Metal-Free Synthesis of N-fused Quinazolino-quinazoline-diones as *MALAT1* RNA triple helix Intercalator

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1. Materials and methods

All the required chemicals and solvents used in this project were purchased from Alfa aesar, TCI india, Thermo Fischer Scientific, Finar, and, Sigma-Aldrich respectively. Column chromatographic purifications were executed using 100−200 and 230−400 Silica gel. All the synthesized molecules were named following IUPAC guidelines as applied by ChemBioDraw Ultra (version 14.0). 400 and 600 MHz spectrometers were used for recording ^{1}H & ^{13}C NMR spectra and are designated as chemical shifts (δ) in parts per million (ppm). ^{1}H NMR multiplicity patterns were given as s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; and coupling constants (J) were denoted as Hertz (Hz). Mass spectral analysis was done using ESI, LCQ-ORBITRAP-XL instrument and EI (magnetic sector, positive ion) mode. UV absorption and fluorescence emission spectra were obtained using Agilent spectrophotometers. Crystal structures were solved with the Bruker Kappa Apex II X-ray crystallography apparatus. 3-Aryl-4(3H)-quinazolinones (II)[1] were synthesized fallowing reported literature.

Molecular docking

The X-ray determined structure of *MALAT1* was retrieved from the PDB database (PDB ID: **4PLX**). Of the three RNA molecules deposited in the PDB, only the most ordered molecule A was considered. The ligand molecules were at first drawn using ChemDraw, energy minimised and randomized after converting them into 3D structures prior to docking. A blind docking study was performed for the ligand wherein the complete receptor lncRNA was considered for search-space. Screening of the molecules by docking them with the *MALAT1* triple using PyRx which is basically Autodock Vina based. Based on the docking scores the molecules were aligned in to the decreasing order of binding energy.

RNA Preparation

All surfaces were cleaned with RNase ZaP prior to handling reagents to avoid RNase contamination. The DNA oligos for *MALAT1* triple helix and duplex were purchased from Bioserve, were amplified using PCR and there is a T7 promoter added to the forward primer. IVT was performed using the Megascript T7 In-Vitro transcription kit using the DNA templates at particular concentration. The concentration of the RNA was measured using absorbance based nanodrop system. RNA extraction was done for purifying the RNA. Sequence length and purity of the *MALAT1* RNA construct was determined using 2.5% agarose gel electrophoresis. The folded triplex was obtained by heating the solutions to 100 °C for 5 min and then keeping on ice for 5 min, followed by a slow return to room temperature. All experiments were performed in 10mM Tris, 100mM KCl buffer at pH 7.4.

MALAT1 triple helix structure establishment through CD spectroscopy

Circular dichroism (CD) spectroscopy was utilized to examine the structural properties associated with triplex formation in both the full-length 94-nucleotide (nt) wild-type sequence and a truncated 73-nt sequence, serving as a control. In order to prevent triplex formation within the control, a strategic deletion of 21-nt from the A-rich strand at the 3' end was executed. CD measurements for both oligonucleotides were conducted at a temperature of 25 °C and a pH of 7.0.

The resulting CD spectra (Figure S1) demonstrated typical characteristics indicative of a nucleic acid duplex adopting the "A" form conformation for both the 94-nt and control 73-nt constructs.

Specifically, a positive band near 265 nm along with a comparable negative band around 210 nm were observed in both cases. However, additional features emerged in the 94-nt sequence, including a weakly positive peak around 219 nm accompanied by a negative counterpart at 243 nm. Conversely, the 73-nt control presented only a minor negative signal at 243 nm.

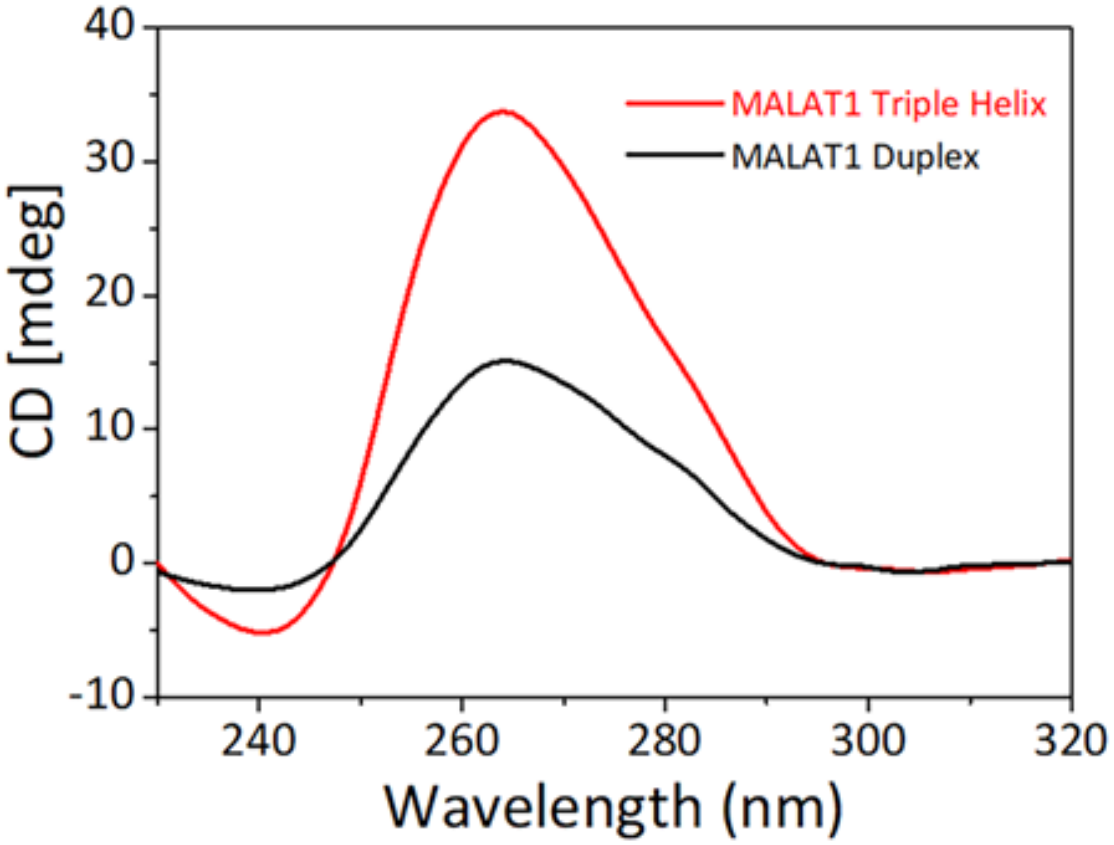


Figure S1: CD spectra of *MALAT1* triplex (red) and control duplex (black), both at 10μM, shows a characteristic triplex-forming signature in the case of the 94-nt triplex.

Notably, the CD spectrum shown in figure S1 derived from the 94-nt sequence showed greater overall intensity compared to that of the duplex control, implying subtle yet significant distinctions in their respective conformations. These discrepancies provide insightful clues regarding the complex nature of triplex formation occurring in the examined oligonucleotides (See reference 7 in manuscript for comparison).

CD Spectroscopy

CD spectra were recorded in a BioLogic MOS-500 spectropolarimeter equipped with a thermoelectrically controlled cell holder and a cuvette with a path length of 1 cm. CD spectra for the triplex and control duplex (both 5 μM) were recorded between 200 and 330 nm at 25 °C, and the spectrum obtained was the average of three scans.

ThT Fluorescence Indicator displacement assay

Lyophilized Calf Thymus (CT) DNA (duplex) dissolved in nuclease free water and concentration was determined by measuring the absorbance at 260 nm. 0.8 µM of CT DNA solution was formed in a cuvette in the 10mM Tris, 100mM KCl buffer at pH 7.4 and Thioflavin T (ThT) was added to 0.2 µM. Then fluorescence was measured by exciting at 350 nm and emission was recorded from 380 nm to 600 nm. Then fluorescence spectra were determined by adding 1 uL of small molecules, starting from 200 nM final concentration. The spectra were recorded by increasing the small molecule concentration until the spectra reached the saturation point. For the shortlisted small molecules to be checked with *MALAT1* triple helix, the RNA was annealed at 95˚ Celsius for 5 min and snap cooled for the 10 mins and brought back to room temperature at a concentration of 50 µM. For fluorescence spectra measurements the RNA concentration was kept at 400 nM in which ThT was added (0.2 µm), fluorescence spectra were determined increasing the small molecule concentration from 200 nM to the point of saturation.

Cell Culture

The HeLa (cell line purchased from National Centre of Cell Science, Pune, India), SKOV-3 cell line purchased from American Type Culture Collection, ATCC, USA) and normal fibroblast cell lines i.e L929 cell line also purchased from National Centre of Cell Science, Pune, India. were maintained in culture flasks containing Dulbecco's Modified Essential Medium (DMEM) and Roswell Park Memorial Institute Medium (RPMI 1640) supplemented with 10% heat-inactivated FBS and 1% antibiotics (100 U/mL penicillin, 100 µg/mL streptomycin). The cells were grown at 37 °C in a humidified incubator set at 5% CO_2. Cells were subcultured after they formed a monolayer on the flask. The cells were detached by treating them with trypsin-EDTA (0.25% trypsin containing 0.01% EDTA) for 5 minutes and then by adding a complete medium to inhibit the reaction.

XTT cell viability assay

EZcount™ XTT Cell Assay Kit was purchased from Himedia, To perform the XTT cell viability assay, XTT solution was prepared according to the manufacturer's protocol. Compound **2z** was resuspended in DMSO to 10 mM stock concentration and then serially diluted in autoclaved water as follows; 50, 20, 8, 2, and 0.5 µM before addition to cell culture. To perform cell viability assay, HeLa, SKOV-3 and normal fibroblast cells were seeded into 96 well plates as 100 cells/well. The next day different working concentrations of the compound **2z** were added in each well of that 96-well plate and incubated for 48 hrs. Control cells were incubated in culture medium only. All aliquot dilution doses were tested in triplicates. After 48 hrs, 25ul of XTT labeling mixture (prepared as stated above) was added to each well of the 96 well plate, and absorbance readouts were performed after 2-4 hrs incubation with XTT at 37 °C and 5% CO_2. The absorbance was measured at 450 nm using an ELISA plate reader (Thermo, USA). The reference wavelength used was 650 nm. Absorbance values obtained were used to determine viability using the following equation:

$$\text{Percent of viability} = \frac{\text{absorbance of sample}}{\text{absorbance of control}} \times 100$$

Half Inhibitory Concentration (IC_{50}) value was determined by using the concentration where 50% cell viability is present.

2. **Table S1:** Binding affinities of 33 synthesized ligands with the *MALAT1* triple helix based on optimal docking model (**PDB ID: 4PLX**).

S.No.	Ligand	Binding Affinity ΔG (kcal/mol)		S.No.	Ligand	Binding Affinity ΔG (kcal/mol)
1	**2z**	**-12.8**		18	2o	-9.6
2	**2n**	**-10.8**		19	2e	-9.6
3	**2h**	**-10.7**		20	2v	-9.6
4	**2g**	**-10.6**		21	4c	-9.4
5	**2l**	**-10.6**		22	4f	-9.4
6	**2s**	**-10.6**		23	2aa	-9.4
7	**2d**	**-10.4**		24	2y	-9.3
8	**2j**	**-10.4**		25	4b	-9.3
9	2i	-10		26	4d	-9.2
10	2q	-10		27	4e	-9.2
11	2k	-10		28	2t	-9
12	2p	-10		29	2a	-8.9
13	2w	-9.9		30	4a	-8.8
14	2f	-9.9		31	2b	-8.8
15	2u	-9.9		32	2c	-8.4
16	2m	-9.7		33	2x	-8.3
17	2r	-9.7				

3. Fluorescence spectroscopy-based screening with double stranded DNA (dsDNA):

The affinity of the small molecules for the dsDNA (calf thymus DNA used) was investigated by measuring the ability of the molecules to alter the fluorescence spectra of Thioflavin T (ThT) bound DNA. ThT (0.2 µM) was added to CTDNA (0.8 µM) in 50 mM Tris/HCl, pH 7.5, and 200 mM KCl, subsequently, the mixture was titrated with the test molecules. The binding of the test molecules to ThT bound DNA manifests alterations in the fluorescence spectra, providing a tangible depiction of the hit molecules forging interactions with dsDNA.

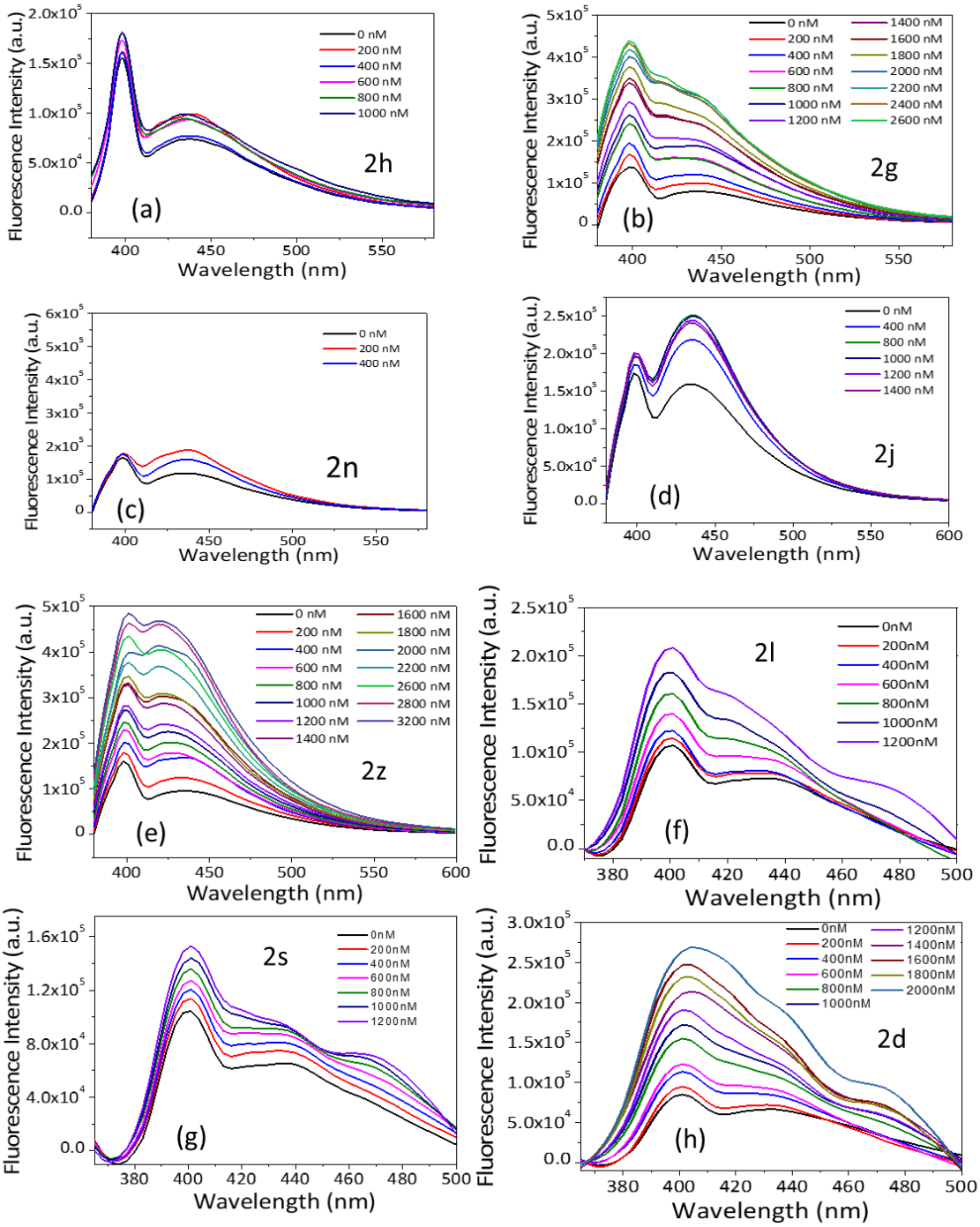


Figure S2: Emission spectra of ThT bound CT DNA in the presence of small molecules with increasing concentration. (a) **2h**, (b) **2g**, (c) **2n**, (d) **2j**, (e) **2z**, (f) **2l**, (g) **2s** and (h) **2d**.

4. Fluorescence spectroscopy-based screening with *MALAT1* triple helix:

The affinity of the small molecules for the *MALAT1* triple helix was investigated by measuring the ability of the molecules to alter the fluorescence spectra of Thioflavin T (ThT) bound RNA. ThT (0.2 µM) was added to RNA (0.4 µM) in 50 mM Tris/HCl, pH 7.5, and 200 mM KCl, subsequently, the mixture was titrated with the test molecules. The binding of the test molecules to ThT bound RNA manifests alterations in the fluorescence spectra, providing a tangible depiction of the hit molecules forging interactions with *MALAT1* triple helix structure.

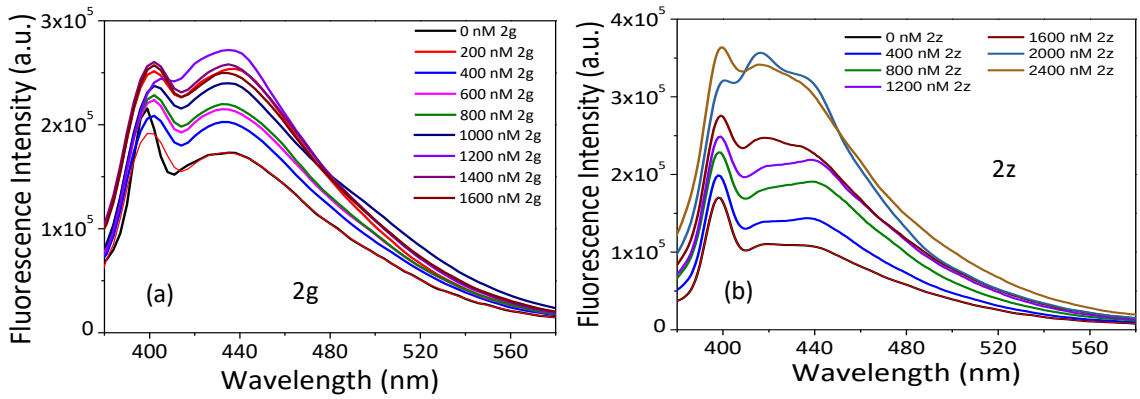


Figure S3: Emission spectra of ThT bound *MALAT1* Triple helix, in the presence of small molecules with increasing concentration. (a) **2g** and (b) **2z.**

5. Temperature dependant CD experiment with *MALAT1* triple helix and 2z.

To check the binding of the molecule **2z** with the *MALAT1* RNA triple helix, we performed the CD melting of the folded *MALAT1* RNA by heating at 95 °C and slowly cooled to 4 °C. The CD spectroscopy was done in presence of 10 mM Tris and 200 mM KCl buffer pH 7.4 and as the temperature was increased from the 25 to 65 °C we observe a change in the peak of the spectrum at 264 nm.

From Figure S4, as the temperature was increased by 10 °C and the spectrum was recorded, we can observe a gradual decrease in the peak intensity at 264 nm in the absence of **2z**. It signifies that increasing the temperature slightly destabilizes the triple helical structure as evident from the decrease in ellipticity observed for *MALAT1* RNA. Nevertheless, the triple helix structure shows significant ellipticity even at 60 °C, indicating that the integrity of the structure is mostly intact. Adding 1 and 2 equivalents of **2z** to the annealed RNA exhibited change in ellipticity which suggests that **2z** binds to *MALAT1* triple helix, but does not significantly alters the conformation of triple helical RNA.

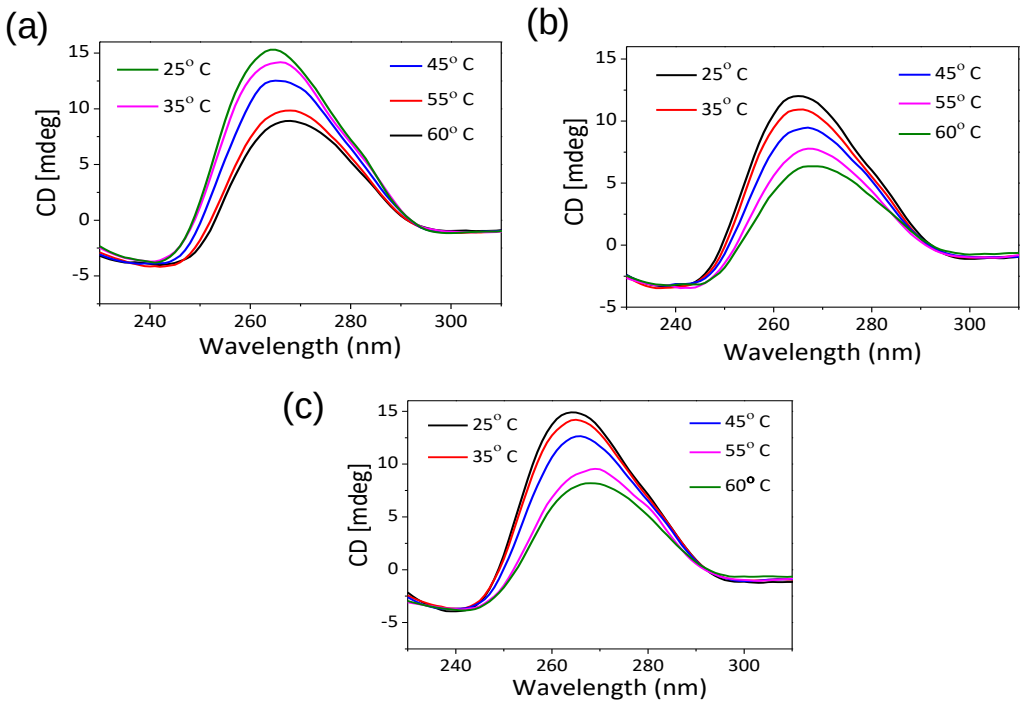
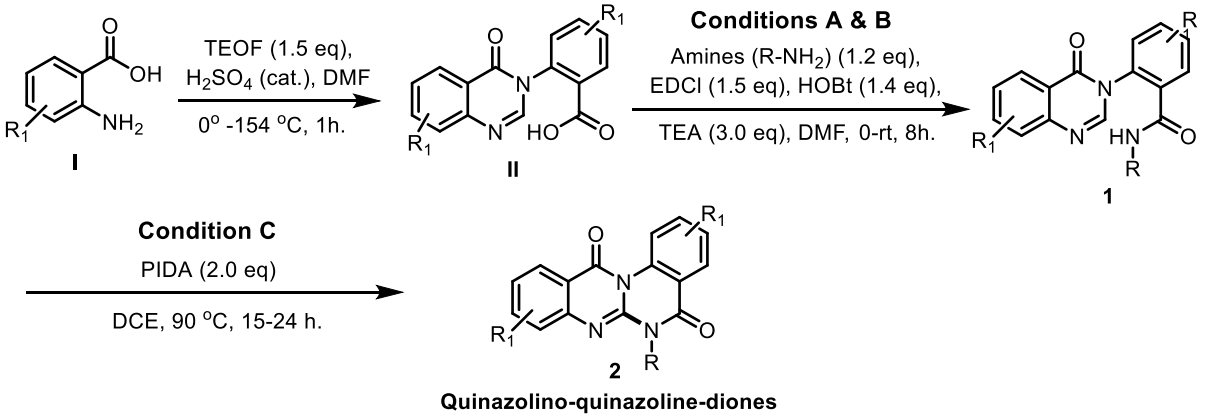


Figure S4: CD melting spectroscopy of *MALAT1* in presence of 10 mM Tris and 200 mM KCl buffer at pH 7.4. (a) CD melting of 2.5 µM *MALAT1* triple helix in absence of **2z**. (b) and (c) CD melting of 2.5 µM *MALAT1* triple helix in presence of 2.5 µM and 5 µM **2z**, respectively.

6. General scheme for the synthesis of quinazolino-quinazoline-diones:



7. General condition A for the synthesis of compounds 1 & 3:

Add **II** (0.5 mmol), EDCl (0.75 mmol), HOBt (0.7 mmol), TEA (1.5 mmol) and dry DMF (1.5 mL) to an oven dried round bottom flask equipped with a magnetic stir bar and stir the reaction mixture for 30 min on an ice bath. After 30 min add amine (0.6 mmol) and allow the reaction mixture to stir for 8 h. After completion of the reaction, reaction mixture was diluted with EtOAc (2 × 30 mL), organic layer was washed with ice cold water (2 × 20 mL) and brine (1 × 15 mL). Combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure to get crude reaction mixture. It was then subjected to Flash chromatography (silica gel 230−400 mesh size, ethyl acetate: pet ether) for further purification to afford desired compounds **1** & **3**.

8. General condition B for the synthesis of compounds 1s and 1u:

Add **II** (0.5 mmol), HATU (0.75 mmol), DIPEA (1.5 mmol) and dry DMF (1.5 mL) to an oven dried round bottom flask equipped with a magnetic stir bar and stir the reaction mixture for 60 min on an ice bath. After 60 min add amine (0.6 mmol) and allow the reaction mixture to stir for 10 h. After completion of the reaction, reaction mixture was diluted with EtOAc (2 × 30 mL), organic layer was washed with ice cold water (2 × 20 mL) and brine (1 × 15 mL). Combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure to get crude reaction mixture. It was then subjected to Flash chromatography (silica gel 230−400 mesh size, ethyl acetate: pet ether) for further purification to afford desired compounds **1s** & **1u**.

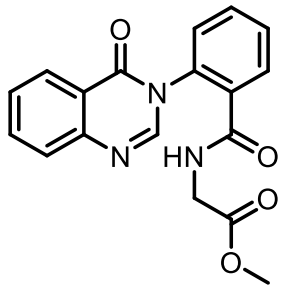
9. General condition C for the synthesis of Quinazolino-quinazoline-diones (2 & 4):

An oven dried sealed tube (10 mL) equipped with a magnetic stir bar was charged **1** or **3** (0.15 mmol), PIDA (0.30 mmol) and dry DCE (1 mL). The sealed tube was capped, and the reaction mixture was stirred at 90 ^{o}C in an oil bath for 15-24 h. After completion of the reaction monitored by TLC, reaction mixture was diluted with DCM (2 × 25 mL), organic layer was washed with distilled deionized water (2 × 15 mL) and brine (1 × 10 mL). combined organic layer was dried over Na_2SO_4, and concentrated in *vacuo* to get crude reaction mixture. It was then subjected to Flash chromatography (silica gel 230−400 mesh size, ethyl acetate: pet ether) for further purification to afford desired compounds **2** & **4**.

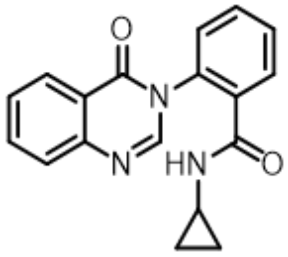
10. Procedure for gram scale synthesis of 2a:

An oven dried sealed tube equipped with a magnetic stir bar was charged **1a** (2.96 mmol), PIDA (5.92 mmol) and dry DCE (15 mL). The sealed tube was capped, and the reaction mixture was stirred at 90 ^{o}C in an oil bath for 15-24 h. After completion of the reaction monitored by TLC, reaction mixture was diluted with DCM (2 × 100 mL), organic layer was washed with distilled deionized water (2 × 50 mL) and brine (1 × 50 mL). combined organic layer was dried over Na_2SO_4, and concentrated in *vacuo* to get crude reaction mixture. It was then subjected to Flash chromatography (silica gel 230−400 mesh size, eluting with 7% ethyl acetate: pet ether) for further purification to afford desired compounds **2a** as white solid (803.9 mg, 81% yield).

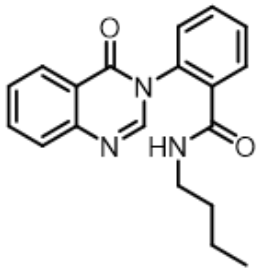
11. Spectral data:



methyl (2-(4-oxoquinazolin-3(4*H*)-yl)benzoyl)glycinate (1a): General condition A was followed, Flash chromatography (SiO_2, eluting with 60% ethyl acetate/pet ether) afforded the desired product as white solid (153.4 mg, 91% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.0 Hz, 1H), 8.12 (s, 1H), 7.81 (d, *J* = 4.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.62-7.53 (m, 3H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.03 (s, 1H), 3.99 (t, *J* = 4.0 Hz, 2H), 3.53 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.73, 166.78, 161.68, 147.67, 146.44, 135.16, 134.95, 134.66, 132.00, 130.22, 129.16, 129.01, 127.81, 127.56, 127.15, 122.17, 52.32, 41.68. **HRMS (ESI):** m/z calculated for $C_{18}H_{16}N_3O_4$ $[M+H]^+$ 338.1135; found 338.1132.

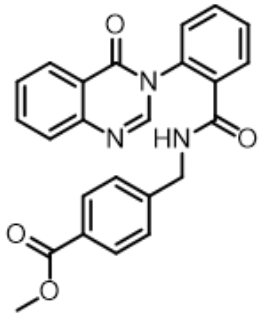


***N*-cyclopropyl-2-(4-oxoquinazolin-3(4*H*)-yl)benzamide (1b):** General condition A was followed, Flash chromatography (SiO_2, eluting with 60% ethyl acetate/pet ether) afforded the desired product as white solid (132.8 mg, 87% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.0 Hz, 1H), 8.09 (s, 1H), 7.81 (d, *J* = 4.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.59-7.49 (m, 3H), 7.29 (d, *J* = 8.0 Hz, 1H), 6.62 (s, 1H), 2.63 (m, 1H), 0.62 (m, 2H), 0.32 (m, 1H), 0.22 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.11, 161.63, 147.55, 146.37, 135.60, 135.15, 134.81, 131.61, 130.17, 128.80, 128.75, 128.02, 127.62, 126.99, 121.91, 22.85, 6.72, 6.40. **HRMS (ESI):** m/z calculated for $C_{18}H_{16}N_3O_2$ $[M+H]^+$ 306.1237; found 306.1240.

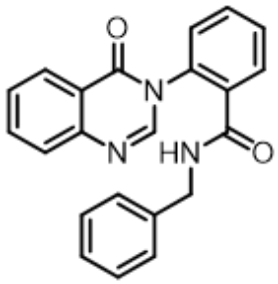


***N*-butyl-2-(4-oxoquinazolin-3(4*H*)-yl)benzamide (1c):** General condition A was followed, Flash chromatography (SiO_2, eluting with 55% ethyl acetate/pet ether) afforded the desired product as yellow sticky solid (143.0 mg, 89% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.0 Hz, 1H),

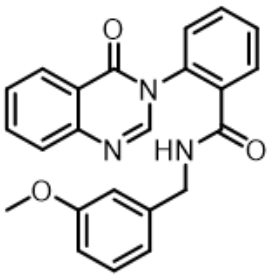
8.04 (s, 1H), 7.78 (d, *J* = 4.0 Hz, 2H), 7.63 (dd, *J* = 8.0 & 4.0 Hz, 1H), 7.65-7.50 (m, 3H), 7.29 (dd, *J* = 8.0 & 4.0 Hz, 1H), 6.50 (s, 1H), 3.26 (m, 1H), 3.08 (m, 1H), 1.21 (m, 2H), 1.08 (m, 2H), 0.65 (t, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.74, 161.94, 148.17, 146.23, 136.34, 134.96, 134.63, 131.34, 130.14, 128.87, 128.81, 127.93, 127.78, 126.94, 122.08, 39.63, 31.44, 19.91, 13.58. **HRMS (ESI):** m/z calculated for $C_{19}H_{20}N_3O_2$ $[M+H]^+$ 322.1550; found 322.1557.



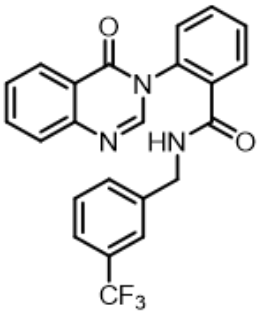
methyl 4-((2-(4-oxoquinazolin-3(4*H*)-yl)benzamido)methyl)benzoate (1d): General condition A was followed, Flash chromatography (SiO_2, eluting with 60% ethyl acetate/pet ether) afforded the desired product as white solid (169.5 mg, 82% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.0 Hz, 1H), 8.00 (s, 1H), 7.78-7.69 (m, 3H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.56 (m, 2H), 7.45 (m, 1H), 7.27 (dd, *J* = 8.0 & 4.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.01 (s, 1H), 4.74 (dd, *J* = 8.0 & 4.0 Hz, 1H), 4.11 (dd, *J* = 8.0 & 4.0 Hz, 1H), 3.89 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.75, 166.68, 162.08, 148.08, 145.84, 142.85, 135.96, 134.93, 134.64, 131.71, 130.34, 129.87, 129.14, 129.06, 128.91, 127.95, 127.80, 127.50, 126.93, 121.80, 52.11, 43.49. **HRMS (ESI):** m/z calculated for $C_{24}H_{20}N_3O_4$ $[M+H]^+$ 414.1448; found 414.1456.



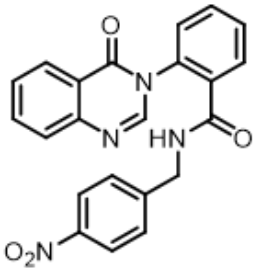
***N*-benzyl-2-(4-oxoquinazolin-3(4*H*)-yl)benzamide (1e):** General condition A was followed, Flash chromatography (SiO_2, eluting with 50% ethyl acetate/pet ether) afforded the desired product as yellow sticky solid (152.8 mg, 86% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.93 (s, 1H), 7.74-7.65 (m, 2H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.48-7.37 (m, 3H), 7.29 (Brs, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 6.98 (s, 5H), 4.41 (dd, *J* = 8.0 & 4.0 Hz, 1H), 4.15 (dd, *J* = 8.0 & 4.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.53, 161.48, 147.88, 146.09, 137.63, 135.41, 134.70, 134.61, 131.25, 129.80, 128.65, 128.26, 127.60, 127.44, 127.34, 127.09, 126.79, 121.82, 43.55. **HRMS (ESI):** m/z calculated for $C_{22}H_{18}N_3O_2$ $[M+H]^+$ 356.1394; found 356.1401.



***N*-(3-methoxybenzyl)-2-(4-oxoquinazolin-3(4*H*)-yl)benzamide (1f):** General condition A was followed, Flash chromatography (SiO_2, eluting with 60% ethyl acetate/pet ether) afforded the desired product as white solid (169.5 mg, 88% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.0 Hz, 1H), 8.03 (s, 1H), 7.80-7.72 (m, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.60-7.50 (m, 2H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 6.91 (t, *J* = 8.0 Hz, 2H), 6.64 (Brs, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 4.53 (dd, *J* = 8.0 & 4.0 Hz, 1H), 4.18 (dd, *J* = 8.0 & 4.0 Hz, 1H), 3.68 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.57, 161.90, 159.63, 148.03, 146.08, 139.16, 135.85, 134.80, 131.60, 130.19, 129.57, 128.95, 128.93, 127.83, 127.68, 126.99, 121.95, 119.84, 113.20, 113.03, 55.15, 43.89. **HRMS (ESI):** m/z calculated for $C_{23}H_{20}N_3O_3$ $[M+H]^+$ 386.1499; found 386.1492.

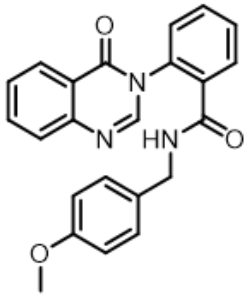


2-(4-oxoquinazolin-3(4*H*)-yl)-*N*-(3-(trifluoromethyl)benzyl)benzamide (1g): General condition A was followed, Flash chromatography (SiO_2, eluting with 50% ethyl acetate/pet ether) afforded the desired product as yellow sticky solid (171.4 mg, 81% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.0 Hz, 1H), 8.03 (s, 1H), 7.81-7.73 (m, 2H), 7.69 (d, *J* = 8.0 & 4.0 Hz, 1H), 7.62-7.53 (m, 3H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.39 (Brs, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 2H), 4.64 (dd, *J* = 8.0 & 4.0 Hz, 1H), 4.23 (dd, *J* = 8.0 & 4.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.88, 162.01, 148.10, 145.95, 138.82, 135.76, 134.98, 134.80, 131.80, 130.96, 130.30, 129.10, 128.94, 128.91, 127.96, 127.88, 126.94, 124.56, 124.52, 124.48, 124.28, 121.85, 43.39. **HRMS (ESI):** m/z calculated for $C_{23}H_{17}F_3N_3O_2$ $[M+H]^+$ 424.1267; found 424.1306.

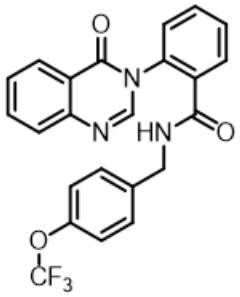


***N*-(4-nitrobenzyl)-2-(4-oxoquinazolin-3(4*H*)-yl)benzamide (1h):** General condition A was followed, Flash chromatography (SiO_2, eluting with 60% ethyl acetate/pet ether) afforded the desired product as yellow solid (160.1 mg, 80% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.78 (s, 1H), 7.78-7.68 (m, 5H), 7.59 (m, 2H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 3H), 4.85 (dd, *J* = 8.0 & 4.0 Hz, 1H), 4.08 (dd, *J* = 8.0 & 4.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.90, 162.10, 148.04, 147.03, 145.79, 145.18, 135.85, 135.23, 134.55,

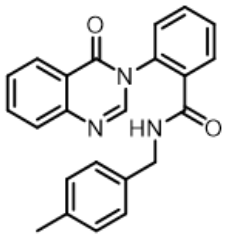
131.84, 130.43, 128.97, 128.90, 128.36, 127.99, 127.86, 126.75, 123.73, 121.60, 43.02. **HRMS (ESI):** m/z calculated for $C_{22}H_{17}N_4O_4$ $[M+H]^+$ 401.1244; found 401.1258.



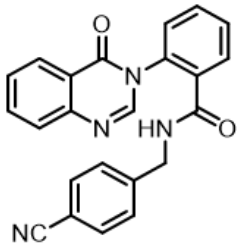
***N*-(4-methoxybenzyl)-2-(4-oxoquinazolin-3(4*H*)-yl)benzamide (1i):** General condition A was followed, Flash chromatography (SiO_2, eluting with 60% ethyl acetate/pet ether) afforded the desired product as white solid (171.5 mg, 89% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.0 Hz, 1H), 8.07 (s, 1H), 7.82-7.75 (m, 2H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.55 (m, 2H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.84 (s, 1H), 6.51 (d, *J* = 8.0 Hz, 2H), 4.54 (dd, *J* = 8.0 & 4.0 Hz, 1H), 4.09 (dd, *J* = 8.0 & 4.0 Hz, 1H), 3.69 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.07, 161.50, 158.45, 147.28, 145.88, 135.63, 134.60, 134.27, 131.24, 129.99, 129.39, 128.76, 128.66, 128.60, 127.43, 127.21, 126.80, 121.53, 113.55, 54.82, 43.05. **HRMS (ESI):** m/z calculated for $C_{23}H_{20}N_3O_3$ $[M+H]^+$ 386.1499; found 386.1498.



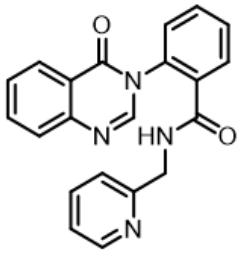
2-(4-oxoquinazolin-3(4*H*)-yl)-*N*-(4-(trifluoromethoxy)benzyl)benzamide (1j): General condition A was followed, Flash chromatography (SiO_2, eluting with 50% ethyl acetate/pet ether) afforded the desired product as white solid (180.1 mg, 82% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.0 Hz, 1H), 8.01 (s, 1H), 7.84-7.68 (m, 3H), 7.61-7.48 (m, 3H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.96 (s, 1H), 6.82 (d, *J* = 8.0 Hz, 2H), 4.65 (dd, *J* = 8.0 & 4.0 Hz, 1H), 4.13 (dd, *J* = 8.0 & 4.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.77, 162.05, 148.40, 148.16, 145.94, 136.38, 135.88, 135.08, 134.72, 131.72, 130.29, 129.03, 128.91, 128.01, 127.85, 126.89, 121.90, 121.74, 120.86, 119.18, 43.08. **HRMS (ESI):** m/z calculated for $C_{23}H_{17}F_3N_3O_3$ $[M+H]^+$ 440.1217; found 440.1220.



***N*-(4-methylbenzyl)-2-(4-oxoquinazolin-3(4*H*)-yl)benzamide (1k):** General condition A was followed, Flash chromatography (SiO_2, eluting with 50% ethyl acetate/pet ether) afforded the desired product as white solid (158.8 mg, 86% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.96 (s, 1H), 7.78-7.63 (m, 3H), 7.54-7.43 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.08 (s, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 8.0 Hz, 2H), 4.58 (dd, *J* = 8.0 & 4.0 Hz, 1H), 4.13 (dd, *J* = 8.0 & 4.0 Hz, 1H), 2.15 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.43, 161.73, 148.00, 146.02, 136.70, 135.76, 134.65, 134.58, 131.31, 129.97, 129.05, 128.86, 128.75, 127.69, 127.48, 127.42, 126.91, 121.85, 43.45, 21.04. **HRMS (ESI):** m/z calculated for $C_{23}H_{20}N_3O_2$ $[M+H]^+$ 370.1550; found 370.1573.

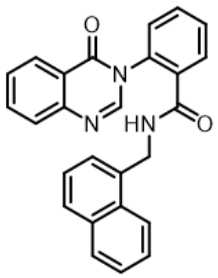


***N*-(4-cyanobenzyl)-2-(4-oxoquinazolin-3(4*H*)-yl)benzamide (1l):** General condition A was followed, Flash chromatography (SiO_2, eluting with 60% ethyl acetate/pet ether) afforded the desired product as white solid (152.1 mg, 80% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.0 Hz, 1H), 8.00 (s, 1H), 7.87 (t, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.61-7.51 (m, 4H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 12.0 Hz, 2H), 7.12 (d, *J* = 12.0 Hz, 2H), 4.78 (dd, *J* = 8.0 & 4.0 Hz, 1H), 4.08 (dd, *J* = 8.0 & 4.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.90, 162.05, 148.01, 145.87, 143.14, 135.81, 135.39, 134.55, 132.25, 131.83, 130.42, 128.96, 128.91, 128.21, 128.03, 128.00, 126.82, 121.69, 118.65, 111.24, 43.32. **HRMS (EI):** m/z calculated for $C_{23}H_{16}N_4O_2$ is 380.1273; found 380.1276.

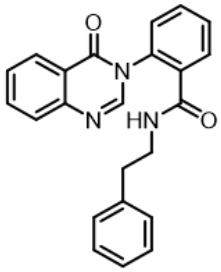


2-(4-oxoquinazolin-3(4*H*)-yl)-*N*-(pyridin-2-ylmethyl)benzamide (1m): General condition A was followed, Flash chromatography (SiO_2, eluting with 90% ethyl acetate/pet ether) afforded the desired product as white solid (138.9 mg, 78% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.0 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 8.06 (s, 1H), 7.80-7.72 (m, 3H), 7.63-7.55 (m, 2H), 7.49 (t, *J* = 8.0 Hz,

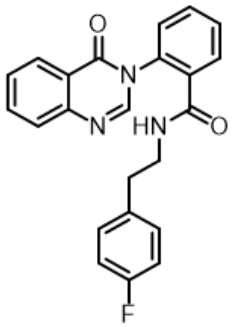
2H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 4.67 (dd, *J* = 8.0 & 4.0 Hz, 1H), 4.45 (dd, *J* = 8.0 & 4.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$ δ 166.61, 161.68, 156.08, 148.77, 148.20, 146.29, 136.80, 135.21, 135.17, 134.70, 131.72, 130.12, 129.11, 127.88, 127.57, 127.12, 122.35, 121.98, 44.91. **HRMS (ESI):** m/z calculated for $C_{21}H_{17}N_4O_2$ $[M+H]^+$ 357.1346; found 357.1363.



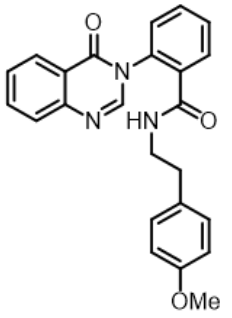
***N*-(naphthalen-1-ylmethyl)-2-(4-oxoquinazolin-3(4*H*)-yl)benzamide (1n):** General condition A was followed, Flash chromatography (SiO_2, eluting with 50% ethyl acetate/pet ether) afforded the desired product as white solid (168.2 mg, 83% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.85 (m, 2H), 7.76-7.62 (m, 5H), 7.57-7.53 (m, 3H), 7.42-7.34 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 2H), 6.98 (s, 1H), 5.09 (dd, *J* = 8.0 & 4.0 Hz, 1H), 4.65 (dd, *J* = 8.0 & 4.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.13, 161.66, 146.84, 146.10, 135.68, 134.84, 134.57, 133.60, 132.88, 131.72, 131.13, 130.37, 129.33, 129.01, 128.79, 128.73, 127.87, 127.32, 126.90, 126.88, 126.70, 125.96, 125.16, 123.14, 121.49, 41.98. **HRMS (ESI):** m/z calculated for $C_{26}H_{20}N_3O_2$ $[M+H]^+$ 406.1550; found 406.1557.



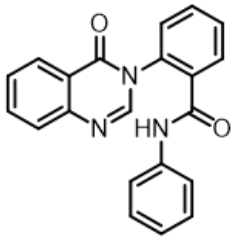
2-(4-oxoquinazolin-3(4*H*)-yl)-N-phenethylbenzamide (1o): General condition A was followed, Flash chromatography (SiO_2, eluting with 50% ethyl acetate/pet ether) afforded the desired product as white solid (157.0 mg, 85% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 8.0 Hz, 1H), 8.06 (s, 1H), 7.83-7.77 (m, 2H), 7.61-7.49 (m, 4H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.44 (s, 1H), 3.47 (m, 2H), 2.64 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.80, 161.75, 148.25, 146.27, 138.67, 135.89, 135.04, 134.93, 131.55, 130.08, 128.91, 128.71, 128.67, 128.64, 128.03, 127.78, 127.01, 126.58, 122.16, 41.09, 35.45. **HRMS (ESI):** m/z calculated for $C_{23}H_{20}N_3O_2$ $[M+H]^+$ 370.1550; found 370.1543.



***N*-(4-fluorophenethyl)-2-(4-oxoquinazolin-3(4*H*)-yl)benzamide (1p):** General condition A was followed, Flash chromatography (SiO_2, eluting with 50% ethyl acetate/pet ether) afforded the desired product as yellow sticky solid (154.9 mg, 80% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.0 Hz, 1H), 8.06 (s, 1H), 7.83-7.77 (m, 2H), 7.60-7.50 (m, 5H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.06-7.02 (m, 2H), 6.88 (t, *J* = 8.0 Hz, 2H), 6.53 (s, 1H), 3.49 (m, 1H), 3.38 (m, 1H), 2.64 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.90, 162.86, 161.77, 160.43, 148.16, 146.27, 135.80, 135.01, 134.30, 131.62, 130.12, 130.03, 128.89, 128.67, 127.99, 127.84, 126.94, 122.05, 115.53, 115.32, 41.09, 34.57. **HRMS (ESI):** m/z calculated for $C_{23}H_{19}FN_3O_2$ $[M+H]^+$ 388.1456; found 388.1448.

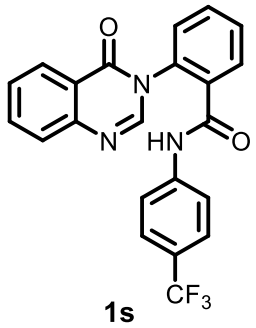


***N*-(4-methoxyphenethyl)-2-(4-oxoquinazolin-3(4*H*)-yl)benzamide (1q):** General condition A was followed, Flash chromatography (SiO_2, eluting with 55% ethyl acetate/pet ether) afforded the desired product as white solid (171.7 mg, 86% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.0 Hz, 1H), 8.05 (s, 1H), 7.82-7.78 (m, 2H), 7.59-7.49 (m, 4H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.46 (s, 1H), 3.75 (s, 3H), 3.42 (m, 1H), 2.64 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.77, 161.70, 158.28, 148.21, 146.27, 135.86, 135.03, 134.90, 131.51, 130.65, 130.04, 129.64, 128.87, 128.62, 127.97, 127.74, 126.97, 122.13, 114.07, 55.31, 41.26, 34.51. **HRMS (ESI):** m/z calculated for $C_{24}H_{22}N_3O_3$ $[M+H]^+$ 400.1656; found 400.1657.



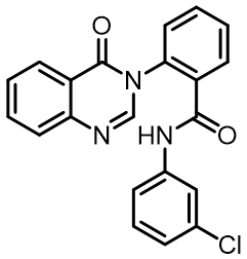
2-(4-oxoquinazolin-3(4*H*)-yl)-*N*-phenylbenzamide (1r): General condition A was followed, Flash chromatography (SiO_2, eluting with 50% ethyl acetate/pet ether) afforded the desired product as pale

yellow solid (124.6 g, 73% yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 10.5 (s, 1H), 8.33 (s, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.88-7.84 (m, 2H), 7.78-7.64 (m, 4H), 7.58-7.53 (m, 3H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** (100 MHz, DMSO-d_6): δ 166.77, 161.70, 158.28, 148.21, 146.27, 135.86, 135.03, 134.90, 131.51, 130.65, 130.04, 129.64, 128.87, 128.62, 127.97, 127.74, 126.97, 122.13, 114.07, 55.31, 41.26, 34.51. **HRMS (ESI):** m/z calculated for $C_{21}H_{16}N_3O_2$ $[M+H]^+$ 342.1237; found 342.1248.

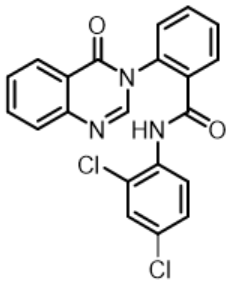


1s

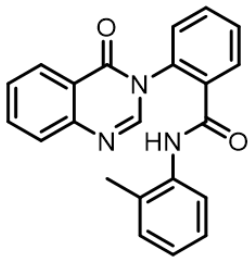
2-(4-oxoquinazolin-3(4H)-yl)-N-(4-(trifluoromethyl)phenyl)benzamide (1s): General condition B was followed, Flash chromatography (SiO_2, eluting with 50% ethyl acetate/pet ether) afforded the desired product as white solid (114.6 mg, 56% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): 8.35 (d, J = 4.0 Hz, 2H), 7.87 (brs, 3H), 7.70 – 7.61 (m, 6H), 7.48 (brs, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 163.62, 160.57, 155.00, 145.00, 144.80, 139.54, 134.64, 134.29, 133.16, 131.61, 129.81, 128.70, 128.63, 127.60, 126.16, 125.31, 125.13, 123.77, 121.97, 120.44, 118.86. **HRMS (ESI):** m/z calculated for $C_{22}H_{15}F_3N_3O_2$ $[M+H]^+$ 410.1111; found 410.1107.



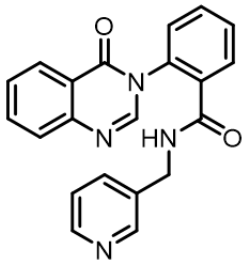
N-(3-chlorophenyl)-2-(4-oxoquinazolin-3(4H)-yl)benzamide (1t): General condition A was followed, Flash chromatography (SiO_2, eluting with 50% ethyl acetate/pet ether) afforded the desired product as white solid (131.5 mg, 70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.82 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 8.19 (s, 1H), 7.82 (d, J = 4.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.63-7.55 (m, 4H), 7.30 (t, J = 8.0 Hz, 2H), 7.10 (t, J = 8.0 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.73, 162.07, 147.40, 146.23, 145.14, 138.93, 135.69, 135.48, 134.67, 132.18, 130.49, 130.00, 129.40, 128.94, 128.37, 127.60, 127.13, 124.74, 121.76, 120.21, 118.07. **HRMS (ESI):** m/z calculated for $C_{21}H_{15}ClN_3O_2$ $[M+H]^+$ 376.0847; found 376.0854.



***N*-(2,4-dichlorophenyl)-2-(4-oxoquinazolin-3(4*H*)-yl)benzamide (1u):** General condition B was followed, Flash chromatography (SiO_2, eluting with 50% ethyl acetate/pet ether) afforded the desired product as pale yellow solid (118.9 mg, 58% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.0 Hz, 2H), 8.18 (s, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 4.0 Hz, 2H), 7.72-7.62 (m, 2H), 7.54-7.50 (m, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 4.0 Hz, 1H), 7.16 (dd, *J* = 8.0 & 4.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.67, 161.35, 147.73, 146.13, 135.46, 135.05, 134.74, 133.14, 132.57, 130.33, 130.08, 129.36, 128.97, 128.61, 127.95, 127.90, 127.68, 127.25, 124.58, 123.17, 122.09. **HRMS (ESI):** m/z calculated for $C_{21}H_{14}Cl_2N_3O_2$ $[M+H]^+$ 410.0458; found 410.0475.

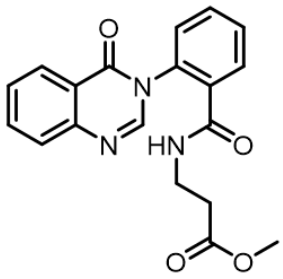


2-(4-oxoquinazolin-3(4H)-yl)-N-(o-tolyl)benzamide (1v): General condition A was followed, Flash chromatography (SiO_2, eluting with 50% ethyl acetate/pet ether) afforded the desired product as pale yellow solid (135.0 mg, 76% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.29 (d, J = 8.0 Hz, 1H), 8.11 (s, 1H), 7.96 (Brs, 1H), 7.83-7.75 (m, 3H), 7.66-7.57 (m, 3H), 7.51 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.11 (t, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 1H), 2.16 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.67, 161.35, 147.73, 146.13, 135.46, 135.05, 134.74, 133.14, 132.57, 130.33, 130.08, 129.36, 128.97, 128.61, 127.95, 127.90, 127.68, 127.25, 124.58, 123.17, 122.09. **HRMS (ESI):** m/z calculated for $C_{22}H_{18}N_3O_2$ $[M+H]^+$ 356.1394; found 356.1413.

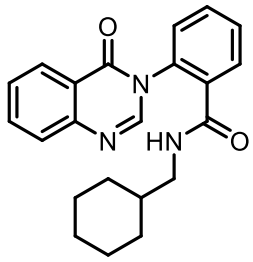


2-(4-oxoquinazolin-3(4H)-yl)-N-(pyridin-3-ylmethyl)benzamide (1w): General condition A was followed, Flash chromatography (SiO_2, eluting with 90% ethyl acetate/pet ether) afforded the desired product as white solid (137.2 mg, 77% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.34 (Brs, 2H), 8.13 (d,

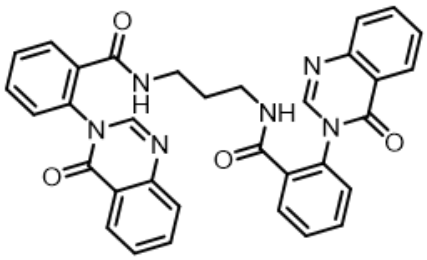
J = 8.0 Hz, 1H), 8.02 (s, 1H), 7.82-7.73 (m, 2H), 7.69 (d, J = 8.0 Hz, 1H), 7.61-7.49 (m, 3H), 7.40 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 4.0 Hz, 1H), 6.90 (s, 1H), 4.58 (dd, J = 8.0 & 16.0 Hz, 1H), 4.20 (dd, J = 8.0 & 16.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.95, 161.88, 148.79, 148.51, 148.15, 146.00, 135.63, 135.59, 135.00, 134.89, 133.67, 131.77, 130.21, 128.86, 128.00, 127.89, 126.96, 123.61, 121.89, 114.70, 41.20. **HRMS (EI):** m/z calculated for $C_{21}H_{16}N_4O_2$ is 356.1273; found 356.1269.



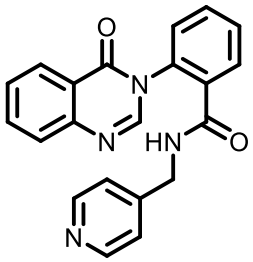
methyl 3-(2-(4-oxoquinazolin-3(4H)-yl)benzamido)propanoate (1x): General condition A was followed, Flash chromatography (SiO_2, eluting with 60% ethyl acetate/pet ether) afforded the desired product as white solid (159.8 mg, 91% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.30 (d, J = 8.0 Hz, 1H), 8.07 (s, 1H), 7.82-7.76 (m, 2H), 7.66-7.51 (m, 4H), 7.33 (d, J = 8.0 Hz, 1H), 6.81 (s, 1H), 3.61 (s, 3H), 3.55 (m, 1H), 3.44 (m, 1H), 2.41 (t, J = 8.0 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 172.76, 166.96, 161.47, 148.23, 146.27, 135.40, 135.18, 134.84, 131.68, 129.99, 128.80, 128.55, 127.94, 127.72, 127.05, 122.24, 51.86, 35.34, 33.44. **HRMS (EI):** m/z calculated for $C_{19}H_{17}N_3O_4$ is 351.1219; found 351.1218.



N-(cyclohexylmethyl)-2-(4-oxoquinazolin-3(4H)-yl)benzamide (1y): General condition A was followed, Flash chromatography (SiO_2, eluting with 50% ethyl acetate/pet ether) afforded the desired product as white solid (162.6 mg, 90% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.32 (d, J = 8.0 Hz, 1H), 8.08 (s, 1H), 7.81 (s, 2H), 7.68-7.66 (m, 1H), 7.60-7.54 (m, 3H), 7.31 (d, J = 8.0 Hz, 1H), 6.45 (s, 1H), 3.22 (m, 1H), 2.89 (m, 1H), 1.50-1.37 (m, 5H), 1.19 (m, 1H), 0.99-0.65 (m, 5H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.79, 161.99, 147.95, 146.27, 136.53, 135.09, 134.45, 131.42, 130.31, 129.14, 128.90, 127.93, 127.89, 127.06, 122.11, 46.21, 37.96, 30.76, 30.68, 26.22, 25.78, 25.61. **HRMS (EI):** m/z calculated for $C_{22}H_{23}N_3O_2$ is 361.1790; found 361.1797.

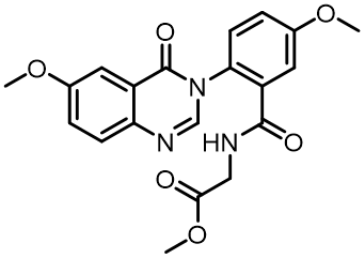


***N,N'*-(propane-1,3-diyl)bis(2-(4-oxoquinazolin-3(4*H*)-yl)benzamide) (1z):** General condition A was followed, Flash chromatography (SiO_2, eluting with 80% ethyl acetate/pet ether) afforded the desired product as pale yellow solid (176.8 mg, 62% yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.37-8.32 (m, 2H), 8.22 (s, 2H), 8.13 (t, *J* = 8.0 Hz, 2H), 7.86 (t, *J* = 8.0 Hz, 2H), 7.73 (t, *J* = 8.0 Hz, 2H), 7.67 (t, *J* = 8.0 Hz, 2H), 7.58-7.56 (m, 4H), 7.55 (d, *J* = 4.0 Hz, 2H), 7.51 (t, *J* = 8.0 Hz, 2H), 3.03 (m, 4H), 1.40 (m, 2H). **^{13}C NMR** (100 MHz, DMSO-d_6): δ 165.97, 160.02, 147.90, 147.40, 135.63, 134.58, 134.47, 131.14, 129.20, 128.08, 127.23, 126.33, 121.86, 72.50, 63.09, 36.24, 36.04. **HRMS (ESI):** m/z calculated for $C_{33}H_{27}N_6O_4$ $[M+H]^+$ 571.2088; found 571.2095.



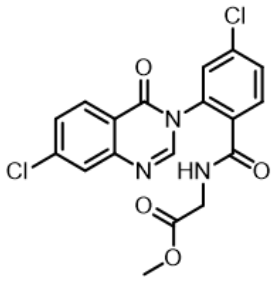
1aa

2-(4-oxoquinazolin-3(4H)-yl)-N-(pyridin-4-ylmethyl)benzamide (1aa): General condition A was followed, Flash chromatography (SiO_2, eluting with 90% ethyl acetate/pet ether) afforded the desired product as pale yellow solid (137.2 mg, 77% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.0 Hz, 2H), 8.16 (d, J = 8.0 Hz, 1H), 8.04 (s, 1H), 7.84 – 7.75 (m, 2H), 7.71 (d, J = 8.0 Hz, 1H), 7.63 – 7.50 (m, 3H), 7.31 (d, J = 8.0 Hz, 1H), 7.23 (brs, 1H), 6.97 (d, J = 4.0 Hz, 2H), 4.63 (dd, J = 8.0 Hz, 1H), 4.18 (dd, J = 8.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.83, 161.66, 149.29, 147.84, 146.72, 145.68, 135.23, 134.91, 134.59, 131.57, 129.93, 128.58, 128.53, 127.77, 127.69, 126.49, 121.96, 121.61, 42.36. **HRMS (EI):** m/z calculated for $C_{21}H_{16}N_4O_2$ is 356.1273; found 356.1269.

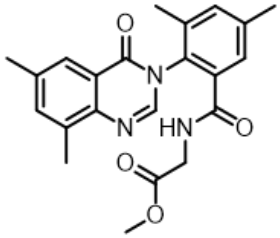


methyl (5-methoxy-2-(6-methoxy-4-oxoquinazolin-3(4H)-yl)benzoyl)glycinate (1ab): General condition A was followed, Flash chromatography (SiO_2, eluting with 60% ethyl acetate/pet ether) afforded the desired product as white solid (176.8 mg, 89% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 4.0 Hz, 1H), 7.39 (dd, J = 8.0 & 4.0 Hz, 1H), 7.24 (d, J = 4.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.10 (dd, J = 8.0 & 4.0 Hz, 1H), 7.04 (s, 1H), 3.99 (d, J =

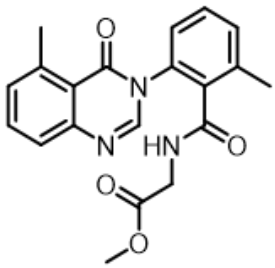
4.0 Hz, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.51 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.64, 166.64, 162.12, 160.49, 159.16, 144.68, 142.43, 135.88, 130.31, 129.20, 127.53, 124.95, 123.05, 117.29, 114.28, 106.70, 56.00, 55.97, 52.31, 41.69. **HRMS (EI):** m/z calculated for $C_{20}H_{19}N_3O_6$ is 397.1274; found 397.1265.



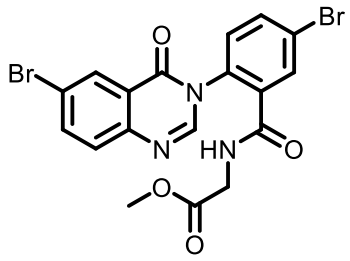
methyl (4-chloro-2-(7-chloro-4-oxoquinazolin-3(4*H*)-yl)benzoyl)glycinate (1ac): General condition A was followed, Flash chromatography (SiO_2, eluting with 50% ethyl acetate/pet ether) afforded the desired product as white solid (174.6 mg, 86% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.0 Hz, 1H), 8.05 (s, 1H), 7.78 (d, *J* = 4.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.56 (dd, *J* = 8.0 & 4.0 Hz, 1H), 7.50 (dd, *J* = 8.0 & 4.0 Hz, 1H), 7.38 (d, *J* = 4.0 Hz, 1H), 6.91 (s, 1H), 3.99 (t, *J* = 8.0 Hz, 2H), 3.60 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.67, 165.82, 160.93, 148.93, 146.96, 141.37, 137.77, 136.21, 132.94, 130.48, 130.01, 129.54, 128.58, 128.50, 127.49, 120.61, 52.48, 41.70. **HRMS (ESI):** m/z calculated for $C_{18}H_{14}Cl_2N_3O_4$ $[M+H]^+$ 406.0356; found 406.0360.



methyl (2-(6,8-dimethyl-4-oxoquinazolin-3(4*H*)-yl)-3,5-dimethylbenzoyl)glycinate (1ad): General condition A was followed, Flash chromatography (SiO_2, eluting with 40% ethyl acetate/pet ether) afforded the desired product as white solid (175.0 mg, 89% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.89 (s, 1H), 7.48 (s, 1H), 7.36 (s, 1H), 7.28 (s, 1H), 6.83 (s, 1H), 3.95 (dd, *J* = 8.0 & 4.0 Hz, 2H), 3.48 (s, 3H), 2.63 (s, 3H), 2.45 (s, 3H), 2.41 (s, 3H), 2.04 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.70, 167.38, 162.26, 144.98, 144.70, 140.33, 137.37, 137.09, 136.79, 136.12, 135.05, 134.04, 131.45, 127.28, 124.27, 122.11, 52.22, 41.65, 21.40, 21.19, 17.77, 17.53. **HRMS (ESI):** m/z calculated for $C_{22}H_{24}N_3O_4$ $[M+H]^+$ 394.1761; found 394.1779.

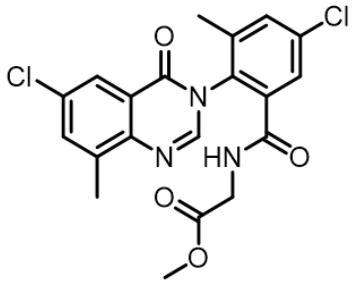


methyl (2-methyl-6-(5-methyl-4-oxoquinazolin-3(4*H*)-yl)benzoyl)glycinate (1ae): General condition A was followed, Flash chromatography (SiO_2, eluting with 50% ethyl acetate/pet ether) afforded the desired product as white solid (158.9 mg, 87% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.64 (d, *J* = 4.0 Hz, 1H), 7.63 (s, 1H), 7.47-7.38 (m, 2H), 7.29 (t, *J* = 4.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.92 (m, 1H), 3.96 (t, *J* = 8.0 Hz, 2H), 3.43 (s, 3H), 2.82 (s, 3H), 2.46 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.35, 167.14, 162.73, 149.44, 146.06, 141.84, 137.86, 136.07, 134.30, 134.14, 132.03, 130.48, 126.01, 125.85, 120.78, 52.17, 41.27, 23.27, 19.42. **HRMS (EI):** m/z calculated for $C_{20}H_{19}N_3O_4$ is 365.1376; found 365.1374.



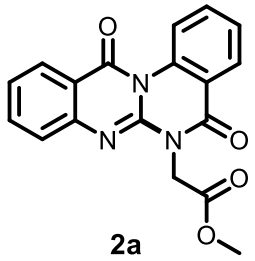
3e

methyl (5-bromo-2-(6-bromo-4-oxoquinazolin-3(4H)-yl)benzoyl)glycinate (1af): General condition A was followed, Flash chromatography (SiO_2, eluting with 50% ethyl acetate/pet ether) afforded the desired product as white solid (173.2 mg, 70% yield). **^{1}H NMR** (400 MHz, DMSO-D6) δ 9.05 (t, J = 4.0 Hz, 1H), 8.17 (s, 1H), 8.13 (s, 1H), 7.95 (dd, J = 8.0 & 2.4 Hz, 1H), 7.88 – 7.85 (m, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 3.83 – 3.73 (m, 2H), 3.44 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D6) δ 169.17, 164.22, 158.34, 147.15, 146.30, 137.02, 134.32, 134.27, 133.93, 131.30, 130.80, 129.20, 127.88, 122.84, 121.87, 119.21, 51.15, 40.47. **HRMS (ESI):** m/z calculated for $C_{18}H_{14}Br_2N_3O_4$ $[M+H]^+$ 493.9346; found 493.9340.



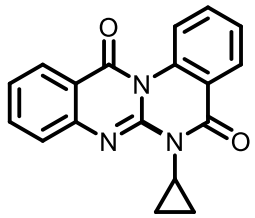
methyl(5-chloro-2-(6-chloro-8-methyl-4-oxoquinazolin-3(4H)-yl)-3-methylbenzoyl)glycinate (1ag): General condition A was followed, Flash chromatography (SiO_2, eluting with 50% ethyl acetate/pet ether) afforded the desired product as white solid (162.8 mg, 75% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.90 (s, 1H), 7.61 (s, 1H), 7.52 (s, 1H), 7.48 (s, 1H), 6.88 (s, 1H), 3.95

(t, J = 4.0 Hz, 2H), 3.56 (s, 3H), 2.63 (s, 3H), 2.13 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.47, 165.85, 160.86, 145.62, 145.17, 139.19, 138.96, 136.45, 135.98, 135.72, 133.23, 133.02, 132.46, 126.64, 124.03, 123.34, 52.41, 41.64, 17.88, 17.52. **HRMS (EI):** m/z calculated for $C_{20}H_{17}Cl_2N_3O_4$ is 433.0596; found 433.0603.



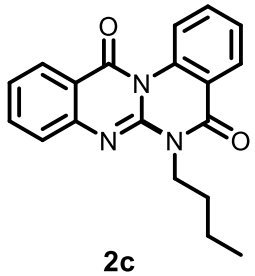
2a

methyl 2-(5,12-dioxo-5H-quinazolino[3,2-a]quinazolin-6(12H)-yl)acetate (2a): General condition C was followed, Flash chromatography (SiO_2, eluting with 7% ethyl acetate/pet ether) afforded the desired product as white solid (42.2 mg, 84% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.22 (d, *J* = 12.0 Hz, 1H), 8.38 (d, *J* = 12.0 Hz, 1H), 8.29 (d, *J* = 6.0 Hz, 1H), 7.79 (t, *J* = 6.0 Hz, 1H), 7.74 (t, *J* = 12.0 Hz, 1H), 7.53 - 7.50 (m, 2H), 7.42 (t, *J* = 6.0 Hz, 1H), 5.21 (s, 2H), 3.79 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 168.00, 161.63, 158.91, 144.83, 142.07, 135.72, 134.86, 134.13, 128.12, 127.23, 126.59, 125.59, 125.23, 120.67, 118.48, 117.68, 52.12, 43.43. **HRMS (EI):** m/z calculated for C18H13N3O4 is 335.0906; found 335.0907.



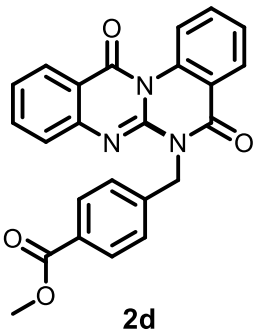
2b

6-cyclopropyl-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2b): General condition C was followed, Flash chromatography (SiO_2, eluting with 7% ethyl acetate/pet ether) afforded the desired product as white solid (24.0 mg, 53% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.06 (d, *J* = 6.0 Hz, 1H), 8.30 (d, *J* = 6.0 Hz, 2H), 7.77 - 7.71 (m, 2H), 7.64 (d, *J* = 6.0 Hz, 1H), 7.49 (t, *J* = 6.0 Hz, 1H), 7.42 (t, *J* = 6.0 Hz, 1H), 3.09 – 3.05 (m, 1H), 1.36 – 1.32 (m, 2H), 0.88 – 0.86 (m, 2H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.67, 160.75, 145.44, 143.79, 135.45, 134.77, 133.32, 127.48, 127.15, 126.40, 125.93, 125.05, 120.89, 119.30, 118.52, 26.91, 9.92. **HRMS (ESI):** m/z calculated for $C_{18}H_{14}N_3O_2$ $[M+H]^+$ 304.1081; found 304.1090.



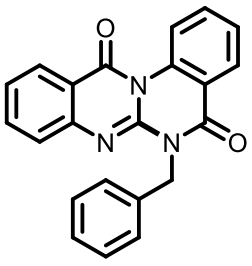
2c

6-butyl-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2c): General condition C was followed, Flash chromatography (SiO_2, eluting with 5% ethyl acetate/pet ether) afforded the desired product as white solid (27.3 mg, 57% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.14 (d, *J* = 8.0 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 8.27 (d, *J* = 4.0 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 4.0 Hz, 1H), 4.48 (t, *J* = 8.0 Hz, 2H), 1.84 – 1.76 (m, 2H), 1.52 - 1.43 (m, 2H), 1.03 (t, *J* = 8.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.44, 159.60, 145.94, 142.77, 136.02, 135.25, 133.98, 128.32, 127.64, 126.90, 126.13, 125.35, 121.00, 118.82, 118.75, 43.18, 29.45, 20.35, 13.92. **HRMS (ESI):** m/z calculated for $C_{19}H_{18}N_3O_2$ $[M+H]^+$ 320.1394; found 320.1393.



2d

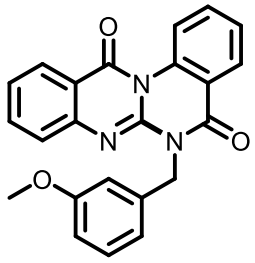
methyl 4-((5,12-dioxo-5H-quinazolino[3,2-a]quinazolin-6(12H)-yl)methyl)benzoate (2d): General condition C was followed, Flash chromatography (SiO_2, eluting with 6% ethyl acetate/pet ether) afforded the desired product as white solid (41.3 mg, 67% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.18 (d, *J* = 12.0 Hz, 1H), 8.41 (d, *J* = 6.0 Hz, 1H), 8.29 (d, *J* = 6.0 Hz, 1H), 7.97 (d, *J* = 6.0 Hz, 2H), 7.79 – 7.73 (m, 2H), 7.65 (d, *J* = 6.0 Hz, 2H), 7.57 (d, *J* = 6.0 Hz, 1H), 7.54 (t, *J* = 6.0 Hz, 1H), 7.42 (t, *J* = 6.0 Hz, 1H), 5.73 (s, 2H), 3.87 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.77, 162.15, 159.70, 145.34, 142.52, 141.95, 135.98, 135.31, 134.35, 129.62, 129.28, 128.80, 128.50, 127.62, 126.98, 125.88, 125.58, 120.96, 118.82, 118.29, 52.01, 45.72. **HRMS (ESI):** m/z calculated for $C_{24}H_{18}N_3O_4$ $[M+H]^+$ 412.1292; found 412.1280.



2e

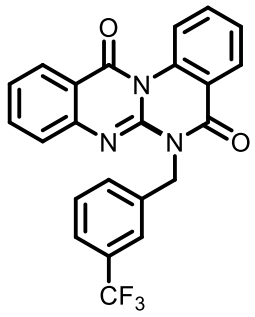
6-benzyl-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2e): General condition C was followed, Flash chromatography (SiO_2, eluting with 5% ethyl acetate/pet ether) afforded the desired product as white solid (27.5 mg, 52% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.17 (d, J = 12.0 Hz, 1H), 8.41 (d, J = 6.0 Hz, 1H), 8.29 (d, J = 6.0 Hz, 1H), 7.77 (t, J = 12.0 Hz, 2H), 7.65 (d, J = 6.0 Hz, 2H), 7.62 (d, J = 6.0 Hz, 1H), 7.53 (t, J = 6.0 Hz, 1H), 7.42 (t, J = 6.0 Hz, 1H), 7.33 (t, J = 12.0 Hz, 2H), 7.27 – 7.24 (m, 1H), 5.71 (s, 2H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.85, 159.29, 145.12, 145.09, 142.28, 136.43, 135.55, 134.82, 133.75, 128.84, 128.05, 127.89, 127.18, 126.48, 125.54,

125.02, 120.51, 118.41, 118.11, 45.48. **HRMS (ESI):** m/z calculated for $C_{22}H_{16}N_3O_2$ $[M+H]^+$ 354.1237; found 354.1247.



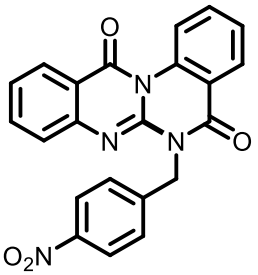
2f

6-(3-methoxybenzyl)-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2f): General condition C was followed, Flash chromatography (SiO_2, eluting with 6% ethyl acetate/pet ether) afforded the desired product as white solid (29.2 mg, 51% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.16 (d, J = 12.0 Hz, 1H), 8.40 (d, J = 6.0 Hz, 1H), 8.29 (d, J = 6.0 Hz, 1H), 7.76 (t, J = 6.0 Hz, 2H), 7.61 (d, J = 6.0 Hz, 1H), 7.52 (t, J = 6.0 Hz, 1H), 7.41 (t, J = 6.0 Hz, 1H), 7.20 (s, 3H), 6.79 (d, J = 6.0 Hz, 1H), 5.68 (s, 2H), 3.77 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.86, 159.27, 159.05, 145.13, 142.32, 137.89, 135.55, 134.85, 133.77, 128.89, 128.08, 127.21, 126.49, 125.51, 125.03, 121.07, 120.52, 118.43, 118.10, 114.51, 112.51, 54.74, 45.42. **HRMS (ESI):** m/z calculated for $C_{23}H_{18}N_3O_3$ $[M+H]^+$ 384.1343; found 384.1343.



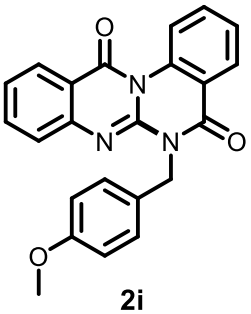
2g

6-(3-(trifluoromethyl)benzyl)-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2g): General condition C was followed, Flash chromatography (SiO_2, eluting with 5% ethyl acetate/pet ether) afforded the desired product as white solid (52.4 mg, 83% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.17 (d, J = 12.0 Hz, 1H), 8.41 (d, J = 6.0 Hz, 1H), 8.28 (d, J = 6.0 Hz, 1H), 7.98 (s, 1H), 7.81 (d, J = 6.0 Hz, 1H), 7.77 (t, J = 6.0 Hz, 2H), 7.60 (d, J = 12.0 Hz, 1H), 7.53 – 7.50 (m, 2H), 7.42 (t, J = 6.0 Hz, 2H), 5.71 (s, 2H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.74, 159.33, 144.91, 142.10, 137.28, 135.59, 135.00, 133.99, 132.23, 130.41, 128.40, 128.13, 127.25, 126.59, 126.24, 125.36, 125.22, 124.54, 124.06, 120.57, 118.44, 117.88, 45.13. **HRMS (ESI):** m/z calculated for $C_{23}H_{15}F_3N_3O_2$ $[M+H]^+$ 422.1111; found 422.1104.



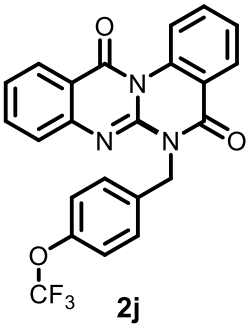
2h

6-(4-nitrobenzyl)-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2h): General condition C was followed, Flash chromatography (SiO_2, eluting with 7% ethyl acetate/pet ether) afforded the desired product as white solid (42.4 mg, 71% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.18 (d, J = 6.0 Hz, 1H), 8.40 (d, J = 6.0 Hz, 1H), 8.29 (d, J = 6.0 Hz, 1H), 8.17 (d, J = 12.0 Hz, 2H), 7.80 – 7.75 (m, 4H), 7.56 – 7.52 (m, 2H), 7.43 (t, J = 6.0 Hz, 1H), 5.75 (s, 2H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.63, 159.30, 146.90, 144.76, 143.78, 142.06, 135.60, 135.04, 134.19, 129.34, 128.13, 127.33, 126.71, 125.39, 123.19, 120.63, 118.46, 117.71, 108.46, 44.99. **HRMS (ESI):** m/z calculated for $C_{22}H_{15}N_4O_4$ $[M+H]^+$ 399.1088; found 399.1090.



2i

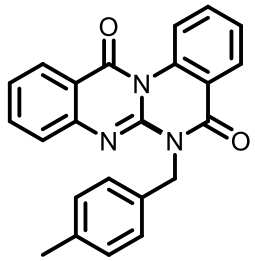
6-(4-methoxybenzyl)-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2i): General condition C was followed, Flash chromatography (SiO_2, eluting with 6% ethyl acetate/pet ether) afforded the desired product as white solid (28.6 mg, 50% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.15 (d, *J* = 12.0 Hz, 1H), 8.40 (d, *J* = 6.0 Hz, 1H), 8.30 (d, *J* = 12.0 Hz, 1H), 7.78 – 7.73 (m, 2H), 7.65 (t, *J* = 6.0 Hz, 3H), 7.52 (t, *J* = 6.0 Hz, 1H), 7.42 (d, *J* = 6.0 Hz, 1H), 6.83 (d, *J* = 6.0 Hz, 2H), 5.65 (s, 2H), 3.75 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.28, 158.64, 145.18, 142.32, 135.96, 135.52, 134.84, 133.69, 130.57, 128.60, 128.01, 127.22, 126.46, 125.52, 124.99, 120.50, 118.42, 118.19, 113.20, 54.76, 44.88. **HRMS (ESI):** m/z calculated for $C_{23}H_{18}N_3O_3$ $[M+H]^+$ 384.1343; found 384.1344.



2j

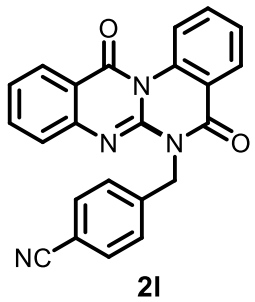
6-(4-(trifluoromethoxy)benzyl)-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2j): General condition C was followed, Flash chromatography (SiO_2, eluting with 5% ethyl acetate/pet ether) afforded the desired product as white solid (57.0 mg, 87% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ

9.16 (d, J = 12.0 Hz, 1H), 8.39 (d, J = 6.0 Hz, 1H), 8.29 (d, J = 6.0 Hz, 1H), 7.77 – 7.74 (m, 2H), 7.70 (d, J = 6.0 Hz, 2H), 7.61 (d, J = 6.0 Hz, 1H), 7.53 (t, J = 12.0 Hz, 1H), 7.43 (t, J = 6.0 Hz, 1H), 7.15 (d, J = 12.0 Hz, 2H), 5.68 (s, 2H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.76, 159.26, 148.19, 144.97, 142.21, 135.55, 135.07, 134.93, 133.92, 130.51, 128.04, 127.27, 126.56, 125.44, 125.18, 120.81, 120.55, 120.35, 118.44, 117.94, 44.70. **HRMS (EI):** m/z calculated for $C_{23}H_{14}F_3N_3O_3$ is 437.0987; found 437.0983.



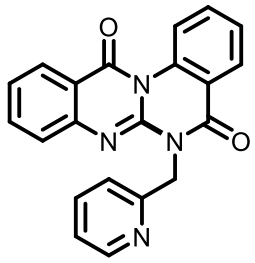
2k

6-(4-methylbenzyl)-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2k): General condition C was followed, Flash chromatography (SiO_2, eluting with 5% ethyl acetate/pet ether) afforded the desired product as white solid (32.5 mg, 59% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.14 (d, J = 8.0 Hz, 1H), 8.39 (d, J = 8.0 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7.75 - 7.70 (m, 2H), 7.61 – 7.47 (m, 4H), 7.39 (t, J = 4.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 2H), 5.65 (s, 2H), 2.29 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.24, 158.66, 144.55, 141.69, 136.32, 134.94, 134.18, 133.08, 132.85, 128.34, 127.96, 127.42, 126.57, 125.83, 124.92, 124.35, 119.89, 117.81, 117.56, 44.62, 20.10. **HRMS (EI):** m/z calculated for $C_{23}H_{17}N_3O_2$ is 367.1321; found 367.1307.



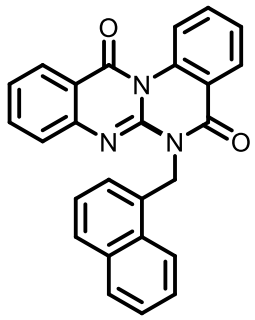
2l

4-((5,12-dioxo-5H-quinazolino[3,2-a]quinazolin-6(12H)-yl)methyl)benzonitrile (2l): General condition C was followed, Flash chromatography (SiO_2, eluting with 7% ethyl acetate/pet ether) afforded the desired product as white solid (43.7 mg, 77% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.17 (d, J = 8.0 Hz, 1H), 8.38 (d, J = 8.0 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H), 7.78 – 7.69 (m, 4H), 7.60 – 7.49 (m, 4H), 7.42 (t, J = 4.0 Hz, 1H), 5.70 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.15, 159.80, 145.31, 142.62, 142.28, 136.11, 135.52, 134.64, 132.30, 129.77, 128.62, 127.83, 127.18, 125.91, 125.86, 121.13, 118.97, 118.78, 118.26, 111.55, 45.74. **HRMS (EI):** m/z calculated for $C_{23}H_{14}N_4O_2$ is 378.1117; found 378.1122.



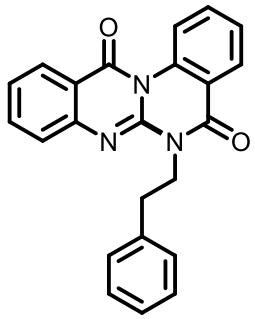
2m

6-(pyridin-2-ylmethyl)-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2m): General condition C was followed, Flash chromatography (SiO_2, eluting with 10% ethyl acetate/pet ether) afforded the desired product as white solid (39.3 mg, 74% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.20 (d, J = 8.0 Hz, 1H), 8.49 (d, J = 4.0 Hz, 1H), 8.41 (d, J = 8.0 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7.78 (t, J = 8.0 Hz, 1H), 7.67 – 7.59 (m, 2H), 7.53 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.37 – 7.30 (m, 2H), 7.13 (t, J = 4.0 Hz, 1H), 5.82 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.38, 159.88, 156.25, 149.46, 145.64, 142.88, 136.52, 136.27, 135.21, 134.33, 128.73, 127.63, 127.00, 126.10, 125.47, 122.10, 121.40, 121.11, 118.94, 118.59, 47.64. **HRMS (EI):** m/z calculated for $C_{21}H_{14}N_4O_2$ is 354.1117; found 354.1130.



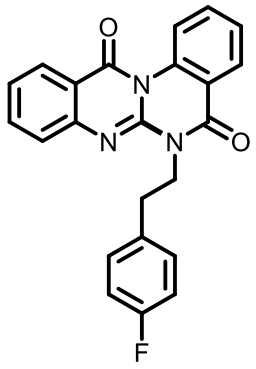
2n

6-(naphthalen-1-ylmethyl)-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2n): General condition C was followed, Flash chromatography (SiO_2, eluting with 5% ethyl acetate/pet ether) afforded the desired product as white solid (31.4 mg, 52% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.21 (d, *J* = 12.0 Hz, 1H), 8.44 (dd, *J* = 12.0, 6.0 Hz, 2H), 8.27 (d, *J* = 6.0 Hz, 1H), 7.88 (d, *J* = 6.0 Hz, 1H), 7.79 (t, *J* = 6.0 Hz, 1H), 7.74 (d, *J* = 6.0 Hz, 1H), 7.64 (t, *J* = 6.0 Hz, 2H), 7.55 (t, *J* = 12.0 Hz, 2H), 7.37 – 7.32 (m, 4H), 6.19 (s, 2H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 162.24, 159.89, 145.45, 142.57, 136.01, 135.12, 134.25, 133.67, 131.95, 131.23, 128.74, 128.58, 127.71, 127.47, 126.94, 126.02, 125.98, 125.59, 125.41, 125.23, 123.94, 123.40, 120.99, 118.79, 118.46, 77.16, 43.44. **HRMS (ESI):** m/z calculated for $C_{26}H_{17}N_3O_2$ $[M+H]^+$ 404.1394; found 404.1388.



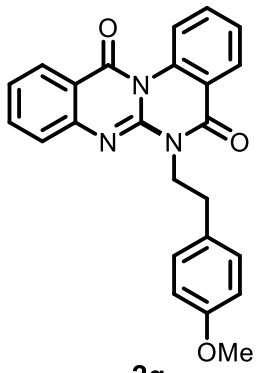
2o

6-phenethyl-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2o): General condition C was followed, Flash chromatography (SiO_2, eluting with 5% ethyl acetate/pet ether) afforded the desired product as white solid (31.9 mg, 58% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.17 (d, J = 12.0 Hz, 1H), 8.37 (d, J = 6.0 Hz, 1H), 8.32 (d, J = 12.0 Hz, 1H), 7.79 – 7.74 (m, 2H), 7.65 (d, J = 12.0 Hz, 1H), 7.53 (t, J = 12.0 Hz, 1H), 7.44 – 7.41 (m, 3H), 7.35 (t, J = 6.0 Hz, 2H), 7.25 (t, J = 6.0 Hz, 1H), 4.70 (t, J = 6.0 Hz, 2H), 3.14 (t, J = 6.0 Hz, 2H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 162.25, 159.35, 145.74, 142.53, 138.69, 135.89, 135.23, 134.02, 128.96, 128.47, 128.20, 127.58, 126.87, 126.46, 126.05, 125.38, 120.92, 118.74, 118.55, 44.57, 33.42. **HRMS (ESI):** m/z calculated for $C_{23}H_{18}N_3O_2$ $[M+H]^+$ 368.1394; found 368.1389.



2p

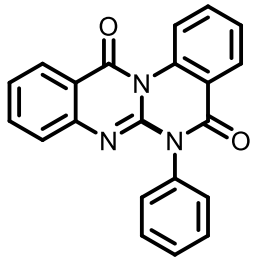
6-(4-fluorophenethyl)-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2p): General condition C was followed, Flash chromatography (SiO_2, eluting with 5% ethyl acetate/pet ether) afforded the desired product as white solid (35.8 mg, 62% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.16 (d, J = 6.0 Hz, 1H), 8.36 (d, J = 12.0 Hz, 1H), 8.32 (d, J = 12.0 Hz, 1H), 7.79 – 7.74 (m, 2H), 7.62 (d, J = 6.0 Hz, 1H), 7.53 (t, J = 12.0 Hz, 1H), 7.44 (t, J = 6.0 Hz, 1H), 7.36 – 7.34 (m, 2H), 7.03 (t, J = 12.0 Hz, 2H), 4.66 (t, J = 6.0 Hz, 2H), 3.11 (t, J = 6.0 Hz, 2H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 162.20, 160.81, 159.36, 145.68, 142.51, 135.87, 135.26, 134.33, 134.08, 130.38, 130.33, 128.19, 127.62, 126.91, 125.97, 125.44, 120.93, 118.74, 118.47, 115.32, 115.18, 44.51, 32.61. **HRMS (ESI):** m/z calculated for $C_{23}H_{17}FN_3O_2$ $[M+H]^+$ 386.1299; found 386.1293.



2q

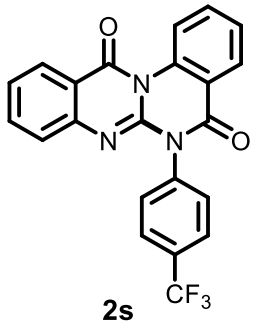
6-(4-methoxyphenethyl)-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2q): General condition C was followed, Flash chromatography (SiO_2, eluting with 6% ethyl acetate/pet ether) afforded the desired product as white solid (30.8 mg, 52% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.17

(d, J = 8.0 Hz, 1H), 8.38 (d, J = 8.0 Hz, 1H), 8.33 (d, J = 8.0 Hz, 1H), 7.80 – 7.74 (m, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 12.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.0 Hz, 2H), 4.68 (t, J = 8.0 Hz, 2H), 3.79 (s, 3H), 3.08 (t, J = 8.0 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.17, 159.27, 158.14, 145.69, 142.48, 135.81, 135.12, 133.90, 130.65, 129.81, 128.11, 127.49, 126.77, 125.94, 125.26, 120.83, 118.66, 118.49, 113.80, 55.12, 44.64, 32.44. **HRMS (ESI):** m/z calculated for $C_{24}H_{20}N_3O_3$ $[M+H]^+$ 398.1499; found 398.1492.



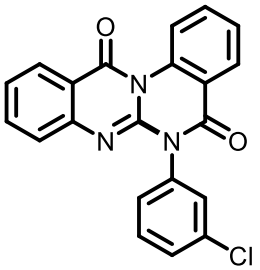
2r

6-phenyl-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2r): General condition C was followed, Flash chromatography (SiO_2, eluting with 6% ethyl acetate/pet ether) afforded the desired product as white solid (25.3 mg, 50% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.23 (d, J = 12.0 Hz, 1H), 8.39 (d, J = 6.0 Hz, 1H), 8.30 (d, J = 6.0 Hz, 1H), 7.82 (t, J = 6.0 Hz, 1H), 7.65 (t, J = 12.0 Hz, 1H), 7.59 – 7.51 (m, 4H), 7.39 – 7.28 (m, 4H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 162.18, 159.85, 145.45, 143.99, 136.47, 136.25, 135.08, 134.39, 129.34, 128.70, 128.60, 128.56, 127.45, 126.96, 126.35, 125.47, 121.11, 118.91, 118.81. **HRMS (ESI):** m/z calculated for $C_{21}H_{14}N_3O_2$ $[M+H]^+$ 340.1081; found 340.1081.



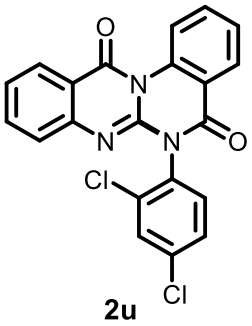
2s

6-(4-(trifluoromethyl)phenyl)-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2s): General condition C was followed, Flash chromatography (SiO_2, eluting with 6% ethyl acetate/pet ether) afforded the desired product as white solid (31.77 mg, 52% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.24 (d, J = 6.0 Hz, 1H), 8.39 (d, J = 12.0 Hz, 1H), 8.31 (d, J = 12.0 Hz, 1H), 7.85 (d, J = 12.0 Hz, 3H), 7.67 (t, J = 6.0 Hz, 1H), 7.57 (t, J = 12.0 Hz, 1H), 7.48 (d, J = 6.0 Hz, 2H), 7.41 (t, J = 6.0 Hz, 1H), 7.30 (d, J = 6.0 Hz, 1H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.62, 159.25, 144.78, 143.20, 139.20, 135.87, 134.88, 134.35, 129.13, 128.26, 127.16, 126.72, 126.14, 126.12, 125.87, 125.38, 124.35, 120.80, 118.49, 118.19. **HRMS (ESI):** m/z calculated for $C_{22}H_{13}F_3N_3O_2$ $[M+H]^+$ 408.0954; found 408.0954.



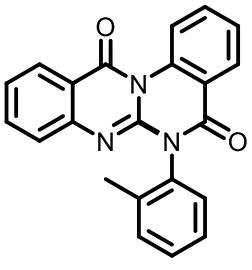
2t

6-(3-chlorophenyl)-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2t): General condition C was followed, Flash chromatography (SiO_2, eluting with 5% ethyl acetate/pet ether) afforded the desired product as white solid (43.7 mg, 78% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.22 (d, J = 6.0 Hz, 1H), 8.38 (d, J = 12.0 Hz, 1H), 8.29 (d, J = 6.0 Hz, 1H), 7.83 (t, J = 12.0 Hz, 1H), 7.67 (t, J = 6.0 Hz, 1H), 7.55 – 7.50 (m, 3H), 7.40 (t, J = 6.0 Hz, 1H), 7.36 (s, 1H), 7.32 (d, J = 6.0 Hz, 1H), 7.24 (d, J = 6.0 Hz, 1H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 162.03, 159.63, 145.24, 143.64, 137.40, 136.21, 135.18, 134.76, 134.60, 130.21, 129.26, 128.93, 128.61, 127.49, 127.21, 127.03, 126.33, 125.65, 121.13, 118.84, 118.64. **HRMS (EI):** m/z calculated for $C_{21}H_{12}ClN_3O_2$ is 373.0618; found 373.0618.



2u

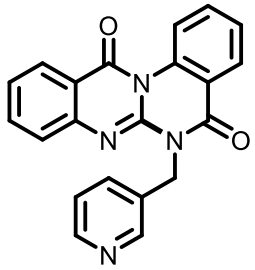
6-(2,4-dichlorophenyl)-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2u): General condition C was followed, Flash chromatography (SiO_2, eluting with 5% ethyl acetate/pet ether) afforded the desired product as white solid (34.9 mg, 57% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.26 (d, J = 6.0 Hz, 1H), 8.39 (d, J = 6.0 Hz, 1H), 8.31 (d, J = 12.0 Hz, 1H), 7.84 (t, J = 6.0 Hz, 1H), 7.68 (t, J = 12.0 Hz, 1H), 7.63 (s, 1H), 7.56 (t, J = 6.0 Hz, 1H), 7.46 (t, J = 6.0 Hz, 1H), 7.41 (t, J = 6.0 Hz, 1H), 7.34 – 7.31 (m, 2H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 162.04, 159.00, 145.32, 142.76, 136.40, 135.30, 135.22, 134.80, 133.70, 132.93, 131.34, 130.20, 128.72, 128.18, 127.56, 127.06, 126.26, 125.72, 121.17, 118.97, 118.31. **HRMS (ESI):** m/z calculated for $C_{21}H_{12}Cl_2N_3O_2$ $[M+H]^+$ 408.0301; found 408.0302.



2v

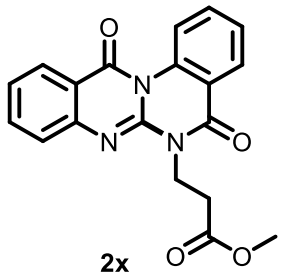
6-(o-tolyl)-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2v): General condition C was followed, Flash chromatography (SiO_2, eluting with 5% ethyl acetate/pet ether) afforded the desired product as white solid (19.0 mg, 36% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.25 (d, J = 8.0 Hz, 1H), 8.41 (d, J = 12.0 Hz, 1H), 8.31 (d, J = 12.0 Hz, 1H), 7.83 (t, J = 8.0 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H),

7.56 (t, J = 8.0 Hz, 1H), 7.43 – 7.35 (m, 4H), 7.30 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 2.15 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.13, 159.23, 145.54, 143.09, 136.24, 135.70, 135.55, 134.93, 134.26, 130.80, 128.73, 128.50, 128.30, 127.32, 126.91, 126.83, 126.25, 125.31, 120.96, 118.70, 118.65, 17.47. **HRMS (ESI):** m/z calculated for $C_{22}H_{16}N_3O_2$ $[M+H]^+$ 354.1237; found 354.1238.



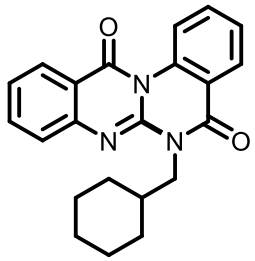
2w

6-(pyridin-3-ylmethyl)-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2w): General condition C was followed, Flash chromatography (SiO_2, eluting with 10 % ethyl acetate/pet ether) afforded the desired product as white solid (34.0 mg, 64% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.07 (d, J = 12.0 Hz, 1H), 8.94 (s, 1H), 8.46 (s, 1H), 8.31 (d, J = 12.0 Hz, 1H), 8.18 (d, J = 6.0 Hz, 1H), 7.93 (d, J = 6.0 Hz, 1H), 7.68 (t, J = 6.0 Hz, 2H), 7.54 (d, J = 12.0 Hz, 1H), 7.44 (t, J = 6.0 Hz, 1H), 7.33 (t, J = 6.0 Hz, 1H), 7.19 (s, 1H), 5.61 (s, 2H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 162.01, 159.65, 150.66, 148.52, 148.49, 145.17, 142.36, 137.38, 135.90, 135.35, 134.37, 128.40, 127.58, 126.95, 125.86, 125.62, 120.92, 118.75, 118.16, 115.21, 43.48. **HRMS (ESI):** m/z calculated for $C_{21}H_{15}N_4O_2$ $[M+H]^+$ 355.1190; found 355.1203.



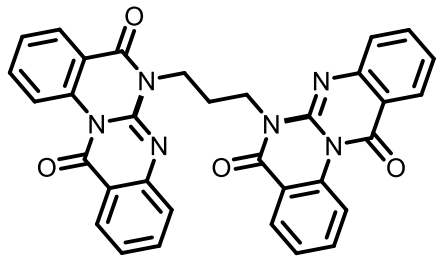
2x

methyl 3-(5,12-dioxo-5H-quinazolino[3,2-a]quinazolin-6(12H)-yl)propanoate (2x): General condition C was followed, Flash chromatography (SiO_2, eluting with 7 % ethyl acetate/pet ether) afforded the desired product as white solid (40.8 mg, 78% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.15 (d, J = 6.0 Hz, 1H), 8.35 (d, J = 6.0 Hz, 1H), 8.29 (d, J = 6.0 Hz, 1H), 7.76 – 7.73 (m, 2H), 7.58 (d, J = 6.0 Hz, 1H), 7.51 (t, J = 6.0 Hz, 1H), 7.42 (t, J = 6.0 Hz, 1H), 4.79 (t, J = 6.0 Hz, 2H), 3.68 (s, 3H), 2.89 (t, J = 6.0 Hz, 2H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.78, 162.12, 159.36, 145.50, 142.41, 135.88, 135.25, 134.16, 128.25, 127.56, 126.91, 125.99, 125.48, 120.96, 118.75, 118.36, 51.78, 38.99, 31.92. **HRMS (ESI):** m/z calculated for $C_{19}H_{16}N_3O_4$ $[M+H]^+$ 350.1135; found 350.1155.



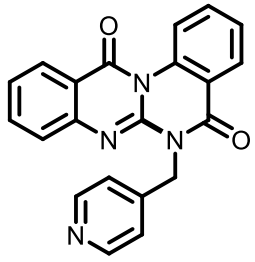
2y

6-(cyclohexylmethyl)-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2y): General condition C was followed, Flash chromatography (SiO_2, eluting with 5% ethyl acetate/pet ether) afforded the desired product as white solid (27.4 mg, 51% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.08 (d, J = 12.0 Hz, 1H), 8.30 (d, J = 12.0 Hz, 1H), 8.24 (d, J = 12.0 Hz, 1H), 7.70 – 7.65 (m, 2H), 7.52 (d, J = 12.0 Hz, 1H), 7.45 (t, J = 12.0 Hz, 1H), 7.35 (t, J = 12.0 Hz, 1H), 4.32 (d, J = 12.0 Hz, 2H), 1.97 (s, 1H), 1.65 (d, J = 6.0 Hz, 4H), 1.56 (d, J = 12.0 Hz, 2H), 1.13 (d, J = 12.0 Hz, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.49, 160.04, 145.87, 143.19, 136.02, 135.28, 134.00, 128.51, 127.67, 126.94, 126.19, 125.39, 120.98, 118.86, 118.70, 48.76, 36.37, 30.97, 26.44, 25.98. **HRMS (ESI):** m/z calculated for $C_{22}H_{22}N_3O_2$ $[M+H]^+$ 360.1707; found 360.1708.



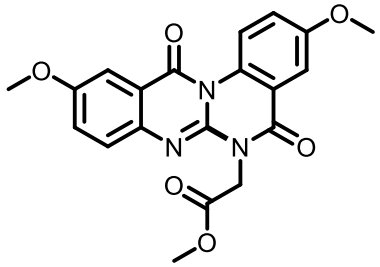
2z

6,6'-(propane-1,3-diyl)bis(5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione) (2z): General condition C was followed, Flash chromatography (SiO_2, eluting with 15% ethyl acetate/pet ether) afforded the desired product as white solid (32.2 mg, 38% yield). **^{1}H NMR** (600 MHz, $CDCl_3$:CD_3OD) δ 9.01 (d, J = 6.0 Hz, 1H), 8.19 (d, J = 6.0 Hz, 1H), 8.13 (d, J = 6.0 Hz, 1H), 7.68 (t, J = 6.0 Hz, 1H), 7.56 (t, J = 6.0 Hz, 1H), 7.41 (t, J = 12.0 Hz, 1H), 7.27 (s, 1H), 7.21 (d, J = 6.0 Hz, 1H), 4.61 (t, J = 6.0 Hz, 2H), 2.42 (p, J = 6.0 Hz, 1H). **^{13}C NMR** (150 MHz, $CDCl_3$:CD_3OD) δ 162.11, 159.62, 145.30, 142.36, 135.61, 135.05, 133.88, 127.94, 127.21, 126.75, 125.65, 125.24, 120.71, 118.35, 118.23, 40.85, 25.20. **HRMS (ESI):** m/z calculated for $C_{33}H_{23}N_6O_4$ $[M+H]^+$ 567.1775; found 567.1760.



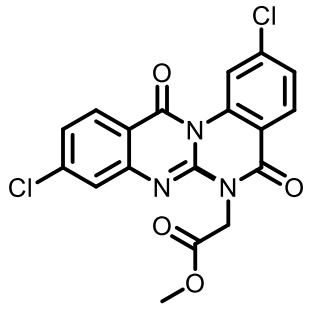
2aa

6-(pyridin-4-ylmethyl)-5H-quinazolino[3,2-a]quinazoline-5,12(6H)-dione (2aa): General condition C was followed, Flash chromatography (SiO_2, eluting with 10% ethyl acetate/pet ether) afforded the desired product as white solid (37.2 mg, 70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.19 (d, J = 8.0 Hz, 1H), 8.59 (brs, 2H), 8.40 (d, J = 8.0 Hz, 1H), 8.29 (d, J = 8.0 Hz, 1H), 7.80 – 7.72 (m, 2H), 7.55 (t, J = 8.0 Hz, 2H), 7.45 – 7.39 (m, 3H), 5.66 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.94, 159.53, 149.61, 145.70, 145.08, 142.34, 135.90, 135.26, 134.42, 128.40, 127.55, 126.95, 125.75, 125.61, 123.31, 120.90, 118.73, 117.99, 44.97. **HRMS (ESI):** m/z calculated for $C_{21}H_{15}N_4O_2$ $[M+H]^+$ 355.1190; found 355.1184.



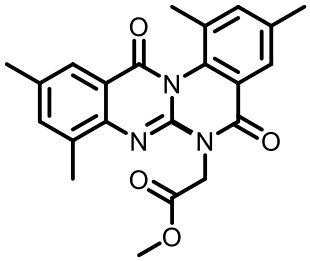
4a

methyl 2-(3,10-dimethoxy-5,12-dioxo-5H-quinazolino[3,2-a]quinazolin-6(12H)-yl)acetate (2ab): General condition C was followed, Flash chromatography (SiO_2, eluting with 8% ethyl acetate/pet ether) afforded the desired product as white solid (46.2 mg, 78% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.18 (d, J = 12.0 Hz, 1H), 7.71 (s, 1H), 7.56 (s, 1H), 7.39 (d, J = 6.0 Hz, 1H), 7.26 (t, J = 12.0 Hz, 2H), 5.13 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.71 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 168.45, 161.65, 159.17, 157.74, 157.45, 140.66, 139.70, 129.90, 127.51, 125.51, 122.91, 122.08, 119.42, 119.24, 109.95, 106.62, 55.76, 52.48, 43.94. **HRMS (ESI):** m/z calculated for $C_{20}H_{18}N_3O_6$ $[M+H]^+$ 396.1190; found 396.1208.



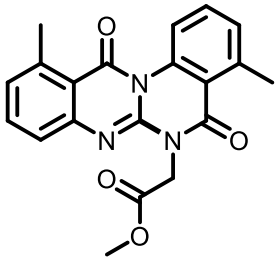
4b

methyl 2-(2,9-dichloro-5,12-dioxo-5H-quinazolino[3,2-a]quinazolin-6(12H)-yl)acetate (2ac): General condition C was followed, Flash chromatography (SiO_2, eluting with 5% ethyl acetate/pet ether) afforded the desired product as white solid (48.5 mg, 80% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.32 (d, J = 4.0 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.52 – 7.49 (m, 2H), 7.37 (dd, J = 4.0 Hz, 1H), 5.16 (s, 2H), 3.80 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.88, 161.06, 158.28, 145.83, 143.06, 141.78, 141.17, 136.39, 129.59, 129.00, 127.58, 126.41, 125.45, 121.19, 116.90, 116.26, 52.50, 43.73. **HRMS (ESI):** m/z calculated for $C_{18}H_{12}Cl_2N_3O_4$ $[M+H]^+$ 404.0199; found 404.0196.



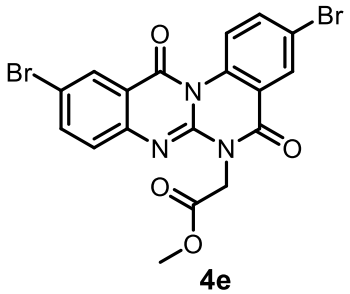
4c

methyl 2-(1,3,8,10-tetramethyl-5,12-dioxo-5H-quinazolino[3,2-a]quinazolin-6(12H)-yl)acetate (2ad): General condition C was followed, Flash chromatography (SiO_2, eluting with 5% ethyl acetate/pet ether) afforded the desired product as white solid (41.6 mg, 71% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.84 (s, 1H), 7.41 (s, 2H), 5.11 (s, 1H), 4.99 (s, 1H), 3.76 (s, 3H), 2.46 (s, 3H), 2.45 (s, 4H), 2.43 (s, 3H), 2.21 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 168.49, 160.80, 160.14, 142.48, 141.89, 137.88, 137.12, 136.88, 134.81, 134.00, 131.97, 131.33, 125.91, 124.07, 120.95, 119.00, 52.28, 43.33, 21.38, 21.08, 20.70, 16.79. **HRMS (ESI):** m/z calculated for $C_{22}H_{22}N_3O_4$ $[M+H]^+$ 392.1605; found 392.1607.



4d

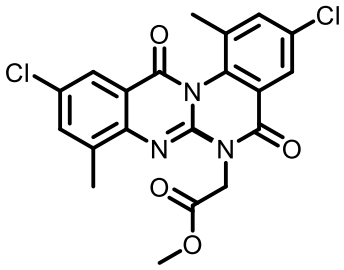
methyl 2-(4,11-dimethyl-5,12-dioxo-5H-quinazolino[3,2-a]quinazolin-6(12H)-yl)acetate (2ae): General condition C was followed, Flash chromatography (SiO_2, eluting with 5% ethyl acetate/pet ether) afforded the desired product as white solid (39.7 mg, 73% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.53 (d, J = 12.0 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.34 (d, J = 6.0 Hz, 1H), 7.27 (d, J = 6.0 Hz, 1H), 7.14 (d, J = 6.0 Hz, 1H), 5.12 (s, 2H), 3.77 (s, 3H), 2.86 (s, 3H), 2.83 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 168.23, 161.88, 159.56, 146.70, 142.06, 141.87, 141.16, 136.12, 133.85, 132.25, 129.91, 127.56, 123.65, 118.72, 117.13, 116.81, 52.06, 42.97, 22.98, 22.53. **HRMS (ESI):** m/z calculated for $C_{20}H_{18}N_3O_4$ $[M+H]^+$ 364.1292; found 364.1286.



4e

methyl 2-(3,10-dibromo-5,12-dioxo-5H-quinazolino[3,2-a]quinazolin-6(12H)-yl)acetate (2af): General condition C was followed, Flash chromatography (SiO_2, eluting with 5% ethyl acetate/pet ether) afforded the desired product as white solid (37.7 mg, 51% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.14 (d, J = 12.0 Hz, 1H), 8.49 (s, 1H), 8.40 (s, 1H), 7.89 (d, J = 12.0 Hz, 1H), 7.82 (d, J = 6.0 Hz, 1H), 7.42 (d, J = 6.0 Hz, 1H), 5.18 (s, 2H), 3.79 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 167.99,

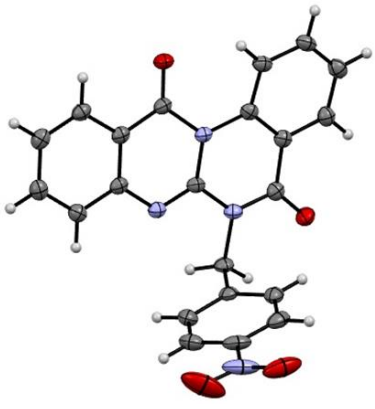
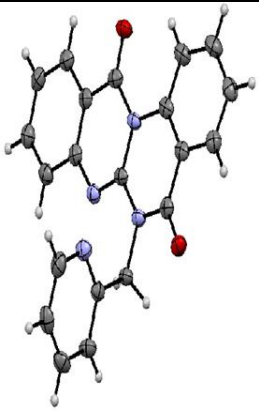
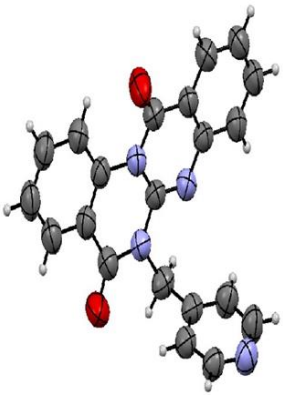
160.66, 158.01, 143.92, 142.32, 138.58, 137.49, 134.82, 131.09, 130.04, 127.86, 122.84, 120.85, 120.00, 119.67, 118.99, 52.63, 43.97. **HRMS (ESI):** m/z calculated for $C_{18}H_{12}Br_2N_3O_4$ $[M+H]^+$ 491.9189; found 491.9174.



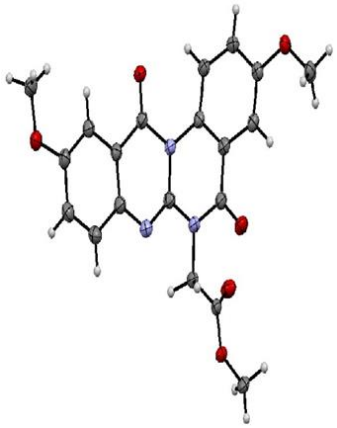
4f

methyl 2-(3,10-dichloro-1,8-dimethyl-5,12-dioxo-5H-quinazolino[3,2-a]quinazolin-6(12H)-yl)acetate (2ag): General condition C was followed, Flash chromatography (SiO_2, eluting with 5% ethyl acetate/pet ether) afforded the desired product as white solid (53.1 mg, 82% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.11 (s, 1H), 8.00 (s, 1H), 7.58 (s, 1H), 7.55 (s, 1H), 5.10 (s, 1H), 4.99 (s, 1H), 3.78 (s, 3H), 2.47 (s, 3H), 2.21 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 168.02, 159.50, 158.85, 143.03, 142.24, 136.75, 136.60, 135.71, 134.31, 133.29, 131.88, 130.57, 125.51, 123.91, 122.36, 119.91, 52.46, 43.46, 21.52, 16.81. **HRMS (ESI):** m/z calculated for $C_{20}H_{16}Cl_2N_3O_4$ $[M+H]^+$ 432.0512; found 432.0523.

12. X-ray crystal data:

Compound	**2h**	**2m**	**2aa**
X-ray crystal structure			
Empirical formula	$C_{22}H_{14}N_4O_4$	$C_{21}H_{14}N_4O_2$	$C_{21}H_{14}N_4O_2$
Formula weight	398.381	354.37	354.371
Crystallizing solvent	$CHCl_3$	$CHCl_3$	$CHCl_3$
Temperature	125.00 K	100 K	297.00 K
Wavelength	1.54178	1.54178	1.54178
Crystal system	Orthorhombic	triclinic	triclinic
Space group	P b c a	P -1	P -1
a [Å]	7.0800(5)	9.1156(5)	7.3072(3)

b [Å] c [Å]	21.6873(17) 22.6977(18)	9.7993(5) 10.6132(5)	10.6416(4) 12.3542(4)
Angles [α, β, γ]	α = 90 β = 90 γ = 90	α = 93.016(2) β = 112.640(2) γ = 111.021(2)	α = 65.804(1) β = 74.301(2) γ = 72.465(2)
Volume [Å3]	3485.1(5)	796.49(7)	823.52(5)
Z	8	2	2
Density [g/cm3][calc.]	1.519	1.4775	1.429
F(000)	1654.101	369.1967	369.277
Radiation	Cu K/a	Cu K\a	Cu K\a
*Θ*Range [°]	4.52 to 67.45	5.62 to 66.83	6.65 to 66.88
Measured reflections	9919	9881	29889
Observed reflections with I >= 2σ(I)	3119	2802	2878
Goodness-of-fit on F2	1.0524	1.0668	1.2779
Final R indexes [I>=2σ (I)]	R_1 = 0.0631, wR_2 = 0.1618	R_1 = 0.0594, wR_2 = 0.1642	R_1 = 0.1107, wR_2 = 0.2912
Final R indexes [all data]	R_1 = 0.0655, wR_2 = 0.1649	R_1 = 0.0624, wR_2 = 0.1676	R_1 = 0.1230, wR_2 = 0.3116
restraints / parameters	0/271	0/244	5/245
Solvent system	Chloroform	Chloroform	Chloroform
Method for crystal growth	Solvent evaporation	Solvent evaporation	Solvent evaporation
CCDC No.	2356882	2356885	2356874

Compound	**2ab**
X-ray crystal structure	

Empirical formula	$C_{20}H_{17}N_3O_6$
Formula weight	395.374
Crystallizing solvent	$CHCl_3$
Temperature	130.00 K
Wavelength	1.54178
Crystal system	triclinic
Space group	P -1
a [Å] b [Å] c [Å]	8.0947(10) 10.0181(13) 11.8931(15)
Angles [α, β, γ]	α = 71.761(4) β = 77.741(4) γ = 86.957(4)
Volume [Å3]	895.0(2)
Z	2
Density [g/cm3][calc.]	1.467
F(000)	413.593
Radiation	Cu K/a
*Θ*Range [°]	7.53 to 66.69
Measured reflections	20381
Observed reflections with I >= 2σ(I)	3068
Goodness-of-fit on F2	1.0611
Final R indexes [I>=2σ (I)]	R_1 = 0.0452, wR_2 = 0.1248
Final R indexes [all data]	R_1 = 0.0463, wR_2 = 0.1263
restraints / parameters	0/265
Solvent system	Chloroform
Method for crystal growth	Solvent evaporation
CCDC No.	2356891

Thermal ellipsoid plots:

Compound **2h**:

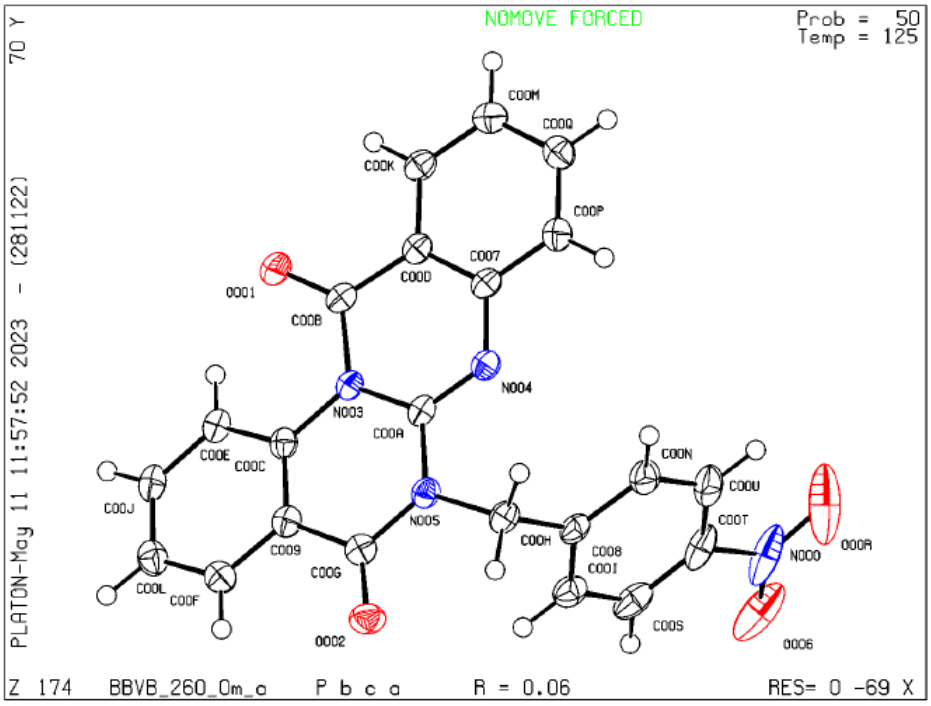


Figure S5: ORTEP diagram of compound **2h**. Thermal ellipsoids are shown at the 50% level.

Compound **2m**:

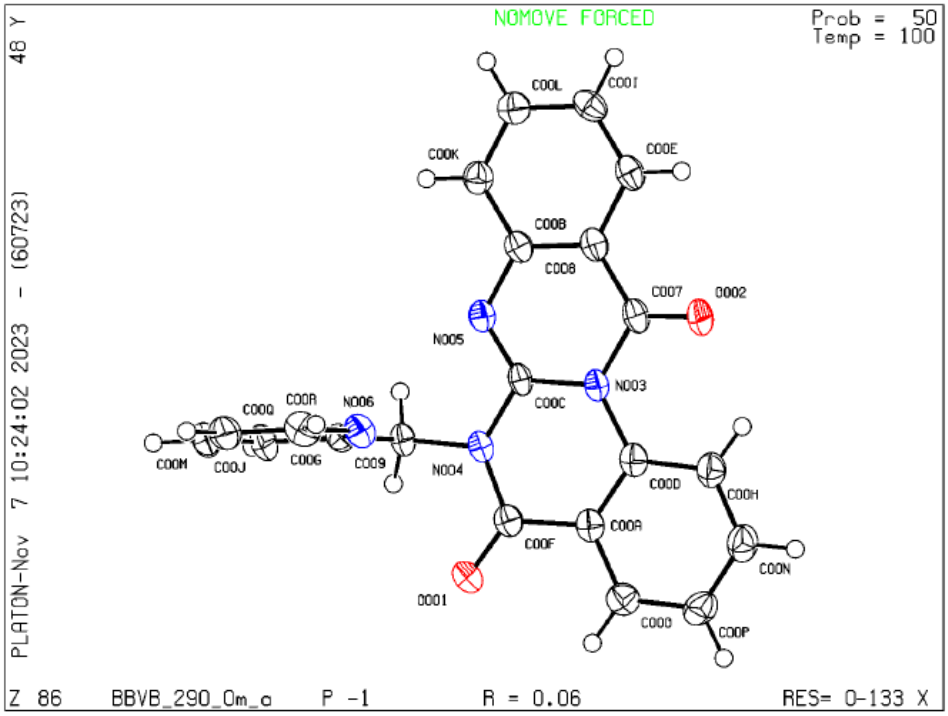


Figure S6: ORTEP diagram of compound **2m**. Thermal ellipsoids are shown at the 50% level.

Compound **2aa**:

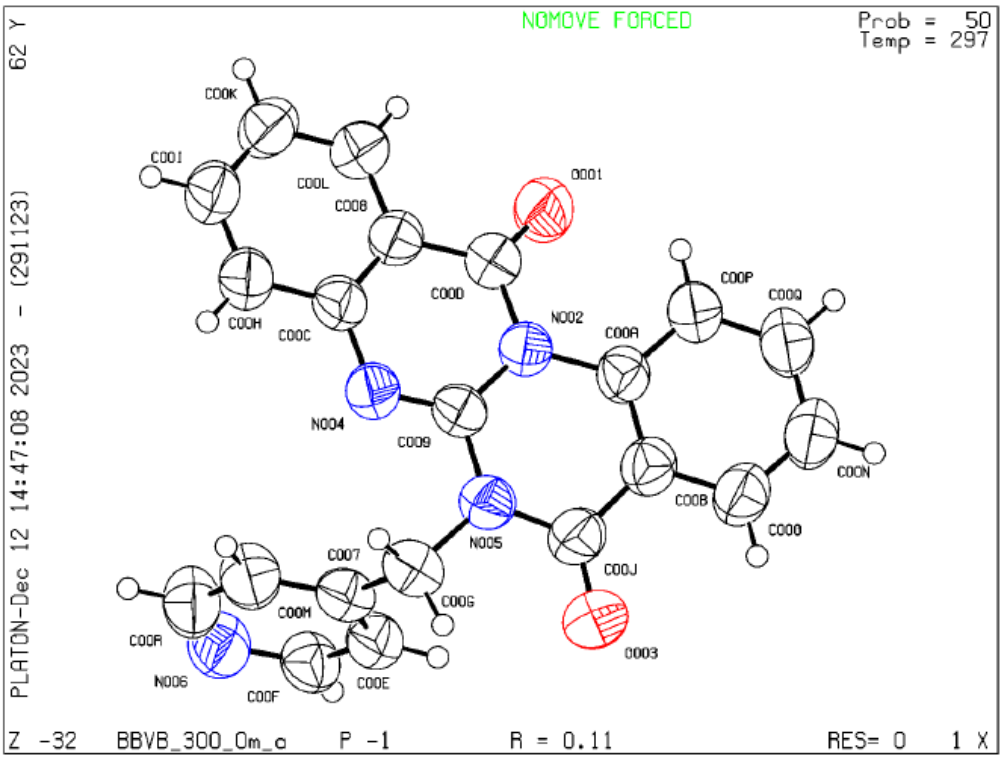


Figure S7: ORTEP diagram of compound **2aa**. Thermal ellipsoids are shown at the 50% level.

Compound **4a**:

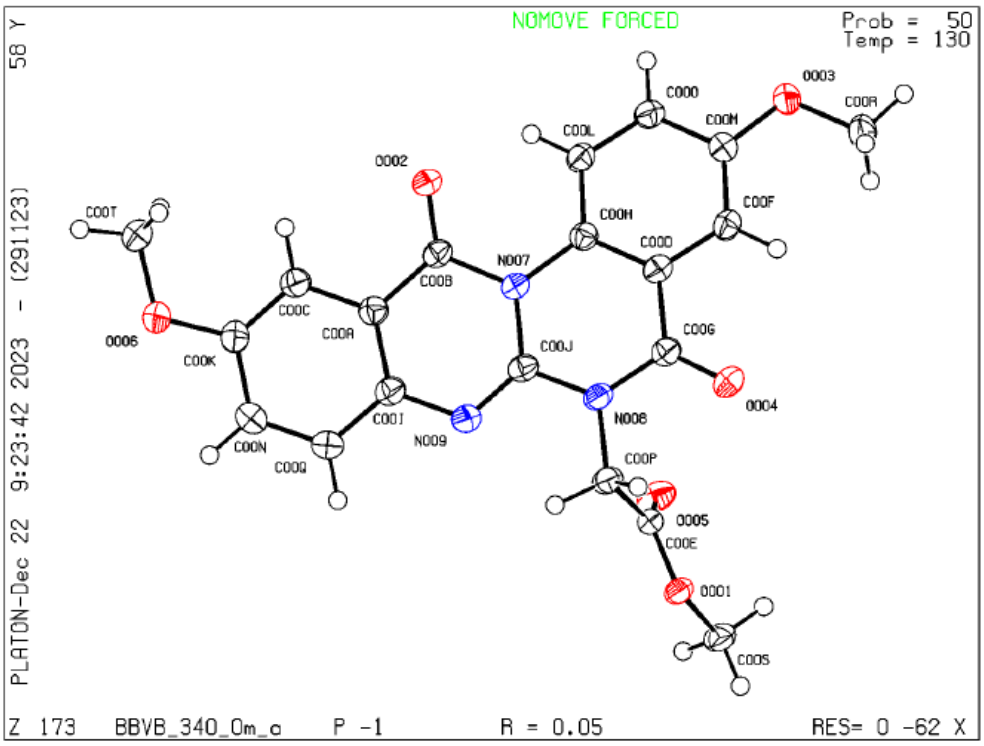
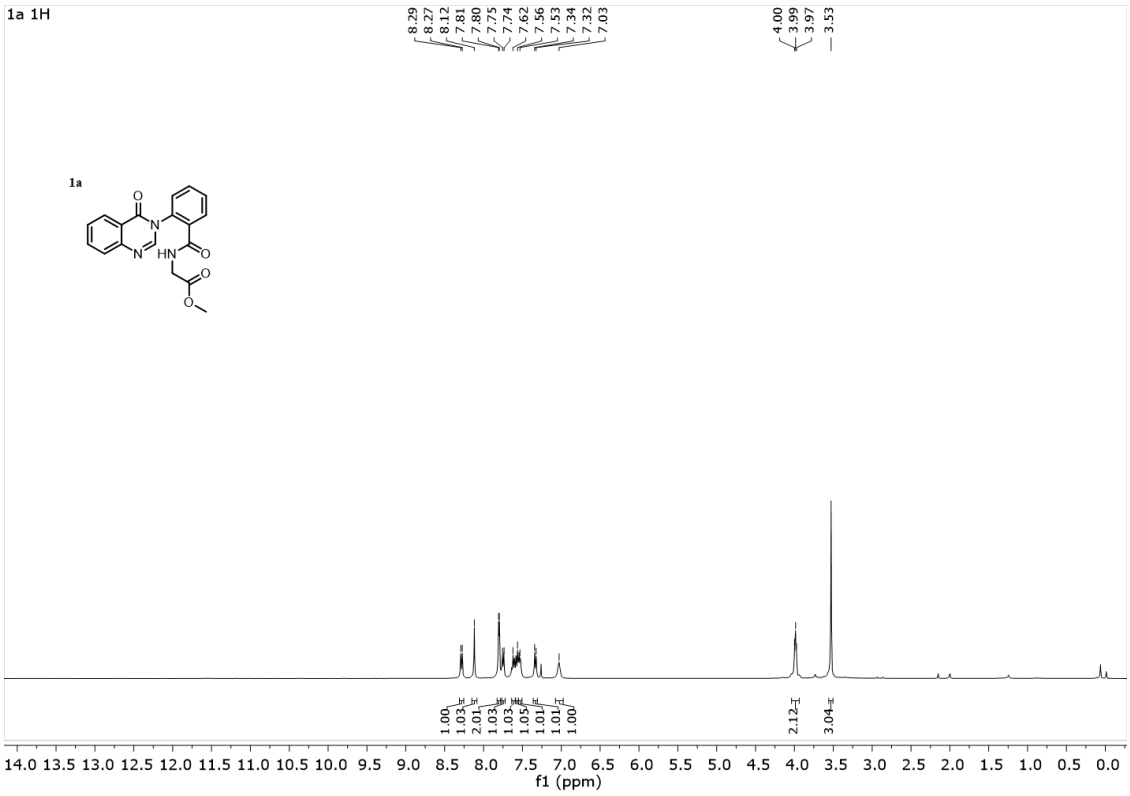


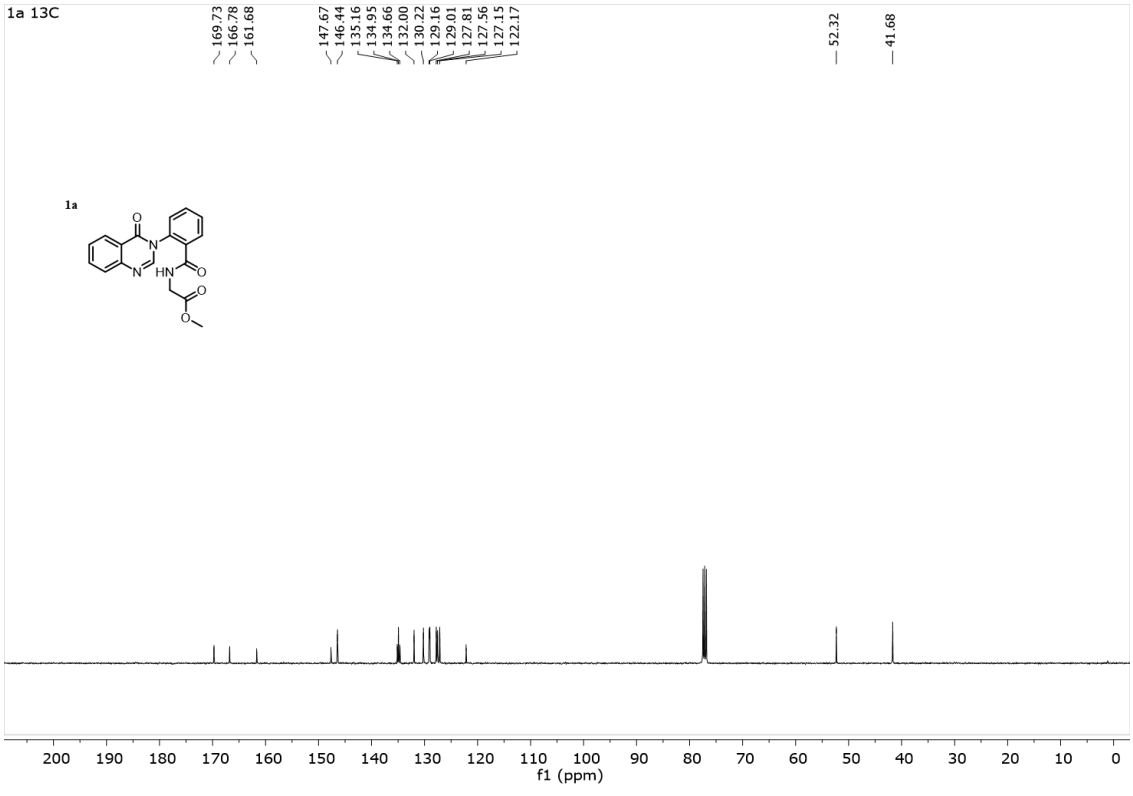
Figure S8: ORTEP diagram of compound **4a**. Thermal ellipsoids are shown at the 50% level.

13. NMR spectra:

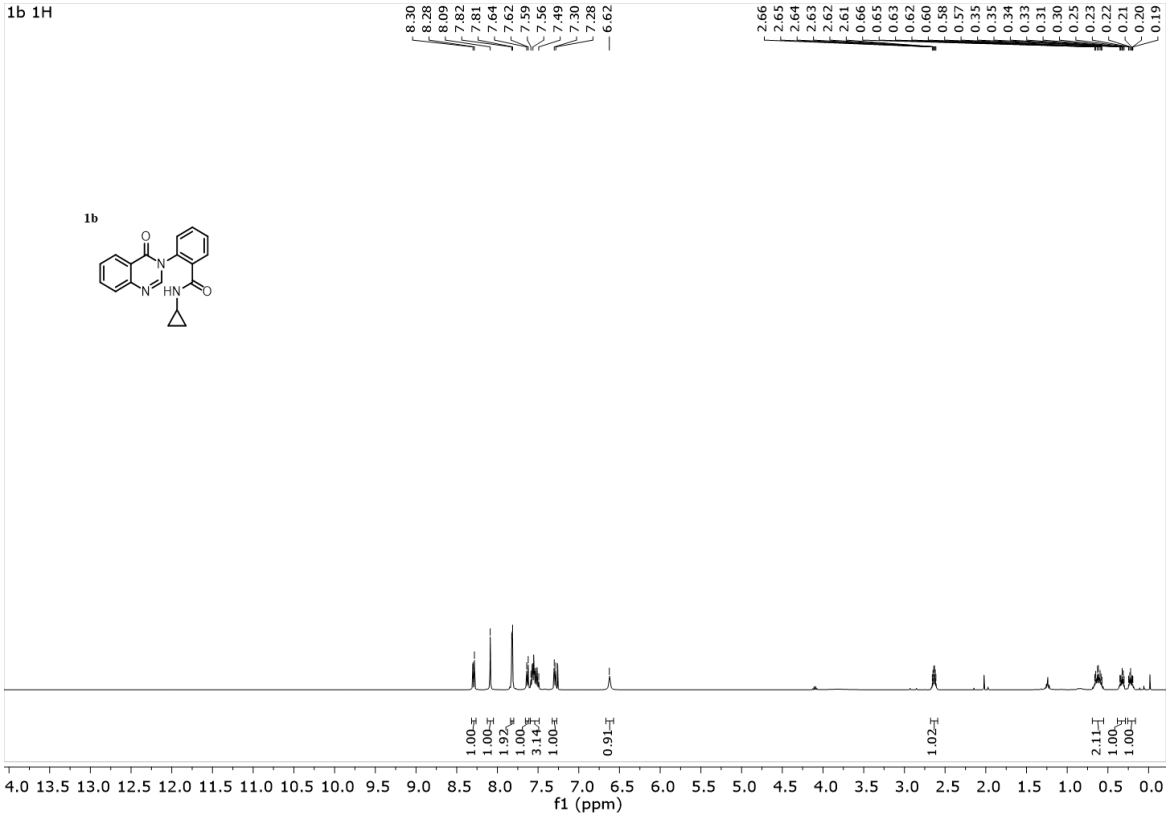
^{1}H in $CDCl_3$ 400 MHz 1a



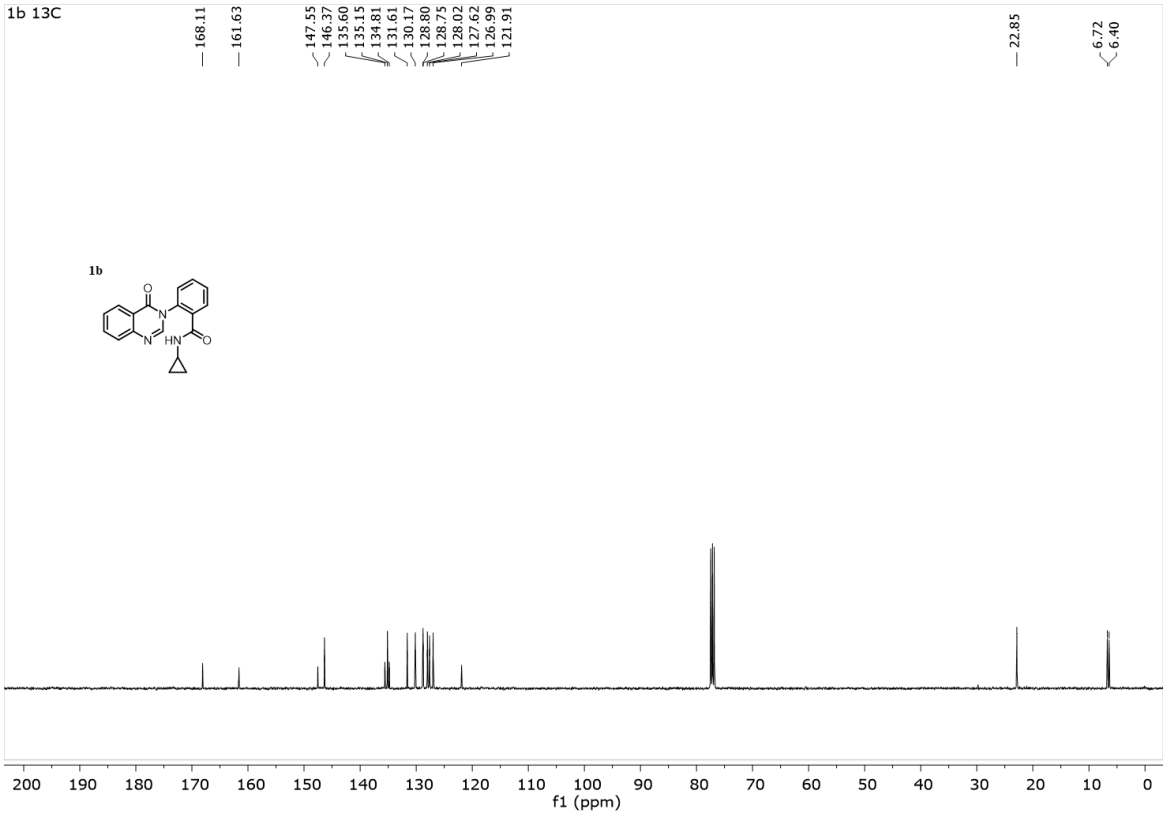
^{13}C in $CDCl_3$ 100 MHz 1a



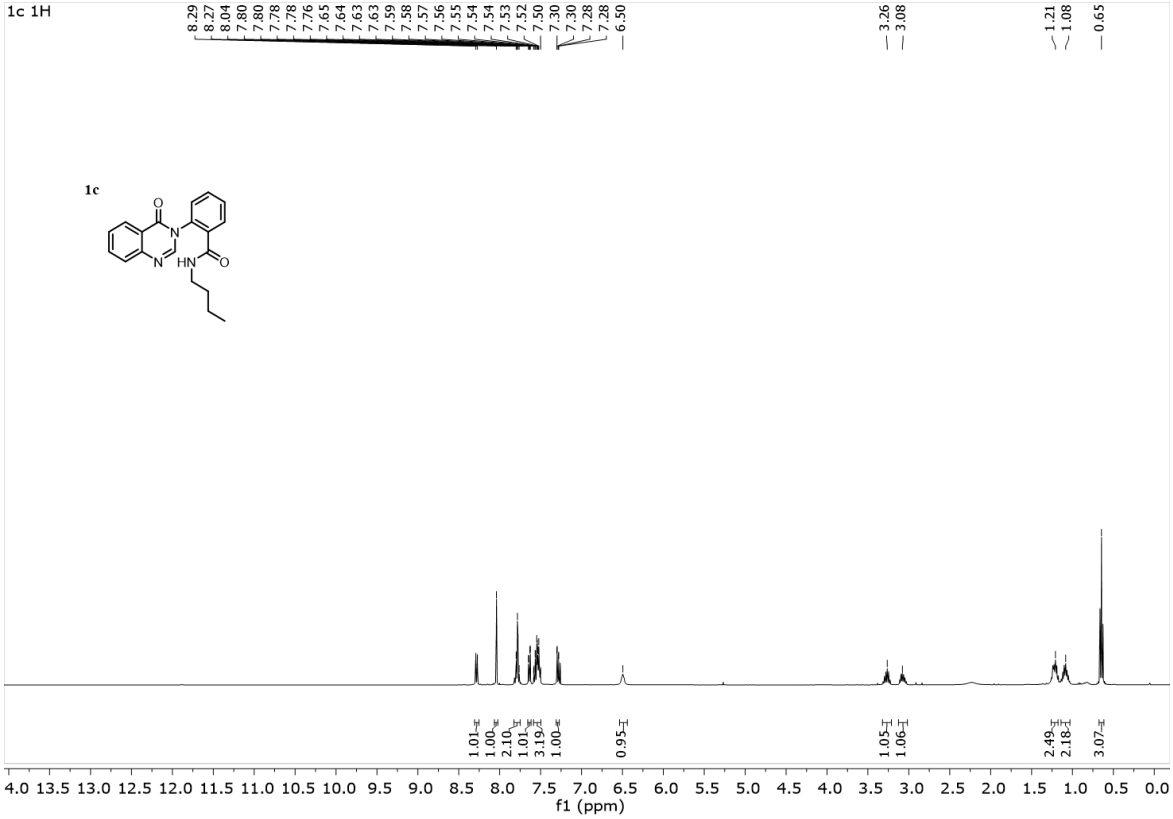
^{1}H in $CDCl_3$ 400 MHz 1b



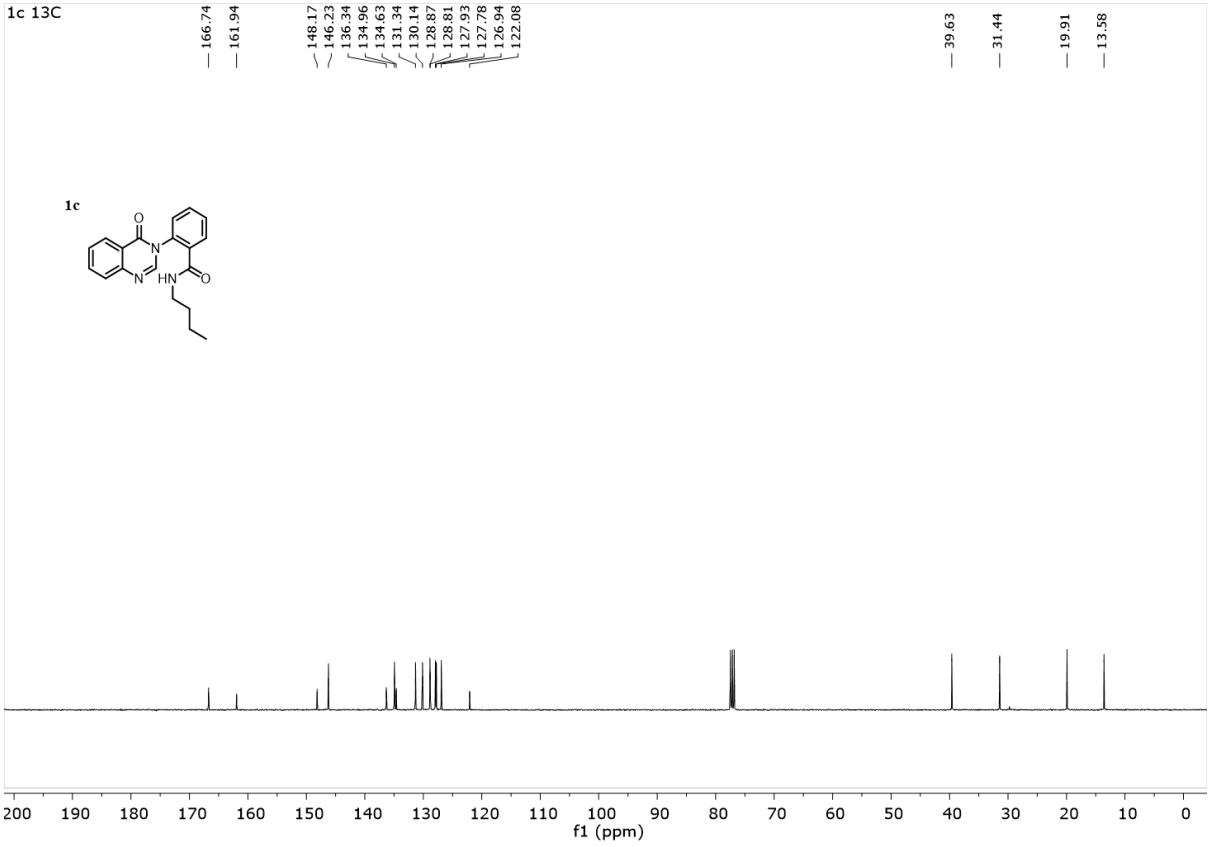
^{13}C in $CDCl_3$ 100 MHz 1b



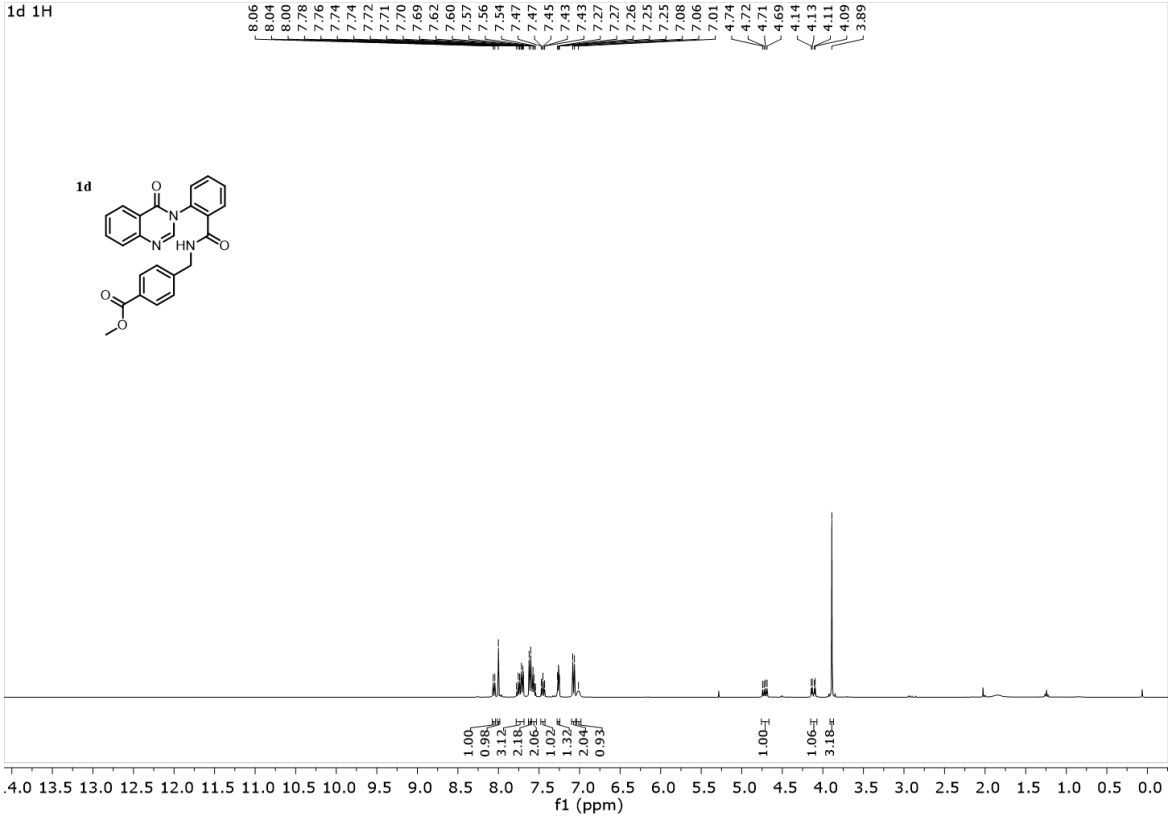
^{1}H in $CDCl_3$ 400 MHz 1c



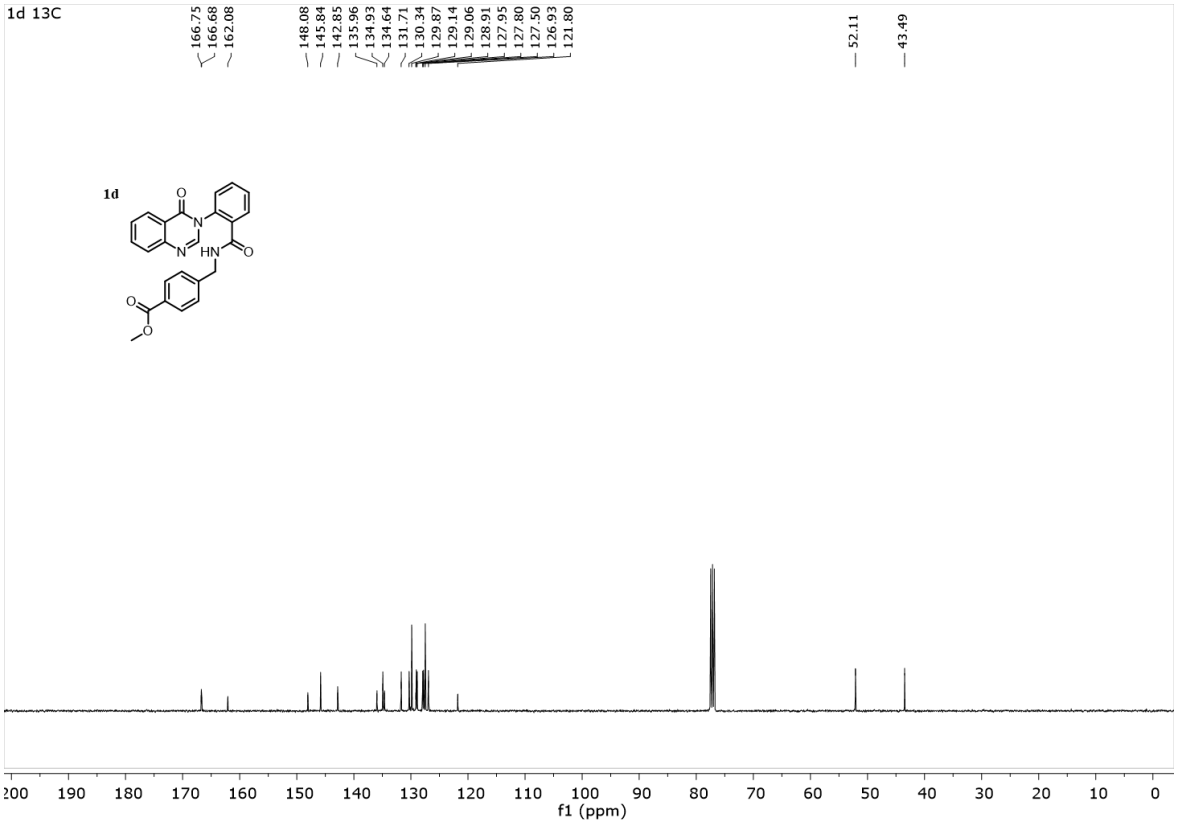
^{13}C in $CDCl_3$ 100 MHz 1c



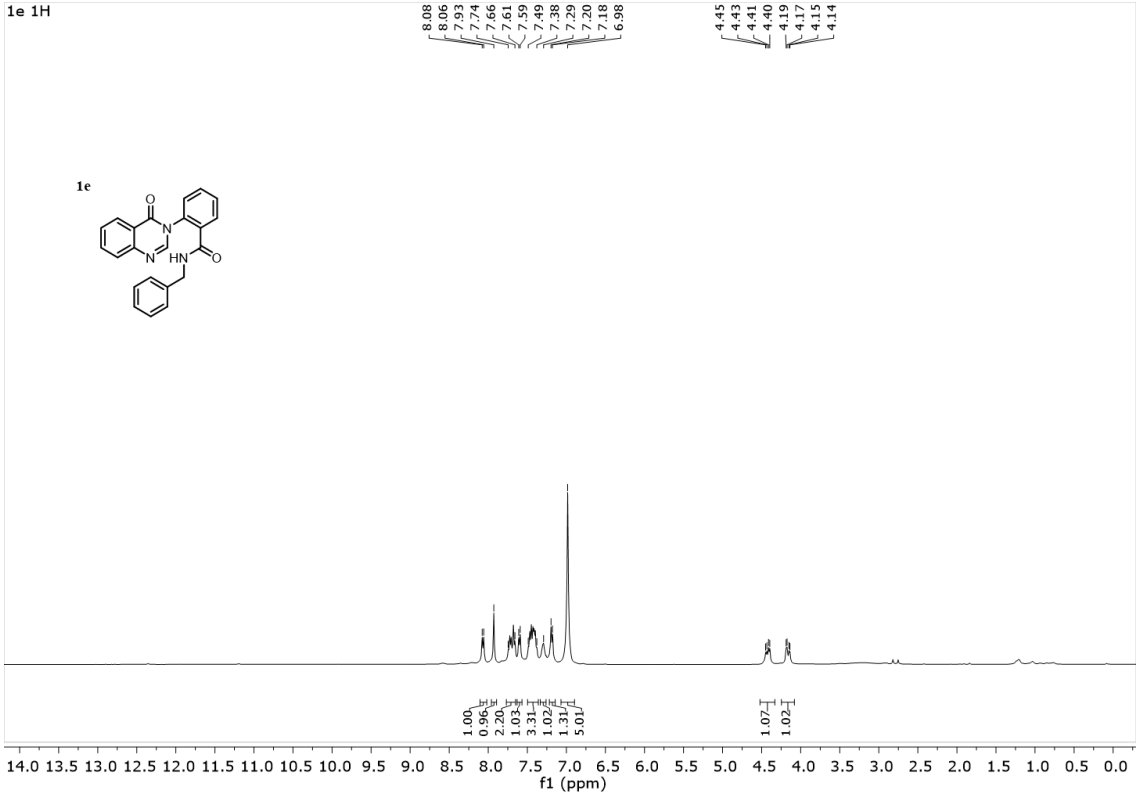
^{1}H in $CDCl_3$ 400 MHz 1d



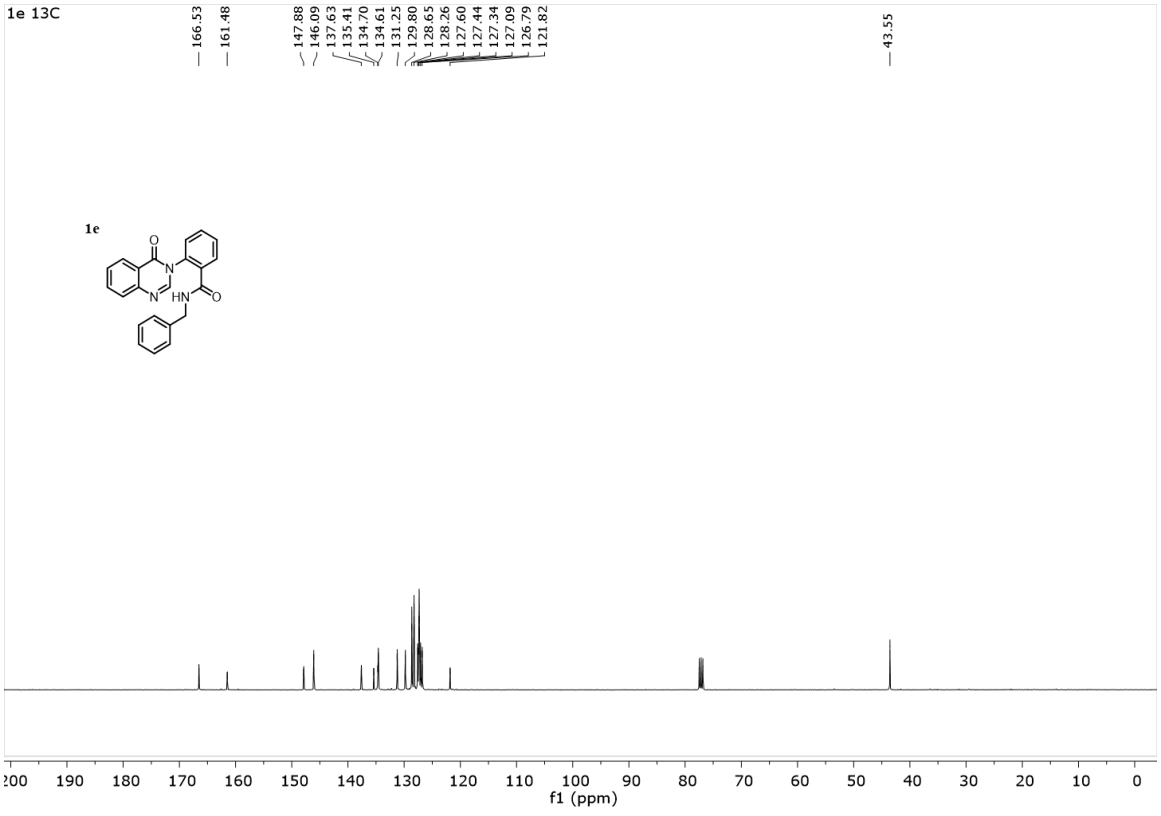
^{13}C in $CDCl_3$ 100 MHz 1d



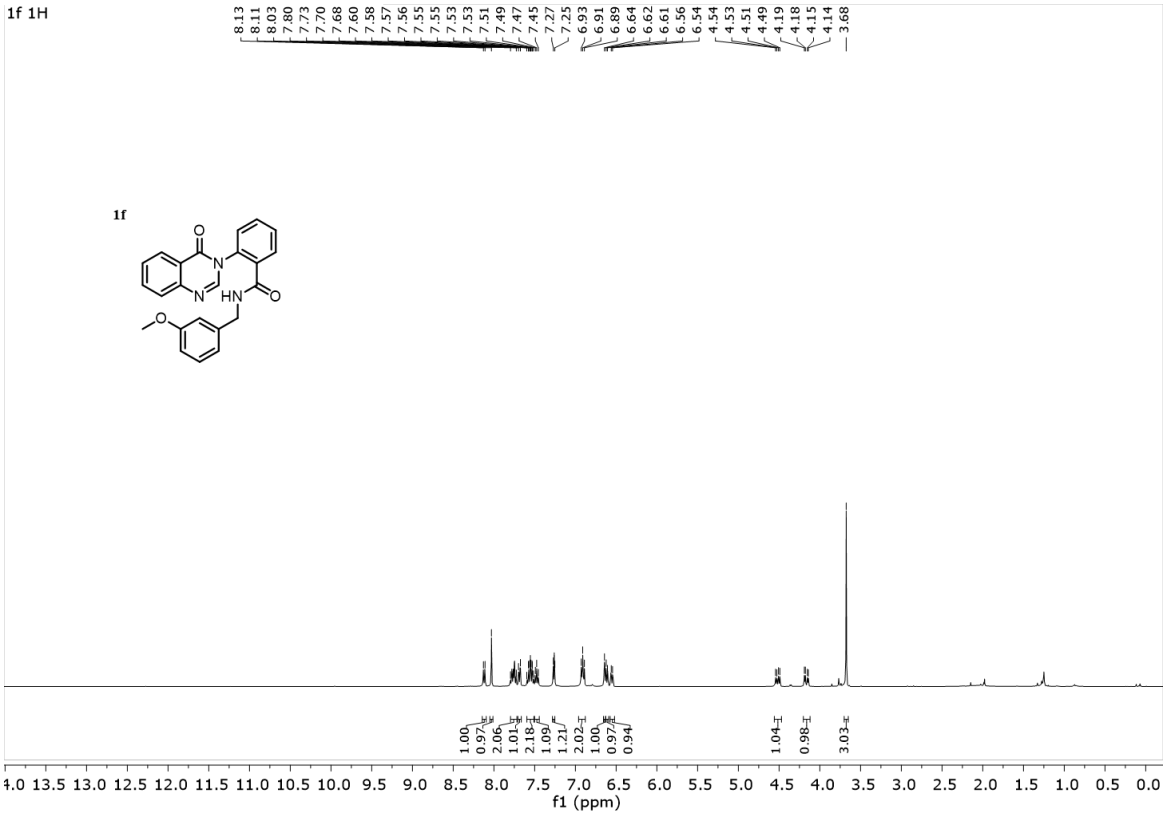
^{1}H in $CDCl_3$ 400 MHz 1e



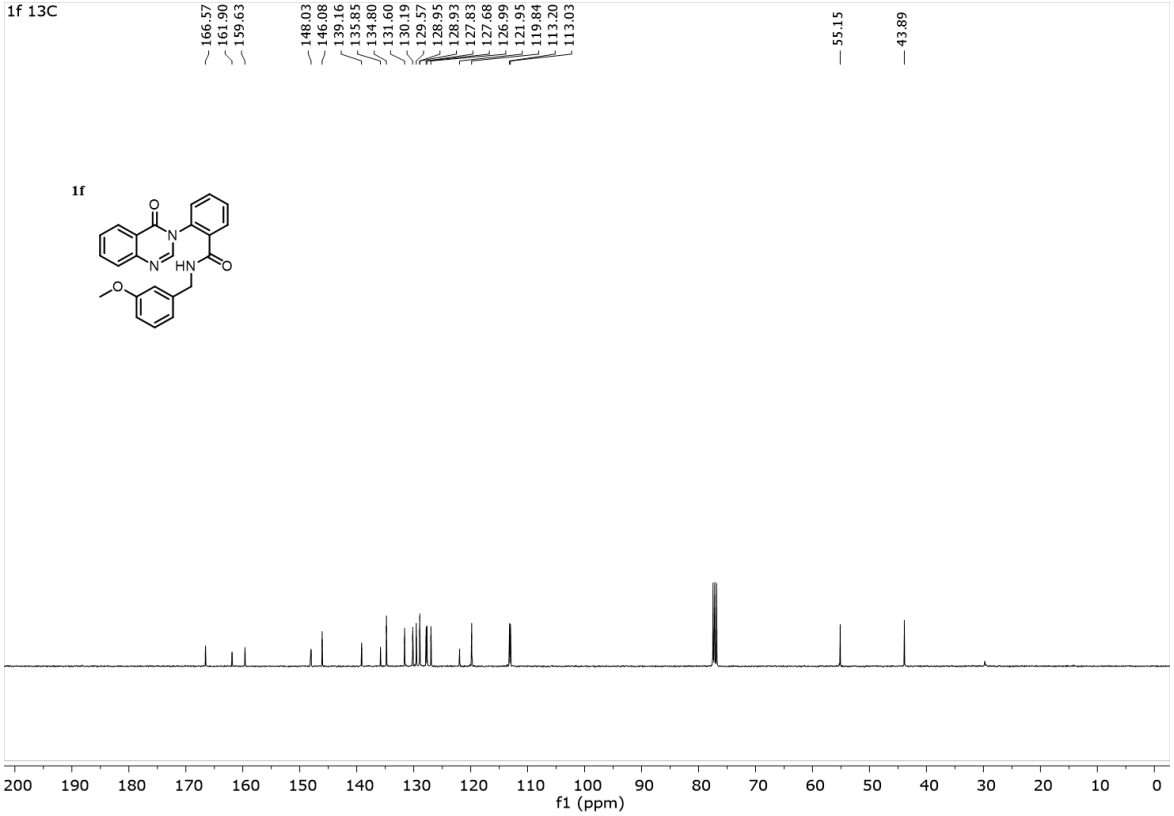
^{13}C in $CDCl_3$ 100 MHz 1e



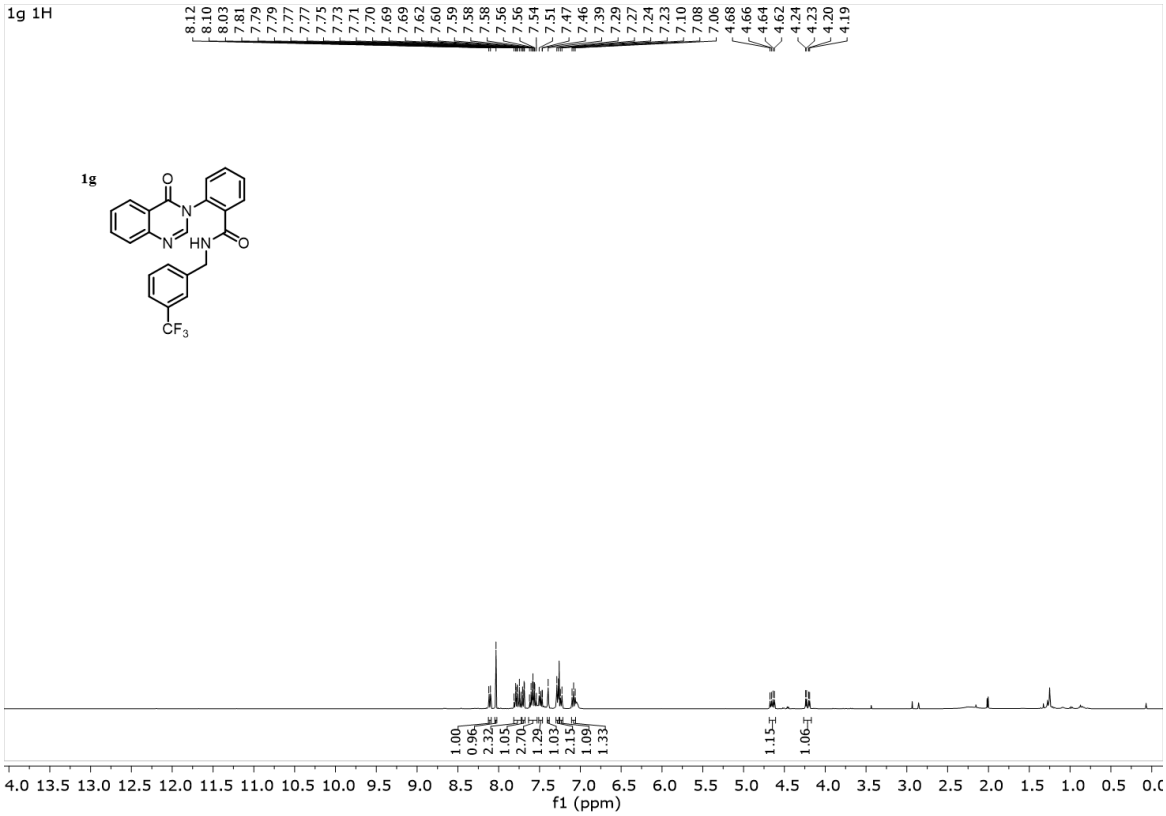
^{1}H in $CDCl_3$ 400 MHz 1f



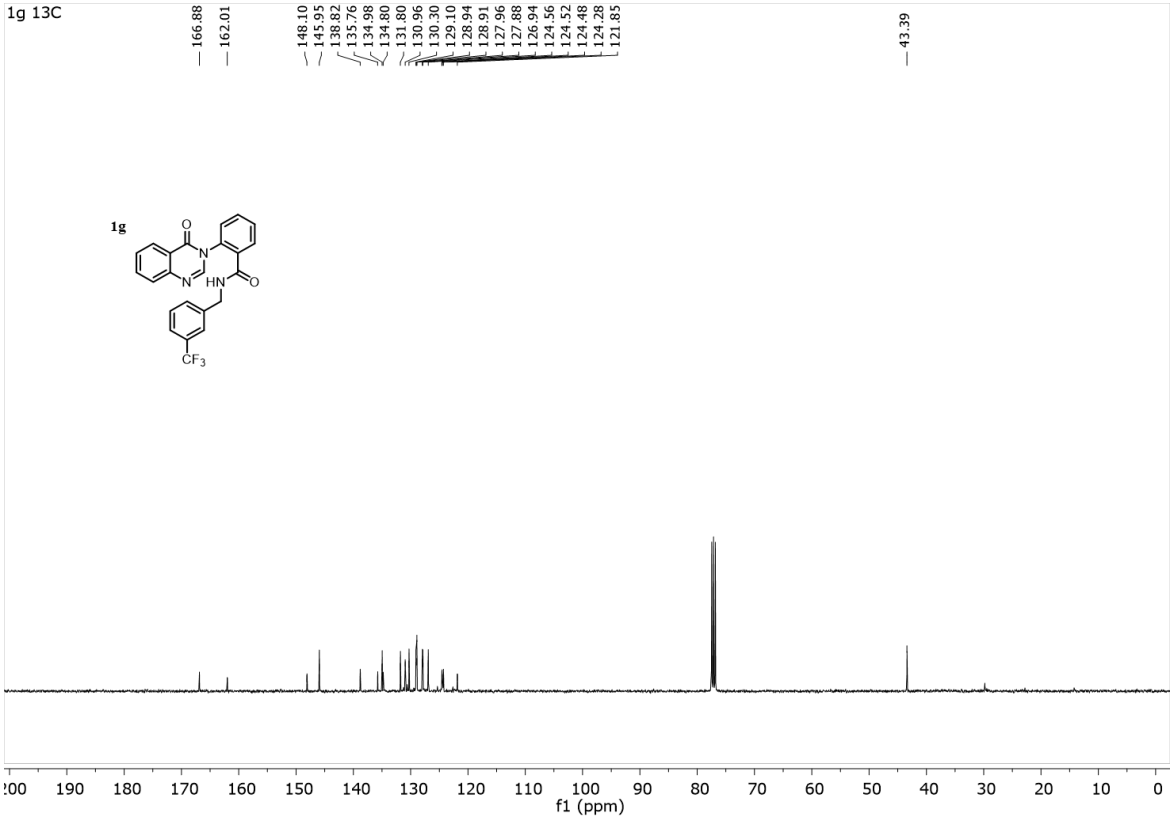
^{13}C in $CDCl_3$ 100 MHz 1f



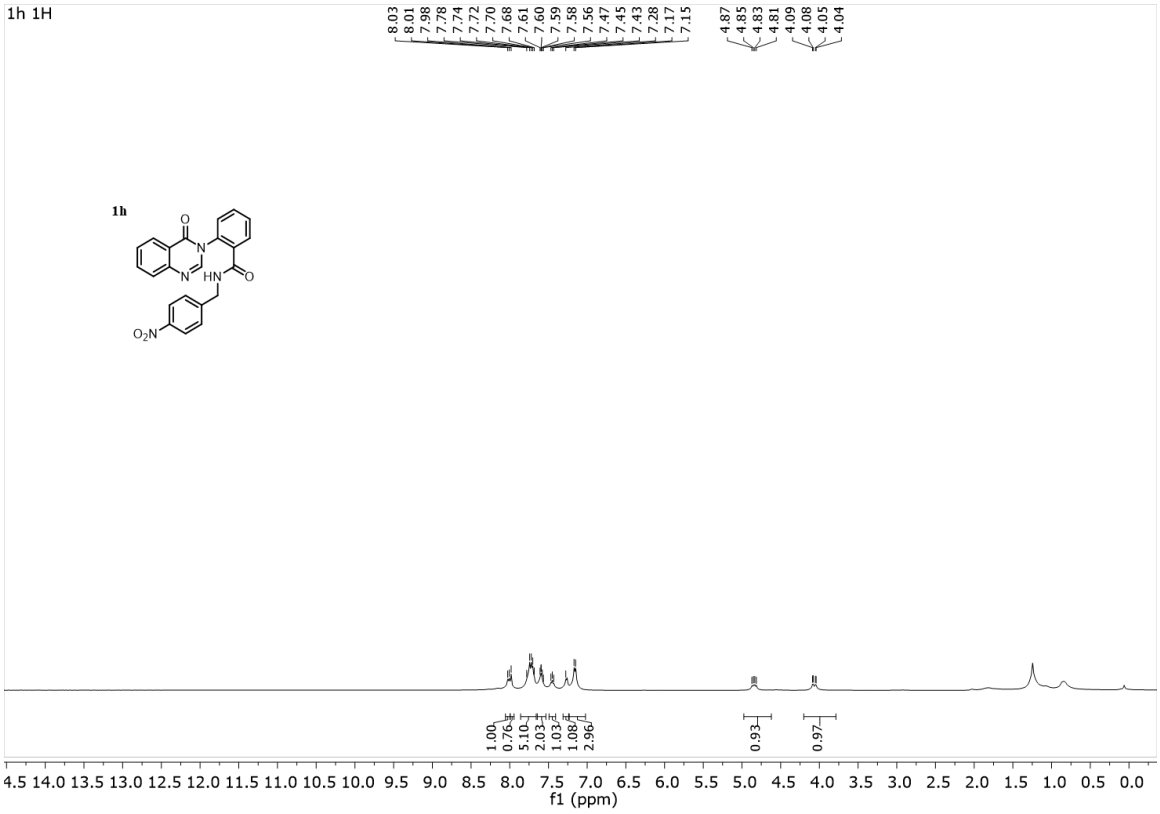
^{1}H in $CDCl_3$ 400 MHz 1g



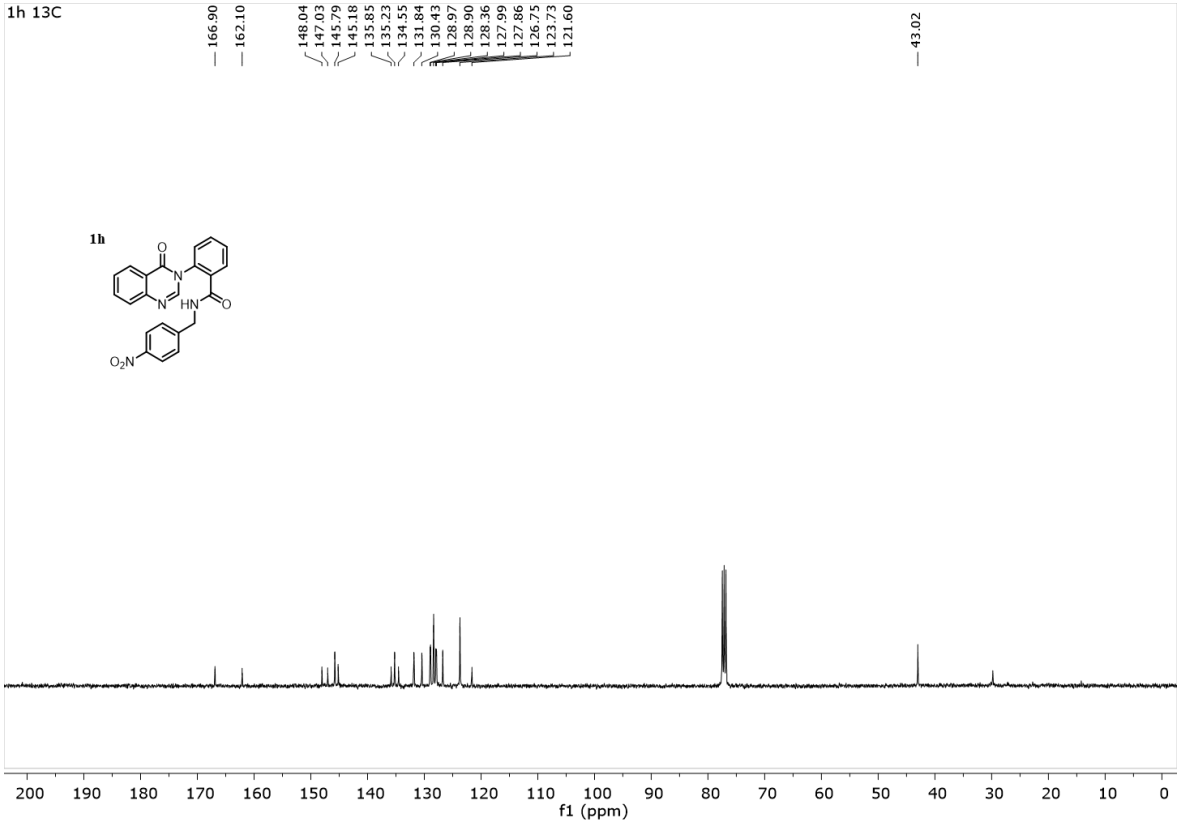
^{13}C in $CDCl_3$ 100 MHz 1g



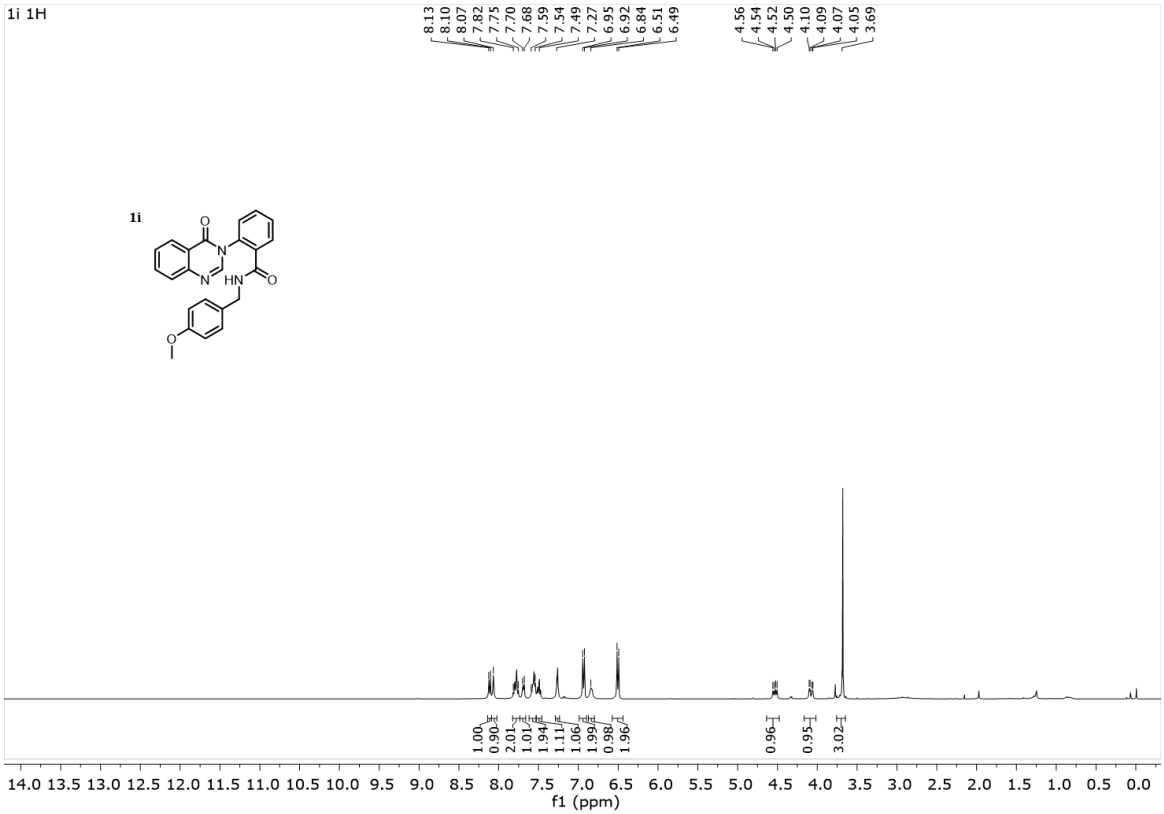
^{1}H in $CDCl_3$ 400 MHz 1h



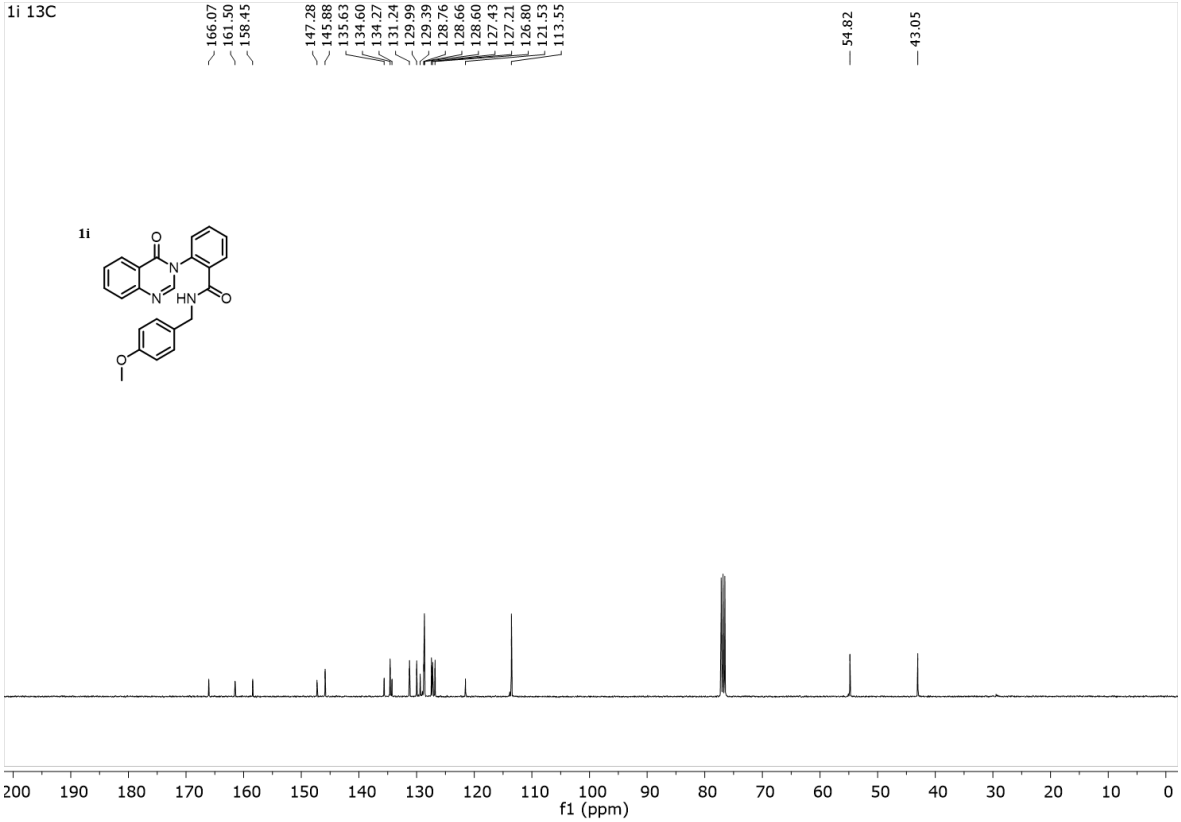
^{13}C in $CDCl_3$ 100 MHz 1h



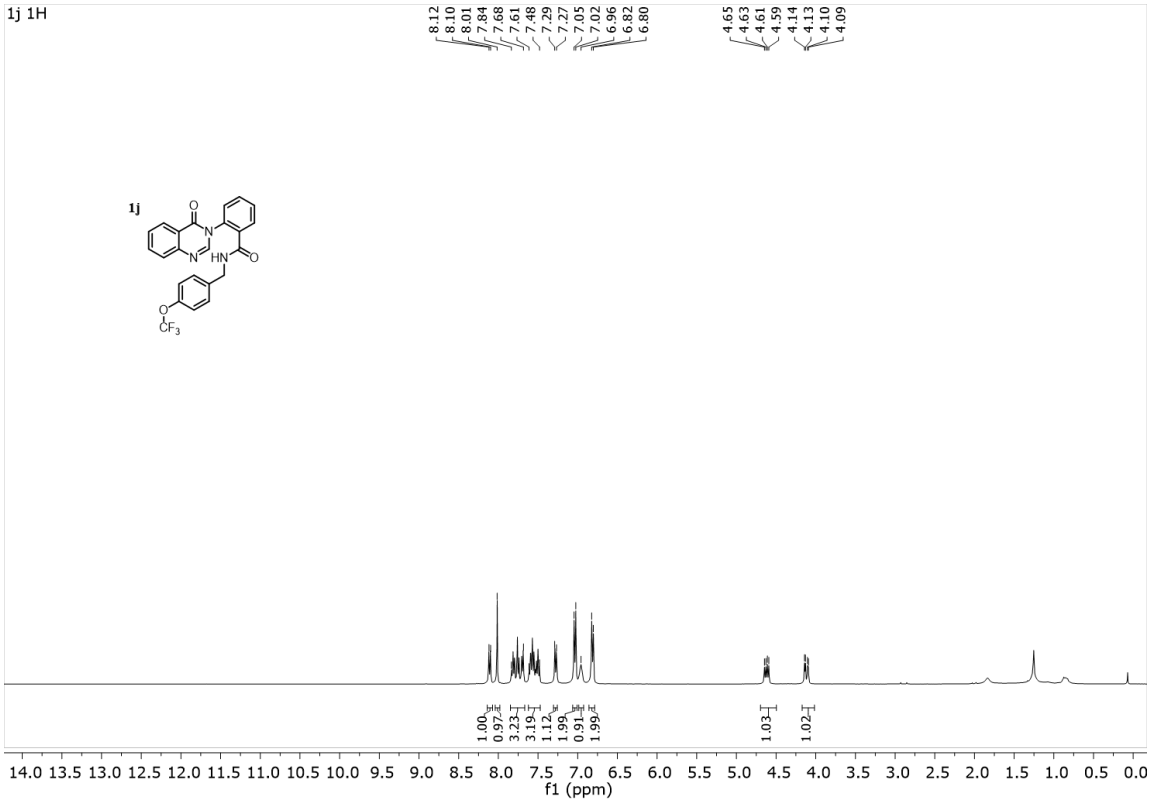
^{1}H in $CDCl_3$ 400 MHz 1i



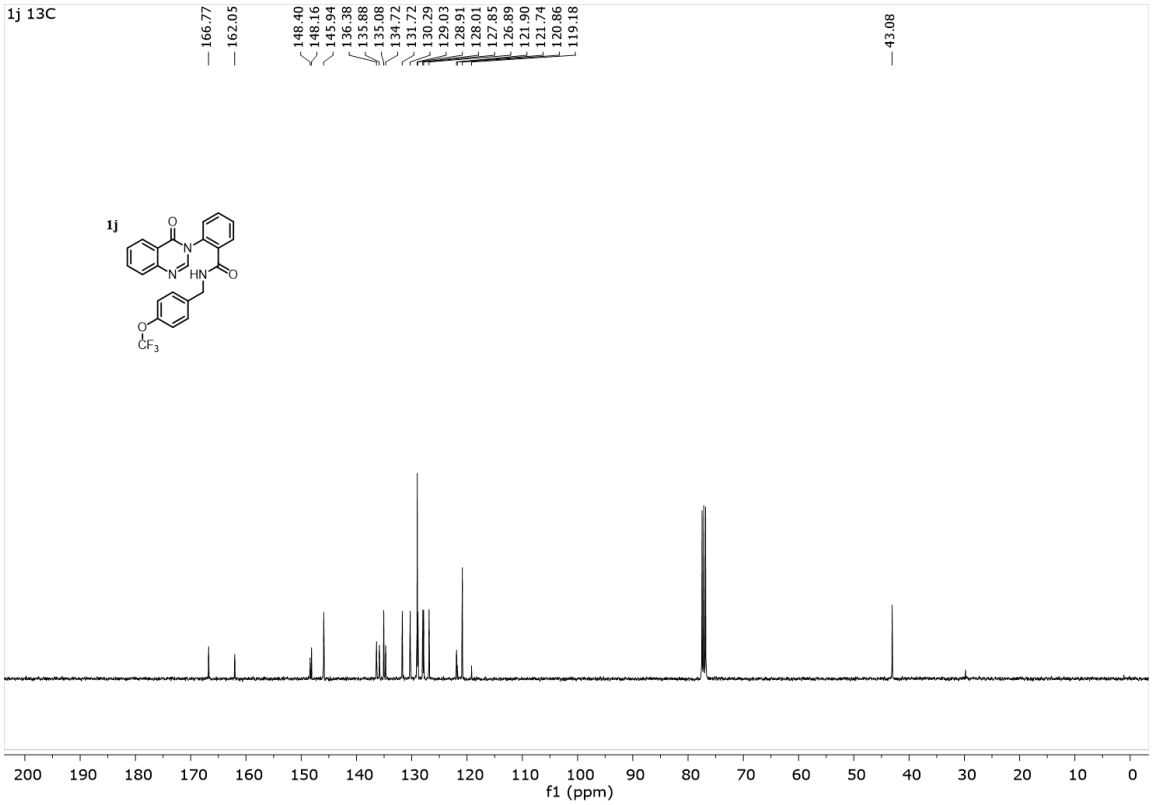
^{13}C in $CDCl_3$ 100 MHz 1i



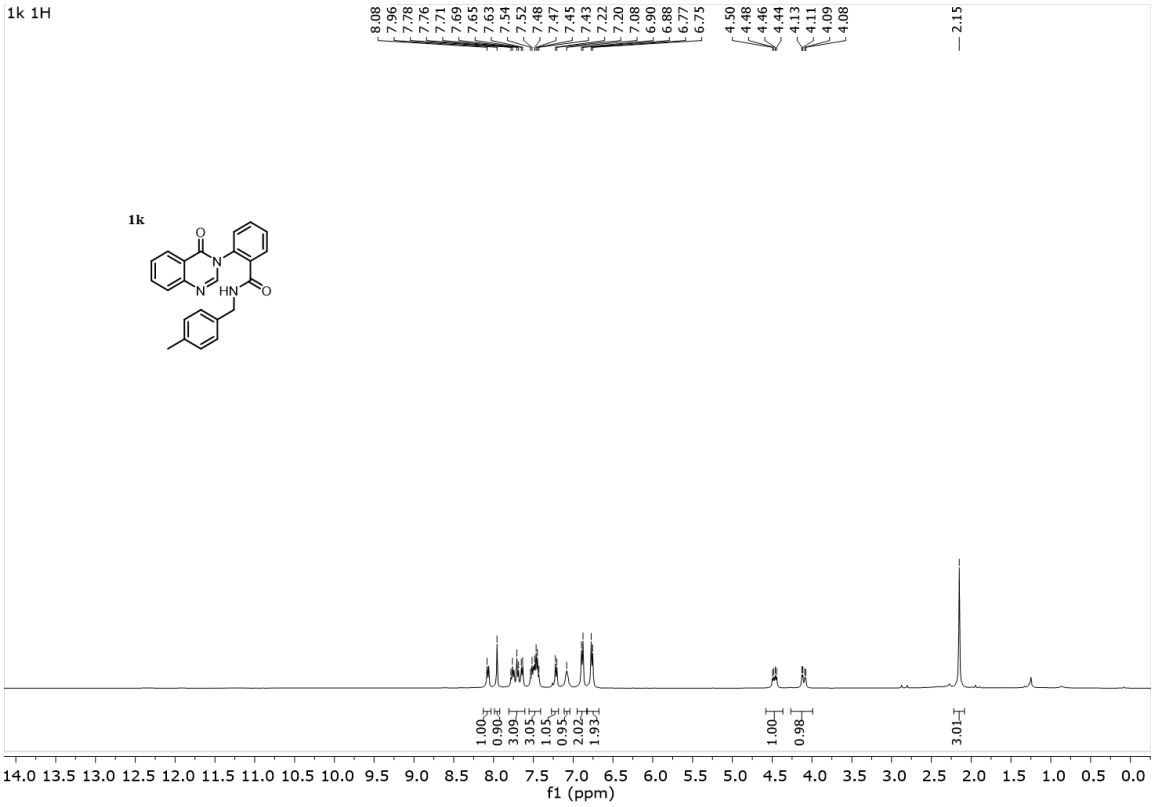
^{1}H in $CDCl_3$ 400 MHz 1j



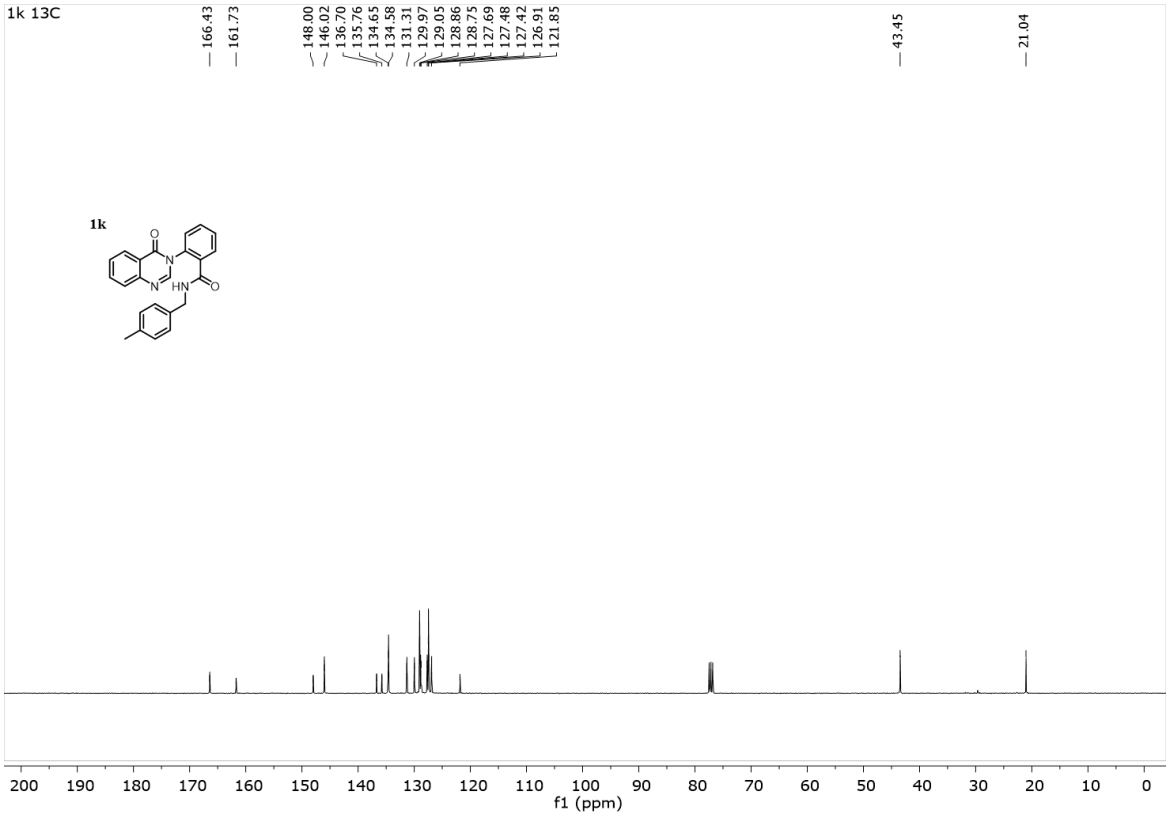
^{13}C in $CDCl_3$ 100 MHz 1j



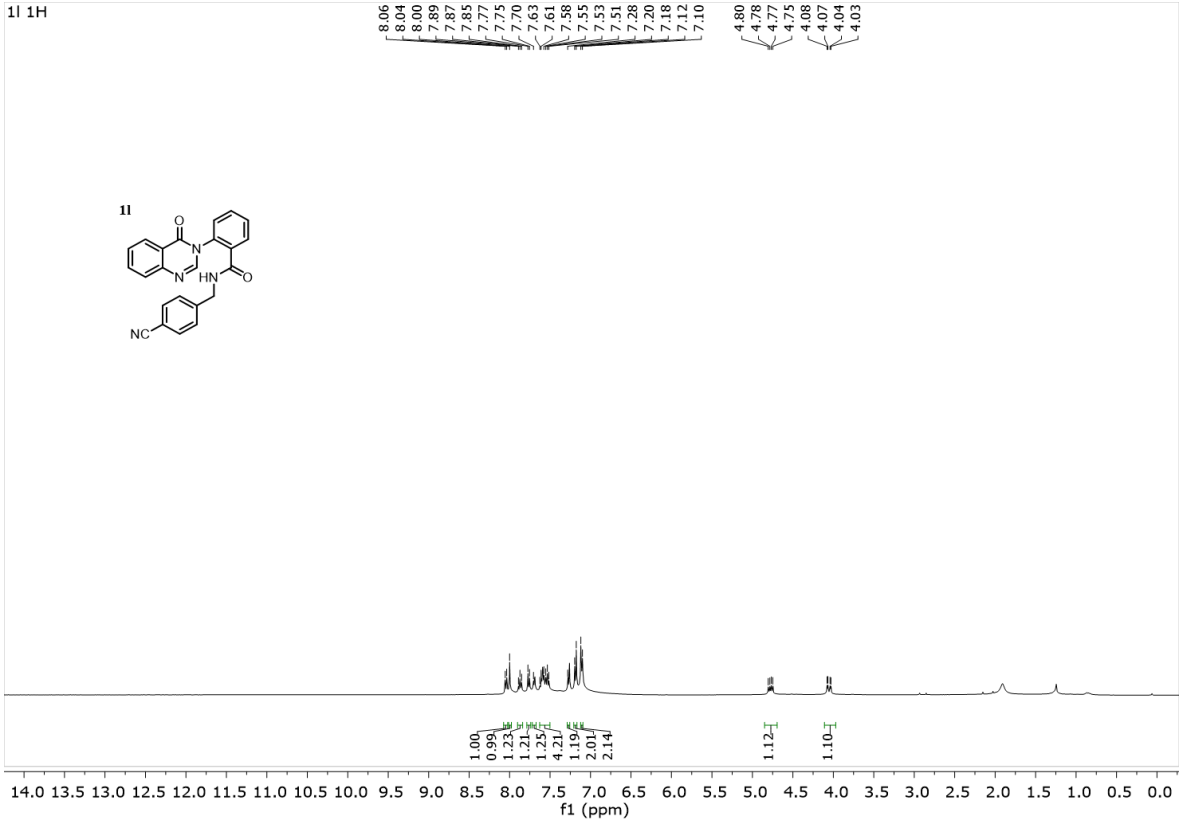
^{1}H in $CDCl_3$ 400 MHz 1k



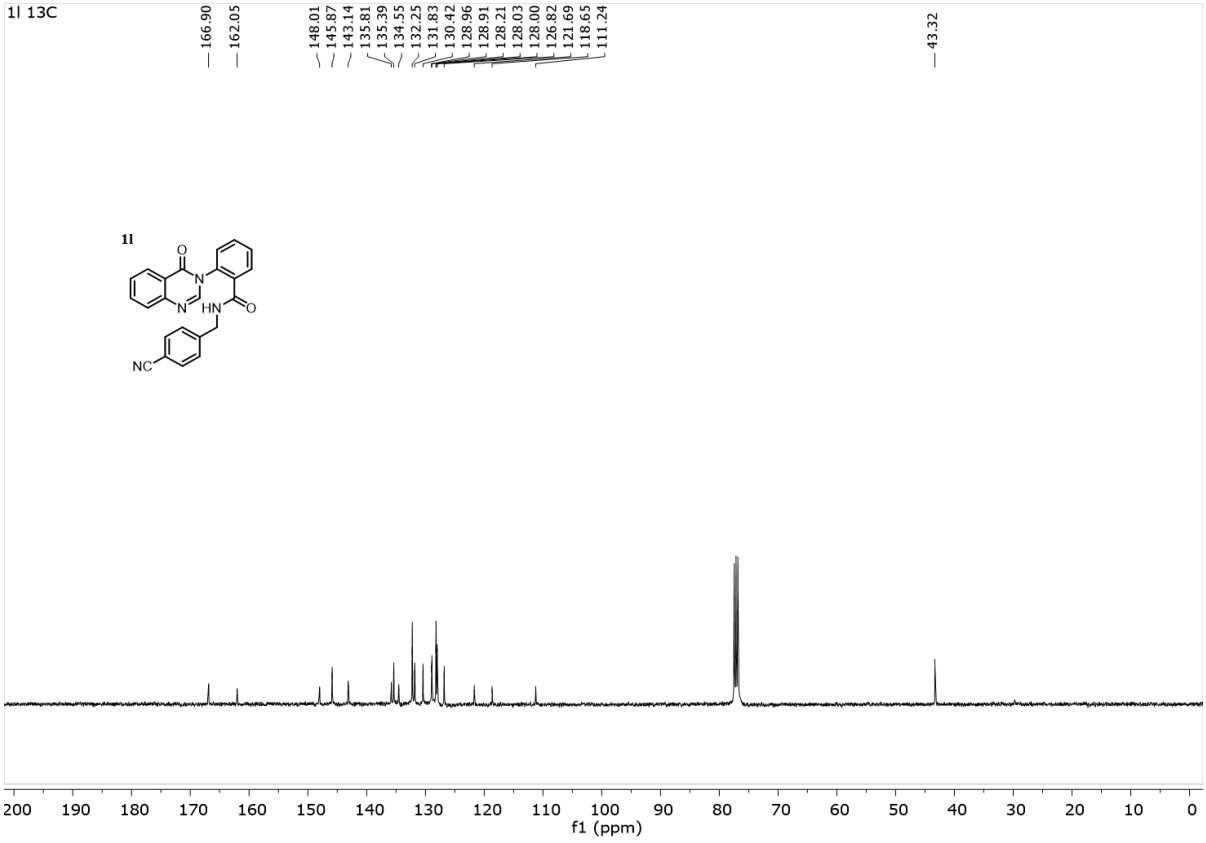
^{13}C in $CDCl_3$ 100 MHz 1k



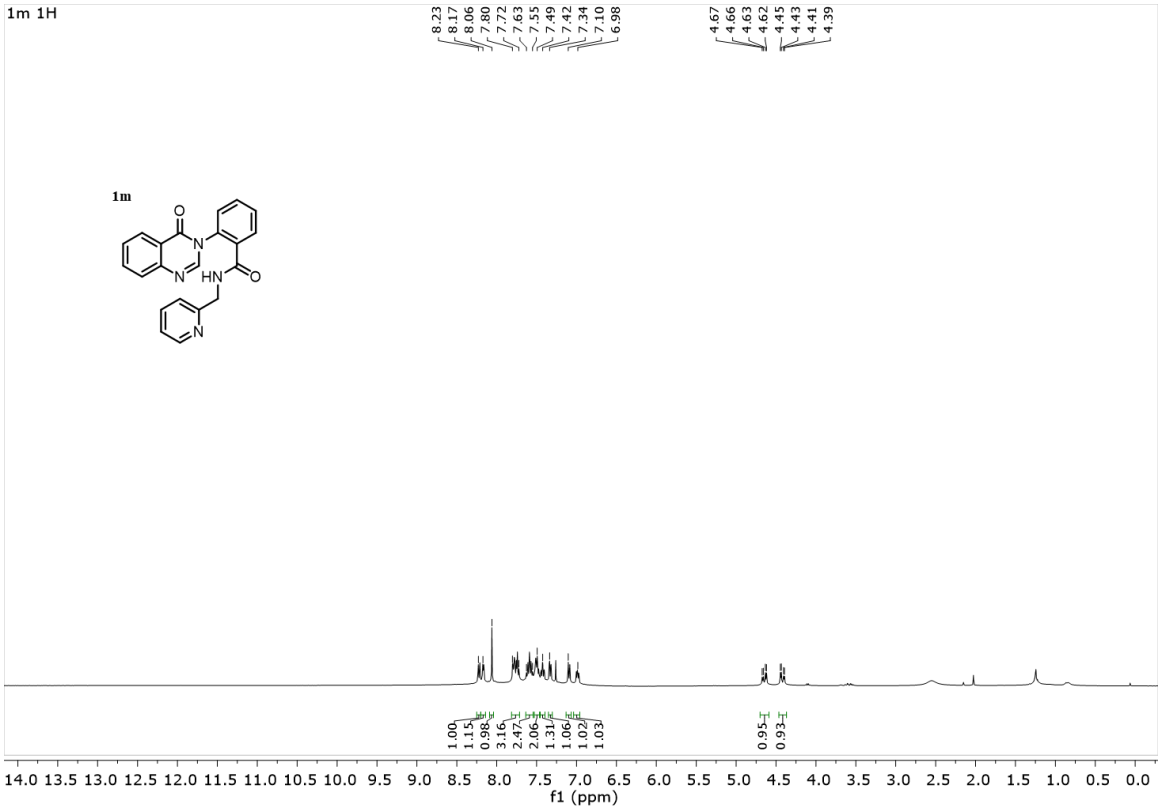
^{1}H in $CDCl_3$ 400 MHz 1l



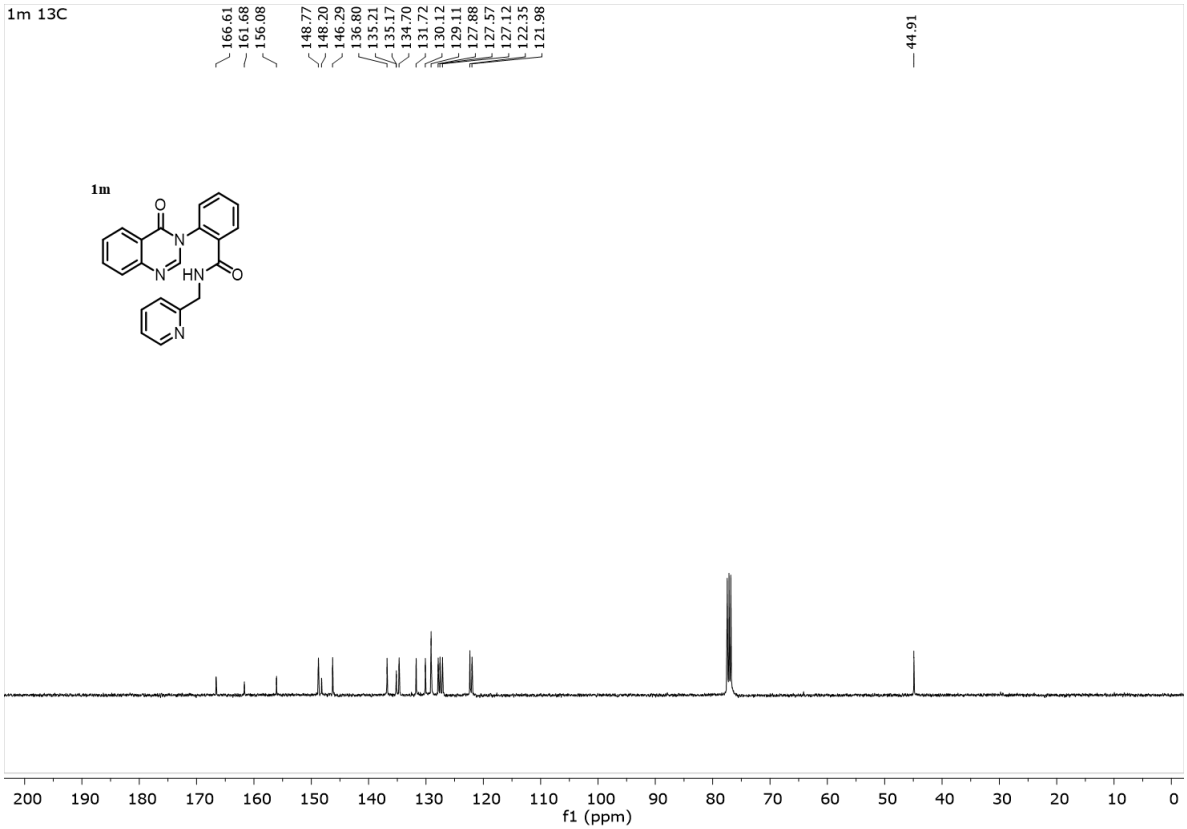
^{13}C in $CDCl_3$ 100 MHz 1l



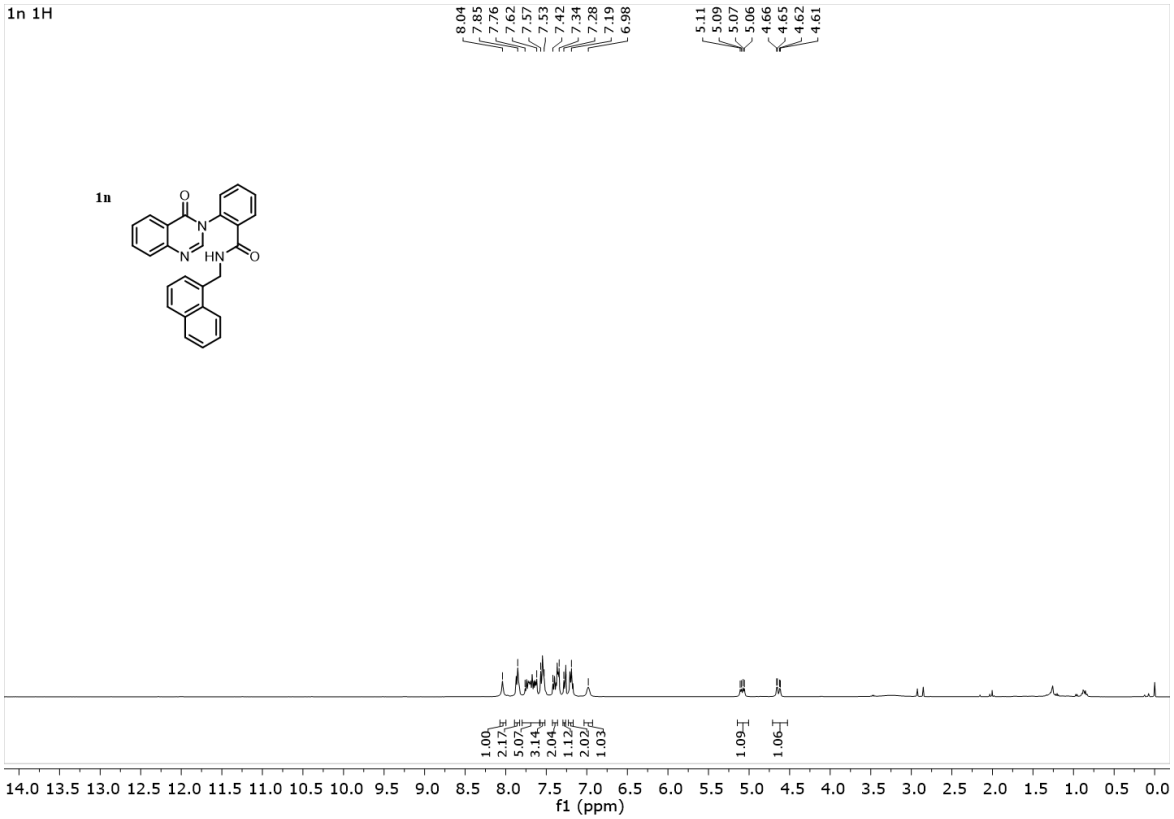
^{1}H in $CDCl_3$ 400 MHz 1m



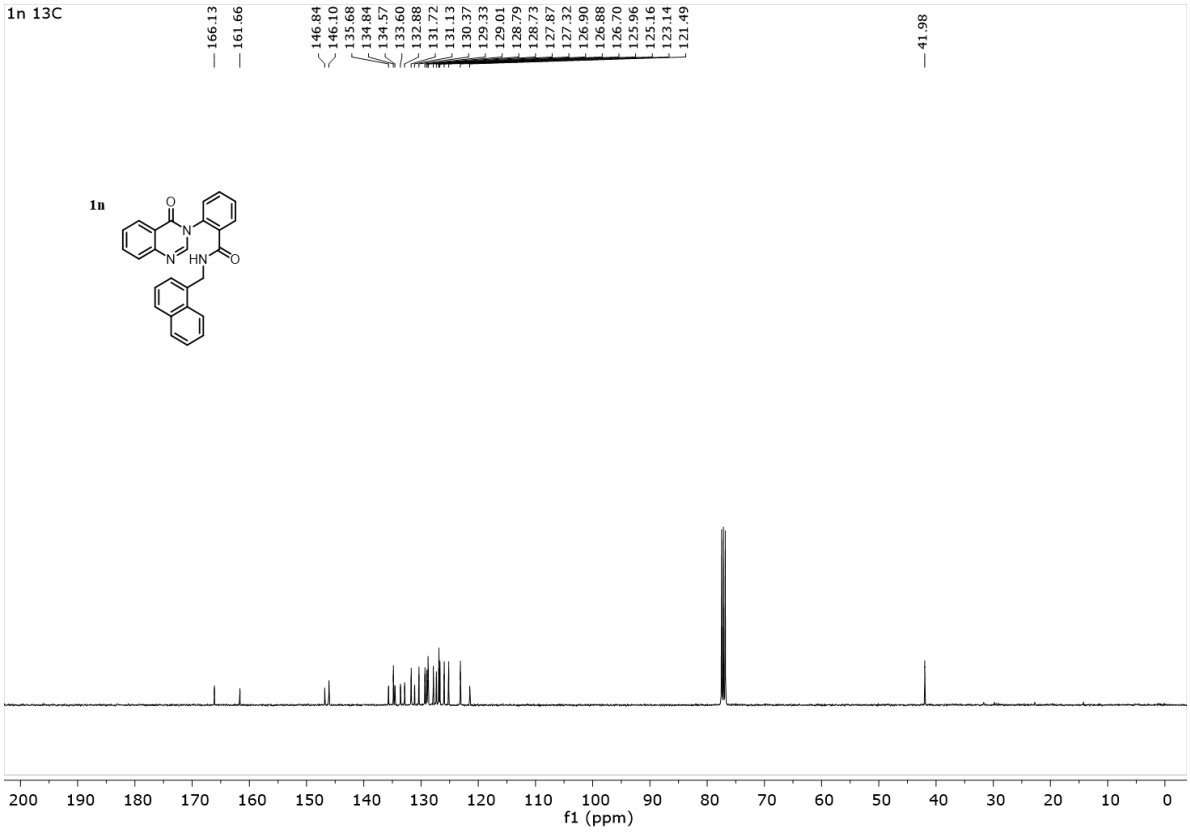
^{13}C in $CDCl_3$ 100 MHz 1m



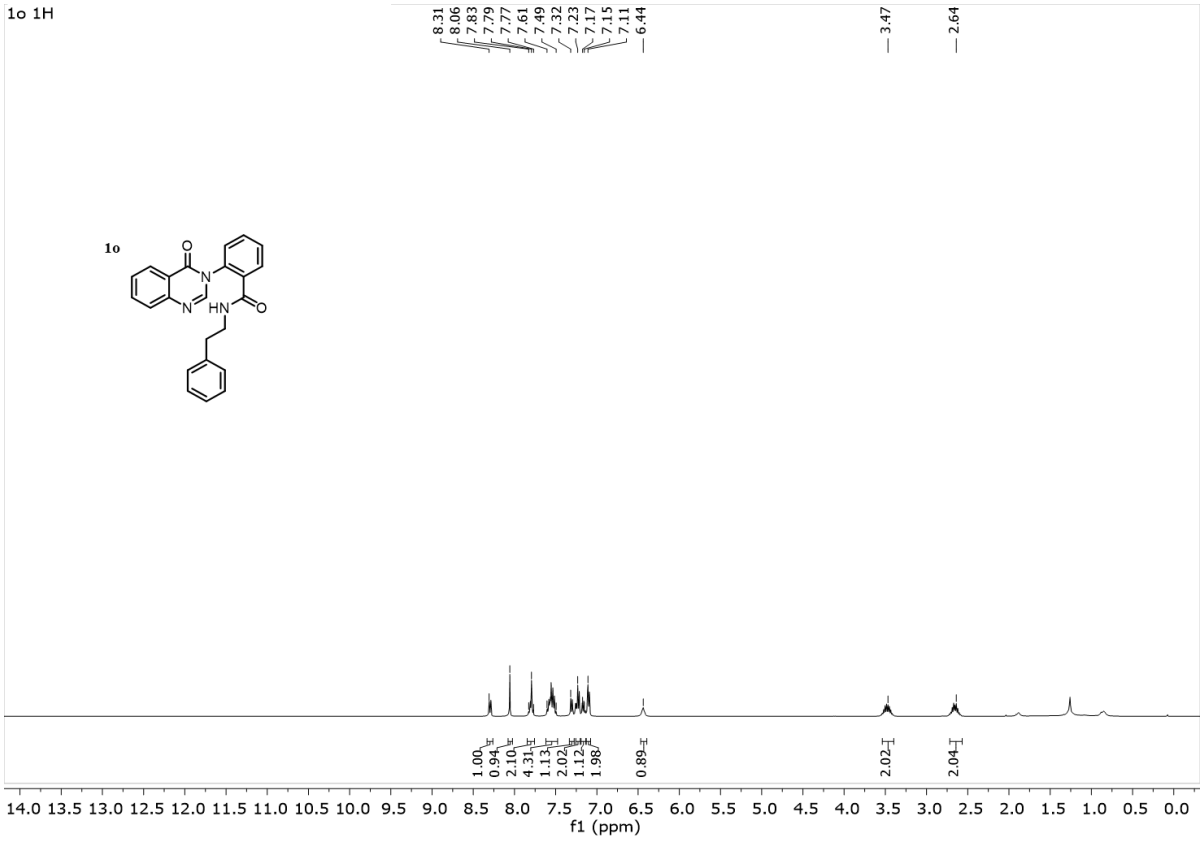
^{1}H in $CDCl_3$ 400 MHz 1n



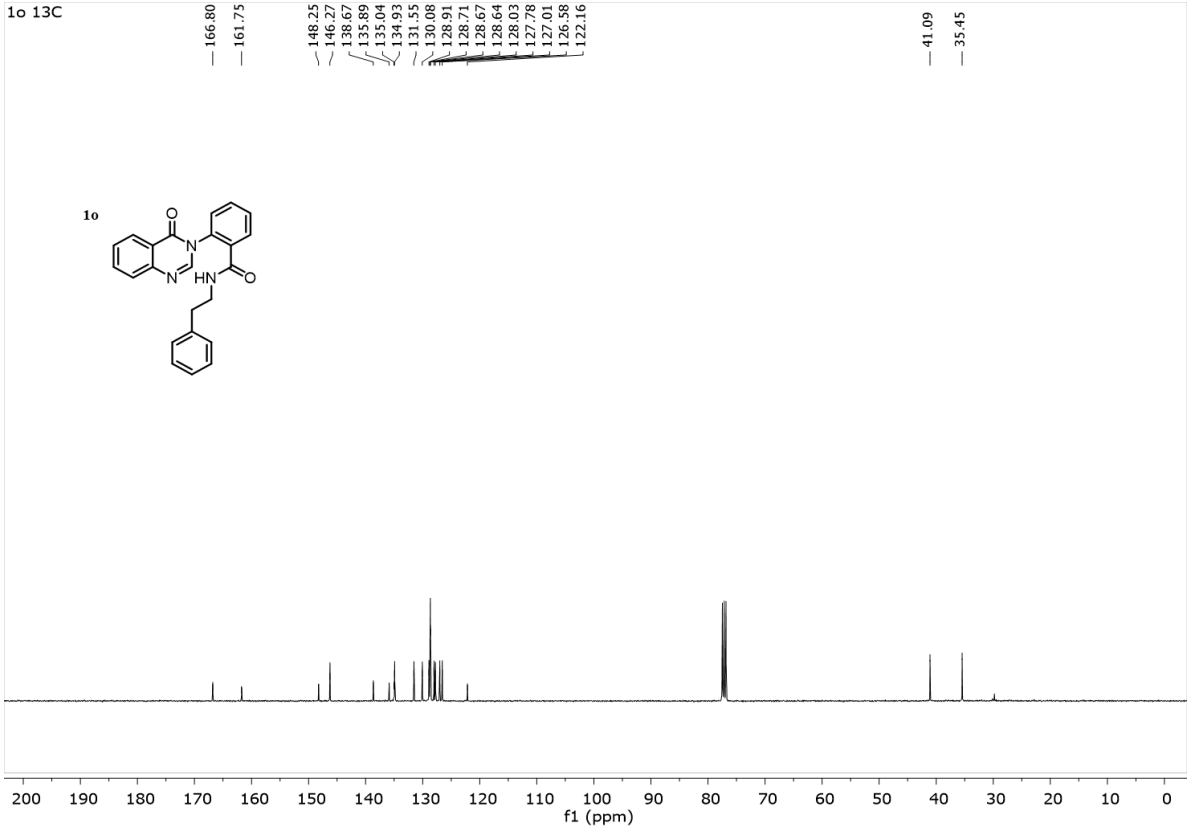
^{13}C in $CDCl_3$ 100 MHz 1n



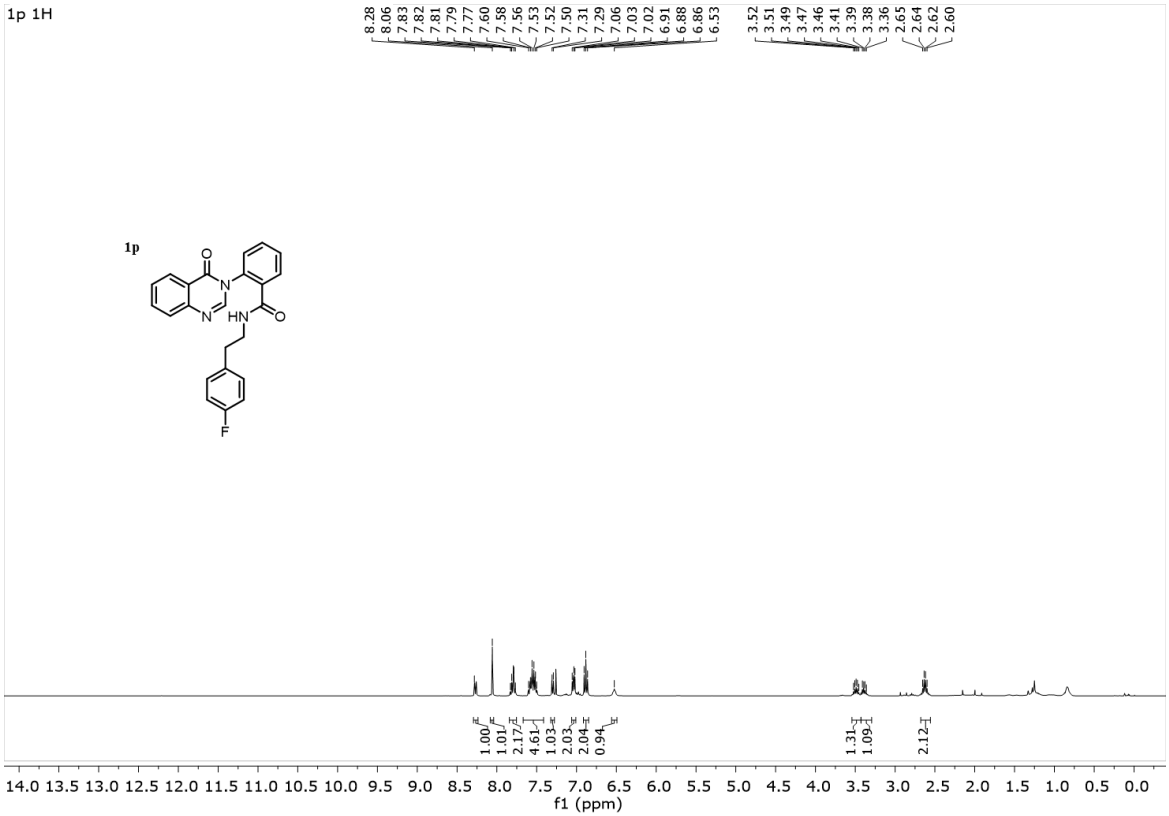
^{1}H in $CDCl_3$ 400 MHz 1o



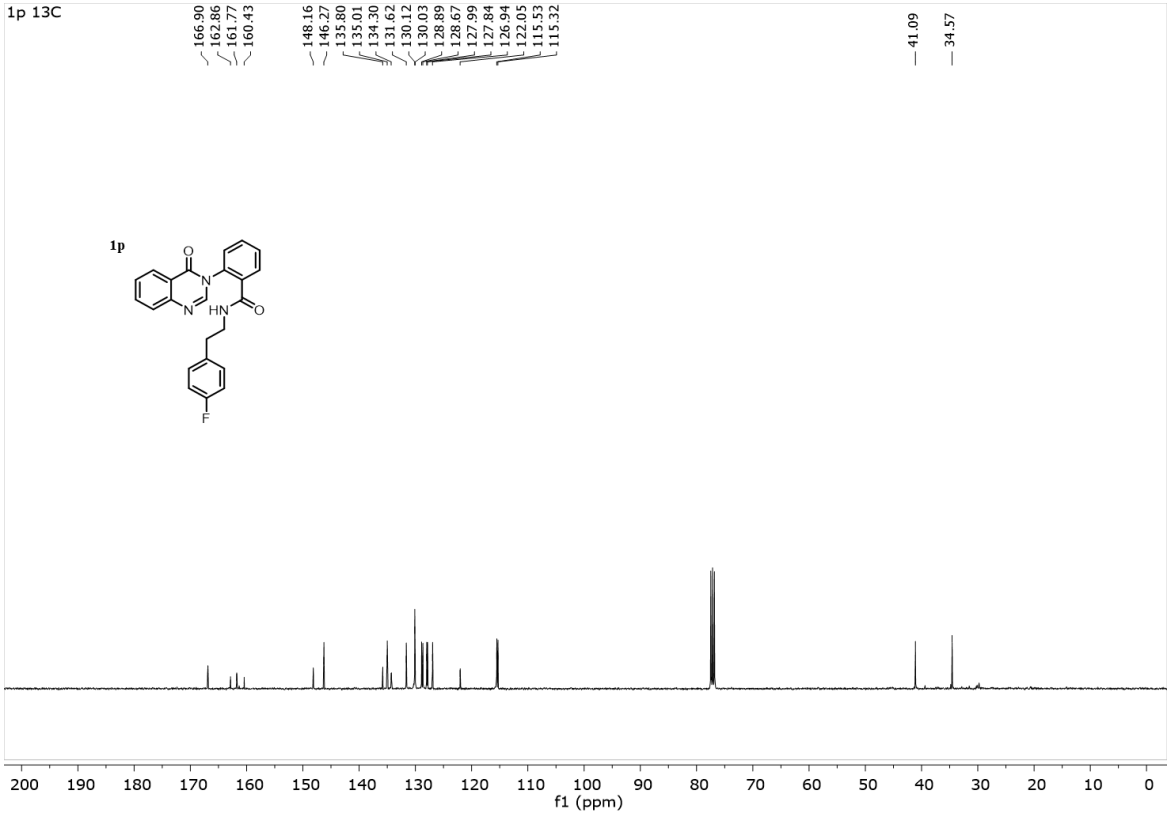
^{13}C in $CDCl_3$ 100 MHz 1o



^{1}H in $CDCl_3$ 400 MHz 1p

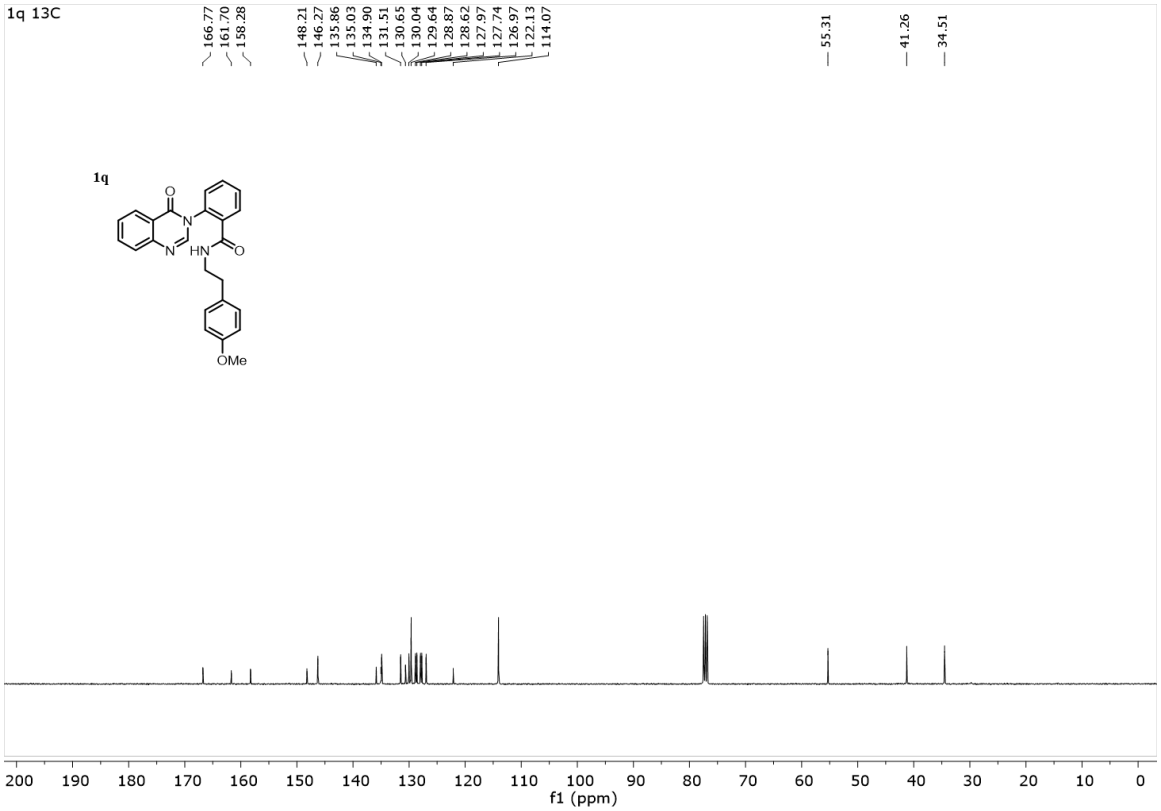


^{13}C in $CDCl_3$ 100 MHz 1p

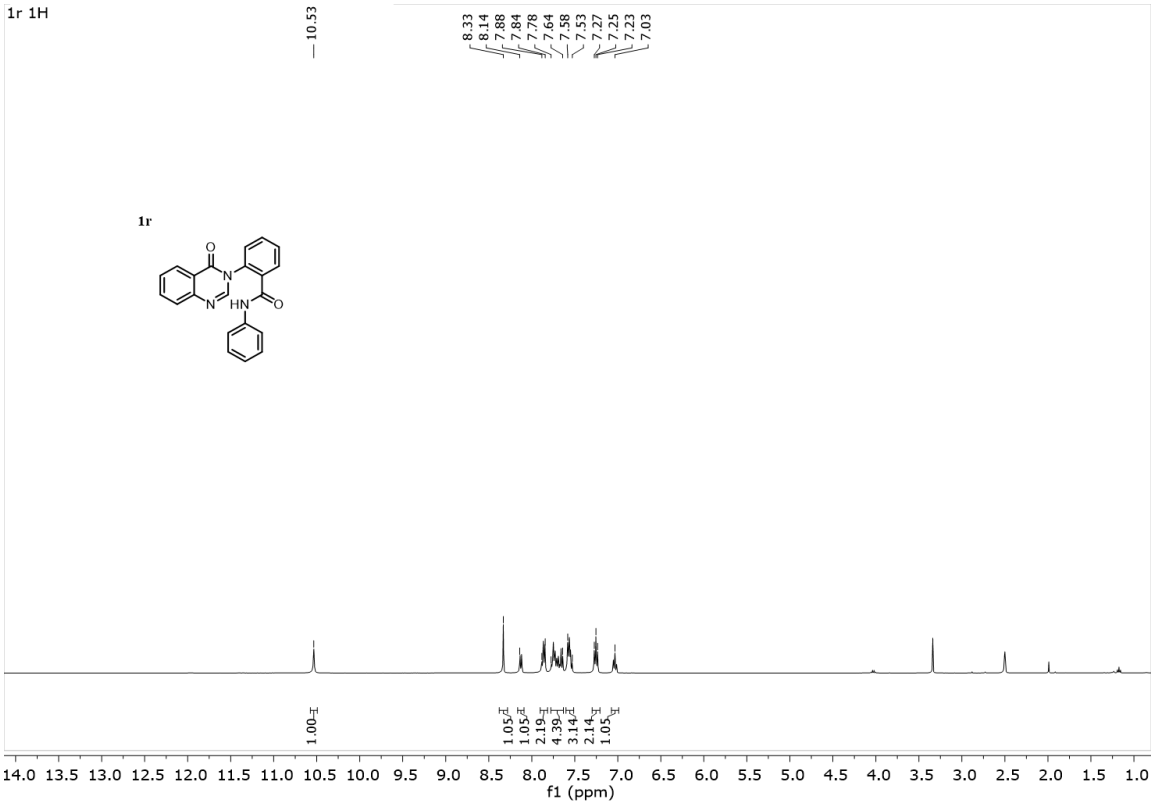


^{1}H in $CDCl_3$ 400 MHz 1q

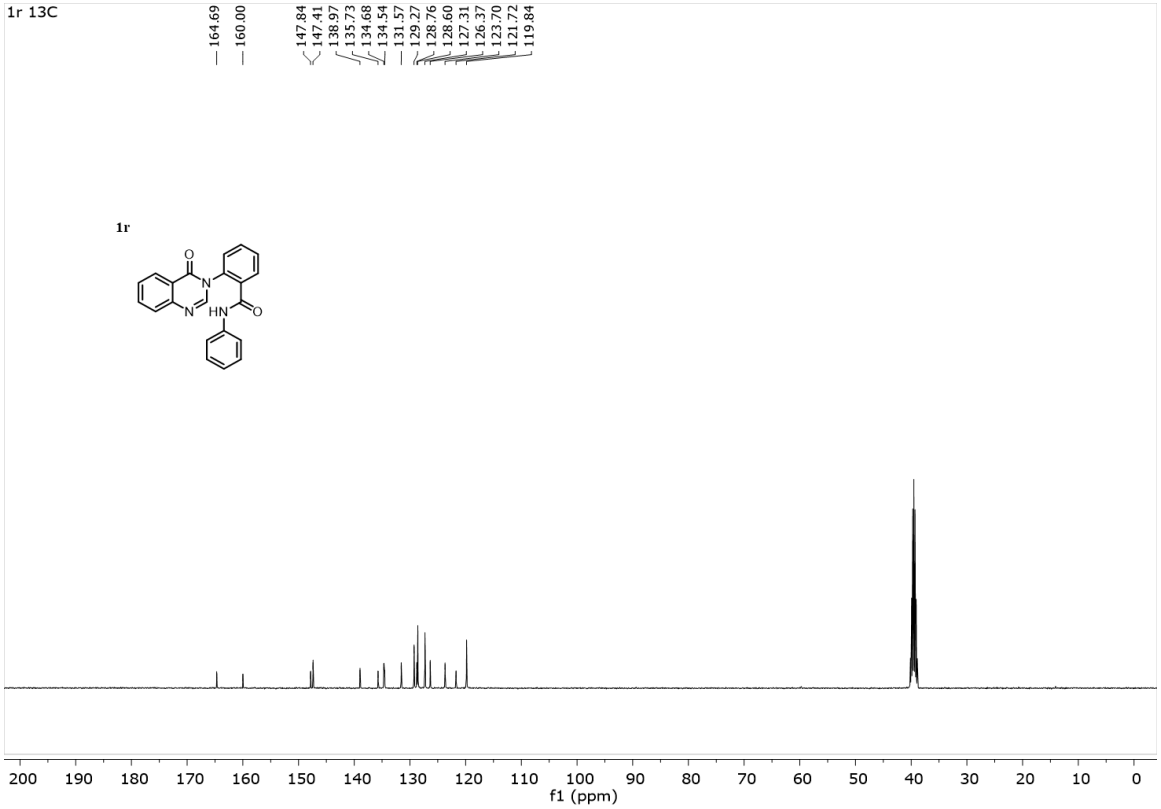
^{13}C in $CDCl_3$ 100 MHz 1q



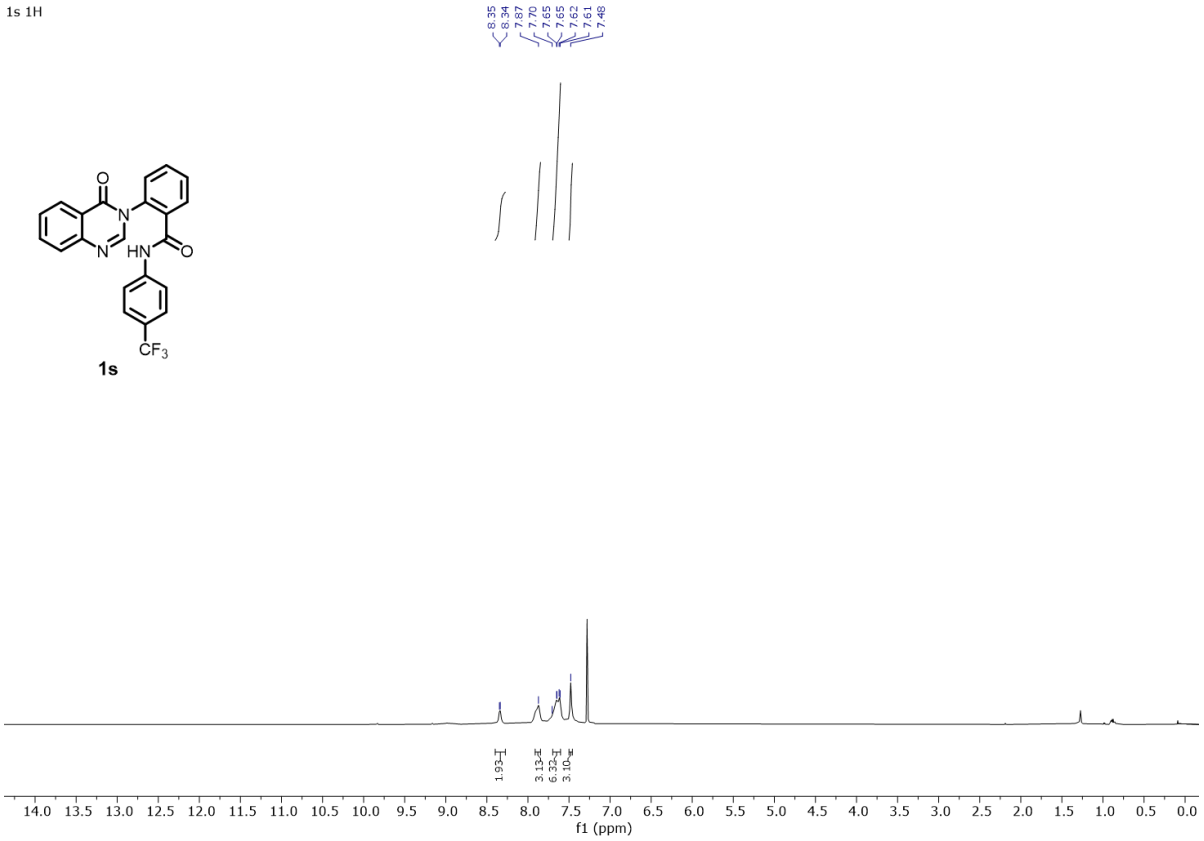
^{1}H in $CDCl_3$ 400 MHz 1r



^{13}C in $CDCl_3$ 100 MHz 1r

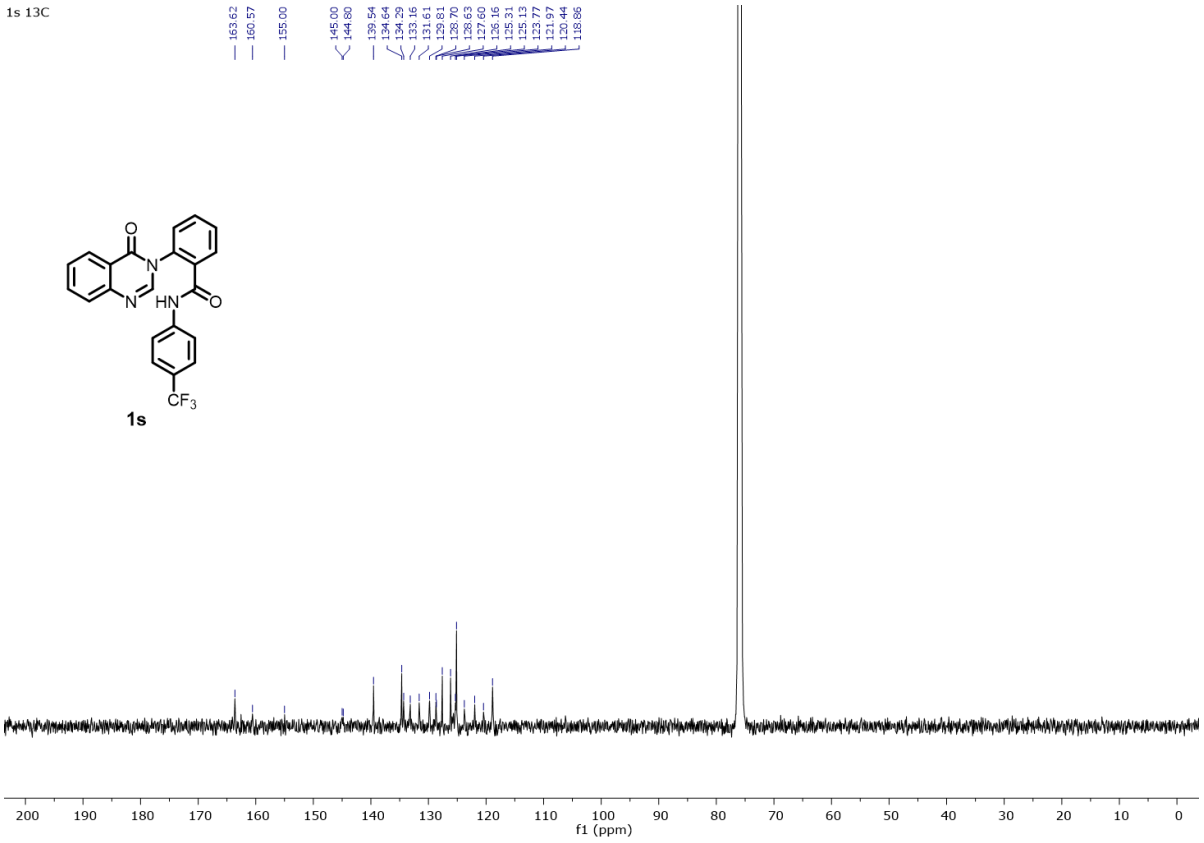


^{1}H in $CDCl_3$ 600 MHz 1s



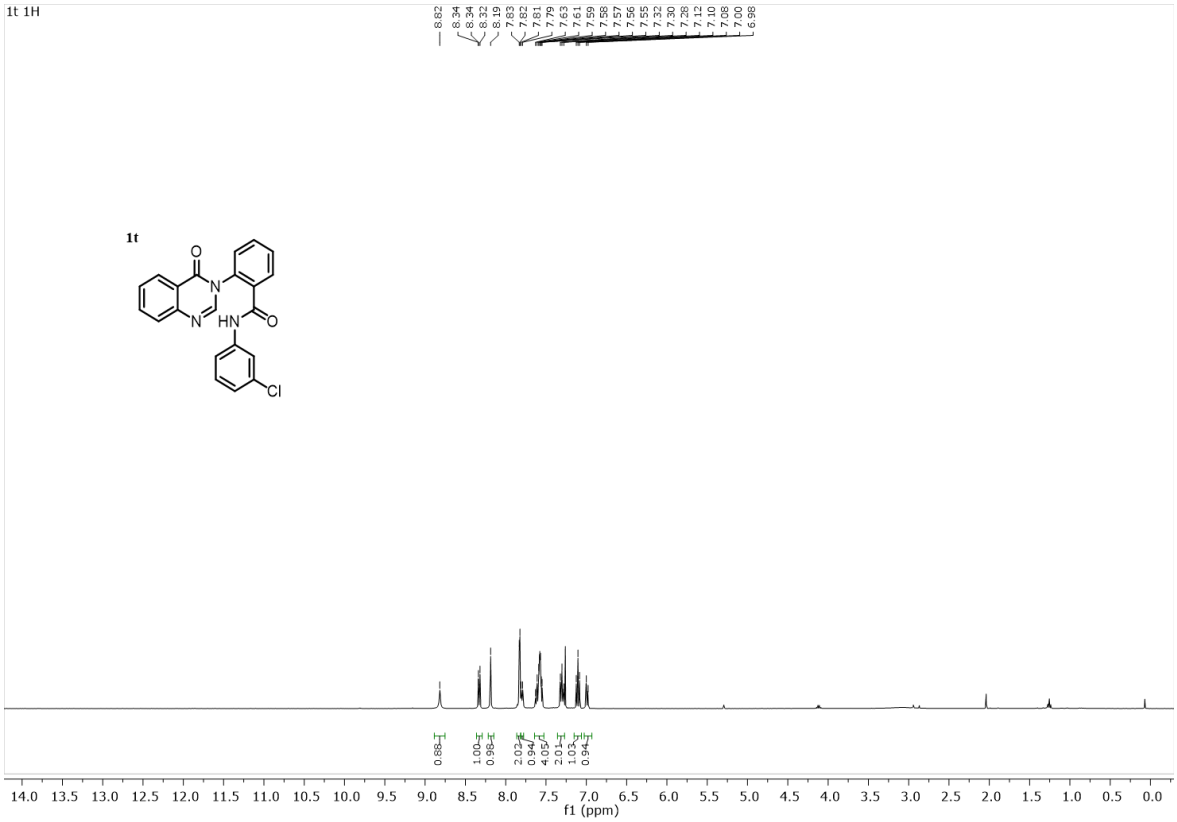
1s

^{13}C in $CDCl_3$ 150 MHz 1s

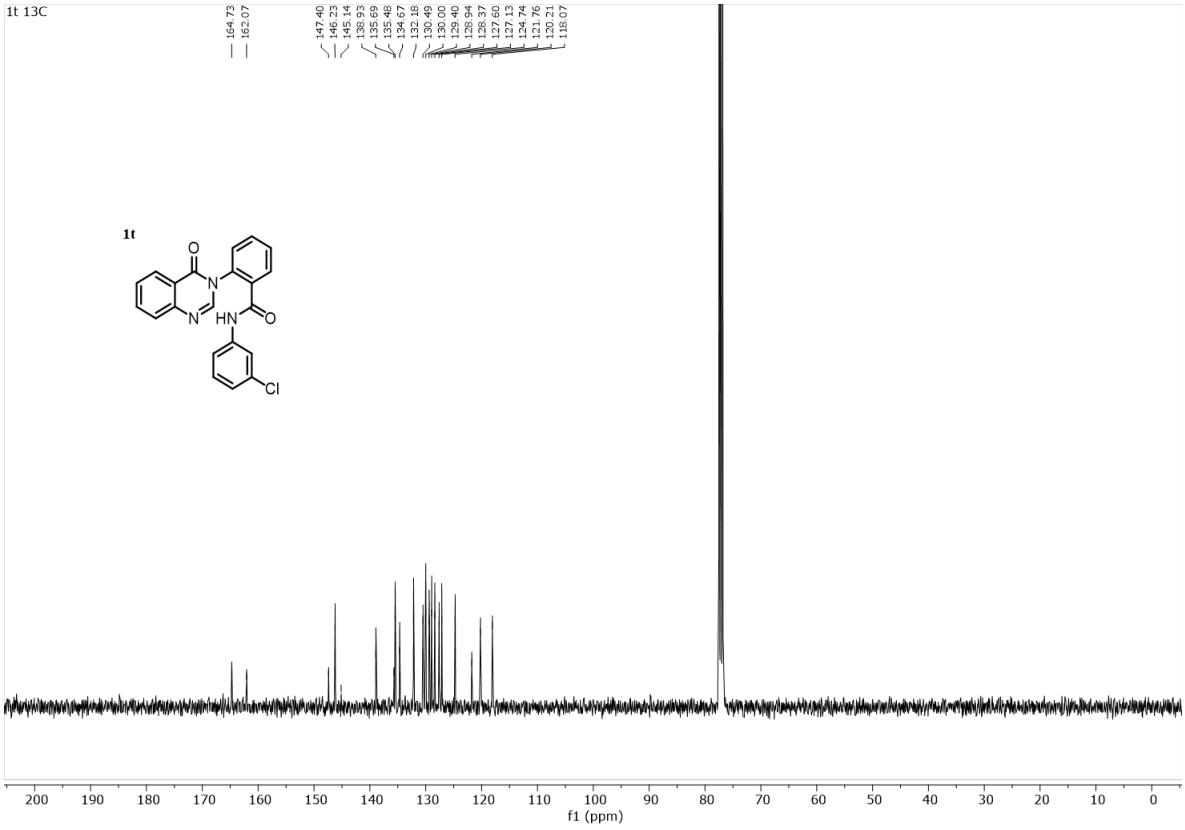


1s

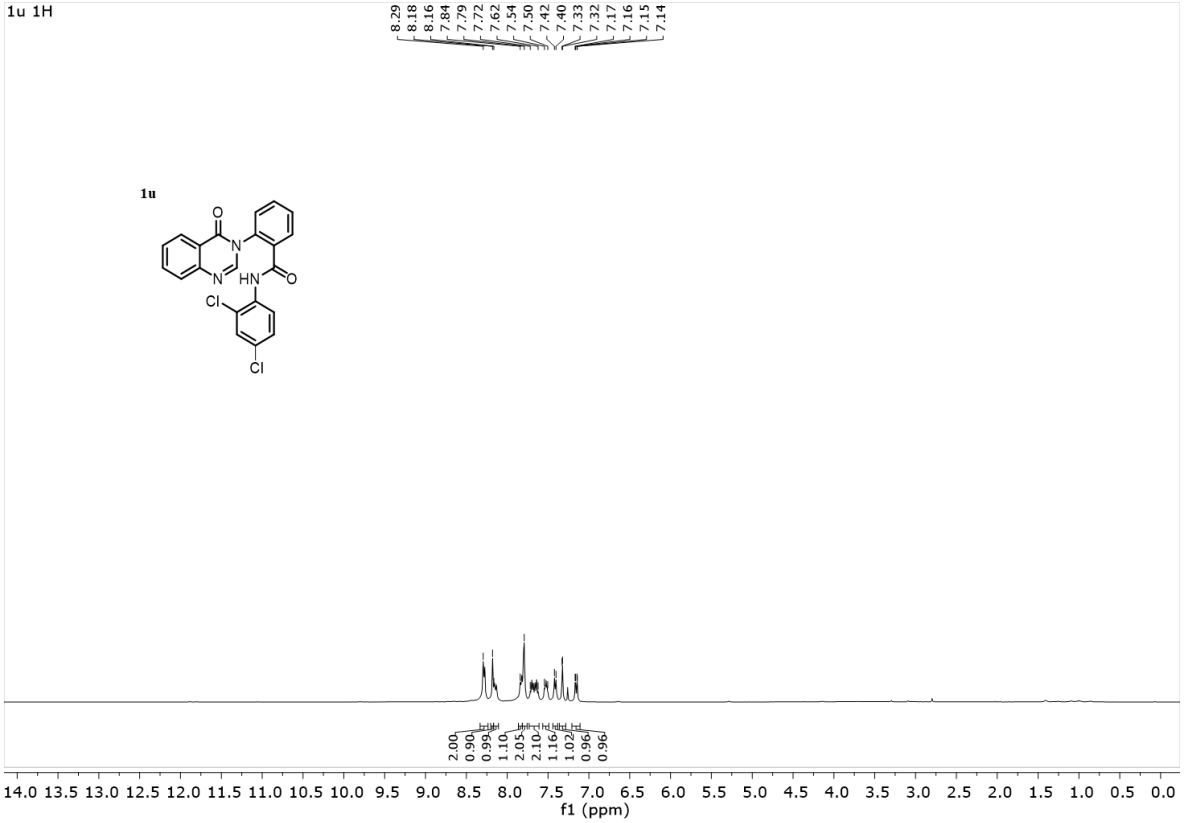
^{1}H in $CDCl_3$ 400 MHz 1t



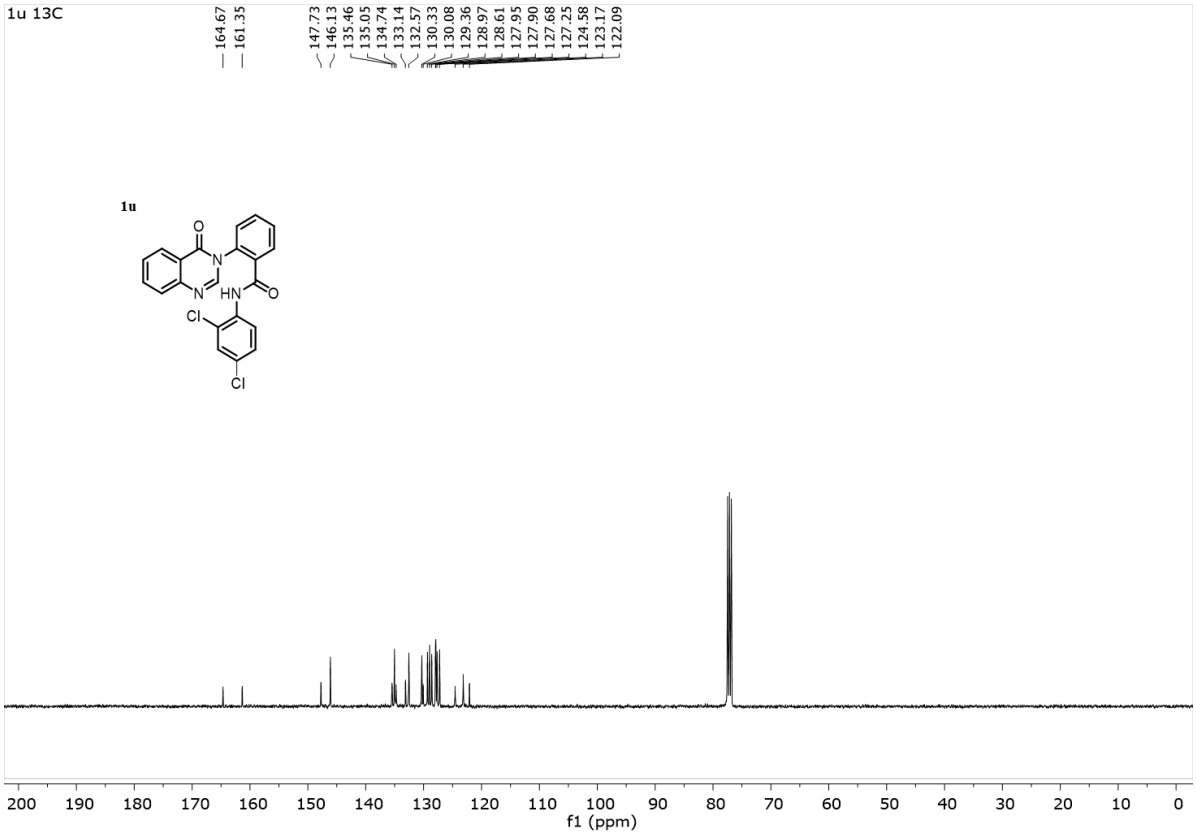
^{13}C in $CDCl_3$ 100 MHz 1t



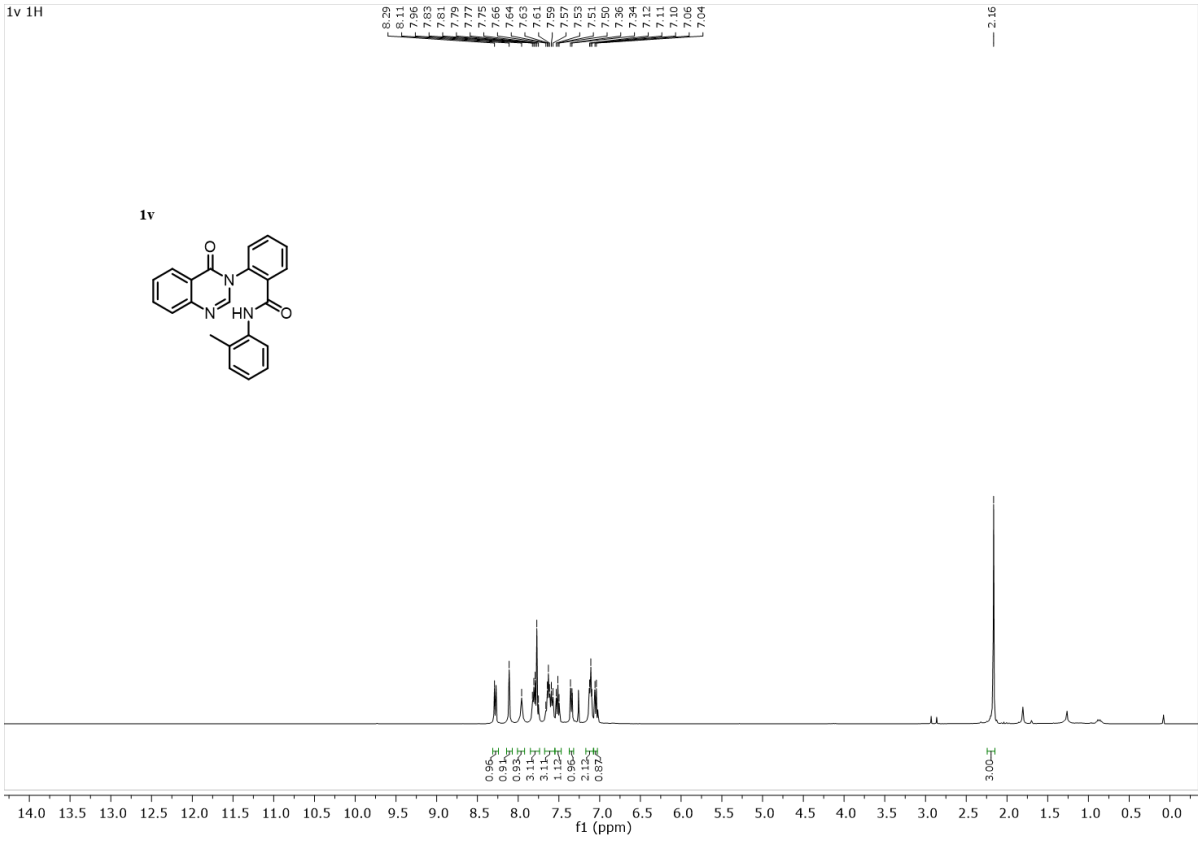
^{1}H in $CDCl_3$ 400 MHz 1u



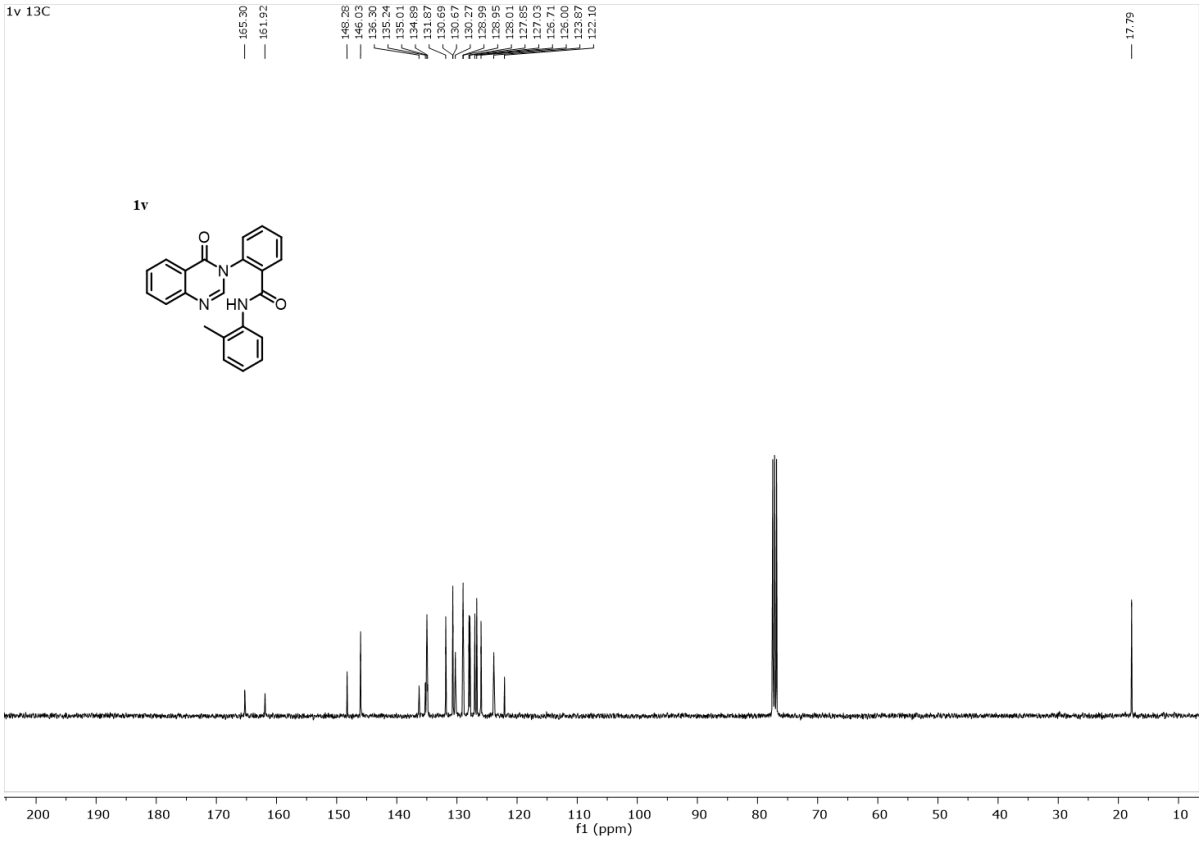
^{13}C in $CDCl_3$ 100 MHz 1u



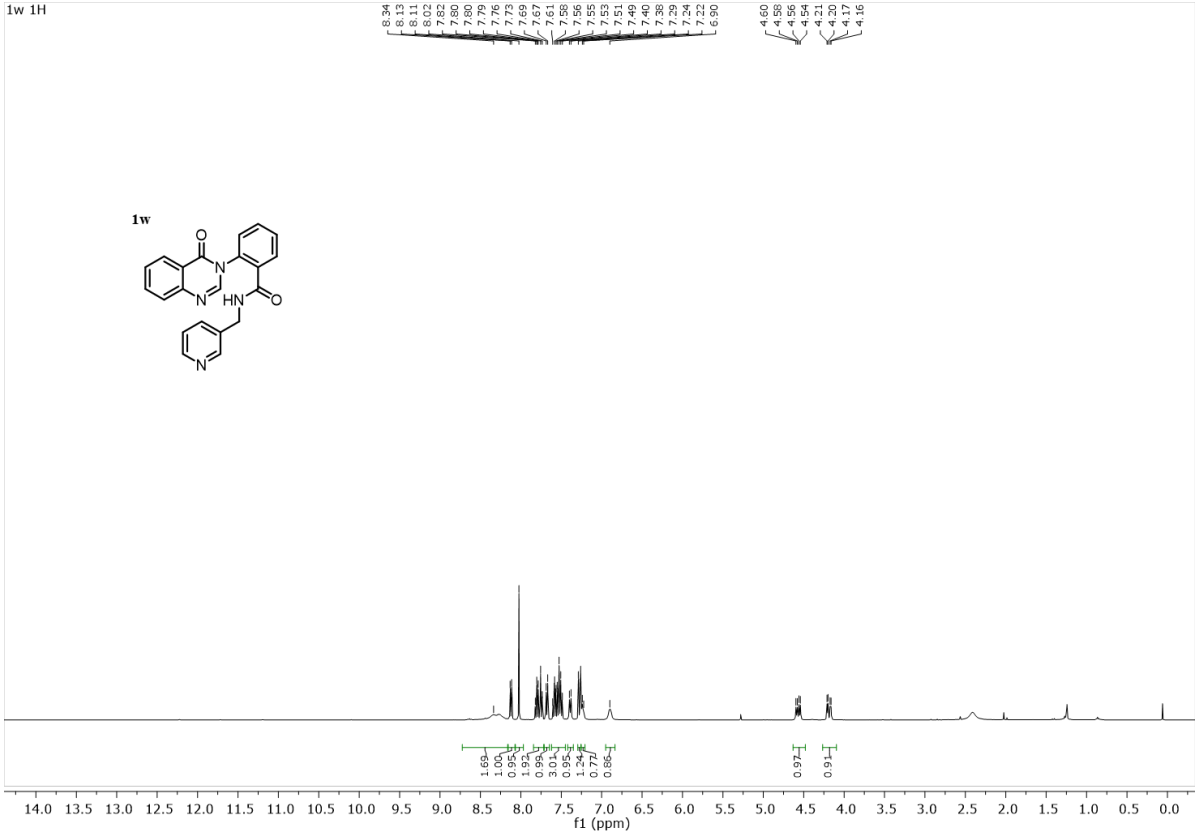
^{1}H in $CDCl_3$ 400 MHz 1v



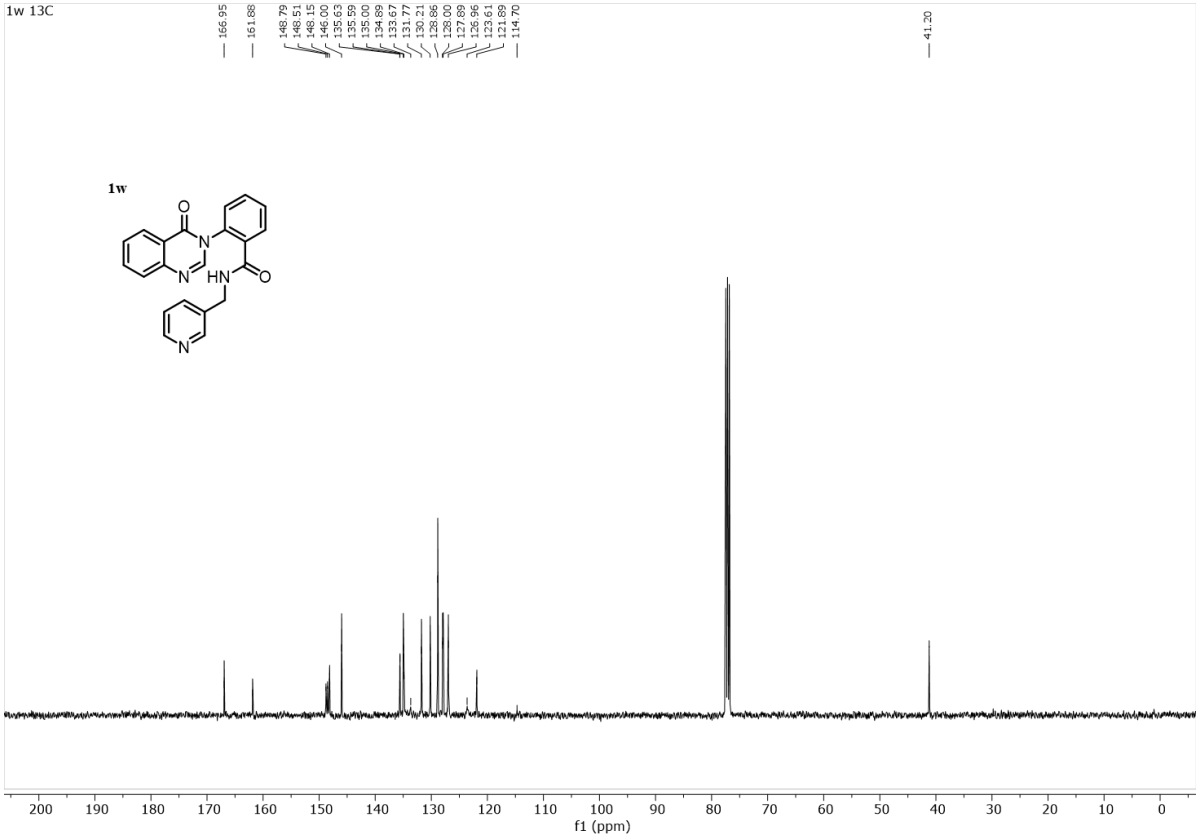
^{13}C in $CDCl_3$ 100 MHz 1v



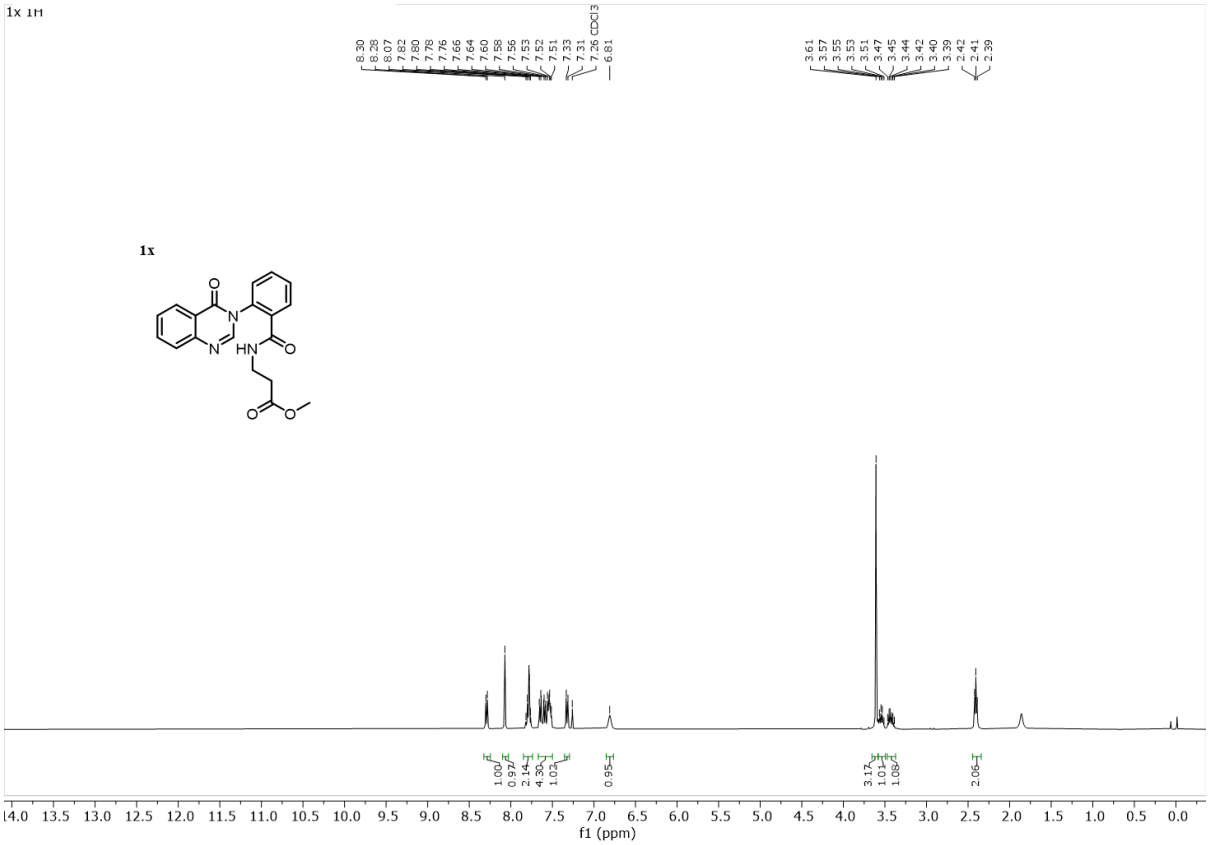
^{1}H in $CDCl_3$ 400 MHz 1w



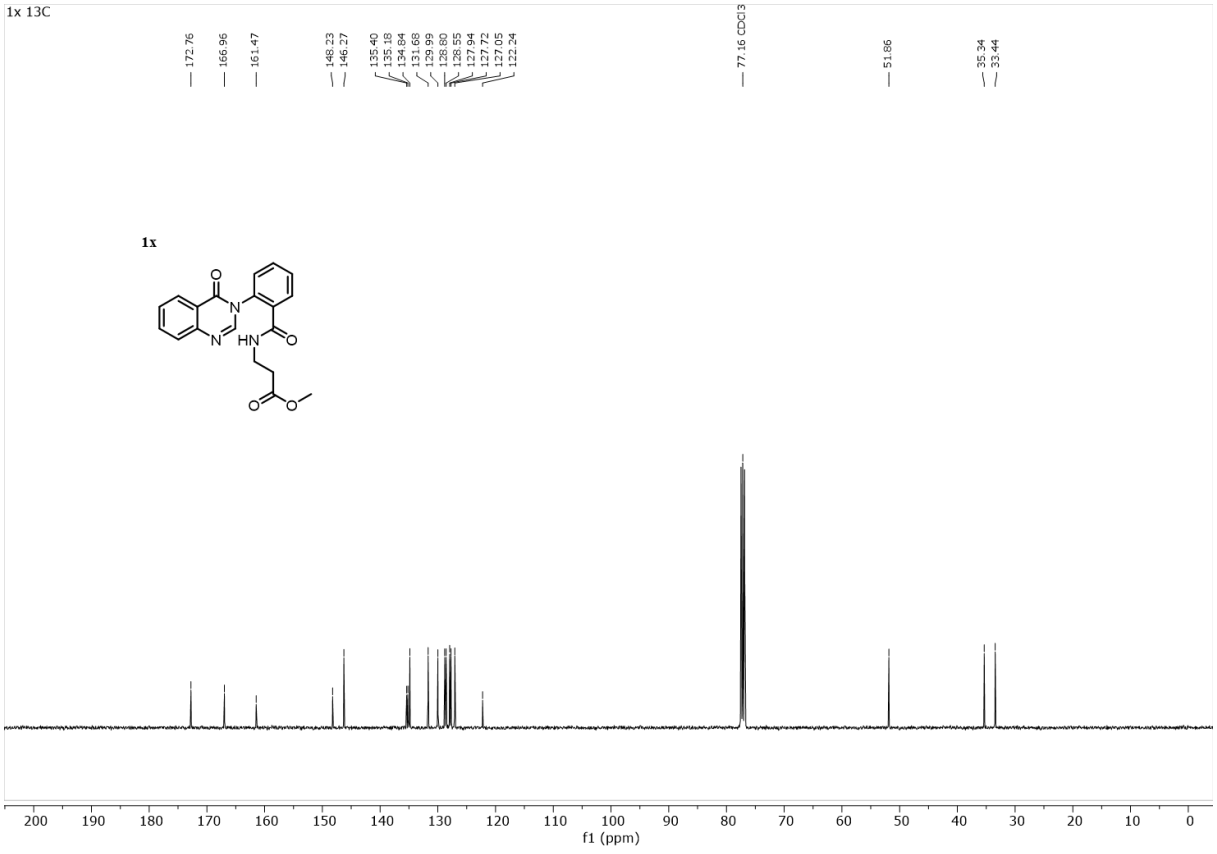
^{13}C in $CDCl_3$ 100 MHz 1w



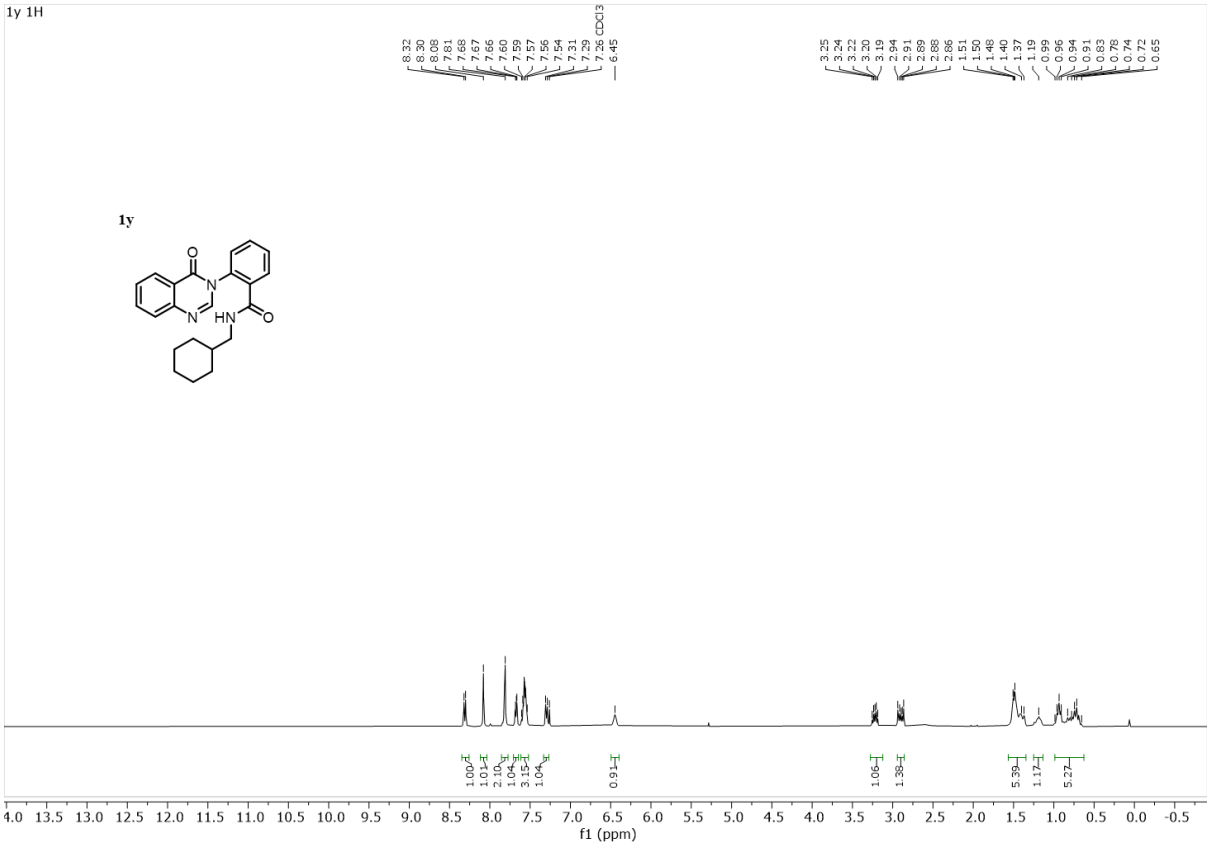
^{1}H in $CDCl_3$ 400 MHz 1x



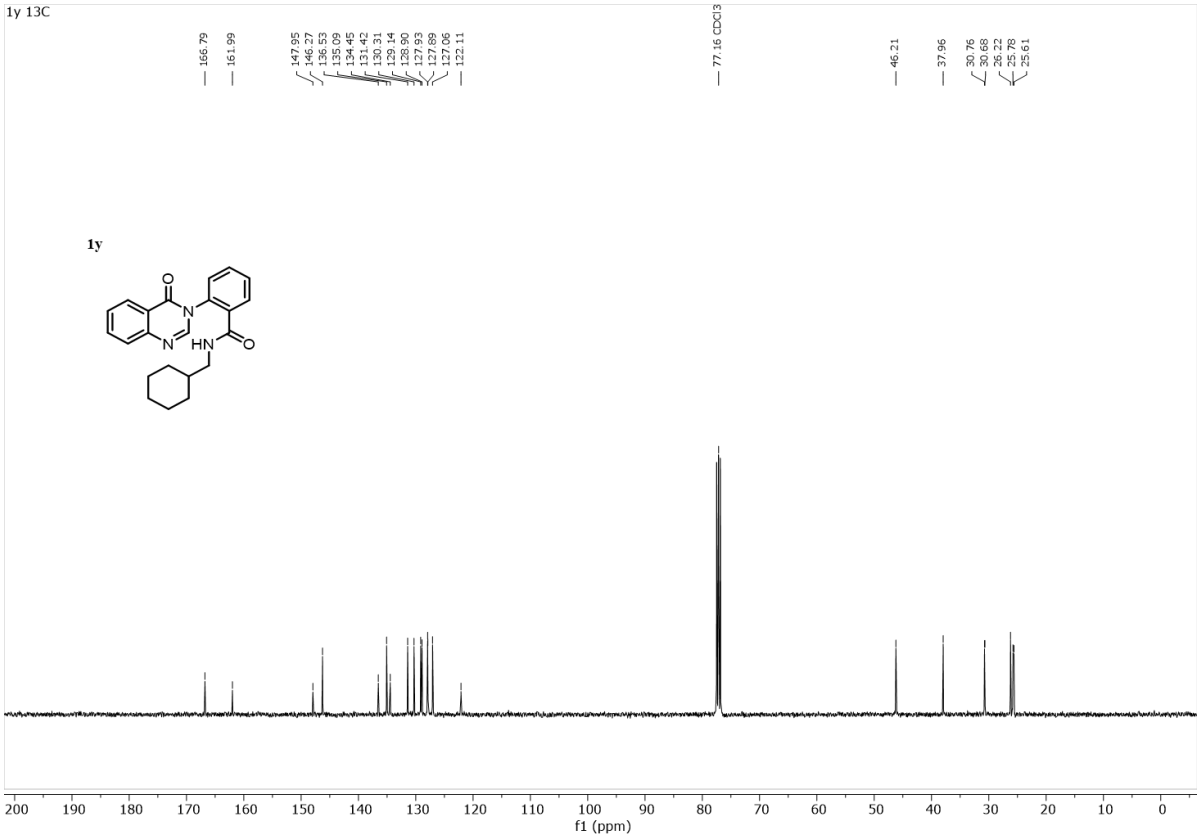
^{13}C in $CDCl_3$ 100 MHz 1x



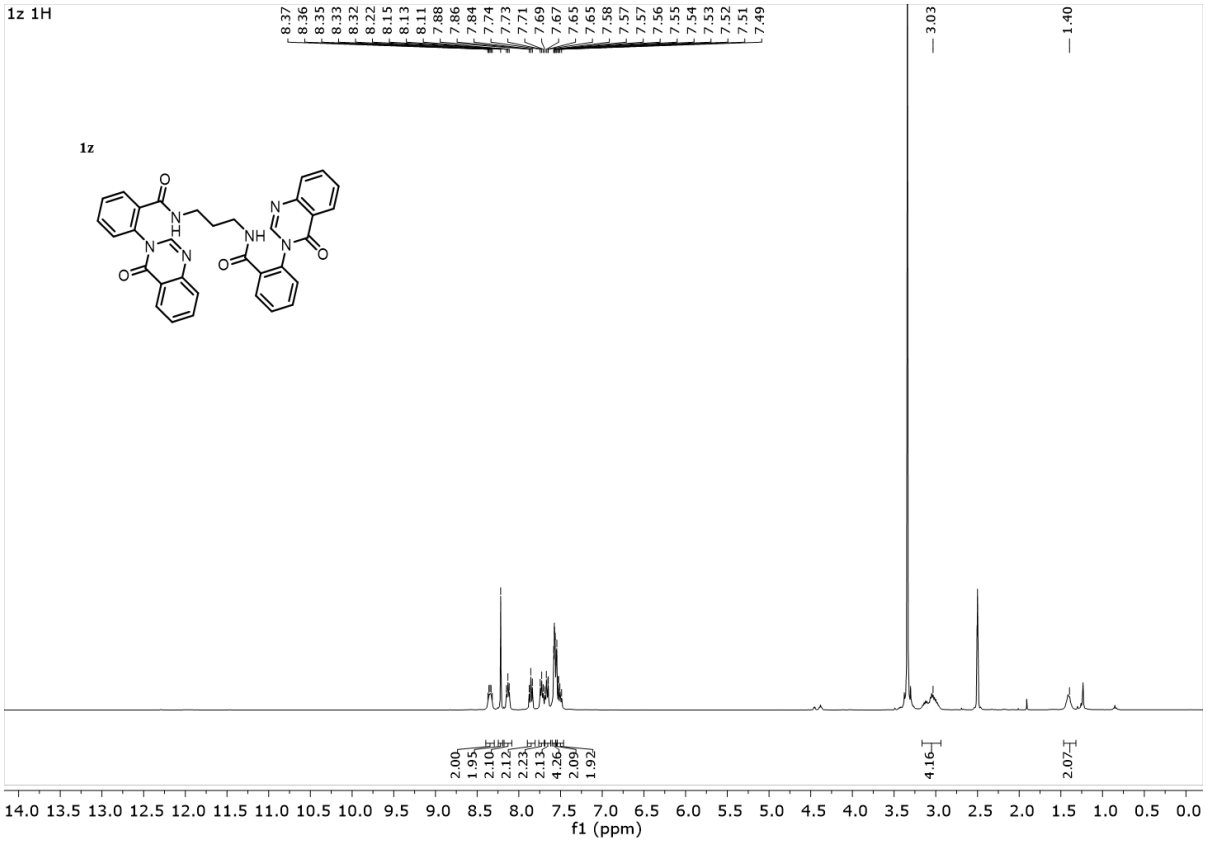
^{1}H in $CDCl_3$ 400 MHz 1y



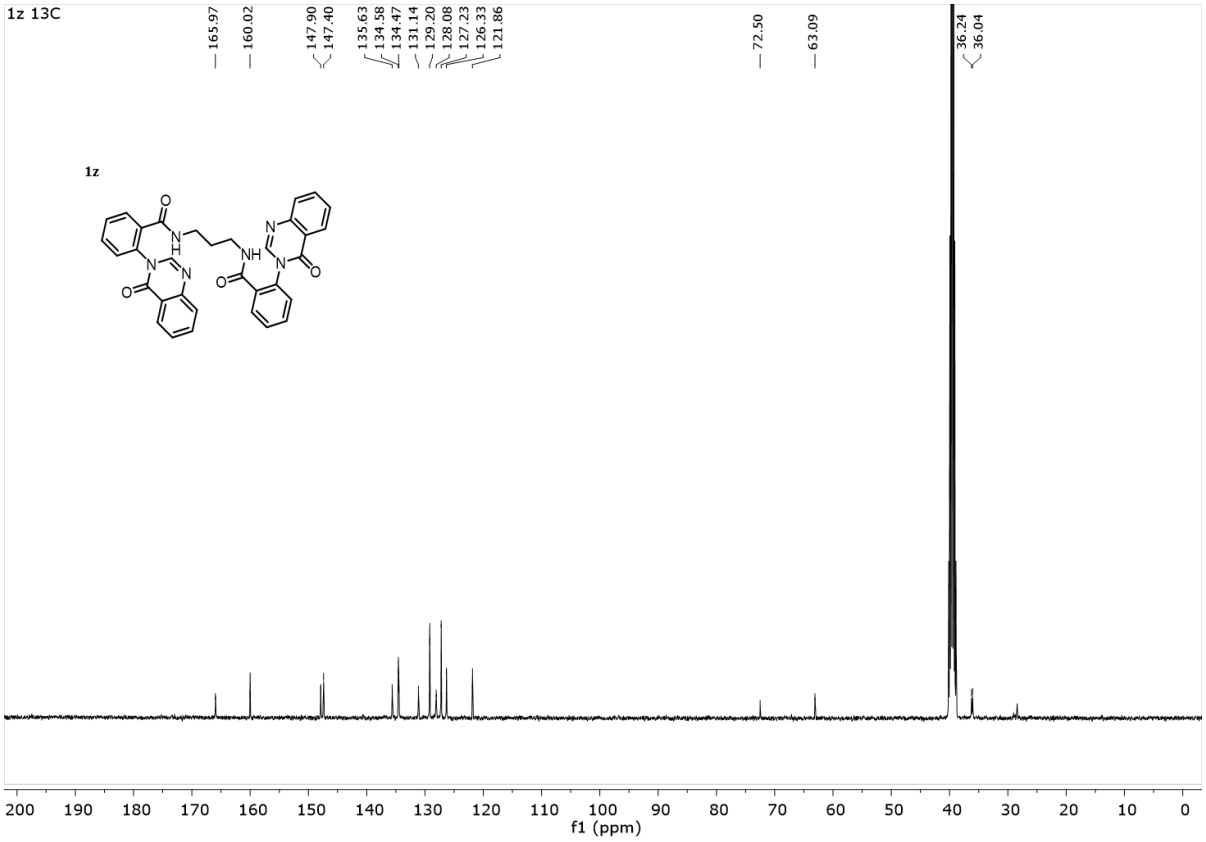
^{13}C in $CDCl_3$ 100 MHz 1y



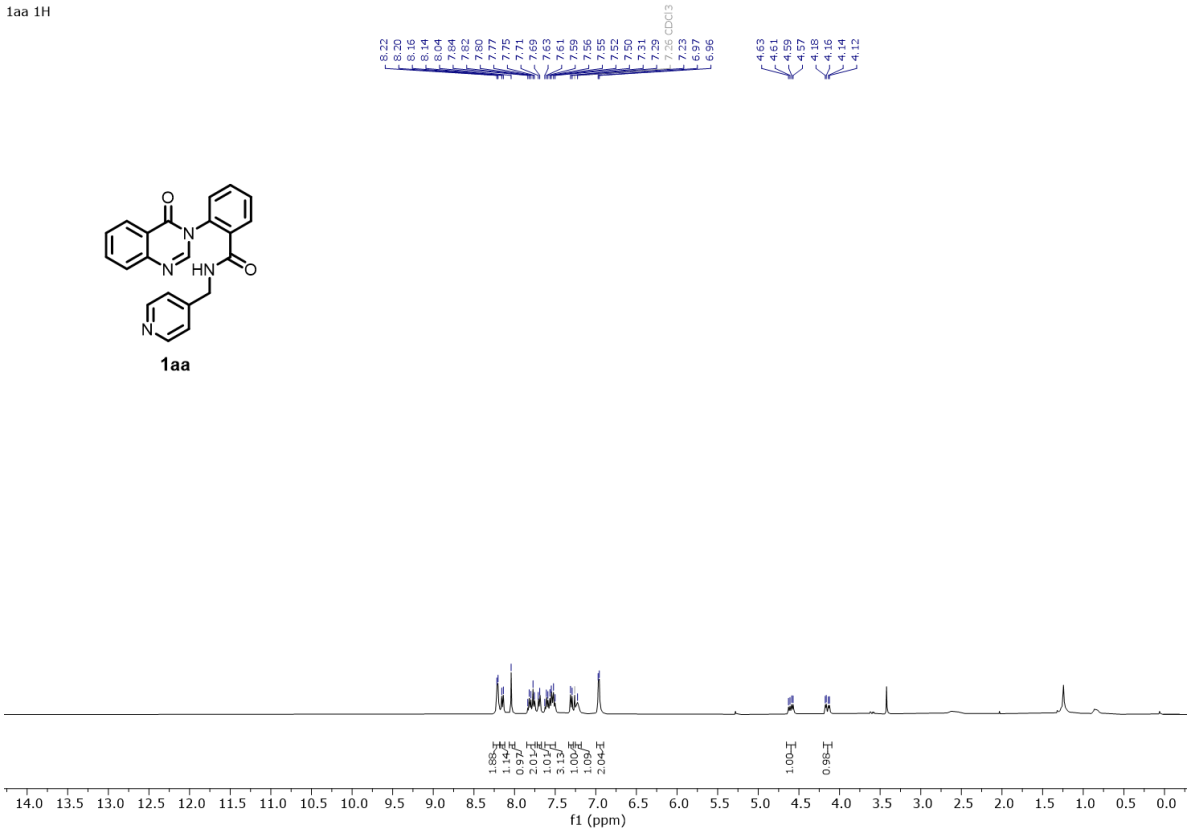
^{1}H in DMSO-d_6 400 MHz 1z



^{13}C in DMSO-d_6 400 MHz 1z

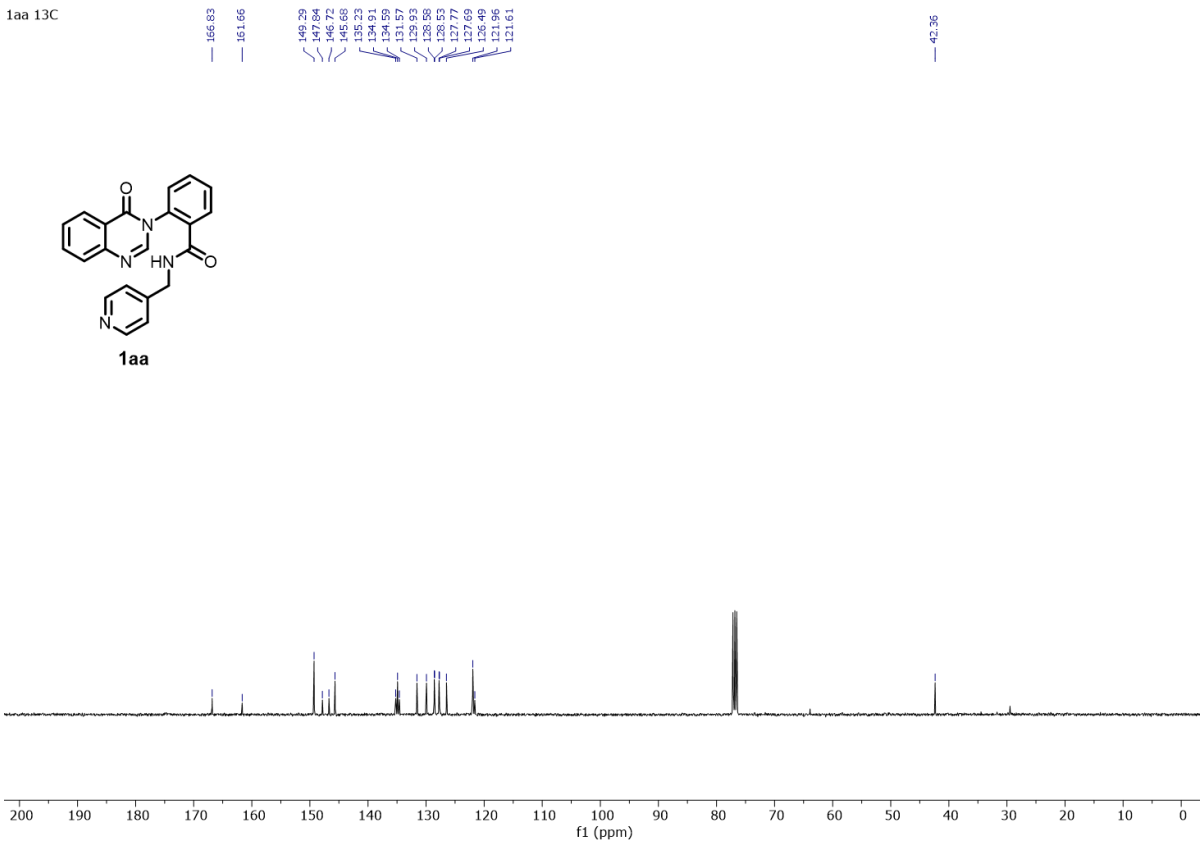


^{1}H in $CDCl_3$ 400 MHz 1aa



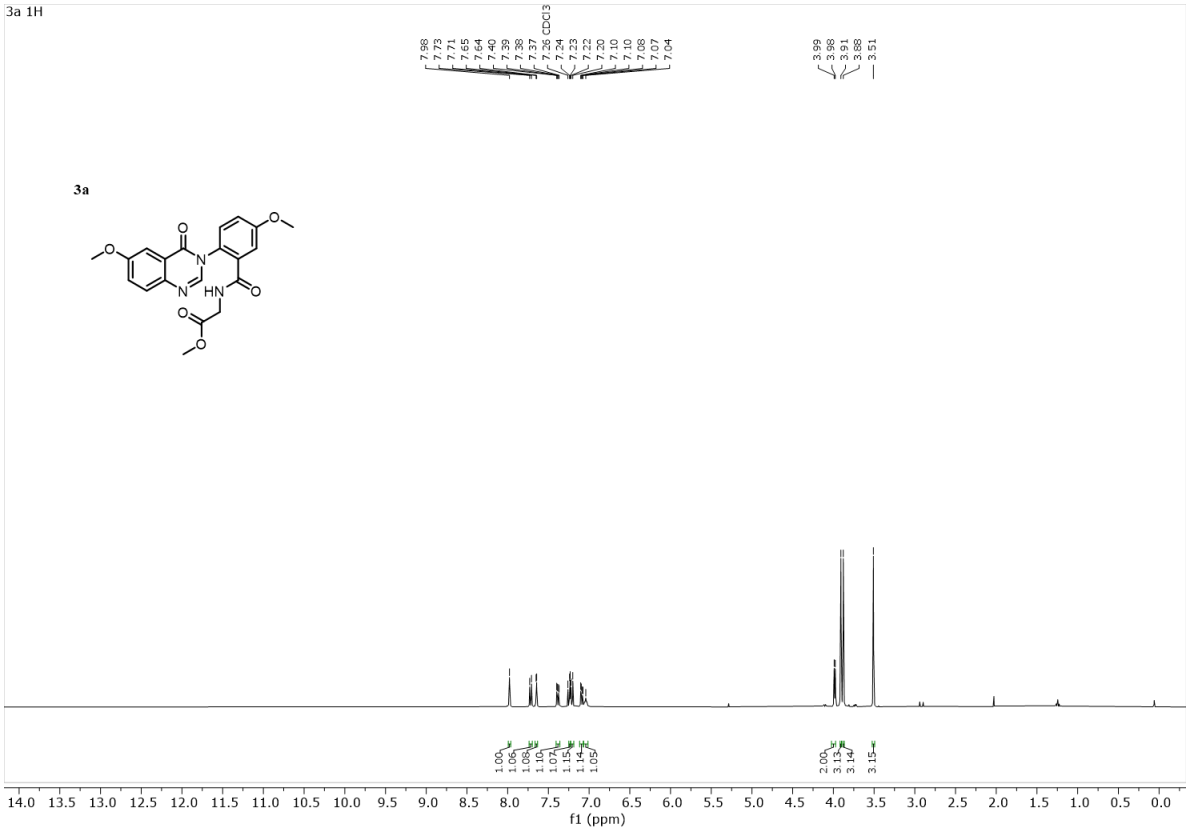
1aa

^{13}C in $CDCl_3$ 100 MHz 1aa

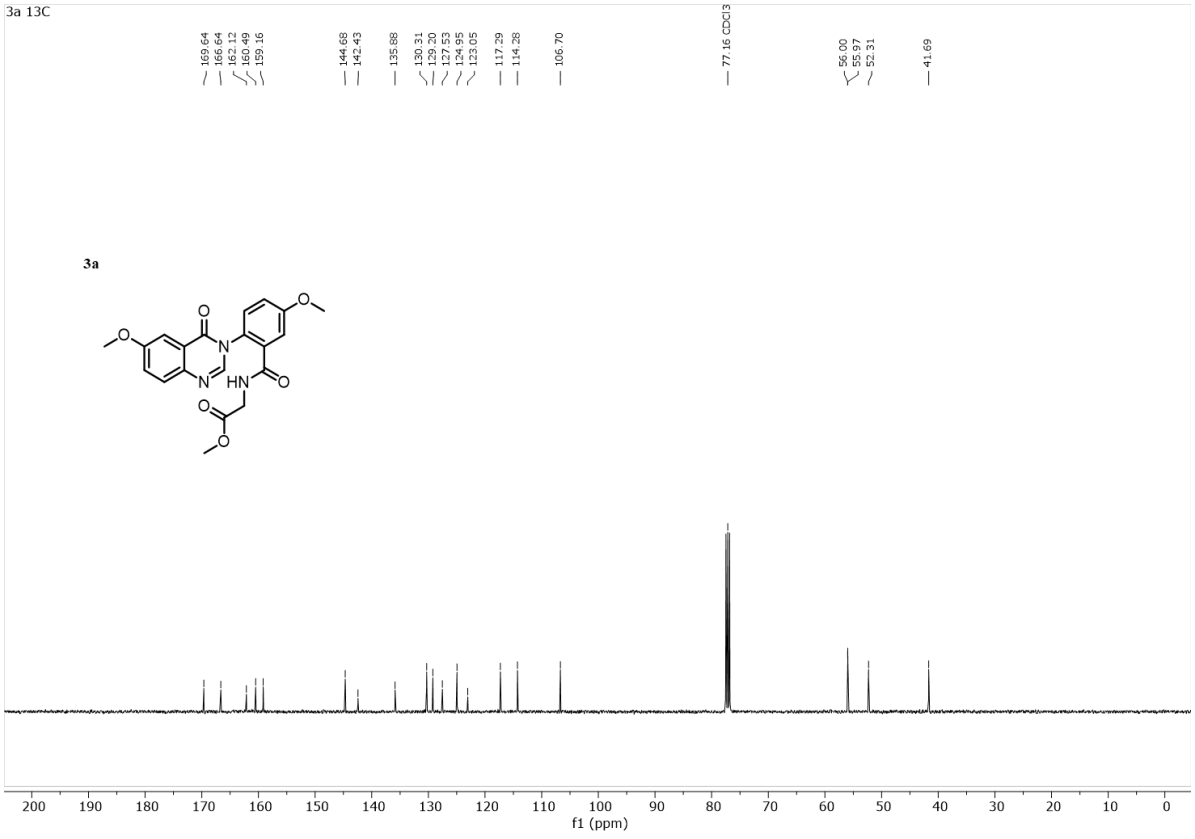


1aa

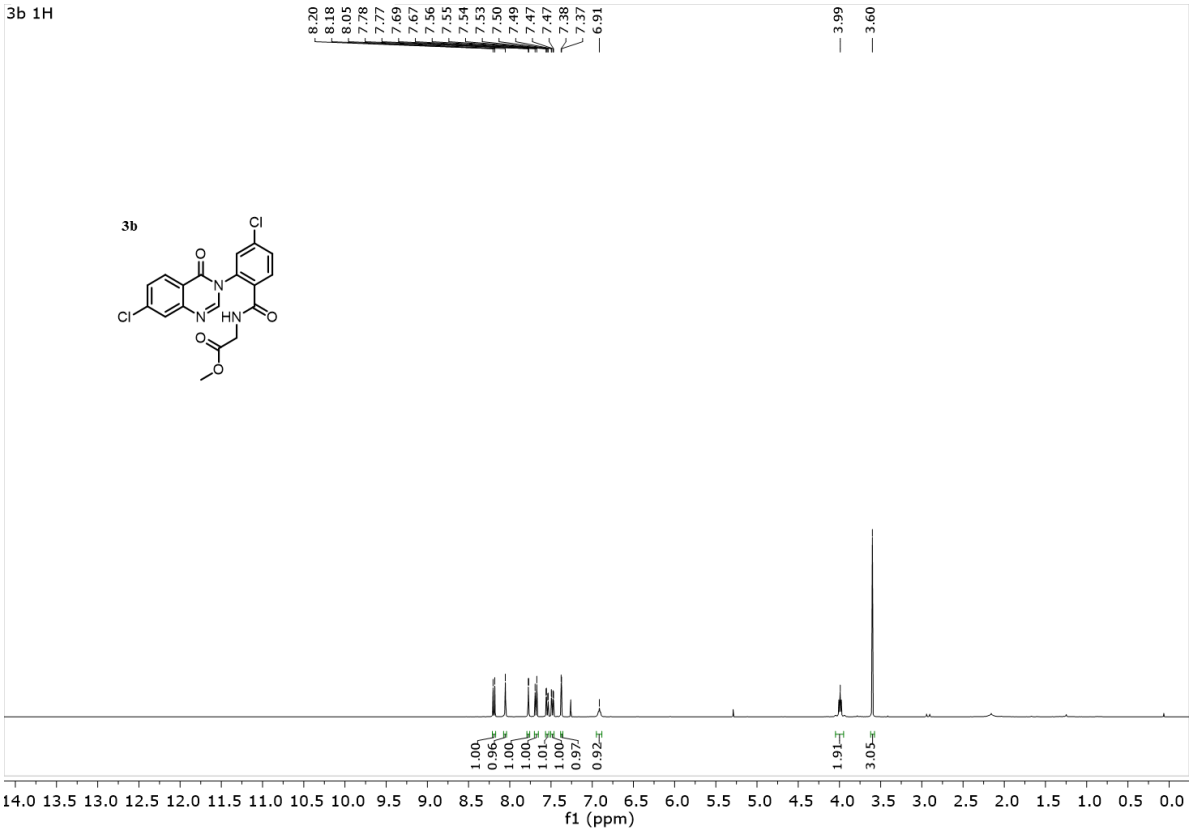
^{1}H in $CDCl_3$ 400 MHz 1ab



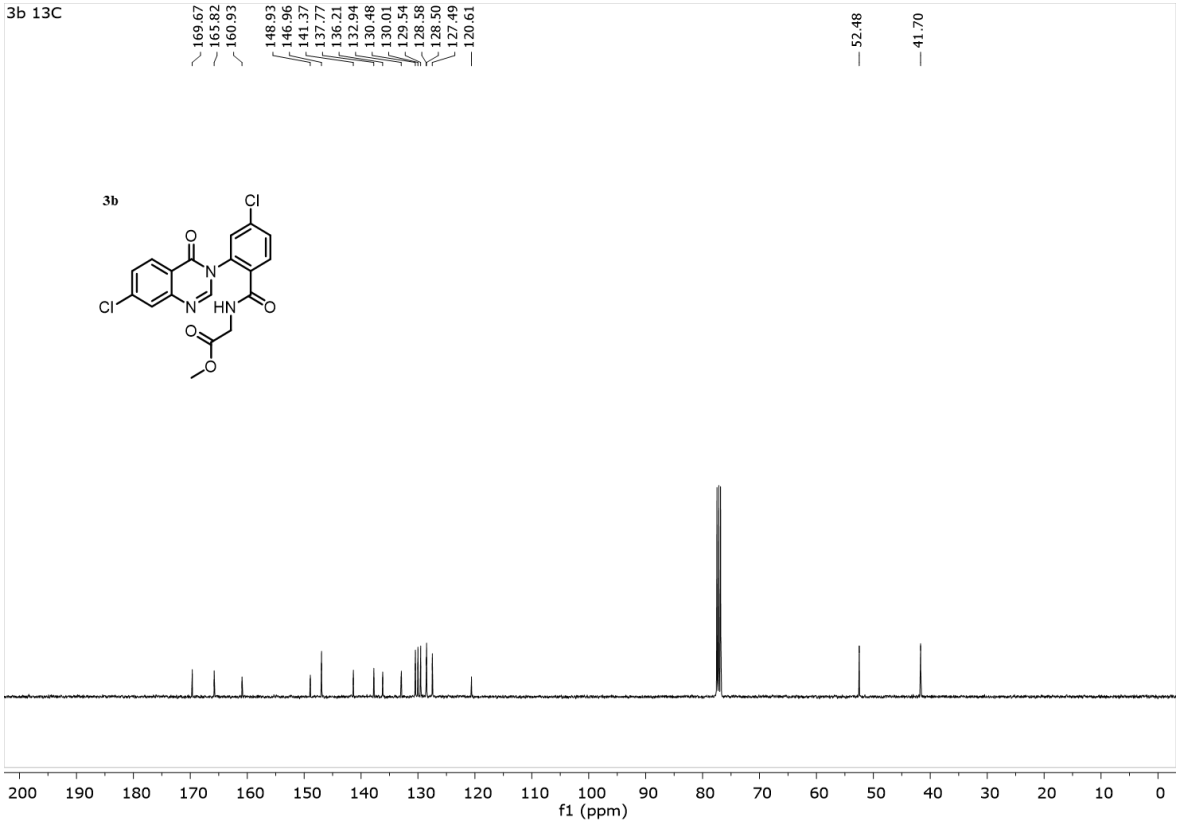
^{13}C in $CDCl_3$ 100 MHz 1ab



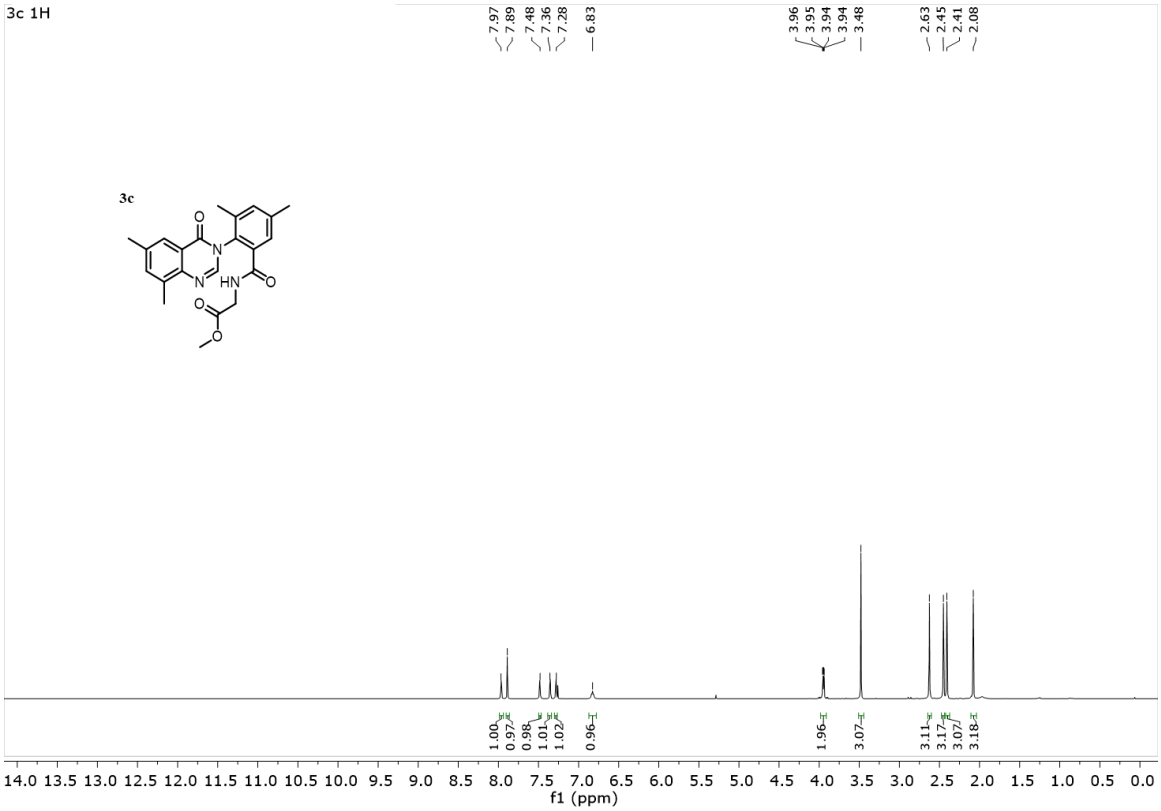
^{1}H in $CDCl_3$ 400 MHz 1ac



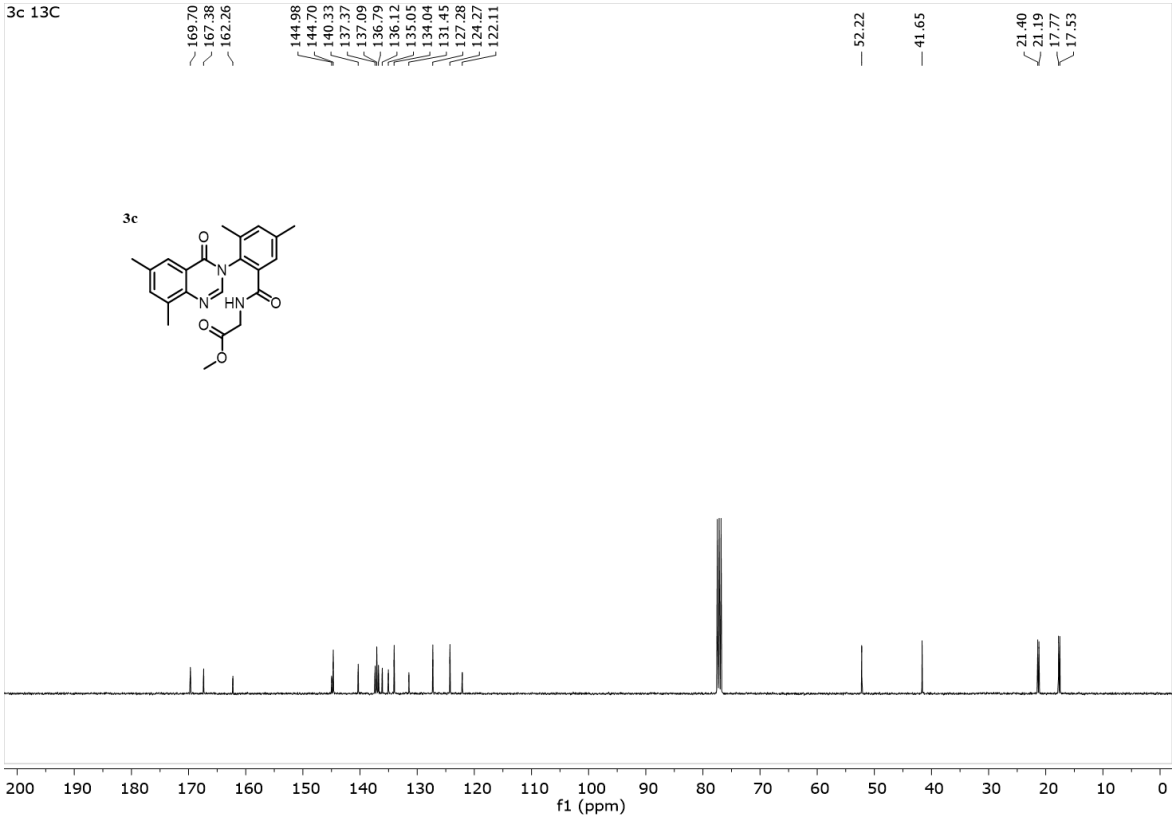
^{13}C in $CDCl_3$ 100 MHz 1ac



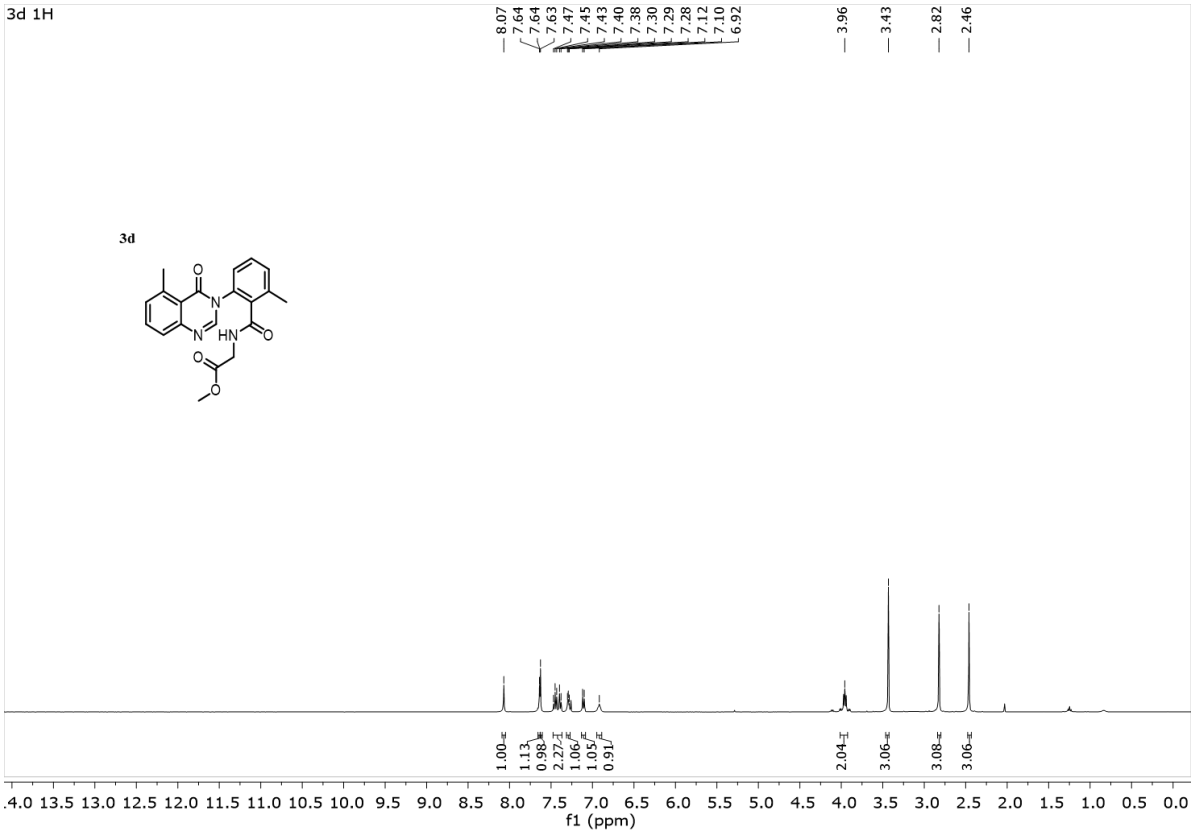
^{1}H in $CDCl_3$ 400 MHz 1ad



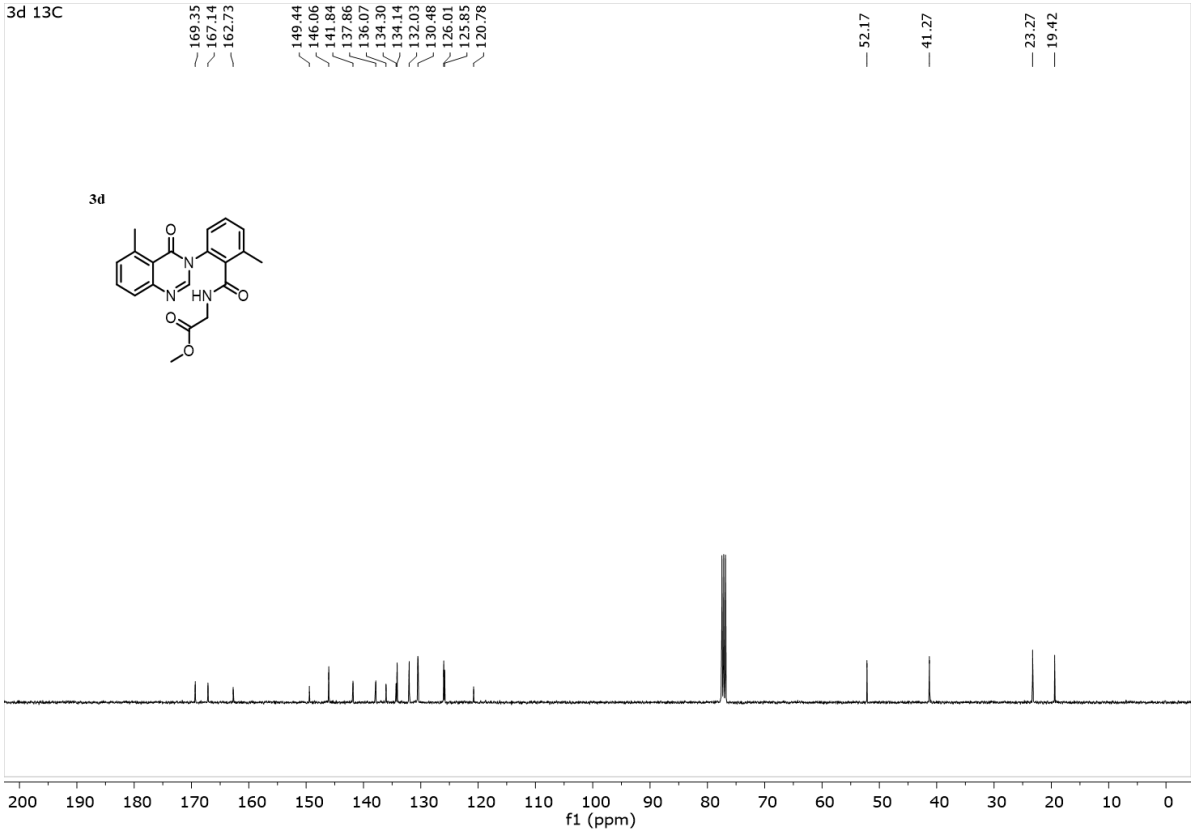
^{13}C in $CDCl_3$ 100 MHz 1ad



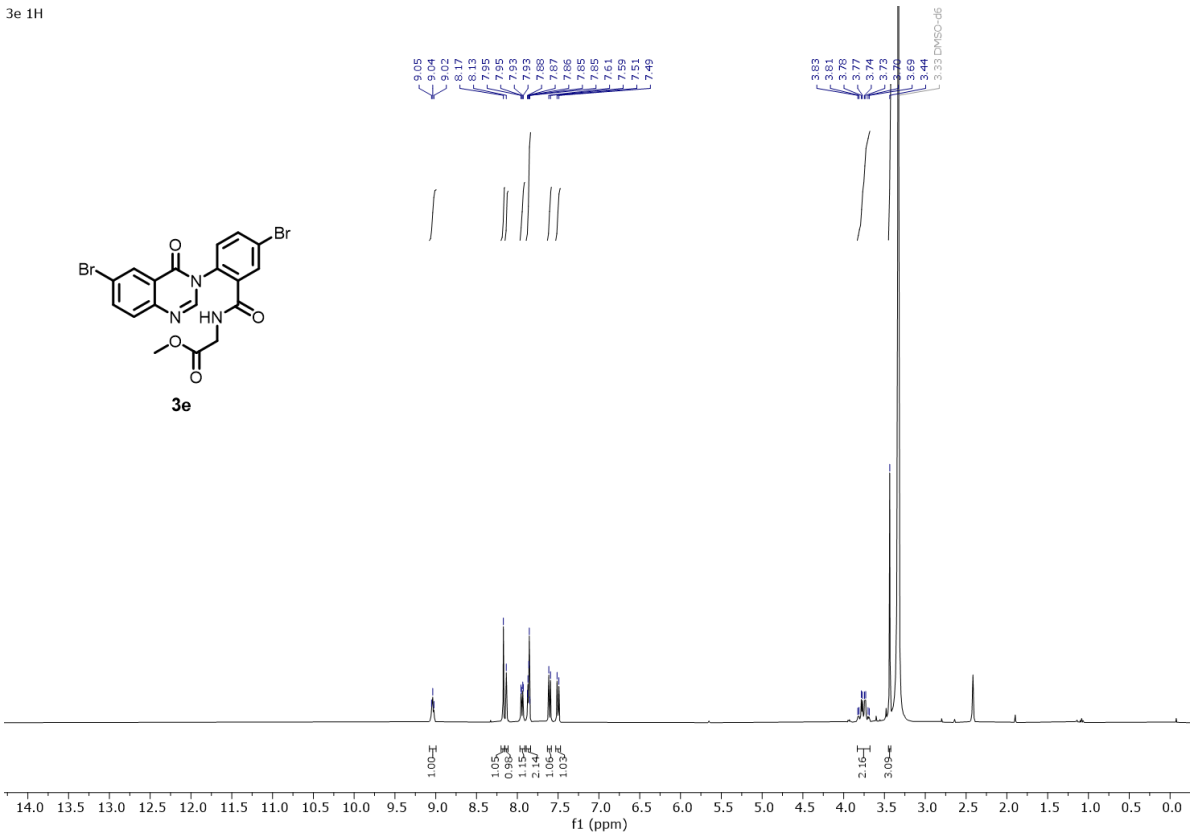
^{1}H in $CDCl_3$ 400 MHz 1ae



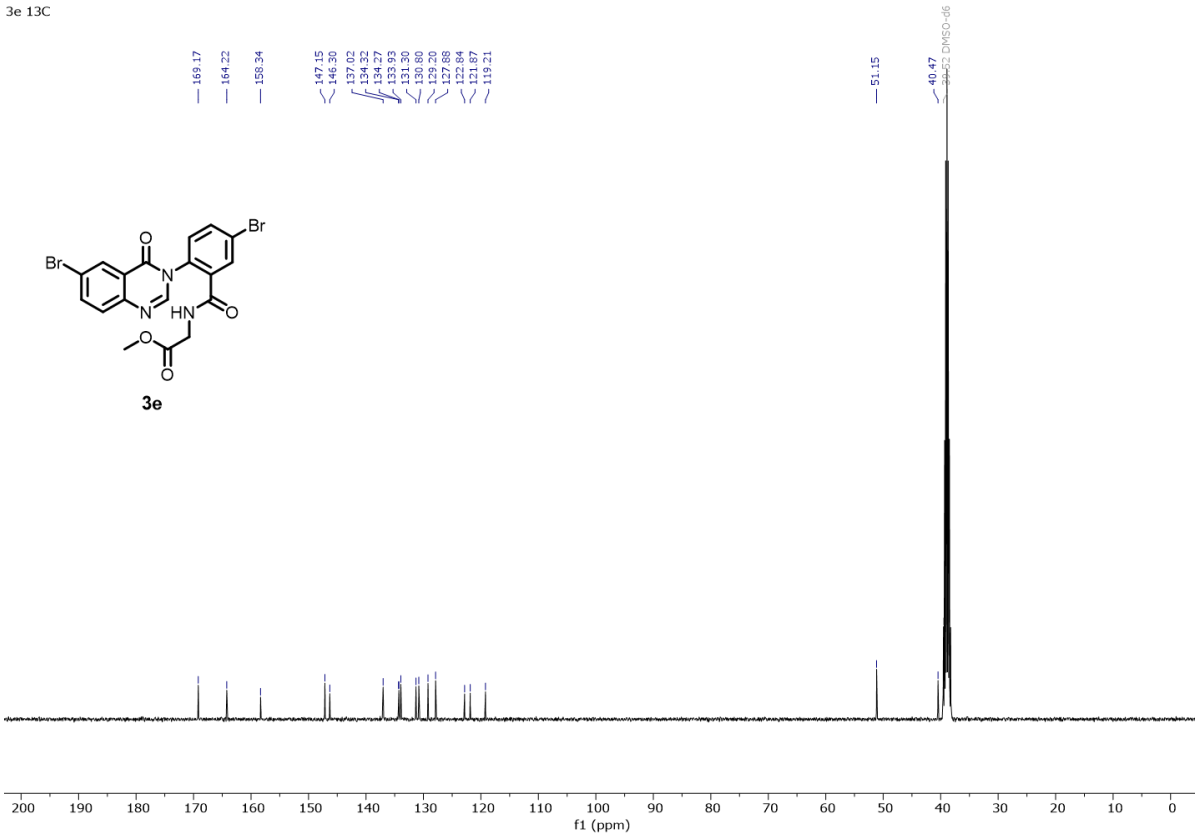
^{13}C in $CDCl_3$ 100 MHz 1ae



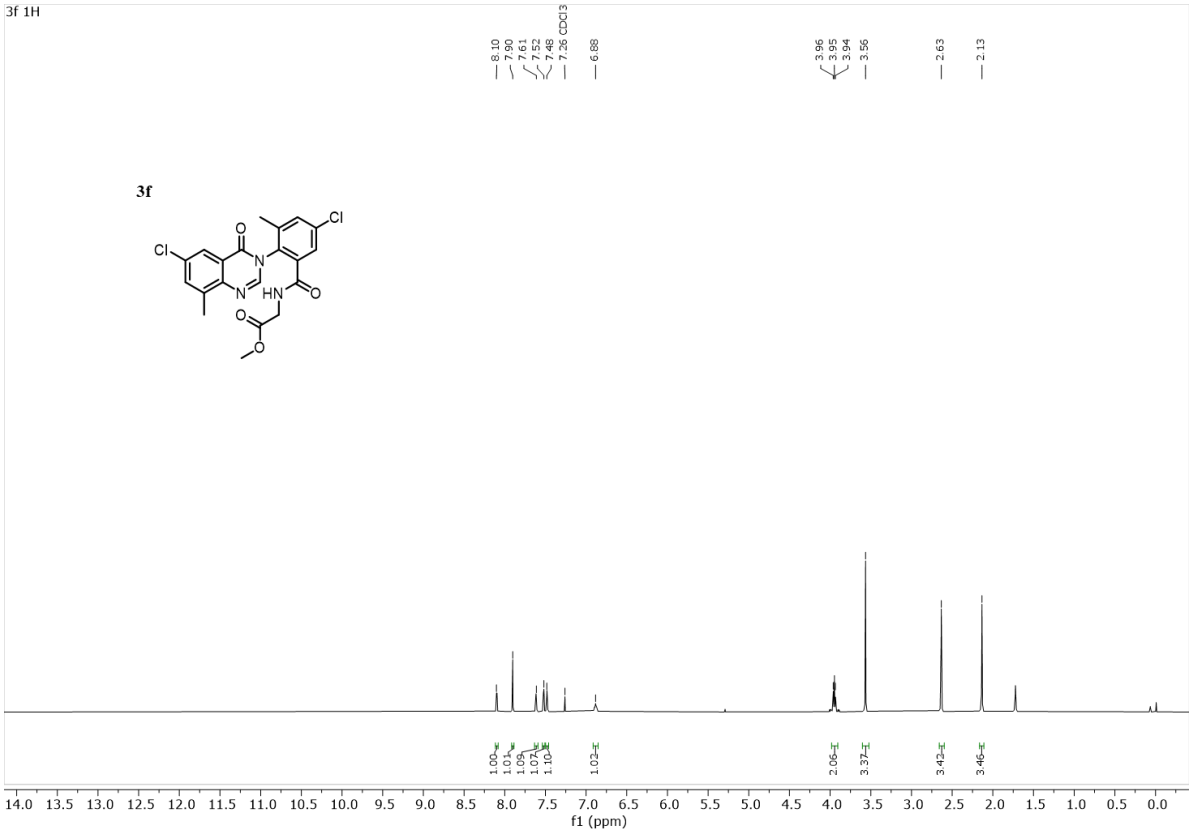
^{1}H in DMSO-d_6 400 MHz 1af



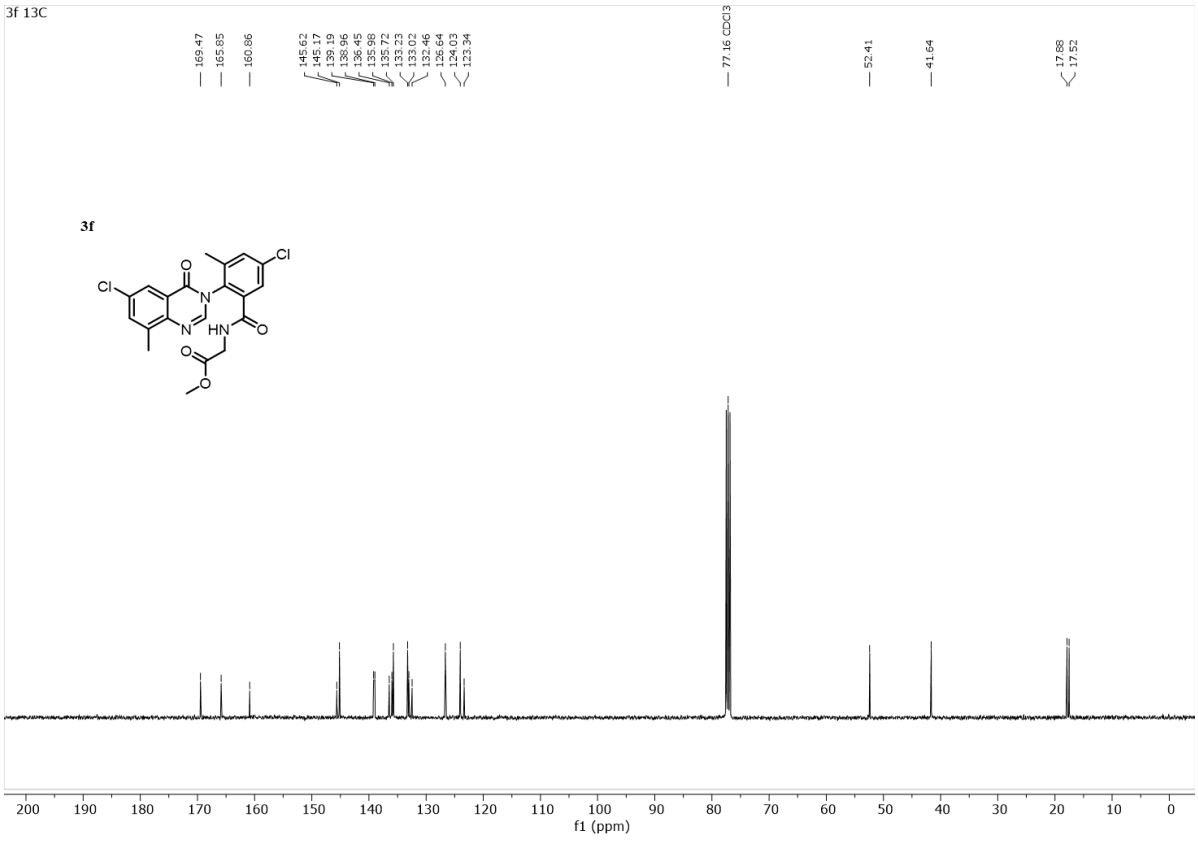
^{13}C in DMSO-d_6 400 MHz 1af



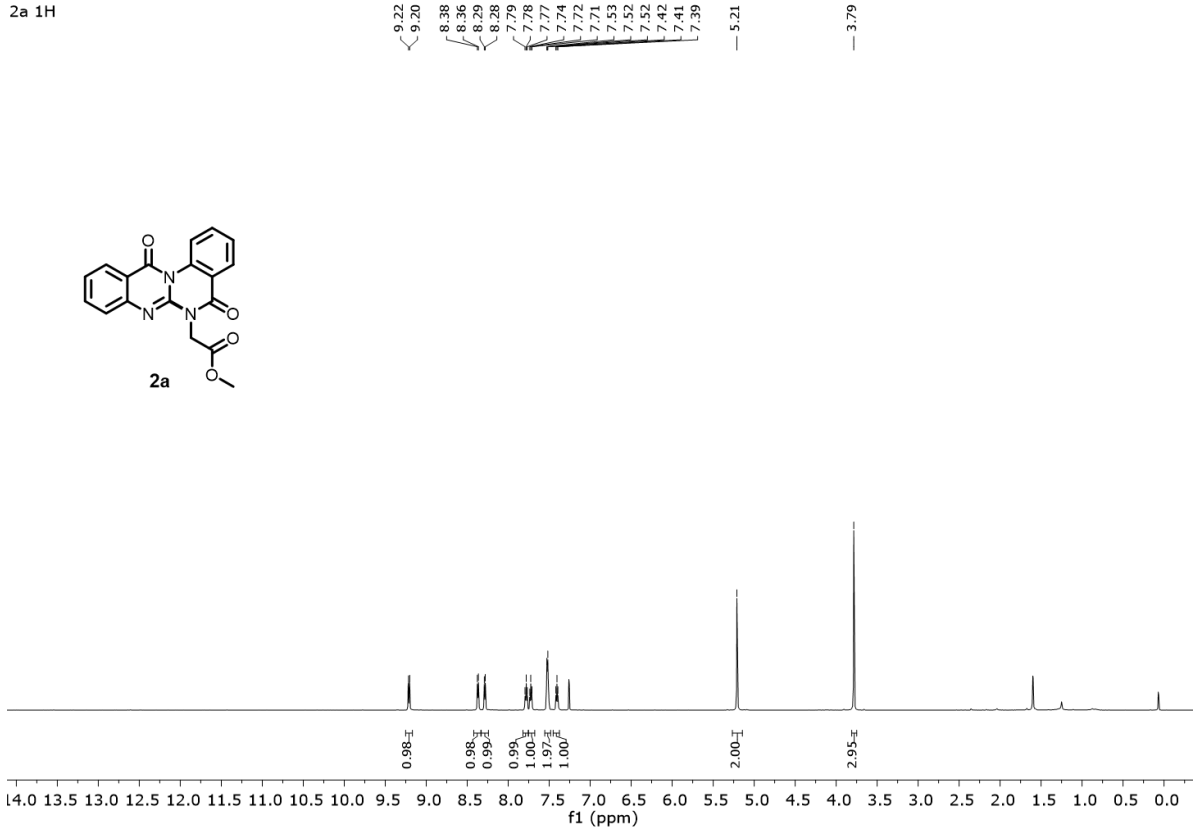
^{1}H in $CDCl_3$ 400 MHz 1ag



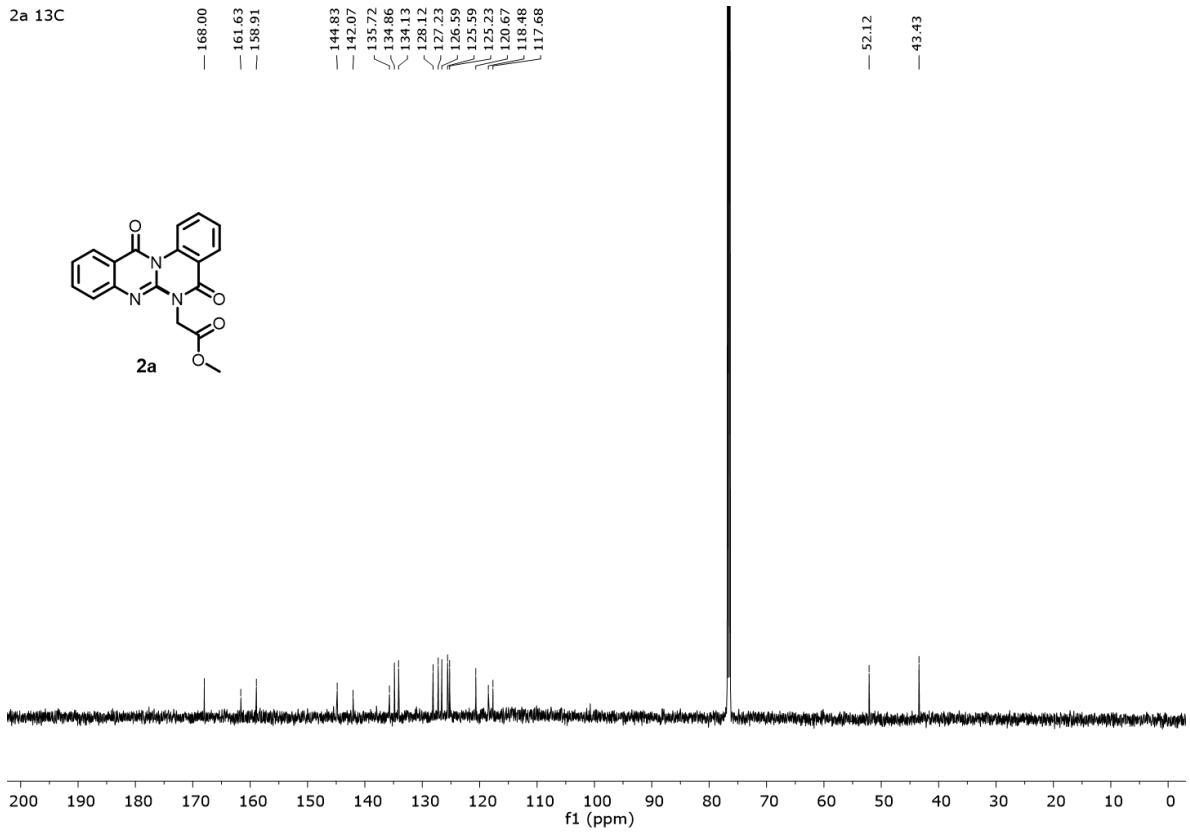
^{13}C in $CDCl_3$ 100 MHz 1ag



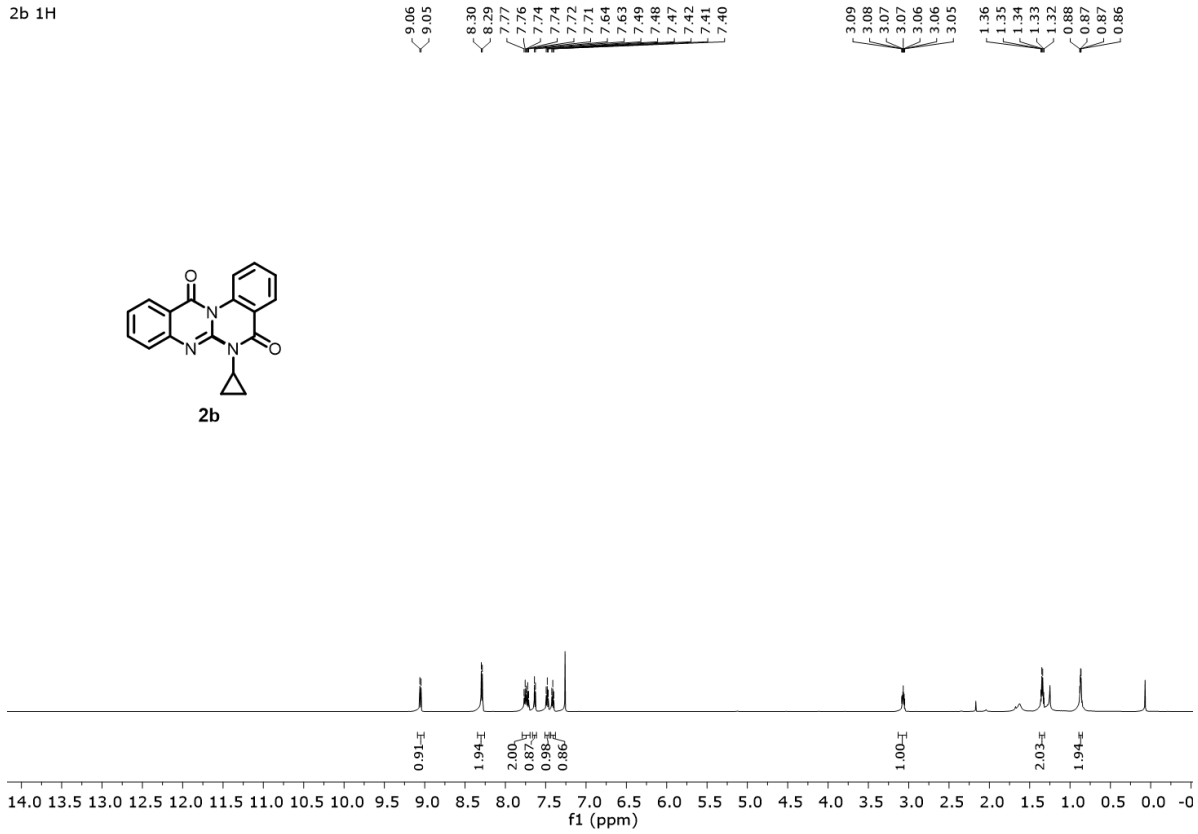
^{1}H in $CDCl_3$ 600 MHz 2a



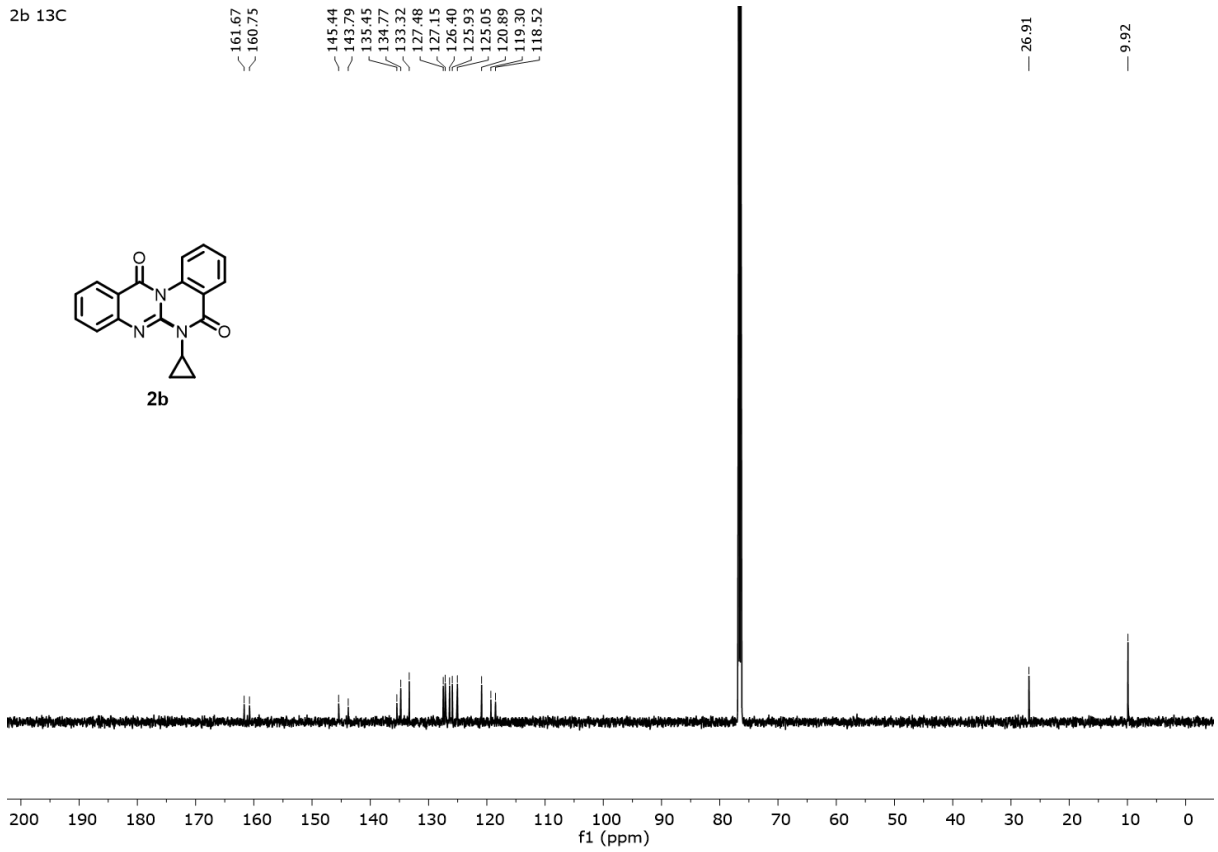
^{13}C in $CDCl_3$ 150 MHz 2a



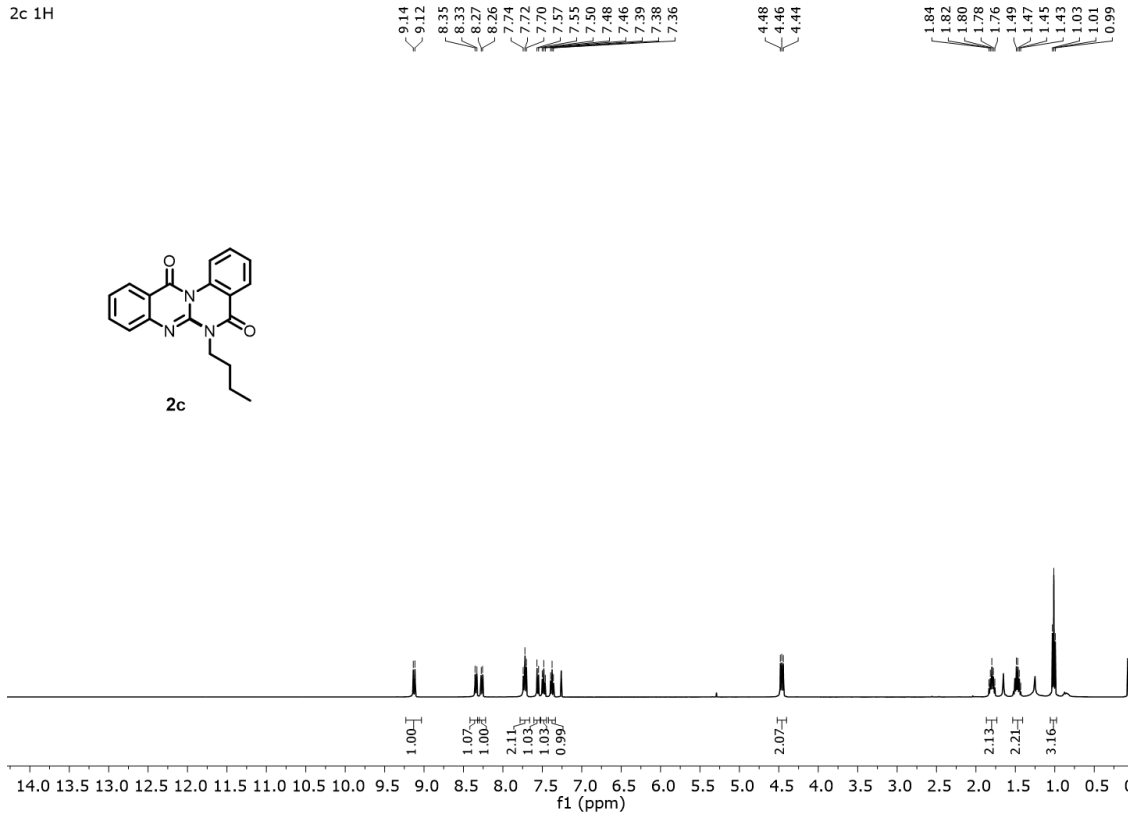
^{1}H in $CDCl_3$ 600 MHz 2b



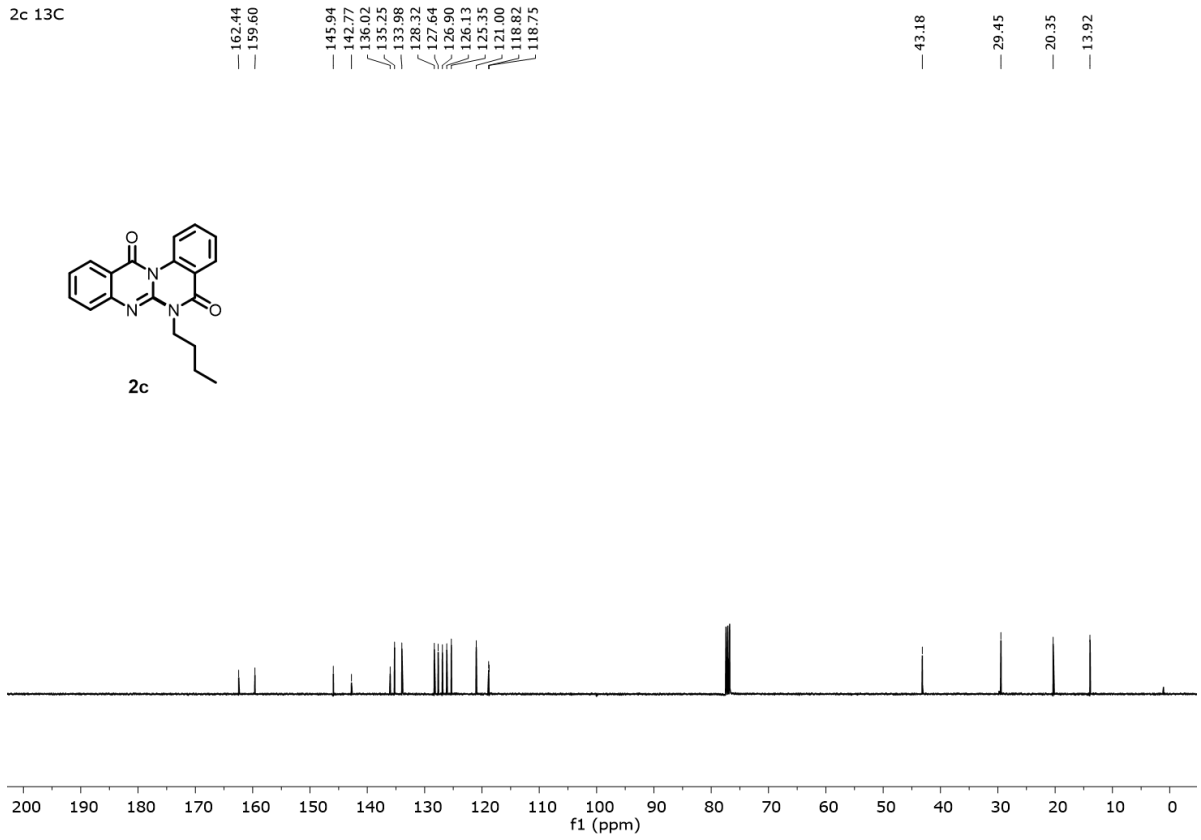
^{13}C in $CDCl_3$ 150 MHz 2b



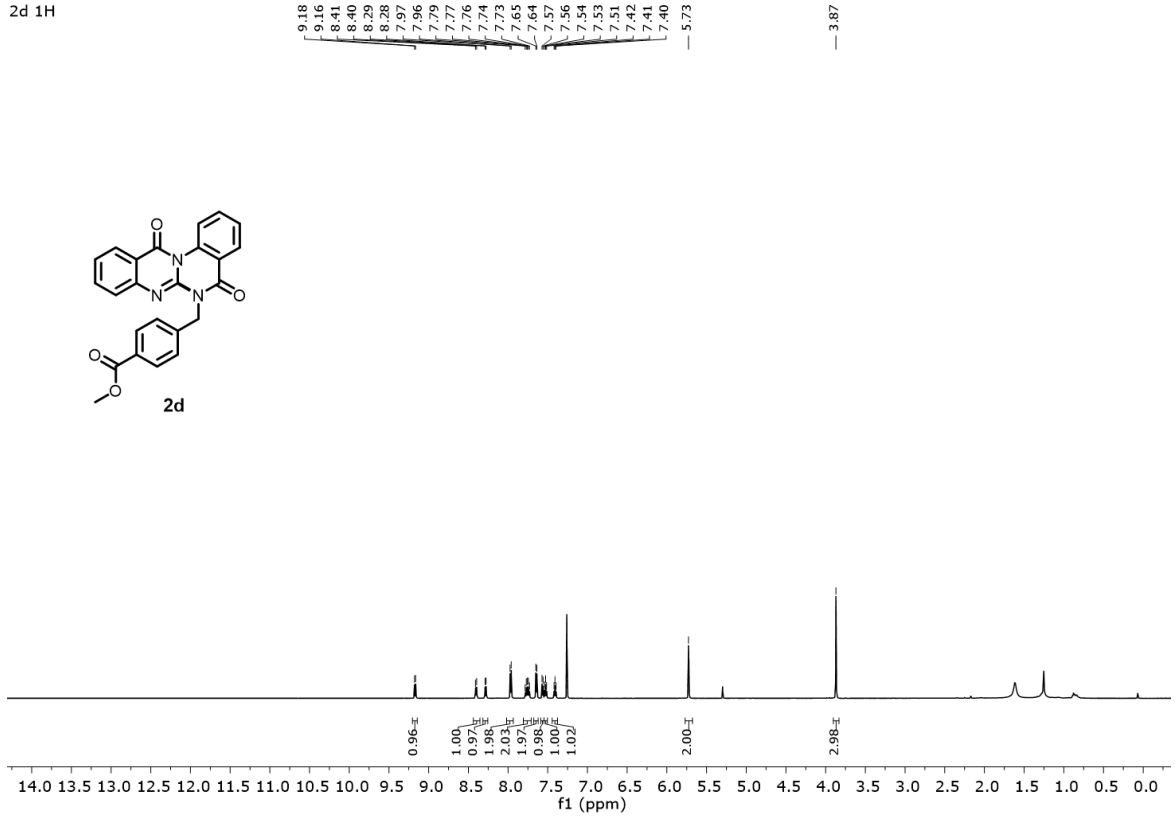
^{1}H in $CDCl_3$ 600 MHz 2c



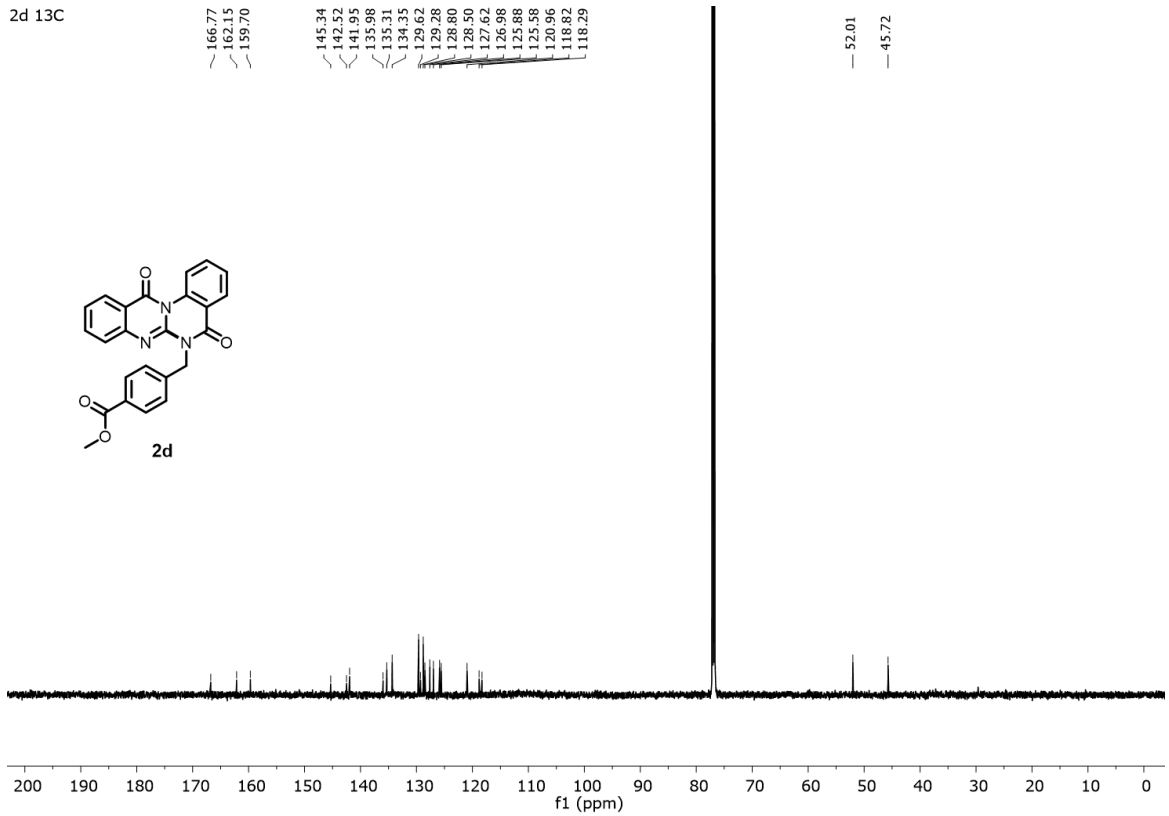
^{13}C in $CDCl_3$ 150 MHz 2c



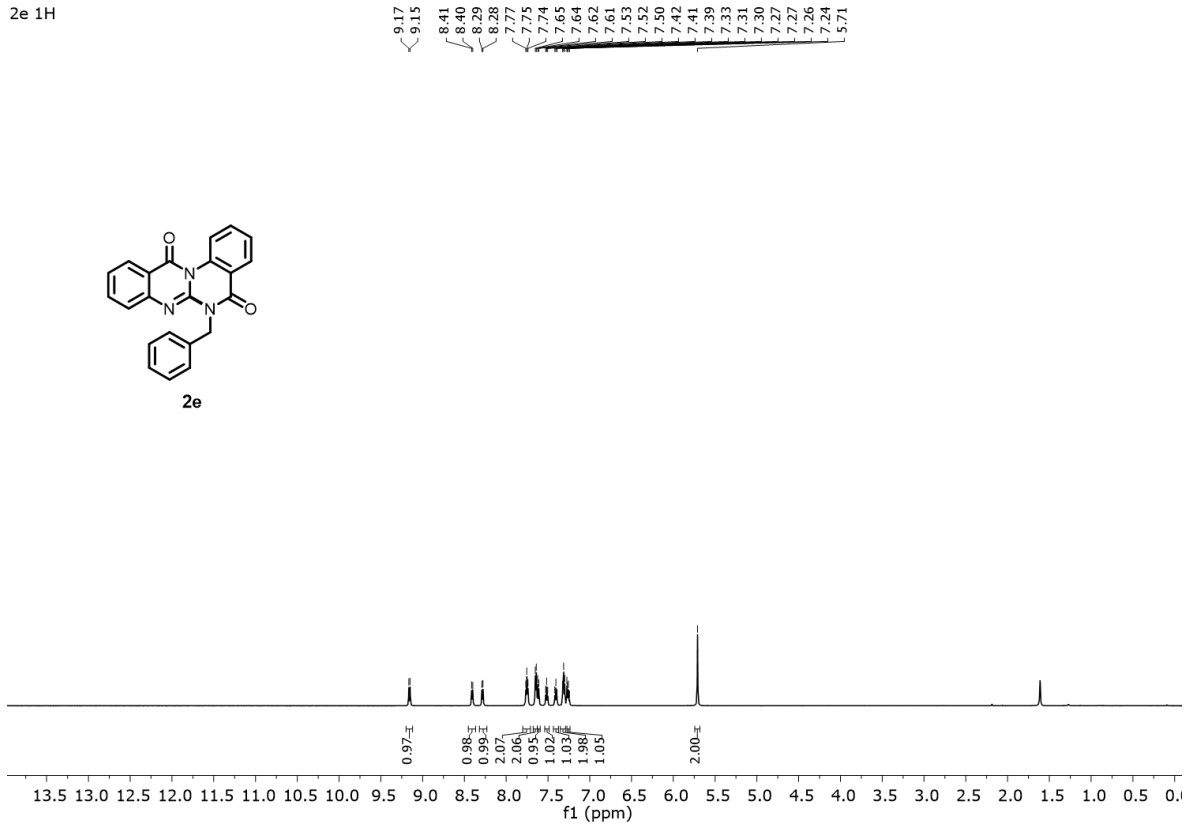
^{1}H in $CDCl_3$ 600 MHz 2d



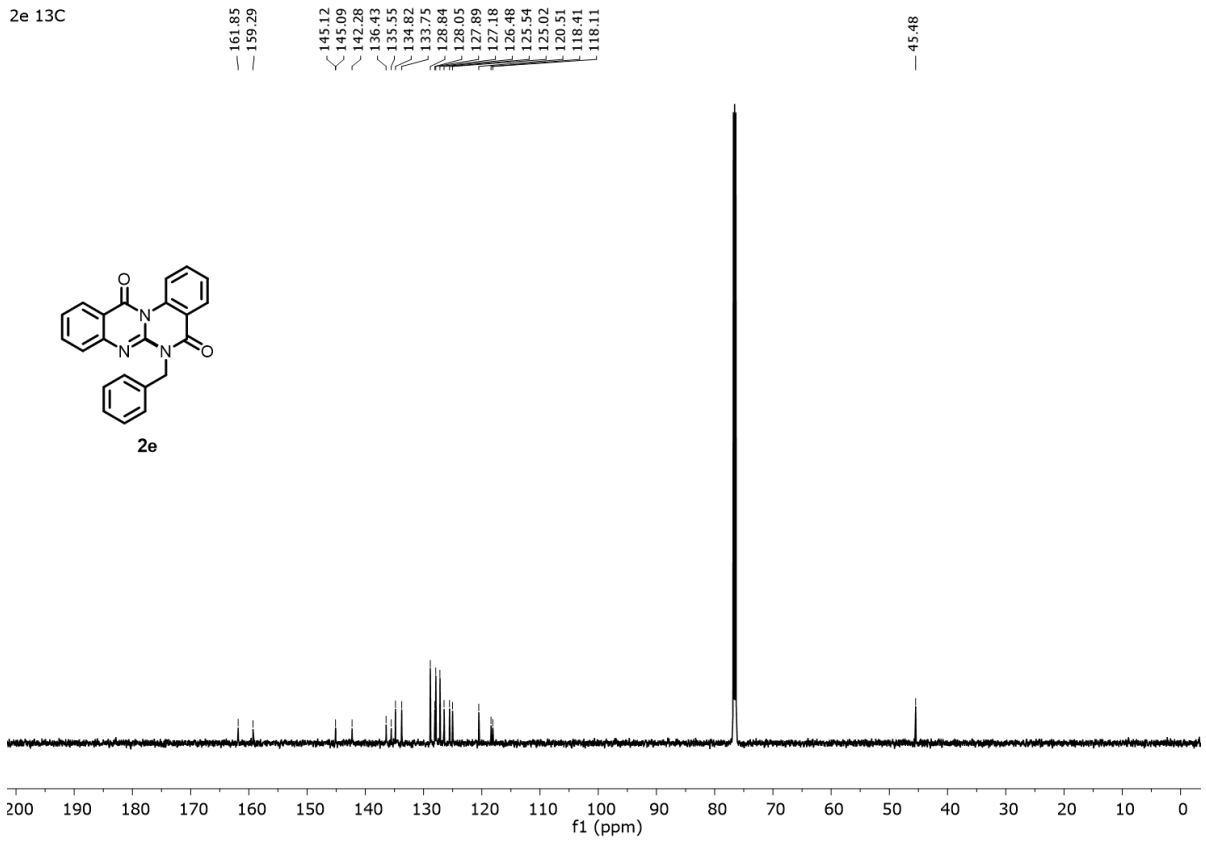
^{13}C in $CDCl_3$ 150 MHz 2d



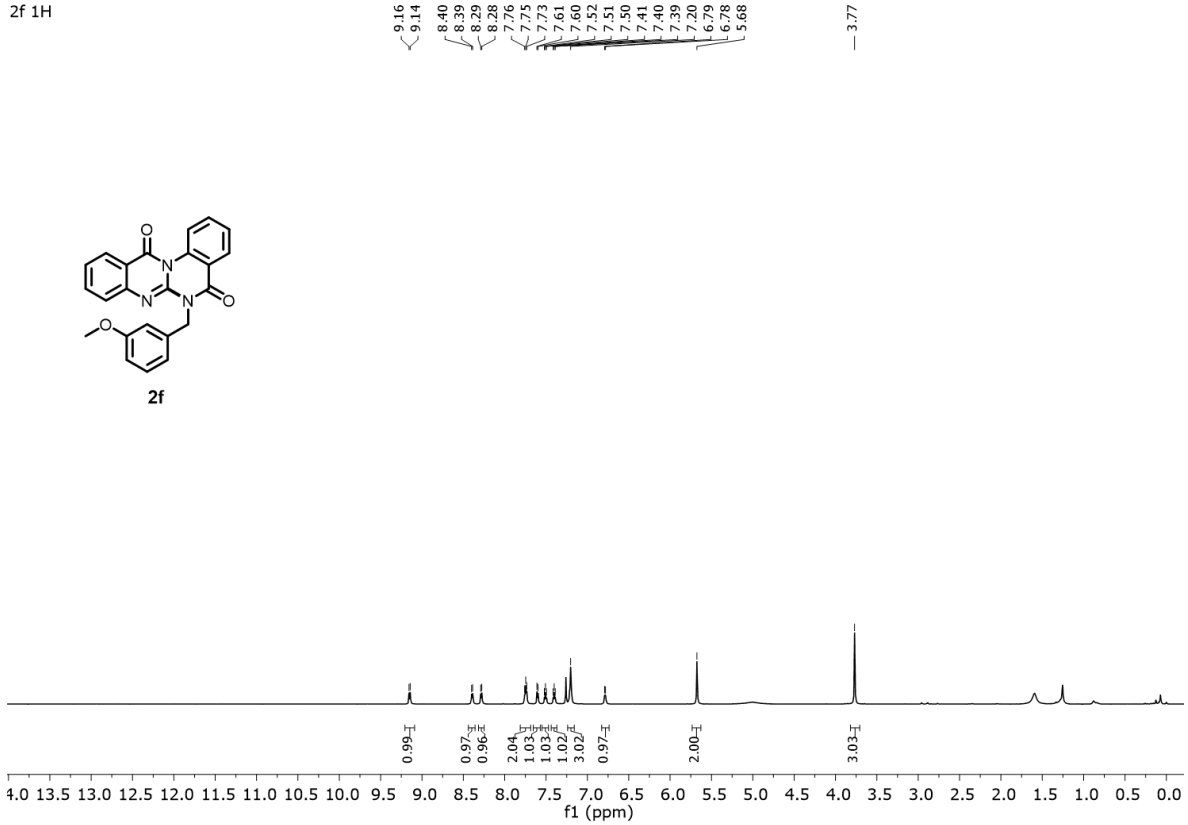
^{1}H in $CDCl_3$ 600 MHz 2e



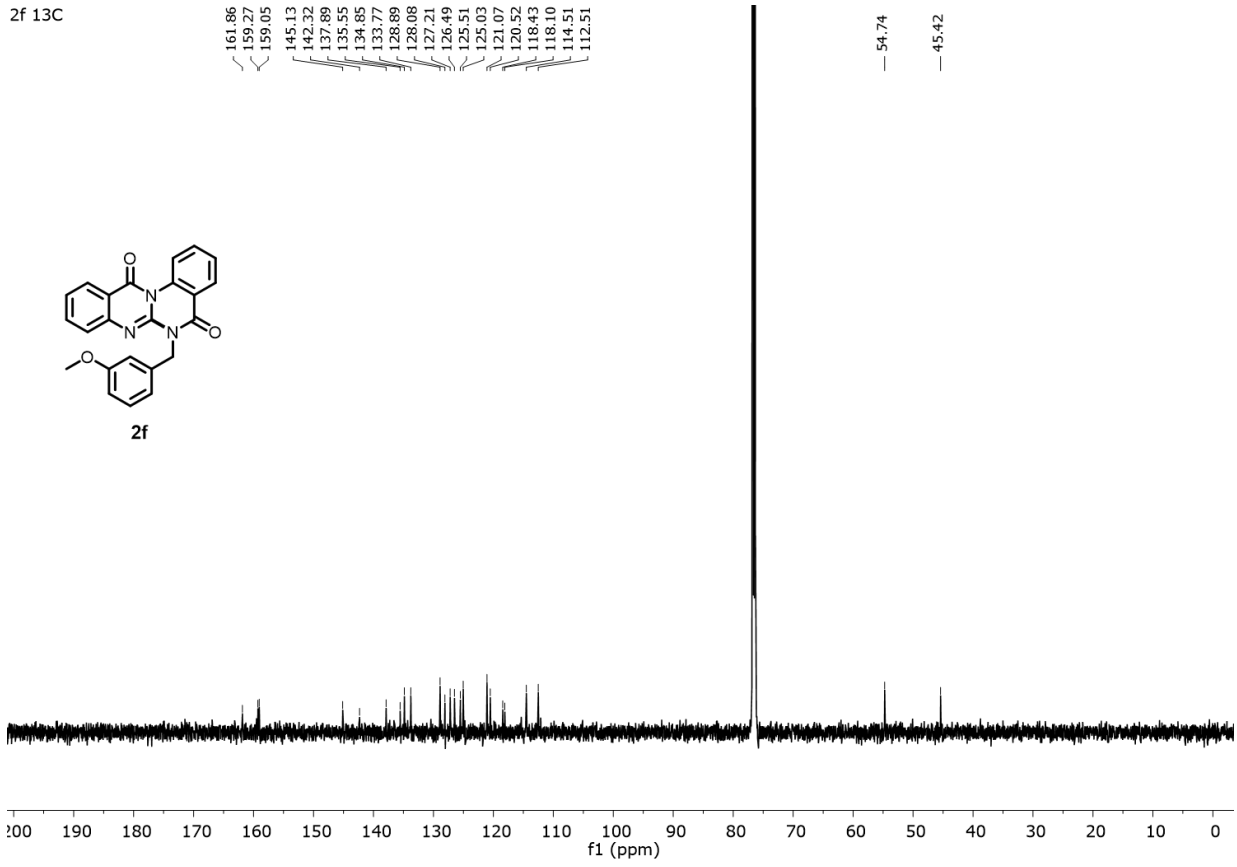
^{13}C in $CDCl_3$ 150 MHz 2e



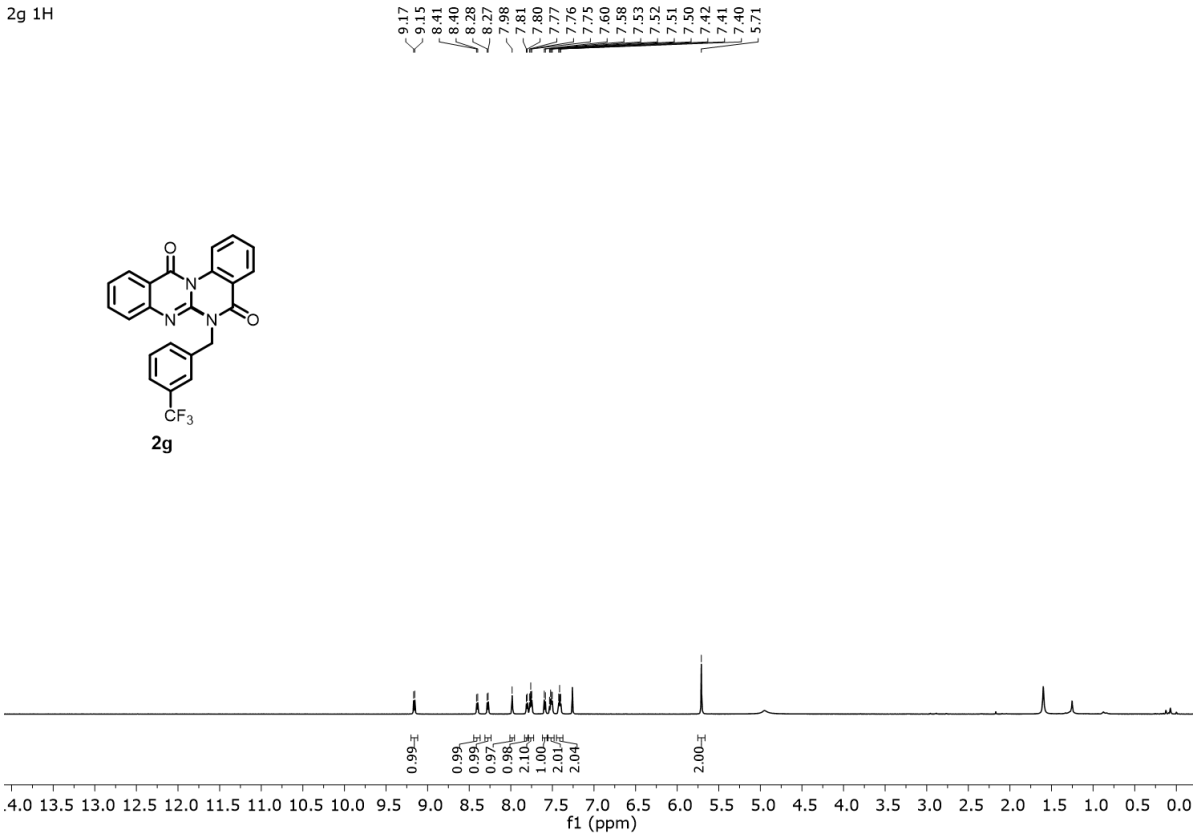
^{1}H in $CDCl_3$ 600 MHz 2f



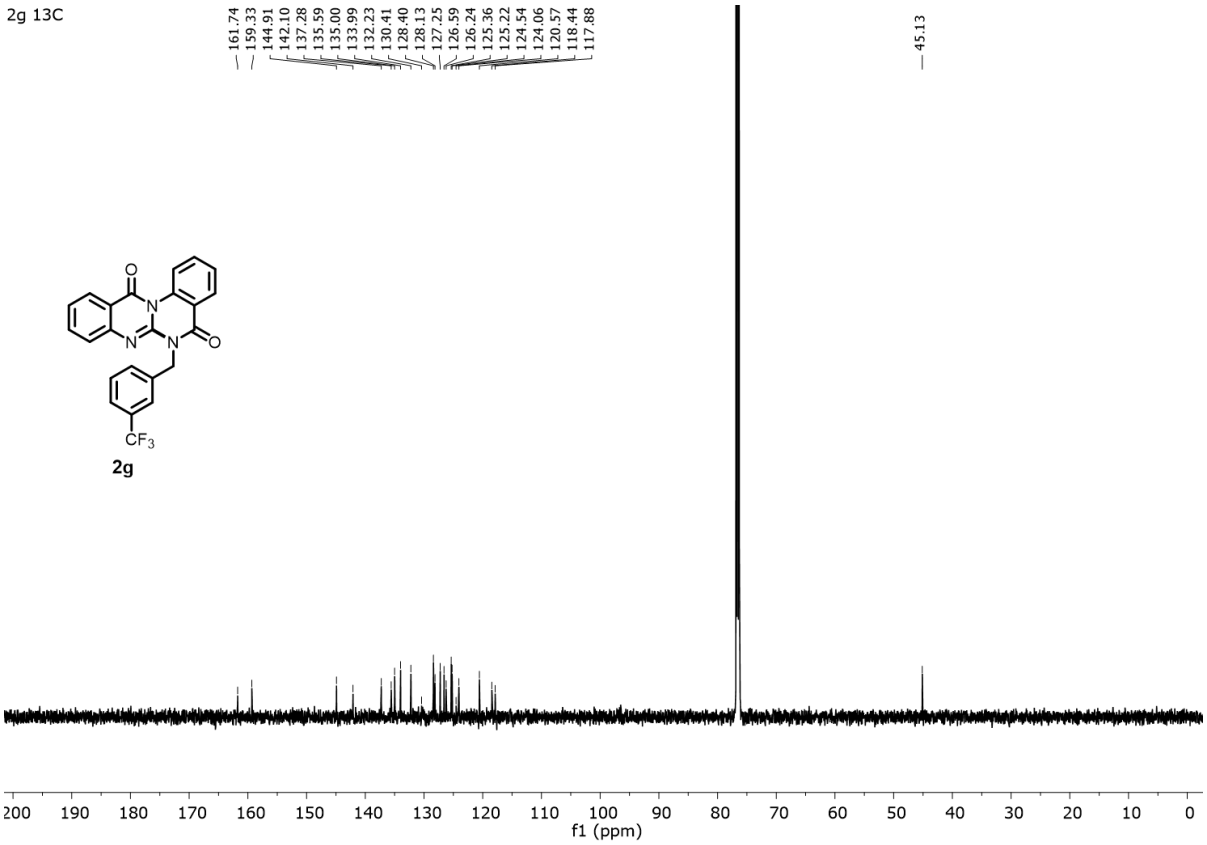
^{13}C in $CDCl_3$ 150 MHz 2f



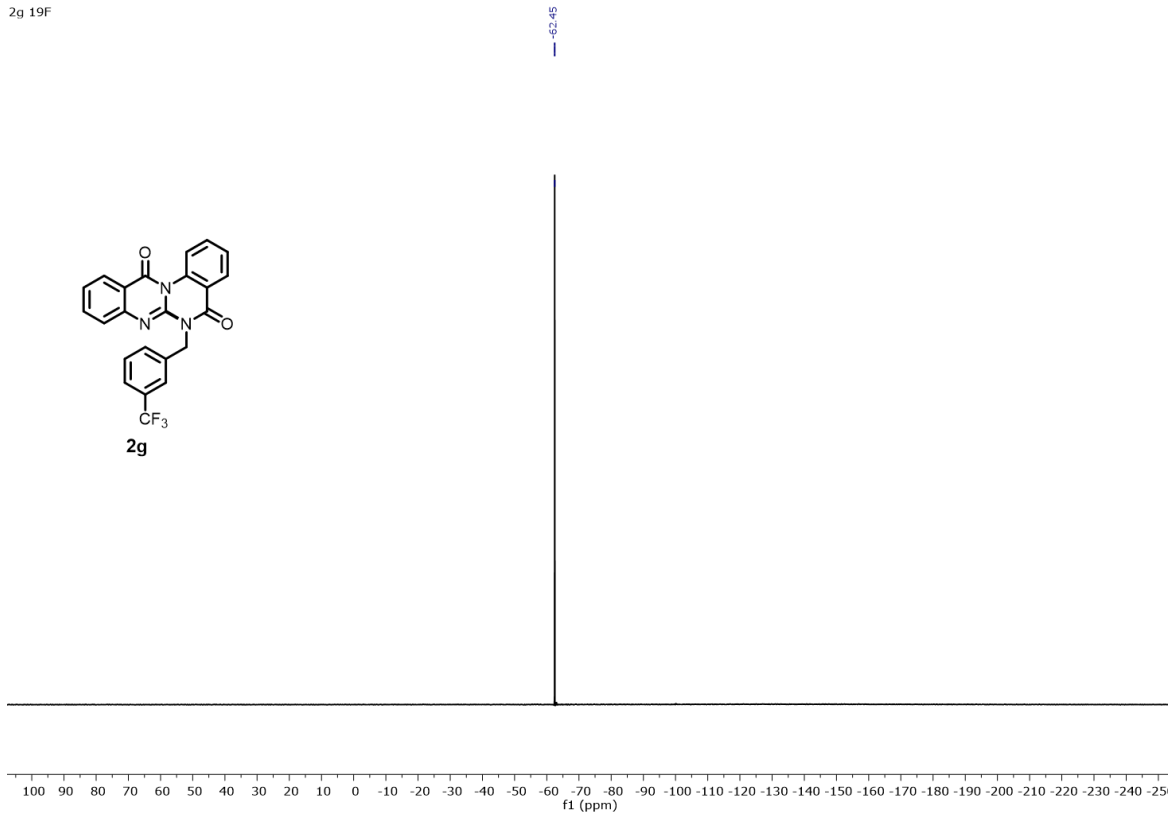
^{1}H in $CDCl_3$ 600 MHz 2g



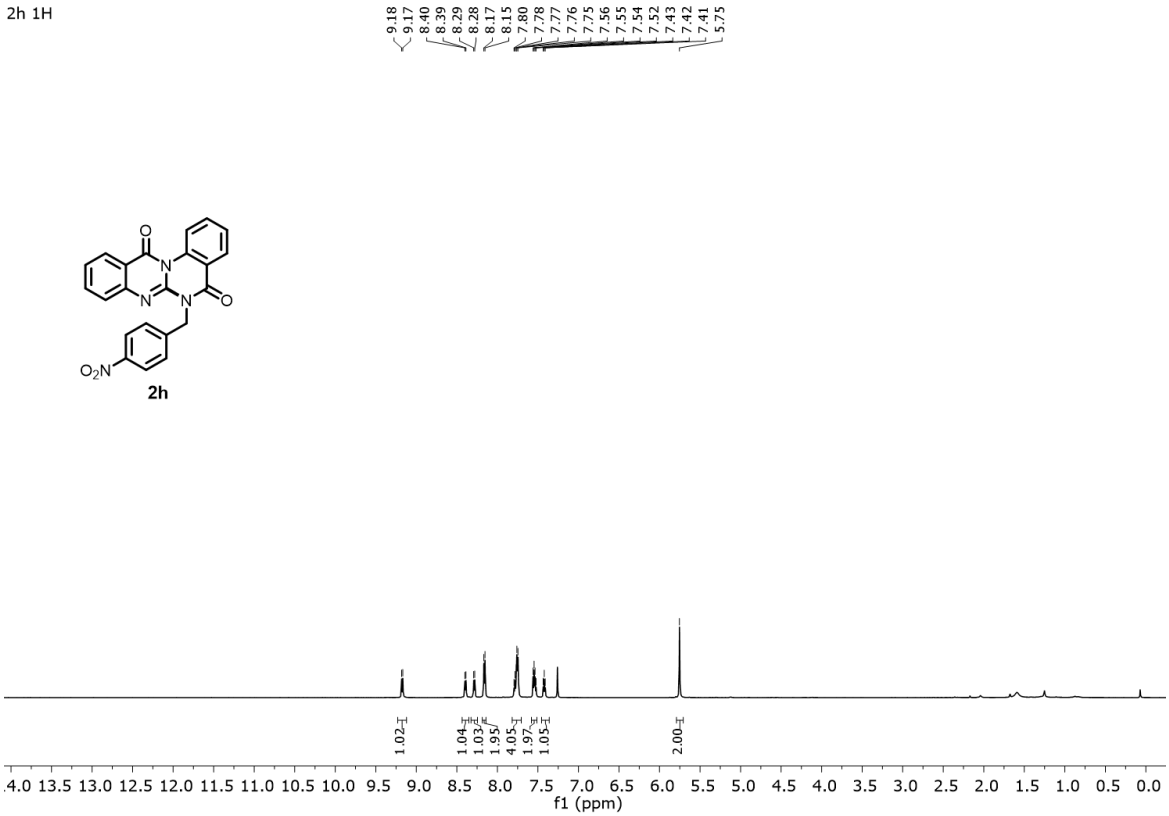
^{13}C in $CDCl_3$ 150 MHz 2g



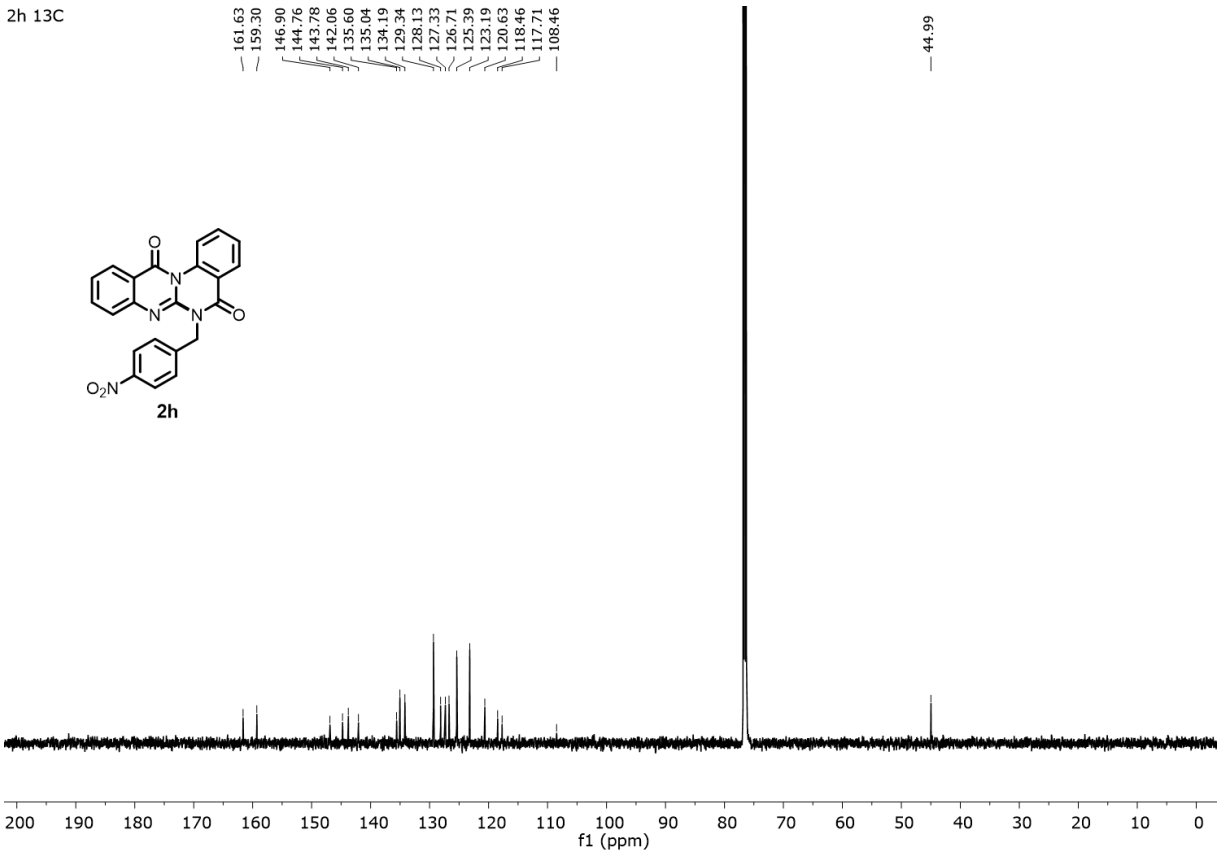
^{19}F in $CDCl_3$ 400 MHz 2g



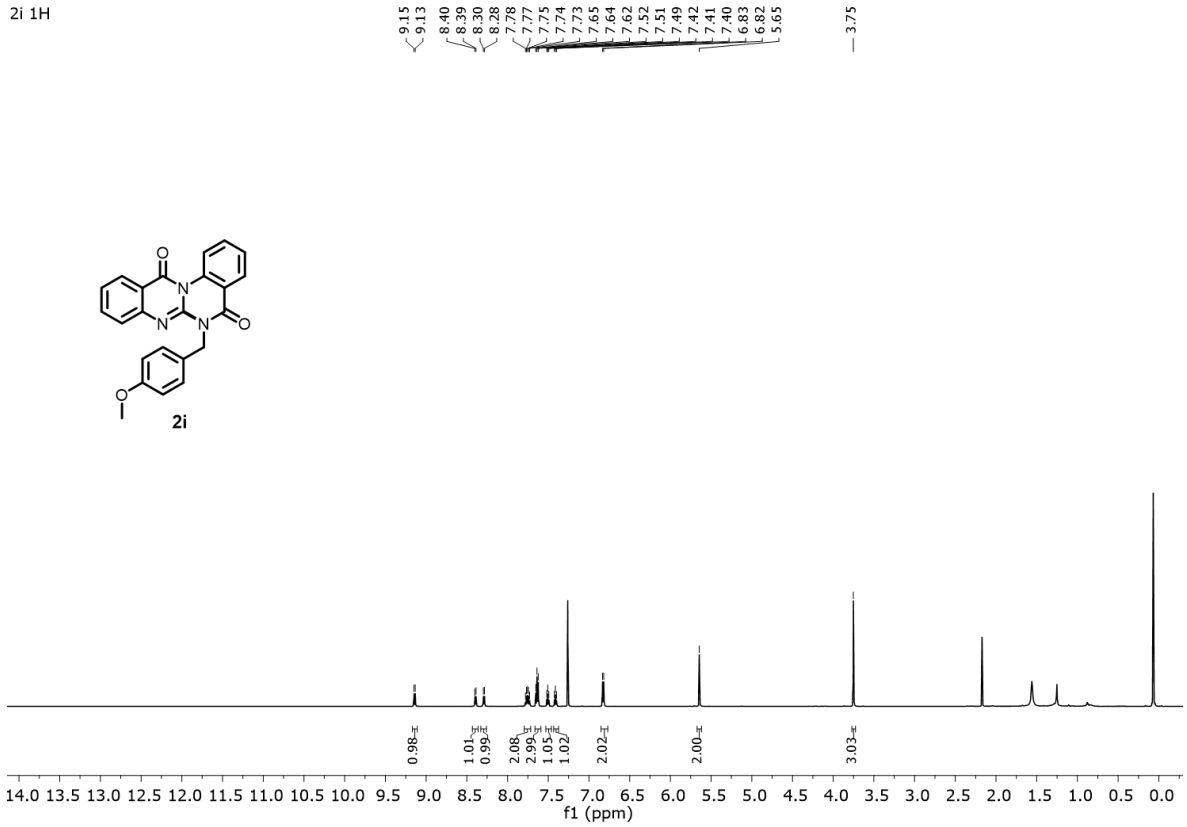
^{1}H in $CDCl_3$ 600 MHz 2h



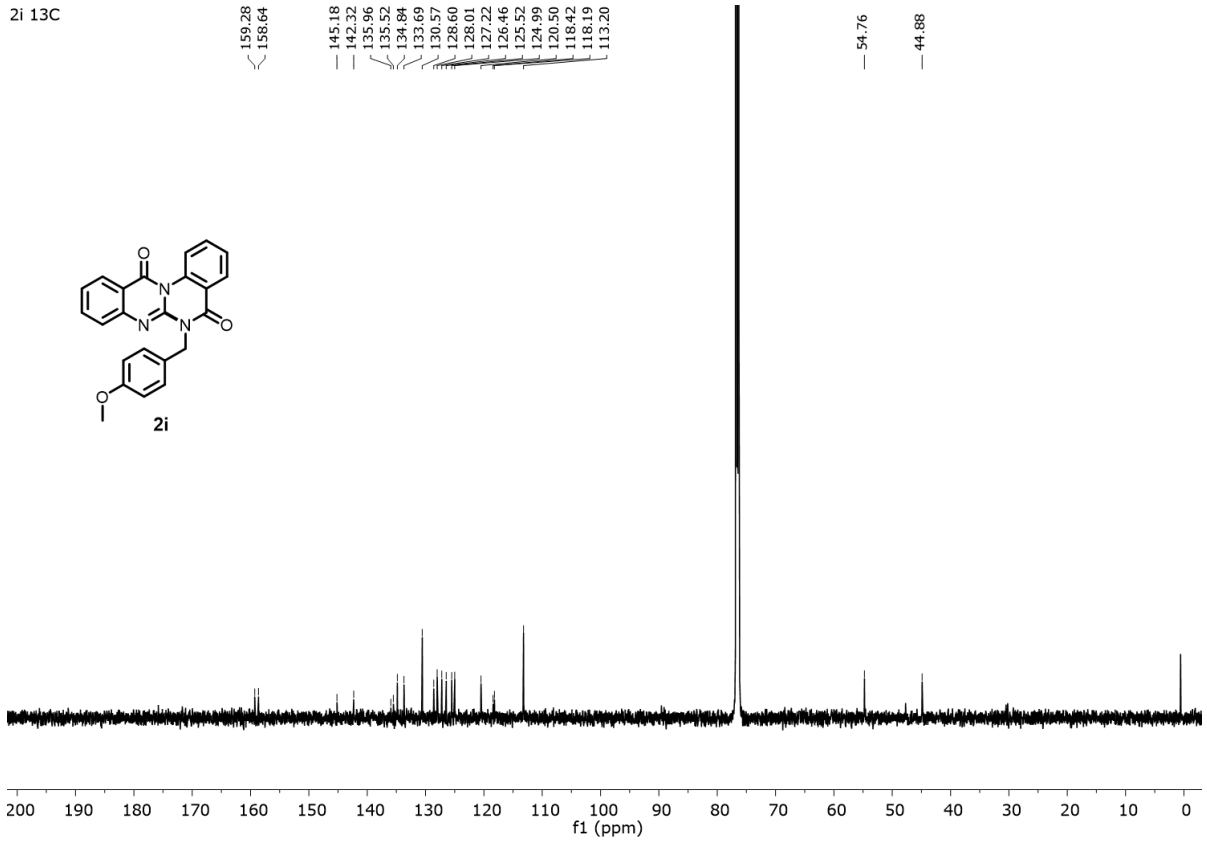
^{13}C in $CDCl_3$ 150 MHz 2h



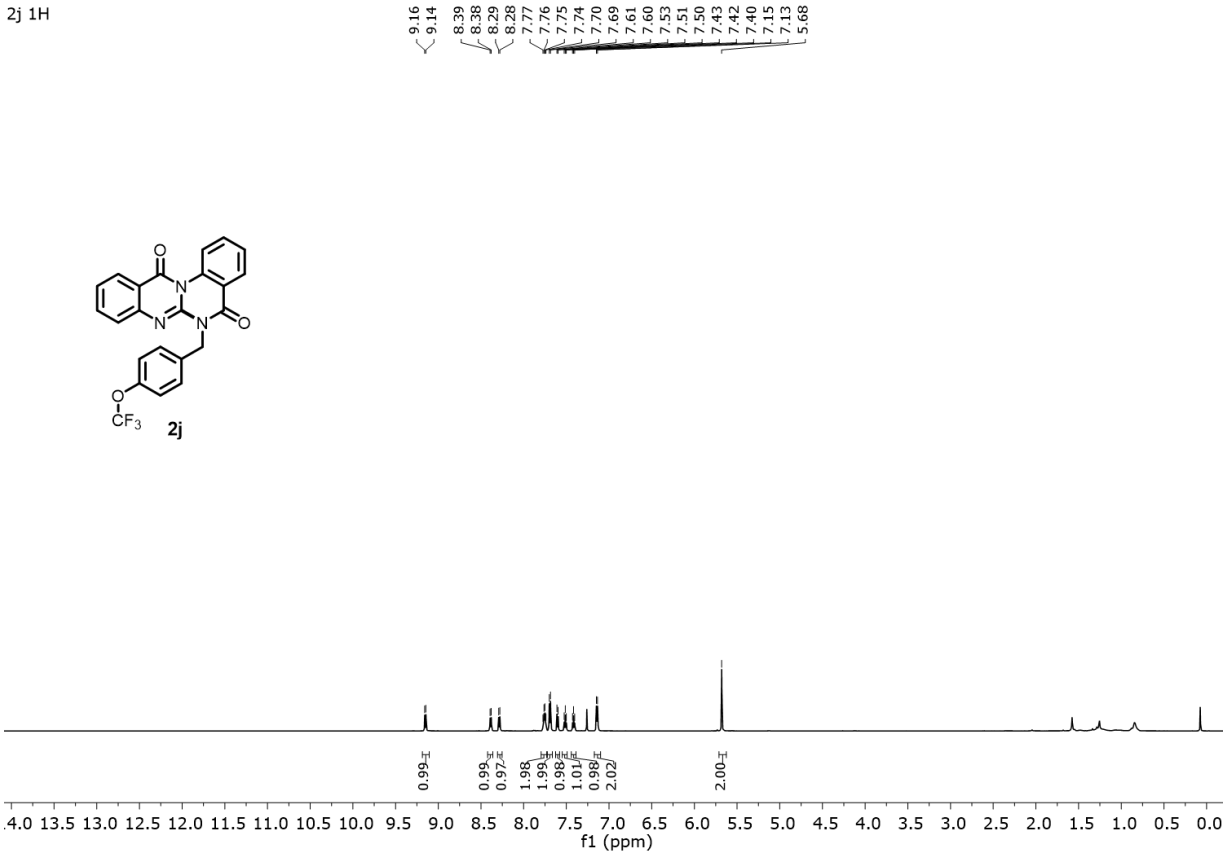
^{1}H in $CDCl_3$ 600 MHz 2i



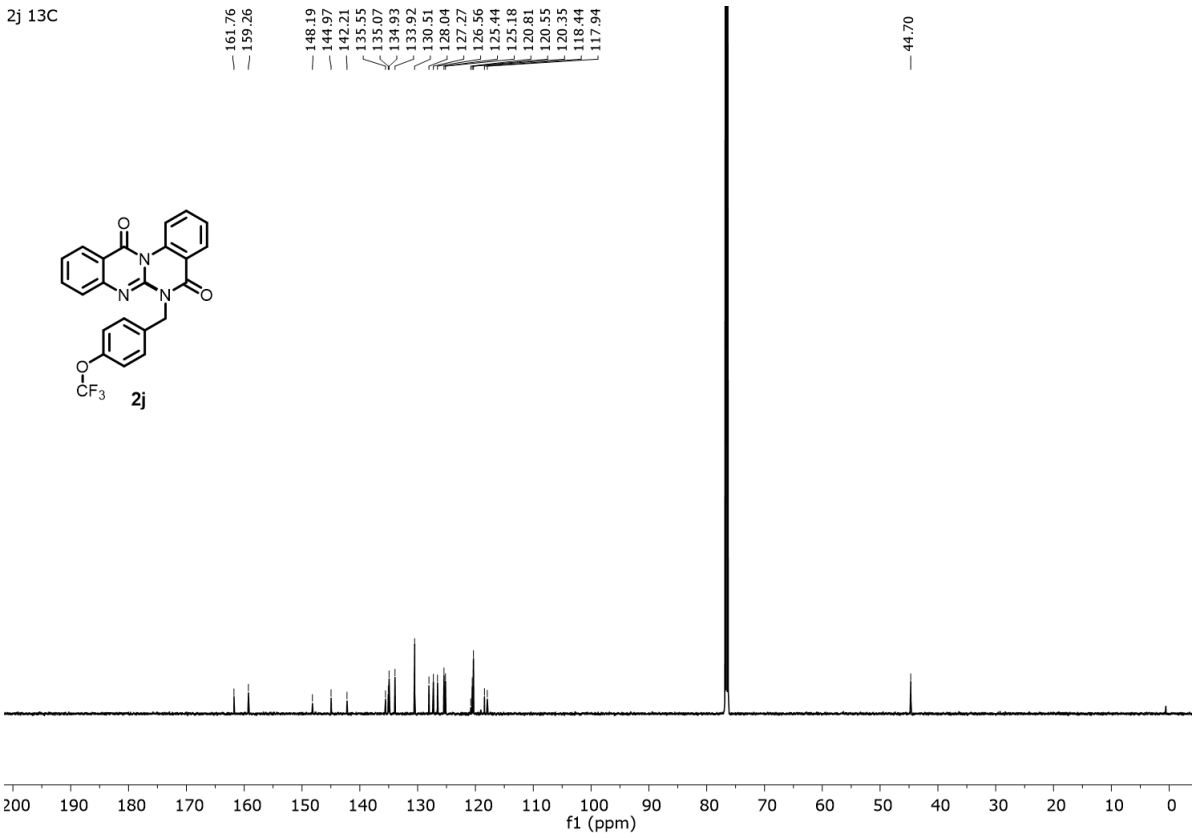
^{13}C in $CDCl_3$ 150 MHz 2i



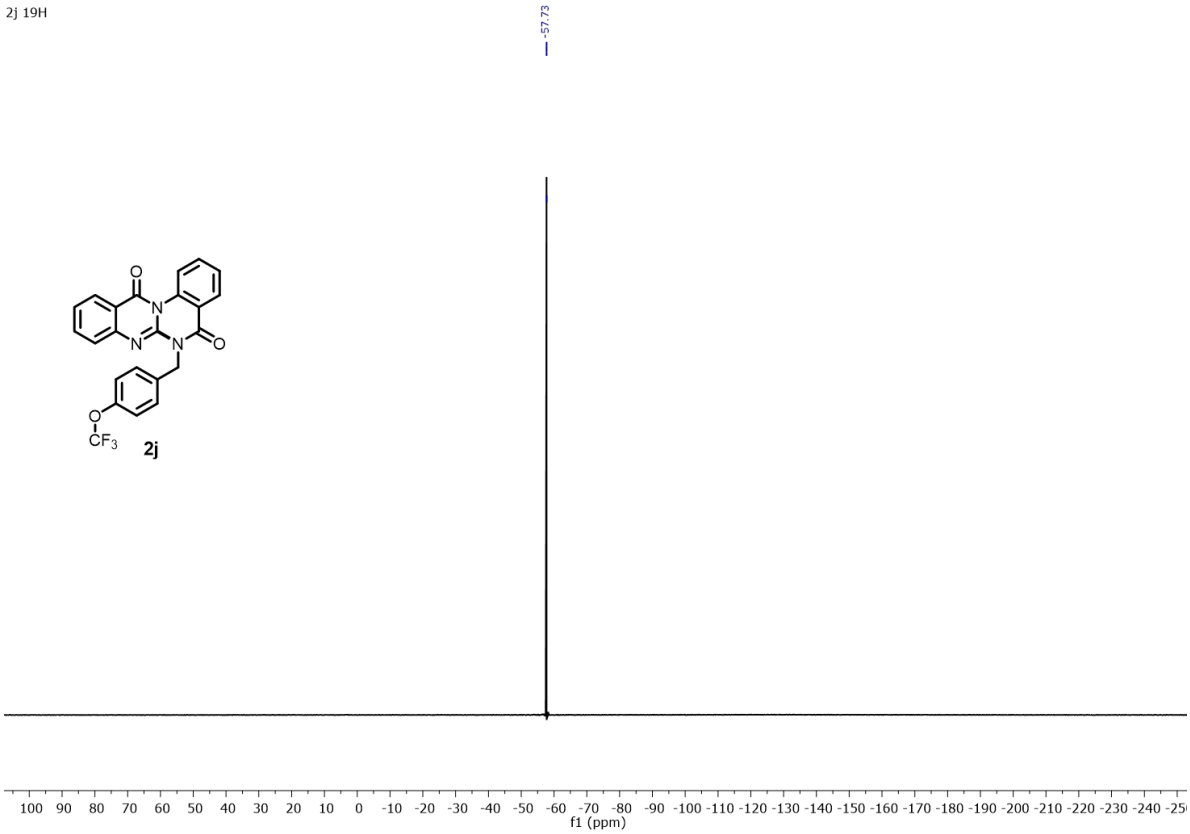
^{1}H in $CDCl_3$ 600 MHz 2j



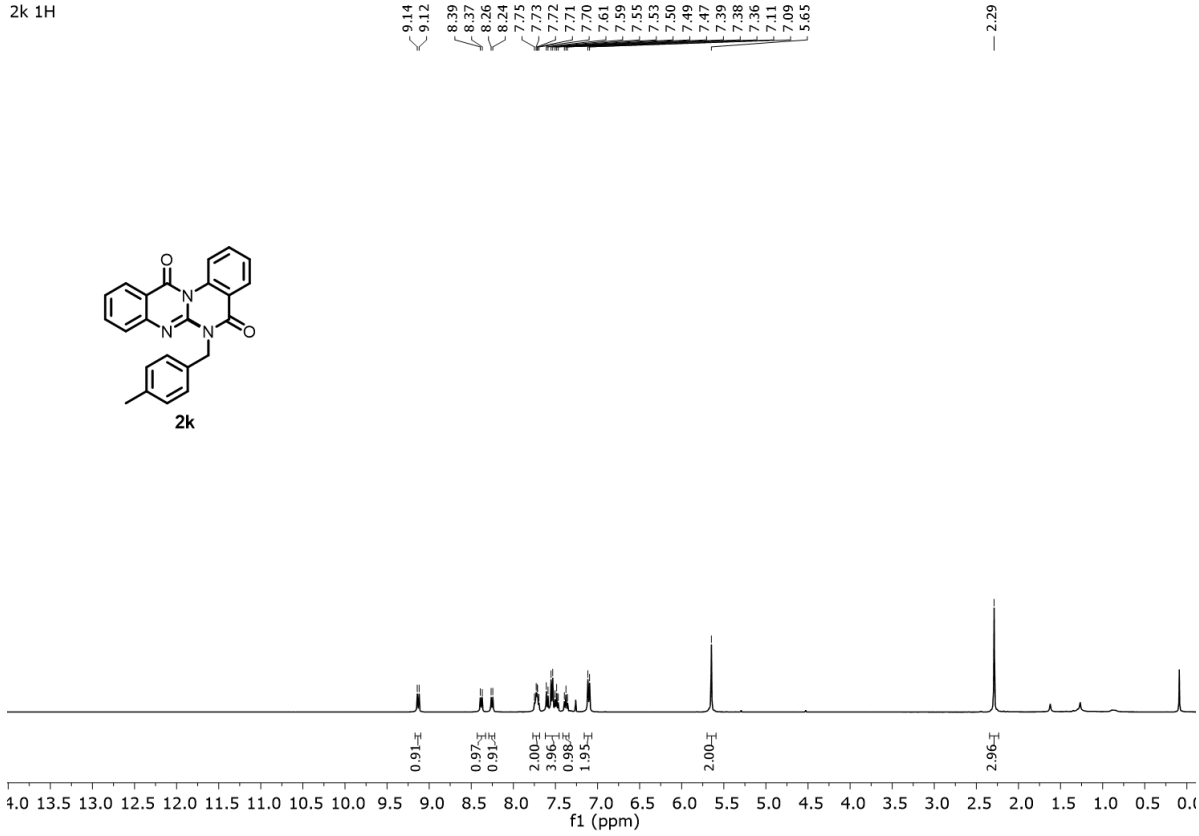
^{13}C in $CDCl_3$ 150 MHz 2j



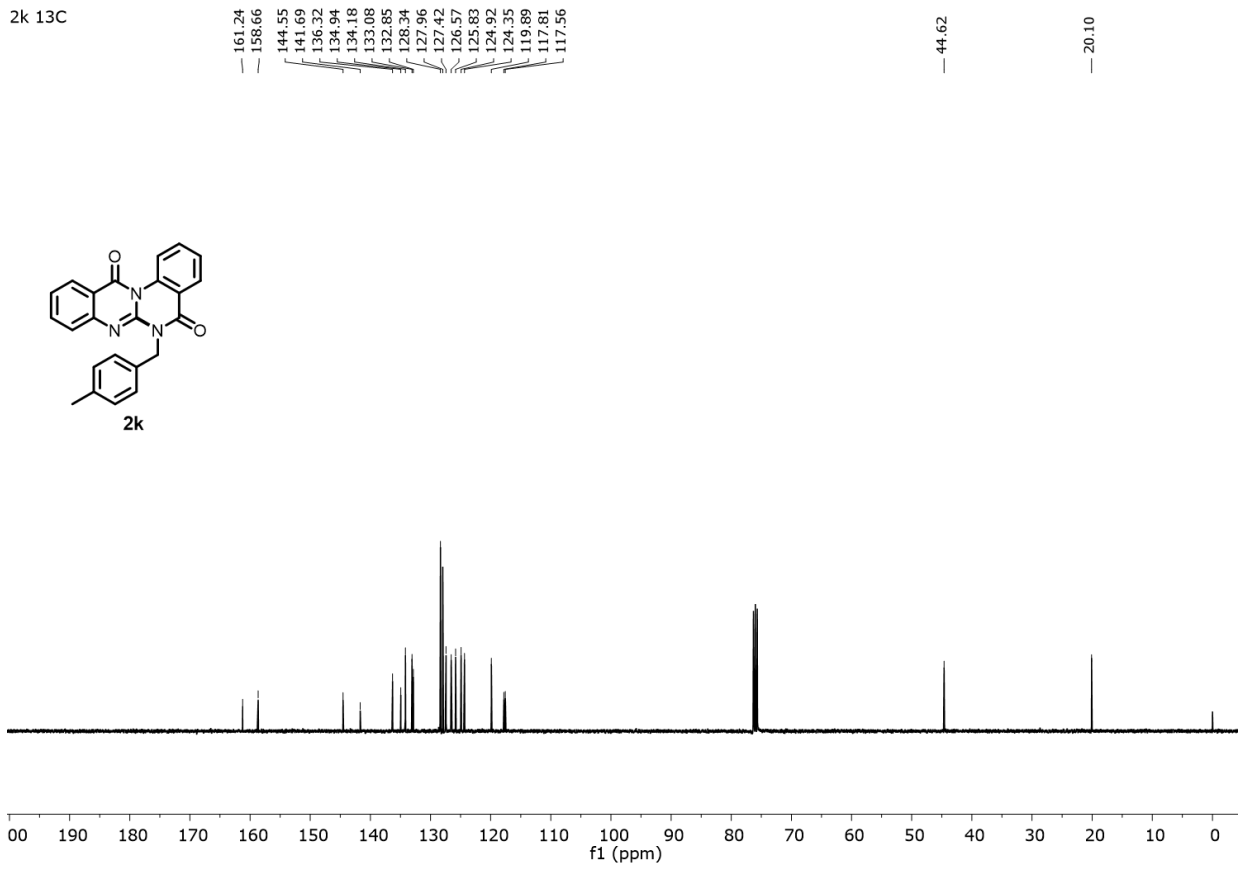
^{19}F in $CDCl_3$ 400 MHz 2j



^{1}H in $CDCl_3$ 600 MHz 2k

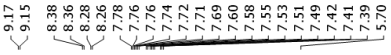


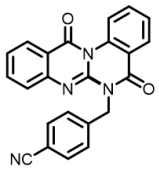
^{13}C in $CDCl_3$ 150 MHz 2k



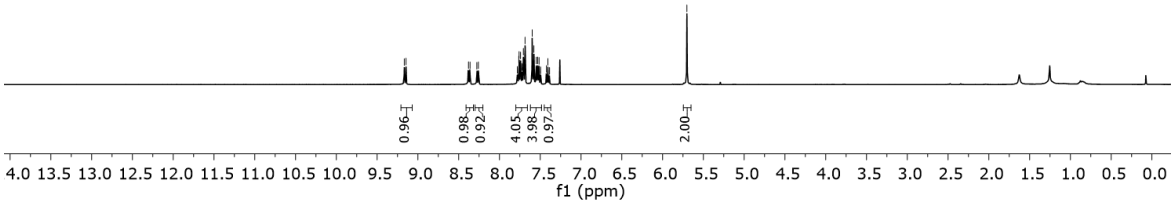
^{1}H in $CDCl_3$ 600 MHz 2l

2l 1H



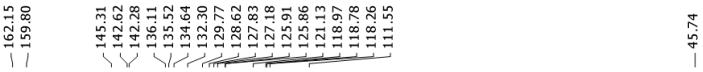


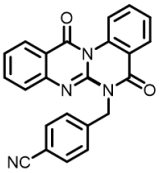
2l



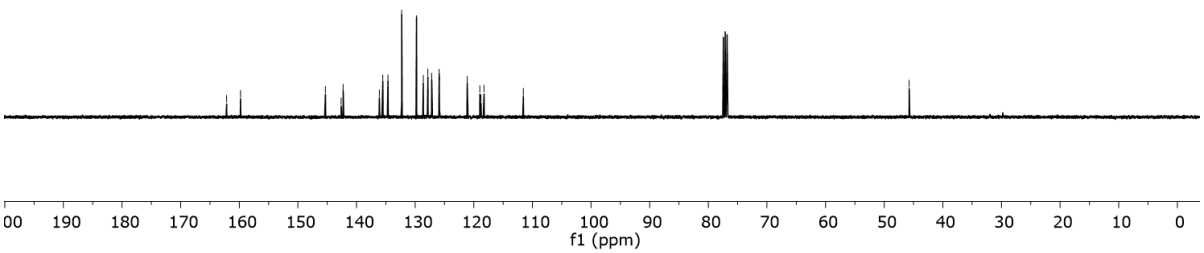
^{13}C in $CDCl_3$ 150 MHz 2l

2l 13C



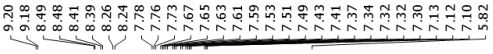


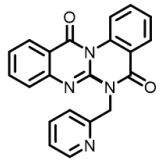
2l



^{1}H in $CDCl_3$ 600 MHz 2m

2m 1H





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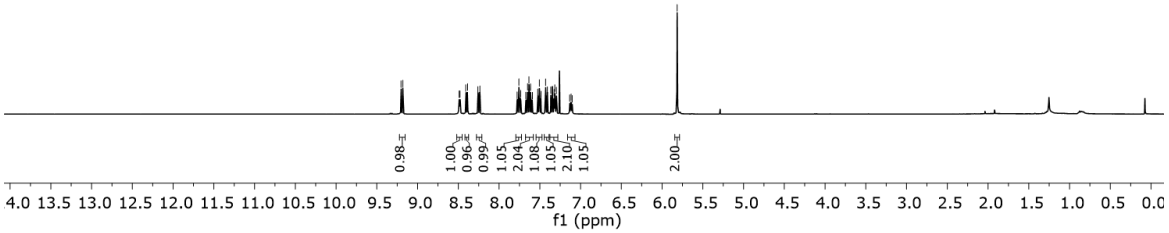
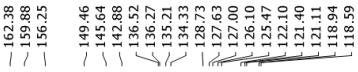
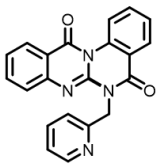


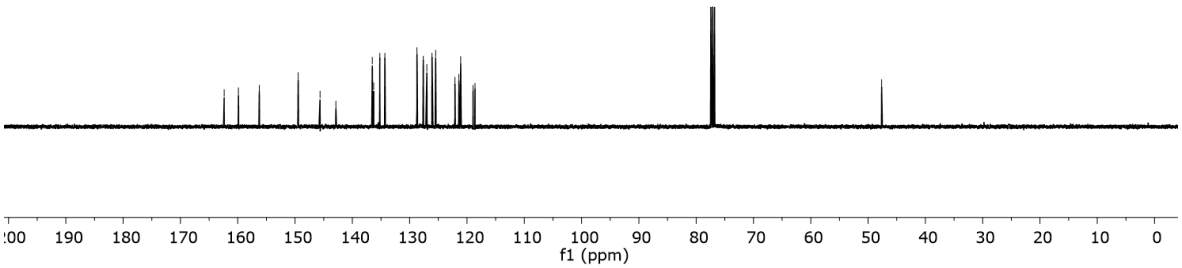
^{13}C in $CDCl_3$ 150 MHz 2m

2m 13C

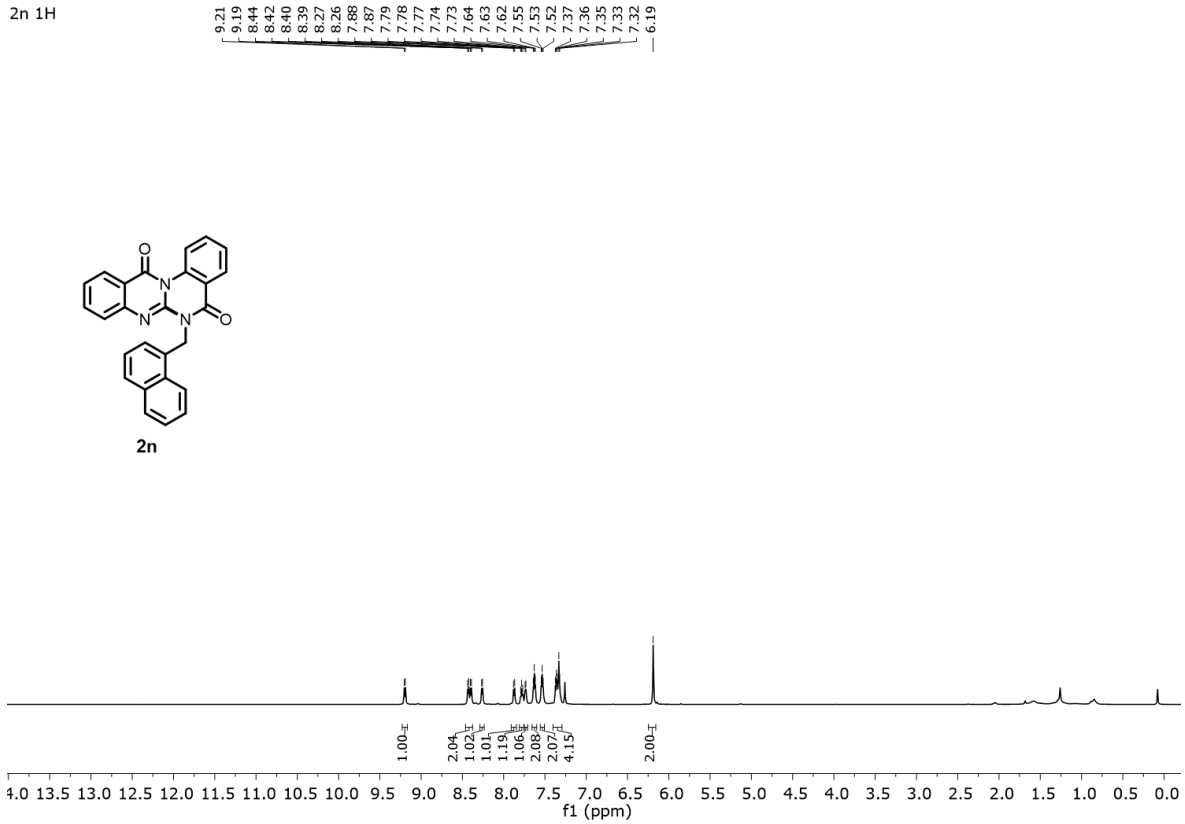




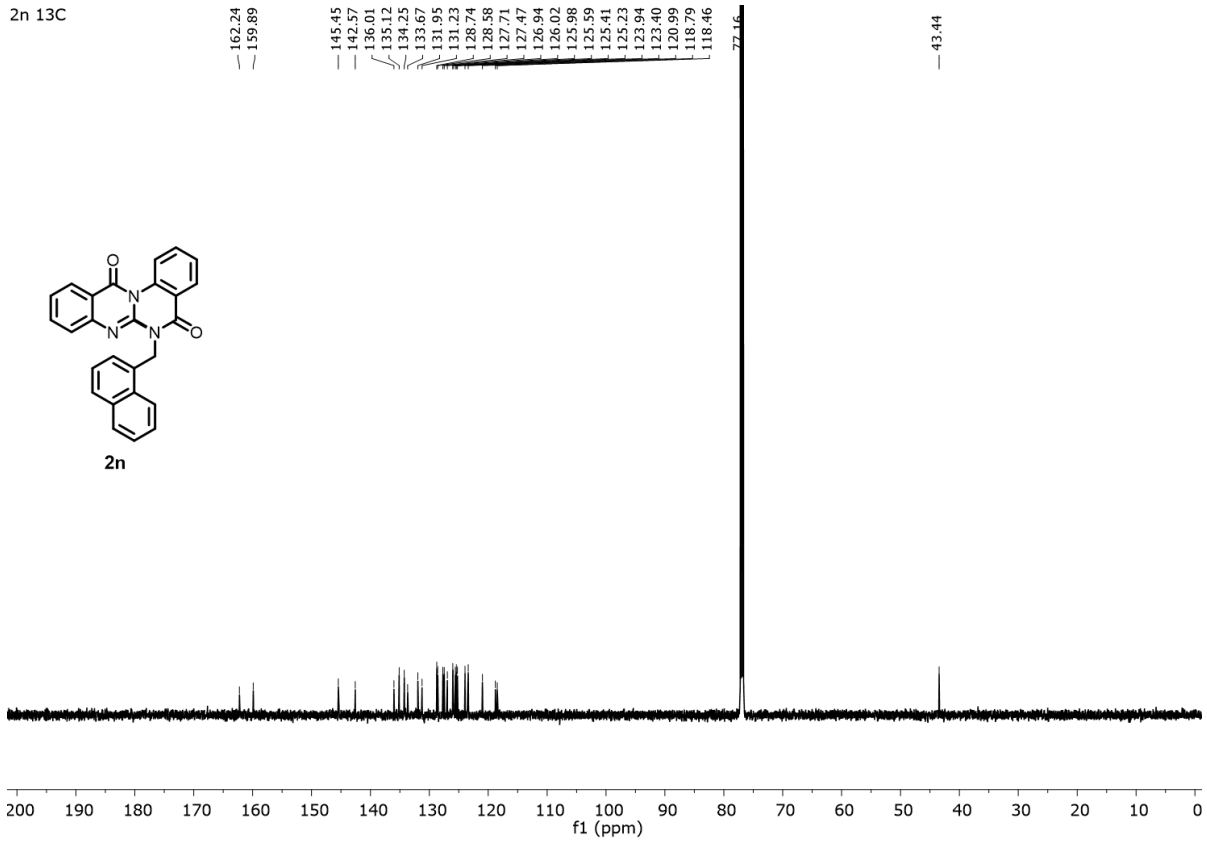
2m



^{1}H in $CDCl_3$ 600 MHz 2n



^{13}C in $CDCl_3$ 150 MHz 2n



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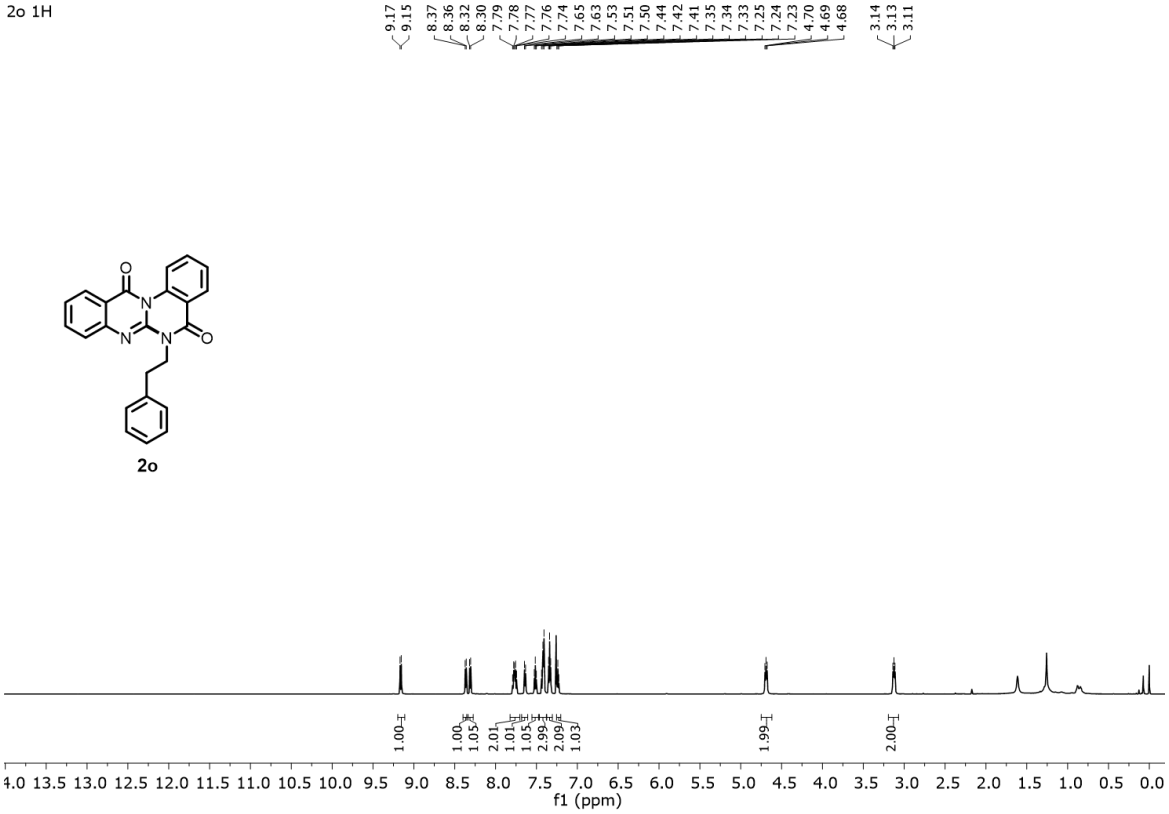
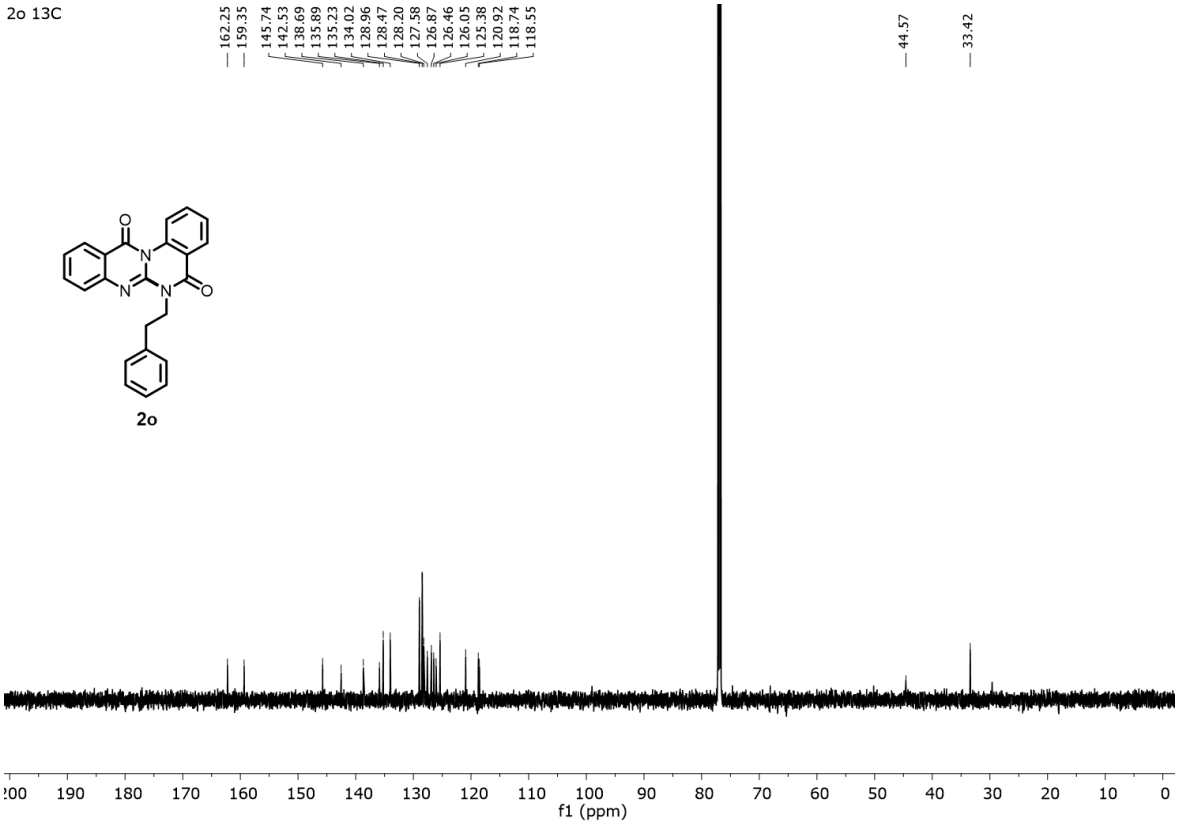
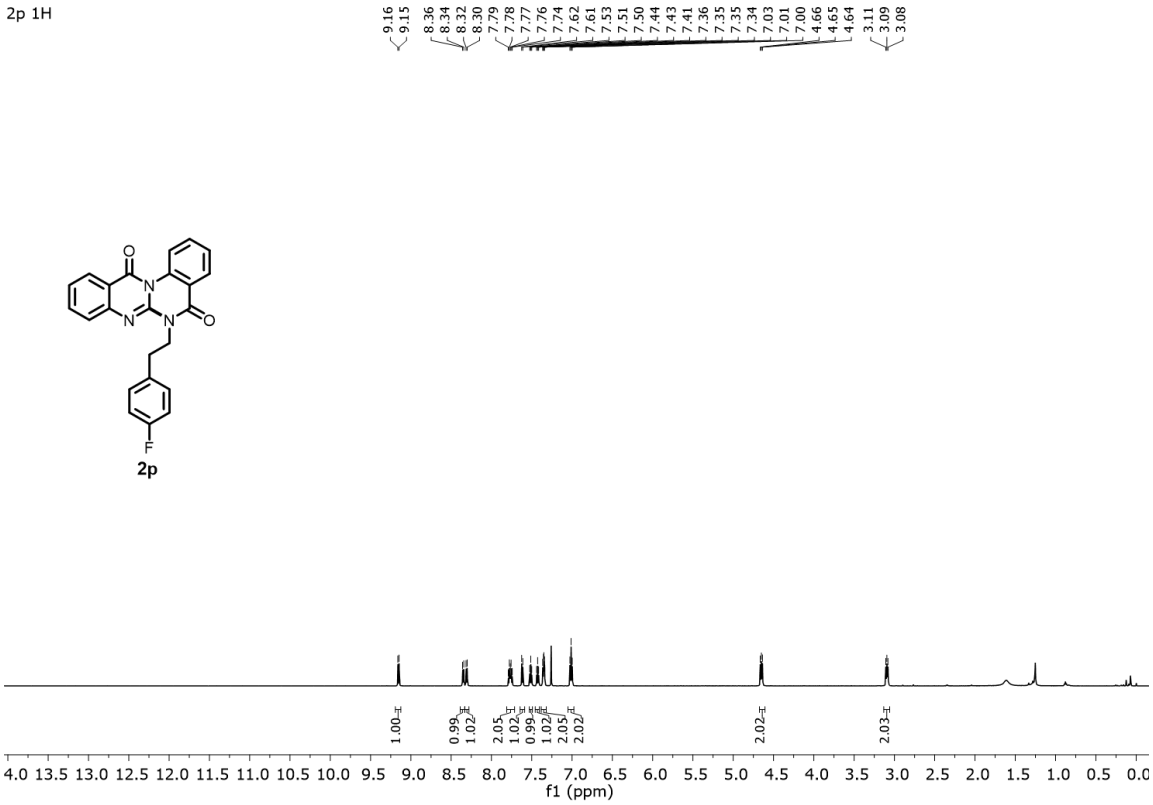


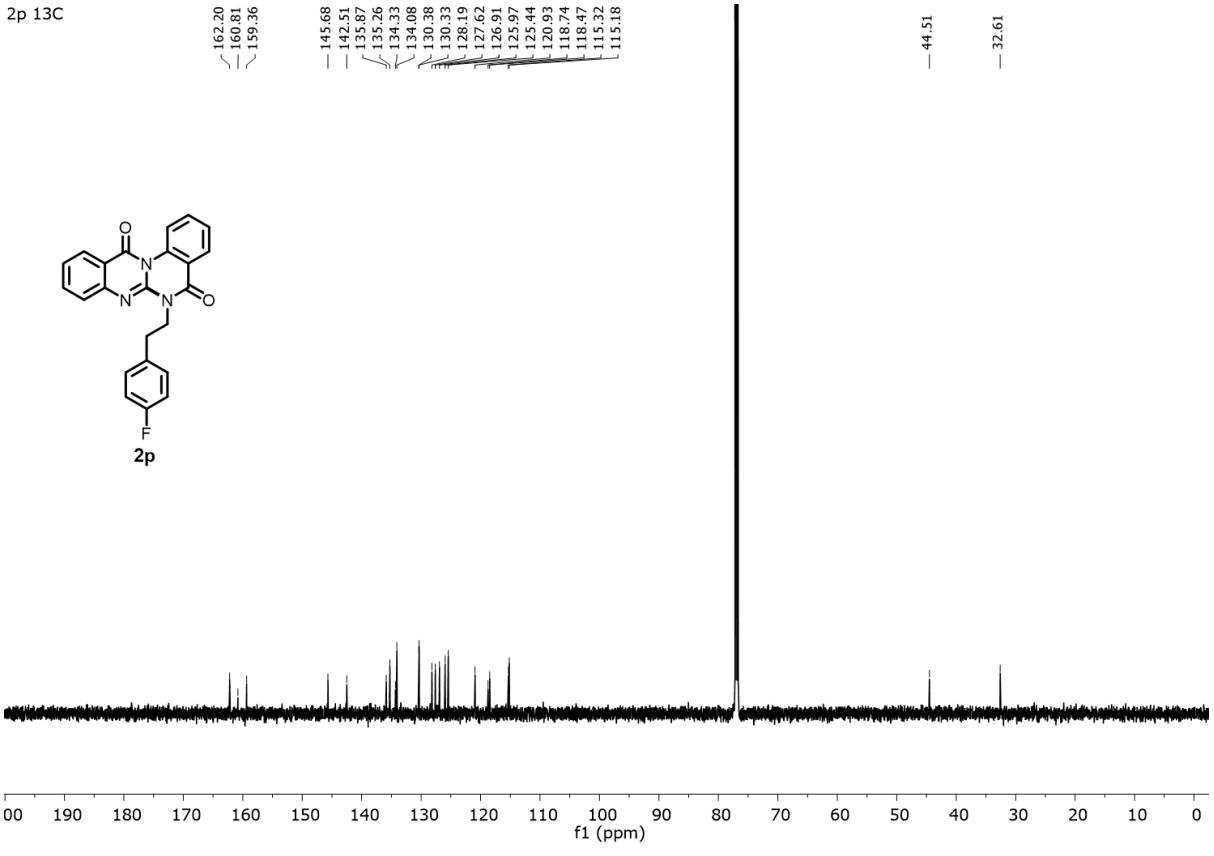
^{13}C in $CDCl_3$ 150 MHz 2o



^{1}H in $CDCl_3$ 600 MHz 2p

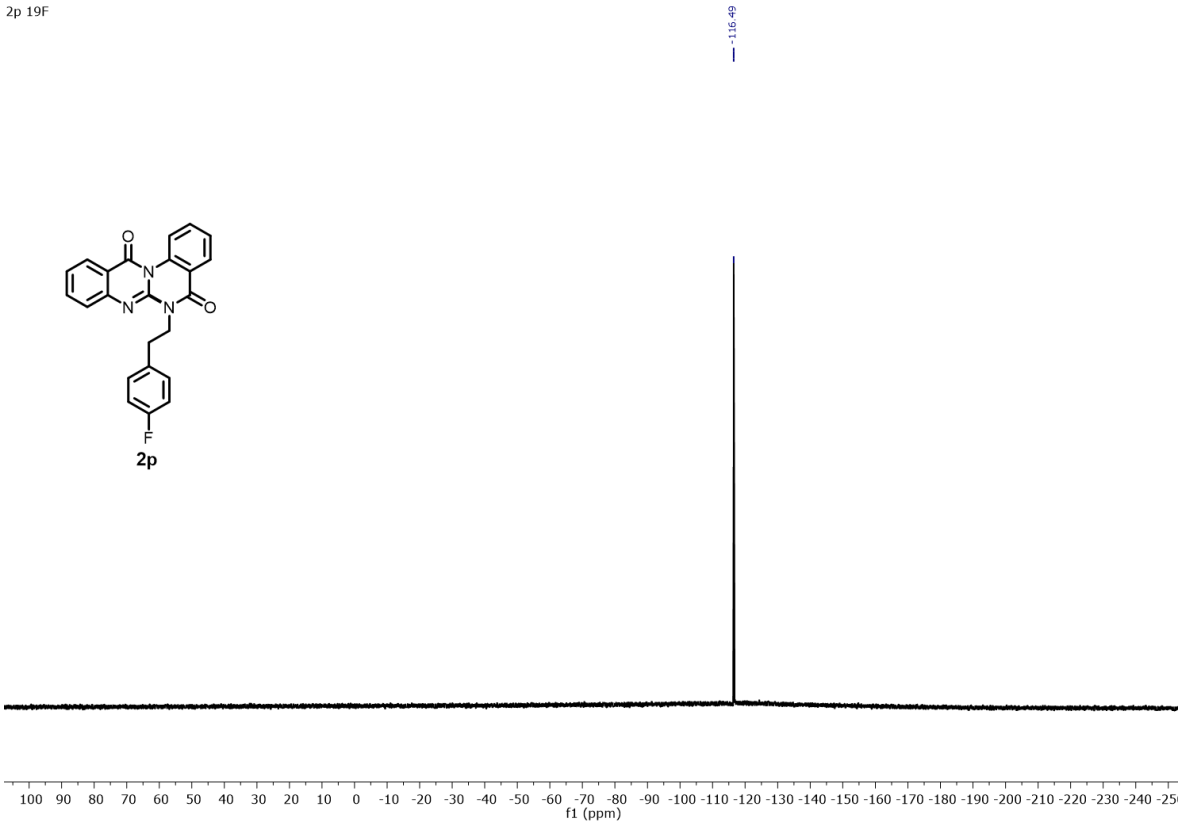


^{13}C in $CDCl_3$ 150 MHz 2p

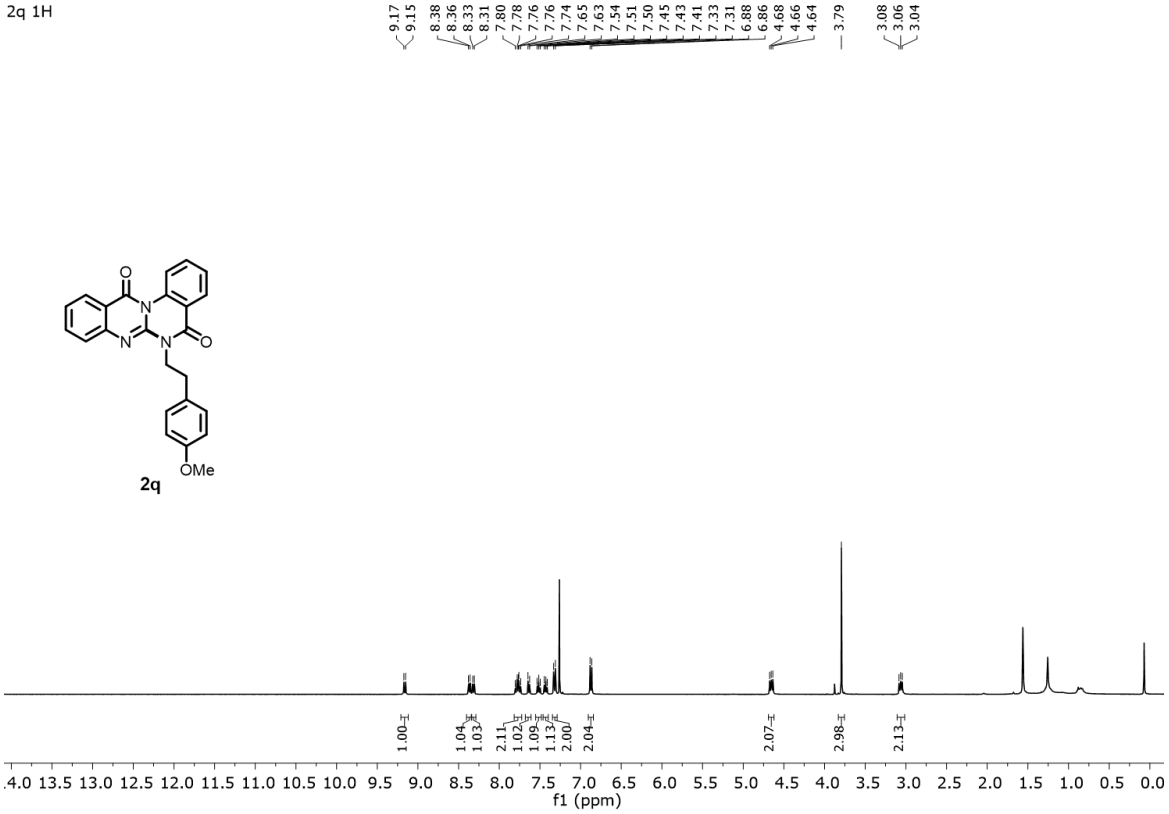


^{19}F in $CDCl_3$ 600 MHz 2p

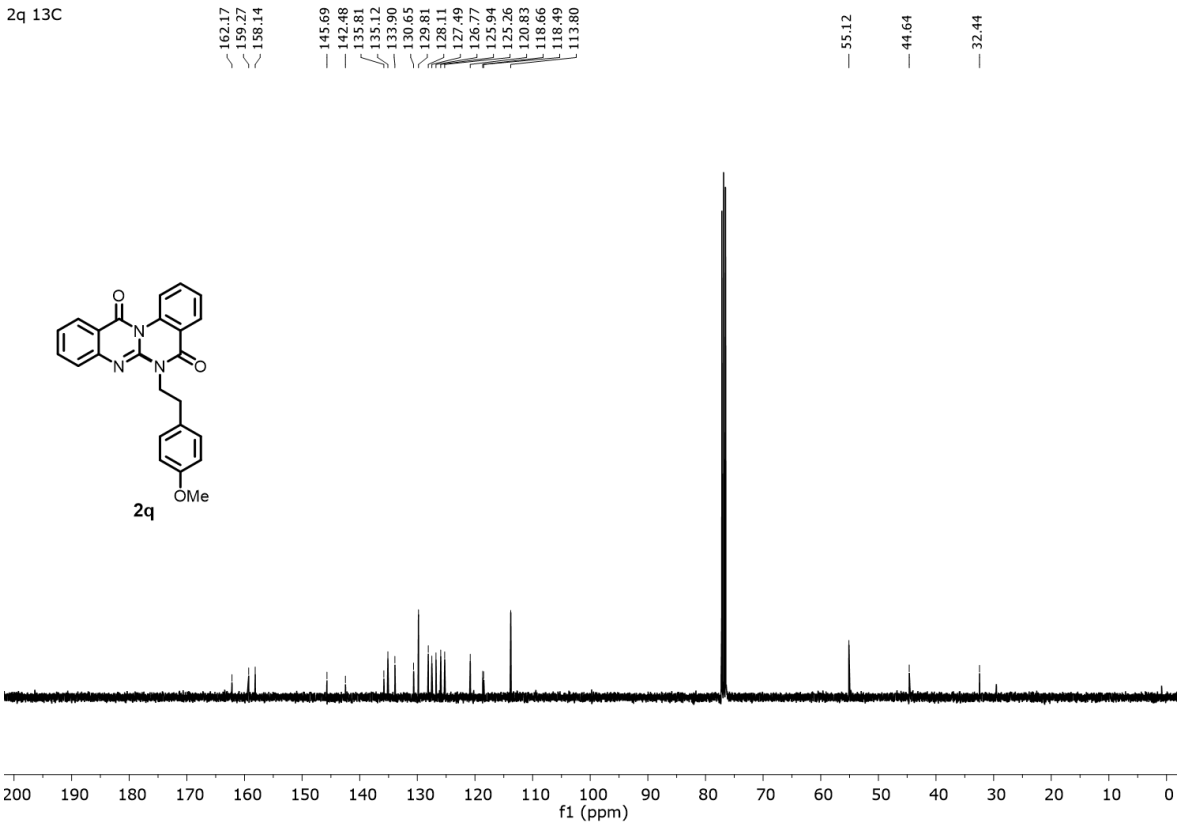
2p 19F



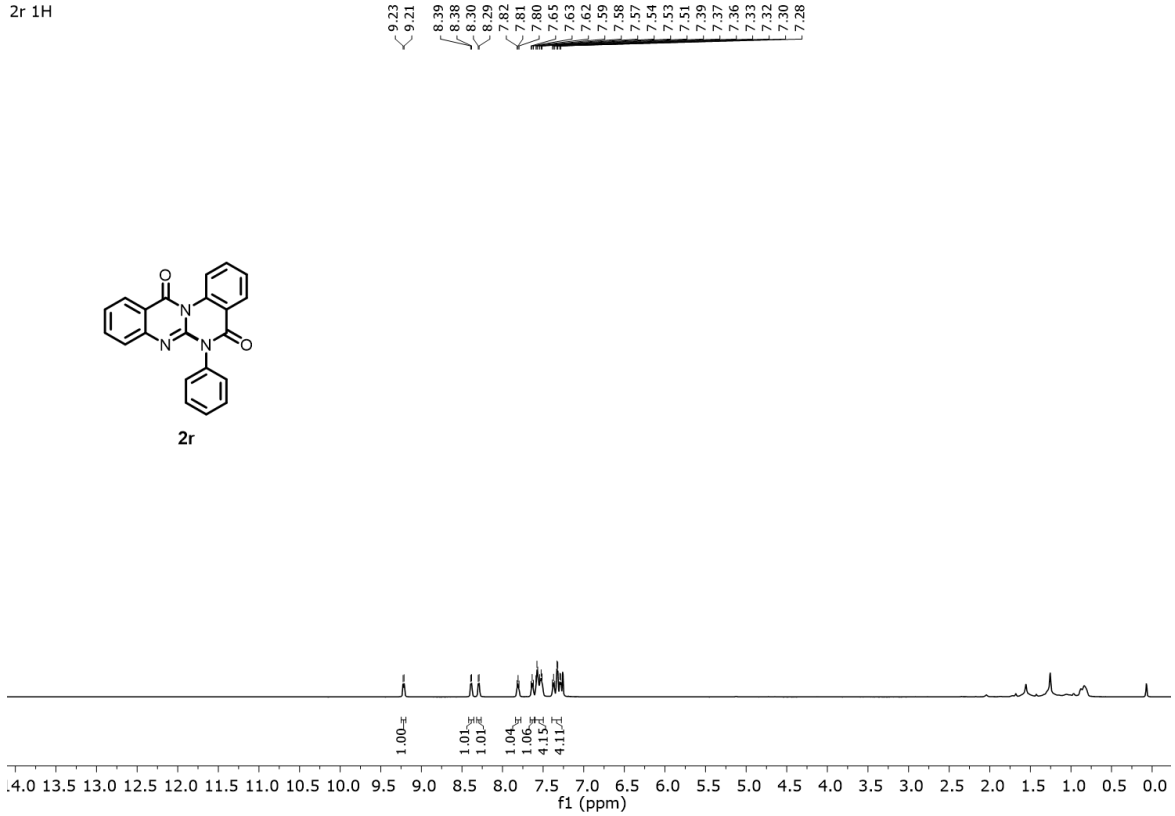
^{1}H in $CDCl_3$ 600 MHz 2q



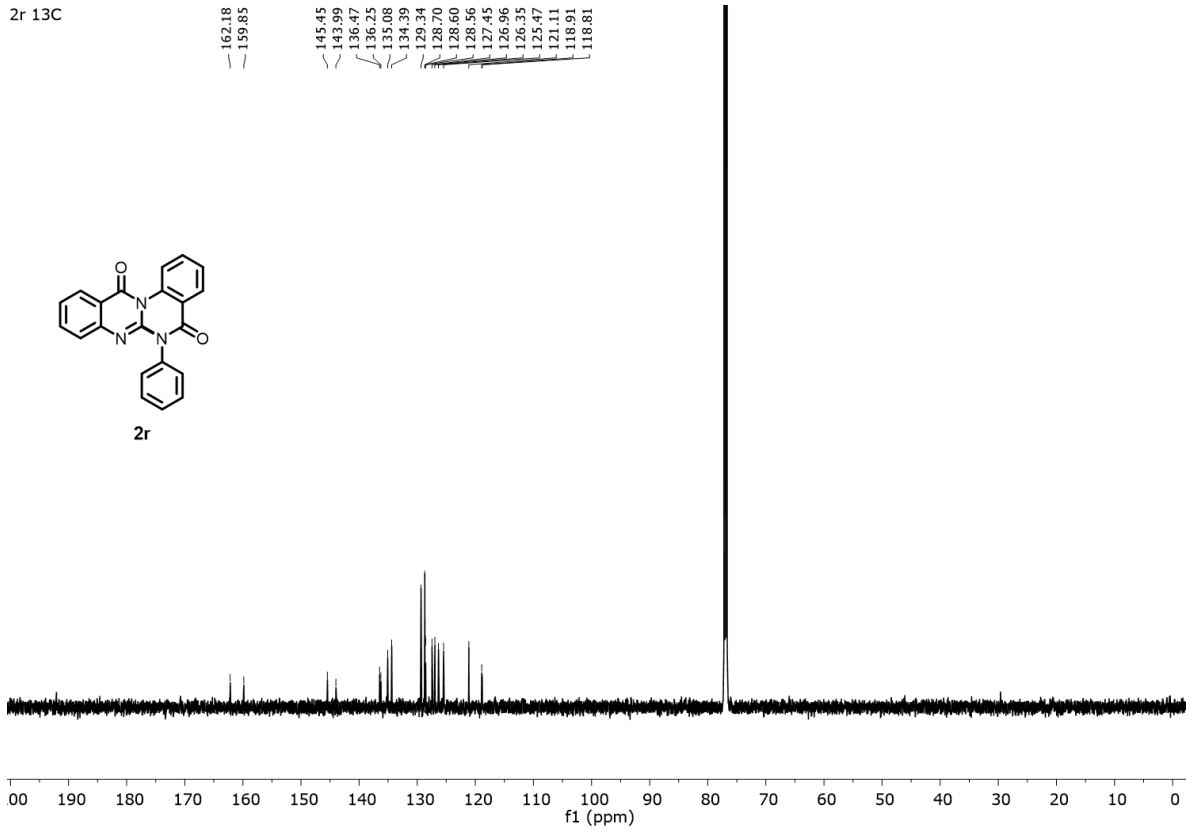
^{13}C in $CDCl_3$ 150 MHz 2q



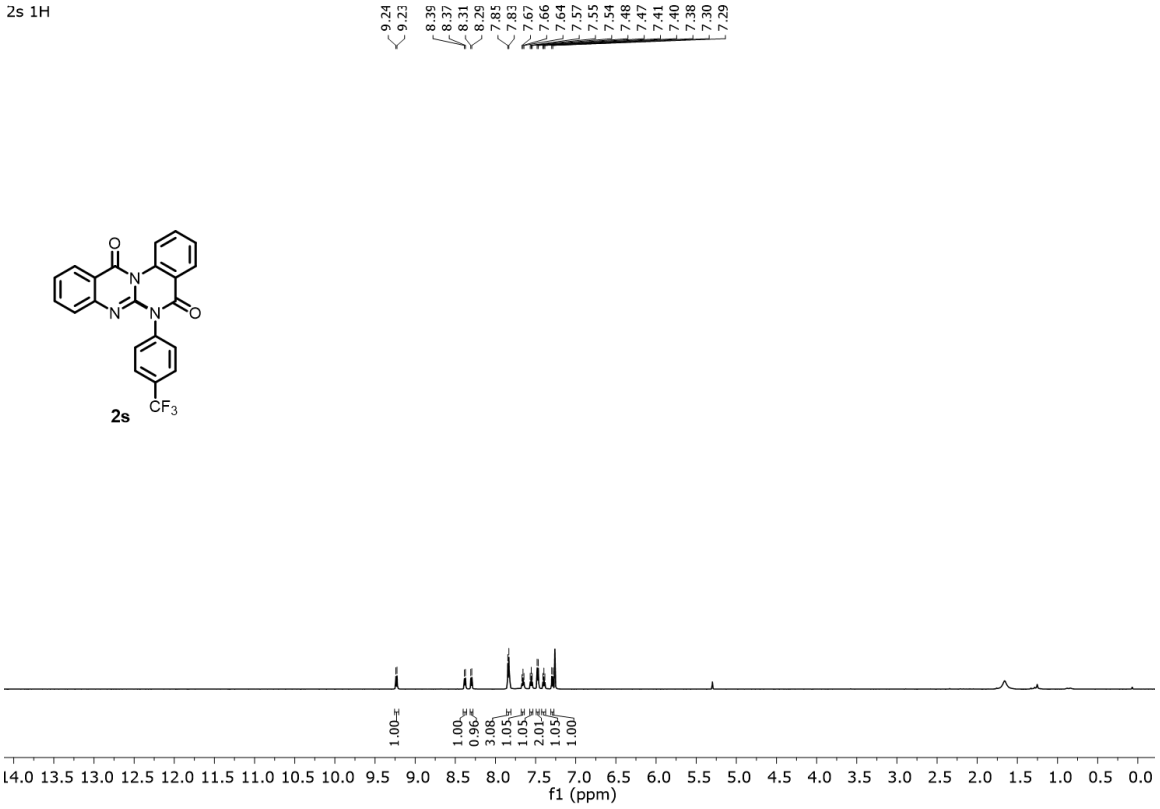
^{1}H in $CDCl_3$ 600 MHz 2r



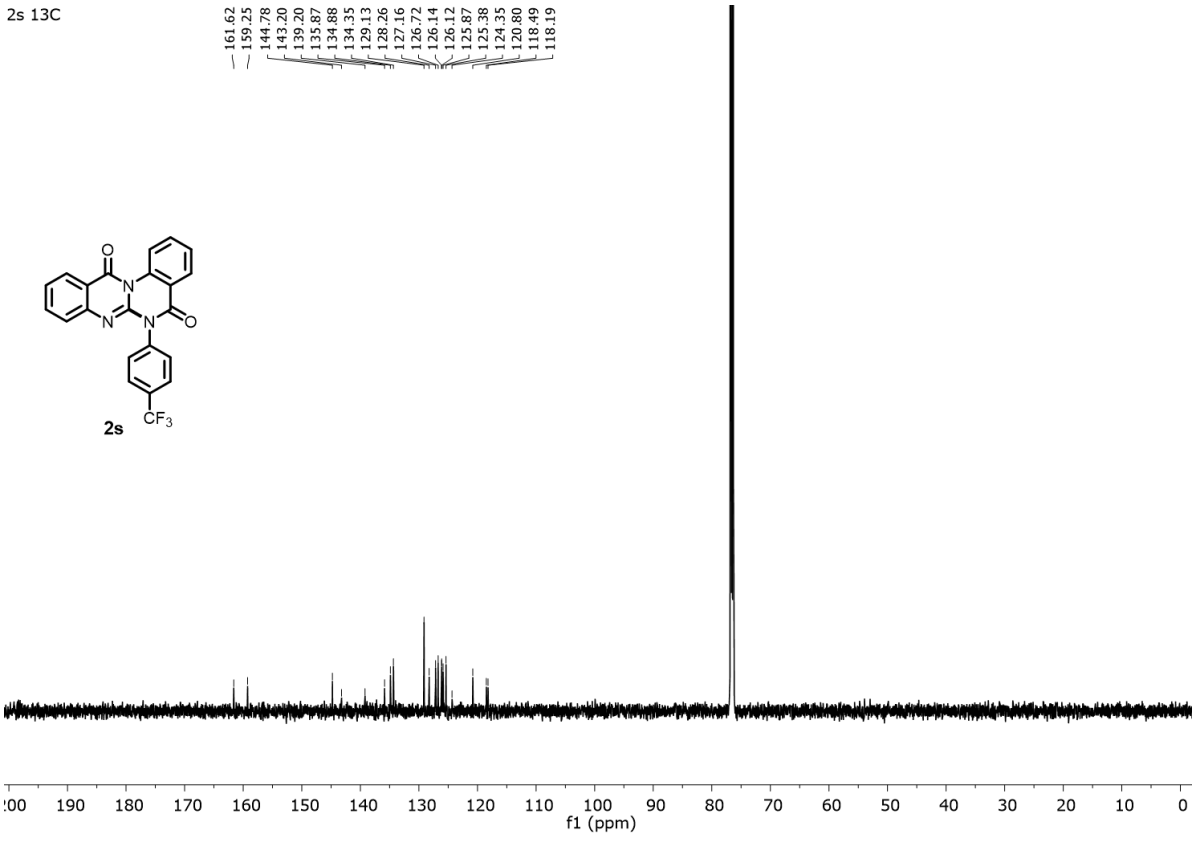
^{13}C in $CDCl_3$ 150 MHz 2r



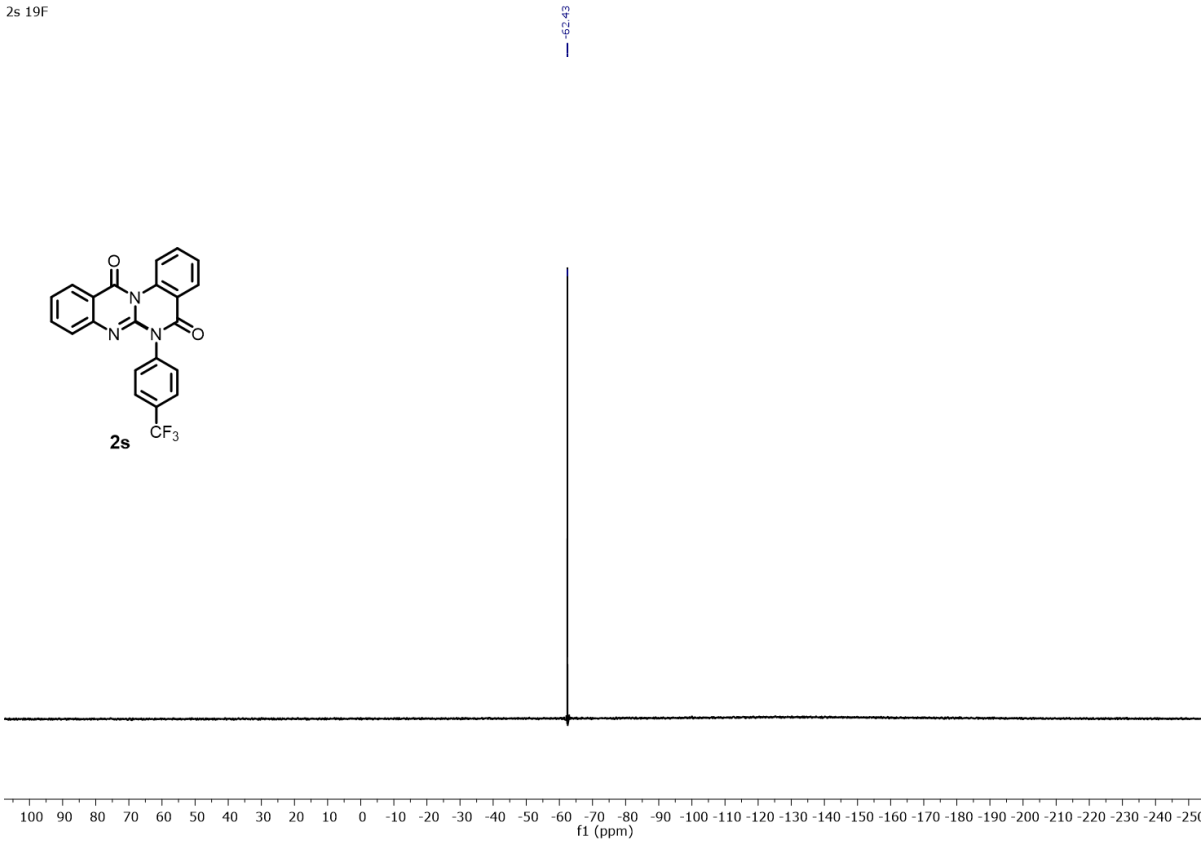
^{1}H in $CDCl_3$ 600 MHz 2s



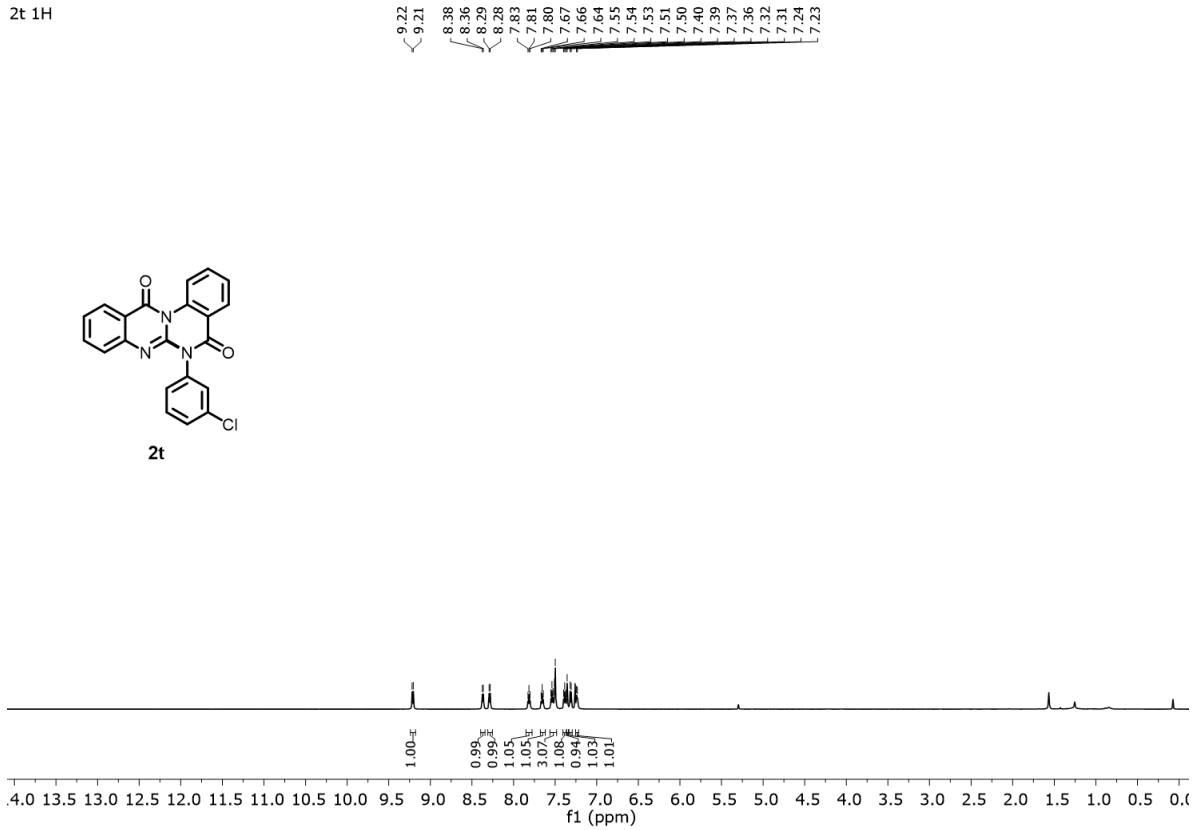
^{13}C in $CDCl_3$ 150 MHz 2s



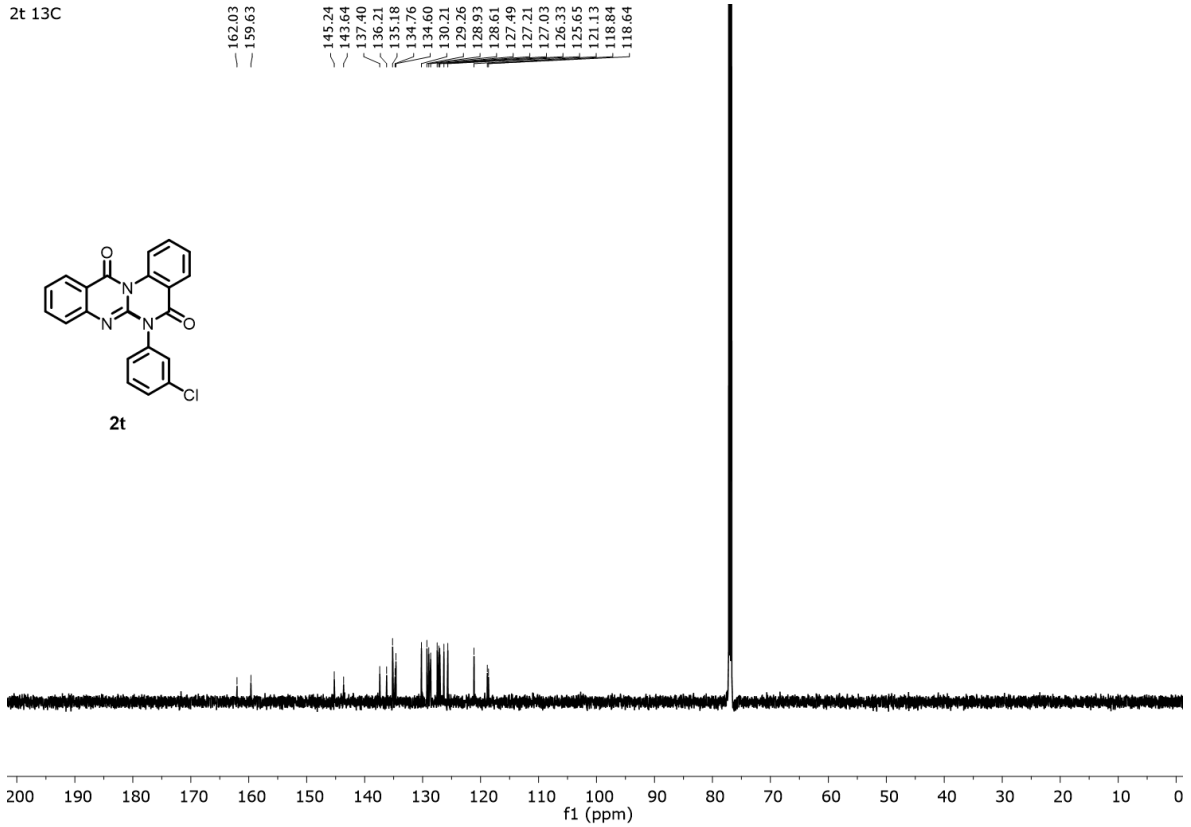
^{19}F in $CDCl_3$ 400 MHz 2s



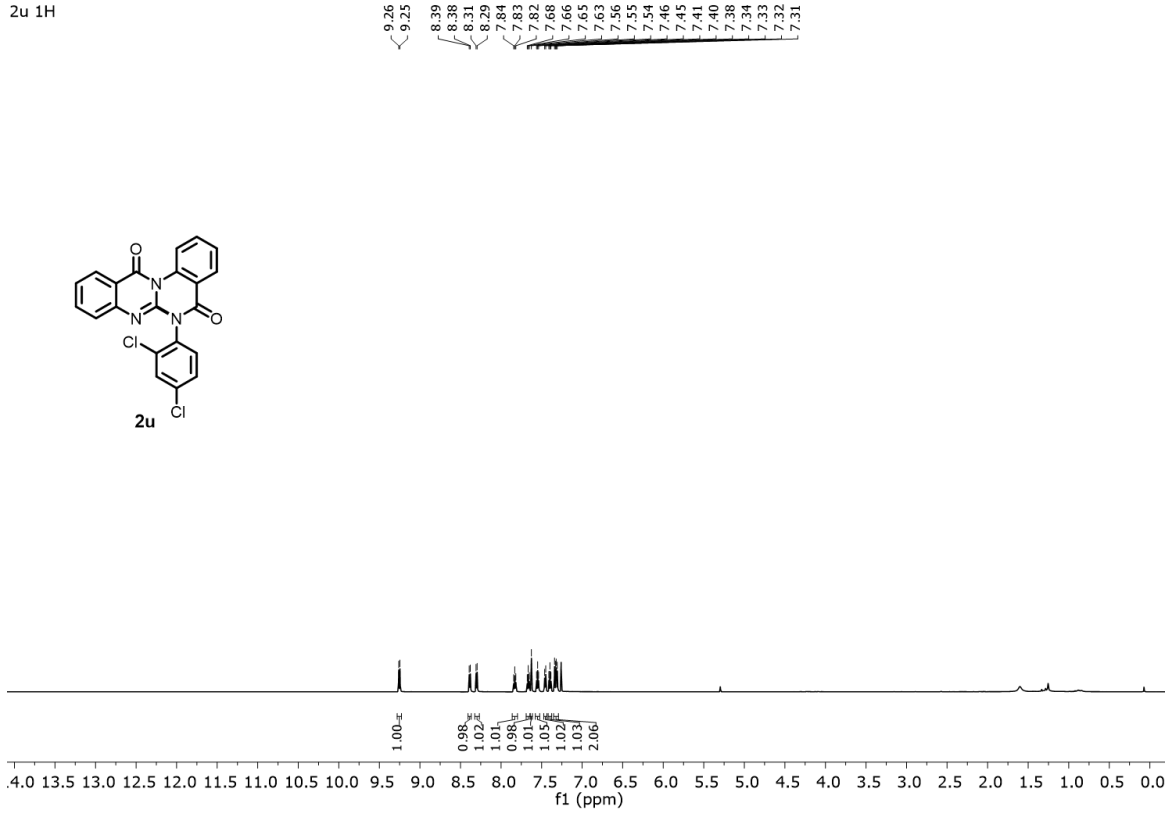
^{1}H in $CDCl_3$ 600 MHz 2t



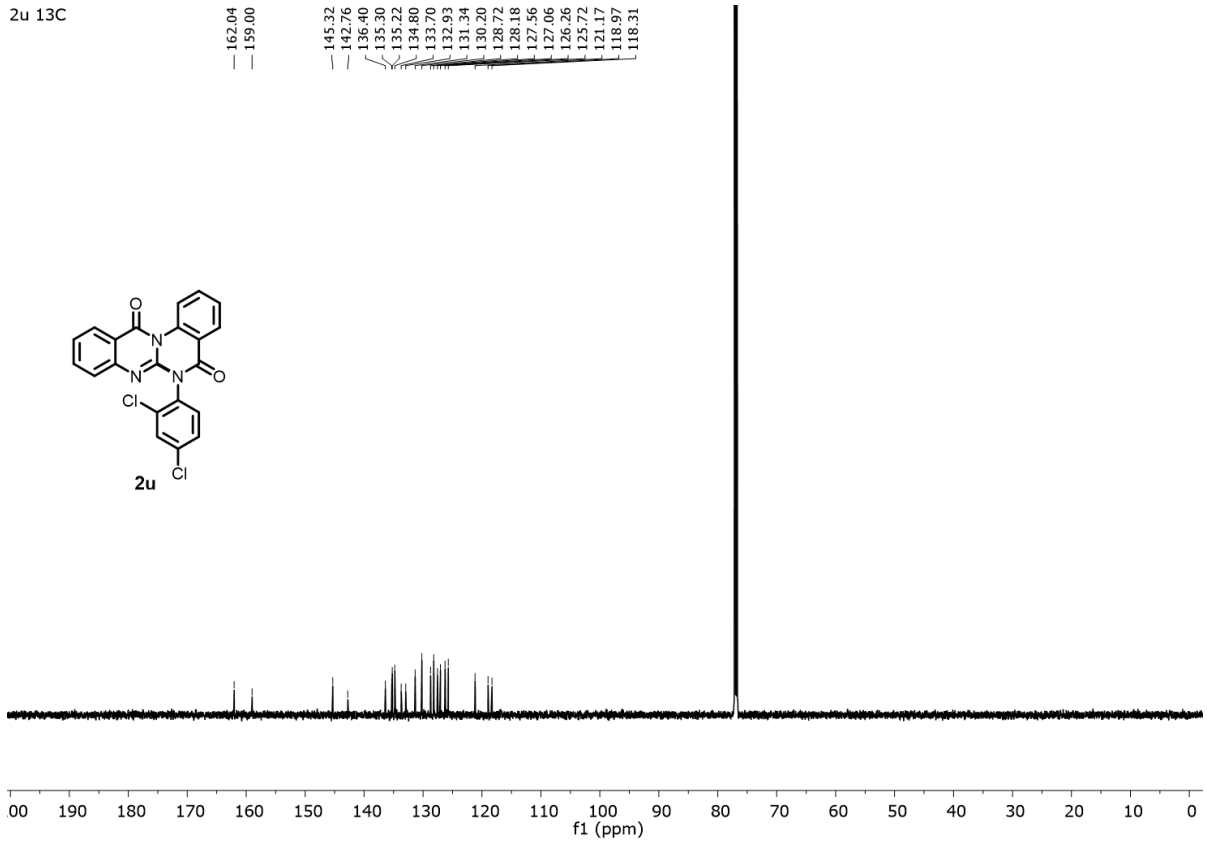
^{13}C in $CDCl_3$ 150 MHz 2t



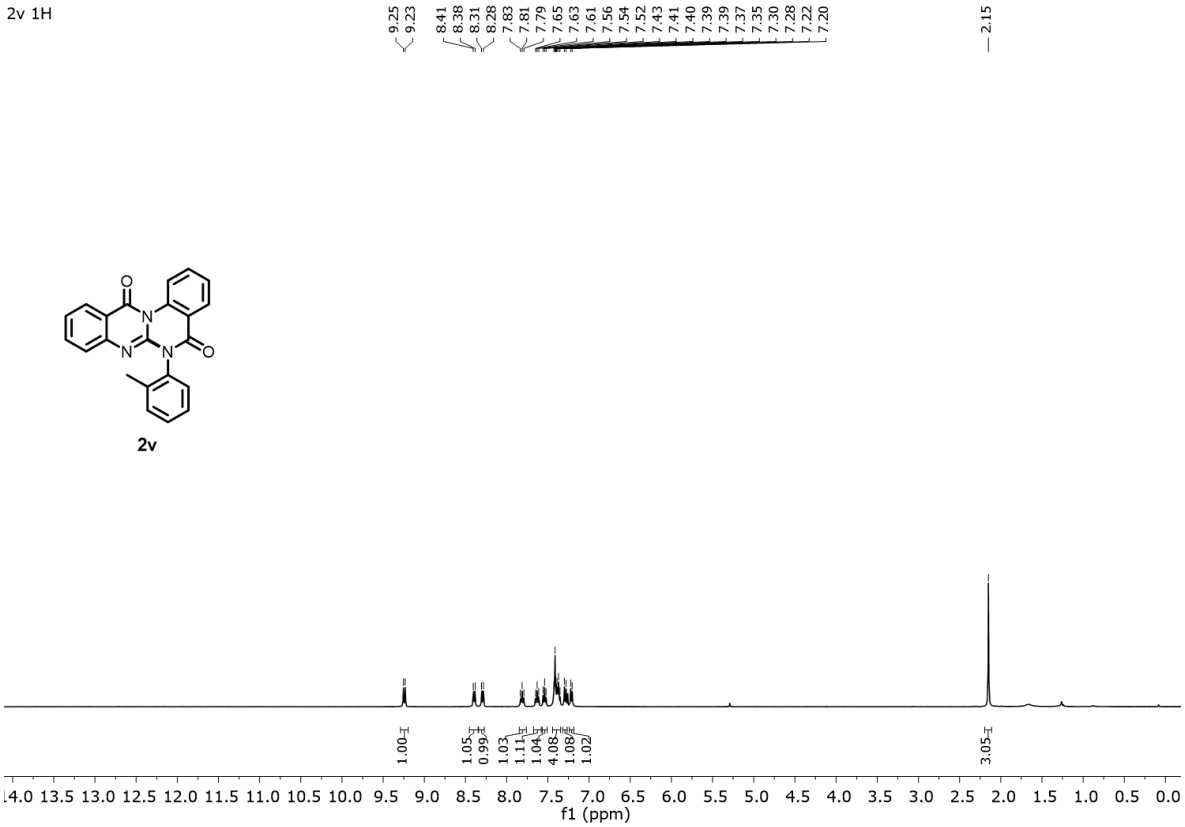
^{1}H in $CDCl_3$ 600 MHz 2u



^{13}C in $CDCl_3$ 150 MHz 2u

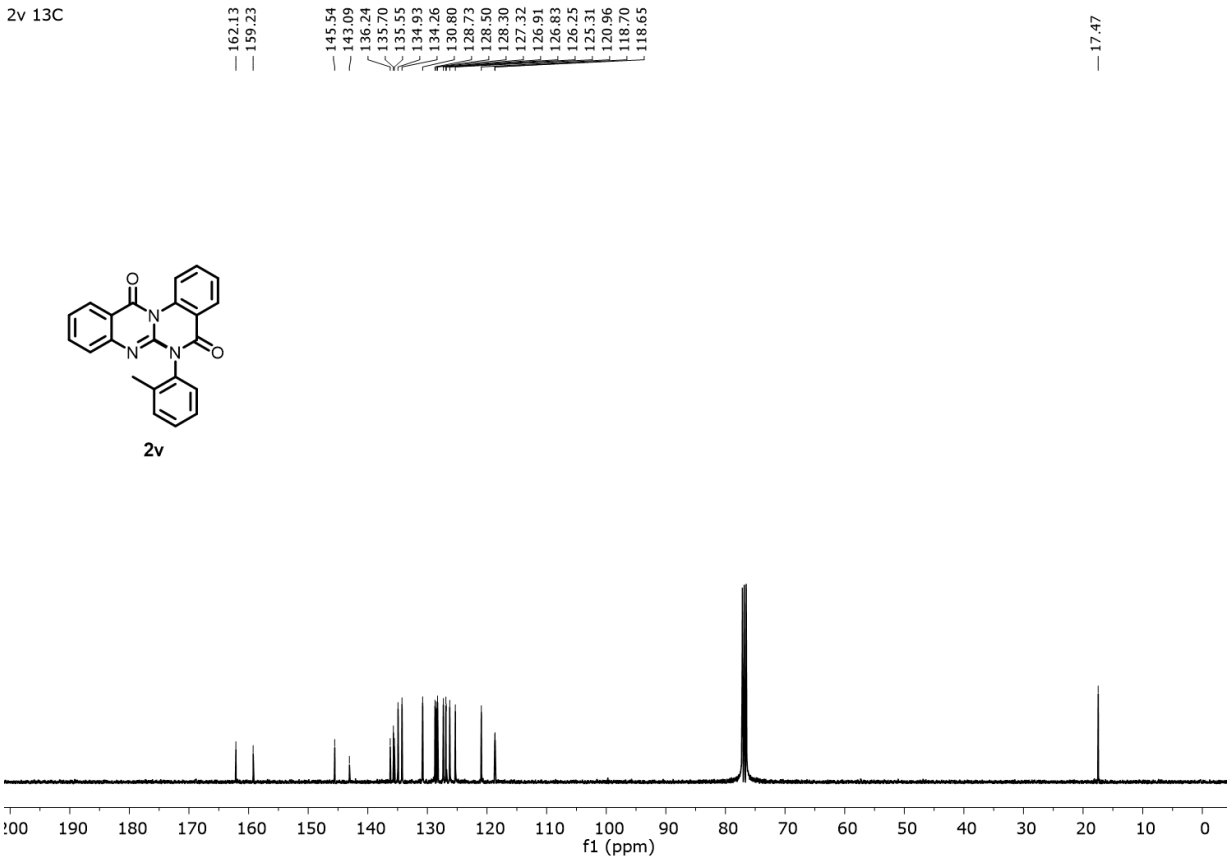


^{1}H in $CDCl_3$ 600 MHz 2v



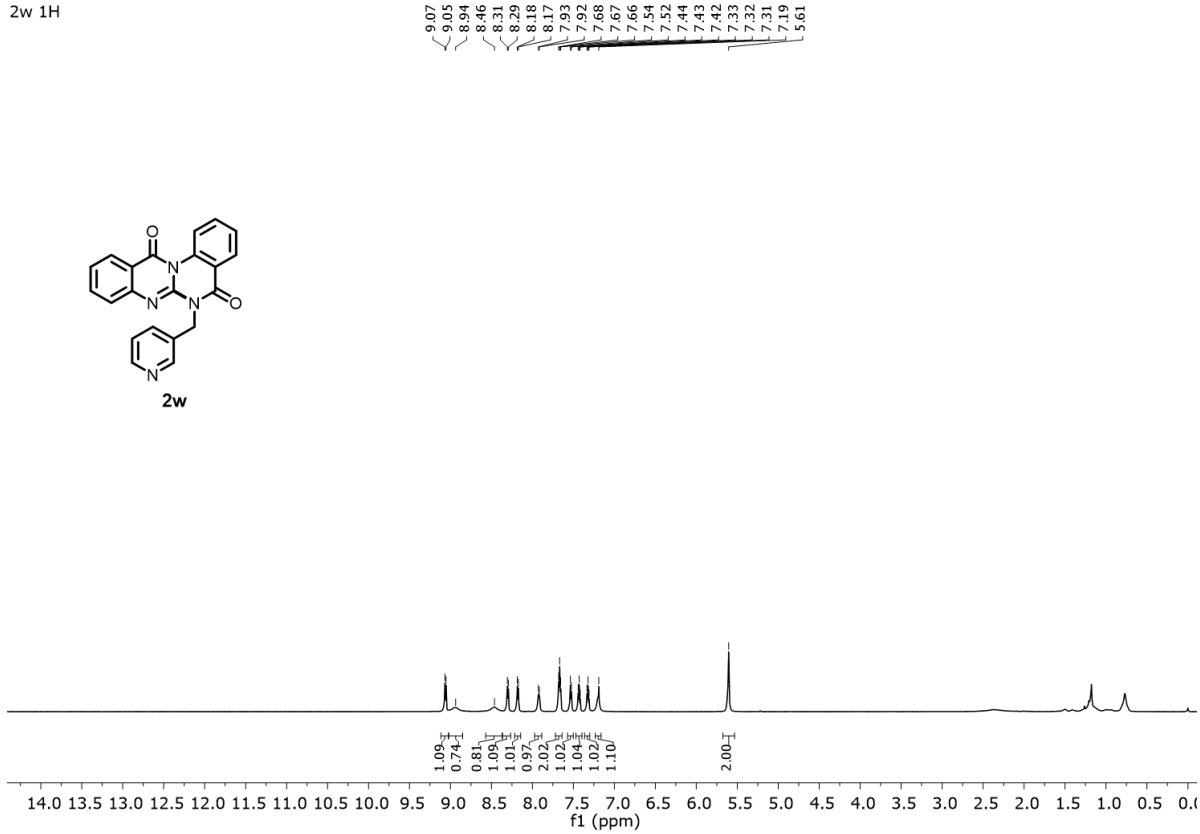
2v

^{13}C in $CDCl_3$ 150 MHz 2v

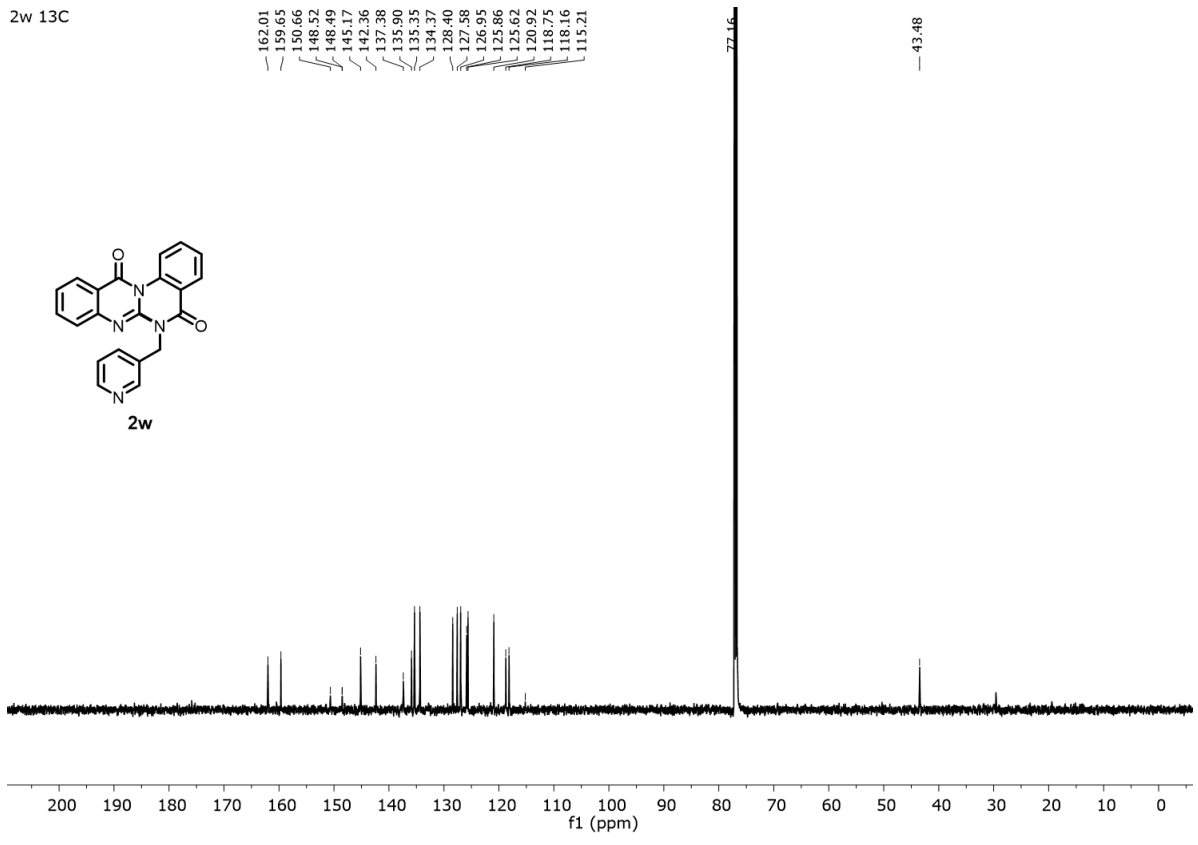


2v

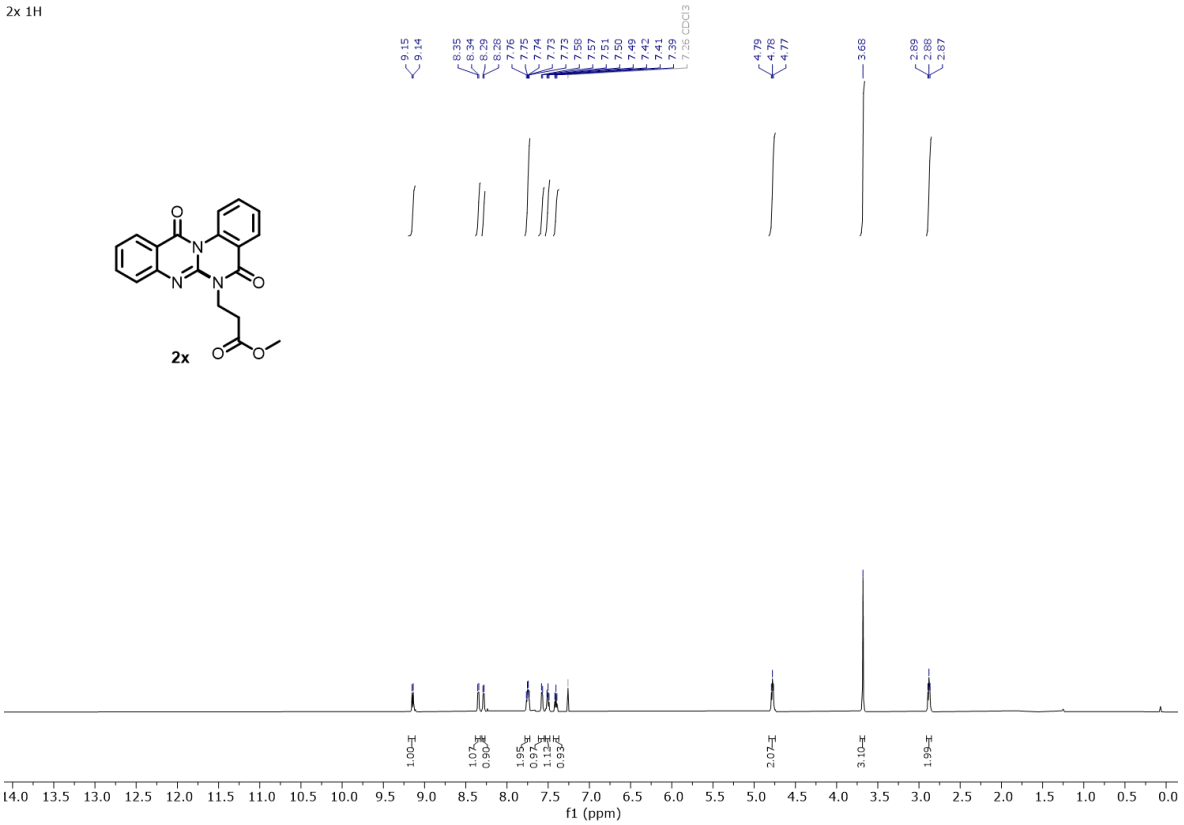
^{1}H in $CDCl_3$ 600 MHz 2w



^{13}C in $CDCl_3$ 150 MHz 2w



^{1}H in $CDCl_3$ 600 MHz 2x



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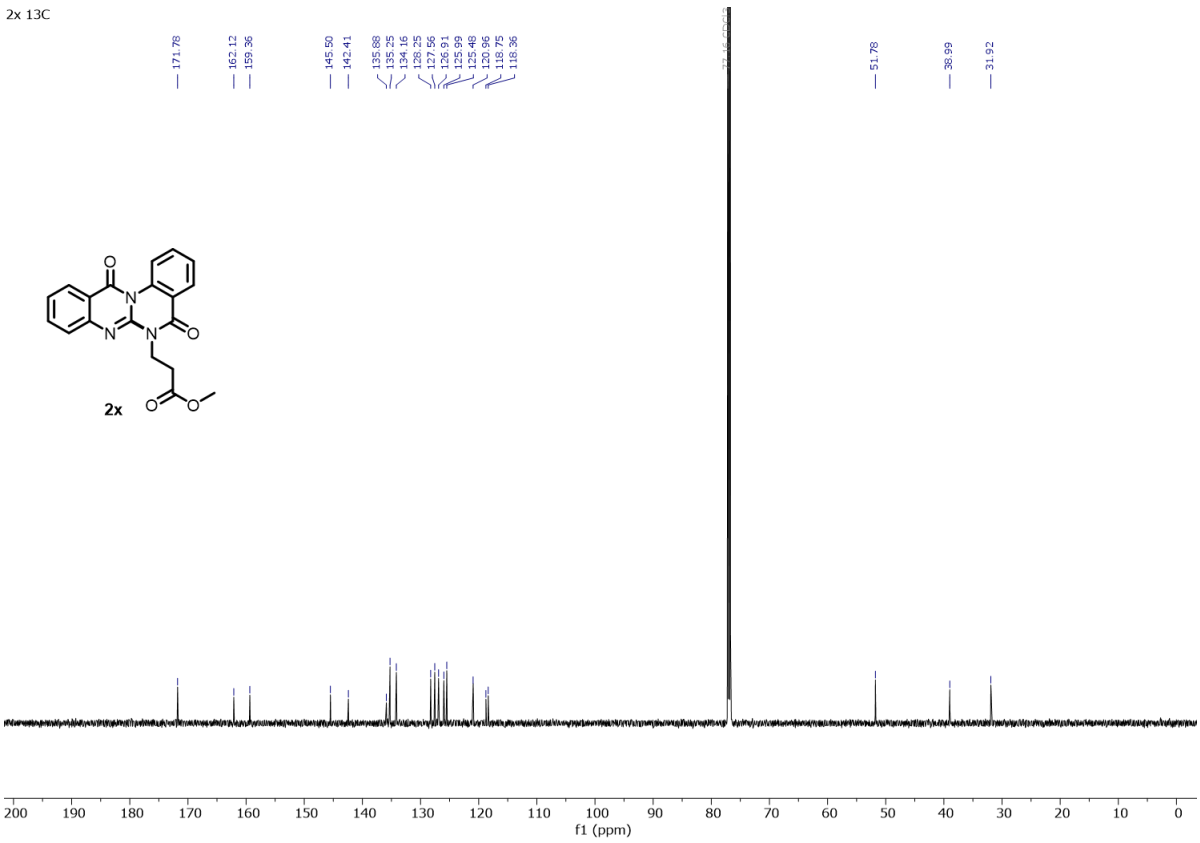
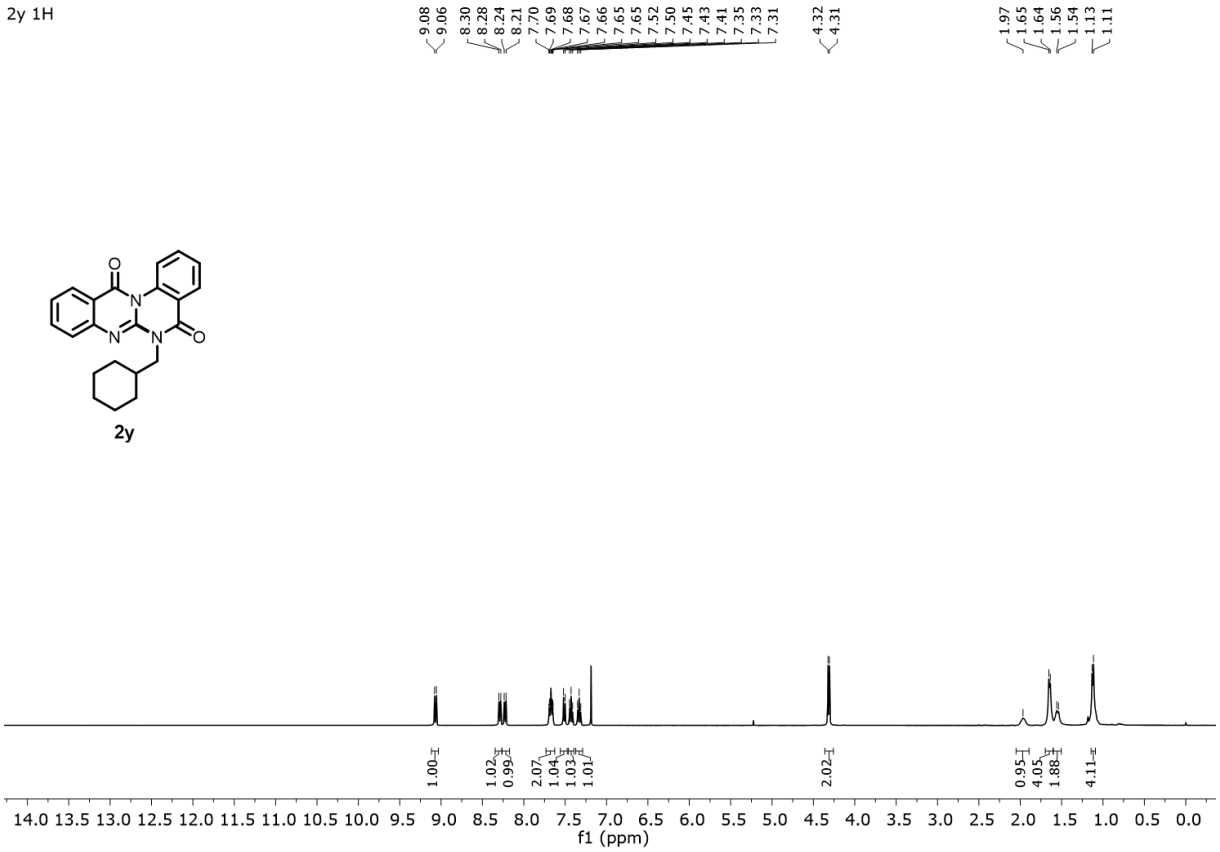


^{1}H in $CDCl_3$ 600 MHz 2y



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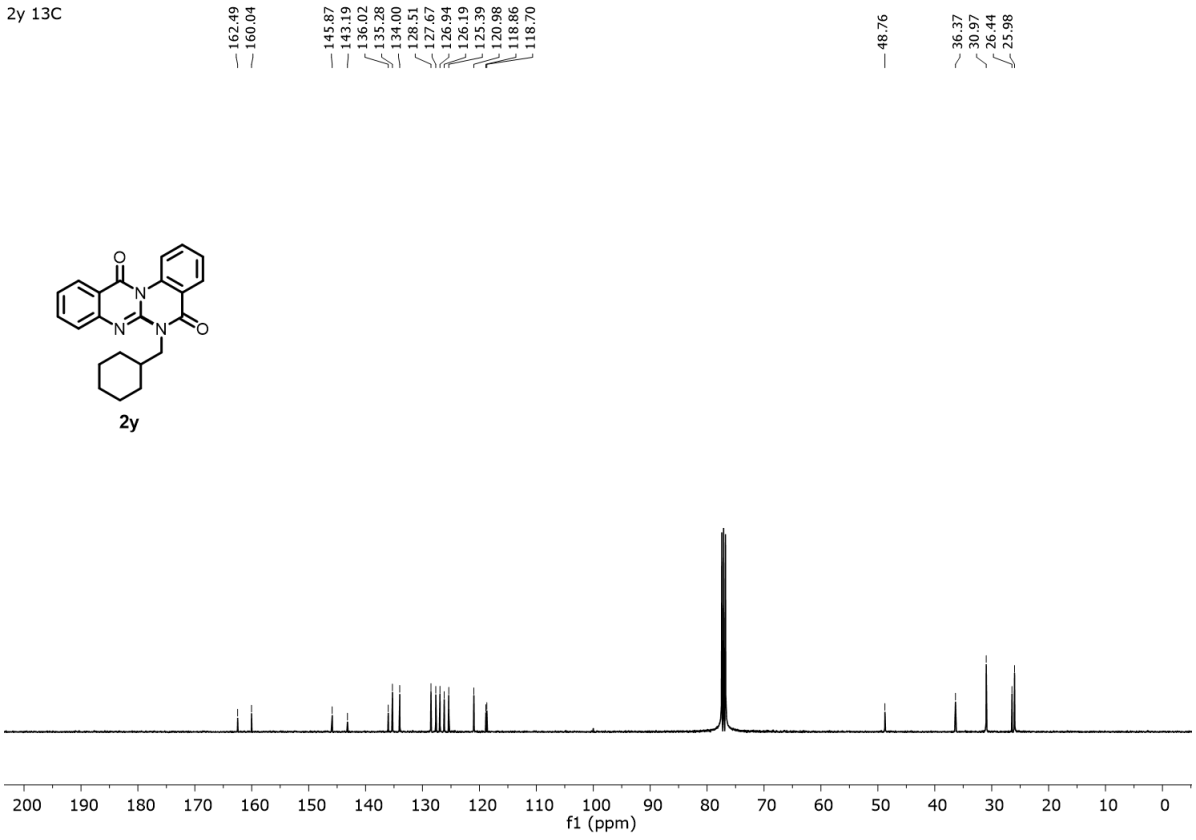
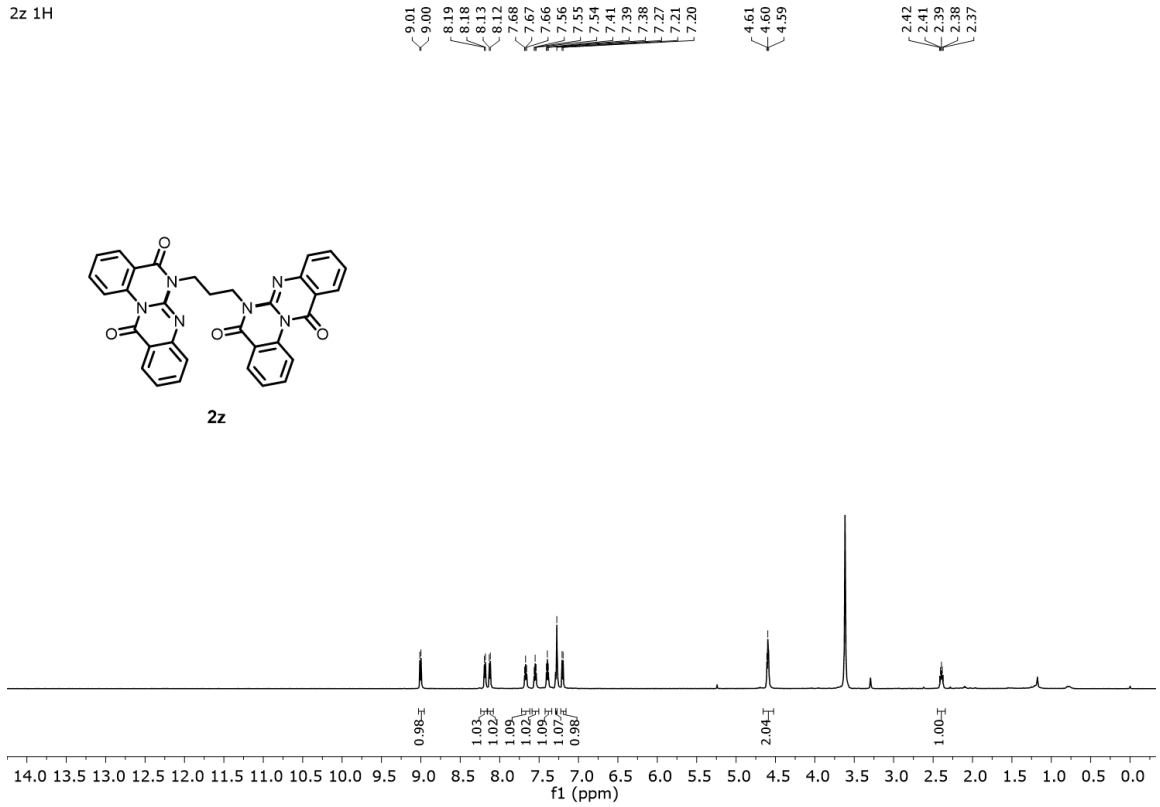
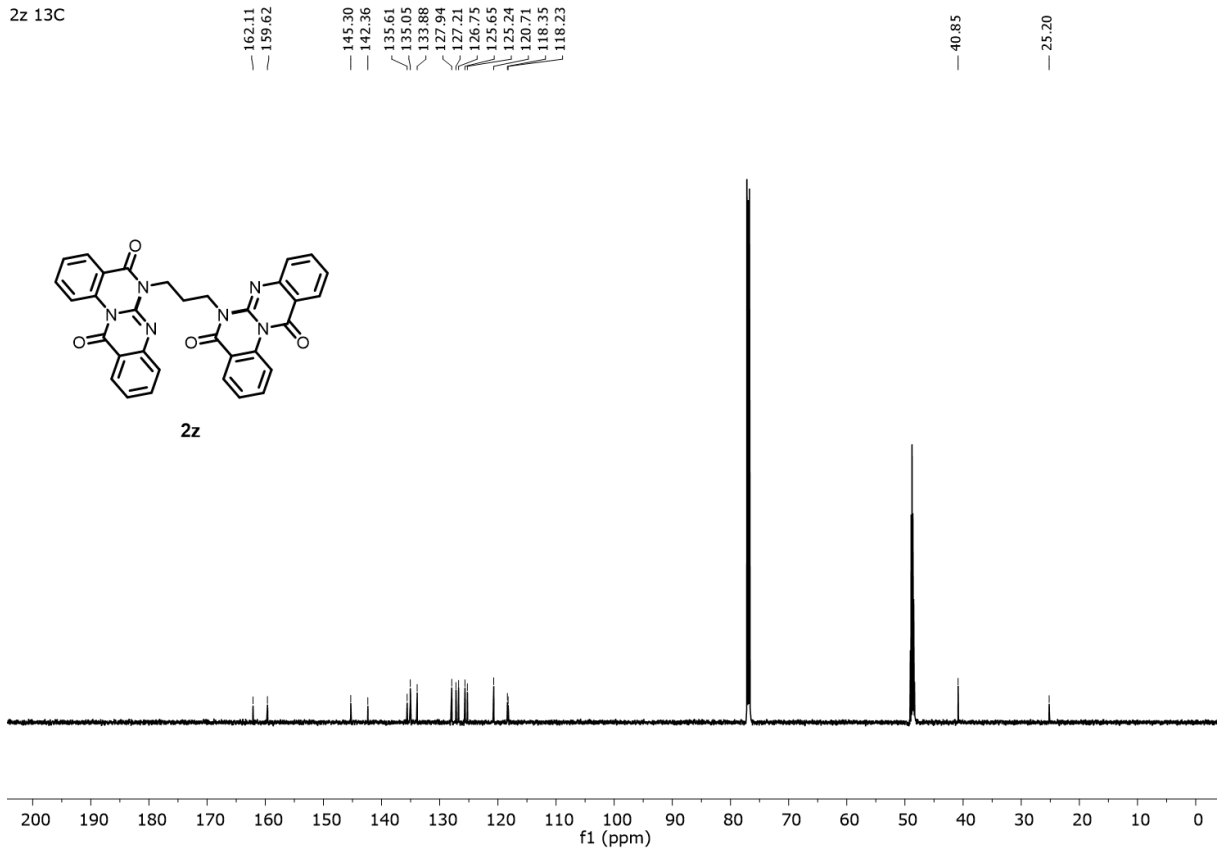


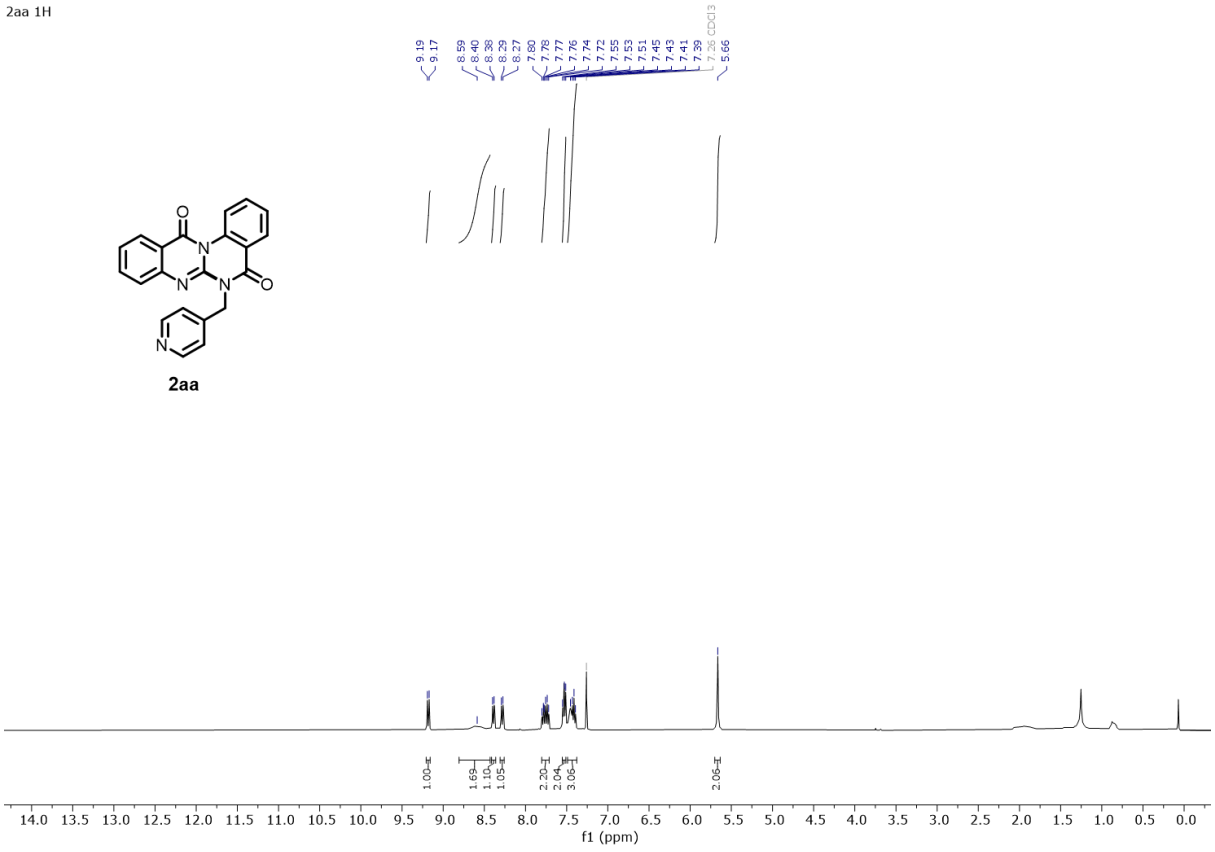
^{1}H in $CDCl_3$ + MD_3OD 600 MHz 2z



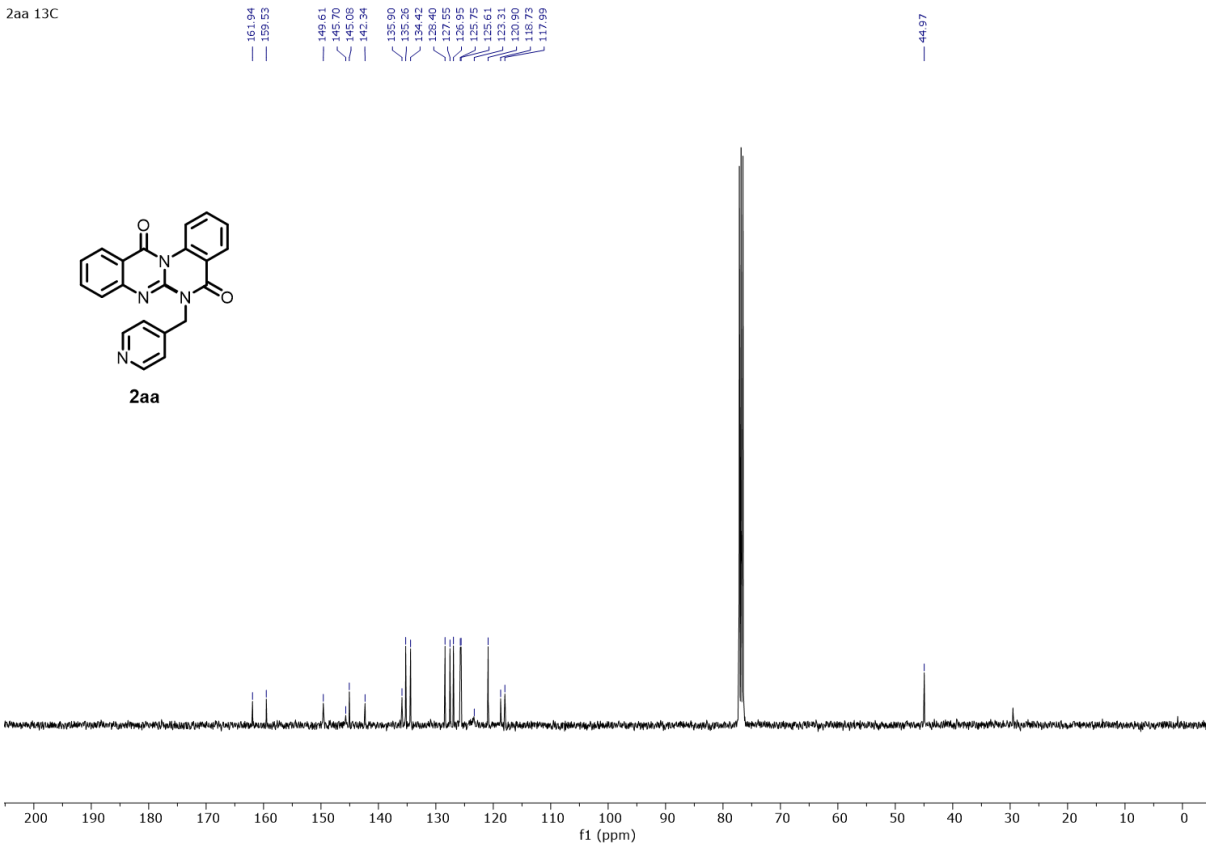
^{13}C in $CDCl_3$ + MD_3OD 600 MHz 2z



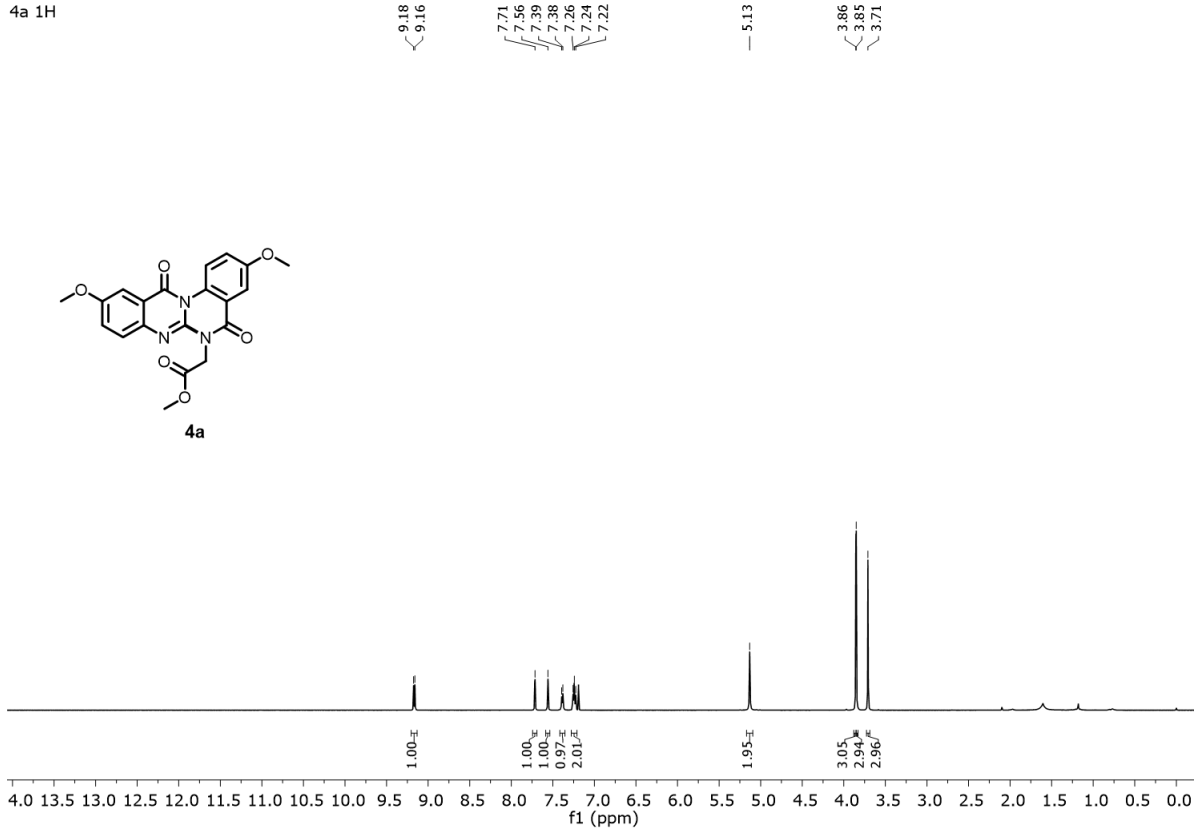
^{1}H in $CDCl_3$ 600 MHz 2aa



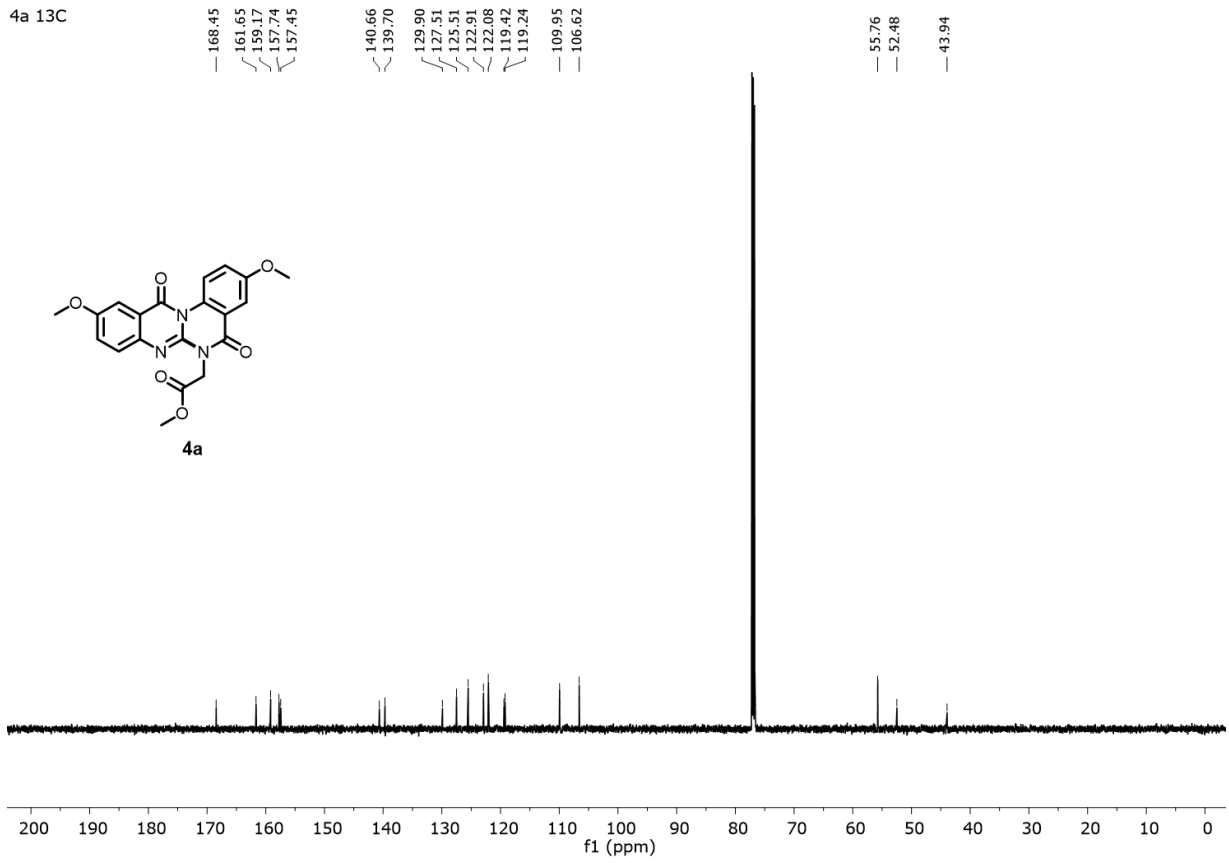
^{13}C in $CDCl_3$ 150 MHz 2aa



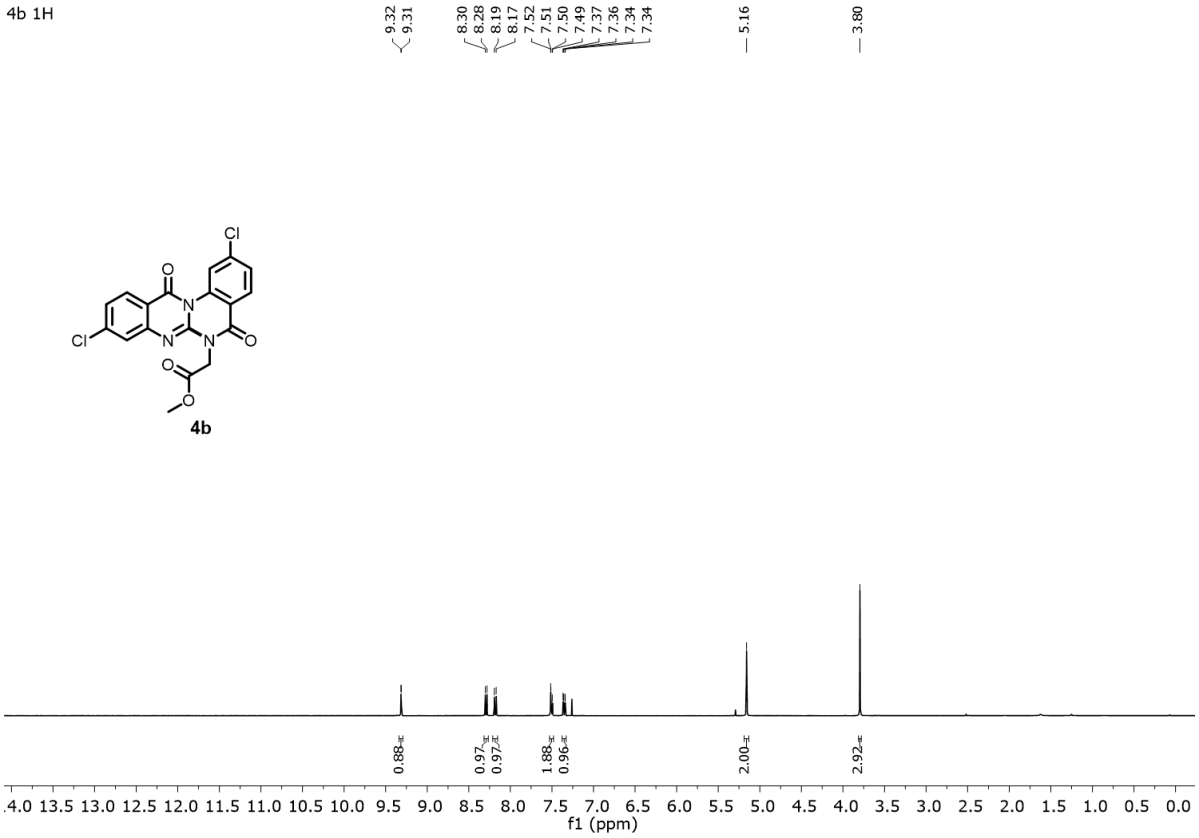
^{1}H in $CDCl_3$ 600 MHz 2ab



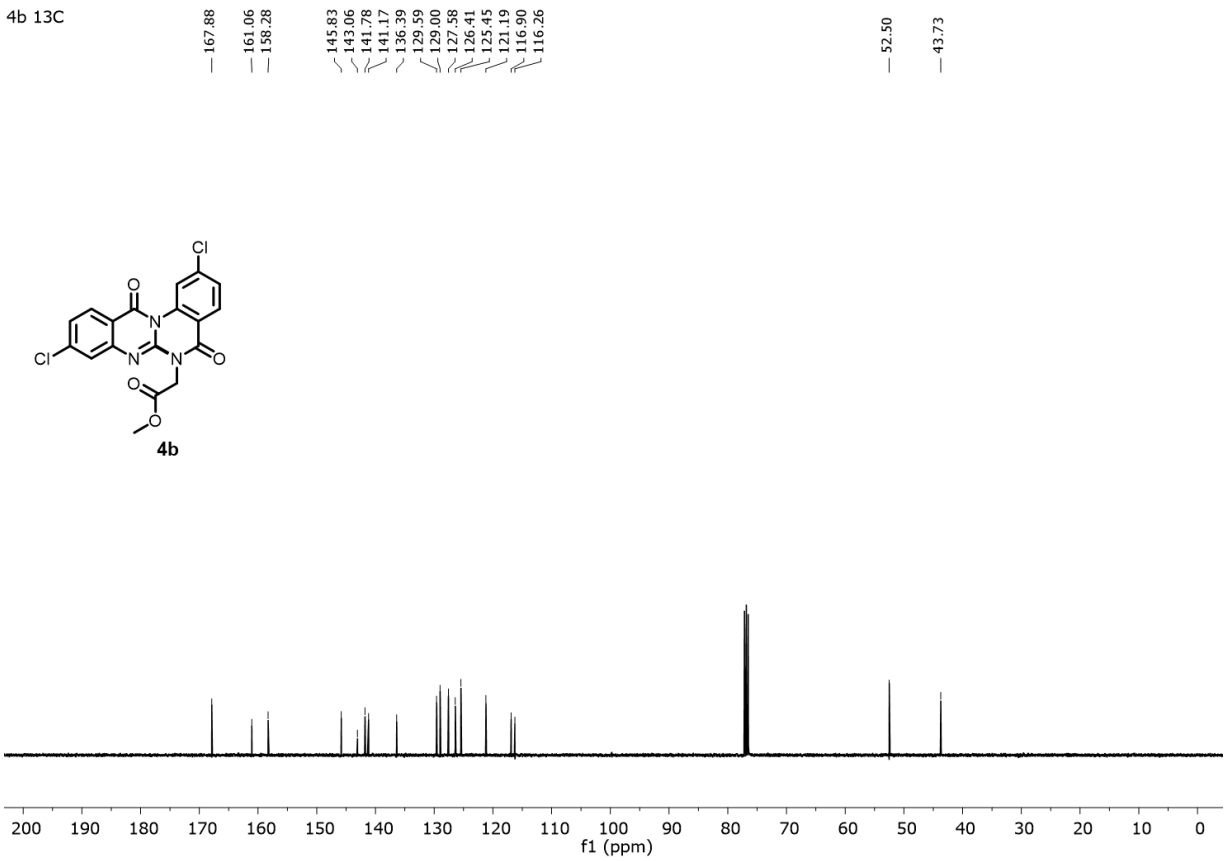
^{13}C in $CDCl_3$ 150 MHz 2ab



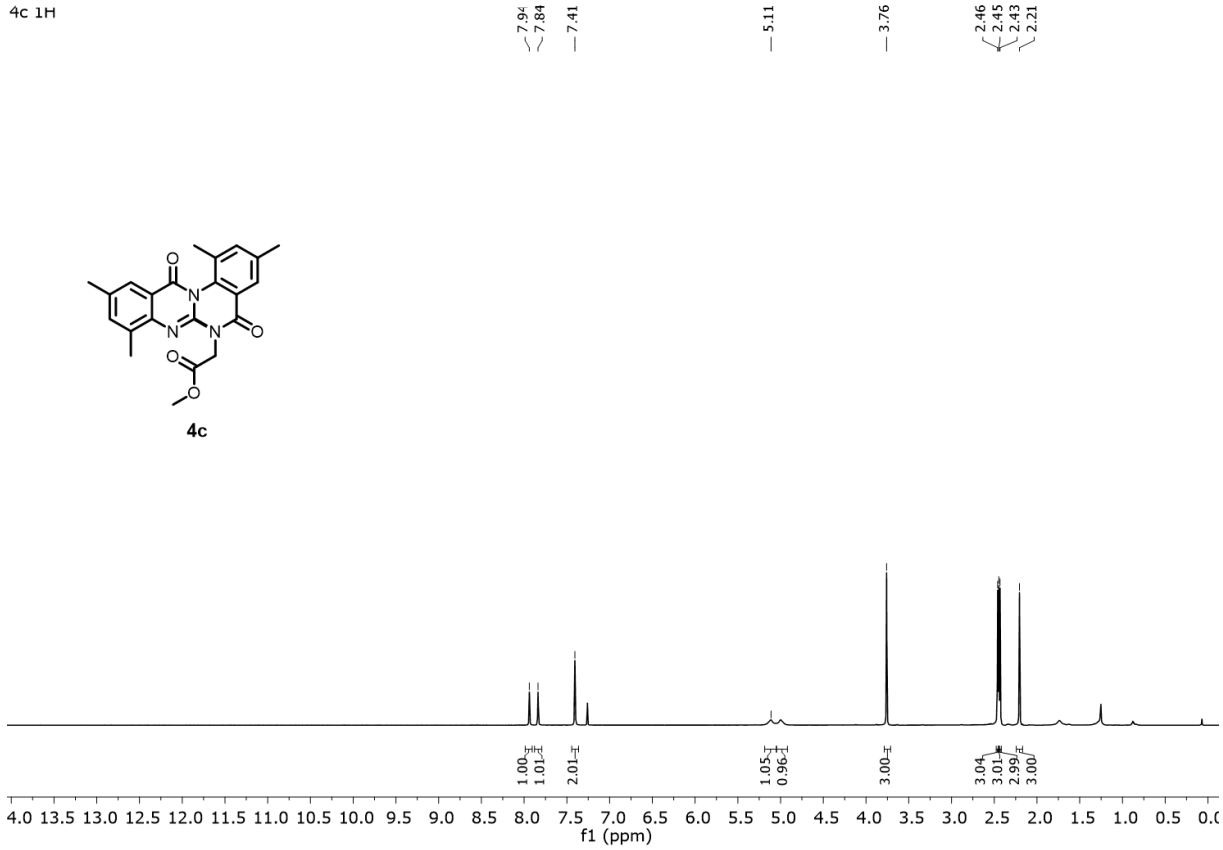
^{1}H in $CDCl_3$ 600 MHz 2ac



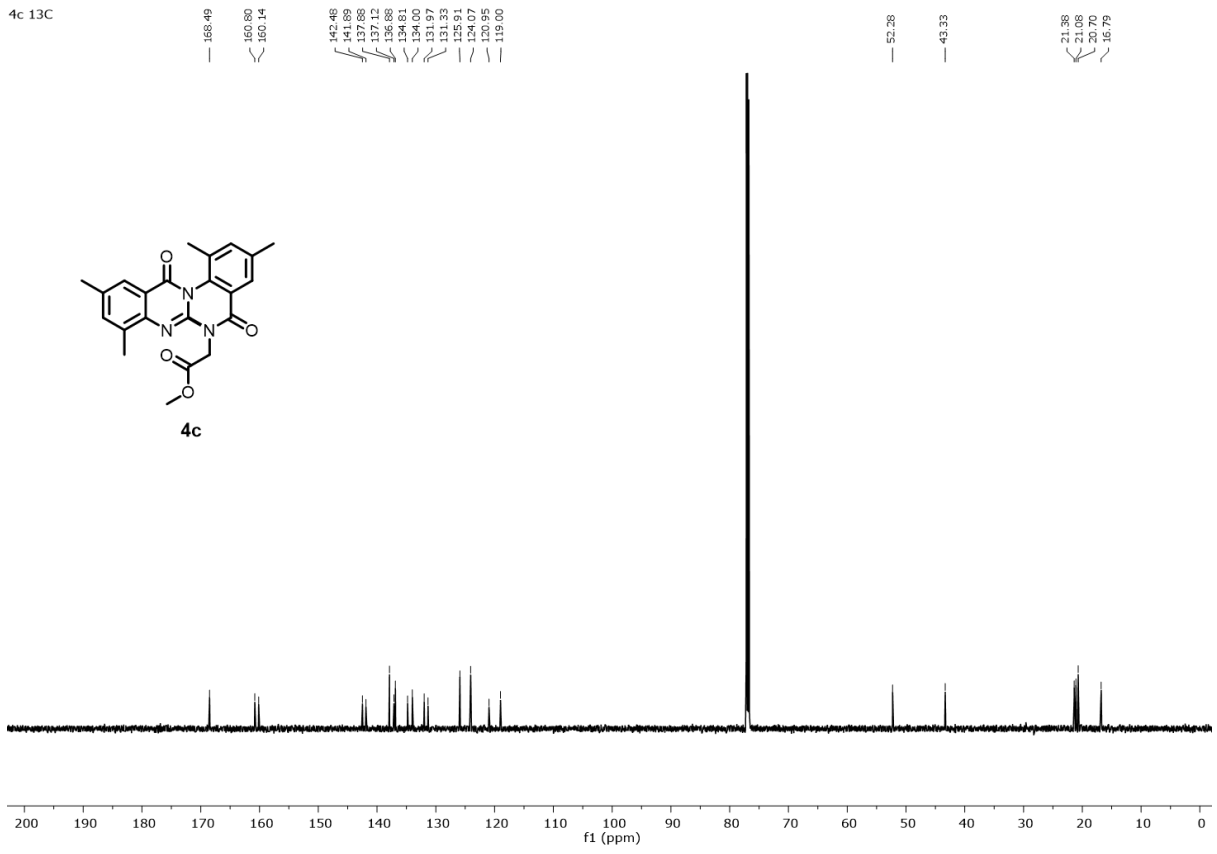
^{13}C in $CDCl_3$ 150 MHz 2ac



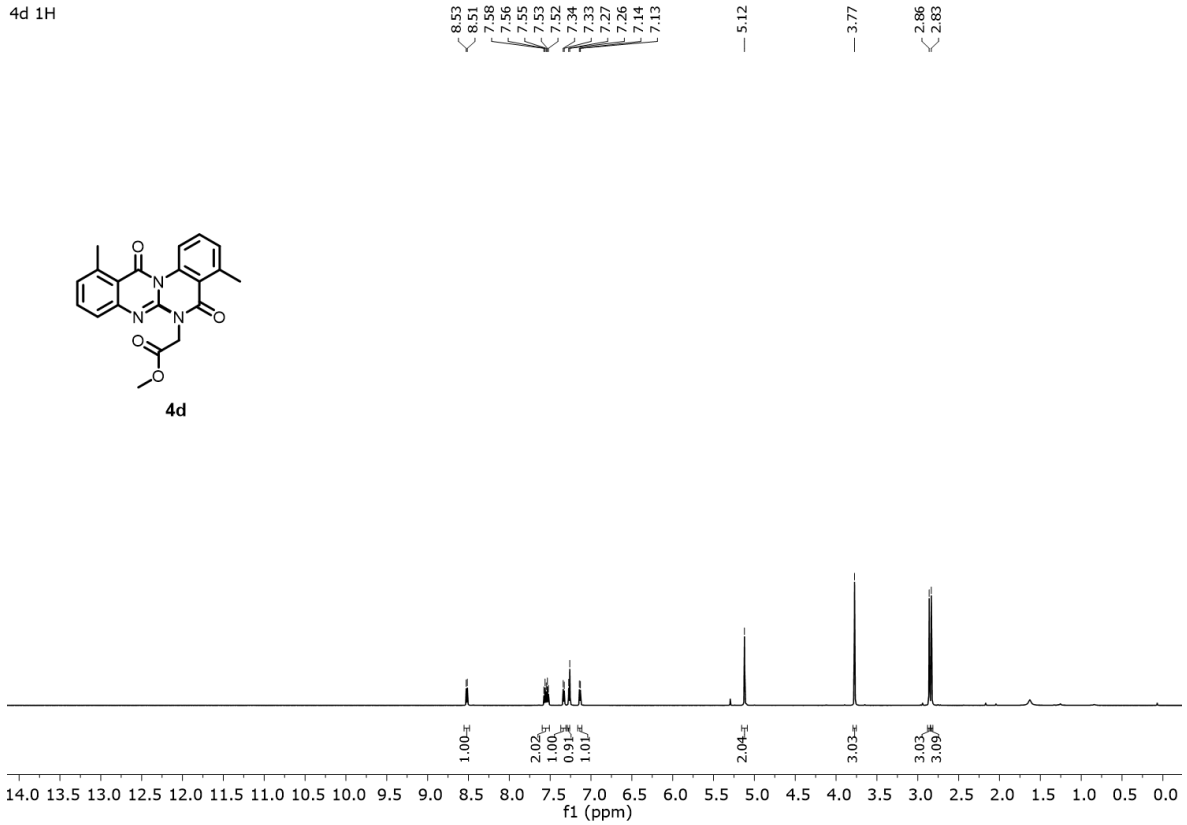
^{1}H in $CDCl_3$ 600 MHz 2ad



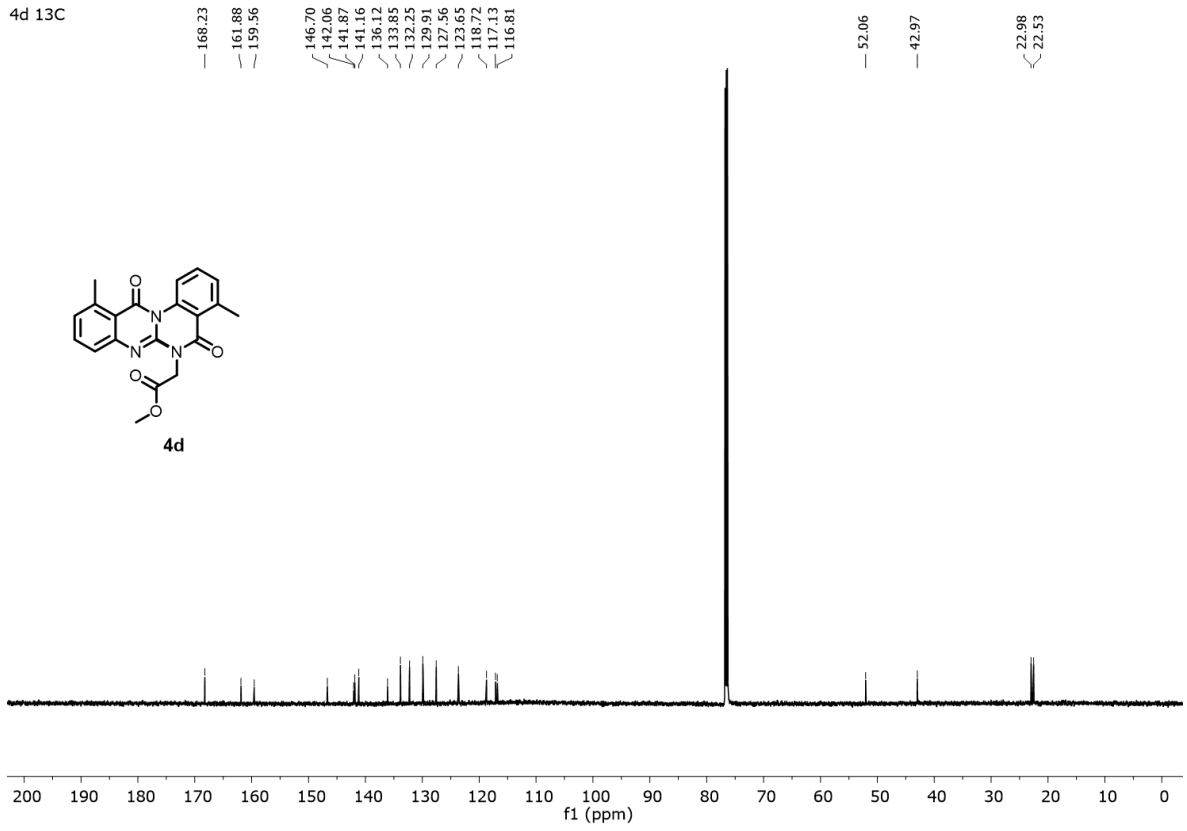
^{13}C in $CDCl_3$ 150 MHz 2ad



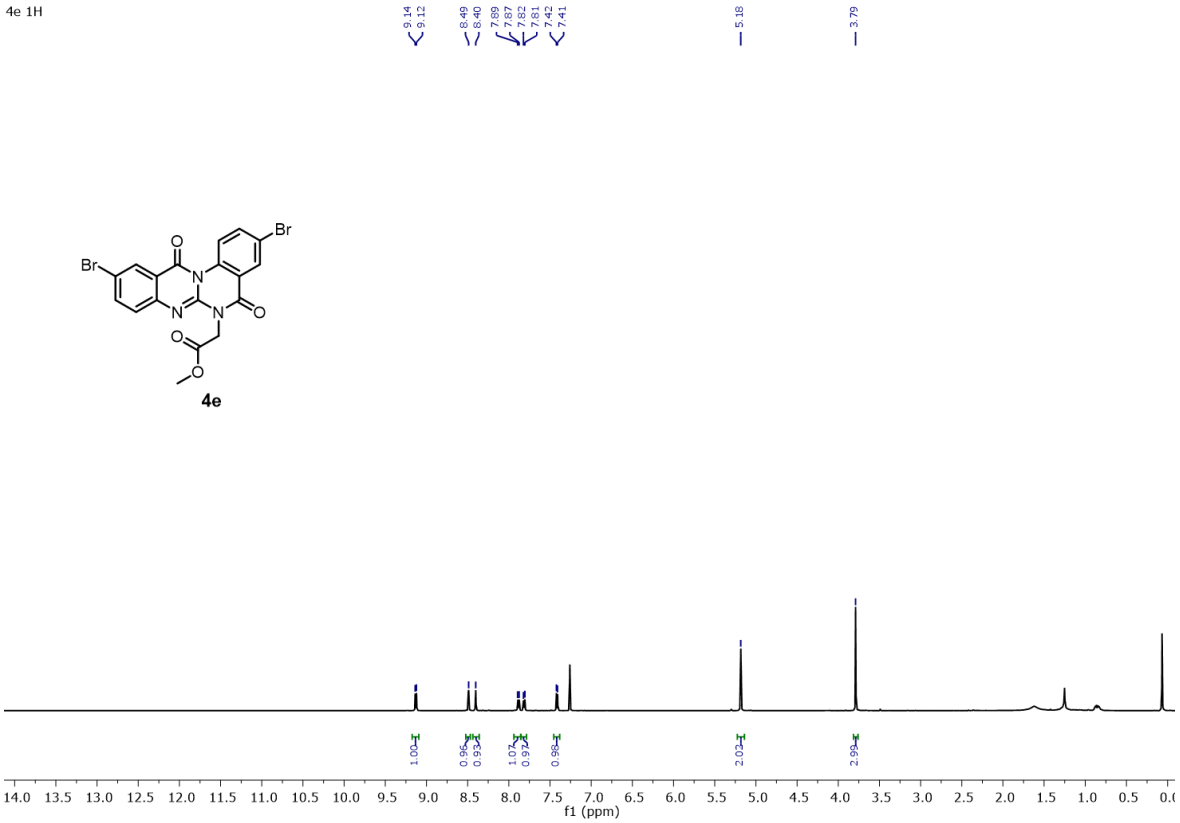
^{1}H in $CDCl_3$ 600 MHz 2ae



^{13}C in $CDCl_3$ 150 MHz 2ae



^{1}H in $CDCl_3$ 600 MHz 2af



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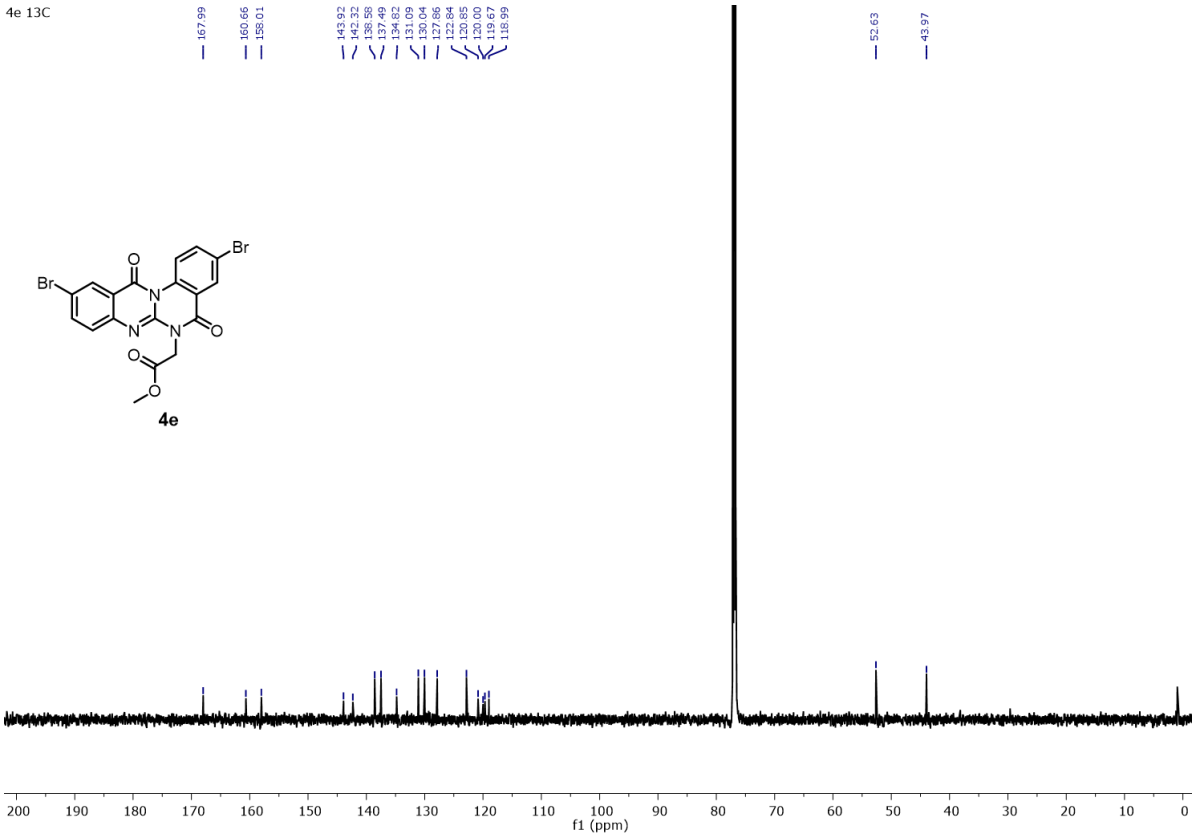
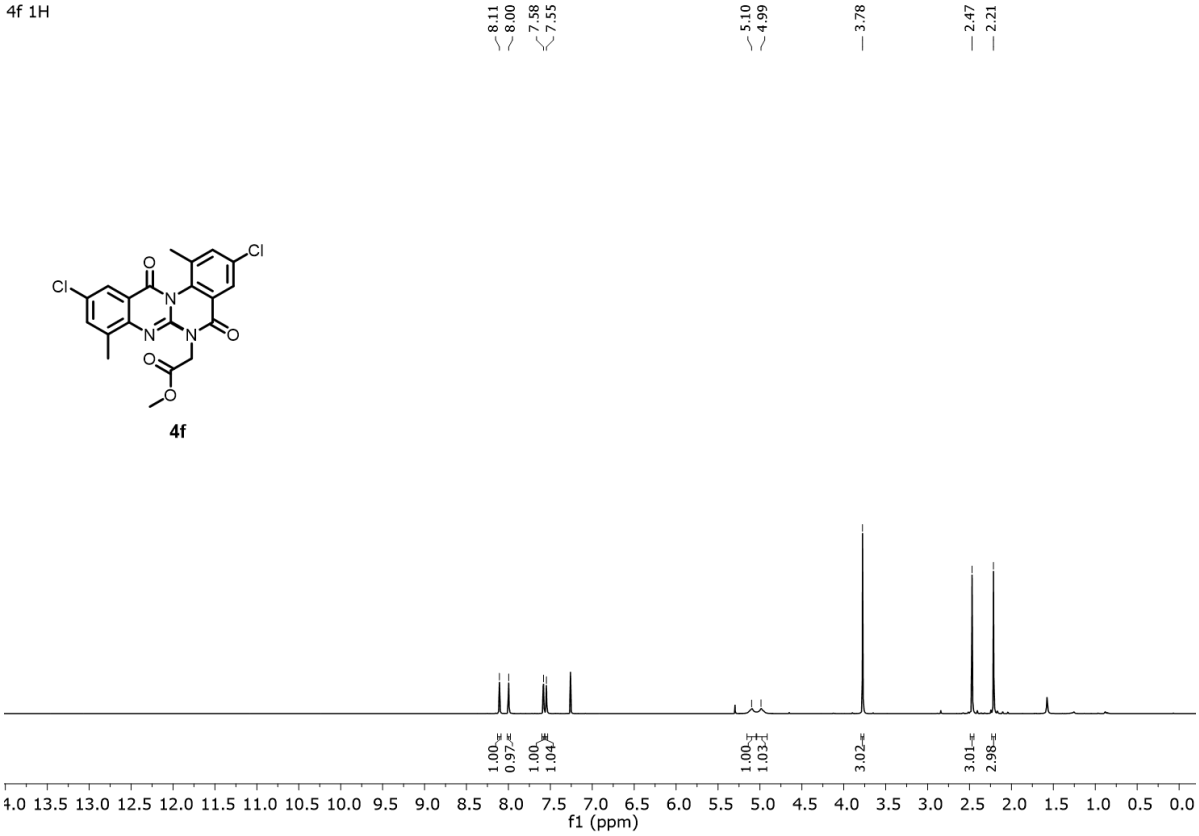
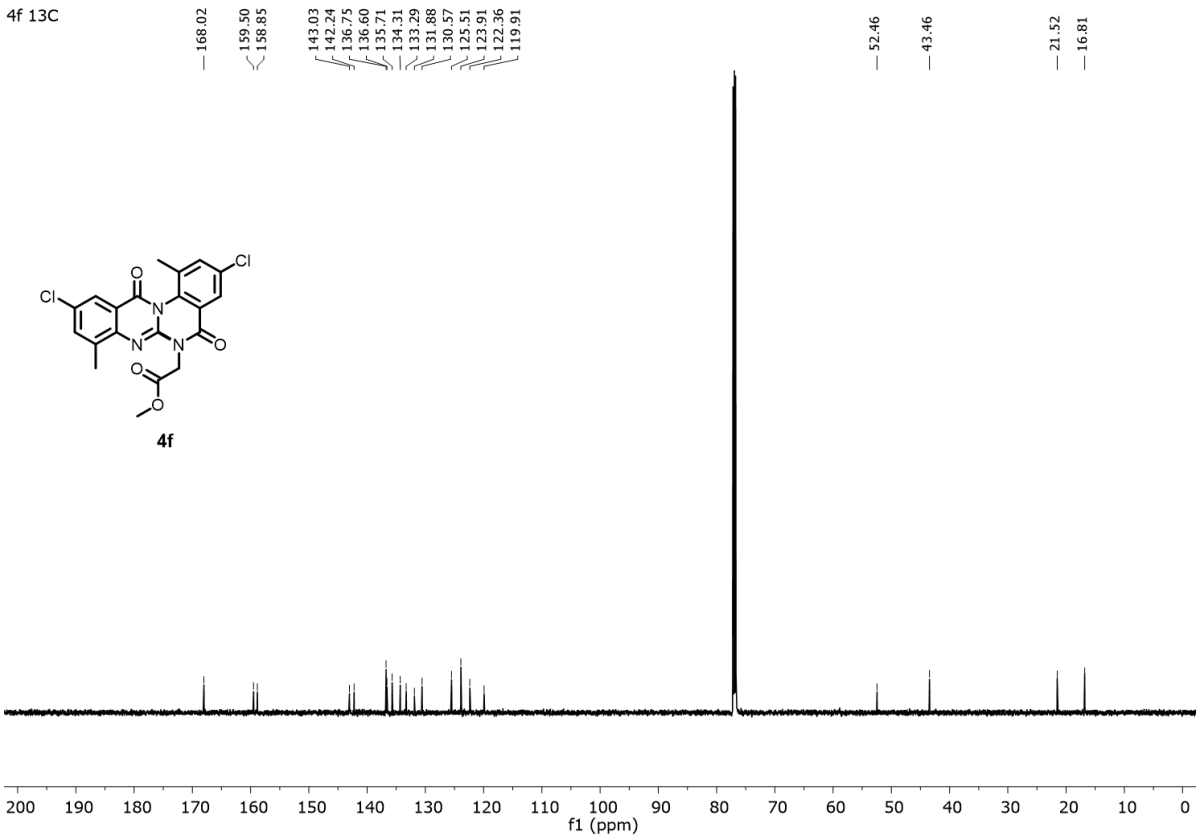


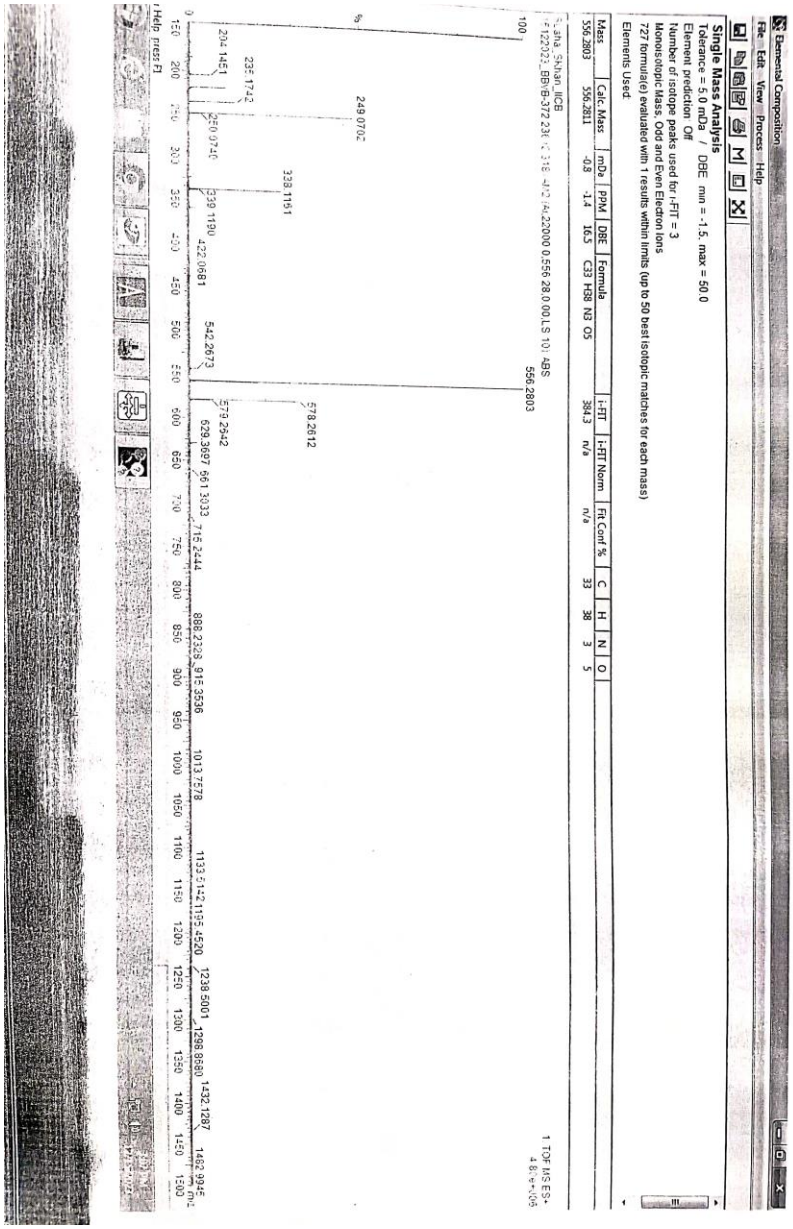
^{1}H in $CDCl_3$ 600 MHz 2ag



^{13}C in $CDCl_3$ 150 MHz 2ag



14. Mass spectra of BHT adduct 2a’



15. References

(1) (a) P. S. Mahajan and S. B. Mhaske, *Organic Letters*, 2018, **20**, 2092–2095. (b) S. L. Cao, M. Zhang, Y. P. Feng, Y. Y. Jiang and N. Zhang, *Synthetic Communications*, 2008, **38**, 2227–2236.