Catalyst-Free Facile Synthesis of Polycyclic Indole/Pyrrole Substituted-1,2,3-triazoles

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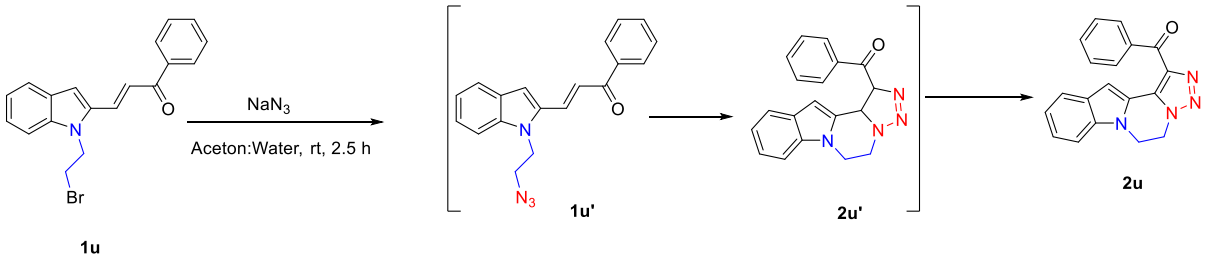
ESI/MS experiments:

ESI/MS experiments were performed to gain evidence for the possible intermediates in the proposed mechanism. The experiment was conducted under the optimal reaction condition and the reaction was monitored after 1.5 h. The ESI/MS analyses showed a peak of intermediates, which was identified as a triazoline species. We tried to isolate and characterize the intermediate. We could not isolate dihydrotirazole, only we were able to isolate 1u' under optimized reaction condition. We characterized and included NMR spectrum of compound **1u'**.



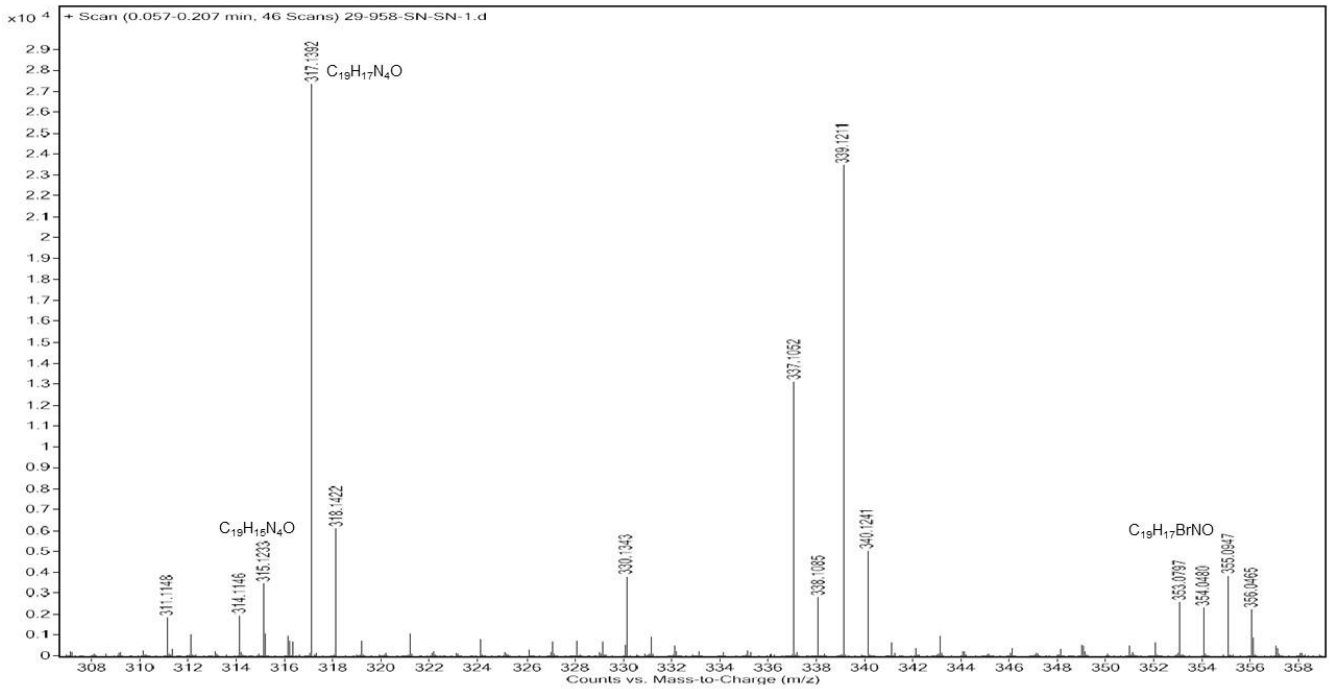
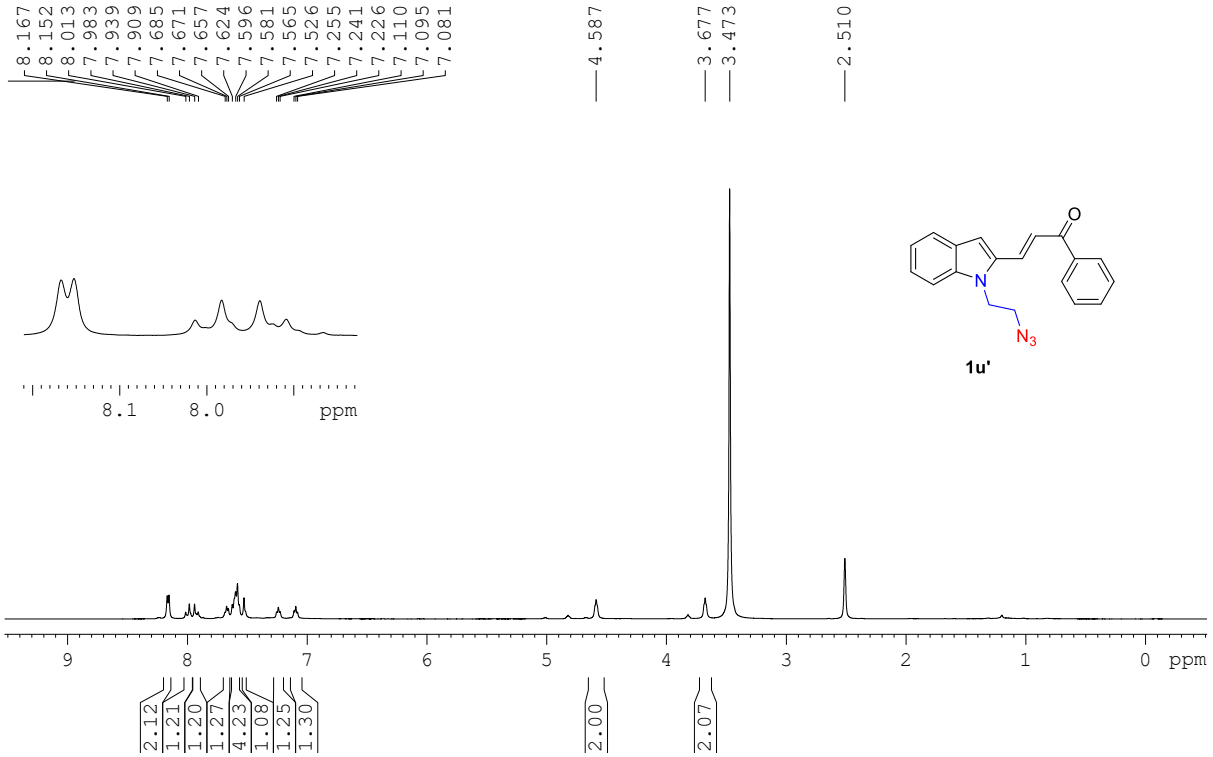
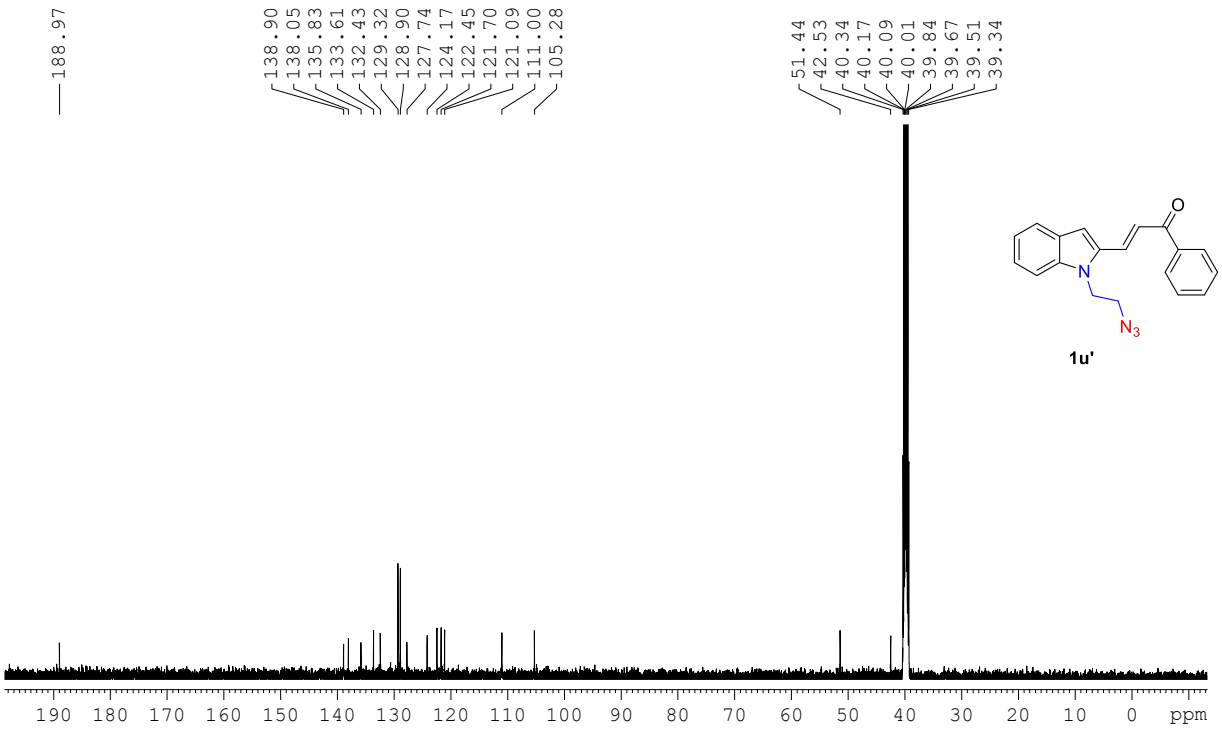


Figure S1: ESI/MS spectra



^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1u'**



^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1u'**

Determination of rate limiting step

The reaction of **1u** (0.1 mmol) and sodium azide (0.13 mmol) was carried out in NMR tube using DMSO-d_6 as a solvent. The reactions were conducted for the specified time (such as 15 min, 30 min, 1 h, 2 h, 3 h, 6 h, 10 h and 20 h), then the progress of the reaction was monitored by ^{1}H NMR spectroscopy. Conversion of **1u** to **1u'** (replacement of bromo to azide) which is giving the corresponding cyclized product (**2u**) was estimated by the relative integration of aliphatic proton(**1u**: 4.82,3.82, **1u'**: 4.59, 3.68 and **2u**: 5.04, 4.69) and α, β-unsaturated ketone protons. The results were listed in figure S2. We observed that the intramolecular azide-alkene cycloaddition is slower than bromo to azide formation (**1u** to **1u'**). Based on the result of figure S2, it may be concluded that the intramolecular azide-alkene cycloaddition step is the rate limiting step.

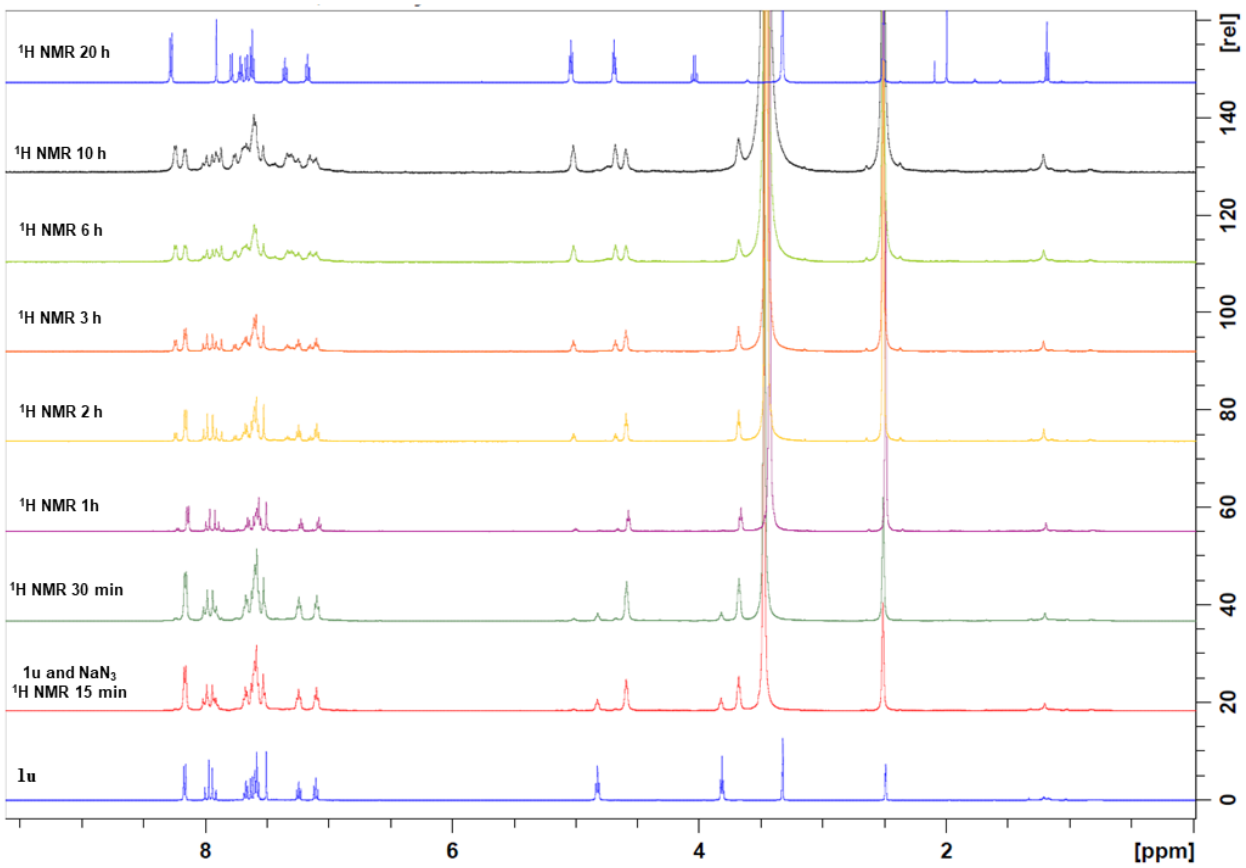
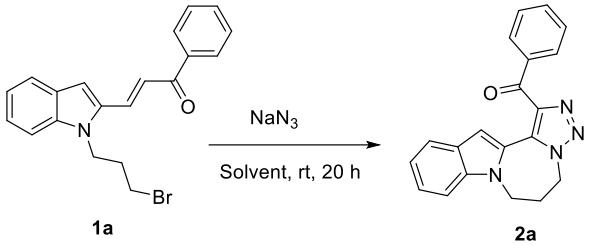


Figure S2: Progress of the reaction (**1u-2u)** monitored by ^{1}H NMR (500 MHz, DMSO-d_6).

Table S1: Screening of solvents[a]



Entry	Catalyst	Solvent	Yield[b](%)
1	None	Chloroform	0
2	None	DMSO	74
3	None	THF	52
4	None	Water	Trace
5	None	Methanol	61
6	None	Ethanol	64
7	None	Water: Methanol (2:1)	Trace
8	None	Water: Methanol (1:1)	11
9	None	Water: Ethanol (1:1)	Trace
10	None	Acetone	60
11	**None**	**Water: Acetone (1:1)**	**86**
12	None	Water: Acetone (2:1)	26
13[c]	None	Water: Acetone (2:1)	56
14[c]	None	Water: Acetone (1:2)	68
14	None	Water: DMF (1:1)	15
15	None	Water: DMSO (1:1)	0

[a]Reaction conditions: **1a** (0.5 mmol) and NaN_3 (0.6 mmol), solvent (5 mL) and the reaction was performed at room temp for 20 h under air atmosphere. [b]Yield of the products. Reaction was performed at room temp for 36 h under air atmosphere

Materials and Method:

Cell Lines

Multiple human cancer cell lines including HT-29 (colorectal adenocarcinoma), A549 (lung carcinoma), PC-3 (prostate adenocarcinoma), MIA PaCa-2 (Pancreatic Carcinoma) and MCF-7 (breast ductal carcinoma) were obtained from ATCC, USA. Early passage cells were resuscitated from liquid nitrogen vapour stocks as needed and cultured according to the manufacturer's instructions. Cells were routinely inspected microscopically for stable phenotype, and all experiments were performed within early passages (within 10) of individual cells.

Evaluation of *in-vitro* anticancer activity of synthetic compounds by Sulphorhodamine B (SRB) calorimetric assay

Efficacy of the compounds as anticancer agents on various cancer cell lines was assessed using standard Sulphorhodamine B (SRB) calorimetric assay for cytotoxicity screening as described by before.[1,2] Briefly, appropriate number of cells in 5% FBS containing medium were seeded in 96 well plates and incubated at 37 °C in a humidified incubator with 5% CO_2 until the cells attached completely. The cells were treated with a single dose of compounds and were incubated for further 48 hours. After an incubation period, cell monolayers were fixed with 10% (wt/vol) trichloroacetic acid followed by washing under slow running tap water. The cells were stained with SRB dye for 30 minutes, after which the excess dye was removed by washing 3-4 times with 1% (vol/vol) acetic acid. The protein-bound dye is dissolved in 10 mM Tris base solution for OD determination at 510 nm using a microplate reader (Epoch Microplate Reader, Biotek, USA). Percentage of cell growth inhibition was calculated using the formula [100-(Absorbance of compound treated cells/ Absorbance of control cells)] X 100.[2]

References

1. Vichai, V.; Kirtikara, K., Sulforhodamine B colorimetric assay for cytotoxicity screening. *Nat. Protoc.* **2006,** *1* , 1112.
2. Maheshwari, S.; Avula, S. R.; Singh, A.; Singh, L. R.; Palnati, G. R.; Arya, R. K.; Cheruvu, S. H.; Shahi, S.; Sharma, T.; Meena, S., Discovery of a Novel Small-Molecule Inhibitor that Targets PP2A–β-Catenin Signaling and Restricts Tumor Growth and Metastasis. *Mol. Cancer Ther*. **2017,** *16*, 1791-1805.

Table S2: Percentage Growth inhibition of the tested compounds against human cancer cell line at 10 μM.

	HT-29 (Colon)	**MCF-7 (Breast)**	**A549 (Lung)**	**MIA PaCa-2 (Pancreatic)**	**PC-3 (Prostate)**
Compound	Average ± SE	Average ± SE	Average ± SE	Average ± SE	Average ± SE
2a	9.95± 6.86	21.2±3.06	8.55±5.79	10.81±0.16	9.47±0.00
2b	15.39±8.9	25.43±0.95	17.22±6.83	14.96±0.03	16.62±2.10
2c	26.91±7.07	24.89±1.33	19.97±5.99	24.84±2.33	13.27±1.38
2d	22.75±4.62	30.39±0.60	14.61±7.15	16.16±0.86	16.78±3.80
2e	7.64±3.87	20.47±0.93	9.69±8.72	0.39±2.43	8.70±0.92
2f	**40.1±5.45**	33.29±1.11	22.79±10.67	30.28±2.17	16.05±4.25
2g	5.71±6.59	19±5.68	8.41±10.22	20.71±12.23	18.89±4.31
2h	15.38±6.20	20.29±4.73	10.24±10.35	17.33±1.53	14.95±3.05
2i	-3.18±8.45	33.43±5.47	5.3±1.38	5.27±0.60	2.27±3.05
2j	8.1±3.24	26.31±7.16	10.86±3.18	19.87±1.39	18.53±1.47
2k	17.13±1.07	32.05±6.15	18.04±2.44	21.09±0.75	7.05±0.91
2m	7.75±1.18	23.07±0.92	13.12±3.60	7.91±1.00	3.07±0.71
2n	**38.51±4.75**	**47.25±0.40**	**40.78±3.74**	**36.42±1.87**	**37.45±1.00**

2o	0.57±3.50	27.79±2.00	8.54±5.04	7.17±0.08	8.36±3.97
2p	3.19±4.41	27.85±6.22	16.68±10.04	7.90±4.42	11.17±0.33
2q	10.5±4.67	34.58±2.81	22.32±3.98	19.90±6.80	29.27±5.74
2r	1.59±2.70	27.4±0.65	13.27±10.46	19.97±10.22	19.67±3.82
2s	19.67±0.56	23.81±2.53	14.41±11.12	18.73±1.95	17.34±2.75
2t	**-3.9±3.48**	**45.48±6.01**	**36.54±1.62**	**37.80±1.83**	**39.64±1.00**
2u	-9.42±5.33	33.07±5.13	14.11±2.52	15.41±1.19	6.30±1.92
2v	-8.57±0.31	23.68±7.18	10.57±0.34	5.10±4.53	-3.20±0.51
2x	**34.57±14.5**	**40.85±6.76**	**38.79±5.19**	**27.89±17.75**	**29.99±1.54**
4a	21.25±0.59	**39.36±7.39**	29.74±2.51	14.62±4.52	20.19±0.47
4b	-13.93±3.28	18.81±2.03	12.68±1.92	26.99±13.70	-8.01±0.21
4c	NT	NT	NT	NT	
4d	-10.4±5.49	33.95±6.31	3.02±1.52	11.92±8.50	-7.34±3.90
4f	8.32±7.39	35.8±4.17	18.8±6.40	21.66±13.92	6.31±0.05
4g	-1.76±3.06	28.37±6.48	13.18±1.24	5.35±0.70	3.37±3.20
4h	-9.07±4.34	18.91±5.65	10.37±1.95	16.71±3.20	-1.61±2.43

NT = Not Tested

Antibiotic susceptibility testing against ESKAP pathogen panel

Antibiotic susceptibility testing was carried out on the newly synthesized compounds by determining the Minimum Inhibitory Concentration (MIC) according to the standard CLSI guidelines.[3,4] MIC is defined as the minimum concentration of compound at which visible bacterial growth is inhibited. Bacterial cultures were grown in Mueller-Hinton cation supplemented broth (CA-MHB). Optical density (OD_{600}) of the cultures was measured, followed by dilution for ~10^6 CFU/mL. This inoculum was added into a series of test wells in a microtitre plate that contained various concentrations of compound under test ranging from 64-0.03 μg/mL. Controls i.e., cells alone and media alone (without compound+cells) and

Levofloxacin used as a reference standard. Plates were incubated at 37 °C for 16-18 h followed by observations of MIC values by the absence or presence of visible growth. For each compound, MIC determinations were performed independently thrice using duplicate samples each time.

References

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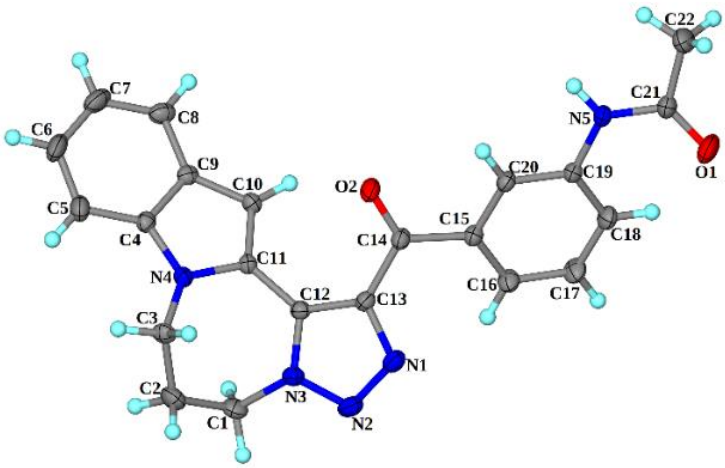
Table S3: MIC (μg/mL) of indolo- and pyrrolo[1,4]diazepines/pyrazines against ESKAP pathogen panel

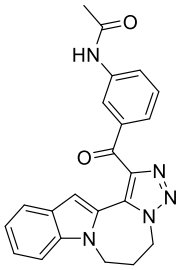
Compound	Gram +ve	Gram -ve			
	***S. aureus* ATCC 29213**	***E. coli* ATCC 25922**	***K. pneumoniae* BAA-1705**	***A. baumannii* BAA 1605**	***P. aeruginosa* ATCC 27853**
2a	>64	>64	>64	>64	>64
2b	64	>64	>64	>64	>64
2c	>64	>64	>64	>64	>64
2d	>64	>64	>64	>64	>64

2e	>64	>64	>64	>64	>64
2f	>64	>64	>64	>64	>64
2g	**16**	>64	>64	>64	>64
2h	>64	>64	>64	>64	>64
2i	>64	>64	>64	>64	>64
2j	>64	>64	>64	>64	>64
2k	**8**	>64	>64	>64	>64
2m	>64	>64	>64	>64	>64
2n	**8**	>64	>64	>64	>64
2o	>64	>64	>64	>64	>64
2p	>64	>64	>64	>64	>64
2q	>64	>64	>64	>64	>64
2r	>64	>64	>64	>64	>64
2s	**32**	>64	>64	>64	>64
2t	>64	>64	>64	>64	>64
2u	>64	>64	>64	>64	>64
2v	>64	>64	>64	>64	>64
2x	NT	NT	NT	NT	NT
4a	>64	>64	>64	>64	>64
4b	NT	NT	NT	NT	NT
4c	>64	>64	>64	>64	>64
4d	>64	>64	>64	>64	>64
4e	NT	NT	NT	NT	NT
4f	>64	>64	>64	>64	>64
4g	>64	>64	>64	>64	>64
4h	>64	>64	>64	>64	>64
Levofloxacin	<0.5	<0.5	64	8	1

NT = Not Tested

X-ray crystallography information and data





2j

Figure S3. The molecular structure of KA555 (compound **2j**) with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radius. **CCDC 1887445** contains the supplementary crystallographic data.

Sample preparation: Compound **2j** was dissolved in ethanol (100 mg in 3 mL ethanol) and allowed for crystallization at room temperature for 7-8 days.

Table S4: Crystal data and structure refinement.

Identification code	KA555
Chemical formula	$C_{22}H_{19}N_5O_2$
Molecular weight	385.42
Temperature	293(2)K
Wavelength	0.71073Å
Crystal system ; space group	monoclinic ; P 21/c
Unit cell dimensions	A = 14.4652(12)Å b = 15.665(3)Å c = 8.435(2)Å α = 90 ° β = 91.931(7) ° γ = 90 °
Volume	1910.2(6) Å³
Z, Calculated density	4, 1.340 g/cm³
Absorption coefficient	0.090 1/mm
F(000)	808
Theta range for data collection	2.600° to 27.500°
Limiting indices	-18 <= h <= 18 ; -20 <= k <= 20 ; -10 <= l <= 10

Reflection collected / unique	34927 / 4384 [R(int) = 0.0710]
Completeness to theta max	99.9 %
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	4384 / 72 / 296
Goodness of fit on F^2	1.172
Final R indices [I>2sigma(I)]	R1 = 0.0533 ; wR2 = 0.1497
Final R indices [all data]	R1 = 0.0772 ; wR2 = 0.1703
Largest diff peak and hole	0.376 and -0.251 e/$Å^3$

Data collection and structure solution of KA555 (2j): Single crystal X-ray data for two compounds were collected at room temperature on a Bruker D8 QUEST equipped with a four-circle kappa diffractometer and Photon 100 detector. An Iμs microfocus Mo source (l=0.71073Å) supplied the multi-mirror monochromated incident beam. A combination of Phi and Omega scans were used to collect the necessary data. Unit cell dimensions were determined using 9898 reflections. Integration and scaling of intensity data were accomplished using SAINT program.[1] The structures were solved by Direct Methods using SHELXS97[2] and refinement was carried out by full-matrix least-squares technique using SHELXL-2014/7.[2-3] Anisotropic displacement parameters were included for all non-hydrogen atoms. All H atoms were positioned geometrically and treated as riding on their parent C atoms with C-H distances of 0.93--0.97 Å, and with $U_{iso}(H) = 1.2U_{eq}$ (C) or $1.5U_{eq}$ for methyl atoms. **CCDC 1887445** contains the supplementary crystallographic data for this paper which can be obtained free of charge at **https://summary.ccdc.cam.ac.uk/structure-summary-form** or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: **deposit@ccdc.cam.ac.uk**.

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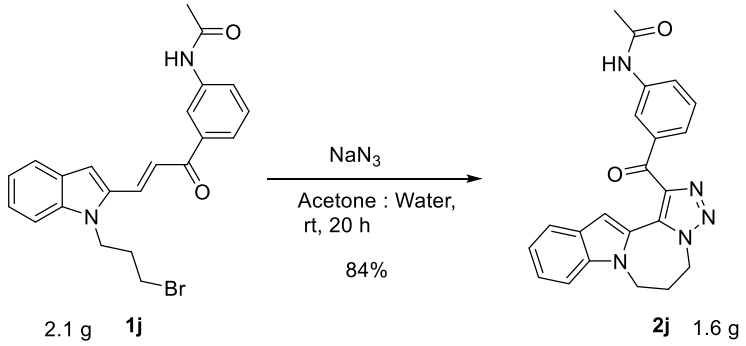
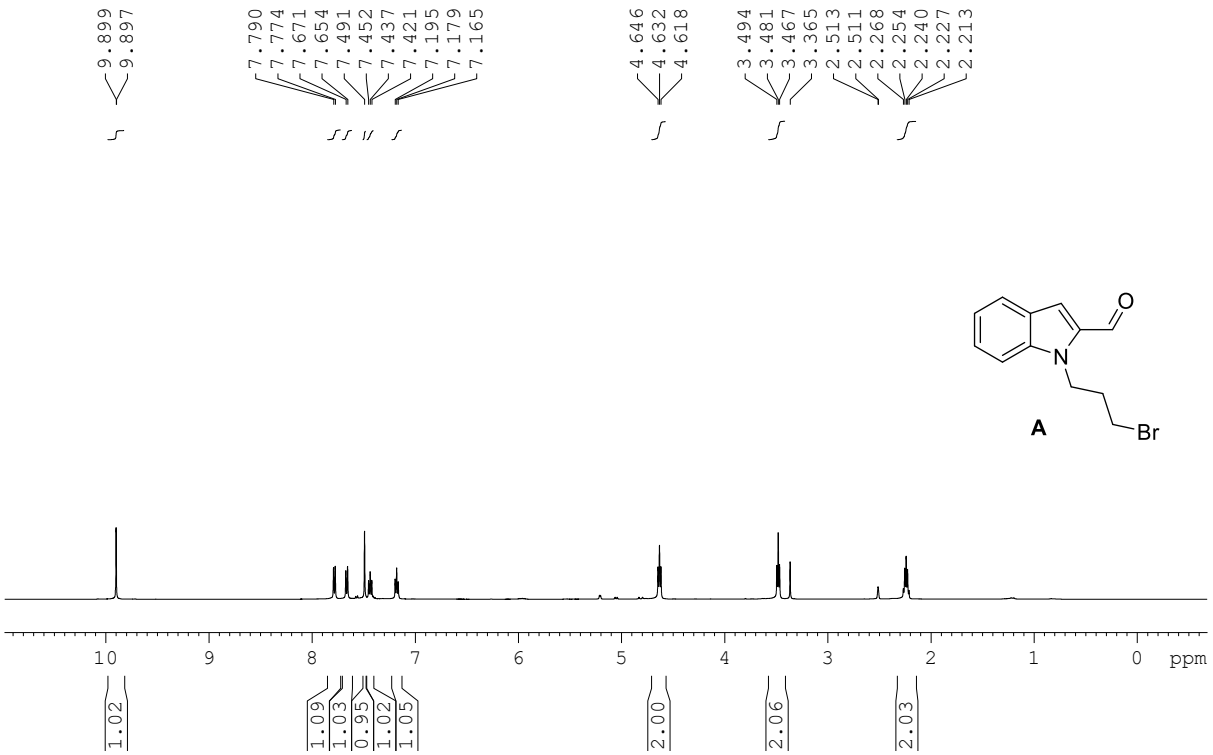
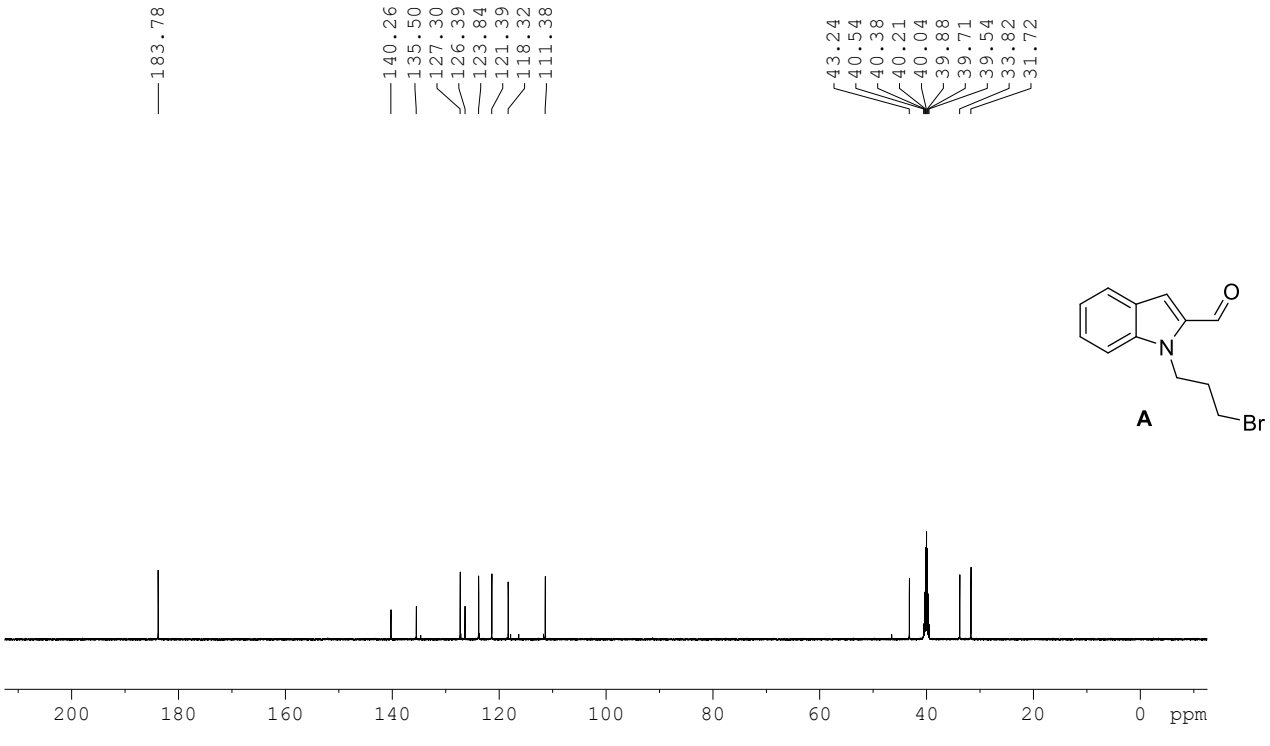


2.1 g **1j** **2j** 1.6 g

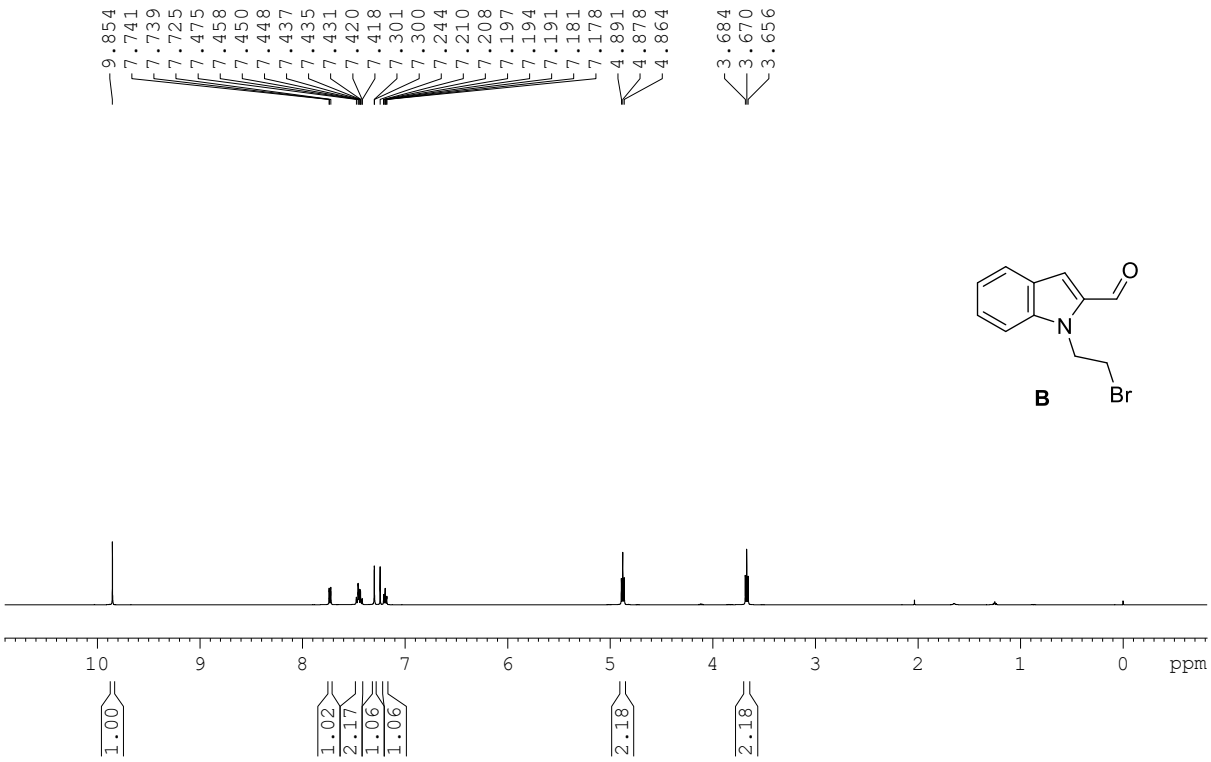
Scheme S1. Gram-scale reaction.



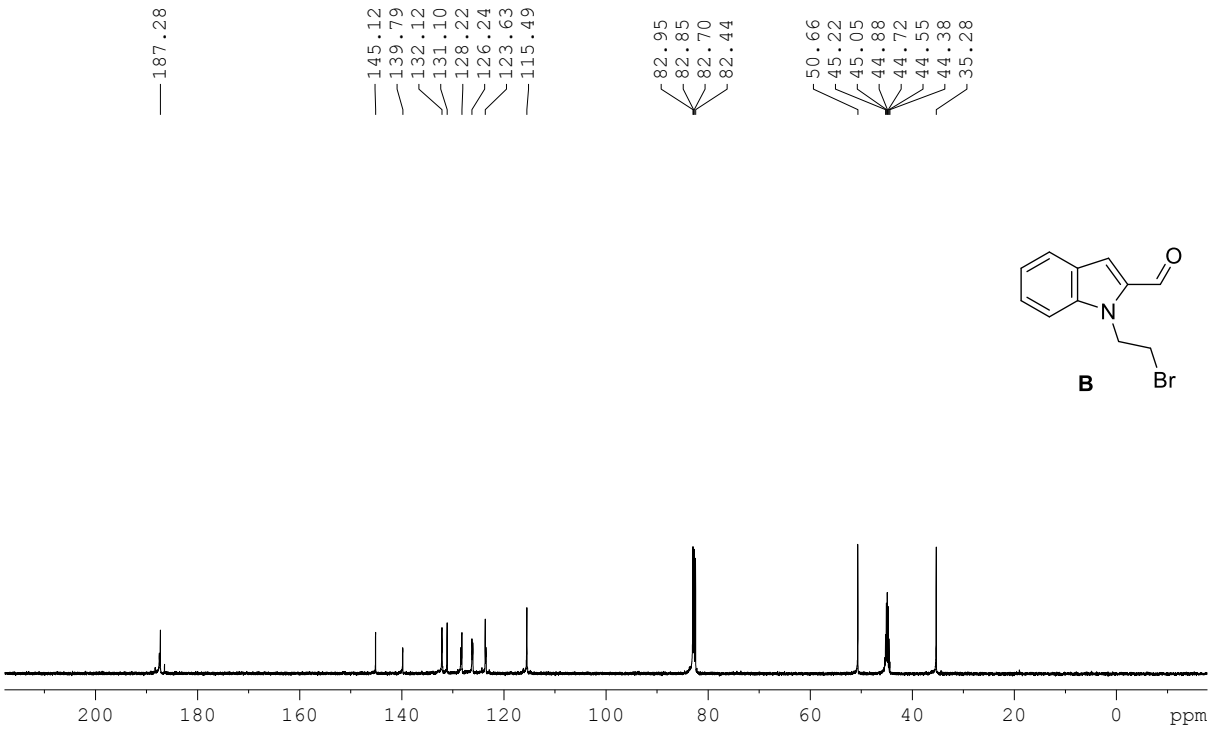
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **A**



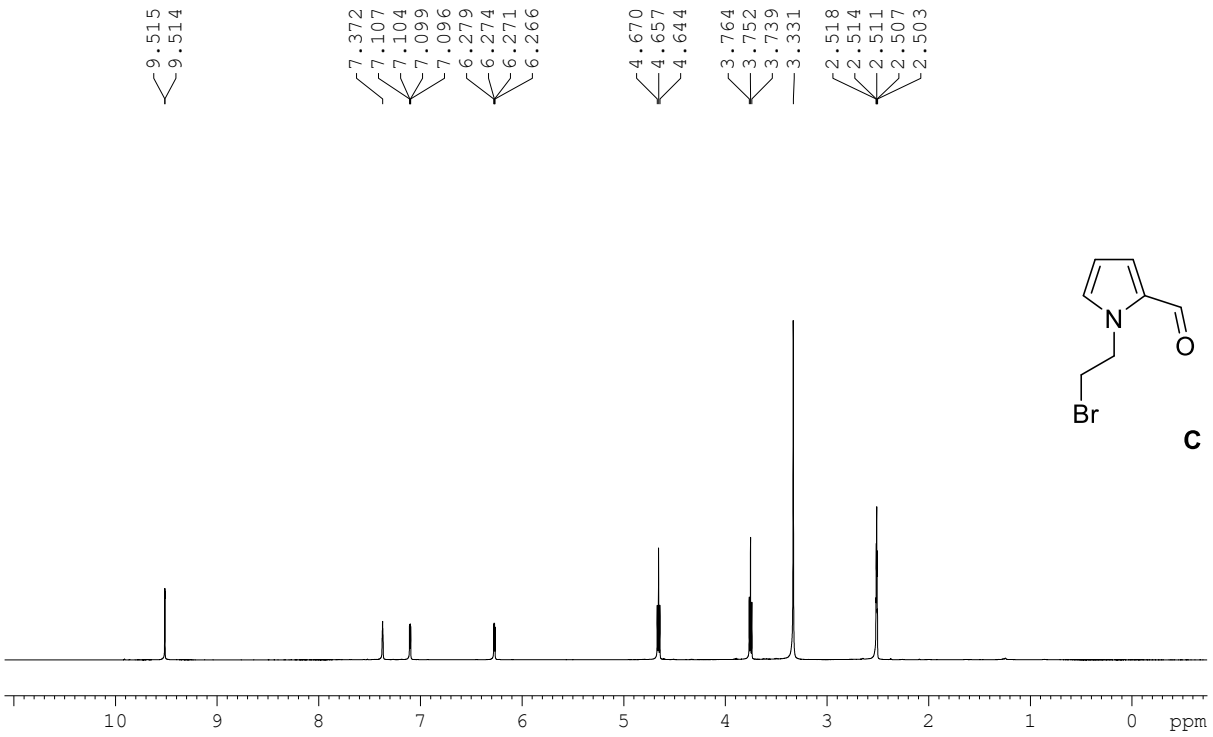
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **A**



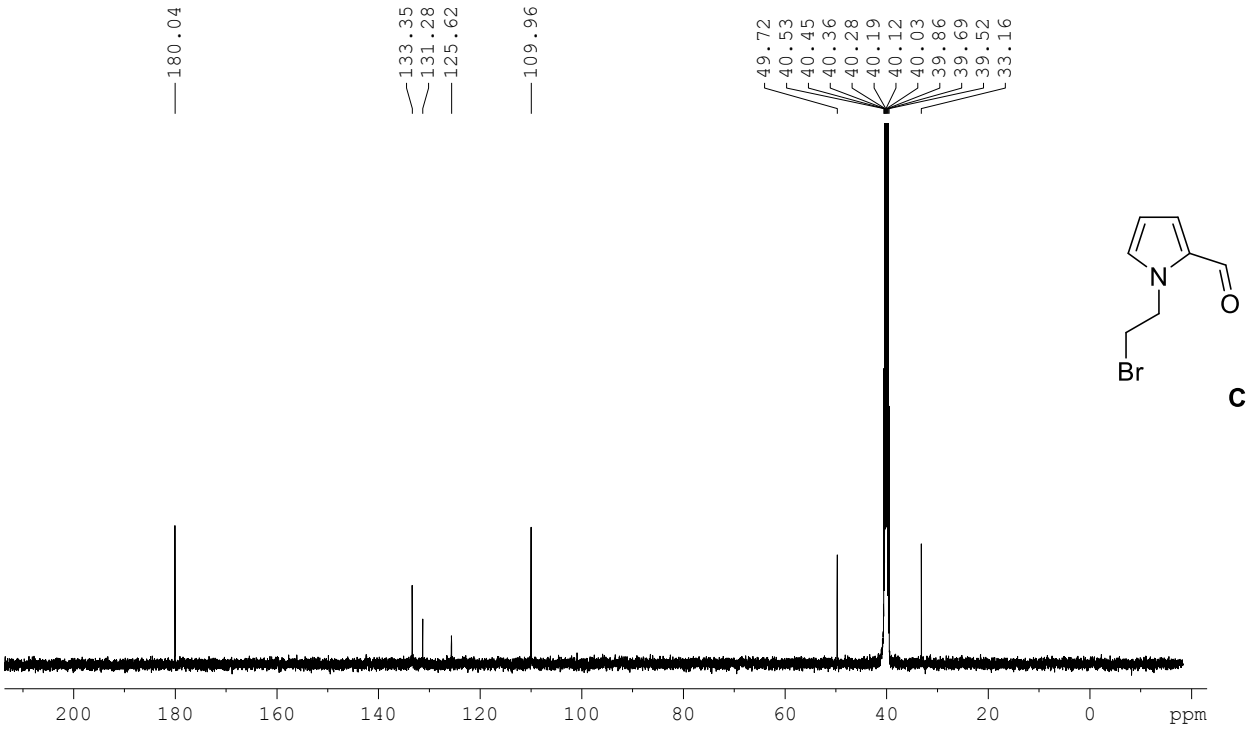
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **B**



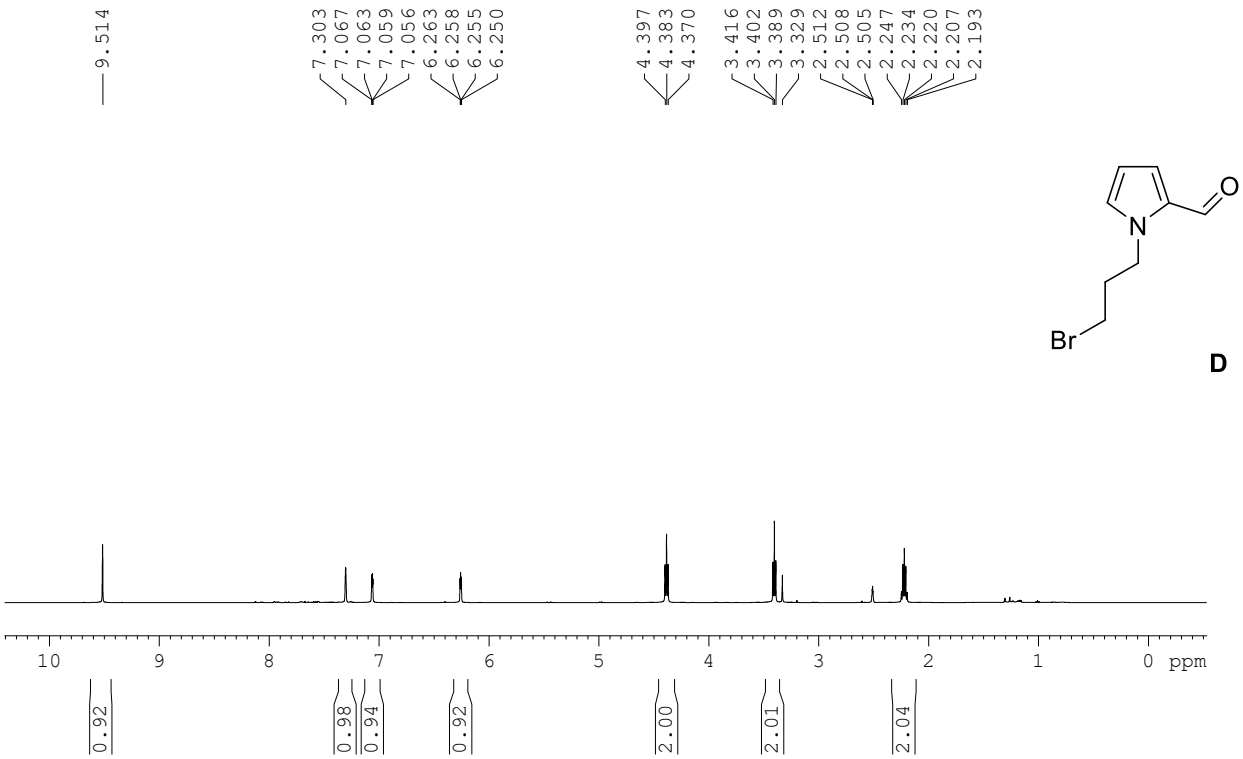
^{13}C NMR (125 MHz, $CDCl_3$ + DMSO-d_6) spectrum of compound **B**



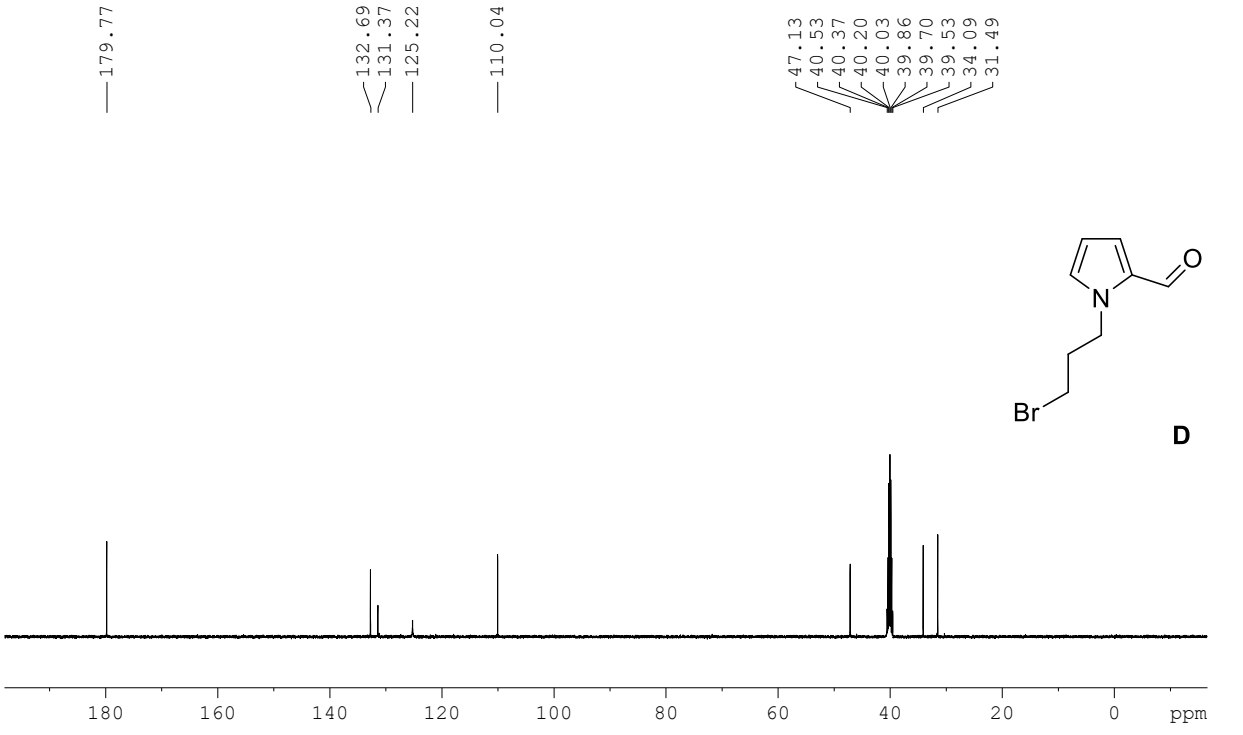
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **C**



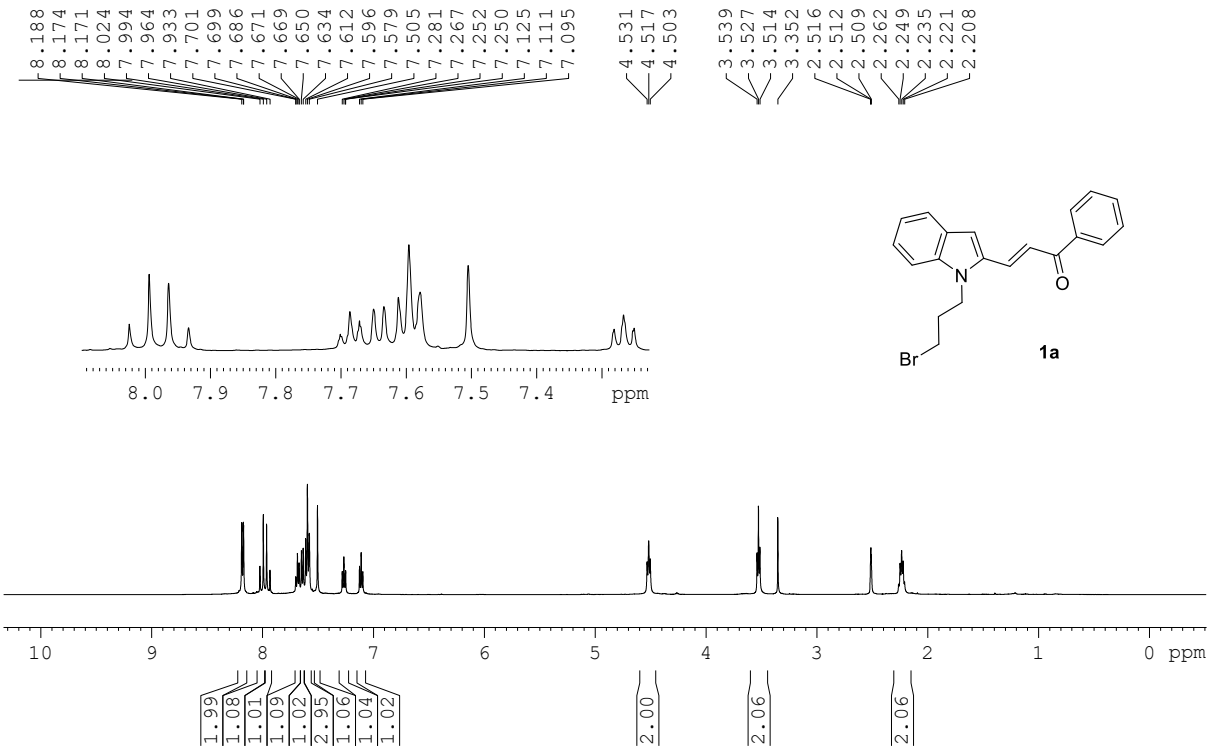
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **C**



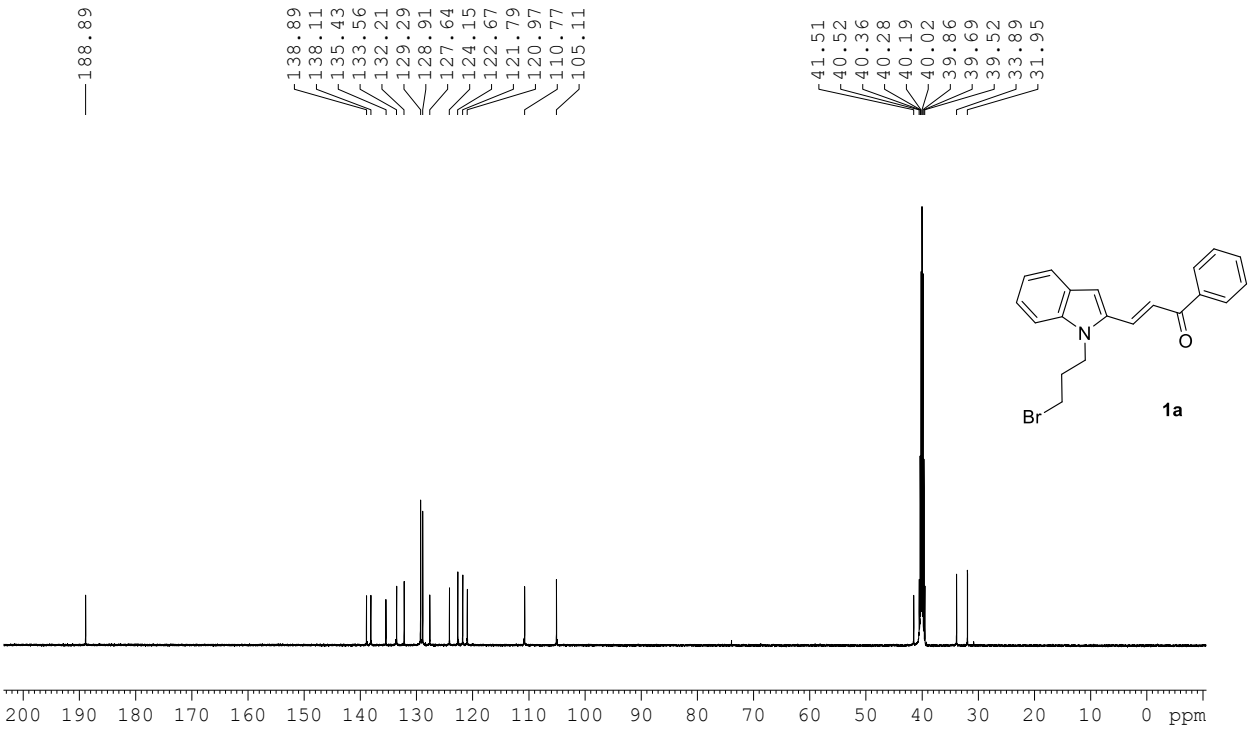
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **D**



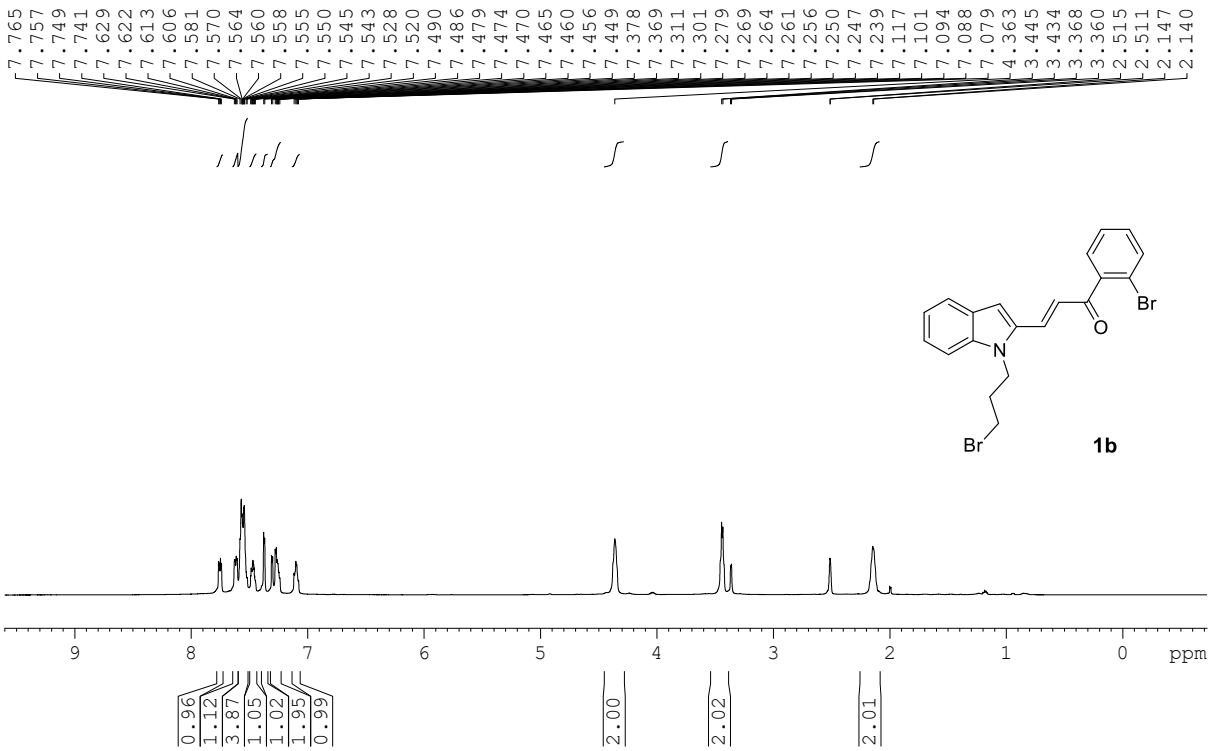
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **D**



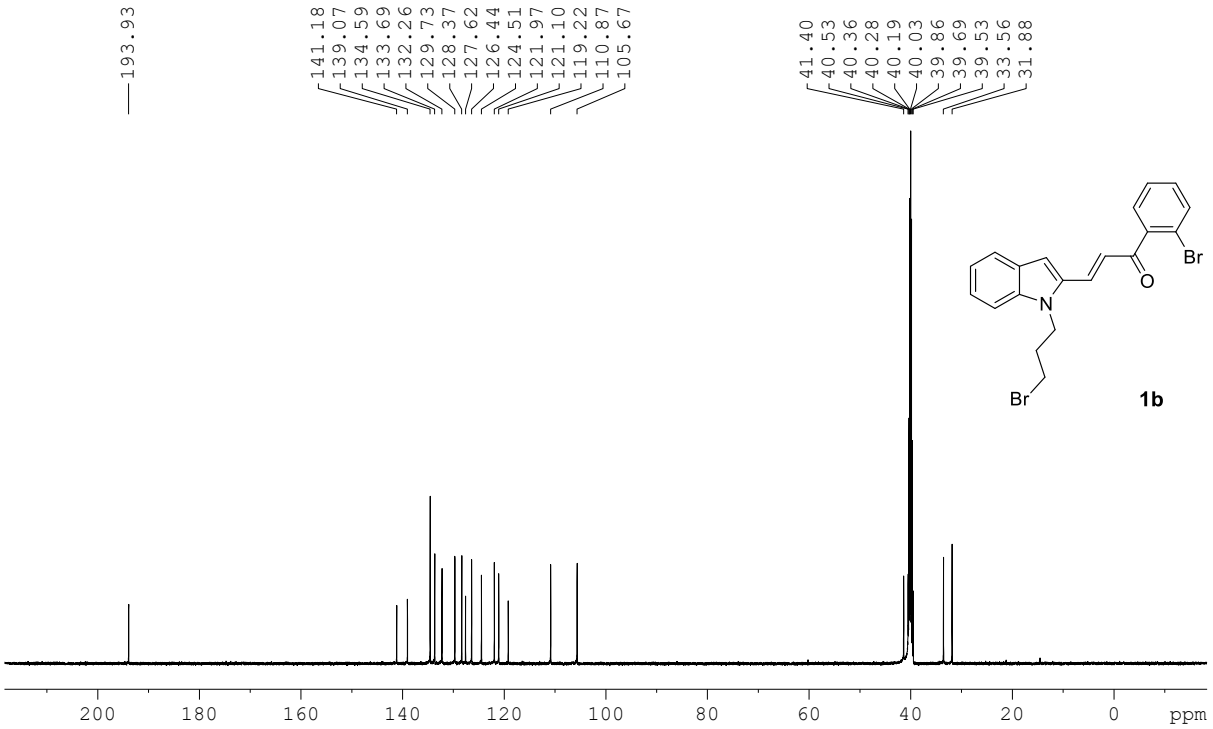
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1a**



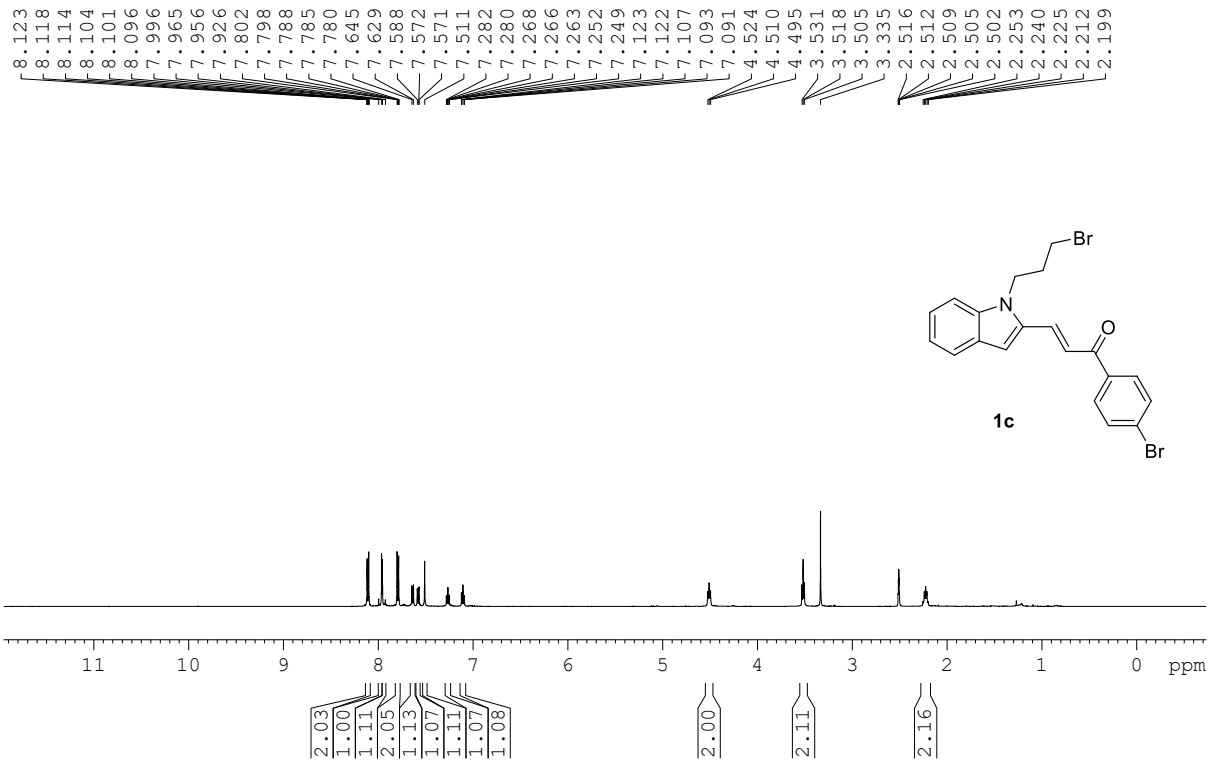
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1a**



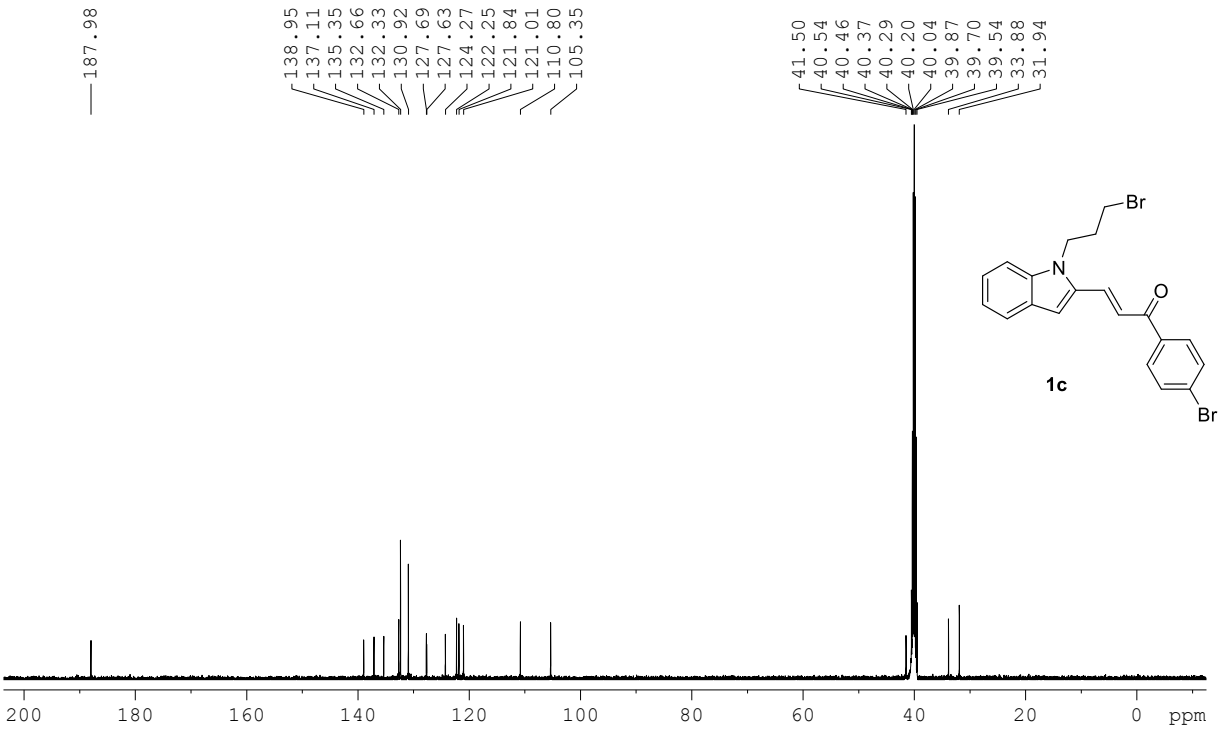
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1b**



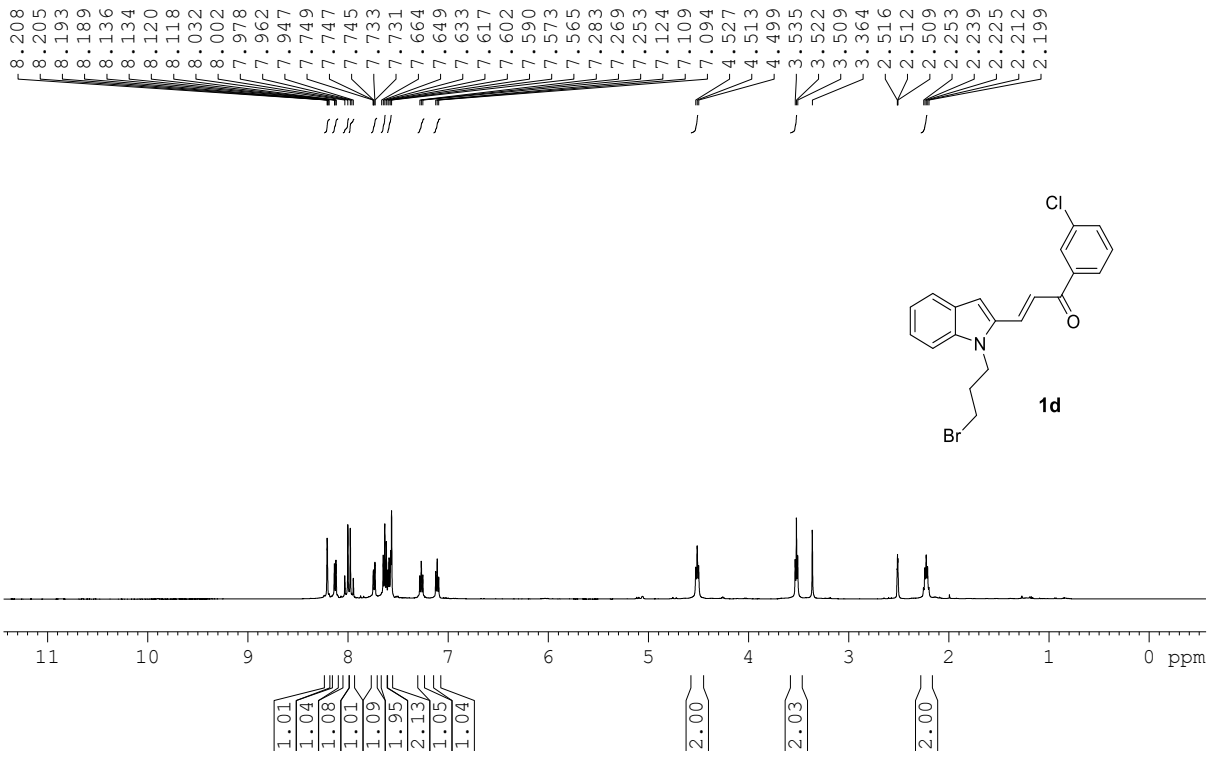
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1b**



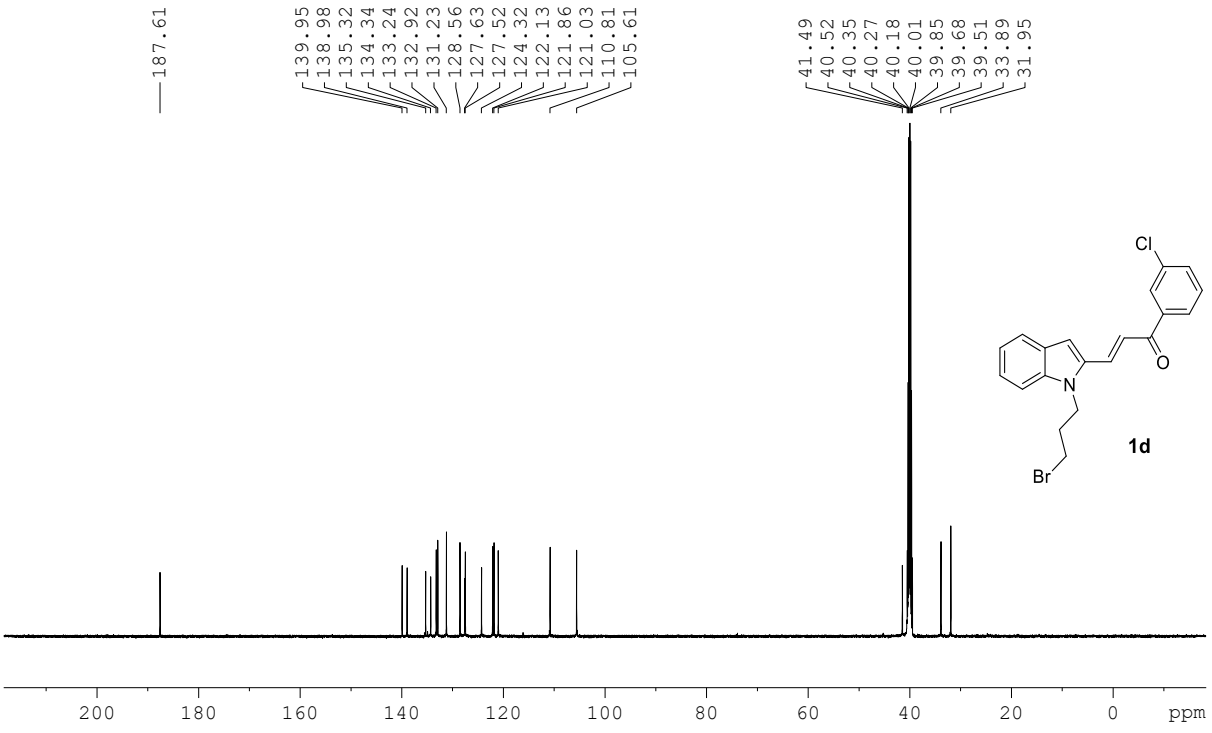
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1c**



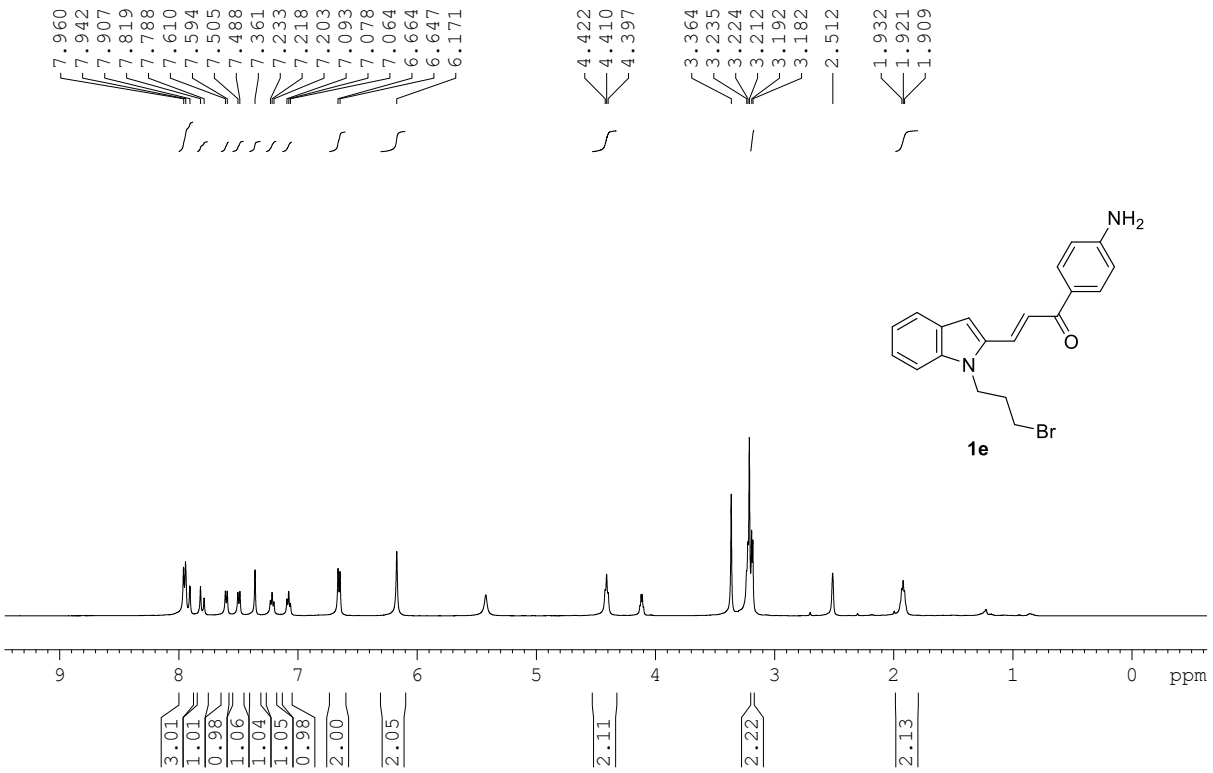
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1c**



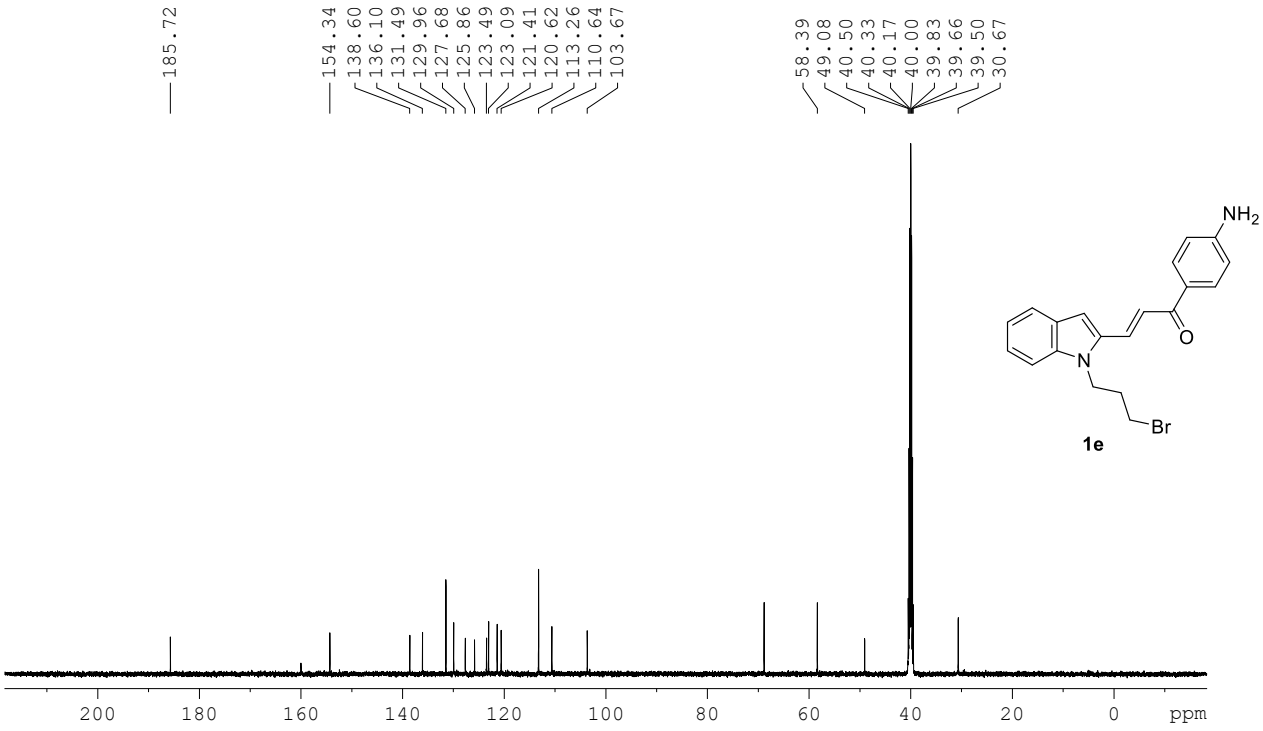
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1d**



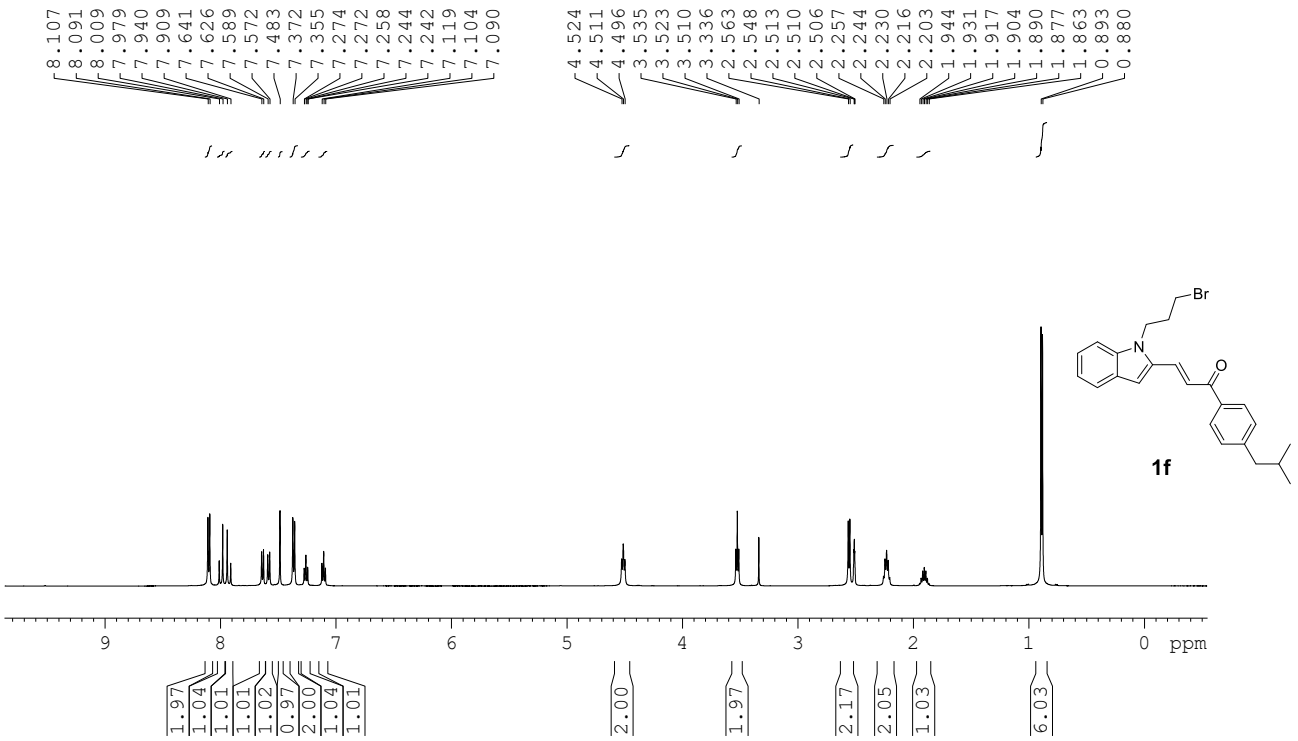
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1d**



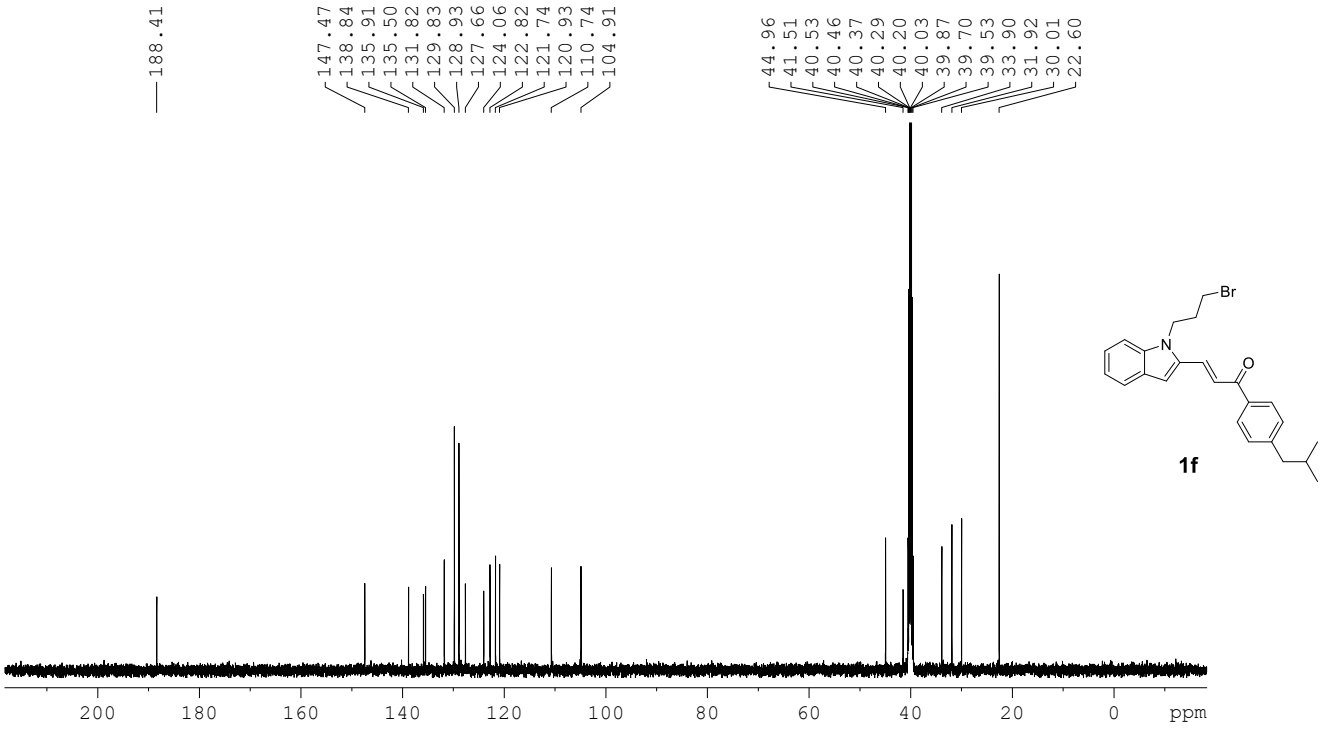
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1e**



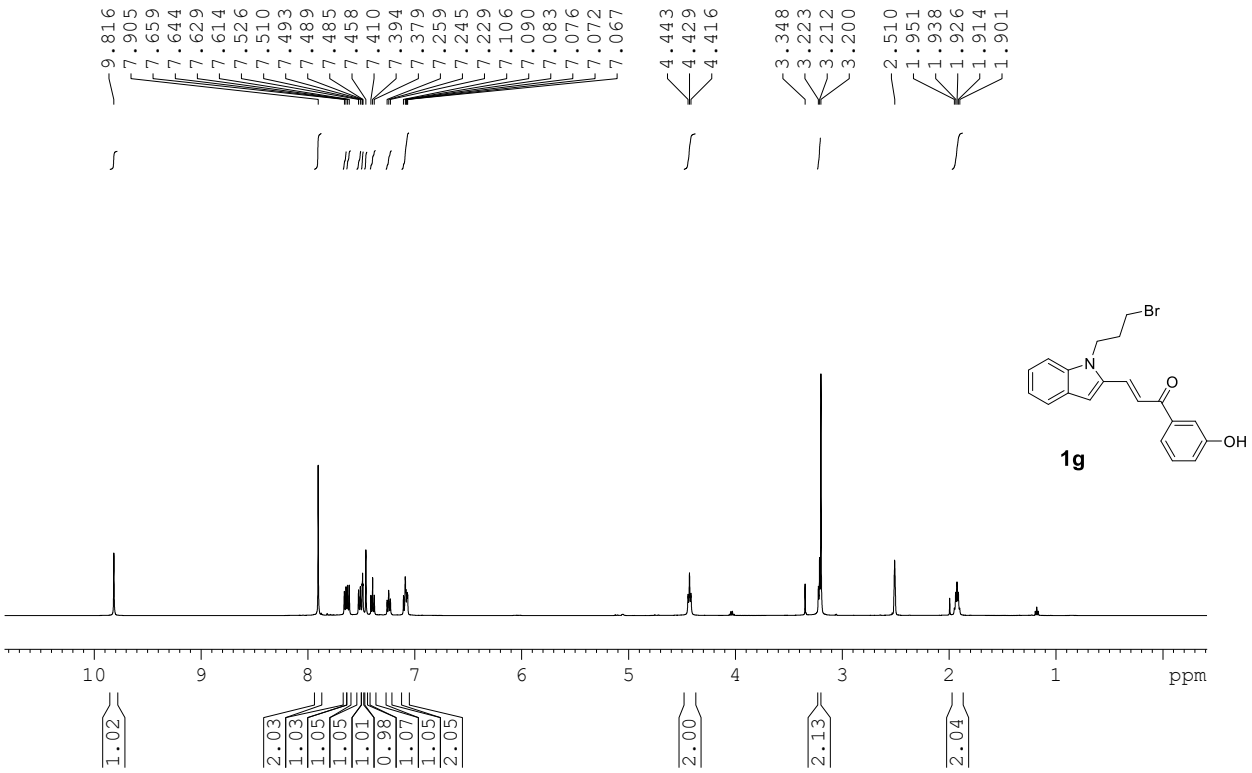
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1e**



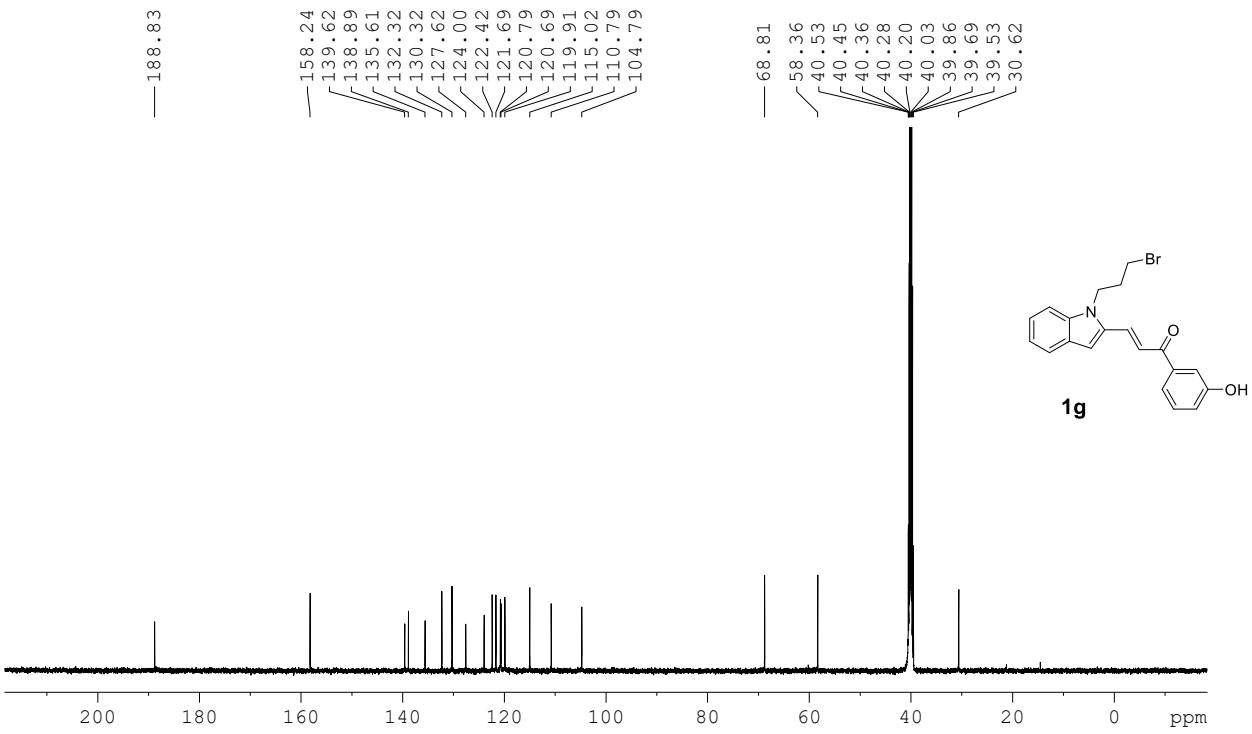
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1f**



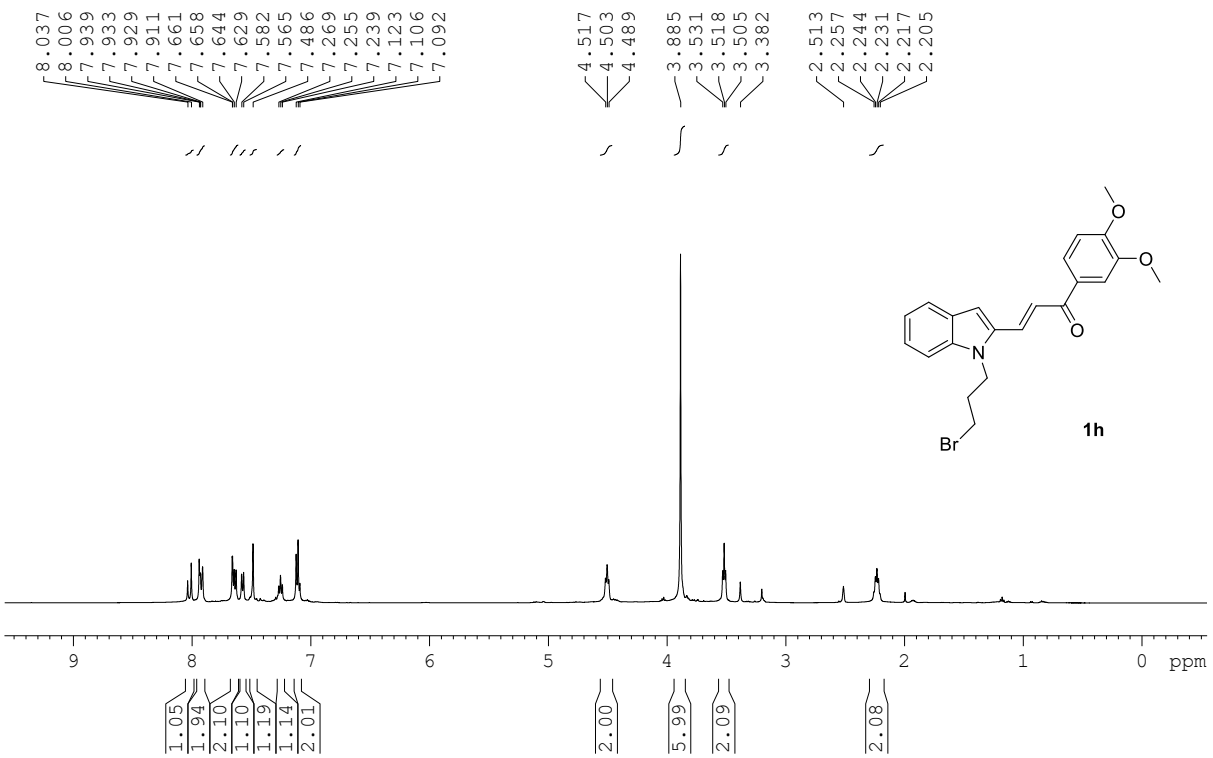
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1f**



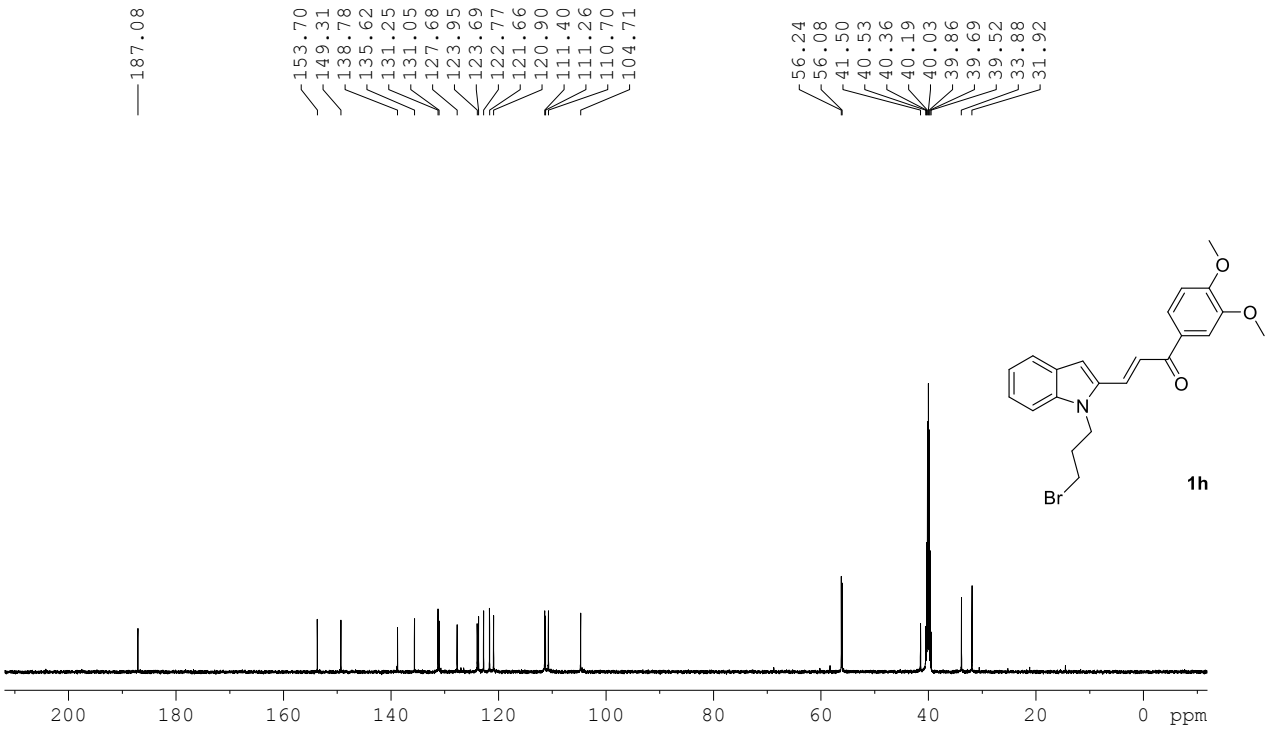
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1g**



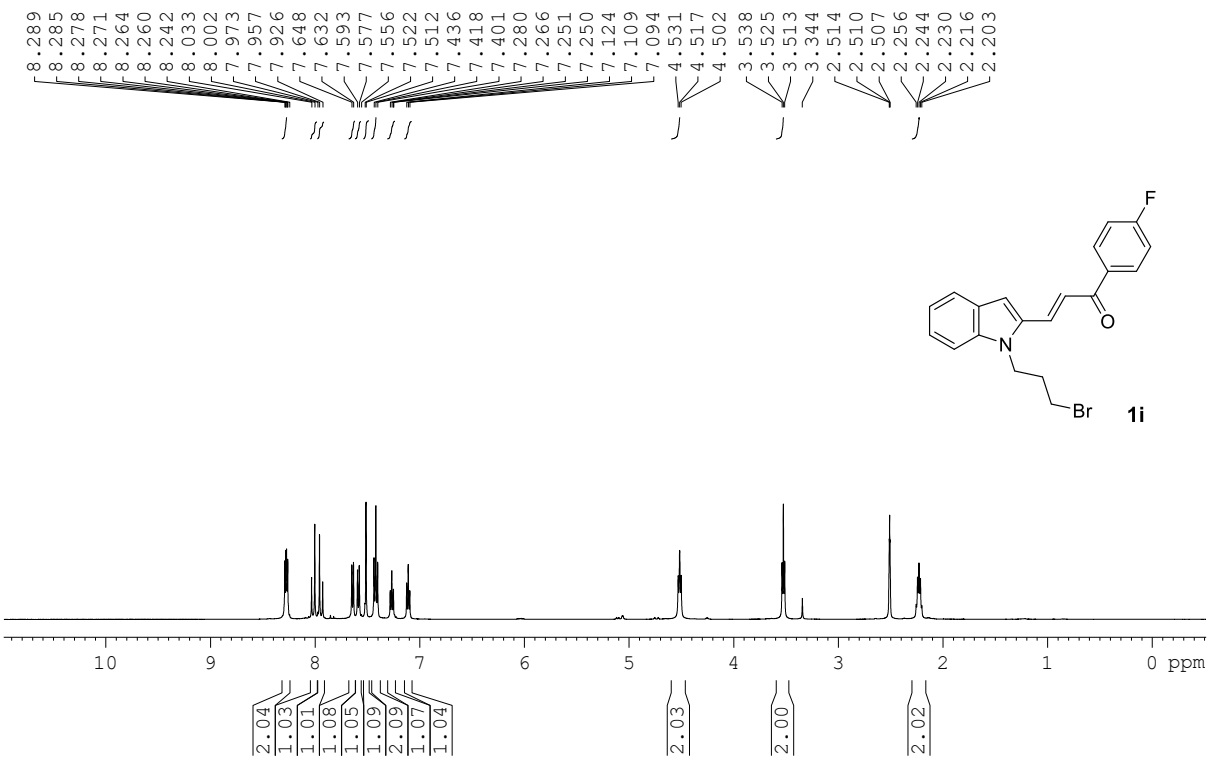
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1g**



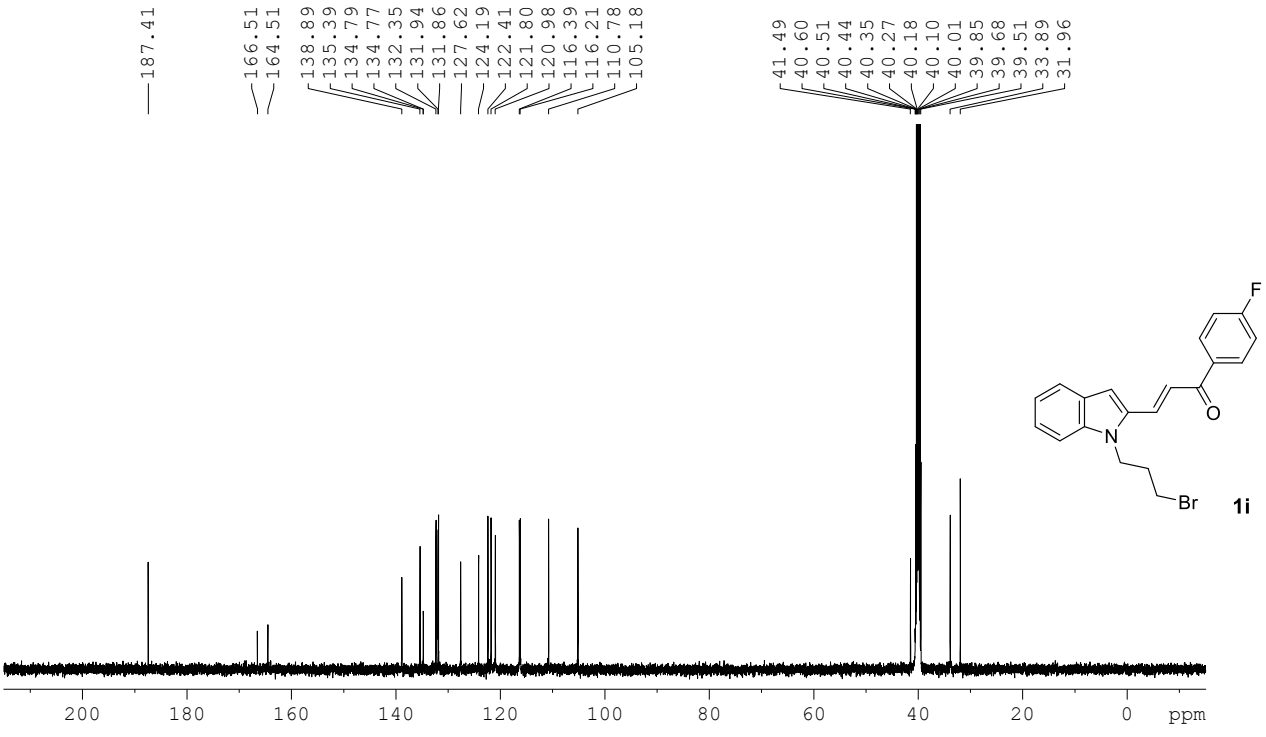
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1h**



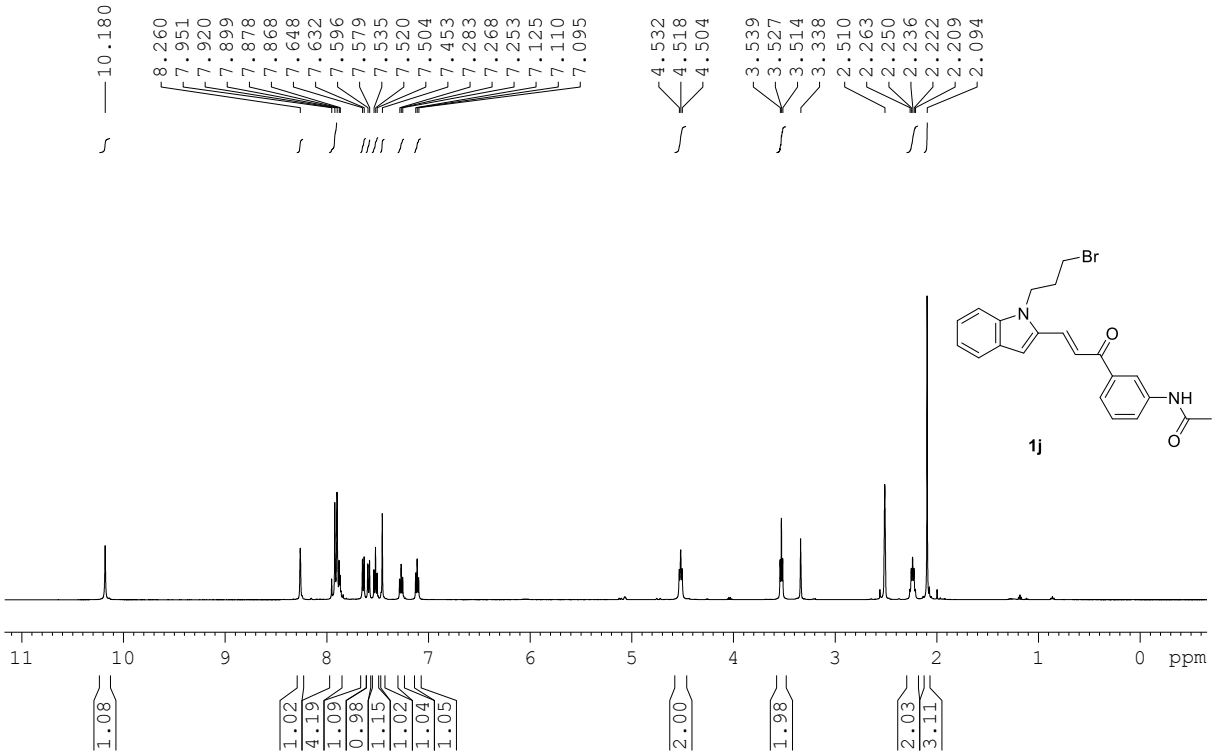
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1h**



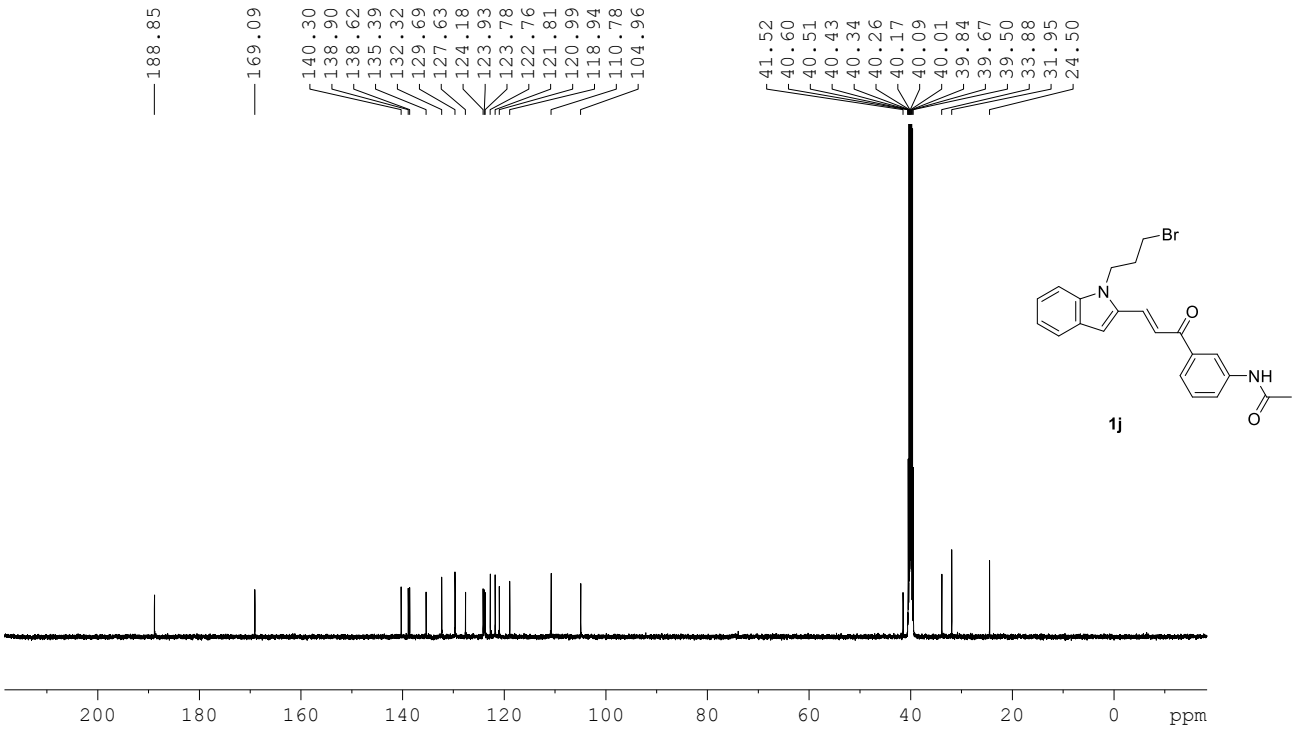
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1i**



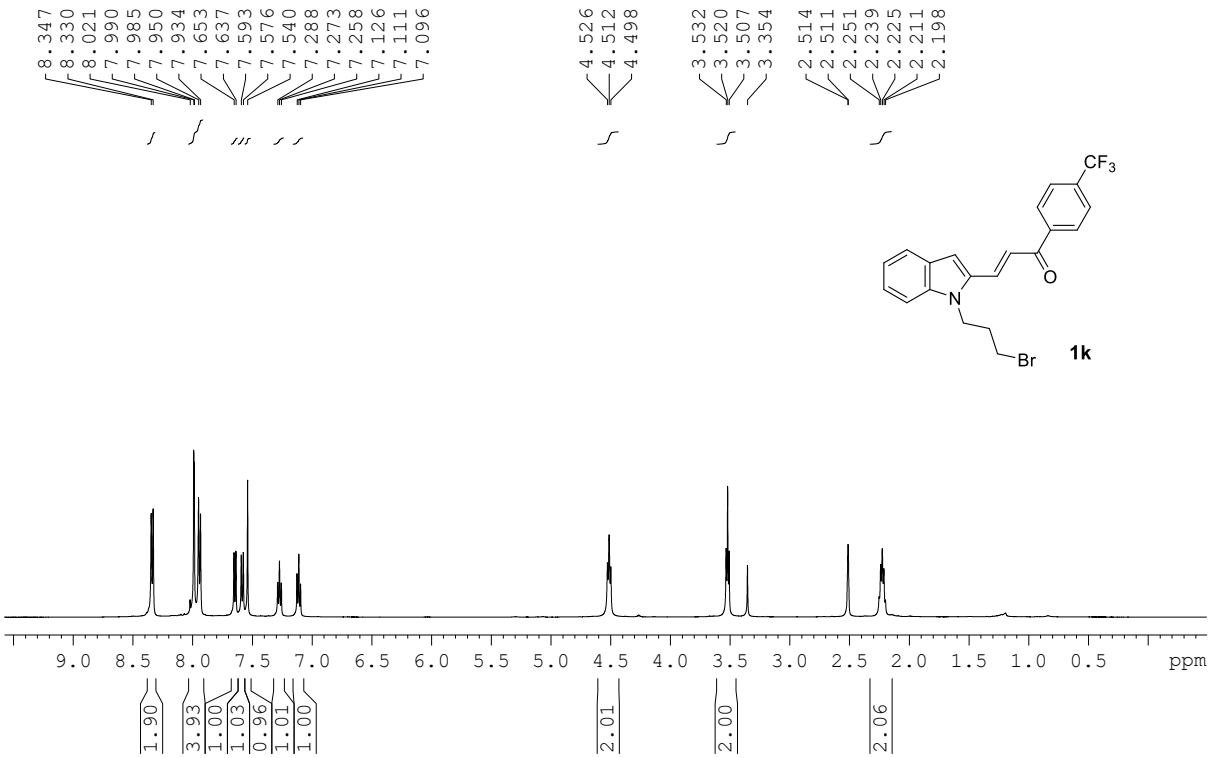
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1i**



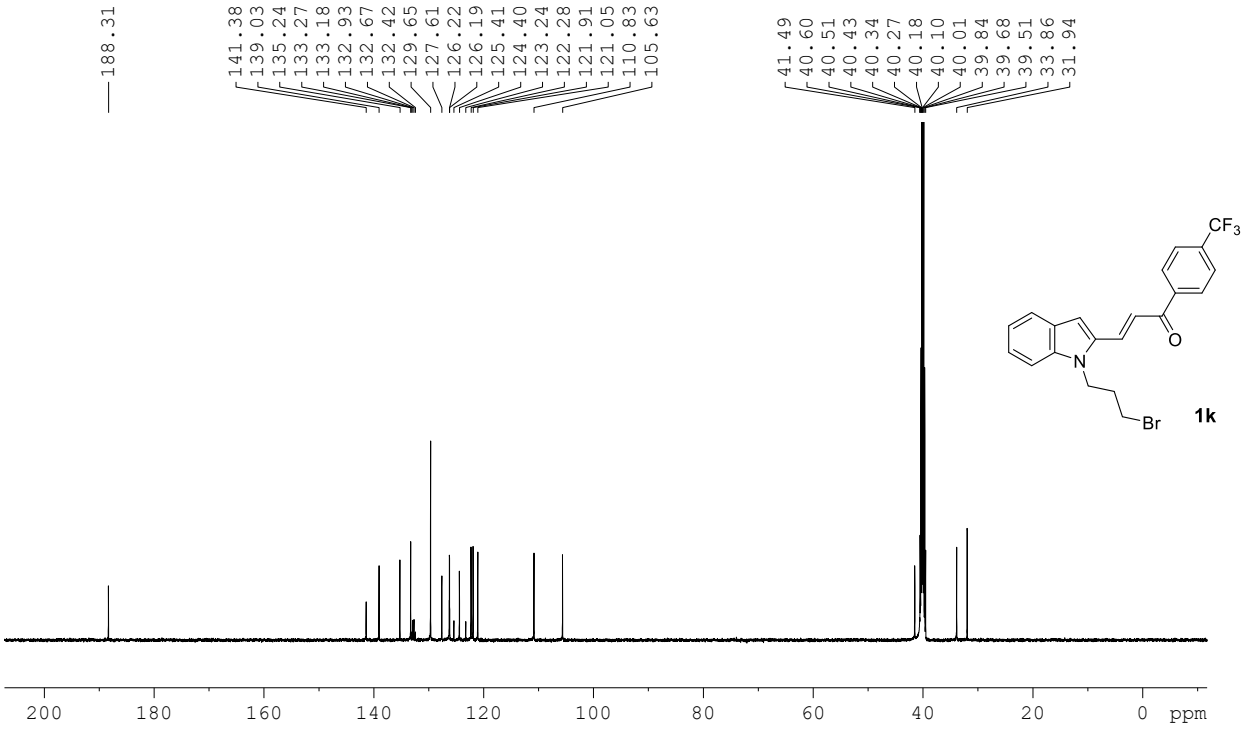
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1j**



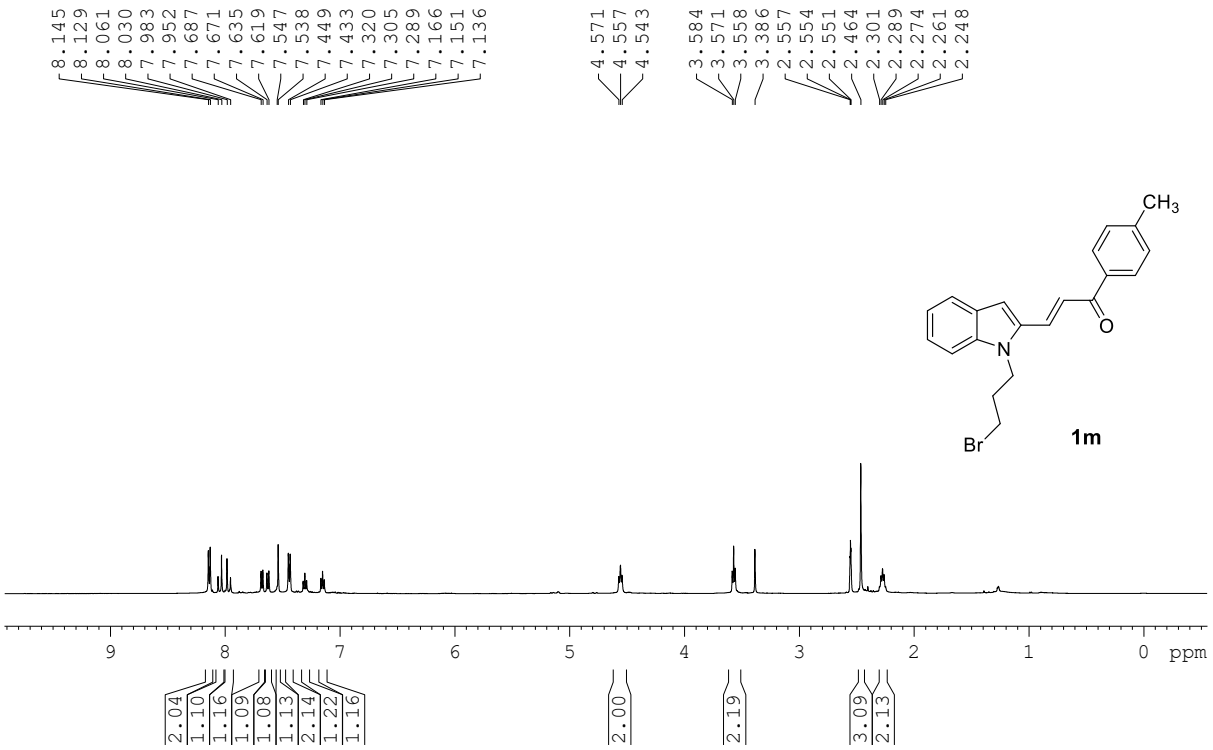
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1j**



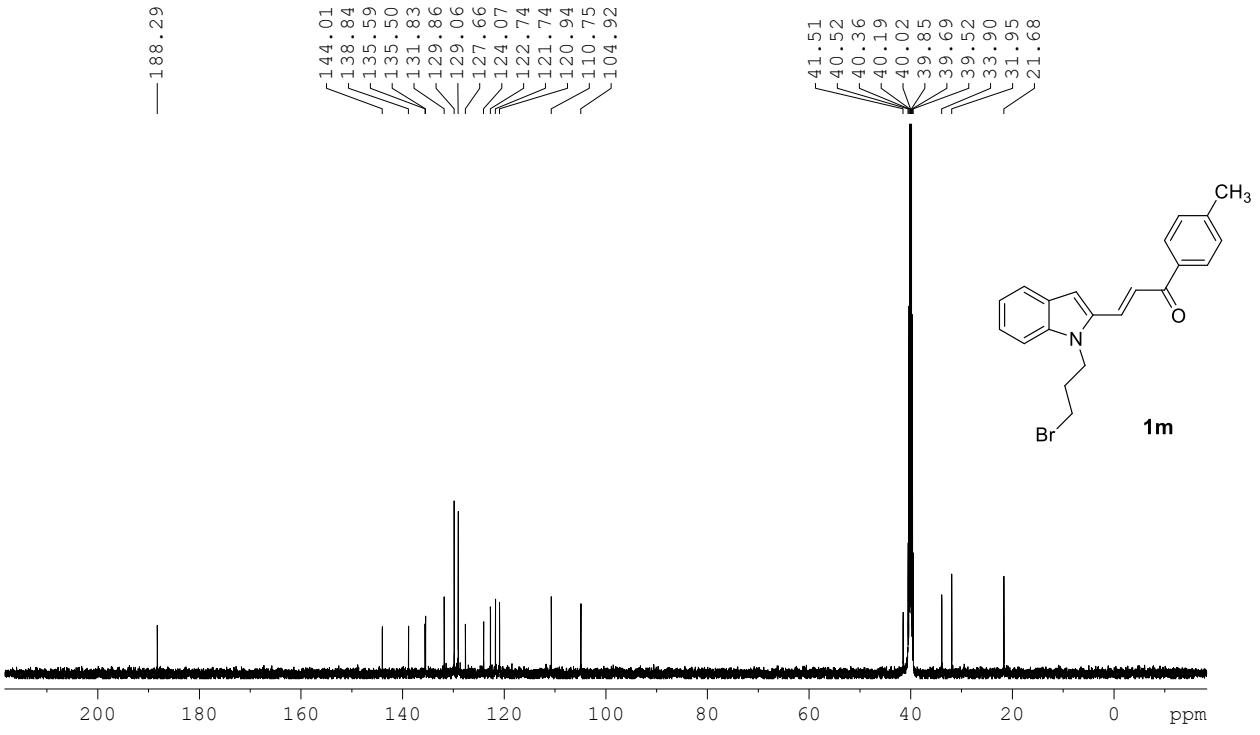
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1k**



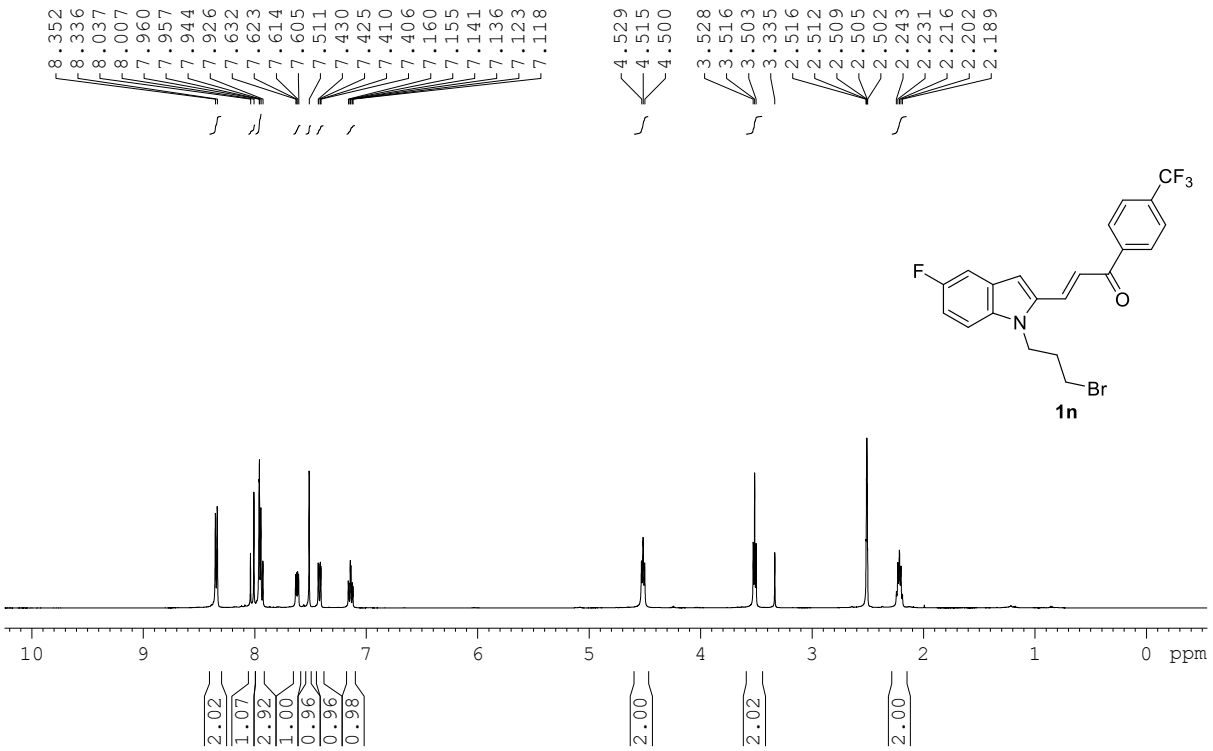
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1k**



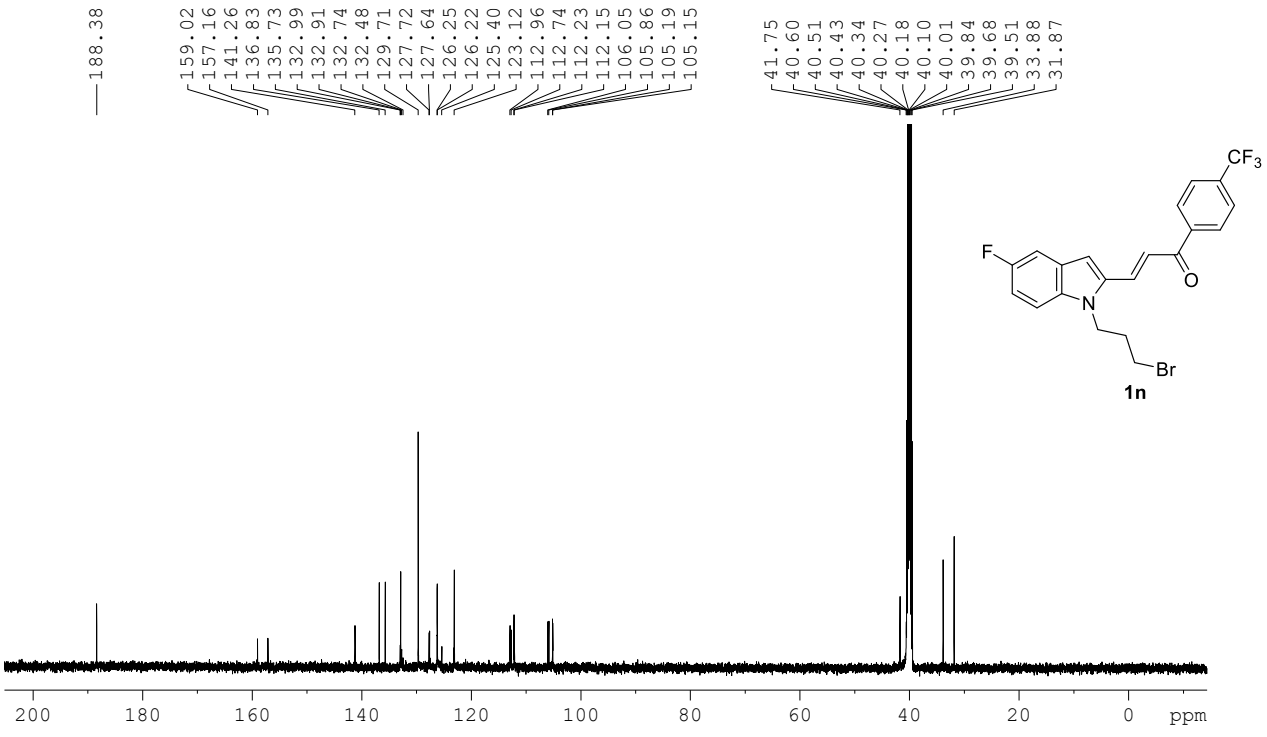
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1m**



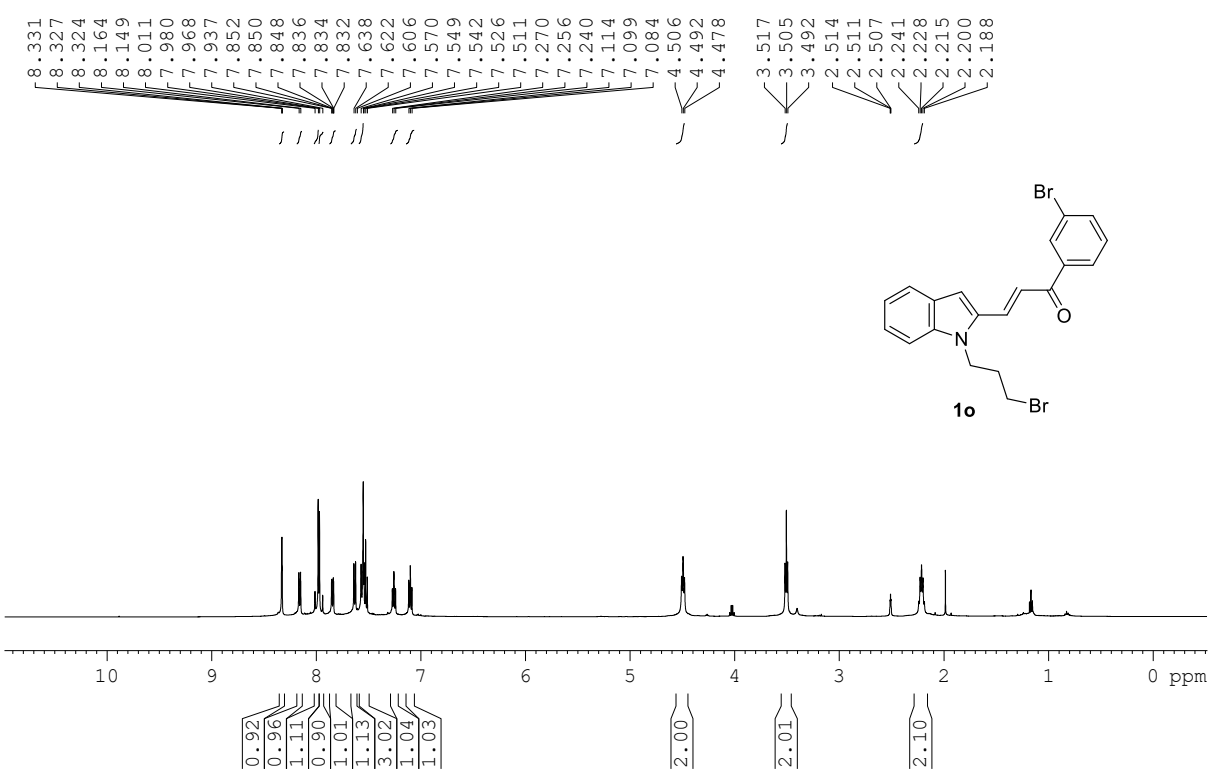
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1m**



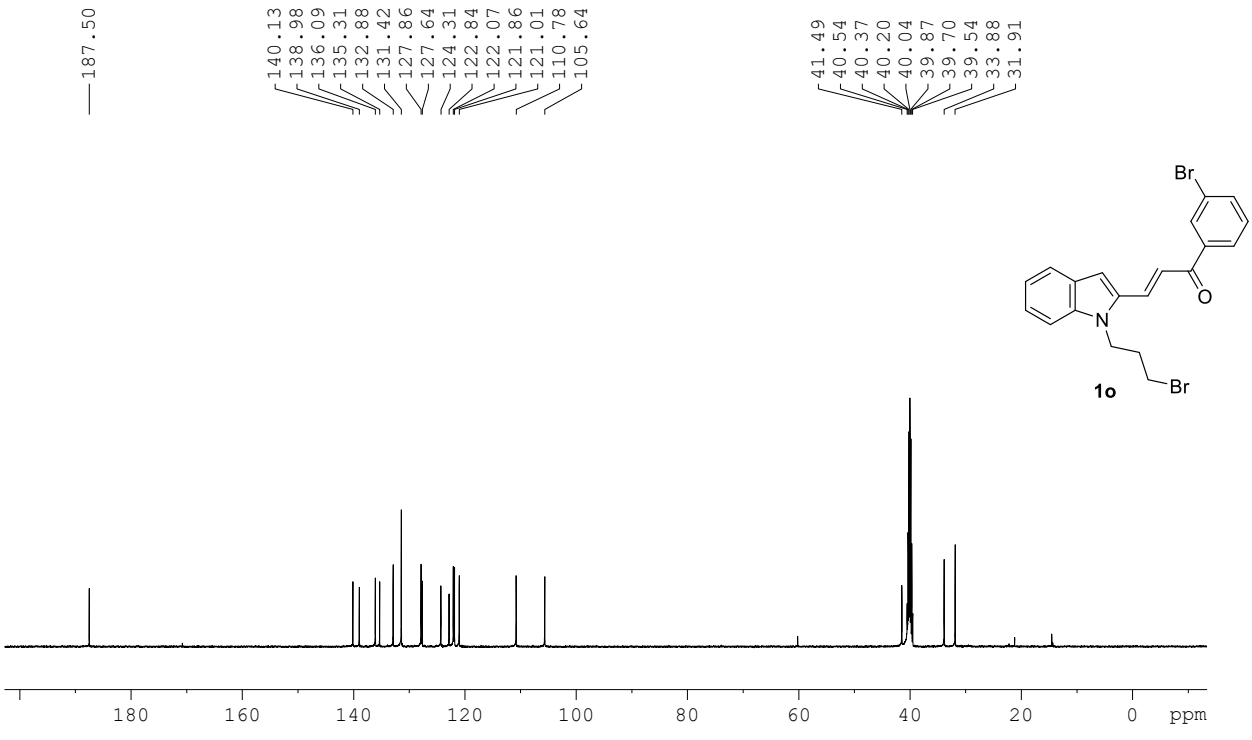
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1n**



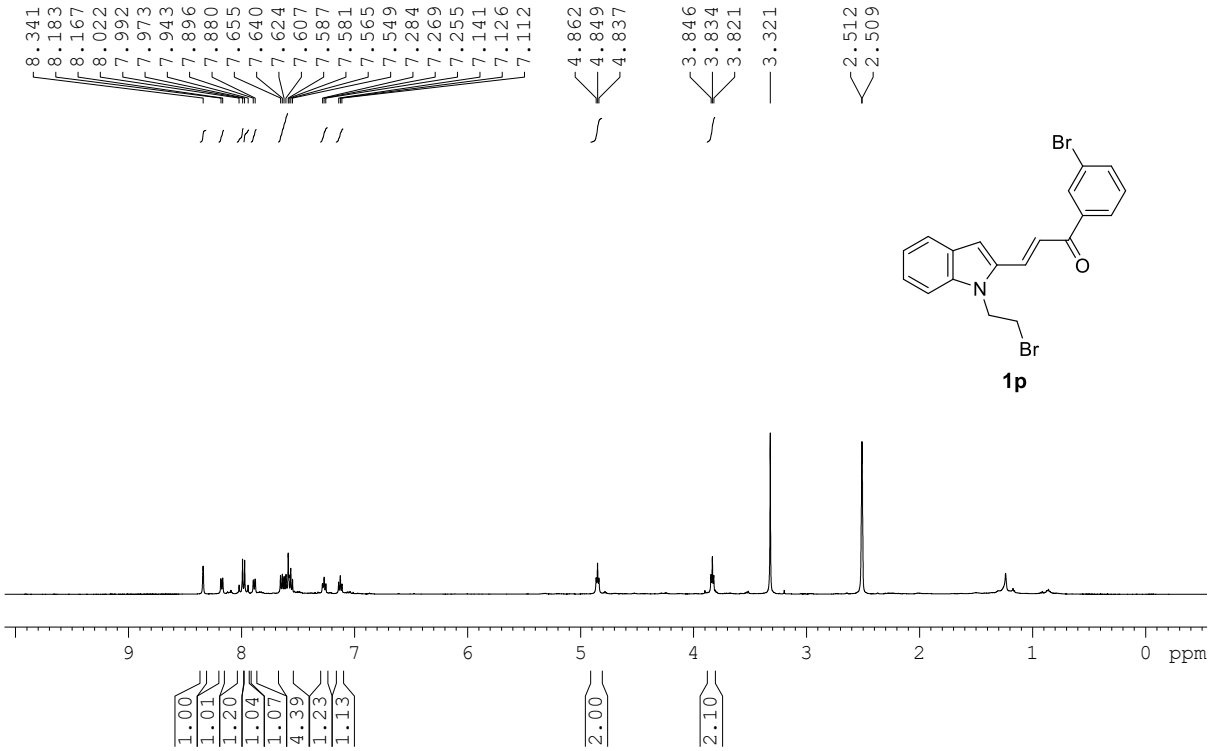
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1n**



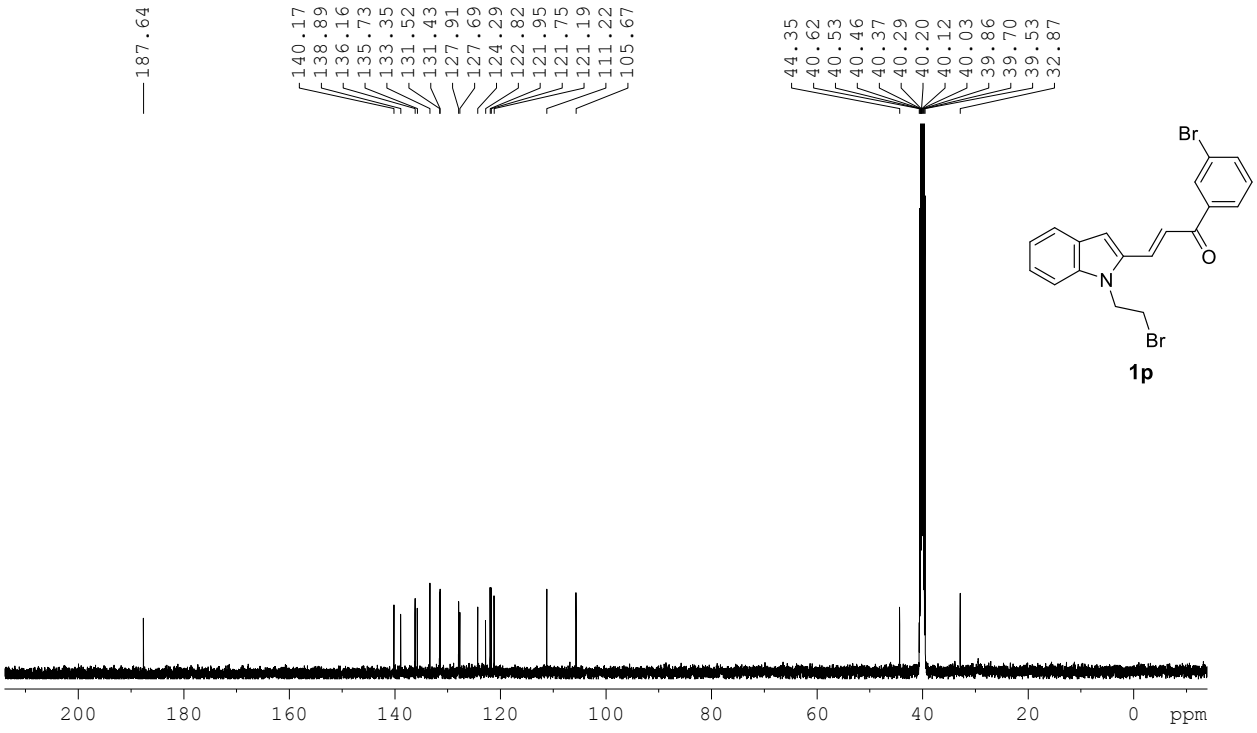
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1o**



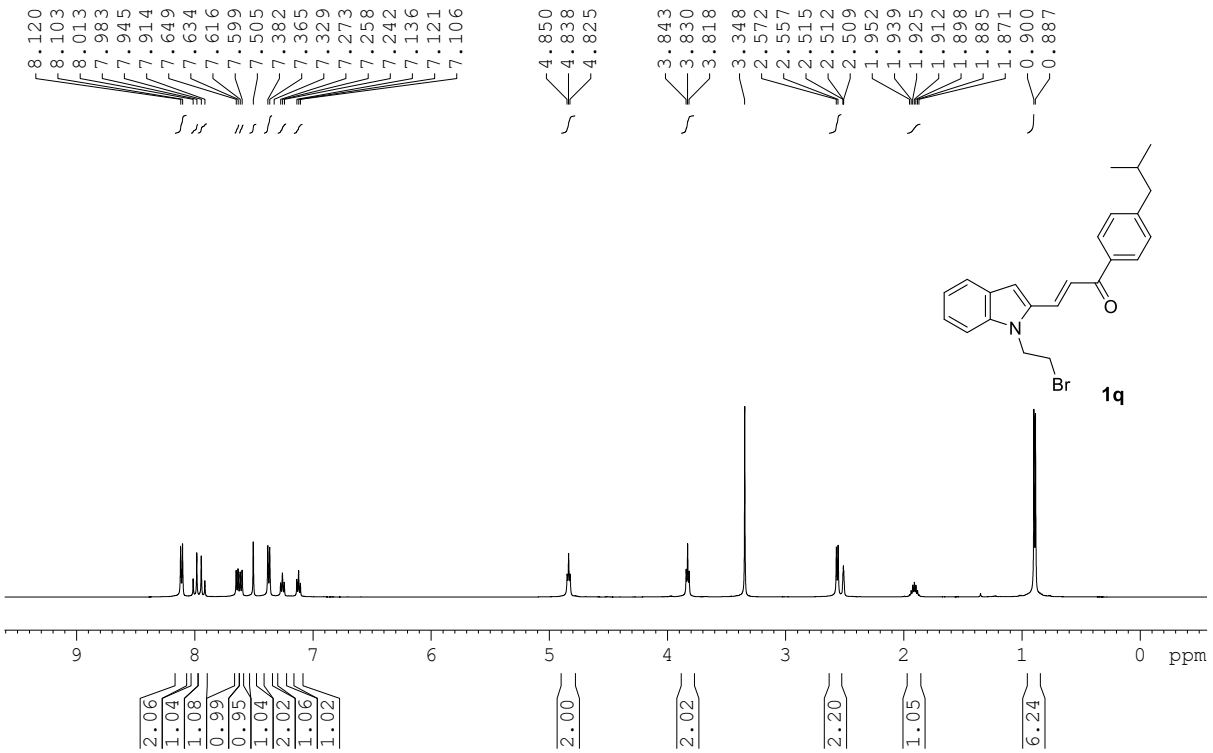
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1o**



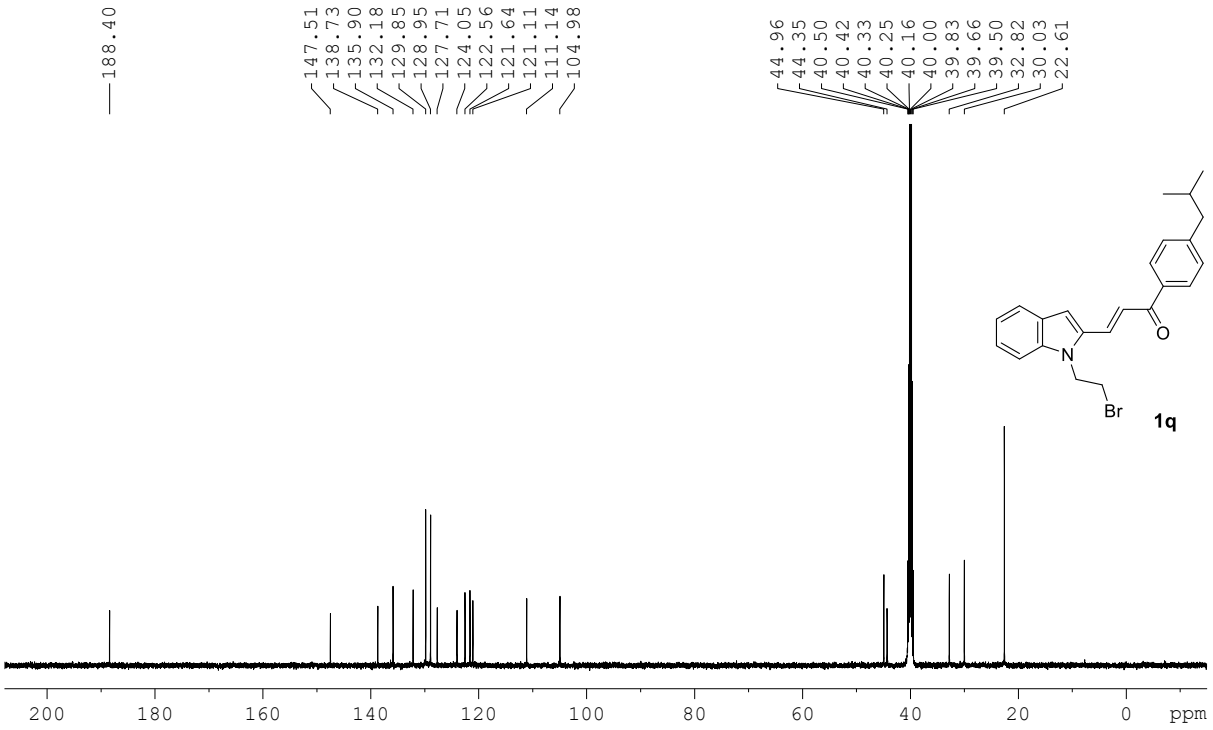
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1p**



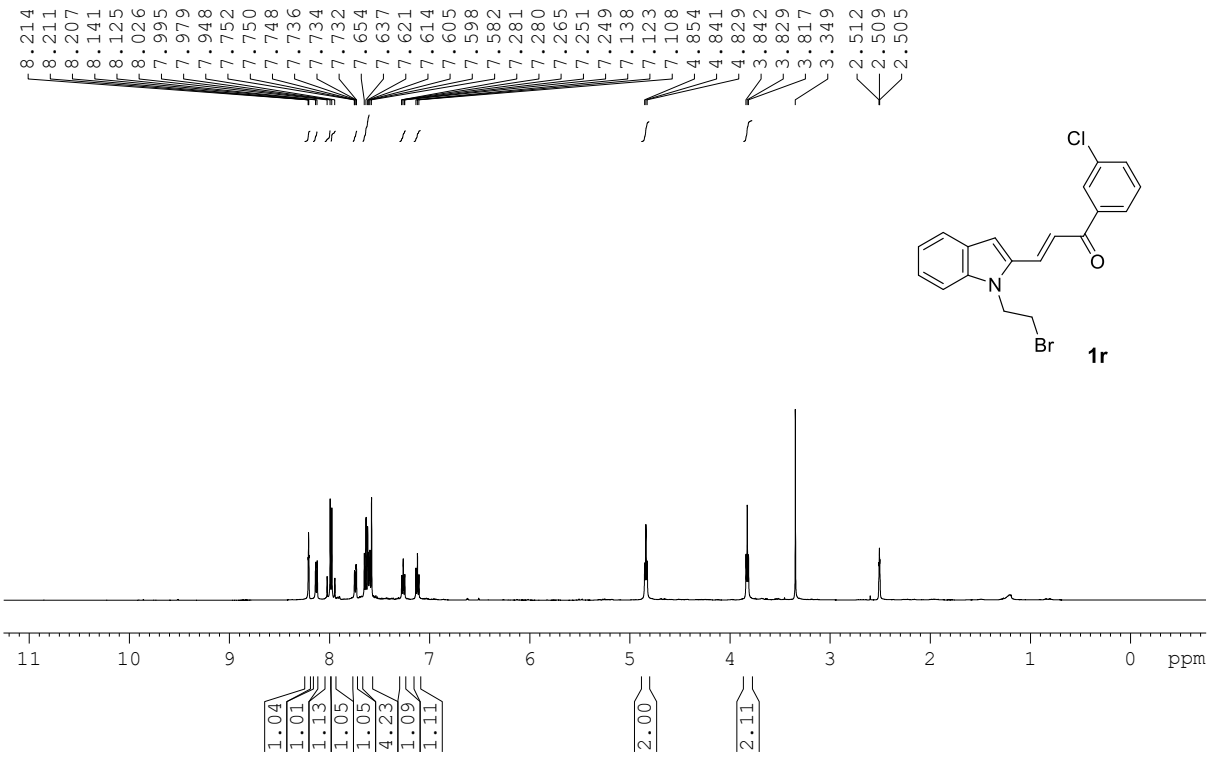
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1p**



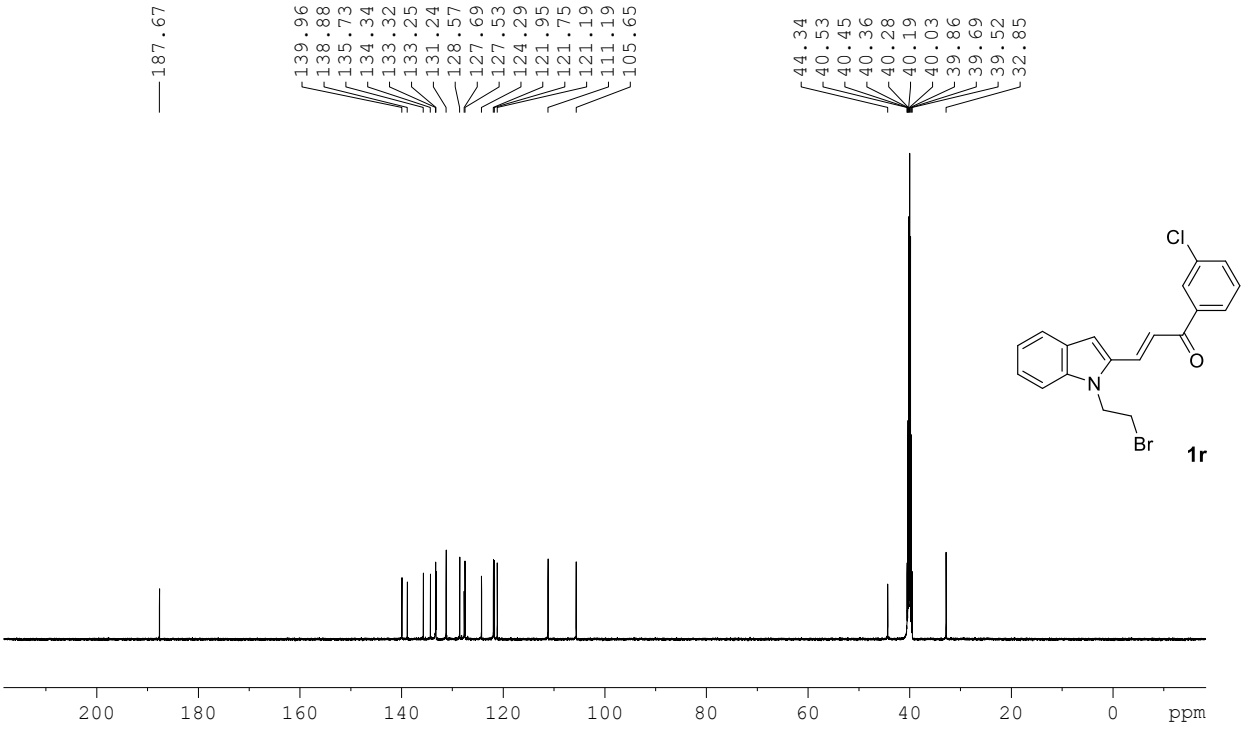
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1q**



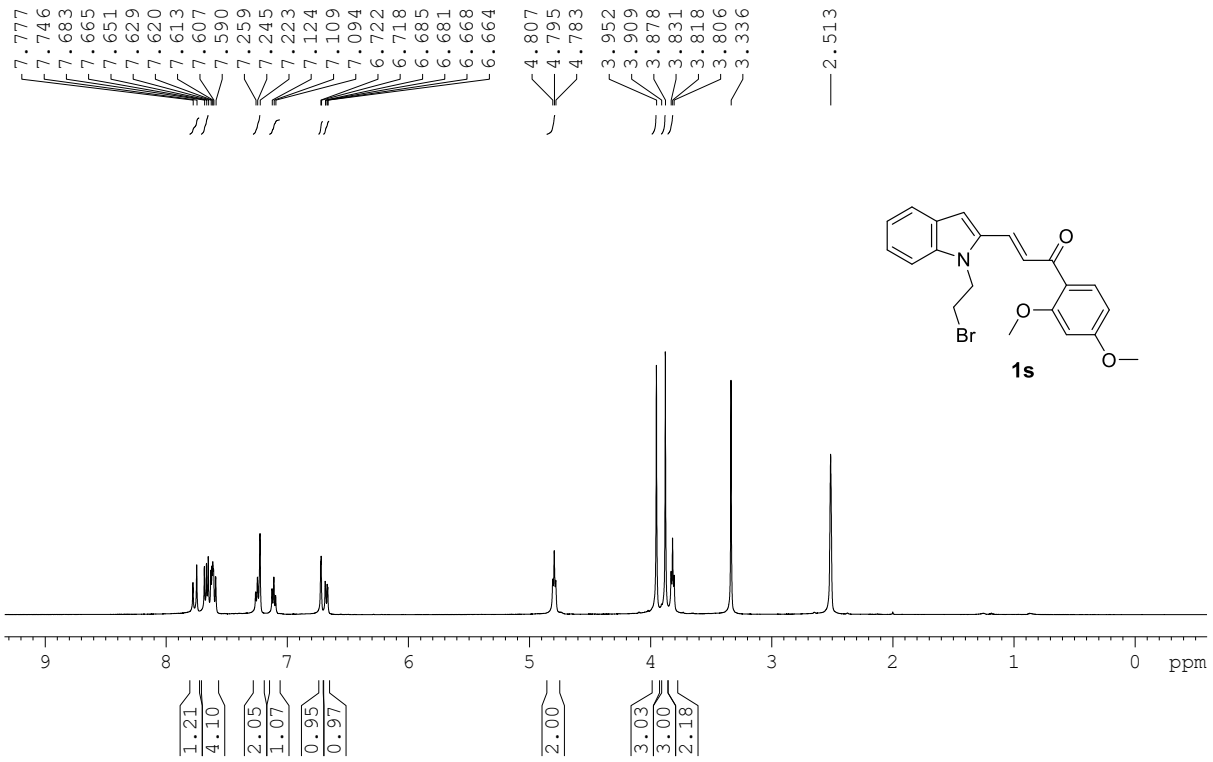
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1q**



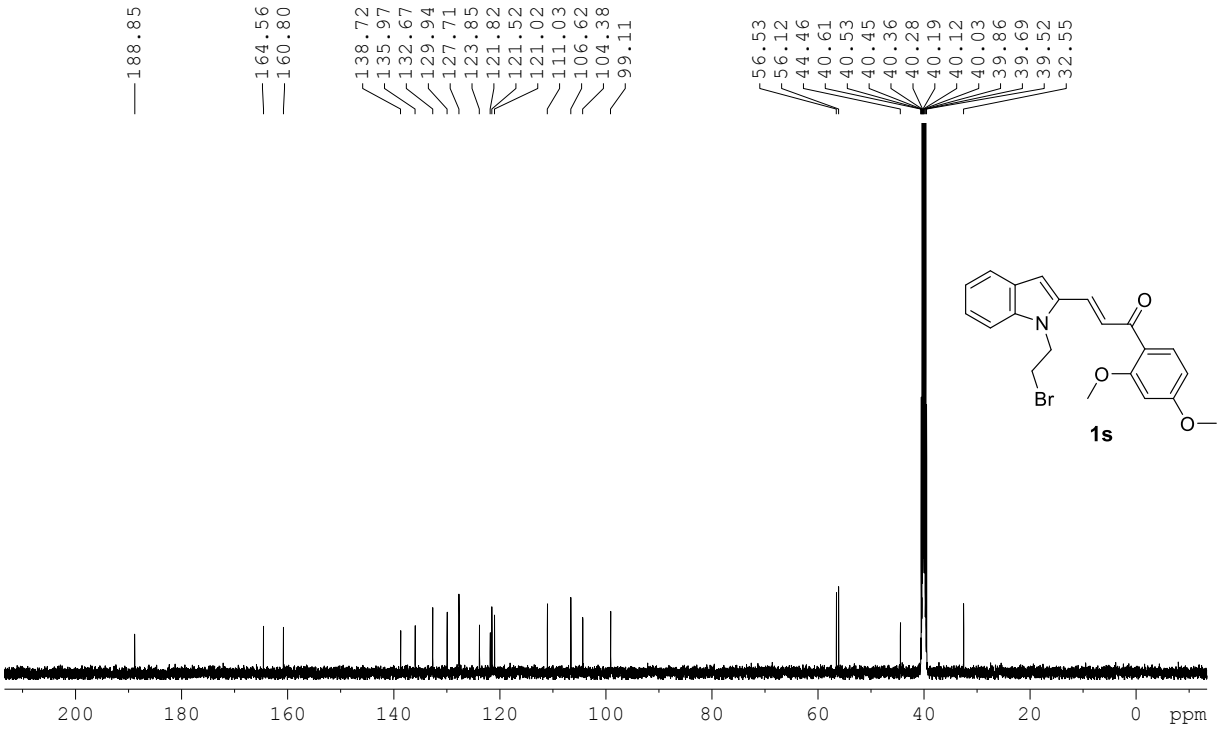
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1r**



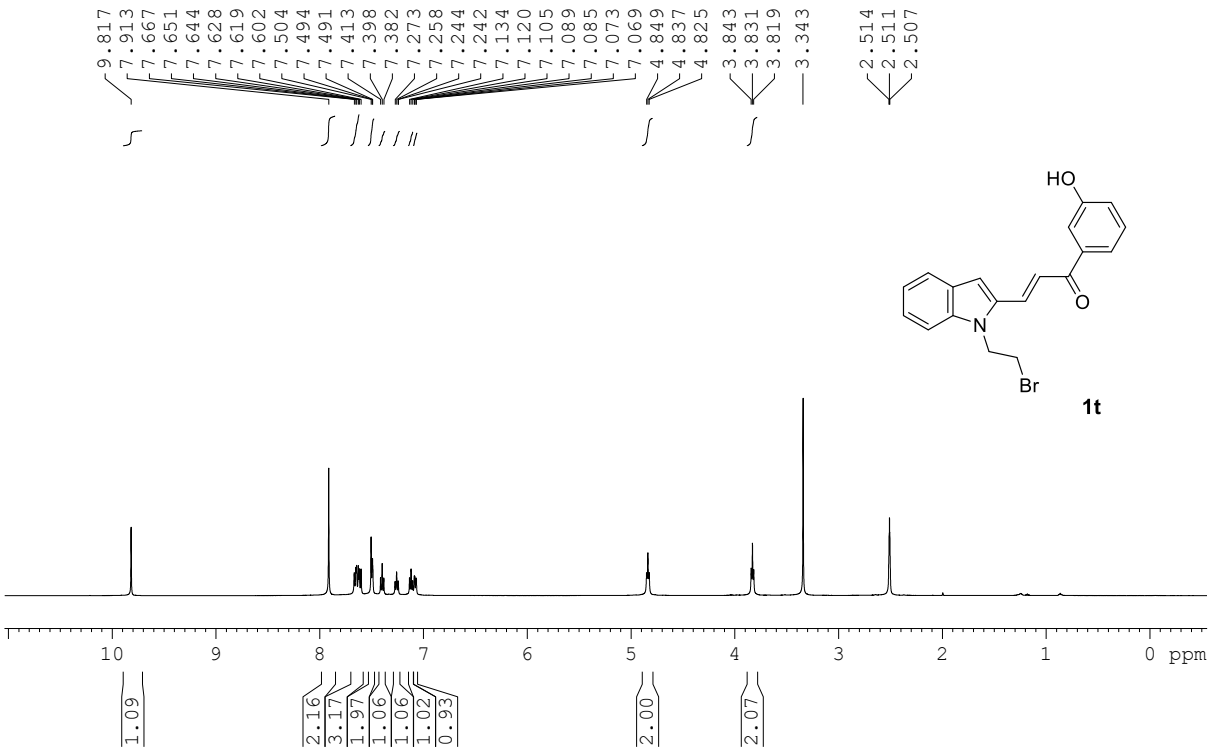
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1r**



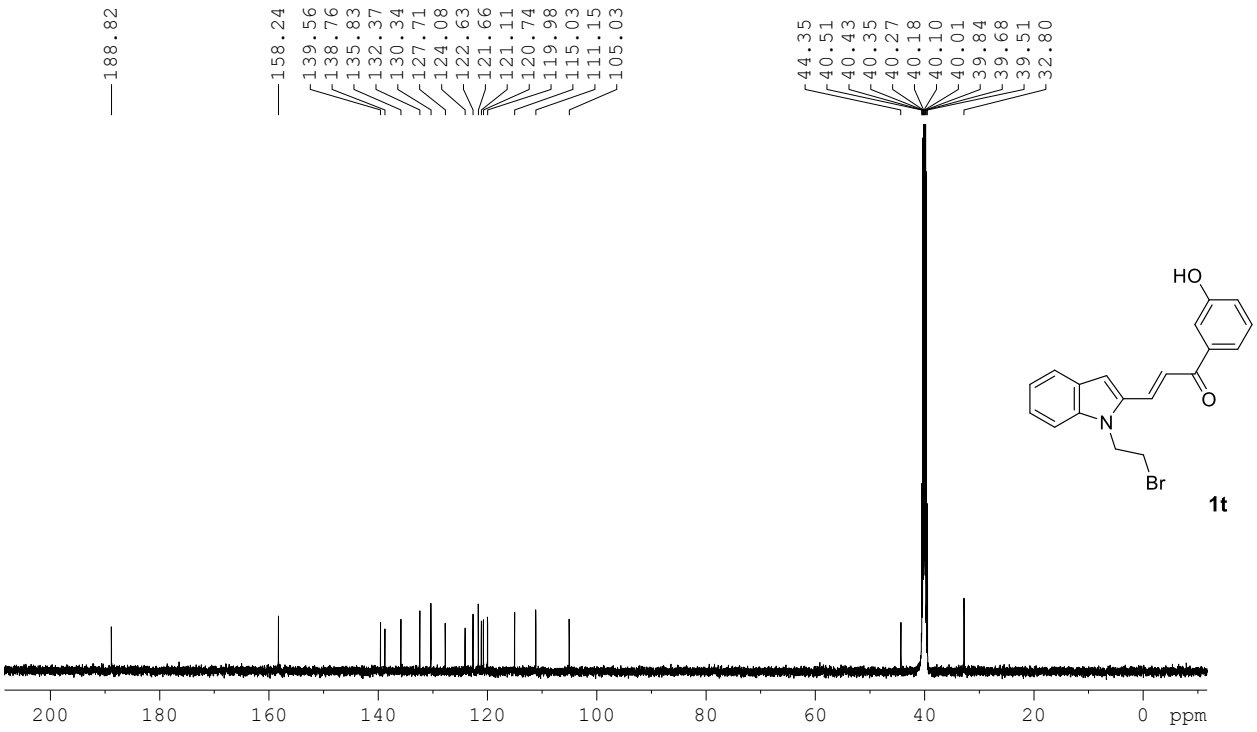
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1s**



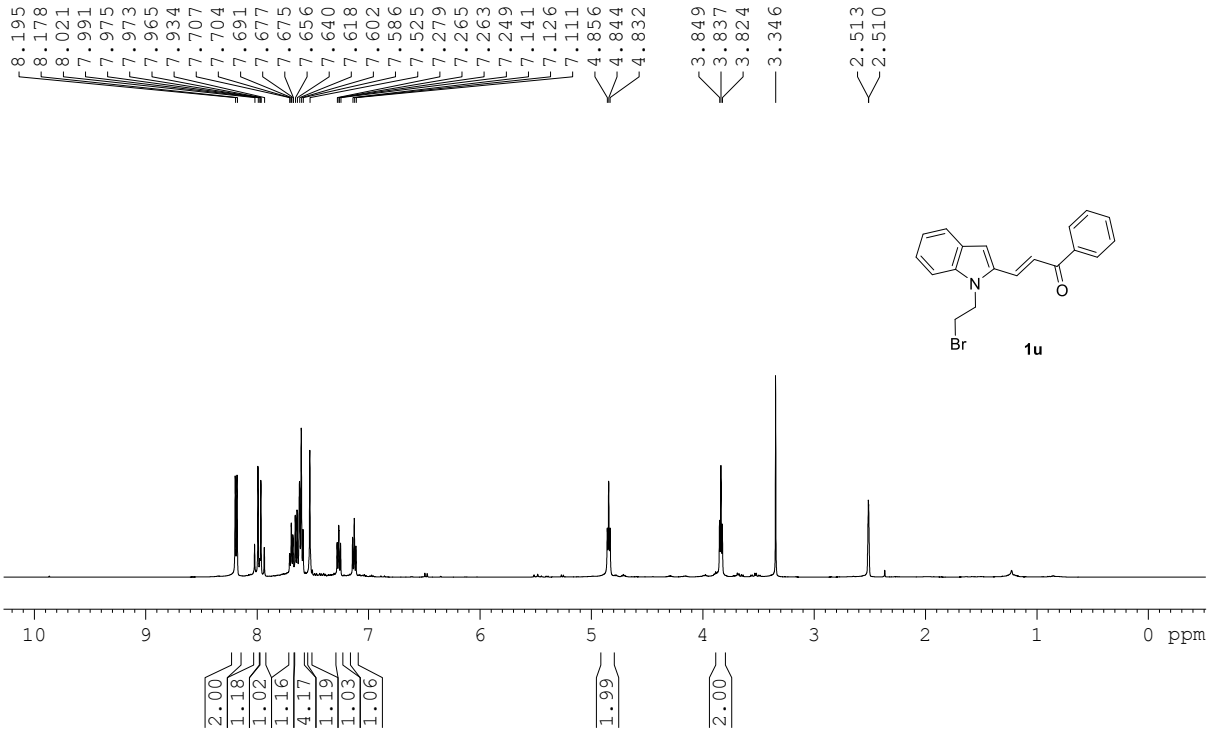
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1s**



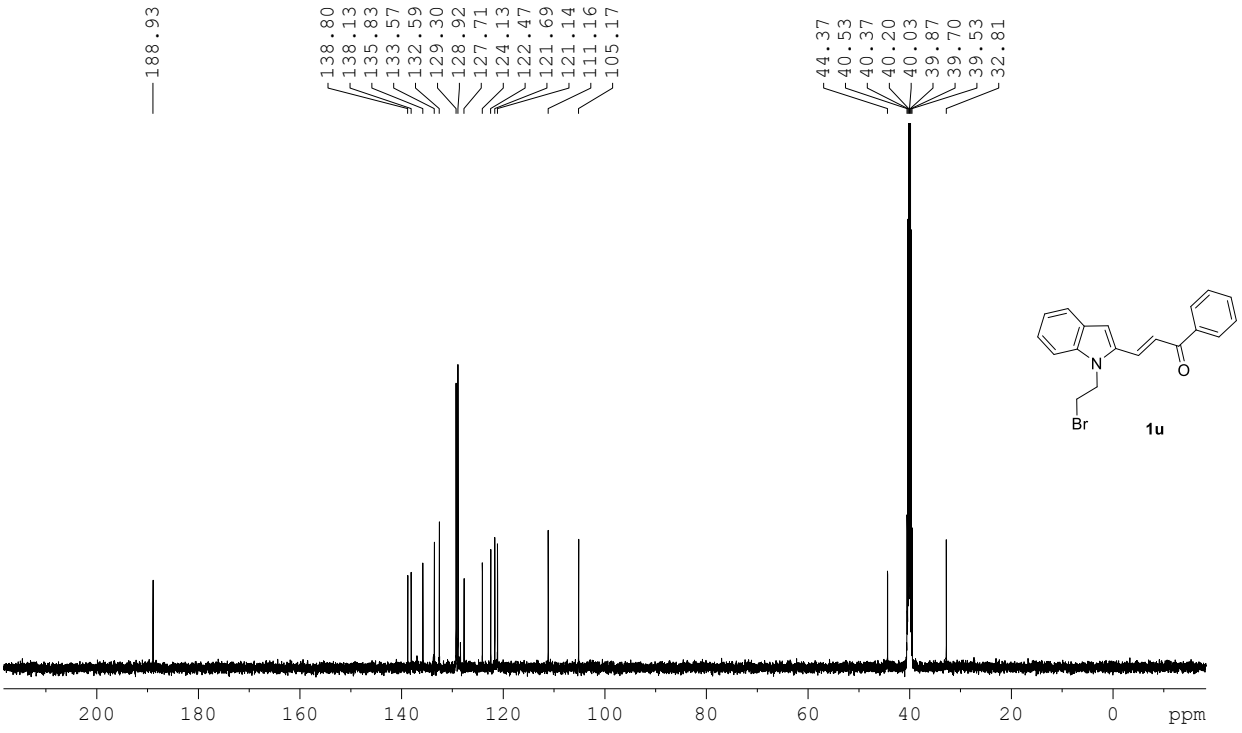
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1t**



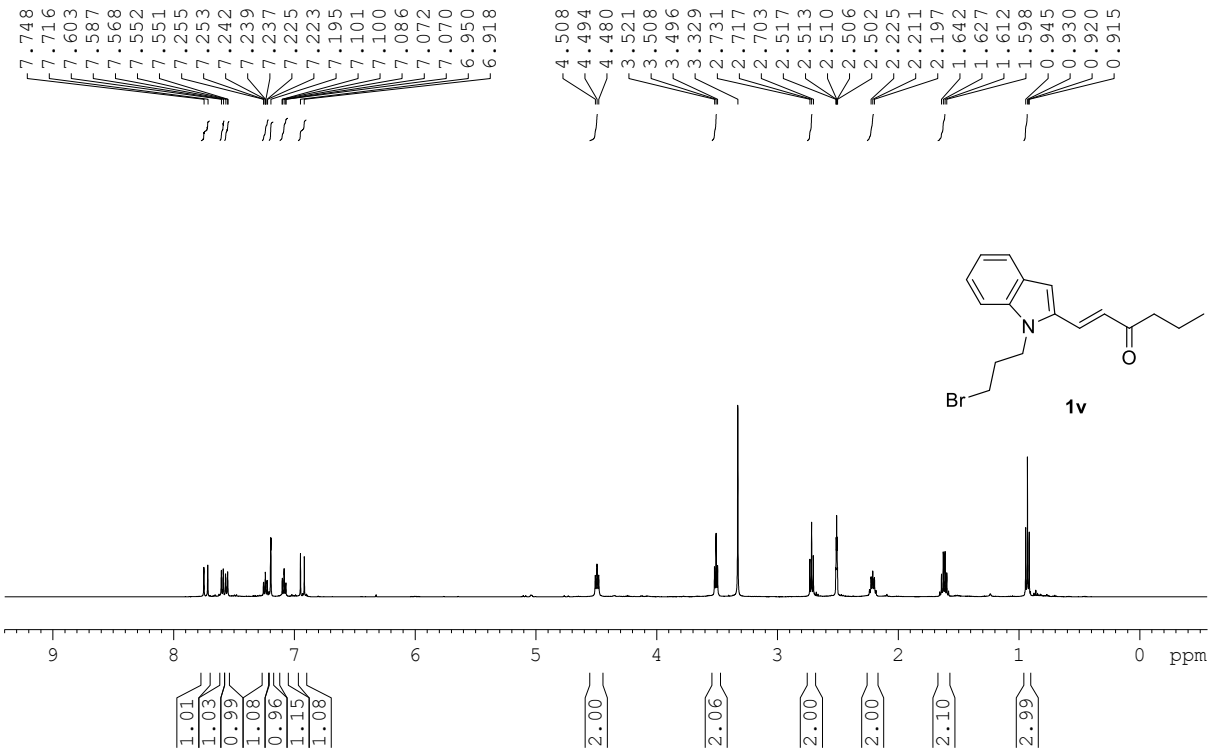
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1t**



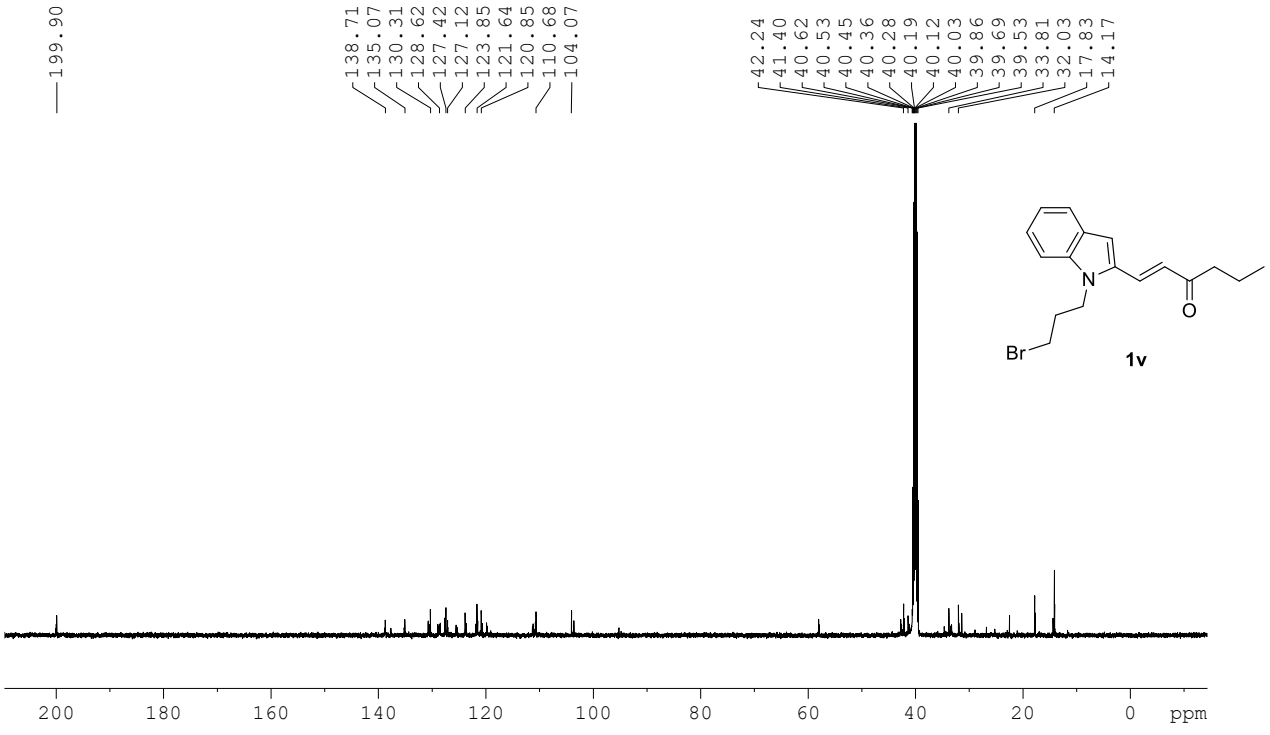
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1u**



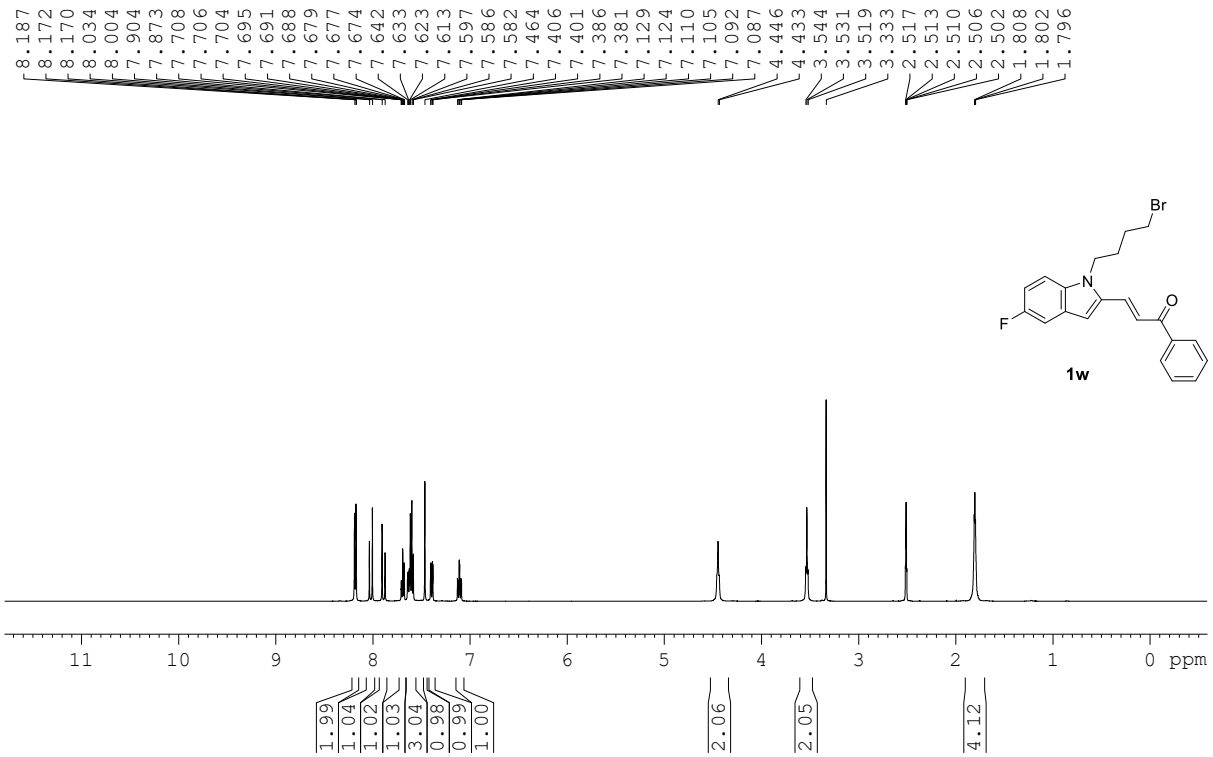
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1u**



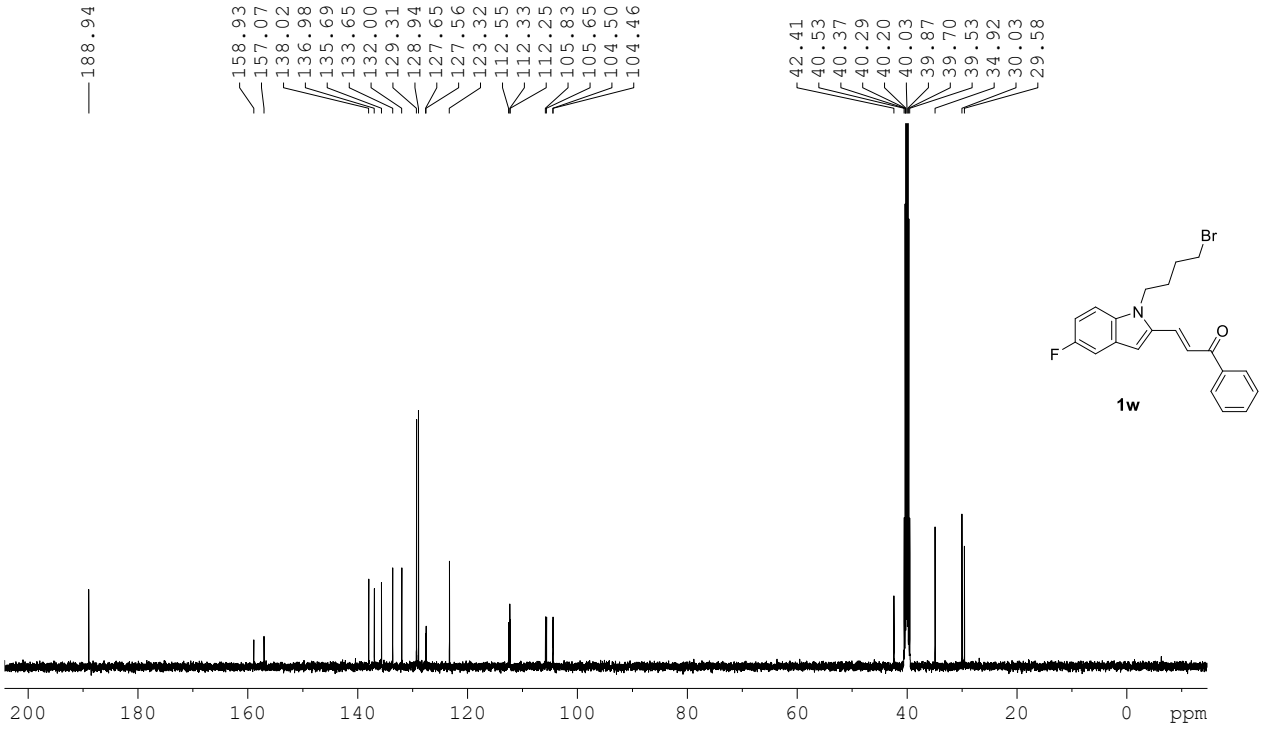
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1v**



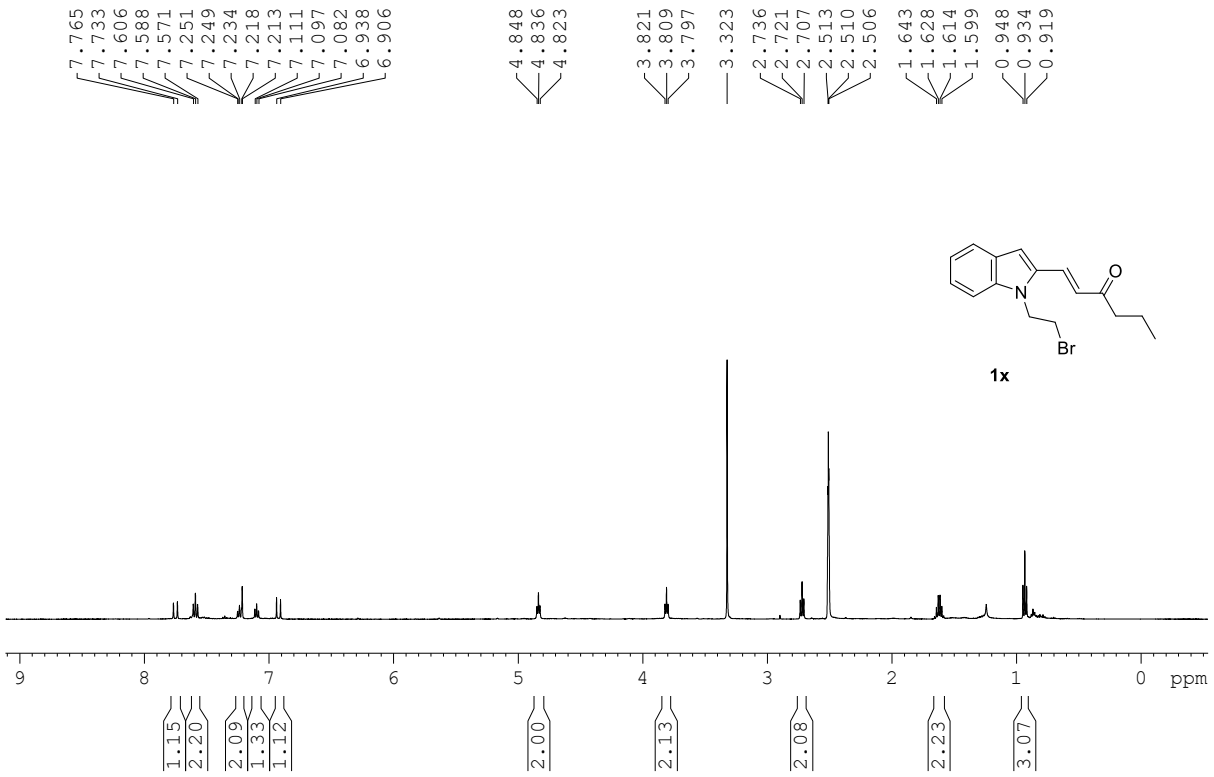
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1v**



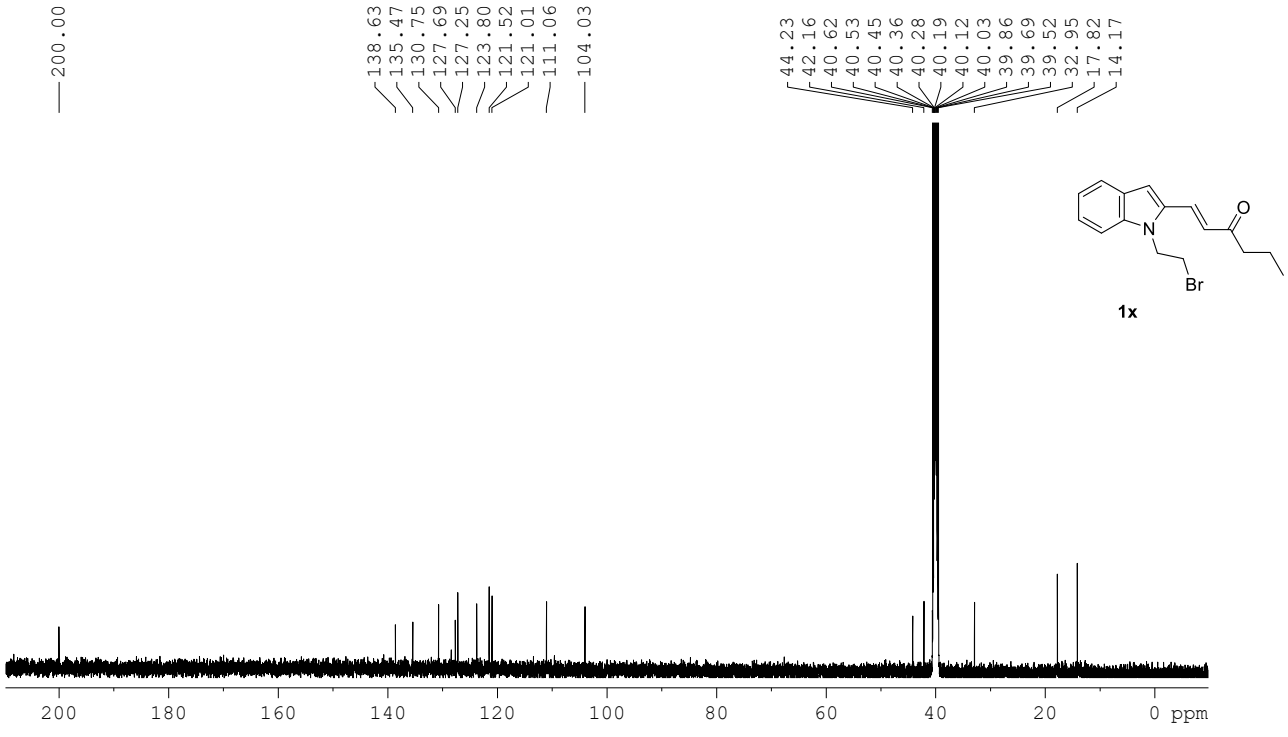
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1w**



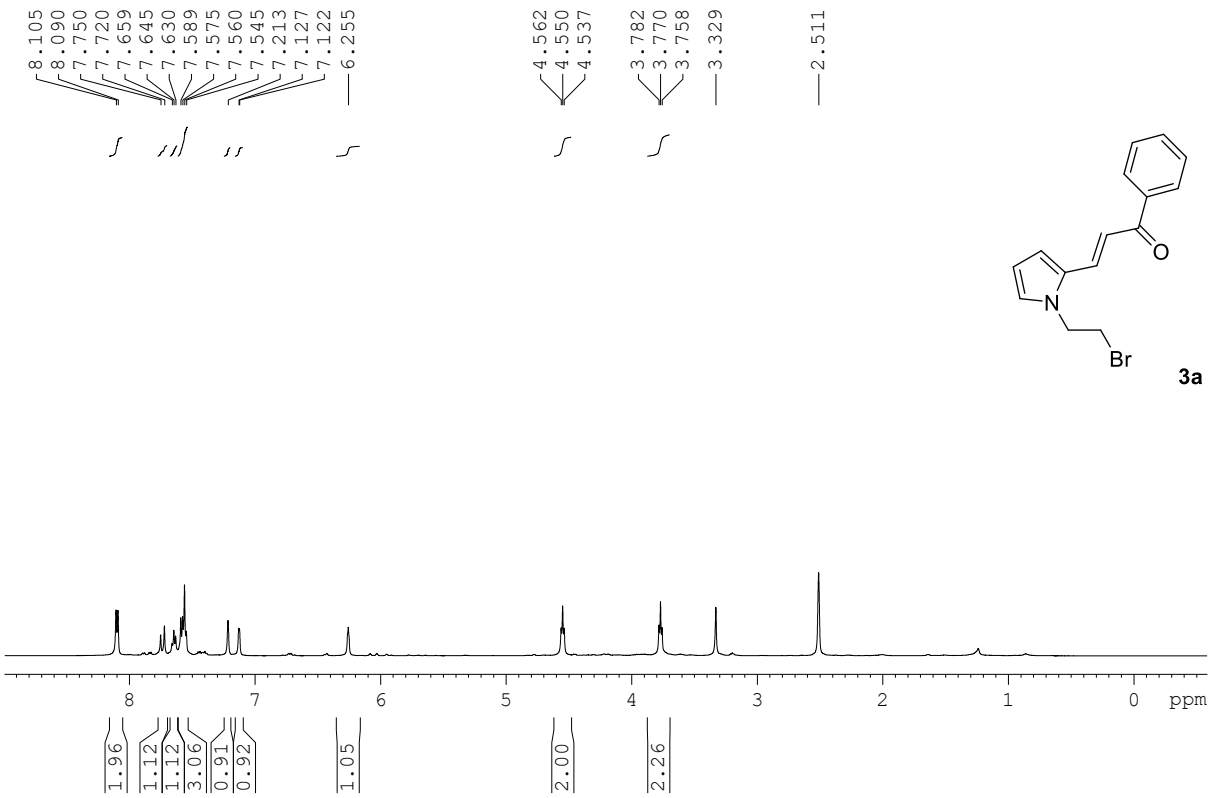
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1w**



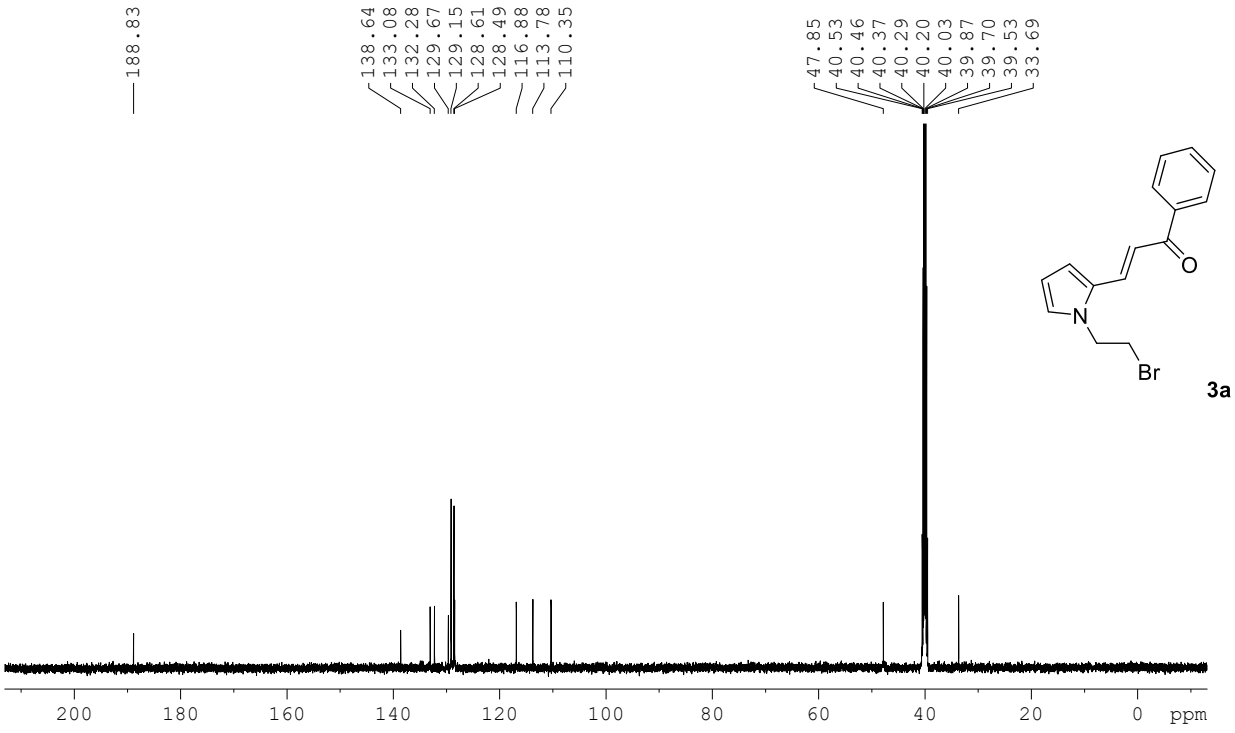
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **1x**



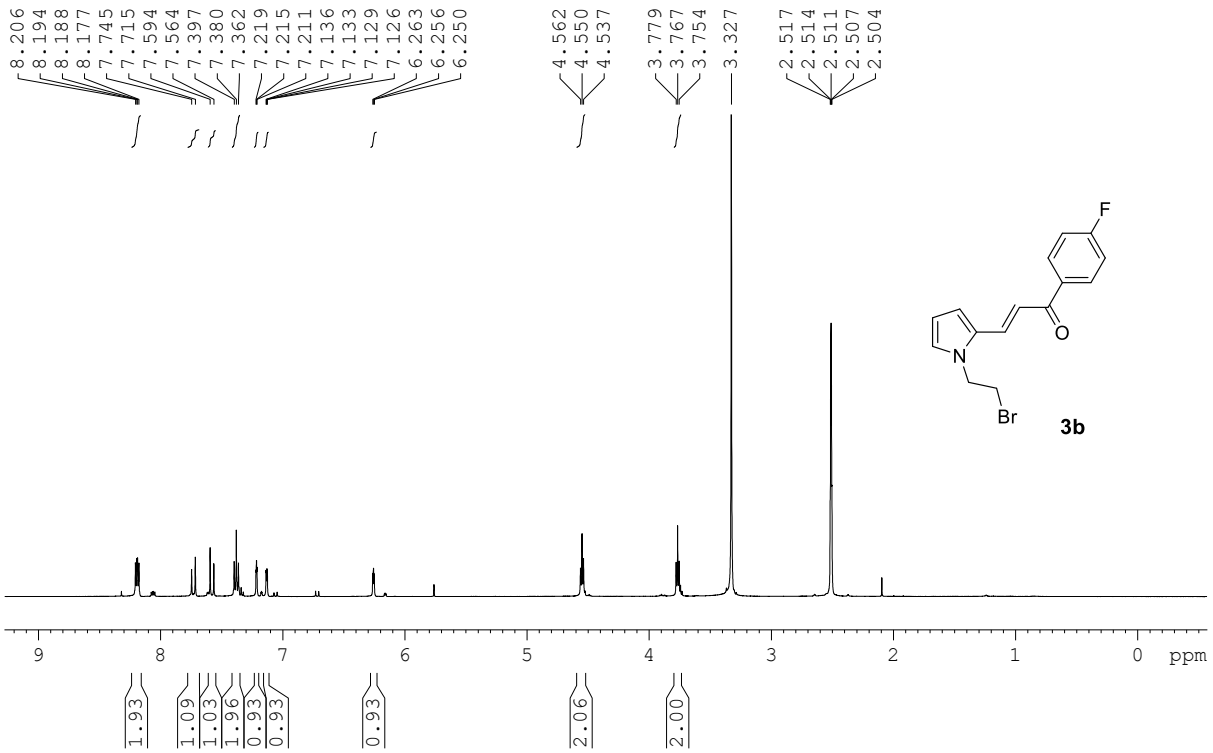
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **1x**



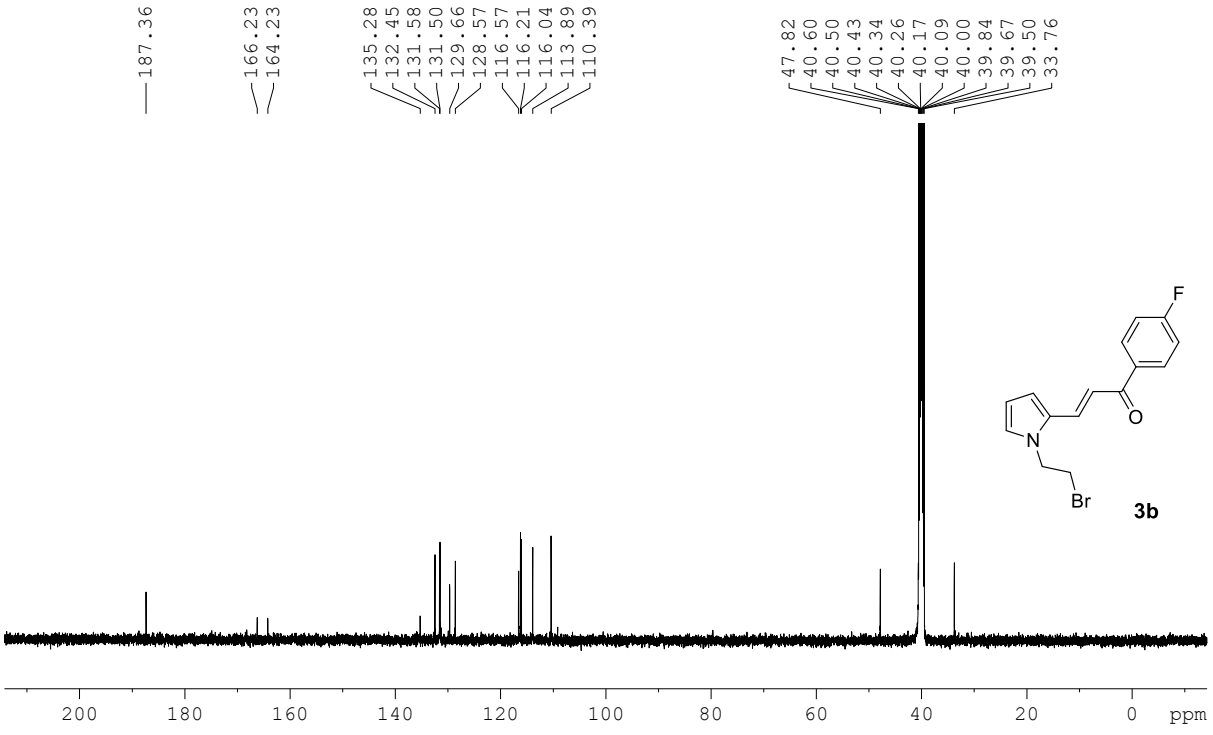
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **3a**



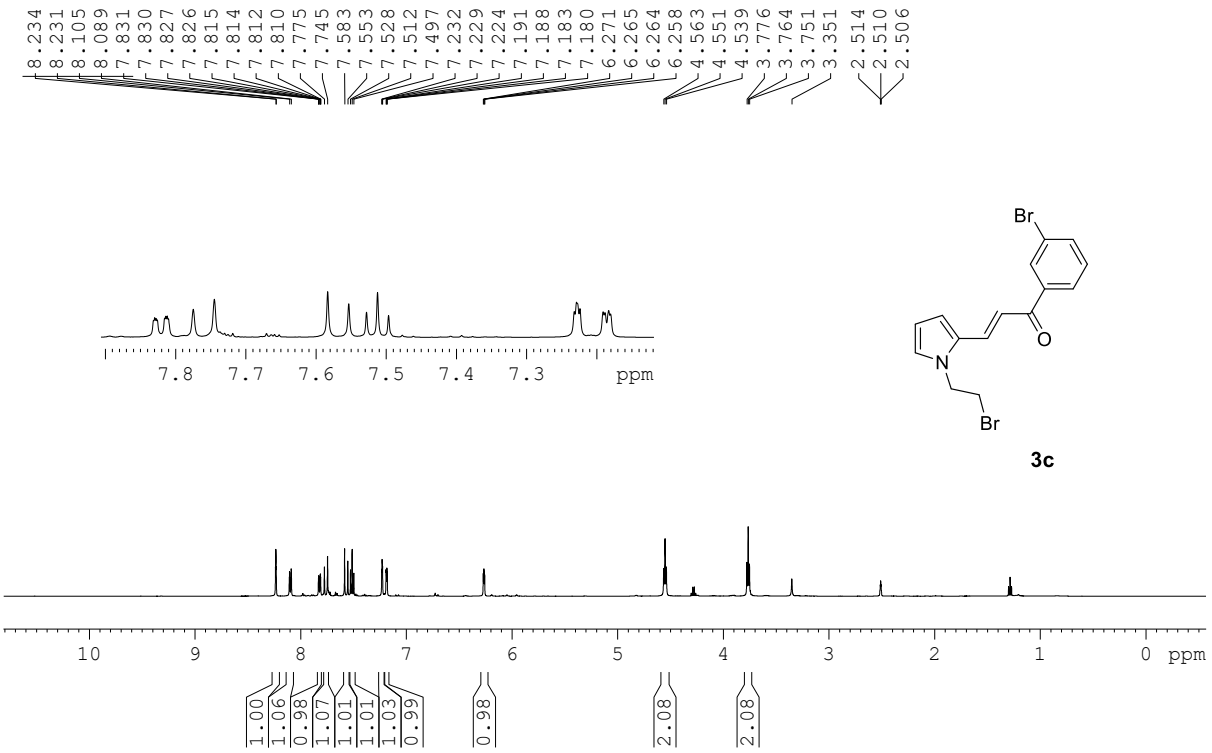
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **3a**



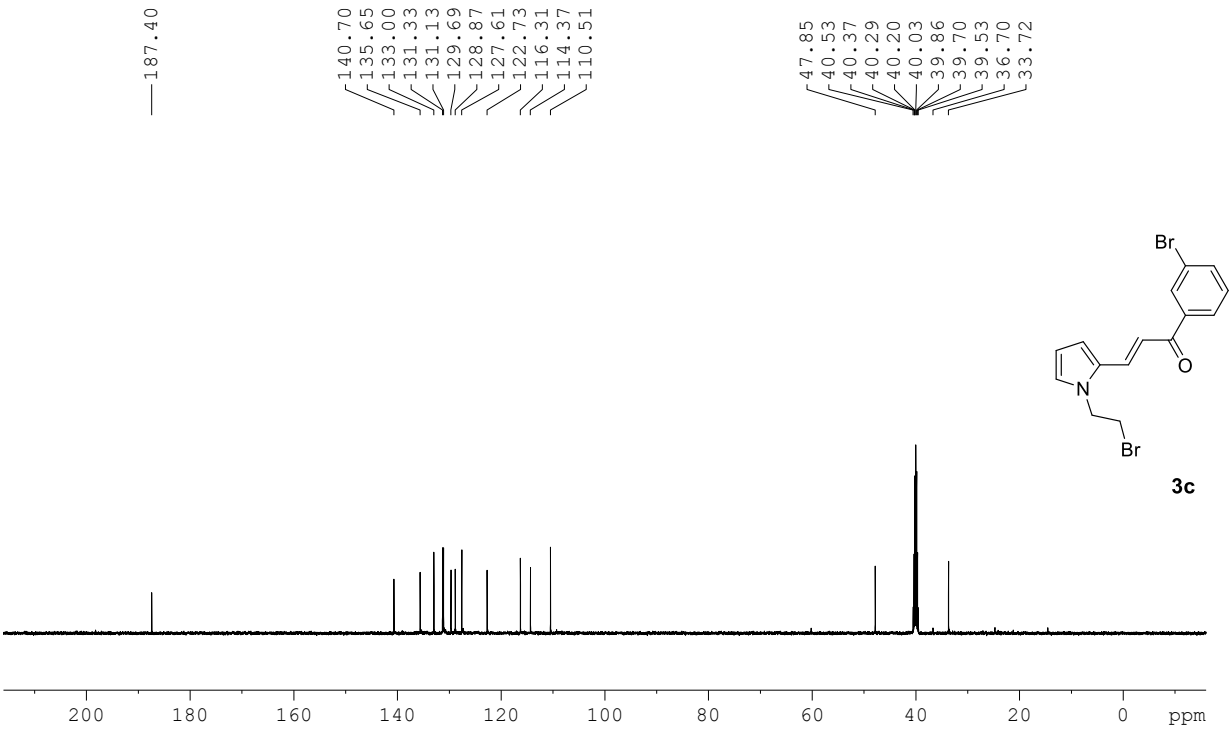
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **3b**



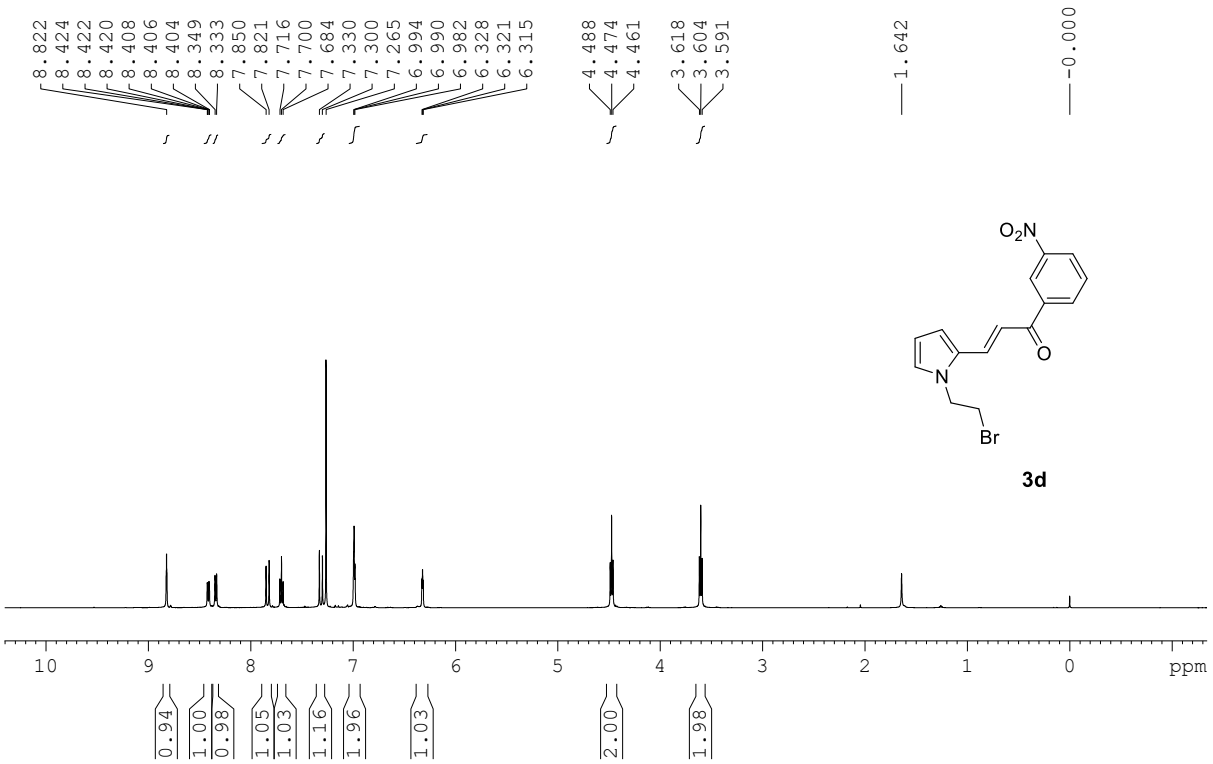
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **3b**



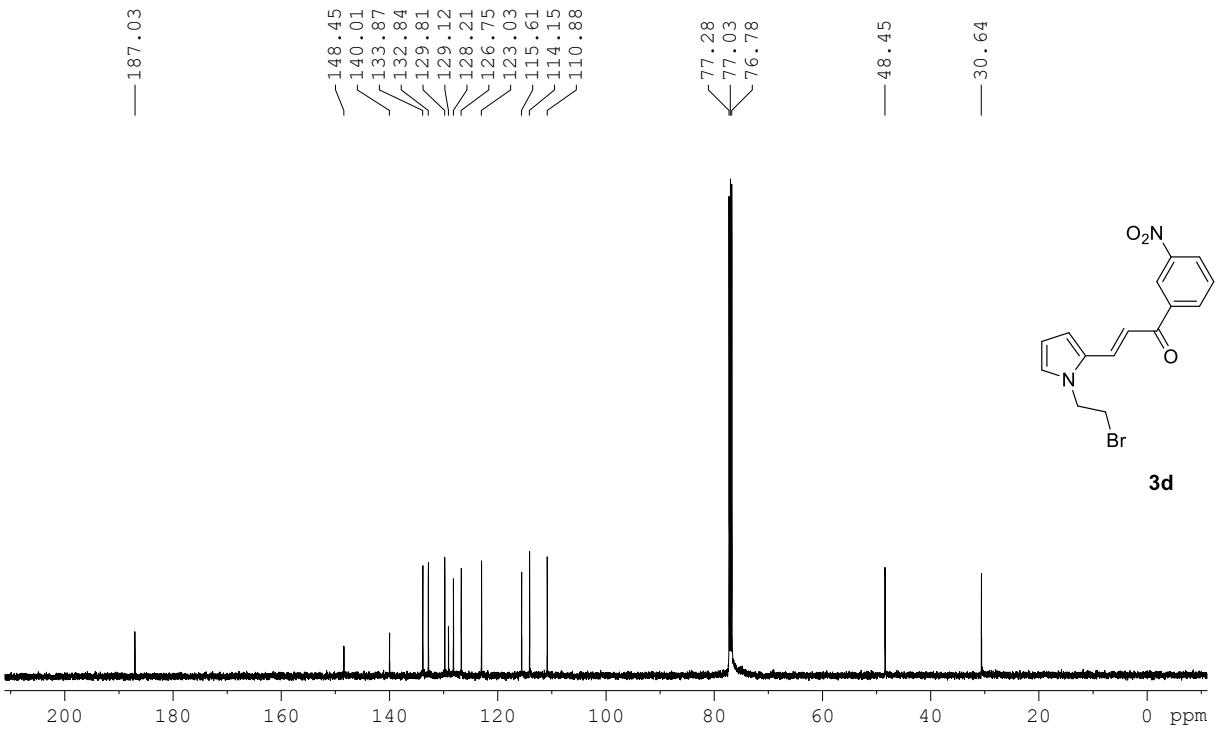
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **3c**



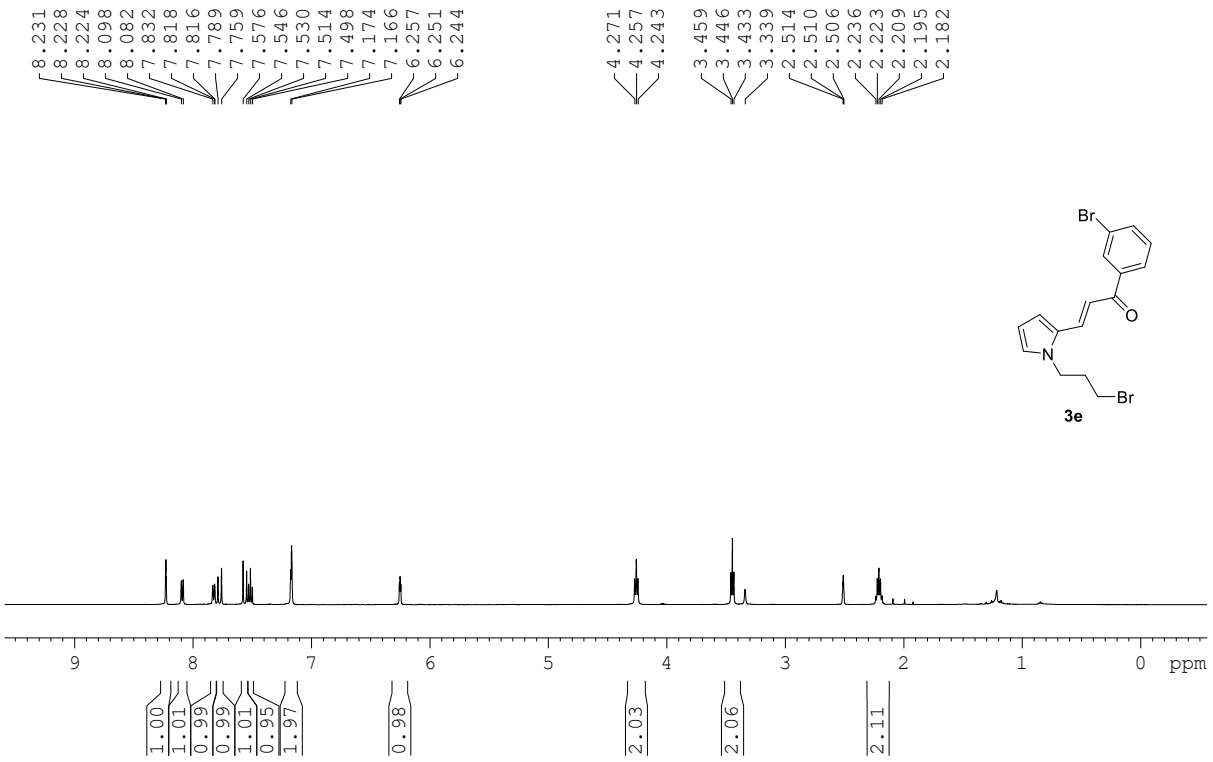
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **3c**



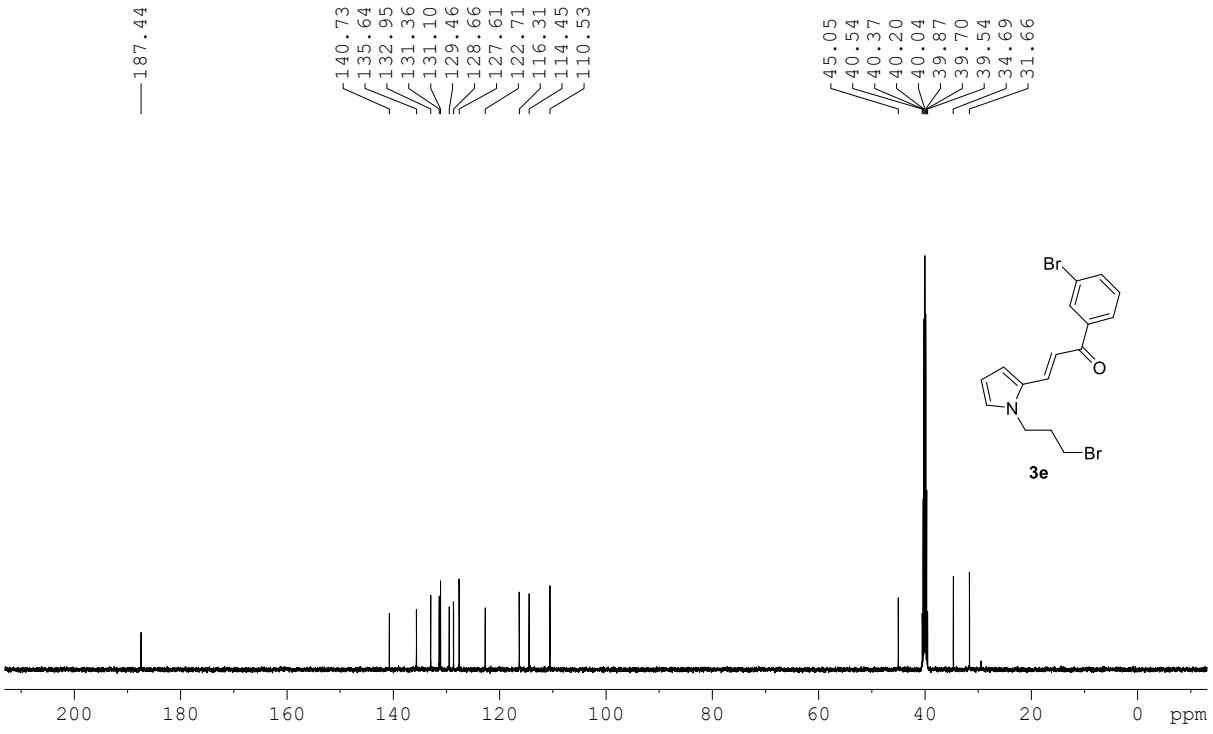
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **3d**



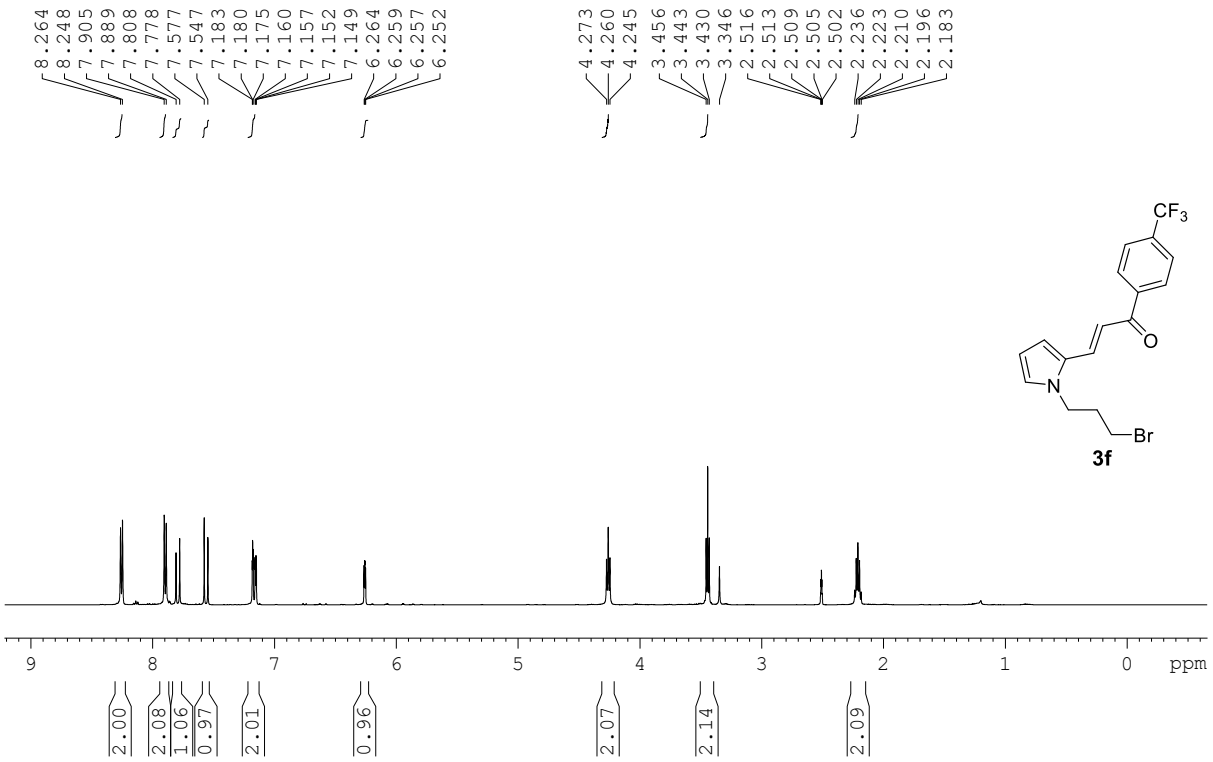
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **3d**



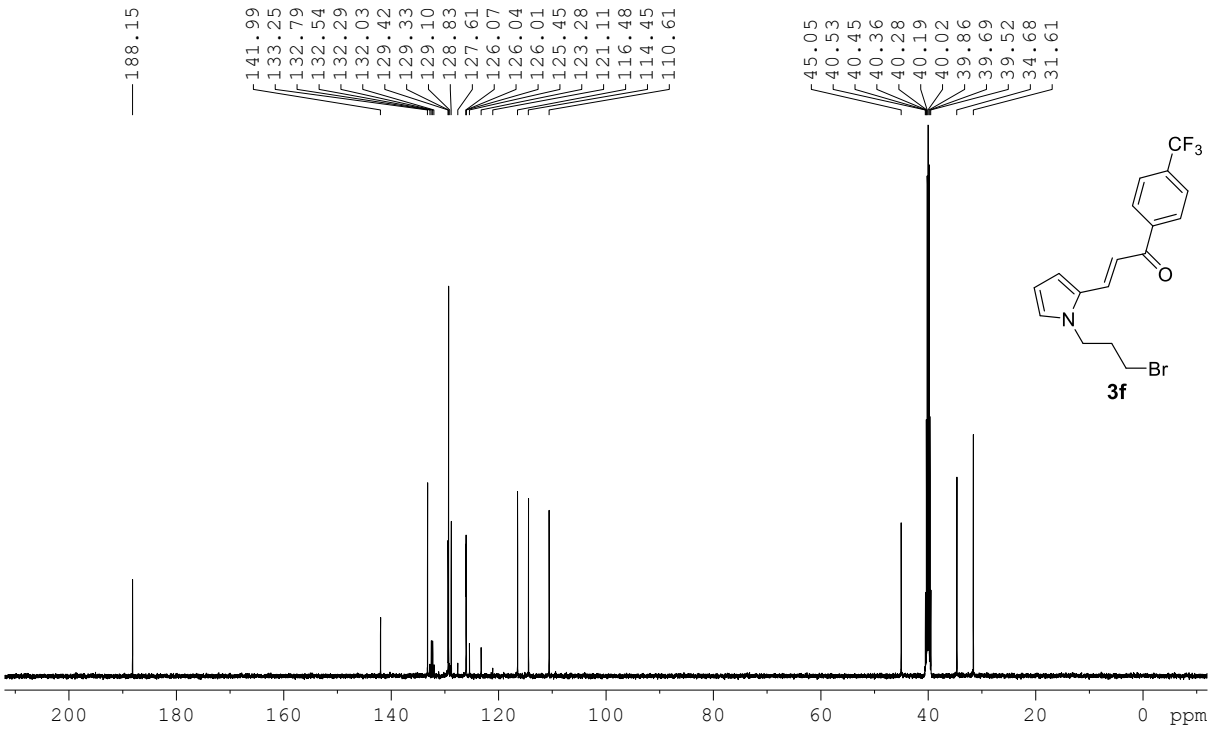
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **3e**



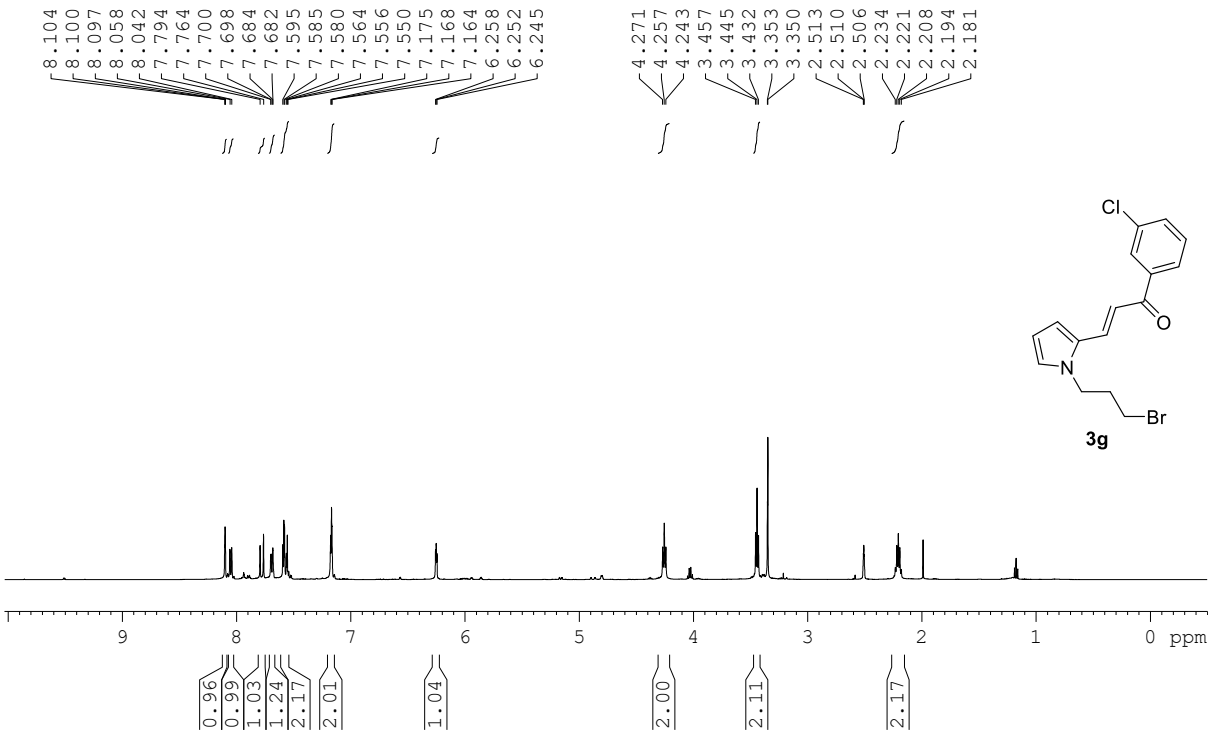
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **3e**



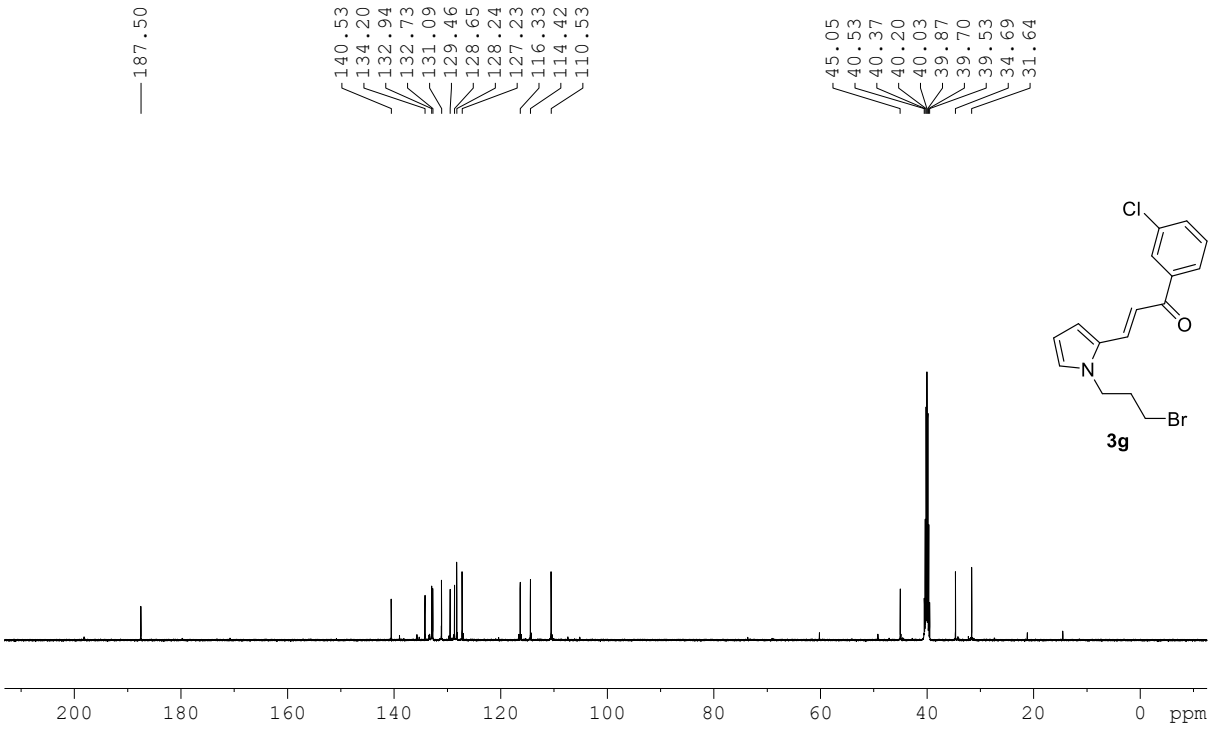
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **3f**



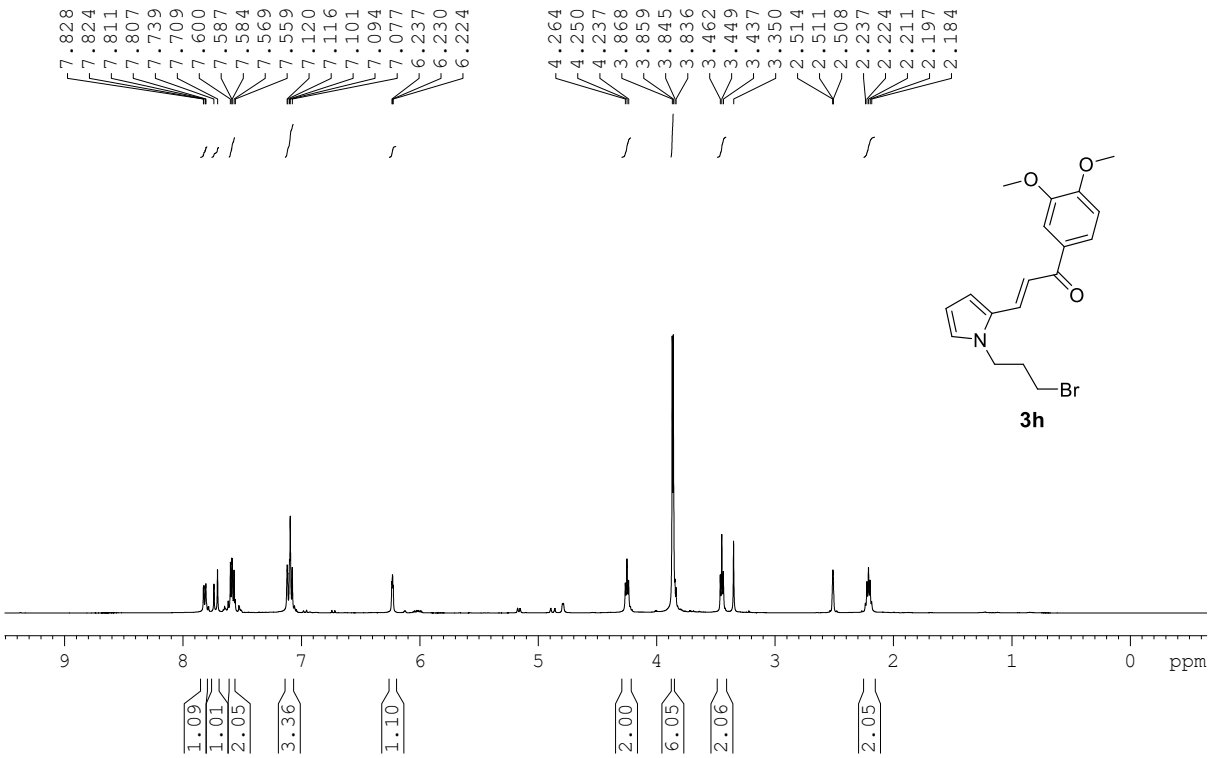
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **3f**



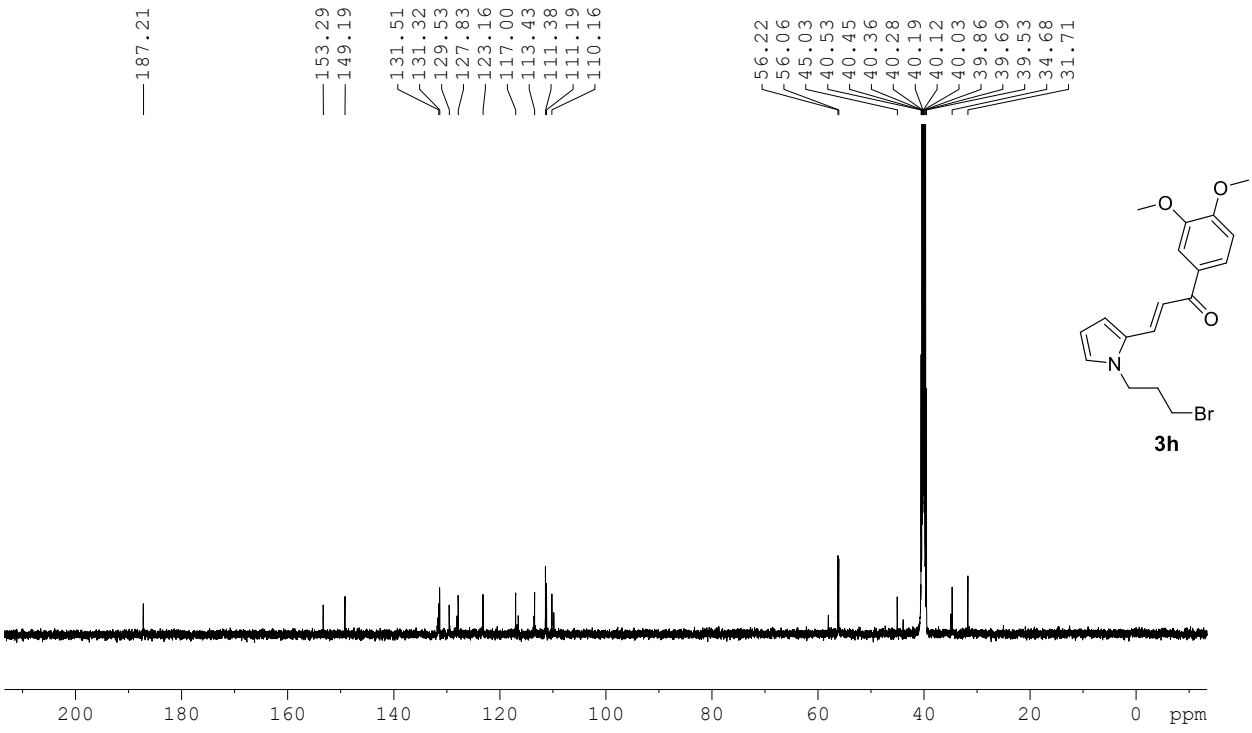
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **3g**



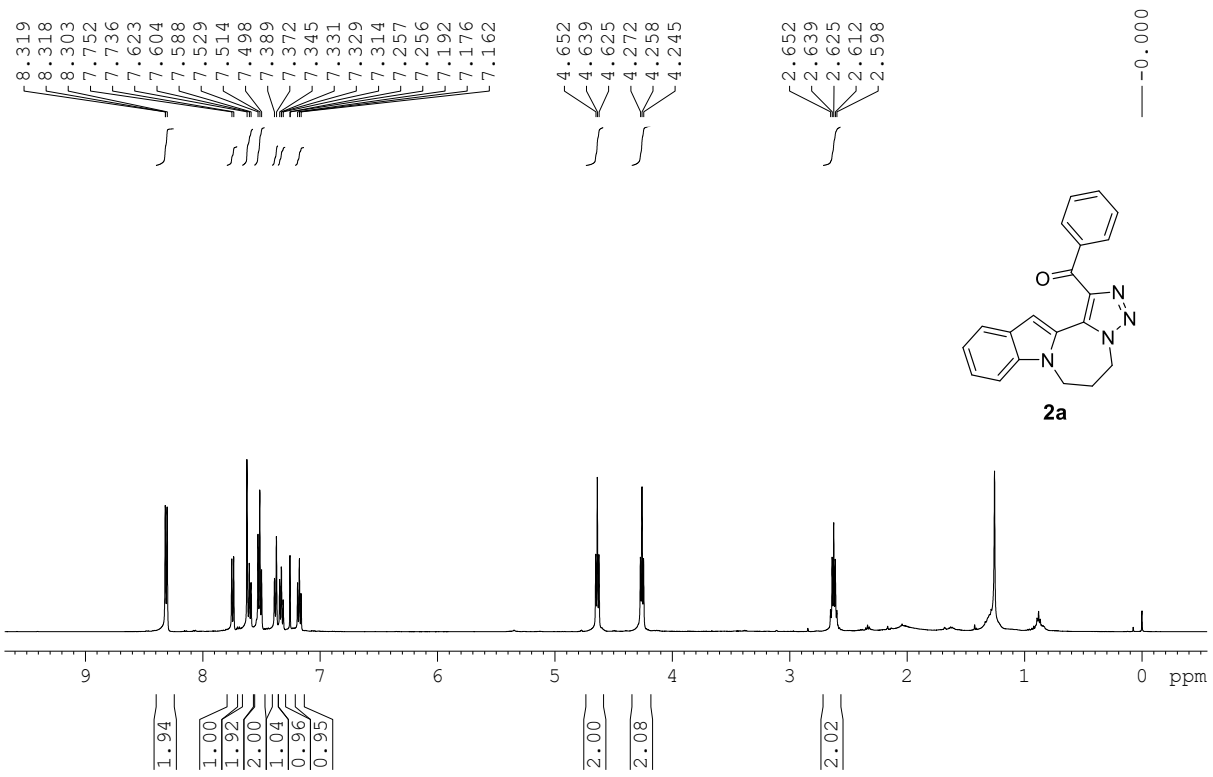
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **3g**



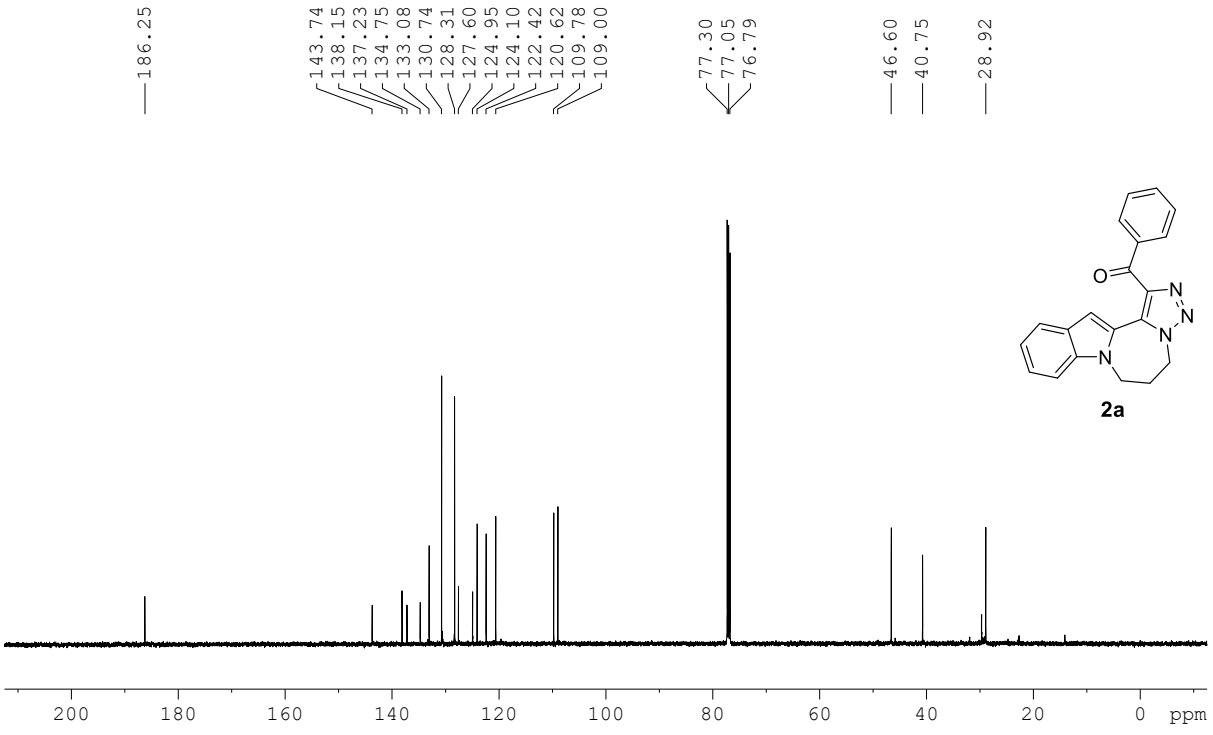
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **3h**



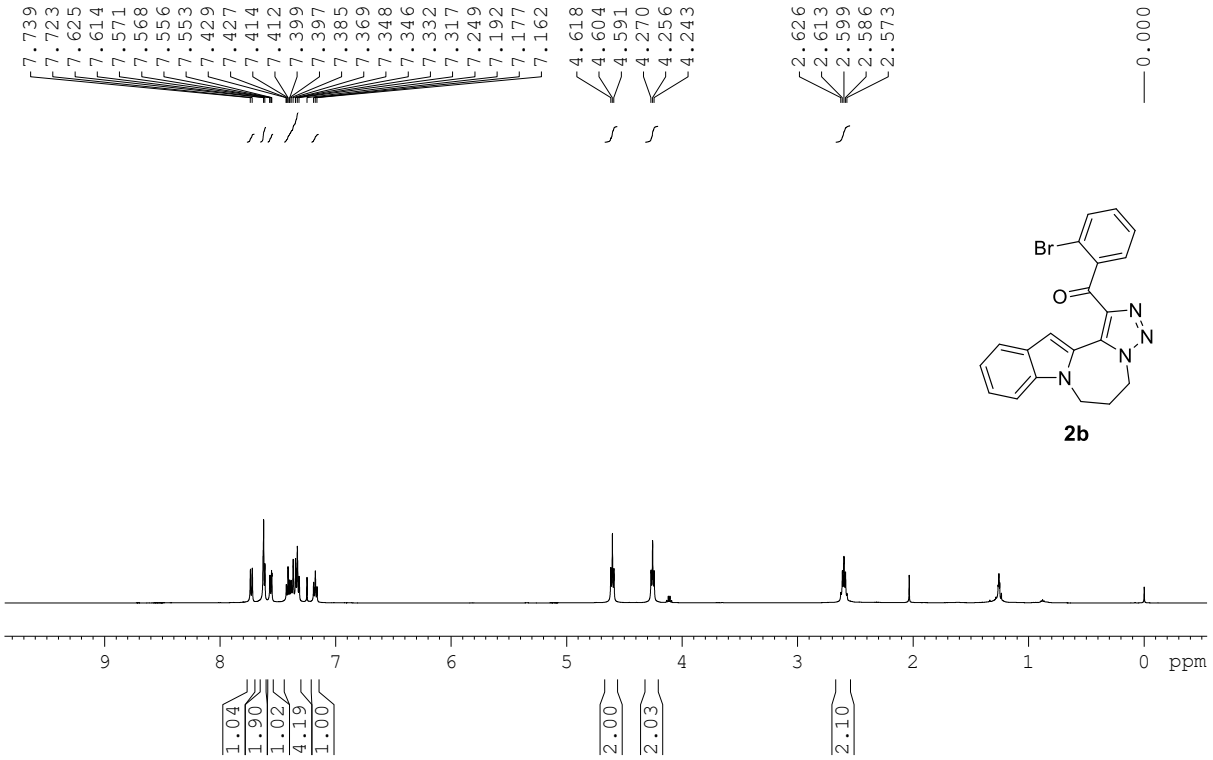
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **3h**



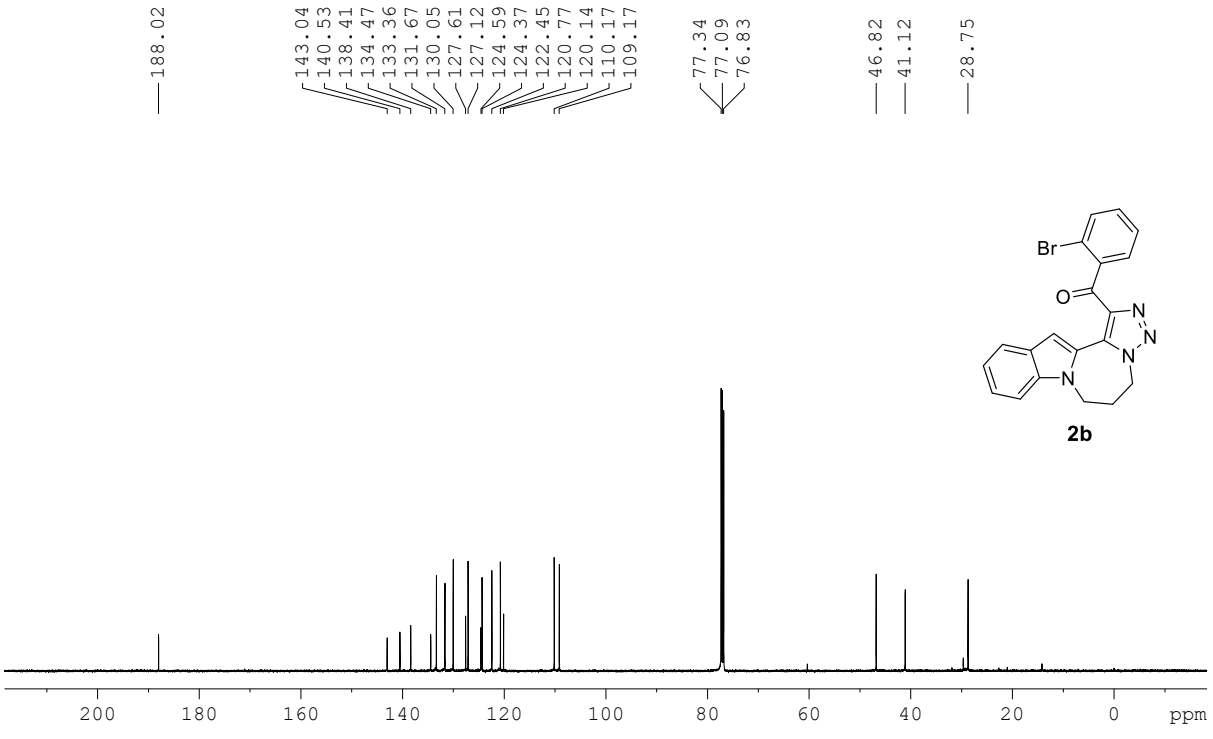
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **2a**



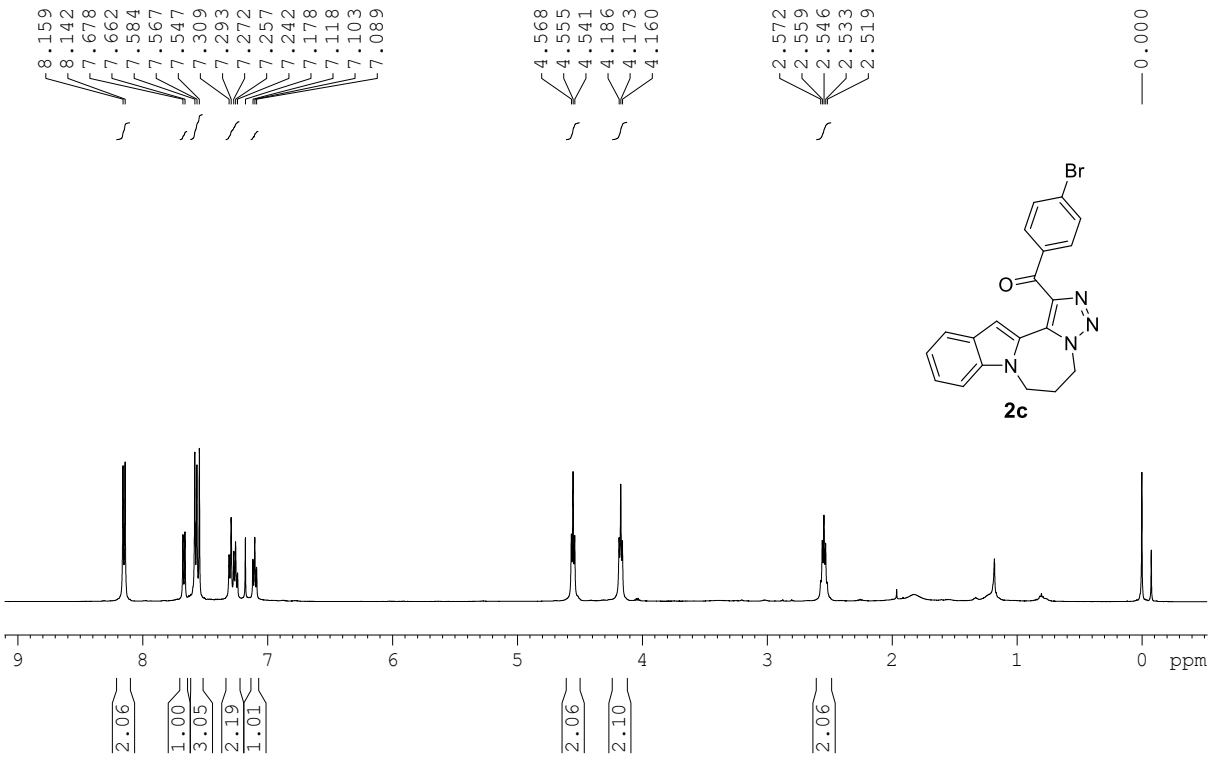
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **2a**



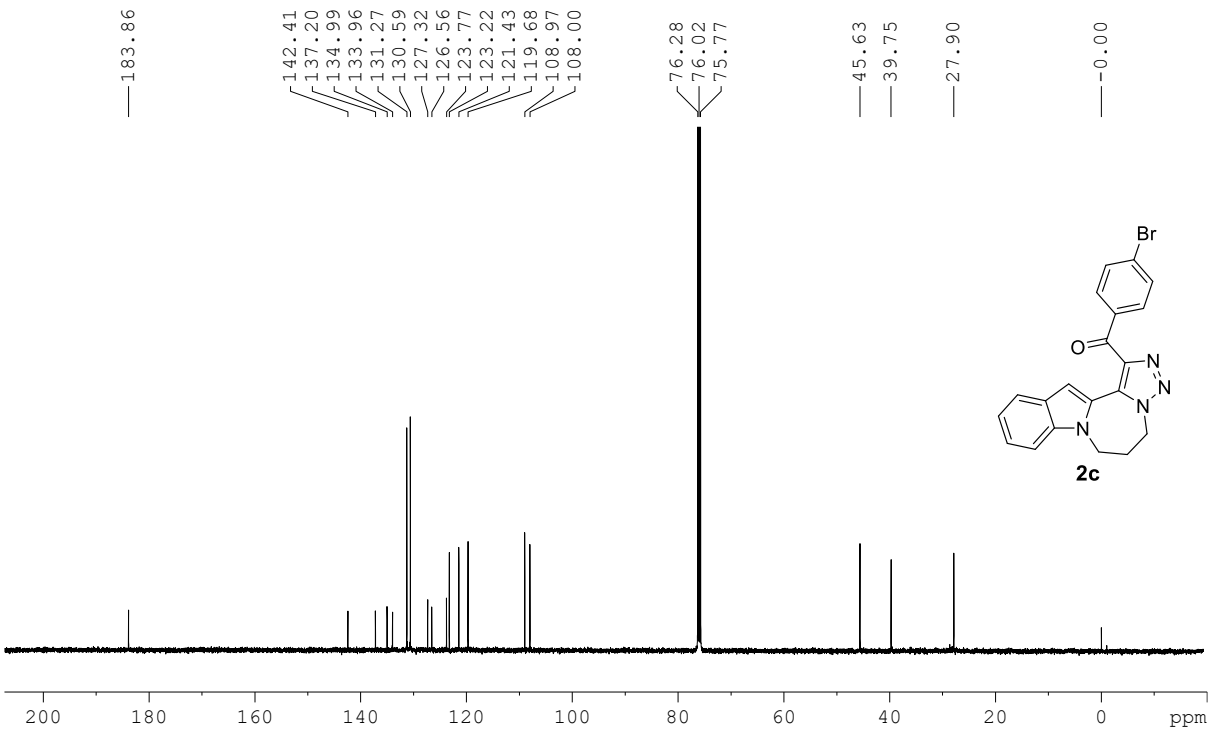
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **2b**



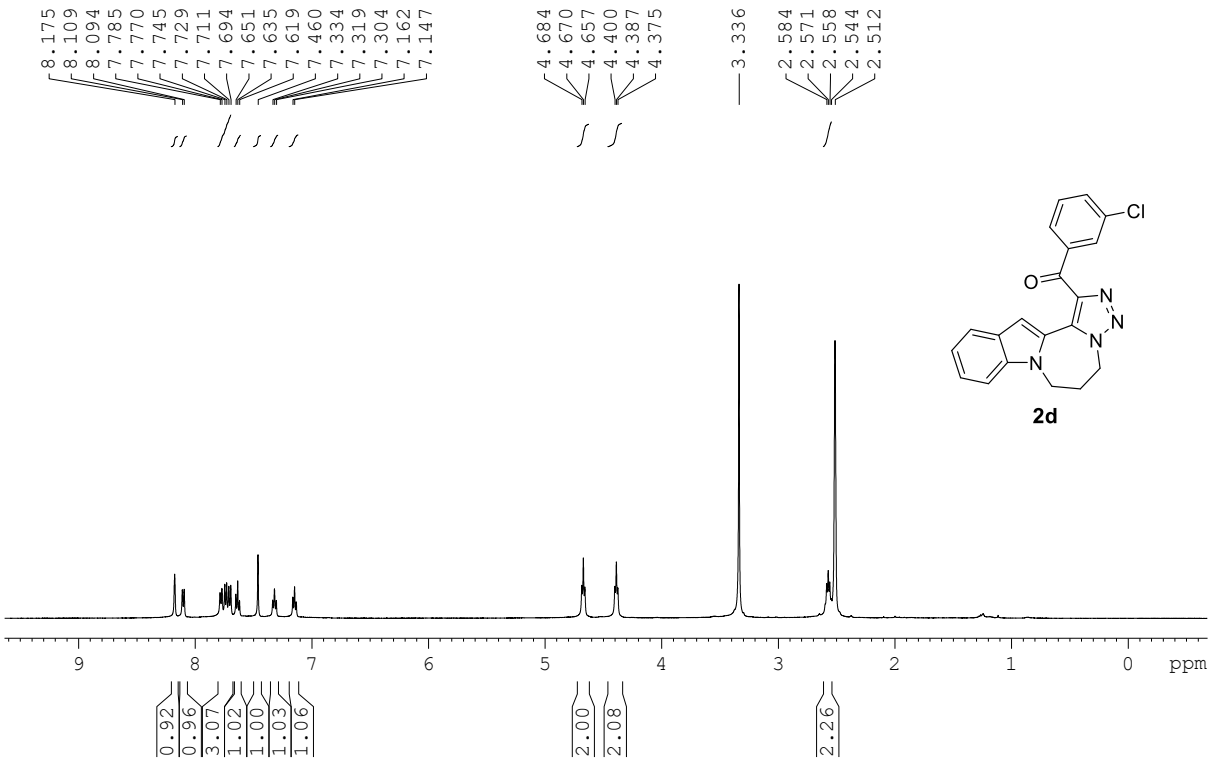
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **2b**



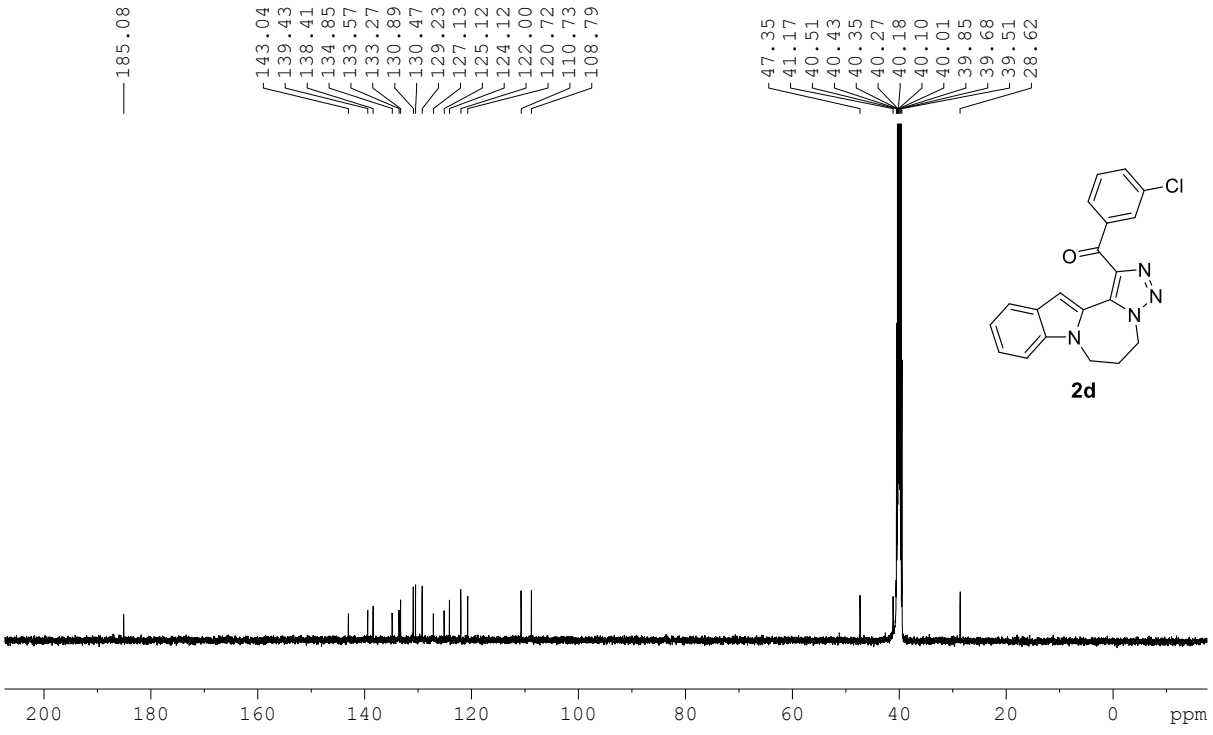
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **2c**



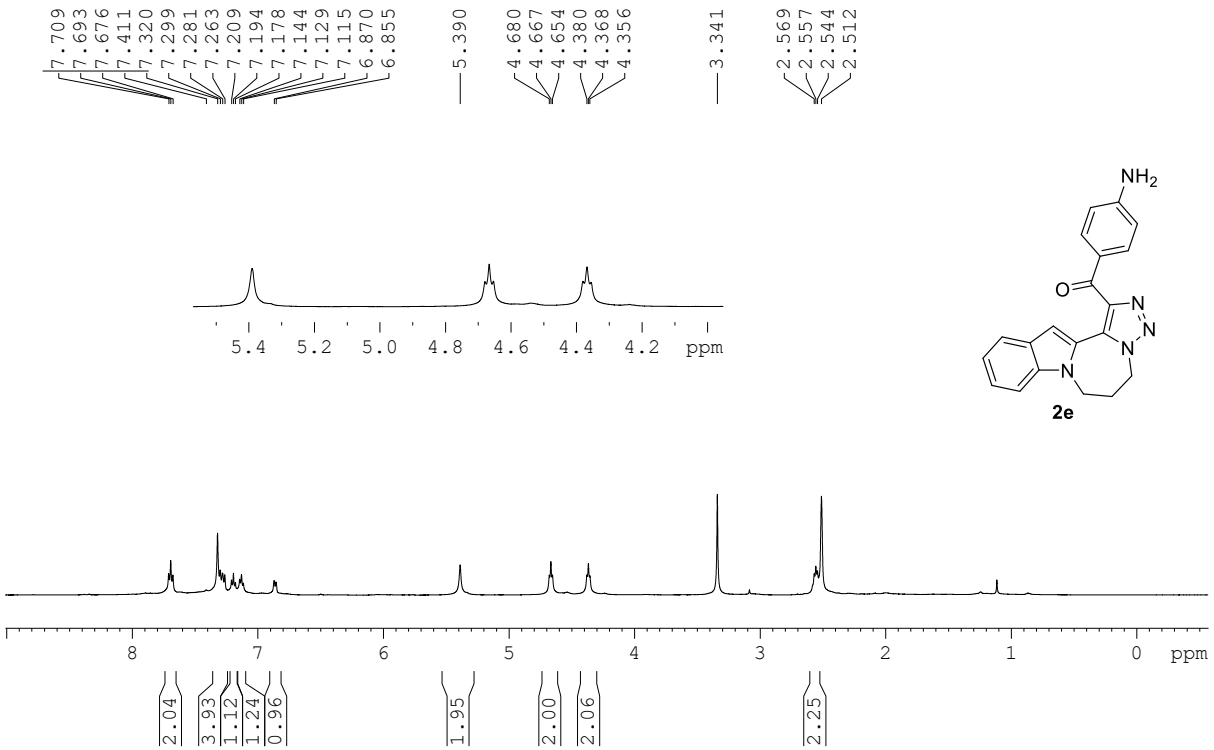
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **2c**



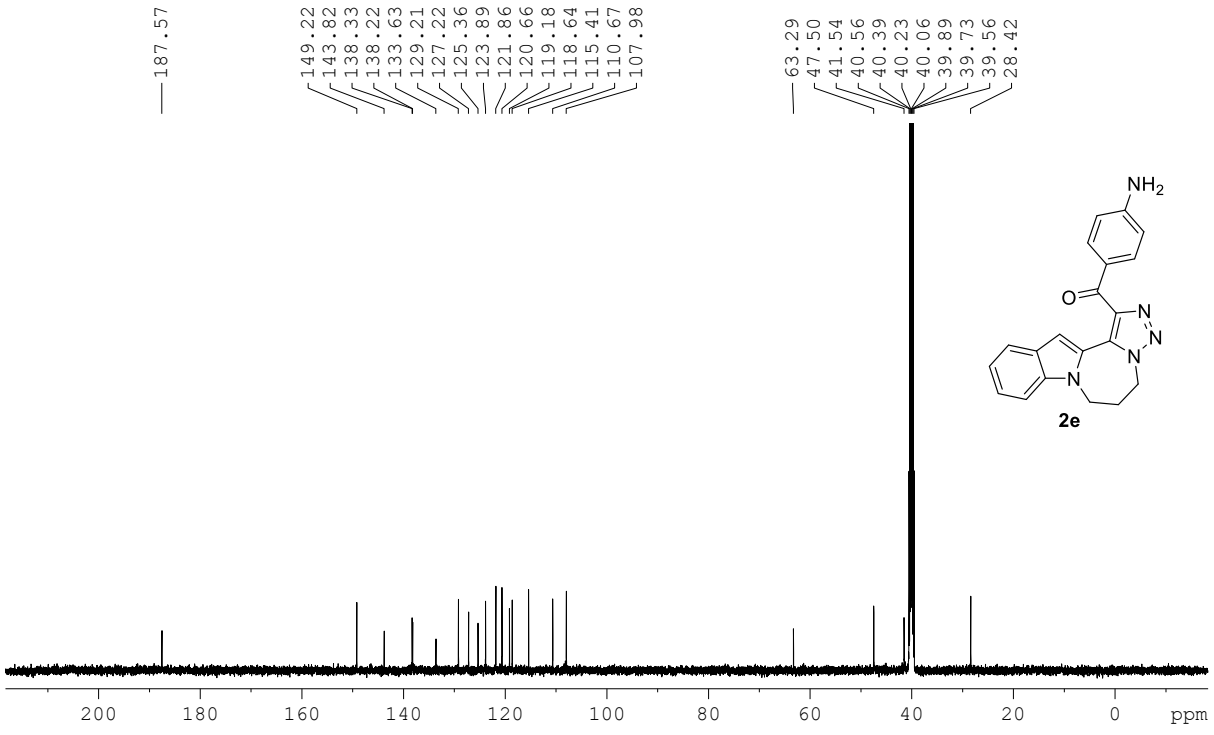
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **2d**



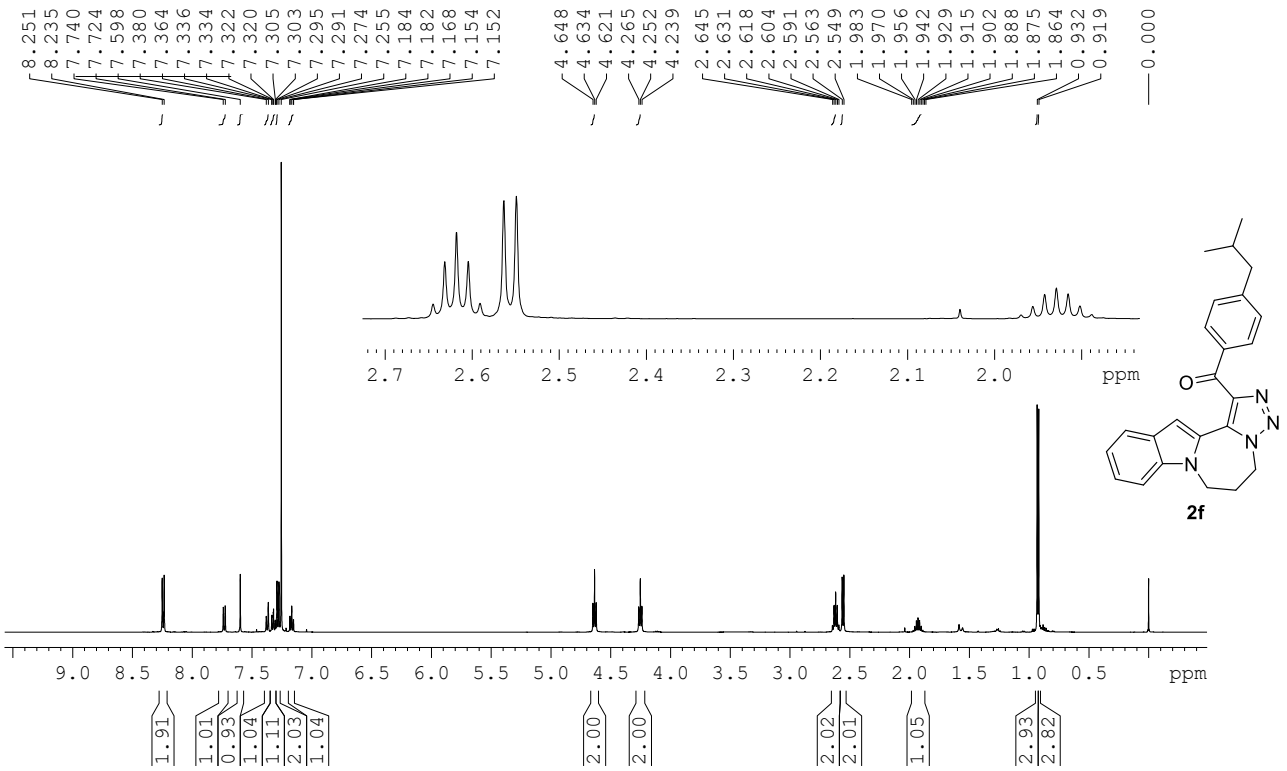
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **2d**



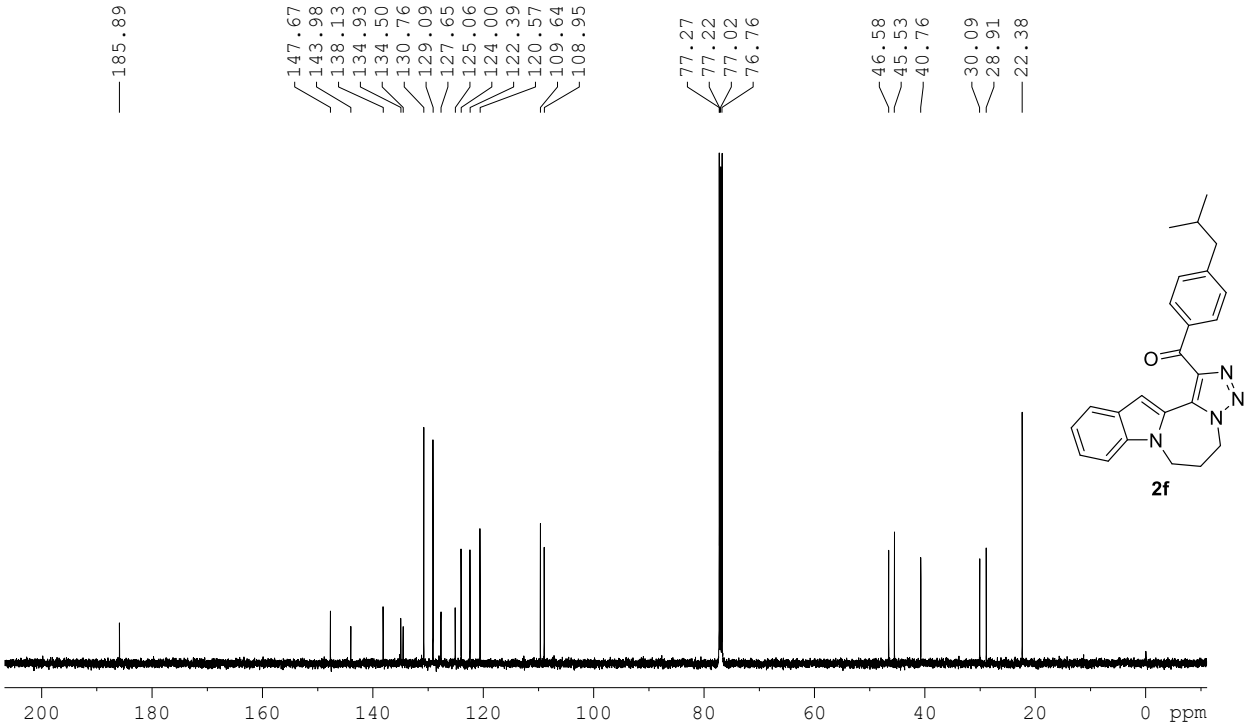
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **2e**



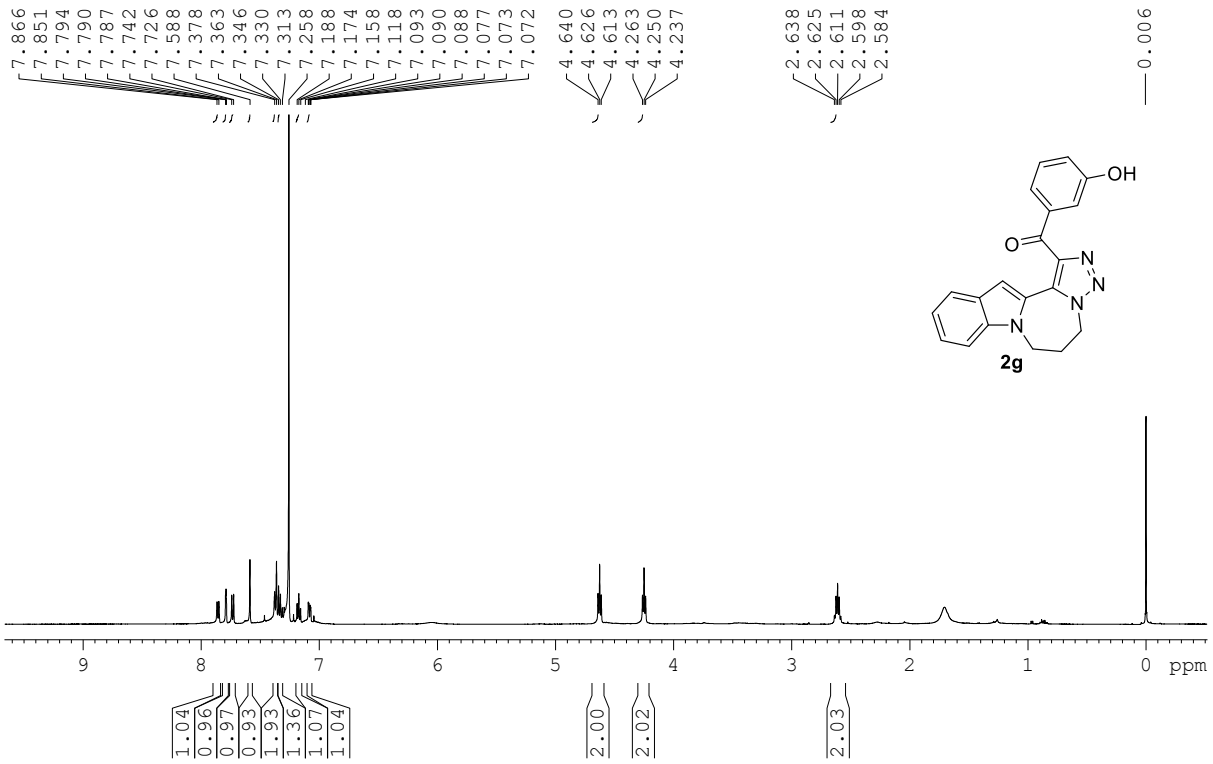
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **2e**



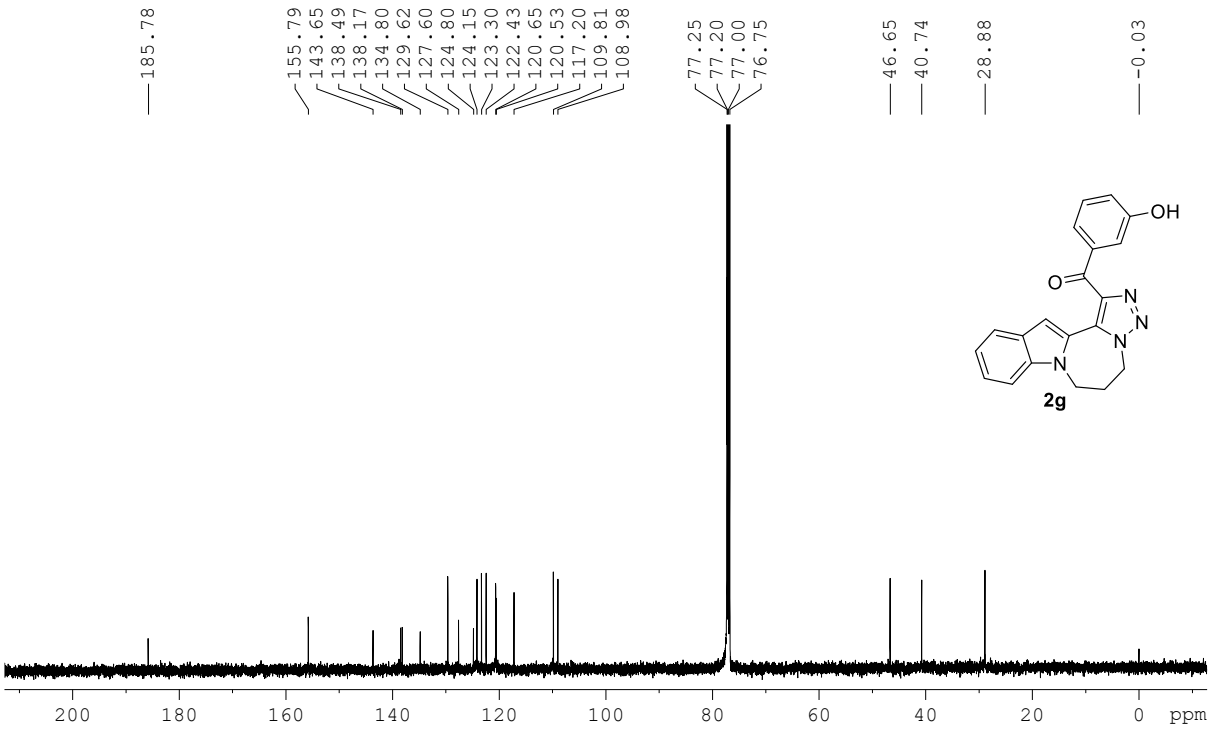
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **2f**



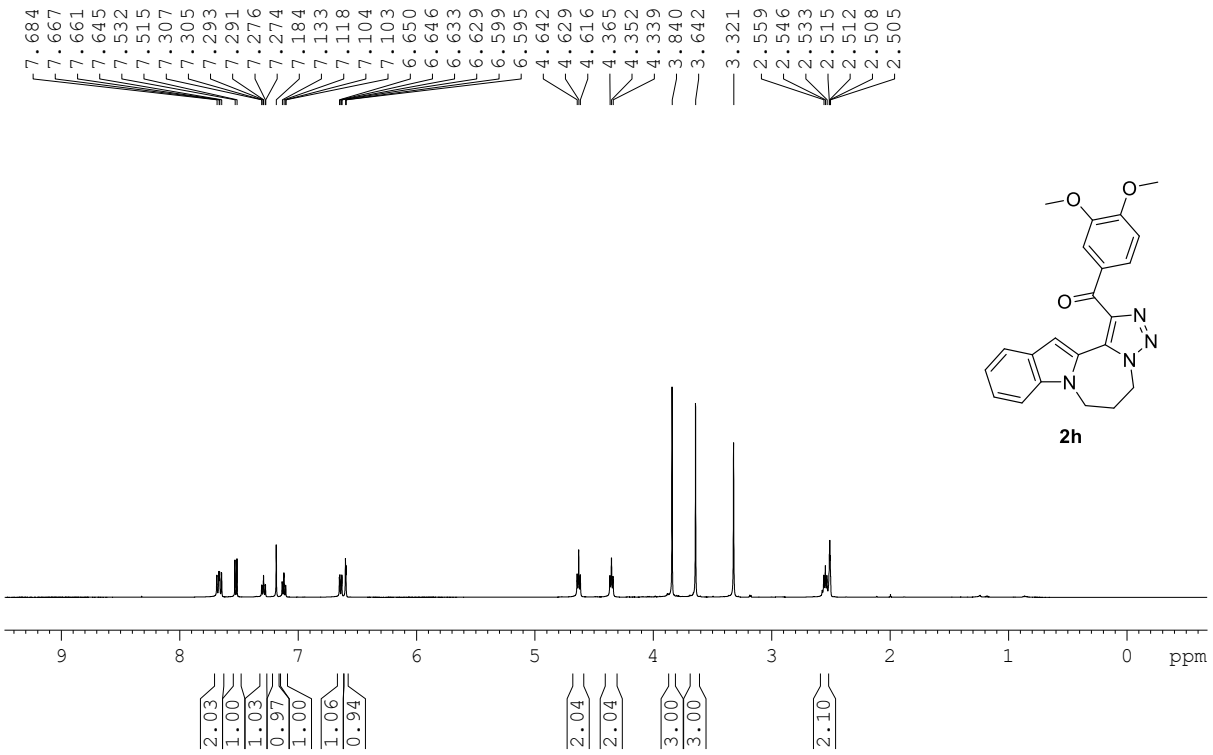
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **2f**



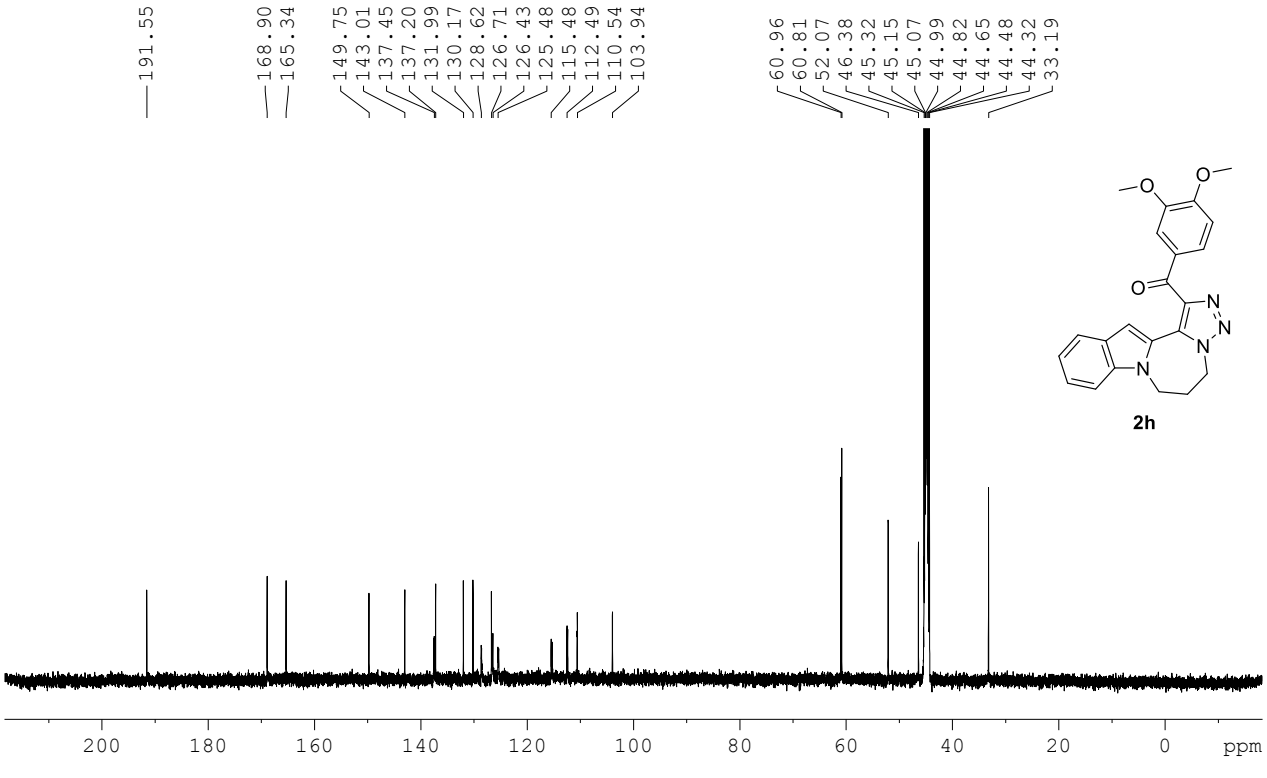
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **2g**



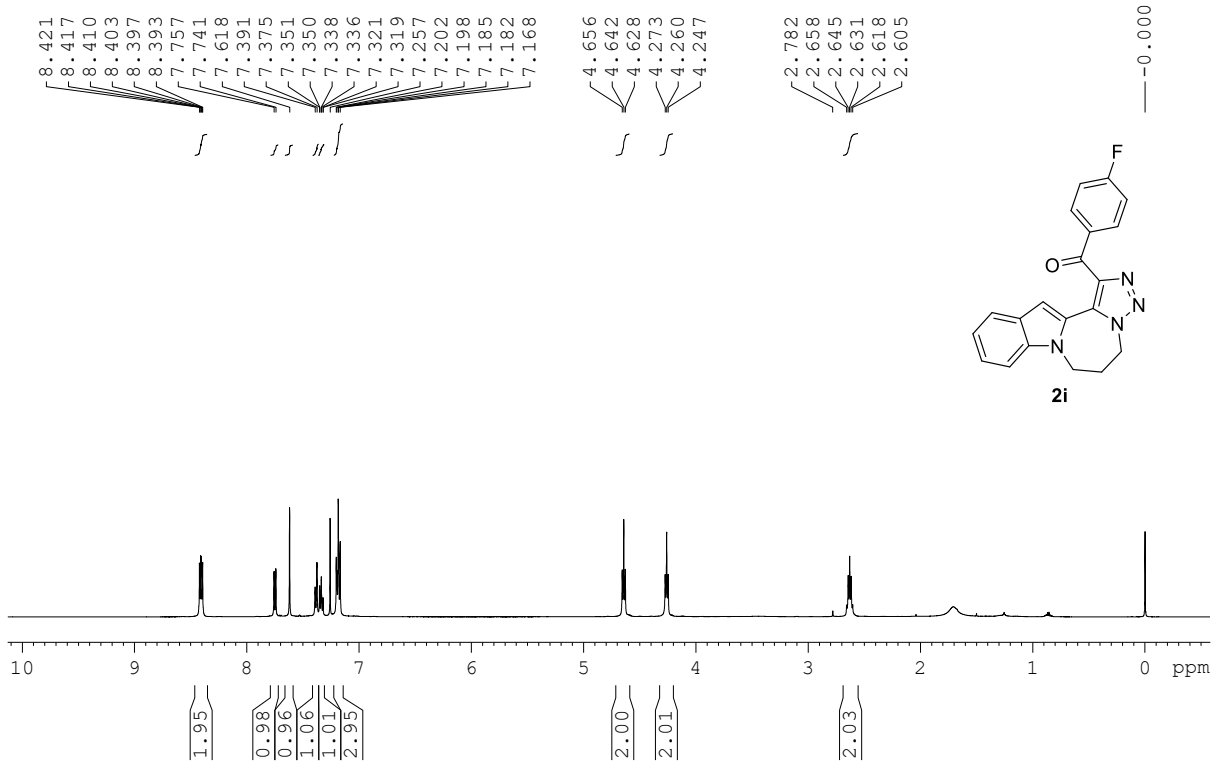
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **2g**



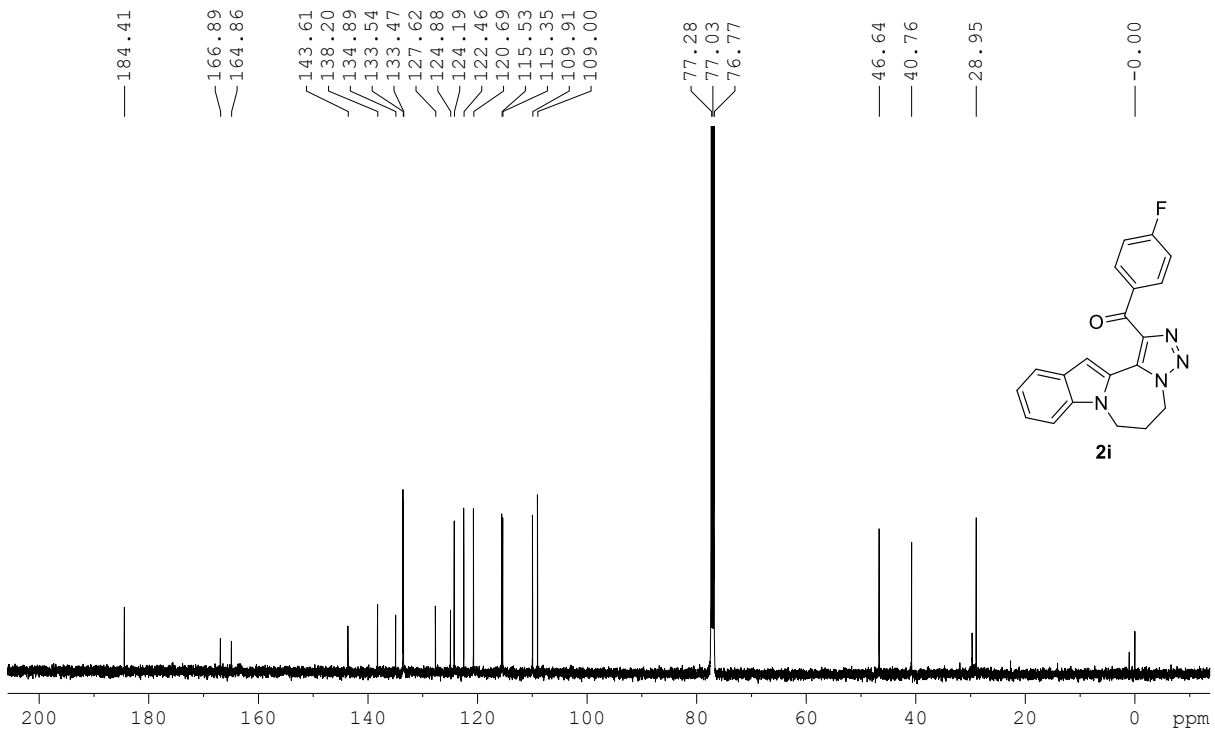
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **2h**



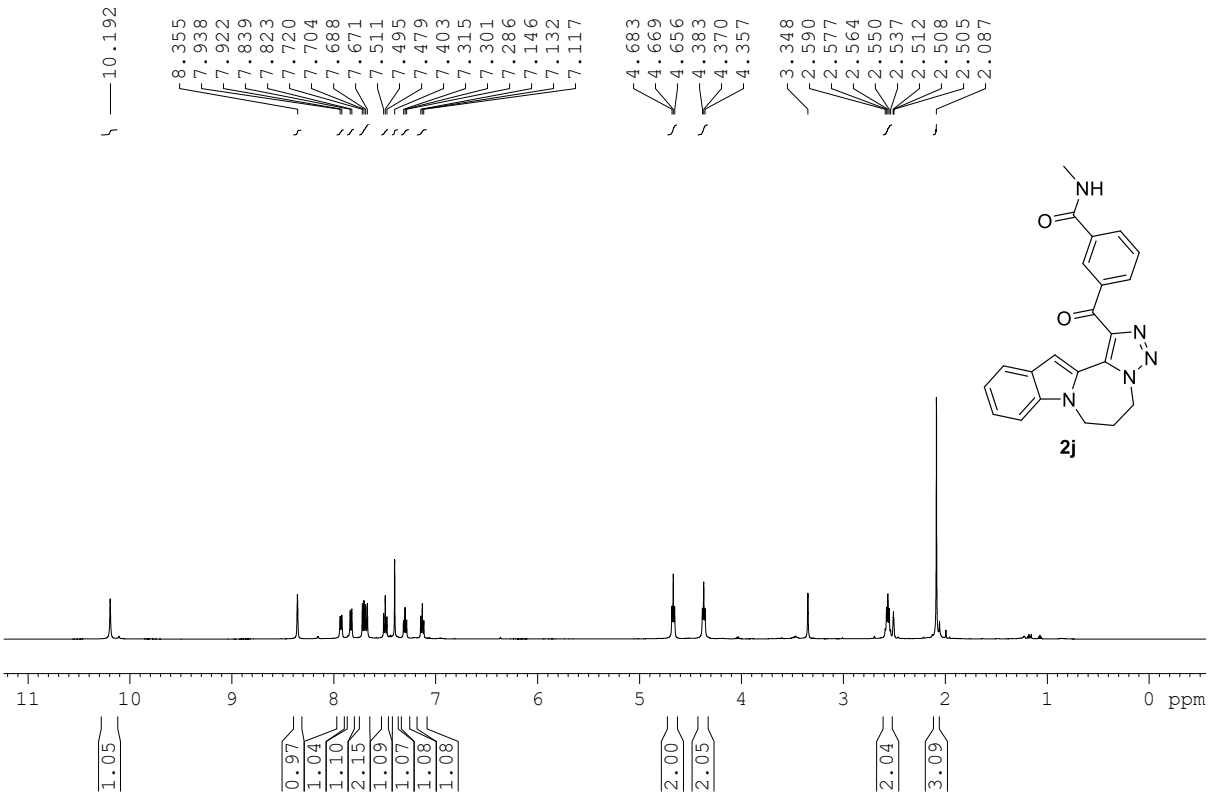
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **2h**



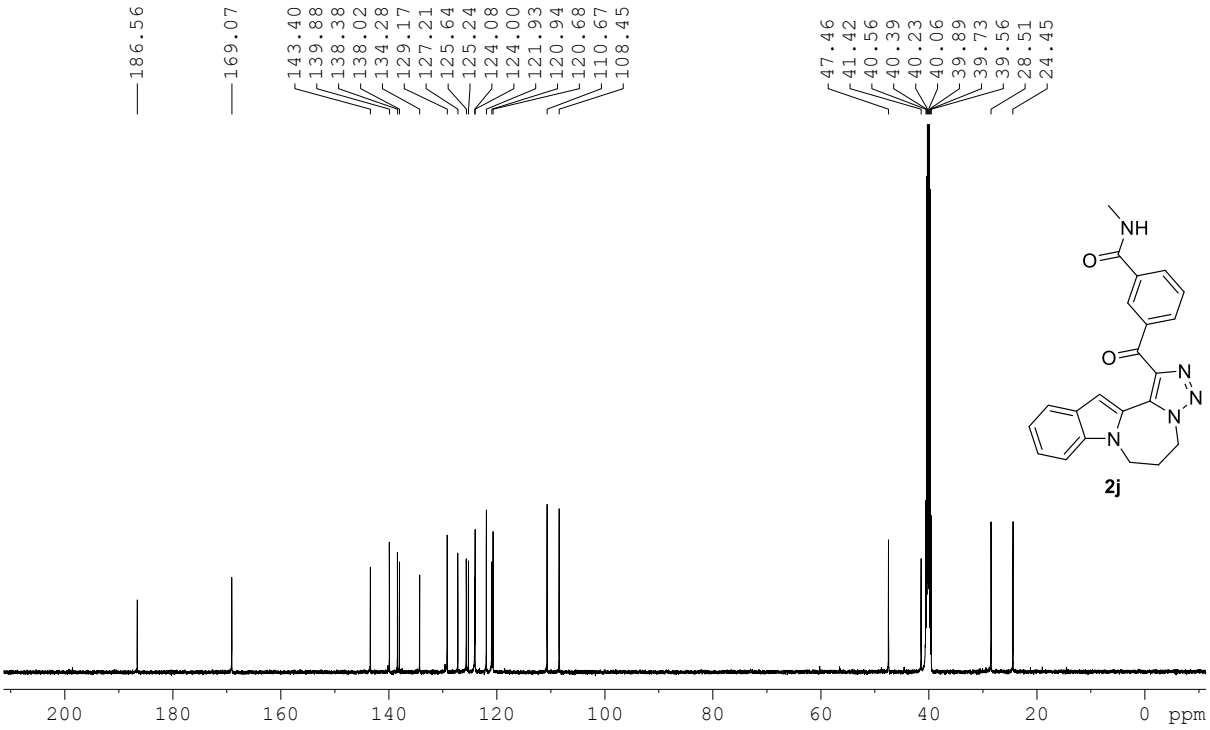
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **2i**



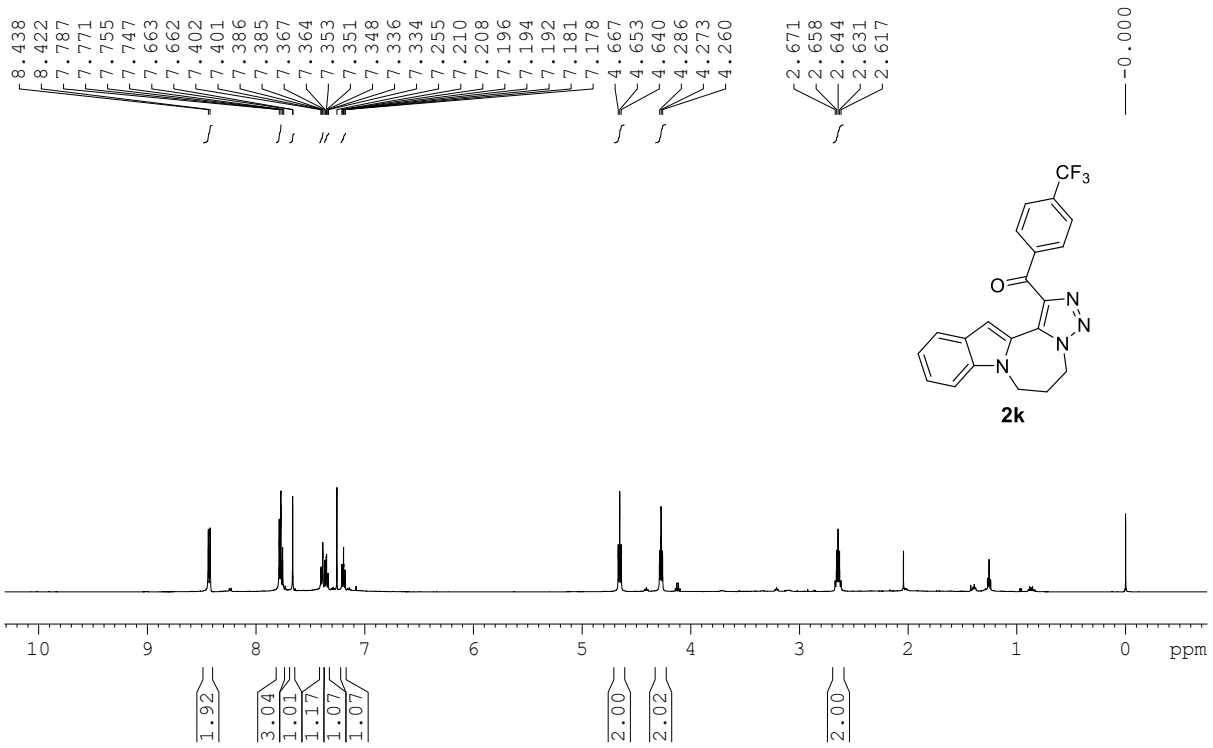
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **2i**



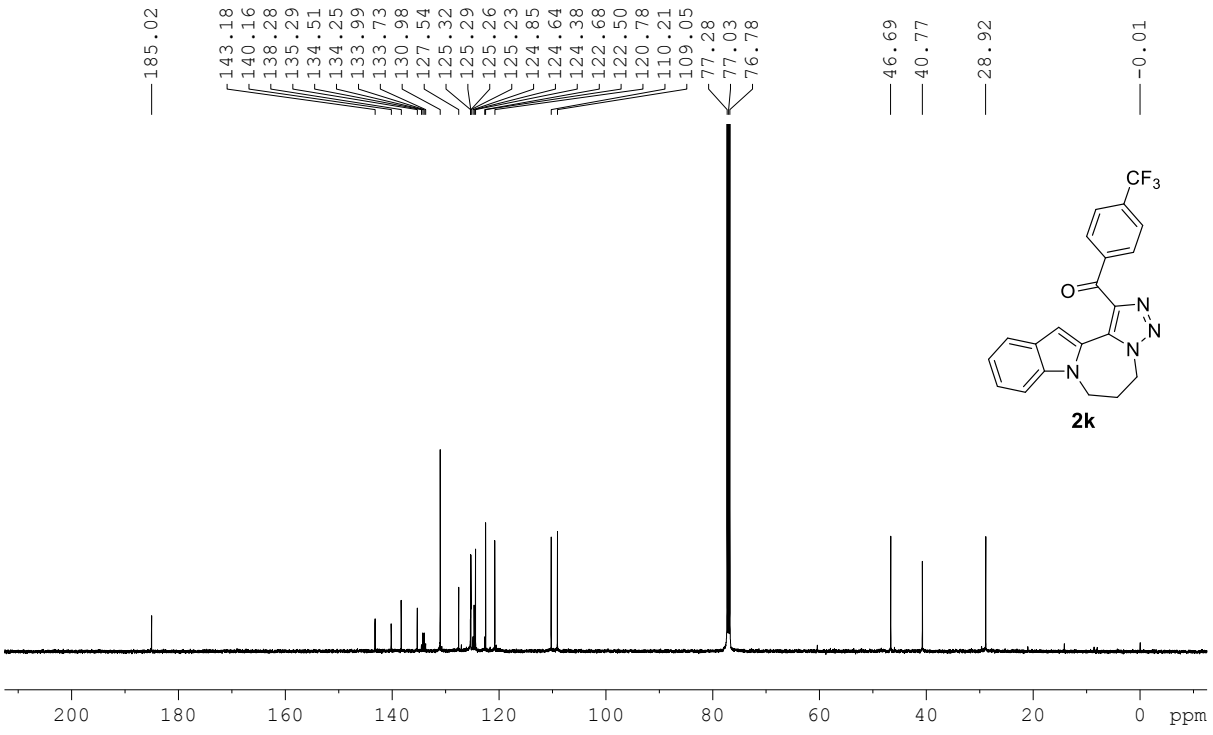
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **2j**



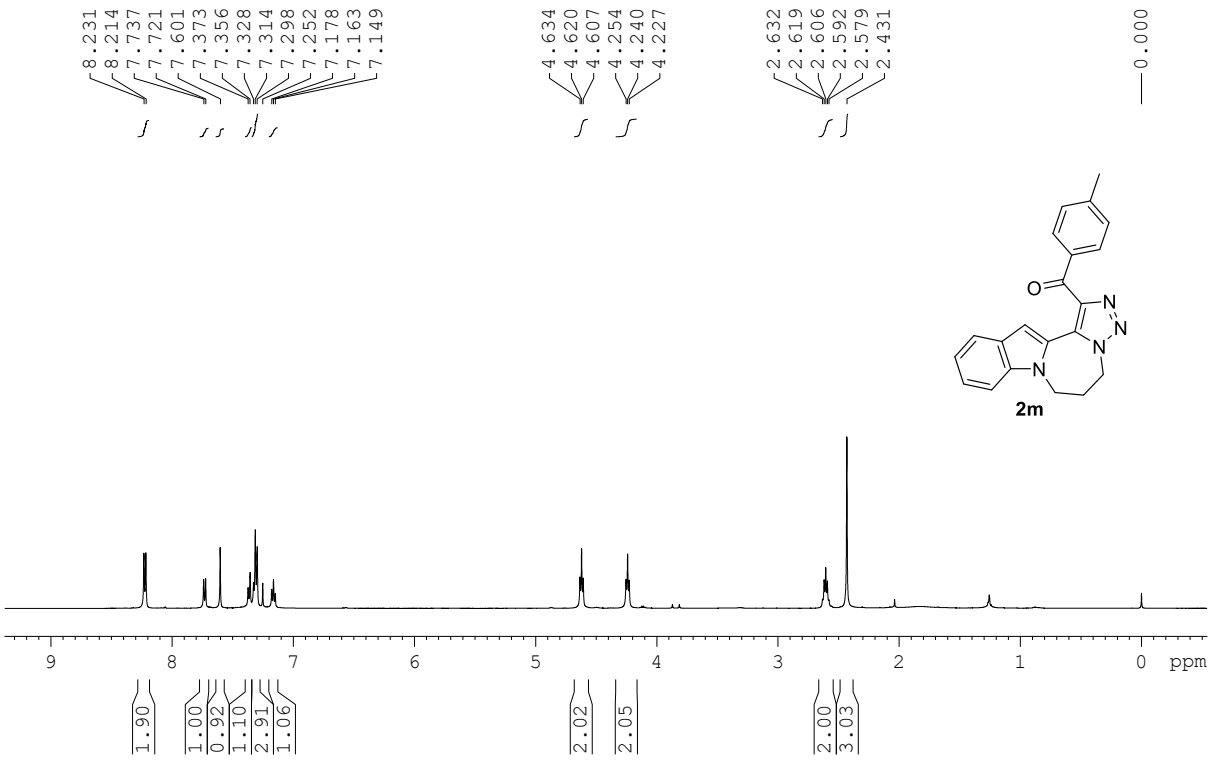
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **2j**



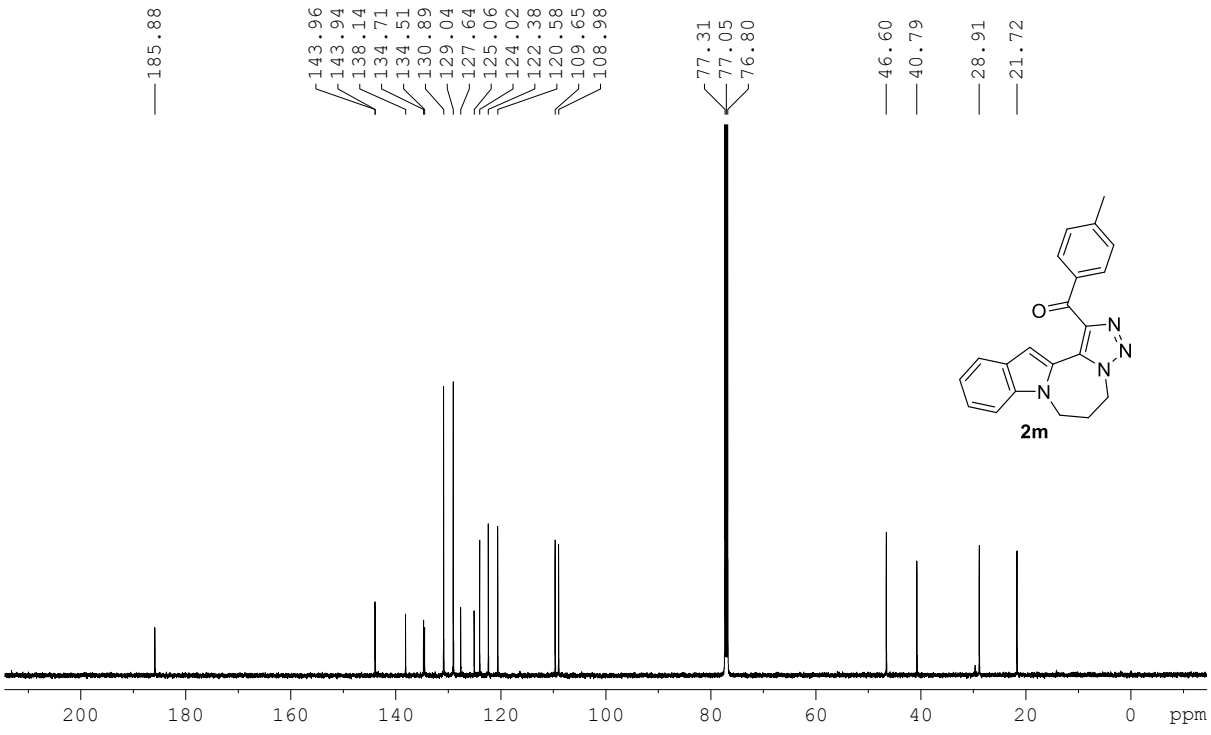
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **2k**



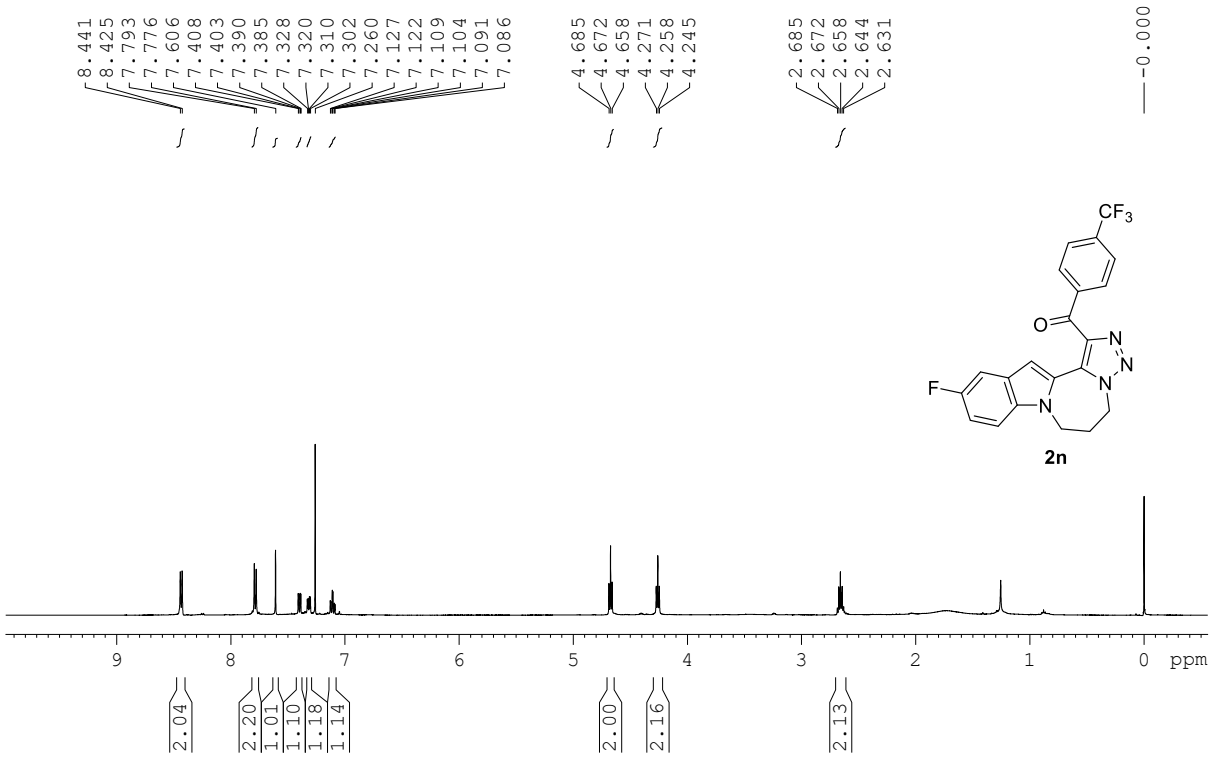
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **2k**



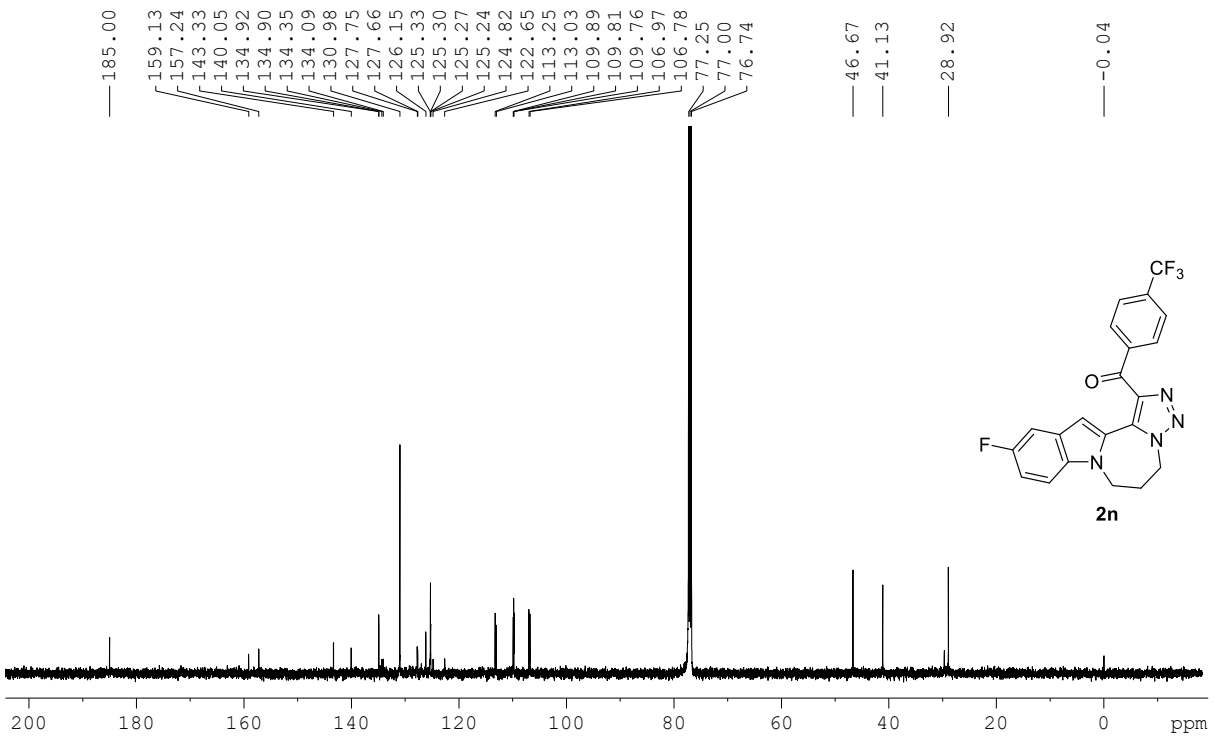
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **2m**



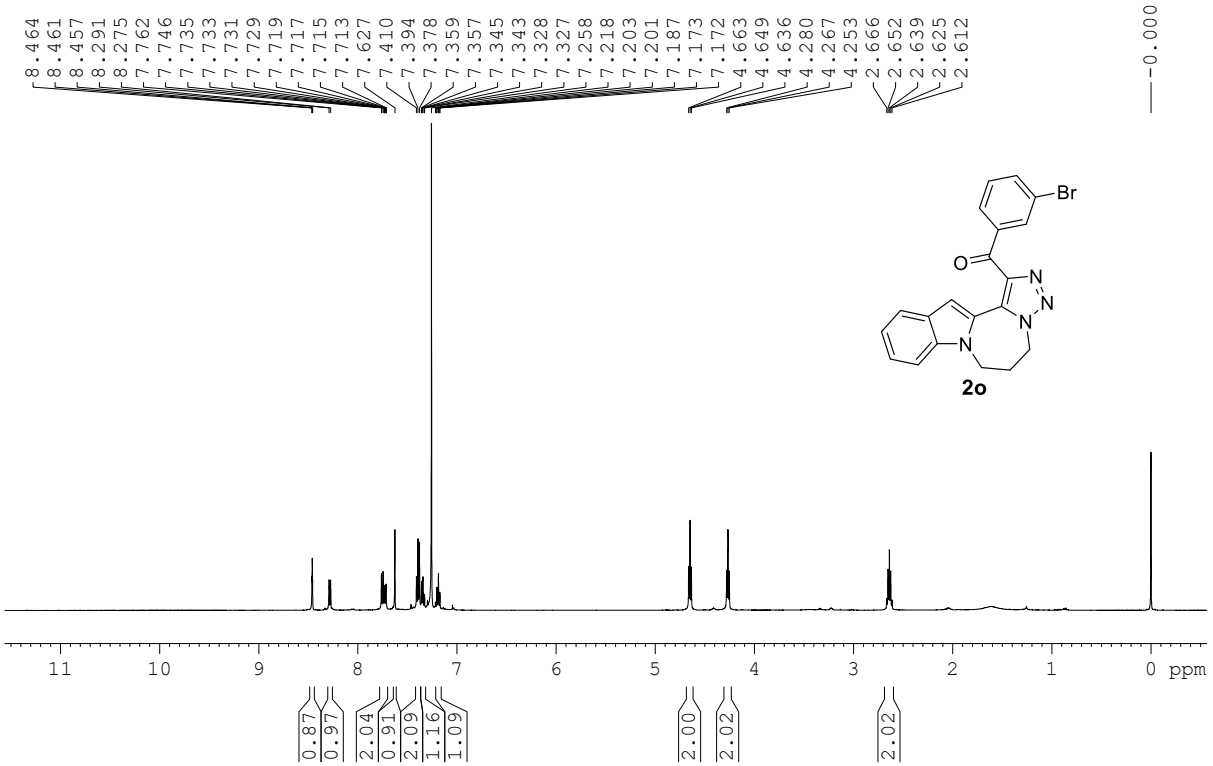
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **2m**



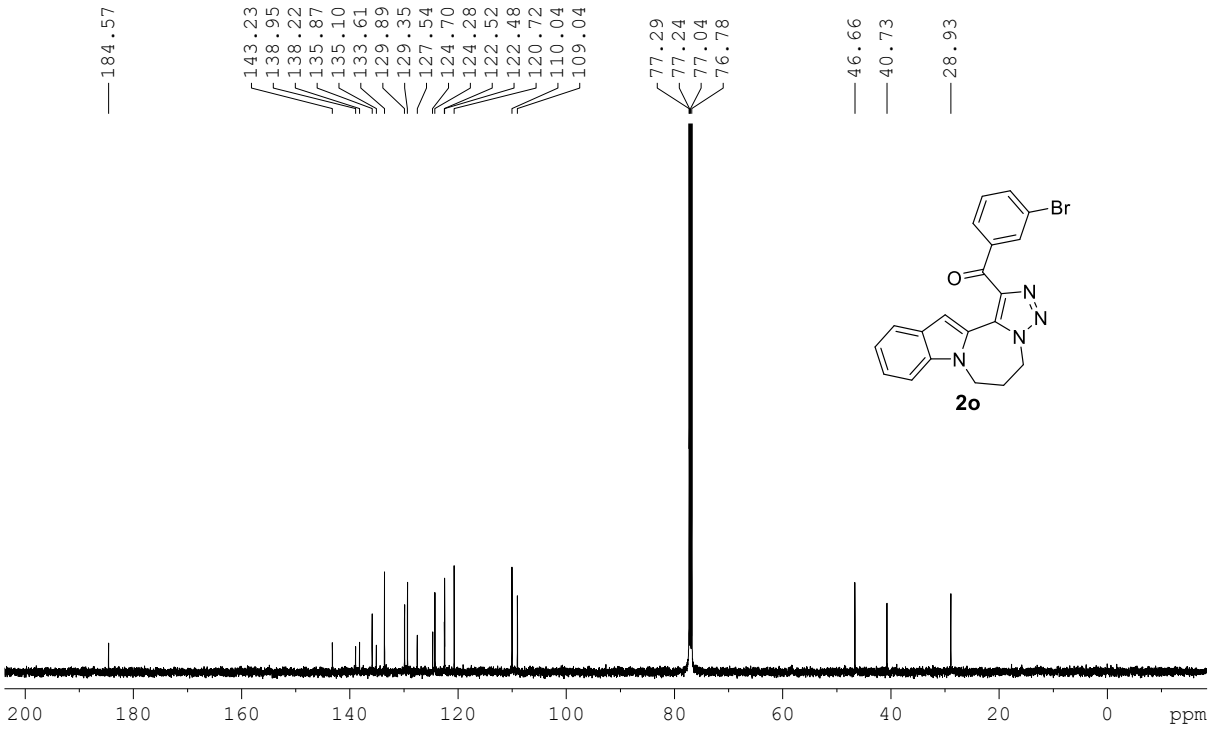
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **2n**



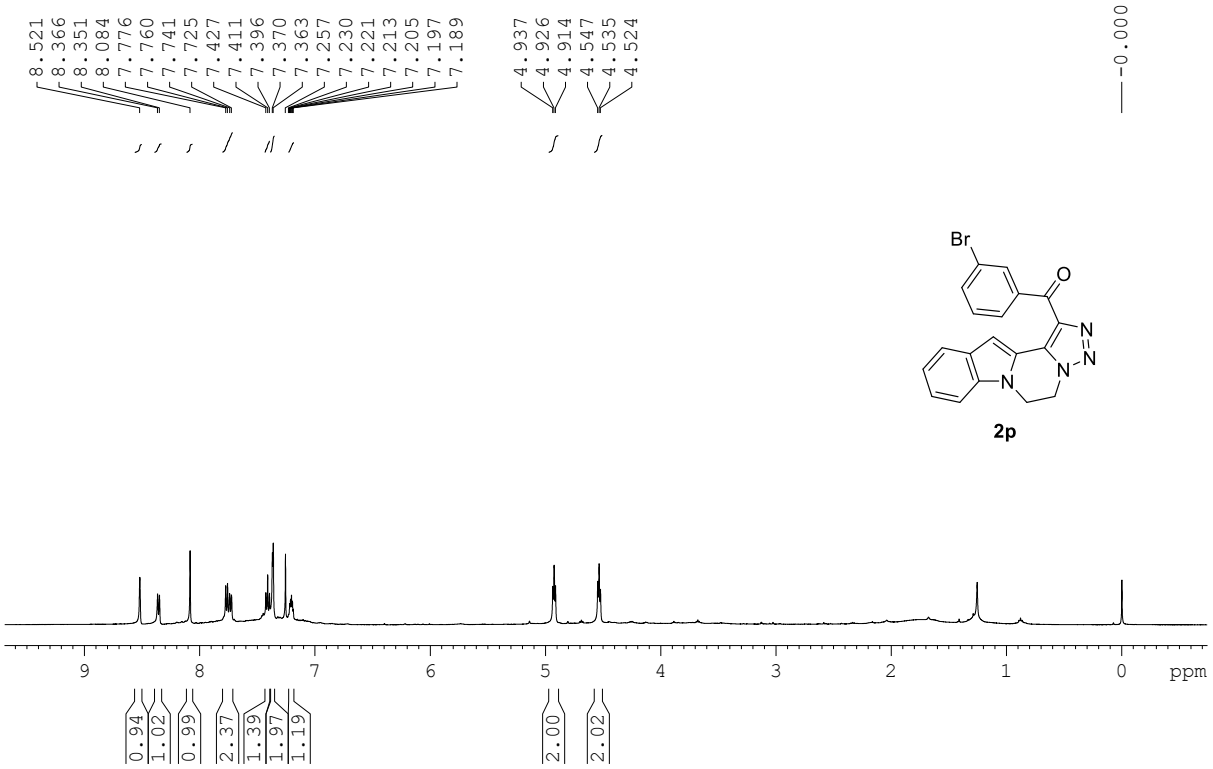
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **2n**



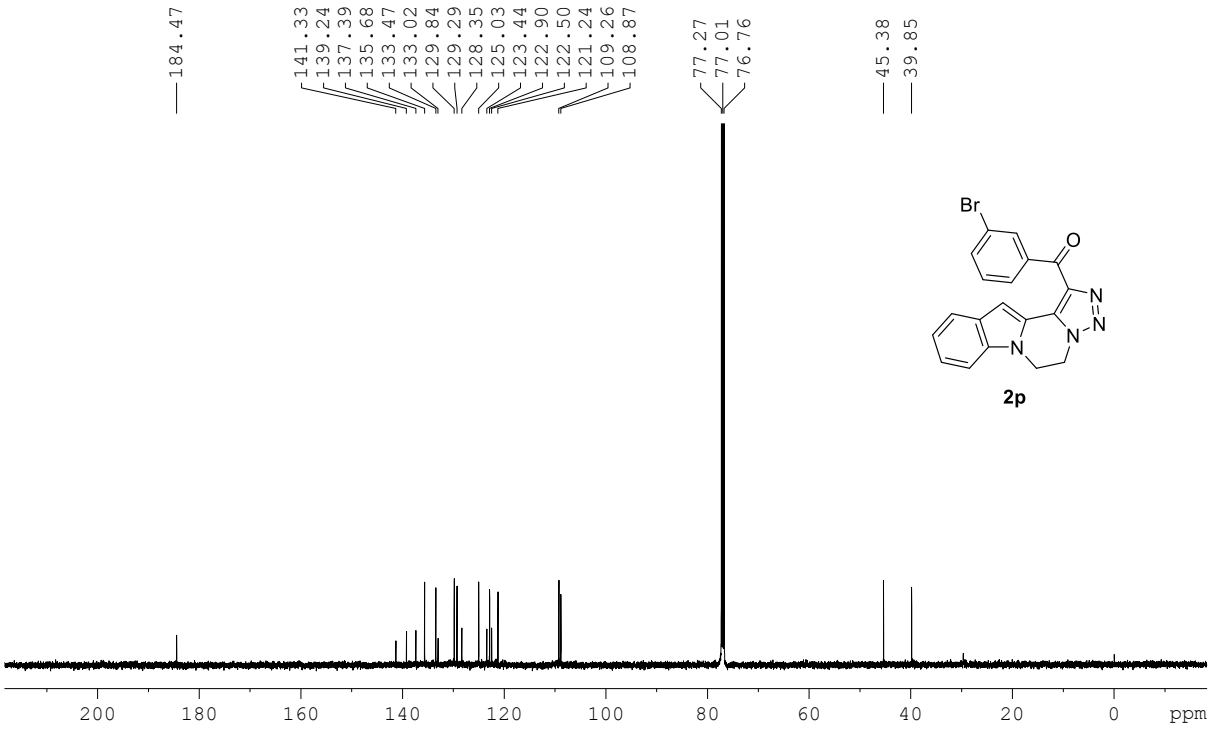
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **2o**



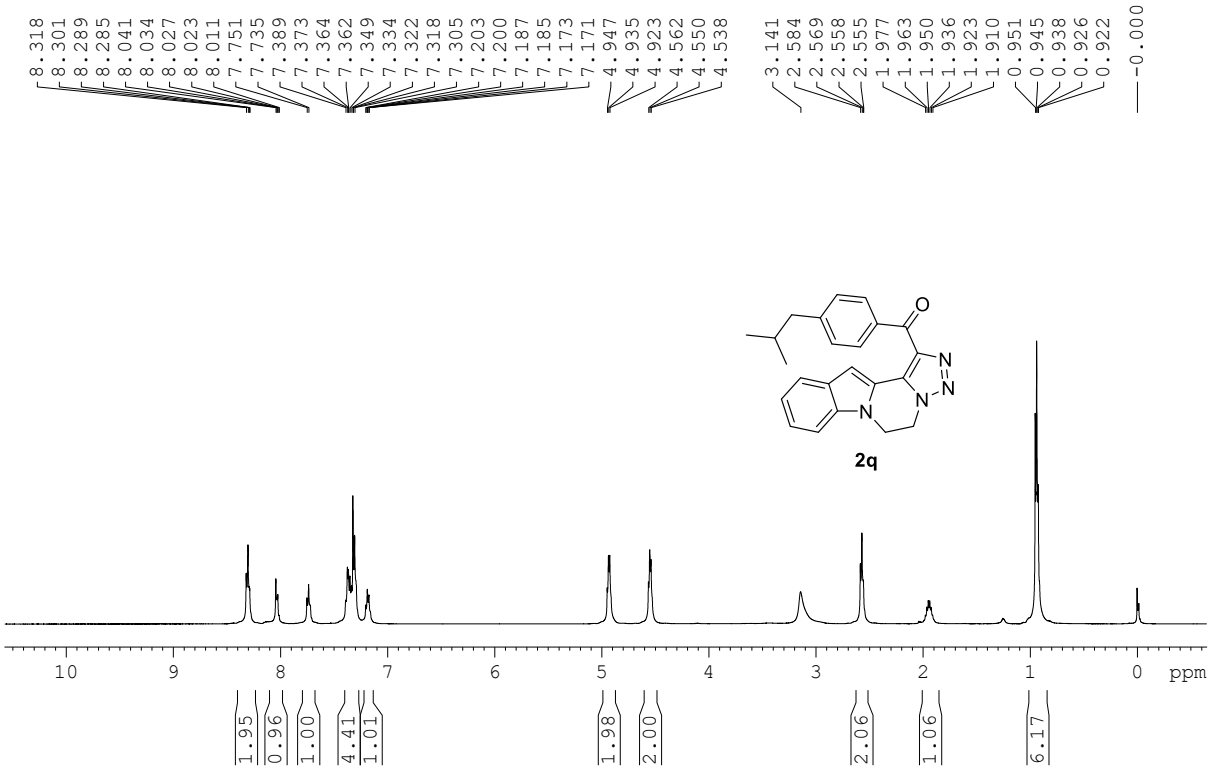
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **2o**



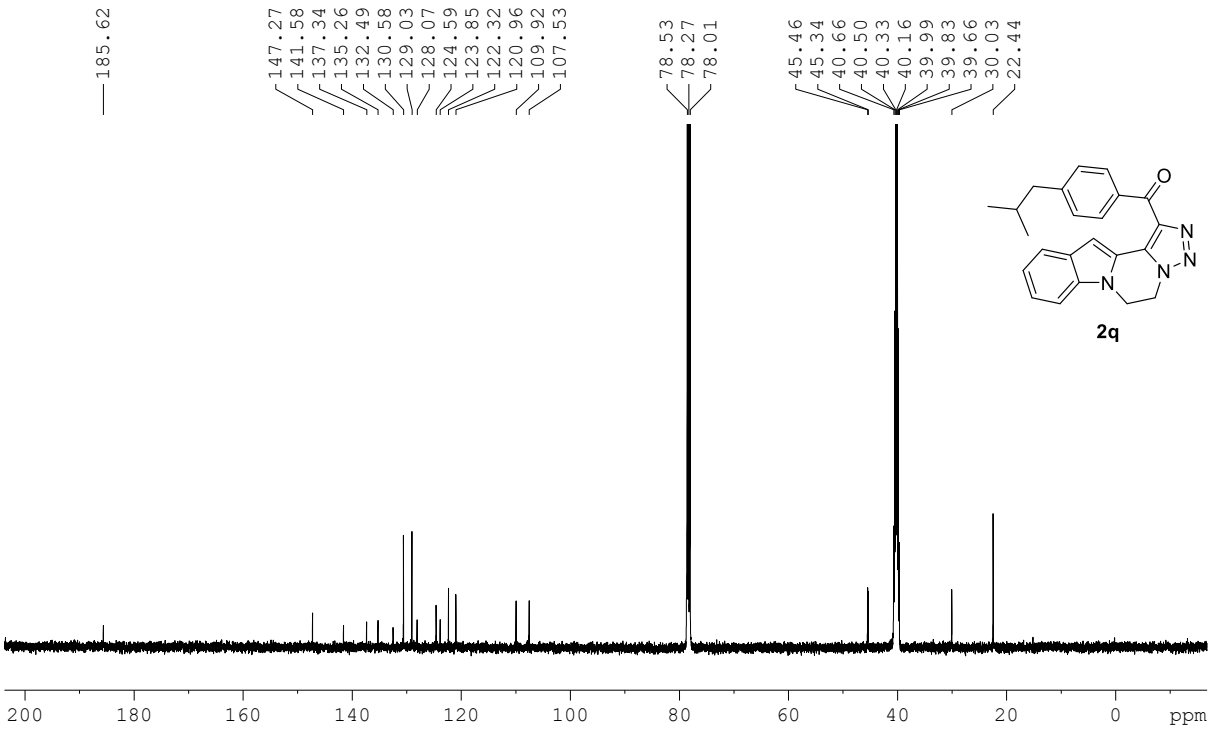
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **2p**



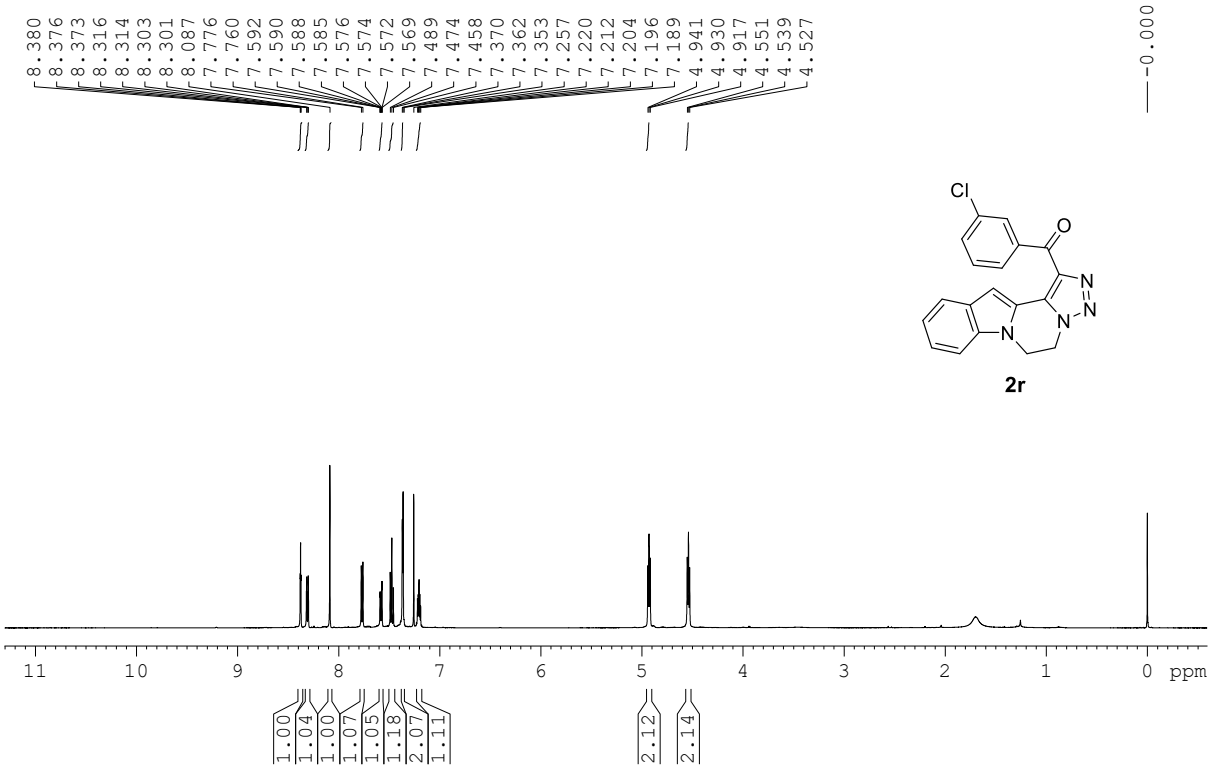
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **2p**



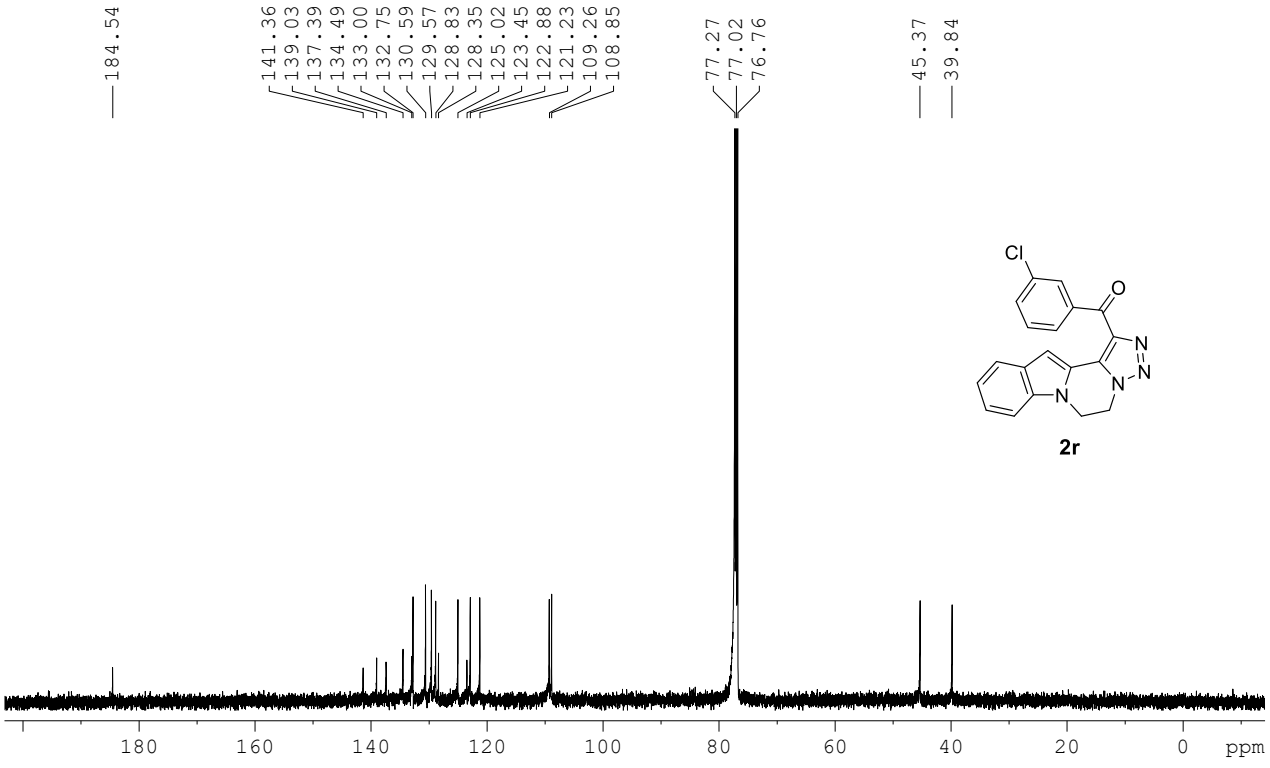
^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6) spectrum of compound **2q**



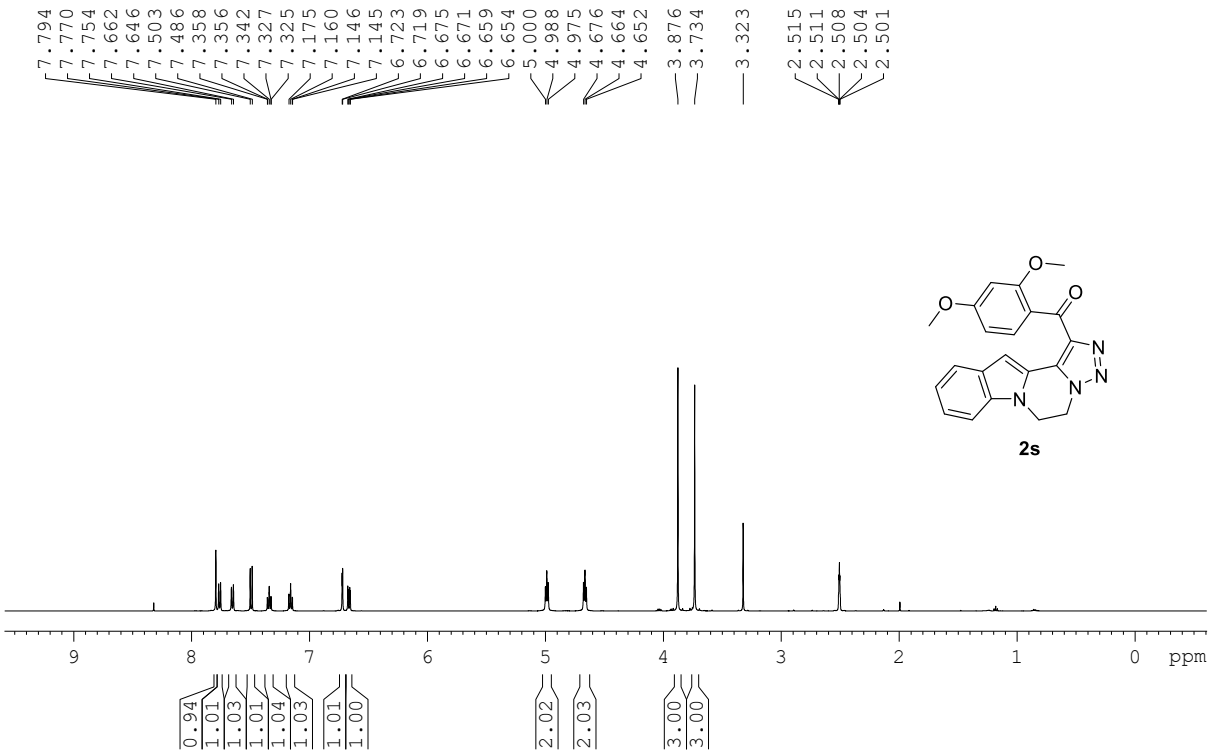
^{13}C NMR (125 MHz, $CDCl_3$ + DMSO-d_6)) spectrum of compound **2q**



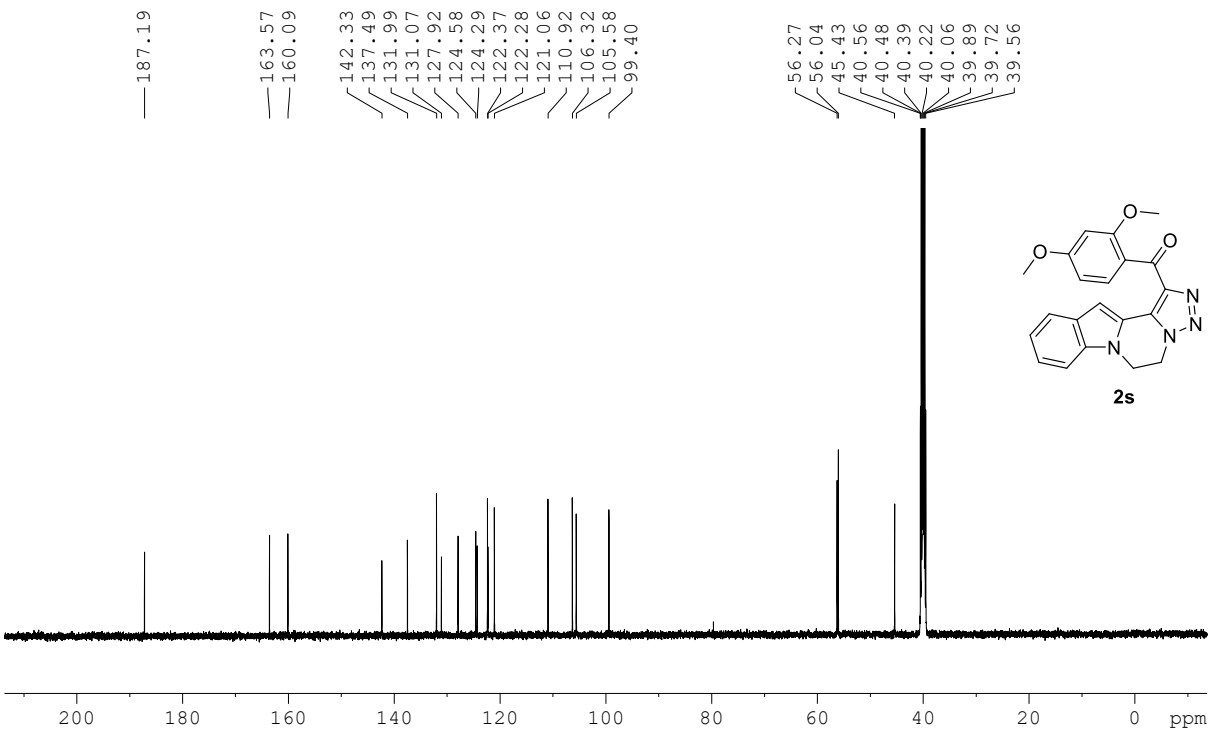
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **2r**



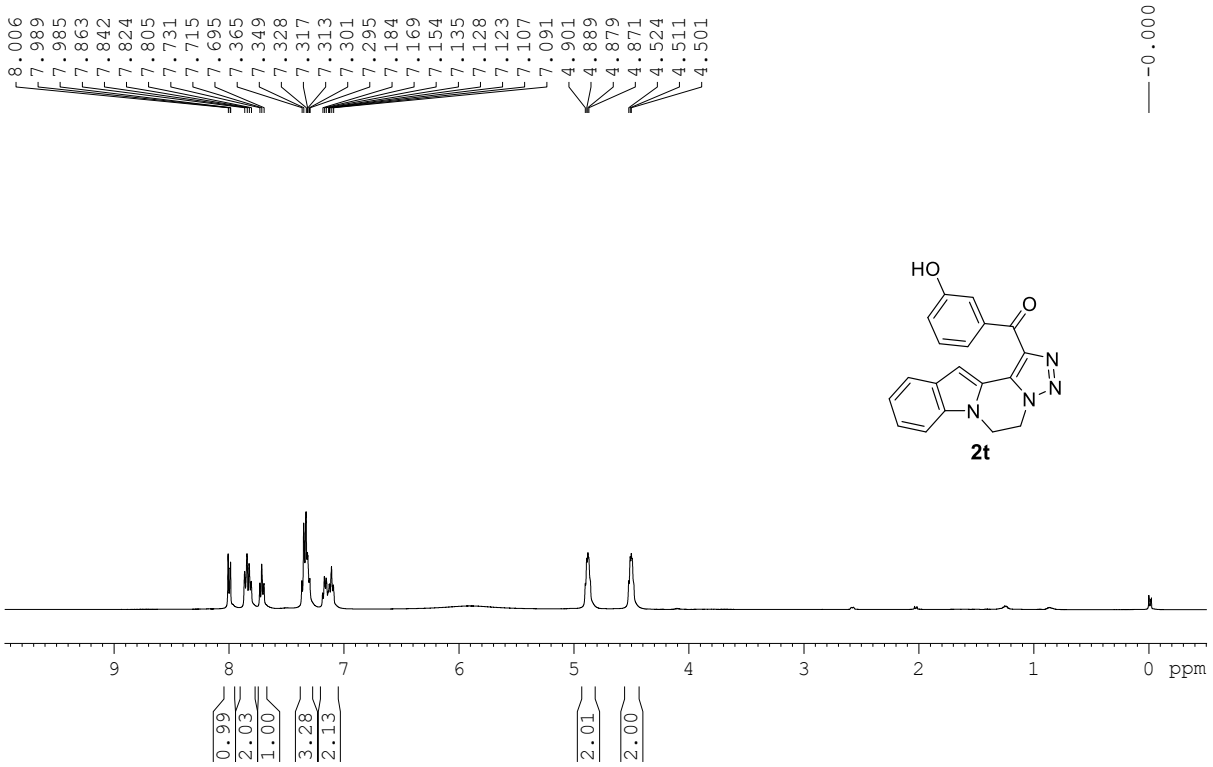
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **2r**



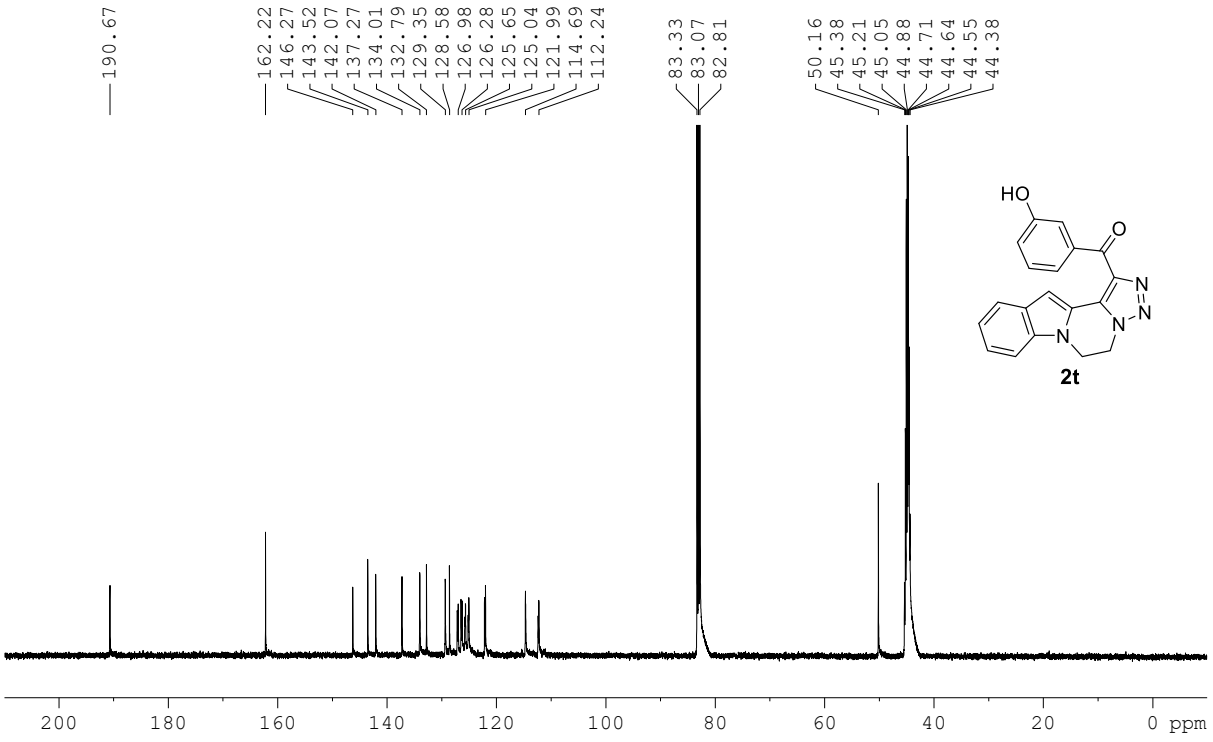
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **2s**



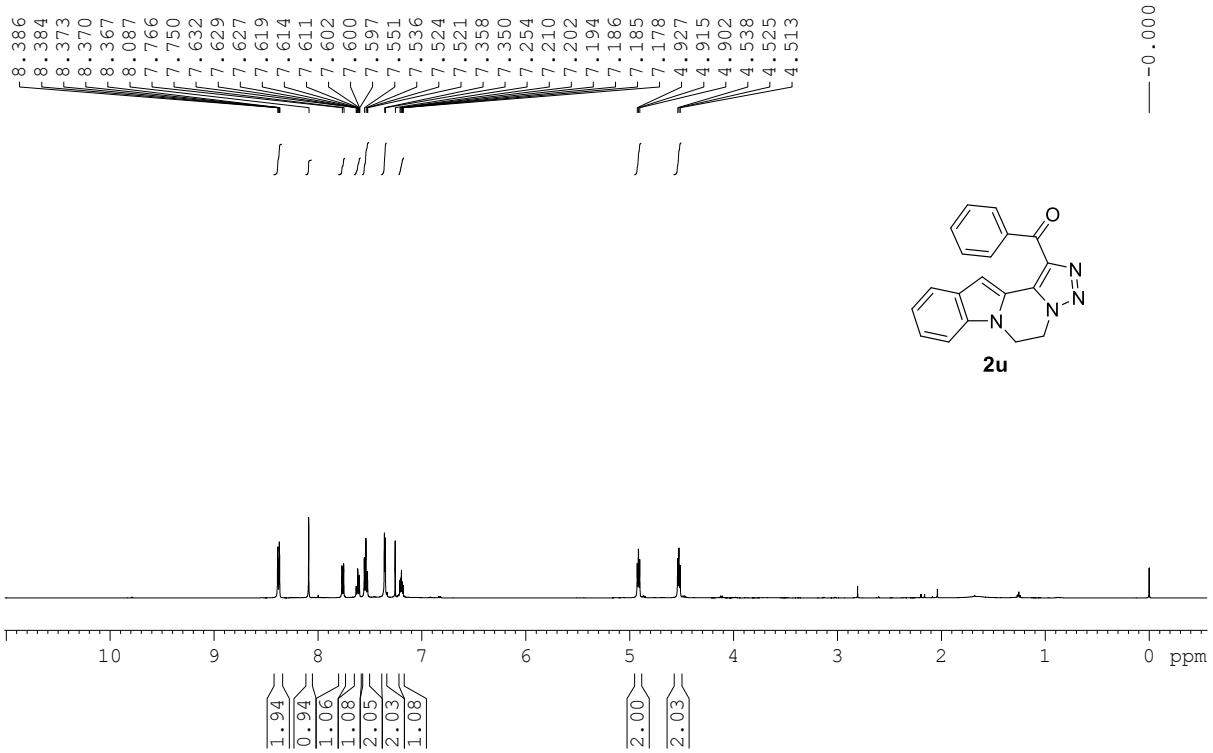
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **2s**



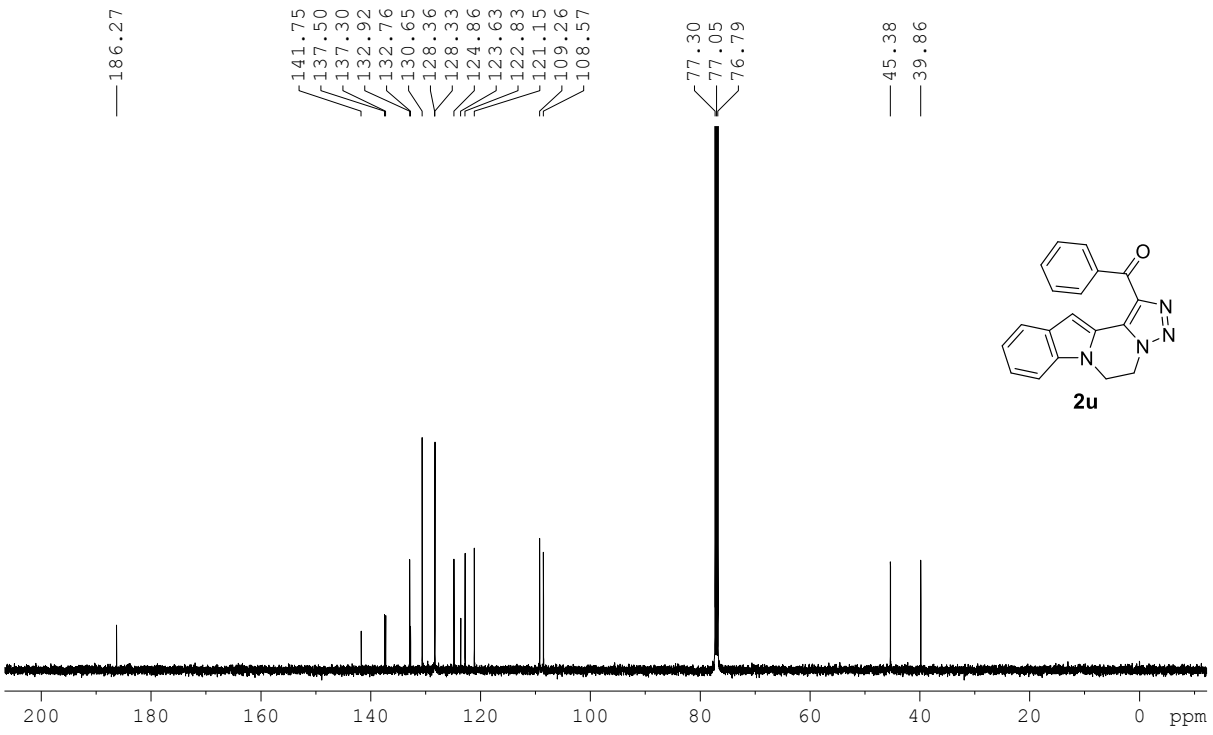
^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6) spectrum of compound **2t**



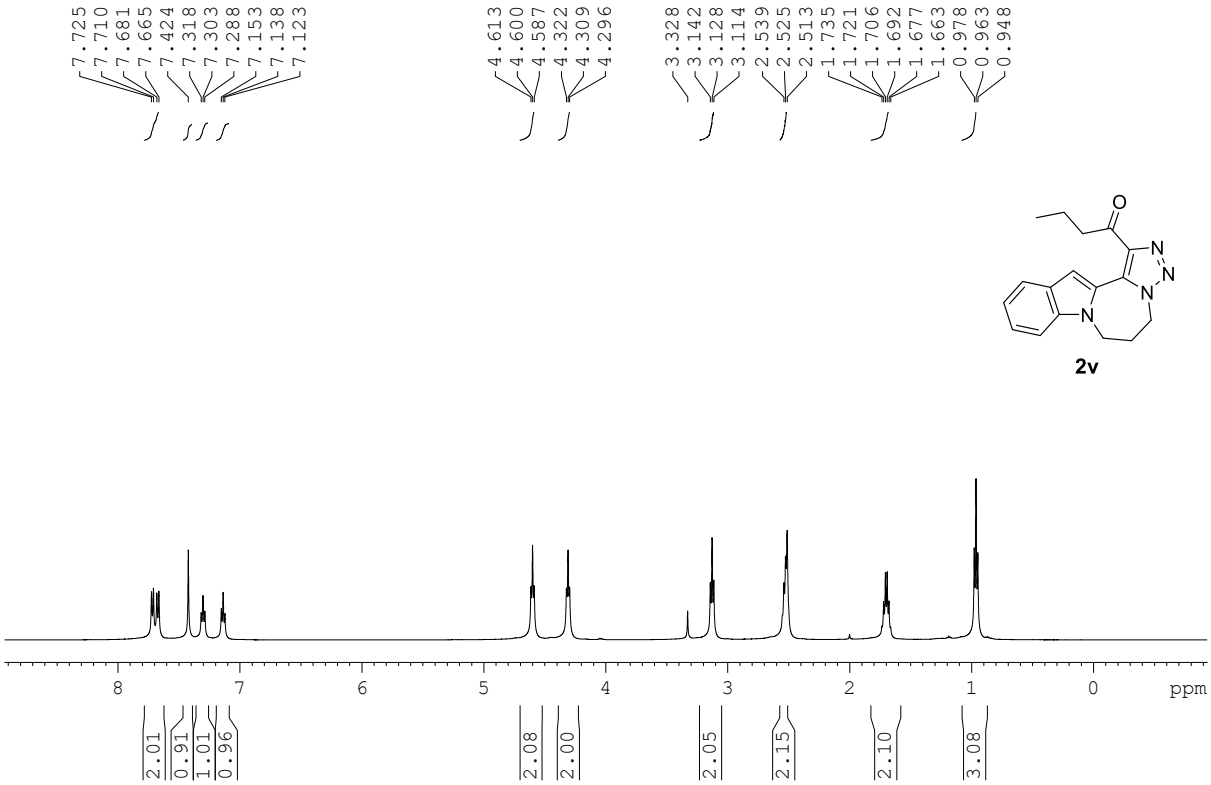
^{13}C NMR (125 MHz, $CDCl_3$ + DMSO-d_6) spectrum of compound **2t**



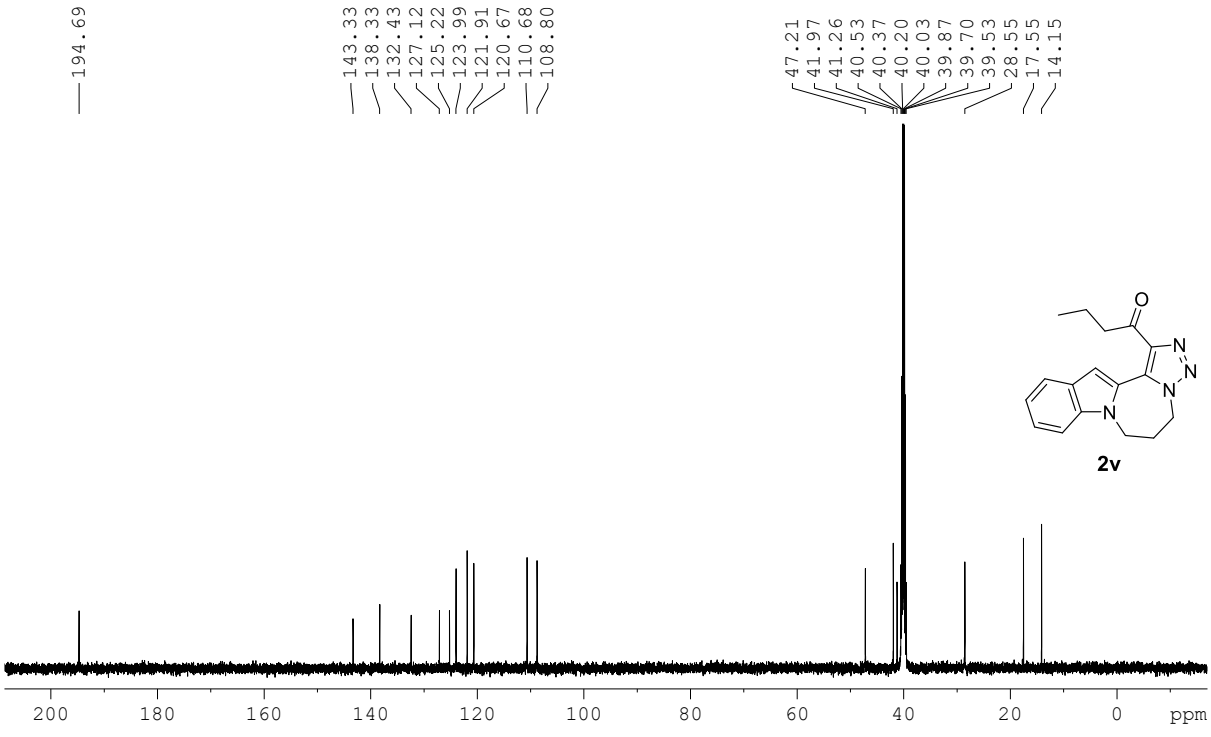
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **2u**



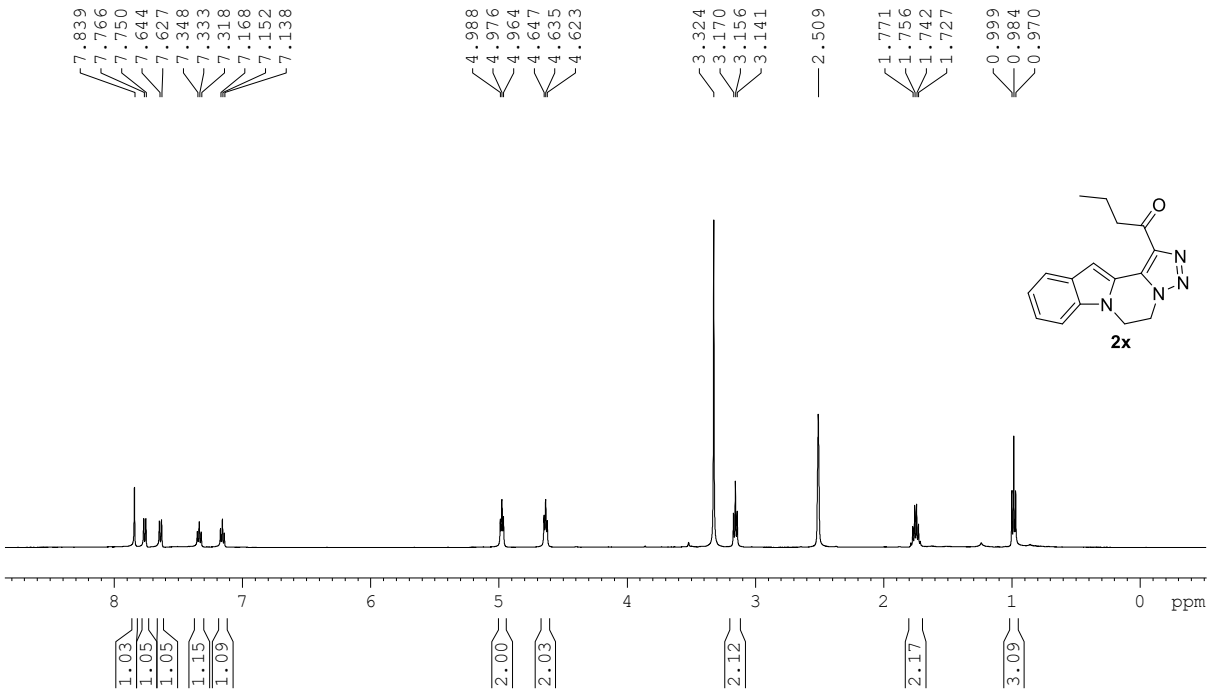
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **2u**



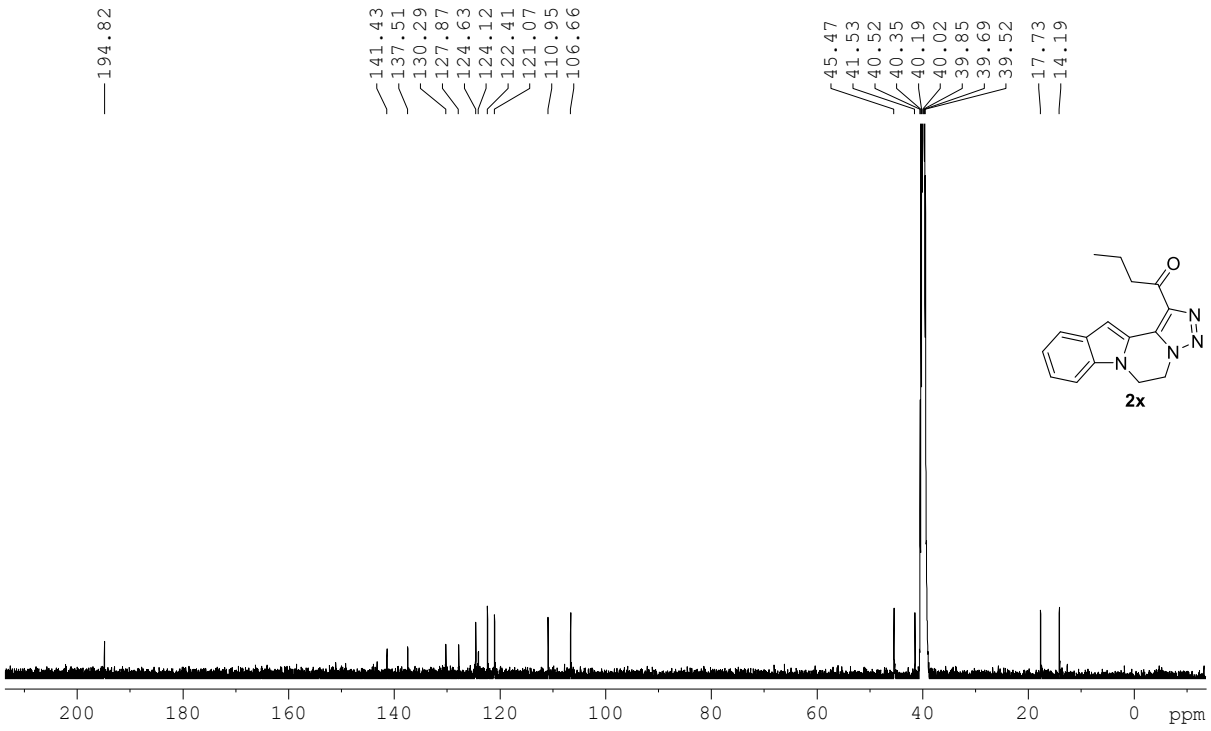
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **2v**



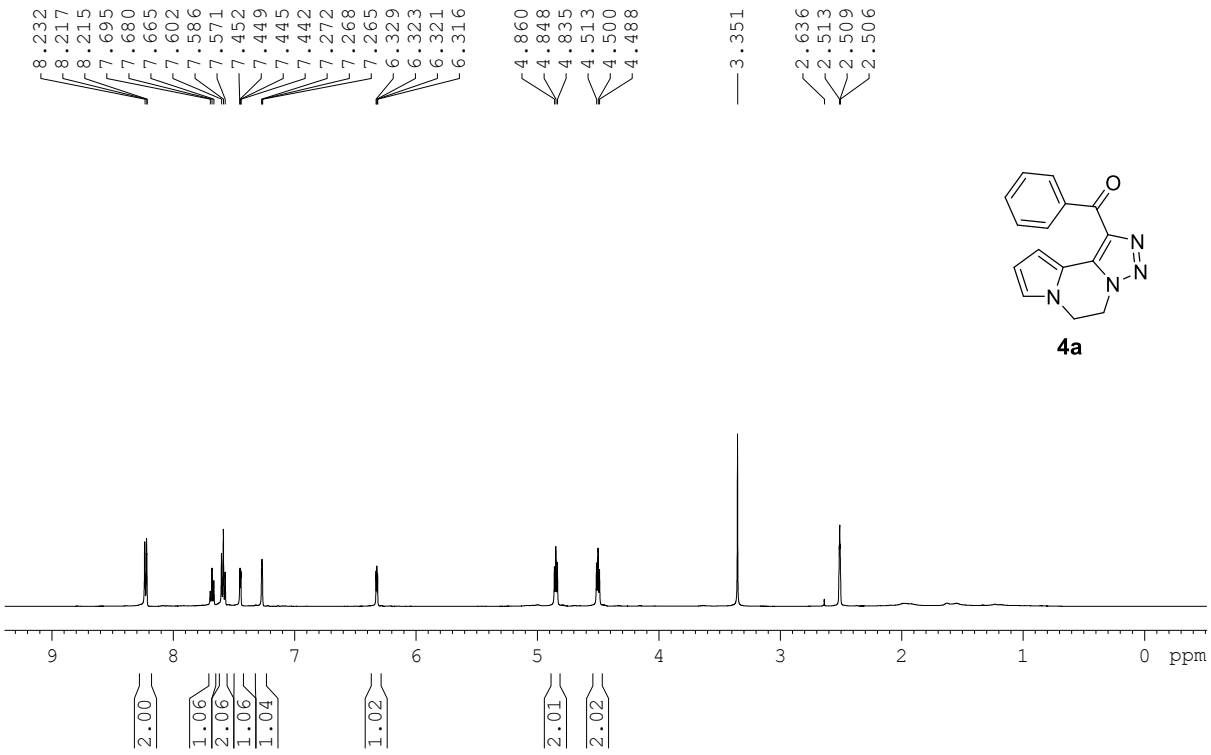
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **2v**



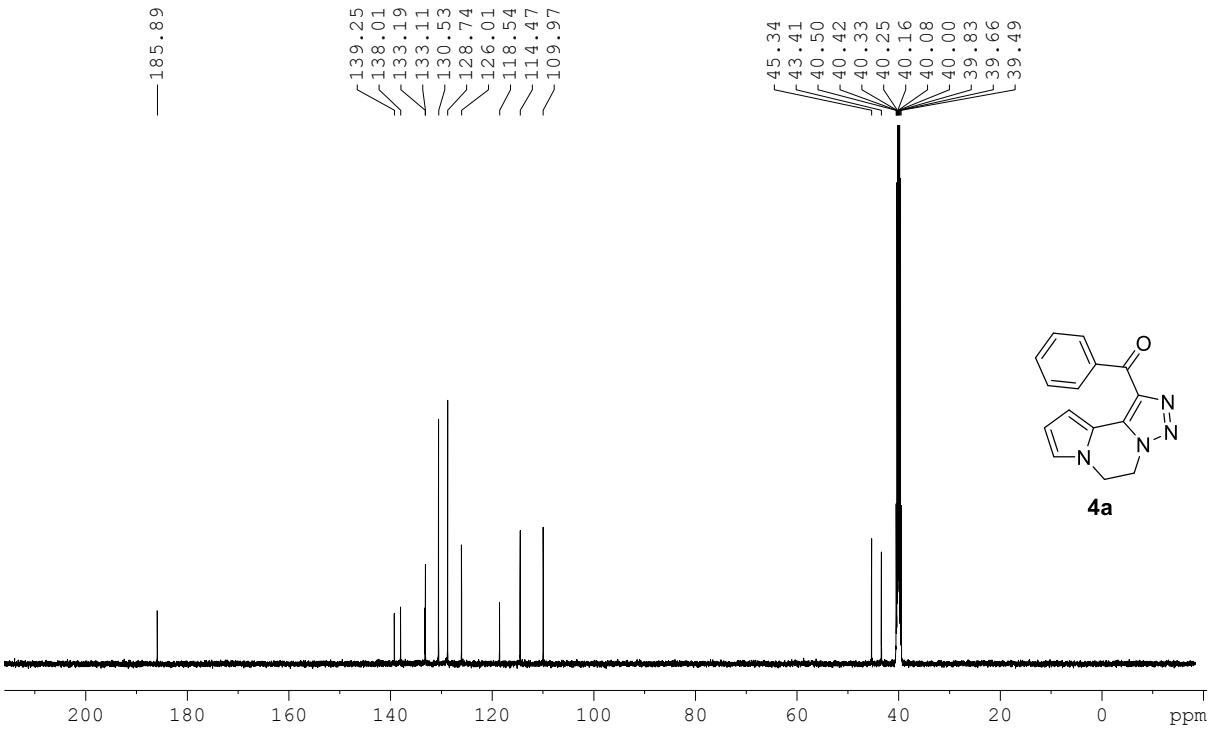
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **2x**



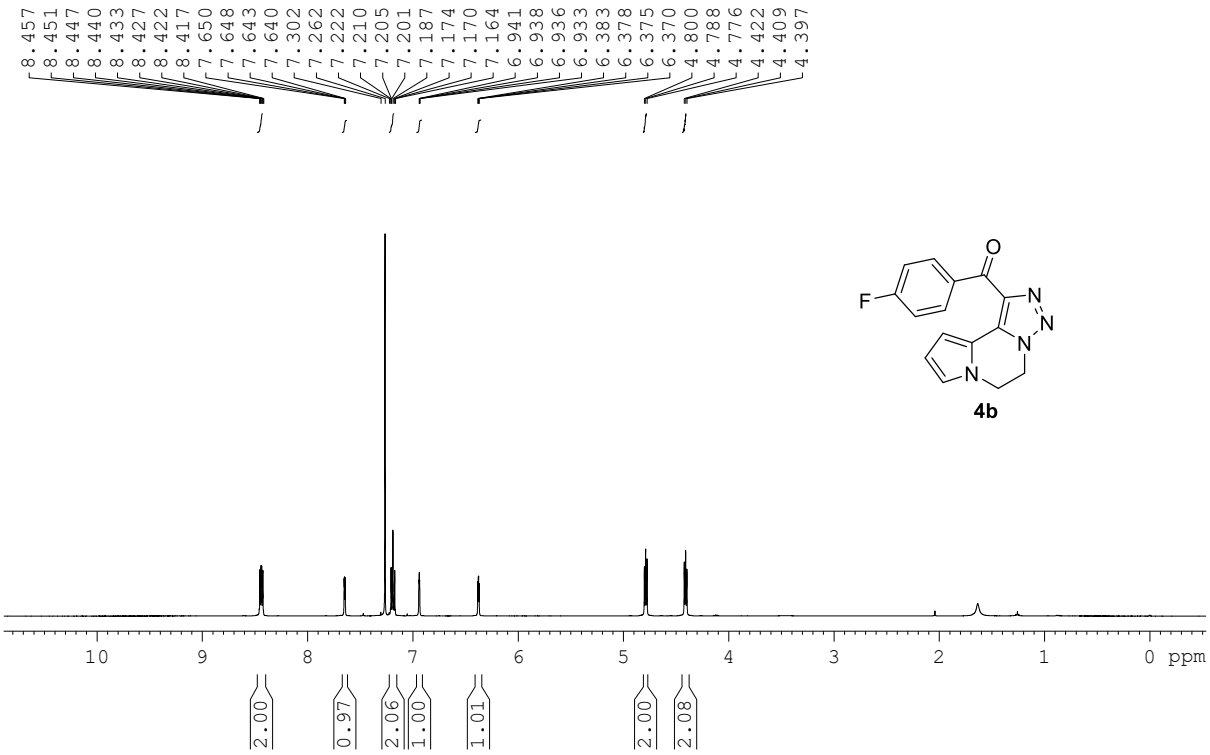
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **2x**



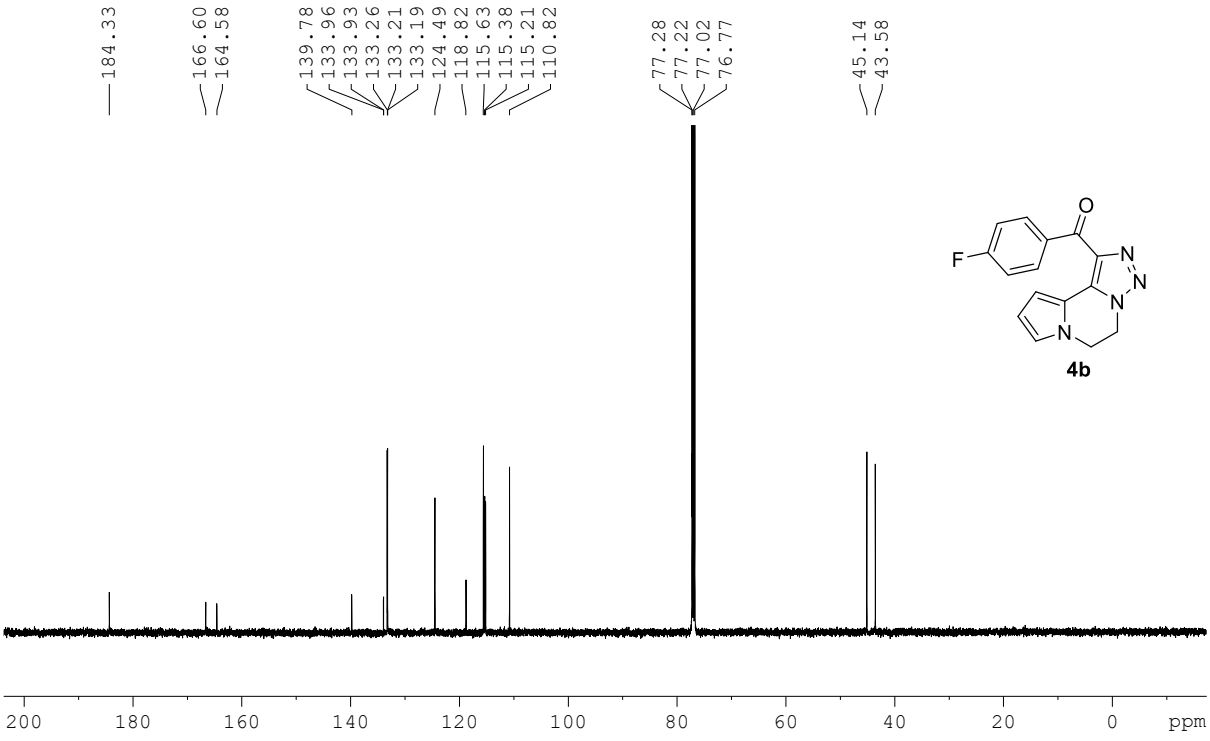
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **4a**



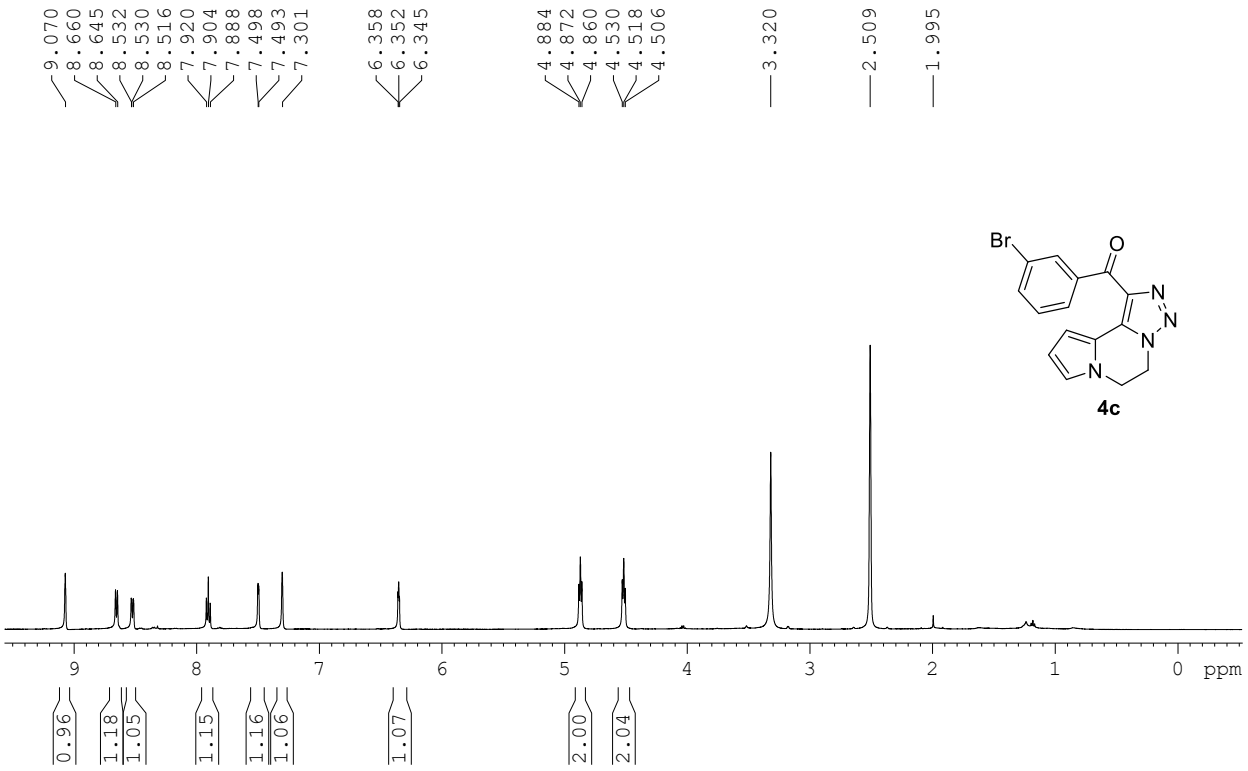
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **4a**



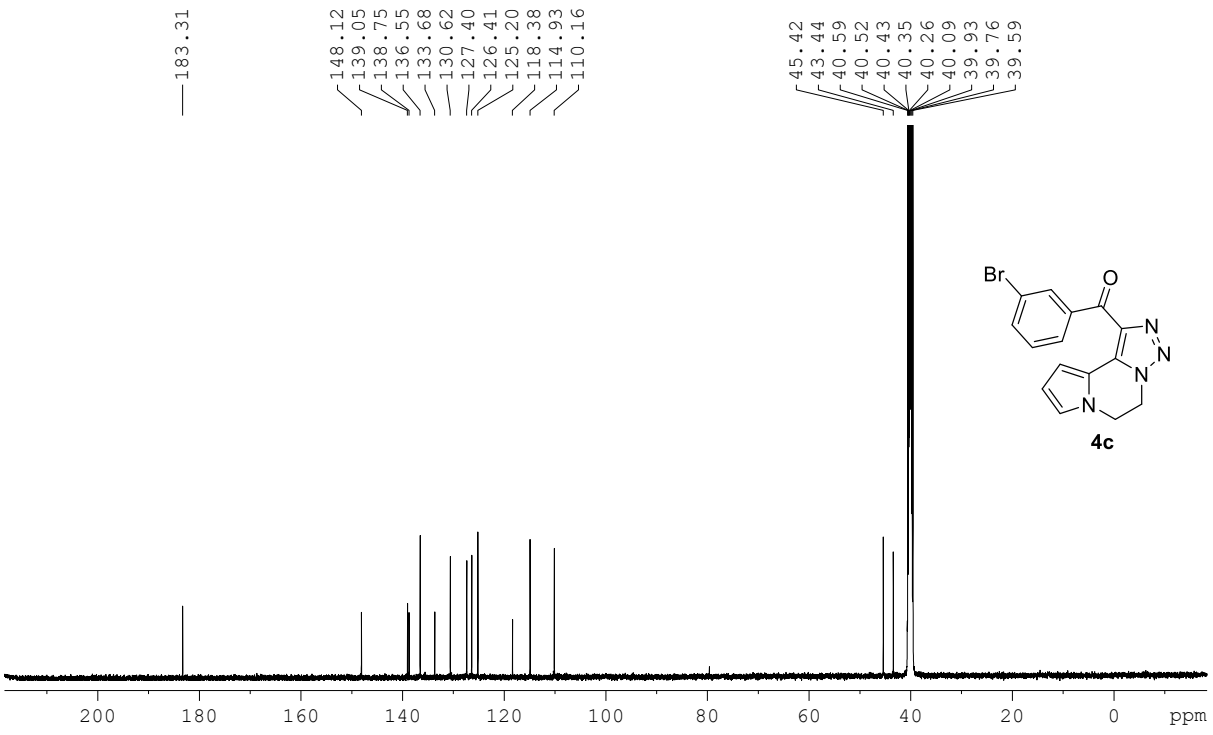
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **4b**



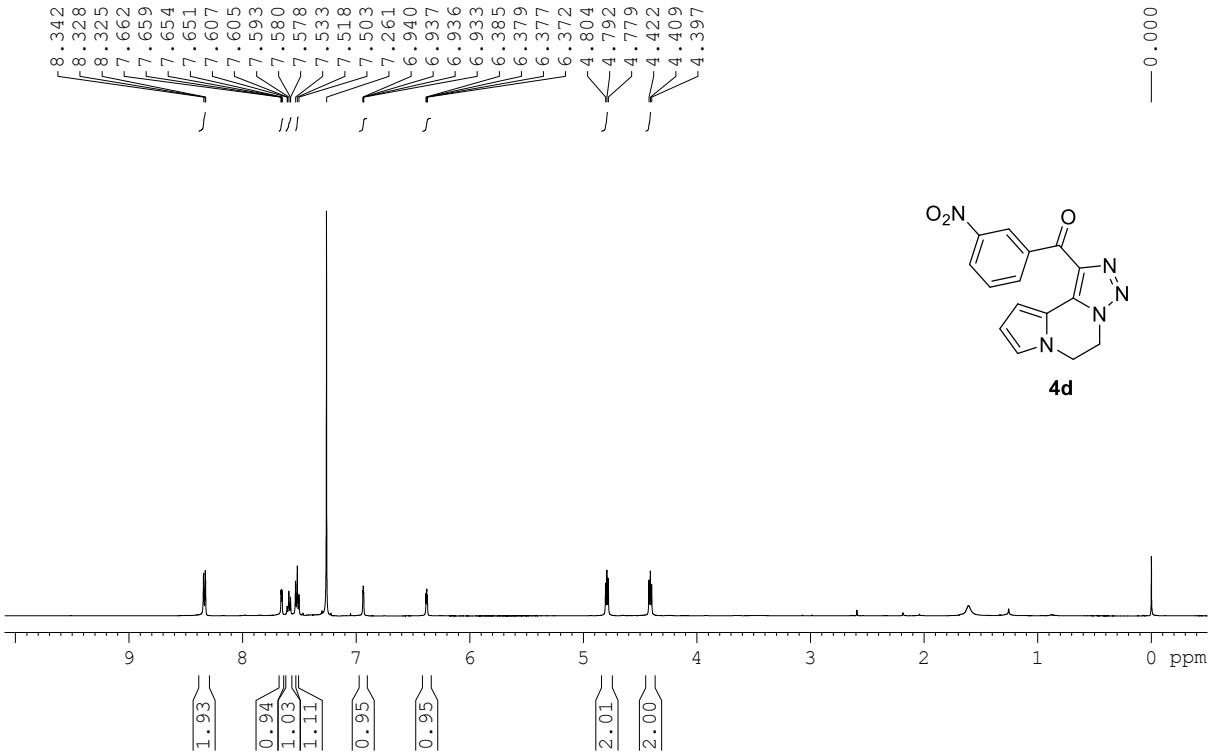
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **4b**



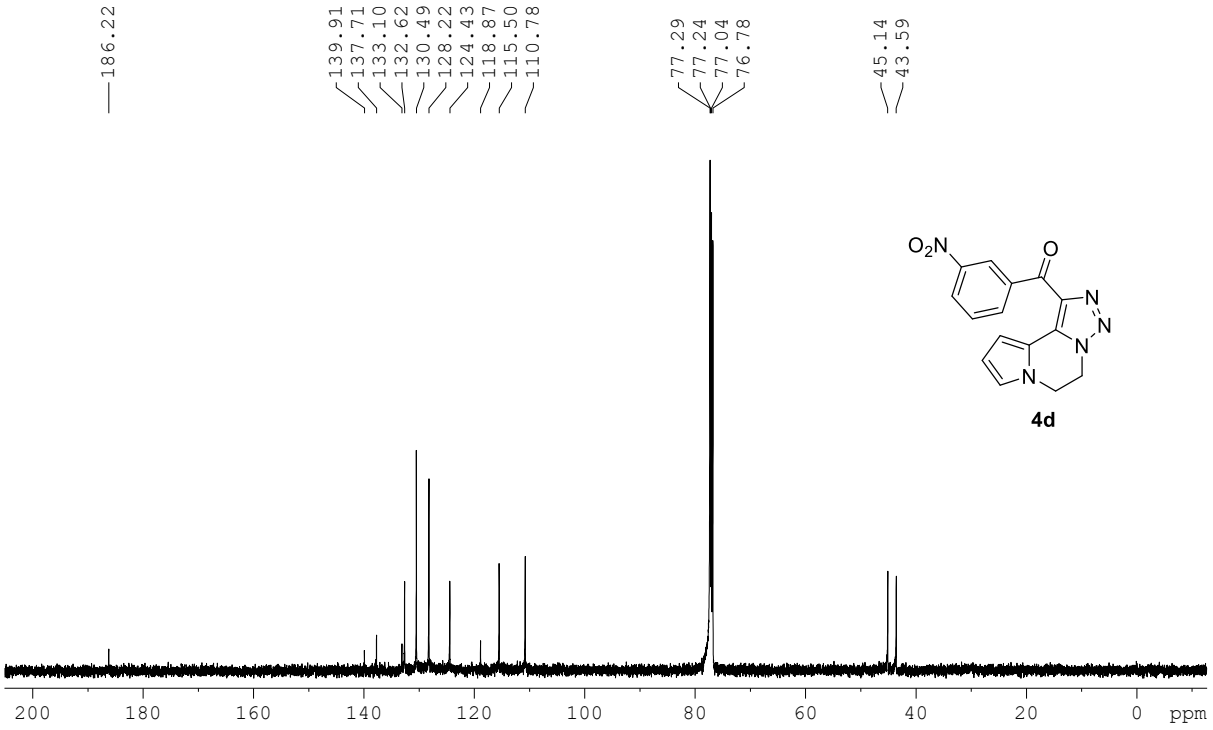
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **4c**



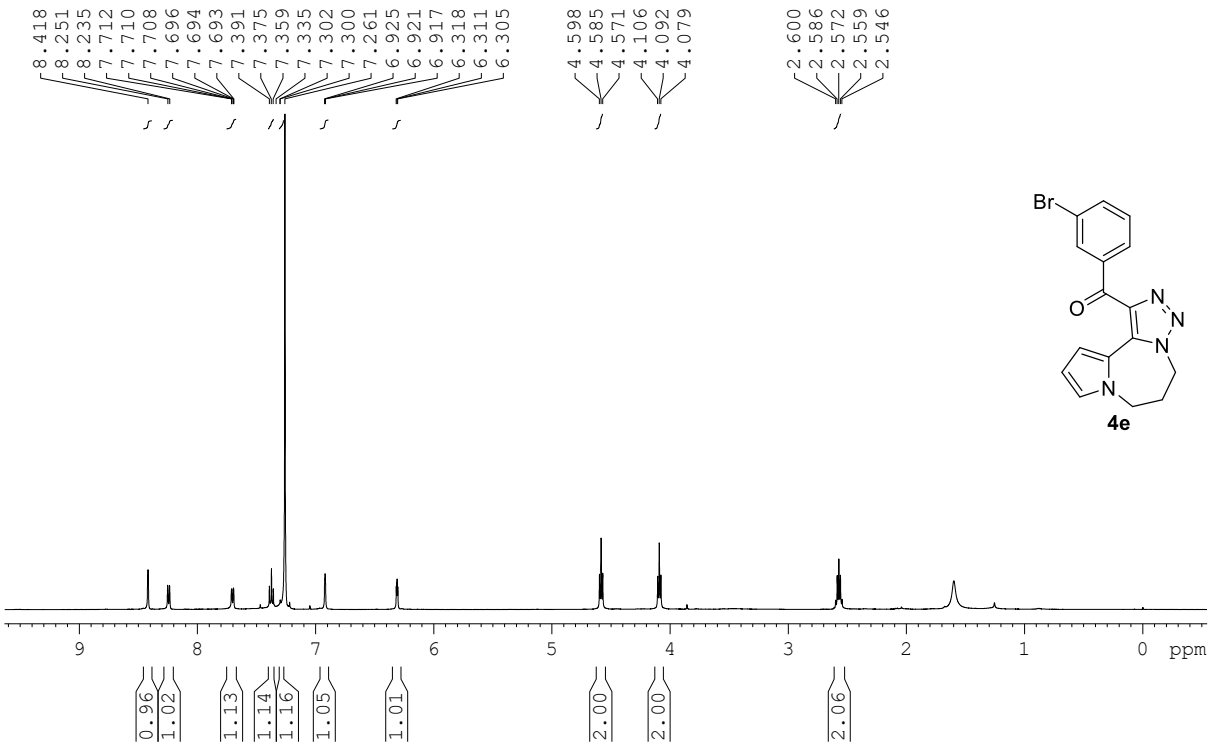
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **4c**



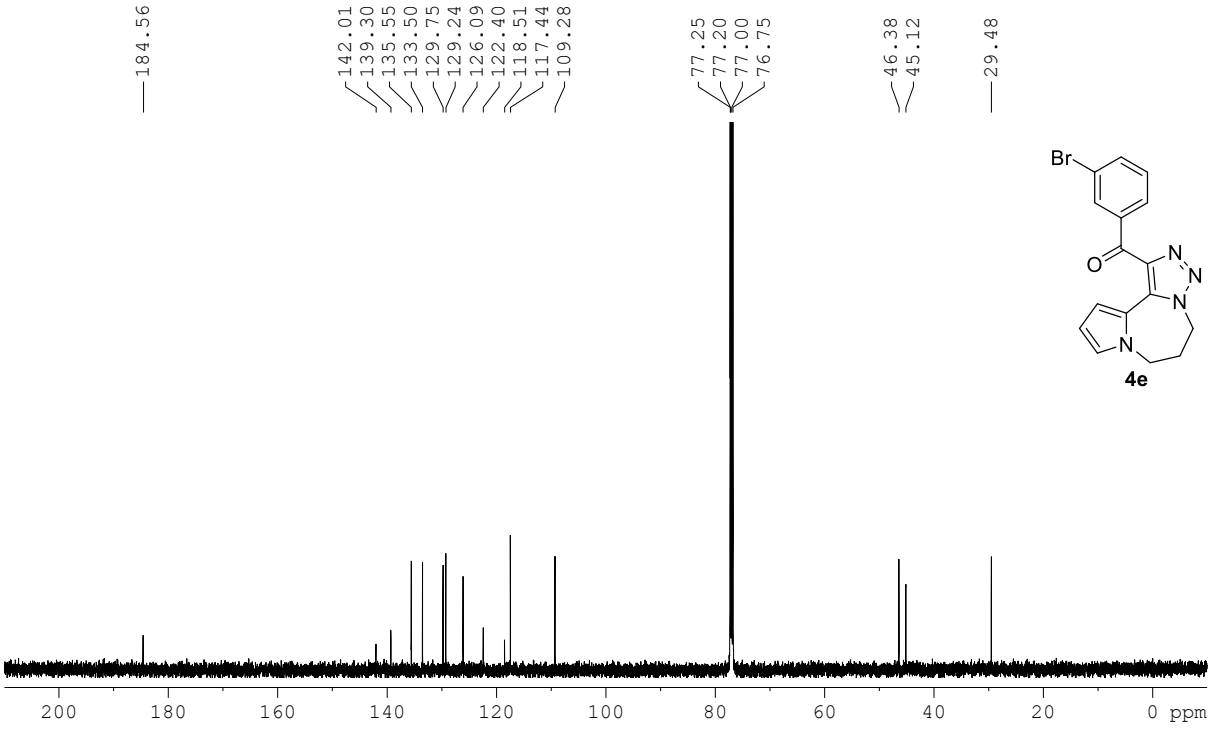
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **4d**



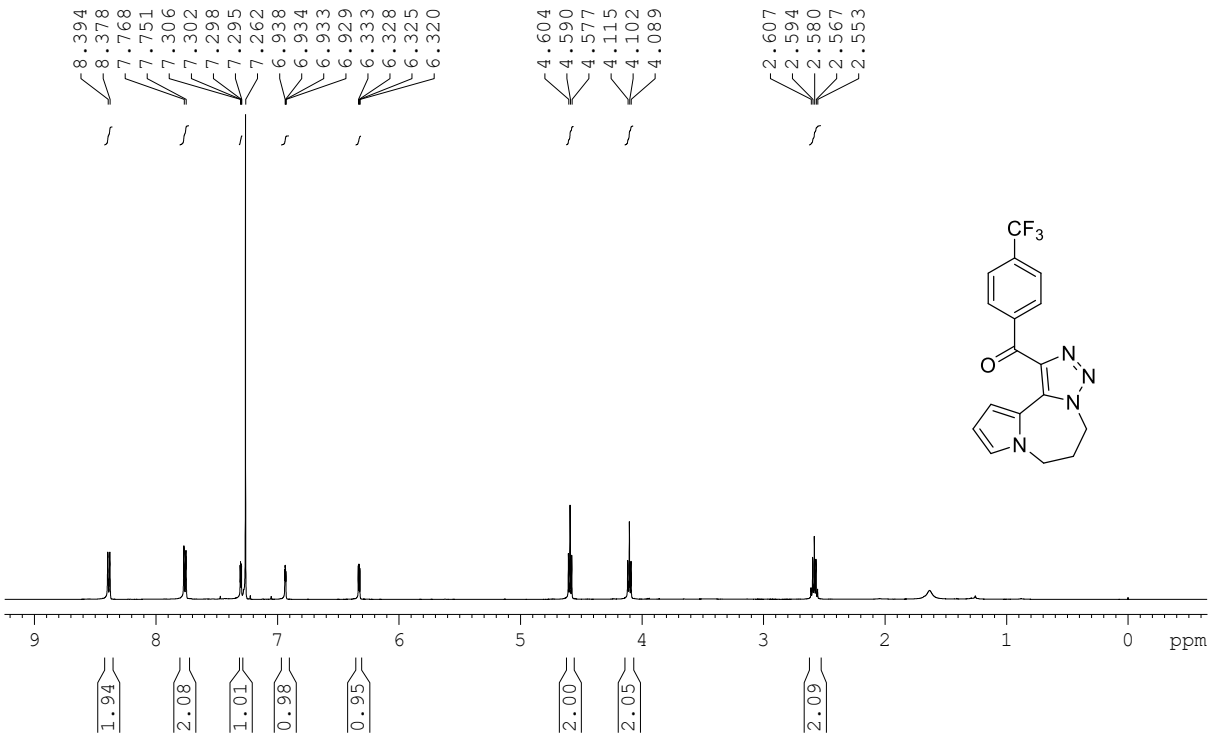
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **4d**



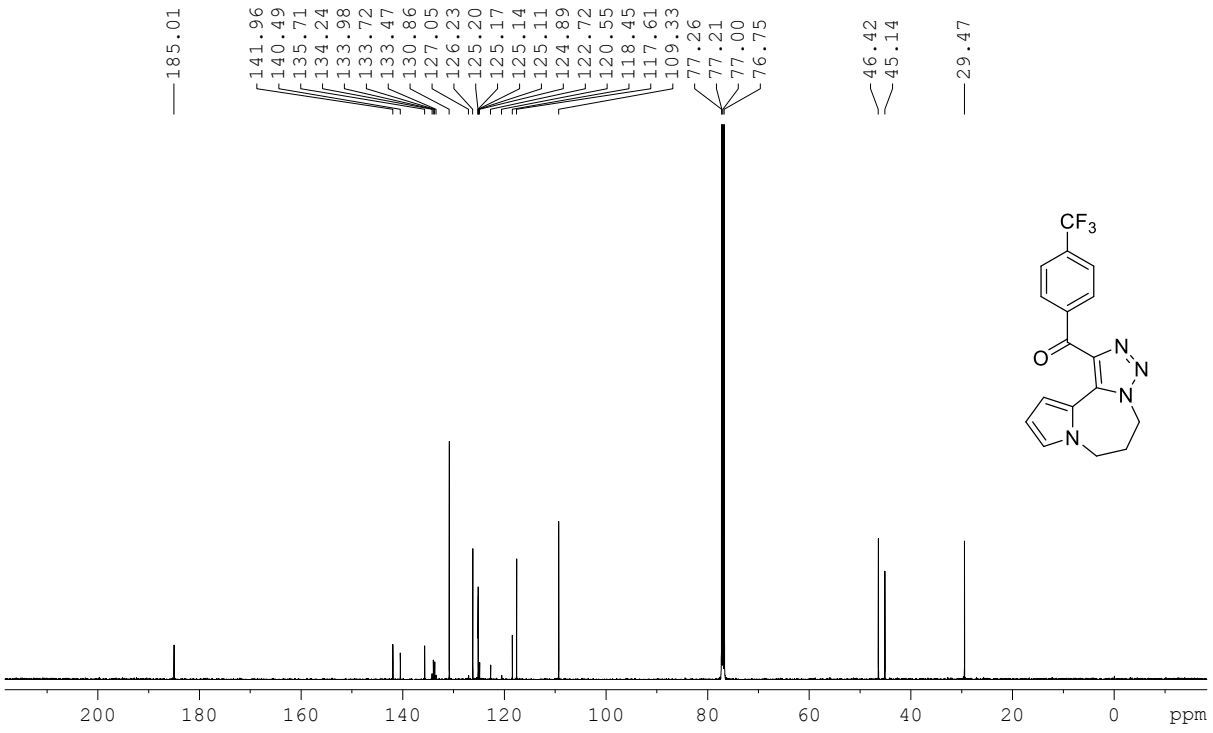
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **4e**



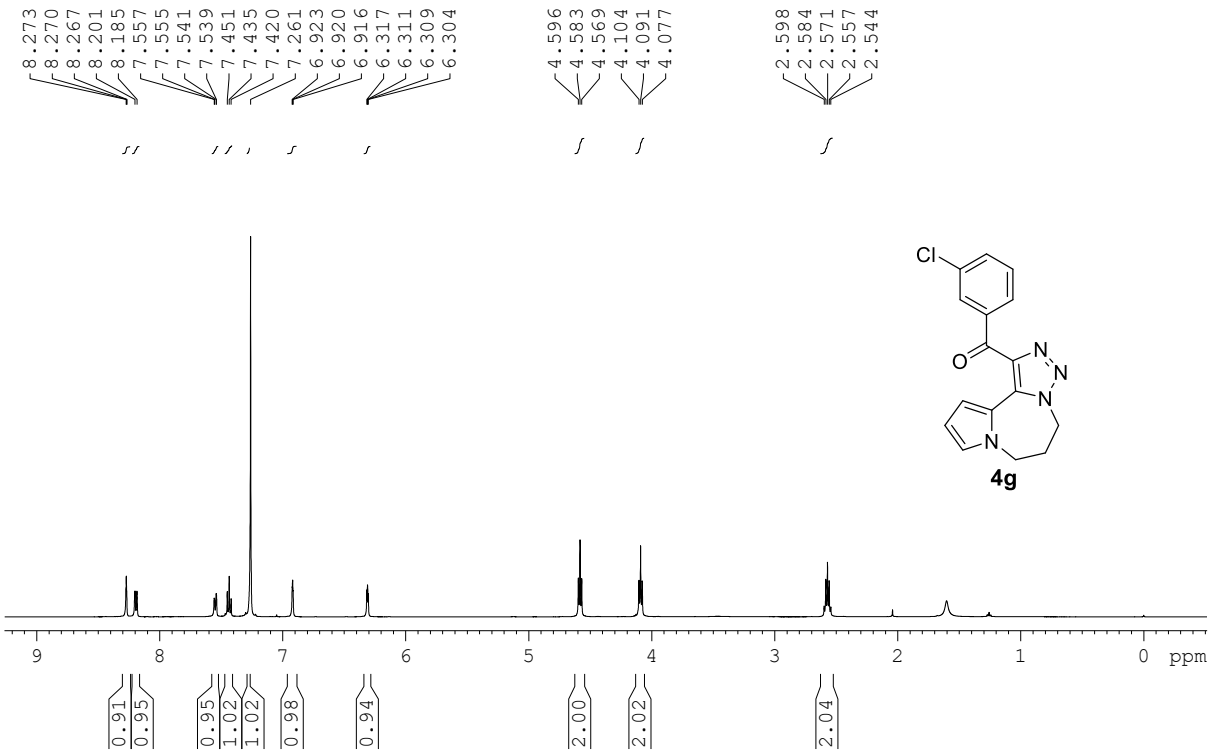
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **4e**



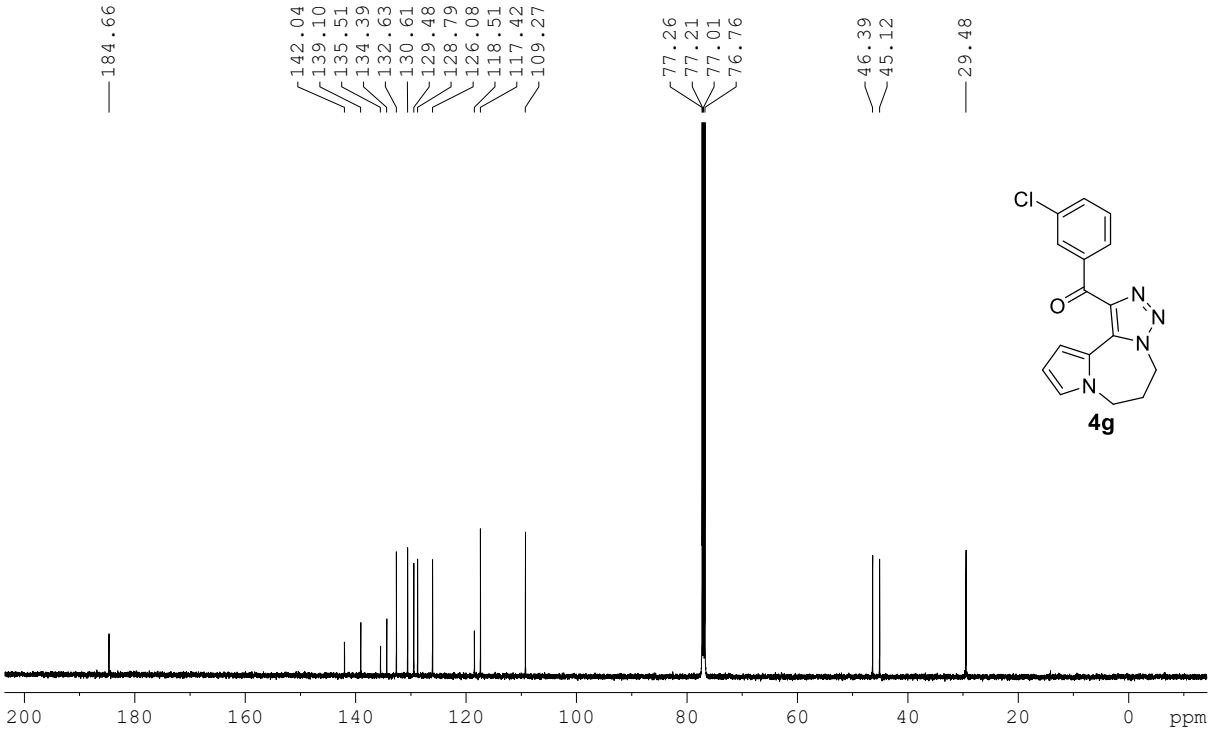
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **4f**



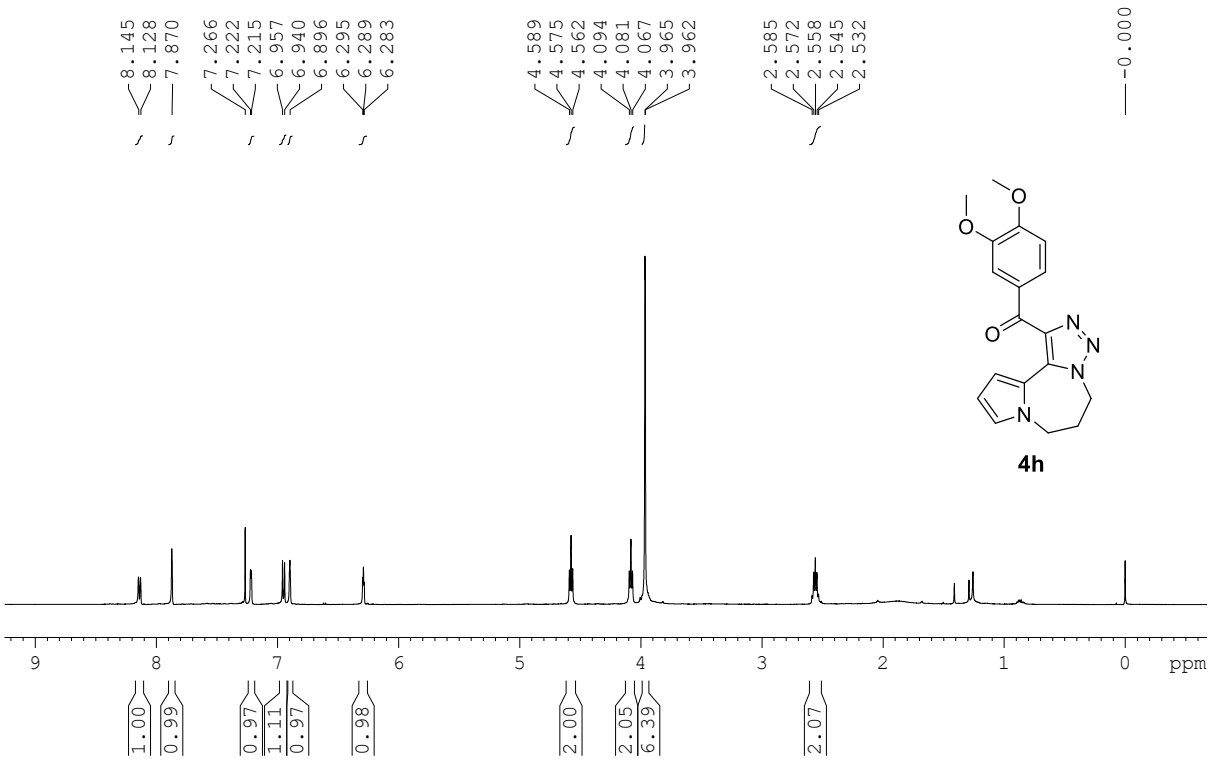
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **4f**



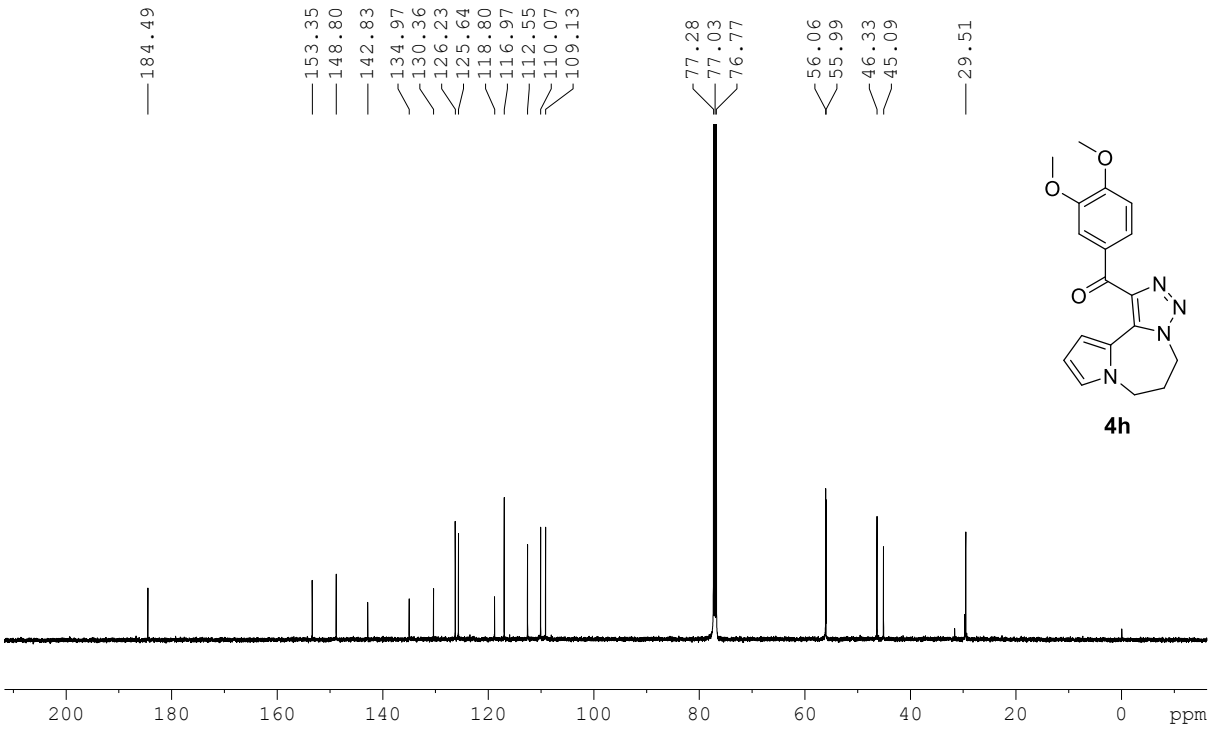
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **4g**



^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **4g**



^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **4h**



^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **4h**