Electronic Supplementary Material (ESI) for New Journal of Chemistry.

SUPPORTING INFORMATION

Bronsted acid catalysed eco friendly synthesis of quaternary centred C-3 functionalized oxindole derivatives

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EXPERIMENTAL GENERAL

Materials and methods

All chemicals were purchased from Sigma Aldrich. All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d6 using TMS as an internal standard on a Bruker Avance spectrometer at 400 Mhz amd 100 Mhz respectively. Mass spectra were recorded using a JEOL GCMate-II–HR mass spectrometer. Analytical TLC was performed on precoated aluminium sheets of siliga gel G/UV-254 of 0.2 mm thickness (Merck, Germany).

Starting materials

3-indolylmethanols **1** had been prepared according to the literature procedure[12]

Pharmacology

In the course of identifying various novel anti-microbial and anti-cancer agents, we are particularly interested in the present work with C-3 functionalished indole which have been identified as a new class of anti-microbial and anti-cancer agents with significant therapeutic efficacy.

Materaials, methods and anti-microbial activity results

The entire 25 compounds were screened for antimicrobial activity against human bacterial pathogens, including Gram-positive bacteria Methicillin resistant *Staphylococcus aureus* (MRSA), the Gram-negative bacteria *Pseudomonas aeruginosa, Escherichia coli and Klebsiella pneumoniae* and a human yeast pathogen, Fluconazole resistant *Candida albicans* (FRCA). Well diffusion assay was carried out to determine the antimicrobial activity[**1**]. For the well diffusion assay, 17 h old bacterial cultures were inoculated over the agar surface of Mueller Hinton agar plates using sterile cotton swabs. After 10 min, wells were cut using a cork borer and each well was loaded with 100 µL of compound from 1 mg/ml stock (100µg/well) along with DMSO control. The plates were incubated at 37°C for 24 h. Susceptibility was assessed on the basis of diameter of the zone of inhibition (ZOI) against the test pathogens and the results are presented Table 1.

The in vitro anti-microbial results are summarized in Table 1. Compounds **3g** & **3m** showed excellent activity against P. aeruginosa, MRSA and C. Albicans. However there was no

activity against *E.coli and K. pneumoniae*. All other tested compound showed moderate to good activities.

The *in vitro* minimum inhibitory concentration (MIC) of the compound against human pathogens was determined by the method of National Committee for Clinical Laboratory (NCCLS).[2] The MIC values are summarized in Table 2. The standard antibiotics, Streptomycin and Fluconazole triclosan were used as controls. The results revealed that the compound **3g** and **3m** have shown very good anti-microbial activity against organism. All other tested compound showed moderate to excellent activities.

Table 1 Antimicrobial activity of the synthesized compounds against human pathogens

Compound	Zone of inhibition (mm)				
	Gram-positive bacterium (MRSA)	Gram-negative bacterium			
		P. aeruginosa	K. Pneumonia	E.coli	Yeast strain FRCA
3a.	18	14	N	N	15
3b.	13	15	N	N	17
3c.	20	10	N	N	16
3d.	24	N	N	N	13
3e.	17	9	N	N	17
3f.	15	16	N	N	18
3g.	27	24	N	N	22
3h.	20	18	N	N	19
3i.	21	13	N	N	17
3j.	N	N	N	N	17
3k.	20	13	N	N	21
3l.	13	N	N	N	15
3m.	26	22	N	N	25
3n.	22	17	N	N	23
5a.	17	16	N	N	19
5b.	14	9	N	N	18
5c.	13	10	N	N	17
5d.	12	10	N	N	20
5e.	11	N	N	N	20
5f.	11	13	N	N	21
5g	N	N	N	N	16
5h.	N	N	N	N	13
5i.	10	11	N	N	16
5j.	12	13	N	N	16
5k.	10	12	N	N	15
P. C.	N	30	N	N	N
N. C.	N	N	N	N	N

P.C : Streptomycin 30µg for MRSA, *P. aeruginosa, S. Typhi* and *E. coli;* Fluconazole 30µg for FRCA; Negative Control (N. C): 10% DMSO;N: No inhibition.

Table 2 Minimum inhibitory concentration of the compounds against human pathogens

Entry	Zone of inhibition (mm)				
	Gram-positive bacterium	Gram-negative bacterium			
	MRSA	P. aeruginosa	K.Pneumonia	E.coli	FRCA
3a.	250	250	ND	ND	250
3b.	500	250	ND	ND	250
3c.	62.5	ND	ND	ND	250
3d.	120	100	ND	ND	250
3e.	100	80	ND	ND	31.25
3f.	125	125	ND	ND	125
3g.	250	62.5	ND	ND	62.5
3h.	155	100	ND	ND	110
3i.	130	120	ND	ND	90
3j.	ND	ND	ND	ND	125
3k.	125	125	ND	ND	62.5
3l.	15.625	ND	ND	ND	15.62
3m.	7.8123	15.625	ND	ND	62.5
3n.	250	500	ND	ND	62.5
5a.	125	145	ND	ND	75
5b.	175	160	ND	ND	80
5c.	187	150	ND	ND	120
5d.	500	500	ND	ND	250
5e.	500	500	ND	ND	62.5
5f.	250	250	ND	ND	500
5g.	ND	ND	ND	ND	31.25
5h.	ND	ND	ND	ND	125
5i.	ND	ND	ND	ND	180
5j.	100	120	ND	ND	190
5k.	90	150	ND	ND	115
P. C.	ND	3.90	ND	ND	ND
N. C.	ND	ND	ND	ND	ND

ND: Not determined as they did not show antimicrobial activity in the well diffusion assay.

Refrences

1. Fazeli. M. R., Amin, G., Attar, M. M. A., Ashtiani, H., Jamalifar, H., Samadi, N. 2007. *Food Control.* **18:** 646.
2. National Committee for Clinical Laboratory Standards, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 5th Edition: Approved Standard M7-A5. National Committee for Clinical Laboratory Standards: Wayne, Pa, Vol. 20, No. 2, 2000.

Anticancer activity

MTT-based cytotoxicity assay

The cytotoxic effect of compounds against human tumor cell lines was determined by a rapid colorimetric assay, using 3-(4, 5 dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) and compared with untreated controls[3]. For screening experiment, the cells were seeded in 96-well plates in 100µL of medium containing 5%FBS, at plating density10,000 cells/well and incubate

(100%) for 48 h. Triplicate was maintained and the medium containing without the sample were served as control.

formazan crystals were solubilised in 100 µL of DMSO and then measured the absorbance at 570 nm using micro plate reader. The percentage cell inhibition was determined using the following formula and summarized in Table 3.

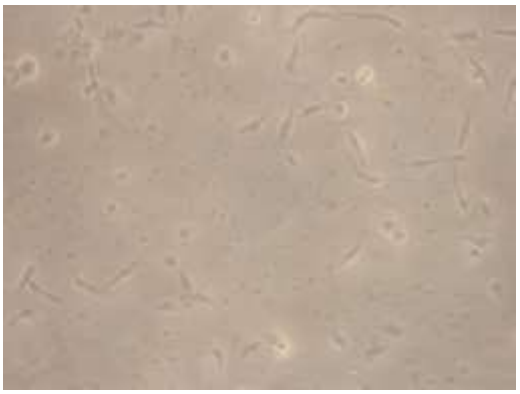
Cell inhibition (%) = 100- Absorbance (Sample)/Absorbance (control) x 100

The compounds **3g** and **3m** were evaluated for anticancer activity against MCF-7 and Hep-2 cancer cell lines using the commercially available standard drug Cisplatin as a positive control.[3] Their IC_{50} concentration are depicted in Table 3. The results demonstrated that N-benzyl oxindole substituted indole derivative **3m** exhibited higher inhibitory activity compares to N-H oxindole substituted indole derivative **3g**. The results indicated that 3-indolyloxindole substituted isoxazole analogs may be useful leads for further biological screening.

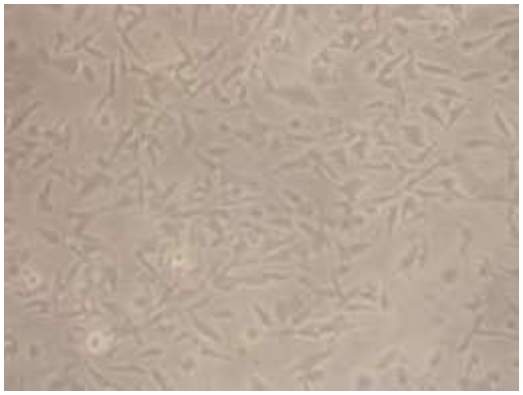
Table 3: IC_{50} values of compound on the growth of human cancer cell lines

Compound	IC_{50} (µg/ml)		
	Hep-2	MCF-7	Vero Cells
3g.	22.09	54.3	123.2
3m.	30.04	45.02	150.2

Hep-2 cells control

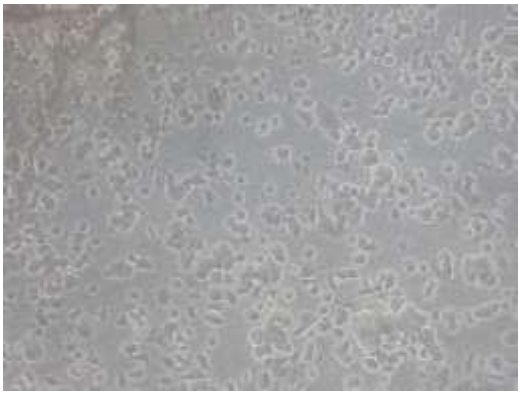


Hep-2 cells treated (3g)



Hep-2 cells treated (3m)

MCF-7 cells control



MCF-7 cells treated (3g)

MCF-7 cells treated (3m)

Vero cells control

Vero cells treated (3g)

Vero cells treated (3m)

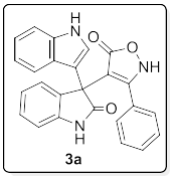
Refrences

3. Mosmann, T. 1983. Rapid colorimetric assay for cellular growth and survival application to proliferation and cytotoxicity assays. *J. Immunol. Methods*, 65: 55-63.

General procedure for the synthesisof 4-(3-(1H-indol-3-yl)-2-oxoindolin-3-yl)-3 phenylisoxazol-5(4H)-one (3a-p) and 3-(1H-indol-3-yl)-3-(3-methyl-5-oxo-1-phenyl-4,5 dihydro-1H-pyrazol-4-yl)indolin-2-one derivatives (5a-k)

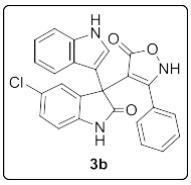
A mixture of 3-Hydroxy-3-indolylindolin-2-ones, **1** (1 mmol), isoxazolone/pyrazolone **2/4**(1 mmole) and p-TSA.H_2O (0.20 mmol) in ethanol (3 mL) was stirred at room temperature for 2-4 h.The crude products were purified by column chromatography (5:95 % MeOH/$CHCl_3$) to obtain pure **3a-p** and **5a-k** in good yields (80-94 %). The identities of products **3a-p** and **5a-k** were confirmed by NMR and EI-HRMS, giving good agreement with the assigned structures.

3a: 4-(3-(1*H*-Indol-3-yl)-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one



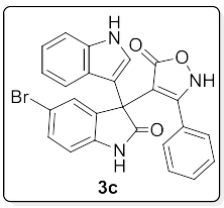
Isolated as white solid, 92 %, m.p: 214-216 ^oC,^1H NMR (400 Mhz, DMSO-d_6): δ $_H$12.45 (1H, s), 10.69 (1H, s), 10.60 (1H, s), 7.53 (1H, d, *J*= 8.0), 7.44 (1H, s), 7.30 (1H, dd, *J*= 8.3, 2.1), 7.08 (4H, dd, *J*= 20.2, 13.9), 7.02 (1H, d, *J*= 8.0), 6.91 (4H, dd, *J*= 20.5, 15.1), 6.79 (1H, t, *J*= 7.5), 6.59 (1H, d, *J*= 2.5)ppm.^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 177.2, 170.7, 164.7, 141.2, 137.1, 135.1, 130.0, 128.5, 128.0, 127.0, 125.8, 125.6, 124.7, 124.0, 121.8, 121.3, 118.6, 111.6, 111.5, 50.9 ppm. EI-HRMS: Anal. Calcd for $C_{25}H_{17}N_3O_3$: 407.1270, Found: 407.1270.

3b:4-(5-Chloro-3-(1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one



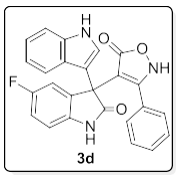
Isolated as white solid, 90 %, m.p: 218-220 ^oC, ^1H NMR (400 Mhz, DMSO-d_6): δ_H 10.61 (1H, s), 10.37 (1H, s), 7.57 (1H, d, *J*= 7.5), 7.48 (1H, d, *J*= 7.0), 7.27 (1H, t, *J*= 7.7), 7.08 (3H, d, *J*= 7.8), 6.99 (1H, d, *J*= 8.0), 6.92 (3H, dd, *J*= 16.7, 8.6), 6.85 (1H, dd, *J*= 10.6, 4.0), 6.77 (1H, t, *J*= 7.4), 6.46 (1H, s) ppm. ^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 177.5, 170.8, 164.7, 142.5, 137.1, 132.9, 129.9, 128.6, 127.8, 127.7, 127.5, 127.3, 127.0, 125.9, 125.8, 125.0, 124.0, 122.2, 121.8, 121.1, 118.3, 112.4, 111.4, 110.0, 50.6 ppm. EI-HRMS: Anal. Calcd for $C_{25}H_{16}ClN_3O_3$: 441.0880, Found: 441.0880.

3c:4-(5-Bromo-3-(1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one



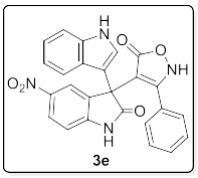
Isolated as white solid, 88 %, m.p: 230-231 ^oC, ^1H NMR (400 Mhz, DMSO-d_6): δ_H12.46 (1H, s), 10.71 (1H, s), 10.62 (1H, s), 7.53 (2H, d, *J*= 12.9), 7.44 (1H, d, *J*= 7.6), 7.11 (3H, d, *J*= 4.8), 7.04 (1H, d, *J*= 7.6), 6.97 (2H, d, *J*= 6.7), 6.87 (2H, d, *J*= 7.3), 6.81 (1H, d, *J*= 7.1), 6.60 (1H, s)ppm. ^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 177.1, 170.7, 164.7, 141.6, 137.1, 135.5, 131.3, 130.0, 127.9, 127.4, 127.1, 125.6, 124.0, 121.7, 121.3, 118.6, 113.5, 112.0, 111.7, 111.6, 50.9 ppm. EI-HRMS: Anal. Calcd for $C_{25}H_{16}$ Br N_3O_3: 485.0375, Found: 485.0373.

3d:4-(5-Fluoro-3-(1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one



Isolated as white solid, 85 %, m.p: 220-222 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 10.68 (1H, s), 10.48 (1H, s), 7.56 (1H, d, *J*= 7.8), 7.31 (1H, d, *J*= 7.5), 7.12 (4H, d, *J*= 6.9), 7.02 (1H, d, *J*= 7.8), 6.98–6.83 (4H, m), 6.81 (1H, d, *J*= 7.6), 6.60 (1H, s) ppm. ^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 177.5, 170.7, 164.8, 159.4, 157.1, 138.5, 137.1, 134.7, 129.9, 128.0, 127.0, 125.6, 124.0, 121.9, 121.2, 118.5, 114.9, 114.6, 112.7, 112.5, 111.9, 111.5, 110.7, 51.2 ppm. EI-HRMS: Anal. Calcd for $C_{25}H_{16}FN_3O_3$: 425.1176, Found: 425.1173.

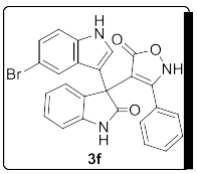
3e:4-(3-(1*H*-indol-3-yl)-5-Nitro-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one



Isolated as white solid, 89 %, m.p: 192-194 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 11.20 (1H, s), 10.78 (1H, d, *J*= 2.1), 8.31 – 8.14 (2H, m), 7.57 (1H, d, *J*= 7.9), 7.15–7.08 (4H, m), 7.05 (1H, d, *J*= 8.0), 6.98 (2H, t, *J*= 7.7), 6.89 (1H, dd, *J*= 10.9, 3.9), 6.83 (1H, t, *J*= 7.5), 6.70 (1H, d, *J*= 2.6).^{13}C NMR (100 Mhz, DMSO-d_6): δ_C177.7, 170.7, 164.7, 148.7, 142.6, 137.2, 133.9, 130.1, 127.9, 127.2, 126.1, 125.5, 124.2, 121.6, 121.4, 120.3, 118.8, 111.7, 110.9, 110.2, 50.6 ppm. EI-HRMS: Anal. Calcd for $C_{25}H_{16}N_4O_5$: 452.1121, Found: 452.1120.

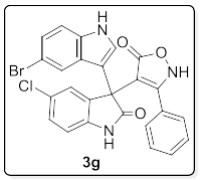
3f:4-(3-(5-Bromo-1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one

Isolated as white solid, 86 %, m.p: 210-212 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 10.85



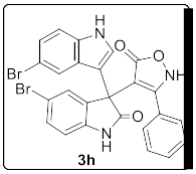
(1H, d, *J*= 2.2), 10.41 (1H, s), 7.73 (1H, s), 7.73 (1H, s), 7.49 (1H, d, *J*= 7.3), 7.30 (2H, td, *J*= 7.7, 0.9), 7.13–7.07 (2H, m), 7.05 (4H, dd, *J*= 8.2, 4.1), 6.93 (1H, q, *J*= 7.6), 6.48 (1 H, d, *J*= 2.6), ppm. ^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 177.5, 170.7, 164.6, 142.7, 135.8, 132.2, 129.9, 128.9, 127.7, 127.6, 126.9, 125.7, 125.1, 124.6, 123.6, 122.0, 113.4, 112.0, 111.3, 110.2, 50.5 ppm. EI-HRMS: Anal. Calcd for $C_{25}H_{16}BrN_3O_3$: 485.0375, Found: 485.0373.

3g:4-(3-(5-Bromo-1*H*-indol-3-yl)-5-chloro-2-oxoindolin-3-yl)-3-phenylisoxazol-5-(2*H*)-one



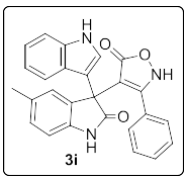
Isolated as white solid, 84 %, m.p: 211-213 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 10.93 (1H, s), 10.59 (1H, s), 7.70 (1H, s), 7.47 (1H, s), 7.35 (1H, dd, *J*= 8.3, 2.1), 7.12–7.02 (3 H, m), 6.94 (5H, dd, *J*= 15.1, 7.8), 6.60 (1H, d, *J*= 2.6) ppm.^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 177.2, 170.6, 164.5, 141.5, 135.8, 130.0, 128.8, 127.8, 127.4, 127.0, 126.0, 125.8, 124.9, 124.4, 123.7, 113.5, 111.6, 111.4, 111.2, 50.8 ppm. EI-HRMS: Anal. Calcd for $C_{25}H_{15}BrClN_3O_3$: 518.9985, Found: 518.9984.

3h:4-(5-Bromo-3-(5-bromo-1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenyli-soxazol-5(2*H*)-one



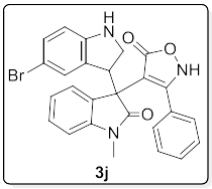
Isolated as white solid, 85 %, m.p: 220-222 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 10.92 (1H, s), 10.60 (1H, s), 7.69 (2H, s), 7.57 (1H, s), 7.48 (1H, dd, *J*= 8.2, 1.7), 7.07 (3H, dd, *J*= 18.8, 7.3), 6.96 (4H, t, *J*= 7.3), 6.88 (1H, d, *J*= 8.2), 6.60 (1H, d, *J*= 2.5) ppm. ^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 177.1, 170.6, 164.5, 141.9, 135.8, 131.7, 127.8, 127.5, 127.4, 127.0, 125.7, 124.4, 123.7, 113.6, 113.5, 112.2, 111.4, 50.8 ppm. EI-HRMS: Anal. Calcd for $C_{25}H_{15}Br_2N_3O_3$: 562.9480, Found: 562.9480.

3i:4-(3-(1H-indol-3-yl)-5-methyl-2-oxo-indolin-3-yl)-3-phenyl-isoxazol-5(2*H*)-one



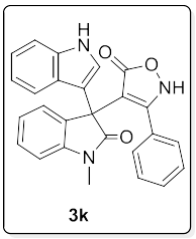
Isolated as white solid, 88 %, m.p: 228-230 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6):δ_H 10.61 (d, *J* = 2.1 Hz, 1H), 10.26 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 7.16 –7.03 (m, 4H), 7.01 (d, *J* = 8.1 Hz, 1H), 6.95 (t, *J* = 7.7 Hz, 2H), 6.84 (dd, *J* = 11.1, 4.1 Hz, 1H), 6.82–6.75 (m, 2H), 6.48 (d, *J* = 2.5 Hz, 1H), 2.31 (s, 3H) ppm. ^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 177.4, 170.9, 164.6, 140.0, 137.1, 133.0, 130.6, 129.9, 128.9, 128.5, 127.9, 127.0, 125.9, 125.9, 125.5, 124.1, 122.2, 121.1, 118.3, 112.6, 111.4, 109.8, 50.7, 21.3 ppm. EI-HRMS: Anal. Calcd for $C_{26}H_{19}N_3O_3$: 421.1426, Found: 421.1424.

3j: 4-(5'-bromo-1-methyl-2-oxo-[3,3'-biindolin]-3-yl)-3-phenylisoxazol-5(2*H*)-one Isolated



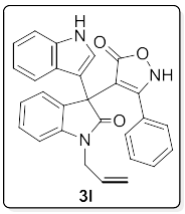
as white solid, 89 %, m.p: 204-207 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 10.67 (1H, s), 7.56 (2H, d, *J*= 7.9), 7.39 (1H, t, *J*= 7.5), 7.16 (2H, d, *J*= 7.4), 7.12–6.99 (5H, m), 6.92–6.84 (1H, m), 6.79 (1H, d, *J*= 7.3), 6.47 (1H, d, *J*= 2.3), 2.97 (3H, s)ppm.^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 175.4, 170.8, 167.0, 143.6, 137.2, 129.5, 128.9, 128.5, 128.2, 127.9, 127.3, 125.9, 124.8, 124.1, 122.7, 122.0, 121.2, 118.4, 111.5, 109.1, 50.0, 26.5 ppm. EI-HRMS: Anal. Calcd for $C_{26}H_{20}BrN_3O_3$: 501.0688, Found: 501.0685.

3k: 4-(3-(1H-indol-3-yl)-1-methyl-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one



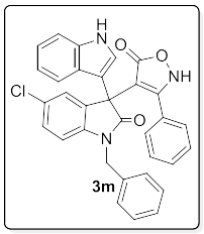
Isolated as white solid, 84 %, m.p: 217-219 ^{o}C,^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 10.89 (1H, s), 7.76 (1H, s), 7.57 (1H, d, *J*= 6.8), 7.41 (1H, d, *J*= 7.3), 7.18 (4H, dd, *J*= 17.3, 9.6), 7.00 (6H, d, *J*= 9.4), 6.51 (1H, s), 2.98 (3 H, s) ppm. ^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 175.6, 170.6, 164.2, 143.9, 137.6, 135.9, 133.3, 131.6, 130.1, 129.1, 128.6, 128.3, 127.8, 127.6, 127.2, 125.8, 124.9, 124.5, 123.7, 122.8, 114.4, 113.5, 111.6, 111.4, 109.2, 49.9, 26.6 ppm. EI-HRMS: Anal. Calcd for $C_{26}H_{19}N_3O_3$: 421.1426, Found: 421.1422.

3l:4-(1-Allyl-3-(1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one



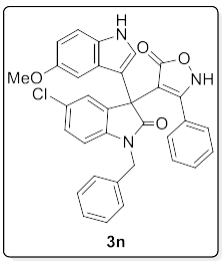
Isolated as white solid, 86 %, m.p: 230-232 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 10.65 (1H, s), 7.57 (2H, t, *J*= 7.8), 7.34 (1H, t, *J*= 7.5), 7.16–7.04 (4H, m), 7.04–6.93 (4H, m), 6.86 (1H, t, *J*= 7.5), 6.79 (1H, t, *J*= 7.4), 6.48 (1H, d, *J*= 2.1), 5.82–5.65 (1H, m), 5.10 (2H, dd, *J*= 36.5, 13.9), 4.26–4.09 (2H, m) ppm. ^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 175.5, 170.7, 164.6, 142.8, 137.2, 132.3, 132.2, 129.9, 128.6, 127.9, 127.1, 125.8, 124.8, 124.0, 122.6, 122.1, 121.2, 118.5, 117.0, 112.2, 111.5, 109.7, 50.2, 42.1 ppm. EI-HRMS: Anal. Calcd for $C_{28}H_{21}N_3O_3$: 447.1583, Found: 447.1580.

3m:4-(1-Benzyl-5-chloro-3-(1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one



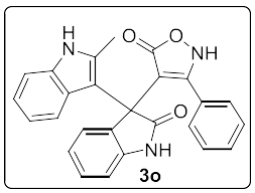
Isolated as white solid, 90 %, m.p: 215-217 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 10.74 (1H, d, *J*= 1.8), 7.54 (2H, dd, *J*= 11.5, 4.7), 7.28 (6H, dd, *J*= 23.9, 12.0), 7.11 (3H, d, *J*= 7.8), 7.03 (1H, d, *J*= 8.0), 6.96 (2H, t, *J*= 7.7), 6.88 (2H, t, *J*= 8.7), 6.81 (1H, t, *J*= 7.3), 6.61 (1H, d, *J*= 2.5), 4.84 (2H, dd, *J*= 55.0, 16.1).ppm.^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 175.6, 170.6, 164.7, 141.5, 137.1, 136.3, 134.3, 130.0, 129.0, 128.9, 128.5, 128.0, 127.7, 127.4, 127.1, 126.8, 125.9, 125.6, 124.7, 124.1, 121.7, 121.4, 118.7, 111.7, 111.4, 111.2, 50.5, 43.5 ppm. EI-HRMS: Anal. Calcd for $C_{32}H_{22}ClN_3O_3$: 531.1350, Found: 531.1350.

3n: 4-(1-Benzyl-5-chloro-3-(5-methoxy-1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenyl -isoxazol-5(2*H*)-one



Isolated as white solid, 80 %, m.p: 218-220 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 10.62 (1H, d, *J*= 2.0), 7.55 (1H, s), 7.28 (6H, dd, *J*= 16.0, 11.9), 7.13 (3H, d, *J*= 7.1), 6.98 (3H, t, *J*= 7.5), 6.89 (2H, d, *J*= 8.5), 6.57 (1H, d, *J*= 2.5), 6.54 (1H, dd, *J*= 8.8, 2.0), 4.84 (2H, dd, *J*= 61.2, 16.2), 3.66 (3 H, s) ppm.^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 175.6, 170.8, 164.8, 153.0, 141.6, 136.3, 134.2, 132.3, 130.1, 128.9, 128.5, 127.9, 127.7, 127.4, 127.1, 126.8, 125.9, 124.8, 124.7, 112.2, 111.6, 111.2, 110.8, 103.8, 55.7, 50.6, 43.4 ppm. EI-HRMS: Anal. Calcd for $C_{33}H_{24}ClN_3O_4$: 561.1455, Found: 561.1453.

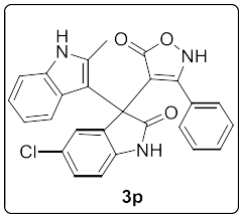
3o: 4-(3-(2-methyl-1*H*-indol-3-*yl*)-2-oxoindolin-3-*yl*)-3-phenylisoxazol-5(2*H*)-one



Isolated as white solid, 82 %, m.p: 204-206 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 10.87 (1 H, s), 10.51 (1H, d, *J* = 10.4), 7.78–7.34 (2H, m), 7.25 (4H, dd, *J* = 50.4, 22.2), 6.92 (4H, dd, *J* = 24.1, 17.5), 6.77–

6.55 (3 H, m), 2.01 (3H, d, *J* 53.7) ppm. ^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 179.8, 178.3, 170.7, 142.2, 141.6, 136.0, 135.4, 135.3, 135.1, 134.3, 132.4, 130.4, 129.5, 128.2, 128.1, 127.9, 127.5, 127.2, 125.9, 125.3, 121.7, 120.2, 120.0, 119.8, 118.3, 118.1, 110.8, 109.9, 52.9, 13.6, 13.4 ppm. EI-HRMS: Anal. Calcd for $C_{26}H_{19}N_3O_3$: 421.1426, Found: 421.1420.

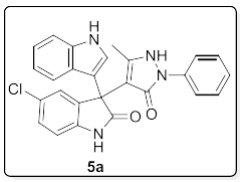
3p:4-(5-chloro-3-(2-methyl-1*H*-indol-3-*yl*)-2-oxoindolin-3-*yl*)-3-phenylisoxazol-5(2*H*)-one



3p

Isolated as white solid, 80 %, m.p: 225-227 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 10.95 (1 H, d, *J* = 14.3), 10.72 (1H, s), 10.55 (1H, s), 7.52–7.24 (5H, m), 7.17 (2H, d, *J* = 7.0), 6.99 (3 H, dd, *J* = 24.5, 15.4), 6.87–6.61 (2H, m), 2.09 (3H, s) ppm. ^{13}C NMR (100 Mhz, DMSO-d_6): 179.4, 178.0, 170.5, 164.8, 140.7, 140.5, 138.0, 136.3, 135.4, 135.1, 135.0, 132.5, 128.2, 128.1, 128.0, 127.9, 127.8, 127.1, 125.9, 125.7, 125.7, 124.6, 120.3, 119.6, 118.7, 111.4, 111.0, 53.2, 13.3 ppm. EI-HRMS: Anal. Calcd for $C_{26}H_{18}ClN_3O_3$: 455.1037, Found: 455.1033

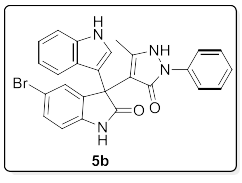
5a:5-Chloro-3-(1*H*-indol-3-yl)-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)indolin-2-one



5a

Isolated as white solid, 85 %, m.p: 202-204 ^{o}C,^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 10.99 (1H, s), 10.38 (1H, s), 7.79 (1H, s), 7.69 (2H, d, *J*= 8.0), 7.49–7.35 (3H, m), 7.28 (2H, d, *J*= 5.0), 7.18 (1H, d, *J*= 6.8), 7.09 (1H, t, *J*= 7.5), 7.01–6.84 (2H, m), 6.67 (1H, s), 1.53 (3H, s) ppm.^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 177.9, 149.2, 141.7, 137.5, 135.8, 129.3, 128.1, 126.5, 125.4, 124.8, 124.0, 122.2, 121.8, 119.0, 118.4, 112.8, 112.1, 111.1, 51.3, 25.5 ppm.EI-HRMS: Anal. Calcd for $C_{26}H_{19}ClN_4O_2$: 454.1197, Found: 454.1195.

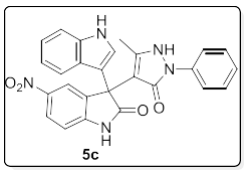
5b:5-Bromo-3-(1*H*-indol-3-yl)-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)indolin-2-one



5b

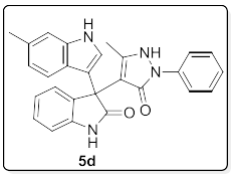
Isolated as white solid, 89 %, m.p: 208-210 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 11.02 (1H, s), 10.44 (1H, s), 7.81–7.66 (3H, m), 7.40 (5H, s), 7.14 (2H, d, *J*= 30.5), 7.01–6.79 (2H, m), 6.68 (1H, s), 1.54 (3 H, s) ppm. ^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 177.9, 148.9, 142.0, 137.6, 137.5, 136.2, 131.0, 129.3, 127.6, 126.5, 124.9, 124.0, 122.2, 121.8, 119.0, 118.8, 113.2, 112.9, 112.2, 111.7, 51.3, 25.6 ppm. EI-HRMS: Anal. Calcd for $C_{26}H_{19}BrN_4O_2$: 498.0691, Found: 498.0690.

5c:3-(1*H*-Indol-3-yl)-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-nitroindolin-2-one



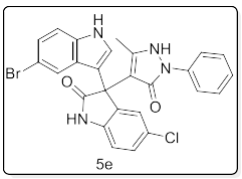
Isolated as white solid, 84 %, m.p: 222-224 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 11.10 (1H, s), 11.02 (1H, s), 8.23 (1H, dd, *J*= 8.6, 2.1), 8.02 (1H, s), 7.81 (1H, d, *J*= 8.0), 7.69 (1H, d, *J*= 7.9), 7.49 (1H, s), 7.41 (3H, s), 7.18 (1H, d, *J*= 7.2), 7.10 (2H, dd, *J*= 18.2, 8.0), 7.00–6.92 (1H, m), 6.79 (1H, d, *J*= 2.1), 1.54 (3H, s) ppm. ^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 178.5, 149.3, 149.0, 142.3, 137.6, 137.4, 134.6, 129.3, 128.5, 126.4, 125.9, 125.0, 124.3, 122.0, 120.9, 120.3, 119.2, 118.8, 112.3, 111.9, 109.8, 51.0, 25.5 ppm. EI-HRMS: Anal. Calcd for $C_{26}H_{19}N_5O_4$: 465.1437, Found: 465.1435.

5d: 3-(6-Methyl-1*H*-indol-3-yl)-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)indolin-2-one



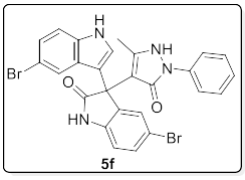
Isolated as white solid, 89 %, m.p: 192-194 ^{o}C,^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 10.94 (1H, d, *J*= 1.8), 10.15 (1H, s), 7.76 (1H, d, *J*= 7.8), 7.70 (2H, d, *J*= 7.8), 7.39 (3H, dd, *J*= 16.9, 8.4), 7.16 (1H, t, *J*= 7.4), 7.1–6.99 (3H, m), 6.92 (1H, t, *J*= 7.6), 6.77 (1H, d, *J*= 7.7), 6.62 (1H, d, *J*= 2.2), 2.27 (s, 3H), 1.53 (3 H, s) ppm.^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 178.3, 148.8, 140.2, 137.8, 137.5, 133.8, 130.2, 129.3, 128.5, 126.7, 125.6, 124.8, 124.1, 122.4, 121.6, 118.8, 113.8, 112.0, 109.4, 51.0, 25.5, 12.3 ppm. EI-HRMS: Anal. Calcd for $C_{27}H_{22}$ N_4O_2: 434.1743, Found: 434.1740.

5e: 3-(5-Bromo-1*H*-indol-3-yl)-5-chloro-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)indolin-2-one



Isolated as white solid, 91 %, m.p: 210-211 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 11.00 (1H, s), 10.30 (1H, s), 7.75 (1H, d, *J*= 7.5), 7.70 (2H, d, *J*= 7.9), 7.40 (3H, dd, *J*= 14.7, 7.7), 7.20–7.11 (2H, m), 7.11–7.04 (1H, m), 6.94 (1H, t, *J*= 7.5), 6.86 (1H, dd, *J*= 8.4, 4.4), 6.69 (1H, d, *J*= 1.9), 1.54 (3 H, s) ppm. ^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 178.3, 159.3, 157.0, 138.8, 137.7, 137.5, 135.5, 135.5, 129.3, 126.5, 124.9, 124.0, 122.2, 121.7, 118.9, 118.8, 114.5, 114.3, 113.1, 112.8, 112.6, 112.1, 110.3, 110.3, 51.5, 25.5 ppm. EI-HRMS: Anal. Calcd for $C_{26}H_{18}$ Br Cl N_4O_2: 532.0302, Found: 532.0301.

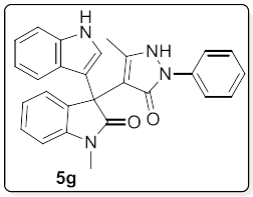
5f: 5-Bromo-3-(5-bromo-1*H*-indol-3-yl)-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)indolin-2-one



Isolated as white solid, 87 %, m.p: 218-220 ^{o}C,^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 11.24 (1H, s), 10.47 (1H, s), 7.95 (1H, s), 7.69 (2H, d, *J*= 5.8), 7.40 (5H, d, *J*= 9.5), 7.20 (2H, s), 6.86 (1H, s), 6.73 (1H, s), 1.52 (3

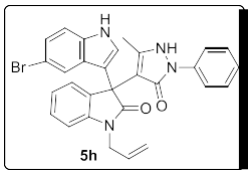
H, s) ppm.^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 177.8, 148.7, 142.0, 137.5, 136.3, 135.7, 131.3, 129.3, 128.5, 128.2, 127.6, 125.9, 125.8, 125.0, 124.4, 124.2, 118.8, 114.3, 113.3, 112.5, 111.8, 111.7, 105.7, 51.1, 25.5 ppm.EI-HRMS: Anal. Calcd for $C_{26}H_{18}Br_2N_4O_2$: 575.9797, Found: 575.9795.

5g: 3-(1H-indol-3-yl)-1-methyl-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)indolin-2-one



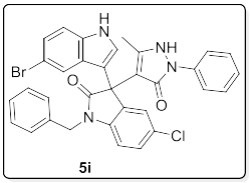
Isolated as white solid, 92 %, m.p: 212-214 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 11.22 (1H, s), 8.02 (1H, s), 7.67 (2H, d, *J*= 7.9), 7.43–7.28 (5H, m), 7.25–7.00 (5H, m), 6.67 (1H, d, *J*= 2.4), 3.0 (3H, s), 1.51 (3 H, s).^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 176.5, 148.5, 144.1, 138.2, 137.5, 136.3, 132.3, 129.4, 129.3, 128.6, 128.5, 128.3, 125.9, 125.8, 124.9, 124.7, 124.4, 124.4, 122.3, 118.8, 114.2, 112.8, 111.6, 108.8, 106.5, 50.3, 26.6, 21.2 ppm. EI-HRMS: Anal. Calcd for $C_{27}H_{22}N_4O_2$: 434.1743, Found: 434.1740.

5h:1-Allyl-3-(5-bromo-1*H*-indol-3-yl)-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)indolin-2-one



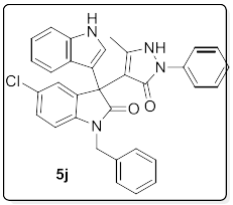
Isolated as white solid, 91 %, m.p: 200-202 ^{o}C,^{1}H NMR (400 Mhz, DMSO-d_6) : δ_H 11.22 (1H, d, *J*= 1.7), 8.03 (1H, s), 7.68 (2H, d, *J*= 7.9), 7.39 (3H, dd, *J*= 15.7, 8.1), 7.30 (2H, dd, *J*= 11.7, 7.5), 7.22 (1H, dd, *J*= 8.6, 1.8), 7.16 (1H, t, *J*= 7.4), 7.08 (1H, d, *J*= 7.5), 6.95 (1H, d, *J*= 7.8), 6.68 (1H, d, *J*= 2.4), 5.82 (1H, dd, *J*= 11.2, 6.0), 5.16 (2H, dd, *J*= 13.8, 11.4), 4.35–4.22 (2H, m), 4.27–4.21 (1H, s), 1.52 (3 H, s) ppm. ^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 176.2, 148.6, 143.1, 137.5, 136.3, 132.6, 132.4, 129.3, 128.6, 128.5, 128.3, 125.9, 125.7, 125.0, 124.8, 124.4, 124.4, 122.3, 118.9, 117.2, 114.3, 113.1, 111.7, 109.5, 106.4, 50.4, 42.1, 21.2 ppm. EI-HRMS: Anal. Calcd for $C_{29}H_{23}BrN_4O_2$: 538.1004, Found: 538.1003.

5i: **1-Benzyl-3-(5-bromo-1*H*-indol-3-yl)-5-chloro-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)indolin-2-one**



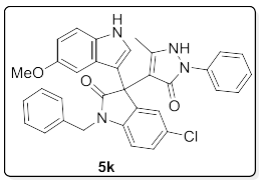
Isolated as white solid, 93 %, m.p: 182-184 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 11.30 (1H, s), 8.03 (1H, s), 7.72 (2H, d, *J*= 7.9), 7.53–7.35 (6H, m), 7.24 (6H, dd, *J*= 15.3, 11.8), 6.83 (1H, d, *J*= 8.4), 6.76 (1H, d, *J*= 2.1), 4.88 (2H, dd, *J*= 28.1, 16.1), 1.50 (3H, s) ppm. ^{13}C NMR (100 Mhz, DMSO-d_6): δ_C176.2, 148.8, 142.0, 137.4, 136.6, 136.4, 134.4, 129.4, 128.9, 128.5, 128.4, 128.2, 127.6, 127.5, 126.6, 125.9, 125.1, 124.9, 124.5, 124.3, 119.0, 114.4, 112.2, 111.8, 110.9, 105.4, 50.7, 43.5, 25.3 ppm. EI-HRMS: Anal. Calcd for $C_{33}H_{24}BrClN_4O_2$: 622.0771, Found: 622.0770.

5j:1-Benzyl-5-chloro-3-(1*H*-indol-3-yl)-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)indolin-2-one



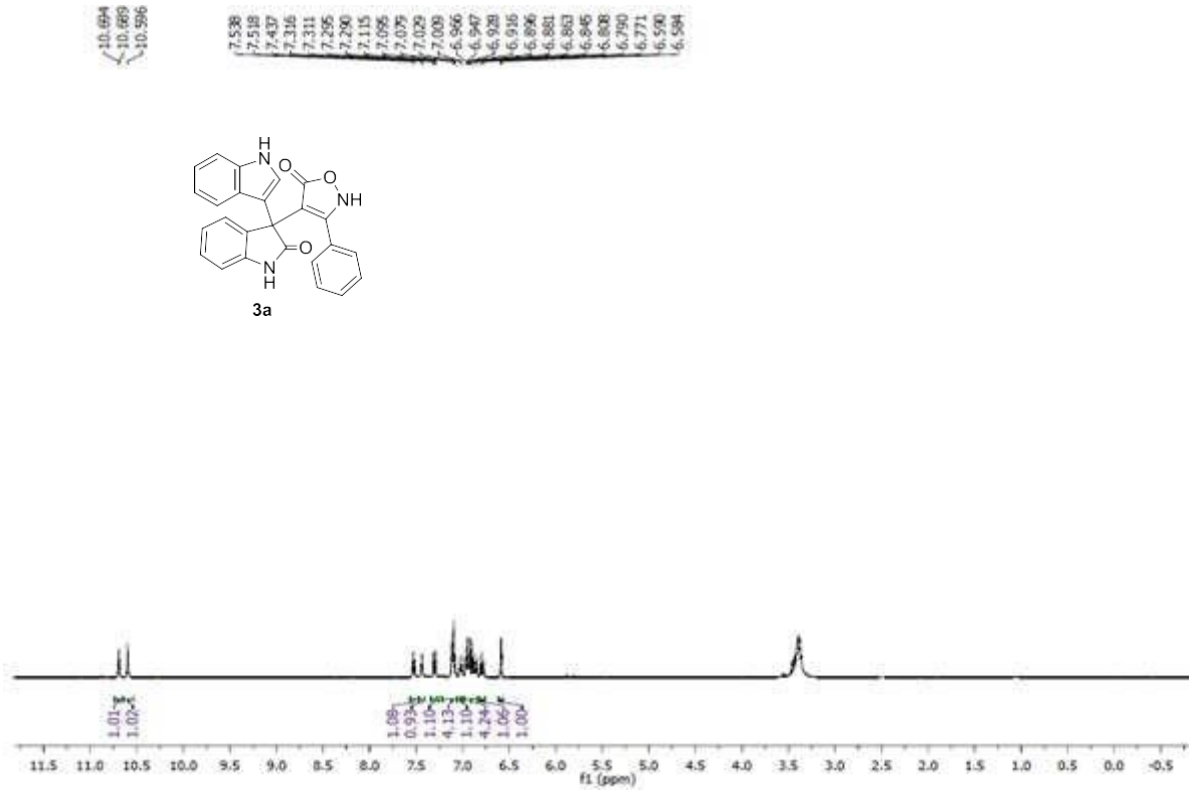
Isolated as white solid, 92 %, m.p: 180-182 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 11.06 (1H, s), 7.81 (1H, d, *J*= 8.0), 7.71 (1H, d, *J*= 7.9), 7.50 (1H, d, *J*= 8.0), 7.44–7.38 (3H, m), 7.35 (2H, d, *J*= 5.5), 7.28–7.18 (5H, m), 7.15–07.07 (2H, m), 6.96 (1H, t, *J*= 7.5), 6.81 (1H, d, *J* = 8.4), 6.68 (1H, d, *J*= 2.3), 4.46 (2H, s), 3.60 (1 H, t, *J*= 6.4), 1.52 (3 H, s) ppm. ^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 176.3, 149.1, 145.9, 142.0, 138.2, 137.6, 137.5, 136.7, 134.9, 129.3, 128.8, 128.5, 128.2, 127.6, 127.5, 126.5, 126.4, 125.9, 125.0, 124.8, 124.1, 122.1, 121.9, 119.1, 119.0, 112.6, 112.3, 110.8, 105.5, 50.9, 43.4, 21.0 ppm. EI-HRMS: Anal. Calcd for $C_{33}H_{25}ClN_4O_2$: 544.1666, Found: 544.1663.

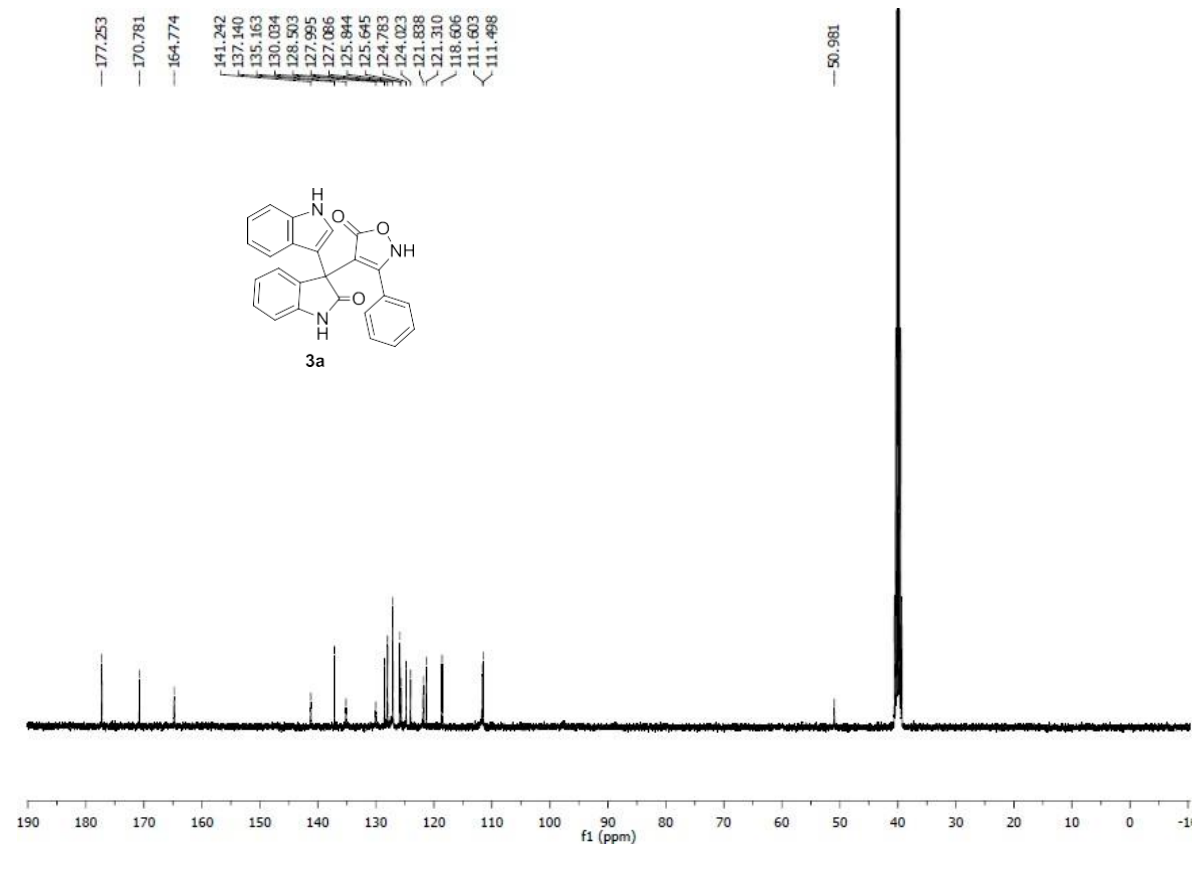
5k:1-Benzyl-5-chloro-3-(5-methoxy-1*H*-indol-3-yl)-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)indolin-2-one



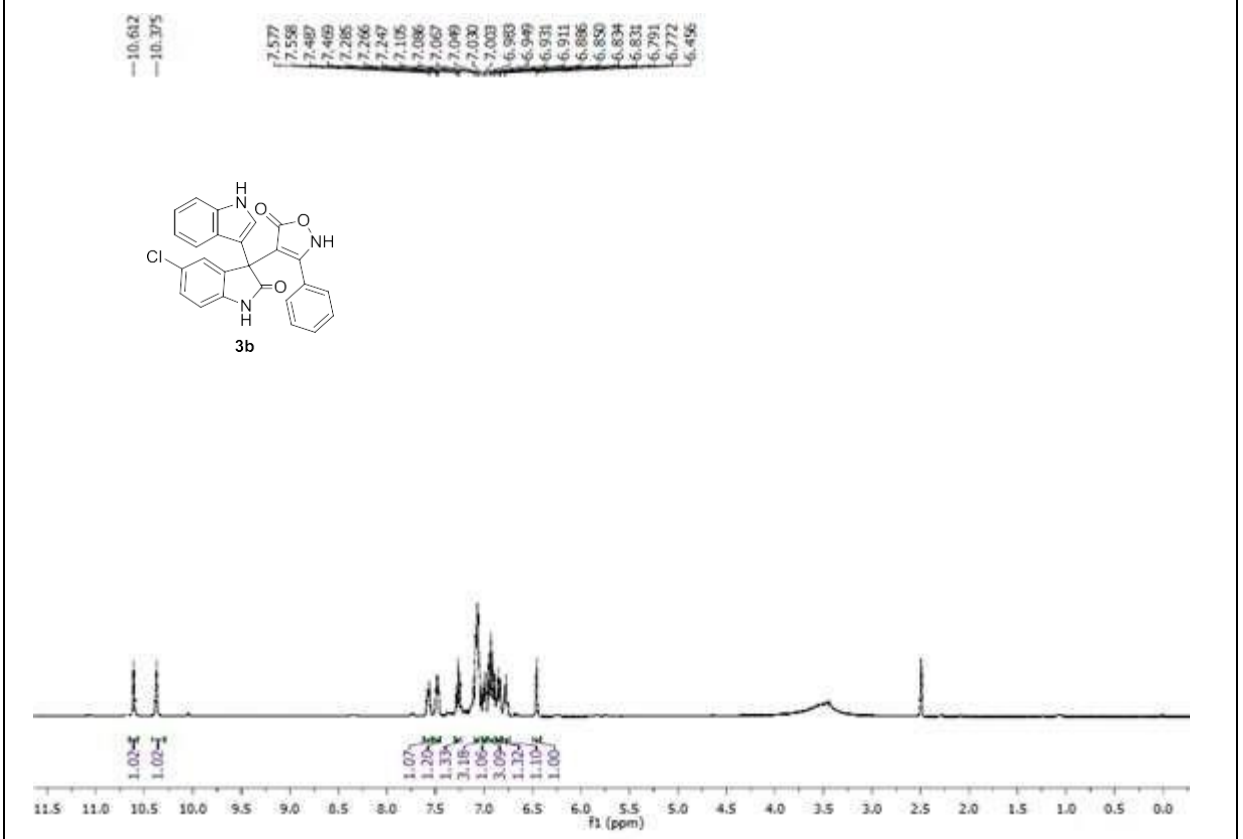
Isolated as white solid, 88%, m.p: 232-234 ^{o}C, ^{1}H NMR (400 Mhz, DMSO-d_6): δ_H 10.93 (1H, s), 7.71 (1H, d, *J*= 7.9), 7.50 (1H, d, *J*= 8.0), 7.43 (2H, t, *J*= 8.0), 7.36 (3H, d, *J*= 2.2), 7.25 (H, dd, *J*= 24.1, 16.3), 7.13 (1H, d, *J*= 7.9), 6.83–6.74 (2H, m), 6.67 (1H, d, *J*= 2.3), 4.20 (2H, s), 3.81 (3H, s), 1.57 (3 H, s) ppm. ^{13}C NMR (100 Mhz, DMSO-d_6): δ_C 176.4, 153.3, 149.2, 142.0, 138.2, 137.5, 136.7, 134.9, 132.8, 129.4, 128.8, 128.6, 128.2, 127.5, 126.9, 126.4, 125.9, 125.1, 124.9, 124.8, 119.0, 112.8, 111.9, 111.7, 110.8, 105.3, 104.3, 55.7, 50.9, 43.4, 21.2 ppm. EI-HRMS: Anal. Calcd for $C_{34}H_{27}ClN_4O_3$: 574.1772, Found: 574.1771.

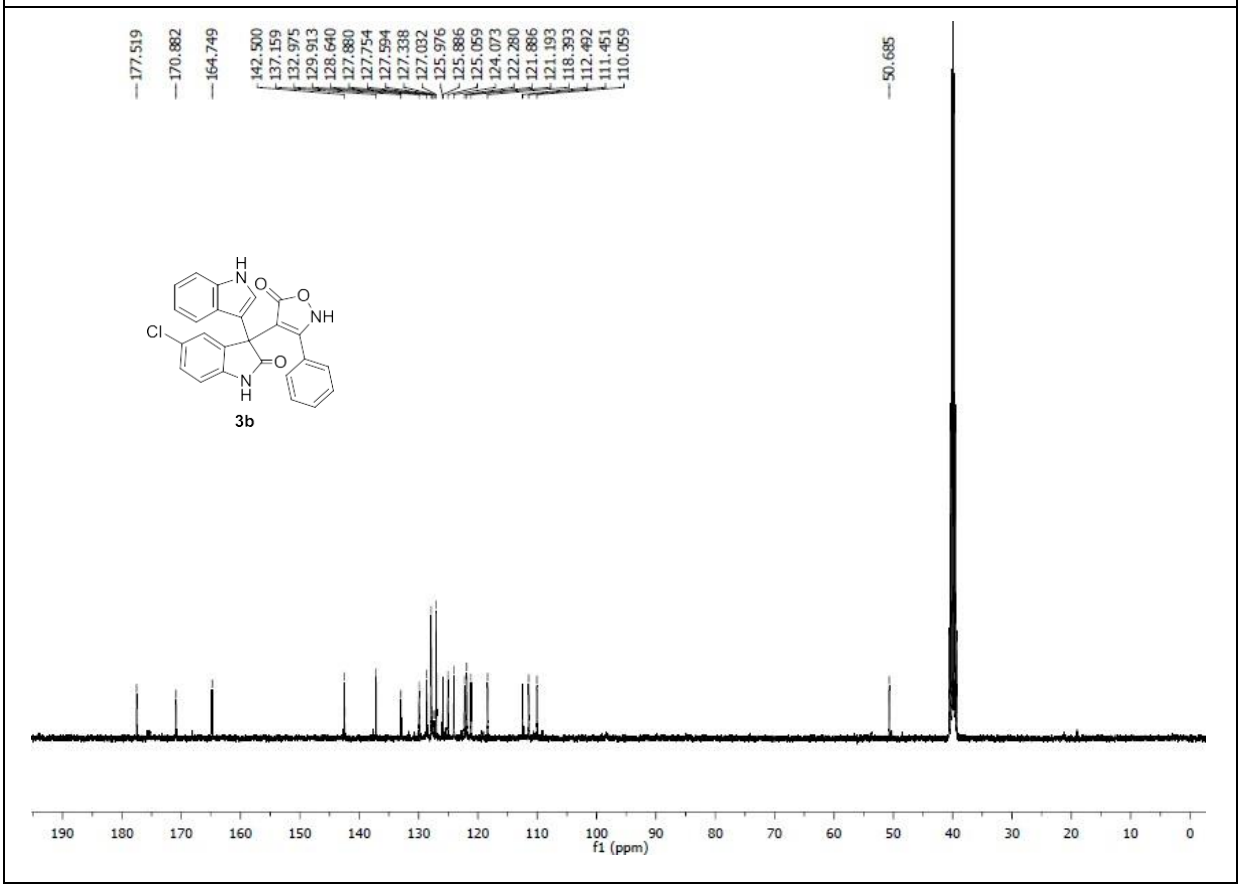
^{1}H and ^{13}C NMR Spectra of Compound (3a)



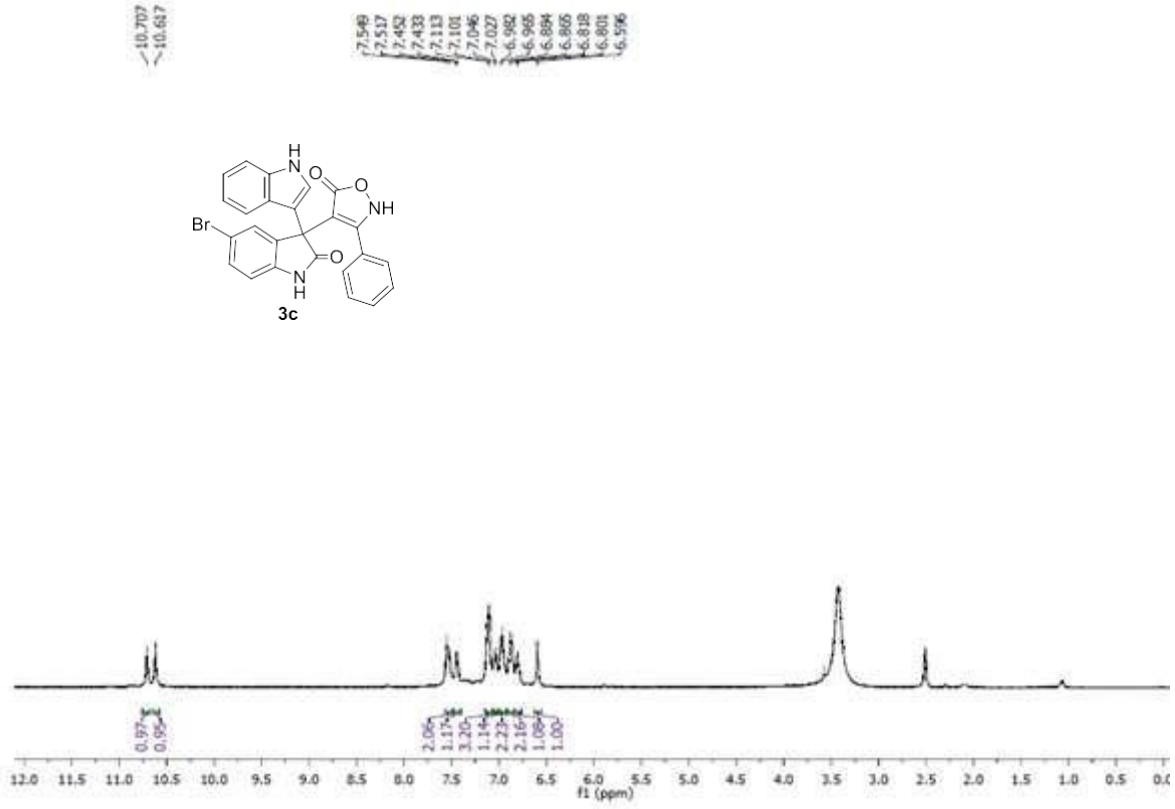


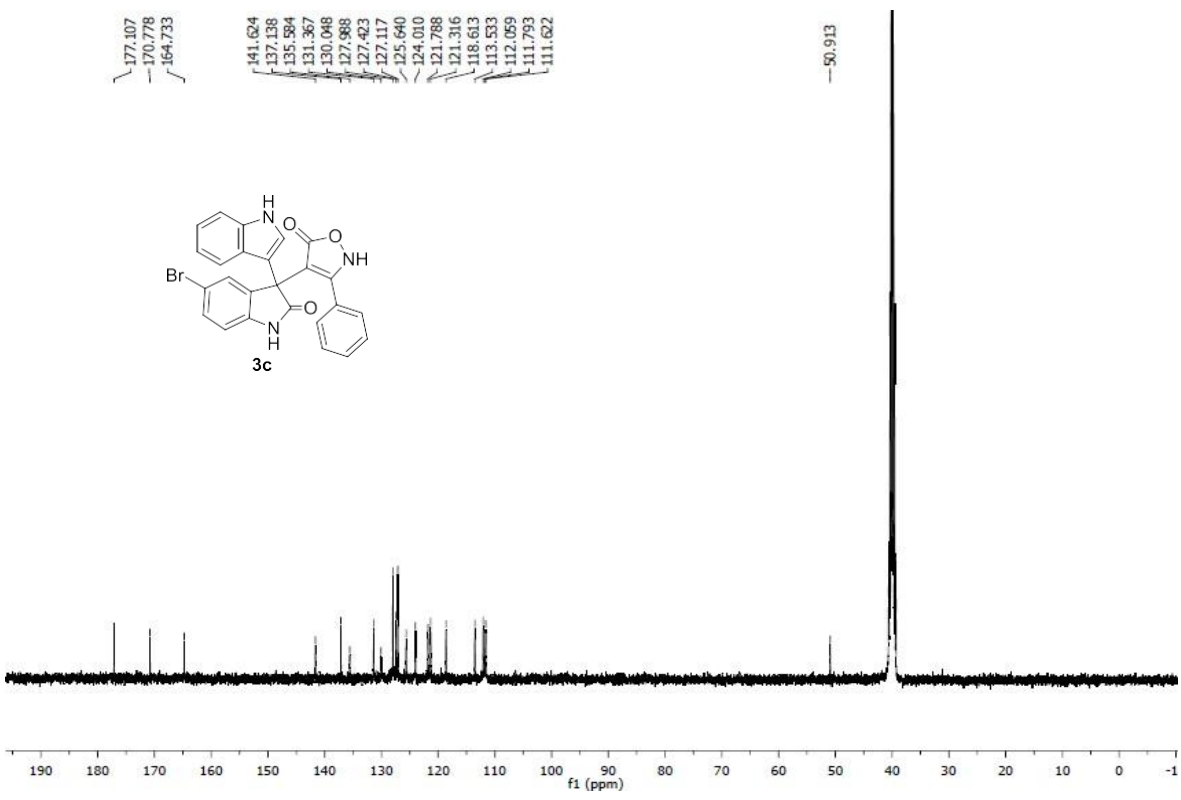
^{1}H and ^{13}C NMR Spectra of Compound (3b)



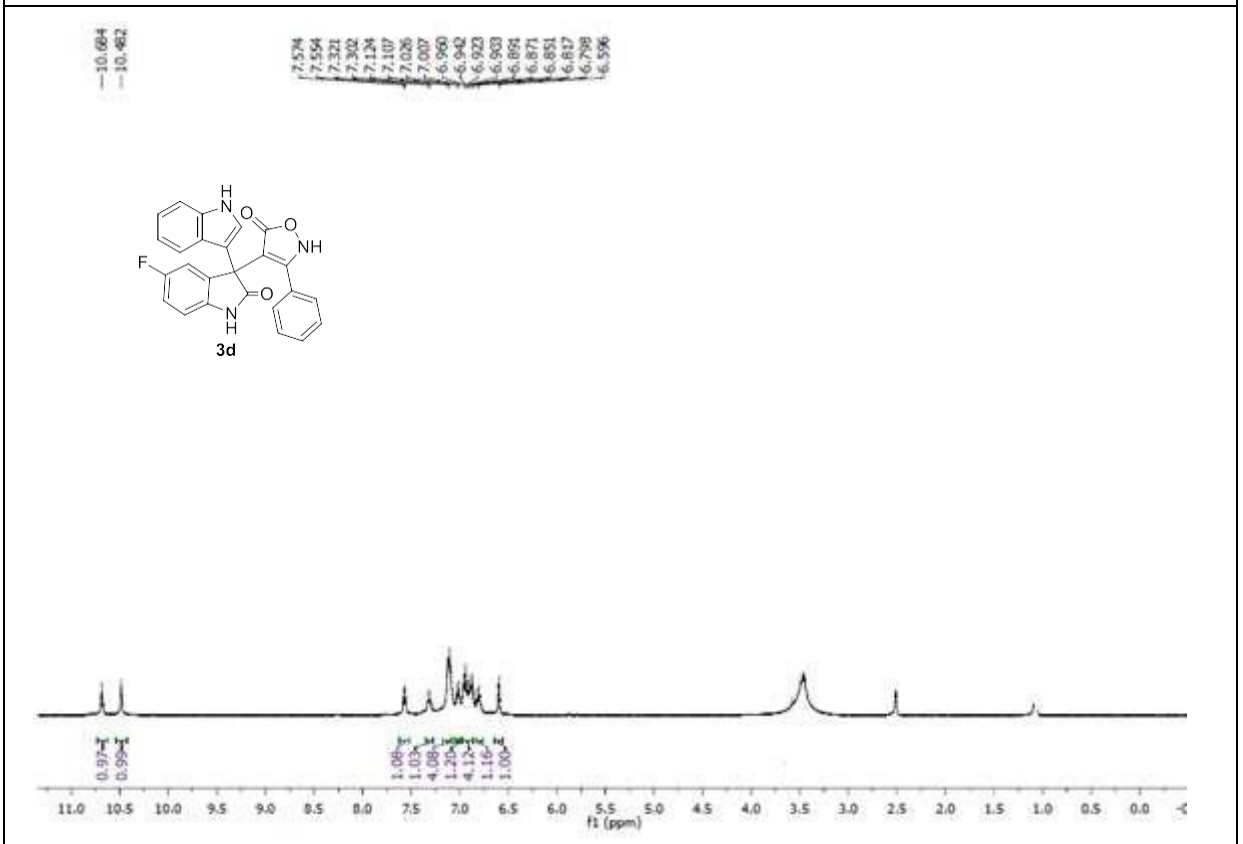


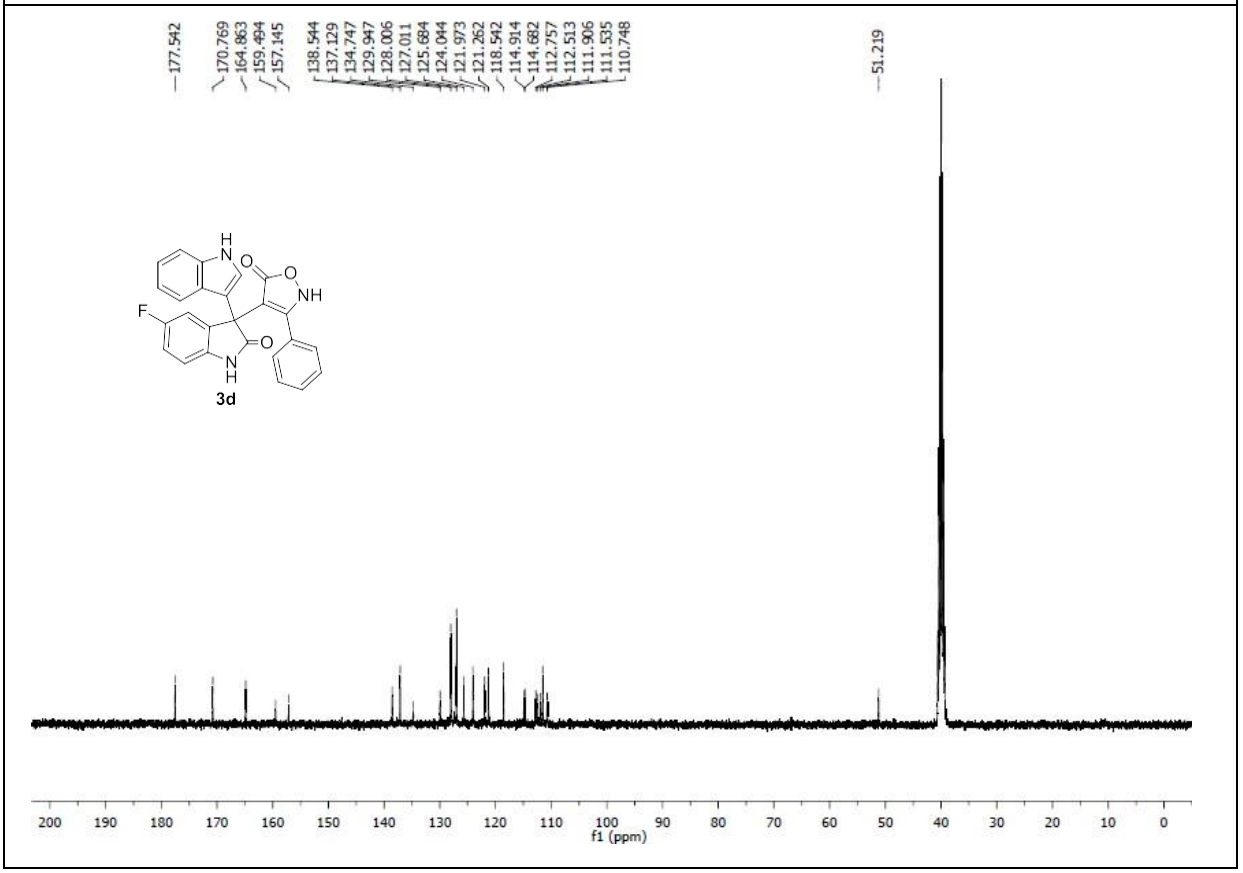
^{1}H and ^{13}C NMR Spectra of Compound (3c)



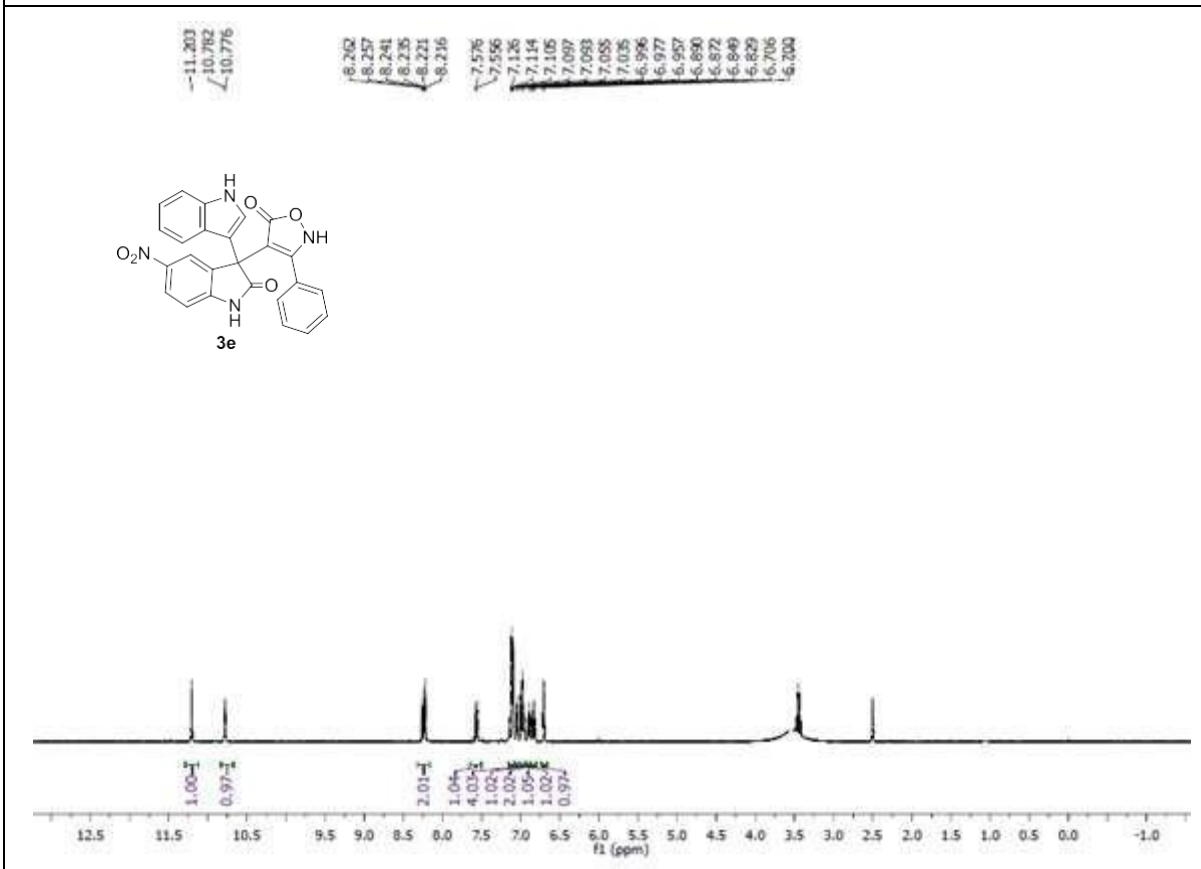


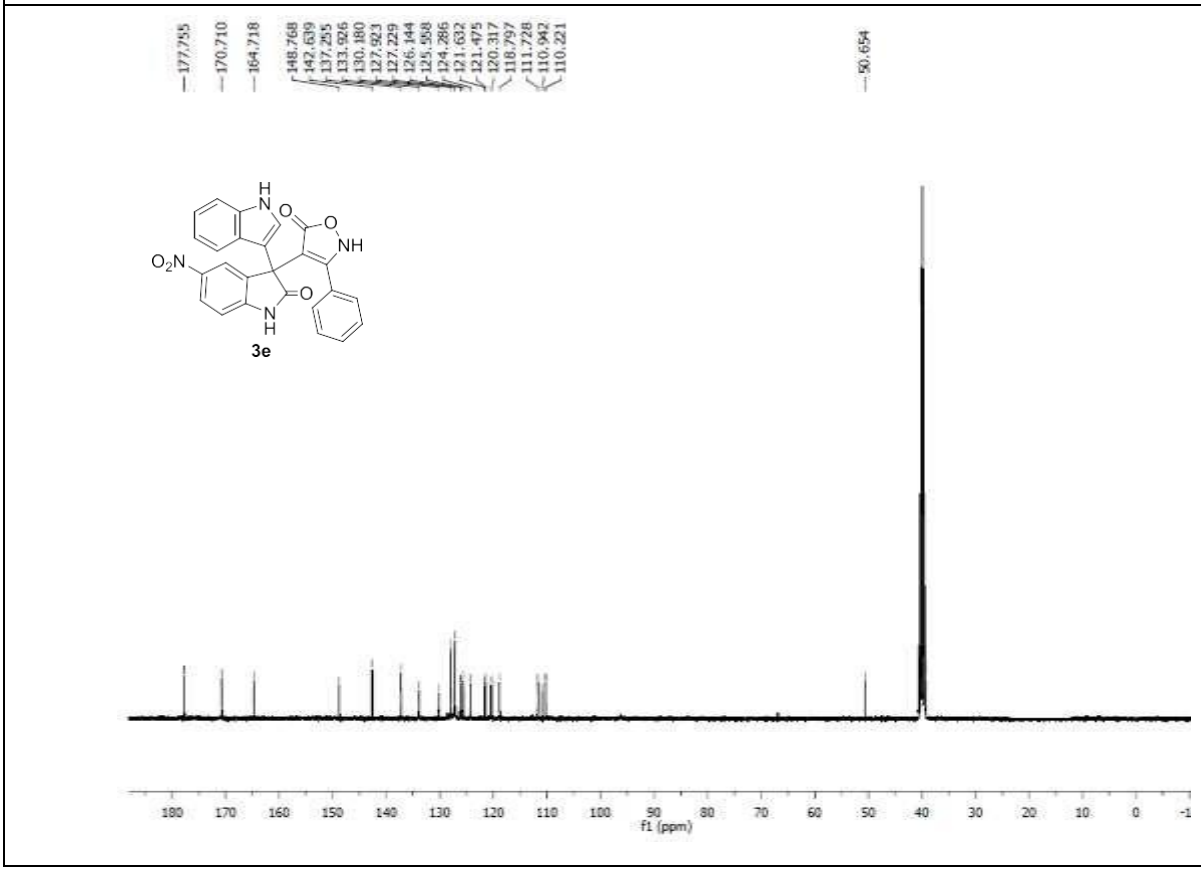
^{1}H and ^{13}C NMR Spectra of Compound (3d)



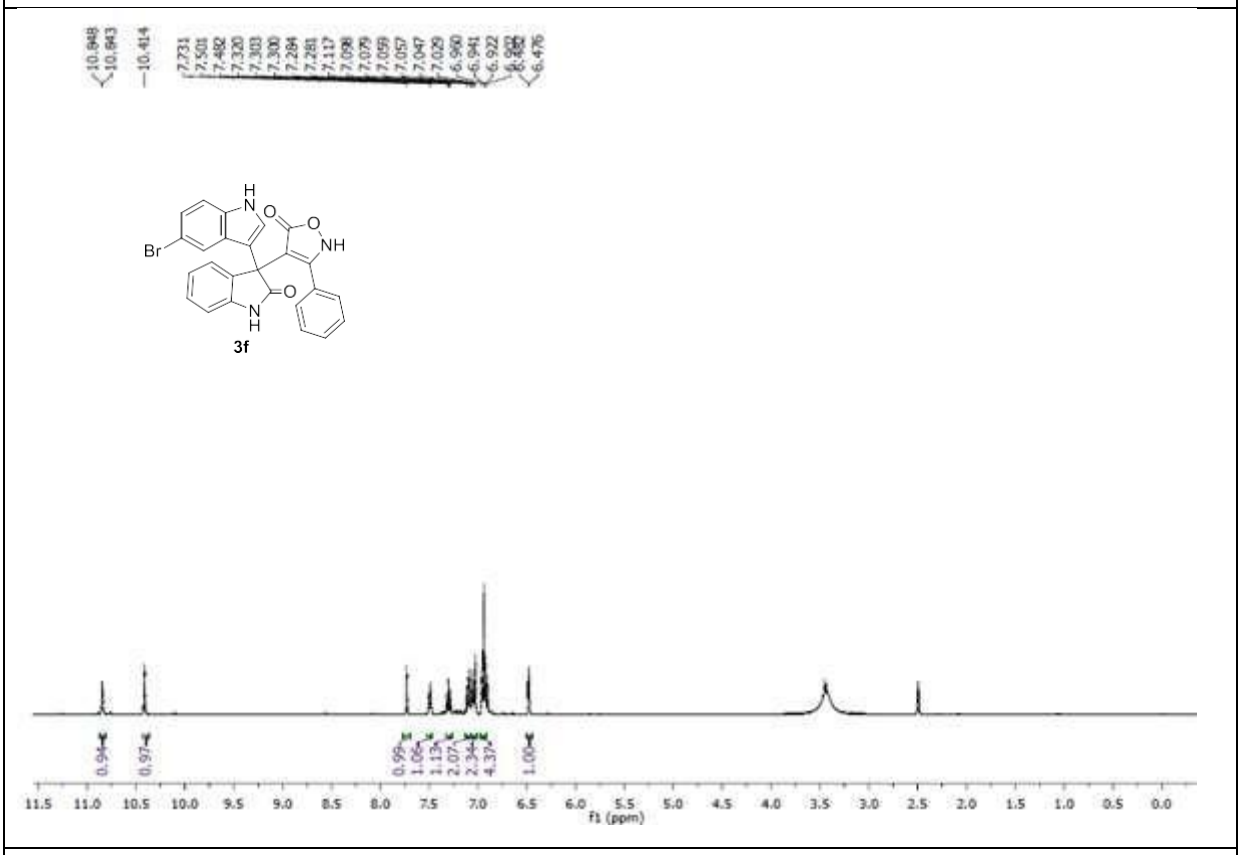


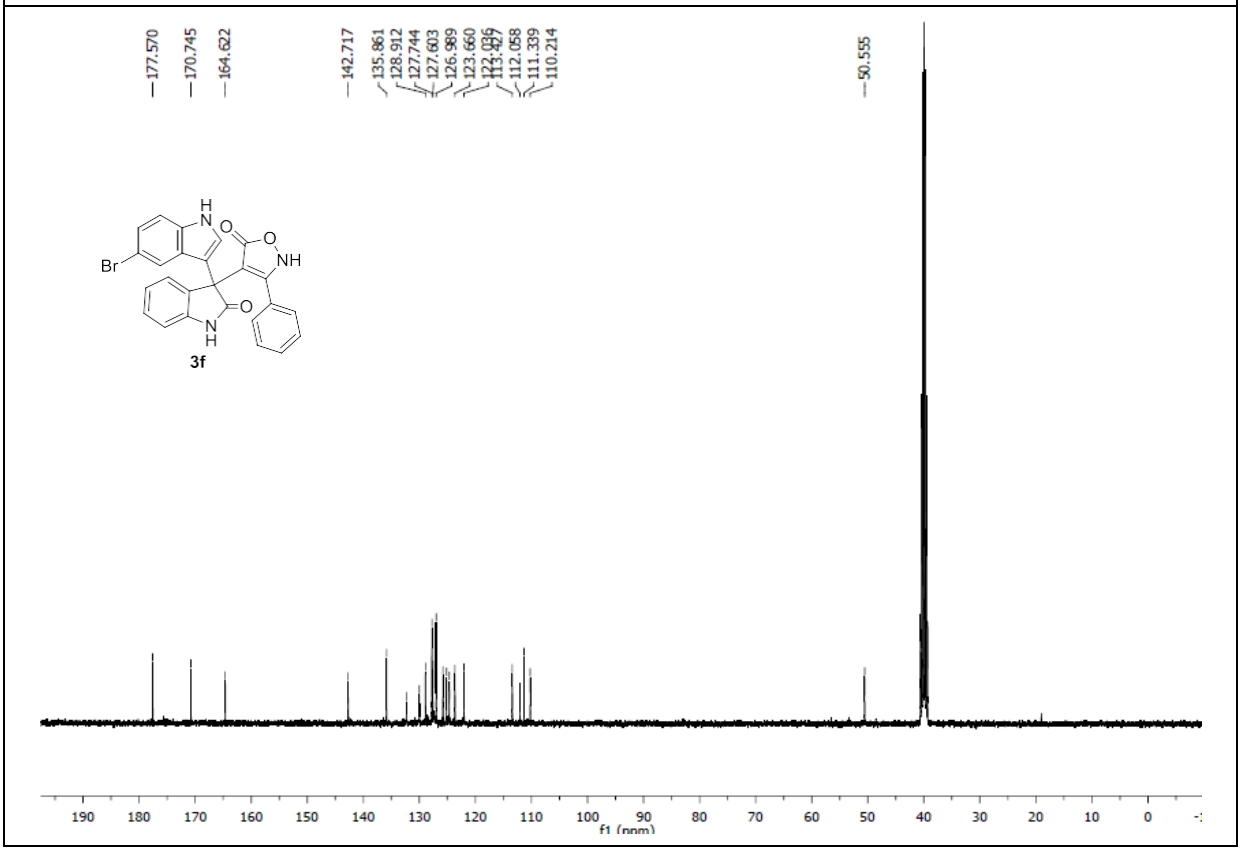
^{1}H and ^{13}C NMR Spectra of Compound (3e)



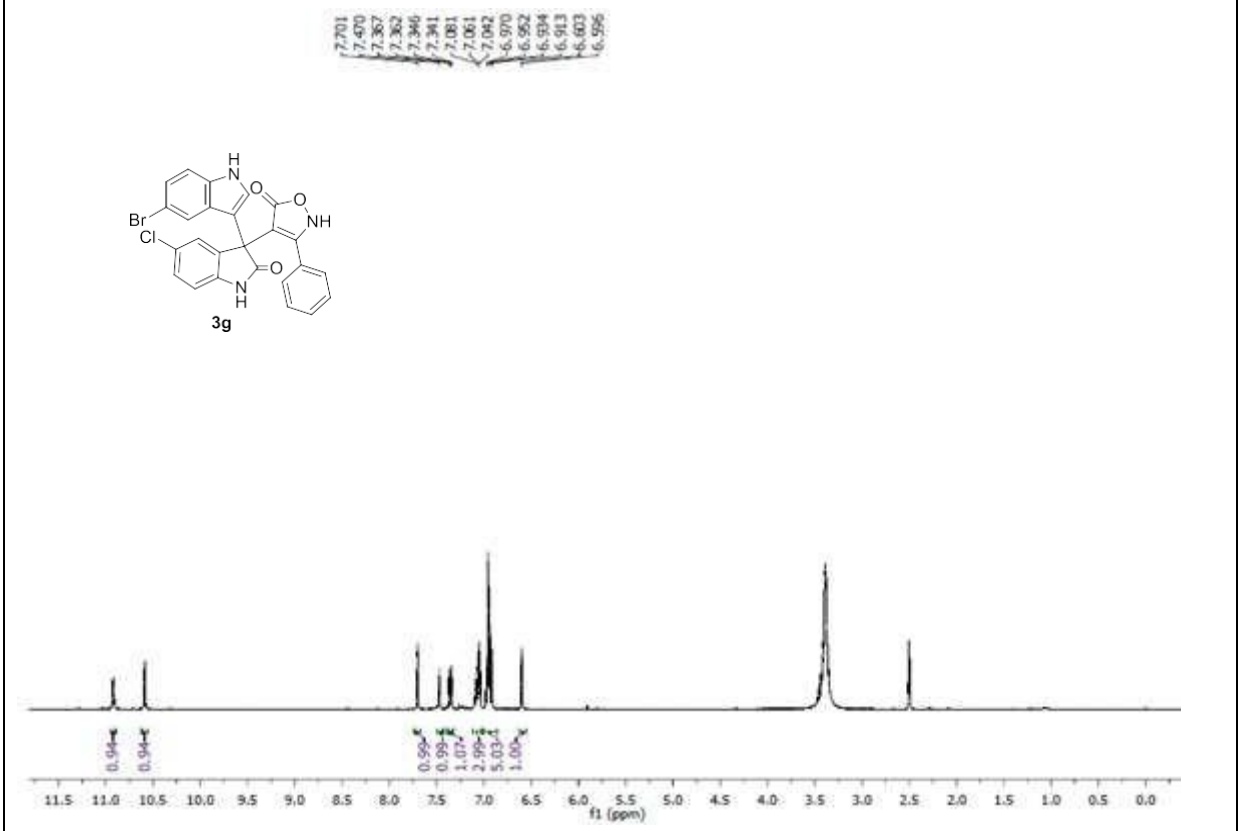


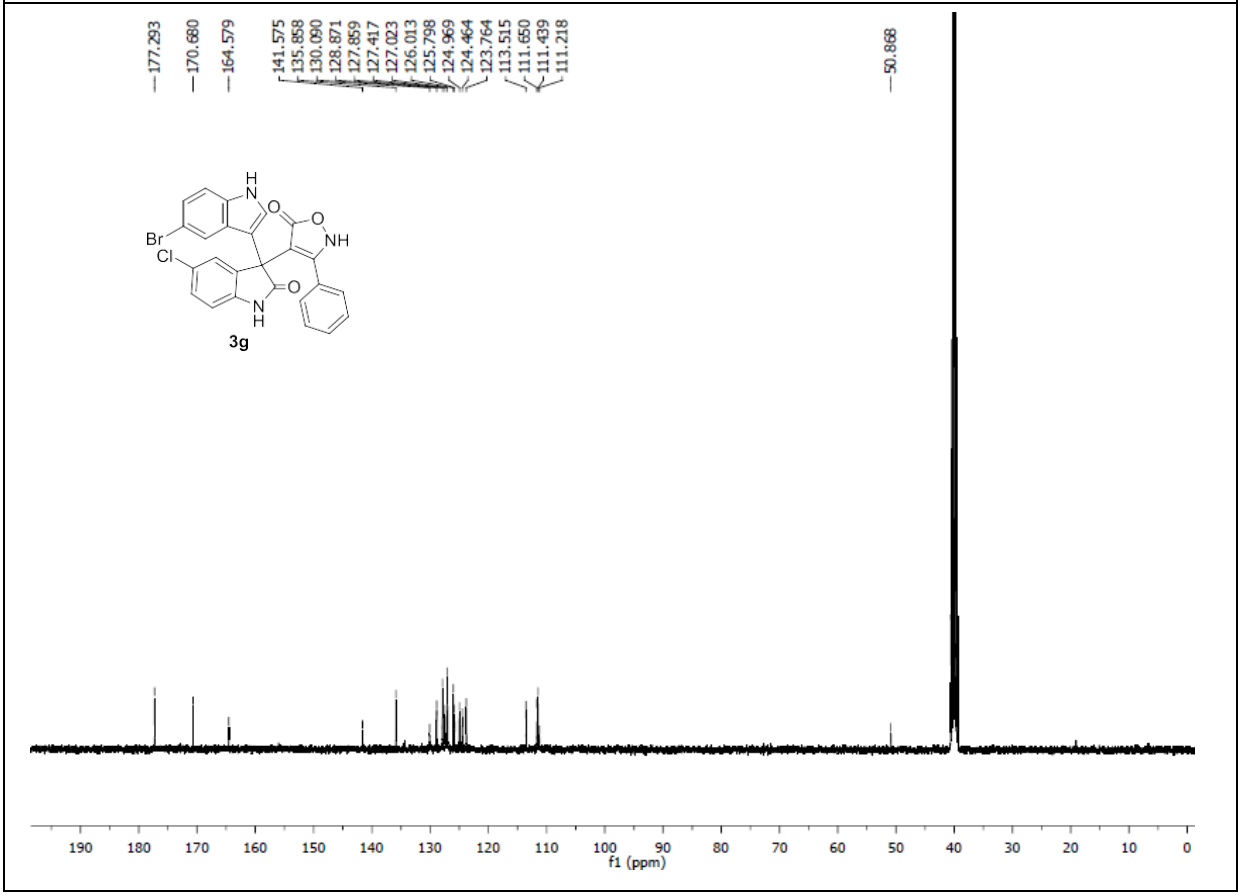
^{1}H and ^{13}C NMR Spectra of Compound (3f)



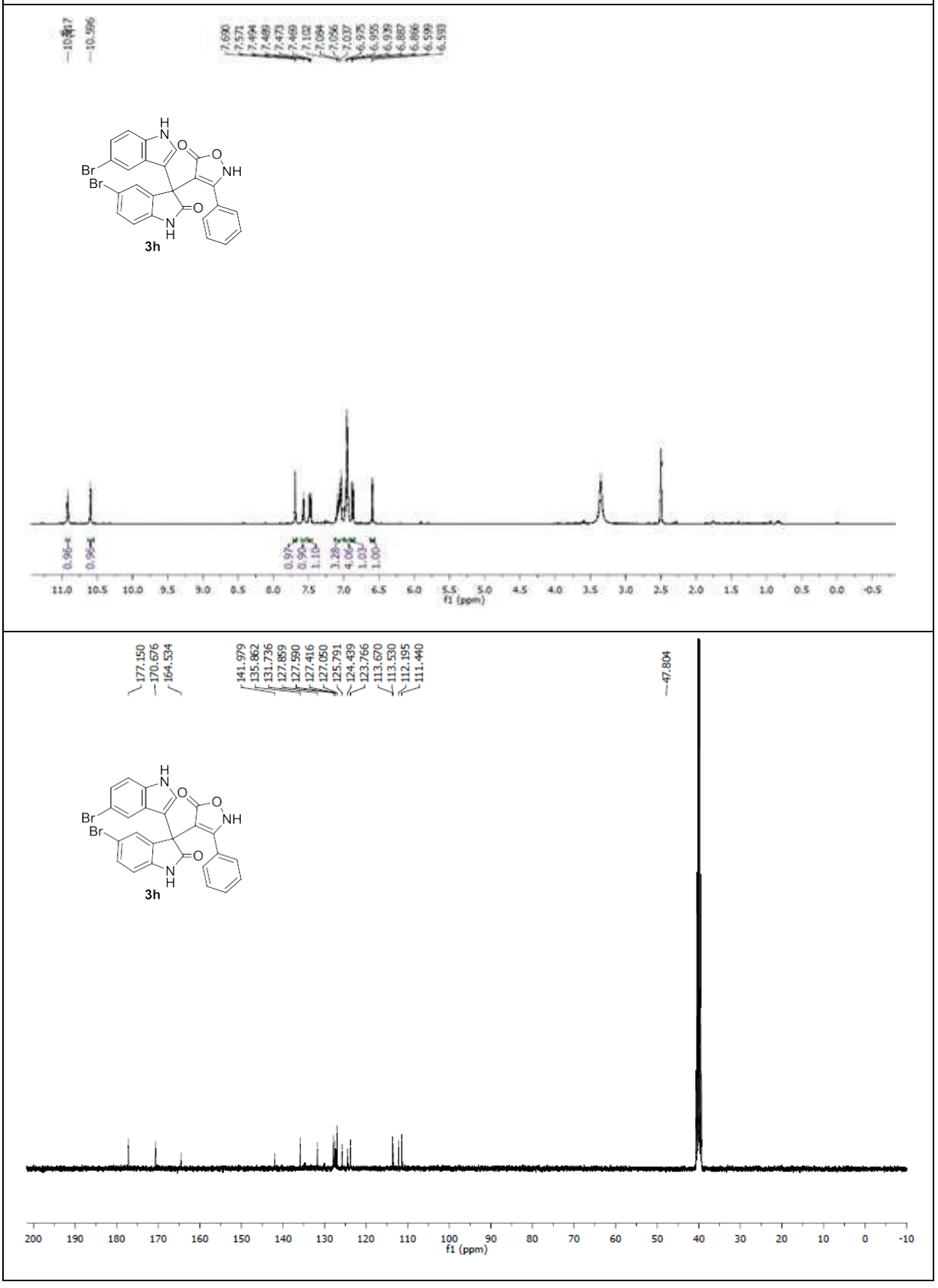


^{1}H and ^{13}C NMR Spectra of Compound (3g)

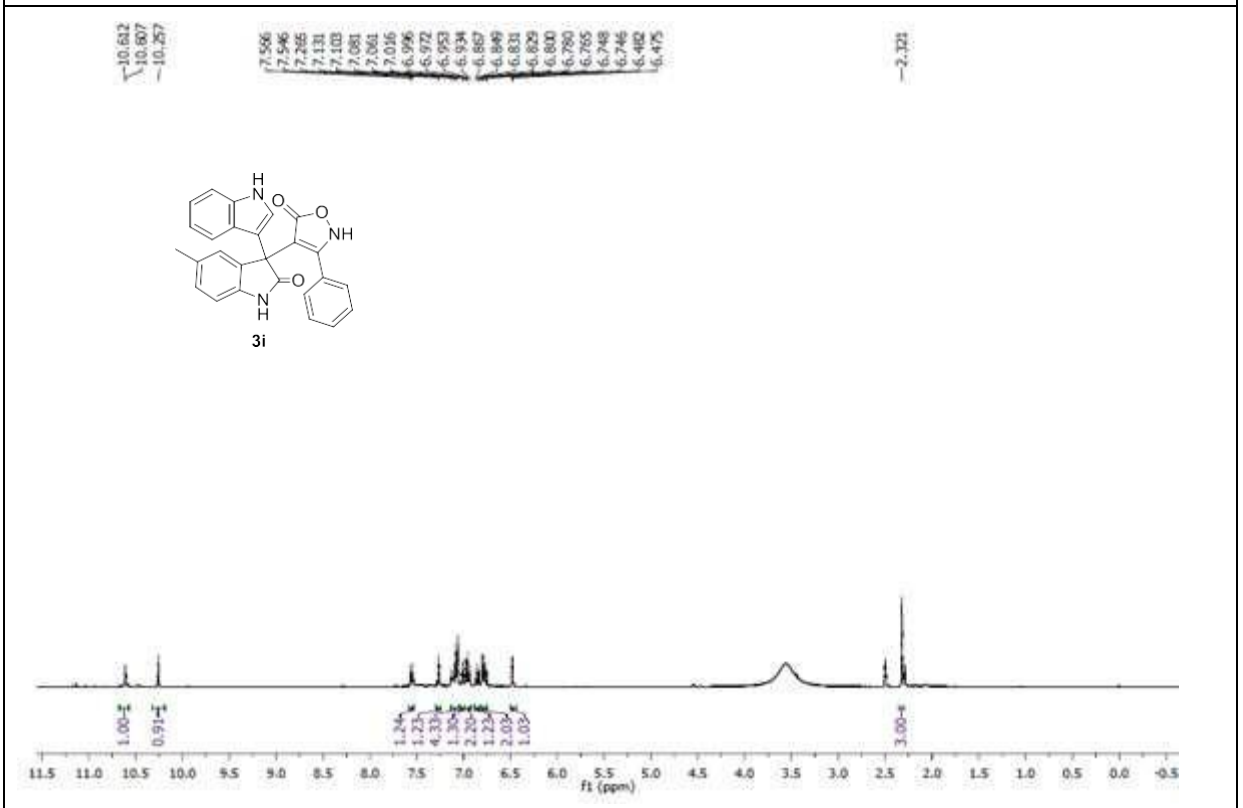


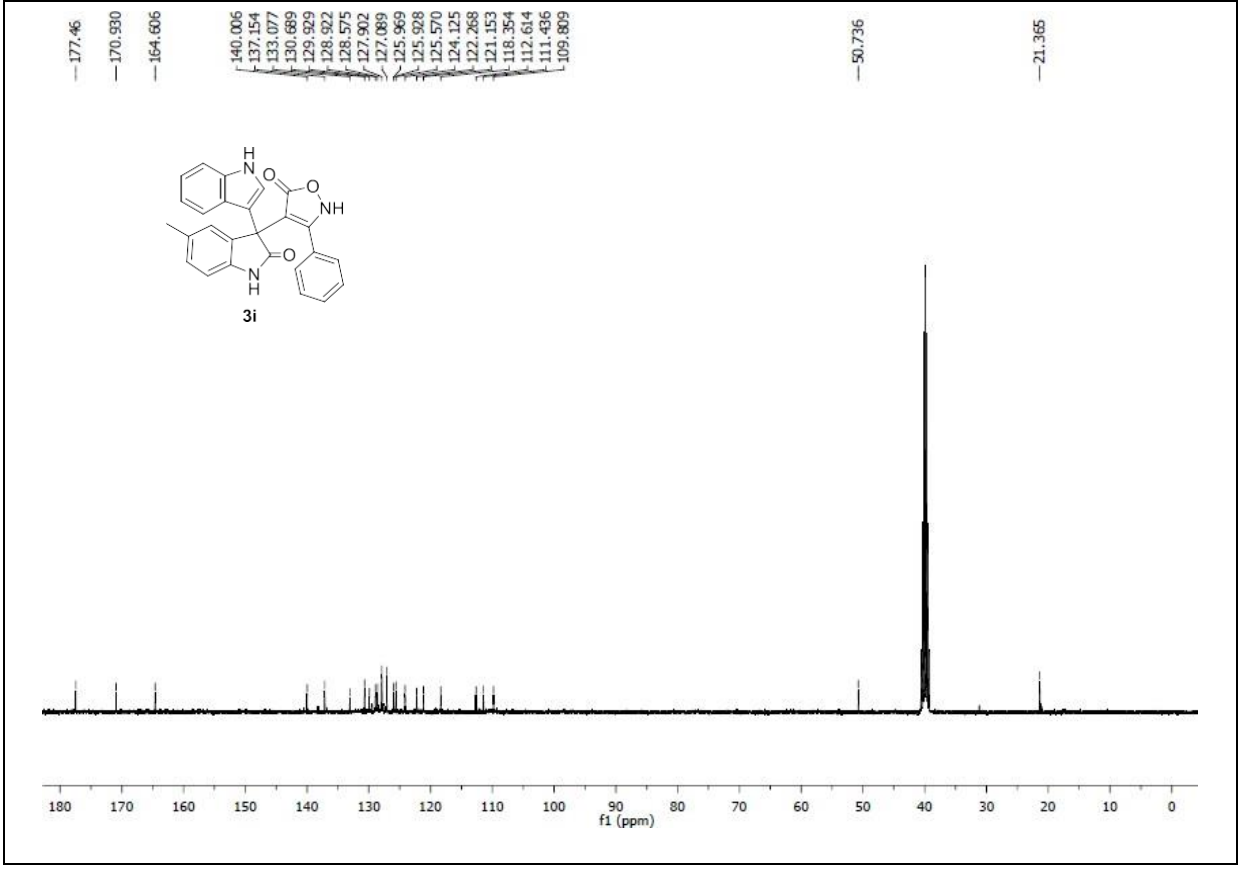


^{1}H and ^{13}C NMR Spectra of Compound (3h)

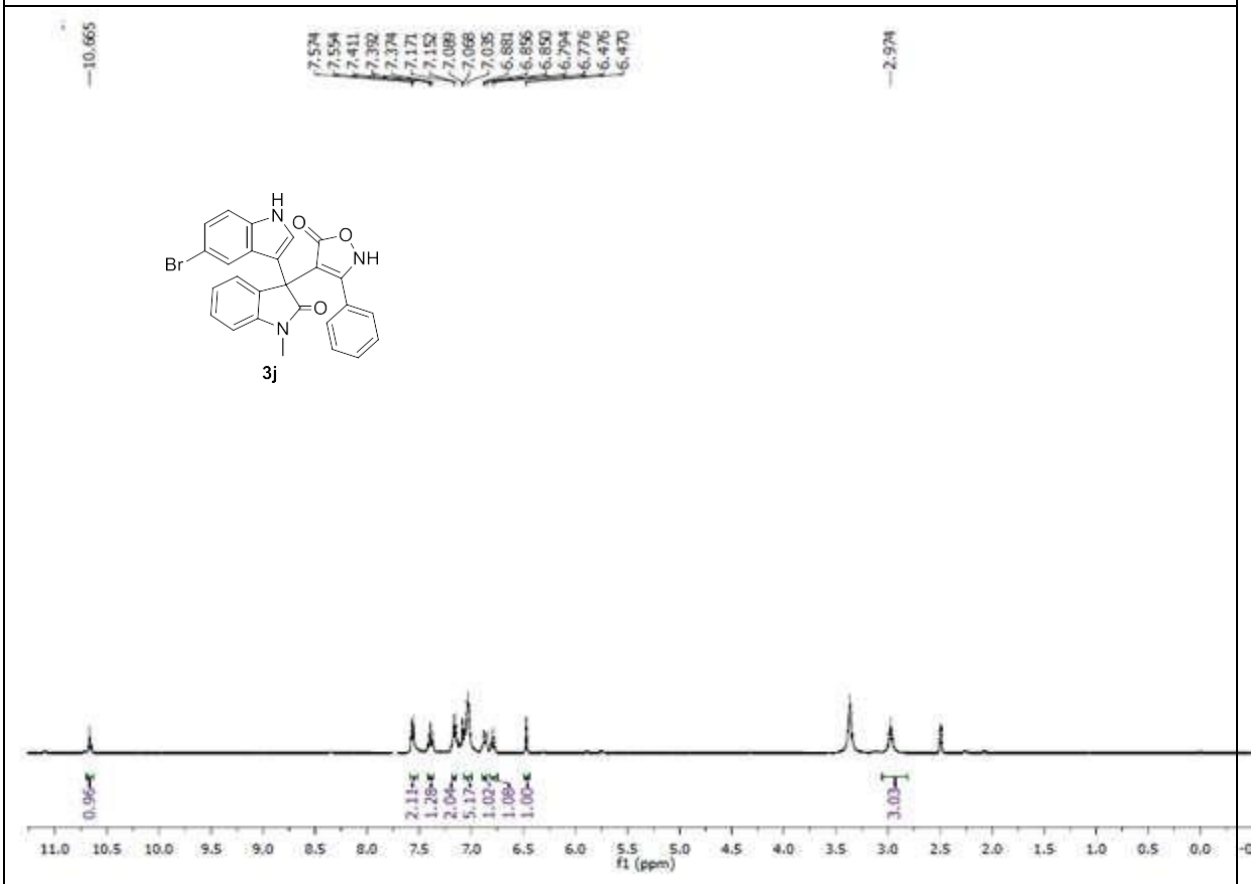


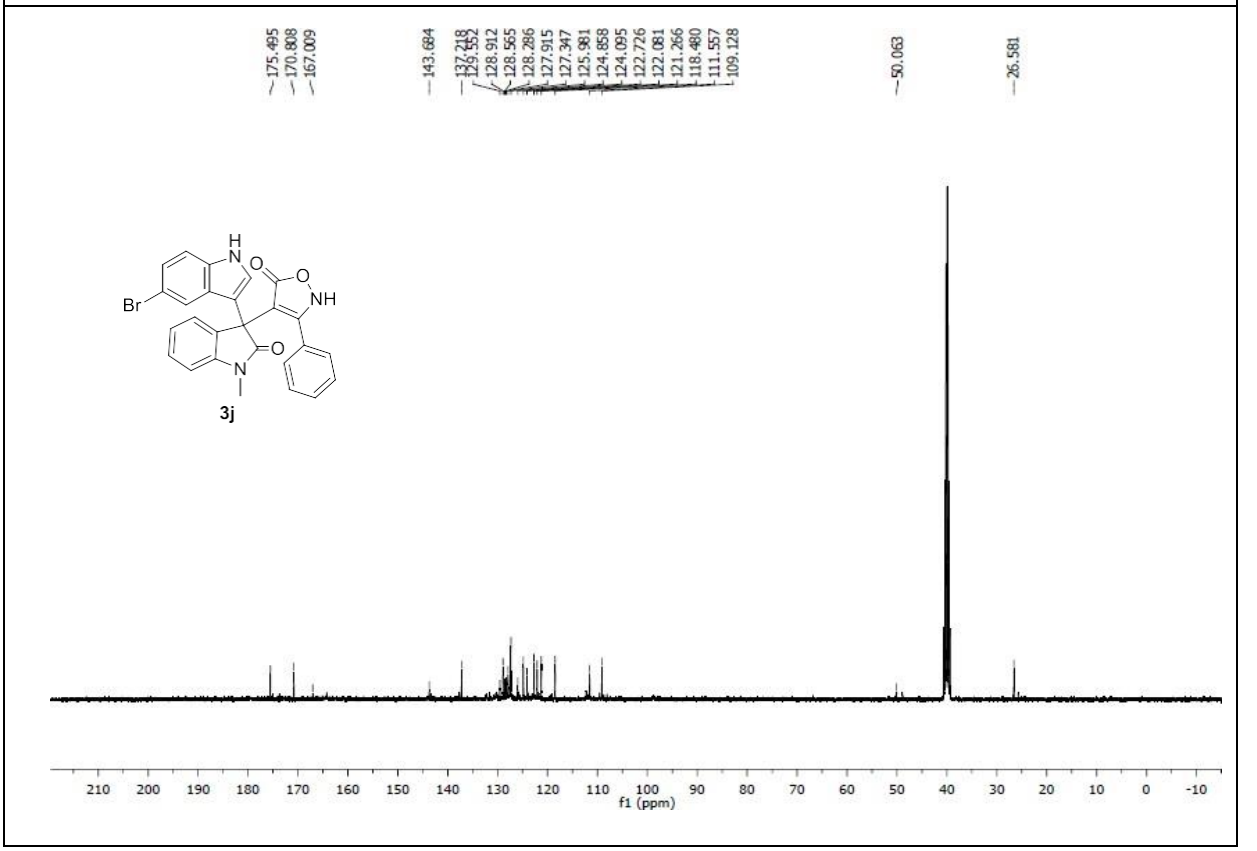
^{1}H and ^{13}C NMR Spectra of Compound (3i)



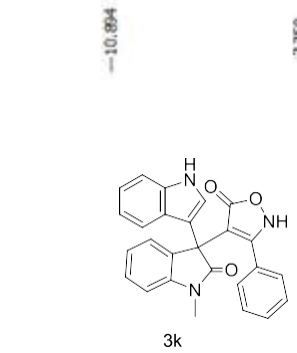


^{1}H and ^{13}C NMR Spectra of Compound (3j)

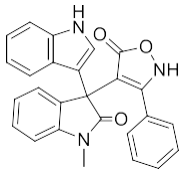




^{1}H and ^{13}C NMR Spectra of Compound (3k)

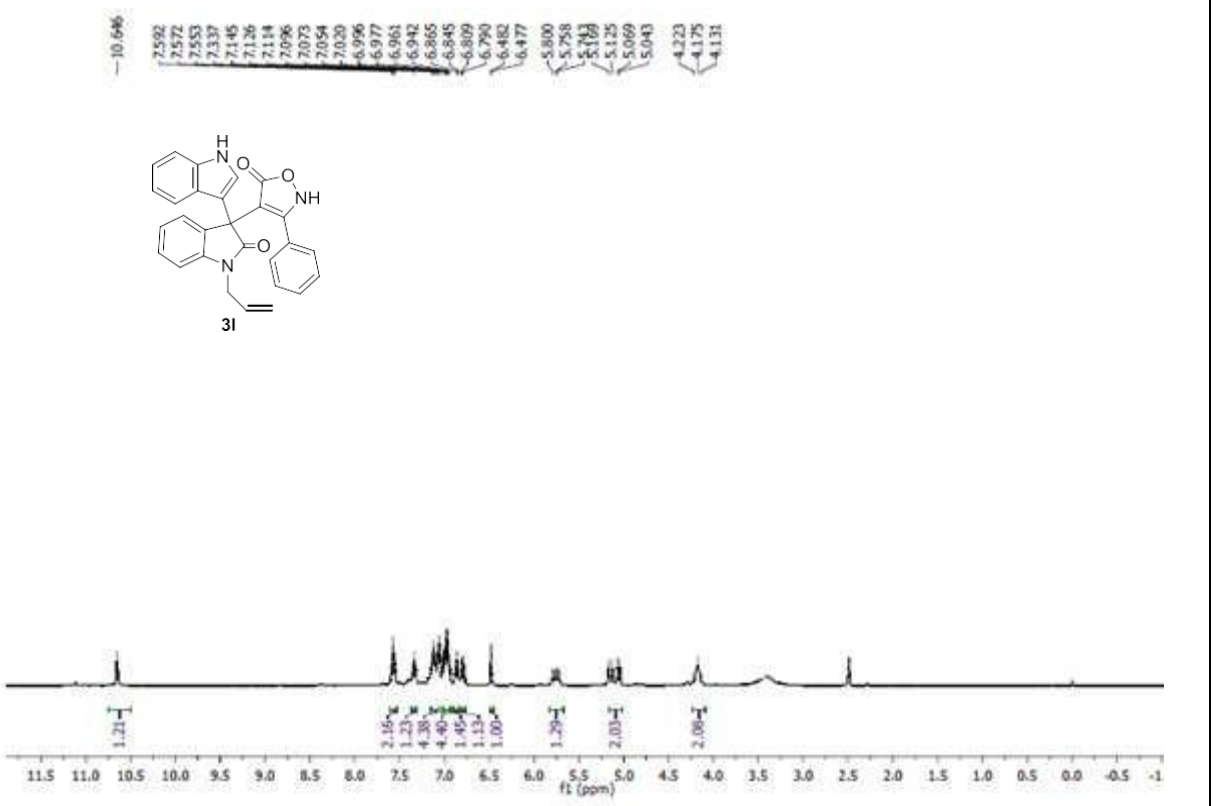


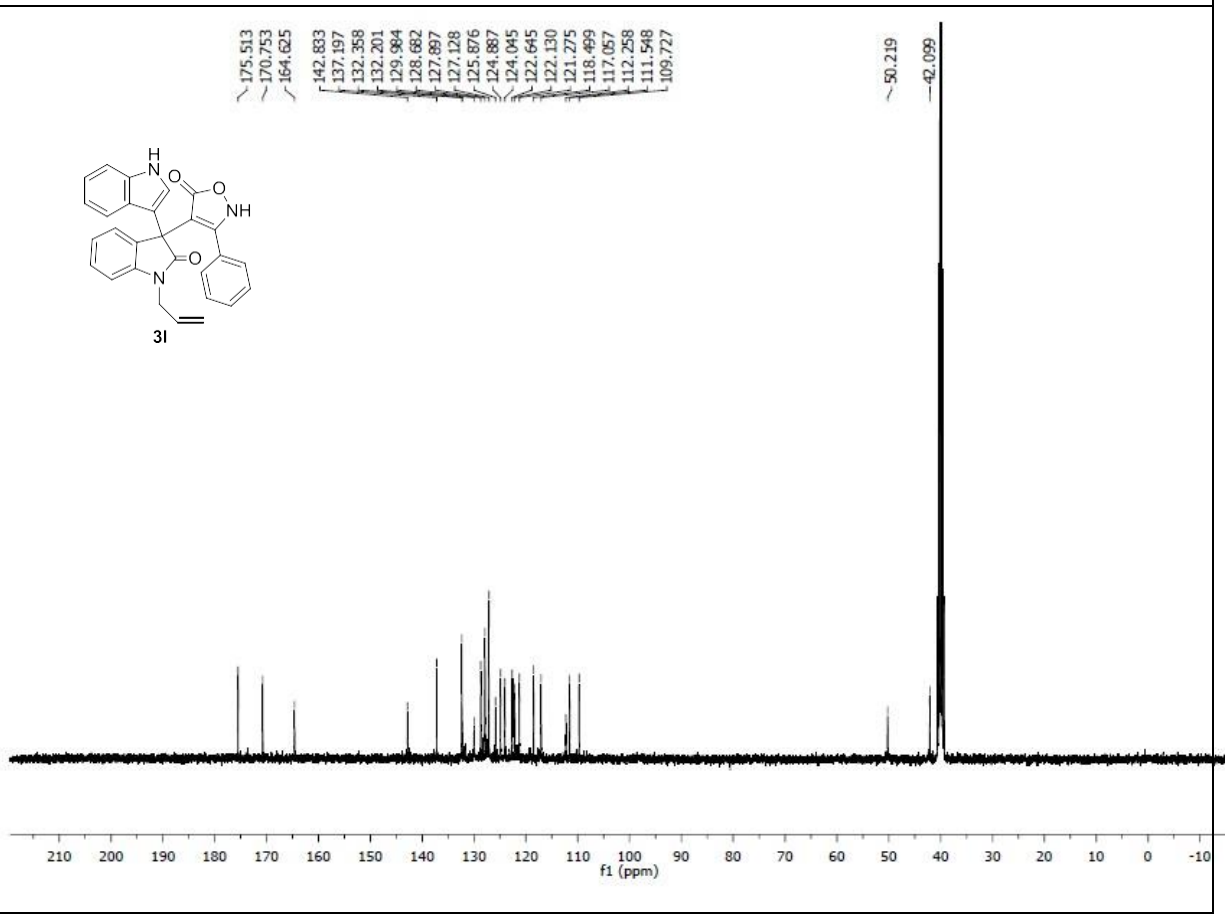
3k



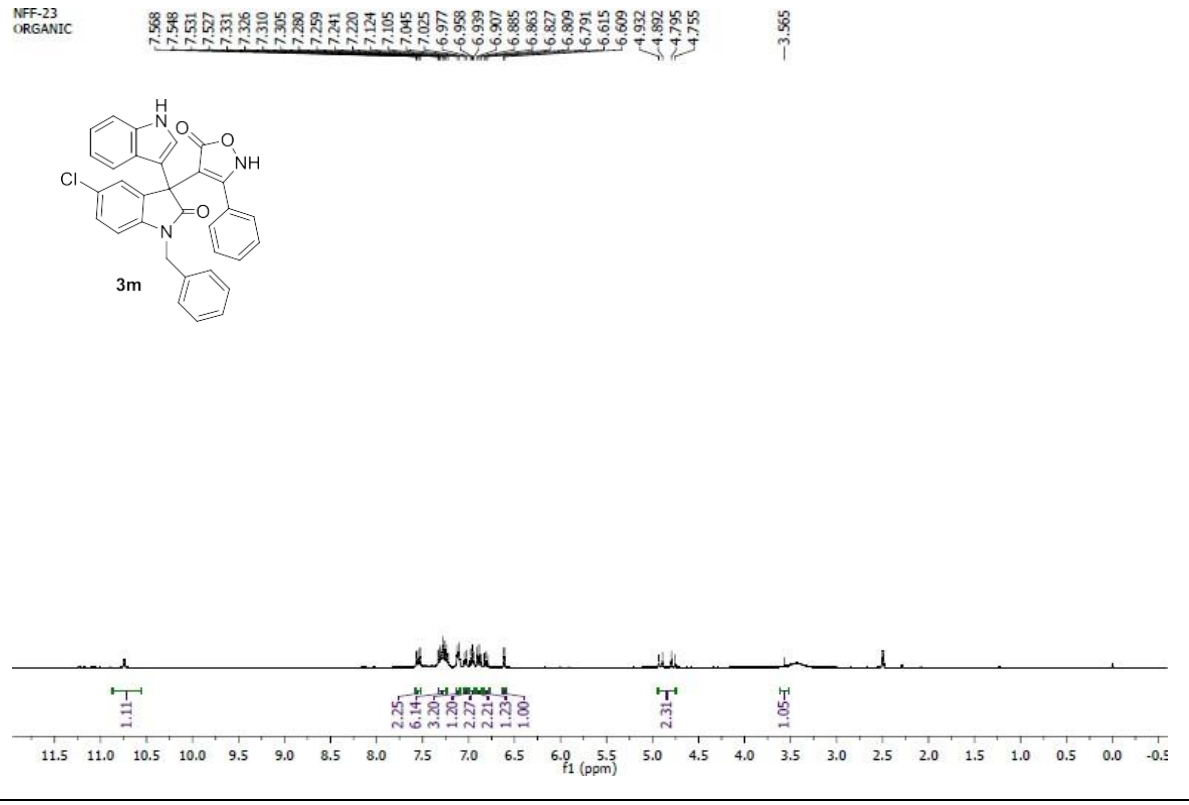
3k

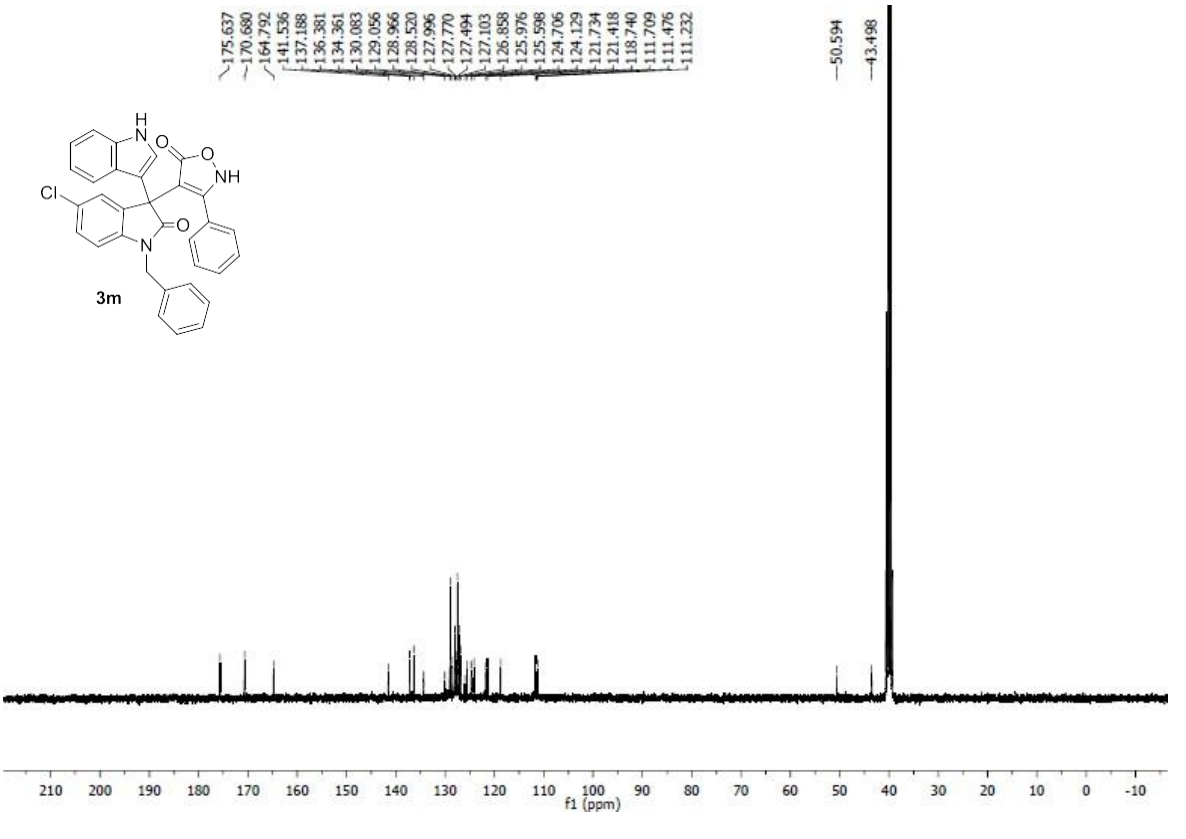
^{1}H and ^{13}C NMR Spectra of Compound (3l)



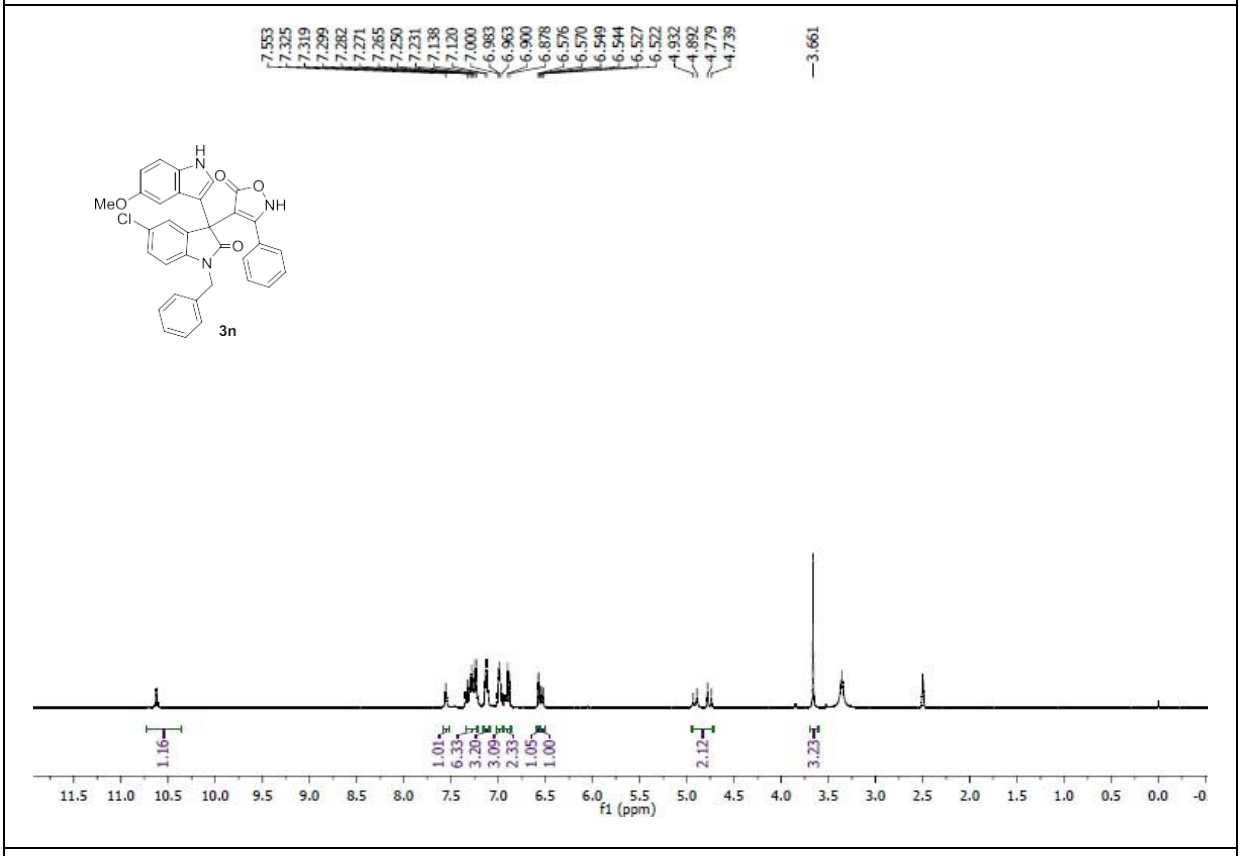


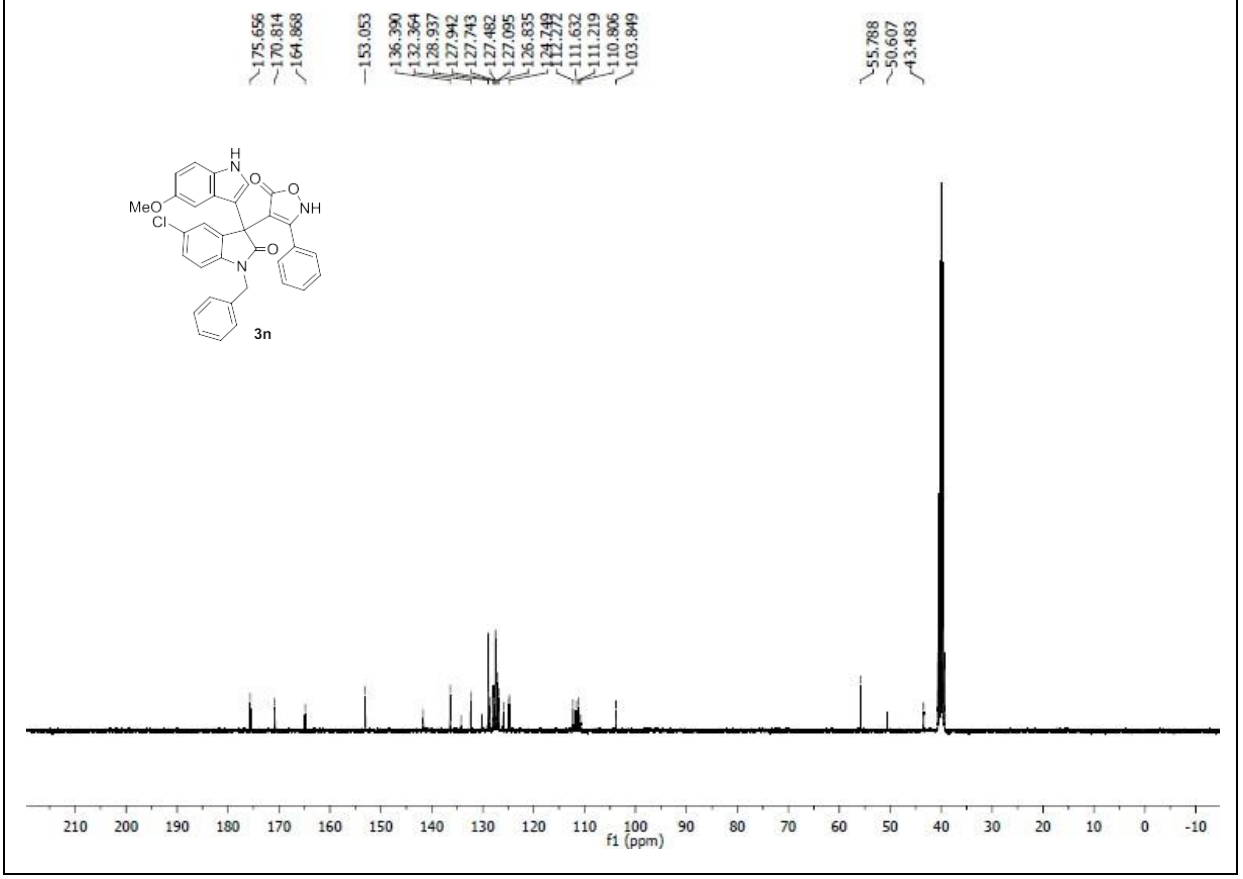
^{1}H and ^{13}C NMR Spectra of Compound (3m)



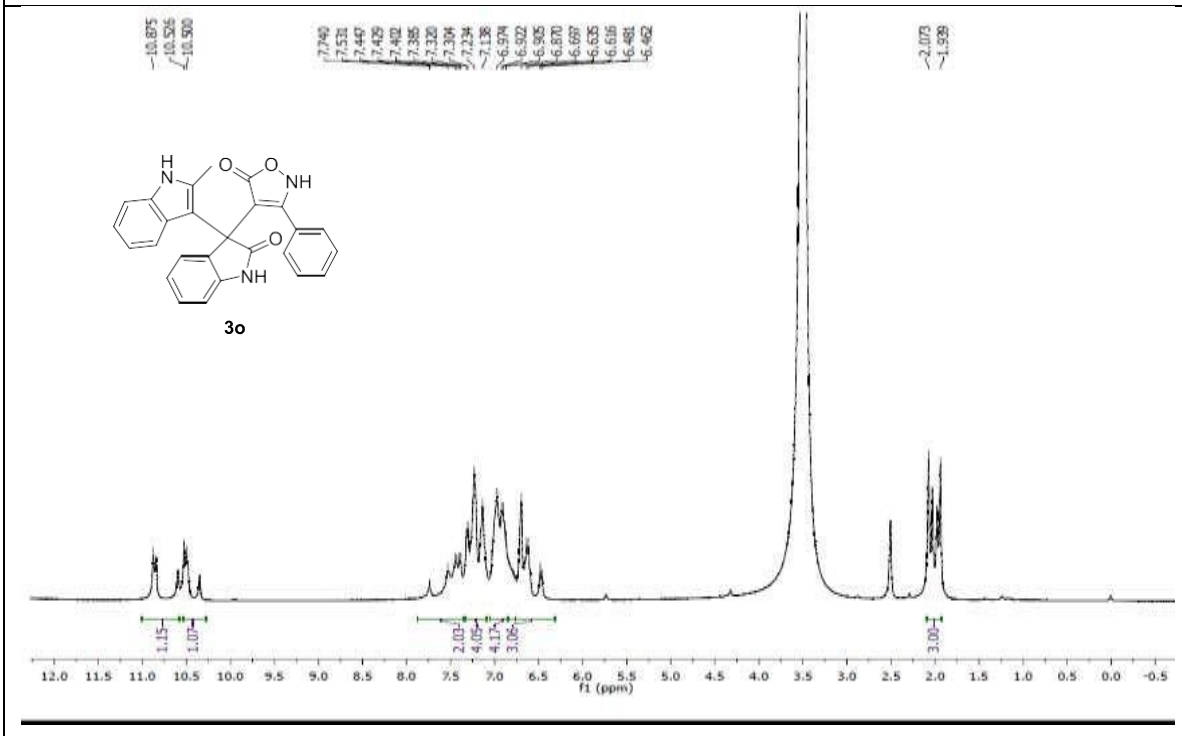


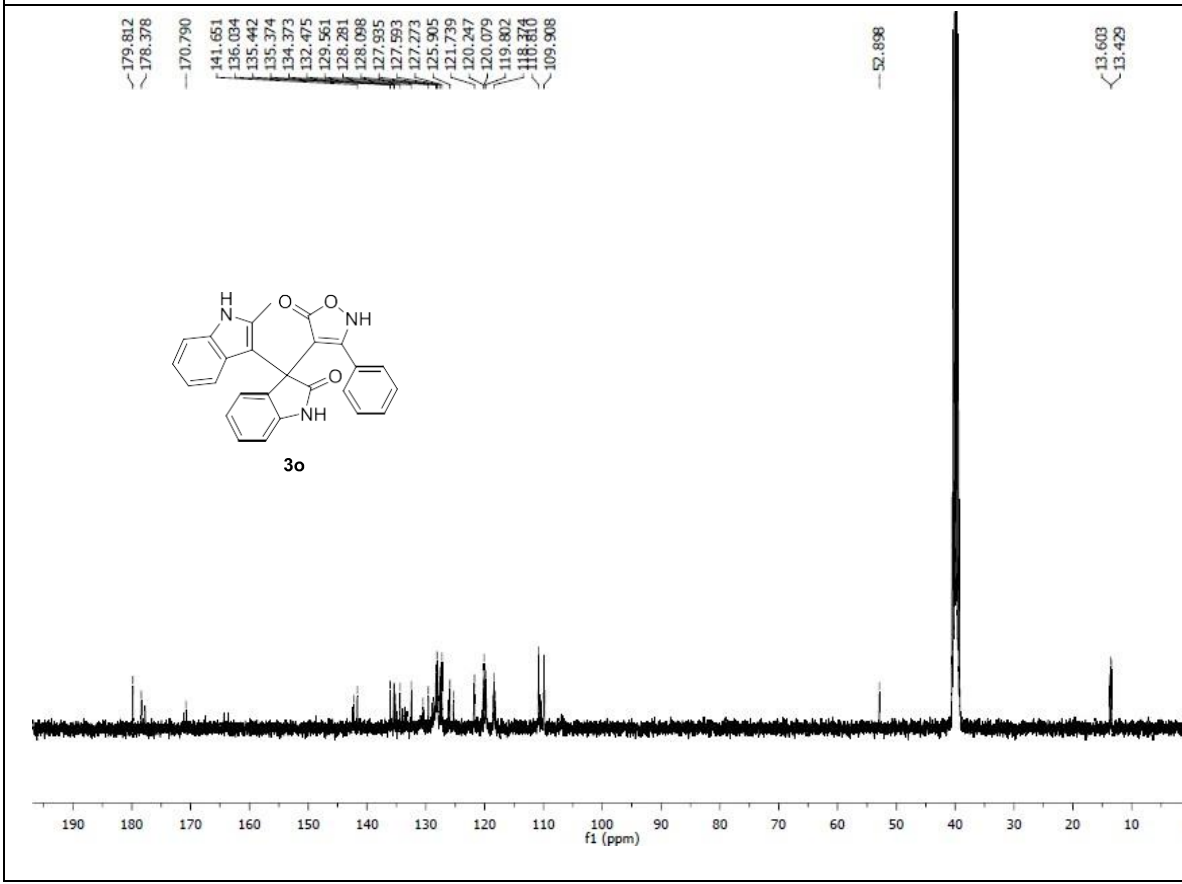
^{1}H and ^{13}C NMR Spectra of Compound (3n)



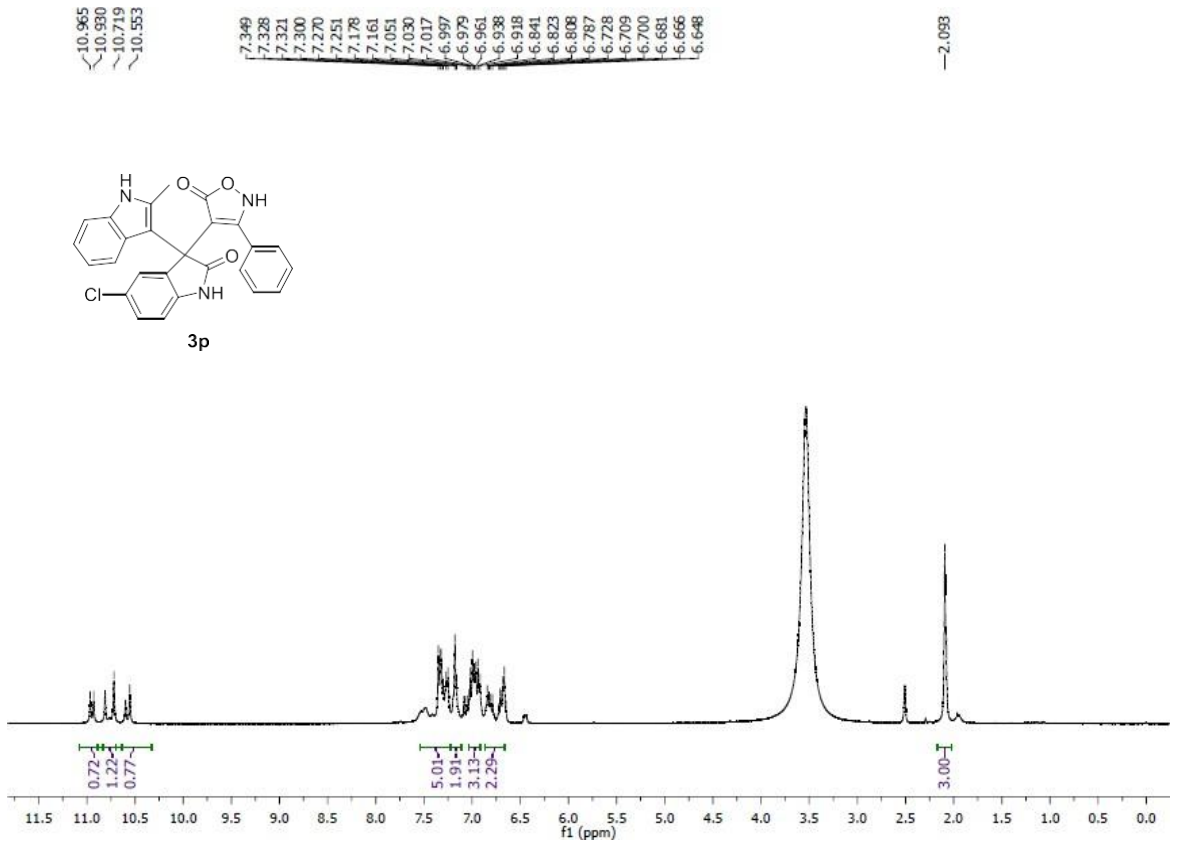


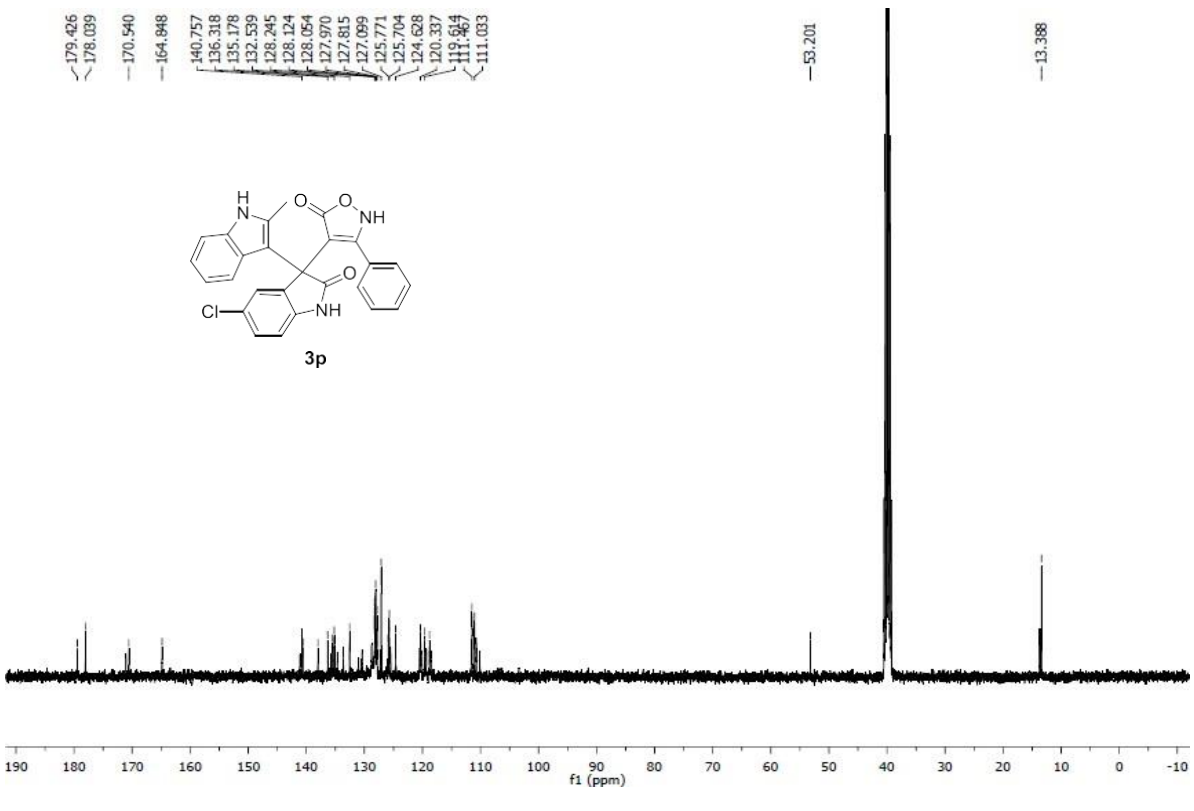
^{1}H and ^{13}C NMR Spectra of Compound (3o)



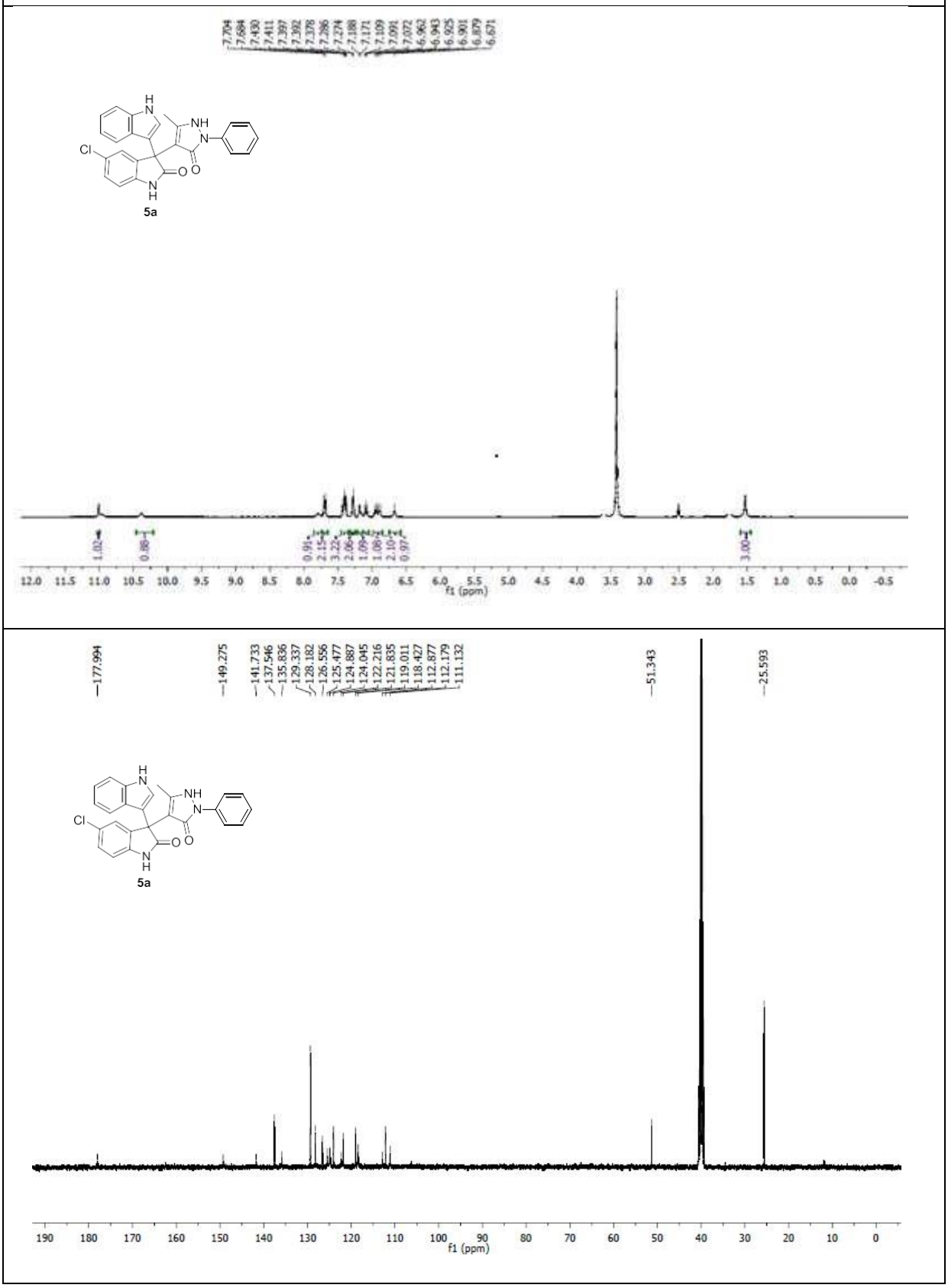


^{1}H and ^{13}C NMR Spectra of Compound (3p)

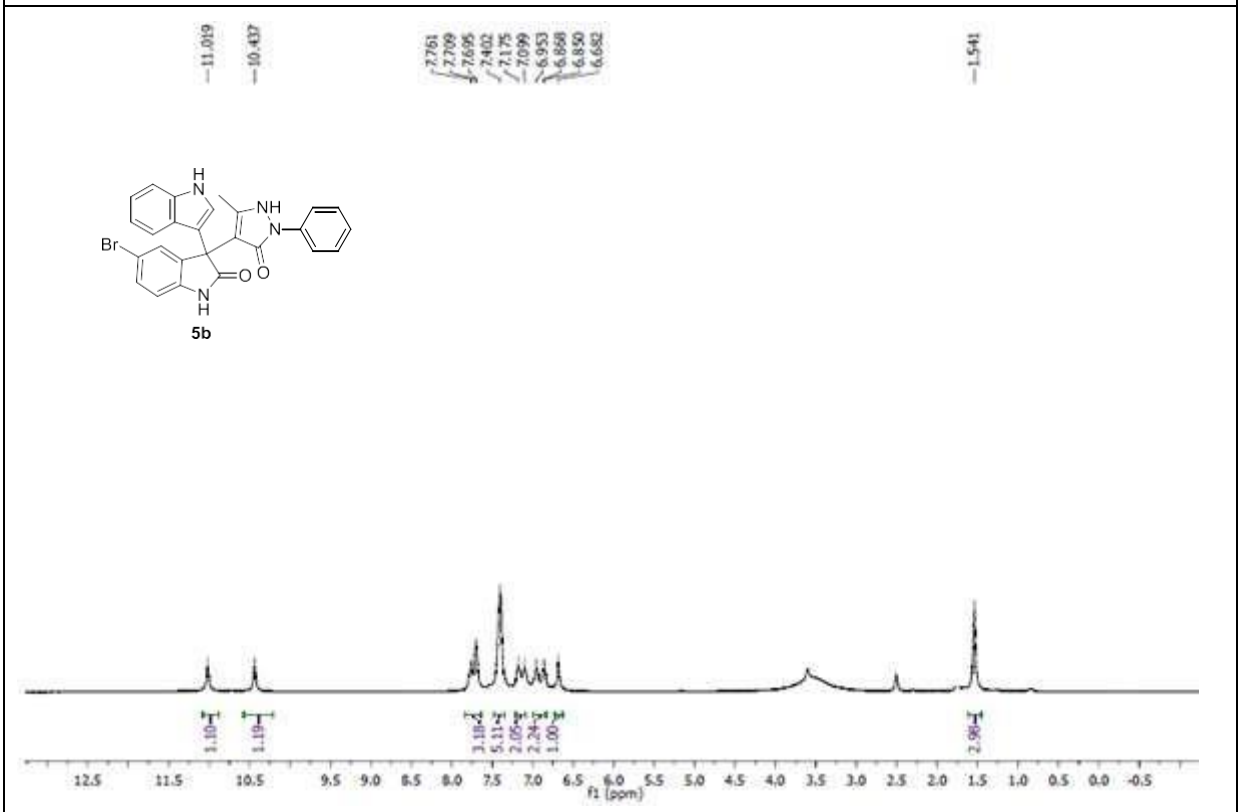


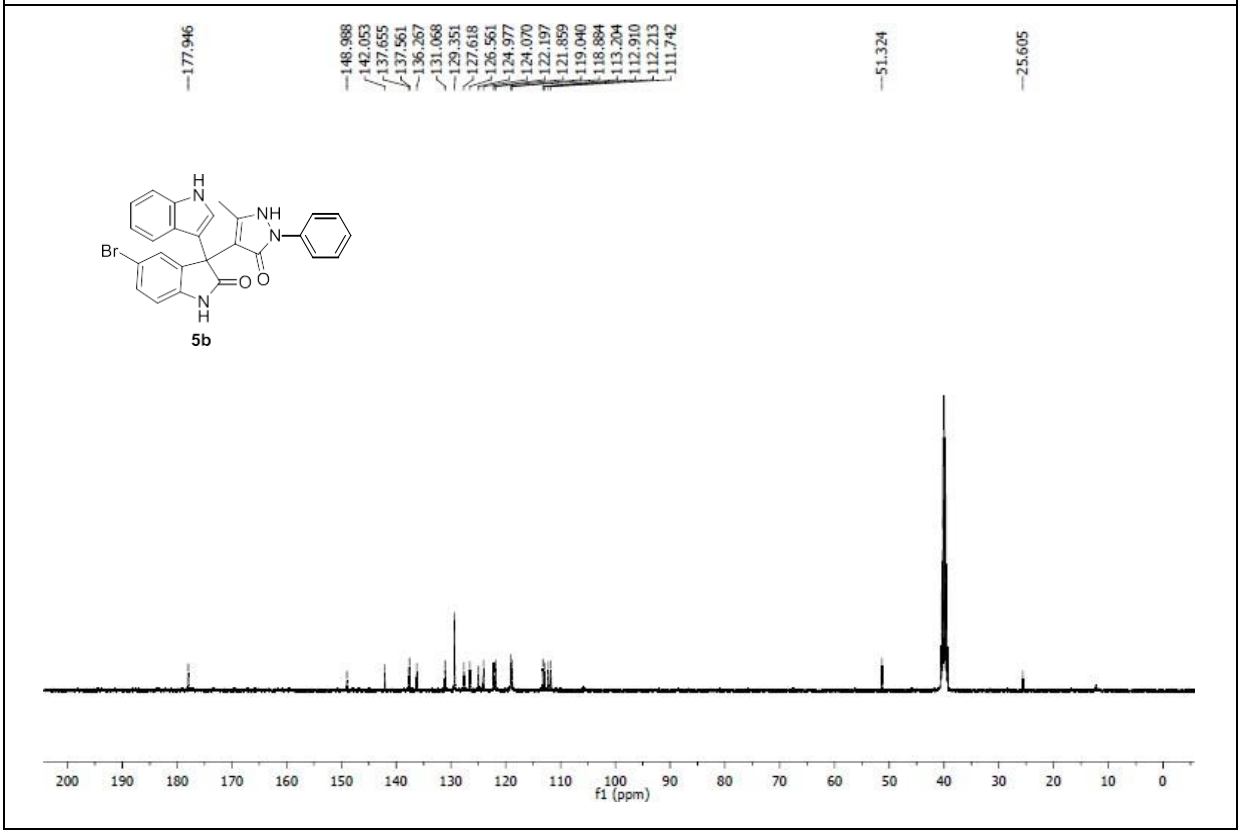


^{1}H and ^{13}C NMR Spectra of Compound (5a)

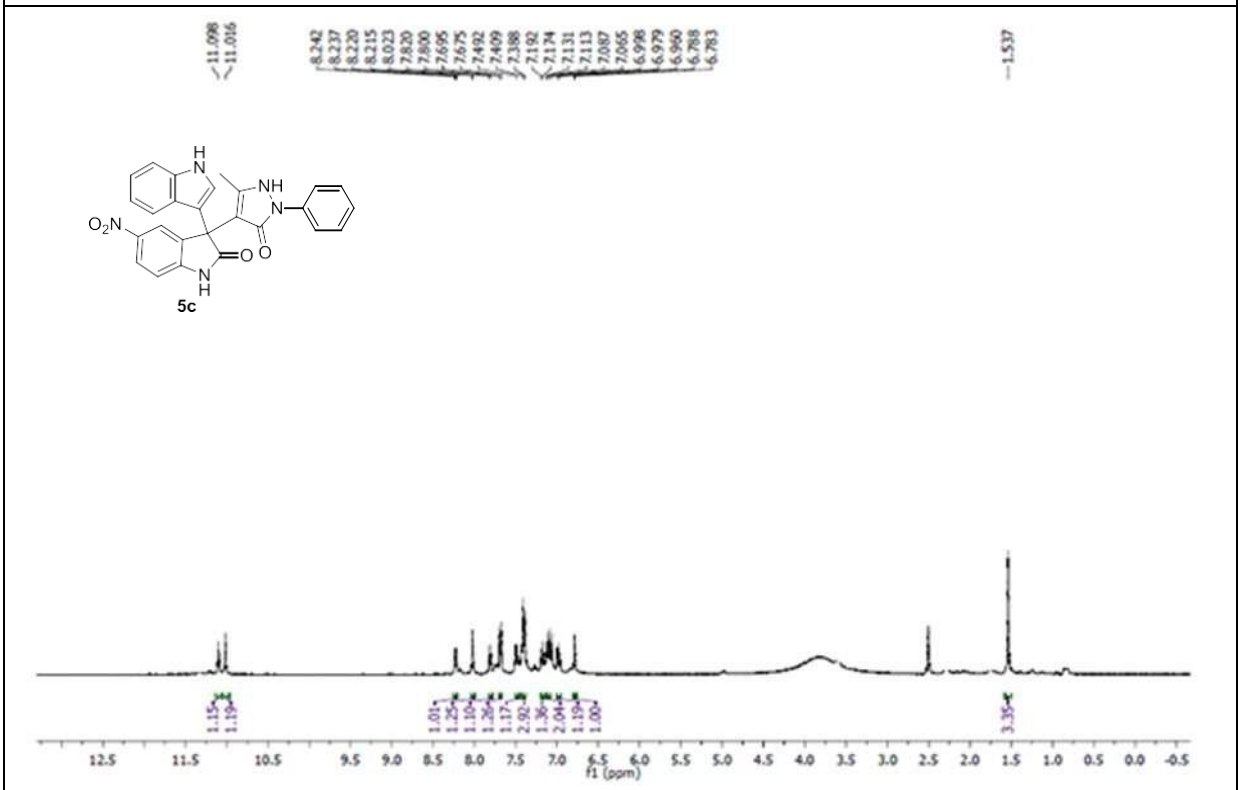


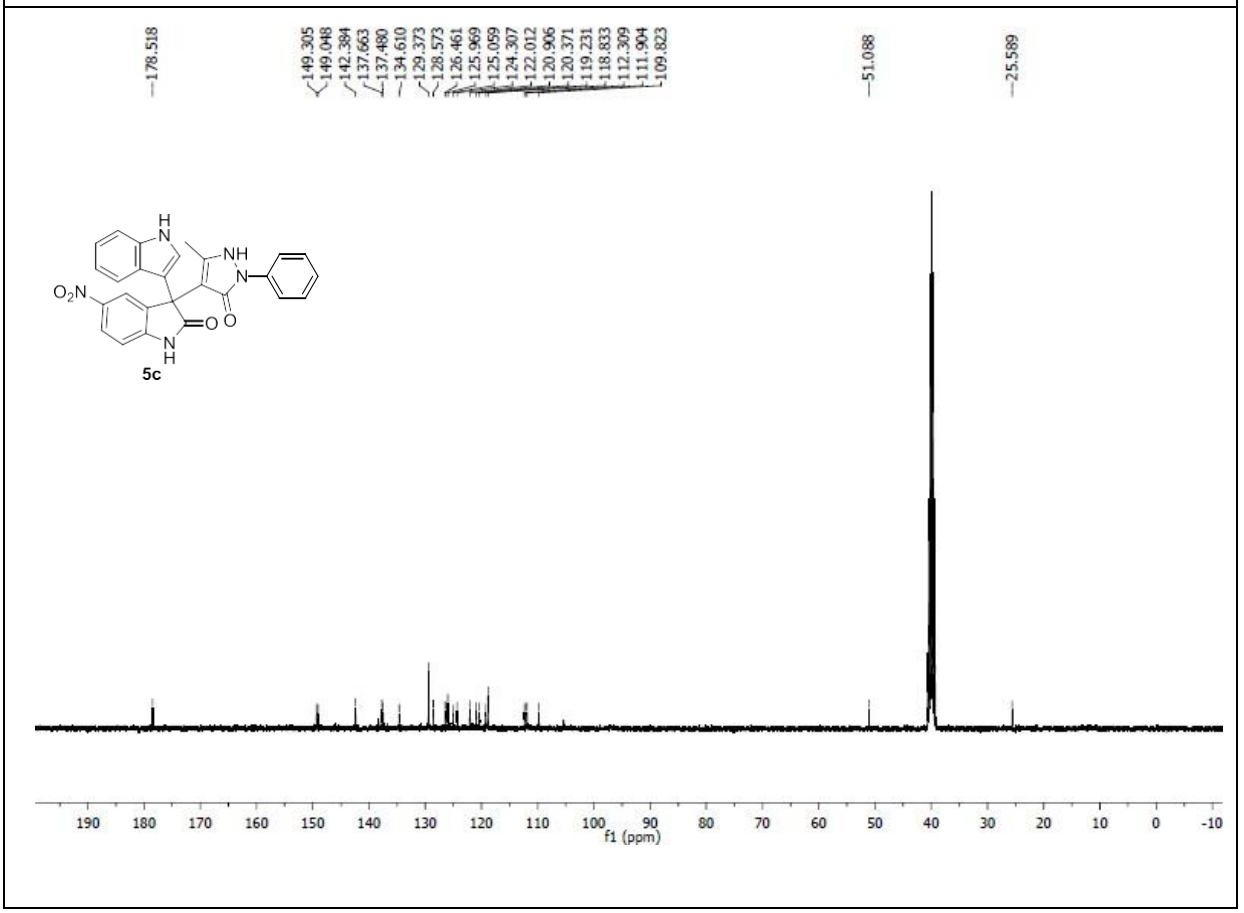
^{1}H and ^{13}C NMR Spectra of Compound (5b)



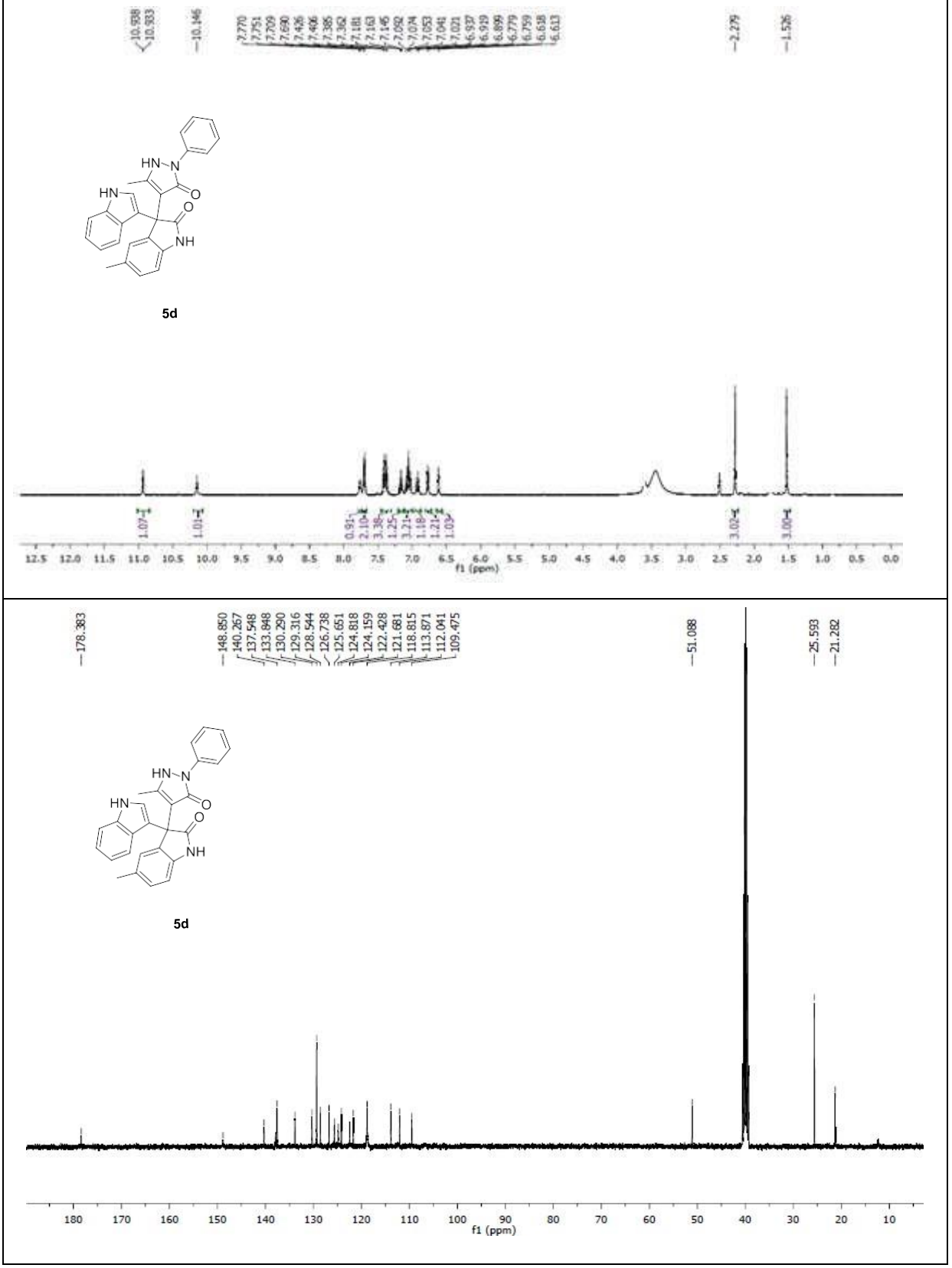


^{1}H and ^{13}C NMR Spectra of Compound (5c)

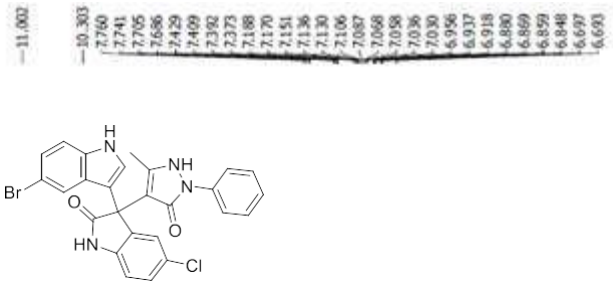




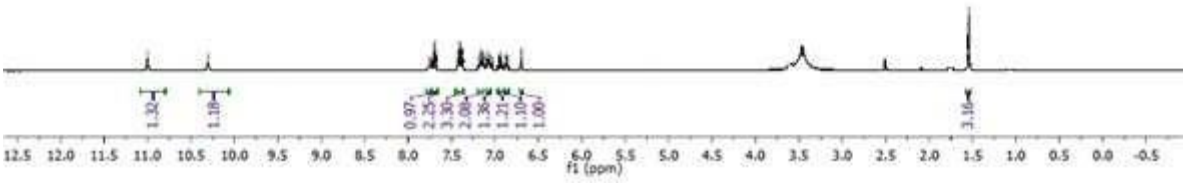
^{1}H and ^{13}C NMR Spectra of Compound (5d)

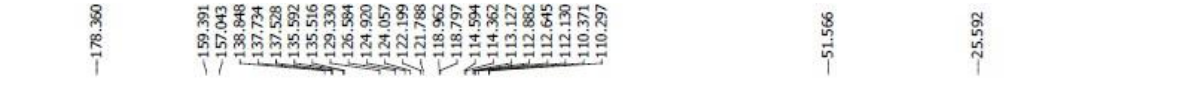


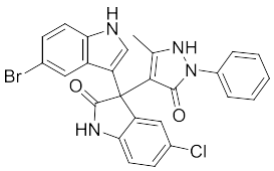
^{1}H and ^{13}C NMR Spectra of Compound (5e)



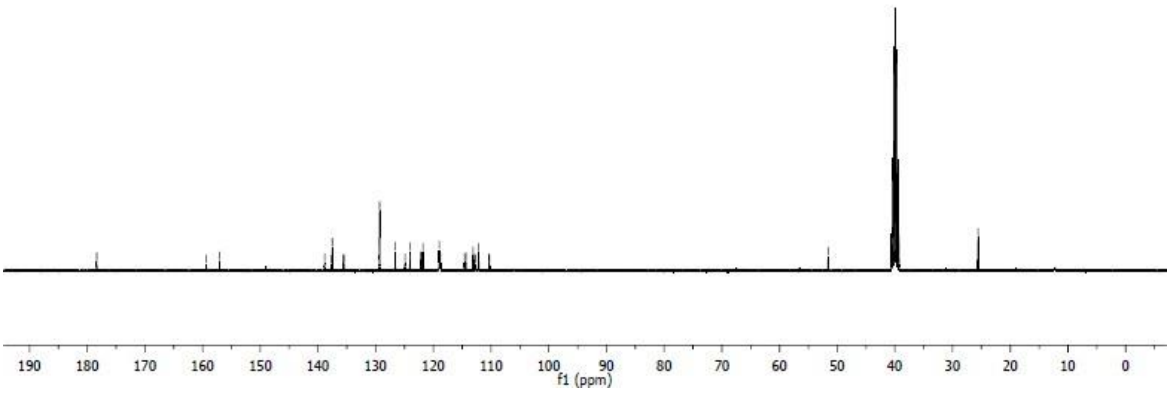
5e



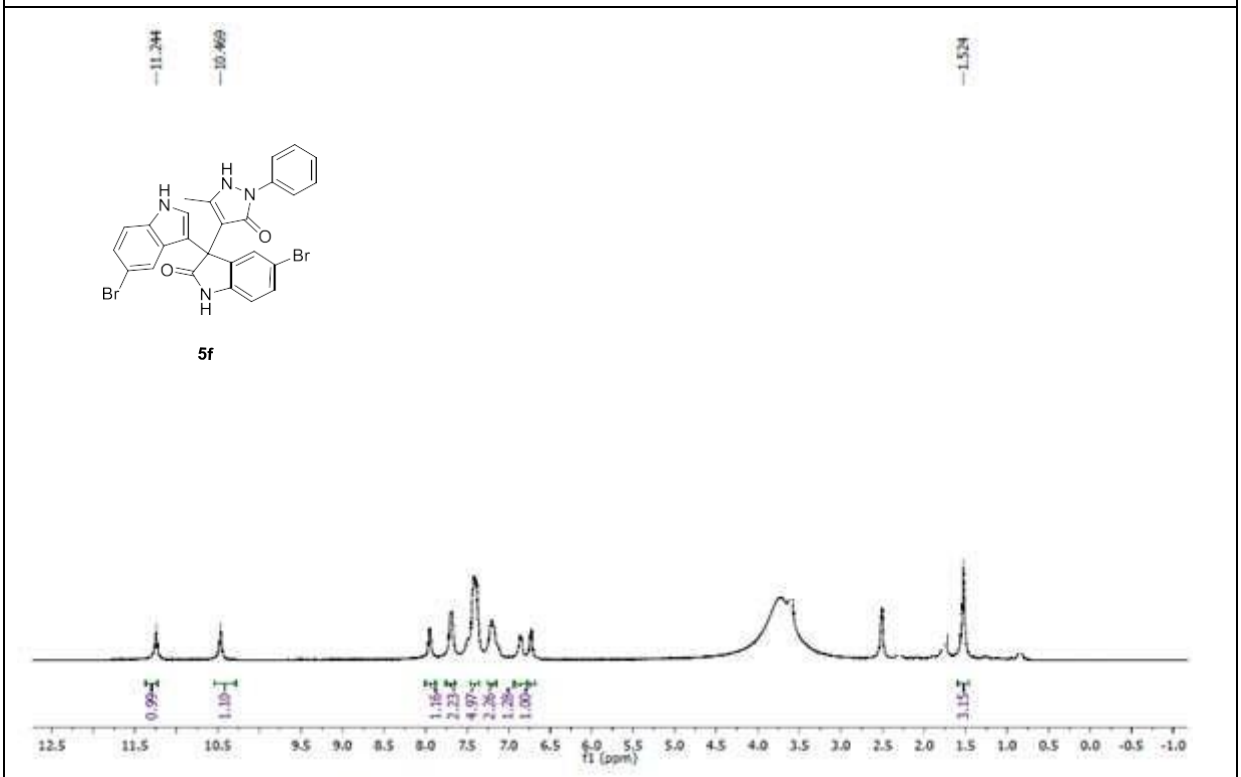


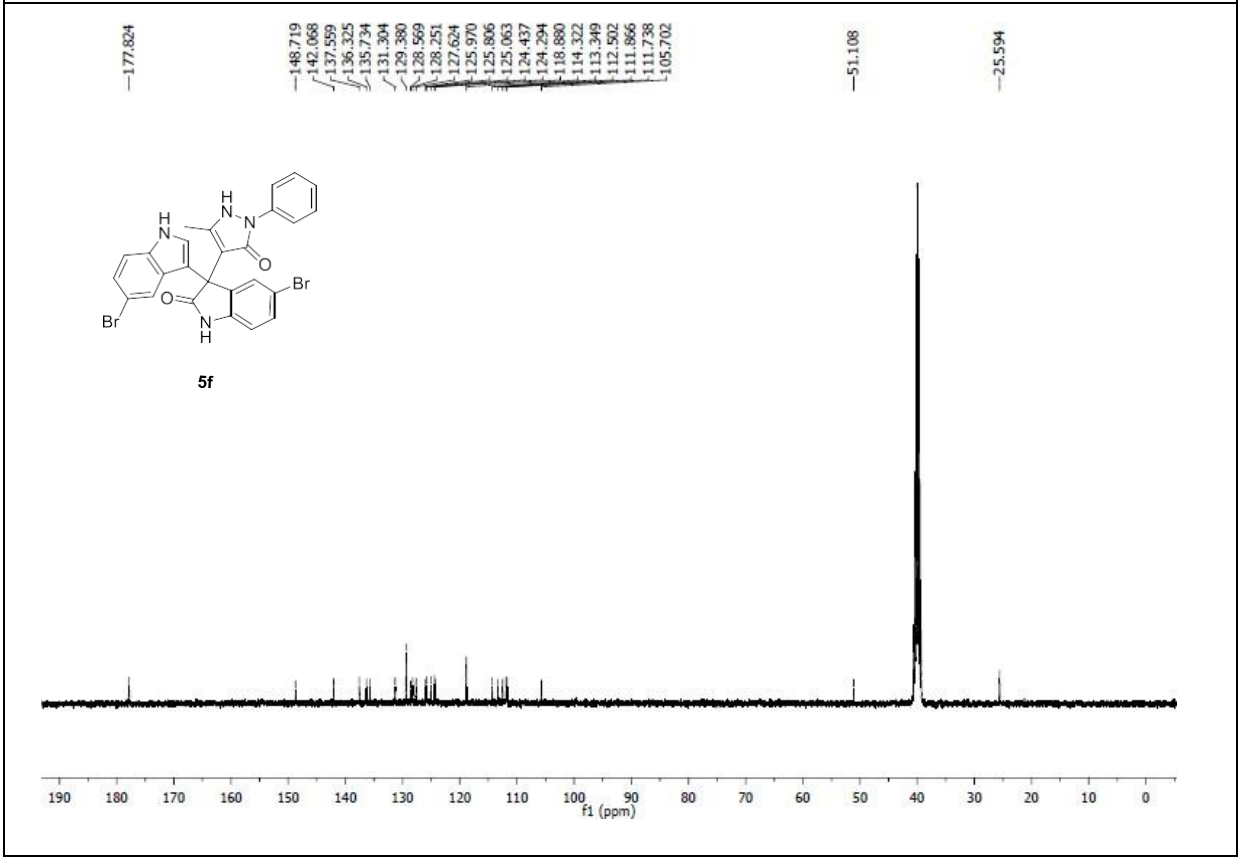


5e

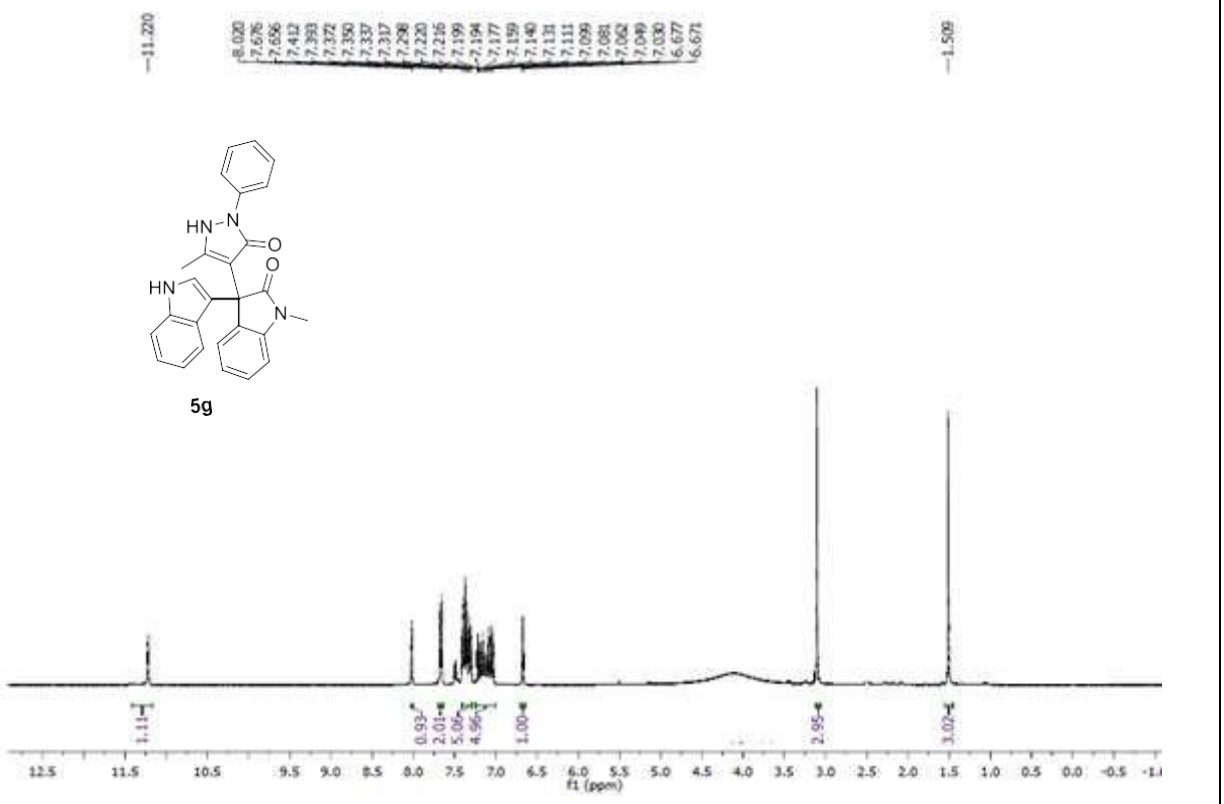


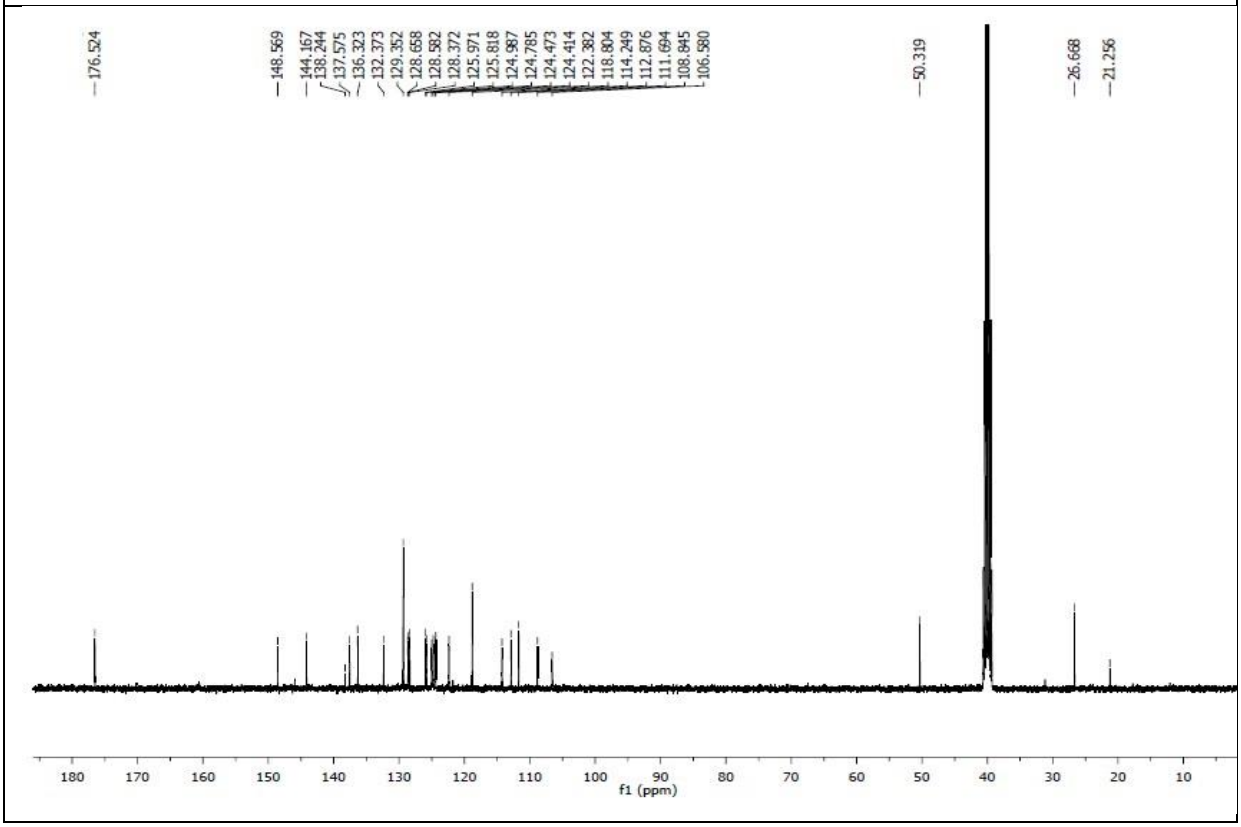
^{1}H and ^{13}C NMR Spectra of Compound (5f)



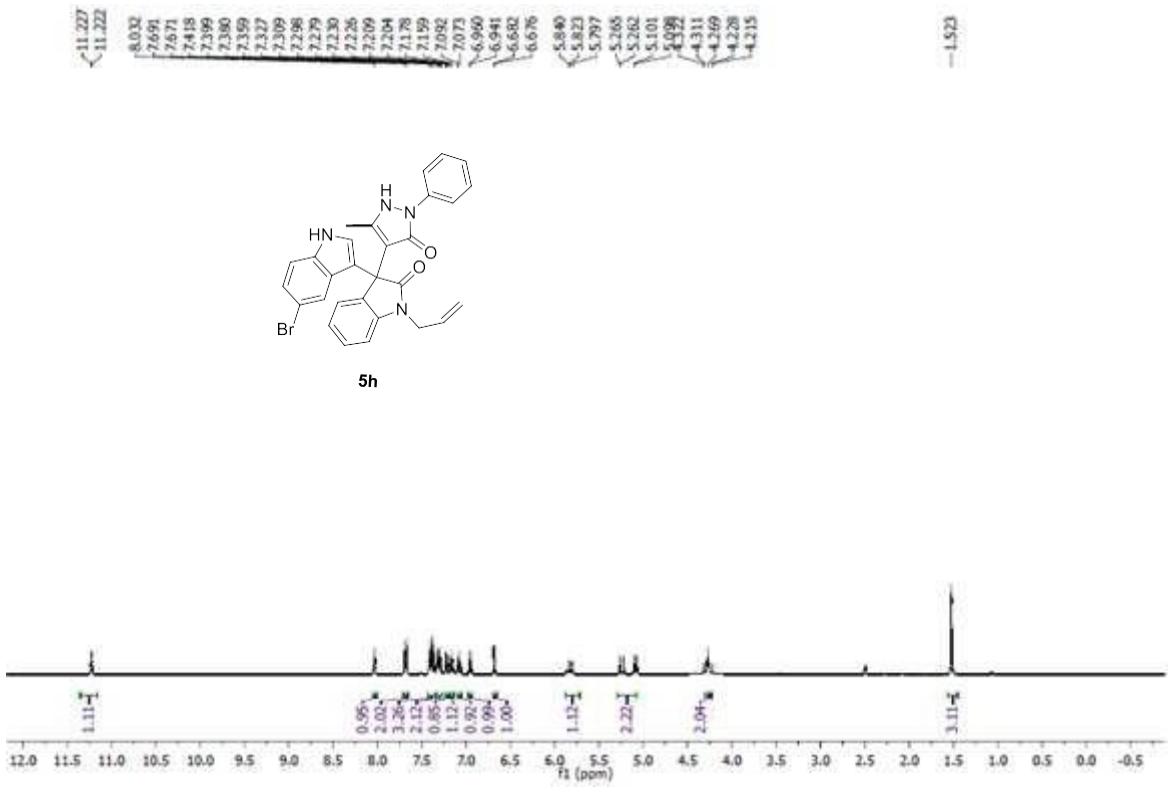


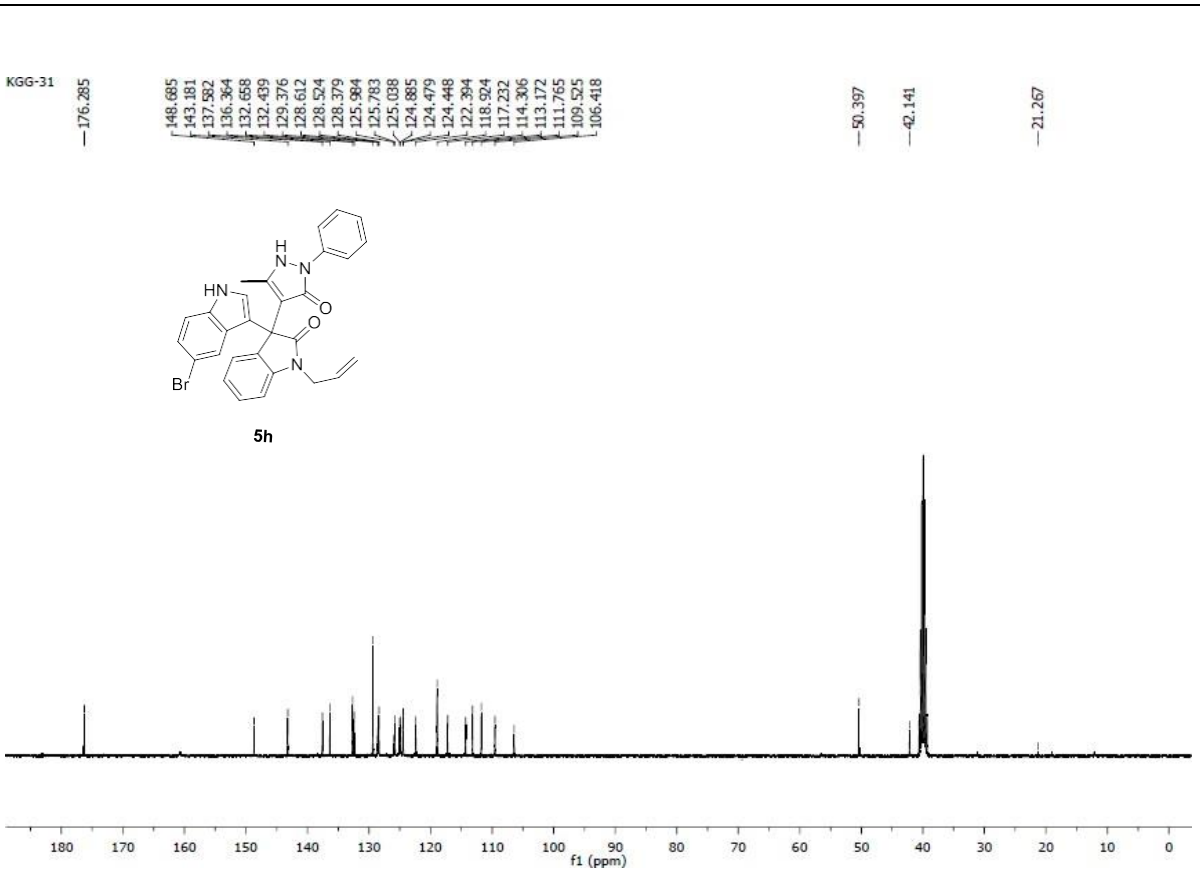
^{1}H and ^{13}C NMR Spectra of Compound (5g)



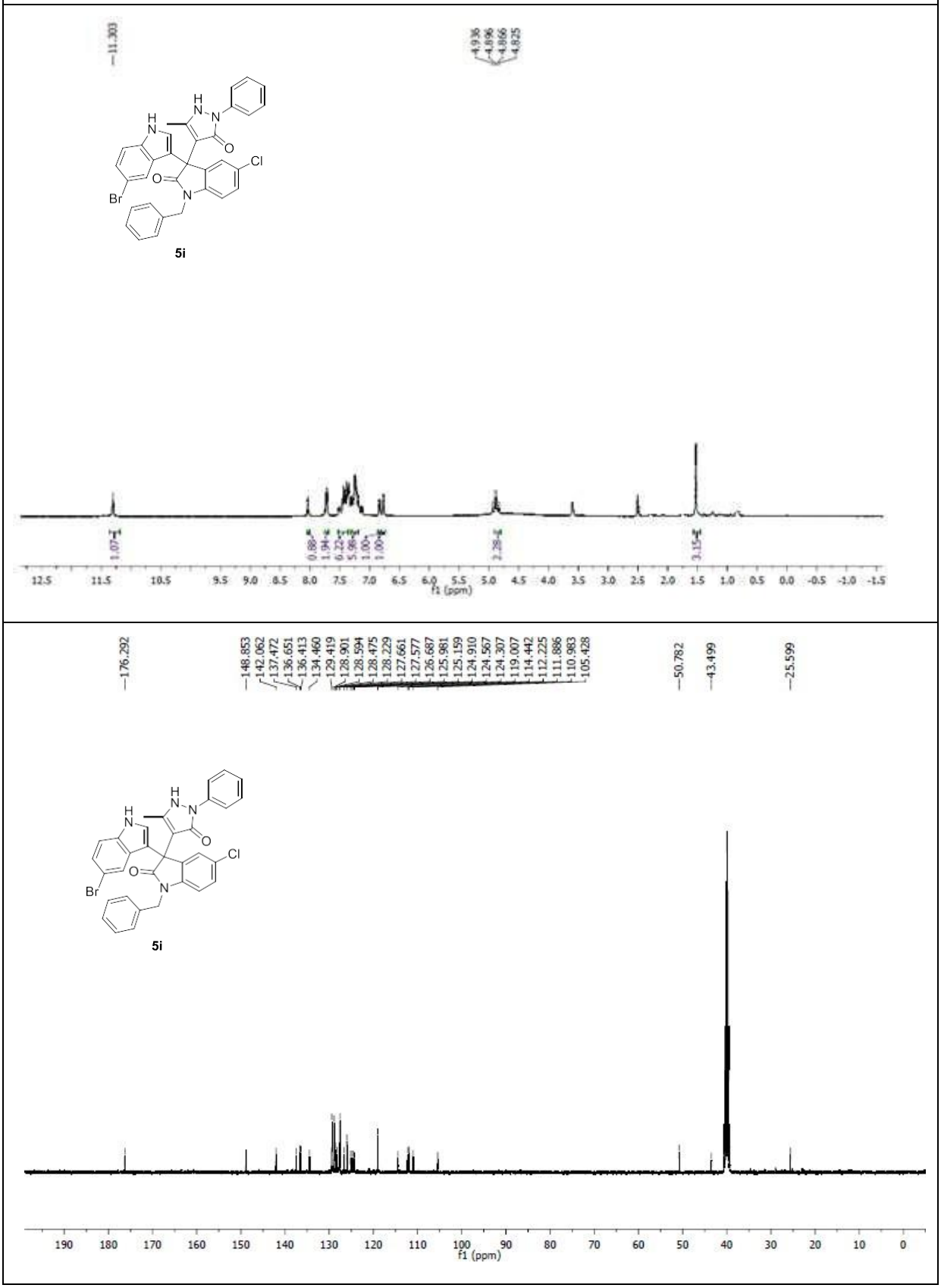


^{1}H and ^{13}C NMR Spectra of Compound (5h)

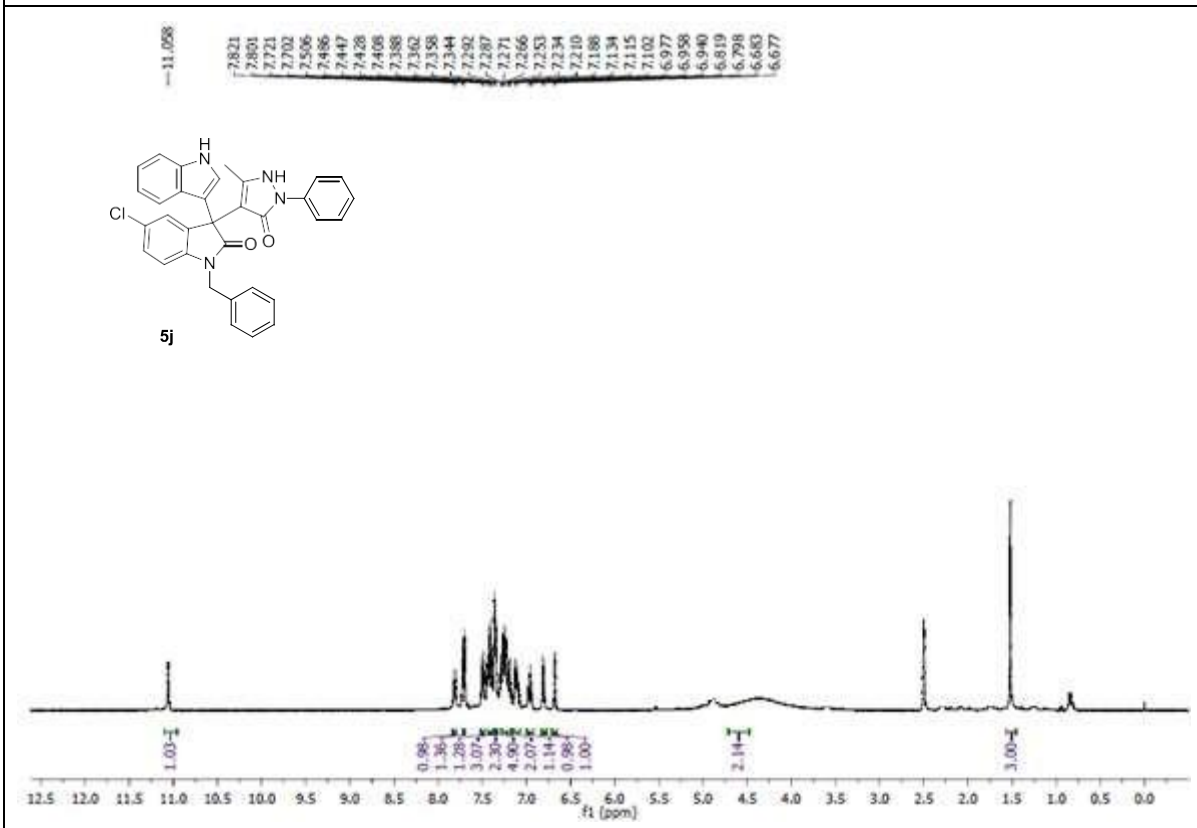


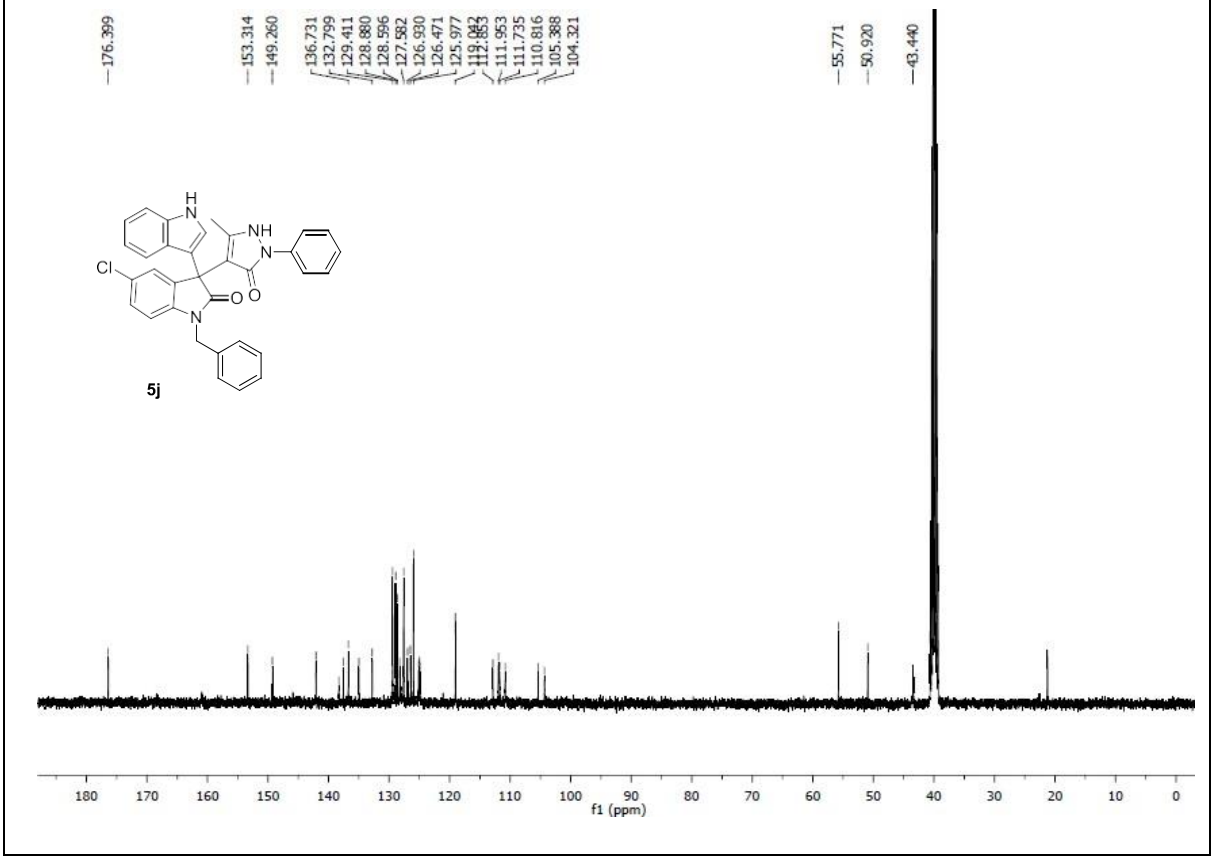


^{1}H and ^{13}C NMR Spectra of Compound (5i)



^{1}H and ^{13}C NMR Spectra of Compound (5j)





^{1}H and ^{13}C NMR Spectra of Compound (5k)