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Supporting Information

DoE-Assisted Development of a 2H–MoS_2-Catalyzed Approach for the Production of Indole Derivatives

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List of Abbreviations

ATR-FTIR Attenuated total reflectance – Fourier transform infrared spectroscopy
^{13}C-NMR carbon nuclear magnetic resonance
^{1}H-NMR proton nuclear magnetic resonance
HPLC High-performance liquid chromatography
OFAT One-factor-at-a-time approach
PTFE Polytetrafluoroethylene
TLC Thin layer chromatography
TMDCs Transition metal dichalcogenides
UV-Vis Ultraviolet-visible spectroscopy

1. General Materials and Methods

Nuclear magnetic resonance (NMR) spectra were recorded on Varian 400 spectrometer (^{1}H: 400 MHz, ^{13}C: 100.5 MHz). The chemical shift (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvent ($CHCl_3$ at 7.26 and 77.16 ppm; respectively). Coupling constants are given in Hertz (Hz). The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublet of doublets; tt, triplet of triplets; ddt, doublet of doublet of triplets; td, triplet of doublets; m, multiplet. HPLC-UV Agilent 1260 Infinity II was used to perform samples analysis. Infinity Lab PoroShell 120 EC-C18 4 µm columns (4.6 x 50 mm or 4.6 x 100 mm) were used for HPLC analysis under the following conditions: solvent A: H_2O + H_2CO_2 (0.1 %); solvent B: acetonitrile; gradient: 0 min (30 % B), 8 min (100 % B), 15 min (100 % B). Powder X-ray diffraction (PXRD) patterns were collected by using a Philips X'pert PRO automatic diffractometer operating at 40 kV and 40 mA, in theta-theta configuration, secondary monochromator with Cu-Kα radiation (λ = 1.5418 Å) and a PIXcel solid state detector (active length in 2θ = 3.347º). Data were collected from 5 to 80°, with a step size of 0.026º and a time per step of 120 s, at room temperature (total time = 23 min, scan speed = 0.056º s^{-1}). 1º fixed soller and divergence slit giving a constant volume of sample illumination were used. The ATR-FTIR spectrum of commercial 2H-MoS_2 was recorded on an IRAffinity 1S spectrophotometer (Shimadzu Corp, Japan), with a total of 240 scans and a spectral resolution of 4 cm^{-1}. Raman spectra were recorded on a Renishaw inVia Raman microscope at room temperature using an exciting laser source of 532 nm. Raman samples were measured in solid state under ambient conditions. X-ray photoelectron spectroscopy (XPS) measurements were carried out using a SPECS SAGE HR 100 spectrometer in high vacuum (10−7 Pa), equipped with a nonmonochromatic X-ray source Mg with a Kα line of 1253.6 eV. An electron flood gun was used to neutralize charge. Measurements were performed directly on the solid material samples, deposited on a sample holder. High-resolution spectra were recorded for C, O, Mo, and S. XPS spectra were processed and fitted using Casa XPS Version 2.3.16 PR 1.6. TEM images were recorded by using a JEOL JEM-2100F/UHR microscope, with a 4-megapixel CMOS camera (TVIPS TemCam-F216). In order to prepare TEM samples, a little bit of powder was ultrasonicated in glass distilled acetone (Electron Microscopy Science) for 10 min, pipetted onto 400 mesh Cu grids coated with a lacey carbon film (Ted Pella, Inc.), and air-dried.

General procedures. All catalytic reactions were set up in glass vials, as also described in section 2.1, unless otherwise stated. Chromatographic purification of products was accomplished using flash chromatography on silica gel (35-70 mesh). Merck pre-coated TLC plates (silica gel 60 GF254, 0.25 mm) were employed, using UV light as the visualizing agent (254 nm), basic aqueous potassium permanganate ($KMnO_4$) stain solution or iodine, and heat as developing agents. Organic solutions were concentrated under reduced pressure on a Büchi rotatory evaporator.

Materials. Commercial reagents and solvents were purchased from Merck, Fluka, Alfa Aesar, Sigma-Aldrich, Fluorochem, and VWR. They were used as received, without further purification, unless otherwise stated. Synthesis grade and anhydrous solvents were used as purchased. The preparation of starting materials.

2. DoE-Assisted Optimization

2.1 General Reaction Procedure

All reactions were carried out in 4-mL glass vials equipped with stirrer bars (7 x 3 mm). Specifically, the catalyst (TMDCs or MoO_2), indole (**1a**), benzaldehyde (**2a**) and the solvent were introduced into the vial. To control the temperature, the vial was placed in an oil bath during the reaction time. The magnetic stirring was kept at 380 rpm.

2.1.1 Catalyst Recycling Experiments

To perform catalyst recycling experiments, 0.5 mmol of benzaldehyde **2a** (53 mg, 51 µL) were introduced into a 15 mL polypropylene centrifuge tube along with an oval stirring bar, acetonitrile (5 mL) and indole **1a** (160 mg, 13.75 mmol). 40 mg of heterogenous catalyst MoS_2-50°C-vac were subsequently added. The centrifuge tube was placed in an oil bath at 70°C and left to react for 2 hours. After the elapsing of the reaction time, the reaction vessel was allowed to cool down and centrifugated at 3200 rpm at 4°C for 20 minutes. The supernatant was collected into a flask and the pellet resuspended in acetonitrile to be thoroughly rinsed. Finally, the collected organic fraction were reunited and evaporated under reduced pressure. The tube was reloaded with benzaldehyde **2a**, indole **1a** and solvent and the procedure repeated. Over three cycles the reaction yield for entry **3a** was >99%, 60%, 25% measured through NMR using 1,3,5-trimethoxybenzene as internal standard.

2.1.2 Scale-Up

Scale up experiments were performed at a 50 mmol scale of the limiting reagent **2a**. 5.30g g of benzaldehyde **2a** (50 mmol) were introduced in a round bottom reaction flask along with 50 mL of acetonitrile, 4 g of MoS_2-50°C-vac and indole **1a** (137.5 mmol, 16.108 g). The reaction mixture was reacted for 2 hours at 70°C. The heterogenous catalyst was separated and recovered by filtration through PTFE membrane. The reaction yield for entry **3a** was 97% at a 50 mmol scale measured through NMR using 1,3,5-trimethoxybenzene as internal standard.

2.2 HPLC Analysis of the Reaction Crude

The amount of product **3a** obtained under the reaction conditions, and in turn the chemical yield of the reaction, was quantified via HPLC analysis. To this end, biphenyl was used as internal standard and added to the reaction crudes. Subsequently, these samples were filtered through a PTFE filter (0,2 µm) to remove the heterogeneous catalyst. Finally, an aliquot of the resulting solution (10 µL) was collected and diluted to 1 mL of acetonitrile. The samples were then analyzed as described in the methods section. Figures S1 and S2 illustrate the resulting chromatograms.

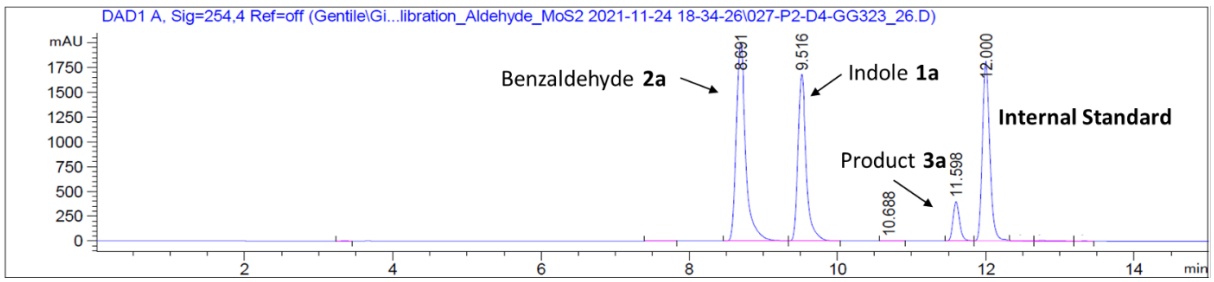


Figure S1 HPLC chromatogram registered at 254 nm with a PoroShell 120 EC-C18 (4µm, 4.6 x 50 mm).

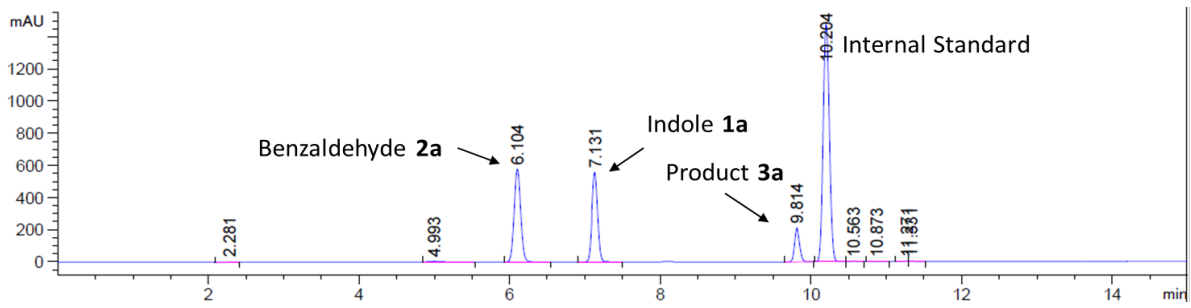


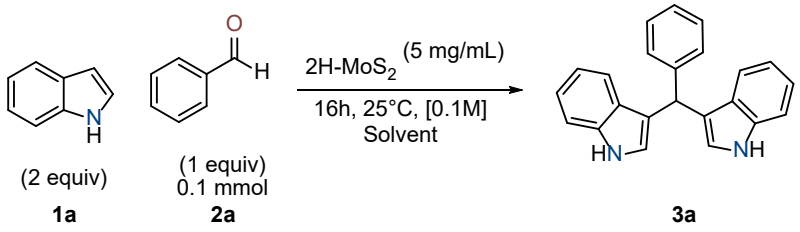
Figure S2 HPLC-UV chromatogram registered at 254 nm with a PoroShell 120 EC-C18 (4µm, 4.6 x 100 mm).

2.3 Design of Experiments (DoE) Results

The DoE optimization and screening studies were carried out to determine which variables had the greatest impact on the yield of compound **3a** and to select optimal conditions for materials confrontation and reaction scope.

All DoE studies were designed and analysed using the DoE software package Modde Pro 13.0.2. The Design wizard tool was used to design and generate the "worksheet" table of experiments in which the value of each factor, for each run, was explicated. All experiments were performed in randomized order. However, to make the design readily understandable, here the experiments are not listed in run order. All experiments were set-up as stated in section 2.1.

2.3.1 OFAT solvent screening



Solvent	Yield%*
Dimethyl Sulfoxide (*DMSO*)	18 ± 2%
Dimethylformamide (*DMF*)	17 ± 2%
Acetonitrile (*ACN*)	48 ± 4%
Water	26 ± 3%
Ethyl Acetate (*EtAc*)	38 ± 4%

* Yield determined by HPLC

Figure S3 OFAT solvent screening: reaction scheme (top), results table (bottom).

2.3.2 DoE optimization

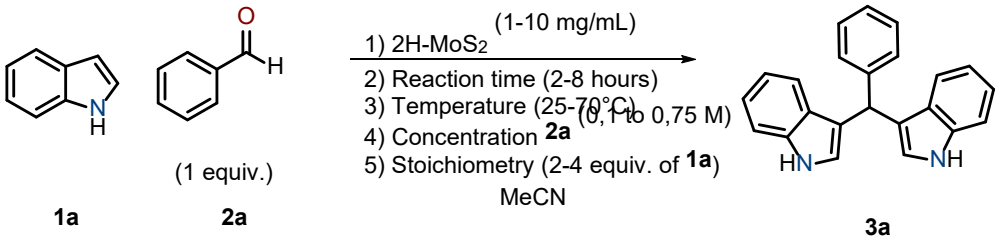


Figure S4 DoE Optimization (reaction scheme and investigated factors with their ranges).

a)

Objective	Optimization (RSM)	
Process model	Quadratic	
Mixture model	--	
Design	**D-Optimal**	
Runs in design	26*	
Center points	3	
Replicated runs	3	
Replicates	0	
N = actual runs	32*	
Maximum runs	12000	
Constraints	No	
Candidate set		
Extreme vertices	256	
Edge points	512	
Centroids of high dim. surfaces	64	
Total runs	832	
D-Optimal		
Potential terms		
Number of inclusions	0	
Constraints	No	
Selected design number	1	
Design statistics	G-efficiency	57,5769
	log(Det. of X'X)	23,7747
	Norm. log(Det. of X'X)	-0,37302
	Condition number	9,22499

b)

Exp No	Concentration (2a)	Temperature °C	Time hours	Loading mg/mL	Stochiometry (1a)
1	-1	-1	-1	-1	-1
2	-0,538	-1	-1	-0,333	1
3	1	-1	-1	-1	0,333
4	0,231	-1	-1	1	-0,333
5	-1	-0,556	-1	0,333	1
6	1	-0,556	-1	1	-1
7	-1	1	-1	1	-1
8	-1	1	-1	-1	1
9	1	1	-1	-1	-1
10	1	1	-1	1	1
11	-1	-1	-0,333	1	0,333
12	0,231	1	-0,333	0,333	-1
13	1	0,111	-0,333	-1	1
14	-1	-1	1	1	-1
15	-1	-1	1	-1	1
16	1	-1	1	-1	-1
17	0,231	-0,556	1	1	1
18	-1	1	1	-1	-1
19	-0,538	1	1	1	1
20	1	1	1	1	-1
21	1	1	1	-1	1
22	1	0,111	1	0	0
23	1	-1	0,333	1	1
24	-0,538	-0,556	0,333	-1	-0,333
25	-1	1	0,333	-0,333	1
26	0,231	0,111	0,333	-1	-1
27	0,231	0,111	0,333	0	0
28	0,231	0,111	0,333	0	0
29	0,231	0,111	0,333	0	0
30	-1	1	-1	1	-1
31	1	1	-1	1	1
32	-1	-1	1	1	-1

Table S1 DoE Optimization D-optimal: a) design summary, b) design experiments matrix.

Exp No	Run Order	Concentration (2a) [M]	Temperature °C	Time hours	Loading mg/mL	Stochiometry (1a)	Yield
1	21	0,1	25	2	1	2	6
5	8	0,1	35	2	7	4	58
7	9	0,1	70	2	10	2	92
8	11	0,1	70	2	1	4	29
30	23	0,1	70	2	10	2	84
11	5	0,1	25	4	10	3,33	53
25	12	0,1	70	6	4	4	65
14	28	0,1	25	8	10	2	57
15	14	0,1	25	8	1	4	22
18	3	0,1	70	8	1	2	22
32	30	0,1	25	8	10	2	51
2	26	0,25	25	2	4	4	24
24	1	0,25	35	6	1	2,66667	15
19	25	0,25	70	8	10	4	65
4	7	0,5	25	2	10	2,66667	37
12	29	0,5	70	4	7	2	68
26	31	0,5	50	6	1	2	20
17	22	0,5	35	8	10	4	48
27	4	0,5	50	6	5,5	3	58
28	24	0,5	50	6	5,5	3	66
29	13	0,5	50	6	5,5	3	60
31	2	0,75	70	2	10	4	73
3	15	0,75	25	2	1	3,33333	2
6	20	0,75	35	2	10	2	37
9	32	0,75	70	2	1	2	11
10	17	0,75	70	2	10	4	72
13	10	0,75	50	4	1	4	12
23	27	0,75	25	6	10	4	41
16	16	0,75	25	8	1	2	3
20	6	0,75	70	8	10	2	80
21	18	0,75	70	8	1	4	18
22	19	0,75	50	8	5,5	3	56

Table S2 DoE optimization D-optimal. Experimental and centre points are in blue and green, respectively.

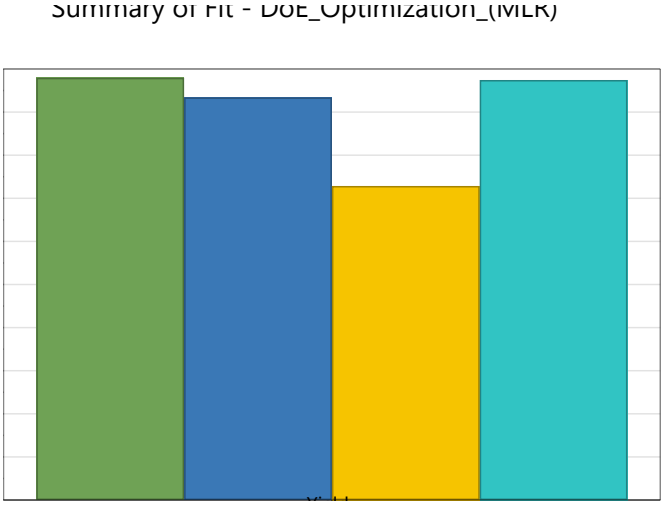


Figure S5 Summary of fit for DoE optimization. Reproducibility is calculated from the standard deviation of the replicated centre points. N = Number of runs, R^2 = goodness of regression model, RSD = residual standard deviation, DF = degrees of freedom, Q^2 = goodness of model prediction.

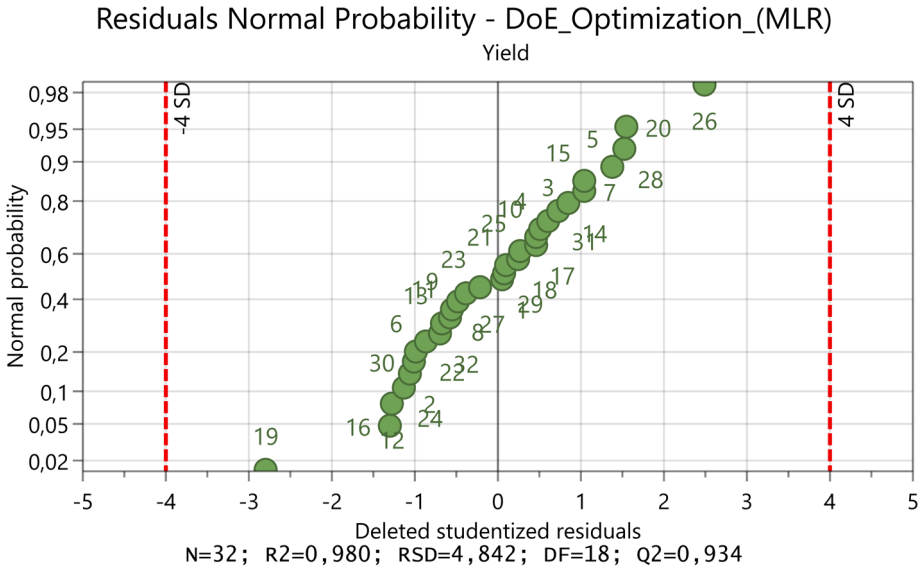


Figure S6 Residuals normal probability plot. In this plot, residuals are plotted on a cumulative probability scale. In the case of normally distributed residuals, the points, each representing an experiment, are scattered close to a straight line. If outliers are present, they deviate from the normal probability line. Red lines indicate four standard deviations.

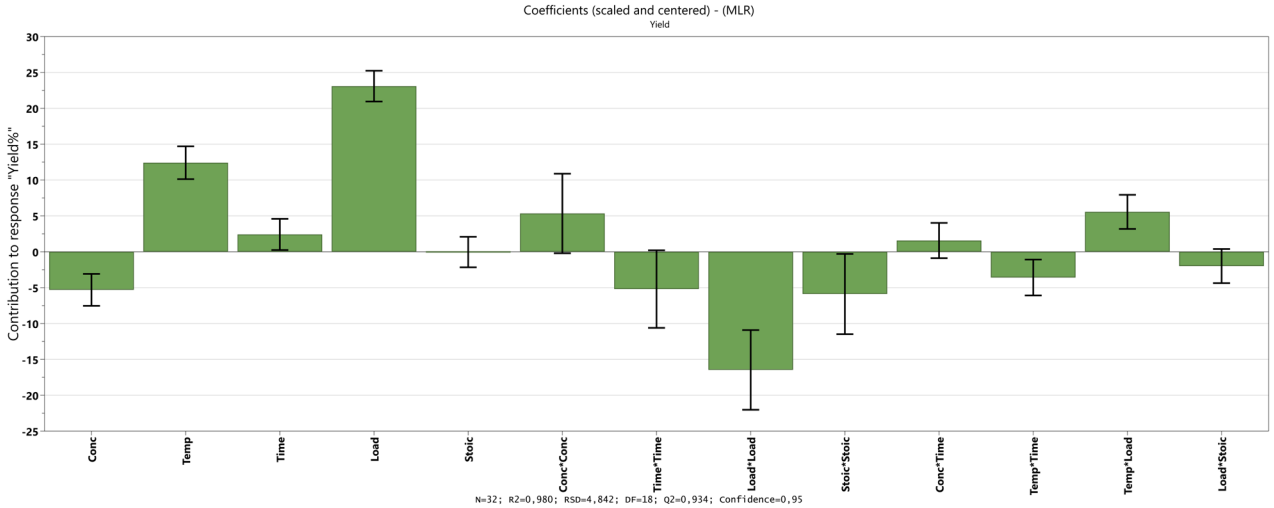


Figure S7 Scaled and centred regression factors calculated from D-Optimal design. Bars with large values have a higher contribution to the response ("Yield%"). A bar with a positive amplitude indicates a factor with a positive influence. On the contrary, a bar with a negative amplitude denotes a factor with a diminishing effect on the response. If a factor regression coefficient has an associated error bar greater than its value, the factor is not significant at the chosen confidence level (specifically, 95%).

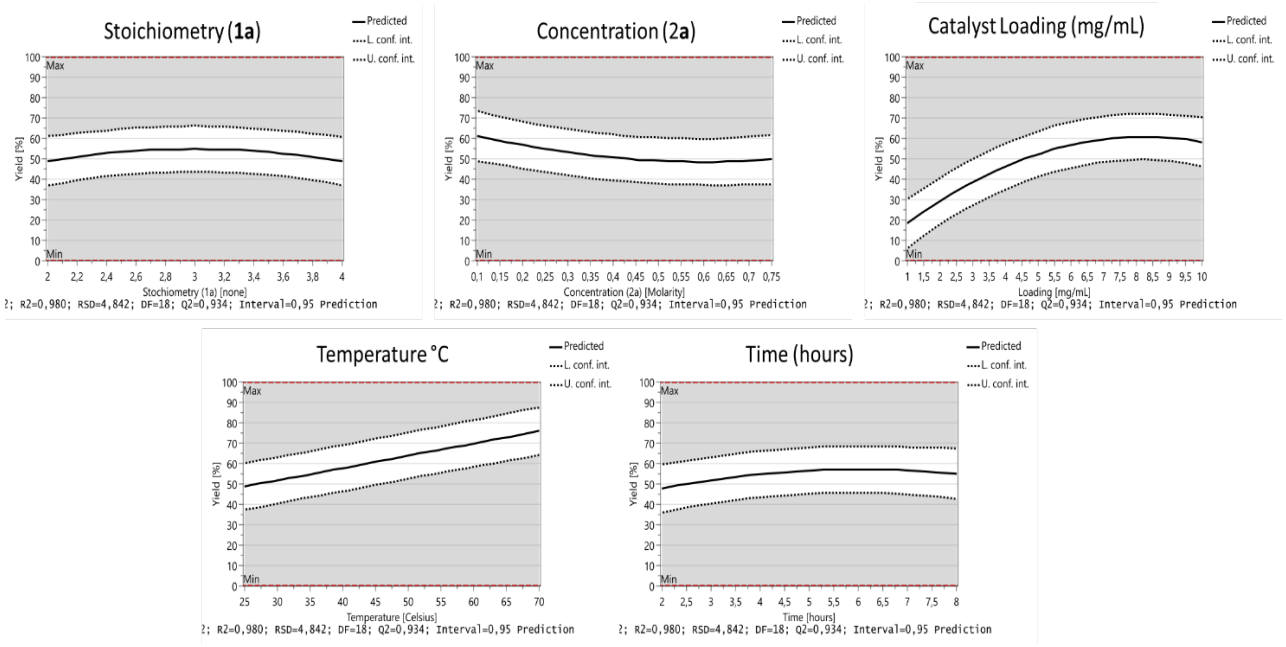


Figure S8 Factor effect plot for the 5 factors under investigation. The plot displays the predicted value of the selected response ("Yield%") when the factor varies over its range.

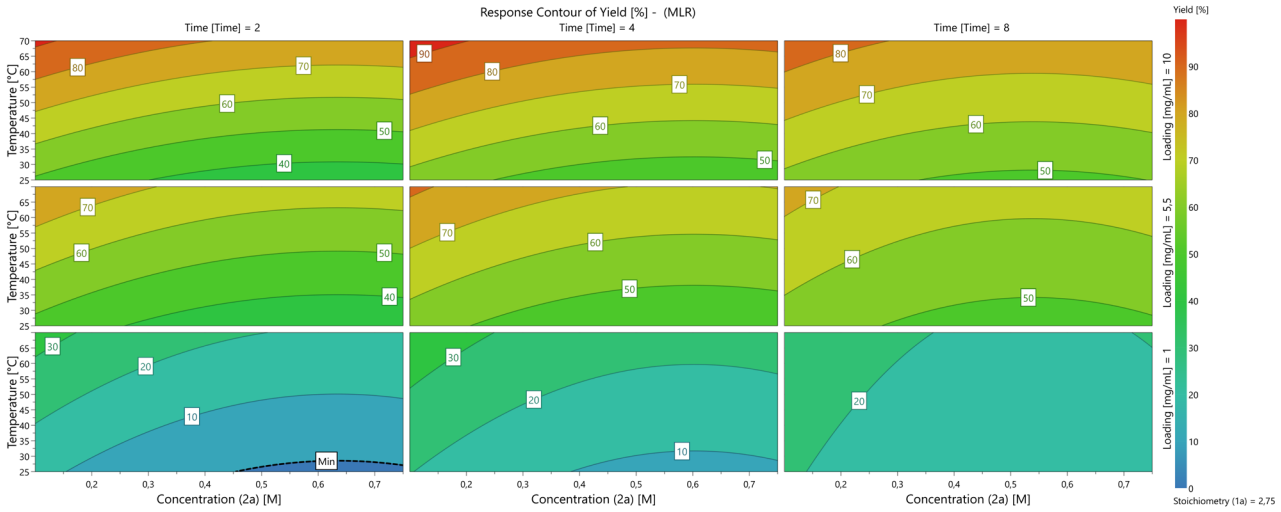


Figure S9 4D-Response contour. Contour plots display the predicted response value for the selected response spanned by two factors (temperature and concentration) in 9-response surface contour plots arranged in a 3x3 grid and spanned by another two factors (time and loading). Stoichiometry (**1a**) = 2.75 equivalents.

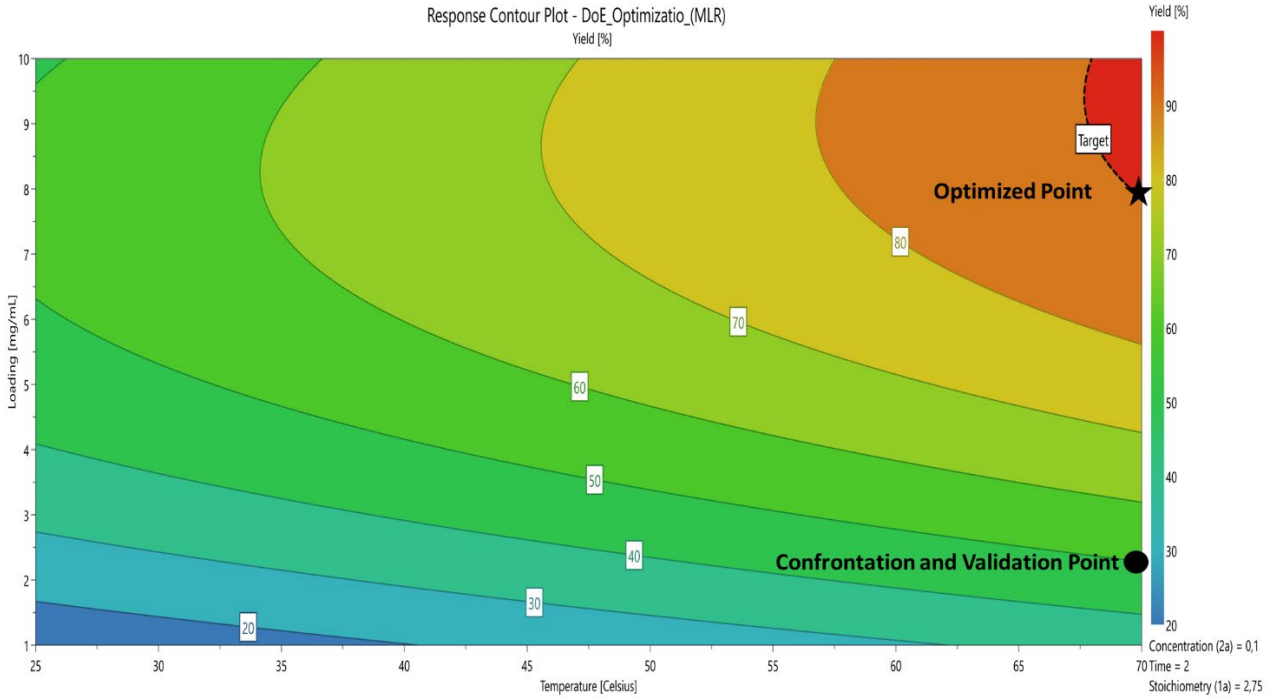


Figure S10 2D-Response contour. Contour plots display the predicted response value for the selected response ("Yield%") over two factors (x-axis= temperature; y-axis= catalyst loading). Stoichiometry (**1a**) = 2.75 equivalents, reaction time = 2 hours, concentration (**2a**) = 0.1 M. The confrontation and optimized points are marked by a black dot and star, respectively.

2.4 Calculation Production Rate

$$Production\ Rate = \frac{(mmol)product\ 3a}{g\ Catalyst * Time\ hours}$$

Equation S1 Equation for calculation of production rate for heterogeneous catalyst.

	Catalyst	*Limiting reagent **(2a)***	*Time (hours)*	*Catalyst (mg)*	*Yield%*	*Production rate mmol $g^{-1}h^{-1}$*
Literature[1]	Nanocomposite of MoS_2-RGO	0.5 mmol	2	55	97	4.40
This work	MoS2-50ºC-vac	0.1 mmol	2	8	95	5.93

Table S3. Confrontation of production rate.

3. Characterization of Commercial Bulk 2H-MoS_2, MoS_2-50ºC-vac, and the Recycled Catalyst

3.1 General Characterization of Commercial Bulk 2H-MoS_2

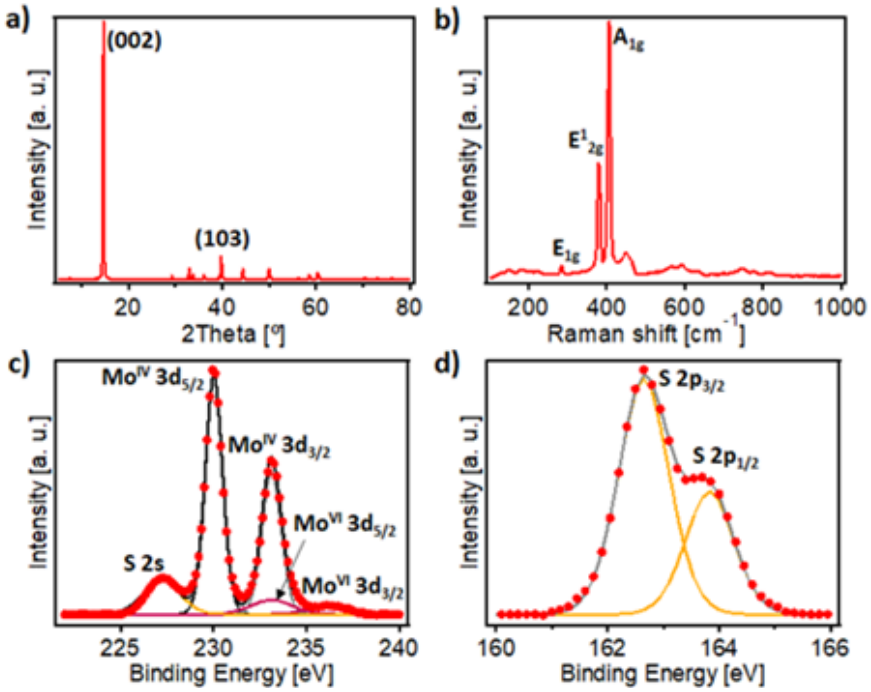


Figure S11 a) PXRD diffractogram of commercial bulk 2H-MoS_2. **b**) Raman spectrum of commercial bulk 2H-MoS_2 at 532 nm. **c**) Mo 3d XPS spectrum of commercial bulk 2H-MoS_2. **d**) S 2p XPS spectrum of commercial bulk 2H-MoS_2

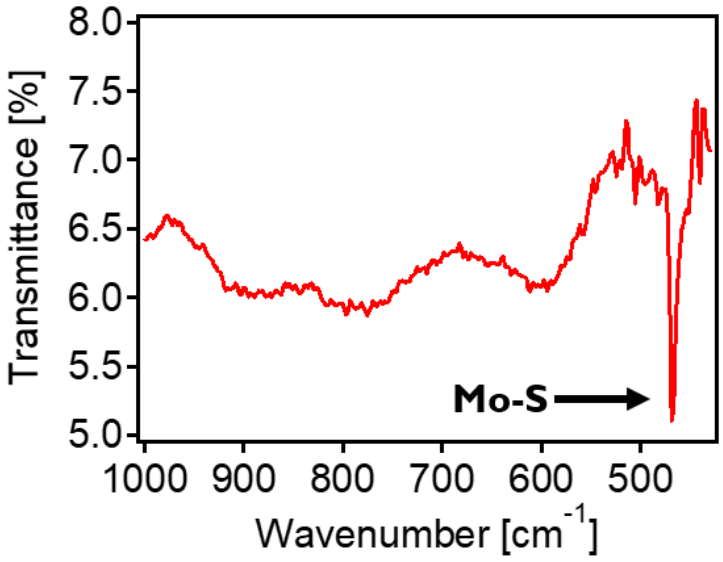


Figure S12 ATR-FTIR spectrum of commercial bulk MoS_2.

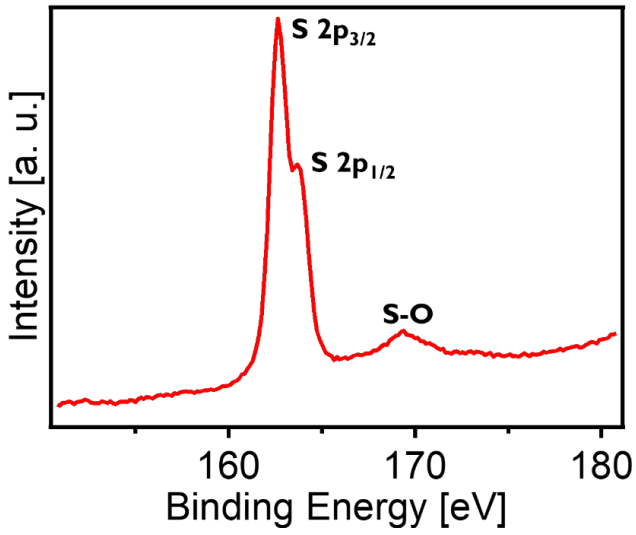


Figure S13 S 2p XPS spectrum of commercial bulk 2H-MoS_2 showing the S-O contribution

3.2 PXRD and ATR-FTIR Characterization of Bulk 2H-MoS_2 and MoS_2-50ºC-vac

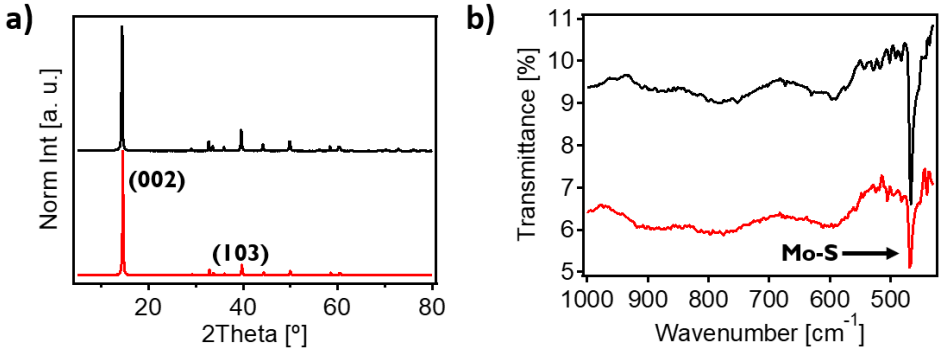


Figure S14 a) Normalized PXRD diffractograms of commercial bulk MoS_2 and MoS_2-50ºC-vac. **b)** ATR-FTIR spectrum of MoS_2-50ºC-vac.

3.3 Chemical Composition of Commercial Bulk 2H-MoS_2 and MoS_2-50ºC-vac

Materials	Core level	Atomic %
Commercial bulk 2H-MoS_2	Mo 3d	13.1
	S 2p	22.1
	C 1s	39.8
	O 1s	25.0
MoS_2-50ºC-vac	Mo 3d	15.9
	S 2p	27.1
	C 1s	43.8
	O 1s	13.2

Table S4. Atomic percentages of commercial bulk MoS_2 and MoS_2-50ºC-vac obtained from the XPS survey spectra.

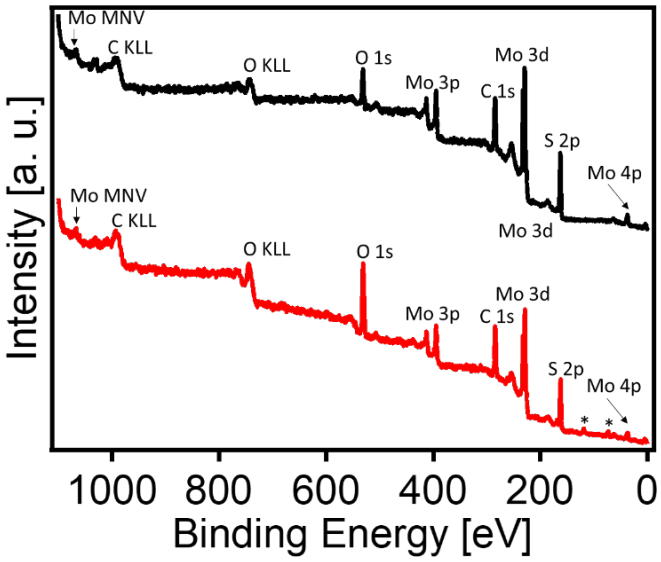


Figure S15 XPS survey spectra of commercial bulk 2H-MoS_2 (in red) and MoS_2-50ºC-vac (in black).

3.4 Characterization of the Recycled Catalyst

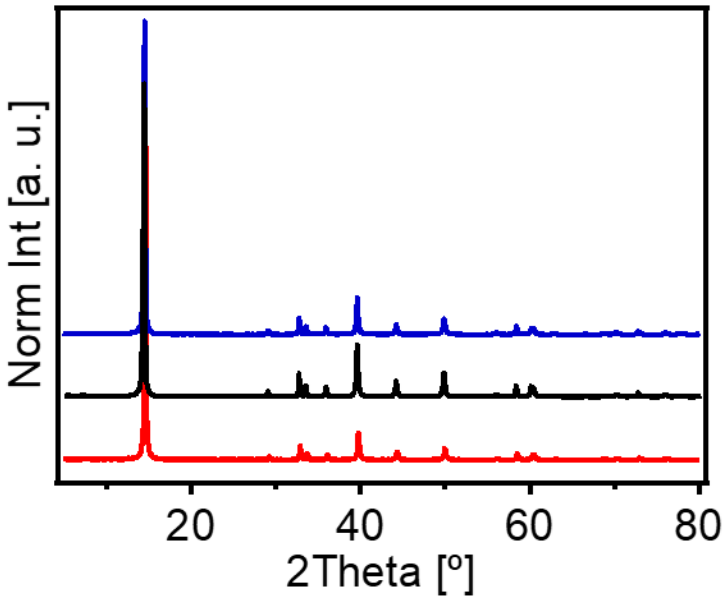


Figure S16 Normalized PXRD diffractograms of commercial bulk 2H-MoS_2 (in red), MoS_2-50ºC-vac (in black), and the recycled catalyst (in blue).

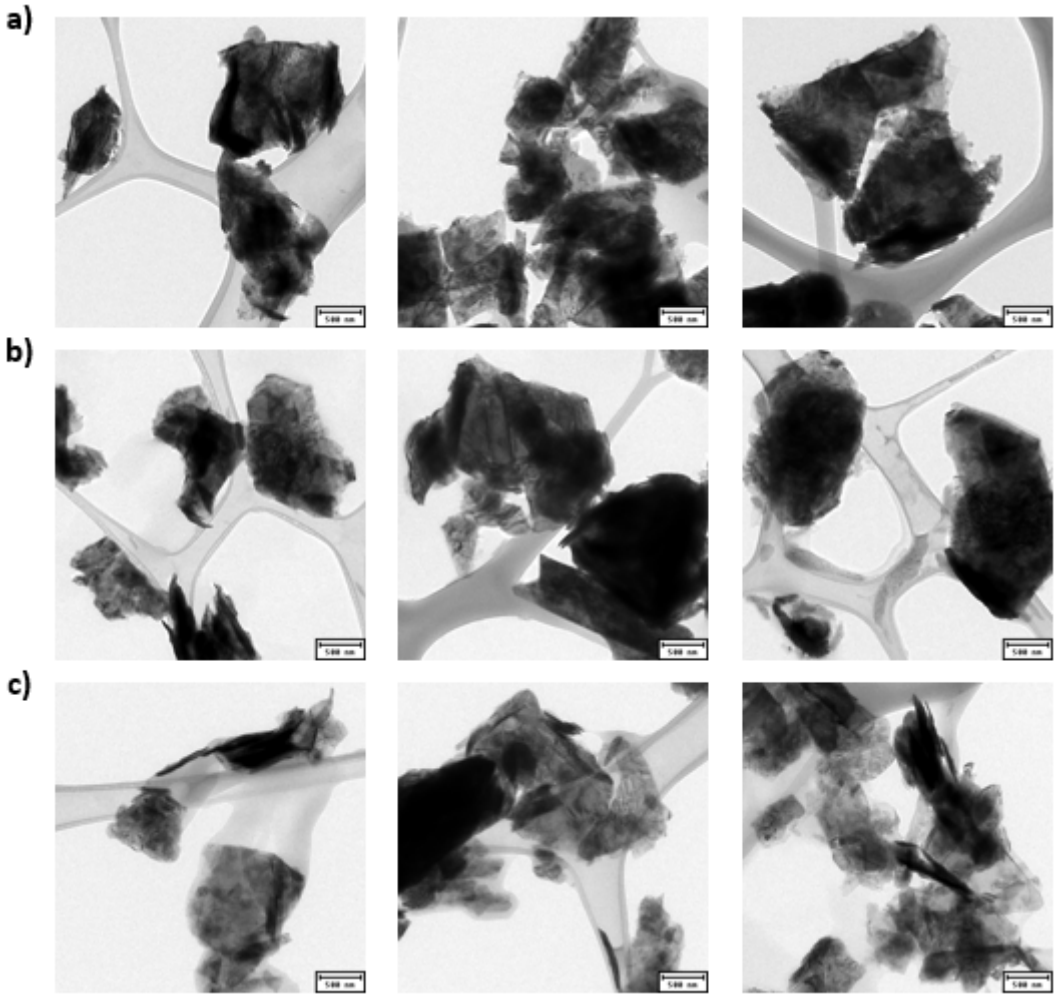


Figure S17 TEM images of a) commercial bulk 2H-MoS_2, b) MoS_2-50ºC-vac, and c) the recycled catalyst. Scale bar = 500 nm.

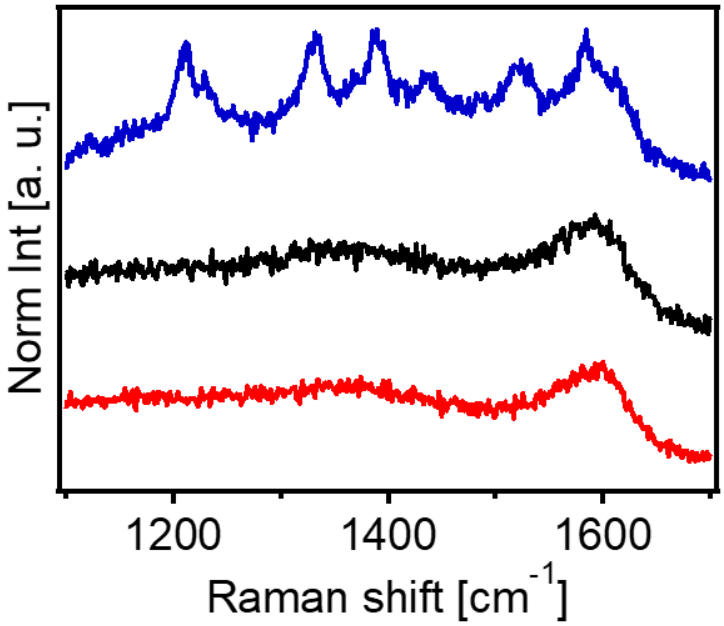
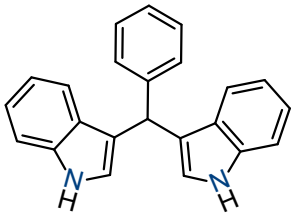
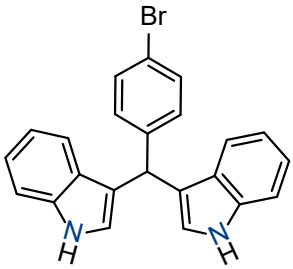


Figure S18. Normalized Raman plots of bulk 2H-MoS_2 (red), MoS_2-50ºC-vac (black), and the recycled catalyst (blue). The loss of the catalytic performance of MoS_2-50ºC-vac after its reutilization is probably due to the adsorption of organic molecules (for instance: the product **3a** after the first catalytic cycle and both reagents **1a** and **2a** and product **3a** after second cycle) onto MoS_2 surface. The presence of these organic molecules may poison the catalyst.

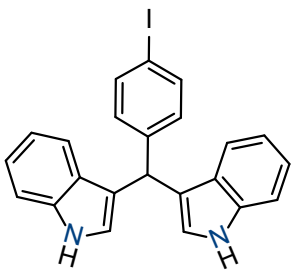
4. Characterization of products 3: NMR Spectra



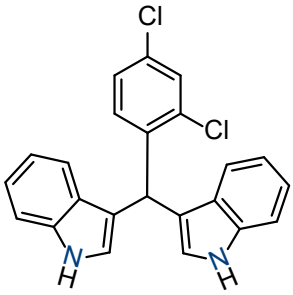
3,3'-(phenylmethylene)bis(1H-indole) (3a) Prepared according to the general procedure using indole **1a** (0.275 mmol, 32.2 mg) and benzaldehyde **2a** (0.1 mmol, 10.6 mg). The product **3a** was obtained as white solid. NMR Yield: 95%
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.43 – 7.38 (m, 2H), 7.38 – 7.32 (m, 4H), 7.32 – 7.26 (m, 2H), 7.25 – 7.15 (m, 3H), 7.02 (m, 2H), 6.63 (dd, *J* = 2.3, 0.9 Hz, 2H), 5.90 (s, 1H).
^{13}C-NMR: (101 MHz, $CDCl_3$): δ 143.99, 136.66, 128.71, 128.21, 127.06, 126.13, 123.61, 121.91, 119.92, 119.68, 119.22, 111.03, 40.19.
The characterization data matched with the reported one.[1]



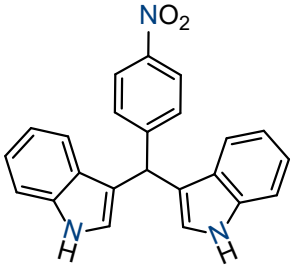
3,3'-((4-chlorophenyl)methylene)bis(1H-indole) (3b) Prepared according to the general procedure using indole **1a** (0.275 mmol, 32.2 mg) and 4-chlorobenzaldehyde **2b** (0.1 mmol, 14.0 mg). The product **3b** was obtained as white solid. NMR Yield: >99%
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 2H), 7.45 – 7.32 (m, 6H), 7.25 – 7.14 (m, 4H), 7.04 (m, 2H), 6.60 (dd, *J* = 2.4, 0.9 Hz, 2H), 5.85 (s, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.41, 137.00, 131.64, 130.82, 127.18, 123.94, 122.41, 120.25, 120.13, 119.69, 119.41, 111.45, 40.01.
The characterization data matched with the reported one.[2]



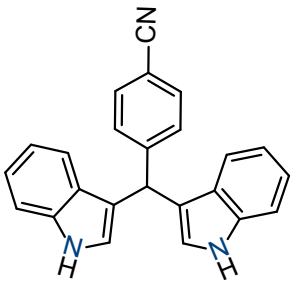
3,3'-((4-iodophenyl)methylene)bis(1H-indole) (3c) Prepared according to the general procedure using indole **1a** (0.275 mmol, 32.2 mg) and 4-iodobenzaldehyde **2c** (0.1 mmol, 23.2 mg). The product **3c** was obtained as white solid. NMR Yield: >99%
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 2H), 7.65 – 7.57 (m, 2H), 7.36 (m, 4H), 7.18 (m, 2H), 7.14 – 7.07 (m, 2H), 7.02 (m, 2H), 6.63 (dd, *J* = 2.4, 0.9 Hz, 2H), 5.83 (s, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.77, 137.27, 136.65, 130.83, 126.84, 123.58, 122.08, 119.79, 119.35, 119.04, 111.08, 91.44, 39.77.
The characterization data matched with the reported one.[3]



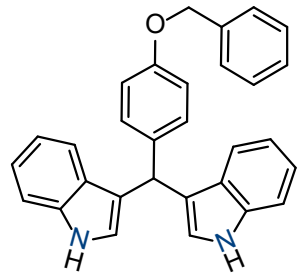
3,3'-((2,4-dichlorophenyl)methylene)bis(1H-indole) (3d) Prepared according to the general procedure using indole **1a** (0.275 mmol, 32.2 mg) and 2,4-dichlorobenzaldehyde **2d** (0.1 mmol, 17.5 mg). The product **3d** was obtained as white solid. NMR Yield: 82%
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 2H), 7.46 (d, *J* = 2.1 Hz, 1H), 7.43 – 7.33 (m, 4H), 7.24 – 7.12 (m, 3H), 7.11 – 7.00 (m, 3H), 6.60 (m, 2H), 6.29 (s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 140.03, 136.70, 134.59, 132.42, 131.15, 129.26, 126.94, 126.79, 123.74, 122.17, 119.71, 119.44, 117.81, 111.14, 36.33.
The characterization data matched with the reported one.[4]



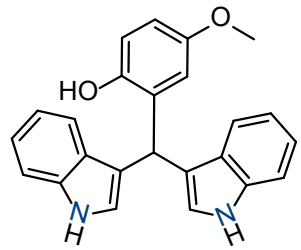
3,3'-((4-nitrophenyl)methylene)bis(1H-indole) (3e) Prepared according to the general procedure using indole **1a** (0.275 mmol, 32.2 mg) and 4-nitrobenzaldehyde **2e** (0.1 mmol, 15.1 mg). The product **3e** was obtained as yellow solid. NMR Yield: 92%
^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.20 – 8.09 (m, 2H), 8.00 (s, 2H), 7.59 – 7.47 (m, 2H), 7.44 – 7.30 (m, 4H), 7.20 (m, 2H), 7.09 – 7.00 (m, 2H), 6.69 (dd, *J* = 2.5, 1.1 Hz, 2H), 6.00 (s,1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ 151.8, 146.4, 136.6, 129.50, 126.6, 123.6, 122.3, 119.6, 119.5, 118.1, 111.2, 110.0, 40.2.
The characterization data matched with the reported one.[1]



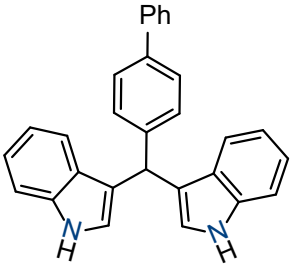
3,3'-((4-cyanophenyl)methylene)bis(1H-indole) (3f) Prepared according to the general procedure using indole **1a** (0.275 mmol, 32.2 mg) and 4-cyanobenzaldehyde **2f** (0.1 mmol, 13.1 mg). The product **3f** was obtained as white solid. NMR Yield: >99%
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 2H), 7.63 – 7.54 (m, 2H), 7.49 – 7.42 (m, 2H), 7.35 (m, 4H), 7.20 (m, 2H), 7.09 – 6.96 (m, 2H), 6.66 (m, 2H), 5.94 (s, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ 149.71, 136.67, 132.17, 129.50, 126.68, 123.64, 122.29, 119.58, 119.55, 119.17, 118.23, 110.02, 40.35.
The characterization data matched with the reported one.[1]



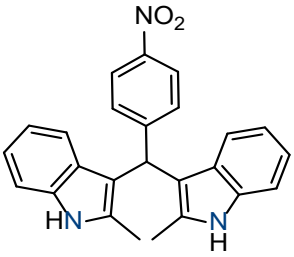
3,3'-((4-(benzyloxy)phenyl)methylene)bis(1H-indole) (3g) Prepared according to the general procedure using indole **1a** (0.275 mmol, 32.2 mg) and 4-(benzyloxy)benzaldehyde **2g** (0.1 mmol, 21.2 mg). The product **3g** was obtained as white solid. NMR Yield: >99%
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.85 (s, 2H), 7.47 – 7.31 (m, 9H), 7.29 – 7.24 (m, 2H), 7.17 (m, 2H), 7.01 (m, 2H), 6.94 – 6.87 (m, 2H), 6.63 (m, 2H), 5.85 (s, 1H), 5.03 (s, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ 157.21, 137.22, 136.68, 136.50, 129.62, 128.53, 127.89, 127.56, 127.05, 123.51, 121.88, 120.00, 119.97, 119.18, 114.49, 111.00, 70.04, 39.34.



3,3'-((2-Hydroxy-5-methoxyphenyl)methylene)bis(1H-indole) (3h) Prepared according to the general procedure using Indole **1a** (0.275 mmol, 32.2 mg) and 2-Hydroxy-5-methoxybenzaldehyde **2h** (0.1 mmol, 15.2 mg). The product **3h** was obtained as white solid. NMR Yield: 87%
^{1}H-NMR (499 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.42 (d, *J* = 7.9 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.23 – 7.15 (m, 2H), 7.03 (m, 2H), 6.82 – 6.68 (m, 5H), 5.96 (s, 1H), 5.06 (s, 1H), 3.67 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ 153.61, 148.40, 136.84, 130.37, 126.79, 123.63, 122.31, 119.83, 119.55, 117.21, 116.98, 115.84, 112.51, 111.21, 55.60, 36.02.

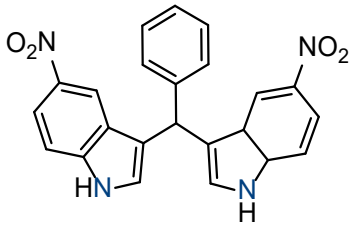


3,3'-([1,1'-biphenyl]-4-ylmethylene)bis(1H-indole) (3i) Prepared according to the general procedure using Indole **1a** (0.275 mmol, 32.2 mg) and 4-phenylbenzaldehyde **2i** (0.1 mmol, 18.2 mg). The product **3i** was obtained as white solid. NMR Yield: 95%.
^{1}H-NMR (499 MHz, $CDCl_3$): δ 7.89 (s, 2H), 7.64 – 7.57 (m, 2H), 7.57 – 7.50 (m, 2H), 7.49 – 7.39 (m, 6H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.24 – 7.17 (m, 2H), 7.03 (m, 2H), 6.77 – 6.69 (m, 2H), 5.94 (s, 1H).
^{13}C-NMR (126 MHz, $CDCl_3$): δ 143.14, 141.06, 138.86, 136.69, 129.09, 128.68, 127.06, 126.97, 126.96, 126.91, 123.61, 121.96, 119.95, 119.62, 119.26, 111.03, 39.86.
The characterization data matched with the reported one.[5]



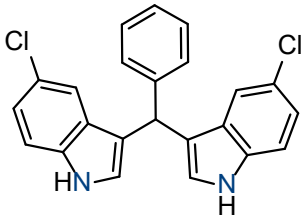
3,3'-((4-nitrophenyl)methylene)bis(2-methyl-1H-indole) (3j) Prepared according to the general procedure using 2-Methylindole **1b** (0.275 mmol, 36.0 mg) and 4-nitrobenzaldehyde **2e** (0.1 mmol, 15.1 mg). The product **3j** was obtained as yellow solid. NMR Yield: >99%

^{1}H-NMR (499 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.7 Hz, 2H), 7.81 (s, 2H), 7.47 – 7.40 (m, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.07 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 2H), 6.97 – 6.84 (m, 4H), 6.06 (s, 1H), 2.09 (s, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ 152.01, 146.34, 135.07, 132.12, 129.83, 128.42, 123.42, 121.02, 119.43, 118.96, 111.84, 110.25, 39.39, 26.92.
The characterization data matched with the reported one.[6]



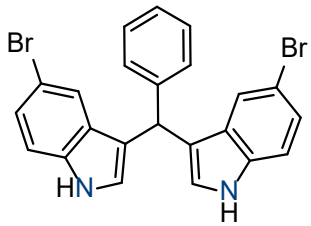
3,3'-(phenylmethylene)bis(5-nitro-1H-indole) (3k) Prepared according to the general procedure using 5-Nitroindole **1c** (0.275 mmol, 44.6 mg) and benzaldehyde **2a** (0.1 mmol, 10.6 mg). The product **3k** was obtained as light-yellow solid. NMR Yield: 45%
^{1}H-NMR (499 MHz, DMSO-d6): δ 11.66 (d, J = 2.4 Hz, 2H), 8.31 (d, J = 2.3 Hz, 2H), 7.96 (dd, J = 9.0, 2.3 Hz, 2H), 7.53 (d, J = 9.0 Hz, 2H), 7.42 – 7.37 (m, 2H), 7.31 (t, J = 7.4, 2H), 7.25 – 7.19 (m, 1H), 7.13 (dd, J = 2.4, 0.9 Hz, 2H), 6.19 (s, 1H).

^{13}C-NMR (126 MHz, DMSO-d6): δ 144.21, 140.65, 140.24, 128.90, 128.65, 128.04, 126.84, 126.23, 120.98, 117.06, 116.66, 112.56, 38.91.
The characterization data matched with the reported one.[1]



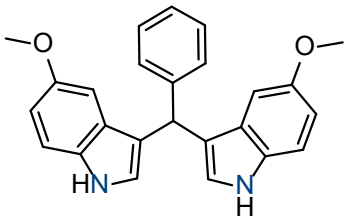
3,3'-(phenylmethylene)bis(5-chloro-1H-indole) (3l) Prepared according to the general procedure using 5-Chloroindole **1d** (0.275 mmol, 41.66 mg) and benzaldehyde **2a** (0.1 mmol, 10.6 mg). The product **3l** was obtained as white solid. NMR Yield: 65%

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.05 (d, *J* = 2.5 Hz, 2H), 7.38 – 7.32 (m, 4H), 7.31 – 7.25 (m, 4H), 7.23 – 7.14 (m, 1H), 7.02 (dd, *J* = 8.6, 2.1 Hz, 2H), 6.90 (dd, *J* = 2.5, 0.8 Hz, 2H), 5.84 (s, 1H).
^{13}C NMR (101 MHz, DMSO-*d6*) δ 144.79, 135.47, 128.66, 128.10, 126.49, 125.84, 123.32, 121.36, 118.61, 118.15, 113.55, 39.41.
The characterization data matched with the reported one.[1]



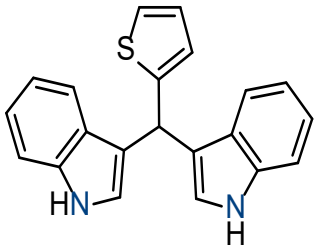
3,3'-(phenylmethylene)bis(5-chloro-1H-indole) (3m) Prepared according to the general procedure using 5-Bromoindole **1e** (0.275 mmol, 53.9 mg) and benzaldehyde **2a** (0.1 mmol, 10.6 mg). The product **3m** was obtained as white solid. NMR Yield: >99%

1H NMR (400 MHz, DMSO-*d6*) δ 11.06 (d, *J* = 2.5 Hz, 2H), 7.41 (d, *J* = 2.0 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 4H), 7.27 (dd, *J* = 8.5, 6.7 Hz, 2H), 7.21 – 7.15 (m, 1H), 7.14 (dd, *J* = 8.6, 2.0 Hz, 2H), 6.87 (dd, *J* = 2.5, 0.8 Hz, 2H), 5.84 (s, 1H).
^{13}C NMR (101 MHz, DMSO-*d6*) δ 144.77, 135.69, 128.81, 128.66, 128.65, 126.50, 125.68, 123.89, 121.64, 118.09, 114.04, 111.34, 39.32.
The characterization data matched with the reported one.[1]



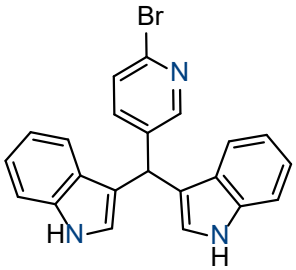
3,3'-(phenylmethylene)bis(5-methoxy-1H-indole) (3n) Prepared according to the general procedure using 5-Methoxyindole **1f** (0.275 mmol, 40.4 mg) and benzaldehyde **2a** (0.1 mmol, 10.6 mg). The product **3n** was obtained as white solid. NMR Yield: 80%

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.7 Hz, 1H), 7.94 (s, 1H), 7.53 – 7.44 (m, 1H), 7.36 – 7.18 (m, 2H), 6.86 (ddd, J = 8.8, 2.4, 0.4 Hz, 1H), 6.75 (d, J = 2.5 Hz, 1H), 6.65 (ddd, J = 2.6, 1.0, 0.4 Hz, 1H), 5.88 (s, 1H), 3.70 (s, 4H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ 153.94, 151.81, 146.51, 131.86, 129.51, 127.10, 124.50, 123.59, 117.64, 112.17, 111.96, 101.68, 55.89, 40.22.
The characterization data matched with the reported one.[1]



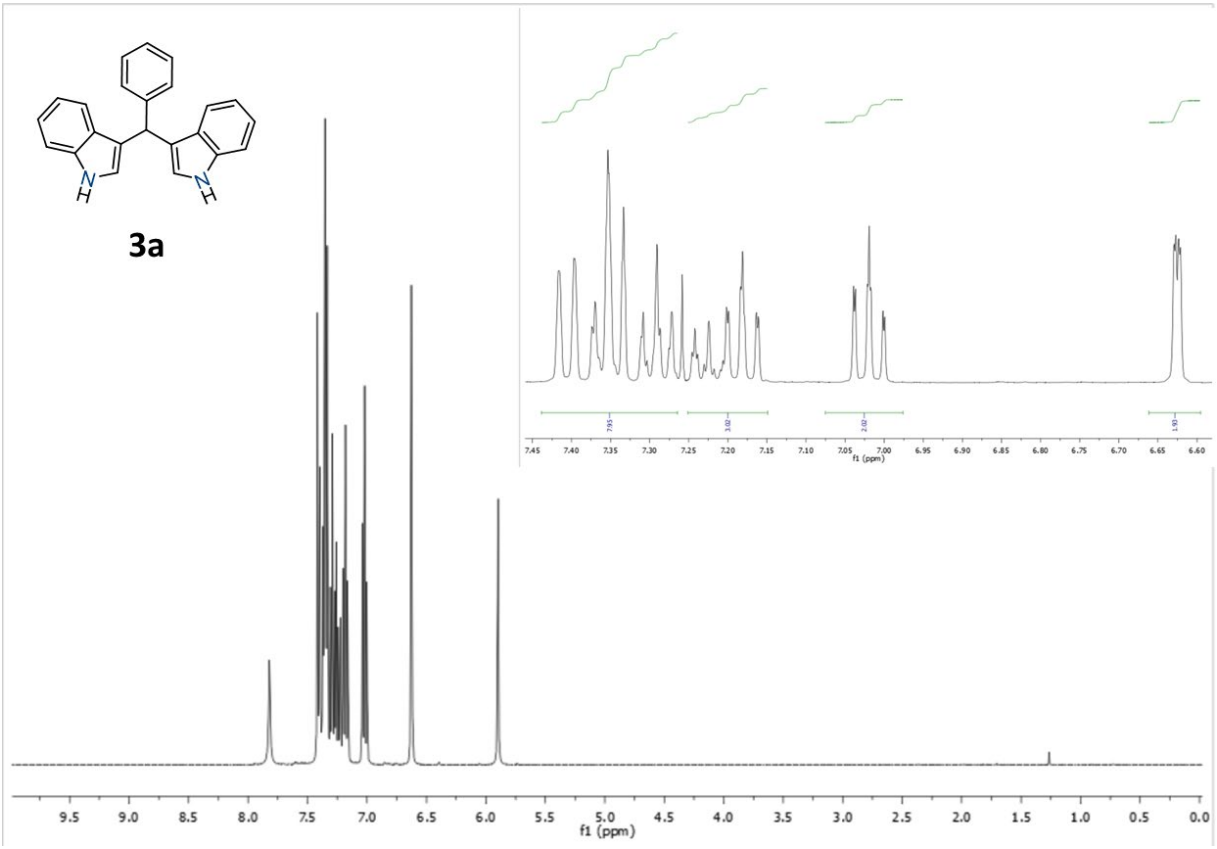
3,3'-(thiophen-2-ylmethylene)bis(1H-indole) (3o) Prepared according to the general procedure using 2-Thiophenecarboxaldehyde **2j** (0.1 mmol, 11.2 mg) and Indole **1a** (0.275 mmol, 32.2 mg). The product **3o** was obtained as white solid. NMR Yield: 78%

^{1}H-NMR (499 MHz, $CDCl_3$): δ 7.77 (s, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 7.23 – 7.17 (m, 3H), 7.11 – 7.04 (m, 2H), 7.00 – 6.89 (m, 2H), 6.76 (d, J = 2.3 Hz, 2H), 6.18 (s, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 148.62, 136.57, 126.75, 126.41, 125.13, 123.60, 123.16, 122.02, 119.76, 119.71, 119.36, 111.10, 35.31.
The characterization data matched with the reported one.[1]

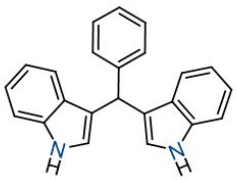


3,3'-((6-bromopyridin-3-yl)methylene)bis(1H-indole) (3p) Prepared according to the general procedure using 6-Bromo-3-pyridinecarboxaldehyde **2k** (0.1 mmol, 18.6 mg) and Indole **1a** (0.275 mmol, 32.2 mg). The product **3p** was obtained as white solid. NMR Yield: >99%

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 2H), 7.47 (dd, *J* = 7.9, 1.0 Hz, 2H), 7.42 – 7.32 (m, 2H), 7.22 – 7.13 (m, 3H), 7.04 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 2H), 6.98 – 6.89 (m, 2H), 6.82 (dd, *J* = 2.4, 1.0 Hz, 2H), 6.17 (s, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ 148.63, 136.56, 126.75, 126.42, 125.14, 123.61, 123.17, 122.02, 119.76, 119.70, 119.37, 111.11, 35.31.



3a



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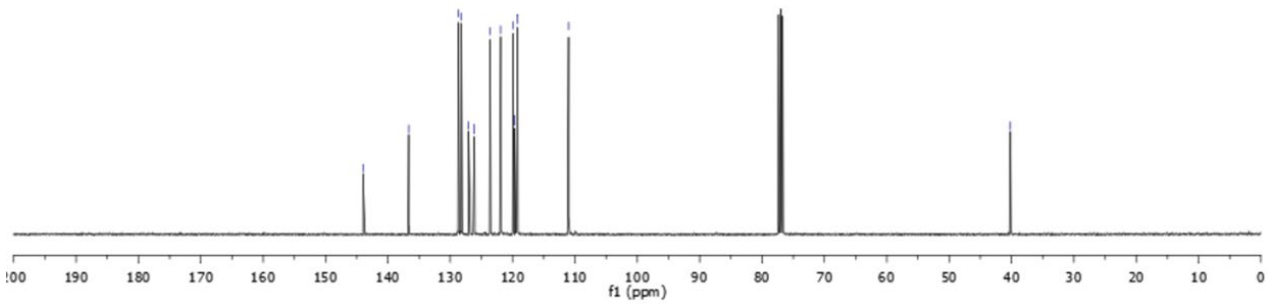
3a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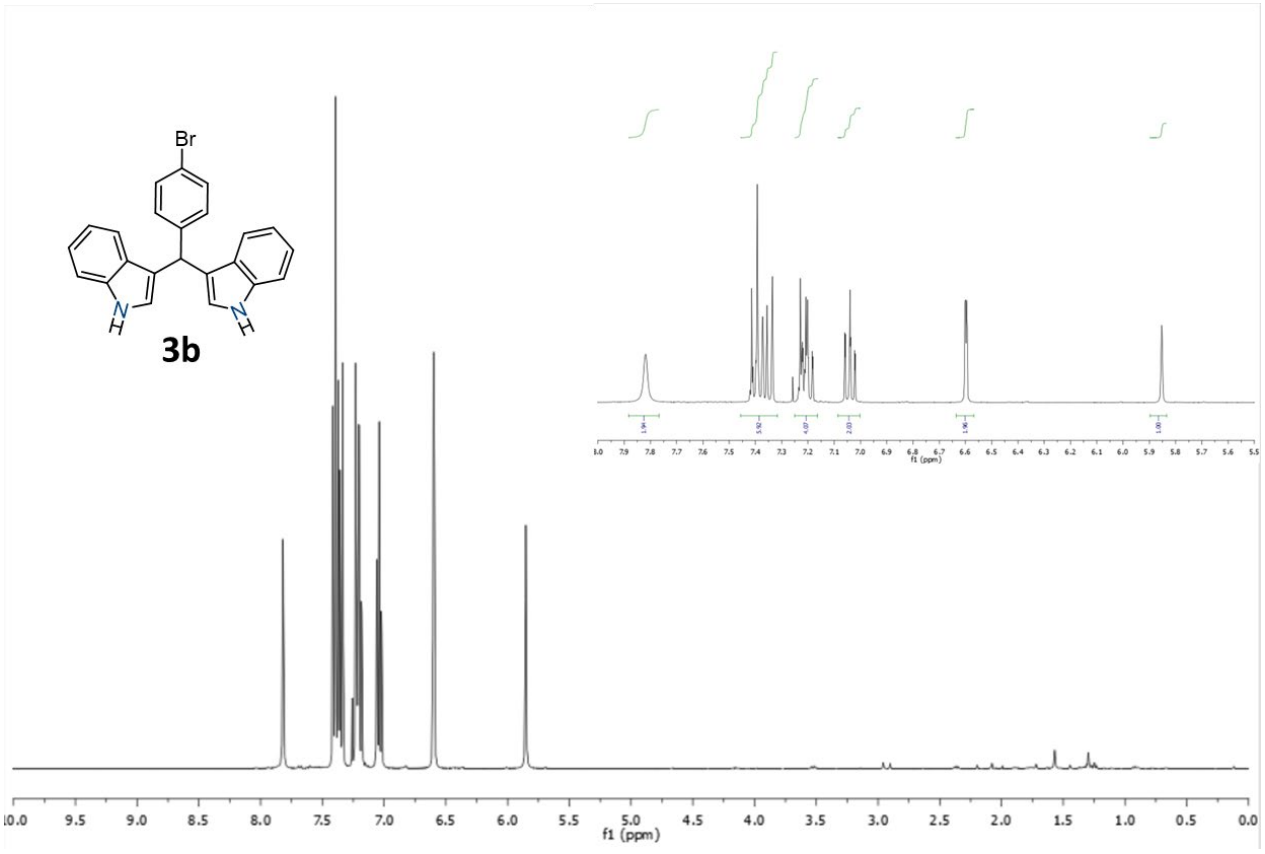
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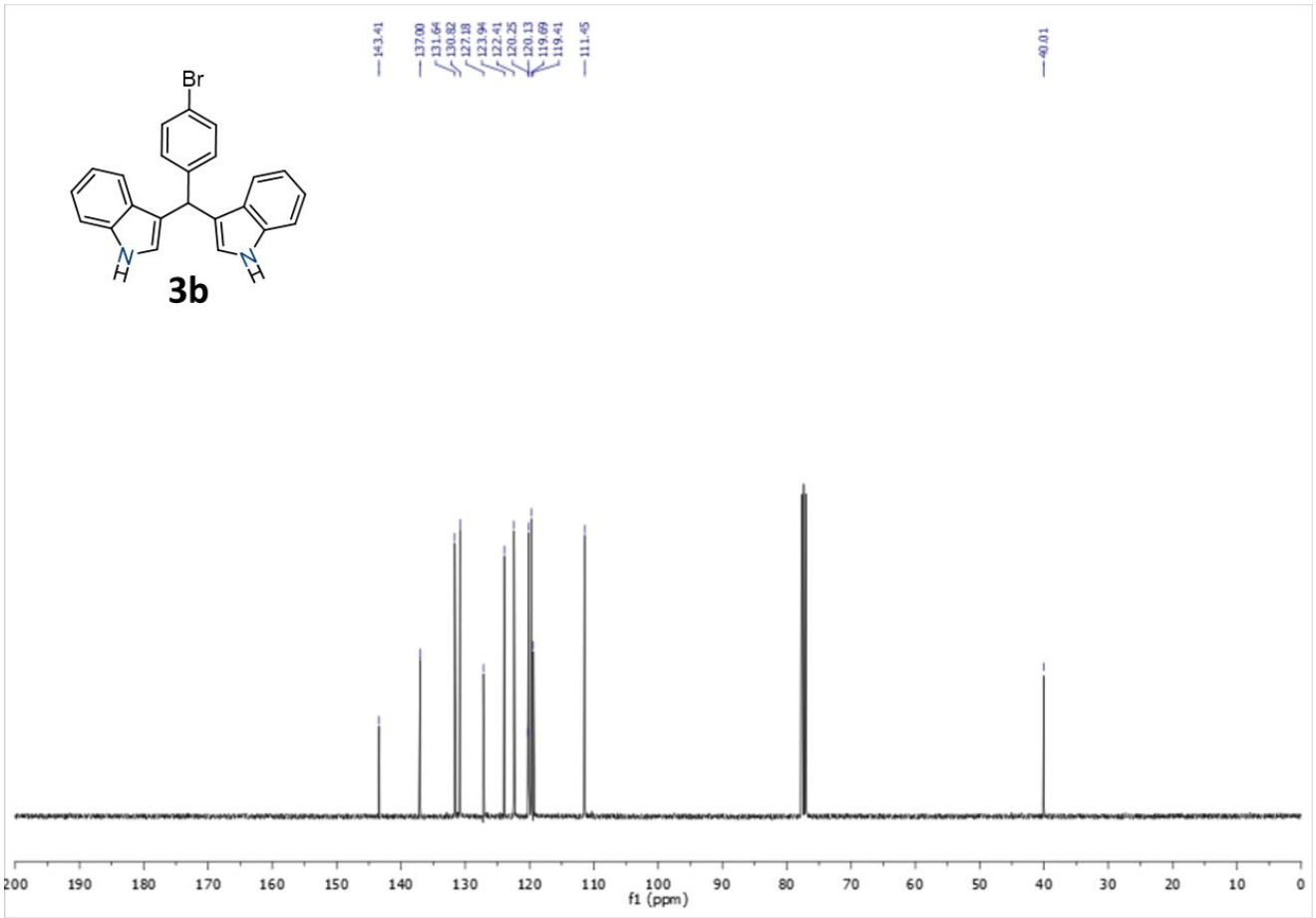
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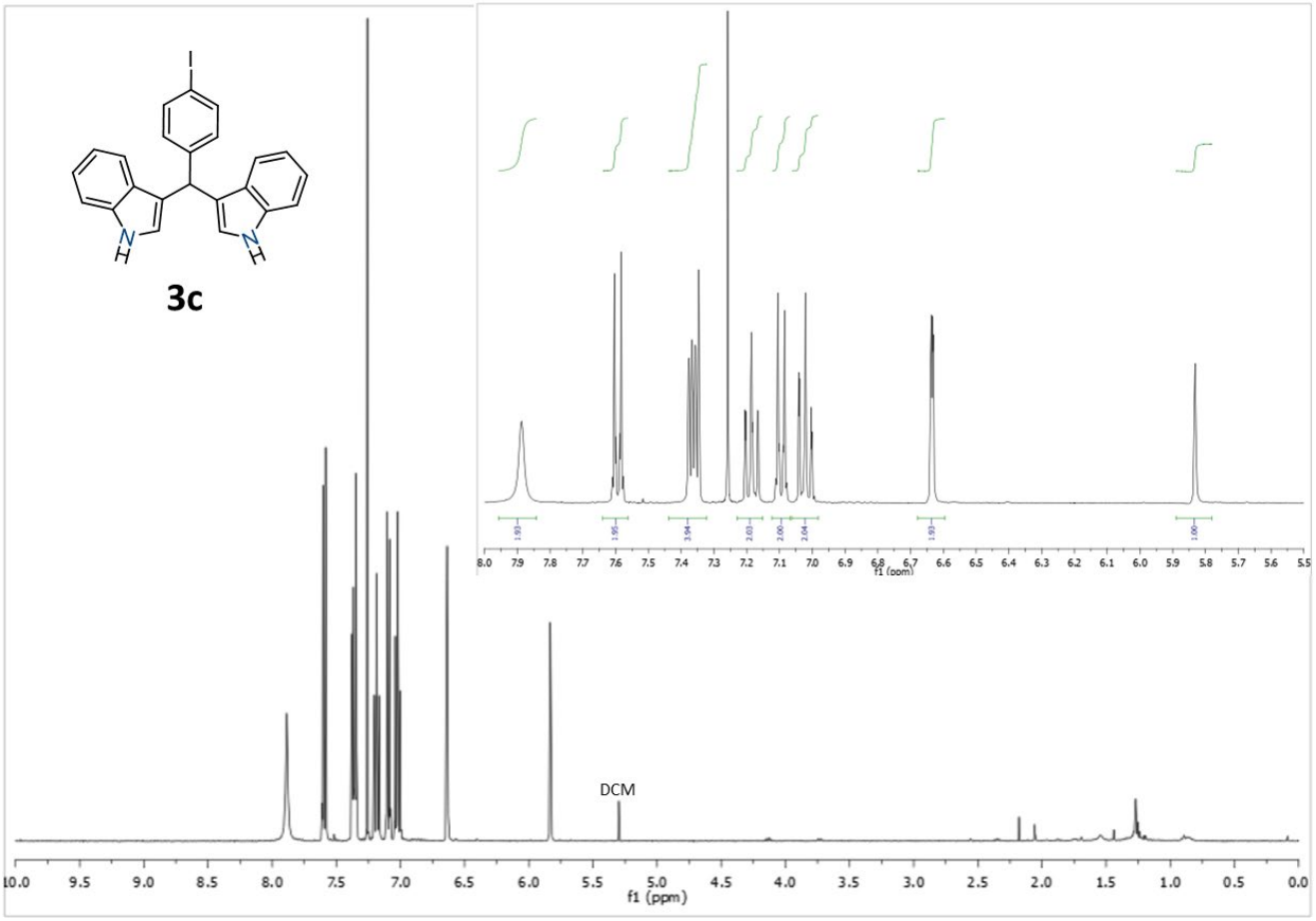
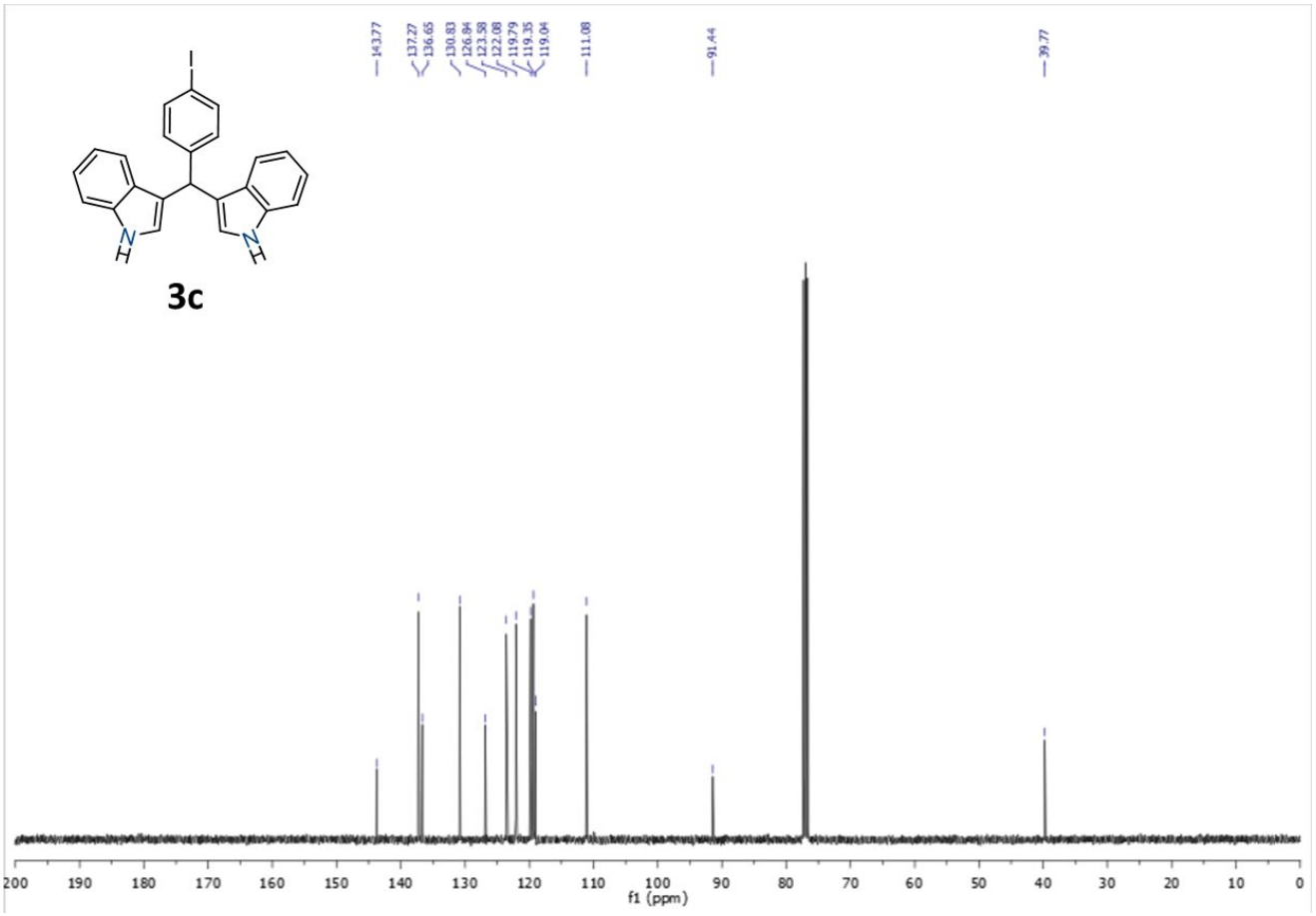
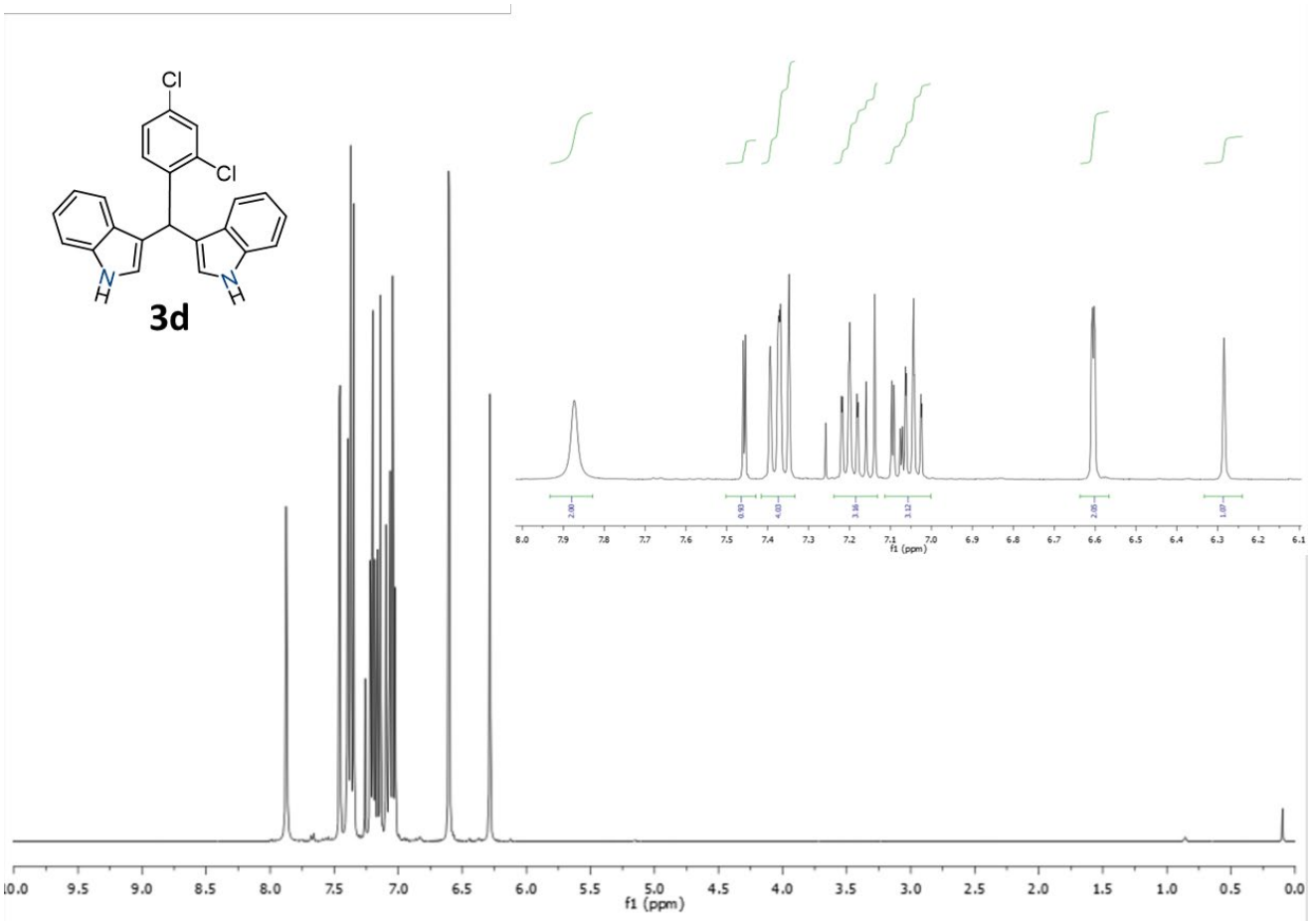
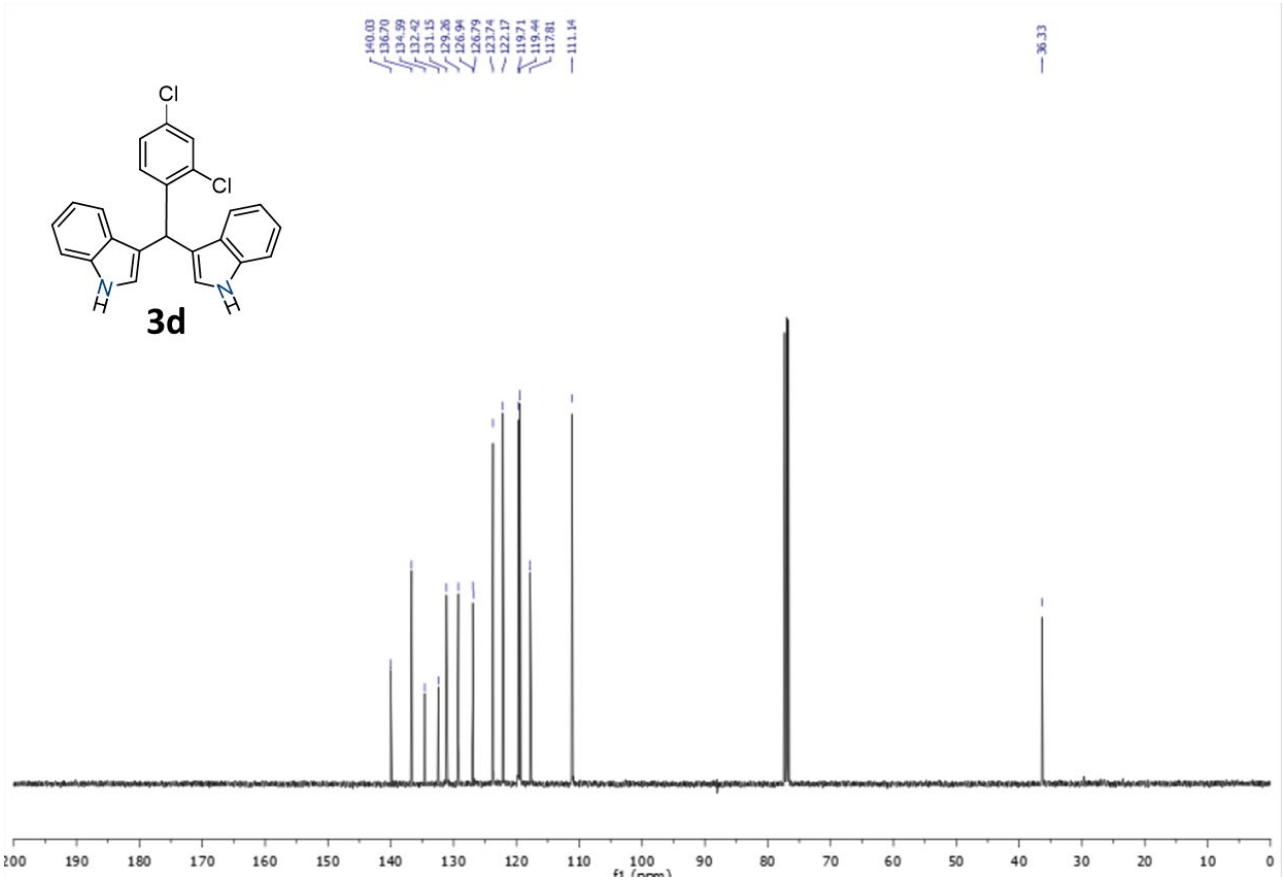
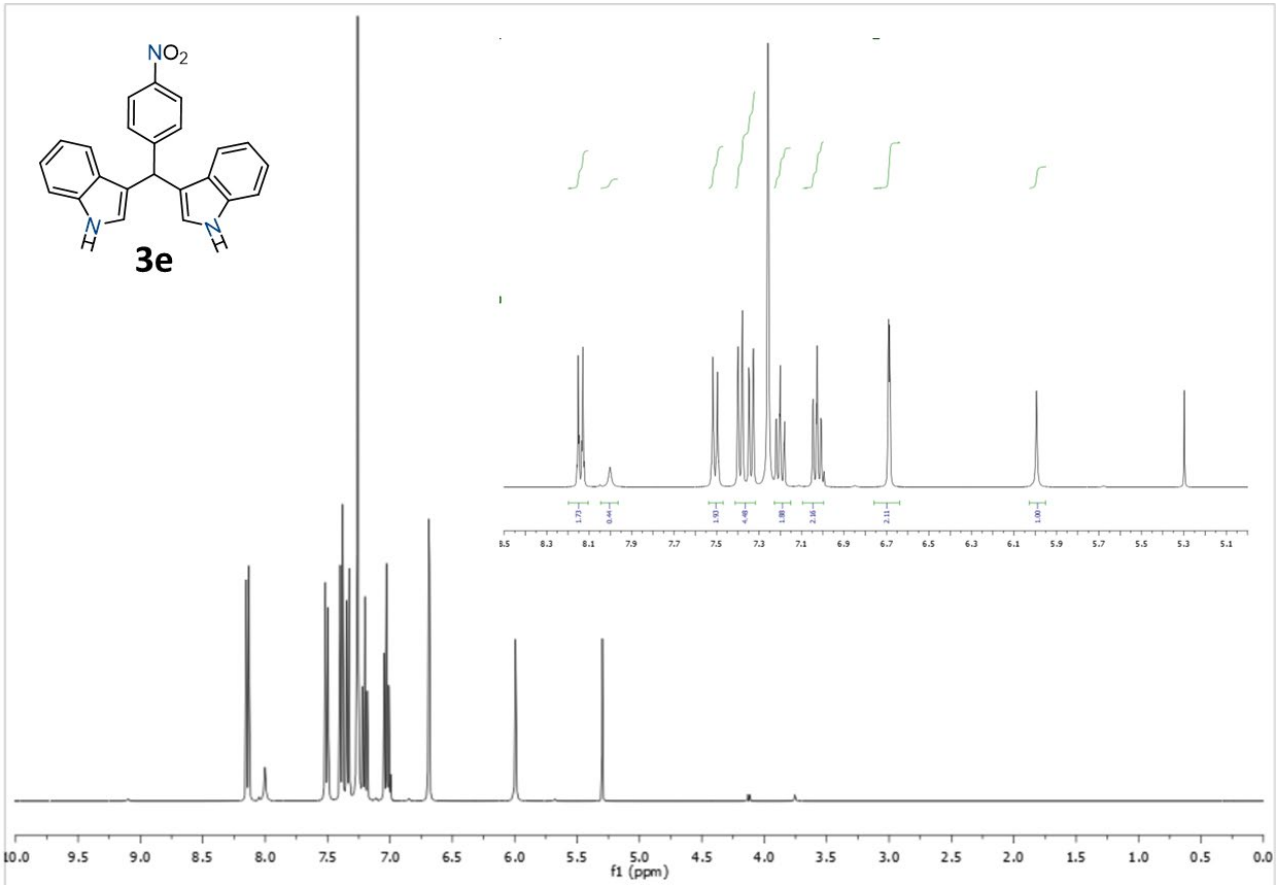
3b
f1 (ppm)

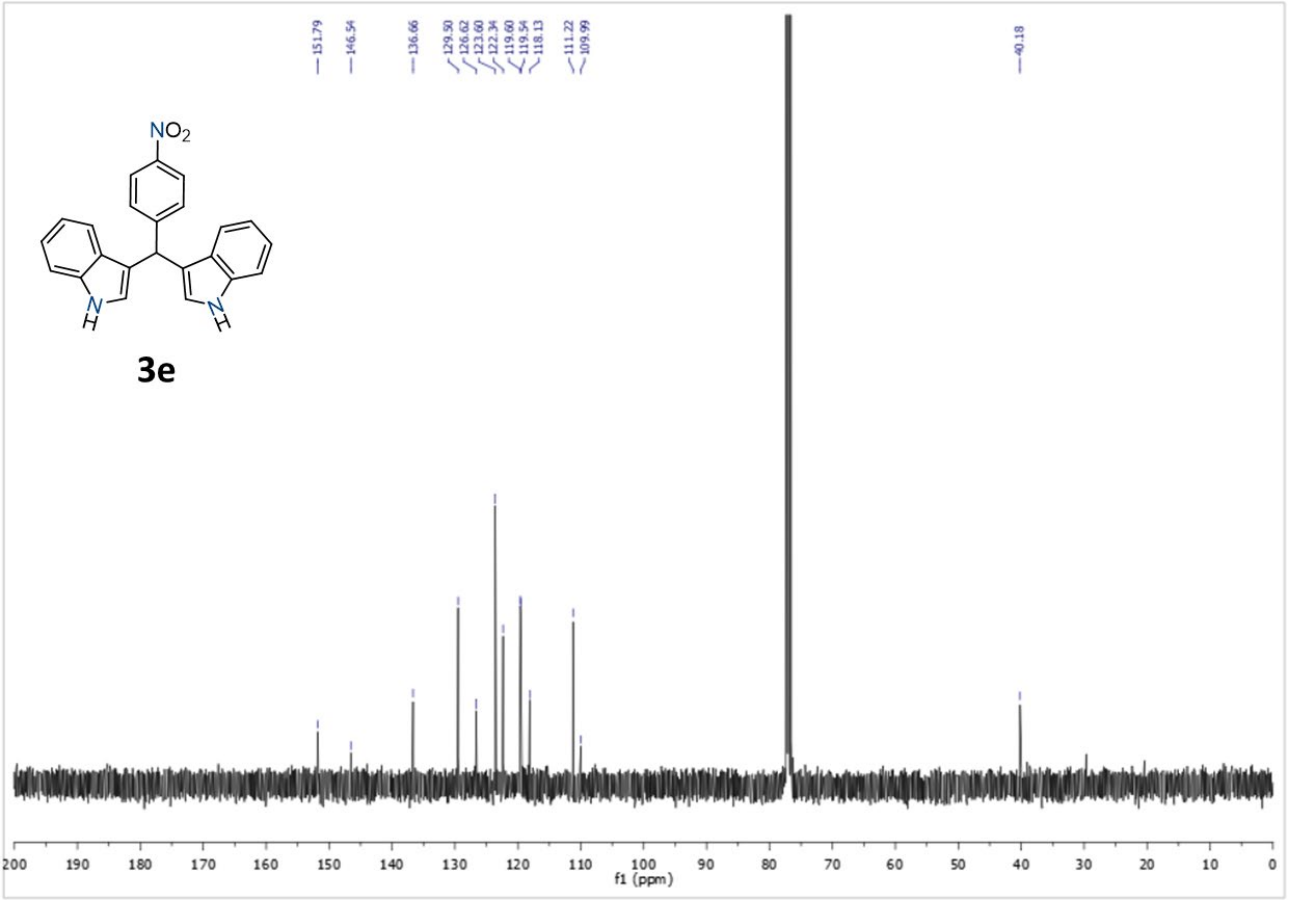

3c
DCM
f1 (ppm)

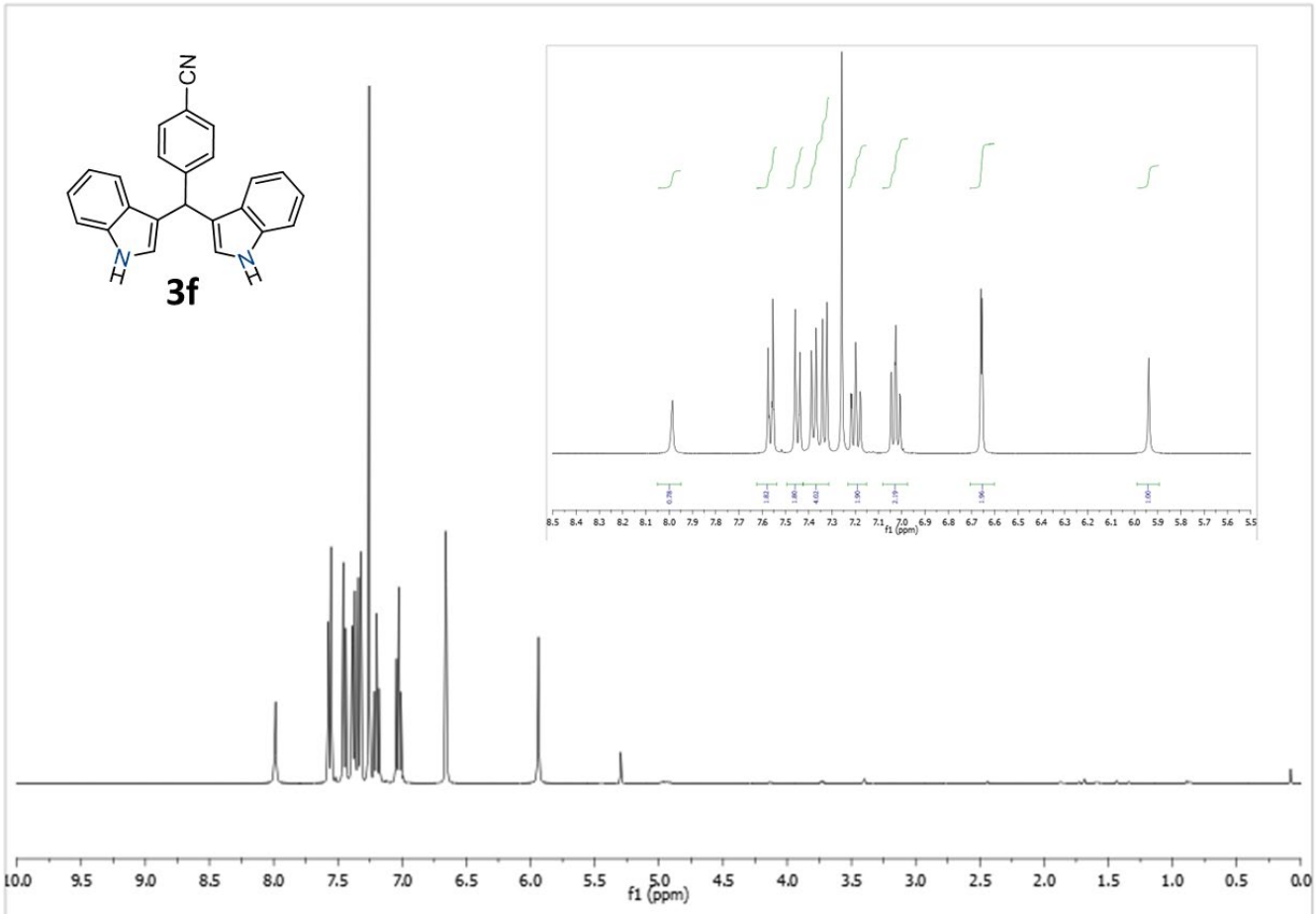

143.77
137.27
136.65
130.83
126.84
123.58
122.08
119.79
119.35
119.04
111.08
91.44
39.77
3c
f1 (ppm)

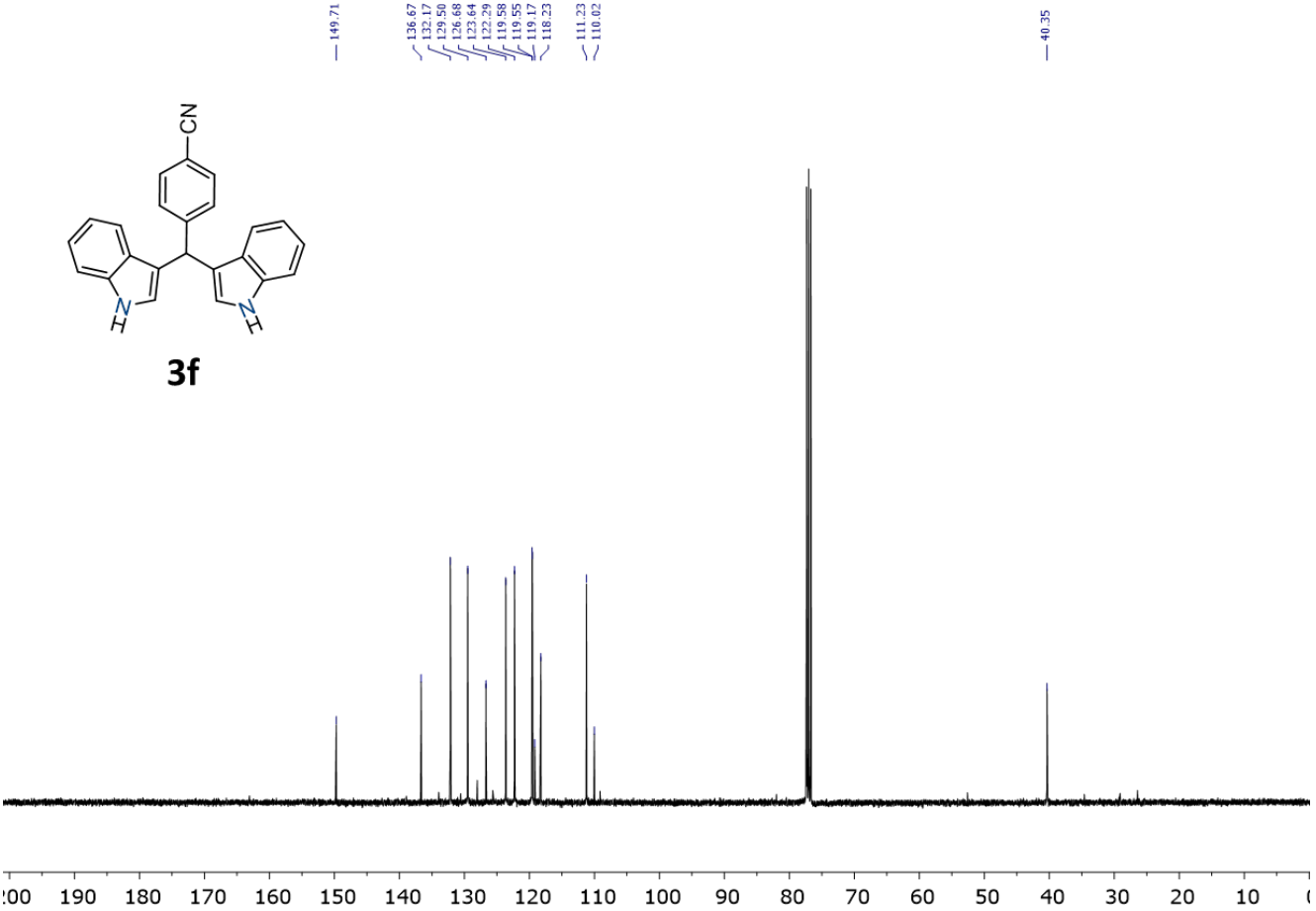

Cl
Cl
N
H
N
H
3d
f1 (ppm)

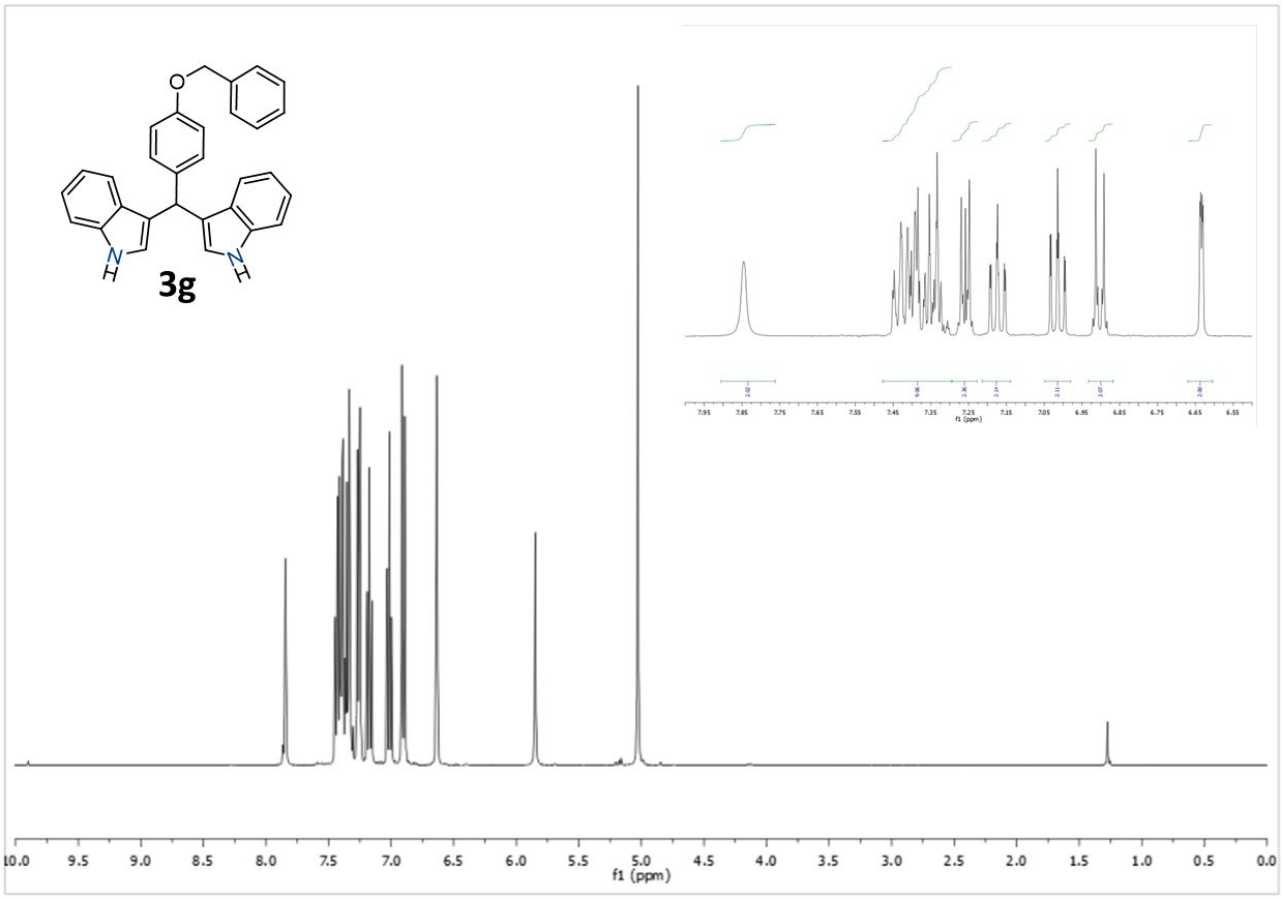

140.03
136.70
134.59
132.42
131.15
129.26
126.94
126.79
123.74
122.17
119.71
119.44
117.81
111.14
36.33
Cl
Cl
N
H
N
H
3d
f1 (ppm)

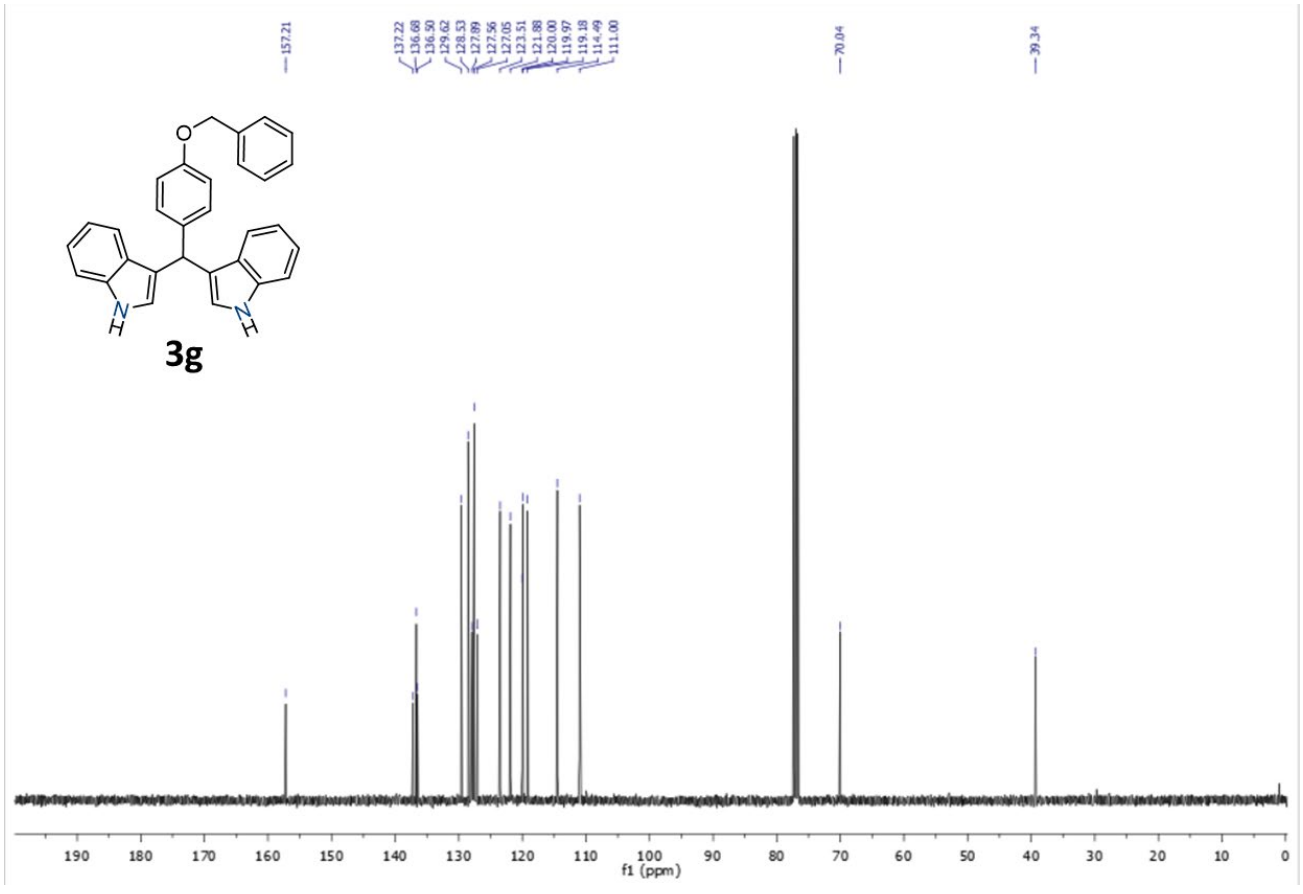

NO2
3e
f1 (ppm)


151.79
146.54
136.66
129.50
126.62
123.60
122.34
119.60
119.54
118.13
111.22
109.99
40.18
NO2
3e
f1 (ppm)


CN
N
H
N
H
3f
f1 (ppm)


149.71
136.67
132.17
129.50
126.68
123.64
122.29
119.58
119.55
119.17
118.23
111.23
110.02
40.35
CN
N
H
N
H
3f
f1 (ppm)


3g
f1 (ppm)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137.22
136.68
136.50
129.62
128.53
127.89
127.56
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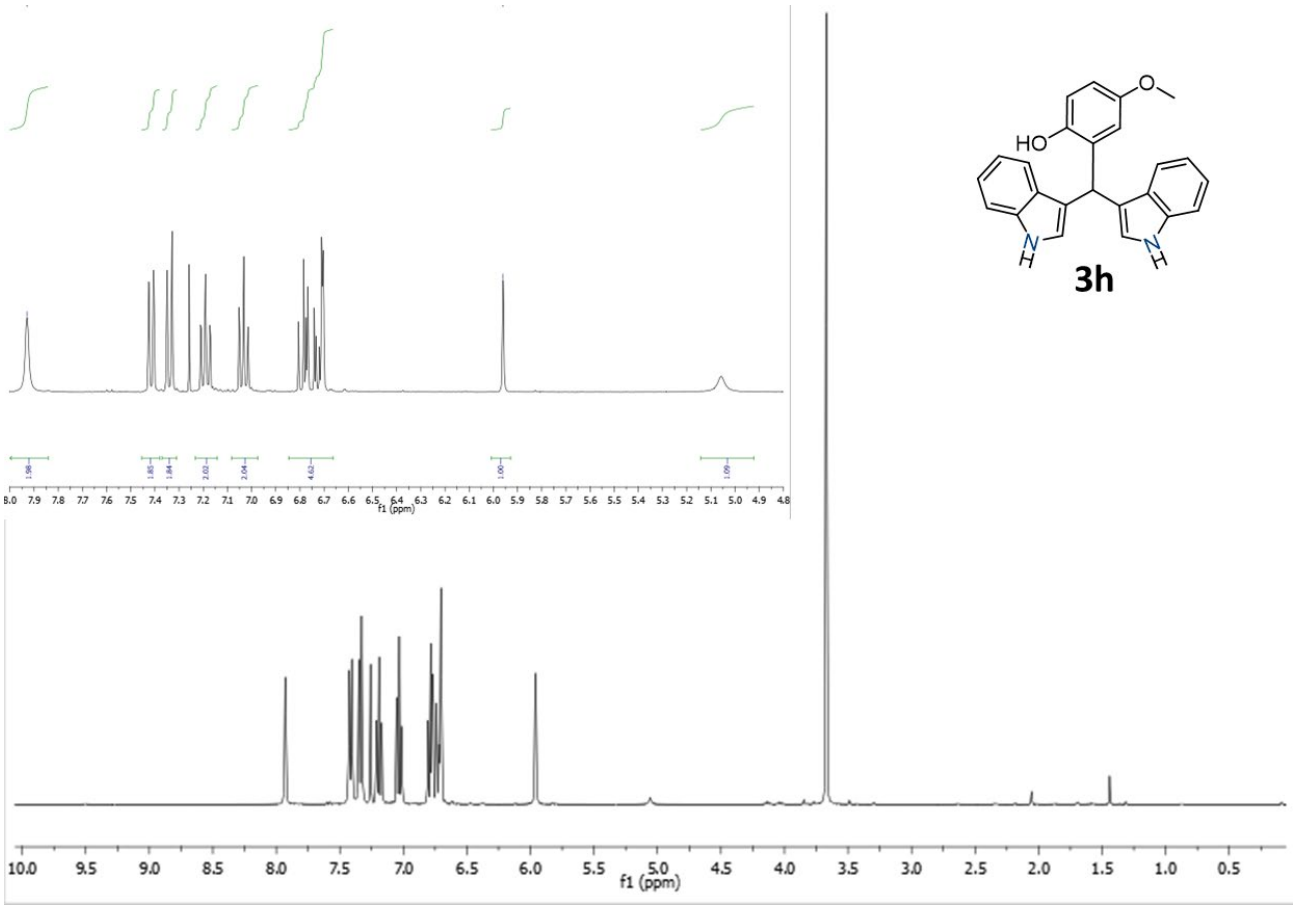
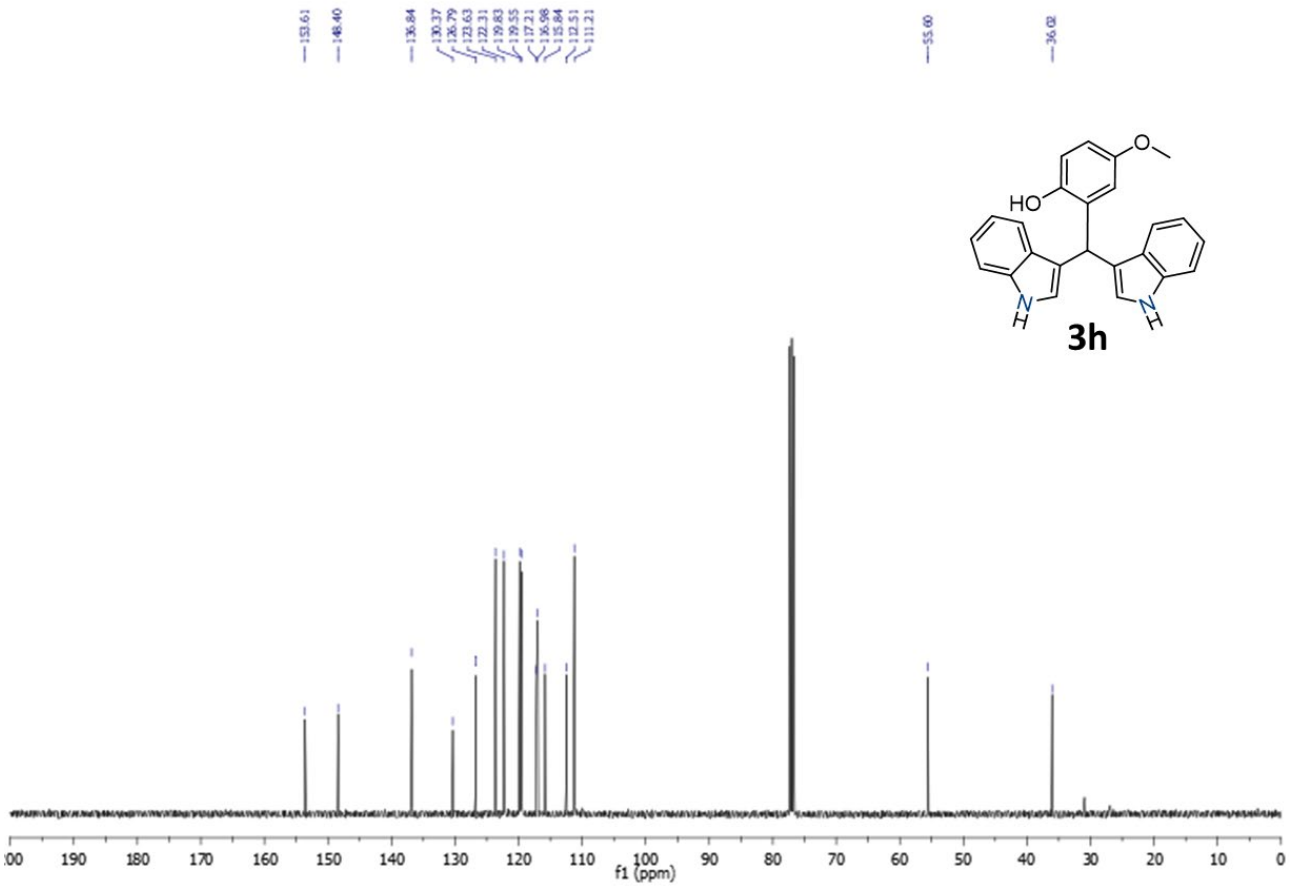
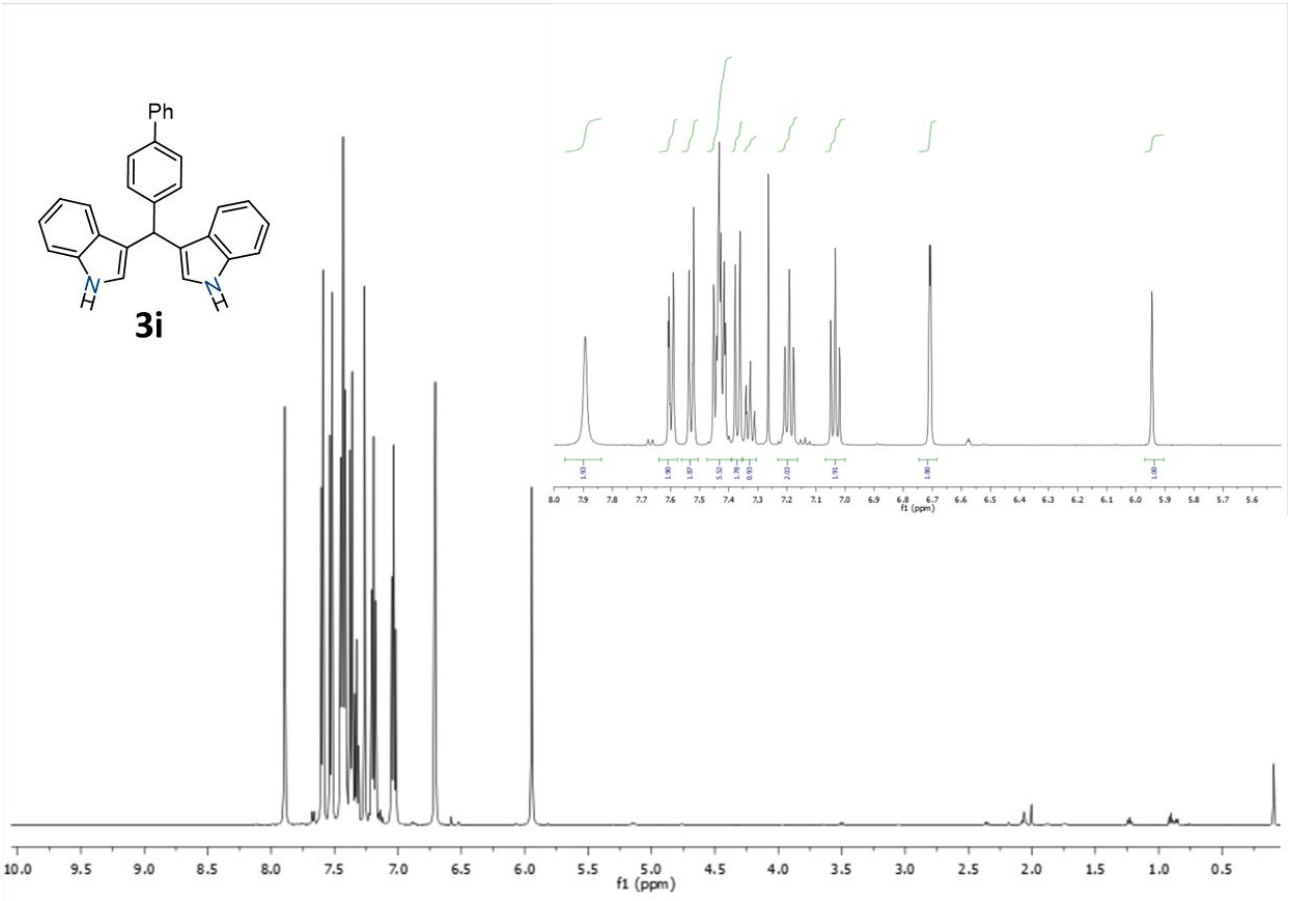
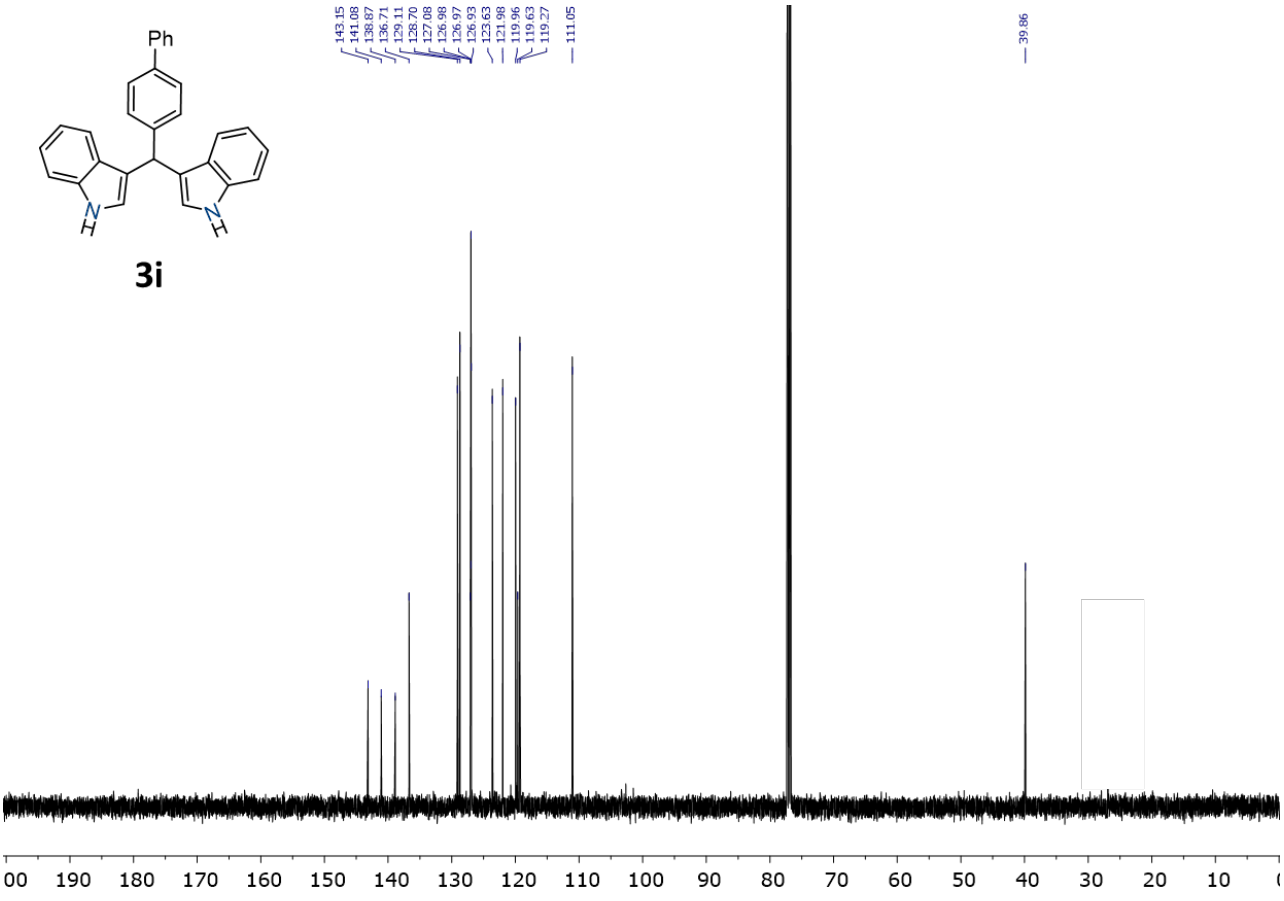
111.00
70.04
39.34
3g
f1 (ppm)


HO
O
N
H
3h
f1 (ppm)

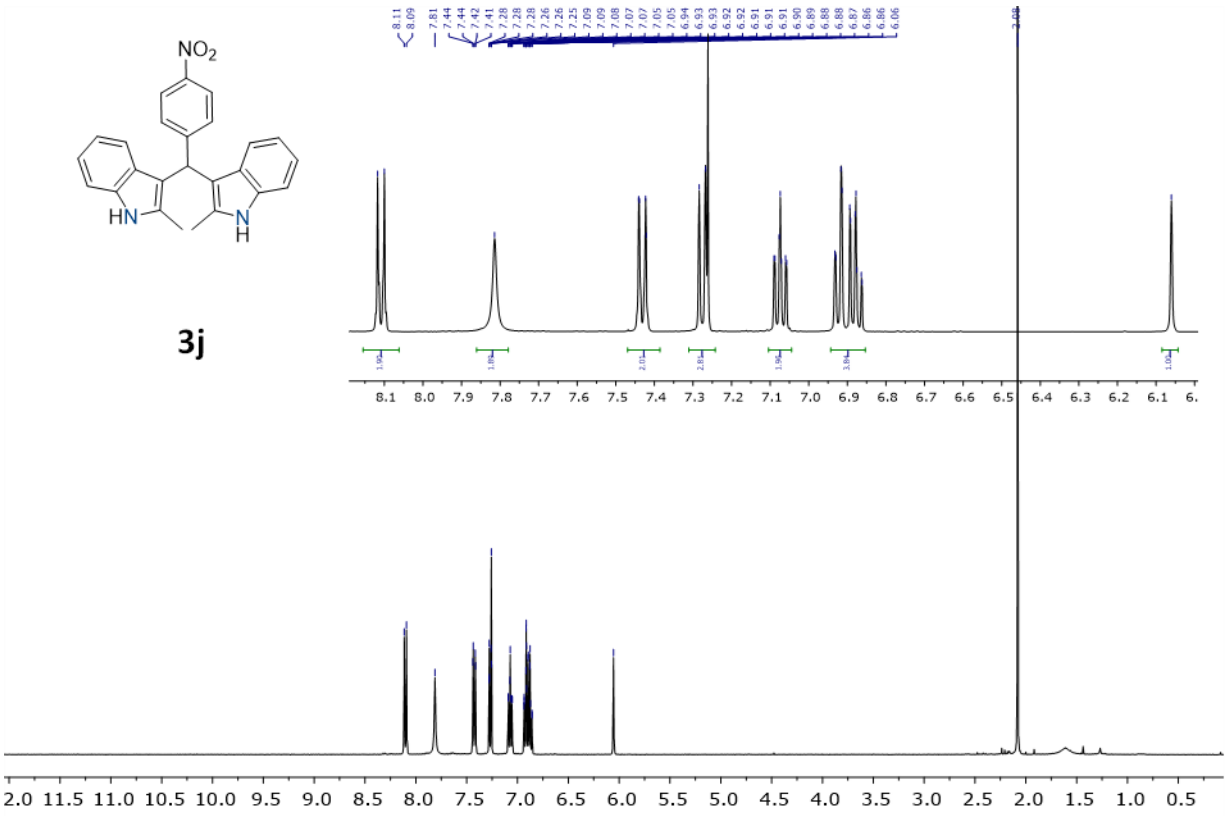

153.61
148.40
136.84
130.37
126.79
123.63
122.31
119.83
119.55
117.21
116.98
115.84
112.51
111.21
55.60
36.02
HO
O
N
H
3h
f1 (ppm)


Ph
3i
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


Ph
3i
143.15
141.08
138.87
136.71
129.11
128.70
127.08
126.98
126.97
126.93
123.63
121.98
119.96
119.63
119.27
111.05
39.86

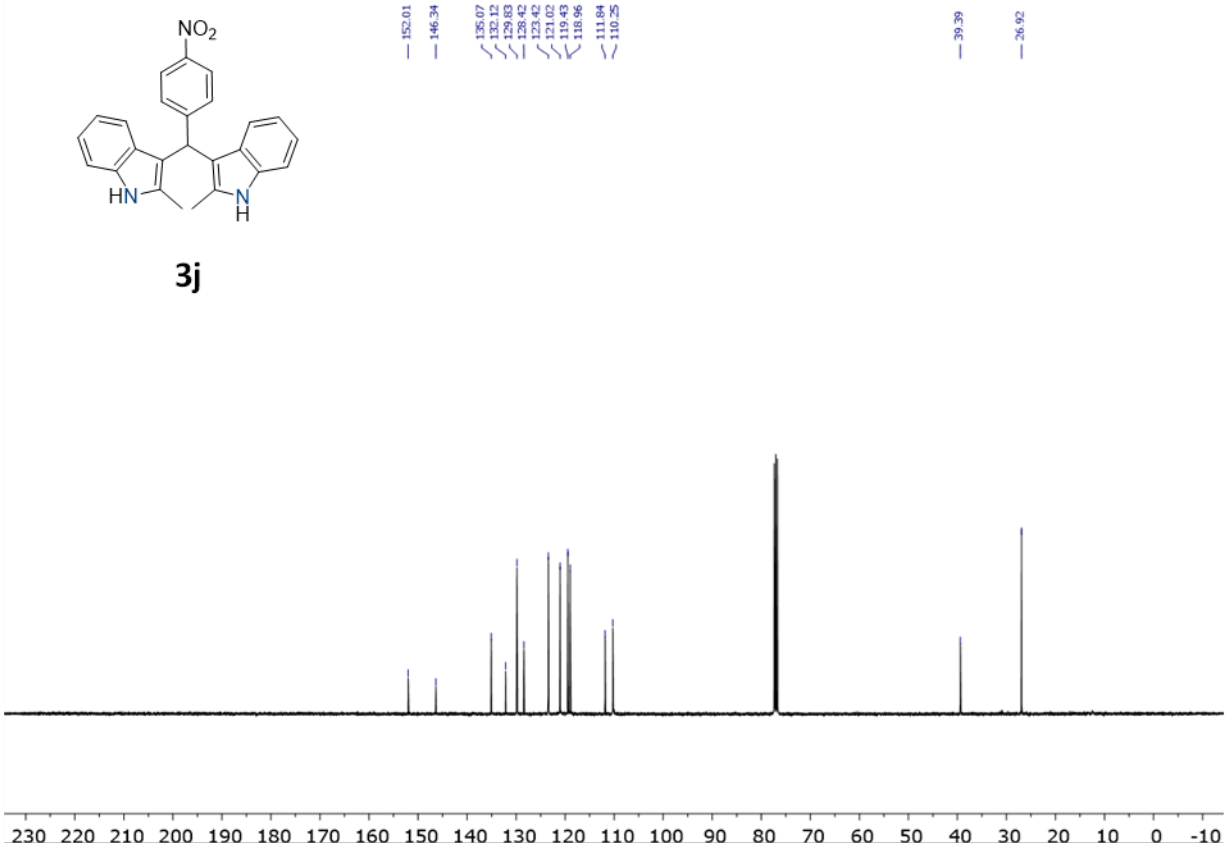
NO2
HN
N
H

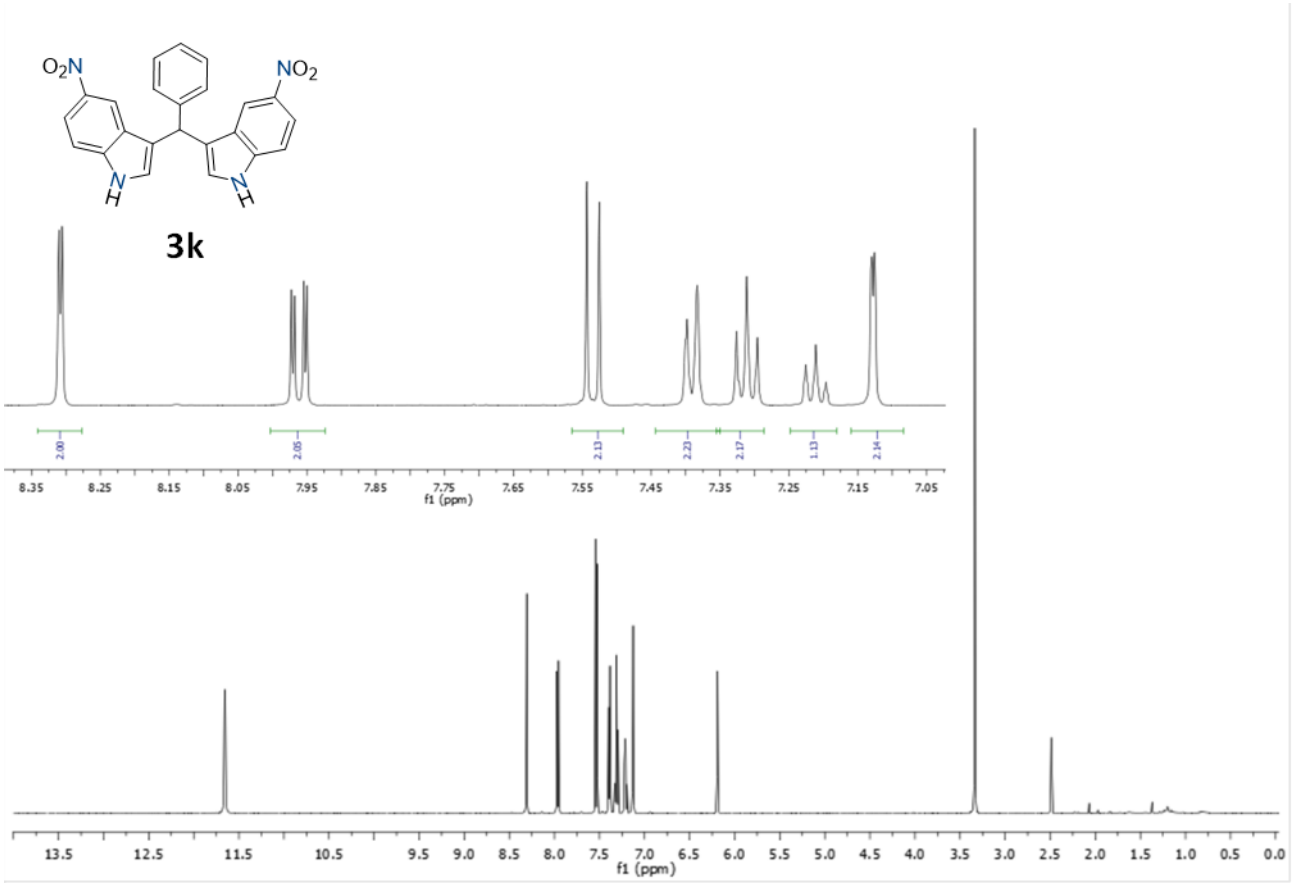
3j

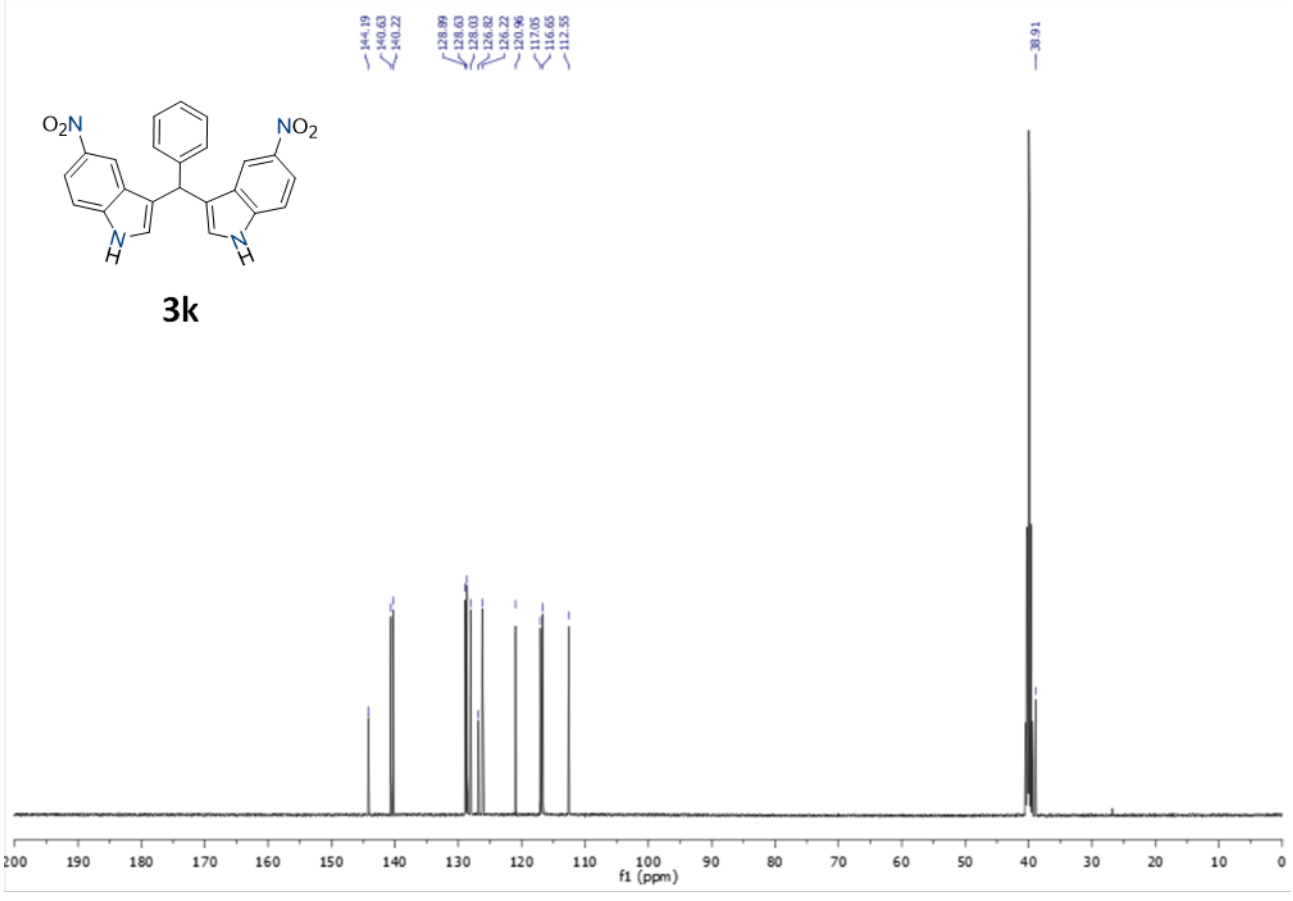

8.11
8.09
7.81
7.44
7.44
7.42
7.41
7.28
7.28
7.28
7.26
7.26
7.25
7.09
7.09
7.08
7.07
7.07
7.05
7.05
6.94
6.93
6.93
6.92
6.92
6.91
6.91
6.91
6.90
6.89
6.88
6.88
6.87
6.86
6.86
6.06
3.08
1.90
1.84
2.01
2.84
1.94
3.84
1.04
8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3 6.2 6.1
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

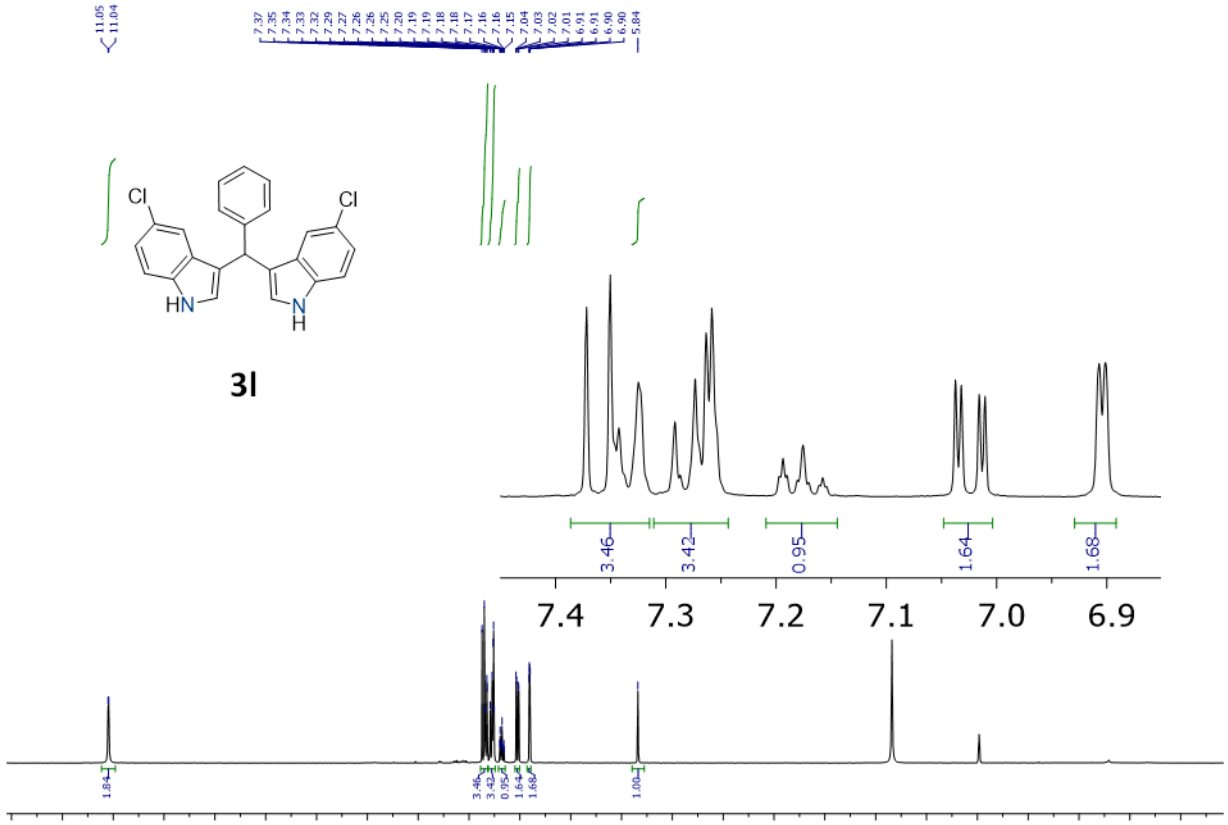
NO2
HN
N
H

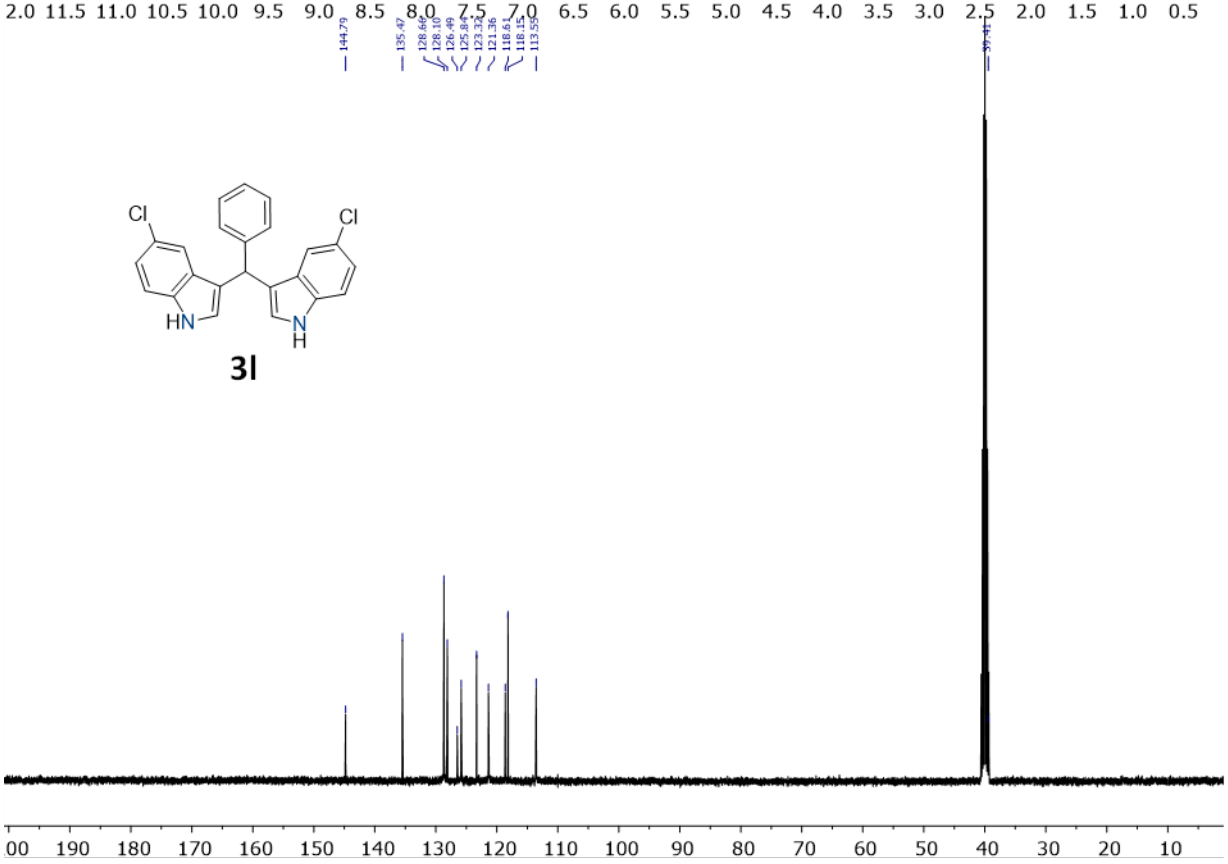
3j

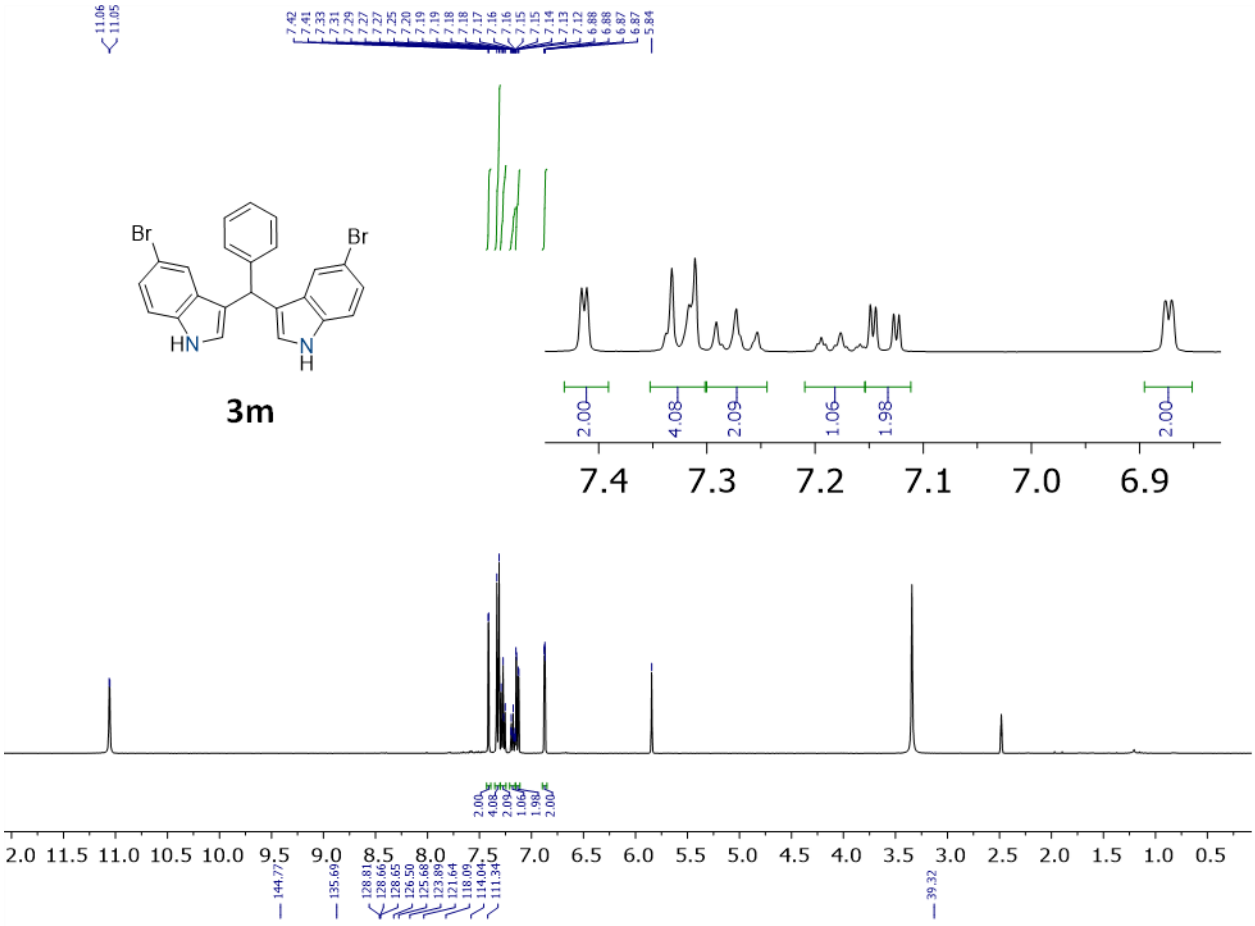

152.01
146.34
135.07
132.12
129.83
128.42
123.42
121.02
119.43
118.96
111.84
110.25
39.39
26.92
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

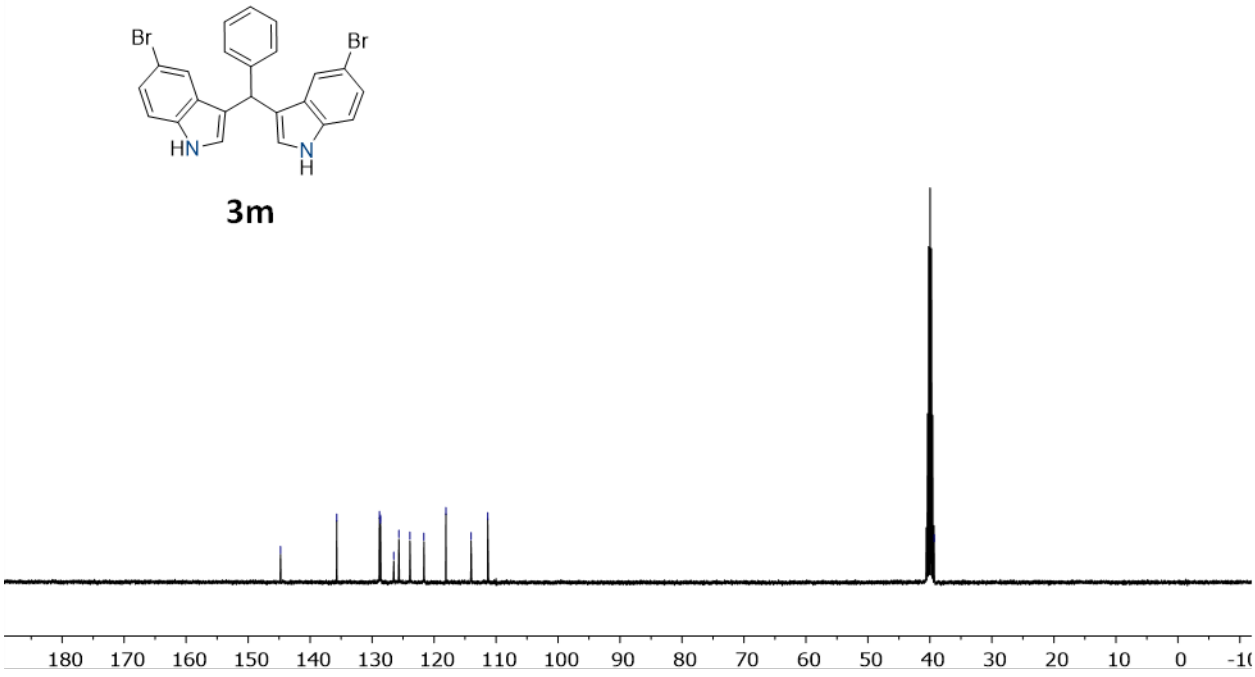

O2N
NO2
N
H
N
H
3k
2.00
2.05
2.13
2.23
2.17
1.13
2.14
8.35
8.25
8.15
8.05
7.95
7.85
7.75
7.65
7.55
7.45
7.35
7.25
7.15
7.05
f1 (ppm)
13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

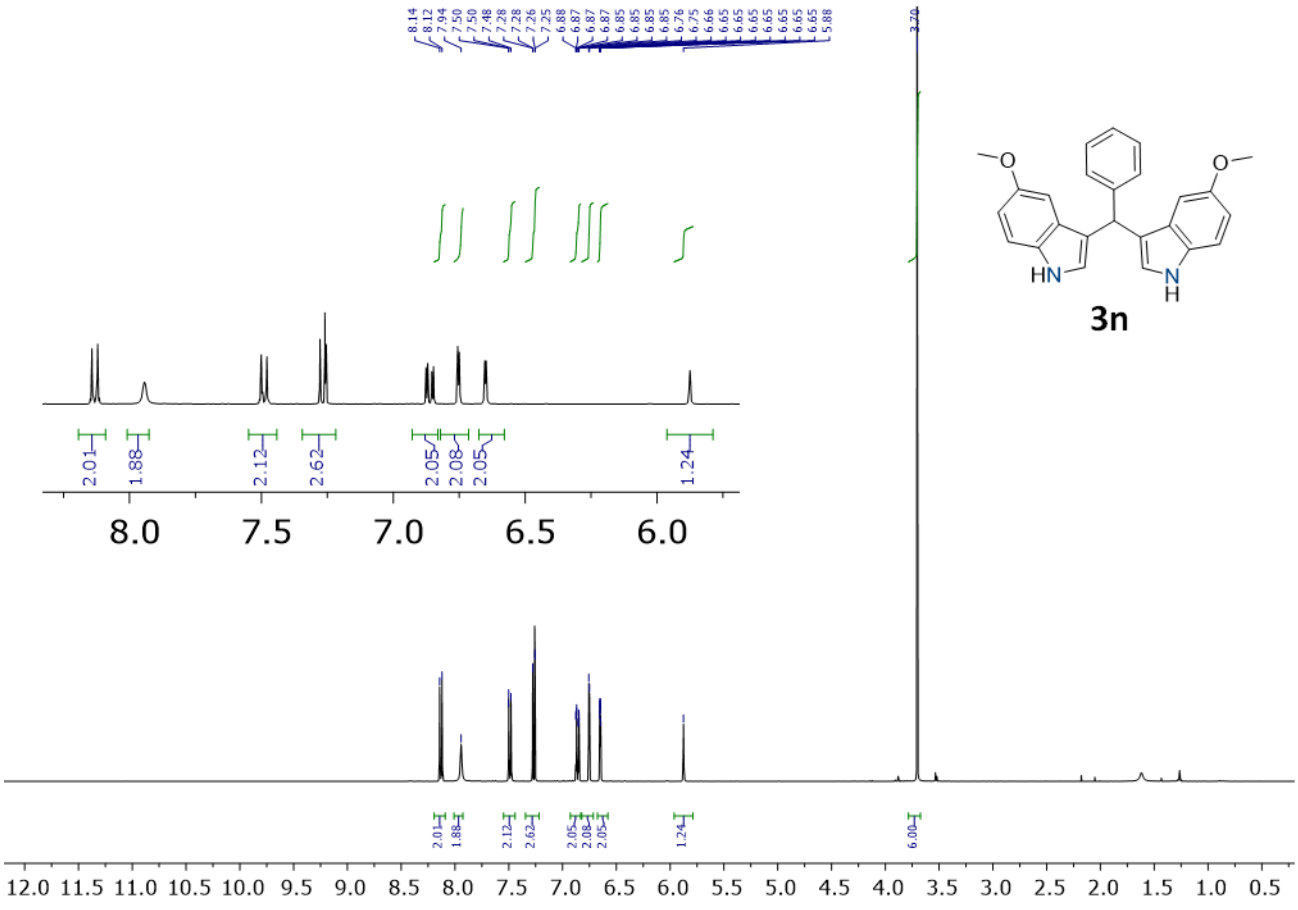

144.19
140.63
140.22
128.89
128.63
128.03
126.82
126.22
120.96
117.05
116.65
112.55
38.91
O2N
NO2
N
H
N
H
3k
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

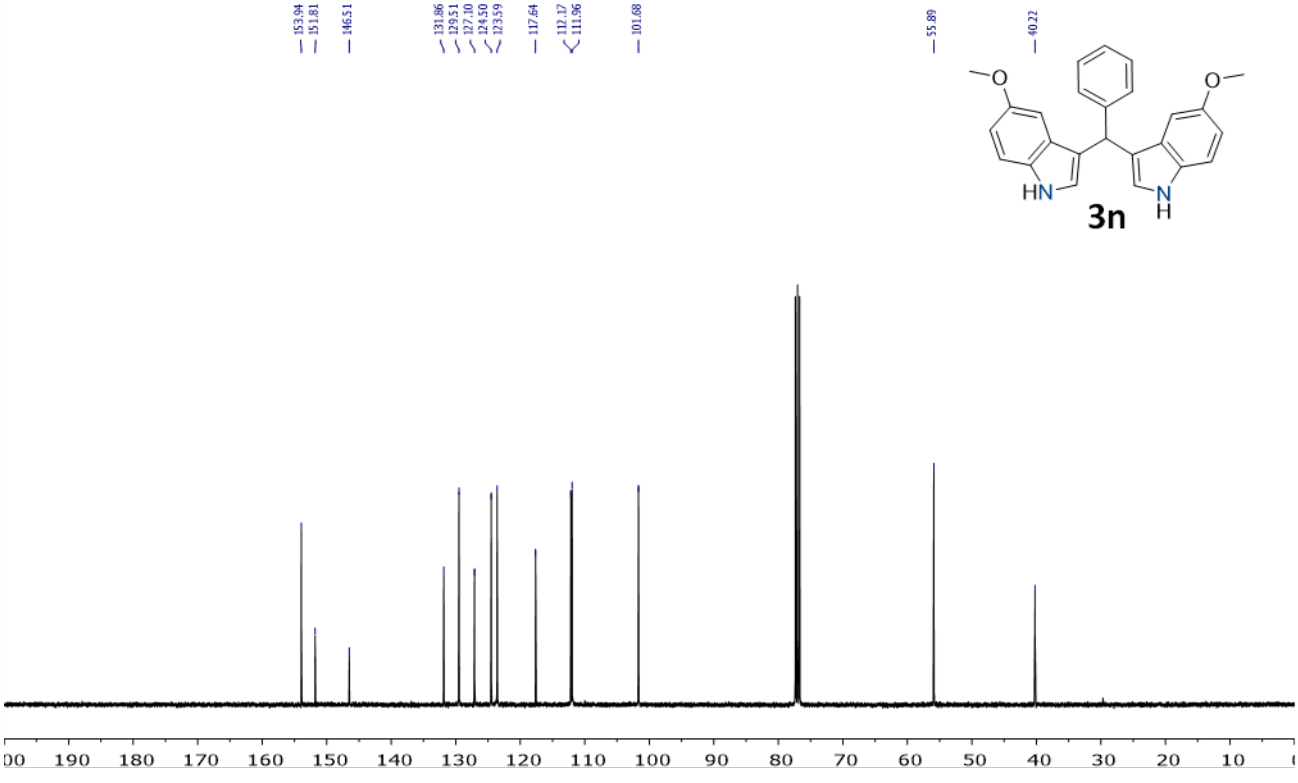

Cl
Cl
HN
N
H
3l
3.46
3.42
0.95
1.64
1.68
7.4
7.3
7.2
7.1
7.0
6.9

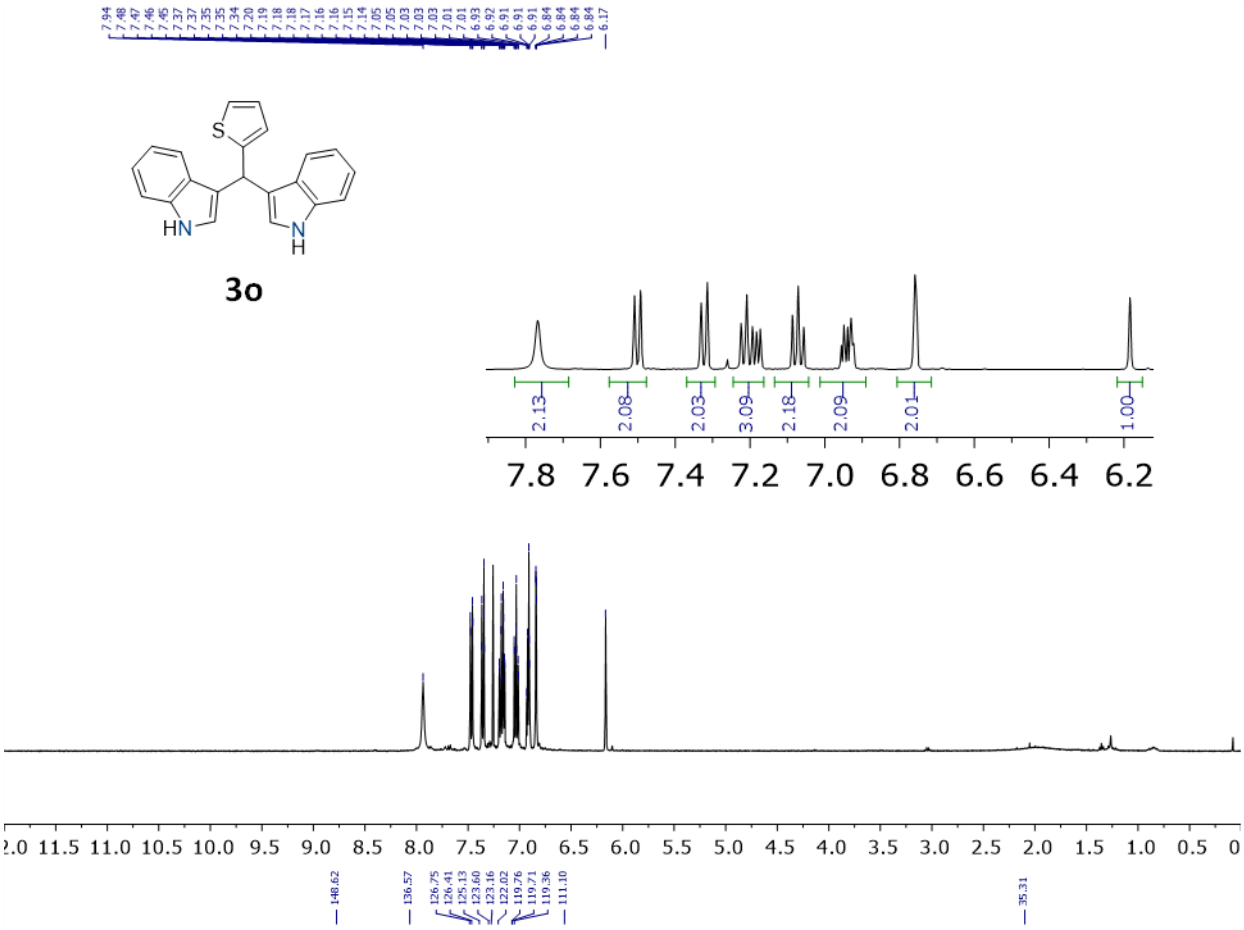

Cl
Cl
HN
N
H
3l

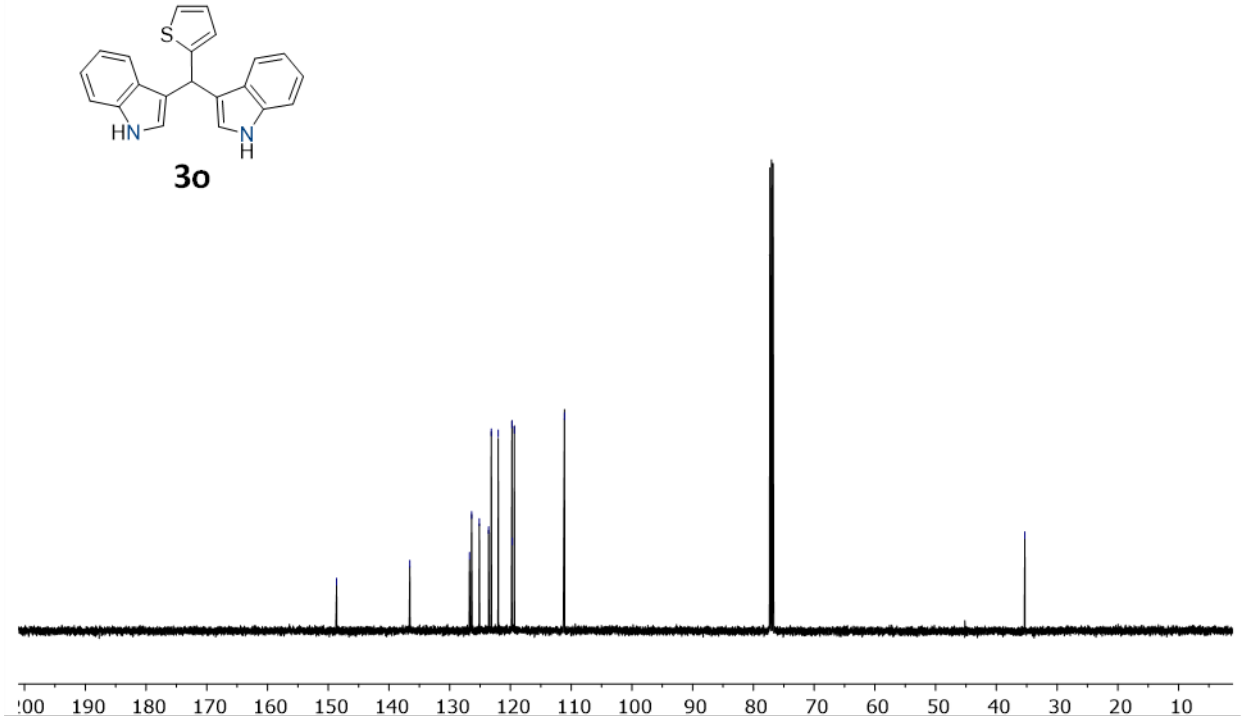

Br
Br
HN
N
H
3m
2.00
4.08
2.09
1.06
1.98
2.00
7.4
7.3
7.2
7.1
7.0
6.9


Br
Br
HN
N
H
3m


3n


3n


7.94 7.48 7.47 7.46 7.45 7.37 7.35 7.34 7.20 7.19 7.18 7.18 7.17 7.16 7.15 7.14 7.05 7.05 7.03 7.03 7.01 7.01 6.93 6.92 6.91 6.91 6.91 6.84 6.84 6.84 6.84 6.17
S
HN
N
H
3o
2.13 2.08 2.03 3.09 2.18 2.09 2.01 1.00
7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
148.62 136.57 126.75 126.41 125.13 123.60 123.16 122.02 119.76 119.71 119.36 111.10 35.31


S
HN
N
H
3o
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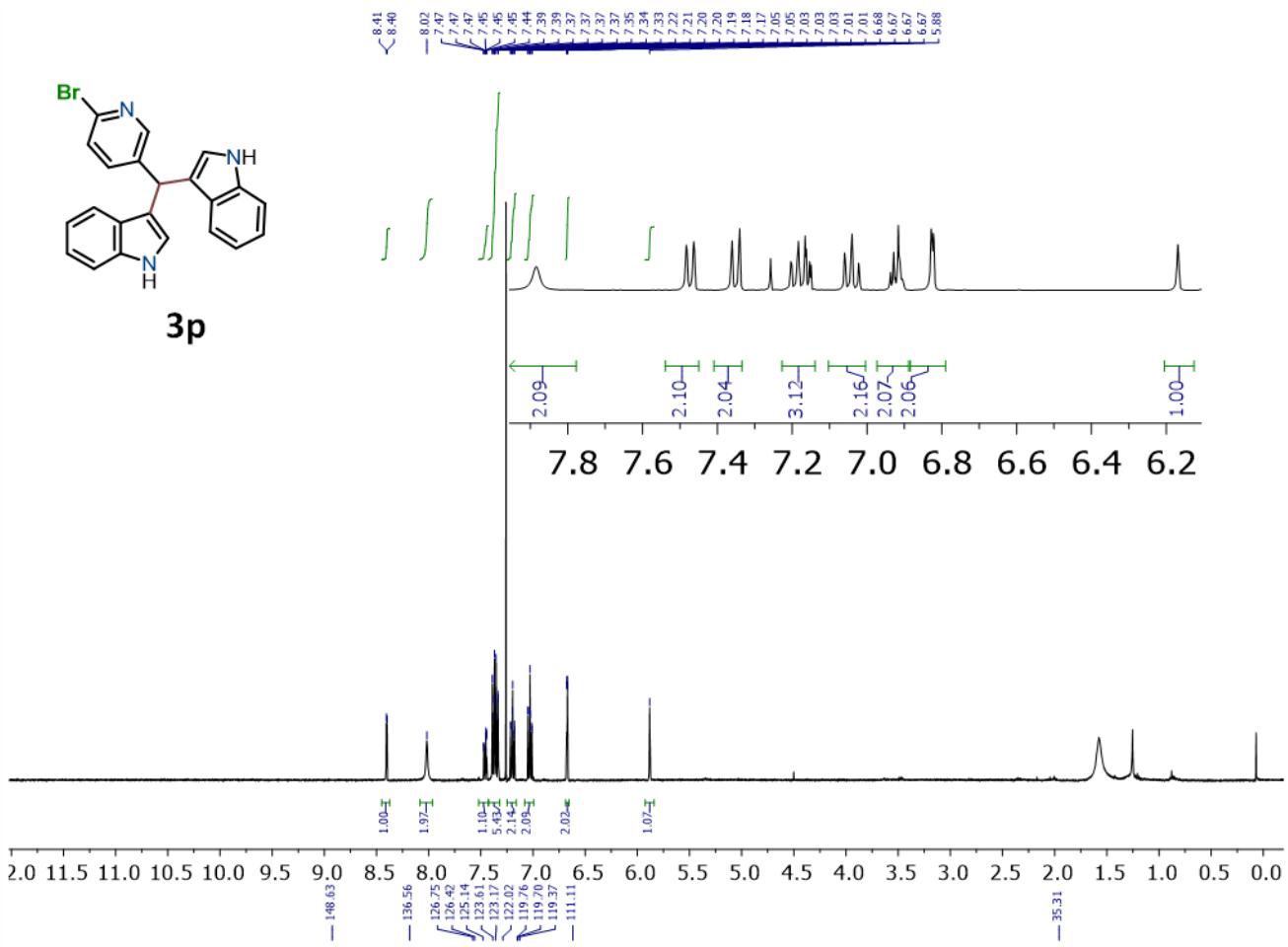
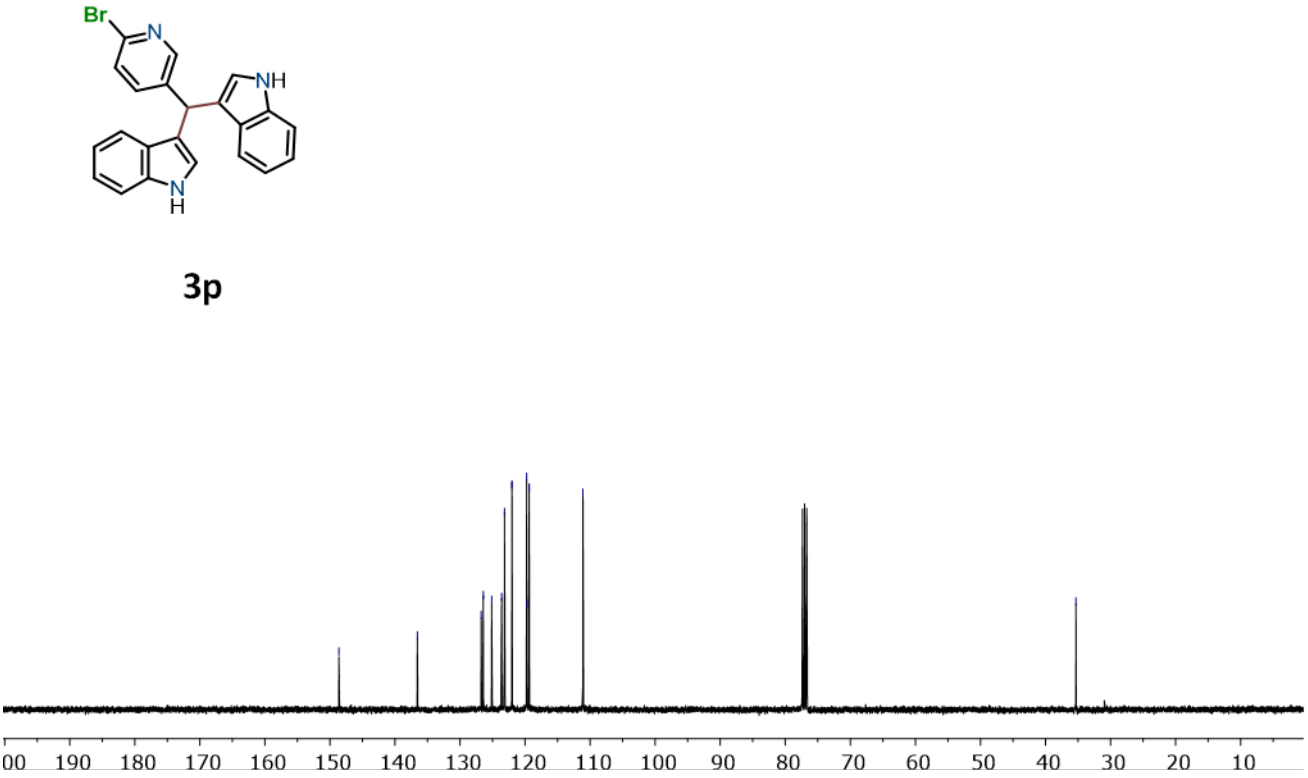

Br
N
NH
N
H
3p
8.41
8.40
8.02
7.47
7.47
7.47
7.45
7.45
7.45
7.44
7.39
7.39
7.37
7.37
7.37
7.37
7.35
7.34
7.33
7.22
7.21
7.20
7.20
7.19
7.18
7.17
7.05
7.05
7.03
7.03
7.03
7.01
7.01
6.68
6.67
6.67
6.67
5.88
2.09
2.10
2.04
3.12
2.16
2.07
2.06
1.00
7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2
1.00
1.97
1.10
5.43
2.14
2.09
2.02
1.07
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
148.63
136.56
126.75
126.42
125.14
123.61
123.17
122.02
119.76
119.70
119.37
111.11
35.31


Br
N
NH
N
H
3p
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

5. References

[1] A. Bahuguna, S. Kumar, V Sharma, K. L. Reddy, K. Bhattacharyya, P. C. Ravikumar, and V. Krishnan**,** *ACS Sustainable Chem. Eng.* 2017, 5, 10, 8551–8567.
[2] A. Modak, J. Mondal, A. Bhaumik, *ChemCatChem* 2013, 5,1749-1753.
[3] X. Liu, S. Ma, P. H. Toy, *Org. Lett.* 2019, 21 (22), 9212–9216.
[4] Y. Wang, R. Sang, Y. Zheng, L. Guo, M. Guan, Y. Wu, *Catal. Commun.* 2017, 89, 138-142.
[5] R. H. Vekariya, K. D. Patel, N. P. Prajapati, H. D. Patel, *Synth. Commun.* 2018, 48 (13), 1505–1533.
[6] Z. Wu, G. Wang, S. Yuan, D. Wu, W. Liu, B. Ma, S. Bi, H. Zhan, X. Chen, *Green Chem.* 2019, 21 (13), 3542–3546.