SYNTHESIS OF BIS(INDOLYL)METHANE DERIVATIVES VIA COPPER-CATALYSED REGIOSELECTIVE C-H FUNCTIONALIZATION OF INDOLE

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Submitted By
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UNDER THE SUPERVISION OF

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SCHOOL OF CHEMISTRY AND BIOCHEMISTRY,
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PATIALA-147001
2019

CERTIFICATE

This is to certify that the thesis entitled "**Synthesis of bis(indolyl)methane derivatives via copper-catalysed regioselective C-H functionalization of indole**" submitted by **Ms. Priya Kamboj** in the partial fulfillment of the requirement for the degree of **Masters of science in Chemistry** from **Thapar Institute of Engineering and Technology, Patiala** is a bonafide piece of work carried out under the guidance and supervision **Dr. Vikas Tyagi**, Assistant Professor, School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala and no part of project has been submitted for award of any other degree in this or any other university.

Priya Kamboj
(PRIYA KAMBOJ)

This is to certify above statement made by student concerned is correct and true to the best of my knowledge.

Dr. Vikas Tyagi
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SELF DECLARATION

The work embodied in the project entitled "**Synthesis of bis(indolyl)methane derivatives via copper-catalysed regioselective C-H functionalization of indole**" has been done by me in the partial fulfillment of the requirement for the Award of degree of **Masters of science in Chemistry**, submitted in the **School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala** is an authentic record of my own carried under the guidance and supervision of **Dr. Amjad Ali**, Professor and Head, and **Dr. Vikas Tyagi**, Assistant Professor, School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala. All the ideas and references has been duly acknowledged.

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Date – July 15, 2019

This is to certify above statement made by student concerned is correct and true to the best of my knowledge.

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Date: July 15, 2019 **PRIYA KAMBOJ**

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ABSTRACT

Considering the wide extent of applications of bis(indolyl)methanes in agrochemical and pharmaceutical industries, new and efficient methodologies for their synthesis have been in continuous demand. The C-H functionalisation of indoles has recently been a hot topic in organic chemistry being atom economic and environment friendly. Despite the usefulness of carbene insertion chemistry for C-H functionalization of indole, it suffers from certain drawbacks of carbene insertion at C-2 and N-1 positions of indoles. In order to invent an competent methodology for designing bis(indolyl)methanes (BIMs) having no substituent at methylene bridge, we described here a new methodology for the development of bis(indolyl)methanes using copper catalysed regioselective C-H functionalization of indoles using indole-3-tosylhydrazone as carbene precursor. Moreover, to the best of our understanding, this is the first report of using carbene insertion chemistry for synthesis of bis(indolyl)methanes. Further, being feasible to one-pot synthesis makes this method highly time saving and economical.

CHAPTER 1: INTRODUCTION & LITERATURE REVIEW

1.1. Introduction: Bis-indoles constitute a structurally fascinating and imperative class of heterocyles as they are broadly found in a number of pharmacologically and biologically important natural along with synthetic compounds.[1] Moreover, bis(indolyl)methanes (BIMs) derivatives contained more than one indole units joined together by a methylene bridge exhibited remarkable biological activities such as anti-inflammatory[2], antihyperglycemic, antiviral[3], antibacterial[4], anticancer[5] and others **(Figure 1)**.[6,7]

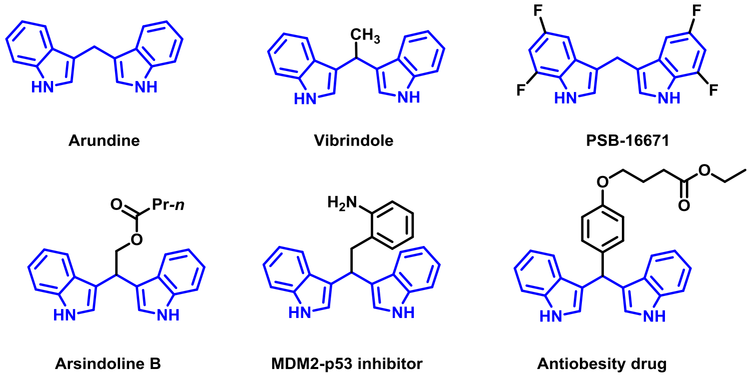


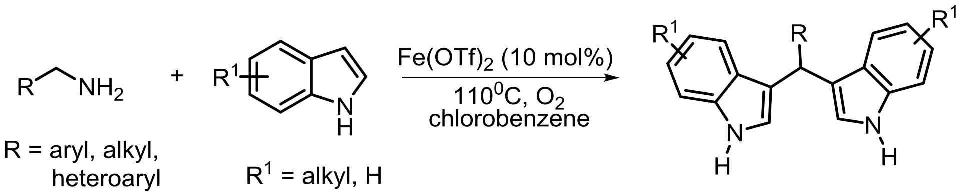
Figure.1: Examples of biologically active bis(indolyl)methane containing natural or synthetic compounds.

Therefore, the preparation of bis(indolyl)methanes derivatives have attracted great attention from the chemical community from previous years. Traditionally, the bis(indolyl)methanes can be synthesized by means of reacting indoles with a number of carbonyl compounds using Lewis/Bronsted acids.[8] Although, the traditional methods have a number of disadvantages such as longer reaction time, more than stoichiometric amounts may be needed, require tedious aqueous work-up and deactivation of Lewis acids or sometimes might be decomposed with nitrogen having compounds.[9] On the other hand, carebene insertion reaction deals with the incorporation of carbene into a C-H or X-H (X=O, S, N) bonds. Further, C-H functionalisation of indoles using carbene insertion reactions has grabbed lot of attention in the last few years since they are eco-friendly and atom-economical.[10] However, regioselectivity is one of the prime concerns in the functionalization of indoles using carbene insertion reactions due to the formation of side products at C-2 and N-1 positions. A number of efforts have been made for the regioselective functionalization of indoles using bulky ligands/catalyst or by protecting the unused positions.[11] Due to increasing attention to cultivate highly efficient methodologies for synthesis of BIMs, we reported here the preparations of bis(indolyl)methanes using copper catalysed regioselective C-H functionalization of indoles.

1.2. Literature Review:

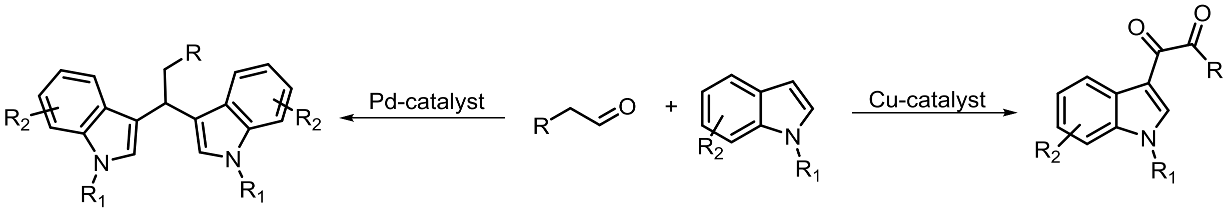
1.2.1. Recent strategies for synthesizing bis(indolyl)methanes: Considering the wide extent of applications of bisindoles, the development of new capable and eco-friendly methods have been in continuous demand. In the recent years, bis(indolyl)methanes have been produced by novel strategies, especially made by transition metals, ionic liquids or nanomaterials catalyzed reactions of different aldehydes or carbonyl compounds with indoles via electrophilic substitution reactions.

In this context, Gopalaiah and co-workers reported iron catalysed oxidative coupling of a number of aliphatic amines with indoles along with molecular oxygen to prepared bis(indolyl)methanes(BIMs). This protocol gives an appealing and normally considerate strategy to synthesize the bis(indolyl)methanes in a one-pot method (**Scheme 1**).[12]



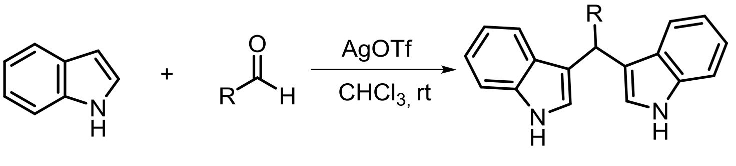
Scheme 1: Oxidative coupling of benzyl amines and indoles

Further, Zhou *et. al.* used copper and palladium based complexes to catalyze the particular C-H functionalization of indoles with diazo compounds(**Scheme 2**).[13]



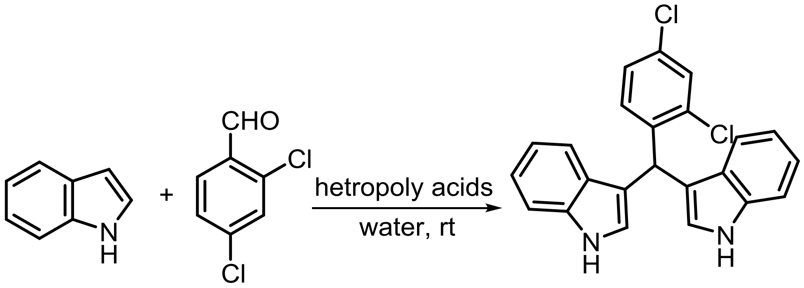
Scheme 2: Chemeoselective preparations of C-3 bis(indolyl)alkanes through Pd/Cu-catalysts.

Further, Beltrá's group developed bis(indolyl)methanes with excellent yields, where AgOTf was used for activation of aldehydes, giving various bisindole derivatives (**Scheme 3**).[14]



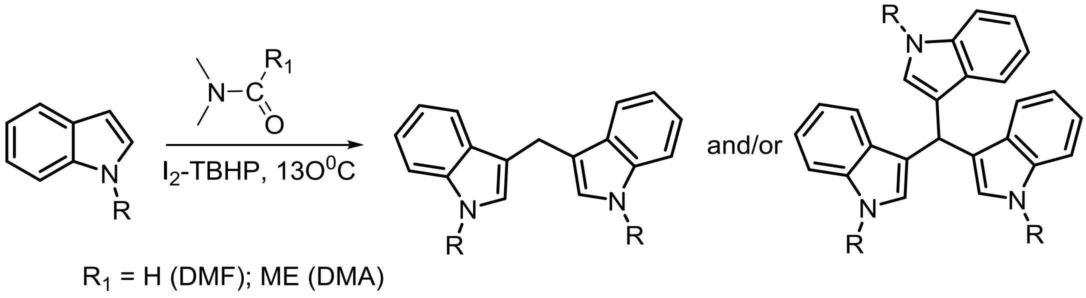
Scheme 3: Catalytic development of BIM derivatives

A very efficient, atom economic and green protocol was designed to synthesize bis(indolyl)methanes by Azizi and co-workers by reacting indole in the company of carbonyl compounds with the presence of heteropoly acids and small quantity of water as a solvent medium (**Scheme 4**).[15]



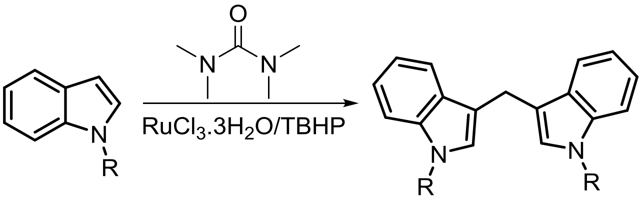
Scheme 4: Reaction of indole with carbonyls using heteropoly acid

Another work uncovered by Deb and co-workers reported the C-H functionalisation of indoles with DMF/DMA in the metal-free environment for preparing bis(indolyl)methanes and tris(indolyl)methanes (**Scheme 5**).[16]



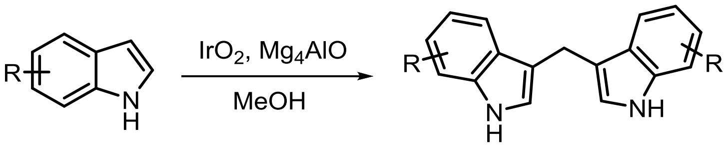
Scheme 5: Synthesis of indoles with DMF/DMA as carbene precursor

1.2.2. Recent approaches for making BIMS without substituent on the methylene bridge: However, the development of bis(indolyl)methanes having unsubstituted methylene bridge is still a challenge. In this context, only a small number of methods are reported in the literature. Deb and co-workers invented the development of bis(indolyl)methanes using Ru(III)/TBHP in the reaction of indoles with tetramethylurea assisted by microwave heating (**Scheme 6**).[17]



Scheme 6: Synthesis of indoles with different carbene precursors

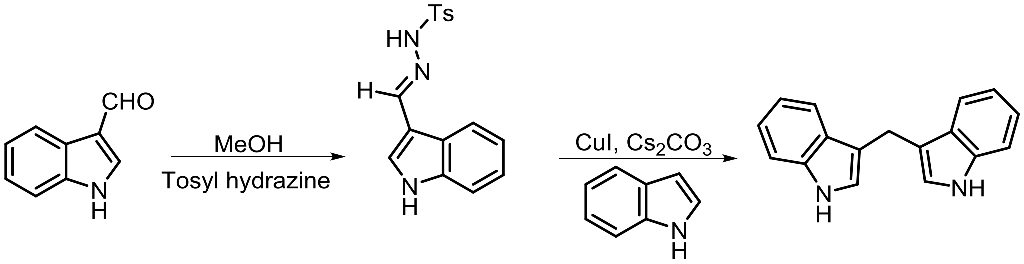
Further, Loh et. al. stated the coupling of indoles with methanol without adding extra substances using Mg-Al blended oxides upheld iridium impetus for the development of bis(indolyl)methanes (**Scheme 7**).[18]



Scheme 7: Coupling of indoles with methanol using Mg-Al blended oxides

1.2.3. Our approach:

Due to continues interest to cultivate extremely valuable methodologies for producing bis(indolyl)methanes having unsubstituted methylene bridge. We designed a methodolgy for the preparation of bis(indolyl)methanes using copper catalysed regioselective C-H functionalization of indole with indole-3-tosylhydrazone as carbene precursor. In this method indole-3-carboxyaldehyde have been prepared using Vilsmeyer-Hack reaction which was further converted to indole-3-tosylhydrazone which acts as a carbene precursor for developing bis(indolyl)methanes containing unsubstituted methylene bridge (**Scheme 8**).

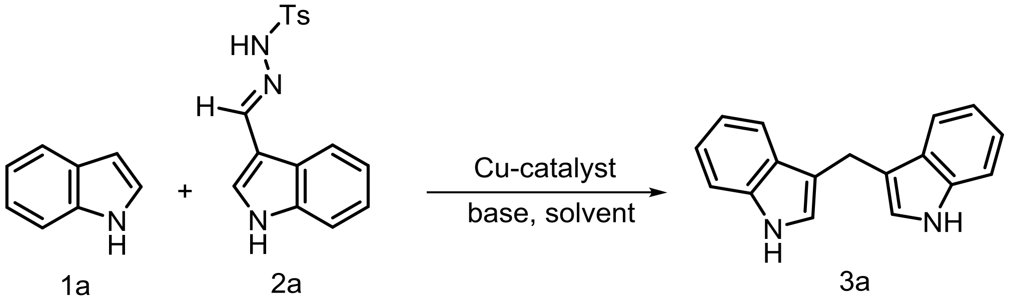


Scheme 8: Development of bis(indolyl)methanes via copper-catalysed regioselective C-H functionalization of indole

CHAPTER 2: RESULTS AND DISCUSSIONS

2.1. Optimisation of reaction parameters: First, we considered the reaction of 1H-indole **1a** and indole-3-tosylhydrazone **2a** as the template reaction for the investigation of the reaction parameters. Moreover, the eventual outcomes of screening various reaction parameters were abbreviated in **Table 1**. First, the reaction of indole (**1a**) and indole-3-tosylhydrazone (**2a**) using 10 mol% of CuI and two equiv. of Cs_2CO_3 in 1,4-dioxane as solvent at 110º C were examined in a sealed tube , and obtained 59% yield for the expected product **3a** (**Table 1,** entry 5).

Table 1. Variations of the reaction parameters for the regioselective C-H functionalization of indole[a]



S.No.	Catalyst	Base	Solvent	%Yield
1	CuI	K_2CO_3	1,4-dioxane	49
2	$Pd(OAc)_2$	K_2CO_3	1,4-dioxane	Trace
3	$Pd(OAc)_2$	KO^tBu	1,4-dioxane	Trace
4	CuI	NaOH	1,4-dioxane	27
5	**CuI**	$\mathbf{Cs_2CO_3}$	**1,4-dioxane**	**59**
6	CuI	KO^tBu	1,4-dioxane	42
7	CuI	LiO^tBu	1,4-dioxane	34
8	CuI	Cs_2CO_3	1,4-dioxane	44[c]
9	$CuSO_4$	Cs_2CO_3	1,4-dioxane	Trace
10	$Cu(OAc)_2$	Cs_2CO_3	1,4-dioxane	Trace
11	CuI	Cs_2CO_3	Toluene	51
12	CuI	Cs_2CO_3	DMF	49
13	CuI	Cs_2CO_3	THF	20
14	-	Cs_2CO_3	1,4-dioxane	0[d]
15	CuI	-	1,4-dioxane	0[d]
16	CuI	Cs_2CO_3	1,4-dioxane	32[c]

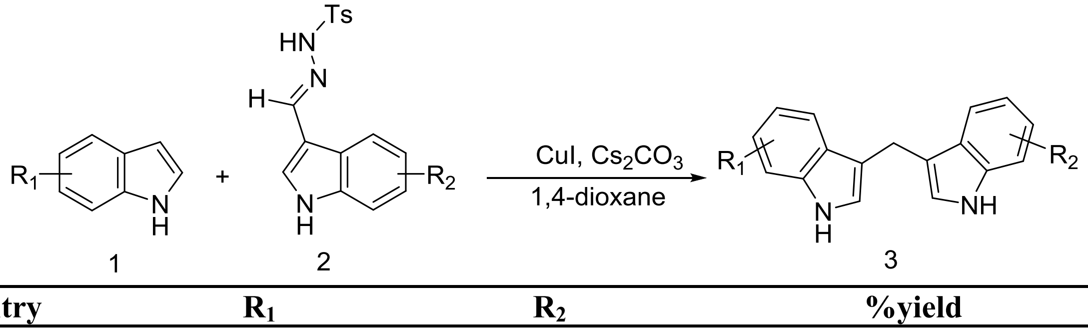
[a]Reaction conditions: All reactions were performed in a 10 mL reaction vial using indole **1a** (1.2 euiv.), indole-3-tosylhydrazone (1.0 equiv.), base (2.0 equiv.), catalyst (10 mol%) and solvent 5mL at 110ºC for 15-18 hours at conventional heating, [b]isolated yield, [c]used 1.0 equiv of base, [d]no reaction, [e]used 5 mol% of catalyst.

This result encouraged us to do further optimisation of reaction conditions to increase the yield of (**3a**). A number of variations in the reaction conditions were tried using different bases, solvents, catalysts and different equivalents of each substrate as stated in **Table 1**. First, the reaction was examined using different metal catalysts and bases and to our delight CuI remained the best catalyst and Cs_2CO_3 as the best base in 1,4-dioxane as the solvent. (**Table 1,** entries 1-7). Further reducing the equivalents of base to half that is 1 equiv that showed comparatively lower yield than the standard reaction conditions (**Table 1,** entry 8). The screening of various solvents using CuI as catalyst along with Cs_2CO_3 as base demonstrated that 1,4-dioxane was the perfect reaction medium while others, for instance, toluene, DMF, THF gave lower yields of bis(indolyl)methanes **3a** (**Table 1,** entries 11-13). Some controlled reaction conditions were moreover endeavoured without catalyst and base anyway the reaction did not occur under these reaction conditions (**Table 1,** entries 14-15). By decreasing the proportion of catalyst to 5 mol% the inferior yield of product **3a** was obtained (**Table 1,** entry 16). As such the general optimized reaction conditions gained were 10 mol% of copper(I) iodide as catalyst and (2equiv.) of Cs_2CO_3 as the base dissolvable in 1,4-dioxane at 110ºC with consistent stirring gave the perfect coupling product **3a**.

2.2. Substrate scope of reaction:

Having the optimized reaction parameters, we assessed the degree of bisindole formations with different indole derivatives and results were listed in **Table 2**. At that point the reaction proceeded effectively for a wide range of substituted as well as unsubstituted indoles **1** to convey the product **3** in decent yields. The reaction of unsubstituted indoles conveyed the product **3** in 59% remarkable yield (**Table 2,** entry 1).

Table 2: Scope of the substrate for the regioselective C-H functionalization of indole using indole-3-tosylhydrazone[a]



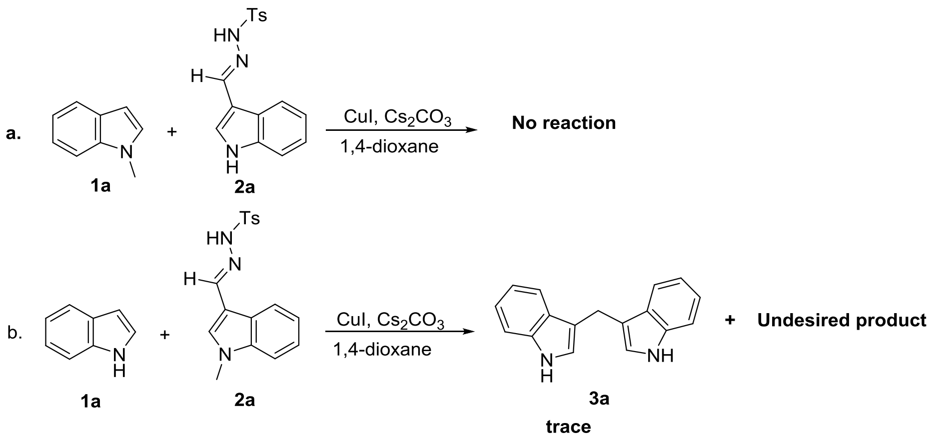
Entry	R₁	R₂	%yield
1	H	H	59
2	5-Br	5-Br	51
3	2-CH_3	2-CH_3	49
4	5-NO_2	5-NO_2	53
5	H	2-CH_3	42
6	H	5-OMe	41

7	H	5-Br	38
8	H	4-Br	37
9	5-Br	2-CH_3	41
10	2-CH_3	4-Br	45
11	5-Br	5-OMe	43
12	5-Br	4-Br	56
13	H	3-CH_3	0

[a]Reaction conditions: All reactions were performed in a 10 mL reaction vial using indole **1a** (1.2 equiv.), indole-3-tosylhydrazone (1.0 equiv.), base (2.0 equiv.), catalyst (10 mol%) and solvent 5 mL.

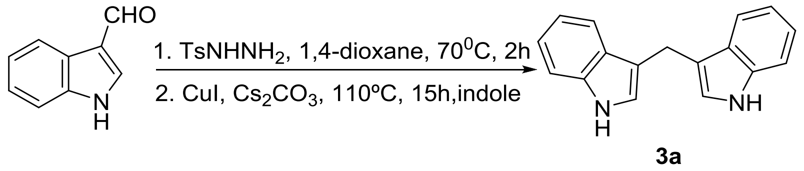
While the proximity of any substituent electron donationg or withdrawing produced a barely lower yield in relation to unsubstituted indoles. The presence of bromo group at 5-position of **1** and **2** produces symmetrical **3** in correspondingly lower amount (**Table 2,** entry 2). Along these, having electron donating group on indole at 2-position does not have much impact on the yield of this transformation (**Table 2,** entry 3). The substrate **1** and **2** having different substitutions produces symmetrical and unsymmetrical bis(indolyl)methane derivatives **3**, where the symmetrical bisindole derivatives conveyed better conversions (**Table 2,** entries 1-4**)** as compared to unsymmetrical bisindoles (**Table 2,** entries 5-12). The transformation of unsubstituted indole **1** with electron donating group associated with **2** made to some degree lower yield as compared to symmetrical bisindoles (**Table 2,** entries 5-8). Further, the reaction of electron donating substituent on indole **1** with electron donating substituent on hydrazone **2** made a better than average yield while electron withdrawing substituent on hydrazone conveyed moderately lower yield (**Table 2,** entries 9-12). Moreover, the reaction of indole **1** with substituent on 3-position of hydrazone made no reaction product (**Table 2,** entry 16).

2.3. Controlled Experiments: A number of controlled trials also carried out to get an informations about the role of substitution at N-1 position (**Scheme 9**). First, the reaction of **1a** and **2a** along with copper iodide (10 mol%), Cs_2CO_3 (2 equiv.) in 1,4-dioxane at 110°C carried out and it showed no reaction (**Scheme 9a**), while the reaction of indole with methylindole-3-tosylhydrazone showed trace amounts of product along with formation of an undesired product which indicates the role of N-H group in the reaction to proceed smoothly (**Scheme 9b**).



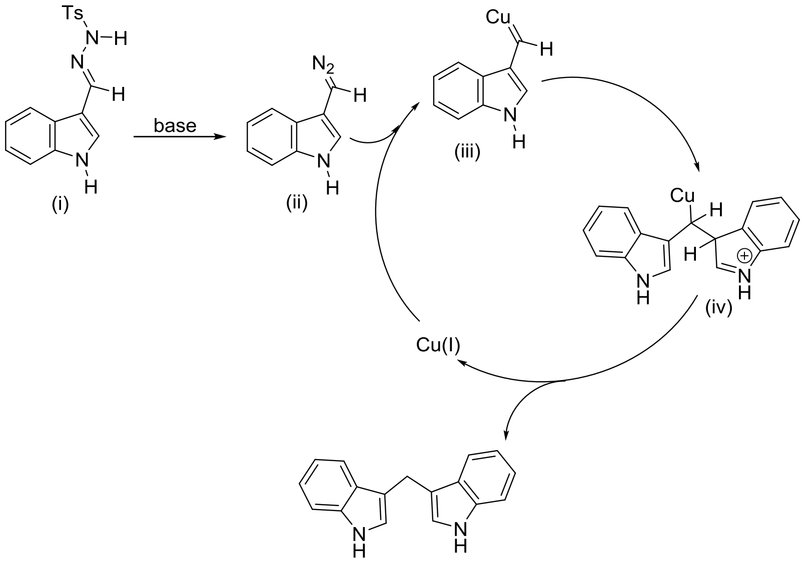
Scheme 9 : Control experiments to examine the role of substitutions on N-1position

2.4. One-pot synthesis: Moreover, we tested the feasibility of reaction in one-pot without purifying the indole based hydrazones (**Scheme 10**). The reaction of indole-3-carboxyaldehyde and tosylhydrazide in 1,4-dioxane was started at 60ºC and observed by TLC and after the complete conversion of indole-3-carboxyaldehyde as indicated by TLC, indole **2a**, Cs_2CO_3 (2 equiv.) and CuI (10 mol%) were mixed and the reaction was kept in sealed tube for 15 hours at 110ºC. The yield of product obtained was 56% which was slightly lower than the stepwise transformation.



Scheme10: One pot C-3 functionalization of bis(indolyl)methanes

2.5. Proposed reaction mechanism: Based on reported literatures and on observations, the plausible reaction mechanism is represented in **Scheme 4**. The reaction started with development of 3-formyl-indoles from indoles via Vilsmeier-Hack reaction[19], which is a very well-known method for the preparation of 3-formyl-indoles. Further, the formation of indole-3-tosylhydrazone from 3-formyl-indole in presence of Tosyl hydrazine in methanol taken place (i). The indole-3-tosyl hydrazone (i) in the presence of base abstract the proton forming diazo intermediate (ii) which on reaction with the copper(I) iodide forms ((1H-indol-3-yl)methylene)copper complex (iii) which is electrophile in nature and undergoes further reaction with indole and gives intermediate (iv), which further gives the bis-indole product and Cu(I) for further catalytic cycle.



Scheme 4 : Possible outcome for the preparations of bis(indolyl)methane

CHAPTER 3: EXPERIMENTAL

3.1. General material:

All the chemicals and solvent was bought from easily available sources and was used without purification. The NMR spectra was recorded using TMS as internal reference in deuterated solvents on Jeol or Bruker spectrometer at 300 (400) and 75 (100) MHz for ^{1}H and ^{13}C-NMR respectively. The chemical shifts δ is reported in ppm and coupling constant J is reported in Hz. The peaks are differentially represented as: singlet (s), doublet (d), triplet (t), multiplet (m), and broad singlet (brs). For checking reaction completion thin layer chromatography (TLC) using silica gel plates was used. The column chromatography was done for product purification using silica gel of particle size 100-120 micron. The compounds were characterised using TLC, ^{1}H NMR, ^{13}C NMR and HRMS techniques.

3.2. General method for the regioselective prepration of bisindolyl methanes:

Initially, the preparations of indole-3-carboxyaldehyde was done using Vilsmeyer-Hack reaction. Next, indole-3-carboxyaldehyde, tosylhydrazine (1.25 equiv.) and p-Toluenesulfonic acid (catalytic amount) in methanol (~ 5 ml) as solvent were added and reflux for overnight to produce indole-3-tosylhydrazone which was purified by filtration and further washed the solid with 5 ml of MeOH (2 times). Next, to set up the final step, indole-3-tosylhydrazone (1 equiv.), indole (1.5 equiv.), CuI (10 mol%), Cs_2CO_3(2 equiv.), and 1,4-dioxane as a solvent were added in a glass sealed tube having a stirring bar and stirred the reaction mixture at 110°C and the development of the conversion was checked by using TLC. Following the complete consumption of indole-3-hydrazone on TLC, reaction was quenched by adding water (5 ml) and extracted the organic layer with ethyl acetate (10 ml x 2). After evaporating the volatiles using high vacuum, the purification of the coupling product was done using column chromatography which afforded the corresponding coupling product in 36-59% yields.

3.3. Characterisation data for Compounds:

di(1H-indol-3-yl)methane (1):

^{1}H NMR (400 MHz, DMSO): δ 10.70 (brs, 2H), 7.48 (d, J = 8Hz, 2H), 7.27 (t, J = 8Hz, 2H), 7.09 (d, J = 2.4Hz, 2H), 7.00-6.96 (m, 2H), 6.88-6.84 (m, 2H), 4.07 (s, 2H) ppm, ^{13}C NMR (100 MHz, DMSO): 136.8, 127.6, 123.2, 121.2, 119.1, 118.5, 114.6, 111.8, 21.4 ppm, HRMS (ESI) Calcd. for $C_{17}H_{14}N_2K$ $[M+39]^+$ 285.0794; Found 285.0789

bis(5-bromo-1H-indol-3-yl)methane (2):

^{1}H NMR (400 MHz, DMSO): δ 10.97 (brs, 2H), 7.65 (s, 2H), 7.31 (d, *J* = 8.4Hz, 2H), 7.25 (s, 2H), 7.15 (d, *J* = 8.4Hz, 2H), 4.10 (s, 2H) ppm, ^{13}C NMR (100 MHz, DMSO): 135.5, 129.4, 125.0, 123.7, 121.3, 114.1, 113.8, 111.2, 21.0 ppm, HRMS (ESI) Calcd. for $C_{17}H_{13}Br_{2}N_{2}$ $[M+H]^{+}$ 402.9445; Found 402.9440.

bis(2-methyl-1H-indol-3-yl)methane (3):

^{1}H NMR (400 MHz, $CDCl_3$ + MeOD): δ 7.30 (t, *J* = 6Hz, 3H), 7.15 (d, *J* = 6.4Hz, 2H), 6.93 (t, *J* = 6Hz, 3H), 6.84 (t, *J* = 5.6Hz, 2H), 4.01 (s, 2H), 2.26 (s, 6H) ppm ^{13}C NMR (100 MHz, $CDCl_3$ + MeOD): 139.2, 135.0, 132.8, 124.0, 122.2, 122.0, 114.2, 113.9, 23.2, 15.4 ppm, HRMS (ESI) Calcd. For $C_{19}H_{18}N_{2}Na$ $[M+23]^{+}$ 297.1368; Found 297.1362.

bis(5-nitro-1H-indol-3-yl)methane (4):

^{1}H NMR (400 MHz, DMSO): δ 11.65 (brs, 2H), 8.55 (s, 2H), 8.02-8.00 (m, 2H), 7.57 (d, *J* = 7.2Hz, 4H), 4.37 (s, 2H) ppm, ^{13}C NMR (100 MHz, DMSO):140.5, 140.0, 127.4, 126.7, 117.0, 116.9, 116.3, 112.3, 20.7 ppm, HRMS (ESI) Calcd. For $C_{17}H_{13}N_{4}O_{4}$ $[M+H]^{+}$ 339.0937; Found 337.0931.

3-((1H-indol-3-yl)methyl)-2-methyl-1H-indole (5):

^{1}H NMR (400 MHz, $CDCl_3$ + MeOD): δ 7.56 (d, *J* = 6.4Hz, 1H), 7.36 (d, *J* = 6.4Hz, 1H), 7.21-7.15 (m, 2H), 7.06 (t, *J* = 6Hz, 1H), 6.99 (s, 2H), 6.90 (t, *J* = 6Hz, 1H), 6.57 (s, 1H), 4.05 (s, 2H), 2.25 (s, 3H) ppm ^{13}C NMR (100 MHz, $CDCl_3$ + MeOD): 136.4, 135.3, 131.5, 128.9, 127.3, 122.2, 121.3, 120.3, 118.9, 118.6, 118.5, 118.3, 115.6, 111.0, 110.1, 109.8, 19.8, 11.4 ppm, HRMS (ESI) Calcd. For $C_{18}H_{16}N_{2}Na$ $[M+23]^{+}$ 283.1211; Found 283.1206.

3-((1H-indol-3yl)methyl-5-methoxy-1H-indole (6):

^{1}H NMR (400 MHz, DMSO): δ 10.71 (brs, 1H), 10.54 (brs, 1H), 7.53 (d, *J* = 7.6Hz, 1H), 7.33 (d, *J* = 8Hz, 1H), 7.22 (d, *J* = 8.8Hz, 1H), 7.14 (s, 1H), 7.07-7.00 (m, 3H), 6.94 (t, *J* = 7.2Hz, 1H), 6.69 (d, *J* = 6.4Hz, 1H), 4.09 (s, 2H), 3.70 (s, 3H) ppm, ^{13}C NMR (100 MHz, DMSO): 153.2, 136.8, 132.0, 127.9, 127.6, 123.9, 123.1, 121.1, 119.1, 118.4, 114.6, 114.4, 112.3, 111.7, 111.1, 101.1, 55.7, 21.3 ppm, HRMS (ESI) Calcd. For $C_{18}H_{16}N_{2}ONa$ $[M+23]^{+}$ 299.1160; Found 299.1155.

3-((1H-indol-3-yl)methyl)-5-bromo-1H-indole (7):

^{1}H NMR (400 MHz, $CDCl_3$ + MeOD): δ 7.84(s, 1H), 7.66(s, 1H), 7.51 (d, *J* = 6.4Hz, 1H), 7.28 (d, *J* = 6.8Hz, 1H), 7.02 (t, *J* = 5.6Hz, 2H), 6.83 (s, 3H), 4.10 (s, 2H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$ + MeOD): 136.4, 135.06, 129.3, 127.4, 124.7, 123.4, 122.1, 121.8, 119.2, 119.1, 115.3, 115.1, 112.5, 111.1, 29.7, 21.1 ppm, HRMS (ESI) Calcd. For $C_{17}H_{14}BrN_2$ $[M+H]^+$ 325.0340; Found 325.0328.

3-((1H-indol-3-yl)methyl)-4-bromo-1H-indole (8):

^{1}H NMR (400 MHz, DMSO): δ 11.10 (brs, 1H), 10.74 (brs, 1H), 7.51 (d, *J* = 7.6Hz, 1H), 7.39-7.35 (t, *J* = 8Hz, 2H), 7.18 (d, *J* = 7.2Hz, 1H), 7.08-6.93 (m, 5H), 4.41 (s, 2H) ppm, ^{13}C NMR (100 MHz, DMSO): 138.3, 136.8, 127.5, 125.9, 125.2, 123.5, 123.0, 122.3, 121.2, 119.0, 118.5, 115.2, 115.0, 113.6, 111.8, 111.6, 22.4 ppm, HRMS (ESI) Calcd. For $C_{17}H_{13}BrN_2Na$ $[M+23]^+$ 347.0160; Found 347.0154.

5-bromo-3-((2-methyl-1H-indol-3-yl)methyl)-1H-indole (9):

^{1}H NMR (400 MHz, DMSO): δ 10.89 (brs, 1H), 10.69 (brs, 1H), 7.60 (s, 1H), 7.36 (d, *J* = 8Hz, 1H), 7.28 (d, *J* = 8.4Hz, 1H), 7.23 (d, *J* = 8Hz, 1H), 7.13 (d, *J* = 8.4Hz, 1H), 7.049 (s, 1H), 6.96 (d, *J* = 7.2Hz, 1H), 6.87 (d, *J* = 7.6Hz, 1H), 4.03 (s, 2H), 2.39 (s, 3H) ppm, ^{13}C NMR (100 MHz, DMSO): 135.7, 135.5, 131.8, 129.3, 128.8, 124.7, 123.5, 121.2, 120.2, 118.3, 118.1, 115.0, 113.7, 111.1, 110.7, 109.5, 19.9, 11.9 ppm, HRMS (ESI) Calcd. For $C_{18}H_{16}BrN_2$ $[M+H]^+$ 339.0497; Found 339.0491.

4-bromo-3-((2-methyl-1H-indol-3-yl)methyl)-1H-indole (10):

^{1}H NMR (400 MHz, DMSO): δ 10.97 (brs, 1H), 10.75 (brs, 1H), 7.36 (d, *J* = 8Hz, 1H), 7.28 (d, *J* = 8Hz, 1H), 7.21 (t, *J* = 6Hz, 2H), 6.98 (t, *J* = 7.6Hz, 2H), 6.86 (d, *J* = 7.2Hz, 1H), 6.53 (s, 1H), 4.390 (s, 2H), 2.324 (s, 3H)ppm, ^{13}C NMR (100 MHz, DMSO):138.4, 135.824, 132.365, 128.864, 125.404, 122.937, 122.393, 120.269, 118.482, 118.130, 115.602, 113.7, 111.7, 110.8, 109.2, 55.3, 21.6, 11.8 ppm, HRMS (ESI) Calcd. For $C_{18}H_{15}BrN_2K$ $[M+39]^+$ 377.0056; Found 377.0050.

5-bromo-3-((5-methoxy-1H-indol-3-yl)methyl)-1H-indole (11):

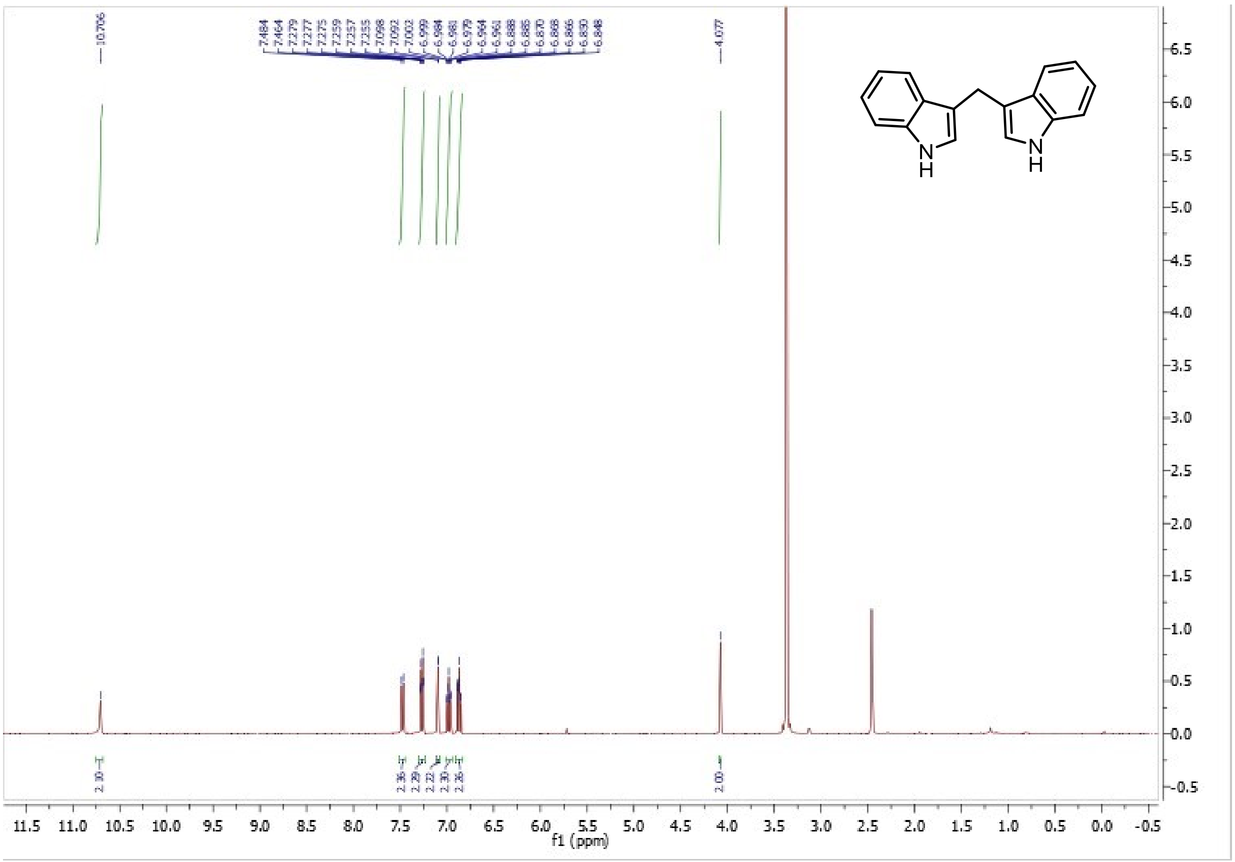
^{1}H NMR (400 MHz, DMSO): δ 10.95 (brs, 1H), 10.57 (brs, 1H), 7.68 (d, *J* = 11.2, 2H), 7.31-7 (d, *J* = 8.4Hz, 1H), 7.24 (d, *J* = 11.2Hz, 1H), 7.15 (d, *J* = 8.4Hz, 1H), 7.10 (s, 1H), 7.01 (s, 1H), 6.71 (d, J = 8.8Hz, 1H), 4.08 (s,2H), 3.71 (s, 3H) ppm, ^{13}C NMR (100 MHz, DMSO):

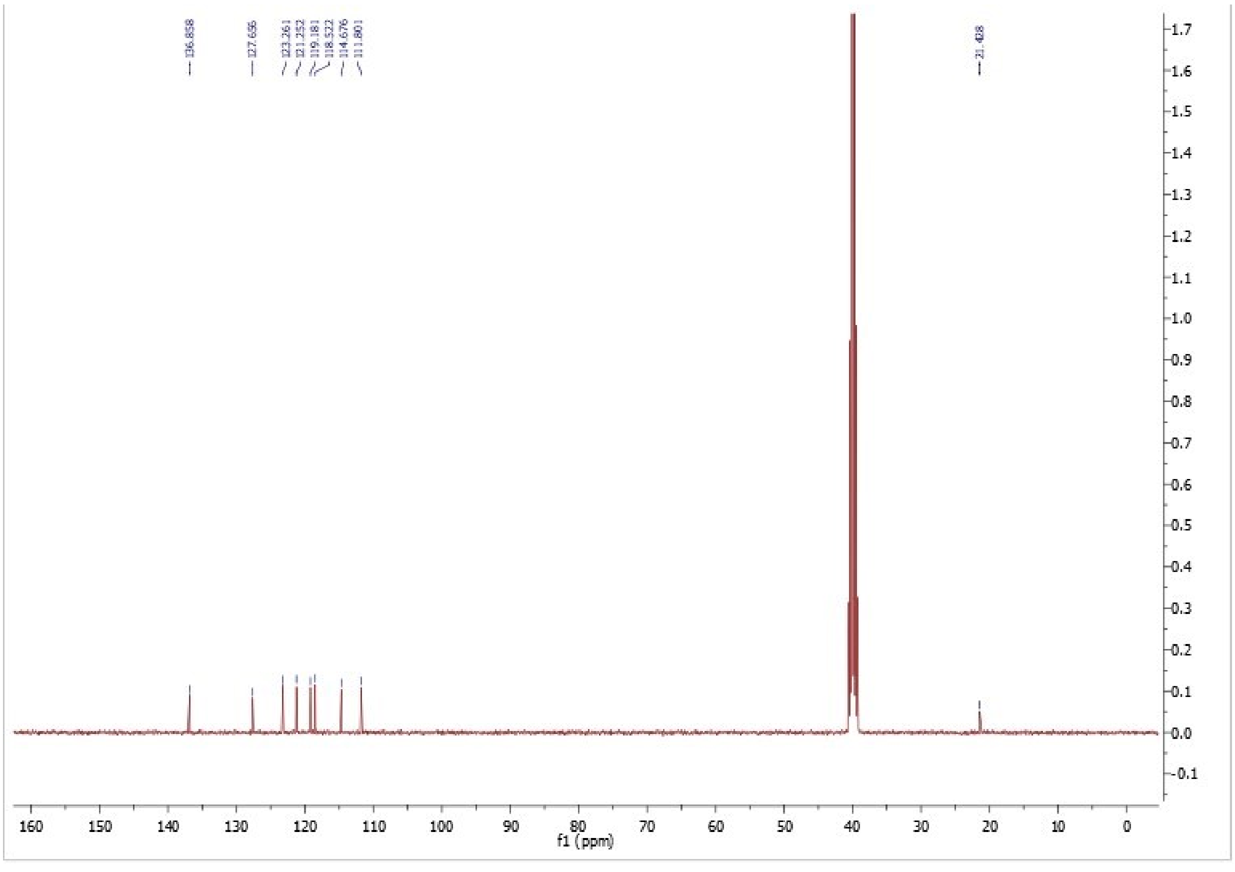
153.2, 135.5, 132.0, 129.5, 127.8, 124.9, 123.6, 121.4, 114.5, 114.0, 113.8, 112.4, 111.2, 111.1, 101.1, 55.7, 21.1 ppm, HRMS (ESI) Calcd. For $C_{18}H_{15}BrN_2OK$ $[M+39]^+$ 393.0005; Found 392.9999.

5-bromo-3-((4-bromo-1H-indol-3-yl)methyl)-1H-indole (12):

^{1}H NMR (400 MHz, DMSO): δ 11.14 (brs, 1H), 10.98 (brs, 1H), 7.64 (s, 1H), 7.39 (d, *J* = 8Hz, 1H), 7.34 (d, *J* = 8.8Hz, 1H), 7.17 (d, *J* = 8Hz, 2H), 7.07-6.95(m, 3H), 4.36(s, 2H) ppm, ^{13}C NMR (100 MHz, DMSO): 138.3, 135.5, 129.3, 125.9, 125.3, 125.1, 123.6, 123.0, 122.4, 121.2, 114.9, 114.7, 113.8, 113.6, 111.7, 111.2, 22.2 ppm, HRMS (ESI) Calcd. For $C_{17}H_{12}Br_2N_2K$ $[M+39]^+$ 440.9004; Found 440.8999

^{1}H NMR & ^{13}C NMR Spectra of Derivative (1)





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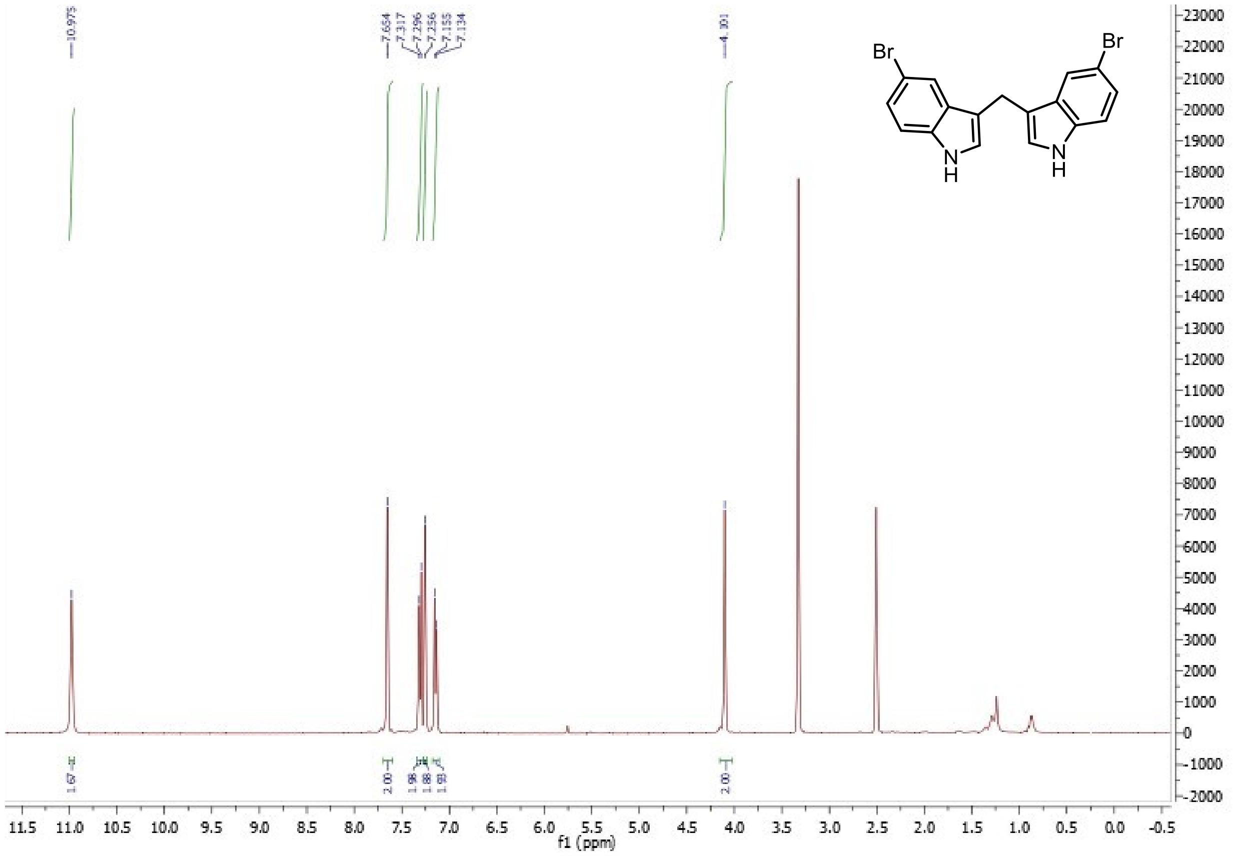
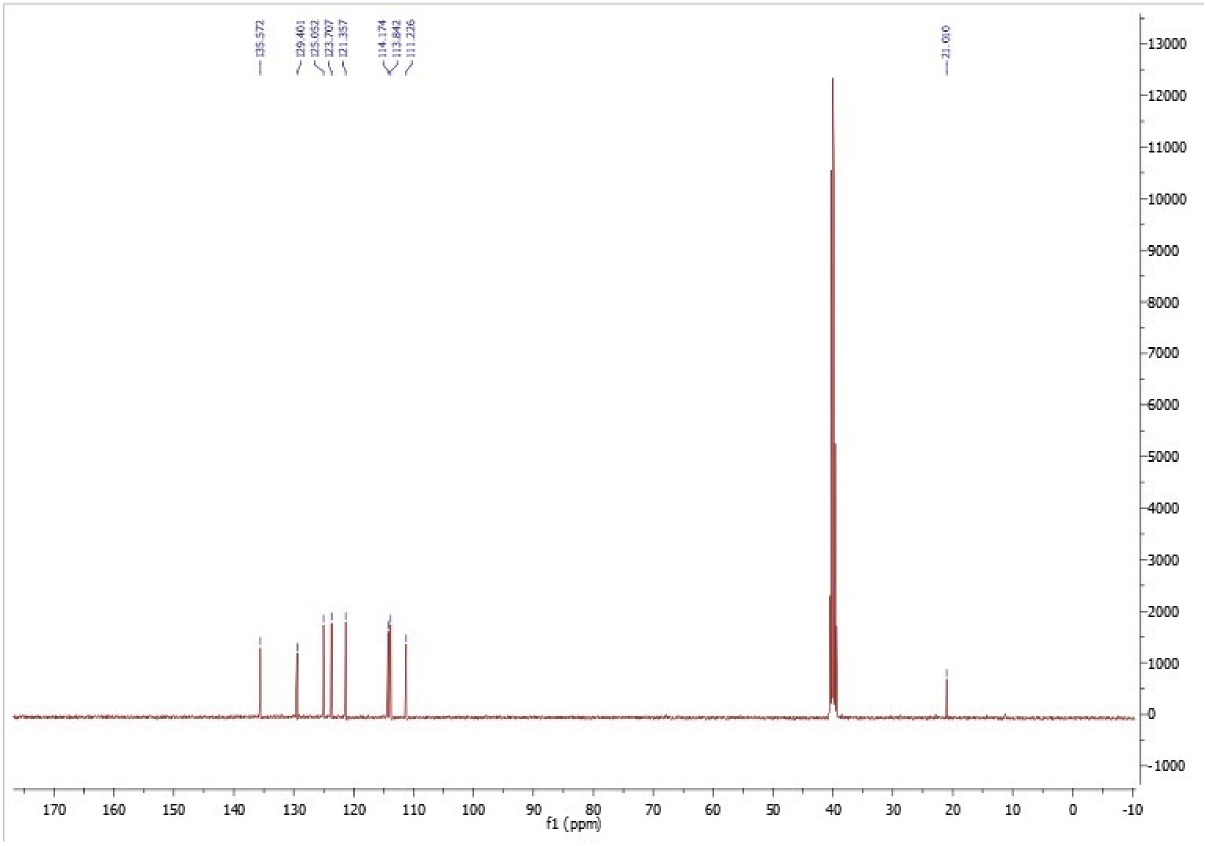
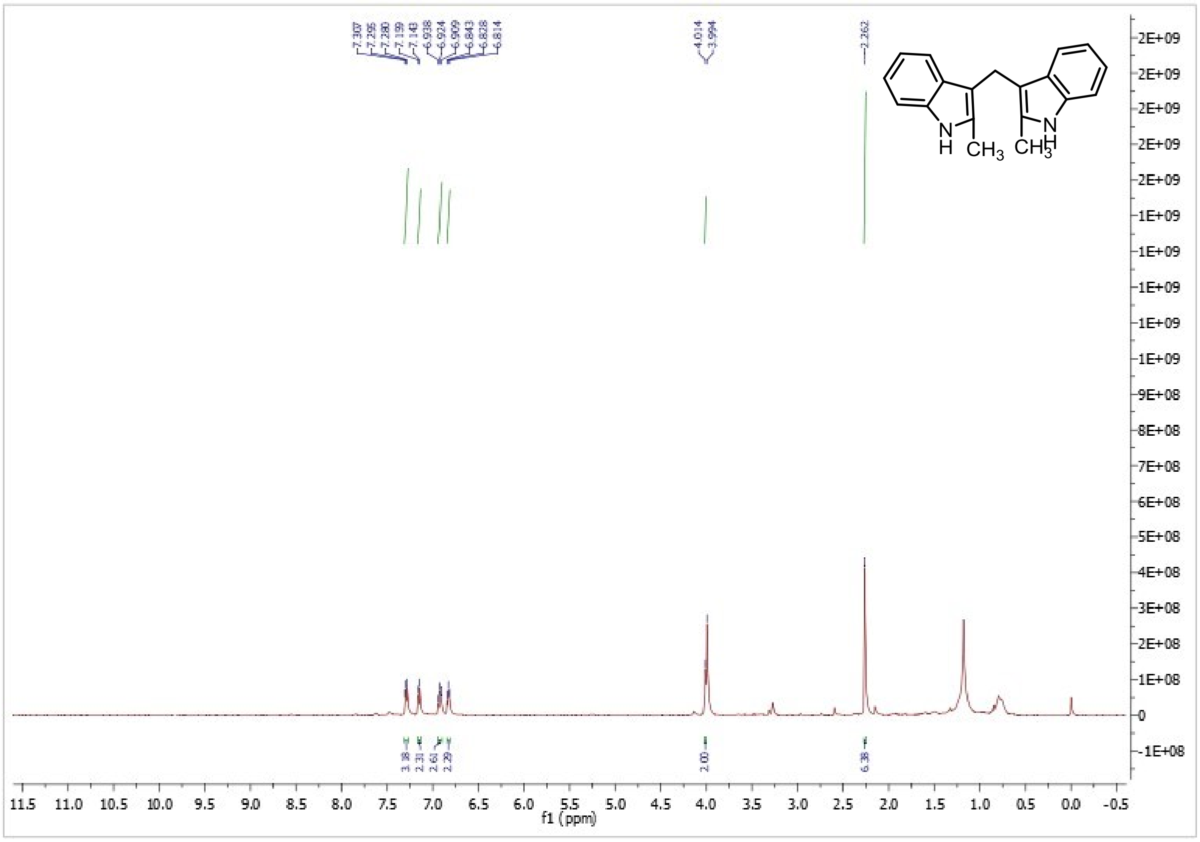
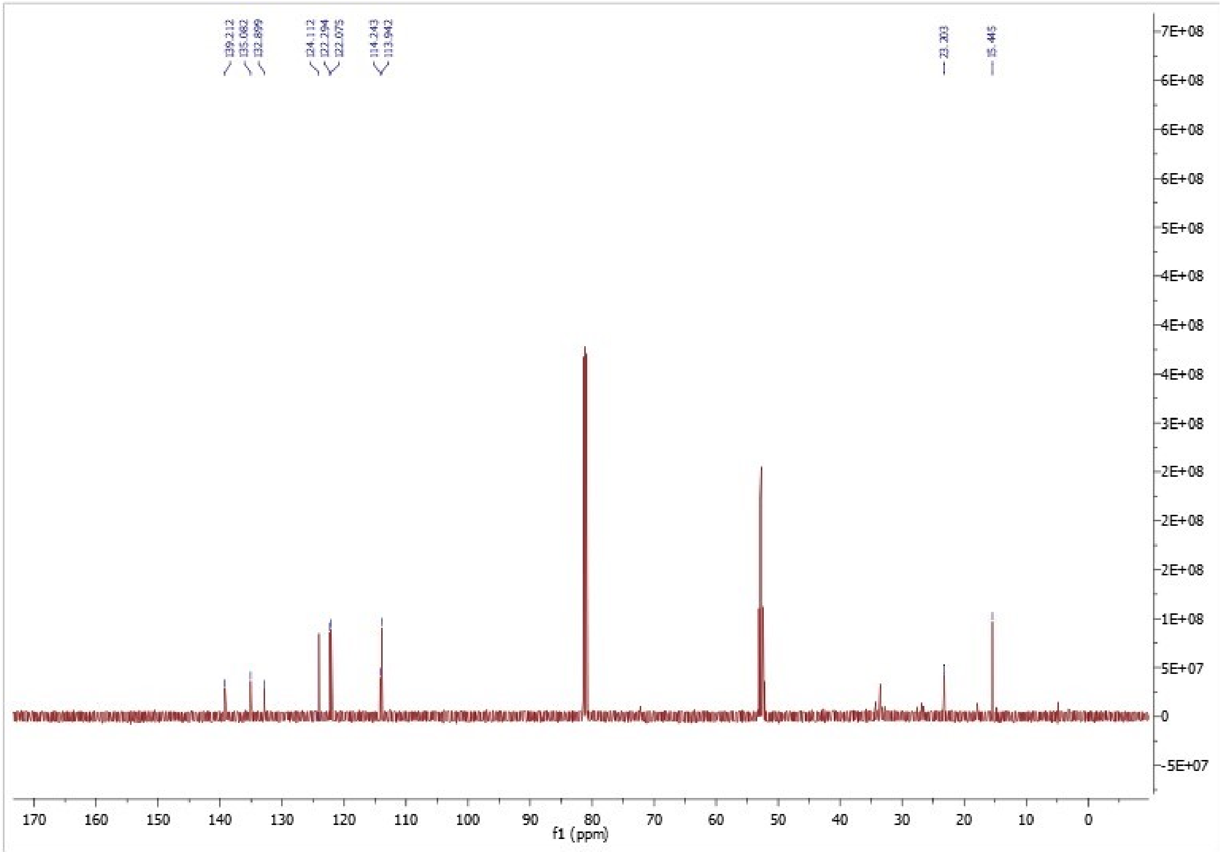


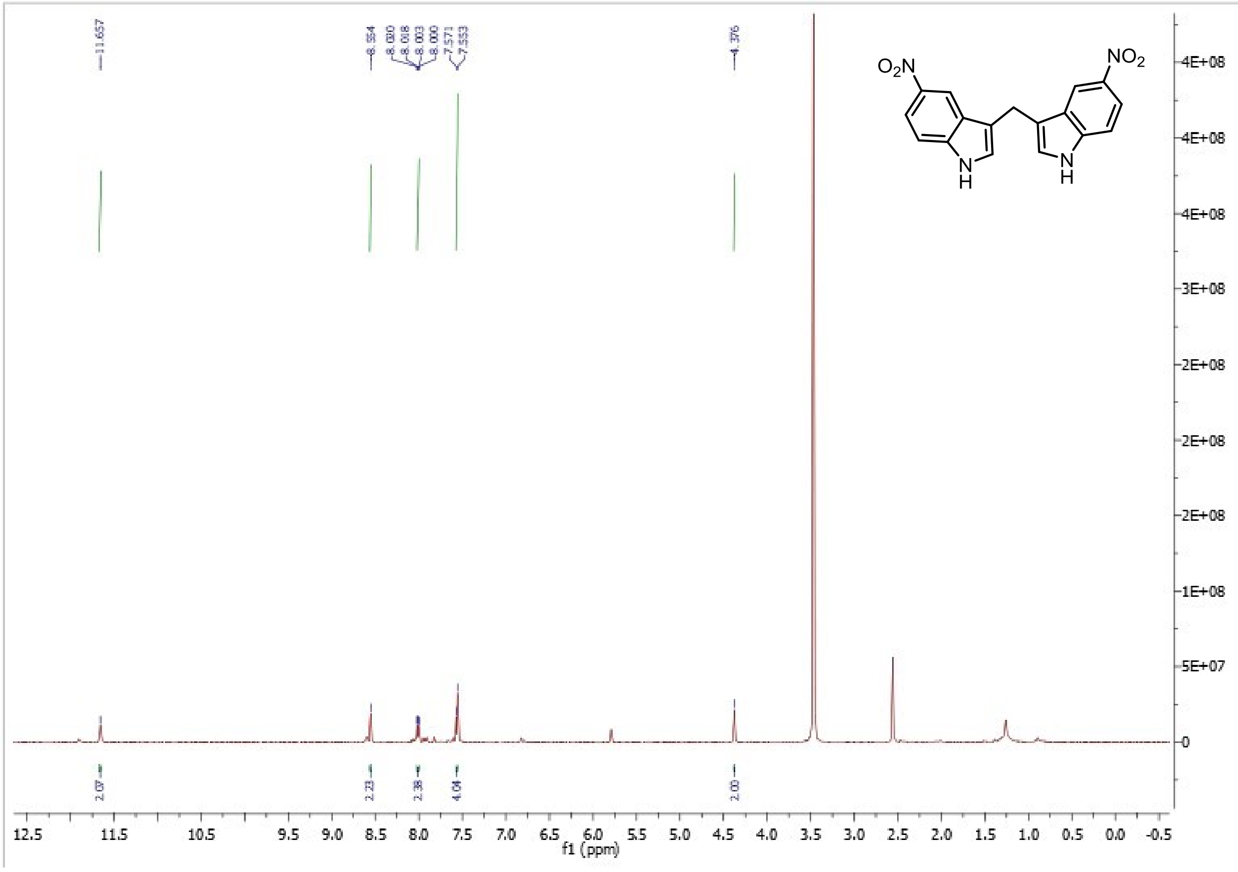


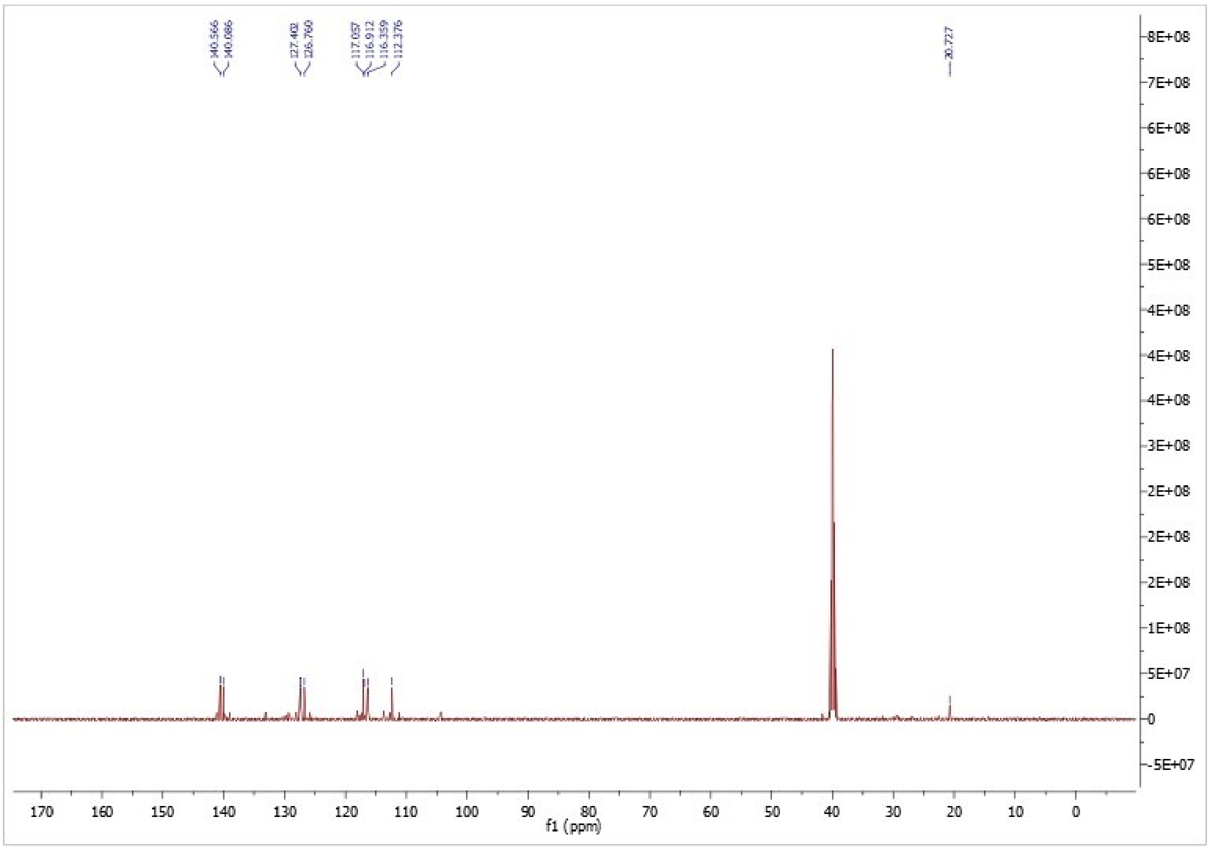
^{1}H NMR & ^{13}C NMR of Derivative (3)



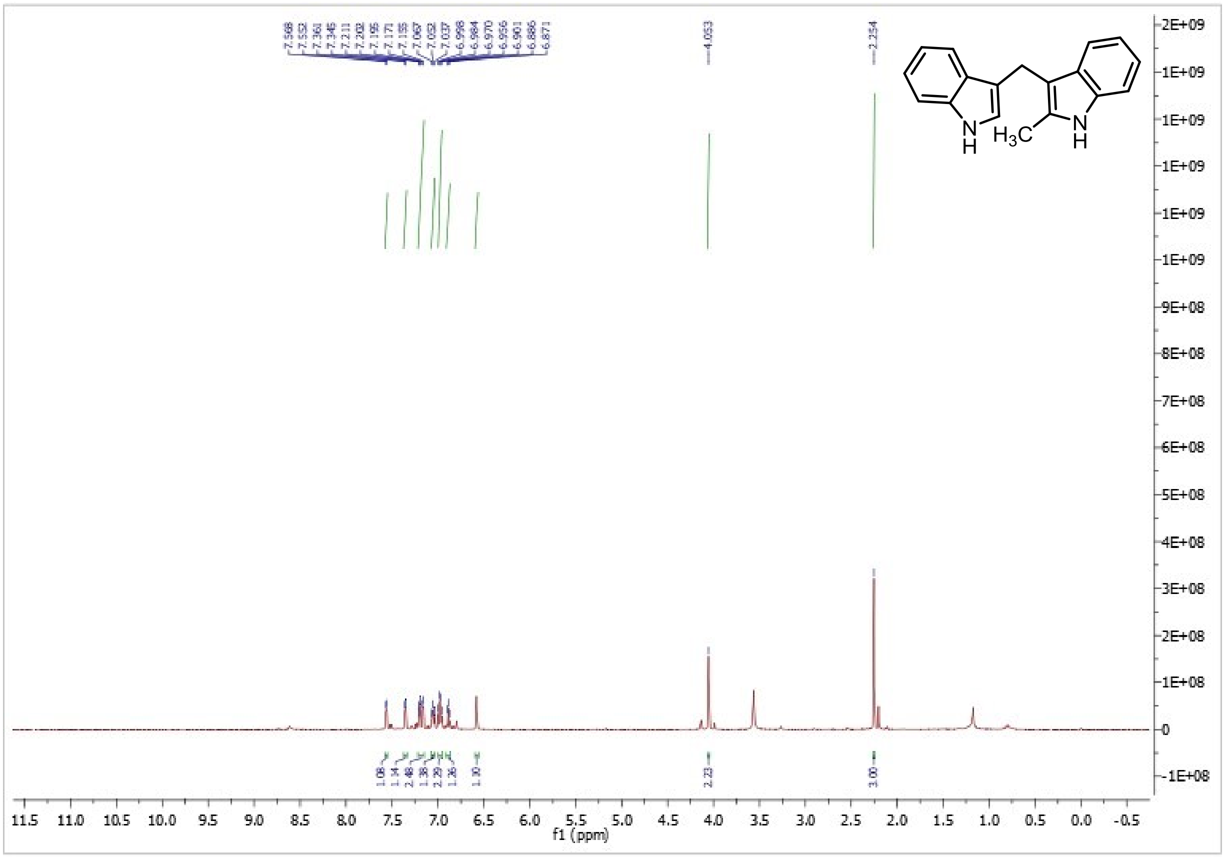


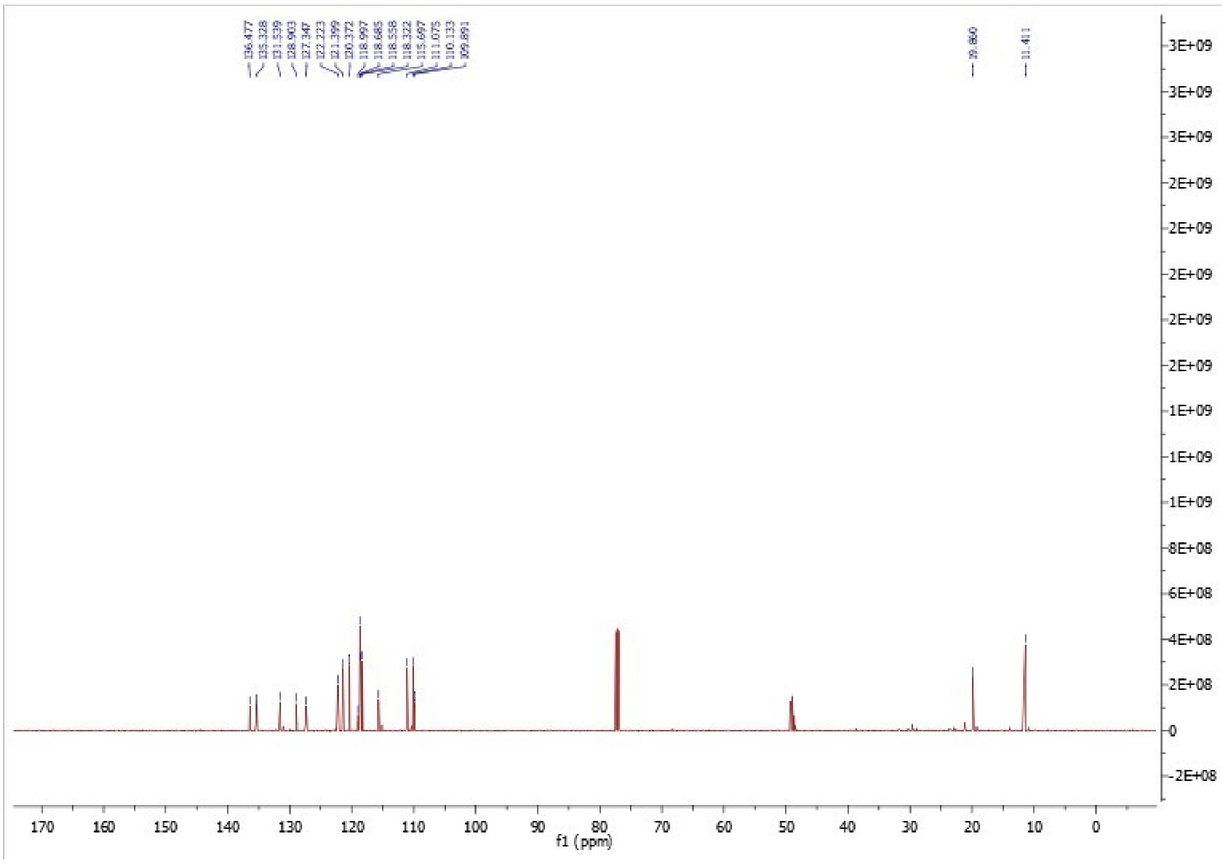
^{1}H NMR & ^{13}C NMR of Derivative (4)



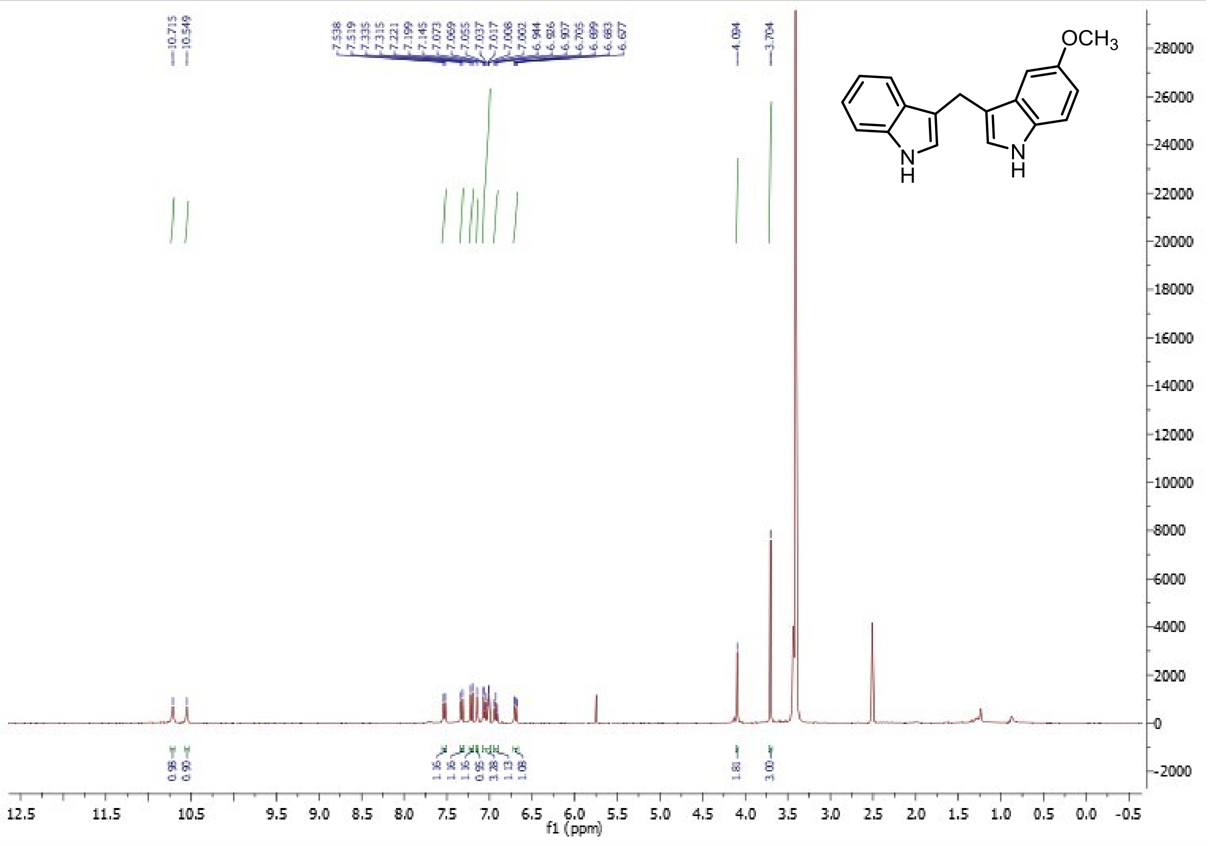


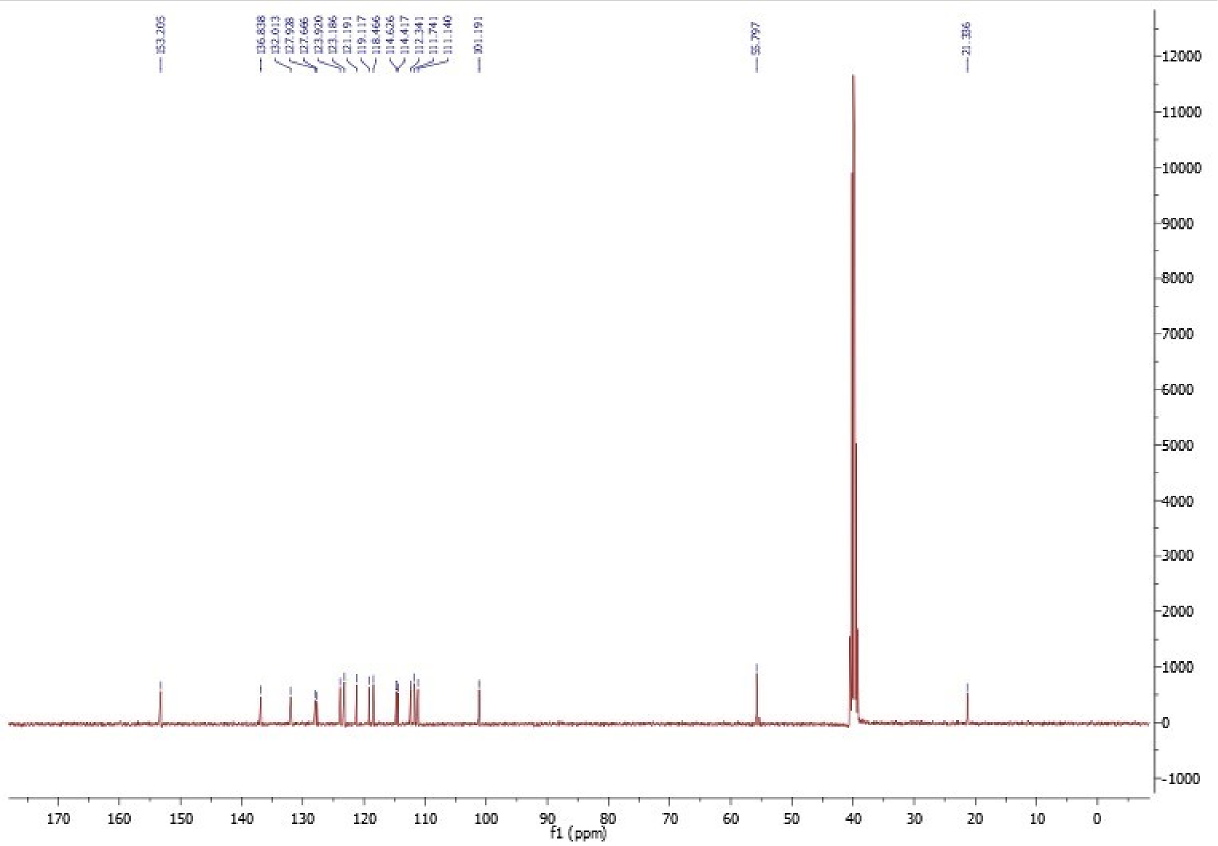
^{1}H NMR & ^{13}C NMR of Derivative (5)



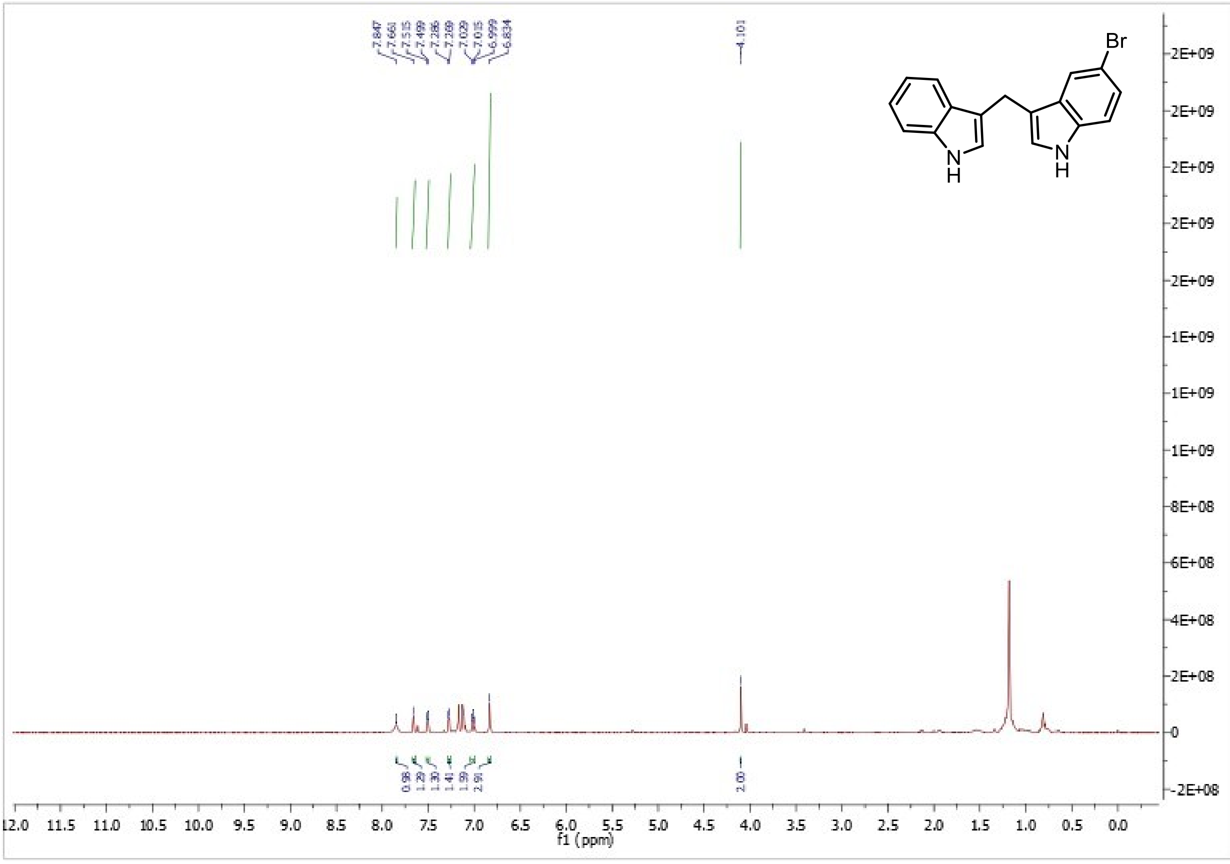


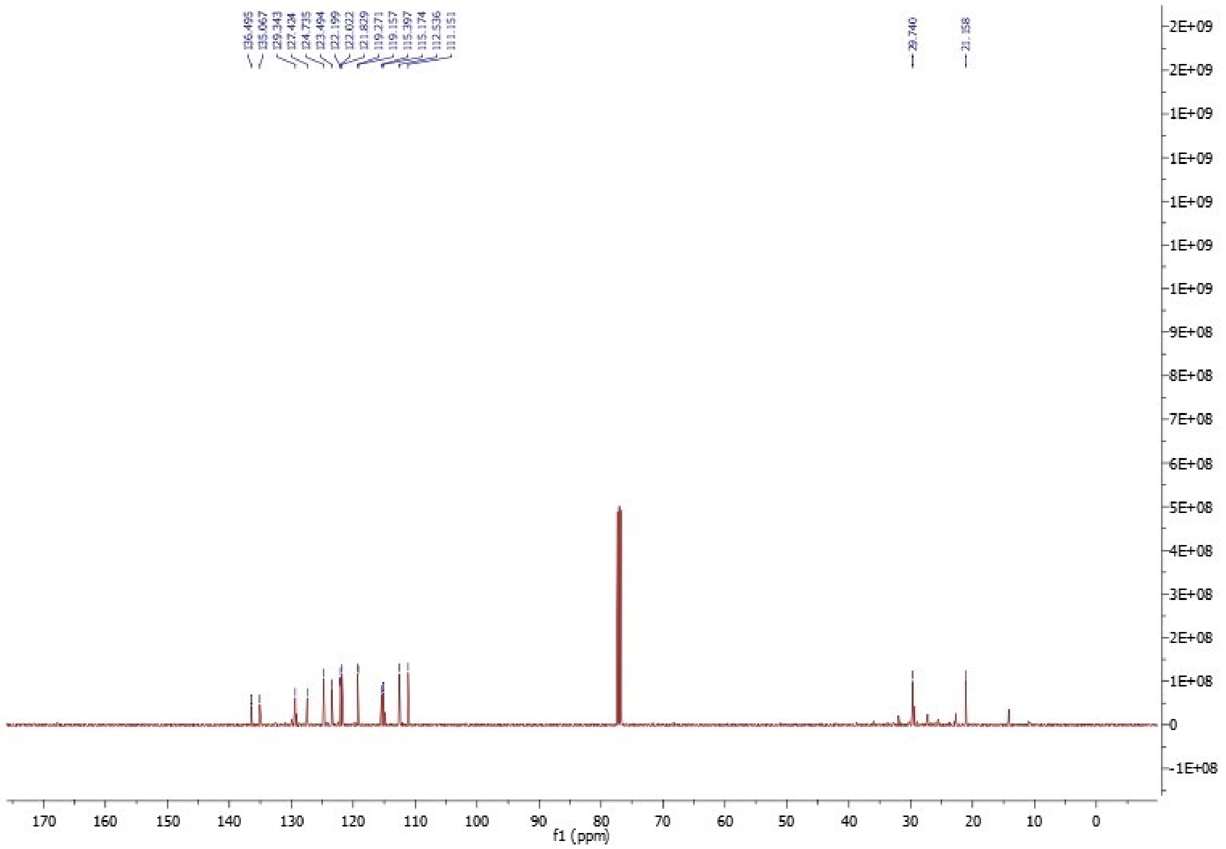
^{1}H NMR & ^{13}C NMR of Derivative (6)





^{1}H NMR & ^{13}C NMR of Derivative (7)





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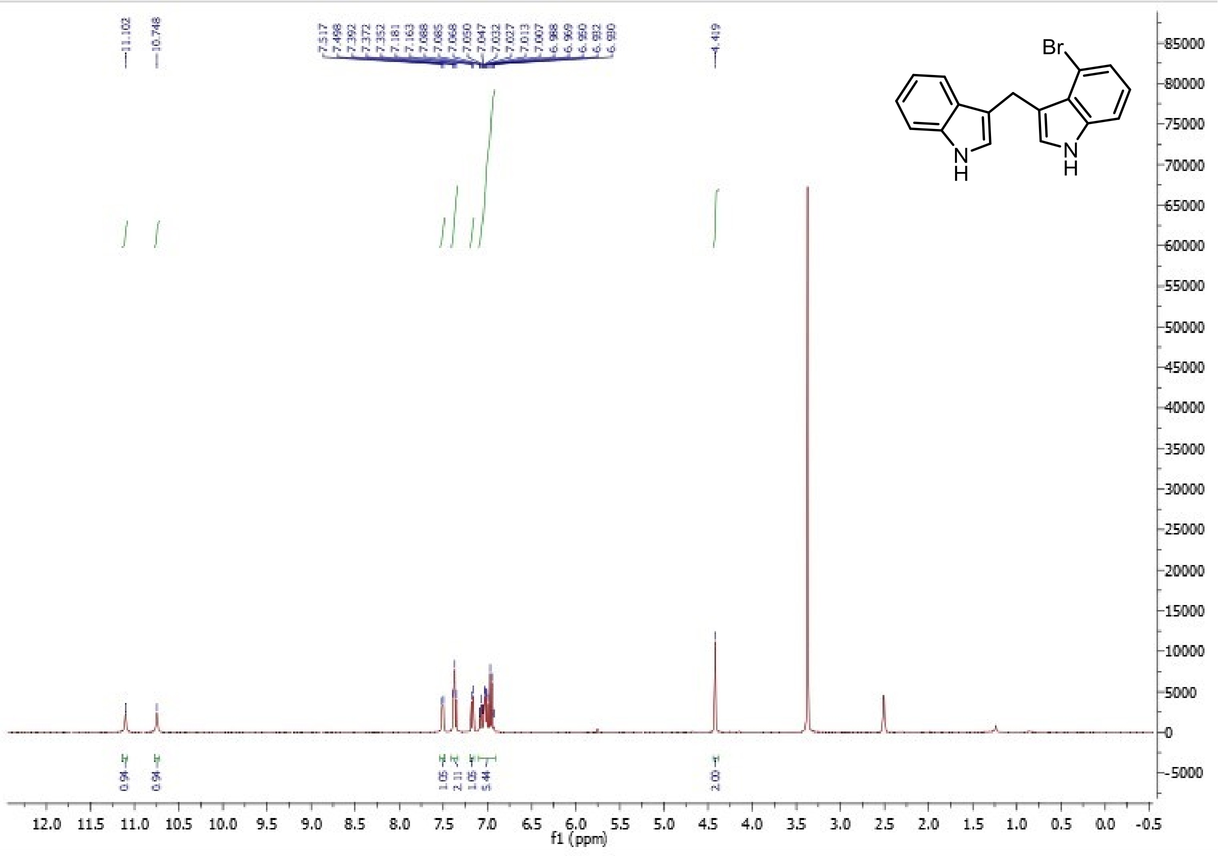
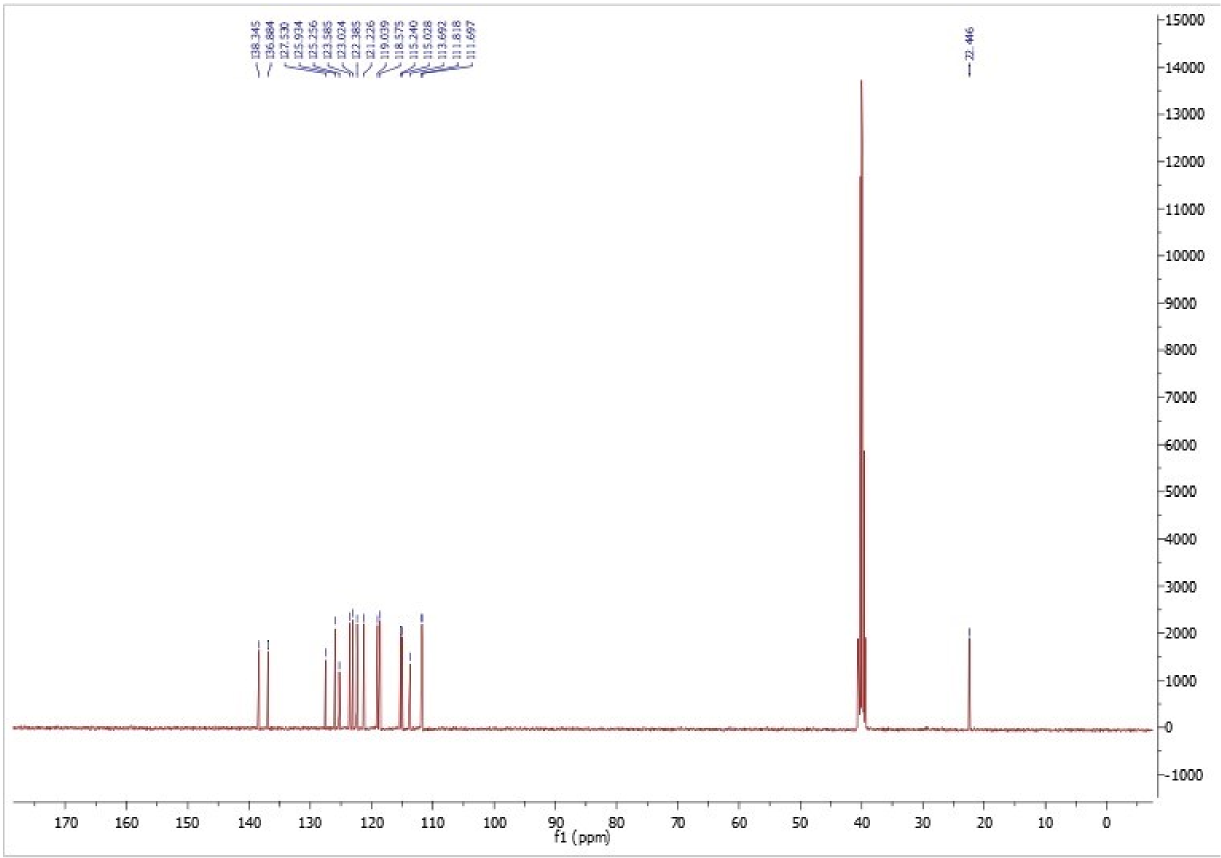
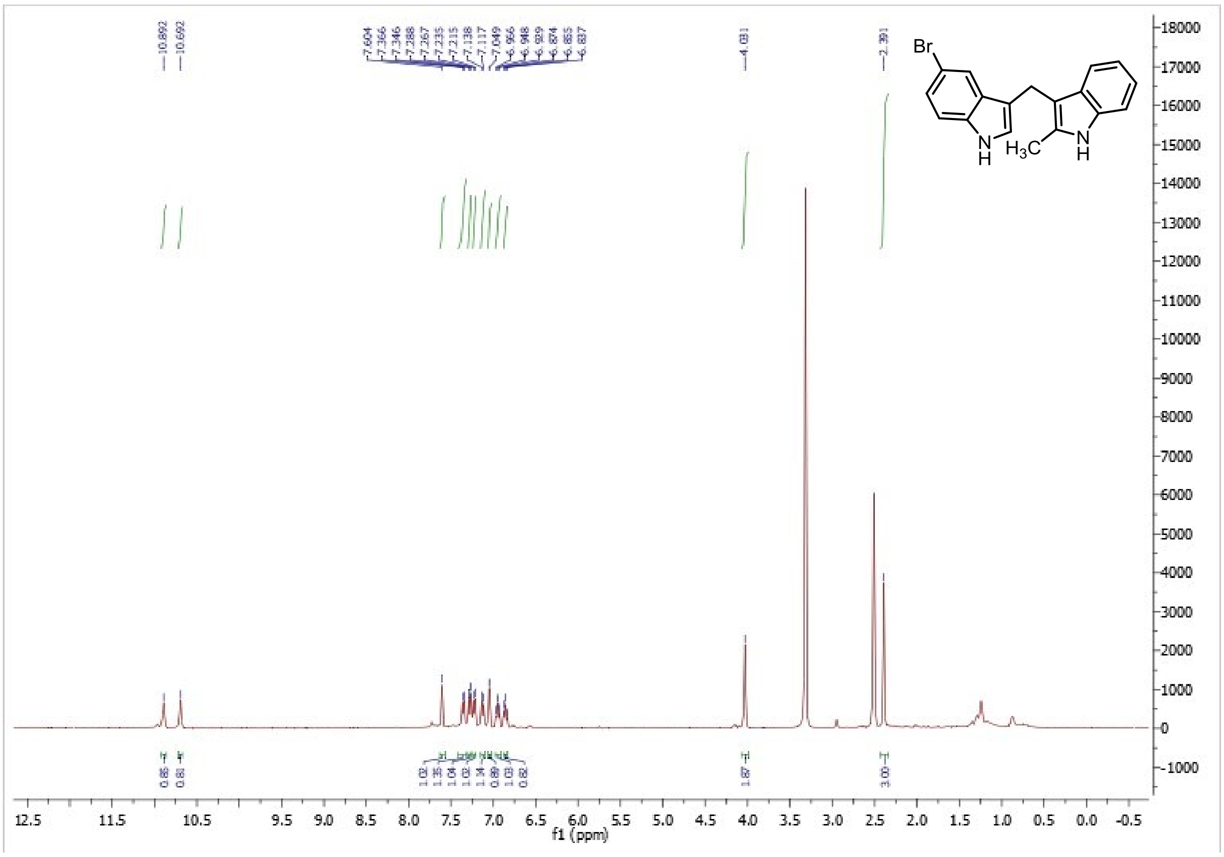
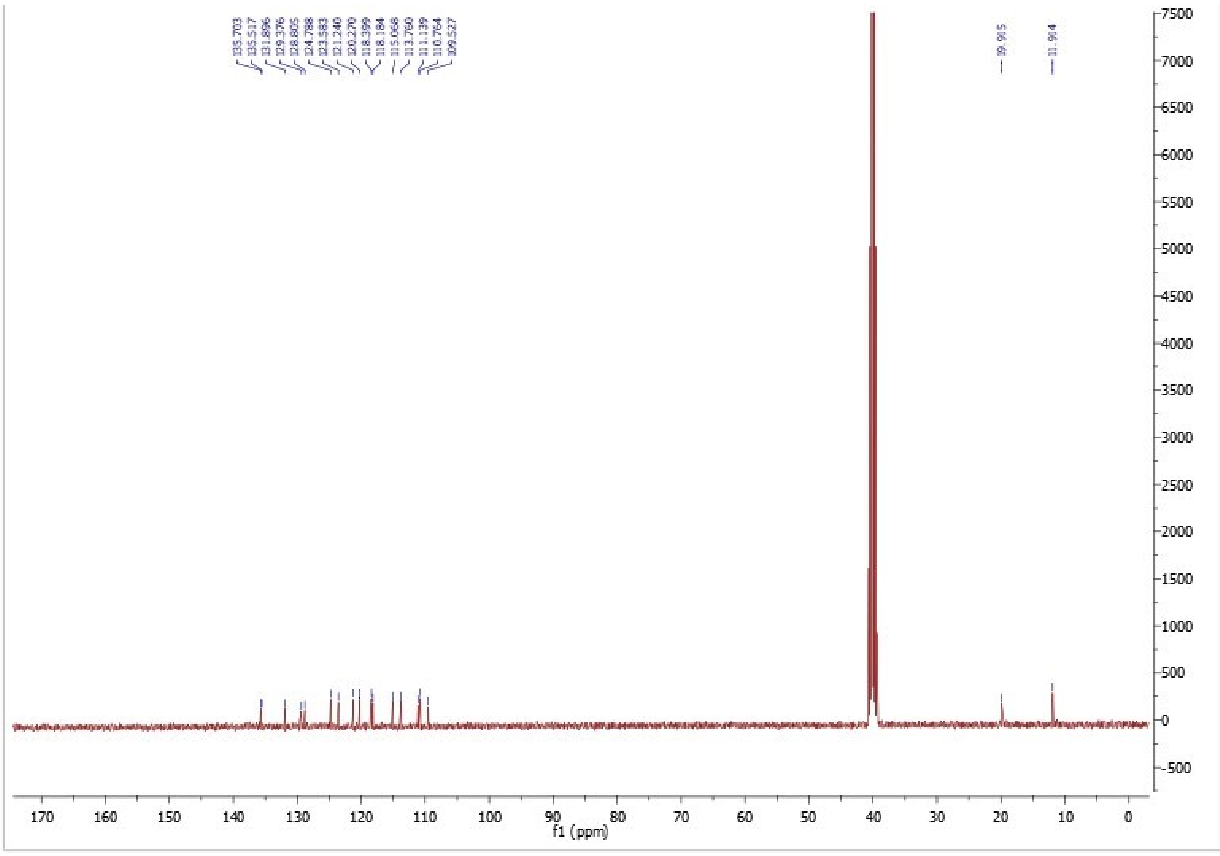


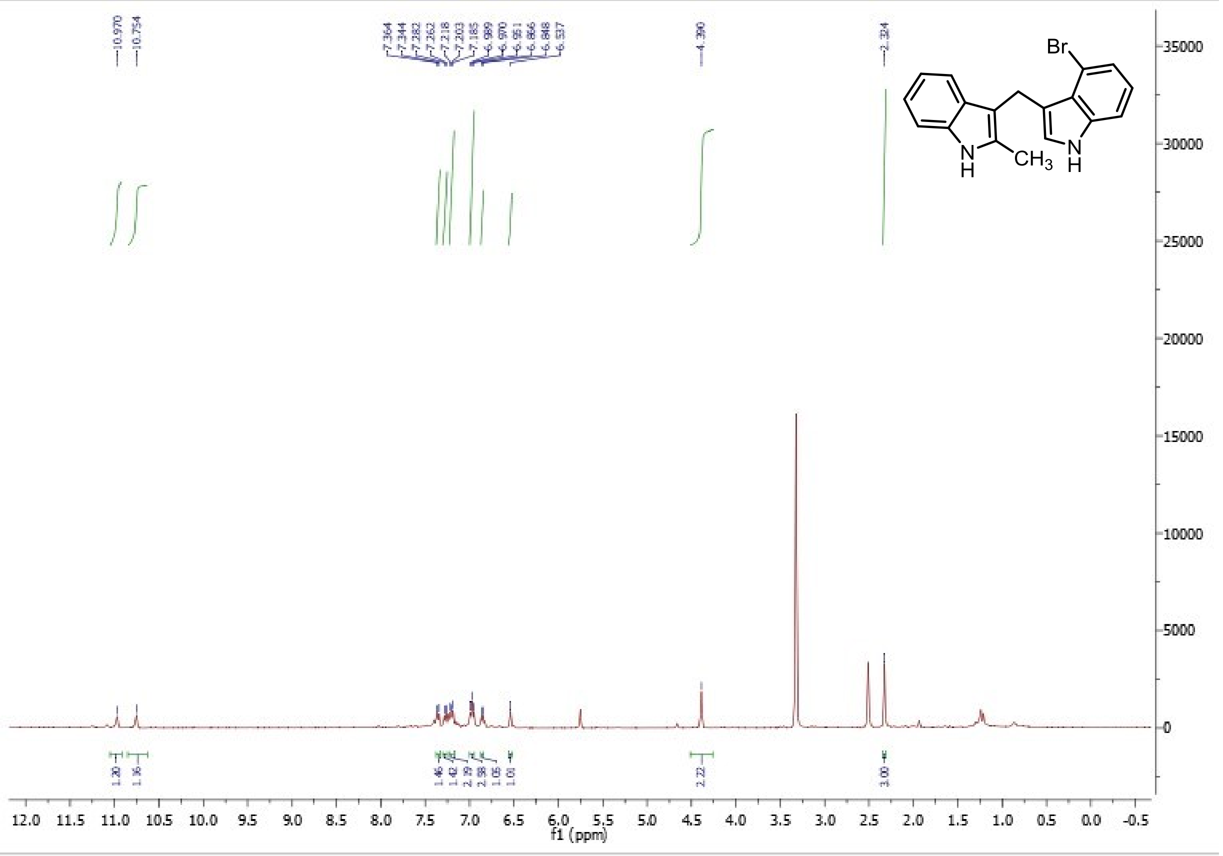


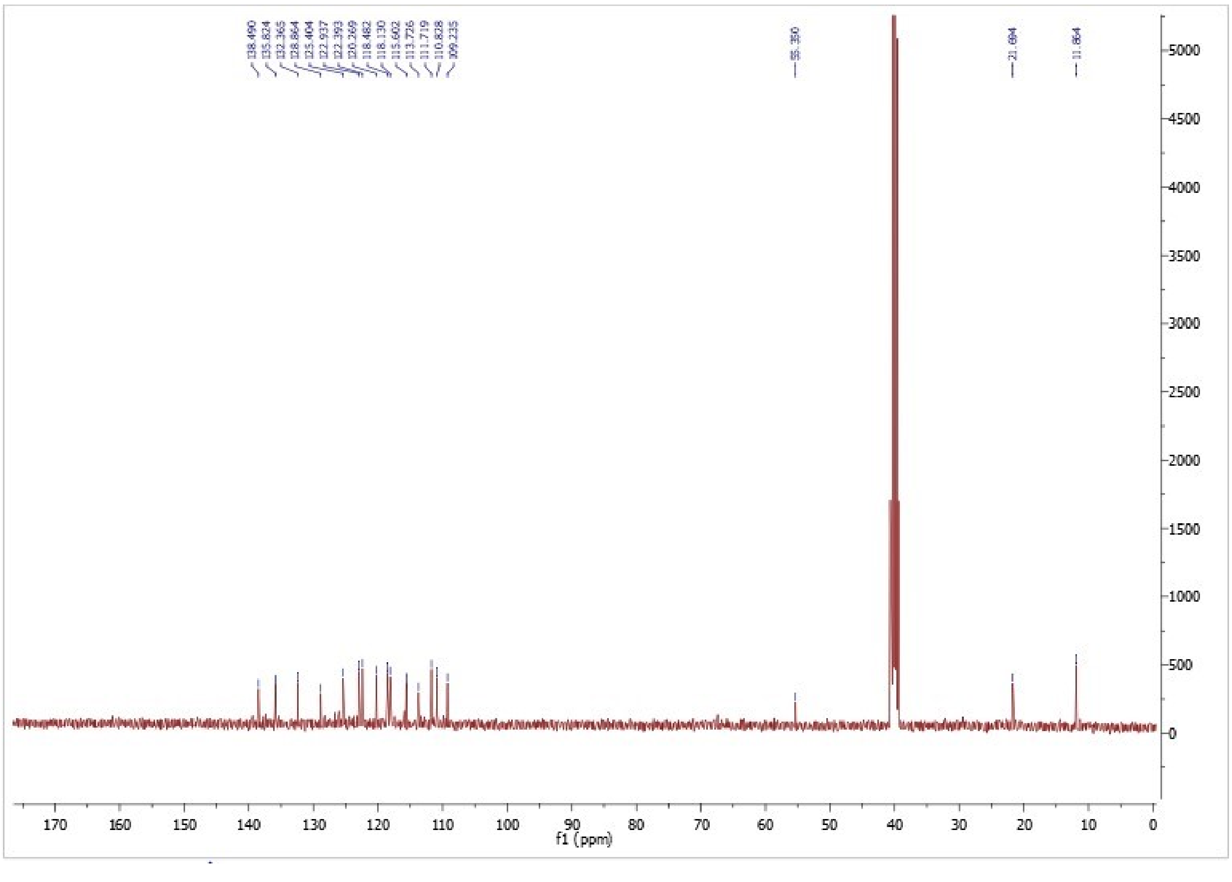
^{1}H NMR & ^{13}C NMR of Derivative (9)



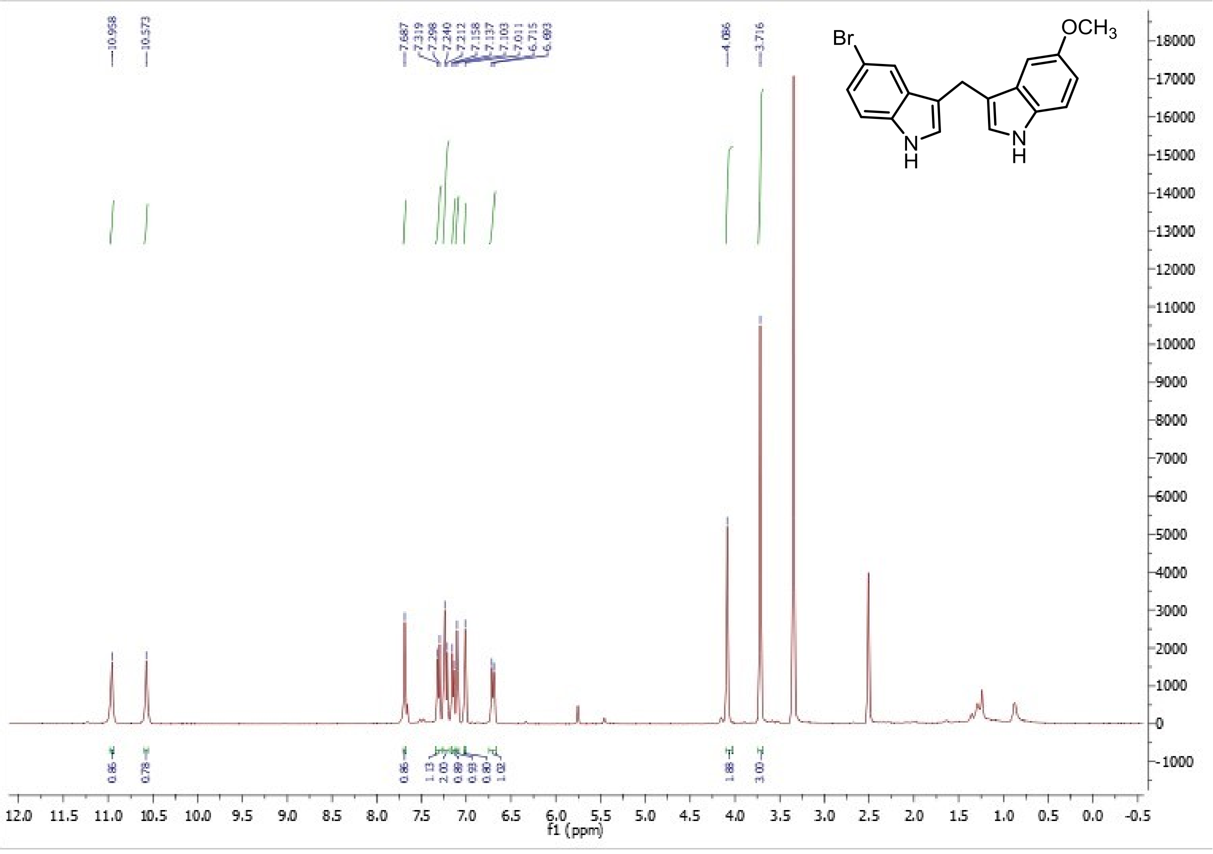


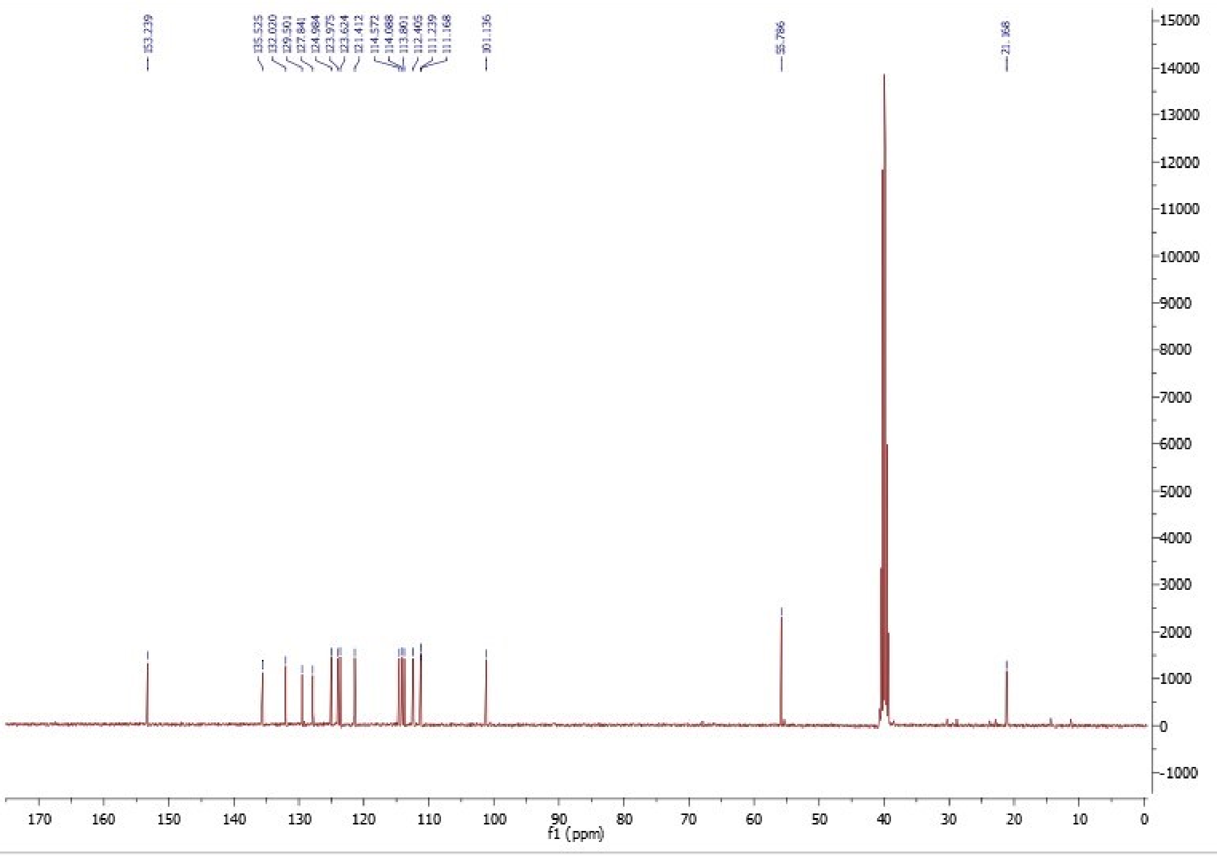
^{1}H NMR & ^{13}C NMR of Derivative (10)



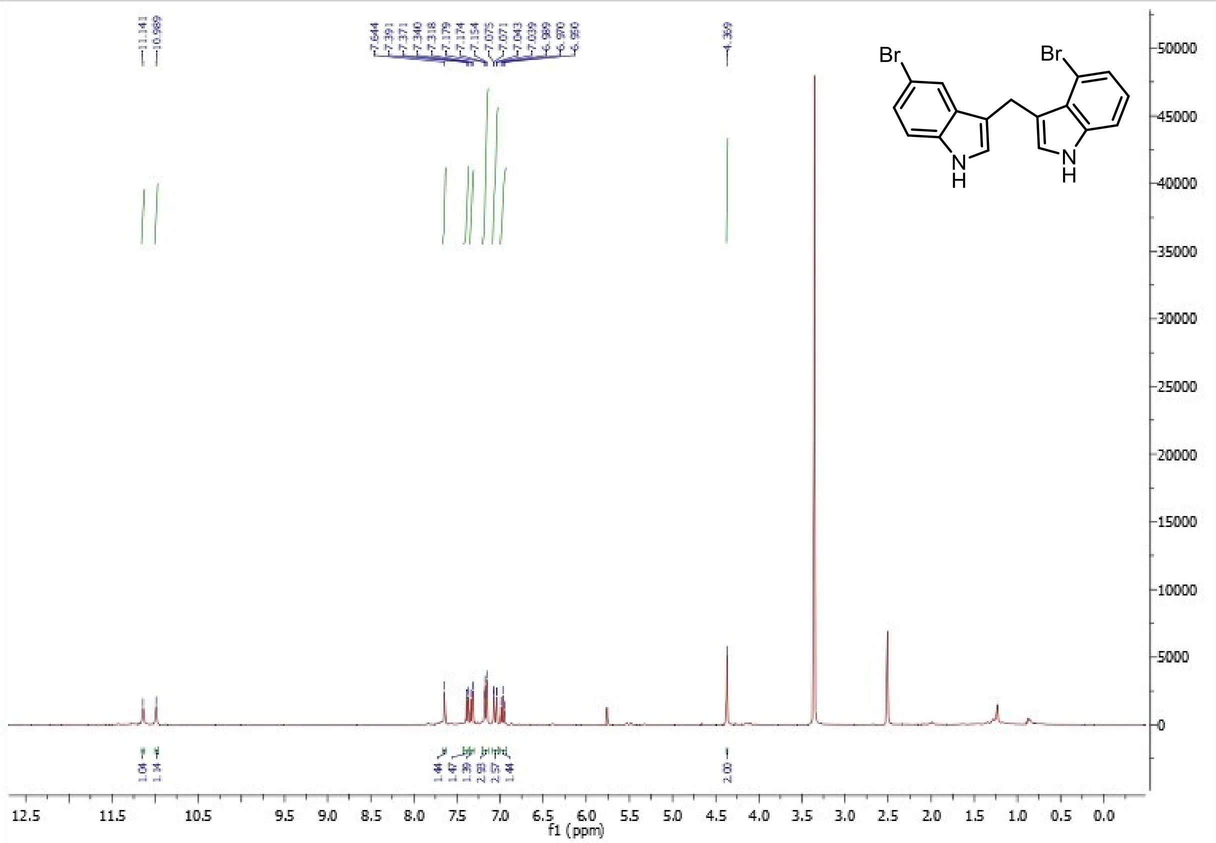


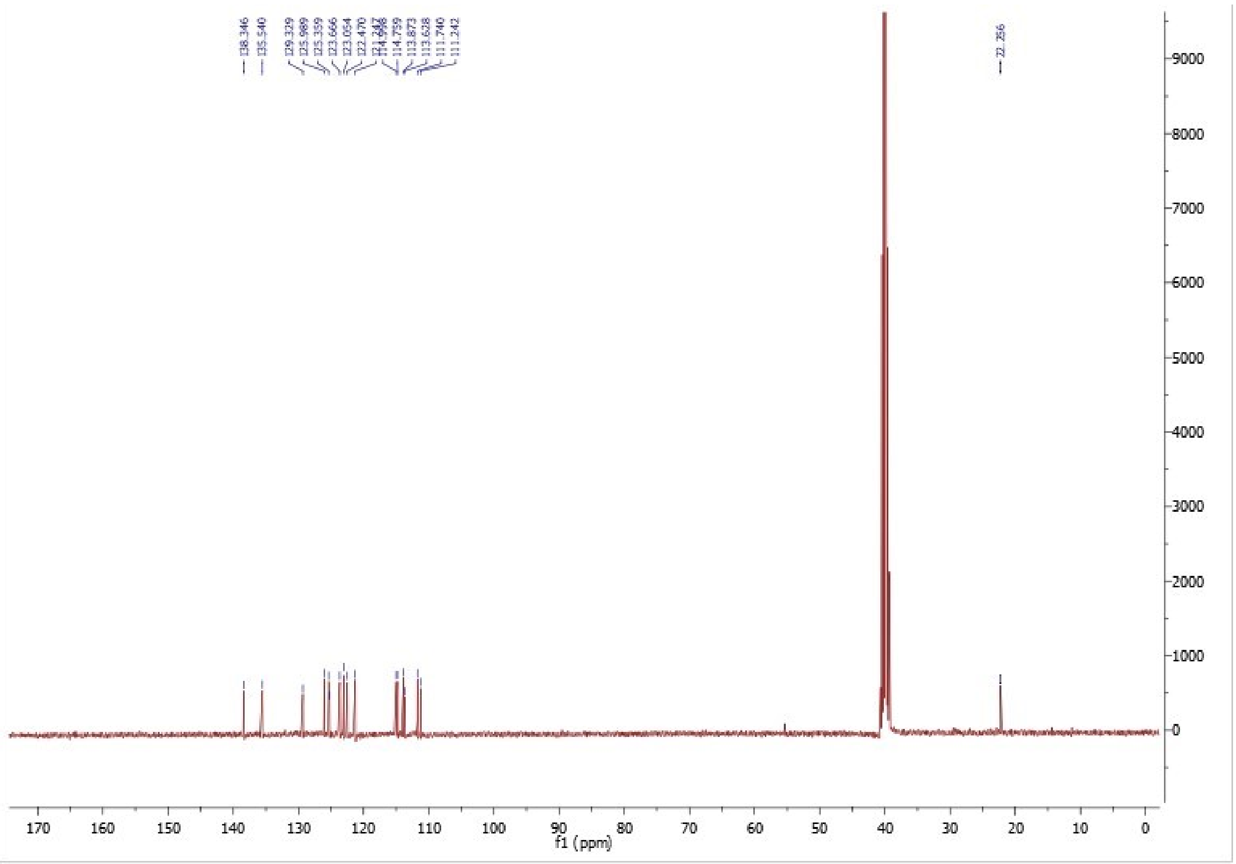
^{1}H NMR & ^{13}C NMR of Derivative (11)





^{1}H NMR & ^{13}C NMR of Derivative (12)





CHAPTER 4: CONCLUSION

In this report, we invented bis(indolyl)methanes using copper catalysed regioselective C-H functionalization of indole using indole-3-tosylhydrazone as carbene precursor giving $3,3'$-bis(indolyl)methanes in superior yields. Moreover, the unsymmetrical bis(indolyl)methanes have also been obtained in good yield by this method. We organized a copper catalyzed regioselective C-H functionalisation of indoles for developing bis(indolyl)methanes which is otherwise difficult to prepare with no substituent at methylene bridge. Development of new procedures for bis(indolyl)methanes using copper catalysed regioselective C-H functionalization of indole would be particularly attractive taking into account the ease of conversion. Moreover, the one-pot synthesis of the reaction starting from indole-3-carboxyaldehyde also produced a good yield comparing to stepwise synthesis which makes it highly efficient method.

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