

# CHAPTER VI

*An efficient synthesis of bis*

*(indolyl) Methanes*

## **INTRODUCTION AND LITRATURE SURVEY:**

### ***An efficient synthesis of bis (indolyl) Methanes***

PEG 400 mediated an expeditious and simple one post synthesis of Bis(indolyl) methane catalysed by Nickle chloride:

Nickel (II) chloride has been applied as an efficient catalyst for the preparation of bis (indolyl) methanes (BIMS) via electrophilic substitution of indoles with aldehyde in PEG-400 as a recyclable green solvent. The catalyst is commercially easily available and inexpensive. The remarkable advantages of this method are the simple experimental procedures, shorter reaction times and high yields of products, use of non-expensive catalyst, room temperature condition and non-hazardous solvent.

Nitrogen containing heterocycles, which contains extensive biological properties, are abundant in natural products <sup>[1]</sup>. Bis(indolyl)alkanes is a useful class of Nitrogen-containing organic compounds. A few bioactive members of this class like Vibrindole-A and others have also been isolated from natural sources<sup>[2]</sup> and are found to be pharmaceutically important <sup>[3]</sup>. Among various indole derivatives, di (1-H-

indolyl-3-yl) methane(DIM) and 1,4-bis[1-H-indole-3-ylmethyl]benzene display diverse pharmacological activities and are useful in the treatment of fibromyalgia, chronic fatigue irritable bowel syndrome<sup>[4]</sup>. Especially, bis(indolyl)methanes is known to promote estrogen metabolism in both women and men and is expected to have an application in the treatment of breast cancer<sup>[5]</sup>. Due to each pharmaceutical importance the synthesis of bis(indolyl)methanes and its derivatives is receiving considerable attention these days<sup>[6]</sup>.

Consequently numerous methods have been reported for the synthesis of bis(indolyl)methanes<sup>[7]</sup>. Of these methods the acid catalyzed electrophilic substitution reaction of indole with aldehyde is one of the most simple and straight forward approaches for the synthesis of bis(indolyl)methanes. Generally, this reaction is promoted using protic acids<sup>[8]</sup>, Lewis acids<sup>[9]</sup>, heteropoly acids<sup>[10]</sup> and heterogeneous catalyst (clay, zeolites and supported reagents)<sup>[11]</sup>.

Other catalyst such as iodine<sup>[12]</sup> CAN<sup>[13]</sup> potassiumhydrogen sulfate<sup>[14]</sup>triphenylphosphoniumperchlorate<sup>[15]</sup>,NBS<sup>[16]</sup>and hexamethylene tetramine bromine<sup>[17]</sup>have also been used to catalysed this reaction. This reaction also proceeds in ionic liquids such as 1-butyl-3-methylimidazoliumtetrafluoroborate and 1-butyl-3-methylimidazolium

hexafluorophosphate<sup>[18]</sup> or in the solid state by employing a high pressure mercury lamp<sup>[19]</sup>. Recently, rare earth perfluorooctanes [RE (PFO)]<sup>[20]</sup>, trichloro-1,3,5-triazine<sup>[21]</sup> zirconium tetrachloride<sup>[22]</sup>

ZrOCl<sub>2</sub>.8H<sub>2</sub>O/silica gel<sup>[23]</sup> AlW<sub>12</sub>PO<sub>40</sub><sup>[24]</sup>, and ionic liquids in conjunction with In(OTf)<sub>3</sub> or FeCl<sub>3</sub>.6H<sub>2</sub>O<sup>[25]</sup> were used for this conversion.

However some of the reported methodologies are associated with several disadvantages, for instance drastic reaction conditions, longer reaction times, low yields of products use of expensive reagents, occurrence of several side products, tedious workup, and use of an additional microwave oven. Therefore search continues for better catalysts for the synthesis of bis(indolyl)methanes derivatives on terms of operation simplicity and economic viability. In the present work we report the synthesis of bis(indolyl)methanes by the condensation of indole with aldehyde in the presence of Nickel (II) chloride in PEG-400 at room temperature, where upon bis(indolyl)methanes derivatives are obtained in high yields (scheme 1.) herein we report that Nickel(II) chloride which act as a mild Lewis acid might be a useful and inexpensive catalyst and PEG-400 as a non-hazardous recoverable solvent for the synthesis bis(indolyl) methanes.

Indoles and their derivatives are known to possess various pharmacological and biological properties, including antibacterial, cytotoxic, anti-oxidative, and insecticidal activities. Furthermore, bis(indolyl)alkanes and their derivatives constitute an important group of bioactive Metabolites of terrestrial and marine origin. During the past decade a large number of natural products containing bis(indolyl)methanes and bis(indolyl)ethanes have been isolated from marine sources. Consequently, a number of synthetic methods for the preparation of bis(indolyl)alkane derivatives by reacting indoles with various aldehydes and ketones in the presence of either a Lewis acid or a protic acid, metal salts, such as  $\text{In}(\text{OTf})_3$ ,  $\text{Dy}(\text{OTf})_3$ ,  $\text{Ln}(\text{OTf})_3$ , and  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ , and molecular iodine, as well as solid acidic catalysts, such as clays and Zeolites, have been reported in the literature.

In addition, it has been reported that the reactions of indoles with various aldehydes were carried out in a protic solvent in the absence of any other catalyst to afford bis(indolyl)methanes. In this study, we report a facile and efficient procedure for the synthesis of bis(indolyl)methanes, bis(thienyl)methanes, and bis(fur-2-yl)methanes under mild conditions using  $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$  as catalyst.

The chemistry of indole has long been known. Indole and pyrroles are well known, a  $\pi$ -electron rich heterocyclic compound which shows Ehrlich Test with *p*-dimethyl amino benzaldehyde. Similarly indoles with aliphatic/aromatic aldehydes and ketones produce azfulvinium salts, These salts upon addition with second molecule of indole yields corresponding bis(indolyl) alkanes.

These derivatives of indole have many important applications in human life. They are known for their antibiotic properties. It helps in promoting the proper estrogen metabolism. Breast cancer prevention and control of cervical dysplasia as strong anti-proliferative effect in human endometrial cancer cells, antibacterial agent etc.

Because of immense important properties of bis (indolyl) alkanes in pharmaceutical industries, many researchers pay much more attention to develop the methods for the synthesis of title compound since many years. Preparation of bis (indolyl) alkanes is carried out by electrophilic substitution reaction of indole with carbonyl compounds using various types of acids as catalyst. Whereas many Lewis acids are prone to undergo decomposition in the presence of nitrogen containing reactants and this necessitates the use of excess and sometimes stoichiometric amount of Lewis acid.

Literature survey reveals several methods for the synthesis of Bis(indolyl)methanes using protic/Lewis acids. Iodine, NBS, MontmorilloniteK-10, and Rare earth Triflate, Ionic liquid, 2, 4, 6-trichloro-1, 3, 5-triazine (TCT). Recently we have reported phosphonitrilic chloride trimer and phenyl phosphonic acid for the rapid synthesis of Bis(indolyl)alkanes under mild conditions. Now a day's heterogeneous solid acid catalysts are playing an important role for the synthesis of organic compounds due to its easy handling, no toxicity and importantly its recyclability. Recently Chemical industries are forced to consider environmental aspects, therefore it becomes necessary to replace liquid acid with solid acid, use of naturally occurring polymers such as starch, cellulose, are attractive candidates to explore for supports for catalysts. Silica sulphuric acid, silica supported NaHSO<sub>4</sub>, cellulose sulphonic acid, starch sulphuric acids are used as solid catalyst for various organic transformations.

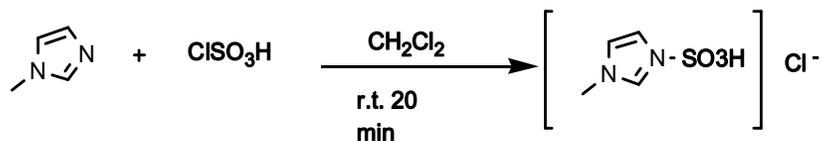
More recently 2, 4, 6-trichloro-1, 3, 5-triazine (TCT) was used for the synthesis of Bis(indolyl) alkanes. Although use of TCT facilitates the transformation cleanly however handling of TCT in laboratory becomes difficult because of its irritative nature. This prompted us to investigate the Sisal supported 2, 4-dichloro-1, 3, 5-triazine, Sisal-DCT as an alternative

catalyst for the synthesis of bis(indolyl)alkanes. Sisal-DCT is a colorless fibrous compound, which is prepared by the modification of Sisal by 2, 4, 6-trichloro-1, 3, 5-triazine. Sisal-DCT containing two labile chloride atoms showed more reactivity towards nucleophiles.

It has two labile chlorine atoms compared to 2, 4, 6-trichloro-1, 3, 5-triazine (TCT) having three labile chlorine atoms. Therefore, catalytic activity of Sisal-DCT is relatively less, but its non-irritating characteristics made it easy to handle. Sisal is easily available as renewable material in the nature and it could be easily modified to Sisal- DCT as a solid acid catalyst. The most useful properties of ionic liquids are the ability to dissolve a wide range of substances, very low vapour pressure, non-inflammability, high thermal stability, safety and the fact that it can be stored for long times without decomposition. Moreover it is often possible to achieve reaction in ionic liquid that proceed with great difficulty. These green solvents have been also extensively used as catalyst in various organic reactions.

Apart of ongoing reaction to extend applications of acidic catalyst and reagents in organic synthesis. They have been prepared 3-methyl-1-sulfonic acid imidazolium chloride as a new Bronsted acidic ionic liquid. In this reaction 1-methyl imidazole with chloro sulfonic acid at room

temperature in presence of dichloromethen gives novel ionic liquid derivative of sulfonic acid.

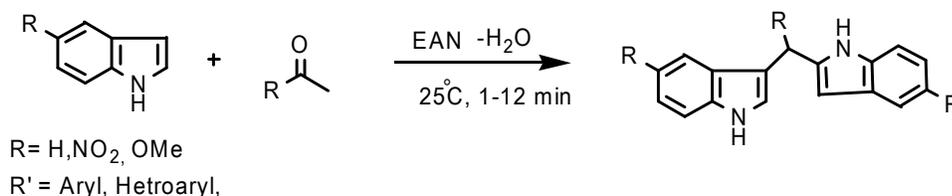


An efficient synthesis of bis (indolyl) methane  $\text{Fe}^{\text{iii}}$  –catalysed electrophilic substitution reactions of indoles with various aldehyde in ionic liquid is described it was found that the ionic liquids involving  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  were the most efficient catalytic systems and could be simply recycled without significant loss of activity.

An efficient synthesis of bis (indolyl) methanes in water and synthesis of di, tri, and tetra bis (indolyl) methanes under thermal conditions catalysed by oxalic acid dihydrate. A simple, clean, and highly efficient green protocol has been developed for synthesis of bis (indolyl) methanes by the reaction of indole with aldehyde and ketones in the presence of oxalic acid dihydrate  $[(\text{COOH})_2 \cdot 2\text{H}_2\text{O}]$  and N-acetyl-N,N,N-tri methyl ammonium bomide [CTAB] in water. Also tri (bis (indolyl)) and tetra (bis (indolyl) methane was under thermal conditions.

An efficient rapid synthesis of bis (indolyl) methane using ethyl ammonium nitarate as ionic liquid. An efficient synthesis of bis

(indolyl) methane in excellent yields using EAN is reusable ionic liquid at room temperature which involves an electrophilic substitution reaction of indoles with several aldehydes.

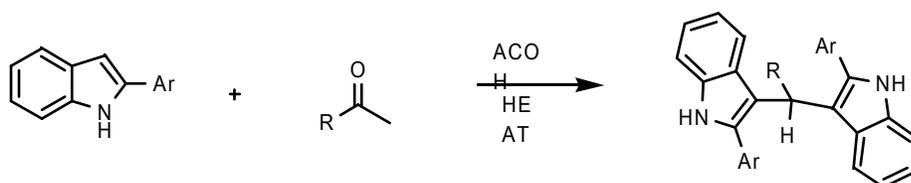


Recently use of ionic liquid attracted an increasing interest in the area of organic synthesis due to their unique properties as well as good solvating capability. And also the ionic liquid catalyzed synthesis of bis (indolyl) methanes [bmim] BF<sub>4</sub>, [bmim] Cl, [bmim] HSO<sub>4</sub> and TMGT, at room temperature have been reported.

However, these methods suffer from certain disadvantages such as very long reaction time and lower product yields. Hence, there has been considerable interest in the development of an elegant, rapid and efficient method for the synthesis of bis (indolyl) methanes using ionic liquids with acidic properties, cheap and easily recoverable, reusable at room temperature, when compared to other ionic liquids. Recently, EAN has been used in various organic reactions such as Kabachnik-Field reaction, Knoevenagel condensation, nitration of phenol and also in the

synthesis of 2-amino-4,6-diphenylpyridine-3-carbonitrile and flavones. The use of ethyl ammonium nitrate as a media and a catalyst in the electrophilic substitution of Indoles with a variety of aldehyde to provide bis (indolyl) methanes at ambient conditions.

An efficient rapid synthesis of bis (indolyl) methanes by the treatment of 2- aryl indole derivatives with aldehyde in presence of glacial acetic acid as an efficient, mild, and inexpensive catalyst under microwave irradiation condition compared with the conventional method afforded excellent yields of biologically important bis (indolyl) methanes and tetra indolyl terephthalyl diamine.

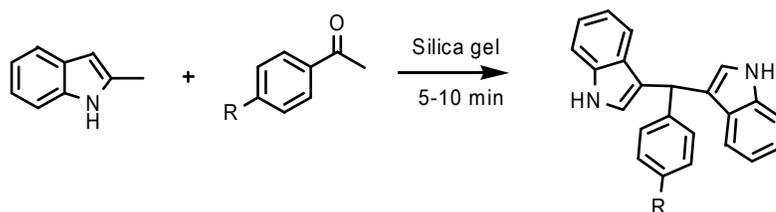


The indole moiety is featured in a variety of pharmacologically and biologically active compounds. Numerous methods describing the synthesis of bis (indolyl) methanes were reported in the literature employing protic acids and Lewis acids. However, there are still some drawbacks.

In this catalytic system including the requirement of large or stoichiometric amount of catalyst, long reaction times, low yields of

products and drastic condition for catalyst preparation. Recently metal triflate in ionic liquid, Fe (III) salts in ionic liquids and ionic liquids were reported.

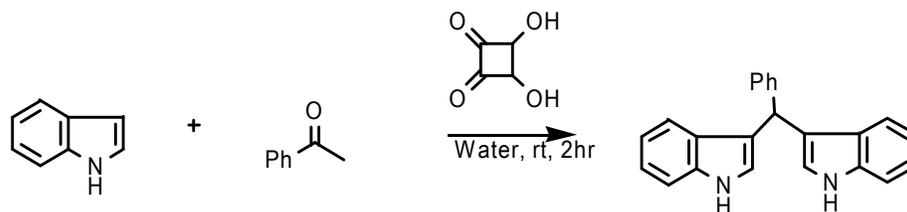
Synthesis of silica supported synthesis of bis (indolyl) methanes derivatives under Microwave irradiation. Numerous methods for synthesis of this have been developed including use of Lewis acid, protic acid, PPA/SiO<sub>2</sub>. Silica sulfuric acid, In(OTf)<sub>3</sub>, I<sub>2</sub>, PCl<sub>5</sub>. However, many of the reported procedure shave significant drawbacks such as requirements of stoichiometric amount catalyst etc.



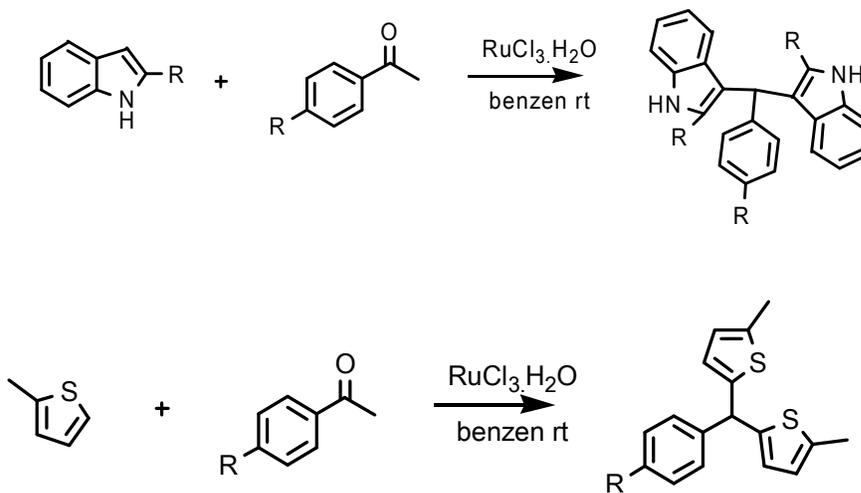
Green procedure bis (indolyl) methanes in water and it is a green and environmentally benign protocol for square acid catalyst electrophilic substitution reaction of indole derivatives, with various aldehydes in water, in good to excellent yields.

A mixture of indole, aldehydes or ketones and water square acid was added and stir vigorously at room temperature, then the reaction mixture was filtered and washed with water and concentrate under reduced pressure, the residue was purified by flash chromatography on silica gel

using ethyl acetate and petroleum ether (1:3), to yield corresponding product.



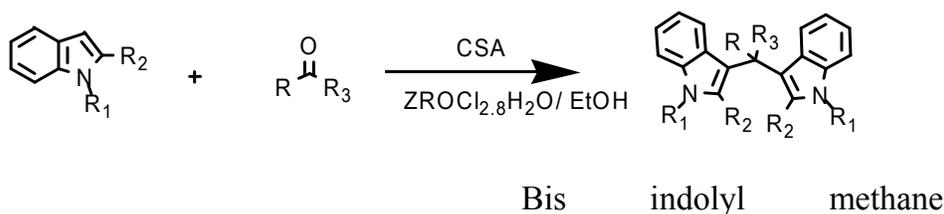
An efficient synthesis of bis (indolyl) methanes under mild conditions of  $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$  catalyzed reactions.  $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$  was found to be an effective catalyst for reaction of indoles, 2-methyl thiophene, and 2-methyl furan with aldehyde to afford the corresponding bis (indolyl) methanes, bis (thienyl) methanes, bis (fur-2-yl) methanes in moderate to excellent yields. A mixture of aryl benzaldehyde and  $\text{RuCl}_3 \cdot \text{H}_2\text{O}$  in benzene was added indole under pressure then mixture was stirred at room temperature.



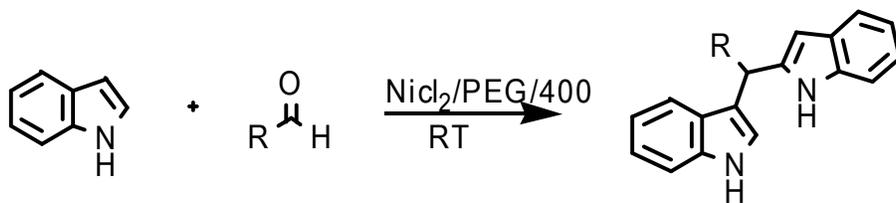
An efficient synthesis of Sisal supported 2, 4-dichloro-1, 3, 5-triazine (Sisal-DCT) was found to be an environmentally renewable, inexpensive solid acid catalyst for the electrophilic substitution reaction of indole with carbonyl compounds to the corresponding bis(indolyl)methanes in excellent yields. The important features of the procedure are cost effectiveness, faster reaction rates and cleaner conversions with simple work.



Synthesis of bis(indolyl)methanes with the help of indole and p-nitro benzaldehyde or aldehydes or ketones in presence of  $\text{ZrOCl}_2 \cdot 2\text{H}_2\text{O}$  catalyst and ethanol.



## Experimental



Indole

Bis (indolyl )methanes

General procedure:

A mixture of indole (2mmol), aldehyde (1mmol) and nickel (II) chloride (0.15mmol) in PEG-400(5mls) was stirred at room temperature for the appropriate time (Table2). The progress of the reaction was monitored by TLC. After completion of reaction, as indicated by TLC, the reaction mixture was cooled and extracted with diethyl ether (3x10 ml). Diethyl ether is evaporated and gives crude product. The crude product were purified by silica gel column chromatography using ethyl acetate/hexane (5:10) as eluent to afford the desired compound in pure form.

**Result and discussion:**

Initially to optimize the reaction conditions we studied the reaction between Indole (2mmol) and 4-chlorobenzaldehyde (1mmol) as a simple model using catalytic amount of Nickel (II) chloride (table 1). We found that the best result was obtained when the reaction was carried out by using 15mol% of the catalyst. (Table I, entry 5). After optimization of the reaction conditions, we studied the generally of these condition for other substrates. Using this method, different kinds of aromatic and aliphatic aldehyde were reacted with indole to produce the corresponding Bis(indolyl)methane.

**Table 6.1**

(Table 2) Effect of catalyst concentration on the reaction<sup>a</sup>

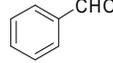
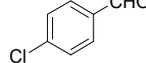
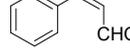
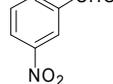
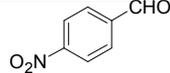
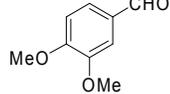
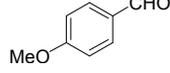
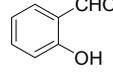
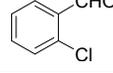
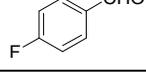
Sr.No.	Catalyst (mol %)	Time (min)	Yield (%)
1	1	150	38
2	2	120	44
3	5	100	55
4	10	90	66
5	15	70	85
6	20	70	85

<sup>a</sup>Reaction Conditions : 4-chloro Benzaldehyde (1mmol), NiCl<sub>2</sub>(15mol%), PEG-400(5ml) <sup>b</sup>isolated yields .

Several aromatic aldehydes with different functional groups were subjected to the condensation reaction and the desired products were synthesized in good to high yields and short reaction time. The use of 15mol% of Nickel(II) chloride was sufficient to progress the reaction and an increase of the amount of the catalyst did not improve the yield (Table 1 entry 6). The substituted functional groups on the aromatic ring of the aldehyde affected the yield and reaction times. In comparison with electron withdrawing groups on the aryl aldehydes, we found that the

presence of electron donating groups on the aryl aldehyde decreased both the reaction rate and yield of product (table 2).

**Table 6.2** (Table 2) Synthesis of Bisindolyl methane<sup>a</sup>:

Entry	Indole	R	Product	Time (min)	Yield % <sup>b</sup>	m.p. <sup>o</sup> C	
						Observed	Reported (7-25)
1			3a	70	87	124-126	128-130
2			3b	60	85	100-102	104-105
3			3c	30	76	100-102	99
4			3d	30	84	261-262	268-270
5			3e	40	81	217-218	220-222
6			3f	55	79	194-196	198-200
7			3g	45	83	186-188	190-192
8			3h	78	78	348-349	340-342
9			3i	76	76	76-77	78-80
10			3j	84	84	72-74	70-72

<sup>a</sup>Reaction Condition: Aldehyde(1mmol), Indole(1mmol), ), NiCl<sub>2</sub>(15mol%), PEG-400(5ml) ) <sup>b</sup>isolated yields .

The rate of the substitution reaction of Indole and aldehyde increases when the reaction was performed in polyethylene glycol (PEG-400). Being a nonvolatile benign solvent, it offers hydrophilic and hydrophobic reactants or solute to dissolve in it and accelerates rate of the reaction. In order find out the use of polyethylene glycol as a recyclable medium, it was recycled with minimum decomposition and loss. Since PEG is immiscible with diethyl ether, the product may be extracted with it and PEG phase may be recovered and can be reused for further reaction without significant loss of activity (Table 3).

**Table 6.3**(Table3): reusability of PEG-400in terms of product yield<sup>3b</sup>.

Cycles	1 <sup>st</sup> cycles	2 <sup>nd</sup> cycles	3 <sup>rd</sup> cycles	4 <sup>th</sup> cycles	5 <sup>th</sup> cycles
Yield% (3b)	85	85	84	84	83

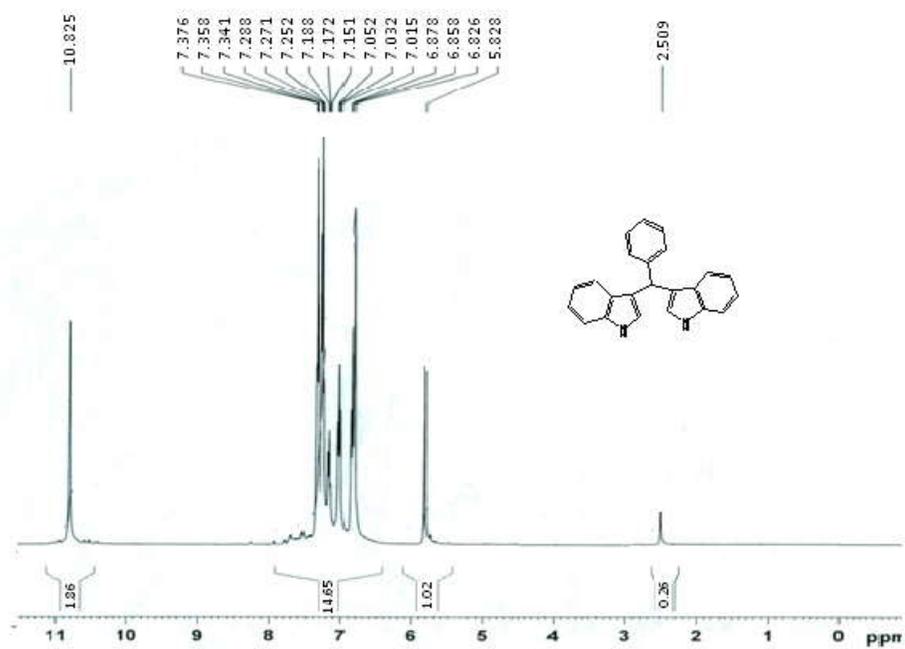
### Spectral Analysis

#### Phenyl (3,3'-bisindolyl)methane (3a)

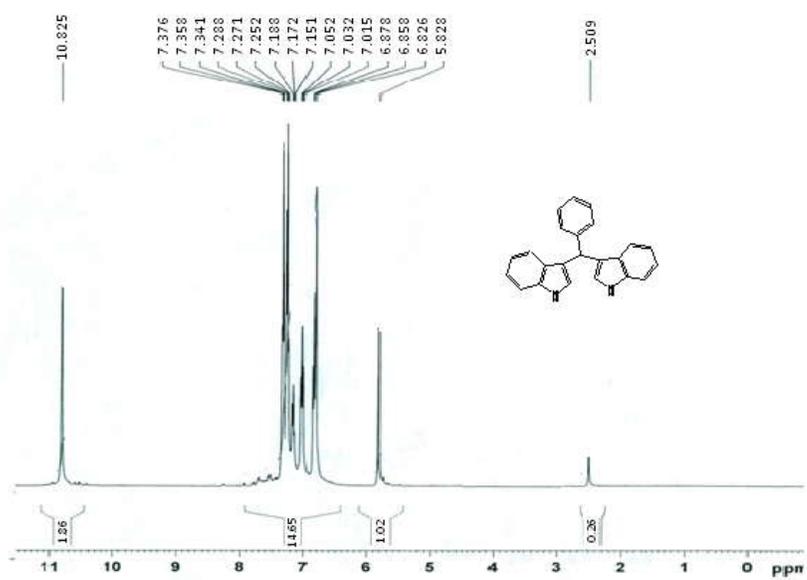
<sup>1</sup>H NMR (400 MHz, DMSO)( δ ppm): 10.825 (2H, s, NH), 7.376-7.151 (9H, m, ArH), 7.032 (2H, t, CH), 6.878-6.826(4H, m, ArH), 5.828 (1H, s, CH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) ( δ ppm): 143.92, 136.61, 129.12, 128.95, 127.55, 127.11, 123.88, 122.01, 119.92, 119.75, 119.22, 111.01, 40.15.

#### 3-nitrophenyl (3,3'-bisindolyl)methane (3b)

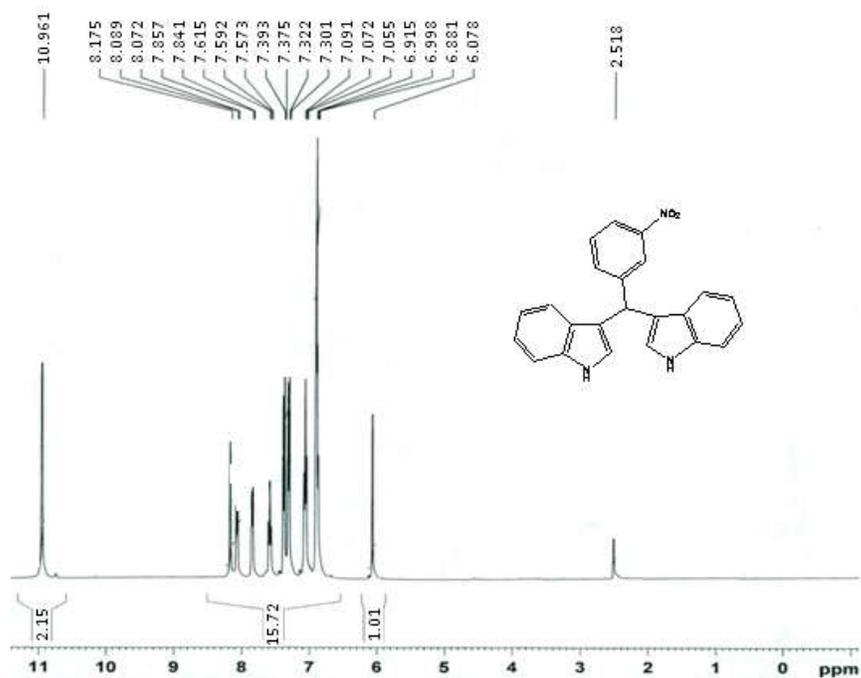
<sup>1</sup>H NMR (400 MHz, DMSO)( δ ppm): 10.95 (2H, s, NH), 8.17 (1H, s, ArH), 8.089 (1H, d, ArH), 7.857 (1H, d, ArH), 7.592 (1H, t, ArH), 7.375 (4H, m, ArH), 7.072 (2H, t, CH), 6.88 (4H, m, ArH), 6.078 (1H, s, CH); <sup>13</sup>C NMR (75MHz, CDCl<sub>3</sub>)( δ ppm): 136.62, 132.32, 131.01, 127.25, 126.73, 124.32, 123.78, 122.15, 119.65, 119.45, 117.55, 111.11, 34.78; .



<sup>1</sup>H NMR Spectrum of Compound 3a



$^{13}\text{C}$  NMR Spectrum of compound 3a



$^1\text{H}$  NMR Spectrum of Compound 3b



**Conclusion:**

In conclusion we have developed a simple convenient method for the synthesis of Bis(indolyl)methanes [aj] by condensation reaction of aldehyde and indole in the presence of Nickel(II) Chloride in PEG-400 as a benign and recoverable medium at room temperature condition. The catalyst is readily available and inexpensive and can conveniently be handled. This method offers some advantages on terms of simplicity of performance; low reaction times, good to excellent yields, and reusable reaction medium and easy work up protocol.

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