

# The Fabrication of Green and Sustainable Pathway for the Synthesis of Bis-indolyl Methane Scaffolds

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The green and efficient procedure for the preparation of substituted bis-indolyl methane via condensation of indole with various aryl aldehydes (3 MCR) in the presence of catalytic amount MFA (Modified Fly Ash; a zeotype catalyst) at reflux temperature in good to excellent yield (85-95%) is reported. This method is utilizing the solvent free condition with the beneficial features such as short reaction time and easy process for isolation. The rate of reactions is found to relay on EDGs and EWGs substituents present on aryl aldehydes at particular positions.

## Introduction

In present constraints, in regards to environmental restrictions on emissions covered in several legislations throughout the world, non-polluting and atom-efficient catalytic technologies are attracting much attention [1]. The acid catalysts are very prominently used in the chemical and refinery industries [2], and the technologies employing highly corrosive, hazardous and polluting liquid acids are being replaced with solid acids [3], for instance, acid treated clays, zeolites [4], zeotypes [5], ion-exchange resins [6] and metal oxides [7].

Fly ash; the solid waste generated from coal, oil and biomass combustion comprises the fine particles that are rise above with flue gases [8]. It is well known fact that efficient disposal of fly ash is a worldwide problem because of the huge amount produced and its harmful effects on the environment [9]. Now days, the synthesis of zeolites with the use of fly ash is attracting lots of attention due to its peculiar properties in catalyzing many reactions [10]. Fly ash acts as a rich source of silica in the synthesis of zeolites, which easily combines with transition metals on hydrothermal or calcination treatment forming molecules with highly branched zeotype geometries [11].

Bis (indolyl) methanes, indole and their derivatives are known as important intermediates in organic synthesis and pharmaceutical chemistry and exhibit various physiological properties [12]. Indole ring system is the most important heterocycle available in natural compounds. Indomethacin and tenidap are indole derivatives found to possess anti-inflammatory activity with analgesic and anti-pyretic properties [13]. They inhibit production of eicosanoids by inhibition of cyclooxygenase (COX) and thereby reduce oedema. Several indole derivatives are reported to have anti-microbial activity [14].

Bisindoles are found in cruciferous plants and promotes beneficial oestrogen metabolism and induce

apo(indolyl) methanes ptosis in human cancer cells [15]. Bis(indolyl) methanes have attracted much interest in recent years. Such compounds are prone to develop interesting bio activity and find useful applications as breast cancer preventive and anti- bacterial agents [16]. The 3, 3-bisindolyl methanes induces potential beneficial effects on the proliferation and induction of apoptosis in human prostate and breast cancer cells [17]. Bis(Indolyl) methane derivatives have been reported to possess promising biological activities including antipyretic, antifungal, anti-inflammatory, anthelmintic, cardiovascular, anticonvulsant, antimicrobial and selective COX-2 inhibitory activities [18]. Therefore synthesis of bis (indolyl) moiety has become interesting target for the synthetic organic chemist in view of their immense biological and pharmaceutical activities [19].

The lead indole derivatives reported in the literature is bis (indolyl) methane [20]. The method of synthesis involves both one step as well as multistep synthesis. Several methods have been reported in the literature for the preparation of bis (indolyl) methanes from indoles and carbonyl compounds acids and Lewis acids.

The present study focuses on the efficient role of MFA (A synthetic catalyst developed from waste) as green reusable catalyst in the synthesis of biologically as well as agro chemically highly important Bis-indolyl derivatives. The study focuses to extend the scope of zeotype catalysts to be a environment friendly catalyst for the synthesis of commercially valuable organic compounds to limit the industrial pollution.

## Experimental

### Materials and methods

All the materials (like ferric chloride, urea, INH and aryl carbonyl compounds) are purchased LR grade from SD Fine Chemicals Pvt. Ltd., Mumbai (India). The fly ash is collected from the nearby area of the thermal power plant, Deep Nagar, Tal- Bhusawal, Dist. Jalgaon 425001 (MS),

India. The fly ash is sampled in equal volumes from four directions of plant and mixed thoroughly to make homogeneous mass.

### Synthesis of MFA zeotype catalyst

The synthesis and characterization of MFA is discussed in our earlier publication [1].

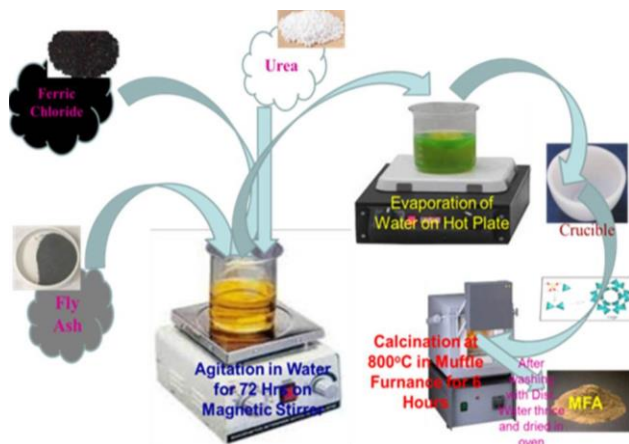


Fig. 1. Schematic diagram of MFA synthesis.

### Reaction scheme

Indole (20 mmol), aromatic aldehydes (10 mmol) (2a-h) and catalytic amount of MFA (10% w/w of reaction mass) are taken in EtOH and mixed thoroughly. The condensation reaction at reflux yields Bis-indolyl methane derivatives in 10-30 min (4a-h). In the synthesis, firstly measured quantity of Indole is taken in round bottom flask, followed by addition of measured quantity of aldehydes. Then the mixture is mixed thoroughly on stirring and addition of MFA is executed. After that the reaction is subjected for reflux. The reaction is continuously monitored on TLC technique for the formation of product. After that reaction mass is filtered and washed with water (3 X 10 ml). The obtained product then recrystallized with pure ethanol separates the MFA as residue on filter paper and pure product reappears in filtrate on cooling.

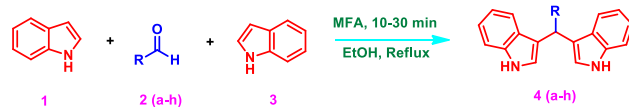


Fig. 2. Schematic diagram of reaction scheme.

### Plausible mechanism

The mechanism proposed reveals the catalytic role of MFA in the synthesis of Bis-indolyl derivatives. The core functional group responsible for its catalytic behaviour is ferrous silicates having the Fe-O-Si linkages present on the surface and in the pore voids of MFA which polarizes the aldehydes and increases the electron deficiency at carbonyl carbon centre. The lone pair of amine nitrogen present in Indole easily attacks on sufficiently electron

deficient carbonyl carbon through conjugation followed by abstraction of acidic proton from chiral centre at 3 position of Indole to form alcohol intermediate. In case of intermediate, the alcoholic -OH again polarized which further access the attack of second molecule of Indole and consecutive dehydration leads to formation of Bis-indolyl derivatives.

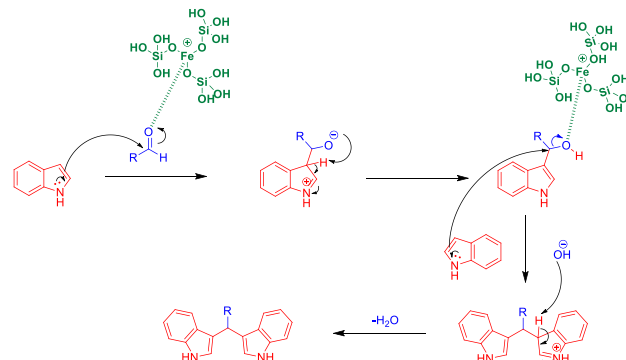


Fig. 3. Schematic diagram of proposed mechanism of reaction.

### Optimization of Efficient Amount of MFA Required for Excellent Yield (4a)

The reaction is tested for different amount of catalyst to optimise the proper amount of catalyst for the best results in terms of time and yield in the synthesis of 3,3'-(phenylmethylene)bis(1H-indole) (4a). The study (Chart 1) depicts the low amount of catalyst leads for long reaction time while high amounts results in the decrease in yields of reaction. The optimistic amount is found to be 10% w/w of reaction mass.

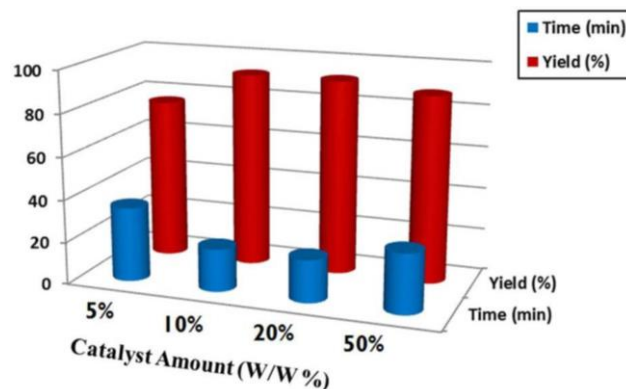


Chart 1. Optimization of effective amount of catalyst.

### Catalyst reusability study

The catalyst is subjected to study its reusability in the synthesis of 3,3'-(phenylmethylene)bis(1H-indole) (4a) (Chart 2). The MFA recovered on filtration from previous step is firstly wash with hot EtOH and water. Thus, purified MFA is subjected for activation at 120oC in oven for 4 hours. The activated MFA is subjected for its catalytic efficiency again in next set of reactions. The study reveals that the MFA can be used efficiently up to 3 times after its recovery from previous synthesis.

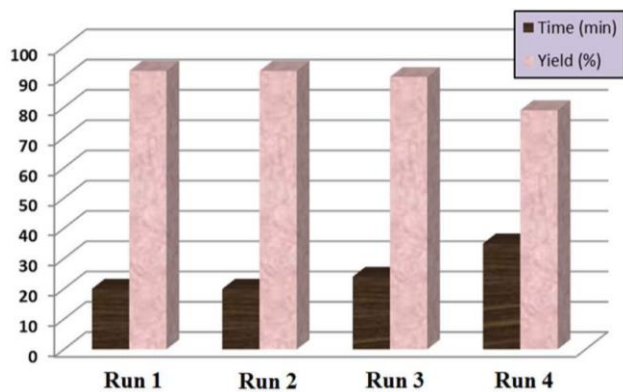










Chart 2. Reusability study of catalyst

## Results and discussion

The time required for reaction and yield of products after replacing the aldehyde derivatives are summarized in **Table 1**. The results depicts the EDGs at 2 and 4 positions in aryl aldehydes reduces the rate of reaction in reference to EWG's requires less time. While the EWG's present at 3 position in aryl aldehydes found to reduce the reaction rate in comparison to EDG's present at respective position.

Table 1. List of synthesized bis-indolyl derivatives.

Sr. No.	Code	R	H	Product	Time (min)	Yield (%)	Melting Point (°C)	Reported Melting Point (°C)
1	4a	C <sub>6</sub> H <sub>5</sub>	H		20	92	124-126	125-127 <sup>54</sup>
2	4b	p-OH-C <sub>6</sub> H <sub>4</sub>	H		24	83	118-120	119-121 <sup>54</sup>
3	4c	m-OH-C <sub>6</sub> H <sub>4</sub>	H		23	80	144-146	--
4	4d	m-Cl-C <sub>6</sub> H <sub>4</sub>	H		28	84	84-86	--
5	4e	p-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	H		12	83	220-222	220-222 <sup>54</sup>
6	4f	m-OCH <sub>3</sub> -p-OH-C <sub>6</sub> H <sub>4</sub>	H		10	86	110-112	111-113 <sup>54</sup>
7	4g	C <sub>6</sub> H <sub>5</sub> S-	H		18	89	182-184	184-186 <sup>54</sup>
8	4h	C <sub>3</sub> H <sub>5</sub>	H		16	90	138-140	--

Note: The table contains the list of synthesized Bis-indolyl derivatives with the required time for the synthesis, their yields and melting points.

The mass spectra of all synthesized scaffolds showing the characteristic M-1 peak as base as reported in earlier reports. HRMS spectra of 4c proves the existence of prescribed molecular formula and molecular weight obtained. The 4a and 4c are also subjected for <sup>1</sup>H NMR and <sup>13</sup>C NMR spectras which confirms their molecular formulas as per the molecular assemblies prescribed in this reports.

## Characterizations of Synthesized Compounds

**(4a) 3,3'-(phenylmethylene)bis(1H-indole)**, Melting Point = 124-126°C, Mass spectra: M-1 peak at 321, <sup>1</sup>H NMR Spectra(δ): 7.865 (s 2H), 7.3852 (d 2H, 7.88 Hz), 7.3391 (d 3H, 7.68 Hz), 7.2409 (d 3H, 7.32 Hz), 7.1305 (d 3H, 7.6 Hz), 7.0065 (d 2H, 7.44 Hz), 6.5970 (s 2H), 5.8244 (s 1H), <sup>13</sup>C NMR Spectra (δ): 144.07, 136.73, 128.79, 128.53, 128.29, 127.29, 127.13, 126.20, 123.69, 121.90, 120.00, 119.75, 119.29, 111.11, 40.29.

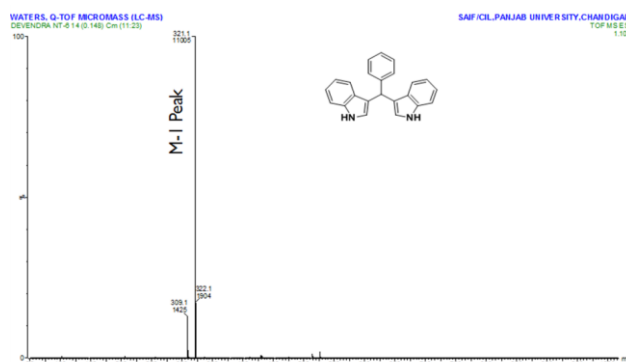


Fig. 4. Mass Spectrum of 4a.

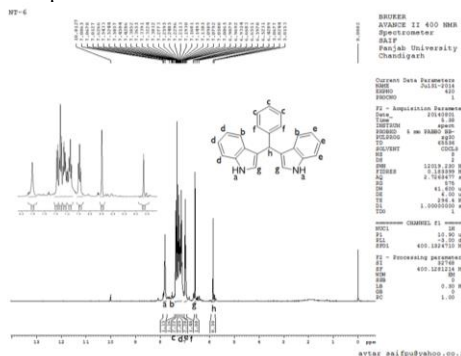


Fig. 5. <sup>1</sup>H NMR Spectrum of 4a.

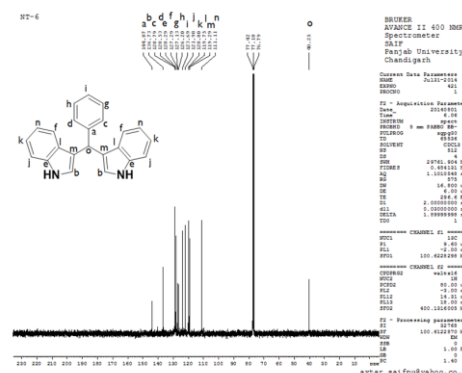


Fig. 6. <sup>13</sup>C NMR Spectrum of 4a.

**(4b) 4-(di(1H-indol-3-yl)methyl)phenol,**

Melting Point = 118-120 °C, Mass Spectra: M-1 peak at 337.

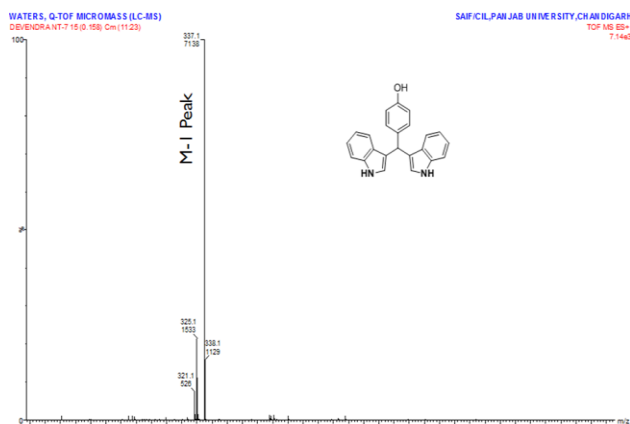


Fig. 7. Mass Spectrum of 4b.

**(4c) 3-(di(1H-indol-3-yl)methyl)phenol**

Melting Point = 144-146 °C, HRMS Spectra: Mass obtained 338.1355 equivalent to molecular formula C<sub>23</sub>H<sub>18</sub>N<sub>2</sub>O, <sup>1</sup>H NMR Spectra(δ): 10.68 (S 2H), 9.0351 (S 1H), 7.3417 (dd 3H, 8.08 Hz, 10.32 Hz, 7.88 Hz), 7.0379 (m 2H, 7.88 Hz), 6.8087 (m 8H, 11.08 Hz, 6.16 Hz, 13.8 Hz), 6.5743 (dd 1H, 1.48 Hz, 6.44 Hz), 5.7176 (S 1H).

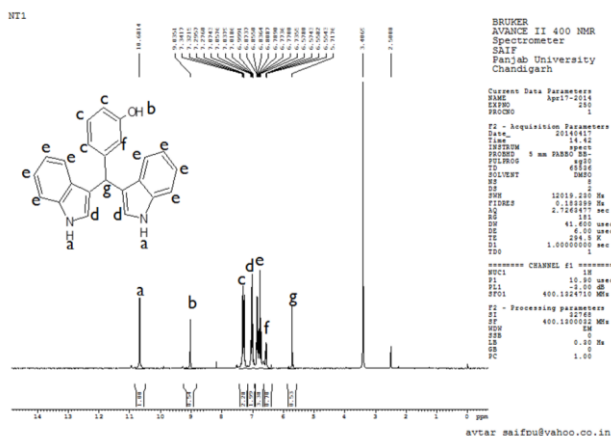


Fig. 8. <sup>1</sup>H NMR Spectrum of 4c.

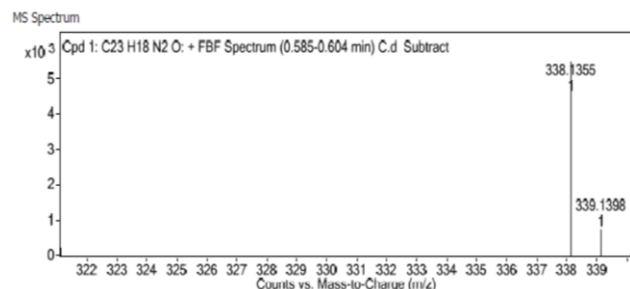


Fig. 9. HRMS Spectrum of 4c.

**(4d) 3,3'-((3-chlorophenyl)methylene)bis(1H-indole),**

Melting Point = 84-86 °C, Mass Spectra: M-1 peak at 355.

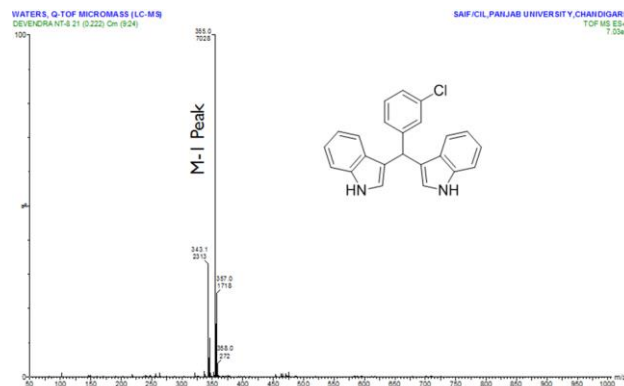


Fig. 10. Mass Spectrum of 4d.

**(4e) 3,3'-((4-nitrophenyl)methylene)bis(1H-indole),**

Melting Point = 220-222 °C, Mass Spectra: M-1 peak at 366.

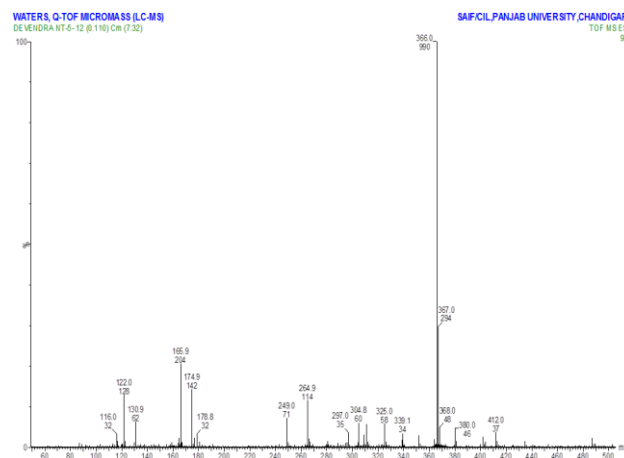


Fig. 11. Mass Spectrum of 4e.

**(4f) 4-(di(1H-indol-3-yl)methyl)-2-methoxyphenol,**

Melting Point = 110-112 °C, Mass Spectra: M-1 peak at 367.

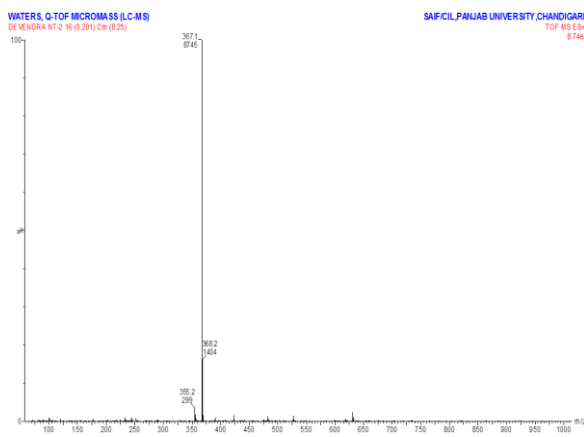


Fig. 12. Mass Spectrum of 4f

(4g) 3,3'-(thiophen-2-ylmethylene)bis(1H-indole),  
Melting Point = 182-184 °C.

(4h) (E)-3,3'-(but-2-ene-1,1-diyl)bis(1H-indole)  
Melting Point = 138-140 °C.

### Conclusion

The present study have elegantly demonstrated the new path for the synthesis of Bis-indolyl methane Scaffold's by the use of newly modified MFA as an efficient heterogeneous catalyst. The method uses EtOH as a green solvent. The current method have several advantages over previous methods, most prominently; it takes less time for the completion of reaction. This study will open up new era for the utilization of zeotype catalysts as a green catalyst in the synthesis of industrially or commercially valuable synthetic products as it efficiently replaces harmful acid catalyst in the reaction method.

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### Supporting information

Supporting informations are available online at journal website.

### Conflicts of interest

There are no conflicts to declare.

### Keywords

MFA, EDGs, EWGs, Bis-indolyl methane, MCR.

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### Authors biography



Dr. Devendra Raghuvanshi is currently working as Team Leader, Research and Development Department, Shiva Pharmachem Pvt. Ltd., Luna, Padra, Vadodara. He has published 5 papers and 1 book chapter in internationally and nationally reputed journals. He has 4 year institutional and 4.5 year industrial research experience. He had presented in more than 12 national/international conferences and workshops and achieved 4 awards on credic including RSC Fellowship Awards. He has delivered lectures and taken practicles of post graduate students.



Prof. Jyotsna Meshram is presently heading the Department of Chemistry at Rashtrasant Tukdoji Maharaj Nagpur University, Nagpur. She had all most 25 year teaching and research experience. She was the member of several national committee bodies. She had published more than 120 research articles in national and internationally reputed journals including RSC Advances, Journal of Toxicology and Luminescence etc. More than 20 students had persude their doctoral degree under her guidance.

### Graphical abstract

