

**Research Article**

**SOLVENT-FREE SYNTHESIS OF ARYL-3,3'-BIS(INDOLYL) METHANES USING  $KAl(SO_4)_2 \cdot 12H_2O$ –ANHYDROUS  $Na_2SO_4$**

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**ABSTRACT**

An efficient pathway for the synthesis of aryl-3,3'-bis(indolyl)methanes (BIMs) from indole/2-methylindole and aromatic aldehyde(s) is described. The aromatic electrophilic substitution reactions of indole with aromatic aldehydes are achieved in the presence of a mixture of potash alum-anhydrous sodium sulphate under solvent-free conditions at room temperature in the absence of light in excellent yields, and in a shorter reaction time.

**Key Words:** *Indole, Bis (Indolyl) Methanes, Solvent-Free, Potash Alum, Anhydrous Sodium Sulphate*

**INTRODUCTION**

Bis(indolyl)methanes (BIMs) and their derivatives have received more attention due to their presence in bioactive metabolites and marine origin (Porter *et al.*, 1977; Osawa and Namiki, 1983; Bell *et al.*, 1994; Garbe *et al.*, 2000). BIMs exhibit antimicrobial, antifungal (Sivaprasad *et al.*, 2006), antibiotic (Kamal *et al.*, 2009), antibacterial (Kobayashi *et al.*, 1994), antiangiogenic, anti-inflammatory, analgesic, (Sujatha *et al.*, 2009) *etc.* activity. The oxidized forms of BIMs are utilized as dyes (Majer, 1960; Budzikiewicz *et al.*, 1972; Novak *et al.*, 1976) as well as colorimetric sensors (He *et al.*, 2006; Martinez *et al.*, 2008; Li *et al.*, 2008). Due to the versatile application possibilities of BIMs, there is a continuous search for more efficient methods for the synthesis of indole derivatives. Varieties of catalytic reagents used in the synthesis of BIMs have been reviewed (Shiri *et al.*, 2010).

However, most of these existing methods suffer toxic metal ions, environmentally non-benign organic volatile solvents, corrosive reagents, longer reaction times (Kamal *et al.*, 1963; Babu *et al.*, 2000), low yield of products (Penieres-Carrillo *et al.*, 2003). hygroscopic nature of catalysts (Lin *et al.*, 2006; Hasaninejad *et al.*, 2007; Ji *et al.*, 2004; Veisi *et al.*, 2009). high catalyst loading, cumbersome work up, conventional heating (Vishvanath *et al.*, 2011), microwave irradiation (Zahran *et al.*, 2008). and ultrasound (Heravi *et al.*, 2009). Many Lewis acids are deactivated or sometimes decomposed by nitrogen-containing reactants. Even when the desired reactions proceed, amino compounds required more than stoichiometric amounts of Lewis acids, as these acids are trapped by nitrogen (Kobayashi *et al.*, 1995). This prompted us to initiate a systematic investigation to look into the feasibility of less hazardous, solvent-free synthesis of aryl-3,3'-bis(indolyl)methane derivatives under modified experimental conditions.

Solvent-free reaction condition has been demonstrated to be an efficient technique for various organic reactions. It often leads to a remarkable decrease in reaction time, increased yields, easier workup, and enhancement of regio- and stereo-selectivity of reaction (Martins *et al.*, 2009; Tanaka *et al.*, 2000). Recently, potash alum [ $KAl(SO_4)_2 \cdot 12H_2O$ ] has been reported as a mild and efficient catalyst for a variety of prominent organic reactions (Suresh *et al.*, 2011; Ghorbani-Vaghei *et al.*, 2010; Dabiri *et al.*, 2007; Azizian *et al.*, 2006). Synthesis of 3,3'-BIMs from indole and carbonyl compounds using potash alum under aqueous medium (Kumar *et al.*, 2009) and by ultrasonic irradiation were reported (Sonar *et al.*, 2009). To the best of our knowledge, there are no previous reports regarding the use of potash alum-anhydrous sodium sulphate mixture as a catalyst for the synthesis of aryl-3,3'-BIMs from indole and

## Research Article

aromatic aldehyde(s) under solvent-free conditions. In the present work, we report an efficient approach for the synthesis of aryl-3,3'-BIMs using potash alum-anhydrous sodium sulphate mixture under solvent-free conditions at room temperature in the absence of light (Figure:1).

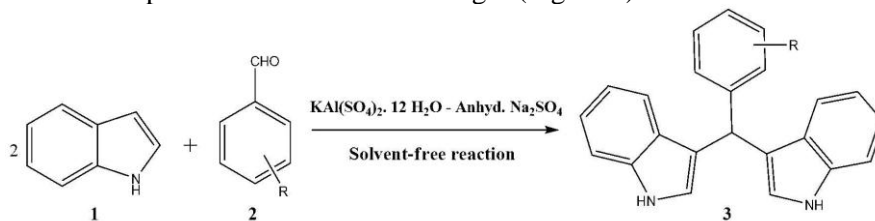


Figure 1: General Reaction Scheme

## MATERIALS AND METHODS

All chemicals were purchased from Merck and Sigma-Aldrich chemical companies and used without purification. The uncorrected melting points of compounds were measured in open capillary in a sulfuric acid bath. The progress of the reactions was monitored by thin-layer chromatography. Thin-layer chromatography was visualized with UV light (254 and 365 nm). FT-IR spectra were recorded from spectral grade KBr disc for solid samples and NaCl window for viscous samples in a JASCO FT-IR Model 410 spectrophotometer. The recording was performed at 4000-400  $\text{cm}^{-1}$  wave number range.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a 300 MHz Varian spectrometer using  $\text{CDCl}_3$  solvent system. The electrospray mass spectra were recorded on a THERMO Finnigan LCQ Advantage max ion trap mass spectrometer. Samples (10  $\mu\text{L}$ ) (dissolved in solvent such as methanol/acetonitrile/water) were introduced into the ESI source through Finnigan surveyor autosampler. Elemental analyses were performed on a Perkin Elmer 2400 series II Elemental CHN analyzer. A BRUKER APEX 2 X-ray (three-circle) diffractometer was employed for crystal screening, unit cell determination, and data collection.

### General procedure for the synthesis of aryl-3,3'-BIMs (3a-n)

A mixture of indole (2 mmol) and aromatic aldehyde (1 mmol) was taken in a dry mortar at room temperature. Potash alum (10 mol%) and anhydrous sodium sulphate (1.5 mmol) were added and ground well in the absence of light. Time for completion of the reaction is shown in Table 1. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was washed with diethyl ether for removing excess indole and aldehyde(s). Then the solid was extracted with hot ethyl acetate. Evaporation of the solvent under vacuum afforded a solid which was again washed with diethyl ether. The product BIMs, thus obtained were found to be pure upon TLC.

### Spectral data for new BIMs

*Ethyl 2-[2-{Bis(1H-indol-3-yl)methyl}-6-methoxyphenoxy] acetate (3g) :*

Pale pink solid, 96 %, mp 150-152  $^{\circ}\text{C}$ ; IR (KBr): 3419 (N-H), 3354 (N-H), 1741(C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.15 (t,  $J = 7.0$  Hz, 3H,  $\text{CH}_3$ ), 3.80 (s, 3H,  $\text{OCH}_3$ ), 4.04 (q,  $J = 7.0$  Hz, 2H,  $\text{OCH}_2$ ), 4.26 (s, 2H,  $\text{OCH}_2\text{O}$ ), 6.44 (s, 1H, methane CH), 6.60 (s, 2H, Ar), 6.75 (d,  $J = 8.0$  Hz, 2H, Ar), 6.89 (t,  $J = 8.0$  Hz, 1H, Ar), 6.96 (t,  $J = 7.0$  Hz, 2H, Ar), 7.12 (t,  $J = 7.0$  Hz, 2H, Ar), 7.28 (d,  $J = 8.0$  Hz, 2H, Ar), 7.41 (d,  $J = 8.0$  Hz, 2H, Ar) 7.87 (s, 2H, NH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 14.1, 33.16, 55.69, 60.80, 69.87, 110.36, 110.93, 119.07, 119.23, 120.07, 121.69, 121.75, 123.60, 124.00, 127.04, 136.64, 138.06, 145.18, 152.10, 169.62; ESI-MS  $m/z$ : 453.2 [ $\text{M}^+$ ], 452.2 [ $\text{M}^+ - \text{H}$ ], 339.2 [ $\text{M}^+ - \text{indole}$ ], 338.2 [ $\text{M}^+ - \text{H} - \text{indole}$ ]; Anal. Calcd. For  $\text{C}_{28}\text{H}_{26}\text{N}_2\text{O}_4$ : C, 73.99; H, 5.77; N, 6.16; Found C, 73.96; H, 5.81; N, 6.20.

*Ethyl 2-[2-{bis(2-methyl-1H-indol-3-yl)methyl}-6-methoxyphenoxy] acetate (3n) :*

Pink solid, 98 %, mp 154-156  $^{\circ}\text{C}$ ; IR (KBr): 3393 (N-H), 3375 (N-H), 1752 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.18 (t,  $J = 7.0$  Hz, 3H,  $\text{CH}_3$ ), 2.07 (s, 6H,  $\text{CH}_3$ -Indole), 3.79 (s, 3H,  $\text{OCH}_3$ ), 3.94 (s, 2H,  $\text{OCH}_2\text{O}$ ), 4.04 (q,  $J = 7.0$  Hz, 2H,  $\text{OCH}_2$ ), 6.37 (s, 1H, methane CH), 6.81 (m, 4H, Ar), 6.91 (t,  $J = 8.0$  Hz, 1H, Ar), 6.95 (d,  $J = 8.0$  Hz, 2H, Ar), 7.00 (t,  $J = 7.5$  Hz, 2H, Ar), 7.21 (d,  $J = 8.0$  Hz, 2H, Ar), 7.71 (s, 2H, NH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 12.24, 14.18, 33.70, 55.75, 60.51, 69.20, 109.90, 110.67,

**Research Article**

113.11, 119.05, 119.43, 120.42, 122.39, 123.69, 129.11, 131.84, 135.01, 138.04, 145.75, 152.15, 169.65; ESI-MS  $m/z$ : 482.2 [ $M^+$ ], 481.2 [ $M^+ - H$ ], 353.1 [ $M^+ - \text{indole}$ ], 352.1 [ $M^+ - H - \text{indole}$ ]; Anal. Calcd. For  $C_{30}H_{30}N_2O_3$ : C, 74.67; H, 6.27; N, 5.18; Found C, 74.60; H, 6.21; N, 6.20.

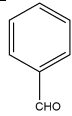
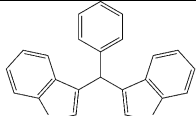
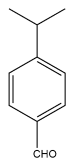
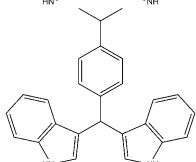
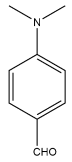
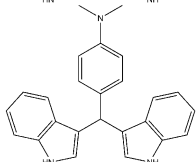
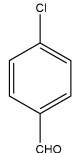
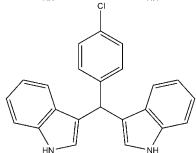
**RESULTS AND DISCUSSION**

As a model reaction, we initially examined the synthesis of 3,3'-bis(indolyl)phenylmethane (**3a**) from indole (**1**) and benzaldehyde (**2**) using potash alum under solvent-free conditions. It was found that, at room temperature the corresponding BIM was not formed exclusively even after 12 h. We observed that the eutectic melt was not hardened, but a by-product (Kumar *et al.*, 2009, Bhuyan *et al.*, 1989) started appearing the degradation of **3a** (Kumar *et al.*, 2009). This situation necessitated us to introduce modification in this adopted procedure.

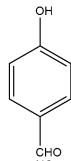
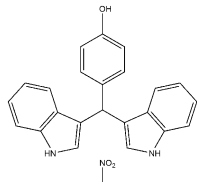
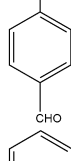
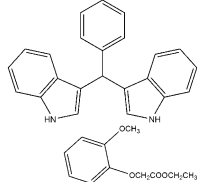
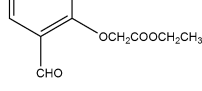
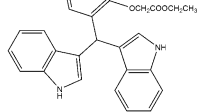
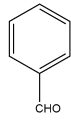
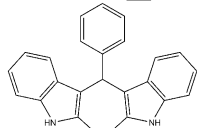
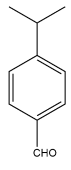
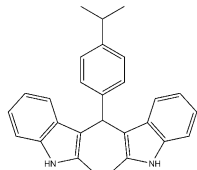
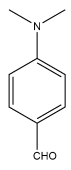
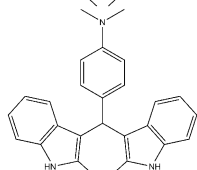
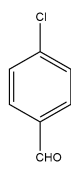
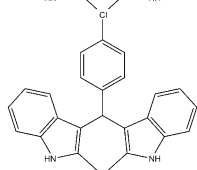
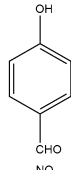
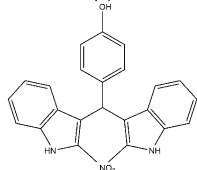
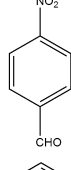
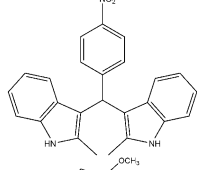
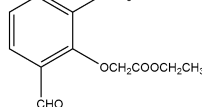
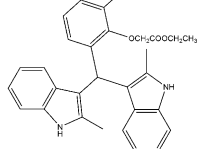
Nevertheless, 2-methylindole afforded the corresponding BIM (**3h**) using potash alum under the solvent-free conditions. This reaction did not yield any other by products even after 24 h as monitored by TLC. Therefore, we concluded that formation of **3a** was rapidly followed by further condensation of the aldehyde (Kumar *et al.*, 2009, Bhuyan *et al.*, 1989) to afford the by product in the presence of potash alum in eutectic melt (pH 2-4). In order to avoid the consecutive condensation leading to the formation of by product, we needed to absorb the water released from the reaction mixture. The same reaction was repeated with excess of anhydrous sodium sulphate alone. But we could not initiate the reaction. Then we used a mixture of potash alum-anhydrous sodium sulphate under solvent-free conditions at room temperature. Now the reaction proceeded to completion in 30 min. Under these conditions, BIM was formed as the major product. The best result was obtained from 10 mol% of potash alum with 1.5 equiv. of anhydrous sodium sulphate at room temperature in the absence of light (Maciejewska *et al.*, 2006) for the synthesis of **3a**. Here potash alum acts as a Lewis acid and anhydrous sodium sulphate acts as a dehydrating agent.

The reaction time and yield of the reactions between indole and various aromatic aldehydes are shown in Table 1.

**Table: 1 Synthesis of Bis(indolyl)methanes**

Sl. No	Aldehyde	Product	Reaction Time (min)	Yield (%)
3a.			30	98
3b.			50	92
3c.			55	90
3d.			25	96

**Research Article**

3e.			45	98
3f.			25	99
3g.			10	96
3h.			10	98
3i.			15	94
3j.			15	94
3k.			10	98
3l.			15	97
3m.			15	99
3n.			10	98

### **Research Article**

With electron releasing groups (Me<sub>2</sub>C, Me<sub>2</sub>N) in the para position of the aromatic aldehydes, the electrophilic character of the carbonyl carbon is less for the aromatic electrophilic substitution reaction, while with electron-withdrawing groups (NO<sub>2</sub>, OH), in the para- position this effect is clearly pronouncing.

When we carried out the experiment with 2-phenylindole under identical conditions, no characteristic reaction was observed. The unreactivity of 2-phenylindole in this case may be attributed to the mild Lewis acidic nature of potash alum as well as the poor nucleophilicity at C-3 of 2-phenylindole.

In summary, we have developed an efficient synthesis of aryl-3,3'-BIMs using potash alum–anhydrous sodium sulphate mixture at room temperature under solvent-free conditions in good to excellent yields. To the best of our knowledge, this is the first report on the synthesis of BIMs using a mixture of potash alum-anhydrous sodium sulphate. Syntheses of biologically important compounds were prepared by using this mixture is under progress in our group.

### **ACKNOWLEDGEMENT**

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### **REFERENCE**

- Azizian J, Mohammadi AA, Karimi AR and Mohammadiazadeh MR (2006).** KAl(SO<sub>4</sub>)<sub>2</sub>·12H<sub>2</sub>O supported on silica gel as a novel heterogeneous system catalyzed biginelli reaction: One-pot synthesis of di-hydropyrimidinones under solvent-free conditions. *Applied Catalysis A: General* **300**(1) 85-88.
- Babu G, Sridhar N and Perumal PT (2000).** A Convenient method of synthesis of bis(indolyl)methanes: indium trichloride catalyzed reactions of indole with aldehydes and schiff's. *Synthetic Communication* **30**(9) 1609-1614.
- Bell R, Carmeli S and Sar N (1994).** Vibrindole A, a Metabolite of the Marine Bacterium, *Vibrio parahaemolyticus*, Isolated from the Toxic Mucus of the Boxfish *Ostracion cubicus*. *Journal of Natural Product* **57**(11) 1587-1590.
- Bhuyan PJ, Borah RC and Sandhu JS (1989).** Synthesis of dihydro- and tetrahydroisoxazolo[3',4':3,4]pyrrolo[1,2-a]indoles via intramolecular cycloadditions. A novel class of mitomycin analogues. *Tetrahedron letters* **30** (11) 1421-1422.
- Budzikiewicz H, Eckau H and Ehrenberg M (1972).** Bis(3-indolyl)-3H-indolylden-methan, ein von *saccharomyces cerevisiae* gebildeter farbstoff. *Tetrahedron Letters* **13**(36) 3807-3810.
- Dabiri M, Baghbanzadeh M, Kiani S, and Vakilzadeh Y (2007).** Alum (KAl(SO<sub>4</sub>)<sub>2</sub> · 12H<sub>2</sub>O) Catalyzed One-Pot Synthesis of Coumarins under Solvent-Free Conditions. *Monatshefte für Chemie* **138** 997-999.
- Garbe TR, Kobayashi M, Shimizu N, Takesue N, Ozawa M and Yukawa H (2000).** Indolyl Carboxylic Acids by Condensation of Indoles with  $\alpha$ -Keto Acids. *Journal of Natural Products* **63**(5) 596-598.
- Ghorbani-Vaghei R, Veisi H, Keypour H and Dehghani-Firouzabadi AA (2010).** A practical and efficient synthesis of bis(indolyl)methanes in water, and synthesis of di-, tri-, and tetra(bisindolyl)methanes under thermal conditions catalyzed by oxalic acid dihydrate. *Molecular Diversity* **14**(1) 87-96.
- Hasaninejad A, Zare A, Sharghi H, Niknam K and Shekouhy M (2007).** P<sub>2</sub>O<sub>5</sub>/ SiO<sub>2</sub> as an efficient, mild, and heterogeneous catalytic system for the condensation of indoles with carbonyl compounds under solvent-free conditions. *ARKIVOC* (xiv) 39-50.

### Research Article

**He X, Hu S, Liu K, Guo Y, Xu J and Shao S (2006).** Oxidized Bis(indolyl)methane: A Simple and Efficient Chromogenic-Sensing Molecule Based on the Proton Transfer Signaling Mode. *Organic Letters* **8**(2) 333-336.

**Heravi MM, Sadjadi S, Sadjadi S, Oskooie HA and Bamoharram FF (2009).** A convenient synthesis of bis(indolyl)alkanes under ultra sonic irradiation using silica-supported Preyssler nano particles. *Ultrasonics Sonochemistry* **16**(6) 718-720.

**Ji SJ, Zhou MF, Gu DG, Jiang ZQ and Loh TP (2004).** Efficient FeIII-Catalyzed Synthesis of Bis(indolyl)methanes in Ionic Liquids. *European Journal of Organic Chemistry* **7** 1584-1587.

**Kamal A and Qureshi AA (1963)** Syntheses of some substituted di-indolylmethanes in aqueous medium at room temperature. *Tetrahedron* **19**(4) 513-520.

**Kamal A, Khan MNA, Reddy KS, Srikanth YVV, Ahmed SK, Kumar KP and Murthy USN (2009).** An efficient synthesis of bis(indolyl)methanes and evaluation of their antimicrobial activities. *Journal of Enzyme Inhibition Medicinal Chemistry* **24**(2) 559-565.

**Kobayashi M, Aoki S, Gato K, Matsunami K, Kurosu M and Kitagawa I (1994).** Marine Natural Products.XXXIV. Trisindole, a New Antibiotic Indole Trimer, Produced by Bacterium of *Vibro* sp. Separated from the Marine Sponge *Hyrtios altum*. *Chemical and Pharmaceutical Bulletin* **42**(12) 2449-2451.

**Kobayashi S, Araki M and Yasuda M (1995).** One-pot Synthesis of [3-Amino Esters from Aldehydes Using Lanthanide Triflate as a Catalyst. *Tetrahedron Letters* **36**(32) 5773-5776.

**Kumar S, Grover IS and Sandhu JS (2009).** Facile and efficient electrophilic substitution reactions of indoles with various carbonyl compounds are carried out using alum [KAl(SO<sub>4</sub>)<sub>2</sub>.12H<sub>2</sub>O], an in-expensive and reusable catalyst, to afford vibrindole and other bis(indolyl)methanes in excellent yields. *Indian Journal of Chemistry* **48B** 585-589.

**Lin XF, Cui SL and Wang YG (2006).** Mild and Efficient Synthesis of bis-Indolylmethanes Catalyzed by Tetrabutylammonium Tribromide. *Synthetic Communication* **36**(21) 3153-3160.

**Maciejewska D, Szpakowska I, Wolska I, Niemyjska M, Mascini M and Maj-Zurawska M (2006).** DNA-based electrochemical biosensors for monitoring of bis-indoles as potential antitumoral agents, chemistry, X-ray crystallography. *Bioelectrochemistry* **69**(1) 1-9.

<sup>a</sup>**Majer JR (1960).** Dyes containing the indole ring-I: Trinuclear trimethincyanines. *Tetrahedron* **9**(1-2) 106-110.

<sup>b</sup>**Majer JR (1960).** Dyes containing the indole ring-II: Trinuclear trimethincyanines. *Tetrahedron* **9**(1-2) 111-115.

**Martinez R, Espinosa A, Tarraga A and Molina P (2008).** Bis(indolyl)methane derivatives as highly selective colourimetric and ratiometric fluorescent molecular chemosensors for Cu<sup>2+</sup> cations. *Tetrahedron* **64**(9) 2184-2191.

**Martins MAP, Frizzo CP, Moreira DN, Buriol L and Machado P (2009).** Solvent-free heterocyclic synthesis. *Chemical Review* **109** 4140-4182.

**Novak TJ, Kramer DN, Klapper H, Daasch LW and Murr BL (1976).** Studies on the Formation of Dyes Derived from Diindolylpyridylmethanes. *The Journal Organic Chemistry* **41**(4) 870-875.

**Osawa T and Namiki M (1983).** Structure elucidation of streptindole, a novel genotoxic metabolite isolated from intestinal bacteria. *Tetrahedron Letters*, **24**(43) 4719-4722.

**Penieres-Carrillo G, Garcia-Estrada JG, Gutierrez-Ramirez JL and Alvarez-Toledano C (2003).** Infrared-assisted eco-friendly selective synthesis of diindolylmethanes. *Green Chemistry* **5** 337-339.

**Porter JK, Bacon CW, Robbins JD, Himmelsbach DS and Higman HC (1977).** Indole Alkaloids from *Balansia epichloe* (Weese). *Journal of Agricultural and Food Chemistry* **25**(1) 88-93.

**Shiri M, Zolfigol MA, Kruger HG and Tanbakouchian Z (2010).** Bis- and trisindolylmethanes (BIMs and TIMs). *Chemical Review* **110** 2250-2293.

**Research Article**

**Sivaprasad G, Perumal PT, Prabavathy VR and Mathivanan N (2006).** Synthesis and anti-microbial activity of pyrazolylbisindoles - Promising anti-fungal compounds. *Bioorganic and Medicinal Chemistry Letter* **16**(24) 6302-6305.

**Sonar SS, Sadaphal SA, Kategaonkar AH, Pokalwar RU, Shingate BB and Shingare MS (2009).** Alum catalyzed simple and efficient synthesis of bis(indolyl)methanes by ultrasound approach. *Bulletin Korean Chemical Society* **30** 825-828.

**Sujatha K, Perumal PT, Muralidharan D and Rajendran M (2009).** Synthesis, analgesic and anti-inflammatory activities of bis(indolyl)methanes. *Indian Journal of Chemistry* **48B** 267-272.

**Suresh Kumar D and Sandhu JS (2011).** Alum [KAl(SO<sub>4</sub>)<sub>2</sub>.12H<sub>2</sub>O], An efficient, novel, clean, catalyst for Doebner Knoevenagel reaction for the efficient production of  $\alpha,\beta$ -unsaturated acids. *Indian Journal of Chemistry* **50B** 1479-1483.

**Tanaka K and Toda F (2000).** Solvent-free organic synthesis. *Chemical Review* **100** 1025.

**Veisi H, Hemmati S and Veisi H (2009).** Highly Efficient Method for Synthesis of Bis(indolyl)methanes Catalyzed by FeCl<sub>3</sub>-based Ionic Liquid. *Journal of Chinese Chemical Society* **56**(1) 240-245.

**Vishvanath DP, Ganesh BD, Priyanka AR and Jaymala JP (2011).** Synthesis of Bis(indolyl) Methanes in Catalyst- and Solvent-Free Reaction. *Synthetic Communication* **41**(5) 736-747.

**Zahran M, Abdin Y and Salama H (2008).** Eco-friendly and efficient synthesis of bis(indolyl) methanes under microwave irradiation. *ARKIVOC* (xi) 256-265.