IJPSR (2013), Vol. 4, Issue 4 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 24 December, 2012; received in revised form, 13 March, 2013; accepted, 29 March, 2013

SYNTHETIC APPROACHES FOR BIS (INDOLYL) METHANES

Partha Pratim Kaishap* and Chandrajit Dohutia

Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh- 786004, Assam, India

Keywords:
Bis (indolyl) Methanes, Indole, Aldehyde, Catalyst, Carbonyl Compounds

Correspondence to Author:

Partha Pratim Kaishap

Vill.- Boalkamari, Po.- Aminkata, Dist.- Kokrajhar-783337, Assam, India

E-mail: pk6511@gmail.com

ABSTRACT: Indole ring system is the most important heterocycle available in natural compounds. Owing to great structural diversity, the indole ring system has become an important structural requirement in many pharmaceutical agents. Indole has been widely identified as a privileged structure or pharmacophore, with its presence in over 3000 natural isolates which are known to possess broad spectrum of biological activities and pharmaceutical applications. The bis (indolyl) methane derivatives are found to be very active compounds in pharmacy field. They are found in cruciferous plants and are known to promote beneficial oestrogen metabolism and induce apoptosis in human cancer cells. In recent years, a lots of bis (indolyl) methane derivatives have been synthesized and found to possess promising biological activities including anticancer, antimicrobial, antifungal, analgesic, anti-inflammatory, anthelmintic, cardiovascular activities. In the present review several synthetic schemes of these compounds are discussed involving non-toxic catalyst and providing high yields.

INTRODUCTION: Bis (indolyl) methanes, indole and their derivatives are known as important intermediates in organic synthesis and pharmaceutical chemistry and exhibit various physiological properties. Indole ring system is the most important heterocycle available in natural compounds. Owing to great structural diversity of biologically active indoles, it is not surprising that the indole ring system has become an important structural requirement in many pharmaceutical agents. Indole has been widely identified as a privileged structure or pharmacophore, with its presence in over 3000 natural isolates [1] which are known to possess broad spectrum of biological activities and pharmaceutical applications [2].

QUICK RESPONSE CODE

IJPSR:
ICV (2011)- 5.07

Article can be accessed online on:
www.ijpsr.com

Indomethacin and tenidap are indole derivatives found to possess anti-inflammatory activity with analgesic and anti-pyretic properties. They inhibit production of ecosanoids by inhibition of cyclo-oxygenase (COX) and thereby reduce oedema. Several indole derivatives are reported to have anti microbial activity.

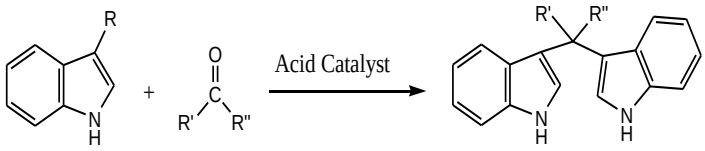
Bis (indolyl) methanes are found in cruciferous plants and are known to promote beneficial oestrogen metabolism and induce apoptosis in human cancer cells [3]. Bis (indolyl) methanes have received much attention in recent years [4].

Such compounds are prone to develop interesting bio activity and find useful applications as breast cancer preventive[5] and anti- bacterial agents [6]. Hong *et al.* [7] and Kedmi *et al.* [8] reported recently the potential beneficial effects of 3, 3-biindolyl methanes on the proliferation and induction of apoptosis in human prostate and breast cancer cells.

Bis(Indolyl) methane derivatives have been reported to possess promising biological activities including antipyretic, antifungal, anti-inflammatory, ant-helmintic, cardiovascular, anticonvulsant, anti-microbial and selective COX-2 inhibitory activities [9]. Therefore synthesis of bis (indolyl) moiety has become interesting target for the synthetic organic chemist in view of their immense biological and pharmaceutical activities.

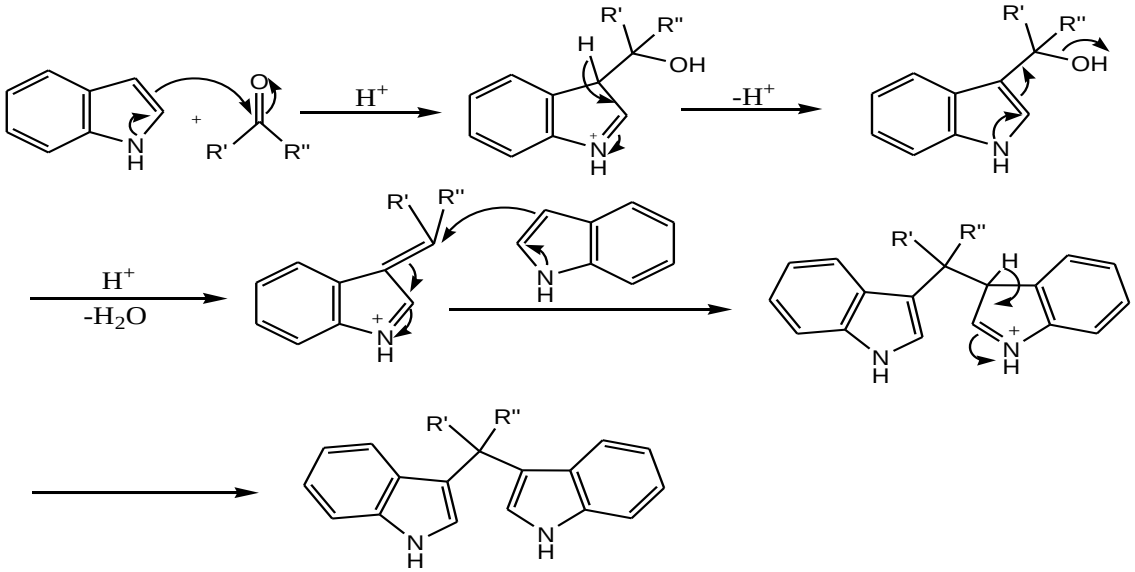
The lead indole derivatives reported in this literature are bis (indolyl) methane. The method of synthesis involves both one step as well as multistep synthesis. Several methods have been reported in this literature for the preparation of bis (indolyl) methanes from indoles and carbonyl compounds using protic acids [10] and Lewis acids [11]. Fischer in 1886 prepared 3, 3-bis (indolyl) methanes for the first time which was a mere acid catalyzed Friedel-Crafts reaction between indole and carbonyl compounds, generally aldehydes and ketones.

The acid catalyzed reaction of electron rich heterocyclic compounds such as indole and pyroles with p-dimethyl aminobenzaldehyde is known as the Ehrlich test [12]. Generally 3,3`-bis (indolyl) methanes are synthesized by an analogous reaction to the Ehrlich test, where indole reacts with aliphatic or aromatic aldehydes or ketones in the presence of an acid catalyst to produce azafulvenium salt which undergoes further addition reaction with a second indole molecule to produce bis (indolyl) methanes.



R' = Alkyl or Aryl
R" = H or Alkyl

Mechanism of the Reaction:



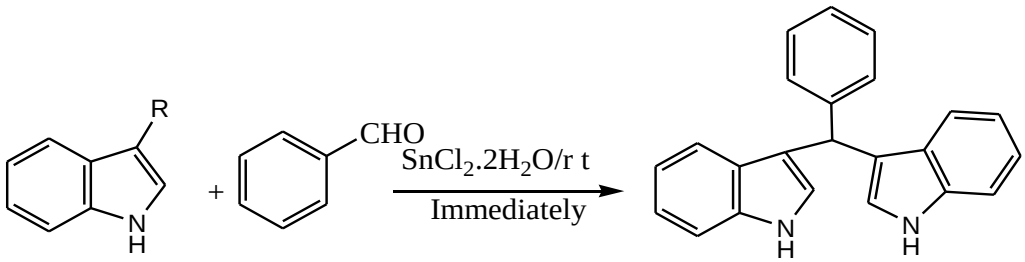
The common route for the synthesis of bis (indolyl) methanes is electrophilic substitution reaction of indoles with the aromatic or aliphatic aldehyde and ketones catalyzed by protic acids or Lewis acids. However, Lewis acids are required in excess because it is destroyed by the presence of even small amount of moisture or when trapped by nitrogen present in heterocycles.

In recent years, synthesis of this class of molecules under mild conditions have been reported with promoters such as $SnCl_2.2H_2O$ [13], TCBDA [14], PCBS [15], Silica H_2SO_4 [16], P_2O_5/SiO_2 [17], $SbCl_3$ [18], Alum [19] etc.

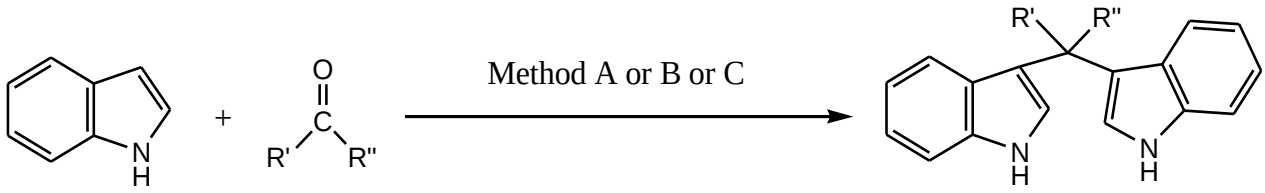
There are various type of method including solvent free, microwave synthesis for the synthesis of bis (indolyl) methanes have been reported in the literature.

Synthetic Schemes:

1. Shaikh *et al* [13] synthesized bis (indolyl) methanes by mixing and crushing a mixture of indole and benzaldehyde in a mortar with pistle in presence of $SnCl_2$. H_2O catalyst. Progress of the reaction was checked by TLC. Water was added to the reaction mixture and filtered. The crude product so obtained is purified by column chromatography (Ethyl acetate: Hexane, 1:9).



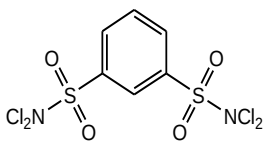
2. Vaghei *et al* [14] used poly (*N,N'*- dichloro-*N*-ethyl-benzene-1,3-disulfonamide) [PCBS] and *N,N,N',N'*-tetrachlorobenzene-1,3-disulfonamide [TCBDA] as novel catalysts in the electrophilic substitutions of indole with a variety of aldehydes and ketones under (*i*) solvent-free, (*ii*) solvent conditions (H_2O and EtOH) to afford bis(indolyl)methanes.



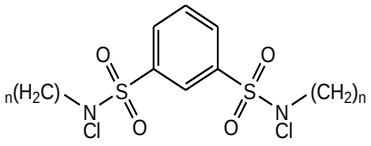
Method A = TCBDA or PCBS in ethanol at room temperature.

Method B = TCBDA or PCBS grinding in solid state at room temperature.

Method C = TCBDA or PCBS in water at room temperature.



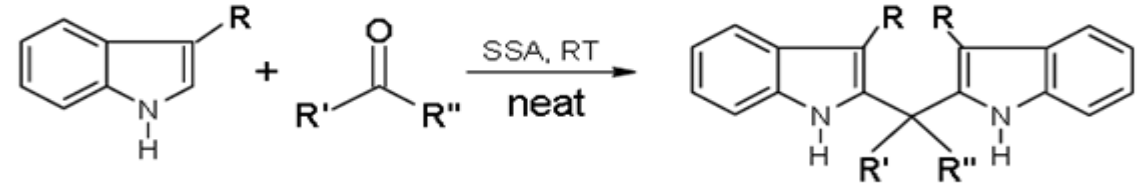
TCBDA



PCBS

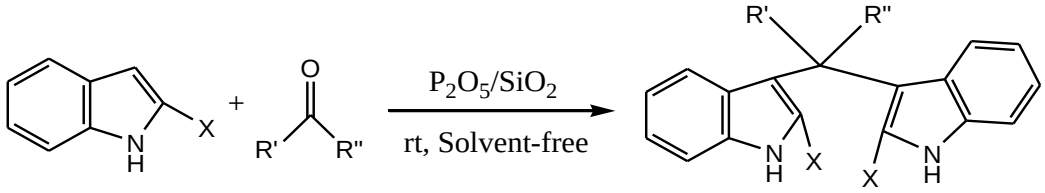
3. Pore *et al* [15] snthesized bis indolyl methanes by stirring a mixture of aldehyde, indole/ indole-3-acetic acid and silica sulphuric acid at room temperature for half an hour. On completion of reaction (TLC) chloroform was added and the reaction mixture was filtered. The catalyst was washed with chloroform. Removal of solvent from combined filtrate gave the residue, which was filtered through a column of silica gel to afford pure bis (indolyl) methanes.

R = H R' = alkyl, phenyl
R" = H, alkyl



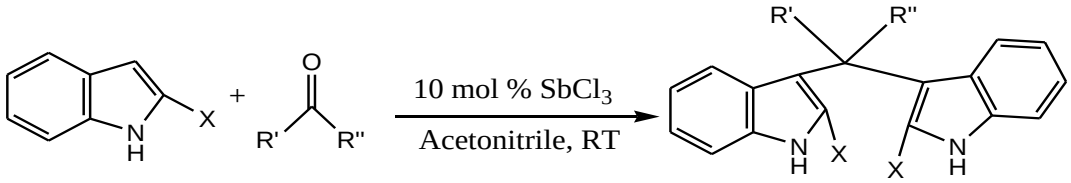
R = $-CH_2COOH$ R' = alkyl, phenyl
R" = H, alkyl

4. Hasaninejad *et al* [16] used P_2O_5/SiO_2 as catalytic system for the condensation of indole with carbonyl compounds under solvent free condition to produce bis (indolyl) methanes derivatives. A mixture of benzaldehyde and well grounded P_2O_5/ SiO_2 was added to indole and the resulting mixture was grounded at room temperature for 40 minutes. An orange coloured reaction was obtained which was the purified by recrystallization to obtain the pure product.



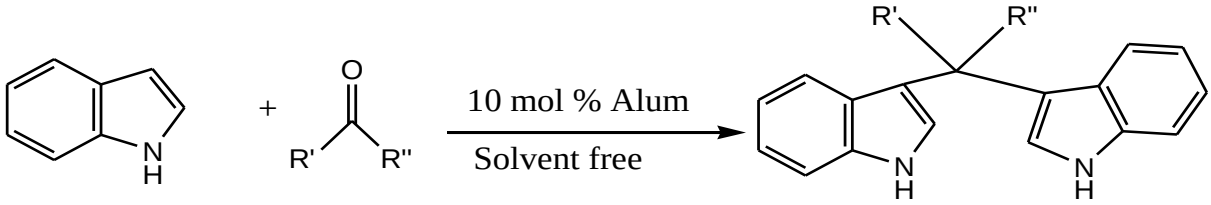
X = H or Methyl
R'= Aryl Or alkyl
R"= H, Alkyl or Aryl

5. Kundu *et al* [17] synthesized bis and tris (indolyl) methanes by the electrophilic addition of indole to the carbonyl compounds in presence of catalytic amount of $SbCl_3$.

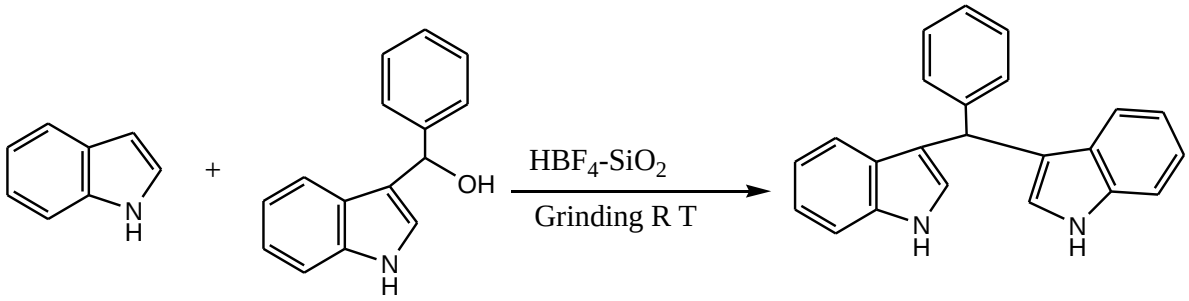


X = H or Methyl
R'= Aryl Or alkyl
R"= H, Alkyl or Aryl

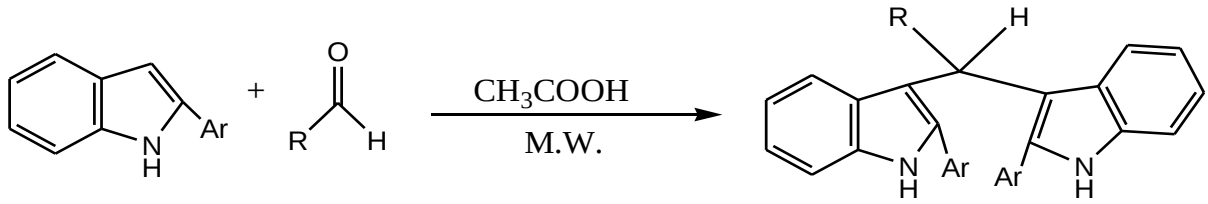
6. Sonar *et al* [18] synthesized bis (indolyl) methanes using alum as catalyst by ultrasound irradiation. A mixture of indole, aldehyde and powdered alum was irradiated under ultrasound irradiation at ambient temperature for appropriate time. After the completion of reaction ice cold water was added to the reaction mixture and the solid obtained was filtered and recrystallized from ethanol to get the pure product.



7. Bandgar *et al* [19] synthesized bis (indolyl) alkanes by using fluoroboric acid absorbed on silica gel as catalyst under mild and solvent free conditions. The reaction of indole with indole-3-phenyl methanol under solvent free condition in presence of HBF_4-SiO_2 yields bis (indolyl) methanes.

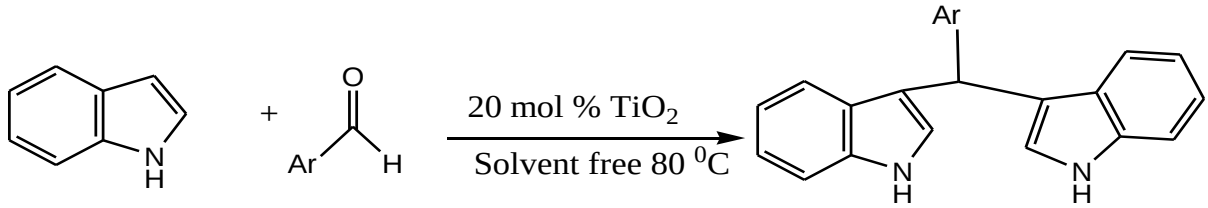


8. Zahran *et al* [20] synthesized bis (indolyl) methanes under microwave irradiation using glacial acetic acid as catalyst. A mixture of 2-arylindole, aldehyde and glacial acetic acid in an open Pyrex-glass vessel was subjected to microwave irradiation. Irradiation was carried out in successive 30 sec periods to avoid overheating of the catalyst. After completion of the reaction as monitored by TLC, the reaction mixture was cooled, and poured onto water. The precipitated solid was filtered off, washed with water, dried and recrystallized.

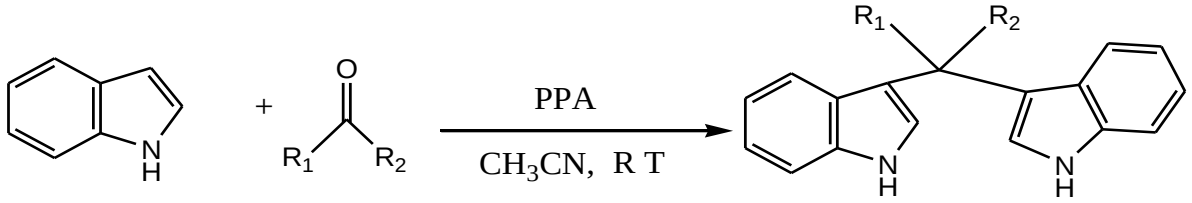


Ar = Aryl
R = Alkyl or aryl

9. Sarvari *et al* [21] synthesized bis (indolyl) methanes under solvent free condition using titania (TiO_2) as catalyst. A mixture of TiO_2, benzaldehyde and indole was added to a test tube and heated in an oil bath at 80°C with stirring. The progress of the reaction was monitored by TLC. After the reaction was completed, the catalyst was filtered, following by washing with ethyl acetate. The volume was concentrated under reduced pressure and the product was purified by column chromatography.

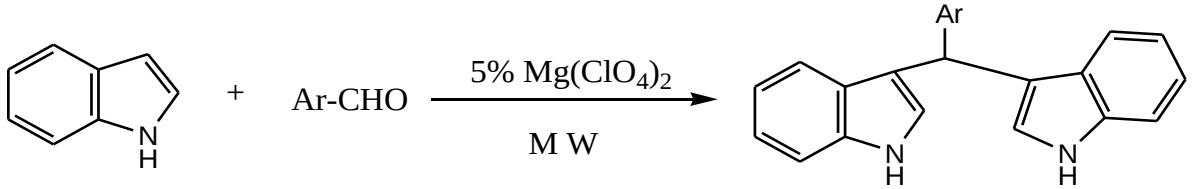


10. Sagar *et al* [22] synthesized bis (indolyl) methanes by the reaction of indole and aldehyde using phenyl phosphoric acid as catalyst in acetonitrile solvent.

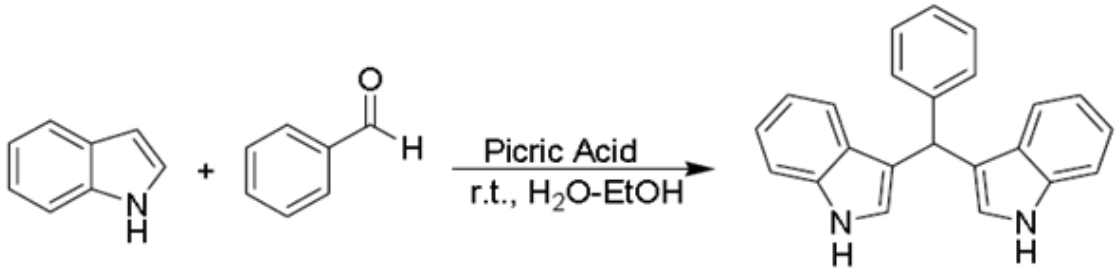


R_1 = H
R_2 = Alkyl, Aryl or Heterocycle

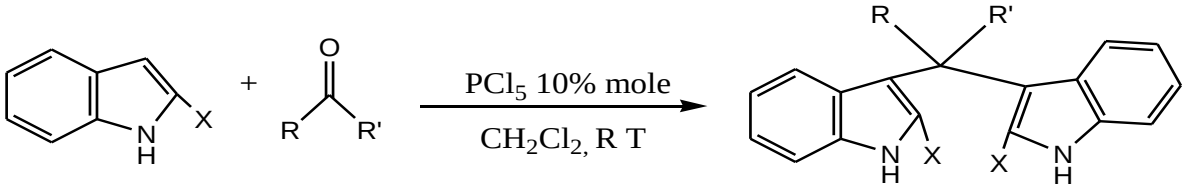
11. Sadaphal *et al* [23] synthesized bis (indolyl) methanes by irradiating the mixture of indole, aldehyde and catalytic amount of $Mg(ClO_4)_2$ in microwave oven at 450 W for appropriate time without using any solvent.



12. Hasaninejad *et al* [24] reported a new, homogeneous, clean and efficient method for condensation of indoles with carbonyl compounds in the presence of catalytic amount of picric acid at room temperature in aqueous media to produce bis (indolyl) methanes.

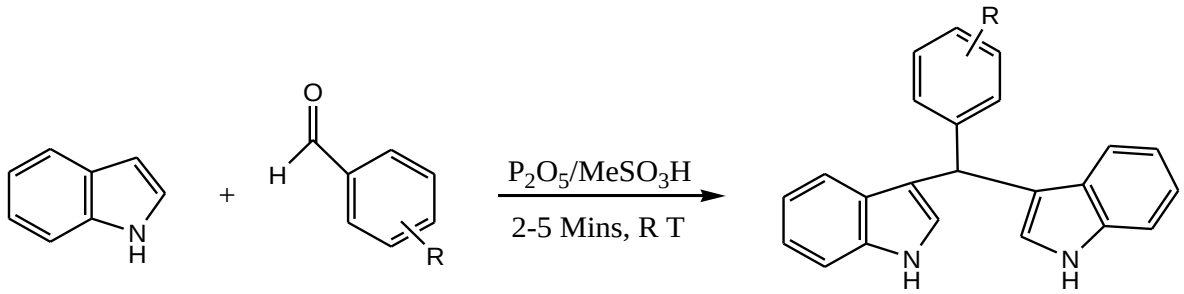


13. Hasaninejad *et al* [25] synthesized bis (indolyl) methanes by the reaction of indole and benzaldehyde using catalytic amount of PCl_5 in dichloromethane at room temperature.

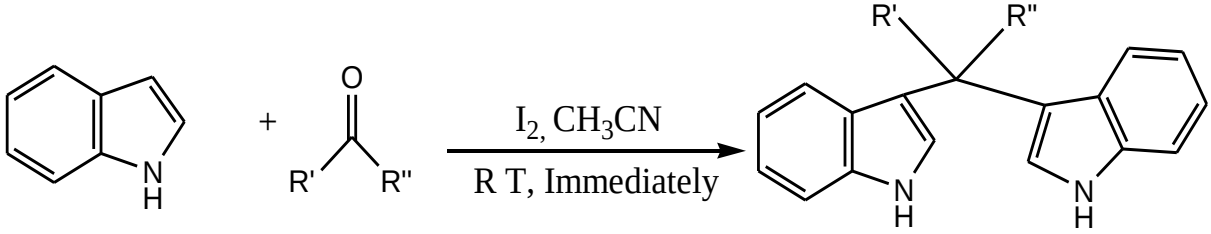


X = H or Me
R = Alkyl or aryl
R' = H or alkyl

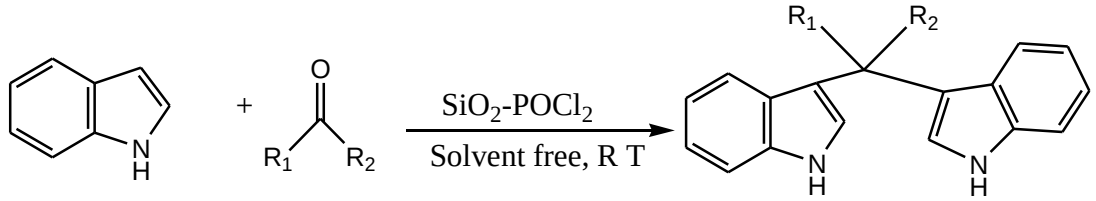
14. Borse *et al* [26] synthesized bis (indolyl) methanes by the reaction of indole with aldehyde using phosphorus pentoxide in methane sulfonic acid as catalyst at room temperature. The solid product separated out, was filtered, washed with sufficient water and dried. The crude product was recrystalized from ethanol-water (1:1) to afford Bis (indolyl) methanes.



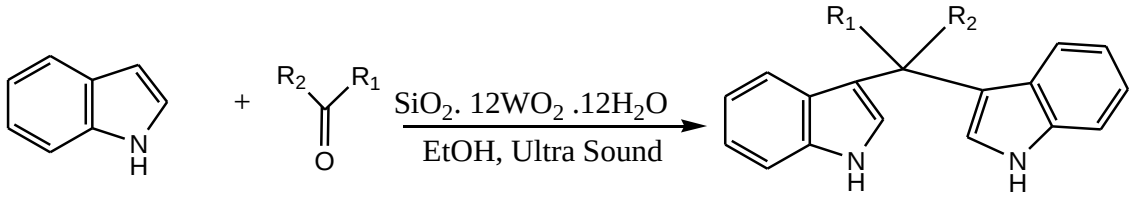
15. Bandgar *et al* [27] reported that when indole was treated with various aldehydes or ketones in the presence of a catalytic amount of I_2 in acetonitrile, bis (indolyl) methanes was formed.



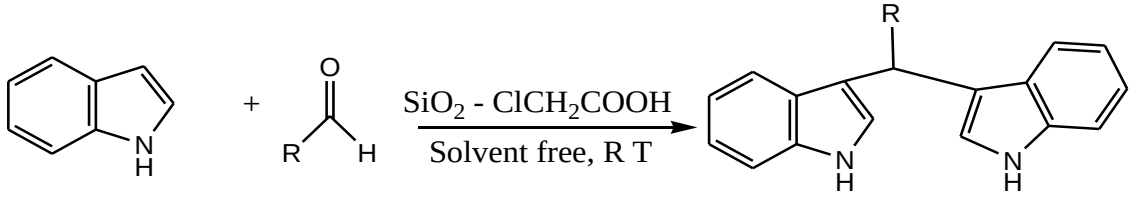
16. Kardak *et al* [28] synthesize bis (indolyl) methanes from corresponding aromatic aldehyde and ketone using silica dichlorophosphate as catalyst under solvent free reaction condition at room temperature.



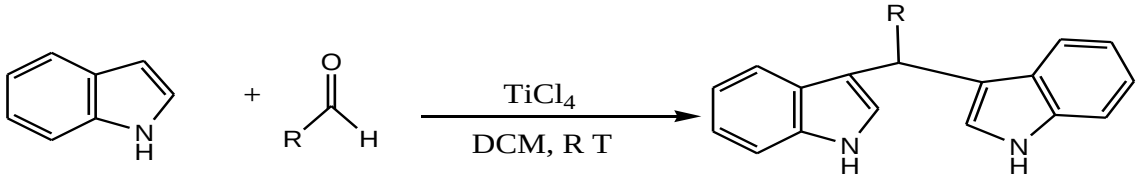
17. Li *et al* [29] carried out Synthesis of bis (indol-3-yl) methanes catalyzed by silicotungstic acid ($SiO_2.12WO_3.24H_2O$) in EtOH at r.t. under ultrasound irradiation.



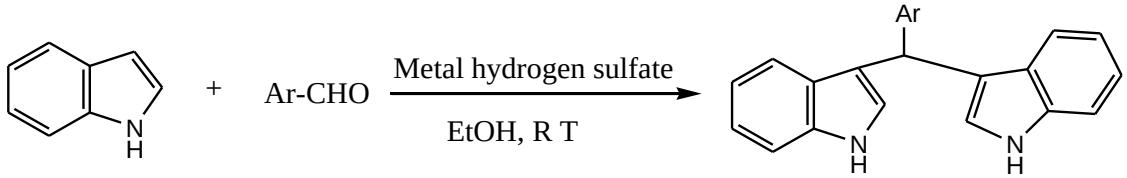
18. Chandam *et al* [30] used Silica supported chloroacetic acid as catalyst for the coupling of aromatic aldehyde and indole to produce bis (indolyl) methanes under solvent free condition.



19. Reddy *et al* [31] used $TiCl_4$ as a catalyst for the reaction of indoles with aromatic aldehydes in dichloromethane to produce corresponding bis (indolyl) methanes at room temperature.

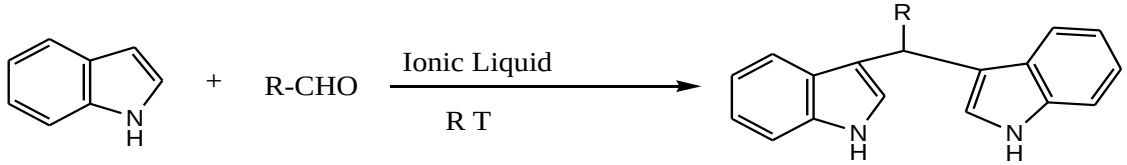


20. Niknam *et al* [32] used metal hydrogen sulphate as catalyst for the reaction of indoles with carbonyl compounds in ethanol to produce bis (indolyl) methanes.



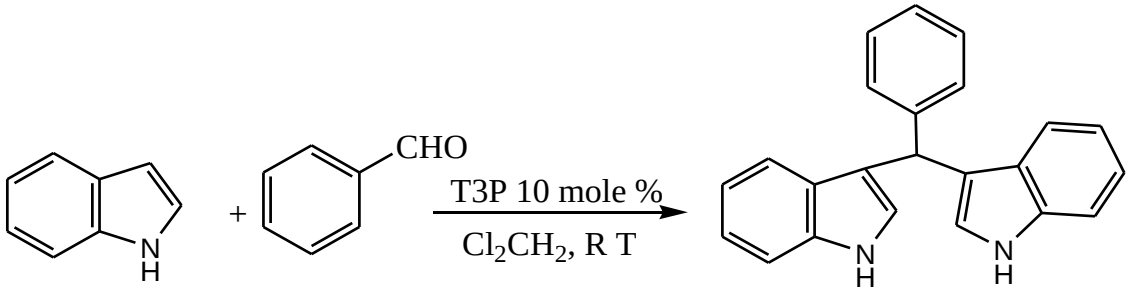
Metal hydrogen sulfate = $Zn(HSO_4)_2$, $Mg(SO_4)_2$, $Ca(SO_4)_2$

21. Dabiri *et al* [33] used ionic liquids [Hmim]Tfa and [Hmim]HSO_4 for the synthesis of bis (indolyl) methanes by reacting indole with carbonyl compounds at room temperature.

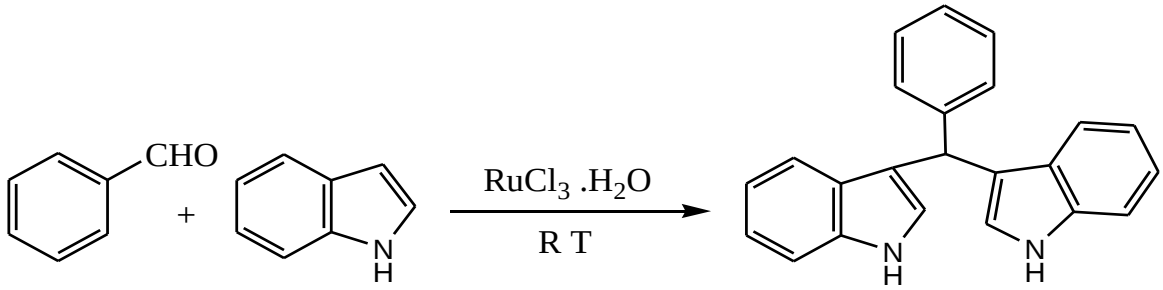


Ionic Liquid = [Hmim]Tfa, [Hmim]HSO_4

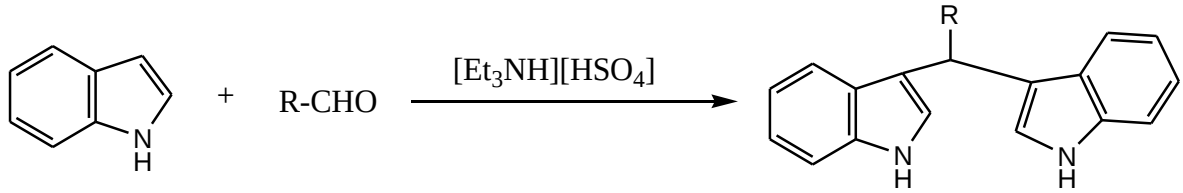
22. Prasanna *et al* [34] synthesized bis (indolyl) methanes using polyphosphoric anhydride (T3P) by the reaction of indole and aldehyde in dichloromethane.



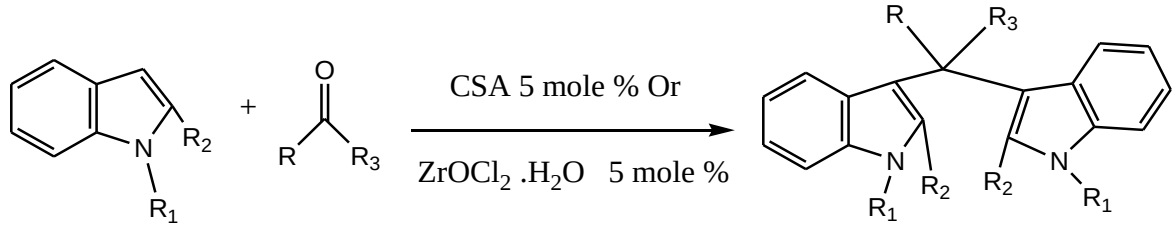
23. Qu *et al* [35] used $RuCl_3.3H_2O$ as catalyst for the synthesis of bis (indolyl) methanes by reacting indole with aldehyde in presence of benzene.



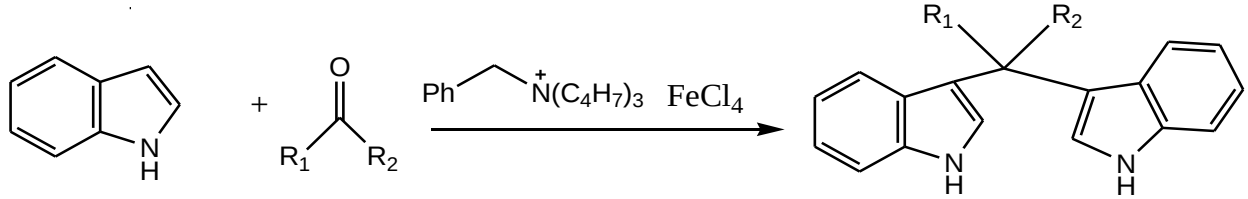
24. Rajendran *et al* [36] used ionic liquid $[Et_3NH][HSO_4]$ as catalyst for the synthesis of bis (indolyl) methane by the reaction of indole and aldehyde.



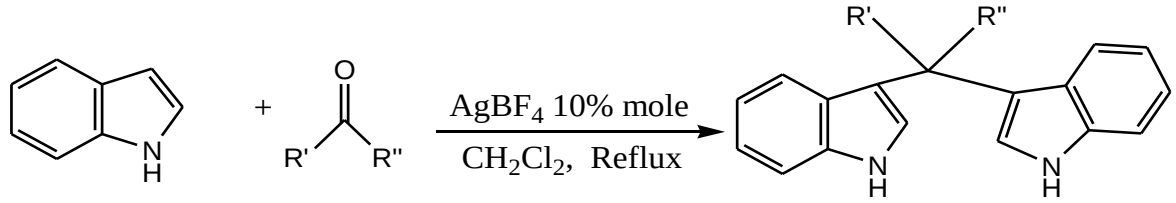
25. Mishra *et al* [37] synthesized bis (indolyl) methanes by reacting indole with aldehyde using camphor sulphonic acid (CSA) and zirconium oxychloride octahydrate ($ZrOCl_2.\ 8H_2O$) in aqueous medium at ambient temperature.



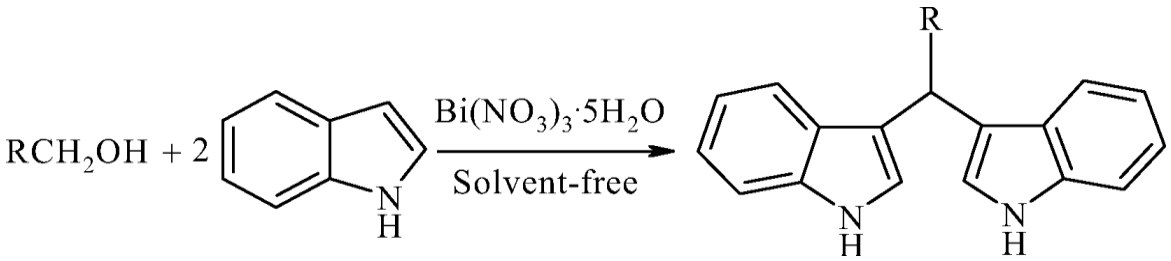
26. Veisi *et al* [38] carried out the synthesis of bis (indolyl) methanes by the reaction of indole with aldehydes and ketones in presence of $FeCl_3$ based ionic liquid.



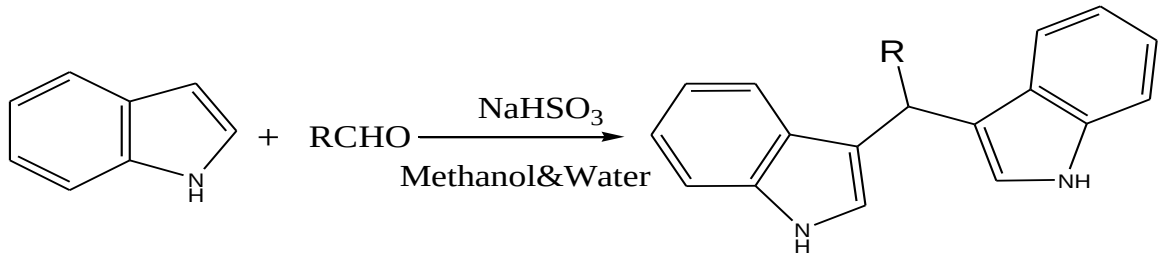
27. Shaikh *et al* [39] synthesized bis (indolyl) methanes by the reaction of indole and carbonyl compounds using $AgBF_4$ as catalyst in dichloromethane.



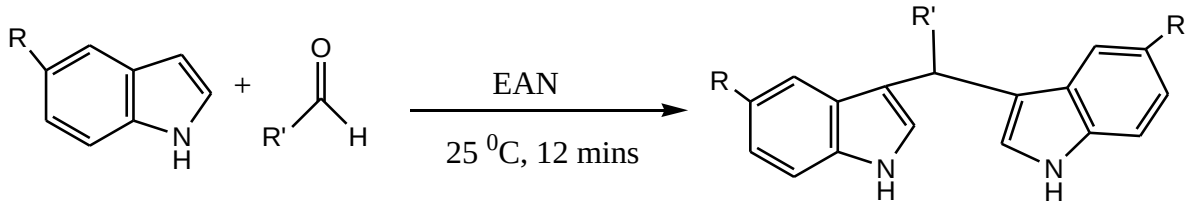
28. Khosropour *et al* [40] reported one pot conversion of primary alcohol to their bis (indolyl) methanes using $Bi(NO_3)_3.5H_2O$ as catalyst. $Bi(NO_3)_3.5H_2O$ was added to benzyl alcohol in a mortar. The mixture was mixed and kept at 65^oC for a few seconds. When indole was mixed in at room temperature., the corresponding bis (indolyl) methanes resulted.



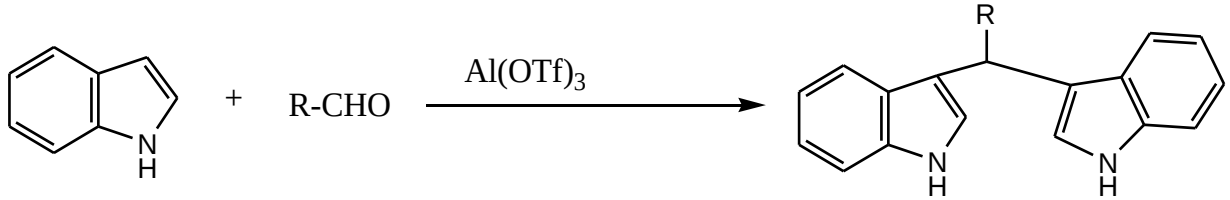
29. Kaishap *et al* [41] synthesized bis (indolyl) methanes by the reaction of indole and aldehyde in presence of $NaHSO_3$ in a solvent containing EtOH and water.



30. Mulla *et al* [42] synthesized bis (indolyl) methanes by the reaction of indole and aldehyde using ethyl ammonium nitrate (EAN) as reusable ionic liquid at room temperature.



31. Kamal *et al* [43] synthesized bis (indolyl) methanes using aluminium triflate as catalyst by reacting indole and carbonyl compounds.



CONCLUSION: This review gives an overview of a number of synthetic procedures using various catalysts, used to form a biologically rich bis (indolyl) methanes moiety. This paper may be helpful for further research work for the development of better medicinal agents and newer compounds containing bis (indolyl) moiety.

ACKNOWLEDGEMENT: The authors are thankful to Prof. Dipak Chetia of Department of Pharm. Sciences, Dibrugarh University for his kind support and help.

REFERENCES:

1. Bell R, Carmeli S, Sar N: Vibrindole A. A metabolite of the marine bacterium, *Vibrio parahaemolyticus*, isolated from the toxic mucus of the boxfish *Ostracion cubicus. J Nat Prod* 1994; 57; 1587.
2. Sundburg RJ: The chemistry of Indoles. Academic Press, New York 1996.
3. Zeligs M; A Diet and estrogen status: the cruciferous connection, J Medicinal Foods J Med Food 1998; 1; 67.
4. Garbe TR, Kobayashi M, Shimuju N, Takesue N, Ozawa M, Yukawa H: Indolyl carboxylic acids by condensation of indoles with alpha-keto acids. J Nat Prod, 2000; 63(5); 596.
5. Garbe TR, Kobayashi M, Shimuju N, Takesue N, Ozawa M, Yukawa H: Indolyl carboxylic acids by condensation of indoles with alpha-keto acids. J Nat Prod, 2000; 63(5);ss 596.
6. Osawa T, NamikiM: Structure elucidation of streptindole, a novel genotoxic metabolite isolated from intestinal bacteria. Tetrahedron Lett, 1983; 24; 4719.
7. Hong C, Firestone GL, Bjeldanes L: FCytostatic effects of 3,3'-diindolylmethane in human endometrial cancer cells result from an estrogen receptor-mediated increase in transforming growth factor-alpha expression. Biochem Pharmacol, 2002; 63;s 1085.
8. Nachshon-Kedmi MN, Yannai S, Haj A, Fares FA: Indole-3-carbinol and 3,3'-diindolylmethane induce apoptosis in human prostate cancer cells. Food Chem Toxicol, 2003; 41; 745.
9. Sujatha K, Perumal. PT, Muralidharan. D, Rajendran M. Indian journal of chemistry, 2009; 48(B); 267-272.
10. Niknam K, Zolfigol MA, Sadabadi, T, Nejati A: Preparation of Indolylmethanes Catalyzed by Metal Hydrogen Sulfates. J. Iran. Chem. Soc. 2006; 3; 318.
11. Murugesan V, Cheralathan KK, Karthik M: Catalysis by materials for fine chemicals production. Bulletin of the Catalysis Society of India 2004; 3; 23.
12. Ehrlich P: Med. Woche, 1901; 151
13. Shaikh KA, Mohammed ZA, Patel NT, Syed SA, Patil VA: SnCl2.2H2O; a precious addition to catalyst range for synthesis of bis (indolyl) methanes. Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2010; 1(4); 730-736.
14. Vaghei RG, Veisi H: Poly(N,N'-dichloro-N-ethyl-benzene-1, 3-disulfonamide) and N,N,N',N' Tetrachlorobenzene-1,3-disulfonamide as Novel Catalytic Reagents for Synthesis of Bis-indolyl, Tris-indolyl, Di(bis-indolyl), Tri(bis-indolyl) and Tetra(bis-indolyl) Methanes under Solid-State, Solvent and Water Conditions. J. Braz. Chem. Soc., 2010; 21(2); 193-201.
15. Pore DM, Desai UV, Thopate TS, Wadgaonkar PP: A mild, expedient, solventless synthesis of bis(indolyl)alkanes using
16. silica sulfuric acid as a reusable catalyst. General Papers, ARKIVOC 2006; 12;s 75-80.
17. Hasaninejad A, Zare A, Sharghi H, Niknam K, Shekouhy M: P2O5/SiO2 as an efficient, mild, and heterogeneous catalytic system for the condensation of indoles with carbonyl compounds undersolvent-free conditions. General Papers, ARKIVOC 2007; 14; 39-50.
18. Sonar SS, Sadaphal SA, Kategaonkar AH, Pokalwar RU, Shingate BB, Shingare MS: Alum Catalyzed Simple and Efficient Synthesis of Bis (indolyl) methanes by Ultrasound Approach. Bull. Korean Chem. Soc., 2009; 30(4); 825.
19. Bandgar BP, Patil AV, Kamble VT: Fluoroboric acid adsorbed on silica gel catalyzed synthesis ofbisindolyl alkanes under mild and solvent-free conditions. General Papers ARKIVOC, 2007; 16; 252-259.
20. Zahran M, Abdin Y, Salama H: Eco-friendly and efficient synthesis of bis(indolyl)methanes under microwave irradiation. General Papers ARKIVOC, 2008;11; 256-265.
21. Sarvari MH: Titania (TiO_2)-Catalyzed Expedient, Solventless and Mild Synthesis of Bis(Indolyl)Methanes. Acta Chim. Slov. 2007; 54; 354–359.
22. Sagar AD, Reddy SM, Pulle JS, Yadav MV: An Efficient Synthesis of Bis(Indolyl) Methanesusing Phenyl Phosphonic Acid. Int. J. Chem. Sci, 2011; 9(4); 1979-1986.
23. Sadaphal SA, Shelke KF, Sonar SS, Madje BR, Shingare MS: Mg(ClO4)2 Promoted Solvent-free Microwave assisted Synthesis of Bis(indolyl) methanes. Bulletin of the Catalysis Scoeity of India, 2008, 7, 111-114.
24. Hasaninejad A, Mohammadizadeh MR, Babamiri SF: A New, Efficient and Mild Method for the Synthesis of Bis (Indolylmethanes) in Aqueouse Media. 2nd International IUPAC Conference on Green Chemistry, Russia, 2008; 14-19.
25. Hasaninejad A, Zare A, Sharghi H, Khalifeh R, Zare ARM: PCL5 As A Mild And Efficient Catalyst For The Synthesis Of Bis(Indolyl)Methanes And Di-Bis(Indolyl)Methanes. Bull. Chem. Soc. Ethiop, 2008; 22(3); 453-458.
26. Borse AU, Patil MN, Patil NL: Expeditious, Mild and Solvent Free Synthesis of Bis(indolyl)methanes, Using a Mixture of Phosphorus Pentoxide in Methanesulfonic Acid. E-Journal of Chemistry, 2012; 9(3); 1313-1319.
27. Bandgar BP, Shaikh KA: Molecular iodine-catalyzed efficient and highly rapid synthesis of bis (indolyl) methanes under mild conditions. Tetrahedron Letters, 2003; 44; 1959–1961.
28. Kardak BG, Gill CH, Gholap SS: Silica Dichlorophosphate [SiO2-POCl2] As An Expeditious Reusable Catalyst For The Synthesis Of Bis-(Indolyl) Methanes Under Solventfree Conditions. Bulletin of the catalysis Society of India, 2009; 8; 126-130.
29. Li JT, Zhang XH, Song YL: Efficient synthesis of bis(indol-3-yl)methanes catalyzed by silicotungstic acid under ultrasound irradiation. International Journal of ChemTech Research, 2010; 2(1); 341-345.
30. Chandama DR, Deshmukha MB, Mulika AG, Patilb PP, Patila DR, Jagdalea SD, Anbhulea PV, Sankpala SA: An efficient synthesis of bis(indolyl) methanes under solvent free condition using Silica supported Chloroacetic Acid as reusable Catalyst. Der Pharmacia Lettre, 2012; 4 (1); 54-60.
31. Reddy YT, Reddy PN, Kumar BS, Rajitha B: An efficient synthesis of bis (indolyl) methanes catalyzed by TiCl4. Indian Journal of Chemistry, 2005; 44(B); 2393-2395.
32. Niknam K, Zolfigol MA, Sadabadi T, Nejati A: Preparation of indolylmethanes catalyzed by metal hydrogen sulfates. Journal of the Iranian Chemical Society, 2006; 3(4); 318-322.

33. Dabiri M, Salehi P, Baghbanzadeh M, Shakouri M, Otokesh S, Ekrami T, Doosti R: Efficient and Eco-Friendly Synthesis of Dihydropyrimidinones, Bis (indolyl) methanes, and N-Alkyl and N-Arylimides in Ionic Liquids. J. Iran. Chem. Soc., 2007; 4(4); 393-401.
34. Prasanna TSR, Raju KM: Quick Access to Bis (indolyl) methanes: T3P as a Novel Catalyst System. Journal of the Korean Chemical Society, 2012; 56(1); 74-77.
35. Qu HE, Xiao C, Wang N, Yu KH, Hu QS, Liu LX: RuCl3•3H2O Catalyzed Reactions: Facile Synthesis of Bis (indolyl) methanes under Mild Conditions. Molecules 2011; 16; 3855-3868.
36. Rajendran A, Raghupathy D, Priyadarshini M: A Domino Green Synthesis of Bis(indolyl)methanes Catalyzed by Ionic Liquid $[Et_3NH][HSO_4]$. International Journal of ChemTech Research, 2011; 3(1); 298-302.
37. Mishra S, Gosh R: Ecofriendly and sustainable efficient synthesis of Bis (indolyl) methanes based on recyclable Bronsted (CSA) and Lewis ($ZrOCl_2$. $8H_2O$) acid catalysts. Indian Journal of Chemistry, 2011; 50(B); 1630-1636.
38. Veisi H, Hemmati S, Veisi H: Highly Efficient Method for Synthesis of Bis(indolyl)methanes Catalyzed by $FeCl_3$-based Ionic Liquid. Journal of the Chinese Chemical Society, 2009; 56; 240-245.
39. Shaikh AC, Chen C: An Easy and Efficient Synthesis of Bisindolylmethanes and Tetraindolylmethane Tröger's Base Catatlyzed by $AgBF_4$. Journal of the Chinese Chemical Society, 2011; 58; 899-905.
40. Khosropour AR, Baltork IM, Khodaei MM, Ghanbary P: Chemoselective One-pot Conversion of Primary Alcohols to their Bis(indolyl)methanes Promoted by $Bi(NO_3)_3$•$5H_2O$. Z. Naturforsch, 2007; 62(b); 537 – 539.
41. Mulla SAR, Sudalai A, Pathan MY, Siddique SA, Inamdar SM, Chavan SS, Reddy RS: Efficient, rapid synthesis of bis(indolyl)methane using ethyl ammonium nitrate as an ionic liquid. RSC Adv., 2012; 2; 3525-352.
42. Kamal A, Khan MN, Srinivasa RK, Srikanth YV, Kaleem AS, Pranay KK, Murthy US: An efficient synthesis of bis (indolyl) methanes and evaluation of their antimicrobial activities. J Enzyme Inhib. Med. Chem. 2009; 24(2); 559-65.

How to cite this article:
Kaishap PP and Dohutia C: Synthetic approaches for bis (indolyl) methanes. *Int J Pharm Sci Res* 2013; 4(4); 1312-1322.