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Recent Advancement in the Green Synthesis of Bis(indolyl) Methane Via One-pot Multicomponent Condensation Strategy: (A Mini Review)

POOJA BEDI[1], RAJBIR KAUR[2], RESHMI BOSE[3], BHOLANATH PAKHIRA[4], MANAS ROY[5]* and TANAY PRAMANIK[3]*

[1,2]Department of Chemistry, SGGS Khalsa College, Mahilpur, Punjab 146105, India.
[3]Department of Chemistry, Institute of Engineering and Management (IEM), University of Engineering and Management, University Area, Action Area III, B/5, Newtown, Kolkata, West Bengal–700160, India.
[4]Department of Chemistry, Sister Nibedita Govt. General Degree College for Girls, Hastings House, Alipore, Kolkata-700027, India.
[5]Department of Chemistry, National Institute of Technology, Agartala, Barjala, Jirania, Tripura-799046, India.
*Corresponding author E-mail: tanay.pramanik@gmail.com, mroyiitk@gmail.com

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ABSTRACT

Bis(indolyl)methane's (BIMs) are highly versatile heterocyclic frameworks that have gained recognition for their wide range of applications in the therapeutic and pharmaceutical sectors, and play an essential role in the drug discovery system. Though several methodological approaches have been adopted for the synthesis of BIMs, these methods have limitations in terms of using hazardous solvents, transition-metal catalysts, and ultimately generating substantial waste. This review emphasized the green synthesis of BIMs, using the one-pot multicomponent condensation (OPMC) method, which offers BIM synthesis via renewable catalysts, green solvents, or a catalyst-free approach. The OPMC method offers numerous advantages, such as reduced time, labour, cost, and waste products. Multicomponent condensation reactions are very effective in synthesizing highly functionalized organic molecules in one step from readily available starting materials. Despite advancements, challenges persist in ensuring the catalyst's stability for optimal yields and compatibility with various substrates. In the present context, only the OPMC synthesis of bis(indolyl) methane was articulated, which provides valuable insights for researchers seeking sustainable pathways for BIM synthesis.

Keywords: Bis(indolyl)methane, Green solvents, Green approaches, One-pot multicomponentcondensation.

INTRODUCTION

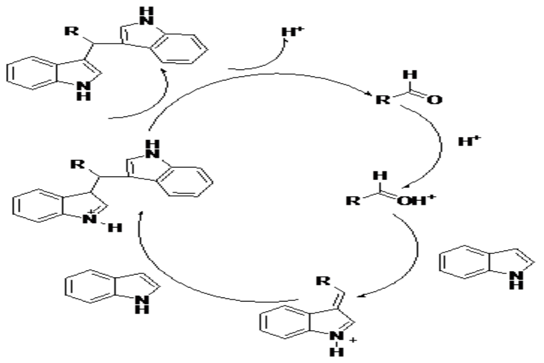
Bis(indolyl)methanes (BIMs) and their derivatives have gained widespread attention as vital nitrogen-containing heterocyclic molecules because they serve as the core structural framework for an array of naturally occurring bioactive compounds[1,2]. BIMs display a diverse array of biological properties, including antibacterial, anti-fungal, antiviral, antibacterial, antioxidant, anti-inflammatory, analgesic, and radical scavenging effects[3,4]. Furthermore, they have many medical uses and are important in treating various types of cancer, such as breast, colon, prostate, and pancreatic cancer. So, in the contemporary era, there has been a growing emphasis among researchers on the synthesis of BIMs.Typically, a series of reactions involving indole and various aromatic or aliphatic aldehydes can synthesize BIMs. This process requires the use of protic or Lewis acids, including ionic liquids, $FeCl_3$, $CeCl_3.7H_2O$, TiO_2, AuCl, I_2, SBA-15/SO_3H, TPPMS/CBr_4, $H_3PW_{12}O_{40}$ pyridinium tribromide, etc[4,5]. Although many of the pointed-out procedures effectively produce BIMs with high yields, they often have limitations in terms of expensive and hazardous heavy metals, such as the requirement for a particular quantity of catalysts that required complicated post-treatment procedures. In addition, the adsorption or polymerization of indole by Lewis's acid sites leads to an excessive consumption of precursors, so a large amount of indole is required to achieve the desired products. Furthermore, nitrogen-containing reactants can deactivate or decompose several Lewis acids and retard their catalytic activity. As a result, there is a requirement for excessive amounts of Lewis acids and the production of harmful waste, which has an adverse impact on the environment[5]. Consequently, the production of BIMs has shown a growing need for eco-friendly catalysts and solvents, which have proven to be beneficial[6].

Green chemistry is a profoundly intriguing approach within the domain of medicinal chemistry. It encompasses distinct branches of chemistry and operates on the preeminent concept of carrying out chemical reactions with the goal of protecting the environment simultaneously. The implementation of green chemistry improves selectivity reducing the reaction time and eliminating the usage of hazardous catalyst/ toxic solvents that simplify separation/purification of product(s)[7–9]. From the perspective of green chemistry, one-pot multicomponent condensation (MCR) reactions are highly favored on account of their fewer number of synthetic steps. In addition, the progress in solvent-free synthesis or the use of aqueous solvent alongside enzyme catalysis, are important strategies to reduce the production of hazardous waste. MCR is particularly appealing on account of the formation of products in a single step, allowing for robust transformation by altering the reacting components, and is extensively implemented as a robust synthetic route for the efficient synthesis of complex heterocyclic molecules. Furthermore, solvent-free MCR offers a wide range of opportunities to carry out efficient organic synthesis via functional group transformations, and the synthesis of BIM is no exception to that.

In the present review, we described the green methodologies for the synthesis of (BIM) via multicomponent condensation of aromatic aldehydes. In addition, this review addresses the adoption of non-toxic solvents like ethylene glycol, glycerol, and aqueous solvents, as well as the absence of solvents and unconventional techniques such as microwaves, ultrasound, and grinding. These approaches are considered crucial and eco-friendly chemical protocols for affordable synthesis. They enable researchers to design robust synthetic sequences compared to substitute multistep methods, synchronising with the principles of green chemistry.

General synthesis methodology of Bis(indolyl) methanes (BIMs)

In general, BIMs were synthesized *via* the condensation of two indole molecules with aldehyde in the presence of a distinct type of catalyst, particularly, Lewis's acids. In the initial stage, a catalyst activates the carbonyl group in the aldehyde, making it electrophilic. Afterwards, another indole molecule reacts with the intermediate alcohol resulting in its aromatization and leading to the formation of the **BIM**[2,10]. The plausible mechanism for synthesising bis(indolyl) methane was asserted in Scheme 1. Several strategies for the synthesis of BIMs have been reported in the literature although many of them suffer disadvantages as they involve the use of harmful catalysts and solvents. These catalysts and solvents are unsafe for the environment and mankind; hence, several environmentally benign methods involving the use of green catalysts and solvents for the synthesis of BIMs have been developed by several research groups.



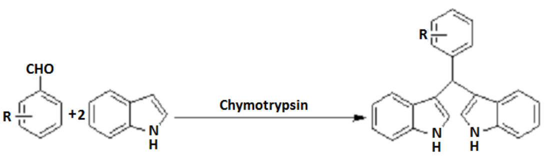
Scheme1. The catalytic cycle of Acid Catalysed synthesis of BIM

Green Synthesis approach to Synthesis of Bis(indolyl) Methane

MCR-based green synthesis offers a promising and strategic approach for facilitating sustainable methods in the synthesis of BIMs. An important benefit of this approach is the application of catalysts such as enzymes, easily accessible, less harmful organic acids, plant extracts, and fruit juice, which serve as substitutes for dangerous alternatives.

Green Catalysts for One-Pot BIM(s) Synthesis

The implementation of green catalysts, such as natural fruit juice, inorganic-organic hybrids like $AlCl_2 \cdot 6H_4O@\beta$-cyclodextrins[11], and biocatalysts such as α-chymotrypsin[11], oxalic acid[12], polymer-supported dichlorophosphate (PEG-$OPOCl_2$)[13], etc. are crucial for the development of sustainable and eco-friendly synthesis of BIMs through one-pot MCR, serve as effective alternatives for typical metal-based catalytic processes. For instance, Xie *et al.,* reported an potent synthetic approach to green synthesis of BIMs using α-chymotrypsin as green bio-catalyst a cascade process between indole and diverse aromatic aldehydes with moderate to good yields (ranging from 68% to 95%) in the presence of ethanol aqueous solution as solvent (Scheme 1)[14].



Scheme 2. α-Chymotrypsin-catalyzed tandem reaction of indole and aldehydes[14]

In a similar experiment, SelvakumarK *et al.,*[15] proposed a one-pot MCR synthesis of BIMs using one mole of aromatic aldehyde and two moles of indole implying heteropoly-11-tungsto-1-natural clay bound vanadophosphoric acid as a catalyst without using any solvent with a substantial yield of the product. BIMs was successfully synthesized by Fu Y *et al.,*[16] using lipase enzyme as a catalyst in pure water by following a simple procedure of stirring the reactants at 55°C. This method offers excellent yield and can tolerate a wide range of substrates. Another efficient protocol for the formation of bis(indolyl)methane was reported by Siadatifard S. H. *et al.,*[17] utilizing tetrabutylammonium hydrogen sulfate as a catalyst. The authors have added a catalyst to the mixture of indole and aldehyde and performed magnetic stirring at 60°C. This protocol offers chemo-selectivity and good yield of product. The waste curd water was used by Rajput J *et al.,*[18] as a catalytic solvent for the synthesis of bis(indolyl) methane good yield. The procedure consists of stirring two moles of indole and one mole of benzaldehyde in the presence of waste curd water at room temperature. Another simple and green methodology for the preparation of bis(indolyl)methane in water with a good yield of products was developed by Azizi N *et al.,*[19] using squaric acid as a catalyst. This method can be used for laboratory as well as industrial-scale synthesis under mild conditions. In the year 2018, Kasar S. B. *et al.,*[20] employed biodegradable itaconic acid as a catalyst in water to obtain bis(indolyl)methane from indole and aldehydes by simply mixing the reaction mixture at 100°C. This procedure offers superiority of high efficiency and reusability of catalyst. Yadav J.S. *et al.,*[21] developed a boric acid catalyzed protocol for the formation of bis(indolyl) methane. They prepared a series of bis(indolyl) methane by simply heating the reaction mixture. This protocol affords above 90% bis(indolyl) methane without the use of any solvent. In the year 2012, Azizi N. *et al.,*[22] used the eutectic mixture of tin(II) chloride dihydrate/choline chloride as a catalyst for the synthesis of bis(indoly)methane by utilizing polyethylene glycol as a solvent. To perform the reaction, a reaction mixture of indole, carbonyl compound, eutectic salt and PEG was vigorously stirred for 60-200 min with substantial yield. A clean and practical approach for the synthesis of BIMs was developed by Ghorbani-Vaghie R *et al.,*[23] in the year 2010. They perform heating of indole, and aldehyde in the presence of oxalic acid dihydrate as catalyst in aqueous medium in the oil bath for

30 minute. All the products were procured in excellent quantity. Bis(indolyl)methane was successfully synthesized by Rajendran A *et al.,*[24] in the year 2011 by utilizing affordable and reusable ionic liquid $[Et_3NH][HSO_4]$. To obtain a high yield of product, a reaction mixture of indole and carbonyl compounds along with a catalyst was stirred at 80°C for 20 minute. In the year 2013, Naidu K.R.M. *et al.,*[25] utilized green catalyst PEG-$OP(O)Cl_2$ for the synthesis of bis(indolyl)methane with simple stirring at room temperature. They beneficially formed the required compound by following cost-effective, practical, and green procedures. Bis(indolyl)methane was successfully obtained from indole and methanol employing supported iridium (Ir/MgxAlO) as an activator of methanol by Qiang W *et al.,* in the year 2019. For this purpose reaction mixture was magnetically stirred (1000rpm) and heated at 150°C for the desired time. The synthetic route for bis(indolyl) methane that was catalyzed by an alum $[KAl(SO_4)_2.12H_2O]$ was described by Kumar S. *et al.,*[26] in the year 2009. The mixture of alum, indole and aldehyde was stirred in water at 80°C for 50 min and a broad range of substituted bis(indolyl) methanes were produced in very good yield. Esmaielpour M. *et al.,*[27] developed a clean and effective methodology for the production of bis(indolyl)methane utilizing heterogeneous catalyst expanded perlite-polyphosphoric acid in the year 2017. This eco-friendly methodology boosting the yield of the BIMs within a short period of reaction time. Poly(4-vinylpyridinium) hydrogen Sulfate catalyzed route for the synthesis of bis(indolyl)methane was reported by Banothu J. *et al.,*[28] in the year 2013. To fulfill the synthetic goal, a mixture of indole and aryl aldehyde in the presence of a catalyst was ground and then stirred after the addition of water for 5 minute. This methodology followed by them resulted in a satisfactory amount of product in pure form. Nemallapudi B.R.*et al.,*[29] came up with meglumine catalyzed approach for the preparation of bis(indolyl) methane at room temperature in the year 2019. The concoction of indole, and carbonyl compound in the presence of meglumine and water was stirred for 15 min and a pure form of the product was formed in high percentage yield. Lewis acids -surfactant-SiO_2- combined catalyst was employed for the synthesis of bis(indolyl)methane by Wu Z. *et al.,*[30] in the year 2019. They successfully obtained a 99% yield of product utilizing Lewis acid–surfactant–SiO_2-combined (LASSC) catalyst and grinding the reactant in the absence of any dissolver for 20 minute. The efficient and eco-friendly methodology that affords a high yield of BIMs in an aqueous solvent implying graphene oxide as a catalyst was reported by Wang Y *et al.,*[31] in the year 2011. To achieve the target, a mixture of benzaldehyde, indole and catalyst was stirred for 3 h at 40°C and the products were procured in excellent yield. In the year 2022, Narsale B.S. *et al.,*[32] came with a pot solvent-free approach for the synthesis of BIMs by using a variety of aromatic aldehydes and indole with the help of xanthan perchloric acid as a catalyst. To accomplish their aim reaction mixture was stirred at room temperature and resulted in a satisfactory outcome. The bis(indolyl)methane was effectively synthesized by Mendes S.R. *et al.,*[33] in the year 2012, by applying silica gel catalyst under solvent free conditions. For this process, the reaction was carried out at a high temperature for 2 h and the results of the reaction were quite relevant in terms of time and output. Mathavam S. *et al.,*[34] described an environment-friendly protocol for the formation of BIMs by utilizing organocatalyst thiamine hydrochloride in the year 2019. The product was produced in good yield just by grinding the reaction mixture at room temperature without any dissolver for 1 hour. Vahdat S.M. *et al.,*[35] reported a clean and green synthetic approach for the synthesis of BIMs by applying Cerium (IV) triflate catalyst in the year 2012. To conduct the reaction, a mixture of indole and carbonyl compounds was stirred at room temperature. All the bis(indolyl)methanes were obtained in excellent quantity. BIMs has been successfully synthesized in high yield by Sadaphal S. A. *et al.,*[36] in the year 2008 from indole and aldehydes employing cellulose sulphuric acid as a catalyst without using any solvent by grinding technique at room temperature. The simple, chemoselective and high-yielding approach for the formation of bis(indolyl)methane has been reported by Kamble V.T *et al.,*[37] in the year 2020. For this purpose, silica chemisorbed SiO_2-BHSB was added in a catalytic amount to a mixture of indole and carbonyl compounds and ground for the desired time at room temperature. In the year 2021, Patil R.C. *et al.,*[38] have developed proficient and environmentally benign methodology for the synthesis of BIMs by stirring reactants using

chickpea leaf exudates as catalysts in isopropyl alcohol at 60°C. This protocol affords a good yield of product at a fast rate of reaction following a simple procedure. The heteropoly acid-catalyzed synthetic route for bis(indolyl)methane was described by AziziN. *et al.,*[39] in the year 2007. They performed vigorous stirring of the reaction mixture in water at room temperature which resulted in 75-90% of the product. Although it takes a longer time it is a good methodology because of its efficiency, mild reaction conditions and high yield. The one-pot green synthesis of BIMs by employing sulfonic acid functionalized silica(SiO_2-Pr-SO_3H) as a catalyst in water was described by Mohammadi Ziarani G. *et al.,*[40] in the year 2015. They stirred the reaction mixture in refluxing water for the required time and resulted in nearly 90% yield of product.

Kalla R.M.N. *et al.,*[66] came up with tetramethylguanidinium chlorosulfonate catalyzed eco-friendly approach for obtaining bis(indolyl) methane in the year 2014. They performed magnetic stirring of the reaction mixture in the absence of any dissolver at room temperature which leads to approximately 90% of product. In 2016 Soliman H.A. *et al.,*[41] proposed a solvent-free protocol forgetting the excellent yield of bis(indolyl)methane employing silicic acid as a catalyst. The mixture of indole and carbonyl compound in the presence of a catalyst was churned at 100°C for 35 min and procured out the desirable product in pure form. Bis(indolyl) methane was successfully prepared by Mulla S. A.R. *et al.,*[42] in the year 2012 following a simple procedure of stirring a concoction of indole, benzaldehyde and ethyl ammonium nitrate as a catalyst at ambient temperature. This protocol had salient features of cost-effective easy work-up, eco-friendly and better outcome ratio. The solvent-free green method for the synthesis of bis(indolyl)methane in the presence of humic acid as a catalyst was described by Mitra B. *et al.,*[43] in the year 2021. They refluxed the reaction mixture of aldehyde and indole at 100°C and obtained a good yield of product utilizing a highly reusable and economical catalyst. The Bis(indolyl)methane was prepared in high yield by grinding a mixture of indole and aldehyde and a catalytic amount of ionic liquid tributyl(carboxymethyl)phosphonium bromide insolvent free environment at room temperature. This approach was reported by Khazaei *et al.,*[44] in the year 2013. SuhanaH. *et al.,*[45] used the economical and eco-friendly catalyst tetrabutylammonium hydrogen sulphate for the formation of bis(indolyl)methane in the year 2014. In the above-mentioned process, the indole, aldehyde, and catalyst were mixed together in aqueous solvent and stirred magnetically for 30 minutes. The resulting products were obtained with a yield of 85-95%. The various derivatives of BIMs have been synthesized successfully from the condensation reaction of indole with aldehyde employing salicylic acid as a catalyst in the presence of aqueous ethanol solvent by swirling the reaction mixture at room temperature. This high-yielding methodology was developed by Banari H. *et al.,*[46] in the year 2018. Bis(indolyl)aryl methane was procured effectively from indole and aromatic aldehyde using choline chloride-oxalic acid catalyst at room temperature just by churning the mixture for 15-20 minutes. This solvent-free facile protocol was proposed by Yadav U.N *et al.,*[47] in the year 2014. The aqueous extract of Sapindustrifoliatus fruit was successfully used as a catalyst for the synthesis of bis(indolyl) methane in the absence of any solvent by simply stirring the reactant at room temperature by Pore S.B. *et al.,*[48] in the year 2016. This methodology offers various superiorities like a fast rate of reaction, good output and cost-effective and easy procedure. Narjundaswamy H.M. *et al.,*[49] came up with a novel green protocol for the preparation of Bims utilizing nanoparticles of gold as promoter and water as a dissolver in the year 2014. This synthetic approach affords excellent yield of product in a shorter time by simply stirring the substrate mixture. A table has shown below for the summary of all the reactions.

In subsequent investigations, Zhang *et al.,* carried out synthesis of BIMs applying composite of networked $AlCl_3 \cdot 6H_2O@\beta$-cyclodextrins (CD) as a green catalyst. using aldehyde and indole as precursors via mechanical grinding with a yield of approximately 84%. $AlCl_3.6H_2O@\beta$-CD has been found to have a unique function as acts as both a catalyst as well as dispersant in the reaction system and triggers the synthesis of bisindolylmethane compounds with outstanding stability, under mechanical grinding[11].

Table 1: Green catalyst for synthesis of BIM

Serial no	Reference	Catalyst	Solvent	Reaction conditions
1	50	Citrus limon juice	water	RT (6 H, 900rpm)
2	51	Grape Juice	water	Reflux (3-4 H)
3	52	Lemon juice	-----	RT (Stir 20 min)
4	53	ProliniumTriflate	CH3CN	RT (Stir 5 H)
5	54	HPVAC	-----	Heat (70°C)
6	55	Aqueous Starfruit juice	-----	Heat(60°C, Stir 4 H, 900rpm)
7	56	Aqueous Tamarind fruit juice	-----	Heat(80°C, Stir 2 H, 800rpm)\
8	57	Chymotrypsin	Water + EtOH	Incubated (50°C, 260rpm, 24 h)
9	16	Lipase	Water	Stir (55°C)
10	58	Citric acid	water	Stir
11	17	TBAHS	EtOAc	Stir (60°C)
12	18	Waste curd water	-------	Stir at RT
13	59	PEG-400	-------	Stir (85°C, 8 h)
14	19	Squaric acid	water	Stir at RT (2-4 h)
15	20	Itaconic acid	Water	Reflux (100°C)
16	59	tin (II) chloride–choline	PEG-200	Stir at RT
17	25	Ir/MgXAlO	-------	Heat (150°C,4 h, N_2)
18	60	$KAl(SO_4)_2.12H_2O$	Water	Stir at 80°C
19	26	EP-PPA	Water	Stir at 60°C
20	61	$P(4\text{-}VPH)HSO_4$	-------	Grinding, RT,
21	29	LASSC	-------	Grind at RT
22	45	GO	Water	Stir at 40°C (3 H)
23	33	-------	-------	Heat (80°C)
24	62	Thiamine Hydrochloride	-------	Grind at RT (1 H)
25	35	-------	-------	Grind at RT
26	36	CSA	-------	Grind at RT
27	37	SiO_2–BHSB	-------	Grind at RT
28	38	CLE	iso-PrOH	Stir at 60°C
29	39	$H_3PW_{12}O_{40}/H_3PMo_{12}O_{40}$	Water	Stir at RT
30	40	SiO_2-Pr-SO_3H	Water	Stir in refluxing H_2O
31	63	TMG-IL	-------	Stir at RT
32	64	Silzic Acid	-------	Heat at 80°C
33	42	EAN	-------	Stir at RT
34	43	Humic acid	-------	Reflux(100ºC)
35	44	PILs	-------	Grind at RT
36	45	$(C_4H_9)_4NHSO_4$	Water	Stir at RT
37	46	Salicylic Acid	EtOH-H2O	Stir at RT
38	47	ChCl-Oxalic acid	-------	Stir at RT
39	65	Fruit extract of Sapindustrifoliatus	-------	Stir at RT

Microwave and Ultrasound assisted methods

Recently, the microwave and ultrasound induced methods have proven to be potent approaches for the one-pot green synthesis of BIMs, as these techniques could potentially lead to advantages including improved reaction efficiencies, yield with a very short period of time, and robust synthetic procedures as compared to conventional methods. In general, microwave irradiation induced reactions offer uniform heating, boosting reaction rate with selectivity of BIM synthesis, whereas ultrasonic technology delivers augmented mass transfer efficacy and a faster reaction rate via acoustic cavitation.

For instance, microwave-assisted ecofriendly synthesis of BIMs was reported by Pal R[66] by using fruit juice of *citrus lemon* under solvent free environment . To carry out the reaction, a mixture of indole, aldehyde and fruit juice of a citrus lemon and neutral Al_2O_3 was ground by the researcher. After grinding he exposed the reaction mixture to MW irradiations for 3 min and procured products in excellent yields. Succinic acid-catalyzed green chemistry approach for the preparation of bis(indolyl) methane was reported by Nasreen A *et al.,*[67]. In this case, the reaction was performed by using indole and a variety of aldehydes in aqueous medium under microwave irradiation and products were prepared in excellent yield (78-96%). Sarva S *et al.,*[68] came up with a new approach to synthesizing BIMs. without the use of any catalyst and solvent by irradiating the mixture of indole and aldehydes with a microwave. This cost-effective method affords a higher yield (90%) and a faster reaction rate. The novel, clean synthetic route for the formation of BIMs was reported by Malkania L *et al.,*[69]. They used lactic acid as a catalyst in an aqueous solution of indole and aldehydes and the reaction mixture was irradiated with microwave radiation of 240 Wand resulting in 70-90% yield of desirable product.

Sadaphal S.A. *et al.,*[70] reported a microwave-assisted synthetic route for BIMs utilizing acidic aluminium oxide as a catalyst in the absence of any solvent. This method proved to be very satisfactory as a high yield of products was obtained in a short reaction time. The catalyst [bnmim][HSO_4] under a solvent-free environment was used for obtaining BIMs by Sadaphal S.A. *et al.,*[71]. In this method, the reaction mixture was exposed to microwave radiation of 450W with substantial yield of product . The glacial acetic acid was employed as a catalyst to prepare bis(indolyl)methane from 2-arylindole and aldehyde by Zahran M *et al.,*[72] using microwave radiation and thermal heating. The results in terms of time and yield were better in the case of microwave radiation in comparison to heating. In the year 2017, Suradkar V.B. *et al.,*[73] employed different natural acids such as sweet lemon, citrus limeta, tamarind, amla, buttermilk and pineapple juice for the synthesis of BIMs. To carry out the reaction, the reaction mixture in water was refluxed at 80°C for 2 h and the same mixture was irradiated with microwave at 750Watt for 2 minute. Both procedures afford a high yield of bis(indolyl)methanes. Deshmukh S.N. *et al.,*[74] synthesized BIMs under a solvent free environment using lanthanumtris(trifluoromethanesulfonate) as a catalyst in the year 2017. For the synthesis of products in excellent yield, they irradiated a reaction mixture of indole, and aromatic aldehyde along with a catalyst under microwave irradiations at 450 watts. A simple, green, and high-yielding approach for the preparation of BIMs was reported by Thorat N.M. *et al.,*[75] utilizing thiamine hydrochloride as a catalyst. They obtained product in good yield by using microwave radiation in the absence of any dissolver and secondly by sonication technique in water. Microwave-assisted, solvent-free methodology for the preparation of BIMs was described by Sulak M.[76]. The product was procured in high yield and in shorter reaction time by grinding a mixture of indole and a carbonyl compound in the presence of nanoparticles of copper and zinc oxide. In the year 2015, Sevedi N. *et al.,*[77] prepared bis (indolyl)methane by irradiating a mixture of indole and carbonyl compounds containing 5 mL of glycerine and 0.02mmol citric acid with microwave (180 Watt) for 3 minute. This efficient and economical method provided good to excellent yield of product in a shorter time. Pal R[78] described a new green approach for the synthesis of bis(indolyl) methane in aqueous ethanol with the help of lemon juice under ultrasound irradiations. All the bis(indolyl) methanes prepared by this method are of high purity and their yields are quite outstanding.

Ultrasonically assisted malic acid catalyzed green protocol for the synthesis of BIMs was developed by Kasar S *et al.,*[79]. This protocol offers the advantages of the use of water as solvent, excellent catalyst recyclability and 85-95% yield of the product. In the year 2022, Chavan K. A. *et al.,*[80] developed an ultrasonic-assisted method for synthesizing BIMs utilizing amino acid taurine as a catalyst in the presence of water as solvent. This one-pot synthesis can be performed with a broad range of substrates under mild reaction con. Though plentiful strategies have been implied for microwave and ultrasound irradiation-induced BIM synthesis, it demands in-depth analysis for its commercial viability in pharmaceutical contexts.

Table 2: MW/US assisted synthesis of BIM

Serial no	Reference	Catalyst	Solvent	Reaction conditions
1	22	Glacial acetic acid	-------	MW or Heat
2	81	Thiamine Hydrochloride	-------	MW
3	34	G-CuO NPs	-------	MW (dry milling)
4	66	Citrus limon juice and neutral Al_2O_3	-----	MW (480W, 3 min)
5	67	Succinic acid	water	MW (300W, 9-35 min)
6	68	-------	-------	MW
7	69	Lactic acid	Water	MW (240W)
8	70	Al_2O_3	-------	MW(450W)
9	71	[bnmim][HSO_4]	-------	MW(450W)
10	82	Citric acid	Glycerin	MWI(180 W, 3 min)
11	83	La(OTf)$_3$	-------	MW(450 W)

Selection of solvent for One-Pot green synthesis of BIM(s)

The selection of solvent is one of the pivotal in the proficient and environmentally viable one-pot green synthesis of BIMs. Generally green solvent particularly water or deep eutectic solvents can accelerate the reaction rate of BIMs synthesis. For example, Pal R *et al.*,[50] reported a green procedure for the formation of BIMs by stirring indole and aldehyde mixture with fruit juice of citrus lemon-water at RT as well as 80°C using aqueous solvent. They found that by raising the temperature reaction time reduced from 6 to 2 hours. Nazeruddin G M *et al.,*[51] described grape juice catalyzed green approach for the synthesis of bis (indolyl)methane. For this purpose, they refluxed a mixture of indole and aldehyde with grape juice for 3-4 h and obtained the products in excellent yields. A natural method for biocondensation of aldehydes and indoles resulting in the formation of bis (indolyl)methanes were described by Ahmed SK *et al.,*[52] This bio condensation was carried out at room temperature by using lemon juice as a natural catalyst. Shiri M *et al.,*[53] used proliniumtriflate, a protic ionic liquid as a catalyst for the preparation of BIMs. This method involves catalyzed condensation of indole with aldehydes using methyl cyanide as a solvent and leads to better yield of products. In the year 2016, an efficient methodology for the preparation of BIMs using natural catalyst cum solvent star fruit juice was developed by Pal R[55]. This methodology requires stirring of reactants for 4 h at 60°C leading to excellent yield of products in pure form. An environment-friendly and economical process for the synthesis of bis(indolyl) methane using tamarind juice as a catalyst in aqueous medium was reported by Pal R[56]. This method includes a one-pot two-component reaction of indole and aldehyde that needed stirring (800rpm) at 80°C for 2 hours. Seyedi N *et al.,*[58] described a simple and effective way of preparing BIMs in the lab by the vigorous stirring of a mixture of indole, and carbonyl compounds in the presence of citric acid as catalyst and water as solvent. This method affords a 93% yield of product in a shorter reaction time. Gurrapur R *et al.,*[59] synthesised BIMs from indole and aldehyde utilizing polyethene glycol as solvent cum activator by following simple stirring at 85°C for 8 hours. This method proves to be efficient, economical and simple to synthesize BIMs. A solvent and catalyst-free green and effective approach for the synthesis of BIMs was developed by Patil V.D. *et al.,*[62] Researchers prepared a series of BIMs by using different carbonyl compounds and Indole by heating at 80°C which resulted in a good yield of BIMs. Dhimuskar K.L. *et al.,*[84] developed a solvent and catalyst-free methodology to prepare BIMs. To accomplish the aim, they performed periodic grinding of indole and aromatic aldehyde every 30 min till the completion of the reaction at room temperature and procured the product in good yield.

CONCLUSION

This review focuses on the synthesis of bisindolylmethanes by green methods making use of inexpensive catalysts, ecofriendly sources of energy or non-toxic solvents. The growing interest of green chemistry in organic synthesis is mainly due to selectivity, energy conservation and the generation of less toxic waste. Therefore, through this review it is addressed to develop greener technologies for the synthesis of organic compounds to preserve the ecosystem and to prevent depletion of natural resources.

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Conflict of Interest

Declared None

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