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Chemistry of trisindolines: natural occurrence, synthesis and bioactivity

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Heterocyclic nitrogen compounds are privileged structures with many applications in the pharmaceutical and nutraceutical industries since they possess wide bioactivities. Trisindolines are heterocyclic nitrogen compounds consisting of an isatin core bearing two indole moieties. Trisindolines have been synthesized by reacting isatins with indoles using various routes and the yield greatly depends on the catalyst used, reaction conditions, and the substituents on both the isatin and indole moieties. Amongst the synthetic routes, acid-catalyzed condensation reaction between isatins and indoles are the most useful due to high yield, wide scope and short reaction times. Trisindolines are biologically active compounds and show anticancer, antimicrobial, antitubercular, antifungal, anticonvulsant, spermicidal, and antioxidant activities, among others. Trisindolines have not previously been reviewed. Therefore, this review aims to provide a comprehensive account of trisindolines including their natural occurrence, routes of synthesis, and biological activities. It aims to inspire the discovery of lead trisindoline drug candidates for further development.

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1. Introduction

Heterocyclic compounds are ubiquitous in nature and possess many bioactivities, making them targets for drug development, health supplements and as highly functional materials. According to the Food and Drug Administration (FDA), 59% of the drug molecules are heterocyclic compounds containing at least one nitrogen atom.¹ One such compound is the indole 1 (Fig. 1) scaffold with a bicyclic structure incorporating a benzene ring fused to a pyrrole ring.² It is among the top ten



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nitrogen heterocyclic scaffolds used for constructing drug molecules.¹ Examples of indole-based drugs include indomethacin, indoxole, and pindolol. Several good reviews covering the chemistry and bioactivity of indoles have been published.^{3–5}

Trisindolines are compounds containing two indole units connected to the 1*H*-indol-2,3-dione **2** (also known as isatin) unit either at its C-3 position to form 3,3-di(3-indolyl)-2-indolone **3** or at its C-2 position to form a 2,2-di(3-indolyl)-3-indolone **4** regioisomeric structure (Fig. 1). Since their first discovery,⁶ trisindolines have attracted considerable attention due to their wide biological activities including anticancer,^{7–9} antimicrobial,¹⁰ antimycobacterial,¹¹ antifungal,¹⁰ anticonvulsant,¹⁰ α -glucosidase inhibition,¹² and spermicidal¹³ activities. The 3,3-di(3-indolyl)-2-indolone **3** isomer is far more interesting

than the 2,2-di(3-indolyl)-3-indolone **4** isomer due to its higher potency and potential as a drug lead compound.⁶ It is worth noting that the widely occurring 1*H*-indol-2,3-dione **2** (isatin) framework is an indole ring bearing two carbonyl groups at C-2 and C-3 (Fig. 1).^{14,15} Isatin forms a core structure of several biologically active molecules and commercial drugs including Sunitinib, Nintedanib, and Semaxanib.^{15,16} The chemistry and bioactivity of isatins have also been covered in several reviews.^{15,17}

To date, no reviews have been published about trisindolines. Hence, this comprehensive review covers the period of 1980–2020 and focuses on the natural occurrence, synthesis, and bioactivities of trisindolines. It highlights the scope, advantages, and limitations of various syntheses of trisindolines. It gives a comprehensive account of the activities reported for



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Following postdoctoral research at Texas A&M University (2003–2006) in the laboratories of Professor Daniel Romo, Ziad joined the department of chemistry at Taibah University as an Assistant Professor (2006–2018). Currently, he is an Associate Professor of organic chemistry at United Arab Emirates University (UAEU). His main research interests include the development of synthetic methodologies and the synthesis and characterization of novel bioactive organic and heterocyclic molecules.



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Dr. Zaher Judeh undertook his undergraduate studies in chemistry at the University of Pune (BSc 1992), and completed his postgraduate studies at the University of Mumbai (MSc 1994) in India and the University of New South Wales (PhD 2000), Australia. Dr Zaher is an Associate Professor of organic chemistry at Nanyang Technological University and has been there since 2004. His main

research interests include the development of synthetic methodologies and the total synthesis of natural products.



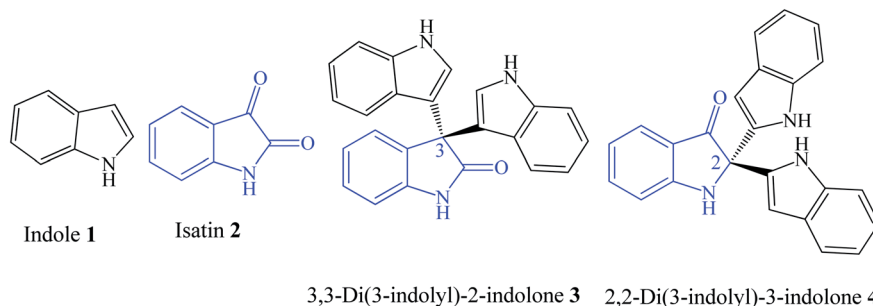


Fig. 1 The structures of indole, isatin and the two regioisomers of trisindolines.

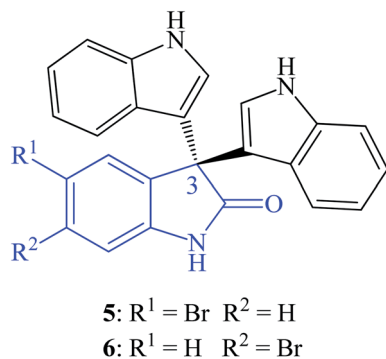


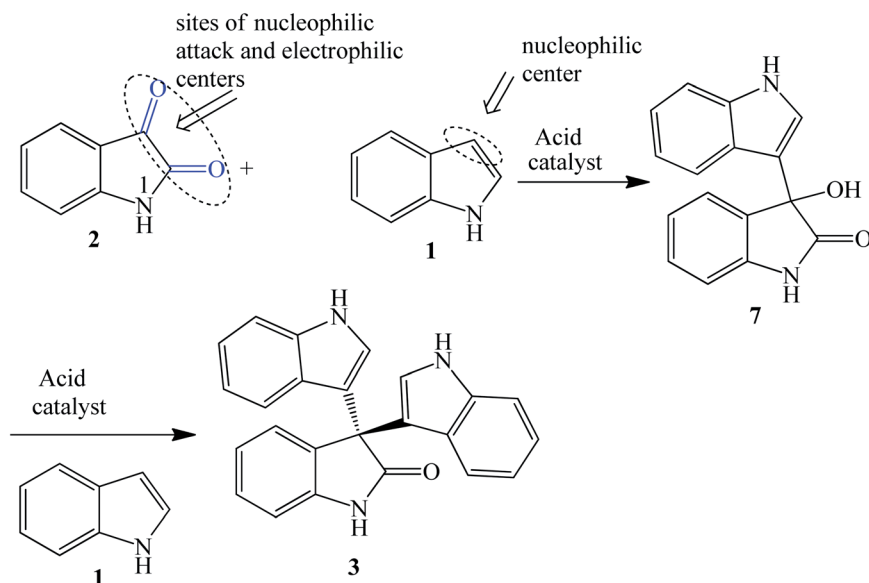
Fig. 2 Trisindoline analogues isolated from the red-sea sponge *Callispongia siphonella*.

trisindolines with a special focus on the structure–activity relationship (SAR) where possible. The review is also meant to be a one-stop reference work for researchers interested in the development of trisindolines as lead drug candidates. Since trisindolines have two isomeric structures, 3,3-di(3-indolyl)-2-indolone 3, and 2,2-di(3-indolyl)-3-indolone 4, we will limit

our discussion to the more common and more biologically active 3,3-di(3-indolyl)-2-indolone 3.

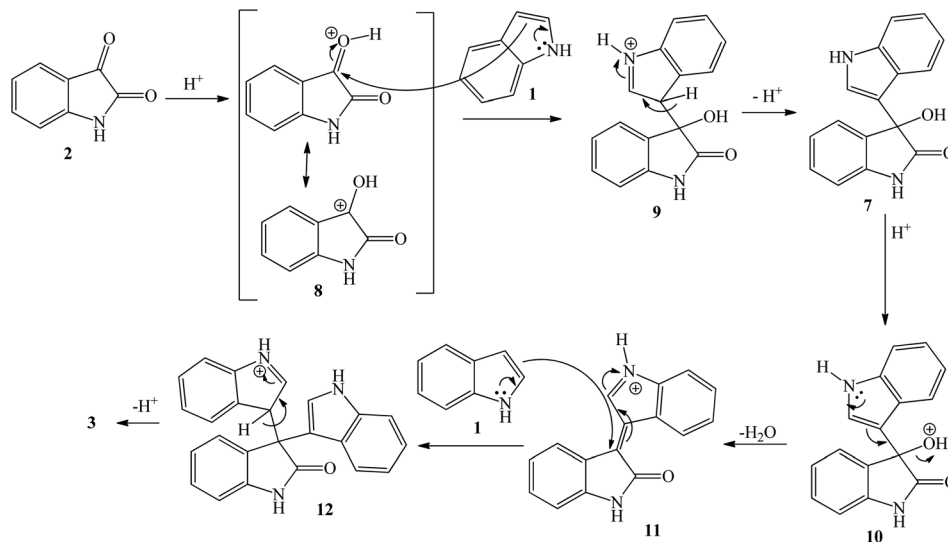
2. Natural occurrence of trisindolines

Trisindolines were isolated from several natural sources including bacteria, sponges and plants. Trisindoline 3 was firstly isolated from cultured marine bacterium *Vibrio* sp. obtained from the Okinawan marine sponge *Hyrtios altum*.⁶ Trisindolines 3 and 4 were also isolated from the marine sponge *Discodermia calyx*.¹⁸ *Aeromonas* sp., a marine-derived bacterium strain CB101, afforded trisindolines 3 and 4 from its ethyl acetate extract.¹⁹ Veluri *et al.* (2003) isolated trisindoline 3 and 4 from the ethyl acetate extracts of cultured *Vibrio parahaemolyticus* Bio249's mycelium.²⁰ Trisindoline 4 was also isolated from the marine bacterium *Vibrio parahaemolyticus* found in the mucus of stressed fish *Ostracion cubicus* species.²¹ Wang *et al.* (2014) also isolated trisindoline 3 from the ethyl acetate extract of the deep-sea bacterium *Shewanella piezotolerans* WP3.²² Trisindoline 3 and its analogues (5-bromo-3,3-di(1*H*-indol-3-yl)indolin-2-one 5 and 6-bromo-3,3-di(1*H*-indol-3-yl)indolin-2-one 6)



Scheme 1 Acid-catalyzed reactions between indole 1 and isatin 2.





Scheme 2 Proposed mechanism of acid-catalyzed formation of trisindoline 3 through reaction between isatin 2 and indole 1.

indolin-2-one 6) were isolated from the red-sea sponge *Callispongia siphonella* (Fig. 2).²³ Fractionation of the indigo metabolites obtained from the extracts of a recombinant *E. coli* gave trisindoline 3.⁹ Besides sponges and bacteria, the extracts from plant *Isatis costata*, Brassicaceae species, also afforded trisindoline 3.^{24,25} These diverse natural sources gave small amounts of trisindolines. To investigate the bioactivities of trisindolines, practical synthetic routes were developed to obtain them in reasonable amounts and diversify their structures to test their structure–activity relationship (SAR).

3. Synthesis of trisindolines

Trisindolines were synthesized (*vide infra*) following several routes. Efficient synthesis of trisindolines depends on the catalyst used, reaction conditions and the reactivity of the indoles and isatins which primarily depends on the position and type (electron donating group or electron withdrawing group) of the substituents on these rings. Additionally, the NH substituents on indoles and isatins rings also impact the efficiency of the reaction. The following sections will highlight these synthetic routes in detail.

The synthetic routes based on acid-catalyzed reaction are the most researched and most efficient with respect to yield, selectivity and reaction time.¹³ Trisindolines have also been synthesized in protic solvents and in the complete absence of acid catalysts. Acid-catalyzed indolylolation of isatin proceeds through a Friedel–Crafts electrophilic aromatic substitution mechanism. Although the indole itself undergoes faster electrophilic aromatic substitution than benzene, a catalyst is usually required for the indolylolation to proceed and give reasonable yields.²⁶ The indolylolation is made efficient by increasing the nucleophilicity of the indole ring *via* appropriately-positioned substituents and by acid-catalyzed activation of the C-3 carbonyl of isatin.²⁷ Mechanistically, the reaction involves two steps where 3-hydroxy-3-indolyl-2-indolone 7 is

formed first and then is converted to 3,3-di(3-indolyl)-2-indolone 3 following the addition of a second equivalent of indole 1 (Scheme 1 and 2). Strong acid catalysts directly afford 3,3-diindolyl-2-oxindole 3.²⁶

The proposed general mechanism of acid-catalyzed formation of trisindoline 3 through reaction between isatin 2 and indole 1 is shown in Scheme 2. Formation of 3,3-di(3-indolyl)-2-indolone 3 proceeds through a pathway in which the C-3 position of isatin 2 is activated to give intermediate 8 which undergoes nucleophilic attack by the indole 1 to generate 9. Deprotonation of the tertiary alcohol 9 to 3-hydroxy-3-(1H-indol-3-yl)indolin-2-one 7 is followed by protonation to form 10. Dehydration of 10 generates α,β -unsaturated iminium ion 11 which is followed by addition of a second molecule of indole 1 and re-aromatization of 12, affording trisindoline 3.

Since many common symmetrical and unsymmetrical trisindolines have been prepared by different routes, we categorized them in Table 1 and 2 and assigned them numbers for easy reference throughout this review. In symmetrical trisindolines, the isatin unit bears the same indole moieties. However, in unsymmetrical trisindolines, the isatin unit bears different indole moieties.

In the below sections, the grouping of the catalysts under different headings is not very strict and is meant for easy reference. This is because some catalysts can fall under several groupings.

3.1 Synthesis of trisindolines from isatin as a coupling partner

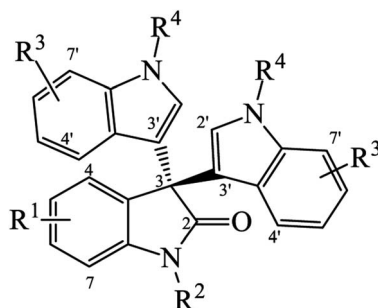
Trisindolines can be synthesized from several coupling partners, the most notable of which is indole 1 and isatin 2. Several reagents and catalysts that promote the coupling process are discussed in the next sub-sections.

3.1.1 Mineral acids-based catalysts

3.1.1.1 Sulfuric acid and related acids catalyzed synthesis. El-Sayed *et al.* (2015) used sulfuric acid to catalyze the reaction



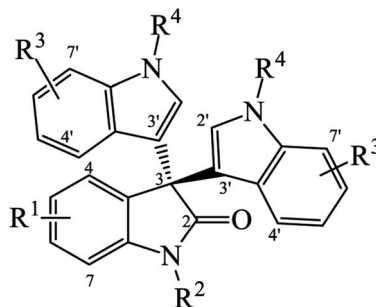
Table 1 List of symmetrical trisindolines



No.	R ¹	R ²	R ³	R ⁴	No.	R ¹	R ²	R ³	R ⁴
13:	5-Br	4-NO ₂ -Bn	5-OH	H	50:	H	H	H	2-F-Bn
14:	5-Br	Bn	H	H	51:	H	H	H	2-Cl-Bn
15:	H	H	5-Br	H	52:	H	H	H	3-F-Bn
16:	H	H	5-OMe	H	53:	H	H	H	4-Br-Bn
17:	H	H	H	Me	54:	H	H	5-CN	H
18:	H	Me	H	H	55:	H	H	5-CO ₂ Me	H
19:	H	Me	H	Me	56:	H	H	5-F	H
20:	H	Me	5-OMe	H	57:	5-Cl	H	H	Me
21:	H	Me	5-Br	H	58:	5-Cl	H	5-F	H
22:	H	H	2-Me	H	59:	5-F	H	5-F	H
23:	H	Me	2-Me	H	60:	5-F	H	5-OMe	H
24:	H	Bn	2-Me	H	61:	5-F	H	H	Me
25:	H	Bn	H	H	62:	5-Br	H	5-OMe	H
26:	H	Bn	H	Me	63:	5-Br	H	5-F	H
27:	5-NO ₂	H	H	H	64:	5-NO ₂	H	5-F	H
28:	5-NO ₂	H	H	Me	65:	5-NO ₂	H	5-OMe	H
29:	5-Br	H	H	Me	66:	H	Me	5-F	H
30:	H	H	5-Cl	H	67:	H	H	H	Et
31:	5-Cl	H	H	H	68:	5-OMe	H	H	Me
32:	5-F	H	H	H	69:	H	H	5-Me	H
33:	5-Me	H	H	H	70:	6-Br	H	H	Me
34:	5-Me	H	5-OMe	H	71:	H	H	6-F	H
35:	7-CF ₃	H	H	H	72:	H	H	4-F	H
36:	6-Cl	H	H	H	73:	H	H	7-F	H
37:	5-OMe	H	H	H	74:	H	H	5-Br	Et
38:	5-OMe	H	5-OMe	H	75:	H	H	2-Me, 5-OMe	H
39:	5,7-Me	H	H	H	76:	H	H	2-Me	Me
40:	5-Me	H	2-Me	H	77:	H	H	2-Me	Et
41:	5-I	H	H	Me	78:	H	H	2-Me	<i>n</i> -Bu
42:	H	H	5-NO ₂	H	79:	H	H	2-Ph	Me
43:	H	H	7-Me	H	80:	H	H	2-Ph	Et
44:	H	H	6-Cl	H	81:	7-Br	H	H	Me
45:	H	H	H	<i>n</i> -Pr	82:	5-Me	H	H	Me
46:	H	H	H	<i>i</i> -Pr	83:	4-Br,5-Me	H	H	Me
47:	H	H	H	<i>n</i> -Bu	84:	5-NO ₂	H	2-Me	H
48:	H	H	H	<i>i</i> -Bu	85:	5-Br	H	2-Me	H
49:	H	H	H	Bn	86:	5-Cl	H	5-Br	H
87:	5-Cl	H	2-Me	H	131:	H	H	H	Cinnamyl
88:	5-Br	H	5-Br	H	132:	H	H	5-Br	Prenyl
89:	H	Ac	H	H	133:	H	Propargyl	5-Br	Prenyl
90:	H	Propargyl	H	H	134:	H	H	H	Propargyl
91:	5-Cl	Propargyl	H	H	135:	H	Bn	H	Propargyl
92:	5-Cl	Bn	H	H	136:	H	Propargyl	H	Propargyl
93:	5,7-Br	H	H	H	137:	H	H	2-Me	Propargyl
94:	5,7-Br	Bn	H	H	138:	H	Me	2-Ph	H
95:	4-Br	H	H	H	139:	5-Me	H	2-Ph, 5-Cl	H
96:	H	H	6-Me	H	140:	H	H	2-Ph, 5-Me	H
97:	H	H	6-NO ₂	H	141:	H	H	2-Ph, 5-CN	H
98:	7-F	H	H	H	142:	H	H	2-Bu	H



Table 1 (Contd.)



No.	R ¹	R ²	R ³	R ⁴	No.	R ¹	R ²	R ³	R ⁴
99:	5-NO ₂	H	5-Br	H	143:	H	Et	H	H
100:	H	Bn	5-Br	H	144:	H	H	4-OMe	H
101:	5-F	H	5-Br	H	145:	H	H	6-OMe	H
102:	5-OMe	H	2-Me	H	146:	5-F	H	4-OMe	H
103:	5-OMe	H	5-Br	H	147:	5-F	H	6-OMe	H
104:	5-F	H	2-Me	H	148:	5-F	H	5-Cl	H
105:	H	H	2-CO ₂ H	H	149:	5-NO ₂	Me	H	H
106:	H	H	2-Me, 5-NO ₂	H	150:	5-NO ₂	Bn	H	H
107:	H	H	2-Ph	H	151:	5-Br	Me	H	H
108:	5-Cl	H	2-Me, 5-NO ₂	H	152:	5-Br	Et	2-Me	H
109:	5-Cl	H	2-Ph	H	153:	H	Allyl	H	H
110:	5-Cl	H	5-CO ₂ Me	H	154:	H	Allyl	5-Br	H
111:	5-Cl	H	5-OMe	H	155:	H	Pr	H	H
112:	5-Cl	H	5-NO ₂	H	156:	H	Pr	5-Br	H
113:	5-Cl	H	6-Cl	H	157:	5-Cl	Bn	2-Me	H
114:	5-Cl	H	7-Me	H	158:	H	Allyl	2-Me	H
115:	5-Me	H	5-Br	H	159:	H	Propargyl	2-Me	H
116:	5-Me	H	5-NO ₂	H	160:	H	Pr	2-Me	H
117:	5-Me	H	7-Me	H	161:	5-Br	Bn	2-Me	H
118:	5-Me	H	6-Cl	H	162:	H	Morpholinomethyl	2-Me	H
119:	H	H	2-CO ₂ Et	H	163:	H	Morpholinomethyl	H	H
120:	H	H	5-OBn	H	164:	5-Br	Me	2-Me	H
121:	4-Br	H	H	Me	165:	5-Br	Bn	H	Me
122:	H	H	7-Et	H	166:	H	H	5-OH	H
123:	H	H	2-Me	Boc	167:	5-CN	H	5-CN	H
124:	5-F	H	5-NO ₂	H	168:	H	Me	5-Me	H
125:	H	H	H	Allyl	169:	H	Ts	H	H
126:	5-NO ₂	H	H	Allyl	170:	H	Ts	2-Me	H
127:	H	H	5-OMe	Allyl	171:	H	Ts	5-Me	H
128:	5-Cl	H	5-OMe	Allyl	172:	H	H	5-COOH	H
129:	5-Br	H	5-OMe	Allyl	173:	H	H	4-OH	H
130:	H	CH ₂ CO ₂ Et	5-OMe	Allyl					

between isatin **2** and indole **1** to prepare trisindoline **3** in 87% yield under reflux conditions in methanol within 2 h.²⁸ Additionally, Annuur *et al.* (2018) employed sulfuric acid to react *N*-benzylisatin substrates **192** and **193** under ambient temperature to obtain trisindolines **13** and **14** in 82% and 81% yield, respectively (Scheme 3).¹¹

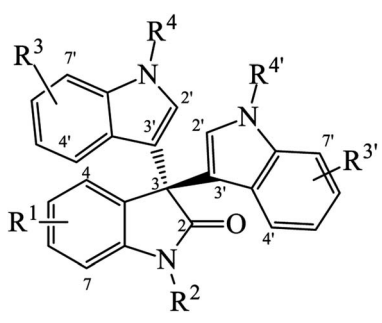
Bartoli indole synthesis involves reaction of 1-bromo-2-nitrobenzene **194** with vinylmagnesium bromide **195** followed by reaction with isatin **2** in the presence of potassium bisulfate (obtained from KOH + H₂SO₄) to give trisindoline **3** in 25% yield. Debromination reaction of the indole ring occurred

simultaneously (Scheme 4).²⁹ This procedure is time consuming and requires several manipulations resulting in low yields.

3.1.1.2 Tungstic acid and related acids catalyzed synthesis. The monohydrated tungsten trioxide, tungstic acid (H₂WO₄, 10 mol%), afforded trisindolines **3** and **15–21** in 88–92% yields within 6 h in ethanol. Remarkably, 5-bromoindole was very reactive with isatin and gave trisindoline **15** in highest 92% yields. The heterogeneous tungstic acid catalyst was recycled by refluxing in dry ethanol for 30 minutes then reused. Other advantages include easy work up and high reactivity under mild conditions especially for NH-substituted indoles and isatins.³⁰



Table 2 List of unsymmetrical trisindolines



No.	R ¹	R ²	R ³	R ^{3'}	R ⁴	R ^{4'}
174:	H	H	H	H	H	Me
175:	H	H	5-Br	H	H	H
176:	5-Br	H	5-Br	H	H	H
177:	H	H	H	2-Me	H	H
178:	H	Bn	H	2-Me	H	H
179:	H	Bn	H	5-Br	H	H
180:	H	H	5-CN	H	H	H
181:	H	Me	H	5-Br	H	H
182:	H	H	H	5-Me	H	H
183:	H	H	H	6-Me	H	H
184:	H	H	H	7-Me	H	H
185:	H	H	2-Me	H	H	Me
186:	H	H	2-Me	5-Br	H	H
187:	H	Bn	H	H	H	Me
188:	5-NO ₂	H	H	5-Cl	H	H
189:	H	Allyl	H	2-Me	H	H
190:	H	Allyl	5-Br	H	H	H
191:	5-Cl	Allyl	H	5-Br	H	H

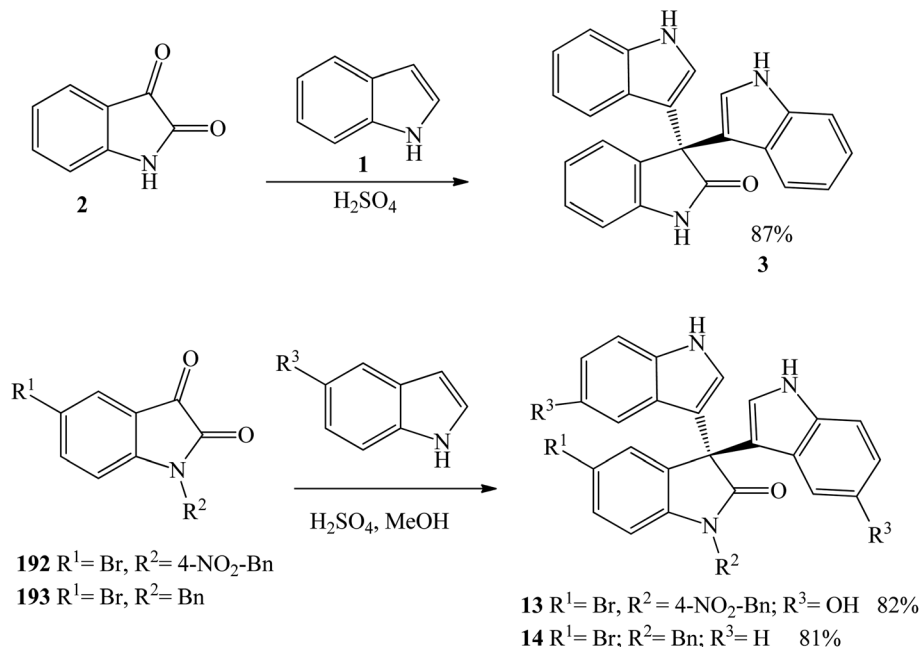
The Wells–Dawson heteropoly acid H₆P₂W₁₈O₆₂ is well-known for its super acidity, stability in solution, and its recyclability. Trisindolines **3**, **5**, **17–19** and **22–29** were successfully synthesized in 86–95% yields using 5 mol% H₆P₂W₁₈O₆₂ in water at 60 °C within 30 minutes. *N*-Alkyl and *N*-benzyl isatins and indoles also reacted to give high yields.³¹

Heteropoly acid silicotungstic acid (H₄SiW₁₂O₄₀, 0.1 mol%) successfully catalyzed the synthesis of trisindolines **3**, **5**, **15**, **17**, **18**, **22–25** and **27–29** in 85–96% yields within 5–70 minutes at room temperature in methanol. However, 5-bromoisatin and 5-bromoindole reacted at a slower rate, giving lower yields.³²

3.1.1.3 Polyphosphoric acid (PPA) catalyzed synthesis. Polyphosphoric acid (PPA) is a mineral acid catalyst used in several organic transformations. However, owing to its high viscosity, the acid exhibited limited use.³³ On a different note, perlite is universal name for amorphous volcanic glass that mainly comprises of alumina-silicate. Perlite expands 4–20 times of its original volume once heated to 760–980 °C. Due to its high surface area, low density, and inertness, expanded perlite can be used as solid support for heterogeneous catalysts.³⁴ Esmailpour *et al.* (2017) fabricated expanded perlite-polyphosphoric acid (EP-PPA) (Scheme 5) and evaluated its catalytic activity for bisindolylmethane (BIM) synthesis. The BIMs were obtained in excellent yields within short reaction times. Nevertheless, trisindoline **3** was obtained in 65% yield within 40 minutes.³³

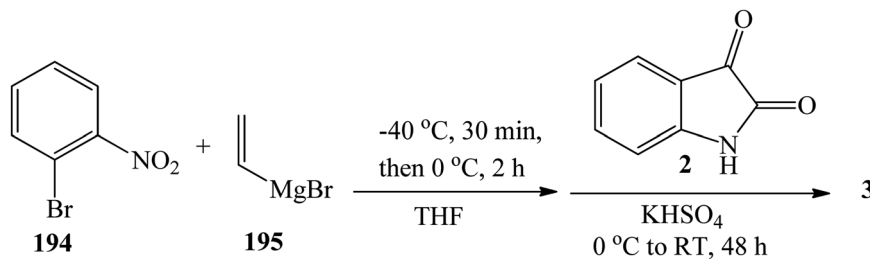
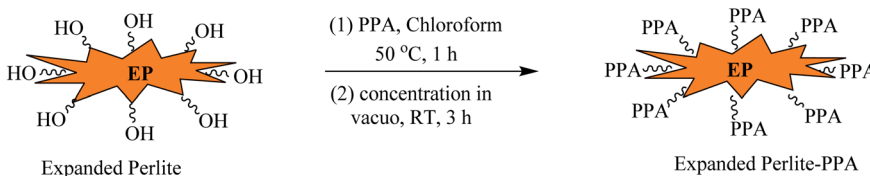
3.1.2 Organic acids-based catalysts. The synthetic routes based on organic acid-catalyzed reactions to afford 3,3-diindolyl-2-oxindoles are generally selective and give high yields under short reaction time. The next subsections discuss the use of various organic acids in this regard.

3.1.2.1 *p*-Toluenesulfonic acid (*p*-TSA)-catalyzed reactions. *p*-Toluenesulfonic acid (*p*-TSA) is a nontoxic, affordable, safe, and readily available catalyst used frequently in many organic

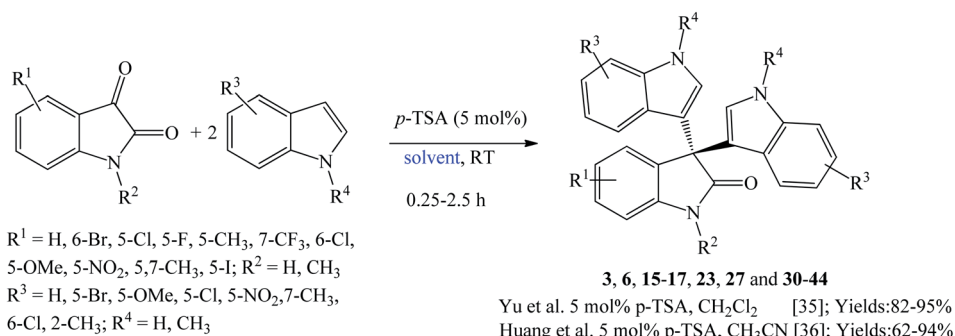


Scheme 3 Trisindoline synthesis using sulfuric acid as catalyst.



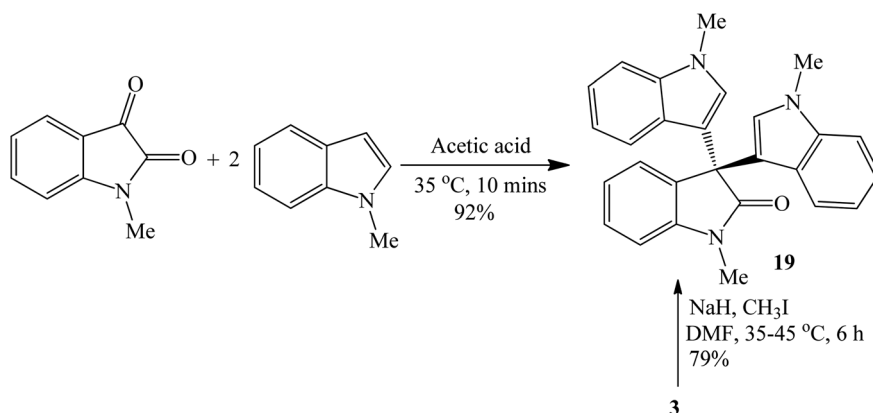
Scheme 4 Synthesis of trisindoline **3** by Bartoli indole synthesis.

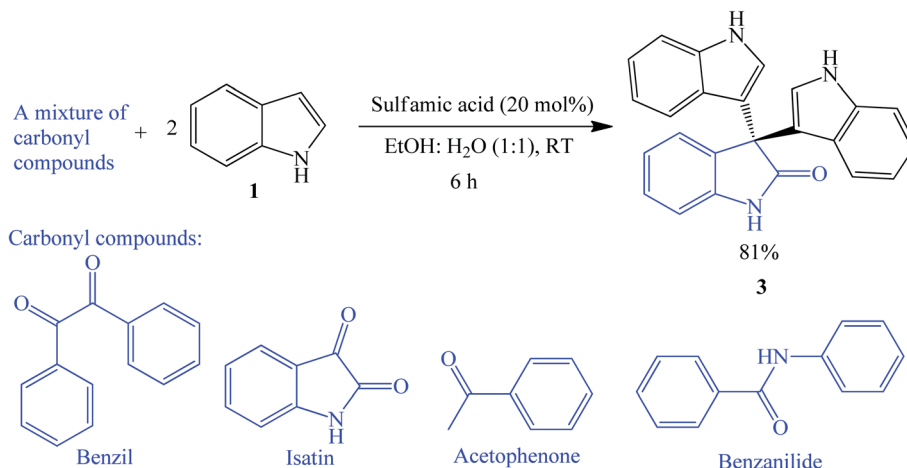
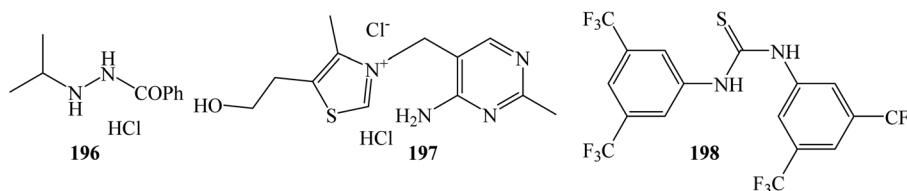
Scheme 5 Synthesis of expanded perlite-PPA (EP-PPA).

Scheme 6 *p*-TSA-catalyzed synthesis of trisindolines **3, 6, 15–17, 23, 27 and 30–44**.

transformations.³⁵ Yu *et al.* (2014) prepared a series of trisindolines **3, 16, 23, 27 and 30–41** in 82–95% yields within 10–150 minutes employing 5 mol% *p*-TSA-catalyzed reaction of isatins and indoles in dichloromethane at room temperature (Scheme 6).³⁵ Reactions of isatins bearing EDG afforded higher

yields under shorter reaction time compared to reactions of isatins bearing EWG. The reaction of electron-rich isatins and electron-rich indoles gave the highest yields within shorter reaction times. Similar reaction results were obtained by Huang *et al.* (2015) (Scheme 6),³⁶ when dichloromethane was replaced

Scheme 7 Synthesis of trisindoline **19**.

Scheme 8 Competitive reaction between indole **1** and carbonyl compounds.Fig. 3 Structures of catalysts **196**, **197** and **198**.

by acetonitrile where trisindolines **3**, **6**, **15–17**, **31**, **33** and **42–44** were obtained in 62–94% yields. *N*-Methylindole reacted smoothly with isatin within 3 h to yield trisindoline **17** in excellent yield (90%). Like the case of Br_2 -catalyzed reactions, *N*-tosylindole did not react even after 24 h.³⁶ In comparison, although the yields of the products are similar, reactions in dichloromethane proceeded at a much faster rate than in acetonitrile (less than 1 h vs. several hours).

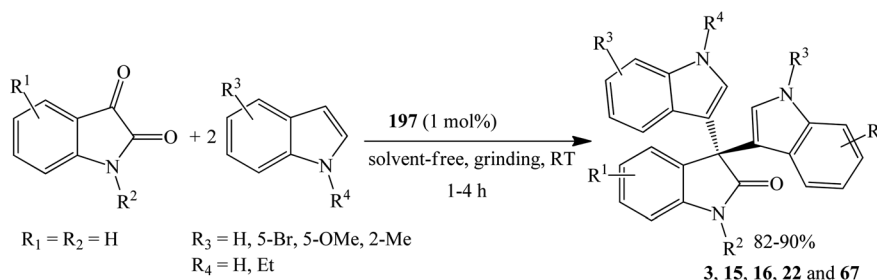
Following that, a series of trisindolines **3**, **5**, **17**, **31**, **33** and **45–53** alkylated and benzylated at the indole rings were synthesized using 10 mol% *p*-TSA in dichloromethane albeit with moderate yields of 50–76%.¹²

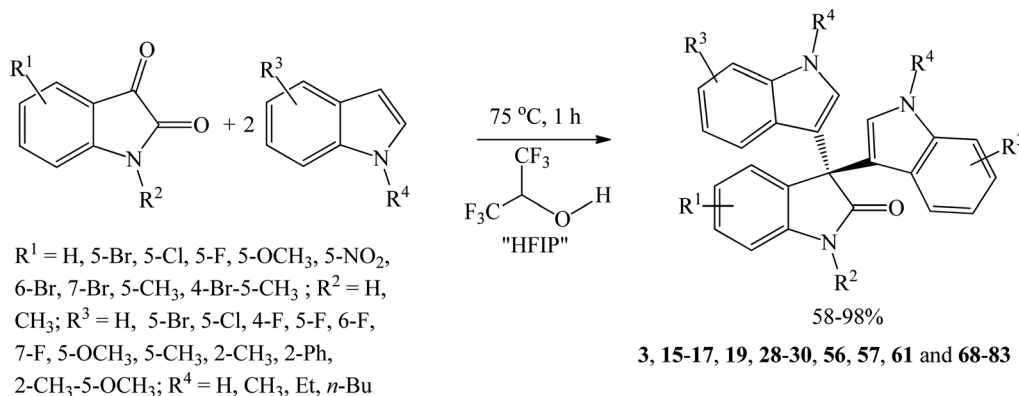
3.1.2.2 Acetic acid-catalyzed reactions. Acetic acid, as both catalyst and solvent, afforded **19** at 35 °C within 10 minutes in 92% yield.³⁷ This method is superior (mild, high yield, short reaction time) to the synthesis by alkylation of trisindoline **3**

using CH_3I (3 equivalents) in the presence of NaH in DMF at 35–45 °C which gave only 79% yield (Scheme 7).

3.1.2.3 Succinimide-*N*-sulfonic acid catalyzed reactions. Trisindolines **3** and **22** were successfully synthesized in 96% and 92% yields, respectively, using 5 mol% succinimide-*N*-sulfonic acid in acetonitrile.³⁸

3.1.2.4 Sulfamic acid-catalyzed reactions. An efficient and simple synthesis of trisindolines **3**, **5**, **15–18**, **20**, **27**, **29**, **31**, **32** and **54–66** was disclosed by Brahmachari *et al.* (2014) using sulfamic acid ($\text{NH}_2\text{SO}_3\text{H}$). Reaction between indoles and isatins using 20 mol% sulfamic acid in ethanol : water (1 : 1, v/v) at ambient temperature gave the desired trisindolines in 84–94% yields within 2–7 h. The electron deficient 5-cyanoindole was unreactive. The catalyst was also reused with a slight decrease in efficiency in the third cycle.³⁹ In a competitive experiment (Scheme 8), when the indole was treated with several carbonyl

Scheme 9 Thiamine hydrochloride **197** catalyzed synthesis of trisindolines **3**, **15**, **16**, **22** and **67**.



Scheme 10 HFIP-catalyzed synthesis of symmetrical trisindolines **3**, **15–17**, **19**, **28–30**, **56**, **57**, **61** and **68–83**.

compounds including benzil, isatin, acetophenone, and benzamide, it selectively reacted with isatin to produce trisindoline **3** in 81% yield. Sharma *et al.* (2016) adopted Brahmachari *et al.* method to synthesize **56** in 87% yield.⁴⁰

3.1.2.5 *N*-isopropylbenzohydrazide hydrochloride-catalyzed reactions. The Friedel–Crafts reaction between isatin **2** and indole **1** was successfully catalyzed using 10 mol% *N*-isopropylbenzohydrazide hydrochloride **196** aminocatalyst in methanol at room temperature to afford trisindoline **3** in 72% yield.⁴¹ No variations of the indoles or isatins were reported (Fig. 3).

3.1.2.6 Thiamine (vitamin B₁) hydrochloride catalyzed reactions. Mathavan *et al.* (2019) utilized the environmentally benign aminocatalyst thiamine (vitamin B₁) hydrochloride **197** (1 mol%) to catalyze the solvent-free condensation reaction between indoles and isatins under grinding conditions (Scheme 9). The reaction at ambient temperature gave trisindolines **3**, **15**, **16**, **22** and **67** in yields ranging from 82–90% after 10 h. Under these conditions, 5-methoxyindole and 5-bromoindole as well as *N*-ethylindole gave high yields of the trisindolines **16**, **15** and **67**. 2-Methylindoles also reacted but gave 82% yield of **22**. Notably, the catalytic activity of the recovered catalyst remained high, giving trisindoline **3** in 96% yield in the first cycle and in 78% yield after ten cycles.⁴²

3.1.2.7 Dodecylsulphonic acid catalyzed reactions. Hazarika *et al.* (2008) used 10 mol% dodecylsulphonic acid (DCA) as a catalyst and water-solubilising agent to catalyze the reaction of indole **1** and isatin **2** to obtain trisindoline **3** in 87% yield within 20 minutes at room temperature. No other variations of the isatins and indoles were evaluated.⁴³

3.1.2.8 Photoacids catalyzed reactions. Photoacids are molecules that become more acidic when absorb light. They can acidify a neutral aqueous solution within very short times (nanoseconds).⁴⁴ *N,N'*-Bis[3,5-bis(trifluoromethyl)phenyl]thiourea **198** also known as Schreiner's thiourea belongs to photoacid organocatalysts that function as proton donors. Trisindole **32** was synthesized in 79% yield using a blue LEDs-activated Schreiner's thiourea **198** in 1,4-dioxane at room temperature for 18 h.⁴⁵ Under these conditions, but using 370 nm LEDs, trisindolines **3** and **18** were synthesized in 69% and 65% yields,

respectively. Unfortunately, the synthesis of trisindoline **32** required 4 equivalents of the indole which is much higher than other routes. This finding reveals that light irradiation plays a prominent role in initiating the reaction.

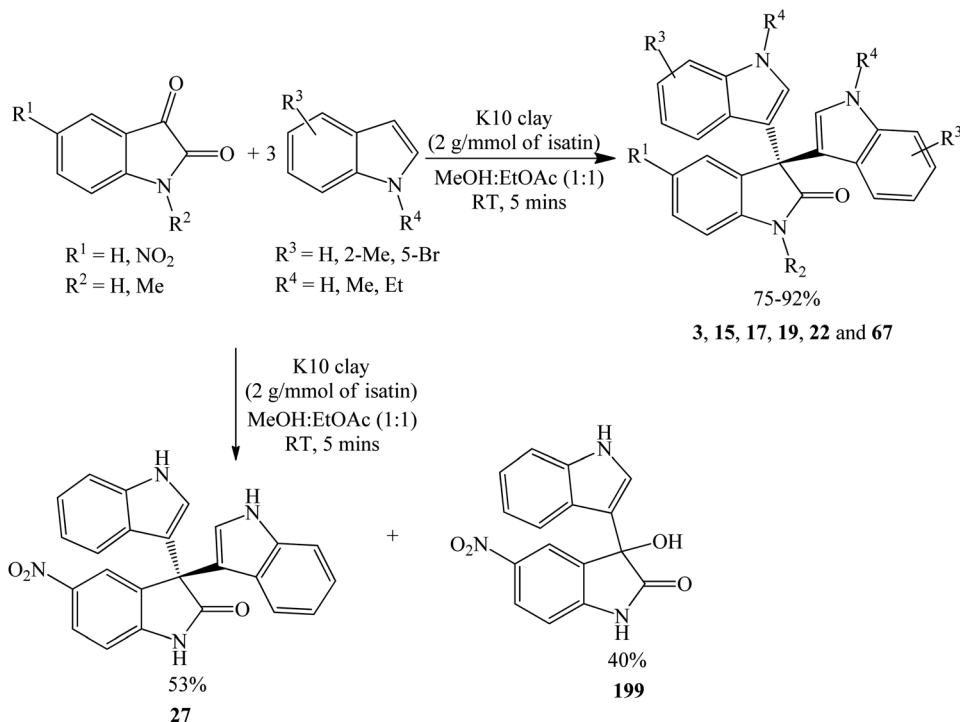
3.1.2.9 Acidic solvent-catalyzed reactions. Yuan *et al.* (2020) used hexafluoro-2-propanol (HFIP, $pK_a = 9.3$) as a strong H-bond donor solvent to obtain a series of trisindolines **3**, **15–17**, **19**, **28–30**, **56**, **57**, **61** and **68–83** in 58–98% yields (Scheme 10).⁴⁶ HFIP activates the C₃ carbonyl group of isatin in the first step and is also involved in subsequent proton transfer reactions during the isomerization and dehydration processes of the next two steps. The reaction conditions work well with *N*-alkylated indoles but are ineffective with indoles bearing substituents (*e.g.* methyl, phenyl) on C-2 of the indole ring. Additionally, no desired products were obtained when indole bearing NO₂ or CN was used as substrate. However, isatin ring tolerates a wide range of substituents such as halogen, nitro, methyl and methoxy substituents.⁴⁶

3.1.3 Heterogeneous and nanoparticle acidic catalysts

3.1.3.1 Amberlyst-15-catalyzed reactions. Amberlyst-15, an acidic cation-exchange resin, is a heterogeneous catalyst that has been used for several organic transformations. Sarrafi *et al.* (2012) reacted various isatins and indoles in the presence of Amberlyst-15 in water (reaction of *N*-benzylisatin using H₂O : acetone (4 : 1)) at 70 °C for 30 minutes, furnishing 88–95% yields of the trisindolines **3**, **5**, **17–19**, **22–29**, **84** and **85**. 5-Nitro- and 5-bromo isatins reacted well with either indole or 5-methylindole while derivatization of the NH of the isatin or indole with electron-donating group did not have any significant effects on reaction rate and product yields.⁴⁷ The catalyst showed outstanding reusable activity. Amberlyst-15 was also found to catalyze the electrophilic substitution reaction of 3-methylindole with isatins to afford the corresponding 2,2-dialkyloxindole **4** in high yield. This is an added advantage since the number of reports on the reaction of isatin with 3-substituted indoles is scant.⁴⁷

3.1.3.2 Clay-catalyzed reactions. Clay is a naturally occurring aluminosilicates solid acid. Modified montmorillonites such as K10 clay and KSF exhibit both Brønsted and Lewis acid properties and are characterized by a large surface area. K10 (250 m²





Scheme 11 K10 clay-catalyzed synthesis of trisindolines.

g^{-1}) offers a remarkably higher surface area compared to KSF (around $10 \text{ m}^2 \text{ g}^{-1}$)⁴⁸ and has been shown to catalyze trisindolines formation much faster than KSF. K10 clay was evaluated by Chakrabarty *et al.* (2005) under ambient temperature for 5 minutes by adsorbing a solution of isatin and 3 equivalents of the indole in ethyl acetate : methanol (1 : 1), furnishing the desired products **3**, **15**, **17**, **19**, **22** and **67** in moderate to excellent yield (75–92%). While methyl-substituted indole on either C-2 or the *N* atom produced higher yields, *N*-Et substitution decreased the reactivity. The reaction of 5-nitroisatin and indole afforded not only the desired trisindoline **27**, but also **199**, which was expected as an intermediate product (Scheme 11).⁴⁹

Intermediate product **199** may be used for the synthesis of unsymmetrical trisindolines.

Nikpassand *et al.* (2010) synthesized symmetrical trisindolines **3**, **5**, **15**, **17**, **22**, **29**, **31** and **85–88** and unsymmetrical trisindoline **174**, **175** and **176** using KSF-catalyzed one-pot reaction of isatin and indoles in refluxing ethanol within 22–35 minutes. Excellent yields of 85–93% for symmetrical and 88–91% for unsymmetrical trisindolines were obtained. 2-Methylindole enhanced the reactivity and the yield. 5-Br isatins showed enhanced reactivity in some cases compared to their chloro analogues. Unsymmetrical trisindolines **174**, **175** and **176** were prepared by initially refluxing equimolar amounts of isatin and

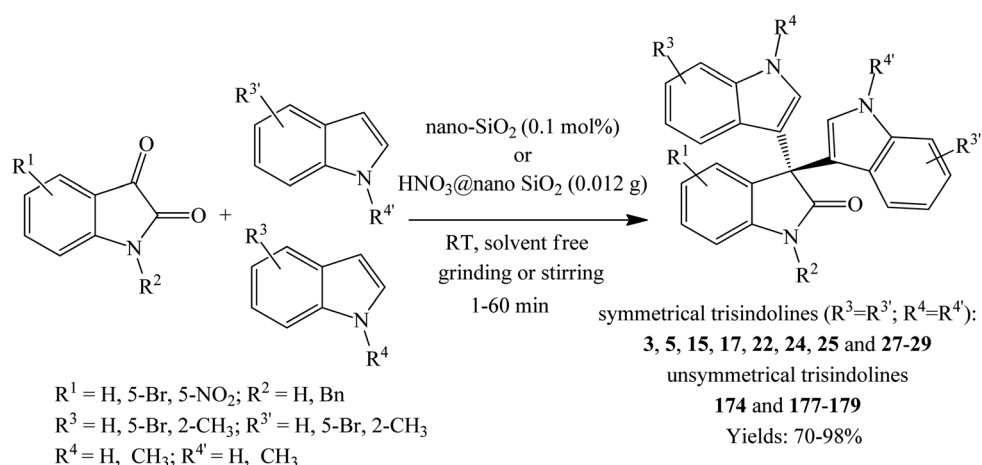
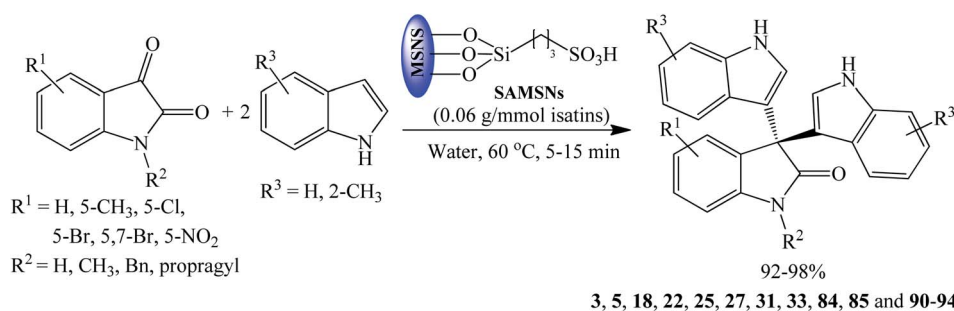
Scheme 12 Coupling of isatins and indoles using nano SiO₂ catalyst and HNO₃@nano SiO₂.

Table 3 Reactions of isatins and indoles using nano-SiO₂ and HNO₃@nano-SiO₂ under stirring and grinding techniques

Catalyst	Nano-SiO ₂ (0.1 mol%) ⁵²				HNO ₃ @nano-SiO ₂ (ref. 53)			
	Symmetrical trisindoline		Unsymmetrical trisindoline		Symmetrical trisindoline		Unsymmetrical trisindoline	
	Stirring	Grinding	Stirring	Grinding	Stirring	Grinding	Stirring	Grinding
Time (min)	15–75	1–6.5	120–150	7–10	20–40	3–5	5–60	5–10
Isolated yields (%)	80–98	63–98	80–83	70–81	80–96	80–95	71–80	72–78

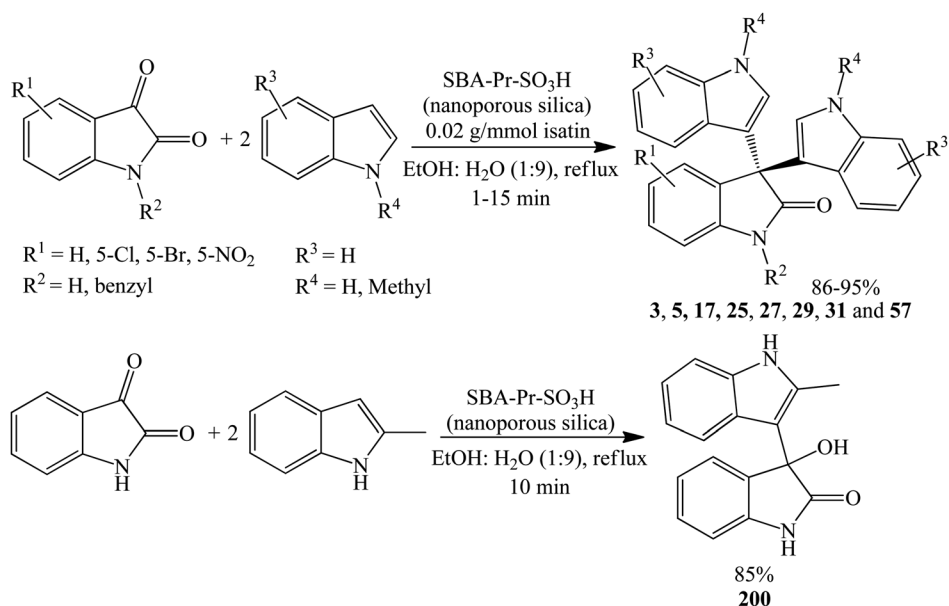
Scheme 13 SAMSNs catalyzed synthesis of trisindolines **3**, **5**, **18**, **22**, **25**, **27**, **31**, **33**, **84**, **85** and **90–94**.

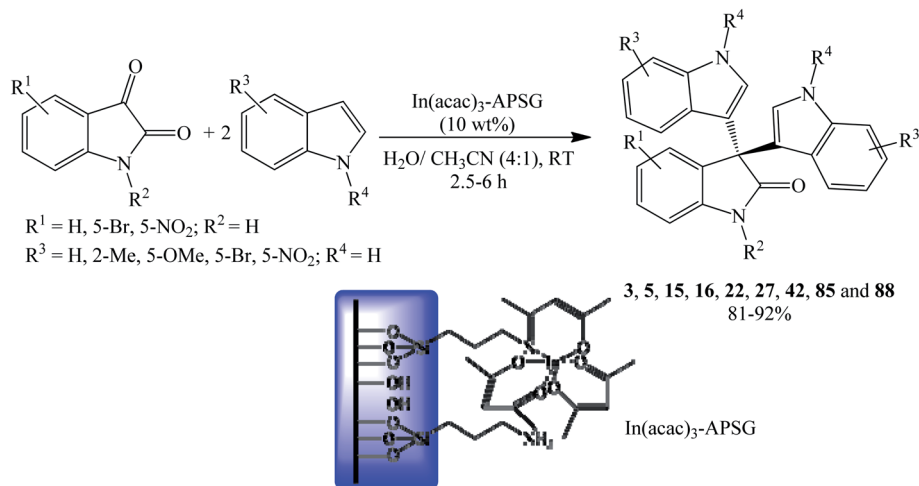
indole substrates, followed by adding a second equivalent of a different indole. Without KSF, the reaction was unsuccessful even when heated at reflux for 12 h. The catalyst was easily recovered and reused without significant loss of reactivity.⁵⁰

3.1.3.3 Cellulose sulfuric acid (CSA) catalyzed reactions. Aliznezhad *et al.* (2010) conduct solvent-free ecofriendly synthesis of trisindolines by grinding a mixture of isatins and indoles with cellulose sulfuric acid (CSA) catalyst at room temperature. 2-Methylindole reacted more smoothly with isatin within 10

minutes to form **22** in 85% yield in comparison to unsubstituted indole which gave **3** in 88% yield within 2 h.⁵¹

3.1.3.4 Acidic nano-SiO₂ catalyzed reactions. Nikoofar and Khalili (2016) conducted one-pot solvent-free condensation reaction of various isatins and indoles in the presence of 0.1 mol% nano-SiO₂ acidic catalyst under ambient temperature using two different techniques. The stirring technique showed wide scope using various substituted indoles and isatins, promoting reactions within 15–75 minutes to yield trisindolines **3**, **15**, **17**, **22**, **24**, **25**, **28** and **29** in 80–98% yield (Scheme 12). On

Scheme 14 SBA-Pr-SO₃H catalyzed synthesis of symmetrical 3,3-di(indolyl)oxindoles **3**, **5**, **17**, **25**, **27**, **29**, **31** and **57** and 3-hydroxy-3-(2-methyl-1H-indol-3-yl)indolin-2-one **200**.

Scheme 15 In(acac)₃-APSG catalyzed synthesis of symmetrical 3,3-di(indolyl)oxindoles.

other side, the grinding method was conducted by mortar and pestle (0.1 mol%, 0.06 g catalyst/1 mmol of isatins), requiring considerably shorter reaction times (1–6.5 minutes) than the preceding method. However, yields were relatively lower ranging from 63 to 98% yields. In the grinding technique, the starting materials were pulverized to fine powder which generated local heat that sped the reaction. Interestingly, nano-SiO₂ catalyst produced best yields of trisindolines (98% for both techniques) with 5-nitroisatin **28**, while *N*-Bn isatins **25** and **24** relatively gave better yield under magnetic stirring (98% yields).⁵² As a notable feature of the protocol and while the attempted multi-step one pot preparation of unsymmetrical 3,3-di(indolyl)indolin-2-ones failed to produce the desired products, nano-SiO₂ efficiently catalyzed the synthesis of various unsymmetrical trisindolines **174** and **177–179** using the two reported methods (Scheme 12).^{52,53}

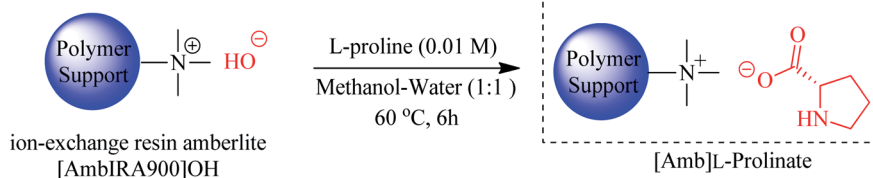
Another mechanical synthesis was achieved using ball-milling technique. The method was introduced as an eco-friendly solvent-free method for the synthesis of trisindoline in the presence of silica gel (SiO₂) as acid catalyst and grinding medium.⁵⁴ Trisindoline **3** was afforded after 7 h of grinding in 62% yield, compared to the grinding technique by mortar and pestle using nano-SiO₂ as a catalyst.⁵²

Azizian *et al.* (2006) demonstrated silica sulfuric acid SiO₂-OSO₃H-catalyzed condensation reaction (0.2 g SiO₂-OSO₃H/1 mmol isatins) of indoles with various isatins in DCM at room temperature for 2–3.5 h. Trisindolines **3**, **5**, **18**, **22–25**, **27**, **33**, **40** and **89** were obtained in 87–94% yields. Unsubstituted

trisindoline **3** was obtained in best yield under shortest reaction time. Both EDG and EWG attached to C-5 isatin did not impact the yield appreciably but substrates with EWG required longer reaction time than those with EDG. Methyl on C-2 of the indole ring and EDG or EWG substituents on the NH of isatin did not affect the yield either. Further, the catalyst was recycled five times without loss in yield.⁵⁵

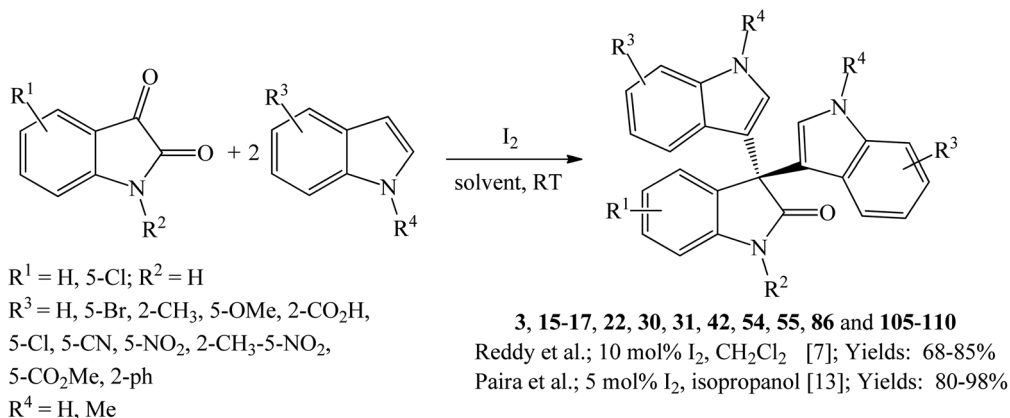
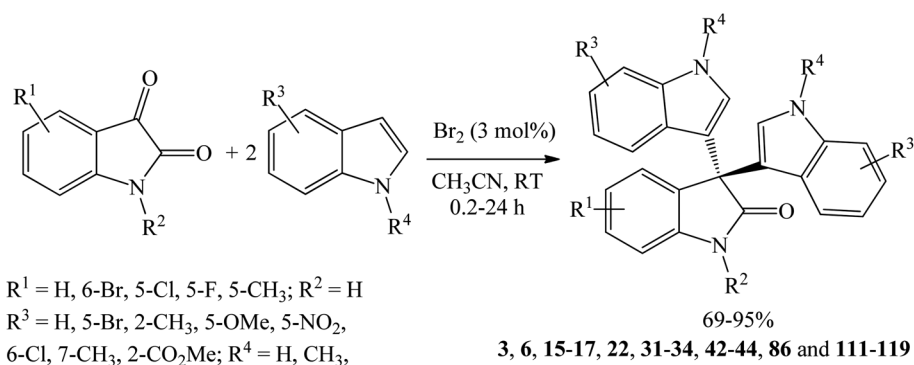
Similarly, Chakrabarty *et al.* (2006) further demonstrated the application of H₃PO₄-SiO₂ in the synthesis of trisindoline **3** (80% yield).⁵⁶

Nikoofar *et al.* (2018) compared the solvent-free stirring and grinding techniques during the synthesis of symmetrical trisindolines **3**, **5**, **15**, **17**, **22**, **24**, **25** and **27–29** using HNO₃@nano SiO₂ catalyst (Table 3). Both methods gave 80–96% yields. However, the reaction using grinding method proceeded within 2–5 minutes while the stirring method required 20–40 minutes. Under both methods, 5-nitroisatin was the most sluggish substrate while trisindoline **3** was produced in >94% yield *albeit* it required longer reaction times. Unsymmetrical trisindolines **174** and **177–179** were also successfully prepared by reacting 1 eq. of isatin and 2 eq. of different indoles. Grinding technique afforded products **174** and **177–179** in 72–78% yields within 5–10 minutes, while stirring technique afforded the same in 71–80% within 5–60 minutes (Scheme 12).⁵³ Compared to a previous method by the same authors using nano-SiO₂ catalyst,⁵² this catalyst was comparable in terms of yield and reaction time for both techniques (Table 3).



Scheme 16 Synthesis of [Amb]L-prolinate ion-pair hybrid.



Scheme 17 Iodine-catalyzed synthesis of trisindolines **3, 15–17, 22, 30, 31, 42, 54, 55, 86** and **105–110**.Scheme 18 Br_2 -catalyzed synthesis of trisindolines **3, 6, 15–17, 22, 31–34, 42–44, 86** and **111–119**.

Sulfonic acid-functionalized mesoporous silica nanoparticles (SAMSNs) were used by Mehrasbi *et al.* (2014) as heterogeneous and recyclable catalyst to synthesize trisindolines **3, 5, 18, 22, 25, 27, 31, 33, 84, 85** and **90–94** in water at 60 °C over 5–25 minutes (Scheme 13). SAMSNs was prepared by incorporating a mercaptopropyl moiety into mesoporous silica nanoparticles, followed by oxidation of the SH group with H_2O_2 to SO_3H . The catalyst showed wide scope for substituted isatins with outstanding yields of 90–98%. Trisindoline **3** gave the best yield within 10 minutes. Generally, isatins bearing EWG gave better yield within short reaction time than methyl-substituted isatin. The catalyst also worked well for bulky isatins, *N*-benzyl-5,7-dibromoisatin and 5,7-dibromoisatin.⁵⁷

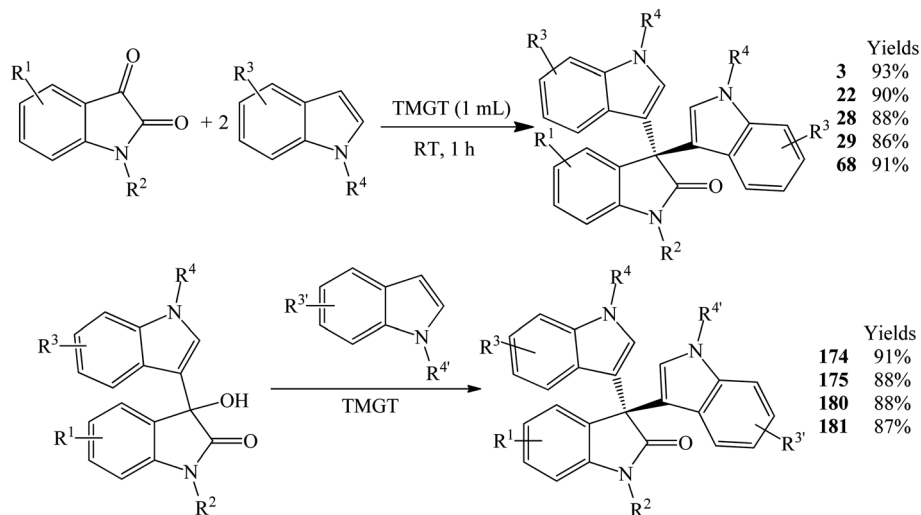
SBA-15 (SBA: Santa Barbara Amorphous) is mesoporous silica which possess uniform-sized nanopores with a large surface area and high thermal stability.⁵⁸ SBA-Pr- SO_3H is a nanoporous solid acid catalyst incorporating sulfonic acid-functionalized silica (SBA-15). Ziarani *et al.* (2015) synthesized **3, 5, 17, 25, 27, 29, 31** and **57** in 86–95% yields within 1–15 minutes by refluxing indoles and isatins in $\text{H}_2\text{O} : \text{EtOH}$ (9 : 1) in the presence of SBA-Pr- SO_3H as reusable catalyst (Scheme 14). Substitution of NH of indoles with methyl groups reduces the reaction time and/or enhances the yields. EWG groups (halogen, nitro) on C-5 of isatin did not affect the reaction time or yield appreciably. *N*-allyl trisindoline was not formed even

after 48 h while *N*-benzyl trisindoline **25** was obtained within 3 minutes in 90% yield. Unexpectedly, instead of forming the desired trisindoline **22**, compound **200** was obtained in 95% yield when 2-methylindole was employed as a substrate.⁵⁹

The modification of silica gel with 3-aminopropyltriethoxy silane results in aminopropylsilica gel (APSG). Subsequent anchoring of indium(III) acetylacetonate complex to aminopropylsilica gel (APSG) gave $\text{In}(\text{acac})_3\text{-APSG}$ which was investigated as a reusable heterogeneous catalyst for oxindole synthesis. Sharma and Sharma (2010) utilized this catalyst (10 wt%) to prepare trisindolines **3, 5, 15, 16, 22, 27, 42, 85** and **88** in 81–93% yield in water/acetonitrile (4 : 1) solvent system within 2.5–6 h (Scheme 15). Indoles with EDGs showed better reactivity than those with EWGs (5-nitroindole) which showed complete inertness when reacted with 5-nitro or 5-bromoisatin. Additionally, 5-bromoindole did not undergo reaction with 5-nitroisatin.⁶⁰

3.1.3.5 Nano- SiO_2 supported boron trifluoride catalyzed reactions. Boron trifluoride-etherate ($\text{BF}_3 \cdot \text{OEt}_2$) is a Lewis acid homogeneous catalyst which has been used in many organic transformations. Heterogenization of BF_3 is possible if anchored on solid materials. One such example is the nano- $\text{SiO}_2\text{-BF}_3\text{-CH}_3\text{OH}_2^+$ which has been synthesized by mixing $\text{BF}_3 \cdot \text{OEt}_2$ and preheated silica gel in MeOH and stirring for 3 h at room temperature. The catalyst was further applied for





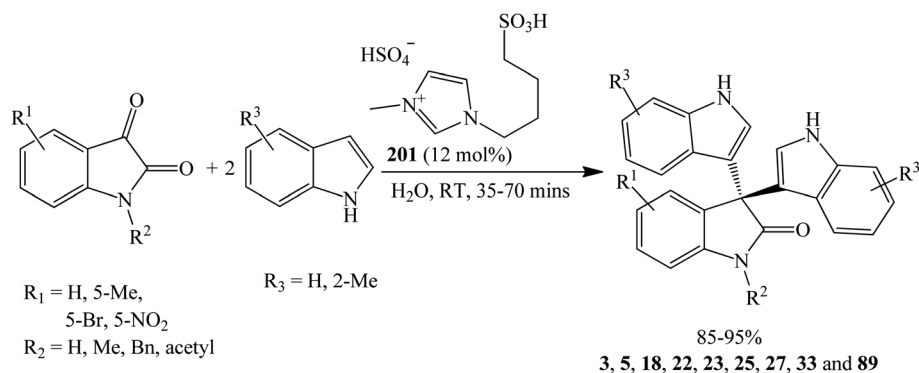
Scheme 19 Preparation of trisindolines catalyzed by TMGT.

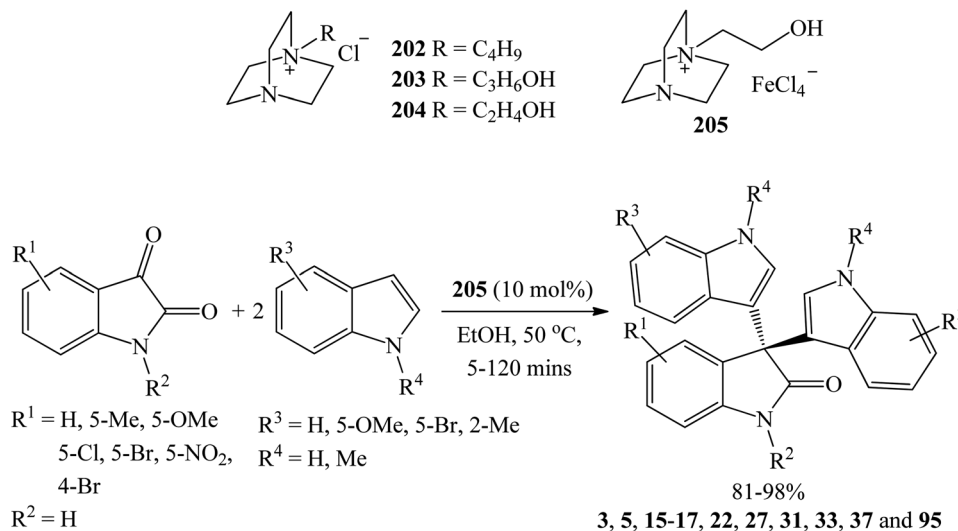
trisindoline synthesis by Saffar-Teluri (2013). Indoles and isatins were treated with a catalytic amount of nano-SiO₂-BF₃-CH₃OH₂⁺ (0.3 g mmol⁻¹ isatins) in methanol under reflux conditions to afford trisindolines **3**, **5**, **18**, **25**, **27** and **33** in 93–97% yields within 0.17–0.5 h. The condensation reaction of this catalytic system depended on the electronic properties of the isatins substrate. For instance, 5-methylisatins reacted much faster than 5-nitroisatins. On the other hand, indoles with EDGs or EWGs reacted very smoothly with isatins, producing outstanding yields of 93–95%. *N*-methyltrisindoline **18** or *N*-benzyltrisindoline **25** were also successfully prepared in 96% and 97% yields, respectively.⁶¹

3.1.3.6 PWA/MCM-41 catalyzed reactions. MCM-41 belongs to mesoporous silica and aluminosilicate materials featuring hexagonal pore arrangement.⁶² Phosphotungstic acid (PWA) supported on silica materials has been extensively utilized in organic transformations, especially in Friedel–Crafts reaction. Xing *et al.* (2018) reported efficient electrophilic coupling reaction between indoles and isatins using 60 wt% PWA/MCM-41 (0.0050 g/0.1 mmol isatins) in THF for 2.5 h at room temperature to give trisindolines **3**, **18**, **22**, **30**, **31**, **33**, **42**, **44**, **56**, **69**, **71** and **95–98** in 55–99% yields. When the ratio of PWA/MCM-41

surpassed 60 wt%, the chemical yields of the trisindolines declined, suggesting that the excess amounts of PWA blocked the MCM-pores, thus highlighting the role of the pores in facilitating the coupling reaction. Unsubstituted trisindoline **3** was formed in excellent 99% yield. Having a methyl group on various positions of the indoles (C-2 or C-5 or C-6) as well as a nitro group on C-5 or C-6 gave moderately lower yields (55–80%) than indoles bearing fluorine, and chlorine substituents on C-5 or C-6 positions (96–98%). On the contrary, 1-methylisatin and 5-methylisatin, as well as 5-chloro, 7-fluoro, or 4-bromo-isatins reacted smoothly with indoles, furnishing trisindolines in excellent 60–99% yields. Interestingly, unlike its 5- and 7-halogenated analogues, 4-bromoisatin showed the least reactivity affording the product **95** in only 60% yield. The catalyst exhibited high activity and was recycled and reused over six cycles with an overall drop of 9% in yield.⁶³

3.1.3.7 Graphene oxide catalyzed reactions. Graphene oxide catalyzed the reaction between indoles and isatins in water media under ambient temperature to give trisindolines **3**, **5**, **15**, **18**, **21–25**, **27**, **31**, **84–88**, **99** and **100** in 65–98% yields within 1.5–5 h.⁶⁴ The best yields were obtained when the indoles were substituted with EDG on C-2 and/or isatins were substituted

Scheme 20 Synthesis of trisindolines **3**, **5**, **18**, **22**, **23**, **25**, **27**, **33** and **89** catalyzed by [(CH₂)₄SO₃HMIM][HSO₄] **201**.



Scheme 21 [Dabco- $\text{C}_2\text{H}_4\text{OH}$][FeCl_4]-catalyzed synthesis of **3**, **5**, **15–17**, **22**, **27**, **31**, **33**, **37** and **95**.

with EWG on C-5. EWG on C-5 of the indole decreased the yield and/or prolonged the reaction time. *N*-Methylisatin exhibited better reactivity than *N*-benzylisatin.

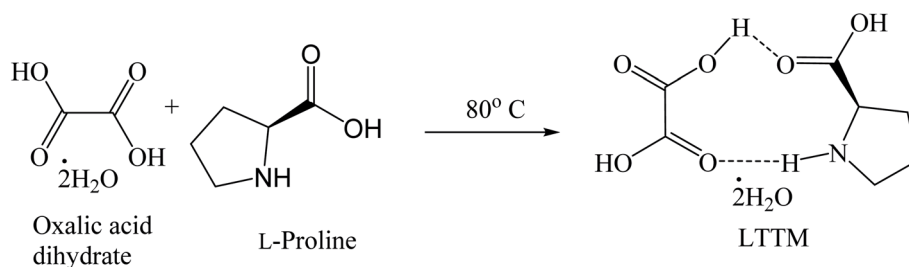
3.1.3.8 [Amb]*L*-prolinate catalyzed reactions. Keshavarz *et al.* (2015) immobilized *L*-proline on the surface of the cationic anion-exchange resin amberlite IRA900OH to obtain [Amb]*L*-prolinate. This was achieved by treating a 1 : 1 methanol/water solution of 0.01 M *L*-proline with amberlite IRA900OH at 60 °C for 6 h (Scheme 16).⁶⁵

When isatins (1 eq.) and indoles (2 eq.) were refluxed in ethanol and treated with 10 mol% [Amb]*L*-prolinate catalyst, trisindolines **3**, **5**, **15**, **17**, **18**, **21–23**, **27**, **31**, **32**, **37**, **57**, **61**, **68**, **84**, **86**, **99** and **101–104** were obtained in 79–99% yields within 8–15 minutes. Both EDG and EWG substituents attached to isatin were well-tolerated. Furthermore, 2-methylindoles were more reactive than indole itself. Interestingly, the heterogeneous catalyst could be reused up to 8 times *albeit* with a slight 5% drop in the yield.⁶⁵ In addition, the catalyst is characterized by very low leaching of *L*-proline during 8 cycles. Another notable feature of this catalyst is its superiority compared to other catalysts in terms of yield and reaction times.

3.1.4 Halogens-based catalysts. The use of halogens-based catalysts to prepare 3,3-diindolyl-2-oxindoles is outlined in the next subsections.

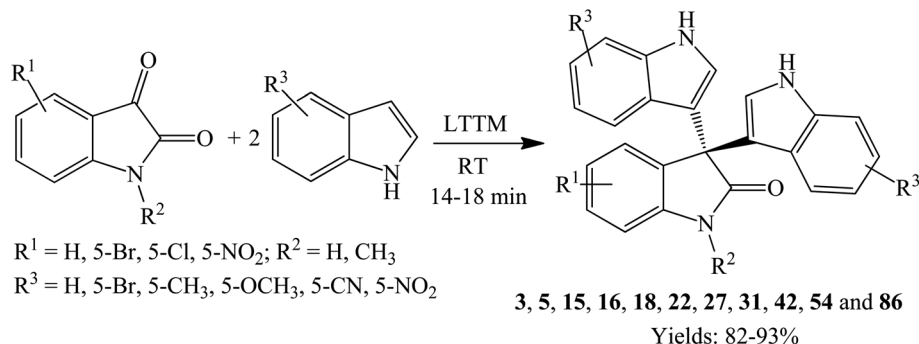
3.1.4.1 Iodine catalyzed reactions. Paira *et al.* (2009) reported that the reaction of isatins with indoles using 5 mol% I_2 in isopropanol at room temperature gave 80–95% yields of trisindolines **3**, **15–17**, **22** and **105** within 15–45 minutes (Scheme 17).¹³ Even electron-deficient indoles reacted very well under these conditions. However, 5-methoxyindole needed 3 h to give 80% yield of trisindoline **19**. Later, Reddy *et al.* (2012) disclosed that 10 mol% of I_2 catalyzed the same reaction in dichloromethane but required longer reaction times (12–22 h) and generally gave lower yields of trisindolines **3**, **15**, **17**, **22**, **30**, **31**, **42**, **54**, **55**, **86** and **106–110** (68–85% yields) especially when 5-chloroisatin was used (Scheme 17). The I_2 -catalyzed reaction showed a wide scope with electron-poor and electron-rich indoles.⁷ In comparison, the method by Paira *et al.* has advantages over Reddy *et al.*'s method in terms of higher yields and shorter reaction times (Scheme 17).

3.1.4.2 Bromine catalyzed reactions. Huang *et al.* (2015) investigated several bromine-based catalysts including Br_2 , *N*-bromosuccinimide (NBS), and 40% HBr in water. Br_2 (3 mol%) was the most active catalyst where trisindolines **3**, **6**, **15–17**, **22**, **31–34**, **42–44**, **86** and **111–119** were obtained in 69–95% yields within 0.2–24 h in acetonitrile at room temperature (Scheme 18).³⁶ Both EDGs and EWGs at any position on indoles gave trisindoline in excellent yields (>90%), except for 2- CO_2Et indole **119** and 5-nitroindole **112** which gave lower yields of 69%

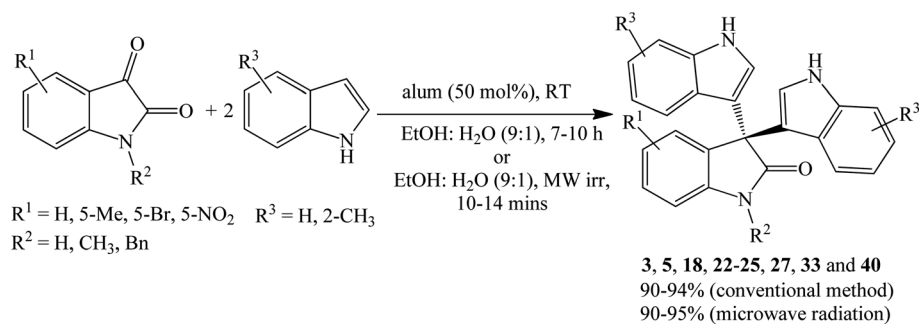


Scheme 22 Preparation of low transition temperature mixture (LTTM).





Scheme 23 Reaction of isatins and indoles using LTTM catalyst.

Scheme 24 KAISO_4 -catalyzed synthesis of 3,3-di(indolyl)oxindoles **3, 5, 18, 22-25, 27, 33** and **40**.

and 77%, respectively. *N*-Tosylindoles and *N*-pivalylindoles were unreactive under these conditions.

3.1.5 Ionic liquids and related catalysts. Ionic liquids have been used extensively as environmentally benign and green reaction solvents and catalysts in many organic transformations due to their special physicochemical characteristics.⁶⁶ Several ionic liquids successfully catalyzed the reaction between indoles and isatins to afford trisindolines.

3.1.5.1 *N,N,N,N*-Tetramethylguanidinium trifluoroacetate catalyzed reactions. The reaction using *N,N,N,N*-tetramethylguanidinium trifluoroacetate (TMGT) as a solvent and a catalyst gave symmetrical trisindolines **3, 22, 28, 29** and **68** in 86–93% yield at room temperature within a short reaction time of 1 h (Scheme 19).²⁷ Both isatins with EWGs and EDGs reacted smoothly. While *N*-methylindoles reacted smoothly, the scope of indoles with EWGs has not been evaluated under these conditions. Asymmetrical trisindolines **174, 175, 180** and **181** (87–91% yields) were also prepared under the same conditions by reacting an equimolar amount of 3-hydroxy-3-indolyl-2-indolones and other indoles (Scheme 19).

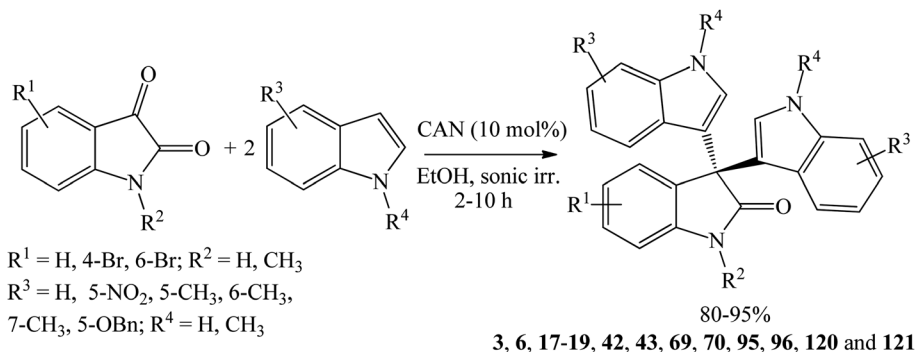
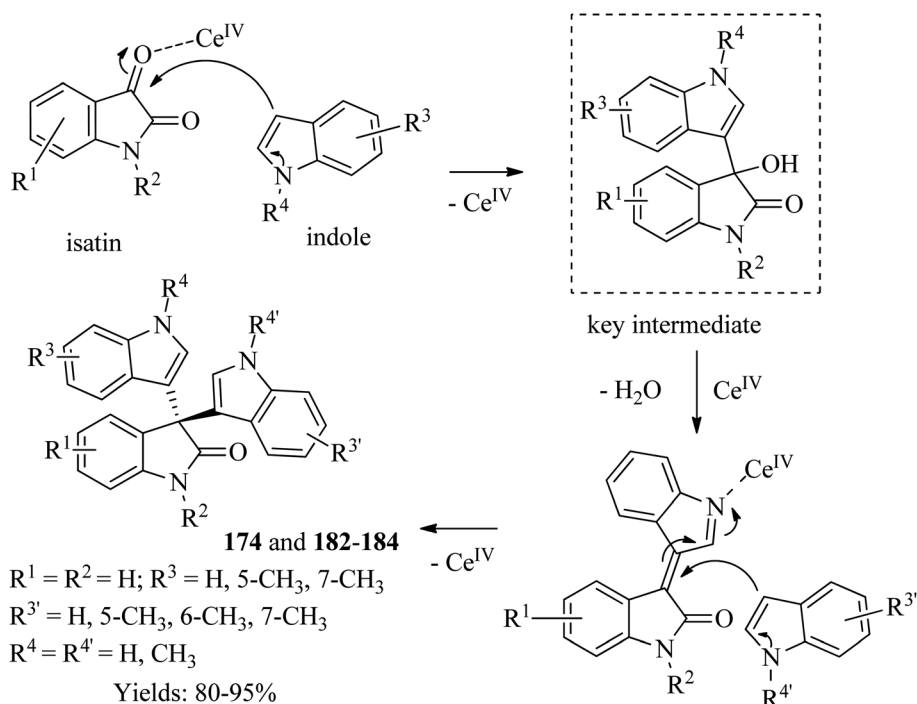
3.1.5.2 1-Butyl-3-methyl-imidazolium hydrogen sulphate catalyzed reactions. Likewise, the Brønsted acid ionic liquid 1-butyl-3-methyl-imidazolium hydrogen sulphate ($[(\text{CH}_2)_4\text{SO}_3\text{HMIM}][\text{HSO}_4]$) **201** (12 mol%) gave the trisindolines **3, 5, 18, 22, 23, 25, 27, 33** and **89** in 85–95% yields in water at room temperature within a shorter reaction time of 35–55 minutes (Scheme 20).⁶⁷ Here again, isatins with either EDGs or EWGs afforded excellent yields. Interestingly, *N*-methylisatin, *N*-

benzylisatin, and *N*-acetylisatin also gave the trisindolines **18, 25** and **89** in >90% yields. The catalyst was recycled and reused five times without significant loss in the yield of the trisindolines.

3.1.5.3 1,4-Diazabicyclo[2.2.2]octane hydrogen sulfate catalyzed reactions. Tong *et al.* (2016) evaluated ionic liquid $[\text{DABCO-H}][\text{HSO}_4]$ (1,4-diazabicyclo[2.2.2]octane hydrogen sulfate) as catalyst for indolylolation of isatin. The reaction furnished 95% yield of trisindoline **3** within 2 h. Substituted indoles or isatins has not been evaluated. Like other ionic liquid catalyst, $[\text{DABCO-H}][\text{HSO}_4]$ was also reused up to six times without significant loss in the catalytic activity.⁶⁸

3.1.5.4 1,4-Diazobicyclo[2.2.2]octanes catalyzed reactions. Gu *et al.* (2018) investigated several 1,4-diazobicyclo[2.2.2]octanes (Dabco) as ionic liquid-based catalysts including $[\text{Dabco-C}_4\text{H}_9]\text{Cl}$ **202**, $[\text{Dabco-C}_3\text{H}_6\text{OH}]\text{Cl}$ **203**, $[\text{Dabco-C}_2\text{H}_4\text{OH}]\text{Cl}$ **204**, and $[\text{Dabco-C}_2\text{H}_4\text{OH}][\text{FeCl}_4]$ **205**. After extensive screening, 10 mol% $[\text{Dabco-C}_2\text{H}_4\text{OH}][\text{FeCl}_4]$ **205** emerged as the best catalyst giving the trisindolines **3, 5, 15-17, 22, 27, 31, 33, 37** and **95** in 85–97% yields in ethanol at 50 °C within 1 h (Scheme 21).⁶⁹ The reaction showed a wide substrate scope where substituted indoles (halogen, methoxy) and isatins (halogen, nitro, methyl) gave the desired trisindolines in excellent yields. However, the reaction between 4-bromoisatin and indole required longer reaction time of 2 h to afford 81% yield of **95**. 5-Nitroisatin and 5-methylisatin reacted smoothly with indole and gave better yield (96% of **27** and 98% of **33**, respectively) than in the case when $[(\text{CH}_2)_4\text{SO}_3\text{HMIM}][\text{HSO}_4]$ was used.⁶⁷ The catalyst **205** was



Scheme 25 CAN-catalyzed synthesis of symmetrical trisindolines **3, 6, 17–19, 42, 43, 69, 70, 95, 96, 120 and 121**.

Scheme 26 Mechanism of CAN-catalyzed synthesis of trisindolines.

recycled and reused six times with a 10% overall decrease in the yield of **3**.⁶⁹

3.1.5.5 Prolinium triflate catalyzed reactions. Since several ionic liquids are air and moisture sensitive, their catalytic activity tends to decrease over time. Protic prolinium triflate (PrOTf), obtained by treating aqueous L-proline with triflic acid, was proposed as water-tolerant ionic liquid. Shiri *et al.* (2013) demonstrated the usefulness of 10 mol% prolinium triflate as a homogeneous catalyst in acetonitrile for the synthesis of trisindolines **3, 18** and **22** in 90%, 89% and 94% yields, respectively.⁷⁰ The reaction proceeded at room temperature but took 5 h for completion.

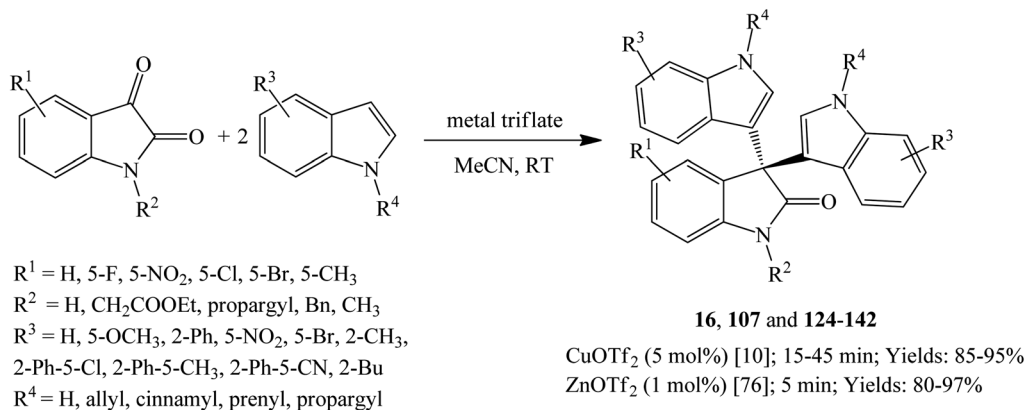
3.1.5.6 Low transition temperature mixtures (LTTMs) catalyzed reactions. Synthesis of trisindolines is also possible using low transition temperature mixtures (LTTMs), also called deep eutectic solvents (DES), comprising oxalic acid dihydrate and L-

proline as the solvent/catalyst (Scheme 22). The reaction tolerates wide substrate scope and produces trisindolines **3, 5, 15, 16, 18, 22, 27, 31, 42, 54** and **86** in 80–93% yields within 14–18 minutes, even in the presence of EWGs such as CN and NO₂ (Scheme 23).⁷¹ This is not surprising as the reactions between isatins and 5-cyanoindole or 5-nitroindole are often difficult and fail to proceed satisfactorily even with catalysts due to poor nucleophilicity.^{39,60,72} LTTM could be recycled and reused five cycles without significant loss of reactivity.⁷¹

3.1.6 Metallic species-based catalysts. Several metal-based catalysts were used to catalyze the reaction between isatins and indoles to trisindolines. The following sub-sections highlight some of the important reagents used.

3.1.6.1 Potassium aluminum sulfate (KAlSO₄) catalyzed reactions. Potassium aluminum sulfate (KAlSO₄), also known as alum, successfully afforded trisindolines **3, 5, 18, 22–25, 27, 33**





Scheme 27 Metal triflates-catalyzed synthesis of trisindolines 16, 107 and 124–142.

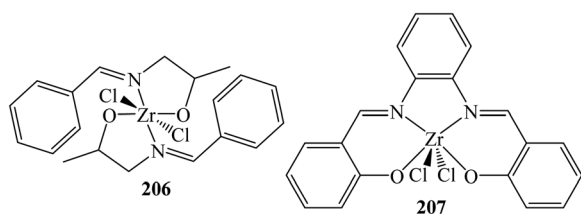


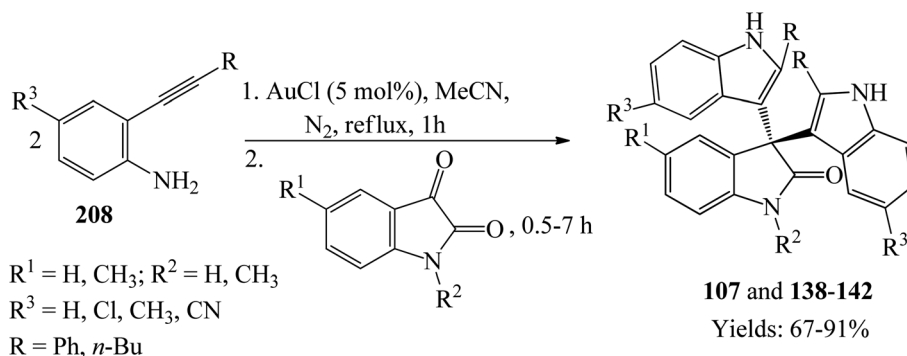
Fig. 4 Zirconium(IV) Schiff base catalysts.

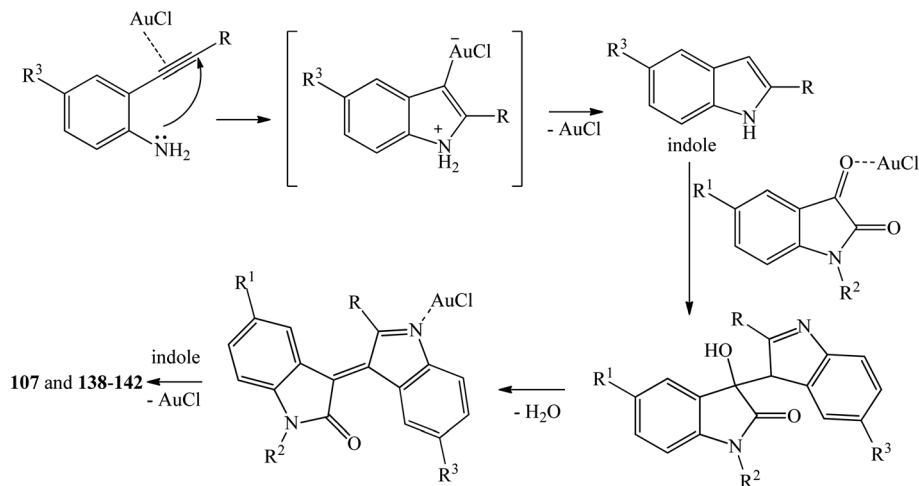
and **40** in excellent yields under conventional and microwave-assisted conditions (Scheme 24).⁷³ The yields of both methods were comparable at >90%. While the microwave reaction in 90% ethanol at 150 watt irradiation was completed within 15 minutes, the conventional reaction in ethanol/water (2 : 3, v/v) at room temperature needed 7 h. However, there were no significant differences in the yields of the products obtained from both methods. The catalyst showed a wide substrate scope where *N*-substituted isatins, and isatins with EWGs and EDGs on C-5 gave excellent yields. Likewise, 2-methylindoles gave excellent yields.

3.1.6.2 Ceric ammonium nitrate (NH₄)₂Ce(NO₃)₆ (CAN) catalyzed reactions. Ceric ammonium nitrate (NH₄)₂Ce(NO₃)₆ (CAN) is well-known catalyst in organic transformation for its mildness, ease of handling and efficiency. 10 mol% CAN catalyzed

the condensation of isatins with indoles under ultrasonic irradiation at room temperature and afforded symmetrical trisindolines **3, 6, 17–19, 42, 43, 69, 70, 95, 96, 120** and **121** in 80–95% yields within 2–10 h (Scheme 25).⁷⁴ Reactions of substituted isatins with unsubstituted indoles took 2–3 h while reactions of unsubstituted isatins with substituted indoles took longer time of 7–8 h. The challenging 5-nitroindole reacted smoothly with isatin to afford trisindoline **42** in 90% yield, but the 7-nitroindole isomer was unreactive. Nevertheless, indoles bearing methyl substituent at any position and isatins bearing bromo substituent at any position were all reactive and gave excellent yields.

The reaction mechanism involves activating the both the carbonyl group of isatin and the indole moiety by the Ce^{IV} atom of CAN (Scheme 26). Thus, in the first step, nucleophilic indole attacks the electrophilic carbonyl group of isatin to generate 3-hydroxy-3-(1*H*-indol-3-yl)indolin-2-one. The tertiary alcohol key intermediate undergoes dehydration to form the α,β -unsaturated imine-Ce^{IV} complex which upon attack by another indole at the β position gives the product and regenerate Ce^{IV}. Evidence for the intermediacy of the 3-hydroxy-3-(1*H*-indol-3-yl)indolin-2-one species had been provided by independently preparing several derivatives of the alcohol key intermediate and converting it to the 3-hydroxy-3-(1*H*-indol-3-yl)indolin-2-one products by the action of CAN. The alcohol intermediate

Scheme 28 AuCl-catalyzed synthesis of trisindolines 107 and 138–142 by cycloisomerization/bis-addition of *o*-ethynylanilines to isatins.



Scheme 29 Plausible reaction mechanism of trisindoline synthesis by cycloisomerization/bis-addition of *o*-ethynylanilines.

was exploited to prepare unsymmetrical trisindolines. Thus, by reacting an equimolar of 3-hydroxy-3-indolyl-2-indolones and indoles, unsymmetrical trisindolines **174** and **182–184** formed in 60–86% yields in 1–5 h (Scheme 26).

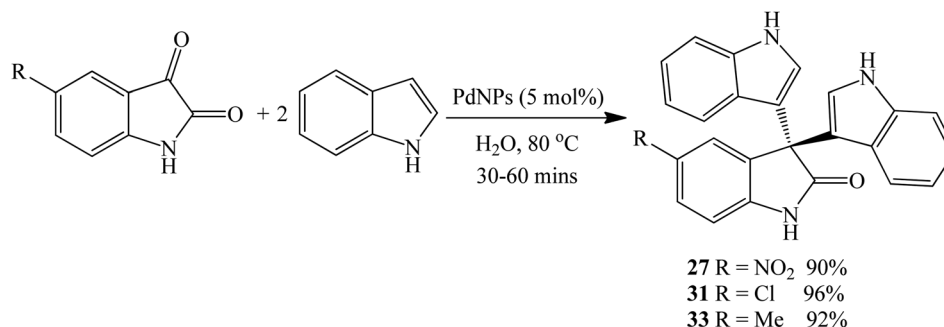
3.1.6.3 Metal triflates catalyzed reactions. Metal triflates such as CuOTf_2 , ZnOTf_2 and BiOTf_2 successfully catalyze the reaction between indoles and isatins to give trisindolines. For example, 2 mol% BiOTf_2 catalyzed the reaction between indoles and isatins at room temperature within 2.5–4 h to give 82–95% yields of trisindolines **3**, **15**, **16**, **22**, **119**, **122** and **123**. Both EWGs and EDGs attached at any position of the indole gave considerably good yields.⁷⁵ Praveen *et al.* examined CuOTf_2 (5 mol%)¹⁰ and ZnOTf_2 (1 mol%)⁷⁶ and found them to be suitable catalysts especially when the NH of the indoles and isatins was substituted with various groups (Scheme 27). Both catalysts worked well to give similar high yields but the reaction with ZnOTf_2 proceeded at a much faster rate within 5 minutes. Moreover, the use of ZnOTf_2 did not cause isomerization of the (*E*)-cinnamyl substituents.^{10,76} Metal triflates seem to be ideal catalysts when NH substituted trisindolines are required.

3.1.6.4 Zirconium catalyzed reactions. Several zirconium-based catalysts were also examined and found effective for the synthesis of trisindolines. 2 mol% zirconium(IV) Schiff base

complex **206** (Fig. 4) gave trisindolines **3** and **22** in 97% yields at 25–27 °C in ethanol within 10–20 minutes.⁷⁷

$\text{Zr}(\text{salphen})\text{Cl}_2$ **207** (1 mol%) afforded trisindoline **22** in 90% yield in less than a minute. The unsubstituted trisindoline **3** was obtained in 85% yield within 25 minutes.⁷⁸ Likewise, the simple zirconium(IV) chloride (ZrCl_4) (5 mol%) promoted the reaction to give trisindolines **3**, **5**, **15**, **17**, **18**, **21**, **22**, **24**, **25**, **27** and **143** in 80–98% yields at 50 °C within 9–120 minutes.⁷⁹ The order of the reactivity of *N*-alkylindole were *N*-methylindole > *N*-benzylindole > *N*-ethylindole. 5-Bromoindole also gave high yield. By adopting the same method, ZrCl_4 catalyst was also evaluated for the synthesis of unsymmetrical trisindoline by reacting 3-hydroxy-3-indolyl-2-indolones (1 eq.) with various indoles (1 eq.) to obtain the desired trisindolines **174**, **175**, **177–179** and **185–187** with excellent 93–97% yields within 10–30 minutes.⁷⁹

3.1.6.5 Gold chloride (AuCl) catalyzed reactions. Synthesis of trisindolines **107** and **138–142** proceeded in one-pot reaction by refluxing two equivalents of *o*-ethynylaniline **208** and one equivalent of the corresponding isatins in the presence of 5 mol% AuCl within 0.5–7 h to give 67–91% yield (Scheme 28).^{80,81} *o*-Ethynylanilines **208** having phenyl substituents showed shorter reaction time and higher yields in comparison with *n*-butyl-*o*-ethynylaniline. EDG (*e.g.* methyl) on C-4 of *o*-



Scheme 30 PdNPs-catalyzed synthesis of di(indolyl)indolin-2-ones **27**, **31** and **33**.



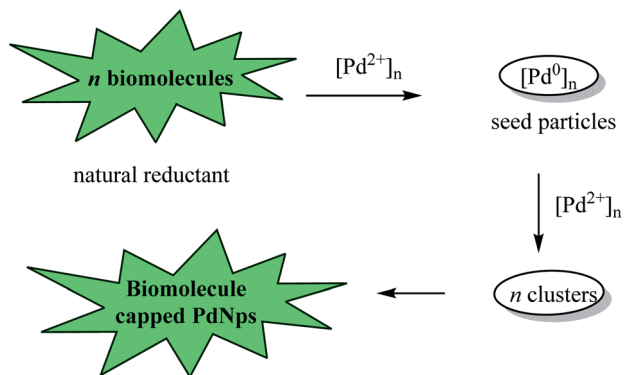


Fig. 5 Proposed mechanism for the synthesis of PdNPs.

ethynylaniline **208** exhibited better reactivity than EWG (*e.g.* cyano).

Praveen *et al.* (2009) proposed a mechanism of this one-pot reaction as shown in Scheme 29.^{80,81} π -coordination of the alkyne residue with Lewis acidic AuCl forms a π -complex intermediate which undergoes intramolecular cyclization and subsequent proto-deauration to generate an indole and give back the AuCl (Scheme 29). The eliminated Lewis acid activates the C3 carbonyl oxygen of isatin, followed by an electrophilic addition reaction at C3 of the indole. The resulting tertiary alcohol undergoes dehydration and coordination with AuCl to form α,β -unsaturated azafulvene derivative, which reacts with another molecule of indole to form the products.

3.1.6.6 Other metallic species catalyzed reactions. RuCl₃·*n*H₂O (5 mol%) gave 78–98% yields of trisindolines **3**, **15**, **17**, **22**, **54** in just 5–30 minutes in methanol at 50 °C. The electron deficient 5-cyanoindole gave 78% yield of **54**.⁸²

Iron salts are less toxic, cheap and environmentally friendly Lewis acid catalysts. Iron(III) chloride (FeCl₃) is a robust catalyst for many organic transformations. However, FeCl₃ is sensitive

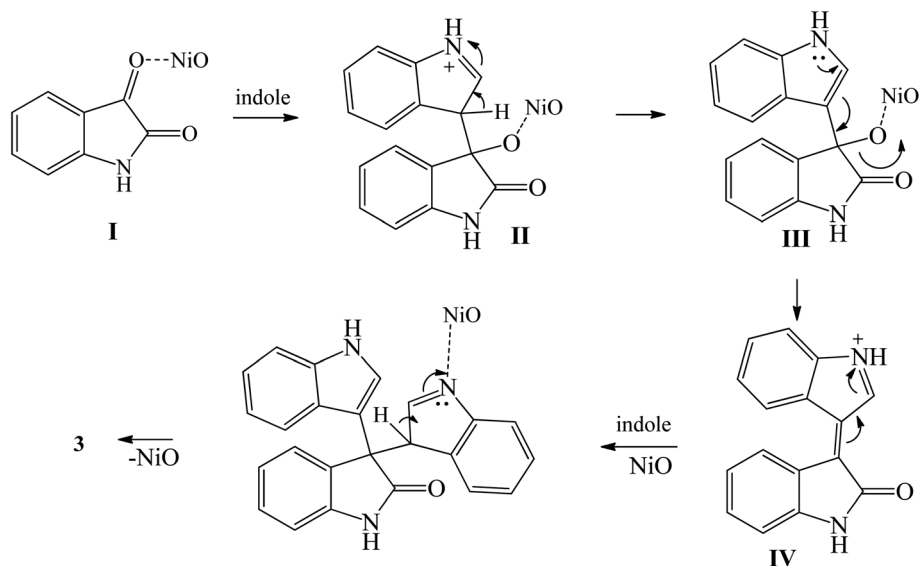
to air and moisture thus requiring special care. Several trisindolines **3**, **15–17**, **30**, **32**, **42**, **60**, **61**, **101**, **124** and **144–148** were obtained in 78–95% yields within 10–60 minutes by employing 5 mol% anhydrous FeCl₃. Both electron-rich and electron-poor indoles reacted smoothly. However, 5-fluoroisatin was less reactive than isatin.⁸

LiClO₄ (20 mol%) afforded 88–93% yields of trisindolines **3**, **17**, **22**, **28**, **31** and **57** when the reaction was performed in ethanol at 60 °C.²⁶

3.1.7 Nanoparticle metal based catalysts

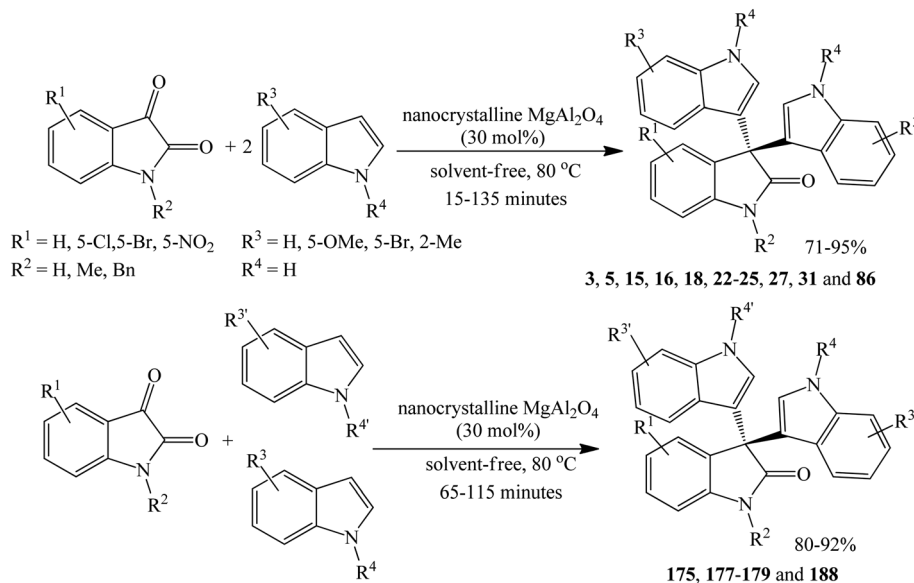
3.1.7.1 Palladium nanoparticle (PdNPs) catalyzed reactions. Nanoparticle metal catalysts are attractive reagents for organic reactions because of their ability to promote faster reaction rates, enhance catalytic activity, recyclability and increase chemical yields. With their nano-sized particles, they are characterized by voluminous surface area.⁸³ Edayadulla *et al.* (2015) evaluated the palladium nanoparticles (PdNPs) for the multi-component synthesis of di(indolyl)indolin-2-ones. The PdNPs (20–30 nm particle size) were obtained by the reduction of palladium chloride (PdCl₂) using *Artemisia annua* leaf extracts as natural reductant. Thus, indole **1** was reacted with 5-substituted isatins (5-methylisatin, 5-chloroisatin and 5-nitroisatin) in water at 80 °C for 30–60 minutes to afford the corresponding products **33**, **31** and **27** in 92%, 96% and 90% yields, respectively (Scheme 30). Optimal chemical yields were obtained in the presence of 5 mol% PdNPs and the catalyst was effective with both, electron-rich and electron-deficient isatin derivatives.⁸⁴ A prominent feature associated with this methodology involves a simple filtration workup procedure where the catalyst is recovered and recycled up to 5 times and the product is isolated without the need for further purification by column chromatography.

The mechanism for the generation of biomolecule capped Pd nanoparticles is shown in Fig. 5. The biomolecules in the aqueous *Artemisia annua* leaf extract coordinate with the Pd²⁺



Scheme 31 Proposed reaction mechanism for the synthesis of trisindoline **3** induced by NiO Nanoparticles.





Scheme 32 Preparation of trisindolines catalyzed by nanocrystalline MgAl_2O_4 .

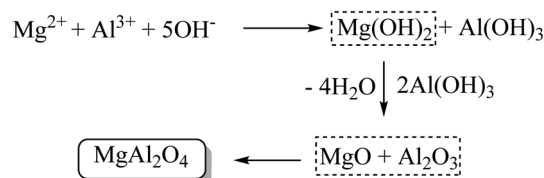
ions to produce metal complexes, which are subsequently reduced to seed Pd^0 particles. The seed particles agglomerate to clusters, which serve as nucleation centres where remaining metal ions get reduced catalytically (Fig. 5).

3.1.7.2 Nickel oxide nanoparticle catalyzed reactions. Nasseri *et al.* (2015) used nickel oxide nanoparticle (average particle size diameter of 11 nm) to catalyze the synthesis of 3,3-diindolylloxindoles by the condensation of indoles with isatin derivatives in water at 70 °C for 0.5–1.5 h.⁸⁵ The reaction was best catalyzed using 0.004 g NiO for every mmol of isatin. NiO nanoparticles were prepared *via* reaction of nickel(II) nitrate hexahydrate with urea in water under heating conditions (115 °C, 1.5 h), followed by calcination at 400 °C for 1 h. The use of nano NiO was advantageous in improving the yield of **1** to 98%, compared to bare NiO (45% yield) and various other catalytic systems (10–68% yield). Furthermore, the NiO catalyst could be recycled at least five times. The optimized reaction conditions gave fair to excellent yields of 3,3-diindolylloxindoles **3, 5, 14, 18, 22, 24, 25, 27, 85, 102** and **149–152** (60–98%). Isatin derivatives bearing electron withdrawing group on C-5 showed higher yield and shorter reaction time than those with EDG at the same position. *N*-Benzylisatin was less reactive, especially upon reacting with unsubstituted indole. The proposed mechanism for the synthesis of **3** from isatin and indole catalyzed by NiO NPs is shown in Scheme 31. Initially, the activated isatin **I** react with indole **1** to produce intermediate **II**. This intermediate undergoes elimination reaction *via* **III** to give intermediate **IV**, which upon addition reaction with the second indole **1** generates trisindoline **3** (Scheme 31).⁸⁵

3.1.7.3 Titanium dioxide nanoparticle catalyzed reactions. Titanium dioxide nanoparticles (TiO_2 NPs) were also evaluated for synthesis of trisindoline. Dwivedi *et al.* (2018) achieved the synthesis of trisindolines **3, 5, 15, 25, 27, 31, 32, 37, 86, 99, 100, 101, 103, 153** and **154** by reacting a mixture of indoles and isatins using 10 mol% nano TiO_2 (40–70 nm) under ambient

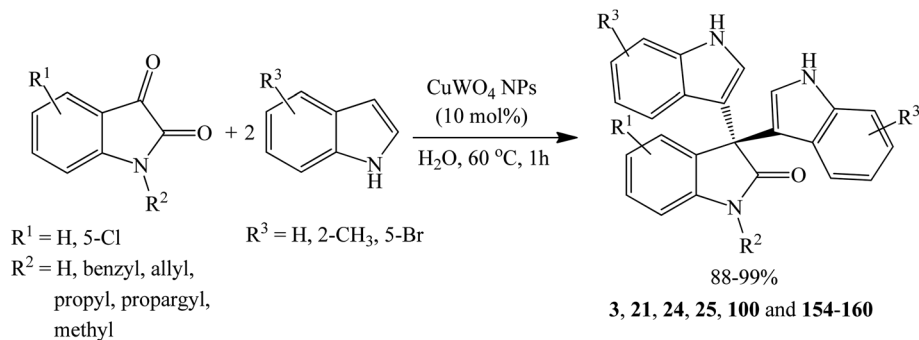
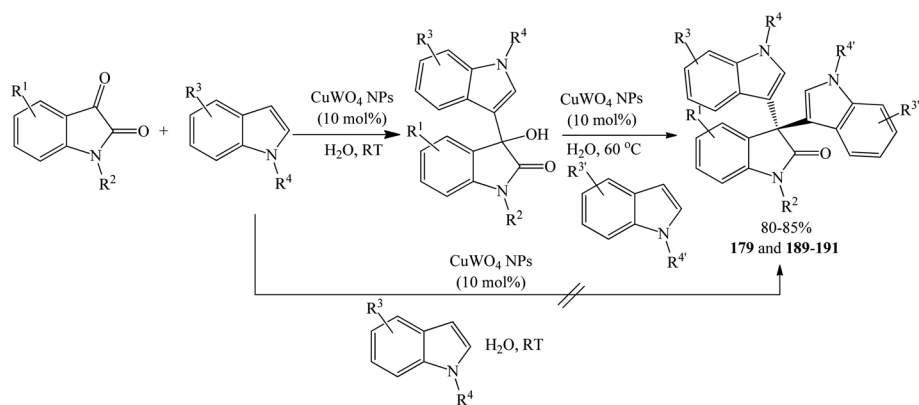
conditions. While quantitative yields for a model reaction was obtained in water as solvent, organic solvents performed relatively poorly, producing less than 80% yields after 1.5 h. The optimized conditions tolerated a wide scope of substrates with yields ranging from 95–99%. All isatins with EDG or EWG substituents on C-5 were reactive as well as those containing halogens on C-5 of the indole unit. Allyl or benzyl substituents attached to *N*-isatin barely affected the yields.⁷² It is noted though, 5-cyano, *N*-methyl, and azo indoles failed to generate the desired products.

3.1.7.4 Magnesium aluminate (MgAl_2O_4) nanoparticle catalyzed reactions. Nikoofar *et al.* (2019) utilized nanocrystalline MgAl_2O_4 (40–50 nm particle diameter) as a recyclable catalyst for the synthesis of symmetrical trisindolines **3, 5, 15, 16, 18, 22–25, 27, 31** and **86** as well as unsymmetrical trisindolines **175, 177–179** and **188** yielding the corresponding products in 71–95% and 80–92% yields, respectively (Scheme 32). The catalyst may be prepared on a gram scale, although the lengthy procedure uses concentrated ammonia. The use of various organic solvents or water produced 56–64% yields with no prospect for yield improvement even under reflux conditions. However, the best yields were realized with 30 mol% catalyst under solvent-free conditions at 80 °C for 15–130 minutes and only 21% yield of **3** was obtained in the absence of any catalyst. While preparing 3-hydroxy-3-indolyl-indolin-2-ones involved using



Scheme 33 Preparation of MgAl_2O_4 catalyst.

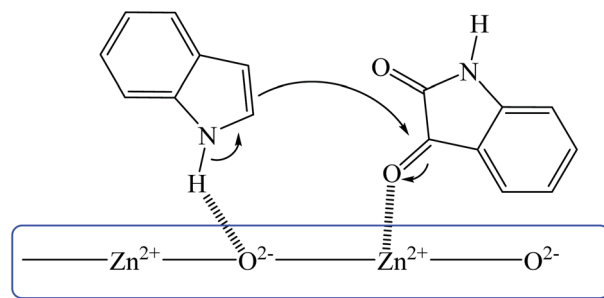


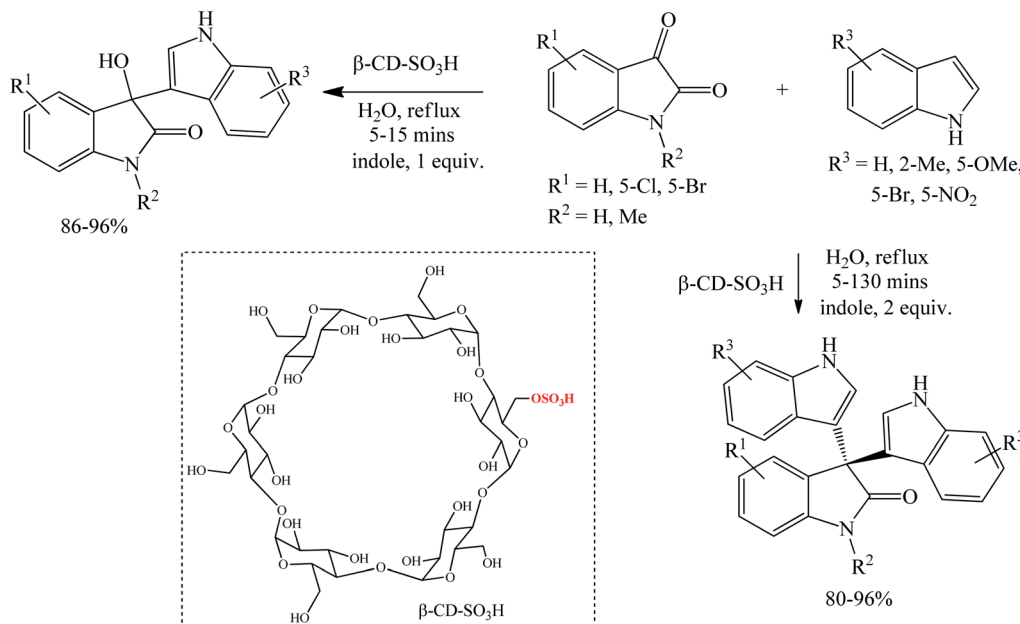
Scheme 34 CuWO_4 NPs-catalyzed synthesis of symmetrical di(indolyl)indolin-2-ones.Scheme 35 CuWO_4 NPs-catalyzed synthesis of unsymmetrical di(indolyl)indolin-2-ones.

equimolar amounts of indoles and isatins substrates, unsymmetrical products **175**, **177–179** and **188** were simply prepared by using a 1 : 1 equimolar mixture of two different indoles with the appropriate matching total molar amount of isatins (Scheme 32). It is noteworthy that the preceding one-step, three-component condensation for the preparation of unsymmetrical oxindoles derivatives from indoles and isatins has rarely been reported in the literature and no by-products of symmetrical oxindoles were observed. Various indoles and isatins with EDGs and EWGs underwent successful condensation. The substituent on isatin (H, CH_3 , Bn) had no noticeable effect on the yield or regiochemistry. Interestingly though, blocking the C-3 position forced the condensation reaction to occur at the less reactive C-2 position.⁸⁶ The preparation of MgAl_2O_4 catalyst is shown in Scheme 33.

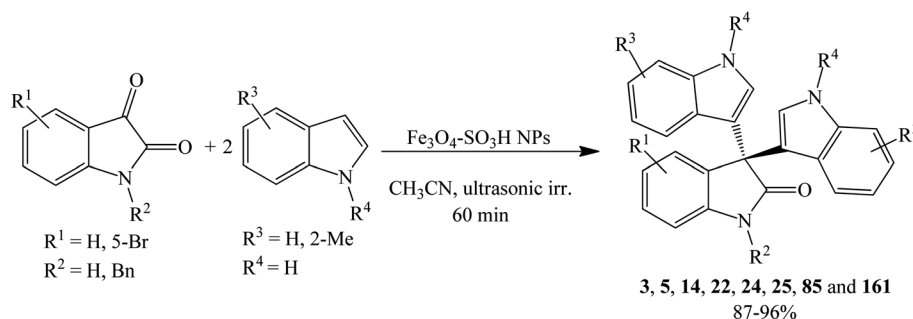
3.1.7.5 Cupric tungstate (CuWO_4) nanoparticle catalyzed reactions. Paplal *et al.* (2020) synthesized a series of symmetrical trisindolines **3**, **21**, **24**, **25**, **100** and **154–160** by treating isatins and indoles with CuWO_4 nanoparticle catalyst (10 mol%) in water at 60 °C for approximately 1 h (Scheme 34). Reaction temperature was critical to the preparation of the trisindolines as room-temperature reactions led to the formation of mono-substituted indolinones (3-hydroxy-3-(indol-3-yl)indolin-2-ones) as sole products. However, this notable feature was exploited to prepare unsymmetrical 3,3'-bis-indolyl-2-oxindoles in good yields (80–85%) (Scheme 35). As such, running

controlled experiments with various starting indoles to produce mono-substituted products at room temperature, followed by further treatment with another indole at 60 °C gave unsymmetrical 3,3'-bis-indolyl-2-oxindoles **179** and **189–191** (80–85% yields). In this study, the reactivity of *N*-substituted isatin, 5-bromo, and 2-methylindole was explored. Trisindolines **3**, **21**, **24**, **25**, **100** and **154–160** were obtained in excellent yields (88–99%), whereas trisindoline **3** ($R^1\text{--}R^3=\text{H}$) was isolated in highest yield (99%) (Scheme 34). The substituents on the *N* atom of isatin ring (*N*-benzyl, *N*-allyl, *N*-propyl, *N*-propargyl, *N*-methyl) and the bromo group attached to C-5 position of indole did not impact the reactivity of substrates or yield of the products. The catalyst was recycled up to 6 cycles without loss of the catalytic

Fig. 6 Interaction of ZnO catalyst isatin **2** with indole **1**.



Scheme 36 Sulfonated β -cyclodextrin-catalyzed synthesis of 3-hydroxy-3-indolyindoline-2-one and trisindolines.



Scheme 37 $\text{Fe}_3\text{O}_4\text{-SO}_3\text{H}$ NPs-catalyzed synthesis of trisindolines **3**, **5**, **14**, **22**, **24**, **25**, **85** and **161**.

activity. XRD analysis of the recovered CuWO_4 after six cycles revealed no change in its morphology suggesting potential for re-use.⁸⁷

3.1.7.6 Zinc oxide (ZnO) nanoparticle catalyzed reactions. Nano zinc oxide (ZnO) has been exploited as catalyst for many organic transformations. Since the surface of nanostructured-ZnO consists of both Lewis acid (Zn^{2+}) and Lewis base (O^{2-}) sites, it is suitable for catalyzing organic reactions (Fig. 6). Recently, Zn^{2+} located on the surface of ZnO disc has been shown to play important role in activating the C-3 carbonyl group of isatin to induce 3-indoylation. To test the importance of surface catalyst, ZnO was covered with hydrophobic stearic acid and the results showed that the coated ZnO-catalyzed reaction did not generate the desired product. Nanodisc ZnO was utilized to prepare a series of trisindolines under solvent-free system at 100 °C within 2 h to produce the desired trisindolines **3**, **16–18** and **54** in 82–88% yields. Interestingly, the reaction of isatin with deactivated indole (bearing cyano group) displayed higher 86% yield compared to the reaction with

activated indole (bearing methoxy substituent). *N*-Methylindole or *N*-methylisatin gave 83% and 88% yields, respectively.⁸⁸

3.1.8 Supramolecular catalysts

3.1.8.1 Sulfonated β -cyclodextrin ($\beta\text{-CD-SO}_3\text{H}$) catalyzed reactions. Supramolecular catalysts are known to accelerate reactions by bringing the two reactants near one another and by reducing activation energy and stabilizing the transition state of the reaction. Tayade *et al.* (2015) synthesized trisindoline **3**, **5**, **15**, **16**, **18**, **20–22**, **31**, **42**, **62**, **86**, **88**, **111** and **112** by refluxing isatins and indoles in water catalyzed by sulfonated β -cyclodextrin ($\beta\text{-CD-SO}_3\text{H}$) for 5–130 minutes (80–96%) (Scheme 36). The yields were modest to excellent where various substrates reacted completely within 5–45 minutes, except for sluggish 5-nitroindole which required 130 minutes for complete conversion. Indole substrate with electron donating group had slightly better yield than that with halogen group (EWD). The presence of 5-methoxy group on indole, a strong electron donating group, accelerated the reaction (complete conversion within 10 minutes) and had an opposite effect to the 5-nitro group. 5-Bromoisatin was comparably less reactive than 5-chloroisatin,



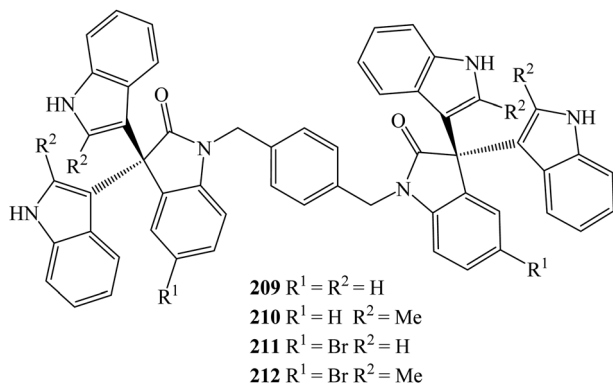


Fig. 7 Bis-[3,3-di(indolyl)indolin-2-ones] **209–212**.

conceivably due to the steric factors associated with the bulky size of the bromo group. Sulfonated β -cyclodextrin displays better solubility in water than β -cyclodextrin owing to the polar sulfonate and hence shows enhanced reactivity profile. β -CD-SO₃H also successfully catalyzed the synthesis of 3-hydroxy-3-indolyindoline-2-ones in water at reflux temperature (86–96% yield). These intermediate products are useful for the synthesis of unsymmetrical trisindolines.⁸⁹

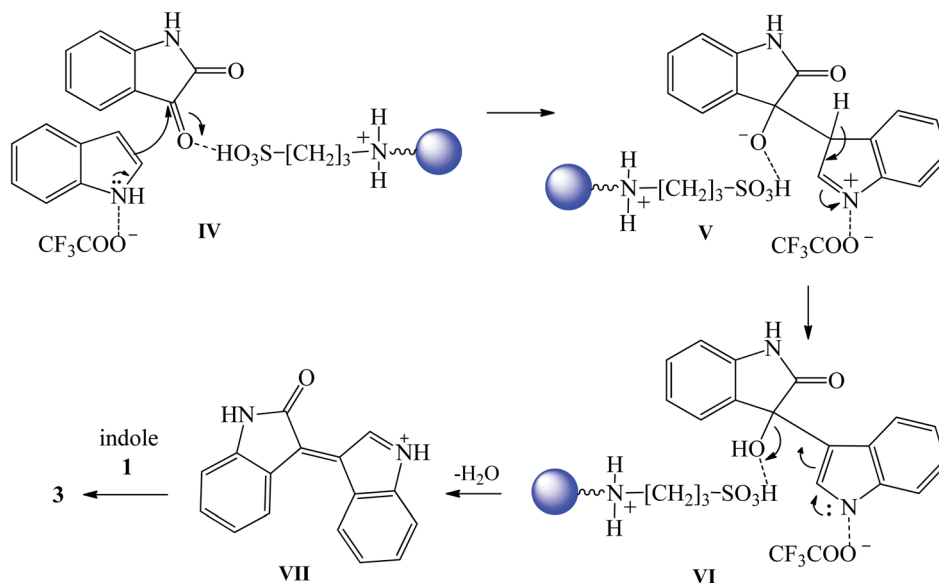
3.1.8.2 β -Cyclodextrin catalyzed reactions. β -Cyclodextrin catalyzed the condensation reaction between isatin and indole in aqueous solvent at 80 °C within 20–100 minutes giving the trisindolines **3**, **15–17**, **22** and **105** in 75–98% yields. Reactions using 2-methylindoles gave 96% yield of trisindoline **22** within a shorter reaction time of 20 minutes while 2-carboxylindoles provided the lowest 75% yield of **105** and required the longest reaction time of 100 minutes. Unsubstituted trisindoline **3** gave the highest isolated yield with fastest reaction time. Interestingly, indoles bearing EDGs such as methoxy or methyl, and EWG such as bromo gave similar yields. The catalyst was

recycled five times without loss of catalytic ability.⁹⁰ The interaction between β -cyclodextrin and the starting materials gave β -cyclodextrin-substrate complexes through non-covalent bond interactions.^{90,91}

3.1.8.3 Sulfonated polyethylene glycol (PEG-OSO₃H) catalyzed reactions. Sulfonated polyethylene glycol (PEG-OSO₃H) (10 mol%) catalyzed synthesis of trisindolines **3**, **5**, **15**, **18**, **21–25**, **27**, **31**, **84–88**, **99** and **100** in acetonitrile at room temperature for 1.5–5 h, affording 65–98% yields. *N*-Methyl- or *N*-benzylisatins gave lower yields compared to others, especially when treated with 5-bromoindole. Consistent with what has been observed with other catalysts, isatin bearing a 5-nitro group required the longest reaction time and afforded the highest yields. PEG-OSO₃H catalyst could be re-obtained and re-used with no significant loss of catalytic activity up to five cycles.⁹²

3.1.9 Magnetic nanoparticle-based catalysts. Catalysis using magnetic materials has recently attracted intensive research as it offers facile separation of catalysts that exhibit magnetic properties by using external magnet, avoiding filtration, centrifugation, or other techniques to separate the reusable catalyst.⁹³ As such, nano magnetic sulfonic acid-supported Fe₃O₄ catalyzed the synthesis of 3,3-di(3-indolyl)-2-indolone **3** in ethanol under reflux for 3 h, providing 92% yield. The high catalytic activity of Fe₃O₄-OSO₃H might presumably be attributed to the combined synergetic action of Fe₃O₄ as a Lewis acid and sulfonic acid as Brønsted acid.⁹⁴

Karimi *et al.* (2015) also employed nanoparticles of magnetically separable sulfonic acid-embedded Fe₃O₄ (Fe₃O₄-SO₃H) to prepare a series of trisindolines **3**, **5**, **14**, **22**, **24**, **25**, **85** and **161**. The magnetic nanoparticles were accessible *via* a one-step procedure by directly reacting chlorosulfonic acid with Fe₃O₄. Mono and bis-[3,3-di(indolyl)indolin-2-ones] **3**, **5**, **14**, **22**, **24**, **25**, **85** and **161** (Scheme 37) and **209–212** were obtained under ultrasonic irradiation in acetonitrile for an hour in 87–96% yields (Fig. 7). The optimum amount of catalyst was 0.15 g



Scheme 38 The proposed mechanism of trisindoline **3** synthesis catalyzed by DABCO-3@FSMNPs.



mol⁻¹ isatin⁹⁵. 5-Bromo substituted isatin improved the yield, while 2-methyl on indole and/or benzyl on *N* atom of isatin reacted smoothly to produce good yields. Generally, compound **3** was obtained in 93% yield within lower reaction time compared to other methods⁹⁴ possibly because ultrasonic irradiation promoted faster and higher yielding reactions.⁹⁵

Another fabricated supported-Fe₃O₄@SiO₂ MNPs, a carboxylic acid-embedded Fe₃O₄@SiO₂ (Fe₃O₄@SiO₂@COOH), gave trisindolines **3**, **5**, **18**, **22**, **23**, **85**, **162** and **163** in 60–98% yields at 80 °C in aqueous solvent within 30–60 minutes. As many reports utilizing ferrite-silica (Fe₃O₄) based catalysts, 5-bromoisatin was excellent electrophile. Furthermore, it produced the highest yield when coupled with the highly nucleophilic 2-methylindole. EDG (methyl, morpholinomethyl) attached on *N*-isatin reduced the reactivity. The catalyst possesses high density of acidic sites and magnetic behaviour.⁹⁶

Fe₃O₄@SiO₂@Bi₂O₃ MNPs was used to prepare trisindolines **3**, **5**, **14**, **18**, **22–25**, **85**, **151** and **164** in 65–97% yields within 25–90 minutes. Methyl or benzyl attached to *N*-isatin render it less electrophilic, promoting slower reactivity and requiring prolonged reaction time to improve the yield. However, the presence of 5-bromo (as electron withdrawing group) on isatin ring led to a remarkably improved yield.⁹⁷

Gupta *et al.* (2019) fabricated silica-coated magnetite-nanoparticle anchored DABCO-derived and acid-functionalized ionic liquid (DABCO-3@FSMNPs) and applied it as recyclable nanocatalyst to prepare a library of trisindolines. The reactions were carried out in H₂O at 90 °C for 2 h to afford products **3**, **5**, **15**, **16**, **31**, **32**, **42**, **60**, **62**, **86**, **101** and **111** in 85–98% yields. Both electron-deficient and electron-rich indoles reacted well with either isatin or halo-substituted isatin. However, 2-methylindole was inert and did not afford any products.⁹⁸ The three-component reaction was found to proceed exclusively *via* H-bonding intermolecular interactions between isatin and indole substrates and the nanocatalyst. The catalyst could be recycled easily without any significant loss in catalytic activity.

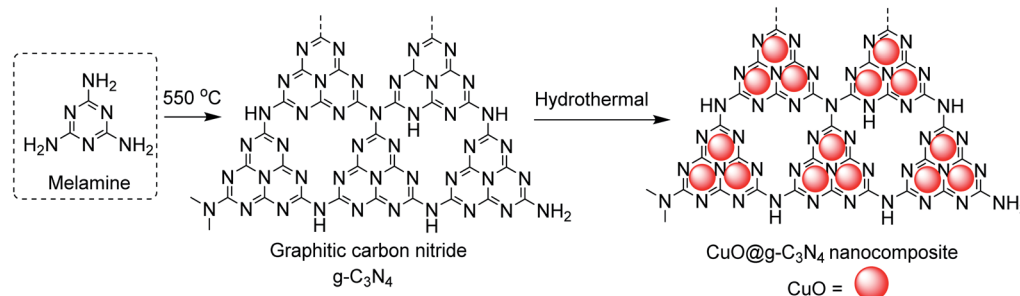
The plausible pathway of trisindoline formation catalyzed by DABCO-3@FSMNPs is illustrated in Scheme 38. Hydrogen bonds are formed by the interaction of both cationic and anionic species of the ionic liquid catalyst with the reactants (indole and isatin) (**IV**). The carbonyl (C-3) of isatin **2** is activated by the proton-donor of the sulfonic acid, making it more

electrophilic. At same time, indole **1** is more nucleophilic due to the participation of trifluoroacetate as proton acceptor from the N-H of indole **1**. Hence, it allows the nucleophilic attack of C-3 indole **1** onto activated carbon of C-3 isatin **2** to render **V**. Intermediate **VII**, generated by the dehydration of **V** to the corresponding α,β -unsaturated iminium ion, is attacked by a second indole **1** molecule to produce trisindoline **3**.

3.1.10 Nanocomposite materials based catalysts

3.1.10.1 TiO₂-impregnated SiO₂ catalyzed reactions. Nanocomposite materials possess large surface areas and unique properties when compared to free nanomaterials. These materials consist of a matrix (graphene or graphene-like) and fillers, which can be metals, metal oxides, *etc*.⁹⁹ Haghghi and Nikoofar (2014) employed nanocomposite TiO₂-impregnated SiO₂ as a Lewis acid to catalyze the synthesis of a series of symmetrical trisindolines under neat conditions at 50 °C for 15–120 minutes, producing the corresponding products **3**, **5**, **15**, **17**, **18**, **22–25**, **27** and **28** in 72–93% yields. The catalyst is prepared by mixing column chromatography grade SiO₂ 60 in CHCl₃ with nano TiO₂ and stirring at room temperature for 1.5 h. Simple evaporation of the solvent at room temperature affords 50% (w/w) nano TiO₂/SiO₂ as white solid. The reaction of 2-methylindole and unsubstituted isatin exhibited the fastest reaction time and the highest yield (93%). Bromo substituent attached to C-5 of either isatin or indole gave longer reaction and the lowest product yield. *N*-benzylated and 5-Br, 5-NO₂-isatins were less reactive and required longer reaction times for complete conversion. Under similar reaction conditions, the catalytic activity of non-supported free nano TiO₂ (70% yield) or SiO₂ (60% yield) did not afford better yields of **3** in comparison with nano TiO₂@SiO₂ (85% yield).¹⁰⁰

3.1.10.2 Al₂O₃/V₂O₅ nanocomposite catalyzed reactions. Hasani *et al.* (2017) used Al₂O₃/V₂O₅ nanocomposite as a heterogeneous catalyst for trisindoline synthesis at 70 °C in water for 10–30 minutes to form trisindolines **3**, **5**, **18**, **22**, **23**, **85**, **162** and **163** in 60–98% yields. The catalyst was reusable but diminished activity was observed following multiple cycles. Reactions of substituted isatin with 2-methylindole led to decreased yields and long reaction times, but the reaction of unsubstituted isatin with 2-methylindole behaved oppositely, generating the highest observed yield of product **22**.¹⁰¹ Further, 2-methylindole was most reactive compared to other substituted indoles with ferrite silica Fe₃O₄@SiO₂@COOH nanoparticles catalyst.⁹⁶



Scheme 39 The synthesis of CuO@g-C₃N₄ nanocomposites.



Table 4 Reaction of isatins and indoles using g-C₃N₄-based catalysts

Trisindolines	SiO ₂ @g-C ₃ N ₄ (ref. 102)		CuO@g-C ₃ N ₄ (ref. 103)		Fe(III)@g-C ₃ N ₄ (ref. 99)	
	Time (min)	Yields (%)	Time (min)	Yields (%)	Time (min)	Yields (%)
3	45	95	60	95	30	96
15	75	83	75	80	40	80
17	35	95	55	95	27	96
18	60	90	75	89	50	90
21	60	83	75	81	50	80
23	55	91	75	90	50	87
24	55	87	75	86	50	83
25	60	81	75	80	50	82
27	70	91	70	95	55	95
29	50	85	60	87	40	90
31	35	93	55	94	30	96
84	60	93	65	95	40	95
86	75	82	75	88	40	85
87	30	95	45	93	30	93
88	75	83	75	83	55	85
99	75	91	75	94	50	92
100	60	82	75	80	50	79
165	45	95	45	95	30	95

3.1.10.3 SiO₂@g-C₃N₄ nanocomposite catalyzed reactions. Allahresani *et al.* (2017) utilized SiO₂@g-C₃N₄ nanocomposite as heterogeneous and recyclable catalyst for Friedel–Crafts reaction between indoles and isatins. The nanocomposite was prepared from the reaction of graphitic carbon nitride nanosheets produced from melamine (g-C₃N₄) and silicon dioxide nanoparticles by heating in a furnace at 550 °C. The synthesized trisindolines **3**, **15**, **17**, **18**, **21**, **23–25**, **27**, **29**, **31**, **84**, **86–88**, **99**, **100** and **165** were produced in high to excellent yields (81–95%) within 30–75 minutes (Table 4). Indoles with electron-releasing substituents at C-2 and isatins bearing EWG at C-5 position reacted synergistically to give the best yields. Although nano-SiO₂ (20 mg) catalyzed the synthesis of trisindolines more efficiently than SiO₂@g-C₃N₄ (60 mg), a tedious separation of nano-SiO₂ from the reaction media as well as agglomeration of nano-SiO₂ rendered it impractical. The remarkable catalytic behavior of SiO₂@g-C₃N₄ nanocomposite has been attributed to the uniformly distributed SiO₂ nanoparticles where size distribution centered at a value of 17.6 nm.¹⁰²

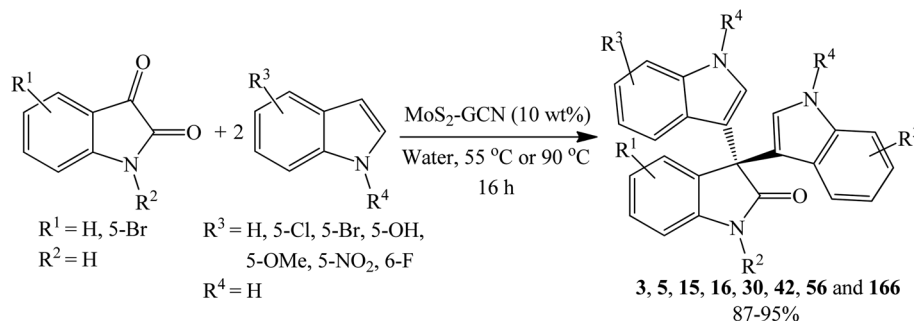
3.1.10.4 CuO@g-C₃N₄ nanocomposite catalyzed reactions. Another doped graphitic carbon nitride catalyst, nanocomposite CuO@g-C₃N₄, was also investigated and applied for trisindoline synthesis by Allahresani (2017) (Scheme 39). The reactions were conducted at room temperature in water to produce the targeted trisindolines **3**, **15**, **17**, **18**, **21**, **23–25**, **27**, **29**, **31**, **84**, **86–88**, **99**, **100** and **165** within 45–75 minutes with yields ranging from 80–95% (Table 4).¹⁰³ The best yields were obtained with 85 mg of the catalyst per mole of isatin. The synthesis of the same trisindolines required longer time than those prepared using SiO₂@g-C₃N₄. Indole bearing electron withdrawing group at C-5 position led to longer reaction time and lower yields (82–83%). The catalyst was however able to match the optimal yields obtained in ref. 102 with isatin bearing EWG on C-5 and indoles having EDG on the C-1 position. The catalytic activity of CuO@g-C₃N₄ has been attributed to the

uniformly distributed CuO nanoparticles impregnated into the pi-conjugated graphitic carbon nitride nanosheets assist in C–C bond formation. One noted disadvantage involves the aggregation of the nanoparticles as observed in the second reuse of SiO₂@g-C₃N₄ catalyst.¹⁰³

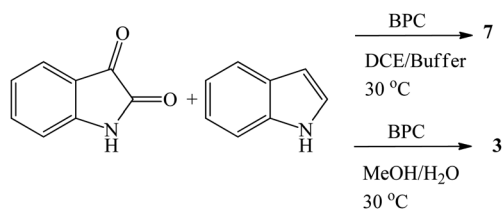
3.1.10.5 Fe(III)@g-C₃N₄ nanocomposite catalyzed reactions. Recyclable Fe(III)@g-C₃N₄ is another nanocomposite catalyst Allahresani and co-workers (2018) studied for oxindoles synthesis (Table 4). Initially, g-C₃N₄ nanosheets were prepared by the oxidation of melamine powder in a heated furnace (550 °C) over 4 h. The catalyst is then prepared by stirring a mixture of FeCl₃ and g-C₃N₄ nanosheets in EtOH at 40 °C for further 6 h. The most effective microscopic and spectroscopic characterization techniques for such nanocomposites include XRD and TEM. For instance, XRD analysis for pure g-C₃N₄ established the hexagonal phase of the nanosheets by two observed distinctive peaks at 13.1 and 27.4°. The signals indicate interlayer stacking and repeated units. Absence of such peaks for Fe(III)@g-C₃N₄ suggests a breakdown of the nanosheet hexagonal phase, interlayer stacking, and planar repeated units due to the incorporation of FeCl₃. On the other hand, while the TEM image of pure g-C₃N₄ shows the expected agglomerated nanosheet, that of Fe(III)@g-C₃N₄ clearly shows the presence of FeCl₃ throughout the surface of the nanocomposite sheets. The condensation of indoles and isatin molecules to give trisindolines **3**, **15**, **17**, **18**, **21**, **23–25**, **27**, **29**, **31**, **84**, **86–88**, **99**, **100** and **165** in 79–96% yields proceeded under reflux in water using 35 mol% Fe(III)@g-C₃N₄ catalyst, and it required shorter reaction time (27–55 minutes). Trisindoline **17** was obtained in 96% yield in just 27 minutes. It is noted that among a dozen other g-C₃N₄-based catalysts, Fe(III)@g-C₃N₄ furnished the highest yield of trisindolines.⁹⁹

In summary, the presence of g-C₃N₄ support limits metal and metal oxide nanoparticles from accumulation to increase the activity and selectivity of the catalyst. Metal or metal oxide





Scheme 40 MoS_2 -GCN-catalyzed synthesis of trisindolines **3**, **5**, **15**, **16**, **30**, **42**, **56** and **166**.



Scheme 41 BPC-catalyzed synthesis of trisindoline **3** and 3-hydroxy-3-(indol-3-yl)-2-indolone **7**.

nanoparticles exhibits a problem in its aggregation, and this problem can be overcome by doping with $g\text{-C}_3\text{N}_4$.¹⁰³ Among above $g\text{-C}_3\text{N}_4$ support catalyst, $\text{Fe(III)}@g\text{-C}_3\text{N}_4$ required shorter reaction times, and no significant differences in the yields of product was observed.

3.1.10.6 MoS_2 -GCN nanocomposite catalyzed reactions. Molybdenum disulfide-supported on graphitic carbon nitride (GCN), MoS_2 -GCN, is a nanocomposite of two dimensional MoS_2 and has been employed as catalyst in several organic reactions. While MoS_2 acts as a Lewis acid catalyst, GCN exhibits basic character due to the nitrogen atoms. The exceptionally high catalytic activity of nanocomposite MoS_2 -GCN may be linked to the synergistic effect of non-bonding Lewis acid-base arrangement and possibly because it possesses relatively larger surface area among many other composites. Bahuguna *et al.* (2018) prepared the catalyst with varying amount of MoS_2 in GCN nanosheets to generate MoS_2 -GCN (1 : 1), MoS_2 -GCN (1 : 2) and MoS_2 -GCN(1 : 4) nanocomposites and applied them for the synthesis of trisindoline **3**. The best of the three catalytic systems was determined to be 10 wt% of MoS_2 -GCN (1 : 1). Reactions of indoles substituted by either EDG or EWG at C-5 with isatin produced notably excellent 87–95% yields of trisindolines **3**, **5**, **15**, **16**, **30**, **42**, **56** and **166** (Scheme 40). The 5-nitroindole substrate, however, required higher reaction temperature of 90 °C.¹⁰⁴

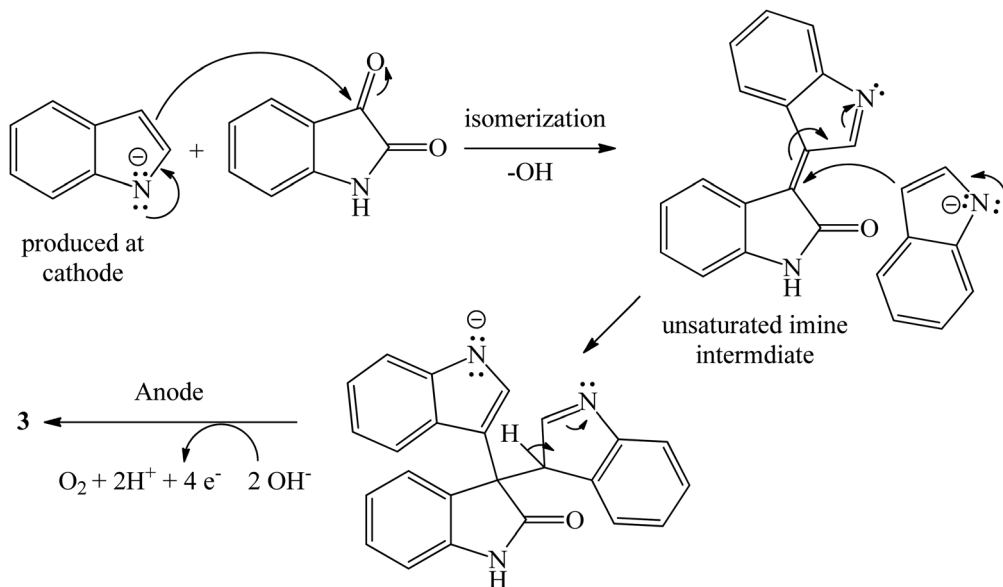
3.1.10.7 Ru(III) -exchanged zeolite Y nanocomposite catalyzed reactions. Khorshidi and Tabatabaeian (2010) treated a mixture of indoles and isatins with Ru(III) -exchanged zeolite Y as a catalyst (10 mol%) in 1,2-dichloroethane for 20–75 minutes to afford trisindolines **3**, **15**, **17**, **19**, **22**, **54** and **167** in 60–98% yields. The catalyst was prepared from zeolite FAU-Y and ruthenium chloride hydrate by stirring a mixture thereof at

room temperature for 1 day. EDG on the indoles (N atom, C-2 or C-3) enhanced the yield or contributed to faster reaction than indoles with EWG. 5-Cyanoindole reacted well with isatin and yielded 80% of **54**. However, reacting 5-cyanoindole with 5-cyanoisatin resulted in the longest reaction time and lowest yield of **167**.¹⁰⁵ In addition, another mild synthesis of trisindoline **3** catalyzed by NaY zeolite functionalized by sulfamic acid/ Cu(OAc)_2 (NaY zeolite- $\text{NH}_2\text{SO}_3\text{H}/\text{Cu(OAc)}_2$) in acetonitrile for 50 minutes gave 96% yield.¹⁰⁶

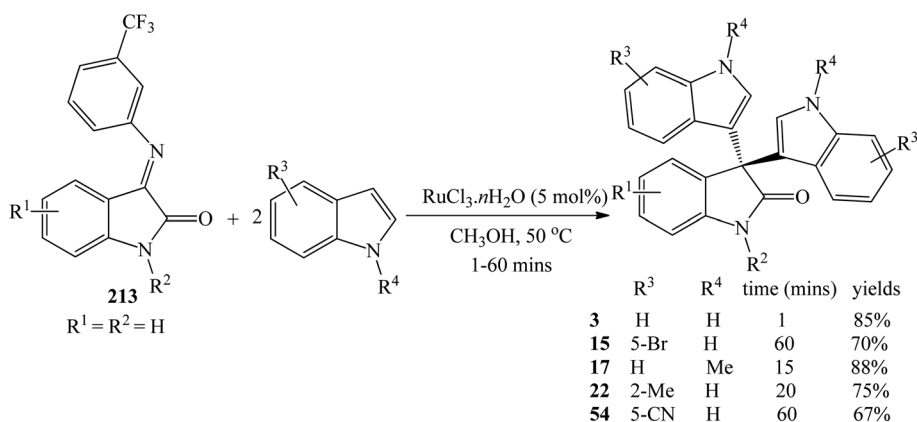
3.1.11 Biocatalyzed reactions. α -Chymotrypsin from bovine pancreas (BPC) was utilized as an enzymatic catalyst for the synthesis of trisindolines by Xue *et al.* (2016). Indoles and isatins were treated with 0.93 kU of bovine pancreas (BPC) in methanol with 20% water at 30 °C for 60–96 h to yield trisindolines **3**, **15–18**, **20**, **27–29**, **32**, **38**, **56–66**, **68** and **69** in 63–97% yields. When polar protic solvent was changed to aprotic solvent, **7** was formed instead of **3**. Trisindoline **3** was obtained in 96% yield after 72 h (Scheme 41). Isatins bearing EDGs or EWGs worked well with the indole and its substituted form. Nevertheless, 5-nitroisatin and 1-methylindole were less reactive, producing relatively lower yields.¹⁰⁷ In general biocatalysts require longer reaction time in comparison with other catalysts.

3.1.12 Electrochemical-based reactions. Trisindoline nanorods **3**, **5**, **15**, **17**, **18**, **22**, **25** and **27** were synthesized in excellent yields (90–96%) by electrochemical methods. Reaction of isatins and indoles were conducted in acetonitrile in unseparated cell under constant current (20 mA) at ambient temperature for 5–150 minutes. LiClO_4 was used as electrolyte, and graphite rods as the cathode and the anode. Overall, the reactions of substituted indoles with isatin proceeded in shorter reaction times and gave better yields than those with indole and substituted isatins. Trisindoline **18** and **25** obtained from *N*-alkylated and *N*-benzylated isatins gave the highest yields of 96%. The proposed mechanism of the reaction producing trisindoline **3** is displayed in Scheme 42.¹⁰⁸ Deprotonation of the indole at the cathode produces indole anion which undergoes the usual nucleophilic addition at the C₃ carbon of isatin to produce, after proton transfer and elimination of hydroxide ion, an α,β -unsaturated imine intermediate. A second molecule of indole anion reacts with the imine, followed by protonation of the indole nitrogen by protons produced at the anode and a final isomerization step to form the product.





Scheme 42 Proposed mechanism of trisindoline synthesis by electrolysis.

Scheme 43 Reaction of isatin-imine with indoles in the presence of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$.

3.1.13 Catalyst-free based synthesis. The catalyst-free reaction between isatins and indoles in water under reflux condition gave trisindolines **3**, **5**, **15**, **22**, **32**, **33**, **40**, **85**, **88**, **101**, **104** and **115** in 80–93% yields.¹⁰⁹ The synthesis was also achieved in water/ethanol (7 : 3) mixture within 5–38 minutes to give 55–86% trisindolines **3**, **15**, **17–19**, **22**, **23**, **69**, **153**, **158** and **168–171**.¹¹⁰ In both cases, the reactivity and yield of the trisindolines increased with EDG on C-5 of the indole ring and decreased in the presence of EWG such as bromine. Furthermore, substituents attached to the NH of isatins decreased the reactivity and yields.

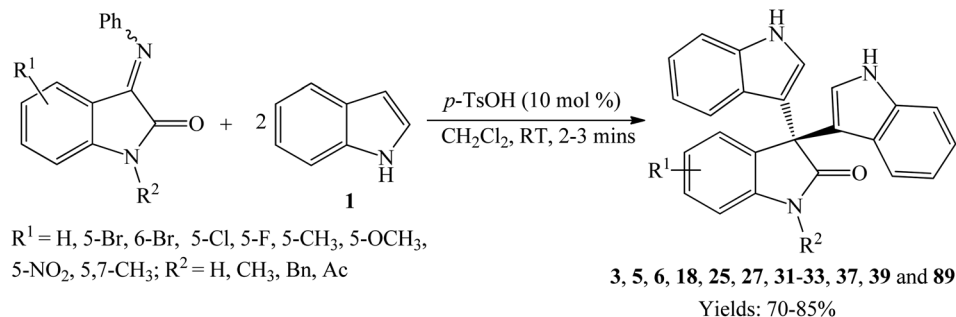
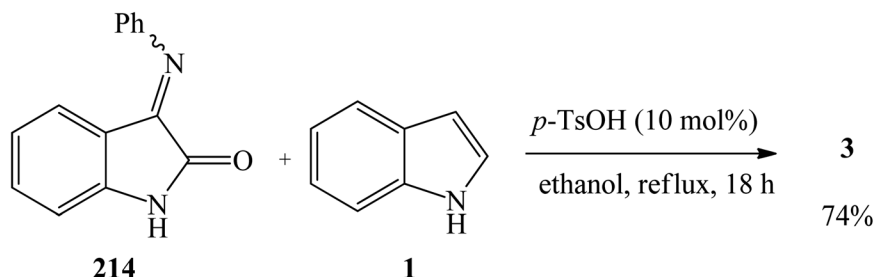
3.2 Synthesis of trisindolines from isatin-imine as coupling partner

3.2.1 Ru(III)- $n\text{H}_2\text{O}$ catalyzed reactions. Ru(III)-catalyst was also used for condensation reactions of CF_3 -attached isatin-imine **213** with several indoles in methanol for 1–60 minutes.

The reactions gave trisindolines **3**, **15**, **17**, **22** and **54** in 67–88% yields (Scheme 43). Reaction of indole and isatin gave trisindoline **3** in 85% yield in just 1 minute. EWGs retarded the reaction and gave lower yields. Accordingly, RuCl_3 worked well in the following order: reaction of isatin and indole > reaction of isatin-derived aldimine and indole > trimerization of indole.⁸²

3.2.2 *p*-TsOH catalyzed reactions. Coupling reaction between isatin-imines and indoles using catalytic amount of *p*-TsOH (10 mol%) in dichloromethane at room temperature proceeded within 2–3 minutes. This method tolerated various indoles and isatins where trisindolines **3**, **5**, **6**, **18**, **25**, **27**, **31–33**, **37**, **39** and **89** were obtained in 70–85% yields (Scheme 44). EDG (OCH_3 , CH_3) attached to isatin ring of (phenylimino)indolin-2-ones gave higher yields compared to the ones with EWG (F, Cl, Br, NO_2). Moreover, the presence of acetyl group on nitrogen rendered isatin-derived aldimine less reactive than those bearing methyl or benzyl group.¹¹¹



Scheme 44 Trisindolines obtained from the reaction of isatin-imine and indoles catalyzed by *p*-TsOH.Scheme 45 Reaction of isatin-imine with indoles in the presence of *p*-TsOH.

Schilling *et al.* (2020) reported the reaction of prepared isatin-imine 1,3-dihydro-3-(phenylimino)-2*H*-indol-2-one **214** (1 equivalent) and indole (two equivalents) in the presence of *p*-TsOH catalyst (10 mol%) under reflux in ethanol for 18 h, generating **3** in 74% yield (Scheme 45).¹¹²

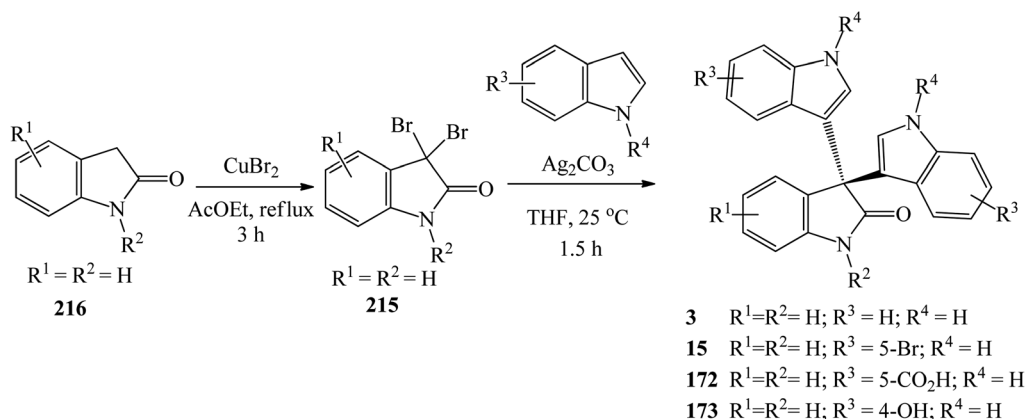
3.3 Synthesis of trisindolines from 3,3-dibromoxindole as coupling partner

Reaction of 3,3-dibromoxindole **215** with indole, catalyzed by silver carbonate at 25 °C for 1.5 h gave trisindoline **3** in 65% yield. Following the same procedure, reaction of 3,3-dibromoxindole **215** with other indoles gave the corresponding trisindolines **15**, **172** and **173**. 3,3-Dibromoxindole **215** was

prepared in 72% yield by refluxing indoline-2-one **216** and copper(II) bromide in ethyl acetate for 3 h (Scheme 46).⁶

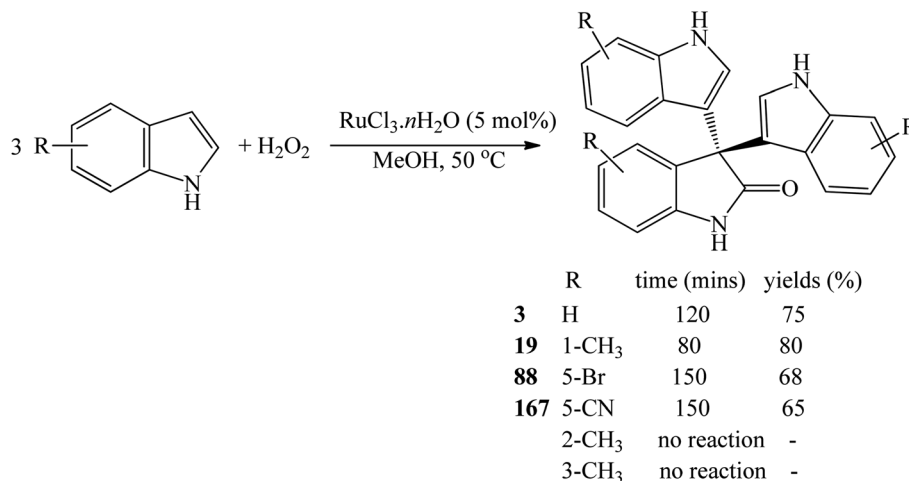
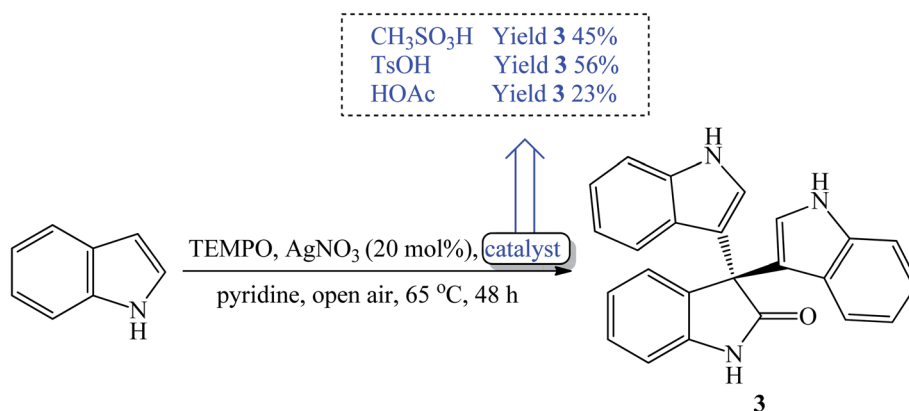
3.4 Synthesis of trisindolines from trimerization reactions of indoles

Tabatabaeian *et al.* (2009) synthesized trisindolines **3**, **19**, **88** and **167** in 65–80% yields by self-condensation reaction of indoles in the presence of hydrogen peroxide and $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (5 mol%) as catalyst in methanol at 50 °C within 80–150 minutes (Scheme 47). Deactivated indoles 5-cyanoindole and 5-bromoindole reacted slower and gave lower yields compared with activated (*N*-methylindole) and unsubstituted indoles. However, 3-methylindole and 2-methylindole were unreactive.⁸²



Scheme 46 Two-step synthesis of trisindolines.



Scheme 47 Trimerization of indoles using RuCl₃·nH₂O.

Scheme 48 Trimerization of indoles using TEMPO.

Trisindoline **3** was prepared by the reaction of indole in the presence of AgNO₃ (20 mol%), acid catalyst additive and TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl radical) as additive, in pyridine under open air at 65 °C for 48 h. For comparison, compound **3** was obtained in 45%, 56%, 23% yields respectively using methanesulfonic acid or *p*-toluenesulfonic acid or acetic acid as catalysts (Scheme 48).¹¹³

4. Bioactivity of trisindolines

4.1 Anticancer activity

Trisindoline **3** was reported to have anticancer activity against colorectal adenocarcinoma (HCT15) and uterine sarcoma (MES-SA). Trisindoline **3** displayed stronger toxicity against both multidrug resistant cell lines HCT15/CL02 and MES-SA/DX5 and exhibited IC₅₀ values of 5.11 ± 0.44 μM and 5.50 ± 0.53 μM, respectively, compared to etoposide which is used for treating ovarian and testicular cancers.⁹ Trisindoline **3** displayed IC₅₀ of 18.4 μM against A-549 cell lines (lung cancer cells) while its isomer, 2,2-di(3-indolyl)-3-indolone **4**, was less potent with IC₅₀ value of 69.7 μM.¹⁹ In other research, trisindoline **3**

showed stronger toxicity against A-549 cell lines with IC₅₀ values of 8.6 μM⁸ and 1.23 ± 0.030 μM.⁷ Trisindoline **3** was also investigated for its anticancer activity against SK-N-SH cell lines (neuroblastoma) and gave IC₅₀ of 11.3 μM⁸ and 0.90 ± 0.06 μM (IC₅₀ of doxorubicin as drug standard was 0.97 ± 0.03 μM).⁷ Furthermore, trisindoline **3** exhibited IC₅₀ value of 5.70 μg mL⁻¹ against HL-60 (human promyelocytic leukemia cell line) and 6.85 μg mL⁻¹ against Bel-7402 (human hepatocellular carcinoma cell line), and was more potent than indoles isolated from *Shewanella piezotolerans* (Table 5).²² Natural brominated trisindolines **5** and **6** showed promising activity against cancer cell lines HT-29 (human colon), OVCAR-3 (human ovarian), and MM.1S (multiple myeloma) (Fig. 8).²³

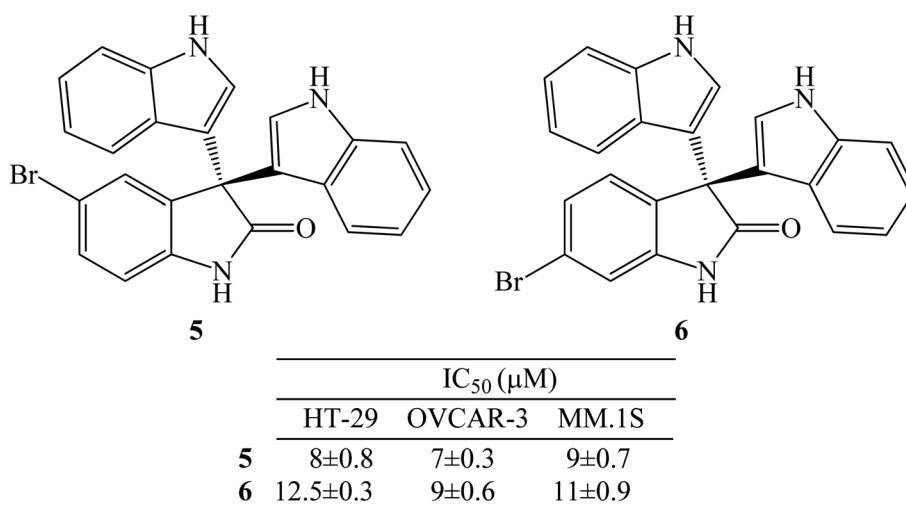
Kamal *et al.* assayed the bioactivity of trisindolines **3**, **15–17**, **30**, **32**, **42**, **60**, **61**, **101**, **124** and **144–148** against lung cancer cell lines (A549), central nerve system cancer cell lines (SK-N-SH), breast cancer cell lines (MCF-7), liver cancer cell lines (Hep G-2), and prostate cancer cell lines (DU-145). Trisindolines **16** and **145** with methoxy substituent at C-5 and C-6 showed lower IC₅₀ of 2.2 μM and 1.2 μM, respectively, against DU-145. In comparison, trisindoline **15** with Br on C-5 gave IC₅₀ value of 3.6



Table 5 IC₅₀ values of trisindoline **3** against cancer and normal cell lines^a

Cancer/tumor cell lines	IC ₅₀			References
	Trisindoline 3	Etoposide (standard)	Doxorubicin (standard)	
HCT-15	6.63 ± 0.43 μM	1.42 ± 0.02 μM		9
HCT-15/CL02	5.11 ± 0.44 μM	11.68 ± 2.38 μM		9
MES-SA	3.51 ± 0.03 μM	0.28 ± 0.02 μM		9
MES-SA/DX5	5.50 ± 0.53 μM	8.14 ± 0.89 μM		9
A549	18.4 μM			19
	8.6 μM			8
	1.23 ± 0.030 μM		15.07 ± 0.13 μM	7
SK-N-SH	11.3 μM			8
	0.90 ± 0.06 μM		0.97 ± 0.03 μM	7
HL-60	5.70 μg mL ⁻¹			22
Bel-7402	6.85 μg mL ⁻¹			22
MCF-7	49.8 μM			8
Hep G-2	20.4 μM			8
DU-145	8.7 μM			8
MDA-MB	Inactive		8.14 ± 0.14 μM	7
MRC-5	>100 μM		14.84 ± 0.25 μM	7

^a HCT-15: colorectal adenocarcinoma; HCT-15/CL02: multidrug-resistant colorectal adenocarcinoma; MES-SA: uterine sarcoma; MES-SA/DX5: multidrug-resistant uterine sarcoma; A549: lung cancer; SK-N-SH: neuroblastoma or central nerve system (CNS) cancer; HL-60: promyelocytic leukemia; Bel-7402: hepatocellular carcinoma; MCF-7: breast cancer; Hep G-2: liver cancer, DU-145: prostate cancer, MDA-MB: breast cancer; MRC-5: human normal lung.

Fig. 8 IC₅₀ values of **5** and **6** against HT-29, OVCAR-3, and MM.1S cell lines.

μM. Trisindoline **146** showed high potency with IC₅₀ value of 7.5 μM against MCF-7 cancer cells. 5-Fluoro-3,3-di(1*H*-indol-3-yl) indolin-2-one **32** also showed anticancer potency against Hep G-2 while other analogues either showed higher IC₅₀ or were inactive. Trisindoline **101** showed the best IC₅₀ against SK-N-SH. In addition to its activity against DU-145, trisindoline **145** displayed IC₅₀ value of 7.8 μM against A549 cell lines, and this value was similar to the ones exhibited by trisindolines **146** and **124**. Overall, the introduction of a methoxy moiety on the indole framework in any position positively enhanced the anticancer activity.⁸

Trisindolines **3**, **15**, **17**, **22**, **30**, **31**, **42**, **54**, **55**, **86** and **106–110** were examined against MDA-MB 231 (breast), SK-N-SH

(neuroblastoma), A549 (lung), and MRC-5 (normal human lung cell) cell lines. Trisindolines **31**, **86**, **108–110** with 5-chloroisatins were not potent against A549 and SK-N-SH. However, the combination of 5-chloroisatin with 5-bromoindole as in trisindoline **86** gave IC₅₀ of 1.04 μM against SK-N-SH cancer cell line. Isatins and indoles bearing electron withdrawing group (except 5-chloro) and/or with methyl on C-2 showed promising activity with IC₅₀ of 0.75–1.23 μM against lung cancer cells (A549) and 0.90–0.99 μM against neuroblastoma cancer cells (SK-N-SH). In the case of lung cancer, they have significantly lower IC₅₀ value compared to doxorubicin with IC₅₀ of 15.07 μM. However, doxorubicin possessed IC₅₀ of 0.97 μM towards neuroblastoma cancer cell lines. The combinations of isatins



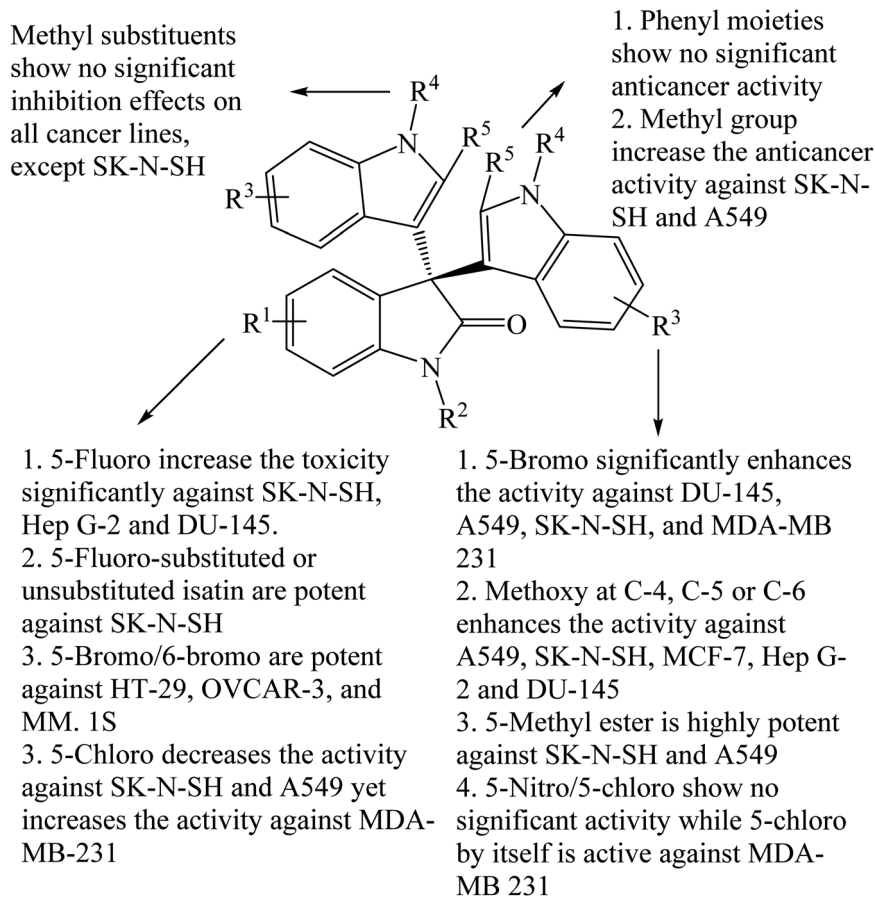


Fig. 9 Effect of various substituents on the anticancer activity of trisindolines.

and indoles bearing EWG (except CO₂Me) or trisindolines with EWG (except halogen) on indoles and chloro on isatin, inhibited the viability of MDA-MB 231 cells and exhibited IC₅₀ value of 9.95–10.05 μM (IC₅₀ of doxorubicin is 8.14 μM). The introduction of 2-phenylindole decreased the activity against three cancer cell lines (MDA-MB 231, SK-N-SH, A549). Trisindolines 15 and 42 were potent during the inhibition of the above cancer cell lines. Interestingly, trisindolines 3, 15, 17, 22, 30, 31, 42, 54, 55, 86 and 106–110 were not toxic to the normal cell (MRC-5) although some were not active as anticancer agents.⁷ A simplified structure–activity relationship (SAR) of trisindolines toward anticancer activity can be seen in Fig. 9.

4.2 Antimicrobial activity

Trisindoline 3 showed antibacterial activity against *E. coli*, *B. subtilis*, *S. aureus* at 10 μg per disk with inhibition zone of 16, 17, and 10 mm respectively.⁶ Trisindoline 3, unlike its analogues, possessed better activity against Gram-negative bacteria compared to Gram-positive bacteria. Trisindolines 172 with 5-carboxylic acid indole and 173 with 4-hydroxyindole did not show any inhibitions while trisindoline 15 with 5-bromoindole exhibited weak activity (at the concentration of 30 μg per disk) against *E. coli*.⁶

Trisindoline 3 was found to have excellent antibacterial activity against *B. cereus*, displaying inhibition zone of 20 mm at

10 μg per paper.¹⁸ The antimicrobial activity of trisindoline 3 and *N*-benzyl-substituted trisindoline 25 was assayed by disc diffusion method using 6 mm paper discs. Compounds 3 and 25 were found to possess inhibition zones of 25 mm and 26 mm against *B. subtilis* respectively, while chloramphenicol and gentamycin (antibiotics) showed inhibition zones of 26 mm and 28 mm respectively. Trisindolines 5, 31 and 27 with halogen or nitro groups on the isatin moiety caused 11–18 mm inhibition zone, while trisindolines 17, 57 and 29 with methyl group on the nitrogen did not show inhibition zones. Compounds that were active against *B. subtilis*, also possessed antimicrobial activity against *S. aureus*, but with lower inhibition zone of 12–16 mm than that of gentamycin with 20 mm inhibition zone. All the

Table 6 Zone of inhibition and MIC values of 5 and 6 against *S. aureus* and *B. subtilis*

Trisindolines	Zone of inhibition (mm)		MIC (μg mL ⁻¹)	
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>S. aureus</i>	<i>B. subtilis</i>
5	17.5 ± 0.8	18 ± 0.1	8	4
6	15 ± 1.1	16.4 ± 0.9	16	4
Amikacin	23.5 ± 0.8	20.2 ± 0.6	—	—
Gentamycin	—	—	16	8



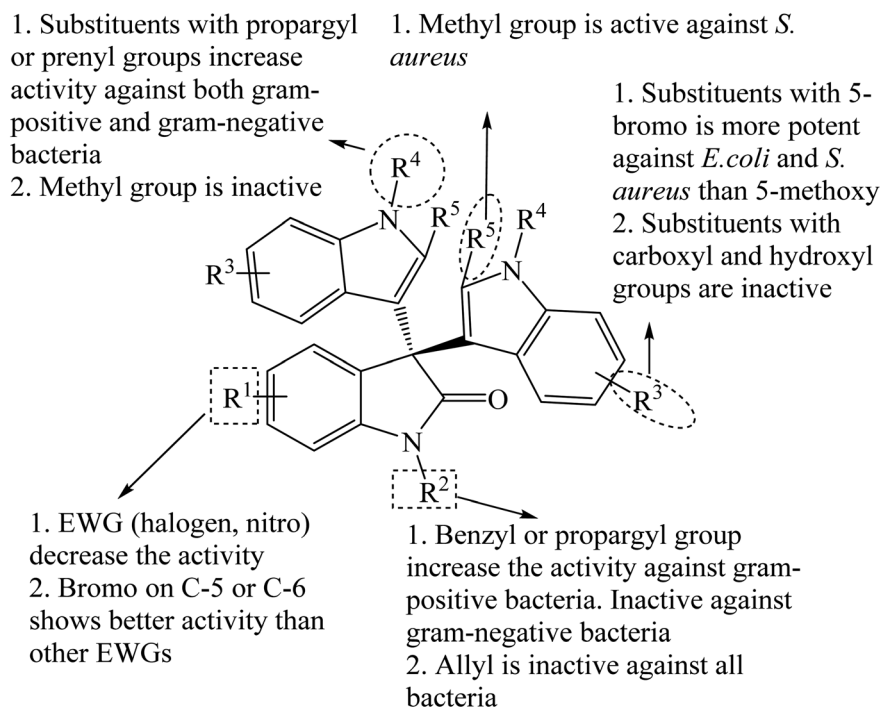


Fig. 10 Structure–activity relationship (SAR) of trisindolines as antibacterial agents.

substituted trisindolines **3**, **5**, **17**, **25**, **27**, **29**, **31** and **57** were not active against *E. coli* and *P. aeruginosa*.⁵⁹

Trisindolines **14** with 5-bromo and *N*-benzyl moieties on isatin showed promising antibacterial activity against *S. aureus* with inhibition zone of 23 mm and MIC of 1.25 $\mu\text{g mL}^{-1}$. Trisindoline **5** without the *N*-benzyl moiety on isatin and trisindoline **161** with 2-methyl on the indole unit exhibited lower activity with inhibition zones of 12 mm (MIC of 10 $\mu\text{g mL}^{-1}$) and 19 mm (MIC of 2.5 $\mu\text{g mL}^{-1}$), respectively. However, trisindolines **5**, **14** and **161** were inactive against *E. coli* and *P. aeruginosa*.⁹⁵

Trisindolines **125–137** inhibited *E. coli* and *S. aureus* successfully. Trisindoline **135** with *N*-benzyl group in the isatin and *N*-propargyl group in indole rings emerged as the most active against *E. coli* with 17 mm inhibition zone as well as the most active against *S. aureus* with 15 mm inhibition zone. Trisindolines **125–134**, **136** and **137** showed zone of inhibitions of 10–15 mm against *E. coli* and 10–15 mm against *S. aureus*. Trisindolines **129**, **133** and **137** were the most potent with 15 mm inhibition zone against *S. aureus*. Under the same conditions, Amikacin exhibited 18- and 17 mm zone of inhibition for *E. coli* and *S. aureus*, respectively.¹⁰ The presence of substituents on the nitrogen of isatin or indole seems to contribute positively to the antibacterial activity against *E. coli*.

The antibacterial activity of trisindolines **5** and **6** was examined against *S. aureus*, *B. subtilis*, *E. coli*, and *P. aeruginosa* by disc diffusion method (Table 6).²³ Trisindoline **5** possessed wider inhibition zone against *S. aureus* (17.5 ± 0.8 mm) and *B. subtilis* (18 ± 0.1 mm) than trisindoline **6**, and both were weaker than amikacin. However, trisindolines **5** and **6** showed better inhibition against *S. aureus* and *B. subtilis* than gentamicin.

Trisindoline **5** with the 5-bromine on isatin is more potent than **6** having 6-bromine. However, both compounds were inactive against Gram-negative bacteria (*E. coli*, and *P. aeruginosa*).¹⁹ The structure–activity relationship (SAR) of the trisindolines as antibacterial agents is seen in Fig. 10.

4.3 Antimycobacterial activity

The potency of trisindoline **3** and its analogues **13** and **14** as antitubercular agents was examined using the resazurin microtiter assay (REMA) method.¹¹ Trisindoline **3** was inactive (MIC > 25 $\mu\text{g mL}^{-1}$) while trisindolines **13** and **14** inhibited the growth of *Mycobacterium tuberculosis* H₃₇Rv with MIC values of 12.5 and <6.25 $\mu\text{g mL}^{-1}$, respectively. Rifampicin reference showed MIC of <6.25 $\mu\text{g mL}^{-1}$ under the same conditions.¹¹

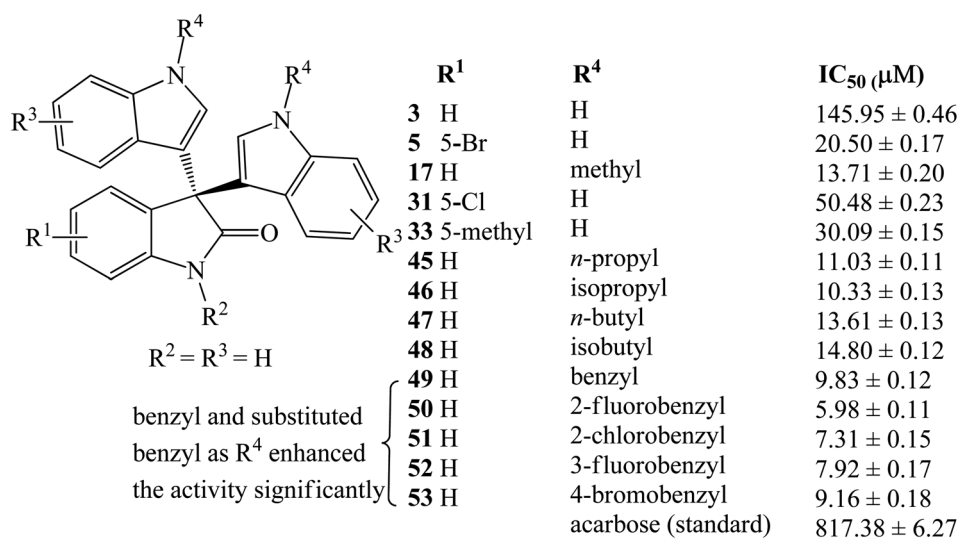
4.4 Antifungal activity

Trisindolines **3**, **5**, **17**, **25**, **27**, **29**, **31** and **57** were found inactive against *Candida albicans* by the disc diffusion method.⁵⁹ Compounds **5**, **14** and **161** were assayed *in vitro* using USP 29-NF25 cylinder plate assay against *Candida albicans*, and none of them were active as antifungal agents.⁹⁵ Surprisingly, trisindolines **125–137** displayed inhibitions against *Candida albicans* by cup plate method. Compounds **126** and **137** showed the best inhibition (15 mm zone of inhibition) while ketonazole as standard antifungal agent showed 16 mm inhibition zone. Other analogues **125** and **127–136** displayed 10–14 mm inhibition zone. The presence of methoxy group on C-5 of the indole increased the activity against *Candida albicans*.¹⁰ The inactivity of trisindolines to inhibit the growth of *C. albicans* was



Table 7 The effect of trisindolines 125–137 on seizures induced by MES in mice

Trisindolines	R ¹	R ²	R ³	R ⁴	Time (s)		
					Flexion	Extensor	Clonus
125	H	H	H	Allyl	5.80 ± 0.20	48.00 ± 0.32	3.60 ± 0.20
126	5-NO ₂	H	H	Allyl	4.80 ± 0.20	39.20 ± 0.40	3.40 ± 0.24
127	H	H	5-OMe	Allyl	4.80 ± 0.18	31.80 ± 0.40	3.20 ± 0.24
128	5-Cl	H	5-OMe	Allyl	5.80 ± 0.20	31.60 ± 0.37	3.40 ± 0.20
129	5-Br	H	5-OMe	Allyl	4.80 ± 0.20	39.20 ± 0.40	3.40 ± 0.24
130	H	CH ₂ CO ₂ Et	5-OMe	Allyl	4.80 ± 0.20	31.60 ± 0.37	3.40 ± 0.24
131	H	H	H	Cinnamyl	4.80 ± 0.20	39.60 ± 0.40	3.60 ± 0.20
132	H	H	5-Br	Prenyl	4.80 ± 0.20	39.60 ± 0.40	3.40 ± 0.24
133	H	Propargyl	5-Br	Prenyl	5.40 ± 0.24	31.60 ± 0.37	2.80 ± 0.24
134	H	H	H	Propargyl	4.80 ± 0.20	39.20 ± 0.40	3.20 ± 0.24
135	H	Bn	H	Propargyl	4.80 ± 0.18	39.20 ± 0.40	3.20 ± 0.24
136	H	Propargyl	H	Propargyl	5.40 ± 0.20	31.80 ± 0.32	3.60 ± 0.20
137	H	H	2-Me	Propargyl	5.40 ± 0.24	31.60 ± 0.37	2.80 ± 0.24
Phenytoin (reference standard)					5.60 ± 0.20	43.00 ± 0.40	3.40 ± 0.24

Fig. 11 IC₅₀ values of trisindolines 3, 5, 17, 31, 33 and 45–53 as α -glucosidase inhibitors.

presumably caused by the absence of substituents on the nitrogen atom in either isatin or indole.

4.5 Anticonvulsant activity

A series of trisindolines 125–137 were tested *in vivo* to examine their anticonvulsant activity by observing seizure in rat.¹⁰ All the tested compounds 125–137 were active at a dose of 20 mg kg⁻¹ and halted convulsion. Compounds 127, 128, 130, 133, 136, 137 markedly showed excellent activities with extensor time of 31.60–31.80 s while standard drug phenytoin's extensor time was 43.00 ± 0.40 s (Table 7). The presence of *N*-propargyl on indole or isatin moieties as well as *N*-allyl moiety reduced the time of tonic extensor remarkably. Methyl substituent on C-2 of the indole increased the activity. Trisindoline 125 was less promising as anticonvulsant since it possessed longer extensor time than phenytoin.¹⁰

4.6 α -Glucosidase inhibition activity

Trisindolines 3, 5, 17, 31, 33 and 45–53 inhibited α -glucosidase activities and possessed significantly lower IC₅₀ values than commercial drug acarbose (Fig. 11).¹² The presence of bromo substituent on isatin ring enhanced the activity. Trisindoles with *N*-benzyl and *N*-substituted benzyl isatins were more active than *N*-alkyl analogues. Trisindoline 3 displayed the lowest inhibition activity and yet was superior to acarbose (Fig. 11).

4.7 Spermicidal activity

Trisindoline 3 and its analogues 15–17, 22 and 105 were investigated for their effects on sperm motility (Table 8). The minimum effective concentrations (MECs) were defined as the minimum concentration that led 100% sperm immobility within 20 seconds without awakening the next motility in Baker's buffer after 1 h of incubation at 37 °C. Trisindoline 16



Table 8 MEC values of trisindolines 3, 15–17, 22 and 105 as spermidal

Trisindolines	MEC (mg mL ⁻¹)	Trisindolines	MEC (mg mL ⁻¹)
3	2.40 ± 0.058	22	2.82 ± 0.057
15	3.18 ± 0.041	16	0.34 ± 0.018
17	2.36 ± 0.045	105	1.11 ± 0.061

showed the best inhibition activity with MEC of 0.34 ± 0.018 mg mL⁻¹. In comparison, nonoxynol-9 (N-9) as standard showed lower MEC of ~0.5.¹³

4.8 Miscellaneous activities

Compound 3 displayed moderate inhibition activity against xanthine oxidase with IC₅₀ of 179.6 ± 0.04 µg mL⁻¹ while standard inhibitor allopurinol showed IC₅₀ value of 7.4 ± 0.07 µg mL⁻¹.²⁵ Xanthine oxidase is an enzyme responsible for catalyzing the transformation of xanthine to uric acid as well as reducing oxygen (O₂) into reactive oxygen species (ROS). The abundance of uric acid causes oxidized lipid membrane, leading to hyperuricemia and obesity.¹¹⁴

Trisindoline 3 showed promising bioactivity as tyrosinase inhibitor with IC₅₀ value of 17.34 ± 0.04 µg mL⁻¹ while reference L-mimosine showed IC₅₀ value of 37.0 ± 0.03 µg mL⁻¹.²⁵ Tyrosinase enzyme is critical to melanogenesis as it catalyzes the production of melanin in skin, hair, and eye pigmentation.¹¹⁵

Trisindoline 3 was less potent as antioxidant since it showed IC₅₀ value of 431 ± 0.09 µg mL⁻¹ compared with the positive control of 3-*tert*-butyl-4-hydroxyanisole (BHA) with IC₅₀ value of 46 ± 0.22 µg mL⁻¹.²⁵

5. Future directions

Various routes and catalysts have been explored for trisindoline synthesis. In majority of cases, acids have been used to catalyze the reaction successfully. Ionic liquid-catalyzed condensation reaction of isatins with indoles have attracted attention since it is considerably environmental benign and requires simple operation giving high yields within short reaction time. Besides, many ionic liquid catalysts could be utilized to synthesize both symmetrical and unsymmetrical trisindolines. On other hand, only a handful of trisindolines have been synthesized using ionic liquids which warrants further exploration. Trisindolines emerge as a new class of bioactive compounds as it displays several promising bioactivities that need developing. However, limited analogues of trisindoline have been well-investigated and the structure activity relationship is reported on limited varieties of compounds especially when trisindolines were explored as antitubercular and α-glucosidase inhibitors. Interestingly, there is also very limited studies on the biological activity of unsymmetrical trisindolines which should be explored.

6. Conclusions

Trisindolines are nitrogen heterocyclic structures with promising biological activities. This review provides comprehensive account of trisindolines including their natural occurrence, synthesis, and biological activities. Various routes of synthesis and catalysts used have been discussed in detail. The biological activities of trisindolines have also been discussed with a special focus on the structure activity relationship. This review aims to inspire further development of trisindolines as lead drug candidates.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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