IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 4, February 2026
Impact Factor: 8.2

Green Synthetic Approaches to Bioactive 3-Substituted 3-Hydroxyoxindole Frameworks

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Abstract: *The 3-substituted 3-hydroxyoxindole scaffold is a biologically important and structurally versatile heterocyclic motif widely found in natural products and pharmacologically active compounds. Growing environmental concerns have encouraged the development of sustainable synthetic methodologies for its efficient construction. This review critically examines environmentally benign strategies for synthesizing bioactive 3-substituted 3-hydroxyoxindoles, with particular focus on water-mediated reactions, ultrasound-assisted synthesis, microwave-assisted transformations, catalytic systems employing recyclable or heterogeneous catalysts, and catalyst-free protocols. Reactions performed in aqueous media enhance safety and reduce toxicity, while ultrasound and microwave irradiation accelerate reaction rates, shorten reaction times, and decrease energy consumption. Catalytic approaches improve atom economy and overall efficiency, whereas catalyst-free methods minimize waste and simplify purification processes. Collectively, these green methodologies offer mild reaction conditions, high selectivity, and improved sustainability compared to conventional procedures. Continued emphasis on reusable catalysts, energy-efficient activation techniques, and scalable eco-friendly protocols will further advance sustainable synthesis and broaden the medicinal relevance of 3-hydroxyoxindole derivatives*

Keywords: *3-Substituted oxindoles, green synthesis, Bioactive heterocycles, Sustainable chemistry, Aqueous medium, Ultrasound-assisted synthesis, Microwave-assisted synthesis, etc*

I. INTRODUCTION

The 3-substituted 3-hydroxyoxindole framework is a highly valuable and biologically important heterocyclic structure that continues to draw strong interest in modern organic and medicinal chemistry. This core structure appears in many natural products and synthetic molecules known for diverse biological activities, including anticancer, antimicrobial, antioxidant, anti-inflammatory, and enzyme inhibitory effects [1]–[4]. Because of its wide-ranging therapeutic potential, developing efficient and reliable methods to construct 3-hydroxyoxindole derivatives has become a significant focus in synthetic chemistry. The presence of a quaternary carbon center at the C-3 position, together with its flexible functionalization possibilities, makes this scaffold both synthetically demanding and pharmacologically attractive.

Over time, numerous strategies have been designed to synthesize 3-substituted 3-hydroxyoxindoles. Traditional methods such as aldol reactions of isatins, nucleophilic additions, metal-catalyzed transformations, and oxidation processes have been widely explored [2], [3]. Although these approaches often provide good yields and structural diversity, they frequently depend on toxic solvents, costly or hazardous metal catalysts, strong oxidizing agents, and long reaction times. These factors raise environmental, safety, and economic concerns, particularly when reactions are scaled up for industrial production [5], [6]. As global awareness of sustainability has increased, researchers have been motivated to redesign synthetic routes with environmental responsibility in mind.

DOI: 10.48175/IJARSCT-31713

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The principles of green chemistry, introduced by Anastas and Warner, encourage minimizing hazardous substances while improving efficiency and reducing waste generation [5]. In response, synthetic research on oxindole derivatives has gradually shifted toward greener methodologies. Among these, the use of water as a reaction medium has gained significant attention. Water-mediated and "on-water" reactions offer practical advantages such as low toxicity, affordability, non-flammability, and ease of handling [7]– [9]. Beyond environmental benefits, aqueous systems can sometimes improve reaction rates and selectivity due to hydrogen bonding and hydrophobic effects.

Alternative energy sources have further strengthened sustainable synthetic practices. Microwave-assisted synthesis enables rapid and uniform heating, dramatically shortening reaction times and often enhancing product yields compared to conventional methods [10], [11]. Ultrasound-assisted techniques generate localized high-energy conditions through acoustic cavitation, improving mass transfer and allowing reactions to proceed efficiently under milder bulk conditions [12]. These technologies contribute to energy savings and cleaner reaction profiles. Catalysis also plays a central role in green synthetic chemistry. Recyclable and heterogeneous catalysts enhance atom economy, reduce waste, and allow easy recovery and reuse, making processes more sustainable [13], [14]. In addition, catalyst-free methodologies simplify reaction systems, decrease chemical load, and reduce purification steps, which is advantageous in pharmaceutical synthesis [15].

Overall, the combined use of water-based systems, microwave and ultrasound activation, recyclable catalysts, and catalyst-free protocols reflects a clear movement toward environmentally responsible synthesis. These approaches not only reduce environmental impact but also improve efficiency, selectivity, and scalability. Continued innovation in this area will be essential for advancing sustainable medicinal chemistry and aligning synthetic practices with global environmental goals.

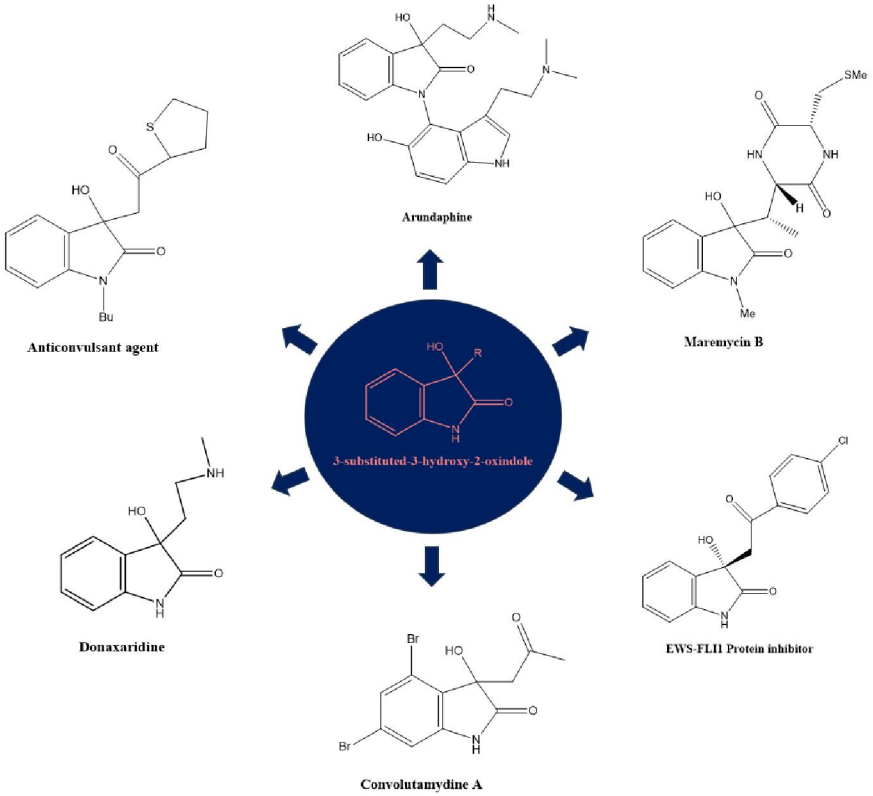

Fig. 1: Some examples of Bioactive 3-Substituted-3-Hydroxy-2-oxindoles.

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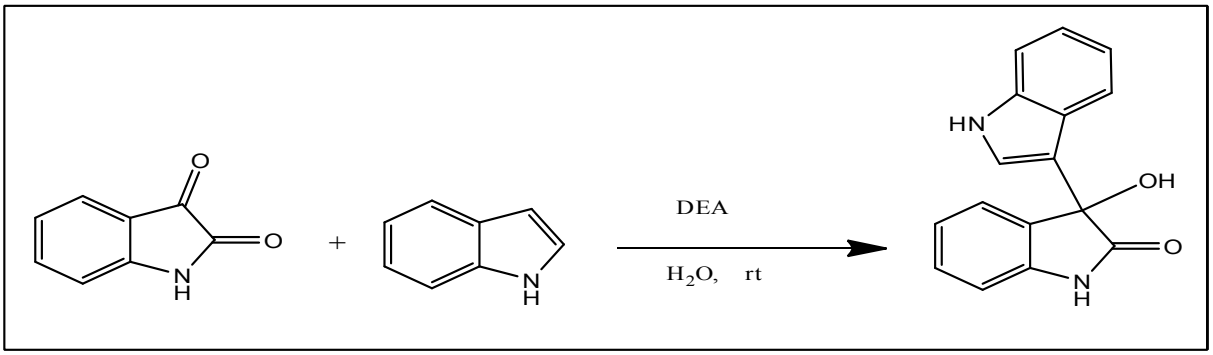
SYNTHESIS OF 3-SUBSTITUTED 3-HYDROXYOXINDOLE SCAFFOLDS BY DIFFERENT GREENER APPROACHES:

Many researchers working in the field of organic synthesis have developed different methods for the synthesis of oxindole molecules [16]. Substituted oxindoles was synthesized using variety of methods which includes microwave irradiation, satalyst free synthesis, synthesis using different catalyst, catalyst free synthesis, etc.

CATALYST FREE ON WATER SYNTHESIS:

Catalyst-free synthesis of 3-substituted-3-hydroxyoxindoles in water has emerged as a sustainable and environmentally benign strategy aligned with green chemistry principles. In this approach, water serves as a non-toxic, inexpensive, and eco-friendly reaction medium that can promote aldol-type additions of isatins with various nucleophiles such as ketones, indoles, and activated methylene compounds without the need for metal or organocatalysts. The unique hydrogen-bonding ability and hydrophobic effect of water often enhance reaction rates and selectivity, facilitating efficient C–C bond formation under mild conditions.[17]-[23] Many protocols report good to excellent yields with simple operational procedures, easy product isolation, and minimal waste generation. Moreover, avoidance of hazardous solvents and catalysts reduces cost and environmental impact while improving functional group tolerance. Although challenges such as limited substrate solubility and longer reaction times may arise, water-mediated, catalyst-free methodologies represent a promising green alternative for constructing biologically important 3-substituted-3-hydroxyoxindole scaffolds. Many researchers have worked on the green synthesis of 3-Substituted oxindole derivatives. Recently water as solvent were used for the synthesis 3-indolyl-3-hydroxy oxindoles from isatin.[24]-[25]



Scheme1: Synthesis of 3-indolyl-3-hydroxy oxindoles from isatin.

Tavakolian et al. reported a visible-light, catalyst-free synthesis of 3-indolyl-3-hydroxy oxindoles in water at room temperature under blue LED irradiation, achieving moderate to good yields (up to ~88%), highlighting a green aqueous photochemical method with potential pharmaceutical scaffold applications.[17]

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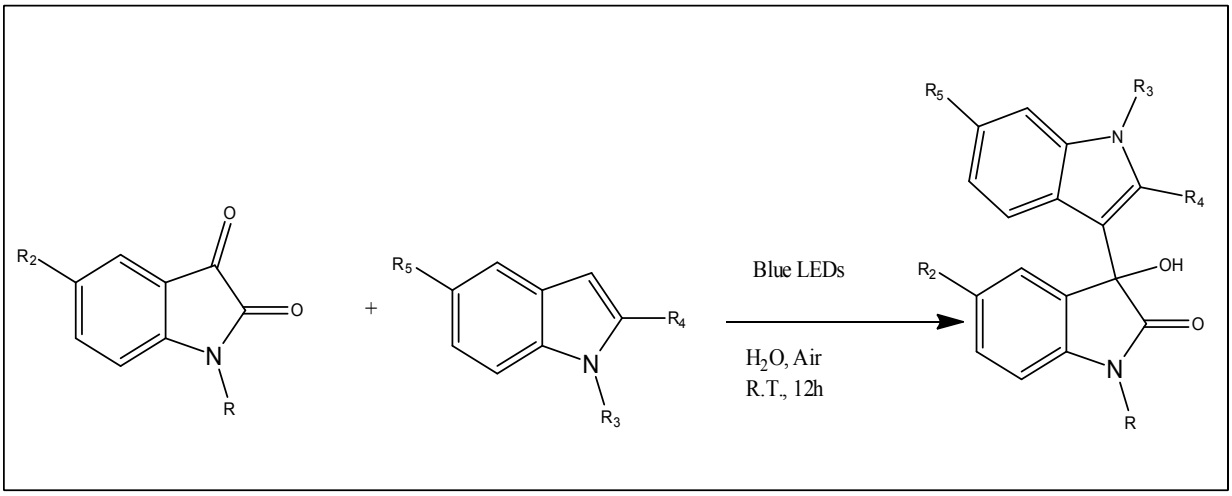
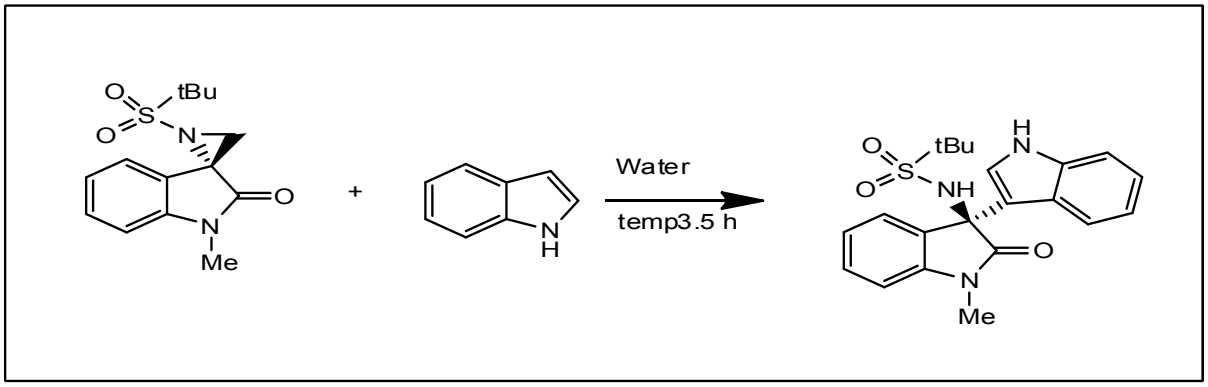


Scheme2: Synthesis of 3-indolyl-3-hydroxy oxindoles.

Hajra et al. disclosed a synthesis of 3-indolyl substituted oxindoles in presence of water. The yield gives up to 92% within a few hours. The metal-free, mild conditions enhance its sustainability profile, although substrate generality remains moderately limited. [18]. About fifteen bioactive derivatives has been reported under catalyst free conditions.



Scheme 3: Synthesis of 3-indolyl substituted oxindoles.

Tiwari et al.described the synthesis of 3-substituted 3-hydroxyoxindole frameworks via acid-catalyzed nucleophilic addition of indoles to isatins. The reaction was carried out in water at room temperature, furnishing products in good to excellent yields within a few hours. The mild, operationally simple conditions make the protocol synthetically practical for accessing pharmacologically relevant oxindole intermediates, although the scope is largely restricted to indole nucleophiles. [19]

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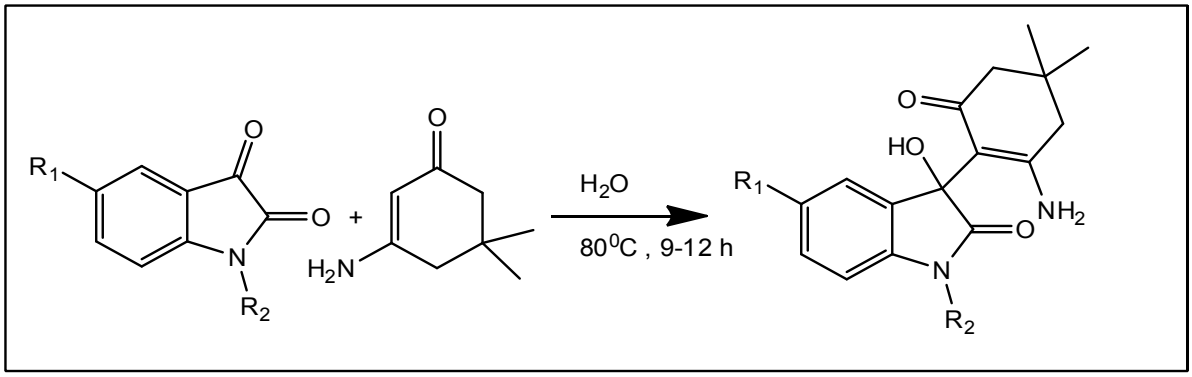
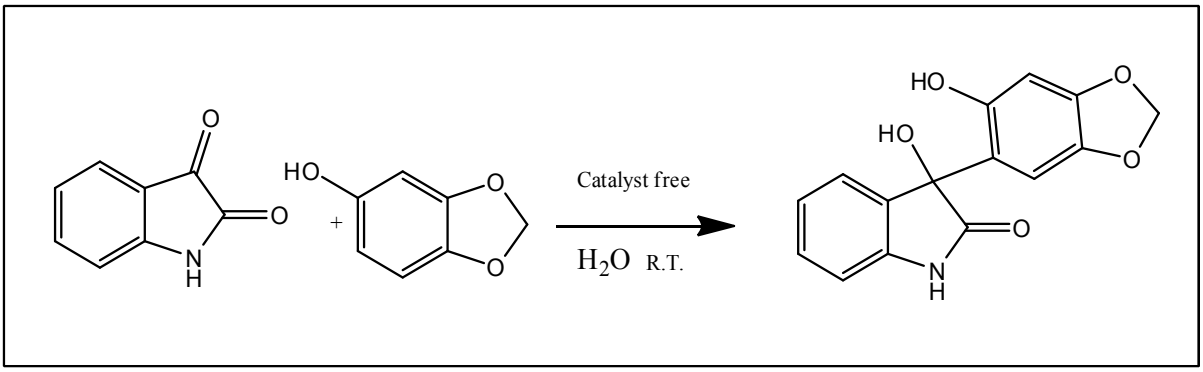


Scheme 4: Synthesis of 3-substituted 3-hydroxyoxindole frameworks via acid-catalyzed nucleophilic addition of indoles to isatins

Kumar et al.reported A catalyst-free green protocol for the synthesis of 3-aryl-substituted 3-hydroxy-2-oxindole frameworks was achieved via direct nucleophilic addition of activated phenols to isatin in aqueous medium. The reaction was performed in water at room temperature without the use of any acid, base, or metal catalyst. Under these mild conditions, the electrophilic C-3 carbonyl group of isatin undergoes Friedel–Crafts type addition with the electron-rich aromatic ring, leading to the formation of a new C–C bond and generating the corresponding 3-hydroxy-3-arylindolin-2-one derivative. The transformation proceeds efficiently due to the inherent reactivity of isatin and hydrogen-bonding assistance from water, affording the products in good yields. The metal-free conditions and stereocontrol make this strategy valuable for accessing chiral 3-substituted 2-oxindole scaffolds relevant to biologically active compounds, although broader substrate generality remains to be established.[20]



Scheme 5: Synthesis of 3-alkyl-substituted 3-hydroxy-2-oxindole frameworks through asymmetric aldol addition of isatins.

Yong Zhang, *et.al* has worked on Direct Organocatalytic Cyanoarylmethylation of Isatins for the Diastereoselective Synthesis of 3-Hydroxy-3-cyanomethyl Oxindoles.[21] He has studied using various catalysts such as DBU, DABCO, DMAP, Diethylamine, Imidazoles, KOH, etc. The Study found that DBU is suitable catalyst to give highest yield of reported product within comparatively short period of time.

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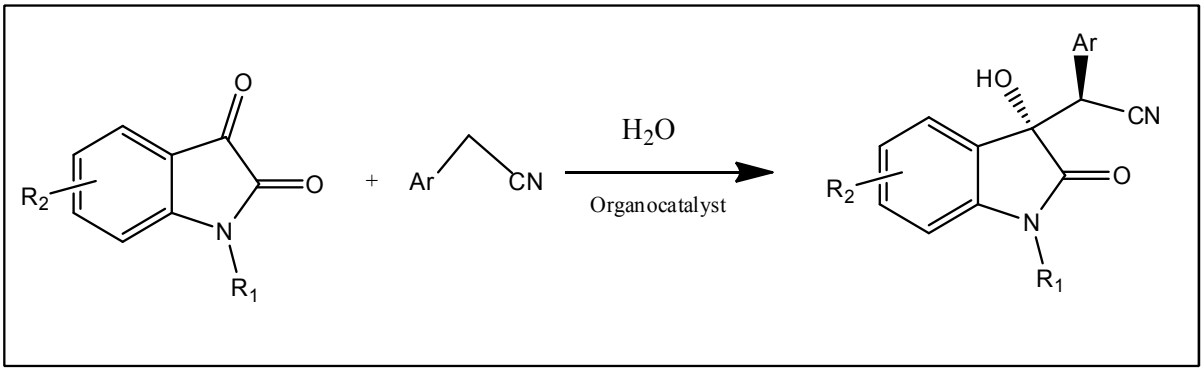
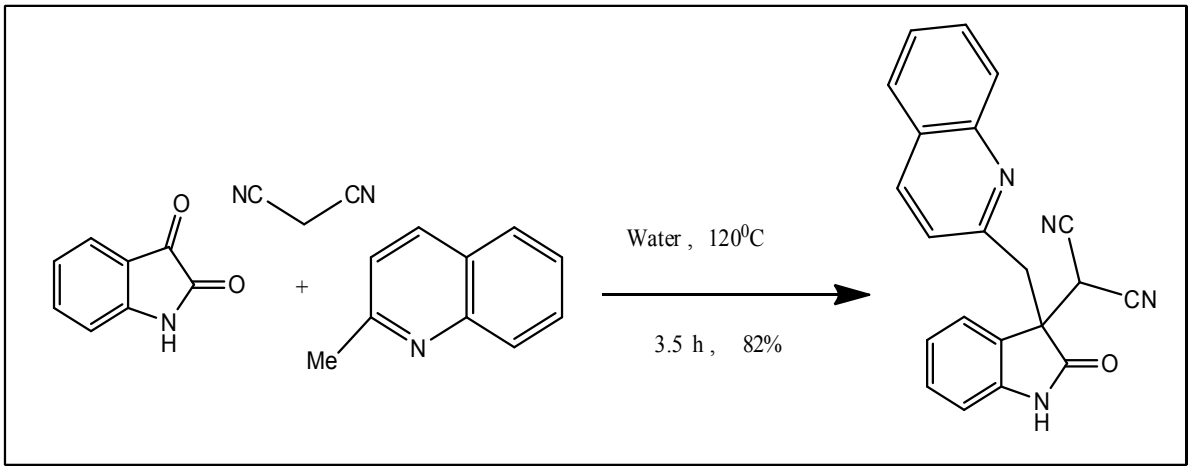


Scheme 6: Synthesis of 3-Hydroxy-3-cyanomethyl Oxindoles.

Srinivasarao Yaragorla, et.al has reported "On Water Synthesis" of Oxindoles bearing quaternary carbon center through C-H (sp3) functionalization of Methyl Azaarenes. This synthesis is three component synthesis with atom economy. Study described the synthesis of 3-indolyl-substituted oxindole frameworks via Lewis acid–catalyzed Friedel–Crafts addition of indoles to isatins. The reaction was carried out in water at 120^0C temperature using a suitable Lewis acid, affording products in good to excellent yields within short reaction times. The method provides efficient access to 3-indolyl-2-oxindole scaffolds of medicinal relevance, although reliance on a metal catalyst slightly limits its green profile. [22]



Scheme 7: Synthesis of3-indolyl-substituted 2-oxindole frameworks via Lewis acid–catalyzed Friedel–Crafts addition of indoles to isatins.

Furthermore, developments in the synthesis of 3-hydroxyoxindoles emphasize environmentally sustainable, catalyst-free approaches utilizing aqueous reaction media, reflecting a paradigm shift toward green chemistry. Pawar et al. [23] introduced an on-water strategy for direct nucleophilic addition to isatins, achieving high yields under mild, eco-friendly conditions. Complementing this, Vaid et al. [24] reported a water-mediated, catalyst-free protocol capable of accommodating a wide range of oxindole derivatives with excellent operational simplicity and functional group tolerance. Ghosh and Hajra [25] extended these methodologies to the preparation of 3-indolyl oxindoles, demonstrating the adaptability of aqueous media in constructing complex oxindole frameworks. Kidwai and Saxena [26] applied similar conditions to 3-aryl oxindoles, achieving efficient conversion at ambient temperatures, while Singh and Batra [27] highlighted an on-water approach that eliminates the need for heating or external catalysts. Patil and Yamamoto

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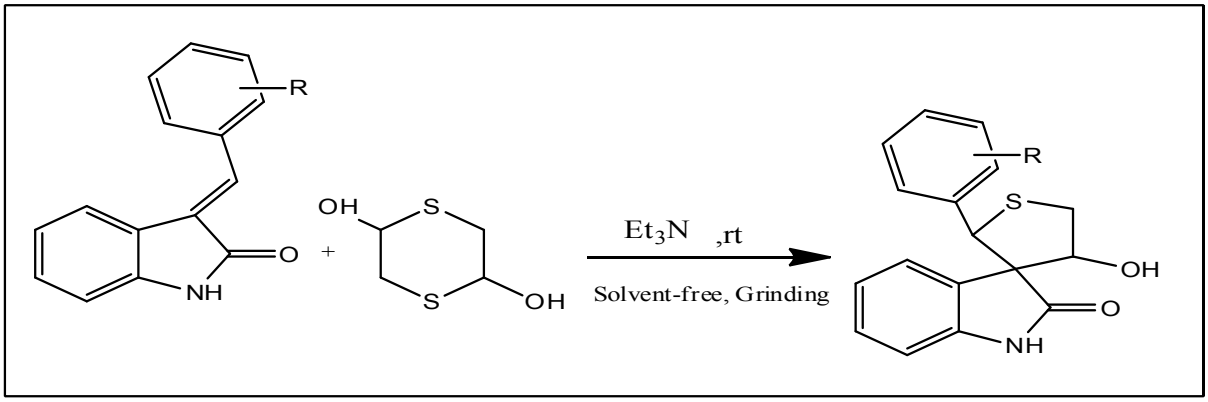
[28] investigated water-mediated additions of indoles to isatins, showing broad substrate compatibility. Aziz and Das [29] and Sharma and Kumar [30] optimized reactions under ambient, pure-water conditions, promoting energy-efficient and sustainable synthesis. Kaur and Puniya [31] emphasized the selectivity and scalability of on-water reactions for substituted 3-hydroxyoxindoles, whereas Chatterjee and Ranu [32] demonstrated room-temperature aqueous synthesis, further minimizing energy requirements. Collectively, these investigations illustrate the growing utility of water as a green solvent, the elimination of toxic catalysts, and the development of operationally simple, high-yielding, and environmentally benign protocols for the synthesis of biologically significant 3-hydroxyoxindole scaffolds.

2.2 SOLVENT FREE SYNTHESIS:

Many researchers working in the field of organic synthesis have developed different methods for the synthesis of oxindole molecules [33]. To find greener approaches researchers found a route to synthesize organic molecules is that the solvent free synthesis of organic scaffolds.**Liu et al.** the synthesis of 3-aryl-substituted 3-hydroxy-2-oxindole frameworks via nucleophilic addition of activated arenes to isatins under acid-catalyzed conditions. The transformation was performed in solvent free condition by grinding method at room temperature, delivering moderate to good yields within short reaction times. The operational simplicity and mild conditions render the method synthetically useful for constructing functionalized 2-oxindole scaffolds, although its applicability is mainly confined to electron-rich aromatic systems[34].



Scheme 8: Synthesis offrameworks via nucleophilic addition of activated arenes to isatins under acid-catalyzed conditions.

The synthesis of 3-aryl-substituted spiro-oxindole frameworks was reported by **Mohamadpour et al**. [35] using an organocatalytic multicomponent condensation of isatins with activated methylene compounds. The reaction, which was carried out in solvent free condition at ambient temperature, produced good to outstanding yields quickly. The catalyst's recycling studies were not thoroughly investigated, but the metal-free and easily operated process offers a productive path to functionalized 3-substituted oxindoles of possible pharmacological importance.

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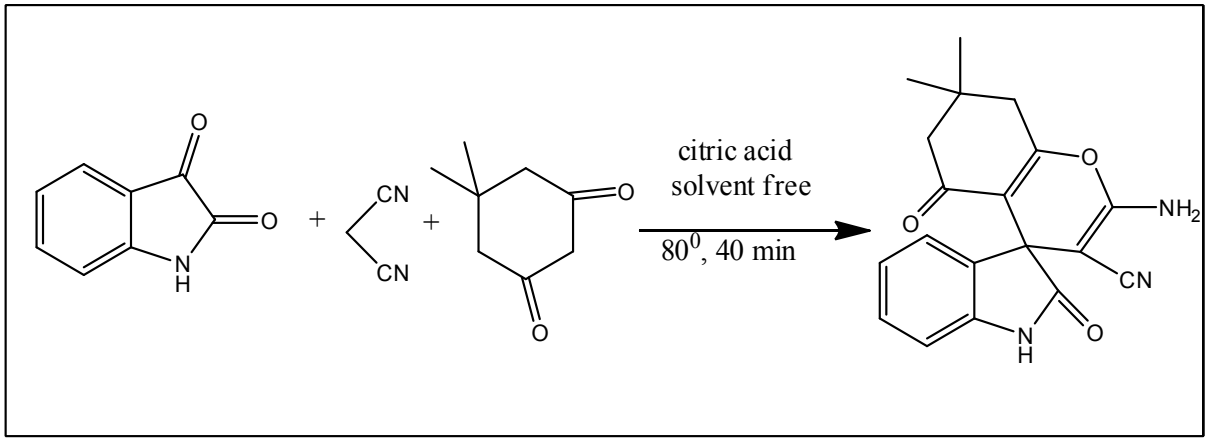

Scheme 9: Synthesis of3-substituted 2-oxindoles.

According to **Xu et al**thespiro-oxindole frameworks were synthesized within a few hours, moderate to good yields were obtained from the reaction, which was carried out utilizing a Ball-milling method. The scaffolds of pharmacological significance can be efficiently produced under mild photochemical conditions, while wider applicability may be limited by reliance on specific CF_3 reagents [36].

Scheme 10: Synthesis of3-trifluoromethyl-substituted 3-hydroxy-2-oxindole frameworks.

2.3 MICROWAVE ASSISTED SYNTHESIS:

A microwave assisted Cannizzaro/aldol reaction of para-formaldehyde and isatins shown below. Para-formaldehyde behaves as both a reductant and an electrophile. Simple and inexpensive inorganic bases are applied as the only catalysts for this process.

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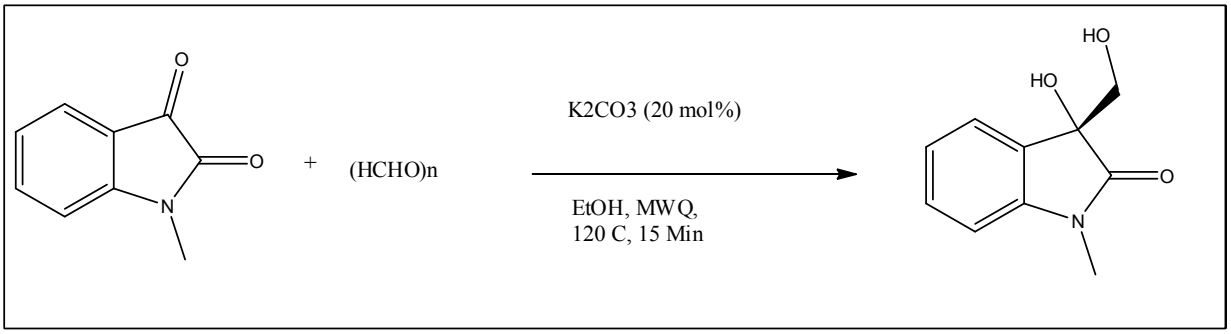
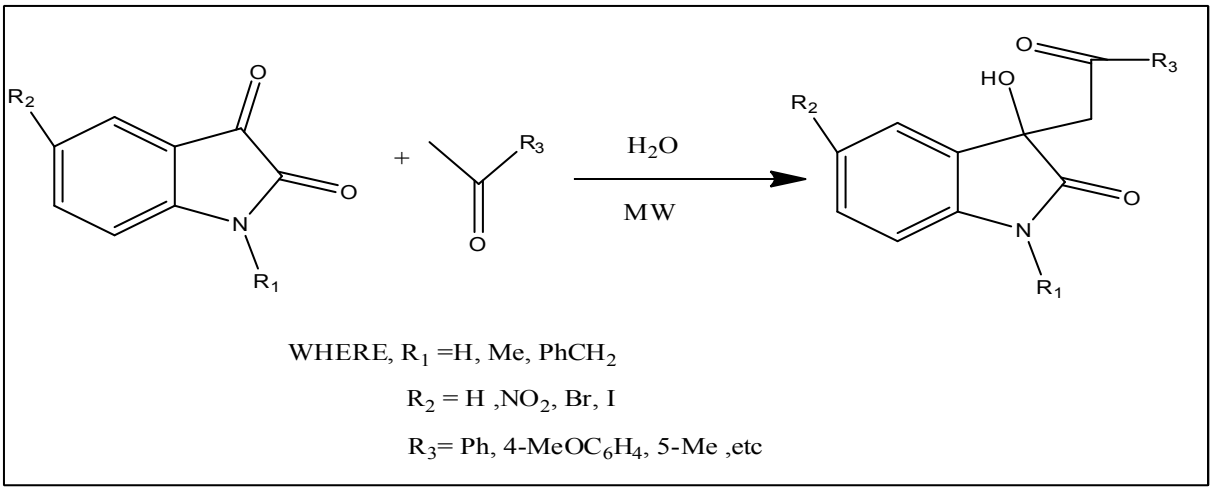


Scheme 11: Synthesis ofpara-formaldehyde substituted oxindoles.

Meshram et al. described the synthesis of 3-substituted 3-hydroxy-2-oxindole frameworks via acid-catalyzed nucleophilic addition of electron-rich arenes to isatins. The reaction was carried out in an organic solvent under reflux conditions, affording moderate to good yields within several hours. The straightforward procedure enables efficient access to functionalized 3-substituted 2-oxindoles of potential biological relevance, although the requirement of acidic conditions and heating reduces its overall green efficiency.[37].



Scheme 12: Synthesis of3-aryl-substituted 3-hydroxy-2-oxindole frameworks

Thakur et al.have mentioned the synthesis of 3-substituted 3-hydroxy-2-oxindole frameworks via Lewis acid–catalyzed Friedel–Crafts addition of indoles to isatins. The reaction was performed in dichloromethane at room temperature, affording good to excellent yields within short reaction times. This efficient protocol enables rapid access to biologically relevant 3-indolyl-2-oxindole scaffolds; however, the requirement of a metal catalyst slightly diminishes its green sustainability profile.[39].

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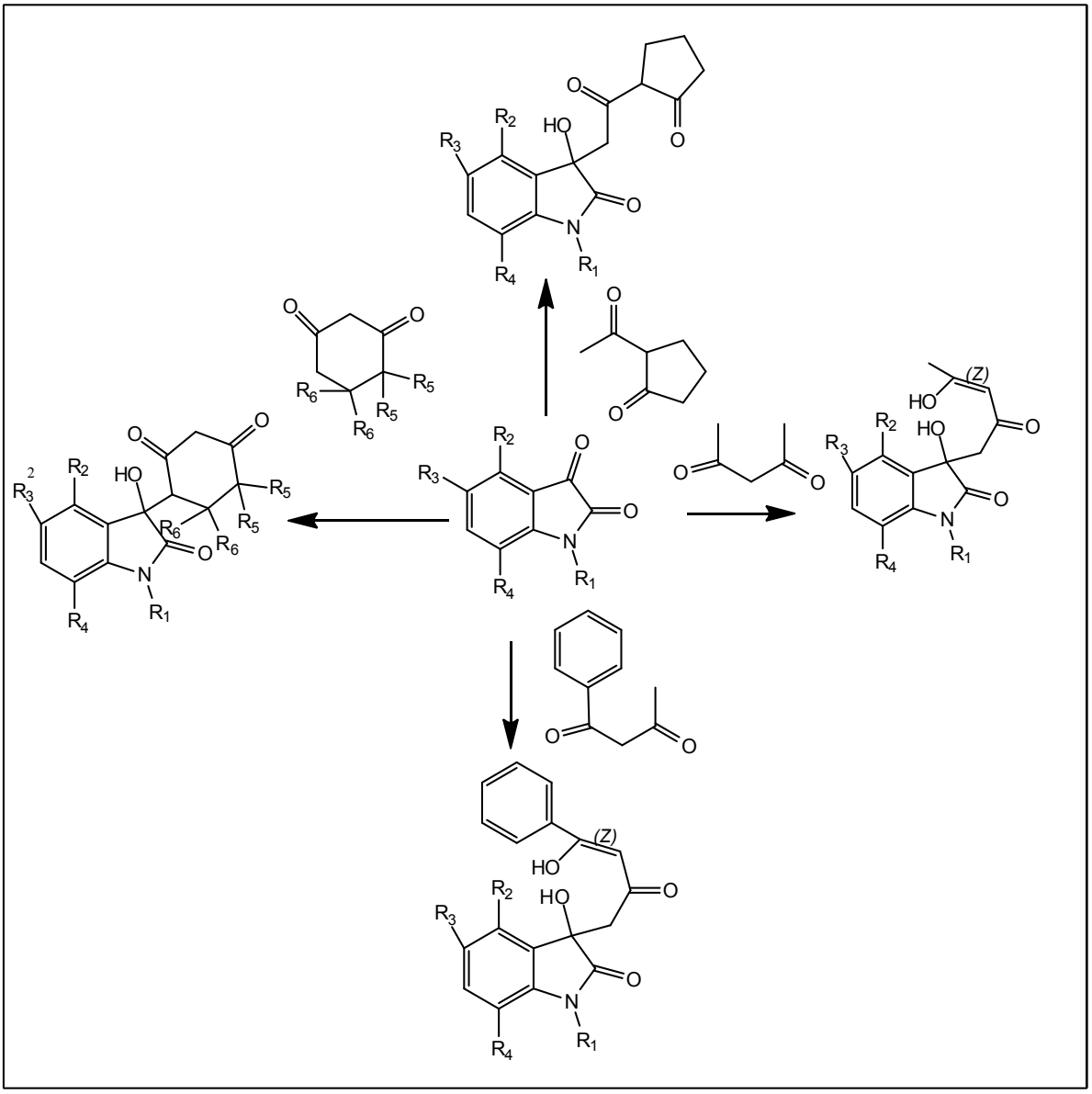

Scheme 13: Synthesis of3-substituted 3-hydroxy-2-oxindole derivatives.

Efremov et al. recently reported the synthesis of 3-substituted 3-hydroxy-2-oxindole derivatives via base-promoted nucleophilic addition of activated aromatic systems to isatins. The transformation was carried out in antriethylamine and 1,4-dioxane solvent under microwave, affording moderate to high yields within 10 minutes. The method enabled access to functionalized 3-substituted 2-oxindoles that were further evaluated for biological activity, highlighting their potential pharmacological relevance, although reaction efficiency depended on electronically activated substrates.[38]

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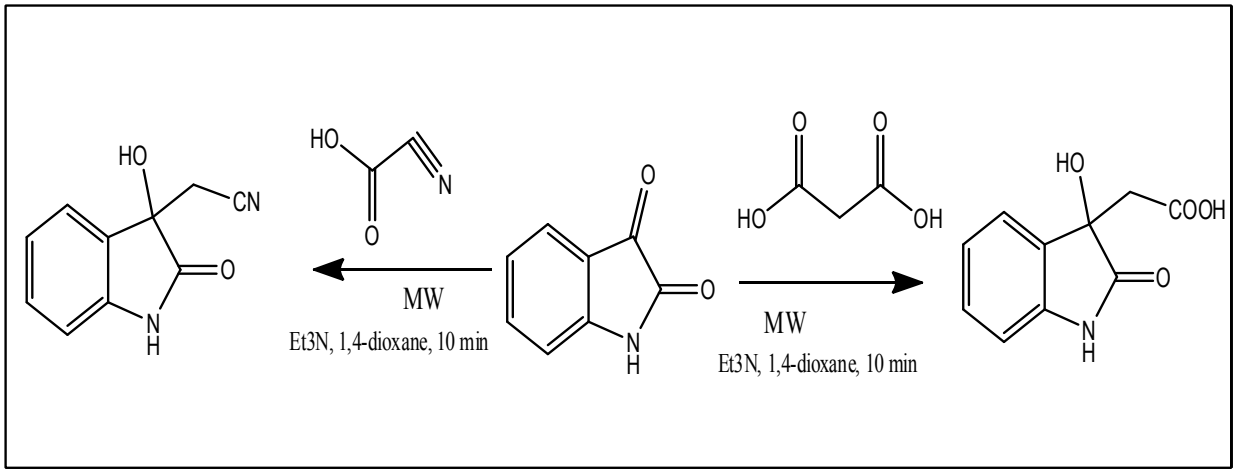

Scheme 14: Synthesis of3-substituted 3-hydroxy-2-oxindole derivatives.

2.4 ULTRASOUND ASSISTED SYNTHESIS:

Ghahremanzadeh et al. developed an ultrasound-assisted synthesis of 3-substituted 3-hydroxy-2-oxindole frameworks via nucleophilic addition of activated methylene compounds to isatins.

Scheme 15: Synthesis of spiro 3-substituted 2-oxindoles.

The reaction was performed in triethyl amine and THF under ultrasonic irradiation at ambient temperature, affording high yields within significantly reduced reaction times. The sonochemical approach enhances reaction efficiency and energy economy, providing a greener route to functionalized 3-substituted 2-oxindoles with potential biological relevance, though scalability under ultrasonic conditions may require optimization.[40].

Kanchrana and colleagues documented the synthesis of spiro 3-substituted 3-hydroxy-2-oxindole frameworks through base-mediated nucleophilic addition of activated methylene compounds to isatins. The reaction was conducted in ethanol under mild heating, affording moderate to excellent yields within a few hours. The operational simplicity and use of relatively benign conditions render the method practical for accessing functionalized 3-substituted 2-oxindoles of potential pharmaceutical interest, although broader substrate diversity warrants further investigation[41]. It was very efficient synthesis of spirooxindoles. About eighteen isatin Schiff bases were synthesized with 80-85% yield under basic medium using triethylamine. These molecules were found showing moderate anti-cancer activity.

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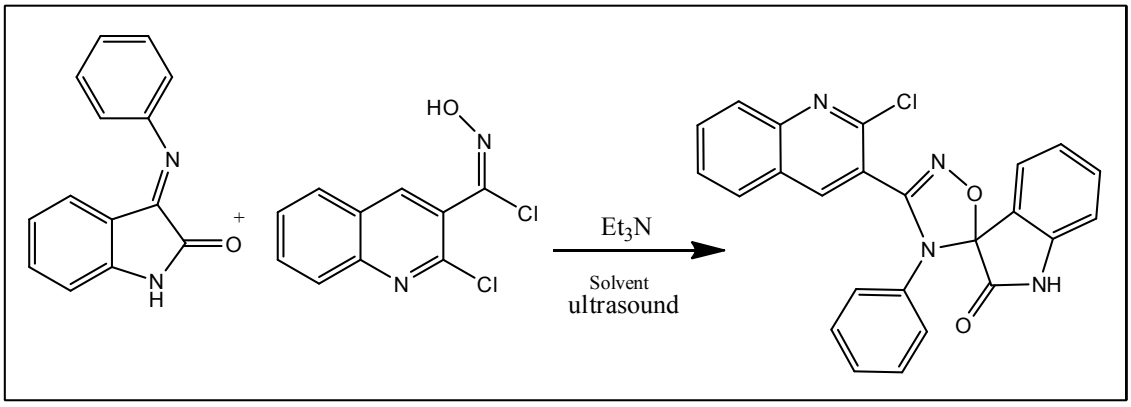
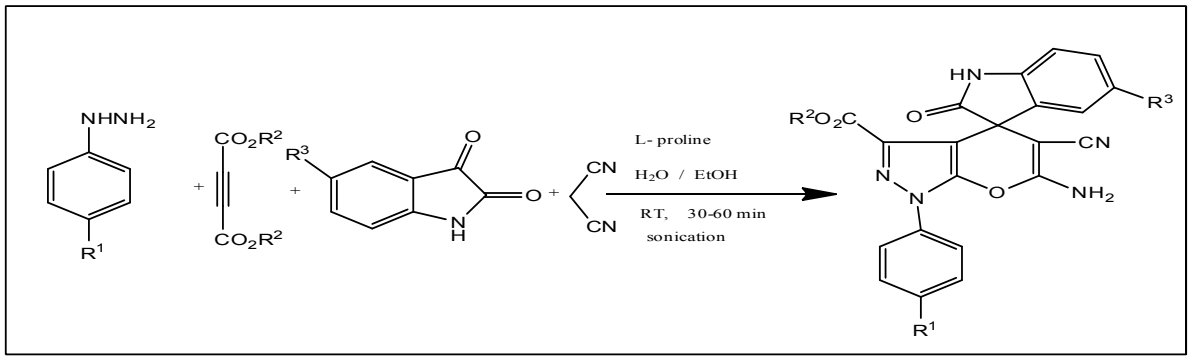


Scheme 16: Synthesis of3-substituted 2-oxindoles.

By nucleophilically adding activated arenes to isatins, **Liju et al.** reported synthesizing 3-aryl-substituted 3-hydroxy-2-oxindole frameworks with the aid of ultrasound. Good to excellent yields were obtained in significantly shorter reaction times when the transformation was performed in ethanol under ultrasonic irradiation at room temperature. Although additional validation may be necessary for large-scale applicability, the sonochemical conditions provide a more environmentally friendly route to bioactive 3-substituted 2-oxindole scaffolds by increasing reaction efficiency and lowering energy usage.[42].



Scheme 17: Synthesis of3-substituted 2-oxindoles

By base-promoted nucleophilic addition of active methylene compounds to isatins, **Xiufang et al.** reported synthesizing 3-alkyl- and 3-aryl-substituted 3-hydroxy-2-oxindole frameworks.

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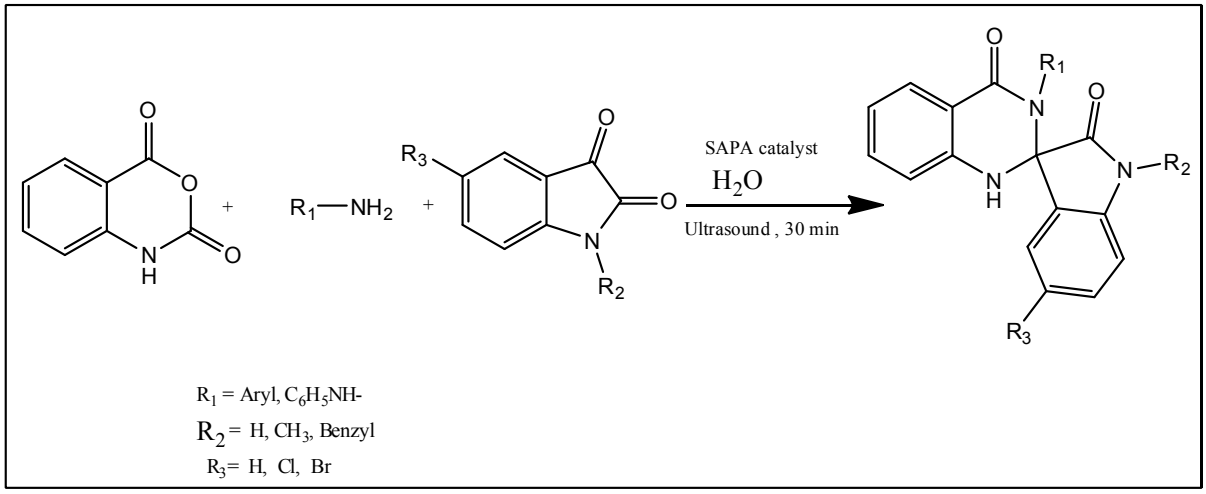

Scheme 18: Synthesis of3-alkyl- and 3-aryl-substituted 3-hydroxy-2-oxindole frameworks

The reaction produced good to outstanding yields in brief reaction times when it was carried out in ethanol under mild heating conditions. Although the technology mainly favors electronically activated substrates, the simple protocol and relatively moderate conditions make it easier to access functionalized 3-substituted 2-oxindoles of potential biological interest. [43].

Ultrasound-assisted methodologies have emerged as a powerful green strategy for the synthesis of 3-hydroxyoxindoles and related oxindole derivatives, offering enhanced reaction rates, selectivity, and operational simplicity. **Khorshidi and Tabatabaeian** [44] reported a one-pot ultrasound-promoted reaction of isatins with indoles to efficiently access 3-indolyl-3-hydroxyoxindoles, demonstrating the ability of sonochemical activation to accelerate bond formation under mild conditions. **Dabiri et al**. [45] extended this approach to multi-component spirooxindole synthesis, highlighting the utility of ultrasonic irradiation in facilitating complex scaffold construction with minimal energy input. **Khorrami et al.** [46] further explored aqueous sonochemical protocols for oxindole derivatives, emphasizing the compatibility of water as a benign solvent in ultrasound-mediated reactions. **Bazgir et al.** [47] showcased an ultrasound-assisted one-pot, three-component assembly of spiro[indoline-3,4′-pyrazolo[3,4-b]pyridine] derivatives, illustrating the method's versatility for constructing fused heterocycles. Recent reviews by **Pagadala** [48], **Draye** [49], and **Choupra et al.** [50] have consolidated these findings, highlighting ultrasound as a sustainable alternative to conventional heating, capable of promoting multicomponent and aqueous-mediated transformations while reducing reaction times, energy consumption, and reliance on hazardous catalysts. Collectively, these studies underscore the growing importance of sonochemistry in the green synthesis of bioactive oxindole scaffolds, demonstrating high efficiency, operational simplicity, and environmental compatibility, making ultrasound-assisted methods increasingly attractive for scalable and sustainable organic synthesis.

2.5 ORGANIC CATALYSTSMEDIATED GREEN SYNTHESIS:

Thakur et al.reported the synthesis of 3-aryl- and 3-indolyl-substituted 3-hydroxy-2-oxindole frameworks via Brønsted acid–catalyzed Friedel–Crafts addition of electron-rich arenes to isatins. The reaction was conducted in THF at ambient temperature, affording good to excellent yields within a few hours. The mild conditions enable efficient access to pharmacologically relevant 3-substituted 2-oxindoles, although the use of acid catalyst and organic solvent slightly limits its green sustainability profile.[51]

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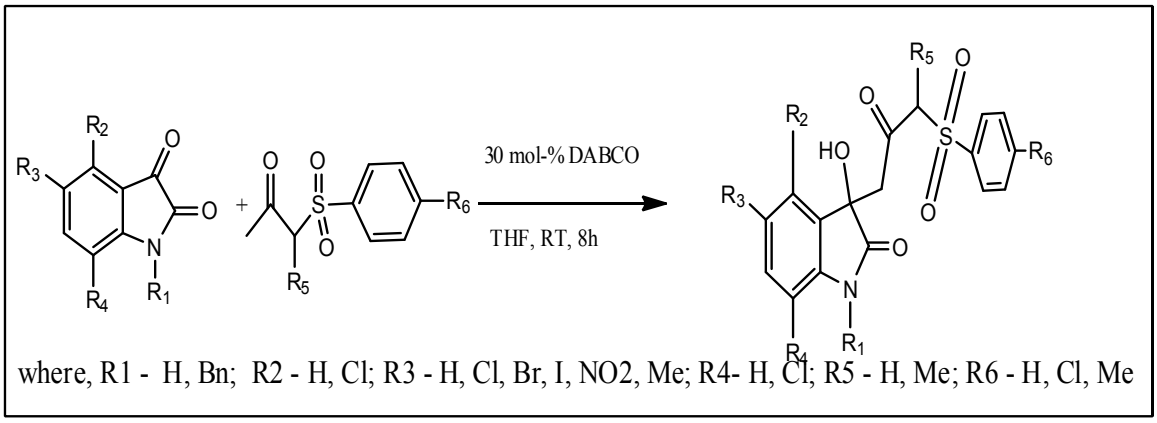
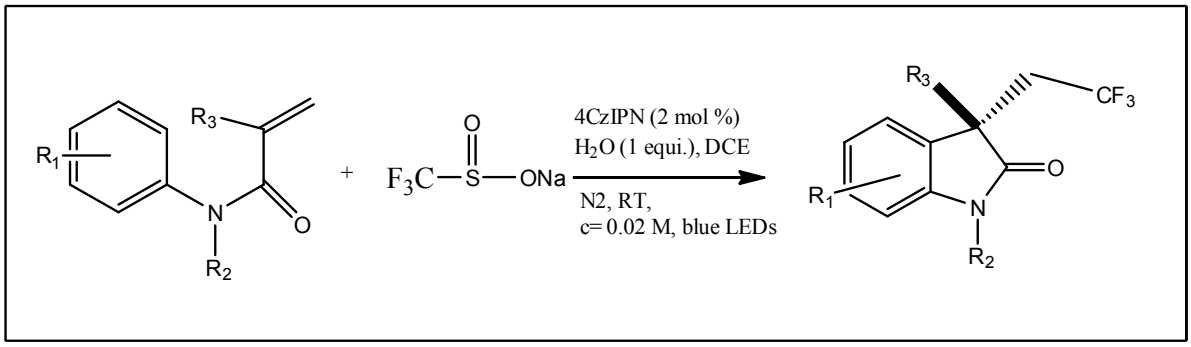


Scheme 19: Synthesis of 3-aryl- and 3-indolyl-substituted 3-hydroxy-2-oxindole

Recent work have been published by **Maojian Lu** and his co-workers on, to synthesize the oxindoles from n-aryl acrylamindes using photoredox catalysts.



Scheme 20: Synthesis ofoxindoles from n-aryl acrylamindes using photoredox catalysts

A chiral organocatalyzed aldol-type addition of isatins to appropriate nucleophiles was used by **Montesinos-Magraner et al.** to synthesize 3,3′-disubstituted-2-oxindole frameworks in an enantioselective manner. Using a bifunctional catalyst, the reaction was performed in an organic solvent at a low temperature, producing good yields with superior enantioselectivity. Although careful adjustment of catalyst loading and substrate scope is necessary, this approach offers effective access to stereodefined 3-substituted 2-oxindoles of pharmacological significance [52].

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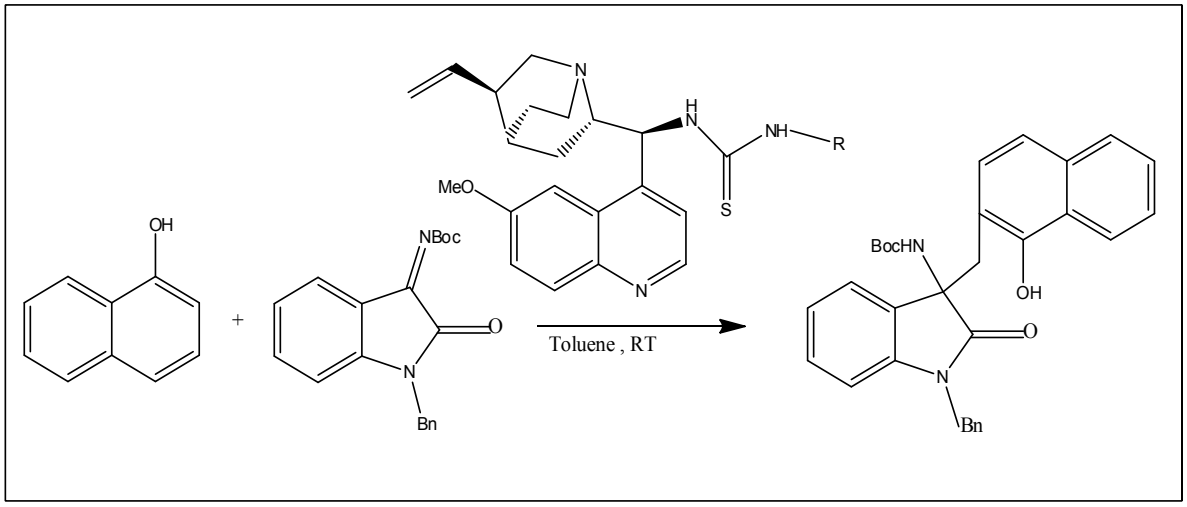
ISSN: 2581-9429
Volume 6, Issue 4, February 2026
Impact Factor: 8.2



Scheme 21: Synthesis of3,3′-disubstituted 2-oxindole frameworks.

Lai et al. [53] reported the enantioselective addition of ketones and aldehydes to isatins to yield 3-alkyl- and 3-aryl-substituted 3-hydroxy-2-oxindoles using a chiral amine organocatalyst in THF at mild temperature. **Tomita et al.** [54] developed a more enantioselective approach employing a chiral heterobimetallic rare-earth/alkali metal catalyst to couple isatins with malonate derivatives, producing 3,3-disubstituted 3-hydroxyoxindoles at low temperature with excellent stereocontrol. **Badillo et al.** [55]reviewed these and other methods, comparing organocatalytic, Lewis acid, and metal-catalyzed protocols, highlighting yields, selectivity, and substrate scope. While Lai's method is simple and mild, Tomita's approach offers superior enantioselectivity, and Badillo emphasizes broader applicability in drug-like oxindole scaffolds. [53]. Rh-, Pd- and Cu-catalyzed additions of boronic acid or silane nucleophiles to isatins.

Scheme 22: Synthesis of3-alkyl- and 3-aryl-substituted 3-hydroxy-2-oxindoles

Condition A [53]: [RhCl(C2H4)2] 2 (5 mol%) / 6 (10 mol%) / KOH (15 mol%) / THF:H2O (20:1) / 50°C / 24 h R = H, PMB, CH3, Bn R1 = Cl, CH3O, CH3

Condition B [54]: Pd(OAc)2 (5 mol%) / 7 (10 mol%) / t-BuOK (0.5 eq) / BF3 . Et2O (4 eq) / THF / rt / 48 h R = Bn R1 = H

Condition C [55]: (i) CuF. 3P(4-F-Ph)3 . 2EtOH (5 to 10 mol%) / 8 (14 mol%) / ZnF2 (30 mol%) / toluene / rt or 80°C (ii) TBAF R = PMB, DMTr R1 = H, Cl, OCH3, CH3, CF.

In a mildly acidic environment, **Prathima et al**. synthesized 3-(2-pyrrolidinyl)-substituted oxindole frameworks by condensation of isatins with cyclic amines and nitroalkenes in a single pot. Using a Bronsted acid catalyst, the reaction was conducted in toluene at -45^{0}C temperature and produced good to outstanding yields in a matter of hours. Although the protocol's substrate breadth was mostly restricted to cyclic amines and electron-deficient nitroalkenes, it offers

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Volume 6, Issue 4, February 2026
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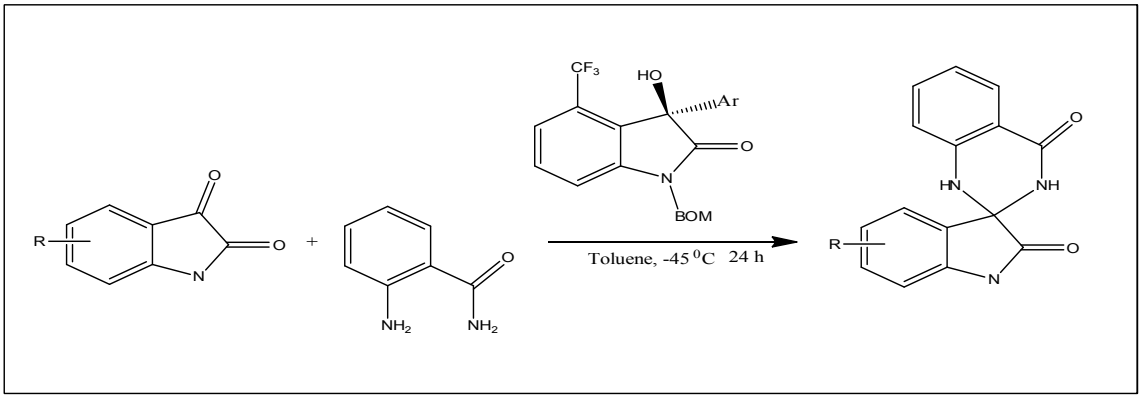
operationally straightforward access to physiologically significant oxindole derivatives with potential anticancer and antibacterial activities.[56]



Scheme 23: Synthesis of3-(2-pyrrolidinyl)-substituted 3-hydroxy-2-oxindole frameworks

In order to get highly functionalized and stereochemically specified scaffolds, recent developments in the synthesis of 3-hydroxyoxindoles have made use of photoredox, enantioselective, and electrochemical techniques. Zhang et al. [57] employed a tandem photoredox and chiral phosphoric acid-catalyzed radical-radical cross-coupling, achieving enantioselective construction of 3-hydroxyoxindoles under mild conditions. Similarly, Tang et al. [58] utilized allylation of isatins to generate 3-allyl-3-hydroxyoxindoles with high diastereo- and enantioselectivity, highlighting the versatility of catalytic asymmetric transformations in modifying the C3 position. Vayer et al. [59] demonstrated electrochemical rearrangement of 3-hydroxyoxindoles to benzoxazinones, presenting a green, energy-efficient alternative for structural diversification of oxindole derivatives.

Parallel approaches have focused on biologically relevant functionalization and the incorporation of reactive motifs. Wei et al. [60] synthesized 3-hydroxy-2-oxindole derivatives bearing sulfonamide groups, demonstrating significant antiviral activity, while Kabra et al. [61] achieved regioselective thioether-linked oxindoles via ring-opening of spiroepoxy intermediates, underscoring the importance of chemoselectivity in medicinally relevant scaffolds. Baur et al. [62] employed oxidative dearomatization of 3-substituted indoles using sulfonium salts to access hydroxyoxindoles directly, providing a straightforward pathway to functionalized derivatives. Sharma et al. [63] further explored homodimerization strategies to construct vicinal quaternary centers, integrating chemical, photochemical, and electrochemical methodologies for complex oxindole architectures.

In addition, microwave-assisted protocols have emerged as efficient alternatives for rapid oxindole synthesis. Huang et al. [64] reported microwave-mediated Cannizzaro and aldol reactions of formaldehyde with isatins and imines, enabling the formation of 3,3-disubstituted oxindoles with high yield and operational simplicity.

III. CONCLUSION

In conclusion, the synthesis of 3-hydroxyoxindoles has seen significant progress through green and sustainable strategies, highlighting water-mediated, catalyst-free, microwave, ultrasound, and organocatalytic methodologies. Water-based protocols offer operational simplicity, high efficiency, and minimal environmental impact, making them ideal for large-scale and eco-friendly production. Microwave-assisted techniques provide rapid reactions with reduced energy consumption and enhanced yields, while ultrasound-promoted approaches exploit cavitation effects for efficient multicomponent and spirooxindole synthesis. Organocatalytic and photoredox strategies enable precise stereocontrol, expanding structural diversity for biologically active derivatives. Solvent-free and heterogeneous catalytic methods further reduce chemical waste and improve reaction sustainability. Considering efficiency, environmental impact, and functional diversity, water-mediated, catalyst-free syntheses are preferred for sustainable production, whereas

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ISSN: 2581-9429 Volume 6, Issue 4, February 2026 Impact Factor: 8.2

microwave and ultrasound-assisted routes are advantageous for rapid and high-yielding transformations. For enantioselective or highly functionalized oxindoles, organic or photoredox catalysts remain the method of choice.

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