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Utility and Applicability of Green Synthesized ISATIN Derivatives with Active Methylene Heterocycles

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Abstract: *ISATIN (1H-indole-2,3-dione), which is derived from the oxidative breakdown of the natural indigo dye, has been proven to be one of the most efficient carbonyl synthons in the field of heterocyclic chemistry. Isatin has been shown to participate in electrophilic reaction of its C-3 carbonyl with various active methylene reagents, including barbituric acid, thiobarbituric acid, malononitrile, cyanoacetamide, pyrazolones, rhodanine, thiazolidinedione and 4-hydroxycoumarin, to furnish various biologically relevant arylidene, spirooxindoles, and indolinone scaffolds. The current review compiles some recent trends on green and sustainable synthesis of isatin active methylene hybrids, where green and sustainable catalytic systems have been used for the synthesis, which include aqueous media and water-on-media reactions, ionic liquids, deep eutectic solvents (DES), reusable magnetic nano-catalysts, grinding and mechanochemical methods, and microwave/ultrasound techniques. Comparing reaction yield, reaction time, and green chemistry parameters, such as E-factor and atom economy, shows that green methods not only excel conventional synthesis by reflux, but also improve the pharmacological potential of synthesized heterocycles. The data obtained through biological testing from the literature indicate that these hybrids have good anticancer, antimicrobial, antidiabetic, antiviral and anti-inflammatory properties, thus making green synthesized isatin-active methylene hybrids good candidates for use in future drug development programs. This review further analyzes the structure activity relationship, Knoevenagel condensation mechanism, and other critical issues that need to be resolved to commercialize green chemistry methods.*

Introduction

Isatin is a bicyclic heterocyclic compound containing benzene ring with a five-membered ring having two adjacent carbonyl moieties at C-2, C-3 positions and a nitrogen at N-1 position. Isatin was synthesized for the first time in 1840 by Erdmann and Laurent via oxidation of indigo and has since then been identified in plants, marine sources and even mammalian organs emphasizing its biological significance [1,5]. The C-3 carbonyl moiety of isatin is significantly electrophilic due to its conjugation with

adjacent amide carbonyl and aromatic system, making it very reactive towards nucleophiles and active methylene reagents giving Schiff's bases, hydrazones and importantly, C-C bonded condensation products via Knoevenagel reaction [1,2].

Active methylene heterocycles are characterized by a ring system with CH2 that is located between two electron withdrawing groups, examples of which include barbituric acid, thiobarbituric acid, malononitrile, cyanoacetamide, pyrazol-5-ones, rhodanine, thiazolidine-2,4-dione, 4-hydroxycoumarin, indane-1,3-dione, etc. The proton from the acidic methylene carbon atom can easily be removed to give rise to a stabilized carbanion that reacts with the carbonyl at the isatin C-3 position to give rise to arylidene (Knoevenagel) compound or a spirocyclic oxindole using multicomponent reaction [8,9,13]. The hybrid systems possess pharmacophoric elements of both indolinone and active methylene heterocycle [3,4].

Historical methods for the synthesis of isatin active methylene condensates have involved prolonged reflux in ethanol or acetic acid, usually in presence of corrosive mineral acid and base catalysts, resulting in significant amounts of waste and prolonged time periods (several hours). Green chemistry, based on the minimization of wastes, use of safer solvents and energy efficiency as well as recyclable catalysts, has led to great efforts for the search of alternative media and catalysts for isatin chemistry during last ten years [1,2]. The present review focuses on the applicability and utility of these isatins which are synthesized according to green methodology and their pharmacological significance.

Isatin: Structure, Reactivity and Role as an Electrophilic Synthon

Reactivity of isatin towards active methylenes is controlled mainly by the C-3 ketonic carbonyl group, which is highly electrophilic compared to C-2 amide carbonyl group due to decreased resonance effect from ring nitrogen and polarization from the fused benzenoid ring [5,6]. The property makes isatin a good candidate for participation in Knoevenagel-like condensation reactions without interference from the second position, and this ability has been used for generation of vast numbers of spirooxindole and arylidene-oxindole collections. Ring substituents of isatin, especially halogen substituents at the 5-position, affect the electrophilicity of C-3 and consequently the speed of condensation and biological properties of the hybrid formed, as demonstrated by numerous SAR studies [2,6].

In addition to being an electrophilic scaffold, isatin has itself various biological activities, such as antimicrobial, antiviral, anticonvulsant, antitubercular, anti-inflammatory, antimalarial and anticancer activities, which persist or increase after hybridization of the compound with various active methylene heterocycles in the form of molecular hybridization techniques [16,6]. It is these unique combination of properties, namely synthetic diversity and inherent bioactivity, which have made isatin derivatives objects of interest for both medicinal and green chemists during the past two decades.

Active Methylene Heterocycles: Chemistry and Selection Rationale

The barbituric acid and its sulfuranalogthiobarbituric acid have a cyclic urea skeleton wherein the C-5 methylene is bonded between two carbonyls, thus making it highly acidic and a very good Knoevenagel donor. Isatin condensation reaction with the barbituric acid analogs occurs with great chemical selectivity and has been shown unambiguously through NMR spectroscopy and single crystal X-ray diffraction analysis [7]. The barbituric acid analogs, whose detailed chemistry has been comprehensively covered by Kaur and co-workers, add antihistamine, sedative-hypnotic, antiviral, anticonvulsive, antimicrobial, and antitumor pharmacophoric properties to the [8].

Another example of a frequently applied active methylene reagent is malononitrile, which is rapidly condensed with isatin without any catalysts in water or in an ethanol-water solution either under visible light irradiation or at room temperature, producing 3-(dicyanomethylene)-oxindoles that are important intermediate products for the synthesis of spiro-pyran and pyridine systems [9,10]. Pyrazolones, rhodanine and thiazolidine-2,4-diones are examples of heterocyclic compounds with active methylene nitrogen or sulphur moiety, which condensation with isatin produces hybrids of special significance in antidiabetic and anticancer drug design, as thiazolidinediones themselves possess insulin sensitising and α-glucosidase inhibiting properties [16,20,21]. Table 1 contains the main active methylene heterocycles that were used for condensation with isatin.

Active Methylene Heterocycle	Reactive Site	Typical Product Class	Principal Pharmacophoric Contribution
Barbituric acid / Thiobarbituric acid	C-5 methylene	5-(Oxindolylidene) barbiturates	Anticonvulsant, antiviral, antimicrobial [7,8]
Malononitrile	Active CH2	3-(Dicyanomethylene)oxindoles	Antiproliferative, precursor to spiro-pyrans [9,10]
Pyrazol-5-one	C-4 methylene	Spiro/arylidene pyrazolone-oxindoles	Anti-inflammatory, antimicrobial [23,25]
Rhodanine	C-5 methylene	5-Oxindolylidene rhodanines	Antimicrobial, antidiabetic [17]
Thiazolidine-2,4-dione	C-5 methylene	Thiazolidinedione–isatin conjugates	Antidiabetic (α-glucosidase inhibition), anticancer [20,21]
4-Hydroxycoumarin / 4-Hydroxythiocoumarin	C-3 methylene	Spirooxindole-coumarins	Antioxidant, anticoagulant-related activity [9]

Green Synthetic Methodologies for Isatin–Active Methylene Condensation

- **Aqueous and On-Water Reactions**

Because water is the cheapest and safest solvent, it has proven to be successful as an environmentally friendly solvent for catalyst-free Knoevenagel condensation between isatin and malononitrile, as well as 1,3-cyclic dicarbonyl compounds, like 4-hydroxycoumarin and barbituric acid. This 'on water' reaction runs efficiently at room temperature in visible light, without the requirement of any additional catalyst, resulting in good-to-excellent yields, which makes it an example of an eco-friendly approach that meets the requirements of atom economy and waste reduction [9,10].

- **Isatin Derivatives Synthesis Using Ionic Liquids**

Owing to negligible vapor pressure, thermal stability, and acid-base property modulation, ionic liquids (ILs) have been extensively studied as a combination of solvent and catalyst for isatin chemistry. Thus, acidic ionic liquids based on DABCO were used as a highly efficient and recyclable catalysts to synthesize 5-arylidene(thio)barbituric acids and related pyrano[2,3-d]pyrimidinone derivatives [1,14]. A review provides a detailed discussion of imidazolium-based ILs as both reaction solvents and Brønsted/Lewis acid catalysts in heterocycle synthesis from isatins [1].

- **Deep Eutectic Solvents (DES)**

The deep eutectic solvents, usually synthesized by mixing hydrogen bond donors and acceptors like choline chloride and urea, have become popular choices for biodegradable and inexpensive, recyclable solvents as opposed to volatile organic solvents. The three-component reaction of isatin, active methylene and β-ketoester in choline chloride and urea (2:1) DES has led to the production of spirooxindoles in the yields of 81-93% with excellent recyclability of the solvent-catalyst system in several runs [22]. The neutral DES solvent has also been successfully employed for the preparation of spiropyrazoline-indolinones from 5-halo-isatins, substituted hydrazines and aromatic ketones with DFT studies also rationalizing the reaction pathway [23]. The natural deep eutectic solvents (NADES), which involve the mixture of choline chloride and lactic acid, have been employed for the construction of spiro[indoline-3,4'-pyrazolo[3,4-b]pyridine] without the need of metals [26,27].

- **Nanocatalysis and Magnetic Recyclable Catalysts**

The novel use of magneto-recoverable nanocatalysts like Fe3O4@L-arginine, guanidine-functionalized Fe3O4 nanoparticles etc. provides an effective combination of high catalytic efficiency with easy removal and recycling, which eliminates one of the major drawbacks of homogenous catalysis systems. The mentioned nanocatalysts have already been employed successfully for solvent-free multicomponent synthesis of spiro[indoline-3,4′-pyrano[2,3-c]pyrazole] derivatives via the reaction between isatin, hydrazines, β-ketoesters and malononitrile, with a repeated catalytic activity of the catalyst established in several cycles according to the results of the SEM, EDX, FTIR and XRD analyses [27,28]. Also, hercynite sulfaguanidine-supported nanocatalysts proved their worth for green synthesis of isatin Schiff bases quinoxaline hybrids used for anticancer evaluation [6].

- **Solvent-free, Grinding and Mechanochemical Approaches**

The mechanochemical grinding of a mixture of appropriate reagents in a mortar and pestle with the help of a catalytic amount of an organic acid like acetic or p-toluenesulfonic has been demonstrated to provide a successful preparation of 5-arylidenebarbituric and thiobarbituric acids in just 5-20 minutes under room temperature conditions, without any organic solvents [12,13].

- **Microwave- and Ultrasound-Assisted Synthesis**

Knoevenagel condensation of barbituric acid and aromatic aldehyde takes place at a very high rate when performed using microwave irradiation, where the reaction time gets shortened from 24 hours using traditional heating method to 5-10 minutes; and the reaction has also been carried out for the isatin derivatives [11]. Ultrasound irradiation with Lewis acid catalysts like Fe(III) salt has led to rapid 3-indolylation and similar functionalization of C-3 of isatins [10].

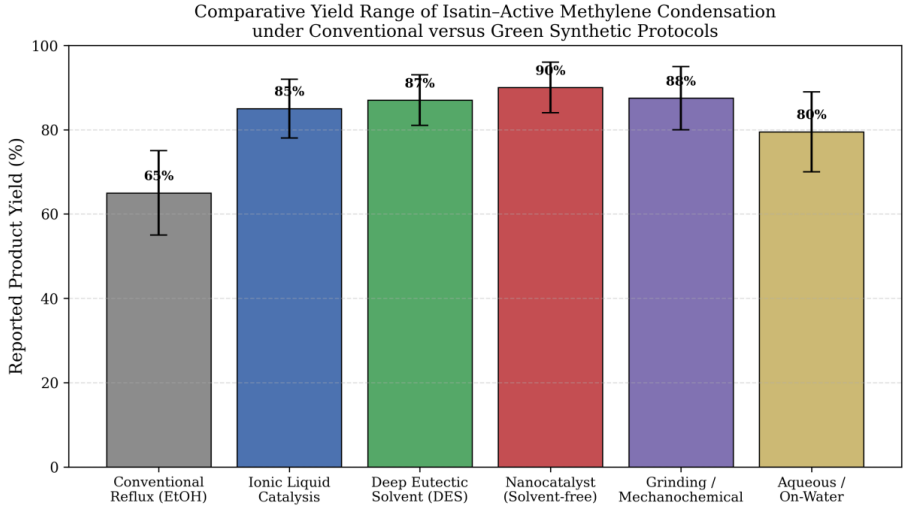

Figure 1: Comparative yield range reported for isatin–active methylene condensation across conventional and green synthetic protocols (data compiled from references [1,7-14,22-28]).

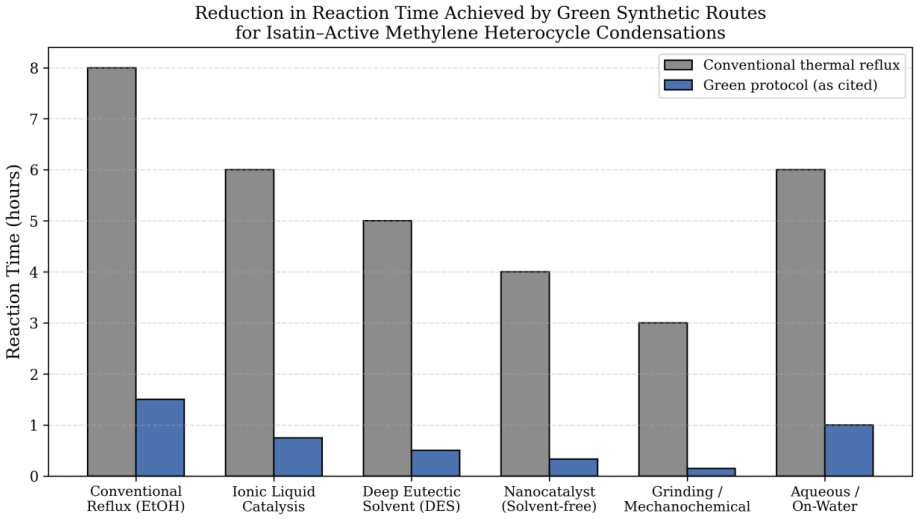

Figure 2: Representative reduction in reaction time achieved by green protocols relative to conventional thermal reflux for the synthesis of isatin–active methylene hybrids.

Mechanistic Considerations

The condensation reaction between isatin and active methylene heterocycles occurs via a standard Knoevenagel pathway where the deprotonation of the active methylene group produces a resonance-stabilized carbanion that then attacks the electrophilic C-3 carbonyl group of isatin to produce a β-hydroxy product. The final dehydration process via acid-base catalysis produces the thermodynamically stable, conjugated arylidene (Knoevenagel) product with an exocyclic double bond on C-3 of the oxindole skeleton [9,13,14]. The hydrogen bonding interaction within the solvent medium such as DES and ionic liquids are postulated to help accelerate the deprotonation process and stabilization of the developing negative charge, thereby explaining the faster reaction rates compared to the normal aprotic and protic organic solvents [22,23]. In the presence of a third component such as a substituted hydrazine or 1,3-dicarbonyl compounds, the initially produced Knoevenagel adduct undergoes intramolecular/intermolecular Michael addition and cyclization reactions to produce spirooxindole products with a new quaternary spiro-center on C-3 of the oxindole structure, reaction which has been thoroughly described in the synthesis of pyrazole, pyran and pyridine spirooxindoles [24,25,26].

Biological and Pharmacological Applications

- **Anticancer Activity**

Antiproliferative activity of green-synthesised isatin-active methylene hybrids has proven to be very significant in several cancer cell lines. Compounds formed through condensation between isatin and indirubin-like active methylene heterocycles have been identified as selective inhibitors of the growth of apoptosis-resistant cancer cells which are difficult targets for chemotherapy [4]. Greenly synthesised thiazolidinone-isatin and thiazolo[3,2-a]benzimidazolone-isatin conjugates have exhibited good potency against MCF-7 and MDA-MB-231 breast cancer cell lines with the more potent derivative showing mitochondrial intrinsic apoptosis mechanism at a very low micromolar concentration [21]. Greenly synthesised isatin derivatives studied as CDK2 inhibitors have been found to be cytotoxic against MCF-7 cancer cell line with IC50 in low micromolar concentrations, which was justified through density functional theory and molecular dynamics studies [2]. Greenly synthesised thiazolidinone-isatin hybrids having benzenesulfonamide moieties have been optimised as isoform-selective inhibitors of the carbonic anhydrase enzymes isoforms IX and XII with nanomolar inhibitory constants [19].

- **Antimicrobial and Antifungal Activity**

The library of isatin bis-indole and isatin bis-imidazothiazole hybrids was tested for activity against Staphylococcus aureus, Escherichia coli, and Candida albicans where selected analogs exhibited inhibitory action at a low microgram-per-milliliter concentration, proving the efficacy of isatin hybrid derivatives as potential antimicrobial candidates against bacterial and fungal pathogens [17]. Significant cytotoxicity of green-synthesized isatin hybrids against Candida albicans and Cryptococcus neoformans, in conjunction with molecular docking against specific bacterial and fungal proteins, has also been reported [20].

- **Antidiabetic Activity**

The design of new hybrid structures containing both thiazolidinediones and isatins has allowed for the generation of new α-glucosidase inhibitors, thus overcoming the undesired effects produced by known drugs used in clinics as antidiabetics. The most effective hybrid had an IC50 of 24.73 μM, which showed better performance in in-vivo studies than the commercial drug acarbose without cytotoxic effects; its binding mode was also validated by docking and dynamic simulation [20,16]. Other hybrid structures such as hydrazineylidene-isatin-triazoles and thiazolidinediones-triazole-isatin have shown an α-glucosidase IC50 of 16.43 μM and also anti-inflammatory properties inhibiting the production of TNF-α, IL-6 and MCP-1 cytokines in monocytic cells [16].

- **Antiviral, Anti-inflammatory and Other Properties**

In literature, it has been reported that isatin-thiazole hybrid structures show activity against HIV, anticonvulsant, and antioxidant properties, apart from their well-known anticancer and antidiabetic properties due to the pharmacological diversity of the isatin-thiazole pharmacophores combination [15]. Spirooxindole-pyrano[2,3-c]pyrazoles prepared by using sulfonic acid functionalized nanoporous silica has shown remarkable antimicrobial properties, emphasizing the relationship between green synthesis [25].

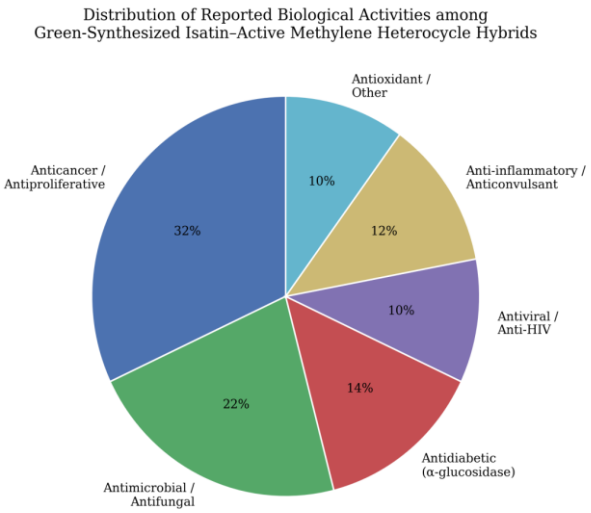

Figure 3: Distribution of principal biological activities reported for green-synthesized isatin–active methylene heterocycle hybrids, based on the surveyed literature [2,4,15-21].

Green Chemistry Metrics: Comparative Analysis

Environmental metrics, in particular environmental factor (E-factor, which is calculated based on the amount of waste produced in relation to the product obtained) and atom economy, give an objective assessment for the comparison of sustainability between various catalytic systems for isatin condensation reactions. As can be seen from Figure 4, the catalytic systems with the use of mineral acids, such as sulfuric and hydrochloric acid, produce significantly higher E-factors due to aqueous extraction, neutralization, and by-product formation, but ionic liquids, deep eutectic solvents, and magnetic nanocatalysts produce significantly less waste and at the same time improve atom economy due to the possibility of catalyst reusability and mild reaction conditions [1,22,27,28]. It is the reason why the high yield, short reaction time and good green metrics make a sufficient reason to use these approaches instead of acid-base catalysts and reflux conditions.

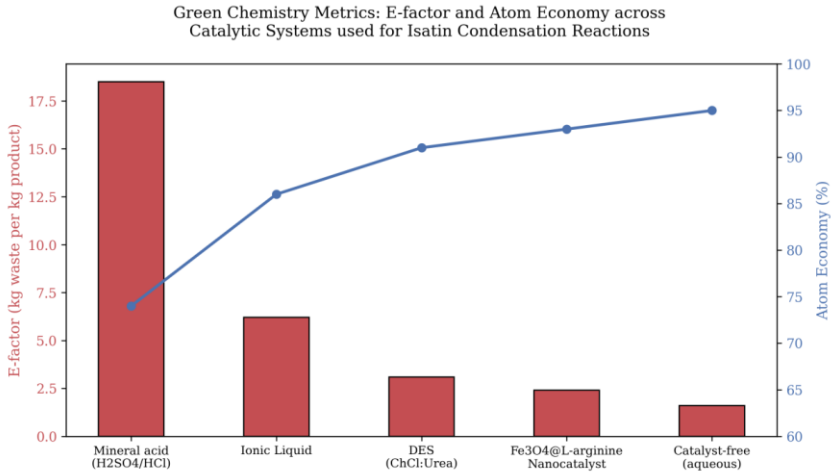

Figure 4: Comparative E-factor (waste generated per unit product) and atom economy across representative catalytic systems used for isatin–active methylene condensation reactions [1,22,27,28].

Structure-Activity Relationship Considerations

Several structural activity relationships that persist across the surveyed literature can be discerned. Halogen substituents that are electron withdrawing, especially at the 5-position on the isatin benzene ring system, increase the electrophilicity of the C-3 position, which correlates with increased anticancer and antimicrobial potency in the resultant hybrid, as seen in chloro- and bromo-substituted spiropyrazoline-indolinones and CDK2 isatinanalogs [2,23]. Lipophilicity and permeability, affected by either alkyl or aryl substitution on the oxindole nitrogen at position N-1, affect the inhibitory activity and selectivity in enzyme inhibitory assays, including carbonic anhydrase inhibitors IX/XII [19]. Another structural factor that affects hybrid biological activity is the heterocycle itself that makes up the active methylene moiety – thiazolidinedione and rhodanines usually lead to the generation of antidiabetic enzyme inhibitors, while barbiturates and pyrazolones preferentially produce anticonvulsants, antimicrobials and anti-inflammatory compounds [8,16,17].

Broader Applicability of Green-Synthesized Isatin Hybrids

Beyond the use in pharmacology through direct administration, these green isatin-based methylene compounds have been proven useful in the preparation of spirocyclic natural product-like frameworks and also in dye and fluorescence chemistry due to their enhanced conjugation and act as model substrates for evaluation of novel green catalytic systems, such as nanocatalysts and biodegradable solvents [1,14,26]. The compatibility of this class of molecules with multicomponent reaction strategy helps in carrying out rapid diversity oriented synthesis of spirooxindoles for biological screening, a much preferred route in the drug discovery process [24,25,27].

Challenges and Future Prospects

Although notable advances have been made, however, there still remain several hurdles that need to be overcome before green synthetic processes for isatin-active methylene hybrids are implemented in industry on a larger scale. Some of these include the viscosity issue of some deep eutectic solvents, life cycle assessment data in order to prove the environmental merits, and the in vivo pharmacokinetic and toxicological investigation of such isatin active methylene hybrids before any translational clinical applications [1,22]. Expected future research trends may include biocatalytic condensation process involving enzymes, continuous flow green synthesis for better scalability and reproducibility of results, and the combined use of computational DFT design and green synthesis [23,2].

Conclusion

Synthesis of isatin derivatives with active methylene heterocycles has been found to be scientifically as well as pharmacologically productive within the field of heterocyclic chemistry. From traditional acidic and basic catalyzed reactions at reflux conditions to environmentally benign strategies such as aqueous media, ionic liquid media, deep eutectic solvents, nanocatalysis and mechanocatalysis, there has been considerable improvement in terms of yields, reaction times as well as sustainability, as illustrated through comparative results and green chemistry parameters in the current review. At the same time, the biologically active isatin-active methylene hybrid derivatives that have been prepared show significant biological activities in the areas of anti-cancer, anti-microbial, anti-diabetic, anti-viral as well as anti-inflammatory activities.

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