IJPSR (2023), Volume 14, Issue 6 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 26 August 2022; received in revised form, 04 November 2022; accepted 18 November 2022; published 01 June 2023

PUTATIVE ROLE OF ISATIN DERIVATIVES SYNTHESIS AND THEIR BIOLOGICAL APPLICATIONS- A REVIEW

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Keywords:

Isatin, Synthesis, Anticonvulsant, Antiviral, Anti-tuberculosis activity, Anti-inflammatory

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ABSTRACT: Isatin (1H-indole-2,3-dione) and its derivatives represent an important class of heterocyclic compounds that can be used as precursors for drug production. Erdmann1 and Laurent2 first discovered isatin in 1840 as an oxidation product of indigo dye for nitric acid and chromic acid. Isatin is one of the most important heterocyclic compounds. For example, Schiff foundations of isatin are used for their medicinal properties. This review understands a variety of synthetic methods in particular, sandmeyer synthesis, stolle synthesis, and gassman synthesis isatin synthesis. This review reports some of the biological applications of Isatin derivatives such as anticancer, antiviral, antifungal, antioxidant, etc. From these studies, Isatin was established as a promising candidate for further research and investigation in a number of fields.

INTRODUCTION: Tribulin was the first name given to Isatin. 1-Hindole-2, 3-Dione is the chemical name for isatin, from which the indole comes. Erdman and Laurent began making this ingredient in 1841 by adding Indigo dye for chromic acid and nitric acid. The compound is found in many plants, such as Isatis tinctoria, Calanthe discolor, and Couroupita guianensis. Isatin is also found in plants, such as melosatin alkaloids (methoxy phenylpentyl isatins) in Melochia tomentosa. Isatin is also found in humans as a metabolic effect of adrenaline [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(6).2678-85

This article can be accessed online on www.ijpsr.com

DOI link: http://doi.org/10.13040/IJPSR.0975-8232.14(6).2678-85

Isatin is a multidisciplinary chemical structure capable of forming a large number of heterocyclic molecules. Isatin can participate in a wide range of synthetic reactions, leading to its widespread use as a precursor to medical chemistry [2]. An in-depth study of the reaction and reactions of isatin, a compound with an indole motif, ketone, and lactam moiety, has revealed interesting chemical reactions and processes [3]. Isatin was also reported to be calculated by HPLC (2 to 20 nMoles / ml) and capillary chromatography.

Isatin was found in the production of parotid glands of Bufo frogs 10. Isatin is found in many plants, such as Isatis, Calanthe discolor Lindl 12, and Couroupita guianen. Satins instead (melosatin alkaloids) are found in plants such as *Melochia tomentosa* [4]. And it is powder. is often employed as a building block in the widespread integration of active organic compounds containing anti-cancer

agents, antiretrovirals, anti-HIV drugs, in addition to anti-tuberculars [5].

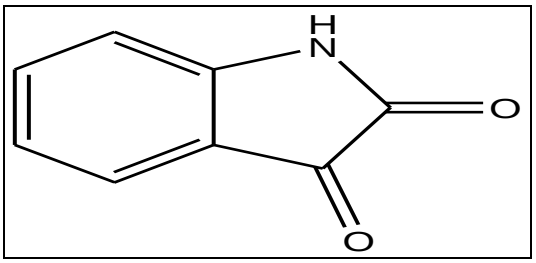
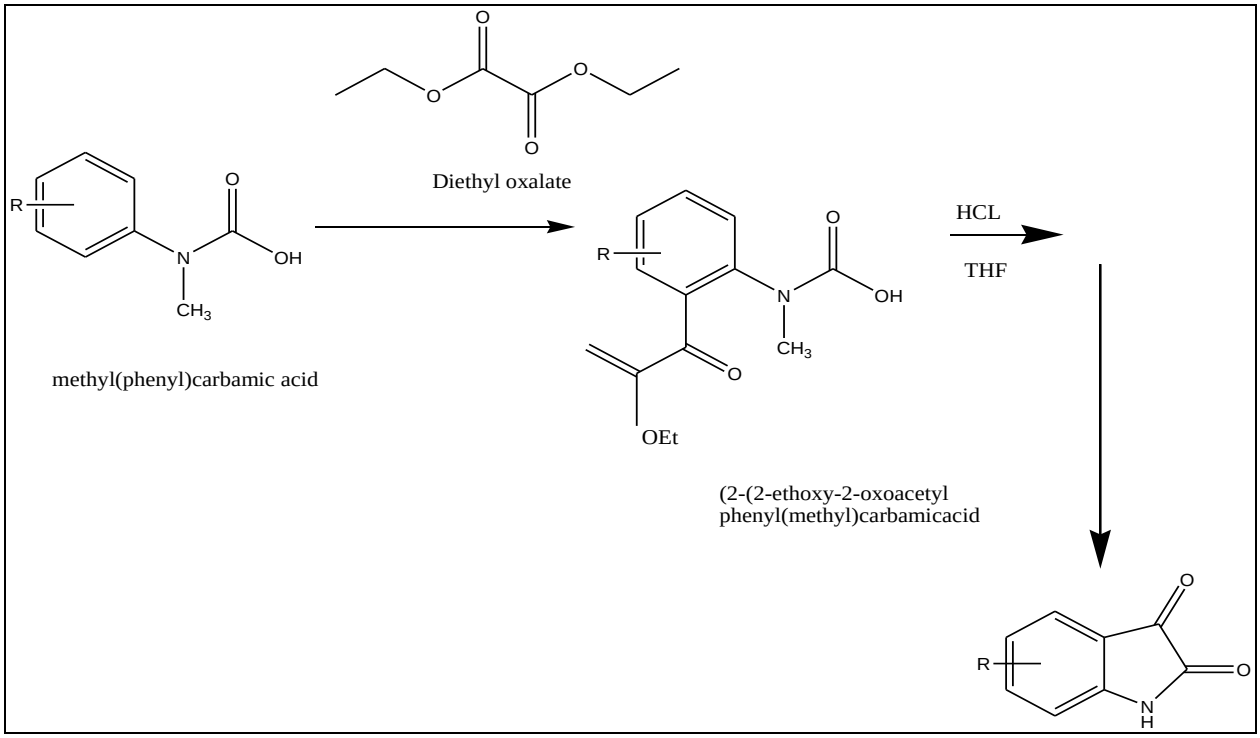


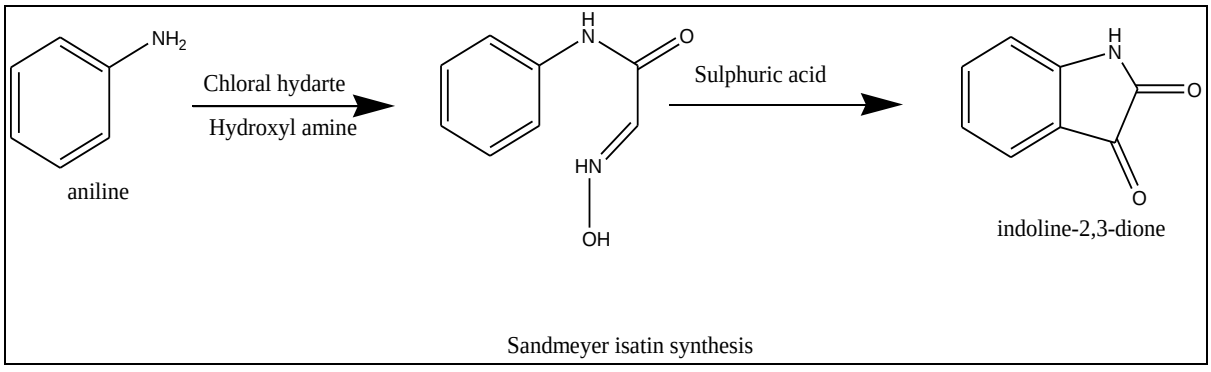
FIG. 1: CHEMICAL STRUCTURE OF ISATIN

Synthesis of Isatin Derivatives:

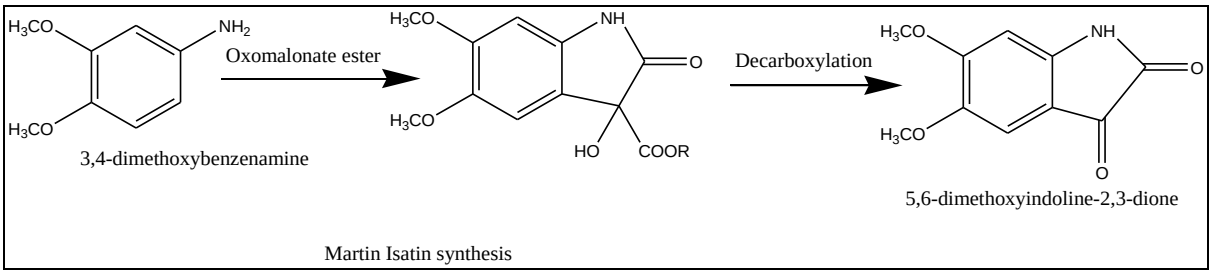
Compilation of Anilide Isatin Compound: A new strategy for creating isatin involves the orthometalation (DoM) of N-pivaloyl- and N-(tbutoxycarbonyl) - anilines are revealed. Dianions are treated with diethyl oxalate after the ban, and cycling in the middle of the road a-ketoesters, and isatins are created (Strategy 1). This process of arranging satin-bound 4 from anilines under the meta has the advantage of being regioselective [6].



Sandmeyer Synthesis: A satin derivative synthesis involving the reaction of chloral hydrate, hydroxylamine and primary arylamine to provide α-isonitrosoacetanilide and subsequent electrophilic cyclization in the presence of strong acids such as concentrated sulfuric acid commonly known as Sandmeyer isatin synthesis (Schedule 1). This method is suitable for aniline-containing electrons with Martinet method (Scheme 2) for the manufacturing of isatins involves satins involves the reaction of an amino aromatic compound with its oxomalonate ester or its hydrate in the presence of acid to produce 3- (3-hydroxy-2) -oxindole) from carboxylicacid after oxidative decarboxylation produces appropriate isatin [7].

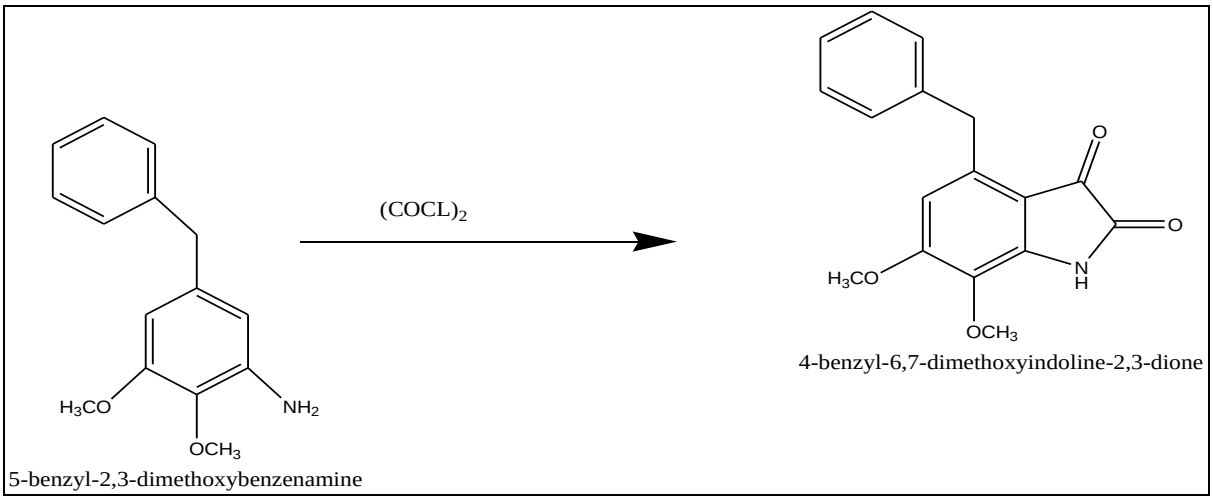


Martinet Isatin Synthesis: The Martinetic (Strategy 2) formulation of isatins involves the reaction of an aminoaromatic compound with its oxomalonate ester or its hydrate in the presence of acid to produce 3- (3-hydroxy-2-oxindole) extracts. carboxylic acid after oxidative. De carboxylation produces appropriate isatin [8].

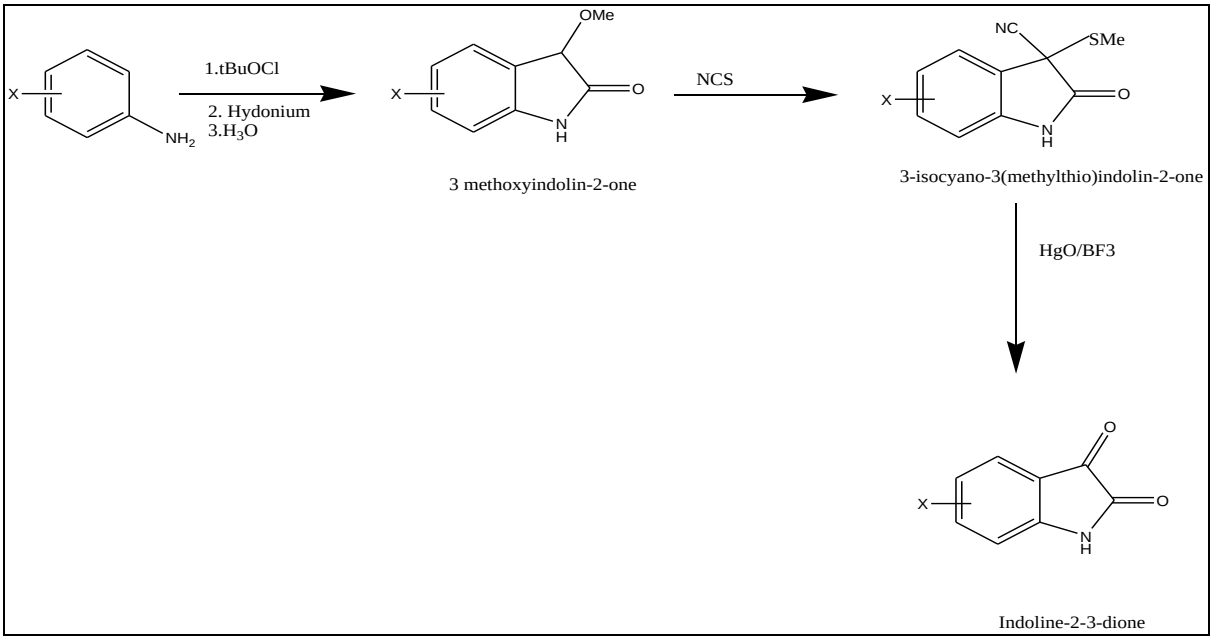


Martin Isatin synthesis

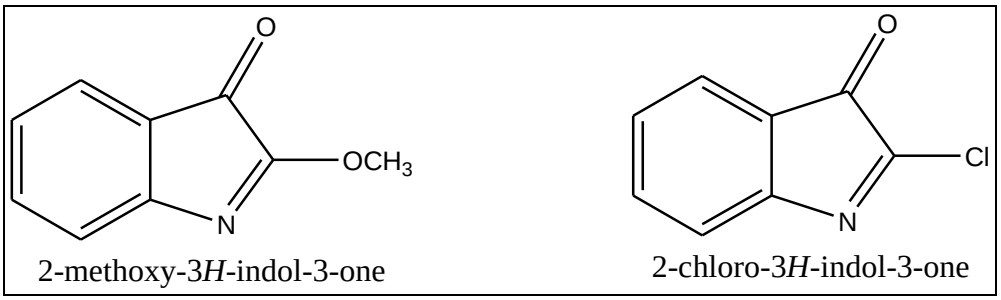
Stolle Method: The most important variant in Sandmeyer synthesis is the Stolle method. In this way the anilines react with oxalyl chloride to form a medium chlorooxalylanilide that can be cycled in the presence of Lewis acid, usually aluminum chloride to provide consistent isatin.



Gasman's Isatin Synthesis: This procedure starts with creating an intermediate 3-methylthio-2-oxindole, which is then oxidized to produce substituted isatin [9].



Structural Characteristics: Tautomerization- In 1882, Baeyer began to suggest that Isatin exists as two forms of tautomeric, lactam and lactam when the transfer of protons between a nitrogen atom and an oxygen present in a second carbon occurs 37. In a solid state, satin is highly present in the structure of lactam. The composition of Oalkylethers and satin-α-chloride support the presence of lactim form. 38 In addition, the 1H NMR spectrum of isatin in CD3OD shows its signals in both lactam and lactim forms, while in -DMSO-d6, only signal due to Lactam forms. In one of our previous works, a theoretical study of the stability of various conformers and tautomers of satellite 3-thiosemicarbazone in the gas and wet phases was reported. Tautomerm has been found to be a keytautomer and one of its compounds comprises about 87% of the gas-laden population [10].

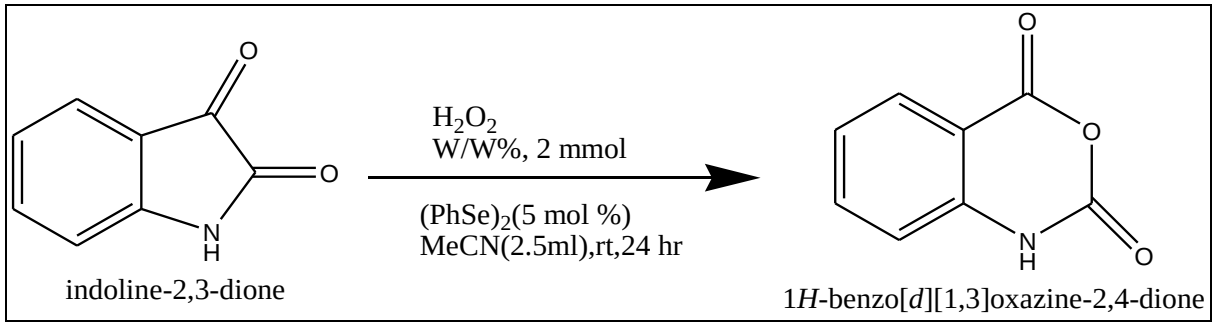


2-methoxy-3*H*-indol-3-one 2-chloro-3*H*-indol-3-one

Spectral Courses: The visible UV spectrum of isatin exhibits high absorption at 260 nm to 350 nm with a$\pi \rightarrow \pi$ * transformation due to the fragrant ring. Absorption the size and durability of the band in this region depends on the ability of the fragrant donor / receiver, where the maxima band varies chromically with the increase of the donor ring capacity. The weak absorption band compared to 350nm to 600 nm is accompanied by n $\rightarrow \pi$ * and intra molecular charge transfer (ICT) for free electron pairs of nitrogen and oxygen. On a medium basis, long wave absorption bands in the 350 nm to 600 nm area disappear and the new band shifts in a Bathochromically way at 400 nm.up to 750 nm. This new group emerged as a result of the construction of the azanion [12].

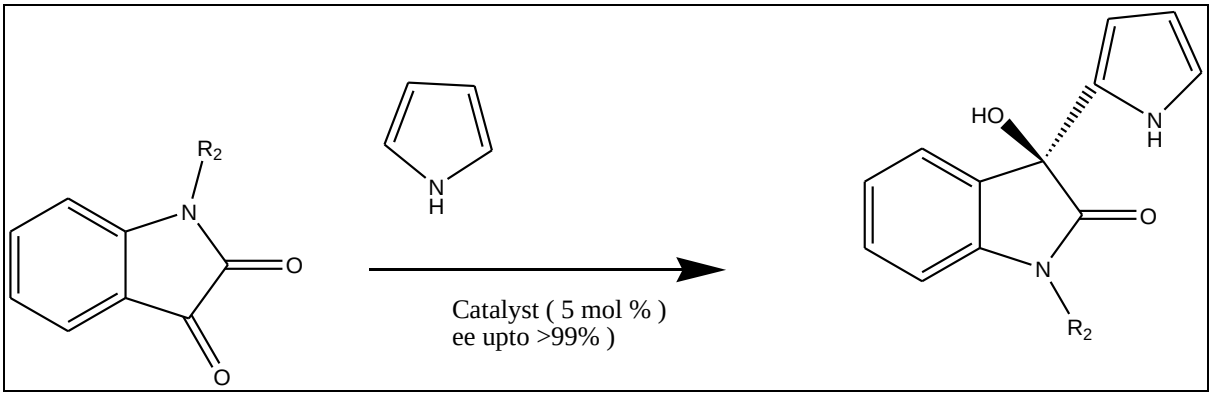
Isatin Chemical Reactions:

Oxidation: Isatoic anhydride, the production of a compound inherbicide compound that is widely used and chemically treated, is obtained by isatin oxidation. Isatin reacts with chromic acid in an acetic acid solution to produce isatoic anhydride 38-43. Reported selective organoselenium-catalyzedclean oxidation of satin with H_2O_2 under mild and neutral. Conditions for providing isatoic anhydride [13].

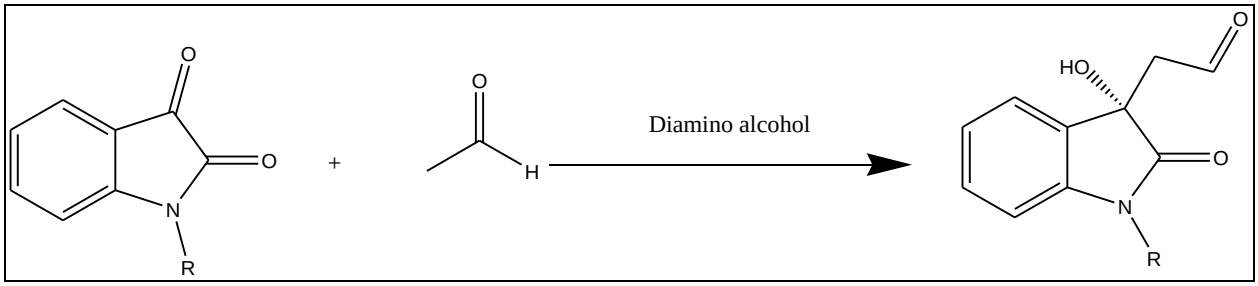


indoline-2,3-dione 1*H*-benzo[*d*][1,3]oxazine-2,4-dione

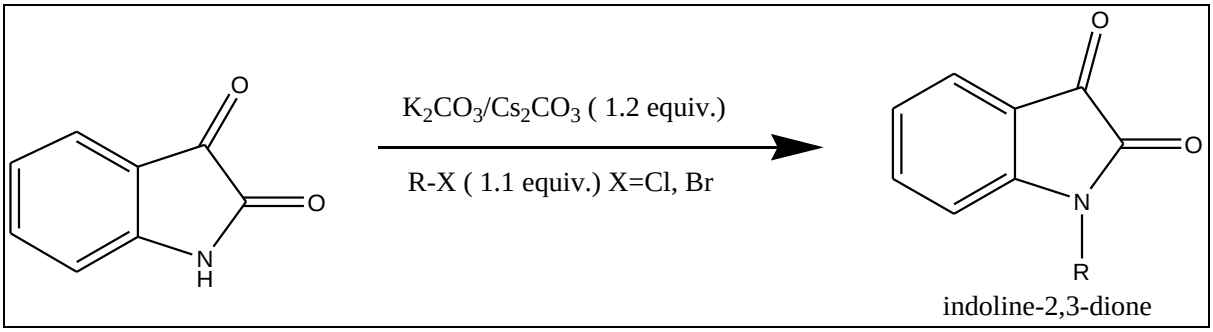
Friedel-Crafts Reaction: Friedel-Crafts reactions are an important class in organic synthesis used to create highly efficient perfumes, which may produce important pharmaceutical compounds. 3-aryl-3-hydroxy-2-oxindoles biologically pleasing and effective. Franz and colleagues reported the first asymmetric and asymmetric of the first Friedel-Crafts alkylation and Isatin with pyrroles to provide oxindoles 50. Moreover, in order to improve the enantioselectivity of synthetic theoxindoles, Wang and colleagues used tridentate Schiff base / Cu as catalyst and hexafluoro-isoproisopro an important ingredient [14].



Aldol Reaction: Aldol reactions produce β-hydroxyl carbonyl compounds, which act as important mediators in the synthesis of biologically active alternatives [15]. The strong adhesion behavior of the H-isatin bond forms a good substrate for thickening reactions. The initial diastereospecific reaction with the selective alleno-aldol of satins containing allenic esters produces carbinol-allenoate instead of tri- and tetra-substituted carbinol-allenoatesusing iron as catalyst [16].



Miscellaneous Reactions: Alkylation of isatin is a synthetically viable reaction that uses an alkylating agent, generally an alkyl or aryl halide, in the presence of a base like Cs_2CO_3 or K_2CO_3. The reaction rate depends on the reactivity of the alky halide used, so the reactions with more reactive alkyl halides require less time for completion [17].



Isatin Biological Applications: Isatin derivatives are well-known soft substances that act as precursors for synthesizing heterocyclic compounds [18]. The extract of Isatin plays an important role in medicine because it is used as an antiseptic for bacterial infections, HIV [19], fungicide, anti-epileptic anti-neoplastic treatment Mycobacterium and anti-instigative, i–anti-convulsants. A isatin derivative like 5-hydroxy isatin and spirobenzodiazepine, used to reduce stress [20]. A few extracts of isatin such as 3-p- (p-(alkoxycarbonyl) phenyl) carbonyl) phenyl) minino-1 aminomethyl-2-indolinone has been found to be effective in combating tuberculosis [21]. 5- [2 (3) -dialkyl aminoalkoxy] Indole 2,3-dione is one of the most important derivatives of satin used against aminoalkane (histamine). Isatin derivatives are used to treat malaria. 4-aminoquinoline derivatives were found to be effective compared with Plasmodium falciparum.

Such discharges can be obtained both from natural and artificial sources. The tryptanthrin well known isatin derivative found in Chinese herbs [22].

Isatin as Anticonvulsants Activity: The Schiff bases of isatin emissions show anticonvulsant activity due to the presence of a hydrophobic HP unit, an electron donor unit, and a hydrogen donor / acceptor (HBD) unit [23]. Palluotto *et al*. reports a combination of 2- aryl-2, 5 dihydropyridazino [4, 3- b] indol-3 (3H). Anticonvulsant activity was observed in synthesized compounds. The onset of clonic and tonic seizures decreased significantly within 45 minutes after intraperitoneal dosing and was equivalent to standard drug administration (Flumazenil). Campagna *et al.* announced the sequence compilation of 2-aryl-2, 5-dihydropyridazino [4, 3-b] idol-3 (3H). The ability of composite compounds to prevent PTZ attacks in experimental mice [24].

Isatin as Anti-inflammatory and Analgesic Aactivity: A recent literature study reveals that extracts from isatin show anti-inflammatory and analgesic activity [25]. Schiff bases of isatin with aminothiazole, its N-mannich bases and Spiro isatin extracts were combined. Anti-inflammatory activity has been tested by carragenin for rat paw edema and computers have been tested for analgesic action by writhing acetic acid-induced writhing method [26]. A series of Schiff novels from the isatin novel were combined with a thickened imesatin with distinctive aldehyde and tested for pain relief in the form of tail immersion. Computers containing electron-donating groups show better analgesic activity than electron-releasing groups [27]. The bases of the novel schiff were combined with a 5-dose imesatin summed with aldehyde with a different scent instead and tested for analgesic activity (tail immersion), anti-inflammatory activity (carrageenan-induced paw edema) function and antibacterial (paper disc diffusion strategy) [28].

Isatin as an Antioxidant Activity: Free radicals of an atom or molecule containing a strange electron in its outer shell [29] are unstable and constantly seek to obtain electrons from any animal species in order to complete its outer shell in order to stabilize them. In our body, during the process of oxygen metabolism any free radicals are produced in mitochondria. Therefore, it is very important to get rid of these free radicals, otherwise they will cause various diseases, especially the harmful neoplastic. disease, cerebral and vascular disease, seizures, heart disease, ulcers, diabetes, heart disease, mucoviscidosis, aging, gastric ulcer and paralysis [30]. Therefore, to overcome this problem antioxidants are used, because their main function is to convert these free radicals into more stable substances. Antioxidants are used in a large number of drugs used to treat diseases caused by free radicles [31]. Here are also the experimental results and theories, associated with (H25MI3ClPT) and (H25MI3PT) with a focus on free radical scavenging in DPPH. Equilibrium increases antioxidant activity. In particular, it is theoretically proven that the antioxidant activity of DPPH products with high volume energy (H25MI3ClPT) - IC_{50} is lower than products (H25MI3PT) –DPPH [32].

Antitubercular Activity: Tuberculosis (TB), mainly caused by Mycobacterium tuberculosis (MTB), is a deadly disease and appears to be the second leading cause of death from infectious diseases worldwide. (Unfortunately, due to the increasing number of drug resistance cases. Drug-resistant tuberculosis is currently increasingly ineffective. In recent years, the isatin scaffold has intensified the discovery of a number of new anti-tuberculosis drugs. The rate at which isatin is reported to indicate significant anti-TB activity [33]. Recently, Hu *et et.* Al. (Reported compounding and in vitro activity against mycobacterium series 1H-1,2,3-triazole-tethered ciprofloxacin (CPFX) satin conjugates against Mycobacterium smegmatis and Mycobacterium tuberculosis (MTB) H37Rv. Preliminary results showed all hybrids showed significant activity against M. smegmatis and show excellent performance against the MTB H37Rv model. Also, hybrids with a carbonyl group were more effective than the corresponding methyloxime hybrids against MTB H37Rv [34].

Antidiabetic Activity: Diabetes mellitus (DM), commonly referred to as diabetes, a disorder characterized by metabolic disorders and high blood sugar (hyperglycemia) either from low levels of the insulin hormone or from resistance to the effect of insulin [44]. The anti-diabetic activity of the novel compound 1- (4- dimethylamino) benzylidene) -5- (2-oxoindolin-3- ylidene)

thiocarbohydrazone has been reported. Administration of a single dose of 50 and 100 mg / kg to diabetic mice showed a significant decrease in blood glucose levels [45] Type 2 diabetes is the most common type of diabetes and is estimated to be 90% of all cases worldwide. A- Glucosidase, a carbohydrate enzyme produced in the intestinal chorionic epithelium, is a therapeutic target for type 2 diabetes. Therefore, the fusion of these two particles into a single molecule can improve drug performance. In this case, a novel series of chromone-isatin secretions were synthesized and tested to evaluate their *in-vitro* α-glucosidase inhibitory activity. All compounds showed excellent inhibitory activity, but combined with the hydroxyl group at 7 chromone and the 4-bromobenzyl group at the N1-isatin positions.

Anthelmintic Activity: A new series of tetradentate Schiff bases was synthesized and screened for anthelmintic activity against earthworm (*Peretima posthuma*) using 5 μg/ml concentration [46]. A series of novel isatin derivatives were synthesized from different substituted chalconised indole-2,3-dione prepared from the different chalconised isatin. Some compounds reported anthelmintic activity against *Pheretima posthuma* [35]. Various 3-(2- hydrazino benzothiazoles)-substituted Indole-2-one derivatives were synthesized and all the synthesized compounds were screened for anthelmintic activity byusing Indian adult earthwarms [36].

Isatin Derivatives with Antianxiety Activity: Isatin derivative like Schiff bases of N-methyl and Nacetylisatin, spirobenzodiazepines, 5-hydroxy isatin and isatinic acid act as antianxiety agents [37]. A new series of 5-hydroxy isatin derivatives were synthesized by the hydroxylation of the aromatic ring in isatin and showed mild antianxiety effect [38].

CONCLUSION: Isatin is one of the most important heterocyclic compounds with special significance for the synthesis of organic compounds. Schiff bases of isatin, 3,3-disubstituted oxindoles, and spirooxindoles are some key compounds that can be synthesized using isatin as a primary substance. In this paper, satin and its derivatives were read and evaluated for their biologically active, Isatin and its derivatives have shown various therapeutic functions, including anticonvulsant, anti-HIV, antiviral, antibacterial, antifungal, anti-tubercular, antidiabetic and anti-inflammatory.

ACKNOWLEDGEMENT: I wish to acknowledge the help provided by the technical and support staff in the Department of Pharmaceutical Chemistry, Mascot college of Pharmacy. I would also like to show my deep appreciation to my all supporting peoples who helped me to finalize the review.

CONFLICTS OF INTEREST: The authors declare no conflict of interest.

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How to cite this article:
Sharma A, Bhardwaj V and Tomar P: Putative role of isatin derivatives synthesis and their biological applications- a review. Int J Pharm Sci & Res 2023; 14(6): 2678-85. doi: 10.13040/IJPSR.0975-8232.14(6). 2678-85.