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Review Article

A REVIEW ON ISATIN AND ITS DERIVATIVES: SYNTHESIS, REACTIONS AND APPLICATIONS

Priyanka V. Gandhi[1], Shubham R. Burande[2], Manoj S. Charde[1], Rita D. Chakole*[1]

[1]*Post Graduate Department of Pharmaceutical Chemistry, Vidyanagar, Karad, Satara, Maharashtra, India*

[2]*Post Graduate Department of Pharmaceutics, Government College of Pharmacy, Vidyanagar, Karad, Satara, Maharashtra, India*

**Corresponding author: kdcritu@gmail.com*

ABSTRACT

Isatin, also known as 1H-Indole-2, 3-Dione, is an eight-carbon containing endogenous compound found in nature. Erdmann and Laurent synthesized isatin in 1840, before it was discovered in nature. It is versatile and distributed in tissues and body fluids. Isatins have also been detected in mammalian tissue, and their function as a biochemical process modulator has been the focus of many debates. The isatin moiety also shows some important chemical reactions such as oxidation, N-Acylation, Friedel-Crafts reaction, N-Halogenation, etc. Antitumor, antimicrobial, anti-inflammatory, anticonvulsant, antiviral, anti-HIV, antioxidant, and CNS depressant functions are all possessed by simple isatin nucleus. Substituted derivatives of this compound also have these properties. The isatin derivatives are effective inhibitors of the urease and α-glucosidase enzymes. This review provides a brief overview on the some commonly used procedures to synthesize the isatin moiety and its derivatives, its physical properties, reactions and biological activities.

Keywords: Isatin, Synthesis, Moiety, Derivatives.

1. INTRODUCTION

Tribulin was the initial name given to Isatin [1]. 1-H indole-2, 3-Dione is the chemical name for isatin, which is an indole derivative. Erdman and Laurent first developed this compound in 1841 by oxidizing Indigo dye with chromic acid and nitric acid. Some plants, such as *Corupita guianensis, Genus Isatis, Isatis tinctoria,* and *Calanthe discolor*, contain this compound. It's also a part of the secretion of the parotid gland in Bufo frogs, and it's a metabolic derivative of adrenaline in humans. Melosatin alkaloids (methoxy phenylpentyl isatins) derived from the Caribbean tumorigenic plant *Melochia tomentosa* are examples of substituted isatins present in plants. The indole moiety in this compound is made up of a pyrrolidine ring fused to benzene to form 2, 3- dihydro indole. It is a monoamino oxidase inhibitor that's been detected in high concentrations in the urine of Parkinson's patients [2-6].

In the field of heterocyclic and pharmaceutical chemistry, isatins are useful intermediates [7, 8]. Isatin is a well-known pharmacophore that can be found in a wide range of synthetic and natural products, and it has a number of significant pharmacological and material-like properties [9-11]. Its derivatives can cross the blood-brain barrier readily [12]. Isatins have long been regarded as important synthetic intermediates in the manufacture of pharmaceuticals and dyes. As a result, a lot of time and effort has passed into developing useful synthetic methods for this class of compounds. Unfortunately, the most commonly used procedures involved strong acid catalysis, which severely limited the method's scope [13].

The following are the three methods for synthesizing isatin derivatives from aniline:

I) Stolle procedure

Aniline is reacted with oxalyl chloride followed by Friedel-Crafts-type intramolecular acylation in the presence of a strong Lewis acid. Only a small amount of product is generated [14].

II) Sandmeyer methodology

This is the most popular and oldest approach for synthesizing isatins which includes primary arylamine and chloral hydrate condensation in the presence of hydroxylamine and sodium sulphate [15].

III) Martinet procedure

Aniline and diethylketomalonate were combined to produce oxindole, which was then treated with sodium hydroxide solution and oxygen to produce isatin [16].

Isatin (1H-indole-2,3-dione) is a synthetically flexible substrate that can be used to make a wide range of

heterocyclic compounds, including indoles and quinolines, as well as a raw material for drug development. Isatin's synthetic versatility has led to widespread use of the compound in organic synthesis [17-19].

Semaxanib, orantinib, sunitinib, and nintedanib, for example, are isatin-based compounds that have been licensed for clinical use or are in advanced clinical trials. More researchers have been encouraged to study isatins and build a large number of structurally diverse derivatives due to the broad spectrum of biological activities coupled with a wide variety of structural modifications as well as active applications in clinical practice [20-23].

2. PHYSICAL PROPERTIES

Isatin is an orange solid with a molecular weight of 147.13g/mol found in nature. It has melting point about 202-203°C. It is soluble in polar organic solvents like methanol, acetone, acetonitrile, DMSO, DMF, and ethyl acetate, partially soluble in CH_2Cl_2, $CHCl_3$, slightly soluble in water, and insoluble in non-polar organic solvents like hexane, toluene, and benzene [24].

3. REACTIVITY OF ISATIN

Isatin reacts primarily at three sites: aromatic substitution at C-5 which increases biological activity, N-alkylation, and carbonyl reactions at C-3 and chemo selective reductions, oxidations, ring-expansions and spiro annulations at C-2. Attack at C-2 may also occur if the system contains electron-withdrawing groups in the benzene ring or at the nitrogen (Fig. 1) [25-27].

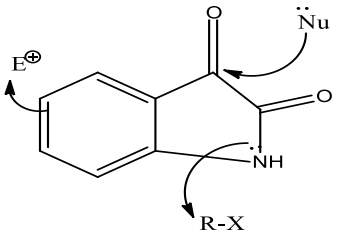
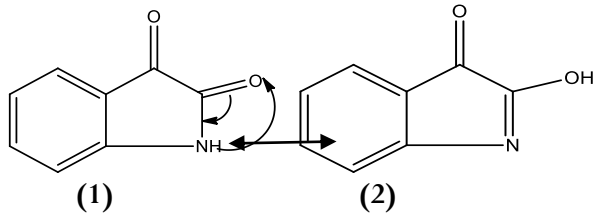


Fig. 1: Reactivity of Isatin

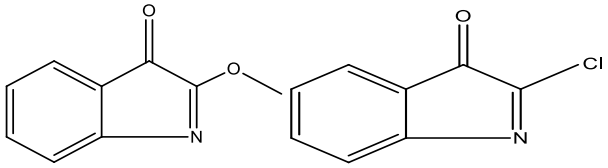
4. STRUCTURAL CHARACTERISTICS

4.1. Tautomerization

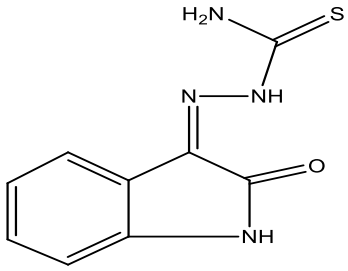
Baeyer suggested in 1882 that isatin has two tautomeric forms, lactam **(1)** and lactim **(2)**, in which a proton transfer occurs between the nitrogen atom and the oxygen present at the second carbon. Isatin is mostly found in the lactam structure in the solid state. The presence of the lactim form is supported by the formation of O-alkyl ethers **(3)** and isatin-chloride **(4)**. In addition, the 1H NMR spectra of isatin in CD_3OD shows signals for both lactam and lactim forms, while only the lactam type signal appears in DMSO-d_6. A theoretical analysis of the stability of the various conformers and tautomers of isatin-3-thiosemicarbazone in the gas phase and aqueous phase was published in one of our previous works. Tautomer **(5)** was discovered to be the main tautomer, with one of its conformers accounting for approximately 87 percent of the population in the gas phase [28].



(1) **(2)**



(3) **(4)**



(5)

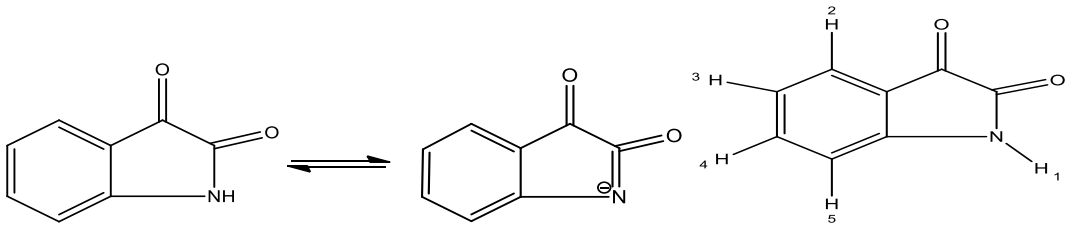
4.2. Spectral studies

Isatin's UV-Visible spectrum displays an absorption maximum in the range of 260 nm to 350 nm, which corresponds to $\pi \rightarrow \pi^*$ transition due to an aromatic ring. The absorption maximum and band strength in this region are determined by the aromatic ring's donor/ acceptor ability, with the maxima band shifting bathochromically as the ring's donor ability increases. The $n \rightarrow \pi^*$ and intramolecular charge transfer (ICT) transitions of the free electron pairs of nitrogen and oxygen lead to a relatively weak absorption band in the range 350nm to 600nm. Long-wavelength absorption bands in the 350 nm to 600 nm region vanish in simple medium, and a new bathochromically shifted band in the

400 nm to 750nm region arises due to the formation of azanion [29].

Isatin has a doublet at δ7.47 ppm and 6.86 ppm, which correspond to H_2 and H_5 respectively, in its 1H-NMR spectrum. At approximately δ11.03 ppm, the hydrogen atom (H_1) bound to nitrogen appears as a singlet. At δ 7.05 ppm and 7.57 ppm, respectively, the protons H_3 and H_4 indicate triplets. In the 1H-NMR spectrum, deprotonation of NH in the isatin moiety causes a downfield shift for the azanion's protons (H_2, H_3, H_4, and H_5) [29].

Furthermore, the carbonyl stretching vibrations are described by two strong bands at 1740 and 1620 cm-1 in the IR spectrum of isatin. At 3188 cm^{-1}, corresponding to N-H stretching, a broad band with some sub-bands appears, which moves to 2370 cm^{-1} on deuteration of N-H [28].



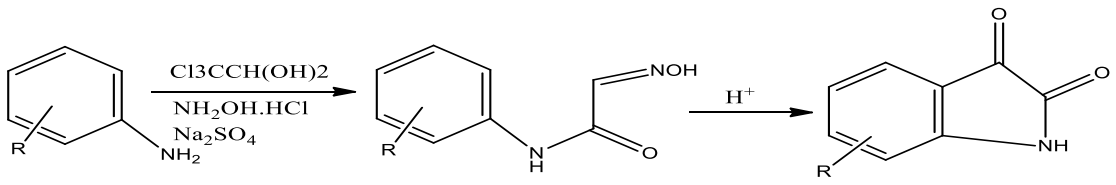
5. SYNTHESIS OF ISATIN

5.1. The Sandmeyer Isatin Synthesis

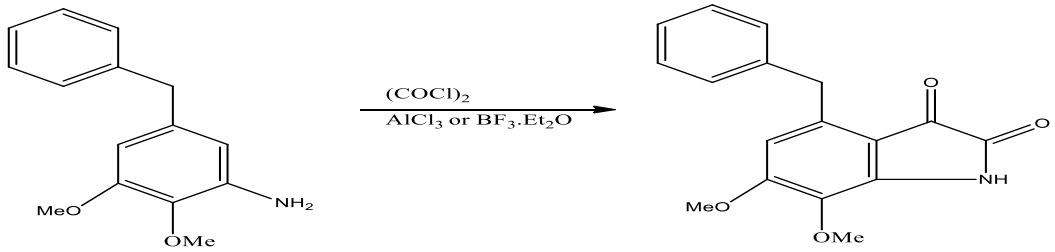
Sandmeyer was the first to report this reaction in 1919. It involves the condensation of chloral (i.e., trichloroacetaldehyde), hydroxylamine, and a primary aryl amine to isonitrosoacetanilide and subsequent electrophilic cyclization of the latter in the presence of a strong acid such as concentrated sulfuric acid to produce an isatin derivative (Scheme 1). The Sandmeyer isatin synthesis, or Sandmeyer synthesis, is the name given to this reaction. Quinolines, acridines, and indophenazines have all been made from the isatin derivatives produced by this reaction [30, 31]. The Sandmeyer method for synthesis of isonitrosoacetanilides is less effective with aniline derivatives that have low solubility in aqueous sodium sulphate medium, but it also fails to work well with anilines that have electron-rich ortho [32].

5.2. The Stolle Procedure

The Stolle approach is the most effective alternative to Sandmeyer's protocol. Anilines react with oxalyl chloride to form an intermediate chloro-oxalylanilide, which can be cyclized in the presence of a Lewis acid, commonly aluminium chloride or BF_3. Et_2O, though $TiCl_4$ has also been used to produce the corresponding isatin (Scheme 2). 1-aryl and polycyclic isatins derived from phenoxazine, phenothiazine, and dibenzoazepine, as well as indoline, have been synthesized using this process [33, 34].



Scheme 1: Sandmeyer Isatin Synthesis



Scheme 2: The Stolle Procedure

5.3. The Martinet Isatin Synthesis

The Martinet method for the synthesis of indole-2,3-diones involves reacting an amino aromatic compound with either an oxomalonate ester or its hydrate in the presence of an acid to produce a 3-(3-hydroxy-2-oxindole)carboxylic acid derivative, which is then oxidatively decarboxylated to yield the desired isatin (Scheme 3). The synthesis of 5, 6-dimethoxyisatin from 4-aminoveratrole was successful using this process, but the use of 2, 4-dimethoxyaniline was less successful [35].

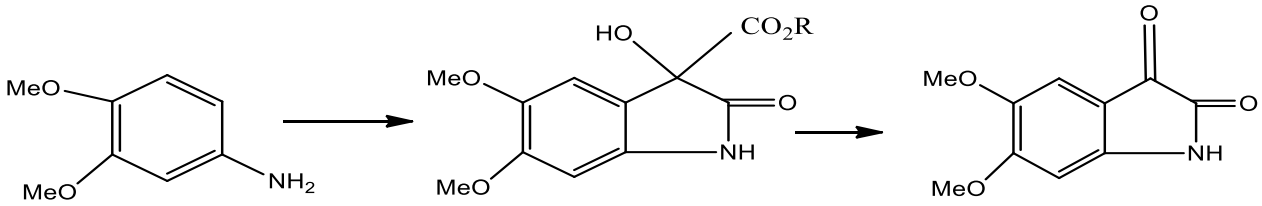
5.4. The Gassman Isatin Synthesis

The conversion of anilines into 3-(methylthio) oxindoles, followed by oxidative removal of the methylthio group through chlorination and subsequent hydrolysis, is the Gassman synthesis of isatins. One of the advantages of the Gassman synthesis is that it can be used for either strongly electron withdrawing or electron-donating groups (Scheme 4) [14].

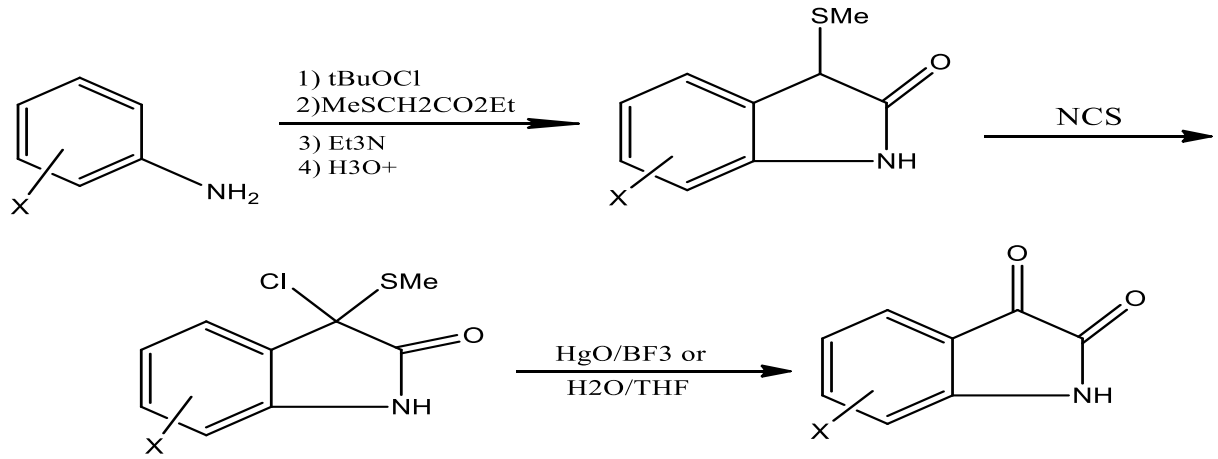
5.5. Miscellaneous

5.5.1. I_2-DMSO promoted Synthesis

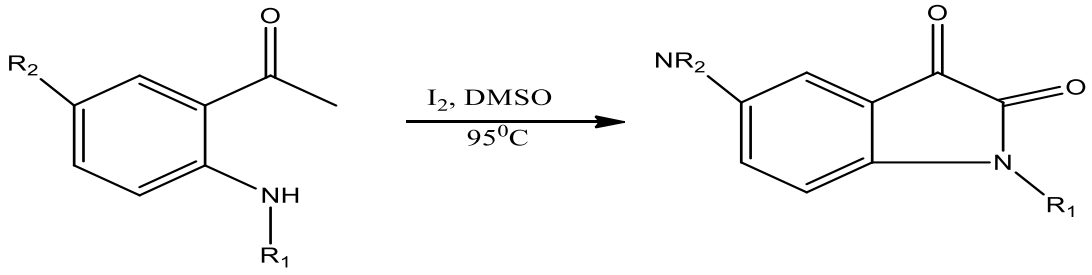
It involves activating C-H bonds to produce isatins from 2-amino acetophenones. It is the I_2-DMSO-catalyzed regioselective synthesis of isatins via dual C-H activation of 2-amino acetophenones and subsequent internal cyclization to form isatins (Scheme 5). When compared to other solvents studied, such as DMF and dioxane, DMSO proved to be the most efficient [36].



Scheme 3: The Martinet Isatin Synthesis



Scheme 4: The Gassman Isatin Synthesis



Scheme 5: I_2-DMSO promoted Synthesis

5.5.2. Electrocatalytic C-H/N-H Coupling

In this method, in the presence of n-Bu_4NI, 2′-aminoacetophenones undergo a C(sp3)-H oxidation followed by intramolecular CN bond formation through a simple electrochemical oxidation, yielding various isatins in moderate to good yields (Scheme 6) [37].

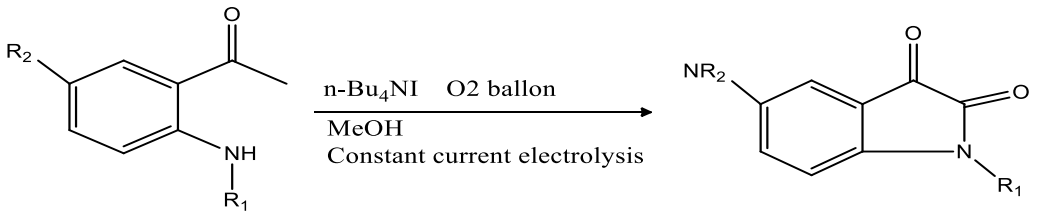
5.5.3. Oxidation of Indoles

N-alkylated indoles could be transformed into the preferred isatins in yields ranging from 58 to 95%. A number of indoles with halides and ester substituents gave the corresponding products under the reaction conditions, in addition to indoles with simple methyl and phenyl substituents. In general, the location of the substituents had little effect on the yield, however indoles with electron-withdrawing substituents tend to be oxidized at a slightly higher rate (Scheme 7) [38].

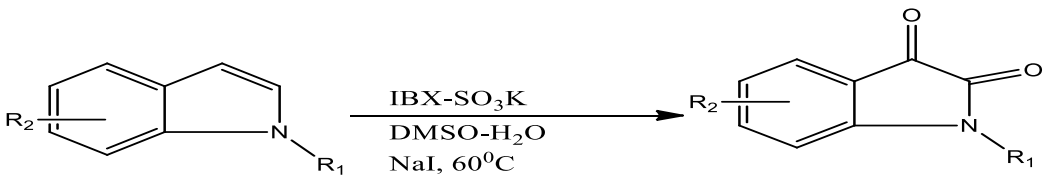
In the presence of a co-oxidant, molecular iodine works efficiently as an oxidant in catalytic quantity and it is environmentally benign compared to metal catalysts [39]. TBHP can also be used for oxidation of indole (Scheme 8). Isatins are synthesized in moderate to good yields [40].

5.5.4. Cyclization of N-Acyl anilines

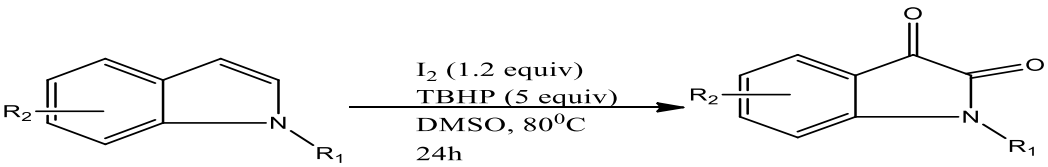
Intramolecular oxidative cyclization reactions of N-acyl anilines take a special place among the latest trends in the synthesis of isatin derivatives. The widespread use of this method for the synthesis of highly functionalized N-alkyl and N-aryl isatins is due to the ease with which these substrates can be synthesized. Catalytic oxidative cyclization of 2-oxo-N-phenylacetamides by oxygen, for example. When meta-substituted glyoxals are used as substrates, a mixture of 4- and 6-substituted isatins results. It should be noted that using $FeCl_3$ as the catalyst resulted in the highest yields of the desired products (70-93%) (Scheme 9) [41].



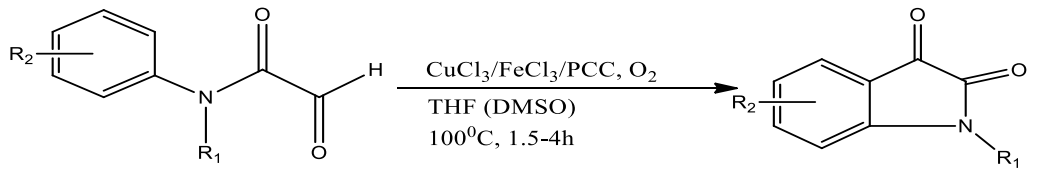
Scheme 6: Electrocatalytic C-H/N-H Coupling



Scheme 7: Oxidation of Indoles



Scheme 8: I_2-TBHP promoted synthesis



Scheme 9: Cyclization of N-Acyl anilines

5.5.5. *One Pot Synthesis*

It is an efficient, and environment friendly method which is developed for converting α-hydroxy N-arylamides into isatins (1H-in- dole-2, 3-diones) by using hydrogen peroxide as oxidant. Under metal-free conditions, the reactions proceeded smoothly and produced the desired products in good to excellent yields. This approach has the benefit of a wide range of substrates and basic operations (Scheme 10) [42].

6. REACTIONS OF ISATIN

6.1. N-Alkylation

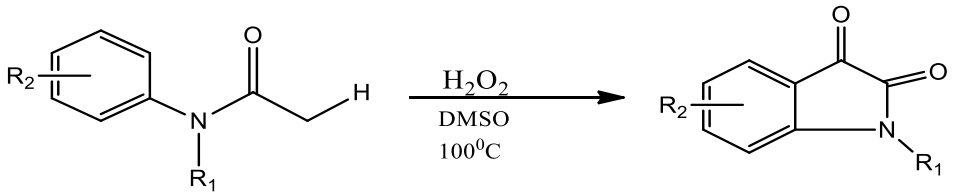
N-alkylated isatins can be successfully prepared under simple conditions using alkyl chlorides, bromides, and iodides, as well as reactive allyl-, benzyl-, and propargyl halides, according to various methods. N-alkylated isatins are frequently produced by conventional heating at temperatures ranging from 40 to 100°C under reflux (Scheme 11) [43].

6.2. N-Arylation

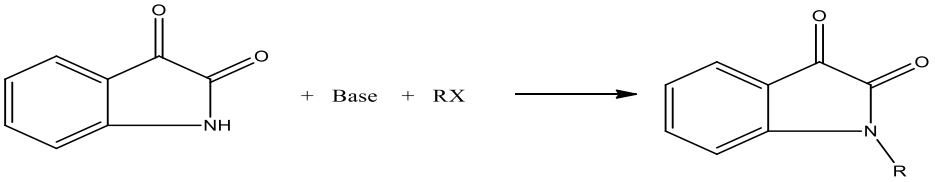
N-Arylisatin can be synthesized from isatin by reacting it with Ph_3Bi $(OAc)_2$ and Cu° in an inert atmosphere [44] or from aryl bromide in the presence of cupric oxide (Scheme 12) [45].

6.3. Pfitzinger reaction

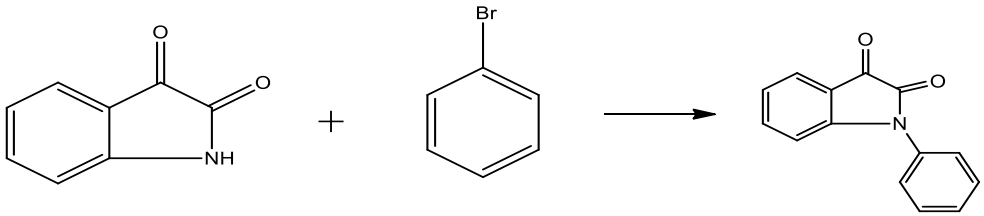
In this reaction, isatin reacted with ketones containing a methylene group adjacent to the carbonyl group in a highly alkaline solution. Quinoline-4-carboxylic acid was the end result of this reaction (Scheme 13) [46].



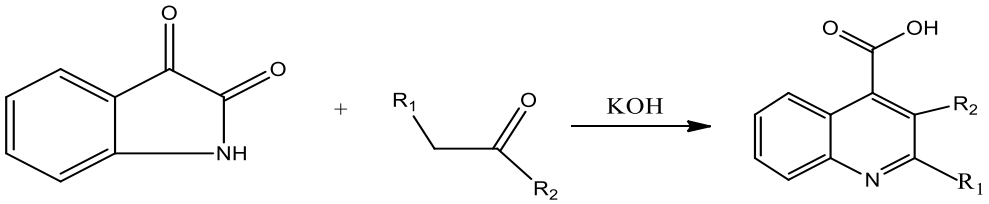
Scheme 10: One pot synthesis



Scheme 11: N-Alkylation of Isatin



Scheme 12: N-Arylation of Isatin



Scheme 13: Pfitzinger reaction

6.4. N-Halogenation

When isatin is treated with sodium hypochlorite in acetic acid, it produces 1-chloroisatin, a mild oxidizing agent that can convert alcohols to aldehydes and ketones, as well as indoles to 3-chloroindoles, with no by-products (Scheme 14) [47].

6.5. Oxidation

Isatin converted to isatoic anhydride, the anhydride form of isatin, in the presence of chromium trioxide. The oxidizing agent introduces the oxygen atom that is added between two adjacent carbonyl groups (Scheme 15) [24, 48].

6.6. Friedel-Crafts reaction

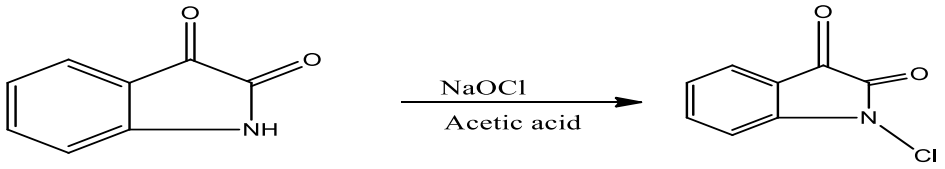
Friedel-Crafts reactions are a form of organic synthesis reaction that produces highly functionalized aromatic compounds, which can then be used to produce pharmaceutically important compounds. The biologically interesting and optically active 3-aryl-3-hydroxy-2-oxindoles are generated by asymmetric Friedel -Crafts alkylation of isatin with electron-rich aromatic compounds. The first and only active asymmetric Friedel- Crafts alkylation of isatins with pyrroles to produce oxindoles was reported by Franz and coworkers (Scheme 16) [28].

6.7. Reduction

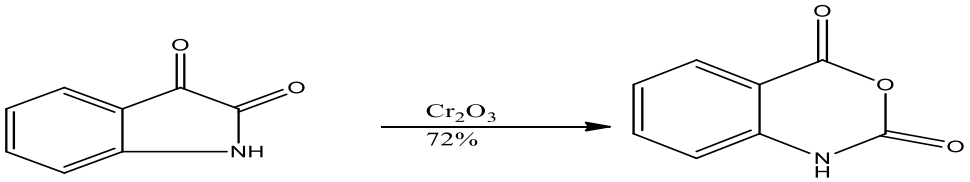
Isatin derivatives when reduced with sodium hydro sulphite or zinc-copper leadsto formation of the corresponding oxindole derivatives (Scheme 17) [33].

6.8. N-Acylation

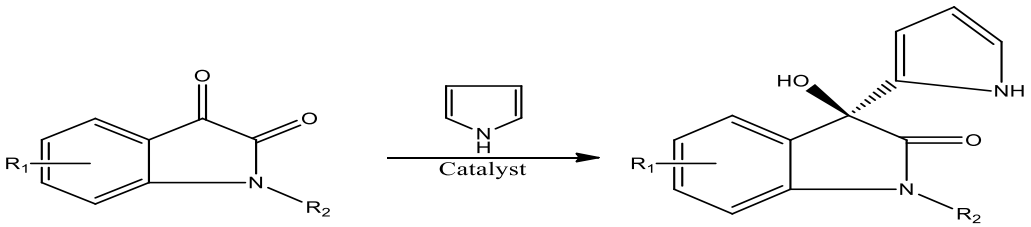
The N-acylisatins were obtained by treating the isatins with acyl chlorides or anhydrides under reflux. Carbonyl groups shows three strong absorption peaks in IR spectra (Scheme 18) [49].



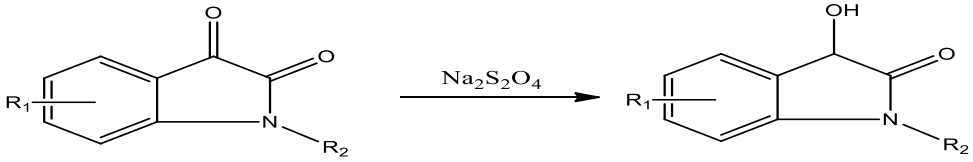
Scheme 14: N-Halogenation of Isatin



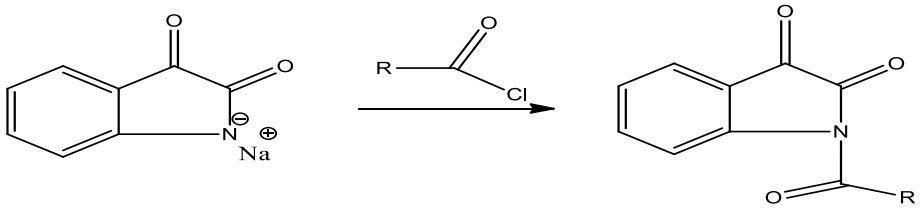
Scheme 15: Oxidation of Isatin



Scheme 16: Friedel-Crafts reaction



Scheme 17: Reduction reaction of Isatin



Scheme 18: N-Acylation of Isatin

7. BIOLOGICAL ACTIVITIES

7.1. Anticonvulsant activity

Schiff bases of isatin derivatives shows the anti-convulsant activity due to the presence of a hydrophobic HP unit, an electron donor group, and a hydrogen donor/acceptor (HBD) unit [50, 51].

Palluotto et al. reported the synthesis of a series of 2-aryl-2, 5 dihydropyridazino [4, 3- b] indol-3(3H) ones. Anticonvulsant activity was observed in the synthesized compounds. The onset of clonic and tonic seizures was substantially decreased 45 minutes after intraperitoneal administration of derivatives and was equivalent to normal drug administration (Flumazenil). Campagna et al. announced the synthesis of a sequence of 2-aryl-2, 5-dihydropyridazino [4, 3-b] indol-3(3H) ones. The ability of the synthesized compounds to avoid PTZ-induced seizures in mice was tested [52].

7.2. Antitubercular activity

Coumarin, isatin, chromene, oxadiazoles, substituted triazoles, and hydrazides such as isoniazid, pyrazinamide, benzhydrazide, and nicotinohydrazide are all essential Schiff bases in the discovery of effective antimycobacterial drugs. The Schiff bases of isatin derivatives, for example, were found to be 20 times more active than isoniazid, the first-line antitubercular drug [53].

Isatin is a biologically versatile structure, and the stability of its indole nucleus has prompted medicinal chemists to work with a variety of pharmacophore moieties in order to develop new anti-TB drugs. Furthermore, an analysis of isatin derivatives' structure-activity relationships (SAR) revealed that 5-halogenation, N-alkylation, N-Mannich base, and 3-thiosemicarbazone formation were successful in increasing inhibition activity against bacteria, fungi, and viruses. As a result, isatin is a feasible alternative for developing new anti-TB drugs. Hybrids of isatin with various heterocycles such as quinoline, thiazole, Tetrahydropyrimidine, Isoniazide, etc. also possesses antitubercular activity [9]. S. Maddela et al synthesized Novel Isatin-Quinoline Hybrids and tested their antitubercular function. The compound had excellent anti-tuberculosis activity against the H37Rv strain of tuberculosis. The pharmacophore method is used to create the isatin-quinoline hybrid [54-56].

7.3. Antimicrobial activity

Using microwave irradiation, Ayman El-Faham et al. synthesized the three series of isatin derivatives [3-hydrazino, 3-thiosemicarbazino, and 3-imino carboxylic acid derivatives]. The antimicrobial activity of the synthesized compounds was tested against a variety of bacteria and fungi. The findings showed that N-alkyl isatin derivatives were biologically active, with a variety of activity spectrums. The majority of 3-hydrazino and 3-thiosemicarbazino isatin derivatives were found to be biologically inactive, and the active derivatives had mild to moderate activity against Gram-positive bacteria [57].

7.4. Antiviral activity

Viruses like the human immunodeficiency virus (HIV) and the hepatitis C virus (HCV) continue to have a devastating impact on the health of human populations around the world. Because isatin and fluoroquinolone derivatives have shown to have antiviral properties, hybridization of isatin with fluoroquinolone can provide more effective candidates [58].

S.N. Pandeya et al. reported the synthesis of Schiff bases and the N-Mannich bases of isatin derivatives with 3-amino-2-methylmercapto quinazolin-4 3H-one and the synthesized compounds screened for anti-HIV activity against replication of HIV-1 III B in MT-4 cells [59].

7.5. Antiplasmodial activity

Clarkson et al. reported the synthesis of a new class of 4-aminoquinoline derivatives based on the natural product isatin scaffold. The synthesized compounds were tested against three strains of the malaria parasite Plasmodium falciparum for biological evaluation. These derivatives had antiplasmodial IC_{50} values of 1.3-0.079 and 2.0-0.050 M, respectively, against a chloroquine-

sensitive (D_{10}) and two resistant (K_1 and W_2) P. falciparum strains [60].

7.6. CNS effects

Isatin affects a wide range of behavioural and metabolic functions. Lower doses are anxiogenic, whereas higher doses are sedative. Its most potent *in vitro* activities are as a NO signalling antagonist and an antagonist of atrial natriuretic peptide (ANP) activity [61].

Isatin-containing synthetic compounds and their derivatives have been linked to a wide range of biological activities, including antipyretic activity [62], analgesic effect [63], anticonvulsant activity [64], and psychotropic agents and MAO inhibitors, according to the literature. All of the recorded activities pave the way for these compounds to be used for CNS activity. Depression is characterized as a depression of mood rather than a mental disturbance. Depression including hallucinations and delusions has been observed. Some isatin derivatives have CNS depressant properties [65].

7.7. Anticancer activity

Isatin derivatives' cytotoxicity has been known for over 30 years. The University of Wollongong began investigating the cytotoxic nature of isatins in 2002, when it was discovered that chloroform extracts of the egg masses of the Australian muricid mollusk Dicathais orbita had cytotoxic activity. Tyrindoleninone, tyriverdin, and 6-bromoisatin were among the extract's components. In a cell-based assay using human monocyte-like, histiocytic lymphoma cells (U937) (IC_{50} = 4 M against U937 cells, 195 M against human mononuclear cells) (IC_{50} = concentration required), tyrindoleninone was found to be the most active component (IC_{50} = concentration required) [66].

Isatin shows cytotoxicity to HL60 cells due to apoptosis induction. Isatin can be used as a chemotherapeutic agent to destroy cancer cells and as a prophylactic agent to prevent free radical-induced cancer [67, 68]. Isatin and its derivatives have a number of biological properties, including antitumor properties. Isatin, for example, is one of the key components of *Indigo naturalis*, a traditional and powerful Chinese medicine for antiproliferation [69] .S. Kumar et al. synthesized and evaluated the Baylis-Hillman adduct-derived N-cinnamyl- substituted isatin derivatives for their anticancer activity. The compound showed a specific cytotoxicity on cancerous cell lines Colo 205, Sup-T1 and C6-glioma, whereas it is non-cytotoxic to non-cancerous cell line (CHO) [70].

7.8. Glucose and Amino acid uptake inhibition

Isatins inhibited Na+-dependent L-Lysine in the rat intestine competitively (27-40%). SH group responding agents had no effect on Isatin. Isatin inhibited Na+-K+-ATPase in the intestine in vitro, but not in vivo. Isatin inhibits the activity of histamine-induced bronchoconstriction. It also has a cardio inhibitory effect, hypertensive, respiratory depressant, and diuretic effects are also possible side effects. It has no effect on inflammation or gastric ailment [24].

8. CONCLUSION

Isatin is a molecule with a lot of synthetic versatility and a pharmacological potential that has been studied extensively by various research groups around the world. Isatin has been synthesized using a variety of methods. As the number and lipophilicity of substituents on the targeted isatin are increased, most traditional methods for their production are inadequate. Sandmeyer's method is one of the most popular classical methods for synthesizing isatin. Since the reagents are inexpensive and readily available, and the yields are generally good, this approach has some economic advantages. Most approach is based on the oxidation of indole and its derivatives with organic and in-organic iodine oxidants, as well as metal-catalysed oxidations with peroxides. The isatin moiety also exhibits important chemical reactions including oxidation, N-acylation, Friedel-Crafts reaction, and N-halogenation, etc. Isatin and its derivatives are used as bactericides, fungicides, anti-HIV, anti-epileptics, anti-instigative, and many other applications. Isatin derivatives can be used to reduce the natural activity of the urease and -glucosidase enzymes. We found from the study that Isatin compounds are potent chemical moieties with a wide variety of activities, and that many Isatin derivatives are currently being researched.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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