Synthesis of Isatin and Its Derivatives and their Applications in Biological System

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ABSTRACT

Here investigations were made to study the variant developments in the synthesis of isatin and its derivatives. This review comprehended the various synthetic methods especially, sandmeyer synthesis, stolle synthesis and gassman synthesis for the synthesis of isatin. The isatin and its derivatives played a key role in biomedical applications. The isatin and its derivatives are used as bactericide, fungicide, anti-HIV, anti-epileptic, anti-instigative and so on. The isatin derivatives are helpful in inhibiting the activity of the urease and α-glucosidase enzymes and reduce the risks of pyelonephritis, gastric problems and diabetes. This review highlighted the synthetic routes for the synthesis of isatin and the beneficial aspects of isatin and its derivatives in biomedical field.

Keywords: Isatin; Urease Inhibition; α-Glucosidase Inhibition; Antioxidant Activity; Sandmeyer Synthesis

Introduction

Isatin is an indole derivative firstly synthesized in the laboratory by Erdmann and Laurent by oxidation of indigo pigment having chronic acid. It is orange-red in color with freezing point 200°C [1,2]. Isatin is heterocyclic compound and acts as important species for the synthesis of various heterocyclic compounds especially, indolic and quinolonic compounds. It is also used in medicines synthesis (Figure 1). Thiosemicarbazide derivatives of isatin were reported as an anti-HIV agent [3]. N-methyl isatin-β-4',4'-diethylthiosemicarbazone prove high inhibition of HIV by their action on contrary transcriptase and viral structural proteins [4]. 3-p-(p-(alkoxycarbonyl) phenyl carbamoyl) phenyl) imino-1-aminomethyl-2-indolinones was by R.S Verma et al. was successfully tested against M. tuberculosis H37Rv [5]. Isatin derivatives are very effective against micro-organism especially, S aureus, S epidermis, Micrococcus luteus, and B cereus. The Schiff base of isatin derivatives 5-substituted and N-acetyl isatin with different substituted aromatic aldehydes was assumed to be very operative against micro-organisms [6,7]. Bis-Schiff bases of isatin were found to possess significant anti-viral, antibacterial and anti-fungal activity [8,9].

Figure 1: Skeleton of Isatin.
The azetidine and thiadiazine derivatives of isatin were also found to possess significant antibacterial activity [10]. 5-Nitro-1H-indole-2,3-dione-3-N-(4H-methyl phenyl)thiosemicarbazones screened for antibacterial activity against *E.coli* and *S.aureus* by the cup-plate method and found active [11]. It also acts as anti-HIV, showing enzyme inhibition activity and as cytotoxic agent against tumor cells [12-14]. In antismallpox [15], inflammatory activities [16], kinase activator [17]. Also, biologically active on echinococcus multilocularis metacestodes [18]. Meshram et al. also developed an isatin-based multicomponent reaction for the synthesis of spirooxindole fused N-heterocyles with anticancer properties [19].

Zhang et al. first reported the vinylogous, henry reaction between isatin and 3,5-dialkyl-4-nitroisoxazole, leading to isoxazole-substituted 3-hydroxy-2-oxindole derivatives, medicinally important compounds [20], also provided the basis for removal of industrial dye wastewater [21]. In this study, we discuss in detail “Synthesis of isatin and its derivatives and their applications in biological system” because isatin play a key effects like ascorbic acid, hydroxyl amino acids, omeprazole, thiol compounds and imidazole etc. which is helpful for the pathogenesis of gastric ulcer and peptic ulcer.

Also discuss antioxidants, which are responsible for converting free radicals into stable substances, especially serious diseases caused by diabetes. We can say, that isatin provides a critical and dynamic role in the pharmaceutical industry.

**Isatin Synthesis**

**Sandmeyer Synthesis**

One of the most famous techniques for the synthesis of isatin is Sandmeyer method. Aniline reacts with chloral hydrate and hydroxylamine hydrochloride conducting aqueous solution of sodium sulfate to produce an isonitrosoacetenilide. In this way, isonitosoacetenilide easily converted into isatin analogs [22] (Figure 2).

**Stolle Synthesis**

This method is very effective for the synthesis of isatin and its derivatives. The substituted isatin is synthesized by converting substituted aniline in the presence of oxalyl chloride and Lewis acids like BF3 or AlCl3. This method is also very useful to synthesize 1-Maryland polycyclic istan from phenothiazine, phenoxazine, dibenzoazepine and indol [23,24] (Figure 3).

**Gassman Synthesis**

Gassman introduced a new approach, to synthesize isatin. This method involves the characteristics relationship between electrons donating, an electron withdrawing group, to convert aniline to intermediate 3-methylthiooxindol. In this intermediate, the methyl group is oxidized by N-chlorosucinamide, which is proceeded by the hydrolysis of the chlorinated intermediate [25,26] (Figure 4).
Isatin Derivatives

Isatin derivatives are well known malleable substances, which are acted as forerunners for the synthesis of heterocyclic compounds [27]. Isatin derivatives play a vital role in the medicines because it used as bactericide [28], used for viral infections [29], anti-HIV [30], fungicide [31], anti-epileptic [32], anti-neoplastic [33], for the treatment of Mycobacterium [34] and anti-invasive [35]. Isatin derivative like 5-hydroxy isatin and spirobenzodiazepine, also used to reduce depression [36] (Figure 5). Few derivatives of isatin like 3-p-(p-(alkoxy carbonyl)phenyl)carbonylphenyl) imino-1-aminomethyl-2-indolinone is found to be effective against tuberculosis [37]. 5-[2(3)-diallyl aminoalkoxy] Indole 2,3-dione is one of the important isatin derivative used against aminallane (histamine) [38]. Isatin derivatives are used for the treatment of malaria. 4-aminoquinoline derivatives were found to be efficacious versus Plasmodium falciparum [39]. Such derivatives can be obtained both from natural and synthetic source. tryptanthrin well-known isatin derivative obtained from Chinese herb [40].

![Figure 5: Structure of 5-hydroxy and spirobenzodiazepine isatin derivative.](image)

Most of this type, derivatives are synthesized in laboratories, such as 5-methyl isatin [41], and 5-aminoindazole and mercapto-acetic acid can easily prepared [42]. By treating alkyl isatin with the compound labeled acidic medium (acetic acid) reflux at 2 hours is converted into 2-amino benzoic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide [43]. Synthesizes, compound involves so many synthetic routes. Then these compounds were dissolved in acidic (acetic acid) in water basic solution [44-48]. The synthesis of Schiff bases, are prepared simply by reacting isatin and its derivatives were also synthesized [59].

Urease Inhibition

Urea, which is well-known fertilizer used for the enhancement of fertility of the soil, urea contains (46%) nitrogen. This urea release nitrogen in the form of ammonia gas due to which its action of fertility is also affected [60]. Urease is a well-known enzyme has nickel in their body structure which convert urea to carbon dioxide and ammonia by hydrolytic catalysis [61]. This typical enzyme is isolated by the same catalysis process from different plants, algae, fungi and bacteria [62,63]. As this enzyme has the same amino acid sequence and having Ni^{2+} in their core structure that is why its origin is very common [62,64,65], and develop various types of diseases in animals and plants especially stomach and gastrointestinal ulcer; hepatic coma auralithiasis and pyelonephritis [66,67]. Recently two new isatin derivatives (1-allyl-2-oxoindolin-3-ylidene)-4-methylbenzenesulfonyl-hydrazide and (1-allyl-2-oxoindolin-3-ylidene)-4-chlorobenzenesulfonyl-hydrazide were synthesized with a high yields. The dynamic stability, reactivity, and affinity of these two derivatives are described. Enzyme inhibition potential test was carried out on urea enzyme of bacillus pasteurii urease and both compounds retarded the enzymatic activity with IC50 values of 39.46 ± 0.12 mM and 148.35 ± 0.16 mM respectively [68] (Figure 6).
Helicobacter pylori is the well-known bacterium which causes gastric and peptic ulcer [69]. This bacterium discharge urease which converts urea to ammonia which is basic in nature which increases the pH of the stomach and provides a good environment for their growth. This enzyme is very useful to eradicate the toxic organism from our body [70]. Recently numerous urease enzymes have been added to literature especially triazoles and coumarin derivatives [71]. Schiff bases derivatives [72], omeprazole [73], plan tool and its thiourea derivatives [74], hydroxamic acid [75], lansoprazole [76], thiol-compound [77], phosphorodiamidates [78,79], imidazoles, for example, rabeprazole [80], hydroxyurea [81], quinine [82] and hydroxamic acid derivatives [83].

**α-Glucosidase Inhibition**

α-glucosidase is also regarded as exoglycosidase enzyme. This enzyme is present in the intestinal tract which hydrolyzed the carbohydrate and converted into glucose. This glucose is then entering the bloodstream and its excess causes postprandial hypoglycemia [84]. The main aim of the α-glucosidase inhibitors is to delay the hydrolysis of carbohydrate to reduce the risks of diabetes [85], that’s why this enzyme is preferably used in anti-diabetic medicines [86]. α-Glucosidase inhibitors retard the function of α-glucidase, which is responsible, to convert carbohydrate into glucose. So, in this, way it, reduces the glucose level in the blood stream and hemoglobin [87]. The main drawback of this enzyme is lack of specify in targeting glycosidase and causes infections especially relating to the stomach and intestines, looseness of the bowel and produce a state of excessive gas in the alimentary canal [88]. The derivatives of benzathiazole-triazole were synthesized, and their characterization was carried out with 1H-NMR and 13C-NMR. The inhibitory activity of α-glucosidase inhibitory in vitro was screened by baker’s yeast α-glucosidase enzyme. Compared to standard IC50 817.38 μm values between 20.7 and 6.11 μm, most compounds exhibit varying degrees of alpha-glucose inhibition activity (Figure 7).

### Antioxidant Activity

Free radicals are atom or molecule with an odd electron in their outmost shell [89], are highly unstable and always in search to gain an electron from any species to complete its outmost shell in order to make itself stable. In our body, during the metabolism process of oxygen, any free radicals are generated in mitochondria. So, it is very important to eradicate these free radicals, if it is not so, they will cause different diseases especially malignant neoplasic disease, disease relating to the brain and the blood vessels, dotage, heart disease, ulceration, diabetes, heart disease, mucoviscidosis, agedness, gastrointestinal ulcer and acquired immune deficiency syndrome [90,91]. So, to overcome this problem antioxidants are used, because their main function is to convert these highly unstable free radicals to stable substances. Antioxidants are used in a large number of medicines which are used to cure the diseases caused by the free radicles [92-94]. Here also experimental and theoretical results, compatible with (H25MI3ClPT) and (H25MI3PT) concentration of free radical scavenging in DPPH. The proportionality increased in the antioxidant activity. In particular, it is theoretically confirmed that the antioxidant activity of DPPH products with high energy volume (H25MI3CIPT) -IC50 is lower than (H25MI3PT)-DPPH products [95].

### Conclusion

In this paper, isatin and its derivatives were studied and evaluate their biological activates, such as urea enzyme inhibition, alpha-glucosamine inhibition and antioxidant activity. Various synthetic methods especially, sandmeyer synthesis, stolle synthesis and gassman synthesis were discussed for the synthesis of isatin. The isatin and its derivatives played a phenomenal role in biomedical applications. The isatin and its derivatives are used as bactericide, fungicide, anti-HIV, anti-epileptic, anti-instigative and so on. The isatin derivatives are useful in constraining the natural action of the urease and α-glucosidase enzymes and reduce the threats to human health like pyelonephritis, gastric problems and diabetes.

### Compliance with Ethical Standards

**Conflict of Interest:** The authors declare that they have no conflict of interest.

**Ethical Approval:** This article does not contain any studies with human participants or animals performed by any of the authors.

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