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Review Paper

Review On Isatin and its Antidiabetic Isatin Scaffolds

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ABSTRACT

Isatin (1H-indole-2,3-dione) is a well-known heterocyclic compound that has gained considerable attention in medicinal chemistry due to its broad range of biological activities. The molecule possesses a bicyclic structure consisting of a benzene ring fused with a five-membered heterocyclic ring containing two carbonyl groups at the C-2 and C-3 positions and a nitrogen atom at the N-1 position. This structural arrangement makes isatin a versatile intermediate for the synthesis of numerous biologically active compounds.A wide variety of isatin derivatives have been reported to exhibit important pharmacological properties, including antimicrobial, antiviral, anticancer, and antidiabetic activities. Historically, isatin was first obtained through the oxidation of indigo dye by the chemists Otto Linné Erdmann and Auguste Laurent using nitric and chromic acids. The compound forms orange-red monoclinic crystals with a melting point close to 200 °C.Isatin has also been identified as an endogenous compound in humans, where it is associated with metabolic pathways related to adrenaline. In addition, it has been detected in the secretions of certain amphibians such as species of the genus Bufo, and several naturally occurring isatin derivatives have been reported in plants. This review highlights recent developments in the synthesis, chemical transformations, and antidiabetic potential of isatin-based derivatives..

INTRODUCTION

Isatin is an important heterocyclic compound that plays a significant role in the synthesis of various heterocyclic molecules, particularly quinoline and indole derivatives. Because of its versatile chemical structure, isatin has been widely used as a starting material in the development of several pharmacologically active compounds. Studies have shown that some isatin derivatives containing thiosemicarbazide groups exhibit notable anti-HIV activity. For example, N-methyl isatin-β-4',4'-diethylthiosemicarbazone has demonstrated

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strong inhibitory activity against HIV by interacting with reverse transcriptase and viral structural proteins. In addition, R. S. Verma and co-workers reported that certain indolinone derivatives such as 3-p-(p-(alkoxycarbonyl)phenyl)carbamoyl phenyl imino-1-aminomethyl-2-indolinones exhibited activity against Mycobacterium tuberculosis H37Rv.

Furthermore, several isatin derivatives have shown significant antimicrobial activity against microorganisms including Staphylococcus aureus, Staphylococcus epidermidis, Micrococcus luteus, and Bacillus cereus. Schiff bases derived from isatin, particularly those formed from 5-substituted and N-acetyl isatin with substituted aromatic aldehydes, have demonstrated strong antimicrobial effects. In addition, bis-Schiff base derivatives of isatin have been reported to possess antiviral, antibacterial, and antifungal properties.

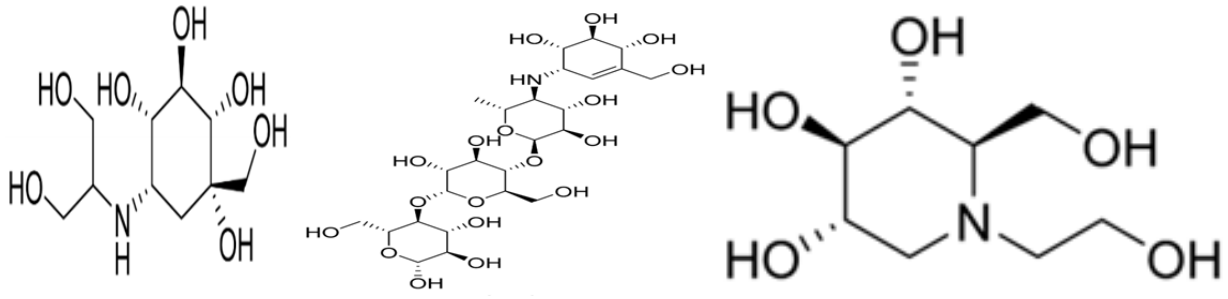
Diabetes mellitus is considered one of the major global health challenges of the twenty-first century. The disease is characterized by persistent hyperglycemia resulting from impaired insulin secretion or insulin resistance. Long-term elevated blood glucose levels may lead to severe complications such as cardiovascular disorders, nephropathy, retinopathy, thrombosis, encephalopathy, and neurodegenerative diseases including Alzheimer's disease. According to the International Diabetes Federation (IDF), diabetes and its associated complications are responsible for millions of deaths worldwide each year.

One of the important therapeutic strategies for controlling postprandial hyperglycemia involves inhibiting the digestion and absorption of dietary carbohydrates. In the digestive system, pancreatic α-amylase breaks down complex carbohydrates into smaller oligosaccharides, while α-glucosidase further hydrolyzes these carbohydrates into glucose molecules. The glucose produced from carbohydrate digestion enters the bloodstream and contributes to elevated blood sugar levels. Therefore, inhibition of α-amylase and α-glucosidase enzymes can delay carbohydrate digestion, slow glucose absorption, and consequently reduce postprandial blood glucose levels.

Although several drugs such as acarbose, voglibose, and miglitol are currently used as α-glucosidase inhibitors, their use is often associated with gastrointestinal side effects including diarrhea, abdominal discomfort, bloating, and flatulence. As a result, the development of new and more effective inhibitors with fewer adverse effects remains an important research objective. In this context, several novel isatin-hydrazide conjugates (1a–1j) have been synthesized and evaluated for their inhibitory activity against α-amylase and α-glucosidase enzymes. Molecular docking studies were also performed to investigate the interaction of these compounds with the active sites of the target proteins.

Over the past decade, medicinal chemists have shown considerable interest in 1,2,3-triazole-linked isatin derivatives because of their wide range of pharmacological activities, including antibacterial, antimycobacterial, antifungal, anticholinesterase, and anticancer effects. These hybrid heterocyclic compounds are also being explored for the treatment of inflammatory disorders and diabetes. For instance, in lipopolysaccharide (LPS)-stimulated THP-1 human monocytic cells, certain triazole-isatin derivatives were found to reduce the production of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1). Additionally, triazolyl-isatin derivatives have demonstrated promising inhibition of the 5-lipoxygenase enzyme. Some hybrid molecules, including hydrazineylideneisatin-phenoxymethyl-1,2,3-triazole and thiazolidinedione-linked triazole-isatin, have also shown significant α-

glucosidase inhibitory activity with IC_{50} values of 24.73 µM and 16.43 µM, respectively.



Acarbose **Voglibose** **Miglitol**

Fig. 1. Clinically used α-glucosidase and α-amylase inhibitors.

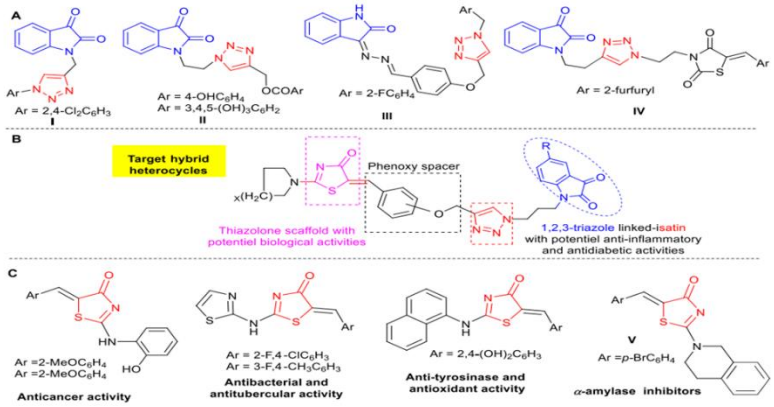


fig.2

Chemistry:

Antidiabetic profile and SAR study :

The antidiabetic potential of the synthesized target compounds was evaluated in vitro by measuring their inhibitory activity against the carbohydrate-digesting enzymes α-amylase and α-glucosidase at concentrations ranging from 10 to 180 µg/mL. The standard drug Acarbose was used as a reference compound to compare the inhibitory effects of the synthesized analogues.The experimental results demonstrated that several compounds exhibited considerable inhibition of both enzymes, indicating that the nature and position of substituents on the molecular framework play an important role in determining enzyme inhibition (Fig. 3). The synthesized analogues showed a wide range of inhibitory activities when compared with the standard drug. The IC_{50} values for α-amylase inhibition ranged from 30.39 ± 1.52 µM to 193.83 ± 9.54 µM, while the values for α-glucosidase inhibition ranged from 65.1 ± 3.11 µM to 208.72 ± 10.38 µM.

Among the tested compounds, analogue 5d exhibited the strongest inhibitory activity, with IC_{50} values of 30.39 ± 1.52 µM for α-amylase and 65.1 ± 3.11 µM for α-glucosidase. The high activity of this compound may be attributed to the presence of an electron-withdrawing chloro (–Cl) substituent attached to the oxoindolin-3-ylidene core. Replacement of the 6-methyl group in compound 5d with a 4-methoxy substituent (compound 5a) resulted in a significant reduction in enzyme inhibitory activity, decreasing the potency by approximately 6.3-fold for α-amylase and 3.2-fold for α-glucosidase. Similarly, compound 5h, which contains a fluoro (–F)

substituent at the C-7 position of the oxoindolin-3-ylidene ring, showed strong inhibitory activity toward both enzymes and was more active than compound 5f, which possesses an electron-donating methyl group at the C-5 position. Furthermore, compound 5e, containing a methyl group at the 6-position of the phenoxy ring and a bromo substituent at the 6-position of the oxoindolin-3-ylidene moiety, exhibited stronger activity compared with compound 5c, which bears a methoxy substituent at the C-4 position of the phenoxy ring (17).

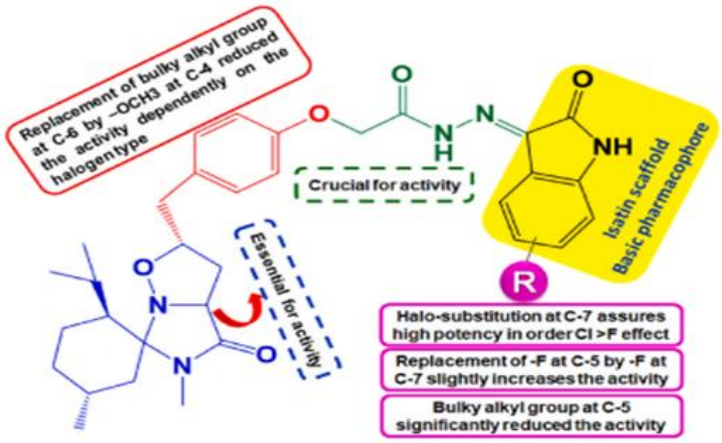
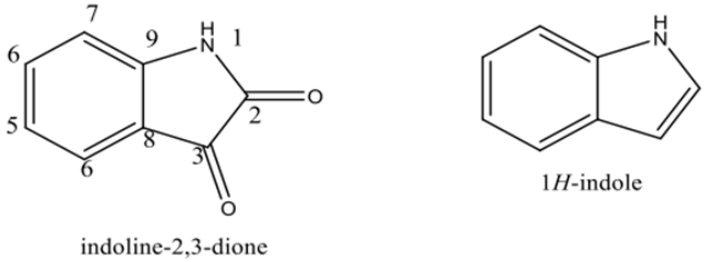


fig.3

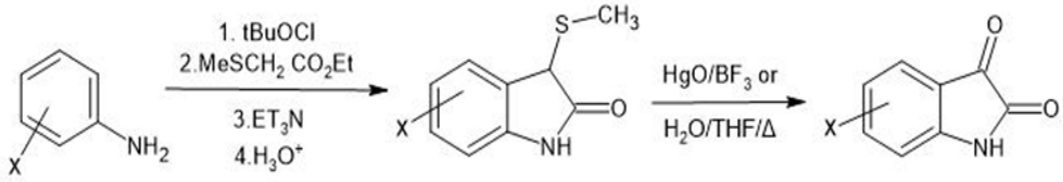


Structure of isatin fig.4

Synthesis of isatin :

1.Gassman isatin synthesis:

3-methylindoline-2-one was the intermediate product of this reaction, which began with aniline. A 3-isocyano-3-(Methyl thio) indoline-2-one was produced by cyclizing the intermediate product N-chlorosuccinimide. It was then combined with boron trifluoride etherate and mercury (II) oxide to produce 1H-indole-2,3-dione (50).

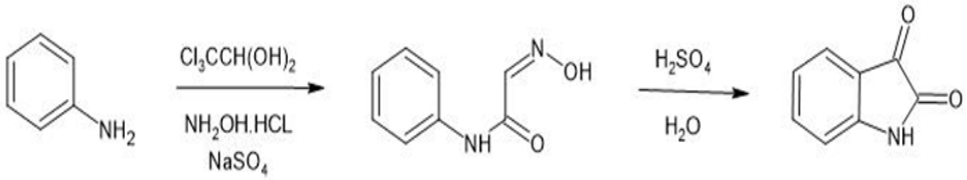


Scheme1.gassman isatin synthesis

2.sandmeyer isatin synthesis:

In 1919, Sandmeyer was the first to document this response. In order to create an isatin derivative, chloral (i.e., trichloroacetaldehyde), hydroxylamine, and a primary aryl amine condense to isonitrosoacetanilide. The latter is then electrophilically cyclized in the presence of a strong acid, such as concentrated sulfuric acid (Scheme 1). This reaction is known as the

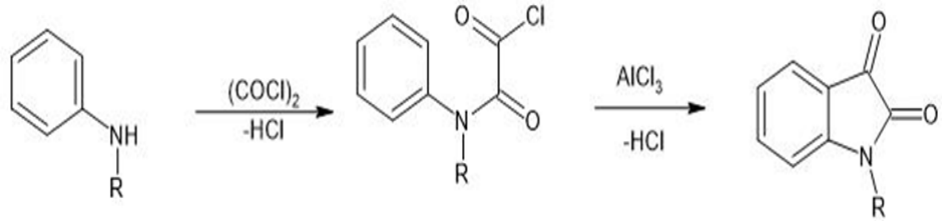
Sandmeyer isatin synthesis, or Sandmeyer synthesis. The isatin derivatives generated by this reaction have been used to make quinolines, acridines, and indophenazines [30, 31]. The production of isonitrosoacetanilides using the Sandmeyer method is less successful when aniline derivatives have limited solubility in an aqueous sodium sulphate media, but it is also ineffective when anilines have electron-rich ortho.(15)



Scheme2. Sandmeyer isatin synthesis.

3.Stolle isatin synthesis:

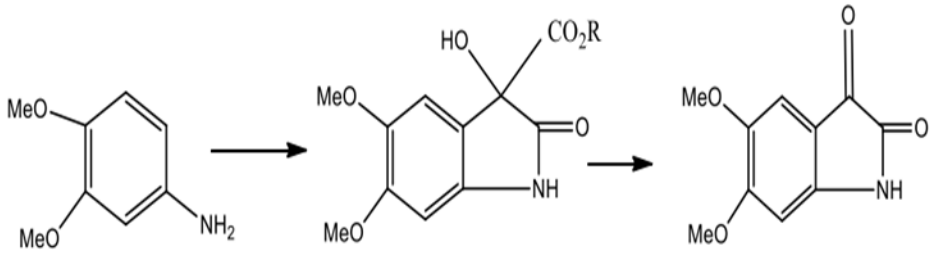
The best substitute for Sandmeyer's protocol is the Stolle method. In the presence of a Lewis acid, typically aluminum chloride or BF3, anilines react with oxalyl chloride to produce an intermediate chloro-oxalylanilide, which can be cyclized. Et2O, while the equivalent isatin has also been produced using TiCl4 (Scheme 2). This method has been used to create 1-aryl and polycyclic isatins from phenoxazine, phenothiazine, dibenzoazepine, and indoline.(15)



Scheme3.stolle isatin synthesis.

4.martinet isatin synthesis:

By reacting an amino aromatic compound with either an oxomalonate ester or its hydrate in the presence of an acid, the Martinet method for the synthesis of indole-2,3-diones yields a 3-(3-hydroxy-2-oxindole)carboxylic acid derivative, which is subsequently oxidatively decarboxylated to yield the desired isatin. This method worked well for the synthesis of 5, 6-dimethoxyisatin from 4-aminoveratrole, but less well for 2, 4-dimethoxyaniline.(15)



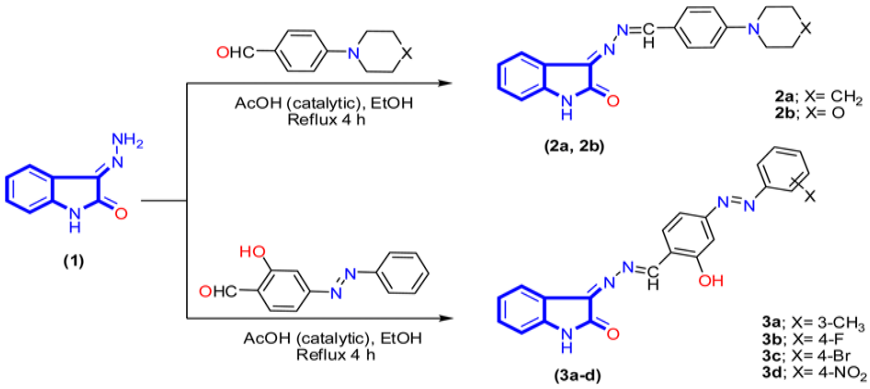
scheme4. Martinet isatin synthesis.

DERIVATIVES OF ISATIN:

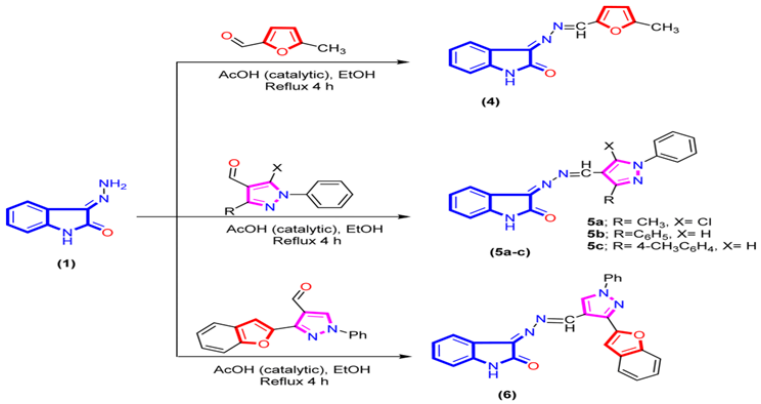
1. Isatin-hydrazide / isatin-hydrazone or Schiff bases:

A novel series of isatin-based Schiff base derivatives was synthesized starting from 3-hydrazonoindolin-2-one (1), which was previously prepared and subsequently reacted with various formyl derivatives. This reaction resulted in the

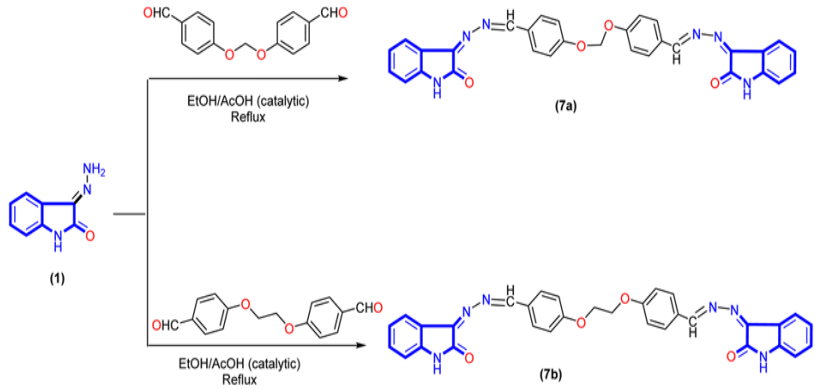
formation of several compounds, including 2a, 2b, 3a–d, 4, 5a–c, 6, 7a, and 7b, and their structures are illustrated in Schemes 6–8.Compound 3-hydrazonoindolin-2-one (1) was reacted with different formyl-containing compounds to obtain three series of derivatives. Series I consisted of aromatic formyl derivatives containing aliphatic or azo (–N=N–) groups (Scheme 6). Series II involved heterocyclic formyl derivatives based on pyrazole or furan cores (Scheme 7), while Series III included bis-formyl derivatives (Scheme 8).The synthesized compounds were evaluated for their antidiabetic activity by examining their ability to inhibit the α-amylase enzyme, which plays a key role in the digestion of starch and oligosaccharides into glucose. Inhibition of α-amylase is therefore considered an important strategy for the management of diabetes mellitus.The inhibitory activities of the synthesized isatin-based Schiff bases (2a, 2b, 3a–d, 4, 5a–c, 6, 7a, and 7b) were compared with the standard drug Acarbose, which showed 69.11 ± 0.15% inhibition of α-amylase. The tested compounds demonstrated moderate to good inhibitory activity, with inhibition values ranging from 26.97 ± 0.06% to 57.64 ± 0.13%.Among the synthesized derivatives, compounds containing a pyrazole moiety (5a–c) and the azo-aryl salicylamide derivative (3b) exhibited comparatively higher inhibitory activity. In particular, compound 3b showed 54.76 ± 0.12% inhibition of the α-amylase enzyme. Similarly, compounds 5a (57.64 ± 0.13%), 5b (55.96 ± 0.12%), and 5c (56.52 ± 0.12%) displayed inhibitory activities close to that of the reference drug. The observed order of activity among these compounds was 5a > 5c > 5b > 3b.



Scheme 6.Synthesis of isatin-based azomethine 2a, 2b, and isatin-azomethine-arylazo 3a–d.



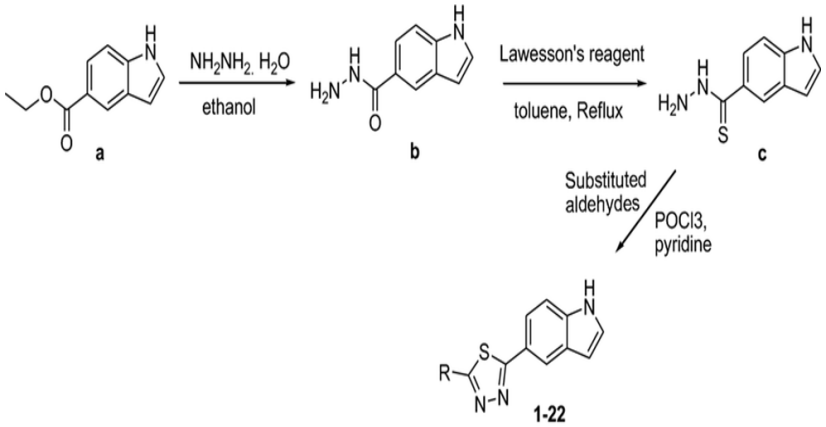
Scheme 7. Synthesis of isatin-azomethine-heterocyclic 4, 5a–c, and 6.



Scheme 8.Synthesis of bis-Schiff bases based on isatin 7a and 7b.

2.Isatin Thiadiazole derivative :

Synthesis of thiadiazole compounds based on indole (1–22): The synthesis of indole-based thiadiazole derivatives (1–22) involved refluxing ethyl 5-cyano-1H-indole-2-carboxylate (I) (2 mmol) with hydrazine hydrate (4 mmol, 2 equivalent) in ethanol for 4 hours to produce 5-cyano-1H-indole-2-carbohydrazide (II). The corresponding cyclized thiadiazole analogs (1–19) were obtained by heating the intermediate product (II) (1 mmol) under reflux with different isothiocyanates (1 mmol, 1 equivalent) in ethanol with triethylamine (1 mmol, 1 equivalent) (Scheme 9). (7)



Scheme.9

3. coumarin isatin derivative

Scheme 10 shows a generic synthesis of coumarin-isatin derivatives 5a–5t. Ethyl 2-((2-oxo-2H-chromen-7-yl)oxy) acetate 2 was produced in good yield by treating 7-hydroxycoumarin 1 with ethyl bromoacetate in the presence of anhydrous K2CO3 in dry acetone. This compound then interacted with hydrazine hydrate to produce the crucial intermediate 3. Finally, by condensing hydrazide 3 with the matching suitable isatins 4a-4t in the presence of glacial acetic acid, the new required compounds 5a-5t were produced in good yields (67.5%-89.1%). Spectral analysis was used to validate the structures of freshly synthesized substances.(8)

Scheme10. Reagents and conditions:

(a) K2CO3, acetone, reflux, 6h; (b) NH2NH2·H2O, EtOH, reflux, 4h; (c) CH3COOH, EtOH, reflux, 2h.(8)

4. Isatin Schiff base derivative:

The general process for creating derivatives of Schiff bases based on isatin Three processes were used to create isatin-based Schiff bases. The first was an esterification, which involved reacting

various carboxylic acids with methanol in sulfuric acid (2–3 ml) at reflux 7 conditions for 12–16 hours. TLC was used to track the reaction's conclusion. Pure esters were obtained by extracting the reaction mixture with hexane after the reaction was finished.(9) After that, esters were refluxed for three hours using hydrazine hydrate in methanol and a few drops of glacial acetic acid. Different hydrazides were obtained by washing the reaction mixture with chloroform after the reaction was finished. After that, each of these hydrazides (1 mmole) was treated for two to four hours with a separate isatin (1 mmole) in methanol containing a catalytic quantity of glacial acetic acid.

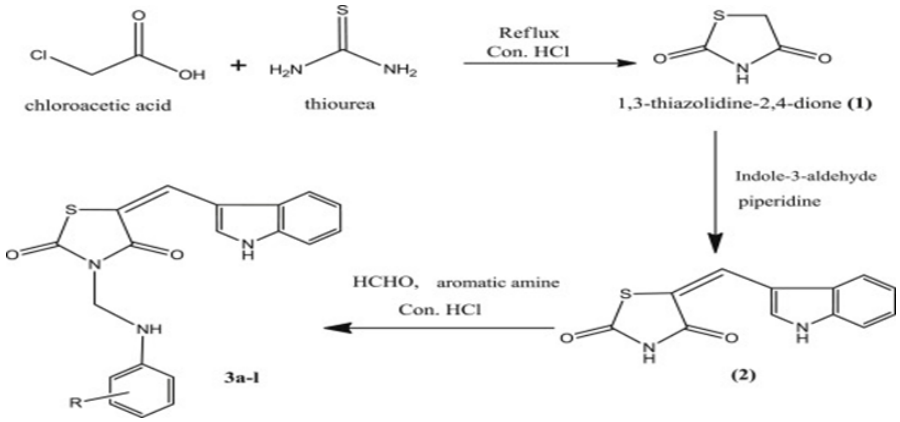
Periodic TLC was used to track the completion of the reaction. To get our desired products, the reaction mixture was cleaned with n-hexane once the reaction was finished. EI-MS and 1HNMR were used to determine each compound's structure.(9)

6.Thiazolidinedione deivatives:

Synthesis of 1,3-thiazolidine-2,4-dione:

Conventional heating method:

In a three-necked round-bottom flask, a stirring solution of thiourea (1.52 g, 20 mmol) was combined with a solution of chloroacetic acid (1.89 g, 20 mmol) in water (5 mL). Until a white precipitate appeared, the reaction mixture was agitated. Using a fitting dropping funnel, a concentrated HCl solution (6 mL) was gradually added dropwise to the reaction mixture. In the center of the flask is a reflux condenser. After being heated to 100–110 °C for ten to twelve hours, the reaction mixture was allowed to cool to room temperature. After filtering off the resultant suspension, the precipitate was thoroughly cleaned with water to get rid of any remaining HCl. Recrystallization from ethanol was used to further purify the product.(11)



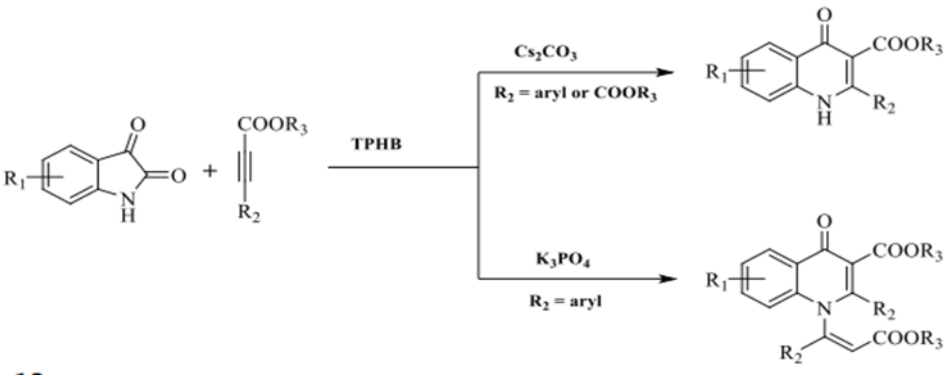
Scheme11. Synthesis of thiazolidine-2, 4-dione using thiourea and chloroacetic acid.(11)

Reactions of isatin:

1.oxidation reaction:

When chromic acid is present in an acetic acid solution, the isatin molecule can undergo an oxidation process that produces isatoic anhydride. Isatoic anhydride is widely used in pharmaceutical chemistry and the manufacturing of herbicides (Sumpter, 1944). An oxidative cyclization process utilizing isatins and alkynes to create structurally varied 4-quinolones was disclosed as part of a straightforward, transition metal-free technique for oxidizing isatins. Interestingly, changing the base of the reaction could provide switchable access to substituted 1-vinyl-3-carboxylate-4-quinolones and 3-carboxylate-4-quinolones. The method's potential for use in organic synthesis could be expanded by allowing the products to undergo additional transformations (Jiang et al., 2018). Scheme 8 shows the oxidation of isatin to

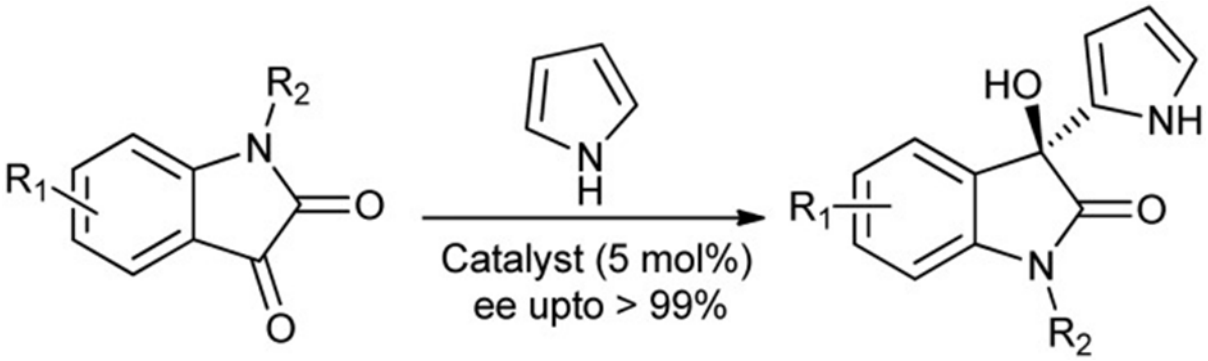
isatoic anhydride, which is catalyzed by organocesium.(16)



Scheme15. Organocesium-catalyzed oxidation of isatin to isatoic anhydride.

2.Friedel–Crafts reaction

A significant family of organic syntheses known as Friedel-Crafts reactions is utilized to create highly functionalized aromatic compounds, which can then produce significant molecules with potential use in medicine.(22, 23) The biologically intriguing and optically active 3-aryl-3-hydroxy-2-oxindoles are produced by the asymmetric Friedel-Crafts alkylation of isatin with electron-rich aromatic chemicals. The first and only effective asymmetric Friedel-Crafts alkylation of isatins with pyrroles to produce oxindoles was reported by Franz and colleagues.(24) Additionally, Wang and colleagues employed a tridentate Schiff base/Cu as a catalyst and hexafluoroisopropanol as an essential additive agent to increase the enantioselectivity of the oxindoles produced (Scheme 17) (25).



Scheme17. Friedel–Crafts alkylation of isatins with pyrroles to give oxindoles.

3.Alkylation of isatin :

An alkylating agent, often an alkyl or aryl halide, is used in the synthetically feasible reaction of alkylation of isatin in the presence of a base, such as Cs2CO3 or K2CO3 (Scheme 22). Reactions with more reactive alkyl halides take less time to complete because the rate of reaction is dependent on the reactivity of the alky halide used.(30)

Scheme 22. Alkylation of isatin in the presence of a base.

5.Aldol reactions:

Aldol reactions yield β-hydroxyl carbonyl molecules, which are crucial intermediates in the creation of derivatives with biological activity. Isatin is an excellent substrate for condensation processes due to its strong H-bond acceptor

activity. Using a metal complex as the catalyst, the first diastereospecific and enantioselective allenoaldol reaction of isatins with allenic esters yields tri- and tetra-substituted carbinol allenoates (Scheme 19).(27)

Pharmacological actions of isatin:

1. Isatins as histone deacetylase (HDAC) inhibitors

The enzymes known as histone deacetylases (HDACs) catalyze the deacetylation of a particular lysine residue in the histone tails. According to literature reviews, HDAC is a desirable target for the creation of new anti-cancer medications, and HDAC inhibitors are a promising class of anti-cancer agents (35).

2. Isatins as carbonic anhydrase inhibitors

Zn2+ ions are present at the active site of carbonic anhydrases (CAs), a family of metalloenzymes. By catalyzing the quick, reversible hydration of carbon dioxide to the bicarbonate anion and proton ($CO2 + H2O \rightleftharpoons HCO3^- + H^+$), they contribute to the pH buffering of extracellular and intracellular regions. The clinical significance of these enzymes in cancer treatment has been emphasized by recent research. Two trans-membrane CA isoforms, hCA IX and hCA XII, are involved in the development of tumors and metastases out of the sixteen isoforms of hCAs that are known to exist in humans. These enzymes are therefore effective candidates for the creation of novel cancer treatments that combat hypoxic malignancies.(36).

3.Isatins as tubulin inhibitors

Microtubules, the key cytoskeletal filaments, play an important role in many cellular processes, such as in maintaining the cell structure and shape, together with mitosis and cell division. A variety of antimitotic agents interfere with the dynamics of microtubules by targeting tubulin, which is a major protein component of microtubules and hence is one of the most important strategic targets for developing novel anti-cancer drugs. Six different families of tubulin have been found so far: α-, β-, γ-, δ-, ε-, and ζ-tubulin. However, microtubules only consist of α- and β-tubulin, and consequently creating inhibitors for them can help in cancer therapy.(37,38)

4. Anti-diabetic activity

Diabetes mellitus (DM), commonly referred to as diabetes, is a syndrome characterized by disordered metabolism and inappropriately high blood sugar (hyperglycemia) resulting either from low levels of the insulin hormone or from abnormal resistance to insulin's effect.(39)The anti-diabetic activity of the novel compound 1-(4-(dimethylamino)benzylidene)-5-(2-oxoindolin-3-ylidene)-thiocarbohydrazone has been reported. Administration of the compound with a single dose of 50 and 100 mg kg–1 to diabetic rats showed a significant reduction in the blood glucose levels in a dose dependent manner.(40)Type 2 diabetes is a more common kind of diabetes and accounts for roughly 90% of all cases worldwide. α-Glucosidase, a carbohydrate enzyme released from the intestinal chorionic epithelium, is a therapeutic target for type 2 diabetes.(41)

A number of chromone(42,43) and isatin(44) derivatives have been reported as α-glucosidase inhibitors. Therefore, combination of these two scaffolds in a single molecule can result in improved pharmacological activity.

5. Anti-bacterial activity

Researchers are investigating the anti-bacterial activity of isatin derivatives, which show therapeutic potential against a range of harmful microorganisms. Schiff bases and Mannich bases of isatin and its derivatives were found to have strong antibacterial activity in a number of investigations.(45–47) SAR analyses of several

isatin compounds showed that 5-halogenation, N-alkylation, and N-Mannich bases also significantly increase the antibacterial activity.6.Anti-convulsant activity

6.Anticonvulsant activity

The most prevalent neurological condition marked by numerous unprovoked seizures is epilepsy, often known as convulsion. It typically starts in childhood and is caused by an electrical activity error in the brain.(48)

7.Anti-viral activity

The most common kind of virus is HIV-1 (human immunodeficiency virus type 1). Highly active anti-retroviral therapy (HAART), a mix of many antiviral medications that target several stages of the virus replication cycle, is the foundation of the currently approved treatment for this illness.(49)

CONCLUSION

The present review highlights the importance of the isatin scaffold in the development of potential antidiabetic agents. Due to its versatile chemical structure, isatin can be modified to produce numerous derivatives with diverse pharmacological properties. Many synthesized derivatives have demonstrated significant inhibitory activity against carbohydrate-digesting enzymes such as α-amylase and α-glucosidase, which are important therapeutic targets in diabetes management.Hybrid molecules incorporating isatin with other pharmacologically active moieties such as thiazole, hydrazone, Schiff base, and coumarin frameworks have shown enhanced biological activity. Structural modifications, particularly the introduction of heterocyclic rings and electron-withdrawing substituents, have been reported to improve enzyme inhibition and pharmacological potency.Overall, isatin remains a promising scaffold for the design of novel antidiabetic agents. Further research involving synthetic modification, biological evaluation, and molecular docking studies may lead to the discovery of safer and more effective therapeutic candidates for the treatment of diabetes mellitus.

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