Isatin Derivatives and Their Pharmacological Potential: Conventional and Green Synthesis Methods

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***Abstract*—Isatin is an eight-carbon containing nitrogenous compound which is available in nature. It is a multifused cyclic compound which is made upon fusion of Six-membered cyclic and Five-membered cyclic ring. Earlier it was discovered by the Erdmann and Laurent in 1964. Before the discovery in nature. It's IUPAC Name: 1-H-indol-2,3-dione .It is also known as Tribulin .The isatin scaffold shows the numerous of chemical reaction such as, N-halogenation, Alkylation, Acylation, N-substitution & such type of naming reaction (Sandmeyer, Clasein etc).It shows biological and pharmacological effect such as- cardioprotective, anti-diabetic, CNS depressant, anti-inflammatory, anti-cancer, anti-microbial etc.It is widely assign and disburse in group of cells and body fluid major intracellular fluid.Isatin is effective in alpha-amylase, Dipeptidyl Peptidase 4 (DPP4), alpha-glucosidase, COX enzyme.**

***Index Terms*—IUPAC, Anti-diabetic Anti-inflammatory, Scaffold, DPP4, COX**

I. INTRODUCTION

Erdmann and Laurent made this compound for the first time in 1841 by using chromic acid and nitric acid to oxidize indigo stains.Isatin is also Derived from plants like Corupita guianensis, Isatis, and Isatis Isatin is a chemical compound that comes from the indole compound. it is also known as Tribulin tinctoria.Before the 1920s, there weren't any good drugs for treating diabetes, which made type-I diabetes a deadly disease.

The isatin (1H-indole-2,3-dione) moiety is ubiquitous in nature, and its derivatives easily cross the blood-brain barrier. Isatin derivatives display a wide range of pharmacological properties due to their capacity to inhibit various enzymes and receptors, such as tubulin, acetylcholinesterase, butyrylcholinesterase, carbonic anhydrase, DNA gyrase, histone deacetylase, reverse transcriptase, serine proteases, and tyrosine kinase. [1–2]

Heterocycles are a very important type of organic compound that makes up more than half of all known organic molecules. They are an important part of many natural products, such as hemoglobin, biomolecules, RNA, DNA, proteins, vitamins, and other biologically active compounds.1. Heterocyclic scaffolds are important building blocks for making a wide range of biologically active compounds. Researchers are looking into a huge number of molecules right now, including nitrogen-containing heterocycles like indoles, pyrimidyl, pyrazolyl, thiazolyl, and pyridyl indoles, to see how they can be used in pharmacology and therapy.2–4 Naturally occurring melatonin is a type of indoleamine that is made and found in a wide range of organisms, including bacteria and eukaryotes. Melatonin is a hormone made by serotonin in the pineal gland. It controls the body's circadian rhythm, sleep and wake cycles, menstrual cycles, aging, immunity, and antioxidants, among other things. Melatonin is made and released more at night, but light exposure stops this.6 Previous studies have shown that melatonin has many effects on the body, such as being an antioxidant, protecting the heart, reducing inflammation, protecting the brain, protecting against strokes, reducing pain, fighting cancer, protecting the liver from damage, and even affecting the metabolism of offspring. Isatin or indenedione is another name for 1H-indole-2,3-dione. It is a flexible molecule with a lot of biological activity. Isatin is the starting point for

many derivatives that could have a wide range of biological and pharmaceutical effects, such as being able to fight cancer in different types of cancers, being an antibiotic, being an anxiogenic, being an antibacterial, being an antidiabetic, being an anticonvulsant, being a sedative, being a carboxylesterase, being an antidepressant, being an antifungal, being an antimicrobial, and so on. Isatin is one of the few things that people produced before they found it in nature.[3]

Isatin and its derivatives possess numerous biological activities, including anticancer, antibacterial, anti-inflammatory, analgesic, anticonvulsant, antiviral, anti-HIV, antioxidant, and central nervous system depressive effects. Linne Erdman and Auguste Laurent discovered isatin in indigo dye in 1941.[4] When nitric acid and chromic acid were used to oxidize indigo, vivid orange monoclinic crystals of isatin were formed.[5]

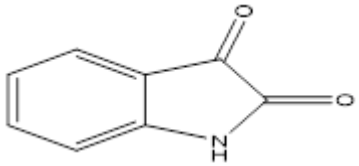
1.1 Chemistry of Isatin

Isatin, is also called indention or indole quinone, is one of these physiologically active heterocyclic moieties. Isatin is an indole building block that has two carbonyl groups at locations C2 and C3, a nitrogen heteroatom at position 1, and a ketone and a-lactam moiety that are attached to the benzene ring. [6–7] Oxindole, which is also called isatin, is a heterocyclic molecule with two nitrogen atoms in a ring with six other atoms. made up of two nitrogen atoms. It is a solid that is colorless and dissolves in benzene, ethers, and alcohols.[8] Isatin is used to make a wide range of chemical molecules, such as drugs, pigments, and scents. It also stops proteases and other enzymes from working. [9, 10] When an acid catalyst is present, formaldehyde and aniline come together to make isatin. The end product is a substituted indole, which can react with other chemicals to make a wide range of derivatives. To make isatin sulfonic acid, which is useful in organic synthesis, you can oxidize isatin. Isatin also goes through aromatic substitution processes, where an aromatic group takes the place of a hydrogen atom in the ring. The end products are useful building blocks for making many different chemical compounds. [11–12]

II. THE PHYSICAL PROPERTIES OF ISATIN

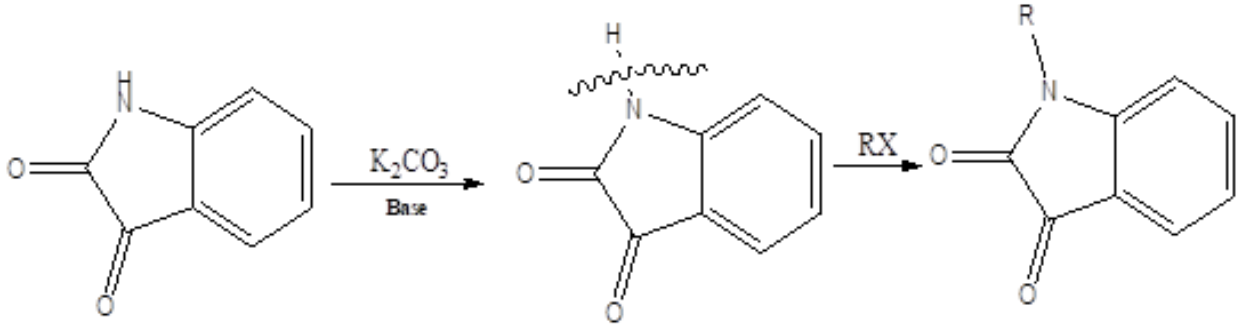
It is a crystalline solid that ranges in color from yellow to orange-brown and has a strong, musty smell. It has a density of 1.3 g/cm3 and boils at 300 °C (572 °F). It dissolves in water, acetone, and ethanol. It also dissolves a little in diethyl ether and benzene. Isatin melts between 165 and 168 °C (329 and 334 °F).[12]

2.1 Structure of Isatin:-



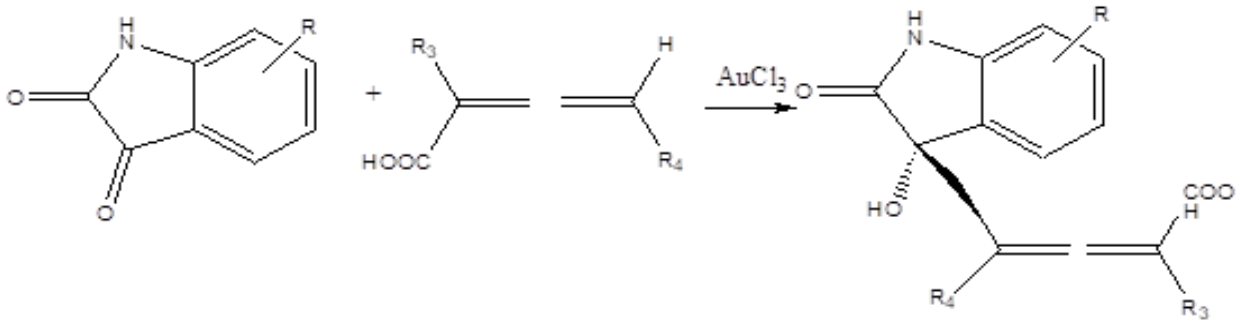
III. SOME REACTIONS OF ISATIN

3.1 N-Alkylation: It can be Synthesized by N-alkylated isatins with alkyl chlorides, bromides, and iodides, as well as allyl-, benzyl-, and propargyl halides that are reactive. Conventional heating is a standard approach to create N-alkylated isatins. It happens when the temperature is between 40 and 100°C and the mixture is constantly stirred.



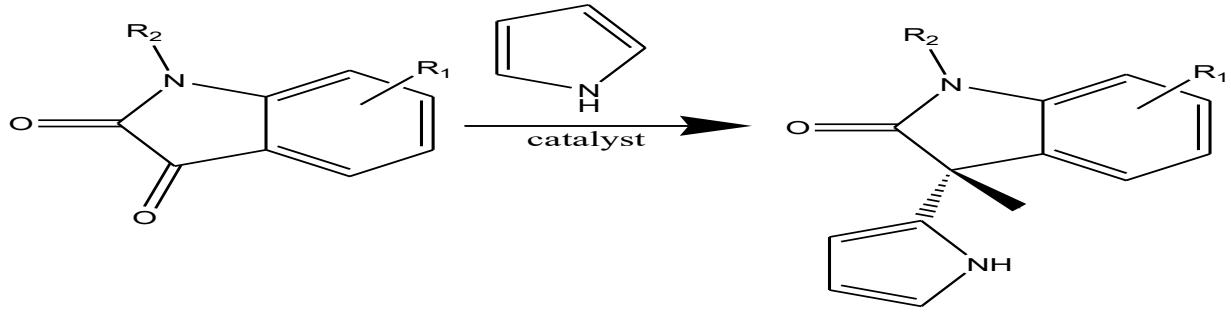
2 3 4

3.2 Aldol Reaction: Aldol reactions Synthesized -hydroxyl carbonyl molecules, which are very important for making derivatives that are biologically active. Isatin is a good substrate for condensation processes because it can easily accept H-bonds Isatin and the first distereospecific and enantioselective alleno-aldol process mix allenic esters to generate tri- and tetra-substituted carbinol-allenoates.



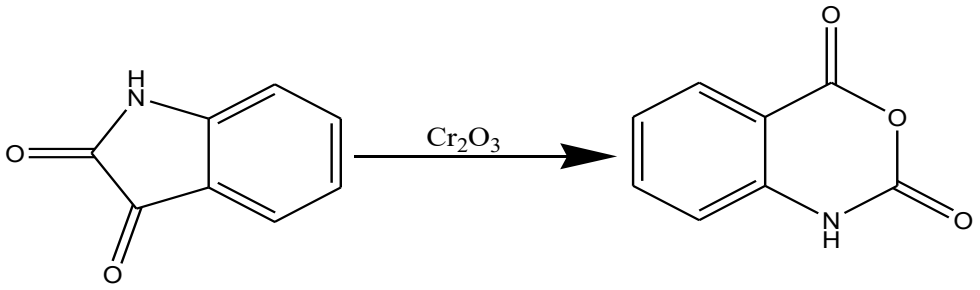
5 6 7

3.3 Friedel-Crafts Reaction: This is a type of organic synthesis process that is used to make aromatic compounds with a lot of functional groups. The asymmetric Friedel-Crafts alkylation of isatin with aromatic chemicals that have a lot of electrons gives 3-aryl 3-hydroxy-2-oxindoles.



8 9

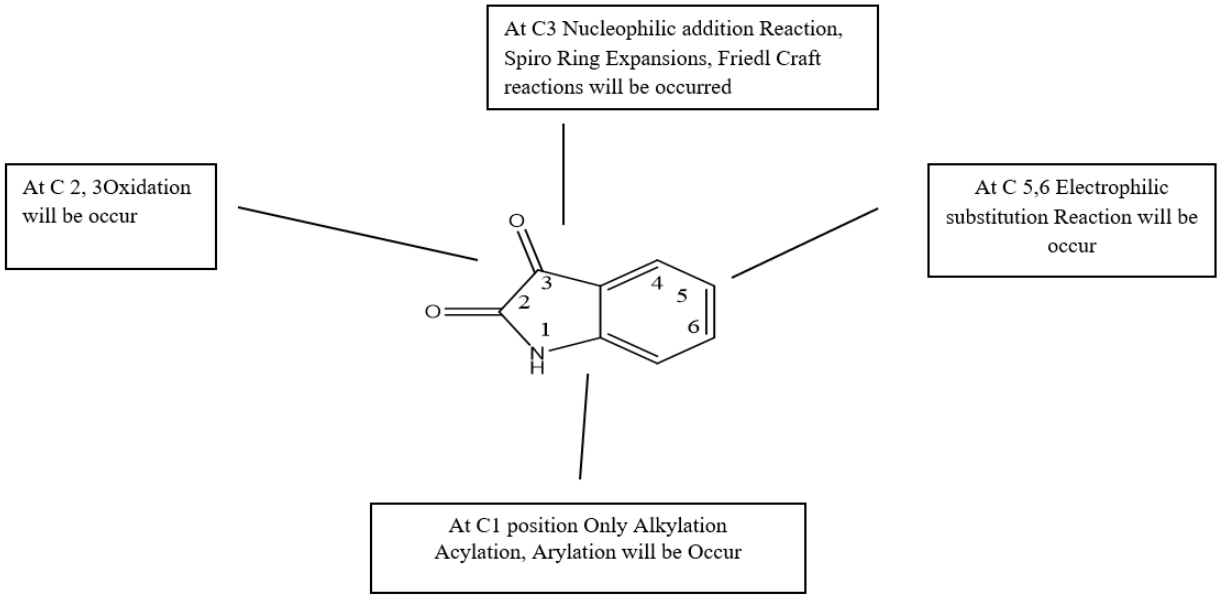
3.4 Oxidation: In Presence of chromium trioxide was present, isatin turned into its anhydride form, isatoic anhydride. The oxidizing agent adds the oxygen atom between the two carbonyl groups that are already there. The first and only active asymmetric Friedel-Crafts alkylation changes isatin into oxindoles.



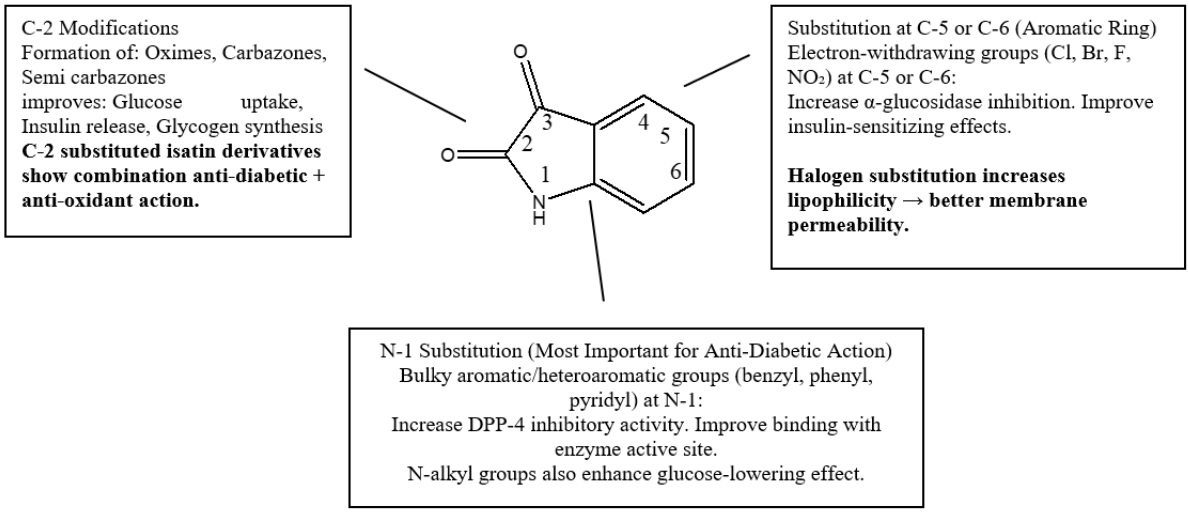
10 11

IV. SAR OF ISATIN

On the basis of reaction

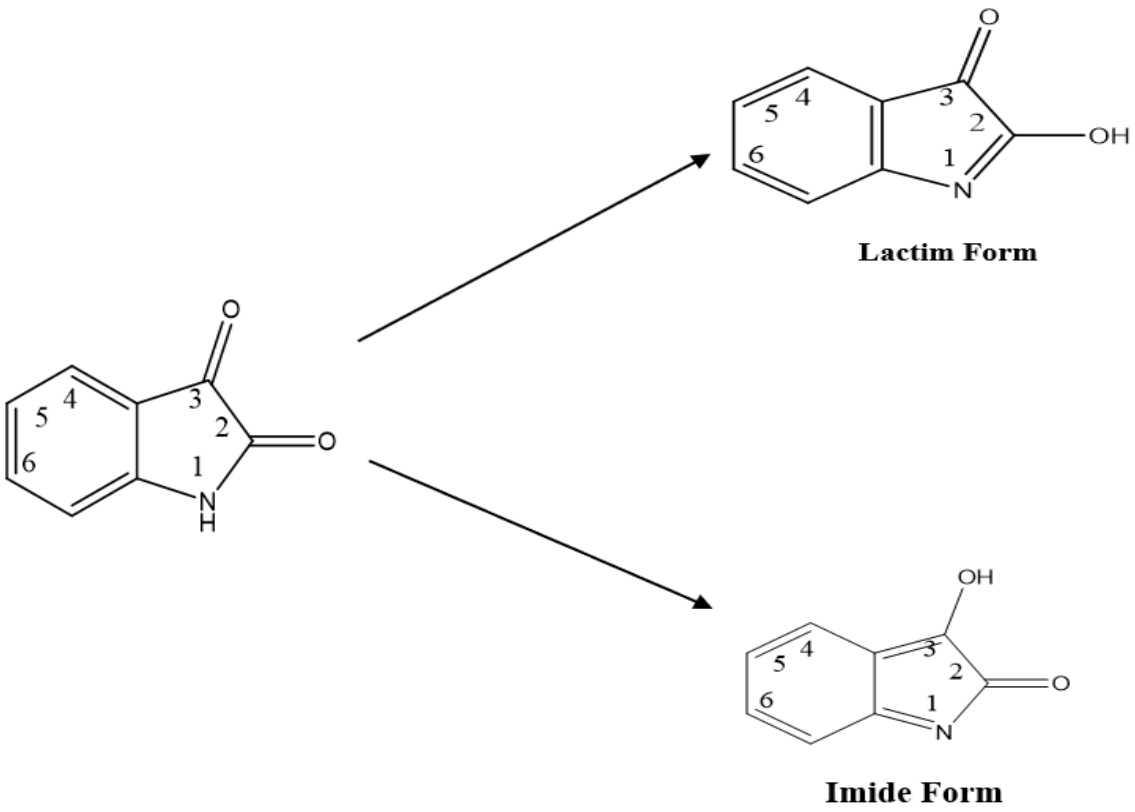


On the basis of position of substituent: -

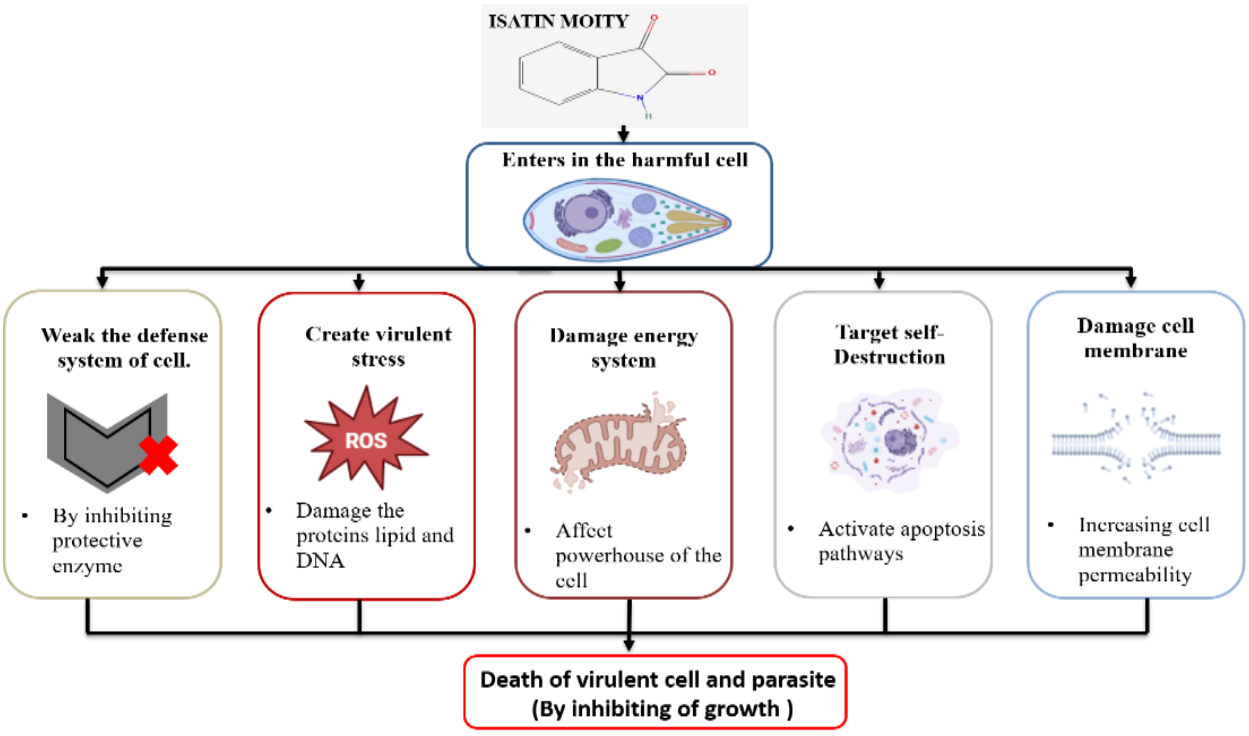


N-1 Substitution (Most Important for Anti-Diabetic Action)
Bulky aromatic/heteroaromatic groups (benzyl, phenyl, pyridyl) at N-1:
Increase DPP-4 inhibitory activity. Improve binding with enzyme active site.
N-alkyl groups also enhance glucose-lowering effect.

Tautomerism of Isatin:



5. Mechanism of Isatin Scaffold's: -



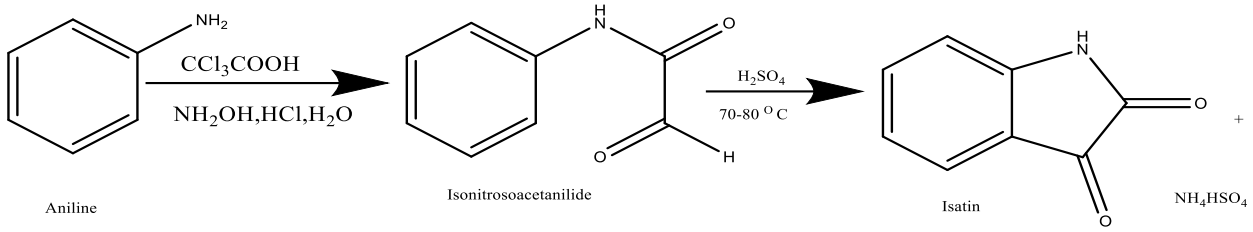
VI. GENERAL METHODS FOR SYNTHESIS OF ISATIN

6.1 Sandmeyer's Synthesis of Isatin:

Isatin is an organic molecule made from indole through a chemical process known as the Sandmeyer synthesis. Leon L. Sandmeyer, Which Introduce this synthesis apparoch After the experiment in laboratories.

To Synthesized iso nitroso acetanilide, from aniline, hydroxylamine hydrochloride, and chloral hydrate were mixed with sodium sulfate in water. This was split up and treated with concentrated sulfuric acid to make isatin, which makes up more than 75% of the final product.[13]

Reaction



Aniline — Isonitrosoacetanilide — Isatin

12 13 14

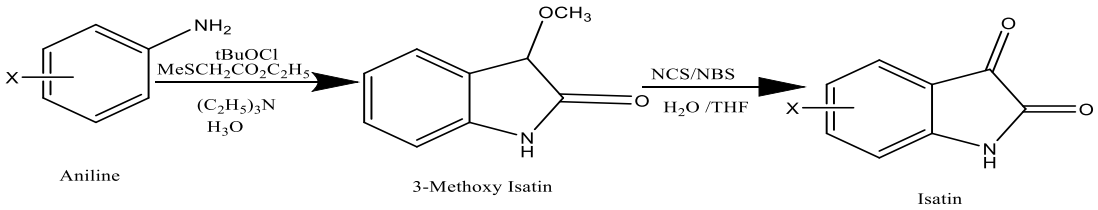
(Scheme – 1)

6.2 Gassman Synthesis of Isatin:

Oscar Gassman, a German organic chemist, came up with this reaction in 1872. It is called Gassman's Isatin Synthesis. It is a very useful Apparoach to make isatin, which is an important chemical that can be used to make many other things.

This process makes an intermediate 3-methylthio-2-oxindole, which is then oxidized to make the corresponding substituted isatin. To make the 3-methylthio-2-oxindoles, two different methods were used. An intermediate called N chloroaniline can be used to make the oxindole derivative when there are groups that pull electrons away from the molecule. After that, this intermediate reacts with a methyl thioacetate ester to make an azasulfonium salt. When the right amount of aniline and chlorosulfonium salt are mixed together, more 3-methylthio-2-oxindoles are obtained. when there are groups that give away electrons and make the N-chloro intermediate unstable. [12,13]

Reaction



Aniline — 3-Methoxy Isatin — Isatin

15 16 17

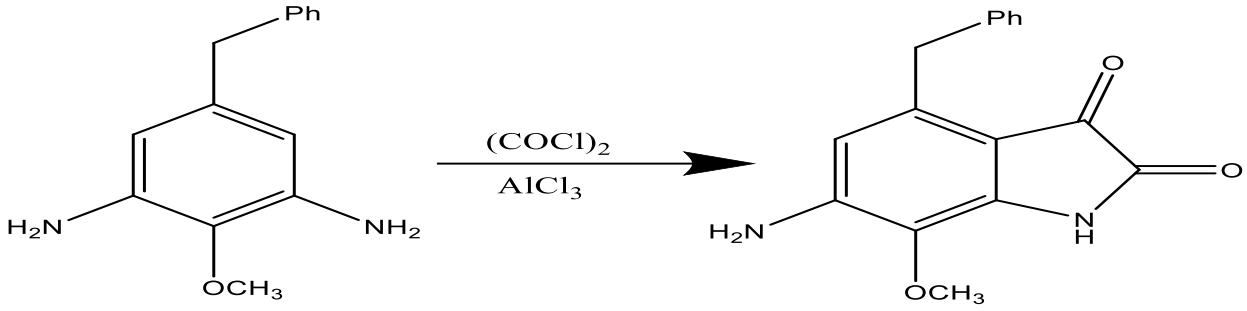
(Scheme – 2)

6.3 Stolle Synthesis of Isatin:

The Stolle technique is a chemical process that makes isatin, an important organic molecule used in dyes, agrochemicals, and medicines. The name of the method comes from Wilhelm Stolle, a German chemist who came up with it in 1896.

This method works especially well for making isatin and its derivatives. When oxalyl chloride is mixed with Lewis's acids like BF3 or AlCl3, substituted aniline changes into substituted isatin. This process is effective for transforming phenothiazine, phenoxazine, dibenzoazepine, and indole into 1-Maryland polycyclic isatin.[12, 13, 14]

Reaction



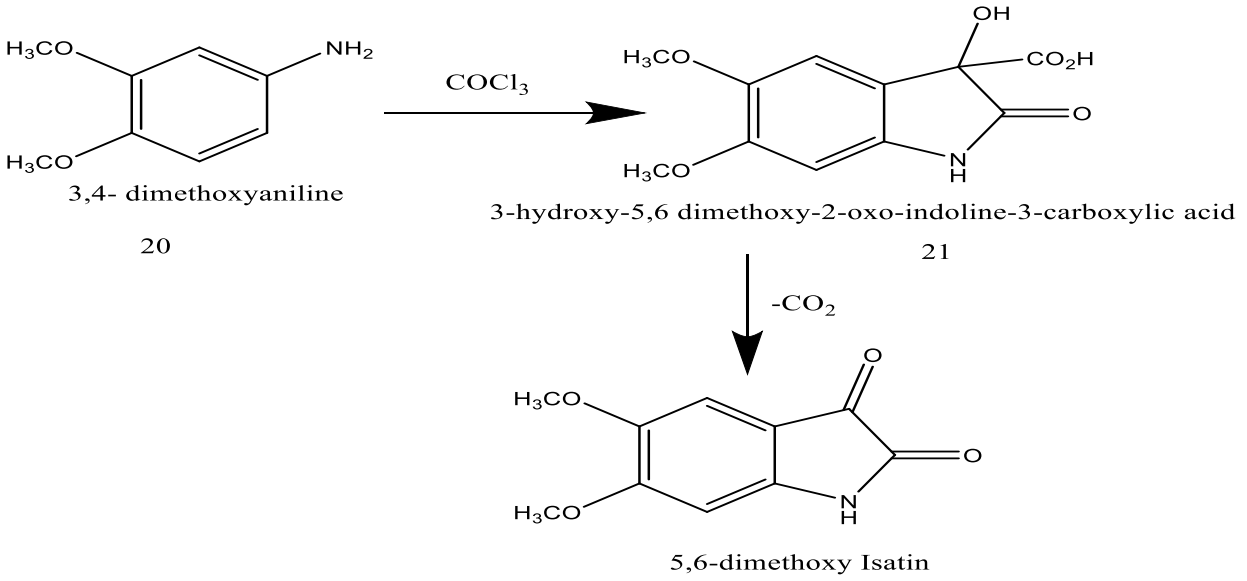
18 19

(Scheme – 3)

6.4 Martinet Synthesis of Isatin:

Henri Martinet, a French chemist, first talked about the reaction in 1891. According to the Martinet method for making indole-2,3-diones, an amino aromatic compound reacts with either an oxomalonate ester or its hydrate in the presence of an acid to make a 3-(3-hydroxy-2 oxindole) carboxylic acid derivative. This derivative then undergoes oxidative decarboxylation to make the right isatin. This method worked well to turn 4-aminoveratrole into 5, 6-dimethoxyisatin, but it didn't work as well with 2, 4-dimethoxyaniline. [15, 16]

Reaction: -



3,4- dimethoxyaniline

20

3-hydroxy-5,6 dimethoxy-2-oxo-indoline-3-carboxylic acid

21

5,6-dimethoxy Isatin

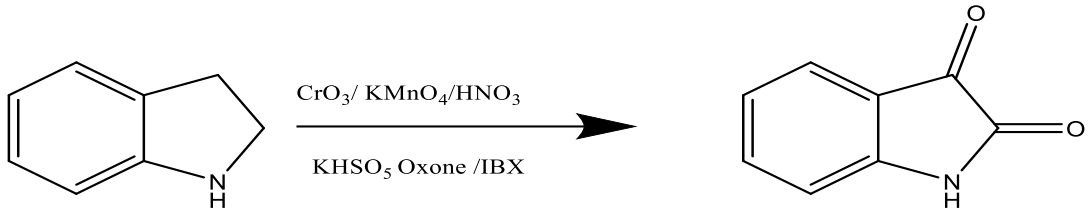
22

(Scheme – 4)

6.5 Oxidation of Indole:

The direct oxidation of indoles is another Apparoach for Synthesis of Isatin.It can be synthesized in the presence of chromium trioxide, potassium permanganate, nitric acid, or modern oxidants like Oxone, IBX, or hypervalent iodine reagents to oxidize the indole nucleus at the 2,3-positions. Indole is turned into isatin as a result. This method works well when there is already an indole framework in place and you only need to add the isatin functionality.

Reaction:



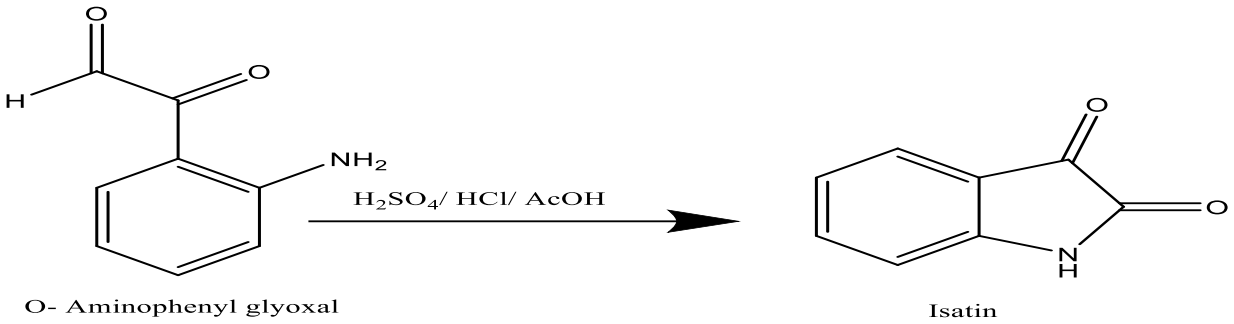
Indole 23 Isatin 24

(Scheme – 5)

6.6From o-Aminophenyl Glyoxals:

This method is effective to synthesized O-aminophenyl glyoxal derivatives.In acidic conditions, these substances undergo intramolecular cyclization, which leads to isatin. Note: This method is often used when functional group tolerance is important or when highly substituted isatins are needed.

Reaction:



O- Aminophenyl glyoxal 25 Isatin 26

(Scheme – 6)

VII. THE MEDICAL SIGNIFICANCE OF ISATIN DERIVATIVES

7.1 Isatin derivatives have anticonvulsant properties.

Numerous isatin derivatives have exhibited anticonvulsant characteristics [17]. The anticonvulsant characteristics of several hydrazines, hydrazides, and related compounds that were condensed with isatin and modified isatins have been documented [18]. By reacting 5-(un)-substituted isatin with particular heterocyclic compounds, a series of Schiff bases was produced, and their neurotoxic and anticonvulsant activities were assessed. 3-(3',4'-dihydro-2'-methylmercapto-4'-oxoquinazolin-3'-yl) iminoisatin was the most effective analog, outperforming valproic acid. All of the drugs were less harmful to the brain than phenytoin and carbamazepine [19]. The maximal electroshock technique (MES) and metrazol-induced convulsions (MET) were utilized to assess the anticonvulsant efficacy of hydrazones, Schiff bases, and Mannich bases generated from isatin. Eight of the chemicals in the series were very good at stopping seizures. The chemical 3-(4-chloro-phenylimino)-5-methyl-1,3-dihydro-indol-2-one was the most effective in the series. All drugs had superior protective effects relative to sodium valproate and decreased neurotoxicity compared to phenytoin [20]. The anticonvulsant efficacy of Schiff bases generated from N-methyl and N-acetyl isatin derivatives, in combination with different aryl amines, has been investigated against MES and Met. N-methyl-5-bromo-3-(p-chlorophenylimino)isatin [21] was more effective than phenytoin, carbamazepine, and valproic acid.

7.2 Isatin derivatives as anticancer agents

Isatin was cytotoxic to HL60 cells due to its induction of apoptosis and its antioxidant properties. Isatin can function as a chemotherapeutic drug to eradicate

cancer cells and as a preventative treatment to avert cancer generated by free radicals [22]. We produced and tested new isatin-based conjugates with pyrazoline and thiazolidine portions to determine if they operated against cancers.

We employed NCI60 cell lines to evaluate the efficacy of synthetic compounds against cancer [23]. Combining isatin Mannich bases with either 2-aminothiazoline or 2-aminobenzimidazole led to the creation of new isatin-thiazoline and isatin-benzimidazole derivatives. Scientists employed the MCF-7 human breast cancer cell line to see how well certain of the chemicals could combat breast cancer [24]. The anticancer activity of new 2,3,5-trisubstituted 4-thiazolidinones with an isatin moiety was assessed. One of the synthesized compounds is (5′Z)-5′- (benzylidene). The anticancer activity of -2,4′(1H)-dione was superior to that of -3′-(4-chlorophenyl) spiro [3H-indole-3,2′-thia-zolidine]-2,4′(1H)-dione and (5′Z)-3′-(4-chlorophenyl)-5′-[4-(1-methylethyl)-benzylidene] [3H-indole-3,2′-thiazolidine]. The recent FDA approval of oxindole sunitinib malate as a kinase inhibitor for the treatment of gastrointestinal stromal tumors and advanced renal carcinoma emphasizes the increasing interest in isatins as a novel class of antineoplastic medicines. In addition to their powerful kinase inhibition [26], other isatin derivatives function by inhibiting or altering proteases, beginning translation, generating new blood vessels, and polymerizing tubulin.

7.3 Derivatives of isatin as antitubercular agents

Isatin derivatives show anti-tubercular effects, which makes isatin a good starting point for creating new anti-tubercular drugs. Tryptanthrin, an alkaloid extracted from the Chinese plant Strobilanthes cusia, demonstrates considerable effectiveness against MTB H37Rv (1 mg/l) [27]. Some of these things are naturally occurring. A new non-nucleoside reverse transcriptase inhibitor with antimycobacterial characteristics was made from an isatinimino lead molecule. It is useful for treating AIDS and AIDS-related TB [28]. We made Schiff bases from isatin derivatives and nalidixic acid carbohydrazide. Four strains of Mycobacterium were used to test the synthetic derivatives' ability to fight TB: Mycobacterium intercellulari, Mycobacterium xenopi, Mycobacterium cheleneo, and Mycobacterium smegmatis. The compounds under investigation exhibited some efficacy against tuberculosis [29].

7.4 Isatin derivatives that work as painkillers and anti-inflammatories

A recent review of the literature indicates that isatin derivatives possess analgesic and anti-inflammatory properties [30].

We developed spiro isatin derivatives, isatin Schiff bases with aminothiazole, and N-mannich bases. We used carragenin to make rat paws swell to check if the compounds had anti-inflammatory effects, and we utilized the acetic acid-induced writhing method to assess how well they worked as pain relievers [31]. By combining imesatin with various aromatic aldehydes, several novel Schiff bases of isatin were produced. They were tested for their pain-relieving effects using the tail-immersion method. Compounds containing electron-donating groups exhibit a more potent analgesic action compared to those with electron-withdrawing groups [32]. We produced new schiff bases by mixing 5-substituted imesatin with different aromatic aldehydes that had been changed. The tail-immersion method, the carrageenan-induced paw edema method, and the paper disc diffusion technique were utilized to evaluate their analgesic, anti-inflammatory, and antibacterial activities [33]. Indomethacin was utilized as a standard to assess the anti-inflammatory, analgesic, and antipyretic effects of several isatin derivatives, including isatin-3-[N2-(2-benzalaminothiazol-4-yl)] hydrazones, in animal models [34].

7.5 Isatin derivatives as antifungal and antibacterial agents

By reacting isatin and substituted isatin with 4-aminoN-carbamimidoyl benzene sulfonamide, we generated a number of Schiff's bases. To make the Mannich bases for these compounds, they were combined with piperidine, which is a secondary amine, and formaldehyde. To see how successfully the synthesized chemicals killed bacteria, we employed the tube dilution approach. The synthesized compounds demonstrated superior antibacterial activity compared to the reference drugs [35]. New isatin-3-isonicotinylhydrazones, isatinazine and its Mannich bases, and spiro (indoline-3, 2'-thiadiazoline)-2-one have been produced. Scientists have examined these compounds on both Gram-positive and Gram-negative bacteria to assess how effectively they operate as antibiotics [36]. There are

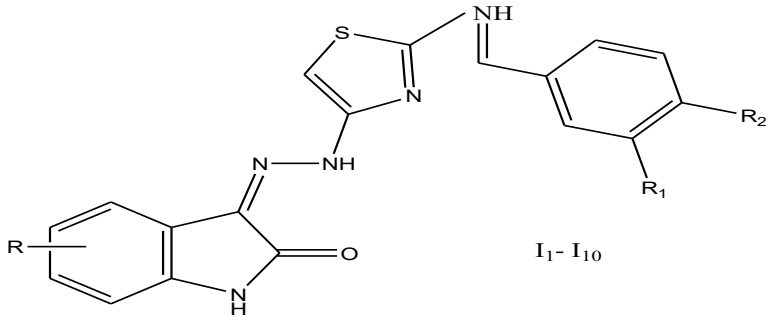
other reports of Schiff bases produced from isatinder showing antibacterial activity [37]. Pandeya and associates utilized twenty-eight clinically relevant microorganisms in their study. One compound was more than 1,000 times better than sulphamethoxazole. There are reports in the literature of other Schiff bases made from isatin, however these compounds don't seem to have any antibacterial properties [38].

7.6 Isatin's antioxidant-active compounds

It has been proven that isatin exhibits antioxidant properties [31]. A new set of 3,3-bis(4-amino-2,5-dimethoxyphenyl)-1,3-dihydroindol-3-one derivatives was created and tested for antioxidant activity based on the interaction between isatin and 2,5-dimethoxyaniline [39]. We looked at the antibacterial and antioxidant effects of certain βIsatin aldehyde-N, N'-thiocarbohydrazone derivatives in a lab setting. Four compounds [40] had the best potential to fight DPPH and get rid of H2O2. We looked at the antibacterial and antioxidant properties of a new type of bisisatin carbohydrazone derivative. We tested the antioxidant activity in vitro using hydrogen peroxide (H_2O_2) and 1,1-diphenyl-2-picryl-hydrazyl. A phosphomolybdenum assay was used to measure the overall antioxidant capacity and the ability to chelate ferrous iron. Researchers observed that most of the chemicals acted as antioxidants [41].

7.7 Antidiabetic and hypolipidemic effects of isatin derivatives

E.Venkateshwarlu et al. found that in a type-2 diabetes model caused by streptozotocin-nicotinamide, the antidiabetic and hypolipidemic effects of isatin derivatives are affected by the formation of isatin-3-[N-(2-benzalaminothiazol-4-yl)] hydrazones. I_4, I_6, I_8, and I_{10} at both doses are the only ones that exhibit a substantial ($P > 0.001$) decline in blood sugar levels compared to the control. This means that they lower blood sugar levels and make it easier for the body to consume glucose. After 14 days, the isatin derivatives Id, If, Ih, and Ij showed a big ($P > 0.001$) drop in blood glucose levels at doses of 10 mg/kg and 100 mg/kg. After 7 days, 100 mg/kg of these compounds generates a big ($P > 0.01$) decline in blood sugar levels. 10 mg/kg also causes a big ($P > 0.05$) drop in blood sugar levels compared to diabetes management. There is a lot of antidiabetic efficacy in glibenclamide between days 7 and 14 ($P > 0.001$) [42].



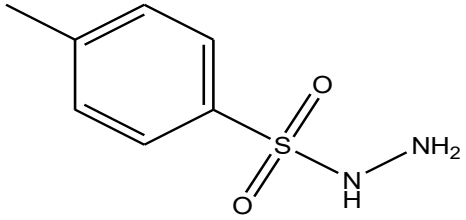
I_1- I_{10}

I_1 ; R=H ,R_1=H , R_2= H
I_2 ; R=H ,R_1=Cl , R_2= H
I_3 ; R=H ,R_1=N $(CH_3)_2$, R_2= H
I_4 ; R=H ,R_1=OH , R_2= OCH_3
I_5 ; R=5-CH_3 ,R_1=Cl , R_2= H
I_6 ; R=5-CH_3 ,R_1=OH , R_2= OCH_3
I_7 ; R=5-CH_3 ,R_1=H , R_2= H
I_8 ; R=5-Cl ,R_1=OH , R_2=OCH_3
I_9 ; R=5-Cl ,R_1=Cl , R_2= H
I_{10} ; R=5-NO_2 ,R_1=OH , R_2= OCH_3

7.8 Urease Inhibition:

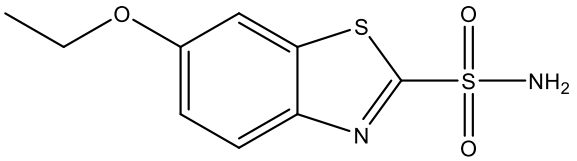
Urea is a well-known fertilizer that improves soil fertility. It is made up of 46% nitrogen. This urea releases nitrogen as ammonia gas, which also affects its ability to make things fertile [43]. Urease is a well-known enzyme that has nickel in its body structure. It changes urea into carbon dioxide and ammonia by hydrolytic catalysis [44]. This common enzyme is separated from a variety of plants, algae, fungus, and bacteria using the same catalytic procedure [45]. This enzyme has the same amino acid sequence and Ni+2 in its core structure. This is why it is very common [46]. It can cause many different diseases in animals and plants, especially stomach and gastrointestinal ulcers, hepatic coma, urolithiasis, and pyelonephritis [47]. Recently, two novel isatin derivatives were made with high yields: (1-allyl-2-oxoindolin-3-ylidene)-4-methylbenezenesulfono-hydrazide and (1-allyl-2-oxoindolin-3-ylidene)-4-chlorobenzenesulfono-hydrazide. This paper talks about the dynamic stability, reactivity, and affinity of these two derivatives. The enzyme inhibition potential test was conducted on the urea enzyme of Bacillus pasteurii urease, revealing that both substances inhibited

enzymatic activity, with IC50 values of 39.46 ± 0.12 mM and 148.35 ± 0.16 mM, respectively [48].



7.9 α-glucosidase Inhibition:

α-glucosidase is also known as an exoglycosidase enzyme. This enzyme is found in the intestines, where it breaks down carbohydrates and turns them into glucose. This glucose subsequently enters the bloodstream, and too much of it produces postprandial hypoglycemia [49]. The primary objective of α-glucosidase inhibitors is to impede the hydrolysis of carbohydrates to mitigate the dangers of diabetes [50]; hence, this enzyme is predominantly utilized in anti-diabetic medications [51]. α-Glucosidase inhibitors slow down the activity of α-glusidase, which is the enzyme that changes carbohydrates into glucose. In this approach, it lowers the amount of glucose in the blood and hemoglobin [52]. The primary disadvantage of this enzyme is its lack of specificity in targeting glycosidase, which leads to infections, particularly in the stomach and intestines, resulting in bowel looseness and excessive gas production in the alimentary canal [53]. We made derivatives of benzothiazole-triazole and used 1H-NMR and 13C-NMR to figure out what they were. Baker's yeast α-glucosidase enzyme was used to test the inhibitory activity of α-glucosidase in vitro. Compared to the conventional IC50 values of 817.38 µm, which range from 20.7 to 61.1 µm, most drugs show different levels of alpha-glucose blocking action.



7.10 Activities of an antioxidant

A free radical is an atom or molecule that has an unusual electron in its outer shell.They are highly unstable and perpetually in quest of stability in order to stabilize itself, to acquire an electron from any species and complete its exterior shell. During the oxygen metabolism process in the human body, mitochondria generate any free radicals.

It is imperative to eliminate these free radicals, as their presence will result in a variety of diseases, including malignant neoplastic disease, brain and blood vessel diseases, dotage, heart disease, ulceration, diabetes, heart disease, mucoviscidosis, aging, gastrointestinal ulcer, and acquired immune deficiency syndrome [54]. Therefore, antioxidants are employed to resolve this issue, as their primary function is to convert these highly unstable free radicals into stable substances. Antioxidants are employed in a multitude of medications with the purpose of treating illnesses that are caused by free radicals [55]. In addition, the experimental and theoretical results presented here are consistent with the concentration of free radical scavenging in DPPH of (H25MI3ClPT) and (H25MI3PT). In the antioxidant activity, the proportionality increased. Particularly, it has been theoretically verified that the antioxidant activity of DPPH products with a high energy volume (H25MI3ClPT) –IC50 is lower than that of (H25MI3PT)-DPPH products [56].

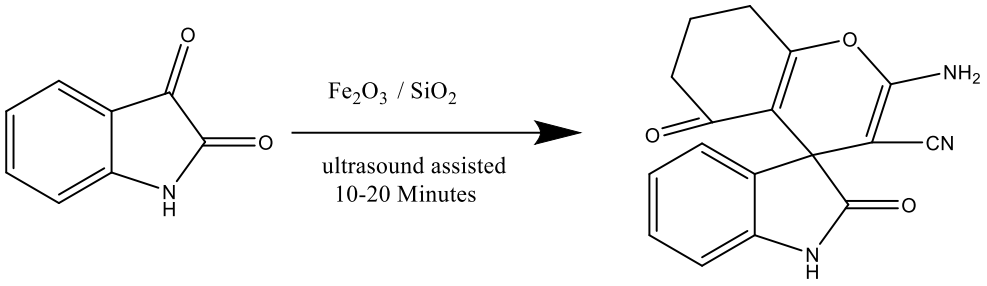
VIII. GREEN PROTOCOLS FOR THE SYNTHESIS OF ISATIN SPIRO COMPOUND

Atom affordable and eco-friendly approaches of performing organic synthesis are particularly significant in today's world [57]. Finding strategies to synthesize biologically significant targets is a big deal in chemical synthesis right now.2,3. Targets are a big aspect of organic synthesis these days [58]. 3,3'-spirooxindoles have gotten a lot of attention in the last two decades since they are biologically important [59]. A lot of natural items and medicines have 3,3'-spirooxindole cores in them [60]. For instance, spirotryptostatins A and B are Spiro oxindoles that are highly good in fighting cancer [61]. The size and placement of the spiro rings, the fact that the chiral spiro carbon is asymmetric, and the unique heterocyclic motifs that are attached to the oxindole scaffold are what mostly determine these compounds' bioactivity and pharmacological profile [62]. There has been a lot of interest in new ways to make Spiro oxindoles using non-covalent organ catalysis [63] and palladium-catalyzed dearomative processes [64].

8.1 Synthesis of Spiro oxindoles in an aqueous medium using heterogeneous catalyst-mediated methods

8.1.1 Nano catalysis of organic Substances

In synthesis, organo-Nano catalysts have become a new type of catalyst. One of these is a metal nanoparticle that is either fused with or covered with an organic molecule that can speed up a chemical reaction. The high turnover number, the ability to recover catalysts through magnetic separation, and the fact that increasing the surface area makes catalysts work better all contribute to better catalytic efficiency [65]. An organic nano catalyst made of Fe_2O_3, SiO_2, and thiamine hydrochloride (Vitamin B1) helped the ultrasound-assisted synthesis of Spiro oxindoles by making isatins, malononitrile/2-amino pyrazoles, and 1,3-dicarbonyl compounds react. The reactions happened in 10 to 20 minutes, and sonication helped the catalyst diffuse widely across the water-based reaction media.



27 28

8.1.2 Nanoparticles as Catalysts

Magnetic copper ferrite [66] and zinc ferrite, which are only a few nanometers wide, are now good catalysts for altering organic molecules. For instance, nanoparticles of $CuFe_2O_4$ and ZnFe2O4 might speed up the interaction between isatin, malononitriles, and 1,3-dicarbonyl compounds, which led to the formation of Spiro oxindoles [67]. Later, it was shown that CuO nanoparticles may be used as a magnetic catalyst to make Spiro oxindoles in an environmentally friendly way.

8.1.3 Immobilized Catalysts: -

It has also been proven that using catalysts that are adhered to the correct surfaces can help make Spiro oxindoles. We made Spiro oxindoles and 3,3'-disubstituted oxindoles in high yields from azaarenes, isatins, and malononitriles using heterogeneous, eco-friendly, and reusable silica-supported dodecatungsto phosphoric acid (DTP/SiO2). The catalyst could be recovered and reused many times without losing much of its activity [68].

8.1.4 Marketed Drug Containing Isatin Moiety:

a) Semaxanib

Type: Tyrosine kinase inhibitor (TKI)

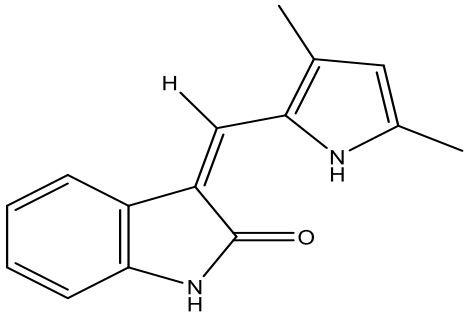
Target: VEGFR-2 (Vascular Endothelial Growth Factor Receptor)

Mechanism:

Stops VEGF signaling, which stops the creation of new blood vessels (angiogenesis).

Tumors need blood to grow; thus, they may be able to fight cancer.

Uses: cancer treatment



Structure of Semaxanib

b) Nintedanib

Type: inhibitor of multi-target tyrosine kinase

Target:

VEGFR FGFR (Fibroblast Growth Factor Receptor)

PDGFR stands for Platelet-Derived Growth Factor Receptor.

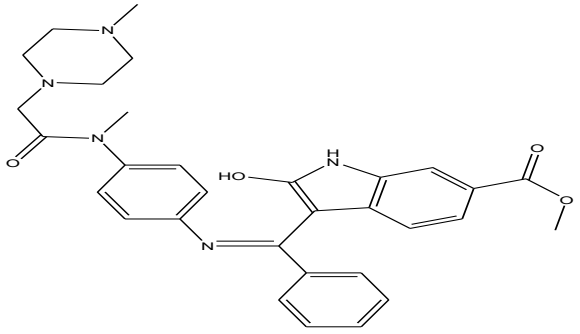
Mechanism:

Blocks many routes for growth factors, which lowers fibrosis and tumor angiogenesis.

Uses:

Idiopathic Pulmonary Fibrosis (IPF)

Lung cancer that isn't small cell (NSCLC)

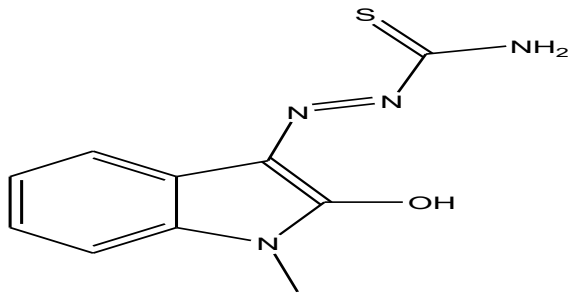


29 Structure of Nintedanib

c) Methisazone
Class: Antiviral (isatin derivative)
Target: VEGFR-2 (Vascular Endothelial Growth Factor Receptor)
Mechanism:

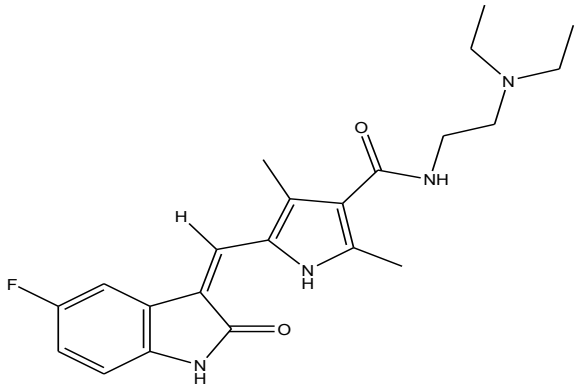
- Stops the production of viral proteins.
- Works especially well against poxviruses

Uses: smallpox



30 Structure of Methisazone

d) Sunitinib
Class: Multi-target TKI
Targets: VEGFR, PDGFR, KIT, and FLT3
Mechanism:
Stops both tumor growth and angiogenesis at the same time
Uses:
RCC, or renal cell carcinoma
Gastrointestinal stromal tumors (GIST)



Structure of Sunitinib

IX. CONCLUSION

Isatin is an important molecule with unique biological features that make it useful for a wide range of medical and pharmaceutical purposes, such as fighting cancer, diabetes, and germs. The review gives a lot of techniques to manufacture isatin derivatives that are important since they fight viruses, bacteria, inflammation, cancer, and other things. Scientists seek to find new, eco-friendly ways to create isatin and fix its issues, thus there has been a lot of research in this area.

Also, researchers have looked into isatin reactions in great detail since they can produce several derivatives with strong biological properties that can be used in a wide range of biological and medical settings.

Its one-of-a-kind indole-based structure makes it easier to change chemically, which leads to the creation of many other derivatives with better pharmacological effects. Isatin and its derivatives have been the subject of intense research over the years for their potential therapeutic uses, encompassing anticancer, antidiabetic, antibacterial, antiviral, and anti-inflammatory properties. These characteristics render isatin a significant framework for the design and development of innovative pharmaceutical candidates. The review stresses the several ways that isatin and its derivatives may be made. These approaches are very important for adding diverse functional groups to the isatin nucleus, which makes it more biologically active and selective. Researchers have looked into both old and new ways to make things, including green and sustainable ones that have less of an effect on the environment. The increased interest in eco-friendly synthesis shows that pharmaceutical research needs safer, cheaper, and

more effective ways to make things. In addition, several studies have looked at how isatin reacts with other chemicals since it may undergo several sorts of reactions, such as condensation, substitution, and cyclization. These interactions make it possible to make structurally different molecules that have a lot of biological promise. Isatin's capacity to make such a wide spectrum of derivatives has made it particularly important for finding and developing new drugs.

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