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Review Article

Review on Isatin and its Antibacterial Derivatives

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ABSTRACT

Isatin or 1H-indole-2,3-dione or 2,3-dioxindole is an indole derivative. Isatin and its analogs are synthetically useful substances where they may be utilized for the production of a broad range of heterocyclic molecules, which are depicting a wide reach of biological and pharmacological activities, as well as anticancer, anti-inflammatory, antiviral, anticonvulsant, antiTB, antidiabetic, anti-microbial, antitumor, antimalarial, anti-HIV, antibacterial, anti-analgesic, and antiplasmodial activities. Isatin is a precursor for many synthesized therapeutic molecules that are amenable to pharmacological action and have excellent biological potential. Isatin has a magnificent scaffold for both the natural and synthetic construction of molecules. These molecules are being used in drug therapy such as anticancer, antibiotic, and antidepressant drugs and have many more clinical applications. Due to its privileged scaffolding, the synthetic versatility of isatin has produced many structurally diverse derivatives, including the substitution of mono-, di- and trisubstitution of the aryl rings A and those derived by derivation of isatin nitrogen and C2 and C3 carbon moieties. As a result, improving and expediting access to isatin-related molecules is a challenging study in synthetic organic chemistry.

INTRODUCTION

Isatin

The isatin (1H-indole-2,3-dione) motif is present everywhere in nature, and its derivatives easily pass through the blood-brain barrier. Isatin derivatives have a wide range of pharmacological properties due to their potential to inhibit numerous enzymes and receptors, including acetylcholinesterase, butyrylcholinesterase, carbonic anhydrase, DNA gyrase, histone deacetylase reverse transcriptase, serine proteases, tyrosine kinase and tubulin. Isatin is one of the few compounds that was synthesized before its

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discovery in nature. Isatin and its derivatives have a wide range of biological properties, including anticancer, antibacterial, anti-inflammatory, analgesic, anticonvulsant, antiviral, antiHIV, antioxidant, and CNS depressive properties. Isatin was discovered in 1941 by Linne Erdman and Auguste Laurent from indigo dye. Indigo was oxidised in the presence of nitric acid and chromic acid, yielding bright orange-coloured monoclinic crystals of Isatin as a product.

Chemistry Of Isatin

Isatin, also known as indention and indole quinone, is one such physiologically active heterocyclic moiety. Isatin, an indole building block, has two carbonyl groups at positions C2 and C3, a nitrogen heteroatom at position 1, and a ketone and a-lactam moiety coupled with the benzene ring. Isatin, also known as oxindole, is a heterocyclic compound with a sixmembered ring containing two nitrogen atoms. It is a colorless solid that is soluble in alcohols, ethers, and benzene. Isatin is used as an intermediate in the synthesis of various organic compounds, such as pharmaceuticals, dyes, and fragrances. It is also used as an inhibitor of proteases and other enzymes. Isatin is formed by the condensation of formaldehyde and aniline in the presence of an acid catalyst. The resulting product is a substituted indole, which can be further reacted to form various derivatives. For example, isatin can be oxidized to form isatin sulfonic acid, a useful reagent in organic synthesis. Isatin also undergoes aromatic substitution reactions, where an aromatic group is substituted for a hydrogen atom in the ring. The resulting products are useful intermediates in the synthesis of a variety of organic compounds.

1. Physical Properties

a. 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 CH2 Cl2 , CHCl3 , slightly soluble in water, and insoluble in non-polar organic solvents like hexane, toluene, and benzene.

2. 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

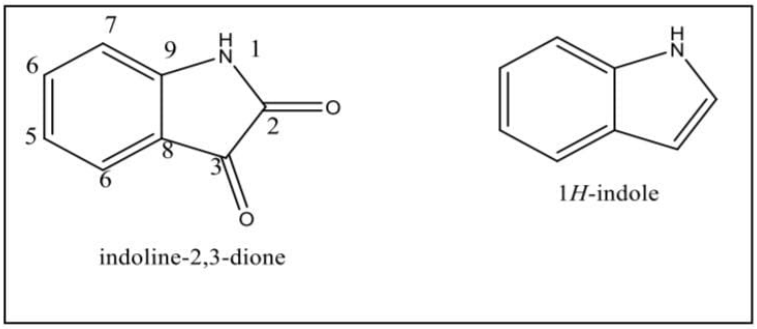
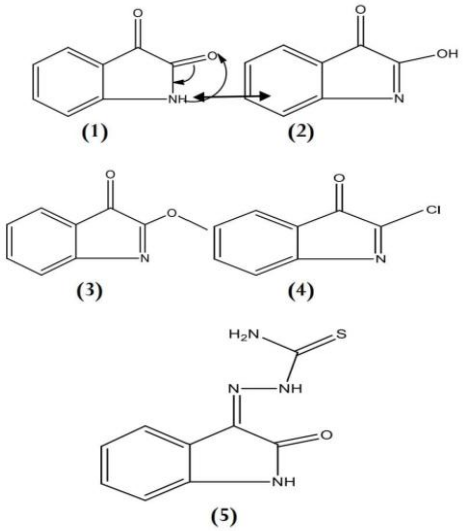


Figure No.1 Structure of Isatin

3. Structural Characteristics

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 CD3 OD shows signals for both lactam and lactim forms, while only the lactam type signal appears in DMSO-d6. 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 conformer's accountings for approximately 87 percent of the population in the gas phase.



Spectral Studies Isatin's.

UV-Visible spectrum displays an absorption maximum in the range of 260 nm to 350 nm, which corresponds to 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 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 . Isatin has a doublet at δ7.47 ppm and 6.86 ppm, which correspond to H2 and H5 respectively, in its 1H-NMR spectrum. At approximately δ11.03 ppm, the hydrogen atom (H1) bound to nitrogen appears as a singlet. At δ 7.05 ppm and 7.57 ppm, respectively, the protons H3 and H4 indicate triplets. In the 1H-NMR spectrum, deprotonation of NH in the isatin moiety causes a downfield shift for the azanion's protons (H2, H3, H4, and H5). 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.

Pharmacological Activities Of Isatin:

Antibacterial Activity of Isatin

Sarrah Sattar Jabbar; synthesized, a new Isatin derivatives (5a-b) hetero cyclization of 5-substituted ethyl-((2-oxo-1-piperedin-1-ylmethyl) indolin-3-ylidene) hydrazine acetohydrazide (4a-b) in the presence of CS2 in ethanolic KOH. These compounds were evaluated for antimicrobial and antifungal activity by the well diffusion method. For antibacterial activity, the zone of inhibition (mm) was measured in comparison to amoxicillin, and for antifungal activity, it was measured in comparison to fluconazole. These compounds were tested against Bacillus cereus, S. aureus and a fungus (C.albicans). The antimicrobial activity was tested in a nutrient agar medium at concentrations (of 250,500 g/well). 5b increases the antimicrobial activity as compared to 5a.

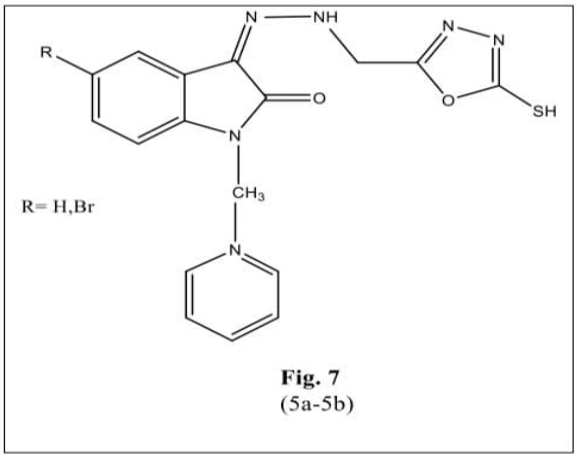


Fig. 7
(5a-5b)

Ankur Patel et al; synthesized some new compounds 3-[(5-benzylidene-2-phenyl)-3, 5-dihydro-4-H-imidazole-4-one-3-(4 bezoylhydrazono)]-indole-2-ones (VIII) from different isatin-hydrazones (II) by condensing with 2-phenyl-5-benzylidene- 3-N (4-acetyl phenyl)-1, 5-dihydro-imidazol-4-on (VII). The disc diffusion method was used to test these compounds for antimicrobial and antifungal activity. The compounds VIIIb, VIIIc, VIIId, and VIIIg demonstrated the highest activity against S. aureus. The results are compared to the standard gentamicin. Compounds VIIIa, VIIId, and VIIIn showed good antifungal activity against A.niger, whereas VIIIb, VIIIc, and VIIId had the best activity against C. albicans. For its inhibitory efficacy against fungus, amphotericin B was used as a reference.

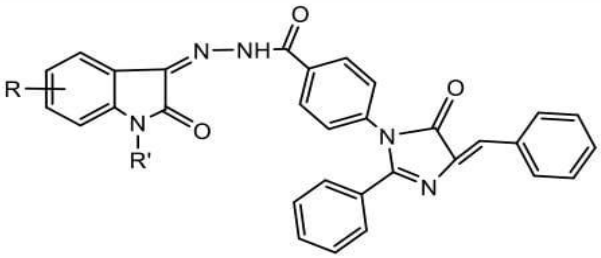
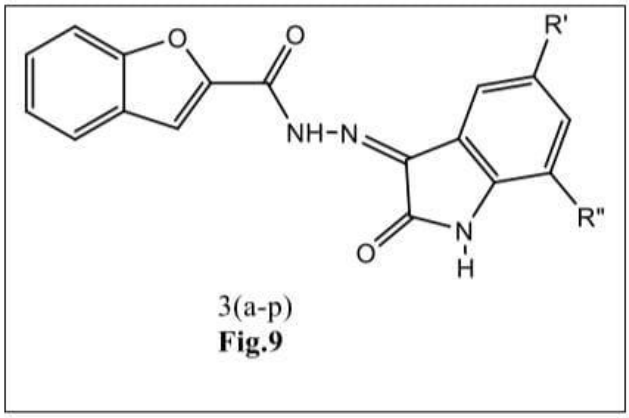


Fig.8 (VIII)

VIIIa; R=H ; R'=H
VIIIb; R= 5-Cl; R'=H
VIIIc; R= 5-F, R'= H
VIIId; R= 5-Br ; R'= H
VIIIe; R= 4-Cl,5-F;R'= H
VIIIf; R= 5-CH_3 ;R' =H
VIIIg; R= 5-NO_2; R'= H
VIIIh; R= 5-COOH; R'= H
VIIIi; R=$_7$-COOH; R'=H
VIIIj; R=$_7$-$COOCH_3$;R'=H
VIIIk;R=H; R'= Acetyl
VIIIl; R= H; R'= Methyl
VIIIm; R=$_5$-Br ; R'= Acetyl
VIIIn; R= 5-Br ; R'=Methyl

Comp	R'	R''	Comp	R'	R''
a	H	H	i	H	Br
b	Br	H	j	H	Cl
c	Cl	H	k	H	OH
d	F	H	l	H	CH_3
e	CH_3	H	m	H	OCH_3
f	OCH_2	H	n	H	OC_2H_5
g	NO_2	H	o	H	NO_2
h	OH	H	p	H	F

Vinod Ugale et al; synthesized a novel series of N-(5 or7 substituted-2-oxoindolin-3-ylidene) benzofuran-2-carbohydrazides by reacting benzofuran-2-carbohydrazide 1 with 5 and 7 substituted-isatin. Compounds 3o and 3p show good antimicrobial activity against E. coli, P. vulgaris, and B. subtilis with MIC values of 31.25 lg/mL. Compounds 3c, 3d, 3i, 3j, 3k, 3m, and 3n show moderate antimicrobial activity against Gram-positive bacteria as well as Gramnegative bacteria with MIC values of 62.50–125 lg/mL. The activity of compounds 3o and 3p against A. niger was good (31.25 lg/mL). When compared to fluconazole, the compounds 3c, 3d, 3g, 3i, 3j, 3m, and 3n displayed moderate antifungal activity (62.50–125 lg/mL). Except for 3o and 3p, none of the investigated compounds 3(a-p) showed strong anti-fungal activity against C. albicans (fluconazole).



3(a-p)
Fig.9

Meryem Chemchem et al; gives a series of twelve isatin Schiff bases (1a-7a, 1b-5b) that were synthesised using green chemistry (microwave (MW) and ultrasound (US) assisted synthesis) by reacting isatin and 5-bromoisatin with different anilines. The antibacterial activity of each compound was evaluated by using the Agar-well diffusion method against E. Coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Staphylococcus aureus. The compound's antibacterial activity was mild to moderate. The compounds 1a and 1b, which have an acid group attached to the aniline moiety, were found to be more effective against Pseudomonas aeruginosa and to have the lowest MIC values (78 mg/mL). Vijai Kumar Reddy Tangadanchu et al; synthesized Isatin-derived azoles as new potential antimicrobial agents. Isatin hybridized 1,2,4-triazole 7a shows excellent inhibitory activity against E. coli with a MIC value of 1 µg/mL, which was 8-fold more potent than the reference drug norfloxacin.

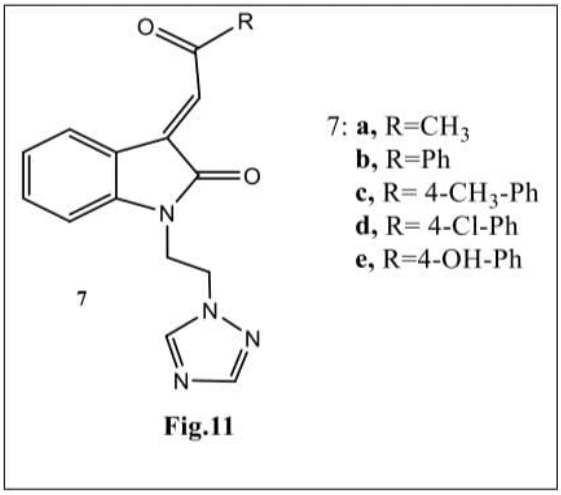


Fig.11

Shobhit Shrivastava et al; synthesized 2,6-aminopyridine Schiff bases of isatin derivatives and evaluate antimicrobial activity by using the broth dilution technique. Compound MS2 and MS4 show good antimicrobial activity against gram-positive and negative bacteria as compared to the standard drug ciprofloxacin (MIC 6.2 µg/ml). Compound MS3 and MS5 have potent antifungal activity against A. niger as compared to standard fluconazole.

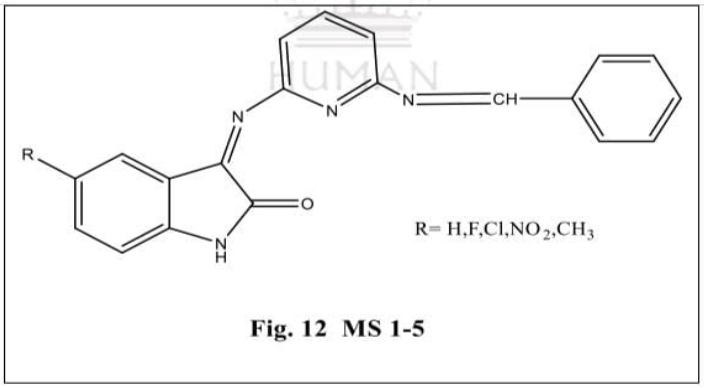


Fig. 12 MS 1-5

Refaie M Kassab et al; synthesized the Isatin-decorated thiazole derivatives for antimicrobial activity. Two bacterial strains, Gram-negative Escherichia coli and Gram-positive MRSA, were used to test the antibacterial properties of isatin derivatives by using the agar well diffusion and cup plate method. Candida albicans was used to measure the anti-fungal activity. Compounds 7b and 7d showed MICs eight times better than chloramphenicol when Citation: Yamini et al. Ijppr.Human, 2023; Vol. 26 (4): 455-477. 466 tested against E. coli. It was discovered that compound 7h had antifungal properties against Candida albicans comparable to that of the standard Nystatin.

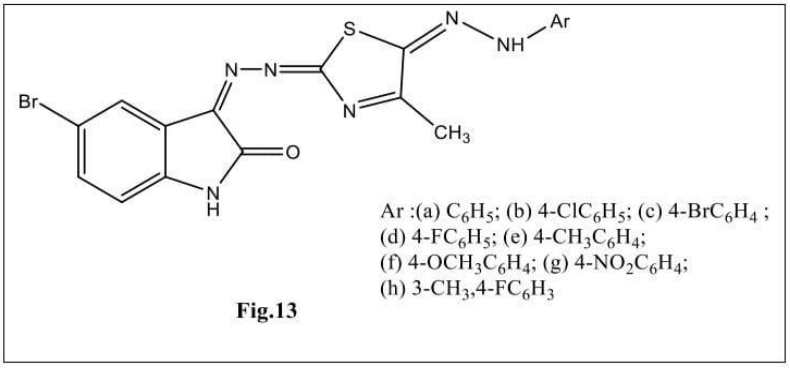


Fig.13

General Methods Of Synthesis Of Isatin:

Sandmeyer's isatin synthesis: The Sandmeyer synthesis is a chemical reaction used to synthesize isatin, which are organic compounds that are derived from indole. It is named after the Swiss chemist Leon L. Sandmeyer, who first reported it in 1883. Aniline, chloral hydrate, and hydroxylamine hydrochloride were combined in aqueous sodium sulphate to produce an isonitroso acetanilide, which was separated and then treated with concentrated sulfuric acid to produce isatin, which accounts for >75 percent of the final product.

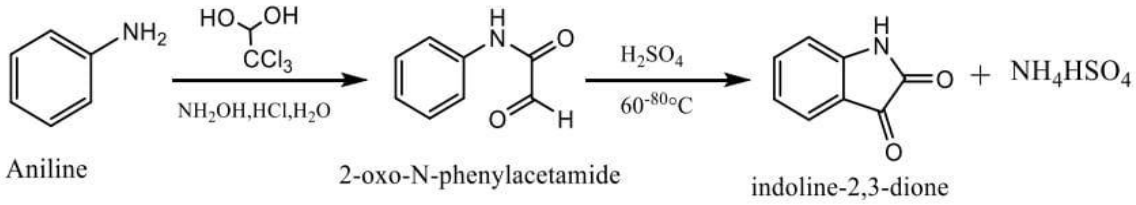


Fig. 2 Sandmeyer's Isatin Synthesis

Stolle's Isatin Synthesis: The Stolle method is a chemical process used to synthesize isatin, an important organic compound used in pharmaceuticals, agrochemicals, and dyes. The method is named after the German chemist Wilhelm Stolle, who developed it in 1896. This process is particularly efficient for preparing isatin and its derivatives. Substituted aniline is converted in the presence of oxalyl chloride and Lewis's acids such as BF3 or AlCl3 to form substituted isatin. This approach is also effective for producing 1-Maryland polycyclic isatin from phenothiazine, phenoxazine, dibenzoazepine, and indole.

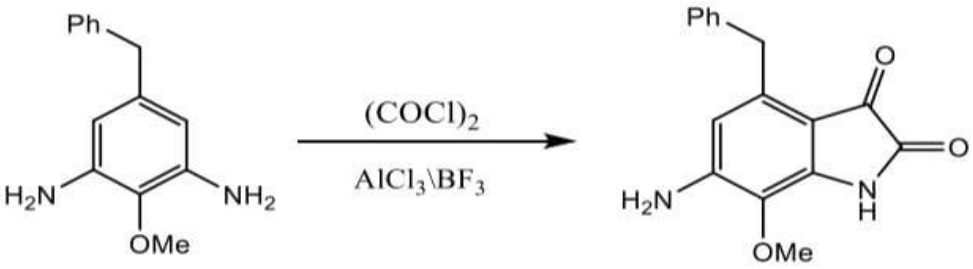


Fig.3 Stolle's Isatin Synthesis

Gassman's Isatin Synthesis: Gassman's Isatin Synthesis is a reaction developed in 1872 by German organic chemist, Oscar Gassman. It is a highly efficient synthetic route for the production of isatin, an important compound that can be used in the synthesis of a variety of organic compounds. In this reaction, an intermediate 3-methylthio-2-oxindole is formed, and it is subsequently oxidized to produce the matching substituted isatin. The 3-methylthio-2-oxindoles were synthesized using two complimentary techniques. The oxindole derivative may be made when electron-withdrawing groups are present by using an intermediate called Nchloroaniline, which then combines with a methyl thioacetate ester to produce an azasulfonium salt. Better yields of the 3-methylthio-2-oxindoles are obtained when the chlorosulfonium salt is reacted with the suitable aniline in the presence of electron-donating groups that destabilize the N-chloro intermediate.

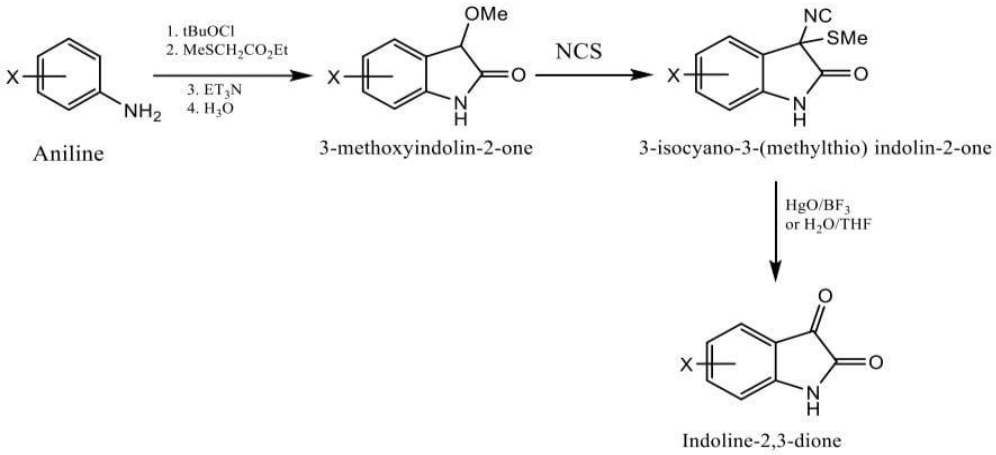


Fig.4 Gassman's Isatin Synthesis

Martinet Isatin Synthesis: The reaction was first reported by French chemist Henri Martinet in 1891. The Martinet method for the synthesis of indole-2,3-diones involves the reaction of 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 upon oxidative decarboxylation results in the appropriate isatin. In contrast to the less successful usage of 2, 4-dimethoxyaniline, this approach was successfully used to synthesize 5, 6- dimethoxyisatin from 4-aminoveratrole

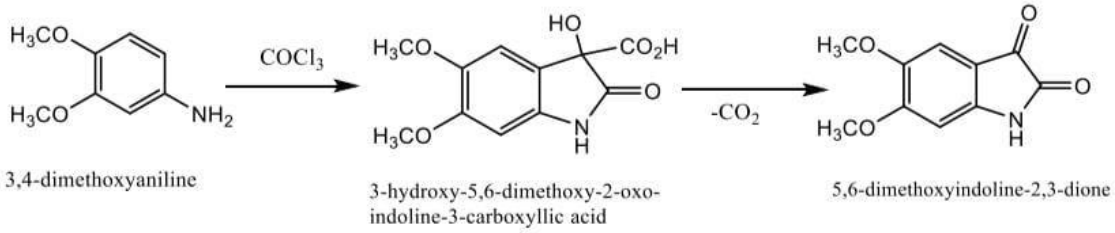


Fig.5 Martinet isatin synthesis

REACTIONS OF ISATIN:

1. N-Alkylation: Alkyl chlorides, bromides, and iodides, as well as reactive allyl-, benzyl-, and propargyl halides, may be used to successfully prepare N-alkylated isatins under simple procedures. At temperatures between 40 and 100°C under reflux, conventional heating is widely used to create N-alkylated isatins.

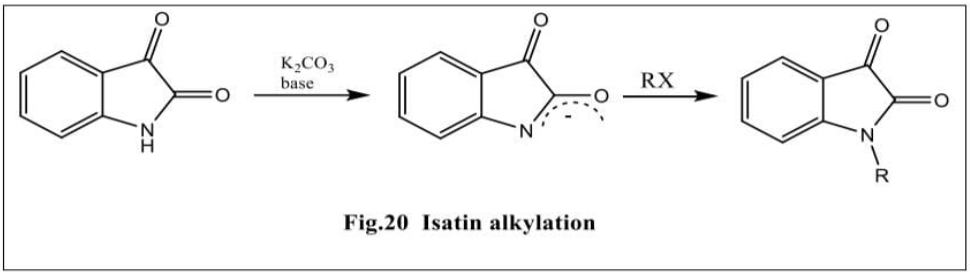


Fig.20 Isatin alkylation

2. Oxidation: In the presence of chromium trioxide, isatin changed into its anhydride form, isatoic anhydride. The oxygen atom that is introduced between two existing carbonyl groups is introduced by the oxidising agent.

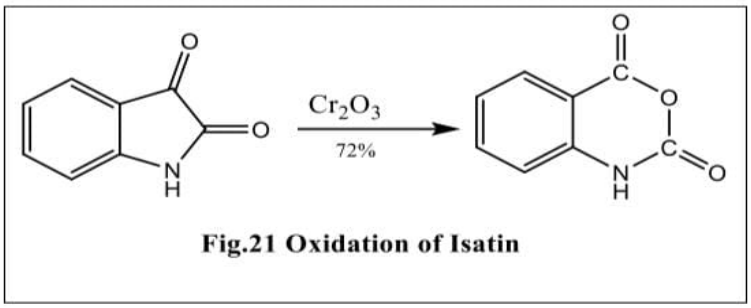


Fig.21 Oxidation of Isatin

3. Friedel-Crafts Reaction: When utilised to create highly functionalized aromatic compounds, Friedel-Crafts reactions are a type of organic synthesis process. These molecules can subsequently be used to create compounds with significant therapeutic value. Via the asymmetric Friedel-Crafts alkylation of isatin with electron-rich aromatic chemicals, 3-aryl3-hydroxy-2-oxindoles—which are visually and physiologically interesting—are produced. Isatin is converted into oxindoles using the first and only active asymmetric Friedel-Crafts alkylation.

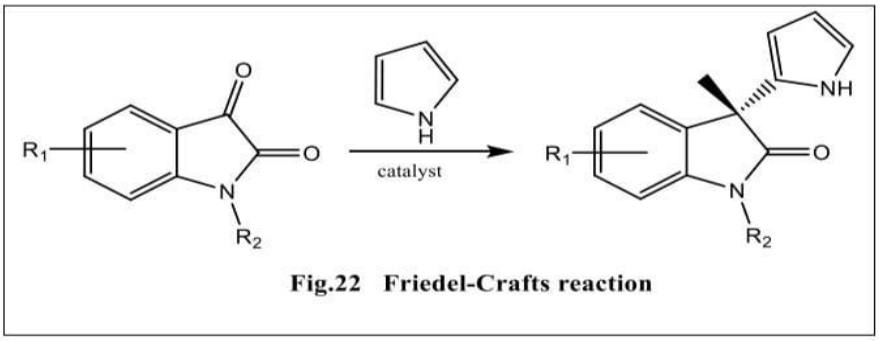


Fig.22 Friedel-Crafts reaction

4. Pfitzinger Reaction, often referred to as the Pfitzinger-Borsche reaction, is a chemical reaction that results in substituted quinoline-4-carboxylic acids when isatin reacts with a base and a carbonyl molecule. Isatin hydrolyzes the amide bond when it reacts with a basic, like potassium hydroxide, to produce keto-acid 2. While it isn't usually done, this intermediate can be separated. An enamine and an imine are produced when an aldehyde or ketone reacts with aniline. The required quinoline is produced via the cyclization and dehydration of the enamine.

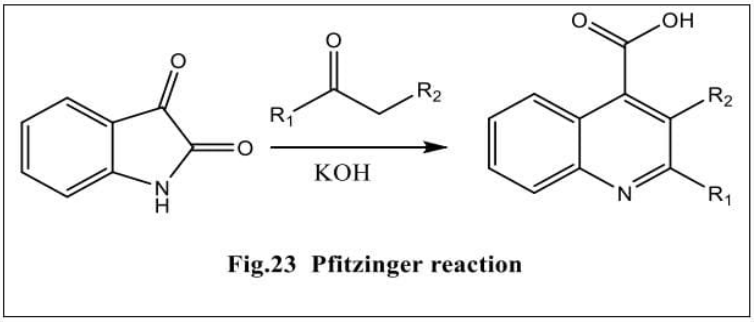


Fig.23 Pfitzinger reaction

5. Aldol Reaction: Aldol reactions result in -hydroxyl carbonyl molecules, which are crucial building blocks in the creation of physiologically active derivatives. Isatin is a useful substrate for condensation processes due to its high H-bond acceptor activity. Isatin and allenic esters are combined in the first distereospecific and enantioselective alleno-aldol reaction to provide carbinol-allenoates that are tri- and tetra-substituted.

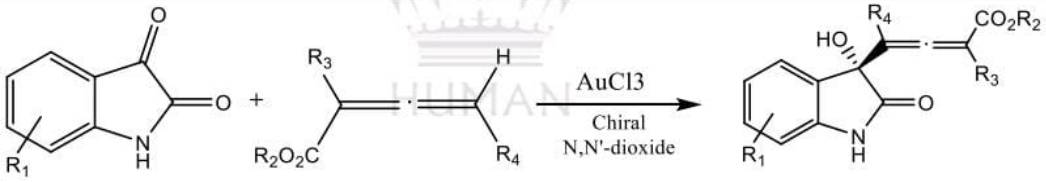
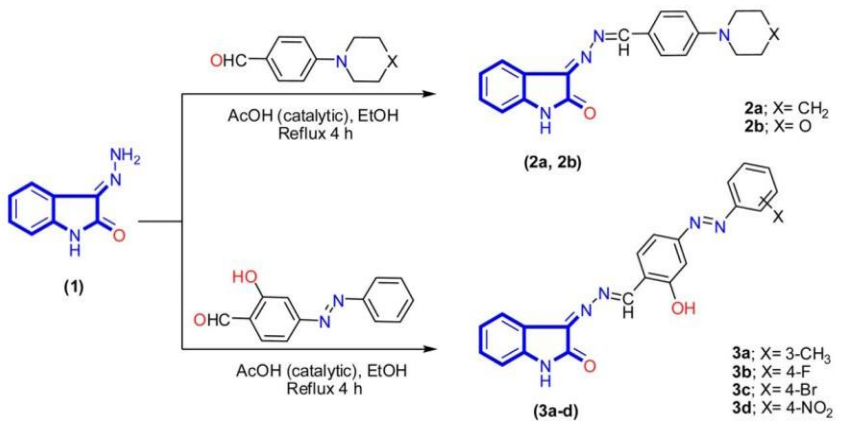


Fig.24 Aldol Reaction

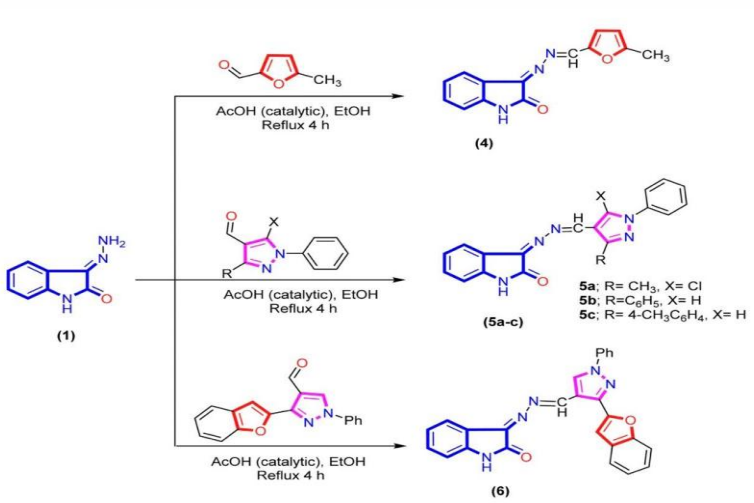
Derivatives Of Isatin:

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

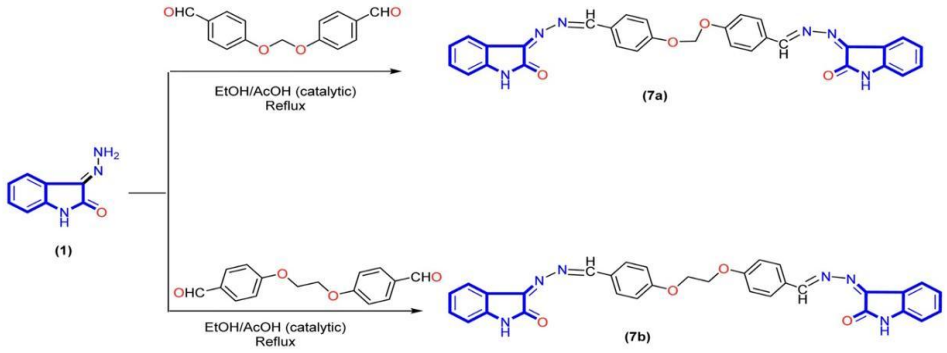
A new series of isatin-based Schiff bases 2a, 2b, 3a–d, 4, 5a–c, 6, 7a, and 7b were synthesized based on a reaction of 3-hydrazonoindolin-2-one (1) that was previously prepared43 with different formyl derivatives, and the structures of the newly designed compounds are outlined in Schemes 6-8. Our research was designed by reaction of 3-hydrazonoindolin-2-one (1) with different formyl cores as series 1 containing aromatic formyl containing aliphatic or azo (NN) group (Scheme 6), series 2 involved heterocyclic formyl based on pyrazole or furane core (Scheme 7), and series 3 including bis-formyl derivatives (Scheme 8).(6) Anti-diabetic activity (α-amylase enzyme inhibition).The α-amylase enzyme is responsible for the breakdown of starch and oligosaccharides. As a result, α-amylase enzyme inhibition is one of the important techniques for diabetes mellitus therapy.50 Accordingly, the anti-diabetic activity of isatin-based Schiff bases 2a, 2b, 3a–d, 4, 5a–c, 6, 7a, and 7b was estimated by determining the ability of these derivatives to inhibit an α-amylase enzyme.51 Acarbose was used as a standard reference (α-amylase inhibition = 69.11 ± 0.15%).(6) As all compounds exhibited moderate to good α-amylase inhibition (%), ranging from 26.97 ± 0.06 to 57.64 ± 0.13%. Among the tested compounds, the Schiff base with pyrazole motif 5a–c and salicylamide containing azo-aryl with para-fluoro atom 3b are relatively more potent than other derivatives. The result of the anti-diabetic activity raveled that the four isatin-based Schiff bases 3b (α-amylase inhibition = 54.76 ± 0.12%), 5a (α-amylase inhibition = 57.64 ± 0.13%), 5b (α-amylase inhibition = 55.96 ± 0.12%), and 5c (α-amylase inhibition = 56.52 ± 0.12%) had anti-diabetic activities nearly close to the acarbose (standard reference), and the order of activity can be represented as 5a > 5c > 5b > 3b.(6)



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

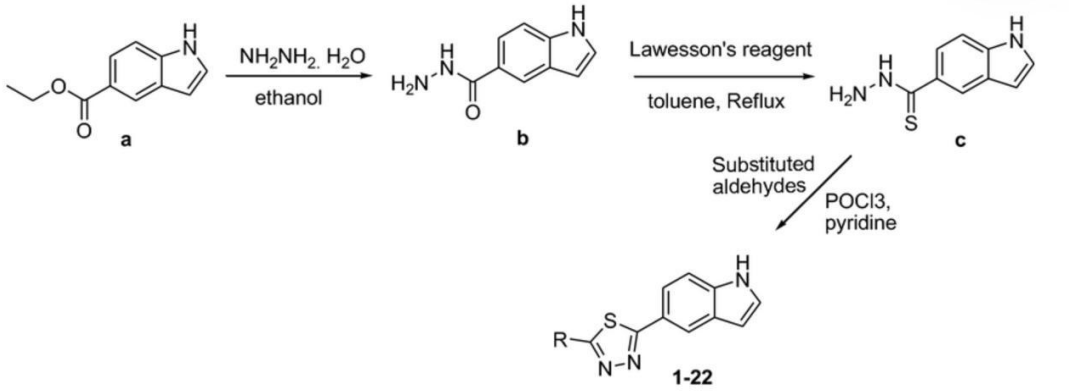


Scheme 7. Synthesis of isatin-azomethine-heterocyclic 4, 5a–c, and 6.



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

2. IsatinThiadiazole derivative:



Scheme.9. Synthesis of indole based thiadiazole derivatives (1–22): Indole-based-thiadiazole derivatives (1–22) were synthesized by refluxing ethyl 5-cyano-1H-indole-2-carboxylate (I) (2 mmol) with hydrazine hydrate (4 mmol, 2 equivalent) in ethanol for 4 hrs to afford 5- cyano-1H-indole-2-carbohydrazide (II). The intermediate product (II) (1 mmol) was then heated under reflux with various isothiocyanate (1 mmol, 1 equivalent) in ethanol with triethylamine (1 mmol, 1 equivalent) yielded corresponding cyclized thiadiazole analogs (1–19) (Scheme9). (7)

3. coumarin isatin derivative:

A general synthesis of coumarin-isatin derivatives 5a-5t is exhibited in Scheme10. Treatment of 7-hydroxycoumarin 1 with ethyl bromoacetate in the presence of anhydrous K2CO3 in dry acetone to afforded ethyl 2-((2-oxo-2H-chromen-7-yl) oxy) acetate 2 in good yield, which reacted with hydrazine hydrate to provide the key intermediate 3. Finally, the new desired compounds 5a-5t were obtained, in good yields (67.5%-89.1%), by condensing hydrazide 3 with the corresponding appropriate isatins 4a-4t in the presence of glacial acetic acid. The structures of newly synthesized compounds were confirmed by their spectral analysis. (8) Scheme10. Reagents and conditions: (a) K2CO3, acetone, reflux, 6h; (b) NH2NH2·H2O, EtOH, reflux, 4h; (c) CH3COOH, EtOH, reflux, 2h. (8)

4. IsatinSchiff base derivative:

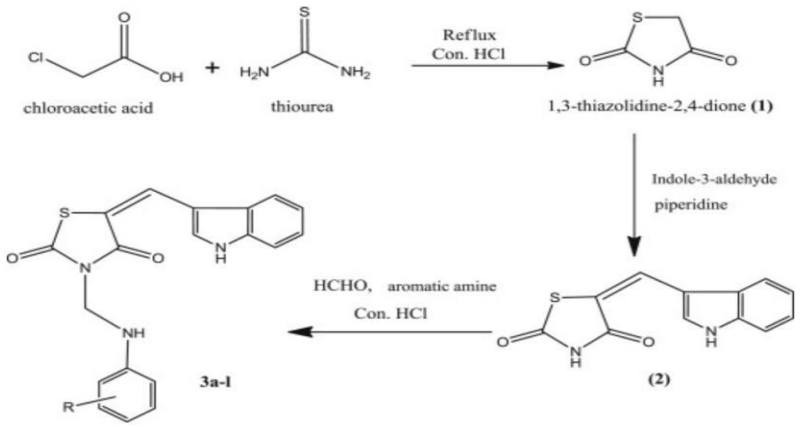
General Procedure for the synthesis of isatin based Schiff bases derivatives Isatin based Schiff bases were synthesized in three steps, first an esterification carried out by reacting different carboxylic acid with methanol in sulphuric acid (2-3ml) under reflux 7 condition for 12-16 hrs. The completion of reaction was monitored by TLC. After completion of reaction, reaction mixture was extracted with hexane to obtained pure esters. (9) Then esters were refluxed with hydrazine hydrate in methanol with few drops of glacial acetic acid for 3 h. After completion of reaction, reaction mixture was washed with chloroform to obtained different hydrazides. These hydrazides (1mmole) each were than treated with different isatin (1mmole) in methanol having catalytic amount of glacial acetic acid for 2-4h. Reaction completion was monitored through periodic TLC. After completion of reaction, reaction mixture was washed with n-hexane to obtain our desired products. The structure of all compounds was established through EI-MS and 1HNMR. (9)

5. Thiazolidinedione deivatives:

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

Conventional heating method:

A solution of chloroacetic acid (1.89 g, 20 mmol) in water (5 mL) was added into a stirring solution of thiourea (1.52 g, 20 mmol) in a three-necked round bottom flask. The reaction mixture was stirred until white precipitate was formed. Concentrated solution of HCl (6 mL) was added dropwise slowly into the reaction mixture by a fitted dropping funnel. A reflux condenser is connected in the middle of the flask. The reaction mixture was heated at 100–110 °C for 10–12 hrs and then cooled down to room temperature. The resulting suspension was filtered off and the precipitate was well washed with water to remove the traces of HCl. The product was further purified by recrystallization from ethanol. (11)



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

CONCLUSION:

Isatin is a significant molecule that possesses special biological characteristics that make it appropriate for a variety of medical and pharmaceutical uses, such as an antibiotic, anticancer, and anti-diabetic drug. The review describes many methods for producing isatin derivatives that have anti-cancer, anti-inflammatory, antiviral, antibacterial, and many other useful properties. As a result, research in this area has significantly increased to identify novel, ecologically friendly approaches to isatin synthesis and solve its problems. Additionally, isatin reactions have been well studied because they open the door to a wide range of novel derivatives with potent biological characteristics that may be used in a wide range of biological and medicinal applications. Isatin is a crucial nucleus and opens up new possibilities for further study for all of the reasons described.

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