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A Review on Pharmacological Attributes of Isatin

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ABSTRACT

Isatin (1H-indole-2,3-dione) and its derivatives have presented a variety of heterocyclic compounds that may be used as building blocks for the production of pharmaceuticals. Many studies have been done on the synthesis, chemical composition, biological uses, and industrial uses of isatin since its discovery. These isatin-containing heterocycles are functional and have exhibited anticancer, anti-inflammatory, antiviral, anticonvulsant, antitubercular, antidiabetic, antibacterial, and many other activities. Different isatin compounds have been evaluated in recent years for their anti-microbial properties, and some of them showed potential in vitro and in vivo effectiveness. In this study, we described several newly reported biological actions of isatin derivatives, such as anti-proliferative, anti-bacterial, anti-diabetic, and others. Their antimicrobial activity has received special attention.

INTRODUCTION

Following the discoveries of synthetic compounds (sulphonamides) by Domagk in 1935 and the potent bactericidal agent penicillin by Fleming in 1929, the modern era of antimicrobial chemotherapy was born.[1] The first synthetic antibacterial chemical, "prontosil," was discovered by German bacteriologist and pathologist Gerhard Domagk, who won the Nobel Prize in 1939.[2] Antimicrobial substances can either be bacteriostatic, which prevents the target bacterium or fungus from growing, or they can be bactericidal, which destroys the target bacterium or fungus. Bactericidal agents are more effective, but bacteriostatic agents can be extremely beneficial because they allow the host's natural defence to destroy microorganisms.[3] Antimicrobial agents are classified based on the type of organism they are active against, such as antibacterial, antiviral, antifungal, antiprotozoal, and anthelmintic drugs. Combining different antimicrobial medicines can also be beneficial for extending the range of their activities and reducing the risk of bacterial resistance development.[4] Some antibiotic combinations work better as a whole than they do as a single drug. This is known as synergism. The most recent treatment for antimicrobials, combination therapy, has demonstrated its efficacy. Both Sulphathiazole and Trimethoprim are bacteriostatic, however, their combination is now frequently used as a bactericidal combination. In combination therapy, two of these bactericidal medications are also employed. All of these antimicrobial medications, which are produced by living creatures and used to cure disease, are collectively referred to as antibiotics in the medical and pharmaceutical fields. Even in minute quantities, these antibiotics can stop the growth of or kill an organism.[5-7]

Aspects of Antimicrobial Agents

- It should be capable of destroying or inhibiting a large range of pathogenic organism species. It should also have a broad spectrum of activity**.**
- It should not cause any allergic reactions, be nontoxic to the host, or have any negative side effects.
- It should be able to reach the site of infection in the human body.
- The cost and ease of production should be low.
- It should be chemically stable.

- It must be soluble in bodily fluids to be active and capable of quickly penetrating body tissues.

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.[8-9] Isatin is one of the few compounds that was synthesized before its discovery in nature.[10] Isatin and its derivatives have a wide range of biological properties, including anticancer,[11] antibacterial,[12] anti-inflammatory,[13] analgesic,[14] anticonvulsant,[15] antiviral,[16] anti-HIV,[17] antioxidant,[18] and CNS depressive[19] properties. Isatin was discovered in 1941 by Linne Erdman and Auguste Laurent from indigo dye.[20] Indigo was oxidised in the presence of nitric acid and chromic acid, yielding bright orange-coloured monoclinic crystals of Isatin as a product.[21]

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.[22-23] Isatin, also known as oxindole, is a heterocyclic compound with a six-membered ring containing two nitrogen atoms. It is a colorless solid that is soluble in alcohols, ethers, and benzene.[24] 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.[25,26]

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.[27-29]

Physical Properties of Isatin

It is a yellow to orange-brown crystalline solid with a pungent, musty odour. It has a density of 1.3 g/cm3 and a boiling point of 300 °C (572 °F). It is soluble in water, ethanol, and acetone. It is also slightly soluble in diethyl ether and benzene. The melting point of isatin is 165–168 °C (329–334 °F).[29]

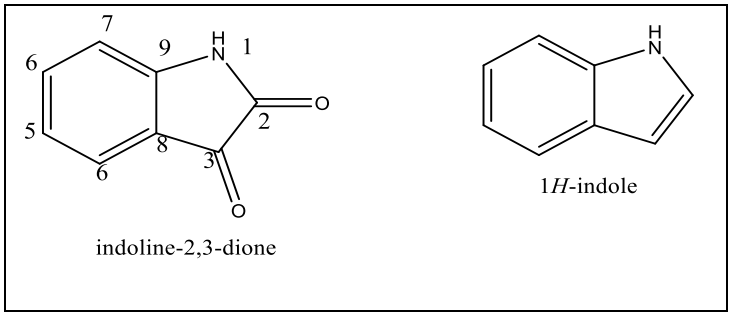


Figure No.1 Structure of Isatin

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.[20,30]

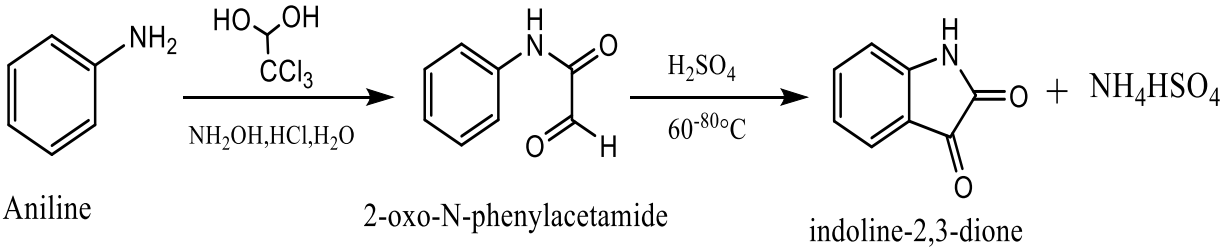


Fig. 2 Sandmeyer's Isatin Synthesis

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.[29,31,32]

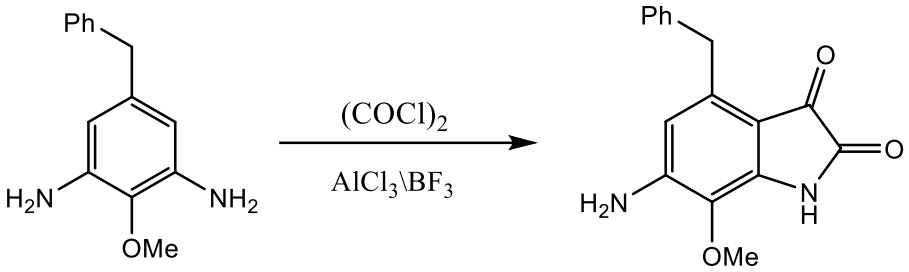


Fig.3 Stolle's Isatin Synthesis

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 N-chloroaniline, 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.[20,29,32]

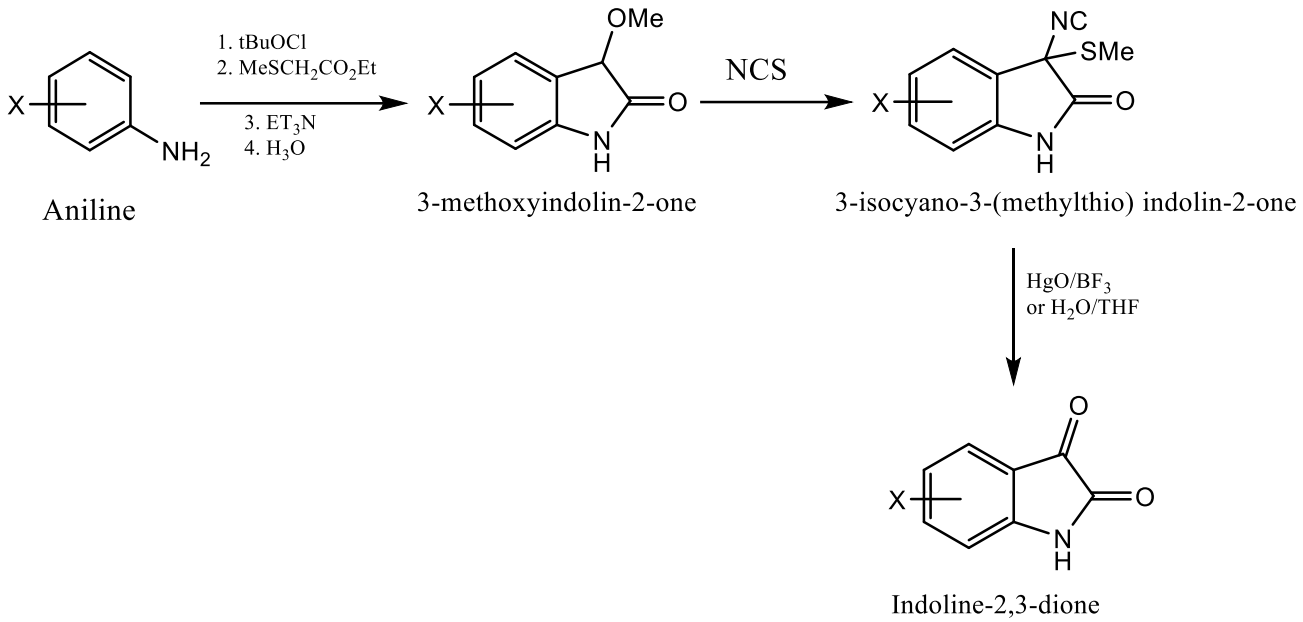


Fig.4 Gassman's Isatin Synthesis

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.[33,34]

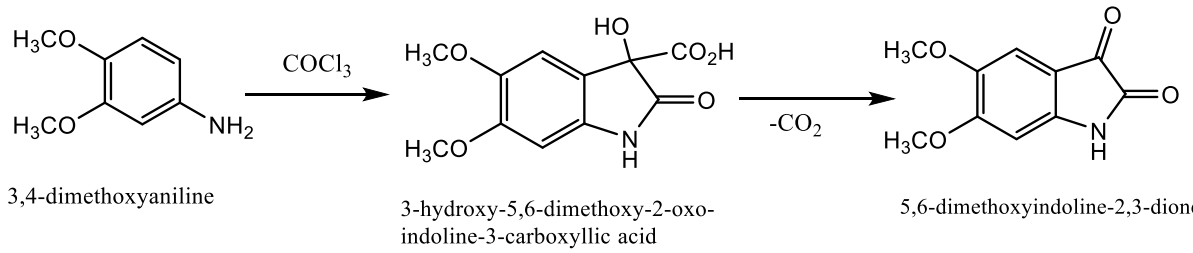
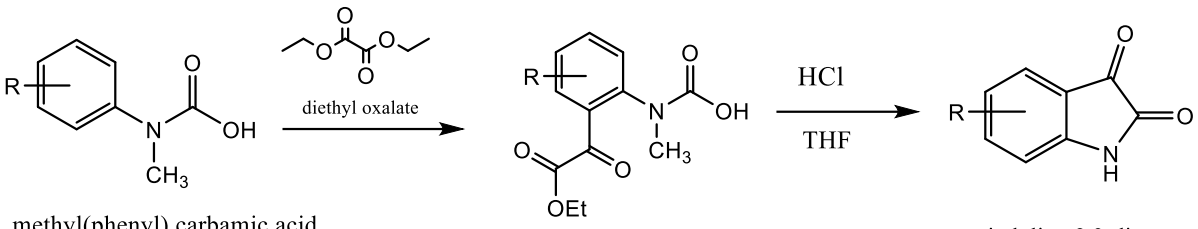


Fig.5 Martinet isatin synthesis

Metalation of Anilide Isatin Synthesis: The most recent method for synthesizing isatin depends on the ortho-metalation (DoM) of N-pivaloyl- and N-(t-butoxycarbonyl)-anilines. Diethyl oxalate is used to treat the dianions, and when the intermediate a-ketoesters are deprotected and cycled, isatins are produced. This method has the benefit of being

regioselective for the synthesis of 4-substituted isatins from meta-substituted anilines(33)(27).



methyl(phenyl) carbamic acid

(2-(2-ethoxy-2-oxoacetyl) phenyl)(methyl)carbamic acid

indoline-2,3-dione

Fig.6 Metalation of anilide isatin synthesis

VARIOUS 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(35).

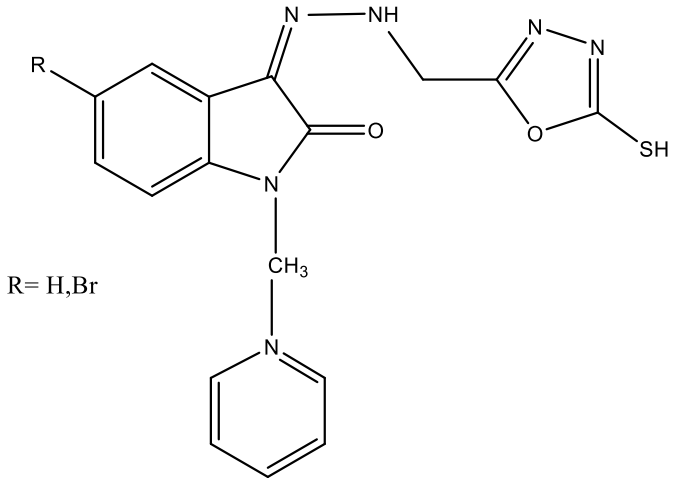


Fig. 7
(5a-5b)

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.[36]

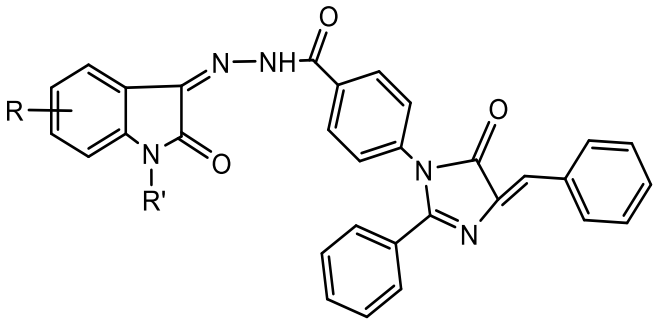


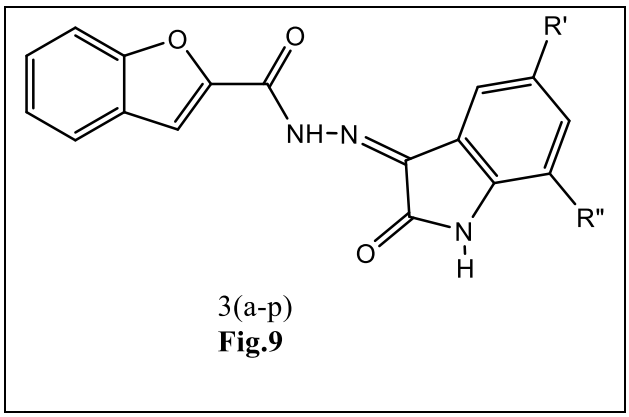
Fig.8 (VIII)

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 Gram-negative 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).[37]



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).[38]

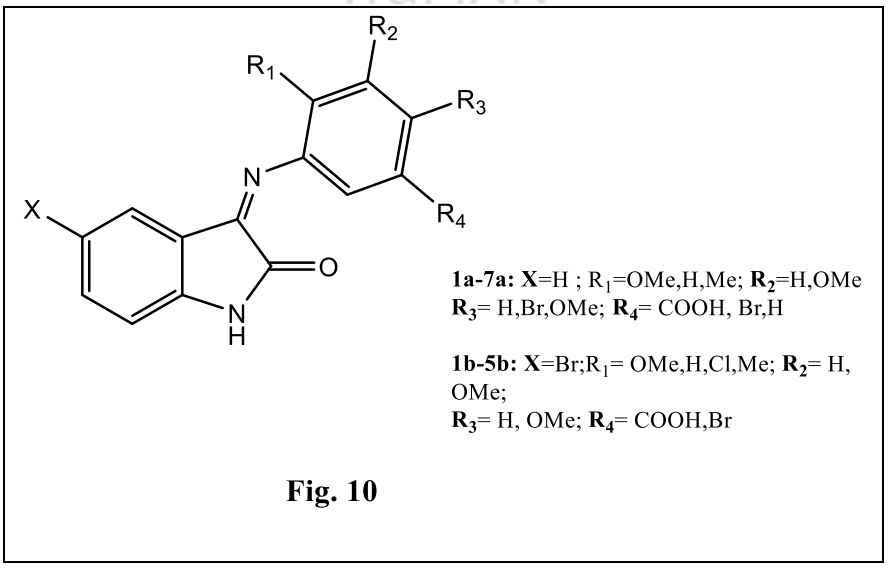


Fig. 10

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.[28]

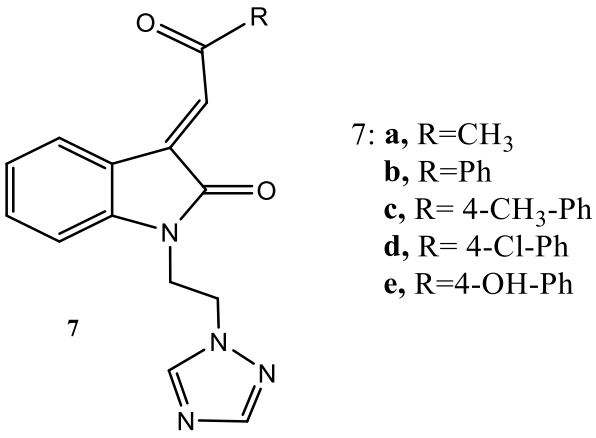


Fig.11

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.[39]

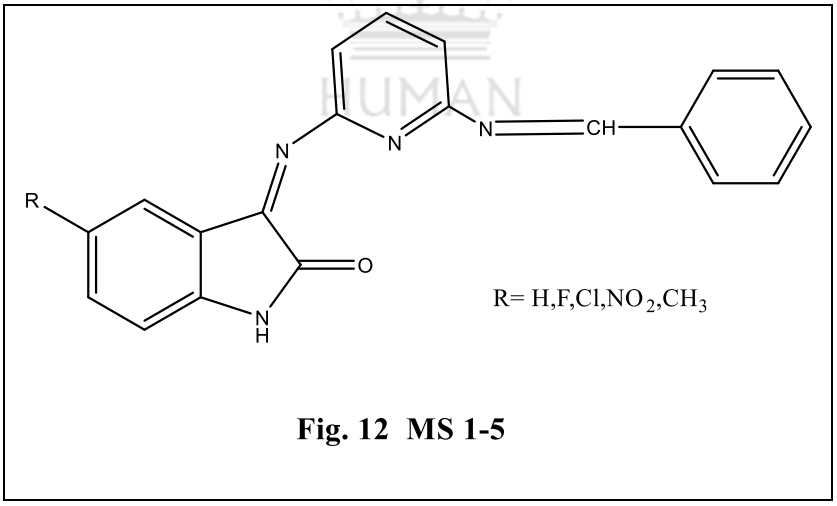
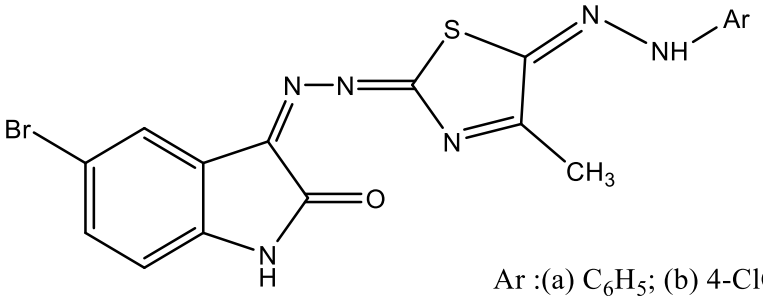


Fig. 12 MS 1-5

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

tested against *E. coli*. It was discovered that compound 7h had antifungal properties against *Candida albicans* comparable to that of the standard Nystatin.[40]



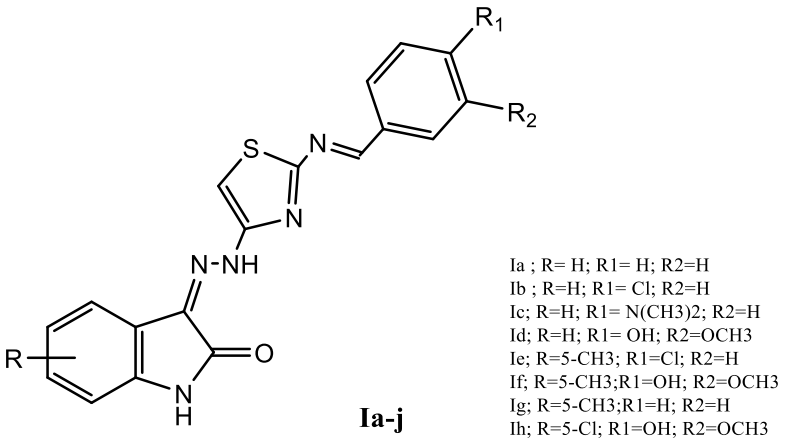
Ar :(a) C_6H_5; (b) 4-ClC_6H_5; (c) 4-BrC_6H_4 ;
(d) 4-FC_6H_5; (e) 4-$CH_3C_6H_4$;
(f) 4-$OCH_3C_6H_4$; (g) 4-$NO_2C_6H_4$;
(h) 3-CH_3,4-FC_6H_3

Fig.13

POTENTIAL PHARMACOLOGICAL ACTIVITIES OF ISATIN:

Anti-Diabetic and Hypolipidemic Activity of Isatin

E. Venkateshwarlu *et al*; synthesized isatin – 3-[N-(2-benzalaminothiazol-4-yl)] hydrazones space determines the antidiabetic and hypolipidemic effects of isatin derivatives in a type-2 diabetes model caused by streptozotocin-nicotinamide. Only Id, If, Ih and Ij at both dosages exhibit a significant (P 0.001) drop in blood glucose level when compared to control, indicating hypoglycemia and glucose tolerance. The antidiabetic action of isatin derivatives (Id, If, Ih, and Ij) exhibited a considerable (P 0.001) decrease in blood glucose levels at 10mg/kg and 100mg/kg dosage levels after 14 days. At 7 days, 100mg/kg of these derivatives results in a significant (P 0.01) decline in blood glucose level, but 10mg /kg also results in a significant (P 0.05) fall in blood glucose when compared to diabetic control. At the 7-14 days interval, glibenclamide has considerable (P 0.001) antidiabetic efficacy.[41]



Ia-j

Ia ; R= H; R1= H; R2=H
Ib ; R=H; R1= Cl; R2=H
Ic; R=H; R1= N(CH3)2; R2=H
Id; R=H; R1= OH; R2=OCH3
Ie; R=5-CH3; R1=Cl; R2=H
If; R=5-CH3;R1=OH; R2=OCH3
Ig; R=5-CH3;R1=H; R2=H
Ih; R=5-Cl; R1=OH; R2=OCH3
Ii; R= 5-Cl; R1= Cl; R2=H
Ij; R= 5-NO2;R1= OH; R2=OCH3

Fig.14

Anti-proliferative Activity

Wagdy M. Eldehna *et al*; reported oxindole-based compounds was replaced with a thiazolo[3,2-a] benzimidazole moiety, resulting in the discovery of potential CDK2 inhibitors with significant antiproliferative activity against breast cancer cell lines. All of the synthesised hybrids (7a-e and 10a-i) were tested for antiproliferative activity against MDA-MB-231 and MCF-7 breast cancer cell lines) and shows excellent activity. In comparison to the reference drug Staurosporine, 7a was the most active derivative against the MCF-7 cell line with an IC50 of 2.02 0.13 M, while 7d was the most active hybrid against the MDA-MB-231 cell line with an IC50 of 3.30 0.21 M. The N-substituted series 10a-i displayed good to excellent activity, with the most active derivative 10a having IC50 values of 2.60 1.47 M and 3.01 0.22 M for the MDA-MB-231 and MCF-7cell lines, respectively.[42]

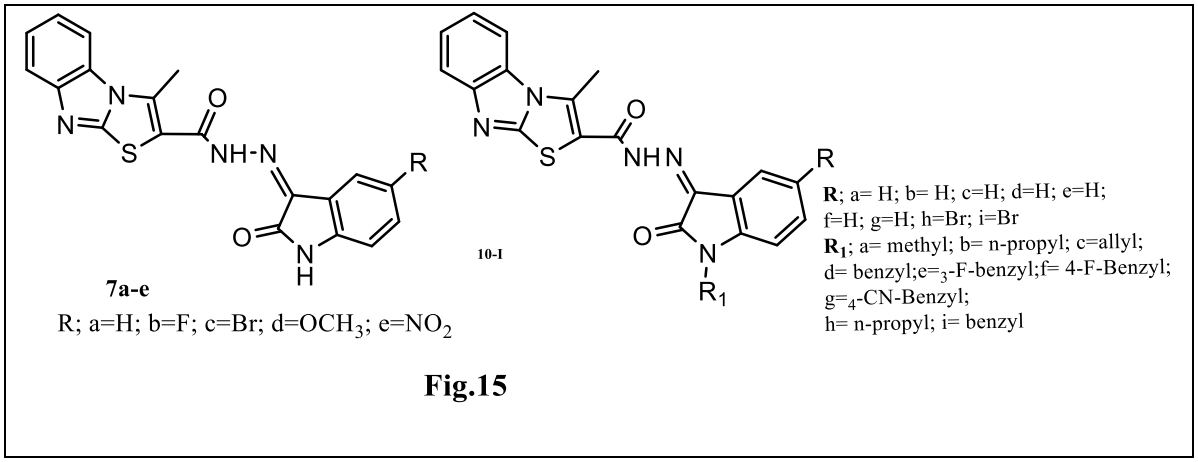
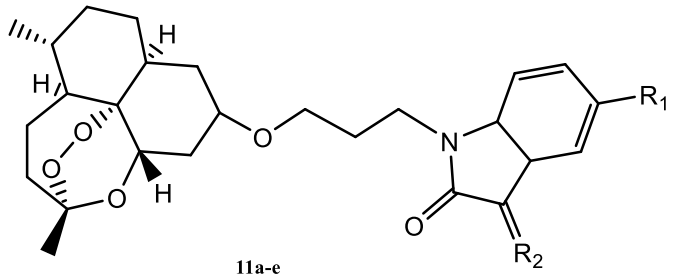


Fig.15

Yanhua Wang *et al*; designed, and synthesized artemisinin-isatin hybrids 8a-i, 10a-c, and 11a-e and evaluate their activity against breast cancer cells (MCF-7, MDA-MB-231, and doxorubicin-resistant MCF-7 (MCF-7/DOX)) as well as the cytotoxicity towards normal MCF-10A breast cells. Among these, hybrids 11c, and d exhibited strong action against the three tested breast cancer cell lines in addition to not being harmful to normal MCF-10A breast cells. Both hybrids 11c,d and doxorubicin were considered potential templates for the development of new anti-breast cancer medications since their activities were comparable to those of the latter drug.[43]



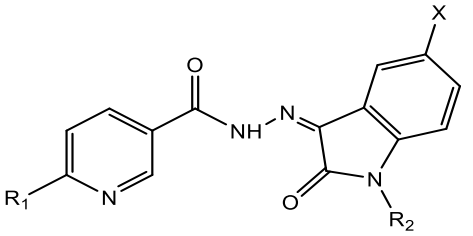
11a-e

11 a: R_1= H, R_2= NOMe
11b: R_1= H, R_2= NOEt
11c: R_1= F, R_2= NOMe
11d: R_1= F, R_2= NOEt
11e: R_1= Me, R_2= NOEt

Fig.16

Antitubercular Activity

Zainab M. Elsayed *et al*; The isatin-3-pyridyl amine hybrid 14 and various sets of isatin-nicotinohydrazide hybrids (5a-m, 9a-c) were designed and prepared. The seventeen newly created 2-oxindolin-3-ylidene nicotinohydrazide derivatives were tested for their anti-mycobacterial activity against M. tuberculosis (ATCC 27294), as well as against the INH and streptomycin-resistant M. tuberculosis (ATCC 35823). MABA32 was tested for anti-tubercular activity against Isoniazid and Streptomycin-resistant *M. tuberculosis* (ATCC 35823). Compounds 5g and 5h, which had the best anti-tubercular effect against *M. tuberculosis* (ATCC 27294), exhibited improved activity (MIC 14 3.9 mg/mL) against a resistant *M. tuberculosis* strain (ATCC 35823), with a 32-fold increase in activity when compared to INH and Streptomycin (MIC > 125 mg/mL). Furthermore, compounds 5d, 5f, and 5j showed good action at MIC 14 15.63 mg/mL, whereas derivatives 5b, 5k, and 14 showed moderate activity at MIC 14 62.5 mg/Ml.[44]



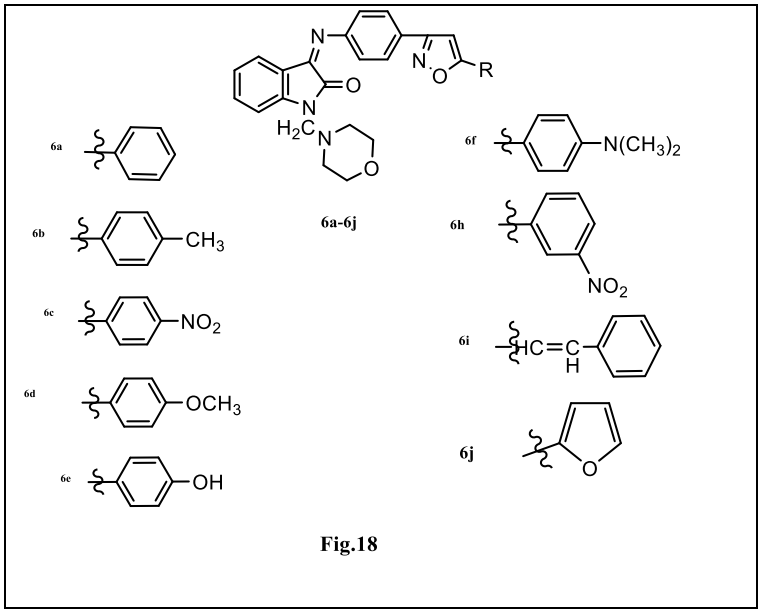
5a-m

5	R_1	X	R_2	5	R_1	X	R_2	5	R_1	X	R_2
a	H	H	propyl	**f**	H	Cl	isobutyl	k	OCH_3	H	isobutyl
b	H	H	isobutyl	**g**	H	Br	propyl	**l**	OCH_3	H	ethylacetate
c	H	H	ethylacetate	**h**	H	Br	propyl	**m**	OCH_3	H	benzyl
d	H	H	benzyl	**i**	H	Br	ethylacetate				
e	H	Cl	propyl	j	OCH_3	H	propyl				

Fig.17

Anticonvulsant Activity

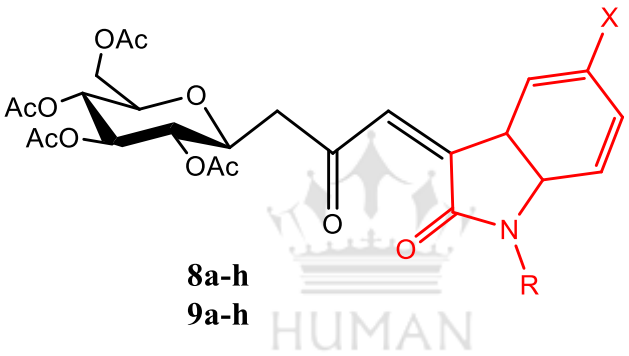
Govindaraj Saravanan *et al*; designed and synthesised novel indole-2,3-dione derivatives to study the pharmacophoric pattern of clinically active AEDs. The majority of isatin-isoxazole coupled derivatives In the MES screening, 6a-6j showed moderate to good antiepileptic efficacy but acryloyl phenyl attached isatin derivatives did not. 5a-5j showed weak activity. Six of the compounds tested in the scPTZ test, 6d, 6e, and 6f, were found to be effective at a dosage of 100 mg/kg after 0.5 hours. The most effective of the synthesized compound was 6f, which showed protection in MES at a dose of 30 mg/kg (i.p.) after 0.5 h and 4h. Interestingly, this compound offered prevention in the scPTZ at doses of 100 mg/kg (0.5 h) and 300 mg/kg(4 h).[45]



6a-6j

Fig.18

Ravi Kumar Thakur *et al*; synthesized a novel series of N-alkylated 3-glycoconjugated-oxopropylidene oxindoles from substituted isatin and glucopyranosyl propanone through a well-known cross-aldol reaction followed by dehydration. The recently formed agents were evaluated for their in vitro antiplasmodial activity against the standard medication chloroquine against chloroquine-sensitive (3D7) and chloroquine-resistant (K1) strains of *P. falciparum*. Compounds 9g, 9f, 9b, 8d, 9d, 9c, and 9e have demonstrated strong antiplasmodial activity, with IC50 values against the chloroquine-sensitive Pf3D7 strain of 0.11, 0.17, 0.18, 0.23, 0.24, 0.26, and 0.32 M, respectively. In addition, compounds 9d, 9b, 9e, 8c, 8f, 9c, and 9a have demonstrated excellent promising activity with IC50 values in the range of 0.1-0.4 M as 0.15, 0.22, 0.25, 0.29, 0.30, 0.31, and 0.40 M, respectively, against chloroquine-resistant PfK1 strain. These values are even better than the standard drug chloroquine, which has an IC50 value of 0.5.[46]



8a-h
9a-h

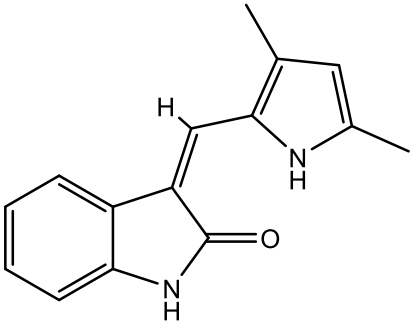
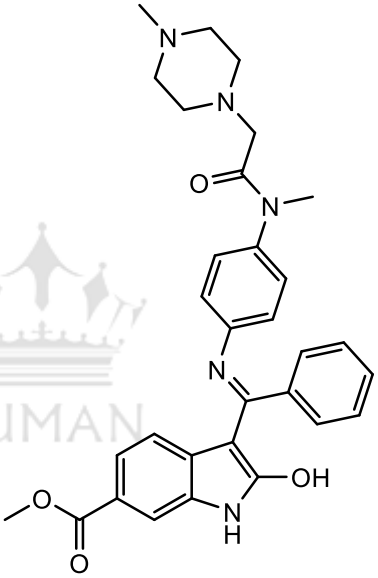
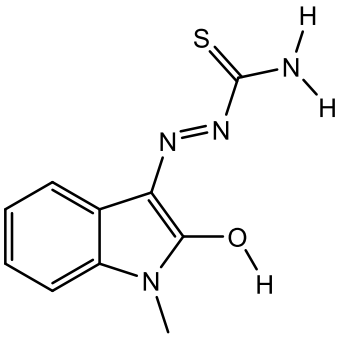
Compound	X	R
8a	H	propyl
8b	H	butyl
8c	H	$PhCH_2$
8d	H	p-Br-$C_6H_4CH_2$
8e	H	p-F-$C_6H_4CH_2$
8f	H	m-Me-$C_6H_4CH_2$
8g	H	$PhCH_2CH_2$
8h	H	H

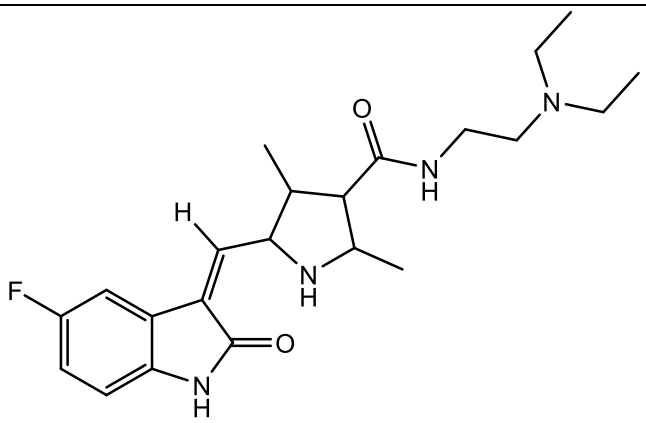
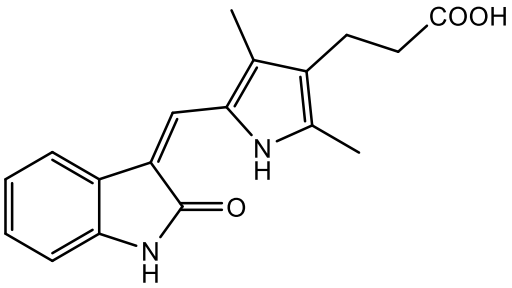
Compound	X	R
9a	Cl	propyl
9b	Cl	butyl
9c	Cl	$PhCH_2$
9d	Cl	p-Br-$C_6H_4CH_2$
9e	Cl	p-F-$C_6H_4CH_2$
9f	Cl	m-Me-$C_6H_4CH_2$
9g	Cl	$PhCH_2CH_2$
9h	Cl	H

Fig.19

Marketed Drug Containing Isatin Moiety:

Table No.1: Marketed drug containing isatin moiety

Semaxanib is a tyrosine-kinase inhibitor drug. In clinical trials semaxanib has shown activity in patients with acute myeloid leukemia and colorectal carcinoma.	 Semaxanib
Nintedanib is used to treat idiopathic pulmonary fibrosis. It helps prevent changes to the lung tissue**.** Nintedanib is in a class of medications called kinase inhibitors. It works by blocking the action of enzymes involved in causing fibrosis**.**	 Nintedanib
Methisazone is an antiviral drug that works by inhibiting mRNA and protein synthesis, especially in pox viruses**.**	 Methisazone

Sunitinib is in a class of medications called kinase inhibitors. It works by blocking the action of the abnormal protein that signals cancer cells to multiply. This helps stop or slow the spread of cancer cells and may help shrink tumors**.**	 Sunitinib
Orantinib used in trials studying the treatment of Lung Cancer, Breast Cancer, Kidney Cancer, Gastric Cancer, and Prostate Cancer, among others.	 Orantinib

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.[29,47,48]

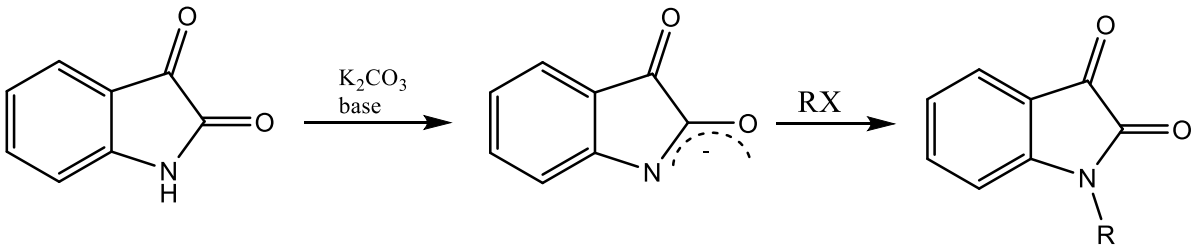


Fig.20 Isatin alkylation

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.[29,49]

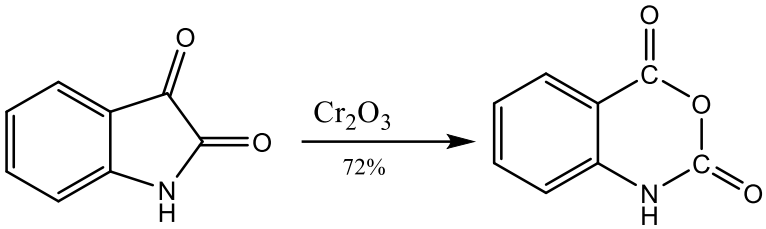


Fig.21 Oxidation of Isatin

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-aryl-3-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.[26,50]

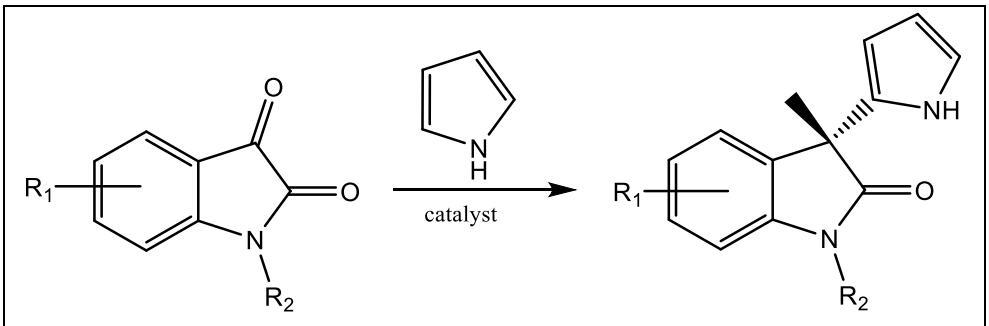


Fig.22 Friedel-Crafts reaction

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.[51,52]

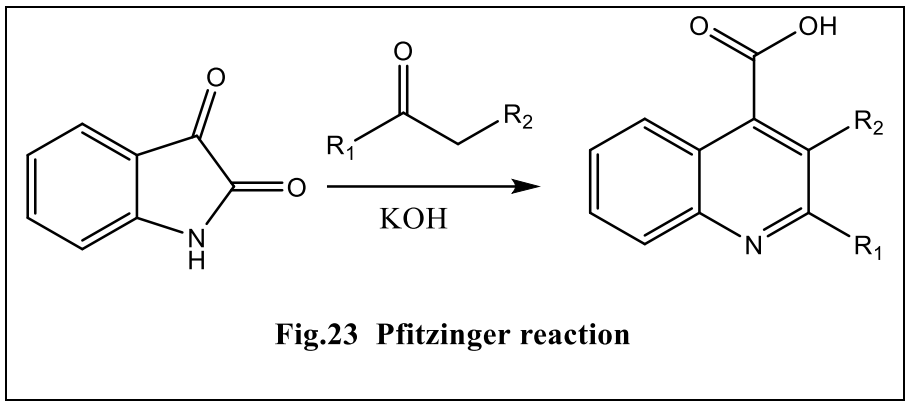


Fig.23 Pfitzinger reaction

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.[49,53]

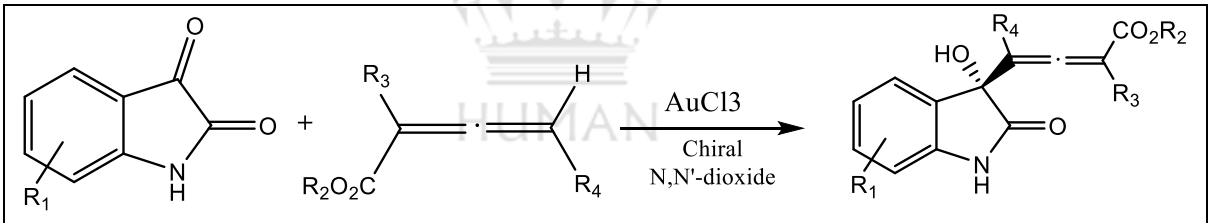


Fig.24 Aldol Reaction

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.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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None

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REFERENCES

1. Sutter VL, Jones MJ, Ghoneim AT. Antimicrobial susceptibilities of bacteria associated with periodontal disease. Antimicrob Agents Chemother. 1983;23(3):483–6.
2. Saga T, Yamaguchi K. History of antimicrobial agents and resistant bacteria. Jmaj. 2009;52(2):103–8.
3. Jain SK, Singhal R. a Review on Pyrazoline Derivatives As Antimicrobial Agent. Int J Pharm Pharm Sci. 2020;21(2):15–24.
4. Lees P, Pelligand L, Giraud E, Toutain P. A history of antimicrobial drugs in animals: Evolution and revolution. J Vet Pharmacol Ther. 2021;44(2):137–71.
5. Journals H. Antimicrobial Activity of a New Antibiotic Adjuvant Entity (AAE) of Ceftriaxone , Sulbactam and EDTA against Clinical Isolates of Gram Negative Bacteria. Int J Pharm Pharm Res. 2020;20(1):609–13.
6. Durand GA, Raoult D, Dubourg G. Antibiotic discovery: history, methods and perspectives. Int J Antimicrob Agents. 2019;53(4):371–82.
7. Tenover FC. Mechanisms of antimicrobial resistance in bacteria. Am J Med. 2006;119(6):S3–10.
8. Zhang YZ, Du HZ, Liu HL, He QS, Xu Z. Isatin dimers and their biological activities. Arch Pharm (Weinheim). 2020;353(3):1–11.
9. Pakravan P, Kashanian S, Khodaei MM, Harding FJ. Biochemical and pharmacological characterization of isatin and its derivatives : from structure to activity. Pharmacol Reports [Internet]. 2013;65(2):313–35. Available from: http://dx.doi.org/10.1016/S1734-1140(13)71007-7
10. Silva B V. Isatin, a versatile molecule: Studies in Brazil. J Braz Chem Soc. 2013;24(5):707–20.
11. Khanapure S, Jagadale M, Bansode P, Choudhari P, Rashinkar G. Anticancer activity of ruthenocenyl chalcones and their molecular docking studies. J Mol Struct [Internet]. 2018;1173:142–7. Available from: https://doi.org/10.1016/j.molstruc.2018.06.091
12. Wang R, Yin X, Zhang Y, Yan W. Design, synthesis and antimicrobial evaluation of propylene-tethered ciprofloxacin-isatin hybrids. Eur J Med Chem [Internet]. 2018;156:580–6. Available from: https://doi.org/10.1016/j.ejmech.2018.07.025
13. Jarapula R, Gangarapu K, Manda S, Rekulapally S. Synthesis , In Vivo Anti-Inflammatory Activity , and Molecular Docking Studies of New Isatin Derivatives. Int J Med Chem. 2016;2016:9.
14. Obafemi CA, Adegbite OB, Fadare OA, Iwalewa EO, Omisore NO, Sanusi K, *et al*. Tryptanthrin from microwave-assisted reduction of isatin using solid-state-supported sodium borohydride: DFT calculations, molecular docking and evaluation of its analgesic and anti-inflammatory activity. Heliyon [Internet]. 2021;7(1):e05756. Available from: https://doi.org/10.1016/j.heliyon.2020.e05756
15. Chirra S, Jupally VR. Study of antimicrobial, analgesic and anticonvulsant activity of novel isatin derivatives. Asian J Pharm Clin Res. 2016;9(5):65–8.
16. Sin N, Venables BL, Combrink KD, Gulgeze HB, Yu KL, Civiello RL, *et al*. Respiratory syncytial virus

fusion inhibitors. Part 7: Structure-activity relationships associated with a series of isatin oximes that demonstrate antiviral activity in vivo. Bioorganic Med Chem Lett [Internet]. 2009;19(16):4857–62. Available from: http://dx.doi.org/10.1016/j.bmcl.2009.06.030
17. Bal TR, Anand B, Yogeeswari P, Sriram D. Synthesis and evaluation of anti-HIV activity of isatin β-thiosemicarbazone derivatives. Bioorganic Med Chem Lett. 2005;15(20):4451–5.
18. Muğlu H, Çavuş MS, Bakır T, Yakan H. Synthesis, characterization, quantum chemical calculations and antioxidant activity of new bis-isatin carbohydrazone and thiocarbohydrazone derivatives. J Mol Struct [Internet]. 2019;1196:819–27. Available from: https://doi.org/10.1016/j.molstruc.2019.07.002
19. Raj V. Review on Cns Activity of Isatin Derivatives. Int J Curr Pharm Res. 2012;4(4):1–9.
20. Bahe AK, Roy A. Synthesis of Isatin and its Derivatives Containing Heterocyclic Compounds. J Turkish Chem Soc. 2021;8(4):1089–98.
21. Nath R, Pathania S, Grover G, Akhtar J. Isatin containing heterocycles for different biological activities : Analysis of structure activity relationship. J Mol Struct [Internet]. 2020;1222:128900. Available from: https://doi.org/10.1016/j.molstruc.2020.128900
22. Silva JFM, Garden SJ, Pinto AC. The Chemistry of Isatins : a Review from 1975 to 1999 2 . Synthesis of Isatins. J Braz Chem Soc. 2001;12(3):273–324.
23. Shakir TH, Al-Mudhafar MMJ. Synthesis and preliminary antimicrobial evaluation of schiff bases of N-Benzyl isatin derivatives. Syst Rev Pharm. 2020;11(12):1950–5.
24. Al-mudhafar MMJ, Omar TN, Abdulhadi SL. Bis-Schiff Bases of Isatin Derivatives Synthesis , and their Biological Activities : A Review. Al Mustansiriyah J Pharm Sci. 2022;22(July):28–48.
25. Mishra R, Chaurasia H, Singh VK, Naaz F, Singh RK. Molecular modeling , QSAR analysis and antimicrobial properties of Schiff base derivatives of isatin. J Mol Struct [Internet]. 2021;1243:130763. Available from: https://doi.org/10.1016/j.molstruc.2021.130763
26. Al-khuzaie MGA, Fahad MM, Al-safi AJ. Biomedicine and Chemical Sciences Synthesis , Reaction and Biological Importance of Isatin Derivatives. Biomed Chem Sci J. 2022;1(3):193–206.
27. Ganim MA, Baloglu MC, Aygun A, Altunoglu YC, Sayiner HS, Kandemirli F, *et al.* PT. Int J Biol Macromol [Internet]. 2018;#pagerange#. Available from: https://doi.org/10.1016/j.ijbiomac.2018.09.084
28. Kumar V, Tangadanchu R, Sui Y, Zhou C. Bioorganic & Medicinal Chemistry Letters Isatin-derived azoles as new potential antimicrobial agents : Design , synthesis and biological evaluation. Bioorg Med Chem Lett [Internet]. 2021;41(January):128030. Available from: https://doi.org/10.1016/j.bmcl.2021.128030
29. Pithawala NA, Jain B. Journal of Advanced Scientific Research. … Adv Sci … [Internet]. 2012;1(2):19–23. Available from: http://www.sciensage.info/journal/1359303580JASR_3006121.pdf
30. Grewal AS. Isatin Derivatives with Several Biological Activities. Int J Pharm Res. 2014;6(September):7.
31. Kurkin A V., Bernovskaya AA, Yurovskaya MA. Comparative study of the different approaches to the synthesis of isatins with a chiral substituent at the nitrogen atom. Chem Heterocycl Compd. 2011;46(10):1208–14.
32. Zi Y, Cai ZJ, Wang SY, Ji SJ. Synthesis of isatins by I2/TBHP mediated oxidation of indoles. Org Lett. 2014;16(11):3094–7.
33. Wakchaure ND, Shejwal SS, Deshmukh VK, R. S, Chaudhari. Review on Common Methods to Synthesize Substituted1H-Indole-2, 3-Dione (Isatin) Derivatives and Their Medicinal Significance. Am J pharmetch resarch. 2012;2(4):289–304.
34. Shukla PK, Singh MP, Patel R. A review on recent advances in chemistry, synthesis and biological applications of isatin derivatives. J Appl Pharm Sci Res. 2018;16–22.
35. Jabbar SS. Synthesis, Characterization and Antimicrobial Activity of New Isatin Derivatives. Int Res J Pharm. 2019;10(1):98–102.
36. Pourahmadi. Ar ch Ar ch هتفاياه. J Clin Psychol. 2009;2(1):205–11.
37. Ugale V, Patel H, Patel B, Bari S. Benzofurano-isatins: Search for antimicrobial agents. Arab J Chem [Internet]. 2017;10:S389–96. Available from: http://dx.doi.org/10.1016/j.arabjc.2012.09.011
38. Chemchem M, Menacer R, Merabet N, Bouridane H, Yahiaoui S, Moussaoui S, et al. Green synthesis, antibacterial evaluation and QSAR analysis of some isatin Schiff bases. J Mol Struct. 2020;1208:10.
39. SHRIVASTAVA S, AHUJA D. Synthesis and Antimicrobial Screening of 2,6-Diaminopyridine Schiff Bases of Isatin Derivatives. Int J Curr Pharm Res. 2023;15(1):47–50.

40. Kassab RM, Al-Hussain SA, Elleboudy NS, Albohy A, Zaki MEA, Abouzid KAM, *et al.* Tackling Microbial Resistance with Isatin-Decorated Thiazole Derivatives: Design, Synthesis, and in vitro Evaluation of Antimicrobial and Antibiofilm Activity. Drug Des Devel Ther. 2022;16(August):2817–32.
41. Author C, Venkateshwarlu E, Sharvana Bhava B, Arvind P, Rakeshkumar Reddy P, Dileep P, *et al*. Evaluation of Anti-Diabetic and Hypolipidemic Activity of Pseudarthria viscida (Whole Plant) in Streptozotocin-Nicotinamide Induced Type II Diabetic Rats. Glob J Pharmacol. 2013;7(2):192–7.
42. Eldehna WM, El Hassab MA, Abo-Ashour MF, Al-Warhi T, Elaasser MM, Safwat NA, et al. Development of isatin-thiazolo[3,2-a]benzimidazole hybrids as novel CDK2 inhibitors with potent in vitro apoptotic anti-proliferative activity: Synthesis, biological and molecular dynamics investigations. Bioorg Chem. 2021;110(December 2020):14.
43. Wang Y, Ding R, Tai Z, Hou H, Gao F, Sun X. Artemisinin-isatin hybrids with potential antiproliferative activity against breast cancer. Arab J Chem [Internet]. 2022;15(3):103639. Available from: https://doi.org/10.1016/j.arabjc.2021.103639
44. Elsayed ZM, Eldehna WM, Abdel-Aziz MM, El Hassab MA, Elkaeed EB, Al-Warhi T, *et al*. Development of novel isatin–nicotinohydrazide hybrids with potent activity against susceptible/resistant Mycobacterium tuberculosis and bronchitis causing–bacteria. J Enzyme Inhib Med Chem [Internet]. 2021;36(1):384–93. Available from: https://doi.org/10.1080/14756366.2020.1868450
45. Saravanan G, Alagarsamy V, Dineshkumar P. Anticonvulsant activity of novel 1-(morpholinomethyl)-3-substituted isatin derivatives. Bull Fac Pharmacy, Cairo Univ [Internet]. 2014;52(1):115–24. Available from: http://dx.doi.org/10.1016/j.bfopcu.2014.02.001
46. Thakur RK, Joshi P, Upadhyaya K, Singh K, Sharma G, Shukla SK, *et al*. Synthesis of isatin based N1-alkylated 3-β-C-glycoconjugated-oxopropylidene oxindoles as potent antiplasmodial agents. Eur J Med Chem [Internet]. 2019;162:448–54. Available from: https://doi.org/10.1016/j.ejmech.2018.11.008
47. Shakir TH, Al-mudhafar MMJ. Synthesis And Preliminary Antimicrobial Evaluation Of Schiff Bases Of N -Benzyl Isatin Derivatives. A multifaceted Rev J F Pharm Synth. 2020;11(12):1950–5.
48. Shmidt MS, Reverdito AM, Kremenchuzky L, Perillo IA. Simple and Efficient Microwave Assisted N-Alkylation of Isatin. Molecules. 2008;13:831–40.
49. Manuscript A. MedChemComm. R Socirty Chem. 2019;1–19.
50. Vodnala N, Singh S, Hazra CK. Lewis Acid-Promoted Typical Friedel–Crafts Reactions Using DMSO as a Carbon Source. J Org Chem. 2022;87(15):10044–53.
51. N Sangshetti J, S Zambare A, Gonjari I, B Shinde D. Pfitzinger reaction in the synthesis of bioactive compounds-a review. Mini Rev Org Chem. 2014;11(2):225–50.
52. Lindwall HG, Maclennan JS. A Condensation of Acetophenone With Isatin By The Knoevenagel Method1. J Am Chem Soc. 1932;54(12):4739–44.
53. Guo Q, Zhao JC-G. Primary amine catalyzed aldol reaction of isatins and acetaldehyde. Tetrahedron Lett. 2012;53(14):1768–71.