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Review on Common Methods to Synthesize Substituted1H-Indole-2, 3-Dione (Isatin) Derivatives and Their Medicinal Significance

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ABSTRACT

Isatin is an important class of heterocyclic compounds. Recently, heterocyclic compounds analogues and their derivatives have attracted strong interest in medicinal chemistry due to their biological and pharmacological properties. The small and simple isatin nucleus possesses numerous biological properties like -antitumor, antimicrobial, anti-inflammatory, anticonvulsant, antiviral, anti HIV, antioxidant, CNS depressant activities. These activities are also possessed by its substituted derivatives as well. The present review outlines some commonly used procedures to synthesize the isatin moiety and its derivatives, with different biological activities.

Keywords: Isatin, Antimicrobial, Anticancer, Anti- inflammatory, Anticonvulsant Activity.

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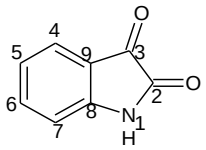
INTRODUCTION

Isatin or 1*H*-indole-2, 3-dione is an indole derivative. The compound was first obtained by Erdman and Laurent in 1841 as a product from the oxidation of indigo dye by nitric acid and chromic acids.[1]

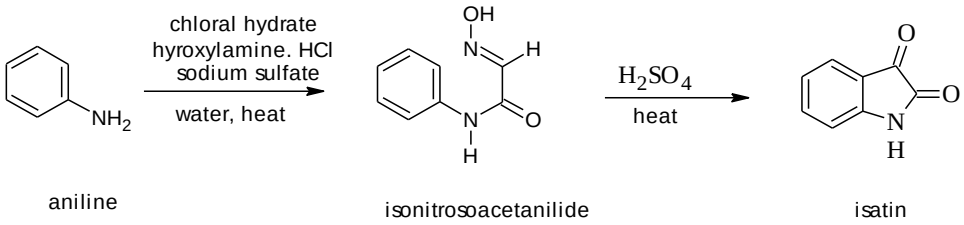


Isatin ring system consists of pyrrole ring fused with benzene ring[2]. A literature survey identified several isatin derivatives in the development phase as potential new drugs. In recent years, isatin are reported to exhibit a broad range of biological and pharmacological properties and are widely used as starting materials for the synthesis of a broad range of heterocyclic compounds and as substrates for drug synthesis[1]. Isatin moeity shows biological activites like antioxidant and anti-inflammatory[3,] antimicrobial[4], antituberculosis[5], anticancer[6], anti-HIV[7], antiviral[8], anticonvulsant[9] activities. To synthesize the isatin moiety and its derivatives to develop new pharmacologically less toxic medicines.

SOME COMMON ROUTES TO SYNTHESIS OF SUBSTITUTED ISATIN DERIVATIVES:

1. The Sandmeyer isatin synthesis

The method developed by Sandmeyer is the oldest and the most frequently used for the synthesis of isatin. It consists in the reaction of aniline with chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulfate to form an isonitrosoacetanilide, which after isolation, when treated with concentrated sulfuric acid, furnishes isatin in >75% overall yield. The method applies well to anilines with electron-withdrawing substituents, such as 2-fluoroaniline, and to some heterocyclic amines, such as 2-aminophenoxathine[10] **(Scheme 1)**.

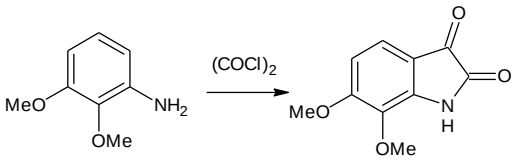


Scheme: 1. Sandmeyer isatin synthesis

2. The Stolle isatin synthesis

The most important alternative to Sandmeyer's procedure is the method of Stolle. In this method anilines are reacted with oxalyl chloride to form an intermediate chlorooxalylanilide which can

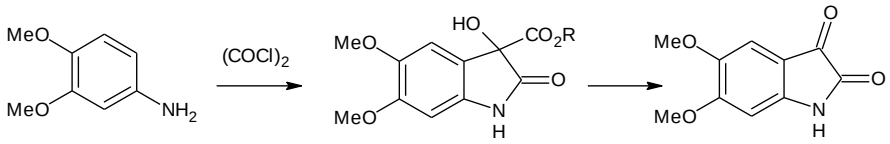
be cyclized in the presence of a Lewis acid, usually aluminum chloride or $BF_3.Et_2O$, although $TiCl_4$ has also been used to give the corresponding isatin[11]. (**Scheme 2).**



Scheme: 2. Stolle isatin synthesis

3. The Martinet isatin synthesis

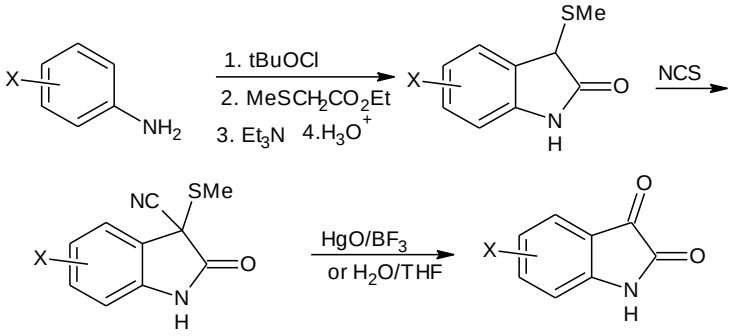
The Martinet procedure for the synthesis of indole-2,3-diones involves the reaction of an aminoaromatic compound and either an oxomalonate ester or its hydrate in the presence of an acid to yield a 3-(3-hydroxy-2-oxindole)carboxylic acid derivative which after oxidative decarboxylation yields the respective isatin. This method was applied with success for the synthesis of 5, 6-dimethoxyisatin from 4-aminoveratrole whereas the use of 2, 4-dimethoxyaniline was less successful.[12] **(Scheme 3).**



Scheme: 3. Martinet isatin synthesis

4. The Gassman isatin synthesis

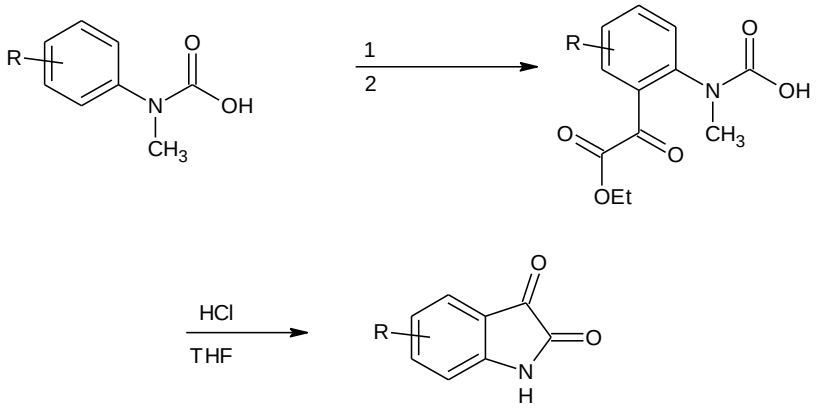
This methodology consists in the formation and subsequent oxidation of an intermediate 3-methylthio-2-oxindole to give the corresponding substituted isatins in 40-81% yield. Two complementary methods for the synthesis of the 3-methylthio-2-oxindoles were developed, and the methodology of choice is dependent upon the electronic effect of substituents bonded to the aromatic ring. When electron-withdrawing groups are present, the oxindole derivative can be synthesized via an *N*-chloroaniline intermediate, which further reacts with a methylthioacetate ester to furnish an azasulfonium salt.[13] **(Scheme 4).**



Scheme: 4. Gassman isatin synthesis

5. **Metalation of anilide isatin synthesis**

A more recent method for the synthesis of isatins is based upon the directed *ortho*-metalation (D*o*M) of *N*-pivaloyl- and *N*-(*t*-butoxycarbonyl)-anilines. The corresponding dianions are treated with diethyl oxalate and the isatins are obtained after deprotection and cyclisation of the intermediate a-ketoesters. This method has the advantage of being regioselective for the synthesis of 4-substituted isatins from *meta*-substituted anilines where the substituent is a metalation directing group.[14] **(Scheme 5).**

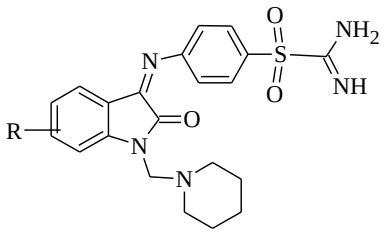


Scheme: 5 Metalation of anilide isatin synthesis

I. **BIOLOGICAL ACTIVITY**

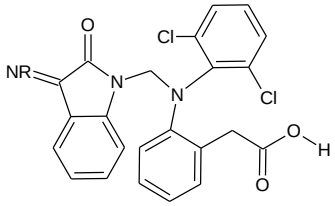
1. **<u>Antimicrobial Activity</u>**

U. K. Singh *et. al*. reported the Synthesis of Schiff's and N-Mannich Bases of Isatin and Its Derivatives with 4-Amino-N-Carbamimidoyl Benzene Sulfonamide **(Figure 1)**, all compounds exhibited very significant and better antibacterial activity.[15]



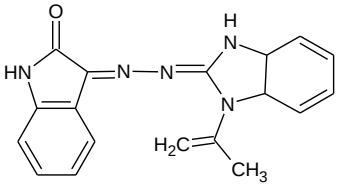
(Figure1) Schiff's and *N*-Mannich Bases of Isatin

V. Ravichandran *et. al.* reported the synthesis of mannich bases of isatin and its derivatives with 2-[(2, 6-dichlorophenyl) amino] Phenyl acetic acid **(Figure 2)**, all the synthesized compounds were tested for their antibacterial activities against Gram + and Gram – bacteria, and antifungal activities.[16]



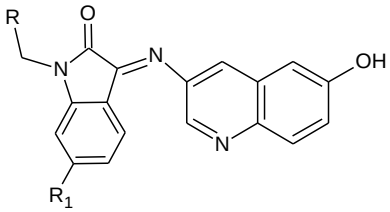
(Figure 2) Mannich Bases of Isatin

Madhu *et al.* reported the synthesis of some new isatin derivatives **(Figure 3)**, tested compounds showed the most favorable antimicrobial activity against S. aureus.[17]



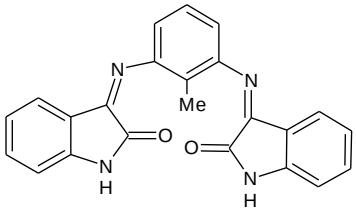
(Figure 3) Isatin Derivatives

Chhajed S.S *et al*. reported the synthesis of schiff and mannich bases of isatin and its derivatives with quinolin **(Figure 4)**, investigation of antimicrobial activity of the compounds was made by the agar dilution method, and the compounds are significantly active against bacteria and fungi.[18]



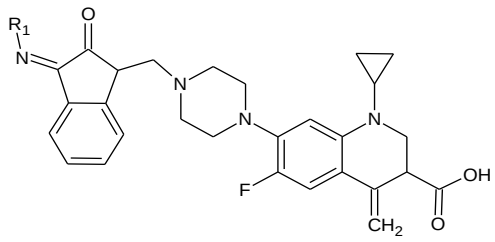
(Figure 4) Schiff's and Mannich Bases of Isatin

Aliasghar Jarrahpour *et. al*. reported the synthesis of some novel bis-schiff bases of isatin and their derivatives and these newly synthesized bis-schiff bases **(Figure 5)** were also tested for their antibacterial and antifungal activities.[19]



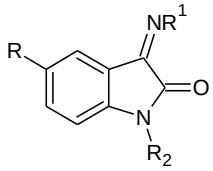
(Figure 5) Bis-Schiff Bases of Isatin

Ramachandran *et. al*. reported the synthesis of schiff and mannich bases of isatin derivatives **(Figure 6)**, most of the compounds shown greater antibacterial and antifungal activities when compared with the standard drugs.[20]



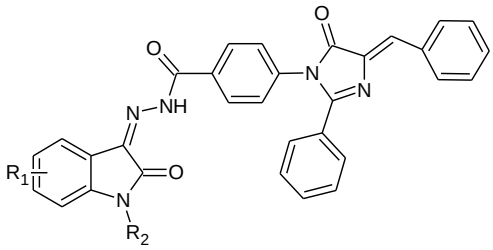
(Figure 6) Schiff's and Mannich Bases of Isatin

Seshaiah Krishnan Sridhar *et al*. reported the synthesis of synthesis of hydrazones, schiff and mannich bases of isatin derivatives **(Figure 7)**, the compounds were screened for antibacterial activity. The minimum inhibitory concentrations of the active compounds were determined. 1-Diphenyl amino-methyl-3-(4-bromo phenylimino)-1, 3-dihydro-indol-3-one and 3-(4-bromo phenylimino)-5-nitro-1, 3-dihydroindol- 3-one were found to be the most active compounds of the series.[21]



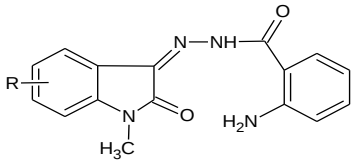
(Figure 7) Schiff's and Mannich Bases of Isatin

Sanjay Bari *et al*. reported the of synthesis and antimicrobial activity of some new isatin derivatives **(Figure 8)**, antimicrobial activity of compounds with 5-Br substitution showed the most favorable antimicrobial activity.[22]



(Figure 8) Isatin Derivatives

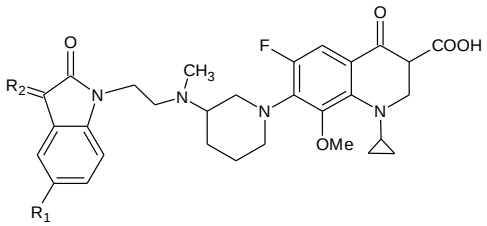
G. Sammaiah *et al*. reported the synthesis of 2-aminobezoic acid (2-oxo-1, 2 dihydro-indol-3-ylidene)-hydrazides, as indol hydrazides have shown proven to be good antimicrobial agents, some new series of indol hydrazides synthecized **(Figure 9)** few 2-amino benzoic acid (2-oxo-1, 2 dihydro-indol-3-ylidene)-hydrazides showed good antimicrobial activity.[23]



(Figure 9) Indol Hydrazides

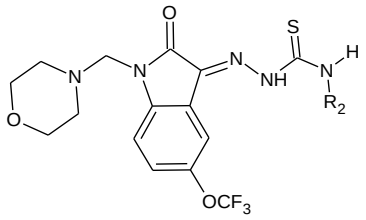
2. Antituberculasis Activity

Lian-Shun Feng, *et al*. reported the synthesis of balofloxacin ethylene isatin derivatives, these derivatives **(Figure 10),** were evaluated for their in vitro activity against some mycobacteria, all of the synthesized compounds were less active than the parent 8-OCH_3 ciprofloxacin against Mycobacteriumsmegmatis CMCC 93202, but most of the methylene isatin derivatives were more active than 8-OCH_3 ciprofloxacin, ciprofloxacin, isoniazid and rifampin against MTB H37Rv ATCC 27294.[24]



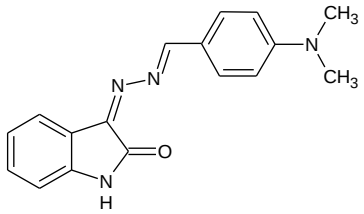
(Figure 10) Balofloxacin Ethylene Isatin Derivatives

Ozlen Guzel *et. al*. reported the synthesis 5-methyl/trifluoromethoxy-1*H*-indole-2, 3-dione 3-thiosemicarbazone derivatives **(Figure 11)**, the synthesized compounds were evaluated for in vitro antituberculosis activity against mycobacterium tuberculosis H37Rv.[25]



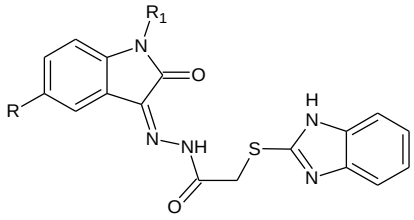
(Figure 11) 5-methyl/trifluoromethoxy-1H-indole-2, 3-dione 3-thiosemicarbazone derivatives

Sangamesh A. Patil *et. al*. reported the synthesis, biological evaluation Co (II), Ni (II),and Mn (II) metal complexes of novel isatin schiff base ligand**(Figure 12)**, the complexes show activity against mycobacterium tuberculosis strain H37Rv.[26]



(Figure 12) Novel Isatin Schiff Base Ligand

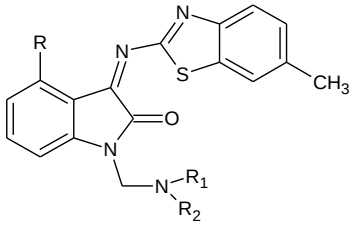
Sandeep K. Gupta *et al*. reported the synthesis some thiobenzimidazolyl derivatives **(Figure 13)** , most of them reported good antitubercular activity against mycobacterium tuberculosis.[27]



(Figure 13) Thiobenzimidazolyl Derivative

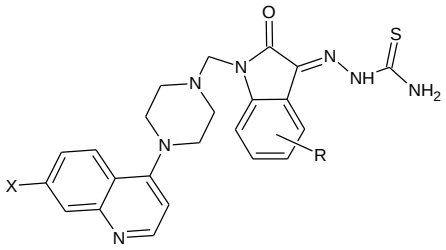
3. Anticancer activity

Hoyun Lee *et al.* reported the hybrid pharmacophore design and synthesis of isatin benzothiazole analogs **(Figure 14)**, all compounds examined were quite effective on all the cancer cell lines examined, the compounds 4-bromo-1-diethylaminomethyl-1H-indole-2,3- dione and 4-chloro-1-dimethylaminomethyl-3-(6-methyl-benzothiazol-2-ylimino)-1,3-dihydroindol- 2-one emerged as the most active compounds of this series.[28]



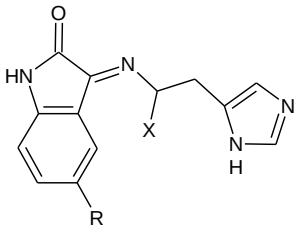
(Figure 14) Hybrid Pharmacophore of Isatin Benzothiazole Analogs

V. Raja Solomon *et al*. reported the design and synthesis of 4-piperazinylquinoline: a hybrid Pharmacophore approach **(Figure 15)**, the compounds were examined for their cytotoxic effects on two human breast tumor cell lines, MDA-MB468 and MCF7, and two non-cancer breast epithelial cell lines, 184B5 and MCF10A.[29]



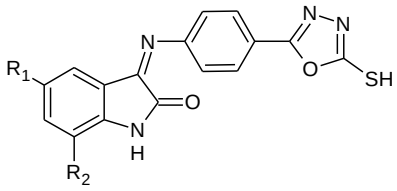
(Figure 15) 4-piperazinylquinoline

Abadi *et al*. reported the synthesis of 3-substituted-2-oxoindoles **(Figure 16)**, compounds were tested for potential antiangiogenic properties, all the final compounds were tested for their in vitro antitumor properties against MCF7 (breast), NCI-H460 (lung) and SF268 (CNS) cancer cell lines.[30]



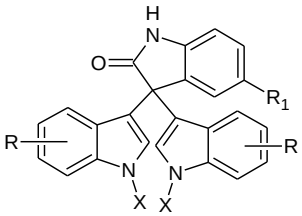
(Figure 16) 3-substituted-2-oxoindoles

Sarangapani Manda *et al*. reported the synthesis of certain 3-{4-(5-mercapto-1, 3, 4-oxadiazole-2- yl)phenylimino}indolin-2-one derivatives, all derivatives **(Figure 17)** were screened for anticancer activity against HeLa cancer cell lines using MTT assay.[31]



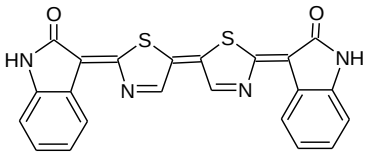
(Figure 17) 3-{4-(5-mercapto-1, 3, 4-oxadiazole-2-yl)phenylimino}indolin-2-one derivatives

Ahmed Kamal *et al*. reported the synthesis of 3-substituted-2-oxoindoles and their evaluation as kinase inhibitors **(Figure 18),** these compounds were evaluated against a panel of five human cancer lines and most of them showed potent cytotoxicity.[32]



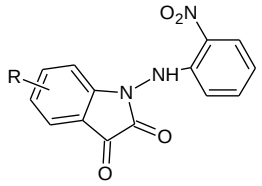
(Figure 18) 3-substituted-2-oxoindoles

Md. Mahbubul Hoque *et al*. reported the synthesis some indophenines and some isatin derivatives **(Figure 19)** was studied by the brine shrimp lethality bioassay. indophenines from thiophene, isatin derivatives showed potential cytotoxicity against brine shrimp nauplii.[33]



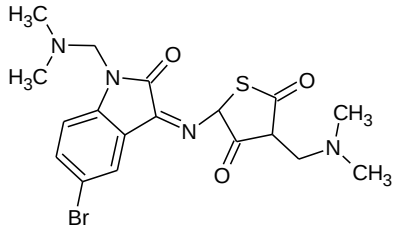
(Figure 19) Indophenines and Isatin Derivatives

F. D. Popp *et. al.* had been synthesized 3-*o*-nitrophenyl hydrazones of isatin by the condensation of isatin with *o*-nitrophenyl hydrazine **(Figure 20)** which shows anticancer activity.[34]



(Figure 20) Isatin with *O*-Nitrophenyl Hydrazine

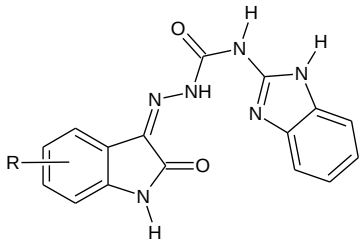
N. H Eshba *et al.* had been synthesized 5-(2-oxo-3-indolinyl) thiazolidine-2,4-dione having positions 1 and 3 of the isatin and thiazolidine rings, respectively, substituted by various Mannich bases **(Figure 21)** and had been shown anticancer activity.[35]



(Figure 21) 5-(2-oxo-3-indolinyl) thiazolidine-2,4-dione

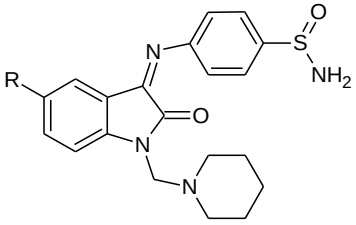
4. Anti-inflammatory Activity

Gummadi Sridhar Babu *et. al*. reported the synthesis, characterization and evaluation of Novel *N*-(1*H* Benzimidazol- 2-Yl)-2-Isatinylidene-Hydrazinecarboxamide **(Figure 22)**, anti-inflammatory data revealed that the compounds possess significant activity which is on a par with the standard ligand.[36]



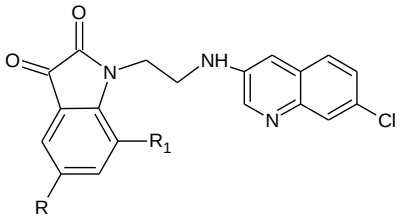
(Figure 22) *N*-(1*H* Benzimidazol- 2-Yl)-2-Isatinylidene-Hydrazinecarboxamide

B. Durga Prasad *et. al*. reported the synthesis, characterization of isatin derivatives **(Figure 23)**, all the synthesized isatin derivatives have been investigated for their anti-inflammatory activity.[37]



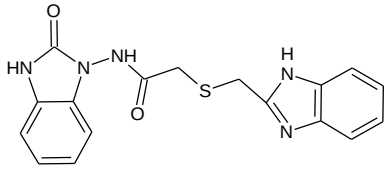
(Figure 23) Isatin Derivatives

Adel Hamed Mandour *et. al*. reported the synthesis of some novel 3-[(*N* -substituted indol-3-yl) methyleneamino]-6-amino- 4-aryl-pyrano(2,3-c)pyrazole-5-carbonitriles and 3,6-diamino-4-(*N*-substituted indol-3-yl)pyrano(2,3-c)pyrazole-5-carbonitriles **(Figure 24)**. The newly synthesized compounds possess significant anti-inflammatory, analgesic and anticonvulsant activities.[38]



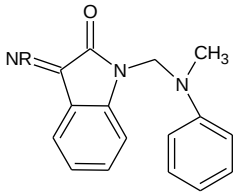
(Figure 24) 3-[(*N* -substituted indol-3-yl) methyleneamino]-6-amino- 4-aryl-pyrano (2,3-c)pyrazole-5-carbonitriles

B. Srinivas *et. al.* repotted the Synthesis and Screening of New Isatin Derivatives **(Figure 25)**, test compounds showed mild to moderate anti-inflammatory activity.[39]



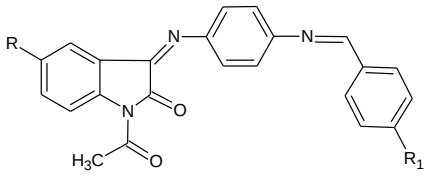
(Figure 25) Isatin Derivatives

Panda *et. al*. reported the synthesis of some isatin nucleus **(Figure 26)**, the synthesized compounds were screened for their analgesic and anti-inflammatory agents.[40]



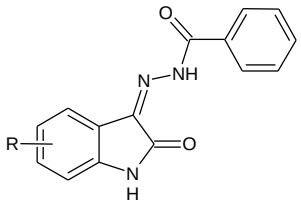
(Figure 26) Isatin Nucleus

Perumal Panneerselvam *et. al*. reported the synthesis of some novel Schiff's bases of 5-subsituted Isatin **(Figure 27)** These synthesized compounds were investigated for analgesic (Tailimmersion method), anti-inflammatory (carrageenan- induced paw oedema method) activity.[41]



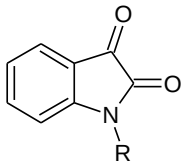
(Figure 27) Schiff's bases of 5-subsituted Isatin

Maharaj Pogula *et. al*. reported the synthesis of new isatin derivatives **(Figure 28)**, the synthesize derivatives were evaluated for In vivo anti-inflammatory activity the compounds VIa(R=H), VI d(R=5-Cl), Vie(R=5-F), VIh(R=6-Br) were found to be have moderate potent activity.[42]



(Figure 28) Isatin Derivatives

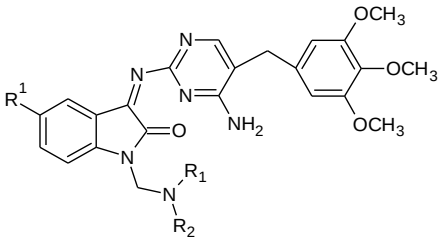
Mathues *et. al*. reported the synthesis of isatin derivatives **(Figure 29)**, the synthesized compounds a-f Inhibited the cyclooxygenase (COX-2) enzymes in RAW 264.7 activated cells.[43]



(Figure 29) Isatin Derivative

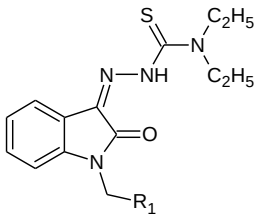
5. <u>Anti-HIV Activity</u>

Dharmarajan Sriram *et. al.* reported the synthesis of Aminopyrimidinimino isatin analogues Compound 1-cyclopropyl-6- fluoro-1,4-dihydro-4-oxo-7[[N4-[3'-(4'-amino 5'trimethoxybenzylpyrimidin-2'-yl)imino-1'-isatinyl] methyl]N1-piperazinyl]-3-quinoline carboxylic acid **(Figure 30)** emerged as the most potent broad-spectrum chemotherapeutic agent active against HIV, HCV. [44]



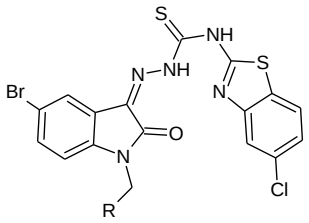
(Figure 30) Aminopyrimidinimino Isatin Analogues

Tanushree Ratan *et. al.* reported the synthesis of isatin *b*-thiosemicarbazone derivatives **(Figure 31)**, three compounds showed significant anti-HIV activity.[45]



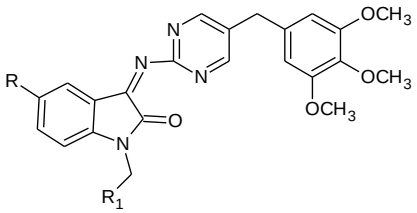
(Figure31) Isatin *b*-Thiosemicarbazone Derivatives

S. N. Pandey *et. al.* reported the synthesis of 1-[N, N-dimethylaminomethyl]isatin-3-[1'(6"-chloro benzothiazol-2"-yl)] by reacting 3-[-1-(-6-chloro benzothiazol-2 yl)thiosemicarbazone] and formalin with dimethylamine **(Figure 32)**. The synthesized compounds were screened for anti-HIV activity at HIV-1(III B) in MT-4 cells.[46]



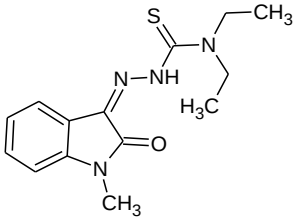
(Figure 32) 1-[N,N-dimethylaminomethyl]isatin-3-[1'(6''-chloro benzothiazol-2''-yl)]

S. N. Pandey *et. al.* reported synthesized Schiff bases of isatin derivatives with sulfodoxine **(Figure 33)**, all the compounds showed notable activity. The piperidino methyl compounds were found to be the most active ones in the series.[47]



(Figure 33) Schiff bases of isatin derivatives with sulfodoxine

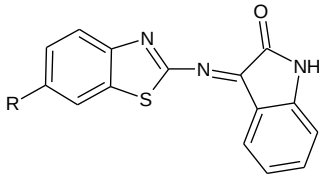
Y. Teiltz et. *al.* reported synthesized *N*-methyl isatin-β-4',4'-diethylthiosemicarbazone **(Figure 34)** and shown inhibition of HIV by their action on reverse transcriptase,viral structural proteins.[48]



(Figure 34) *N*-methyl isatin-β-4',4'-diethylthiosemicarbazone

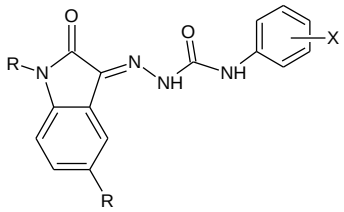
6. <u>CNS Depressant Activity</u>

Prince P Sharma *et. al.* reported the synthesis of some novel isatin schiff's bases **(Figure 35)**, these compound screened for anticonvulsant activity.[49]



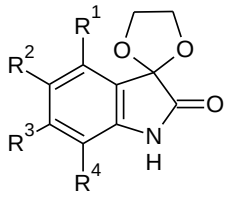
(Figure 35) Isatin Schiff's Bases

Sivakumar Smitha *et. al*. reported the synthesis of *N*-Acetyl/Methyl Isatin derivatives **(Figure 36),** the synthesized compounds were screened for their Anticonvulsant and Sedative-Hypnotic activities, the synthesized compounds showed significant sedative-hypnotic activity.[50]



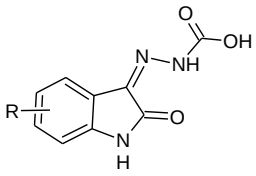
(Figure 36) *N*-Acetyl/Methyl Isatin derivatives

Gisele Zapata-Sudo *et. al.* reported the synthesis of novel isatin ketals **(Figure 37)** The dioxolane ketals were more potent than dioxane ketals for inducing sedative–hypnotic states, causing up to a three-fold increase in pentobarbital hypnosis. The dioxolane ketals produced sedation. Hypnosis and anesthesia were observed during intravenous infusion of 5′-chlorospiro-[1, 3-dioxolane-2,3′-indolin]-2′-one in conscious Wistar rats.[51]



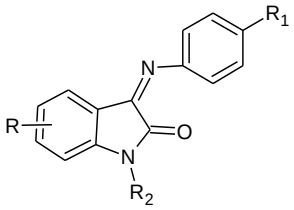
(Figure 37) Isatin Ketals

S N Pandey *et. al.* had been synthesized Isatin-3-hydrazone by istain, para bromo and phenoxy acetyl hydrazide with glaceial acetic acid **(Figure 38)** which shows anticonvulsant activity.[52]



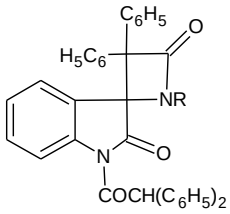
(Figure 38) Isatin-3-hydrazone

Krishan Nand Singh *et. al.* had been synthesized (3*Z*)-5-bromo-1-methyl-3-[(4-nitrophenyl)imino]-1,3-dihydro-2*H*-indol-2-one by reacting 5-substituted *N*-methyl/*N*-acetyl isatin and aromatic amine **(Figure 39)** with glacial acetic acid and was shown to possess good anticonvulsant activity.[53]



(Figure 39) (3*Z*)-5-bromo-1-methyl-3-[(4-nitrophenyl) imino]-1,3-dihydro-2*H*-indol-2-one

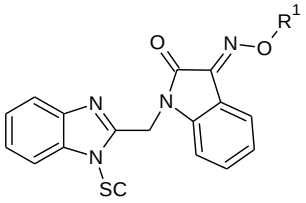
Singh *et al.* synthesized a series of isatin-based spiroazetidinones **(Figure 40)** and screened them for their anticonvulsant activity.[54]



(Figure 40) Isatin-Based Spiroazetidinones

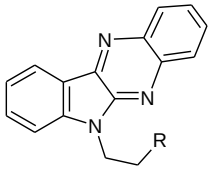
7. Antiviral activity

Ny Sin, Brian L *et. al*. were reported the Structure–activity relationships associated with a series of isatin oximes **(Figure 41)** These studies identified several compounds demonstrated antiviral activity in the BALB/c mouse model of RSV infection following oral dosing.[55]



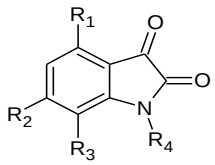
(Figure 41) Isatin Oximes

Shibinskya *et. al.* were reported the Synthesis of some new 6-(2-aminoethyl)-6-*H*-indolo [2, 3-b] quinoxalines **(Figure 42),** The selective index (SI) value as the integral parameter of the antiviral effectiveness was determined as the ratio of the CC50 to the IC50 (SI =CC50).[56]



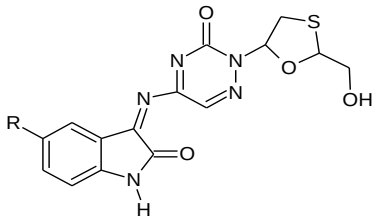
(Figure 42) 6-(2-aminoethyl)-6-*H*-indolo [2, 3-b] quinoxalines

Chen *et. al*. were reported synthesis of *N*-substituted isatin derivatives **(Figure 43).** Three compounds shown as potent and selective inhibitorsagainst SARS Coronaviral 3CL Protease with IC50 values ranging from 0.95 to 17.50 µM and isatin exhibited more potent inhibition for SARS Coronavirus Protease.[57]



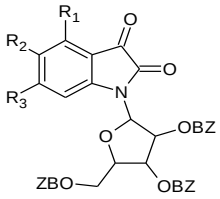
(Figure 43) *N*-substituted isatin derivatives

Sriram *et. al*. were reported the synthesis of a novel series of lamivudine prodrugs involving *N*4-substitution with isatin derivatives **(Figure 44)**, the synthesized compounds showed *in-vitro* antiretroviral activities and one compound was found to be equipotent to lamivudine with EC50 OF 0.0742 ± 0.04 µM.[58]



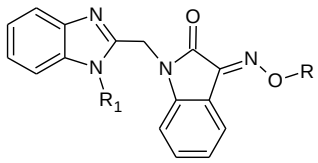
(Figure 44) Lamivudine Prodrugs Involving *N*4-substitution with Isatin Derivatives

Oliveira *et. al.* were reported Synthesis of a series of novel substituted isatin ribonucleosides **(Figure 45)** compounds showed antiviral activity on HSV-1 infected cells.[59]



(Figure 45) Substituted Isatin Ribonucleosides

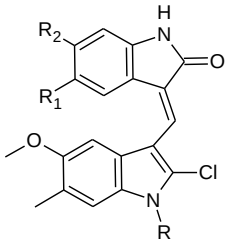
Sin N *et. al.* were reported synthesis of a series benzimidazole-isatin oximes **(Figure 46)**, the synthesized compounds 16a, 16b and 16c showed the antiviral activity and as inhibitors of respiratory syncytial virus (RSV) replication in cell culture with EC50 ranging from 18 to 50 µM, with excellent HLM stability.[60]



(Figure 46) Benzimidazole-Isatin Oximes

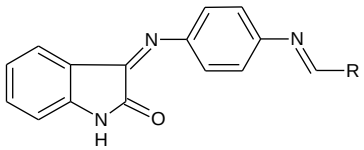
8. Antioxidant activity

Aldo Andreani *et. al*. were reported New isatin derivatives **(Figure 47).** The antioxidant activity of the compounds isolated was evaluated with two methods. 3, 3-Bis (4-amino-2, 5-dimethoxyphenyl)-1, 3-dihydroindol-2-one and the three antitumor agents showed a good chemical antioxidant activity.[61]



(Figure 47) Isatin Derivatives

C.R. Prakash *et. al*, reported the synthesis of some novel isatin derivatives and analogs (Figure:48), these compounds were screened for antioxidant activity, in this method, the compound 3-(4-(4-dimethylaminobenzylideneamino) phenylimino) indoline-2-oneshowed highest antioxidant activity.[62]



(Figure 48) Isatin Derivatives and Analogs

CONCLUSION

Isatin belongs to an important class of heterocyclic compounds and exhibits a wide range of biological properties and due to its potent activities, thus the synthesis of isatin is an area of current interest. Several methods for the synthesis of isatin have been reported. The most common classical methods for the synthesis of isatin are sandmeyer's method. Because, this method has some economic advantages, as the reagents are cheap and readily available, and the yields are usually high. Recently, the sandmeyer methodology has been modified by the incorporation of ethanol as a co-solvent. The survey of the literature revealed that, Isatin is a versatile lead molecule for designing potential bioactive agents, and its derivatives were reported to possess broad-spectrum antiviral, antimicrobial, cytotoxic, anti-inflammatory, CNS depressant, analgesic, antioxidant, anti HIV, antiviral activities. It has been observed so far, that the alterations on isatin moiety displayed valuable biological activities and these alterations can be utilized to develop potentially active agents in future investigations. The isatin substituted at

position-1 by mannich base and position-3 by Schiff base reaction, show potent pharmacological activities, such as antimicrobial, anticancer, anti-inflammatory and anticonvulsant activities.

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