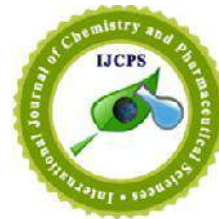




## Review Article

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## Isatine: A Versatile Heterocyclic Molecule

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### Abstract

Heterocyclic compounds are present in many of our medicines used today. This article gives detailed information on isatine which is one of the versatile heterocyclic molecule. It is a synthetically versatile molecule, a precursor for a large number of pharmacologically active compounds. Isatin and its derivatives have aroused great attention in recent years due to their wide variety of biological and pharmacological activities 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 purpose of this review is to provide an overview of the pharmacological activities of isatin and its synthetic and natural derivatives.

**Keywords:** Isatine, anticonvulsant, antimicrobial, antitumor

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## 1. Introduction

Heterocyclic chemistry has now become a separate field of chemistry with long history, present society and future prospects. The earliest compounds known to mankind were of heterocyclic origin. Life, like ours, is totally dependent on the heterocyclic compounds, it takes birth with purine / pyrimidine bases, which nourishes carbohydrates and in case of disease, is cured from medicines, many of which are heterocyclic in nature. Today, the heterocyclic chemistry delivers reagents and synthetic methods of its own traditional activity in synthesis of drugs, pesticides and detergents as well as into the related fields such as biochemistry, polymers and material sciences. Isatin or 1H-indole-2,3-dione is an indole derivative fig.1. Isatin (1H-indole-2,3-dione) was first obtained by Erdman and Laurent in 1841 as a product from the oxidation of indigo by nitric and chromic acids. The compound is found in many plants. In recent years, indole derivatives have acquired conspicuous significance due to their wide spectrum of biological activities [1]. It is an endogenous indole found in the mammalian brain, peripheral tissues and body fluids [2,3,4,5]. In nature, isatin is found in plants of the genus *Isatis*, in *Calanthe*. Isatin is the biologically active chemical produced by an *Altermones* sp. strain inhibiting the surface of embryos of the cardian shrimp

*Palaemon macrodectylus*, have a power to protect them from the pathogenic fungus *Lagenidium callinectes* [4]. The isatin moiety is also present in a range of compounds which can act as inhibitors of apoptosis [6,7], anticonvulsants [8] and other antiviral [9,10], anti-bacterial and anti-fungal [11] agents. It is possible that drugs containing the isatin moiety, may compete with endogenous isatin, and the latter have capacity to influence their therapeutic effect. Analysis of the isatin content of the body, its metabolic routes, and its interactions may not only be of importance for understanding more about the function of this endogenous regulator, but also for understanding its possible role as a functional agonist/antagonist of drugs.

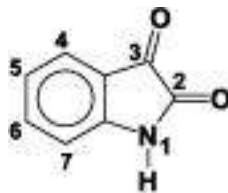


Figure 1.

### 1.1 Isatin origin and metabolism

The pathways of endogenous isatin formation fig.2 still require better experimental support there is in vitro evidence that isatin can be formed from indole. It is typically produced by tryptophan catabolism in the gut, and its catabolism involves microsomal cytochrome P450 enzymes present in gut walls [12]. Besides excretion with urine, the catabolic pathways of isatin include further, possibly spontaneous, oxidation followed by dimerization yielding the indigoid pigments, indigo and indirubin [12,13], hydrogen peroxide-dependent conversion into anthranilic acid [14] and NADPH-dependent reduction to 3-hydroxy-2-oxoindole [15]. All these compounds have been found in urine [14,15]. However, it remains unclear whether indigoid formation precedes urinary excretion and aerobic transformation of the urinary components. During in vitro oxidation of indole by cytochrome P450 enzymes, isatin was an intermediate, which was then transformed into the indigoid pigment major end products [12].

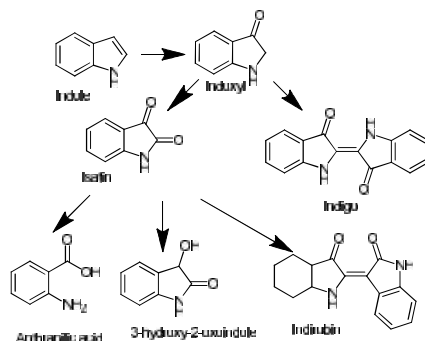


Figure 2: Scheme of isatin origin and metabolism

## 2. Chemistry of isatin and its derivatives

### 2.1 Fundamental reactivity of isatin and its derivatives

Isatin ring system consists of pyrrole ring fused with benzene ring. Pyrrole ring is a five-member ring containing one nitrogen in the ring system. The presence of several reaction centers in isatin and its derivatives render them capable of participating in a large number of reactions. The keto group at position 2 and particularly at position 3 can enter into addition reactions at the C-O bond and into condensation reactions. Through the primary amine group, compounds of the isatin series are capable of entering into N-alkylation and N-acylation and into Mannich and Michael reactions [16]. These reactions are described in detail below.

### 2.2 Carbonyl reaction

Schiff bases of isatin can be synthesized by condensation of the keto group of isatin with different aromatic primary amines fig.3 [17]. Bis-Schiff bases of isatin can be prepared by reactions with aromatic diamines in the presence of catalytic amounts of glacial acetic acid in EtOH under reflux conditions [18,19].

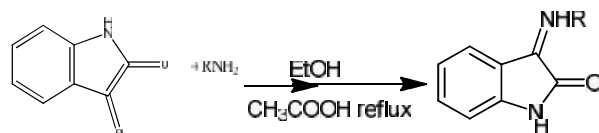


Figure 3: Schiff reaction

### 2.3 N-Alkylation

N-substituted isatins have been frequently used as intermediates and synthetic precursors for the preparation of a wide variety of heterocyclic compounds. N-substituted isatin derivatives can be synthesized via substitution reaction. The reaction between isatin and haloalkanes can be carried out in NaOEt using EtOH as solvent or in the presence of NaOH using DMF as solvent fig.4 [20].

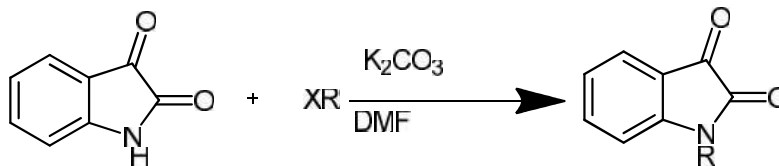


Figure 4: N Alkylation

#### 2.4 N-arylation

N-Arylisatin can be obtained from isatin in good yields by reaction with  $\text{Ph}_3\text{Bi}(\text{OAc})_2$  and CuO under an inert atmosphere [21] or from aryl bromides and cupric oxide [22].

#### 2.5 N-methyleneamino derivatives

The Mannich reaction is readily applied to isatins. The Mannich bases of this reaction, i.e the N-aminomethyl isatins, can also be prepared from the N-hydroxymethyl derivatives by reaction with an amine [23] or by reaction with acetyl chloride to yield N-chloromethylisatin which can be further treated with potassium phthalimide or alcohols to give the corresponding N-phthalimidomethyl or N-alkoxymethyl isatins [24]. The Mannich reaction can also be performed with isatin derivatives, such as isatin-3-hydrazone [25] and isatin-3-thiosemicarbazones [26].

#### 2.6 N-acylation and N-sulfonylation

The synthesis of N-acylisatins under a variety of conditions has been described using acyl chlorides or anhydrides under reflux, either alone [27] or using perchloric acid in benzene, triethylamine in benzene [28], pyridine in benzene [29], or triethylamine in chloroform [30], [31] as catalysts; or by conversion of isatin to sodium isatide using NaH in toluene under reflux and subsequent reaction with acyl chlorides [32].

The use of diacyl chlorides, e.g. oxalyl chloride [33], octanedioyl or nonanedioyl chlorides [34], yields bis-acylisatins. Attempts to use 2, 2-dimethylmalonyl chloride to furnish 2,2-dimethylmalonyl-bis-isatin failed, and led instead to an unusual tricyclic compound which was characterized by spectroscopic methods and by X-ray diffraction [35] fig.5

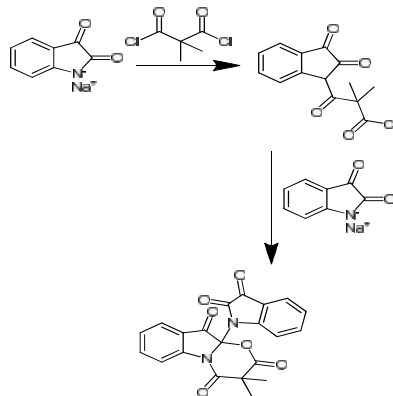


Figure 5: Tricyclic compound

N-Sulfonylisatins are obtained from the reaction of isatin and sulfonyl chlorides by applying the same methodologies as used for obtaining 1-acylisatins. For example, 1-tosylisatin is formed in 71-74% yield by mixing tosyl chloride with isatin in the presence of  $\text{Et}_3\text{N}$  or with the sodium salt of isatin [36].

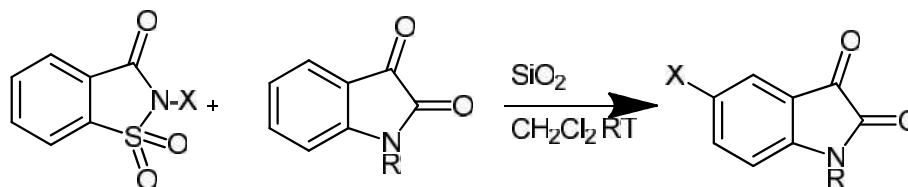
#### 2.7 N-Halo derivatives

The treatment of isatin with sodium hypochlorite in acetic acid leads to 1-chloroisatin, which is a mild effective oxidizing agent for the conversion of alcohols to aldehydes and ketones [37] and of indoles to 3-chloroindoles without formation of by-products [38]. N-[phenyliodine(III)] bisisatin can be obtained from the sodium salt of isatin and phenyliodine (III) bistrifluoroacetate in 85% yield. This compound is a member of a group of iodine (III) imides, have a mild oxidizing properties [39].

#### 2.8 Electrophilic aromatic substitution of isatin

In 1925, Calvery, Noller and Adams reported the nitration of isatin at the C-5 position using fuming nitric acid in concentrated sulfuric acid [40]. However, a more convenient method to synthesize 5-nitroisatin involves the drop wise addition of a solution of isatin in sulfuric acid to a solution of potassium nitrate dissolved in concentrated sulfuric acid at  $0-4^\circ\text{C}$  [41]. 5-Nitroindoline-2,3-dione has been prepared by refluxing of indoline-2,3-dione with a

mixture of 95% sulfuric acid and 70% nitric acid in water bath at 60°C for 1 h [42]. Mono-halogenation (-Cl, -I, -Br) of isatin can be achieved via reacting N-halosaccharins with isatin in the presence of SiO<sub>2</sub> at room temperature to specifically produce the 5-halo derivatives as reported by De Souza et al. fig.6 [43]. This method is an alternative to the use of highly toxic and corrosive Cl<sub>2</sub> and Br<sub>2</sub>, which can lead to other products such as 5,7-dibromo-3,3-dialkoxyindole when the bromination of isatin is attempted in alcoholic media [44]. Moreover, others have reported using the relatively stable reagent trichloroisocyanuric acid (TICA), as an efficient new source of electrophilic chlorine and this provides a relatively inexpensive route to the chlorination of isatins [45, 46].



**Figure 6:** Monohalogenation of isatin (-Cl, -Br, -I)

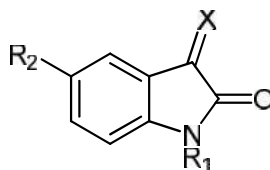
### 3. Isatin with its analogues and drugs

Although the interaction between isatin and its analogues, and drugs at specific biological targets still requires detailed analysis, there is evidence that isatin protects MAO B against irreversible inhibition by mechanism based inhibitors phenelzine [47] and pargyline. Deprenyl in its turn inhibited isatin binding to GAPDH and this effect was rather specific because the other mechanism based MAO inhibitor, tranylcypromine, was ineffective [48]. Deprenyl was somewhat more effective in inhibition of RNase activity of GAPDH than isatin, and during their combined addition the effect of RNase inhibition was somewhat less pronounced than in the case of independent action of deprenyl [48]. Thus it is possible that being less effective than the drug, deprenyl, isatin may attenuate some of its effects. 5-Hydroxyisatin and to a lesser extent N-methylisatin inhibited ubiquitin binding to amino-isatin immobilized onto a cuvette of optical biosensor Biacore [49]. The latter suggests that endogenous isatin may attenuate interaction of some biological targets with drugs containing isatin moiety and therefore influence expected therapeutic effect.

## 4. Crystallographic and spectral analysis

### 4.1 Crystallographic data

The crystallographic data for isatin reveals that it is almost planar, with a bond length between the two carbonyls of 1.55 Å. This value was attributed to lone pair electron repulsion between the two oxygen atoms [50, 51], though this interpretation was subsequently refuted by comparison of bond lengths of cis and trans 1,2-diketones where no systematic or substantial difference between the bond lengths was observed [52]. A similar bond length was observed for 1-acetylisatin [53], 1-chloroacetylisatin [54], diethyl (2,3-dihydro-2-oxo-3-indolylidene) propanedioate [55], 1,1-oxalylbisatin [56] and 1-methylisatin [57], as well as in derivatives where C-3 is tetrahedral, such as 3,3-dichloro-1H-indol-2(3H)-one [58] and 5-bromospiro-[1,3-dioxolano-2,3-indolin]-2-one [59], as well as in 3-methyleneoxindoles [60] (Table 1) and in products obtained by nucleophilic ring opening of 1-acetylisatin, where the 1,2-dicarbonyl system assumes a s-trans conformation [61]. The crystal structure of 2-methoxy isonitrosoacetanilide, an intermediate in the Sandmeyer procedure for the synthesis of 7-methoxyisatin has also been determined [62].



**Table 1**

X	R <sub>1</sub>	R <sub>2</sub>	C <sub>2</sub> -C <sub>3</sub>
O	H	H	1.55
O	Ac	H	1.538
O	Me	H	1.545
Cl, Cl	H	H	1.556
OCH <sub>2</sub> CH <sub>2</sub> O	H	Br	1.539
CHCH=C(CH <sub>3</sub> ) <sub>2</sub>	H	H	1.508

#### 4.2 Infrared spectroscopy

The infrared spectrum of isatin shows two strong bands at 1740 and 1620  $\text{cm}^{-1}$  corresponding to the carbonyl stretching vibrations. A broad band occurs at 3190  $\text{cm}^{-1}$  due to the N-H stretching, and it is accompanied by many sub-bands, all of which are moved to a lower frequency on deuteration, which also affects several bands in the region of 1400-1100  $\text{cm}^{-1}$ , associated with N-H in-plane bending [63, 64]. Although the  $\text{C}=\text{O}$  values are not modified by N-alkylation, N-acetylation leads to a hypsochromic shift of the lactam absorption of about 50-70  $\text{cm}^{-1}$ , while the ketone band shifts to 1750  $\text{cm}^{-1}$ , as a consequence of the extension of conjugation of the nitrogen lone pair with the acetyl group [65]. On the other hand, 3-methyleneoxindoles show a bathochromic shift for the lactam band of around 20 to 30  $\text{cm}^{-1}$ , this shift being greater when there are groups at the C-3 position, such as OH, which can form a hydrogen bond with the lactam carbonyl. In this case,  $\text{C}=\text{O}$  appears at 1660  $\text{cm}^{-1}$  [66]. 3,3-Difluoroindoles reveal a hypsochromic shift of about 20  $\text{cm}^{-1}$  in comparison to the respective isatin [67].

#### 4.3 $^1\text{H}$ NMR spectroscopy

The  $^1\text{H}$  NMR spectrum of isatin shows the signals of the aromatic nucleus signals at 6.86 (doublet), 7.00 (triplet), 7.47 (doublet) and 7.53 (triplet) ppm (DMSO- $d_6$ ), corresponding to H-7, H-5, H-4 and H-6 respectively. While this pattern is not altered by N-alkylation, N-acetylation leads to a downfield shift of all the signals, but H-7 most significantly due to the anisotropic effect of the carbonyl group. A downfield shift of H-4 by about 0.6-1.0 ppm appears in a similar fashion of 3-methyleneoxindoles bearing cyano groups, with no significant effect over the other signals [68, 69] (Table 2).

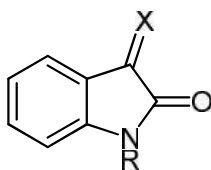


Table 2

X	R	H-4	H-5	H-6	H-7	$\text{CH}_3\text{CO}$	Solvent
O	H	7.50d	7.07t	7.60t	6.92d	-	DMSO- $d_6$
O	Me	7.59d	7.12t	7.61t	6.91t	-	DMSO- $d_6$
O	Ac	7.27d	7.33t	7.70t	8.38d	2.73s	DMSO- $d_6$
$\text{C}(\text{CN})_2$	H	7.87d	7.12t	7.59t	6.94d	-	DMSO- $d_6$

#### 4.4 $^{13}\text{C}$ NMR spectroscopy

The  $^{13}\text{C}$  NMR spectrum of isatin was the object of controversy in the literature. Different proposals for assignment of the signals have been published [70, 71, 72, 73]. This question was resolved by the abstention of the HETCOR spectrum, which revealed that the assignment proposed by Galasso, based on quantum mechanical calculations using the CNDO/S wave functions, was correct [72]. This result allowed the correction of the assignments of the spectra of 1-acetylisatin [74, 75, 76] and of 1-methylisatin and 3-dicyanomethylene oxindole [77, 78]. Again, acetylation of N-1 implies an important change in the pattern of the spectra, with a deshielding effect over C-7 [74] (Table 3).

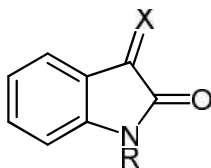


Table 3

X	O	O	O	$\text{C}(\text{CN})_2$
R	H	Ac	Me	H
C-2	159.6	157.8	158.1	163.6
C-3	184.6	180.1	183.2	146.4
C-3a	118.0	119.1	117.2	137.8
C-4	124.8	126.1	125.0	122.9
C-5	123.0	125.2	123.7	118.5
C-6	138.6	138.6	138.4	125.7
C-7	112.4	118.1	109.9	111.6
C-7a	150.9	148.5	151.3	150.4
Reference	72	74	78	78

#### 4.5 - Mass spectrometry

The electron-impact mass spectra of isatin [79], 1-alkylisatins [80] and derivatives, such as hydrazones [81], usually show an intense molecular ion peak. In the case of 3,3-dissubstituted oxindoles [82], the base peak corresponds to the loss of the substituent at C-3. A peak corresponding to the loss of CO (ion a) can also be observed, whose intensity decreases with the increase in size of the alkyl chain of 1-alkylisatins [83]. Ion a usually loses HCN, leading to a fulvene ion (ion b). An arene aziridine is also observed (ion c), which arises from a second loss of CO [84-86]. The ions b and c are also observed in the gas-phase pyrolysis of isatin [87]. In a general manner, the mass spectra of 3-substituted isatins show a sequential loss of neutral molecules [88] fig.7.

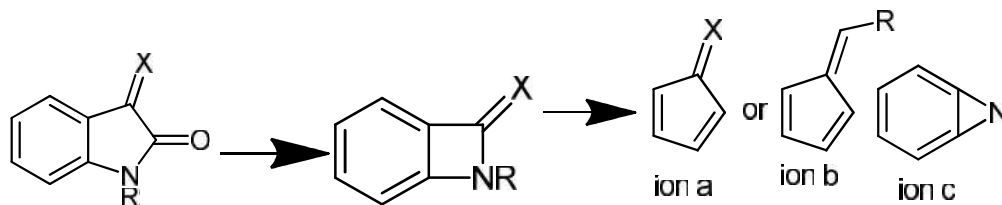


Figure 7: Mass spectra of 3-substituted isatins

A different pattern is observed in the mass spectra of isatin-3-oximes, where a peak corresponding to the loss of CO is not found; this is attributed to a Beckmann rearrangement of the molecular ion leading to a heterocyclic ring opened ion [89]. In the case of the acetylated derivatives, the molecular ion obtained is usually of low intensity. The fragmentation pattern shows loss of ketene (ion d) and of CO (ion e) fig. 8.

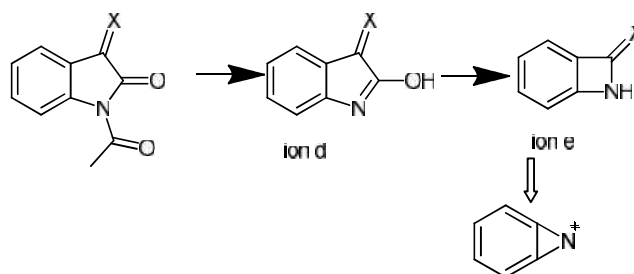


Figure 8: Fragmentation pattern of Isatin

#### 4.6 - $^{14}\text{N}$ NQR

The  $^{14}\text{N}$  nuclear quadrupole resonance of isatins and derivatives has been thoroughly studied as this method can furnish important information with respect to the electronic distribution around the nitrogen atom. The results obtained confirmed the existence of H bonds between isatin molecules in the solid state [90], and showed a linear relationship between the depletion of charge of the C-N bonds and the electron withdrawing character of the substituents attached to the aromatic nucleus, as represented by the inductive Taft parameter [91]. The results also revealed that the lone pair of electrons of the nitrogen atom is involved in conjugation with the aromatic ring [92].

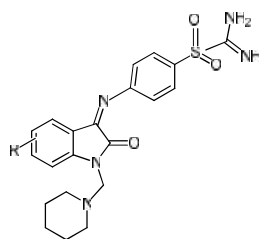
#### 4.7 - Further spectroscopic data

The electronic absorption spectra of isatin [93-95], isatin-3-arylhydrazones [96], isatin and 1-methylisatin anion radicals [97] were studied and correlated with theoretical calculations with good results. The electron spin resonance spectra of the isatin anion radical was also recorded and revealed that the monoanion radical exists in equilibrium with the dianion radical in the solvents employed [97]. DSC thermograms of some alkylisatins were also recorded [98].

## 5. Biological activity

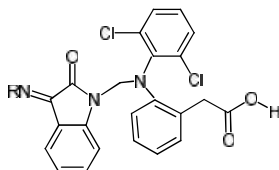
### 5.1. Antimicrobial activity

Antimicrobial drugs are effective in the treatment of infection because of their selective toxicity; they have the power to injure or kill an invading microorganism without harming the host [99]. It is evident from literature that isatin derivatives are known to be associated with broad spectrum of biological activities like antibacterial, antifungal. Bis-schiff bases, N-mannich bases, phthalimidoxy substituted and spiro-thiazolidinone derivatives of isatin & spiroindoles and imidazolines derivatives possess antimicrobial activity and it act against variety of gram +ve and gram -ve bacteria, some fungi and viruses. 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 fig. 9, all compounds exhibited very significant and better antibacterial activity [100].



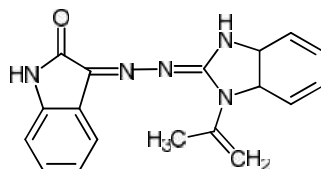
**Figure 9:** Schiff's and N-Mannich bases of isatin

V. Ravichandran et al. reported the synthesis of mannich bases of isatin and its derivatives with 2-[(2, 6-dichlorophenyl) amino] Phenyl acetic acid fig. 10, all the synthesized compounds were tested for their antibacterial activities against Gram + and Gram - bacteria, and antifungal activities [101].



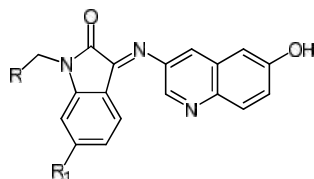
**Figure 10:** Mannich bases of isatin

Madhu et al. reported the synthesis of some new isatin derivatives fig. 11, tested compounds showed the most favorable antimicrobial activity against *S. aureus* [102].



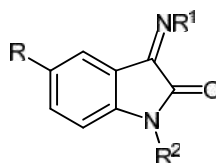
**Figure 11:** Isatin derivative

Chhajed S.S et al. reported the synthesis of schiff and mannich bases of isatin and its derivatives with quinolin fig. 12, investigation of antimicrobial activity of the compounds was made by the agar dilution method, and the compounds are significantly active against bacteria and fungi [103].



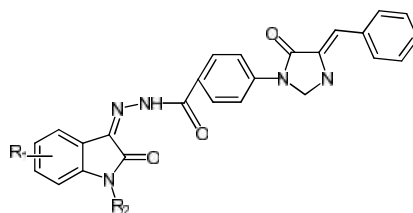
**Figure 12:** Schiff's and Mannich Bases of Isatin

Seshaiah Krishnan Sridhar et al. reported the synthesis of hydrazones, schiff and mannich bases of isatin derivatives fig. 13, 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 [104].



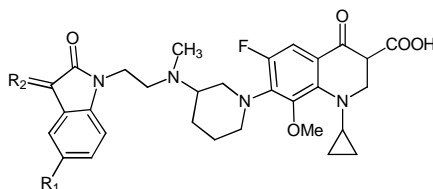
**Fig. 13 Schiff's and Mannich Bases of Isatin**

Sanjay Bari et al. reported the synthesis and antimicrobial activity of some new isatin derivatives fig. 14, antimicrobial activity of compounds with 5-Br substitution showed the most favorable antimicrobial activity [105].



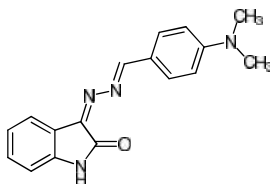
**Figure 14:** Isatin Derivatives

Lian-Shun Feng, et al. reported the synthesis of balofloxacin ethylene isatin derivatives, these derivatives fig. 15, were evaluated for their in vitro activity against some mycobacteria, all of the synthesized compounds were less active than the parent 8-OCH<sub>3</sub> ciprofloxacin against *Mycobacterium smegmatis* CMCC 93202, but most of the methylene isatin derivatives were more active than 8-OCH<sub>3</sub> ciprofloxacin, ciprofloxacin, isoniazid and rifampin against MTB H37Rv ATCC 27294 [106].



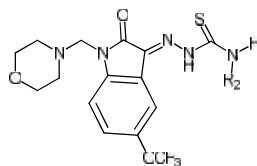
**Figure 15:** Balofloxacin Ethylene Isatin Derivatives

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 fig.16, the complexes show activity against mycobacterium tuberculosis strain H37Rv [107].



**Figure 16:** Novel Isatin Schiff Base Ligand

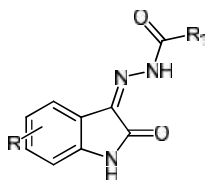
Ozlen Guzel et. al. reported the synthesis 5-methyl/trifluoromethoxy-1H-indole-2, 3-dione 3- thiosemicarbazone derivatives fig. 17, the synthesized compounds were evaluated for in vitro antituberculosis activity against mycobacterium tuberculosis H37Rv [108].



**Figure 17:** 5-methyl/trifluoromethoxy-1H-indole-2, 3-dione 3-thiosemicarbazone derivatives

## 5.2. CNS depressant activity

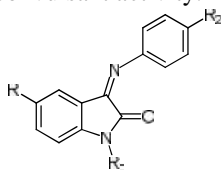
Depression is defined as disorders of mood rather than disturbances of thought or cognition. Depression accompanied by hallucination and delusion [109]. Some of isatin derivatives show CNS depressant activity. Semicarbazones, thiosemicarbazole, heterocyclic derivatives of isatin and Isatin-based spiroazetidinones shows anticonvulsant activity. S N Pandey [110] et al had been synthesized Isatin-3-hydrazone fig.18 by isatin, parabromo and phenoxy acetyl hydrazide with glacial acetic acid which shows anticonvulsant activity.



**Figure 18:** Semicarbazone isatin derivatives



Krishan Nand Singh [111] et al had been synthesized (3Z)-5-bromo-1-methyl-3-[(4-nitrophenyl) imino]-1,3-dihydro-2H-indol-2-one fig.19, by reacting 5-substituted N-methyl/N-acetyl isatin and aromatic amine with glacial acetic acid and was shown to possess good anticonvulsant activity.



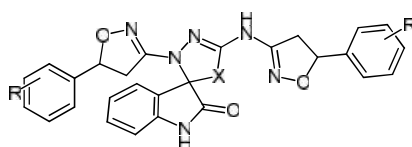
**Figure 19:** Schiff bases of isatin derivatives

Singh et al. synthesized a series of isatin-based spiroazetidinone fig. 20 and screened them for their anticonvulsant activity [112].

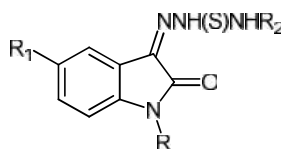


**Figure 20:** Isatin-Based Spiroazetidinones

Ashok Kumar [113] et al had been synthesized 3-Spiro[1', 3', 4'-oxa/thiadiazolyl-2'-{5''-(substitutedphenyl-3''-amino)-4'-{5''-(substituted phenylisoxazolynyl)}}-5'-indol-2-ones fig. 21 by the reaction of 3-Spiro-[1', 3', 4'-oxadiazolyl-2'-{1''-acetyl-5''-(2-hydroxyphenyl-3''-amino)-4'-{1''-acetyl-5''-(2-hydroxyphenyl) pyrazolynyl}}]-5'-indol-2-ones with methanol, hydroxyl amine and NaOH solution which shows anticonvulsant and antipsycotic activity. 3-aryloxy, arylthioxy acetyl hydrazono-2-indolinones fig. 22 had been synthesized by Gursoy and Karali [114] et al.

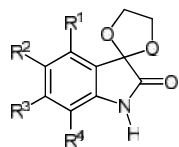


**Figure 21:** Pyrazolynyl / isoxazolynyl indol-2-ones derivatives



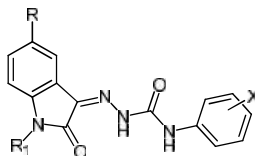
**Figure 22:** Hydrazono-2-indolinones

Gisele Zapata-Sudo et. al. reported the synthesis of novel isatin ketals fig. 23. 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 [115].



**Figure 23:** Isatin Ketals

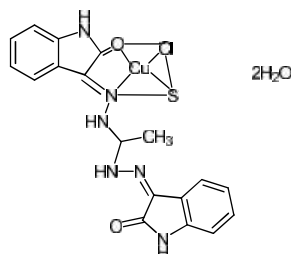
N-methyl/acetyl-5-(un)-substituted isatin-3-semicarbazones fig. 24 were formed by Sivakumar Smith [116] and coworkers by reacting N-methyl/acetyl isatin, 5-bromo/nitro-N-acetyl isatin and p-substituted phenyl semicarbazides. The compounds possess anticonvulsant and sedative activity.



**Figure 24:** Thiosemicarbazole isatin derivatives

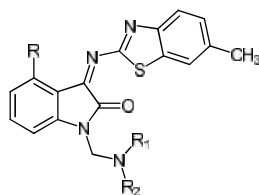
### 5.3. Anticancer activity

Cancer is a disease characterised by uncontrolled multiplication and spread of abnormal forms of the body's own cells. From literature survey it is well known that isatin heterocycles exhibit manifold importance in the field of medicinal chemistry as a potent chemotherapeutic agent. Bis-isatin thiocarbohydrazone Metal Complexes, Bis-Isatin Thiocarbohydrazone Metal Complexes, 3- o-Nitrophenyl hydrazones of isatin possess cytotoxicity activity. Co(II), Ni(II), Cu(II), and Zn(II) complexes of thiocarbohydrazone ligand fig. 25 were formed by reacting with ethanolic solution of metal chloride or aqueous ethanolic solution of metal acetates with specific amount of the ligand. Compound shows antitumour activity [117].



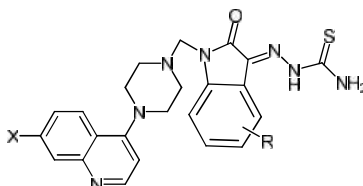
**Figure 25: Bis-Isatin Thiocarbohydrazone Metal Complexes**

Hoyun Lee et al. reported the hybrid pharmacophore design and synthesis of isatin benzothiazole analogs fig. 26, all compounds examined were quite effective on all the cancer cell lines examined, the compounds 4-bromo-1-diethyl aminomethyl-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 [118].



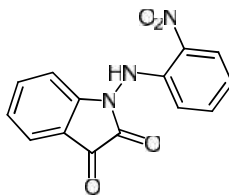
**Figure 26: Hybrid Pharmacophore of Isatin Benzothiazole Analogs**

V. Raja Solomon et al. reported the design and synthesis of 4-piperazinylquinoline: a hybrid Pharmacophore approach fig. 27, 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 [119].



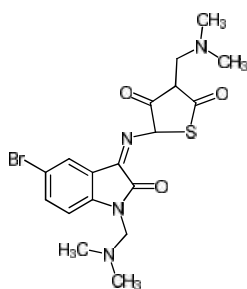
**Figure 27: 4-piperazinylquinoline**

F. D. Popp et. al. had been synthesized 3-o-nitrophenyl hydrazones of isatin by the condensation of isatin with o-nitrophenyl hydrazine fig. 28 which shows anticancer activity [120].



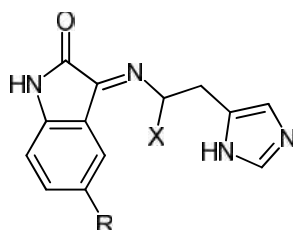
**Figure 28: Isatin with O-Nitrophenyl Hydrazine**

N.H Eshba [121] et al had been synthesized 5-(2-oxo-3-indoliny) thiazolidine-2,4-dione fig. 29 having positions 1 and 3 of the isatin and thiazolidine rings, respectively, substituted by various Mannich bases and had been shown anticancer activity.



**Figure 29:** 5-(2-Oxo-3-indolinylidene) thiazolidine-2,4-dione

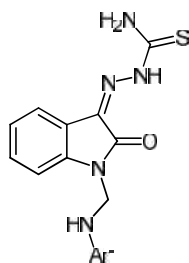
Abadi et al. reported the synthesis of 3-substituted-2-oxoindoles fig. 30, compounds were tested for potential antiangiogenic properties, all the final compounds were tested for their in vitro antitumor properties against MCF7 (breast), NCI-H460 (lung) and SF268 (CNS) cancer cell lines [122].



**Figure 30:** 3-substituted-2-oxoindoles

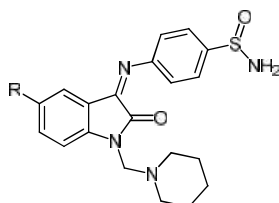
#### 5.4 Analgesic and anti-inflammatory activity

Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbial agents [123]. It inhibits Prostaglandin synthesis at the site of injury [124]. Analgesic drug is used to control the pain. Prostaglandin E2 (PGE2) is thought to sensitize nerve ending to the action of bradykinin, histamine and other chemical mediators released locally by the inflammation process [123]. thiosemicarbazino isatin, Isatin-3-p-chlorophenylimine, Azetidinone derivatives of isatin possess analgesic and anti-inflammatory activity. The anti-inflammatory activity was studied by Carrageenan induced paw oedema method and analgesic activity studied by tail flick and hot plate method. 1-(phenylaminomethyl)3-thiosemicarbazino isatin fig. 31 was formed by 3-thiosemicarbazino isatin and appropriate aromatic amine reacted with formaldehyde. The compound possesses analgesic activity [125].



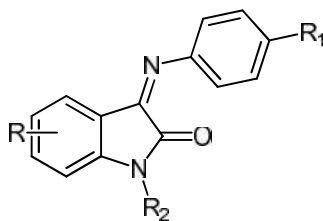
**Figure 31: Thiosemicarbazino isatin**

B. Durga Prasad et. al. reported the synthesis, characterization of isatin derivatives fig. 32, all the synthesized isatin derivatives have been investigated for their anti-inflammatory activity [126].



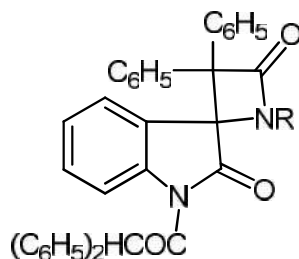
**Figure 32: Isatin Derivatives**

B. Srinivas et. al. reported the Synthesis and Screening of New Isatin Derivatives fig. 33, test compounds showed mild to moderate anti-inflammatory activity [127].



**Figure 33:** (3Z)-5-bromo-1-methyl-3-[(4-nitrophenyl) imino]-1,3-dihydro-2H-indol-2-one

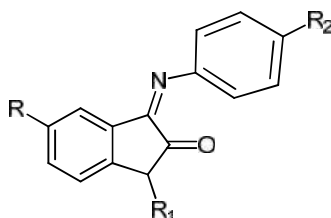
Panda et. al. reported the synthesis of some isatin nucleus fig. 34, the synthesized compounds were screened for their analgesic and anti-inflammatory agents [128].



**Figure 34:** Isatin-Based Spiroazetidiones

### 5.5 Antianxiety activities

Anxiety is an unpleasant of tension, apprehension, or uneasiness a fear that seems to arise from a sometimes unknown source. The physiological symptoms of severe anxiety are similar to those of fear and involve sympathetic activation. It enhances the response to GABA by facilitating the opening of GABA-activated chloride channel. Isatin derivative like Schiff bases of N-methyl and N-acetyl isatin, Spiro benzodiazepines, 5-Hydroxy isatin and isatinic acid act as antianxiety agents. G.S.Palit [129] et al had been synthesized Schiff bases of N-methyl and N-acetyl isatin derivatives fig. 35. They studied the behavioral effects of isatin, a putative biological factor in rhesus monkeys. Isatin, one of the constituents of tribulin, a postulated endocoid marker of stress and anxiety, has been shown to induce anxiety in rodents.



**Figure 35:** Schiff bases of isatin

### 5.6 Anticonvulsant activity

Isatin is endogenously produced in the central nervous system. Its effect as a selective monoaminoxidase (MAO) inhibitor is its most potent in vitro action Isatin has been reported to possess anti-MES (maximal electroshock) activity and it appears to have a range of actions in the brain [130]. Derivatives have also been proposed as antiepileptic drugs [130]. Many isatin derivatives, such as isatin hydrazone, isatin Mannich bases, isatin based spiroazetidiones and 3-(methylene) indolin-2-ones, have also been reported to possess neuroprotective activity [131]. 3-Hydroxy-3-substituted oxindoles derived from isatin, 3-(4-thiazolidone-2-hydrazone)-isatin, 1-morpholinomethyl-3-(aryloxy-arylthio-acetyl hydrazone)- isatin and isatin based spiroazetidiones are known to possess anticonvulsant activity. Therefore, it would be expected that hydrazones, Schiff and Mannich bases of isatin would also exhibit significant anticonvulsant activity.

## 6. Conclusion

The creation of novel isatin derivatives as drug targets is an active area of medicinal chemistry. The review compiles published data on the biological action of new isatin derivatives. 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.

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