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A Review On Isatin and Its Pharmacological Profile

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ABSTRACT

Isatin is an endogeneous and an important class of heterocyclic compound. It possess indole nucleus having both keto and lactam moiety with a diverse pharmacological properties like antimicrobial, antitubercular, anticonvulsant activity etc. Isatin derivatives are synthetically important substrates, which can be used for the synthesis of a large variety of heterocyclic compounds, and as raw material for drug synthesis. Recently, isatin derivatives have attracted strong interest in organic and medicinal chemistry due to their potent biological and pharmacological activities. The purpose of this review is to provide information on the pharmacological activities of isatin and its derivative.

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

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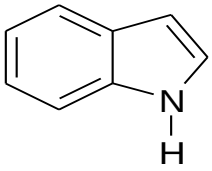
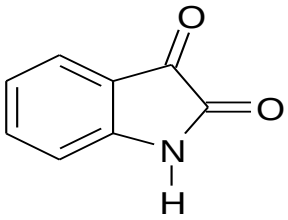
INTRODUCTION

Isatin or 1H-indole-2,3-dione is an indole derivative and an important group of heterocyclic compounds which are biologically active and of significant importance in medicinal chemistry.[1] 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. It is a synthetically versatile substrate, where it can be used for the synthesis of a large variety of heterocyclic compounds, such as indoles and quinolines, and as a raw material for drug synthesis.



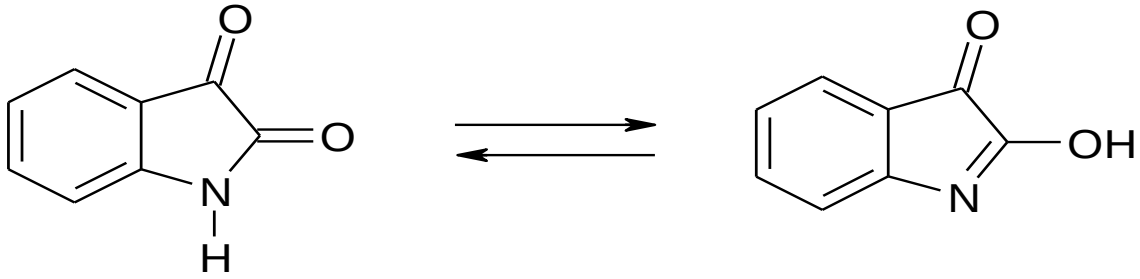
Indole



Isatin

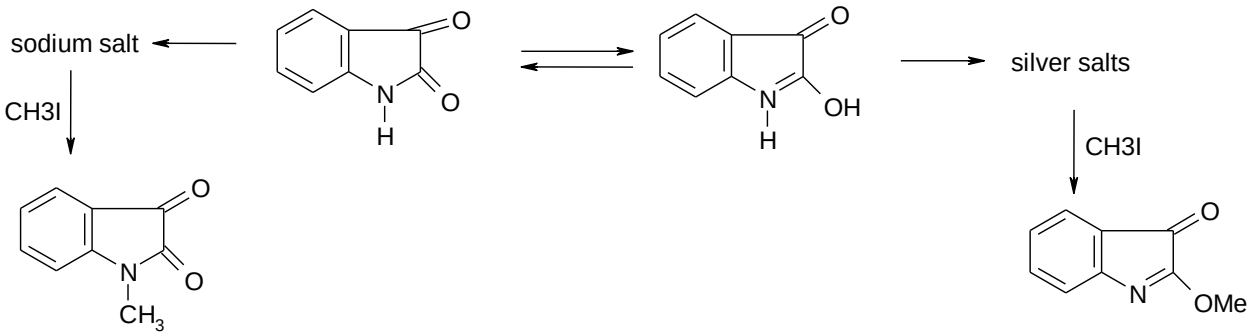
Three reviews have been published regarding the chemistry of this compound: the first by Sumpter in 1954, a second by Popp in 1975 and the third on the utility of isatin as a precursor for the synthesis of other heterocyclic compounds.[2] It occurs in the leaves and roots of the *Strobilanthes cusia* (Nees) and was first isolated from the plants of the Isatins *tinctoria, Couroupita guianesis* and *Calanthe discolor* in 1840.[3] These plants are abundant in northern and central china and are of ethnic importance in traditional therapeutics. It has also been found as a component of the secretion from the parotid gland of Bufo frogs and other biotic like Caribbean tumorigenic plant, *Melochia tomentosa*, fungi, marine mollusks[3] & in humans as it is a metabolic derivative of adrenaline.

Isatin ring system consists of pyrrole ring fused with benzene ring. Pyrrole ring is a five-membered ring containing one nitrogen in the ring system.[4] It was the first compound to exhibit the phenomenon of tautomerism. It is an example of *lactam-lactim* tautomerism system; the two forms are:



Lactam Lactim

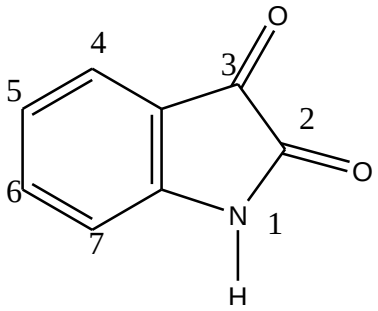
The existence of the above tautomeric system in isatin is proved by the formation of N- and O-alkyl isatins. The former is formed by treating the sodium salt of isatin with methyl iodide whereas the latter is formed by treating the silver salt of isatin with methyl iodide.[5]



Isatin moiety shows biological activities like antimicrobial, CNS depressant, anti-HIV, cytotoxicity, anti-inflammatory, analgesic, antitubercular, anticonvulsant and many other activities and are capable of crossing the blood-brain barrier.[4] It was identified in animals as a major component of the endogenous monoamine oxidase inhibitor. The various substituent at third position of the isatin which were reported various substituted phenyl ring moieties, heterocyclic rings and aliphatic system.[1]

The good biological profile of isatin derivatives prompted us to synthesize some mannich bases of isatin and evaluate their antibacterial, antifungal activities etc. Schiff bases are used as substrates in the preparation of number of industrial and biologically active compounds and mannich bases of isatin have gained importance due to their application in pharmaceutical chemistry.[6]

STRUCTURE ACTIVITY RELATIONSHIP



1. Substitution at position 5, 6 and 7 improves the CNS activity.[7]

2. Nitration at C5 enhanced the anticancer activity by a factor 4, while the addition of a methoxy group mildly increases the cytotoxicity.

3. Halogenation yielded most active compounds with 5-bromo, 5-iodo, 5-fluoro isatin being 5-10 times more active than the unsubstituted parent compound.[8]

4. N-alkylation and acylation can be done on position 1.

5. If substituted phenyl ring is substituted at position 3, then it enhances antimicrobial activity.[9]

6. Little variation at position 2, 3 produce different degree of biological activity.[7]

PHARMACOLOGICAL ACTIVITY

1. **Antimicrobial Activity**

Antimicrobial drugs are effective in the treatment of infection because of their selective toxicity; that is, they have the ability to injure or kill an invading microorganism without harming the host.[10] It is evident from literature that isatin derivatives are known to be associated with broad spectrum of biological activities like antibacterial, antifungal. Isatin analogues are important due to their therapeutic potential against a variety of pathogenic microbes. In a study, thiosemicarbazone and dispiropyrrolidine derivatives of isatin have been reported to inhibit the growth of *Mycobacterium tuberculosis*.[11-12] During in vitro studies, isatin-3-phenylhydrazone has been described to show more antimicrobial activity against *Proteus vulgaris*, *Proteus aeruginosa*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* than the reference compounds amoxicillin and norfloxacin.[13] Moreover, one-pot synthesis of spiroxindoles derived from isatin has been reported to exhibit good and moderate antimicrobial activity against various bacterial and fungal strains.[14] However, metal complexes of lanthanides have been reported to increase the antifungal potential of isatin bishydrazones by affecting various factors including lipophilicity of the molecule.[15]

Patro VJ, Panda CS, Panda V , Panda SS, Sahoo B and Mishra NK reported the synthesis of 1H-indole-2,3-dione derivatives **(Figure 1)** and the investigation of antimicrobial activity of the mannich bases was done by cup plate method against pathogenic bacteria and fungi. Compound with chloro substitution showed the most favourable antimicrobial activity.[16]

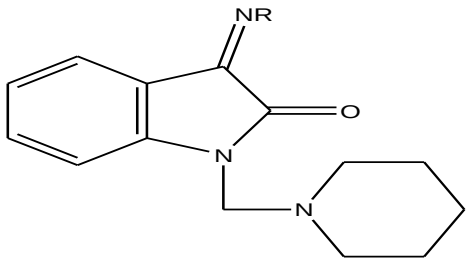


Figure 1: 1H-indole-2,3-dione derivatives

Basavaraj M, Sathyanarayana YD, Subhash K reported the synthesis of isatin derivatives **(Figure 2)** and the synthesized compounds were screened for the invitro antimicrobial activity against Staphylococcus aureus, Escherichia coli and Bacillus subtilis by cup plate method. Compound (A), (B), (C) showed excellent antimicrobial activity as compared to standard drug Norfloxacin.[17]

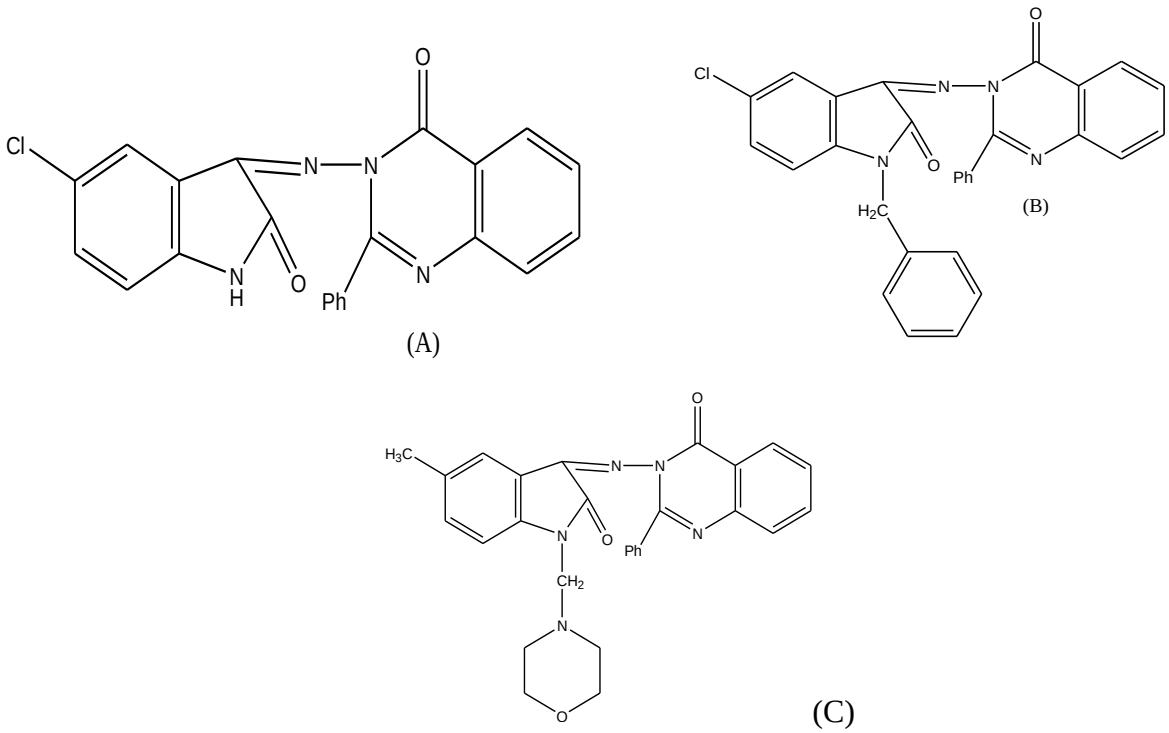


Figure 2 : 5-substituted isatin derivatives

Chaluvaraju KC, Zaranappa reported the synthesis of N-mannich bases of isatin **(Figure 3)** and the synthesized compound were tested for invitro antibacterial activity by cup plate agar diffusion method against the reference compound amoxicillin and antifungal activity against the reference compound fluconazole. All the compounds tested showed mild to moderate activity against tested bacteria and showed lesser activity to standard against tested fungi.[18]

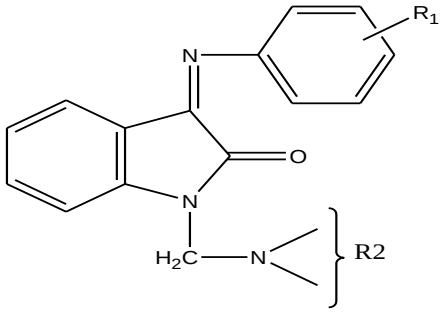


Figure 3: Substituted N-Mannich bases of Isatin

Verma RS, Kumar A, Srivastava VK, Panwar H reported the synthesis of isatin thiadiazino derivatives **(Figure 4)** and the compounds were evaluated for their antimicrobial susceptibility test against *S.aureus, E.coli, K.Pneumoniae, P.vulgaris, A.fumigatus, C.albicans* and the compound showed significant antibacterial and antifungal activity.[19]

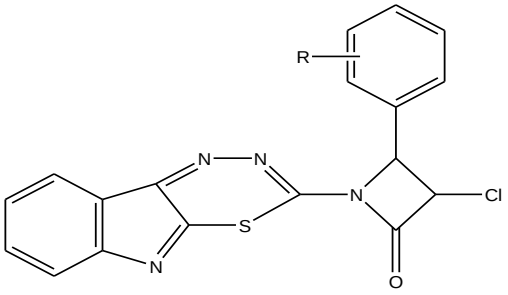


Figure 4: Isatin thiadiazino derivatives

Singh SK, Pandey SN, Bhasin PS reported the synthesis of a series of schiff and mannich bases of isatin **(Figure 5)** and the synthesized compound showed significant antimicrobial activity.[20]

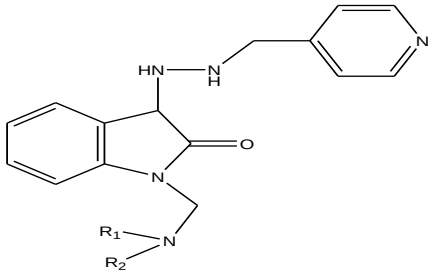


Figure 5: Substituted schiff and mannich bases of Isatin

Patel A, Bari S, Talele G, Patel J, Sarangapani M reported the synthesis of some new isatin derivatives **(Figure 6)** from different isatin hydrazones by condensing with 2-phenyl-5-benzylidene-3-N(4-acetylphenyl)-1,5-dihydroimidazolone. Among the compounds tested for antimicrobial activity, the compound with 5-Br substitution showed the most favourable antimicrobial activity.[21]

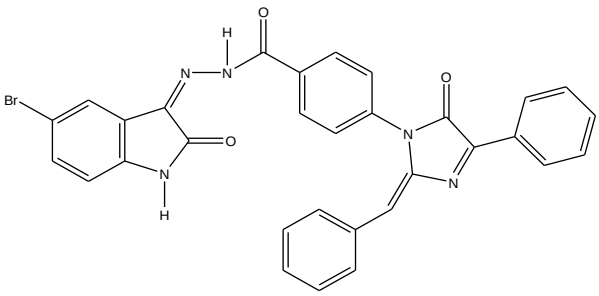


Figure 6: Substituted isatin derivative

Singh BN, Shukla SK, Singh M. reported the synthesis of sulphadiazine schiff and mannich bases of isatin **(Figure 7)** and the compound were screened for their antibacterial and antifungal activity.[22]

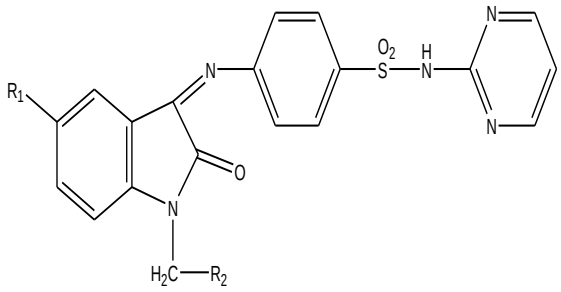


Figure 7: Substituted sulphadiazine schiff and mannich bases of isatin

2. Anticonvulsant activity

Depression is defined as disorders of mood rather than disturbances of thought or cognition. Depression accompanied by hallucination and delusion.[23] Some of isatin derivatives show CNS depressant activity. Semicarbazones, thiosemicarbazole, heterocyclic derivatives of isatin and Isatin-based spiroazetidinones shows anticonvulsant activity.

Prakash CR, Raja S, Saravanan G reported the synthesis of novel schiff base of isatin derivatives.**(Figure 8)** It was synthesized by condensation of imesatin with different aromatic aldehydes. The isatins were synthesized by reaction of isatin with *p*-phenylenediamine. All the synthesized compounds screened for anticonvulsant activities against maximal electroshock (MES) and subcutaneous metrazole (ScMet). Among the compounds synthesized 3-(4-(3, 4,5,-trimethoxybenzylideneamino) phenylimino) indoline-2-one showed excellent anticonvulsant activity with lower dose in MES as well as in ScMet methods.[24]

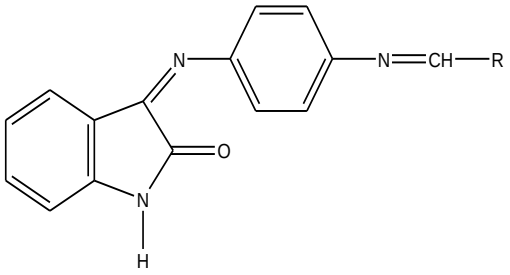


Figure 8: Novel Schiff base of isatin derivative

Subudhi BB, Pandaa PK, Bhattaa D, Jenab A reported the synthesis of metal complexes of isatin 3-glycine **(Figure 9)** and evaluated for the anticonvulsant activity of Cu (II), Zn (II) and Co (II) complex of isatin 3-glycine. The role of Cu, Zn and Co in human physiology is well documented. Isatin and glycine have inhibitory effects on central nervous system. The Cu (II) complex was found to be most active among the compounds.[25]

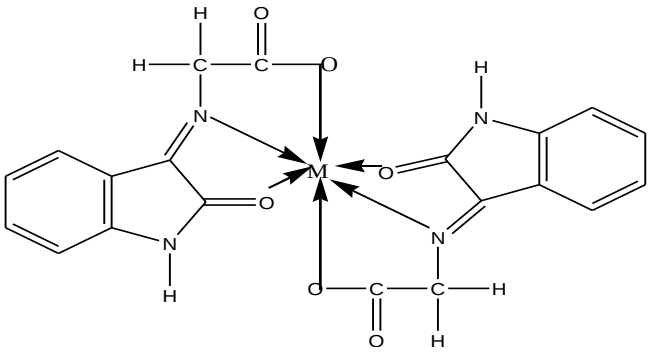


Figure 9: Metal Complexes of isatin 3-glycine

Kumar A, Kaur H, Kumar S reported the synthesis of 3-Spiro[1', 3', 4'-oxa/thiadiazolyl-2'-{5"-(substitutedphenyl-3"-amino)-4'-{5"- (substituted phenylisoxazolinyl)}]-5'-indol-2-ones **(Figure 10)** by the reaction of 3-Spiro-[1', 3', 4'-oxadiazolyl-2'-{1"-acetyl-5"- (2-hydroxyphenyl-3"-amino)-4'-{1"-acetyl-5"- (2-hydroxyphenyl) pyrazolinyl}]-5'-indol-2-ones with methanol, hydroxyl amine and NaOH solution which showed anticovulsant and antipsycotic activity.[26]

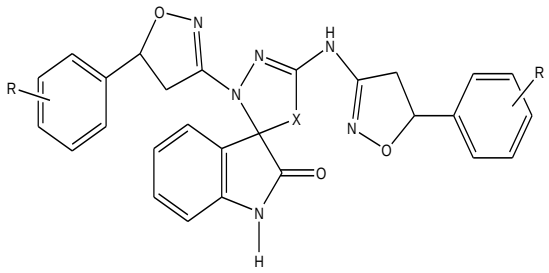


Figure 10: Pyrazolinyl/isoxazolinyl indol-2-ones derivative

Kiran G, Rajyalakshmi, Reddy RN, Rao JV, Sarangapani M reported the synthesis of isatin-5-sulphonamide **(Figure 11)** and the compounds were evaluated for anticonvulsant ability using phenytoin as standard. All the synthesized compounds showed excellent anticonvulsant activity against electric shock induced and Pentylenetetrazole induced seizures.[27]

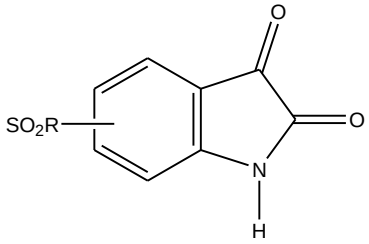


Figure 11: Isatin 5-sulphonamide derivative

Jain R, Bansal M reported the synthesis of heterocyclic derivatives of isatin formed by reacting a heterocyclic system like isatin/5-fluoroisatin with ethyl cyano acetate and substituted ketones. Compound with 5-fluoro group **(Figure 12)** which showed better anticonvulsant activity.[28]

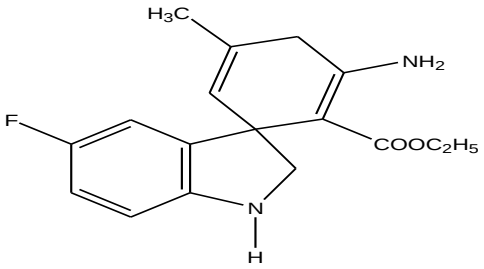


Figure 12: Substituted heterocyclic derivatives of isatin

Sharma PP, Pandeya SN, Roy RK, Gupta S reported the synthesis of a series of 3-(-4-(4-hydroxy-3-methoxylbenzylideneamino)phenylimino) indoline-2-one **(Figure 13)** by the isatin and p-phenylenediamine by dissolving in sufficient quantity of methanol in the presence of acetic acid. Various aromatic aldehydes were allowed to react to obtain final compounds. The compounds showed excellent anticovulsant activity.[29]

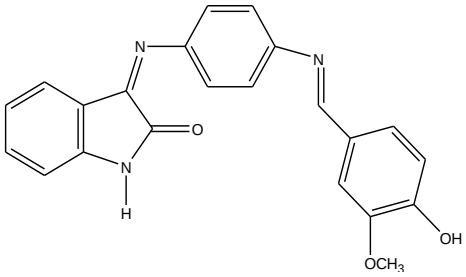


Figure 13: Phenylimino Schiff bases of isatin

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 heterocyclic exhibit manifold importance in the field of medicinal chemistry as a potent chemotherapeutic agent.

Arifuzzaman M, Kandahary RK, Islam RM reported the synthesis of Bis-diisatin [3,3´] furan **(Figure 14)** on treatment with furan in presence of diethylamine under intensive stirring. The compounds were evaluated for cytotoxicity study on the brine shrimp as a test organism.[30]

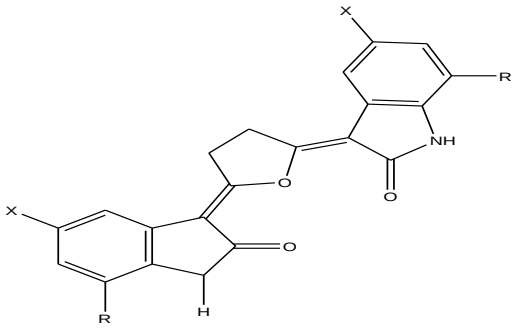
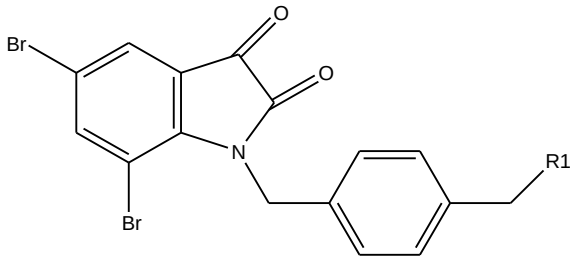


Figure 14: Bis-diisatin derivatives

Krishnegowda G *et. al.* reported the synthesis of novel series of 5,7-dibromoisatin analogs **(Figure 15)** were and synthesized derivatives were evaluated for the anticancer activity.[31]



R1 = S-C=S, N=C=S

Figure 15: Isatin benzothiazole derivative

Solomon VR, Changkun H, Hoyun L reported the synthesis of the compounds 4-bromo-1-(4-(7-chloro-quinolin-4-yl)piperazin-1-ylmethyl)-1H-indole-2,3-dione and N'-(4-(7-trifluoromethyl-quinolin-4-yl))-piperazin-1-ylmethyl-4-chloro-1H-indole-2,3dione-3-thiosemicarbazone **(Figure 16)** emerged as the most active against anti-breast cancer.[32]

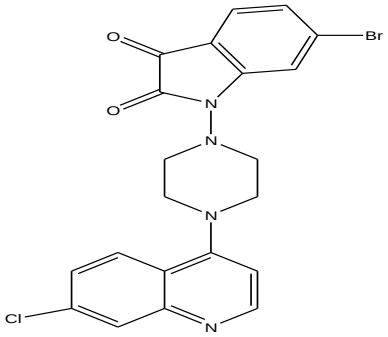


Figure 16: Substituted isatin thiosemicarbazone derivatives

Rabiul IM, Mohsin M reported that the spiro 1,3,4 oxadiazoline derivatives of isatin having chlorine atom at 5th position **(Figure 17)** showed cytotoxic effect on brine shrimp more significantly than other compounds substituted derivatives.[33]

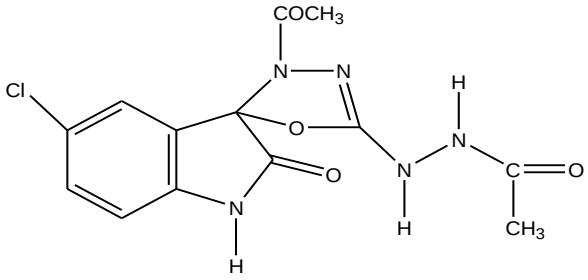


Figure 17: Oxadiazoline derivative of isatin

Rajyalakshmi G, Rama NR , Sarangapani M synthesized a series of 5-or 7-substituted 3-(4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenylimino)-indolin-2-one derivatives. Among the synthesized compounds 5-chloro derivative **(Figure 18)** showed improved anti-cancer activity.[34]

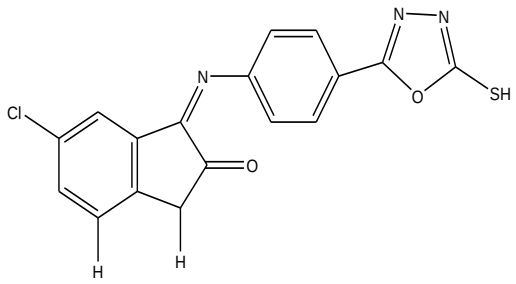


Figure 18 : 5 or 7 substituted 3-(4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenylimino)-indolin-2-one derivatives

4. Anti- HIV activity

HIV is an RNA retrovirus. Two forms are known HIV-1 is an organism responsible for human AIDS. The HIV-2 organism is similar to the HIV-1 virus in that it also causes immune suppression, but it is less virutent. HIV-1 is distributed around the world, whereas the HIV-2 virus is confined to parts of Africa.[35]

Bal TR, Anand B, Yogeeswari P, Sriram D had synthesized and evaluated anti-HIV activity of isatin β-thiosemicarbazone derivatives. **(Figure 19)** On the basis of pharmacophoric modelling studies a series of isatin β- thiosemicarbazone derivative was synthesized and evaluated for their anti-HIV activity in HTLV-IIIB strain in the CEM cell line. The synthesized compounds showed significant anti-HIV activity.[36]

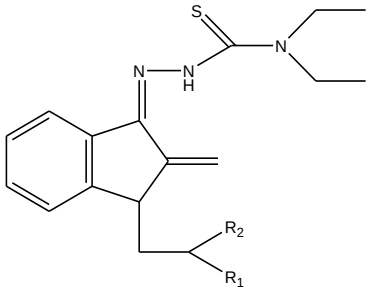


Figure 19: Isatin β-thiosemicarbazone derivatives

Selvam.P, Murgesh M, Chandramohan M, Clerco ED reported the synthesis of novel isatin sulphonamides **(Figure 20)** and the compounds were tested for anti-HIV activity against the replication of HIV-1 (IIIB) in MT-4 cells.[37]

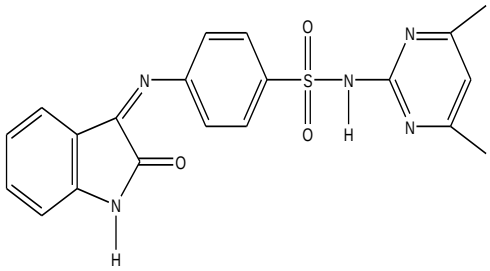


Figure 20: Novel isatin sulphonamides

5. Antioxidant Activity

Antioxidants play a significant role in several important biological processes such as immunity, protection against tissue damage, reproduction and growth or development. They reduce damage to cells and biochemicals caused by free radicals, which are normal products of metabolism.[38] Isatin and its derivatives are among an extensive diversity of heterocycles that have been explored for developing pharmaceutically important lead compounds. They are biologically active and have significant importance in medicinal chemistry.

Naik N, Kumar HV, Vidyashree PB reported the synthesis and evaluation of antioxidant potential of novel isatin analogues. **(Figure 21)** A series of novel isatin conjugated with aniline and substituted anilines were synthesized and examined for their antioxidant activity to probe the most potent analogues by using two in vitro models like 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay and inhibition of microsomal lipid peroxidation (LPO) assay.[39]

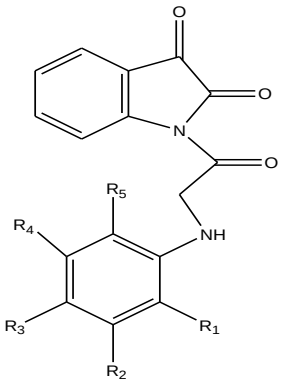


Figure 21 : Novel isatin derivative

Mondal P, Jana S, Kanthal LK reported the synthesis of novel mercapto-pyrimidine and amino-pyrimidine derivatives of indoline-2-one as potential antioxidant. **(Figure 22)** It was synthesized from different substituted chalconised indole 2,3 dione. The synthesized compounds were screened for their antioxidant activity by reducing power method .Evaluation of the compounds revealed remarkable antioxidant activity.[40]

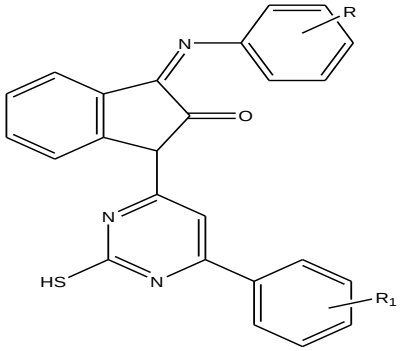


Figure 22: Mercapto-pyrimidine and amino-pyrimidine derivatives of indoline-2-one

6. Anti-inflammatory and analgesic activity

Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbial agents.[41] It inhibits prostaglandin synthesis at the site of injury.[42] 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.[41]

Pal M, Sharma NK, Priyanka, Jha KK reported the synthesis of 3-thiosemicarbazino isatin. Among the synthesized carbazone derivatives aniline methyl substituent at N1 position **(Figure 23)** showed good anti-inflammatory activity.[43]

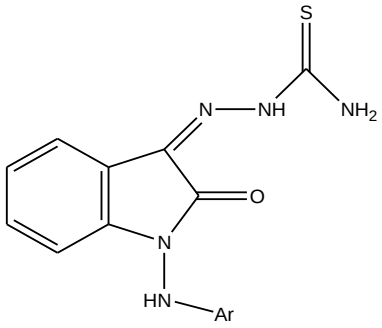


Figure 23 : 3-thiosemicarbazino isatin

Priyanka, Pal M, Sharma NK, Jha KK reported the synthesis of isatin-3-*p*-chlorophenylinine. Among the synthesized compounds the spiro derivative **(Figure 24)** showed superior anti-inflammatory activity.[44]

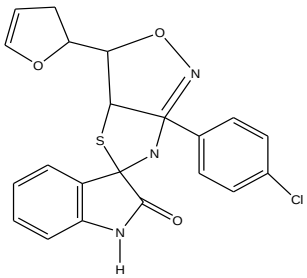


Figure 24 : Isatin-3-p-chlorophenylinine

Sridhar G, Pal M, Sharma NK, Priyanka, Jha KK reported the synthesis of a series of isatin derivatives by condensation. Among the synthesized derivatives the following compound **(Figure 25)** shows good anti-inflammatory.[45]

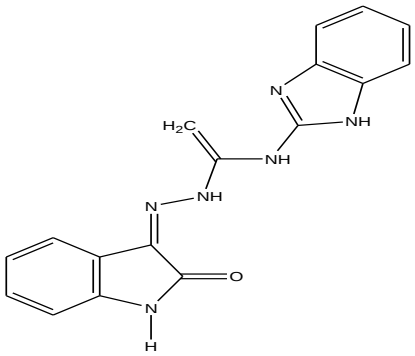


Figure 25: Substituted isatin derivatives

Ramachandran S, Uma MV reported the synthesis, analgesic and ulcerogenic evaluation of some novel schiff and mannich bases of isatin derivatives **(Figure 26)** All the compounds were evaluated for analgesic and ulcerogenic activities. Most of the compounds showed significant analgesic activity and lesser ulcerogenic property, when compared with the standard drugs.[46]

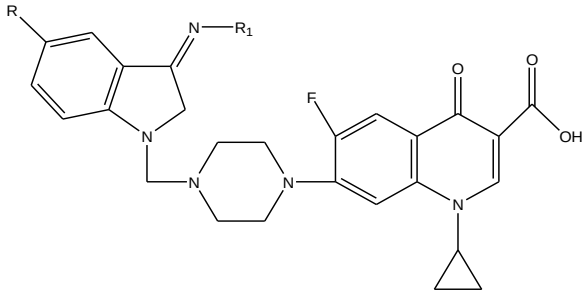


Figure 26 : Novel Schiff and mannich bases of isatin derivatives

7. Antitubercular activity

Tuberculosis (TB) is a chronic bacterial infection, spread through the air, and caused by a bacterium called *Mycobacterium tuberculosis* (MTB). It is most often found in the lungs. Most people who are exposed to TB never develop symptoms because the bacteria can live in an inactive form in the body. But if the immune system weakens, such as in people with HIV or elderly adults, TB bacteria can become active. In their active state, TB bacteria cause death of tissue in the organs they infect. Active TB disease can be fatal if left untreated.

Banerjee D, Yogeeswari P, Bhat P, Thomas A, Srividya M, Sriram D reported the synthesis of a series of novel 5-substituted -1-(arylmethyl)-1-H indole-2,3-dione-3-(N- hydroxyl / methoxythiosemicarbazone) analogues and evaluated for their anti-HIV activity and antitubercular activity. Among the synthesized compound with 5-chloro and dimethyl aminomethyl at N1 position **(Figure 27)** exhibited better results.[47]

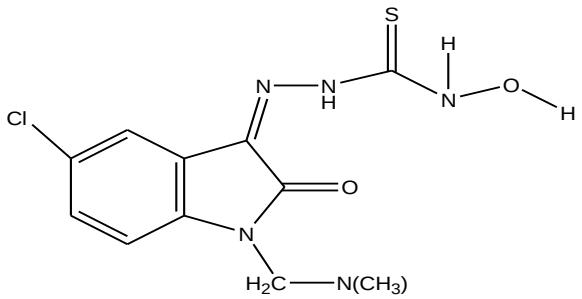


Figure 27: Novel 5-substituted -1-(arylmethyl)-1-H indole-2,3-dione-3-(N- hydroxyl / methoxythiosemicarbazone)

Tarek AF, Fayzah AJ, Omima AW reported the synthesis of different schiff and mannich bases of 1H-Indole-2,3-diones derivatives and tested for anti-TB activity against *M.tuberculosis*. Benzyl substituted at N1 analog **(Figure 28)** reported to exhibit maximum anti-TB activity.[48]

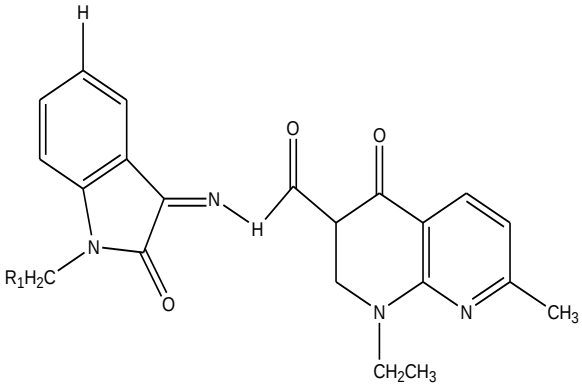
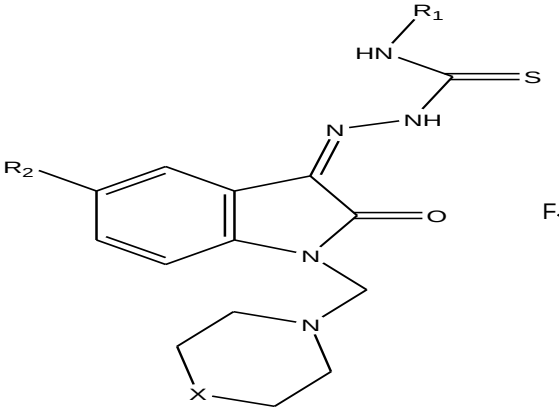
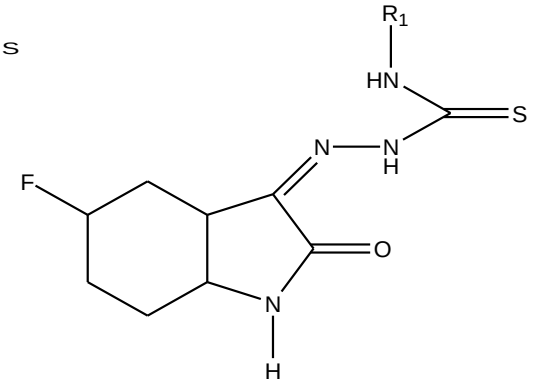


Figure 28 : Schiff and mannich bases of 1H-Indole-2,3-diones derivatives

Karali *et. al.* reported the synthesis of a new series of 1H-indole-2,3-dione derivatives **(Figure 29)** and evaluated for in vitro antituberculosis activity against *Mycobacterium tuberculosis* H37Rv*l*. Among the tested compounds, 5-nitro-1H-indole-2,3-dione-3-thiosemicarbazones and its 1-morpholinomethyl (a), (b),(c), and(d) derivatives exhibited significant inhibitory activity with MIC values - 75%.[49]



(a) R_1= CH_3 , R_2= NO_2



(d) R_1=4-$CH_3C_6H_4$

(b) R_1= C_6H_5, R_2= NO_2

(c) R_1=4-$CH_3C_6H_4$

Figure 29: New series of 1H-indole-2,3-dione derivatives

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