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Review Article

# REVIEW ON CNS ACTIVITY OF ISATIN DERIVATIVES

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**ABSTRACT**

Isatin derivatives are one of most potent anticonvulsant agent of natural origin. It has display potent anticonvulsant effect in a wide variety of preclinical anticonvulsant models. Till date various isatin derivatives have been synthesized and evaluated for anticonvulsant activity. This review is an attempt to compile the medicinal chemistry of various synthesized isatin analogs. Isatin and its analogs are versatile substrates, which can be used for the synthesis of numerous heterocyclic compounds. Isatin and its derivatives are used in organic synthesis and they are used in evaluating new product that possesses different, biological activities. In the past few decades, Isatin and its derivatives have received much attention due to their chemo- therapeutic values. This review covers updated information on the most active isatin derivatives that have been reported to show considerable pharmacological actions such as, anticonvulsant, antianixity and antipsychoactives activity. From these results, ideas for future molecular modifications leading to compounds with greater favorable pharmacological properties may be derived.

**Keyword**: Isatin derivatives, Anticonvulsant, Structure-activity relationship.

## INTRODUCTION

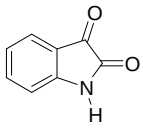


**Fig. 1: Isatin**

Isatin or 1*H*-indole-2, 3-dione (Fig.1.) is an indole derivative. The compound was first obtained by Erdman[1] and Laurent[2] in 1841 as a product from the oxidation of indigo dye by nitric acid and chromic acids. Isatin forms a blue dye if it is mixed with sulfuric acid and crude benzene. The formation of the blue indophenin was long believed to be a reaction with benzene. Victor Meyer was able to isolate the substance responsible for this reaction from benzene. This new heterocyclic compound was thiophene[3]. Isatin is exert broad spectrum of biological activity like antipyretic activity, analgesic effect anticonvulsant activity, few compounds were also reported as psychotropic agents and MAO inhibitors.

In nature, isatin is found in plants of the genus *Isatis*[4], in *Calanthe discolor*[5], in *Couroupita guianensis* Aubl[6], has also been found as a component of the secretion from the parotid gland of *Bufo* frogs[7] and in humans as it is a metabolic derivative of adrenaline[8, 10]. Substituted isatins are also found in plants, for example the melosatin alkaloids (methox phenylpentyl isatins) obtained from the Caribbean tumorigenic plant *Melochia tomentosa*[11, 13]as well as from fungi: 6-(3'-methylbuten-2'-yl)isatin was isolated from *Streptomyces albus*[14] and 5-(3'-methylbuten-2'-yl)isatin from *Chaetomium globosum*[15].The various substituents at 1[rd]and 3[rd] position of the isatin which were reported various substituted phenyl ring moieties, heterocyclic rings and aliphatic system. Isatin is one of the most promising new classes of heterocyclic molecules having many interesting activity profiles and well-tolerated in human[16, 17].

## PREPARATION

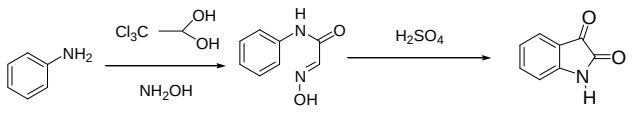


**Fig. 2: Synthesis of isatin**

It may be prepared from cyclicizing the condensation product of chloral hydrate, aniline and hydroxylamine in sulfuric acid[18, 19].This reaction is called the Sandmeyer isonitrosoacetanilide isatin synthesis (Fig.2.) and discovered by Traugott Sandmeyer in 1919. The method applies well to anilines with electron-withdrawing substituents, such as fluoroaniline [20].

## MECHANISM OF ACTION: ISATIN

In 1988, isatin was identified as a major constituent of tribulin, a low-molecular-weight inhibitor of MAO type B (MAO-B) [21] and furthermore, urinary concentrations of isatin in patients with Parkinson.s disease tend to increase according to the severity of disease. These results suggest that urinary isatin may become a diagnostic marker for the clinical severity of Parkinson.s disease and that endogenous isatin, a new biological modulator, may play a role in the regulation of the brain levels of ACh by increasing the level of DA under stress, identified isatin in the urineand the brain[22, 23] of stroke-prone spontaneously hypertensive rats (SHRSP). Tribulin may contain metabolites of isatin or related endogenous compounds[24]. The physiological and pathological roles of isatin and tribulin are not yet clear. In humans, tribulin levels increase as a result of exercise[25] and old age[26]. Tribulin excretion is significantly higher in females than males[27]. Tribulin output is transiently raised following alcohol withdrawal[28], benzodiazepine withdrawal, lactate-induced panic attacks[29], and migraine attacks [30]. Tribulin output thus appears to be raised in a variety of different conditions related to stress, agitation, or anxiety. These observations suggest that during stress, activated catecholamine-synthesizing cells and corticotropin-releasing factor cells, both of which play central roles in stress responses, may be involved in isatin production[31]. Cold immobilization stress, for example, has been associated with the serotonergic system[32].

Cold restraint stress increases tribulin in the rat heart and kidney[33]. Tribulin acts on central benzodiazepine receptors, and has been proposed to be an anxiety-promoting agent[34]. The potency of the MAO inhibitory and benzodiazepine-receptor-binding inhibitory components of tribulin are roughly equal[35]. It is a selective MAO-B inhibitor. At much higher concentrations, it inhibits a variety of other enzymes, such as alkaline phosphatase[36]. Tribulin can be extracted from tissue and body fluids with ethyl acetate. Isatin is believed to be a component of tribulin and a selective inhibitor of MAO-B. Other components of tribulin, the ethyl and methyl esters of indoleacetic and 4-hydroxyphenylacetic acid selectively inhibit MAO-A [37].The synthetic and metabolic pathways of isatin have not been established. It has been suggested that dietary tryptophan may be converted into an indole by the gut flora and then transported to the liver where it is oxidized. Urinary isatin concentration is significantly reduced in germ-free rats (0.22 mg/mL) compared to control rats (0.66 mg/mL) [38]. This suggests that isatin is derived, at least in part, from the interaction of gut flora with tryptophan-containing food.

Kumar *et al*.[39]reported that isatin inhibits acetylcholine esterase (AChE) activity in rat brain and erythrocytes. To elucidate the physiological role of isatin in the regulation of acetylcholine (ACh) levels in the rat brain, the levels of ACh, choline (Ch), and DA in rat tissues at 2 h after isatin administration (50 or 200 mg/kg, i.p.), ACh and Ch levels in the striatum of the group receiving isatin increased significantly. Striatum DA levels also increased after isatin treatment.In other words, at a single dose isatin simultaneously increased ACh and DA levels in the WKY striatum. In our *in vitro* study, isatin at 10.4 M induced an approximate 93% inhibition of MAO and a 5% inhibition of AChE in the rat brain. It is clear that isatin has a higher affinity for MAO than AChE. Isatin administration also increased Ch, an AChE metabolite of ACh, in many brain regions. These results suggested that isatin increased ACh levels not by inhibiting AChE activity but rather by affecting another pathway[40]. Isatin has a wide spectrum of biological properties: (a) its physiological effects protect against stress and certain infections; and (b) it affects the central nervous system.Isatin has been shown to inhibit a number of enzymes in various tissues, such as acid phosphatase [41], alkaline phosphatase, and xanthine oxidase, hyaluronidase[42]as well as MAO. In a variety of tests isatin has been found to act as an antiseizure agent [43], it potentiates the antiseizure action of propranolol [44].

Yuwiler[45] was found some indirect evidence that isatin acts *in vivo* as a benzodiazepine blocker. The most potent action of isatin *in vitro* is the inhibition of the atrial natriuretic peptide (ANP) binding to its receptor. Isatin attenuates ANP-stimulated guanylate cyclase activity in the rat brain, heart, and kidney[46]. Recent studies also suggest that the anxiogenic effect of isatin may be explained by its antagonism of ANP. Thus isatin may provide a link between the function of the monoamines involved in stress and the control of the natriuretic system by ANP [47]. Isatin-induced anxiogenic action can be blocked by 5-HT3 receptor antagonists [48]. In vivo studies suggest that isatin may be functioning as an agonist at the 5-HT3 receptors; although this effect was not evident in recent *in vitro* binding studies [49].Isatin was found in mammalian tissues to be one of the components of tribulin[50]. In the rat brain, the highest levels of isatin have been found in the hippocampus and the cerebellum, whereas striatal concentrations are higher in the human brain [51]. Isatin has a wide spectrum of biological properties: (a) a marker of stress and anxiety (b) an inhibitor of a number of enzymes; (c) an ant-seizure agent; (d) an inhibitor of ANP binding to its receptors; (e) an agonist at the 5-HT3 receptors; and (f) an inhibitor of benzodiazepine receptors, among others.

**STRUCHURE ACTIVITY RELATIONSHIP**

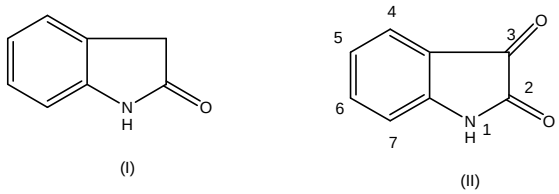



**Fig. 3: 2-indolinone (I) and 2, 3-indolindione (II)**

**1**. Bond acceptor at the position (3)

**2**. Free rotation bond O#H

**3.** Bond donor (1)

**4.** Polar surface area-37.38

**5.** C5, C6and C7 substitution generally enhanced CNS activity with some di and tri halogenated isatin (Fig.3).

Thomson *et al.*[52] were found that a little variation at position 3 of 2-indolinone (I) and 2, 3-indolindione (II) produce different degree of biological activity.

**(1) Anticonvulsant activity**

Popp *et al.*[53] studied Comparative anticonvulsant activity of different compounds (Fig.4). The found that 3-hydroxy-3-acetonyloxindole (XIIA) which was obtained from the condensation of isatin and acetone, exhibits greater anticonvulsant activity than 3-hydroxyl-3-pehenacycloindole (XIIB).Various analogues of 3-hydroxy-3-acetonyloxindole (XIIA) were also prepared with varying degree of anticonvulsant activity. The compounds 3-acetonyldeneoxindole (XIIIA) and 3-acetophenylideneoxindole (XIIIB) showed somewhat less anticonvulsant activity. Another compound 3-cyclohexenonyl oxindole (XIIIC) showed increase activity in MES screen from 300 to100 mg/kg. The compound 3-hydroxy-3-cyclohexanonyloxindole (XIIC) was found as potent anticonvulsant drug showing activity at 300mg/ kg by body weight in the MES test.

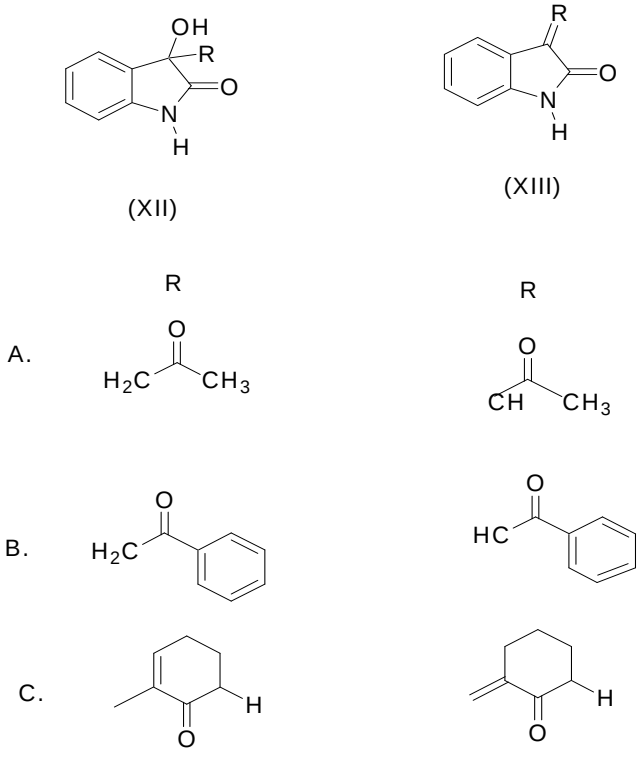
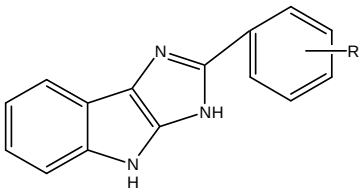



**Fig. 4: 3-hydroxy-3-phenacyloxindole Analogs**

Kumar, N. *et al.*[54a] were found that a little variation at position of compound (Fig.5) Ib and Ic have chloro and nitro substitution at para position of the phenyl ring which showed excellent anticonvulsant activity compared to substitution at any other position. The anticonvulsant activity of synthesized compounds having substitutions N, N-dimethyl, 4-chloro, 2-nitro, 2, 4-dinitro was found to be 5.16, 2.83, 3.33, 4.36, 5.5 kg/mg respectly which showed moderate potency when compound to standard drug diazepam. Among the synthesized compounds such as (1b) 3, 4-dihydro-2-(4-nitro phenyl) imidazo(4, 5, 6), indol and (1c) 2-(4-chloro phenyl) -3, 4-dihydro-imidazo (4, 5, 6) indole showed excellent anticonvulsant activity.It may be assumed that further modifications may produce compounds of better activity with less toxic effects.

Muller *et al.*[55]were found that oxindole (I), isatin (II) and N-methyl Isatin-3-thiosemicarbazene (III b) injected (1/p) in the rat, inhibited monoamine oxides in liver homogenate, Isatin-3-hydrazone (VIIIa) was much less effective as an inhibitor, introdertion of Br group at the position 5 in certain analognes afforded 5-bromoisatine (IX a), 5-bromo-N-methylisatin (IX b) and 5-bromoisatin-3-hydrazone (VIII).The bromo group markedly increased the inhibitory effectiveness of the unsubstituted compounds




Ib = 4-nitrophenyl

Ic = 4-chlorophenyl

**Fig. 5: Phenyl indoloimidazole derivatives**

**(2)Antipsychotic activity**

Fischer *et al.* [56]were found that Isatin (II) and its derivatives contraction of terminal guinea pig ileum in-vitro.Several of these compounds also contracted rat stomach strips and rabbit aorta strips and the effects exerted through 5-HT receptors in the guinea pig ileum but were not specified for D-or M-receptor.Some of these compounds also act as non-competitive antagonists of 5-HT and tryptamine at the receptors. The antiserotoninergic activity of the isatin was enhanced by the substituents in the positions-3 and 5 diminished by substituents in the position-1.

**(3)MAO inhibitor activity**

Medvedev *et at.*[57] were found that indole and 2, 3-dioxindole analogues an inhibitor of MAO-A and B.The compounds exhibited reversible and competitive MAO inhibition. The substituents at C-2 and C-3 of indole ring for selective MAO-A inhibitor. The presence of hydroxyl group at C-5 of isatin increased selectivity of MAO-A inhibitor. However, simultaneous insertion of substituents into both positions of indole ring (5-hydroxy-2-phenylindole) led to a decrease of MAO-A inhibitor. The planar molecules demonstrating potent MAO- A inhibition have the average sizes 7A in length and 6A in width. The MAO-B inhibition also depended on the sizes of planar molecules. However, distribution of electron density in the molecules was another precondition for the selective inhibition of the enzyme.

Virsis *et at.*[58] were found that relationship between the structure of 2-indolines (I), 2, 3-indolinediones(II) and their biological activity. The analytical data obtained from in-vivo studies of 2-indolinone (I) and 2, 3-indolindione (II) compounds, which showed MAO inhibiting activities. He also examined that the inhibiting activity is due to both the hydrophobic properties of the molecule and details of electronic structure, especially, the presence of carbonyl group at C-3 and a substitution at C-5 that has a post-R-effect.

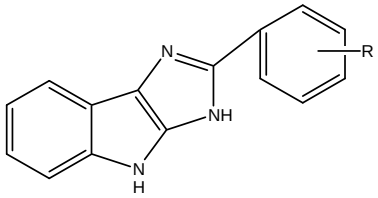
Above review letrature survey found that, if change at positon 3[nd] of isatin (II) likes as hydrazied and schiff base also give novel isatin derivatives which show CNS activity. Halogens at position 5, 6, and 7 increase the activity of isatin derivatives compound.

**CNS ACTIVITY OF ISATIN**

From literature that isatin containing synthetic compounds and their derivatives are known to be associated with broad spectrum of biological activity like antipyretic activity, analgesic effect[59, 60]anticonvulsant activity[61], few compounds were also reported as psychotropic agents[62] and MAO inhibitors[63]. All the reported activities provide way for utilization of these compounds for CNS activity. Depression is defined as disorders of mood rather than disturbances of thought. Depression accompanied by hallucination and delusion [64]. Some of isatin derivatives show CNS depressant activity.

**1. Anticonvulsant activity**

Kumar, N. *et al.* [54b] synthesized and evaluated for anticonvulsant activity of a number of new N-phenyl-3-substituted pheny indolo(2, 3) imidazole derivatives(Fig.6).The titled compound were obtained by condensing different aromatic aldehyde with N-phenyl isatin in presence of ammonium acetate and glacial acetic acid. All the newly synthesized compounds were screened for their anticonvulsants activity using maximal electroshock seizers method taking diazepam as standard drug. Compound Ib and Ic showed highly significant anticonvulsant activity. Compound Ib and Ic have chloro and nitro substitution at para position of the phenyl ring which showed excellent anticonvulsant activity compared to substitution at any other position. The anticonvulsants activity of synthesized compounds having substitutions N, N-dimethyl, 4-chloro, 2-nitro, 2, 4-dinitro was found to be 5.16, 2.83, 3.33, 4.36, 5.5kg/mg respectively which showed moderate potency when compound to standard drug diazepam. Among the synthesized compounds such as (1b) 3, 4-dihydro-2-(4-nitro phenyl) imidazo(4, 5, 6), indol and (1c) 2-(4-chloro phenyl) -3, 4-dihydro-imidazo(4, 5, 6) indole showed excellent anticonvulsant activity. It may be assumed that further modifications may produce compounds of better activity with less toxic effects.




Ib = 4-nitrophenyl

Ic = 4-chlorophenyl

**Fig. 6: N-phenyl-3-substituted pheny indolo(2, 3) imidazole derivatives**

Pandey S. N. *et al.*[65] synthesized a series of Isatin-3-hydrazone (fig.7), a series of substituted isatin semicarbazones and related bioisosteric hydrazones were designed and synthesised to meet the structural requirements essential for anticonvulsant properties. All compounds were evaluated for their anticonvulsant activity by maximal electroshock (MES), subcutaneous metrazol (ScMet) and subcutaneous strychnine (ScSty) induced seizure methods and their neurotoxic effects were determined by rotorod test. Some of them showed good anticonvulsant activity in MES test in rats after per oral administration at the dose of 30mg/kg. The bioisosteric hydrazone derivatives were inactive in all tests. Compound 6-chloroisatin-3- (4-bromophenyl)-semicarbazone has emerged as the most active analogue of the series showing good activity in all the three tests and was more active than phenytoin and valproic acid. Para bromo and phenoxy acetyl hydrazide with glaceial acetic acid and tested their anticonvulsant activity.

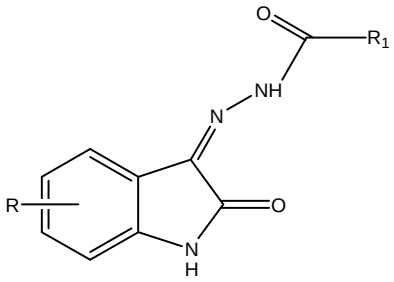


**Fig. 7: Semicarbazone isatin derivatives**

Krishan Nand Singh *et al.* [66] synthesized a series of (3*Z*)-5-bromo-1-methyl-3-[(4-nitrophenyl) imino]-1, 3-dihydro-2*H*-indol-2- one (fig.8) by reacting 5-substituted *N*-methyl/*N*-acetyl isatin and aromatic amine with glacial acetic acid. Schiff bases of N-methyl and N-acetyl isatin derivatives with different aryl amines have been synthesized and screened for anticonvulsant activities against maximal electroshock (MES) and subcutaneous metrazole (ScMet). N-methyl-5-bromo-3-(p-chlorophenylimino) isatin 2 exhibited anticonvulsant activity in MES and ScMet with LD50 > 600 mg kg (-1), showing better activity than the standard drugs phenytoin, carbamazepine and valproic acid. Thus, compound 2 may be chosen as a prototype for development of new anticonvulsants.

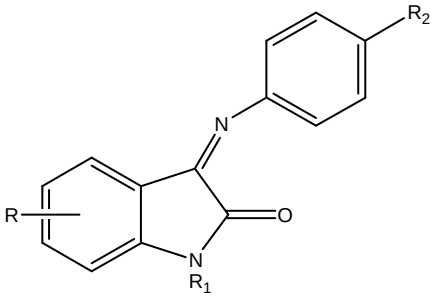


**Fig. 8: Shiff bases of isatin derivatives**

Sivakumar Smith *et al.*[67a] synthesized a series of N-methyl/acetyl-5-(un)-substituted isatin-3-semicarbazones (fig.9) were formed by and coworkers by reacting N-methyl/acetyl isatin, 5-bromo/nitro-N-acetyl isatin and p-substituted phenyl semicarbazides and tested their anticonvulsant and sedative activity.

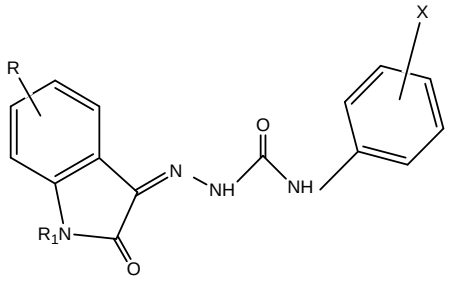
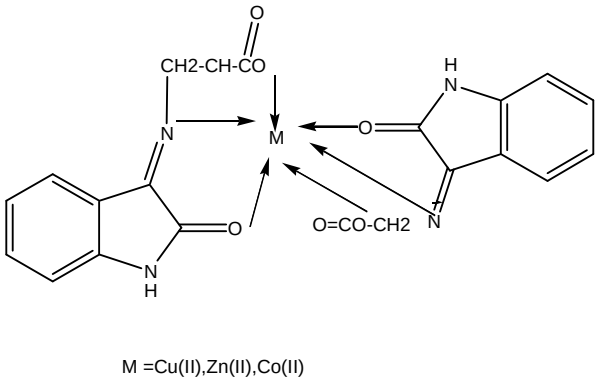


**Fig. 9: Thiosemicarbazole isatin derivatives**

Bharat Bhusan Subudhia *et al.*[68]synthesized metal complexes of isatin-3-glycine (Fig.10) and evaluated for activity.The role of Cu, Zn and Co in human physiology is well documented. Isatin and glycine have inhibitory effects on central nervous system. To capitalize on these features metal complexes of isatin-3-glycine were prepared and evaluated for activity. The Cu (II) complex was found to be most active among the compounds. All of the animals showing convulsion died within 40 min. The incidences of convulsion indicate the percentage of animals exhibiting convulsion. The isatin-3-glycine and its metal complexes with Cu (II), Zn (II)and Co (II) increased onset of convulsion, significantly ($p$<0.01) compared to the control. As expected the Cu (II) complex exhibited maximum anticonvulsant action .Complexation with Zn (II) seems to have decreased the anticonvulsant property of the ligand. The activity was enhanced on complexation with Cu (II) and Co (II).However; the complexes did not provide full protection against convulsion.



M =Cu(II),Zn(II),Co(II)

**Fig. 10: Metal complexes of isatin-3-glycine derivatives**

Ashok Kumar *et al.*[69a] synthesized a series of 3-Spiro[1', 3', 4'-oxa/thiadiazolyl-2'-{5''-(substitutedphenyl-3''-amino)-4'-{5''-(substituted phenylisoxazolinyl)}]-5'-indol-2-ones (fig.11.) 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 and tested their anticovulsant and antipsycotic activity. Compounds having thiadiazole ring (i.e. 3e-3h, 4e-4h and 5e-5h) show better antipsychotic and anticonvulsant activity than the compounds having oxadiazole ring (i.e.3a-3d, 4a-4d and 5a-5d).Pyrazoline derivatives (i.e. 4a-4h) exhibited better activity than isoxazoline derivatives(i.e. 5a-5h) with isoxazoline ring. Compounds having 4-N (CH3)2 C6H4-substitution at Vth position of pyrazoline ring showed more potent activity than other substituted pyrazolines.

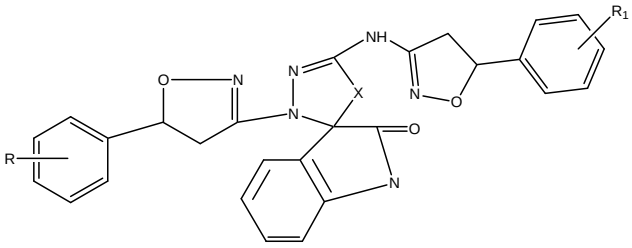


**Fig. 11: Pyrazolinyl/isoxazolinyl indol-2-ones derivatives**

Jain, R. *et al.*[70] synthesized a series of heterocyclic derivatives of isatin (fig.12.) were formed by reacting a heterocyclic system like isatin/5-fluoroisatin with ethyl cyano acetate and substituted ketones which shows anticonvulsant activity.

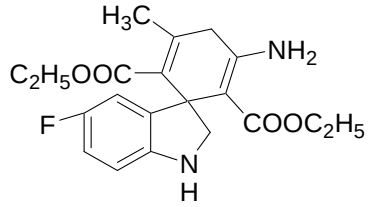


**Fig. 12: Heterocyclic derivatives of isatin**

Gursoy *et al.* [71] Synthesized a series of 3-aryloxyl, arylthioxy acetyl hydrazono-2-indolinones (fig.13) in this study a new series of 3-aryloxy/arylthioxyacetylhydrazono-2-indolinones obtained by condensation of isatin with aryloxy/arythioxyacetylhydrazines were treated with morpholine and formaldehyde to yield 1-morpholinomethyl-3-aryloxy/ aryl thioxyacetylhydrazono-2-indolinones. Anticonvulsant evaluation of the compounds revealed varying degrees of activity against pentylenentetrazole induced seizures.

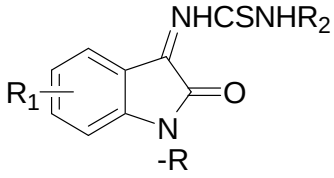



**Fig. 13: Hydrazono-2-indolinones derivatives**

Singh *et al.*[72] synthesized (fig.14) a series of 1-aryl/cyclohexyl-3, 3-diphenyl-1'-(diphenylacetyl)-2-oxospiro azetidin-4, 3'-indolin-2'-ones 9a-h by the reaction of diphenylketene, generated in situ from the thermal decomposition of 2-diazo-1, 2-diphenylethanone 1 with 3-N-aryl/cyclohexyliminoindolin-2-ones 2a-h in 2:1 molar ratio. These spiroazetidinones, also obtainable by an equimolar reaction of diphenyketene with 1-diphenylacetyl derivatives 3 of the latter and screened for their anticonvulsant activity. Two compounds 14e and 14h exhibit highly significant activity against MES.

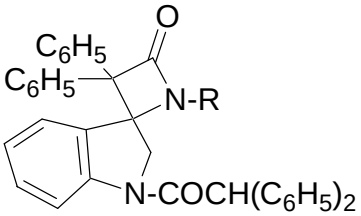



**Fig. 14: Isatin-based spiroazetidinones derivatives**

Prakash, C.R. *et al.* [73] synthesized a series of 3-(-4-(4-hydroxy-3-methoxy lbenzylideneamino) phenyl imino) indoline-2-one (fig.15) 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.

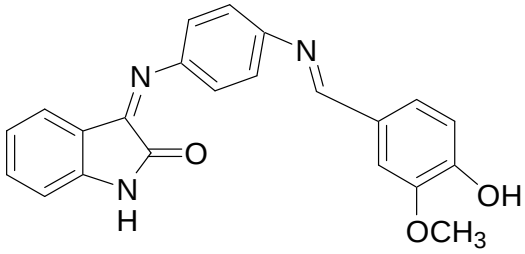



**Fig. 15: Phenylimino Schiff bases of isatin derivatives**

Prince P. Sharma *et al.* [74]synthesized a series of Isatin Schiff's bases (fig.16) were formed by the 6-(un)substituted 1, 3 benzothiazol-2-amine and insole 2, 3-dione by dissolving 20 ml of absolute alcohol and were refluxed in presence of few drops of glacial acetic acid. All the compounds were screened for anticonvulsant properties, compounds 16a, 16b and 16d shown potent anticonvulsant activity.

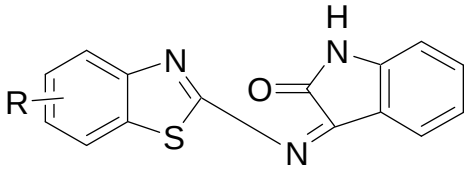



**Fig. 16: Isatin Schiff bases derivatives**

Sarangapani, M. *et al.*[75] synthesized a series of Isatin Isatin-5-Sulphonamide derivatives (fig. 17) and the anticonvulsant activity of some new isatin-5-sulphonamide derivatives against maximum electric shock induced and Pentylenetetrazol (PTZ) induced seizures in mice using phenytoin as standard. All the five test compounds were effective against electric shock and PTZ induced convulsions at a dose of 100mg/kg. The anticonvulsant activities of test compounds were comparable with standard anticonvulsant, Phenytoin.

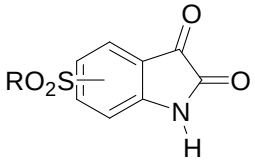
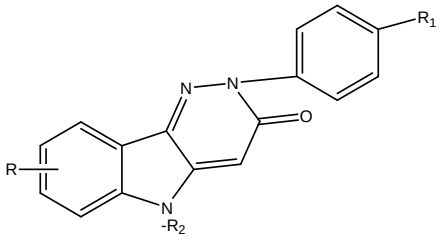



**Fig. 17: Isatin-5-Sulphonamide derivatives**

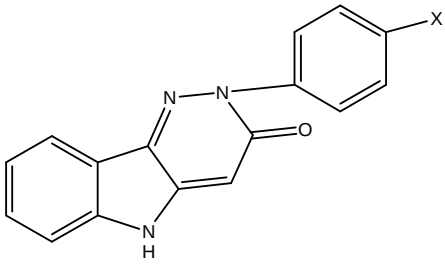
Palluotto *et al.*[76]Synthesized of a series of 2-aryl-2, 5 dihydropyridazino [4, 3- b]indol-3(3H)ones (Fig.18) The synthesized compounds 18a, 18b, 18c and 18d showed anticonvulsant activity. The onsets of clonic and tonic seizures were significantly reduced 45 min. after ip.(intraperitoneal) administration of derivatives 18(a, d) an comparable with standard drug (Flumazenil).




R=H,R1=P-Cl,p-Br,p-OCH3,R2=H,CH3

**Fig. 18: 2-aryl-2, 5 dihydropyridazino[4, 3- b]indol-3(3H)ones derivatives**

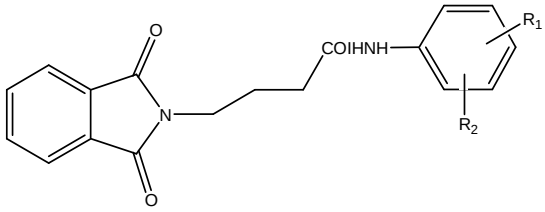
Campagna *et al.*[77] Synthesized of a series of a 2-aryl -2, 5 dihydropyridazino [43-b] indol-3(3H) ones (Fig.19)compounds 19a, 19b and 19c were evaluated for their good ability to prevent pentylenetetrazole (PTZ)induced seizures in mice.




X=H,Cl,Br

**Fig. 19: 2-aryl-2, 5 dihydropyridazino [43-b] indol-3(3H) ones derivatives**

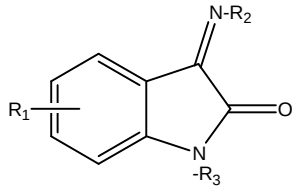
Rajavendran *et al.* [78] Synthesized of aryl/alkylidene-4-(1, 3-dioxo-1, 3-dihydro-2*H* isoindol-2-yl) butanoyl hydrazides/butanamides (Fig.20) Anticonvulsant activity was determined using four animal models of seizures which included MES, subcutaneous (sc PTZ) intraperitoneal Picritoxin (ip PIC) induced seizures threshold test. Compounds were ineffective in MES test up to 300 mg/kg and showed protection in sc PTZ screen included 20i, 20ii, and 20iii. These compounds were found to be more potent when compared to standard drug phenytoin and ethosuximide, and were effective at dose 30 mg/kg.




R1=2-CH3,3-Cl,R2=4CH3,2-CH3,R3=CH3,R4=4-CH3-C6H4

**Fig. 20: Aryl/alkylidene-4-(1, 3-dioxo-1, 3-dihydro-2*H* isoindol-2-yl)butanoyl hydrazides/butanamides**

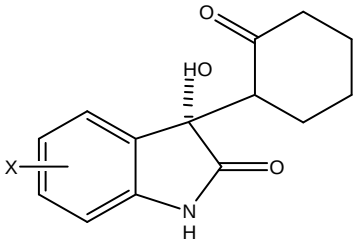
Sridhar *et al.*[79]Synthesized a series of 3-(4-chloro-phenylimino)-5-methyl-1, 3 dihydro-indole-2-one(Fig.21)**.** The anticonvulsant activity of hydrazones, Schiff and Mannich bases of isatin were evaluated by maximal electroshock method (MES) and metrazol-induced convulsions (MET) at 30, 100 and 300 mg/kg dose levels. Eight compounds of the series exhibited significant anticonvulsant activity at 30 mg/kg dose level. 3-(4-chloro-phenylimino)-5-methyl-1, 3-dihydro-indol-2-one was found to be the most potent compound of the series with 87% protection at 100 mg/kg and an $ED_{50}$ of 53.61 mg/kg (MET). All the compounds exhibited lesser neurotoxicity compared to phenytoin. All the active compounds showed greater protection than sodium valproate.The synthesized compounds 21a, 21b, 21c were active in MES test and compound 21b was found to be most active compound.




R1=H,CH3,CH3,4-Methylphenyl,4-chlorophenyl,1-napthyl,R3=H

**Fig. 21: 3-(4-chloro-phenylimino)-5-methyl-1, 3 dihydro-indole-2-one derivatives**

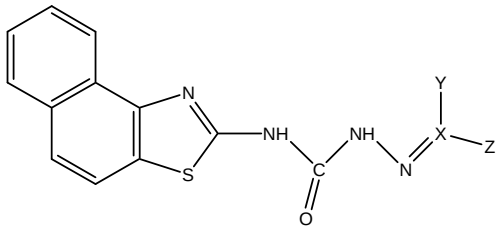
Veerasamy *et al.*[80] synthesized a series of 3-cycloalkanone-3, 4-hydroxy-2-oxindoles derivatives (Fig.22) by using primary-tertiary diamine-Bronsted acid catalyst in both organic medium and aqueous medium were reported by synthesized compound 22a and 22b showed the MES test and PTZ test. Compound 22a was active in PTZ seizure threshold test (PTZ), thus act as a potential anticonvulsant.




X=Br,Cl

**Fig. 22: 3-cycloalkanone-3, 4-hydroxy-2-oxindoles derivatives**

Azam *et al.* [81] Synthesized a series of *N4*-(naphtha [1, 2-d] thiazol-2-yl) semicarbazides (Fig.23) and synthesized to meet the structural requirements essential for anticonvulsant activity. Anticonvulsant activity was determined after intraperitoneal (i.p.) administration to mice by maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ)-induced seizure tests and minimal motor impairment was determined by rotorod test. A majority of the compounds exhibited significant anticonvulsant activity after intraperitoneal administration. Some of the selected compounds were evaluated orally in rats for activity in scPTZ test at several time points (50 mg/kg). The most active compounds carry bromo, fluoro and nitro substituents at 4-position in the phenyl ring. The biochemical estimations of malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) from brain homogenate not only clearly implicated the role of free radicals in PTZ-induced convulsion but also explained the possible mechanism of protective effect of semicarbazides, through the reduced formation of MDA and increased formation of SOD and GSH-Px..The synthesized 23a, 23b and 23c with chloro, bromo and flouro substituents respectively, showed activity at 100 mg/kg after 0.5 h in MES test is comparable to the standard drug Phenobarbital, indicating that they have rapid onset of action and shorter duration of action.




X=C,Y=H,Z=4BrC6H5,4ClC6H4,4FC6H4

**Fig. 23: N4-(naphtha [1, 2-d] thiazol-2-yl) semicarbazides derivatives**

**(2) Sedative activity**

Sivakumar Smith *et al.* [67b]synthesized a series of N-methyl/acetyl-5-(un)-substituted isatin-3-semicarbazones (fig.24) were formed by and coworkers by reacting N-methyl/acetyl isatin, 5-bromo/nitro-N-acetyl isatin and p-substituted phenyl semicarbazides and tested their anticonvulsant and sedative activity.

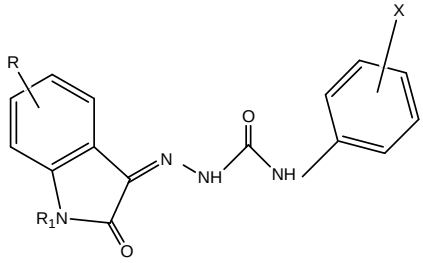



**Fig. 24: Thiosemicarbazole isatin derivatives**

**(3) CNS depression activity**

Raghunandan Nerella *et al.*[82] synthesized a series of new 1-N-Substituted amino methyl-3-(3-phenyl quinazolin-4-one-methylene-2-yl) indolin-2-one (Fig.25) by subjecting an appropriate 3-(3-phenyl quinazolin-4-one methylene-2-yl) indolin-2-ones (VII) to mannich reaction with three different secondary amines viz. dicyclohexylamine, piperidine and morpholine in presence of formaldehyde and alcohol. All the synthesized compounds were screened for CNS activity. The gross behavioral studies of test compounds reveal that all the test compounds exhibited CNS depression in the mice. All the test compounds showed a decrease in Locomotor activity. Except 25b increased locomotor activity which is found to be not significant. Compounds 25d, 25a, 25c and 25g were next to compound 25e in the order of reduction of locomotor activity. Compound 25e (R=5-methyl, R1 = piperdino) has exhibited more effect among all the compounds.

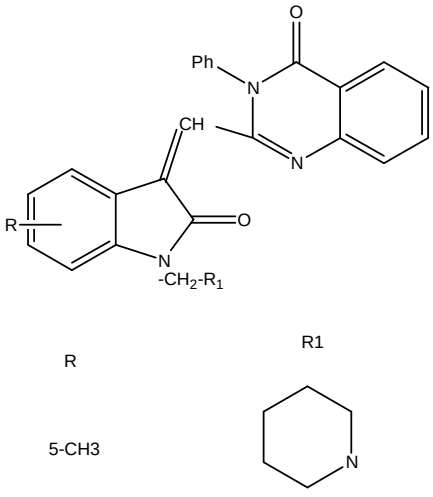



**Fig. 25: 1-N-Substituted amino methyl-3-(3-phenyl quinazolin-4-one-methylene-2-yl) indolin-2-one derivatives**

Bethi Srinivas *et al.* [83] synthesized a series of isatin derivatives containing 1, 2, 3, 4-tetrahydrocarbazole moiety (Fig.26). Synthesized compound are subjected to screen for the central nervous system activity. All the new compounds were screened for gross behavioural studies.The gross behavioural studies of the test compounds revealed that all the test compounds exhibited central nervous system depression in the mice, pertaining to the gross behavioural studies of N-(2-oxo-1, 2 dihydro- 3H-indol-3-ylidene)-2-(1, 2, 3, 4-tetrahydro-9H-carbazol-9- yl)acetohydrazides (26) shows that all the compounds did not show alertness. Among the test compounds, 26d, 26c, and 26a showed more depressant activity than the rest of the compounds.The locomotor activity was studied by actophotometer. The compound 26d (R=5-Br) exhibited more effect among all the compounds with 82.41% reduction in the locomotor activity. The compound 26c (R= Cl) reduced the locomotor activity by 75.86%. Compounds 26c, 26a, 26g, 26f, 26h, 26e & 26b were next in the order of reduction of locomotor activity. Compounds containing halogen atoms exhibited more depressant activity as compared to other compounds.

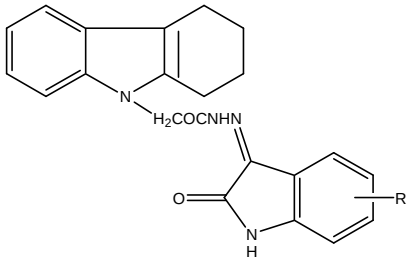



**Fig. 26: Isatin derivatives containing 1, 2, 3, 4-tetrahydrocarbazole moiety**

**(4) Psychotic activity**

Ashok Kumar *et al.* [69b] synthesized a series of 3-Spiro[1', 3', 4'-oxa/thiadiazolyl-2'-{5''-(substitutedphenyl-3''-amino)-4'-{5''-(substituted phenylisoxazolinyl)}]-5'-indol-2-ones (fig.27.) 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 and tested their anticovulsant and antipsycotic activity. Compounds having thiadiazole ring (i.e. 3e-3h, 4e-4h and 5e-5h) show better antipsychotic and anticonvulsant activity than the compounds having oxadiazole ring (i.e.3a-3d, 4a-4d and 5a-5d).Pyrazoline derivatives (i.e. 4a-4h) exhibited better activity than isoxazoline derivatives(i.e. 5a-5h) with isoxazoline ring. Compounds having 4-N $(CH_3)_2$ $C_6H_4$-substitution at Vth position of pyrazoline ring showed more potent activity than other substituted pyrazolines.

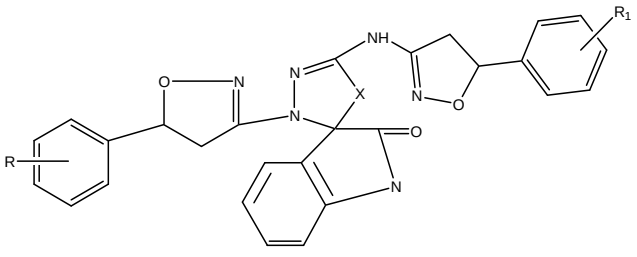



**Fig. 27: Pyrazolinyl/isoxazolinyl indol-2-ones derivatives**

**(5) Antianixiety Activity**

Anxiety (also called angst or worry) is a psychological and physiological state characterized by somatic, emotional, cognitive, and behavioral components[84, 85]. It is the displeasing feeling of fear and concern[86].The root meaning of the word anxiety is to vex or trouble, in either presence or absence of psychological stress, anxiety can create feelings of fear, worry, uneasiness, and dread [87]. 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 [88]. It enhances the response to GABA by facilitating the opening of GABA-activated chloride channel [89].

G.S.Palit *et al.* [90] synthesized a series of Schiff bases of *N*-methyl and *N*-acetyl isatin derivatives (fig.28). They studied the behavioral effects of isatin, one of the constituents of tribulin, a postulated endocoid marker of stress and anxiety has been shown to induce anxiety in rodents. In the present study, the behavioural effects of isatin were investigated in unrestrained rhesus monkeys (Macaca mulatta) living in social colonies. Pentylenetetrazol (PTZ), an anxiogenic agent, was used for comparison. Plasma cortisol levels were also estimated. Isatin (20 mg/kg, i.m.) induced behavioural responses comparable to those produced by PTZ (20 and 30 mg/kg, i.m.) which were indicative of anxiety and agitation. However, an increase in the dose (50 mg/kg, i.m.) of isatin resulted in reduction or loss of anxiogenic activity. Diazepam (1 mg/kg, i.v.) inhibited the behavioural effects of isatin (20 mg/kg, i.m.) and PTZ (20 mg/kg, i.m.), and the increase in plasma cortisol levels produced by them. The results indicate that, isatin induces an anxiogenic response in primates within a narrow dose range.

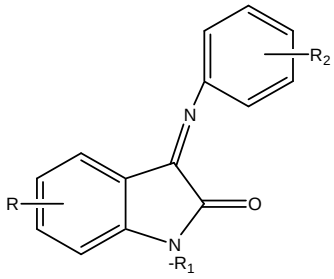



**Fig. 28: Schiff bases of isatin derivatives**

**DISCUSSION**

Isatin (1H-indole-2, 3- dione) are synthetically versatile substrates, where they can be used for the synthesis of a large variety of heterocyclic compounds, and as raw material for drug synthesis. The advances in the use of isatin for organic synthesis during the last twenty-five years, as well as a survey of its biological and pharmacological properties are reported in this review and in the accompanying supplementary information. 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 anticonvulsant, anxiety activities and other biological activity. Further we can conclude that many other derivatives of isatin can be synthesized which will be expected to show potent pharmacological activities.

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