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 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 new product that possesses different, biological activities.

INTRODUCTION

Isatin or 1H-indole-2, 3-dione (Fig.1) is an indole derivative. The compound was first obtained by Erdman and Laurent in 1841 as a product from the oxidation of indigo dye by nitric acid and chromic acids. Isatin forms a blue dye if it is mixed with sulfuric acid and crude benzene. The formation of the blue indophenol 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. 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, in Calanthe discolor, in Couroupita guianensis Aubl, has also been found as a component of the secretion from the parotid gland of Bufo frogs and in humans as it is a metabolic derivative of adrenaline. Substituted isatins are also found in plants, for example the melosatin alkaloids (methoxypentylisatins) obtained from the Caribbean tumorigenic plant Melochia tomentosa as well as from fungi: 6-(3'-methylbuten-2'-yl)isatin was isolated from Streptomyces albus and 5-(3'-methylbuten-2'-yl)isatin from Chaetomium globosum. The various substituents at 1'and 3'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.

PREPARATION

It may be prepared from cyclizing the condensation product of chloral hydrate, aniline and hydroxyamine in sulfuric acid. 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.

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) 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. Isatin is also reported as psychotropic agents and MAO inhibitors.

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Kumar et al. 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. 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, alkaline phosphatase, and xanthine oxidase, hyaluronidase as well as MAO. In a variety of tests isatin has been found to act as an antiseizure agent, it potentiates the antiseizure action of propranolol.

Yuwiler 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. 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. Isatin-induced anxiogenic action can be blocked by 5-HT3 receptor antagonists. 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. Isatin was found in mammalian tissues to be one of the components of the tribulin. 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. 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 antiseizure 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.

**STRUCTURE ACTIVITY RELATIONSHIP**

![Fig. 3: 2-indolinone (I) and 2-indolindione (II)](image)

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, C6, and C7 substitution generally enhanced CNS activity with some di and tri halogenated isatin (Fig. 3).

Thomson et al. found that a little variation at position 3 of 2-indolinone (I) and 2-indolindione (II) produced different degrees of biological activity.

**1 Anticonvulsant activity**

Popp et al. 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-hydroxy-3-phenacycloindole (XIIIB). Various analogues of 3-hydroxy-3-acetonyloxindole (XIIIA) and 3-acetophenylideneoxindole (XIIIB) showed somewhat less anticonvulsant activity. Another compound 3-cyclohexenonyloxindole (XIIIC) showed increase activity in MES screen from 300 to 100 mg/kg. The compound 3-hydroxy-3-cyclohexanonyloxindole (XIIIC) 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](image)
Kumar, N. et al.\textsuperscript{34} 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 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.

Mueller et al.\textsuperscript{[5]} were found that oxindole (I) isatin (II) and N-methyl isatin-3-thiosemicarbazone (III b) injected (1/p) in the rat, inhibited monoamine oxides in liver homogenate. Isatin-3-hydrazone (VIII a) was much less effective as an inhibitor, introduction of Br group at the position 5 in certain analogues 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.

\[ \text{Fig. 5: Phenyl indoloimidazole derivatives} \]

\[ \text{lb = 4-nitrophosphyl} \]
\[ \text{lc = 4-chlorophenyl} \]

Above review literature survey found that, if change at position 3\textsuperscript{rd} of isatin (II) like as hydrated 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 antipretyp tic activity, analgesic effect\textsuperscript{59}, anticonvulsant activity\textsuperscript{61}, few compounds were also reported as psychotropic agents\textsuperscript{62} and MAO inhibitors\textsuperscript{63}.

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\textsuperscript{64}. Some of isatin derivatives show CNS depressant activity.

**1. Anticonvulsant Activity**

Kumar, N. et al.\textsuperscript{59} 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, 5.5 kg/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-chlorophenyl) -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.

\[ \text{Fig. 6: N-phenyl-3-substituted pheny indolo(2, 3) imidazole derivatives} \]

\[ \text{lb = 4-nitrophosphyl} \]
\[ \text{lc = 4-chlorophenyl} \]
Fig. 7: Semicarbazone isatin derivatives

Krishan Nand Singh et al. synthesized a series of (3Z)-5-bromo-1-methyl-3-(4-nitrophenyl)-1, 3-dihydro-2H-indol-2-one (Fig. 7B) 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 (Fig. 7C) 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: Schiff bases of isatin derivatives

Sivakumar Smith et al. synthesized a series of N-methyl/acetyl-3-(un)-substituted isatin-3-semicarbazones (Fig. 8) 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. synthesized metal complexes of isatin-3-glycine (Fig. 9) 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.

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

Ashok Kumar et al. 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. 10) by the reaction of 3-Spiro[1', 3', 4'-oxa/thiadiazolyl-2'-{1''-acetyl-5''-(2'-hydroxyphenyl)-3''-amino}-4'-{1''-acetyl-5''-(2'-hydroxyphenyl) pyrazolyl}]-5''-indol-2-ones with methanol, hydroxyl amine and NaOH solution and tested their anticonvulsant and antipsychotic activity. Compounds having thiazolole 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. synthesized a series of heterocyclic derivatives of isatin (Fig. 11) 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.

Fig. 12: Heterocyclic derivatives of isatin

Gursoy et al. synthesized a series of 3-aryloxyl arythioacyl acetyl hydradrazono-2-indolinones (Fig. 12) in this study a new series of 3-aryloxyl arythioacyl acetyl hydradrazono-2-indolinones obtained by condensation of isatin with aryloxy/arythioacylhydrazines were treated with morpholine and formaldehyde to yield 1-morpholinomethyl-3-aryloxyl/aryl thioacyl acetyl hydradrazono-2-indolinones. Anticonvulsant evaluation of the compounds revealed varying degrees of activity against pentylentetrazole induced seizures.
Fig. 13: Hydrazono-2-indolinones derivatives
Singh et al. 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 diphenylketene 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. synthesized a series of 3-[4-(4-hydroxy-3-methoxy benzylideneamino) 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 anticonvulsant activity.

Fig. 15: Phenylimino Schiff bases of isatin derivatives
Prince P. Sharma et al. synthesized a series of Isatin Schiff’s bases (fig.16) were formed by the 6-[un]substituted 1, 3 benzoimidazole-2-amino 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. synthesized a series of Isatin 5-Sulphonamide derivatives (fig. 17) and the anticonvulsant activity of some new isatin-5-sulphonamide derivatives against maximum electric shock induced and Pentylentetrazol (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. synthesized 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).

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

Fig. 19: 2-aryl-2, 5 dihydropyridazino [43-b] indol-3(3H) ones derivatives
Rajavendran et al. synthesized of aryl/alkylidene-4-(1, 3-dioxo-1, 3-dihydro-2H 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.
Sridhar et al. 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 ED50 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.

Veerasamy et al. 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.

Azam et al. 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 pentyleneetrazole (scPTZ)-induced seizure tests and minimal motor impairment was determined by rotored 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 fluoro 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.
Bethi Srinivas et al. 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-y)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, 26d, 26h, 26e & 26f 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. synthesized a series of 3-Spiro[1’, 3’, 4’-oxa/thiadiazolyl-2’-(5’-substitutedphenyl-3’-amino)4’-f5’] (substituted phenylisoxazolyl)])-1’-indol-2-ones (Fig. 27) by the reaction of 3-Spiro[1’, 3’, 4’-oxadiazipozyl-2’-(1’-acetyl-5’- (2-hydroxyphenyl) pyrazolyl)])-5’-indol-2-ones with methanol, hydroxyl amine and NaOH solution and tested their anticonvulsant and antipsycotic activity. Compounds having thiadiazole ring (i.e. 3a-3d, 4a-4d and 5e-5h) show better antipsycotic 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 oxazoline derivatives (i.e. 5a-5h) with isoxazoline ring. Compounds having 4-N (CH3)-C=O-substitution at Vth position of pyrazoline ring showed more potent activity than other substituted pyrazolines.

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

(5) Antianxiety Activity
Anxiety (also called angst or worry) is a psychological and physiological state characterized by somatic, emotional, cognitive, and behavioral components. It is the displeasing feeling of fear and concern. 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. Anxiety is an unpleasant of tension, apprehension, or uneasiness 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.

G.S.Palit et al. 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 behavioral effects of isatin were investigated in unrestrained rhesus monkeys (Macaca mulatta) living in social colonies. Pentyleneetrazol (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 of anxiogen 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.

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 pharmaceutical 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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