ISATIN – A POTENT ANTICONVULSANT AGENT

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ABSTRACT
Convulsion or epilepsy is the most common serious disorder of the brain and is characterized by recurrent unprovoked seizures. It is estimated that there are 50 million people with convolution worldwide and the majority of cases are in the developing countries. This means almost 1 in 100 people has the condition. Convulsion usually begins during childhood, although it can start at any age. In general, heterocyclic systems consisting mainly nitrogen, oxygen, and sulfur atom form a huge class of compounds of biological and medicinal interest. A vast number of heterocyclic systems which consists mainly five and six membered analogues represent a varied group of molecular scaffolds. A number of such heterocyclic scaffolds have been effectively incorporated into new drug leads and therapeutic agents. On the other hand, Schiff and Mannich bases, the condensation products of aromatic aldehydes with aromatic amines, have been recognized to have a wide variety of biological applications. Furthermore, Schiff and Mannich bases derived from different heterocyclic scaffolds especially isatin covers a wide range of pharmacological potential which includes mainly anticonvulsant activity. In addition literature review also indicates that Schiff and Mannich base of isatin derivatives showed outstanding anticonvulsant activity. The present review summarizes anticonvulsant activities of isatin analogs.

KEYWORDS: Isatin, Indole-2,3-dione, Anticonvulsant, Neurotoxicity, MES.

INTRODUCTION
The discovery of novel drugs and drug compounds has forever been the aim of pharmaceutical sciences and, especially, of medicinal chemistry, which arises from pharmaceutical chemistry.[1,2] Drug design in its wide sense and structure-activity relationship studies are important and at the heart of medicinal chemistry, and it are the advancement and progress of this field of research that has made medicinal chemistry the contemporary and extremely productive science it has become in current decades. Majority of the currently available medicinal compounds consist one or more heterocyclic ring system. From the contemporary medicinal chemistry investigation it was found that isatin is one such significant heterocyclic system has been gained magnitude due to the broad array of biological activities.

Isatin I (1H-indole-2,3-dione) was original obtained by Erdman and Laurent in 1841 as a product from the oxidation of indigo by chromic acids and nitric acid. The synthetic versatility of isatin has led to the extensive use of this compound in organic synthesis.[3]

Figure 1: Chemical structure of isatin
Subsequent the discovery of isatin ring a numeral of structural modifications have been made consecutively to elevate the biological actions such as anticonvulsant, anti-inflammatory, analgesic, antifungal, antibacterial, antihistaminic, anticancer, anti-HIV, anti-oxidant, anti-diabetic and anti-tubercular activity which paying attention the interest of medicinal and pharmaceutical chemists. A meticulous literature review is depicted in this for anticonvulsant activity of isatin ring.

ANTICONVULSANT POTENTIAL OF ISATINS
In the early days Popp and his co-workers have been proved the anticonvulsant activity of indole-2,3-dione (isatin) moiety I. They screened the isatin against
different seizure types. Isatin shows the significant activity,[4] Jain et al., designed some heterocyclic analogs of isatin and prepared by reaction of a heterocyclic nuclear system like isatin/5-fluoroisatin 2 with ethyl nitrile acetate and different substituted ketones which shows significant anticonvulsant activity.[5]

Gursoy and Karali et al., designed and synthesized by incorporating arylthiooxacetyl, 3-aryloxy, hydrazono-2-indolinones based some novel isatin derivatives 3. These synthesized compounds are evaluated for its anticonvulsant activity. Tested compounds showed promising results.[6] Singh et al., was designed and synthesized a series of novel isatin based spiroazetidinones 4. All the novel derivatives are screened for antiepileptic activity by subcutaneous metrazol induced convulsions (scMET), subcutaneous strychnine (scSTY) induced seizure model and maximal electroshock method (MES) at different dose levels. They also screened neurotoxicity by rotorod test. Results showed promising activity compared to standard drug phenytoin.[7]

Pandeya et al., in 2002 disclosed a group of semicarbazones 5 reaction with isatin and showed its anticonvulsant activity. They also studied the key structural requirements which are needed for the effective anticonvulsant activity. This study also concluded the importance of hydrogen binding and they opened the novel pharmacophore concept with its binding sites for the maximal activity.[8] Sridhar et al., in 2002 reported the anticonvulsant activity of series of novel hydrazones, Schiff and Mannich bases of indole-2,3-dione derivatives 6 by metrazol induced convulsions (MET) and maximal electroshock method (MES) at different dose levels. Neurotoxicity of the novel synthesized derivatives was also assessed at the same dose levels. Eight out of twenty compounds showed exceptional anticonvulsant activity. 3-(4-chlorophenylimino)-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 synthesized compounds exhibited lesser neurotoxicity when compared to the standard drug phenytoin.[9]

When N-methyl / acetyl group introduction in N-1 position of isatin-3-thiosemicarbazone showed a significant improvement in anticonvulsant action and also showed significant sedative hypnotic activity. Pandey et al., reported a series of C-5 substituted and un substituted isatin-3-thiosemicarbazones as Schiff and N-1-methyl / acetyl group substituted Mannich bases. Among the compounds synthesized compound bearing N-methyl 7 and N-acetyl 8 isatin-3-thiosemicarbazone derivatives exhibited as the most active compounds by the protection they exhibit in MES, scSTY and scPTZ screens. All the compounds showed significant sedative hypnotic activity.[10]

Yogeeswari et al., disclosed when halogens introduced at C-5 position of isatin substituted by different semicarbazones at C-3 showed anticonvulsant activity in the MES and scPTZ screens with acute neurotoxicity. Among the different unique semicarbazone derivatives, C-5 chloro 9 and fluoro 10 substituted isatin compounds showed mild protection in scPTZ screen and in the MES screen, respectively.[11] Verma and his co worker in 2004 synthesized different Schiff bases of N-methyl and N-acetyl isatin derivatives with various aryl amines and evaluated for their anticonvulsant activities against maximal electroshock (MES) and subcutaneous

![Figure 2: Chemical structure of anticonvulsant isatins 1-8](image-url)
metrazole (scMET). Among the different derivatives compound N-methyl-5-bromo-3-(p-chlorophenylimino) isatin 11 exhibited potent anticonvulsant activity in MES and scMET with LD₅₀ greater than 600 mg/kg, showing better activity than the standard drugs carbamazepine, phenytoin and valproic acid.²¹

Yogeeswari and her research team unconfined the results when compared the anticonvulsant activity of 6-substituted benzothiazolyl isatinimino derivatives with benzylidene or acetophenone derivatives by maximal electroshock induced seizure (MES) and subcutaneous pentylenetetrazole (scPTZ) induced seizure models in mice. Because the MES and scPTZ tests have become the two most widely employed seizure models for the early identification and high throughput screening of investigational antiepileptic drugs. Generally the isatinimino derivatives 12 were found to show better anticonvulsant activity profile than benzylidene or acetophenone derivatives when the 6-position in benzothiazole moiety was either methyl or methoxy. These results indicate that the substituent at 6-position of benzothiazole moiety should be an electron donating group in combination with isatin nucleus as an auxiliary aryl group. All the compounds exhibited less significant or no neurotoxicity compared to phenytoin.¹³

In 2007 Sudo and co-workers took the research work on isatin ketals as sedative and hypnotic agents. They found the lead molecule 13 with good hypnosis and sedation effect without any toxic effects on respiratory and cardiac tissues.⁴¹ Smitha and his research team disclosed the synthesis of some new N-substituted isatin analogues 14. All the prepared compounds have been evaluated against antiepileptic and hypnotic sedative activity using MES, scPTZ and scSTY models. Several compounds showed better activity compared with standard drugs used.⁴²

Sharma et al., revealed in their reported the anticonvulsant activity of series of novel Schiff bases of isatin derivatives by subcutaneous metrazol induced convulsions (scMET) and maximal electroshock method (MES) at different dose levels. They also screened neurotoxicity by rotorod test. Few investigated molecules exhibit momentous activity. Compounds with electron releasing group like dimethylamino and methoxy substituted derivatives 15 showed incomparable activity.⁴³ Kiran and his co-workers reported the novel isatin sulphonamides derivatives 16. All the synthesized compounds have been evaluated against anticonvulsant activity using pentylenetetrazol induced seizure model. Phenytoin was used as standard for this study. Many compounds showed comparable antiepileptic activity.⁴⁴

Novel metal complexes of isatin derivatives are synthesized by Subudhi and his co-workers in 2009. The metal complexes of isatin further reacted with an amino acid glycine. The copper (II) metal complex 17 was emerged as lead molecule.¹⁸

Kumar et al., has been prepared 3-spiro-5'-indol-2-ones 18 by the condensation 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 hydroxyl amine, methanol, and sodium hydroxide solution. Report clearly indicates the unreliable degree of anticancer activity exhibited by these compounds.¹⁹ Prakash et al., designed and synthesized some novel

 ![Chemical structure of anticonvulsant isatins 9-17](image-url)
Schiff base of isatin derivatives 19. It was prepared by reaction of imesatin with different types of aromatic aldehydes. The initial imesatins were prepared by condensation of isatin with p-phenylendiamine. All of the synthesized compounds were screened for their anticonvulsant activities against subcutaneous metrazole (scMET) and maximal electroshock (MES). Among the compounds synthesized 3-(4-(3,4,5-trimethoxy benzylideneamino) phenylimino)indoline-2-one showed significant anticonvulsant activity with lesser dose in scMET as well as in MES methods.[20]

Praveen et al., in 2011 synthesized several substituted N-allyl and N-propargyldi(indolyl)indolin-2-ones derivatives 20. As speculated many compounds produced antiepileptic activity in their screening. Additionally these series of compounds also tested for their antimicrobial activity using two bacterial strains and one fungal strain. Compounds showed promising activity.[21] Pandeya and his co worker have been synthesized novel substituted isatin-3-oximes 21 to derive structure activity relationship (SAR). The synthesized compounds have been screened against scMET (subcutaneous Metrazol) induced seizures, MES (maximal electroshock), and 6Hz induced shock. Moreover neurotoxicity has been tested with rotorod test. Compound 5-bromo substituted isatin-3-oxime was showed more active in both 6Hz test and MES with no neurotoxicity even up to 300 mg/kg.[22]

Kumar et al., in their latest report revealed that the synthesis of various Schiff and Mannich bases of indoline derivatives with 2-aminopyridine. These synthesized derivatives were evaluated for their anticonvulsant activity by dissimilar chemical induced convulsion models such as thiosemicarbazide, isoniazid and 4-aminopyridine, respectively. The synthesized compounds were also evaluated for their neurotoxicity by rotorod method. The decoded result showed that few of the pyridine containing compounds 22 & 23 is highly active against different chemo induced convulsion models, proving their diverse mode of actions in the course of convulsive seizures.[23]

Eggadi et al., in 2013 synthesized and reported anticonvulsant activity of isatin derivatives 24 to decrease the side effects and augment the percentage protection from different stages of convulsions. No animals showed toxic effects up to 2000 mg/kg. Greater part of compounds showed antiepileptic effect at the dose levels of 10 and 100 mg/kg in PTZ induced convulsions test and MES test. The isatin motifs which proved antiepileptic activity in both PTZ induced convulsion and MES models are selected and screened brain GABA levels. They showed significant enhance of GABA levels in brain.[24]

A new series of dibromo substituted isatin semicarbazones 25 are prepared by Kumar et al. All the compounds are evaluated for CNS depressant activity and antiepileptic activity. Antiepileptic activity tested using MES seizure model. Compounds showed diversified biological activity.[25] Saravanan et al., reported a novel series of isatin derivatives as antiepileptic activity. The fusion of isatin moiety with morpholine derivatives 26 showed an enhanced antiepileptic activity. The antiepileptic activity was screened against MES and scPTZ models. They also screened neurotoxicity study for the newly synthesized compounds.[26]

Figure 4: Chemical structure of anticonvulsant isatins 18-26
CONCLUSION
Isatin which is chemically known as indole-2,3-dione was a fused heterocyclic compound possessing various pharmacological actions. Emerging research interest on isatin moiety already has been proven by various search groups in the literature. The great interest associated with isatin and their derivatives is based on their versatility as synthetic building blocks. This review paper comprises of up to date information of anticonvulsant isatin analogs. Results of isatin derivatives and their substitutions effect on anticonvulsant activity were also presented. Though many procedures are established for the synthesis of isatin core, but very few of them yielded isatin with better percentage, but much more effort yet to be given to develop new synthetic strategies. Furthermore, anticonvulsant activity with new dimension needs to be explored for isatin. Therefore this review may useful for medicinal chemist.

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