

ISATIN – A POTENT ANTICONVULSANT AGENT

G. Saravanan^{1*}, V. Alagarsamy¹, P. Dinesh Kumar², T. Panneer Selvam³ and C.R. Prakash

¹*MNR College of Pharmacy, Fasalwadi, Sangareddy – 502294, Telangana, India.

²Hindu College of Pharmacy, Amaravathi Road, Guntur – 522002, Andhra Pradesh, India.

³International Research Center, Kalasalingam University, Anand Nagar, Krishnan Koil – 626190, Tamil Nadu, India.

***Corresponding Author: Dr. G. Saravanan**

MNR College of Pharmacy, Fasalwadi, Sangareddy – 502294, Telangana, India.

Article Received on 14/06/2017

Article Revised on 04/07/2017

Article Accepted on 24/07/2017

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 convulsion 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** (1*H*-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]

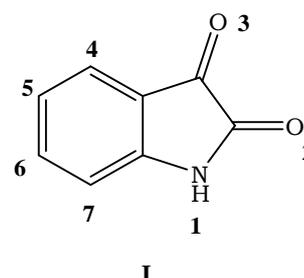


Figure 1: Chemical structure of isatin

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 **1**. 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 arylthioxyacetyl, 3-aryloxy, hydrazone-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 spiroazetidines **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 bonding 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. Pandeya *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]

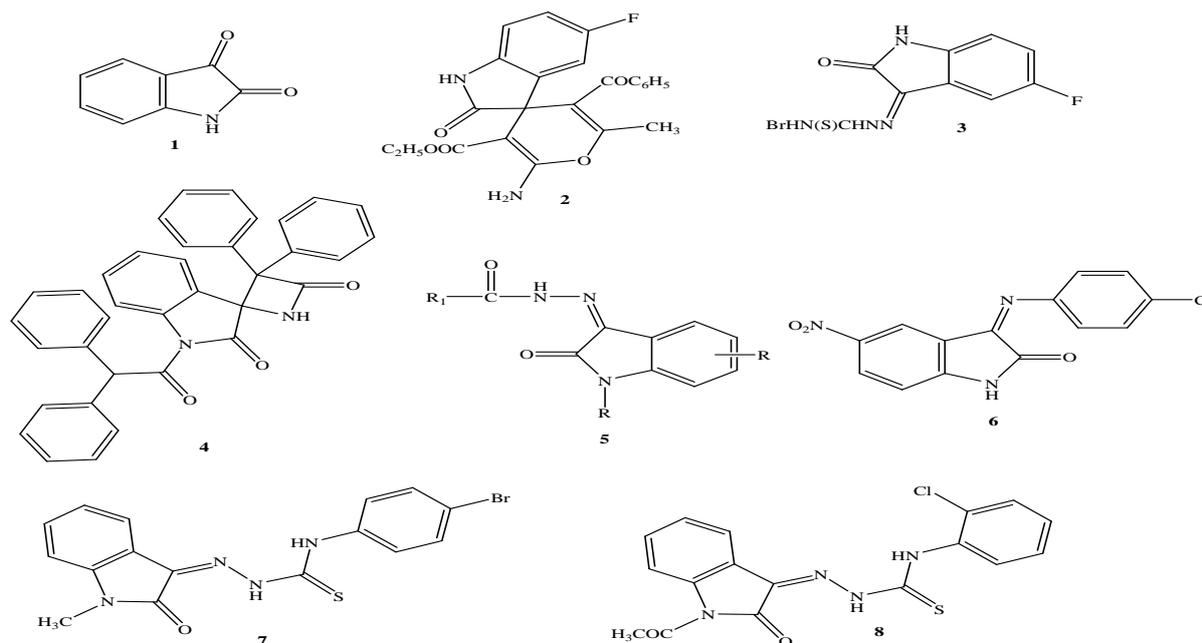


Figure 2: Chemical structure of anticonvulsant isatins 1-8

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

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.^[12]

Yogeewari 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 type 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.^[14] Smitha and his research team^[26] 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.^[15]

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.^[16] 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.^[17]

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]

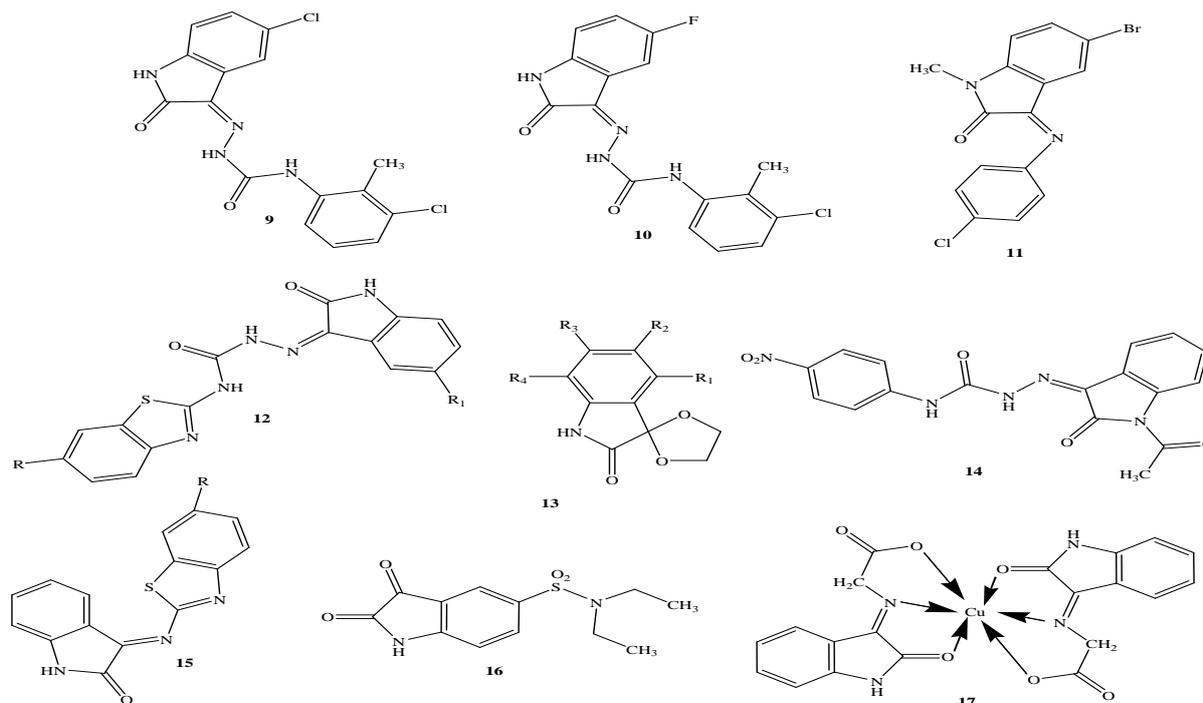


Figure 3: Chemical structure of anticonvulsant isatins 9-17

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)pyrazolanyl}]'-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

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*-phenylenediamine. 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-trimethoxybenzylideneamino) 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-amino pyridine. 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]

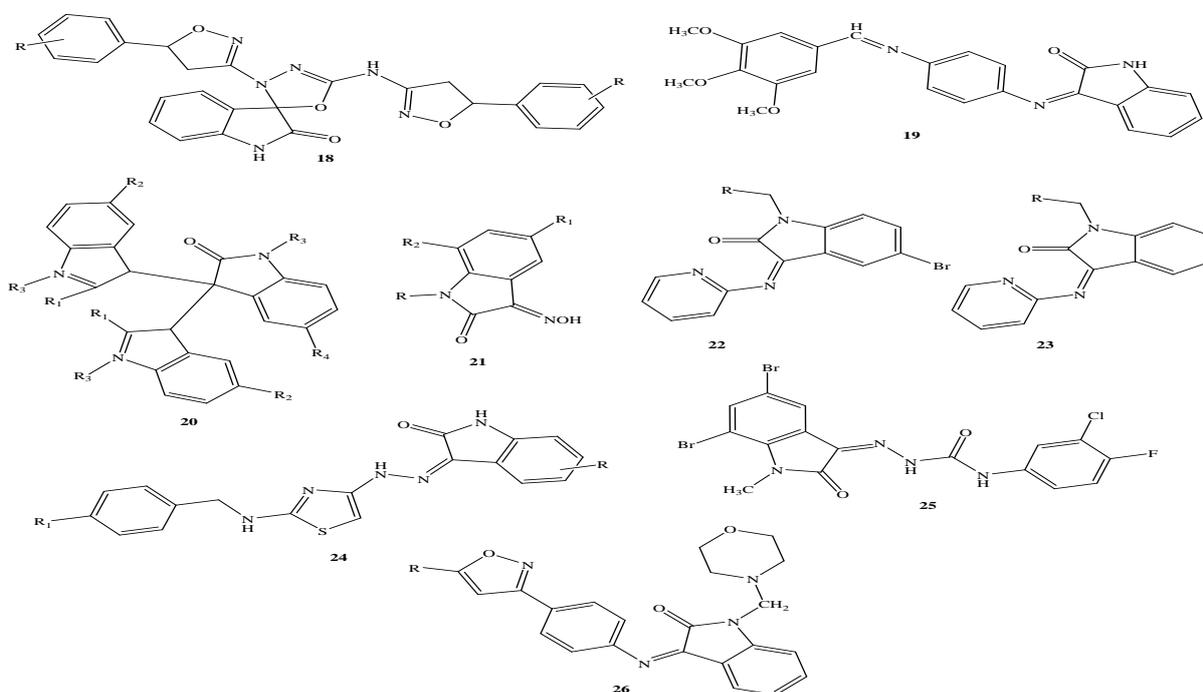


Figure 4: Chemical structure of anticonvulsant isatins 18-26

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.

ACKNOWLEDGEMENT

Authors are thankful to the management of MNR College of Pharmacy, Fasalwadi, Sangareddy, Telangana, India, for providing necessary facilities to carry out this work successfully.

REFERENCES

1. Andrejus K. Essentials of medicinal chemistry. 1988; 2nd edition: 3-4.
2. Wilson and Giswold. Text book of organic medicinal and pharmaceutical chemistry. J.B. Lippincott Company, USA, 1991; 9th edition: 1-2.
3. Robert CE. Heterocyclic compounds. University of Michigam, 1957; 6: 325-45.
4. Popp FD. Potential anticonvulsants – IX: Some isatin hydrazones and related compounds. J Hetero Chem, 1984; 21: 1641-5.
5. Jain R, Bansal. A facile synthesis and central nervous system activities of fluorine containing spiro-[3*H*-indole-3,4(4*H*)-pyran]-2(1*H*)-ones. Pharmazie, 1995; 50: 224-5.
6. Gursoy A, Karali N. Some 3-hydrazono-2-indolinones and *N*-Mannich bases as potential anticonvulsants. Farmaco, 1996; 51: 437-42.
7. Singh GS, Singh T, Lakhan R. Synthesis and biological activity of azetidinones from hydrazine thieno pyrimidine. Indian J Chem, 1997; 36B: 951-4.
8. Pandeya SN, Raja AS. Synthesis of isatin semicarbazones as novel anticonvulsants: Role of hydrogen binding. J Pharm Pharm Sci, 2002; 5(3): 266-71.
9. Sridhar SK, Pandeya SN, Stables JP, Ramesh A. Anticonvulsant activity of hydrazones, Schiff and Mannich bases of isatin derivatives. Eur J Pharm Sci, 2002; 16: 129-32.
10. Pandeya SN, Smitha S, Stables JP. Anticonvulsant and sedative hypnotic activities of *N*-substituted isatin semicarbazones. Arch Pharm Pharm Med Chem, 2002; 4: 129-34.
11. Yogeewari P, Thirumurugan R, Kavya R, Samuel JS, Stables J, Sriram D. 3-Chloro-2-methylphenyl-substituted semicarbazones: Synthesis and anticonvulsant activity. Eur J Med Chem, 2004; 39: 729-34.
12. Verma M, Pandeya SN, Singh KN, Stables JP. Anticonvulsant activity of Schiff bases of isatin derivatives. Acta Pharm, 2004; 54: 49-56.
13. Yogeewari P, Sriram D, Mehta S, Nigam D, Kumar M, Murugesan S, Stables JP. Anticonvulsant and neurotoxicity evaluation of some 6-substituted benzothiazolyl-2-thiosemicarbazones. IL Farmaco, 2005; 60: 1-5.
14. Sudo GZ, Pontes LB, Gabriel D, Mendes TC, Ribeiro NM, Pinto AC, Trachez MM, Sudo RT. Sedative hypnotic profile of novel isatin ketals. Pharmacol Biochem Beha, 2007; 86: 678-85.
15. Smitha S, Pandeya SN, Stables JP, Ganapathy S. Anticonvulsant and sedative hypnotic activities of *N*-acetyl / methyl isatin derivatives. Sci Pharm, 2008; 76: 621-36.
16. Sharma PP, Pandeya SN, Roy RK, Anurag, Verma K, Gupta S. Synthesis and anticonvulsant activity of some novel isatin Schiff's bases. Int J Chem Tech Res, 2009; 1(3): 758-63.
17. Kiran G, Rajyalakshmi G, Reddy RN, Rao JV, Sarangapani M. Anticonvulsant activity of some isatin-5-sulphonamide derivatives. J Pharm Res., 2009; 2(3): 388-90.
18. Subudhi BB, Bhattaa D, Jenab A. Anticonvulsant and antimicrobial activity of Cu (II), Zn (II) and Co (II) complex of isatin 3-glycine. Ira J Pharm Sci, 2009; 5(2): 83-8.
19. Kumar A, Kaur H, Kumar S. Synthesis, antipsychotic and anticonvulsant activity of some new pyrazolinyl / isoxazolinylindol-2-ones. Int J Chem Tech Res, 2010; 2(2): 1010-9.
20. Prakash CR, Raja S, Saravanan G. Synthesis, characterization and anticonvulsant activity of novel Schiff base of isatin derivatives. J Pharm Pharm Sci, 2010; 2(4): 77-81.
21. Praveen C, Ayyanar A, Perumal PT. Practical synthesis, anticonvulsant, and antimicrobial activity of *N*-allyl and *N*-propargyl di(indolyl)indolin-2-ones. Bioorg Med Chem Lett, 2011; 21: 4072-77.
22. Pandeya SN, Singh UK, Srivastava BK, Kukreja P. Synthesis and anticonvulsant activity of substituted isatin-3-oximes. J Drug Chem, 2012; 2(8): 1-7.
23. Kumar CA, Pandeya SN. Synthesis & anticonvulsant activity (chemo shock) of Schiff and Mannich bases of isatin derivatives with 2-amino pyridine (mechanism of action). Int J Pharm Tech Res, 2012; 4(2): 590-8.
24. Eggadi V, Kulandaivelu U, Sharvanabhava BS, Jupally VR. Screening of the anticonvulsant activity of some isatin derivatives in experimental seizure models and its effect on brain GABA levels in mice. Am J Pharmacol Sci, 2013; 1(3): 42-6.
25. Kumar D, Sharma VK, Kumar R, Singh T, Singh H, Singh AD, Roy RK. Design, synthesis and anticonvulsant activity of some new 5,7-

dibromoisatin semicarbazones derivatives. *Exp Cli J*, 2013; 12: 628-40.

26. Saravanan G, Alagarsamy V, Dineshkumar P. Anticonvulsant activity of novel 1-(morpholinomethyl)-3-substituted isatin derivatives. *Bull Facul Pharm*, 2014; 52: 115-124.