WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A Review on *N*-Mannich Base Derivatives of Anticonvulsant Drugs

Raveena Praveen*, D Visagaperumal, Vineeth Chandy

Department of Pharamaceutical Chemistry, T. John College of Pharmacy, 560083, Bangalore, Karnataka

A B S T R A C T

The present review focuses on the various synthesis of *N*-Mannich base derivatives of different anticonvulsants or seizures this is the basic requirement for the drug to reach the brain, the target site for the convulsion. The *N*-Mannich base approach will help the various anticonvulsant drugs to reach the brain. This is because of the increase in lipophilicity of the drugs containing *N*-Mannich base group. Various derivatives of such researches have been compiled for thesame.

Keywords:*N*-Mannich base, Anticonvulsants, Brain, lipophilicity

1. Introduction

Convulsions

Anticonvulsants are also knowns antiepileptic drugs that are used to treat epilepsy as well as non-epileptic convulsive disorders.[1] Epilepsy is a chronic neurological disorder which is characterized by recurrent unprovoked seizures. These seizures are signs and/or symptoms of abnormal, excessive or synchronous neuronal activity in the brain.[2] Epilepsy is a common neurological disorder that affects 0.5 to 1% of the global population (45-100 million people).[3] Epilepsy can be controlled, but can not be cured, with medication, and surgery may be considered in some chronic cases. Over 30% of people with epilepsy do not have seizure control even with the use of best medications. Epilepsy is not considered as a single disorder, but it's a group of syndromes which has vastly divergent symptoms but all involves episodic abnormal electrical activity in the brain.[4]

1.1. Mechanism of Action of Antiepileptic

The word "antiepileptic medicine" is actually a misnomer. These medications are antiseizure or anticonvulsant, but they have little effect on epilepsy's natural course. The AEDs are not completely antiepileptic since they only treat the symptoms of seizure suppression. A medication must operate on one or more target molecules in the brain that are involved in seizures to have anticonvulsant activity. There are currently no treatments that target the epileptogenic process's cascade of signalling changes in the brain. Rather, almost all of the available AEDs, both old and modern, are directed at the seizure, which is the end product of epileptogenesis. This is usually achieved by altering the bursting properties of neurons and decreasing synchronisation in both localised and generalised neuronal networks. With the exception of absence seizures, where the target is more thalamocortical circuitry, the drugs target one or more molecules in the brain to achieve these objectives. Almost all of them are designed to either increase GABA-mediated inhibition or decrease glutamate-mediated excitation.[5]

* *Corresponding author.*
E-mail address: raveenakhan96@gmail.com

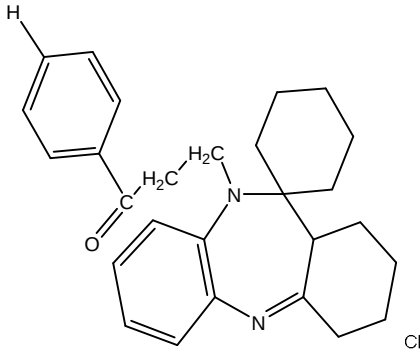
1.2. Mannich Bases

The quest for antiepileptic compounds with more selective activity and lower toxicity remains a focus of medicinal chemistry research. Several approaches to a rational drug design method for a new anticonvulsant have been proposed.[6] The first approach is to find new goals by gaining a deeper understanding of epilepsy's molecular mechanisms. Another choice is to change already existing drugs and formulations for example derivatives of mannich bases.

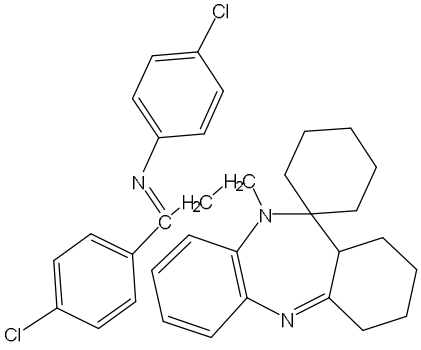
The Mannich reaction produces Mannich bases, also known as beta-amino ketone carrying compounds. Mannich reaction forms a carbon-carbon bond involving nucleophilic addition reaction and it is also a important step in the synthesis of various compounds including natural products, pharmaceuticals, and so on. For the construction of nitrogen-containing compounds, the Mannich reaction is essential. There are a number of aminoalkyl chain bearing Mannich bases that act as pharmacophores or bioactive leads of high curative value, such as fluoxetine, atropine, ethacrynic acid, trihexyphenidyl, and so on. Mannich bases are highly reactive and have a wide range of properties, like anti-inflammatory, anti-cancer, antibacterial, antifungal, anticonvulsant, anthelmintic, antitubercular, analgesic, anti-HIV, antimalarial, antipsychotic, and several others. The formation of,-unsaturated ketone by deamination of hydrogen atoms in the amine group is primarily responsible for Mannich bases' biological activity. Mannich bases are known to play a important role in the development of synthetic pharmaceutical chemistry.[7]

2. Review of Literature

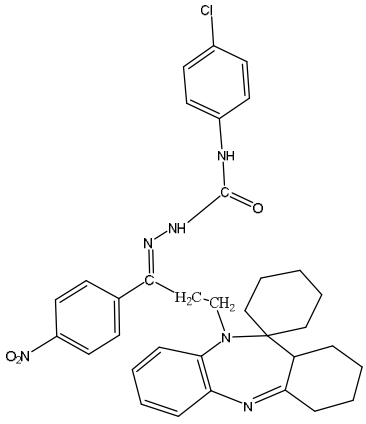
Pandeya SN *et al.*,had synthesized and screened anthiconvulsant activity of various 1,5-Benzodiazepine derivatives and they were biologically important molecules with extensive activity, motor function, appetitive behaviour. 1,5-Benzodiazepine were synthesized by condensation of *o*-phenylenediamine and ketones, eg., cyclohexane and acetone in presence of sulfated zirconia. a1 and a2 were found to be most active among all compound in isoniazid induced model. a3 and a4 were found to be most active in thiosemicarbazide induced model. a5 and a6 shows good anticonvulsant activity and have an advantage over that they are not sedative.[8]



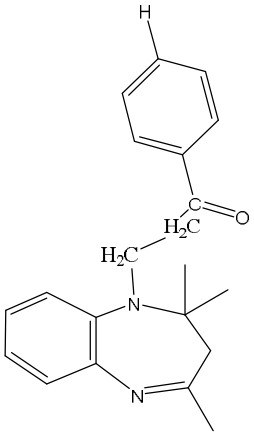
a1.



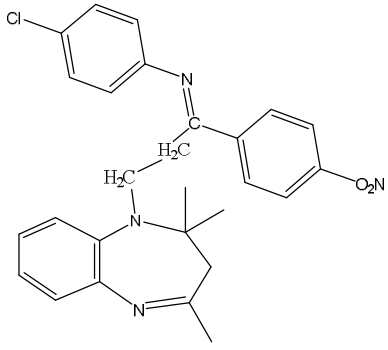
a2



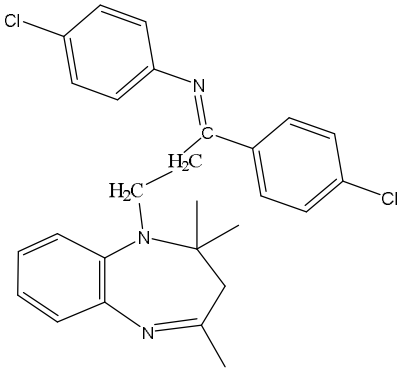
a3.



a4.

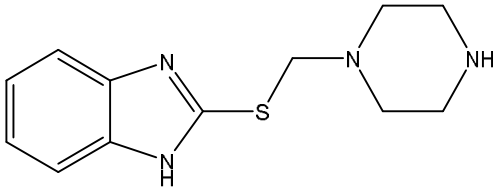


a5.

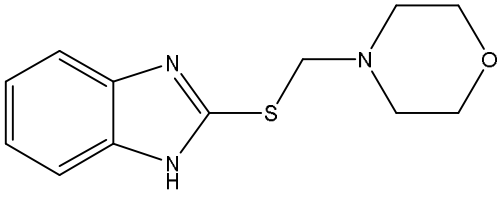


a6.

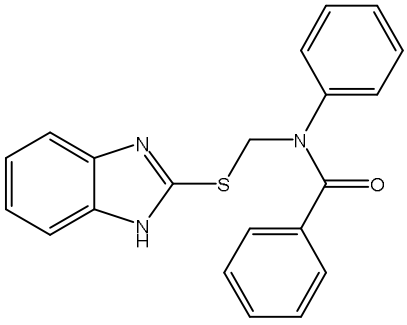
Anandarajagopal K *et al.*,have synthesized various 2-mercaptobenzimidazole derivatives, one of the most impoartant derivatives of benzimidazole exhibited a wide variety of interesting biological activities such as antimicrobial, antihistamine, neurotropic and analgesics activities. A series of novel mannich bases of 2-mercaptobenzimidazole derivatives were synthesised using the mannich reaction, which involves the reaction of secondary amine-containing compounds with formaldehyde. All of the synthesised compounds have a strong tendency to shorten the length of the stimulated extensor process. All the synthesized compounds at a dose of 20 mg/kg, ip exhibited anticonvulsant activity (26.10 – 85.98 % protection) against maximum electrical shock induced convulsion compared with the standard drug phenytoin. Compounds **b1**, **b2** and **b3** exhibited excellent anticonvulsant activity.[9]



b1.

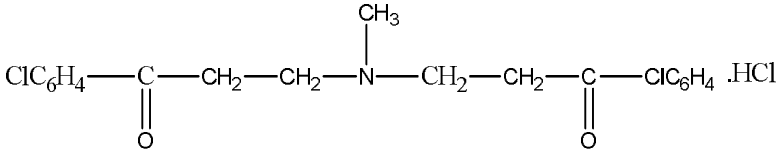


b2.

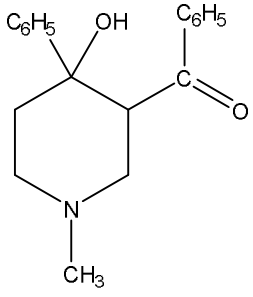


b3.

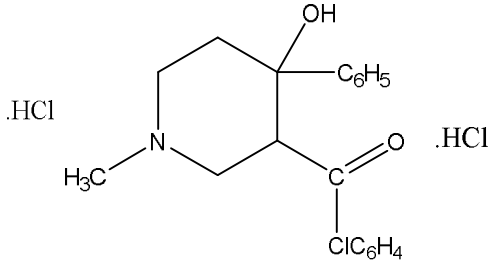
Gul HI*et al.*,have synthesizedsome acetophenone derived bis Mannich bases (**c1**) and piperidine (**c2, c3**), which are the structural isomers of **c1**, and also quaternary piperidine derivative and studied for anticonvulsant activity. According to the data obtained from the in vivo studies **c1, c2** and **c3** were determined to have significantly high anticonvulsant activity against the MES seizures at a dose range of 30 to 300 mg/kg. It should be noted that for compound **c2** significant neurotoxicity was observed at a dose level of 300 mg/kg, while no neurotoxicity was detected for the compounds **c1** and **c3.** Therefore compounds **c1** and **c3** seem to be promising compounds for their potential anticonvulsant activity as neurotoxicity was not detected.[10]



c1.

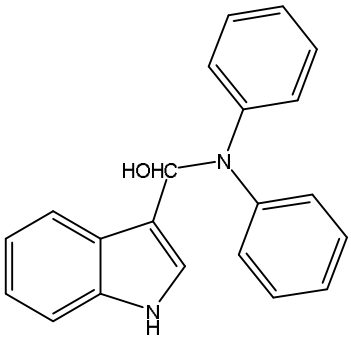


c2.

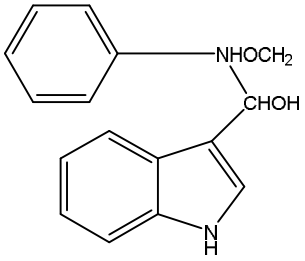


c3.

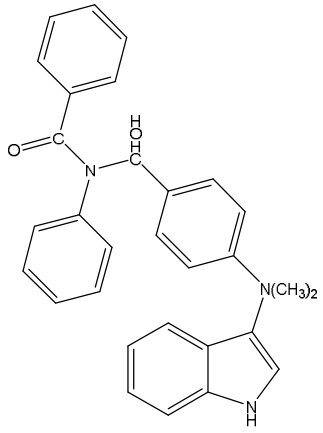
Kulkarni SD*et al.*,had synthesizedMannich bases of indole derivatives which have various pharmacological profile such as antiepileptic, analgesics and biological profile such as antimicrobial including anticonvulsant activity. Novel Mannich bases of indole were synthesized by using a series of aldehyde and secondary amine in presence of ethanol with magnetic stirrer for 4-6 hours. in cold condition. Phenytoin was used as a standard drug.The compounds synthesized were evaluated for anticonvulsant activity by maximum electroshock induced convulsion method. Most of the compounds have shown significant anticonvulsant activity. Compound **d1, d2** and **d3** have showed maximum anticonvulsant activity.[11]



d1.

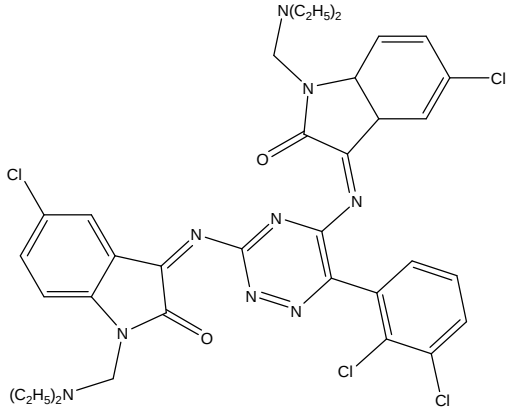


d2.

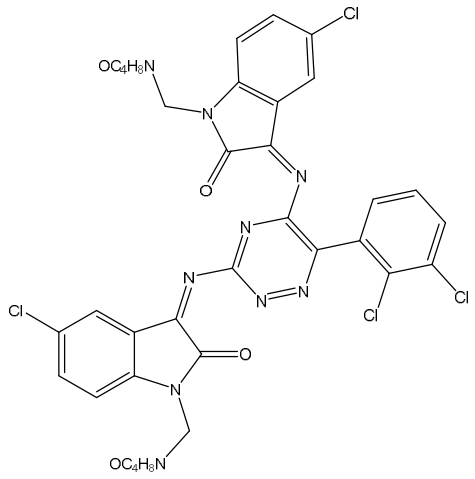


d3.

Kulkarni AA*et al.*,have synthesized a novel series of Mannich and Schiff base derivatives of lamotrigine and all the compounds were screened for anticonvulsant activity using MES method. The anticonvulsant evaluations of synthesized compounds were done in rat at 10 mg kg1 by i.p. route. As standard medications, phenobarbitone sodium and lamotrigine were used, and the percentage of time spent in extension, flexion, clonus, and stupor by the animals was measured. Compounds **e1**and **e2** showed more potent anticonvulsant activity when compared with that of the standard drug. Remaining all compounds show moderate activity.[12]

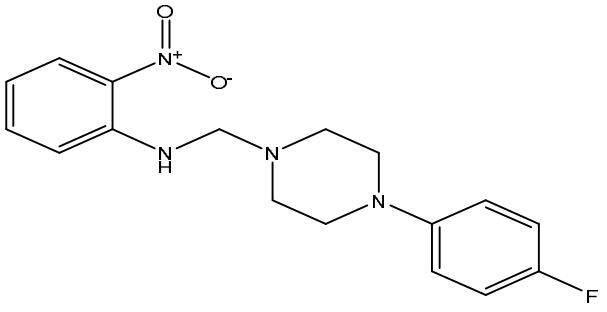


e1.

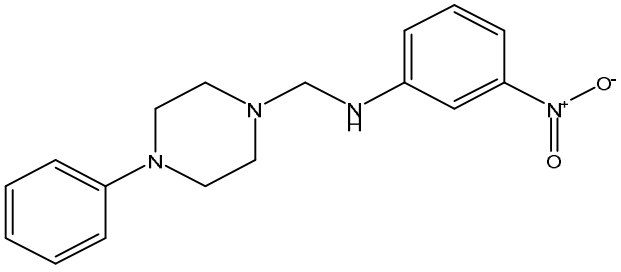


e2

Prasanthi Ghas synthesized the Mannich bases of substituted piperazine derivatives *via* feasible Mannich reaction. Compound **f1** showed significant anti PTZ activity and compound **f2** showed good protection against shock induced seizures. Both the compounds are less active than reference standard drugs diazepam and phenytoin respectively.[13]

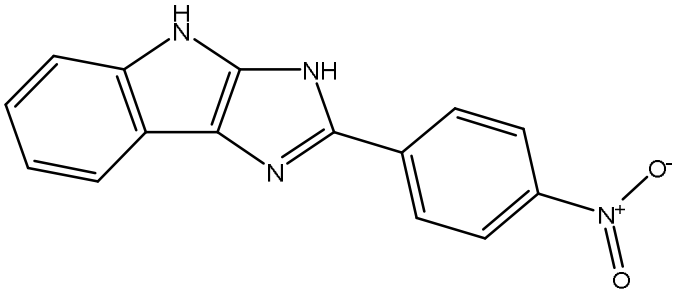


f1.

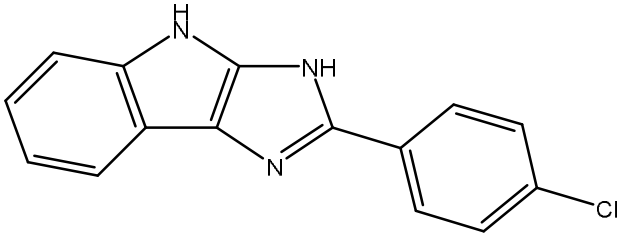


f2.

Kumar N*et al.*, have synthesized a number of new Phenyl Indoloimidazole derivatives and evaluated for their anticonvulsant activity. The compounds were obtained when condensation was done in the presence of glacial acetic acid and ammonium acetate in different aromatic aldehyde with *N*-1-phenyl isatin. The maximum electroshock seizure procedure was used to screen all newly synthesised drugs, with diazepam as the standard drug Among all the compound obtained during the reaction, only **g1** and **g2** showed highly significant anticonvulsant activity.[14]

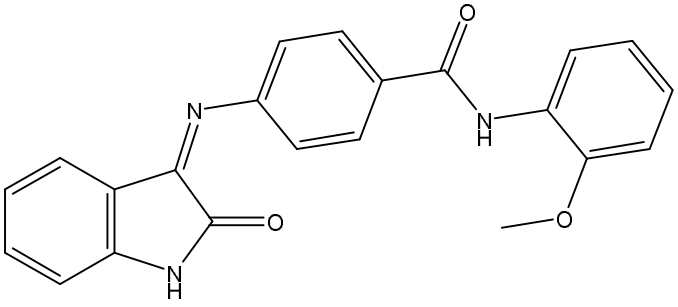


g1.

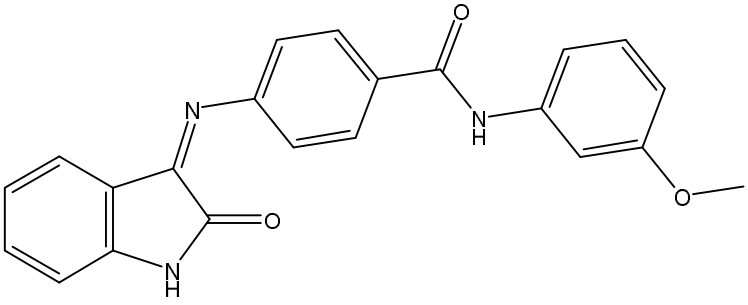


g2.

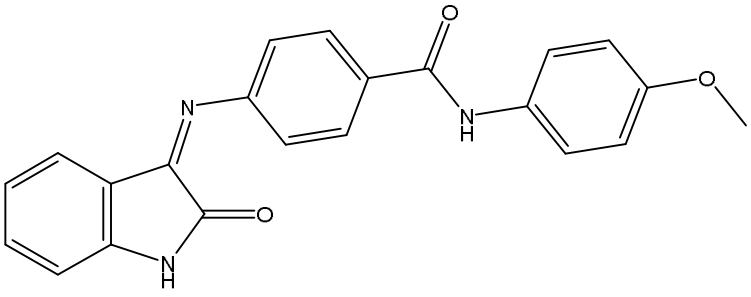
Khajouei MR*et al.*,reported that theIsatin- containing derivatives were synthesized by formation the immine between isatin and p-aminobenzoic acid. A new class of isatin-based anti-seizure derivatives was developed, synthesised, and tested in mice using the MES and PTZ models. All methoxylated derivative (**h1, h2, h3**) has showed significant anti-convulsant activity in MES model. Compound **h1** and **h3** also shows potent activity against PTZ.[15]



h1.

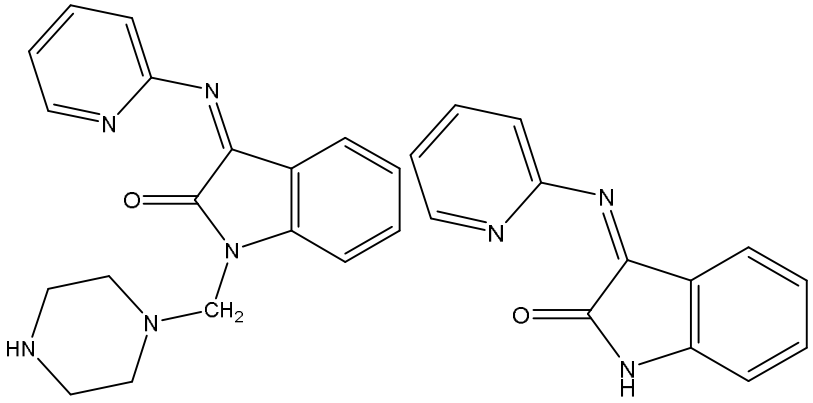


h2.

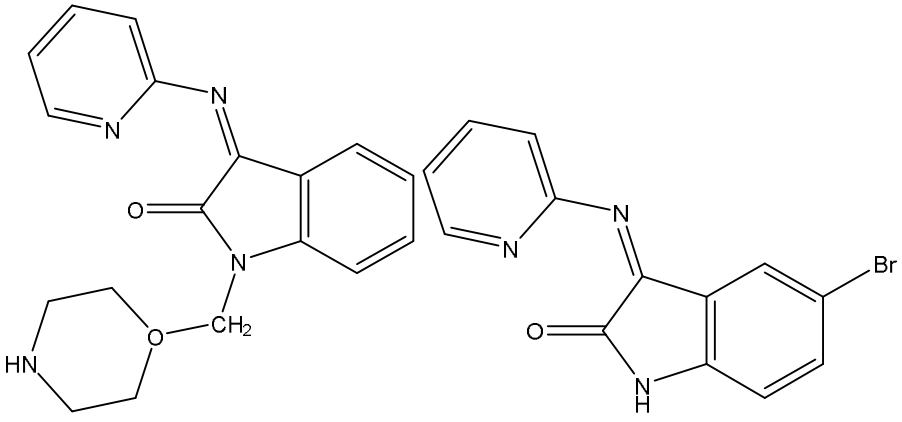


h3.

Chaubey AK*et al.*,have synthesized Isatin derivatives with 2-Amino pyridine.All the synthesized derivatives were evaluated at the dose of 30mg/kg body weight and have shown good anticonvulsant activity. The compound **i1, i2, i3**&**i4** were found to be most active against thiosemicarbazide induced model, as well as against thiosemicarbazide induced model. The standards used were Diazepam 10 mg/kg and Phenytoin 30mg/kg body weight.[16]

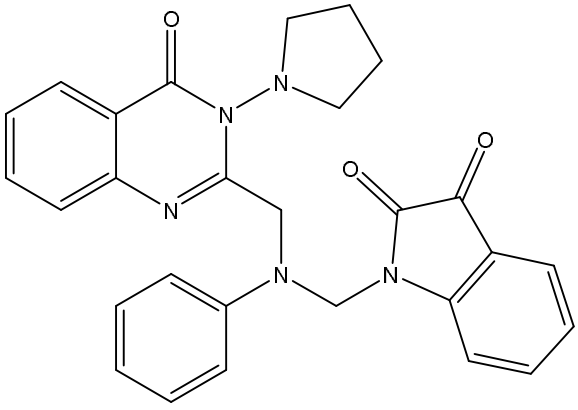


i1. **i2.**



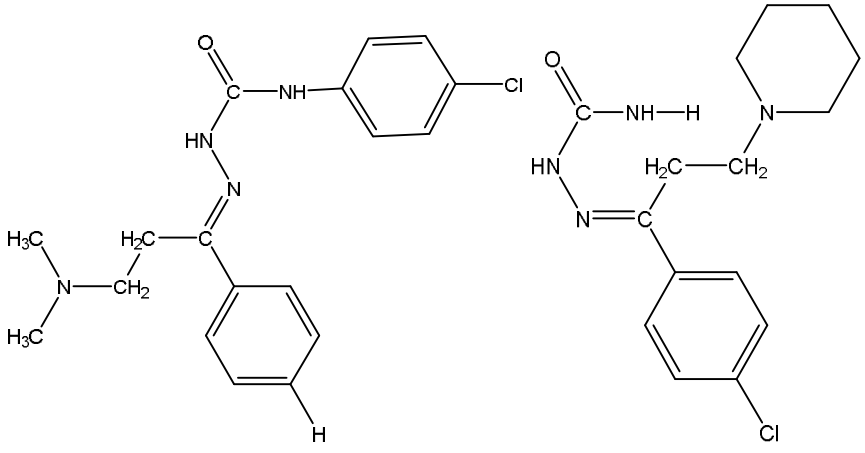
i3. **i4**

Yadav MK*et al.*, have synthesized new *N*-methyl isatin (*N*-methyl-3-ary-3*H*-quinazoline-4-one) derivatives screened for anticonvulsant activity by strychnine, isoniazid (INH) and thiosemicarbazide induced chemo shock convulsion models. Diazepam was taken as a standard drug. Compound **l1** was showing good activity against chemo shock models of epilepsy.[17]

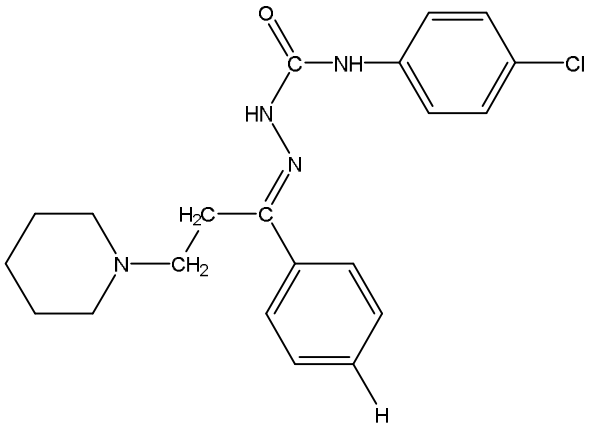


l1.

Pandaya SN *et al.*,has been synthesized a series of compound involving semicarbazide/p-chlorophenyl semicarbazide and Mannich bases of acetophenone/p-acetophenone and the anticonvulsant activity of compounds were screened against MES and scPTZ test. P-chlorophenyl semicarbazone of *N*, *N* dimethylaminopropiophenone has been found to be the most active in all these screening tests. Compound **m1, m2** and **m3** has showed broad spectrum anticonvulsant activity.[18]

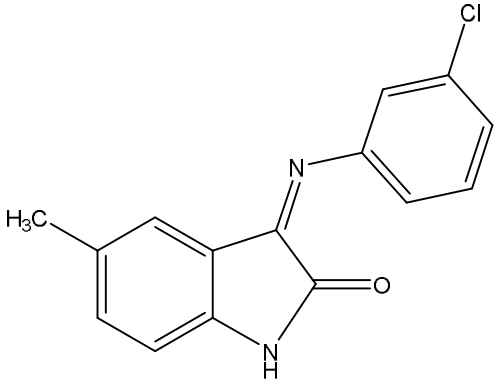


m1 **m2.**



m3.

Sridhar SK*et al.*,havesynthesized various derivatives of isatin and all derivative compounds exhibited lesser neurotoxicity compared to phenytoin and greater protection than sodium valproate. Compound **n1** was found to be the most potent compound and possessed 87% protection at 100 mg/kg dose level with an ED value of 53.61 mg/kg (MET).[19]



n1.

3. Conclusion

The various *N*-Mannich base derivatives increase the lipophilicity of the anticonvulsants so that they can cross the blood brain barrier efficiently and show their action on the target site of the brain. Various synthesis of different *N*-Mannich base derivatives of anti convulsant drugs have been discussed such as, 1,-5 Benzodiazepine; 2-Mercaptobanzimidazole derivatives; Piperidinols derivatives, 1-anilinocyclohexane-1-amide derivatives etc.

4. Acknowledgements

The authors are thankful to the management,T John College of Pharmacy, Bangalore, India for providing facilities and technical assistance. They express their thanks to the Head and the Department of Pharmaceutical Chemistry, T John College of Pharmacy, Bangalore, India, for their continuous encouragementand support during the course of study.

REFERENCES

1) Rang HP, Dale MM, Ritter JM, Flower RJ. Rang and Dale's Pharmacology. 4th ed., Elsevier Limited: 2007, pp. 579.
2) Croucher MJ, Meldrum BS, Krogsgaard-Larsen P. Anticonvulsant activity of GABA uptake inhibitors and their prodrugs following central or systemic administration. EurJPharmacol. 1983; 89: 217-28.
3) Malawska M. New Anticonvulsant Agents. Curr Top Med Chem, 2005; 5(1): 69-85.
4) Meldrum BS. Gabaergic Mechanism in the pathogenesis and treatment of epilepsy. Br J ClPharmacol. 1989; 27(1): 3-11.
5) Elizabeth J, Donner O, Carter Snead III. New Generation Anticonvulsants for the Treatment of Epilepsy in Children. NeuroRx, 2006; 3(2): 170-80.
6) Bruno-Blanch L, Ga´lvez J, Garcı´a-Domenech R. Topological Virtual Screening: A Way to Find New Anticonvulsant Drugs from Chemical Diversity. Bioorg Med Chem Lett, 2003; 13: 2749–54.
7) Bala S, Sharma N, Kajal A, *et al*. Mannich bases: an important pharmacophore in present scenario. Int J Med Chem, 2014; 2014: 191072.
8) Pandeya SN, Rajput N. Synthesis and anticonvulsant activity of various and Schiff bases of 1,5-benzodiazepine. Int J Med Chem, 2012; 2012: 237965.
9) Anandarajagopal K, Tiwari NR, Bothara KG, Sunilson JAJ, Dineshkumar C, Promwichit P. 2-Mercaptobenzimidazole deriatives: synthesis and anticonvulsant activity. Adv Appl Sci Res, 2010; 1(2): 132-8.
10) Gul HI, Calis U, Vepasalainen J. Synthesis and evaluation of anticonvulsant activities of some bis mannich bases and corresponding piperidinols. Araneum-Forach/ Drug Res, 2002; 52(12): 863-9.
11) Kulkarni SD, Tankar AN, Patwardhan KB, Govindwar RB, Anandarajgopal K, Ravi TN. Evaluation of Anticonvulsant Activity of Novel Indole Derivatives. Int J Chem Sci, 2008; 6(2): 926-32.
12) Kulkarni AA, Wankhede SB, Dhawale ND, Yadav PB, Deore VV, Ganjori ID. Synthesis, characterization and biological behavior of some sciff's and mannich base derivative of lamotrigine. Arab J Chem, 2017; 10: S184-9.
13) Prasanthi G. Synthesis and evaluaton of mannich base of substituted piperazine derivatives as anticonvulsant agents. J Glob Trends Pharm Sci, 2014; 5(1): 1475-1479.
14) Kumar N, Sharma PK, Garg VK, Singh P. Synthesis and anticonvulsant activity of novel substituted phenyl indoloimidazole derivatives. Curr Res Chem, 2011; 3(2): 114-20.
15) Khajouei MR, Mohammadi AF, Moradi A, Aliabadi A. Synthesis and evaluation of anticonvulsant activity of (z)-4-(2-oxoindolin-3-ylideneamino)-N-phenylbenzamide derivative in mice. Res Pharm Sci, 2018; 13(3): 262-272.
16) Chaubey AK, Pandeya SN. Synthesis & anticonvulsant activity (chemo shock) of schiff and mannich baes of isatin derivatives with 2-aminopyridine (mechanism of action). Int J Pharmtech Res, 2012; 4(2): 590-8.
17) Yadav MK, Tripathi L. Synthesis, anticonvulsant (chemo shock) activity of isatin mannich bases of quinazolone derivative. MIT Int J Pharm Sci, 2016; 2(1): 38-42.
18) Pandeya SN, Sowmyalakshmi V, Panda SS, Pandeya A, Stable JP. Anticonvulsant activity of semicarbazone derivatives of mannich bases. Indian J Chem, 2003; 42B: 2657-61.
19) Sridhar SK, Pandeya SN, Stabble JP, Ramesh A. Anticonvulsants activity of hydrazones, sciff and mannich bases of isatin derivatives. Eur J Pharm Sci, 2002; 16: 129-132.