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Review on Synthesis of N-Mannich Base Derivatives of Anticonvulsant Drugs

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ABSTRACT

Mannich bases are the end product of Mannich reactions and are known as beta-amino ketone-carrying compounds. Mannich reaction is important for the construction of nitrogen-containing compounds. 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 syntheses of different N-Mannich base derivatives of anticonvulsant drugs have been discussed such as 1,-5 Benzodiazepine; 2-Mercaptobanzimidazole derivatives. These anticonvulsant drugs with N- mannich base group will have an increase in lipophilic character and thus, have better penetration through the Blood-brain barrier as the need for anticonvulsant drugs.

INTRODUCTION:

The term anticonvulsant is used synonymously with antiepileptic to describe drugs that are used to treat epilepsy (which does not necessarily cause convulsions) as well as non-epileptic convulsive disorders(1). Epilepsy is defined as a common chronic neurological disorder which is characterized by recurrent unprovoked seizures. These seizures are transient signs and/or symptoms of abnormal, excessive, or synchronous neuronal activity in the brain(2). Epilepsy can be controlled, but not cured, with medication, although surgery may be considered in difficult cases. However, over 30% of people with epilepsy do not have seizure control even with the best available medications. Not all epilepsy syndromes are life long some forms are confined to particular stages of childhood. Epilepsy should not be understood as a single disorder, but rather as a group of syndromes with vastly divergent symptoms but all involving episodic abnormal electrical activity in the brain(3,4,5).

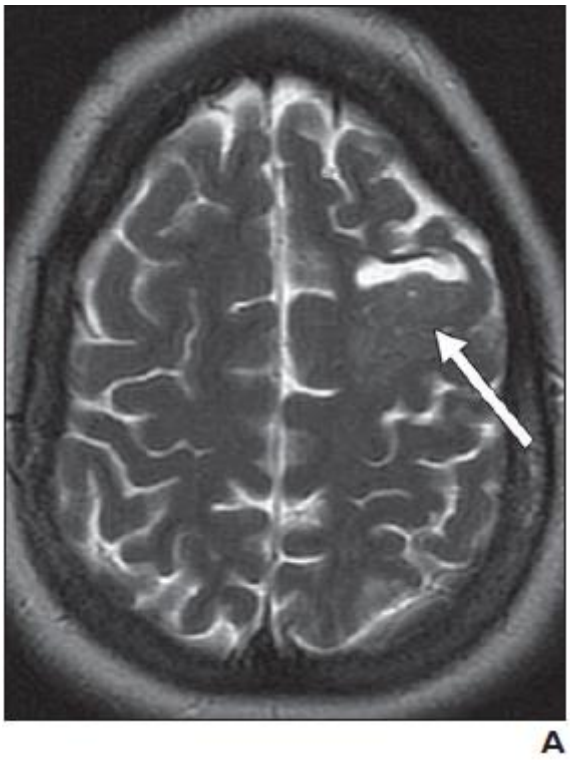


Figure No. 1: A 25-year-old woman with epilepsy. Axial T2-weighted MR image shows T2-hyperintense cortical thickening in the left frontal lobe with adjacent white matter cystic change (*arrow*). Imaging findings may reflect cortical dysplasia or low-grade neoplasm. Biopsy results revealing gliosis were deemed to reflect nonrepresentative sampling(6,7).

Mannich Bases:

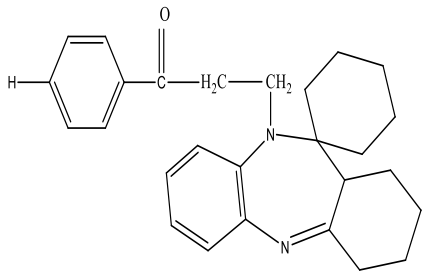
Mannich bases are the end products of the Mannich reaction and are known as beta-amino ketone-carrying compounds. Mannich reaction is a carbon-carbon bond-forming nucleophilic addition reaction and is a key step in the synthesis of a wide variety of natural products, pharmaceuticals, and so forth. Mannich reaction is important for the construction of nitrogen-containing compounds. Several aminoalkyl chains are bearing Mannich bases like fluoxetine, atropine, ethacrynic acid, trihexyphenidyl, and so forth with high curative value. The literature studies enlighten the fact thatMannich bases are very reactive and recognized to possess potent diverse activities like anti-inflammatory, anticancer, antifilarial, antibacterial, antifungal, anticonvulsant, anthelmintic, antitubercular, analgesic, anti-HIV, antimalarial, antipsychotic, antiviral activities, and so forth. The biological activity of Mannich bases is mainly attributed to α, β-unsaturated ketone which can be generated by deamination of the hydrogen atom of the amine group(8).

Mannich bases, beta-amino ketones carrying compounds, are the end products of the Mannich reaction. Mannich reaction is a nucleophilic addition reaction that involves the condensation of a compound with active hydrogen(s) with an amine (primary or secondary) and formaldehyde (any aldehyde)(9,10).

Mannich bases also act as important pharmacophores or bioactive leads which are further used for the synthesis of various potential agents of high medicinal value which possess aminoalkyl chain. The examples of clinically useful Mannich bases which consist of aminoalkyl chain are cocaine, fluoxetine, atropine, ethacrynic acid, trihexyphenidyl, procyclidine, ranitidine, biperiden(11,12), and so forth. Mannich bases are known to play a vital role in the development of synthetic pharmaceutical chemistry. The literature studies revealed that Mannich bases are very reactive and can be easily converted to other compounds, for example, reduced to form physiologically active amino alcohols. Mannich bases are known to possess potent activities like anti-inflammatory(13,14), anticancer, antibacterial, antifungal, anticonvulsant. Prodrugs of Mannich bases of various active compounds have been prepared to overcome the limitations. Mannich bases (optically pure chiral) of 2-naphthol are employed for catalysis (ligand accelerated and metal-mediated) of the enantioselective carbon-carbon bond formation(15,16). Mannich bases and their derivatives are intermediates for the synthesis of bioactive molecules. Mannich reaction is widely used for the construction of nitrogen-containing compounds(17,18,19).

Some of N- Mannich base derivatives having Anticonvulsant activities are discussed below:

1. Synthesis and Anticonvulsant Activity of various Mannich and Schiff bases of 1,5 Benzodiazepine. 1,5-Benzodiazepine are biologically important molecules are extensive activity, motor function, appetitive behavior. 1,5-Benzodiazepine were synthesized by condensation of o-phenylenediamine and ketones, eg., cyclohexane, and acetone in presence of sulfated zirconia. 1 and 2 were found to be most active among all compounds in the isoniazid induced model. 4 and 5 were found to be most active in the thiosemicarbazide induced model. 2, 3 and 6 show good anticonvulsant activity and have an advantage over that they are not sedative(20).



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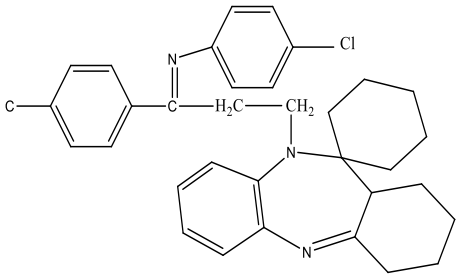

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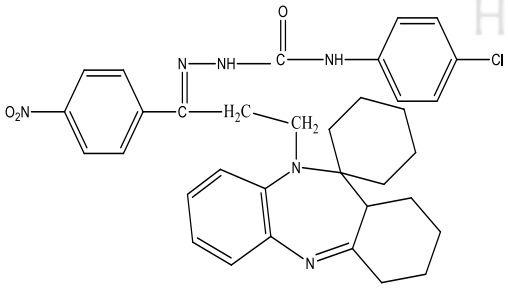

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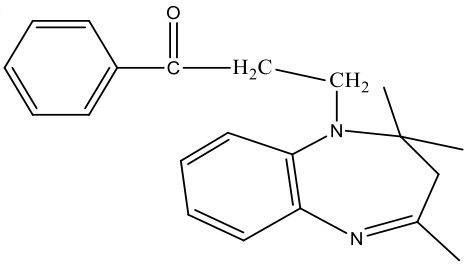

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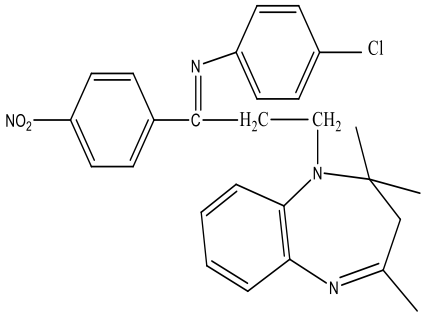

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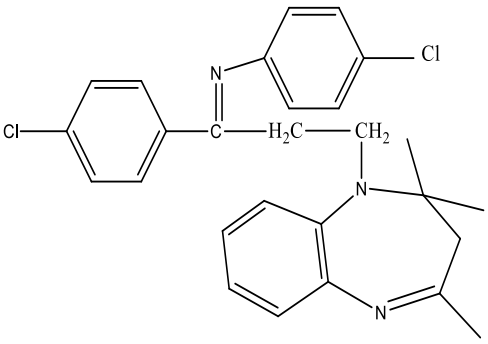

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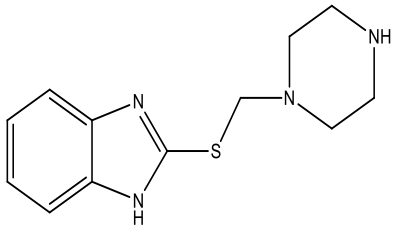
2. 2-Mercaptobenzimidazole Derivative: Synthesis and Anticonvulsant Activity.2-mercaptobenzimidazole derivatives, one of the most important derivatives of benzimidazole exhibited a wide variety of interesting biological activities such as antimicrobial, antihistamine, neurotropic, and analgesics activities. Compounds 7, 8, and 9 exhibited excellent anticonvulsant activity(21).



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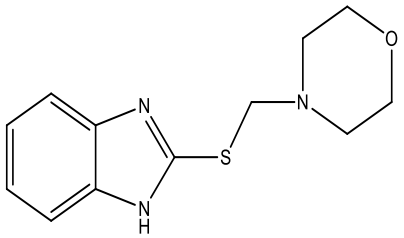

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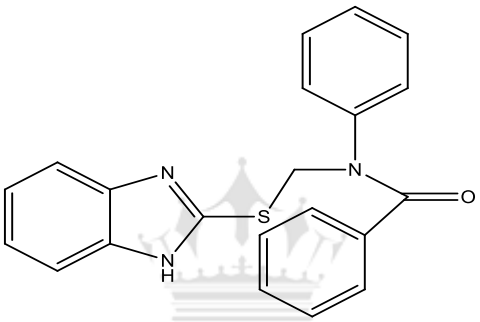
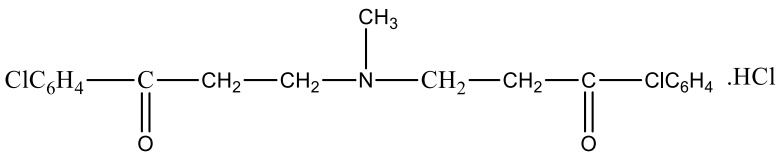


9.

3. Synthesis and Evaluation of Anticonvulsants Activities of some Bis Mannich Bases and Corresponding Piperidinols. Some acetophenone derived bis Mannich bases (10) and piperidine (11,12), which are the structural isomers of 10, and also quaternary piperidine derivative were synthesized and studied for anticonvulsant activity. 10, 11, and 12 were determined to have significantly high anticonvulsant activity against the MMESC Maximal Electroshock seizures(22).



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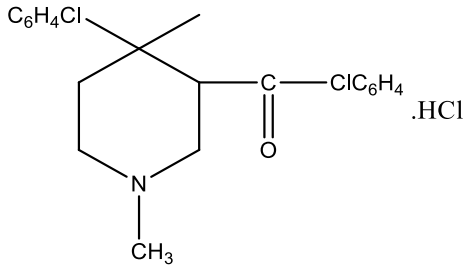

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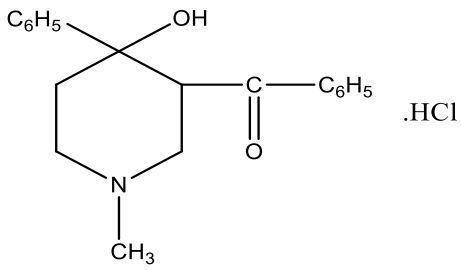
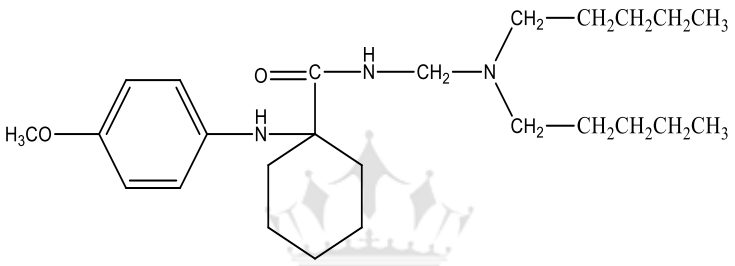


12.

4. A study of Anticonvulsant Activity N-substituted Derivative of 1-Anilinocyclohexane 1-Amide. N-substituted derivatives 1-qnilno cyclohexane 1-amide are neuropharmacologically active. The p-methoxy substitution (MB-7, MB-9, MB10) increases anticonvulsant activity and reduces sedative activity. Most active compounds have either dibenzylamino (MB-8) or morpholino substitution (MB-11)(23).



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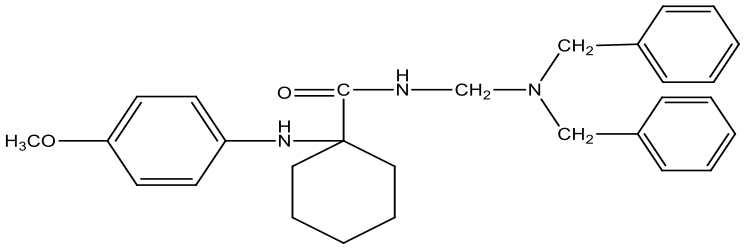

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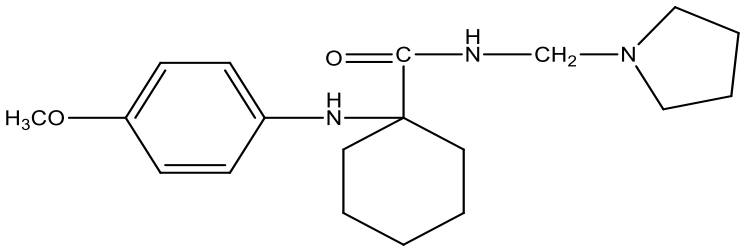

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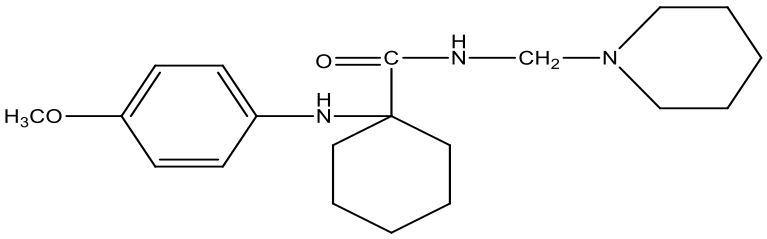

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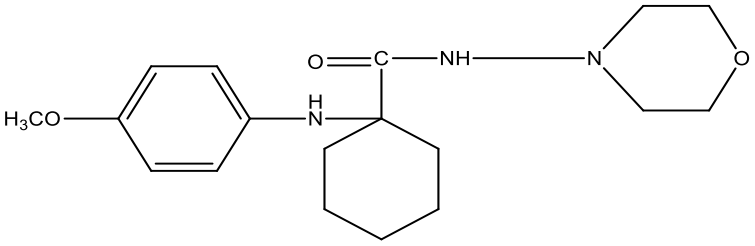

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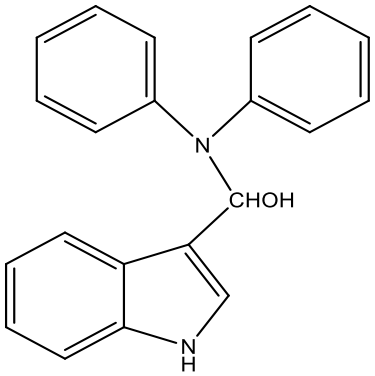
5. Evaluation of Anticonvulsant Activity of Novel Indole Derivative. Mannich bases of indole have a pharmacological profile such as antiepileptic, analgesics, and biological profile such as antimicrobial. Novel Mannich bases of indole were synthesized by using a series of aldehyde and secondary amine in presence of ethanol with a magnetic stirrer for 4-6 hr. in cold condition. Compounds 18, 19, and 20 have shown maximum anticonvulsant activity(23).



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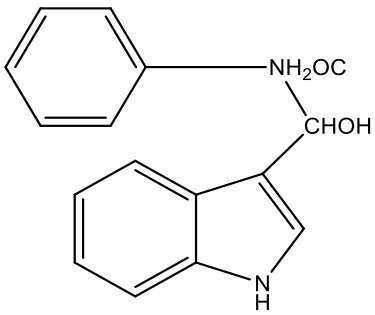

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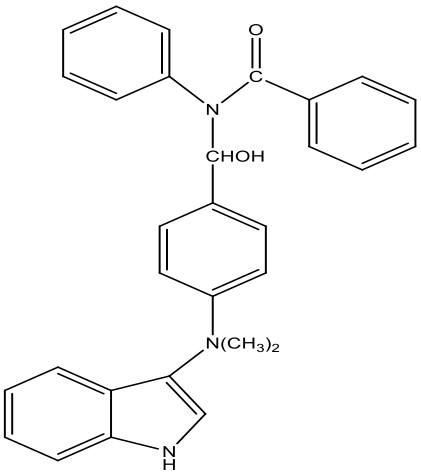
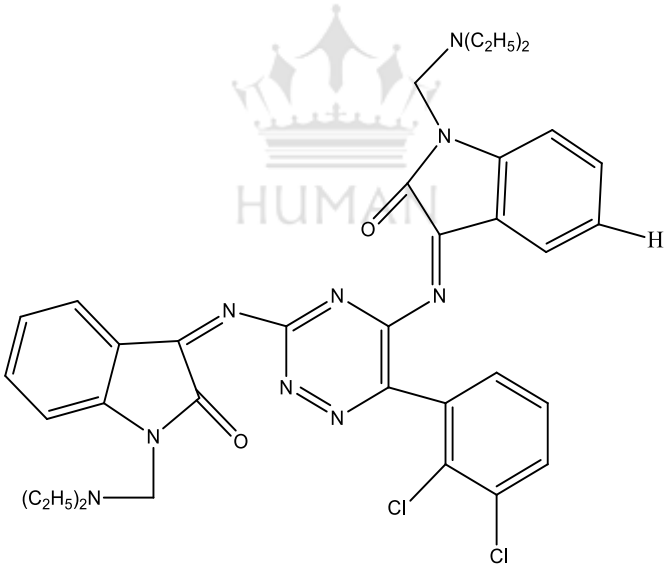


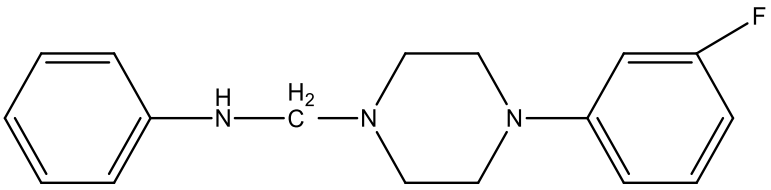
20.

6. Synthesis, characterization, and biological behavior of some Schiff's and Mannich Base Derivatives of Lamotrigine. Lamotrigine reacts with isatin& substituted isatin gave Schiff's bases. Compound 21 showed significant anticonvulsant activity when compared with that of standard drugs. The remaining all compounds show moderate activity(24).



21.

7. Synthesis and Evaluation of Mannich Bases of substituted Piperazine Derivative as Anticonvulsant Agents. The Mannich bases of substituted piperazine derivative were synthesized via feasible Mannich reaction. Compound 22 showed significant anti-PTZ activity and compound 23 showed good protection against shock-induced seizures(25).



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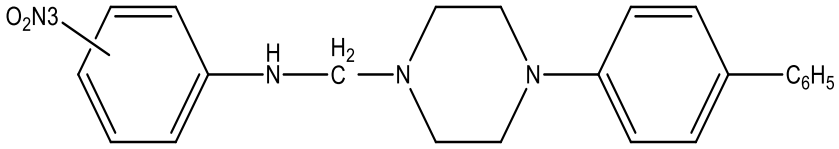
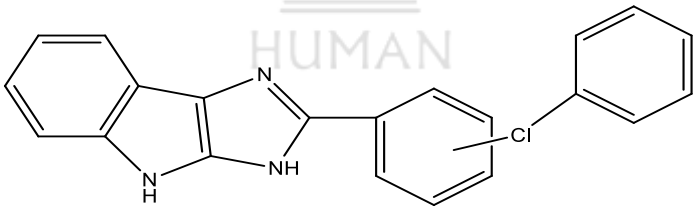


23.

8. Synthesis and Anticonvulsant Activity of Novel substituted Phenyl Indoloimidazole Derivative. Phenyl Indoloimidazole derivatives were obtained by condensing different aromatic aldehyde with N-1-Phenyl isatin in presence of ammonium acetate and glacial acetic acid. Among all the compounds, 24 and 25 showed highly significant anticonvulsant activity(26).



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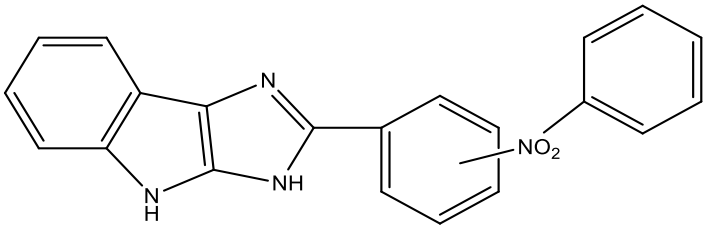

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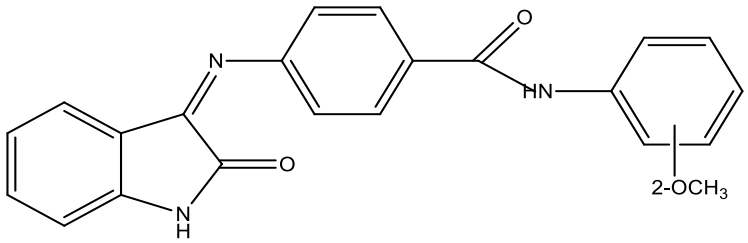
9. Synthesis and Evaluation of Anticonvulsant Activity of (z)-4(2-oxoindolin-3-yildeneamino)-N-Phenylbenzamide Derivative in Mice. Isatin-containing derivatives were synthesized via the immune formation between isatin and p-aminobenzoic acid. All

methoxylated derivatives (26, 27, 28) showed significant anti-seizure activity in the MES model. 26 and 28 also show potent activity against PTZ(27).



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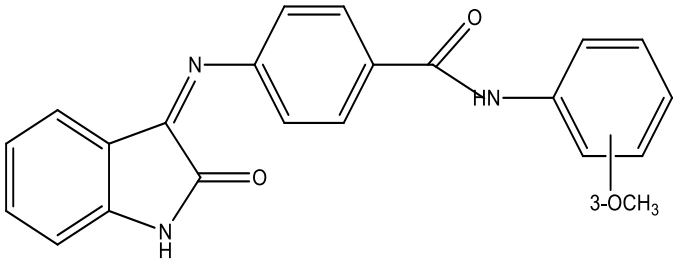

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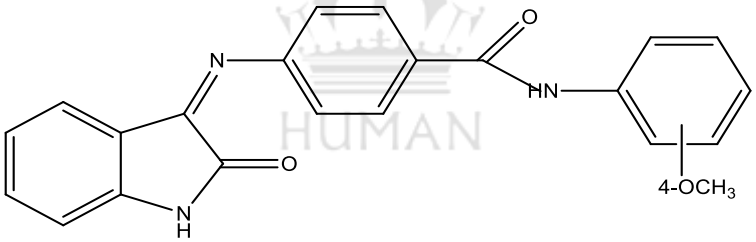
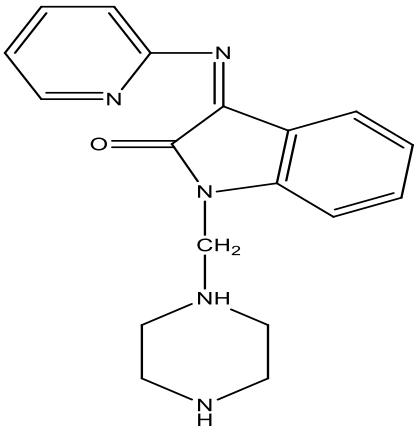


28.

10. Synthesis and Anticonvulsant Activity (Chemo Shock) of Schiff's and Mannich Bases of Isatin Derivatives with 2-Amino Pyridine. All the synthesized derivatives were evaluated they shown good anticonvulsant activity. The compounds 29, 30, 31 &32 were found to be most active against the thiosemicarbazide-induced model(28).



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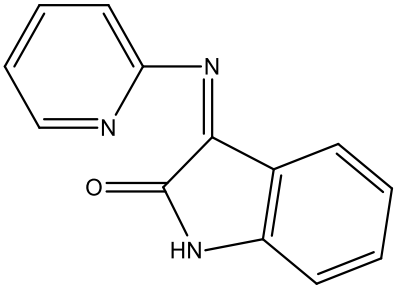

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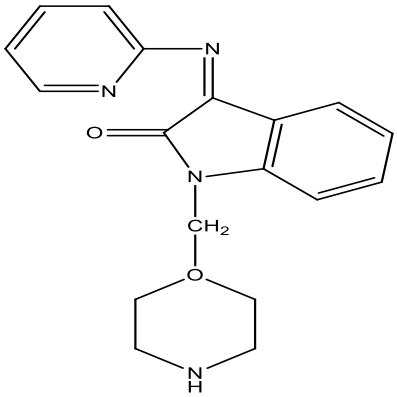

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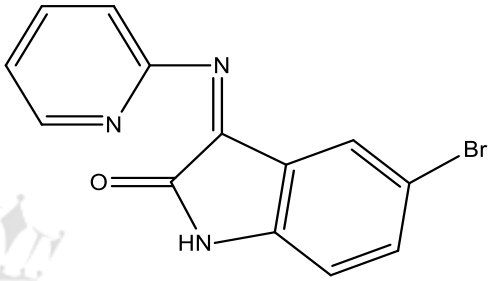
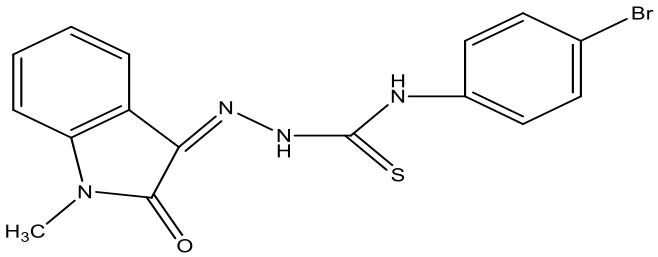


32.

11. Isatin-A Potent Anticonvulsant Agent. In the isatin ring, a numeral of structural modifications has been made consecutively to elevate the biological actions such as anticonvulsant, anti-inflammatory, analgesic, antifungal, anti-cancer, anti-HIV, antibacterial, anti-diabetic and anti-tubercular activity. Among all, compounds bearing N-methyl (33) and N-acetyl (34) isatin-3-thiosemicarbazone derivative exhibited as the most active compounds by the protection they exhibit in MES, scSTY, and scPTZ screen(29).



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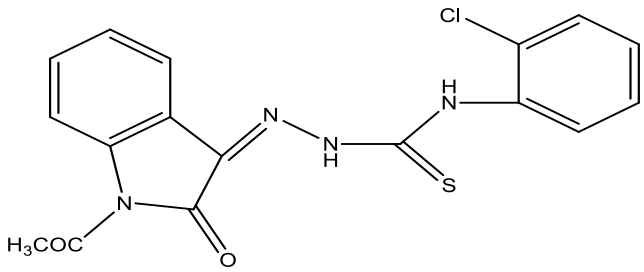
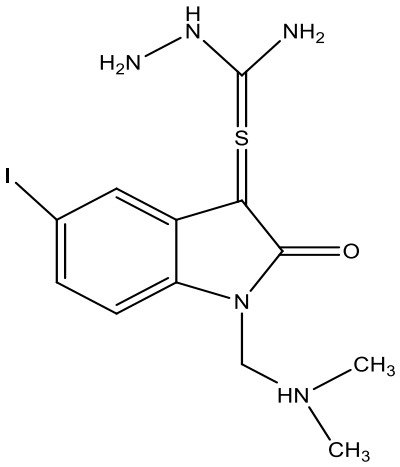


34.

12. Synthesis and Anticonvulsant Activity of some different Schiff's and Mannich Bases of 5-substituted-1H Indole-2,3 diones. A series of different mannich bases were synthesized from Schiff's bases of different 5-substituted-1H Indole-2,3 diones with different secondary aromatic in presence of formaldehyde. Compounds 35, 36, and 37 were screened for anticonvulsant activity, with an increase in latency time and reduction in duration of convulsion when compared with sod. Valproate 300mg/kg(30).



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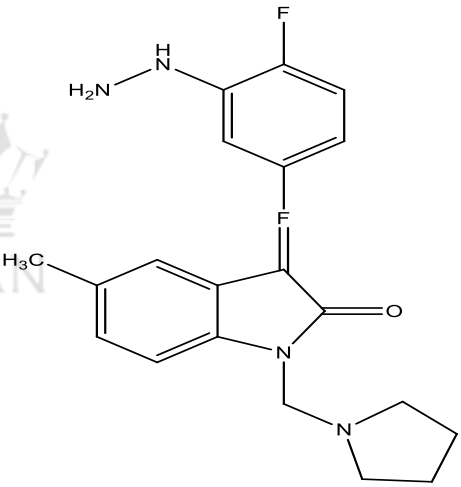

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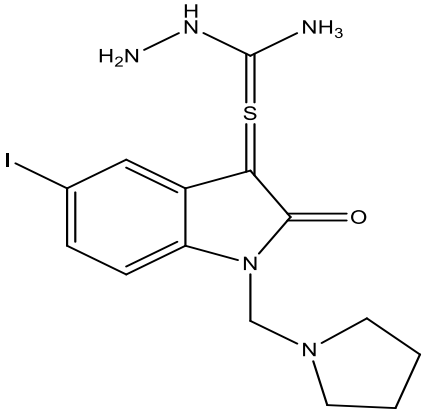
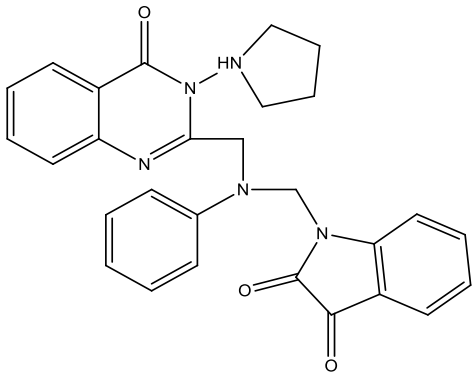


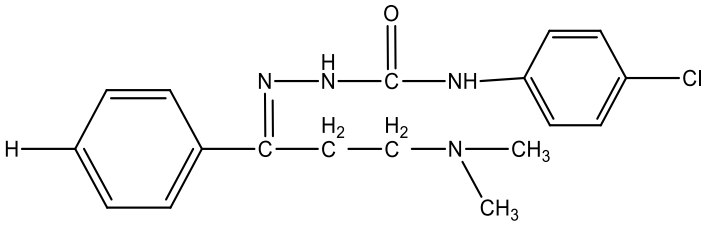
37.

13. Synthesis, Anticonvulsant (Chemo shock) Activity of IsatinMannich Bases of Quinozolone Derivative. New N-methyl isatin (N-methyl-3-ary-3H-quinazoline-4-one) derivatives were synthesized compound 38 was showing good activity against chemo shock models of epilepsy(31).

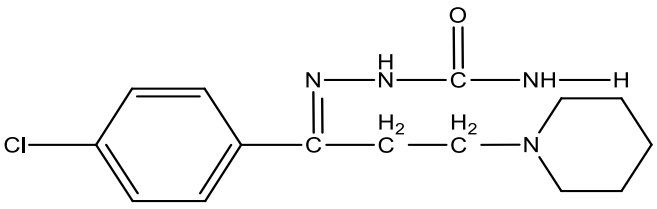


38.

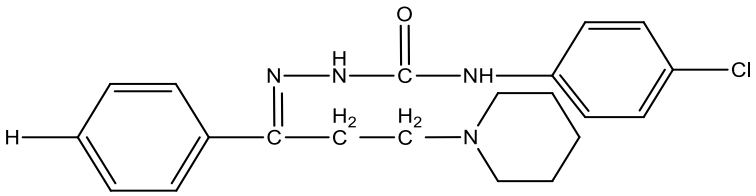
14. Anticonvulsant Activity of Semicarbazone Derivative of Mannich Bases. A series of semicarbazide/p-chlorophenyl semicarbazide and Mannich bases of acetophenone/p-acetophenone have been synthesized and their anticonvulsant activity screened against MES and scPTZ test. P-chlorophenyl semicarbazone of N, N dimethylaminopropiophenone is the most active in all these tests. Compounds 39,40 and 41 showed broad-spectrum activity(32).



39.

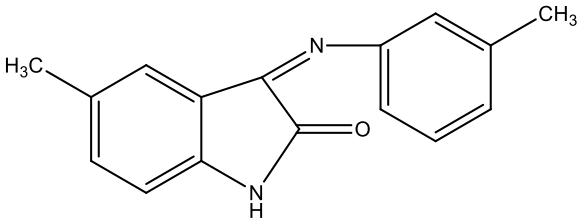


40.



41.

15. Anticonvulsant Activity of Hydrazones, Schiff's and Mannich Bases of Isatin Derivatives. Various derivatives were synthesized and all derivative compounds exhibited lesser neurotoxicity compared to phenytoin and greater protection than sodium valproate. Compound 42 was found to be the most potent compound(33).



42.

CONCLUSION:

Anticonvulsant drugs need to cross the Blood-brain barrier and thus should be highly lipophilic. The most recent study suggests preparation of N- Mannich base derivatives increase the lipid solubility or lipophilicity of drug molecule. The various N-Mannich base derivatives of antiepileptic drugs, increase the lipophilicity so that they can cross the blood-brain barrier efficiently and show their action on the target site of the brain. Various syntheses of different N-Mannich base derivatives of anticonvulsant drugs have been discussed such as 1,-5 Benzodiazepine; 2-Mercaptobanzimidazole derivatives, etc. This approach thus can be used to prepare various active analogs to cure epilepsy.

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