Original Article

Anti-epileptic agents: Recent developments and structure-activity relationship studies

Bhaskar Sahu, Ravi Ranjan Kumar, Bhupinder Kumar*

Department of Pharmaceutical Chemistry, ISF College of Pharmacy, Ghal Kalan, Moga, Punjab, India

Correspondence:
Dr. Bhupinder Kumar, Department of Pharmaceutical Chemistry, ISF College of Pharmacy, Ghal Kalan, G.T Road, Moga - 142 001, Punjab, India.
E-mail: bhupinderkumar25@gmail.com
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ABSTRACT

Epilepsy is a chronic neurological disorder which is affecting around 50 million people worldwide with 80% living in a developed country. Epilepsy is generalized due to imbalance of excitatory and inhibitory neurotransmitters that how could be they are responsible for the causing seizer. Hence, in this review summarized the deferent type of epileptic seizer and characterization of the seizures. In addition, classified the antiepileptic drugs and discussed their adverse effects. Moreover, the mechanism of epilepsy has complexed it may be a type of convulsion. Furthermore, the chemistry of the antiepileptic drugs has there discussed by the survey of different research papers. In this review, we have provided critical highlights on current developments in designing and synthesis of piperazine based antidepressant (2015 onwards) compounds along with their SAR studies.

Keywords: Anti-epileptic drugs, chemistry of epilepsy, epilepsy, recent developments

INTRODUCTION

Epilepsy is the chronic neurological state considered the fourth most common problems after the Alzheimer's and Migraine.[1,2] According to the WHO, an estimated 50 million people are suffering from epilepsy worldwide and almost 80% of the people with epilepsy are living in developing countries.[3,4] Epilepsy is characterized by uncontrolled episodes defined as condition one or more epileptic seizer. Multiple seizers can be occurring in a more than 24 h period.[5,6] The major of seizer characterized into two category partial seizer[7] and epilepsy (generalized seizure)[8] [Table 1]. Epilepsy further characterized by focal seizer is being in the local area of the brain.[9] This type of seizer further sub-divided into simple seizer with no alteration in consciousness[10] and complex partial seizer with alteration of consciousness.[11] Individual generalized seizer type includes absence,[12] myoclonic,[13] tonic-clonic,[14] atonic,[15] tonic,[15] and clonic symptom.[16] Epilepsy seizer can be caused due to an excessively synchronous and sustained discharge of a group of neurons. The single feature of all epileptic syndromes is a determined increase of neuronal excitability.[2,17,18] Pathophysiological mechanisms of some epilepsy (partially) are understood but there no specific relevant factors are inductee in about half of the patients suffering from epilepsy.[19,20]

In additive, antiepileptic drugs [Table 2] are usually used as long-term treatments need for more effective and safer but demonstrated that various side effects such as sedation, headache, hypotension, blur vision, slurred speech, poor judgment, and loss of coordination and imperative 30% of the cases do not respond.[21,22] Moreover, many of the existing antiepileptic drugs have multiple and complex mechanisms.[23]

CHEMISTRY OF EPILEPSY

Kocharov *et al*. synthesized 3-p-isopropoxy phenyl pyrrolidine-2,5-dione derivatives and evaluated antiepileptic activities using maximal electroshock-induced seizer test in mice.[24] From the result of MES test, it was observed that compounds **1** and **2** possess better activity. The time to peak of maximum antiepileptic effect ranged between 15 and 20 min, respectively. However, bio-screening results proposed that the binding phenyl or substituted phenyl radical with succinimide N-atom through CH_2-NH-bridge is preferable to direct binding in

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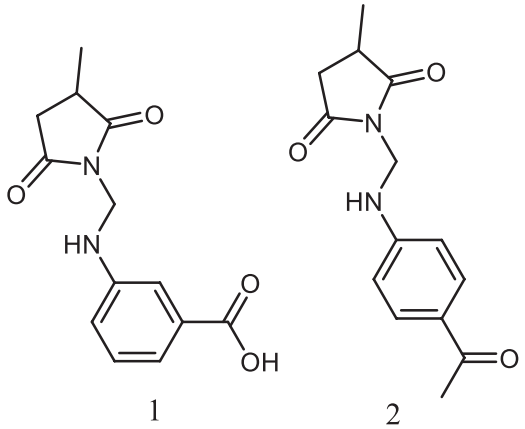
Table 1: Classification of major type epilepsies

Epilepsy			
Generalized seizures		Partial seizures	
Sub-types	**Observe**	**Sub-type**	**Observe**
Tonic-clonic seizure (major epilepsy, grand mal)	Duration 1–2 min, aura-cry-unconsciousness and patient falls	Simple partial seizure	Duration 30–90 s sudden onset unilateral clonic jerking of a group of muscles
Absence seizure (minor epilepsy)	30 s to 1 min, prevalent in children, loss of consciousness, no patient fall	Complex partial seizure (temporal lobe epilepsy)	Duration 1–2 min, dream-like behavior, confusion
Atonic seizure (akinetic epilepsy)	Loss of conscious, relax of all muscles	Simple partial or complex partial seizure	Generalized tonic-clonic seizure with loss of consciousness
Myoclonic sei	Shock like momentary contraction of muscles		
Infantile spasms (hypsarrhythmia)	See in infants, probably not a form of epilepsy		

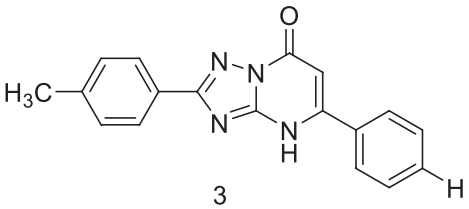
Table 2: Classification of antiepileptic drug

Drug	Mechanism of action	Adverse effects
Phenytoin	Prolongation of Na^+ channel inactivation	Headache, nausea, vomiting, constipation, drowsiness, feeling of spinning
Carbamazepine		
Fosphenytoin		Hypotension, cardiac arrhythmias, local dermatological reaction
Oxcarbazepine		Fatigue, drowsiness, diplopia, long term use cause hyponatremia
Eslicarbazepine		
Valproate sod	Prolongation of Na^+ channel inactivation and inhibit of Type Ca^+ current	Stomach pain, feeling sick, diarrhea, sour mouth, swollen gums
Divalproex	Increase the GABA in the brain	Dizziness, drowsiness, hair loss, blurred vision
Lamotrigine	Block Na^+ and Ca^+ channel	Tremor, loss of coordination, back pain
Topiramate		Loss of appetite or weight loss
Zonisamide		Increase seizure's, shortness of breath
Lacosamide	Enhancing Na^+ channel inactivation	Ataxia, vertigo, diplopia, tremor
Phenobarbital	Enhance of $GABA_A$ receptor-mediated synaptic inhibition	Confusion, poor judgment, slurred speech, irritability, insomnia
Primidone	Interaction with voltage-gated Na^+ channel inhibit high-frequency	Slow speech, loss control
Levetiracetam	Inhibition of "T" type Ca^+ current	Mood change, agitation, headache
Ethosuximide		
Clonazepam	Positive allosteric modulator on $GABA_A$ receptor	Loss of muscle coordination, slurred speech
Diazepam		
Lorazepam		
Clobazam		

terms of a higher level of anticonvulsant activity of the compounds **1** and **2**.

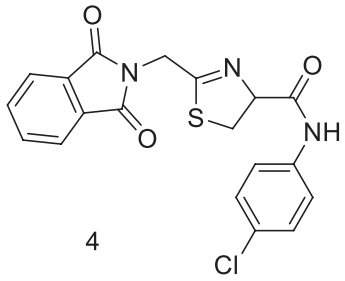


Ding *et al.* synthesized series of pyrimidine-7(4H)-one and triazolo-[1,5-a]-pyrimidine amine derivatives on the based marine natural product Essramycin.[25] Antiepileptic activities were performed using 4-aminopyridine (4-AP) induced hyperexcitability model *in vivo*. The result *in vivo* test pyrimidine-7(4H)-one based compound showed positive antiepileptic activities. Compound **3** was possessed potent activity with an IC_{50} value of 2.35 μM. However, SAR studies were performed and found that the pyrimidine-7(4H)-one was important for antiepileptic activities. Moreover, docking studies were performed using of $GABA_A$. Compound **3** showed a good affinity with binding energy 7.85 and bind with the active site of the $GABA_A$ receptors amino residues ARG-142, ASP-146.



Tabatabaei *et al.* synthesized that phthalimide-4,5-dihydrothiazole-amide series of novel compounds were evaluated antiepileptic activities against the pentylenetetrazole (PTZ)-induced seizure

in mice.[26] Compound **4** was showed potent activity with zero mortality. Further docking studies were performed to investigate the binding mode with the $GABA_A$ receptor. Docking result proposed compound **4** had a high binding affinity and low binding energy −9.60. Compound **4** formed three hydrogen bonds with amino residue Tyr159 and Thr142 and Thr206. Besides, π-interactions were formed with amino residues of Met130 and Leu140. Additional Phthalimide and N-substituted phthalimide were important in compounds that possessed good biological activity. Compound **4** was scored 2.52 lipophilicity can easily cross BBB.



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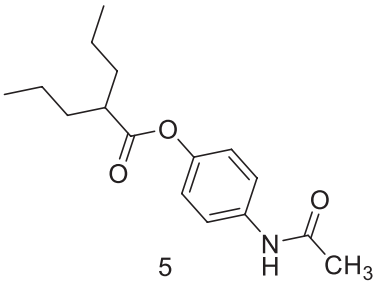
Song *et al.* synthesized two type valproic acid derivative compounds **5** and **6** by an esterification condensation reaction for the treatment of epilepsy with the lower toxic side effect.[27] The maximum shock seizure test of the compounds **5** and **6** was performed for the cytotoxicity and survival effects investigations. The result no convulsion occurred for compounds **5** of 50 mg/kg and compound **6** of 25 mg/kg and 50 mg /kg in low weight mice. Moreover, compound **5** was more effective than compound **6** to preventing H_2O_2 induced cell death. Additional cytotoxicity activity was performed in compound **5** and **6** possessed effective to respond.

Rawat *et al.* design synthesized a series of chroman derivative compounds and evaluated their antiepileptic activity using the PTZ seizure test *in vivo* in mice.[28] Resultant antiepileptic activity of the compounds **7**, **8**, and **9** possessed potential activity than the reference sodium valproate. Additional neurotoxicity of compounds was performed at the dose level of 30 mg/kg, 100 mg/kg, and 300 mg/kg using a Rotarod test. All the compounds showed good safety index of toxicity.

Gunia-Krzyżak *et al.* reported a series of (E)-N-cinnamoyl derivatives as an anticonvulsant activity using a rodent model of seizures.[29] The biological activities of the compounds maximal electroshock and subcutaneous pentylenetetrazole tests as well as a model of resistant seizures test were performed. The result compounds **10**, **11**, and **12** were showed positive anticonvulsant activity. In addition, all compounds



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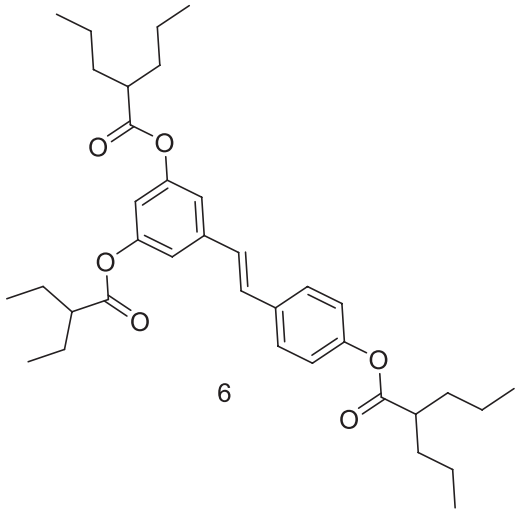

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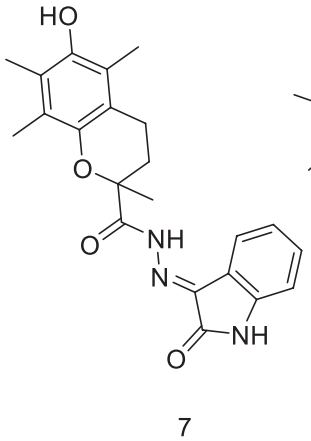

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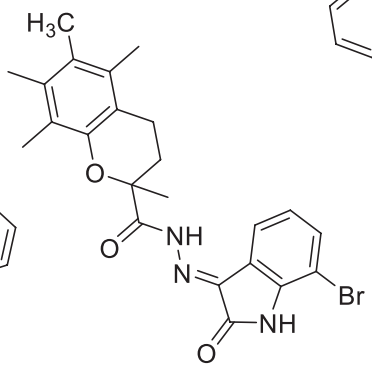

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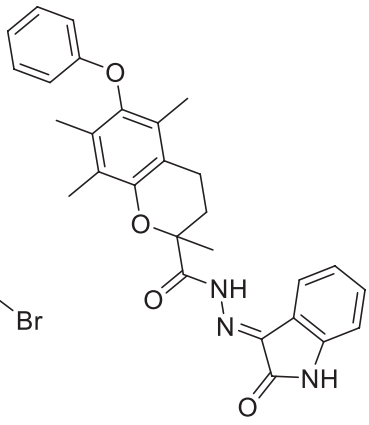

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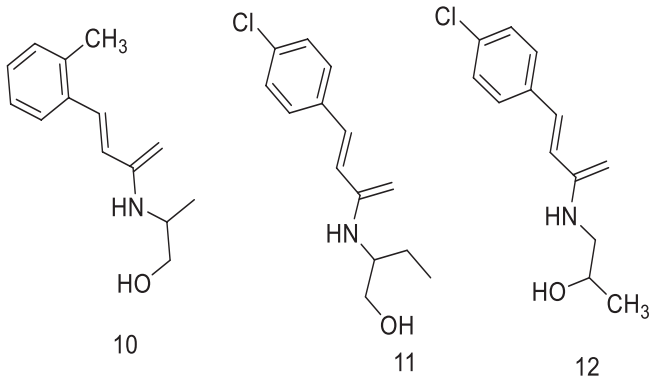
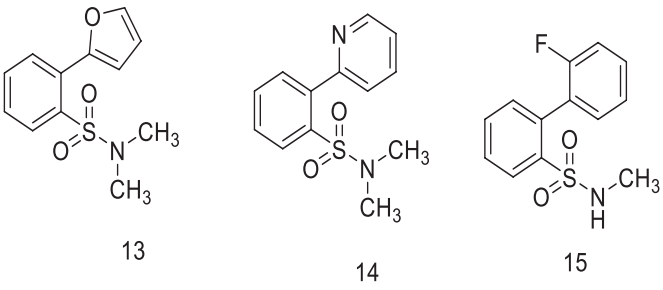
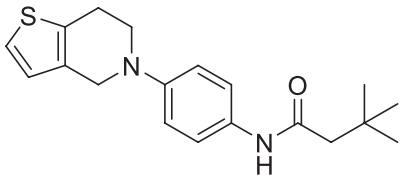
showed serotonin binding affinity, compounds **10** and **11** showed benzodiazepine receptor antagonistic activity. *In vitro* binding studies for 80 targets did not solve molecular mechanism of action of compounds **10**, **11**, and **12**. However, in SAR studies were performed and found that chlorine atom in position para or methyl group in the ortho position of phenyl ring was beneficial for anticonvulsant activity and Methyl group in position para of phenyl ring decreased anticonvulsant activity.



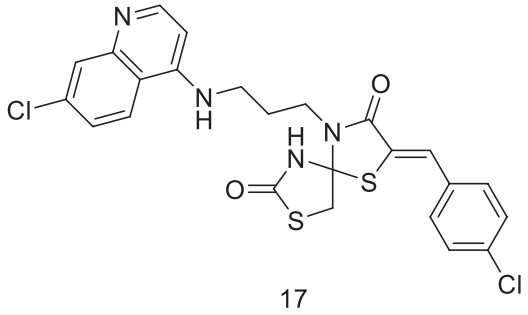
Tanaka *et al*. developed phenyl sulfonamide derivatives as putative antiepileptic activities scaffold and initiated the biological activity *in vivo* test in mice MES and sc-PTZ models.[30] Compounds **13** and **14** were possessed a potential lead compound for compound **15** discover. Compound **13** showed potential anti-MES activities and compound **14** showed anti-PTZ only at the dose level of 100 mg/kg. Further in SAR studies found that the compounds **13** and **14** were a lead compound for the development of potent compound **15**. Furthermore, compound **15** possessed best anticonvulsant activities at the dose level of 100 mg/kg.



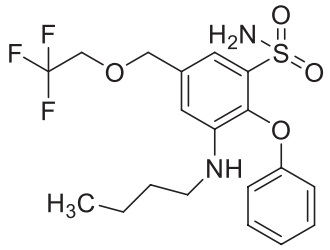
Yang *et al*. design and synthesized a series of N-phenylbutanamide derivatives targeted to the KCNQ opening activities *in vitro* and *in vivo* antiepileptic drugs.[31] *In vitro* result suggested that compound **16** was possessed potential anticonvulsant activities KCNQ activation ratio 84.24% at dose level 10 μM with lower adverse effects. Furthermore, compound **16** *in vivo* studies using rotating-rod test were found favorable pharmacokinetics profile. Compound **16** showed zero present neurotoxicity.



Dwivedi *et al*. design and synthesized spirothiazolidinone derivatives potential anti-epileptic activities.[32] Synthesized compounds biological activities were evaluated using maximum electro seizure (MES) *in vivo* test. From the result, compound **17** was possessed potential activity against epilepsy treatments compared with diazepam standard drug. The tonic flexion and extension along with clonic stupor were observed for control synthesized compound and standard. Compound **17** was found a potential compound with 20.2 SEM mortality at the dose level 100 mg/kg. Further, in pharmacokinetic test compound, **17** had better lipophilicity due to chloro groups which turn responsible for permeability enhanced in the cell.



Auer *et al*. design and characterized by bumetanide based derivatives NKCC1/NKCC2 antagonistic activities for the epilepsy treatments.[33] Design compounds pharmacological activities were evaluated using *in vivo* and *in vitro*. The result, **18** (BUM97) a novel compound possess remarkable strong anticonvulsant activities. The antiepileptic effects of compound **18** were evaluated using the unilateral KA mouse model of TLE. BUM97 + Phenobarbitone suppressed the number spike train 49 ± 19 % within the 1st h in epileptic animals. The SAR studies were performed and suggested benzylamine of butanamide exhibit potential biological activities and responsible for the NKCC inhibition log *P* = 3.71.



CONCLUSION

In this review, we have discussed the epileptic disorder having different pathophysiology and mechanism. Epilepsy is the major problem as large population are affected. The seizer classified into different types and discussed the etiology. Antiepileptic drugs used to treatment of epilepsy show many side effects so it is important to reduce the adverse effect of antiepileptic drugs, available drugs are not responding in different cases. Further literature survey supposed that the newly derived scaffold gives better activity. There is an opportunity to optimized scaffold for antiepileptic drug and reduce the adverse effects.

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