REVIEW ARTICLE

SOME HETEROCYCLICS WITH ANTICONVULSANT PROPERTIES

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The anticonvulsants are Food and Drug Administration approved, for the prevention and/or treatment of various seizure disorders either as monotherapy or adjunctive therapy. The goal of an anticonvulsant is to suppress the rapid and excessive firing of neurons that start a seizure. Due to the non-selectivity of the anticonvulsants and the undesirable side effects posed by them the use of current antiepileptic drugs has been questioned. This led to an intensive investigation in this area worldwide during the past 10 years. As far as drug efficacy and safety is concerned there have been some significant outcomes and the findings are promising. This review covers the brief description of epilepsy and various heterocyclic moieties that have shown encouraging anticonvulsant activity and less neurotoxicity.

Key words: Heterocyclics, Anticonvulsant activity, Neurotoxicity, Epilepsy.

INTRODUCTION

More than a century ago, John Hughlings Jackson, the father of modern concepts of epilepsy, proposed that seizures were caused by “occasional, sudden, severe, excessive, rapid and local discharges of gray matter”, and that a generalized convulsion resulted when normal brain tissue invaded by the seizure activity initiated in the abnormal focus. This insightful proposal provided a valuable framework for thinking about mechanism of epilepsy. The advent of the electroencephalogram in the 1930s permitted the recording of electrical activity from the scalp of humans with epilepsy and demonstrated that the epilepsies are disorders of neuronal excitability (Brunton et al 2006). According to International League against Epilepsy and International Beaurue of Epilepsy, an epileptic seizure is a transient occurrence of signs and or symptoms due to abnormal excessive or asynchronous neuronal activity in the brain. Epilepsy is the disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of the condition (Fisher et al 2005). Epileptic episodes are called seizures and have different manifestation ranging from brief lapses of lack of attention to limited motor, sensory, or psychological changes. In severe cases they include prolonged loss of consciousness with convulsive motor activity (Gavernet et al 2007). The definition of epilepsy requires the occurrence of at least one epileptic seizure. Epileptic seizures are classified into various categories: A) Partial-onset seizures: Partial-onset seizures are further classified as simple partial seizures, complex partial seizures. All partial seizures are characterized by onset in a limited area, or focus, of one cerebral hemisphere. B) Generalized-onset seizures are classified into 6 major categories: (i) absence seizures, (ii) tonic seizures, (iii) clonic seizures,
produce adverse effects such as ataxia, sedation, or other toxicity studies. A series of substituted benzothiazole carboxamides were synthesized: monosubstituted benzothiazolamines and evaluated for anticonvulsant activity with established anticonvulsants agents. Kumar et al. 2012 have designed and synthesized a series of 2-[2-(substituted)hydrazinyl]-1,3-benzothiazole 3 and 2-(1,3-benzothiazol-2-yl-sulfanyl)-N-(substituted)acetohydrazide 4. The anticonvulsant activity of the titled compounds was assessed using the 6 Hz psychomotor seizure test. A series of substituted benzo[d]thiazol-2-yl-carbamates 5, 6 were synthesized and evaluated for anticonvulsant activity by Navale et al. 2013. Two series of analogues of riluzole, a blocker of excitatory amino acid mediated neurotransmission, have been synthesized: monosubstituted-2-benzothiazolamines 7 and 3-substituted derivatives 8 by Jimonet et al. 1999. A series of 1,3-benzothiazol-2-yl-benzamides 9 were prepared in satisfactory yield by Rana et al. 2008 and evaluated for their anticonvulsant, neurotoxicity, CNS depressant study and other toxicity studies. Siddiqui et al. 2007b have prepared a series of 1,3-benzothiazol-2-yl-semicarbazones 10 in satisfactory yield and evaluated for their anticonvulsant, neurotoxicity and other toxicity studies. A series of 6-substituted -[3-substituted-prop-2-eneamido] benzothiazole 11 and 6-substituted -[1-acetyl-

(iv) myoclonic seizures, (v) primary generalized tonic-clonic seizures, and (vi) tonic seizures. Generalized tonic-clonic (grand mal) is characterized by sudden cry, fall, rigidity, followed by muscle jerks, shallow breathing or temporarily suspended breathing, bluish skin, possible loss of bladder control (usually lasts a couple of minutes).

In recent years the field of antiepileptic drug development is quite dynamic, affording many promising research opportunities (Yogeesswari et al. 2003). Despite the development of several anticonvulsants, the treatment of epilepsy still remains inadequate. Studies indicate that a significant group of patients (20-30%) are responding to currently used therapeutic agents (Curry and Kulling, 1998) and about 1/3rd of patients do not respond well to currently available treatment even if multiple drugs with complimentary activities are used.

A major cause of this is the lack of understanding of underlying mechanism. However the pivotal role of synapses in mediating communication among neurons in the mammalian brain suggested that defective synaptic function might lead to a seizure i.e. a reduction of inhibitory synaptic activity or enhancement of excitatory synaptic activity might be expected to trigger a seizure; pharmacological studies of seizures supported this notion. The neurotransmitters mediating the bulk of synaptic transmission in the mammalian brain are amino acids, with γ-aminobutyric acid (GABA) and glutamate being the principal inhibitory and excitatory neurotransmitters, respectively.

Pharmacological studies disclosed that antagonists of the GABA<sub>A</sub> receptor or agonists of different glutamate-receptor subtypes (NMDA, AMPA, or kainic acid) trigger seizures in experimental animals in vivo. Conversely, pharmacological agents that enhance GABA-mediated synaptic inhibition suppress seizures in diverse models. Glutamate-receptor antagonists also inhibit seizures in diverse models, including seizures evoked by electroshock and chemical convulsants such as pentyleneetetrazole. Another major problem caused by available drugs is the side effect associated with them. The established antiepileptic agents viz. valproic acid, phenytoin, carbamazepine, though widely prescribed, produce adverse effects such as ataxia, hepatotoxicity, gingival hyperplasia and megaloblastic anemia (Curry and Kulling, 1998). Thus, there is still a need for new antiepileptic drugs as the clinical efficacy, tolerability, toxicity, or pharmacokinetic properties of existing AEDs may not be satisfactory. Rufinamide is the newest approved antiepileptic drug, which is a triazole derivative with no structural similarity to any other AEDs and is suggested to be effective against partial and generalized seizures (Jia and Lu, 2011). Other six drugs viz. brivaracetam, carisbamate, eslicarbazepine, lacosamide, retigabine and stiripentol are in phase III of drug development.

This lead to the search for antiepileptic compounds with more selective activity and lower toxicity continues to be an area of investigation. This review focuses on different heterocyclic moieties showing anticonvulsant activity.

**Benzothiazoles**

A new series of N-(6-chlorobenzothiazol-2-yl)-2-substituted-acetamides 1 and N-(6-chlorobenzothiazol-2-yl)-2-(substituted - benzylidene) hydrazinecarbothioamides 2 were synthesized by Amir et al. 2012 and in vivo anticonvulsant and acute toxicity screening of all the synthesized compounds have been performed. 3D four-point pharmacophore measurements of compounds were also carried out to match these with established anticonvulsants agents. Kumar et al. 2012 have designed and synthesized a series of 2-[2-(substituted)hydrazinyl]-1,3-benzothiazole 3 and 2-(1,3-benzothiazol-2-yl-sulfanyl)-N-(substituted)acetohydrazide 4. The anticonvulsant activity of the titled compounds was assessed using the 6 Hz psychomotor seizure test. A series of substituted benzo[d]thiazol-2-yl-carbamates 5, 6 were synthesized and evaluated for anticonvulsant activity by Navale et al. 2013. Two series of analogues of riluzole, a blocker of excitatory amino acid mediated neurotransmission, have been synthesized: monosubstituted-2-benzothiazolamines 7 and 3-substituted derivatives 8 by Jimonet et al. 1999. A series of 1,3-benzothiazol-2-yl-benzamides 9 were prepared in satisfactory yield by Rana et al. 2008 and evaluated for their anticonvulsant, neurotoxicity, CNS depressant study and other toxicity studies. Siddiqui et al. 2007b have prepared a series of 1,3-benzothiazol-2-yl-semicarbazones 10 in satisfactory yield and evaluated for their anticonvulsant, neurotoxicity and other toxicity studies. A series of 6-substituted - [3-substituted-prop-2-eneamido] benzothiazole 11 and 6-substituted-2-[(1-acetyl-
5-substituted) 2-pyrazolin-3-yl] aminobenzo thiazole 12 were synthesized by Amnerkar and Bhusari, 2010 using appropriate synthetic route and evaluated experimentally against maximal electroshock test. Selected compounds were evaluated for neurotoxicity, hepatotoxicity and behavioral study. A series of N-(substituted benzothiazol-2-yl) amide derivatives 13 were synthesized by the EDC coupling reactions of substituted-benzothiazol-2-amine with 4-oxo-4-phenylbutanoic acid-2-benzoyl benzoic acid and evaluated for their anticonvulsant and neuroprotective effect by Hassan et al 2012. A series of 6-bromo-2-ethyl-3-(substituted-benzo[d]thiazol-2-yl)quinazolin-4(3H)-one 14 were synthesized using appropriate synthetic route and evaluated experimentally by the Maximal Electro Shock (MES) and the PTZ-induced seizure methods by Ugale et al 2012. A series of sulphonamide derivatives 15 were synthesized in good yield by Siddiqui et al 2007a and evaluated for their possible anticonvulsant activity and neurotoxic study (Figure 1).
Isatins

Palluotto et al 1996 synthesized a series of 2-aryl-2,5-dihydropyridazino[4, 3-b]indol-3-(3H)-ones 16. The synthesized compounds showed anticonvulsant activity. The onsets of clonic and tonic seizures were significantly reduced 45 min. after i.p. administration of derivatives and comparable with standard drug (Flumazenil). Campagna et al 1993 synthesized a new series of 2-aryl-2,5-dihydropyridazino[4,3-b]indol-3-(3H)
-ones. The synthesized compounds were evaluated for their good ability to prevent pentyleneterazol (PTZ) induced seizures in mice. Rajavendran et al 2007 designed a series of \( N^4\)-aryl / alkylidene-4-(1,3-dioxo-1,3-dihydro-2H-isoxindol-2-yl)butanoylhydrazides / butanamides. Anticonvulsant activity was determined using four animal models of seizures which included MES, subcutaneous pentylenetetrazole (scPTZ), intraperitoneal picrotoxin (ipPIC) induced seizures threshold test. Compounds showed protection in scPTZ screen. These compounds were found to be more potent when compared to standard drug phenytoin and ethosuximide, and were effective at dose 30 mg/kg. Azam et al 2009 designed a new series of \( N^4\)-[naphtha[1, 2-d][thiazol-2-yl]semicarbazides. The synthesized compounds with chloro, bromo and fluoro substituents, showed activity at 100 mg/kg after 0.5 h in MES test is comparable to the standard drug Phenobarbital, indicating that they have rapid onset of action and shorter duration of action. Sridhar et al 2002 designed a series of 3-(4-chlorophenylimino)-5-methyl-1, 3-dihydro-indole-2-one. The synthesized compounds were active in MES test and showed 87% protection at 100 mg/kg dose level with \( \text{ED}_{50} \) value of 53.61 mg/kg (Figure 2).

![Figure 2](image_url)

**Fig. 2.** Structures of diverse substituted isatins

**Oxadiazoles**

Zarghi et al 2005 synthesized a series of new 2-substituted-5 - (2-benzoxoxyphenyl)-1,3,4-oxadiazoles and evaluated them as anticonvulsant agents. Compounds showed considerable anticonvulsant activity both in scPTZ and MES models. It seems this effect is mediated through benzodiazepine receptors mechanism. Rajak et al 2010 synthesized a series of \( N^4\)-[(naphthalene-2-yl)oxymethyl] - 1,3,4-oxadiazol-2-yl] - \( N^4\) - (4-substituted benzaldehyde)-semicarbazone on the basis of semicarbazone based pharmacophoric model to meet the structural requirements necessary for anti-
convulsant activity. The anticonvulsant activities of the compounds were investigated using maximal electroshock seizure (MES), subcutaneous pentylenetetrazole (scPTZ) and subcutaneous strychnine (scSTY) models. Some of the selected active compounds were subjected to GABA assay to confirm their mode of action. Lankau et al. 2007 synthesized a new series of 3- and 5-aryl-1,2,4-oxadiazole derivatives 23 and tested for anticonvulsant activity in a variety of models. These 1, 2, 4-oxadiazoles exhibit considerable activity in both pentylenetetrazole (PTZ) and maximal electroshock seizure (MES) models. They found several oxadiazoles that acted as selective GABA potentiating compounds with no interaction to the benzodiazepine binding site. Gadegoni and Manda, 2013 designed a series of novel 3-[5-(1H-indol-3-ylmethyl) - 2-oxo-[1,3,4] - oxadiazol-3-yl] propionitrile 24. The chemical structures of the newly synthesized compounds were elucidated by their IR, 1H NMR and MS. Almasirad et al. 2004 synthesized a new series of 2-substituted-5-[2-(2-fluoro phenoxy) phenyl]-1,3,4-oxadiazoles 25 and evaluated their anticonvulsant activities (Figure 3).

Fig. 3. Structures of diverse substituted oxadiazoles
Pyridines

Pattan et al 2008 synthesized a new series of 1,4-dihydropyridine 26 and their derivatives and the structures of the compounds have been confirmed by IR and NMR. Some of the compounds have been found to exhibit excellent anticonvulsant activity. Ulloora et al 2013a synthesized a new series of imidazo-[1,2-a]-pyridines carrying biologically active cyano-pyridine 27. The target compounds were screened for their in vivo anticonvulsant activity following MES and subcutaneous pentylene tetrazole (scPTZ) methods at a small test dose of 10 mg/kg. Enhanced activity profile was observed for new compounds in PTZ method over MES method (Figure 4).

Fig. 4. Structures of diverse substituted pyridines
Prasanthi et al 2013 developed the study of dialkyl-4-(benzo \([d]\) \[1,3\] dioxol-6-yl)-1,4-dihydro-2,6-dimethyl-1-substituted pyridine-3,5-dicarboxylate derivatives 28 as isosteric analogues of isradipine and nifedipine, by the replacement of benzofurazanyl and 2-nitrophenyl groups respectively with benzo[\(d\)] \[1,3\]dioxo-6-yl group, as potential anticonvulsants. Fifteen new derivatives were synthesized and tested for anticonvulsant activity using maximal electroshock and subcutaneous pentylenetetrazole induced seizure methods. Compound possessing free NH group in 1,4-dihydropyridine ring, diethyl ester functionality at the positions 3 and 5 showed significant anticonvulsant activities.

Ulloora et al 2013b designed a series of imidazo [1,2-\(a\)]pyridines carrying active pharmacophore as potential anticonvulsant agents. The newly synthesized target compounds were characterized by FTIR, \(^1\)H NMR, \(^{13}\)C NMR, and mass spectroscopy. Preliminary anti-convulsant screening study of target compounds was carried out following MES and scPTZ methods. Compound 29 possessing electron rich aryl substituent at position-2 and tolyl substituted oxazolone moiety at the position-3 of imidazo[1,2-\(a\)] pyridine ring, exhibited activity comparable to standard drug diazepam and emerged as lead compounds. New compounds displayed enhanced activity in scPTZ method. Their neurotoxicity study by Rotarod test showed that they are nontoxic at all tested doses. Tripathi et al 2011 designed a new series of \(N\-[\)substituted] pyridine-4-carbohydrazides synthesized keeping in view the structural requirement of pharmacophore and evaluated for anticonvulsant activity and neurotoxicity. The most active compound of the series was \(N\-[4-(4-fluorophenoxy)benzylidene] pyridine-4-carbohydrazide 30, which showed a MES ED\(_{50}\) value of 128.3 mg/kg and 6 Hz ED\(_{50}\) value of 53.3 mg/kg in mice. A computational study was also carried out, including calculation of the pharmacophore pattern, prediction of pharmacokinetic properties and docking studies.

Pyrimidines

Alam et al 2010 synthesized a number of \(N-(4,6\)-substituted diphenyl pyrimidin-2-yl) semicarbazones 31 and tested for their anticonvulsant activity against the two seizure models, maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ).

All the synthesized compounds possessed the four essential pharmacophoric elements for good anticonvulsant activity. Most of the compounds displayed good anticonvulsant activity with lesser neurotoxicity.

To assess the unwanted effects of the compounds on liver, estimation of enzymes and proteins were carried out.

Deng et al 2011 designed a new series of anticonvulsant activities of 7-(\(substituted phenyl)- 6,7\)-dihydropyrazolo [1,2,4] triazolo [1,5-\(a\)] pyrimidin-5(4H)-ones 32 and their derivatives. Most of the synthesized compounds exhibited potent anticonvulsant activities in the maximal electroshock test (MES).

The potency of compounds against seizures induced by Pentylene tetrazole, Isoniazid, Thiosemi- carbazide, 3-Mercaptopropionic acid, and Bicuculline in the chemical-induced seizure tests suggested that compound displayed broad spectrum activity in several models, and it is likely to have several mechanisms of action including inhibiting voltage-gated ion channels and modulating GABAergic activity.

Wang et al 2012 synthesized new series of 5-alkoxytetrazolo [1,5-\(a\)] thi eno [2,3-\(e\)] pyrimidine 33 and their anticonvulsant potential was evaluated. Said et al 2009 synthesized new series of fused triazolopyrimidine 34 using 4-phenyl-but-3-en-2-one (Figure 5).
Initially the acute toxicity of the compounds was assayed via the determination of their LD$_{50}$ All the compounds were interestingly less toxic than the reference drug. The pharmacological screening showed that many of these obtained compounds have good anticonvulsant and activities comparable to Carbamazepine as reference drug.

**Indoles**

Praveen et al 2011 synthesized a new series of novel di(indoly)indolin-2-ones via Cu(OTf)$_2$ catalyzed bis-addition of N-allyl and N-propargylindole with isatin 36. This methodology allowed achieving the products in excellent yields without requiring purification technique like column chromatography. All the synthesized compounds were evaluated for their in vivo anticonvulsant activity against maximal electroshock test. Raj et al 2010 designed a new series of highly enantioselective catalytic synthesis of 3-cycloalkanone-3-hydroxy-2-oxindoles 37 was achieved by using primary-tertiary diamine-Brønsted acid catalyst in both organic medium and aqueous medium. The products, thus obtained act as potential anticonvulsants. Siddiqui et al 2011 synthesized a new series of various 1-(amino-N-arylmethanethio)-3-(1-substituted benzyl-2, 3-dioxoindolin-5-yl)urea 38 keeping in view the structural requirements suggested in the pharmacophore model for anticonvulsant activity. Their in vivo anticonvulsant screenings were performed by two most adopted seizure models, maximal electroshock seizure (MES) and subcutaneous pentylentetrazole (scPTZ). Some compounds were found active in MES screening while some compounds showed significant anticonvulsant activity in both the screenings and were devoid of any neurotoxicity. Sarges et al 1989 reported a series of l-aryl-3-(aminoalkylidene) oxindoles 39 (Figure 6).
The compounds were found to be potent enhancers of benzodiazepine binding and they antagonize cyclic GMP elevations induced by isoniazid and have potential therapeutic utility as anticonvulsants or anxiolytics. Salituro et al 1992 synthesized and tested as an antagonist for the strychnine-insensitive glycine binding site of the NMDA receptor 40. Chlorine and other small electron withdrawing substituents in the 4\textsuperscript{th} and 6\textsuperscript{th} positions of the indole ring greatly enhanced binding and selectivity for the glycine site over the glutamate site of the NMDA receptor.

**Figure 6.** Structures of diverse substituted indoles

**Benzimidazoles**

Shaharyar et al 2011 synthesized a series of 2-[2-(phenoxyethyl)-1H-benzimidazol-1-yl]aceto hydrazide 41 by using various aromatic aldehyde, cyanogens bromide and carbon disulfide/potassium hydroxide. These were elucidated by IR, NMR and elemental analysis and their in vivo anticonvulsant screening was performed using MES and scPTZ. Two compounds were found to be potent in both the screens and their protective index was found to be better than standard drugs used (Figure 7).
Shukla et al. 1982 synthesized a series of 1-heterocyclic amino/iminomethyl-2-substituted benzimidazoles 42 and were screened for their neuropharmacological and monoamine-oxidase inhibitory properties. A number of such compounds showed anticonvulsant, CNS stimulant and mono amine oxidase inhibitory activities. Synthesis of novel 1-H-pyrrolo(1,2-a)benzimidazole-1-one derivatives 43 were reported by Chimirri et al. 2001. Compounds showed good result by maximum electroshock method, at dose level 25 mg/kg orally. Shingalapur et al. 2010 synthesized a new series of benzimidazole derivatives, a group of 4-thiazolidinones 44 containing 2-mercapto benzimidazole moiety and screened for in vivo anticonvulsant activity by Maximal Electroshock (MES) model. Compounds exhibited potent anticonvulsant result and also pharmacophore derived from active molecules suggested that presence of -OH group was a common feature in all active compounds.

**Triazoles**

Siddiqui and Ahsan, 2010 designed a new series of 3-[4-(substituted phenyl)-1,3-thiazol-2-yl-amino]-4-(substituted phenyl)-4,5-dihydro-1H-1,2,4-triazole-5-thiones 45. Thiazole and triazole moieties being anticonvulsants were clubbed together to get the titled compounds and their in vivo anticonvulsant screening were performed by two most adopted seizure models, maximal electroshock seizure (MES) and subcutaneous pentylene tetrozole (scPTZ). They displayed a wide margin of safety with Protective index (PI), median hypnotic dose (HD_{50}) and median lethal dose (LD_{50}) much higher than the standard drugs.

Piao et al. 2011 synthesized a new series of novel 8-alkoxy-5,6-dihydro-4H-[1,2,4] triazolo [4,3-a] benzazepin-1-one derivatives 46 for their anticonvulsant activities by the maximal electroshock (MES) test, subcutaneous pentylene tetrozol (scPTZ) test, and their neurotoxicity was evaluated by the rotarod neurotoxicity test. Plech et al. 2013 synthesized a new series of 4-alkyl-1,2,4-triazole-3-thione derivatives 47 showed significant anticonvulsant activity, determined in the maximal electroshock-induced seizure (MES) test (Figure 8).
The chemical structure of all new compounds was confirmed by spectral methods (1H NMR, 13C NMR, IR, MS). A sensitive and selective method was elaborated for the determination of the anticonvulsant compounds levels in mice brain tissue, based on HPLC with diode array detector (DAD). Dawood et al. 2006 synthesized a new series of benzotriazoles by treatment of 2-bromoacetyl-benzofuran with 1H-benzotriazole afforded 1-(benzofuran-2-yl)2-(benzotriazol-1-yl)ethanone 48 which reacted with phenyl isothiocyanate to give the corresponding thioacetalilide derivatives. The newly synthesized compounds were found to possess anticonvulsant activities with the same mechanism of action of selective COX-2 inhibitor. A series of 4- (4-alkoxyphenyl) - 3-ethyl-4H-1,2,4-triazole derivatives 49 was synthesized by Chen et al. 2007 as open-chain analogues of 7-alkoxy-4,5-dihydro [1,2,4] triazolo [4,3-d] quinolines. Their anticonvulsant activities were evaluated by the maximal electroshock test (MES test) and their neurotoxicity was evaluated by the rotarod neurotoxicity test.

**Pyrazoles**

Falco et al. 2005 synthesized a new series of 3-amino-4,5-dihydro-1H-pyrazolo[3,4-b]pyridin-6-(7H)-ones and their N1-alkyl derivatives 50 as new scaffolds for designing non-benzodiazepine BZ receptor ligands.

Kaushik et al. 2010 synthesized a new series of N1-[(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylene]-2/4-substituted hydrazides 51 using appropriate synthetic route and characterized by elemental analysis and spectral data. The anticonvulsant activities of some of the synthesized compounds were evaluated against maximal electroshock induced seizure (MES) and subcutaneous pentylentetrazole (scPTZ) induced seizure models in mice. The neurotoxicity was assessed using the rotarod method. All the test compounds were administered at doses of 30, 100, and 300 mg/kg body weight and the anticonvulsant activity was noted at 0.5 and 4 h time intervals after the drug administration. Abdel-Aziz et al. 2009 synthesized a new series of substituted carboxylic acid hydrazides 52 which reacted with ethenetetracarbonitrile in dimethyl formamide with the formation of diacylhydrazines and 5-amino-1-substituted pyrazole-3,4-tricarbonitriles. The prepared compounds were evaluated for their anticonvulsant activity against scPTZ induced seizures in mice. The results of anticonvulsant activity are nearly close to phenobarbital sodium at a dose level of 30 mg/kg and more potent than phenytoin sodium at a dose level of 30 mg/kg.

Beyhan et al. 2013 designed a new series of 3, 5-disubstituted-4, 5-dihydro-1H-pyrazole-1-carboxamides 53 by refluxing selected chalcones and thiosemi-carbazide in alkaline medium. Structures of the synthesized compounds were confirmed by elemental analysis and spectral (UV, IR, 1H NMR, 13C NMR,
and mass) data, which were in line with the proposed structures. All compounds were tested for their anticonvulsant activity using pentylenetetrazole induced seizure (PTZ) and maximal electroshock seizure (MES) tests in mice at a dose level of 50 mg/kg. Yang et al 2004 synthesized a series of 3-(4-phenoxyphenyl)-1H-pyrazoles 54 and characterized as potent state-dependent sodium channel blockers. A limited SAR study was carried out to delineate the chemical requirements for potency. The results indicate that the distal phenyl group is critical for activity but will tolerate lipophilic (+δ) electronegative (+δ) substituents at o- and/or p-position. Substitution at pyrazole nitrogen with H-bond donor improves potency (Figure 9).

Fig. 9. Structures of diverse substituted pyrazoles
CONCLUSION
The present study revealed different heterocyclic moieties and their derivatives possessing anticonvulsant activity. Further studies and the modifications in these moieties can lead to generation of promising candidates in controlling epileptic seizures in future investigation.

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