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REVIEW ARTICLE

SOME HETEROCYCLICS WITH ANTICONVULSANT PROPERTIES

Birjees Nusrat[1], Ruhi Ali[1], Nadeem Siddiqui[1]* and Anwar Habib[2]

[1]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard, Hamdard Nagar, New Delhi-110 062, India*
[2]*Department of Medicine, HIMSAR, Jamia Hamdard, Hamdard Nagar, New Delhi-110 062, India*

**E-mail*: nadeems_03@yahoo.co.in
Tel.: +91 11 26059688, *Fax*: +91 11 26059688.

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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,

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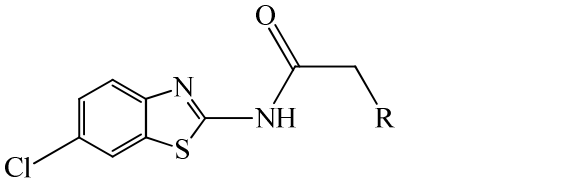
(iv) myoclonic seizures, (v) primary generalized tonic-clonic seizures, and (vi) atonic seizures.
Generalized tonic-clonic (grand mal) is characterized by sudden cry, fall, rigidity, followed by muscle jerks, shallow breathing or temporarily suspended breathing, bluish skin, possible loss of bladder control (usually lasts a couple of minutes).
In recent years the field of antiepileptic drug development is quite dynamic, affording many promising research opportunities (Yogeeswari *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 $GABA_A$ 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 pentylenetetrazole. Another major problem caused by available drugs is the side effect associated with them. The established antiepileptic agents *viz.* valproic acid, phenytoin, carbamazapine, 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-chloro-benzothiazol-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-

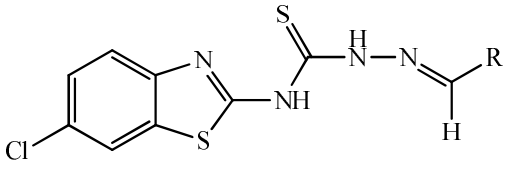
5-substituted) - 2-pyrazolin-3-yl] aminobenzo thiazole **12** were synthesized by Amnerkar and Bhusari, 2010 using appropriate synthetic route and evaluated experimentally against maximal electroshock test.

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-phenyl-butanoic 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(3*H*)-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**).



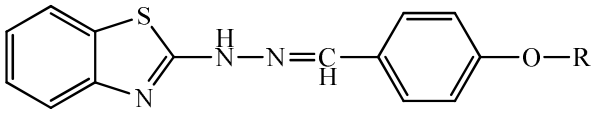
R= tert-butylamino, 4-chlorophenylamino, diphenylamino

(1)



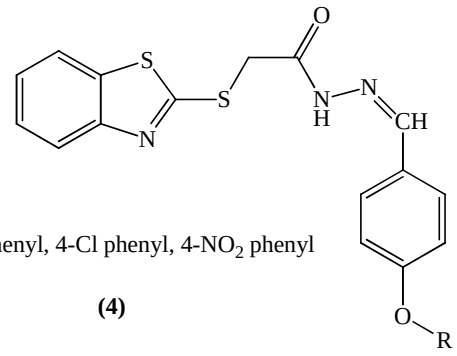
R= phenyl, 4-Cl phenyl, 4-Fphenyl, 2-Cl phenyl

(2)



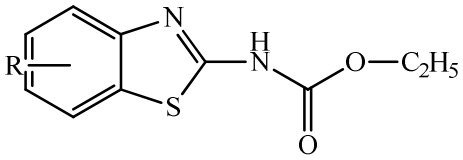
R= phenyl, 4-Cl phenyl, 4-NO_2 phenyl

(3)



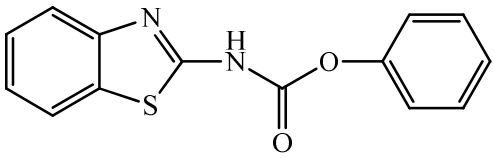
R= phenyl, 4-Cl phenyl, 4-NO_2 phenyl

(4)



R= H, 6-CH_3, 6-C_2H_5

(5)



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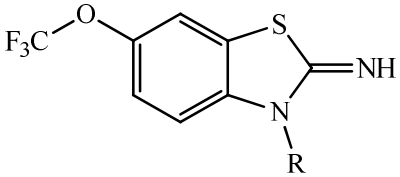
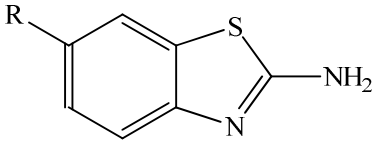


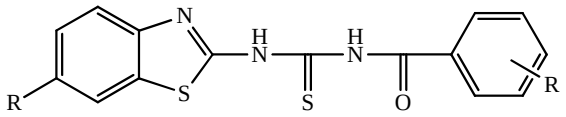
R= CH_3, C_2H_5, C_3H_7, allyl

(7)



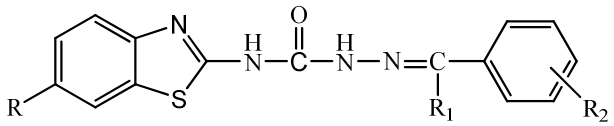
R= H, Cl, Br, OCF_3

(8)



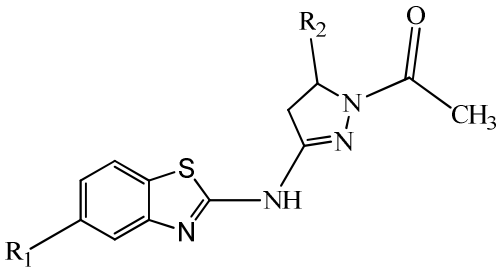
R= F, Cl, Br, NO_2
R1= H, 2-Cl, 4-Cl, 4-OCH_3

(9)



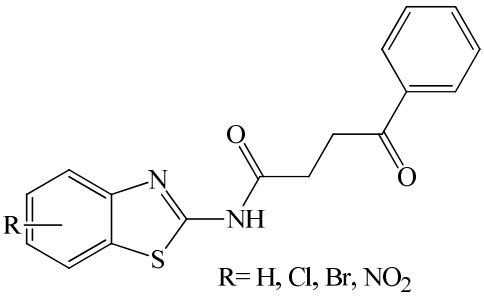
R= Cl, CH_3, OCH_3, R_1= CH_3, C_6H_5, R_2= H, OH, NO_2

(10)



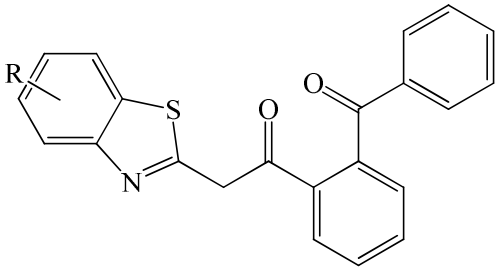
R_1= H, Cl, NO_2,
R_2= phenyl, 4-OH phenyl, 4-Cl phenyl

(11)



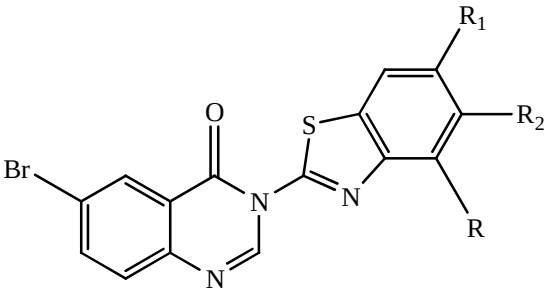
R= H, Cl, Br, NO_2

(12)



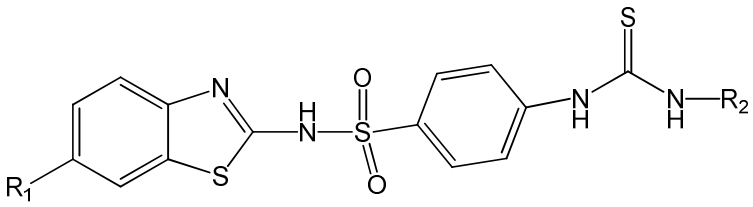
R- H, Cl, Br

(13)



R, R_1, R_2= H, Cl, CH_3, OCH_3

(14)



R1= F, Cl, OCH_3 R2= CH_3, C_2H_5

(15)

Fig.1. Structures of diverse substituted benzothiazoles

Isatins

Palluotto *et al* 1996 synthesized a series of 2-aryl-2,5-dihydropyridazino[4, 3-b]indol-3-(3*H*)-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-(3*H*)

-ones **17**. The synthesized compounds were evaluated for their good ability to prevent pentylenetetrazole (PTZ) induced seizures in mice. Rajavendran *et al* 2007 designed a series of *N*-aryl / alkylidene-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butanoylhydrazides / butanamides **18**. 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 **19**. The synthesized compounds with chloro, bromo and flouro 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 **20**. The synthesized compounds were active in MES test and showed 87% protection at 100 mg/kg dose level with ED_{50} value of 53.61 mg/kg (**Figure 2**).

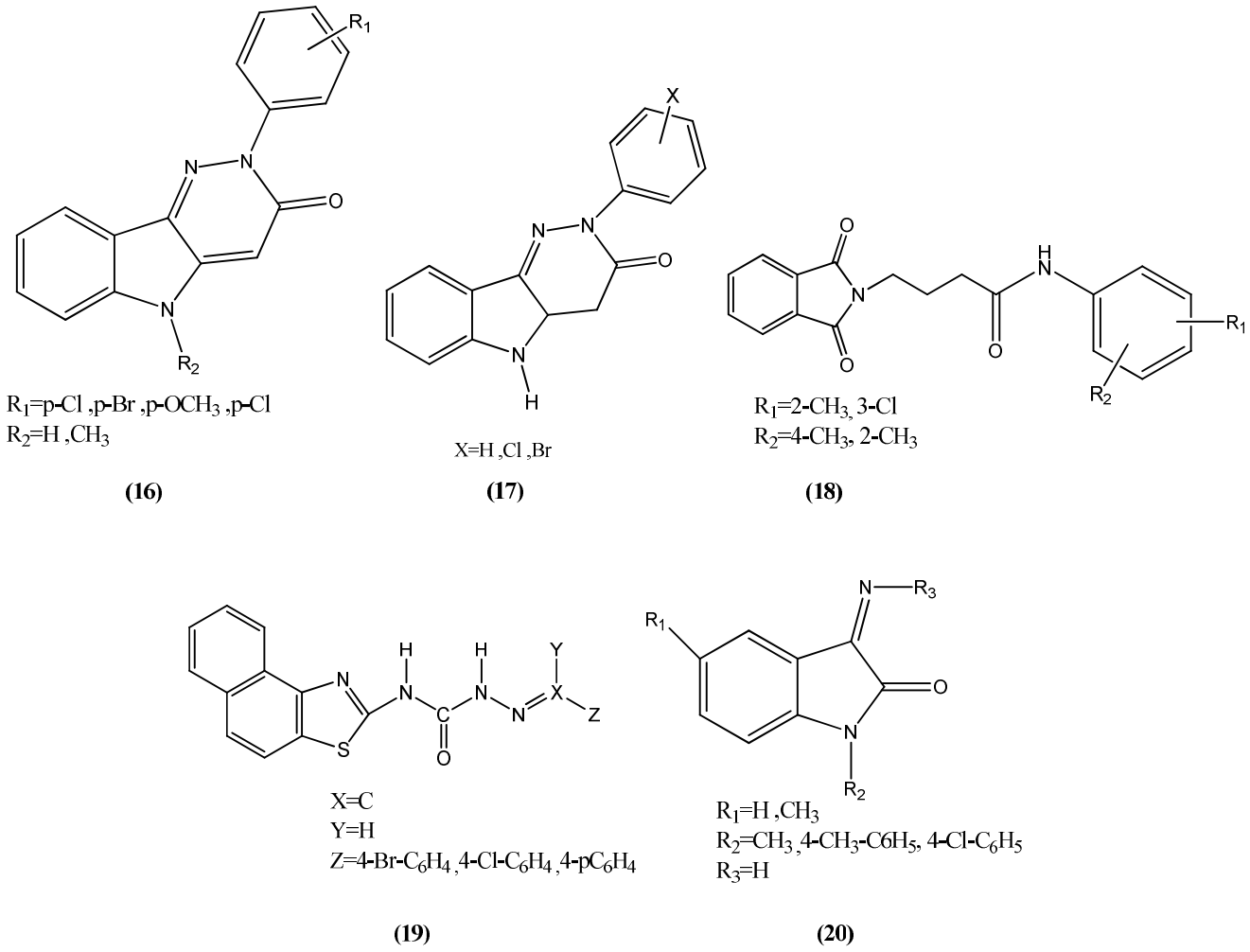


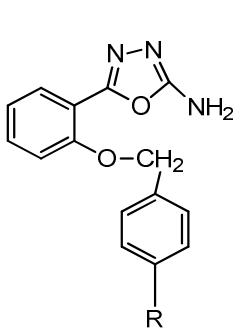
Fig. 2. Structures of diverse substituted isatins

Oxadiazoles

Zarghi *et al* 2005 synthesized a series of new 2-substituted-5 - (2-benzyloxyphenyl)-1,3,4-oxadiazoles **21** 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^1-{5-[(naphthalene-2-yloxy)methyl] - 1,3,4-oxadiazol-2-yl} - N^4 - (4-substituted benzaldehyde)-semi carbazone **22** on the basis of semicarbazone based pharmacophoric model to meet the structural requirements necessary for anti-

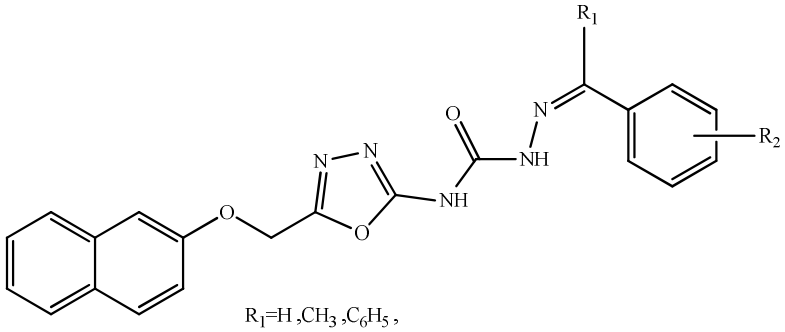
convulsant activity. The anticonvulsant activities of the compounds were investigated using maximal electroshock seizure (MES), subcutaneous pentylenetrtrazole (scPTZ) and subcutaneous strychnine (scSTY) models. Some of the selected active compounds were subjected to GABA assay to confirm their mode 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-(1*H*-indol-3-yl-methyl) - 2-oxo-[1,3,4] - oxadiazol-3-yl] propio-nitrile **24**. The chemical structures of the newly synthesized compounds were elucidated by their IR, ^{1}H 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**).



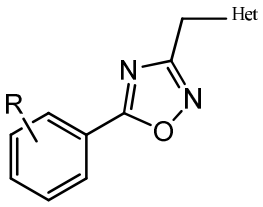
R=F, Cl, H

(21)



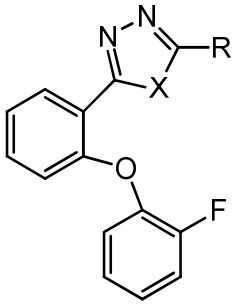
R_1=H ,CH_3 ,C_6H_5 ,
R_2=H ,4-Cl ,4-NO_2 ,4-OH,4-CH_3, 4-OCH_3

(22)



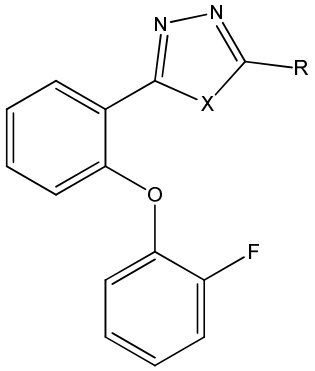
R=H ,4-Cl ,2-F, 3-F ,4-F ,3-CH_3 ,4-CH_3

(23)



R=NH_2 ,SH , OH , SCH_3 ,OC_2H_5
X=O , NH

(24)



X= O, N
R= SH, OH, NH_2

(25)

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**).

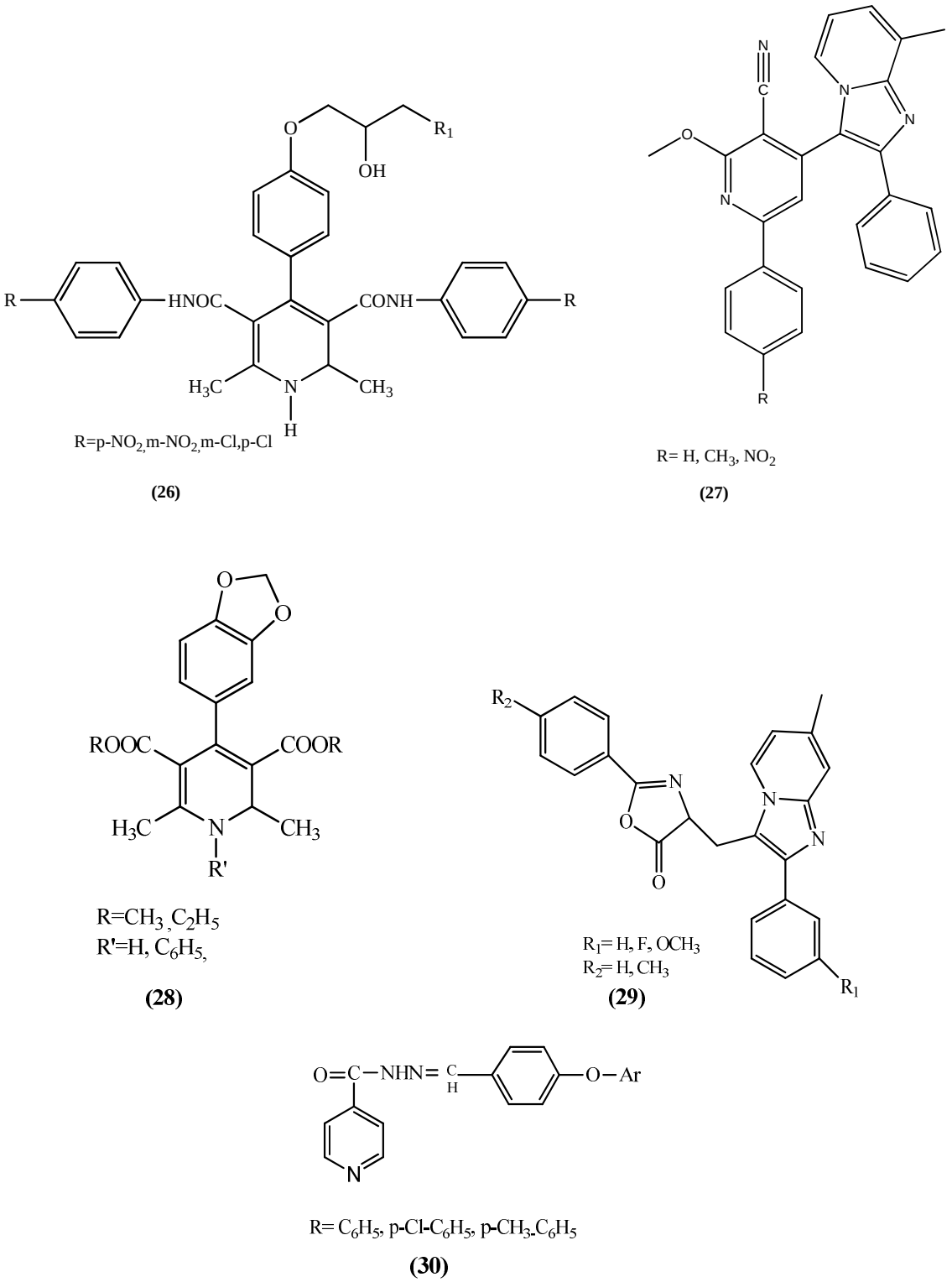


Fig. 4. Structures of diverse substituted pyridines

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-nitro-phenyl groups respectively with benzo*[d]* [1,3]dioxo-6-yl group, as potential anti-convulsants. 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 pharmaco kinetic 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).

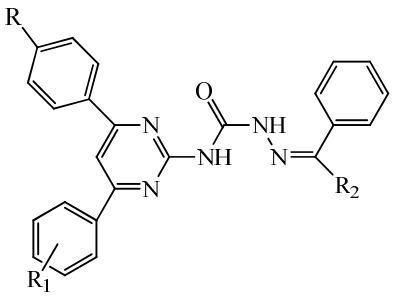
All the synthesized compounds possessed the four essential pharmacophoric elements for good anticonvulsant activity. Most of the compounds displayed good anticonvulsant activity with lesser neurotoxicity.

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-dihydro- [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*] thieno [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**).

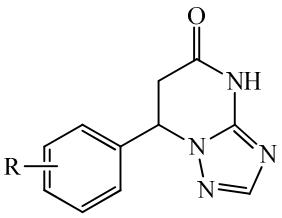


R=4-F ,4-Cl

R_1= 3,4 di-OCH_3 , 2,4,-diOCH_3 ,4-NO_2 ,4-CH_3 ,4-OCH_3 ,

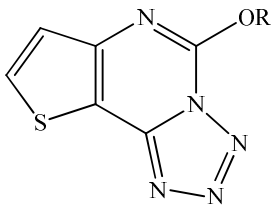
R_2=H , CH_3

(31)



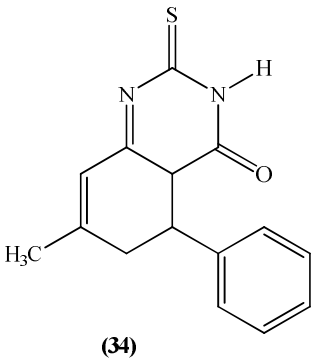
R=H ,2-F ,3-F ,2-Cl ,3-Cl ,4-Cl ,2-Br ,3-Br ,4-Br ,3-CF_3 ,4-CH_3 ,2-OCH_3 ,4-OCH_3 ,$CH_2C_6H_5$, C_6H_{13}

(32)



R=C_6H_4(o-Cl) ,C_6H_4(p-Cl) ,C_6H_4(m-Cl) ,C_6H_5 ,8-Quinoline , C_6H_4(p-CF_3) C_6H_4(o-NH_2) , C_6H_4(m-NH_2) ,C_6H_5 (2,4-Cl) ,C_6H_4(m-F|)

(33)



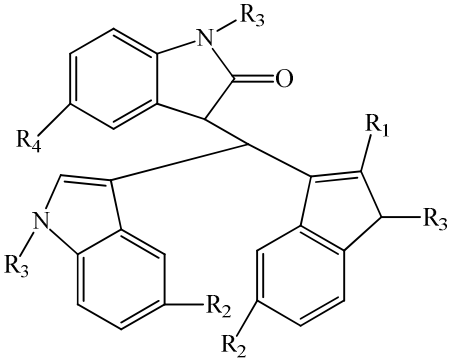
(34)

Fig. 5. Structures of diverse substituted pyrimidines

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.

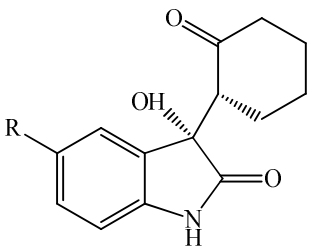
Indoles

Praveen *et al* 2011 synthesized a new series of novel di(indolyl)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 pentylenetetrazole (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**).



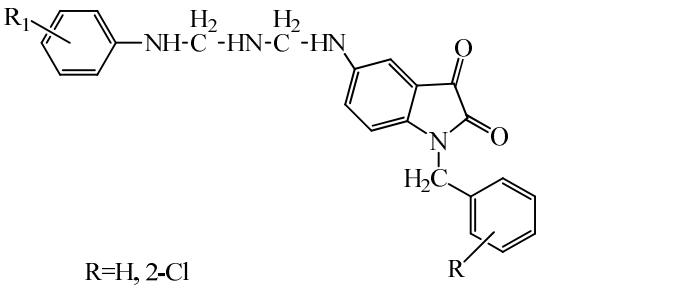
R=H ,Me
R_1=allyl, prenyl, cinnamyl, propargyl,
R_2=H, OMe, Br
R_3=H, benzyl, propargyl,CH_2COOEt
R_4=H, Cl,Br, NO_2

(36)



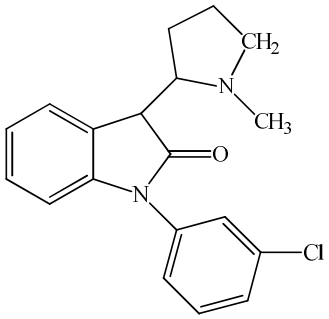
R=H, Cl,Br

(37)

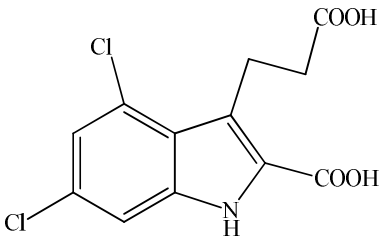


R=H, 2-Cl
R_1=H,2-Cl,2-CH_3, 3-CH_3, 4-CH_3, 2-$OCH_3$3-OCH_3, 4-OCH_3

(38)



(39)



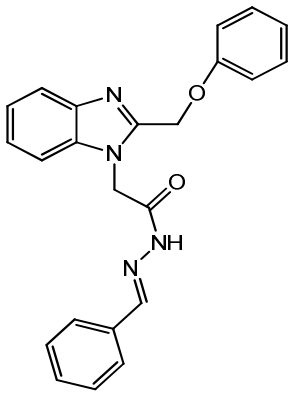
(40)

Fig. 6. Structures of diverse substituted indoles

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 4th and 6th positions of the indole ring greatly enhanced binding and selectivity for the glycine site over the glutamate site of the NMDA receptor.

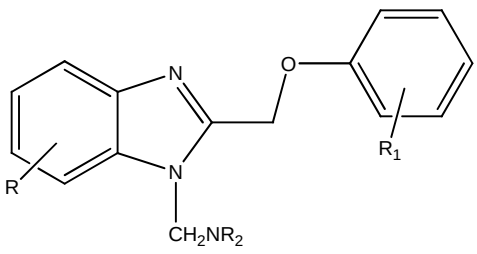
Benzimidazoles

Shaharyar *et al* 2011 synthesized a series of 2-[2-(phenoxymethyl)-1*H*-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**).



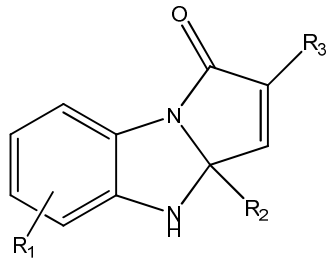
R=H,2-Cl,4-Cl,4-OCH_3,3-OCH_3,4-F,4-NH_2,NO_2,3,4-di$OCH_3$4,4,dimethylamino

(41)



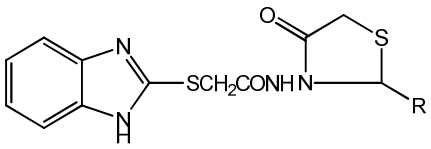
R=H, Cl, F
R_1=H, C_2H_5, CH_3
R_2=H, C_6H_5

(42)



R_1=Cl, F, H
R_2=C_6H_5,CH_3
R_3=H

(43)



R= C_6H_5, m-OH-C_6H_5, p-NH_2-CUH_5, p-Cl-C_6H_5

(44)

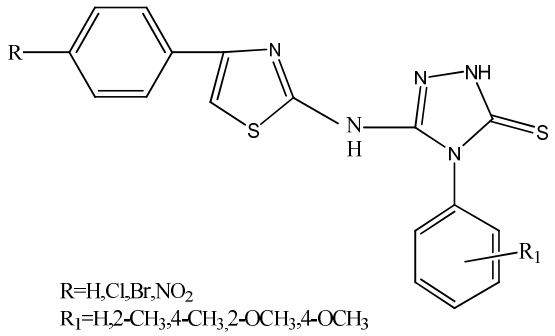
Fig. 7. Structures of diverse substituted benzimidazoles

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

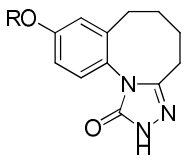
Siddiqui and Ahsan, 2010 designed a new series of 3-[4-(substituted phenyl)-1,3-thiazol-2-yl-amino]-4-(substituted phenyl)-4,5-dihydro-1*H*-1,2,4-triazole-5-thiones **45**. Thiazole and triazole moieties being anticonvulsants were clubbed together to get the titled compounds and their *in vivo* anticonvulsant screening were performed by two most adopted seizure models, maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (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-4*H*- [1,2,4] triazolo [4,3-*a*] benzazepin-1-one derivatives **46** for their anticonvulsant activities by the maximal electroshock (MES) test, subcutaneous pentylene tetrazol (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**).



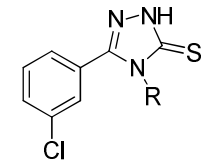
R=H,Cl,Br,NO_2
R_1=H,2-CH_3,4-CH_3,2-OCH_3,4-OCH_3

(45)



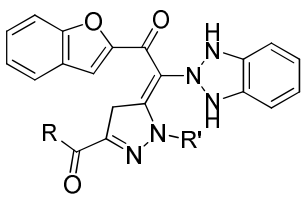
R=$C_{17}H_{15}$, C_6H_{13}, C_5H_{11}

(46)



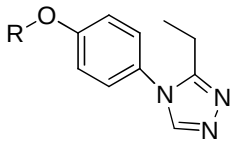
R=$C_{10}H_{21}$, $C_{12}H_{25}$

(47)



R=CH_3, OC_2H_5

(48)



R=-n-C_7H_{15}, n-C_8H_{17}

(49)

Fig. 8. Structures of diverse substituted triazoles

The chemical structure of all new compounds was confirmed by spectral methods (^{1}H NMR, ^{13}C 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 thio acetanilide derivatives. The newly synthesized compounds were found to possess anti-convulsant activities with the same mechanism of action of selective COX-2 inhibitor**.** A series of 4 - (4-alkoxylphenyl) - 3-ethyl-4*H*-1,2,4-triazole derivatives **49** was synthesized by Chen *et al* 2007 as open-chain analogues of 7-alkoxyl-4,5-dihydro [1,2,4] triazolo [4,3-α] quinolines. Their anticonvulsant activities were evaluated by the maximal electroshock test (MES test) and their neurotoxicity was evaluated by the rotarod neurotoxicity test.

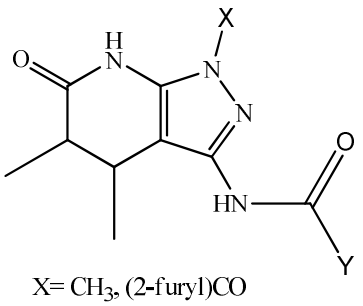
Pyrazoles

Falco *et al* 2005 synthesized a new series of 3-amino-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6-(7*H*)-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 *N'*-[(5-chloro-3-methyl-1-phenyl-1*H*-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 pentylenetetrazole (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 diacyl-hydrazines and 5-amino-1-substiuted pyrazole-3,3,4-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.

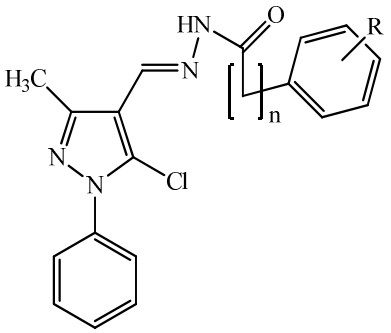
Beyhan *et al* 2013 designed a new series of 3, 5-disubstituted-4, 5-dihydro-1*H*-pyrazole-1-carbothioamides **53** by refluxing selected chalcones and thiosemi- carbazide in alkaline medium. Structures of the synthesized compounds were confirmed by elemental analysis and spectral (UV, IR, ^{1}H NMR, ^{13}C 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)-1*H*-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**).



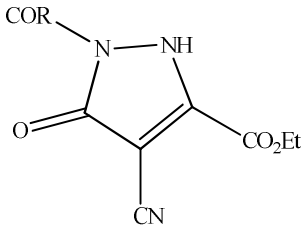
X= CH_3, (2-furyl)CO
Y= CH_3, C_6H_5, C_6H_5NH

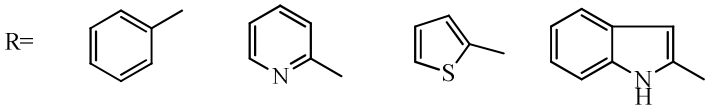
(50)



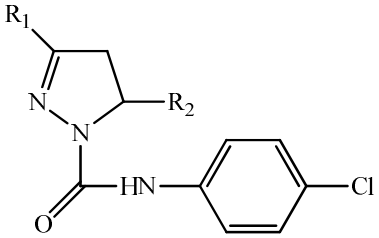
R=H, CH_3 , p-F, p-Cl, p-NO_2, o-Cl ,2,4-Dichloro, iso-butyl

(51)



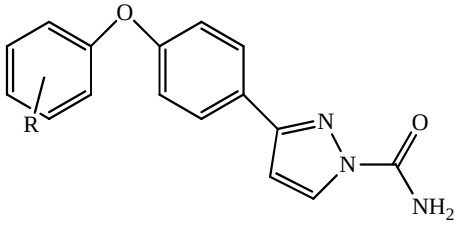


(52)



R_1=Phenyl, 4-Methylsulfonylphenyl, Thiophen-2-yl, 5-Bromothiophen-2-yl, 5-chlorothiophen-2-yl
R_2=2,6,Dichlorophenyl

(53)



R=4-NO_2, H, 4-F, 2,4-F_2

(54)

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.

REFERENCES

Alam O, Mullick P, Verma SP, Gilani SJ, Khan SA, Siddiqui N, Ahsan W. Synthesis, anticonvulsant and toxicity screening of newer pyrimidine semicarbazone derivatives. *Eur. J. Med. Chem.* 2010;45(6):2467-72. [DOI: 10.1016/j.ejmech.2010.02.031].

Almasirad A, Tabatabai SA, Faizi M, Kebriaeezadeh A, Mehrabi N, Dalvandi A, Shafiee A. Synthesis and anticonvulsant activity of new 2-substituted-5-[2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazoles and 1,2,4-triazoles. *Bioorg. Med. Chem. Lett.* 2004;(14):6057-59. [DOI:10.1016/j.bmcl.2004.09.072].

Amir M, Asif S, Ali I, Hassan MZ. Synthesis of benzothiazole derivatives having acetamido and carbothioamido pharmacophore as anticonvulsant agents. *Med. Chem. Res.* 2012;21:2661-70. [DOI: 10.1007/s00044-011-9791-1].

Amnerkar ND, Bhusari KP. Synthesis, anticonvulsant activity and 3D-QSAR study of some prop-2-eneamido and 1-acetyl-pyrazolin derivatives of aminobenzothiazole. *Eur. J. Med. Chem.* 2010;45(1):149-59. [DOI:10.1016/j.ejmech.2009.09.037].

Azam F, Alkskas IA, Khokra SL, Prakash O. Synthesis of some novel N4-(naphtha [1,2-*d*] thiazol-2-yl) semicarbazides as potential anticonvulsants. *Eur. J. Med. Chem.* 2009;44(1):203-11. [DOI: 10.1016/j.ejmech.2008.02.007] .

Abdel-Aziz M, Abou-Rahma GEA, Hassan AA. Synthesis of novel pyrazole derivatives and evaluation of their antidepressant and anticonvulsant activities. *Eur. J. Med. Chem.* 2009;44(9):3480-7. [DOI: 10.1016/j.ejmech.2009.01.032]

Beyhan N, Kocyigit-Kaymakcioglu B, Gumru S, Aricioglu F. Synthesis and anticonvulsant activity of some 2-pyrazolines derived from chalcones. *Arab. J. Chem.* 2013 (In press). [DOI: 10.1016/j.arabjc.2013.07.037]

Brunton LL, Lazo JS, Parker KL. Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 11th edition, McGraw-Hill Medical Publishing Division: 2006; 610-11.

Campagna F, Carotti A, Casini G, Palluotto F, Genchi G, De Sarro GB. 2-Aryl-2, 5-dihydropyridazino[4,3-*b*]indol-3(3*H*)ones: Novel rigid planar benzodiazepine receptor ligands. *Bioorg. Med. Chem.* 1993;1(6):437-46. [DOI: 10.1016/S0968-0896(00)82154-9]

Chen J, Sun X-Y, Chai K-Y, Lee J-S, Song M-S, Quan Z-S. Synthesis and anticonvulsant evaluation of 4-(4-alkoxylphenyl)-3-ethyl-4*H*-1,2,4-triazoles as open-chain analogues of 7-alkoxyl-4,5-dihydro[1,2,4]triazolo[4,3-*a*] quinolones. *Bioorg. Med. Chem.* 2007;15(21):6775-81. [DOI: 10.1016/j.bmc.2007.08.004]

Chimirri A, Sarro AD, De Sarro G, Gitto R, Zappala M. Synthesis and anticonvulsant properties of 2,3,3a,4-tetrahydro-1*H*-pyrrolo (1,2-*a*) benzimidazol-1-one-derivatives. *Farmaco* 2001;56(11):821-6.

Curry WJ, Kulling DL. Newer antiepileptic drugs: gabapentin, lamotrigine, felbamate, topiramate and fosphenytoin. *Am. Fam. Physician* 1998;57(3):513-20.

Dawood KM, Abdel-Gawad H, Rageb EA, Ellithey M, Mohamed HA. Synthesis, anticonvulsant, and anti-inflammatory evaluation of some new benzotriazole and benzofuran-based heterocycles. *Bioorg. Med. Chem.* 2006; 14(11):3672-80. [DOI: 10.1016/j.bmc.2006.01.033]

Deng XQ, Quan LN, Song MX, Wei CX, Quan ZS. Synthesis and anticonvulsant activity of 7-phenyl-6,7-dihydro-[1,2,4] triazolo [1,5-*a*] pyrimidin-5(4*H*)-ones and their derivatives. *Eur. J. Med. Chem.* 2011;46(7):2955-63. [DOI: 10.1016/j.ejmech.2011.04.020]

Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, Engel J Jr. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005;46(4):470-2. [DOI: 10.1111/j.0013-9580.2005.66104.x]

Falco JL, Lloveras M, Buira I, Teixido J, Borrell JI, Mendez E, Terencio J, Palomer A, Guglietta A. Design, synthesis and biological activity of acyl substituted 3-amino-5-methyl-1,4,5,7-tetrahydropyrazolo [3,4-*b*] pyridin-6-ones as potential hypnotic drugs. *Eur. J. Med. Chem.* 2005;40(11): 1179-87. [DOI:10.1016/j.ejmech.2005.06.008]

Gadegoni H, Manda S. Synthesis and screening of some novel substituted indoles contained 1,3,4-oxadiazole and 1,2,4-triazole moiety. *Chin. Chem. Lett.* 2013;24(2):127-30. [DOI: 10.1016/j.cclet.2013.01.001]

Gavernet L, Barrios IA, Sella Cravero M, Bruno-Blanch LE. Design, synthesis, and anticonvulsant activity of some sulfamides. *Bioorg. Med. Chem. Lett.* 2007;15(16):5604-14. [DOI: 10.1016/j.bmc.2007.05.024]

Hassan MZ, Khan SA, Amir M. Design, synthesis and evaluation of *N*-(substituted benzothiazol-2-yl)amides as anticonvulsant and neuroprotective. *Eur. J. Med. Chem.* 2012;58(12):206-13. [DOI: 10.1016/j.ejmech.2012.10.002].

Jia J, Lu D. Ethyl 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxylate. *Acta Crystallogr. Sect. E. Struct. Rep. Online* 2011;67(1):o127. [DOI: 10.1107/S1600536810050014]

Jimonet P, Audiau F, Barreau M, Blanchard JC, Boireau A, Bour Y, Coleno MA, Doble A, Doerflinger G, Huu CD, Donat MH, Duchesne JM, Ganil P, Gueremy C, Honor E, Just B, Kerphirique R, Gontier S, Hubert P, Laduron PM, Le Blevec J, Meunier M, Miquet J-M, Nemecek C, Pasquet M, Piot O, Pratt J, Rataud J, Reibaud M, Stutzmann J-M, Mignani S. Riluzole Series. Synthesis and in vivo "Antiglutamate" activity of 6-substituted-2-benzothiazolamines and 3-substituted-2-imino-benzothiazolines. *J. Med. Chem.* 1999; 42(15):2828-43. [DOI: 10.1021/jm980202u].

Kaushik D, Khan SA, Chawla G, Kumar S. *N*'-[(5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl) methylene] 2/4-substituted hydrazides: Synthesis and anticonvulsant activity. *Eur. J. Med. Chem.* 2010;45(9):3943-9. [DOI: 10.1016/j.ejmech.2010.05.049]

Kumar P, Shrivastava B, Pandeya SN, Tripathi L, Stables JP. Design, synthesis, and anticonvulsant evaluation of some novel 1,3-benzothiazol-2-yl hydrazones/aceto-hydrazones. *Med. Chem. Res.* 2012;21(9):2428-42. [DOI: 10.1007/s00044-011-9768-0].

Lankau H-J, Unverferth K, Grunwald C, Hartenhauer H, Heinecke K, Bernoster K, Dost R, Egerland U, Rundfeldt C. New GABA-modulating 1,2,4-oxadiazole derivatives and their anticonvulsant activity. *Eur. J. Med Chem.* 2007; 42(6):873-9. [DOI: 10.1016/j.ejmech.2006.12.022]

Navale A, Pawar S, Deodhar M, Kale A. Synthesis of substituted benzo[*d*]thiazol-2-ylcarbamates as potential anticonvulsants. *Med. Chem. Res.* 2013;22(9):4316-21. [DOI: 10.1007/s00044-012-0434-y].

Palluotto F, Carotti A, Casini G, Campagna F, Genchi G, Rizzo M, De Sarro GB. Structure-activity relationships of 2-aryl-2,5-dihydropyridazino[4,3-*b*]indol-3(3*H*)-ones at the benzodiazepine receptor. *Bioorg. Med. Chem.* 1996;4(12):2091-104. [DOI: 10.1016/S0968-0896(96)00220-9]

Pattan SR, Purohit SS, Rasal VP, Mallya S, Marihal SC, Khade AB, Paschapur MS. Synthesis and pharmacological screening of some 1,4-dihydropyridine and their derivatives for anticonvulsant activity. *Ind. J. Chem.* 2008; 47B(04):626-9.

Piao FY, Han RB, Zhang W, Zhang WB, Jiang RS. Synthesis and anticonvulsant activity of 8-alkoxy-5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-*a*][1]benzazepin-1-one derivatives. *Eur. J. Med. Chem.* 2011;46(4):1050-5. [DOI: 10.1016/j.ejmech.2011.01.017]

Plech T, Luszczki JJ, Wujec M, Flieger J, Pizon M. Synthesis, characterization and preliminary anticonvulsant evaluation of some 4-alkyl-1,2,4-triazoles. *Eur. J. Med. Chem.* 2013;60:208-15. [DOI: 10.1016/j.ejmech.2012.11.026]

Prasanthi G, Prasad K, Bharathi K. Design, synthesis and evaluation of dialkyl 4-(benzo[*d*][1,3]dioxol-6-yl)-1,4-dihydro-2,6-dimethyl-1-substituted pyridine-3,5-dicarboxylates as potential anticonvulsants and their molecular properties prediction. *Eur. J. Med. Chem.* 2013; 66:516-25. [DOI: 10.1016/j.ejmech.2013.06.006]

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(13):4072-7. [DOI: 10.1016/j.bmcl.2011.04.117]

Ragavendran JV, Sriram D, Patel SK, Reddy IV, Bharathwajan N, Stables J, Yogeeswari P. Design and synthesis of anticonvulsants from a combined phthalimide-GABA-anilide and hydrazone pharmacophore. *Eur. J. Med. Chem.* 2007;42(2):146-51. [DOI: 10.1016/j.ejmech.2006.08.010]

Raj M, Veerasamy N, Singh VK. Highly enantioselective synthesis of 3-cycloalkanone-3-hydroxy-2-oxindoles, potential anticonvulsants. *Tetrahedron Lett.* 2010;51(16): 2157-9. [DOI: 10.1016/j.tetlet.2010.02.082]

Rajak H, Deshmukh R, Veerasamy R, Sharma AK, Mishra P, Kharya MD. Novel semicarbazones based 2,5-disubstituted-1,3,4-oxadiazoles: One more step towards establishing four binding site pharmacophoric model hypothesis for anticonvulsant activity. *Bioorg. Med. Chem. Lett.* 2010;20(14):4168-72. [DOI: 10.1016/j.bmcl.2010.05.059]

Rana A, Siddiqui N, Khan SA, Haque SE, Bhat MA. N-{[(6-Substituted-1,3-benzothiazole-2-yl)amino] carbonthio-yl}-2/4-substituted benzamides: Synthesis and pharmacological evaluation. *Eur. J. Med. Chem.* 2008; 43(5):1114-21. [DOI: 10.1016/j.ejmech.2007.07.008]

Said SA, Amr A-G, Sabry NM, Abdalla MM. Analgesic, anticonvulsant and anti-inflammatory activities of some synthesized benzodiazipine, triazolopyrimidine and bis-imide derivatives. *Eur. J. Med. Chem.* 2009;44(12):4787-92. [DOI: 10.1016/j.ejmech.2009.07.013]

Salituro FG, Harrison BL, Baron BM, Nyce PL, Stewart KT, Kehne JH, White HS, McDonald IA. 3-(2-Carboxyindol-3-yl)propionic acid-based antagonists of the N-methyl-D-aspartic acid receptor associated glycine binding site. *J. Med. Chem.* 1992;35(10):1791-9. [DOI: 10.1021/jm00088a014]

Sarges R, Howard HR, Koe BK, Weissman A. A novel class of "GABAergic" agents: 1-aryl-3-(aminoalkylidene) oxindoles. *J. Med. Chem.* 1989;32(2):437-44. [DOI: 10.1021/jm00122a025]

Shaharyar M, Mazumder A, Salahuddin, Garg R, Pandey RD. Synthesis, characterization and pharmacological screening of novel benzimidazole derivatives. *Arab J. Chem.* 2011 (In press). [DOI: 10.1016/j.arabjc.2011.04.013]

Shingalapur RV, Hosamani KM, Keri RS, Hugar MH. Derivatives of benzimidazole pharmacophore: Synthesis, anticonvulsant, antidiabetic and DNA cleavage studies. *Eur. J. Med. Chem.* 2010;45(5):1753-9. [DOI: 10.1016/j.ejmech.2010.01.007]

Shukla JS, Saxena S, Rastogi R. Synthesis of some newer 1-hetrocyclic amino/iminomethyl-2-substituted benzimidazoles as a potent CNS, anticonvulsant and monoamineoxidase inhibitory agents. *Curr. Sci.* 1982; 51(17):820-22.

Siddiqui N, Ahsan W. Triazole incorporated thiazoles as a new class of anticonvulsants: Design, synthesis and in vivo screening. *Eur. J. Med. Chem.* 2010;45(4):1536-43. [DOI: 10.1016/j.ejmech.2009.12.062]

Siddiqui N, Alam MS, Stables JP. Synthesis and anticonvulsant properties of 1-(amino-N-arylmethane thio)-3-(1-substituted benzyl-2, 3-dioxoindolin-5-yl) urea derivatives. *Eur. J. Med Chem.* 2011;46(6):2236-42. [DOI: 10.1016/j.ejmech.2011.03.004]

Siddiqui N, Pandeya SN, Khan SA, Stables J, Rana A, Alam M, Arshad MF, Bhat MA. Synthesis and anticonvulsant activity of sulphonamide derivatives-hydrophobic domain. *Bioorg. Med. Chem. Lett.* 2007;17(1):255-9. [DOI: 10.1016/j.bmcl.2006.09.053].

Siddiqui N, Rana A, Khan SA, Bhat MA, Haque SE. Synthesis of benzothiazole semicarbazones as novel anticonvulsants-The role of hydrophobic domain. *Bioorg. Med. Chem. Lett.* 2007;17(15):4178-82. [DOI: 10.1016/j.bmcl.2007.05.048].

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(3): 129-32. [DOI: 10.1016/S0928-0987(02)00077-5]

Tripathi L, Singh R, Stables JP. Design and synthesis of *N*'-[substituted]pyridine-4-carbohydrazides as potential anticonvulsant agents. *Eur. J. Med. Chem.* 2011;46(2):509-18. [DOI: 10.1016/j.ejmech.2010.11.030]

Ugale VG, Patel HM, Wadodkar SG, Bari SB, Shirkhedkar AA, Surana SJ. Quinazolino-benzothiazoles: Fused pharmacophores as anticonvulsant agents. *Eur. J. Med. Chem.* 2012;53:107-13. [DOI: 10.1016/j.ejmech.2012.03.045].

Ulloora S, Adhikari AV, Shabaraya R. Synthesis and antiepileptic studies of new imidazo[1,2-*a*]pyridine derivatives. *Chin. Chem. Lett.* 2013;24(9):853-6. [DOI: 10.1016/j.cclet.2013.05.030]

Ulloora S, Shabaraya R, Aamir S, Adhikari AV. New imidazo[1,2-*a*]pyridines carrying active pharmacophores: Synthesis and anticonvulsant studies. *Bioorg. Med. Chem. Lett.* 2013;23(5):1502-6. [DOI: 10.1016/j.bmcl.2012.12.035]

Wang SB, Deng XQ, Zheng Y, Yuan YP, Quan ZS, Guan LP. Synthesis and evaluation of anticonvulsant and anti-depressant activities of 5-alkoxytetrazolo[1,5-*c*]thieno [2,3-*e*]pyrimidine derivatives. *Eur. J. Med. Chem.* 2012;56: 139-44. [DOI: 10.1016/j.ejmech.2012.08.027]

Yang J, Gharagozloo P, Yao J, Ilyin VI, Carter RB, Nguyen P, Robledo S, Woodward RM, Hogenkamp DJ. 3-(4-Phenoxy phenyl)pyrazoles: A novel class of sodium channel blockers. *J. Med. Chem.* 2004;47(6):1547-52. [DOI: 10.1021/jm030498q]

Yogeeswari P, Sriram D, Saraswat V, Ragavendran JV, Mohan Kumar M, Murugesan S, Thirumurugan R, Stables JP. Synthesis and anticonvulsant and neurotoxicity evaluation of N4-phthalimido phenyl (thio) semi-carbazides. *Eur. J. Pharm. Sci.* 2003;20(3):341-6. [DOI: 10.1016/j.ejps.2003.08.002]

Zarghi A, Tabatabai SA, Faizi M, Ahadian A, Navabi P, Zanganeh V, Shafiee A. Synthesis and anticonvulsant activity of new 2-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles. *Bioorg. Med. Chem. Lett.* 2005;15(7):1863-5. [DOI: 10.1016/j.bmcl.2005.02.014]

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