ISSN 0976 – 3333

Available Online at www.ijpba.info.

International Journal of Pharmaceutical & Biological Archives 2010; 1(5): 404-415

REVIEW ARTICLE

An Updated Review: Emerging Anticonvulsants

Nadeem Siddiqui*[1], Md. Jawaid Akhtar, Ruhi Ali, Bishmillah Azad, Andalip

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard University, Hamdard Nagar, New Delhi 110062, India

Received 28 Oct 2010; Revised 21 Nov 2010; Accepted 30 Nov 2010

Abstract

Anticonvulsants are a diverse group of pharmaceuticals used in the treatment of epileptic seizures. The goal of an anticonvulsant is to suppress the rapid and excessive firing of neurons that start a seizure. The use of current antiepileptic drugs has been questioned due to the non selectivity of the drugs and the undesirable side effects posed by them.This lead to the search for antiepileptic compounds with more selective activity and lower toxicity continues to be an area of investigation in medicinal chemistry. This review describes various moieties representing anticonvulsant activity.

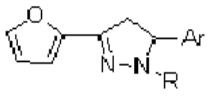
Keywords: Anticonvulsant, maximal electroshock, subcutaneous pentylene tetrazole induced seizure.

INTRODUCTION

Epilepsy, a ubiquitous disease characterized by recurrent seizure which results from a temporary electrical disturbance of the brain due to imbalance between excitatory and inhibitory neurotransmitters inflicts more than 60 million people worldwide. Nearly 95% of clinically available drugs for the treatment of epilepsy were approved before 1985 and they could provide seizure control for 60-70% of patient, but their use is often limited by adverse effects such as drowsiness, ataxia, gastrointestinal disturbance, hepatotoxicity and megaloblastic anaemia and even life threatening condition. Therefore, the need for more effective and less toxic antiepileptic drugs still exists .In the effort to get those agents, we have reported several heterocyclic compounds which have shown considerable anticonvulsant activities. Mainly two kinds of epilepsy have been identified, one with grandmal and other with petitmal. Anticonvulsant drugs with MES (maximal electroshock) activity are generally useful in grandmal, while ScMet (subcutaneous metrazole) antagonist are effective in petitmal.

Pyrazole

Ozdemir *et al* [1] synthesized twelve 1-phenyl, 1-thiocarbamoyl, and 1N-substituted thiocarbamoyl-3-(2-furyl)-5-phenyl)(2-furyl-2)-pyrazoline derivatives **(1)**. Anticonvulsant activity of the compounds were detected by maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (metrazol) (scMet) tests. Neurotoxicity was determined by rotarod toxicity test on albino mice. The compound with substituent in structure **(1)** was found to be protective against MES and ScMet.



(1)

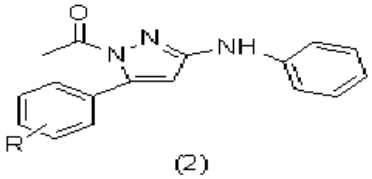
Ar=2-C_4H_4O,C_6H_5

R=C_6H_5,$CSNH_2$,$CSNHC_3H_5$,$CSNHCH_3$, $CSNHC_2H_5$,$CSNHC_3H_5$,$CSNHC_6H_5$

Singh *et al* [2] synthesized a series of 1-[(4,5-dihydro-5-phenyl-3-(phenylamino)pyrazole-1-yl)] ethanone derivatives **(2)** from chalcones of anilides and evaluated for their anticonvulsant activity against electric shock induced convulsion method in rat at a dose of 125 mg/kg and 250 mg/kg ip. All the compounds synthesized possess anticonvulsant activity. Chlorine substitution at the position-2 in compound 1-[(4,5-dihydro-5-(2-chloro)phenyl-3-(phenylamino)pyrazole-1-yl)]ethanone **(2a)** and position 2,4 in compound 1-[(4,5-dihydro-5-(2,4-

***Corresponding Author: Nadeem Siddiqui**, **Email:** nadeems_03@yahoo.co.in.

dichloro)phenyl-3-(phenylamino)pyrazol-1- yl)] ethanone **(2b)** have significant activity.

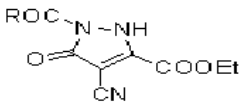


(2)

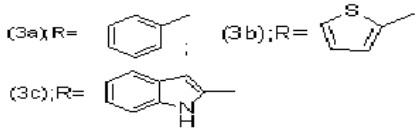
(2a); R=2-Cl

(2b); R=2,4-Cl_2

Abdel Aziz *et al* [3] synthesized a set of pyrazolone derivatives **(3)** and screened for their anticonvulsant activity. The compounds, ethyl-1-benzoyl-4-cyano-5-oxo-2,5-dihydro-1*H*-pyrazole-3-carboxylate **(3a),** ethyl-1-(thiophene-2-carbonyl)-4-cyano-5-oxo-2,5-dihydro-1*H*- pyrazole-3-carboxylate **(3b)** and ethyl-1-(1*H*-indole-2-carbonyl)-4-cyano-5-oxo-2,5-di hydro1-*H* pyrazole-3-carboxylate **(3c)** exhibited remarkable protective effect against clonic seizure induced by i.p injection of PTZ at a dose level of 20 mg/kg. Anticonvulsant activity found to be nearly close to phenobarbital sod. At a dose level of 30 mg/kg and more potent than phenytoin sod. at a dose level of 30 mg/kg.

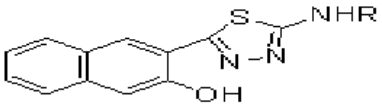


(3)



Thiadiazole

Dogan *et al* [4] synthesized a series of 2,5-disustituted- 1,3,4- thiadiazole **(4)**.These compounds afforded protection at a dose of 100 mg/kg against pentylenetetrazole- induced convulsion in mice. Compounds 2-ethylamino-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole **(4a)** and 2-(3-Fluorophenyl amino-5-(3-hydroxy-2-naphthyl)-1,3,4- thiadiazole **(4b)** showed maximum protection.

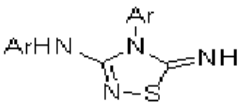


(4)

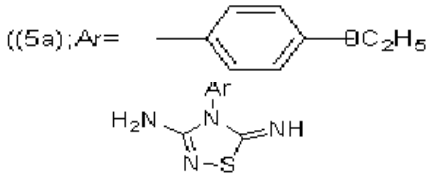
(4a); R= $-C_2H_5$

(4b); R= 3-FC_6H_4

Gupta *et al* [5] synthesized a series of 3-aryl amino/amino-4 aryl-5-imino-Δ^{2-} 1,2,4thiadiazoline derivative **(5,6)**. Synthesized compound was evaluated against MES and (ScPTZ) induced seizure model in mice. Compound **(5a)** was found to be active in ScPTZ test. Whereas all **6(a-i)** showed protection from MES seizure.



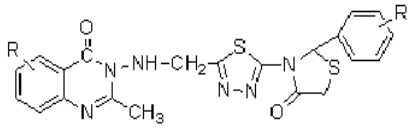
(5)



(6)

Ar-1 napthyl,4 ethoxy,4 fluorophenyl, 2' pyridyl,3' pyridyl,4'pyridyl,4 phenoxy methyl,4 bromophenyl,4 chlorophenyl

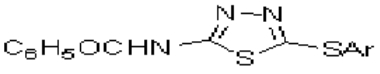
Archana *et al* [6] synthesized 3-({4-[2-(alkylphenyl)-4-oxo-1,3-thiazolidine-3-yl]-1,3,4-thiadiazol-2-yl} methylamino)-2-methyl-6-monosubstituted quina zoline-4(3*H*)-one **(7)**.Of all these compound synthesized, the most active was 3-({4-2(3-methoxy-p-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1,3,4 thiadiazol-2-yl}methylamino)-2-methyl-6-bromoquinazolin-4(3*H*)-one **(7a)**.



(7)

(7a); X= 6-Br, R= 3-OCH_3, 4-OH

Pattanayak *et al* [7] synthesized 2-amino-5-sulfonyl-1,3,4-thiadiazoles **(8)** derivatives by varying the substituents in the thiadiazole moiety. The newly synthesized compounds 4-(5-benzoylamine-[1,3,4-thiadiazole-2-yl-sulfanyl]-benzene sulfonyl chloride **(8a),** N-[5-(4-sulfamoyl- phenyl sulfanyl)-[1,3,4] thiadiazol-2-yl]-benzamide **(8b)** and N-[5-(4-fluoro-phenyl sulfanyl)-[1,3,4]thiadiazole-2-yl]-benzamide **(8c)** were found to possess significant anticonvulsant activity against both MES and PTZ animal model.



(8)

(8a); Ar= 4-$C_6H_4SO_2Cl$

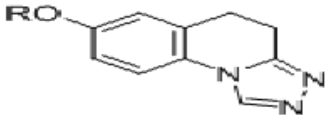
(8b); Ar= 4-$C_6H_4SO_2NH_2$

(8c); Ar= 4-C_6H_4F

Quinolines

Xie *et al* [8] synthesized a series of 7-alkoxy-4,5-dihydro-[1,2,4]triazole[4,3-a]quinoline derivatives **(9)** from 6-hydroxy-3,4-dihydro-1*H*-quinoline-2-one as starting material. Anticonvulsant activity was evaluated by (MES test) and subcutaneous (Sc) pentylenetetrazole test (ScMet test) and

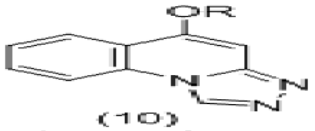
neurotoxicity test. MES and ScMet test shows that 7-(4-flourobenzyloxy)-4,5-dihydro-(1,2,4)triazolo [4,3-a]quinoline **(9a)** was found to be most potent.



(9)

(9a); R= $-CH_2C_6H_4(4\text{-}F)$

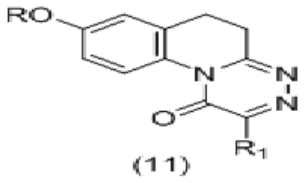
Guo *et al* [9] synthesized a series of 5-alkoxy-[1,2,4]triazolo[4,3-a]quinoline derivatives **(10)** using 4-hydroxyquinolin-2-[1*H*]-one as a starting material. Anticonvulsant activity was evaluated by MES and neurotoxicity by rotarod test. Compound 5-hexyloxy-[1,2,4]triazolo[4,3-a]quinoline **(10a)** was the most potent anticonvulsant and compound 5-benzyloxy-[1,2,4]triazolo[4,3a]quinoline **(10b)** exhibited little weaker activity than the first one in controlling seizure induced by MES test but possessed lower neurotoxicity.



(10)

(10a); R= $-C_6H_{13}$
(10b); R= $-CH_2Ph$

Sun *et al* [10] synthesized a series of 8-alkoxy-5,6-dihydro-(1,2,4)triazino[4,3-a]quinoline-1-one derivatives **(11)**. Anticonvulsant activity were evaluated by MES and neurotoxicities were evaluated by rotarod neurotoxicity test. Compound 8-heptyloxy-5,6-dihydro-[1,2,4]triazino[4,3a] quinoline-1-one **(11a)** was the most potent.

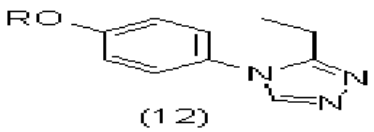


(11)

(11a); R= n-C_7H_{15}, R_1= H

Chen *et al* [11] synthesized a series of 4-(4-alkoxyphenyl)-3-ethyl-4*H*-1,2,4-triazole derivatives **(12)** as open chain analogues of 7-alkoxy-4,5-dihydro[1,2,4]triazolo[4,3a]quinolines.

Anticonvulsant activity was evaluated by MES and neurotoxicity by rotarod neurotoxicity test. Compound 3-ethyl-4-(4-heptyloxyphenyl)-4*H*-1,2,4-triazole **(12a)** found to be most potent. Whereas, 3-ethyl-4- (4-octyloxyphenyl)-4*H*-1,2,4-triazole (**12b**) exhibited better PI value which was much greater than prototype drug phenytoin.

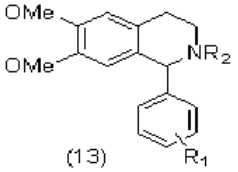


(12)

(12a); R= n - C_7H_{15}
(12b); R= n - C_8H_{17}

Isoquinoline

Gitto *et al* [12] synthesized a novel series of 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives **(13)** as potential AMPA (non-competitive) receptor antagonist. Some of the compounds showed high anticonvulsant activity against sound induced seizure in DBA/2 mice.

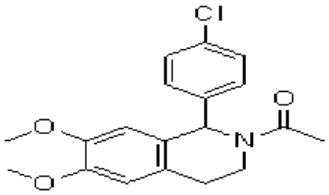


(13)

R_1= **4**-Cl, 4-Br, **4**-F, 3-NO_2, 4-NO_2, 3-NH_2, **4**-NH_2,3-Cl, 3-Br, 3-F, 2,3-F_2, 3,4-F_2, 2,3-Cl_2, 3,4-Cl_2, 3,5-Cl_2

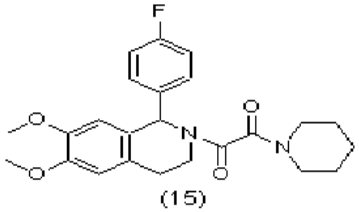
R_2= H, Ac

Gitto *et al* [13] identified (R, S)-2-acetyl-1-(4'-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro iso quinoline **(14)** as a potent non competitive AMPA receptor antagonist able to prevent epileptic seizures. The biological tests of single enantiomers revealed higher anticonvulsant and antagonistic effects, resides in (R)-enantiomer as also suggested by molecular modelling.



(14)

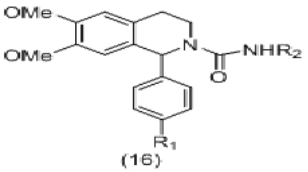
Gitto *et al* [14] synthesized new N-substituted isoquinolines based on ligand based approach which is identified as noncompetitive AMPA receptor antagonist. Compounds were screened against audiogenic seizure and some showed anticonvulsant properties. Compound 1-(4-fluorophenyl)-6,7-dimethoxy-2-[oxo(piperidine-1-yl)acetyl]-1,2,3,4-tetrahydroisoquinoline **(15)** most active of the series was also tested in-vitro using patch-clamp techniques and proved to antagonize AMPA mediated effects.



(15)

Gitto *et al* [15] planned a solution phase parallel synthesis of new N-substituted-3,4-dihydro isoquinoline-2[1*H*]-carboxamide exploring the introduction of different (cyclo) alkyl groups **(16)** at carboxamide moiety linked to N-2 atom of isoquinoline scaffold. Anticonvulsant effects were evaluated against audiogenic seizures in DBA/2 mice. Some new derivatives were more active than valproate, instead modification did not improve anticonvulsant efficacy with respect to their precursors.

Oxadiazole

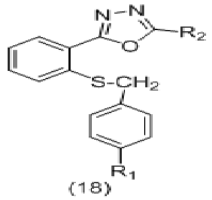


(16)

R_1= H,Cl,Br,F

R_2= $-C_2H_5$, n-C_3H_7, iso-C_3H_7, n-C_4H_9, t-C_4H_9, $-C_5H_9$, $-C_5H_{11}$, $-C_6H_{13}$

Gitto *et al* [16] synthesized a series of 1-aryl-6, 7-dimethoxy-3,4-dihydroisoquinoline-2-(1*H*) sulphonamides **(17)**. New compound incorporate Zarghi *et al* [17] synthesized a series of new 2-substituted-5-(2-benzylthiophenyl)-1,3,4-oxadiazole **(18)** and evaluated for anticonvulsant agent with the help of conformational analysis and superimposition of energy minima conformer of the designed molecules reveals that, it is well matched with main proposed benzodiazepine pharmacophores (estazolam, a known benzodiazepine agonist).Electroshock and PTZ induced lethal convulsion test showed that introduction of amino group in position 2 of 1,3,4-oxadiazole ring and fluoro substituent at para position of benzylthio moiety had the best anticonvulsant activity which seems to be mediated through benzodiazepine receptor mechanism.



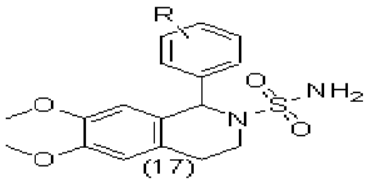
(18)

R_1= H, Cl, F

R_2= NH_2, SH, SMe, SEt, SBz

Almasirad *et al* [18] synthesized a series of new 2-substituted- 5-[2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazoles **(19)** and screened for anticonvulsant activity. Compound 2-amino-5-[2-(2-flouro phenoxy)phenyl]-1,3,4-oxadiazole **(19a)** shows considerable anticonvulsant activity in both PTZ and MES models which seems to be mediated by benzodiazepine receptors and other unknown mechanism.

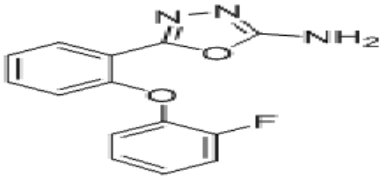
the main features of the anticonvulsant and sulfonamide function capable to inhibit the enzymes carbonic anhydrase which represent an attractive targets in epilepsy. Pharmacological effects were evaluated in vivo against audiogenic seizure in DBA/2 mice. Some of the new compound shows anticonvulsant properties better than topiramate. Among the compounds i.e. 1-(4`-chlorophenyl)-6, 7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-sulfonamide **(17a)** and 1-(4`-aminophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2-(1*H*)-sulfonamide **(17b)** proved to be most potent than topiramate against audiogenic seizure in DBA/2 in mice.



(17)

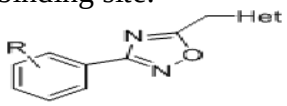
(17a); R=4-Cl

(17b); R=4-NH_2



(19a)

Lankau *et al* [19] prepared a series of 3- and 5-aryl-1,2,4-oxadiazole derivatives **(20)** and tested for anticonvulsant activity in variety of models. Compound 5-phenyl-3-[1,2,4]triazole-1-ylmethyl [1,2,4]oxadiazole **(20a)** was protective in the PTZ model and MES model in rat. It was found that several oxadiazole that acted as selective GABA potentiating compound with no interaction to the benzodiazepine binding site.

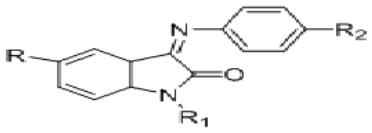


(20)

(20a); Het= 1-[1,2,4]triazolyl
R= H

Isatin

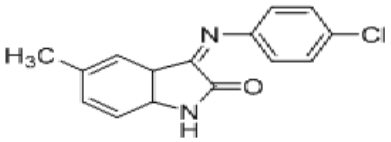
Verma *et al* [20] synthesized Schiff base of N-methyl and N-acetyl isatin derivatives with different aryl amines and screened for anticonvulsant activities against MES & subcutaneous metrazole (ScMet). N-methyl-5-bromo-3(4-chlorophenylimino)isatin **(21)** exhibited anticonvulsant activity in MES &Sc MET with LD50 >600 mg/kg showing better activity than the standard drug phenytoin, carbamazepine and valproic acid.



(21)

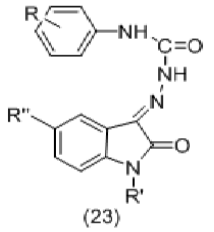
R= Br, R_1= CH_3, R_2= Cl

Sridhar *et al* [21] evaluated anticonvulsant activity of hydrazones, schiff and mannich base of isatin by MES and metrazol-induced convulsion (MET) at different dose level. Among the eight compounds 3-(4- chloro-phenylimino)-5-methyl-1,3-dihydro-indol-2-one **(22)** was found to be most potent compound of the series with 87% protection at 100 mg/kg and ED_{50} of 53.61mg/kg (MET). The entire active compound showed greater protection than sod.valproate.



(22)

Pandeya *et al* [22] synthesized a series of N-methyl/acetyl 5-(un)-substituted isatin semicarbazone **(23)** and screened for anticonvulsant and sedative-hypnotic activities. It was observed that compounds showed protection in all screens i.e MES, Sc PTZ and Sc STY. Compounds **(23a), (23b)** emerged as the most active compounds as indicated by the protection they exhibit in MES, Sc PTZ, and Sc STY screens.

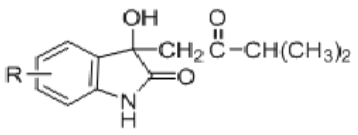


(23)

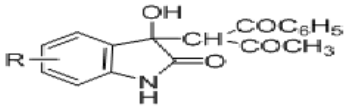
(23a) R= 4-Br, R'= -CH_3, R"= H-

(23b) R= 2-Cl, R'= -$COCH_3$, R"= H

Popp *et al* [23] synthesized a series of new 3-hydroxy-3-substituted oxindoles **(24), (25)** and screened for their anticonvulsant activity. A number of these 3-hydropxyoxindole had shown activity in maximal electroshock seizure test.

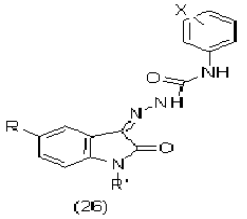


(24)



(25)

Smitha *et al* [24] synthesized a series of N-methyl/acetyl 5-(un)-substituted isatin-3-semicarbazole **(26)** and screened for their anticonvulsant activity. Anticonvulsant activities of the compounds were detected by maximal electroshock (MES), subcutaneous pentylenetetrazole (scPTZ) and subcutaneous strychnine (scSTY) screens. Among all the compounds 1-acetyl-1*H*-indole-2,3-dione3-[N-(4-chlorophenyl)semicarbazone] **(26a)**, 1-acetyl-1*H*-indole-2,3-dione3-[N-(4-nitrophenyl)semicarbazone] **(26b)**, 4-({[2-(1-acetyl-5-bromo-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazino]carbonyl} amino)benzenesulfonamide (**26c**) emerged as broad-spectrum compounds as indicated by their protection in MES, sc PTZ and sc STY screens.



(26)

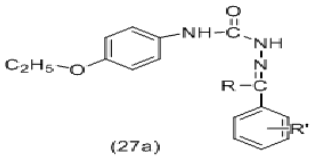
(26a); R=H, R'= -$COCH_3$, X= 4-Cl

(26b); R=H, R'= -$COCH_3$, X= 4-NH_2

(26c); R=5-Br, R'=-$COCH_3$, X=4-SO_2NH_2

Semicarbazone

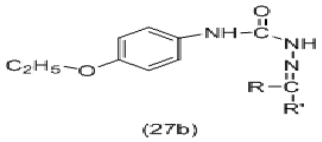
Yogeeswari *et al* [25] synthesized a series of 4-ethoxyphenyl semicarbazones (**27a**), **(27b)** and evaluated against MES and and ScPTZ induced seizure in mice. Among, the compound tested the compound with substituent shown above showed protection from seizure in both animal models.



(27a)

R= H, CH_3

R'= 2-Cl, 2-OH, 4-OH, 4-Cl



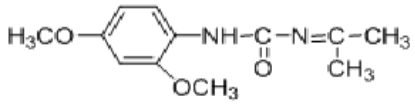
(27b)

R= - CH_3

R"= -CH_2COCH_3, -$CH_2CH(CH_3)_2$

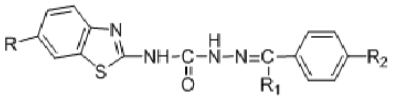
Thirumurugan *et al* [26] synthesized 2,4-dimethoxyphenylsemicarbazones starting from 2,4-dimethoxyaniline via phenylcarbamate. The anticonvulsant activity of the synthesized compound were evaluated by intraperitoneal administration in three seizure model which include MES, Sc PTZ and Sc strychnine induced seizure.

Mostly exhibit protection in all three seizure model in which N^1-(2,4-dimethoxyphenyl)-N^4-(propan-2-one)semicarbazone **(28)** found to be most active with no neurotoxicity. The compound was also found to elevate *y*-amino butyric acid (GABA) level in the mid brain and medulla oblongata region.



(28)

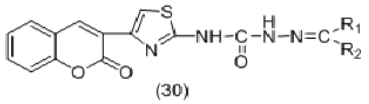
Siddiqui *et al* [27] synthesized a series of 1,3-benzothizole-2-yl-semicarbazones **(29)** and evaluated for their anticonvulsant, neurotoxicity and other toxicity studies. Majority of the compounds were active in MES screens.



(29)

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

Siddiqui *et al* [28] synthesized several heteroaryl semicarbazone by the reaction of heteroaryl hydrazine carboxamide with aryl aldehyde or ketone. Compound were tested for anticonvulsant activity utilising PTZ and MES and found that (1E)-1-arylalkane-1-one-N-[4-(2-oxo-2H-chromen-2-yl)-1,3-thiazol-2-yl]semicarbazone **(30)** exhibited significant anticonvulsant activity at 30 mg/kg dose level comparable to the standard drug taken as phenytoin.

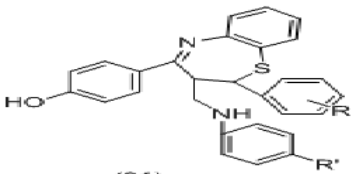


(30)

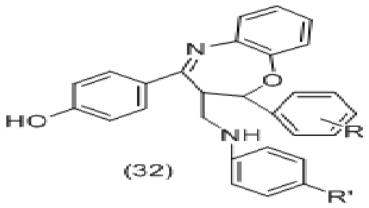
R_1= 3,4-ClC_6H_3, 2-$OCH_3C_6H_4$, 4-BrC_6H_4
R_2= -CH_3,

Benzoxazepine

Garg *et al* [29] synthesized a new series of 4-(4'-hydroxyphenyl)-2-(3-substitutedphenyl)-3-(4-substituted phenylamino-methylene)-2,3-dihydro-1,5-benzothiazepine **(31)** and 4-(4'-hydroxy phenyl)-2-(3-substitutedphenyl)-3-(4-substituted phenylaminomethylene)-2,3-dihydro-1,5-benzo xazepine **(32)** and evaluated for their anticonvulsant activity. Compound 4-(4'-hydroxyphenyl)-2-(2-chlorophenyl)-3-[(4-methoxy phenylaminomethylene)]-2,3-dihydro-1,5-benzo thizepine **(31a)** was found to be most potent of this series and was compared with reference drug phenytoin.

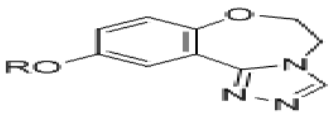


(31)
(31a); 2-Cl, 4-OCH_3



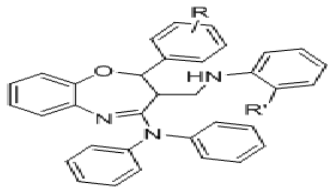
(32)

Deng *et al* [30] synthesized a series of 10-alkoxy -5,6-dihydro- triazolo [4,3-d] benzo(f)[1,4] oxazepine derivatives **(33)** and screened for their anticonvulsant activity by MES and their neurotoxicity by rotarod neurotoxicity test. In the MES test compound 10-Heptyloxy-5,6-dihydro-triazolo[4,3-d]benzo[f]1,4-oxazepine **(33a)** was found to possess better anticonvulsant activity and higher safety than marketed drug carbamazepine and phenytoin.



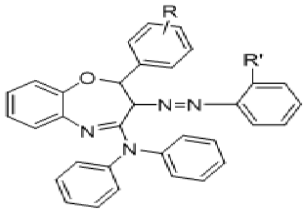
(33)
(33a); R= n-C_7H_{15}

Bajaj *et al* [31] synthesized a series of 2-substitutedphenyl-3-(substitutedphenylamino)methyl 2,3-dihydro-4-diphenylamino-1,5-benzoxazepine **(34)** and 2-substitutedphenyl-3-substitutedphenylazo-2,3-di hydro-4-diphenylamino-1,5-benzoxazepine**(35)** from 2-substitutedphenyl- 2,3-dihydro-4-diphenyl amino-1,5-benzoxazepine by mannich reaction and diazotization reaction. Compounds were screened for their anticonvulsant activity and acute toxicity studies.Compound 2-(3-methoxy-4-hydroxyphenyl) -3(2-methoxyphenylamino)methyl-2,3-dihydro-4-diphenylamino-1,5-benzoxazepine **(34a)** and 2-(3-methoxy-4-hydroxyphenyl)-3-(2-methoxy phenylazo) -2,3-dihydro-4-diphenyl amino-1,5-benzoxazepine **(35a)** were found to be most potent of the series and compared with lamotrigine, phenytoin sod. and sod.valproate.



(34)

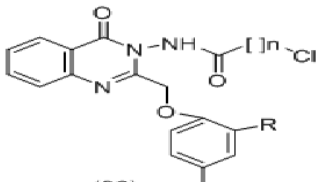
(34a),(35a) R=3-OCH_3,4-OH
R'=2-OCH_3



(35)

Quinazoline

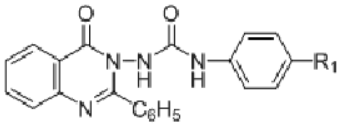
Georgey *et al* [32] synthesized number of 3-substituted-2-(substituted-phenoxymethyl) quinazolin-4 (3H) one derivatives **(36)**. Prepared compounds were evaluated for anticonvulsant activity and some of them exhibit moderate to significant activity compared to diazepam standard. Compound 3-chloro-N-2-((2,4-dichlorophenoxy methyl)-4-oxo-quinazolin-3(4*H*)-yl) propanamide **(36a)** was found to be most potent.



(36)

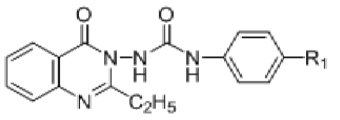
(36a); R, R_1= -Cl ; n= 2

Kashaw *et al* [33] synthesized new 1-(4-substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-4*H*-quinazolin-3-yl)-urea **(37), (38)** and screened for anticonvulsant activity by MES and ScPTZ induced seizure models and neurotoxicity by rotarod method. All of the compounds shown found to be active. All the compounds were found to exhibit potent CNS depressants activity.



(37)

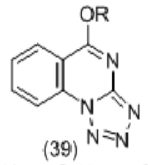
R_1= -Cl, -Br, $-NO_2$



(38)

R_1= H, $-NO_2$, CH_3, $-OC_2H_5$, $-OCH_3$

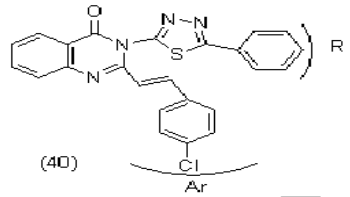
Wang *et al* [34] synthesized several derivatives of 5-alkoxy-tetrazolo[1,5-a]quinazoline **(39)** by reacting 2,4-dichloroquinazoline with various phenol or aliphatic alcohol and then with sodium azide. Anticonvulsant activity was evaluated against MES test. Most of the synthesized compound display weak anticonvulsant activity at a dose of 300 mg/kg.



(39)

R= iso-C_3H_7, n-C_5H_{11}, n-C_9H_{19}, $-C_6H_5$, $-C_6H_4$(4-OCH_3), $-C_6H_4$(3-CH_3), $-C_6H_4$(4-Cl)

Jatav *et al* [35] synthesized a new series of 3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4-(3*H*)-ones **(40)** and evaluated for anticonvulsant activities. The compounds were evaluated by MES and ScPTZ induced seizure models in mice. The three derivatives were shown to be active as anticonvulsant agents in one or more test models.

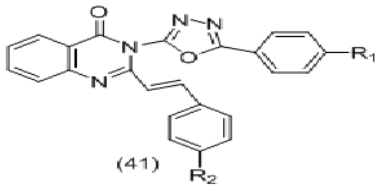


(40)

Ar= $-C_6H_4$(4-Cl), C_6H_4(4-Cl),

R= $-C_6H_5$, C_6H_4(3-Cl), C_6H_4(4-Cl)

Kashaw *et al* [36] synthesized few novel 3-[5-(4-substituted) phenyl-1,3,4-oxadiazole-2-yl]-2-styryl quinazoline-4-(3*H*)-ones **(41)** and evaluated for anticonvulsant activity. Synthesized compounds were examined in the maximal electroshock induced seizures (MES) and subcutaneous pentylene tetrazole (ScPTZ) induced seizure model in mice. Out of synthesized compounds **(41a)** and **(41b)** showed anticonvulsant activity at various doses in one or more test models.



(41)

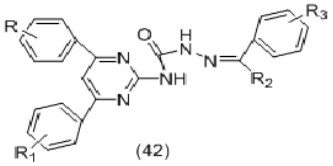
(41a); R_1= -Cl, R_2= $-CH_3$

(41b); R_1= $N(CH_3)_2$, R_2= -Cl

Pyrimidine

Alam *et al* [37] synthesized a number of N-(4,6-substituted diphenylpyrimidine -2-yl) semicar bazones **(42)** derivatives and tested for their anticonvulsant activity against two seizure models, MES and ScPTZ. All compounds possessed the four essential pharmacophoric element for good anticonvulsant activity. Most of the compounds shows good anticonvulsant activity. CompoundN^1-

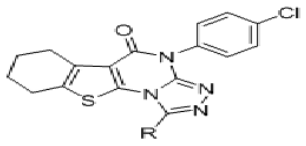
[4-(4-fluorophenyl)-6-(4-methylphenyl)pyrimidin-2-yl]-N^4-chloroacetophenone) semicarbazone **(42a)**, N^1-[4-(4-chlorophenyl)-6-(3,4-dimethoxy phenyl) pyrimidin-2-yl]-N^4-(4-nitrobenzaldehyde)-semi carbazone **(42b)** and N^1-[4-(4-chlorophenyl)-6-(4-methylphenyl)pyrimidin-2-yl]-N^4-(4-chloro aceto phenone) semicarbazone **(42c)** were found to be significantly active at lower dose of 30 mg/kg after 0.5 hr and also show the activity after 4hrs but at higher doses, thus show rapid onset and long duration of action. It was observed that the substitution at para position of hydrophobic domain by electron withdrawing groups and substitution at para position of distal aryl ring by electron releasing groups resulted in increased anticonvulsant activity. Substitution at the other aryl ring and the semicarbazone did not have any marked effect on activity.



(42)

(42a); R= 4-F, R_1= 4 -CH_3, R_2= -CH_3, R_3 = 4-Cl
(42b); R= 4-Cl, R_1= 3,4 -OCH_3, R_2= H, R_3 = 4-NO_2
(42c); R= 4-Cl, R_1= 4 -CH_3, R_2= -CH_3, R_3 = 4-Cl

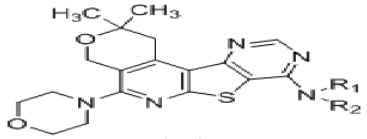
Gupta *et al* [38] synthesized a series of triazolo[4,3-a]tetrahydrobenzo(b)thieno[3,2-e]pyrimidine- 5(4 *H*)-ones **(43)**. These five derivatives exhibited good activity when tested for anticonvulsant activity in mice at different dose level.



(43)

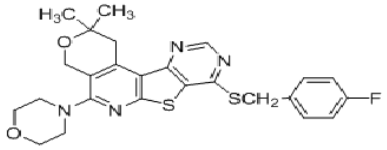
R; -CH_3, -C_2H_5, -C_3H_7, -NH_2, -SH

Paronikyan *et al* [39] synthesized a series of new derivatives of condensed thieno[3,2-d]pyrimidines and anticonvulsant activities of these synthesized compounds were studied. Several compounds **(44a), (44b)** and **(45)** had shown possessing specific anticonvulsant activity with respect to carbazole-induced convulsion.



(44)

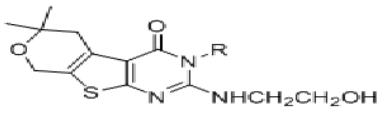
(44a); R_1,R_2= -CH_2CH_2OH
(44b); R_1=H, R_2= -$(CH_2)_5CH_3$



(45)

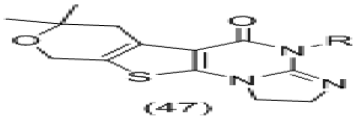
Oganisyan *et al* [40] synthesized 4-substituted 6,7-dihydro-7,7-dimethyl-5-oxo-9H-pyrano-[4'3';4,5]-thieno[3,2-e]imidazo-[1,2-a]pyrimidines.

Anticonvulsant activity of synthesized compounds were studied and found that **(46) ,(47a)** and **(47b)** exhibited weak anticonvulsant effects.



(46)

R= -C_6H_5

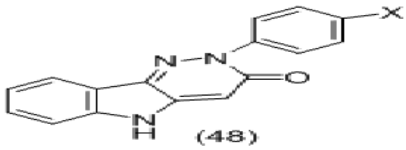


(47)

(47a); R= -C_6H_5
(47b); R= -$CH_2C_6H_5$

Indole

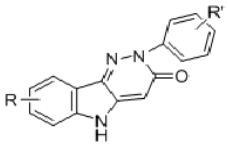
Campagna *et al* [41] synthesized a series of 2-aryl-2,5-dihydropyridazino[4,3-b]indol-3(3*H*)ones **(48)** and evaluated for their activity to prevent sound and pentylenetetrazole (PTZ) induced seizures in mice by inhibiting radioligand binding to benzodiazepine receptor BZR, and found that **(48a)** possess the best anticonvulsant activity.



(48)

(48a); X= -Br

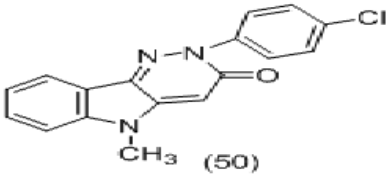
Palluoto *et al* [42]synthesized a large series of 2-aryl-2,5-dihydropyridazino [4,3-b] indol-3 (3*H*)-ones having properly selected substituents at the indole and N2-phenyl ring and tested for anticonvulsant agents as central benzodiazepine receptor(BZR) ligands. Compounds with substituents as shown in structure (**49a-f)** and **(50)** reduces the onset of clonic and tonic seizures, 45 min after i.p administration of derivatives. The latter N5-methylated congener, displayed highest anticonvulsant activity.



(49)

R = H

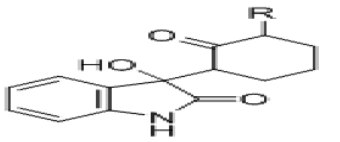
R'= p-Cl, m-Cl, p-Br, p-OCH_3, p-CH_3, p-NO_2



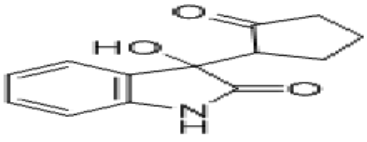
(50)

Raj *et al* [43] synthesized 3-cycloalkanone-3-hydroxy-2-oxindoles **(51), (52)** by highly enantioselective catalysis synthesis using primary-tertiary diamine-Bronsted acid catalyst in both

organic medium and aqueous medium. The products obtained are active in maximal electroshock seizure test (MES) and pentylene-tetrazol seizure threshold test (PTZ) and act as potential anticonvulsant.

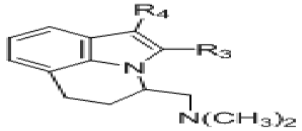


(51)
R: H, Me

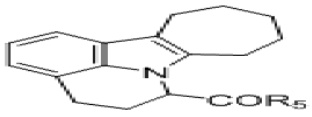


(52)

tanton *et al* [44] synthesized related series of cycloalkyl [4,5] Pyrrolo [3,2,1-ij] quinolines and tested for anticonvulsant activity. The products were tested in rat maximal electroshock for anticonvulsant activity. The compounds 6-[(dimethyl-amino)methyl]-4,5,6,8,9,10-hexahydro cyclopenta [4,5] pyrrolo [3,2,1-ij] quinolines **(53)** and N-methyl-4,5,6,8,9,10,11,12-octahydro cyclohepta [4,5] pyrrolo [3,2,1-ij] quinoline-6-carboxamide **(54)** showed good activity.



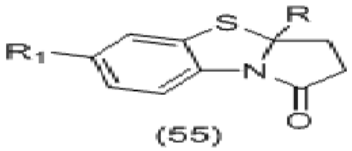
(53)
R_3, R_4: $-(CH_2)_3$



(54)
R^5 : $-N(CH_3)_2$

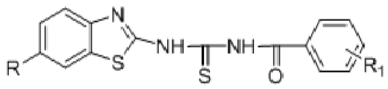
Benzothiazole

Trapani *et al* [45] synthesized tetrahydropyrrolo[2,1-b]benzothiazole-1-ones **(55)** and its analogues and tested for anticonvulsant activity. Some of the compounds were effective against bicuculline induced seizures in mice, which reduces ,at very high concentration ,the binding of [^{35}S]-tert-butylbicyclophosphorothionate ([^{35}S]TBPS) to recognition sites located at GABA-coupled chloride channel,but there is lack of co-relation between anticonvulsant activity of these compounds and their capability to displace [^{35}S] TBPS binding. The most active compounds was 3a-methyl 1,2,3,3a-tetrahydropyrrolo [2,1-b] benzothiazol-1-one **(55a)**.



(55)
(55a);R=CH_3,R_1=H

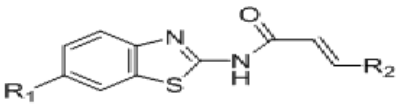
Rana *et al* [46] synthesized a series of 1,3-benzothiazol-2-yl-benzamide **(56)** and evaluated for their anticonvulsant activity. Majority of the compounds were active in MES and sc PTZ screen.



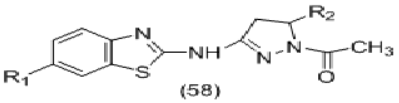
(56)

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

Amnerkar *et al* [47] synthesized a series of 6-substituted-[3-substituted-prop-2-eneamido]-benzo thiazole **(57)** and 6-substituted-2-[(1-acetyl-5-substituted)-2-pyrazoline-3-yl] amino benzothiazole **(58)** and evaluated experimentally against maximal electroshock test. The most active compound 6-methyl-2-[(1-acetyl-5-(4-chloro phenyl))-2-pyrazolin-3-yl]aminobenzthiazole **(58a)** exhibited an ED_{50} of 25.49 umol/kg, TD of 123.87umol/mg and high protective index 4.86 as compared to standard drug phenytoin.

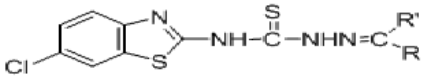


(57)



(58)
(58a); R_1= $-CH_3$, R_2= $4-ClC_6H_5$

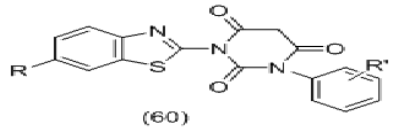
Yogeeswari *et al* [48] synthesized 6-chlorobenzthiazolyl-2-thiosemicarbazones **(59)** and screened for anticonvulsant activity. Most of the compounds showed anticonvulsant activity against both maximal electroshock seizures(MES) and subcutaneous pentylenetetrazole screens. Compound [4-(6-chlorobenzothiazol-2-yl)-1-(3-isatinimino)thiosemicarbazone] **(59a)** emerged as the most promising one.



(59)
(59a); CRR' = 3-isatinyl

Siddiqui *et al* [49] synthesized a series of 1-(6-substituted-1,3-benzothiazol-2-yl)-3-(substituted phenyl)hexahydro-2,4,6-pyrimidinetriones **(60)**, using substituted anilines as starting material. Synthesized compounds contain two active anticonvulsant pharmacophore, benzothiazole and barbituric acids and evaluated for their anticonvulsant activity. Compounds 1-(6-chloro-

1,3-benzothiazol-2-yl)-3-(2-methoxyphenyl) hexahydro-2,4,6-pyrimidinetrione **(60a)**, 1-(6-chloro-1,3-benzothiazol-2-yl)-3-(4-methoxyphenyl) hexahydro-2,4,6-pyrimidinetrione **(60b)** and 1-(4-methoxyphenyl)-3-(6-nitro-1,3-benzothiazol-2-yl)hexahydro-2,4,6-pyrimidine trione **(60c)** showed promising anticonvulsant activities in maximal electroshock seizure test(MES) and subcutaneous pentylenetetrazole test (sc PTZ).



(60)

(60a); R= -Cl, R'= 2-OCH_3
(60b); R= -Cl, R'= 4-OCH_3
(60c); R= -NO_2, R'= 4-OCH_3

Conclusion: The present study revealed that all mentioned heterocyclic moieties and their derivatives, under this review showed promising anticonvulsant activities. These compounds and their modification can be considered as lead molecule for further investigation and thus to control epileptic seizure in patients.

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