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Review Article

Anticonvulsant and Comparative Structure Activity Relationship of Pyridazine Derivatives with Currently Clinically Used Anticonvulsants

Mohammad Asif

Guru Ram Das (PG) Institute of Management and Technology, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Dehradun, 248009 India

***Corresponding Author:**
aasif321@gmail.com

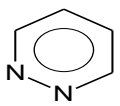
ABSTRACT

There has been considerable interest in the development of novel pyridazine and pyridazinone compounds with their anticonvulsant activity. Pyridazine and pyridazinones possessing a magic azometine –NH-N=CH- moiety. The pyridazinone also possessing cyclic amide moiety in their ring structures, constitute an important class of compounds for new drug development and the effect of a hydrophobic unit, hydrogen bonding domain and electron-donor group on the compound's anticonvulsant activity. Therefore, many researchers have synthesized these compounds as target structures and evaluated their different pharmacological activities. These observations have been guiding for the development of new pyridazinones that possess potent anticonvulsant activity with less toxic or side effects.

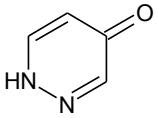
Keywords: Pyidazinone, pyridazine, anticonvulsant, pharmacological activity

INTRODUCTION

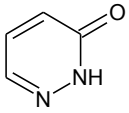
Pyridazine (**I**) is one of the three possible isomeric diazines (pyridazine, pyrimidine and pyrazine). The pyridazine (1,2-diazine) is a compounds formally derived from benzene by the replacement of two of the ring carbon atom by nitrogen atoms are present adjacent to each other. Appropriately substituted pyridazines exhibits tautomerism. This 3 & 4-hydroxylpyridazines (**II**) & (**III**) exist predominantly in the oxo form.



(I)

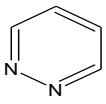


(II)

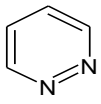


(III)

This ring system does not form a part of any natural product and thus has been less extensively investigated than other diazine. Pyridazine was obtained as early as 1886 by Fischer & was first synthesized by Tauber in 1895. Pyridazinones are the derivatives of pyridazine which belong to an important group of heterocyclic compounds containing two nitrogen atoms at 1 and 2 positions in a six member ring and carbonyl group at 3 positions are most commonly. Pyridazine is assumed to be a planer six membered ring & is represented as a resonance hybrid of two structure (**I-a**) & (**I-b**) with a greater contribution from the canonical structure. This is supported by the result of electron diffraction, microwave spectroscopy data & X-ray analysis, which all indicate that the N-N bond has single bond character[1,2].



(I- a)



(I-b)

Pyridazine and pyridazinones are mostly synthesized by heating the appropriate substituted hydrazines/hydrazides with substituted diketones or keto acids.

In recent years a substantial number of Pyridazines and pyridazinones that containing the different moiety or substituent have been demonstrated to possess, anti-inflammatory & analgesic[3,4], antipyretics[5], antiplatelet[6], anticancer[7], antidiabetic[8], antihypertensive[9-12], antidepressant & anxiolytic[13,14], anticonvulsant[15-28], antifungal, antibacterial, antitubercular[29-31], bronchial asthma & allergy[32] and other anticipated biological properties. In particular, a large number of pyridazinones are well known as intermediates for drugs and agrochemicals[33].

Epilepsy is one of the most common neurological disorders, affecting about 1% of the world's population and characterized by recurrent seizure attacks *i.e.* a group of syndromes that involve spontaneous, intermittent, abnormal electrical activity in the brain. The pharmacotherapy of epilepsy has been achieved during the last decade. Current clinically available drugs produce satisfactory seizure control in 60–70% of patients. Furthermore, the drugs available have shown significant side-effects, and many have narrow therapeutic indices and are difficult to formulate. For example, to exert its anticonvulsant therapeutic effect, the drug must reach its receptors in the central nervous system. Yet, many of the drugs exhibit physicochemical and protein-binding properties that would not permit crossing of the blood-brain barrier (BBB). Approximately 25% epilepsies are inadequately controlled by currently used medication[34-35].

To investigate the new anticonvulsant drug with more potent and less toxic effects, different pyridazines and pyridazinones were synthesized and evaluated for their anticonvulsant activity in different animal models of seizures, *viz.* maximal electroshock (MES), subcutaneous pentylenetetrazole (scPTZ), strychnine, picrotoxin, 3-mercaptopropionic acid (MP), bicuculline, and quinolinic acid-induced seizures models. The MES test and the scPTZ test are the most widely used animal models of epilepsy to characterize the anticonvulsant activity. Phenytoin, phenobarbitone, diazepam, ethosuximide, carbamazepine, and sodium valproate were used as standard antiepileptic drugs for biological screening[15-28].

A study of anticonvulsant agents also reveals that the presence of an amide moiety, cyclic or not, is present in most anticonvulsants[15]. Hence this feature of the ring system was tapped for the presence of any anticonvulsant activity. According to them, the most common structural elements of clinically active drugs against epilepsy appeared to be a nitrogen hetero atomic system[16]. Therefore, the need for more effective and less toxic antiepileptic drugs still exists as it has not been possible to control every kind of seizure with the currently available antiepileptic drugs.

General mechanisms of action of anticonvulsant agents

The mechanisms of action of anticonvulsant drugs fall into three major categories. Drugs effective against the most common forms of epileptic seizures, partial and secondarily generalized tonic-clonic seizures, appear to work by one of two mechanisms. One is to limit the sustained, repetitive firing of neurons, an effect mediated by promoting the inactivated state of voltage-activated Na^+ channels (Carbamazepine, lamotrigine, phenytoin, topiramate, valproic acid, zonisamide). A second mechanism appears to involve enhanced γ-aminobutyric acid (GABA)-mediated synaptic inhibition, an effect mediated either by a presynaptic or postsynaptic action (benzodiazepines and barbiturates). Drugs effective against absence seizure, a less common form of epileptic seizure, limit activation of a particular voltage-activated Ca^{2+} channel known as the T current (ethosuximide, valproic acid)[38-42].

Side effects of currently used anticonvulsant agents

The most common adverse effects of anticonvulsants are dizziness, vertigo, drowsiness, lethargy, somnolence, tremor, fatigue, ataxia, anorexia, weight loss, blurred vision, nausea, vomiting, rash and nervousness. Effects on the CNS include sedation, hypnosis (barbiturates, benzodiazepines, valporoic acid) and tremor. In some patients alopecia, and weight gain occurs due to valporoic acid therapy. Several effects on hepatic function, acute pancreatitis, hyperammonemia also produce teratogenic effects such as neural tube defects (carbamazepine, valporoic acid), parkinson like symptoms, photophobia, urticaria and other skin reactions, including Stevens-Johnson syndrome, as well as systemic lupus erythematosus, eosinophilia, leukopenia, thrombocytopenia, pancytopenia, and aplastic anemia (carbamazepine, ethosuximide). Behavioral disturbances, especially in children, these include aggression, hyperactivity, irritability, and difficulty in concentration. Both anorexia and hyperphagia have been reported. They also increase salivary and bronchial secretions. Cardiovascular and respiratory depression may occur (ethosuximide, benzodiazepine). Nystagmus and ataxia may occur at excessive dosage of barbiturates. A late complication of therapy is retention of water, with decreased osmolality and Na^+ ions in plasma, especially in elderly with cardiac diseases (carbamazepine). It can precipitate renal calculi, which is most likely due to inhibition of carbonic anhydrase (acetazolamide, zonisamide)[38-42].

Reported anticonvulsant activity of pyridazines and pyridazinones

In searching for effective anticonvulsant agents containing pyridazine moiety against different models of antiepileptic, mostly compounds showed significant effect to protect different types of seizures induced by different agents.

In order to explore the anticonvulsant activities of various 5-substituted benzylidene-6-methyl-4,5-dihydro pyridazine-3(2H)-one derivatives[15], 6-substituted pyridazinones (**IV**) or thiopyridazinones[16] (**V**), some 6-substituted aryl-4-substituted benzylidene-2,3,5-trihydropyridazinon-3-ones[23] (**VI**) and some 6-(3'-nitrophenyl)-4-substitutedbenzylidene-2,3,5-trihydropyridazinon-3-ones against maximal electroshock seizure test (MES) model (**VII, VIII**)[24].

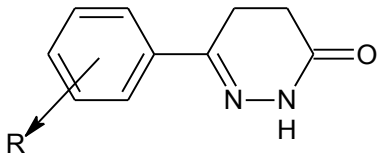


Fig. IV 6-substituted pyridazinones

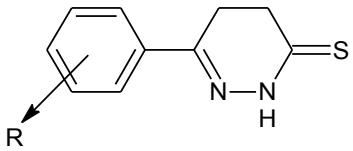


Fig. V 6-substituted thiopyridazinones

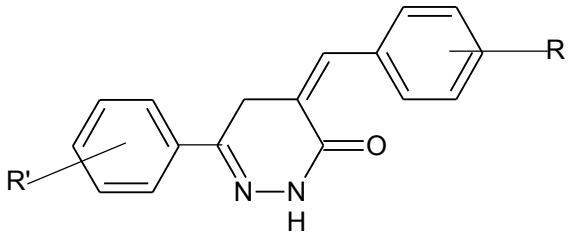


Fig. VI 6-substituted aryl-4-substituted benzylidene-2,3,5-trihydropyridazinon-3-ones.

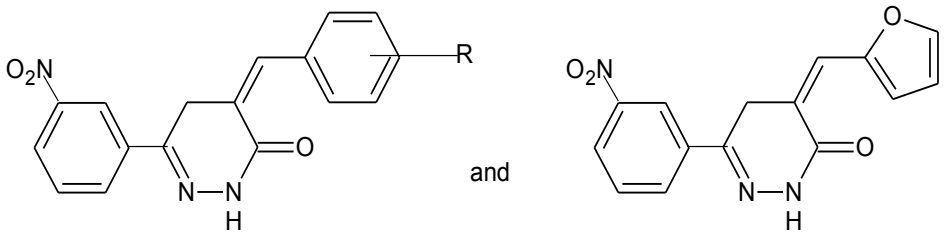


Fig. VII &VIII 6-(3'-nitrophenyl)-4-substituted benzylidene-2,3,5-trihydropyridazinon-3-ones.

In searching for effective anticonvulsant agent some5-benzylidene-6-methyl-4,5-dihydropyridazine- 3(2H)-one their ester, hydrazide and acetic acid derivatives were evaluated for anticonvulsant activities by PTZ seizure model[17]. The pharmacological evaluation of novel 1-substituted-1,2-dihydro-pyridazine-3,6-diones as potential anticonvulsant agents (**X**). The compound which have maximum protection against MES induced seizures were 1-[3-(2-aminophenylamino)-2-hydroxy propyl)-1,2-dihydro-pyridazine-3,6-dione, 2-hydroxy-3-piperazin1-yl-propyl)-1,2-di hydropyridazine -3,6-dione and 1-[2-hydroxy-3-imidazol-1-yl-propyl)-1,2-dihydro-pyridazine-3,6-dione. Whereas all these compounds failed to protect the animals from scPTZ (Metrozol) seizure threshold test[18]. Fourteen 6-(substituted-phenyl)-4,5-dihydro-3(2H) pyridazinones and fifteen 6-(substituted phenyl)-3(2H) pyridazinones have been evaluated in mice against maximal electroshock (MES) induced seizure. The ED50 values showed that 6-(2',4'-dichlorophenyl)-3(2H) pyridazinone was the most potent anticonvulsant in these compounds[19]. Analogues of 3-amino-7-(2,6-dichlorobenzyl)-6-methyltriazolo[4,3-b]pyridazine PC25 containing amide or carboxylic acid function. The compounds having the imidazole ring substituted with an amide group have been found to be generally more active against maximal electroshock-induced seizures. Furthermore, maximum activity was generally associated with a 2,6-dichlorobenzyl substitution pattern. 3-Amido-7-(2,6-dichlorobenzyl)-6-methyltriazolo[4,3-b]pyridazine was also protective in the PTZ-induced seizures test and blocked strychnine-induced seizures[20]. A series of 6-aryl-3-(hydroxypolymethylene amino) pyridazines derivatives were evaluated for anticonvulsant activity against MES and bicuculline-induced seizures; and neurotoxicity evaluated in the rotorod test[21].

Two amino-phenyl-pyridazine derivatives (**IX**), SR 41378 and CM 40907, have been reported to antagonize seizures with comparable potencies. Structurally, SR 41378 differs from CM 40907 by additional chlorine in position 6 of the phenyl ring. Anticonvulsant activities were compared with that of diazepam, pentobarbital, meprobamate and valproate[22]. The 3-aryl-5,6-dihydro-6-oxo-1(4H)-pyridazine acetic acid derivatives were prepared by alkylation of 6-aryl-4,5-dihydro-3(2H)-pyridazinones. A number of 3-aryl-5,6-dihydro-6-oxo-1(4H)-pyridazineacetic acid derivatives showed weak anticonvulsant activity, while nearly all displayed a sedative profile[25].

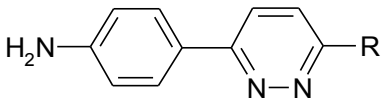


Fig. IX Amino-pyridazine derivatives.

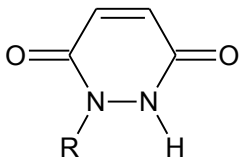


Fig. X Pyridazine-3, 6-dione derivatives

In recent years considerable emphasis has been placed on the hypothesis that enhancement of GABA transmission could be beneficial in some types of epilepsy. The alpha-(aryl)-4-morpholineacetonitrile obtained by the interaction of aryl aldehydes, morpholine and potassium cyanide, have been used to synthesize 3-(aroyl)-propionic acids and esters by 1,4-additions to acrylonitrile or acrylic ester. 3-(Aroyl) propionic acids reacting

with hydrazine can yield 6-aryl-4,5-dihydro-3(2H) pyridazinones which are dehydrogenated by bromine (via bromination dehydrobromination) to give 6-aryl-3(2H) pyridazinones. The latter compounds were converted into 3-(N-GABA)-6-(substituted phenyl) pyridazines and 3-(N-butyryllactamyl)-6-(substituted phenyl) pyridazines by the chlorination (by means of phosphorus oxychloride) and then reaction with GABA. Seventeen 3-GABA derivatives of 6-(substituted-phenyl) pyridazines were synthesized. The anticonvulsant activities (MES) of these compounds were also tested. 3-(N-GABA)-6-(2',4'-dichloro) phenylpyridazine; potent anticonvulsant (ED50 = 21.05 mg/kg)[26].

Novel *N*-(3-oxobutyl)-hydroxy- and acetoxypyrido[2,3-*d*]pyridazinones were synthesized and tested *in vivo* for their sedative and anticonvulsant activity. The *Michael*-type reaction of quinolinic acid hydrazide and methyl vinyl ketone afforded a mixture of two isomers, 5-hydroxy-*N* 7.(3-oxobutyl)-pyrido[2,3-*d*]pyridazin-8(7*H*)-one and 8-hydroxy-*N* 6-(3-oxobutyl)-pyrido[2,3,-*d*]pyridazin-5-(6*H*)-one, in a ratio of 2:1 which were separated by crystallization. Subsequent acetylation of both isomers yielded the corresponding 5- and 8-acetoxy compounds. Preliminary pharmacological tests showed low acute toxicity with a LD_{50} > 1000 mg/kg in the mouse and sedative activity for the title compounds. 5-Acetoxy-N^7-(3-oxobutyl)-pyrido[2,3-*d*]pyridazin-8(7*H*)-one displayed a borderline anticonvulsant activity in the metrazole test model[27].

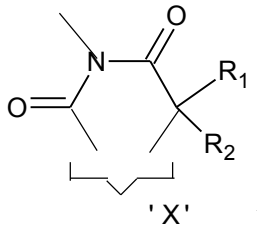
A series of 6-Alkoxy-[1,2,4]triazolo[4,3-*b*]pyridazine derivatives (**XI**) were synthesized for their anticonvulsant activities against maximal electroshock test and their neurotoxicity was evaluated by the rotarod neurotoxicity test. In initial screening, compound 6-(2,4-Dichlorophenoxy)-[1,2,4]triazolo[4,3-b]pyridazine (**IIr)** was among the most active agents, exhibiting in the same time the lowest toxicity. In the anti-MES test, it showed median effective dose (ED_{50}) of 17.3 mg/kg and median toxicity dose (TD_{50}) of 380.3 mg/kg, and the protective index (PI) of 22.0, which is much better than PI of the reference drugs. In a subsequent test, compound **IIr** had median hypnotic dose (HD_{50}) of 746.6 mg/kg, thus demonstrating much better margin of safety compared to reference drugs. Compound **2r** also showed oral activity against MES-induced seizures and lower oral neurotoxicity[28].

Fig. XI General structure of 6-alkoxy-[1,2,4]triazolo[4,3-b]pyridazine (**IIa**–**r**)

R = Butyl **(**IIa**)**, Pentyl **(**IIb**)**, 6-Hexyl (IIc), Heptyl (IId), Octyl (IIe), Nonyl (IIf), Decyl (IIg) Ar = 2-Tolyl (IIh), Tolyl IIi), 4-Tolyl, 2-Methoxyphenyl (IIk), 4-Methoxyphenyl (IIl), 2-Chlorophenyl (2m), 3-Chlorophenyl (IIn), 4-Fluorophenyl (IIo), 4-Chlorophenyl (IIp) 4-bromophenyl (IIq), 2,4-Dichlorophenyl (**IIr**).

Fig. XII Flunitrazepam and alprazolam.

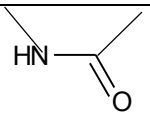
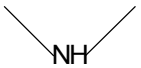
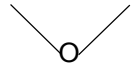
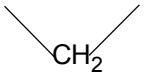
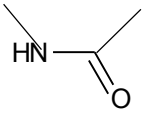
Structure Activity Relationship of currently used anticonvulsants



Ureide moiety

Fig. XIII General structure of anticonvulsant drugs with ureide moiety

Table 1 Structure activity relationship and structural features of anticonvulsant drugs

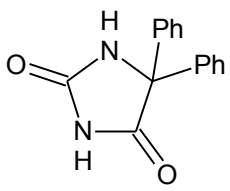
Group of compound	'X'	Amide group containing anticonvulsant	N hetero atom present in the ring
Barbiturates		Phenacetamide	Benzodiazepines
Hydantoins		Carbamazepine	Lomatrigine
Oxazolidinediones		Levetiracetam	Sultiame
Succinimide		Felbamate	Zonisamide
Primidone		Acetazolamide	

In currently clinically used mostly anticonvulsant agents possess cyclic amide or acyclic amide or hetero atom present in the ring (in mostly compounds N hetero atom, it numbered may be 1 or 2 or 3, few compounds also contain S and O hetero atom). For example tiagabine (S), Sultiame (S, N), acetazolamide (S, N), topiramate (O), zonisamide (O, N), trimethadione (O, N), some compounds do not containing any hetero atom like (phenacetamide, carbamazepine, gabapentin, felbamate, valporoic acid) and some compounds without amide groups (gabapentin, valporoic acid).

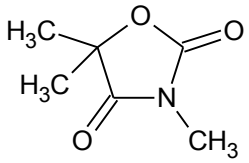
An overall pattern in the foregoing is that R & R' should both be hydrocarbon radicals. If both R & R' are lower alkyl, the tendency is to be active against absence seizures (petit mal) or partial seizures. If one of the hydrocarbon substituent is an aryl group, activity tends to derive toward generalized tonic clonic and partial seizure & no anti absence activity. A conformational analysis of the aryl containing anti generalized tonic clonic agents indicate that the conformational arrangement of the hydrophobic group is important[41,42].

Substituted heterocyclic/substituted aryl group at the 5-position of the barbituric or thiobarbituric acids nucleus remarkably increases the antiepileptic activity. Maximal antiseizure activity is obtained when one substituent at carbon 5 position is a phenyl group. Alkyl substituents in position 5 contribute to sedation, a property absent in phenytoin. The 5,5-diphenyl derivative has less antiseizure potency than does phenobarbital, but it is virtually devoid of hypnotic activity. By contrast, 5,5-dibenzyl barbituric acid causes convulsions. The Methsuximide has phenyl substituents and is more active against maximal electroshock seizures. Ethosuximide, with alkyl

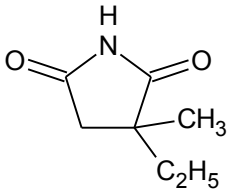
substituents, is the most active of the succinimides against seizures induced by PTZ and is the most selective for absence seizures. However, in Valporic acid, increasing the number of carbon atoms to nine introduces marked sedative properties. Straight-chain acids have little or no activity[38-42].



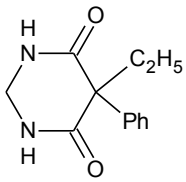
Phenytoin



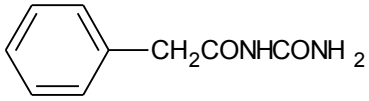
Trimethadione



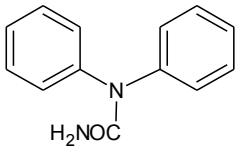
Ethosuccimide



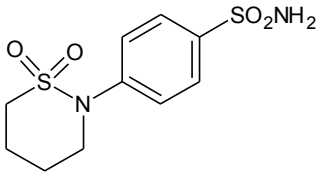
Primidone



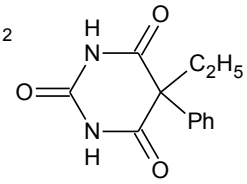
Phenacetamide



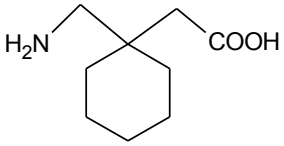
Carbamazepine



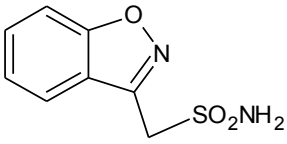
Sultiame



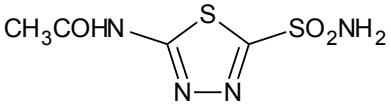
Phenobarbiturate



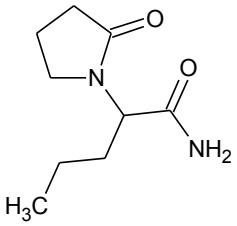
Gabapentin



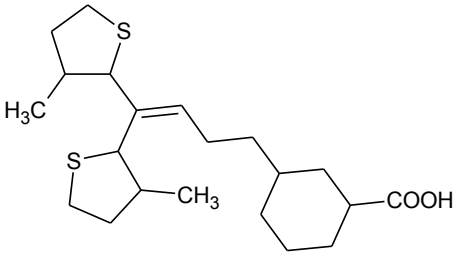
Zonisamide



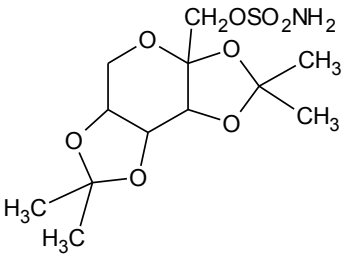
Acetazolamide



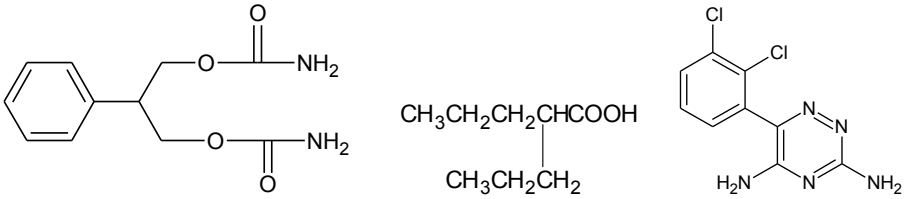
Levetiracetam



Tiagabine



Topiramate



Felbamate Valporic acid Lomatrigine

Fig. XIV Structures of clinically used anticonvulsants.

SAR study of reported pyridazine and pyridazinones

Many investigations indicated that the presence of at least one aryl group, one or two electron donor atoms and/or an NH group in a special spatial arrangement is necessary for anticonvulsant activity. The pyridazinone ring system agrees with this salient feature and many papers have reported anticonvulsant activities of pyridazine derivatives. In order to explore the activity associated with the structural moiety =N-NH-CO-CH- or presence of an amide moiety, cyclic or not, is present in most anticonvulsants. The most common structural elements of clinically active drugs against epilepsy appeared to be a nitrogen hetero atomic system[15-16].

The biological results revealed that in general, a number of aryl pyridazinones possessed greater protection in the MES screen. It has been proposed that for activity in the MES test, a compound should have a large hydrophobic group in the close proximity to at least two electron donor atoms. The pyridazinones containing a hydrophobic moiety (aryl ring) as well as two electron donor atoms in the ring have been shown to possess activity in MES as well as scPTZ screen.This study reported that higher is the hydrophobic parameter pi of the substituent on phenyl ring, more potent anticonvulsant is the compound and also, only the compounds with an electron withdrawing substituent on the phenyl ring exhibited appreciable anticonvulsant activity[19, 20, 36].

A series of 6-aryl-3-(hydroxypoly methylene amino) pyridazines derivatives, the compounds with a phenyl ring in the 6-position of the pyridazine ring exhibited appreciable anticonvulsant activity. Furthermore, a 4-hydroxypiperidine side chain in the 3-position of the pyridazine ring appeared essential for anticonvulsant activity. Substituting the hydrogen (from –NH in pyridazine nucleus) with methyl and acetyl group enhanced the lipophilicity of the compounds. Lipophilic drugs must pass through BBB and reach to its receptors in the central nervous system (CNS)[34].

DISCUSSION

Pyridazine and pyridazinones have documented consistent advances in the design of novel anticonvulsant agents, through the reported literature. Therapy is symptomatic with the available antiseizure drugs. Compliance with medicine is a major problem because of the long-term therapy together with unwanted effects of many drugs. Unfortunately, the drugs used currently not only fail to control seizure activity in some patients, but also they frequently cause unwanted effects that rang in severity from minimal impairment of CNS to death from aplastic anemia or hepatic failure. A wide variety of agents have the capacity to depress the function of the central nervous system[34-36].

To exert its anticonvulsant therapeutic effect, the drug must reach its receptors in the central nervous system (CNS). Yet, many of the drugs exhibit physicochemical and protein-binding properties that would not permit crossing of the blood-brain barrier (BBB) like phenytoin. However, its low solubility in water, both as free acid and sodium salt, makes its administration to patients difficult and seldom satisfactory [34].

The classic prodrug approach to improve membrane permeability of drug molecules employs lipophilic derivatives to increase passive membrane penetration. In recent years, different nutrient transporters (oligopeptides, amino acids, and glucose) have been identified and cloned. The active nutrient transport systems have become a target for prodrug design for the attempted to demonstrate the feasibility of utilizing natural amino acids and benzhydrols as a promoiety that can transport a compound across the BBB[34].

According to previous literature, in pyridazine compounds should have a large hydrophobic moiety (aryl or substituted aryl ring) in the close proximity to at least one electron donor atom have been shown to possess anticonvulsant activity. Substituting the hydrogen (from –NH in pyridazine nucleus) with methyl and acetyl group enhanced the lipophilicity of the compounds[36].

The results of the investigations indicate that from our earlier studies the three essential structural features to interact at the binding site for exhibited appreciable anticonvulsant activity are

- The compounds with an electron withdrawing substituent on the phenyl ring.
- One or two electron donor atoms and/or an NH group in a special spatial arrangement are necessary.
- A lipophilic moeity (4-bromophenyl, 4-chlorophenyl or 4-nitrophenyl).
- A hydrogen bonding domain (amide function -NH-CO-NH-)

We conclude that further structural modifications of these molecules might lead to the discovery of more potent anticonvulsant agents with still lower neurotoxicity. The classic prodrug approach to improve membrane permeability of drug molecules employs lipophilic derivatives to increase passive membrane penetration. The previous results indicate that the amino acids (especially phenylalanine and alanine) and benzhydrol linked with phenytoin are increases the anticonvulsant activity of phenytoin and decrease neurotoxicity[35]. In recent years, different nutrient transporters have been used for to become a target for prodrug design. Although many treatments are available, much more effort is being developed to novel approaches. The ideal antiseizure drug would suppress all seizures without causing any unwanted effects.

Therapeutic Aspects

The ideal antiseizure drug would suppress all seizures without causing any undesirable effects. Unfortunately, the drugs used currently not only fail to control seizure activity in some patients, but frequently cause undesirable effects. To minimize toxicity, treatment with a single drug is preferred. If seizures are not controlled with the initial agent, substitution of a second drug is preferred to the concurrent administration of another agent. However, multiple-drug therapy may be required, especially when two or more types of seizure occur in the same patient. The classic prodrug approach to improve membrane permeability of drug molecules employs lipophilic derivatives to increase passive membrane penetration. In recent years, different nutrient transporters (i.e. oligopeptide, amino acid, and glucose transporters) have been identified and cloned. The active nutrient transport systems have become a target for prodrug design[34-37].

Choice of drugs for the therapy of the convulsion

To minimize dose-related adverse effects, therapy with many drugs is initiated at reduced dosage. Dosage is increased at appropriate intervals, as required for control of seizures or as limited by toxicity. If compliance has been confirmed yet seizures persist, another drug should be substituted. Unless serious adverse effects of the drug dictate otherwise, dosage always should be reduced gradually when a drug is being discontinued to minimize risk of seizure recurrence. In the event that therapy with a second single drug also is inadequate, many physicians resort to treatment with two drugs simultaneously. This decision should not be taken lightly, because most patients obtain optimal seizure control with fewest unwanted effects when taking a single drug. Nonetheless, some patients will not be controlled adequately without the simultaneous use of two or more

antiseizure agents. It seems wise to select two drugs that act by distinct mechanisms (*e.g.,* one that promotes Na^+ channel inactivation and another that enhances GABA-mediated synaptic inhibition). During the therapy careful consideration of the unwanted effects of each drug and the potential drug interactions[39-42].

CONCLUSION

The ideal antiseizure drug would suppress all seizures without causing any unwanted effects. The results of the investigations indicate that from our earlier studies the three essential structural features to interact at the binding site are a lipophilic moiety (aryl), hydrogen bonding domain (amide) and an electron withdrawing substituent on the phenyl ring, should have a large hydrophobic group in the close proximity to electron donor atom(s) exhibited appreciable anticonvulsant activity.

Although many treatments are available, much more effort is being developed to novel approaches. The ideal antiseizure drug would suppress all seizures without causing any unwanted effects [36]. We conclude that further structural modifications of these molecules might lead to the discovery of more potent anticonvulsant agents with still lower neurotoxicity[35].

Due to hydrophobic nature of substituted electron withdrawing group in phenyl moiety of pyridazines are more active, further introduction of alkyl group at NH group of pyridazines has also increased the lipophilicity of the compound, which will enhance the absorption of the molecule. The acetyl group can also be easily hydrolysed to give a free N-H containing compound necessary for hydrogen bonding which may be responsible for the bioactivity, In conclusion compound could be the lead compounds for further beneficial modification in the design of pyridazinones as anticonvulsants. The classic prodrug approach to improve membrane permeability of drug molecules employs lipophilic derivatives to increase passive membrane penetration[34].

In this study, we have attempted to demonstrate the anticonvulsant activity, structure activity relationship, reduce toxicity, prodrug formation by feasibility of utilizing natural amino acids and benzhydrols as a promoiety that can transport a model compound across the BBB[34]. Overall, there has been progress in recent year in the introduction of anti seizure drugs. Most of the progress has been involved voltage gated sodium channel blocking drugs. Furthermore, although for the last thirty years new antiepileptic drugs have been introduced into clinical practice.

REFERENCES

1. Katritzky A R Chairman of the editorial board, Charles WR, FRS Co chairman of the EB, FRS, Comprehensive heterocyclic chemistry: The structure, reaction synthesis & use of heterocyclic compounds, 1984, Vol-3 pergamon press, UK p-2.
2. Matyus P and Czako, K. Trend in heterocyclic chemistry. 1993 P-3, 249.
3. GökçeM, Colak MS, Küpeli E, Sahin MF. *Arzneimittelforschung*, 2009; 59(7):357-63.
4. Dogruer, DS, Sahin MF, Kupeli E, Yesilada E. *Turk. J. Chem.* 2003; 27: 727-738.
5. Sato M. *Nippon Yakurigaku Zasshi*, 1979; 75(7):695-706.
6. Cherng SC, Huang WH, Shiau CY, Lee AR, Chou TC. *Eur J Pharmacol.* 2006; 532(1-2):32-37.
7. Malinka W, Redzicka A, Lozach O. *Il Farmaco,* 2004; 59: 457-462.
8. Rathish IG, Javed K, Bano S, Ahmad S, Alam MS, Pillai KK. *Eur J Med Chem*, 2009; 44(6):2673-8.
9. Ranju B, Dinesh K, Rosalia C, Carmen DLC, Dharam PJ. *Acta Pharm,* 2008; 58: 393–405.
10. Kumar D, Carron R, La Calle CD, Jindal DP, Bansal R. *Acta Pharm,* 2008; 58(4):393-405.
11. Wang T, Dong Y, Wang LC, Xiang BR, Chen Z, Qu LB. *Arzneimittelforschung*, 2008; 58(11):569-73.
12. Bansal R, Kumar D, Carron R, de la Calle C. *Eur J Med Chem*, 2009; 44(11):4441-7.

13. Laura K, Wing HA, Behanna LJ, Van ED, Martin W, and Hantamalala, RR. *Current Alzheimer Research*, 2006; 3: 205-214.
14. Griebel G, Perrault G, Tan S, Schoemaker H, Sanger DJ. *Behav Pharmacol*, 1999; 10(5):483-95.
15. Rubat C, Coudert P, Albuisson E, Bastide J, Couquelet J, Tronche P. *Journal of Pharmaceutical Sciences,* 1992; 81:1084-1087.
16. Pooja SB, Sharma PK, Rajesh KN. *International Journal of Chem Tech Research*, 2009; 1(3):522-525.
17. Oya Ü, Ayla B, Cenk A, Berna TM, Zafer G. *FABAD J. Pharm. Sci*, 2004; 29:185-194.
18. Sivakumar R, Anbalagan N, Gunasekaran V, Leonard JT. *Biol Pharm Bull*. 2003; 26(10):1407-11.
19. Xu P, Wang SY, Chenb Y, Liu WQ, Tao C. *Yao Xue Xue Bao,* 1991a; 26(9):656-60.
20. Moreau S, Coudert P, Rubat C, Vallee-Goyet D, Gardette D, Gramain JC, Couquelet J. *Bioorg Med Chem Lett*, 1998; 6(7):983-91.
21. Hallot A, Brodin R, Merlier J, Brochard J, Chambon JP, Biziere K. *J Med Chem*, 1986; 29(3):369-75.
22. Perio A, Chambon JP, Calassi R, Heaulme M, Biziere K. *J Pharmacol Exp Ther*, 1986; 239(2):542-7.
23. Siddiqui AA, Islam M, Asif M, Asthana C. *Journal of Ultra fine chem*. 2007; 3(2): 23
24. Deniz SD, Tijen O, Semiha O, Selda O, M Fethi S. *Turk J Chem*, 2008; 32:469 - 479.
25. Mojahidul I, Anees AS, Ramadoss R, Afroz B, Sunil G. *Acta Poloniae Pharmaceutica*, 2008; 65 (3): 353-362.
26. Mojahidul I, Anees AS, Ramadoss R. *Acta Poloniae Pharmaceutica*, 2008; 65 (3): 353-362.
27. Nagai H, Suda H, Iwama T, Daikoku M, Yanagihara Y, Koda A. *Int Arch Allergy Immunol*, 1992; 98(1):57-63.
28. Cao S, Qian X, Song G, Chai B, Jiang Z. *J Agric Food Chem*, 2003; 51:152-155.
29. Meenakshi D, Pravin S, Ashok B, Kapil J, Rahul D, Pramod S. *Turk J Chem,* 2009; 33:1-7.
30. Mahendra RS, Mangesh G, Kailash GB, Shashikant VB, Ana N, Kalyan CA, Nisheeth CD, Prashant J B. *ARKIVOC,* 2007; 14: 58-74.
31. Maryam S, Marya BM, Sharifzadeh M, Abbas S. *Iranian Journal of Pharmaceutical Research*, 2005; 1:33-36.
32. Sivakumar S, Surendra NP, James PS, Suthakar G. *Sci Pharm*, 2008; 76: 621–636
33. Pyridazine and phthalazine derivatives, process of their preparation and their use as anticonvulsants. *European Patent Application,* EP0975605.
34. Siddiqui AA, Abdullah MM, Arora M, Islam M, Ahmad SR. *Indian drugs*, 2006; 43 (10): 790-794.
35. Kane JM, Huber EW, Miller FP, Kehne JH. *Pharmazie*, 1992; 47(4):249-51.
36. Li-Ping G, Xin S, Xian-Qing D, Ying-Chun Q and Zhe-Shan Q. *European Journal of Medicinal Chemistry*, 2010, Article in Press, Corrected Proof - Note to users.
37. Edith G, Ales K, Winfried W and Marija K. *Monatshefte für Chemie, 2002;* 133 (9): 1177-1185.
38. Xu P, Wang SY, Liu WQ. *Yao Xue Xue Bao*, 1991b;26(9):650-5
39. Goodman & Gilman's, The pharmacological basis of therapeutics-11th ed. 2006; Chapter 19. Pharmacotherapy of the epilepsies - *James O. Mcnamara*
40. Rang and Dale's Pharmacology. 5th Ed. Section 4, chapter 39, page 550-559.
41. Katzung pharmacology, 9th edition. Section V. Drugs that act in the central nervous system chapter 24. Antiseizure drugs.
42. Foye's principal of medicinal chemistry, 6th ed. Thomas L lemke, David A William, Victoria F Rochey, S Willium Zito. Lippin Cott William and Wilkin published by Wolter Kluwer (India) Pvt Ltd, new Delhi. Page 521- 540.
43. Wilson & Gisvold's, Text book of Organic medicinal and pharmaceutical chemistry, 11th ed. Lippin Cott William and Wilkin. Page 503-508.