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Novel Fused quinazolinones: Further studies on the anticonvulsant activity of 1,2,9,11 tetrasubstituted-7*H*-thieno[2',3':4,5]pyrimido[6,1-b]-quinazolin-7-one and 1,3,10,12-tetrasubstituted-8*H*-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one

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Abstract:

Background: Epilepsy is one of the most common neurological disorders, affecting about 1% of the world's population. The currently available anticonvulsants are effective in reducing the severity and number of seizures in less than 70% of patients. Moreover, their usage is associated with undesirable side effects ranging from cosmetic (gingival hyperplasia) to life threatening (hepatotoxicity, megaloblastic anemia). Therefore, the continued search for the safer and more effective antiepileptic drugs is urgently necessary. Literature survey reveals that various derivatives of quinazolinone, thienopyrimidine and pyridopyrimidine shown very promising anticonvulsant activity along with other pharmacological activities. So we concentrate our aim to screen novel quinazolinone fused with thienopyrimidine/pyridopyrimidine.

Result: A novel series of 1,2,9,11-tetrasubstituted-7*H*-thieno[2',3':4,5]pyrimido[6,1-b]-quinazolin-7-ones (**1–15**) and 1,3,10,12-tetrasubstituted-8*H*-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-ones (**16-36**) were synthesized by reported method. The anticonvulsant activity of all the new compounds (**1-15** and **16-36**) was evaluated against Maximum Electroshock (MES) induced seizures and against subcutaneous pentylenetetrazole (scPTZ) induced seizures model in mice. The neurotoxicity was assessed using the Rotorod procedure. All the compounds tested were administered intraperitoneally at a various dose levels ranging from 15-175 mg/Kg body weight and the median toxic dose (TD50) and the protection index (PI) values were determined. All test compounds exhibited good activity. The structure–activity relationships based on the results obtained for these series were also studied.

Conclusion: The present study indicates that fused quinazolinones shown very good anticonvulsant agents. In both series, electron-withdrawing substitutions showed more activity. Among all the tested compounds, 10,12-dibromo-1-(4-chloro-phenyl)-3-(4-tolyl)-8*H*-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one **29** and 10,12-dibromo-3-(4-chloro-phenyl)-1-phenyl-8*H*-pyrido[2',3':4,5] pyrimido[6,1-b]quinazolin-8-one **25** were found to be most potent.

Keywords: Anticonvulsant activity, Fused quinazolinones, Maximum Electroshock, Neurotoxicity, Pentylenetetrazole.

Introduction

Epilepsy, a ubiquitous disease characterized by recurrent seizures, inflicts more than 60 million people worldwide according to epidemiological studies [1]. In recent years, antiepileptic drug development has been one of the most important research areas [2]. Absence (petit mal) seizures are treated well in most cases; significant therapeutic improvement is still needed for the treatment of partial-complex (focal) and generalized tonic-clonic (grand mal) seizures [3]. Anticonvulsant drugs are estimated to be useful in treating 90% of the epileptic patients. However, all the anticonvulsant drugs currently approved, and which are already in use, have dose related toxicity and idiosyncratic side effects [4]. Therefore, the research for new anti-epileptic agents with lower toxicity and fewer side effects are the challenges for medicinal chemist and a wide-variety of compounds has been synthesized for this purpose [5,6].

Recently a great number of fused pyrimidine derivatives became known as potential drug molecules against various types of diseases. One of the most important compound families are quinazolinones. The quinazolinone moiety is a building block for

approximately 150 naturally occurring alkaloids and drugs [7]. Literature survey reveals that natural quinazolinones and their synthetic analogs possess a variety of pharmacological activities, including PDE inhibitory activity [8-12], anticonvulsant [5,6], bronchodilator [13], anti-inflammatory [14,15], antimalarial [16], antituberculous [17], anti-HIV [18], narcotic antagonist [19], anti-tumor [20], tyrosine kinase inhibitor [21], adenosine antagonist [22], antimicrobial [14], etc. Similarly thienopyrimidine [23,24] and pyridopyrimidine[25], the bioisosters of quinazolinones are known to possess good anticonvulsant activity.

We are especially interested in developing novel quinazolinones fused with various heterocycles at 2 and 3 positions. Previously we have reported synthesis and pharmacological evaluation of various quinazolinone derivatives [5,11,14,26-28]. In previous report [5] we have described the number of quinazolinones and their possible anticonvulsant activity. These compounds (**see Figure 1**) have some sort of similarity with the well known methaqualone. These compounds showed a very promising anticonvulsant activity with less neurotoxicity. Among the twenty six compounds tested, the compound 2-phenyl-3-(4-methoxybenzothiazol-2-yl)-4[3*H*]-quinazolinone in the 2-phenyl-3-(benzothiazole-2-yl)-4[3*H*]-quinazolinone series and 6,8-dibromo-2-phenyl-3-(4-6-dimethylbenzothiazol-2-yl)quinazolin-4[3*H*]-one in the 6,8-dibromo-2-phenyl-3-(benzothiazole-2-yl)-4 [3*H*]-quinazolinone series were found to be the most potent.

While searching for anticonvulsant compound, we have found that quinazolinone ring is one of the moieties on which studies have been concentrated [14]. Thienopyrimidine and pyridopyrimidine are also bioisosters of quinazolinone, and anticonvulsant activity have been extensively investigated and performed. All of these have made us think that thienopyrimidine/pyridopyrimidine fused quinazolinones are promising compounds for finding a drug with anticonvulsant action.

In spite of the fact that according to the literature thousands of quinazolinones, thienopyrimidine and pyridopyrimidine related compounds have been synthesized and tested for a possible central nervous system depressant and anticonvulsant activity, no attempt has been made to incorporate the thienopyrimidine/pyridopyrimidine moiety and the quinazolinone nucleus in a single molecular framework. So we attempted to synthesize various analogues of 7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]-quinazolin-7-one **1-15** [26] and 8*H*-pyrido[2',3':4,5]pyrimido[6,1-*b*]quinazolin-8-ones **16-36** [27]. Moreover, it was considered of interest to substitute various groups on the thienopyrimidine/pyridopyrimidine nucleus to investigate the influence of such structural variation on the anticipated biological activities. Thus in the present investigation, thirty six different derivatives of thienopyrimidine/pyridopyrimidine fused with quinazolinone were evaluated for their anticonvulsant activity using Maximum Electroshock (MES) induced seizures and subcutaneous pentylenetetrazole (scPTZ) induced seizures model in mice. In addition to anticipated anticonvulsant activity, neurotoxicity of title compounds was assessed using the Rotorod procedure.

The preliminary SAR features (based on the results obtained) of these new heterocyclic anticonvulsants are discussed herein.

Results and Discussion

Chemistry

A series of some new 1,2,9,11-tetrasubstituted-7*H*-thieno[2',3':4,5]pyrimido[6,1-*b*]-quinazolin-7-one **1-15** and 1,3,10,12-tetrasubstituted-8*H*-pyrido[2',3':4,5]pyrimido[6,1-*b*]quinazolin-8-ones **16-36** have been synthesized using appropriate routes. Details of the synthesis and characterization have been well documented [26, 27].

Pharmacology

Continuing our studies on quinazolinones heterocycles [5,11,14, 26-28] that are attractive candidates [5] as anticonvulsant agents, we have designed a novel thienopyrimidine fused quinazolinones and pyridopyrimidine fused quinazolinones. In the pharmacological study, we have investigated anticonvulsant activity as well as the neurotoxicity.

The pre-clinical discovery and development of new chemical agents for the treatment of epilepsy are based mainly on the use of predictable animal models, from which the MES and scPTZ screens are recognized as the ‘‘gold standards’’ in the early stages of testing [29].

Initial anticonvulsant activity and neurotoxicity (NT) data for the thienopyrimidine/pyridopyrimidine fused quinazolinones **1-36** are given in Table 1 and most of the compounds showed remarkable anticonvulsant activity. The title compounds revealed diversified anticonvulsant properties.

The MES model has served to identify currently available anticonvulsants that are functionally similar to phenytoin, and most of these compounds display in common the ability to inactivate voltage-dependent Na^+ channels in a use-dependent fashion. Activity in this model seems highly predictive of the ability of those currently available anticonvulsants to protect against partial and secondarily generalized tonic-clonic seizures. The scPTZ model has proven to be a good predictor of clinical efficacy against generalized spike-wave epilepsies of the absence type. Thus, the MES and scPTZ screens have become the most widely employed seizure models for early identification of candidate anticonvulsants.

The Anti-MES and Anti-scPTZ (ED50 values in Tables 1) indicated significant anticonvulsant activity for the tested compounds **1-15** and **16-36**. However, they were found to be less potent when compared with the reference standard phenytoin (ED50 value in MES model 6.48 at t=0.5h and 7.1 at t = 4h) and Phenobarbital (ED50 value in MES model 16.8 at t=0.5h and 21.8 at t = 4h; ED50 value in scPTZ model 11.5 at t=0.5h and 13.2 at t = 4h). The different substituent at the aromatic ring and heterocycles exerts a significant influence on the biological activity by modulating the lipophilicity and thereby facilitating penetration across the blood-brain barrier. The presence of electron withdrawing groups (Bromo) at the quinazoline nucleus in general increases the potency of the tested compounds compared to compounds having no bromo group. In general dibromo substituted compounds are more potent than the monobromo and than non bromo compounds. This is because of the increased lipophilicity, which in turn increases the permeability across biological membrane. In general, among all the compounds evaluated, pyridopyrimidine (dibromo substituted) fused quinazolinones are more potent than thienopyrimidine (dibromo substituted) fused quinazolinones. Further it has been found that the ED50 andTD50 values of the tested compounds increase significantly at t = 4 h, compared to t = 0.5 h, in contrast to the reference compound, indicating that the tested compounds were metabolized with time in the biological environment. This trend was found to be more pronounced in compounds having electron withdrawing substituent on the ring compared to electron releasing substituent. To confirm this phenomenon *in vivo*, it will be necessary to carry out a kinetic study in an animal model. Based upon the results, it will also be necessary to optimize the lead compound by substituting a series of electron withdrawing groups at the aromatic ring and selectively modifying the quinazoline nucleus. The protection index (PI) values are found to be more significant for determining the relation between lipophilicity and toxicity. Tables 1 show that PI values were found for more potent compounds in contrast to less lipophilic compounds. Thus, as the lipophilicity increases, so does the toxicity and therefore also the protection index (PI). Among the compounds tested, 10,12-dibromo-1-(4-chloro-phenyl)-3-(4-tolyl)-8*H*-pyrido [2',3':4,5]pyrimido[6,1-b]quinazolin-8-one **29** (ED50 value in MES model 18.5at t=0.5h and 24.7 at t = 4h; ED50 value in scPTZ model 19.8 at t=0.5h and 25.3at t = 4h; TD50 value 83.8 at t=0.5h and 98.5 at t = 4h; PI 4.52973 in MES and 4.232323 in scPTZ) and 10,12-dibromo-3-(4-chloro-phenyl)-1-phenyl-8*H*-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one **25** (ED50 value in MES model 20.1at t=0.5h and 24.7at t = 4h; ED50 value in scPTZ model 19.3 at t=0.5h and 23.8 at t = 4h; TD50 value 90.3 at t=0.5h and 110.3 at t = 4h; PI 4.492537 in MES and 4.678756 in scPTZ).

Compound **1-15** exhibited little more activity against seizure induced by scPTZ than seizure induced by MES. While in compound **16-36** we observed that these compounds showed little stronger activity against seizure induced by MES than the seizure induced by scPTZ. Further studies are in progress to optimize this lead compound and fully characterize its mode of action.

SAR studies of 1,2,9,11-tetrasubstituted-7H-thieno[2',3':4,5]pyrimido[6,1-b]-quinazolin-7-one 1-15.

Structure activity relationship (SAR) studies indicated that different substitution on the aromatic ring, exerted varied anticonvulsant activity. The electronic nature of the substituent group in aromatic ring led to a significant variation in anticonvulsant activity. For example electronic withdrawing group (mainly bromo substitutions) enhanced the anticonvulsant activity whereas non bromo analogues showed less activity and the order of activity was dibromo analogues **(6-10)>** monobromo analogues **(11-15) >** non bromo analogues **(1-5)**. The substituent over thiophene nucleus also led to significant variation in anticonvulsant activity. Aromatic substitution in thiophene ring increased the anticonvulsant activity over the aliphatic substituted compounds. In general the order of

the activity was R_1= p-chlorophenyl; R_2= H > R_1 =R_2 = -$(CH_2)_4$- > R_1=p-methyl-phenyl; R_2 = H > R_1 = p-methoxy-phenyl; R_2 = H > R_1 = R_2 = methyl. Among this series, 9,11-dibromo-1-(4-chlorophenyl)-7*H*-thieno[2',3':4,5]pyrimido[6,1-b]quinazolin-7-one **8** was the most potent (ED50 value in MES model 34.3 at t=0.5h and 37.8 at t = 4h; ED50 value in scPTZ model 33.9 at t=0.5h and 37.2 at t = 4h; TD50 value 97.9 at t=0.5h and 122.7 at t = 4h;PI 2.854227 in MES and 2.887906 in scPTZ).

SAR studies of 1,3,10,12-tetrasubstituted-8*H*-pyrido[2',3':4,5]pyrimido[6,1-*b*]quinazolin-8-ones 16-36.

Structure activity relationship (SAR) studies in this series indicated that the R_1 and R_2 substituent over the pyridine ring, exerted varied anticonvulsant activity. It has been found that anticonvulsant activity increases as R_2 = electron releasing groups, whereas if R_2= electron withdrawing groups, then it decreases the activity. The compound with R_1 = electron releasing groups was showed more anticonvulsant activity than the compounds with R_1= electron withdrawing groups. Among all the compounds in this series, 10,12-dibromo-1-(4-chloro-phenyl)-3-(4-tolyl)-8*H*-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one **29** (ED50 value in MES model 18.5 at t=0.5h and 24.7 at t = 4h; ED50 value in scPTZ model 19.8 at t=0.5h and 25.3 at t = 4h; TD50 value 83.8 at t=0.5h and 98.5 at t = 4h; PI 4.52973 in MES and 4.232323 in scPTZ) and 10,12-dibromo-3-(4-chloro-phenyl)-1-phenyl-8*H*-pyrido [2',3':4,5]pyrimido[6,1-b]quinazolin-8-one **25** (ED50 value in MES model 20.1 at t=0.5h and 24.7 at t = 4h; ED50 value in scPTZ model 19.3 at t=0.5h and 23.8 at t = 4h; TD50 value 90.3 at t=0.5h and 110.3 at t = 4h; PI 4.492537 in MES and 4.678756 in scPTZ).

Attempted correlation of anticonvulsant activity with C log P data

To be effective as antiepileptic agents, antiepileptic drugs have to cross the blood brain barrier (BBB) [30]. Entry into the brain is therefore a crucial step in developing effective drug therapies for cerebral disorders. *In vitro* determination of brain-blood partitioning is difficult, time-consuming, expensive and not suitable to screen a large collection of chemicals. Therefore, we used alternative method based on computerized models. Lipophilic substances are able to permeate into the brain interstitium in a relatively easy way [31,32]. First, we calculated the C log P value for each compound in order to reflect the overall lipophilicity of the thienopyrimidine/pyridopyrimidine fused quinazolinones (Table 1). It is postulated that a C Log P value of at least 2.0 is required to cross the BBB [33,34].

The C log P data for all novel anticonvulsant compounds (**1-15** & **16-36**) were mentioned in Table 1 and ranged from 7.89724 to 2.89725. All the compounds have C Log P value above 2 which is required for effective penetration in the brain. As such no significant correlation could be established between C log P values and anticonvulsant activity of the title compounds. In general it was found that compounds having more C Log P values having less TD50 value. Table 1 shows that compounds with a weak C log P (compound **5**) are able to protect the mice against convulsions but shown the least activity among all the compounds. Compounds **29** and **25** share an optimal C log P value and exhibit also an optimal anticonvulsant effect. In general, it was found that the correlation between the C log P and the *in vivo* anticonvulsant activity is not really straightforward.

Experimental

Albino mice of either sex weighing between 20-25 g, obtained from National Center for Laboratory Animal Sciences, Hyderabad, India, were used in the present study. Animals were housed in wire-mesh cages under the laboratory conditions (23 ± 2° C), 12 h light. Animals were allowed to acclimatize with free access to food and water for a 24 h period before testing. All animals had free access to standard pellet diet (Hindustan Leaver Ltd. Mumbai) and water, in a constant light-dark cycle. During the course of the experiment, the general behavior of the animal was normal. All the experimental protocols were approved by the institutional animal ethical committee and the experiments were conducted in accordance with the standard guidelines. The animals were divided into three groups (control, standard and test) and each group consisted of six animals. The homogenous suspension of the tested compounds (**1-15** and **16-36**) and the standard drugs (phenytoin/Phenobarbital) were prepared in polyethylene glycol and distilled water (1:9/mL). All the test compounds were administered intraperitoneally (ip) at a dose in the range of 15–175 mg/kg body weight 30 min prior to the start of the experiments. The maximal Electroshock Seizures (MES) were induced by electroconvulsometer (Techno Instruments, Lucknow).

A Pentium IV Core 2 Duo computer (with 4GB RAM) with Windows Vista operating system was used. The calculated partition coefficient (C Log P) values were determined by using ChemDraw Ultra, computer software by CambridgeSoft.com.

Anticonvulsant activity

Anticonvulsant activity of the title compounds (**1-36**) was evaluated by MES and scPTZ and Rotorod test for neurological toxicity (NT). Male albino mice were used as experimental animals.

The MES were induced by electroconvulsometer (Techno Instruments, Lucknow), using a technique described earlier [35]. The animals were subjected to electroshock (60 mA/0.2 s) via the transauricular electrodes. Further the compounds were evaluated against scPTZ model in mice. The anticonvulsant effect was assessed by recording the Tonic Hind-limb Extension at various dose levels at t = 0.5 and 4 h. Absence of seizure component like hind limb tonic extension with drug treatment was considered to be evidence of protection. Medium effective dose (ED50) was calculated for each compound and is presented in Tables 1. Acute neurotoxicity of all the test compounds was assessed in mice using the method described by Dunham and Miya [36]. Briefly, group of animals (mice) were trained to balance on a rotating rod (3 cm diameter and 6 rpm speed) and they were allowed three attempts to remain on the rotating rod for 20 s. Such trained animals were treated with the tested compounds at a various dose levels between 40–170 mg/Kg body weight by intraperitoneal administration. The tested compounds were considered to be neurotoxic at a particular dose level if the trained animal showed lack of Rolling Roller Performance. Each of the trained animals was tested in this manner at 30 min and 4 h after the drug administration, and the neurotoxic effect was recorded in terms of TD50. Based upon these results PI values were calculated as shown in Tables 1.

Theoretical C Log P calculation

The chemical structure of the molecules was drawn by the ChemDraw Ultra software. The theoretical C Log P values of all the title compounds were calculated using ChemBioOffice.

Conclusion

In this paper, we have described the anticonvulsant activity of novel thienopyrimidine/pyridopyrimidine fused quinazolinone derivatives. The results obtained revealed that number of novel thienopyrimidine/pyridopyrimidine fused quinazolinone derivatives were effective in the MES and scPTZ screens, the most widely employed seizure models for early identification of candidate anticonvulsants. The most active was 10,12-dibromo-1-(4-chloro-phenyl)-3-(4-tolyl)-8*H*-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one **29** (ED50 value in MES model 18.5 at t=0.5h and 24.7 at t = 4h; ED50 value in scPTZ model 19.8 at t=0.5h and 25.3 at t = 4h; TD50 value 83.8 at t=0.5h and 98.5 at t = 4h; PI 4.52973 in MES and 4.232323 in scPTZ). There was no distinct correlation between the lipophilicity and anticonvulsant efficacy.

Executive summary – In this study, attempts were made to design compounds that exhibit anticonvulsant activity.

- ☐ Initially we designed these compounds considering the anticonvulsant potency of thienopyrimidine, pyridopyrimidine and quinazolinones. We observed that no attempt has been made to incorporate the thienopyrimidine/pyridopyrimidine moiety and the quinazolinone nucleus in a single molecular framework. So we attempted to synthesize compounds having thienopyrimidine/pyridopyrimidine and quinazolinone nucleus in a single frame work, in hope of good anticonvulsant activity.
- ☐ From the study carried out on the title compounds, it was found that they exhibit good anticonvulsant activity with good protection index.
- ☐ n both series, 10,12-dibromo-1-(4-chloro-phenyl)-3-(4-tolyl)-8*H*-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one **29** (ED50 value in MES model 18.5 at t=0.5h and 24.7 at t = 4h; ED50 value in scPTZ model 19.8 at t=0.5h and 25.3 at t = 4h; TD50 value 83.8 at t=0.5h and 98.5 at t = 4h; PI 4.52973 in MES and 4.232323 in scPTZ) and 10,12-dibromo-3-(4-chloro-phenyl)-1-phenyl-8*H*-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one **25** (ED50 value in MES model 20.1 at t=0.5h and 24.7 at t = 4h; ED50 value in scPTZ model 19.3 at t=0.5h and 23.8 at t = 4h; TD50 value 90.3 at t=0.5h and 110.3 at t = 4h; PI 4.492537 in MES and 4.678756 in scPTZ) exhibited potent anticonvulsant activity with good protection index.

Future perspective

As most of the compounds were shown a promising anticonvulsant activity with good protection, it will worthwhile if we develop this pharmacophore with help of computational tools. As these compounds have very good Clog P values, we are on the way to check out these compounds against neurodegenerative diseases.

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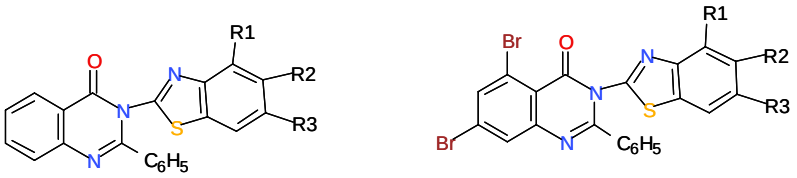
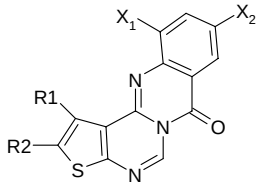
Figure 1. Previously synthesized compounds by our lab showing anticonvulsant activity.



Where R1, R2, and R3 = H, CH3,OCH3, OC2H5,Cl,Br and NO2

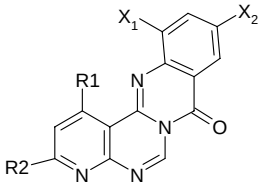
Figure 2. Compound **1-36** for pharmacological evaluation



1: R1= R2= -(CH2-)4; X1=X2=H
2: R1=p-Cl-phenyl; R2= H; X1=X2=H
3: R1=p-Me-phenyl; R2= H; X1=X2=H
4: R1=p-MeO-phenyl; R2= H; X1=X2=H
5: R1=R2= Me; X1=X2=H

6: R1= R2= -(CH2-)4; X1=X2=Br
7: R1=R2= Me; X1=X2=Br
8: R1=p-Cl-phenyl; R2= H; X1=X2=Br
9: R1=p-Me-phenyl; R2= H; X1=X2=Br
10: R1=p-MeO-phenyl; R2= H; X1=X2=Br

11: R1= R2= -(CH2-)4; X1=H;X2=Br
12: R1=R2= Me; X1=H; X2=Br
13: R1=p-Cl-phenyl; R2= H; X1=H; X2=Br
14: R1=p-Me-phenyl; R2= H; X1=H; X2=Br
15: R1=p-MeO-phenyl; R2= H; X1=H; X2=Br



16: R1= 2-furfuryl; R2= 4-tolyl; X1=X2=H
17: R1=p-MeO-phenyl; R2= phenyl; X1=X2=H
18: R1=phenyl; R2= 4-Cl-phenyl; X1=X2=H
19: R1=3-NO2-phenyl; R2= 4-MeO-phenyl; X1=X2=H
20: R1=4-NO2-phenyl; R2= 4-NO2-phenyl; X1=X2=H
21: R1=4-tolyl; R2= phenyl; X1=X2=H
22: R1=4-Cl-phenyl; R2= 4-tolyl; X1=X2=H

23: R1= 2-furfuryl; R2= 4-tolyl; X1=X2=Br
24: R1=p-MeO-phenyl; R2= phenyl; X1=X2=Br
25: R1=phenyl; R2= 4-Cl-phenyl; X1=X2=Br
26: R1=3-NO2-phenyl; R2= 4-MeO-phenyl; X1=X2=Br
27: R1=4-NO2-phenyl; R2= 4-NO2-phenyl; X1=X2=Br
28: R1=4-tolyl; R2= phenyl; X1=X2=Br
29: R1=4-Cl-phenyl; R2= 4-tolyl; X1=X2=Br

30: R1= 2-furfuryl; R2= 4-tolyl; X1=H; X2=Br
31: R1=p-MeO-phenyl; R2= phenyl; X1=H; X2=Br
32: R1=phenyl; R2= 4-Cl-phenyl; X1=H; X2=Br
33: R1=3-NO2-phenyl; R2= 4-MeO-phenyl; X1=H; X2=Br
34: R1=4-NO2-phenyl; R2= 4-NO2-phenyl; X1=H; X2=Br
35: R1=4-tolyl; R2= phenyl; X1=H; X2=Br
36: R1=4-Cl-phenyl; R2= 4-tolyl; X1=H; X2=Br

Table 1. C Log P value, Anticonvulsant Activity and Neurotoxicity of Compounds **1-36** in Mice[a].

Comp.	C Log P	MES		scPTZ		Toxicity		PI	
		0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	MES	scPTZ
1	3.52125	54.1(49–55)	62.3(53–65)	54.0(48–56)	61.9(50–66)	146.3(140–149)	168.8(162–170)	2.704251	2.709259
2	4.55061	52.7(48–54)	59.9(52–63)	52.2(48–54)	58.3(49–60)	129.1(124–132)	153.4(150–155)	2.449715	2.47318
3									

	4.33625	55.3(50–58)	63.9(56–66)	55.1(50–60)	64.2(56–66)	137.7(130–142)	159.9(154–166)	2.490054	2.499093
4	3.77647	56.9(51–60)	64.8(58–68)	56.5(50–61)	64.2(55–70)	138.5(130–140)	161.1(155–168)	2.434095	2.451327
5	2.89725	60.2(55–63)	68.7(60–70)	59.8(56–64)	68.2(60–70)	149.8(145–155)	172.1(165–174)	2.488372	2.505017
6	5.24709	37.3(35–39)	42.2(40–45)	36.9(35–40)	42.8(40–46)	112.1(110–116)	137.8(133–140)	3.005362	3.03794
7	6.27645	42.1(40–44)	46.7(44–50)	41.2(40–45)	45.3(40–48)	91.6(90–96)	115.2(110–118)	2.175772	2.223301
8	6.06209	34.3(31–38)	37.8(35–40)	33.9(30–35)	37.2(30–46)	97.9(94–98)	122.7(120–125)	2.854227	2.887906
9	5.5023	38.8(35–40)	43.8(40–46)	38.2(35–40)	43.1(40–46)	101.9(98–105)	128.8(125–130)	2.626289	2.667539
10	4.62309	39.1(35–41)	44.5(40–46)	39.5(35–42)	44.1(40–47)	126.9(124–128)	149.8(145–152)	3.245524	3.212658
11	4.38414	46.7(45–48)	51.3(48–53)	45.9(42–46)	50.8(48–53)	134.6(132–136)	158.1(155–160)	2.882227	2.932462
12	5.4135	50.8(48–53)	56.9(54–58)	50.2(48–52)	56.8(53–58)	109.7(105–111)	131.5(128–133)	2.159449	2.185259
13	5.19914	44.3(43–46)	49.8(46–52)	43.8(42–45)	49.1(45–51)	115.3(112–117)	139.1(135–140)	2.602709	2.63242
14	4.63936	48.9(46–50)	53.7(51–55)	47.8(46–49)	52.9(51–54)	125.2(122–127)	148.5(145–150)	2.560327	2.619247
15	3.76014	49.3(47–52)	54.5(52–56)	48.2(45–50)	53.8(51–55)	142.9(140–144)	164.7(162–168)	2.89858	2.96473
16	4.8434	53.7(51–55)	59.8(57–61)	52.7(51–55)	59.4(57–61)	121.8(120–123)	143.1(140–145)	2.268156	2.311195
17	4.96783	54.5(52–58)	63.7(61–65)	55.1(53–58)	62.9(60–64)	119.8(115–121)	141.3(140–144)	2.198165	2.174229
18	5.67212	48.2(45–50)	53.3(51–55)	47.9(45–50)	53.8(51–55)	99.1(97–101)	125.4(123–127)	2.056017	2.068894
19	4.71209	50.1(48–52)	57.7(55–60)	49.8(47–51)	57.5(55–59)	123.3(120–125)	146.8(144–148)	2.461078	2.475904
20	4.44648	56.1(54–58)	60.3(58–61)	56.8(54–58)	59.9(57–61)	131.4(128–133)	156.6(154–158)	2.342246	2.31338
21	5.4574	52.8(50–54)	60.3(58–62)	53.5(50–55)	59.9(58–62)	106.1(104–108)	129.0(125–130)	2.00947	1.983178
22	6.17112	46.3(45–47)	50.2(48–52)	46.8(45–48)	50.8(48–52)	97.4(95–99)	120.5(118–122)	2.103672	2.081197
23	5.70649	21.5(20–25)	30.3(25–32)	22.7(20–25)	31.2(30–35)	98.0(95–99)	123.7(120–125)	4.55814	4.317181
24	5.83093	27.2(25–30)	34.3(30–36)	26.9(22–28)	36.1(33–38)	98.7(95–100)	124.1(122–125)	3.628676	3.669145
25	6.53521	20.1(18–22)	24.7(20–26)	19.3(16–22)	23.8(20–25)	90.3(88–92)	110.3(108–112)	4.492537	4.678756
26	5.57519	21.3(18–24)	27.3(25–30)	20.9(18–22)	26.9(24–28)	101.4(100–103)	128.2(125–130)	4.760563	4.851675
27	5.30958	28.9(25–30)	35.1(34–40)	29.2(26–32)	34.9(32–36)	110.9(108–112)	133.3(130–135)	3.83737	3.797945
28	6.32049	22.3(20–25)	30.8(28–32)	23.0(20–25)	31.0(28–34)	95.8(92–97)	118.1(115–120)	4.295964	4.165217
29	7.03421	18.5(15–20)	24.7(22–26)	19.8(16–22)	25.3(22–28)	83.8(80–85)	98.5(95–100)	4.52973	4.232323
30	6.56952	38.1(35–40)	43.7(40–45)	38.3(35–40)	44.1(42–46)	87.5(85–90)	101.2(100–103)	2.296588	2.284595
31	6.69396	42.7(40–45)	46.1(42–48)	42.0(40–45)	45.3(42–46)	85.9(83–87)	98.7(95–100)	2.01171	2.045238
32	7.39832	31.3(30–34)	38.3(35–40)	30.8(28–32)	34.7(30–35)	58.9(55–60)	71.3(68–72)	1.881789	1.912338
33	6.43822	34.7(32–36)	39.9(37–42)	34.2(30–35)	41.1(37–44)	93.6(90–95)	111.9(108–113)	2.697406	2.736842
34	6.17261	42.9(40–45)	47.5(45–50)	43.2(40–45)	47.9(45–50)	94.1(90–92)	117.2(115–119)	2.193473	2.178241
35	7.18352	40.3(38–43)	48.2(45–50)	40.6(38–44)	47.9(45–50)	60.8(58–62)	78.5(75–80)	1.508685	1.497537
36	7.89724	29.8(26–31)	34.2(32–36)	29.5(25–32)	33.9(30–35)	52.6(50–54)	68.2(65–69)	1.765101	1.783051
Phenytoin	2.085	6.48(5.5-8.5)	7.1(6-8.7)	Not tested	Not tested	42.8 (36–48)	44(37–51)	6.60	Not tested
Phenobarbital	1.365	16.8 (10–	21.8 (21.8-	11.5 (8.3-	13.2 (10-	55.0 (52.8-	69.0 (62.8-	3.27381	4.782609

		18)	25.5)	12.9)	15.3)	62.9)	72.9)		

[a]All test compounds were administered by ip injection at doses spanning the range 15-175 mg kg^{-1}, 30 min and 4 h before evaluation of activity. At least 6 animals were used to calculate each ED50 and TD50 value. In scPTZ induced seizures test, 200 µL/kg body wt. of 10 µM solution of PTZ was administered by subcutaneous route 15 min after the ip injection of the tested compounds; the anticonvulsant activity was recorded at t = 0.5 and 4 h and represented in terms of the ED50, i.e., dose of tested compound required to assure anticonvulsant protection in 50% of animals from hind limb tonic extension (tonic phase); the TD50, dose eliciting minimal neurological toxicity in 50% of animals as assessed by the Rotorod test (locomotor deficit); the PI, protection index (PI = TD50/ED50) from MES/scPTZ induced seizures after 0.5 h; ED50 and TD50 values are given as mg kg^{-1}.