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Studies on anticonvulsant agents. Achievements and prospects

Sh Pandey, Sh Shukla, D Pandey, R S Srivastava

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Abstract. The data published over the past 15 years on the search for newer anticonvulsant drugs are generalized. Pyrrolidinedione, quinazolinone, xanthone, hydrazine and thiadiazole derivatives manifesting anticonvulsant activity in model *in vivo* tests in rodents are considered. The bibliography includes 69 references.

I. Introduction

The World Health Organization (WHO) estimates that epilepsy affects 50 million people globally, and almost 85% of them live in the developing countries.[1–4] About 10% of the world's population who live a normal lifespan can expect to have at least one epileptic seizure and nearly 70% of population fail to receive proper medical treatment.[5] Untreated epilepsy is a critical public health issue, as people with untreated epilepsy face potentially devastating social consequences and poor health outcomes. Epilepsy is among the most common disorders encountered by neurologists, it is characterized by the occurrence of at least two or more unprovoked seizures. Generally, seizures can be caused by multiple factors, mainly by the disruption of the mechanisms that balance the excitation and inhibition. Epilepsy is a neurological condition that knows no geographic, social, or racial boundaries, occurring in men and women and affecting people of all ages, though more frequently affecting young people in their first two decades of life and people over the age of 60.[6]

The majority of available antiepileptic drugs cause serious undesirable side effects, and lifelong medication seriously worsens the health condition of the patients.[7, 8] Approximately 20% – 30% of patients show resistance to the currently available therapeutic agents. The efficacy of epilepsy treatment is not up to the mark and none of the currently approved antiepileptic drugs is perfect. About 70% of patients with epilepsy are well controlled by monotherapy with currently available antiepileptic drugs and another 5% – 10% of patients could be stabilized by the addition of one more antiepileptic drug, but the seizures are not efficiently controlled in remaining 20% of patients.[9] Moreover, the last two decades witnessed the growth of the number of studies in molecular pharmacology and the development of new anticonvulsant agents. Countless research efforts are being made worldwide to find novel antiepileptic agents with more selective activity and lower toxicity suitable for monotherapy, but the biggest hurdle in designing the new drug for epilepsy is incomplete information about the cellular mechanism of their action in humans.

The currently available antiepileptic drugs can broadly be classified into four categories on the basis of the main molecular mechanisms through which they act, in particular: 1) modulation of voltage-dependent Na^+ or Ca^{2+} channels, 2) enhancement of γ-aminobutyric acid (GABA) mediated inhibition or another effect on the GABA system, 3) inhibition of synaptic excitation mediated by ionotropic glutamate receptors and 4) modulation in synaptic release.[7, 10, 11] The understanding of the mechanisms of seizure generation and propagation helps identifying new targets for potential antiepileptic drugs. However, this classification has limited value because the majority of antiepileptic drugs act through more than one mechanism of action, which is very significant for their efficacy. Drugs like Carbamazepine, Gabapentin, Lamotrigine, Oxcarbaze-

Sh Pandey, Sh Shukla, D Pandey, R S Srivastava Institute of Technology and Institute of Medical Sciences, Banaras Hindu University, 221005 Varanasi, Uttar Pradesh, India. Fax (91-542) 236 84 28, (91-542) 236 75 68 tel. (91-988) 991 09 00, e-mail: spandey.rs.phe@itbhu.ac.in (Sh Pandey), tel. (91-953) 286 36 72, e-mail: shubpharma@rediffmail.com (Sh Shukla), tel. (91-979) 535 61 08, e-mail: pandey99itbhu@gmail.com (D Pandey), tel. (91-933) 691 15 53, e-mail: rssitbhu@yahoo.com (R S Srivastava)

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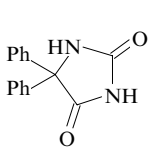
pine, Phenobarbital, Phenytoin, Topiramate, Valproate, *etc.* , which are effective against generalized tonic–clonic and partial seizures, are believed to act by blocking sustained repetitive firing in individual neurons, this effect being mainly due to the blockade of voltage-dependent sodium or calcium channels. Antiepileptic agents like benzodiazepines, Gabapentin, Phenobarbital, Tiagabine, Topiramate, Vigabatrin, Valproate, *etc.* act by enhancing the inhibitory events mediated by γ-aminobutyric acid. Meanwhile, drugs like Ethosuximide and Zonisamide were found to be active against absence seizures, and they act as T-type calcium channel blockers. Few antiepileptic drugs, *e.g.*, Felbamate, Phenobarbital and Topiramate, may also reduce some events mediated by excitatory amino acid glutamate.

The success in the discovery of novel antiepileptic drugs mainly relies upon the preclinical employment of animal models to establish the efficacy and safety prior to the introduction of the antiepileptic drugs in human volunteers.[12] The more predictive the animal model for any given seizure type the greater the possibility to demonstrate the efficacy in human clinical trials. Maximal electroshock seizure (MES) test and chemically induced seizure (by subcutaneous administration of pentylenetetrazole, scPTZ) test have been continuously used in high throughput screening for anticonvulsant agents. Furthermore, these animal models can provide insight into pharmacokinetic–pharmacodynamic relationships, which is essential for clinical trials. The protective index (PI) is considered as an index characterizing safety and tolerability between anticonvulsant doses and doses of compounds exerting acute adverse effects (sedation, ataxia, impairment of motor coordination or other neurotoxic manifestations) in preclinical studies. Quantitatively, PI is the ratio of the toxic dose (TD_{50}) evaluated in the Rotarod test in rodents (where the animals are placed on a rotating rod) to the therapeutic dose (ED_{50}) determined separately in the MES test and for various chemically induced seizures. The admissible protective index (PI) for a new drug (synthesized compound) should be greater than unity, indicating its pharmacological activity in safe doses. The protective index can be compared with the therapeutic index, but the former is mainly concerned with the toxic (TD_{50}) rather than lethal (LD_{50}) dose. Finally, PI is a more accurate measure of the benefit-to-risk ratio than the therapeutic index, but is less objectively defined. The protective indices of some reference drugs are as follows: Phenytoin, 4.6; Carbamazepine, 4.8; Valproate, 1.68 and Phenobarbital, 3.21.[13]

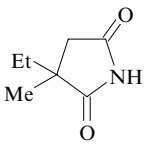
Nevertheless, there is a continuous need for new anticonvulsant agents especially for focal and secondary generalized seizures. This review presents studies dealing with the search for better pharmacophores that can potentially play an important role in the development of novel anticonvulsant agents effective against pharmacoresistant forms of epilepsy.

II. Pyrrolidinedione derivatives

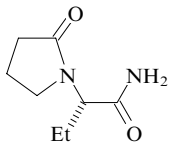
The anticonvulsant activity of compounds incorporating a nitrogen heterocycle (often a cyclic imide), at least one carbonyl group and an alkyl or an aryl substituent in the heterocycle was discovered long ago. The well-known drugs Phenytoin, Ethosuximide and more recent drug Levetiracetam as well as Brivaracetam and Seletracetam that are currently under clinical trials can serve as examples.



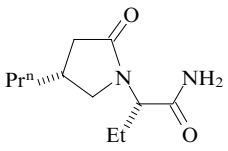
Phenytoin



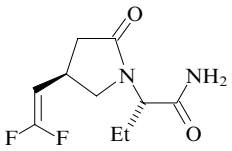
Ethosuximide



Levetiracetam



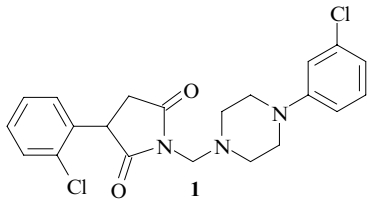
Brivaracetam



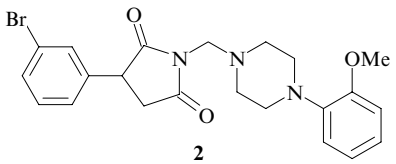
Seletracetam

In the past two decades, a series of research into substituted pyrrolidinediones was carried out by Obniska and co-workers.[14–23] For early identification of candidate anticonvulsants, the synthesized compounds were evaluated using *in vivo* tests in rodents, as a rule, the MES and scPTZ seizure threshold tests. The systematic structure–activity relationship (SAR) investigations have revealed[19–23] the essential roles of the phenyl fragment in position 3 of the pyrrolidinedione ring and the nature and positions of substituents in this phenyl fragment. The substituent at the nitrogen atom is also of considerable importance: *N*-(4-arylpiperazino)alkyl derivatives were most active. The replacement of the piperazine fragment by the pyridyl, aryl or aminophenyl fragment markedly reduced the anticonvulsant activity of the respective compounds.

In a series of *N*-(4-arylpiperazino)methyl derivatives of 3-arylpyrrolidine-2,5-dione, Mannich bases **1** and **2** were the most promising in MES tests (oral administration in rats), ED_{50} were 14.18 and 33.64 mg kg^{-1}, respectively, PI were 8.8 and 2.47, respectively.[19–23]



1

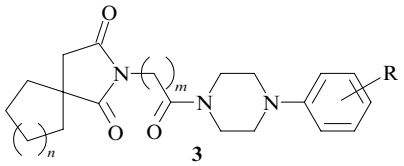


2

In continuation of these studies, a series of derivatives with the methyl group instead of the aryl substituent in the piperazine ring were synthesized and evaluated.[18] Simultaneously, the number of methylene groups in the bridge connecting the pyrrolidinedione and piperazine fragments was varied, and, in addition, a spiro cycloalkyl fragment instead of the phenyl group was introduced in position 3 of the pyrrolidinedione ring of some derivatives. The results provided the conclusion that at least one phenyl ring is necessary for the compound to exhibit anticonvulsant activity: the spirocycloalkyl derivatives with the methyl group in the piperazine ring proved inactive.

In view of the necessity of the presence of amide group in the potential anticonvulsant agents, compounds of gen-

eral formula **3** containing an additional amide group were subsequently studied.[16, 17]

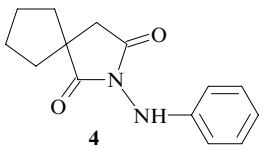


3

n, *m* = 1, 2; R = H, 2-F, 2-Cl, 3-Cl, 2-Me, 2-OMe, *etc.*

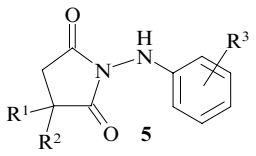
Compound **3** ($n = m = 2$, R = 2-OMe) manifested activity in both MES and scPTZ tests, the other were effective only against one seizure model (or inactive in both tests). The obtained results showed that the introduction of an additional amide function does not enhance the anticonvulsant activity of the compounds. Elongation of the methylene bridge connecting the pyrrolidinedione and piperazine fragments ($m = 2$) reduces the efficiency of the derivatives. The replacement of the acetopiperazide fragment in compound **3** ($m = 1$) by acetanilide or *N*-benzylacetamide fragment resulted in the loss of anticonvulsant activity. This confirmed once again the important role of the 4-arylpiperazine fragment as the pharmacophore responsible for the anticonvulsant activity of compounds of this series.

Some of *N*-anilinoazaspirans demonstrated the anticonvulsant activities. Derivative **4** showed ED_{50} of 76.27 mg kg^{-1} and PI of 3.44 in the MES test in rats [intraperitoneal (i.p.) administration].



4

The synthesis and study of the anticonvulsant activity of a number of *N*-anilinopyrrolidine-2,5-diones **5** with two alkyl substituents in position 3 of the heterocycle were reported.[15] These compounds can be considered as analogues of Ethosuximide, one of the few drugs effective against absence seizures.



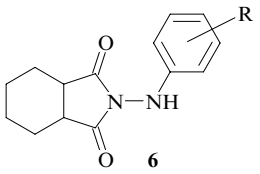
5

R^1 = Me, Et; R^2 = Me, Et, Pr^n, Bu^n; R^3 = H, 2-Me, 4-Me, 2-Cl, 3-Cl, *etc.*

The anticonvulsant activities of compounds were preliminarily estimated in MES and scPTZ tests (i.p. administration in mice). The most effective agents were subsequently studied in the MES test in rats (oral administration). The most active compound **5** with $R^1 = R^2 = Me$, $R^3 = H$ showed ED_{50} of 69.89 mg kg^{-1} and PI of 7.15. Note that the anticonvulsant activity decreased with increase in the length of the alkyl substituent in position 3 of the heterocycle and was also dependent on the nature and position of substituent in the benzene ring.

Some of the compounds were active in the scPTZ test in rats (oral administration) and in the psychomotor seizure test at 6-Hz [so-called 6-Hz-test based on transcorneal stimulation by low-frequency (6 Hz) electrical pulses, the model of therapy-resistant epilepsy].

A number of hexahydroisoindole-1,3-dione derivatives **6** were synthesized and evaluated, *i.e.*, the above-described spiro coupling of the cyclohexane and imide rings was replaced by fusion of the rings through the shared bond.

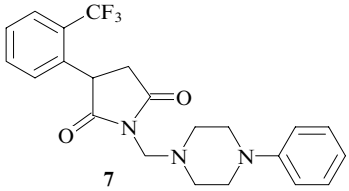


6

R = H, 2-Cl, 3-Cl, 4-Cl, 4-Me, *etc.*

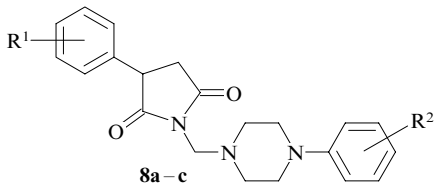
The results of MES and scPTZ tests in rodents demonstrated that this change in the structure of the bicyclic system did not enhance the anticonvulsant activities.

Among *N*-(4-arylpiperazino)pyrrolidine-2,5-diones, high activity in the MES test in rodents was demonstrated by compounds **1** (see above) and **7** (ED_{50} 20.78 mg kg^{-1}, PI 24.1).



7

The synthesis of some new Mannich bases **8** was reported.[14]



8a–c

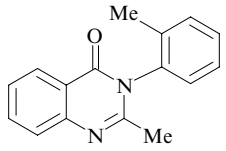
R^1 = 3-Cl: R^2 = 4-Cl (**a**), 3-CF_3 (**b**); $R^1 = R^2$ = 2-Cl (**c**).

Compounds **8** were obtained by the Mannich reaction of the appropriate succinimide derivatives, formaldehyde and 4-arylpiperazines. The anticonvulsant activities of the new compounds were estimated in MES and scPTZ tests in rodents. The highest activities were found for compounds **8a** (ED_{50} 21.4 mg kg^{-1}, PI 23.37) and **8b** (ED_{50} 28.83 mg kg^{-1}, PI 5.30), which were more effective in the MES test than the known drug Phenytoin. Piperazinomethylpyrrolidinediones **8**, which did not manifest activities in the MES or scPTZ tests, were investigated in the 6-HZ test where compound **8c** showed the highest protection with ED_{50} of 78 mg kg^{-1}.

The results of preliminary screening revealed the dependence of the anticonvulsant activity of Mannich bases **8** on the nature and position of the substituent in the benzene ring at the heterocycle C(3) atom and in the 4-arylpiperazine fragment.

III. Quinazolinone derivatives

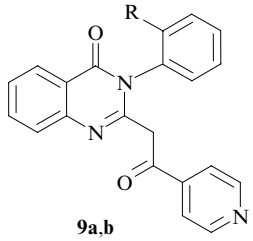
Quinazolin-4(3*H*)-one is one of the most frequently encountered heterocyclic compounds in medicinal chemistry. Its derivatives show antibacterial, antifungal, antiinflammatory, sedative–hypnotic properties, and many of them demonstrate remarkable anticonvulsant action on screening in rodents.[24–35] For example, Methaqualone [2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one] has a pronounced sedative effect.



Methaqualone

Some scientists suggest that sedative-hypnotic and central nervous system (CNS) depressant action and anticonvulsant action of a quinazolinone compound require the presence of a methyl group in position 2 and a substituted aromatic ring in position 3 of the heterocycle.

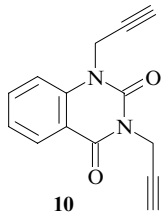
Wolfe *et al.*[35] synthesized some quinazolin-4(3*H*)-ones structurally related to Methaqualone, and these compounds were evaluated for anticonvulsant activity. In preliminary screening of this series, 3-aryl-2-isonicotinoylmethylquinazolin-4(3*H*)-ones with a single *ortho*- substituent in the 3-phenyl group were most promising as regards the anticonvulsant activity. Among these compounds, quinazolinones **9a**,**b** showed excellent protection against MES and scPTZ-induced seizures in rodents but simultaneously they showed high neurotoxicity.



9a,**b**

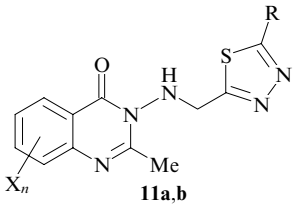
R = Me (**a**), Cl (**b**).

Acetylenic derivatives of quinazolinones and quinazolinediones were synthesized and evaluated for their anticonvulsant activity by Usifoh and Scriba.[33] Few compounds from this series demonstrated seizure-protection in MES test with little or no acute neurotoxicity. Only three compounds were found to be active in the seizure threshold (scPTZ) test. Based on the ED_{50} value in the MES test, compound **10** was almost tenfold less active than the reference compound Phenytoin or Carbamazepine but it was comparable in activity with Mesuximide.

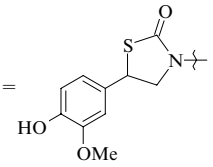


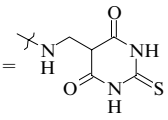
10

A series of thiadiazolyl and thiazolidinyl quinazolin-4(3*H*)-ones have also been screened for anticonvulsant activity in MES and scPTZ tests.[32] In this series, the most active compound **11a** showed better activity than the reference drugs Phenytoin and Lamotrigine. In the scPTZ model, this compound exhibited better anticonvulsant activity than sodium valproate. The SAR studies revealed that 3-amino-6-bromo-2-methylquinazolinones provide a better protection against seizures than similar derivatives containing no bromine in position 6.



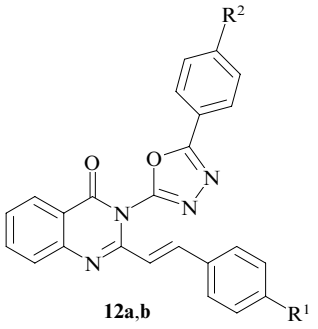
11a,**b**

R =  , X_n = 6-Br (**a**);

R =  , X_n = 6,7-Br_2 (**b**).

1,3,4-Thiadiazole derivatives containing barbituric acid and quinazolinone fragments showed significant anticonvulsant activity; the most active compound **11b** was effective in both the MES and scPTZ seizure tests (i.p. administration in mice).

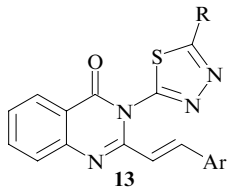
A series of quinazolin-4(3*H*)-ones containing a 1,3,4-oxadiazole fragment with *para*-substituted phenyl group at C(5) in position 3 and a styryl fragment in position 2 were studied in the MES and scPTZ tests (i.p. administration in mice).[25] Some of the compounds exhibited high anticonvulsant activity. Thus compounds **12a**,**b** were tested for anticonvulsant activity in various doses using one or several seizure models.



12a,**b**

R^1 = Me, R^2 = Cl (**a**); R^1 = Cl, R^2 = NMe_2 (**b**).

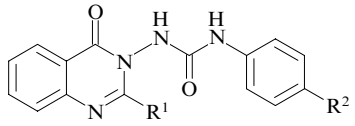
Another series containing a thiadiazole fragment instead of the oxadiazole fragment was evaluated for anticonvulsant activities in MES-induced seizures and scPTZ-induced seizure models (mice and rats, i.p. administration).[28,29] Compounds **13** showed anticonvulsant activity in one or more anticonvulsant test models.



13

R = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, *etc.*;
Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$.

In other works, the same authors investigated the anticonvulsant activities of a number of analogous quinazolinone derivatives containing an urea fragment instead of a heterocyclic fragment in position 3.[26,27] Compounds **14a**–**g** were active in the MES test, whereas compounds **14a**,**f**–**h** were active in the scPTZ test in mice. However, all compounds considered in these works showed more pronounced sedative-hypnotic and CNS depressant action than the anticonvulsant action, 2-phenyl substituted compounds having a higher CNS depressant activity as compared with 2-ethyl substituted compounds.



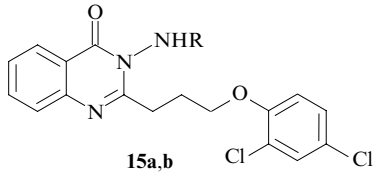
14a–**h**

R^1 = Et: R^2 = H (**a**), NO_2 (**b**), Me (**c**), OEt (**d**);
R^1 = Ph: R^2 = Cl (**e**), Br (**f**), NO_2 (**g**), OMe (**h**), *etc.*

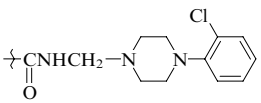
SAR studies of various quinazolinone derivatives showed that a substituted aromatic ring in position 3 and a methyl group in position 2 are required for a significant anticonvulsant activity of the compound. Substituted methyl group also supports anticonvulsant action; on replacement of the CH_3 group in position 2 by an alkyloxymethyl or alkylthiomethyl groups, the anticonvulsant activity was retained.

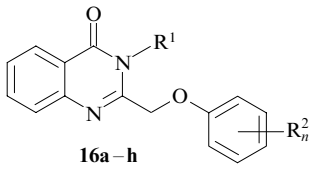
Non-competitive binding to AMPA receptors [AMPA is α-amino-β-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid] is considered as a possible mechanism of the anticonvulsant action of quinazolinone derivatives.[30] Some scientists believe that the proper quinazolinone nucleus is responsible for the anticonvulsant action. Thus substitution in positions 2 and 3 of Methaqualone produces CNS active agents.

The anticonvulsant activities of a number of 2,3-disubstituted quinazolinones were measured in the MES test.[30,31] Compounds **15a**,**b** demonstrated a noticeable activity;[31] therefore, subsequently a broad range of analogous derivatives **16a**–**h** were synthesized and studied.

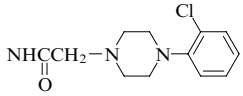


15a,**b**

R = H (**a**),  (**b**).



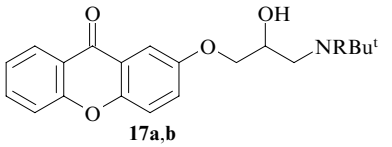
16a–**h**

Compound **16**	R^1	R^2_n
a	$C(=NH)NH_2$	2,4-Cl_2
b	$NHC(O)CH_2Cl$	2-Cl
c	$NHC(O)CH_2Cl$	2,4-Cl_2
d	$NHC(O)CH_2CH_2Cl$	H
e	$NHC(O)CH_2CH_2Cl$	2-Cl
f	$NHC(O)CH_2CH_2Cl$	2,4-Cl_2
g		H
h	$NHCH_2NHC_6H_4OMe$-4	2,4-Cl_2

Derivatives with different substituents in position 2 were arranged in the following activity series: 2,4-dichlorophenoxymethyl > 2-chlorophenoxymethyl > phenoxymethyl. Compound **16g** was an exception to this trend. The SAR studies confirmed the significance of 3-substitution in quinazolinone for manifestation of the anticonvulsant activity by a compound. Thus 3-(3-chloropropionamido) derivatives **16d,f** were more efficient that 3-chloroacetamido derivatives (for example, **16c**). Similarly, 3-carboxamidino and 3-hydroxy derivatives are more active than 3-amino derivatives. Generally, the studied compounds can be arranged in the following series in the order of decreasing anticonvulsant activity: **16f** > **16c** > **16b** ≈ **16h** > **16a** > **16e** > > **16d** ≈ **16g**.

IV. Xanthone derivatives

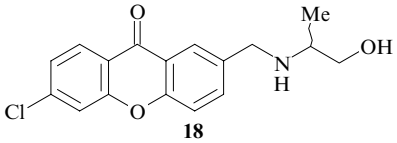
Marona and co-workers[36–43] reported some amino alcohols, derivatives of 9*H*-xanthen-9-one, having anticonvulsant activity. Compound **17a** showed high activity (PI 4.5) in the MES test in mice (i.p. administration); the reference drug Carbamazepine has PI of 4.9 in a similar test.[36]



17a,**b**

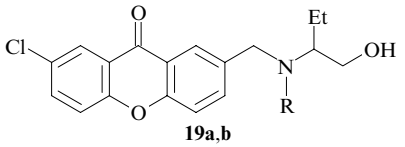
R = H (**a**), Me (**b**).

Another series of appropriate xanthone derivatives containing amino alcohol and amide fragments were evaluated for anticonvulsant activities in MES and scPTZ seizure tests. The most promising results were shown by 6-chloroxanthones. Among them, *R*- and *S*-enantiomers **18** displayed good anticonvulsant activity in the MES test (mice, i.p.), their protective index being 6.23 *versus* 6.85 shown by Phenytoin, Carbamazepine and Valproate drugs in this test.



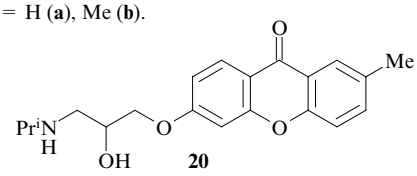
18

Derivatives **19a** showed ED_{50} of 56.2 mg kg^{-1} with PI of 5.84 in the same test. According to radioligand binding assays, compound (*S*)-**18** has an affinity to the BDZ receptors (BDZ is benzodiazepine) and to voltage-dependent Ca^{2+} channels. Most of compounds of these series showed excellent protection, mainly against MES-induced seizures, with low neurotoxicity.



19a,**b**

R = H (**a**), Me (**b**).



20

A number of xanthone derivatives with hydroxyalkylamino and aminohydroxyalkoxy substituents in positions 2, 3, 6 and 7 have also been evaluated for anticonvulsant activity in the MES and scPTZ tests. Some of the compounds were found to be active in both tests. Among 2-, 3- or 6-(3-amino-2-hydroxypropoxy) xanthene derivatives, promising results were obtained for compounds **17a,b** and **20**, compound **20** being active in both tests.

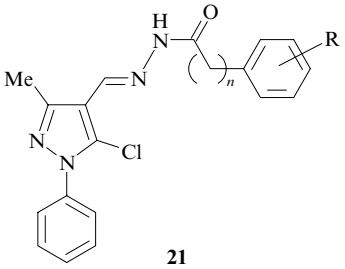
Compound	ED_{50} /mg kg^{-1}	PI
17a	42.2	1.9
17b	110.0	>4.5
20	173.45	0.80

7-Chloroxanthone derivatives with 2-amino or 2-*N*-methylaminobutan-1-ol fragments have shown noticeable anticonvulsant activity in the MES test in mice (i.p.). Note that both the racemate and the *R*-enantiomer of compound **19a** displayed fair anticonvulsant activity: the ED_{50} values in the MES test were 27 and 33.4 mg kg^{-1}, respectively, and the PI were 3.28 and 2.848, respectively.

Among derivatives of 6-methoxy- or 6-chloroxanthone, the highest anticonvulsant activity in the MES test in mice (i.p.) was found for compounds with the 2-aminopropan-1-ol, 1-aminopropan-2-ol and 1-aminobutan-2-ol fragments (their ED_{50} values ranged from 33.89 to 56.2 mg kg^{-1}).

V. Hydrazine derivatives

A series of acid hydrazide-hydrazones **21** have been synthesized.[44]

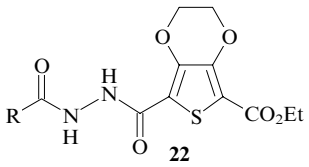


21

R = H, 4-Me, 4-OMe, 4-F, 4-Br, 4-Cl, *etc.*; n = 0–2.

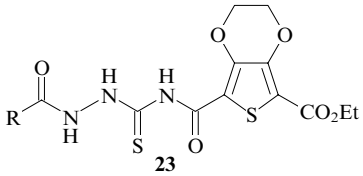
The synthesized compounds were evaluated for anticonvulsant activities against the MES- and scPTZ-induced seizure models in mice. Most of the compounds showed efficiency in the protection from seizures. However, some compounds demonstrated lower CNS depression and neurotoxicity compared to Phenytoin.[44]

The anticonvulsant activities (in the MES and scPTZ tests) of a series of hydrazine derivatives inclusing compounds **22** and **23** were studied.[45]



22

R = 2-thienyl, 2-naphthyloxymethyl, phenoxymethyl, 3-methyl-2-thienyl, *etc.*

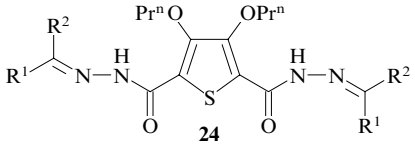


23

R = Ph, 2-naphthyloxymethyl, phenoxymethyl, 2-bromo-5-thienyl, *etc.*

These compounds were synthesized through the condensation of ethyl 7-(chlorocarbonyl)-2,3-dihydrothieno[3,4-*b*]-[1,4]dioxine-5-carboxylate with suitable hydrazides. The results of this study show that the substituted naphthyloxy derivatives have significant anticonvulsant activity in various seizure models. Furthermore, thenoylhydrazides substituted with a hetero-aromatic system exhibit improved activities than the rest of the compounds in the series. According to SAR studies, the methyl group in the peripheral ring is responsible for the superior activity of this compound in flexion and recovery phases, while bromo derivatives are most active against the generalized clonic seizure and the stupor stage.

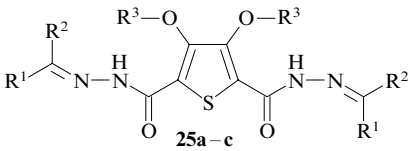
Yet another series of 3,4-dialkoxythiophene derivatives with two hydrazone substituents in positions 2 and 5 (**24**) were evaluated for their anticonvulsant action in MES and scPTZ models.[46] Compound **24** with R^1 = Me, R^2 = 2-thienyl was most potent among this series, and also showed low neurotoxicity. This activity was attributed to the presence of hydrophobic aryl fragments, NHCO groups capable of hydrogen binding and electron donating substituents in the central thiophene ring.



24

R^1 = H, Me; R^2 = Me, Bu^n, Ph, 2-thienyl, 2-Py, 4-Py, *etc.*

The same authors studied a series of analogous compounds **25** with various substituents in the thiophene ring and in the hydrazide fragments.[47]

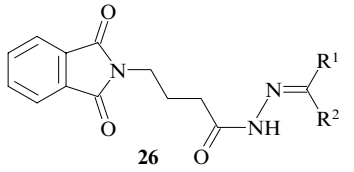


25a–c

R^1 = H, R^2 = 4-$O_2NC_6H_4$, R^3 = n-C_7H_{15} (**a**);
R^1 = Me, R^2 = 3-thienyl, R^3 = Pr^n (**b**);
R^1 = H, R^2 = 2-HOC_6H_4, R^3 = Pr^n (**c**), *etc*.

The anticonvulsant activities were studied using MES and scPTZ tests and psychomotor seizure test at 6-Hz (6 Hz test) (i.p.). Compound **25a** demonstrated clear-cut activity with no neurotoxicity. A systematic screening of compounds with varied substituents in positions 3 and 4 of the thiophene ring and the terminal substituent in the hydrazide fragments for the antiepileptic activities was performed. Amongst the tested models, the 6 Hz screening results were promising. Compounds **25b**,**c** came out as potential candidates for further investigations. It was concluded that increase in the hydrophobicity of molecules entails the enhanced anticonvulsant activity in this series. According to SAR studies, the 3,4-dialkoxythiophene central fragment is responsible for the broad spectrum of antiepileptic activities, while changes in the peripheral rings influence the activity and toxicity of the corresponding derivatives.

Ragavendran *et al.*[48] reported the synthesis of hydrazones based on γ-aminobutyric acid (GABA) hydrazides **26** and evaluation of their anticonvulsant activities in different animal models of epilepsy including MES and scPTZ tests and subcutaneous strychnine-induced (scSTY) and intraperitoneal (i.p.) picrotoxin-induced seizure tests.

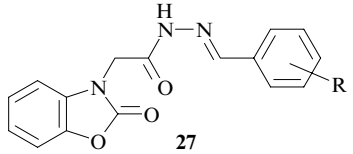


26

R^1 = H, Me, Et, Ph; R^2 = Me, Ph, 2-HOC_6H_4, 4-HOC_6H_4, 4-MeC_6H_4, 3-$O_2NC_6H_4$, *etc*.

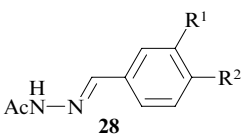
γ-Aminobutyric acid is the principal inhibitory neurotransmitter in the mammalian brain. Some hydrazones based on GABA hydrazides were effective as anticonvulsant agents in various seizure models.[48]

New hydrazones **27** were synthesized and their anticonvulsant activity was assessed in the scPTZ test.[49] The compound with R = 4-F proved to be most active.

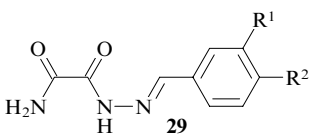


27

A series of new hydrazones were studied by Dimmock *et al.*[50] Acetylhydrazones **28** demonstrated high anticonvulsant activity, while oxamoylhydrazones **29** were less active.



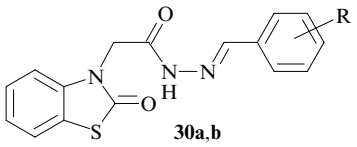
28



29

A broad range of acetylhydrazones, oxamoylhydrazones and semicarbazones of aromatic aldehydes and related compounds were evaluated in the MES and scPTZ tests (mice, i.p.). These compounds showed rapid action and superior protection in the MES anticonvulsant screening. Detailed studies of structure–property relationship showed that the fragment responsible for hydrophobic binding may accommodate groups other than aromatic rings. In addition, acetylhydrazones were found to provide greater protection in the MES tests than oxamoylhydrazones due to the higher negative charge on the oxygen atom.

A number of *N*-substituted hydrazones of benzaldehyde were evaluated for anticonvulsant activity.[51] Compounds **30a**,**b** were found to be most promising.



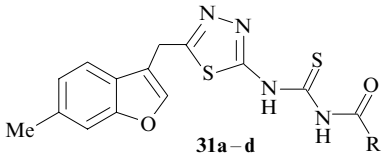
30a,**b**

R = 4-Me (**a**), 2-OH (**b**).

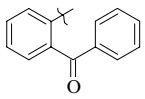
Darias *et al.*[52] also reported the anticonvulsant activities of some aryl- and heteroarylsulfonylhydrazones. It was noted[53] that as regards the anticonvulsant activities in the MES test, the hydrazones of benzenesulfonylhydrazide are comparable with valproic acid.[53] Anticonvulsant activities were also identified[54] for the hydrazones of some heterocyclic aldehydes.

VI. Thiazole and thiadiazole derivatives

Among substituted thiazole and thiadiazole derivatives, many compounds proved themselves as having significant anticonvulsant activity.[55–64] A series of disubstituted 1,3,4-thiadiazoles **31a–d** were evaluated for the anticonvulsant activity.



31a–d

R = 2-ClC_6H_4 (**a**), 4-$O_2NC_6H_4$ (**b**), 2-naphthyl (**c**),  (**d**).

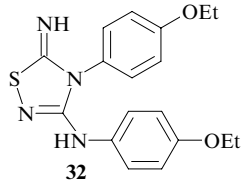
The results of this study confirmed that the pharmacophore model with four binding sites is crucial for the anticonvulsant activity. The structure–activity relationship studies demonstrated that the anticonvulsant activity of test compounds changes on varying the *p*-substituent in the aryl moiety, the activity series being as follows: OH > OMe > > NO_2 > Cl. Compounds with the substituted phenyl ring (**31a**,**b**) were more active than compounds with the naphthyl or benzoylphenyl group (**31c**,**d**). The decrease in the activity was attributed to the increase in the lipophilicity of the aromatic hydrophobic binding site. It is noteworthy that improved anticonvulsant activity of compounds **31a**,**b** is caused by the additional van der Waals interaction of the binding site upon substitution in the benzene ring.[55]

Gupta *et al.*[56] reported screening of some substituted thiadiazoles for anticonvulsant activity. Most of the compounds showed protection against MES seizures in rats

(i.p.) at higher doses. All of the synthesized compounds were more active in the MES test than in the scPTZ test and exhibited the ability to reduce tonic–clonic seizures.

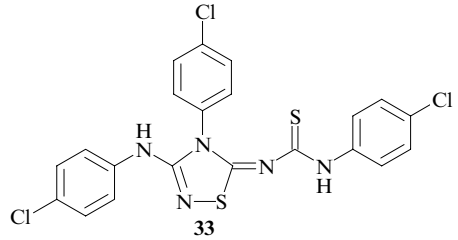
1,3,4-Thiadiazole derivatives containing a quinazolinone fragment in position 2 (instead of the benzofuran fragment in compounds **31**) were evaluated for the anticonvulsant activity (MES and scPTZ tests)[29] (see compounds **13** in Section III).

4-Aryl-3-arylamino-5-iminothiadiazolines were studied[57] for the anticonvulsant activities in the MES and scPTZ tests in mice. Many members of this series exhibited one or another type of anticonvulsant activity. Most of compounds were efficient in the MES test, while one derivative (**32**) proved active in the scPTZ test.



32

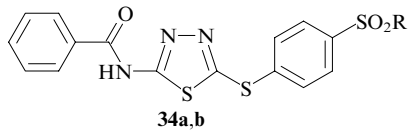
Siddiqui *et al.*[57,58] reported good anticonvulsant activity of some 1,2,4-thiadiazole derivatives. Compound **33** with *para*-chlorophenyl substituents showed the highest activity in the MES test and moderate activity in blocking the strychnine-induced seizures, whereas other compounds of the series were less active.[57]



33

A number of 1,3,4-thiadiazole derivatives with a dihydropyrimidinone fragment as substituent in position 2 were evaluated for anticonvulsant activity in rodents.[57]

Pattanayak *et al.*[59] reported some 2-amino-5-sulfanyl-1,3,4-thiadiazole derivatives that exhibited anticonvulsant, antidepressant and anxiolytic activities. Compounds **34a**,**b** exhibited excellent anticonvulsant activity in comparison with the reference drug Phenytoin.

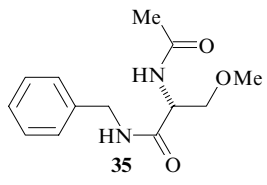


34a,**b**

R = Cl (**a**), NH_2 (**b**).

VII. Miscellaneous compounds

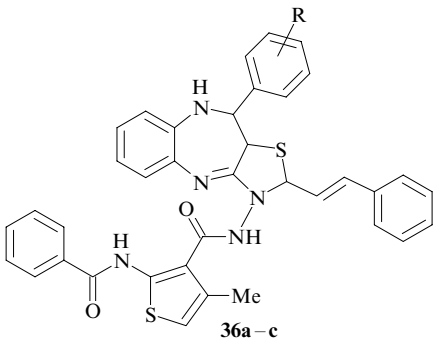
The anticonvulsant screening of some substituted propionamides in the MES and scPTZ tests was reported.[65–68] The best results were found for compound **35** [(*R*)-lacosamide].



35

The SAR studies of a number of derivatives with an *N*-benzyl group showed that compounds containing non-bulky substituents exhibit superb anticonvulsant activities irrespective of the electronic properties of the substituents. The screening of derivatives with various groups in position 3 revealed that the presence of a small, non-bulky 3-alkoxy group ensures the greatest seizure protection (mice, i.p.), the efficiency increasing upon the decrease in the substituent size. Some structural modifications concerning the benzyl and methoxy substituents do not reduce the anticonvulsant properties of compounds. The replacement of the alkoxy group in position 3 by phenoxy group considerably reduces the activity of compounds in the MES test. Note that none of the studied compounds of this series was active in the scPTZ test.

The anticonvulsant activity of benzodiazepines can be associated with the γ-aminobutyric acid (GABA) mediated synaptic inhibition. Many anticonvulsant drugs are known to act by increasing the GABA level in the brain. A series of substituted benzodiazepines fused with thiazolidine were evaluated for the anticonvulsant activity.[69]



36a–c

R = 2-OH (**a**), 4-OMe (**b**), 4-F (**c**).

Compounds **36a**,**b** exhibited significant anticonvulsant activity on intraperitoneal administration. The 2-OH and 4-OMe substituents in the phenyl ring located in position 10 of the thiazolidinobenzodiazepine system (compounds **36a** and **36b**, respectively) are crucial for the anticonvulsant action. According to SAR studies, the presence of a small polar electron-enriched group contributes significantly to the anticonvulsant activity, while an electronegative substituent (compound **36c**) reduces the efficiency with respect to the locomotor activity. Finally, the presence of the thiazolidine ring is exceptionally important for manifestation of the anticonvulsant activity by compounds of this series.

VIII. Conclusion

This review surveys numerous investigations concerning the development of novel chemical agents for treatment of diverse forms of epilepsy. Various chemical classes of compounds were extensively studied against various seizure models to evaluate their efficiency and identify the possible side effects. For a number of reported potential structures, structure–activity relationships were studied systematically to elucidate the effects of substituents in different positions of the structural nucleus on the anticonvulsant activity. Most of the compounds have been evaluated in accordance with the Antiepileptic Drug Development Program of the National Institutes of Health, USA, and the anticonvulsant activity has been confirmed through various *in vivo* screening tests in rodents. Nevertheless, the specific mechanism of

action for most of the compounds is still unclear. This review will be useful for researchers who are engaged in the development of new anticonvulsant agents by the rational structural modification of existing compounds or consider some specific objectives through modification of the target of the anticonvulsant agents. A large pool of chemically and structurally diverse classes of compounds (active leads) discussed in this review would assist the scientists in the establishment of the precise mechanism of action for new anticonvulsant agents in the future. Certainly, these new compounds should surpass the existing ones in safety, tolerability and pharmacokinetic parameters.

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