Current Neuropharmacology, 2022, *20*, 1519-1553

REVIEW ARTICLE

Overview of Chemistry and Therapeutic Potential of Non-Nitrogen Heterocyclics as Anticonvulsant Agents

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ARTICLE HISTORY

Received: May 28, 2021
Revised: June 14, 2021
Accepted: July 20, 2021

DOI:
10.2174/1570159X19666210803144815

Abstract: Epilepsy is a chronic neurological disorder, characterized by the predisposition of unprovoked seizures affecting the neurobiological, psychological, cognitive, economic, and social well-being of the patient. As per the 2019 report by World Health Organization, it affects nearly 80% of the population, which comes from middle to low-income countries. It has been suggested that 70% of such cases can be treated effectively if properly diagnosed. It is one of the most common neurological diseases affecting 50 million people globally. Most of the antiepileptic drugs used in clinical practice are only 60-80% effective in controlling the disease. These drugs suffer from serious drawbacks of non-selectivity and toxicity that limit their clinical usefulness. Hence, there is a need to search for safe, potent, and effective anti-epileptic drugs. One of the emerging strategies to discover and develop selective and non-toxic anticonvulsant molecules focuses on the design of non-nitrogen heterocyclic compounds (NNHC). Drugs such as valproic acid, gabapentin, viagabatrin, fluorofelbamate, tiagabine, progabide, pregabalin, gamma amino butyric acid (GABA), *etc.* do not contain a nitrogen heterocyclic ring but are as effective anticonvulsants as conventional heterocyclic nitrogen compounds. This review covers the various classes of NNHC which have been developed in the recent past as anticonvulsants along with their chemistry, percentage yield, structure-activity relationship and biological activity. The most potent compound in each series has been identified for comparative studies, for further structural modification and to improve the pharmacokinetic profile. Various optimized synthetic pathways and diverse functionalities other than nitrogen-containing rings discussed in the article may help medicinal chemists to design safe and effective anticonvulsant drugs in near future.

Keywords: Non-nitrogen heterocyclics, anticonvulsant, amide, GABA, epilepsy, structure activity relationship, antiepileptic drugs.

1. INTRODUCTION

Epilepsy is characterised as a chronic non-communicable disease of the brain. According to the WHO survey, around 50 million people worldwide suffer from epilepsy. Every year, approximately five million people are diagnosed with epilepsy. The rate of epilepsy occurrence also depends upon the income of the countries. The prevalence of epilepsy is much higher in the low-income countries (49 per 10000) rather than the middle-income countries (139 per 100000). This is likely because of the expanded danger of endemic conditions like jungle fever (malaria) or neurocysticercosis; the higher frequency of street traffic wounds; birth-related injuries; and varieties in the clinical foundation, the accessibility of preventive well-being programs, and available consideration [1]. Epilepsy is the fourth most regular neurological disease after headaches, stroke, and Alzheimer's affecting nearly 1% of the world population and is one of the common neurological problems [2]. Epilepsy is considered recurrent seizure attacks with or without the loss of consciousness. The pathophysiology of epilepsy is very complex and still unknown. Many diseases can lead to the development of epilepsy. The reasons for epilepsy are partitioned into the accompanying classifications: structural, infectious, metabolic, genetic, immune, and unknown. In 2017, the International League against Epilepsy (ILAE) updated its classification of seizures from two to three, a change dependent on three key highlights of seizures: *i.e.,* seizures start in the mind, level of awareness during the course of seizure, and other highlights of the seizures, like motor skills and auras [3]. Seizures can be controlled with the help of medication in 70% of cases [4]. In contrast, most antiepileptic drugs are in limited use because of their toxicity and are effective in only 60-80% of patients [5-8]. Herbes *et al.* suggested that the alkyl derivatives of nitrogen heterocyclic compounds

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1875-6190/22 $65.00+.00

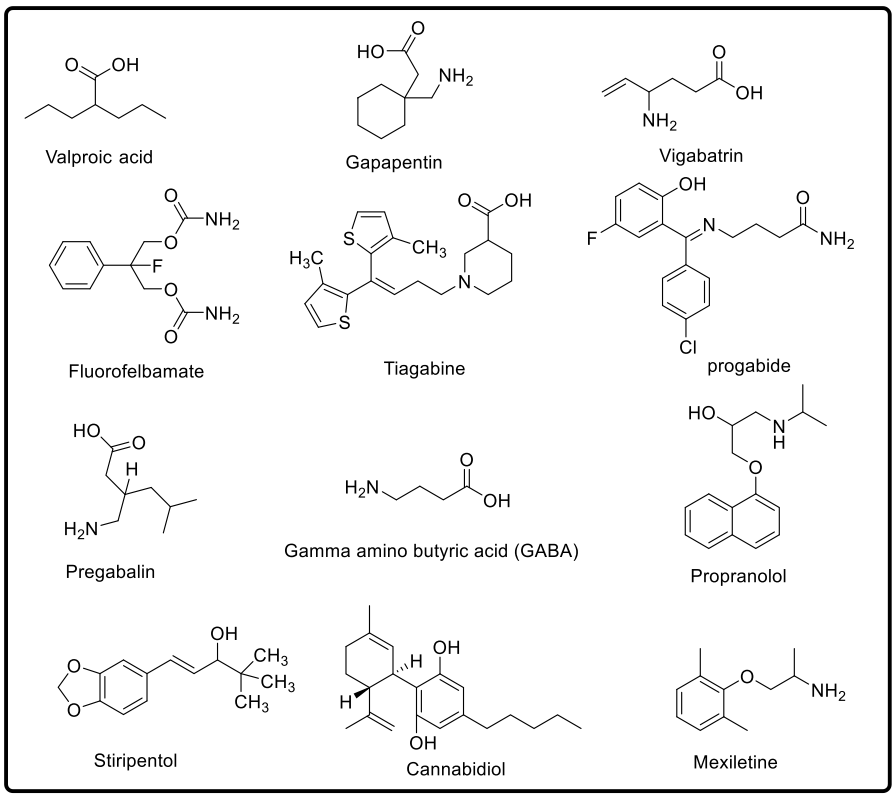


Fig. (1). The compounds showing non-nitrogen heterocyclic rings having anticonvulsant actions.

displayed environmental risk [9]. These compounds also increase the biological degradations [10]. The newer drugs, such as lamotrigine, topiramate, felbamate, and levetiracetam are approved antiepileptic drugs but are not as effective as established antiepileptic drugs (AEDs) [11]. Further, the currently used clinical drugs are associated with various side effects such as ataxia, gingival hyperplasia, hirsutism, megaloblastic anaemia, and gastrointestinal disturbances [12, 13]. It is a challenging task for a medicinal chemist to design and synthesize more effective, optimized pharmacokinetic profile, low dose, and safer antiepileptic drugs. Most of the available clinically effective anticonvulsant drugs have a nitrogen heterocyclic ring system containing a carbonyl group with a hetero-aromatic or aromatic system [7]. The drugs with 5 membered-heterocycles such as oxadiazole, thiadiazole, triazole are well known in literature [6, 14-17]. However, there are a large number of chemical groups apart from nitrogen-containing rings that show potent anticonvulsant action and are effective in various seizures [18]. One such example is amide and its derived cyclized form which is present in most of the anticonvulsant drugs right from phenytoin to recently approved cenobamate (sold under brand name Xcopri) are used to treat partial-onset seizures in adults. Another recently approved drug by FDA includes brivaracetam and stiripentol. Drugs such as valproic acid, gapapentin, viagabatrin, fluorofelbamate, tiagabine, progabide, pregabalin, gamma amino butyric acid (GABA) *etc.*, do not contain a nitrogen heterocyclic ring but are equally effective as a potent anticonvulsant. The other non-nitrogen containing drugs class such as propranalol and mexilitene possess anticonvulsant action by stabilizing the neuronal cellular membrane potential [8] (Fig. **1**). Some patent details on compounds other than nitrogen-containing rings as anticonvulsants are represented in (Table **1**). In the last decade, various research groups have published excellent review on the design from the pharmacophore of the established anticonvulsant, synthesis, and their biological evaluation as AEDs. Grover *et al.* published a very detailed review article on the nitrogen-containing heterocycles as anticonvulsant and AEDs along with their biological and medicinal importance [14]. Perhaps in the last two decades, there is no published review or article on the non-nitrogen heterocyclics or aliphatic groups in the development of anticonvulsant agents. The importance of non-nitrogen heterocyclics in the development of AEDs is to reduce the side effects associated with the nitrogen-containing heterocycles, low dose, and to produce the desired amount of therapeutic potential. The newer anticonvulsant compounds were designed and synthesized from the pharmacophoric groups present in the existing drugs. The designed drugs were further validated by the hypothesis suggested by Dimmock's *et al.* parameters *i.e.,* having aryl hydrophobic unit (R), electron donor group (D), and hydrogen bonding domain (hydrogen acceptor and hydrogen donor) [19]. In this review, it is of interest to include amides, amines, sulphonamides, and furan-containing compounds as an anticonvulsant.

This review explicitly covers the design strategies, synthesis, SAR, and the anticonvulsant potential of the non-nitrogen-containing compounds reported by various researchers in the past decade (2010-2020) as a promising class of anticonvulsant agents. Thus, this review may fulfill the existing gap and will prove to be useful to the various researchers working on groups other than nitrogen-containing rings to develop anticonvulsant agents.

Table 1. Some patent details on compounds other than nitrogen-containing rings as an anticonvulsant.

Sr. No.	Title	Inventors	Patent No.
1.	New anticonvulsant drugs	Susanna Askanazovna, Inessa Ivanovna	WO1999023056A1 [20] https://patents.google.com/patent/WO1999023056A1/en
2.	Process for the synthesis of antiepileptic drug lacosamide	MuthukrishnanMurugan, Mohammad Mujahid, Prashant Pramod Mujumdar	US20140012044A1 [21] https://patents.google.com/patent/US20140012044A1/en
3.	Active derivative of valproic acid for the treatment of neurological and psychotic disorders and a method for their preparation	Meir Blaler, Boris Yagen, Niv Papo	US6323365B1 [22] https://patents.google.com/patent/US6323365B1/en
4.	Synthesis and biological studies of an isomeric mixture of (E/Z) isoxylitones and its analogues	Atta-ur Rahman, M. Iqbal Choudhary, Farzana Shaheen, Shabana Usman Simjee, Noureen Kahn, Saima Mahmood Malhi, Syed Uzair Ali Shah, MuhammadNadeem Ashraf	US20140221682A1 [23] https://patents.google.com/patent/US20140221682A1/en
5.	Imepitoin for use in treating epileptic disorders in a feline	OdiloRandolf Engel, Annalena Michel, Frerich De Vries	EP3122361A1 [24] https://patents.google.com/patent/EP3122361A1/en
6.	Anticonvulsant sulfamate derivatives	Bruce E. Maryanoff, Joseph F. Gardocki	US4513006A [25] https://patents.google.com/patent/US4513006A/en
7.	Certain barbituric acid derivatives used as anticonvulsant agents	Carlos M. Samour, Julius A. Vida	US4046894A [26] https://patents.google.com/patent/US4046894A/en
8.	1-aryl-5-(2-oxo-1-pyrrolidinyl)-1,2,3-triazolines as novel anticonvulsants	Pankaja K. Kadaba	US4820721A [27] https://patents.google.com/patent/US4820721
9.	Phospholipid derivatives of valproic acid and mixtures thereof	Alexander Kozak	US20040033987A1 [28] https://patents.google.com/patent/US20040033987A1/en
10.	Amide derivatives of valproic acid and uses thereof	Meir Bialer, Boris Yagen, Dan Kaufmann, Marshall Devor	US8829242B2 [29] https://patents.google.com/patent/US8829242B2/en
11.	Fructose 1,6 bisphosphate - a novel anticonvulsant drug	Xiao-Yuan, Lian, Janat, L. Sringer	US20100197610A1 [30] https://patents.google.com/patent/US20100197610A1/en
12.	Hydrazones, hydrazines, semicarbazones and thiosemicarbazones derived from pyridyl ketones as anticonvulsant drugs and excitatory amino acid antagonists	Pankaja K. Kadaba, Zhaiwei Lin	US5942527A [31] https://patents.google.com/patent/US5942527A/en
13.	Anticonvulsant activity of turmeric oil and bisabolene sesquiterpenoids	Peter A. M. De Witte, Camila V. Esguerra, Alexander D. Crawford, Adriana Monserrath Orellana Paucar	US9782361B2 [32] https://patents.google.com/patent/US9782361/fi
14.	Use of cannabidiol in the treatment of epilepsy	Geoffrey Guy, Stephen Wright, Alice Mwad, Elizabeth Thiele	US20160166514A1 [33] https://patents.google.com/patent/US20160166514A1/en_2
15.	Rufinamide and derivatives and their use in modulating the gating process of human voltage-gated sodium channels	Frank Bosmans	WO2014120994A1 [34] https://patents.google.com/patent/WO2014120994A1/zh
14.	Oleamide in epilepsy	George Lees	WO2001035939 [35] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2001035939
15.	Hesperidin for the treatment of epilepsy, migraine, schizophrenia, depression and drug abuse	Wilfried Prof. Dr. Dimpfel	EP1721613A1 [36] https://patents.google.com/patent/EP1721613A1/fr
16.	Ambroxol for treating epilepsy	Thomas WeiserWolfram GaidaKlaus Klinder	EP1648436A1 [37] https://patents.google.com/patent/EP1648436A1/sv

2. SYNTHETIC PATHWAY OF NON-NITROGEN HETEROCYCLIC COMPOUNDS AS POTENTIAL ANTICONVULSANT AGENTS

2.1. Amides

Amide is an important functional group that has been known to play an important role in drug design and discovery. It has been widely used for the synthesis of medicinal compounds. Amide functionality of aromatic systems, such as benzamides *e.g.* metoclopramide and clebopride show neuroleptic properties by blocking dopaminergic receptors [38]. Apart from common heteroaromatic fragment imide attached with alkyl or phenyl such as phenytoin and ethosuximide and few newer anticonvulsants such as levetiracetam, seletracetam and brivaracetam are observed for side-chain amide groups [39]. The *N*-palmitoylethanolamide (PEA) was tested for anticonvulsant effect on electroshock induced convulsion in mice. The amide was found to show dose-dependent protection at non-toxic doses [40]. Guan *et al.* synthesized a series of *N*-(2-hydroxyethyl)amide derivatives and evaluated them for their anticonvulsant activity by using the maximal electroshock (MES) test. The compounds were prepared in a one-step reaction by using trimethylamine, methyl chloroformate, carboxylic acid, and ethanolamine at room temperature about 8-10 h in high yield (Scheme **1**). The methyl chloroformate helps in introducing the methoxycarbonyl group and then its attack and removal from ethanolamine to form a final amide bond. The percentage yields of most active compounds **1**, **2**, and **3** were found to be 81, 82, and 81%, respectively. Among the compound *N*-(2-hydroxyethyl)decanamide **1**, *N*-(2-hydroxyethyl) palmitamide **2**, and *N*-(2-hydroxyethyl)stearamide **3** were found to possess potent anticonvulsant activity with an ED_{50} value of 22.0, 23.3, and 20.5 mg/kg and protective index of 27.5 > 42.9 > 48.8. The compounds showed lower toxicity as compared to standard drug valproate. The compounds showed strong antagonistic activity against seizures induced by the 3-mercaptopropionic acid, bicuculline, and thiosemicarbazide. The results further confirmed that it inhibits GABA-α-oxoglutarate aminotransferase (GABA-T) and activates the glutamate decarboxylase (GAD) [40]. The typical amide formation using EDC/HOBt has been reported by Rafiei *et al.* The group synthesized a series of phthalimide-4,5-dihydrothiazole-amide derivatives and screened them for antiepileptic activity against the pentylenetetrazole (PTZ)-induced seizures in mice. Phthalimide-4,5-dihydrithiazole-amide derivatives were prepared by the nucleophilic substitution, cyclization, and amidation reaction. Initially, potassium phthalimide **(a)** was reacted with chloroacetonitrile **(b)** in the presence of DMF to yield the compound **(c)**. The second step involves the reaction of cysteine and compound **(c)** in the presence of solvent buffer (prepared by taking sodium bicarbonate and hydrochloric acid) to give the compound **(d)** (4-5-dihydrothiazole ring). Finally, to obtain the desired final product *i.e. N*-(4-chlorophenyl)-2-((1,3-dioxoisoindolin-2-yl)methyl)-4,5-dihydrothiazole-4-carboxamide) **4**, amidation reaction was carried out between compound **(d)** and 4-chloroaniline (Scheme **2**). The synthesis of these derivatives was performed under highly specified conditions with pH = 2 and good yields were found after the amidation in the final step of the reactions *i.e.,* 65%. Among the synthesized, compounds **4**; *N*-(4-chlorophenyl)-2-((1,3-dioxoisoindolin-2-yl)methyl)-4,5-dihydrothiazole-4-carboxamide was found to be most potent which possesses more protective effect than thalidomide ($P < 0.05$) with zero mortality in PTZ test. Docking studies of compound **4** using autodock tools (ver. 1.5.6) further validate the *in vivo* activity and showed binding deep inside the pocket of the $GABA_A$ receptors as compared to the standard drug thalidomide [41]. A similar approach was undertaken by Hassan *et al.* in benzothiazole amide derivatives synthesis. They synthesised a series of *N*-(substituted benzothiazole-2-yl)amide derivatives and screened them for anticonvulsant activity against the MES and scPTZ. Friedel craft acylation of benzene with succinic anhydride in the presence of Lewis acid gives 4-oxo-4-phenylbutanoic acid in the first step and then it was coupled with substituted-2-aminobenzothiazoleto to form an amide bond. The reaction was performed with the help of EDC, HOBT in DCM for the generation of activated acyl compound (*in-situ)* and then reacted with substituted-2-aminobenzothiazole to yield the desired product *N*-(6-methoxybenzothiazol-2-yl)-4-oxo-4-phenylbutanamide **5** with 72% yield (Scheme **3**). Compound **5** exhibited the most potent anticonvulsant activity and protected against the seizures in the MES test with an ED_{50} value of 40.96 mg/kg whereas, in scPTZ the ED_{50} value was 85.16 mg/kg. The compound was effective at a dose of 30 mg/kg dose after 0.5 and 4.0 h of the administration. The result indicated the compound showed quick onset of action and prolonged action at a lower dose. The protective index of the compound for MES and scPTZ is 8.4 and 4.0. The compounds showed GABA-mediatory action that might be due to the molecular hybridization of the lipophilic benzothiazole ring system. Molecular docking was carried out by using Maestro 9.0 program (Schrodinger Inc. USA) and the compound showed strong hydrogen bond interaction reasoned being is that the delocalization of lone pair of nitrogen in amide bond and CH-π interaction due to benzothiazole ring [42]. Compared to thionyl chloride a much better approach is the use of CDI in the preparation of urea dipeptides because carbonylimidazole is much easily handled and it also avoids side-reaction due to its lower reactivity. Compound **5** was also evaluated for mechanistic study using GABA estimation assay and results revealed that **5** increased the GABA level by18 fold than the control group [43]. The use of CDI for amide formation is utilized by Kayal *et al*., in the year 2019 for the synthesis of a series of 2-(2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl) acetamide and evaluated for their anticonvulsant activity against PTZ induced seizures in mice. The derivatives were synthesized by reacting methyl 2-isothiocyanatobenzoate **(a)** and glycine **(b)** in the presence of base triethylamine and solvent isopropanol to give compound 2-(4-oxo-2-thioxo-1,4-dihydroquinazolin-3(2*H*)-yl) acetic acid **(c)**. The compound **(c)** on oxidation with hydrogen peroxide gives the compound 2-(2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl) acetic acid **(d)**. The last step is the coupling of the compound 2-(2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl) acetic acid **(d)** with corresponding amines **(f)** in the presence of *N*,*N*-carbonydiimidazole **(e)** in solvent dioxane to obtain the final product 2-(2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)-*N*-substituted-acetamide (Scheme **4**). The compounds **6**, **7**, **8** and **9** were obtained in good percentage yields with 82, 75, 82 and 78%, respectively better than earlier methods of direct amide cyclization to peptides using anthranilic acid. The compounds **6, 7, 8, 9** possess potent anticonvulsant activity with 40.0%, 33.3%,

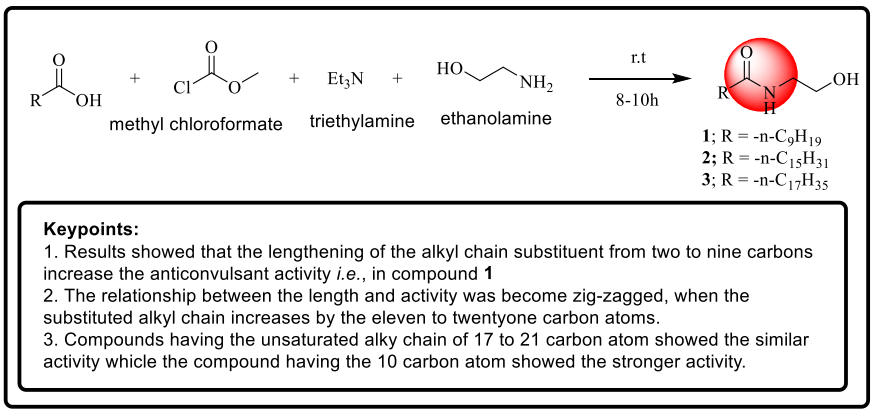
40.0%, and 0% lethality at the dose of 100 mg/kg. Compound **9** showed zero percent lethality and was superior to sodium valproate. Docking studies of the potent compounds were carried out using SCIGRESS software (Fujitsu, Fukuoka, Japan (license 742F6852C191) and the compounds showed the best affinity inside the receptors (PDB 4COF, 3F8E and 1 EOU). The presence of an aromatic ring increases the lipophilicity of the compounds and facilitates their penetration through the blood-brain barrier [44]. Ibrahim *et al.,* introduced thiosemicarbazide carbonyl after reacting acetohydrazide with phenylisothiocyanate. The group synthesized a series 2-(3-methyl-2-oxoquinoxalin-1(2*H*)-yl)-*N*-(4-substitutedphenyl) acetamides derivatives and screened them for their anticonvulsant activity against PTZ induced convulsions in mice. Initially, *ortho*-phenylenediamine was reacted with sodium pyruvate to afford 3-methylquinoxalin-2(1*H*)one and then converted into potassium salt on treatment with alcoholic potassium hydroxide. On heating, the potassium salt with ethyl-4-(2-chloroacetamido)benzoate gave the ethyl ester derivatives **(a)**. The reaction of ethyl ester **(a)** with hydrazine hydrate afforded intermediate *N*-(4-(hydrazinecarbonyl)phenyl)-2-(3-methyl-2-oxoquinoxalin-1(2*H*)-yl)acetamide **(b)**. Finally, the reaction of intermediate **(b)** with acetic anhydride and isothiocyanates produced thiosemicarbazide derivative **10** with a 75% yield. Condensation of intermediate **(b)** with substituted aromatic aldehydes gives Schiff's bases **11** with 80% yield (Scheme **5**). All the synthesized compounds showed good to moderate anticonvulsant activity. Among them, compounds **11** and **10** showed the most potent activity with an ED_{50} value of 75 mg/kg for both the compounds with 83% protection (compound **10**) and 100% protection (compound **11**) at a dose of 200 mg/kg. The potency of the compounds was 0.33 and 0.32 and was noted to be higher than standard phenobarbital sodium [45]. Another procedure for the synthesis of a series of *N*-substituted 2-anilinophenylacetamides was reported by Shindikar *et al.* Compound **12** was recrystallized using ethanol and dark brown crystals to produce 53.62% yield. The final compounds were synthesized *via* two pathways shown in Scheme **6**. Path A yields 43% of 2-[2-(phenylamino) phenyl] acetic acid whereas, path B yields 85.5%. Path B is more efficient in terms of cost and number of steps. The compounds were screened for anticonvulsant activity in swiss albino mice by MES and scPTZ induced seizures tests. All the synthesized compounds were found to be potent among which compound **12** demonstrate the most potent anticonvulsant with an ED_{50} value of 24.0 mg/kg. Compound **12** showed the absence of neurotoxicity in the rotarod test with a high protective index of 20.3 as compared to standard (Scheme **6**) [46]. The previously trained animals were made to balance the accelerating rod at test dose of 30, 100 and 300 mg/kg after 0.5 and 4 h of time interval in rotarod test. The animals were placed in rotarod of 3.2 cm diameter rotating at 10 rpm. The inability to balance was checked for minimum 1 min and the dose at which 50% of the animal not able to balance indicates motor impairment [47]. Introduction of amide group by the removal of methanol after condensation reaction of ester with ammonia was performed by Ghidini *et al.* The intermediates (ester derivative) were decontaminated by trituration using such solvent as methanol and further liquified in an ammonia solution (conversion of ester into amide take place). Compounds **13** (40%), **14** (45%) and **15** (48%) were obtained in moderate to good percentage yields. With this a series of aminoacetamides was synthesized and screened for anticonvulsant activity against electrical and chemical stimuli induced convulsions in mice (Scheme **7**). The compounds containing a bicyclic (tetralinyl, indanyl) group linked to aminoacetamide chain were found to be potent. Among all the synthesized, compounds **13, 14,** and **15** were observed to be the most potent anticonvulsant activity with an ED_{50} value of 43, 36 and 21 mg/kg. For the mechanistic study radioligand [^{3}H] batrachotoxin using rat brain (voltage-gated sodium channel binding assay) was performed for compounds **13**, **14** and **15**. The results revealed **15** to exhibit noteworthy activity with K*i* = 8.8 μM [48].

2.2. Chalcone

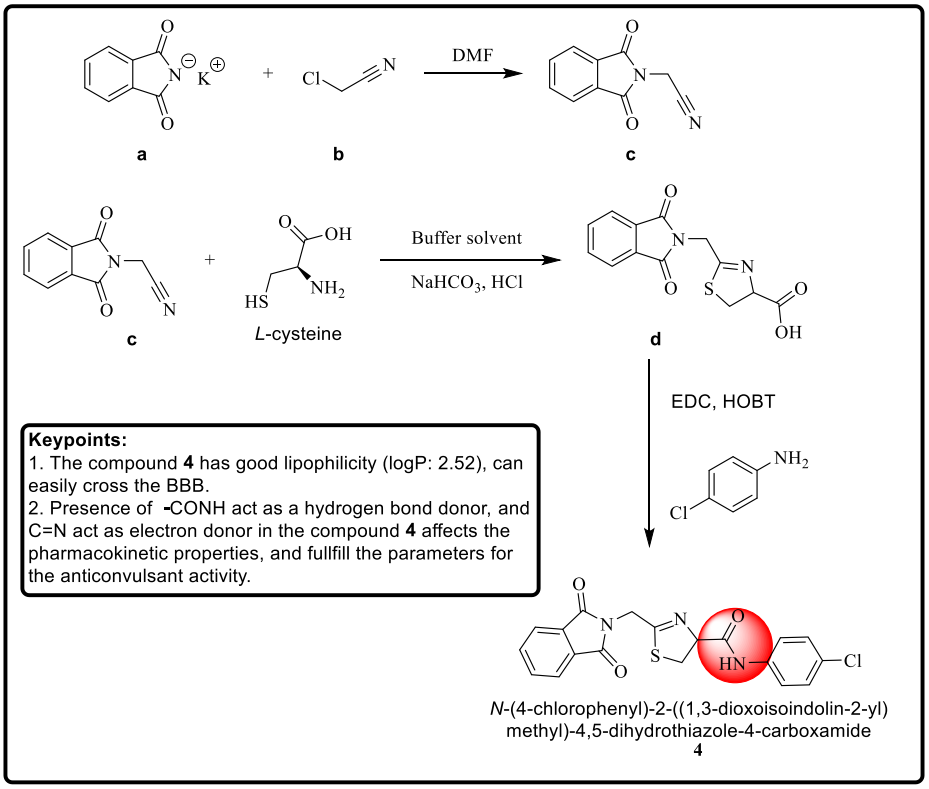
Chalcone serves as the backbone for the synthesis of a variety of heterocyclic compounds. The synthesized chalcones and their conversion into different derivatives remain always attractive methods for the medicinal chemist to design compounds of medicinal importance. Sudhakararao *et al.*, in the year 2015 synthesized a series of chalcone-based pyrazoline compounds and screened them for anticonvulsant activity by using MES. Among them, compound **16** with a percentage yield 73% was found to be the most potent anticonvulsant compound in the series. Compound **16** showed 100.43% protection in the MES test with 65.68% potency [49] (Scheme **8**). Chalcone with semicarbazone has been investigated for anticonvulsant potential by Singh *et al.*, using standard MES test. Among them, compound **17** with 65 % yield was found to be the most potent anticonvulsant at the dose of 100 mg/kg after 0.5h and 300mg/kg after 4h in MES and scPTZ study. The compound showed a 373 mean ± SEM activity score after 24 h at the dose of 30 mg/kg. The compound showed 100% protection in the MES test. In the neurotoxicity test compound **17** was found to be non-toxic [50] (Scheme **9**).

2.3. Coumarin and Flavones

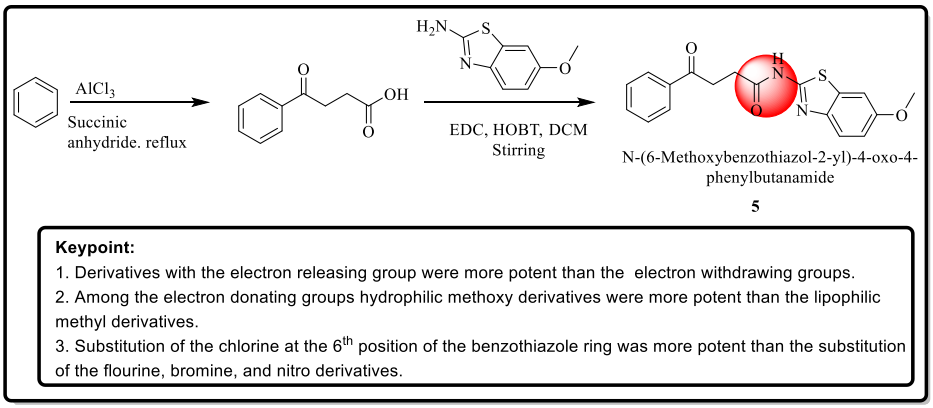
Coumarin ring system contains 2*H*-chromen-2-one and occurs naturally in various natural products. It is also found in the drug warfarin which is used as an anticoagulant. Some studies have demonstrated coumarin derivatives for their possibility as a supportive treatment for epileptic seizures [51]. A good result of acridone-based 1,2,4-oxadiazole derivatives by Khanaposhtani *et al.* in the year 2016 synthesized another series of coumarin-1,2,4-oxadiazole hybrids in the year 2019 [6]. The compounds were checked for anticonvulsant properties against PTZ and MES-induced seizures in mice. The substituted coumarin was made to react with 3-aryl-5-(chloromethyl)-1,2,4-oxadiazole derivatives in the presence of potassium iodide and potassium carbonate to afford desired products coumarin-1,2,4-oxadiazole hybrids with good percentage yield (greater than 70%). In the MES test compounds **18, 19,** and **20** exhibited the most potent anticonvulsant activity against the MES test. Compound **18** binding efficiency got reduced after treatment with flumazenil which confirms that the compound mimics benzodiazepine mechanism for anticonvulsant activity. Further docking study using autodock tools (ver. 1.5.6) also validate benzodiazepine mechanism of action as compound **18** binds well inside the BZD receptor (BZD-binding site of $GABA_A$). Blood-brain barrier (BBB) penetration was carried out online



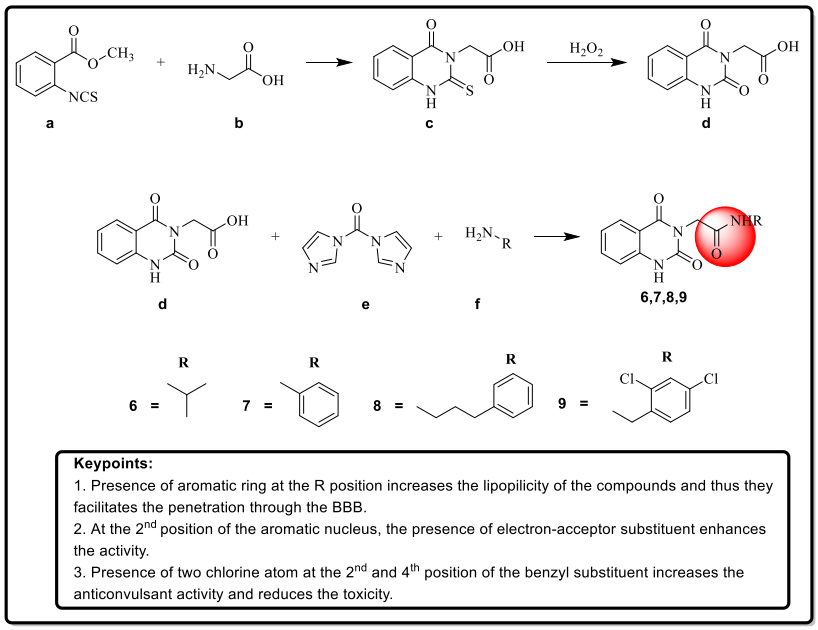
Scheme 1. Synthesis of *N*-(2-hydroxyethyl)amide derivatives as potent anticonvulsant.



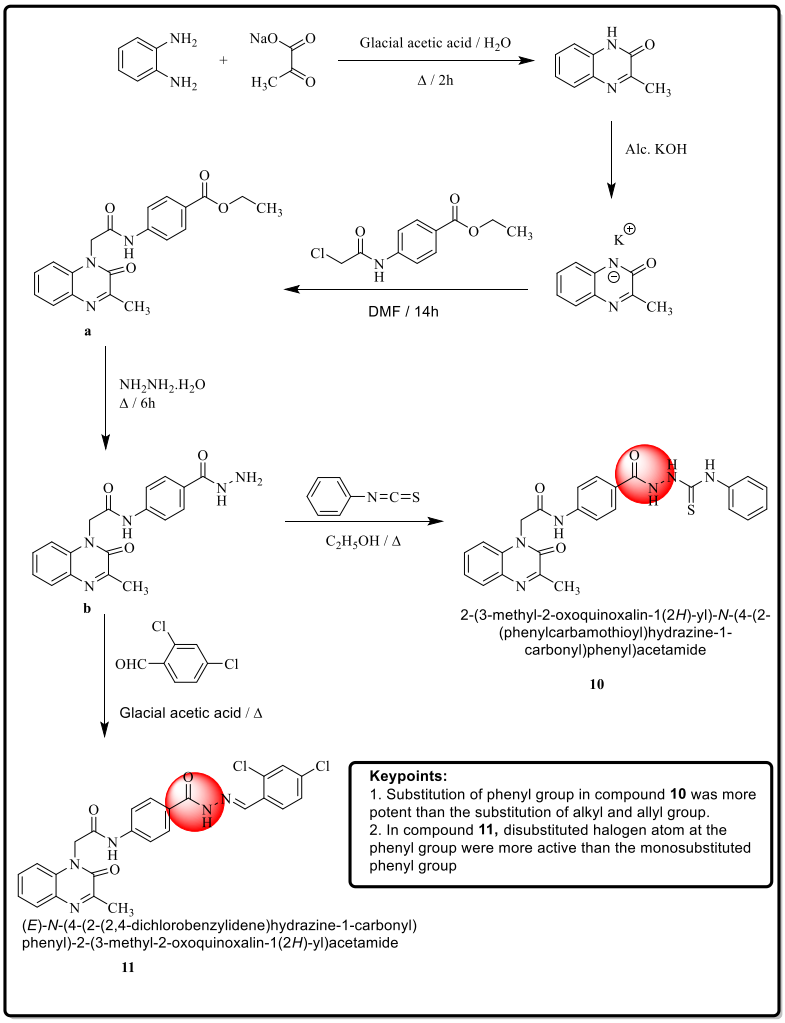
Scheme 2. Synthesis of phthalimide-4-5-dihydrithiazole-amide derivatives as antiepileptic.



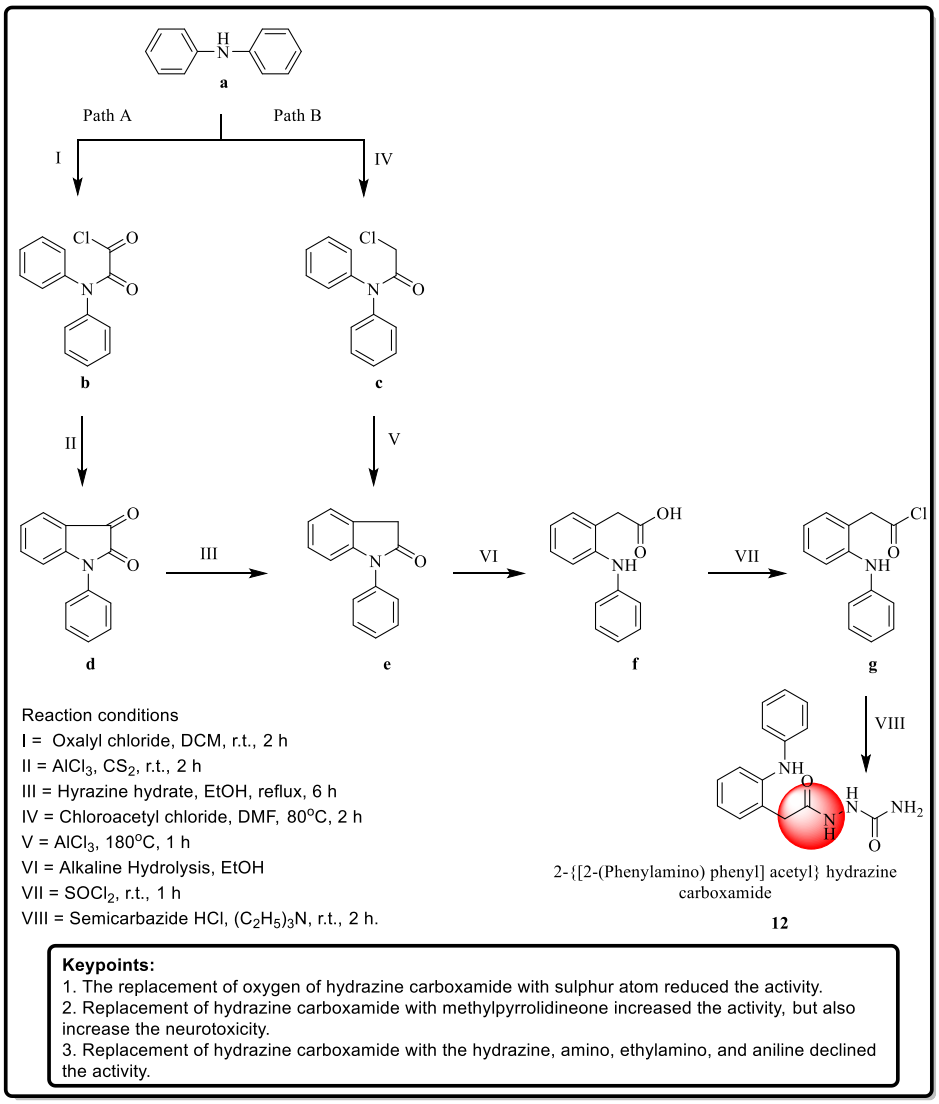
Scheme 3. The synthesis of benzothiazole amide derivatives as potent anticonvulsant.



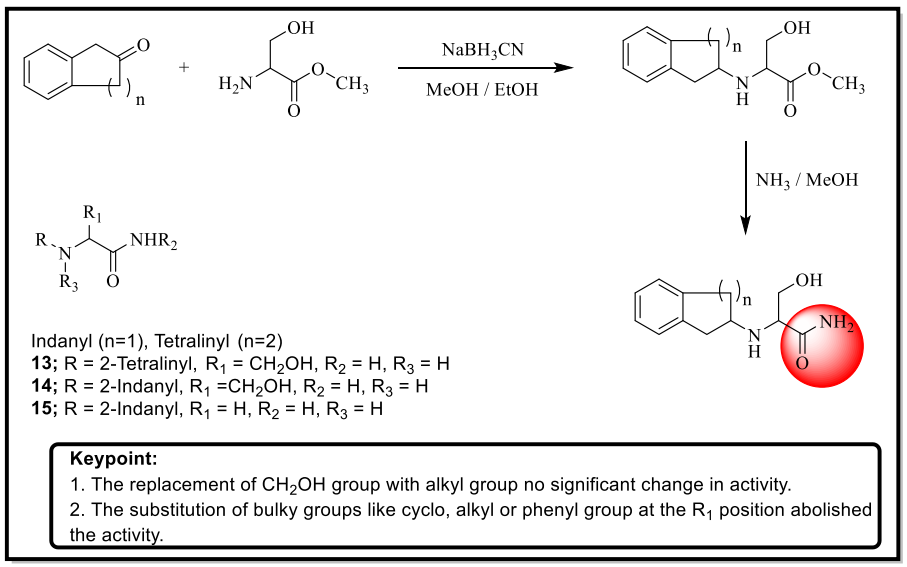
Scheme 4. Synthesis of 2-(2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)acetamide derivatives in good percentage yield and with significant anticonvulsant activity.



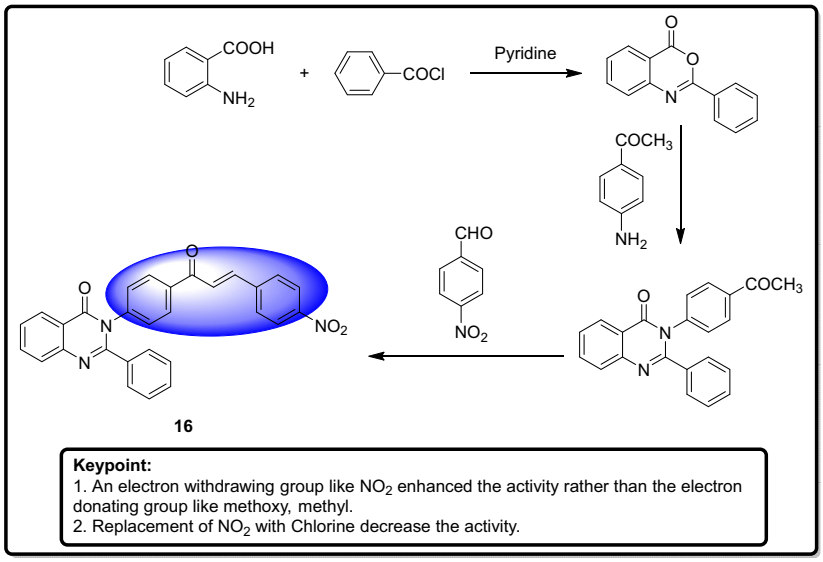
Scheme 5. Synthesis of some novel 2-(3-methyl-2-oxoquinoxalin-1 (2H)-yl)-N-(4-(substituted) phenyl) acetamide derivatives as anticonvulsant.



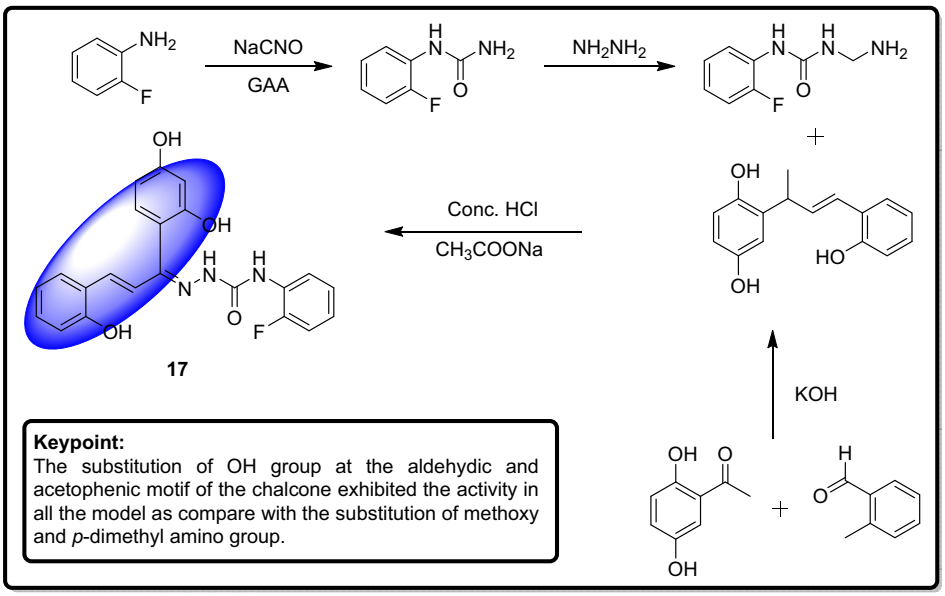
Scheme 6. The procedure for the synthesis of *N*-substituted 2-anilinophenylacetamides derivatives with significant anticonvulsant activity.



Scheme 7. The bicyclic tetralinyl/indanyl linked to aminoacetamide chain for potent anticonvulsant activity.

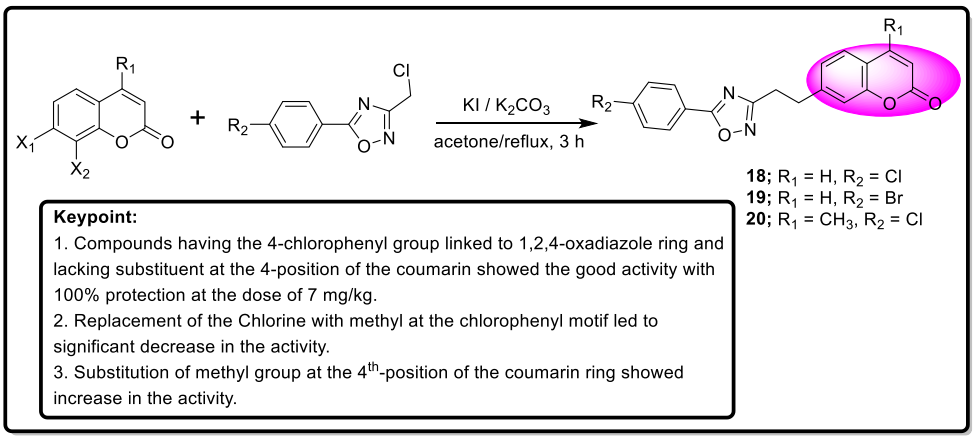


Scheme 8. The chalcone-based pyrazoline compounds having potent anticonvulsant activity.

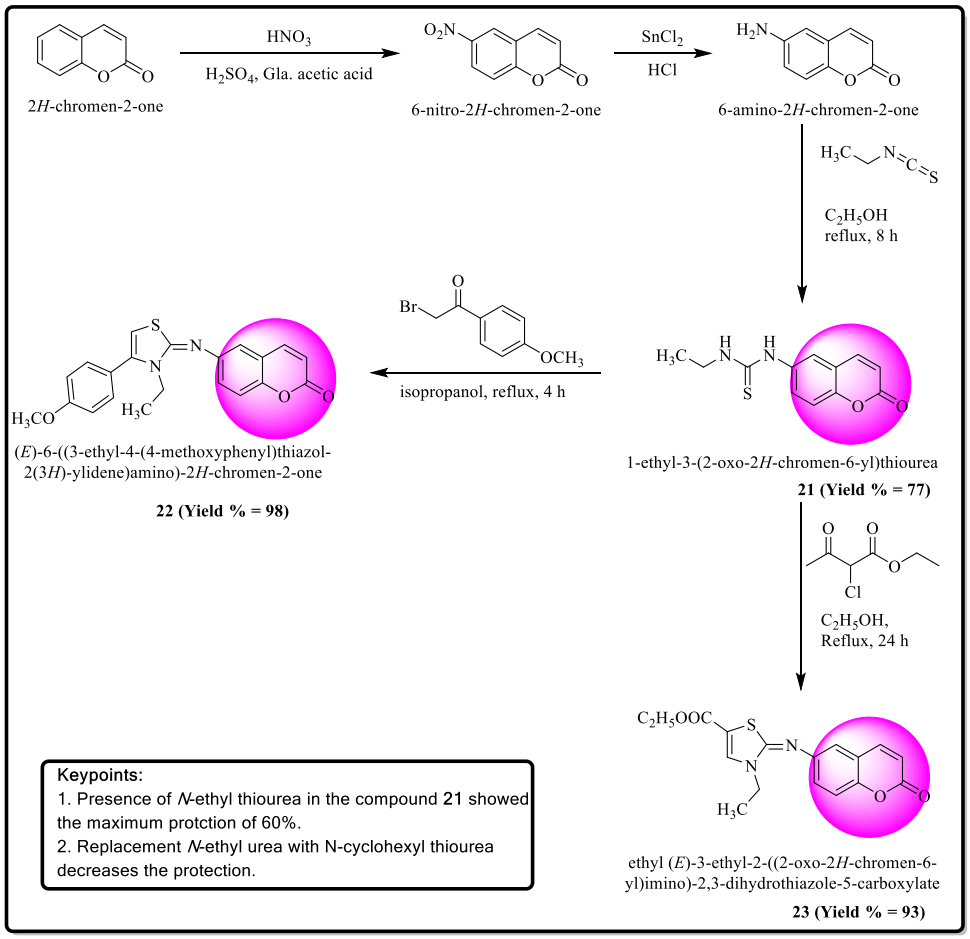


Scheme 9. Chalcone with semicarbazone showed good percentage of protection against MES.

by BBB predictor (www.cbligand.org) [6] (Scheme **10**). Coumarin with pyrazoles, 4-thiazolidinones, 1,3,4-oxadiazoles and pyrazolines-5-ones showed enhanced biological properties [52]. This led Amin *et al.,* to synthesize a series of coumarinyl-thiazolines, coumarinyl-thiazolidin-4-ones, and substituted chromenothiazoles. All the synthesized series of compounds were checked for their anticonvulsant potential against PTZ-induced and strychnine-induced seizures in mice. Among them, compounds **21, 22,** and **23** showed highest anticonvulsant potencies. The yields of the compounds are mentioned in Scheme **11**. In scPTZ test, these compounds showed protection of 60%, 60%, and 80%, respectively at a dose of 100 mg/kg. Compound **22** also exhibited hypnotic and sedative activity with LD_{50} value 1453.78 mg/kg which was higher than standard drug phenobarbital [53] (Scheme **11**). In another study, Siddiqui *et al.* synthesized a series of heteroaryl semicarbazones and screened them for their anticonvulsant activity against the two models *i.e.,* PTZ and MES. Among them, compounds **24, 25** and **26** were found to be the most potent among the series (yield of the compounds are mentioned in Scheme **12**). Compound **24** was found to be active at a dose of 30 mg/kg after 0.5h and at 300 mg/kg after 4.0h in the MES test. The result indicated the compound as fast-acting at a lower dose but having prolonged action at a higher dose. In scPTZ test, the compound was active at a dose of 100 mg/kg after 0.5h with no sign of neurotoxicity. Similarly, compound **25** was quite active at a dose of 30 mg/kg after 0.5h and 300 mg/kg after 4.0h in the MES test whereas, in the scPTZ, the compound displayed activity at a dose of 100 mg/kg after 0.5h. The compound was neurotoxic at the higher dose of 300 mg/kg. In the MES test, compound **26** was quite active at a lower dose 30 mg/kg after 0.5h and 4h time intervals. This confirms the most active compound among the series as it was fast-acting with

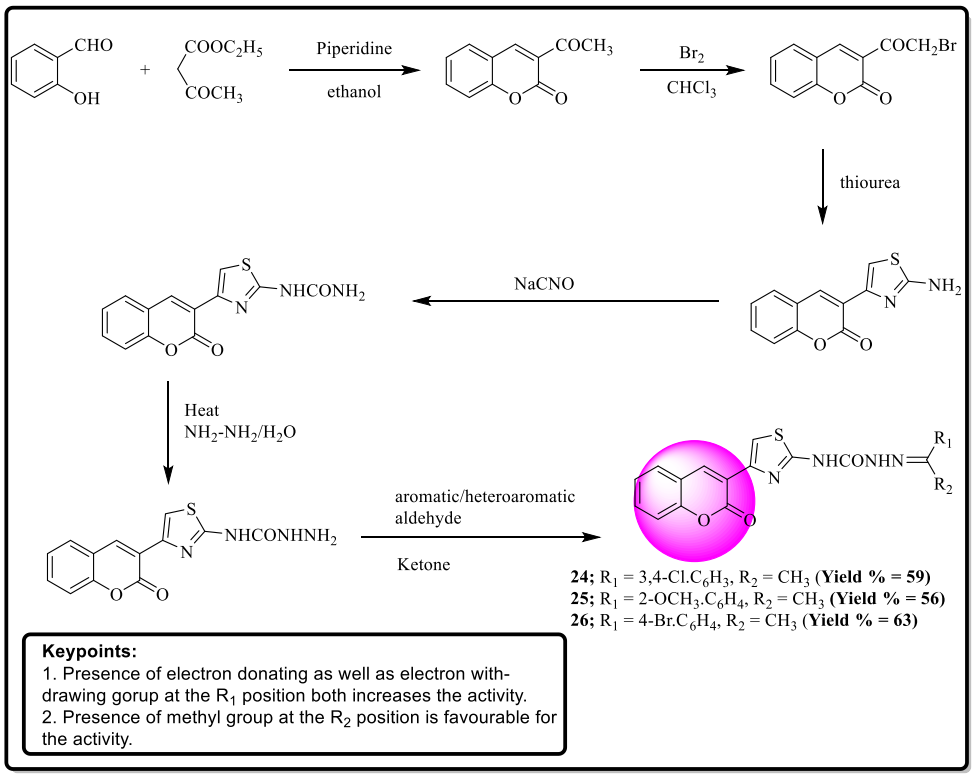


Scheme 10. Synthesis of acridone-based 1,2,4-oxadiazole derivatives with good percentage yield and potent anticonvulsant activity.

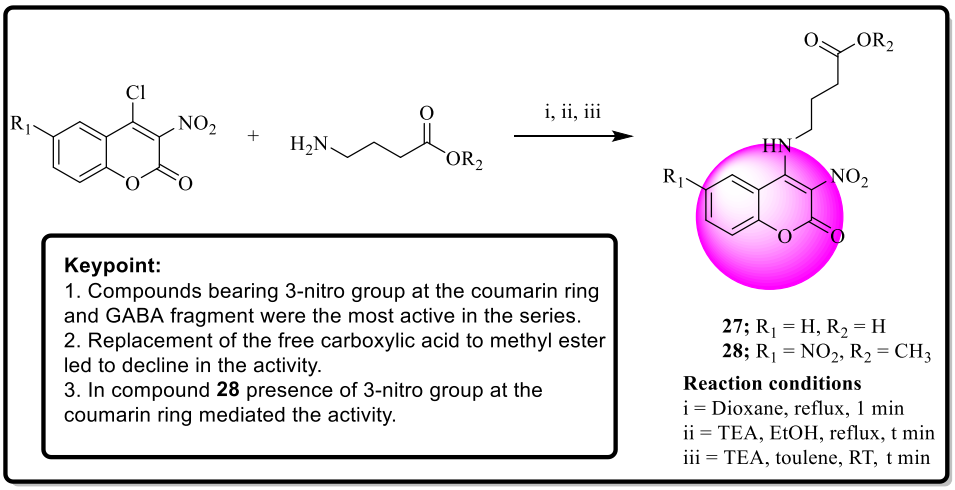


Scheme 11. The synthesis of coumarinyl-thiazolines, coumarinyl-thiazolidin-4-ones, and substituted chromenothiazoles with potential anti-convulsant against PTZ-induced and strychnine-induced seizures in mice.

prolonged action at a lower dose. In scPTZ test, the compound was most active at 100 mg/kg after 0.5h and at 300 mg/kg after 4.0h. Compound **26** was found to be neurotoxic at the dose of 100 mg/kg after 0.5h and at 300 mg/kg after 4.0h [54] (Scheme **12**). Amino-coumarin is considered an important class of organic compounds because of its diverse biological properties and absorption in the visible region of the spectrum [55]. Amino-coumarin has been investigated for anticonvulsant activity by Mokrov *et al.* They reported the synthesis of *N*-substituted 4-amino-3-nitrocoumarins in a single step by reacting 4-chloro-3-nitrocoumarins 2 with ω-amino acids and their esters. Compounds were synthesized by using three different methods. The first involved refluxing of 4-chlorocoumarins with an excess of amino acid in dioxane. Dioxane was chosen as solvent since the starting reactants were dissolved in it however the products obtained were poorly soluble. The second set comprised refluxing in EtOH with equimolar amounts of 4-chlorocoumarins and

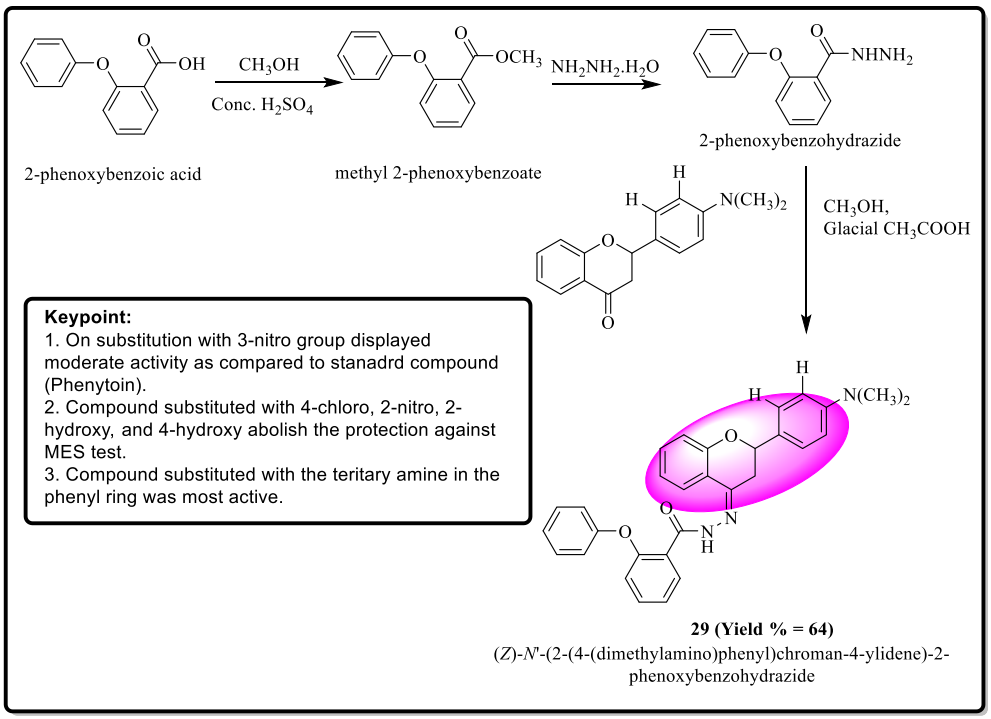


Scheme 12. Synthesis of heteroaryl semicarbazones derivatives as active anticonvulsant.



Scheme 13. Synthesis of *N*-substituted 4-amino-3-nitrocoumarins *via* a single step having good anticonvulsant activity.

amino acids in the presence of triethylamine (TEA). The reactions gave high yields regardless of the used conditions (**27** and **28** were obtained in 86 and 84% yield). The final products were easily purified *via* recrystallization from EtOH. Additionally, the reaction of 4-chlorocoumarin with GABA methyl ester occurred significantly faster than with GABA under milder conditions at room temperature in toluene and in the presence of TEA. The synthesized compounds were tested against the MES test in mice and corazole antagonism test. The compound *N*-(3-nitrocoumarin-4-yl)-4-aminobutyric acid **27** at the dose of 60 and 80 mg/kg and compound methyl *N*-(3,6-dinitrocoumarin-4-yl)-4-aminobutyrate **28** at 20 and 40 mg/kg dose were found to be active [56] (Scheme **13**). Another phenylchromen-4-one comprises of flavones ring system. The flavonoids are found in fruits and vegetables and are considered important in the epileptic patient as they protect the brain from oxidative stress [57]. The importance of flavonoid in the epileptic patient led Kumar *et al.,* synthesized a series of flavones that incorporated hydrazide derivatives and evaluated them for anticonvulsant activity against MES model in male Wistar rats taking phenytoin as a standard drug. Esterification of phenoxy benzoic acid gave the methyl-2-phenoxybenzoate which after reaction with hydrazine hydrate yield 2-phenoxybenzohydrazide. The final compound (Z)-*N*'-(2-(4-(dimethylamino) phenyl) chroman-4-ylidene)-2-phenoxy-benzohydrazide were obtained after the reaction with



Scheme 14. Synthesis of a series of flavones incorporated hydrazide derivatives with potent anticonvulsant activity profile as compared to standard phenytoin.

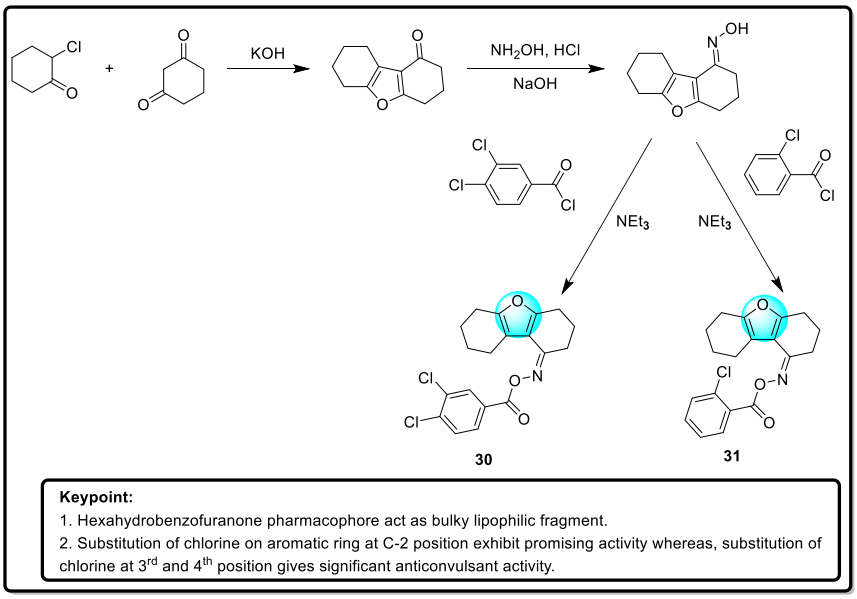
2-phenoxybenzohydrazide and flavone derivatives *i.e.* 2-(4-(dimethylamino)phenyl)chroman-4-one. The synthesized derivatives compound *N'*-(2-(4(dimethylamino)phenyl)chroman-4-ylidene)-2-phenoxybenzohydrazide **29** (Yield, 64 %) was appeared to be more active as compared to standard drug phenytoin. It showed 68.59 % protection at the dose of 30 mg/kg with 86.70% of potency [58] (Scheme **14**).

2.4. Furan

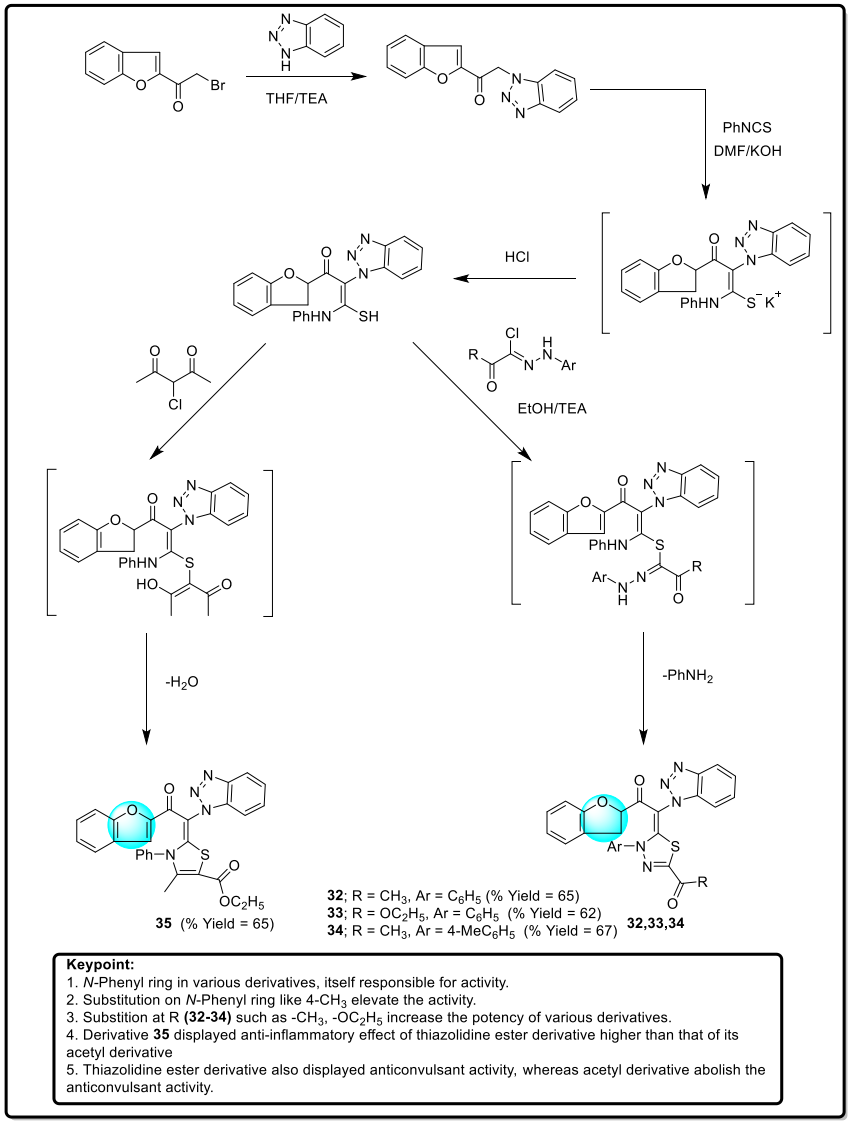
Furan is a five-membered heterocyclic ring and is an important moiety with diverse biological activities. The furan derivatives evaluated by the Parchenko *et al i.e.,* 5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-thiones were of prime importance and were reported to have equivalent strength as compared to the reference compounds mydocalmum and phenobarbital [59]. Synthesis of furan ring containing dibenzofuranone-oxime derivatives was carried out by Zhmurenko *et al*. The compounds were screened for their anticonvulsant activity by using MES and corazole-induced convulsions. Initially, 2-chlorocyclohexanone and 1,3-cyclohexanedione were reacted in the basic medium of KOH in methanol to give the 3,4,6,7,8,9 hexahydrodibenzo[b,d]furan-1(2*H*)-one (DBF). The intermediates were then reacted with hydroxylamine hydrochloride in the presence of NaOH to afford DBF oxime. DBF Oxime was refluxed in benzene with chlorosubstituted acyl chlorides in the presence of triethylamine (Et_3N) to afford the final product compound **30** and **31** with 88 and 84% yields (Scheme **15**). The initial results indicated that most of them are potent but compounds **30** and **31** were found to be the highly active. Compound **30** was quite active in the dose range of 20-100 mg/kg in the MES test. Survival of animals after the injection was increased by 50% relative to the control. Compound **31** at the dose of 20 mg/kg showed 100% survival of the animals as compared to the standard control [60]. Dawood *et al.* worked on a series of benzofuran derivatives (percentage yield mentioned in Scheme **16**) to investigate their role as potential anticonvulsants using MES and scMet. The results showed that compounds **32, 33, 34,** and **35** were the most active in the series. In MES the compounds **32** and **33** were found to be potent as compared to reference drug phenytoin whereas, compounds **34** and **35** were active in the scMET test as compared with standard drug valproic acid [61] (Scheme **16**). Salat *et al*., synthesized a series of dihydrofuran-2-one, and anticonvulsant activities were carried out by Więckowski *et al* using MES. The compound 3-[4-(3-trifluoromethylphenyl)-piperazine was reacted with 3-bromo-dihydrofuran-2-one in anhydrous K_2CO_3 and solvent dry acetonitrile to yield the desired product (3-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)dihydrofuran-2(3*H*)-one) **36** with good percentage yield (62%). Synthesis required complete dry condition from reagent to solvents and after completion of reaction compound **36** was purified by recrystallization from 2-propanol. The compound **36** exhibited the most potent in the synthesized series. In the MES test, the compound **36** exhibited the ED_{50} value of 112 mg/kg in mice. Compound, **36** was active after 4h thus demonstrated prolonged protection. Further, it was noticed that the presence of an electron-withdrawing trifluoromethyl group in the aromatic ring increases the anticonvulsant activity of the compound [62, 63] (Scheme **17**).

2.5. Amines

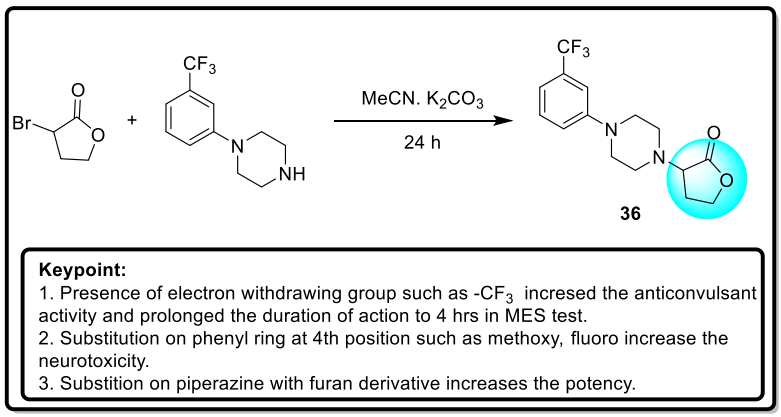
Amines especially cerebral monoamines manipulation play an important role in epilepsy. A simple correlation can be demonstrated as depletion of brain serotonin (5-hydroxytryptamine) causes fall in seizures in mice, rats whereas, increase in brain concentration of 5-hydroxytryptophan in the presence of monoamine-oxidase inhibitor



Scheme 15. Synthesis of furan ring containing dibenzofuranone-oxime derivatives as highly active anticonvulsant.



Scheme 16. Synthesis of benzofuran derivatives as active anticonvulsant.

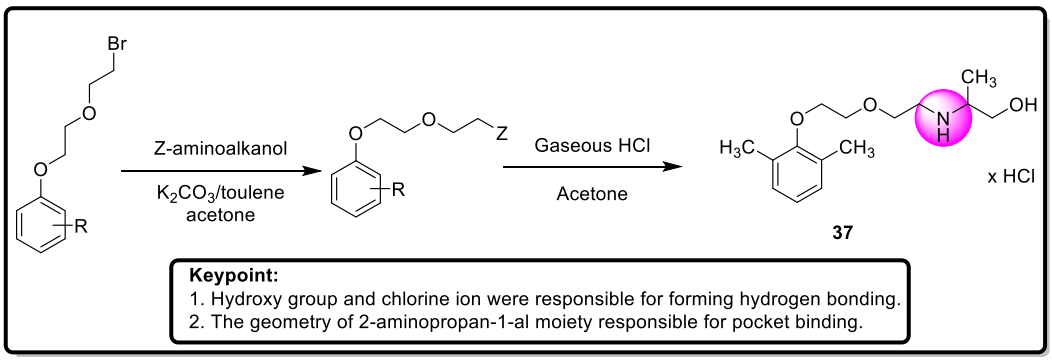


Scheme 17. Synthesis of dihydrofuran-2-one derivatives with good anticonvulsant activities against MES.

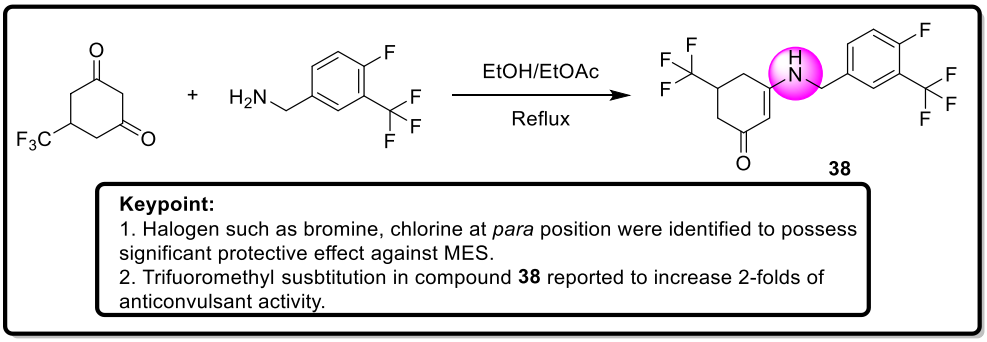
led to an elevation in the seizure threshold. Even alone monoamine oxidase inhibitors are found to help epileptic patients in increasing the seizure threshold [64]. One series of amine-containing compounds *viz., N*-(phenoxy)alkyl or *N*-{2-[2-(phenoxy)ethoxy]ethyl}aminoalkanols were synthesized by Waszkielewicz *et al*. and screened them for their anticonvulsant activity in mice by using MES, 6Hz test, and pilocarpine-induced status epilepticus. The synthesis procedures involved the reaction between (2-(2-bromoethoxy)ethoxy) benzene with *Z*-amino alkanol in base potassium carbonate in toluene/acetone followed with exposure to gaseous HCl in acetone to yield the *N*-alkylated final compound **37** (yield = 85%). The synthesized compound **37** was found to be the most potent anticonvulsant agent with an ED_{50} value of 12.92 mg/kg in the MES test and the TD_{50} value of 33.26 mg/kg in the rotarod test [18]. (Scheme **18**). Other benzyl methylamine derivatives with trifluoromethyl substitution play an important role in alleviating the symptoms of epilepsy. Fluorine increases the hydrophobicity and may increase the better CNS action. This led Apraku *et al.,* reported the synthesis of a series of trifluoromethylated enaminone derivatives and screened them for anticonvulsant activity in rats by using MES and scPTZ test and for the neurotoxicity, rotarod test was used. Condensation of 5-trifluromethyl diketone with corresponding phenyl, heteroaromatic amine, and benzylamine derivatives in the presence of dry methanol/ethyl acetate gave the final product. The final product (compound **38**) was purified by column chromatography in a 76% yield. It was the most potent anticonvulsant agent with an ED_{50} value of 23.47 mg/kg in comparison to standard carbamazepine having an ED_{50} value of 28.20 mg/kg. All the tested compounds were given orally to the rats. Further, the compound was not found to be neurotoxic at a maximum dose level of 300 mg/kg [65] (Scheme **19**). One carbon-less benzylamine derivative were also checked for anticonvulsant activity. Eddington *et al.,* synthesized a series of 5-methyl-2-cyclohexene enaminones and screened them for their anticonvulsant activity by using MES. The β-hydroxy keto esters treated with different substituted aniline heated under the appropriate conditions (solvent mixture of benzene and ethyl acetate mixture refluxed and stirred in Dean-stark apparatus) gave the final desired product. In the synthetic procedure noteworthy precaution should be taken as enaminones are quite stable at pH 7.0 and 7.4 in the absence of esterase. Among them, compound **39** exhibited potent anticonvulsant activity. In the MES test the compound showed ED_{50} of 16.7 mg/kg, TD_{50} of 110.7 mg/kg and a protective index of 6.6 mg/kg in mice whereas, in rats the value of ED_{50} was 3.0 mg/kg, TD_{50} of 250 mg/kg and protective index of 83.3. The results demonstrate that compound **39** acts as the most potent anticonvulsant agent and works by blocking the sodium channel. The enaminone ester has a lipophilic nature thus permits passive diffusion across the blood-brain barrier, however active efflux mechanism for its sustained action. The synthesized ester enaminones were active in the Na^+ channel assay [66] (Scheme **20**). Another study for the amine-containing compounds as anticonvulsant was reported by Malik *et al*. A series of (5-amino-3-substituted-1,2,4-triazin-6-yl)(2-(6-halo-substitutedbenzo[d]isoxazol-3-yl) pyrrolidin-1-yl) was tested for their anticonvulsant activity by MES test and neurotoxicity by the rotarod test. The mixture of triazine ester reacted with 6-fluoro-3-(pyrrolidin-2-yl)benzo[d]isoxazole in the presence of base DBU at room temperature and stirred for 48h to obtain the desired product compound **40** with 85% yield. The most potent compound **40** showed an ED_{50} value of 6.20 mg/kg and a protective index of > 48.38. The protective index of compound **40** was greater as compared to the standard drug phenytoin > 35.38. Compound **40** showed anticonvulsant activity by blocking the sodium channel. To determine the possible mechanism of synthesized compounds, sodium channel binding assay ([^{3}H] BTX Radioligand assay) was performed. The neuronal activity revealed **40** as the most potent candidate with an IC_{50} value of 84.7 [67] (Scheme **21**).

2.6. Sulfonamide

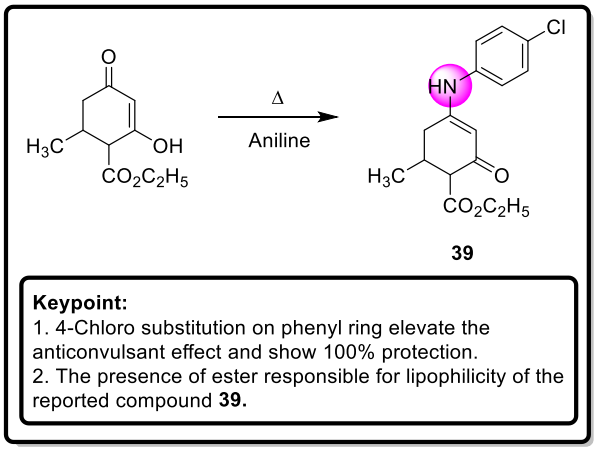
Sulfonamide derivatives were initially developed as potential antimicrobial agents but also showed efficacy in epilepsy [68]. One such approved sulfonamide containing drug is zonisamide which is used as an adjunct in partial seizures [69]. Shimshoni *et al.,* designed and synthesized a series of tetramethyl cyclopropane carboxamide derivatives containing a benzene ring as newer antiepileptic drug (AEDs). The compounds were evaluated for anticonvulsant activity using scMet seizure and MES test. For the synthesis of aromatic tetramethyl cyclopropane carboxamide derivatives, compound 2,2,3,3- tetramethyl cyclopropane carboxylic acid (TMCA) was used as the starting material for the synthesis. Product **41** was crystallized using the solvent ethyl acetate/petroleum ether mixture (1:3; yield; 61%) (Scheme **22**).



Scheme 18. Synthesis of *N*-{2-[2-(phenoxy)ethoxy]ethyl}aminoalkanols as potent anticonvulsant.

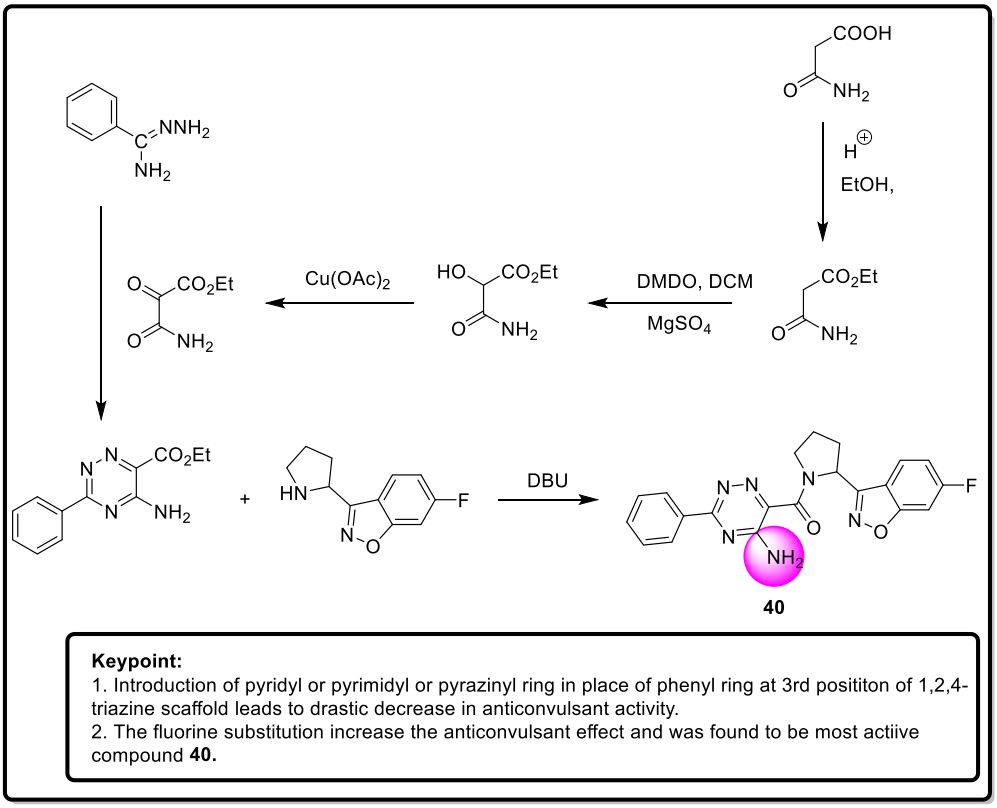


Scheme 19. Synthesis of trifluoromethylated enaminone derivatives to increase hydrophobicity and acts as better CNS anticonvulsant.

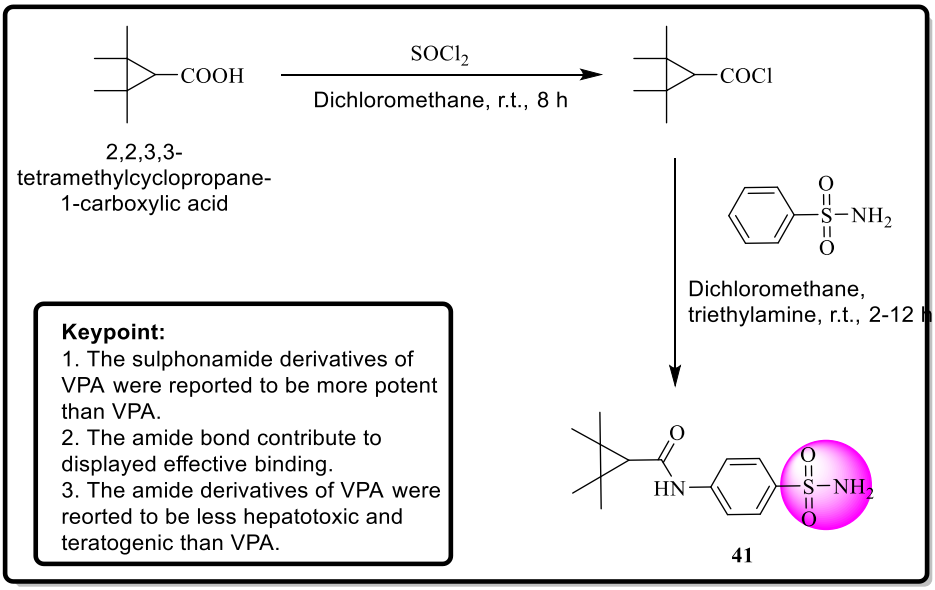


Scheme 20. The synthetic scheme for 5-methyl-2-cyclohexene enaminones derivatives as potent anticonvulsant.

From the series, compounds *N*-(2,2,3,3-tetramethylcyclopropanecarboxamide)-*p*-phenyl-sulfonamide **41** was identified as the most potent with an ED_{50} value of 26 mg/kg in the rat-MES test and a remarkable PI (PI = TD_{50}/ED_{50}) value above 19. The synthesized derivatives possessed wider safety margin in comparison to standard valproic acid (VPA) and zonisamide. Adding a methylene or ethylene spacer linking the phenyl ring and the amine led to reduction in the anticonvulsant activity [70]. Keeping the general requirement of basic pharmacophore and fulfilling the Lipinski rule of five criteria, Ajeet *et al.,* perform the design and synthesis of a series of substituted 4-amino-benzene sulphonamides and screened anticonvulsant activity by MES model. The result displayed that compound 4-[2-(4-acetyl-phenylamino)-ethyl]-benzene sulfonamide **42** as most potent among the series of the synthesized compounds with a minimum 2.92 sec extensor phase (yield in percentage is mentioned in Scheme **23**). The author also suggested the possible mechanism for the synthesized compounds is *via* inhibition of carbonic anhydrase enzyme. Docking studies were carried out with the help of AutoDock Vina (PyRx-Python Prescription 0.8 software with PDB ID 1AZM (Lyase-Human Carbonic Anhydrase). Compound **42** showed strong hydrogen bonding and binding affinity of 7.3 Kcal/mol [71] (Scheme **23**). One such procedure for the synthesis of sulfonamide derivatives were reported by Farag *et al.* The author synthesized many derivatives of heterocyclic compounds having sulfonamide thiazole moiety. A mixture of 4-amino-*N*-(thiazol-2-yl)benzene sulfonamide (0.01 mol) and ethyl cyanoacetate was reacted to give cyanoacetanilide which was further reacted with malononitrile



Scheme 21. The (5-amino-3-substituted-1,2,4-triazin-6-yl)(2-(6-halo-substitutedbenzo[d]isoxazol-3-yl)pyrrolidin-1-yl) derivatives with greater protective index than standard phenytoin.



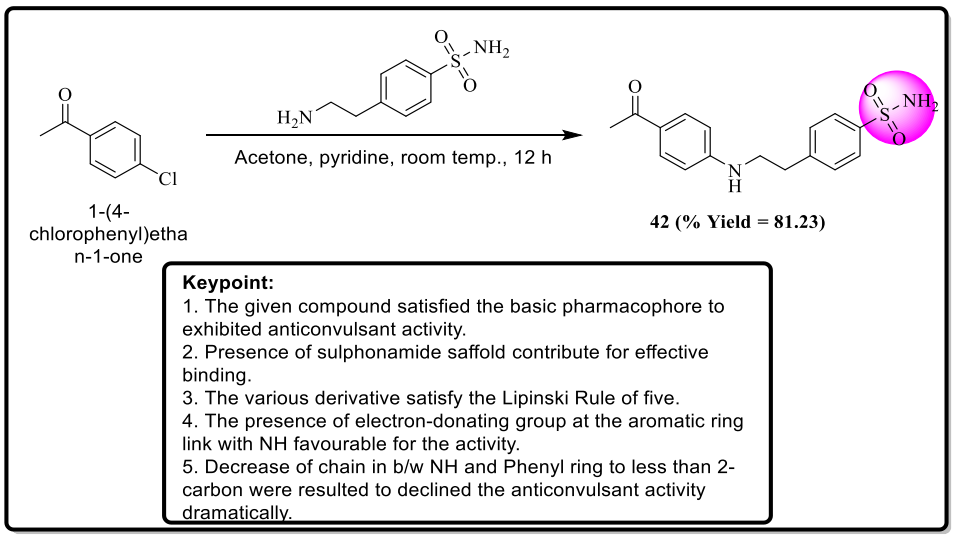
Scheme 22. Synthesis of tetramethyl cyclopropane carboxamide derivatives as newer anticonvulsant.

(0.01 mol) and aldehyde in ethanol (30 ml) in the presence of piperidine as the base (0.5 mL), heated under reflux for 3h. The product obtained was filtered and recrystallized from ethanol to give **43** with a percentage yield of 63%. One-pot synthesis was also reported with cyanoacetanilide derivatives with malononitrile and aldehyde at the reflux temperature in the presence of pyridine. The anticonvulsant activities of a series of compounds were estimated by picrotoxin-induced convulsion method. The compound, 4-(6-amino-3,5-dicyano-4-(4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)-*N*-(thiazol-2-yl)-benzenesulfonamide **43** exhibited the significant anticonvulsant effect. Picrotoxin is known to block the chloride channel linked to $GABA_A$ and thus prevent the entry of chloride into the brain. Thus, the compounds by enhancing the GABAergic neurotransmission exerted a protective effect or antagonistic action against picrotoxin-induced seizures.

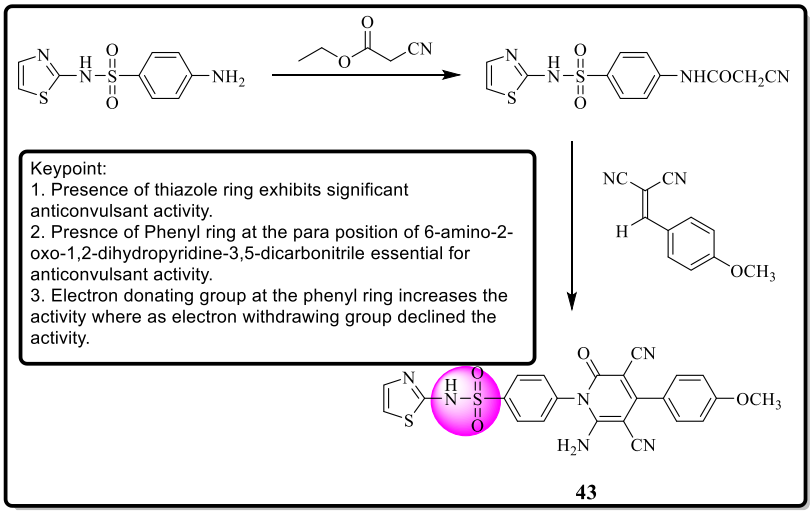
Moreover, compound **43** exhibited 100% protection and was also able to abolish the tonic extensor phase. There was no mice death reported in the study [72] (Scheme **24**). Sulfonamide between the two phenyl rings dramatically increases the anticonvulsant action. Some derivatives were designed and synthesised by Khokra *et al*. The compounds 3 and 4 substituted benzene sulfonamides were linked *via* phenyl ring to a benzothiazole moiety. The reaction started with the use of 3-aminobenzoic acid with 2-aminothiophenol added dropwise and placed in a mortar. The reaction completion was monitored by TLC, the crude product was recrystallized in methanol to obtain 3-(benzo[d]thiazol-2-yl)aniline. Simultaneously chlorobenzene and chlorosulfonic acid reacted in the presence of calcium chloride in a reflux condenser to afford the 3-chlorobenzenesulfonyl chloride. The final step is the reaction between 3-(benzo[d]thiazol-2-yl) aniline and 3-chlorobenzenesulfonyl chloride in acetic anhydride and pyridine to yield the final desired product *N*-(4-(benzo[d]thiazol-yl) phenyl)-3-chlorobenzenesulfonamide **44** with 49% yield. The synthesised compounds were further evaluated for their anticonvulsant potential, neurotoxicity screening and computational studies. The MES model taking standard drug phenytoin in mice displays compound **44** to possess the most potent anticonvulsant effect. The computational analysis (Molegro Virtual Docker; MVD) revealed three hydrogen bond interactions with the nicotinic acetylcholine ion gated receptors (PDB ID: 2BG9). The compound **44** resulted in better flexion in terms of mean ± SEM as 1.8 ± 0.37 and recovery in comparison to standard drug *i.e.,* phenytoin 3.6 ± 0.68 and diazepam 171.8 ± 2.92. The compound **44** emerged as the lead candidate for anticonvulsant action [73] (Scheme **25**). Replacing one of the phenyls with thiazolidinone *i.e.,* sulfonamaide between phenyl and thiazolidinone ring results in good lipophilic compounds to act on CNS. The compounds of 4-thiazolidinone containing sulfonamide group were designed and synthesised by Siddiqui *et al.* In the first step, *p*-bromoanisole was treated with chlorosulfuric acid to form 2-methoxybenzenesulfonyl chloride. In the subsequent step, the prepared 2-methoxybenzenesulfonyl chloride was treated with hydrazine hydrate to yield 5-bromo-2-methoxybenzenesulfonylhydrazide. The hydrazide derivatives were then refluxed with the aromatic aldehyde or ketones in glacial acetic acid to form 5-bromo-2-methoxy-N'-[(1*E*)-arylmethylene/arylethylidene] benzenesulfonohydrazide **(a)**. The final compounds were synthesised by cyclization of **(a)** into thiazolidinone ring in the presence of zinc chloride and thioglycolic acid. All final products obtained have a good percentage yield (greater than 60%). The synthesised compounds were then subjected to the anticonvulsant activity by MES and scPTZ animal models. The results displayed that compounds **45, 46** and **47** showed the most significant potency against the MES test at a dose level of 30 mg/kg after 0.5 h time interval. The lipophilicity of compounds **45, 46** and **47** was found to be 2.14, 3.47 and 3.65 (logP) respectively. The Compounds inhibited the GABA-T enzyme after 4 h in the in vitro GABA-T inhibition assay. Among them, compound **45** showed the maximum inhibition of 12%. The anticonvulsant action was predicted as CO_2 retention and then inhibition of red cell and brain enzymes [74]. (Scheme **26**). A novel series of derivatives consisting *N*-(2-(1,1-dimethyl-5,7-dioxo-4,6-diazaspiro[2.4]heptan-6-yl) ethyl) sulphonamide **(b)** was developed by Li *et al.* The compounds were prepared using sulfonyl chloride dissolved in anhydrous THF slowly added with continuous stirring to the mixture of the 6-(2-aminoethyl)-1,1-dimethyl-4,6-diazaspiro [2.4] heptane-5,7-dione **(a)** in solvent dry dichloromethane and base TEA. The stirring of reaction mixture was continued for another 6h at room temperature. In the next step, water and saturated brine was used for washing the mixture, dried over Na_2SO_4 under reduced pressure to remove the traces of solvent and the product obtained as a crude product (oily). The oil product was then subjected to silica-gel column chromatography to give compound **48** (% yield = 83) and **49** (% yield = 85). The synthesized compounds were subjected for their anticonvulsant activity by using MES and scPTZ seizure models in mice. The result revealed that compound *N*-(2-(1,1-dimethyl-5,7-dioxo-4,6-diazaspiro[2.4] heptan-6-yl)ethyl)-4-methyl benzene sulfonamide **48** and *N*-(2-(1,1-dimethyl-5,7-dioxo-4,6-diazaspiro [2.4]heptan-6-yl) ethyl)-4-fluorobenzenesulfonamide **49** displayed encouraging anticonvulsant activity in MES model. The most potent compound **48** was found to show anticonvulsant activity with an ED_{50} value of 28.05 mg/kg and TD_{50} value of 561 mg/kg against MEM-induced seizure in mice intraperitoneally. Moreover, the protective index (TD_{50}/ ED_{50}) of compound **48** comes out to be 20 in the MES test. Furthermore, the neurotoxicity profile was evaluated by using the rotarod toxicity method that indicated compound **48** to be non-neurotoxic. The mechanism of the anticonvulsant action was proposed as inhibition of Na^+ channel as the compounds has hydantoin core similar to phenytoin [75] (Scheme **27**).

2.7. Urea Derivatives

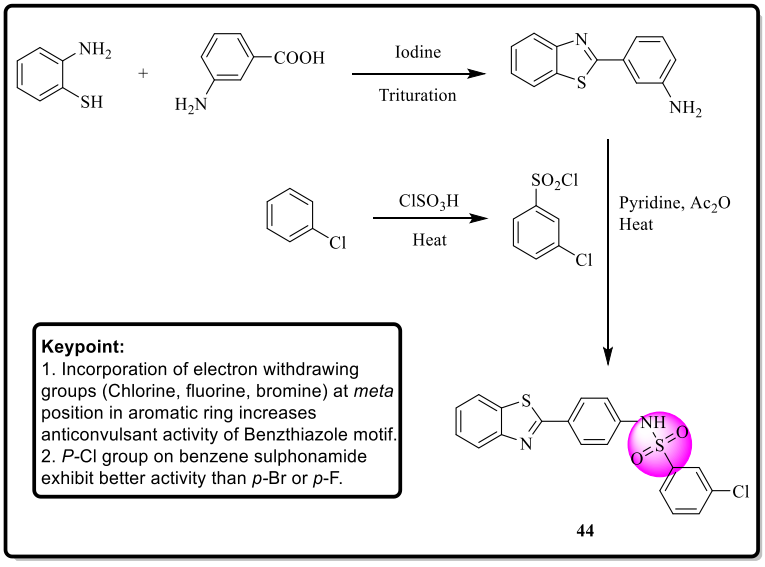
Urea derivatives are considered under the ureide class and are congener or structurally related to barbiturates. Urea derivatives are known to have broad anticonvulsant action with reduced hepatotoxicity and teratogenicity. Urea is also found in many heterocyclic rings containing AEDs such as phenobarbital, phenytoin, and carbamazepine [2]. Siddiqui *et al.* synthesised various derivatives containing 1-(amino-*N*-arylmethanethio)-3-(1-substituted benzyl-2,3-dioxoindolin-5-yl) urea as the basic pharmacophore, by keeping the basic structural requirements for anticonvulsant activity. The nitration of the indoline-2,3-dione at 5th position **(a)** was carried out by refluxing with a mixture of 95-100% sulfuric acid and 70% nitric acid in a water bath at 60^o C for 1h. The free NH of the 5-nitroindoline-2,3-dione was substituted with different benzyl derivatives after the reaction with different substituted benzyl chloride in the presence of anhydrous potassium carbonate in acetone **(b, c).** The reduction of the free nitro **(b, c)** gives compound **(d, e)** on heating with a mixture of iron powder and hydrochloric acid. The resulted compounds **(d, e)** were stirred with sodium cyanate in solvent glacial acetic acid into corresponding urea derivatives. Lastly, the required titled compounds 1-(amino-*N*-aryl methane thio)-3-(1-substituted benzyl-2,3-dioxoindolin-5-yl) urea were prepared on refluxing with different substituted phenyl isothiocyanates. Compounds **50** (87%), **51** (55%), **52** (68%), **53** (82%) and **54** (58%) gave good percentage yields. The series of compounds were evaluated by *in vivo* anticonvulsant screenings *i.e*., MES and scPTZ. Compound **50** was identified as the most active compound in MES screening whereas, compounds **51**, **52, 53** and **54** displayed significant activities in both the screening models and were devoid of any neurotoxicity. Two of the compounds *i.e.*, **51** and **52** resulted



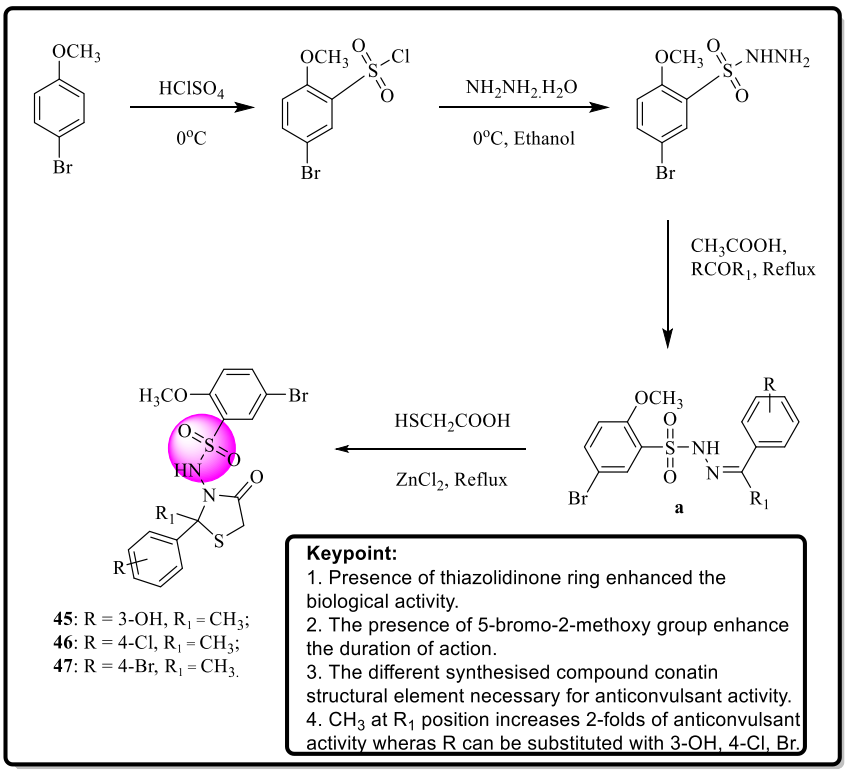
Scheme 23. Synthesis of substituted 4-amino-benzene sulphonamides derivatives as anticonvulsant and acts *via* carbonic anhydrase inhibitor.



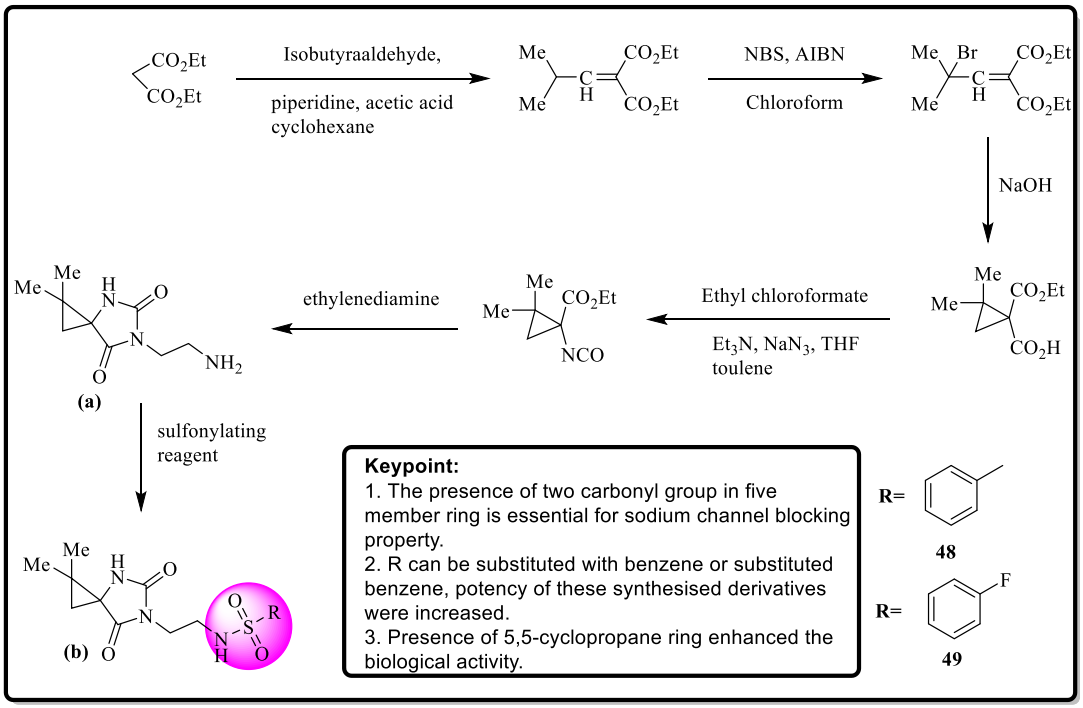
Scheme 24. The synthesis of sulfonamide thiazole derivatives with good percentage protection *via* enhancing GABAergic neurotransmission.



Scheme 25. Benzothiazole phenyl linked sulfonamide derivatives with increased anticonvulsant action.



Scheme 26. Thiazolidinone phenyl linked sulfonamide derivatives showing good lipophilic CNS anticonvulsant.



Scheme 27. *N*-(2-(1,1-dimethyl-5,7-dioxo-4,6-diazaspiro[2.4]heptan-6-yl)ethyl)sulphonamide derivatives as non-neurotoxic anticonvulsant.

in marked protection at 300 mg/kg against both the models [76] (Scheme **28**). He *et al.* studied the design and synthesis a new series of 1-(2-(8-(benzyloxy)quinolin-2-yl)-1-butyryl-cyclopropyl)-3-substituted urea derivatives as a potent anti-convulsant. The activities were carried out by using two standard models *i.e.,* MES and scPTZ and neurotoxicity by the rotarod test. The compounds **55, 56,** and **57** showed the most promising activity in both models. The compound **56** displayed protection against seizure induced by MES resulting in ED_{50} value of 14.3 mg/kg and TD_{50} value of 434 mg/kg after intraperitoneal injection to mice. Furthermore, compound **56** showed protective index of 30.3 (TD_{50}/ED_{50})

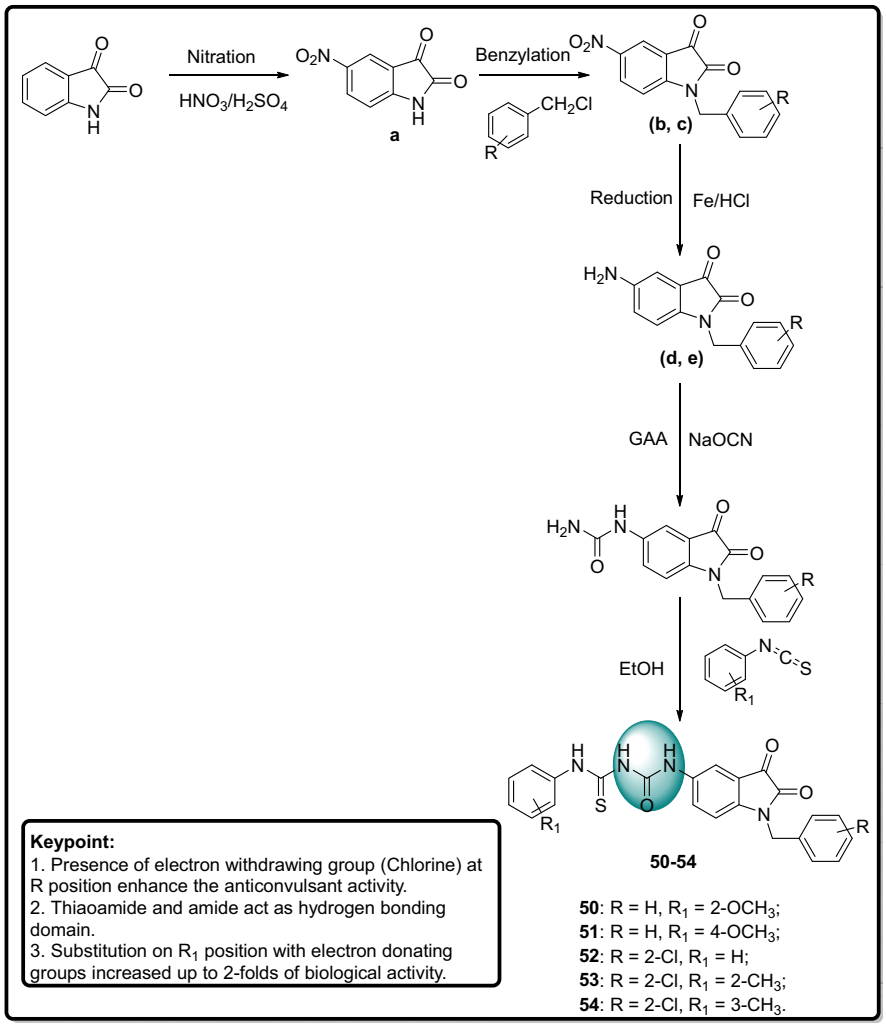
in the MES test (percentage yield incorporated in Scheme **39**). The final compounds are chemically bioisosteres of cyclic acyl urea of phenytoin. Thus, the mechanism proposed was influenced by Na^+ 2HCl K^+ [77] (Scheme **29**). Kashaw *et al.,* synthesised various derivatives of 1-(4-substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-4*H*-quinazolin-3-yl)-urea derivatives justifying the basic pharmacophore. All the synthesized derivatives were obtained in more than 50% yield. The compounds **58-64** were found to be active in the MES screening whereas, the compounds **58, 66, 64** and **65** were found to be active in scPTZ screening model. All compounds displayed a more than 50% decrease in locomotor activity after 1h of drug administration through actophotometer screening method. The bulkier group is more lipophilic and cross blood-brain-barrier easily. Further, it was noted that phenyl substituted derivatives showed better activity than alkyl derivatives [78] (Scheme **30**). Mishra *et al.,* performed the design and synthesis of the series of derivatives titled 1-phenyl-3/4-[4-(aryl/heteroaryl/alkyl-piperazine1-yl)-phenyl-urea. The prepared derivatives were examined for anticonvulsant screening using MES, scPTZ seizure tests and the acute neurotoxicity was evaluated by rotarod assay. Compound **66** (1-{4-[4-(4-chloro-phenyl)-piperazin1-yl]-phenyl}-3-phenyl-urea) (the yield percentage is mentioned in Scheme **31**) showed remarkable anticonvulsant activity in animal seizure models. In the phase II anticonvulsant quantification, compound **66** has the ED_{50} value of 28.5 mg/kg in MES induced seizure. Moreover, in pilocarpine-induced status epilepsy in rats, compound **66** displayed significant protections. The induced seizure by 3-mercaptopropionic acid and thiosemicarbazide was remarkably reduced by compound **66**. The overall profile of compound **66** indicated it to be the most potent as it displayed anticonvulsant activity by different mechanisms. The compound was not able to produce significant activity against 4-AP (K^+ channel antagonist) induced seizures even at high doses, thus not interacting with the K^+ channel. The compound inhibits PTZ, 3-MPA, and TSC showing its broad-spectrum anticonvulsant action [79] (Scheme **31**). Prakash *et al.,* synthesized twenty novels substituted benzylidene-3-(1-(morpholino/ piperidinomethyl)-2,3-dioxoindolin-5-yl) urea derivatives and evaluated for their anticonvulsant screening by methods of scPTZ and MES antiepileptic seizures and neurotoxicity by rotarod test. The compounds **67, 68, 69,** and **70** were found to be the most potent in MES model whereas, compound **71** displayed remarkable anticonvulsant activity in scPTZ screening model (the percentage yields of the compounds synthesized are mentioned in Scheme **32**). Furthermore, these five compounds were given orally to rats among which compounds **67, 68,** and **70** displayed better anticonvulsant action as compared to the standard drug phenytoin. Furthermore compounds **67** showed MES protection at a dose of 30 mg/kg after 0.5h and 4h of drug administration whereas, it provided protection against scPTZ induced seizure at maximum dose of 300 mg/kg after both time intervals. This indicates that the compounds are very much effective against generalized tonic-clonic seizure at a lower dose of 30 mg/kg but increases seizure threshold at the higher dose of 300 mg/kg. The antiepileptic activity was proposed to be due to the presence of extra electronegative oxygen of morpholine as compared to piperidine accounted for participating in hydrogen bond within the receptors [80] (Scheme **32**).

2.8. Naphthalene Derivatives

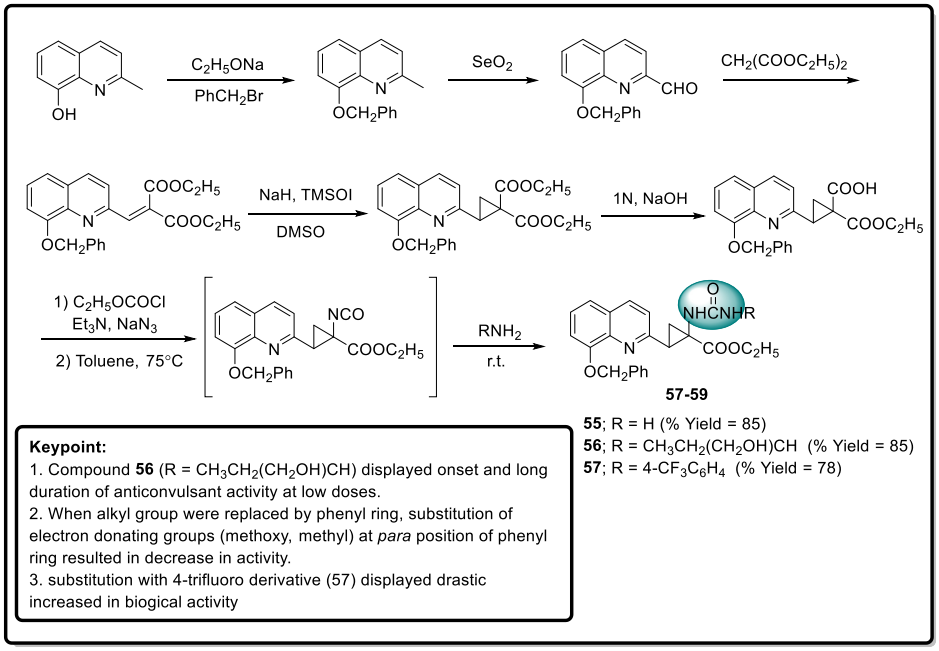
Several naphthalene derivatives were synthesized in the last decade as AEDs. The first naphthalene derivative to be used as an anticonvulsant is Nafimidone. It belongs to the structurally different class and is found to be more potent than phenytoin but is associated with toxicity and low potencies [81]. Azam *et al.,* designed and synthesized the series of 1-(substituted benzylidene/ethylidene)-4-(naphthalen-1-yl) semicarbazide derivatives. The activity was carried out by the established anticonvulsant models *i.e.,* MES and scPTZ. Compound **72** was found to be the most potent and depicted the highest protection profile against MES and scPTZ model. To determine the vital structural features of compounds showing anticonvulsant activity, quantum chemical studies were carried out. Compound **72** (percentage yield incorporated in Scheme **33**) displayed the highest energy gap *i.e.,* ΔE (HUMO-LUMO) = -5.529. The compound further displayed protection of 25%, 100%, 75% and 50% against the tested animals after 0.25h, 0.5h, 1h and 2h, respectively. Reduction in SOD (superoxide dismutase), GSH-Px (Glutathione peroxidase), GSH (Glutathione) and increase in malondialdehyde (MDA) are important markers of PTZ-induced epilepsy. MDA is the product of membrane lipid peroxidation (LPO) and the brain is vulnerable to injury by LPO. The compound was able to protect from the PTZ effect and protected the brain from oxidative stress [82] (Scheme **33**). Another naphthalen-2-yl acetate derivative as a potential anticonvulsant agent was reported by Ghareb *et al.* Synthetic procedure involved naphthalen-2-yl acetate solution in chloroform, bromine (previously dissolved in chloroform) was added in 15 min with the dropping funnel. The reaction was completed after 2h at room temperature. The desired product was obtained in 82% yield higher than other common methods. These compounds were subjected for anticonvulsant activity against strychnine (4 mg/kg, *i.p.*) induced seizure model at the dose of 100 mg/kg. Among them, compound **73** showed the highest remarkable prevention ($P < 0.0001$) against strychnine-induced seizure compared to the standard drug phenobarbital. Docking studies (Schrodinger 10.1. software) were carried out taking flurazepam allosteric sites. Compounds docked well inside the BDZ binding sites. The plausible mechanism was the strongest binding to the benzodiazepine sites of the GABA-A homolog. The author stated the possible mechanism of action is delaying the strychnine-induced seizure (compound **73** may involve glycinergic inhibitory action) [83] (Scheme **34**).

2.9. Steroids

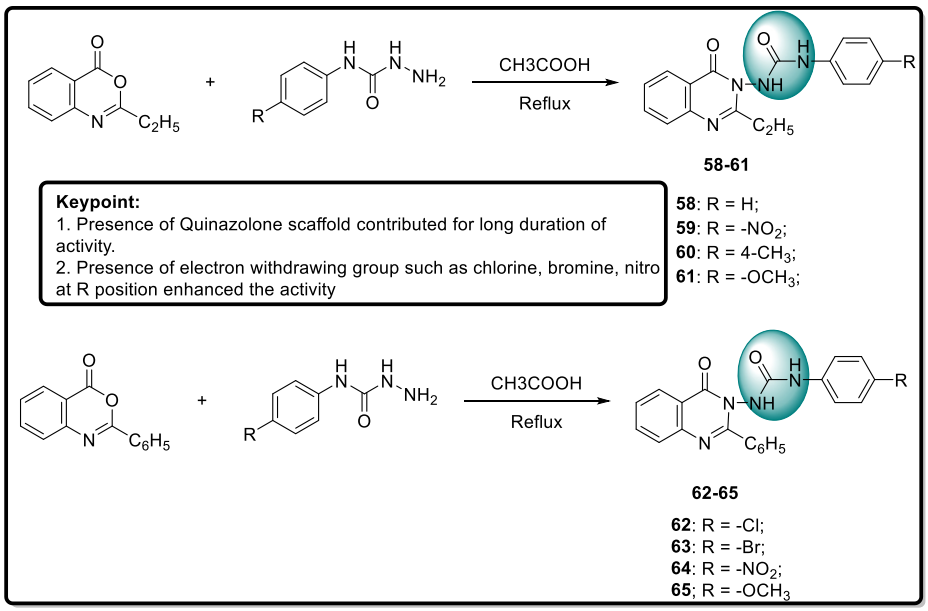
Steroids were studied as an anticonvulsant as their derivatives were found to modulate the neuroactive steroid site on the $GABA_A$ receptor site. This can be a new direction for the treatment strategies for patient suffering from epilepsy. Neuroactive steroids, diazepam and phenobarbital are very much effective against PTZ-induced clonic convulsions [84]. Neurosteroids are broad-spectrum anticonvulsant and provide protection in many animal models. The two such steroids which are positive modulators of $GABA\text{-}_A$ receptors include allopregnanolone (3α-hydroxy-5α-pregnane-20-one) and allotetrahydrodeoxycorticosterone (3α,21-dihydroxy-5α-pregnan-20-one) receptors [85]. Upasani *et al.,* synthesized a series of 3α-hydroxy-3β-(phenylethynyl)pregnan-20-ones



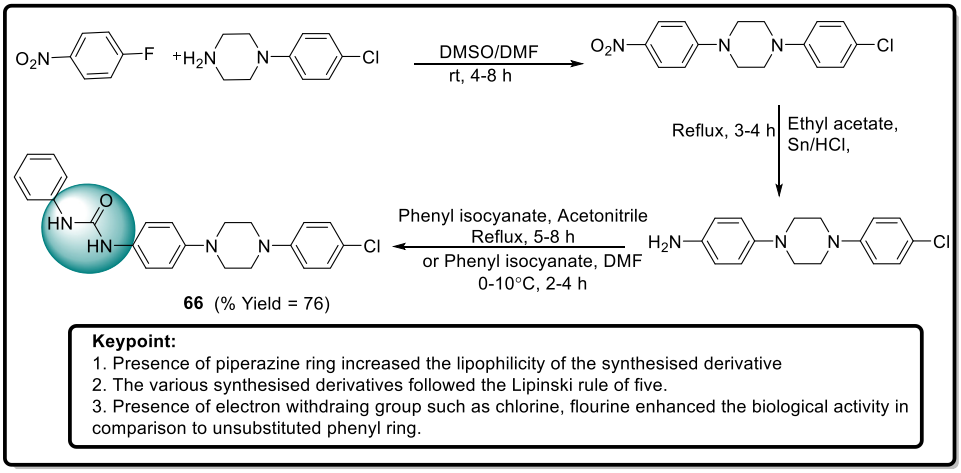
Scheme 28. The 1-(amino-*N*-arylmethanethio)-3-(1-substituted benzyl-2,3-dioxoindolin-5-yl) urea as basic pharmacophore for potent anti-convulsant activity.



Scheme 29. Synthesis of 1-(2-(8-(benzyloxy)quinolin-2-yl)-1-butyrylcyclopropyl)-3-substituted urea derivatives as potential anticonvulsant.

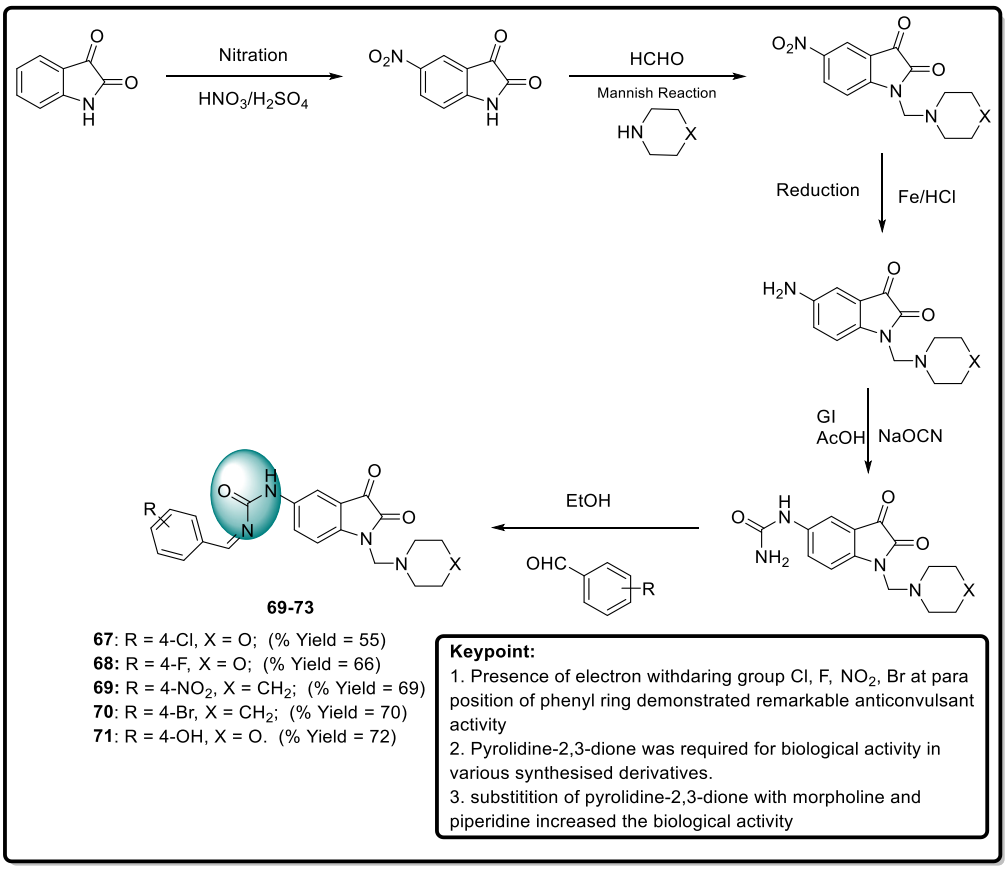


Scheme 30. The 1-(4-substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-4*H*-quinazolin-3-yl)-urea derivatives having basic pharmacophore with potent anticonvulsant against MES and scPTZ induced seizures.

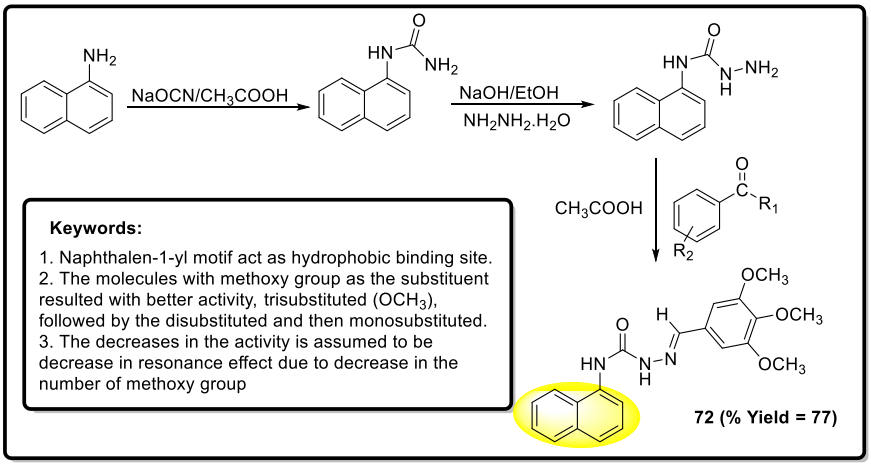


Scheme 31. Synthesis of 1-phenyl-3/4-[4-(aryl/heteroaryl/alkyl-piperazine1-yl)-phenyl-urea derivatives with remarkable anticonvulsant activity.

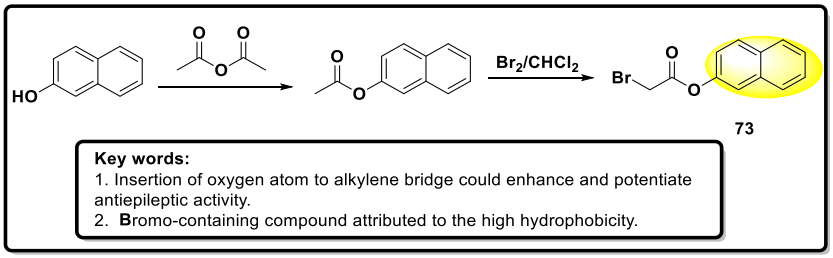
derivatives and evaluated for anticonvulsant activities with the help of PTZ and MES tests. The derivative of 3*β*-[(4-acetylphenyl)ethynyl]-19-nor, **74** displayed the remarkable anticonvulsant profile with an ED_{50} value of 2.8 and 9.2 mg/kg in PTZ and MES tests, respectively. Compound **74** was synthesized (30% yield) from 4-iodoacetophenone and 3*β*-ethynyl-3α-hydroxy-5α-19-norpregnan-20-one [86]. Neuroactive steroids are limited by rapid metabolization either conjugation of 3α-hydroxy group or oxidation to ketone and can be blocked by adding the substituents. The compound **74** was highly potent in both potentiation of the GABA-evoked currents in Xenopus oocytes with high affinity (IC_{50} = 10nM) measured electrophysiologically oocytes expressing $\alpha_1\beta_2\gamma_2L$ receptors and inhibiting [35S]-tert-butylbicyclo-phosphorothionate (TBPS) binding in rat brain (Scheme **35**). Runyon *et al.,* reported the various derivatives of 17β-Nitro-5α-androstan-3α-ol and its 3β-methyl. The anticonvulsant effect was evaluated against PTZ and 6 Hz seizure models in the mouse. The result revealed that compound **75** showed protection in a dose-dependent fashion in both models. Compound **76** also displayed a similar pattern to that of compound **75**. When the results were compared with pregnanolone 5α-Pregnan-3β-ol-20-one (allopregnanolone), compounds **75** and **76** displayed similar potency as that of allopregnanolone in the PTZ model whereas, in the 6 Hz the compounds appeared to be more potent. The compounds **75** and **76** possessed ED_{50} = 12.9 (9.8-16.9), 10 (8.9-11.2) and 5.3 (4.6-6.1), 8.8 (7.1-10.8) mg/kg in PTZ and 6 Hz model, respectively [87]. The finding of the study shows that in the compounds, the nitro group at the 17th position works as bioisosteres to the acetyl group present in the allopregnanolone. The compounds modulate $GABA_A$ receptors evaluated through [^{35}S]t-butylbicyclo-phosphorothionate and [3H] flunitrazepam binding with potencies equal to or greater than 1 (Scheme **36**).



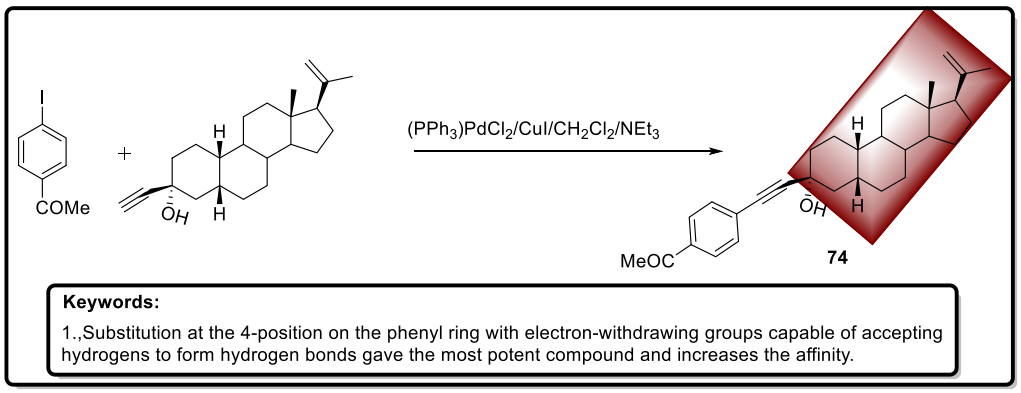
Scheme 32. The synthetic scheme of benzylidene-3-(1-(morpholino/piperidinomethyl)-2,3-dioxoindolin-5-yl) urea derivatives as antiepileptics.



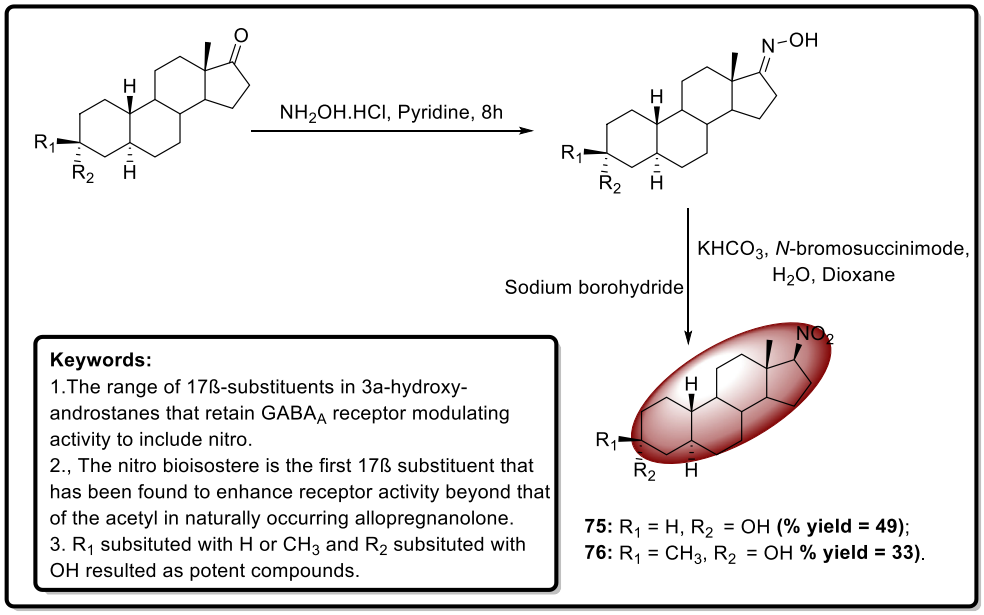
Scheme 33. Synthesis of series of 1-(substituted benzylidene/ethylidene)-4-(naphthalen-1-yl)semicarbazide derivatives with high protection profile as anticonvulsant.



Scheme 34. Synthetic scheme of naphthalen-2-yl acetate derivatives as potential anticonvulsant.



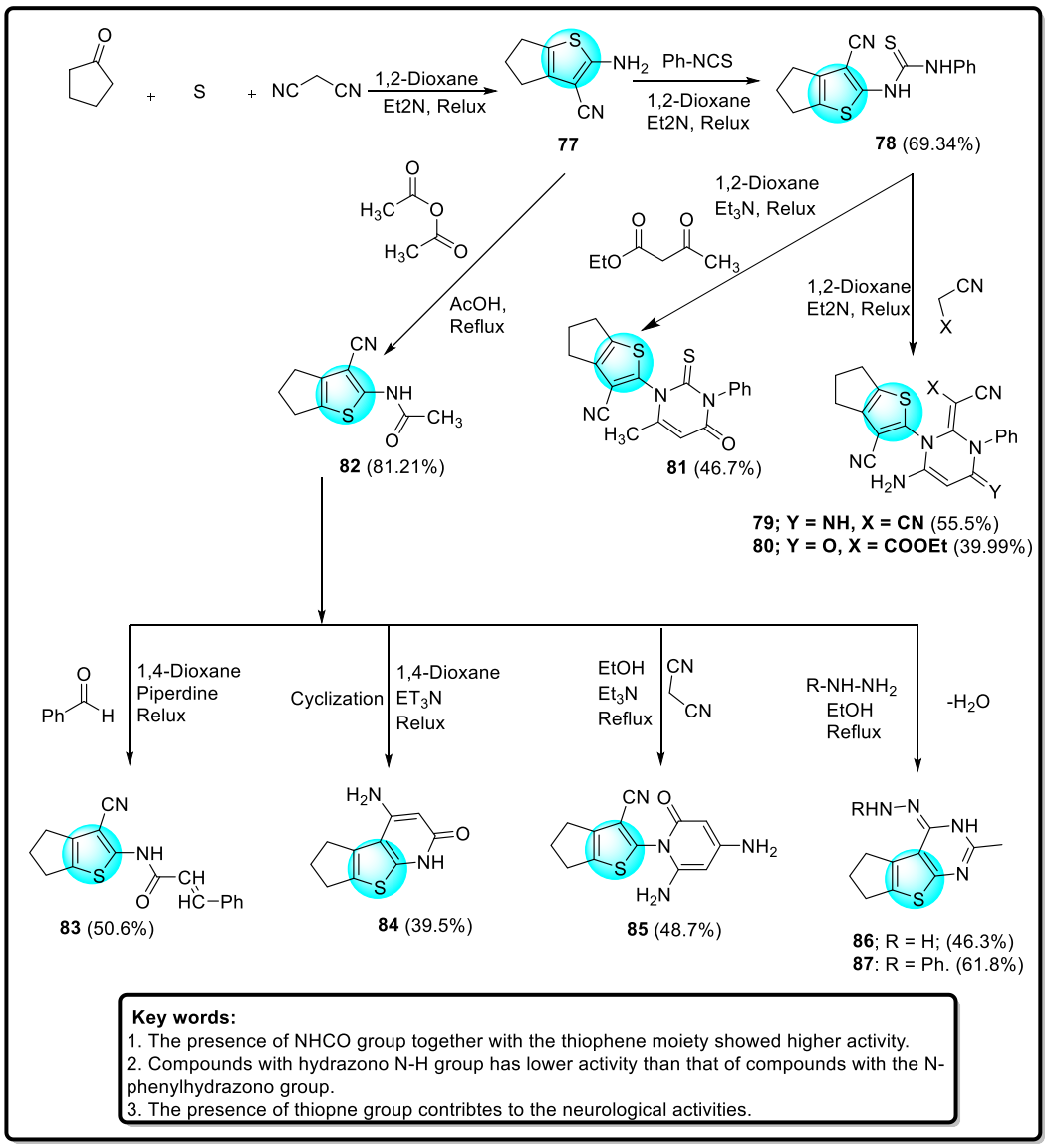
Scheme 35. The synthetic scheme for 3α-hydroxy-3β-(phenylethynyl)pregnan-20-ones derivatives as potent anticonvulsant.



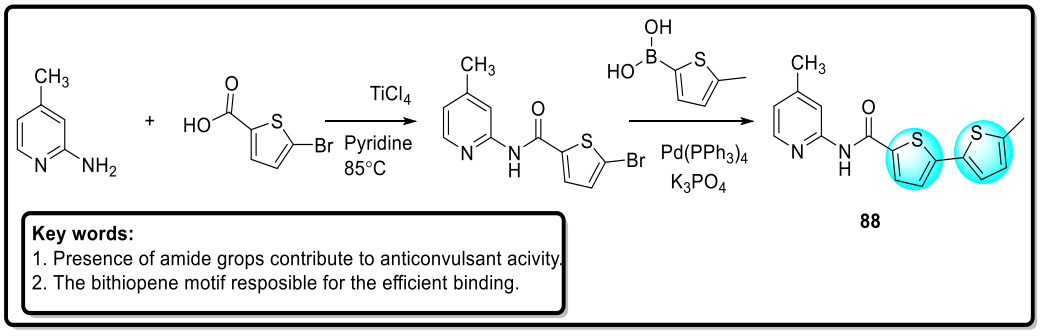
Scheme 36. Synthesis of various derivatives of 17β-Nitro-5α-androstan-3α-ol and its 3β-methyl with potent anticonvulsant activity compared to allopregnanolone.

2.10. Thiophene

Thiophene derivatives have been stated to possess a wide spectrum of biological activities such as anti-inflammatory, antidepressant, analgesic, and anticonvulsant [88]. One drug containing the thiophene nucleus is tiagabine, third-generation antiepileptics and selective GABA (gamma-aminobutyric acid) reuptake inhibitor as it interacts with GAT1 [89]. El-Sharkawy *et al.* reported and tested the various derivatives of cyclopenta[b]thiophene with more than 50% yield of all compounds (the individual percentage are mentioned in Scheme **37**) for anticonvulsant activity against the MES, scPTZ seizure threshold tests and minimal motor impairment test by rotarod (neurotoxicity, NT) at different doses of 30, 100 and 300 mg/kg. The results revealed that compounds **77, 78, 80, 82**, **83** and **84** were non-neurotoxic at a maximum administered dose of 300 mg/kg. The compounds **77**, **80**, **81, 82, 85** and **86** showed protection at a dose of 100 mg/kg after both the time interval of 0.5h and 4h in the MES screening test. In scPTZ screening, the compounds **77, 78, 79, 82, 83, 84** and **87** were effective at higher dose of 300 mg/kg after 0.5h [90] (Scheme **37**). Ahmad *et al.,* designed and synthesized a series of thiophene carboxamide analogue. Titanium tetrachloride ($TiCl_4$) was used for the formation of an amide bond in the first step and in the next step, Suzuki coupling reaction was employed with $Pd(PPh_3)_4$ as a catalyst. The desired carboxamide derivatives were obtained in moderate to good yields (35-84%). The acute PTZ model was used for the evaluation of anticonvulsant activities for various derivatives. Among the tested, compound **88** showed the most significant anticonvulsant effect. The compound **88** resulted in 50% and 80% protection at a dose of 10 mg/kg and 30 mg/kg respectively. The compound was docked on GABAergic receptors carried out using Molecular Operating Environment (MOE 2016.0208) software package in human GABA-$_A$ receptor (PDB 4COF) complexed with benzamidine as native ligand. The compound is bound to the active sites of the receptor. *In silico* pharmacokinetic parameters (AdmetSAR online server (lmmd.ecust.edu.cn/ admetsar1/) suggest for plasma protein bindings with low to moderate blood-brain barrier penetration, low solubility [91] (Scheme **38**). Amr *et al.,* reported the various hybrid of thiophene fused with other different heterocyclic moieties. All

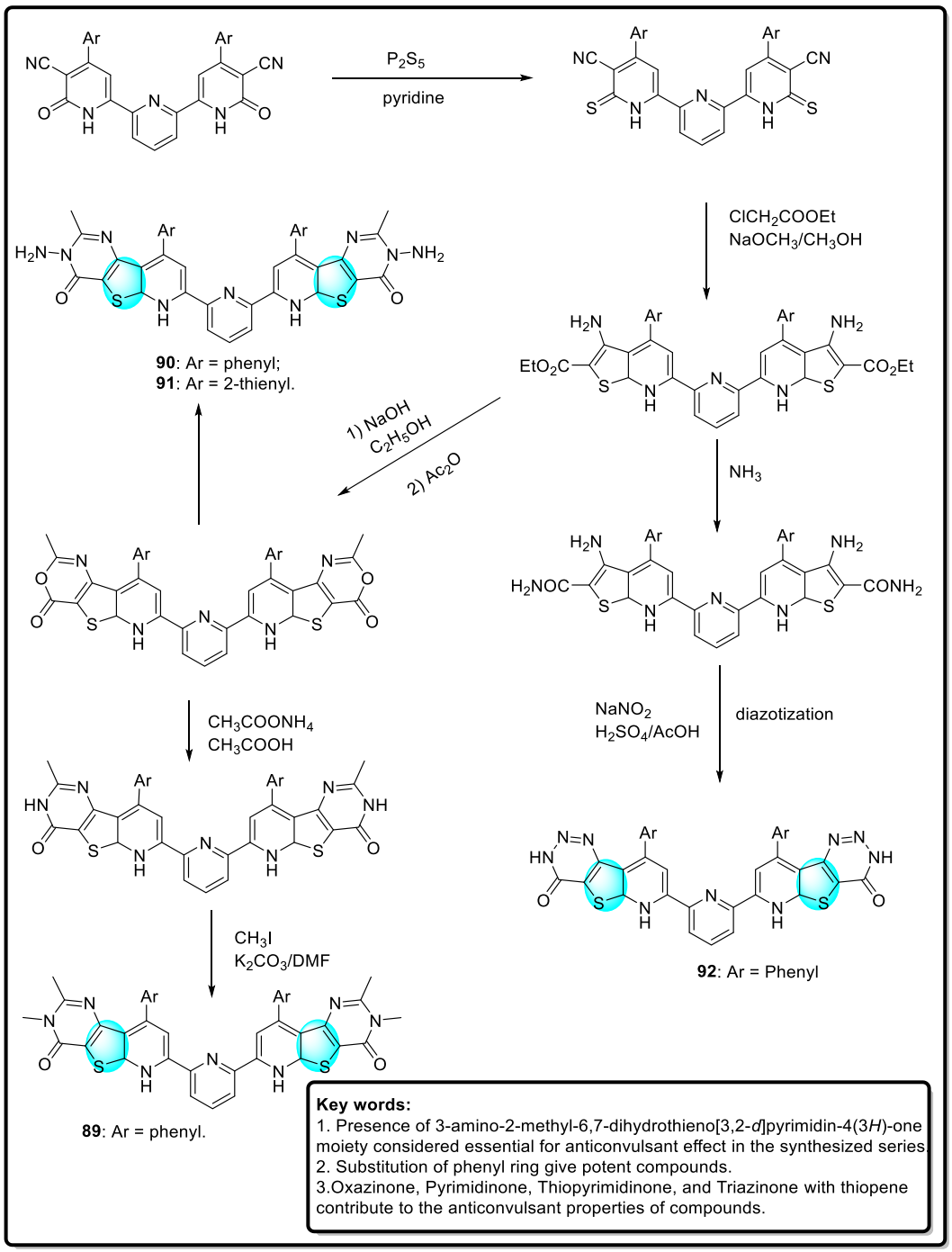


Scheme 37. The various derivatives of cyclopenta[b]thiophene as non-neurotoxic anticonvulsant.



Scheme 38. The synthetic scheme for thiophene carboxamide analogue with significant anticonvulsant activity.

the reported compounds showed more than 80% yield. The various derivatives were subjected to the anticonvulsant evaluation against the yohimbine-induced seizures model in mice. The compounds **89, 90, 91** and **92** displayed the most significant anticonvulsant effect with relative potencies of 0.94, 0.7, 1.93 and 2.23 as compared with the standard drug carbamazepine. The ED_{50} of the **89, 90, 91** and **92** were reported as 31, 35, 15 and 13 mg/kg, respectively [92] (Scheme **39**). Kulandasamy *et al.*, reported a series of novel 3,4-dipropyloxy-N_2,N_5-bis(substituted)thiophene-2,5-dicarbohydrazides taking diethyl 2,2'-thiodiacetate and diethyl oxalate as the starting material (percentage yield is mentioned in

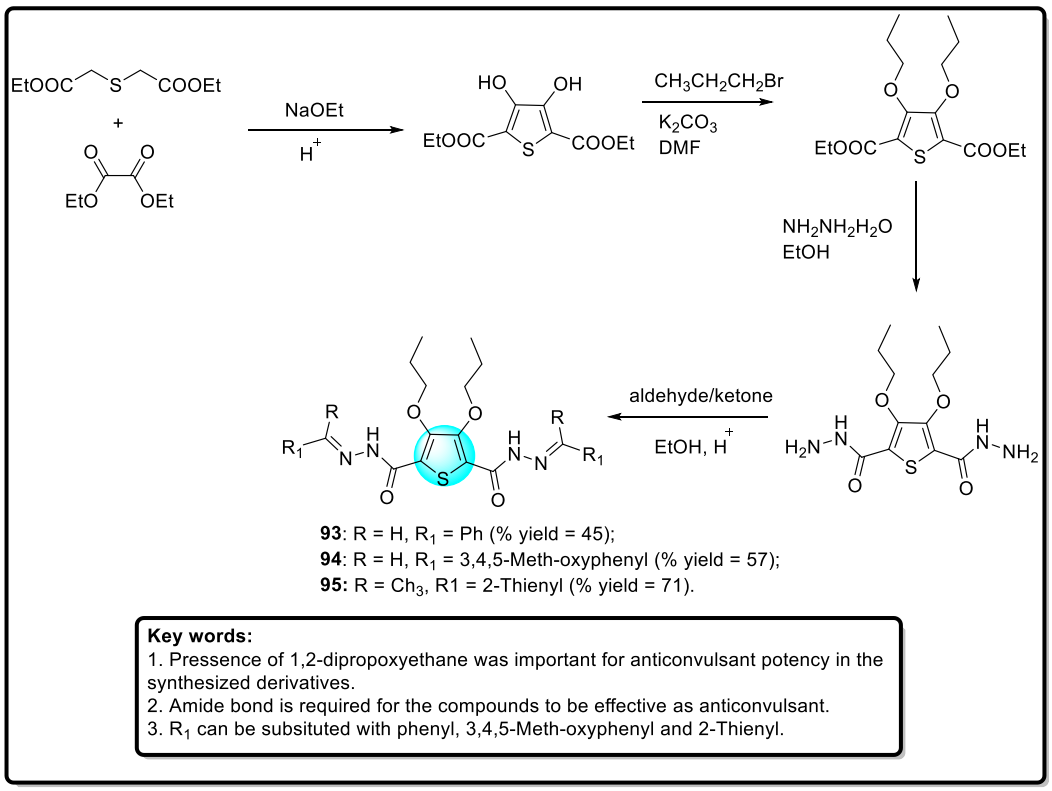


Scheme 39. The synthesis of thiophene fused with other different heterocyclic moieties possessing significant anticonvulsant activity.

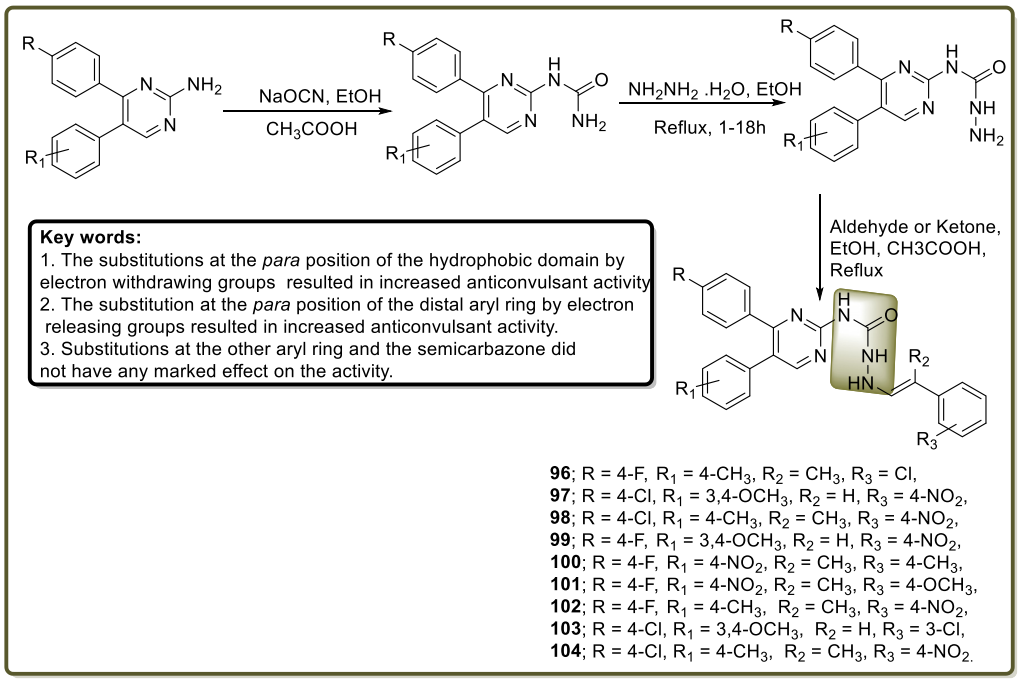
Scheme **40**). The anticonvulsant activity was evaluated against MES, scMET, 6 Hz models and the minimal neurotoxicity was tested by rotarod technique. From the various evaluation results, it was concluded that compounds **93** and **94** possessed significant anticonvulsant effect and marginal efficacy and lesser neurotoxic at a higher dose of 300 mg/kg. In scMET model, 1/5 of the animals were found to be protected after 4h. Compounds **93, 94,** and **95** also exhibited good anticonvulsant activity at a dose of 100 mg/kg in the 6 Hz model. The 3,4-dipropyloxythiophene was considered to be an important pharmacophore for anticonvulsant activity [93] (Scheme **40**).

2.11. Semicarbazone

Semicarbazone is synthesized from the semicarbazide and aldehydes/ketones. The semicarbazones derivatives were found to possess varied biological activities *i.e.,* anticancer, anticonvulsant, antimicrobial, and anticonvulsant activities. Dimmock *et al.* have extensively explored semicarbazones as anticonvulsants [94, 95]. Alam *et al.*, accomplished the synthesis of semicarbazone-containing compounds for their anticonvulsant effect in MES and scPTZ models. The synthetic procedure includes the reaction of 4,6-substituted diphenylpyrimidin-2-amines with sodium cyanate and acetic acid. The intermediate (diphenylpyrimidin-2-ureas) formed

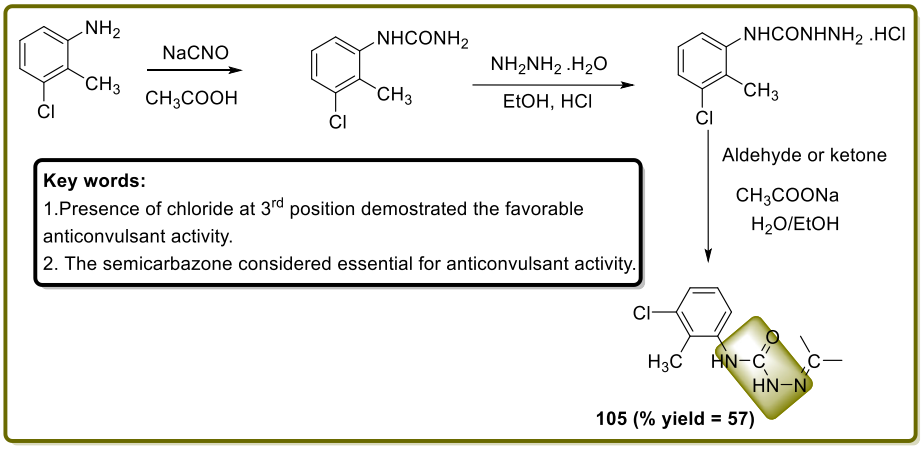


Scheme 40. Synthetic scheme for novel 3,4-dipropyloxy-N_2,N_5-bis(substituted)thiophene-2,5-dicarbohydrazides.

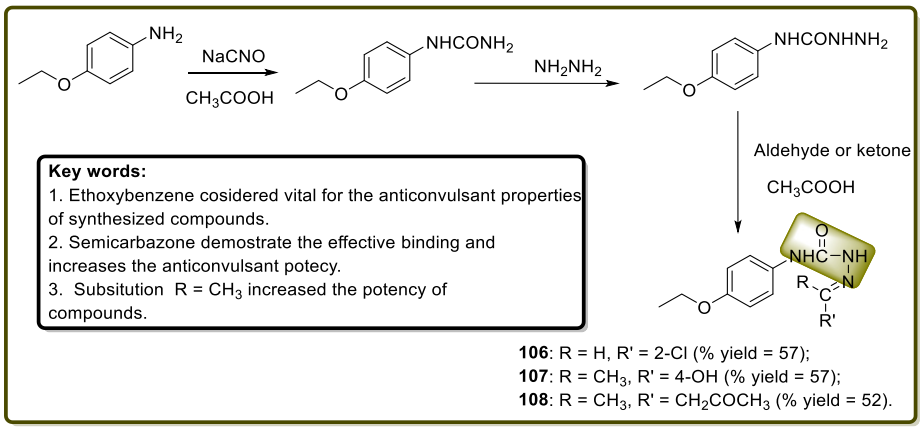


Scheme 41. The synthesis of pyrimidine semicarbazone derivatives with rapid onset and prolonged duration anticonvulsant.

were further subjected to refluxing with hydrazine hydrate in ethanol. The different semicarbazides formed in the last steps were converted to semicarbazones on condensation with substituted aromatic aldehydes and ketone and desired product was obtained in good yields of 65-85%. Compounds **96, 97** and **98** were found to be most potent. They showed protection at 30 mg/kg after 0.5h and at a maximum dose of 300 mg/kg after 4.0h. The activity results suggest a rapid onset of action along with a prolonged duration of action at higher doses. The compounds **99, 100, 101, 102, 103** and **104** showed protection at 100 mg/kg after 0.5h. The chemshock investigation insight that compound **97** showed phenomenal activity because it continued to be active at the dose of 100 mg/kg even after 4h. The compounds were less neurotoxic



Scheme 42. Synthetic scheme for 3-chloro-2-methylphenyl substituted semicarbazones as active anticonvulsant.

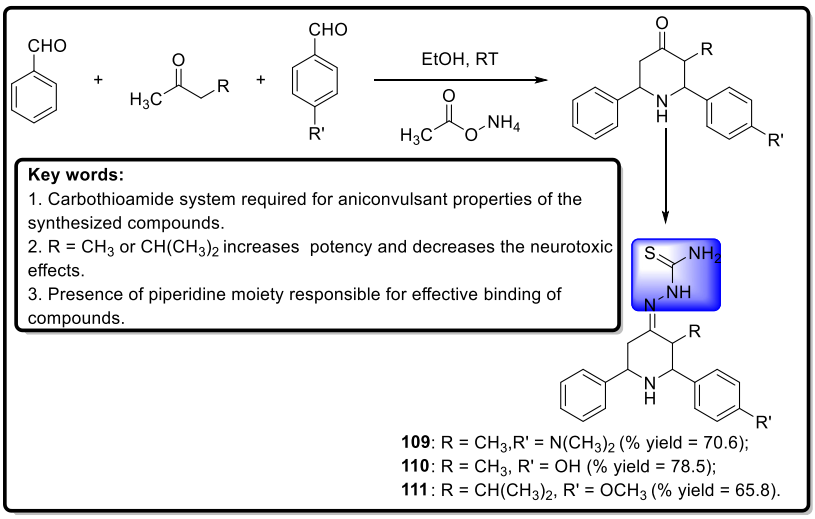


Scheme 43. The 4-ethoxyphenyl semicarbazones derivatives as effective against convulsion.

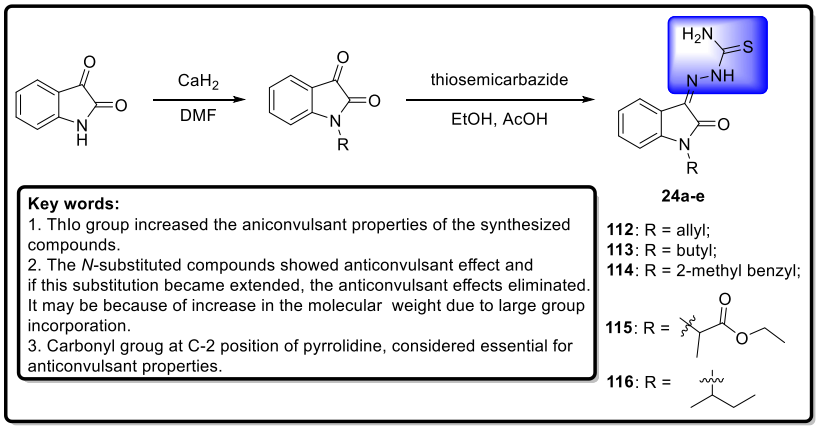
and hepatotoxic indicating better tolerability [96] (Scheme **41**). Yogeeswari *et al.*, reported the series of 3-chloro-2-methylphenyl substituted semicarbazones and tested the analogues as anticonvulsant agents. The various derivatives were tested with the help of MES, scPTZ, subcutaneous strychnine (scSTY)-induced seizure and neurotoxicity screening models. The percentage yield of the compound is mentioned in (Scheme **42**). Among all the synthesized derivatives compound **105** depicted anticonvulsant effects against all the selected models. Moreover, compound **105** was also observed as lesser neurotoxic in comparison to phenytoin [97] (Scheme **42**). Yogeeswari *et al.* synthesized another series of 4-ethoxyphenyl semicarbazones in good yield mentioned in Scheme **43** and evaluated them for their anticonvulsant activity against MES and scPTZ induced seizure in mice. The neurotoxicity was evaluated by the rotarod test. Compounds **106, 107** and **108** showed significant protection from seizures in both the screening test. Compound **106** was found to be active in MES at 100 mg/kg dose after 30min and at 300 mg/kg after 4h of drug administration whereas, in scPTZ it was active at 300 mg/kg dose after 0.5h. In MES compound **107** and **108** were found to be active at a dose of 100 mg/kg after 0.5h and at the higher dose of 300 mg/kg after 4h whereas, in scPTZ compound **107** was active at 100 mg/kg after 0.5h and at the higher dose of 300 mg/kg after 4h. In scPTZ study, compound **108** was found to be active at dose of 300 mg/kg after 0.5 and 4h. Compounds **107** and **108** showed neurotoxic effect but at the maximum dose of 300 mg/kg whereas, compound **106** was non-neurotoxic. The GABA estimation test revealed that, synthesized derivative **107** increases (GABA) levels in the medulla oblongata region whereas, compound **108** increases GABA in both medulla oblongata and the olfactory lobe of the rat brain. Compound **107** showed the 10% inhibition after 8h only [98] (Scheme **43**).

2.12. Thiosemicarbazones

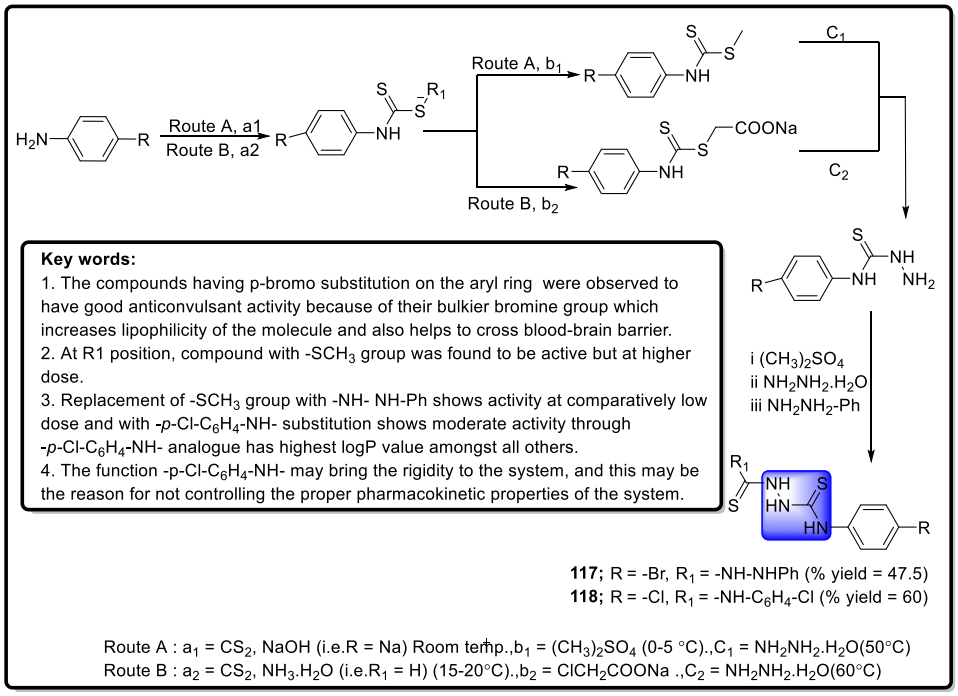
Yogeeswari *et al.*, have reported many studies on thiosemicarbazide and thiosemicarbazones and highlighted their anticonvulsant spectrum [99]. The requirement for any compounds to be potent anticonvulsant is that in MES large hydrophobic groups are needed between two-electron donor groups whereas a less hydrophobic group is required to be present nearer to the two-electron donor system. The requirement is very much fulfilled by aryl semicarbazides/semicarbazones [100]. Rastogi *et al.* prepared various thiosemicarbazone derivatives of 2,6-diaryl-3-methyl-4-piperidones. The percentage yield of the compounds is mentioned in (Scheme **44**). The reactions were carried out with the help of the microwave which reduces the time from 12-16 h to only a few minutes (4-7 min). The yield of one of the compounds **110** is 79% and showed lesser impurities on TLC as compared to conventional methods. Compounds **109**, **110** and **111** showed phenomenal activity as compared with



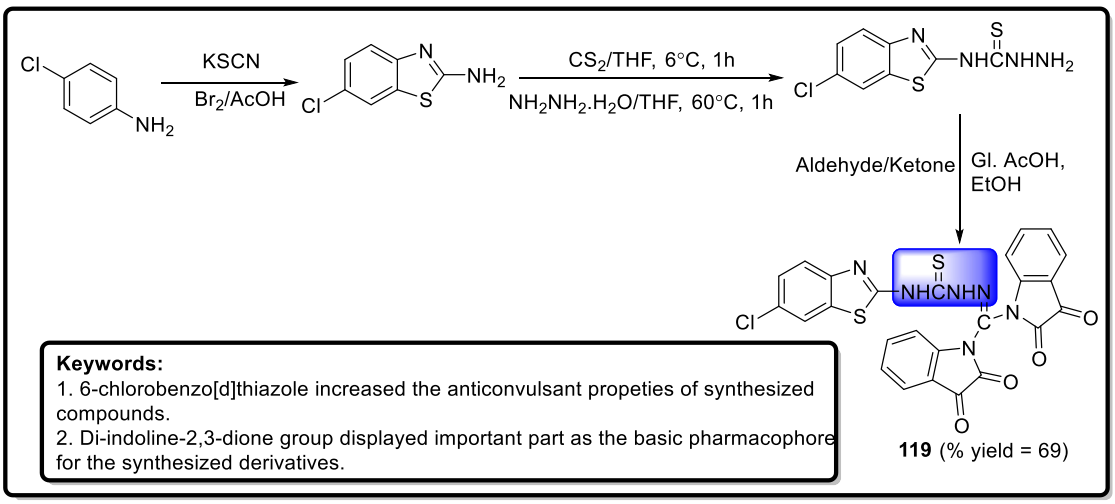
Scheme 44. Synthetic scheme of thiosemicarbazone derivatives of 2,6-diaryl-3-methyl-4-piperidones derivatives as potential anticonvulsant.



Scheme 45. Semicarbazone and thiosemicarbazone derivatives of isatin displayed remarkable anticonvulsant activity.



Scheme 46. Synthetic scheme of novel thiosemicarbazide derivatives and active against MES and scPTZ induced seizure.

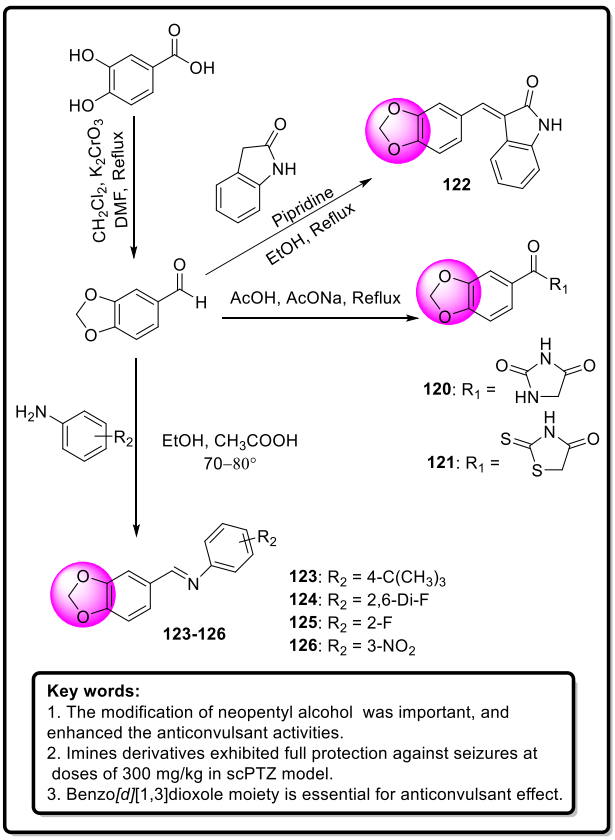


Scheme 47. One pot synthesis of derivatives of 6-chlorobenzothiazolyl-2-thiosemicarbazones as anticonvulsant.

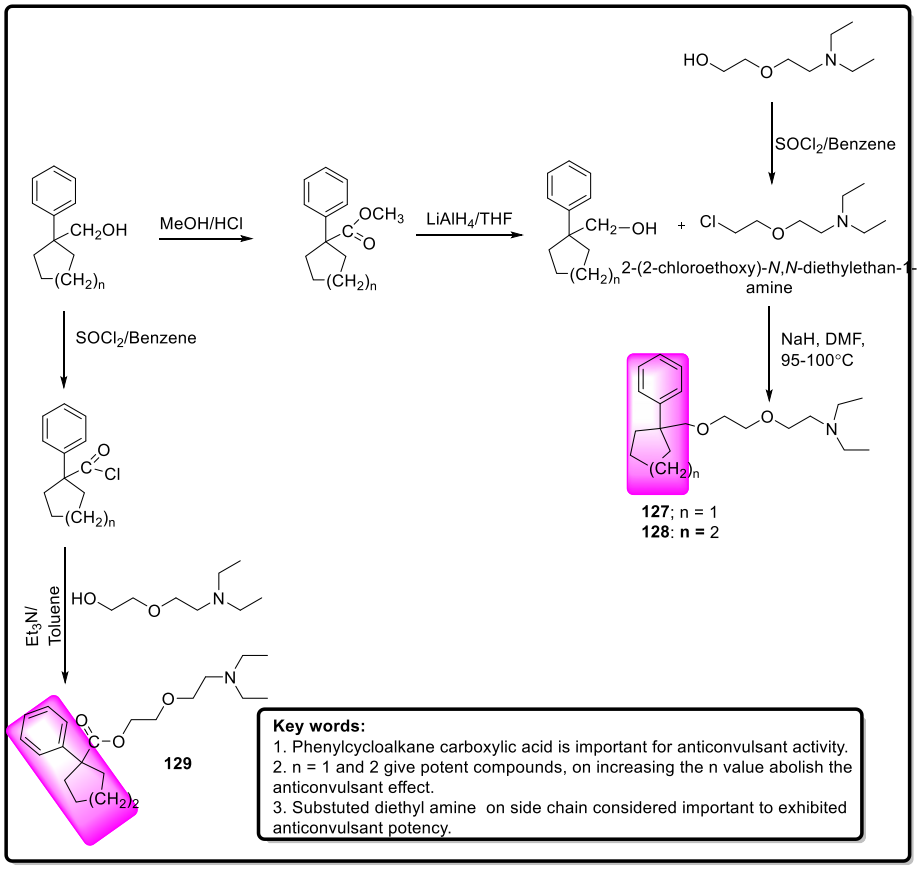
the standard in maximal MES screening method [101] (Scheme **44**). In another study various thiosemicarbazone derivatives were synthesized and evaluated for anticonvulsant activity by Divar *et al.* In the first step, alkylation of isatin was done with the help of calcium hydride in DMF. In the next step, *N*-substituted isatins were used to synthesize the desired semicarbazone and thiosemicarbazone analogs of isatin with good percentage yields *i.e.,* more than 85%. The compounds were tested against the PTZ model (acute) in male mice (85 mg/kg) and the chemical kindling model (chronic) in male rats (37.5 mg/kg each 48h for 14-20 days). Inhibition of PTZ induced seizures is useful for treating myoclonic and absence seizures in humans whereas the kindling model was investigated for complex partial seizures and drug-resistant one. Compounds **112, 113, 114, 115** and **116** displayed remarkable anticonvulsant activities at three doses of 10, 20 and 30 mg/kg. In the kindling model, two derivatives were found to be the most effective compounds *i.e.,***112** and **113** at the doses of 10, 30 mg/kg. Both compounds were able to show 100% protection in the epileptogenesis process [102] (Scheme **45**). Nevagi *et al.*, reported the novel series of thiosemicarbazide derivatives (percentage yield is shown in the Scheme **46**). Two routes were described for the synthesis of thiosemicarbazides. In route one, *p*-chloroaniline was treated with carbon disulphide to form dimethyl sulphate in basic condition and then reacted with hydrazine hydrate to get *p*-chlorophenyl thosemicarbazide. In another aniline was treated with carbon disulphide to give dithiocarbamate in the presence of ammonia and sodium chloroacetate. The dithiocarbamate on reaction with hydrazine hydrate yielded thiosemicarbazide. The second method is more efficient in terms of yield and time. The anticonvulsant activities were carried out against MES and PTZ induced convulsion to check for grand mal and petit mal epilepsy, respectively. Neurotoxicity of the compounds was carried out by the rotarod screening method. Among all the synthesized compounds, **117** emerged as the most active compound in both MES and PTZ induced seizure models with the absence of neurotoxicity effect. Compound **118** was identified as the most selective agent for grand mal epilepsy because it reduced the duration of hind limb extension in MES induced seizures model. The compound **118** was active after 30 min and 4h, which displayed fast onset and longer-acting drug with no sign of neurotoxicity [103] (Scheme **46**). Yogeeswari *et al.*, synthesized the various derivatives of 6-chlorobenzothiazolyl-2-thiosemicarbazones in one-pot procedure. The thiourea was generated *in-situ* and then oxidized to (6-chloro-2-benzothiazolamine) which on reaction with carbon disulphide (benzothiazolyl dithiocarbamate) and hydrazine hydrate yielded the final product. The synthesized compounds were tested for anticonvulsant activity against the MES and PTZ testing methods. Compound **119** (percentage yield of 69%) was the most potent compound with an ED_{50} value of 17.86 and 6.07 in mice after *i.p.* and rat *p.o.* administration. The compound **119** was found to be as potent as standard drug valproate against both MES and scPTZ-induced seizures. Moreover, it was also found to be more potent than ethosuximide against MES-induced seizures. Compound **119** showed a protective index (PI) of 8.77 in the rat *p.o.* administration against MES screen. It was observed that isatin-imino derivatives were more potent than benzylidene/acetophenone but more toxic than benzylidene derivatives [104] (Scheme **47**).

2.13. Miscellaneous

Dong *et al.*, synthesized a series of novel benzo[d](1,3) dioxole derivatives with good percentage yield (more than 75%) and evaluated them for anticonvulsant activity against the MES and scPTZ models screening methods. The various synthesized compounds were also subjected to rotarod test for neurotoxicity. Among the series of compounds, six of them showed satisfactory anticonvulsant activities in the MES model *i.e.,* **120-125**. The compounds **126** and **123** showed complete protection from seizures in the scPTZ test at a maximum dose of 300 mg/kg. Moreover, compound **122** exhibited the most potent activity with high protection against the MES-induced seizures. Compound **122** showed an ED_{50} value of 9.8 mg/kg and a TD_{50} value of 229.4 mg/kg after *i.p.* injection into mice. It also showed a high protective index (TD_{50}/ED_{50}) = 23.4 as compared to the reference antiepileptic drugs *i.e.,* phenytoin (6.9) and phenobarbital (3.2) [105] (Scheme **48**). Calderon *et al.*, synthesized a series of 1-phenylcycloalkanecarboxylic acid analogs with moderate to good percentage yield (27-55%). The compounds were



Scheme 48. Synthetic scheme for novel benzo[d](1,3)dioxole derivatives with high percentage yield and better anticonvulsant profile.



Scheme 49. Synthesis of 1-phenylcycloalkanecarboxylic acid analogs with promising anticonvulsant effect.

designed taking carbetapentane as prototype molecules as the ester functionality of the drug is susceptible to metabolic degradation. The synthesis of the compounds was tried with different increasing temperature, but decomposition led to a side-chain elimination product. The most appropriate temperature of the reaction between 2-(2-chloroethoxy)-*N,N*-diethylethan-1-amine and 1-phenylcyclopentanemethano to get **127** and **128** was 95-100 ºC. The reduction of the ester group with sodium borohydride-boron trifluoride etherate was unsuccessful. The method adopted was a reduction with $LiAlH_4$ in solvent THF. The various synthesized analogues were investigated for their anticonvulsant activity in rat against MES. Compounds **127, 128** and **129** showed promising anticonvulsant effects with an ED_{50} value of 16, 86 and 173 µmol/kg respectively. Moreover, compound **127** was identified as the most potent than the prototype anticonvulsant drug *i.e.*, diphenylhydantoin [106] (Scheme **49**).

CONCLUSION

Right from the patent, approved marketed drugs and the extensive research carried out by different research groups, it can be suggested that there are groups other than nitrogen-containing rings which play a vital role in decreasing the severity of convulsions in epileptic patients. First, the group of linkers is provided by amides, semicarbazone, and thiosemicarbazone, which serve in compounds as proving linkers. The second group is chalcone which provides space for the development of many heterocyclic compounds as anticonvulsant agents. The third group includes coumarin and flavones which are documented to show a high percentage of protection when combined with amides/heterocyclic moieties. The fourth group provides the naphthalene and steroid derivatives that play important roles in providing the hydrophobic part in the compounds; one of the essential features required for any compound to cross the blood-brain barrier. Other important ring systems discussed include furan and thiophene and their possibility to convert into more potent compounds. Targeting the receptors through sulfonamide derivatives provides an interesting route for the development of anticonvulsant agents with better protection. These functionalities other than nitrogen-containing rings may help medicinal chemists to design many more effective anticonvulsant drugs in near future.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors are thankful to the management of ISF College of Pharmacy, Moga, Punjab, India and College of Pharmacy, National University of Science and Technology, Muscat, Oman for their continuous support and encouragement.

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