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REVIEW ARTICLE

A review on the synthesis and applications of molecules as anticonvulsant drug agent candidates

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Abstract

Epilepsy is one of the most common neurological disorders worldwide and it requires a long-term or life-long treatment. Current standard treatment includes the use of antiepileptic drugs. To date, many organic compounds have been synthesized by chemists as potential antiepileptic drugs and their anticonvulsant properties have been investigated. While evaluating the anticonvulsant activities of these newly synthesized molecules, known antiepileptic drugs are used as reference. Thus, many novel molecules with anticonvulsant properties have been added to the literature. It is clear that these new molecules will be effective in the treatment of epilepsy. In this review, we investigated the synthesis and properties of organic compounds with anticonvulsant properties.

Keywords Synthesis · Anticonvulsant activity · Epilepsy · Antiepileptic drug

Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent seizures and affects 1–2% of world population (Kumar et al. 2016; Kaindl et al. 2006; Cárdenas-Rodríguez et al. 2020). According to the recent studies about 70 million people have epilepsy worldwide and the vast majority of these patients live in developing countries (Benlier et al. 2020). In addition, epilepsy was estimated to affect ~10 million children worldwide (Gadgil et al. 2019). Epilepsy is clinically characterized by sudden attacks involving only one part of the brain or both hemispheres and epileptic seizures may result from transient interruption of normal brain function (Bora et al. 2015). Genetic predisposition, various diseases and several environmental triggers play a role in the etiology of epilepsy (Fisher et al. 2005). Epileptic seizures are fundamentally divided into two major groups as partial (simple partial, complex partial) and generalized (absence, myoclonic, clonic, tonic, tonic–clonic, and atonic).

The treatment epilepsy requires long-term or lifetime treatment depending on the type of seizures with the use of antiepileptic drugs (LoPinto-Khoury and Mintzer 2010). Anticonvulsants or antiepileptic drugs are pharmacological agents used in the treatment of these epileptic seizures. Antiepileptic drugs work through different mechanism such as the enhancement of γ-amino butyric acid (GABA) neurotransmission or the modulation of voltage-gated ion channels (sodium and calcium) (Saravanan et al. 2012). Levetiracetam, phenytoin, phenobarbital, carbamazepine, felbamate, ethosuximide, diazepam, valproate, gabapentin, and tiagabine (Fig. 1) are some of the commonly used drugs in the treatment of epilepsy.

Animal seizure models have played a significant role in epilepsy research including synthesis, characterization, and identification of new anticonvulsant drugs (Rogawski 2006). The most commonly employed tests in animal models in the search for newly synthesized compounds with anticonvulsant activities are the maximal electroshock-induced seizure (MES) and the subcutaneous pentylenetetrazol-induced seizure (PTZ) tests (Júnior et al. 2008). MES test identifies the compounds that prevent the spread of seizures and the s.c.PTZ test primarily identifies the compounds that raise the seizure

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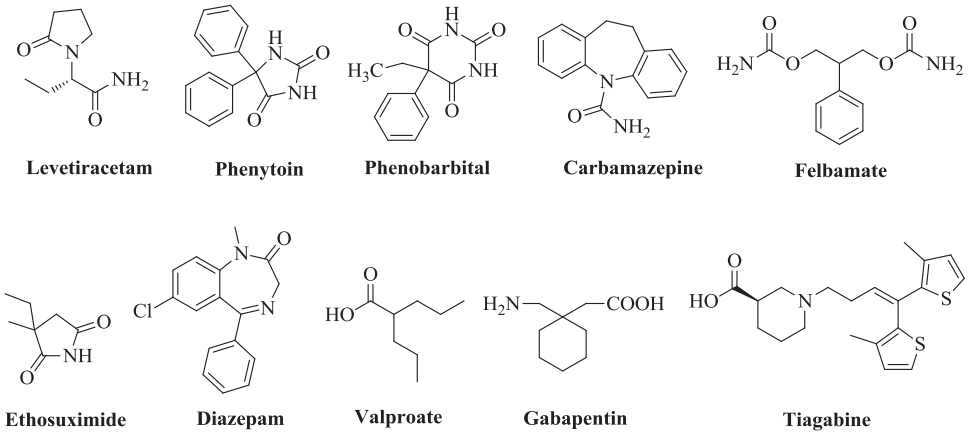


Fig. 1 Antiepileptic drugs used in epilepsy treatment

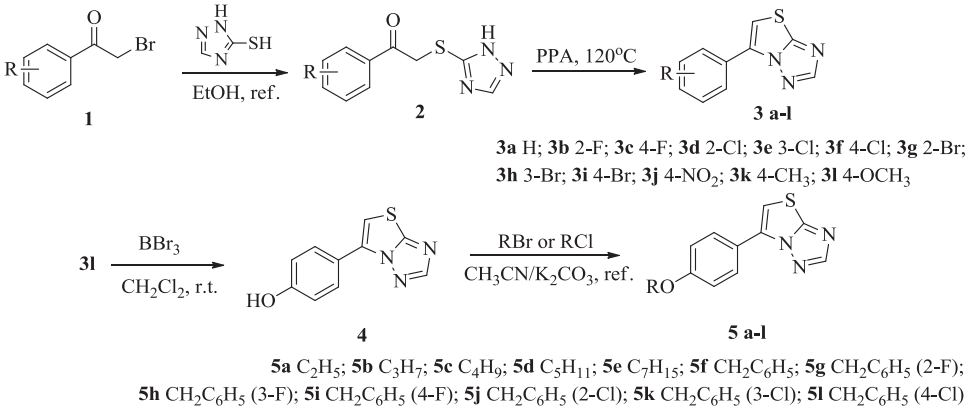


Fig. 2 Synthesis of triazole derivatives **(3** and **5 a–l)**

threshold in these animal seizure models (Sanjay et al. 2007).

The structure–activity relationship is the connection between the chemical structure of a synthesized molecule and its biological activity. Chemists use various synthesis techniques to insert different groups into the bioactive compounds and test them for their biological activity. In the recent years, organic chemists have been working hard to describe the synthesis and properties of new compounds that may show anticonvulsant activity. In this review, the synthesis and properties of molecules with anticonvulsant effects were investigated.

Synthesis of organic compounds with anticonvulsant activity

Deng et al. (2014a) synthesized 6-(substituted phenyl)thiazolo[3,2-*b*][1,2,4] triazole derivatives **(3** and **5 a–l)** (Fig. 2) and studied for their anticonvulsant activity using MES and PTZ tests. In this report, 6-(4-fluorophenyl)thiazolo[3,2-*b*][1,2,4]triazole **(3b)** and 6-(4-propoxyphenyl)thiazolo[3,2-*b*][1,2,4]triazole **(5c)** were found to be active in both tests. In addition, in PTZ screening, compound 6-(4-Propoxyphenyl) thiazolo[3,2-*b*][1,2,4]triazole was reported to have a higher PI (TD_{50}/ED_{50}) value compared with carbamazepine a commonly used drug in epilepsy treatment.

Zayed et al. (2017) synthesized novel fluorinated quinazoline derivatives **(10 a–j)** (Fig. 3) and investigated the anticonvulsant activity and neurotoxic properties of these newly synthesized molecules using mice experiments. All of the synthesized molecules in this study were shown to have significant anticonvulsant activity in PTZ and MES tests (Fig. 4). In addition, the three of the compounds **(10 b**, **c**, and **d)** showed the highest binding affinities to the GABA-A receptor. These three compounds **(10 b–d)** were reported to show higher anticonvulsant activity (PI values are 1.78, 2.12, and 2.29, respectively) in experimental mice than reference epilepsy drugs, metacalon (PI value 2) and valproate (PI value of 1.5).

Khokra et al. (2019) synthesized ¾ substituted benzene sulfonamides **(16**, **17 a–g)** (Fig. 5) linked via phenyl ring to a benzothiazole moiety **(13** and **14)**. In this study, the anticonvulsant potentials of these newly synthesized molecules were evaluated. According to their results, *N*-[4-(benzothiazole-2-yl)phenyl]3-substituted benzene sulfonamide **(16 a–g)** derivatives possessed better anticonvulsant activity in comparison with 4-substituted benzene

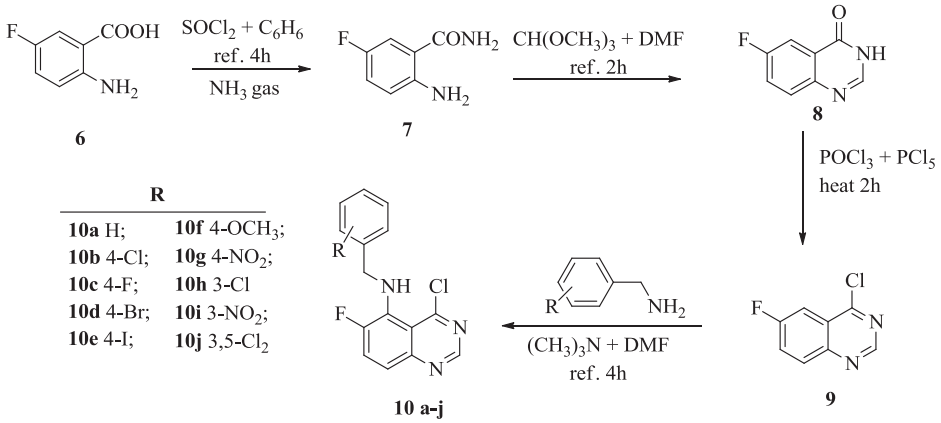


Fig. 3 Synthesis of fluorinated quinazoline derivatives **(10 a–j)**

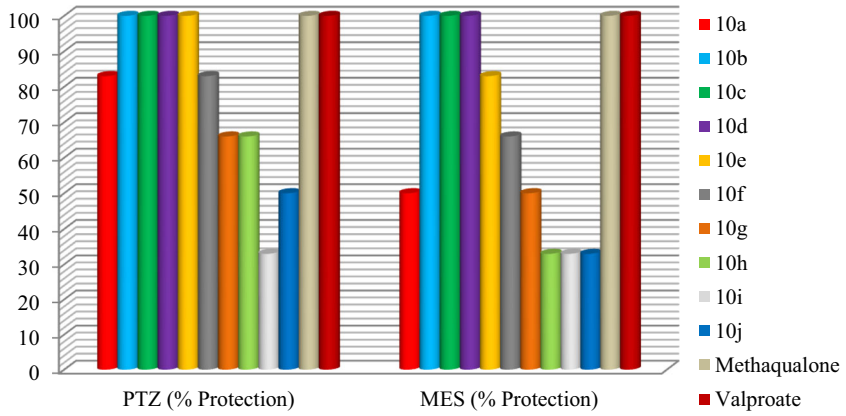


Fig. 4 Anticonvulsant effects of quinazoline derivatives **(10 a–j)**

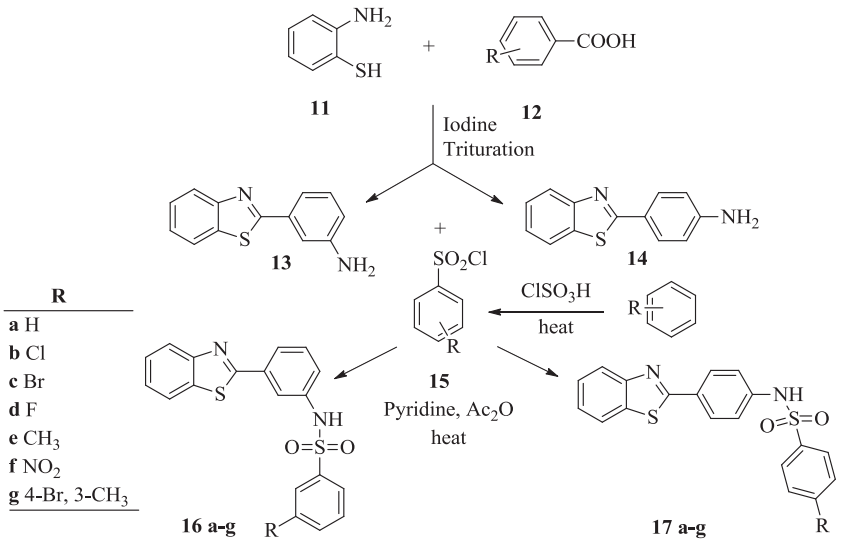


Fig. 5 Synthesis of ¾ substituted benzene sulfonamides **(16** and **17 a–g)**

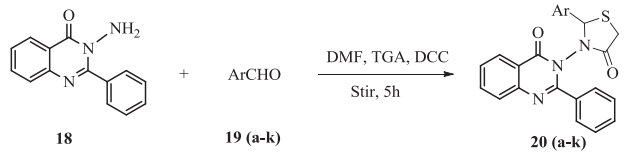
sulfonamide derivatives **(17 a–g)**. Amongst all the synthesized compounds in this work, **16b** was reported to be the strongest anticonvulsant agent in MES test performed in mice.

In a study by Jangam et al. (2019) 3-(2-substituted)-4-oxothiazolidin-3-yl)-2-phenylquinazolin-4(3*H*)-one compounds **(20 a–k)** (Fig. 6) were synthesized according to two-component reaction using 3-amino-2-phenylquinazolin-4(3*H*)-one **(18)**, substituted aromatic aldehydes **(19 a–k)**, TGA and DCC in *N,N*-dimethyl formamide as a solvent. In vivo anticonvulsant activities of these compounds were performed by maximal electroshock induced convulsion model. Six of the

newly synthesized molecules **(20 b**, **c**, **d**, **e**, **f**, and **i)** were reported to have a higher anticonvulsant activity compared with phenytoin which was used as a reference in this study (Fig. 7).

Malik and Khan (2014) performed the synthesis of a series of novel (5-amino-3-substituted-1,2,4-triazin-6-yl)(2-(6-halo-substituted benzo[*d*]isoxazol-3-yl)pyrrolidin-1-yl) methanone derivatives **(25 a–r)** (Fig. 8). These newly synthesized compounds were evaluated in terms of their anticonvulsant and neurotoxic properties. It was reported that the (5-amino-3-phenyl-1,2,4-triazin-6-yl)(2-(6-fluorobenzo[*d*]isoxazol-3-yl)pyrrolidin-1-yl) methanone **(25c)** molecule had a stronger anticonvulsant property (PI values of 48.38) than the standard antiepileptic drug phenytoin (PI values of 35.58). Also, they reported that compounds of **25b**, **25i**, and **25o** showed good anticonvulsant activity in this study.

Harish et al. (2013) synthesized a series of new pyrazine substituted 1,3,4-thiadiazole derivative **(35 a–o)** (Fig. 9). In this study, the new compounds were screened for their anticonvulsant activity using MES seizure method. In addition, the neurotoxicity of the compounds was determined in order to assess their clinical usability. Among the synthesized compounds, **35d** and **35g** were reported to



Ar: a) Ph, **b)** 4-OHPh **c)** 4-OCH_3Ph **d)** 4-NO_2Ph **e)** 3-OHPh **f)** 3-NO_2Ph **g)** 4-$N(CH_3)_2$Ph **h)** 3-ClPh **i)** 3,4-OCH_3Ph **j)** 2-ClPh **k)** 4-FPh

Fig. 6 Synthesis of 3-(2-substituted)-4-oxothiazolidin-3-yl)-2-phenylquinazolin-4(3*H*)-one derivatives **(20 a–k)**

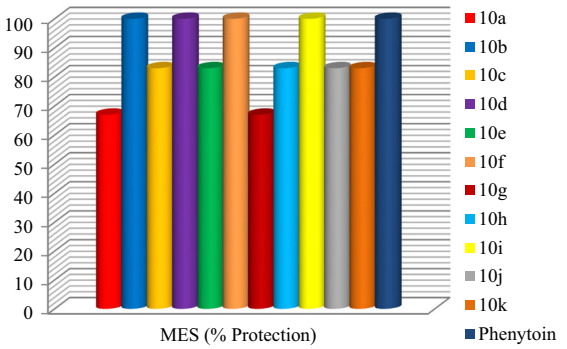
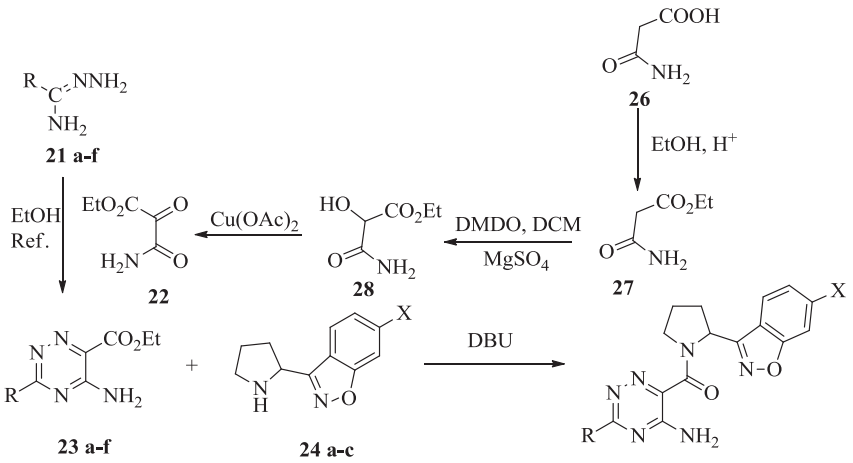


Fig. 7 Anticonvulsant activity of 3-(2-substituted)-4-oxothiazolidin-3-yl)-2-phenylquinazolin-4(3*H*)-one derivatives **(20 a–k)**

Fig. 8 Synthesis of (5-amino-3-substituted-1,2,4-triazin-6-yl)(2-(6-halo-substituted benzo[*d*] isoxazol-3-yl)pyrrolidin-1-yl) methanone derivatives **(25 a–r)**



Compd.	25a	25b	25c	25d	25e	25f
R	$-CH_3$	$-NH_2$	$-C_6H_5$	2-pyridyl	2-pyrimidyl	2-pyrazinyl
X	-F	-F	-F	-F	-F	-F
	25g	**25h**	**25i**	**25j**	**25k**	**25l**
R	$-CH_3$	$-NH_2$	$-C_6H_5$	2-pyridyl	2-pyrimidyl	2-pyrazinyl
X	-Cl	-Cl	-Cl	-Cl	-Cl	-Cl
	25g	**25h**	**25i**	**25j**	**25k**	**25l**
R	$-CH_3$	$-NH_2$	$-C_6H_5$	2-pyridyl	2-pyrimidyl	2-pyrazinyl
X	-Br	-Br	-Br	-Br	-Br	-Br

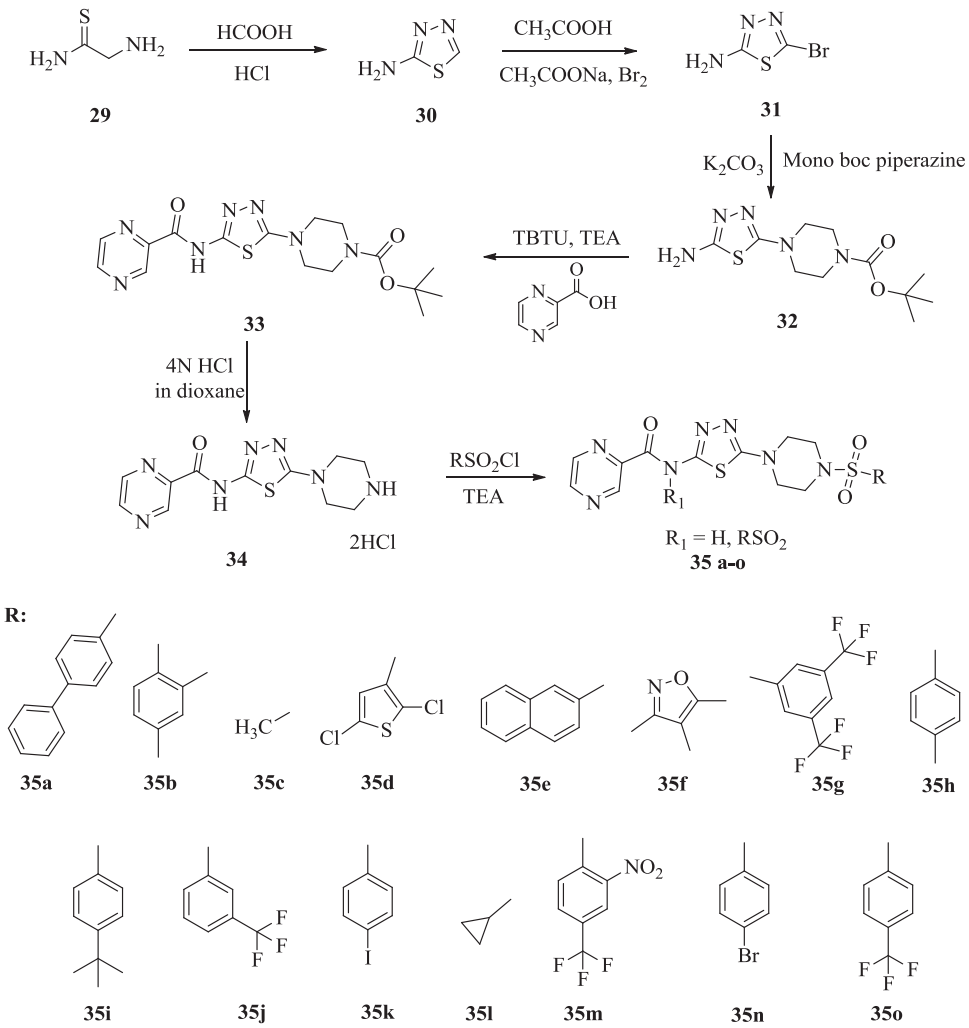


Fig. 9 Synthesis of pyrazine substituted 1,3,4-thiadiazole derivative **(35 a–o)**

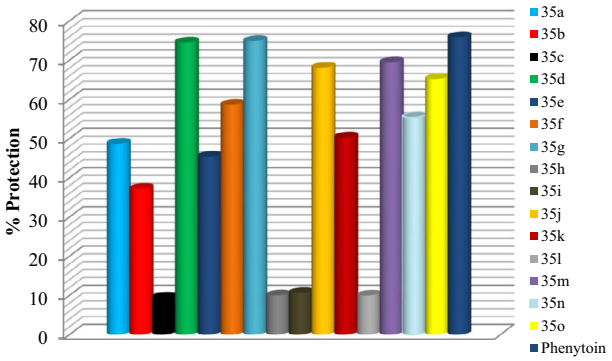


Fig. 10 % Protection of pyrazine substituted 1,3,4-thiadiazole derivative **(35 a–o)** in the MES test

exhibit excellent anticonvulsant activity and proposed as potential antiepileptic compounds (Fig. 10).

Thirteen novel cyclopentanecarbaldehyde-based 2,4-disubstituted 1,3-thiazoles compounds **(38 a–m)** (Fig. 11) were synthesized by Łaczkowski et al. (2016a) and these compounds were evaluated for their in vivo anticonvulsant activities. The results of these the anticonvulsant tests revealed that seven compounds, **38a**, **38b**, **38d**, **38e**, **38f**, **38k**, and **38m** demonstrated the most significant anticonvulsant activity in the PTZ model. In addition, compounds **38a** and **38b** were reported to delay the onset of clonic seizures and reduce the number of seizure episodes in mice models.

Iman et al. (2017) synthesized a number of compounds **(41–45** and **48)** (Fig. 12) related to the ameltolide and examined their anticonvulsant activities in mice. Phenytoin was used as the reference antiepileptic drug in this study, and the compounds showed better anticonvulsant activity relative to the reference and their activity were maximum 30 min after administration. Furthermore, it was reported that the effect of compound **42** (62.46 ± 6.48) on clonic seizure was stronger than that of phenytoin (49.20 ± 1.09).

3-alkoxy-4-(4-(hexyloxy/heptyloxy)phenyl)-4*H*-1,2,4-triazole derivatives **(53 a–t)** (Fig. 13) were synthesized by

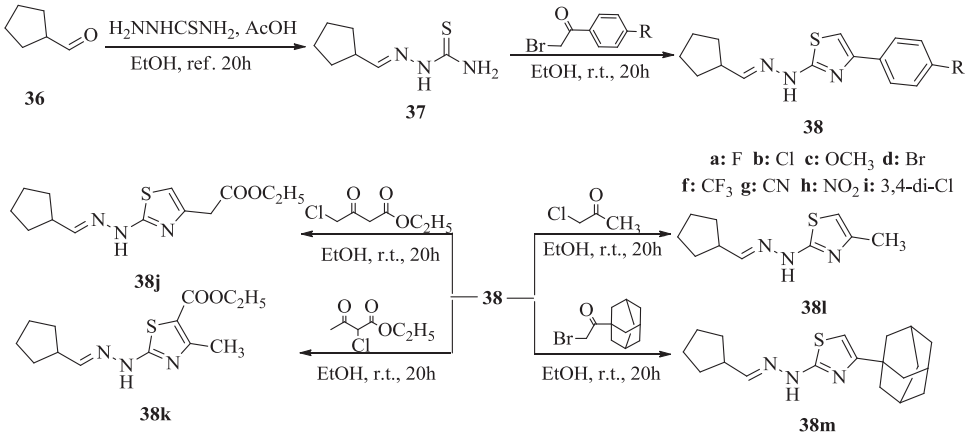


Fig. 11 Synthesis of cyclopentanecarbaldehyde-based 2,4-disubstituted 1,3-thiazoles **(38 a–m)**

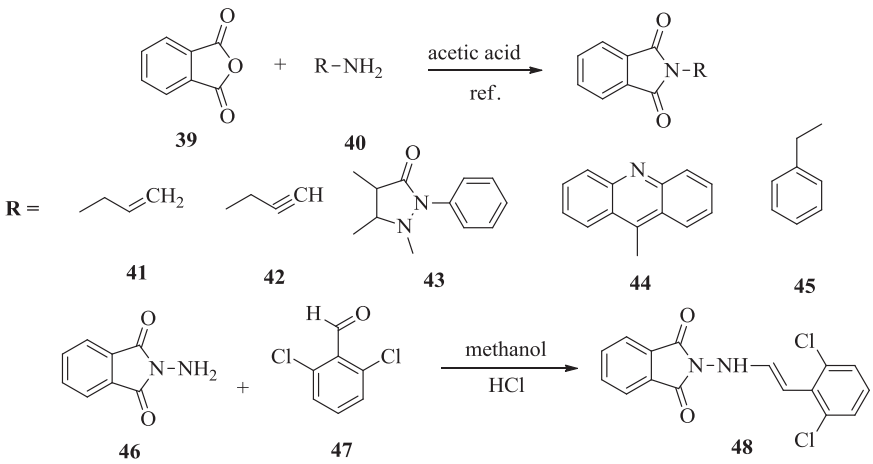
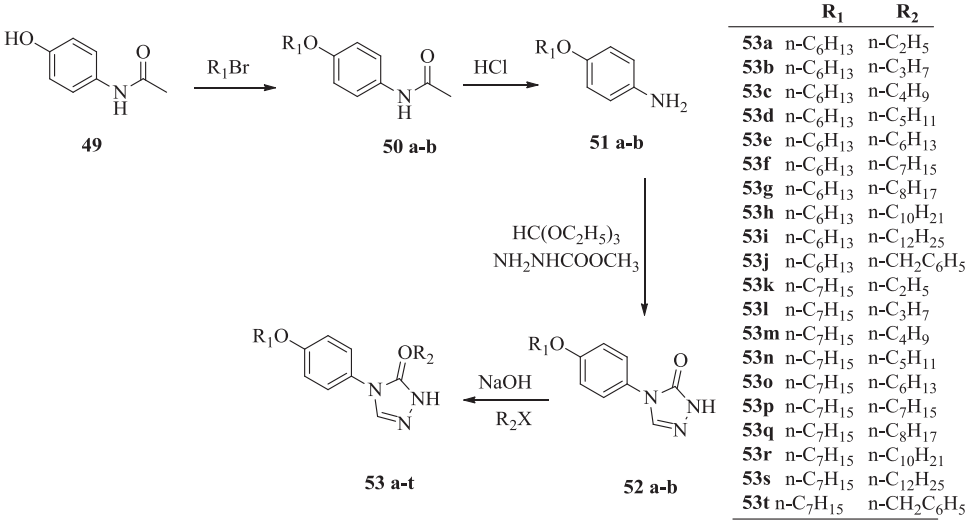


Fig. 12 Synthesis of *N*-substituted phthalimide derivatives **(41–45** and **48)**



	R_1	R_2
53a	n-C_6H_{13}	n-C_2H_5
53b	n-C_6H_{13}	n-C_3H_7
53c	n-C_6H_{13}	n-C_4H_9
53d	n-C_6H_{13}	n-C_5H_{11}
53e	n-C_6H_{13}	n-C_6H_{13}
53f	n-C_6H_{13}	n-C_7H_{15}
53g	n-C_6H_{13}	n-C_8H_{17}
53h	n-C_6H_{13}	n-$C_{10}H_{21}$
53i	n-C_6H_{13}	n-$C_{12}H_{25}$
53j	n-C_6H_{13}	n-$CH_2C_6H_5$
53k	n-C_7H_{15}	n-C_2H_5
53l	n-C_7H_{15}	n-C_3H_7
53m	n-C_7H_{15}	n-C_4H_9
53n	n-C_7H_{15}	n-C_5H_{11}
53o	n-C_7H_{15}	n-C_6H_{13}
53p	n-C_7H_{15}	n-C_7H_{15}
53q	n-C_7H_{15}	n-C_8H_{17}
53r	n-C_7H_{15}	n-$C_{10}H_{21}$
53s	n-C_7H_{15}	n-$C_{12}H_{25}$
53t	n-C_7H_{15}	n-$CH_2C_6H_5$

Fig. 13 Synthesis of 3-alkoxy-4-(4-(hexyloxy/heptyloxy) phenyl)-4*H*-1,2,4-triazole **(53 a–t)**

Fang et al. (2015). The anticonvulsant effect and neurotoxicity of the compounds were investigated using MES and rotarod tests applied in mice. According to the results obtained from these mice experiments, compound 3-heptyloxy-4-(4-(hexyloxy)phenyl)-4*H*-1,2,4-triazole **(53f)** was the most effective (Fig. 14) one and had the lowest toxicity among compounds tested. In addition, compound **53f** was observed to be more effective as an anticonvulsant than pentylenetetrazole, 3-mercaptopropionic acid and bicuculline.

Kubowicz et al. (2015) reported the synthesis, antiepileptic activity and biotransformation of three chiral,

N-aminoalkyl derivatives **(57–59)** (Fig. 15). Antiepileptic activity of these the compounds were studied using MES and scMet tests. Valproate was used as the reference antiepileptic drug in the study and it was found that compounds **57**, **58**, and **59** had good antiepileptic activity in vivo, comparable with that of valproate. The authors stated that *trans*-2-aminocyclohexane-1-ol derivatives were the most promising chemical structures in terms of antiepileptic activity.

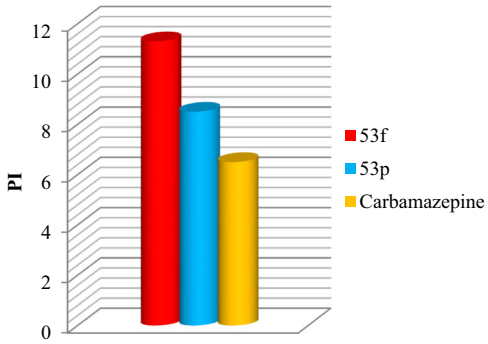


Fig. 14 PI values of **52f** and **52p**

Dibenzofuranone-oxime derivatives **(65 a–h)** (Fig. 16) were synthesized by Zhmurenko et al. (2018). The anticonvulsant effect of the compounds was investigated using MES test applied in mice. According to the results obtained from these mice experiments, compounds with a single Cl atom on the phenyl ring or two Cl atoms at the *meta*- and *para*- positions are more active than other compounds.

6-substituted-[1,2,4]triazolo[3,4-a](tetrazolo[5,1-a]) phthalazine derivatives **(69–105)** (Fig. 17) were synthesized by Bian et al. (2013). Anticonvulsant activities of the all synthesized compounds were determined using MES tests. They reported that the compound **82** had a very strong effect compared with the standard antiepileptic drug carbamazepine (Fig. 18). They also reported that compound **82** showed a broad spectrum of activity against different types of epileptic seizures.

3a,4-dihydro-3*H*-indeno[1,2-c]pyrazole-2-carboxamide/carbothioamide **(108 a–n)** (Fig. 19) analogs were synthesized by Ahsan et al. (2013) and the synthesized compounds were evaluated for their anticonvulsant activity according to the Antiepileptic Drug Development Program protocol. In the study phenytoin, carbamazepine, and sodium valproate were preferred as reference

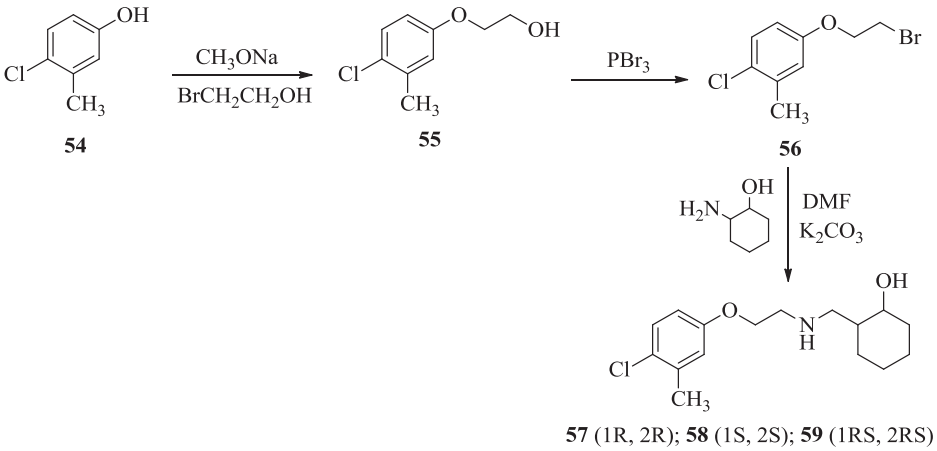
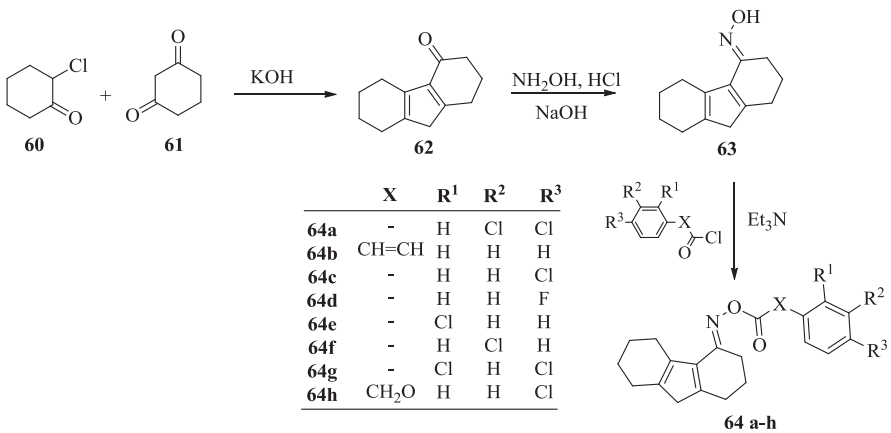


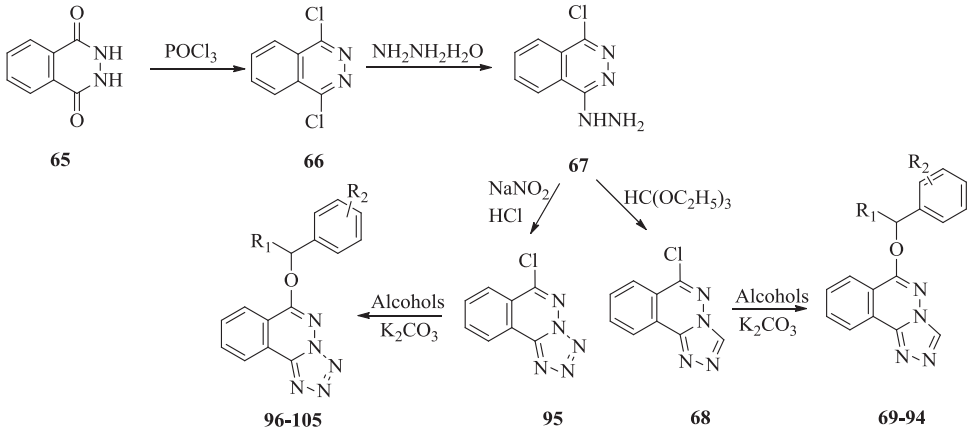
Fig. 15 Synthesis of *N*-aminoalkyl derivatives **(57–59)**



	X	R^1	R^2	R^3
64a	-	H	Cl	Cl
64b	CH=CH	H	H	H
64c	-	H	H	Cl
64d	-	H	H	F
64e	-	Cl	H	H
64f	-	H	Cl	H
64g	-	Cl	H	Cl
64h	CH_2O	H	H	Cl

Fig. 16 Synthesis of dibenzofuranone-oxime derivatives **(64 a–h)**

Fig. 17 Synthesis of 6-substituted-[1,2,4]triazolo[3,4-a](tetrazolo[5,1-a])phthalazine derivatives **(69–105)**



65 66 67 95 68 96-105 69-94

	R_1	R_2
69	H	H
70	H	*o*-F
71	H	*m*-F
72	H	*p*-F
73	H	*o*-*Cl*
74	H	*m*-Cl
75	H	*p*-Cl
76	H	*o*-Br
77	H	*m*-Br
78	H	*o*-OCH_3
79	H	*m*-OCH_3
80	H	*p*-OCH_3
81	H	*o*-CF_3

	R_1	R_2
83	H	*p*-CF_3
84	H	*o*-CH_3
85	H	*cyclohexil*
86	H	H
87	H	*p*-F
88	H	*p*-Cl
89	CH_3	*p*-OCH_3
90	CH_3	*p*-CH_3
91	CH_3	H
92	CH_3	*p*-F
93	CH_3	*p*-Cl
94	C_6H_4(*p*-F)	*p*-F
95	C_6H_4(*p*-Cl)	*p*-Cl

	R_1	R_2
96	H	H
97	H	*p*-F
98	H	*o*-Cl
99	H	*p*-Cl
100	H	*m*-Br
101	H	*m*-CF_3
102	H	*p*-CH_3
103	H	*p*-F
104	CH_3	*p*-F
105	C_6H_4(*p*-F)	*p*-F

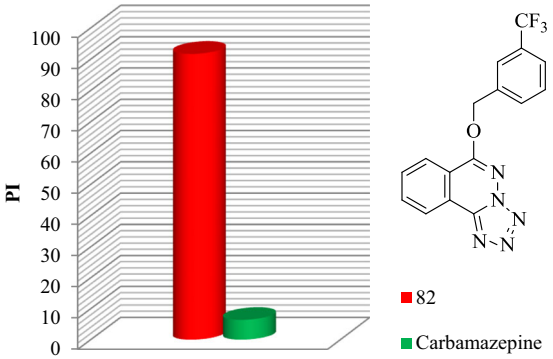


Fig. 18 The PI values of compounds **82** and carbamazepine

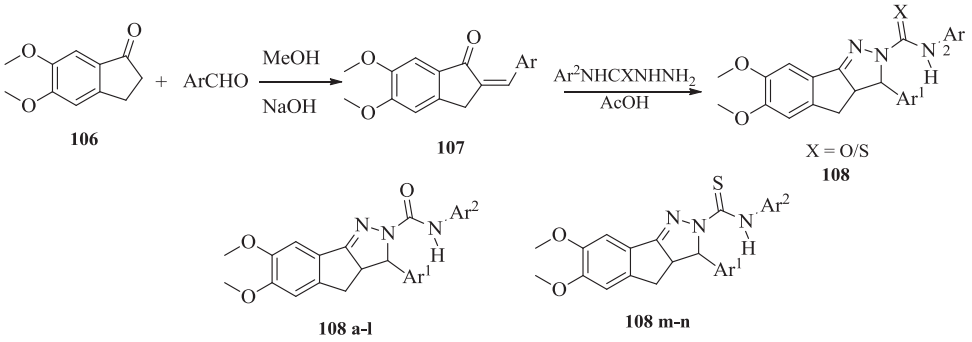
antiepileptics. They reported that compound **108c** had the most effective anticonvulsant properties compared with other compounds tested, according to the MES and subcutaneous metrazole seizure (scMET) tests. It was also reported that this compound protected against minimum clonic seizures without any toxicity.

Piao et al. (2012) synthesized 9-alkoxy-6,7-dihydro-2*H*-benzo[*c*][1,2,4]triazolo[4,3-a] azepin-3(5*H*)-one derivatives **(112 a–n)** (Fig. 20) starting from 2,3,4,5-tetrahydro-7-hydroxy-1*H*-2-benzazepin-1-one **(109)**. While the anticonvulsant activities of these compounds **(112 a–n)** were determined by MES test, their neurotoxic effects were investigated by using the rotarod neurotoxicity test. Compound **112k** was reported to have the strongest anticonvulsant activity and exhibit antagonistic activity against seizures caused by PTZ in mice models.

Six pyrazolo[1,5-a][1,3,5]triazines **(115** and **118 a–c)** (Fig. 21) obtained by one-step reaction from S,S-diethylaroyl-/hetaroylimidodithiocarbonates **(113** and **116 a–c)** and 5-aminopyrazoles **(114)** were synthesized by Insuasty et al. (2014). The analysis of the anticonvulsant effects of these six compounds was performed in vivo by the MES test in mice. The toxicities of these compounds were also investigated by the authors. According to the results obtained, compound **115b** was reported to have anticonvulsant-like effects in some types of seizures (generalized tonic clonic seizures and refractory partial seizures).

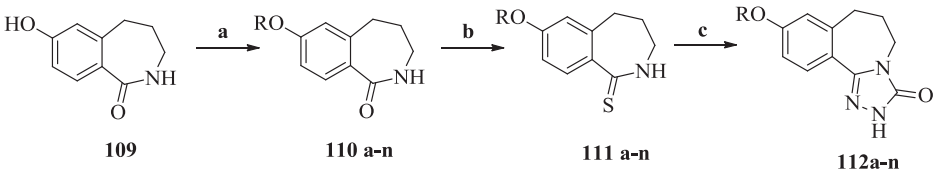
Celen et al. (2011) synthesized thiourea derivatives **(120 a–l)** (Fig. 22) as product of the reaction of isothiocyanate with 4-aminophenyl acetic acid **(119)**. Anticonvulsant activities of these compounds were investigated using PTZ and MES tests in mice. As a result of the tests performed, they found that compound **120b** was more active than the other compounds tested.

Fig. 19 Synthesis of 3a,4-dihydro-3*H*-indeno[1,2-c] pyrazole-2-carboxamide derivative **(108 a–n)**



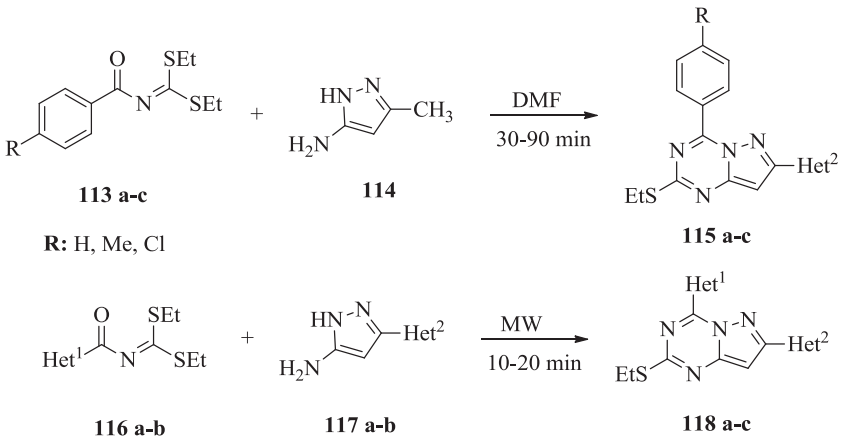
	Ar^1	Ar^2
108a	4-Pyridinyl-	4-Fluorophenyl-
108b	2-Chlorophenyl-	4-Bromophenyl-
108c	4-Fluorophenyl-	4-Bromophenyl-
108d	3,4-Dimethoxyphenyl-	4-Bromophenyl-
108e	4-Methoxyphenyl-	4-Bromophenyl-
108f	4-Pyridinyl-	4-Chlorophenyl-
108g	3,4-Dimethoxyphenyl-	4-Chlorophenyl-
108h	Phenyl-	4-Chlorophenyl-
108i	4-Pyridinyl-	3-Chloro-4-fluorophenyl-
108j	2-Chlorophenyl-	H
108k	3,4-Dimethoxyphenyl-	H
108l	Phenyl-	H
108m	3,4-Dimethoxyphenyl-	H
108n	Phenyl-	H

Fig. 20 Synthesis of 9-alkoxy-6,7-dihydro-2*H*-benzo[*c*][1,2,4] triazolo[4,3-a] azepin-3(5*H*)-one derivatives **(112 a–n)**

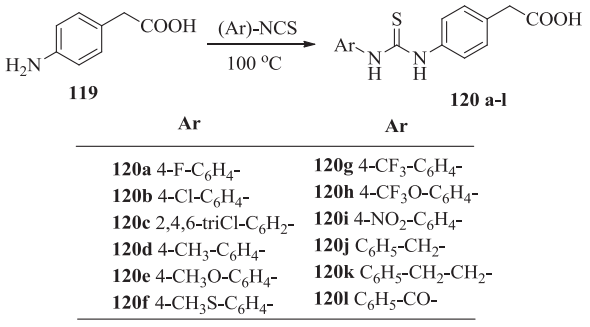


Reagents: (a) RX/C_2H_5OH, 80–92 °C; (b) P_2S_5, $(C_2H_5)_3N/CH_3CN$, 86–92 °C, 5–7 h; (c) $H_2NNHCOOCH_3$/ $(CH_3)(CH_2)_3OH$, 140–150 °C, 5–8 d where R: **a** = n-C_4H_9, **b** = n-C_5H_{11}, **c** = n-C_6H_{13}, **d** = CH_3, **f** = $CH_2C_6H_4$(*m*-F), **g** = $CH_2C_6H_4$(*p*-F), **i** = $CH_2C_6H_4$(*m*-Cl), **j** = $CH_2C_6H_4$(*p*-Cl), **k** = $CH_2C_6H_4$(*o*-Cl), **m** = $CH_2C_6H_4$(*p*-Br), **n** = $CH_2C_6H_5$

Fig. 21 Synthesis of pyrazolo [1,5-a][1,3,5]triazines **(115** and **118 a–c)**



a) $Het^1 = Het^2$ = 2-furyl; **b)** $Het^1 = Het^2$ = 2-thienyl; **c)** Het^1 = 2-thienyl Het^2 = 2-furyl

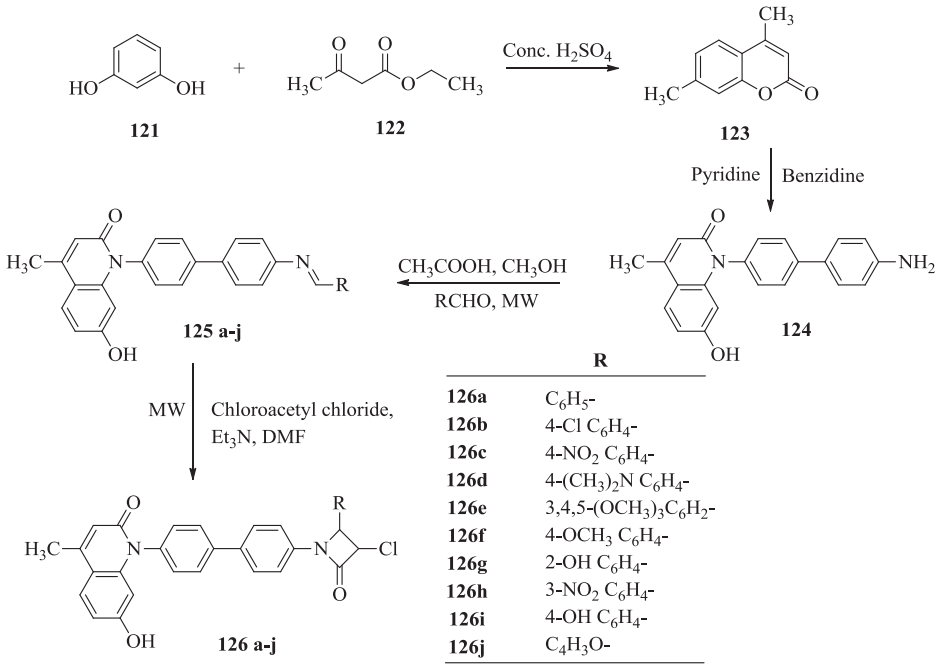


Ar	Ar
120a 4-F-C_6H_4-	**120g** 4-CF_3-C_6H_4-
120b 4-Cl-C_6H_4-	**120h** 4-CF_3O-C_6H_4-
120c 2,4,6-triCl-C_6H_2-	**120i** 4-NO_2-C_6H_4-
120d 4-CH_3-C_6H_4-	**120j** C_6H_5-CH_2-
120e 4-CH_3O-C_6H_4-	**120k** C_6H_5-CH_2-CH_2-
120f 4-CH_3S-C_6H_4-	**120l** C_6H_5-CO-

Fig. 22 Synthesis of thiourea derivatives (**120 a–l**)

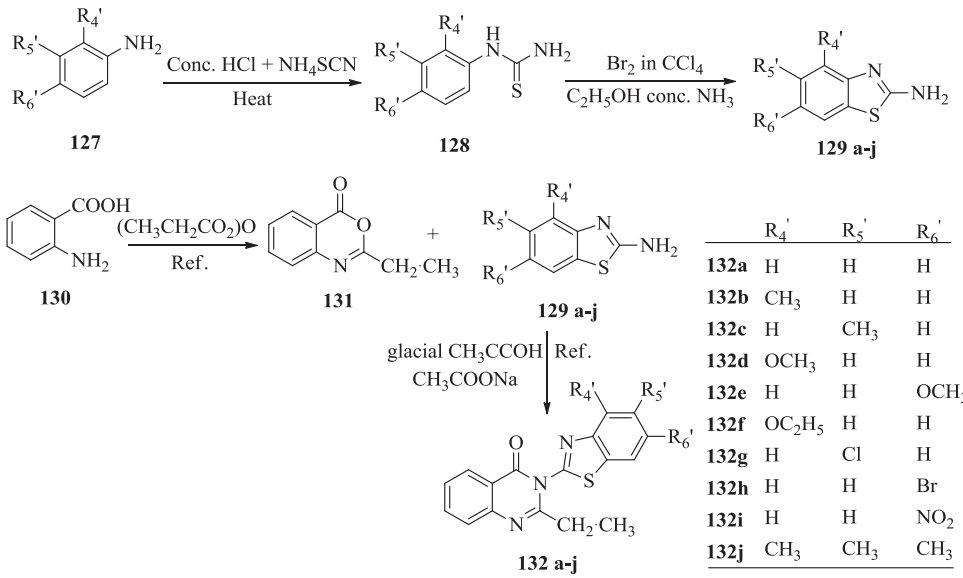
The derivatives of 1-{4′-[3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl]-biphenyl-4-yl}-7-hydroxy-4-methyl-1*H*-quinolin-2-one (**126 a–j**) (Fig. 23), starting with the ethylacetoacetate (**122**) reaction of resorcinol (**121**) and obtained as a result of a series of reactions, were synthesized by Pawar et al. (2010). The anticonvulsant effects of these synthesized compounds were analyse using the MES tests in mice. In the study where Diazepam, which is an anti-epileptic drug, was used as a standard, it has been reported that **125j** and **126a** compounds showed excellent anticonvulsant properties.

Fig. 23 Synthesis of 1-{4′-[3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl]-biphenyl-4-yl}-7-hydroxy-4-methyl-1*H*-quinolin-2-one (**126 a–j**)



R	
126a	C_6H_5-
126b	4-Cl C_6H_4-
126c	4-NO_2 C_6H_4-
126d	4-$(CH_3)_2N$ C_6H_4-
126e	3,4,5-$(OCH_3)_3C_6H_2$-
126f	4-OCH_3 C_6H_4-
126g	2-OH C_6H_4-
126h	3-NO_2 C_6H_4-
126i	4-OH C_6H_4-
126j	C_4H_3O-

Fig. 24 Synthesis of 2-ethyl-3-(substituted benzothiazole-20-yl)–[3*H*]-quinazolin-4-ones derivatives (**132 a–j**)



	R_4'	R_5'	R_6'
132a	H	H	H
132b	CH_3	H	H
132c	H	CH_3	H
132d	OCH_3	H	H
132e	H	H	OCH_3
132f	OC_2H_5	H	H
132g	H	Cl	H
132h	H	H	Br
132i	H	H	NO_2
132j	CH_3	CH_3	CH_3

Kabra et al. (2011) synthesized 2-ethyl-3-(substituted benzothiazole-20-yl)–[3*H*]-quinazolin-4-ones derivatives **(132 a–j)** (Fig. 24). They studied anticonvulsant activities of these newly synthesized compounds with the maximum electroshock method. They used phenytoin as a control and showed that compound **132b** might have an anticonvulsant effect (Fig. 25).

Synthesis of phenytoin-derived **(135** and **137 a–c)** (Fig. 26) molecules was carried out by Deodhar et al. (2009). They used different amino acids, 2,5-Dioxo-4,4-diphenylimidazolidine-1-carboxylic acid **(134)** and substituted benzhydrols as starting materials. They investigated the anticonvulsant activities of these newly synthesized phenytoin derivatives **(135 a–c** and **137 a–c)**. Anticonvulsant activity tests were investigated using PTZ and MES tests in mice. Also, in the study, motor impairment in mice was measured by the rotorod test. They reported that amino acids (especially phenylalanine and alanine) and benzhydrol, which binds to phenytoin, actually increase the anticonvulsant activity of phenytoin and reduce its neurotoxicity in mice.

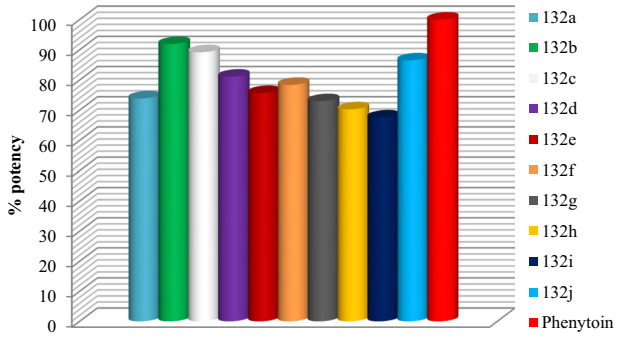


Fig. 25 Anticonvulsant effects of synthesis of 2-ethyl-3-(substituted benzothiazole-20-yl)–[3*H*]-quinazolin-4-ones derivatives **(132 a–j)**

The synthesis, pharmacological evaluation and molecular modeling studies of 1,6-dithia-4,9-diazaspiro [4.4]nonane-3,8-dione derivatives **(141–152)** (Fig. 27) as potential anticonvulsant agents were carried out by Ghareb et al. (2017). The synthesized compounds were tested in vivo for their anticonvulsant activity in mice. They reported that the newly synthesized compounds were highly effective against strike-induced seizures and had strong anticonvulsant properties compared with standard drug phenobarbital. These compounds were found to be more potent in terms of anticonvulsant activity, especially when compared with diazaspirononan **(145)** and 1-(2-naphthyl)-2-bromoethanone phenobarbital **(140)**.

Methylsulfonyl phenyl derivatives **(156 a–k)** were synthesized by Mishra et al. (2018) (Fig. 28) in order to evaluate their COX-2 inhibitory activities along with anticonvulsant potential. Compound **156b** was reported to show excellent protection against scPTZ-induced seizures in acute epilepsy models. In addition, **156b** was effective for a long period of time and showed 67% seizure protection after 6 h following its administration. In addition, **156b** was also been found to show satisfactory protection in the chronic epilepsy model caused by PTZ, compared with the standard COX-2 inhibitor ETX (Fig. 29). The toxicity test performed in this study proved

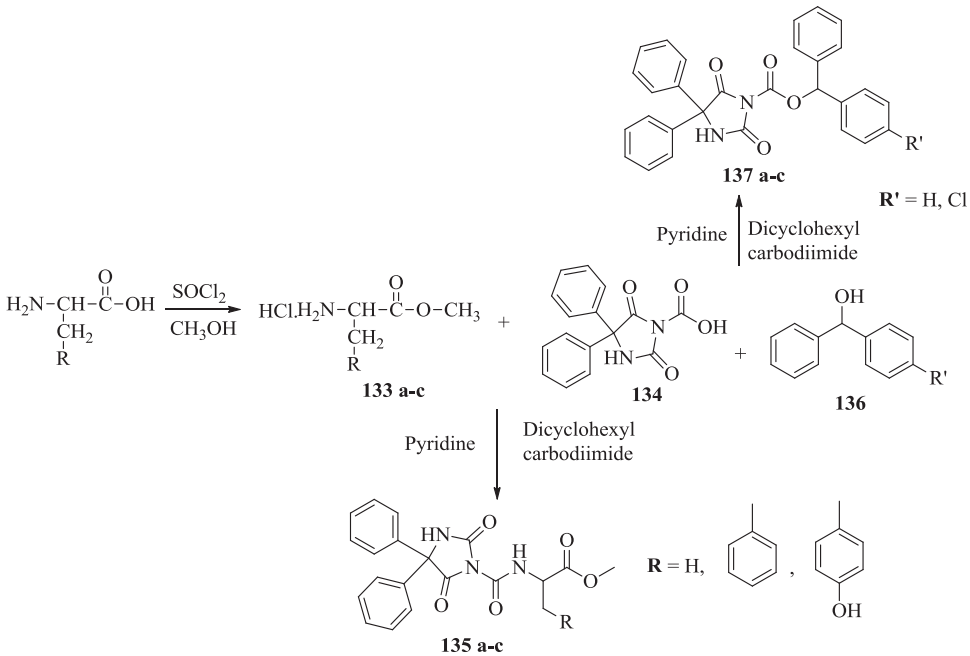


Fig. 26 Synthesis of phenytoin-derived molecules **(135** and **137 a–c)**

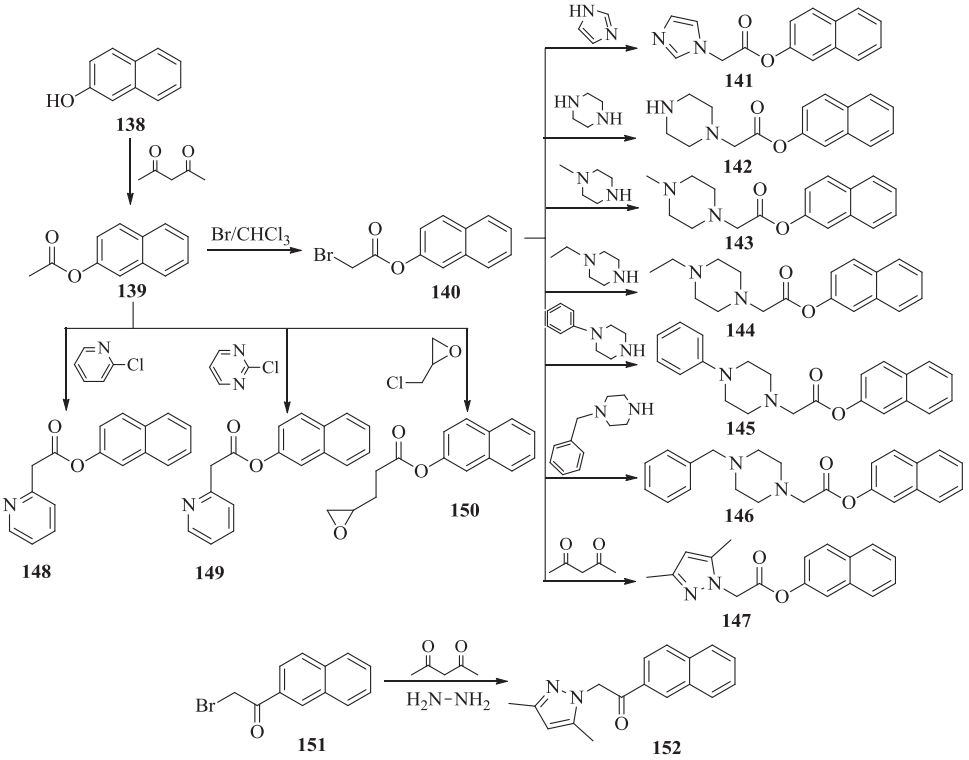
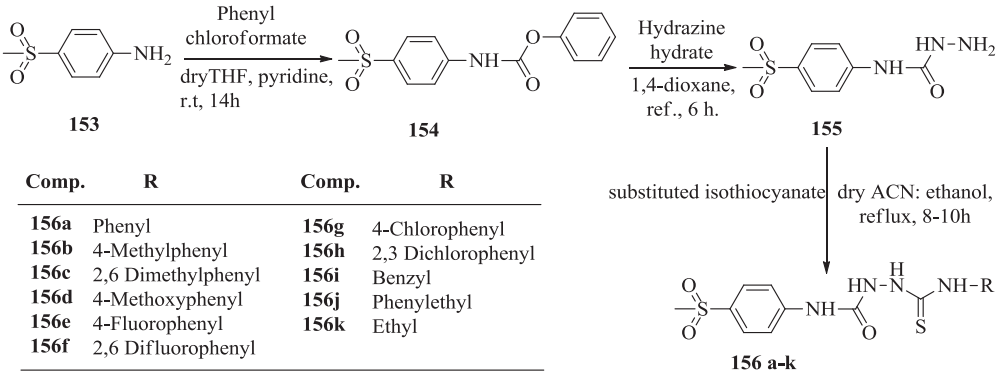


Fig. 27 Synthesis of 1,6-dithia-4,9-diazaspiro [4.4]nonane-3,8-dione derivatives **(141–152)**



Comp.	R	Comp.	R
156a	Phenyl	**156g**	4-Chlorophenyl
156b	4-Methylphenyl	**156h**	2,3 Dichlorophenyl
156c	2,6 Dimethylphenyl	**156i**	Benzyl
156d	4-Methoxyphenyl	**156j**	Phenylethyl
156e	4-Fluorophenyl	**156k**	Ethyl
156f	2,6 Difluorophenyl		

Fig. 28 Synthesis of methylsulfonyl phenyl derivatives **(156 a–k)**

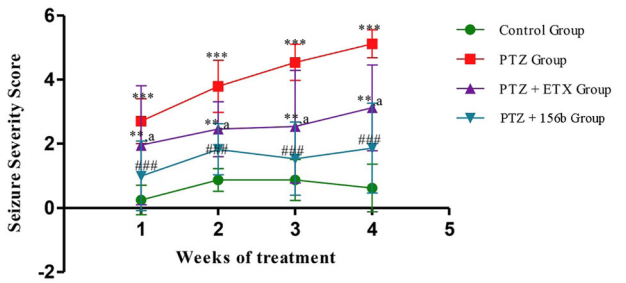


Fig. 29 The visual assessment of seizure scores in PTZ + **156b** and other groups for a period of 1 month

that the compound **(156b)** was nontoxic in these mice models.

In this study, the COX-2 docking study to determine the molecular interaction of **156b** is given in Fig. 30.

Khajouei et al. (2018) synthesized isatin-based compound derivatives **(160 a–l)** (Fig. 31) investigated their anticonvulsant activities using MES and PTZ models in mice. All methoxylated derivatives **(160j**, **160k**, **160l)** were reported to show significant anti-seizure activity in the MES model. In addition, all derivatives tested were proved to have a low toxicity using Rotarod protocol.

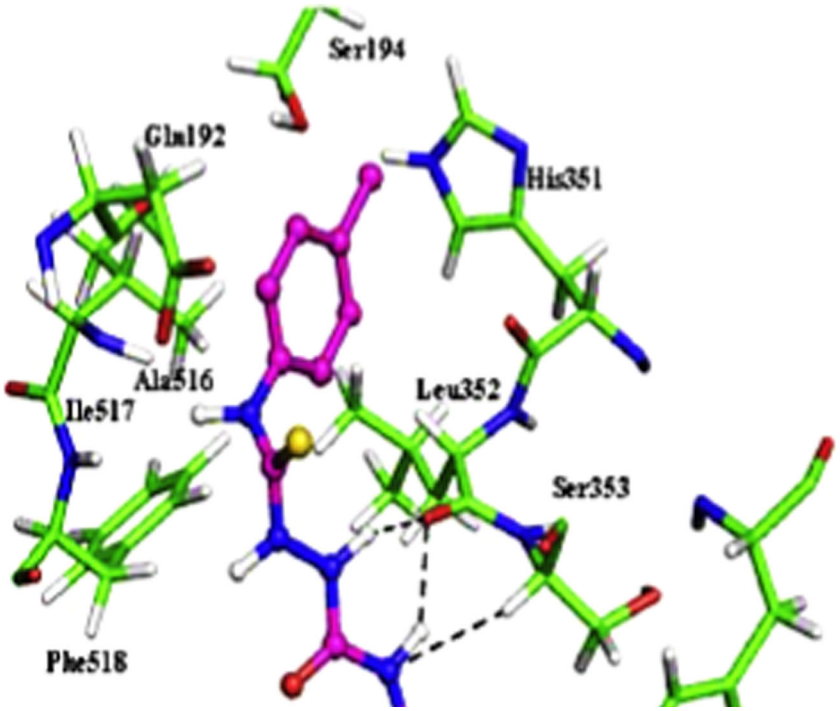
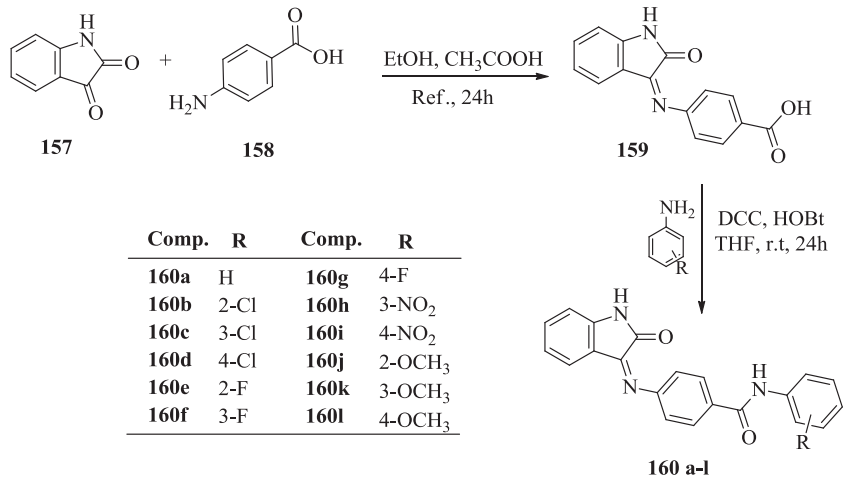


Fig. 30 Molecular doking study for compund **156b**



Comp.	R	Comp.	R
160a	H	**160g**	4-F
160b	2-Cl	**160h**	3-NO_2
160c	3-Cl	**160i**	4-NO_2
160d	4-Cl	**160j**	2-OCH_3
160e	2-F	**160k**	3-OCH_3
160f	3-F	**160l**	4-OCH_3

Fig. 31 Synthesis of isatin-based compound derivatives **(160 a–l)**

7-(benzylamino)-1*H*-benzo[*b*][1,4]diazepine-2,4(3*H*,5*H*)-dione derivatives **(165** and **168 a–i)** (Fig. 32) were synthesized by Shao et al. (2018) and their anticonvulsant activities were screened with MES and scPTZ tests. In addition, their neurotoxicity was evaluated by the rotarod neurotoxicity test as previously mentioned. In this article carbamazepine, sodium valproate, and phenytoin were used as reference antiepileptic drugs. The synthesized compounds were reported to have a moderate anticonvulsant effects and compound **168c** (7-(4-fluorobenzylamino)-1,5-dimethyl-1*H*-benzo[*b*][1,4]diazepine-2,4(3*H*,5*H*)-dione) exhibited more effective anticonvulsant properties relative to other compounds tested, in both MES and scPTZ test (Fig. 33).

1,2,4-trisubstituted 5-imidazolinone derivatives **(176–181 a** and **b)** (Fig. 34) were synthesized by Moorthy et al. (2012) using different aldehydes **(173)** of benzoylglycine **(174)** in the presence of sodium acetate and acetic anhydride. The authors used phenobarbital as a reference antiepileptic drug and reported that the anticonvulsant activity of the synthesized compounds ranged from 10 to 60%. Compounds containing *p*-OCH_3, *p*-OH and *o*-Cl were shown to exhibit better anticonvulsant activity than those which do not contain these chemical moieties.

Pyrazolyl thiosemicarbazone derivatives **(186 a–k)** (Fig. 35) were synthesized by Deng and Song (2014), and evaluated

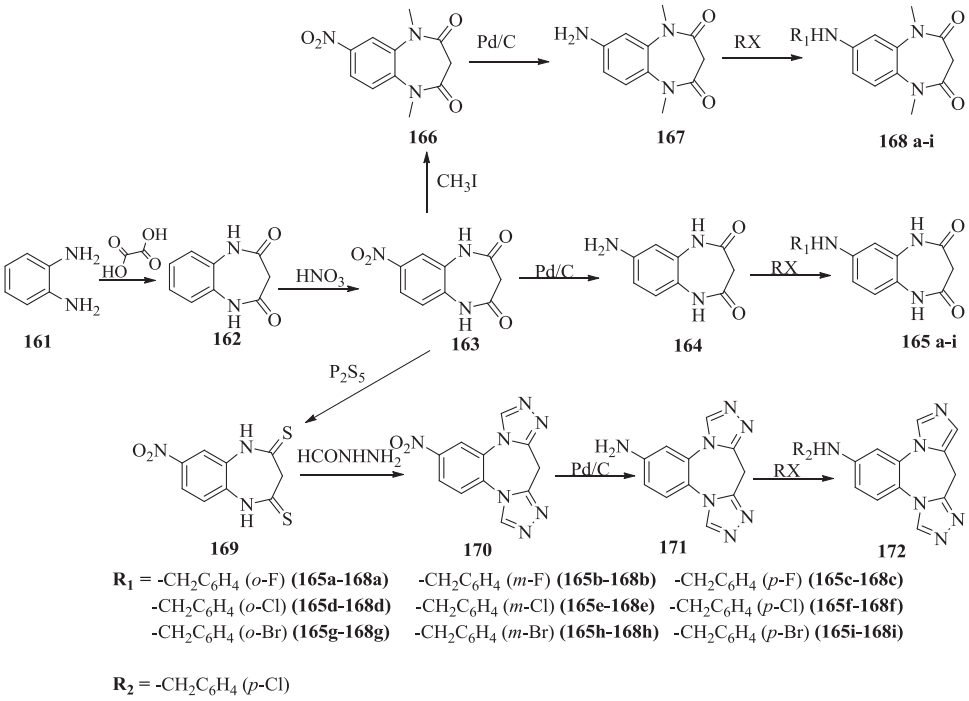


Fig. 32 Synthesis of 7-(benzylamino)-1*H*-benzo[*b*][1,4]diazepine-2,4(3*H*,5*H*)-dione derivatives (**165** and **168 a–i**)

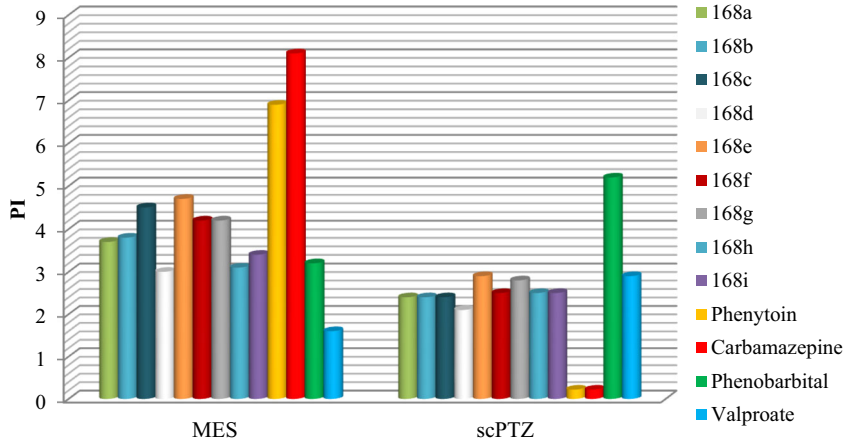
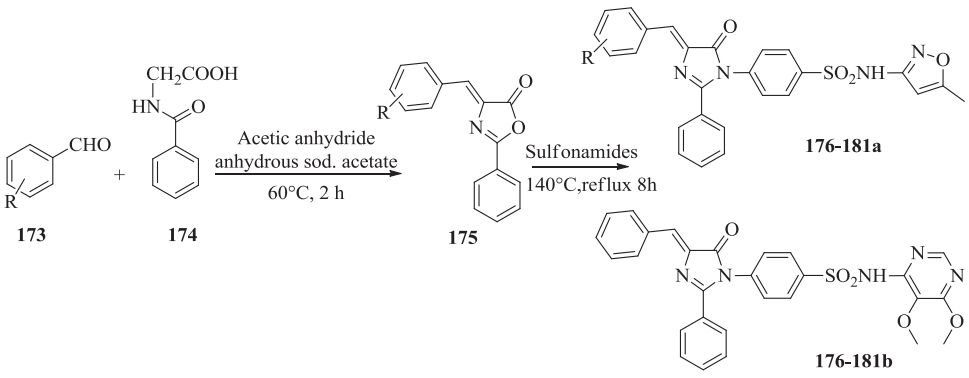


Fig. 33 The PI values of 7-(benzylamino)-1*H*-benzo[*b*][1,4]diazepine-2,4(3*H*,5*H*)-dione derivatives (**168 a–i**)



Structures: **176** = H, **177** = *p*-dimethylamino, **178** = *p*-OH, **179** = *p*-OCH3, **180** = *o*-Cl, **181** = *o*-OH

Fig. 34 Synthesis of 1,2,4-trisubstituted 5-imidazolinone derivatives (**176–181 a** and **b**)

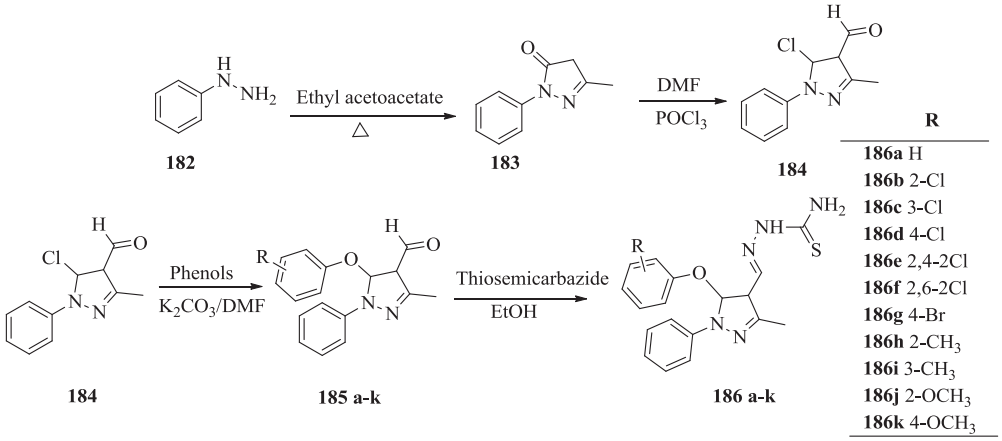


Fig. 35 Synthesis of pyrazolyl thiosemicarbazone derivatives **(186 a–k)**

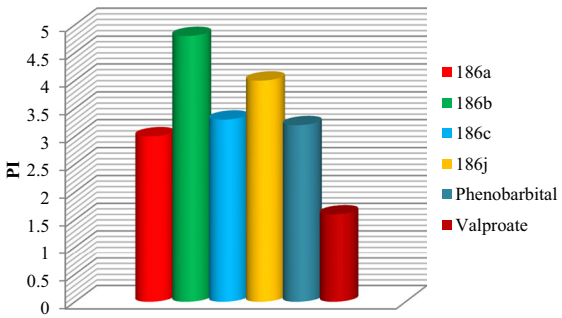


Fig. 36 The PI values of compound **186a**, **186b**, **186c**, **186j**

for their anticonvulsant activity using MES method. Among them, compound **186b** was considered to be the most promising compound (PI value of 4.8) which was superior to phenobarbital (PI value of 3.2) and valproate (PI value of 1.6) (Fig. 36).

Ahangar et al. (2011) synthesized thiazole derivatives **(190–194 a–b)** (Fig. 37) and investigated anticonvulsant properties of these novel compounds in mice using maximum electroshock and pentylenetetrazole models. Of these compounds, **193a** and **193b** were reported to exhibit significant anticonvulsant activity with a protection range of 33–100% in both pentylenetetrazole and maximal electroshock tests.

As potential antiepileptic compounds, 8-alkoxy-4,5-dihydrobenzo[*b*][1,2,4]triazolo[4,3-*d*][1,4]thiazepine derivatives **(201** and **202 a–q)** (Fig. 38) were synthesized by Deng et al. (2014b). These compounds were evaluated for their anticonvulsant activity in mice models using the MES method. In this study where carbamazepine (PI value of 4.5), phenobarbital (PI value of 3.2), and valproate (PI value of 1.6) were used as reference antiepileptic drugs, compound **202j** (PI value of 12.6) was found to have a very good anticonvulsive effect (Fig. 39). In addition, a calculation study was conducted to estimate the pharmacokinetic properties of these newly synthesized compounds and it was reported by the authors that these compounds might be used as promising antiepileptic agents in the future after clinical phase trials were conducted in humans.

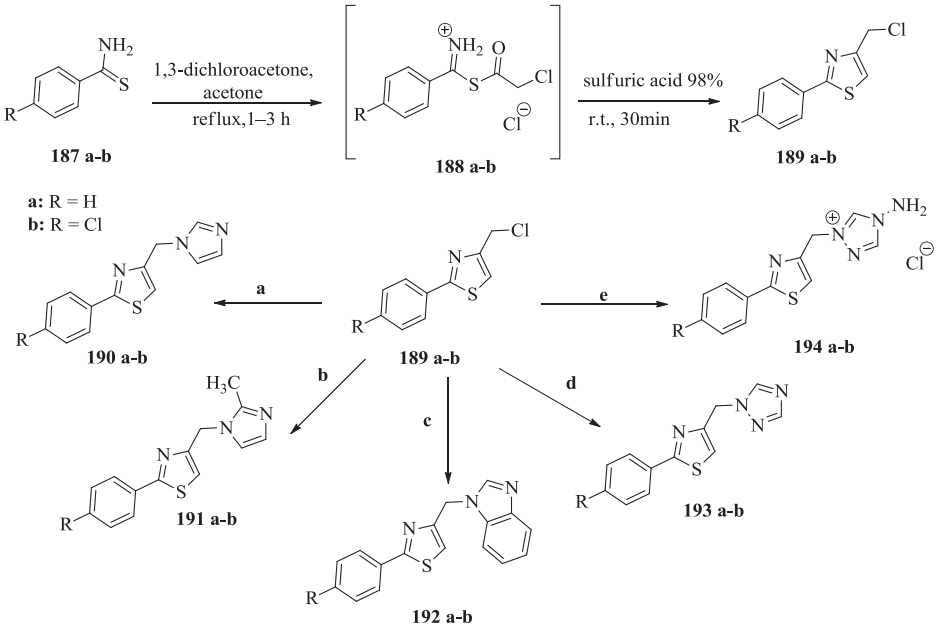
Mahdavi et al. (2010) synthesized 3-amino-5-(4-chloro-2-phenoxyphenyl)-4*H*-1,2,4-triazole derivatives **(207 a–b)** (Fig. 40) and tested their anticonvulsant activities using the PTZ model. They reported that the 3-amino-5-[4-chloro-2-(2-flurophenoxy)phenyl]-4*H*-1,2,4-triazole **(207a)** showed better anticonvulsant activity than that of diazepam in mice models.

Łaczkowski et al. (2016b) synthesized 22 compounds consisting of thiazole and selenazole derivatives **(211 a–u)** (Fig. 41). They investigated the antimicrobial and anticonvulsant properties of these newly synthesized compounds by their group. Anticonvulsant screening results reported that compounds **211a**, **211b**, **211m**, and **211n** showed significant anticonvulsant activity in the pentylenetetrazole model, while **211a** and **211n** reported to provide protection in the 6-Hz psychomotor seizure model.

Acar et al. (2019) synthesized nafimidone derivatives **(216 a–o)** (Fig. 42) and they tested the anticonvulsant effects of these compounds with the MES method in both mice and rats. They reported that compounds **216b**, **216c**, and **216i** showed exceptional activity in the rat MES tests, while compound **216l** showed anticonvulsive activity against 6 Hz and corneal-kindled mice models.

They also reported that **216l** showed affinity to the benzodiazepine binding site of A-type GABA receptor via molecular docking simulations (Fig. 43).

Mohammed Hasan (2019) synthesized a chalcone derivative **(219)** (Fig. 44) and then prepared their polymers **(222 a–d)**. In this study, the anticonvulsant potentials of these newly synthesized molecules were evaluated. Synthesized molecule structures were supported by FTIR, ^{1}H-NMR, elemental analysis, thermal analysis (TGA and DSC). The



Reagents and conditions: **(a)** imidazole, K_2CO_3, acetone, reflux, 8–10 h; **(b)** 2-methylimidazole, K_2CO_3, acetone, reflux, 5–8 h; **(c)** benzimidazole, K_2CO_3, acetone, reflux, 7–10 h; **(d)** 4-amino-1,2,4-triazole, 2-propanol, reflux, 24–36 h; **(e)** $NaNO_2$, concentrated HCl, H_2O, 0–5 °C then rt.

Fig. 37 Synthesis of thiazole derivatives **(190–194 a–b)**

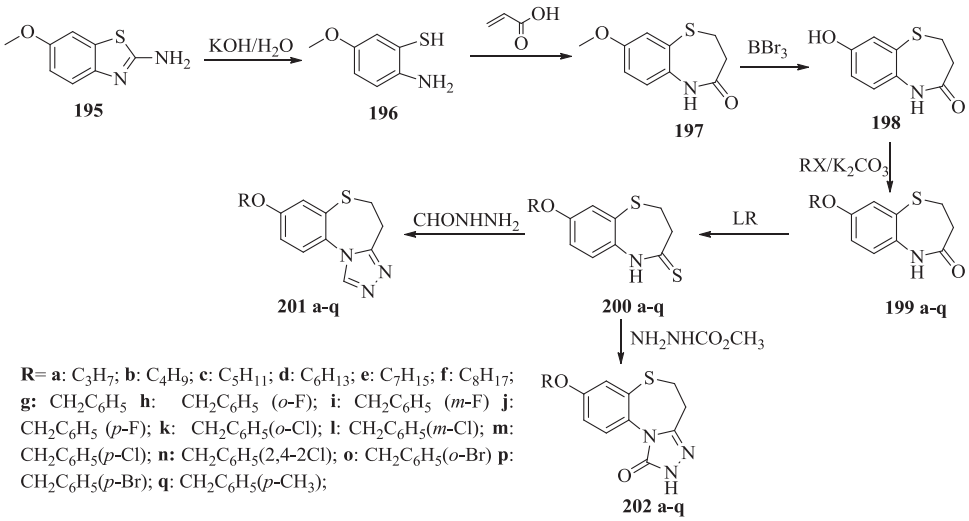


Fig. 38 Synthesis of 8-alkoxy-4,5-dihydrobenzo[*b*][1,2,4] triazolo[4,3-*d*][1,4]thiazepine derivatives **(201** and **202 a–q)**

author investigated the anticonvulsant properties of these structures using MES method and reported that most derivatives have comparably stronger activity than that of reference phenytion.

Singh et al. (2020) synthesized a series of fifteen nipecotic acid 1,3,4-oxadiazole based hybrids **(226 a–o)** (Fig. 45) After the structures of all the synthesized compounds were characterized by spectroscopic methods (FT-IR, ^{1}H-, ^{13}C NMR, and elemental analysis), they carried out anticonvulsant test studies. Anticonvulsive activity tests were performed in mice using scPTZ and MES methods. **226i**,

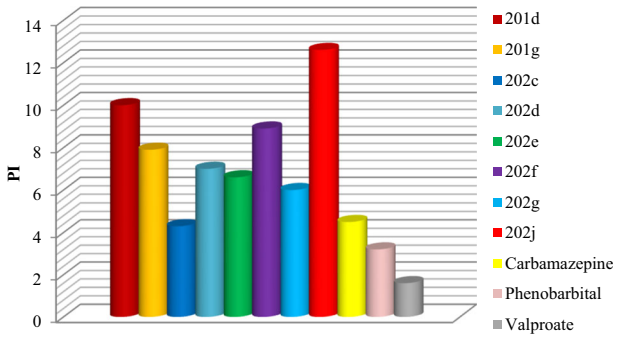


Fig. 39 The PI values of most active compounds

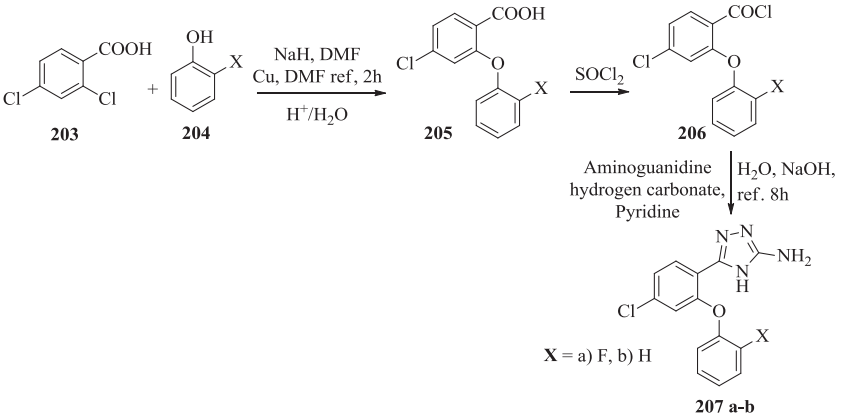


Fig. 40 Synthesis of 3-amino-5-(4-chloro-2-phenoxyphenyl)-4*H*-1,2,4-triazole derivatives **(207 a–b)**

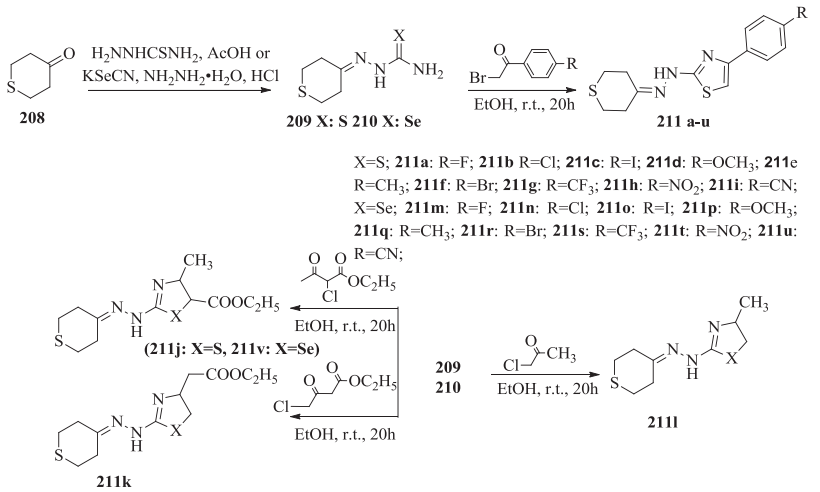


Fig. 41 Synthesis of thiazole and selenazole derivatives **(211 a–u)**

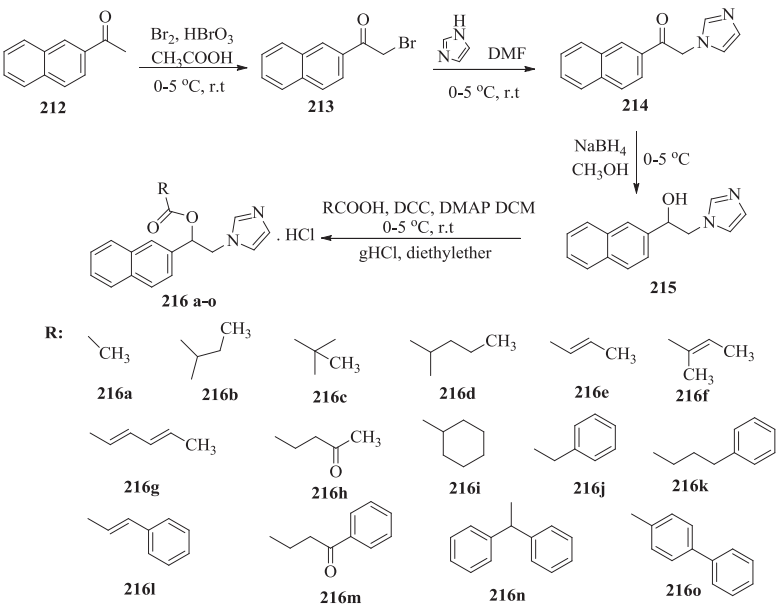


Fig. 42 Synthesis of nafimidone derivatives **(216 a–o)**

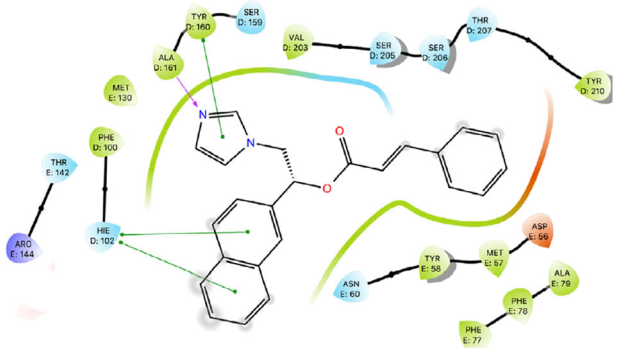


Fig. 43 2D interaction diagram of compound **216l** with $GABA_AR$

226m, and **226n** of the synthesized compounds have been reported to show significant activity against scPTZ-induced seizures (Fig. 46) and also, they studied docking of compound **226m** (most active compound) with GABA (Fig. 47). In addition, it has been reported that the compounds are promising in terms of their antidepressant properties and that none of the compounds show neurotoxicity in mice.

Twenty different (*E*)-3-(5-(substituted aminomethyl)-1,3,4-thiadiazol-2-yl)-2-substituted styrylquinazolin-4-(3*H*)-one derivatives **(234 a–u)** (Fig. 48) were synthesized by Bhattacharya and Kashaw (2019). The synthesized compounds have been evaluated for their anticonvulsant potential

Fig. 44 Synthesis of polymers **(222 a–d)**

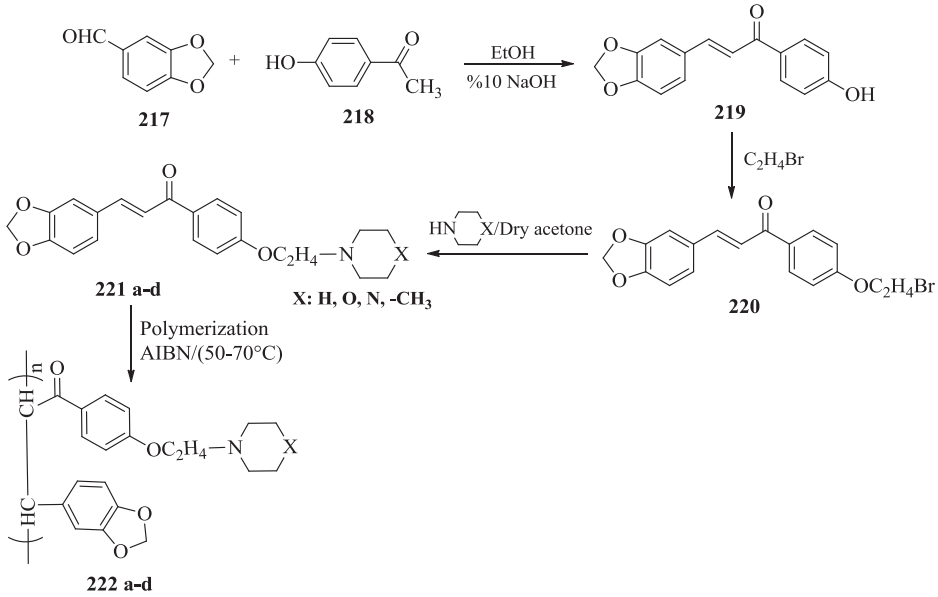
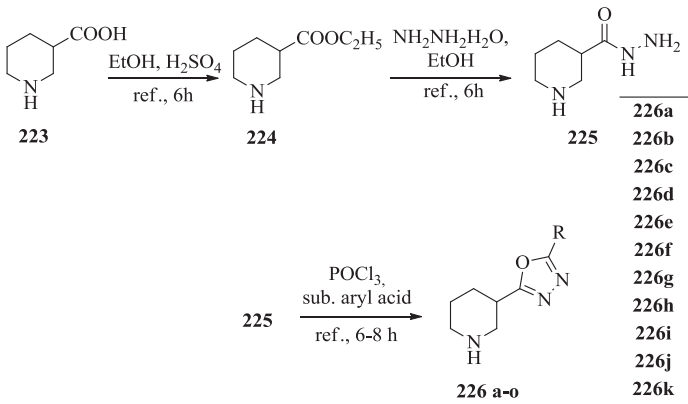


Fig. 45 Synthesis of nipecotic acid 1,3,4-oxadiazole based hybrids **(226 a–o)**



	R
226a	Phenyl
226b	4-Chlorophenyl
226c	3-Chlorophenyl
226d	3-Cyanophenyl
226e	2,4-Dihydroxyphenyl
226f	4-Methoxyphenyl
226g	3-Methoxyphenyl
226h	2,4-Dichlorophenyl
226i	4-Nitrophenyl
226j	2-Hydroxyphenyl
226k	3-Nitrophenyl
226l	2,4,5-Trifluorophenyl
226m	3,5-Dinitrophenyl
226n	4-Aminophenyl
226o	2-Amino-4,5-dimethoxyphenyl

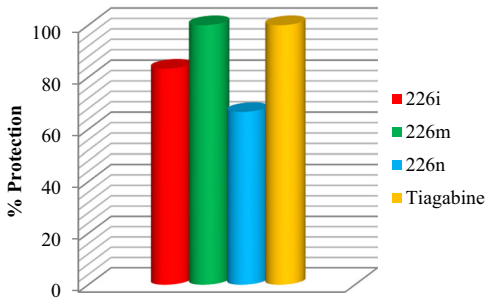


Fig. 46 % Protection values of **226i**, **226m**, and **226n**

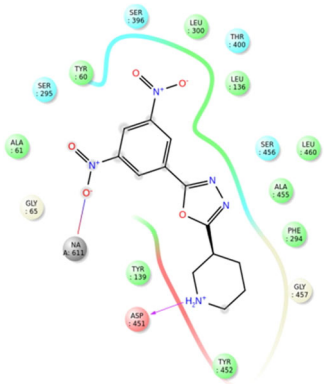


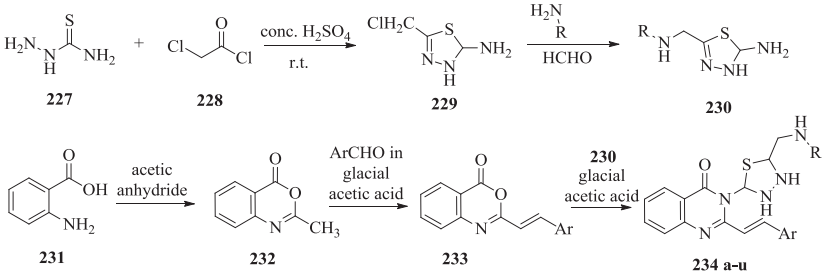
Fig. 47 2D interaction diagram of compound **226m** with GABA

by scPTZ and MES model and compared with the reference drugs, phenytoin and carbamazepine. According to the results obtained, **234f**, **234l**, **234n**, and **234s** have been reported to be highly active in terms of anticonvulsant activity compared with standard drugs.

Microwave assisted synthesis of benzimidazole derivatives **(237 a–e)** (Fig. 49) were performed by Sahoo et al. (2019). They synthesized benzimidazole derivatives with ortho phenylenediamine **(235)** and benzaldehydes **(236 a–e)** according to Claisen–Schmidt condensation method. All the synthesized compounds were investigated for their anticonvulsant activity based on MES models and their neurotoxicities were evaluated by rotarod test. According to the results obtained from all the compounds screened in terms of their anticonvulsant potential, it was reported that the compound **236e** had more anticonvulsant activity than the Phenytoin (Fig. 50).

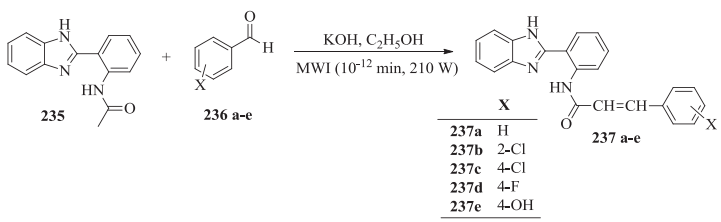
Thieno[2,3-*b*]pyridine derivatives **(241 a–c, 243 a–e)** (Fig. 51) were synthesized by Paronikyana et al. (2020). The anticonvulsant activity of the synthesized compounds was assessed by their effects on PTZ seizures. In the study, male and female white mice weighing 18–24 g were used. Anticonvulsant activity test results showed that compound **242f** could prevent PTZ-induced clonic seizures in 60% of animals. In addition, among thieno[2,3-*b*]pyridine deriva-

Fig. 48 Synthesis of (*E*)-3-(5-(substituted aminomethyl)-1,3,4-thiadiazol-2-yl)-2-substituted styrylquinazolin-4-(3*H*)-one derivatives **(234 a–u)**



	Ar	R		Ar	R
234a	$-C_6H_5$	$-C_6H_5Cl$	**234k**	$-C_6H_5Cl$	$-C_6H_5OC_2H_5$
234b	$-C_6H_5$	$-C_6H_5Br$	**234l**	$-C_6H_5NO_2$	$-C_6H_5Cl$
234c	$-C_6H_5$	$-C_6H_5NO_2$	**234m**	$-C_6H_5NO_2$	$-C_6H_5Br$
234d	$-C_6H_5Cl$	$-C_6H_5Cl$	**234n**	$-C_6H_5NO_2$	$-C_6H_5NO_2$
234e	$-C_6H_5Cl$	$-C_6H_5Br$	**234o**	$-C_6H_5NO_2$	$-C_6H_5F$
234f	$-C_6H_5Cl$	$-C_6H_5NO_2$	**234p**	$-C_6H_5CH_3$	$-C_6H_5Cl$
234g	$-C_6H_5Cl$	$-C_6H_5F$	**234r**	$-C_6H_5CH_3$	$-C_6H_5Br$
234h	$-C_6H_5Cl$	$-C_6H_5CH_3$	**234s**	$-C_6H_5OCH_3$	$-C_6H_5Cl$
234i	$-C_6H_5Cl$	$-C_6H_5C_2H_5$	**234t**	$-C_6H_5OCH_3$	$-C_6H_5Br$
234j	$-C_6H_5Cl$	$-C_6H_5OCH_3$	**234u**	$-C_6H_5OCH_3$	$-C_6H_5F$

Fig. 49 Synthesis of benzimidazole derivatives **(237 a–e)**



X	
237a	H
237b	2-Cl
237c	4-Cl
237d	4-F
237e	4-OH

tives (**241 a–c, 243 a–e**), the most active compounds are reported to be **241a**, **242b**, and **243a**–**243e**.

Siddiqui et al. (2020) have identified several pyridazinone-based compounds (**246 a–s**) (Fig. 52). Pyridazinone derivatives are known to have anticonvulsant effects. Based on this, they tested the anticonvulsant activities of the molecules they synthesized. They reported that **246e** has a significant anticonvulsant effect acting through GABA mediated mechanism, among all synthesized compounds (Fig. 53).

They performed the docking study of the compound **246e** with the $GABA_A$ receptor. They reported that the compound **246e** could be physicallysurrounded by the $GABA_A$ receptors (Fig. 54).

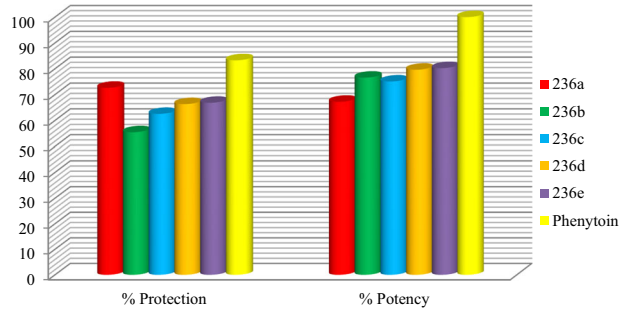


Fig. 50 Anticonvulsant activity of benzimidazole derivatives (**237 a–e**)

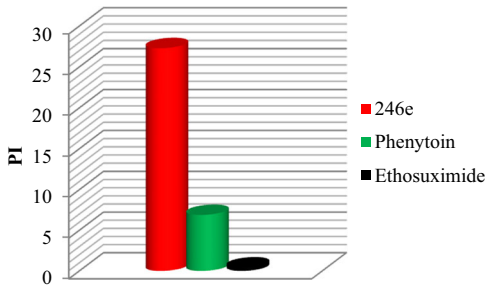
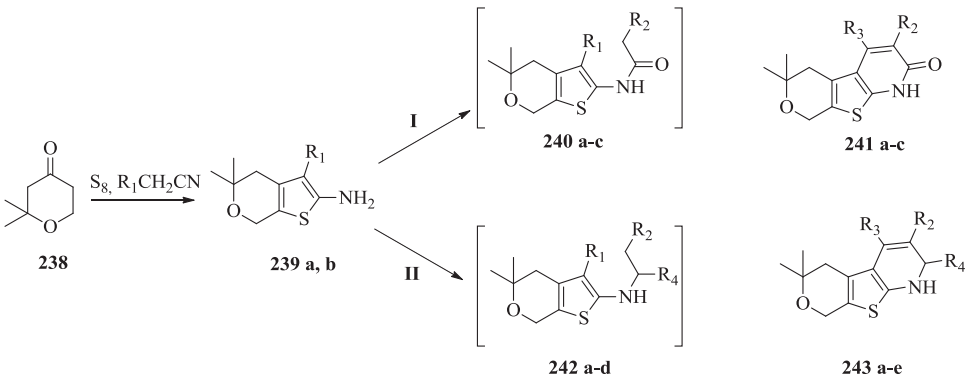


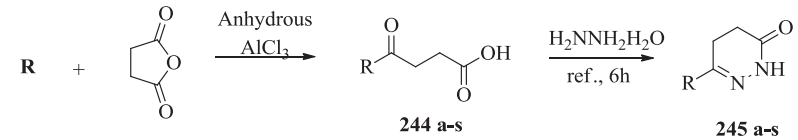
Fig. 53 PI value of **246e**

Fig. 51 Synthesis of thieno[2,3-*b*]pyridine derivatives (**241 a–c, 243 a–e**)

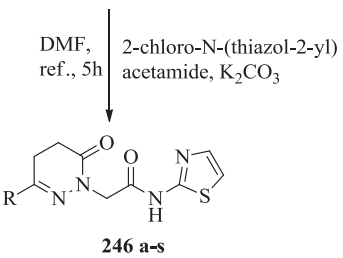


239a, **240a**, **240c**, **242a**, R_1 = COOEt; **239b**, **240b**, **242b–242d**, R_1 = CN; **240a**, **240b**, **241a**, **241b**, **242b**, **243b**, R_2 = CN; **242a**, **242d**, **243a**, **243d**, R_2 = COOEt; **240c**, **241c**, R_2 = Ph; **242c**, **243c**, R_2 = $CONH_2$; **243e**, R_2 = COOH; **241a**, **241c**, **243a**, R_3 = OH; **241b**, **243b–243e**, R_3 = NH_2; **242a**, **242d**, **243a**, **243d**, **243e**, R_4 = Me; **242b**, **242c**, **243b**, **243c**, R_4 = NH_2

Fig. 52 Synthesis of pyridazinone-based compounds (**246 a–s**)



R		R	
234a	Phenyl	**234j**	*p*-Isobutyl phenyl
234b	*p*-Fluro-phenyl	**234k**	Naphthyl
234c	*p*-Tolyl	**234l**	3,4-Dichloro-phenyl
234d	*p*-Anisyl	**234m**	*p*-Benzyl phenyl
234e	*p*-Chloro-phenyl	**234n**	*p*-Phenoxy phenyl
234f	*p*-Ethyl phenyl	**234o**	*p*- Propyl phenyl
234g	3,4-Dimethylphenyl	**234p**	*p*-Biphenyl
234h	2,5-Dimethylphenyl	**234r**	*p*-Bromo-phenyl
234i	2,4-Dimethylphenyl	**234s**	2-Thienyl



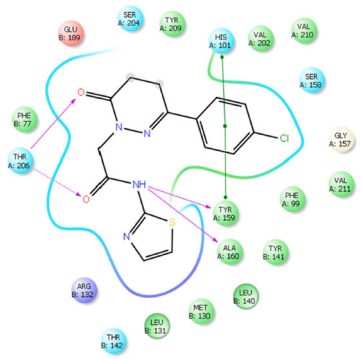


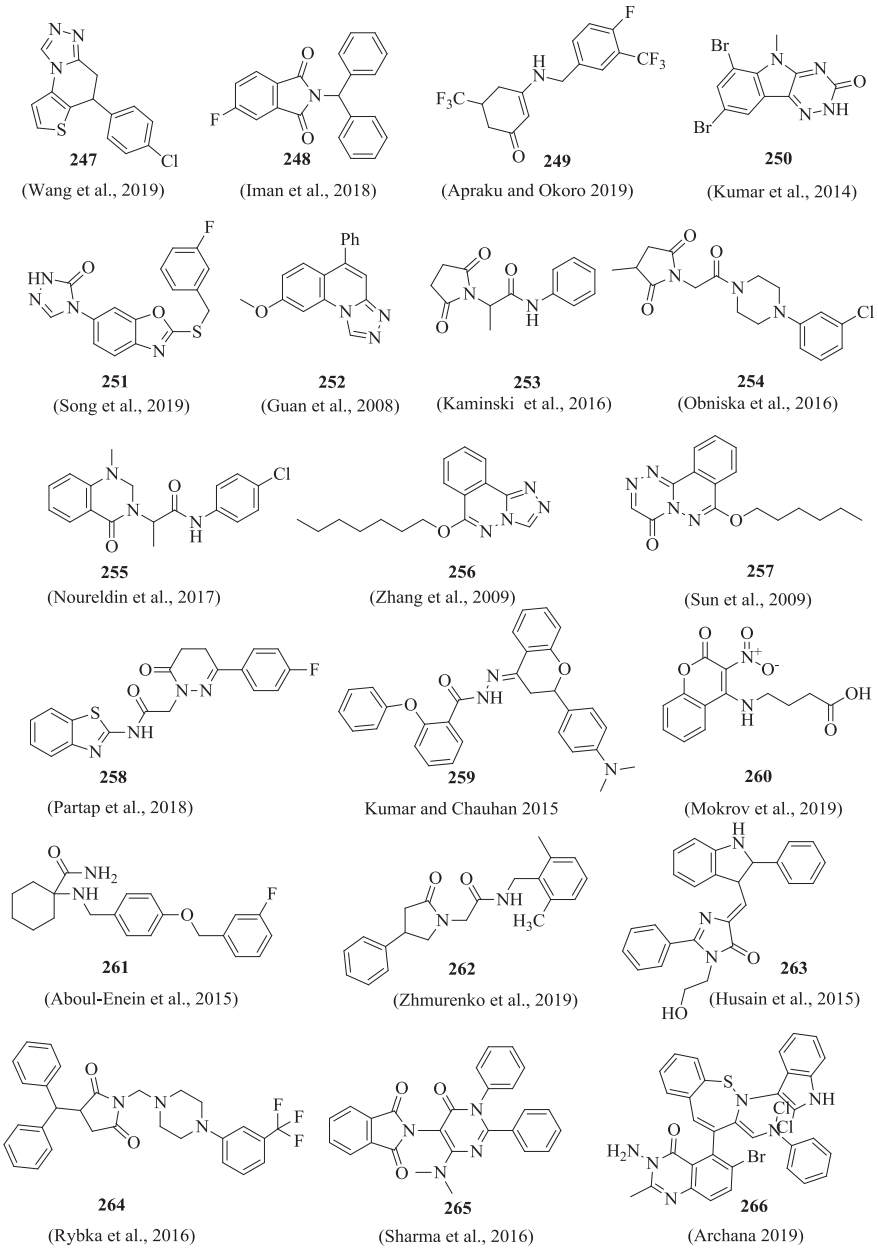
Fig. 54 $GABA_A$ interaction with compound **246e**

In addition to these studies, molecules that are synthesized and show good anticonvulsant properties are shown in Figs 55–57.

Conclusion

Each compound synthesized by chemists has its own biological characteristics such as anticancer, antimicrobial, antiantioxidant, antitubercular and anticonvulsant features, etc (Özbek et al. 2017; Gürdere et al. 2020; Gürdere et al. 2017). There are thousands of studies in the literature, reporting on the synthesis and characterization of drug active substances.

Fig. 55 Molecules with anticonvulsant properties **(247–266)**



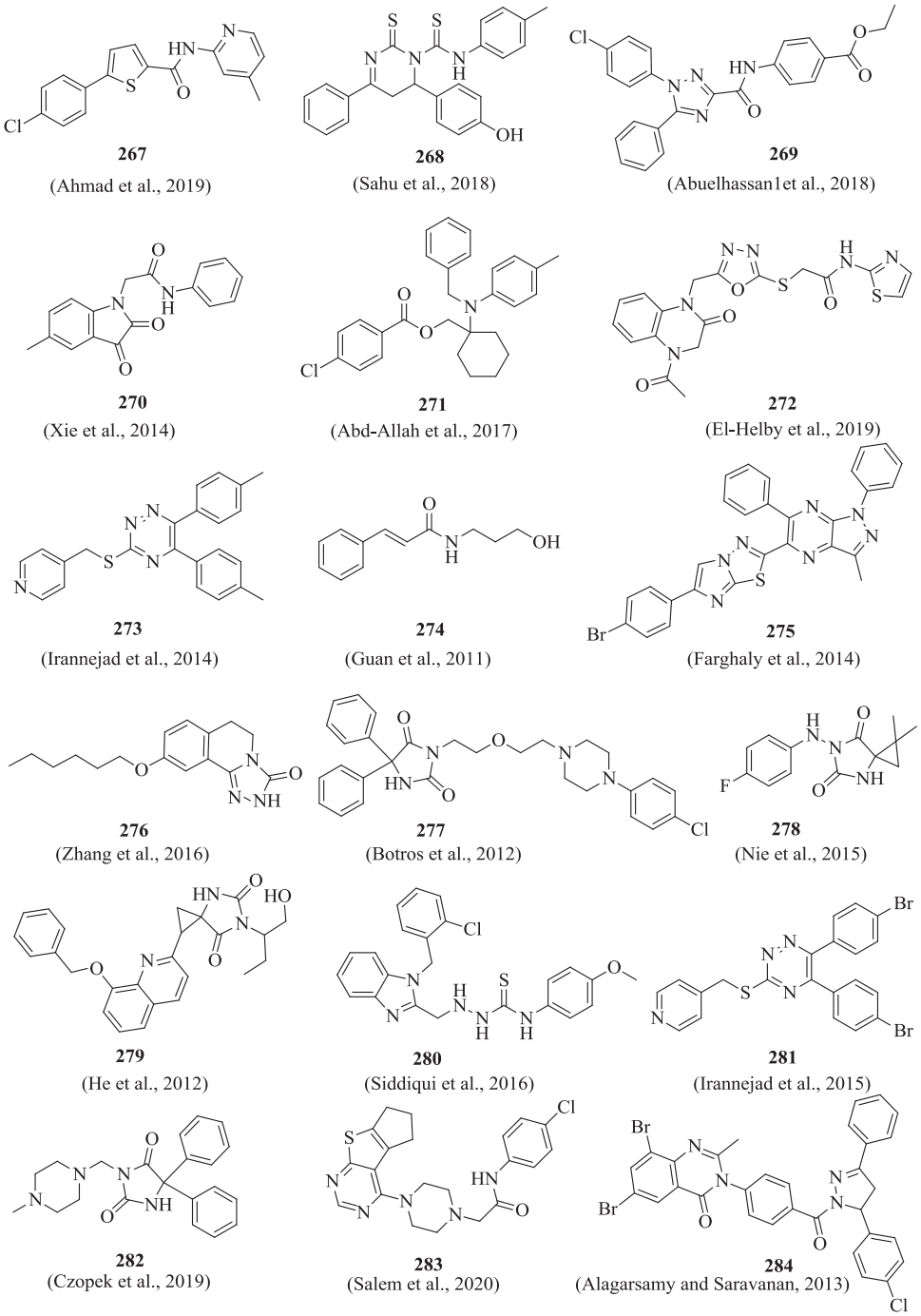


Fig. 56 Molecules with anticonvulsant properties **(267–284)**

Novel anticonvulsant drug active substance research has an important place among these studies. The current standard treatment of epilepsy, which is a common chronic disease worldwide, is carried out with the prescription of various antiepileptic drugs which have limited efficacies. For the purpose of providing more potent antiepileptic drugs, new molecules are synthesized in the labs by researchers and their anticonvulsant properties are tested in animal models. These studies, with no doubt, are of great importance in the discovery of new drugs which have the potential to be used in the clinic for the improvement of human health. Preclinical evaluation of some studies presented in this review has been completed (Obniska et al. 2016; Kaminski et al. 2016; Matias et al. 2017; Kaproń a et al. 2020). In other studies, positive results were obtained on mice and better results than standard antiepileptics have been reported in the

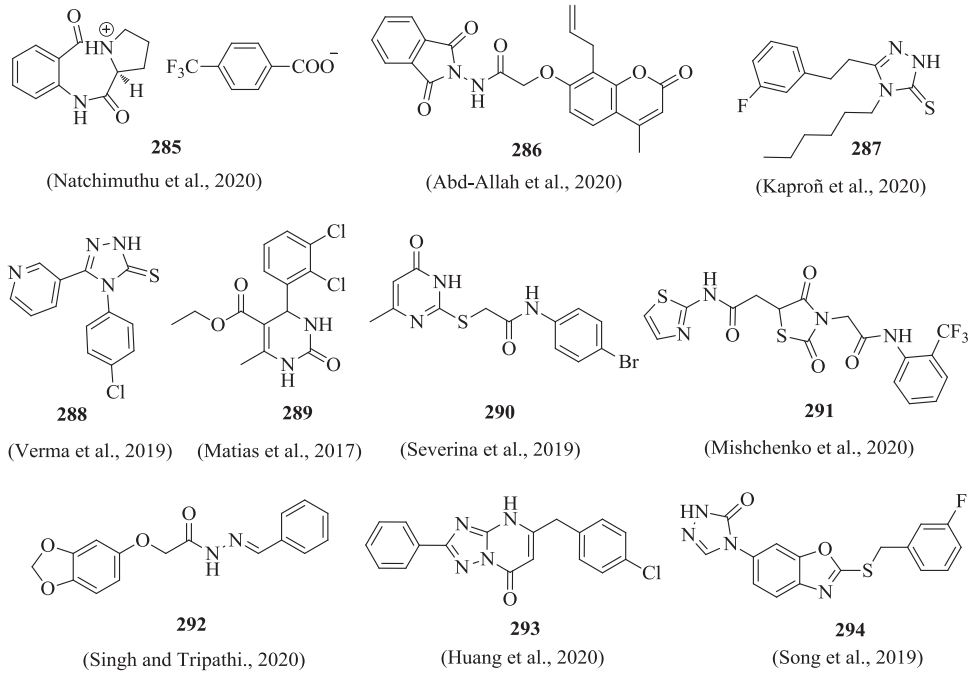


Fig. 57 Molecules with anticonvulsant properties **(285–294)**

vast majority of this studies. We believe that in the future, the molecules presented in this review and their strong anticonvulsant effects will guide the researchers working on this area.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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