Section: Research Paper

A REVIEW OF SYNTHESIS OF NEW ANTIEPILEPTIC DRUGS

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Abstract

Epilepsy is one of the most not unusual neurological disorders global and it calls for a protracted-term or lifestyles-lengthy treatment. Present day standard treatment includes the usage of antiepileptic capsules. So far, many organic compounds were synthesized by means of chemists as ability antiepileptic capsules and their anticonvulsant houses had been investigated. At the same time as evaluating the anticonvulsant sports of these newly synthesized molecules, regarded antiepileptic tablets are used as reference. Therefore, many novel molecules with anticonvulsant homes were delivered to the literature. It is clean that these new molecules can be powerful in the remedy of epilepsy. In this article investigation of the synthesis and homes of natural compounds with anticonvulsant residences is detailed.

Keywords: Anticonvulsant, Seizure, Electroshock, Molecular Modelling

Introduction

Epilepsy is a persistent neurological ailment characterised by way of recurrent seizures and influences 1–2% of global population (1) (2) (3). Consistent with the latest studies about 70 million humans have epilepsy global and the vast majority of those sufferers live in growing nations (4). Further, epilepsy became predicted to have an effect on ~10 million youngsters international (5). Epilepsy is clinically characterised through sudden assaults concerning simplest one part of the brain or both hemispheres and epileptic seizures may additionally end result from brief interruption of ordinary mind characteristic (6). Genetic predisposition, diverse sicknesses and numerous environmental triggers play a function in the etiology of epilepsy (7, 29). Epileptic seizures are fundamentally divided into predominant businesses as partial (easy partial, complicated partial) and generalized (absence, myoclonic, clonic, tonic, tonic–clonic, and atonic).

The treatment epilepsy calls for long-time period or lifetime treatment relying at the sort of seizures with the use of antiepileptic capsules (8). Anticonvulsants or antiepileptic tablets are pharmacological sellers used inside the treatment of these epileptic seizures. Antiepileptic capsules paintings via distinctive mechanism inclusive of the enhancement of γ-amino butyric acid (GABA) neurotransmission or the modulation of voltage-gated ion channels (sodium and calcium) (9). Levetiracetam, phenytoin, phenobarbital, carbamazepine, felbamate, ethosuximide, diazepam, valproate, gabapentin, and tiagabine are some of the commonly used drugs within the treatment of epilepsy.

Animal seizure models have played a substantial position in epilepsy research which includes synthesis, characterization, and identity of recent anticonvulsant capsules (10). The most usually hired checks in animal models inside the look for newly synthesized compounds with anticonvulsant sports are the maximal electroshock-precipitated seizure (MES) and the subcutaneous pentylenetetrazol-prompted seizure (PTZ) checks . MES check identifies the compounds that prevent the unfold of seizures and the s.C.PTZ check mainly identifies the compounds that improve the seizure threshold in these animal seizure fashions (10).

The structure–pastime relationship is the connection between the chemical structure of a synthesized molecule and its organic activity. Chemists use various synthesis techniques to insert one-of-a-kind organizations into the bioactive compounds and test them for his or her biological hobby. In the current years, organic chemists were operating difficult to explain the synthesis and homes of new compounds that may display anticonvulsant interest. In this overview, the synthesis and residences of molecules with anticonvulsant results have been investigated.

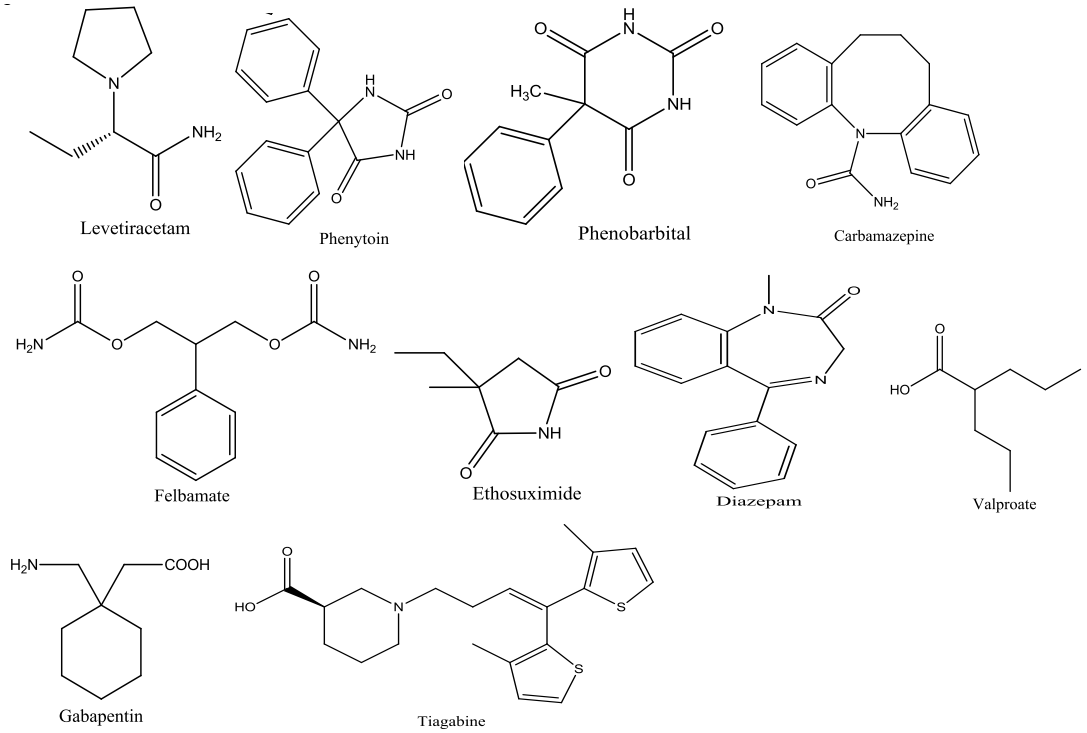


Fig.1Antiepileptic drugs for epilepsy

Synthesis Of Organic Compounds with Antiepileptic Activity

Deng et al. (2014a) synthesized 6-(substituted phenyl)thiazolo[3,2-b][1,2,4] triazole derivatives (three and five a–l) and studied for their anticonvulsant activity using MES and PTZ tests. On this file, 6-(four-fluorophenyl)thiazolo[3,2-b] [1,2,4]triazole (3b) and 6-(4-propoxyphenyl)thiazolo[3,2-b] [1,2,4]triazole (5c) had been found to be active in both tests. Further, in PTZ screening, compound 6-(4-Propoxyphenyl) thiazolo[3,2-b][1,2,4]triazole

turned into mentioned to have a higher PI (TD50/ED50) price in comparison with carbamazepine a commonly used drug in epilepsy treatment.(11)

Khokra et al. (2019) synthesized ¾ substituted benzene sulfonamides (sixteen, 17 a–g) related through phenyl ring to a benzothiazole moiety (thirteen and 14). On this take a look at, the anticonvulsant potentials of these newly synthesized molecules have been evaluated. In keeping with their consequences, N-[4- (benzothiazole-2-yl)phenyl]three-substituted benzene sulfonamide (sixteen a–g) derivatives possessed better anticonvulsant hobby in evaluation with 4-substituted benzene sulfonamide derivatives (17 a–g). Amongst all of the synthesized compounds on this work, 16b was mentioned to be the most powerful anticonvulsant agent in MES check carried out in mice.(12,30)

Zayed et al. (2017) synthesized novel fluorinated quinazoline derivatives (10 a–j) and investigated the anticonvulsant interest and neurotoxic residences of those newly synthesized molecules the use of mice experiments. All of the synthesized molecules in this observe were proven to have significant anticonvulsant hobby in PTZ and MES checks . Further, the 3 of the compounds (10 b, c, and d) confirmed the very best binding affinities to the GABA-A receptor. These three compounds (10 b–d) had been pronounced to expose higher anticonvulsant activity (PI values are 1.Seventy eight, 2.12, and a pair of.29, respectively) in experimental mice than reference epilepsy drugs, metacalon (PI fee 2) and valproate (PI fee of one.5).

Malik and Khan (2014) carried out the synthesis of a series of novel (5-amino-three-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). Those newly synthesized compounds were evaluated in phrases of their anticonvulsant and neurotoxic residences. It was stated that the (five-amino-3-phenyl-1,2,4-triazin-6-yl)(2-(6-fluorobenzo[d]isoxazol-3-yl)pyrrolidin-1-yl) methanone (25c) molecule had a more potent anticonvulsant property (PI values of 48.38) than the usual antiepileptic drug phenytoin (PI values of 35.Fifty eight). Additionally, they suggested that compounds of 25b, 25i, and 25o showed properly anticonvulsant pastime in this observe.(13,31)

In a observe by way of Jangam et al. (2019) 3-(2-substituted)-4- oxothiazolidin-three-yl)-2-phenylquinazolin-4(3H)-one compounds (20 a–okay) had been synthesized consistent with issue response the use of three-amino-2-phenylquinazolin-4(3H)- one (18), substituted fragrant aldehydes (19 a–okay), TGA and DCC in N,N-dimethyl formamide as a solvent. In vivo anticonvulsant activities of those compounds have been executed by way of maximal electroshock brought on convulsion model. Six of the zero 10 20 30 40 50 60 70 eighty 90 a hundred PTZ (% safety) MES (% safety) 10a 10b 10c 10d 10e 10f 10g 10h 10i 10j Methaqualone Valproate Fig. 4 Anticonvulsant effects of quinazoline derivatives (10 a–j) . Five Synthesis of ¾ substituted benzene sulfonamides (16 and 17 a–g) Fig. Three Synthesis of fluorinated quinazoline derivatives (10 a–j) Medicinal Chemistry studies newly synthesized molecules (20 b, c, d, e, f, and that i) had been mentioned to have a better anticonvulsant pastime in comparison with phenytoin which became used as a reference on this have a look at (14).

Harish et al. (2013) synthesized a series of latest pyrazine substituted 1,3, four-thiadiazole by-product (35 a–o) (Fig. 9). On this look at, the brand-new compounds were screened for their anticonvulsant pastime the use of MES seizure approach. Similarly, the neurotoxicity of the compounds became determined with a purpose to determine their scientific usability. Some of the synthesized compounds, 35d and 35g had been stated to show off wonderful anticonvulsant hobby and proposed as potential antiepileptic compounds (15).

Thirteen novel cyclopentanecarbaldehyde-based totally 2,four-disubstituted 1,three-thiazoles compounds (38 a–m) had been synthesized by using Łaczkowski et al. and those compounds have been evaluated for their in vivo anticonvulsant activities. The consequences of those the anticonvulsant assessments discovered that seven compounds, 38a, 38b, 38d, 38e, 38f, 38k, and 38m established the maximum vast anticonvulsant pastime inside the PTZ version. In addition, compounds 38a and 38b have been reported to delay the onset of clonic seizures and reduce the wide variety of seizure episodes in mice model.

Iman et al. (2017) synthesized a number of compounds (forty-one–forty-five and 48) associated with the ameltolide and tested their anticonvulsant activities in mice. Phenytoin changed into used because the reference antiepileptic drug on this look at, and the compounds confirmed higher anticonvulsant hobby relative to the reference and their interest had been most 30 min after management. Furthermore, it become reported that the effect of compound 42 (62.46 ± 6.Forty eight) on clonic seizure was stronger than that of phenytoin (forty nine.20 ± 1.09).

3-alkoxy-4-(4-(hexyloxy/heptyloxy)phenyl)-4H-1,2,4- triazole derivatives (53 a–t) were synthesized by 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)-4H-1,2,4-triazole (53f) was the most effective 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.(16)(17)

Kubowicz et al. (2015) reported the synthesis, antiepileptic activity and biotransformation of three chiral, N-aminoalkyl derivatives (57–59) .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.(18)

Dibenzofuranone-oxime derivatives (65 a–h) 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.

3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide/ carbothioamide (108 a–n) (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 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.(19) 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-2H-benzo[c][1,2,4]triazolo[4,3-a] azepin-3(5H)-one derivatives (112 a–n) (Fig. 20) starting from 2,3,4,5-tetrahydro-7- hydroxy-1H-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) 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).(20)(21)(22) 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) (23) as product of the reaction of isothiocyanate with 4-aminophenyl acetic acid . 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.The derivatives of 1-{4′-[3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl]-biphenyl-4-yl}-7-hydroxy-4- methyl-1H-quinolin-2-one (126 a–j), 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 antiepileptic drug, was used as a standard, it has been reported that 125j and 126a compounds showed excellent anticonvulsant properties.(24)

Kabra et al. (2011) synthesized 2-ethyl-3-(substituted benzothiazole-20-yl)–[3H]-quinazolin-4-ones derivatives (132 a–j) . 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 .

Synthesis of phenytoin-derived 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 mic.

The synthesis, pharmacological evaluation and molecular modeling studies of 1,6-dithia-4,9-diazaspiro [4.4]nonane-3,8-dione derivatives (141–152) 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-bromoetha-none phenobarbital.(25)

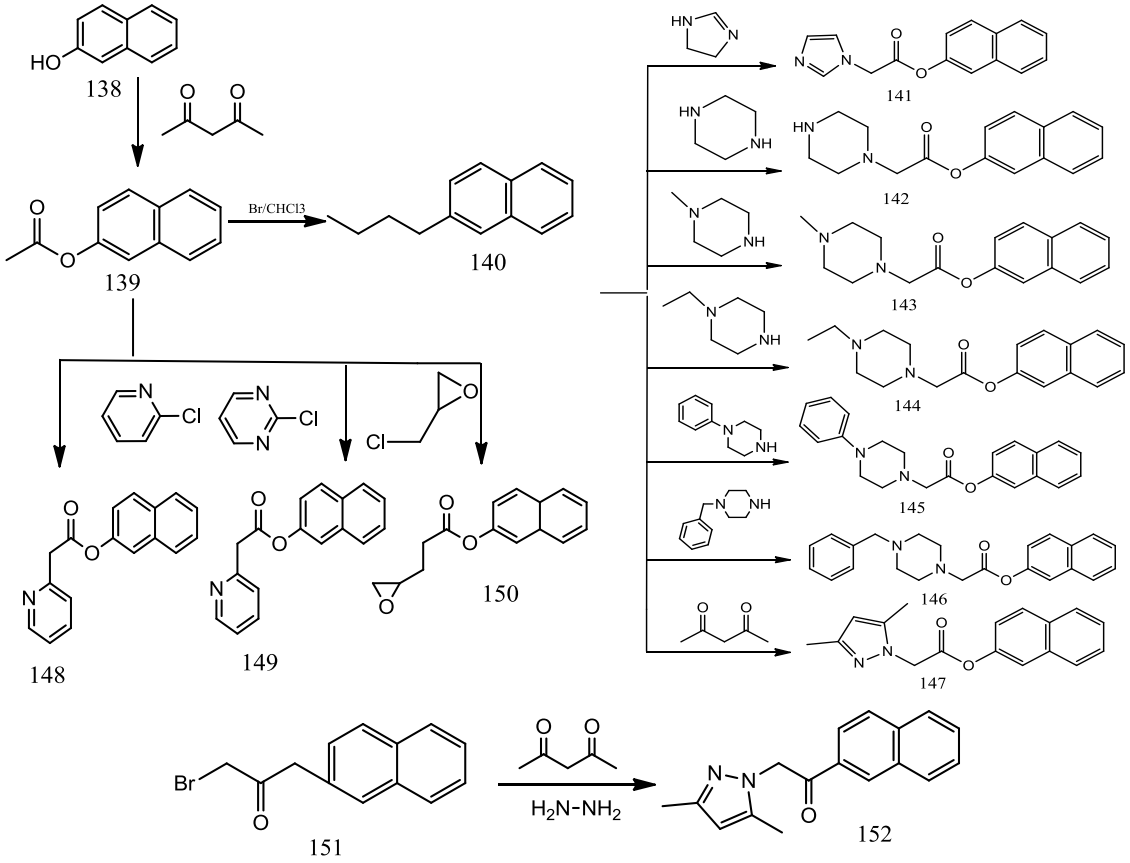
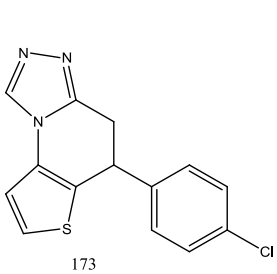


Fig.2 Synthesis of 1,6-dithia-4,9-diazaspiro [4.4]nonane-3,8-dione derivatives (141-152)

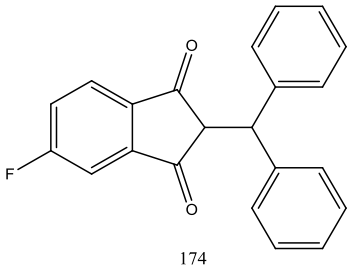
Methylsulfonyl phenyl derivatives (156 a–k) were synthesized by Mishra et al. (2018) in order to evaluate their COX-2 inhibitory activities along with anticonvulsant potential. Compound 156b was reported to show excellent protection against scPTZ-induced seizures in acute epilepsy models. In addition, 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 .The toxicity test performed in this study proved that the compound (156b) was nontoxic in these mice models.(26).

Khajouei et al. (2018) synthesized isatin-based compound derivatives (160 a–l) 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.(27) In addition, all derivatives tested were proved to have a low toxicity using Rotarod protocol.7-

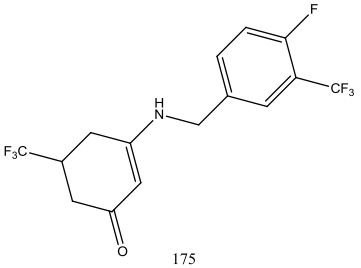
(benzylamino)-1H-benzo[b][1,4]diazepine-2,4(3H,5H)- dione derivatives (165 and 168 a–i) were synthesized by Shao et al. (2018) and their anticonvulsant activities were screened with MES and scPTZ tests. In addition, their neurotoxicity was evaluated by the rotarod neurotoxicity test as previously mentioned. 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-1H-benzo[b][1,4]diazepine-2,4(3H,5H)-dione) exhibited more effective anticonvulsant properties relative to other compounds tested, in both MES and scPTZ test (28).



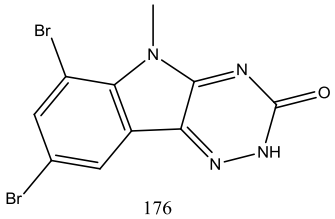
173
(Wang et al., 2019)



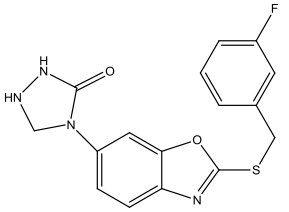
174
(Iman et al., 2018)



175
(Apraku and Okoro 2019)



176
(Kumar et al., 2014)



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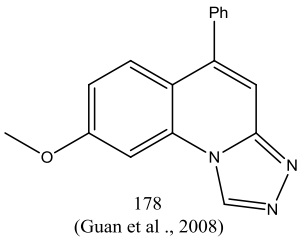
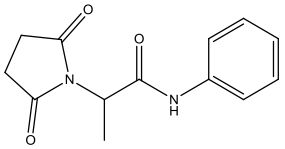
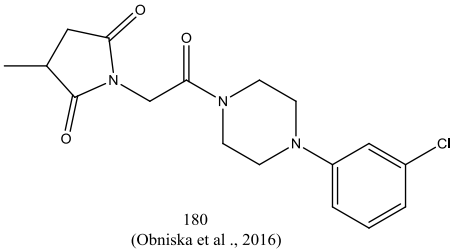
(Song et al., 2019)



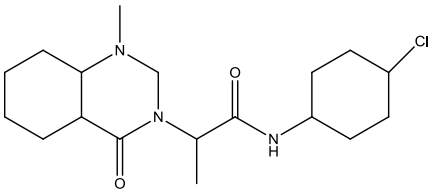
178
(Guan et al ., 2008)



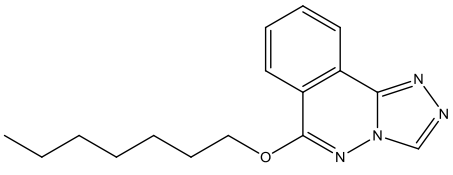
179
(Kaminski et al ., 2016)



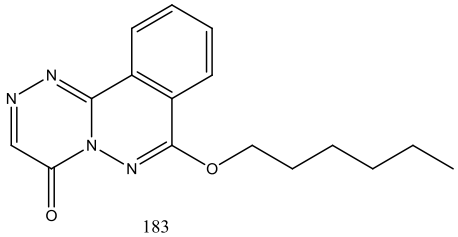
180
(Obniska et al ., 2016)



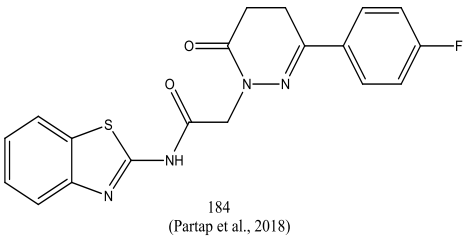
181
(Noureldin et al., 2017)



182
(Zhang et al., 2009)



183
(Sun et al., 2009)



184
(Partap et al., 2018)

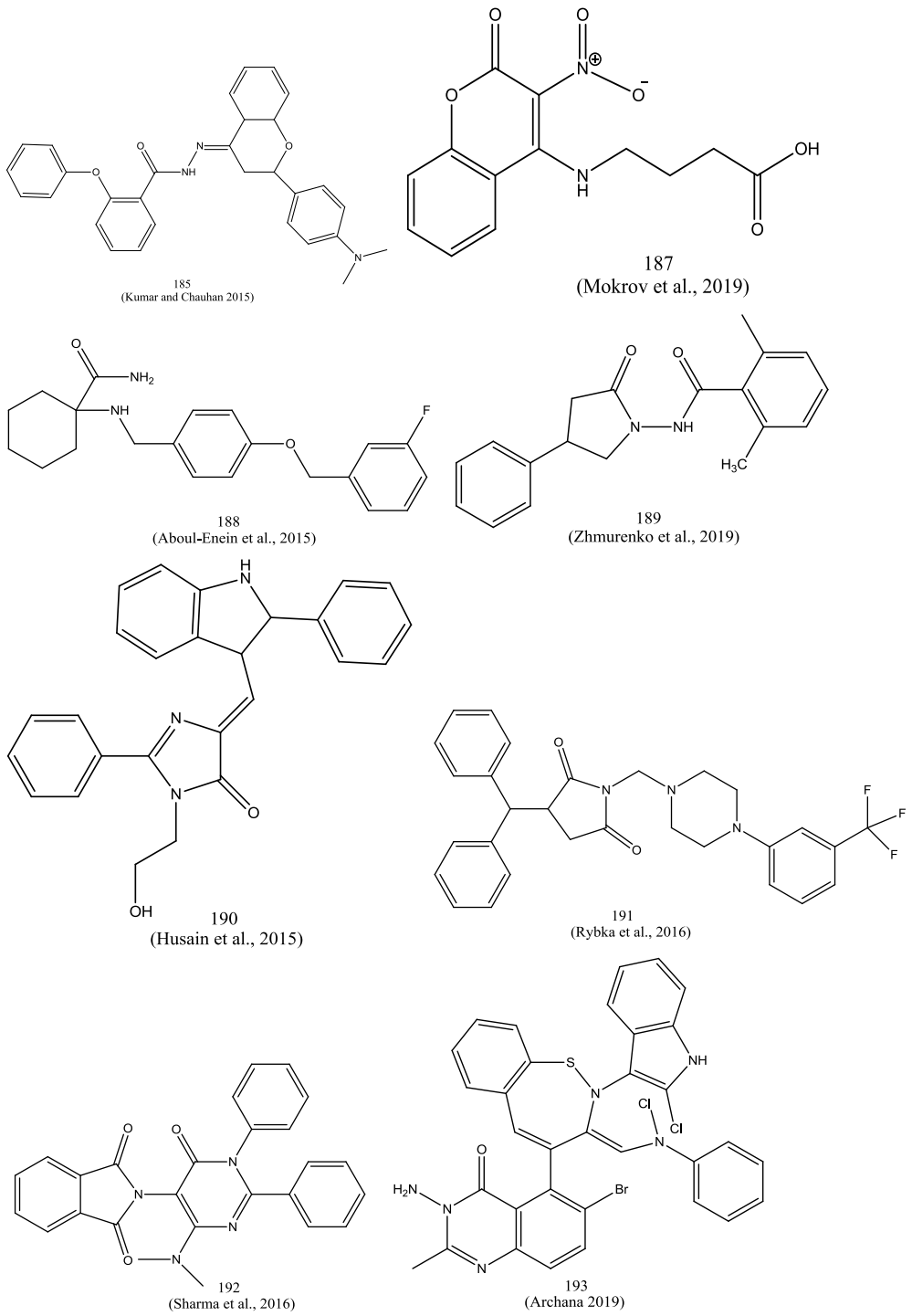


Fig.3 Molecules with anticonvulsant properties

Conclusion

Every compound synthesized by using chemists has its personal organic traits such as anticancer, antimicrobial, antiantioxidant, antitubercular and anticonvulsant capabilities, etc There are lots of research inside the literature, reporting on the synthesis and characterization of drug energetic materials. Novel anticonvulsant drug energetic substance research has a crucial

vicinity among these studies. The present-day standard remedy of epilepsy, that's a commonplace persistent disorder worldwide, is completed with the prescription of various antiepileptic capsules which have constrained efficacies. For the purpose of offering stronger antiepileptic capsules, new molecules are synthesized in the labs by using researchers and their anticonvulsant homes are examined in animal models. Those studies, with no question, are of great importance within the discovery of latest capsules that have the ability for use within the sanatorium for the improvement of human fitness. Preclinical evaluation of a few research provided on this review has been finished. In different research, high-quality consequences have been obtained on mice and better effects than preferred antiepileptics have been suggested inside the large majority of this studies. We trust that within the destiny, the molecules provided in this assessment and their strong anticonvulsant consequences will manual the researchers running in this place.

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