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Epilepsy and Quinazolinones: The Renewable Relationship

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Review Article

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Abstract

Epilepsy is a global public health issue requiring a global response. Epilepsy is present everywhere and affects people of various ages, genders, ethnicities, and social backgrounds, regardless of geographical locations. Excess discharge from the cortical neurons in the cortical section of brain is generally responsible for epileptic state. Understanding the classification of epileptic seizures is the first step toward the correct diagnosis, treatment and prognostication of the condition. Specific seizure types or syndromes often respond better to specific medications or surgical approaches. Multidrug resistant syndrome and refractory epilepsy are the biggest challenge in treatment of epilepsy, they lead to defect access of Anti-Epileptic Drugs AEDs to their target in CNS. Moreover, the marketed drugs carry severe side effects such as drowsiness, hepatotoxicity, anemia, and teratogenicity. Therefore, there is pivotal need to discover more safe and effective drugs. Quinazolinones analogues represent molecules which are capable of binding at multiple sites with high affinity and facilitate more rapid discovery of useful medicinally active compounds. Series of new quinazolinone derivatives were synthesized by many sceintists around the world, screened virtually and evaluated for the anticonvulsant activity against different types of seizures. They are to be a vital part of the solution of epilepsy in the future.

Keywords: Epilepsy, Quinazolinones, Seizures

Abbreviations: NCC**:** Neurocysticercosis; WHO: World Health Organization; EEG: Electroencephalography; AEDs: Antiepileptic Drugs; GAD: Glutamic Acid Decarboxylase; CNS: Central Nervous System; SC2A: Synaptic Vesicle Protein 2A

Introduction

Prevalence and Incidence of Epilepsy

Epilepsy is a global public health issue requiring a global response. Epilepsy is present everywhere and affects people of various ages, genders, ethnicities, and social backgrounds, regardless of geographical locations [1]. It is the most common chronic serious neurological disease as it affected 50 million people worldwide and nearly 80% of them are found in developing regions[2]. Globally, an estimated 5 million people are diagnosed with epilepsy each year. In high-income countries, annual new cases are around 49 per 100,000 people in the general population. In low-income and middle-income countries, this figure can be up to 2 times higher as 139 per 100,000 [2-4]. This is likely due to the increased risk of endemic conditions, such as malaria or

neurocysticercosis (NCC), the higher incidence of road traffic injuries and birth-related injuries in addition to that most people in developing countries with epilepsy receive no medical attention at all [5]. Consequently, although diagnostic and therapeutic innovations remain important goals, the greatest challenge for world health lies in appropriately identifying epileptic patients with providing the best available treatment [4,6]. The prevalence of epilepsy in developed countries ranges from 4 to 10 cases per 1000, while in the developing and tropical countries studies have reported higher prevalence rates of epilepsy, ranging from 14 to 57 cases per 1000 persons [7,9]. In Saudi Arabia the prevalence of epilepsy is 6.5 per 1000 and it is probably 2 times higher in children and young adult compared to other groups and with a lower rate in middle age people. The prevalence rate of epilepsy in Saudi Arabia is within the range reported in most other communities [10-12]. The prevalence of epilepsy of some countries is summarized in (Figure 1)[13].

The prevalence of active epilepsy is 6.4 per 1,000 and the lifetime prevalence is 7.6 per 1,000. The prevalence tends to increase with age, with peaks in the oldest age groups and in socially deprived individuals. The incidence of epilepsy is 61.4 per 100,000 person-years. Epilepsy has a bimodal distribution according to age with peaks in the youngest individuals and in the elderly. The increased incidence of seizures and epilepsy in the elderly can be attributed to the increase of age-related and aging-related epileptogenic conditions [14].

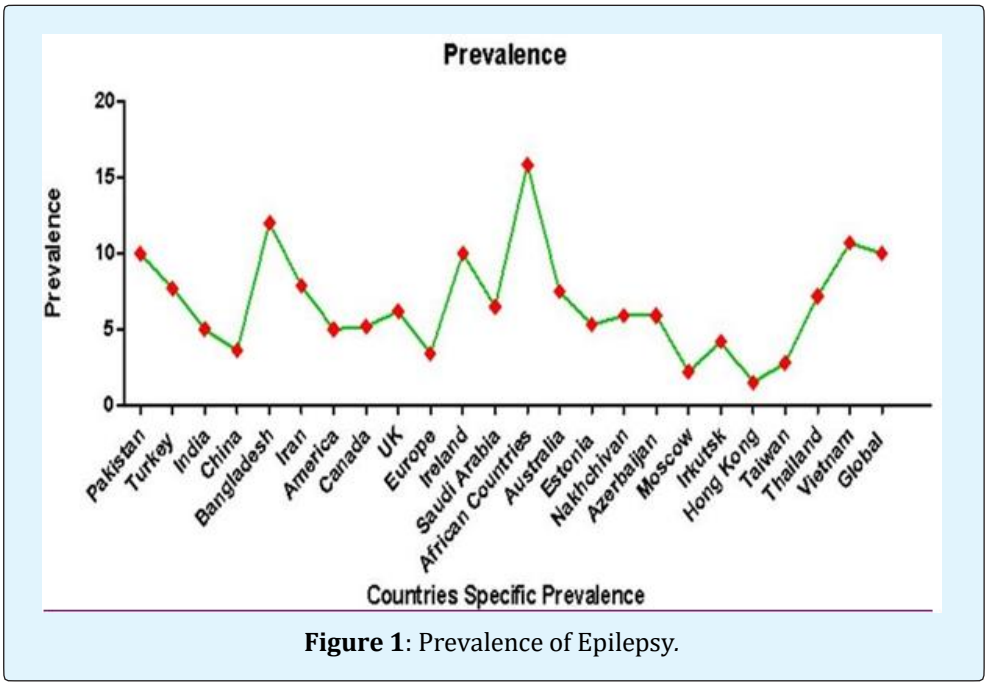


Figure 1: Prevalence of Epilepsy.

According to World Health Organization (WHO), (2001b), epilepsy is a neurological disorder characterized by recurrent seizures resulting from excessive electrical activity in either part or the whole of the brain [15]. People with epilepsy suffer from discrimination, misunderstanding, and social stigma. Besides that, uncontrolled seizures lead to major morbidity and mortality, including physical injury such as head trauma, fractures and burns, also psychosocial problems such as depression and anxiety, and sudden unexpected death [16,17].

Causes of Epilepsy

Excess discharge from the cortical neurons in the cortical section of brain is generally responsible for epileptic state. Transition from normal behavior to seizure behavior may be caused by a number of factors including greater spread and neuronal recruitment secondary to a combination of enhanced connectivity, enhanced excitatory transmission, a failure of inhibitory mechanisms, and changes in intrinsic neuronal properties [18,19].

Previously, the causes of epilepsy were classified as idiopathic, symptomatic, or cryptogenic [20]. The International League Against Epilepsy ILAE in 2010 proposed that to replace the old classification by the following categories: genetically, in which genetic factors have a major role in the causation of the epilepsy and in which the causative or susceptibility genes are inherited or result from de-novo mutations that might or might not be further inherited, structural or metabolic, in which there is a clear genetically or non- genetically determined cause that is structural or metabolic (e.g, stroke, trauma, brain tumor, aminoacidopathies), and unknown. The structural or metabolic categories are under discussion for further clarifying to extend and include immune and infectious causes [21].

The likely underlying cause of epilepsy varies with age as shown in (Figure 2) [22]. Congenital factors (including genetic conditions) are predominating in infancy and perinatal stage. Idiopathic (genetic) epilepsies remain common in later childhood and adolescence but are the cause in only 20-30% of people with epilepsy overall. In middle life, trauma becomes more common as a cause of seizures (although it is only responsible for about 3-4% of cases in the population as a whole), while tumor, although the most feared cause of seizures, is responsible for only about 6% of incident cases of epilepsy (approximately 13% in the elderly). Cerebrovascular disease is the commonest identified etiology of seizures overall, being the cause in approximately 15%. In the older age groups, it is responsible for only 30-50% of cases. Even with modern neuroimaging and other modes of investigation, no cause can be identified in the majority of people developing seizures [23].

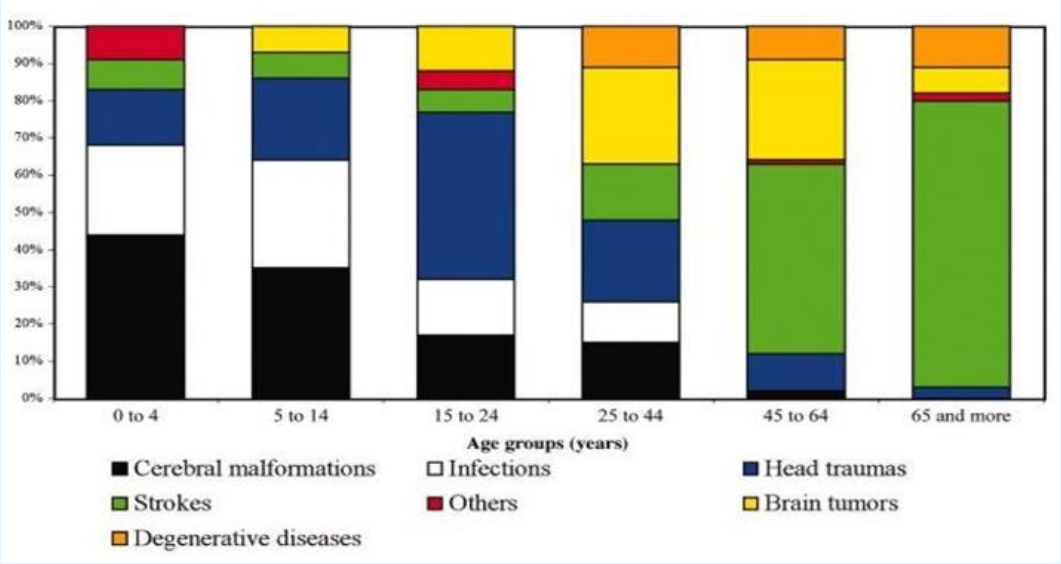


Figure 2*:* Proportion of epilepsy cases according to the etiologic categories within age groups.

Classification of Epileptic Seizures

Understanding the classification of epileptic seizures is the first step toward the correct diagnosis, treatment and prognostication of the condition. Specific seizure types or syndromes often respond better to specific medications or surgical approaches. Some seizure types or syndromes carry a benign prognosis or high likelihood of seizure remission by a certain age. Other seizure syndromes may carry a far poorer prognosis, and early knowledge of this allows focused treatment and lifestyle modifications for patients and families [24]. A revised operational classification of seizure types was presented by the ILAE. The purpose of such a revision is to recognize that some seizure types can have either focal or generalized onset, to allow classification when the onset is unobserved, to include some missing seizure types, and to adopt more transparent names. Because current knowledge is insufficient to form a scientifically based classification, the 2017 Classification is operational (practical) and based on the 1981 Classification which extended in 2010 (Figure 3)[25].

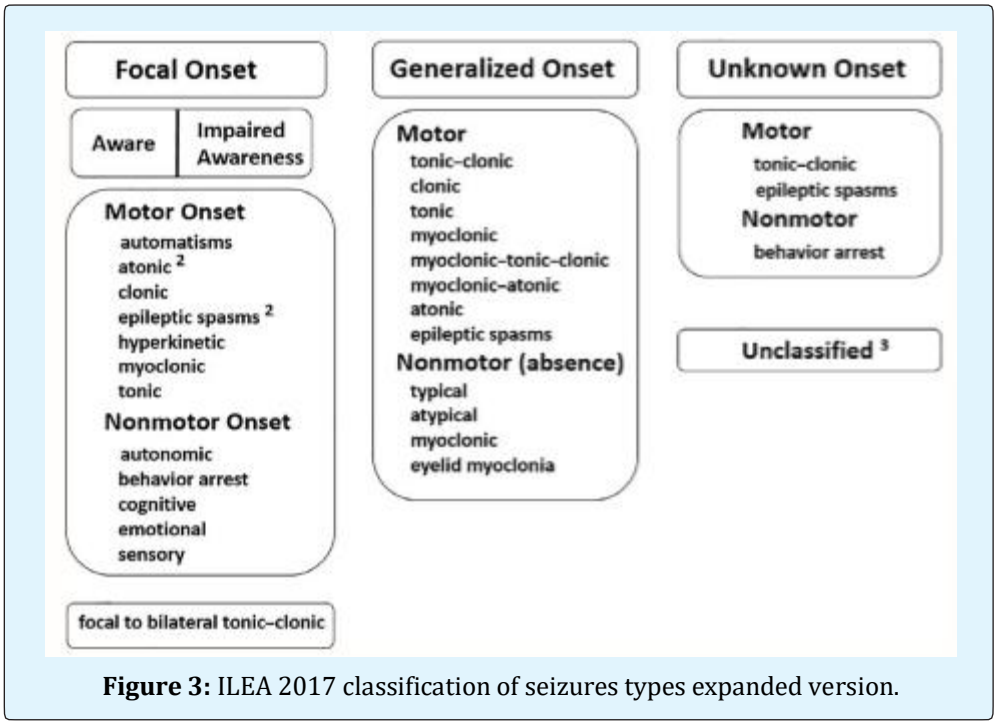


Figure 3: ILEA 2017 classification of seizures types expanded version.

The ILEA classifies seizures by their site of onset. Electroencephalography (EEG) plays an essential role beside the clinical observation in differentiation between types of seizures and diagnosis of epilepsy [26].

Generalized seizure: Generalized seizures start throughout the entire cortex at the same time and therefore cause loss of consciousness because cortical neurons that maintain consciousness are not able to perform their normal functions. The abnormal electrical activity involves both hemispheres of brain. There are several types of generalized seizers, the most common is absence seizure usually have onset on childhood but can persist on adulthood. It is usually brief loss of conciseness. The other type is the tonic-clonic seizure which start with sudden loss of consciousness and tonic activity (stiffening) followed by clonic activity (rhythmic jerking) of the limb. Tonic seizure involves stiffening of the muscles as the primary seizer manifestation with brief loss of consciousness. While clonic seizure involves rhythmic generalized jerking, commonly occur in neonates and infants. Atonic seizure is manifested as sudden loss of muscle tone and subsequent falling or dropping to the floor unprotected. Myoclonic seizure is brief, lightning-like muscular jerks. The most common signs are bilateral hand or arm jerks [23,26,27].

Partial (focal) seizure: Partial seizures have onset on one side of the brain, resulting in focal symptoms. Partial seizures are classified as simple or complex according to loss of consciousness. In simple partial seizure there is no alteration in consciousness or memory. It can be motor seizures with twitching, or non-motor with abnormal sensations; abnormal visions, and sounds or smells. Seizure activity can spread to the autonomic nervous system. Complex partial seizure characterized by loss or impaired of consciousness and involuntary motor actions (Automatism) [23,26,27].

Treatment of Epilepsy

The objective of treatment is to bring the electrical activity in the brain under control while maintaining quality of life. The standard medical treatment of epilepsy is with antiepileptic drugs (AEDs), which are known generally as anticonvulsants. Antiepileptic drugs can be effective, but like all drugs acting on central nervous system (CNS) have side effects. Although the majority of people with epilepsy can anticipate good seizure control with the correct antiepileptic drugs, about 30% of people continue to have seizures. Non- pharmacological treatments which include ketogenic diet, surgical resection, and vagal nerve stimulation can be helpful to reduce seizure frequency for patients with refractory seizures [15,28].

Antiepileptic drugs (AEDs): AEDs are the first choice of treatment of epilepsy. The main goal of anticonvulsant treatment is a significant reduction in seizure frequency and severity and maintaining normal lifestyle for epileptic patient. The selection of AED is principally determined by several factors including efficacy, toxicity, type of seizure, the Physicist's familiarity with drug, and AED cost [29,30]. All AEDs have the ability to decrease neuronal excitation or increase neuronal inhibition by one or more of pharmacological processes, including modification of voltage-gated ion channels (Na^+, Ca^{+2}, K^+), potentiation of GABA-ergic activity, inhibition of glutamatergic process and modification of neurotransmitter release [31]. A new AED is successful if it has at least one of the following properties: greater efficacy than other drugs in the treatment refractory epilepsy, the ability to prevent or delay the epileptic onset, broad usefulness in other non-epileptic CNS disorders, fewer side effects than available drugs and ease of use such as linear pharmacokinetic, lack of drug interaction and once or twice daily dosing [32,33].

Mechanism of Action of AEDs

- **Voltage Gated Na^+ Channels**

Ion channels are extremely important membrane integral proteins that regulate trans-membrane potential of the cell. Voltage gated Na^+ channels generate the upstroke of the action potential by allowing Na^+ to rapidly enter the cell upon reaching the threshold voltage. Some AEDs are thought to principally affect the voltage-dependent Na^+ channels. The traditional AEDs, Phenytoin and Carbamazepine are thought to exert their anti-epileptic effects by prolonging the inactivation of Na^+ channels that may account for the termination of the sustained, rapid and repetitive firing induced in neurons by a trans-membrane current pulse. At high concentrations, Valproate could contribute to the long-lasting inactivation of Na^+ channels. Lamotrigine one of the newer AEDs, also prolongs the inactivation of Na^+ channels. Abolition of the sustained, rapid and repetitive firing of isolated neurons was also observed with, Topiramate and Zonismaide (Figure 4). These drugs block high-frequency repetitive spike firing, which is believed to occur during the spread of seizure activity, without affecting ordinary on-going neural activity. This elucidates their ability to protect against seizures without causing a generalized impairment of brain function [34-36].

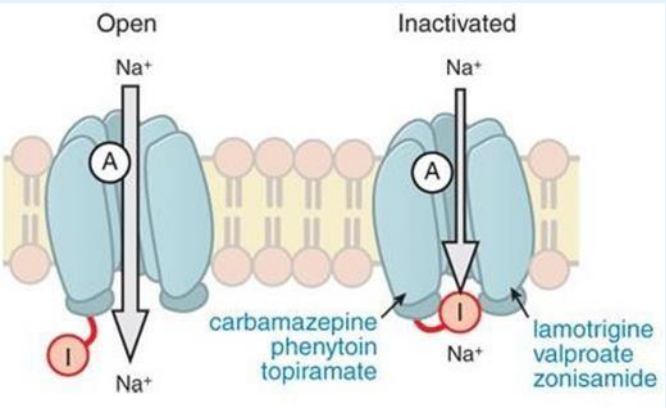


Figure 4: Anti-seizure drugs enhanced Na^+ channel inactivation.

- **Voltage Gated Ca^{+2} Channels**

Voltage gated calcium channels molecular structure and mechanism of inactivation are similar to the voltage-gated sodium channels. They are divided into several subtypes, L, N, P/Q, T and R, according to their electrophysiological characteristics. Blockade of N or P/Q channels inhibits the presynaptic release of excitatory amino acids. However, a potential role for these channels in AED action has not been elucidated. The low-voltage calcium channel T-type opens with slight depolarization, and are quickly inactivated. The low-threshold Ca^{2+}current regulate repetitive electrical activity of thalamic neurons and probably participate in generating generalized absence seizures. Ethosuximide is one of AEDs that inhibit this T- calcium channel, (Figure 5)[35-37].

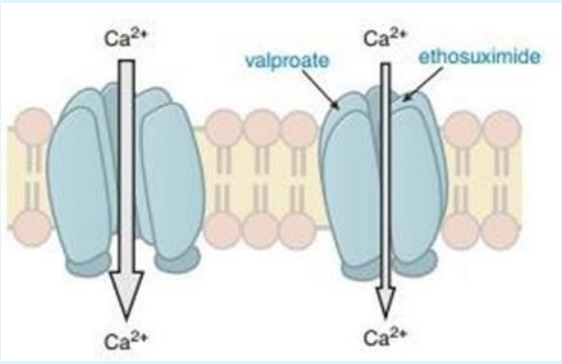


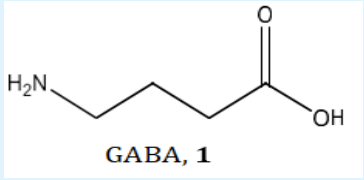
Figure 5: anti-epileptic drugs enhanced Ca^{+2} channel inactivation.

• Potassium Channels

K^+ channels with distinct subcellular localization, biophysical properties, modulation, and pharmacologic profile are primary regulators of intrinsic electrical properties of neurons and their responsiveness to synaptic inputs. An increase in membrane conductance to K^+ ions causes neuronal hyperpolarization and reduces firing frequency, exerting a strong inhibitory function on neuronal excitability. Involvement of K^+ channels in mechanism of action- with exception of Retigabine- remains unknown [38].

• The GABA-ergic System

γ-Aminobutyric acid **1** (GABA) is recognized as the main inhibitory neurotransmitter in the cerebral cortex. GABA is formed within GABA-ergic axon terminals by decarboxylation of glutamic acid by glutamic acid decarboxylase (GAD) to GABA. It is released into the synaptic junction and then acts at one of two types of GABA receptors: $GABA_A$ receptors and $GABA_B$ receptors. The $GABA_A$ receptors are ligand-gated ion channels that hyperpolarize the neuron by increasing inward chloride conductance and have a rapid inhibitory effect. The $GABA_A$ - receptor complex is a pentameric heterooligomer that contains binding sites for GABA, barbiturates, benzodiazepines, picrotoxin, and neuro-steroid. $GABA_B$ receptors are G protein– linked receptors that hyperpolarize the neuron by increasing potassium conductance. $GABA_B$ receptors decrease calcium entry and have a slow inhibitory effect. After release from the presynaptic axon terminals, GABA is rapidly removed by uptake into both glia and presynaptic nerve terminals and then is catabolized by GABA transaminase. Four transporters (GAT1-4) participate in GABA uptake. An enhancement of GABA-ergic inhibitory transmission is responsible for the antiepileptic effects of drugs that directly bind and activate GABA receptors or influence GABA synthesis, transport and metabolism, (figure 6) [39,40]. Drugs that act through these mechanisms typically have broad spectrum of antiepileptic activity in human seizure disorders [35].



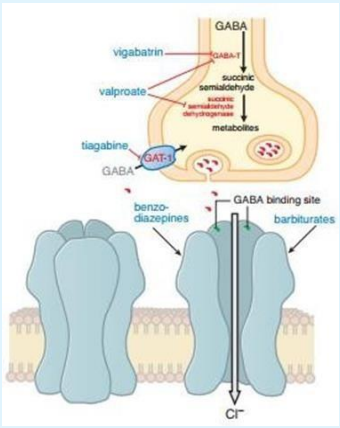


Figure 6: Enhanced GABA synaptic transmission.

• **Glutamate Receptor**

Glutamate is the main excitatory neurotransmitter in the CNS. When Glutamate binds to glutamate receptors, the receptors facilitate the flow of both sodium and calcium ions into the cell, while potassium ions flow out of the cell, resulting in excitation. Four glutamate receptor types have been identified within the CNS. Three of these receptors, α-amino-3-hydroxy-5- methyl-4isoxazolepropionic acid (AMPA), N-methyl-D-aspartate (NMDA), and kainate, are coupled to ion channels. The fourth type of glutamate receptor is the metabotropic glutamate receptor that acts via G protein influence on various second messenger systems and ion channel activity. AEDs that modify these receptors are antagonistic to glutamate [40,41].

• **Synaptic Vesicles Protein 2A (SV2A)**

SV2 is an integral membrane protein present on all synaptic vesicles; it is consisting of three isoforms, designated SV2A, SV2B, and SV2C. SV2A is the most widely distributed isoform, being nearly ubiquitous in the CNS; SV2A appears to be integral to the process of neurotransmitter exocytosis into the synaptic cleft. Inhibition of this protein appears to result in abroad-spectrum attenuation of excitatory activity. Levetiracetam is the first of several agents able to inhibit the synaptic vesicle protein 2A (SV2A) as well as Brivaracetam [42].

• **Classification of Antiepileptic Drugs**

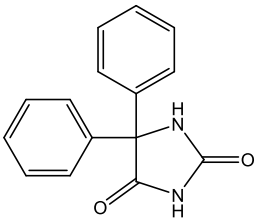
It is very difficult to classify AEDs depending on their mechanism of action because some of them act by several mechanisms, new modes of action are discovered, and in some cases the mechanisms of anticonvulsant action are incompletely described. All these facts make the mechanism-based selection of anticonvulsant drugs a difficult mission [43]. They are classified chronologically to the following generations:

• **First Generation**

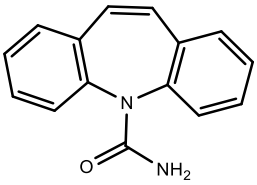
Most of the first generation or old AED_S are very effective and continue to be used up-to- date. These include phenytoin **2**, Carbamazepine **3,** Valproate **4**, Benzodiazepines, Phenobarbital **5**, Primidone **6**, and Ethosuximide **7**. The drawbacks for these drugs are there effect on metabolic enzymes either induction or inhibition. That makes new alternative antiepileptic recommended [44,45]. The clinical indications and efficacy of these drugs are summarized in (Table 1) [46].

Antiepileptic Drugs	Partial	Generalized toinc-clonic	Absence	Myoclonic	Tonic/ atonic
Phenytoin	X	X	_	_	_
Carbamazepine	X	X	_	_	_
Valproate	X	X	X	X	X
Benzodiazepines	A	_	E	A	A
Phenobarbital	X	X	_	_	X
Primidone	X	X	_	E	_
Ethosuximide	_	_	X	_	_

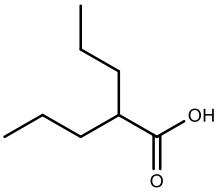
Table 1: Efficacy and indication of antiepileptic drugs by seizure type (United State or European indication)
A: adjunctive only**, E**: some evidence of efficacy without indication, **X**: monotherapy



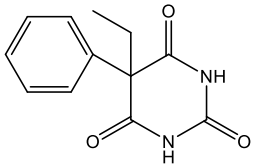
Phenytoin **2**



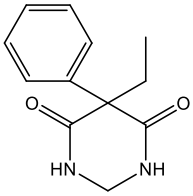
Carbamazepine **3**



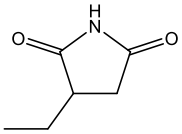
Valproic Acid **4**



Phenobarbital **5**



Primidone **6**



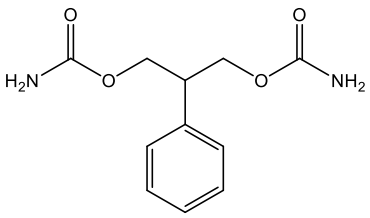
Ethosuximide **7**

• **Second Generation**

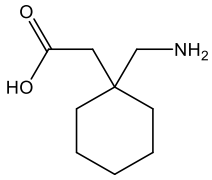
The choice of AEDs was limited to the old agents till the new second generation discovered and approved. These include Felbamate **8**, Gabapentin **9,** Lamotrigine **10**, Topiramate **11**, Tiagabine **12**, Oxcarbazepine **13**, Levetiracetam **14,** Pregabalin **15,** Zonisamide **16** and Vigabatrin**17**. They are better tolerated and safer than old drugs. They also have advantages of fewer side effects (table 2) minimum drug interactions in addition to the wide spectrum of activity. All the drugs in this group are approved to manage partial seizure. Falbamate, lamotrigine and Topiramate are used to control generalized seizure in addition to the partial type [47-51].

AED	Serious	Non serious
Felbamate	Aplastic anemia, hepatotoxicity	Anorexia, insomnia
Gabapentin	None	Sedation, weight gain
Lamotrigine	Stevens-Johnson syndrome	Insomnia
Topiramate	Kidney stones, glaucoma	Paresthesia, cognitive impairment, weight loss
Tiagabine	Spike-wave stupor	Tremor, sedation, impaired Concentration
Levetiracetam	None	Sedation, behavioral change
Oxcarbazepine	Hyponatremia, rash	Ataxia, diplopia
Zonisamide	Kidney stones Rash	Paresthesia, weight loss
Pregabalin	None	Sedation, weight gain

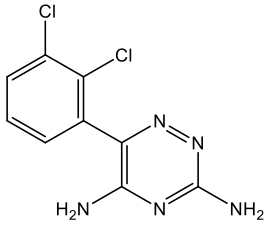
Table 2: Summary of adverse effects.



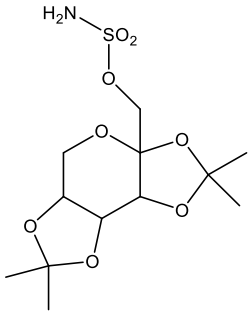
Flbamate **8**



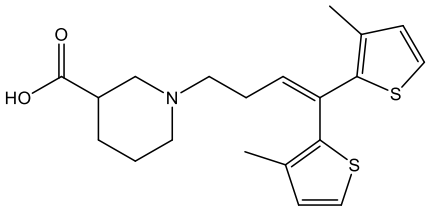
Gabapentin **9**



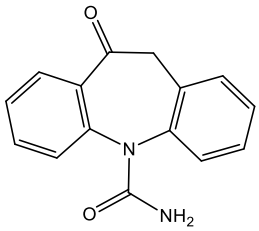
Lamotrigine **10**



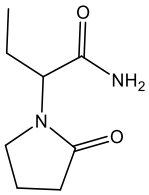
Topiramat **11**



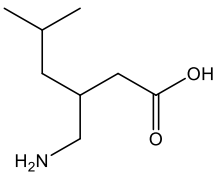
Tiagabine **12**



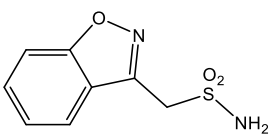
Oxacarbazepine **13**



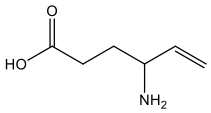
Levetiracetam **14**



Pregabalin **15**



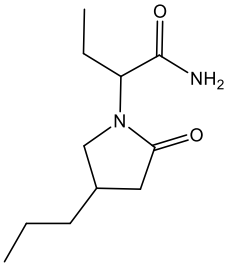
Zonismaide **16**



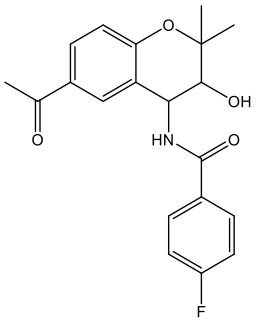
Vigabatrin **17**

• **Third Generation**

There are advanced AEDs have been developed and licensed latterly by pharmaceutical companies, which include Brivaracetam **18,** Carabersat **19**, Carisbamate **20**, Eslicarbazepine **21**, Fluorofelbamate **22**, Fosphenytoin **23**, Ganaxolone **24**, Lacosamide **25,** Remacemide **26**, Retigabine **27**, Rufinamide **28**, Safinamide **29**, Seletracetam **30**, Soretolide **31**, Talampanel **32**, Stiripentol **33** Valrocemide **34** and Losigamone **35**. They present a new and preferable approach to curing epilepsy, these attributed to their multiple diverse molecular mechanisms of action. Comparing to previous generations of AEDs the third-generation agents show superior tolerability, milder side effects, less drug and hormone interactions and enhance pharmacokinetics profiles [52-54]. The mechanism of action of AEDs of different generations could be summarized in (Table 3) [42].



Brivaracetam **18**



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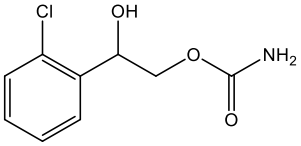
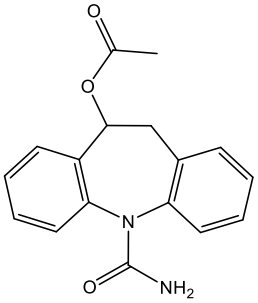
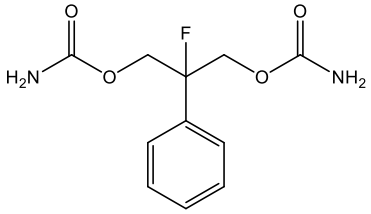


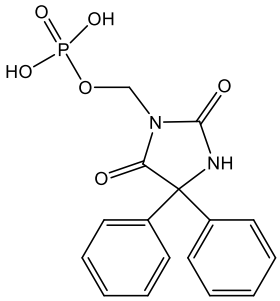
Carisbamate **20**



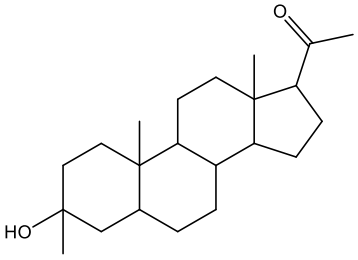
Eslicarbazepine **21**



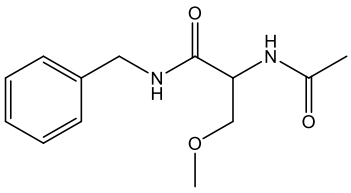
Fluorofelbamate **22**



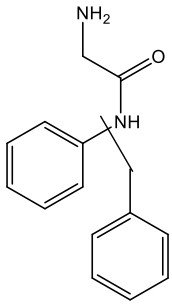
Fosphenytoin**23**



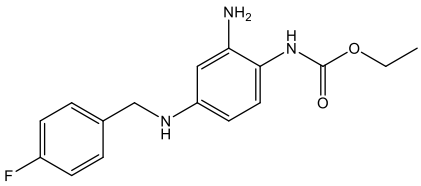
Ganaxolone **24**



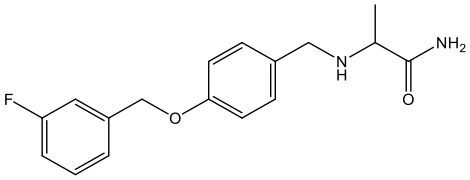
Lacosamide **25**



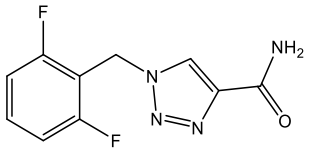
Ramacemide **26**



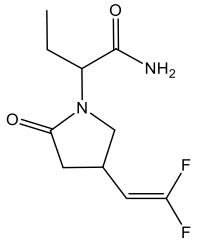
Retigabine **27**



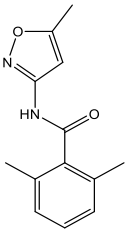
Rufinamide **28**



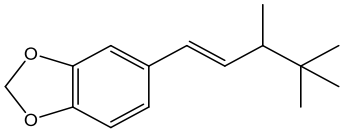
Safinamide **29**



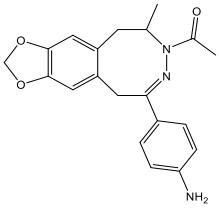
Seletracem **30**



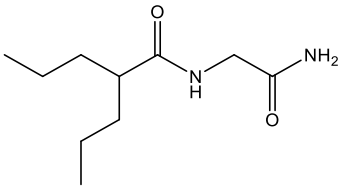
Soretolide **31**



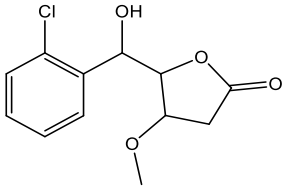
Talampanel **32**



Stiripentol **33**



Valrocemide **34**



Logamone **35**

Mechanism of action	Effect on neuronal transmission	First-generation AEDs	Second/third-generation AEDs
Na+ channel blocked (fast inactivation)	Slowed recovery from inactivated state	Phenytoin	Topiramate
		Carbamazepine	Zonisamide
		Valproate	Oxcarbazepine
			Lamotrigine
			Felbamate
			Rufinamide
Ca^{+2} channel blocked	Post-synaptic inhibitory action	Ethosuximide (T- type) Valproate	Topiramate
			Zonisamide
			Gabapentin
			Lamotrigine
			Pregabalin
GABA agonism/potentiation	Inhibitory activity by permitting hyperpolarization	Benzodiazepines	Felbamate
		Barbiturates	Topiramate
		Valproate	Vigabatrin
			Stiripentol
			Retigabine
NMDA receptor Blockade	Decreased excitatory synaptic activity		Felbamate
AMPA receptor Blockade	Decreased excitatory synaptic activity		Topiramate
SV2 A vesicle Inhibition	Decreased excitatory synaptic activity		Levetiracetam Seletracetam
Sodium channel Blockade (slow inactivation)	Recovery of neurons Oxcarbazepine from prolonged depolarization		Lacosamide
Potassium channel Blockade			Retigabine

Table 3: Summary of antiepileptic drugs' proposed mechanisms

New Concept for Developing Anticonvulsant Drugs

Although there are more than 20 approved AEDs with different chemical structures and targets of mechanism, they can provide seizure control for 60 - 70% of patients. Multidrug resistant syndrome and refractory epilepsy are the biggest challenge in treatment of epilepsy, they lead to defect access of AED to their target in CNS. Moreover, the marketed drugs carry severe side effects such as drowsiness, hepatotoxicity, anemia, and teratogenicity. Therefore, there is pivotal need to discover more safe and effective drugs [33,55,56]. It is difficult to use rational methodologies in the discovery of new antiepileptic drugs; this is attributed to the insufficient information on the cellular mechanism of epilepsy in human with the complex mechanism of action of most of the antiepileptic drugs. Consequently, another design approach based on the existence of different pharmacophores that were established through the analysis of structural characteristics of clinically effective drugs as well as other antiepileptic compounds was adopted. In the literatures, it is well documented that one of the important core fragments is defined by the presence of hydrogen donor/acceptor unit, one electron donor atom, and a hydrophobic domain (aryl ring substituted/un-substituted). These structural features were found in the first-generation drugs such as Carbamazepine or Phenytoin, and the newest drugs e.g, Felbamate and Retigabine (Figure 7) [43,57,58].

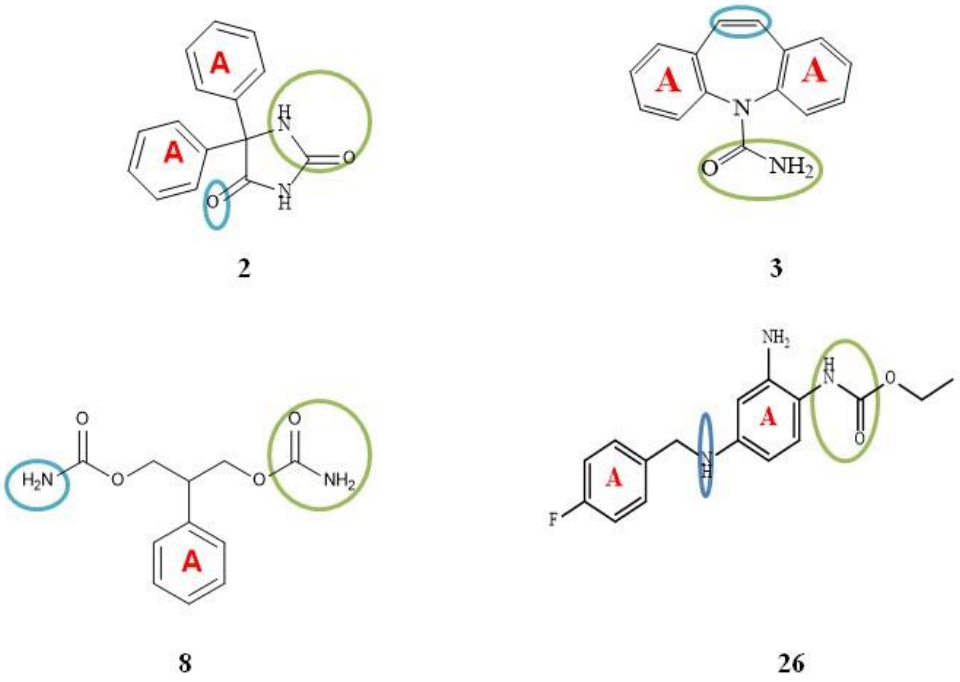


Figure 7: Pharmacophoric pattern of antiepileptic drugs. **A** hydrophobic domain; electron donor atom; hydrogen accepter/donor domain.

Compounds contain heterocyclic quinazolines and quinazolinones are considering available scaffolds in drug research as they possess vital pharmacological properties. These nucleuses can be termed as 'Master key' for antiepileptic therapy as it is an important scaffold of many reported anticonvulsant drugs (Figure 8) [59,60].

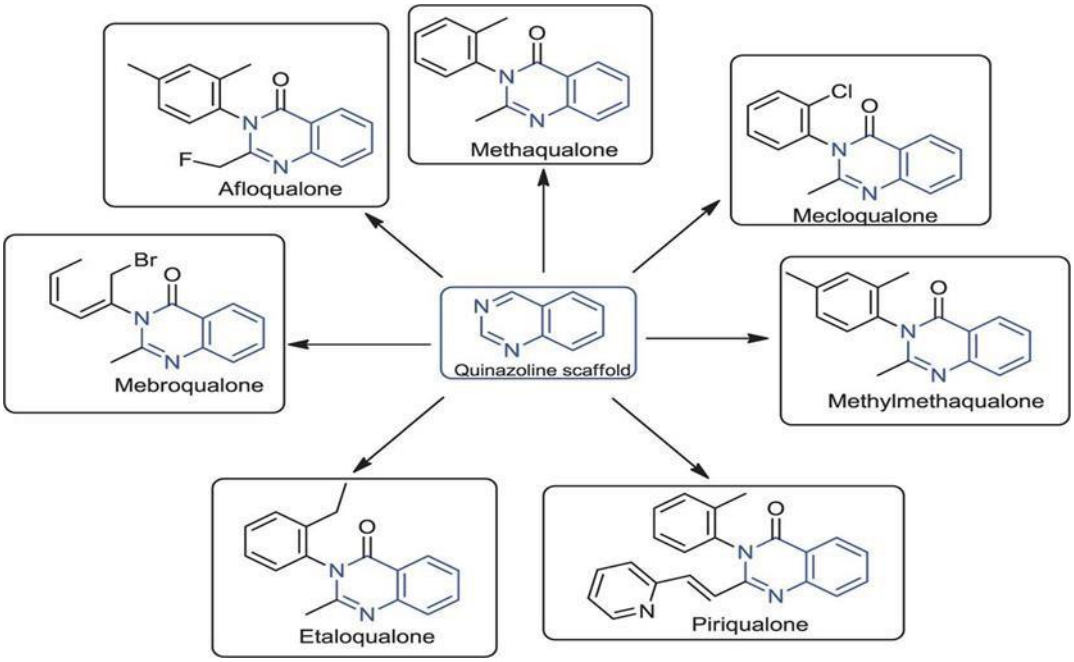
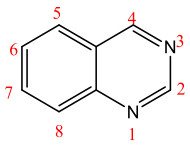


Figure 8: Potent anticonvulsant drugs bearing 4(3H)- quinazolinone ring.

Chemistry of Quinazolinone

Quinazolinone and their derivatives represent a building block for more or less 150 naturally occurring alkaloids isolated from numerous families of plant kingdom, animals and microorganisms [461-64]. Quinazolinone is a heterocyclic chemical compound with two joined aromatic rings, benzene ring and pyrimidine ring **36**, and one of the carbons oxidized to ketone oxygen. This 4-oxo derivative of quinazoline is called 4(3*H*)-quinazolinone **37**.

According to the keto or oxo group position, these compounds may be classified into three types: 2(1*H*) quinazolinones **38**, 4(3*H*) quinazolinones **37** and 2, 4(1*H*, 3*H*) quinazolinediones **39**. The 4(3*H*) quinazolinones are most abundant and significant in medicinal chemistry possessing a multitude of pharmacological action. Moreover, they are prevalent either as intermediates or as natural products in many proposed biosynthetic pathways.



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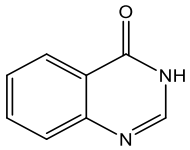

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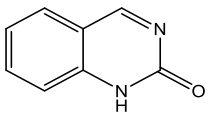

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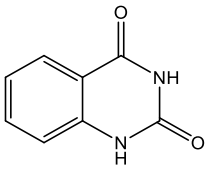

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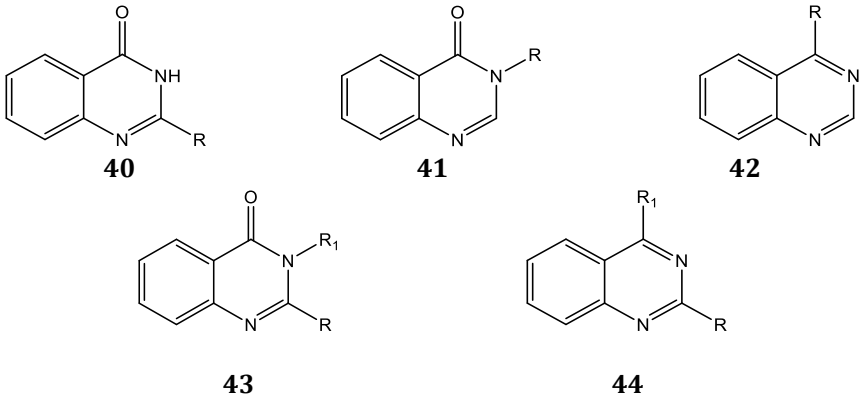
Furthermore, quinazolinones can be classified into the following five categories, based on the substitution patterns of the ring system [461,64-68].

- 2-Substituted-4(3*H*)-quinazolinones **40**.
- 3-Substituted-4(3*H*)-quinazolinones **41**.
- 4-Substituted-quinazolines **42**
- 2,3-Disubstituted-4(3*H*)-quinazolinones **43**.
- 2,4-Disubstituted-4(3*H*)-quinazolines **44**.



40 **41** **42**

43 **44**

Screenings of quinazolinones structure show that there are strong lactam-lactim tautomeric interactions, (Figure 9). This tautomeric effect has significance in enhancement of the reactivity of substituted 4(3*H*)-quinazolinones [55,69].

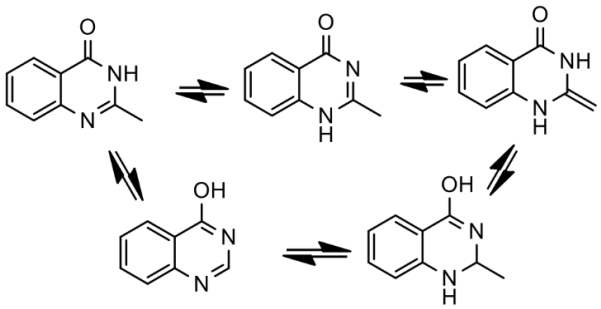


Figure 9: Tautomerism in Quinazolinone.

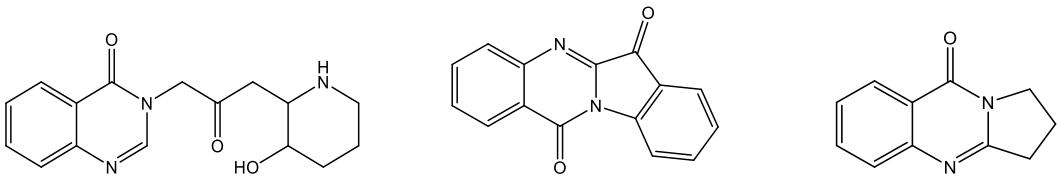
The presence of a fused benzene ring alters the properties of the pyrimidine ring considerably. The two nitrogen atoms are not equivalent. The properties of substituted quinazolines depend largely on the nature of the substituents, whether they are in the pyrimidine ring or in the benzene ring, and whether or not complete conjugation is present in the pyrimidine ring [65,66,70,71].

Physical Properties of Quinazolinone

Commonly, quinazolinones are solid in nature with high melting points. These are water insoluble substances but readily soluble in alkali and form stable salts. Moreover, quinazolinones are stable to distillation and crystallization [69].

Biological Activity of Quinazolinone Ring

Utility of qunazolinones in medicinal chemistry was triggered in the early of 1950s with discovery of febrifugine **45**, a quinazolinone alkaloid, which was isolated from the Chinese plant Aseru (*Dichroa febrifuga Lour*) and was reported to possessing antimalarial potential [72]. Moreover, trypanthrin **46** has been the active principle of a Japanese traditional herbal remedy for fungal infections. It also has antibacterial, antitubercular and antileishmanial activities. Deoxyvascinon **47** has been extensively used in herbal medicines for cough, cold, bronchitis and asthma [73].



45 **46** **47**

Quinazolinones analogues have been described as privileged structures. These structures represent molecules which are capable of binding at multiple sites with high affinity and facilitate more rapid discovery of useful medicinally active compounds [74].

On the bases of various literature survey, quinazolinones derivatives show various pharmacological activities such as antimalarial [75], anti-inflammatory [76], anticonvulsant [77], sedative and hypnotic [78], antihypertensive [79], anti-diabetic [80], antimicrobial [81-85], antioxidant [86], anticancer [87-89], anti-histamine [90], anti-asthmatic [91], and anti-parkinsonism [92]. Furthermore, several of these compounds exhibited dihydrofolate reductase inhibition [93,94], and also used as kinase inhibitors [95] . Presently, a large number of quinazolinone derivatives are patented and available in the market as potential drugs for various diseases (Table 4) [69,96].

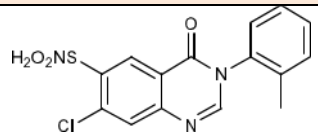
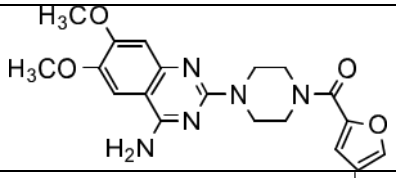
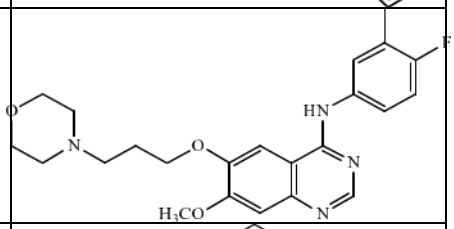
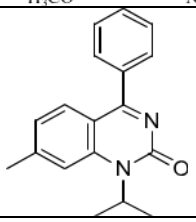
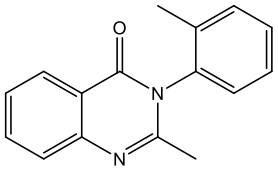
Name of drug	Category	Structure
Metolazone	Diuretic	
Prazosin	Antihypertensive	
Gefitinib	Tyrosine kinase inhibitor: anticancer	
Proquazone	NSAID	

Table 4: Successful quinazolinone based clinically available drugs.

The choice of a suitable substitution pattern including electron-donating and electron withdrawing groups as well as some heterocyclic moieties on the basic skeleton plays a key role in regulating the biological potential of the synthesized compounds. This would also help medicinal chemists to choose appropriate functional groups in order to design more effective and safer molecules for treatment of various disorders [63].

Anticonvulsant Activity

Quinazolin-4(3*H*)-one constitutes a good template for the preparation of some new anticonvulsant agents, since such heterocyclic system has the required pharmacophoric moiety [97]. Methaqualone **48** considered as an important landmark in the area of synthetic anticonvulsants owned quinazolinone core responsible for its activity [98,99]. It is analogue Mecloqualone **49** was found to possess marked anticonvulsant action [100]. Although numerous quinazolinones structurally related to methaqualone were synthesized and biologically tested for their anticonvulsant activity, none of them is clinically used. A persistent problem with these compounds attributed to their neurotoxicity [101-104].



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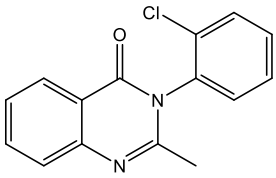

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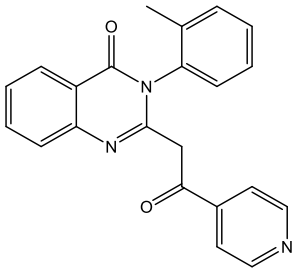
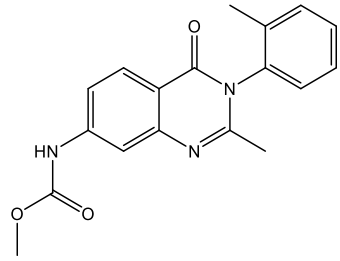
Some scientists suggested that presence of methyl group in position 2 and substituted aromatic ring in position 3 of quinazolinone compound are required for its CNS depression and anticonvulsant activities[105]. Boltz et al, and Wolfe et al, gave hypothesis stated that methyl group at second position of 4(3*H*)-qunazolinnones is not always necessary for the CNS activity and other groups when placed at this position can also lead to potent CNS activity [106]. Wolfe et al, synthesized some quinazolin-4(3*H*)-ones structurally related to Methaqualone. These compounds were evaluated for anticonvulsant activity. In the screening of these series 2-[2-oxo-2-(4-pyridyl)ethyl]-3-aryl-4(3H)- quinazolin-4(3*H*)-ones with a single *ortho*- substituted in 3-phenyl ring were most promising as regard as anticonvulsant agent. Among these compounds quinazolinone **50** shown excellent protection against maximal electroshock seizure (MES) and subcutaneous pentylenetetrazol ($_{sc}$PTZ)- induced seizures in rodents with high neurotoxicity [102].



50

Adel El-Azab et al, synthesized a new series of trisubstituted- 4(3*H*)-quinazolinone derivatives, evaluated for their anticonvulsant activity against MES and chemically PTZ, picrotoxin and strychnine- induced seizures. Compounds **51, 52, 53, 54, 55** and **56** showed advanced anticonvulsant activity as well as lower neurotoxicity than reference drugs Methaqualone and Valproate. The obtained new findings point to the Schiff's bass, 2-substituted-thiozoladin-4-ones or ethoxycarbonyl amino moieties at position 7 which are important for the anticonvulsant activity of these compounds [107].



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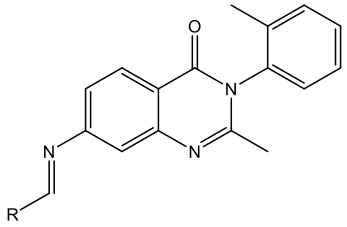
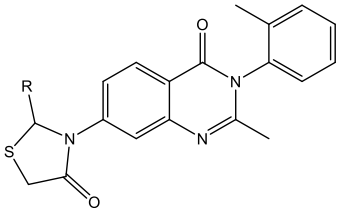


52 R= 4-Ph

53 R = 4-Cl

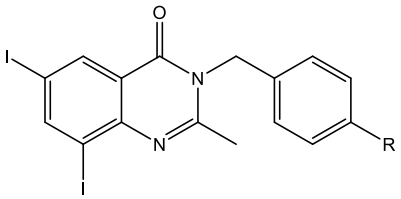


54 R=Ph

55 R= 4-F-Ph

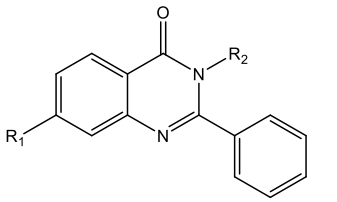
56=R =4-Cl-Ph

Novel derivatives of 6,8-diiodo-2-methyl-3-substituted benzyl-quinazolin-4(3*H*)-ones were synthesized by Zayad et al, and evaluated for their anticonvulsant activity by the MES-induced seizure and $_{SC}$ PTZ tests. The neurotoxicity was assessed using rotarod test. All the tested compounds showed considerable anticonvulsant activity in at least one of the anticonvulsant tests. Compounds **57-59** proved to the most potent compounds of this series with relatively low neurotoxicity with the reference drugs. The presence of electron-withdrawing group at aromatic ring enhanced the activity when compared to un-substituted or electron-donating group in the benzyl ring [103].



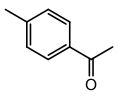
57 R= 4-Cl
58 R= 4-F
59 R= 4-Br

Series of new quinazolinone derivatives were synthesized by Patel et al, Screened virtually and evaluated for the anticonvulsant activity against MES and $_{SC}$PTZ- induced seizures, Methaqualone and Sodium Valproate were taken as reference drugs. Compounds **60-62** was found to be the most potent compound of the series accompanied with relatively low toxicity as compared with the reference drugs. Moreover, the obtained results showed that compounds **60-62** could be useful as a model for future design, optimization, and investigation to create more active analogues. Structure-activity correlation of the investigated quinazolinones proved that, the compounds having chloro functional group at 7 position of quinazoline had significant anticonvulsant activity, presence of 2-amino phenyl at the 3rd position results into the most active compound of the series. In case of acetyl phenyl substitution at 3rd position of quinazolinone, para- substituted was more potent as compare to the *ortho*- and *meta*- [108].



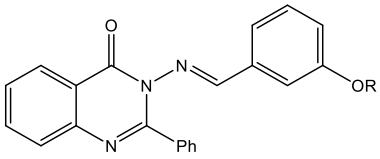
60 R_1 = H ; R_2 = 

61 R_1 = Cl ; R_2 = 

62 R_1 = Cl ; R_2 = 

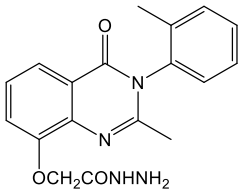
Ali et al, Synthesized a new series of 2-phenyl-3-(3-(substituted –benzylideneamino)) quinazolin-4-(3*H*)-one derivatives. The synthesized quinazolinone derivatives were screened for their anticonvulsant activity against standard models MES for their ability to reduce seizure spread. Motor impairment screening was also carried out by Rotarod Test method. The active compounds were tested against CNS depressant activity. Phenytoin and Carbamazepine were used as standard reference drugs. The data obtained for screened compounds represented

that compounds **63** and **64** having R = ethyl and n-propyl groups, respectively were found to be the most active of the series with no motor impairment effect. Moreover, they showed reduced CNS depressant effect in comparison to the standard drug Carbamazepine. On the basis of these finding, it can be conclude that the activity may be attributed to the presence of adequate long and straight aliphatic chain ethyl and propyl that provide adequate lipophilicity which lead to enhancement in the blood brain barrier (BBB) crossing capacity of the compounds in addition to well fitted to receptor site [109].



63 R = C_2H_5
64 R = C_3H_7

Novel 2,3,8- trisubstituted-4(*3H*)-quinazolinone derivatives were prepared by El-Azab et al, the compounds assessed as antiepileptic agents, being compared with the reference drugs Methaqualone and Sodium Valproate. Compounds **65 -67** produced the strongest activity in this class with relatively low neurotoxicity. The structural activity correlation revealed that compounds having acetic acid hydrazide fragments at position 8 possess significant anticonvulsant activity **65-67**. More interestingly, the ester or thioester of acetic acid hydrazide such as compounds, **66** and **67** showed the most potent activity in compared with its parent acetic acid hydrazide **65**; this may be attributed to their high lipid solubility [110].



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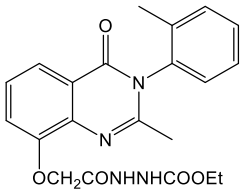

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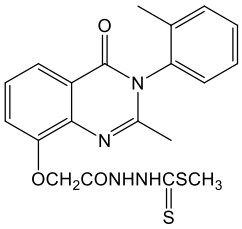
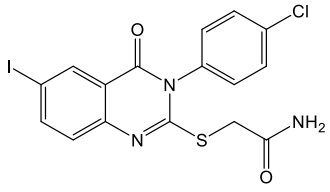


67

Kadi et al, produced a new class of 2-mercapto-3-(4-chlorophenyl)-4-oxo-6- iodoquinazolines. The antiepileptic potency of the new derivatives was evaluated using the PTZ seizure- threshold test. Compounds **68–72** showed significant anticonvulsant activity with complete disappearance of seizures during the course of the assay. According to the obtained data, these compounds showed potent CNS depressant effects, accompanied by sedation and hypnosis [111].



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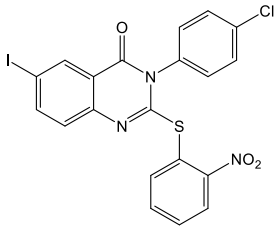

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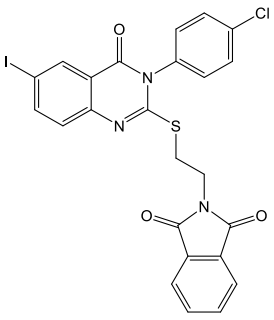

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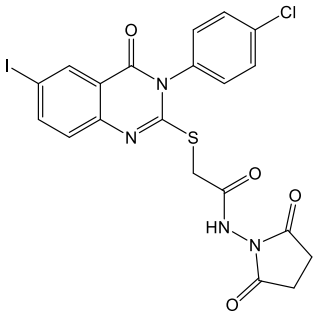

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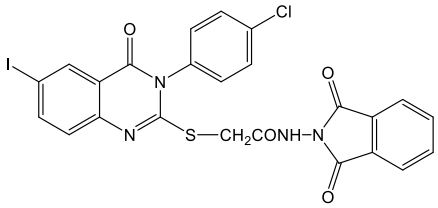
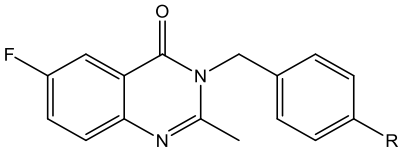


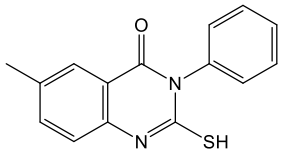
72

Zayed et al, demonstrated the synthesis of a novel series of 6-fluorinated quinazolinone derivatives. The synthesized compounds were tested for their anticonvulsant activity and neurotoxicity. The anticonvulsant activity as well as the neurotoxicity of the newly synthesized compounds was compared to that of Phenytoin as a reference drug. Four compounds showed significant anticonvulsant activity with low neurotoxicity when compared with the reference drug **73-76**.The inspection of the structure– activity relationship of these compounds suggests that the presence of a halogen substituent at the 6th position from the distal aromatic ring of the quinazolinone moiety greatly enhanced the anticonvulsant activity of the newly synthesized compounds when compared with other compounds. Moreover, the substitution pattern on the distal aromatic ring of the quinazolinone system by electron-donating group play a key role in their anticonvulsant activity [112].



73: R = Cl
74: R = F
75: R = I
76: R= Br

El-Subbag et al, designed a new series of quinazolinone derivatives and evaluated for their anticonvulsant potency using four animal models; MES, PTZ, picrotoxin and bicuculline induced seizures. Different compounds with moderate and strong activity were documented. The active compounds may act directly as $GABA_A$ receptor agonists or indirectly by increasing GABA synthesis or its release as a brain inhibitory neurotransmitter. This suggestion attributed to the fact that all active compounds produced high percentage of protection against picrotoxin chloride channel blocker and bicuculline GABA receptor blocker. The structural activity correlation of the active compounds shown that replacement of 3-phenyl of moderately active compound **77** to 3-benzyl lead to loss of the activity while, replacement of the 2-sulfhydryl function of **77** by N-(tetrachloro phthalimido)-2-thioacetamide moiety to get **78** preserved the moderate anticonvulsant activity; but its replacement with N-(1,8-naphthalimido)-2-thioacetamide **79** lead to total loss of activity. The contrary was observed in the 3-benzyl series, compound **80** with it is N-(1,8-naphthalimido)-2-thioacetamide showed protection against PTZ-induced convulsions, while its N-tetrachloro phthalimido analogs **81** and **82** showed no sign of anticonvulsant activity. The most potent compound 3-amino analog **83** showed 100% protection against PTZ-induced convulsion. Benzoylation of the 3-amino function and introduction of phthalimido function at position 3- produced **84** and **85** respectively with same potent activity. Increasing the bulkiness of the substituents at position 3- such as the tetrachloro phthalimido analogs **87**produced inactive compounds comparing to compound **86** [113].



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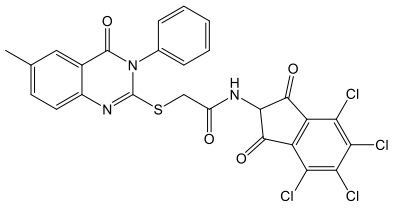

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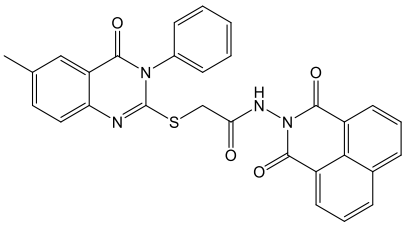

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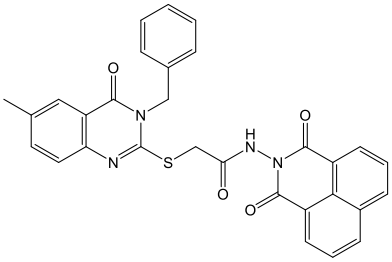

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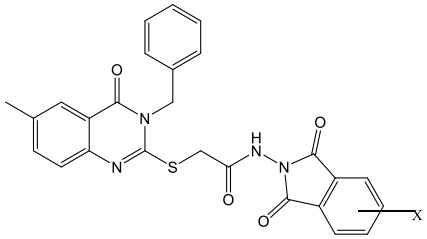
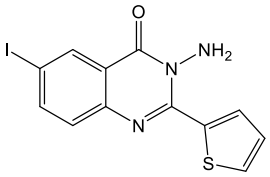


81: X = tetrachloro
82: X = tetrabromo



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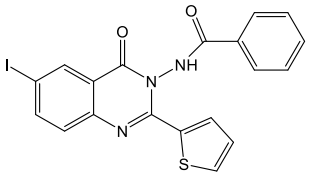

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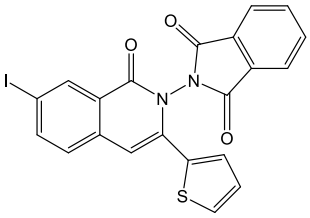

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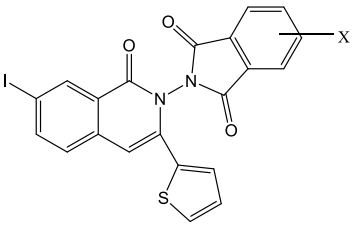
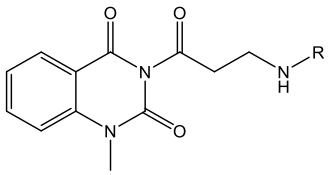


86: X = H
87: X=tetrachloro

A novel class of N-substituted methylquinazoline-2,4(1*H*, 3*H*)-dione derivatives were synthesized by Prashanth et al, MES test was performed to evaluate their anticonvulsant activity using Phenytoin as standard reference drug. Neurotoxicity of these compounds was evaluated using Rotoarod Test. Compounds **88** and **89** were found to have good protective effect from seizures. Titled compounds were designed by considering the hypothesis that presence of an aryl hydrophobic binding site, hydrogen bonding domain, an electron donor group and another hydrophobic-hydrophilic site controlling the pharmacokinetic properties of the anticonvulsants. Findings of this study indicated that different substitutions on the distal aromatic ring resulted in variation in antiepileptic effect. The simple phenyl ring with fluoro or chloro substitution in *para*-position exhibited the most potent activity and did not exhibit neurotoxicity at highest administered dose [114].

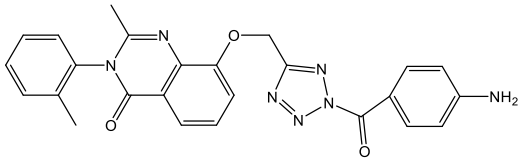


88 R =

89 R =

Khan et al, reported 25 new synthesis derivatives of quinazolinon-4(3*H*)-one and evaluated for anticonvulsant activity using MES and $_{SC}$PTZ. Neurotoxicity was performed using Rotarod Test. From the biological

activity of the synthesized compounds, it was observed that compounds, **90** and **91** proved to be of clinical significance. The quinazolinone nuclei pretended as the mainstay for the inducing the anticonvulsant activity. The introduction of the benzyloxy tetrazole moiety as the core fragment synergized the activity. The amplification of the anticonvulsant stimulus attributed to the presence of the free carbonyl. Moreover, the major role was played by the heterocyclic pyridinyl moiety conjugated through the alkyl linkage to the tetrazole nuclei [97].



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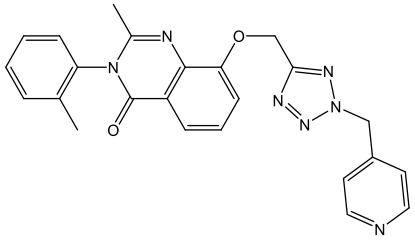

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