

Current Trends in Anticonvulsant 4(3H)-quinazolinone: A Review

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Summary

A variety of antiepileptic drugs (AEDs) are available today, but still there is a need for new drugs. The goal of epilepsy management is complete control of seizures with little or no adverse effects. Although epilepsy can be idiopathic, it is estimated that up to 50% of all epilepsy cases are initiated by neurological disturbances and are called acquired epilepsy (AE)¹. AE develops in 3 phases: the injury (central nervous system² [CNS] insult), epileptogenesis³ (latency), and the chronic epileptic (spontaneous recurrent seizure) phases. Status epilepticus (SE), stroke, and traumatic brain injury (TBI) are 3 major examples of common brain injuries that can lead to the development of AE⁶. The signalling cascades associated with the development of epileptogenesis and maintenance of the chronic epileptic state are required to understand the development of AE and for developing novel interventional target to prevent or even cure AE⁷. AMPA glutamate receptors (AMPA receptors) have structural features that allow for multiple sites to which ligands can act to modulate receptor functions²⁴. Other non-competitive AMPAR antagonists containing quinazolin-4-one skeleton were developed by Pfizer research group^{33,34}. Compound CP-465,022 (+)-(aS)-(2-chlorophenyl)-2-[(E)-2-[6 (diethylaminomethyl)pyridin-2-yl]-vinyl]-6-fluoroquinazolin-4(3H)-one (**9**) consisted of three features: (1) the quinazolin-4-one ring, with a small C-6 substituent, (2) the orthogonal N-3 phenyl ring containing a single ortho substituent, and (3) the aryl ring attached to C-2 through a two-atom spacer showed anticonvulsant efficacy when tested against pentylenetetrazole and AMPA induced seizures (4.0 mg/Kgsc)^{36,37}

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Introduction

Epilepsy is the most common neurological disorder after stroke and is characterized by seizure of various types which result from episodic neuronal discharges^{1,2}. Nearly, 1-2% of the world population is affected by epilepsy³. It shows an estimated 7 million people in India and 50 million worldwide, approximately 40% of them are women⁴. A minority of patients (20-30%) may develop chronic epilepsy, and in such cases, treatment is more complicated. There is an increased mortality in people with epilepsy and most studies have given overall standardized mortality ratios between two & three times higher than that of the general population⁵. Although epilepsy can be idiopathic, it is estimated that up to 50% of all epilepsy cases are initiated by neurological disturbances and are called acquired epilepsy (AE). AE develops in 3 phases¹: the injury (central nervous system² [CNS] insult), epileptogenesis (latency), and the chronic epileptic³ (spontaneous recurrent seizure) phases. Status epilepticus (SE), stroke, and traumatic brain injury (TBI) are 3 major examples of common brain injuries that can lead to the development of AE⁶.

In India, the prevalence rate of epilepsy varies from 1,710 to 9,780 cases per million⁷. Nearly, 95% of clinically approved drugs for epilepsy treatment were approved prior to 1985, and they can provide satisfactory seizure control for 60–70% of patients. These drugs, however, also cause notable adverse side effects such as drowsiness, ataxia, gastrointestinal disturbance, hepatotoxicity and megaloblastic anaemia and even life threatening conditions⁸⁻¹⁰. Most antiepileptic drugs are associated with adverse effects, such as sedation, ataxia and weight loss (e.g. topiramate) or weight gain (e.g. valproate, tiagabine, and vigabatrin). Rare adverse effects can be life threatening such as rashes leading to Stevens-Johnson syndrome (e.g. lamotrigine) or aplastic anaemia (e.g. felbamate)¹¹. A seizure is a paroxysmal event due to abnormal, excessive, hyper-synchronous neuronal discharges in central nervous system (CNS)¹³. These are thought to arise from the cerebral cortex, major part of the cerebrum (largest part of the brain divided into left and right hemispheres) which control wide array of behaviours^{12,13}. The different kinds of epilepsies consider from different neurophysiologic abnormalities¹⁴. Seizures are fundamentally divided into two major groups: partial and generalized. In partial (focal, local) seizures the attacks have a localized onset in the brain, usually in a portion of one hemisphere, while generalized seizures are those in which evidence for a localized onset is lacking. It may also generalize throughout the brain via cortical and sub-cortical routes, including colossal and thalamocortical pathways. The area from which the abnormal discharge originates is known as the epileptic focus. An EEG recording carried out during one of these abnormal discharges may show a variety of atypical signs, depending on which area of the brain is involved, its progression and how the discharging areas project to the superficial cortex for understanding the cure of epilepsy¹⁵.

Gamma-amino butyric acid (GABA) is the inhibitory neurotransmitter in the vertebrate central nervous system. There are two classes of GABA receptors: GABA_A and GABA_B. GABA_A receptors are ligand-gated ion channels (also known as ionotropic receptors), whereas GABA_B receptors are G protein-coupled receptors (also known as metabotropic receptors). Glutamate receptors are responsible for the glutamate-mediated post-synaptic excitation of neural cells, and are important for neural communication, memory formation, learning, and regulation. Inhibitory neurotransmitter GABA or an increase in excitatory neurotransmitters such as glutamate would promote abnormal neuronal activity. A relative deficiency of excitatory glutamate, a amino acid neurotransmitter in the CNS mainly involved in epilepsy whereas γ -amino butyric acid is the major inhibitory amino acid neurotransmitter in central nervous system¹⁷⁻¹⁹.

Mechanism of Action: Main proposed mechanism of newer antiepileptic drug in the inhibitory, GABAergic and the excitatory glutamatergic synapse as shown in **Figure 1**.

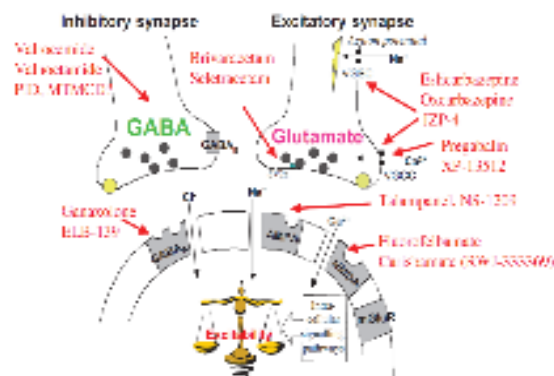


Figure 1: New generation of antiepileptic drugs.

The black spots are reuptake protein for GABA and glutamate. The grey receptor metabotropic receptors, GABA_B for GABA and mGluR (metabotropic glutaminergic receptor), for glutamate. SV2a: synaptic vesicle protein 2a, the specific binding site for levetiracetam, VGCC and VGSC are Ca²⁺ and Na⁺ channels. Glutamatergic neurotransmission involves ionotropic and metabotropic receptors (iGluRs and mGluR) that's are activated.²⁰

A new generation of AEDs are having improved efficacy and tolerability are shown in **Table 1**

New Compound	Parent AED	Improvement	Characteristics
Brivaracetam	Levetiracetam	Efficacy	More potent binding to SV2A
Oxcarbazepine Eslicarzepine	Carbamazepine	Tolerability	Improved pharmacokinetic properties
Fluorofelbamate	Felbamate	Tolerability	Non-toxic metabolite
JZP-4	Lamotrigine	Efficacy	Improved pharmacokinetic properties
Pregabalin	Gabapentin	Efficacy	Equally potency to gabapentin
Valrocecimide, valnoctamide, Propylisopropyl acetamide (MTMCD),NDS-1776, Tetramethylcyclopropanecarbonyl urea (TMCU)	Valproate	Tolerability	Less toxic metabolites, less teratogenic potential

The iGluRs are ligand gated ion channels which are further subdivided into three classes based on their affinity for specific agonists: the N-methyl-D-aspartic acid (NMDA), the kainic acid (KA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subtypes allow for sodium, potassium and calcium flux upon glutamate binding. (Figure 2) iGluR agonists.

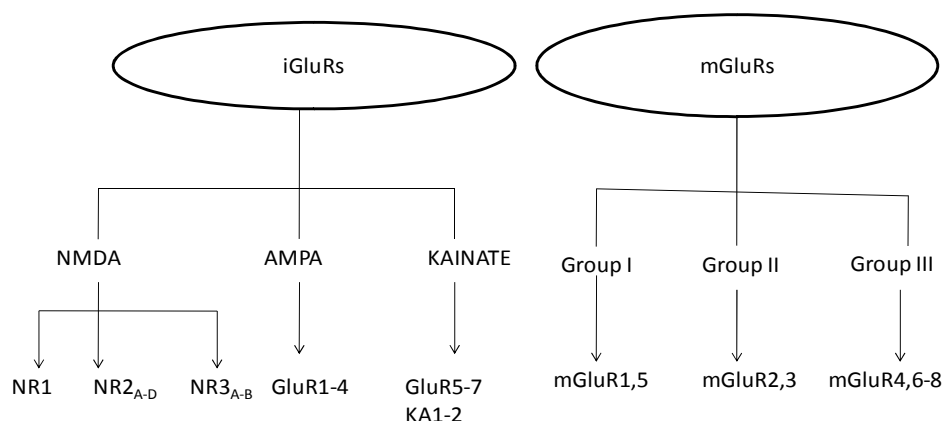


Figure 2: iGluR agonists.

AMPA receptors (AMPA receptors) are expressed in the key epileptogenic regions of the brain including the cerebral cortex, the thalamus, the amygdala, the hippocampus, and even the basal ganglia which receive inputs from these regions^{21,22}. The potential of AMPA receptor antagonists to attenuate epileptic seizures has not yet been fully investigated. At present, talampanel is the only AMPA receptor antagonist in phase II clinical trial use for the amelioration of epileptic seizures. AMPA glutamate receptors (AMPA receptors) have structural features that allow for multiple sites to which ligands can act to modulate receptor functions²³. AMPARs are tetramers built from closely related subunits, called both GluR 1-4 and GluR A-D, assembled from homo or heteromeric complexes surrounding a central cation conducting pore mediating fast excitatory postsynaptic potentials by the flux of Na^+ and Ca^{2+} ions^{24,25}. Release of glutamate from the presynaptic neuron and its binding to AMPARs of the postsynaptic neuron leads to cations influx into the cells, but also causes the receptor to desensitize thus prevention against excitotoxic processes. Each of GluR1-4 subunit can exist as two forms, flip and flop, due to variable gene splicing and consists of a long extracellular amino terminus, jointed to three transmembrane spanning domains (TM1, TM3 and TM4), a membrane imbedded re-entry loop (M2) that connects TM1 and TM3, and a short intracellular C-terminus as showed in (Figure 4) for GluR2. Two discontinuous extracellular domains (S1, S2) contain the glutamate binding site, responsible for binding the neurotransmitter and the competitive agonists/antagonists²⁶.

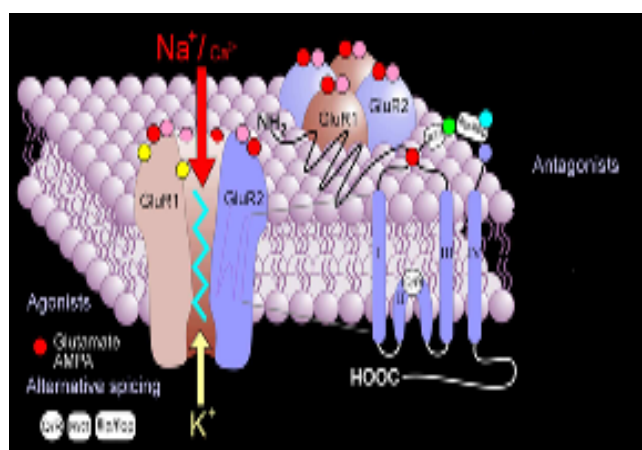
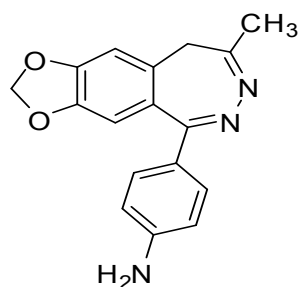


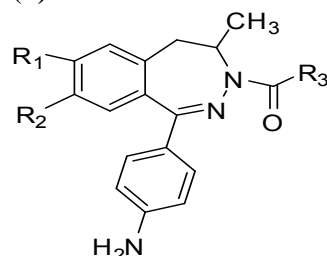
Figure 3: GluR2 subunit of AMPA receptor.²⁷

Chemistry:

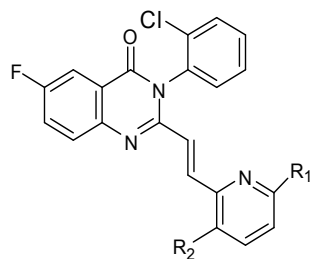
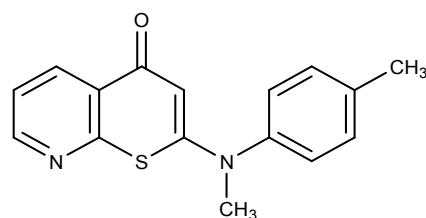
The first non-competitive AMPA antagonist was 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (GYKI 52466, **1**)²⁸, discovered in 1989 and used as template to develop novel more potent and less toxic AMPAR modulator. Stereoselectivity in AMPA receptor is also confirmed by the higher activity of R-enantiomers such as (-) GYKI53733 (**2**, also named LY300164 or talampanel) and (-) GYKI 53784 (**3**)²⁹⁻³⁰.



1. GYKI52466

2. (-) R₁, R₂ = -OCH₂O-, R₃ = CH₃
GYKI 53733 talampanel3. R₁, R₂ = OCH₂O- R₃ = NHCH₃ GYKI 53784

Other non-competitive AMPAR antagonists containing quinazolin-4-one skeleton were developed by Pfizer research group^{31,32}. (Figure 5). Compound CP-465,022, (+)-(aS)- (2-chlorophenyl)-2-[(E)-2-[6(diethylamino-methyl)pyridin-2-yl]-vinyl]-6-fluoroquinazolin-4(3H)-one (**4**) showed anticonvulsant efficacy when tested against pentylenetetrazole and AMPA induced seizures (4.0 mg/kg sc).^{33,34} The 2-[N-(4 chlorophenyl)-N-methylamino]-4H-pyrido[3,2-e]-1,3-thiazin-4-one (**6**, YM928) exerts significant anticonvulsant effects in various seizures models (e.g. MES, ED₅₀ = 4.0-7.4 mg/kg p.o. both in mice and rats), it is orally active^{35,36}. Compound (**6**) demonstrated to prevent audiogenic seizures in DBA/2 mice after oral administration at 3mg/kg. Another compound, irampanel (**7**, BIIR 561CL, dimethyl-[2-[2-(3-phenyl-[1,2,4]oxadiazol-5-yl)-phenoxy]-ethyl]amine

4. R₁ = CH₂NEt₂, R₂ = H; CP-465,0225. R₁ = H, R₂ = CN; CP-526,427

6. YM 928

hydrochloride) showed anticonvulsant effect; its mechanism is due to the combination of antagonistic action at AMPA receptors and Na⁺ channel blocking properties, in a maximal electroshock model in mice with an ED₅₀ value of 2.8 mg/kg after subcutaneous administration³⁷.

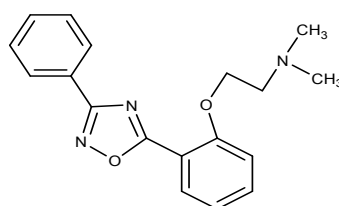
Irampanel (**7**)

Figure 4: Different non-competitive AMPA receptor antagonists.

Directly investigation of quinazolinones showed that there is a strong lactam-lactim tautomeric interaction.³⁸ The significance of these extended tautomeric effect as shown in (Figure 7) is that they enhance the reactivity of the substituted 4(3H)-quinazolinone.³⁹ One of the most frequently encountered heterocycles in medicinal chemistry is 4(3H)-quinazolinone with diverse biological activity such as PDE-1inhibitor⁴⁰, anticancer⁴¹, analgesic and anti-inflammatory⁴², antimalarial⁴³, antiviral⁴⁴ and antihypertensive activity⁴⁵.

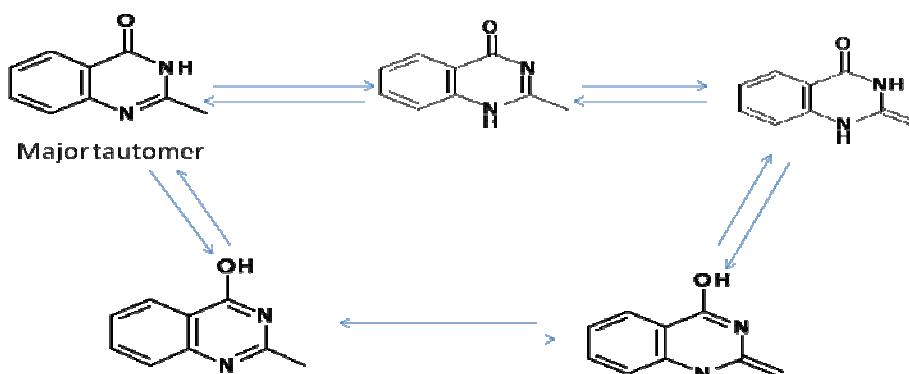
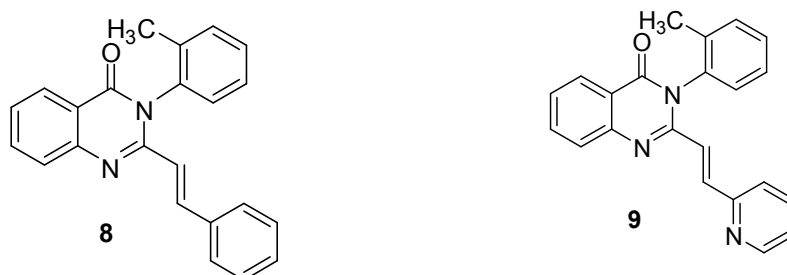
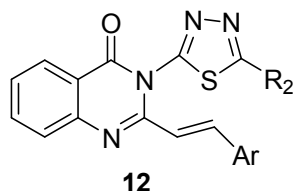


Figure 5: Tautomeric effect.

Some of the few reports available in literature revealed that substituted quinazolin-4(3H)-one exhibit anticonvulsant activity. Boltze *et. al.* has reported the synthesis of 2-(2-aryletenyl)-3-o-tolyl-4(3H)quinazolinone derivatives and among them analogues (**8**) and (**9**) displayed very good anticonvulsant activity.



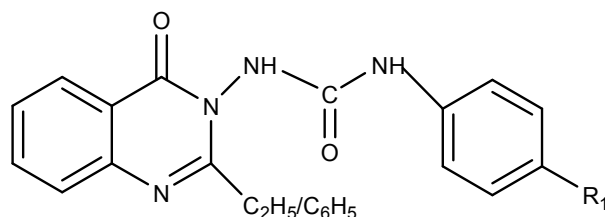
Varshav jataw *et. Al*⁴⁶ reported 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styrylquinazolinone-4(3H)-ones derivative. Some of the synthesised analogues showed mild to moderate anticonvulsant activity, among these analogues 4d & 4e displayed moderate to good activity.



4d. Ar = p- ClC₆H₄, R₂= p- ClC₆H₄

4e. Ar = p- ClC₆H₄, R₂= m- ClC₆H₄

Recently, Sushil K. Kashaw *et. al.*⁴⁷ has reported the synthesis and anticonvulsant activity of series of 1-(4-substituted phenyl)3-(4-oxo-2-phenyl/ ethyl-4H-quinazo3-yl)-urea derivative (**13**).

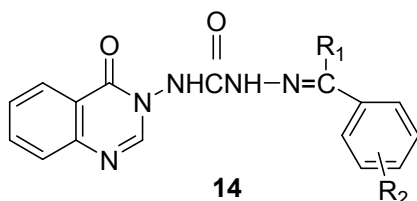
**13**

E10. R₁= C₂H₅ **P10.** R₁= C₂H₅

P5. R₁= I **P7.** R₁= o-OCH₃

P8. R₁= m-OCH₃

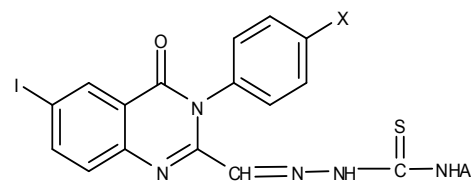
Among these compounds E10, P10, P5, P7, P8 showed good anticonvulsant activity. Ponnilarasan Ilangovan *et. al.*⁴⁷ reported the synthesis of 2-Aryl-3-amino-4(3H)quinazolinone semicarbazone analogues (**14**) for anticonvulsant activity.

**14**

10b. X= F, Ar = H

10d. X= F, Ar = CH₃

10f. X= F, Ar = C₂H₅

**15**

1. R₁= H , R₂= 4-N-(CH₃)₂ **2.** R₁= H, R₂= 3-OCH₃,4-OH

4. R₁= H, R₂= 3-NO₂ **6.** R₁= H, R₂= 2-OH

7. R₁= CH₃,R₂= H **8.** R₁= H, R₂= Ar-Furan

9. R₁= H, R₂= 2-OCH₃ **10.** R₁= CH₃,R₂= 4-Cl

The analogues **1**, **2**, **4**, **6** and **8** were active at 30mg/kg only at 0.5h, indicating that they have rapid onset and shorter duration of action. Moshsen M. Aly *et. al.*⁴⁹ reported the synthesis of quinazolinone based thiosemicarbazone derivative showing mild to moderate anticonvulsant activity. Among these compound 10b, 10d and 10f were formed to exhibit moderate anticonvulsant activity.

Structural Activity Relationship

It showed that a substituted aromatic ring in position 3 and a methyl group in position 2 are required for a significant anticonvulsant activity of the compound. Substituted methyl group also supports anticonvulsant action. The replacement of the CH₃ group in position 2 by an alkyloxymethyl or alkylthiomethyl groups, the anticonvulsant activity was retained.

Conclusion

Non-competitive binding to AMPA receptors [AMPA is α -amino- β -(3-hydroxy-5-methylisoxazol-4-yl) propionic acid] is considered as a possible mechanism of the anticonvulsant action of quinazolinone derivatives. Some scientists believe that the proper quinazolinone nucleus is responsible for the anticonvulsant action⁵⁰.

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