CHEMISTRY AND MECHANISTIC APPROACHES OF HETEROCYCLES AS ANTIEPILEPTIC AGENTS

Jayalakshmi C[1], Dr. Hima C. S[2], Dr. S. M Sandhya[3], Dr. Shaiju S Dharan[4]

[1] M Pharm Student, Department of Pharmaceutical Chemistry, Ezhuthachan College of Pharmaceutical Sciences,

[2] Professor, Department of Pharmaceutical Chemistry, Ezhuthachan College of Pharmaceutical Sciences,

[3] Professor, HOD, Department of Pharmaceutical Chemistry, Ezhuthachan College of Pharmaceutical Sciences,

[4] Principal, Ezhuthachan College of Pharmaceutical Sciences,

Corresponding Author: Jayalakshmi.C

Abstract

Epilepsy is a persistent neurological condition characterized by spontaneous and recurrent seizures, with nearly one-third of patients showing poor response to existing antiepileptic medications. This limitation emphasizes the need for innovative therapeutic agents offering superior safety and efficacy. Heterocyclic frameworks, owing to their wide structural variability, favorable pharmacokinetic behavior, and ability to engage multiple central nervous system (CNS) targets, have gained considerable attention in anticonvulsant drug research. This review discusses significant heterocyclic families, such as oxadiazoles, thiazoles, imidazoles, thiadiazoles, triazoles, pyridines, pyrimidines, piperazines, benzodiazepines, benzothiazoles, quinazolines, indoles, chromenes, and benzofurans—focusing on their structure–activity relationships, modes of action, and recent synthetic advances. Primary mechanisms include enhancement of GABAergic signaling, inhibition of ion channels, antagonism of glutamate receptors, and neuroprotective effects. Persistent challenges like drug resistance, limited brain bioavailability, and toxicity are examined alongside promising solutions, including AI-assisted drug design, multi-target ligands, and sustainable synthesis approaches, to advance next-generation antiepileptic agents.

Keywords

Epilepsy, Heterocyclic Compounds, Antiepileptic Agents, Structure-Activity Relationship

INTRODUCTION

Epilepsy is an immedicable neurological disorder characterized by a higher susceptibility to unprovoked and recurrent seizures. These events are caused by abnormal bursts of electrical activity in the brain and may affect muscle movements, awareness, sensation, or consciousness. Their manifestation may also differ markedly, from mild behavioral modifications or muscular violent contractions to severe and protracted convulsions. It can occur due to genetic mutations, brain injuries, infections, developmental disorders, or metabolic errors. In many cases, however, the precise trigger is not known. Seizure onset determines that epilepsy can be generally divided into focal, generalized, and unknown onset categories. Diagnosis is based on clinical history, electroencephalogram (EEG) recordings, and neuroimaging methods, including MRI, for the detection of structural damage[1].

Antiepileptic drugs (AEDs) are the treatment of choice for patients with epilepsy, with most experts recommending AEDs for >70% of patients with the condition. Valproic acid, carbamazepine, lamotrigine, and levetiracetam are examples of widely used AEDs. In drug-resistant epilepsy, other forms of treatment, including surgical resection of the epileptogenic focus, vagal nerve stimulation, responsive neurostimulation, or implementation of a ketogenic diet, can be explored. Although treatment is available, epilepsy remains challenging due to resistance to medication, drug-induced adverse events, psychosocial issues, and associated stigma. Patients with epilepsy may also display comorbidities, including depression, anxiety, or cognitive impairment, which can contribute to the complexity of the treatment management[1]. Current studies of genetics, neurobiology, and drug discovery have resulted in increased knowledge of the disorder and expanded treatment choices. Novel approaches, such as in silico drug screening and neuroimaging biomarkers, provide hope for personalized treatment approaches[2].

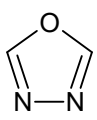
Heterocyclic chemistry, focuses on the synthesis, characteristics, and biological functions of ring structures contains one non-carbon atom- nitrogen, oxygen, or sulfur. Heterocyclic compounds are crucial in discovering and developing anticonvulsant medications due to their diverse structures, favorable pharmacokinetics, and capacity to interact with multiple neural targets. Most approved and experimental AEDs feature heterocyclic frameworks, underscoring their significance in epilepsy treatment from both mechanistic and therapeutic perspectives[2].

Heterocycles Having Anticonvulsant Activity

Five Membered Rings	Six Membered Rings	Fused Membered Rings	Hybrid Heterocycles
• Oxadiazole • Thiazole • Imidazole • Thiadiazole • Triazole	• Pyridine • Pyrimidine • Piperazine	• Benzodiazepine • Benzothiazole • Quinazoline • Indole	• Chromene (Benzopyran) • Benzofuran

1. Five-Membered Heterocycles

- **Oxadiazole**

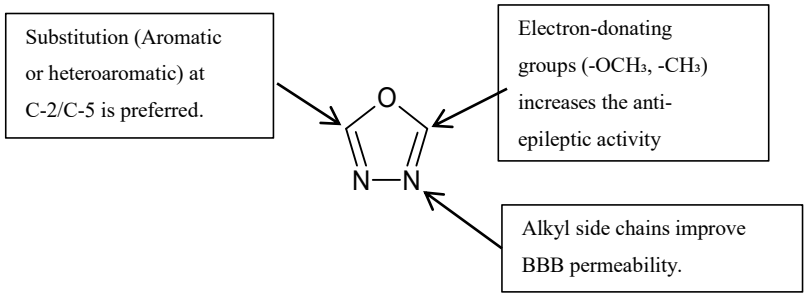


1,3,4-oxadiazole

Oxadiazoles are heterocyclic compounds having a five membered ring composed of 2 nitrogen atoms and 1 oxygen atom. They belong to azole family, and they exist in four isomeric forms: 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, and 1,3,4-oxadiazole. Among these, the 1,3,4-oxadiazole isomer- the most widely encountered. These scaffolds are known for their favorable pharmacokinetic properties, such as good CNS penetration, metabolic stability, and low toxicity, which make them promising candidates in the development of AEDs[3].

Structure-Activity Relationship (SAR)

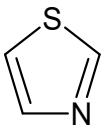
The core oxadiazole ring, especially 1,3,4- is essential for activity. Aromatic or heteroaromatic groups at positions 2 and 5 enhance the potency. Aromatic Rings like phenyl and substituted phenyl enhance the CNS activity through π-π interactions and lipophilicity. Electron-donating groups like methoxy and methyl increase the antiepileptic activity by enhancing interaction with GABA receptors. Electron-withdrawing substituents such as chlorine and nitro on aryl groups improve the efficacy. Lipophilic side chains enhance blood-brain barrier permeability. Heterocyclic substituents like pyridine and thiophene broaden the activity spectrum, potentially engaging multiple CNS targets. Amide or hydrazone linkages facilitate hydrogen bonding with biological targets, thereby improving the affinity. Hybrid molecules with benzodiazepines, piperazines, or thiadiazoles boost the receptor affinity and pharmacokinetics[3,4].



Mechanism of Action

Oxadiazole-based compounds exhibit anticonvulsant activity through modulation of GABAergic neurotransmission by enhancing $GABA_A$ receptor activity, leading to increased inhibitory synaptic transmission. Sodium channel blockade by inhibiting voltage-gated Na^+ channels (VGSC), stabilizes the neurons, and reduces excitability. Calcium channel inhibition by attenuation of T-type calcium currents, which are implicated in absence seizures[4,5].

- **Thiazole**

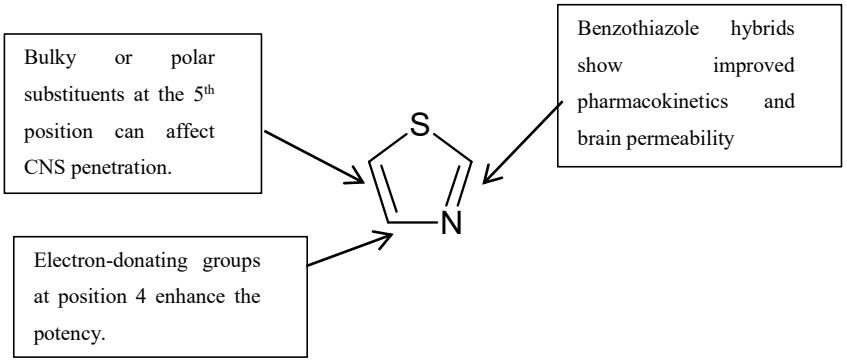


1,3-thiazole

Thiazole is a five-membered heterocyclic ring structure made up of both N and S atoms, which is a useful scaffold in drug design because of its spatial arrangement, that imparts unique electronic and structural properties. Thiazole-based compounds have attracted more and more attention in the field of medicinal chemistry over time. Their anticonvulsant potential is particularly noteworthy, as many of their derivatives have shown a notable capacity to regulate neuronal excitability and inhibit seizure activity. The thiazole ring is therefore a promising building block for the creation of novel antiepileptic drugs[6,7].

Structure–Activity Relationship (SAR)

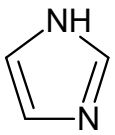
Bulky or heteroaryl substitutions at position-2 enhance CNS activity; amine or carbonyl groups modulate solubility. Electron-donating groups at position-4 increase potency whereas electron-withdrawing groups reduce activity. Polar or bulky groups at position-5 influence BBB penetration and may affect toxicity. Linking thiazole with hydantoins, benzodiazepines, oxadiazoles, or triazoles enhances potency through multitarget effects (e.g., Na^+ channel inhibition, GABAergic potentiation). Benzothiazole hybrids show improved pharmacokinetics and brain permeability[6]. Electron-donating substituents at key positions improve receptor binding and anticonvulsant activity. Electron-withdrawing substituents decrease efficacy but can enhance metabolic stability[7]. A moderate lipophilic balance (logP ~2–4) optimizes BBB crossing without increasing nonspecific CNS toxicity[8].



Mechanism of Action

Thiazole derivatives act as $GABA_A$ receptor agonists or positive allosteric modulators thereby enhance chloride ion influx which causes neuronal hyperpolarization which leads to seizure suppression. Also act as GABA transaminase inhibitors which reduce GABA degradation by increasing GABA levels in the synaptic cleft. Also act by blocking VGSCs thereby stabilizes neuronal membrane and preventing excessive firing. Inhibits T-type Ca^{2+} channels which are involved in absence seizures and rhythmic firing of thalamic neurons. Thiazole-containing molecules may antagonise NMDA receptors, reducing excitatory neurotransmission[9].

- **Imidazole**

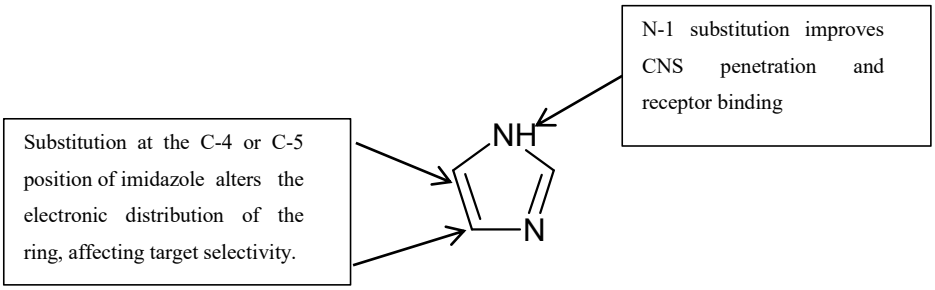


1H-imidazole

Imidazole, is one of the five-membered ring with 2 nitrogen atoms at positions 1 & 3, a versatile pharmacophore. Its physicochemical properties-such as moderate lipophilicity and strong hydrogen-bonding potential and make it particularly effective in designing central nervous system (CNS) active agents, including those with antiepileptic activity. Recent investigations have highlighted imidazole-containing molecules for their potential in seizure suppression. These compounds can modulate various molecular targets associated with the onset and progression of epileptic episodes. These molecules often influence GABAergic transmission[10,11].

Structure–Activity Relationship (SAR)

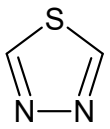
N_1-substitution with aromatic or lipophilic groups enhances brain permeability and activity. Introduction of electron-releasing substituents on phenyl rings tends to improve efficacy. Formation of hybrid molecules that incorporate other pharmacophores like sulfonamides, triazoles often results in multi-target agents with improved therapeutic profiles[11].



Mechanism of Action

Imidazole based compounds exhibit anticonvulsant effects primarily through GABAergic enhancement, this occurs either through direct interaction with $GABA_A$ receptors or by modulating GABA release and uptake, thereby promoting neuronal inhibition. These compounds often interfere with sodium or calcium channels in neurons, preventing excessive electrical discharge, a key event in seizure activity[12]. Inhibits glutamatergic signaling-particularly via NMDA or AMPA receptors-thus reducing excitatory transmission[13]. These derivatives influence neuronal excitability by altering intracellular pH through carbonic anhydrase inhibition, a mechanism shared with clinically used drugs like topiramate[14].

- **Thiadiazole**



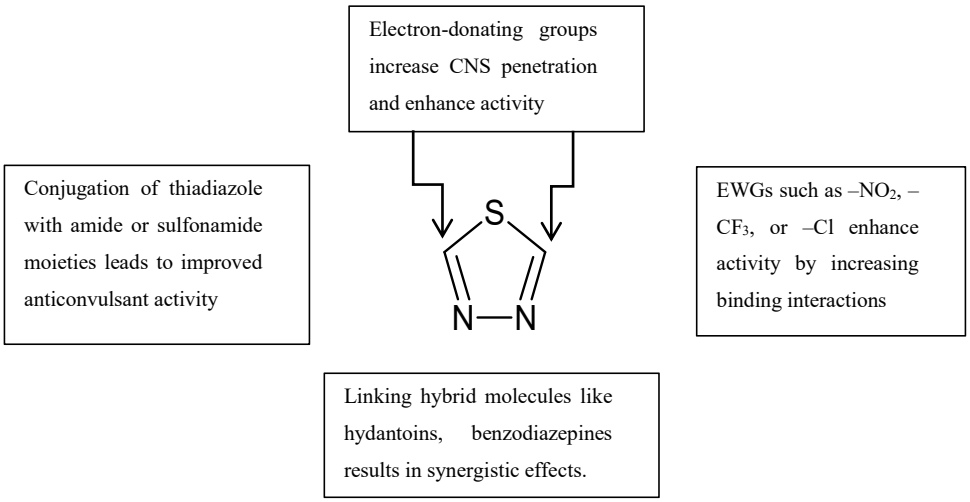
1,3,4-thiadiazole

Thiadiazole is a 5 membered heterocyclic system containing 2 nitrogen atoms and 1 sulfur atom, with three main isomers: 1,2,3-thiadiazole, 1,2,4-thiadiazole, and 1,3,4-thiadiazole. Among these, the 1,3,4-thiadiazole isomer is widely studied for its biological activities, including potent anticonvulsant effects. Thiadiazole derivatives have attracted significant interest in epilepsy research due to their ability to modulate neuronal excitability[15, 16].

Structure-Activity Relationship (SAR)

The 1,3,4-thiadiazole core is crucial for anticonvulsant activity, and substituents at the 2nd and 5th positions of 1,3,4-thiadiazole ring play a vital role in modulating anticonvulsant activity. Lipophilic or electron-donating groups like alkyl, aryl, or halogens at these positions generally increase CNS penetration and enhance activity. Introduction of aromatic or heteroaromatic rings at these positions often improves receptor binding affinity and bioavailability. Linking with known anticonvulsant pharmacophores such as hydantoins, benzodiazepines, or pyridines often results in synergistic effects and increased efficacy. These hybrids can act via multiple mechanisms, such as sodium channel inhibition and GABA receptor modulation. Electron-withdrawing groups enhance activity by increasing binding interactions at the receptor level, though excessive electron deficiency can reduce CNS bioavailability. Conjugation with amide or sulfonamide moieties often leads to improved anticonvulsant profiles due to enhanced hydrogen bonding and receptor interactions.

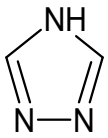
Moderate alkyl chain length or steric bulk is generally favorable for activity, but excessive size can hinder BBB permeability and reduce efficacy[17,18].



Mechanism of Action

Thiadiazole rings mainly act by enhancing the GABAergic activity which leads to hyperpolarization of neuronal membranes, reducing the likelihood of abnormal firing and seizure activity. They can block VGSCs, preventing rapid depolarization, thereby stabilizing the neuronal membrane and stopping seizure initiation and spread[19]. In certain types of epilepsy, especially absence seizures, thiadiazole analogs inhibit T-type calcium channels , reducing thalamocortical oscillations linked with seizures. Also inhibits carbonic anhydrase enzyme, leading to altered brain pH and neuronal excitability, which contributes to anticonvulsant effects. Thiadiazoles protect neurons from seizure-related oxidative damage, indirectly contributing to anticonvulsant effects [20, 21].

- **Triazole**



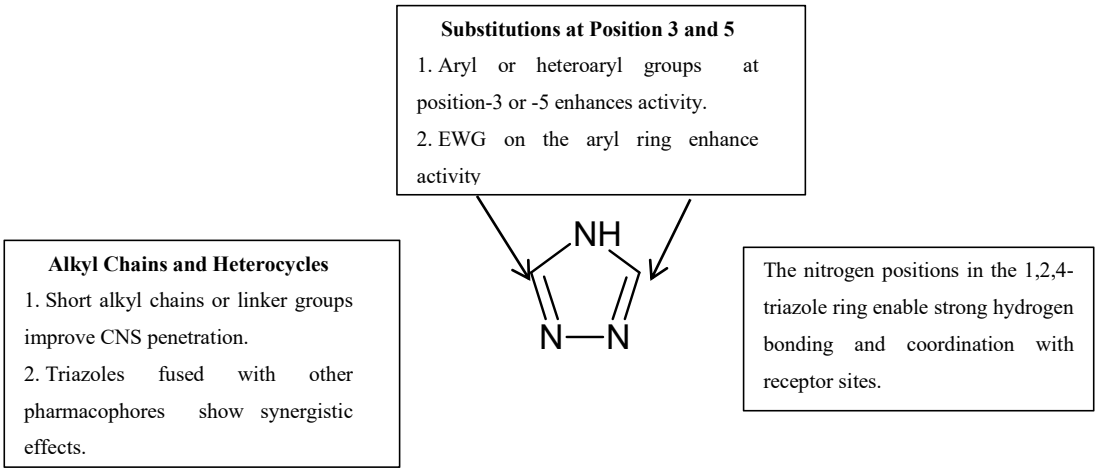
4H-1,2,4-triazole

Triazoles are a class of 5 membered heterocyclic compounds containing 3 nitrogen atoms & 2 carbon atoms. They exist mainly in two isomeric forms: 1,2,3-triazoles and 1,2,4-triazoles. Triazole derivatives exhibit anticonvulsant activity by interacting with various central nervous system targets, these interactions help stabilize neuronal membranes and inhibit abnormal electrical discharges in the brain[22,23].

Moreover, triazole rings are often used as bioisosteres to replace amide or ester groups, enhancing metabolic stability and blood-brain barrier penetration, making them favorable for CNS-active agents. Additionally, the triazole moiety's ability to form hydrogen bond and π stacking interaction contribute to high binding affinity with neuronal receptors[23, 24].

Structure-Activity Relationship (SAR)

1,2,4-Triazoles are more widely studied for antiepileptic activity compared to 1,2,3-isomers. The nitrogen positions in the 1,2,4-triazole ring enable strong hydrogen bonding and coordination with receptor sites. Substitution with aryl or heteroaryl groups (e.g., phenyl, pyridyl) at position-3 or -5 enhances activity due to increased lipophilicity and π–π interactions[25]. Electron-withdrawing groups (Cl, NO_2, CF_3) on the aryl ring enhance activity by stabilizing the triazole-receptor interaction. Short alkyl chains or linker groups improve CNS penetration[26]. Triazoles fused with other pharmacophores (e.g., benzodiazepines, pyridines) show synergistic effects. A balance between polar groups (for solubility) and hydrophobic regions (for membrane penetration) is crucial for bioavailability[27].

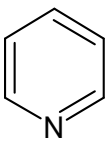


Mechanism of Action

Triazole-containing compounds exert their antiepileptic activity primarily by modulating neuronal excitability through various central nervous system (CNS) targets. They have been shown to enhance GABAergic neurotransmission, which increases the inhibitory tone in the CNS. This occurs either through positive allosteric modulation of $GABA_A$ receptors or by inhibition of GABA transaminase, leads to increased synaptic GABA levels which prevents hyperexcitability of neurons responsible for seizures[25]. Some triazole compounds inhibit VGSCs, stabilizes the neuronal membrane and reducing repetitive firing of action potentials. These derivatives inhibit NMDA or AMPA receptors, which mediate excitatory neurotransmission, which leads to a reduction in excitatory synaptic currents, thus suppressing seizure activity[28]. Some triazoles also interact with enzymes like carbonic anhydrase or monoamine oxidase (MAO), indirectly contributing to CNS effects[29].

2. Six-Membered Heterocycles

- **Pyridine**



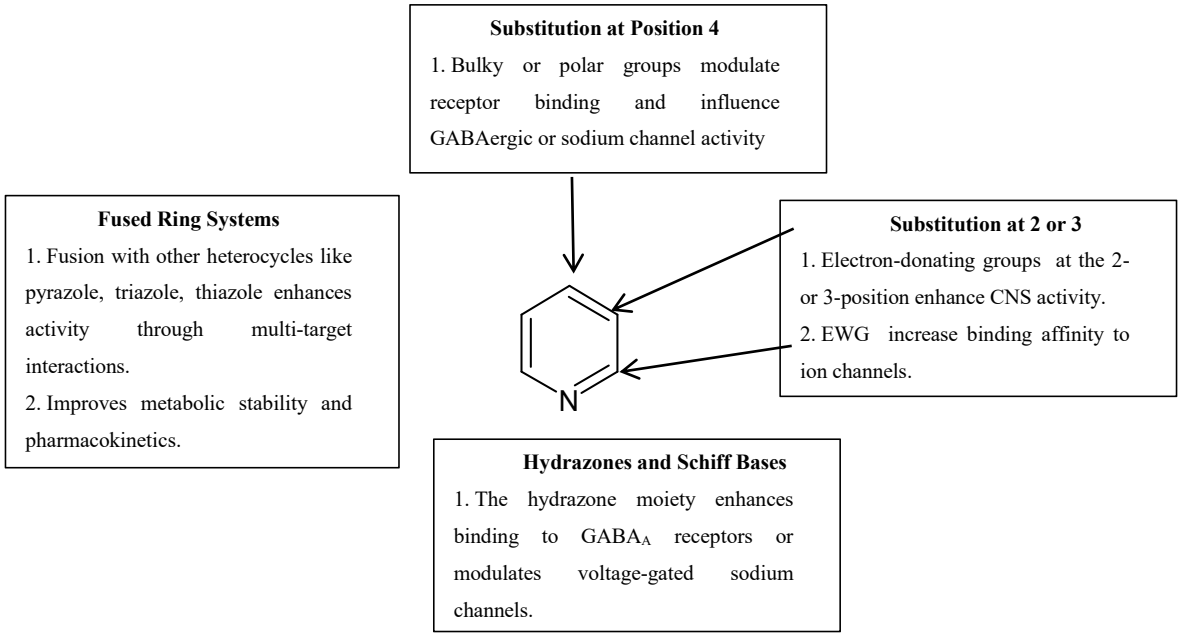
Pyridine

Pyridine, a six-membered heterocyclic aromatic ring containing one nitrogen atom, plays a vital role in the design and development of numerous pharmacologically active compounds, including antiepileptic agents. Although pyridine itself is not used directly as an antiepileptic drug, its derivatives and analogs have demonstrated promising anticonvulsant

properties through various mechanisms. Many synthetic antiepileptic compounds incorporate the pyridine ring as a core scaffold due to its electron-rich nature, which facilitates binding to specific targets in the central nervous system (CNS). Pyridine derivatives exert their antiepileptic effects primarily by modulating ion channels (e.g., sodium and calcium channels), enhancing GABAergic neurotransmission (inhibitory pathways), or inhibiting excitatory neurotransmitters such as glutamate[30].

Structure–Activity Relationship (SAR)

Electron-donating groups like $–CH_3$, $–OCH_3$ at 2- or 3-position often enhance CNS activity by improving lipophilicity and BBB permeability and electron-withdrawing groups like $–NO_2$, –Cl may increase binding affinity to ion channels but can reduce selectivity and increase toxicity. Introduction of bulky or polar groups like $–NH_2$, $–CONH_2$, aryl groups at the 4th position may modulate receptor binding and can influence GABAergic or sodium channel activity[31]. 4-Aminopyridine derivatives have been explored for their potassium channel blocking properties, which can indirectly enhance excitability and may be useful in specific seizure subtypes. Fusion of the pyridine ring with heterocycles such as pyrazole, triazole, thiazole enhances activity through multi-target interactions, improving efficacy in resistant forms of epilepsy. Fused systems also improve metabolic stability and pharmacokinetics and pyridine-based hydrazones and Schiff base derivatives often show potent activity in MES and PTZ models, which enhanced binding to $GABA_A$ receptors and also modulated voltage-gated sodium channels[31, 32].



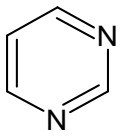
Mechanism of Action

Pyridine-containing molecules produce anticonvulsant effects by influencing various molecular systems that control nerve cell excitability and neurotransmission. Many of these derivatives bind preferentially to the inactivated form of voltage-gated sodium channels (VGSCs), reducing repetitive neuronal discharges during seizures. This action is similar to that of lamotrigine, which also incorporates a pyridine-like structure. By limiting VGSC activity, these compounds restrict the spread of action potentials in hyperactive neurons. Certain pyridine-based agents also boost inhibitory GABAergic signaling. They may act as positive allosteric modulators of $GABA_A$ receptors or inhibit GABA transaminase, thereby elevating GABA concentrations in the synaptic cleft. Others dampen excitatory drive by blocking

NMDA or AMPA receptors or by suppressing glutamate release, helping to restore excitatory–inhibitory balance in the brain[31].

Some analogues target T-type calcium channels, whose activity contributes to absence seizures, thereby preventing the burst firing patterns typical of this seizure type. Compounds like 4-aminopyridine instead act on potassium channels, modifying neuronal membrane potentials and firing thresholds. Additionally, hybrid molecules, such as pyridine–triazole and pyridine–thiazole derivatives are capable of engaging multiple CNS targets simultaneously, offering improved therapeutic potential and a reduced likelihood of resistance development[31].

- **Pyrimidine**

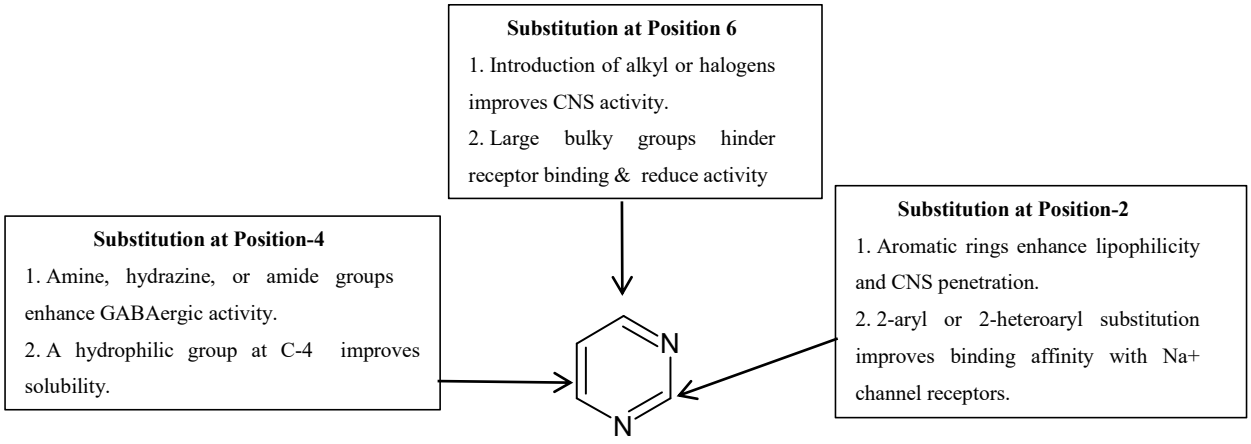


Pyrimidine

Pyrimidine, a 6 membered aromatic heterocycle containing 2 nitrogen atoms at positions 1 & 3, plays a vital role in medicinal chemistry due to its structural resemblance to nucleic acid bases. Its derivatives have demonstrated promising anticonvulsant properties, making them potential candidates for epilepsy treatment[33].

Structure–Activity Relationship (SAR)

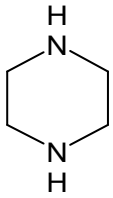
Structure–Activity Relationship (SAR) studies of pyrimidine derivatives have revealed that aromatic rings like phenyl, substituted phenyl at position-2 enhance lipophilicity and CNS penetration. Electron-withdrawing groups on the aromatic ring improve activity in MES models. Heterocycles like triazole and oxadiazole at C-4 increase potency and metabolic stability. 2-aryl or 2-heteroaryl substitution generally improves binding affinity with sodium channel receptors. Amine, hydrazine, or amide groups at position-4 enhances GABAergic activity. Substitution with alkyl or alkoxy groups at C-4 improves lipophilicity but may reduce receptor binding if too bulky. A hydrophilic group at C-4 helps in modulating ion channels and improves solubility. Introduction of alkyl or halogens improves CNS activity by balancing lipophilicity. Large bulky groups may hinder receptor binding and reduce activity. Small hydrophobic groups at this position are favored for optimal receptor fit and bioavailability. Pyrimidine fused with triazole, thiadiazole, or imidazole enhances potency and receptor specificity[34].



Mechanism of Action

Pyrimidine derivatives inhibit VGSCs, by stabilizing inactive state of sodium channels, these compounds reduce neuronal hyperexcitability, this mechanism is particularly effective against tonic–clonic seizures (MES test). Also helps in positive allosteric modulation of $GABA_A$ receptors or inhibition of GABA transaminase. Some pyrimidine derivatives inhibit low-threshold (T-type) calcium channels, which are involved in thalamocortical rhythms related to absence epilepsy[33]. Inhibition of these channels reduces burst firing and abnormal synchronization. Hybrid pyrimidines like pyrimidine–triazole reduce excitatory neurotransmission by blocking NMDA or AMPA glutamate receptors which helps to counteract excitotoxicity during seizures. Many modern pyrimidine-based agents exhibit dual or multitarget activity, combining sodium channel inhibition with GABAergic potentiation or glutamate antagonism. This improves efficacy and broadens the spectrum of anticonvulsant action[34].

- **Piperazine**

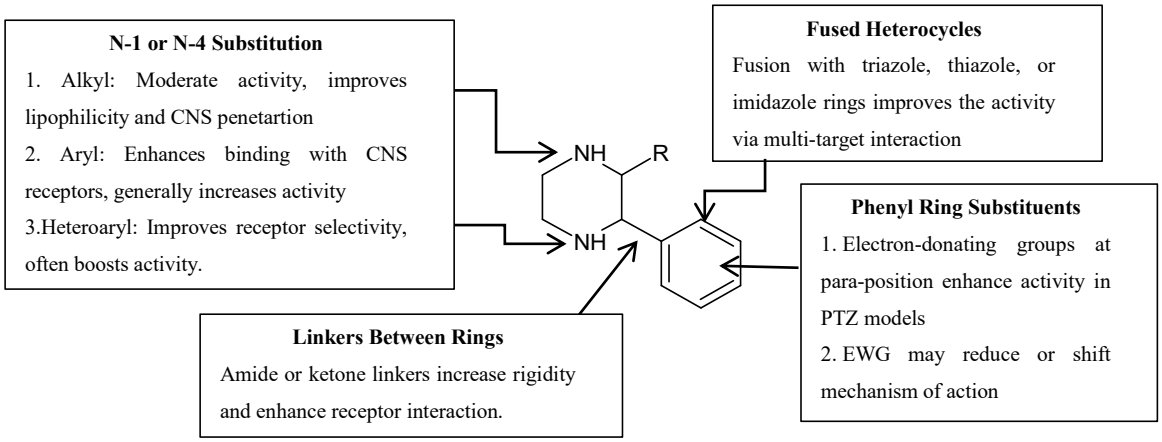


Piperazine

Piperazine, saturated 6 membered heterocycle with N atoms located at opposite positions in ring (1,4-diazacyclohexane). Initially developed as an anthelmintic agent, it has become an important structural motif in medicinal chemistry, largely due to its diverse central nervous system activities, including promising anticonvulsant effects. The presence of a piperazine ring in drug molecules can improve their capacity to cross BBB, enhance metabolic stability, and strengthen receptor-binding interactions[35].

Structure–Activity Relationship (SAR)

Substituting aryl or heteroaryl groups at the N-1 or N-4 position improves binding to CNS targets and anticonvulsant activity. Electron-donating groups on attached aromatic rings improve activity in PTZ seizure models, suggesting GABAergic enhancement. Rigidification of the structure via amide/ketone linkers often results in better potency and selectivity. Hybridization with azole or hydantoin rings increases spectrum and potency, showing efficacy in both tonic–clonic and absence seizures[36].

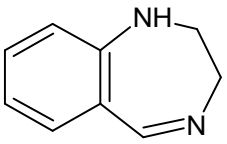


Mechanism of Action

Piperazine derivatives act as positive allosteric modulators of $GABA_A$ receptors, enhancing the inhibitory neurotransmitter. This increases chloride ion influx, which leads to hyperpolarization of the neuronal membrane, and reducing neuronal excitability. They inhibit GABA transaminase, leading to rise in GABA levels in synaptic cleft. Also arylpiperazine derivatives block voltage-gated sodium channels, stabilizing the inactivated state and reducing repetitive neuronal firing[36]. Some piperazine compounds inhibit low-threshold T-type Ca^{2+} channels, which suppresses burst firing in thalamic neurons. Few derivatives display antagonistic activity at NMDA receptors, thereby reducing glutamate-mediated excitotoxicity and excitatory transmission. These derivatives interact with $5\text{-}HT_{1A}$ or $5\text{-}HT_2$ receptors, modulating serotonergic tone. Alteration of serotonin levels can influence seizure susceptibility through effects on neuronal circuits[37].

3. Fused Heterocycles

➢ Benzodiazepine

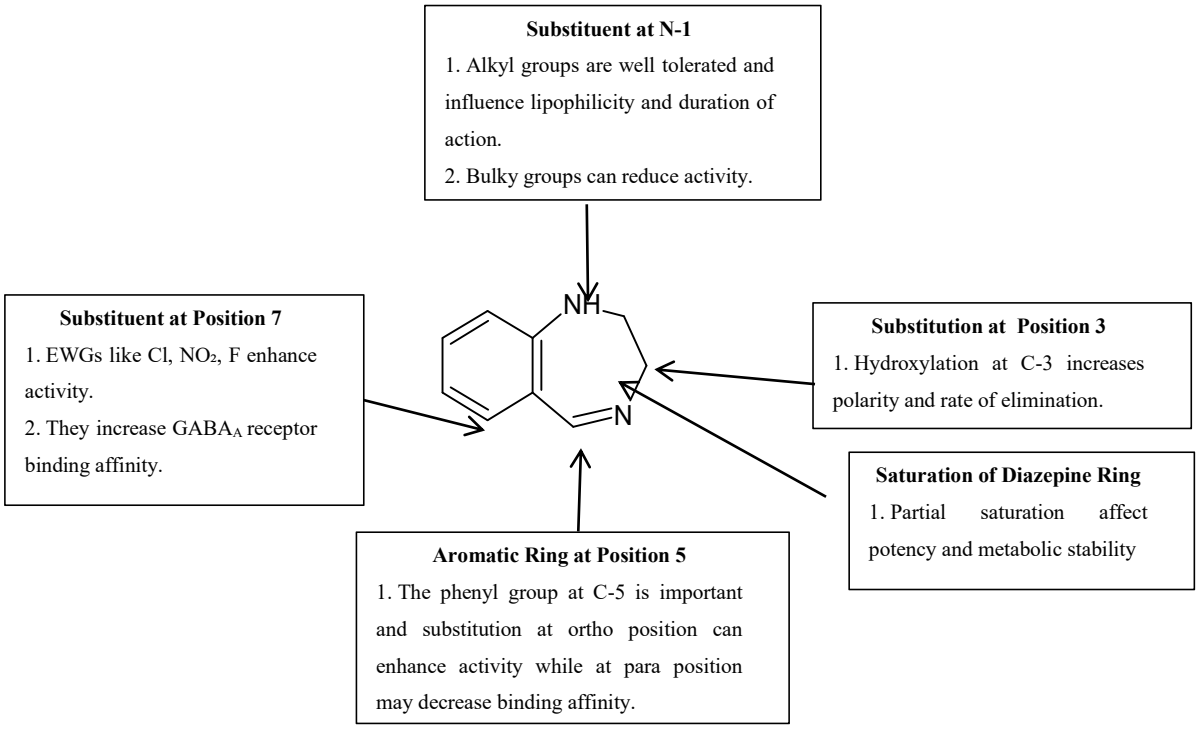


2,3-dihydro-1H-1,4-benzodiazepine

Benzodiazepines represent a significant group of heterocyclic compounds known for their broad spectrum of pharmacological effects, especially those targeting CNS. Their chemical framework is built around the 1,4-benzodiazepine core, a benzene ring fused to a 7-membered diazepine ring containing N atoms at the first and fourth positions. Structural modifications to this scaffold have produced numerous derivatives with varied therapeutic actions, including anticonvulsant, sedative-hypnotic, anxiolytic, and muscle relaxant activities[38, 39].

Structure–Activity Relationship (SAR)

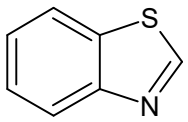
The benzodiazepine core is essential for activity. The diazepine ring fused with a benzene ring is critical for binding to the $GABA_A$ receptor. Electron-withdrawing groups like Cl, NO_2, F at C-7 enhance activity, which thereby increases $GABA_A$ receptor binding affinity. For example: 7-chloro substituent in diazepam is vital for its potency. Alkyl groups (e.g., methyl) at N-1 are well tolerated and influence lipophilicity and duration of action. Bulky groups at N-1 can reduce activity and also affect oral bioavailability. Usually a keto group at 2^{nd} position is essential for hydrogen bonding at the receptor site, which is required for agonistic activity. The phenyl group at position-5 is important for π–π stacking with receptor sites. Substitution on this phenyl ring can modulate activity: Ortho-substitution (e.g., Cl, F) enhances activity, whereas para-substitution decrease binding affinity. Partial saturation (e.g., 3,4-dihydro) of the diazepam ring may affect potency and metabolic stability. Additional fused rings, such as triazolo, imidazo like in alprazolam, midazolam, improve receptor selectivity, potency, and half-life. Hydroxylation at position-3 (e.g., temazepam) increases polarity and rate of elimination thereby shortens duration[39, 40].



Mechanism of Action

Benzodiazepines exert their CNS depressant and antiepileptic effects by enhancing the action of γ-aminobutyric acid. Benzodiazepines bind to a specific allosteric site on the $GABA_A$ receptor, which is a ligand-gated chloride ion channel. The benzodiazepine binding site is located between the α and γ subunits, distinct from the GABA binding site. They do not activate the receptor directly. Instead, increases the frequency of chloride channel opening only when GABA is present. This leads to a greater influx of Cl^- ions into the neuron. Chloride influx causes hyperpolarization of the neuronal membrane. This makes the neuron less likely to fire action potentials, reducing neuronal excitability[40, 41, 42].

- **Benzothiazole**



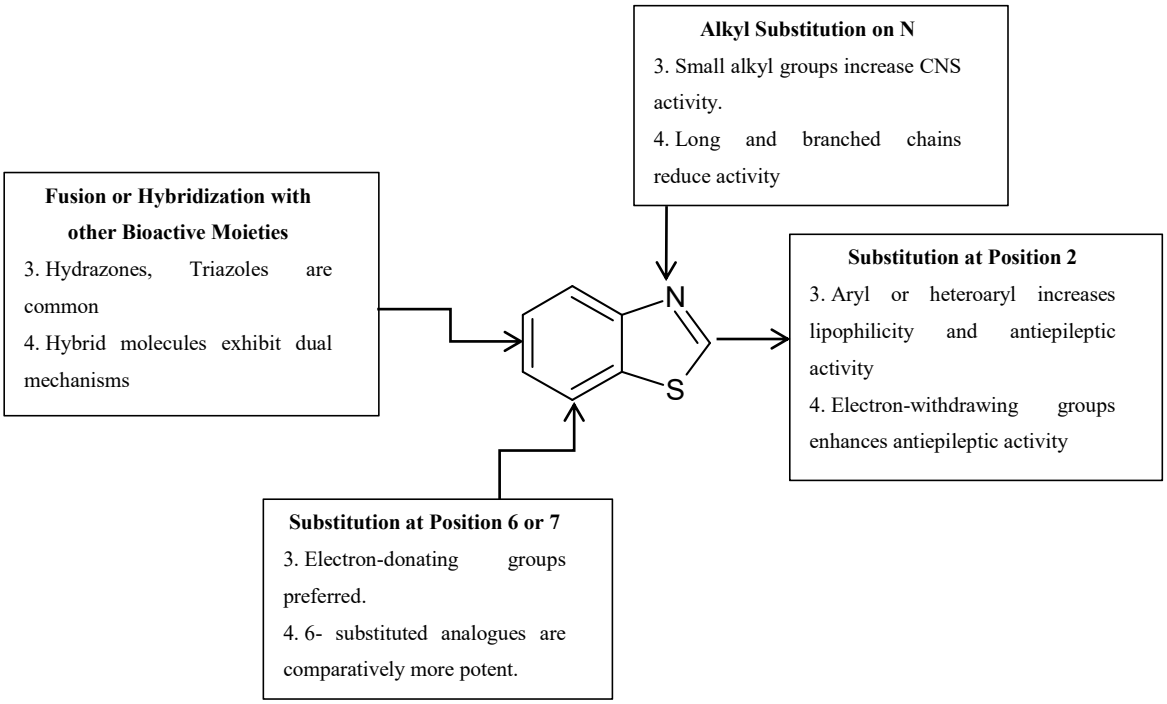
1,3-benzothiazole

Benzothiazole, a fused heterocyclic compound containing both a benzene and a thiazole ring, has gained attention in medicinal chemistry for its diverse biological properties, including antiepileptic activity. The structural versatility of benzothiazole allows for functional modifications that can significantly enhance its interaction with central nervous system (CNS) targets[43].

Structure–Activity Relationship (SAR)

The benzothiazole nucleus, due to its rigid planar structure and ability to engage in multiple binding interactions within the CNS. Aryl or heteroaryl substitution like phenyl, pyridyl at C-2 increases lipophilicity and enhances blood–brain barrier (BBB) penetration. Electron-withdrawing groups on the aryl ring improve activity in MES and PTZ models.

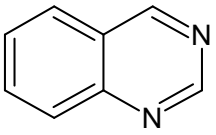
Bulky groups may hinder receptor binding, reducing efficacy. Electron-donating groups at position-7 can modulate the electronic nature of the molecule and enhance receptor affinity. Halogen substitution (–F, –Cl) at C-7 also improves metabolic stability and activity; fluorine often enhances CNS penetration. 6-substituted derivatives are often more potent than 7-substituted analogs. Hydrazones, triazoles, oxadiazoles, or thiadiazoles attached to the ring improve pharmacological profile. Such hybrids often show dual mechanisms, like GABAergic modulation along with sodium channel blockade. Short alkyl chains like methyl, ethyl at nitrogen may improve solubility and CNS delivery. Long or branched chains at C-7 often reduce anticonvulsant activity due to steric hindrance. Adding pyridine, imidazole, or pyrrole rings can increase receptor selectivity and improve efficacy[43, 44].



Mechanism of Action

Benzothiazole and its derivatives exhibit antiepileptic activity primarily through modulation of neuronal excitability and neurotransmission. Some benzothiazole derivatives enhance the activity of GABA by acting as $GABA_A$ receptor agonists or positive allosteric modulators, increasing chloride ion influx and resulting in hyperpolarization of neuronal membranes, thus reducing seizure activity. Benzothiazoles can also block voltage-gated sodium channels, stabilizing the inactive state of the channel & preventing repetitive firing of action potentials seen in epileptic seizures. Some of the derivatives inhibit T-type calcium channels, particularly in thalamic neurons, reducing low-threshold calcium spikes and burst firing, which is especially relevant in absence seizures. These analogues also exert glutamate antagonistic effects, thereby inhibiting excitatory neurotransmission mediated by NMDA or AMPA receptors, which are often overactivated in epilepsy. Certain benzothiazole compounds exhibit antioxidant and neuroprotective properties, mitigating oxidative stress and excitotoxicity associated with epileptogenesis[45, 46].

- **Quinazoline**

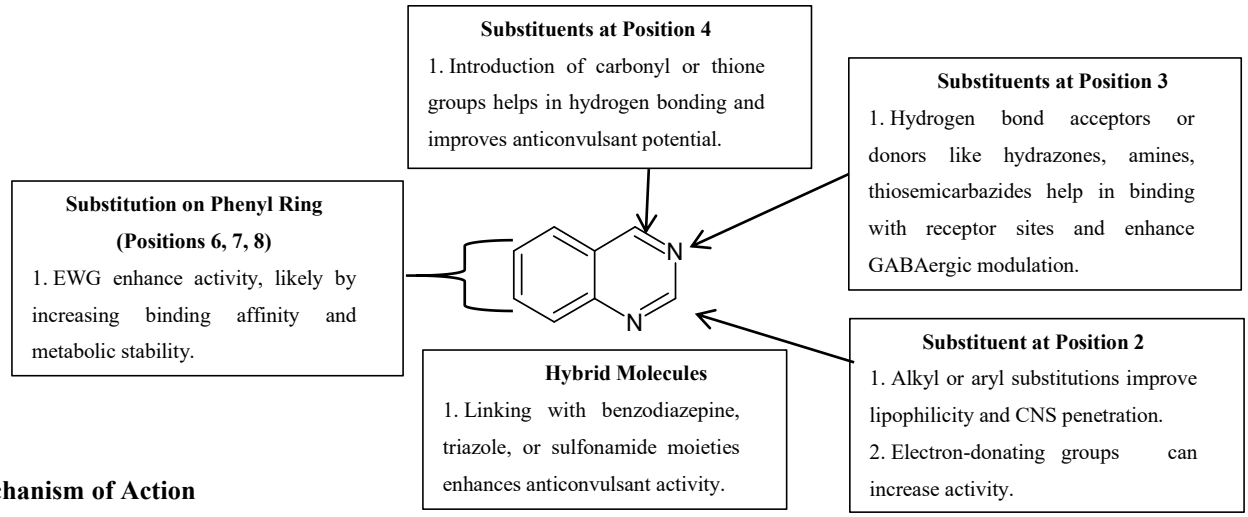


Quinazoline

Quinazoline, a bicyclic heterocyclic compound comprising a fused benzene and pyrimidine ring system. Among its diverse therapeutic applications, quinazoline derivatives have shown promise as antiepileptic agents, owing to their ability to modulate central nervous system (CNS) activity[47].

Structure–Activity Relationship (SAR)

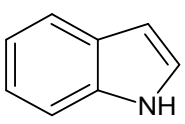
The quinazoline nucleus is essential for anticonvulsant activity. Substitutions on the ring system significantly influence the pharmacological activity. Alkyl or aryl substitutions at position-2 improve lipophilicity and CNS penetration. Electron-donating groups at position-2 can increase activity. Bulky groups at this position may hinder binding to the receptor and reduce activity. Position-3 is often used for hydrogen bond acceptors or donors such as hydrazones, amines and thiosemicarbazides. These groups help in binding with receptor sites and enhance GABAergic modulation. Introduction of carbonyl or thione groups at position-4 helps in hydrogen bonding and improves anticonvulsant potential. Electron-withdrawing groups at position-6, 7, and 8 enhance activity, by increasing binding affinity and metabolic stability. Halogens at position-6 or -8 have shown significant improvement in CNS bioavailability and activity. Linking the quinazoline nucleus with other pharmacophores like benzodiazepine, triazole, or sulfonamide moieties enhances anticonvulsant activity via multiple mechanisms[47, 48].



Mechanism of Action

Quinazoline and its derivatives exhibit anticonvulsant activity primarily through modulation of neurotransmission in the central nervous system (CNS). Certain quinazoline derivatives enhance GABAergic transmission by acting as positive allosteric modulators of the $GABA_A$ receptor, which increases the chloride ion influx, leading to neuronal hyperpolarization, and suppresses seizure activity. Some quinazoline derivatives block VGSCs, this mechanism is similar to that of phenytoin or carbamazepine. A few analogs act by blocking T-type calcium channels, especially in the thalamic neurons, which is useful in treating absence seizures. Some quinazoline-based compounds have been reported to inhibit excitatory neurotransmission by acting as antagonists at NMDA receptors, reducing glutamate-mediated excitotoxicity. Quinazoline derivatives may also provide neuroprotection through antioxidant activity, reducing oxidative stress that contributes to seizure-induced neuronal damage[47, 49].

- **Indole**

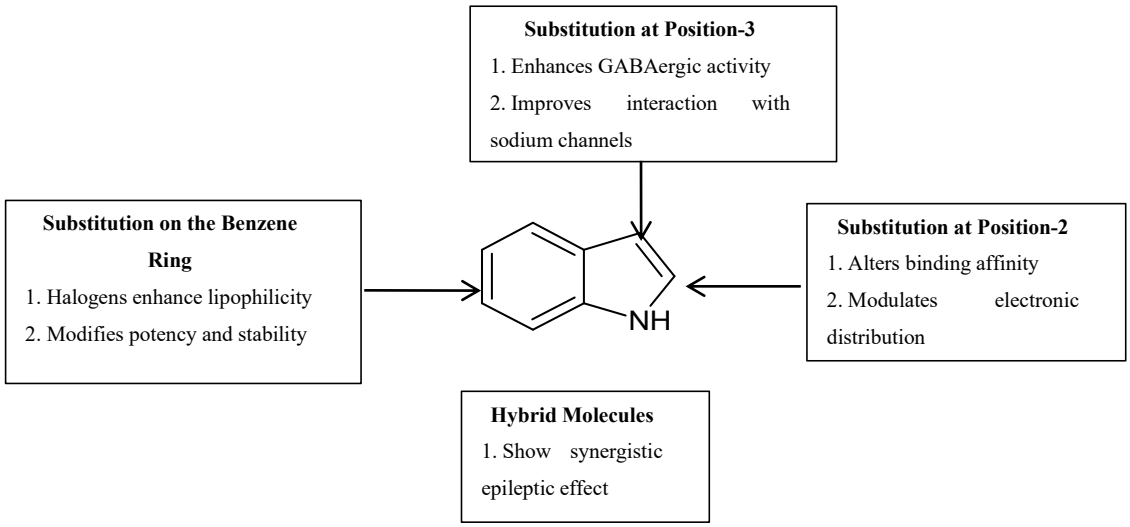


1H-indole

Indole, a bicyclic heterocycle consisting of a benzene ring fused to a five-membered nitrogen-containing pyrrole ring, is a key structural motif in numerous biologically active compounds. In recent years, indole and its derivatives have gained considerable attention as potential antiepileptic agents due to their favorable pharmacological profiles and ability to modulate central nervous system (CNS) activity[50, 51].

Structure–Activity Relationship (SAR)

The indole scaffold offers multiple substitution points, allowing extensive modification for enhancing anticonvulsant activity. Substitution at C-3 is the key site for side chain addition (amide, hydrazide, ketone, etc.) which enhances interaction with GABAergic and sodium channel targets. Substitution at C-2 affects binding affinity and electronic distribution. Substitution on the benzene ring (Positions 4–7) alters lipophilicity, electron density, and metabolic stability. N-1 substitution influences pharmacokinetics and target specificity. Indole fused with other pharmacophores like benzodiazepine, thiazole, oxadiazole rings show synergistic effects[52, 53].

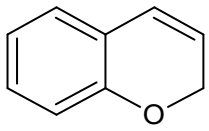


Mechanism of Action

Indole derivatives exert their anticonvulsant activity primarily by enhancing γ-aminobutyric acid (GABA) neurotransmission. Acting as positive allosteric modulators of GABAA receptors, they promote increased chloride ion influx, leading to hyperpolarization of neuronal membranes and a consequent reduction in neuronal excitability. In addition, these compounds can inhibit voltage-gated sodium channels in their inactivated state, thereby preventing repetitive neuronal firing. Some agents also modulate T-type and N-type calcium channels, reducing calcium entry into neurons and limiting neurotransmitter release, which in turn suppresses excitatory synaptic transmission. Moreover, certain indole-based molecules antagonize ionotropic glutamate receptors (such as NMDA and AMPA subtypes), further decreasing excitatory signaling and protecting against seizure-induced overactivation. Beyond ion channel modulation, they may provide neuroprotective benefits by scavenging reactive oxygen species and mitigating oxidative stress, thereby helping to prevent neuronal injury during epileptic episodes[53, 54].

4. Miscellaneous and Hybrid Heterocycles

- **Chromenes (Benzopyrans)**

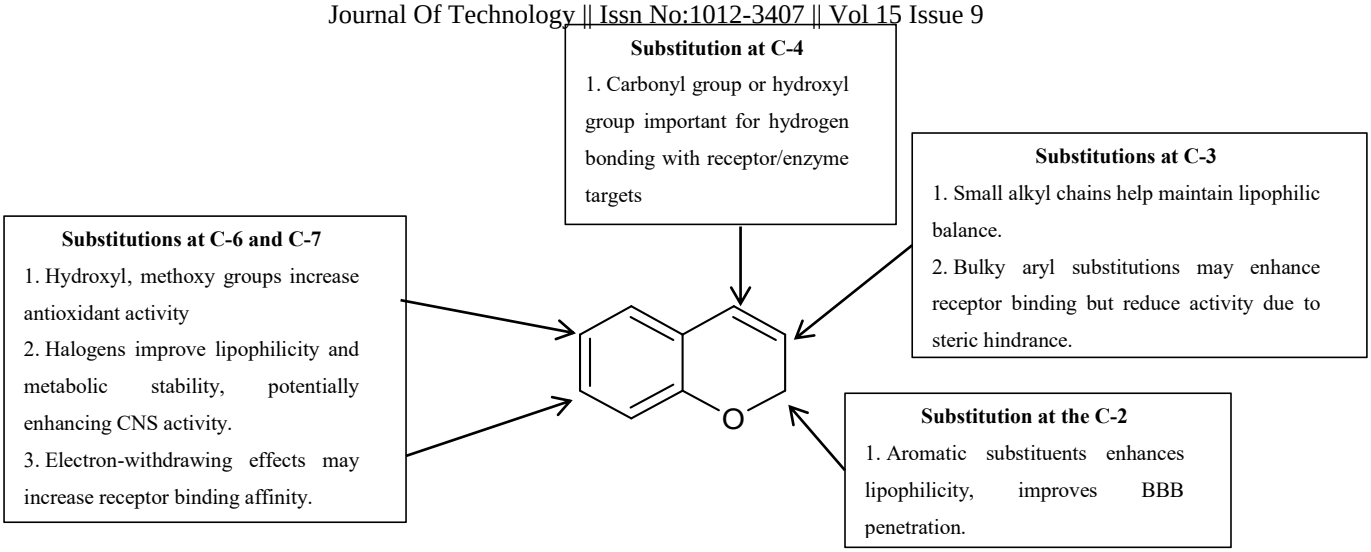


2H-1-benzopyran

Chromenes, commonly called benzopyrans, are bicyclic heterocycles formed by the fusion of benzene ring with a pyran ring containing oxygen. This core structure is found in numerous naturally occurring substances as well as synthetic analogues. Due to their adaptable chemical nature, chromenes demonstrate diverse pharmacological actions, notably antioxidant, anti-inflammatory, and antiepileptic effects. Within epilepsy research, these compounds have drawn significant attention for their capacity to modulate ion channel activity and neurotransmitter signaling—mechanisms closely linked to the development and suppression of seizures[55, 56].

Structure–Activity Relationship (SAR)

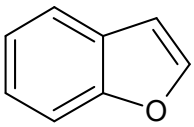
The benzopyran nucleus is crucial for anticonvulsant activity. The planar, aromatic chromene skeleton favors CNS activity by interacting with targets like GABA receptors and ion channels. Both 2H-chromenes and 4H-chromenes are biologically active, with 4H-chromenes often showing stronger activity in seizure models. Aromatic substituents like phenyl and substituted phenyl at C-2 enhances lipophilicity, improving blood-brain barrier (BBB) penetration. EDGs on the phenyl ring at C-2 increases GABAergic modulation and antioxidant effects. EWGs on the phenyl ring at C-2 enhances binding affinity to voltage-gated ion channels. Heteroaryl groups pyridyl, thienyl at C-2 provide additional polar interactions and sometimes improve target selectivity. Alkyl groups (e.g., methyl, ethyl) substituents at the C-3 position help maintain lipophilic balance and improve pharmacokinetic properties. Aryl substitutions at C-2 enhance receptor binding but excessive steric hindrance may reduce activity. Some active 3-aryl-4H-chromenes inhibit calcium channels, contributing to anticonvulsant effects. Carbonyl group or hydroxyl group is important for hydrogen bonding with receptor/enzyme targets. Maintains molecular polarity necessary for biological interaction. 4H-chromene derivatives often show higher MES test activity. Substitutions at C-6 and C-7 like hydroxyl or methoxy groups increase antioxidant activity by indirectly protecting neurons during seizures. Also modulates the electron density of the chromene ring, influencing binding to GABA receptors. Halogens like Cl, F, Br improve lipophilicity and metabolic stability, potentially enhancing CNS activity. Electron-withdrawing effects may increase receptor binding affinity. Halogenation (especially fluorine) at C-8 position enhances BBB penetration and binding affinity. Small polar substituents at C-8 improve solubility. Fusion with heterocycles like imidazole, thiophene, or benzothiazole increases molecular rigidity and pharmacophoric complexity. These derivatives often exhibit multi-target action like GABAergic, ion channels, and antioxidant activity. Incorporation of amino, hydrazone, or amide groups improves solubility in physiological conditions, potential for forming hydrogen bonds with biological targets.and enhanced anticonvulsant activity in some series[56, 57].



Mechanism of Action

Chromene derivatives enhance GABA neurotransmission. Positive allosteric modulation of $GABA_A$ receptors, leads to increased chloride influx and neuronal hyperpolarization. Inhibition of GABA transaminase, prevents GABA degradation and increasing its synaptic levels. Results in enhanced inhibitory neurotransmission, reducing seizure propagation. Some chromene derivatives block Na^+ channels, stabilizing the inactive state and preventing excessive neuronal firing during seizures. Inhibition of T-type or L-type calcium channels, reducing calcium influx and suppressing neurotransmitter release. Important in modulating burst firing in thalamic neurons, a mechanism linked to generalized seizures. Chromenes with phenolic or methoxy groups scavenge ROS. Oxidative stress contributes to neuronal damage and seizure susceptibility by reducing oxidative damage, chromenes protect neurons and stabilize neuronal membranes. Some chromenes reduce glutamate release or antagonize NMDA/AMPA receptors, decreasing excitatory neurotransmission. This balances the excitatory-inhibitory tone in the brain. Chromenes with anti-inflammatory properties inhibit pro-inflammatory cytokines like TNF-α and IL-1β, indirectly reducing seizure susceptibility. Some chromenes may inhibit enzymes such as acetylcholinesterase (AChE), indirectly modulating neurotransmitter levels associated with seizure activity[58].

- **Benzofuran**

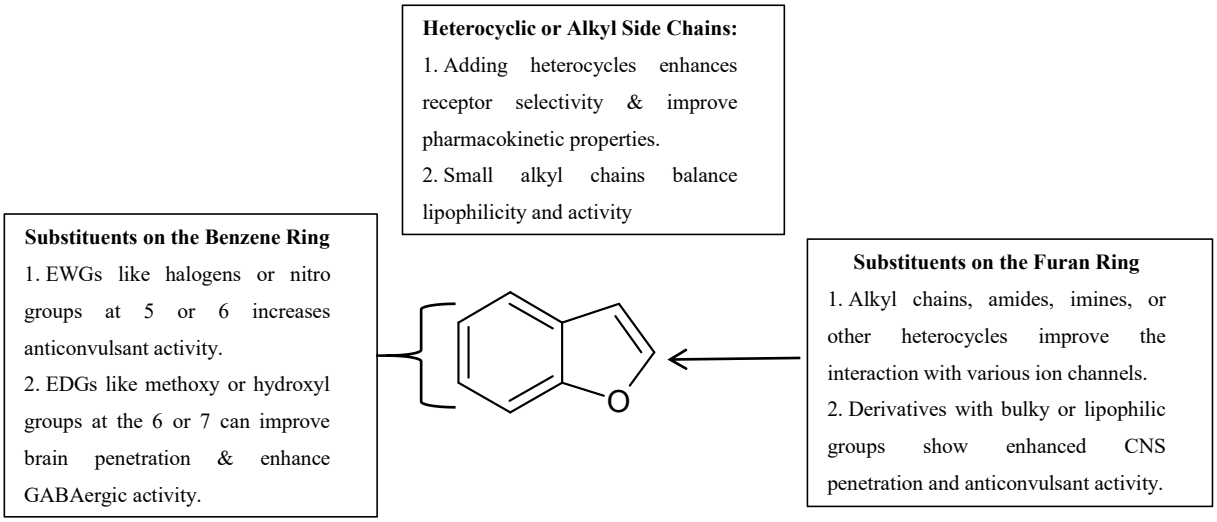


1-Benzofuran

Benzofuran, a heterocyclic compound consisting of a fused benzene and furan ring. Due to its planar structure and the presence of oxygen, it can interact with various biological targets, making it a versatile scaffold in medicinal chemistry. Recent studies have highlighted the anticonvulsant potential of benzofuran derivatives in various in vivo models such as the maximal electroshock seizure (MES) test and pentylenetetrazole (PTZ)-induced seizure models. These derivatives show activity by modulating GABAergic transmission, blocking VGSCs, or inhibiting T-type Ca^{2+} channels, which are common mechanisms targeted by current AEDs[63].

Structure–Activity Relationship (SAR)

The benzofuran nucleus is essential for activity, providing π-π stacking and hydrogen bonding interactions with biological targets like GABA receptors, sodium channels, or calcium channels. Halogens (Cl, Br, F) or nitro groups at the 5- or 6-position of benzofuran generally increase anticonvulsant activity, possibly by enhancing receptor binding. Example: 5-chloro and 6-nitro substitutions often improve potency. Methoxy (-OCH_3) or hydroxyl (-OH) groups at the 6- or 7-position can also improve brain penetration and enhance GABAergic activity. Alkyl chains, amides, imines, or other heterocycles 2nd position improve the interaction with various ion channels. Some derivatives with bulky or lipophilic groups at this position show enhanced CNS penetration and anticonvulsant activity. Adding heterocycles (such as piperazine, imidazole, or pyrrolidine) enhances receptor selectivity and may improve pharmacokinetic properties. Small alkyl chains (methyl, ethyl) sometimes balance lipophilicity and activity. Optimal lipophilicity (LogP ~2–4) is required for blood-brain barrier (BBB) penetration. Excessive lipophilicity may cause off-target effects or toxicity, whereas insufficient lipophilicity reduces CNS availability. Incorporation of amide or urea linkages connecting benzofuran to pharmacophoric fragments has been reported to increase anticonvulsant potency, possibly by increasing hydrogen bonding with target proteins[64, 65].



Mechanism of Action

Benzofuran derivatives exhibit antiepileptic activity primarily through their interaction with key neurotransmitter systems and ion channels that regulate neuronal excitability. Some benzofuran derivatives act as positive modulators of $GABA_A$ receptors, enhancing GABAergic inhibitory neurotransmission. Results in the stabilization of neuronal membranes & the suppression of hyperexcitability, which is a key feature in seizure disorders. These compounds have been shown to inhibit voltage-gated sodium (Na^+) and calcium (Ca^{2+}) channels, that are essential for the propagation of action potentials in neurons. By blocking these channels, benzofurans reduce neuronal firing rates and prevent seizure propagation. Some benzofuran derivatives may antagonize NMDA (N-methyl-D-aspartate) or AMPA receptors, reducing excitatory glutamatergic transmission. This helps in preventing excitotoxicity, a phenomenon often associated with seizure activity. These compounds also possess antioxidant activity, which may protect neurons from oxidative stress-induced damage that contributes to epilepsy pathology. Certain benzofuran analogs are suggested to open potassium (K^+) channels, promoting membrane hyperpolarization and reducing neuronal excitability[64].

Recent Advances in Heterocyclic Anticonvulsants

Over the last decade, research into heterocyclic compounds as potential antiepileptic agents has intensified. Various scaffolds, including oxadiazoles, triazoles, thiazoles, and indoles, have been modified to enhance efficacy, CNS

penetration, and selectivity toward molecular targets such as $GABA_A$ receptors, sodium channels, or calcium channels.

- Hybrid structures (e.g., triazole-indoles, benzofuran-thiazoles) improve multi-target interaction.
- Introduction of electron-withdrawing groups (Cl, NO_2, CF_3) enhances potency.
- Lipophilic substituents often improve blood-brain barrier permeability[1, 66].

Current Challenges in Anticonvulsant Drug Development

Despite the significant progress in identifying heterocyclic compounds with anticonvulsant activity, several challenges continue to hinder their clinical success:

1. Drug Resistance

A major limitation of existing antiepileptic drugs (AEDs) is the development of pharmacoresistance, especially in patients with refractory epilepsy. About 30% of epilepsy cases do not respond adequately to current therapies. This is often due to:

- Overexpression of efflux transporters at BBB.
- Mutations or alterations in drug targets (e.g., sodium channels, GABA receptors)

2. Central Nervous System (CNS) Penetration

Effective anticonvulsants must cross the blood-brain barrier (BBB) in therapeutic concentrations. However, many promising heterocyclic compounds:

- Have poor lipophilicity or are too polar
- Are rapidly metabolized or effluxed by P-glycoprotein
- Structural modifications to enhance BBB permeability often compromise solubility, stability, or safety.

3. Neurotoxicity and Off-Target Effects

Toxicity remains a major concern, particularly with heterocyclic compounds that interact with multiple CNS targets. Common side effects include:

- Sedation
- Cognitive impairment
- Hepatotoxicity and teratogenicity (e.g., valproic acid analogs)[1, 66].

Future Perspectives and Emerging Strategies

1. *In Silico* Screening and AI-Assisted Drug Design

Computational approaches have become integral to modern anticonvulsant drug discovery:

- Molecular docking and pharmacophore modeling aid in predicting binding affinity and guiding scaffold optimization.
- Machine learning (ML) and artificial intelligence (AI) are used to:
  - Predicts ADMET properties
  - Design novel heterocyclic libraries with CNS activity
  - Identify lead compounds from big chemical databases (e.g., ZINC, ChEMBL)

2.Multi-Target Directed Ligands (MTDLs)

Hybrid molecules that act on more than one target (e.g., GABA modulators + sodium channel blockers) are gaining interest for resistant epilepsy. Designing heterocycles that combine different pharmacophores offers synergistic effects with fewer side effects.

3. Green Chemistry and Safer Synthesis

Eco-friendly synthesis routes, including microwave-assisted synthesis and use of benign solvents, are being adopted to reduce environmental impact and improve the sustainability of heterocyclic drug production.

4. Biomarker-Guided Therapy and Personalized Medicine

In the future, anticonvulsant therapy may be guided by individual genetic and metabolic profiles. Identifying biomarkers associated with drug response could tailor the use of specific heterocyclic compounds to individual patients[66].

CONCLUSION

Epilepsy is a chronic neurological disorder that continues to pose significant medical and social challenges, particularly due to drug resistance and the limitations of current therapies. Heterocyclic compounds, owing to their structural diversity and capacity to modulate multiple molecular targets, have emerged as promising scaffolds in the search for novel antiepileptic agents. Various heterocyclic classes, including azoles, benzodiazepines, thiadiazoles, and chromenes, demonstrate potent anticonvulsant activity through mechanisms such as GABAergic enhancement, ion channel regulation, and inhibition of excitatory neurotransmission. Structure-activity relationship studies emphasize that targeted substitutions, electronic effects, and hybrid designs can markedly improve activity, selectivity, and brain penetration. The integration of medicinal chemistry with computational drug design and high-throughput screening is expected to accelerate discovery. Continued research on heterocyclic frameworks offers a viable path toward developing safer, more effective, and personalized treatments, addressing unmet needs in epilepsy management and improving patient quality of life.

REFERENCES

1. Loscher W. Critical review of current animal models of seizures and epilepsy used in the discovery and development of new antiepileptic drugs. Seizure. 2011;20(5):359-68.
2. Grover G, Nath R, Bhatia R, Akhtar MJ. Synthetic and therapeutic perspectives of nitrogen containing heterocycles as anti-convulsants. Bioorganic & Medicinal Chemistry. 2020;28(15):115585.
3. Lankau HJ, Unverferth K, Grunwald C, Hartenhauer H, Heinecke K, Bernöster K, Dost R, Egerland U, Rundfeldt C. New GABA-modulating 1, 2, 4-oxadiazole derivatives and their anticonvulsant activity. European journal of medicinal chemistry. 2007;42(6):873-9.
4. Wang S, Liu H, Wang X, Lei K, Li G, Li J, Liu R, Quan Z. Synthesis of 1, 3, 4-oxadiazole derivatives with anticonvulsant activity and their binding to the GABAA receptor. European Journal of Medicinal Chemistry. 2020;206:112672.
5. Balachandra A, Deshpande SN, Raj A, Revanasiddappa BC. Synthesis, Molecular Docking, and Anticonvulsant Activity of 1, 3, 4-Oxadiazole Derivatives. Journal of Health and Allied Sciences NU. 2025;15(01):063-9.
6. Mishchenko M, Shtrygol S, Kaminskyy D, Lesyk R. Thiazole-bearing 4-thiazolidinones as new anticonvulsant agents. Scientia Pharmaceutica. 2020;88(1):16.
7. Siddiqui N, Ahsan W. Triazole incorporated thiazoles as a new class of anticonvulsants: Design, synthesis and in vivo screening. European journal of medicinal chemistry. 2010;45(4):1536-43.
8. Laczkowski KZ, Konklewska N, Biernasiuk A, Malm A, Salat K, Furgala A, Dzitko K, Bekier A, Baranowska-Laczkowska A, Paneth A. Thiazoles with cyclopropyl fragment as antifungal, anticonvulsant, and anti-Toxoplasma gondii agents: synthesis, toxicity evaluation, and molecular docking study. Medicinal Chemistry Research. 2018;27(9):2125-40.
9. Yamsani N, Sundararajan R. Design, in-silico studies, synthesis, characterization, and anticonvulsant activities of novel thiazolidin-4-one substituted thiazole derivatives. Biointerface Res Appl Chem. 2022;13(4):366.
10. Ganguly S, Mishra R. Comparative Molecular Similarity Indices Analysis of 1-(Naphthylalky1)–1H-imidazole Analogs with Antiepileptic Activity. Journal of Young Pharmacists. 2010;2(4):388-93.
11. Marzouk AA, Bass AK, Ahmed MS, Abdelhamid AA, Elshaier YA, Salman AM, Aly OM. Design, synthesis and anticonvulsant activity of new imidazolidindione and imidazole derivatives. Bioorganic Chemistry. 2020;101:104020.
12. Mawasi H, Bibi D, Bialer M. Design and comparative anticonvulsant activity assessment of CNS-active alkyl-carbamoyl imidazole derivatives. Bioorganic & Medicinal Chemistry. 2016;24(18):4246-53.
13. Husain A, Siddiqui N, Sarafroz MD, Khatoon Y, Rasid M, Ahmad N. Synthesis, anticonvulsant and neurotoxicity screening of some novel 1, 2, 4-trisubstituted-1H-imidazole derivatives. Acta Pol Pharm. 2011;68(5):657-63.
14. Robertson DW, Beedle EE, Lawson R, Leander JD. Imidazole anticonvulsants: structure-activity relationships of [(biphenylyloxy) alkyl] imidazoles. Journal of medicinal chemistry. 1987;30(5):939-43.
15. Anthwal T, Nain S. 1, 3, 4-thiadiazole scaffold: As anti-epileptic agents. Frontiers in Chemistry. 2022;9:671212.
16. Kumar K, Manna K, Bhatt H. Synthesis and Pharmacological Evaluation of Substituted 1, 3, 4-Thiadiazole Derivatives as Anticonvulsant Agents. Nirma University Journal of Pharmaceutical Sciences. 2019;6(1):15-26.
17. Anthwal T, Pant S, Rana P, Nain S. Design, synthesis, and in vitro, in vivo, and in silico evaluation of novel substituted 1, 3, 4-thiadiazole derivatives as anticonvulsant agents. Frontiers in Chemistry. 2025;12:1515866.
18. Mullick P, Khan SA, Verma S, Alam O. Thiadiazole derivatives as potential anticonvulsant agents. Bulletin of the Korean Chemical Society. 2011;32(3):1011-6.
19. Luszczki JJ, Karpińska M, Matysiak J, Niewiadomy A. Characterization and preliminary anticonvulsant assessment of some 1, 3, 4-thiadiazole derivatives. Pharmacological Reports. 2015;67(3):588-92.

20. Sharma B, Verma A, Prajapati S, Sharma UK. Synthetic methods, chemistry, and the anticonvulsant activity of thiadiazoles. International journal of medicinal chemistry. 2013;2013(1):348948.
21. Gupta A, Mishra P, Pandeya SN, Kashaw SK, Kashaw V, Stables JP. Synthesis and anticonvulsant activity of some substituted 1, 2, 4-thiadiazoles. European journal of medicinal chemistry. 2009;44(3):1100-5.
22. Song MX, Deng XQ. Recent developments on triazole nucleus in anticonvulsant compounds: a review. Journal of enzyme inhibition and medicinal chemistry. 2018;33(1):453-78.
23. K Kamboj V, K Verma P, Dhanda A, Ranjan S. 1, 2, 4-triazole derivatives as potential scaffold for anticonvulsant activity. Central Nervous System Agents in Medicinal Chemistry. 2015;15(1):17-22.
24. Ayati A, Emami S, Foroumadi A. The importance of triazole scaffold in the development of anticonvulsant agents. European journal of medicinal chemistry. 2016;109:380-92.
25. Kapron B, Luszczki JJ, Plazinska A, Siwek A, Karcz T, Grybos A, Nowak G, Makuch-Kocka A, Walczak K, Langner E, Szalast K. Development of the 1, 2, 4-triazole-based anticonvulsant drug candidates acting on the voltage-gated sodium channels. Insights from in-vivo, in-vitro, and in-silico studies. European journal of pharmaceutical sciences. 2019;129:42-57.
26. Kapron B, Czarnomysy R, Wysokinski M, Andrys R, Musilek K, Angeli A, Supuran CT, Plech T. 1, 2, 4-Triazole-based anticonvulsant agents with additional ROS scavenging activity are effective in a model of pharmacoresistant epilepsy. Journal of Enzyme Inhibition and Medicinal Chemistry. 2020;35(1):993-1002.
27. Song M, Zhao W, Zhu Y, Liu W, Deng X, Huang Y. Design, synthesis, and evaluation of anticonvulsant activities of new triazolopyrimidine derivatives. Frontiers in Chemistry. 2022;10:925281.
28. Lai MC, Wu SN, Huang CW. Rufinamide, a triazole-derived antiepileptic drug, stimulates Ca^{2+}-activated K^{+} currents while inhibiting voltage-gated Na^{+} currents. International journal of molecular sciences. 2022;23(22):13677.
29. Jain RP, Kashaw SK, Jain V, Kohli DV. Design, synthesis, in silico studies, and pharmacological evaluation of 5-aryl-4-(chloroacetylamino)-3-mercapto-1, 2, 4-triazole derivatives as anticonvulsant agents. International Journal of Applied Pharmaceutics. 2024;16(6):190-200.
30. Tripathi L, Singh R, Stables JP. Design & synthesis of N′-[substituted] pyridine-4-carbohydrazides as potential anticonvulsant agents. European journal of medicinal chemistry. 2011;46(2):509-18.
31. Ulloora S, Adhikari AV, Shabaraya R. Synthesis and antiepileptic studies of new imidazo [1, 2-a] pyridine derivatives. Chinese Chemical Letters. 2013;24(9):853-6.
32. Sirakanyan SN, Spinelli D, Petrou A, Geronikaki A, Kartsev VG, Hakobyan EK, Yegoryan HA, Zuppiroli L, Zuppiroli R, Ayvazyan AG, Paronikyan RG. New Bicyclic Pyridine-Based Hybrids Linked to the 1, 2, 3-Triazole Unit: Synthesis via Click Reaction and Evaluation of Neurotropic Activity and Molecular Docking. Molecules. 2023;28(3):921.
33. Alam O, Mullick P, Verma SP, Gilani SJ, Khan SA, Siddiqui N, Ahsan W. Synthesis, anticonvulsant and toxicity screening of newer pyrimidine semicarbazone derivatives. European Journal of Medicinal Chemistry. 2010;45(6):2467-72.
34. Dawood D, Saleh D, Mustafa P, Farid O, Nossier E. Synthesis and Molecular Modeling Study of New Pyrimidine-Based Derivatives as Anticonvulsant Agents. Egyptian Journal of Chemistry. 2025;68(1):109-22.
35. Tripathi S, Kumar R, Debnath A, Singh H, Yadav RK. Design, synthesis, docking, DFT, and MD simulation studies of new piperazine, 1, 3, 4-oxadiazole, and quinoline conjugates: A search for potent antiepileptic agents. Bioorganic Chemistry. 2025; (1):108595.
36. Kumari S, Mishra CB, Tiwari M. Design, synthesis and pharmacological evaluation of N-[4-(4-(alkyl/aryl/heteroaryl)-piperazin-1-yl)-phenyl]-carbamic acid ethyl ester derivatives as novel anticonvulsant agents. Bioorganic & Medicinal Chemistry Letters. 2015;25(5):1092-9.

37. Kaminski K, Wiklik B, Obniska J. Synthesis and anticonvulsant activity of new N-phenyl-2-(4-phenylpiperazin-1-yl) acetamide derivatives. Medicinal Chemistry Research. 2015;24(7):3047-61.
38. Sobanska AW, Zydek G, Wlodno P, Brzezinska E. Comparative (Q) SAR analysis of benzodiazepine derivatives with different biological activity. European Journal of Medicinal Chemistry. 2015;89:147-55.
39. Ochoa JG, Kilgo WA. The role of benzodiazepines in the treatment of epilepsy. Current treatment options in neurology. 2016;18(4):18.
40. Tolu-Bolaji OO, Sojinu SO, Okedere AP, Ajani OO. A review on the chemistry and pharmacological properties of benzodiazepine motifs in drug design. Arab Journal of Basic and Applied Sciences. 2022;29(1):287-306.
41. Aastha P, Navneet K, Anshu A, Pratima S, Dharma K. 1, 5 Benzodiazepines: overview of properties and synthetic aspects. Research Journal of Chemical Sciences. 2013;2231:606X.
42. Shafie A, Mohammadi-Khanaposhtani M, Asadi M, Rahimi N, Ranjbar PR, Ghasemi JB, Larijani B, Mahdavi M, Shafaroodi H, Dehpour AR. Novel fused 1, 2, 3-triazolo-benzodiazepine derivatives as potent anticonvulsant agents: design, synthesis, in vivo, and in silico evaluations. Molecular diversity. 2020;24(1):179-89.
43. Chauhan B, Kumar R, Salahuddin, Singh H, Afzal O, Altamimi AS, Abdullah MM, Yar MS, Ahsan MJ, Kumar N, Yadav SK. Design, synthesis, in vivo, and in Silico evaluation of Benzothiazoles bearing a 1, 3, 4-Oxadiazole moiety as new antiepileptic agents. ACS omega. 2023;8(2):2520-30.
44. Gagoria J, Kumar Verma P, Khatkar A. Anticonvulsant and neurological profile of benzothiazoles: a mini-review. Central Nervous System Agents in Medicinal ChemistryChemistry-Central Nervous System Agents). 2015;15(1):11-6.
45. Gilani SJ, Hassan MZ, Imam SS, Kala C, Dixit SP. Novel benzothiazole hydrazine carboxamide hybrid scaffolds as potential in vitro GABA AT enzyme inhibitors: Synthesis, molecular docking and antiepileptic evaluation. Bioorganic & Medicinal Chemistry Letters. 2019;29(14):1825-30.
46. Liu DC, Zhang HJ, Jin CM, Quan ZS. Synthesis and biological evaluation of novel benzothiazole derivatives as potential anticonvulsant agents. Molecules. 2016;21(3):164.
47. Zayed MF. New fluorinated quinazolinone derivatives as anticonvulsant agents. Journal of Taibah University Medical Sciences. 2014;9(2):104-9.
48. Abuelizz HA, El Dib R, Marzouk M, Anouar EH, Maklad YA, Attia HN, Al-Salahi R. Molecular docking and anticonvulsant activity of newly synthesized quinazoline derivatives. Molecules. 2017;22(7):1094.
49. Zheng J, Jeon S, Jiang W, Burbulla LF, Ysselstein D, Oevel K, Krainc D, Silverman RB. Conversion of quinazoline modulators from inhibitors to activators of β-glucocerebrosidase. Journal of medicinal chemistry. 2019;62(3):1218-30.
50. Ahuja P, Siddiqui N. Anticonvulsant evaluation of clubbed indole-1, 2, 4-triazine derivatives: A synthetic approach. European Journal of Medicinal Chemistry. 2014;80:509-22.
51. Khan MS, Dhar N, Husain A. Indole derivatives with anticonvulsant activity against two seizure models. Pharmacophore. 2012;3(1-2012):55-61.
52. Swathi K, Sarangapani M. Evaluation of Anti-Epileptic Effect of New Indole Derivatives by Estimation of Biogenic Amines Concentrations in Rat Brain. Adv Exp Med Biol. 2017;988:39–48.
53. Dinnimath BM, Manjunath L, Munishamgowda Y. Synthesis and developing of new thiazolidones and thiotriazole-indoles as potent anticonvulsant agents. Int J Pharm Res. 2013;5:78-82.
54. Kerzare DR, Menghani SS, Rarokar NR, Khedekar PB. Development of novel indole-linked pyrazoles as anticonvulsant agents: A molecular hybridization approach. Archiv der Pharmazie. 2021;354(1):2000100.
55. Angelova VT, Andreeva-Gateva PA, Vassilev NG, Tafradjiiska-Hadjiolova R, Surcheva S, Tchekalarova J. Anticonvulsant activity of newly synthesized 2H-chromene based hydrazones in ICR mice. Compt. Rend. Acad. Bulg. Sci. 2016;69:513-20.

56. Raj V, Lee J. 2H/4H-Chromenes—A versatile biologically attractive Scaffold. Frontiers in Chemistry. 2020;8:623.
57. Kushwaha RK, Singh K, Kumar P, Chandra D. Review on Chromen derivatives and their Pharmacological Activities. Research Journal of Pharmacy and Technology. 2019;12(11):5566-74.
58. Angelova VT, Voynikov Y, Andreeva-Gateva P, Surcheva S, Vassilev N, Pencheva T, Tchekalarova J. In vitro and in silico evaluation of chromene based aroyl hydrazones as anticonvulsant agents. Medicinal Chemistry Research. 2017;26(9):1884-96.
59. Abd-Allah WH, Osman EE, Anwar MA, Attia HN, El Moghazy SM. Design, synthesis and docking studies of novel benzopyrone derivatives as anticonvulsants. Bioorganic chemistry. 2020;98:103738.
60. Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: a summary of the Eleventh Eilat Conference (EILAT XI). Epilepsy research. 2013;103(1):2-30.
61. Parsons AA, Bingham S, Raval P, Read S, Thompson M, Upton N. Tonabersat (SB-220453) a novel benzopyran with anticonvulsant properties attenuates trigeminal nerve-induced neurovascular reflexes. British journal of pharmacology. 2001;132(7):1549-57.
62. Keri RS, Budagumpi S, Balappa Somappa S. Synthetic and natural coumarins as potent anticonvulsant agents: A review with structure–activity relationship. Journal of clinical pharmacy and therapeutics. 2022;47(7):915-31.
63. Shakya AK, Kamal M, Balaramnavar VM, Bardaweel SK, Naik RR, Saxena AK, Siddiqui HH. Design, synthesis and evaluation of benzofuran-acetamide scaffold as potential anticonvulsant agent. Acta Pharmaceutica. 2016;66(3):353-72.
64. El-Sawy ER, Ebaid MS, Abo-Salem HM, Al-Sehemi AG, Mandour AH. Synthesis, anti-inflammatory, analgesic and anticonvulsant activities of some new 4, 6-dimethoxy-5-(heterocycles) benzofuran starting from naturally occurring visnagin. Arabian Journal of Chemistry. 2014;7(6):914-23.
65. Mushtaq A, Zahoor AF, Ahmad S, Saif MJ, ul Haq A, Khan SG, Al-Mutairi AA, Irfan A, Al-Hussain SA, Zaki ME. A comprehensive review on benzofuran synthesis featuring innovative and catalytic strategies. ACS omega. 2024;9(19):20728-52.
66. Fawcett J, Davis S, Manford M. Further advances in epilepsy. Journal of Neurology. 2023;270(11):5655-70.