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Benzotriazole derivatives in Epilepsy: A Review of the Latest Research

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ABSTRACT

Epilepsy, a prevalent neurological disorder, necessitates the continuous search for novel therapeutic strategies, particularly for drug-resistant cases. Benzimidazole, a versatile heterocyclic scaffold, has garnered significant attention in medicinal chemistry due to its diverse pharmacological activities, including anticonvulsant properties. This review synthesizes the latest research on benzimidazole derivatives in epilepsy, focusing on preclinical investigations over the last five years. The article explores the efficacy of these compounds in various animal models of seizures, highlighting promising results in maximal electroshock, pentylenetetrazole, and kindling models. Potential mechanisms of action, such as modulation of GABAergic neurotransmission, blockade of sodium channels, and kappa-opioid receptor agonism, are discussed. Furthermore, the review delves into structure-activity relationship studies, elucidating the impact of specific structural modifications on anticonvulsant activity. Emerging trends, including the development of multi-target ligands and greener synthetic methodologies, are also examined. While preclinical findings are encouraging, the review addresses the challenges in translating these compounds to clinical use, including bioavailability, safety, and drug resistance. The potential clinical relevance of benzimidazole derivatives in epilepsy treatment is considered, emphasizing the need for further translational research to fully unlock their therapeutic potential for this debilitating condition.

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1. Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures, affecting a significant portion of the global population.[1] While current antiepileptic drugs (AEDs) can effectively control seizures in approximately two-thirds of patients, substantial challenges persist concerning their overall effectiveness, the emergence of drug resistance, the occurrence of often debilitating side effects, and the critical need for treatment strategies tailored to individual patients.[1] In a notable percentage of cases, the disease may become refractory to specific anticonvulsant medications, leading to the continued occurrence of seizures despite consistent drug use.[3] This highlights a critical unmet medical need, as it is estimated that in a considerable fraction of individuals with epilepsy, currently available AEDs do not provide complete relief or control of seizures.[4] These limitations underscore the urgent necessity for the development of novel therapeutic agents that offer improved efficacy and enhanced safety profiles for individuals living with epilepsy.[3]

Benzotriazole (Figure 1) is a versatile bicyclic heterocyclic compound that has garnered significant interest in medicinal chemistry due to its broad spectrum of biological activities.[4] These activities include antimicrobial, antiparasitic, antitumor, analgesic, antioxidant, and anti-inflammatory properties.[4]

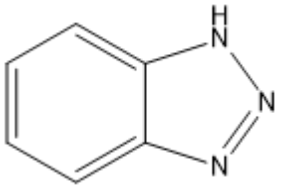

Figure 1. Benzotriazole nucleus

This diverse pharmacological profile suggests that benzotriazole may possess the ability to interact with multiple biological targets that are relevant to the pathophysiology of epilepsy, potentially offering multi-faceted therapeutic benefits for seizure management. Furthermore, benzotriazole has been recognized for its utility as a "tagging molecule" [4], a strategy in drug design where it can be chemically linked to other pharmacologically active heterocyclic nuclei, potentially enhancing their desired properties, such as anticonvulsant activity or improved pharmacokinetic characteristics. Given the existing limitations of current AEDs and the promising array of biological activities exhibited by benzotriazole derivatives, recent scientific research has increasingly focused on exploring their potential as novel antiepileptic agents.[5] This review aims to provide a comprehensive overview of the latest research, primarily from the period of 2020 to 2025, concerning the anticonvulsant activity of benzotriazole derivatives. The scope of this review will encompass their synthesis, preclinical evaluation in various seizure models, proposed mechanisms of action at the molecular level, structure-activity relationships that govern their efficacy, assessments of their safety and toxicity, and their potential trajectory for future therapeutic development in the context of epilepsy.

2. Synthesis and Chemical Properties of Benzotriazole Derivatives

The synthesis of benzotriazole can be achieved through well-established chemical methods, notably the diazotization of *o*-phenylenediamine using sodium nitrite in the presence of acetic acid.[7] This foundational compound serves as a key intermediate for the creation of a diverse range of derivatives. These derivatives are often synthesized by employing various chemical modifications, including N-alkylation, where alkyl groups are attached to one of the nitrogen atoms, and N-acylation, involving the addition of acyl groups.[4] Additionally, the benzotriazole moiety can be strategically incorporated into larger, more complex heterocyclic systems to generate novel compounds with potentially enhanced biological activities.[4] In the pursuit of more efficient and environmentally conscious synthetic approaches, researchers have also developed solvent-free techniques and methods utilizing microwave irradiation to facilitate the synthesis of benzotriazole derivatives.[7] The development of such efficient and environmentally friendly synthesis methods is of paramount importance for the potential large-scale production of promising benzotriazole derivatives, particularly if these compounds

demonstrate significant efficacy and safety in preclinical studies and subsequently advance to clinical trials for human use.

The fundamental chemical structure of benzotriazole (C6H5N3) comprises a benzene ring that is fused to a 1,2,3-triazole ring, which is characterized by the presence of three nitrogen atoms within the five-membered heterocyclic ring.[7] This unique arrangement allows benzotriazole to exist in different tautomeric forms, which are isomers that differ in the position of a hydrogen atom and a double bond.[9] The molecule's inherent polarity, stemming from the presence of nitrogen atoms, coupled with its capacity to participate in hydrogen bonding and coordinate with metal ions, significantly contributes to the diverse array of biological activities it exhibits.[15] It is highly probable that the presence of multiple nitrogen atoms within the triazole ring system plays a crucial role in the interaction of benzotriazole derivatives with specific biological targets within the central nervous system, thereby influencing their potential to exert anticonvulsant effects.[9]

3. Preclinical Evaluation of Anticonvulsant Activity

Initial investigations into the potential of benzotriazole derivatives as antiepileptic agents have involved *in vitro* studies, which explore their effects on neuronal activity at the cellular level. Some of these studies have indicated that certain benzotriazole derivatives may interact with gamma-aminobutyric acid (GABA) receptors [1], which are key inhibitory neurotransmitter receptors in the brain, and also with voltage -sensitive sodium channels (VGSCs) [3], which are critical for the generation and propagation of action potentials in neurons. Furthermore, research on structurally related triazole-containing derivatives has demonstrated their ability to inhibit neuronal voltage-sensitive sodium channels and L-type calcium channels [27], suggesting a potential mechanism for seizure control. These *in vitro* findings provide crucial preliminary evidence regarding the potential mechanisms of action of benzotriazole derivatives, thereby guiding subsequent *in vivo* studies in animal models and informing the rational design of more targeted and effective drug candidates. The observed involvement of GABA receptors and VGSCs is particularly noteworthy as these are well-established mechanisms of action for many currently used AEDs.

The anticonvulsant potential of benzotriazole derivatives has been extensively evaluated in *in vivo* studies utilizing various animal models of epilepsy. The maximal electroshock (MES) test is a widely recognized preclinical model that is predictive of a compound's efficacy against generalized tonic-clonic seizures, which are characterized by loss of consciousness and major convulsions.[1] Numerous synthesized benzotriazole derivatives have demonstrated significant anticonvulsant effects in the MES model, indicating their ability to prevent the spread of seizure activity in the brain.[1] For instance, certain 1-(substituted)-5-[(N-benzotriazolo-methyl)-1,3,4-thiadiazolyl]-imidazole-2-thione derivatives have shown promising anticonvulsant effects in this model.[4] Similarly, a specific compound, 2-(1H-benzotriazol-1-yl)-N'-[4-(1,3-benzodioxol-5-yloxy)benzylidene] acetohydrazide, also known as BTA 9, exhibited notable anti-MES activity in mice.[5] Furthermore, triazolopyrimidine derivatives, which incorporate a triazole ring system, have also shown anticonvulsive activity in the MES model, with some compounds demonstrating potency greater than that of established AEDs such as valproate, carbamazepine, and diazepam.[1] The consistent observation of anticonvulsant activity in the MES model across various structural classes of benzotriazole derivatives strongly suggests a potential therapeutic avenue for the treatment of generalized tonic-clonic seizures.

The subcutaneous pentylenetetrazol (scPTZ) test is another widely used preclinical model, often employed to assess a compound's efficacy against absence seizures, which are characterized by brief lapses of consciousness, and myoclonic seizures, which involve sudden, brief muscle jerks.[1] Several benzotriazole derivatives have also demonstrated significant activity in the scPTZ model, indicating their potential to control these types of seizures.[1] Of particular interest is compound 6d, a triazolopyrimidine

derivative, which was found to be highly potent against seizures induced by both MES and PTZ, suggesting a broad spectrum of anticonvulsant activity.[1] Additionally, some benzotriazole-based oxadiazole derivatives have also shown activity in the scPTZ model, further expanding the potential therapeutic applications of this class of compounds.[2] The demonstrated efficacy of certain benzotriazole derivatives in the scPTZ model suggests their potential to treat a wider range of seizure types beyond generalized tonic-clonic seizures, including absence and myoclonic seizures.

Beyond the primary MES and scPTZ models, some research has explored the effectiveness of benzotriazole derivatives in other seizure models. For instance, certain triazole-thione derivatives, which share structural similarities with benzotriazole, have shown efficacy in the 6 Hz model, which is relevant to pharmacoresistant epilepsy, a particularly challenging form of the disorder where seizures do not respond to standard medications.[27] Furthermore, the previously mentioned compound 6d also exhibited efficacy in seizure models induced by 3-mercaptopropionic acid and bicuculline, providing further evidence of its broad spectrum of anticonvulsant activity.[1] The demonstrated effectiveness in models of pharmacoresistant epilepsy is a particularly significant finding, as it suggests the potential for benzotriazole derivatives to overcome the limitations of existing AEDs in patients whose seizures are not adequately controlled by current treatments.

4. Mechanisms of Action of Benzotriazole Derivatives in Epilepsy

Research into how benzotriazole derivatives exert their anticonvulsant effects has pointed towards several potential mechanisms of action. One prominent area of investigation is the modulation of voltage-gated ion channels (VGICs), particularly voltage-gated sodium channels (VGSCs).[3] VGSCs are essential proteins in nerve cells responsible for generating and transmitting electrical signals, and their dysfunction is implicated in epilepsy. Notably, one study found that the presence of unbranched alkyl chains of specific lengths attached to a triazole core, a structural motif related to benzotriazole, was crucial for both anticonvulsant activity and strong interaction with VGSCs.[3] Additionally, computational docking studies have indicated that some synthesized benzotriazole derivatives can bind to voltage-gated calcium channels (VGCCs) and N-methyl-D-aspartate (NMDA) receptors, both of which play critical roles in neuronal excitability and seizure activity.[2] Targeting VGSCs is a well-established mechanism of action for many currently available AEDs, making this a plausible and promising avenue for the anticonvulsant effects of benzotriazole derivatives. The specific structure-activity relationship finding that links the length of alkyl chains to VGSC interaction provides valuable information for the future rational design and optimization of more potent benzotriazole-based anticonvulsants that target these channels.

Another significant mechanism under investigation is the potential of benzotriazole derivatives to enhance GABAergic neurotransmission.[1] GABA is the primary inhibitory neurotransmitter in the brain, and enhancing its activity can help to suppress excessive neuronal firing that leads to seizures. Research has indicated the involvement of GABA receptors in the anticonvulsant activity of certain benzotriazole derivatives.[1] For example, studies on compound 6d, a triazolopyrimidine derivative, have confirmed its interaction with GABA receptors, specifically the benzodiazepine (BZD) receptor subtype.[1] Benzodiazepines are a class of well-known anticonvulsant drugs that exert their effects by binding to and modulating GABA receptors.[25] This suggests that some benzotriazole derivatives may work through a mechanism similar to benzodiazepines, which are effective in controlling seizures but are also associated with side effects such as sedation.

Beyond these primary mechanisms, other potential modes of action have been proposed. Some studies suggest that certain benzotriazole derivatives might exert their anticonvulsant effects by increasing the levels of GABA in the brain.[28] Additionally, research on triazole-grafted benzenesulfonamide derivatives has proposed the inhibition of carbonic anhydrase isoforms II and VII, enzymes implicated in epilepsy, as a potential mechanism of action.[57] The variety of proposed mechanisms of action highlights the complexity of epilepsy and suggests that benzotriazole derivatives may possess the ability to act through different path-

ways, potentially leading to broader efficacy across various seizure types or the ability to target specific subtypes of epilepsy more effectively.

5. Structure-Activity Relationship (SAR) Studies

Structure-activity relationship (SAR) studies aim to identify the specific structural features of a molecule that are responsible for its biological activity. In the context of benzotriazole derivatives and epilepsy, several key SAR findings have emerged from recent research. Studies on triazole derivatives, which share a core triazole ring with benzotriazole, have demonstrated that the length and nature of alkyl chains attached to the triazole ring are critical determinants of anticonvulsant activity and the ability to interact with voltage-gated sodium channels (VGSCs).[3] Specifically, unbranched alkyl chains of certain lengths have been found to be crucial for both efficacy and VGSC interaction.[3] This finding provides a specific structural motif that can be further explored and optimized in the design of more potent benzotriazole-based anticonvulsants that target VGSCs.

In studies involving benzothiazole-urea derivatives, which are structurally related heterocyclic compounds, specific substitutions on the aromatic rings have been linked to anticonvulsant activity.[44] For example, the presence of a chlorine atom on the benzyl thiol ring and a bromine atom on the phenyl urea ring were associated with good anticonvulsant activity in these compounds.[44] This observation suggests that the strategic placement of specific substituents on the aromatic portions of related heterocyclic compounds can significantly influence their ability to control seizures, implying that similar principles might be applicable to the design of benzotriazole derivatives with enhanced efficacy.

Furthermore, research has shown that combining the 3-mercapto-1,2,4-triazole and benzothiazole chemical moieties with an amide linkage has resulted in the synthesis of potent anticonvulsant compounds.[29] This finding suggests that the creation of hybrid molecules that incorporate the benzotriazole scaffold with other known pharmacophores, which are structural features known to confer biological activity, could be a promising strategy for the development of novel AEDs with improved properties.

Finally, it is important to note that benzotriazole itself can function as a "tagging molecule" [4], meaning it can be used to deliver other pharmacologically active heterocyclic nuclei to their targets within the body. This strategy has the potential to enhance the anticonvulsant properties of these other molecules by improving their pharmacokinetic characteristics, such as absorption, distribution, metabolism, and excretion, or by increasing their specificity for particular targets in the central nervous system.

6. Toxicity and Safety Assessment

An important aspect of evaluating the potential of any new therapeutic agent is the assessment of its toxicity and safety profile. Preclinical studies on benzotriazole derivatives have generally indicated a relatively low level of toxicity.[3] In several instances, compounds that demonstrated high anticonvulsant activity in the MES and scPTZ seizure models did not exhibit observable neurotoxic effects at the doses tested in animal models.[2] For example, the previously mentioned compound BTA 9, which showed promising anti-MES activity, did not cause neurotoxicity in the Rotorod test, a common assessment of motor coordination and balance in rodents.[5] Similarly, compound 4g, a triazolone derivative, demonstrated a higher protective index, which is a measure of the drug's efficacy relative to its toxicity, compared to established AEDs like carbamazepine and valproate.[28] The indication of low neurotoxicity in several promising benzotriazole derivatives is an encouraging sign for their potential translation into clinical use, as it suggests the possibility of a better safety profile compared to some currently available AEDs, which are known to cause a range of side effects. Furthermore, some benzotriazole derivatives have shown comparable or even better protective indices than standard drugs such as phenytoin, phenobarbital, carbamazepine, and valproate in preclinical models.[1] A superior protective index suggests the potential for a wider therapeutic window, meaning that a higher dose can be administered to achieve greater efficacy without causing significant toxic effects.

However, while the initial safety data for many

benzotriazole derivatives appear promising, it is crucial to emphasize that a thorough and comprehensive evaluation of the toxicity profile of each individual compound is absolutely necessary to identify any specific adverse effects that may arise. It is well-known that anticonvulsant drugs, as a general class, can be associated with various side effects, including drowsiness, dizziness, and cognitive impairment.[3] Therefore, despite the encouraging initial indications of safety observed in preclinical studies, it remains essential to conduct comprehensive preclinical toxicology studies to fully characterize the safety profile of any benzotriazole derivative that shows promise as a potential antiepileptic drug before considering its evaluation in human clinical trials.

7. Comparison with Existing Antiepileptic Drugs

When evaluating the potential of benzotriazole derivatives in the treatment of epilepsy, it is crucial to compare their efficacy, safety, and mechanisms of action with those of existing antiepileptic drugs (AEDs). In terms of efficacy, some benzotriazole derivatives, particularly triazolopyrimidines, have demonstrated anticonvulsant activity in preclinical models that is comparable to or even exceeds that of well-established AEDs such as valproate, carbamazepine, and diazepam.[1] Furthermore, certain compounds within this class have shown efficacy across a broad spectrum of different seizure models, suggesting a potential for controlling various types of seizures.[1] This potential for superior efficacy offers hope for patients with epilepsy who may not respond adequately to currently available treatments.

In terms of safety, several benzotriazole derivatives have exhibited lower levels of neurotoxicity and higher protective indices in animal studies when compared to conventional AEDs.[2] A better safety profile would represent a significant advantage in epilepsy management, potentially leading to improved patient compliance with medication regimens and an overall enhancement in their quality of life by minimizing drug-related side effects.

Regarding the mechanisms of action, research suggests that benzotriazole derivatives may exert their anticonvulsant effects through pathways that are similar to those of some existing AEDs. These include the modulation of voltage-gated ion channels, which are critical for neuronal excitability, and the enhancement of GABAergic neurotransmission, the brain's primary inhibitory system.[1] A thorough understanding of the precise mechanisms by which these derivatives act is crucial for predicting potential drug interactions if they were to be used in combination with other medications, and also for the rational design of even more effective and targeted therapies for epilepsy in the future.

8. Future Directions and Potential Clinical Relevance

The promising findings from recent research on benzotriazole derivatives in preclinical models of epilepsy warrant further investigation to fully realize their therapeutic potential. Continued research efforts should focus on several key areas. Firstly, it is essential to fully elucidate the precise mechanisms of action by which these compounds exert their anticonvulsant effects at the molecular and cellular levels.[3] This deeper understanding will not only aid in predicting their pharmacological properties and potential interactions but also guide the rational design of even more effective derivatives. Secondly, further studies are needed to optimize the structure-activity relationships of the most promising compounds. By systematically modifying their chemical structures and evaluating the resulting changes in anticonvulsant activity and safety, researchers can identify the key structural features that contribute to their efficacy and minimize potential side effects. Thirdly, comprehensive pharmacokinetic studies are necessary to determine how these compounds are absorbed, distributed, metabolized, and excreted by the body. This information is crucial for predicting their dosage requirements and potential for drug interactions in humans. Finally, thorough toxicological studies must be conducted to fully characterize their safety profiles before they can be considered for clinical trials.

Looking ahead, future research could also focus on evaluating the efficacy of specific benzotriazole derivatives in animal models that closely mimic different epilepsy syndromes observed in humans. This targeted approach

could help to determine their potential for treating specific types of epilepsy, potentially leading to more personalized and effective therapeutic strategies. Given the inherent versatility of the benzotriazole scaffold, which allows for a wide range of structural modifications, continued exploration of novel derivatives holds significant promise for the discovery of even more potent and safer anticonvulsant agents.[4] Ultimately, if the results from these continued preclinical investigations remain promising and demonstrate a favorable balance of efficacy and safety, selected benzotriazole derivatives could advance to clinical trials in human patients with epilepsy. Successful clinical trials would represent a substantial step forward in the development of new and much-needed treatment options for individuals living with this challenging neurological disorder.

9. Conclusion

Recent research has compellingly highlighted the significant potential of benzotriazole derivatives as a novel class of anticonvulsant agents. Numerous derivatives have demonstrated promising efficacy in preclinical animal models of seizures, often exhibiting low toxicity and favorable protective indices when compared to currently available antiepileptic drugs. These findings suggest that benzotriazole derivatives represent a promising and exciting area of ongoing research for the development of new and improved therapies for epilepsy. Continued and dedicated investigation into their mechanisms of action, structure-activity relationships, pharmacokinetic properties, and safety profiles is warranted to fully unlock their therapeutic potential and ultimately translate these encouraging preclinical findings into tangible clinical benefits for patients affected by epilepsy.

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