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BENZOTHIAZOLE - PHARMACOLOGICAL ACTIVITIES IN EPILEPSY

Mr. V. Bharathraj[1], Dr. P. Udhayakumar[2]

[1]B. Pharm Final Year Student, (P.S.V College Of Pharmaceutical Science And Research, Krishnagiri – 635001, Tamilnadu, India.

[2]Assistant Professor, (P.S.V College Of Pharmaceutical Science And Research, Krishnagiri – 635001, Tamilnadu, India.

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ABSTRACT

The study investigates the potential use of benzothiazole derivatives as new anticonvulsant drugs, concentrating on their pharmacological mechanisms, effectiveness in seizure models, and therapeutic benefits compared to existing antiepileptic medications (AEDs). An exhaustive review of synthetic benzothiazole compounds was performed, integrating molecular docking, structure-activity relationship (SAR) analysis, and preclinical evaluations using maximal electroshock (MES) and subcutaneous pentylenetetrazol (scPTZ) models. Computational methods, such as virtual screening and pharmacophore modeling, were utilized to estimate binding affinities and neurochemical interactions. Benzothiazole derivatives showed significant anticonvulsant activity, with compounds 7a, 7f, and 8b demonstrating protective effects similar to phenytoin in MES assessments. Substituents that donate electrons (e.g., −CH3, −Cl) improved lipophilicity and efficacy. Investigations into the mechanisms revealed that GABAergic modulation, glutamate suppression, and ion channel stabilization are crucial pathways. The toxicity profiles were positive, with minimal neurotoxicity noted in chronic trials. Benzothiazoles offer a promising framework for the development of safer, multitarget AEDs that also provide neuroprotective advantages. Further clinical validation is needed to tackle refractory epilepsy and reduce side effects linked to traditional treatments.

Keywords: *Benzothiazole derivatives, Anticonvulsant agents, Molecular docking, MES model, GABA modulation, Epilepsy treatment.*

1. INTRODUCTION

Epilepsy is a neurological disorder that is often linked to stigma and mental health challenges.Meta-analyses of community-based studies suggest that up to 3 million adults in the United States have active epilepsy, which corresponds to a point prevalence of approximately 1.1% of the adult population. Epilepsy, as defined by The International League Against Epilepsy, affects approximately 80% of all people with epilepsy in both low and middle-income countries (LMIC) and high-income countries (HIC).Currently, barbiturates and benzodiazepines are the most widely used AEDs. But for the other 70%, these drugs don't prevent seizures. Newer AEDs (eg, lamotrigine, vigabatrin, pregabalin, levetiracetam, and gabapentin) are also seeing a rise in prescription, but the neurotoxicity, hirsutism, nausea, weight gain, and gastrointestinal side effects are no less.

Phenobarbital is a first line drug in Indian children with epilepsy. The CSA varies between seizure type and person, including tolerance and retention, respectively. The anticonvulsants drugs marketed in India are also Keppra/Spritam, Topamax, Lamictal, and Trileptal etc., Great interest is also concentrated on benzothiazoles type of heterocyclic compounds, due to their significant biological activities and are used as a leading compound for the design of drug in future.

Studies are investigating these compounds for potential applications in the treatment of numerous diseases and targeted therapies. 1,3,4-Oxadiazole is a heterocycle with the formula $C_2H_2N_2O$, which is classified as an azole.

Of the four isomers, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole are being of great pharmaceutical value, different drugs like fenadiazole, raltegravir, oxalamine and pleconaril are synthesized from these compounds. The standard routes to novel drug discovery are time-consuming and expensive: in order to complement the disadvantages of the traditional strategies, simple and rational methods that enable us to obtain some structure information via virtual screening have been established.

Virtual screening techniques can be used in both structure-based and ligand-based drug design. Structure-based methods for drug design reveal molecular connectivity, while ligand-based methods consider the connection between QSAR (quantitative structure-activity relationship) and pharmacophore modeling. The molecular docking technique examines the interaction between a compound and its target molecule. It predicts how these molecules will interact and the binding affinity that allows them to form a stable supramolecular complex. This is achieved by determining the most stable orientation based on low free energy.

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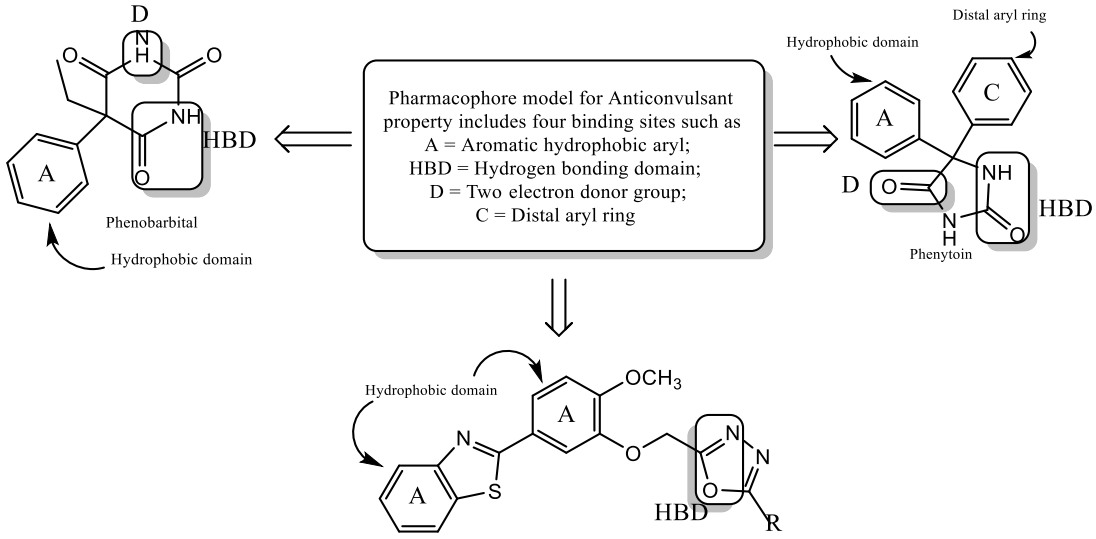
In spite of the shape complementarity and simulation, molecular docking may still fall into three different classes of categories. The present study was designated to explore in silico molecular docking of some newly synthesized benzothiazole derivatives as potent anticonvulsant agents. It is commonly used in the bioorganlc and medicinal chemistry fields as a reagent for product synthesis. Sulfur and nitrogen atoms are the vital constituents of thiazole and other pharmacologically and biologically active compounds. The 1,3-benzothiazole ring has been confirmed as a flexible pharmacophore with mechanism of action mediated by increasing overall brain levels of GABA (possibly by inhibiting the enzyme Gamma-aminobutyric acid aminotransferase (GABA-AT))



2-[4-Methoxy-3-(5-sibstituted-[1,3,4]oxadiazol-2-ylmethoxy)-phenyl]-benzothiazole (6a-n)

Fig 1:

Activity of Anti-epilepsy drug and using MES method also involved:

The preparation of a number of N-{[(6-substituted-1,3-benzothiazole-2-yl)amino]carbonothioyl}-2/4-Substituted benzamides has been found to be significant against convulsions when tested on the known animal models (MES and scPTZ).

Subsequently synthesized derivative with H, 2-Cl and 4-Cl substitution at various positions in benzothiazole nucleus was reported to be more potent.

1-(4-substituted phenyl) ethan-1-one-N-(6-substituted-1,3-benzothiazol-2-yl) semicarbazones were also prepared and investigation of their anti-convulsant activity was carried out.

Derivatives with higher lipophilic substitutions, namely -CH_3 and -Cl on benzothi- azole ring, have been found to be more protective, the study demonstrated. In addition, the -NO_2 group substituted at the distal aryl ring of the analogues was superior to the -OH group on the hydrophobic aryl ring to the MES animal model.

In addition, the design of novel benzothiazolyl guanidines as anticonvulsants was explored. The 4-CH_3 and 4-Cl derivatives demonstrated a protective action in the MES test, scPTZ and partially against strychnine-induced seizures.

Finally, the anticonvulsant activity and synthesis of 2-(4-arylthiosemicarbazidocarbonylthio)-benzothiazoles was performed on pentylenetetrazole induced convulsions in mice. A large number of 2-amastigote(3H)benzothiazolone analogues was prepared and tested for protection against convulsions in mice and many of them showed significant protection.

Mice were shocked with a current of 48 mA for 2 seconds by ear electrodes, after 60 min of receiving the test preparation. The standard reference was Phenytoin. Compounds 7a, 7f and 8b were shown to be potent amongst the tested compounds in mice at a dose of 200 mg/kg. The reference phenytoin inhibited the seizures in the mice in 4.36 s, while compounds 7a and 7f acted in 4.62 and 4.44 s. Compound 8b also displayed a significantly extended duration of seizure inhibition (6.37 s compared to control). 27 Compounds with electron releasing groups attached to the benzothiazole ring had significant activity unlike all of the other compounds.

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Table 1:

Group	Onset of action(sec) mean ± SEM	Total durations(sec) mean ± SEM	% of protection
7a	2.635 (± 0.80)	30.1(± 2.73)**	50%
7f	4.447(±1.16)*	35.8(± 3.10)**	66.66%
8b	6.3725 (±1.86)**	51.76(± 2.23)	50%

Pharmacological activites :

1. **Partial seizures :** (simple partial seizures) (eg, jacksonian), in affects one part of the body at onset, Focal with motor, sensory or speech signs, localized in a limited area of the body or single muscle group, Seizure-symptoms do not change over time, No alternation of consciousness.

2. Complex partial seizures : (Temporal Lobe epilepsy or Psychomotor Seizures) Causes confusion and strange,rural or dazed behavior. Movement exists as non-reflex function. Automatisms repetitive coordinated movements.Conciousness is impaired or lost. Site at which the seizure originates. Found in 40% of epileptic syndromes.

A) A Generalized Tonic-Clonic Seizures : Trace recruitment of neurons in the entire cerebrum. General convulsions (generally there in 2 stages: Tonic and Clonic) Seizure: Motoric symptom, May or may not be accompanied by motor, Excessive neuronal discharge. Convulsion are a feature of simple partial (Jacksonian) and complex partial (psychomotor) seizure, among which the focal neuronal discharge involve motor centres, occur in all generalized tonic – clonic seizure irrespective of the source of origin ;

And atonic, akinetic, absences of seizures are non-convulsive(Tonic phase: maintained muscular contraction powerful comprising all body musculature in which breath holding.) (ClONlc PHASE: The plunging action alternating with reflex relaxation leads to a back and forth movement, which may be bilateral (or) progressive movement.

This is the most frequent and most severe type of epilepsy. It start with tonic extension of trunk and limbs (tonic phase) that last 10-20 sec, then is follow by rhythmic contraction of the extremities (clonic phase). Absent of consciousness and autonomic signs; followed by a period of confusion and exhaustion which may last for several minutes after the seizures episodes; do not usually respond to anticonvulsant treatment.

B) Absence seizures (Petite mal) : sudden and transient loss of consciouness, absent look, may be with on motor component. Mild twitching limited to eyes and/or face, usual: 2.5-3.5 Hz spike-and-wave, often brief or rare (5-10 sec), but may cluster many times per day; no loss of postural control.

C) Tonic Seizures : Opisthotonus, loss of consciousness, Marked autonomic features.

D) Atonic Seizures (atypical) : Loss of muscle tone, with head dropping / falling, Can loss consciousness, -Children.

E) Clonic Seizures : Clonic seizure; Rhythmic clonic contraction on all muscles, loss of consciousness, with marked autonomic manifestations.

F) Myoclonic Seizures : Isolated clonic jerks, transient shock like muscle contraction involving only one part / one extremity accompanied by rapid, repetitive jagged spike-waves.

G) Infantile spasms : Epileptic syndrome, attacks although incomplete are usually bilateral. Consists of the brief myoclonic body jerks of sudden flexion or extension of body and limbs.

Cellular Mechanisms of Epileptic Seizures :

1. **Excitation (too much) :** ionic inward Na^+ (2) Ca^{++} currents (4) Neurotransmitter : glutamate, aspartate.
2. **Inhibition (too little) :** About Ionic inward Cl; outward K^+ currents, Neurotransmitter : GABA

Treatment of Seizures:

Goals :

Block repetitive neuronal firing ,

Block synchronization of neuronal discharges,

Block propagation of seizures.

Control side effects of drug with the easiest regimen.

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Most patients are treated with : →

Monotherapy is recommend in most cases :

Strategies :

- Modification of ion conductances,
- Increase inhibition (GABA) transmission,
- Decrease excitatory (glutamatergic) activity.

Drug of phenobarbital ;

- It is deemed to be one of the safest drugs, and its has sedative effects.
- If most use them as the drug of choice for seizure, though only in infant
- Beneficial for the partial, generalized tonic and clonic seizures, and febrile seizures.
- If they opening (Cl+) calcium channels.
- And blocks excitatory GLU (AMPA) responses,
- Blocks Ca2+ current (L,N).
- Suppresses the repetitive high frequency firing of neurons exclusively at the high concentrations.

Toxicity:

Sedation, Cognitive impairment, behavioral changes, induction of the liver enzymes, and may exacerbate absence and atonic seizu

Terms & Condition of Epilepticus :

Status epilepticus is when there are recurring seizures within a brief span of time, e.g., baseline consciousness is never regained between the seizures. They are lasting for a minimum of 30 min. Can result in systemic hypoxia, acidemia, hyperpyrexia, cardiovascular collapse, and renal failure.

The most frequent generalized tonic-clonic status epilepticus is life-threatening and should be treated as soon as possible with concomitant cardiovascular, respiratory and metabolic management.

Treatment of status epilepticus in adult :

Intial :

a. Diazepam (5-10 mg, (1-2 mg/min)), repeat dose (5-10 mg, every 20-30 min).
b. Lorazepam (2-6 mg, (1 mg/min)), repeat dose (2-6 mg, every 20-30 min) .
c. Phenobarbital (10-20 mg/Kg (25-30 mg/min)), repeat dose (120-240 mg) every 20 min).

Infantile spasms :

The attack while occasionally fragmentary are, most commonly, bilateral and combined for practical reasons with the generalized seizures.

Characterized by the recurrent myoclonic jerks with sudden flexions or extension of body and limbs; the form of infantile spasms, however quite heterogeneous. And most patients are mentally retarded, presumably from the same cause of the spasms.

Treatment Protocols :

In clinical settings, epilepsy is treated with daily doses that vary between 200 and 1200 mg per day, administered in one or two divided doses.The process of determining the optimal dosage commences with relatively low levels, as the patient's response is carefully monitored over time. In spite of the availability of many synthetic drugs with the potential to control epileptic seizures, their toxicity and pharmacokinetic profiles tend to restrict their use in acute clinical settings.

Therefore, a large number of research projects have been devoted to the finding of novel safe and efficient anticonvulsants for the treatment of epilepsy. In the therapeutic area of epilepsy, benzothiazole and derivatives thereof have been recognized as substances possessing the ability to inhibit epileptic seizures by mechanisms that include neurotransmitters, hormonal levels, or antioxidant activities.

Apart from their application in epilepsy management, these substances also exhibit wider biological activities, such as anticonvulsant, antiallergic, antitubercular, and anti-inflammatory activity.

The anticonvulsant effect in epilepsy is mediated by modulating excitatory and inhibitory neurotransmitters-glutamate and gamma-aminobutyric acid (GABA), respectively-and by modulating the activity of sodium, calcium, and potassium ion channels in neuronal membranes.

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Safety and Toxicology:

Studies of safety and toxicology in benzothiazole derivatives revealed that repeated-administration treatments yield no abnormal clinical observations and subtle changes in sleep duration, though with a slight reduction of body weight gain at elevated doses.

Subacute toxicity tests for all derivatives show identical biochemical profiles.

Behavioral and neurochemical toxicity studies reveal that some compounds, e.g., antioxidant-based 2-arylbenzothiazole derivatives, are not neurotoxic and do not impair cerebrovascular function in a negative way.

Additionally, subchronic and chronic toxicity studies show very few signs of adverse effects in rodents and dogs and an excellent safety profile equivalent to clobazam. The clinically effective antiepileptic LCS-1 has demonstrated both anticonvulsant and neuroprotective activity; however, its chronic administration in animals needs tolerance and toxicity monitoring.

Anticonvulsant and possible anticonvulsant activities of related compounds have also been tested using induced convulsion models, expanding their utility to neurodegenerative disorders involving oxidative stress and inflammation. Biochemical experiments show that metabolism through the glutathione-dependent mercapturic acid pathway is not expected to hinder the clinical cancer chemopreventive activity of 2-arylbenzothiazoles.

These results reinforce the active involvement of benzothiazole derivatives in epilepsy and related central nervous system disorders.

Recent Research Developments:

New Benzothiazole Derivatives ;

Pharmacological activities against several diseases, such as antibacterial, oral contraceptive, and carbonic anhydrase inhibitor, have been reported for 2-mercaptobenzothiazole derivatives. Chen et al. subsequently synthesized 2-mercaptobenzothiazole derivatives containing a pyrazole fragment and evaluated their anticonvulsant activity.

Compound 26 demonstrated the most potent activity against maximal electroshock seizures, surpassing that of carbamazepine. Jiang et al. synthesized benzothiazole derivatives substituted with pyrazole fragments, and compound 27 exhibited the strongest anticonvulsant activity, with an ED50 value of 49 mg/kg in the PTZ test and a protective index of 10.2, exceeding the activity of valproate.

Recent Clinical Trials:

The anticonvulsant properties of benzothiazole derivatives have also been explored in several clinical trials. Kahn conducted a controlled trial to evaluate the anticonvulsant effect of the benzothiazole derivative, SDB-VS-201 in refractory epileptic patients; this investigation assessed related behavioral disorders and potential toxicological side effects. Moreover, Amit et al. carried out a clinical investigation on the pharmacokinetics and urinary excretion of the benzothiazole derivative R 78 998 in healthy male volunteers following single and multiple oral doses.

Clinical Trials :

Antiepileptic drugs are typically viewed as the most suitable treatment option for epilepsy. However, in many patients, these drugs produce undesirable adverse effects. Although these adverse effects vary in their severity, they can have a serious impact on a patient's quality of life. Current research therefore focuses on the development of anticonvulsant agents with improved profiles of effectiveness and side effects.

Benzothiazole, a nitrogen–sulfur heterocyclic compound, is a promising pharmacophore that forms the basis of many clinically prescribed drugs for various diseases. In experimental models of epilepsy, benzothiazole derivatives have demonstrated anticonvulsant activity. The major mechanism underlying these effects is the regulation of the balance between excitatory and inhibitory neurotransmitters.

Benzothiazole derivatives also exhibit neuroprotective, antioxidant, and anti-inflammatory effects. For deeper insight, comprehensive studies have been conducted to develop novel anticonvulsant agents derived from this nucleus. Benzothiazole displays significant anticonvulsant properties by altering the functional state of ion channels. The latter property influences the pharmacokinetic profile and the absorption and distribution of this drug in target tissues. Benzothiazole derivatives are employed to treat focal and generalized epilepsies and are frequently used in combination with other agents.

Clinical Phases of Benzothiazole Study:

The development of benzothiazole as an anti-epileptic drug has been a deliberate one. For a first preclinical step, the drug needs first to show a suppressant effect on seizures in seizure animal models, and to have a good toxicology profile. Preliminary testing in animal models is performed during the pre-clinical phase to study these properties.

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The phase I studies are then followed by administration to a small number of healthy volunteers to determine the maximum tolerated dose with evaluation for pharmacokinetics, absorption, distribution in body fluids, metabolism, and elimination. Phase II trials have two goals: to identify the optimal dose, in terms of both efficacy and toxicity, and to provide preliminary evidence of efficacy within the target population of patients. Phase III trials are intended to corroborate the therapeutic index and assess late toxicity.

Any drug that shows reasonable efficacy in epilepsy also implicates a block in the pilocarpine-induced seizures. Benzothiazole is still under investigation for epilepsy therapy but its side effects, such as rashes, pyrexia, leucopenia, multi-organ insufficiency, angioedema, and serum sickness, have caused it to lose ground as a first-line drug.

The severity of these side effects differ from person to person, but can be life threatening. Against this background, currently benzothiazole stands in the third line of antiepileptic drugs with a special indication in certain refractory forms of epilepsy.

Preclinical Trials:

At this point in time benzothiazole is investigated in epilepsy, but is not registered for this condition. It finds application in various other applications. Several animal studies had demonstrated the compound's efficacy in epilepsy.

Its MOA has been well characterized, as have its PK properties. This fact is all the more exciting since the preclinical experience with benzothiazole has been developed and advanced in a way that closely resembles that of the more recent AEDs (levetiracetam, tiagabine, topiramate, lamotrigine, zonisamide).

In many cases, antiepileptic drugs are analogs of an endogenous compound. Preclinical development, a molecule in a new chemical class usually begins as an idea or an hypothesis in the lab and progresses through basic research to phase an stage of preclinical in vitro (isolated tissues) and in vivo (animal) test to provide some initial data about the new drug and establish safety and tolerability).

If candidates pass preclinical testing, they enter the clinical stages of testing, which tests the new compound in humans for effectiveness and safety.For epilepsy, animal experiments are needed to do proof of concept studies.

Key objectives in prospective analyses are:

1. The mechanism of action of the test compound;
2. The epilepsy syndrome that can be considered sensitive; and
3. The dose range to be effective in man and consequently the dose to be applied to man upon initiation of clinical trials (usually referred to as the „dose of first administration").

Phase I Trials:

First-in-man studies are the first stage of testing in human subjects. The purpose of these trials to define the safety, tolerability, pharmacokinetics and pharmacodynamics of the new agent. They are typically carried out in a single cohort and often in healthy volunteers (though exceptions may exist for interventions in which high immediate risk is known). The length of this stage differs and is determined essentially by the agent's half-life and the study performed.

To date, none of the ~30 benzothiazole based derivatives have advanced to Phase I trials which represents the initial phase of clinical assessment. These are studies in which the normal tolerance of the drug is evaluated by giving it to healthy volunteers.

The first time use in human of new medicinal products is regulated by regulatory authorities worldwide; for example, the USFDA is responsible for approval of new active substances, biological drugs, new dosage forms and formulation change (fixed-dose combinations). A new patent involves a benzothiazole-albumin conjugate intended for the treatment of primary brain disorders, such a Parkinson's disease and epilepsy.

Phase II Trials:

A sulfhydryl-substituted derivative of benzothiazole, which is a valuable compound in its own right, is designated as an antiseizure agent in the Naturally Occurring Anticonvulsant Drugs Category.

Epilepsy affects approximately 1% of the population, with a significant proportion being children, and constitutes a disorder of the central nervous system. It is marked by repeated seizures arising from abnormal and excessive nerve discharges, resulting in disturbances of consciousness or sensory and motor anomalies. Selenium, a trace element exhibiting antioxidant effects, has been proposed as a potential agent in the prophylaxis of several neurological disorders.

Benzothiazole is currently in clinical development for the treatment of epilepsy. Phase II trials evaluate the effectiveness of a new treatment for a specific condition in patients, with closely monitoring for safety. Similar to

other novel agents, benzothiazole also exhibits some side effects when used to treat refractory epilepsy. The Phase II stage of clinical development forms part of the regulatory process governing drug approvals.

Phase III Trials:

The third phase of research, the phase III trial(s), demands that the trial should be well conducted in a way appropriate to define the benefit/risk ratio of the drug for the target indication and to offer a sound basis for an estimation of the overall benefit/risk ratio of the drug. Phase III trials are generally performed in the general population and with longer duration of therapy compared to phase II trials. Inconclusive or negative findings are as useful as positive findings in phase III trials.

Special care must be taken in defining the dose and the group because two doses (low and high) are used in most cases; the high dose is chosen with considerations of the effective dose range and the optimal efficacy/safety or tolerance ratio shown in phase II trials. An upper limit must also be found, beyond which the frequency of the unwanted effects is very likely to be unacceptable; such a ceiling dose is helpful to define even if the effective dose has not been reached.

The low dose is often a fraction of the high dose or the lowest effective dose. A single trial success is theoretically enough for approval, but a second trial is normally run unless the first trial was a large group of patients in an appropriately characterized population. Such postapproval studies can be conceived as being phase IV trials.

Case Studies:

A rapid, direct, and hematin-sensitive assay known as the five ookinete-motility assay (FSOMA) was created for high and medium-throughput screening of compounds that prevent the transmission of the Plasmodium parasite from humans to mosquito vectors. FSOMA facilitates the screening of a large number of substances to pinpoint those that impede the locomotion of ookinetes.

This assay employs light microscopy along with a computer-controlled image-processing program to evaluate the path lengths of ookinetes.FSOMA assesses the effect of chemotherapy, gene knockdown, or gene knockout on the motility of ookinetes by utilizing a parasite gene-regulation system.

Mature ookinetes, cultured in vitro and purified from Pbs16-GFP STAT-transgenic Plasmodium berghei, are placed into 96-well microtiter plates either with or without experimental compounds. Observations are made using a light microscope at a 4× magnification, and recordings of motile ookinetes are captured in 45-second video segments using a camera attached to the microscope.

The assay is performed at temperatures between 20–21 °C. Despite control measures like insecticides, disease vectors continue to survive.New insecticides, repellents, and delivery systems of these compounds to repellent vectors are needed.

2. CONCLUSION

The benzothiazole system holds promise for the development of new anticonvulsant medications with neuroprotective and antioxidant actions. Epilepsy, which is caused by abnormal electric brain activity, interferes with consciousness and mental patterns. While there are many anticonvulsant medications available, their efficacy is primarily focused on pharmacodynamics, and some of the benzothiazoles exhibit pertinent anticonvulsant activity. Other anticonvulsant medications include GABA-agonists that act on GABA receptor sites and anticonvulsants that influence sodium ion channels.

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