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A STUDY OF SYNTHESIZE 1, 5 BENZOTHIAZEPINE DERIVATIVES FROM ACETOPHENONE AND SUBSTITUTED ALDEHYDE

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ABSTRCT
Since the synthesis of anticonvulsant drugs based on 1,5-benzothiazepine derivatives from acetophenone and substituted aldehyde is very straightforward, there has been a lot of attention in the field of medicinal chemistry. More effective, safer, and more patient-friendly anticonvulsant drugs are needed, and this study aimed to contribute to that effort. Epilepsy is a neurological disorder that affects millions of people worldwide and results in recurrent seizures. Although several anticonvulsant drugs are available today, many of them have significant limitations. Therefore, there is an urgent need for the development of new anticonvulsant medicines with enhanced therapeutic qualities. The 1,5-benzothiazepine derivatives are an interesting class of compounds because they may be effective as anticonvulsants. These compounds have a peculiar chemical structure, which means that the pharmacological effects may be modified by adding different substituents to the benzene ring. This variety in molecular structure permits optimal biological activity, selectivity, and physical properties to be engineered.

KEYWORDS:- Benzothiazepine Derivatives, Acetophenone, Substituted Aldehyde, anticonvulsant drugs, biological activity, molecular structure, pharmacological effects

INTRODUCTION

Epilepsy has been a major health problem for humans practically since the beginning of written history, as evidenced by the earliest medical records. Historically, people had a spiritual explanation for the ailment. An ancient Akkadian literature, written approximately 2000 BC, has the first known description of an epileptic patient. People who suffer from epileptic seizures are mentioned in the Edwin Smith Papyrus (about 1700 BC).

The ancient Greeks held contrasting perspectives on epilepsy. They viewed epilepsy as a type of demonic possession, but they also connected it to brilliance and the divine. Bromide, the first truly successful anti-seizure medicine, was released around the middle of the 1800s. In 1912, barbiturates—the first modern treatment—were created, and by 1938, phenytoin had made a comeback[1].

When aberrant electrical activity begins in the brain, the result is epilepsy. There is a certain pattern to the electrical signals sent between brain cells. Seizures in epilepsy are brought on by a "electrical storm" caused by aberrant electrical impulses. Depending on the kind of epilepsy, these storms may be localized to a specific region of the brain or they may affect the entire brain [2].

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There is great variation in the manifestation and impact of seizures. Once the brain is stimulated by seizure discharges, normal brain activity can occur during a seizure. Some people refer to these occurrences as "electrical storms" (a burst of energy) in the brain. Sometimes it's hard to spot the causes of a seizure or separate them. The following stages and symptoms are not always present in people who experience seizures. Seizure symptoms are often stereotypical (happen in the same way each time), episodic (come and go), and sometimes unexpected.

"an episodic disturbance of movement, feeling, or consciousness caused by sudden synchronous, inappropriate, and excessive electrical discharges in the cerebral cortex" [3] describes what happens during a seizure. The patient's personal and professional life, such as their relationships, education, and career, may suffer as a result of epileptic seizures. Untreated epilepsy increases the chance of death by unexpected causes and is connected with physical and psychological disability, dependence, low quality of life, and premature mortality. Since the goal of treating epilepsy is to allow patients to lead as normal of a life as possible by completely controlling seizures with no or minimal side effects, antiepileptic drugs (AEDs) are commonly prescribed to patients as soon as they report experiencing more than one documented or witnessed seizure[4].

Injuries to a normally functioning brain, such as those caused by trauma, infection, ischemia, or the presence of a malformation or mass lesion, initiate the process of epileptogenesis. Some acute injury occurs with following gradual damage based on the patient's age and genetic history. Despite the brain's best efforts to heal itself, hyperexcitability and seizures can arise after a protracted delay (perhaps years)[5].

Epilepsy comes from the Greek epilamvanein, which means "to be seized" or "to be attacked" in English. These expressions are indicative of the mindset of the time, which believed that demonic spirits were to blame for this illness.[6]

HISTORY OF EPILEPSY

Epilepsy is said to be one of the first human ailments based on its depiction in early medical books. Myths and legends arose around the concept of epilepsy in ancient societies since its mechanism was unknown and its patients showed odd behavior. Epilepsy was originally referenced in ancient Indian medicine (about 4500-1500 B.C.). Epilepsy was described as "apasmara," which means "loss of consciousness," in India's traditional Ayurvedic medical practice.

Information on the symptom complex, aetiology, diagnosis, and treatment of epilepsy were all covered in depth [7] in this document.

Over three million years ago, ancient Babylonian scientists understood the causes and symptoms of epilepsy. Epilepsy was blamed on angering Selene, the Greek moon goddess, in ancient Greek mythology. Since the earliest documented connection between epilepsy and the brain was discovered by the Greek physician Hippocrates, renowned as the "Father of Medicine," about 400 B.C., he may have been the first to explain epilepsy using scientific reasoning. A new school of thought evolved throughout the Renaissance that demonic possession was not to blame for epilepsy. Some Romans believed epileptics to be prophetic or special because to the prevalence of the disorder among prominent Romans such as Julius

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Caesar and Petrarch. The prevalent assumption that epilepsy was contagious from the late 1600s onward led to the isolation of persons with the condition in mental institutions. Between the years 1858 and 1905, three Western neurologists—William Richard Gowers, Russell Reynolds, and John Hughlings Jackson—laid the framework for a more enlightened approach to epilepsy as a medical concern. According to Jackson, "a seizure is an occasional, excessive, and disorderly discharge of nerve tissue on muscles"[8].

Since then, many studies of the brain and the pathophysiology of epilepsy have been done, expanding our understanding of the disorder and ushering in the era of pharmacological intervention for its treatment.

EPIDEMIOLOGY OF EPILEPSY

The prevalence of epilepsy is estimated to be between 5 and 10 per 1,000 in a typical European population, excluding cases of single seizures and febrile convulsions in children [9]. The incidence rate of epilepsy is between 50 and 70 per 100,000 people per year in most developed countries.

Epilepsy is more common in developing countries than in developed ones, according to a recent research [10]; the likely median incidence of epilepsy is 43.4 per 100,000 people in affluent countries and 68.7 per 100,000 people in developing nations. In the developed world, the epilepsy incidence "U-shaped curve" peaks in young children and then again in the elderly around age 55. Higher rates of occurrence are seen in children and young adults than in the elderly are seen in the developing nations [11]. The incidence of a first seizure is 52–59 per 100,000 people between the ages of 40 and 59, and 127 per 100,000 people aged 60 and up [12]. The high prevalence of epilepsy in the elderly may be attributable to the common occurrence of epilepsy risk factors in people of retirement age. Most cases of epilepsy have vascular causes (such as stroke or a brain hemorrhage) [13]. Metabolic brain abnormalities, calcium metabolism problems, brain tumors, and degenerative diseases like Alzheimer's disease are other possible causes. The origin of some cases of epilepsy, known as cryptogenic, remains a mystery.

Regarding sex, the global population as a whole seems to agree that males (50.7/100,000) have a greater epilepsy incidence rate than females (46.2/100,000) (10). This difference between the sexes can be explained by the fact that women are less likely to be exposed to the risk factors of epilepsy, such as stroke (ischemic, hemorrhagic, etc.), brain traumas, and central nervous system infection; even seizures caused by alcohol are more common in males.

Latin America and several African countries were found to have an especially high incidence of epilepsy, possibly due to certain parasitic infections with brain involvement, perinatal brain damage, or hereditary factors, among developing countries with a higher incidence of epilepsy compared to developed ones[14].

Partial seizures, with or without subsequent generalization (localization-related epilepsies), make up the bulk of seizures across all age groups.

Four to ten people out of every thousand in the industrialized world have active epilepsy [16]. Conversely, the prevalence of active epilepsy varies widely among developing regions,

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with rates as high as 57 per 1,000 people in South America, 43 per 1,000 in Africa, and 1.5 per 1,000 in Asia [11].

The estimated number of people in Europe who are currently living with epilepsy is around 3.1 million (based on a prevalence of 6/1000), excluding Russia, Belarus, and Ukraine (due to a lack of data on the epidemiology of epilepsy in a large population) [17].

CLASSIFICATION OF SEIZURES AND EPILEPSY SYNDROMES

Patients with different types of epilepsy have different prognoses, thus it's important to correctly identify the patient's seizure type before deciding which AED to use. In terms of epileptic seizures (Commission, 1981) and epilepsy syndromes (Commission, 1989), the ILAE's categorization is the most widely utilized in clinical practice.

According to the International League Against Epilepsy (ILAE) categorization of epileptic seizures (Commission, 1981), they are separated into three groups: general, partial (localization-related), and unclassified seizures. Seizures that affect both hemispheres of the brain at once are called generalized seizures. The electrical discharge in partial seizures originates from isolated regions of the brain. Tonic-clonic seizures, absence seizures, myoclonic seizures, atonic seizures, tonic seizures, and clonic seizures are all subtypes of generalized seizures. However, partial seizures can be either simple, in which the patient's awareness remains unaffected, or complicated, in which the patient's consciousness is diminished throughout the seizure. Secondary generalization occurs when seizures that began as partial owing to a discharge from a focal in the brain spread to include the whole cerebral hemisphere.

Table 1. 1 International classification of epileptic seizures:

Seizures type	Description
Partial seizures (with localised onset)	Simple partial seizures (consciousness preserved) with motor symptoms with somatosensory or special sensory symptoms with autonomic symptoms with psychic symptoms
	Complex partial seizures (consciousness impaired) simple partial seizures onset followed by impaired consciousness impaired consciousness at onset
	Partial seizures with secondary generalized seizures
Generalised Seizures	Absence seizures (whether typical or atypical)
	Myoclonic seizures
	Clonic seizures
	Tonic seizures
	Tonic-clonic seizures
	Atonic seizures

Unclassified Seizures	Includes all seizures unclassified due to inadequate or incomplete data e.g. some neonatal seizures presented as rhythmic eye movements or chewing

A revised categorization, taking into account additional criteria than the 1981 one, was proposed by ILAE in 1989. Type of seizure; electroencephalogram (EEG); prognosis; pathophysiological and aetiological facts; genetics; year of diagnosis; etc. The three most common forms of seizures—generalized, partial, and unclassified—have been preserved in this new system. However, depending on the underlying etiology, epilepsy can be further classified as idiopathic, symptomatic, or cryptogenic. Epilepsy can be either idiopathic, where the cause is unknown, or symptomatic, when a problem in the central nervous system is to blame. Only disorders in which the underlying focal cause is unknown are classified as cryptogenic forms of epilepsy.

When looking at the aetiology of epilepsy, several different factors have been uncovered in these individuals' brains. Ischemia and hemorrhage are forms of cerebrovascular illness; other forms include trauma, tumors, infections of the brain (both bacterial and viral), degenerative diseases, and birth defects. About 40% of people with epilepsy had no identifiable cause [17].

Although these two categories are still in use today, the International League Against Epilepsy (ILAE) established them more than two decades ago, and this has prompted some epilepsy specialists to look for an updated version of seizures classification [18]. There is always a beginning, middle, and finish to a seizure.

Beginning

A seizure can occur at any time, although sometimes people have warning signs in the hours or days leading up to it. These sensations don't really happen during a seizure, but they can be a warning indicator. Although not everyone may experience these symptoms, being aware of them can help those who do adjust their level of activity, remember to take their medicine, make the most of a therapy, or take other precautions to avoid harm.

Middle:

The ictal phase is the time during a seizure when symptoms are at their worst. This is associated with the brain's electrical activity. In most cases, the duration of outward symptoms exceeds that of EEG seizure activity. Some of the outward signs may be secondary to a seizure or unrelated to it altogether.

Common Symptoms during middle of the Seizure.

Awareness, Sensory, Emotional or Thought Changes:

- Unawareness (often called “black out”)
- Confused
- Periods of forgetfulness or memory lapses
- Distracted, daydreaming
- Loss of consciousness, unconscious
- Low to hear

- Sounds may be strange / totally different
- Unusual smells (often unpleasant smells like burning rubber)
- Unusual tastes
- Loss of vision or unable to see
- Blurry vision
- Flashing lights
- Formed visual hallucinations
- Numbness, tingling
- Out of body sensations
- Feeling detached
- Feeling of panic, fear, (feeling that something bad will happen)
- Pleasant feelings

Physical Changes:

- Speech impairment (including stuttering, slurring, or incoherent utterances).
- Incapacity to swallow; Repetitive eye blinking, gaze shifting to the side or up, or fixed staring
- Weakness or loss of muscle tone (inability to move, loss of tone in the neck, which can cause the head to drop forward, and loss of muscular tone in the body, which can cause the person to droop or fall forward)
- Shaking, twitching, or jerking (may affect one or both sides of the face, arms, legs, or the entire body; may begin in one region and spread to others, or may be localized and remain constant)
- Muscle stiffness or tension (one can feel so tight all over that they could topple over if they tried to stand).
- Automatisms, or repetitive, involuntary motions, can affect any part of the body, including the face, arms, and legs.
- Repeated, deliberate motions (the affected individual may go on with the activity they were engaged in prior to the seizure).
- Convulsion (unconsciousness followed by rigidity and jerking motions)
- Unpredictable incontinence (of either pee or defecation)
- Sweating
- Change in skin color tone (looks pale or flushed)
- Pupils may dilate or seems larger than normal
- Biting of tongue
- Difficulty breathing
- Heart racing

Ending

The postictal phase marks the end of a seizure and the beginning of recovery. Some people seem to bounce back quickly, while for others it may take a few minutes or a few hours. The severity of the injury (how long it may persist and what may happen during it) and the kind of seizure both play a role in the amount of time it takes to recover.

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Typical Reactions to a Seizure.

Awareness, Sensory, Emotional, or Thought Changes:

- • Unable to respond quickly enough or at all
- Sleepy
- Confused
- Memory loss
- Difficulty talking or writing
- Feeling fuzzy, lightlheaded, or dizzy
- Feeling depressed, sad, upset
- Scared
- Anxious
- Frustrated, embarrassed, ashamed

Physical Changes:

- May have injuries, like cuts, broken bones, or head injury if fall in seizure
- May feel tired, exhausted.
- Headache or various other pain
- Nausea or dyspepsia
- Thirsty
- General weakness or weak in one part or side of the body
- Urge to go to the lavatory or lose control of bowel or bladder[19]

Symptoms of epilepsy

Symptoms differ from person to person and according to the different type of seizure.

Focal (partial) seizures

A simple partial seizure doesn‟t involve loss of consciousness. Symptoms include:

- Change in sense of taste, smell, sight, hearing, or touch
- dizziness
- tingling and cramp of limbs

Complex partial seizures show the loss of awareness or consciousness. Alternative symptoms include:

- staring without expression
- slow to response
- performing repetitive movements

Generalized seizures

Generalized seizures where whole brain is involve. There are six types:

Absence seizures, which used to be called “petit mal seizures,” cause a blank stare. This type of seizure may also cause repetitive movements like blinking etc. There‟s also typically a brief loss of awareness.

Tonic seizures cause muscle stiffness.

Atonic seizures cause loss of muscle control and can make people fall down suddenly.

Clonic seizures are characterized by repeated, jerky muscle movements of the face, neck, and arms.

Myoclonic seizures cause spontaneous sudden cramp of the arms and legs.

Tonic-clonic seizures used to be known "grand mal seizures." Where Symptoms include: Stiffening of the body, loss of bladder or bowel control, biting of the tongue and loss of consciousness etc.

Some people are able to identify things or some causes that can trigger seizures.

A few of the **commonly known triggers** are:

- lack of sleep
- illness or fever
- stress
- bright lights or flashing lights
- intake of caffeine, alcohol, medicines, or drugs
- skipping meals, overeating, or due to incompatibility specific food ingredients

Causes epilepsy [20]

It's possible that the reasons behind this shift with age. Six out of every ten persons who have epilepsy have no identifiable trigger for their condition.

There may be a hereditary kind of epilepsy that causes seizures in certain persons for no apparent reason.

Some infants and toddlers may be born with a structural defect in the brain that makes them more susceptible to developing epilepsy.

Brain infections are a common culprit. Though antibiotics can clear up the acute infection, the brain damage it might cause can lead to seizures in the road.

Although young adults are at the most risk for catastrophic brain injuries, anybody can suffer one.

Strokes, cancers, and injuries all tend to be more common in middle age.

Stroke is the leading cause of new-onset seizures in adults over the age of 65. Seizures can be brought on by a variety of illnesses, including brain disorders and Alzheimer's disease.

Common causes by age:

In Newborns:

- Brain malformations
- Lack of oxygen during birth
- Low levels of blood sugar or other electrolyte problems
- Inborn errors of metabolism
- Intracranial hemorrhage
- Maternal drug use In Infants and Children:
- Fever (febrile seizures)
- Brain tumor (rarely)
- Infections

In Children and Adults:

- Congenital conditions (Down's syndrome; Angelman's syndrome; tuberous sclerosis and neurofibromatosis)
- Genetic factors

- Progressive brain dysfunction (rare)
- Head trauma

In seniors:

- Stroke
- Alzheimer's disease
- Trauma

Mechanism

Neurons in the brain don't usually fire in sync with one another, but they do so in a systematic manner when messages go from one part of the brain to another. A wide variety of intracellular and extracellular variables control its function. The variety, abundance, and location of ion channels, as well as alterations in receptors and gene expression, are all important factors within neurons.

Although the precise cause of epileptic sickness remains unknown, its cellular and network processes have been somewhat elucidated. It is unclear, however, at what point the brain's excessive synchronization results in the activity of a seizure.

Neurons with epilepsy have a reduced threshold for firing when triggered. This may be the consequence of alterations in ion channels or abnormal inhibitory neuronal activity, and the resulting epileptic "seizure focus" is characterized by a localized location from which seizures originate. Seizures can occur for a variety of reasons, including the up-regulation of excitatory circuits or the down-regulation of inhibitory circuits that may occur after brain damage. Epileptogenesis refers to the mechanisms that cause these subsequent forms of epilepsy. The breakdown of the blood-brain barrier, which would allow chemicals in the blood to enter the brain, might possibly be a contributing factor.

Epilepsy is not a random phenomenon, but there is some evidence to suggest otherwise. Stress, alcoholism, flashing lights, lack of sleep, and other sleep disturbances are common triggers for seizures.

CONCLUSION

Using computational methods, the purpose of this study is to examine the pharmacokinetics, drug-likeness, and toxicity of synthesized antiepileptic compounds based on the concept of several physiochemical parameters. Our ADMET studies allow us to evaluate a set of anticonvulsant lead compounds and determine which desirable parameter is crucial for future lead optimization efforts. The evaluation in silico confirmed that the compounds possessed "druglike" properties.

All specified substances have appropriate molecular weights (MWT 500). Compared to compounds with a high molecular weight, low molecular weight molecules are more readily ingested, diffused, and transported. There is no violation of Lipinski's rule of five because the number of H-bond acceptors and H-bond donors in each of the chosen antiepileptic derivatives falls within the permissible range.

The drug-likeness, log P, molecular weight, and PSA of the synthesized compounds were determined, revealing their overall potential as drug candidates.

A few numbers indicate greater drug similarity within the acceptable range. The designed compounds have molecular weights between 311-450 dalton. Fifty designed compounds

exhibited one Lipinski violation with pharmacological properties comparable to 90% of available medications with high to moderate oral bioavailability. If Lipinski violation is greater than one, there is an issue with oral bioavailability.

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