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Research Article

Design and Synthesis of Benzotriazole Derivatives for Anti-convulsant Activity

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ABSTRACT

Design and Synthesis of Benzotriazole Derivatives for Anticonvulsant Activity Epilepsy is a prevalent neurological disorder significantly impacting global health and economy, necessitating the development of novel therapeutic agents. Benzotriazole derivatives, known for their diverse biological activities, present a promising scaffold for new antiepileptic drugs. This study aimed to synthesize novel benzotriazole-linked triazine derivatives, characterize their physicochemical properties, and evaluate their potential anticonvulsant activity through in silico ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) and docking studies, as well as in vivo maximal electroshock seizure (MES) model testing. Our approach involved a five-step synthesis of five benzotriazole derivatives (PTB1-5), including the formation of benzotriazole, N-esterification, nucleophilic substitution, cyclization to triazine, and Schiff's base formation. Characterization was performed using melting point, solubility, and spectral analysis (^{1}H-NMR, FT-IR). In silico studies predicted drug-likeness and ADMET properties . Anticonvulsant activity was assessed in Wistar albino rats using the MES model, observing hind limb extension and clonus. Results showed that compounds PTB1, PTB2, and PTB5 significantly reduced the onset of hind limb extension in the MES model, demonstrating considerable anticonvulsant action. PTB3 and PTB4 also showed reduction in onset. All synthesized compounds exhibited good drug-likeness and favorable ADMET properties, with high intestinal absorption. Docking studies indicated binding affinity to the GABA-AT receptor, suggesting a potential mechanism of action In conclusion, this research successfully synthesized novel benzotriazole-linked triazine derivatives with promising anticonvulsant activity and favorable pharmacokinetic profiles, warranting further investigation as potential antiepileptic drug candidates.

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INTRODUCTION

1.1 Benzotriazole

Heterocyclic compounds have explored new avenues in the field of medicinal and organic chemistry. Among large pool of heterocyclic compounds, benzotriazole (Figure 1.1) took the chemist and druggist to the surprise by its miraculous characteristic in context of electron donating nature, group release, anion director in surrounding etc. Benzotriazole is easy to introduce into molecules by a variety of condensation, addition and substitution reactions. Its derivatives have a wide spectrum of biological, chemical and industrial activities. Benzotriazole comprises two fused rings; its five membered rings can show tautomerism.

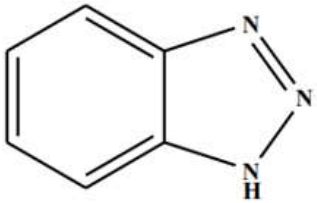


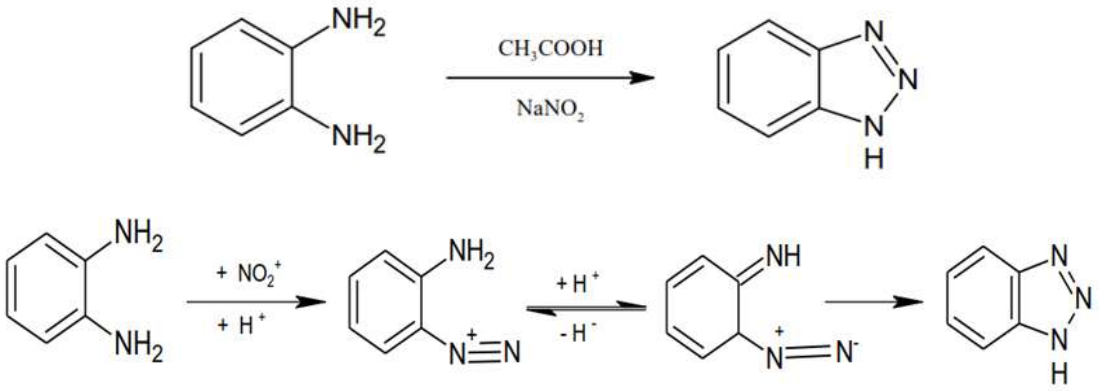
Figure 1.1 1H-Benzotriazole

The physical properties of benzotriazole reveal molecular formula C6H5N3, with a molecular mass of 119.12 and melting range of 98.5-100°C. The compound is white to brown crystalline powder and exhibits density of 1.36 g/cm3. It is moderately soluble in water and has a UV absorption maximum of 286 nm.

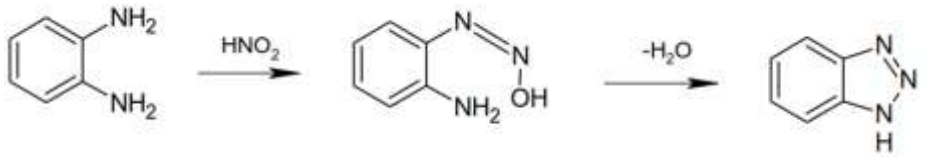
In general, nitrogen and sulfur containing organic compounds and their metal complexes display a wide range of biological activity as antitumor, antibacterial, antifungal and antiviral agents [1]. Benzotriazoles are often used as corrosion inhibitors, radioprotectors, and photo stabilizer in the production of plastic, rubber and chemical fiber. Along with these activities, benzotriazole is also important as a precursor in the synthesis of peptides, acid azides, preparation of 3-hydroxymethyl-2,3-dihydrobenzofurans and 3-hydroxymethylbenzofurans [2].

1.2 Methods of Synthesis of Benzotriazole

Benzotriazole is commonly synthesized by diazotization process using benzene-1,2-diamine with sodium nitrite and acetic acid. The reaction involved the simple heating the reagents together. Conversion of the diamine into the monodiazonium derivative is followed by spontaneous cyclization [3].



Another method of synthesizing benzotriazole involves direct action of nitrous acid on o-phenylenediamine and by the hydrolysis of an acylated or aroylated benzotriazole which has been previously prepared by the action of nitrous acid on the corresponding mono acylated or aroylated o-phenylenediamine.



N-substituted derivatives of benzotriazole have been prepared by N-Alkylation of Benzotriazole under Solvent-Free Conditions: An efficient, simple and solvent-free method for highly regioselective N-alkylation of benzotriazole in the presence of SiO2, K2CO3 and tetrabutylammonium bromide (TBAB) under thermal and microwave conditions has been described.

1.3 Epilepsy

Epilepsy is the most common neurological disorder which significantly affects the quality of life and poses a health as well as economic burden on society. Epilepsy affects an approximately 70 million people in the world [4]. In the United States, more than 300,000 people with epilepsy are younger than 14 and more than 500,000 are older than 65. With age, the incidence rate of epilepsy is fluctuating as high levels in childhood followed by decreasing order in early adult life which precedes by second high rate at the age of more than 65 years old [5]. Epilepsy diminishes health related quality of people as there is increased risk of injuries during seizures and higher mortality as compared to normal people. Epilepsy affects an estimated 1.5 million women in the United States [6]. The estimation of the corresponding rates is higher in low- and middle-income countries. In India, the prevalence of epilepsy is 6–10 per 1000 people [7].

The pathophysiology of epilepsy involves conversion of a normal network into a hyper excitable network. It is associated with a group of processes which disturb extracellular ion homeostasis, alter energy metabolism, change receptor function and alter transmitter uptake. In CNS, the brain consists of nerve cells and these nerve cells communicate and interact with each other through axons by discharging tiny electrical impulses. The brain along with nerve cells works on the phenomenon of electricity. The output of these electrical impulses is the release of chemicals called neurotransmitters from the axon end which in turn interacts with the next cell. These chemicals (neurotransmitters) can be excitatory or inhibitory. The balance of these excitatory and inhibitory impulses is very important to maintain the action potential of neurons [8]. Release of excessive excitatory glutamate overactivates NMDA receptors resulting in excessive influx of Ca2+ ions. The overflow of Ca2+ levels caused deteriorate condition which activates cytoplasmic proteases (such as calpain I), which proteolysis cytoskeletal and other proteins, neuronal nitric oxide synthase (nNOS), which increases nitric oxide production in turn generating the free radical peroxynitrite that damages DNA which ultimately lead to neuronal cell death (Figure 1.2).

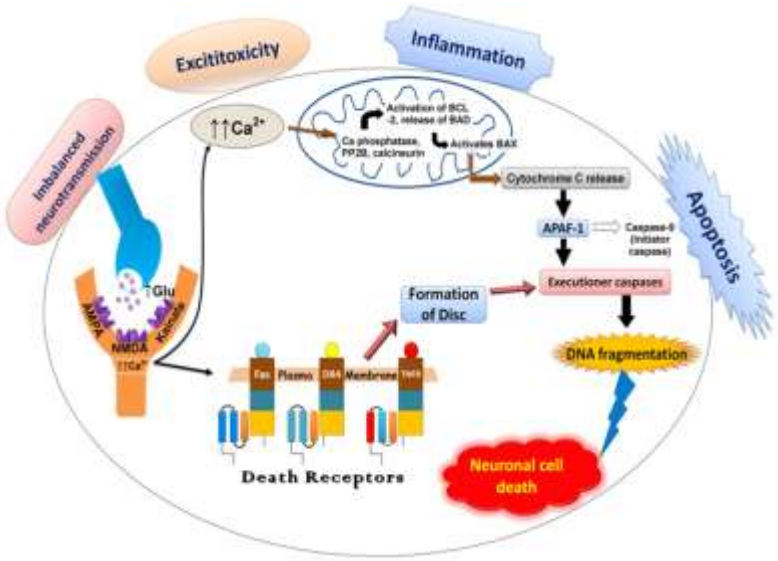


Figure 1.2. Pathophysiology of epilepsy

1.4 Anti-epileptic drugs

A number of anti-epileptic drugs (AEDs) are clinically used for managing the symptoms associated with epilepsy. Several pharmacological targets help in designing of newer AEDs continuously (Table 1.1).

Table 1.1 AEDs and their target site

Target site	AED
Sodium Ion channel	Phenytoin
	Carbamazepine
	Lamotrigine
	Lacosamide
	Zonisamide
	Rufinamide
	Valproate, divalproex
Potassium Ion channel	Retigabine
Calcium Ion channel	Gabapentine
	Pregabaline
	Ethosuximide
GABAA receptor	Benzodiazepines
	Barbiturates
	Topiramate
	Stiripentol
	Ganaxolone
NMDA receptor	Felbamate

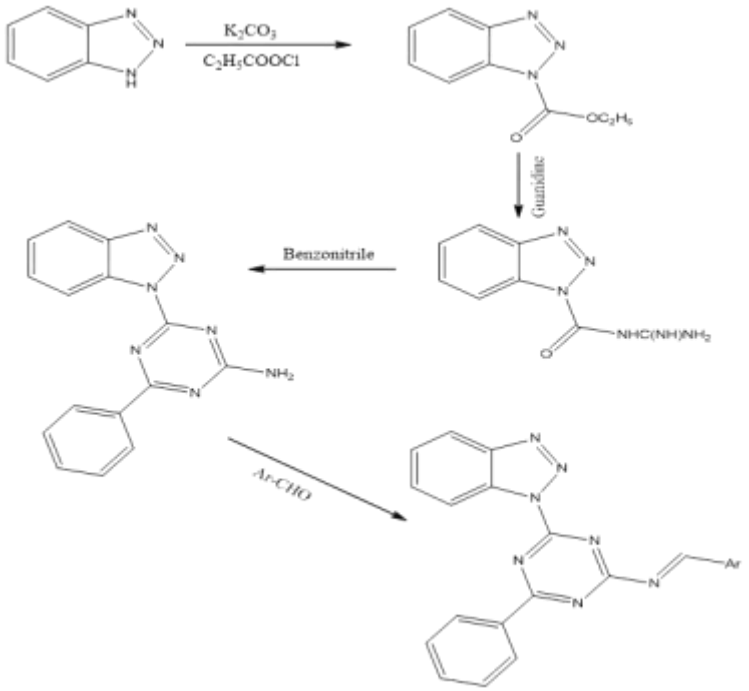
MATERIAL AND METHODS

The objective of the present work was to synthesize benzotriazole derivatives and perform the *in silico* ADMET and docking studies and evaluate anti-epileptic activity of the compounds.

List of Chemical Used

Sr.No.	Name	Source
1	Orhtophenylenediamine	CDH
2	Sodium nitrite	CDH
3	Glacial acetic acid	Finar
4	Benzonitrile	Sigma
5	Guanidine	Sigma
6	Ethylchloroformate	Sigma
7	Potassium carbonate	Sigma
8	Ethanol	Sigma
9	Hexane	Finar
10	Ethyl acetate	Loba
11	Methanol	Loba
12	Benzaldehyde	China
13	Dimethylsulfoxide (DMSO)	Loba
14	Distilled Water	Freshly prepared
15	4-Chlorobenzaldehyde	Sigma
16	4-Nitrobenzaldehyde	Sigma
17	4-Hydroxybenzaldehyde	Sigma
18	4-Methylbenzaldehyde	Sigma

The steps adopted in the synthesis of the benzotriazole derivatives (Scheme 1) are depicted in the scheme below which is adopted from the literature and modified as per requirement.



Scheme 1. Synthesis of benzotriazole derivatives

The steps involved in the synthesis of target compounds involved

1. Synthesis of benzotriazole
2. N-Esterification of benzotriazole
3. Nucleophilic substitution of the alkyl group
4. Cyclization to obtain triazine side chain
5. Formation of Schiffs base

Synthesis of benzotriazole

In a round bottom flask, 10.8g of ortho phenylenediamine was dissolved in a mixture of 12g glacial acetic acid and 30 mL of water, with the aid of moderate heat. The clear solution was cooled to 15°C and stirred on a magnetic stirrer. To the solution was added slowly a solution of 7.5g sodium nitrite in 15 mL water. The temperature of the solution increases to 85°C and the mixture was allowed to cool. The color of the solution changes while cooling and the mixture was continued stirring till temperature reaches 30°C. The mixture was then chilled in an ice-bath for 30 min. The product was collected by vacuum filtration and washed thrice with cold water. The product was recrystallized using hot water to obtain the benzotriazole [9].

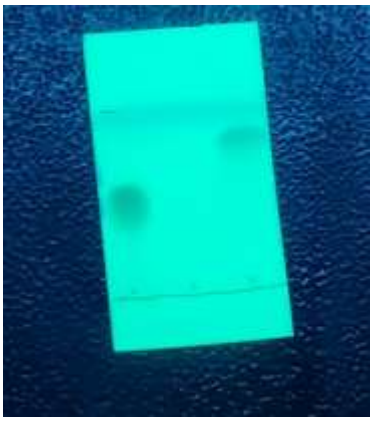


Figure 4.1 (A) TLC of product

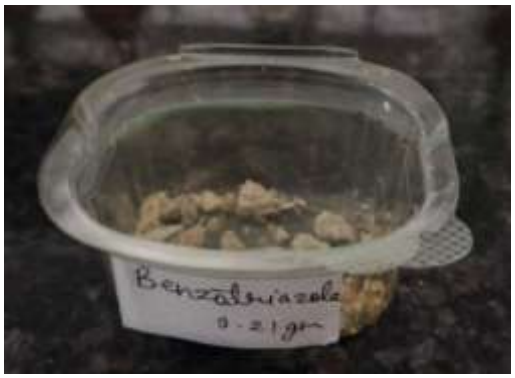


Figure 4.1 (B) Dried benzotriazole

Synthesis on N-Ethylester of benzotriazole

Anhydrous K2CO3 was added to a solution of the benzotriazole and ethylchlorformate dissolved in anhydrous DMF in a round bottom flask and allowed the reaction to refluxed for 1-2 hr. After the completion of reaction checked by TLC, crushed ice was added into reaction mixture compounds got ppt out. Filter the solid and washed with cold water [10].

Figure 4.2 (A) TLC of N-ethylester derivative of benzotriazole

Figure 4.2 (B) Dried N-ethylester derivative of benzotriazole

Synthesis of Guanidine derivative

0.01 mole of guanidine was added to added to 0.01 mole of the N-Ethylester of benzotriazole obtained from the previous step in 5 mL of ethanol. The reaction mixture was refluxed in microwave at 120 Watt power for 5 min. The mixture was cooled to obtain the solid, which was recrystallized from ethanol to obtain the guanidine derivative [11].

Figure 4.3 (A) TLC of Guanidine derivative of benzotriazole

Figure 4.3 (B) Dried Guanidine derivative of benzotriazole

Synthesis of triazine derivative

To a solution of 0.001 mole of the guanidine derivative synthesized in previous step in ethanol (5 mL), 0.001 mole of benzonitrile was added. The reaction mixture was refluxed for 15 min in microwave at 120-Watt power. The mixture was cooled and the product obtained was collected by filtration.

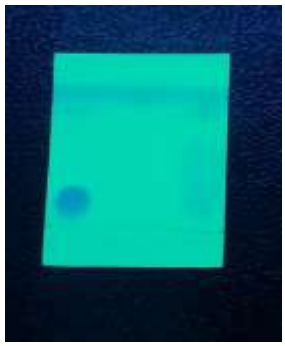


Figure 4.4 (A) TLC of triazine derivative of benzotriazole

Figure 4.4 (B) Dried triazine derivative of benzotriazole

General method for synthesis of schiffs base

In a round bottom flask (0.003 mol) of aromatic aldehyde, (0.003 mol) of triazine derivative were mixed in 5 mL of ethanol and heated on heating mantle for 5 to 10 min. The catalytic amount of zinc chloride (1 to 2g) was added to the mixture and the mixture was heated until the completion of the reaction (approximately 15 to 20 min.) On cooling a solid separated which was filtered and recrystallised using methanol to give the desired product. Completion of the reaction was monitored by the TLC [12].

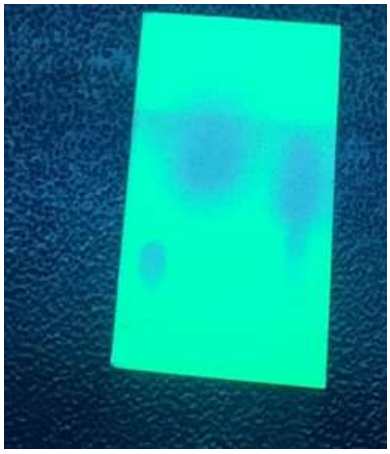


Figure 4.5 (A) TLC of Schiff's base derivative

Figure 4.5 (B) Schiff's base derivative of benzotriazole

Synthesis of (E)-4-(1H-benzo[d][1,2,3]triazol-1-yl)-N-benzylidene-6-phenyl-1,3,5-triazin-2-amine (PTB1)

In a round bottom flask (0.003 mol) of benzaldehyde, (0.003 mol) of triazine derivative were mixed in 5 mL of ethanol and heated on heating mantle for 5 to 10 min. The catalytic amount of zinc chloride (1 to 2g) was added to the mixture and the mixture was heated until the completion of the reaction (approximately 15 to 20 min.) On cooling a solid separated which was filtered and recrystallised using methanol to give the desired product. Completion of the reaction was monitored by the TLC.

Synthesis of (E)-4-(1H-benzo[d][1,2,3]triazol-1-yl)-N-(4-chlorobenzylidene)-6-phenyl-1,3,5-triazin-2-amine (PTB2)

In a round bottom flask (0.003 mol) of 4-chlorobenzaldehyde, (0.003 mol) of triazine derivative were mixed in 5 mL of ethanol and heated on heating mantle for 5 to 10 min. The catalytic amount of zinc chloride (1 to 2g) was added to the mixture and the mixture was heated until the completion of the reaction (approximately 15 to 20 min.) On cooling a solid separated which was filtered and recrystallised using methanol to give the desired product. Completion of the reaction was monitored by the TLC.

Synthesis of (E)-4-(1H-benzo[d][1,2,3]triazol-1-yl)-N-(3-nitrobenzylidene)-6-phenyl-1,3,5-triazin-2-amine (PTB3)

In a round bottom flask (0.003 mol) of 4-nitrobenzaldehyde, (0.003 mol) of triazine derivative were mixed in 5 mL of ethanol and heated on heating mantle for 5 to 10 min. The catalytic amount of zinc chloride (1 to 2g) was added to the mixture and the mixture was heated until the completion of the reaction (approximately 15 to 20 min.) On cooling a solid separated which was filtered and recrystallised using methanol to give the desired product. Completion of the reaction was monitored by the TLC.

Synthesis of (E)-2-(((4-(1H-benzo[d][1,2,3]triazol-1-yl)-6-phenyl-1,3,5-triazin-2-yl)imino)methyl)phenol (PTB4)

In a round bottom flask (0.003 mol) of 4-hydroxybenzaldehyde, (0.003 mol) of triazine derivative were mixed in 5 mL of ethanol and heated on heating mantle for 5 to 10 min. The catalytic amount of zinc chloride (1 to 2g) was added to the mixture and the mixture was heated until the completion of the reaction (approximately 15 to 20 min.) On cooling a solid separated which was filtered and recrystallised using methanol to give the desired product. Completion of the reaction was monitored by the TLC.

Synthesis of (E)-4-(1H-benzo[d][1,2,3]triazol-1-yl)-N-(4-methoxybenzylidene)-6-phenyl-1,3,5-triazin-2-amine (PTB5)

In a round bottom flask (0.003 mol) of 4-methylbenzaldehyde, (0.003 mol) of triazine derivative were mixed in 5 mL of ethanol and heated on heating mantle for 5 to 10 min. The catalytic amount of zinc chloride (1 to 2g) was added to the mixture and the mixture was heated until the completion of the reaction (approximately 15 to 20 min.) On cooling a solid separated which was filtered and recrystallised using methanol to give the desired product. Completion of the reaction was monitored by the TLC.

Figure 4.6 Performing reaction in lab

Chemical Characterization of the synthesized compounds [13]

The characterization of the physicochemical properties of these compounds was done as follows:

1. The **melting points** were determined by open capillary method and are uncorrected.

2. The purity and homogeneity of the compounds was determined by **thin layer chromatography [14]**, using silica gel G as the stationary phase on glass plates. Iodine vapors were used for development of the chromatogram. The solvent system used for running the compounds was hexane-ethylacetate in the ratio 2:8.

3. The **solubility** of the synthesized compounds was assessed by shaking a small quantity of the compound in 1mL of solvent (Chloroform, DMSO, methanol, water) and visualizing for undissolved particles if any.

4. **Infrared spectroscopy**: The FT-IR spectra of the synthesized compounds were obtained using FT-IR spectrophotometer.

5. **NMR spectroscopy**: NMR are performed on $CDCl_3$ using Bruker NMR Spectrophotometer.

Docking study

The docking study of the synthesized compounds on the active site of GABA-AT was performed with the help of Autodock software. The GABA protein structure (1ohw) for docking was downloaded from protein database. The macromolecule was prepared for docking by removal of water molecules, addition of charges and hydrogen. The ligand structure were drawn using Chemdraw ultra 12.0 software and saved as SDF file. The ligand structure for docking was prepared by saving the structure as pdbqt file. Docking study was carried and the binding affinity scores were calculated. The interactions ligand with various amino acid residues in the helix of the enzyme was also observed.

***In silico* ADMET study**

The 2D structures of the ligands were sketched on ChemDraw Ultra 12.0 and then transferred on Chem 3D to create the three dimensional structures. The canonical SMILES (simplified molecular-input line-entry system) were generated using ChemDraw and then submitted to SwissADME as well as pkCSM online tools for the ADMET analysis, the prediction of physicochemical parameters and the drug-likeness using the Lipinski rule of five. The so-called Rule-of-five of Lipinski delineated the relationship between pharmacokinetic and physicochemical parameters.

Evaluation of Anti-epileptic Activity

Preparation of test solutions

The synthesized compounds were individually dissolved in required volume of dimethylsulfoxide (DMSO) and diluted using phosphate buffer solution (PBS) (pH = 7.8) for the final range of concentrations (2-10 μM).

Maximal electroshock seizure [MES] model [15]

Experimental design

Wistar albino rats weighed around 150-250g were used for the study. Rats were divided into seven groups of 5 animals each.

- Group I - Vehicle control [Equivalent normal saline, oral]
- Group II - Standard [Diazepam 5 mg/Kg, oral]
- Group III-VII - Synthesized compounds, 75 mg/kg orally

Animals in the control group [Group 1] were been administered equivalent volume of normal saline by oral route. Animals in Group 2 were been administered standard drug Daizepam. In Groups 3 to 7 the synthesized compounds (75 mg/kg) was administered by oral route in 1% Sodium lauryl sulphate solution respectively.

After 30 minutes of administration of above drugs, all the rats were been given electroshock with electro convulsiometer through ear electrodes [after moistening the ear of animals with drop of normal saline] at intensity of 150 mA, 60Hz for 0.2 seconds. Thereafter the animal were observed for number of convulsions. The percent protection and duration of tonic hind limb extension (i.e., the hind limbs of animals outstretched at 180° to the plane of the body axis) was observed. Protection was defined as complete absence of tonic hind limb extension.

RESULTS AND DISCUSSION

The synthesis of the compounds was achieved in five steps and five derivatives of benzotriazole

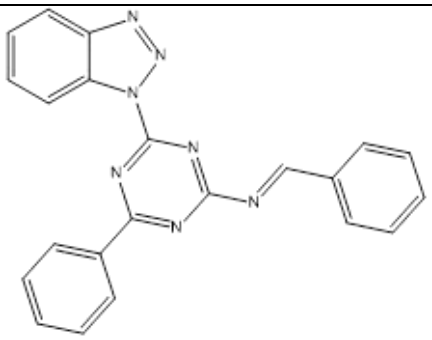
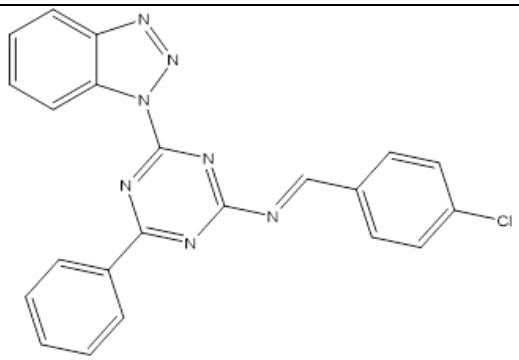
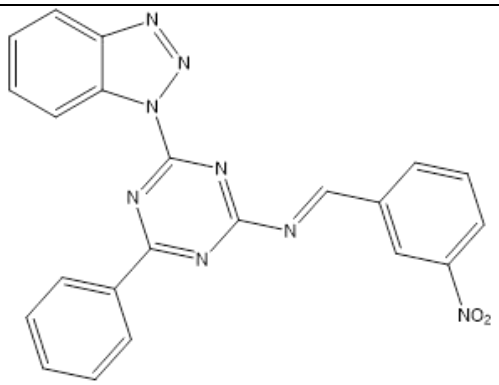
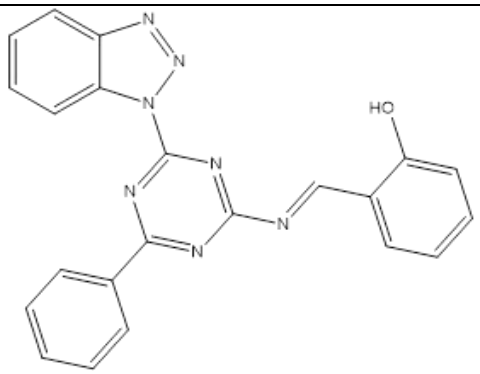
linked triazines were synthesized. The compounds were characterized for their physicochemical features and anti-epileptic activity. The results obtained are presented in the following section.

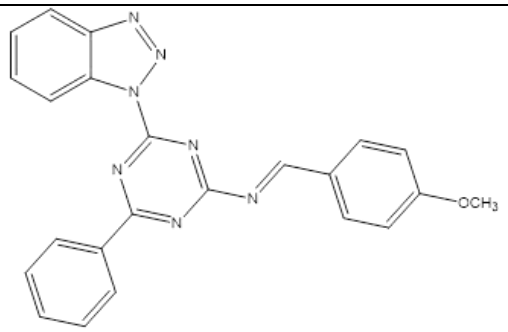
Results

Chemistry

Five benzotriazole derivatives (**PTB_{1-5}**) were synthesized and structure and IUPAC names of the synthesized derivatives is presented in table 5.1.

Table 5.1 Structure of synthesized benzotriazole derivatives

Code	Structural Formula	IUPAC Name
PTB_1		(E)-4-(1H-benzo[d][1,2,3]triazol-1-yl)-N-benzylidene-6-phenyl-1,3,5-triazin-2-amine
PTB_2		(E)-4-(1H-benzo[d][1,2,3]triazol-1-yl)-N-(4-chlorobenzylidene)-6-phenyl-1,3,5-triazin-2-amine
PTB_3		(E)-4-(1H-benzo[d][1,2,3]triazol-1-yl)-N-(3-nitrobenzylidene)-6-phenyl-1,3,5-triazin-2-amine
PTB_4		(E)-2-(((4-(1H-benzo[d][1,2,3]triazol-1-yl)-6-phenyl-1,3,5-triazin-2-yl)imino)methyl)phenol

PTB_5		(E)-4-(1H-benzo[d][1,2,3]triazol-1-yl)-N-(4-methoxybenzylidene)-6-phenyl-1,3,5-triazin-2-amine

The yield and melting point of the synthesized derivatives is presented in table 5.2. The yield of the compounds was in the range of 62-69%.

Table 5.2 Physicochemical properties of the compounds

Code	Yield	Molecular Weight	Melting point
PTB_1	62	377.40	266-268 °C
PTB_2	68	411.85	235-237 °C
PTB_3	69	422.40	242-244 °C
PTB_4	64	393.40	260-262 °C
PTB_5	66	407.43	248-250 °C

All the compounds were soluble in chloroform and DMSO whereas insoluble in water and methanol.

Spectral characterization of synthesized derivatives

The ^{1}H-NMR and FTIR spectra of the synthesized compound was observed for the vibrations of functional groups in the FTIR spectra and protons in the ^{1}H-NMR spectra.

Spectral characterization of PTB_1

Color: White, Form – Crystals

^{1}H-NMR (δ ppm): 7.09-8.20 (aromatic protons), 9.08 (imine proton)

FTIR (cm^{-1}): 3050.55 (C-H), 1327.08-1225.82 (C-C, aromatic), 850.64 (C-N)

Spectral characterization of PTB_2

Color: White, Form – Crystals

^{1}H-NMR (δ ppm): 7.43-8.22 (aromatic protons), 9.15 (imine proton)

FTIR (cm^{-1}): 3050.55 (C-H), 1327.08-1225.82 (C-C, aromatic), 850.64 (C-N)

Spectral characterization of PTB_3

Color: White, Form – Crystals

^{1}H-NMR (δ ppm): 6.98-8.15 (aromatic protons), 9.13 (imine proton), 10.95 (hydroxyl proton)

FTIR (cm^{-1}): 3017.39 (C-H), 1399.26-1253.77 (C-C, aromatic), 821.51 (C-N)

Spectral characterization of PTB_4

Color: White, Form – Crystals

^{1}H-NMR (δ ppm): 7.51-8.26 (aromatic protons), 9.15 (imine proton)

FTIR (cm-1): 3029.11 (C-H), 1325.36-1221.91 (C-C, aromatic), 867.04 (C-N)

Spectral characterization of PTB_5

Color: White, Form – Crystals

^{1}H-NMR (δ ppm): 7.08-8.27 (aromatic protons), 9.11 (imine proton), 3.25 (methyl protons)

FTIR (cm^{-1}): 2972.32 (C-H), 1412.08-1296.02 (C-C, aromatic), 851.13 (C-N)

Antiepileptic activity

The result of the present study shows that the synthesized compounds significantly delayed the onset of hind limb extension and decreased the duration of extension (Table 5.3).

Table 5.3 Effect of PTB_{1-5} on seizures

Group	Onset Time (sec)		Recovery/ Mortality
	Extension	Clonus	
Control	3.36 ± 0.089	30.68 ± 0.614	Recovery
Standard	15.66 ± 0.403	0	Recovery
PTB_1	12.06 ± 0.336	0	Recovery
PTB_2	12.66 ± 0.260	0	Recovery
PTB_3	7.48 ± 0.192	0	Recovery
PTB_4	9.66 ± 0.207	0	Recovery
PTB_5	10.62 ± 0.414	0	Recovery

As evident from the Table 5.3, PTB_{1-5} were able to abolish the phase of convulsion in MES induced convulsion (clonus, involuntary muscle movement) models.

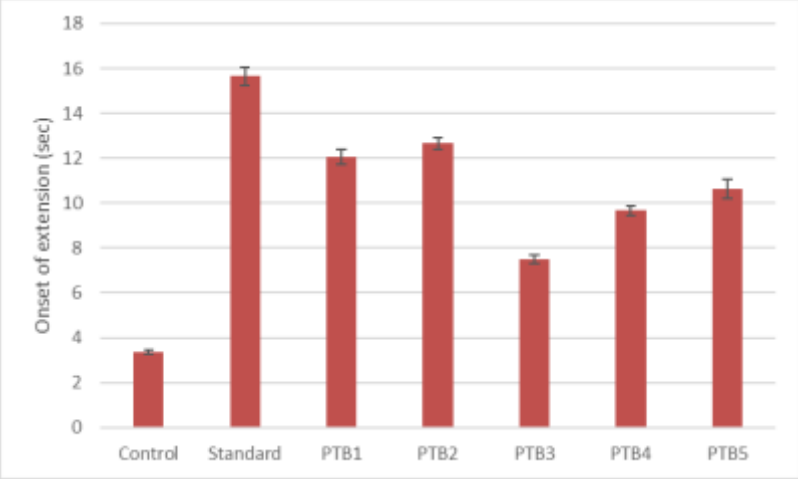


Figure 5.1 Comparison of onset of extension in various treatment groups

In silico ADMET properties of synthesized derivatives

The SMILES of the synthesized derivatives PTB1-5 was generated using chemdraw ultra 12.0 software. The physicochemical properties of the compounds predicted in silico by SwissADME are presented in table 5.4 and the ADMET properties predicted by pkCSM are presented in table 5.5.

Table 5.4 Physicochemical properties of PTB1-5

Compound Code	HBD	HBA	Log P	NRB	PSA (A)	MR	Log S
PTB1	0	6	3.56	4	81.74	111.38	-5.41
PTB2	0	6	4.19	4	81.74	116.39	-6.00
PTB3	0	8	3.53	5	127.56	120.20	-5.45
PTB4	1	7	3.66	4	101.97	113.40	-5.26
PTB5	0	7	3.97	5	90.97	117.87	-5.47

Table 5.5 ADMET of PTB1-5

ADMET Parameters	PTB1	PTB2	PTB3	PTB4	PTB5
Absorption					
Water solubility (log mol/L)	-4.267	-4.511	-4.122	-4.245	-3.973
Caco2 permeability (log Papp in 10^{-6} cm/s)	1.198	1.097	0.471	1.486	1.165
Intestinal absorption (human) (% Absorbed)	98.306	96.81	100	100	98.631

Skin Permeability (log Kp)	-2.731	-2.734	-2.735	-2.735	-2.735
Distribution					
VDss (human) (log L/kg)	0.266	0.114	-0.132	-0.004	-0.023
BBB permeability (log BB)	-0.976	-1.159	-1.533	-1.208	-1.219
CNS permeability (log PS)	-2.053	-1.942	-2.313	-3.131	-3.812
Metabolism					
CYP2D6 substrate	No	No	No	No	No
CYP3A4 substrate	Yes	Yes	Yes	Yes	Yes
Excretion					
Total Clearance (log ml/min/kg)	0.101	0.121	0.036	0.037	0.049
Renal OCT2 substrate	No	No	No	No	No
Toxicity					
AMES toxicity	Yes	Yes	Yes	Yes	Yes
Hepatotoxicity	Yes	Yes	Yes	Yes	Yes
Oral Rat Acute Toxicity (LD50) (mol/kg)	2.969	2.736	2.778	2.843	2.788

Figure 5.2 Physicochemical properties diagram of PTB1

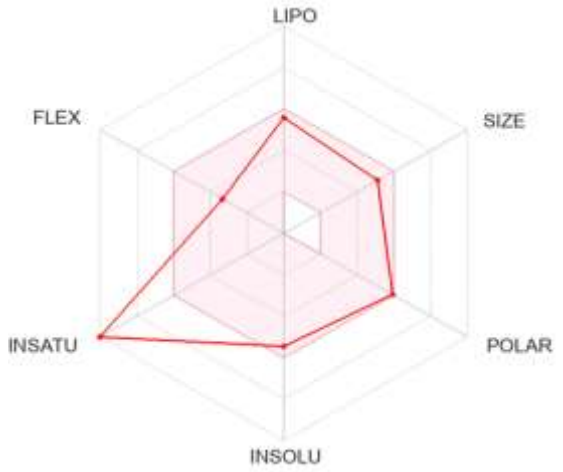


Figure 5.4 Physicochemical properties diagram of PTB3

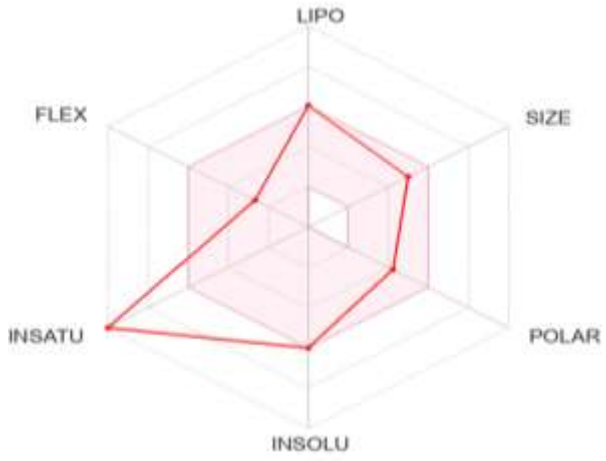


Figure 5.3 Physicochemical properties diagram of PTB2

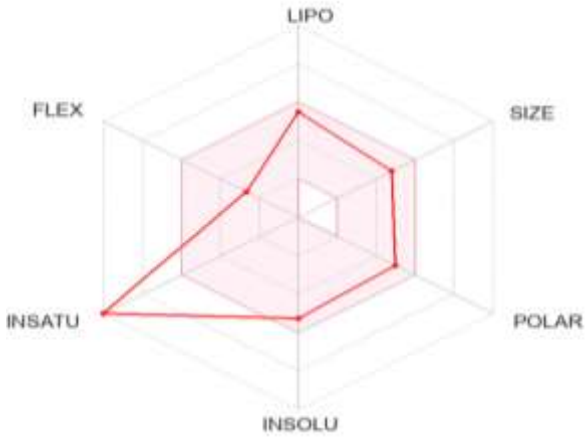


Figure 5.5 Physicochemical properties diagram of PTB4

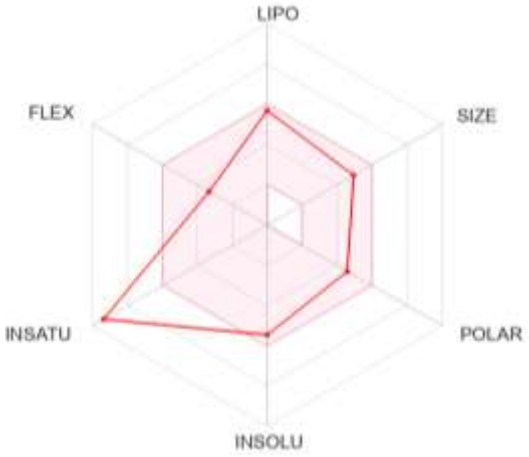


Figure 5.6 Physicochemical properties diagram of PTB5

DISCUSSION

Chemistry

The spectral characterization of the synthesized derivatives revealed the presence of aromatic protons, and the protons of imine in all the compounds. The protons of methyl were present in PTB5. The FTIR spectrum exhibited the stretching vibrations due to C-H, C-C, C=C, C-O and C-N in the compounds.

Physicochemical property is an important parameter of a molecule that influences efficacy, safety or metabolism which could be predicted by using Lipinski's rule of five, Veber's rule or Muegge's rule. We have used the Lipinski's rule that defines an orally active drug, which confirms to the number of hydrogen bonds acceptor (HBA) ≤ 10, hydrogen bonds donor (HBD) ≤ 5, molecular weight (MW) < 500 Da and Log P (the logarithm of octanol water partition coefficient) ≤ 5. The physicochemical properties include molecular weight, number of the rotatable bonds (NRB), HBA, HBD, molar refractivity (MR, in m3.mol-1) and polar surface area (PSA, in Å). The compounds exhibited drug likeliness as they presented no violations in Lipinski, Ghose, Veber, Egan and Muegge rules but could not present lead likeliness as they had molecular weight of more than 350 and XlogP3 more than 3.35. The other two significant determinant are lipophilicity and solubility that are monitored for favorable drug development. Table 5.4 reveals that all compounds meet every single criterion of Lipinski's rule of five and thus fully obey the rule. Consequently, all the investigated compounds present a good drug-likeness profile, since they are predicted to be easily absorbed and have good permeability and bioavailability. The boiled egg diagram is a tool to predict the BBB permeability of molecules. It was observed that none of the molecules were permeating the BBB and exhibited high absorption in the gastrointestinal region (Figure 5.7).

Figure 5.7 Boiled Egg diagram of PTB1-5

The ADMET properties of the compounds was predicted in silico by using academic tool pKCSM online. The compounds exhibited hepatotoxicity, low renal clearance and high intestinal absorption (Table 5.5)

Antiepileptic activity

The maximal electroshock induced convulsion in animals represents grand mal type of epilepsy. The tonic extensor phase is selectively abolished by the drugs effective in generalized tonic clonic seizure [31]. As seen in Figure 5.1, the onset of extension of hind limb was significantly reduced in standard, PTB_1, PTB_2 and PTB_5 ($p<0.001$) in comparison to the control group. PTB3 and PTB4 were able to reduce the onset ($p<0.05$). This results were found to be almost in consonance with the boiled egg predictions were molecules 1, 2 and 5 were displaying physicochemical features closed to the yolk region representing blood brain barrier. Also as the ADMET properties were predicted, the compounds PTB3 and PTB4 were showing 100% gastrointestinal absorption.

Docking Study

The docking study was conducted to predict the binding affinity of the synthesized molecules to GABA receptor. GABA is the primary inhibitory neurotransmitter in the brain and agonists of GABA, in particular GABA-A help in increasing the inhibition potential of this receptor.

SUMMARY AND CONCLUSION

The objective of the present work was to synthesize benzotriazole linked triazine derivatives and perform the *in silico* ADMET and docking studies and evaluate anti-epileptic activity of the compounds.

Summary

The steps involved in the synthesis of target compounds involved

1. Synthesis of benzotriazole
2. N-Esterification of benzotriazole
3. Nucleophilic substitution of the alkyl group
4. Cyclization to obtain triazine side chain
5. Formation of Schiffs base

The characterization of the compounds was done for melting point, solubility, yield and spectral characterization.

The docking study of the synthesized compounds on the active site of Human Gamma Amino Butyric Acid (GABA-A) receptor was performed with the help of Autodock software. The GABA-A protein structure (8bhk) for docking was downloaded from protein database.

The canonical SMILES (simplified molecular-input line-entry system) were generated using ChemDraw and then submitted to SwissADME as well as pkCSM online tools for the ADMET analysis, the prediction of physicochemical parameters and the drug-likeness.

The anti-epileptic activity of the synthesized compounds was studied by Maximal Electroshock Method (MES).

The yield of the compounds was in the range of 62-69%. All the compounds were soluble in chloroform and DMSO whereas insoluble in water and methanol. The spectral characterization of the synthesized derivatives revealed the presence of aromatic protons, and the protons of imine in all the compounds. The protons of methyl were present in PTB_5. The FTIR spectrum exhibited the stretching vibrations due to C-H, C-C, C=C, C-O and C-N in the compounds.

All compounds meet every single criterion of Lipinski's rule of five and thus fully obey the rule.

the onset of extension of hind limb was significantly reduced in standard, PTB_1, PTB_2 and PTB_5 ($p<0.001$) in comparison to the control group. PTB3 and PTB4 were able to reduce the onset ($p<0.05$). These results were found to be almost in consonance with the boiled egg predictions were molecules 1, 2 and 5 were displaying physicochemical features closed to the yolk region representing blood brain barrier. Also, as the ADMET properties were predicted, the compounds PTB3 and PTB4 were showing 100% gastrointestinal absorption.

CONCLUSION

In this work, benzotriazole nucleus was linked to 1,3,5-triazine and Schiff's base derivatives were synthesized and evaluated for anti-epileptic action. Compound PTB_1, PTB_2 and PTB_5 were able to produce significant anti-epileptic action.

CONSENT FOR PUBLICATION: Not Applicable

CONFLICTS OF INTEREST: The authors declare that there are no conflicts of interest, whether financial or otherwise.

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