

SYNTHESIS, CHARACTERIZATION & BIOLOGICAL EVALUATION OF NOVEL 1H-SUBSTITUTED 2,4,5-TRIPHENYL IMIDAZOLE DERIVATIVES AS ANTICONVULSANT ACTIVITY

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ABSTRACT

Epilepsy is a neuro pharmacological disorder that significantly impacts mental and physical well-being, with GABA inhibitors being a long-standing treatment option for convulsions. However, early attempts to utilize these inhibitors were limited by side effects associated with their irreversible mechanisms. Over time, researchers have shifted focus towards developing reversible and selective GABA-A inhibitors. In this study, we synthesized and evaluated novel triphenyl-1H-imidazole derivatives (N1to N6) for their anticonvulsant properties. The compounds were synthesized through a two-step procedure involving refluxing and characterized using various analytical techniques such as FT-IR, MS, and NMR. The anticonvulsant activity of the synthesized derivatives was assessed using the maximal electroshock seizure (MES) model in Swiss albino mice. Among the compounds tested, **N2**, **N3**, and **N5** demonstrated significant anticonvulsant effects comparable to the standard drug, Phenytoin sodium. These findings suggest that these derivatives could serve as potential candidates for the treatment of epilepsy and other neuro pharmacological disorders. Further research on structural modifications, selectivity, and reversibility is needed to optimize their efficacy and minimize side effects. Additionally, these compounds may be explored for other biological activities such as antioxidant, anti-inflammatory, and antidepressant properties, which could open new therapeutic avenues for the treatment of neurodegenerative disorders.

Keywords: Epilepsy, Anticonvulsant, Triphenyl-1H-imidazole, GABA inhibitors, Maximal Electroshock Seizure (MES).

INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent spontaneous seizures, which are caused by abnormal, excessive, or synchronous neuronal activity in the brain. It affects

approximately 50 million people globally, which accounts for around 1-2% of the population¹⁻². The condition is particularly prevalent in developing countries, where 80% of epileptic patients reside. A significant and concerning risk associated with epilepsy is sudden unexpected death in epilepsy (SUDEP), which claims one life in every 1,000 individuals. Despite ongoing research, the precise pathophysiology of epilepsy remains incompletely understood. However, it is recognized that an imbalance between excitatory and inhibitory neurotransmission plays a critical role in the development of seizures. Excessive release of the excitatory neurotransmitter glutamate, particularly through NMDA and AMPA receptors, is a key factor in seizure initiation³. In contrast, gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter, counteracts excessive neuronal firing, and its function can be enhanced through pharmacological intervention⁴⁻⁵.

Seizures in epilepsy are classified into generalized and partial types. Generalized seizures, such as tonic-clonic and absence seizures, affect both hemispheres of the brain, while partial seizures typically begin in one region and may or may not spread to other areas. Understanding the underlying mechanisms of these seizures is essential for designing effective treatments⁶. Structural brain abnormalities, genetic factors, neuroinflammation, and neurotransmitter imbalances all contribute to the pathogenesis of epilepsy. Neurochemical dysregulation⁷, particularly involving GABA and glutamate, plays a central role in epileptic seizures, and targeting these pathways is a promising therapeutic strategy⁸.

Anticonvulsant drugs are the primary treatment for epilepsy, although they do not provide a cure⁹. These drugs work by either inhibiting excitatory neurotransmission or enhancing inhibitory mechanisms to prevent the onset of seizures¹⁰. Over the years, a variety of anticonvulsants, such as phenobarbital, phenytoin, carbamazepine, and valproic acid, have been developed and are widely used in clinical practice. However, these drugs often come with side effects, and their efficacy varies among patients, underscoring the need for new and more effective therapeutic options.

IMIDAZOLE PROFILE

Imidazole is a five-membered heterocyclic organic compound composed of three carbon atoms and two nitrogen atoms at positions 1 and 3 of the ring. It is a highly versatile chemical building block widely employed in natural and synthetic compounds, including pharmaceuticals, agrochemicals, and materials science¹¹. The structure of imidazole allows it to interact with a variety of enzymes and receptors, making it an important component in medicinal chemistry¹²⁻¹³. Imidazole

derivatives exhibit a broad range of biological activities, and their ability to modulate biological processes has led to their use in numerous therapeutic applications.

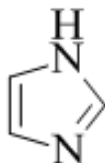


Figure 1: Structure of 1*H*-imidazole

Imidazole was first synthesized in 1858 by German chemist Heinrich Debus, although derivatives of the compound were discovered as early as the 1840s. The simplest form of the imidazole family is the compound itself, with the empirical formula $C_3H_4N_2$. Imidazole is also known by its systematic name, 1,3-diazole, and is characterized by a five-membered ring structure where nitrogen atoms occupy the 1 and 3 positions¹⁴. The structure is unique in that it has two equivalent tautomeric forms, with the hydrogen atom capable of binding to either nitrogen atom in the ring. This tautomerism is one of the distinguishing features of imidazole.

Imidazole belongs to a class of compounds referred to as substituted aromatics, where the aromatic sextet of π -electrons is formed from contributions by both nitrogen atoms and the remaining carbon atoms in the ring^{4,14}. The compound is amphoteric in nature, meaning it can act as both a base and an acid. Imidazole is more basic than pyridine, with an acidic proton located at the N1 position. Its pKa value of approximately 6 makes it more acidic than alcohols but less acidic than carboxylic acids and imides¹⁵.

One of the most significant biological roles of imidazole is its presence in the amino acid histidine, which contains an imidazole side chain. Histidine plays a crucial role in several biological processes, including protein function and enzyme catalysis¹⁶. The imidazole group is also important in the structure and function of hemoglobin, where it influences oxygen binding and release.

Due to its diverse biological properties, imidazole and its derivatives are utilized in a wide array of applications, ranging from pharmaceuticals to agrochemicals. The compound's ability to interact with biological systems, its structural versatility, and its role in essential biochemical processes make imidazole a key target for further research and development in medicinal chemistry⁵.

Table 1: Physiological Properties of imidazole

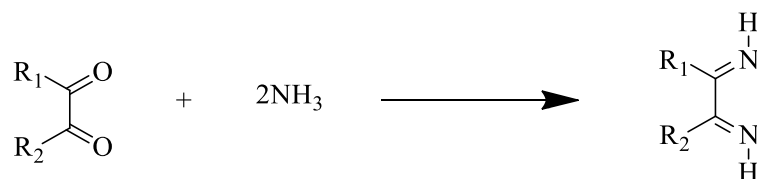
Physical properties	Values
Molecular formula	C3H4N2
IUPAC name	1H-Imidazole
Other name	1,3-Diazacyclopenta-2,4-diene, 1,3-Diazole Glyoxaline
Molar mass	68.077 g/mol
Appearance	White or pale-yellow solid
Density	1.23 g/cm ³ solid
Melting point	89 to 91 C
Boiling point	256 C
Solubility	Slightly soluble in water (633 g/l)
Acidity (pKa)	6.95 for the conjugate acid)

General synthesis of imidazole**Debus synthesis**

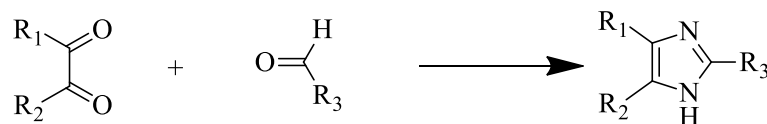
Debus Radziszewski imidazole synthesis is used to synthesize imidazole from aldehyde and ammonia, di carbonyl, the di carbonyl constituent is frequently glyoxal, but can contain many 1,2 Biketones and ketone aldehydes. These methods are used to yield various imidazoles¹⁰.

It can be considered that the reaction in two stages. The di carbonyl group and ammonia are condensed attain the di imine.

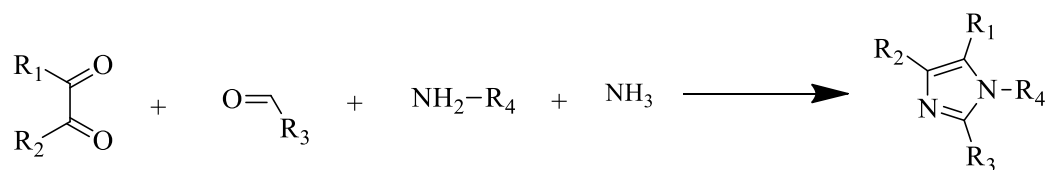
The di-carbonyl group and ammonia shrink to give di imine.



Second stage, the diimine is condensed with aldehyde:

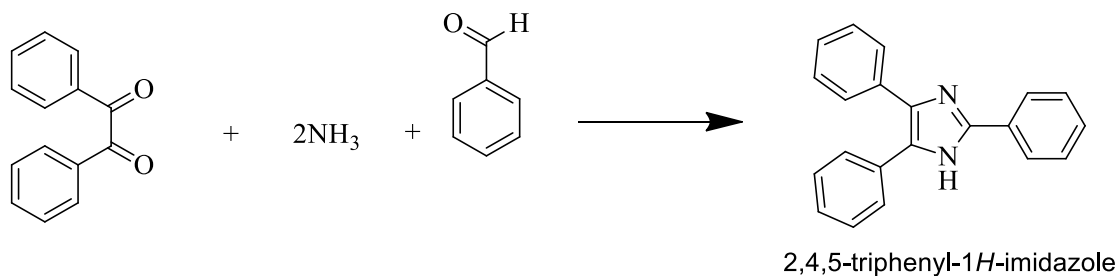


Ammonia is substituted by an amine and provides N-substituted imidazole.



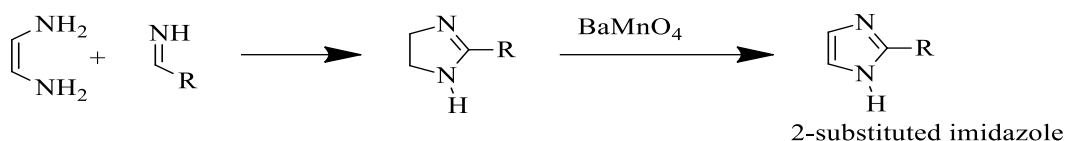
Radiszewski synthesis:

The preparation of imidazole derivative with condensing a Bi-carbonyl compound, an aldehyde, and equivalents of dry ammonia in alcohol are commonly called as the Radziszewski reaction. This reaction produces low yield and undergoes few sides' reaction. The reaction is very beneficial for the synthesis of imidazoles with a substituent at the 2-position of adjacent bi-carbonyl compounds⁹. This reaction was modified through the condensation of acetone, aqueous ammonia, and cupric acetate to provide imidazole in essentially good yields¹⁰.



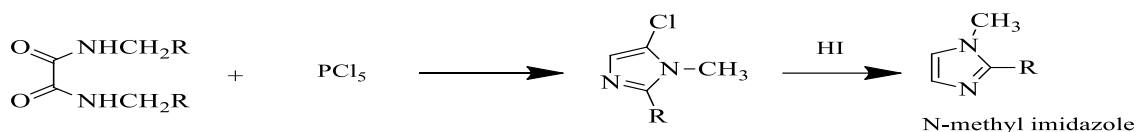
Dehydrogenation of imidazoline:

Knapp was explained that imidazoles were formed from imidazolines in the existence of S. imidazolines was formed from alkyl nitrile and 1,2 ethane diamines.



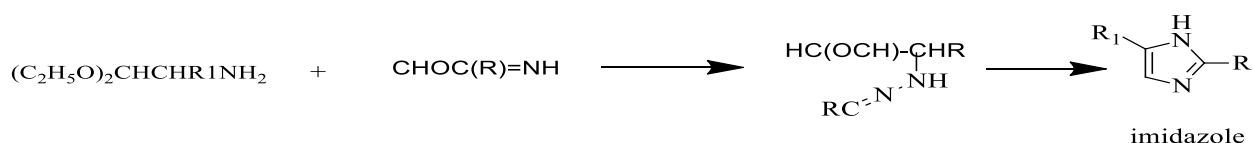
Wallach synthesis

Wallach told that, when N,N-dimethyl oxamide is reacted with PCl₅, a Cl holding compound is attained which proceeding reduction by HCl give (N-methyl imidazole). Below the N,N-diethyl oxamide is transformed to a chloride compound, which proceeding reduction gives 1-ethyl-2-methyl imidazole¹⁷.



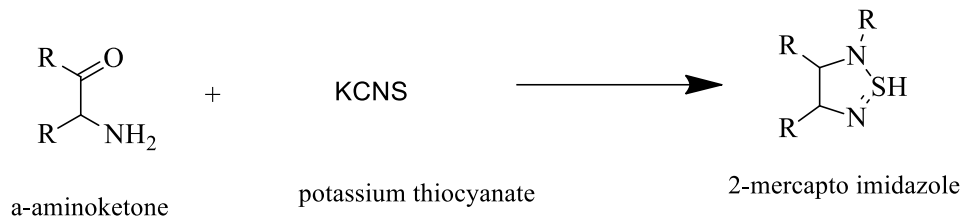
Bond Formation

The bond is designed by the reaction of imide with amino aldehyde or amino acetal, outcomes imidine to imidazole⁴. The example apply to imidazole where R and R₁H.



Markwald synthesis

The 2-mercaptoimidazole was prepared from amino ketone or aldehyde and potassium thiocyanate or alkyl isothiocyanate. Sulfur can be removed by several oxidation methods to obtain the desired imidazole. The amino aldehydes or ketones, are not easily available, which may be the limitation of Markwald synthesis¹⁰.



Triphenylimidazole is a best nucleus and biologically active molecule. Now a day this is interesting research nucleus of substituted derivative. The aim of the present study was to obtain triphenyl imidazole as biologically effective agent with good therapeutic values and minimum toxic levels. In this research work substitute the different aldehyde in the reaction of benzil and ammonium acetate in step I and substitute the different amine in the reaction of triphenyl imidazole and formaldehyde in step II.

MATERIALS AND METHODS

Scheme:

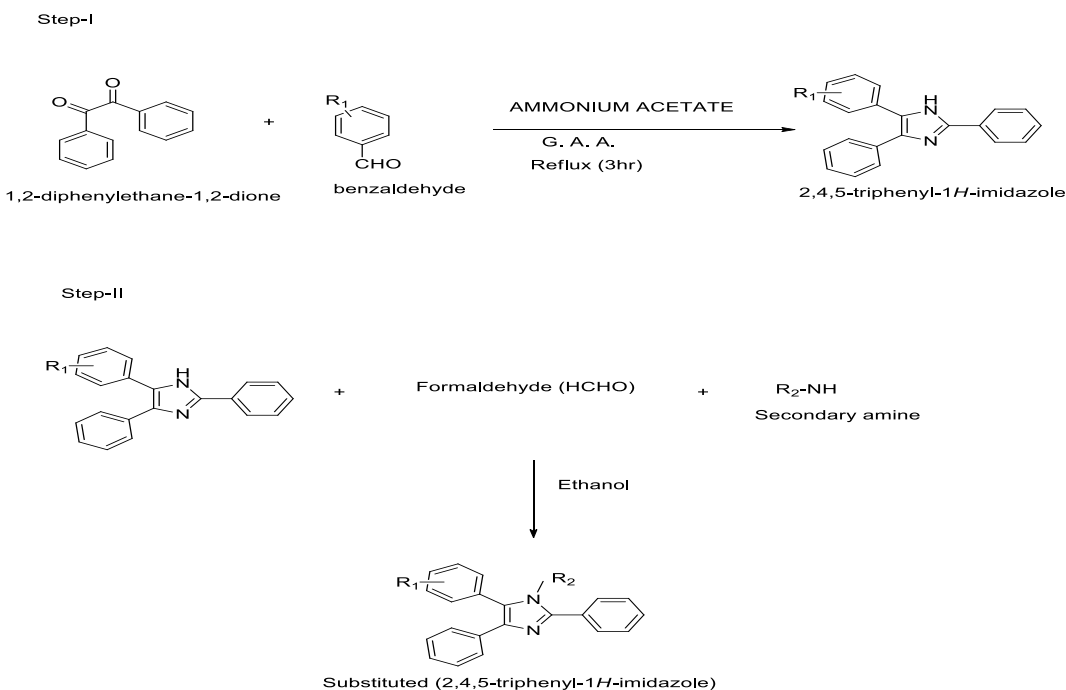
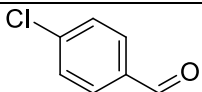
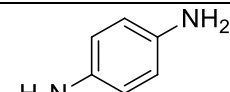
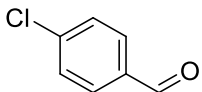
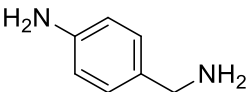
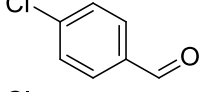
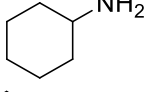
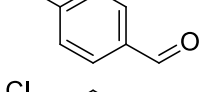
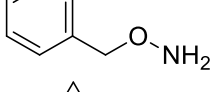
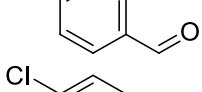
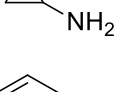
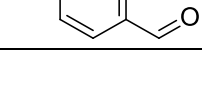
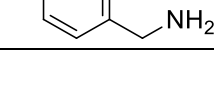


Table 2: Substituted R1 and R2

Compound	R1	R2
N1		
N2		
N3		
N4		
N5		
N6		

Methods:

The compliance of triphenyl-1H-imidazole derivatives was synthesized in tow steps using standard technique (Refluxing). Triphenyl-1H-imidazole was synthesized using a reported procedure and these benzyl were then treated with *p*-chlorobenzaldehyde, in the presence of glacial acetic acid (GAA) and ammonium acetate, to produce intermediate compound 5-(4-chlorophenyl)-2,4-diphenyl-1H-imidazole. The 5-(4-chlorophenyl)-2,4-diphenyl-1H-imidazole and formaldehyde was added slowly-slowly to the ethanolic solution of substituted secondary amine is stirred one hours at room temperature, kept it over night in refrigerator the solid form of compound is filtered and is washed with ethanol the was obtained substituted triphenyl-1H-imidazole. Compound purity was assessed by recoated TLC plate, and n- hexane – ethyl acetate (9:1) as the evolving solvent, and the spots were subjected to UV light, Melting point, elemental analysis and spectral information (FT-IR, MS, H1-NMR) were applied to characterize all synthesized compounds (N1-N6)¹⁸.

Synthesis of triphenyl-1H-imidazole

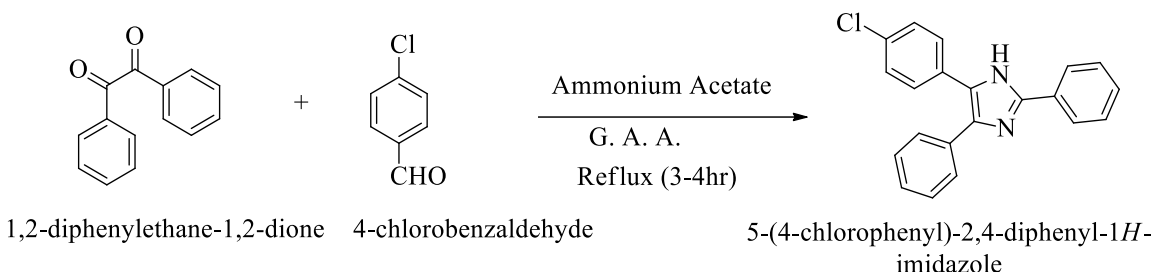
Step-I: General procedure for Synthesis of triphenyl-1H-imidazole

A combination of **2.0g** (0.0167mol) of Benzyl, **2g** (0.0167mol) of Ammonium acetate and **4ml** (0.0356) of *p*-chlorobenzaldehyde with **3ml** of glacial acetic acid reflux for **3-4 hours** the reaction mixture was allowed to be stand at room temperature. To that added **300ml** of distilled water the

solid thus obtained was filtered. The filter is neutralized with ammonium hydroxide or sodium carbonate to give solid pasty mass and filtered. Then the solid mass was washed with toluene. Recrystallisation will be done with methanol to get **5-(4-chlorophenyl)-2,4-diphenyl-1*H*-imidazole**.

Reaction involved

Step-I



Step-II: General procedure for Synthesis of Substituted triphenyl-1*H*-imidazole (N1-N6)

The crude of **0.01M** 5-(4-chlorophenyl)-2,4-diphenyl-1*H*-imidazole and **3gm** of formaldehyde was added slowly-slowly to the ethanolic solution of substituted secondary amine is stirred one hours at room temperature, kept it over night in refrigerator the solid form of compound is filtered and is washed with ethanol the was obtained substituted triphenyl-1*H*-imidazole. Compound purity was assessed by recoated TLC plate, and n- hexane – ethyl acetate (**9:1**) as the evolving solvent, and the spots were subjected to UV light, Melting point, elemental analysis and spectral information (FT-IR, MS, H1-NMR) were applied to characterize all synthesized compounds (**N1-N6**)¹⁹.

Reaction involved

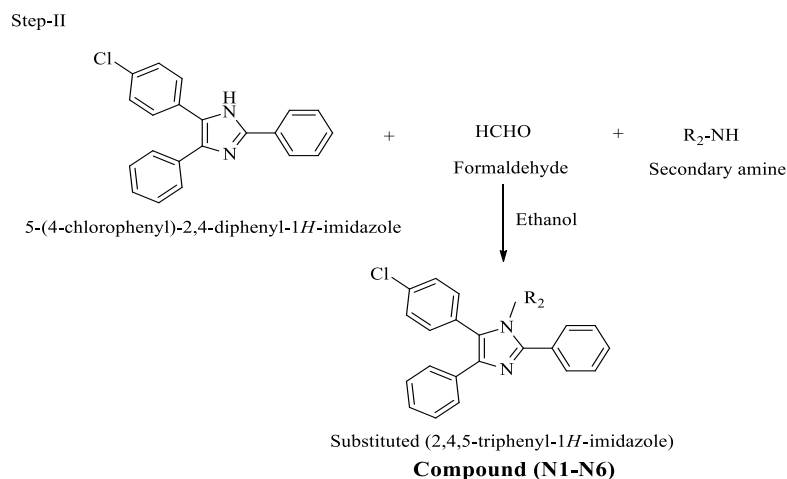


Table 3: Solubility test of synthesized compounds (N1-N6)

Compound	Water	Methanol	Chloroform	n-hexane	Petroleum Ether	Acetone	DMFO
N1	-	++	++	++	-	++	++
N2	-	++	++	++	-	++	++
N3	-	+	++	++	-	++	++
N4	-	+	++	++	-	++	++
N5	-	+	++	++	-	++	++
N6	-	++	++	++	-	++	++

Freely soluble: (++), partially soluble: (+), Insoluble: (-)

Synthesis of triphenyl-1H-imidazole

Step-I: General procedure for Synthesis of triphenyl-1H-imidazole

A combination of **2.0g** (0.0167mol) of Benzyl, **2g** (0.0167mol) of Ammonium acetate and **4ml** (0.0356) of p-chlorobenzaldehyde with **3ml** of glacial acetic acid reflux for **3-4 hours** the reaction mixture was allowed to be stand at room temperature. To that added **300ml** of distilled water the solid thus obtained was filtered. The filter is neutralized with ammonium hydroxide or sodium carbonate to give solid pasty mass and filtered. Then the solid mass was washed with toluene. Recrystallisation will be done with methanol to get **5-(4-chlorophenyl)-2,4-diphenyl-1H-imidazole**.

Spectral characterization of all synthesized compounds (N1-N6)

Compound (N1)

FTIR: C-Cl (Aromatic) 600-840 791.53, C-N stretching 1180-1360 1347.02, C=C (Aromatic) 1440-1625 1615.88, C-C (Aromatic) 1585-1600 1596.65, C-H (Aromatic) 3000-3100 2996.65, N-H (Amine) stretching 3250-3550 3385.39, C-NH₂ (Amine) stretching 3310-3550 3439.14

¹H NMR: ¹H NMR [DMSO-d₆] δ (ppm): 4.0 (s, NH, 1H), 6.27 (s, NH₂, 2H), 6.38-8.28 (m, Ar-CH, 18H).

Mass: MS-ESI [M⁺]: 436.4 (95%)

Compound (N2)

FTIR: C-Cl (Aromatic) 600-840 756.44, C-N stretching 1180-1360 1253.57, C=C (Aromatic) 1440-1625 1464.97, C-C (Aromatic) 1585-1600 1591.20, C-H (Aromatic) 3000-3100 3003.72, N-H (Amine) stretching 3250-3550 3362.96, C-NH₂ (Amine) stretching 3310-3550 3575.34

¹H NMR: ¹H NMR [DMSO-d₆] δ (ppm): 4.0 (s, NH, 1H), 4.36 (s, CH, 1H), 6.51-8.28 (m, Ar-CH, 18H), 8.68 (s, NH₂, 2H).

Mass: MS-ESI [M⁺]: 450.5 (93%)

Compound (N3)

FTIR: C-Cl (Aromatic) 600-840 771.94, C-N stretching 1180-1360 1219.56, C=C (Aromatic) 1440-1625 1517.45, C-C (Aromatic) 1585-1600 1619.23, C-H (Aromatic) 3000-3100 3003.72, N-H (Amine) stretching 3250-3550 3268.04, C-NH₂ (Amine) stretching 3310-3550 3364.46

¹H NMR: ¹H NMR [DMSO-d₆] δ (ppm): 1.48-2.28 (m, CH, 20H), 5.11 (d, NH₂, 2H).

Mass: MS-ESI [M⁺]: 427.2 (98%)

Compound (N4)

FTIR: C-Cl (Aromatic) 600-840 771.58, C-N stretching 1180-1360 1219.30, C=C (Aromatic) 1440-1625 1626.51, C-C (Aromatic) 1585-1600 1526.97, C-H (Aromatic) 3000-3100 3003.72, N-H (Amine) stretching 3250-3550 3292.02, C-NH₂ (Amine) stretching 3310-3550 3401.02

¹H NMR: ¹H NMR [DMSO-d₆] δ (ppm): 0.57-8.28 (m, Ar CH, 17H), 2.0 (s, NH, 1H).

Mass: MS-ESI [M⁺]: 385.1 (99%)

Compound (N5)

FTIR: C-Cl (Aromatic) 600-840 772.15, C-O stretching 1000-1360 1220.15, C-N stretching 1180-1360 1347.02, C=C (Aromatic) 1440-1625 1524.03, C-C (Aromatic) 1585-1600 1615.80, C-H (Aromatic) 3000-3100 3172.15, N-H (Amine) stretching 3250-3550 3492.15, C-NH₂ (Amine) stretching 3310-3550 3359.06

¹H NMR: ¹H NMR [DMSO-d₆] δ (ppm): 2.0 (d, NH₂, 2H), 4.79 (s, CH, 1H), 7.29-8.28 (m, Ar-CH, 18H).

Mass: MS-ESI [M⁺]: 451.1 (90%)

Compound (N6)

FTIR: C-Cl (Aromatic) 600-840 759.60, C-F stretching 1180-1360 1142.73, C-N stretching 1180-1360 1254.10, C=C (Aromatic) 1440-1625 1462.61, C-C (Aromatic) 1585-1600 1609.85, C-H (Aromatic) 3000-3100 3012.27, N-H (Amine) stretching 3250-3550 3362.83, C-NH₂ (Amine) stretching 3310-3550 3291.57

¹H NMR: ¹H NMR [DMSO-d₆] δ (ppm): 2.0 (s, NH, 1H), 4.28 (s, CH, 1H), 7.12-8.28 (m, Ar-CH, 18H).

Mass: MS-ESI [M⁺]: 453.1 (98%)

RESULT AND DISCUSSION

Chemistry:

The anticonvulsant properties of 6 new compounds that include the triphenyl-1H-imidazole scaffold were assessed in this work. The synthesis of triphenyl-1H-imidazole derivatives was achieved through a 2-step process using standard techniques including refluxing. First, we synthesized 5-(4-chlorophenyl)-2,4-diphenyl-1H-imidazole using a reported procedure. We then added polyphosphoric acid this compound and refluxing ethanol, producing triphenyl-1H-imidazole. Finally, we obtained triphenyl-1H-imidazole. We evaluated the purity of the synthesized compounds using precoated TLC plates and subjected the spots to UV light. All synthesized compounds (N1 to N6) were characterized by various physiochemical parameters like melting point, physical state, and solubility.

IR spectra of the synthesized triphenyl-1H-imidazole derivatives (N1 to N6) showed absorption bands in the 3500-3100 cm^{-1} range for primary amine (N-H stretching) and C-H stretching bands were observed in 3000-3100 cm^{-1} . The C=C and C-C stretching bands were detected in 1440-1625 cm^{-1} and 1185-1600 cm^{-1} , respectively. Other prominent characteristic absorption peaks at 1640-1550 cm^{-1} amine (N-H bending) were also observed. MS-ESI [M^+ & M^-] peaks were observed in the mass spectra, consistent with the proposed structures. Similarly, NMR spectra with chemical shifts were consistent with the proposed structure. Rest assured that we have performed rigorous quality control procedures to ensure the accuracy and reliability of our results.

Biological activity

MES induce seizure model

The MES seizure model was used to conduct an initial assessment of every synthesized chemical. The anticonvulsant efficacy of all the substances was encouraging. The compounds N2, N3, and N5 had the highest level of activity against the MES test, with a dose level of 100 mg/kg. Maximum inhibition of extensor phase was observed with phenytoin, a medicine used as standard²⁰.

Table-4: in vivo anticonvulsant activity of synthesized compounds

Compound	Dose(mg/kg)	Hind limb extensor (Mean $\pm$ SEM)
Disease control	Normalsaline	19.40 $\pm$ 0.35
Std.(Phenytoinsodium)	25	2.0 $\pm$ 0.13***
N1	100	17.0 $\pm$ 0.12
N2	100	3.60 $\pm$ 0.15***
N3	100	3.80 $\pm$ 0.14***
N4	100	5.40 $\pm$ 0.19
N5	100	4.40 $\pm$ 0.19***
N6	100	5.40 $\pm$ 0.19

All the values are uttered as Mean $\pm$ SEM of five animal of each group. ***($p=0.001$) shows the level of statistical consequence as associated with control.

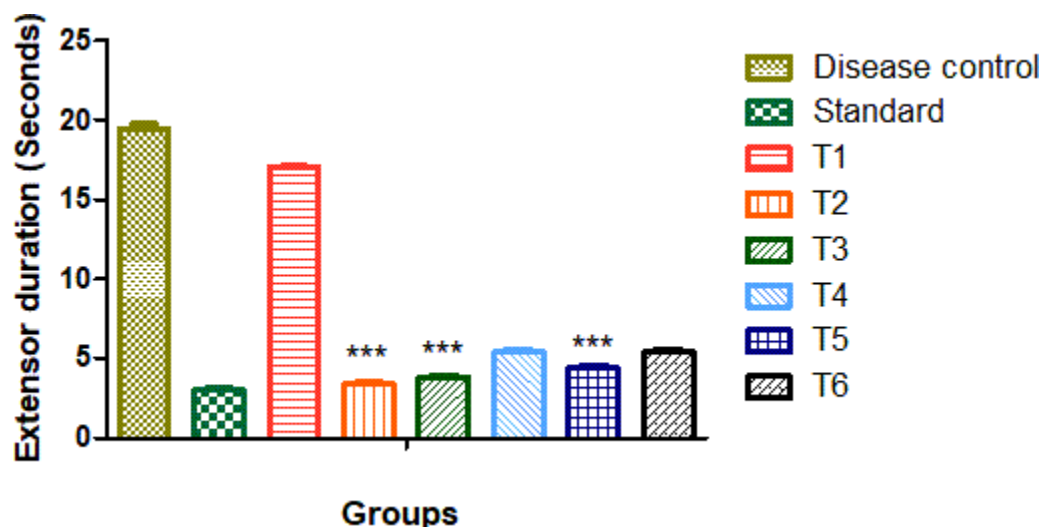


Figure 2: in vivo anticonvulsant activity of synthesized compounds

DISCUSSION

The Epilepsy is one of the most challenging neurological problems in the society. The compliance of triphenyl-1H-imidazole derivatives was synthesized in first step using standard techniques (reflux).

The synthesis of triphenyl-1H-imidazole derivatives was synthesized in tow steps using standard technique (Refluxing). Triphenyl-1H-imidazole was synthesized using a reported procedure and these benzyl were then treated with *p*-chlorobenzaldehyde, in the presence of glacial acetic acid (GAA) and ammonium acetate, to produce intermediate compound 5-(4-chlorophenyl)-2,4-diphenyl-1H-imidazole. The 5-(4-chlorophenyl)-2,4-diphenyl-1H-imidazole and formaldehyde was added slowly-slowly to the ethanolic solution of substituted secondary amine is stirred one hours at room temperature, kept it overnight in refrigerator the solid form of compound is filtered and is washed with ethanol the was obtained substituted triphenyl-1H-imidazole. Finally, we obtained triphenyl-1H-imidazole derivatives (N1 to N6). Spectral study FT-IR, MASS, and ^1H NMR, were used to describe each of the synthesized compounds (N1 to N6) and characterized by various physiochemical parameters like melting point, physical state, and solubility.

Given the bioactivity of triphenyl-1H-imidazole, it was determined to carry out an ecological evaluation on all new forms of triphenyl-1H-imidazole and their compounds (N1 to N6).

Therefore, all synthesized compounds have been evaluated for anticonvulsant activity. The in vivo anticonvulsant activity effect of the new triphenyl-1H-imidazole was explored using a MES model. The mice were given an intraparitoneal injected of standard drug phenytoin solution, after a one-hour period by the help of Maximal Electroshock Seizure (MES) induces at 50 Hz for 0.2 seconds. Note the various seizure stages. Most potent compounds are N2, N3 and N5.

CONCLUSION

In this study, novel triphenyl-1H-imidazole derivatives were synthesized and characterized using IR, NMR, and Mass spectrometry. The pharmacological evaluation using the maximal electroshock-induced seizure (MES) method revealed that compounds N2, N3, and N5 exhibited the highest anticonvulsive potential, with significant differences (***($p=0.001$)) when compared to

the standard phenytoin sodium. On the other hand, compounds N4 and N6 demonstrated lower potency. The findings suggest that the triphenyl-1H-imidazole scaffold, when combined with other heterocyclic rings, could serve as a promising lead for the development of potent anti-convulsive agents. The reduction in convulsion intensity at various time intervals supports the potential of these novel derivatives as anticonvulsants. Additionally, the modification of the triphenyl-1H-imidazole core with substituted groups further enhances its therapeutic value, making it a strong candidate for further exploration in the search for effective anticonvulsive treatments. Overall, this study highlights the potential of triphenyl-1H-imidazole derivatives, particularly in combination with other heterocyclic, as a valuable lead in the development of new anticonvulsive agents with improved pharmacological profiles. Further research is needed to explore their full therapeutic potential and optimize their efficacy in the treatment of seizures.

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