WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 17, 107-113. Review Article ISSN 2277– 7105

REVIEW ON ANTICONVULSANT EVALUATION OF SOME NEWER BENZIMIDAZOLEDERIVATIVES: DESIGN AND SYNTHESIS

Palmate Ankita L.*, Bavge S. B., Patel A. C. and Ingle P. V.

Student At. P kamkheda Latur Maharashtra India.

Article Received on
28 October 2022,

Revised on 18 Nov. 2022,
Accepted on 08 Dec. 2022

DOI: 10.20959/wjpr202217-26273

***Corresponding Author**
Palmate Ankita l.
Student At. P kamkheda
Latur Maharashtra India.

ABSTRACT

A series of new 2-[(1-substituted phenylethylidine) hydrazine]-N-phenyl-1H-benzo[d]imidazole-1-carbothioamides (4a-n) were designed and synthesized to have the pharmacophoric elements essential for anti-convulsant activity. The key step in the synthesis of the title compounds involves the reaction of 2-mercapto-benzimidazole with hydrazine hydrate, substituted acetophenones and phenylisothiocyanate to get the com-pounds in good yields. All the newly synthesized compounds were screened by two most adopted models, max-imal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ). Interestingly, compounds 4e, 4f, 4g, 4h and 4j exhibited potent anticonvulsant results and in the neurotoxicity screening, most of the com-pounds were devoid of toxicity at the dose of 60 and 100 mg/kg.

KEYWORD: 2 mercaptobenzimdiazole, Maximal elctroahock seziure test, Subcutaneous pentylenetetrazole, Anticonvulsant activity, Neurotoxcitiy.

INTRODUCTION OF EPILEPSY

Epilepsy is a central nervous system (neurological) disorder in which brain activity becomes abnormal, causing seizures or periods of unusual behavior, sensations and sometimes loss of awareness.

A disorder in which nerve cell activity in the brain is disturbed, causing seizures.

Epilepsy may occur as a result of a genetic disorder or an acquired brain injury, such as a trauma or stroke.

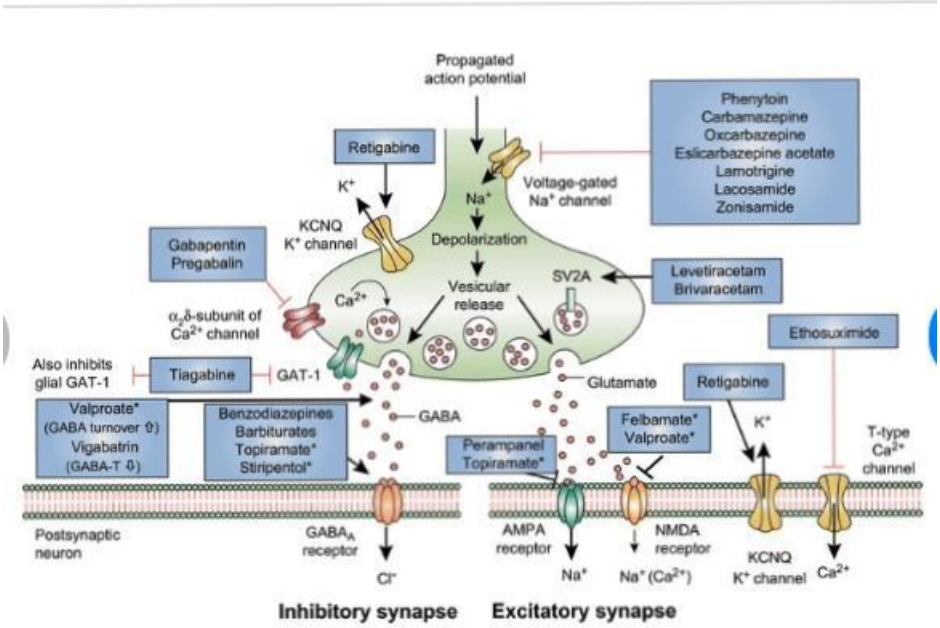
Epilepsy also called as seizure disorder.

Symptoms

Because epilepsy is caused by abnormal activity in the brain, seizures can affect any process your brain coordinates. Seizure signs and symptoms may include:

1. Temporary confusion
2. A staring spell
3. Stiff muscles
4. Uncontrollable jerking movements of the arms and legs
5. Loss of consciousness or awareness
6. Psychological symptoms such as fear, anxiety

Mechanism of action



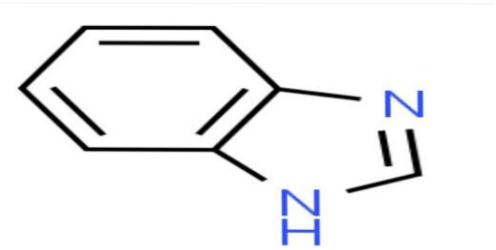
Established antiepileptic drugs (AEDs) decrease membrane excitability by interacting with neurotransmitter receptors or ion channels. AEDs developed before 1980 appear to act on sodium channels, gamma-aminobutyric acid type A (GABAA) receptors, or calcium channels.

Benzodiazepines and barbiturates enhance GABAA receptor-mediated inhibition. Phenytoin (PHT), carbamazepine (CBZ), and possibly valproate (VPA) decrease high-frequency repetitive firing of action potentials by enhancing sodium-channel inactivation.

Ethosuximide (ESM) and VPA reduce a low threshold (T-type) calcium-channel current. The mechanisms of action of the new AEDs are not fully established. Gabapentin (GBP) binds to

a high-affinity site on neuronal membranes in a restricted regional distribution of the central nervous system. This binding site may be related to a possible active transport process of GBP into neurons; however, this has not been proven, and the mechanism of action of GBP remains uncertain. Lamotrigine (LTG) decreases sustained high-frequency repetitive firing of voltage-dependent sodium action potentials that may result in a preferential decreased release of presynaptic glutamate.

Benzimidazole



Benzimidazole is one of the oldest known nitrogen heterocycles and was first synthesized by Hoebrecker and later by Ladenberg and Wundt during 1872-1878.

This bicyclic compound may be viewed as fused rings of the aromatic compounds benzene and imidazole.
Chemical formula: C7H6N2
Melting point: 170 to 172 °C (338 to 342 °F; 443 to 445 K)
Acidity (pKa): 12.8 (for benzimidazole) and 5.6 (for the conjugate acid).

Pharmacology of benzimidazole

Benzimidazoles are a class of heterocyclic, aromatic compounds which share a fundamental structural characteristic of six-membered benzene fused to five-membered imidazole moiety. Molecules having benzimidazole motifs showed promising application in biological and clinical studies. Nowadays it is a moiety of choice which possesses many pharmacological properties extensively explored with a potent inhibitor of various enzymes involved in a wide range of therapeutic uses which are antidiabetic, anticancer, antimicrobial, antiparasitic, analgesics, antiviral, and antihistamine.

As well as used in cardiovascular disease, neurology, endocrinology, ophthalmology, and more. The increased interest for benzimidazole compounds has been due to their excellent properties, like increased stability, bioavailability, and significant biological activity.

Chemistry of benzimidazole

All of the chemicals used in synthesis wereobtained from s.d. Fine Chem.,Spectrochem Pvt.Ltd., and Qualigens. The purity of synthesized compound was tested by thin layer chromatography onsilica gel G coated plates and solvent system usedwas benzene : acetone (7:3 v/v). Melting points weredetermined in open glass capillaries using Hiconmelting point apparatus (Hicon, India) and areuncorrected. The infrared spectra of the compoundswere recorded in KBr discs on Shimadzu 8416 FT-IR (λmax in cm-1). The proton magnetic resonance (1HNMR) spectra were recorded on Bruker DRX 300 inDMSO-d6 at 300 MHz using TMS as an internalstandard and mass spectrum on Jeol SX 102/DA-6000 mass spectrometer using methanol as solvent.Iodine chamber and UV lamp were used for visualization of TLC spots. Elemental analysis was per-formed on CHN analyzer, Carlo Erba 1108. All thechemicals used werevisuali-zation of TLC spots. Elemental analysis was per-formed on CHN analyzer, Carlo Erba 1108. All thechemicals used were of L.R. grade and used without purification.

Synthesis of compound

General procedure for synthesisof 1-(1H-benzo[d]imidazole-2-yl) hydrazine (2)To the warm hydrazine hydrate solution (0.02mol) of 2-mercapto-1benzo[d]imidazole(0.01mol), ethanol (10 mL) was added and thenaqueoussolution of sodium hydroxide (10%)added and the reaction mixture was refluxed for 6h. The solid obtained was filtered, dried in vacuumdessicator and recrystallized from absolute ethanolto yield compound 2, (68.34%), m.p. 298ñ300OC.

Genaral procedure of synthesis of 1-(1H-benzo[d]imidazole-2-yl)-2-[(1-substituted-phenylethylidene] hydrazones (3a-n)Equimolar quantity of 1-(1H-benzo[d]imida-zole-2-yl)hydrazine (2) (0.12 mmol) and substitutedacetophenones (0.12 mmol) in ethanol (10 mL) wasrefluxed for 6.5 h. After refluxing, the reaction mix-ture was poured onto crushed ice. The solid obtainedwas filtered, dried and recrystallized from ethanol togive compounds 3añn.

Maximal electroshock seizure test (MES)

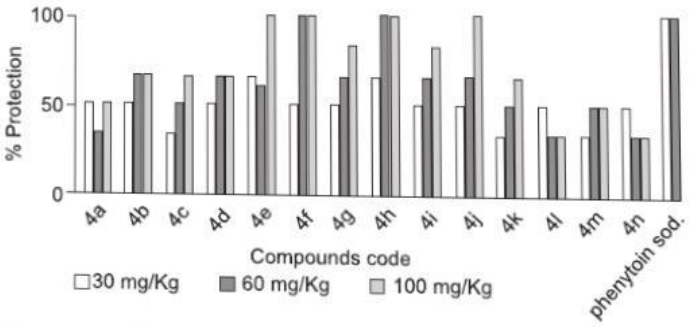


Figure 1. Graphical representation of anticonvulsant activity by MES test

Each compound was administered through anoral route at dose level of 30, 60 and 100 mg/kgbody weight. The maximal electroshocks seizureswere elicited in rats by delivering 60 Hz, 150 mAelectrical stimuli for 0.2 s via ear clip. The MES-convulsions are divided into five phasessuch as (a) tonic flexion (b) tonic extensor (c) clonicconvulsion (d) stupor € recovery or death. Thetime (s) spent by the animal in each phase of theconvulsions was noted. A compound is known topossess anticonvulsant property if it reduces or abol-ishes the hind limb tonic extensor phase of MES-convulsions.

scPTZ- induce seizure test

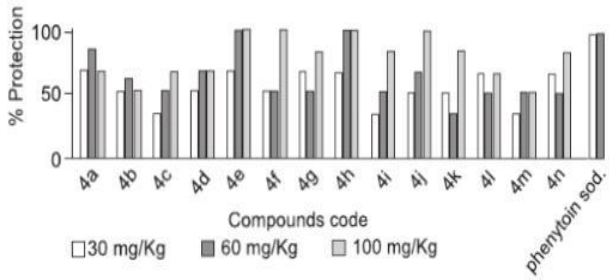


Figure 2. Graphical representation of anticonvulsant activity by scPTZ test

He scPTZ test utilizes a dose of pentylenete-trazole (70 mg/kg in rats). This produces clonicseizures lasting for a period of at least 5 s. The timeneeded for the development of clonic seizure activi-ty involving limbs and duration of seizure was care-fully noted. Seizure free period of 1 h was consid-ered as protection. The number of animals protectedin each group was recorded and percentage of pro-tection was calculated.

Neurotoxicity screening

The minimal motor impairement was measured in rats by the rotorod test. The albino rats (100-250g) were trained to stay on an accelerating rotorod (diameter 3.2 cm) that rotated at 10 rpm. Only thoserats were taken for the test, which can stay on therevolving rod for at least one minute. Trained ani-mals were injected i.p. with the test compounds atdoses of 100 mg/kg. Neurotoxicity was indicated bythe inability of the animal to maintain equilibrationon the rod for at least one minute.

CONCLUSION

A simple and convenient methodhas been developed to synthesize novel 2-[€2-(1-phenylethylidine)hydrazinyl]-N-phenyl-1H-benzo[d]imidazole-1-carbothioamides (4a-n).Further, the study highlights the importance of thestructural features responsible for the anticonvulsantactivity. These compounds, being active in both thescreens, proved to have broad spectrum of action indealing with the convulsions. These new data mightbe beneficial in the future development of benzimi-dazole derivatives as novel anticonvulsants.

REFERENCES

1. Leonard J.T., Jeyaseeli L., Kumar M., Sivakumar R.: Asian J. Chem, 2006; 18: 1104.
2. Srinivasan N., Balaji A., Nagrajan G., Suthakaran R., Kumar Y., Jagdesh D.: Asian J. Chem, 2008; 20: 4934.
3. Deshmukh M.B., Suryavanshi A.W., Deshmukh S.A., Jagtap S.S.: Ind. J. Chem, 2009; 86B: 302.
4. Ansari K.F., Lal C.: Eur. J. Med. Chem, 2009; 44: 2294.
5. Devivar R.V., Kawashima E.: J. Med. Chem, 1994; 37: 2942.
6. Gellis A., Kovacic H., Boufatah N., Vanelle P.:Eur. J. Med. Chem, 2008; 43: 1858.
7. Vezquez G.N., Vilchis M.D., Mulia L.Y., Melendez V., Gerena L., Compos A.H.: Eur. J.Med. Chem, 2006; 41: 135.
8. Bariwal J.B., Shah A.K., Kathiravan M.K., Somani R.S., Jagtap J.R., Jain K.S.: Ind. Pharm. Educ. Res, 2008; 42: 225.
9. Tripathi T., Mishra J.P.: Indian Drugs, 2008; 45: 809.
10. Ate∫-Alagoz Z., Ku∫ C., Coban T.: J. Enz. Inhib. Med. Chem, 2005; 20: 325.
11. Kumar B.B., Rao P.V.: Asian J. Chem, 2006; 18: 3060.
12. Alonso F.P., Cook H.J.: Eur. J. Med. Chem, 2009; 44: 1794.

13. Orjales A., Cires L.A., Tudanca P.L., Tapia I., Mosquera R., Labeaga L.: Eur. J. Med. Chem, 1999; 34: 415.
14. Sondhi S.M., Rajvanshi S., Johar M., Bharti N., Azam A., Singh A.K.: Eur. J. Med. Chem, 2002; 37: 835.