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Review Article

Benzotriazole Derivatives And Its Pharmacological Activity

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ABSTRACT

Azoles are heterocyclic chemicals that were first identified in late 1960 and make up the largest class of currently accessible antifungal medications. A particular chemical element that gives azoles their activity is the imidazole ring. Triazoles are made by making a small alteration to this ring, and derivatives of triazoles have been found to have equal or better actions as well as fewer negative effects. It follows that the discovery of biological activity in benzimidazole/benzotriazole compounds is not unexpected. Due to the extensive research on benzimidazole, the focus of this review is on defining the role of benzotriazole derivatives in biomedical research, highlighting their diverse biological characteristics, the mechanism of action, and Structure Activity Relationship (SAR) studies for a variety of antimicrobial, antiparasitic, and even antitumor, cholesterol-lowering agents.

INTRODUCTION

Benzotriazole is a type of heterocyclic organic compound containing, a ring System & 3 nitrogen atom a fused benzene ring exhibit a broad range of biological activity. This is Synthesis of 1,2-Phenylenediamine by diazotization with sodium nitrate and acetic acid[1]

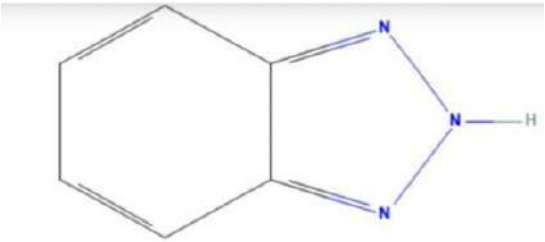

Fig no.1: General structure of benzotriazole

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Table no. 1.Physicochemical Properties of Benzotriazole

Molecular formula	C6H5N3
Molecular weight	119.1240 gm
Melting point	98.5 - 100°C
Nature	White to brown crystalline
Density	1.36g/cm3
UV Absorbance	286nm

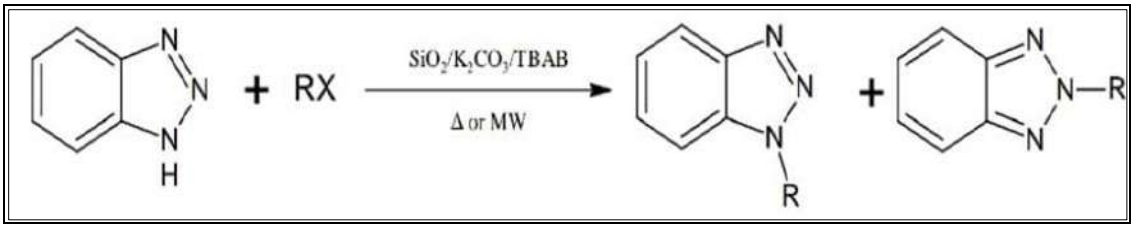


Fig No.2: General reaction of benzotriazole

1.2 Mechanism of Benzotriazole:-[15]

Benzotriazole

↓

Ability to permit /enter into cell membrane

↓

Membrane of microbes

↓

Damages the membrane of the microbe's cell membrane

↓

Leakage out the content

↓

Death of microbes

2. Synthesis of Benzotriazole

2.1. Scheme-1 for synthesis of benzotriazole

By cyclocondensing o-phenylenediamines with sodium nitrite in acetic acid, benzotriazoles are created. The reagents were simply heated together to initiate the reaction. After the diamine is transformed into the monodiazonium derivative, spontaneous cyclization occurs.[3]

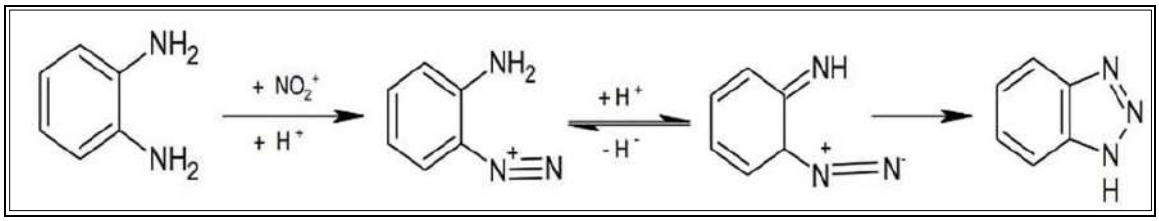


Fig no.3: Synthesis of Benzotriazole

2.2. Scheme-2

The hydrolysis of an acylated or aroylated benzotriazole that had previously been synthesized by the action of nitrous acid on the corresponding mono acylated or aroylated o-phenylenediamine led to the direct preparation of 1,2,3-benzotriazole. The process described above is direct and produces better overall yields than methods involving a number of intermediate steps.[16]

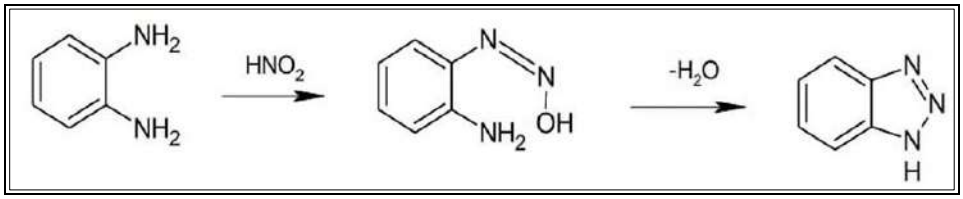
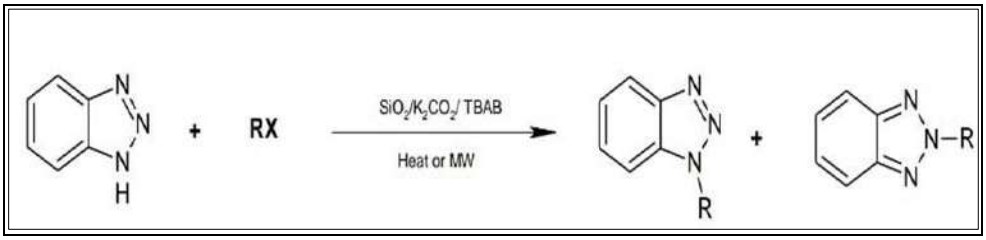


Fig no.4: Hydrolysis of O-Phenylenediamin

2.3. Scheme-3

N-Alkylation of benzotriazole in the absence of solvent: In the presence of SiO2, K2CO3, and tetrabutylammonium bromide (TBAB) under thermal and microwave conditions, a highly efficient, straightforward, and solvent-free approach for the N-alkylation of benzotriazole has been created. 1-alkyl benzotriazoles were produced using this technique. with quick reaction times and moderate to high yields, regioselectivity[17]



R= Alkyl, Aryl

Fig no.5: Alkylation of benzotriazole

By cooling and stirring benzene-1,2-diamine and carboxylic acid, benzotriazoles are created.

3. Pharmacological effect of benzotriazole:

3.1. Antimicrobial activity of benzotriazole : Since the late 1980s, benzotriazole derivative, antimicrobial activity has been thoroughly studied, and along with all azolic ring, they have emerged as one of the latest active highlights. The discovery and advancement on antimicrobial medication were significant scientific breakthrough in the early twentieth century. Despite the investment made in the research of antimicrobial drugs. [1] Acantamoeba castellanil , a protozoan has been evaluated in vitro using 1H-benzotrialole and their chloro, bromo, and methyl counter parts as well as their N- alkyl derivatives according to the findings, chloro-hexidine and 5,6-dibromo-1H-benzotriazole are less effective against protozoa than 5,6-diabromo-1H-benzotriazole and 5,6-dibromo-1H-benzotriazole. [3]

antifungal properties of the benzotriazole moiety (Compound B showed good efficacy).[17]

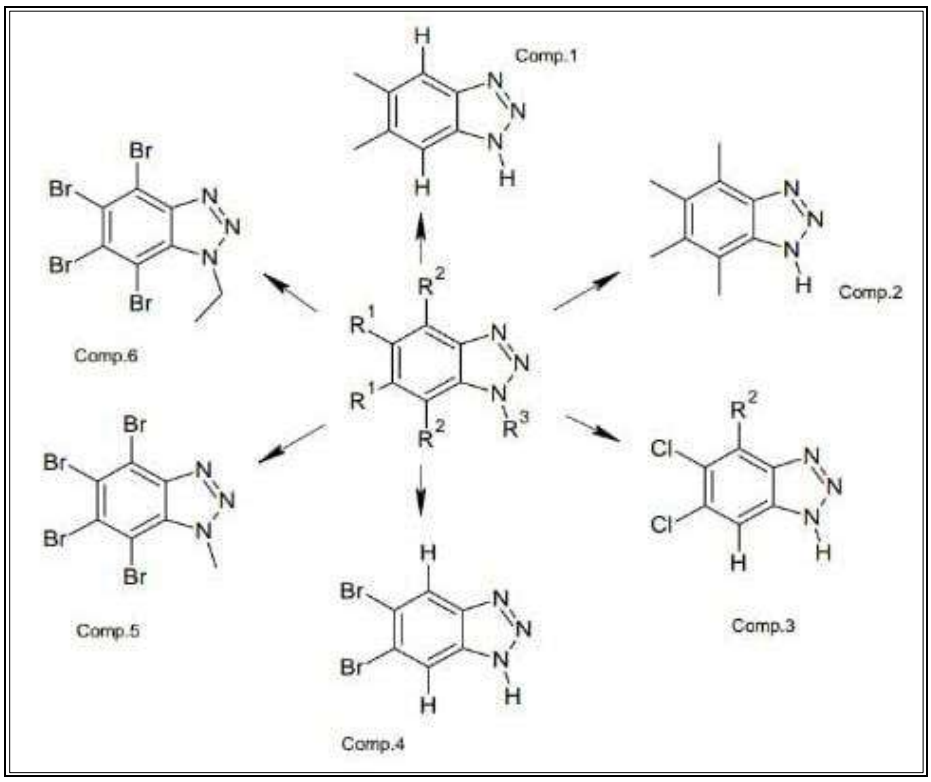


Fig no.6: Derivatives of Antimicrobial Benzotriazole

3.2. Antiviral activity of benzotriazole:-

Virus is pathogens that can lead to serious illness in both humans and animals, resuting in a loss of a life, financial losses, and greater production costs. They were divided int DNA and RNA viruses by bacteria.[2] There are many targets that have been identified that antiviral drugs are most likely to be effective against a primer target drug discovery include essential metabolic enzymes like polymers, protease and helicase widespread research is being done on nucleoside and non – nucleoside inhibitor to expand the pharmacological toolbox and procedure more effective and targeted antiviral medicines. [1]

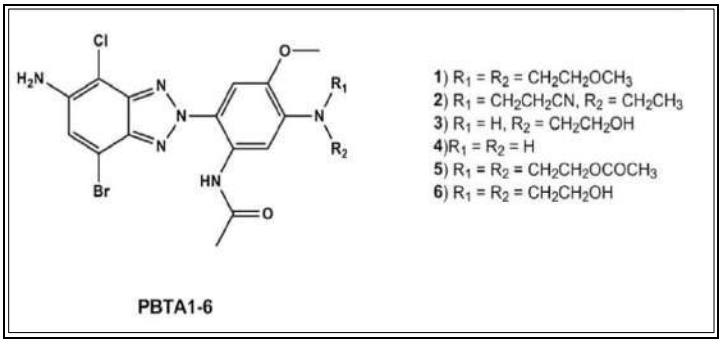


Fig no.7: Phenyl benzotriazole derivative recognized as mutagenic agent

It was discovered that a novel series of Benzotriazole compounds with dialkylamino side of benzotriazole compounds with dialkylamino side chains are most effective when taken together as possible inhibitor of the respiratory synthctial virus.[8] The halogenated benzotriazole nucleoside were effective inhibitor of the west

Nile virus enzyme with RNA substrate [1C50 – 0.3m] and also revealed selective antiviral activity was tested against the hepatic C virus and other viral NTpase/helicases.[3]

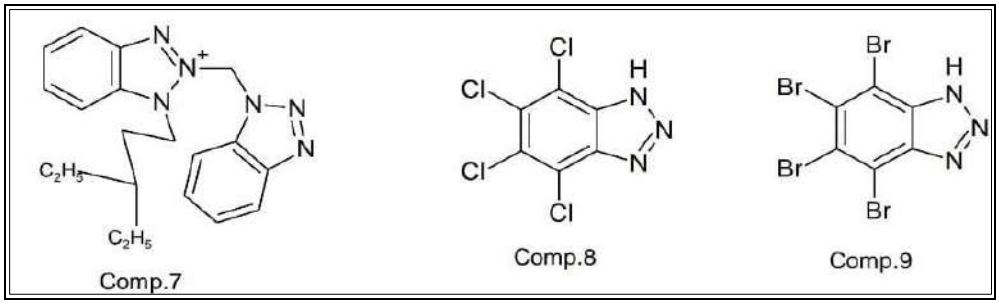


Fig no.8: Derivatives of antiviral benzotriazole

3.3. Antitubercular activity of benzotrizole :-

Mycobacterium tuberculosis is the main cause of the highly contagious disease known as tuberculosis (TB). Several antitubercular medications, including isoniazid and rifampicin, are offered in clinics.[13] The use of clinical anti-TB medications has been constrained by their diminished efficacy and unavoidable toxic side effects due to the prevalence of resistant strains, clinical adverse drug reactions of the stomach and gut, as well as liver damage. Therefore, it is essential to create new, powerful anti-tubercular medications that lack cross resistance with established antimycobacterial treatments.[1] More studies have recently revealed the significant potential for nitrogen heterocyclic benzotriazole compounds to cure tuberculosis. It has been demonstrated that replacing the halogen atoms on the benzene ring with benzotriazole rings is an effective strategy to increase the bioactivity.[19] Some amide benzotriazloe derivatives synthesized from syndromes fragment were reported to display good antitubercular activities. Mycobacterium tuberculosis is the main cause of the highly contagious disease known as tuberculosis (TB). Several antitubercular medications, including isoniazid and rifampicin, are offered in clinics.[20] The use of clinical anti-TB medications has been constrained by their diminished efficacy and unavoidable toxic side effects due to the prevalence of resistant strains, clinical adverse drug reactions of the stomach and gut, as well as liver damage. Therefore, it is essential to create new, powerful anti-tubercular medications that lack cross resistance with established antimycobacterial treatments.[3]

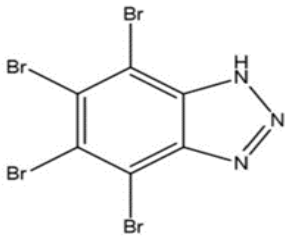


Fig no.9: Benzotriazole-based cancer drugs

3.4. Antioxidant activity of benzotriazole:-

Free radicals, represented by reactive oxygen nitrogen species from human metabolism, could produce harmful substances by a variety of metabolic pathways, and then cause health problems, such as aging, cancer and many neurodegenerative diseases. Therefore, eliminating the excessive oxidized free radicals, improving the antioxidative activities of the body to resolve the aging-related diseases has been an increasingly important challenge. Antioxidants are reducing agents used to stabilize some free radicals produced by cellular metabolism. Benzotriazole compounds have shown remarkable antioxidative activities and large potentiality to be novel antioxidative agents or candidates.[16] Primaquine (PQ) derivatives are well known and wide-used antimalarial drugs, meanwhile they are interesting molecules to develop potential

antioxidative agents due to their prooxidant effects in blood. Benzotriazole substituted primaquine 58 showed a higher interaction (73.8%) than the parent compound primaquine (31%), and it also exhibited a good lipoxygenase inhibitory (LOX) inhibition. In addition, benzotriazole derivative had perfect DPPH interaction value (85%), which was comparable to that of the reference compound nordihydroguaiaretic acid (91%) at the same concentration. This compound also displayed a good lipid peroxidation (LP) inhibition of 31%.[3] Reactive oxygen and nitrogen species (free radicals) from human metabolism can produce hazardous compounds through a number of metabolic pathways, which can eventually lead to health issues like aging, cancer, and numerous neurological illnesses. Therefore, reducing the body's excessive levels of oxidized free radicals and enhancing its antioxidative capabilities to treat disorders associated with aging have become more essential challenges. In order to stabilize some free radicals created by cellular metabolism, antioxidants are used as reducing agents. The antioxidative properties of benzotriazole compounds are exceptional, and they offer a lot of potential as novel antioxidative agents or candidates.[3] Due to their prooxidant effects in blood, derivatives of the well-known and widely-used antimalarial medication primaquine (PQ) provide intriguing compounds for the development of possible antioxidative medicines. Primaquine 58 with a benzotriazole replacement exhibited a stronger interaction (73.8%) than the parent compound primaquine (31%), and it also exhibited a good lipoxygenase inhibitory (LOX) inhibition. In addition, benzotriazole derivative had perfect DPPH interaction value (85%), which was comparable to that of the reference compound nordihydroguaiaretic acid (91%) at the same concentration. [3] Karali et al. reported the synthesis of Spiro[benzothiazole-indol]conjugates and examined their antioxidant activities, including the Fe3+/ascorbate system-induced inhibition of lipid peroxidation (LP) in liposomes, trolox equivalent antioxidant capacity (TEAC), DPPH scavenging activity, and reducing power (RP). The most effective antioxidant was a methyl-substituted compound. The substitution of methyl or halogen on the spiroindolinones resulted in an enhancement in the antioxidant capabilities. Trifluoromethoxy or nitro groups that replaced methyl or halogen groups exhibited decreased anti-oxidant activity. Using the ferric reducing antioxidant power (FRAP) method, Tzanova and colleagues reported on a number of 5-hydroxybenzoyl-benzothiazolone derivatives and their in vitro antioxidant activity. These substances' cytotoxicity was assessed against the three cell lines MCF7, hTERT-HME1, and H9c2.[7]

3.5. Anti-inflammatory action of Benzotriazole:

Its ability to reduce inflammation. The substance benzotriazole-6- carboxylic acid was found to inhibit CPLA2 and have substantial anti-inflammatory effects. The anti-inflammatory activity was diminished when the carboxyl benzotriazole scaffold was replaced with a carboxyl indole or carboxyl benzimidazole moiety.[6]

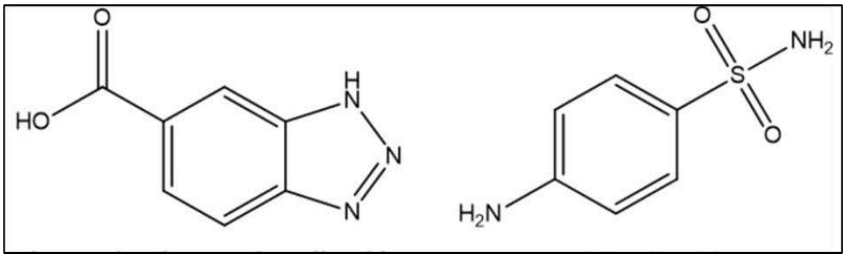


Fig no. 10 : benzotriazole-6-carboxylicacid

The tetrazole-linked sulfanilamide benzotriazole derivative demonstrated significantly more anti-inflammatory effect when compared to the commonly used paracetamol-based benzotriazole anti-inflammatory medicines. The anti-inflammatory effects of the compound are enhanced by the addition of the benzotriazole and the substituted sulfonyl moiety. [18]

3.6. Antibacterial activity of Benzotriazole:-

Tazobactam, an antibacterial used as an anticonvulsant in combination with -lactam antibiotics, is one of the clinically effective derivatives of 1,2,3-triazole. Rizatriptan, Trazodone (Fig. 11), an antidepressant, Dapiprazole (Fig. 10), a miotic, Ribavirin (Fig. 13), an antiviral, Israpafant, an anti-asthmatic, Lotrifen (Fig. 14), an abortifacient, and Rilmazafone (Fig. 15), a strong sedative and hypnotic.[6]

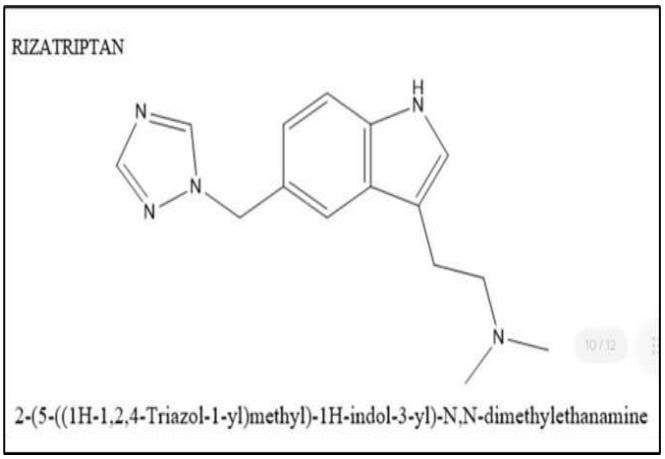


Fig no. 11 : Rizatriptan

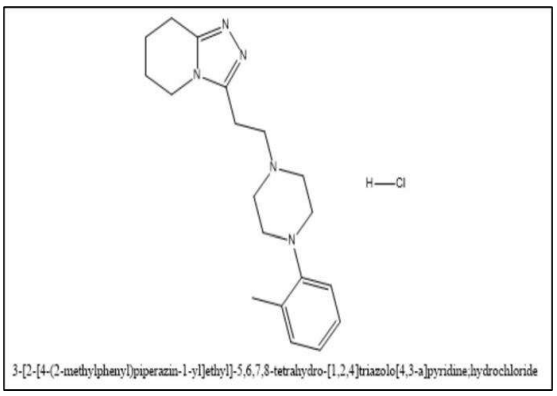


Fig no. 12 : Dapiprazole

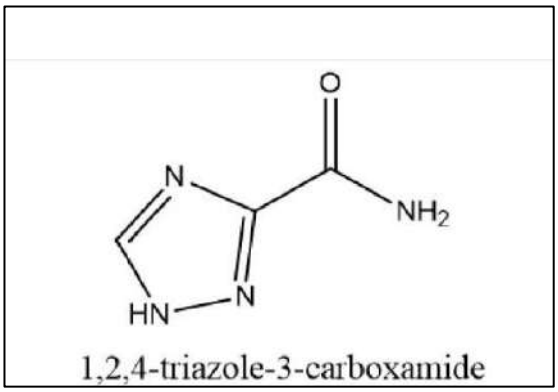


Fig no. 13 : Ribavirin

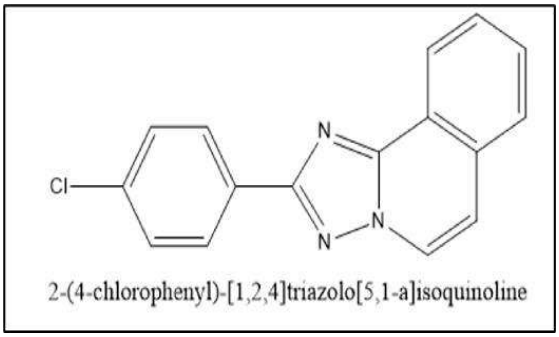


Fig no.14 : Lotrifen

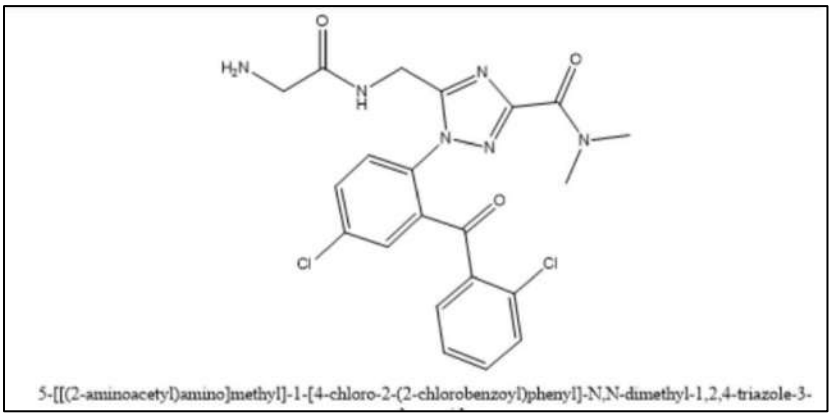


Fig no.15 : Rilmazafon

CONCLUSION

The study indicates that pharmacological activities exhibited by benzotriazole derivatives. Benzotriazole derivatives is focused on screening of biological activities such as antibacterial, antiviral, antitubercular, antimicrobial, anti-inflammatory, analgesic, antioxidant etc. in which benzotriazole is act as a tagging molecule to deliver other pharmacologically active heterocyclic nuclei. The investigated reports in this review definitely suggest the possibility to develop a lead compound in which benzotriazole is used as a tagging molecule to emerge new chemical entities (NCE's) of benzotriazole having potential pharmacological activity. The study shows that benzotriazole compounds have pharmacological properties. The biological characteristics of these new benzotriazole generations would serve as a sound foundation for the continued development of improved pharmaceuticals. Benzotriazole serves as a tagging molecule to deliver other pharmacologically active heterocyclic nuclei. Benzotriazole derivatives are concentrated on screening biological activities such as antibacterial, antifungal, antiviral, antitubercular, anticancer, anti-inflammatory, anticonvulsant, analgesic, and antioxidant. The reviewed articles that were looked into strongly imply that it may be possible to create a lead compound in which benzotriazole is employed as a tagging molecule to produce novel chemical entities (NCEs) of benzotriazole that have the potential to exhibit pharmacological action.

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