IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Review Of Benzotriazole

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Abstract:-

Benzotriazole is a bicyclic heterocyclic system consisting of three nitrogen atoms and fused benzene ring, shows wide range of biological and pharmacological activities. Benzotriazole can be synthesized using benzene-1, 2-diamine and carboxylic acid. Benzotriazole posses wide spectrum of biological activities like including antibacterial, antifungal, antiviral, anti-inflammatory, antihypertensive, analgesic properties. The present reviews attempted to gather the various developments in synthesis and biological activities of benzotriazole derivatives.

Key words: - Benzotriazole, Biological activities, Synthesis, Pharmacological activities.

Introduction

Benzotriazole are a class of heterocyclic organic compound having a ring system containing three nitrogen atoms and fused benzene ring shows wide range of biological activities. It is synthesised by diazotization process using benzene-1,2-diamine with sodium nitrite and acetic acid [1].

As the micro-organisms are rapidly undergoing genetic changes and developing resistance against many antibiotics and therapeutic agents for various diseases more quickly than new drugs are being made available so the war against the infectious diseases has become a never ending process. Bess. Over the past few decades, there are great interest of triazole class arising due to their wide use in industry and agriculture. Benzotriazole and its derivatives have great significance in medicinal chemistry [2].

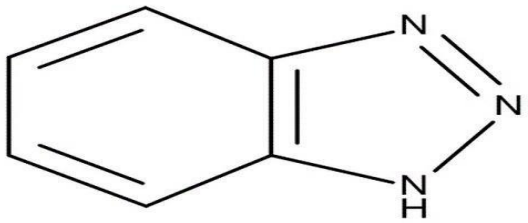
The incorporation of the Benzotriazole nuclei is an important synthetic strategy in drug discovery. The high therapeutic properties of the related drugs have encouraged the medicinal chemists to synthesize the large number of novel chemotherapeutic agents [3].

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 [4]. Benzotriazoles are often used as corrosion inhibitors, radioprotectors, and photo stabilizer in the production of plastic, rubber and chemical fiber 3. Along with these activities, benzotriazole is also important as a precursor in

the synthesis of peptides, acid azides,preparation of 3hydroxymethyl-2,3-dihydrobenzofurans and 3-hydroxymethylbenzofurans[5].

N-Substituted benzotriazoles exist as two isomers: 1H-and 2H-substituted, it is generally agreed that 1H-substituted dominated in solid and solution, whereas the proportion of the 2H-tautomer increased in the gas phase [6]. However, the energy difference between the two isomers is very little [7]. Similarly, benzotriazoles containing Marinich bases have recently been synthesized also by amine exchange reactions, from the N,N-dimethylaminopropiophenone hydrochlorides and benzotriazole, respectively [8].

Benzotrizole structure



Physical properties

Molecular formula C6H5N3

Molecular weight 119.1240

Melting point 98.5-100°C

Nature White to brown crystalline powder

Density 1.36 g/cm3

Solubility in water g/100 ml is 2 (moderate)

CAS Registry Number 95-14-7

UV absorbance 286 nm

Application:

Benzotriazole has been known for its great versatility. It has already been used as a restrainer (or anti-fogging agent) in photographic emulsions or developing solutions, and as a reagent for the analytical determination of silver. More importantly, it has been extensively used as a corrosion inhibitor in the atmosphere and underwater. Also, its derivatives and their effectiveness as drug precursors have been drawing attention. Besides all the applications mentioned above, the BTA can be used as antifreezes, heating and cooling systems, hydraulic fluids, and vapor-phase inhibitors as well [31].

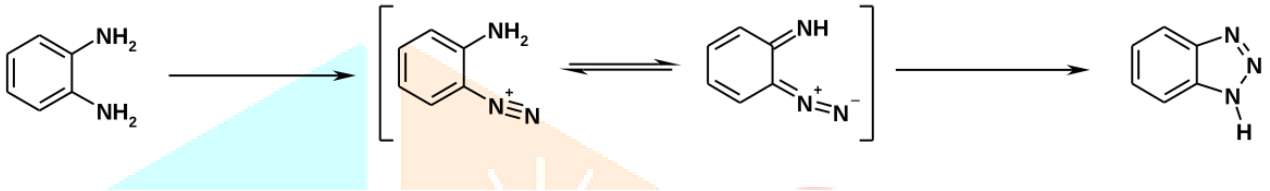
Environmental relevance :

Benzotriazole is fairly water-soluble, not readily degradable and has a limited sorption tendency. Hence, it is only partly removed in wastewater treatment plants and a substantial fraction reaches surface water such as rivers and lakes[32]. It is considered to be of low toxicity and a low health hazard to humans although exhibiting some antiestrogenic properties [33].

Synthesis

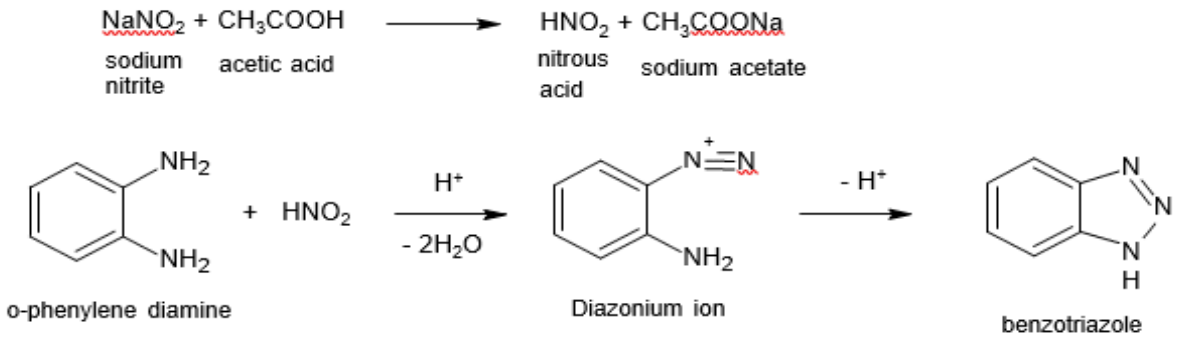
Scheme-1 for synthesis of benzotriazole

Benzotriazoles are synthesized by cyclocondensation of o-phenylenediamines with sodium nitrite in acetic acid. The reaction involved the simple heating the reagents together. Conversion of the diamine into the monodiazontum. derivative is followed by spontaneous cyclization [9].



Scheme-II

1,2,3-Benzotriazole has been prepared directly by the 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. The above procedure is the direct method and gives better over-all yields than the methods involving several intermediate step[10].



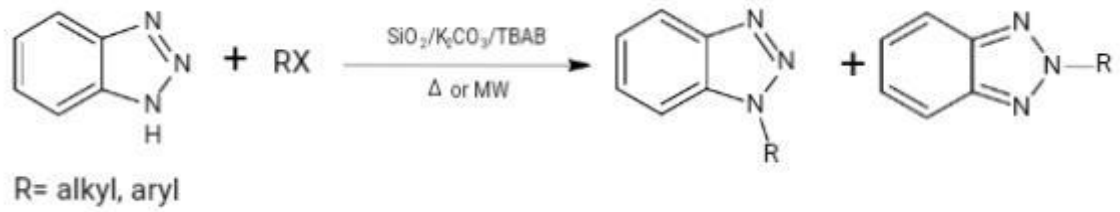
Scheme-III N-Alkylation of Benzotriazole under Solvent-Free Conditions

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. In this method, 1-alkyl benzotriazoles were obtained

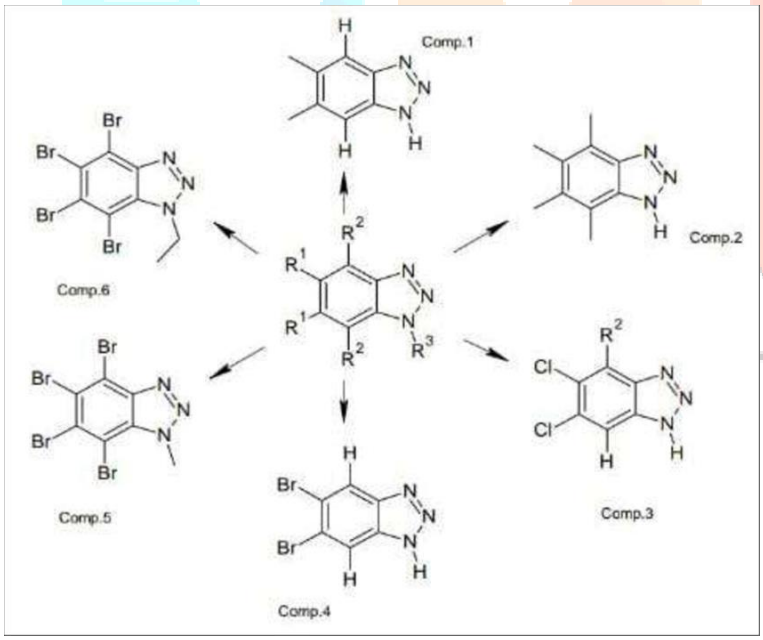
regioselectively in moderate to high yields and short reaction times [11]



Pharmacologic activity

Antimicrobial activity of benzotriazole :

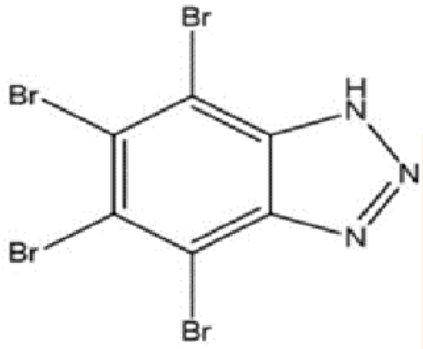
Since the late 1980s, benzotriazole derivative, antimicrobial activity has been thoroughly studied, and along with all azolic ring, they have emerged as one of the latest active highlights. The discovery and advancement on antimicrobial medication were significant scientific breakthrough in the early twentieth century. Despite the investment antifungal properties of the benzotriazole moiety[12]. made in the research of antimicrobial drugs. [13] 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[14].



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.[15] 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.[13] 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.[16] 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.[17] 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[14].



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.[11] 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.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[18].

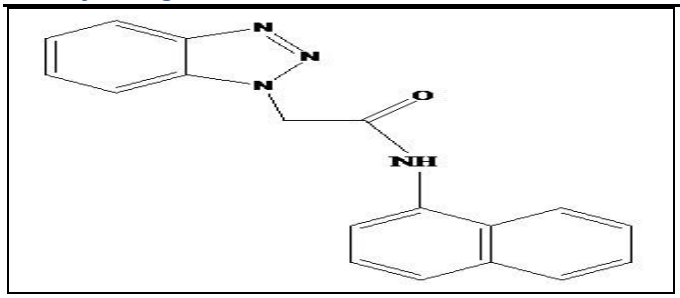


FIG. 11: SHOW ANTIOXIDATIVE ACTIVITY

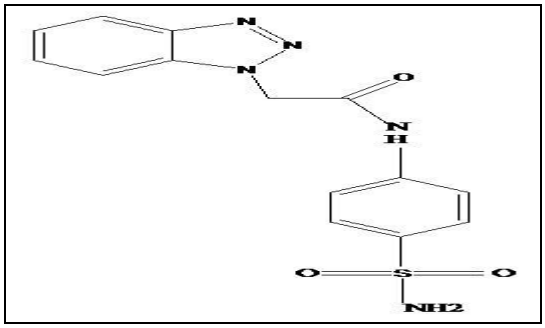
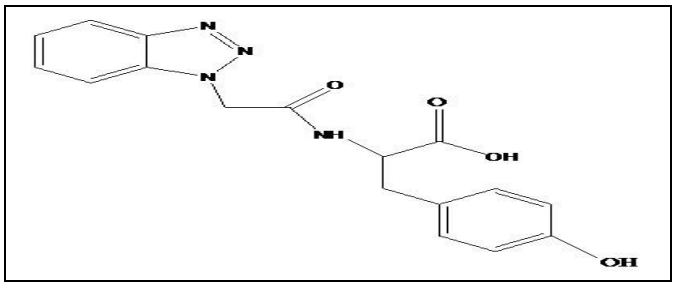


FIG. 12: SHOW ANTIOXIDATIVE ACTIVITY



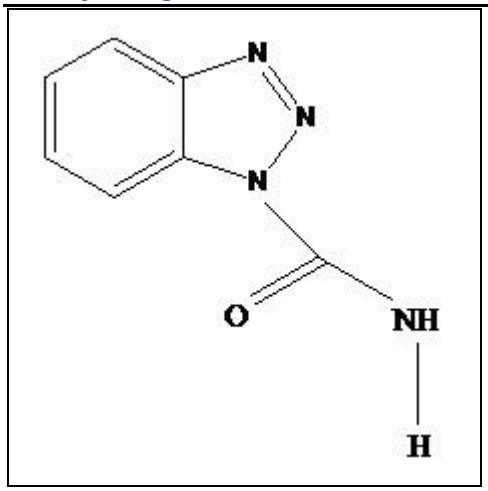
Antifungal Activity:

During the past two decades, the frequency of invasive and systemic fungal infections has increased dramatically due mainly to Candida species. During the past two decades, the frequency of fungal infection increased dramatically due mainly to candida species[19]. Recently, the expansion of antifungal drug research has occurred because there is a critical need for new antifungal agents to treat these life-threatening invasive fungal infections[20]. Among different kinds of antifungal agents, azole compounds have been rapidly developed as the mainstream for fungal infection treatment and are widely used in Clinic[21-23]

A variety of antifungal azoles representing as an important class of nitrogen-containing heterocycles with desirable electron-rich properties, have been early discovered and successfully used to develop clinical agents.

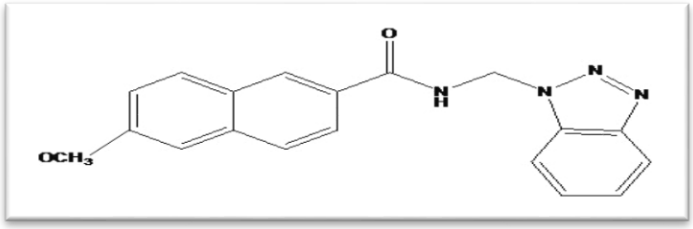
1-Carbamoyl-1H-benzotriazole(benzotriazole-1-carboxamide,2n), an effective carbamoyl chloride substitute, and a range of its analogs can be synthesized in good yields in simple steps from 1,2-diaminobenzene.

Christopher John Perry et al., in 2008 gives different substituted of benzotriazole with good antifungal activity[24].



Anticancer Activity:

Cancer is actually the second leading cause of death worldwide after cardiovascular diseases, accounting for about 8 million deaths. Viswanathan CL and Co-workers[25]. New series were synthesized of the Benzotriazole derivatives Fig. The entire compound was investigated for anticancer activity. Derivative designed and synthesized further to improve the chemosensitizing activity of the drug. The synthesized drug shows the 29.9% inhibition of the growth of the cells in murine lymphocytic leukemia cell, which was best than the standard drug Verapamil which inhibit 9.3% cell growth at 80 µg/ml. concentration.



Anthelmintic Agent:

Anthelmintis are a group of antiparasitic drugs that expel parasitic worms and other internal parasites from the body by either stunning or killing them and without causing significance damage to the host they may also be called vermicides. They affect the poorest and most deprived communities and are recognized as cause of chronic ill-health amongst the people living in tropical and subtropical areas Benzotriazole derivatives effectively working as aanthelmintic agent. Benzotriazoles with 1 and 2-carbamoyl substituents give anthelmintic activity

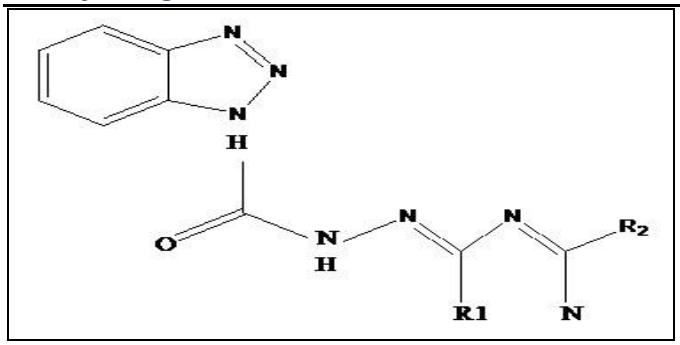
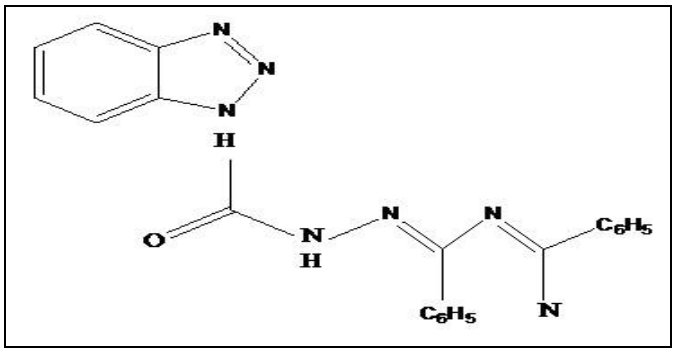


FIG. 6: SHOW ANTHELMINTIC ACIVITY

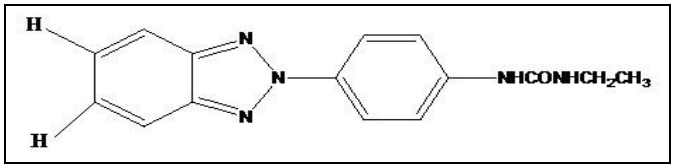


Antiviral Activity:

Viruses can cause major diseases both in humans and animals and determine life lost economic losses and higher production costs. The current antiviral agents can not only inhibit the growth of the virus instead of directly destroying and killing them but also damage the host cell. For these reasons, large numbers of investigations have been focused on the design and development of non-nucleoside compounds as novel antiviral drugs in recent decades. The exploitation of new antiviral benzotriazole compounds has opened a new opportunity in this field.

Orthohantaviruses are classified as emerging viruses that cause two life-threatening diseases: hemorrhagic fever with renal syndrome (HFRS) and orthohanta viruses pulmonary syndrome (HPS), also known as hantavirus cardiopulmonary syndrome (HCPS)[26]. Research group has published several 1(2)H-benzo[d][1,2,3]triazole, usually called benzotriazole, derivatives that have shown marked antiviral activity against many viruses [27-30].

The researcher performed the same broad antiviral screening on a series of 2-phenyl-benzotriazole from the library, or newly synthesized all showed in Fig.



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.

Reference

1. Furmiss BS, Hannaford AJ, Smith PWG, Tatchell AR. Vogel's textbook of practical organic chemistry. Pearson. 2008, (5), 1163.
2. VK Singh, PoonamRishishwar, Peeyush Bhardwaj and ShashiAlok (2017). Benzotriazole. A Heterocyclic Molecule with Diversified Pharmacological Activities, IJPSR, 8(2), 446-456.
3. Khalafi-Nezhad A, Soltani Rad MN, Mohabatkar H, Asrari Z and Hemimateenejad B. (2005). Design, synthesis, antibacterial and QSAR studies of benzimidazole and imidazole chloroaryloxyalkyl derivatives. Bioorgan Med Chem, 13, 1931-1938.
4. Arjmand F, Mohani Band Ahmad S. (2005). Synthesis, antibacterial, antifungal activity and interaction of CTDNA with a new benzimidazole derived Cu (II) complex. Eur J Med Chem, 40, 1103-1110.
5. Jamkhandi CM, Disouza J1, Asgekar S D, Sutar TB and Kumbhar PS. (2015) Synthesis, Characterization, in-vitro anti-inflammatory activity and QSAR evaluation of benzotriazolyl-3-(5-(carboxymethyl) diazenyl) Zhydroxyphenyl prop-2-enoic acid derivatives. European journal of pharmaceutical and medical research, 2, 302-306.
6. Tomasf, catalan J, perez p and Elguero J.(1994), on the acidity and basicity of azoles: the fraft scheme for electrostatic proximity effect J.orb.Chen.59.2799
7. Wang H, Burda C,persy G and wirz J. (2000). Photochemistry of 1H-Benzotriazole in aqueous solution:A potolatent Base J.Am.Chen.soc.122,5849.
8. Abonia R, insuastya-B, QuirogaAJ, noguerash M and merierc H. (2004).mini-reviews inorganic chemistry1,387.
9. Vogel's Textbook of Practical Organic Chemistry by Brian S. Furniss, Antony J. Hannaford, Peter W. G. Smith & Austin R. Tatchell, 1163.
10. Khalafi A, zare A, Parhami A, soltani Rad MN and nejabat GR, (2007). Highly regioselective N-alkylation of benzotriazole under solvents-free conditions, J-iranian Chen.soc,4(3)271-278.

11. Namdeo KP, Singh VK and Prajapati SK. (2009) Synthesis of some 2-(substituted)-5-((N-benzotriazolomethyl)- 1,3,4-thiadiazolyl-4-thiazolidinones for their antifungal activity Indian J. Pharma. Educ. Res, 43(3), 266-271.
12. Khalafi A, Zare A, Parhami A, Soltani Rad MN and Nejabat GR. (2007), "Highly regioselective N-alkylation of benzotriazole under solvent-free conditions", J. Iranian Chem. Soc, 4(3),271-278.
13. Briguglio, S. Piras, P. Corona, E. Gavini, M. Nieddu, G. Boatto, A. Carta, "Benzotriazole: An overview on its versatile biological behavior". Bhavior! European Journal of Medicinal Chemistry [2014] page no. 1-37
14. 3.A. vahad Datta, Asnani Alpana, mohurl Shrikant, Kumar Praitysh, Bais Abhinav and Tale Ruchita, "Review on Synthetic Study of Benzotriazole" GSC Biological and Pharmaceutical sciences[2020] Page No-205-225
15. Zhou Qi Shi, You-Sheng Liu, Qian Xiong. Wen-Wen Cai, Guang-Guo Ying."Occurrence, toxicity and transformation of six typical benzotriazoles in the environment: A review", Science of the Total Environment 661 (2019) 407-421.
16. VK Singh, PoonamRishishwar, Peeyush Bhardwaj and (2017). "Benzotriazole: ShashiAlok. Heterocyclic A Molecule with Diversified Pharmacological Activities" IJPSR, 8(2), 446-456.
17. Paolo Sanna, Antonio Carta, Mohammad E. Rahbar Nikookar, "Synthesis and antitubercular activity of 3-aryl substituted-2-(1H(2H)benzotriazol-1(2)-yl)acrylonitriles" Eur. J. Med. Chem. 35 (2000) 535-543
18. Rangappa S. Keri, Mahadeo R. Patil, Siddappa A. Patil, Srinivasa Budagumpi, "A comprehensive review in current developments of benzothiazole-based molecules in medicinal chemistry". European Journal of Medicinal Chemistry 89 (2015) 207-251http://dx.doi.org/10.1016/j.ejmech 2014.10.059
19. Cara Briguglio A. Riess Cema S. Both P. Nied Chunched M. Man P. Glen ME and hudiano F Quinolinstriesofic Design synthesis cvslation of the arrival activity of the aes classes of RNA persem RNA polymerate inhibitors Bisory, Med Chon 2011 7070-54.
20. Girasd F. Geillon R. Loge C. Page F. Piet Cand Borge ML Synthesis and mucture-actiiry of L-phenyl-1-pyridinyl and piperidinylmethylaminol 3418-12-4-marol-1-yl) propan-2-as antifangal agents Bionryn Med Chen Latt 2000, 19: 301.04
21. Andriole VT: current and future anti fungal therapy: New target for antifungal therapy. Int J Antimicrob Ag 200p;16:317-21
22. Zhu CH and Mi JL. Preparatum of Floorimazole ether derivatives ammirobal agents C Pa CN101391886 (A) 2009
23. Lokhande TN, Vuwanathun CL and Juukar AS: Chem Phurts thali 2008, 56 24.06.
24. Perry CJ and Holding K and Tyrrell E: "simple, novel synthesis for 1carnamoni II 1H-benzotriazole and some of its analoges" synthetic communication: An international Journal for Rapid communication of synthetic organic chemistry 2009.

25. Lokhande TN, Vuwanathun CL and Juukar AS: Chem Phurts thali 2008, 56 24.06.
26. Schmaljohn C and Hooper JW: Bunyaviridae: The viruses and their replication. In Fields Virology, 4th ed.; Knipe, D.M., Howley, P.M., Griffin, D.E., Lamb, R.A., Martin, M.A., Roizman, B., Straus, S.E., Eds.; Lippincott Williams & Wilkins: Philadelphia, PA, USA, 2001; 1581-1602.
27. Corona PS, PIbba R, Riu F, Sanna G, Madeddu S, Delogu I, Loddo and Carta R: A novel benzotriazole derivatives as selective inhibitors of Coxsackies B5 virus: 1-[4-(5,6dimethyl(H)-1H(2H)-benzotriazol-1(2)-yl)phenyl]-3alkyl(aryl)urea. Med Chem 2020: 16: 1.
28. Carta, Loriga A, Piras G, Paglietti S, Ferrone G, Fermeglia M, Pricl M, Colla SL, Secci B and Collu G: Synthesis and in-vitro evaluation of the anti-viral activity of N-[4(1H(2H) benzotriazol-1(2)-yl)phenyl]alkylcarboxamides. Med Chem 2006; 2: 577-89.
29. Carta, Loriga A, Piras M, Paglietti S, Ferrone G, Fermeglia M, Pricl M, Colla SL, Collu G and Sanna T: Synthesis and anti-picornaviridae in-vitro activity of a new class of helicase inhibitors the N,N'-bis[4 -(1H(2H)-benzotriazol1(2)-yl)phenyl] alkyldicarboxamides. Med Chem 2007; 3: 520-32.
30. Pricl CA, Piras S, Fermeglia S, Colla ML and Loddo R: Activity and molecular modeling of a new small molecule active against NNRTI-resistant HIV-1 mutants. Eur. J. Med Chem 2009; 44: 5117-22.
31. Sease, Catherine (May 1978). "Benzotriazole: A Review for Conservators". Studies in Conservation. 2. 23 (2): 76–85. doi:10.2307/1505798. JSTOR 1505798.
32. Giger, W; Schaffner, C; Kohler, HP (2006). "Benzotriazole and tolyltriazole as aquatic contaminants. 1. Input and occurrence in rivers and lakes". Environmental Science & Technology. 40 (23): 7186–92. doi:10.1021/es061565j. PMID 17180965.
33. Farré, Marinel la; Pérez, Sandra; Kantiani, Lina; Barceló, Damià (2008). "Fate and toxicity of emerging pollutants, their metabolites and transformation products in the aquatic environment". TrAC Trends in Analytical Chemistry. 27 (11): 991–1007. doi:10.1016/j.trac.2008.09.010. ISSN 0165-9936.