Review on synthetic study of benzotriazole

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Abstract

Benzotriazole is nitrogen containing heterocycle derivative containing three nitrogen atoms at 1st, 2nd, 3rd positions. Lone pairs of each nitrogen atom are present in unshared form. The unshared lone pair of electrons enables five-membered ring to exhibit that can exist in tautomeric forms. Benzotriazole belongs to a fused heterocycles, which has a benzene ring fused with with a triazole ring. Benzotriazole and its derivatives have great significance in medicinal chemistry. The derivatives are used by several chemists for therapeutic conditions. The current paper concise several synthetic methods utilized for synthesizing derivatives which acts as antimicrobials, antibacterial, antifungal, antiviral, antitubercular, anticancer, anti-inflammatory, anticonvulsant, analgesic and antioxidant agents. The article will also help the researchers to understand the structure activity relationships and improvise the concepts in their researches.

Keywords: Benzotriazole; Antimicrobial; Anticancer; Antifungal; Fused heterocycles

1. Introduction

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. 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 [1].

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 [2].

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 [3]. 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 [4].

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 [5]. However, the energy difference between the two isomers is very little [6]. Similarly, benzotriazoles containing Mannich bases have recently been synthesized also by amine exchange reactions, from the N,N-dimethylaminopropiophenone hydrochlorides and benzotriazole, respectively [7].

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1.1. Structure of Benzotriazole with their properties

Molecular Formula: C₆H₅N₃
Formula Weight: 119.124
Composition: C(60.50%) H(4.23%) N(35.27%)
Molar Refractivity: 34.71 ± 0.3 cm³
Molar Volume: 88.3 ± 3.0 cm³
Index of Refraction: 1.715 ± 0.02
Surface Tension: 73.9 ± 3.0 dyne/cm
Density: 1.348 ± 0.06 g/cm³
Dielectric Constant: Not available
Polarizability: 13.76 ± 0.5 10⁻²⁴ cm³

2. Synthesis

2.1. Scheme-I 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 monodiazonium derivative is followed by spontaneous cyclization [8].

2.2. 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 steps [9].

2.3. 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 [10].
Benzotriazoles are formed by cooling and stirring of benzene-1,2-diamine with carboxylic acid. Benzotriazole moiety possessing antifungal activity (Compound b had good activity) [11].

3. Pharmacological Study

3.1. Antimicrobial activity

Chloro-, bromo- and methyl- analogues of 1H-benzimidazole and 1H-benzotriazole and their N-alkyl derivatives have been synthesized and tested in vitro against the protozoa Acanthamoeba castellanii. The results indicate that 5,6-dimethyl-1H-benzotriazole and 5,6-dibromo-1H-benzotriazole have higher efficacy than the antiprotozoal agent chlorohexidine.

3.2. Antiviral activity

A novel series of dialkylamino side chain derivatives of benzotriazole were synthesized and reported as potential inhibitors of respiratory syncytial virus was found to be most potent in series.
Halogenated benzotriazole nucleosides were synthesized and antiviral activity was tested against hepatitis C virus and other viral NTPase/helicases was found to be good inhibitor of the West Nile virus enzyme with an RNA substrate (IC50-0.3 µm) also reported selective antiviral activity.

3.3. Antifungal activity

1-Carbamoyl-1H-benzotriazole (benzotriazole-1-carboxamide, 2a), an effective carbamoyl chloride substitute, and a range of its analogs can be synthesized in good yields in two very simple steps from 1,2-diaminobenzene. The facile preparation of the intermediate o-aminophenylurea is key to this process. Evaluated antifungal derivatives.

3.4. Anticancer activity

4, 5, 6, 7-tetrabromobenzotriazole was found to be most effective with high selective inhibition against protein kinase CK2 reported excellent anticancer activity.

3.5. Antitubercular Benzotriazole

Tuberculosis (TB) is a highly infectious disease primarily caused by Mycobacterium tuberculosis. Several types of antitubercular agents such as isoniazide and rifampicin are available for clinic. However, with the frequent occurrence of resistant strains and clinical adverse drug reactions of stomach and gut as well as liver damage, the uses of clinical anti-TB drugs have been limited by the reduced efficacy and inevitable toxic side effects. Therefore, there is necessary to develop new potent anti-tubercular drugs without cross resistance from known antimycobacterial agents. Recently, more and more researches have shown that the nitrogen heterocyclic benzotriazole compounds have considerable potentiality to treat tuberculosis. The substitution of benzotriazole ring by halogen atoms on the benzene ring has been proved to be a useful way to enhance the bioactivity of benzotriazole derivatives. Sydnones have drawn increasing attention in the fields of both heterocyclic chemistry and medicinal chemistry due to their structural features and biological activities. Some amide benzotriazole derivatives synthesized from sydnone fragment were reported to
display good antitubercular activities. For instance, amino benzo triazole was manifested to be a potent antitubercular agent with better inhibition against M. tuberculosis than standard drugs streptomycin and pyrazinamide. Pyrazole N-aryl derivatives have been deeply investigated in the pharmaceutical field due to their wide range of bioactivities such as anti-hyperglycemic, analgesic, antiinflammatory, antipyretic and antibacterial activities. The introduction of pyrazole ring in molecules could increase the electron density of the system and makes the chromophore more resistant towards enzymatic reduction by radical species [25].

3.6. Antioxidative Benzotriazoles

Free radicals, represented by reactive oxygen nitrogen species from human metabolism, could produce harmful substances by a variety of metabolic pathways, then cause healthy 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 [26]. Benzotriazole compounds have shown remarkable antioxidative activities and large potentiality to be novel antioxidative agents or candidates. Primaquine (PQ) derivatives are wellknown 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 lipoxgenase inhibitory (LOX) inhibition [27]. 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%. These results proved the promising efficiency of the benzotriazole group as a new scaffold in the rational design of new antioxidant compounds. Ketoprofen (Ket) is a non-steroidal antiinflammatory drug (NSAID) with pronounced analgesic and antipyretic activities. Recently, the structural modification of ketoprofen molecule has afforded a series of derivatives with minimized side-effects, prolonged plasma half life, increased solubility and considerable antioxidative potentiality. For example, ketoprofenzbenzotriazole derivative possessed good interaction with 1, 1-diphenyl-2-picrylhydrazyl (DPPH) which was a stable free radical with spared electron delocalization over the whole molecule. The interaction between compound and DPPH indicated its radical scavenging ability in an iron-free system as well as its reducing activity. Moreover, it was proved to be an excellent inhibitor of LP of 98%, which was significantly higher than that of the standard ketoprofen (69.3%). This compound also exhibited remarkable soybean LOX activity of 95% [28]. The replacement of benzotriazole ring by other substituent such as pyrrolyl or piperidyl fragment could obviously reduce the antioxidant activity, which indicated that then presence of benzotriazole was benifical to its antioxidant propriety [28].

Table 1 Various pharmacological activities with their derivatives of Benzotriazole

| Sr. No | Authors | Compounds | Derivatives | Activities |
|--------|---------|-----------|-------------|------------|
| 1      | Farag et al; 1997 | ![Compound1](image1.png) | R 1 CH₃ C₆H₅ 2 CH₃ MeC₆H₄ 3 CH₃ ClC₆H₄ 4 OC₂H₅ C₆H₅ 5 OC₂H₅ MeC₆H₄ 6 OC₂H₅ ClC₆H₄ | Anticonvulsant and Antiinflammato ry [12] |
| 2      | Fatima Al-Omran et al; 2002 | ![Compound2](image2.png) | R 1 O 2 O 3 Ph Me CN | Antimicrobial and Antifungal [13] |
|   |   | ![Chemical Structures](image) |
|---|---|---|
| 3 | Yu K. L., Zhang Y et al; 2003 | ![Chemical Structures](image) |
|   |   | ![Chemical Structures](image) |
|   |   | ![Chemical Structures](image) |
| 4 | KatarzynaKapanska et al; 2004 | ![Chemical Structures](image) |
|   |   | ![Chemical Structures](image) |
|   |   | ![Chemical Structures](image) |
| 5 | Maria Bretner, Andrea Baier, et al; 2005 | ![Chemical Structures](image) |
|   |   | ![Chemical Structures](image) |
|   |   | ![Chemical Structures](image) |

1. R=R1=R2=R3=R4= Br
2. R=R1=R2=R3=R4= Cl

Antiviral [14]

1. R1=HCH3 R2=R3= H
2. R1=R2= CH3 R3=H
3. R1=Cl R2=R3=H
4. R1=Br R2=R3=H
5. R1=R2=Br R3= CH3
6. R1=R2=Br R3=C2H5

Antimicrobial [15]

1. R= CH3 R1 = H
2. R = H R1 = CH3
3. R = C2H R1 = H
4. R = C2H5 R1 = H
5. R = C2H R1 = H
6. R = H R1 = C2H7
7. R = C2H5OH R1 = H
8. R = H R1 = C2H5OH

Cytotoxicity against NTPase / helicase (Flavivirdae), Antiviral [16]
| 6 | Asati KC et al; 2006 | ![BTA- Benzotriazole](image) | Ar - ClC\textsubscript{6}H\textsubscript{4}, -CH\textsubscript{2}C\textsubscript{6}H\textsubscript{4}, -NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}, -Br C\textsubscript{6}H\textsubscript{4} | Analgesic and Antimicrobial activity [17] |
|---|---|---|---|---|
| 7 | Christopher John Perry et al; 2008 | ![Compound](image) | 1- R = O R\textsubscript{1} = H  
2- R = S R\textsubscript{1} = H  
3- R = O R\textsubscript{1} = C\textsubscript{6}H\textsubscript{5}CH\textsubscript{3} | Antifungal [18] |
| | | | A- R = S R\textsubscript{1} = C\textsubscript{6}H\textsubscript{5}CH\textsubscript{3}  
B- R = S R\textsubscript{1} = C\textsubscript{11}H\textsubscript{10} | |
| 8 | JUN WAN et al; 2009 | ![Compound](image) | 1- R\textsubscript{1} = 3-OCH\textsubscript{3} R\textsubscript{2} = 3-C\textsubscript{6}H\textsubscript{5}N \n2- R\textsubscript{1} = 3-OCH\textsubscript{3} R\textsubscript{2} = 4-C\textsubscript{6}H\textsubscript{5}N \n3- R\textsubscript{1} = 3-OCH\textsubscript{3} R\textsubscript{2} = C\textsubscript{6}H\textsubscript{6} \n4- R\textsubscript{1} = 3-OCH\textsubscript{3} R\textsubscript{2} = C\textsubscript{6}H\textsubscript{5}Cl \n5- R\textsubscript{1} = 3-OCH\textsubscript{3} R\textsubscript{2} = C\textsubscript{6}H\textsubscript{5}Cl \n6- R\textsubscript{1} = CH\textsubscript{3} R\textsubscript{2} = C\textsubscript{6}H\textsubscript{6} \n7- R\textsubscript{1} = CH\textsubscript{3} R\textsubscript{2} = C\textsubscript{6}H\textsubscript{5}Cl \n8- R\textsubscript{1} = CH\textsubscript{3} R\textsubscript{2} = C\textsubscript{6}H\textsubscript{10} \n9- R\textsubscript{1} = CH\textsubscript{3} R\textsubscript{2} = 4-Cl C\textsubscript{6}H\textsubscript{5} \n10- R\textsubscript{1} = CH\textsubscript{3} R\textsubscript{2} = 2-Cl C\textsubscript{6}H\textsubscript{5} \n11- R\textsubscript{1} = 3-Cl R\textsubscript{2} = 2-Cl C\textsubscript{6}H\textsubscript{5} \n12- R\textsubscript{1} = 3-Cl R\textsubscript{2} = 4-C\textsubscript{6}H\textsubscript{5}N \n13- R\textsubscript{1} = 4-Br R\textsubscript{2} = 3-C\textsubscript{6}H\textsubscript{5}N \n14- R\textsubscript{1} = 4-Br R\textsubscript{2} = 4-C\textsubscript{6}H\textsubscript{5}N \n15- R\textsubscript{1} = 4-Br R\textsubscript{2} = 4-Cl C\textsubscript{6}H\textsubscript{5} \n16- R\textsubscript{1} = 4-Br R\textsubscript{2} = 2-Cl C\textsubscript{6}H\textsubscript{5} \n17- R\textsubscript{1} = 4-Br R\textsubscript{2} = p-tolyl \n18- R\textsubscript{1} = 4-Br R\textsubscript{2} = o-tolyl \n19- R\textsubscript{1} = 4-Br R\textsubscript{2} = H \n20- R\textsubscript{1} = 2-CH\textsubscript{3} R\textsubscript{2} = 3-C\textsubscript{6}H\textsubscript{5}N \n21- R\textsubscript{1} = 2-CH\textsubscript{3} R\textsubscript{2} = 4-C\textsubscript{6}H\textsubscript{5}N \n22- R\textsubscript{1} = 2-CH\textsubscript{3} R\textsubscript{2} = 4-Cl C\textsubscript{6}H\textsubscript{5} \n23- R\textsubscript{1} = 2-CH\textsubscript{3} R\textsubscript{2} = 2-Cl C\textsubscript{6}H\textsubscript{5} | Antibacterial [19] |

All compounds shows the activity against Gram positive bacterial strains. The most potent antibacterial activity shows compound 4, 7, 16, 18, 19. The moderate antibacterial activity shows compound 17, 24, 25 [12].
|   | Name                              | Structures                                                      | R1, R2 | Functional Activity          | Reference |
|---|-----------------------------------|-----------------------------------------------------------------|--------|-----------------------------|-----------|
| 9 | Adesh Dubey et al; 2010           | ![BTA- Benzotriazole](image)                                      | R = 2-Cl, 4-Cl, 2-Br, 3-Br, 2-NO₂, 4-NO₂, 2-OCH₃, 4-OCH₃ | Antitubercular [20] |          |
| 10| S. Khabnadideh et al; 2011         | ![Structure A](image) ![Structure B](image) ![Structure C](image) | A- C₈H₁₈  B- C₈H₂₀  C- C₁₁H₂₄ | Antifungal [21] |          |
| 11| C. M. Jamkhandi et al; 2013        | ![Structure A](image) ![Structure B](image) ![Structure C](image) ![Structure D](image) ![Structure E](image) ![Structure F](image) | R₁, R₂ | Anti-oxidant Activity [22] |          |
|   |   |   |   |
|---|---|---|---|
| **12** | J. J. Shah, Krishnapriya Mohanra et al; 2014 | R = Cl, C₆H₅N, C₆H₆N, C₄H₁₁N | **Antifungal [23]** |
|   |   |   |   |
|   |   | R = Cl, C₆H₅N, C₆H₆N, C₄H₁₁N |   |
|   |   |   |   |
| **13** | Gitanjali K. Patil et al; 2015 | \( R_{1} \) \( R_{2} \) | **Anticancer [24]** |
| R¹ | Br | H |   |
| R² | Br | (CH₂)₂OH |   |
|   | Br | (CH₂)₂NH₂ |   |

**4. Conclusion**

The plethora of research subscribed in this review indicates a wide spectrum of pharmacological activities exhibited by benzotriazole derivatives. The biological profiles of these new generations of benzotriazole would represent a healthy matrix for further development of better medicinal agents. Benzotriazole derivatives is focussed on screening of biological activities such as antibacterial, antifungal, antiviral, antitubercular, anticancer, antimicrobial, anti-inflammatory, anticonvulsant, 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 suggests 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.

On the one hand, an increasing effort is the structural modification by the introduction of benzotriazole ring into available drugs, and focused more on new strucutralbenzotriazolecontaining compounds with novel mechanisms of action. The electron-rich benzotriazole ring with a large conjugated system is an attracting molecular skeleton, which is not only easily modified by various types of functional groups, but also employed to combine with other bioactive fragments to afford more active compounds with remarkable physicochemical properties.
Compliance with ethical standards

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Disclosure of conflict of interest
The authors declare that there are no conflicts of interest.

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