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Synthetic Stratrgy and Pharmacological Approaches of Benzotriazole; A-Review

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ABSTRACT: This review attempts to bring tighter various developments in synthesis and biological activities of benzotriazole derivatives. Benzotriazole is bicyclic heterocyclic compound contain three nitrogen atom fused in benzene ring. This has wide range of biological and pharmacological activity. Literature study reveals that Nitrogen containing heterocyclic compound reported various biological effect specially benzotriazole which is containing three nitrogens at 1,3,4 position which is essential for synthesis of novel molecules.

KEYWORDS: Benzotriazole, Biological Activity, synthesis, pharmacological activity.

I. INTRODUCTION

BENZOATRIAZOLE

In late 1960, azoles are a heterocyclic compound class that constitutes the largest group of available antifungal drugs. Particularly, the imidazole ring is the chemical component that confers activity to azoles. Triazoles are obtained by a slight modification of this ring and similar or improved activities as well as fewer adverse effects are reported for triazole derivatives. Consequently, it is not surprising that benzimidazole/benzotriazole derivatives are biologically active[1].

Benzo-fused azoles are a class of heterocyclic compounds of great interest in the pharmaceutical chemistry area. Benzimidazole and its derivatives have been studied for decades, and drugs having this heterocycle moiety as a main element have been widely used in clinics, for instance as anthelmintic in humans[2,3]. Benzo-condensed azole containing three heteroatom's, such as bezoxadiazole, benzothiazole, and benzotriazole has been extensively studied for their broad range of biological activity[4,5].

The primary triazole molecule is comprised of a five-member heterocyclic compound with three nitrogen atoms and a vicinal pair of carbon atoms. Two isomers are presented, with the hydrogen present in either the 1-H (Figure 2(a)) or 2-H configuration (Figure 2(b)). Benzotriazole is formed when a benzene ring is fused to the triazole (e.g., Figure 1(a)). ManyBenzotriazole compounds exist, but those with a high production volume (HPV) and which have been reported as being present in the environment most commonly follow these two configurations.

Although a significant numbers of engine valve-actuation systems including cam-based and cam less mechanisms have been already introduced by several researches and companies, only few types of these systems (mainly cam-based) have been employed on commercial vehicles due to the liability, durability and cost issues. Cam-based valve systems offer reliable and durable functionality, the cam less valve trains can vary valve lift and more timing to a greater extent comparing to the cam-based types. Among various categories of cam less mechanisms, the electromagnetic actuator system is the most desired one.

Benzotriazoles used as anticorrosive additives have hydrogen oriented in the 1-H position (Figure 1(a)). In addition, two BZTs used extensively for this purpose are methylated, with the functional group at either the 4′ or 5′positions (e.g., 4-TT and 5-TT) (Figure 1(b–d)). Conversely, the UV-stabilizing BZTs (UV-BZTs) generally have a phenolic moiety positioned at 2-H (e.g., Figure 2e). Overall, the phenolic BZTs are higher in molecular weight (MW) and structurally more complex. These compounds often include an ester, chlorine atom, or additional functional groups (e.g., phenol and methyl) as part of the molecule.

Stability is a key characteristic and desired attribute of most commercially used Benzotriazole. The parent structure will in many instances readily undergo a range of reactions; however, the triazole moiety in most cases remains unchanged[6]. For applications utilizing their anticorrosiveproperties, Benzotriazoles form highly stable metal complexes

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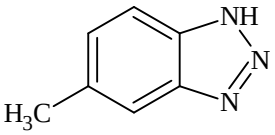
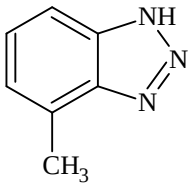
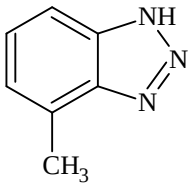
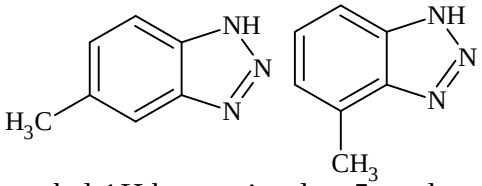
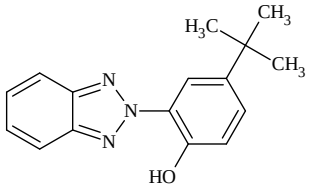
with numerous metals and alloys, particularly copper, which protect them against corrosive attack. In this application, the Benzotriazole–metal complex forms a passive layer on the metal surface, preventing surface reactions [7].

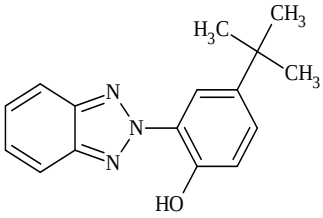
a)

5-methyl-1*H*-benzotriazole

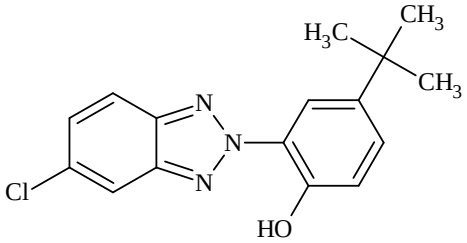
b)

4-methyl-1*H*-benzotriazole

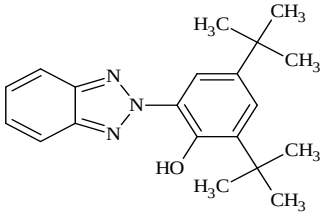
c)

4-methyl-1*H*-benzotriazole

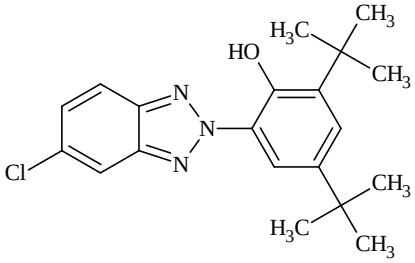
d)

4-methyl-1*H*-benzotriazole—5-methyl-1*H*-benzotriazole (1/1)

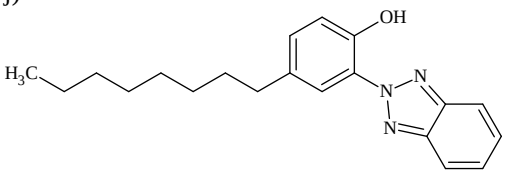
e)

2-(2*H*-benzotriazol-2-yl)-4-*tert*-butylphenol

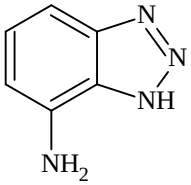
f)

2-(2*H*-benzotriazol-2-yl)-4-*tert*-butylphenol

g)

4-*tert*-butyl-2-(5-chloro-2*H*-benzotriazol-2-yl)phenol

h)

2-(2*H*-benzotriazol-2-yl)-4,6-di-*tert*-butylphenol

i)

2,4-di-*tert*-butyl-6-(5-chloro-2*H*-benzotriazol-2-yl)phenol

j)

2-(2*H*-benzotriazol-2-yl)-4-octylphenol

k)

1*H*-benzotriazol-7-amine

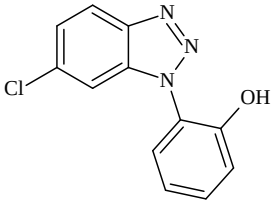
l)

2-(6-chloro-1*H*-benzotriazol-1-yl)phenol

FIGURE 1 Structures, names of select Benzotriazole compounds

Structure of benzotriazole

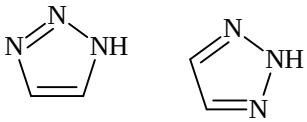


FIGURE 2 Structures of 1-H (a) and 2-H (b) triazole.

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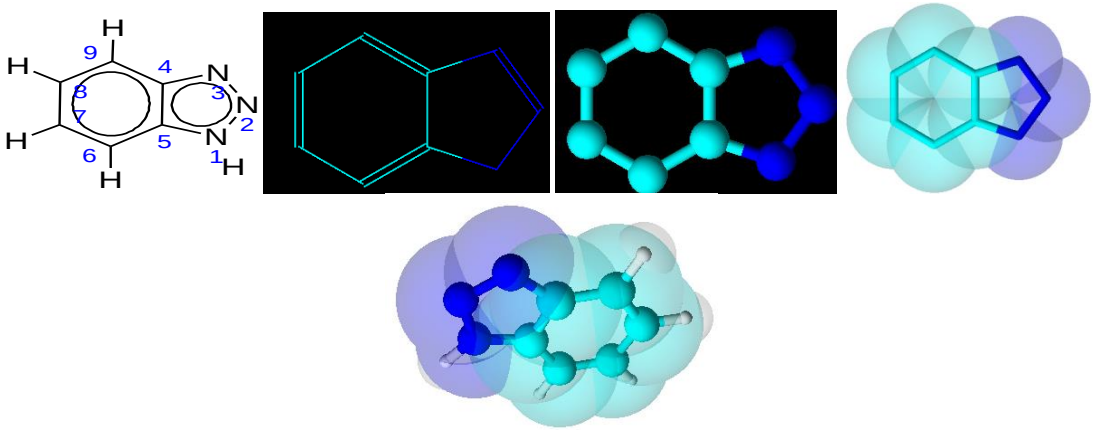


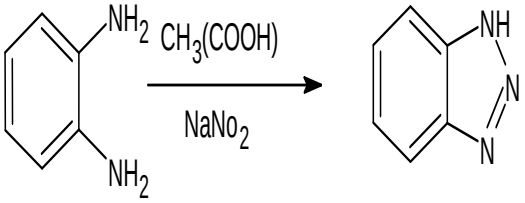
Physicochemical properties

Molecular Formula:	H2N2
Formula Weight:	30.02928
Composition:	H(6.71%) N(93.29%)
Molar Refractivity:	6.36 ± 0.5 cm3
Molar Volume:	24.3 ± 7.0 cm3
Parachor:	68.6 ± 8.0 cm3
Index of Refraction:	1.435 ± 0.05
Surface Tension:	63.0 ± 7.0 dyne/cm
Density:	1.23 ± 0.1 g/cm3
Dielectric Constant:	Not available
Polarizability:	2.52 ± 0.5 10-24cm3
RDBE:	1
Monoisotopic Mass:	30.021798 Da
Nominal Mass:	30 Da
Average Mass:	30.0293 Da
M+:	30.021249 Da
M-:	30.022347 Da
[M+H]+:	31.029075 Da
[M+H]-:	31.030172 Da
[M-H]+:	29.013424 Da
[M-H]-:	29.014522 Da

Chemistry and synthesis of Benzotriazole-

Benzotriazole display a broad range of biological activities and are found in many potent, biologically active compounds. So far, modifications of the benzotriazole ring have proven highly effective with improved potency and lesser toxicity.Benzotriazole also has three tautomers. Namely two IH-forms and one 2H-form. In solution, the equilibrium lies almost entirely on the side of the IH-forms [8].

It is synthesized by diazotization process using benzene-1,2-diamine with sodium nitrite and acetic acid.



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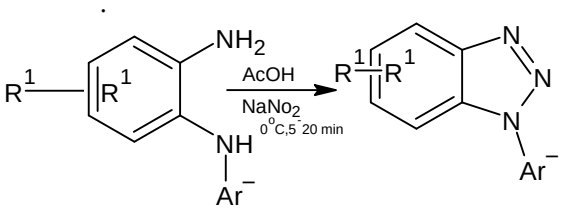
Cyclocondensation of (arylamino)aryliminophosphoranes :(9)

A cyclocondensation of 2-(arylamino) aryliminophosphoranes enables the synthesis of1-aryl-1,2,3-benzotriazoles under mild conditions. The reaction involves a three-step,Halogen-free route starting from simple nitroarenes and aryl amines

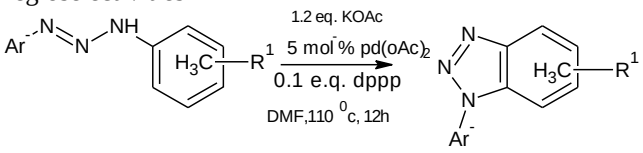


C-H activation of aryl triazene: (10)

C-H activation of aryl triazene compoundsfollowed by intermolecular amination in the presence of a catalytic amount ofPd(OAc)2 provides 1-aryl-1H-benzotriazoles at moderate temperature

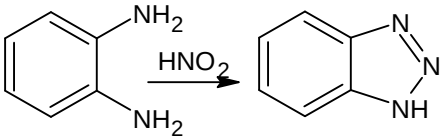
1, 7-palladium migration-cyclization-dealkylation(11)

A 1, 7-palladium migration-cyclization-dealkylation sequence for the regioselective synthesis of benzotriazoles proceed in excellent yields with high regioselectivities



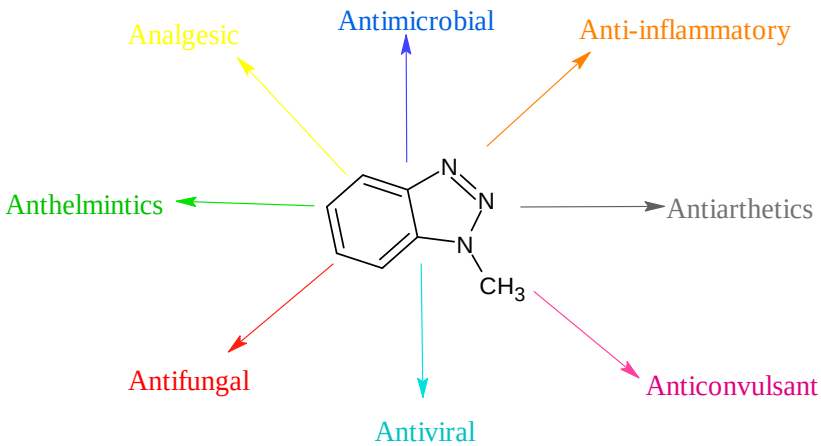
Cyclocondensation of o-phenylenediamines (12)

The standard synthesis ofbenzotriazoles is the cyclocondensation of o phenylenediamines with sodium nitrite in acetic acid.



Biological activity-

Synthetic compounds of derivatives of Benzotriazole have shown analgesic, antibacterial, antifungal activities1-6 ant filarial activities, and Benzotriazole also reported for anticonvulsant and anti-inflammatory, antitumor activities; literature study reveals the antiviral activity[13]



Antifungal activity

Rezaei Z.et. alwas reported Design, synthesis, and antifungal activity of triazole and benzotriazole derivatives. In this study a series of new 1,2,4-triazole and benzotriazoles related to clotrimazole and fluconazolewere synthesized and then the compounds docked in the active site of 14a-demethylase using Autodock program. In

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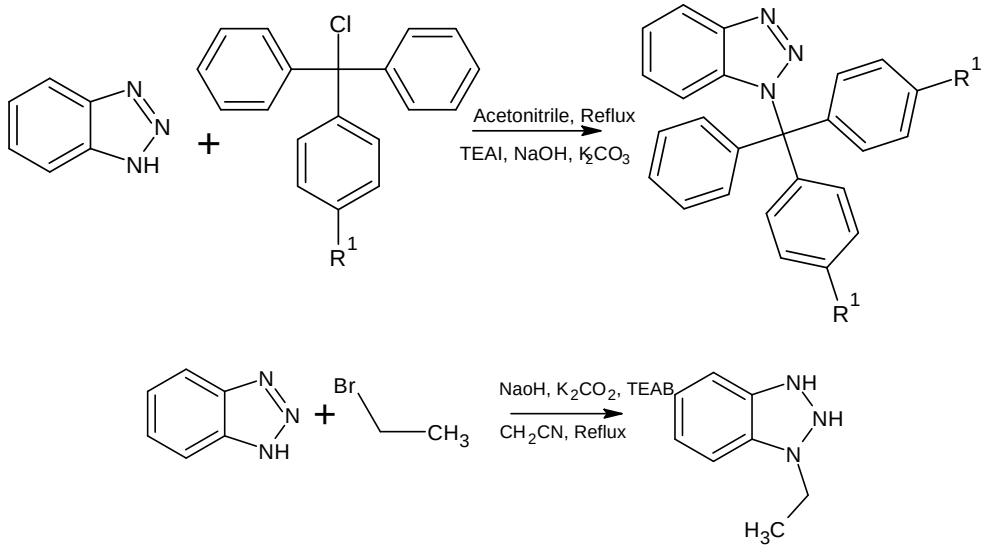
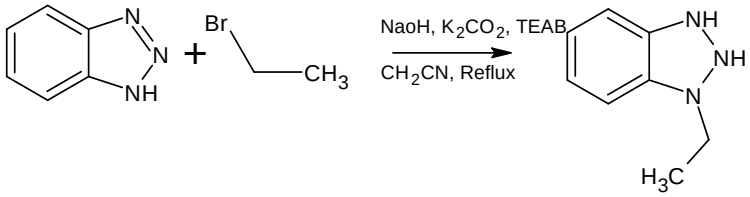
addition we investigated the activity of the compounds against Microsporumcanis, Trichophyton mentagrophyte, Trichophyton rubrum, Epidermophyton floccosum, andCandidaalbicans.(14)

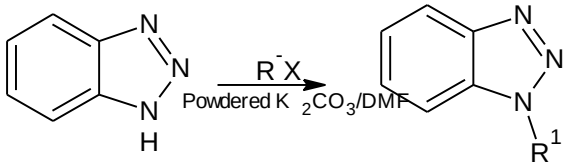


S. Khabnadideh et. Al were reported Synthesis and antifungal activity of benzimidazole, benzotriazole and aminothiazole derivatives the compound synthesized by the reaction of benzotriazole with bromo-alkanesthesynthesized product showsantifungalactivity. (15)

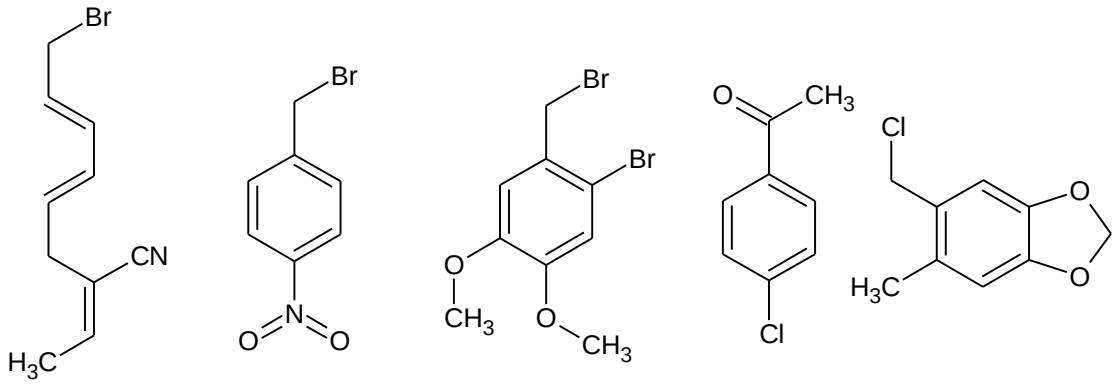


Antimicrobial activity

S. Nanjunda Swamy et.alwas reported Microwave-assisted synthesis of N-alkylated benzotriazole derivatives: Antimicrobial studies.(16)



Where: R-X=



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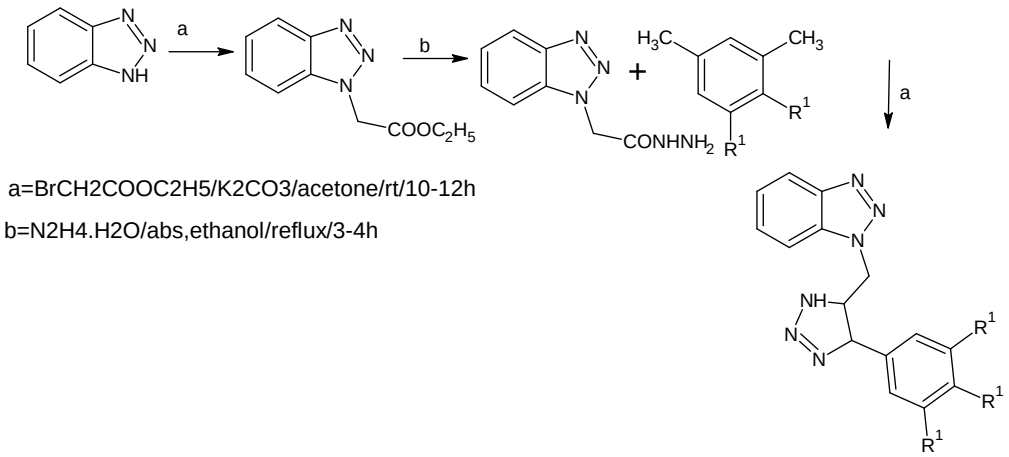
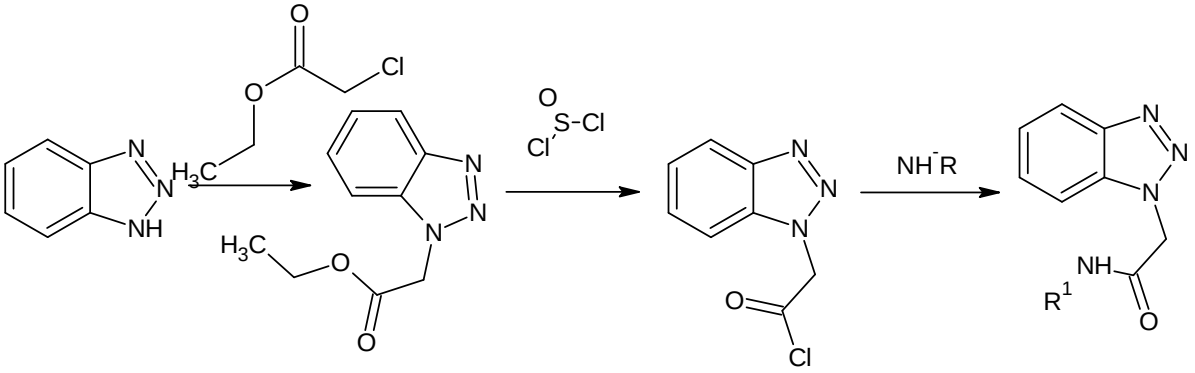
Mahesh chand et .al were reported Synthesis and antimicrobial and antioxidant activities of hybrid molecules containing benzotriazole and 1,2,4-triazole.(17-18)

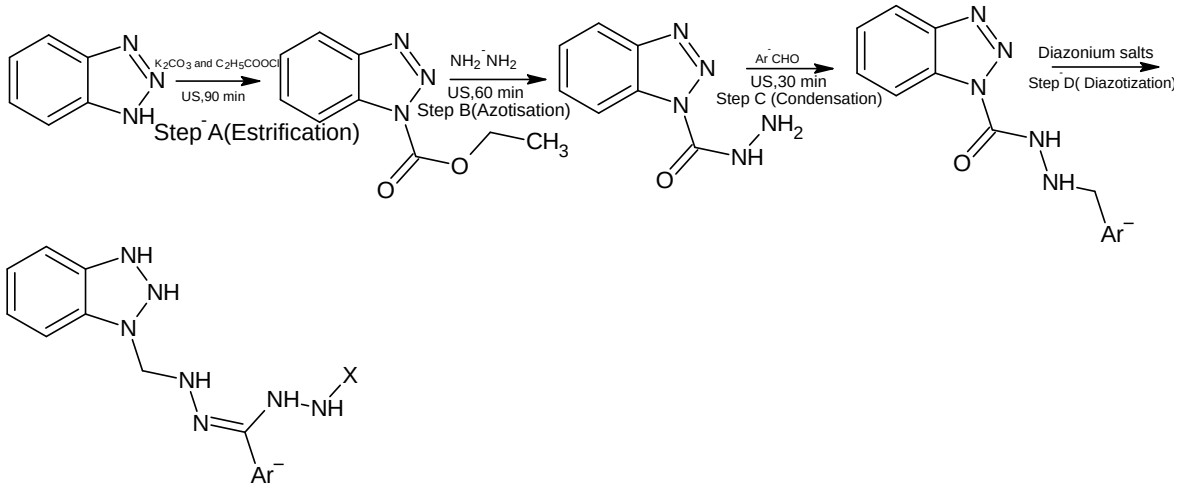


C. M. Jamkhandi et al were reported Synthesis and Antimicrobial Evaluation of 2-(1H-1,2,3-Benzotriazol-1-yl)- N-Phenylacetamide Derivatives.(19)



Anthelmintic activity

M.S Sudhir et.al were reported Evaluation of in vitro anthelmintic activities of novel 1,2,3 e benzotriazole derivatives synthesized in ultrasonic and solvent free conditions.(20)



Anti-inflammatory Activity

aiyalurajasekaranet al were reported Synthesis of some novel triazole derivatives as anti-nociceptive and anti-inflammatory agents.(21)

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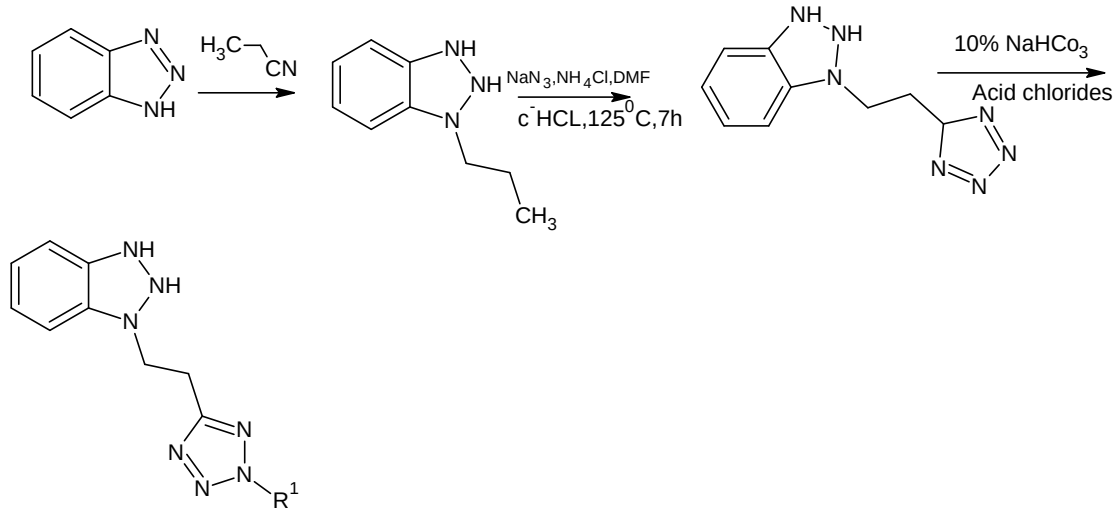
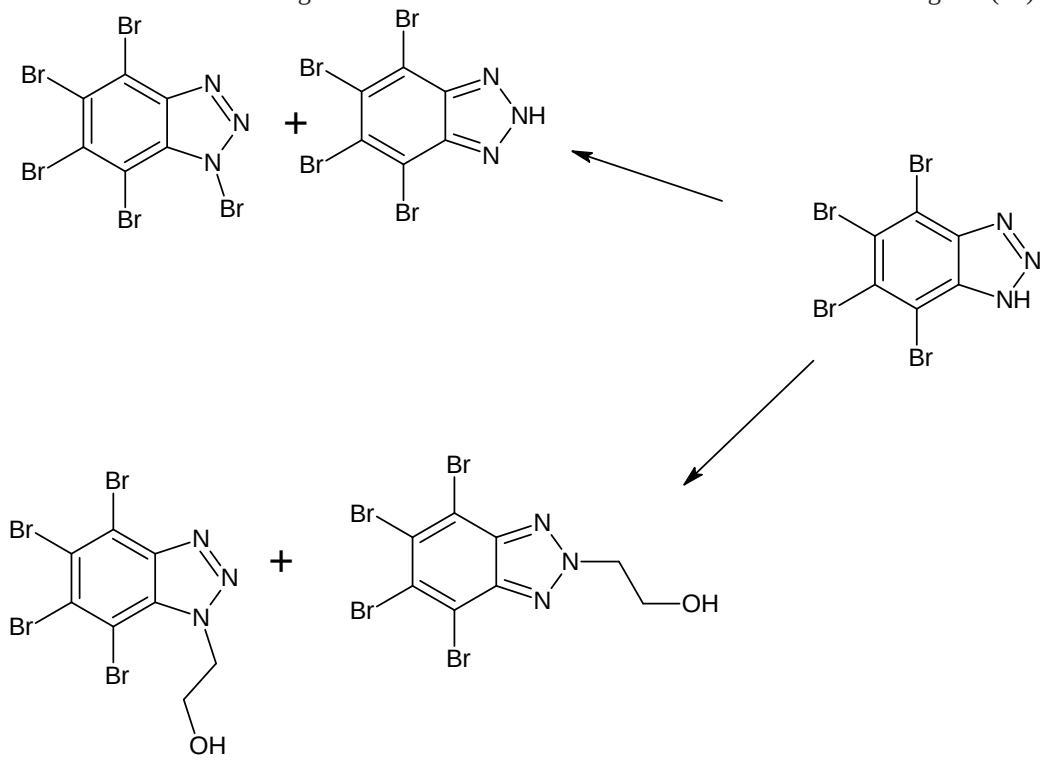


Antiviral agent

Briguglio et al were reported versatile biological behaviour of benzotriazole. Nucleosides and non-nucleosides inhibitors are widely investigated to implement the pharmacological arsenal and to obtain more potent and selective antiviral agents. Several benzotriazole derivatives acted as antiviral agents.(22)



REFERENCES

[1]. Maertens JA. History of the development of azole derivatives. Clinical Microbiology and Infection. 2004 Mar;10:1-0.

[2]. K.P. Barot, S. Nikolova, I. Ivanov, M.D. Ghate, Novel research strategies of benzimidale derivatives: a review, Mini Rev. Med. Chem. 13 (2013) 1421e1447.

[3]. Q.A. McKellar, E.W. Scott, The benzimidazole anthelmintic agents e a review, J. Vet. Pharmacol. Ther. 13 (1990) 223e247.

[4]. A.P. Piccionello, A. Guarcello, Bioactive compounds containing benzoxadiazole,

International Journal of Pharmaceutical research and Applications
Volume 8, Issue 4, Jul.-Aug. 2023, pp: 559-566 www.ijprajournal.com ISSN: 2456-4494

benzothiadiazole, benzotriazole, Curr. Bioact. Compd. 6 (2010) 266e283.
[5]. B.V. Suma, N.N. Natesh, V. Madhavan, Benzotriazole in medicinal chemistry: an overview, J. Chem. Pharm. Res. 3 (2011) 375e381.
[6]. L.N. Davis, J. Santodonato, P. Howard, J. Saxena, Investigation of Selected Potential Environmental Contaminants: Benzotriazoles. Final Report Prepared for Office of Toxic Substances, US Environmental Protection Agency, Washington, DC, 1977.
[7]. C. Sease, Stud. Conserv 23 (2) (1978) 76–85.
[8]. Catalan J, Perez P, Elguero J. Structure of benzotriazole in the gas phase: a UV experimental study. The Journal of Organic Chemistry. 1993 Sep;58(19):5276-7.
[9]. Łukasik E, Wrobel Z. 2-(Arylamino) aryliminophosphoranes as easily available and convenient starting materials in the synthesis of 1, 2, 3-benzotriazoles. Synlett. 2014 Sep; 25(14):1987-90.
[10]. Kumar RK, Ali MA, Punniyamurthy T. Pd-Catalyzed C− H Activation/C− N Bond Formation: A New Route to 1-Aryl-1 H-benzotriazoles. Organic letters. 2011 Apr 15;13(8):2102-5.
[11]. Zhou J, He J, Wang B, Yang W, Ren H. 1, 7-Palladium migration via C− H activation, followed by intramolecular amination: regioselective synthesis of benzotriazoles. Journal of the American Chemical Society. 2011 May 11;133(18):6868-70.
[12]. Furniss BS, editor. Vogel's textbook of practical organic chemistry. Pearson Education India; 2011.
[13]. Jamkhandi CM, Disouza JI. Synthesis and Antimicrobial Evaluation of 2-(1H-1, 2, 3-Benzotriazol-1-yl) N-PhenylacetamideDerivatives. Research Journal of Pharmacy and Technology. 2012;5(8):1072-5.
[14]. Rezaei Z, Khabnadideh S, Pakshir K, Hossaini Z, Amiri F, Assadpour E. Design, synthesis, and antifungal activity of triazole and benzotriazole derivatives. European journal of medicinal chemistry. 2009 Jul 1;44(7):3064-7.
[15]. Khabnadideh S, Rezaei Z, Pakshir K, Zomorodian K, Ghafari N. Synthesis and antifungal activity of benzimidazole, benzotriazole and aminothiazole derivatives.
[16]. Swamy SN, Sarala G, Priya BS, Gaonkar SL, Prasad JS, Rangappa KS. Microwave-assisted synthesis of N-alkylated benzotriazole derivatives: antimicrobial studies. Bioorganic & medicinal chemistry letters. 2006 Feb 15;16(4):999-1004.
[17]. Chand M, Kaushik R, Jain SC. Synthesis and antimicrobial and antioxidant activities of hybrid molecules containing benzotriazole and 1, 2, 4-triazole. Turkish Journal of Chemistry. 2018;42(6):1663-77.
[18]. Ramachandran R, Rani M, Senthan S, Jeong YT, Kabilan S. Synthesis, spectral, crystal structure and in vitro antimicrobial evaluation of imidazole/benzotriazole substituted piperidin-4-one derivatives. European journal of medicinal chemistry. 2011 May 1;46(5):1926-34.
[19]. Jamkhandi CM, Disouza JI. Synthesis and Antimicrobial Evaluation of 2-(1H-1, 2, 3-Benzotriazol-1-yl) N-Phenylacetamide Derivatives. Research Journal of Pharmacy and Technology. 2012;5(8):1072-5.
[20]. Sudhir MS, Nadh RV. Evaluation of in vitro anthelmintic activities of novel 1, 2, 3–benzotriazole derivatives synthesized in ultrasonic and solvent free conditions. Journal of Pharmacy Research. 2013 Jan 1;7(1):47-52.
[21]. Rajasekaran A, Rajagopal K. Synthesis of some novel triazole derivatives as anti-nociceptive and anti-inflammatory agents. Acta pharmaceutica. 2009 Sep 1;59(3):355-64.
[22]. Briguglio I, Piras S, Corona P, Gavini E, Nieddu M, Boatto G, Carta A. Benzotriazole: An overview on its versatile biological behaviour. European journal of medicinal chemistry. 2015 Jun 5; 97:612-48.