INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Review Article

AN EXPLORATION OF SUNDRY NATURE OF BENZOTRIAZOLE DERIVATIVES: A REVIEW

Navneet Singh *, Vanika Priya, Ridhima Bhasin, Kunika Verma
Department of Chemistry, School of Chemical Engineering and Physical Sciences, Lovely Professional University, Punjab, India
*Corresponding Author Email: drnavneet10@gmail.com

Article Received on: 03/12/18 Approved for publication: 05/02/19

DOI: 10.7897/2230-8407.100374

ABSTRACT

Benzotriazole has been a matter of discussion among scientific community due to its potential characteristics and touched areas such as medicinal, pharmacological, clinical, industrial etc. On screening the literature, this work for the first time gave a comprehensive review on the latest and remarkable developments of benzotriazole derivatives covering multifarious number of activities such as antifungal, antibacterial, anticancer, anthelmintic, antidepressant, antioxidative, antitubercular, antiviral, anticorrosive, plant growth inhibitor, anti-inflammatory, etc. The purpose of this study was to explore its sundry nature, to investigate the most active site and to generate a data base for prominent methods of synthesis for benzotriazole derivatives in a single review article which has not been done before. The investigation through this review article has revealed that, the credit for sundry nature of benzotriazole derivatives goes to 1-position nitrogen in benzotriazoles. The study has put a light on the fact that, when various substituents are added to 1-position nitrogen in benzotriazoles it effectively contributes toward its diverse nature.

Keywords: Benzotriazole, antifungal, antibacterial, anticancer, anticorrosive, anti-inflammatory.

INTRODUCTION

Heterocyclic compounds have explored new avenues in the field of medicinal and organic chemistry. Among large pool of heterocyclic compounds, benzotriazole took the chemist and druggist to the surprise by its miraculous characteristic in context of electron donating nature, group release, anion director in surrounding etc. Benzotriazole is easy to introduce into molecules by a variety of condensation, addition and substitution reactions. Its derivatives have a wide spectrum of biological, chemical and industrial activities. Benzotriazole comprises two fused rings; its five membered rings can show tautomerism. Its common structure is stated in figure 1[1].

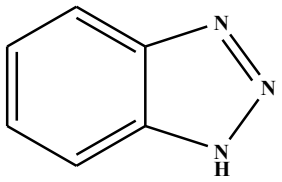


Figure 1:1H-benzotriazole

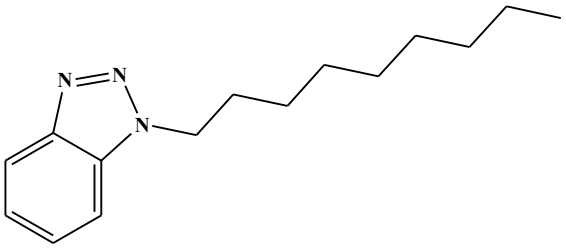
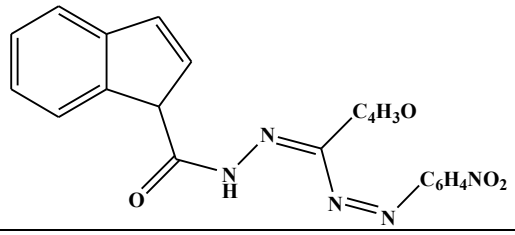
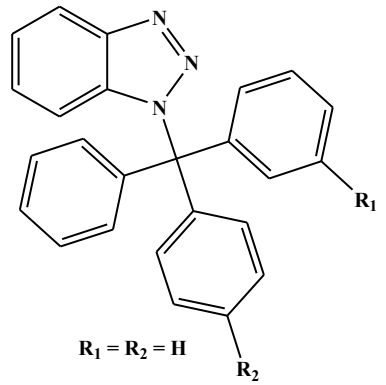
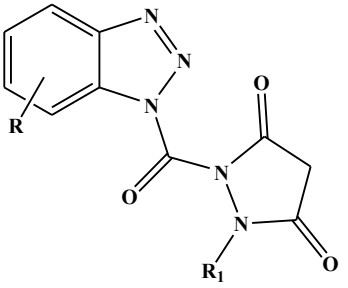
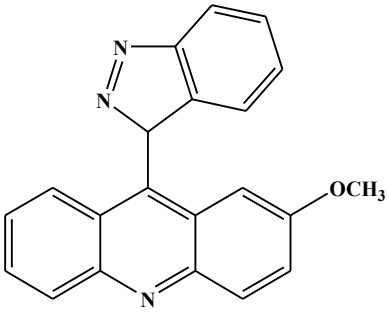
A large number of compounds containing 1, 2, 3-benzotriazole system have been investigated for broad spectrum of activities which include anticorrosive[2], antiviral[3], anti-inflammatory, anticonvulsant[4], enzyme inhibitor[5], DNA cleavage[6], antifungal[7], herbicidal[8], antitubercular[9], antimicrobial[10], antiproliferative[11] etc.

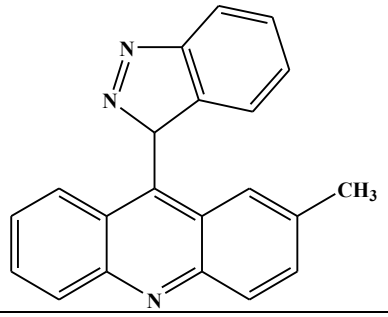
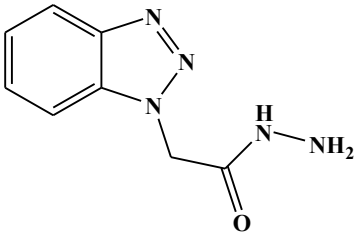
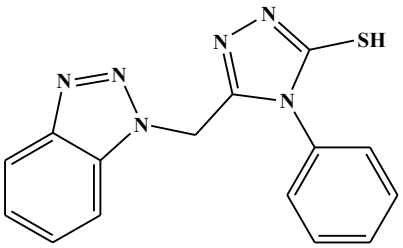
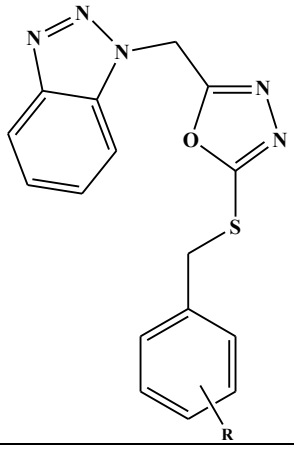
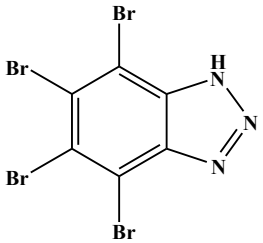
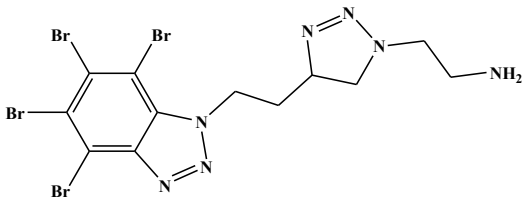
The literature search has reported that benzotriazole derivatives are found active against a wide spectrum of target species. Special focus is therefore given to analyse the benzotriazoles of biological and industrial importance, to find most active sites of benzotriazoles and to investigate target species. The prominent methods of synthesis for these benzotriazole derivatives have also been given in this review article which is not done before. One of the outcomes of this work is that, 1-position nitrogen is the most prominent point of activity.

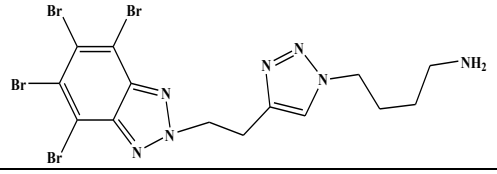
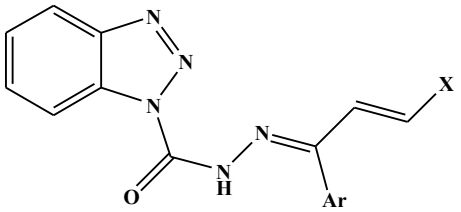
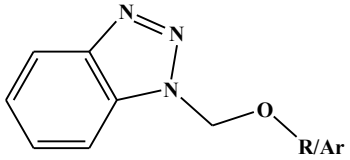
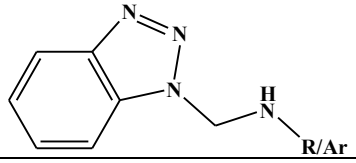
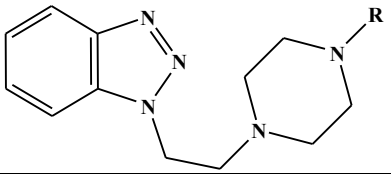
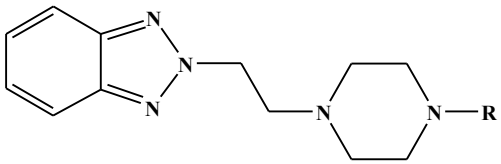
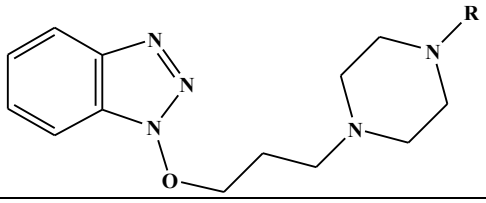
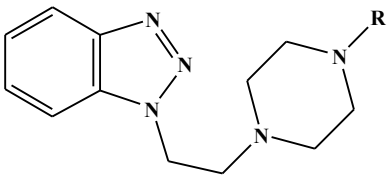
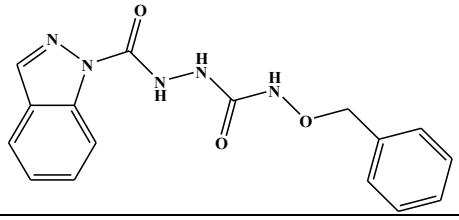
AN INSIGHT INTO SUNDRY NATURE

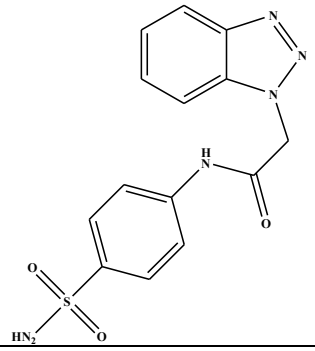
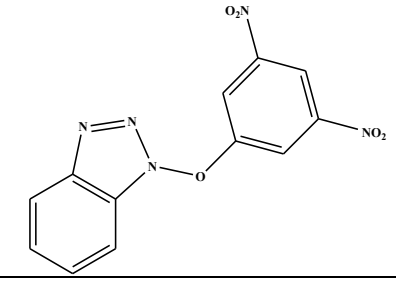
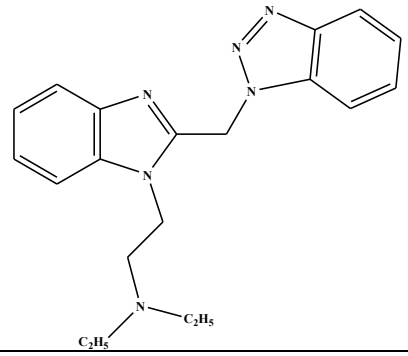
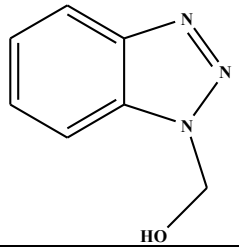
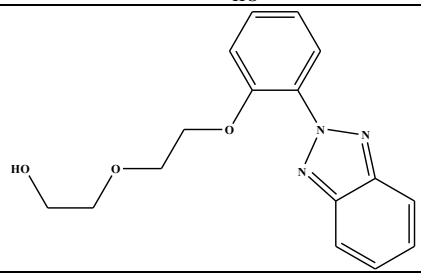
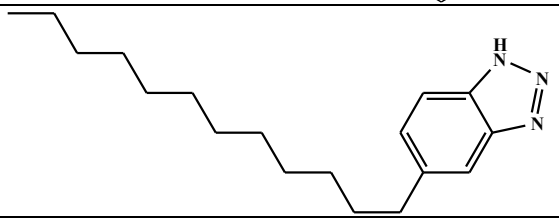
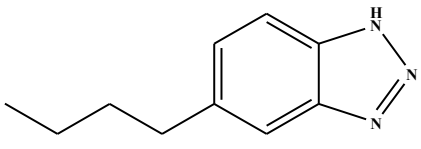
The researchers all over globe have explored benzotriazoles' activity in key areas such as medicinal, pharmacological, clinical, industrial etc. which optimized its scientific value. A spectrum of sundry nature of benzotriazole derivatives is given in table 1 which embraced three derivatives for antifungal activity, five derivatives for antibacterial activity, four derivatives for anticancer activity, three derivatives for anthelmintic activity, four derivatives for antidepressant activity, two derivatives for antioxidative activity, one derivative for antitubercular activity, one derivative for antiviral, seven derivatives for anticorrosive activity, one derivative for plant growth inhibitor activity, one derivative for HIV-1 activity, one derivative for anti-inflammatory activity and one derivative for T modulators. This investigation has revealed that benzotriazole and its derivatives possessed diverse biological nature which explored new channels for future studies.

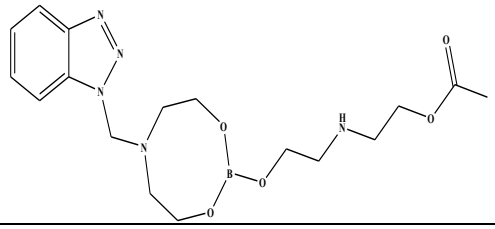
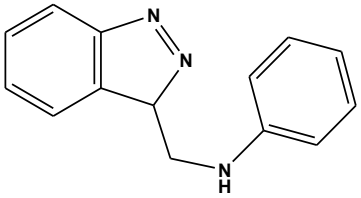
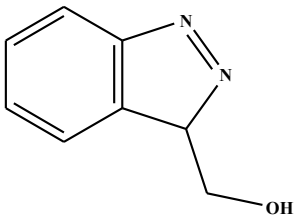
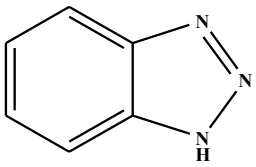
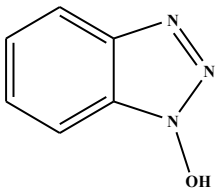
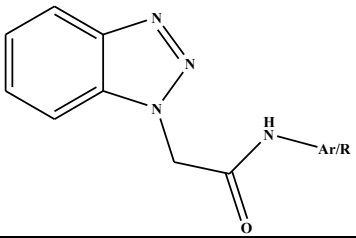
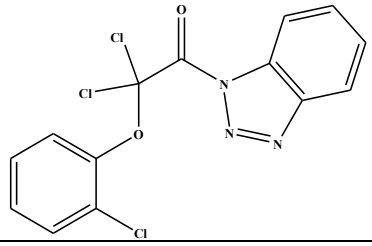
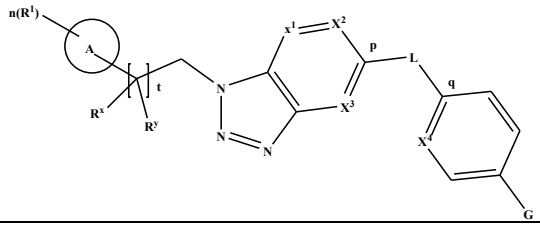
Table 1: Spectrum of Sundry nature of Benzotriazole derivatives

Compound	Biological properties	Effective for species	Reference
	Antifungal	*Candadia* (fungal infection)	12
	Antifungal	*Trichophyton rubrum, Epidermophyton floccosum*	13
	Antifungal	*Microsporum canis*, *Trichophyton mentagrophyte*, *Trichophyton rubrum*, *Epidermophyton floccosum*	14
	Antibacterial	*Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Proteus valgaris*	15
	Antibacterial	*Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Proteus vulgaris, Klebsiella pneumoniae, Salmonella typhi*	16

	Antibacterial	*Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Proteus vulgaris, Klebsiella pneumoniae, Salmonella typhi*	16
	Antibacterial	*Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Proteus vulgaris, Klebsiella pneumoniae, Salmonella typhi*	17
	Antibacterial	*Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Proteus vulgaris, Klebsiella pneumoniae, Salmonella typhi*	17
	Anticancer	Human Leukaemia jurkat T- cell line, Murine Leukaemia L1210 cell Line, Estrogen resistant human breast adenocarcinoma MDA_MD231 cell line, Estrogen sensitive human adenocarcinoma MDF-7 Cell line	18
	Anticancer	CK2 (Caesin Kinase)	19
	Anticancer	CK2 (Caesin Kinase)	19

	Anticancer	CK2 (Caesin Kinase)	19
	Anthelmintic	*P. posthuma*	20
	Anthelmintic	*P posthuma*	21
	Anthelmintic	*P posthuma*	21
	Antidepressant	inhibits the activity of serotonin	22
	Antidepressant	inhibits the activity of serotonin	22
	Antidepressant	inhibits the activity of serotonin	22
	Antidepressant	inhibits the activity of serotonin	22
	Antioxidative	Cancer diseases	23

	Antioxidative	Reactive Oxygen Species	23
	Antitubercular	Mycobacterium tuberculosis (bacterial species)	24
	Antiviral	Hepatitis c (virus)	25
	Anticorrosive	Brass	26
	Anticorrosive	Copper	27
	Anticorrosive	Bronze	28
	Anticorrosive	Copper	29

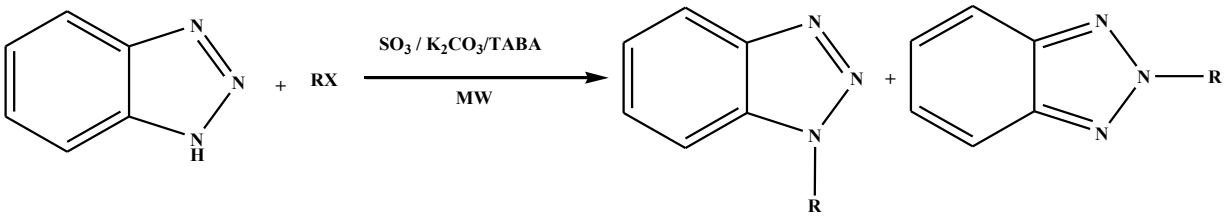
	Anticorrosive	Mild steel	30
	Anticorrosive	Mild steel	31
	Anticorrosive	Mild steel	31
	Plant growth inhibitor	Alfa alfa, Pumpkin	32
	HIV-1	SUMOylation of phosphorylated STAT5	33
	Anti-inflammatory	attack of antigen	34
	Anti-inflammatory	Edema	35
	T modulators	ROR gamma	36

The discussed benzotriazoles are found effective against various target species. The study further elaborated that maximum activities are done at 1-position nitrogen in benzotriazole derivatives with few exceptions such as one derivative each in anticancer, antidepressant activities and three derivatives for anticorrosive activity. It is not exaggerating to say that 1-position nitrogen takes credit for sundry nature of benzotriazoles.

PROMINENT METHODS OF SYNTHESIS

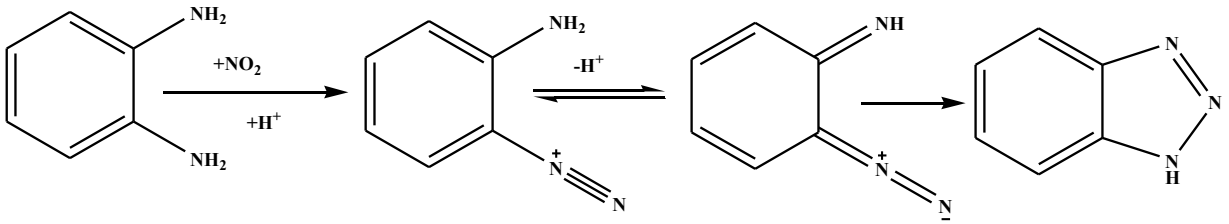
Numbers of methods have been used in literature for the synthesis of benzotriazole derivatives which are quite relevant even today. Latest research can't be completed without giving due credits to the researchers of century and is given as below.

Khalafi-Nezhad et al. synthesized *N*-alkylation of benzotriazole in the presence of SiO_2, K_2CO_3 and tetrabutylammonium bromide (TBAB) under thermal and microwave conditions. In this method, 1-alkyl benzotriazoles were obtained regioselectively in moderate to high yields and short reaction times as per scheme 1.[37]



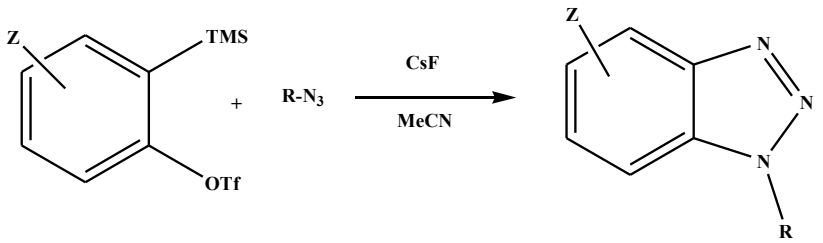
Scheme 1

Vogel et al. reported that benzotriazoles were 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 mono-diazonium derivative is followed by spontaneous cyclization as shown in scheme 2.[38]



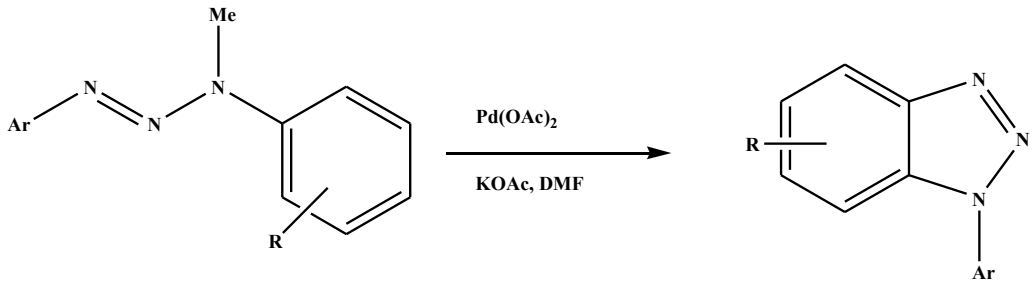
Scheme 2

Shi et al. synthesized a large number of substituted benzotriazoles by [3 + 2] cycloaddition of azides to benzynes. The reaction method was easy so further substitution could occur under the mild conditions as per scheme 3.[39]



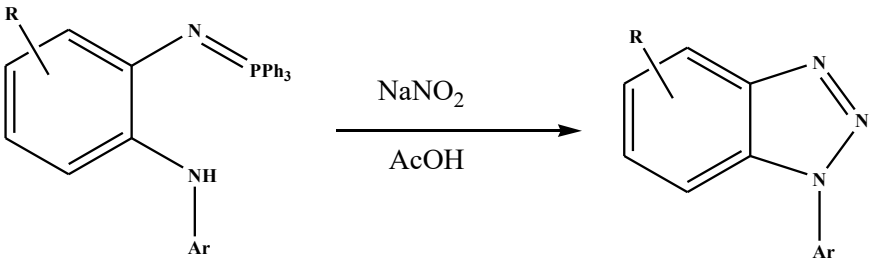
Scheme 3

Zhou et al. explored method for the regioselective synthesis of benzotriazoles using 1, 7-palladium migration cyclization dealkylation sequence. These reactions showed high regioselectivity and high yields as shown in scheme 4.[40]



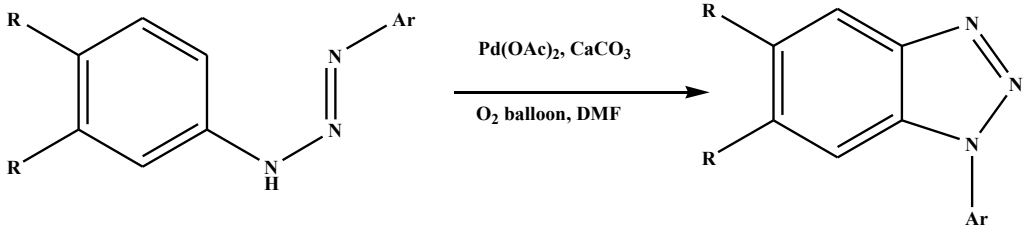
Scheme 4

Lukasik et al. synthesized 1-aryl-1, 2, 3-benzotriazole via cyclocondensation of 2-(arylamino) aryliminophosphoranes in mild conditions. It involved three-step, halogen-free route of synthesis from simple nitroarenes and arylamines as per scheme 5.[41]



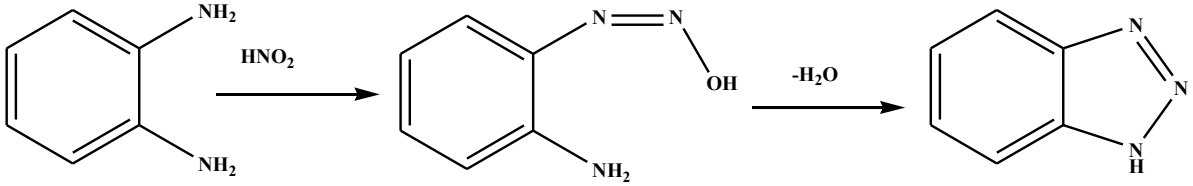
Scheme 5

Kumar et al. synthesized 1-aryl-1H-benzotriazoles by using catalytic amount of $Pd(OAc)_2$ that affected cyclization at moderate temperature. The method is shown in scheme 6.[42]



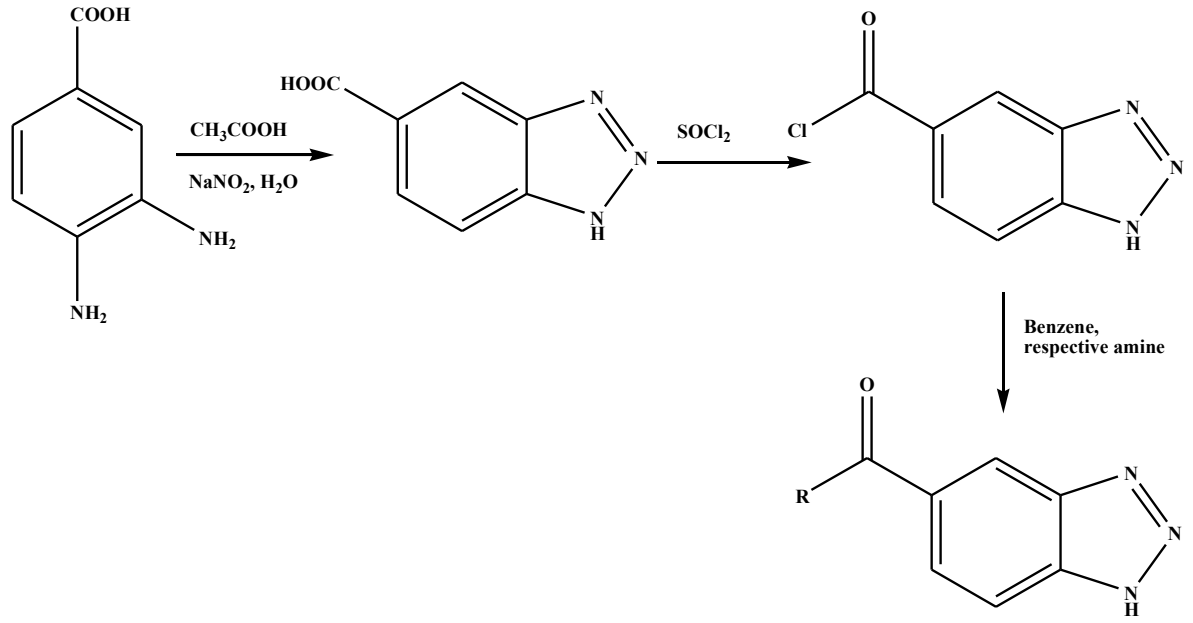
Scheme 6

Damschroder et al. prepared 1, 2, 3-benzotriazole by reacting nitrous acid with o-phenylenediamine and then hydrolysed. This was direct method involving many intermediate steps. The scheme 7[43] is given as below.



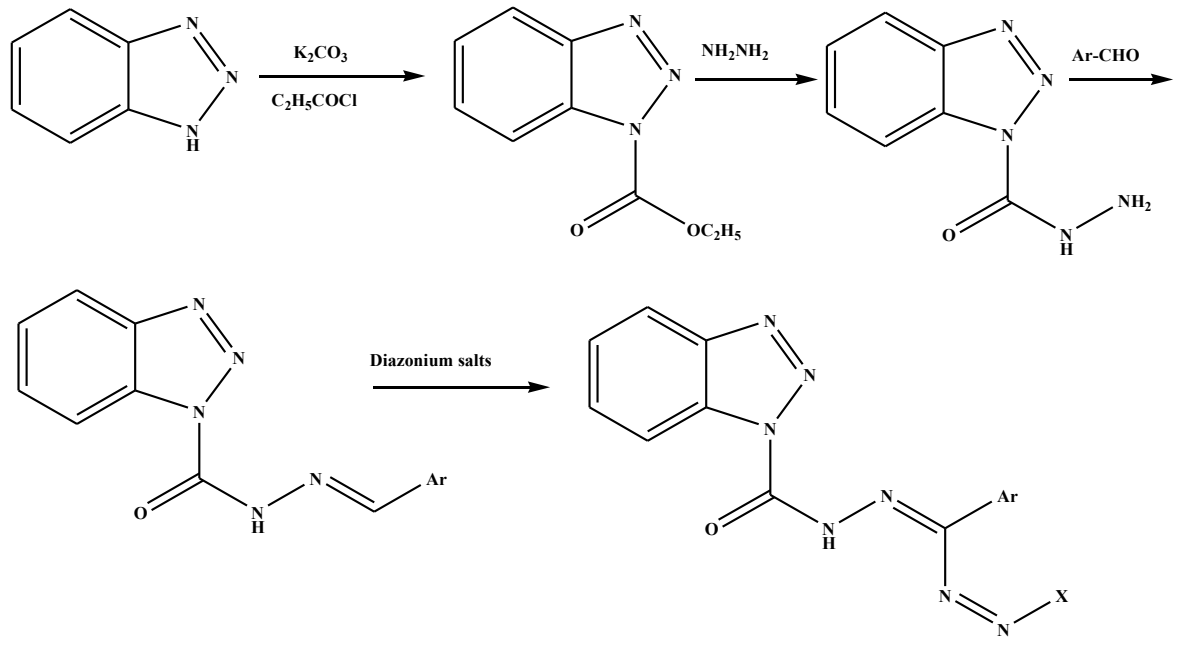
Scheme 7

Shah et al. explored the conventional and microwave synthesis of benzotriazole as per scheme 8.[44]



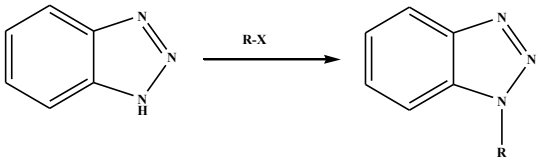
Scheme 8

Nadendlaa et al. synthesized 1, 2, 3 benzotriazole derivatives using conventional and microwave ultrasonification as shown in scheme 9.[45]



Scheme 9

Swamy et al. **s**ynthesized N-alkylated benzotriaziole derivatives. The *N*-alkylation of the benzotriazole was done with different bioactive alkyl halides in the presence of powdered K_2CO_3 in DMF solution by the microwave irradiation method as per scheme 10.[46]



Scheme 10

Literature search unfolds that most of the research activities revolves around the 1-position nitrogen which is further supported by methods of synthesis through schemes 1, 3, 4, 5, 6, 9 and 10. Various substituents are attached at this position through conventional or microwave mode of synthesis.

CONCLUSION

This study shows that sundry nature of benzotriazoles is due to attachment of various substituents at 1-position nitrogen which is supported by number of activities against various target species followed by methods of synthesis adopted by number of researchers. In general, antifungal activity is demonstrated against target species- *Candadia, Trichophyton rubrum, Epidermophyton floccosum, Microsporum canis*, *and Trichophyton mentagrophyte*. Antibacterial activity is demonstrated against target species- *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Proteus valgaris, Pseudomonas aeruginosa, Klebsiella pneumoniae, Salmonella typhi.* Anticancer activity is demonstrated against target species Human Leukaemia jurkat T- cell line, Murine Leukaemia L1210 cell line, Estrogen resistant human breast adenocarcinoma MDA_MD231 cell line, Estrogen sensitive human adenocarcinoma MDF-7 Cell line, CK2(Caesin Kinase). Anthelmintic activity is demonstrated against target species- *P. posthuma.* Antidepressant activity is demonstrated against target species- serotonin, Antioxidative activity is demonstrated against target species- Cancer diseases, Reactive Oxygen Species, Antitubercular is demonstrated against target species- *M. tuberculosis*, Antiviral activity is demonstrated against target species- Hepatitis c, Anticorrosive is demonstrated against target species- Brass, Copper, Mild steel, Plant growth inhibitor activity is demonstrated against target species- Alfalfa, Pumpkin, HIV-1 activity is demonstrated against target species- SUMOylation of phosphorylated STAT5, Anti-inflammatory activity is demonstrated against target species- antigen, edema. It is not exaggerating to say that benzotriazoles have scientific value beyond expectation and imagination.

In addition to that methods of synthesis as reported through schemes, 1, 3, 4, 5, 6, 9 and 10 endorses further that 1-position nitrogen has got attention for maximum synthetic activities. This has been the reason; researches of so many decades focused on 1-position nitrogen and accordingly planned the synthetic routes for benzotriazoles.

This work professes that benzotriazole moiety not only show sundry nature but also enjoy celebrity status among medicinal or pharmacological community. Now a day, many research groups are doing collaborative research to explore further, the latent potential of benzotriazole derivatives. It is found that incorporation of indole, tetrazole, benzimidazole etc. moieties into benzotriazole and benzatriazole derivatives resulted in the improvement of biological action of the compounds. Therefore,

efforts are being done to expand the spectrum of sundry nature of benzotriazole derivatives through new synthetic route of conventional and microwave approaches.

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Cite this article as:

Navneet Singh *et al.* An exploration of sundry nature of benzotriazole derivatives: A review. Int. Res. J. Pharm. 2019;10(3):25-35 http://dx.doi.org/10.7897/2230-8407.100374

Source of support: Nil, Conflict of interest: None Declared