



ISSN No: 0975-7384  
CODEN(USA): JCPRC5

*J. Chem. Pharm. Res.*, 2011, 3(6):375-381

## Benzotriazole in medicinal chemistry: An overview

B. V. Suma<sup>\*1</sup>, N. N. Natesh<sup>1</sup> and V. Madhavan<sup>2</sup>

<sup>1</sup>Department of Pharmaceutical Chemistry, M. S. Ramaiah College of Pharmacy, Bengaluru, India

<sup>2</sup>Department of Pharmacognosy, M. S. Ramaiah College of Pharmacy, Bengaluru, India

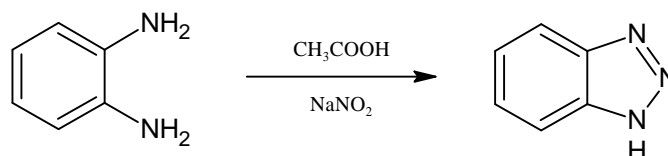
### ABSTRACT

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]



Physical properties are listed in the below table:

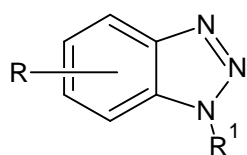
Molecular formula	C <sub>6</sub> H <sub>5</sub> N <sub>3</sub>
Molecular weight	119.1240
Melting point	98.5-100°C
Nature	White to brown crystalline powder
Density	1.36 g/cm <sup>3</sup>
Solubility in water	g/100 ml is 2 (moderate)
CAS Registry Number	95-14-7
UV absorbance	286 nm

Substance is found to be harmful for aquatic organisms. On long term exposure it may cause skin sensitization. Substance can be absorbed into the body inhalation of its aerosol and by ingestion. Stable in acids and alkali's.

### The other synthetic methods:

#### a) Copper-free 'click': 1, 3-dipolar cycloaddition of azides and arynes:

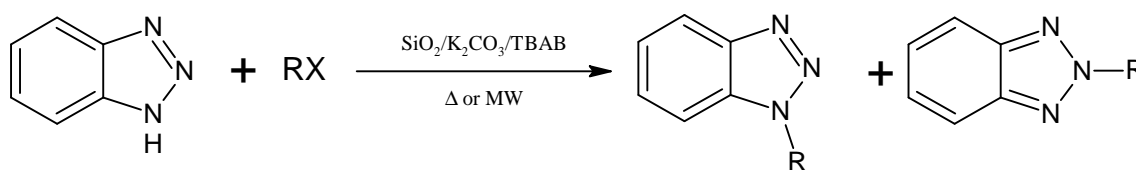
Copper-free 'click': 1, 3-dipolar cycloaddition of azides and arynes has been developed while attempting to synthesize substituted benzotriazoles. The steps involved are: Arynes are formed through fluoride-promoted *ortho*-elimination of *o*-(trimethylsilyl) aryl triflates which can undergo [3 + 2] cycloaddition with various azides to form substituted benzotriazoles. The rapid reaction times and mild conditions make this an attractive variation of the classical 'click' reaction of azides and alkynes. [2]



R	R <sup>1</sup>
Et O <sub>2</sub> CCH <sub>2</sub>	H
Cinnamyl	H
p-Fluorobenzyl	H

#### b) N-Alkylation of Benzotriazole under Solvent-Free Conditions:

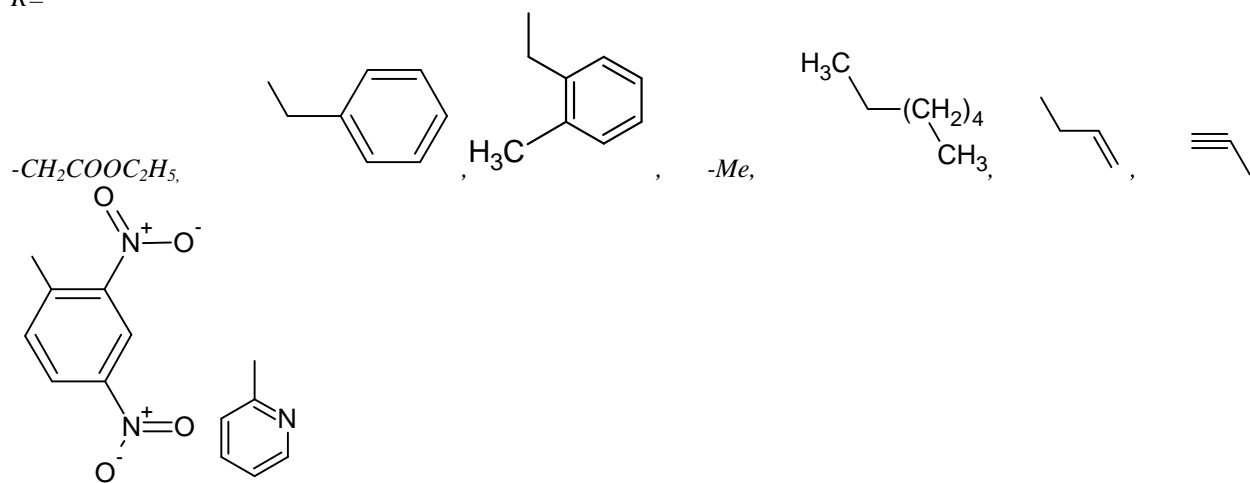
An efficient, simple and solvent-free method for highly regioselective *N*-alkylation of benzotriazole in the presence of SiO<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub> and tetrabutylammonium bromide (TBAB) under thermal and microwave conditions has been described. In this method, 1-alkyl benzotriazoles were obtained regioselectively in moderate to high yields and short reaction times. [3]

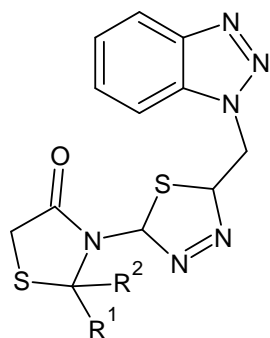


R= alkyl, aryl

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). [4]

R=

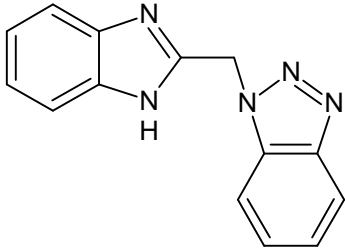
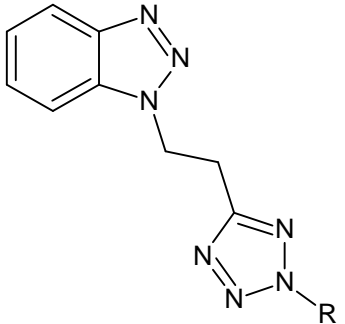
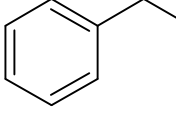
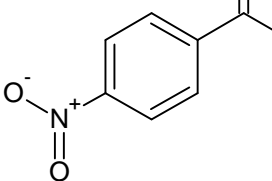
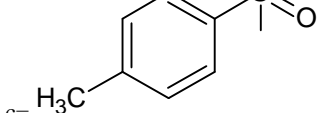
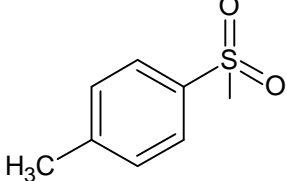
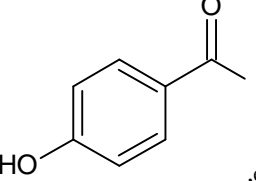
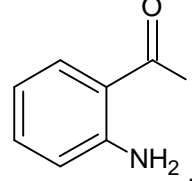
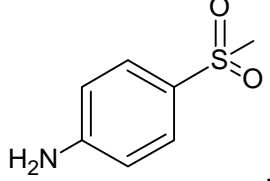
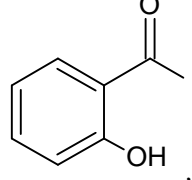
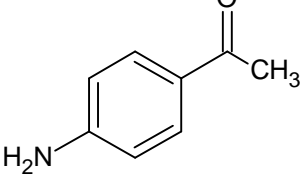
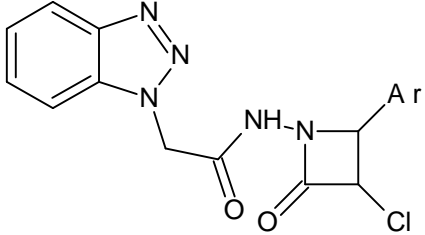


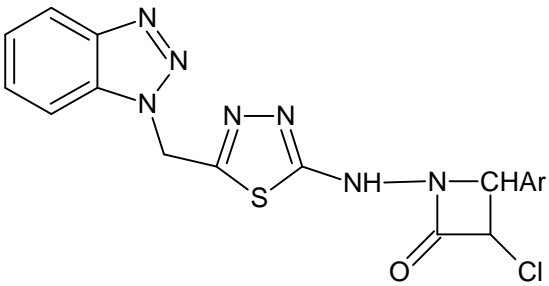
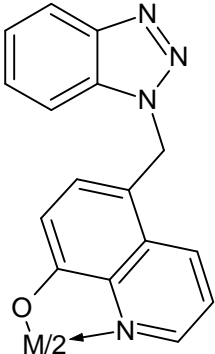
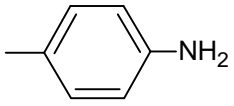
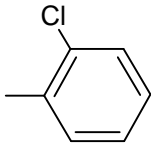
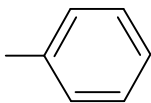
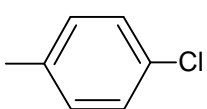
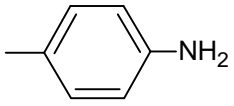
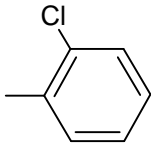
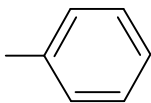
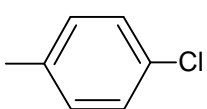
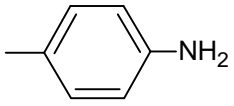
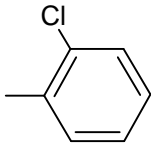
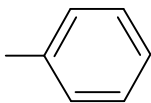
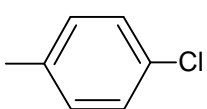


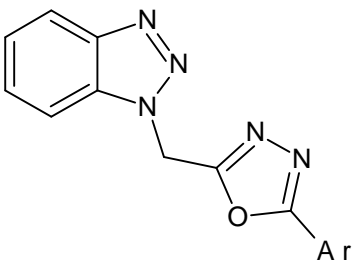
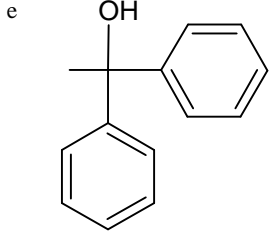
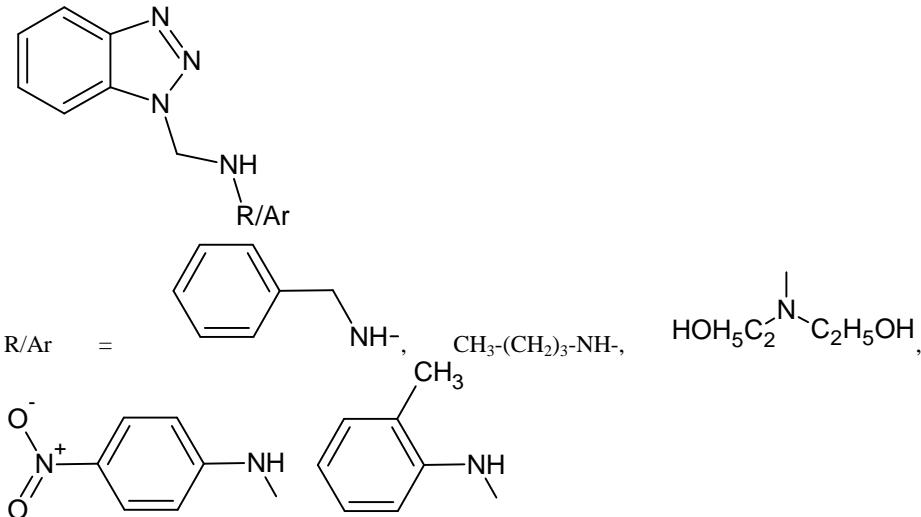
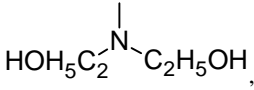
	R1	R2
a	H	-C6H5
b	-C6H5	-4-Br-C6H4
c	H	-4-Cl-C6H4
d	CH3	-C6H5
e	CH3	-C2H5
f	C6H5	-C6H5

Various pharmacological activities of Benzotriazole:-

Sl.No	Authors	Structure and Pharmacological Activity																														
1.	Prasad K.K et al; 2008	<p>Compound d showed highest activity Antifungal activity [5]</p> <table border="1"> <thead> <tr> <th>Compounds</th> <th>Ar</th> </tr> </thead> <tbody> <tr><td>a</td><td>H</td></tr> <tr><td>b</td><td>2-Br C<sub>6</sub>H<sub>4</sub></td></tr> <tr><td>c</td><td>3-Br C<sub>6</sub>H<sub>4</sub></td></tr> <tr><td>d</td><td>4-Br C<sub>6</sub>H<sub>4</sub></td></tr> <tr><td>e</td><td>2-Cl C<sub>6</sub>H<sub>4</sub></td></tr> <tr><td>f</td><td>3-Cl C<sub>6</sub>H<sub>4</sub></td></tr> <tr><td>g</td><td>4-Cl C<sub>6</sub>H<sub>4</sub></td></tr> <tr><td>h</td><td>2-NO<sub>2</sub> C<sub>6</sub>H<sub>4</sub></td></tr> <tr><td>i</td><td>3-NO<sub>2</sub> C<sub>6</sub>H<sub>4</sub></td></tr> <tr><td>j</td><td>4-NO<sub>2</sub> C<sub>6</sub>H<sub>4</sub></td></tr> <tr><td>k</td><td>2-OCH<sub>3</sub> C<sub>6</sub>H<sub>4</sub></td></tr> <tr><td>l</td><td>3-OCH<sub>3</sub> C<sub>6</sub>H<sub>4</sub></td></tr> <tr><td>m</td><td>4-OCH<sub>3</sub> C<sub>6</sub>H<sub>4</sub></td></tr> <tr><td>n</td><td>4,4'-N (CH<sub>3</sub>)<sub>2</sub> C<sub>6</sub>H<sub>4</sub></td></tr> </tbody> </table>	Compounds	Ar	a	H	b	2-Br C <sub>6</sub> H <sub>4</sub>	c	3-Br C <sub>6</sub> H <sub>4</sub>	d	4-Br C <sub>6</sub> H <sub>4</sub>	e	2-Cl C <sub>6</sub> H <sub>4</sub>	f	3-Cl C <sub>6</sub> H <sub>4</sub>	g	4-Cl C <sub>6</sub> H <sub>4</sub>	h	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	i	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	j	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	k	2-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	l	3-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	m	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	n	4,4'-N (CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>
Compounds	Ar																															
a	H																															
b	2-Br C <sub>6</sub> H <sub>4</sub>																															
c	3-Br C <sub>6</sub> H <sub>4</sub>																															
d	4-Br C <sub>6</sub> H <sub>4</sub>																															
e	2-Cl C <sub>6</sub> H <sub>4</sub>																															
f	3-Cl C <sub>6</sub> H <sub>4</sub>																															
g	4-Cl C <sub>6</sub> H <sub>4</sub>																															
h	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>																															
i	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>																															
j	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>																															
k	2-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>																															
l	3-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>																															
m	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>																															
n	4,4'-N (CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>																															
2.	Ewa Augustynowicz-Kopec et al; 2008	<p>Antimicrobial activity [6]</p> <table border="1"> <tbody> <tr><td>a</td><td>R<sub>1-4</sub> = Cl, R<sub>5</sub> = 2- Nitrobenzyl</td></tr> <tr><td>b</td><td>R<sub>1-4</sub> = Cl, R<sub>5</sub> = 3- Nitrobenzyl</td></tr> <tr><td>c</td><td>R<sub>1-4</sub> = Cl, R<sub>5</sub> = 4- Nitrobenzyl</td></tr> <tr><td>d</td><td>R<sub>1-4</sub> = Cl, R<sub>5</sub> = 3,5- Nitrobenzyl</td></tr> <tr><td>e</td><td>R<sub>1-4</sub> = Cl, R<sub>5</sub> = 2,4- Nitrobenzyl</td></tr> </tbody> </table>	a	R <sub>1-4</sub> = Cl, R <sub>5</sub> = 2- Nitrobenzyl	b	R <sub>1-4</sub> = Cl, R <sub>5</sub> = 3- Nitrobenzyl	c	R <sub>1-4</sub> = Cl, R <sub>5</sub> = 4- Nitrobenzyl	d	R <sub>1-4</sub> = Cl, R <sub>5</sub> = 3,5- Nitrobenzyl	e	R <sub>1-4</sub> = Cl, R <sub>5</sub> = 2,4- Nitrobenzyl																				
a	R <sub>1-4</sub> = Cl, R <sub>5</sub> = 2- Nitrobenzyl																															
b	R <sub>1-4</sub> = Cl, R <sub>5</sub> = 3- Nitrobenzyl																															
c	R <sub>1-4</sub> = Cl, R <sub>5</sub> = 4- Nitrobenzyl																															
d	R <sub>1-4</sub> = Cl, R <sub>5</sub> = 3,5- Nitrobenzyl																															
e	R <sub>1-4</sub> = Cl, R <sub>5</sub> = 2,4- Nitrobenzyl																															
3.	Asati KC et al; 2006	<p>Ar : - Cl C<sub>6</sub>H<sub>4</sub>, -CH<sub>3</sub> C<sub>6</sub>H<sub>4</sub>, -NO<sub>2</sub> C<sub>6</sub>H<sub>4</sub>, -Br C<sub>6</sub>H<sub>4</sub> Analgesic and Antimicrobial activity [7]</p>																														

<p>4.</p>	<p>Kuo-Long Yu et al; 2003</p>	 <p>Antiviral activity [8]</p>
<p>5.</p>	<p>Aiyalu Rajasekaran et al; 2009</p>	 <p>R = a=  , b=  , c=  , d=   e=  , f=  , g=   h=  , h= </p> <p>Compound d, e, g and h had significant anti-nociceptive activity, compound c and f exhibited mild anti-inflammatory activity.  Anti-nociceptive and Anti-inflammatory agents [9]</p>
<p>6.</p>	<p>Mrunmayee P Toraskar et al; 2009</p>	 <p>Ar a 4-Cl-C<sub>6</sub>H<sub>4</sub>-  b 4-N(CH<sub>3</sub>)<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>-  c 4-OCH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>-  d 2-OH-C<sub>6</sub>H<sub>4</sub>-  e 3-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>-  f 4-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>-  G 2-Cl-C<sub>6</sub>H<sub>4</sub>-  h C<sub>5</sub>H<sub>4</sub>N-  i 4-OH-C<sub>6</sub>H<sub>4</sub>-  j C<sub>14</sub>H<sub>9</sub>-</p> <p>Compounds h, i and j had good activity.  Antifungal activity [10]</p>

7.	Shukhla DK and Srivastava SD; 2008	 <p>Antimicrobial activity [11]</p> <table data-bbox="1045 600 1433 943"> <thead> <tr> <th>Compounds</th> <th>Ar</th> </tr> </thead> <tbody> <tr> <td>a</td> <td>C<sub>6</sub>H<sub>5</sub></td> </tr> <tr> <td>b</td> <td>C<sub>4</sub>H<sub>3</sub>O</td> </tr> <tr> <td>c</td> <td>4- OCH<sub>3</sub> .C<sub>6</sub>H<sub>4</sub></td> </tr> <tr> <td>d</td> <td>2- Cl .C<sub>6</sub>H<sub>4</sub></td> </tr> <tr> <td>e</td> <td>2- OH .C<sub>6</sub>H<sub>4</sub></td> </tr> <tr> <td>f</td> <td>4- Cl .C<sub>6</sub>H<sub>4</sub></td> </tr> <tr> <td>g</td> <td>4- OH .C<sub>6</sub>H<sub>4</sub></td> </tr> <tr> <td>h</td> <td>- CH = CH .C<sub>6</sub>H<sub>4</sub></td> </tr> <tr> <td>i</td> <td>4- N (CH<sub>3</sub>)<sub>2</sub> C<sub>6</sub>H<sub>4</sub></td> </tr> <tr> <td>j</td> <td>4- OH -3- O CH<sub>3</sub> . C<sub>6</sub>H<sub>3</sub></td> </tr> <tr> <td>k</td> <td>2- NO<sub>2</sub> .C<sub>6</sub>H<sub>4</sub></td> </tr> </tbody> </table>	Compounds	Ar	a	C <sub>6</sub> H <sub>5</sub>	b	C <sub>4</sub> H <sub>3</sub> O	c	4- OCH <sub>3</sub> .C <sub>6</sub> H <sub>4</sub>	d	2- Cl .C <sub>6</sub> H <sub>4</sub>	e	2- OH .C <sub>6</sub> H <sub>4</sub>	f	4- Cl .C <sub>6</sub> H <sub>4</sub>	g	4- OH .C <sub>6</sub> H <sub>4</sub>	h	- CH = CH .C <sub>6</sub> H <sub>4</sub>	i	4- N (CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	j	4- OH -3- O CH <sub>3</sub> . C <sub>6</sub> H <sub>3</sub>	k	2- NO <sub>2</sub> .C <sub>6</sub> H <sub>4</sub>
Compounds	Ar																									
a	C <sub>6</sub> H <sub>5</sub>																									
b	C <sub>4</sub> H <sub>3</sub> O																									
c	4- OCH <sub>3</sub> .C <sub>6</sub> H <sub>4</sub>																									
d	2- Cl .C <sub>6</sub> H <sub>4</sub>																									
e	2- OH .C <sub>6</sub> H <sub>4</sub>																									
f	4- Cl .C <sub>6</sub> H <sub>4</sub>																									
g	4- OH .C <sub>6</sub> H <sub>4</sub>																									
h	- CH = CH .C <sub>6</sub> H <sub>4</sub>																									
i	4- N (CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>																									
j	4- OH -3- O CH <sub>3</sub> . C <sub>6</sub> H <sub>3</sub>																									
k	2- NO <sub>2</sub> .C <sub>6</sub> H <sub>4</sub>																									
8.	Patel HS, Oza KK ; 2008	 <p>BTMQ – metal chelates where M is Cu<sup>2+</sup>, Ni<sup>2+</sup>, Co<sup>2+</sup>, Zn<sup>2+</sup>, Mn<sup>2+</sup> Antimicrobial activity [12]</p>																								
9.	Rakesh Saini et al; 2010	<table data-bbox="1145 1384 1423 1877"> <tbody> <tr> <td>a</td> <td></td> </tr> <tr> <td>b</td> <td></td> </tr> <tr> <td>c</td> <td></td> </tr> <tr> <td>d</td> <td></td> </tr> </tbody> </table>	a		b		c		d																	
a																										
b																										
c																										
d																										

		 <p>Compound b was found to be more effective. Antifungal activity [13]</p>	
10.	Pawar SS et al; 2010	 <p>Compound d had a good activity. Anthelmintic activity [14]</p>	

Apart from pharmaceutical use benzotriazole is used in industry as fixing agent in photographic emulsion as anti-tarnish agents for copper and its alloy and as a corrosion inhibitor in anti-freeze and water coolant systems. More recently benzotriazoles has also been used as an additive in anti-tarnish clothes. [15]

## 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. An attempt is made to focus on some synthetic methods of benzotriazole including *N*-Alkylation of benzotriazole under Solvent-Free Conditions and Copper-free 'click' methods. It can act as an important tool for medicinal chemists to develop newer compounds possessing benzotriazole moiety that could be better agents in terms of efficacy and safety.

## REFERENCES

- [1] Furmiss BS, Hannaford AJ, Smith PWG, Tatchell AR. Vogel's textbook of practical organic chemistry. Pearson . **2008**, (5), 1163.
- [2] Lachlan Campbell-Verduyn, Philip Elsinga H, Leila Mirfeirzi, Rudi Dierckx A and Ben L. Feringa, *Org Biomol Chem*, **2008**, (6), 3461-3463.
- [3] Khalafi A, Zare A, Parhami A, Soltani Rad M.N and Nejabat G.R. *J. Iranian Chem. Soc.* **2007** September; 4(3),271-278.

- [4] Namdeo KP, Singh VK and Prajapati SK. *Indian J. Pharma. Educ. Res* **2009** July-Sept, 43(3), 266-271.
- [5] Prasad K.K., Toraskar MP, Kulkarni VM and Kadam VJ. *Indian Drugs* **2008** December: 45(12).
- [6] Ewa Augustynowicz-Kopec, Zofia Zwolska, Andrzej Orzeszko. *Acta Polo Pharma* **2008**, 65(4), 435-439.
- [7] Asati KC, Srivastava SK and Srivastava SD. *Indian J. Chem.* **2006** February; 45B, 526-531.
- [8] Kuo-Long Yu, Yi Zhang, Rita L.Civiello, Kathleen F. Kadow, Christopher Cianci, Mark Krystal and Nicholas A.Meanwell. *Bioorg. Med. Chem Letters* **2003**, 13, 2141-2144.
- [9] Aiyalu Rajasekaran, Kalasalingam Ananda Rajagopal.. *Acta Pharm.***2009**, 59, 355–364.
- [10] Mrunmayee P Toraskar, Vilasrao J Kadam , Vithal M Kulkarni.. *International Journal of Chem Tech Research* **2009**, 1(4), 1194-1199.
- [11] Shukhla DK and Srivastava SD. *Indian J. Chem.* **2008** March, 47B, 463-469.
- [12] Patel HS, Oza KK. *E-Journal of Chemistry* **2009**, 6(2),371-376.
- [13] Rakesh Saini, Saurabh Chaturvedi, Achyut Narayan Kesari, Swatrantra Kushwaha.. *Der Pharma Chemica*, **2010**, 2(2), 297-302.
- [14] Pawar SS, Gorde PL, Kakde RB. *Archives of Applied Science Research*, **2010**, 2 (1), 80-85.
- [15] <http://cameo.mfa.org/browse/record.asp?subkey=1091>.