Journal Of Harmonized Research (JOHR)

Journal Of Harmonized Research in Pharmacy
4(4), 2015, 344-352

ISSN 2321 – 0958

Review Article

BENZOTRIAZOLES: A VALUABLE INSIGHT INTO RECENT DEVELOPMENTS AND BIOLOGICAL ACTIVITIES

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Abstract: In recent years, heterocyclic compounds, analogs, and derivatives have attracted strong interest due to their useful biological and pharmacological properties. The small and simple benzotriazole nucleus is present in compounds aimed at evaluating new entities that possess anti-microbial, anti-tumor, antitubercular, anti-convulsant, anti-depressant, antimalarial, and anti-inflammatory activities. Benzotriazoles 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. The present review highlights the recently synthesized benzotriazoles possessing important biological activities.

Key Words: Benzotriazoles; Antifungal; Antitubercular; Anticancer; Antiviral; Anticonvulsant; Anti-inflammatory; Antidepressant; Antimalarial

Introduction

Benzotriazoles are heterocyclic compounds featuring a benzene ring fused with five membered ring of two carbon atoms and three nitrogen atoms as part of the aromatic five-membered ring. Benztriazole refers to chemical compounds (Fig. 1) with the molecular formula $C_6H_5N_3$. The :

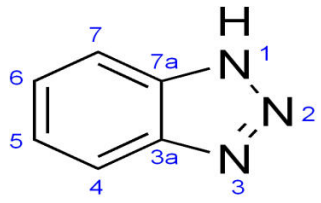

Fig. 1 Structures of Benzotriazoles

1,2,3-Benzotriazole forms colorless, sweet-tasting, hygroscopic crystals, mp 100 °C, bp 350 °C, which is soluble in water. The chemistry of fused heterocycles derived from benzotriazole has received considerable attention in recent years due to their usefulness in different areas of biological activities and as

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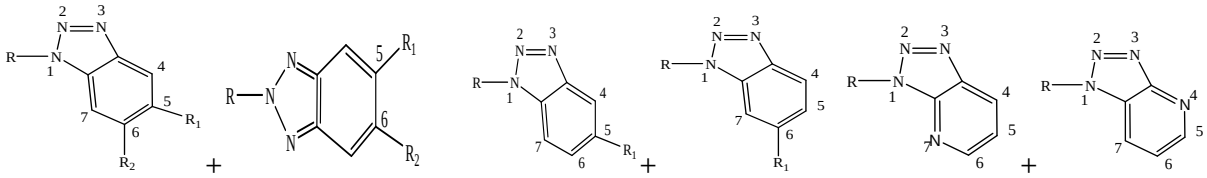
Received on: December 2015
Accepted after revision: December 2015

industrial intermediates. Benzotriazole derivatives are known to exhibit antifungal [1–5], antiprotozonal [21], antitubercular [6-7], anticancer [10-12], anticonvulsant [9], anti-inflammatory [8], analgesic activities [10] and antidepressant activities [14]. The Benzotriazole nucleus has been incorporated into a wide variety of therapeutically interesting drug candidates. Some of the modern day drugs having fused heterocyclic with a benzotriazole moiety were synthesized and evaluated for the activity.

Biological Activities Of Benzotriazole Derivatives

Antifungal activity

Talele *et al.* [15**]** synthesized a series of compounds 5,6-dimethylbenzotriazol-2-yl derivative), 1d (5-chlorobenzotriazol-1-yl derivative) and 1e (6-methylbenzotriazol- 1-yl derivative) exhibited potent antifungal activity, with the MICs for Candida spp. and Aspergillus niger **[**11**]**.

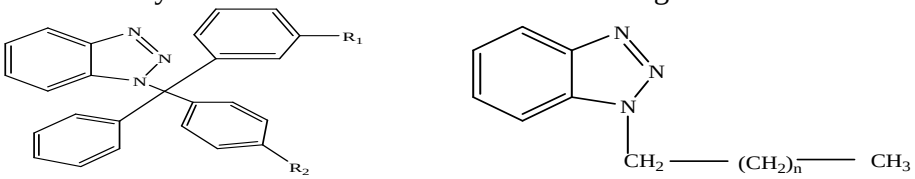


(major + minor) (major + minor) (major + minor)

	R_1	R_2			R_1	R_2			R_1			
1a:	H	H	(9:1)	1a':	H	H	1c	NO_2	(8:2)	1c'	NO_2	1h (9:1) 1h'
1b:	CH_3	CH_3	(6:4)	1b':	CH	CH_3	1d	Cl	(7:3)	1d'	Cl	
							1e	CH_3	(8:2)	1e'	CH_3	
							1f	F	(7:3)	1f'	F	
							1g	OCH_3	(9:1)	1g'	OCH_3	

Figure 2: Synthesis of target compounds 1a - 1h and 1b'- 1f'

Rezaei *et al* [16**]** described the synthesis and evaluation of a novel series of benzotriazoles **2** and **3** as inhibitors of cytochrome P450 14α-demethylase (14DM). Compounds were designed by generating a virtual library and docking them into the enzyme active site. The analogs **2a, 2b**, and **2c** had low antifungal activity. The activity was decreased by the presence of a methoxy group substituted on the benzotriazole moiety (compounds **2b** and **2c**). Compound **3a** possessed potent inhibitory effect on tested fungi.



(a)$R_1 = R_2 = H$ (a) n = 3

(b)$R_1 = H$, $R_2 = OCH_3$ (b) n = 6

(c)$R_1 = R_2 = OCH_3$

2 3

Figure 2: Synthesis of target compounds 2a – 2c and 3a- 3b

***S. Kabilan et al* [**17**]** synthesized benzotriazole analogues substituted piperidin-4-one derivatives by various substituted compounds of which compound 1-(2-(1H-benzotriazol-1-yl)acetyl)-3,5-dimethyl-2,6-bis(p methoxyphenyl) piperidine-4-one is found to be active. The synthesized compounds were subjected to their in vitro antibacterial and

antifungal activities against pathogenic microbial strains. The results pointed out that compound **4(**Figure 4) explored superior inhibition activity against B. subtilis and E. coli.

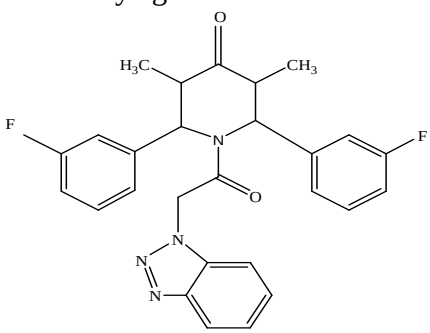


Figure 4: Structure of the active compound 4 of the synthesized series.

Vivek D. Bobade et al **[**18**]** synthesized coumpound 1-(2-(1H-benzo[d][1,2,3]triazol-1-yl)-1-(4-substitutedphenyl) ethylidene)-2-(4-(substitutedphenyl) thiazol-2-yl)hydrazine 5a–y as shown in Figure no.5. All the synthesized compounds were screened for their in vitro antibacterial activity against the standard strains Bacillus subtilis, Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa and for their antifungal activity against Candida albicans and Aspergillus niger. Of the compounds 5a–y tested, compounds with electron-withdrawing F, Cl, Br, CF_3, and NO_2 at the phenyl ring expressed a moderate to good activity against most of the tested pathogens; they inhibited the Gram-positive and Gram-negative pathogens equally.

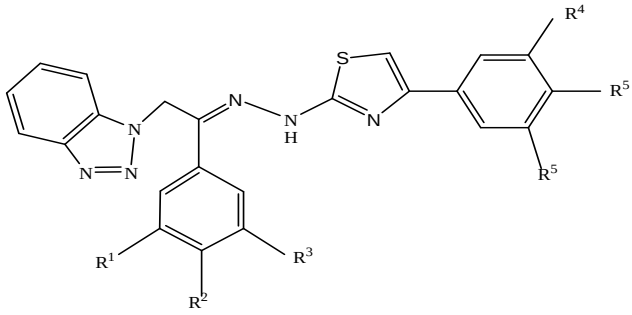


Figure 5: Synthesis of the target compounds 5a-y.

Compound	R1	R2	R3	R4	R5	R6
5a	H	F	H	H	F	H
5b	H	F	H	H	Cl	H
5c	H	F	H	H	Br	H
5d	H	F	H	H	NO2	H
5e	H	F	H	CF3	H	CF3
5f	H	Cl	H	H	F	H
5g	H	Cl	H	H	Cl	H
5h	H	Cl	H	H	Br	H
5i	H	Cl	H	H	NO2	H
5j	H	Cl	H	CF3	H	CF3
5k	H	Br	H	H	F	H
5l	H	Br	H	H	Cl	H
5m	H	Br	H	H	Br	H
5n	H	Br	H	H	NO2	H
5o	H	Br	H	CF3	H	CF3
5p	H	NO2	H	H	F	H
5q	H	NO2	H	H	Cl	H
5r	H	NO2	H	H	Br	H
5s	H	NO2	H	H	NO2	H
5t	H	NO2	H	CF3	H	CF3
5u	CF3	H	CF3	H	F	H
5v	CF3	H	CF3	H	Cl	H
5w	CF3	H	CF3	H	Br	H
5x	CF3	H	CF3	H	NO2	H
5y	CF3	H	CF3	CF3	H	CF3

Antitubercular activity

Paolo Sanna et al **[**6**]** synthesized a series of 3-aryl substituted-2-(1*H*(2*H*)-benzotriazol-1(2)-yl)acrylonitriles for a preliminary in vitro evaluation of antitubercular activity. Several compounds showed an interesting activity in the preliminary screening with a percent growth inhibition of the virulent *Mycobacterium tuberculosis* between 40 and 99% at the concentration of 12.5 μg/mL. The most effective derivatives of the synthesized compound of E-isomer and Z-isomer was found to be E-**6a and E-6e** were also tested against *M. avium* in vitro.

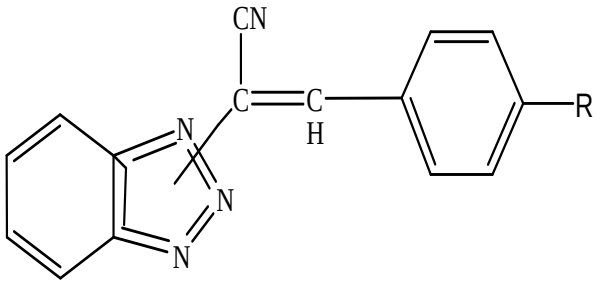
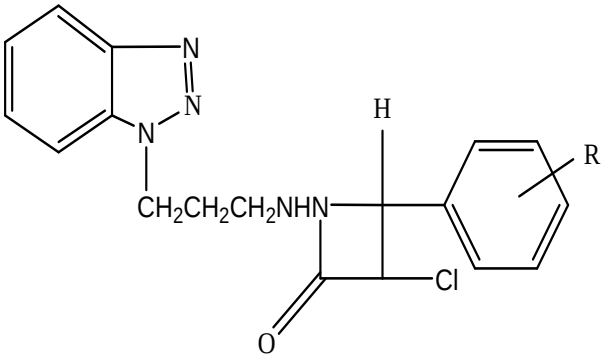


Figure 5: Synthesis of the target compounds E - 6a-h and Z-6b, h, f.

Compound	R
a	**H**
b	**CH_3**
c	**F**
d	**Cl**
e	**Br**
f	**CF_3**
g	**COOH**
h	**NO_2**

Adesh Dubey et al **[**7**]** synthesized compounds of series **7a–i** were evaluated for their antitubercular activity against Mycobacterium tuberculosis H37RV and antimicrobial activity against some selected microorganism. All the synthesized compounds of series (**7a–i**) were screened against Mycobacterium tuberculosis for their antitubercular activity and against some microorganisms for their antimicrobial activities. Generally compounds possessing electron withdrawing groups showed good antibacterial and antitubercular activity. Some derivatives (**7b, 7c, 7d, 7f, 7g**) containing electron withdrawing groups (–Cl, –Br, –NO2) have shown promising activity against M. tuberculosis and some bacteria. Compounds possessing electron donating groups (**7h, 7i**) have shown good antifungal activity.

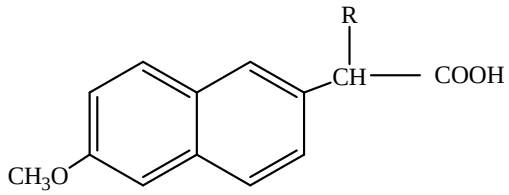


R=-H, 2-CL, 4-CL, 2-Br, 2-NO_2, 4-NO_2, 2-OCH_3, 4-OCH_3

Figure 6: Synthesis of the target compounds 7a-i.

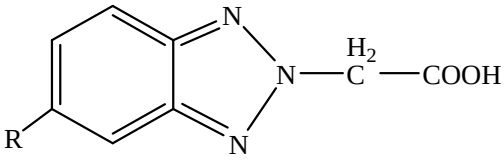
Anti-inflammatory activity

Fabio Sparatore et al **[**8**]** sets of benzotriazol-1/2-ylalkanoic acids (1, 2, 3) and benzotriazol-1-yloxyalkanoic acids (4, 5) were prepared and tested for antiinflammatory activity; when significant activity was observed also the antinociceptive activity was explored. While the acids of structure 1, 4 and 5 were devoid of antiinflammatory action, most 2-(benzotriazol-1/2-yl)propionic acids (2, 3) exhibited significant activity as anti inflammatory and anti nociceptive agents, with compound 2c and 3a being the most active in the two assays, respectively. The dextrorotatory enantiomer of 2c ((_)-2c) was also prepared and found to be practically as active as the racemic mixture, though some differences in the steepness of the dose_ response curves were observed.

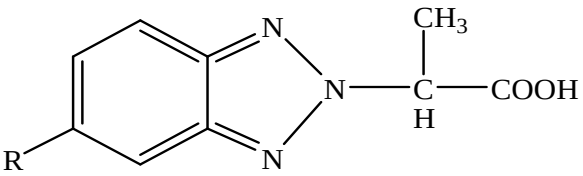


R= H: 6-MNA

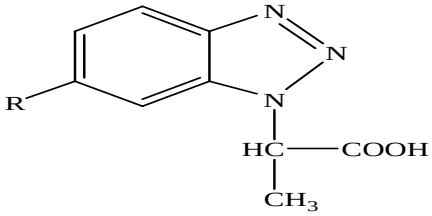
CH_3: naproxen



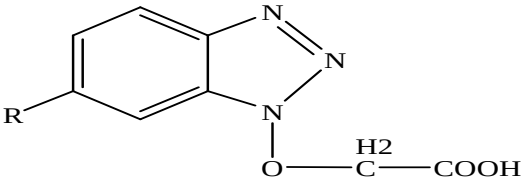
1a; 1b



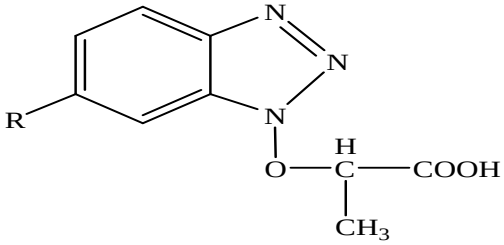
2a – 2e



3a – 3c



4a; 4b



5a-5e

R= H (a); O-CH_3 (b); CH_3 (c); Cl (d); CF_3 (e)

Figure 7: Synthesis of the target compounds 1-5.

Anticonvulsant activities

Kamal M. Dawood et al **[**9**]** synthesized compound by treatment of 2 bromoacetylbenzofuran with 1H-benzotriazole afforded 1-(benzofuran-2-yl)-2-(benzotriazol-1-yl)ethanone which reacted with phenylisothiocyanate to give the corresponding thioacetanilide derivatives. Treatment of the latter ethanone and thioacetanilide derivatives with hydrazonoyl chlorides afforded the corresponding pyrazole and 1,3,4-thiadiazole derivatives. The thioacetanilide derivative reacted with a-haloketones and a-halodiketones to afford thiophene and thiazole derivatives, respectively. The newly synthesized compounds were found to possess anticonvulsant and anti-inflammatory activities with the same mechanism of action of selective COX-2 inhibitors.

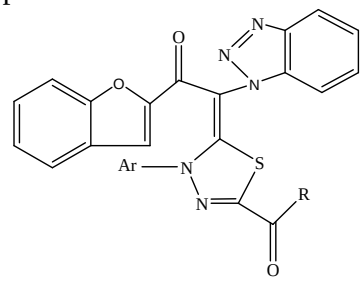


Figure 8: Synthesis of the target compounds 8 a-f.

Compound	**R**	**Ar**
a	CH_3	C_6H_5
b	CH_3	4-MeC_6H_4
c	CH_3	4-ClC_6H_4
d	OC_2H_5	C_6H_5
e	OC_2H_5	4-MeC_6H_4
f	OC_2H_5	4-ClC_6H_4

Anticancer activities

Hai-Liang Zhu et al synthesized a series of new 1,3,4-oxadiazole derivatives containing benzotriazole moiety as potential focal adhesion kinase (FAK) inhibitors. All the synthesized

compounds were firstly reported. Among the compounds, compound 9 (Figure 9) shows the most potent inhibitory activity against MCF-7 and HT29 cell lines with IC50 values of 5.68 lg/ml and 10.21 lg/ml, respectively.

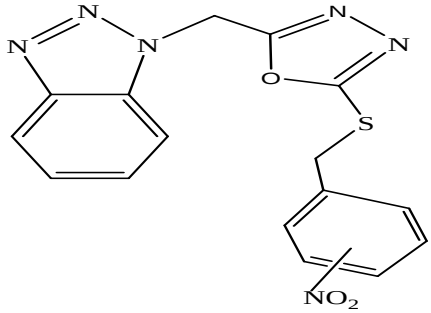


Figure 9: Structure of the active compound 9 of the synthesized series.

Antonio Carta et al synthesized a new series of variously substituted 3-aryl-2-[1*H*(2*H*)-benzotriazol-1(2)-yl]acrylonitriles and tested for antiproliferative and antitubercular activity as part of our continuing research program in the antimicrobial and antitumor fields. The most cytotoxic derivatives (**5a,g,i,j,l** and **7b**) (CC50 < 3.0 μM against MT-4 cells) were evaluated against a panel of human cell lines derived from hematological and solid tumors, using 6-mercaptopurine (6-MP) and etoposide as reference drugs.

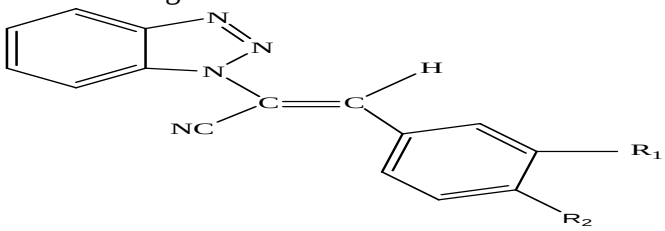


Figure 10: Synthesis of the target compounds 10 a-f.

a) R_1= H; R_2= Cl
b) R_1= H; R_2= Br
c) R_1= H; R_2= CH_3
d) R_1= H; R_2= OCH_3
e) R_1= NO_2; R_2= H
f) R_1= OCH_3; R_2= H
g) R_1-R_2= OCH_2O.

Bin Qu et al synthesized bioactive compound, 3-(1H-benzo [d] [1, 2, 3] triazol-1-yl)-1-(4-methoxyphenyl)-1-oxopropan-2-yl benzoate (BmOB), which is a novel benzotriazole derivative. BmOB displayed anti-proliferative effects on several human tumor cell lines. Human hepatocarcinoma BEL-7402 cell line was selected as a model to illustrate BmOB's inhibition effect and its potential mechanism, since it was the highest susceptible cell line to BmOB. It was shown that treatment with BmOB resulted in generation of reactive oxygen species, disruption of mitochondrial membrane potential (ΔΨm), and cell death in BEL-7402 cells. BmOB induced cytotoxicity could be prevented by antioxidant vitamin C and mitochondrial permeability transition inhibitor cyclosporine A. cyclosporine A could also protect the BmOB induced collapse of ΔΨm in BEL7402 cells, while vitamin C did not show similar effects. The results suggest that BmOB could inhibit BEL-7402 cell proliferation, and the cell death may occur through the modulation of mitochondrial functions regulated by reactive oxygen species.

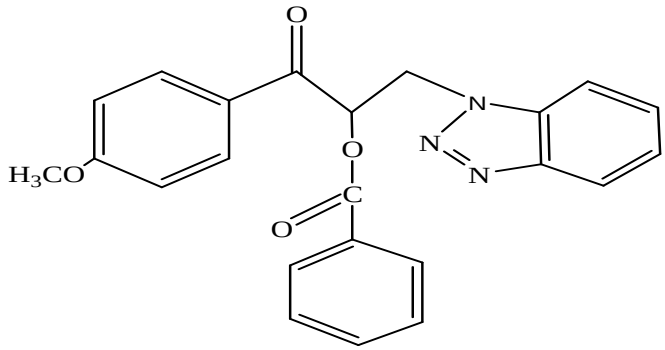
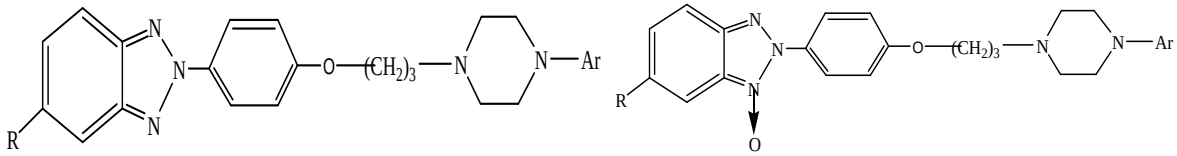


Figure 11: Structure of the active compound of the synthesized series.

Antidepressant activities

Anna Sparatore et al synthesized a small set of 2-{4-[3-(4-aryl: heteroaryl- piperazinyl) propoxy] phenyl}-2*H*-benzotriazoles and corresponding N-oxides. The synthesized compounds were able to bind on some serotonin (5-HT1A, 5-HT2A) and dopamine (D2, D3) receptors, while displaying poor or no affinity for 5-HT1B, 5-HT2C, 5-HT3, and 5-HT4 subtypes. The strong contribution of the N-oxide function for the binding on 5-HT1A, D2

and D3 receptors is noteworthy. The most selective compounds in this regard are **13a**, followed by **12b** and **12c**, which inhibit [3H]ketanserin binding to 5-HT2A receptors at about 10_7 M while, until the highest concentration tested (10_5 M), not affecting [3H]mesulergine binding to 5-HT2C receptors. For 2-{4-[3-[4-(2-methoxyphenyl)-1-piperazinyl] propoxy]phenyl}-2*H*-benzotriazol-1-oxide (**13b**), the binding constants (*K*i) were 11.9 (5-HT1A) and 10.5 nM (D3).



12 13

Ar = Phenyl (a); 2-methoxyphenyl (b); 2-pyridyl (c); 2-pyrimidyl (d)

Figure 12: Synthesis of the target compounds 12 a-d and 13 a-d.

Antianthemintic activities

R. Venkata Nadh et al **[**14**]** synthesized 1e(1Hebenzo[d][1,2,3]triazole-1-carbonyl) derivatives using"1Hebenzo[d][1,2,3]triazole" (1)as the starting material under ultrasonicated and solvent-free conditions. All the products were assayed for anthelmintic activity against Pheretima posthuma using albendazole and mebendazole as reference compounds. All the newer 1,2,3 e benzotriazole derivatives synthesized by ultrasound activation in solvent free condition were obtained in moderate to good yields in the range of 71-82%. The data interpretation of the spectral values with reference to standard values confirmed the structures of the synthesized compounds. Out of the sixteen synthesized derivatives, four compounds (14B, 14F, 14J and 14N) showed anthelmintic activity in dose-dependent manner giving shortest time of paralysis and death with different concentrations of the derivatives. Among these four derivatives, 14J showed superior activity.

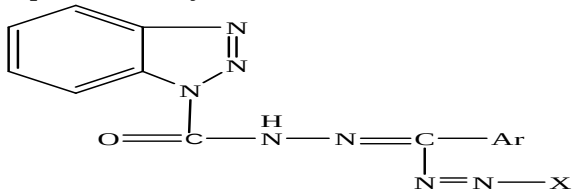


Figure 8: Synthesis of the target compounds 14 A-P.

Current Aspects Of Benzotriazoles

There are number of benzotriazoles reported possessing different biological activities comparable to clinically synthetic compounds. It has been noticed that modifications on the benzotriazole moiety displayed valuable biological activities. It will be interesting to observe whether these modifications can be utilized for the development of potent therapeutic agents in the future. Thus the quest to explore many more modifications on the benzotriazole moiety needs to be continued.

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