REVIEW ARTICLE

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A Review on Biological Activities of Benzotriazole Derivatives

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ABSTRACT

Benzotriazoles have various chemical properties that play a vital role in the development of new benzotriazole derivatives. The biological activities of several benzotriazole derivatives were evaluated. The aim of this review is to provide an overview of the biological activities of benzotriazole derivatives. This review covers the compounds that have benzotriazole moiety have wide range of spectrum that include antibacterial, antifungal, anti-inflammatory, analgesic, antitumor and miscellaneous activity. These findings have been guiding for development of new benzotriazole compounds.

Keywords: - Benzotriazole, IND, FDA, DLX-4, antifungal

INTRODUCTION

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.

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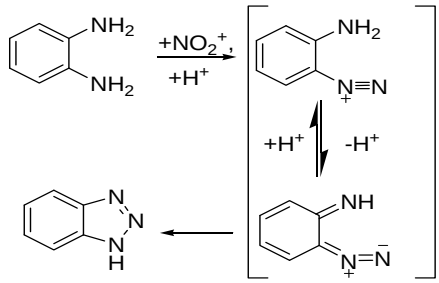
Benzotriazole derivatives are nitrogen containing bicyclic ring system and have been demonstrated many biological activities, such as, antibacterial, antifungal, anticancer, anti-inflammatory, analgesic, antimalarial and antitubercular activity [1]. Benzotriazole derivatives also possess antihelminthics and antiprotozoal action. For example, 5,6-dimethyl-1*H*-benzotriazole and 5,6-dibromo-1*H*-benzotriazole are antiprotozoal and active against *Acanthamoeba castellani*, *N*-heteroaryl benzotriazole derivatives are antihelminthics, 5-arylidene-2-aryl-3- benzotriazoloacetamidyl)-

1,3-thiazolidin-4-ones are antibacterial, 1-[3-(4-benzotriazol-1 /2-yl- 3-fluoro -phenyl) -2-oxooxazolidin -5- ylmethyl]-3- substituted-thiourea derivatives are reported antitubercular activity [2]. Benzotriazole derivatives act as agonists for many proteins. Benzotriazoles are often used as corrosion inhibitors, radio protectors, and photo stabilizer in the production of plastic, rubber and chemical fiber [3]. Along with activity benzotriazole is important as a precursor in the synthesis of peptides, acid azides, preparation of 3-hydroxymethyl-2,3-dihydrobenzofurans and 3-hydroxymethylbenzofurans [2].

Benzotriazole have three tautomers, namely two 1*H*-forms and one 2*H*-form. In solution, the equilibrium lie almost entirely on the side of the 1*H*-forms [4]. Benzotriazole is an extremely weak base, but with a *pKa* = 8.2, it is a stronger NH-acid than indazole, benzimidazole or 1,2,3-triazole [5].

Synthesis

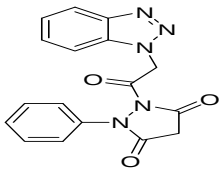
Benzotriazoles are synthesized by cyclocondensation of *o*-phenylenediamines with sodium nitrite in acetic acid. The reaction involved the simple heating the reagents together. Conversion of the diamine into the mono-diazonium derivative is followed by spontaneous cyclization [6].



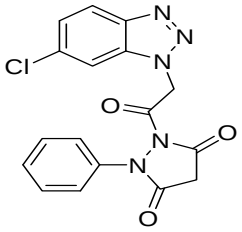
Biological activity-

2.1 Anti-bacterial activity-

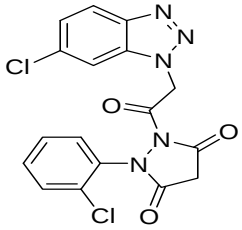
A series of 1, 2, 3, benzotriazole derivatives containing pyrazolidine 3, 5 dione moiety (**1a-1i**) were synthesized by diazotization of benzene-1, 2-diamine with Glacial acetic acid. Synthesized derivatives were evaluated for antibacterial activities, against gram-positive organisms like *S. aureus* & *B. subtilis* & gram-negative organisms like *E.Coli* & *P. vulgaris* by diffusion agar media technique. Compound **1b** was found to be good activity against *E.coli*. Compound **1h** was found to be more effective against *S. aureus*. Compound **1f** was found to have good activity against *B.subtilis*. Compound **1g** was found to have good activity against *P. vulgaris*. Ciprofloxacin and Amoxicillin (100 µg/ml) were used as standard for screening [1].



Compound 1h

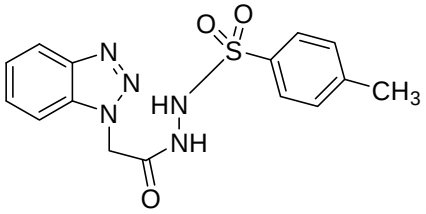


Compound 1b

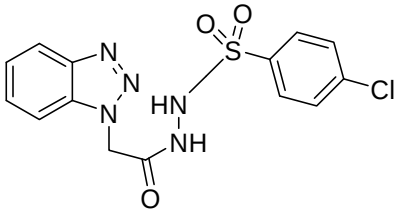


Compound 1f

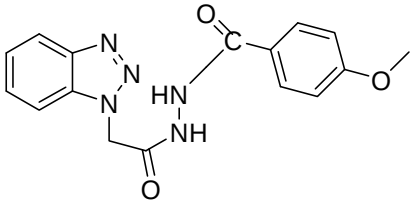
N-Substituted 2-(1*H*-benzotriazol-1-yl)-acetohydrazide series (**2a-2f**) were synthesized from *o*-phenylene diamine and evaluated for antibacterial activity by agar plate disc diffusion method. Compound **2b**, **2c** and **2e** showed good antibacterial activity against *S.aureus, B.subtilis* and *E.coli* but less potent than sulphacetamide [7].



Compound 2b

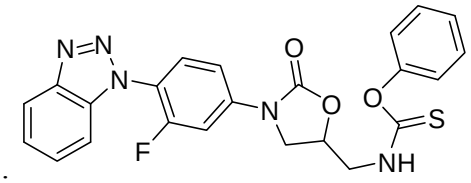


Compound 2c



Compound 2e

A series of oxazolidinone containing benzotriazole derivatives were synthesized and exhibited antibacterial activity against many antibiotic- resistant microbial strains. Compound **3** showed excellent antibacterial activity against antibiotic- resistant microbial strains [8].



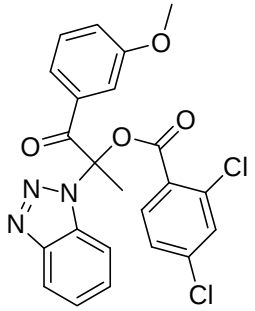
Compound 3

A series of *N*-alkylated benzotriazole derivatives were synthesized and evaluated for antimicrobial activity. Compound **4** showed significant antimicrobial activity against many gram positive and gram negative bacteria [9].

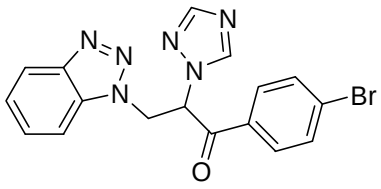
Compound 4

A novel series of *N*-Substituted benzotriazole derivatives containing mannich bases (**5a-5x**) were synthesized by amine exchange reactions, from the *N*,*N*-dimethylamino propiophenone hydrochlorides and benzotriazole. Antibacterial activities of the synthesized compounds was

tested against *B. subtilis, S. aureus, S. faecalis, E. coli, P. aeruginosa* and *E. cloacae* using MH medium. Compounds **5d**, **5g**, **5p 5r** and **5x** exhibited significant activity with MIC values of 1·56 µg/mL against *B. subtilis*. Compound **5s** showed the most favourable antibacterial activity against *B. subtilis*, *S. aureus*, *S. faecalis*, *P. aeruginosa*, *E. coli* and *E. cloacae* with MIC of 1·562 µg/mL, 1·562 µg/mL, 1·562 µg/mL, 3·125 µg/ mL, 6·25 µg/mL and 6·25 µg/mL respectively [10].

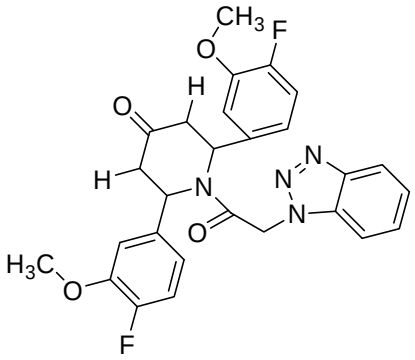


Compound 5d



Compound 5s

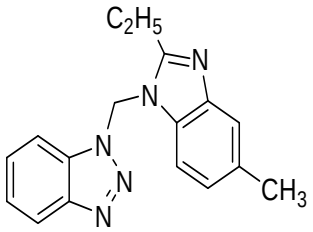
A series of imidazole/benzotriazole substituted piperidine-4-one derivatives (**6a–6j**) were synthesized. The synthesized compounds investigated the antimicrobial activity against selected bacterial strains. Among the compounds, fluoro and methoxy group substituted compound **6d** showed good antimicrobial activity at minimum concentration [11].



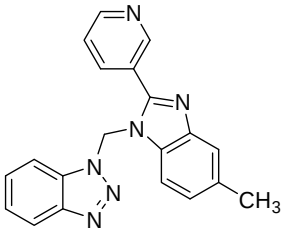
Compound 6d

2.2 Antifungal activity-

Substituted 1,2,3-benzotriazole derivatives (**7a-7e**) are synthesized from benzimidazoles with 1- chloro methylbenzotriazoles and evaluated for their antifungal activity against *P.oryzae, B.cinerea, A. niger, C.albicans and T.rubrum* at 1000 ppm, 500 ppm and 100 ppm concentrations by solidified agar method. Compound **7b** and **7e** showed excellent antifungal activity. The inhibitory activity was compared with griseofulvin (standard drug) [12].

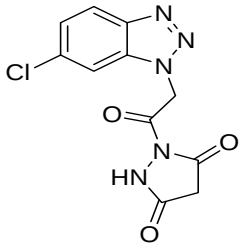


Compound 7b

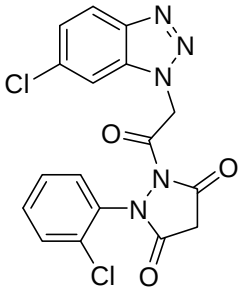


Compound 7e

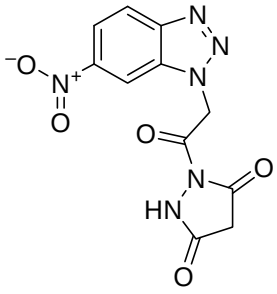
Substituted benzotriazole derivatives containing pyrazolidine dione moiety (**8a-8i**) were synthesized and their antifungal activity was tested against *A. niger* and *C. albicans* by cup plate diffusion method by measuring the zone of inhibition in mm. Compounds **8e, 8h** and **8i** were found to have good activity against *A.niger* while compound **8c** was found to have good activity against *C.albicans.* Ketoconazole and Clotrimazole were used as a standard for screening [1].



Compound 8e

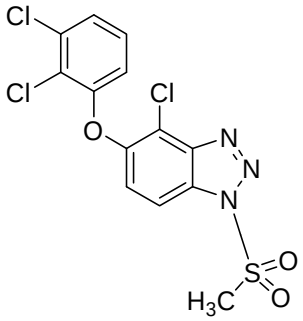


Compound 8h



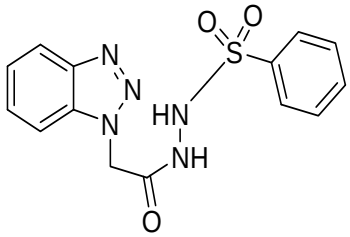
Compound 8i

Novel benzotriazolesulfonic acid derivatives were synthesized and have reported plant-protecting properties and have antifungal activity against *Oomycetes.* Compound **9** showed excellent antifungal activity [13].



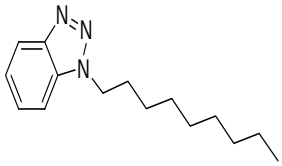
Compound 9

N-Substituted 2-(1*H*-benzotriazol-1-yl)-acetohydrazide series (**10a-10f**) were synthesized and have reported antifungal activity against *Candida albicans*. Antifungal activity was evaluated by filter disc method. Compound **10a** showed good anti-fungal activity against *Candida albicans* at 1000ug/ml concentration [7].

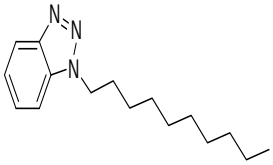


Compound 10a

A series of 1*H*-1,2,3-benzotriazole derivatives were synthesized and evaluated for antifungal activity against clinical species of *Candida. Compound **11a** and **11c** showed desirable antifungal activity* [14].

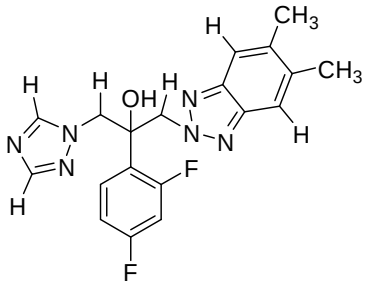


Compound 11a



Compound 11c

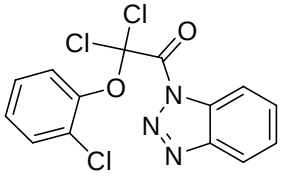
A series of 5(6)-(un)substituted benzotriazole derivatives (**12a-12f**) were synthesized using a crystalline oxirane intermediate**.** All the compounds were evaluated for inhibitory activity against various species of *Candida* and *Aspergillus*. Compounds **12b**, **12c**, **12d** and **12e** exhibited potent antifungal activity, with the MICs for *Candida spp.* and *Aspergillus niger*, ranging from 1.6 µg/mL to 25 µg/mL and 12.5 µg/mL to 25 µg/mL, respectively [15].



Compound 12b

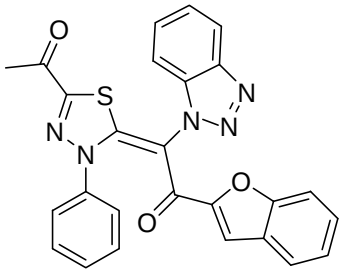
2.3 Antiinflammatory activity-

Some new chlorosubstituted phenoxy acetyl and propionyl benotriazoles were synthesised and evaluated for their anti-inflammatory activity. Trichlorophenoxy acetyl benzotriazole (compound **13**) exhibited better anti-inflammatory activity than its propionyl derivatives [16].



Compound 13

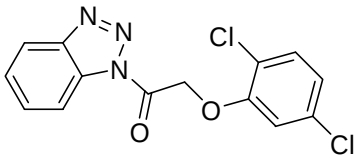
A series of benzotriazole containing 1,3,4-thiadiazole derivatives (**14a-14f**) were synthesized by 2-bromoacetylbenzofuran with 1(*H*)-benzotriazole. The anti-inflammatory activity of the synthesized compounds was evaluated by carrageenan-induced edema method. Compound **14a** was the most potent anti-inflammatory compound and decrease in the edema size 45% after 2h. Ibuprofen was used as a reference for evaluation of anti-inflammatory activity [17].



Compound 14a

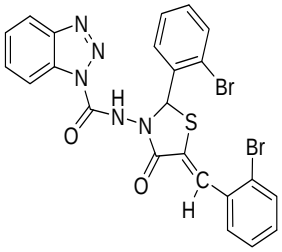
2.4 Analgesic activity-

A series of chlorosubstituted phenoxy acetyl and propionyl benzotriazoles were synthesised and evaluated for analgesic activity. The 2,5-dichlorophenoxy acetyl benzotriazole (compound **15**) exibited moderately better analgesic activity among the series [16].

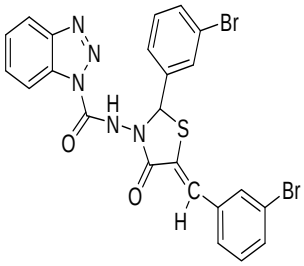


Compound 15

5-Arylidene-2-aryl-3-(benzotriazoloacetamidyl)-1,3-thiazolidin-4-ones derivatives (**16a-16j**) were synthesized from ethyl acetoacetate and evaluated the analgesic activity by eddy and leimbach method. Compound **16h**, **16i** and **16j** were found to be better analgesic activity. Acetylsalicylic acid was employed as a reference drug [18].



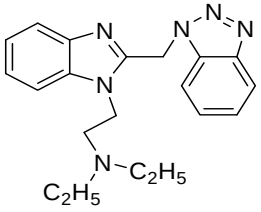
Compound 16h



Compound 16i

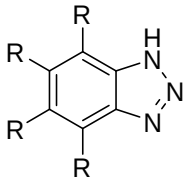
2.5 Antiviral activity-

A novel series of dialkylamino side chain derivatives of benzotriazole were synthesized and reported as potential inhibitors of respiratory syncytial virus. Compound **17** was found to be most potent in series [19].



Compound 17

Halogenated benzotriazole nucleosides were synthesized and antiviral activity was tested against hepatitis C virus and other viral NTPase/helicases. Compound **18a** was found to be good inhibitor of the West Nile virus enzyme with an RNA substrate (IC_{50}-0.3um). Compound 18b also reported selective antiviral activity [20].

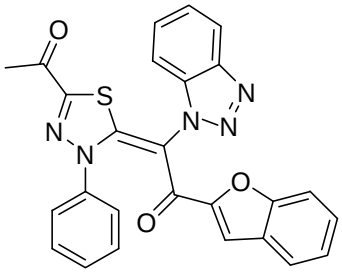


Compound

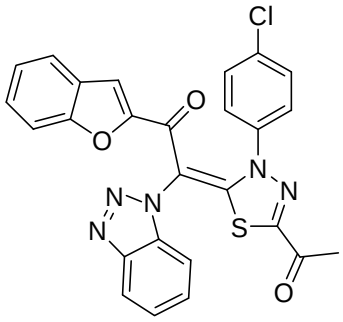
R	
Cl	**18a**
Br	**18b**

2.6 Anticonvulsant activity-

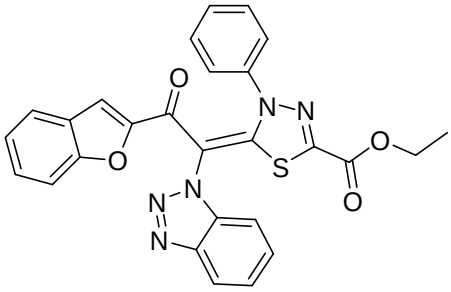
A series of benzotriazole containing 1,3,4-thiadiazole derivatives (**19a-19f**) were synthesized and evaluated for anticonvulsant activity in maximal electroshock seizure (MES) and subcutaneous metrazole (ScMet) test. Compounds **19a** and **19d** were found to be active in ScMet only, whereas the test compounds **19c** was active in MES. Activity of compound **19c** was similar to the second reference drug phenytoin. Valproic acid was used as a first reference drug [17].



Compound 19a



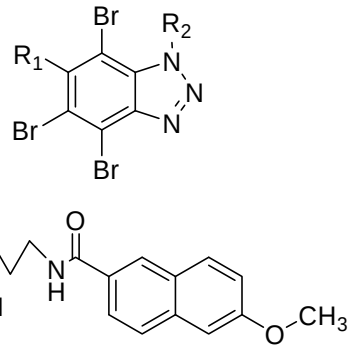
Compound 19c



Compound 19d

2.7 Anticancer activity-

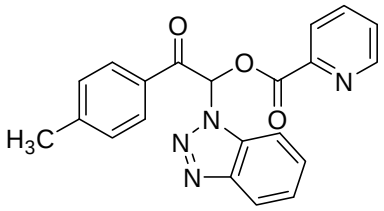
There are various benzotriazole derivatives are synthesized and evaluated for anticancer activity. 4,5,6,7-tetrabromobenzotriazole (compound **20a**) was found to be most effective with high selective inhibition against protein kinase CK2. Compound **20b** also reported excellent anticancer ativity [21].



R_1 Br **Compound 20a**

R_2 Br **Compound 20b**

Benzotriazole-substituted benzoate derivative (compound **21a)** was synthesized and evaluated for its anti-proliferative activity against several cancer cell lines. It could effectively inhibit the proliferation of human hepatocarcinoma BEL-7402 cell with low IC50 value of 0.082 mg/mL [22].



Compound 21a

Conclusion

The present study focussed on screening of biological activity of benzotriazole derivatives. In the past two decades, it can be reasonable to expect that benzotriazole derivatives will play remarkable roles in medicinal chemistry. Currently, these reports of investigations suggest the possibility of emerging a lead

compound of benzotriazole having a potential pharmacological activity.

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