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BENZOTRIAZOLE: A HETEROCYCLIC MOLECULE WITH DIVERSIFIED PHARMACOLOGICAL ACTIVITIES

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ABSTRACT: 1,2,3-Benzotriazole (BTA) is a heterocyclic compound with three nitrogen atoms. The enormous investigations on derivatives of benzotriazole reveals wide applicability of this molecules for tagging and delivering huge number of heterocyclic nuclei. This molecule has been used for the analytical determination of silver as well as a restrainer in photographic emulsions. The effectiveness of 1,2,3-Benzotriazole (BTA) as drug precursors have been drawing attention for a long period. The derivatives of benzotriazole act as agonists for many biologically active proteins. For instance, corozole and alizapride have the inhibitory properties against different proteins and Benzotriazole esters have been reported to work as mechanism-based inactivators for severe acute respiratory syndrome (SARS) 3CL protease. The various derivatives synthesized by different research workers showed antimicrobial activities such as antibacterial, antifungal, antiviral, anthelmintics, antiprotozoal and antimycobacterial activity. The present article throws light on the different derivatives of benzotriazole and their related biological activity, and is reported chronologically. The chronologic development in the synthesis of its derivatives and related changes in therapeutic activity opens new channels for the researchers to work on benzotriazole molecules to develop some highly effective lead molecules.

INTRODUCTION: As the micro-organisms are rapidly undergoing genetic changes and developing resistance against many antibiotics and therapeutic agents for various diseases more quickly than new drugs are being made available so the war against the infectious diseases has become a never ending process. 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 for 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-1H-benzotriazole and 5,6-dibromo-1H-benzotriazole are antiprotozoal and active against *Acanthamoeba castellani*, N-heteroaryl benzotriazole derivatives are anti helminthics, 5-arylidene – 2 – aryl - 3- benzotri azoloacetamidyl) - 1,3-thiazolidin-4-ones are antibacterial, 1-[3-(4-benzotriazol-1/2-yl- 3-fluoro - phenyl) - 2 - oxooxazolidin -5- yl methyl] - 3 – substituted thiourea derivatives are reported antitubercular activity [2]. Benzotriazole derivatives act as agonists for many proteins.

Benzotriazoles are often used as corrosion inhibitors, radioprotectors, and photo stabilizer in the production of plastic, rubber and chemical fiber [3]. Along with these activities, benzotriazole is also 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 1H-forms and one 2H-form. In solution, the equilibrium lie almost entirely on the side of the 1H-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].

The literature survey reveals that heterocyclic compounds bearing benzotriazoles as part of main molecule showed versatile biological activities particularly antibacterial, antifungal, antiviral, anti-inflammatory, anticonvulsant and anticancer activity. Benztriazole derivatives have effectively been proven as antimicrobials.

Synthesis: Benzotriazoles are synthesized by cyclocondensation of o-phenylenediamines with sodium nitrite in acetic acid (**Fig. 1**). The reaction involved the simple heating the reagents together. Conversion of the diamine into the mono-diazonium derivative is followed by spontaneous cyclization [6].

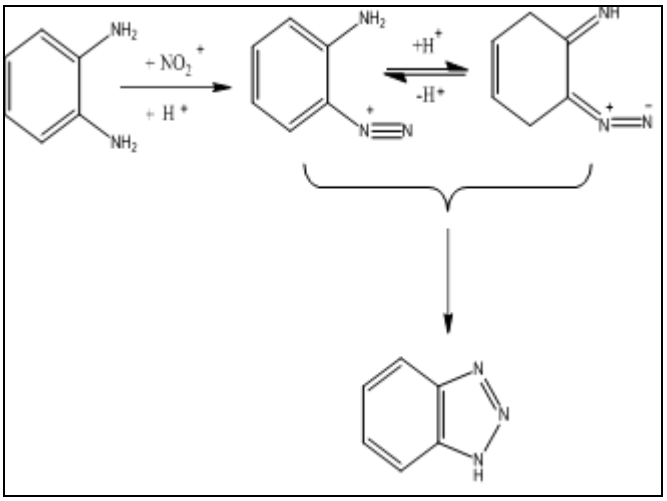
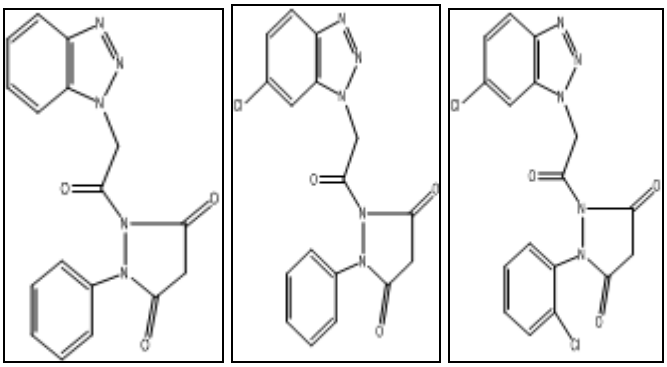


FIG. 1: SCHEME FOR SYNTHESIS OF BENZOTRIAZOLE

Biological Activity:

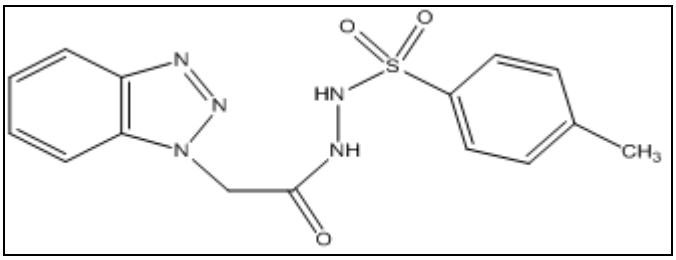
Antibacterial activity: A series of 1, 2, 3, benzotriazole derivatives containing pyrazolidine 3, 5 dione moiety were synthesized by diazotization of benzene-1,2-diamine with glacial acetic acid and were evaluated for antibacterial activities, against gram-positive organisms like *S. aureus* and *B.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



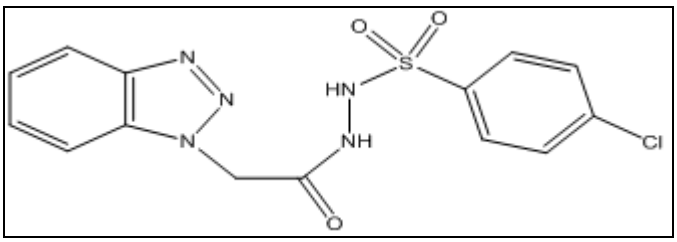
Compound 1h **Compound 1b** **Compound 1g**

FIG. 2: COMPOUND 1h, 1b AND 1g

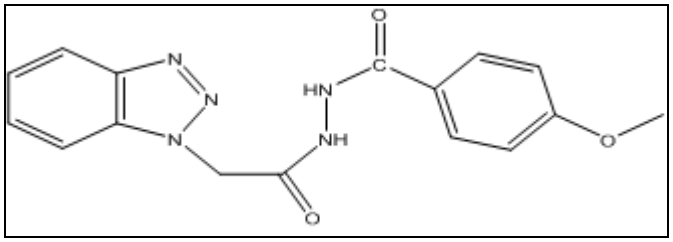
N-Substituted 2- (1H-benzotriazol – 1 - yl) - aceto hydrazide series (2a-2f) were synthesized from o-phenylenediamine and evaluated for antibacterial activity by agar plate disc diffusion method. Compound 2b, 2c and 2e (**Fig. 3**) showed good antibacterial activity against *S. aureus, B. subtilis* and *E. coli* but less potent than sulphacetamide [7].



Compound 2b



Compound 2c



Compound 2e

FIG. 3: COMPOUND 2b, 2c and 2e

A series of oxazolidinone containing benzotriazole derivatives were synthesized and exhibited antibacterial activity against many antibiotic-resistant microbial strains. Compound 3 (**Fig. 4**) showed excellent antibacterial activity against antibiotic resistant microbial strains [8].

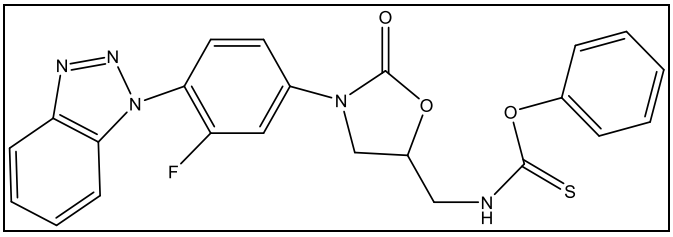


FIG. 4: COMPOUND 3

A series of N-alkylated benzotriazole derivatives were synthesized and evaluated for antimicrobial activity. Compound 4 (**Fig. 5**) showed significant antimicrobial activity against many gram positive and gram negative bacteria [9].

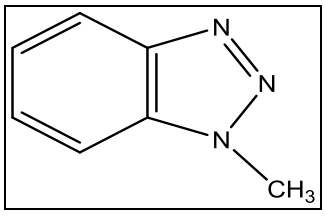
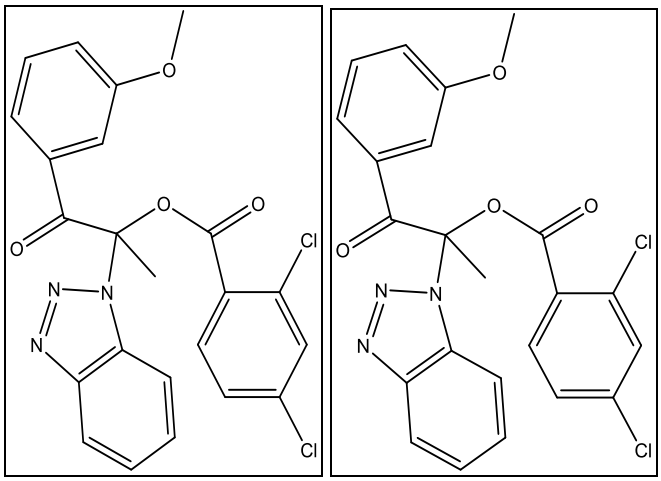


FIG. 5: COMPOUND 4

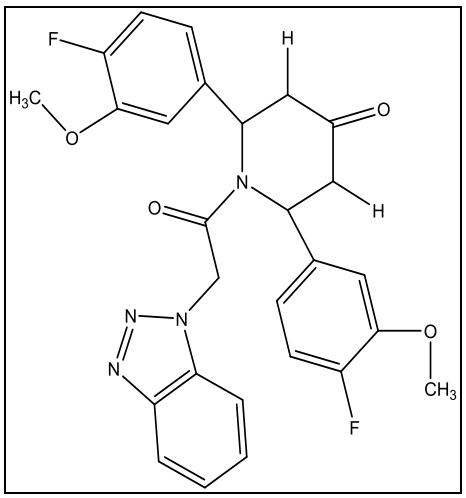
A novel series of N-Substituted benzotriazole derivatives containing mannich bases (5a-5x) were synthesized by amine exchange reactions, from the N,N-dimethylaminopropiophenone hydrochlorides and benzotriazole. Antibacterial activities of the synthesized compounds were tested against *B. subtilis, S. aureus, S. faecalis, E. coli, P. aeruginosa* and *E. cloacae* using MHA media. Compounds 5d (**Fig. 6**), 5g, 5p 5r and 5x exhibited significant activity with MIC values of 1·56 µg/mL against *B. subtilis*. Compound 5s (**Fig. 6**) 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, 1·562µg/mL, 3·125 µg/ mL, 6·25 µg/mL and 6·25µg/mL respectively [10].



Compound 5d **Compound 5s**

FIG. 6: COMPOUND 5d AND 5s

A series of imidazole / benzotriazole substituted piperidine-4-one derivatives (6a–6j) were synthesized. The synthesized compounds were investigated for antimicrobial activity against selected bacterial strains. Among the compounds, fluoro and methoxy group substituted compound 6d (**Fig. 7)** showed good antimicrobial activity at minimum concentration [11].

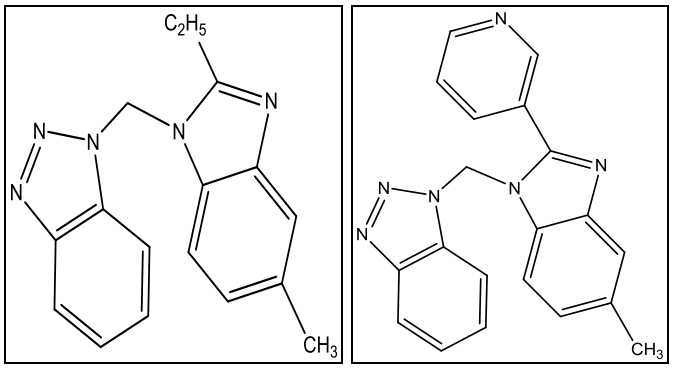


Compound 6d

FIG. 7: COMPOUND 6d

Antifungal activity: Substituted 1,2,3-benzotriazole derivatives (7a-7e) are synthesized from benzimidazoles with 1-chloromethyl benzotriazoles 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.

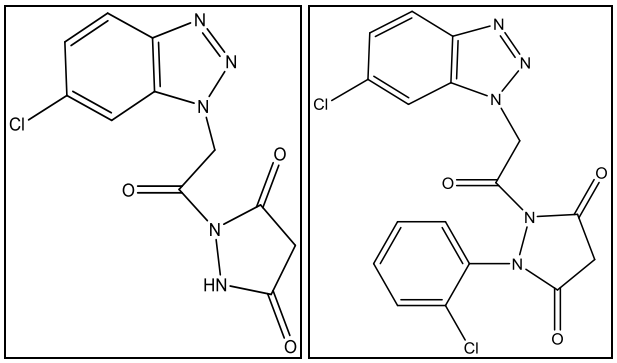
Compound 7b and 7e (**Fig. 8**) showed excellent antifungal activity. The inhibitory activity was compared with griseofulvin (standard drug) [12].



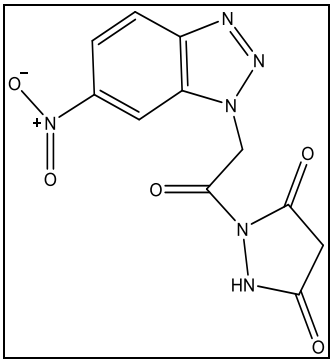
Compound 7b **Compound 7e**

FIG. 8: COMPOUND 7b AND 7e

Substituted benzotriazole derivatives containing pyrazolidinedione 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 (**Fig. 9**) 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].



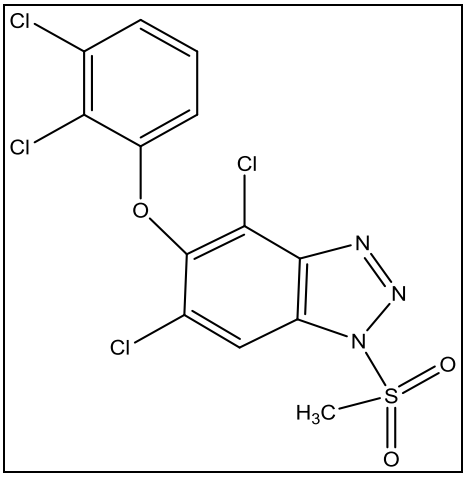
Compound 8e **Compound 8h**



Compound 8i

FIG. 9: COMPOUND 8e, 8h AND 8i

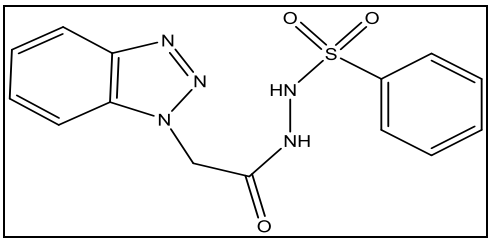
Novel benzotriazolesulfonic acid derivatives were synthesized and have reported plant protecting properties and have antifungal activity against Oomycetes. Compound 9 (**Fig. 10**) showed excellent antifungal activity [13].



Compound 9

FIG 10: COMPOUND 9

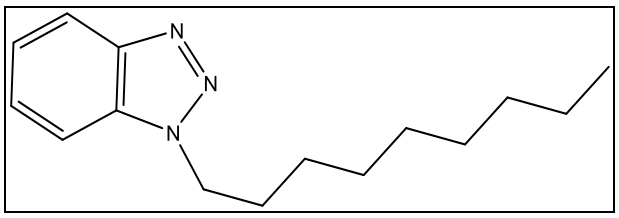
N-Substituted 2 - (1H-benzotriazol-1-yl) - aceto hydrazide series (10a-10f) were synthesized and have reported antifungal activity against *Candida albicans*. Antifungal activity was evaluated by filter disc method. Compound 10a (**Fig. 11**) showed good anti-fungal activity against *Candida albicans* at 1000ug/ml concentration [7].



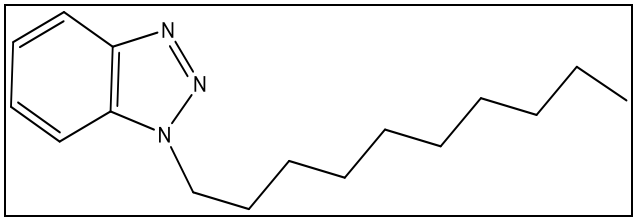
Compound 10a

FIG. 11: COMPOUND 10a

A series of 1H-1,2,3-benzotriazole derivatives were synthesized and evaluated for antifungal activity against clinical species of *Candida*. Compound 11a and 11c (**Fig. 12**) showed desirable antifungal activity [14].



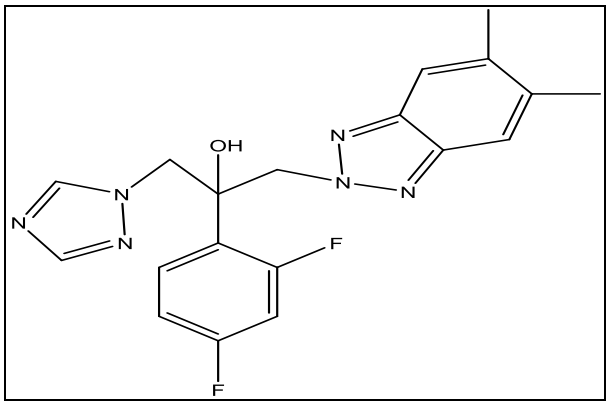
Compound 11a



Compound 11c

FIG. 12: COMPOUND 11a and 11c

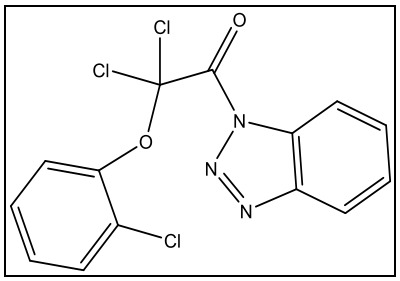
A series of 5(6)-(1N)-substituted benzotriazole derivatives (12a-12f) were synthesized using a crystalline oxirane intermediate. All the compounds were evaluated for inhibitory activity against various species of *Candida* and *Aspergillus*. Compounds 12b (**Fig. 13**), 12c, 12d and 12e exhibited potent antifungal activity, with the MICs for *Candida spp.* and *Aspergillus niger*, ranging from1.6 μg/mL to 25 μg/mL and 12.5 μg/mL to 25 μg/mL, respectively [15].



Compound 12b

FIG. 13: COMPOUND 12b

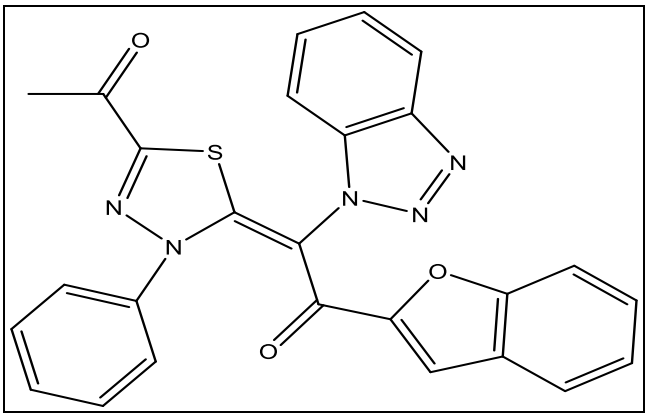
Anti-inflammatory activity: Some new chlorosubstituted phenoxyacetyl and propionylbenotriazoles were synthesised and evaluated for their anti-inflammatory activity. Trichlorophenoxy acetyl benzotriazole (compound 13) (**Fig. 14**) exhibited better anti-inflammatory activity than its propionyl derivatives [16].



Compound 13

FIG. 14C: OMPOUND 13

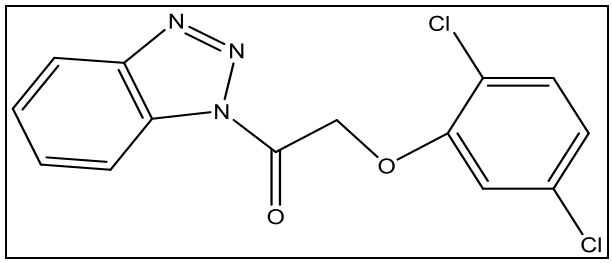
A series of benzotriazole containing 1,3,4-thiadiazole derivatives (14a-14f) were synthesized by 2-bromoacetyl benzofuran with-(H)-benzotriazole. The anti-inflammatory activity of the synthesized compounds was evaluated by carrageenan-induced edema method. Compound 14a (**Fig. 15**) was the most potent 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

FIG. 15: COMPOUND 14a

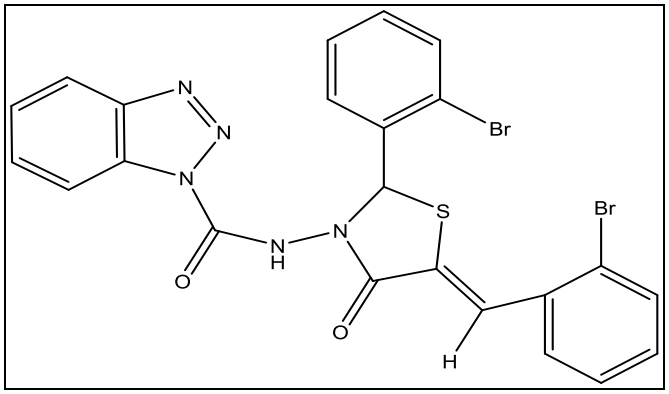
Analgesic activity: A series of chlorosubstituted phenoxyacetyl and propionylbenzotriazoles were synthesised and evaluated for analgesic activity. The 2,5-dichlorophenoxy acetyl benzotriazole (compound 15) (**Fig. 16**) exhibited moderately better analgesic activity among the series [16].



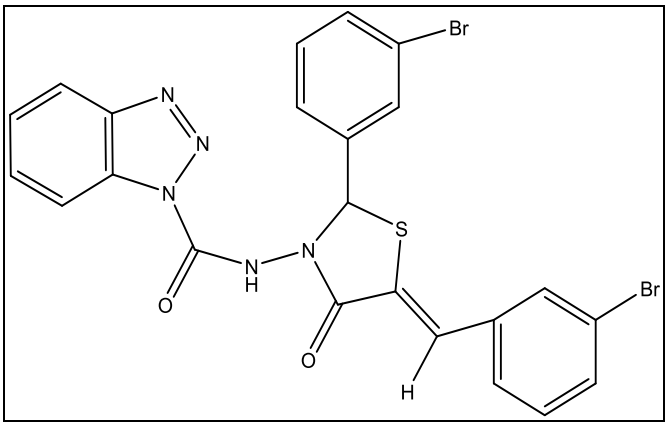
Compound 15

FIG. 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 (**Fig. 17)** and 16j were found to be better analgesic activity. Acetylsalicylic acid was employed as a reference drug [18].



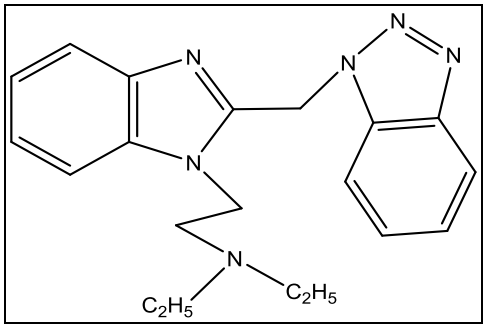
Compound 16h



Compound 16i

FIG. 17: COMPOUND 16h AND 16i

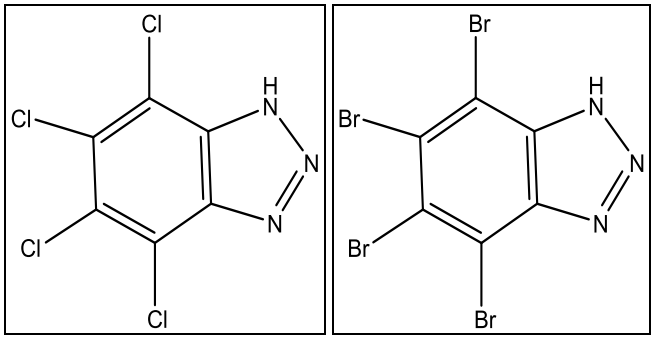
Antiviral activity: A novel series of dialkylamino side chain derivatives of benzotriazole were synthesized and reported as potential inhibitors of respiratory syncytial virus. Compound 17 (**Fig. 18**) was found to be most potent in series [19].



Compound 17

FIG. 18: COMPOUND 17

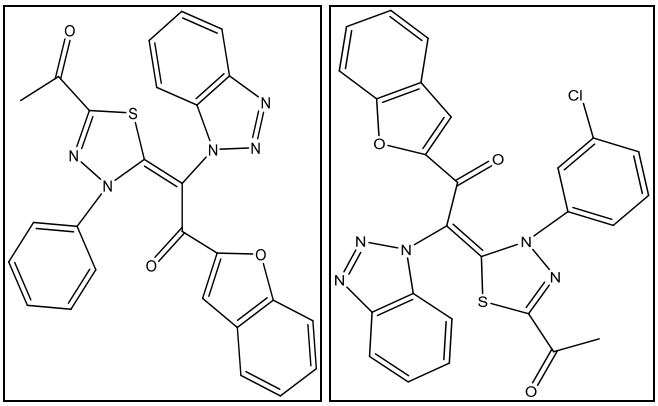
Halogenated benzotriazole nucleosides were synthesized and antiviral activity was tested against hepatitis C virus and other viral NTPase/helicases. Compound 18a (**Fig. 19**) was found to be good inhibitor of the West Nile virus enzyme with an RNA substrate (IC50-0.3um). Compound 18b (**Fig. 19**) also reported selective antiviral activity [20].



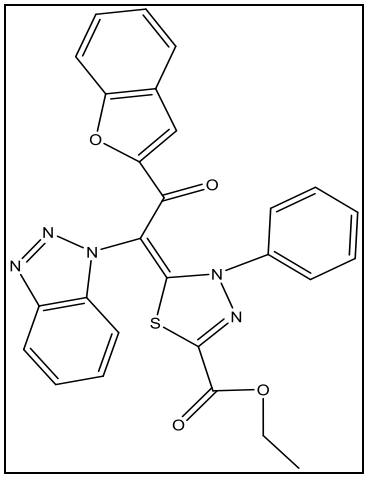
Compound 18a **Compound 18b**

FIG. 19: COMPOUND 18a AND 18b

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 (**Fig. 20**) 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].



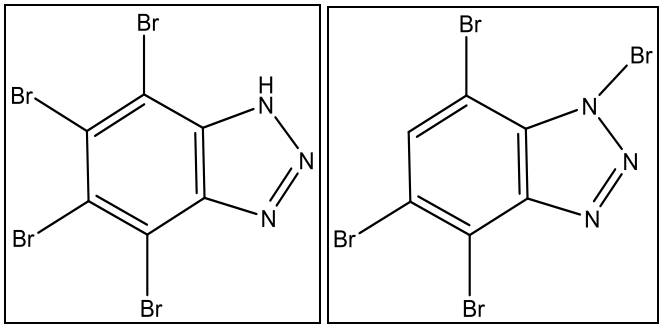
Compound 19a **Compound 19c**



Compound 19d

FIG. 20: COMPOUND 19a, 19c AND 19d

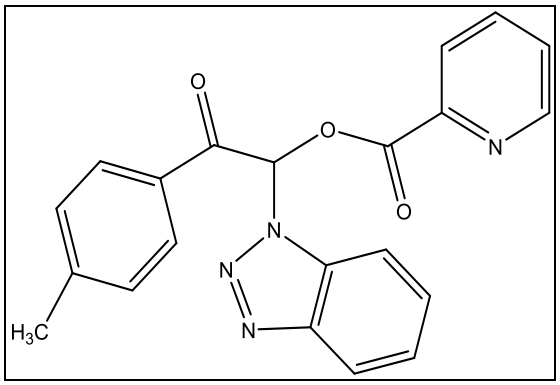
Anticancer activity: There are various benzotriazole derivatives are synthesized and evaluated for anticancer activity. 4, 5, 6, 7-tetrabromobenzotriazole (compound 20a) (**Fig. 21**) was found to be most effective with high selective inhibition against proteinkinase CK2. Compound 20b (**Fig. 21**) also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



Compound 20a **Compound 20b**

FIG. 21: COMPOUND 20a AND 20b

Benzotriazole-substituted benzoate derivative (compound 21a) (**Fig. 22**) 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 IC_{50} value of 0.082 mg/mL [22].



Compound 21a

FIG. 22: COMPOUND 21a

Anti-mycobacterial activity: Development of anti-tubercular agents is very tedious process therefore only one or two new drugs will arrive in the market from these efforts. The treatment of tuberculosis with combination of drugs has even not satisfactory in combating the disease due to bacterial resistance. There is need for effective anti-tubercular agents to win the battle against this millenary scourge [23], new class of benzotriazole derivatives triazoloquinolones were active against multidrug resistant *M. tuberculosis* (MDR-Mtb) was reported by Carta Antonio *et al*., 2011.

Anti-protozoal activity: The 5, 6-dimethyl and 5,6-dibromo derivatives of Benzotriazole were reported active against *Acanthamoebacastellani* by Katarzyna K *et al*., in 2004.

Anthelmentic activity: Benzotriazole derivatives of N-heteroaryl/diphenyl amino acetyl/propionyl were tested for anthelmentic activity. Apart from antimicrobial activity the Benzotriazole is important as a synthetic auxiliary [24-26], in synthesis of peptides [27], acid azides [28], preparation of 3-hydroxymethyl-2,3-dihydrobenzofurans and 3-hydroxymethylbenzofurans has been developed using benzotriazole mediated benzofuran ring closure was reported [29]. Some derivatives of Benzotriazole are reported to have antiproliferative activity [30-33], pharmacological activities like analgesic, anticonvulsant, anti-inflammatory [34-35], inhibitors of human (CK2) protein kinase [36], agonist for 5-Ht receptor [37], metal corrosion inhibitors [38], cytochalasin B-mimetic activity [39], synthesis and biological activities of Benzotriazole derivatives was reviewed by BV Suma *et al*., [40].

The antimicrobial activity of Benzotriazole derivatives with reference and main investigator is arranged in chronological order in **Table 1**.

TABLE 1: ANTIMICROBIAL ACTIVITY OF BENZOTRIAZOLE DERIVATIVES

Year	Benzotriazole derivatives synthesized	Author / Investigators	Reported activity	Ref. No
1992	Chlorosubstitutedphenoxy acetyl and propionylbenotriazoles	M. Purohit and S.K. Srivastava	Antibacterial, Antifungal	41
1994	Benzotriazolesulfinicacid derivatives	P. Ackerman and M. Schellenbaum	Antifungal	43
1995	Derivatives of 1-(N-heteroyl/ diphenyl aminoacetyl/propionyl) benzotriazole	R. K. Upadhaya and S. D. Srivastava	Antibacterial, Antifungal, Anthelmentic	42
2000	Derivatives of 3-aryl substituted -2-(1*H*(2*H*)-benzotriazol-1(2)-yl) acrylonitrile	S. Paolo *et al*.	Antitubercular	44

2002	Benzotriazole derivatives of 2-aminothiophene-3carbonitrile, 2-thioxopyridine-3carbonitrile, 1,8 -naphthyridine-2-one, thieno [2,3-*b*] pyridine-5-carbonitrile andthieno[2,3-*d*]pyrimidine	A. O. Fatima *et al.*	Antibacterial, antifungal	45
2003	Dialkylamino side chain substituted on the Benzotriazole	Kuo-Long Yu *et al.*	Respiratory syncytial virus Inhibitor	46
2004	5,6-dimethyl-1Hbenzotriazole and5,6-dibromo-1H-benzotriazole	K. Katarzyna *et al*.	inhibitor of *Acanthamoebac astellanii*	47
2005	Oxazolidinone derivatives with positional and geometrical substitutions on benzotriazole	J. Das *et al.*	Antibacterial activity	48
2005	Benzotriazolyloxazolidinone derivatives	P.D. Prasad and co-workers	Antibacterial activity	49
2005	N-alkyl derivatives of 1H - benzotriazole	M. Bretner *et al*.	Antihelicase Activity Against Flaviviridae	50
2006	5-arylidene-2-aryl-3-(benzotriazoloacetamidyl)-1,3- thiazolidin-4-ones	K. C. Asati *et al.*	Antibacterial activity	18
2006	Derivatives of N-alkylated benzotriazole	S. N. Swamy *et al*.	Antibacterial activity, Antifungal	51
2006	Benzotriazole esters	Chung-Yi Wu *et al*.	Anticoronovirus	52
2006	Derivatives of 1-[3-(4-benzotriazol-1/2-yl-3-fluoro-phenyl)-2-oxooxazolidin-5-ylmethyl]-3-substituted-thiourea	P. D. Prasad and co-workers	Antitubercular activity	53
2008	Derivatives of 5-[2-(1,2,3-benztriazole)-1-yl-methyl]-1′-arylidene hydrazine-1,3,4-thiadiazoles and 5-[2-(1,2,3-benztriazole)-1-yl-methyl]-1′-(4′-substituted aryl-3′-chloro-2′-oxoazetidine)]-amino-1,3,4-thiadiazoles	D. K. Shukla and S.D. Srivastava	Antibacterial and Antifungal activity	54
2008	Derivatives of Benzotriazoleesters1-(4-Dimethylamino-benzoyloxy)-Benzotriazole	H. V. Koen *et al*.	Anticorono-virus(SARS) activity	55
2009	2-(substituted)-5[(N-Benztriazolomethyl)-1,3,4-Thiadiazolyl]-4 thiazolidinones	K. P. Namdeo *et al*.	Antifungal	56
2009	Derivatives of 1-Trityl-1H-1,2,3-benzotriazole	Z. Rezaei *et al.*	Antifungal	57
2010	1H-Benzotriazolylpropanone and2H-benzotriazolylpropanones	J. Wan and co-workers	Antibacterial activity	58
2010	Acridine substituted Benzotriazolederivative	N. P. Singh *et al.*	Antibacterial activity	59
2010	Derivatives of 2-(2,4-difluorophenyl)-1-(2,3-dihydro-1*H*benzotriazol-1-yl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol	D.P. Pallav *et al*.	Antifungal	60
2011	Imidazole/benzotriazole substitutedpiperidin-4-one derivatives	R. Ramachandran *et al.*	Antibacterial activity, Antifungal	61
2011	Azetidinone derivatives ofbenzotriazole.	A. Dubey and co-workers	Antitubercular activity	62
2011	Triazoloquinolones	C. Antonio *et al.*	Antitubercular activity	63
2012	Benzotriazole derivatives substitutedwiththiazole moiety.	N. D. Gaikwad and co-workers	Antibacterial activity, Antifungal.	64
2012	*N*-Substituted 2-(1*H*benzotriazol-1-yl)-acetohydrazide derivatives	J. S. Patel *et al.*	Antibacterial activity, Antifungal	65
2012	Benzotriazole substituted withpyrozolidine 3, 5-dione.	B.V. Suma *et al*.	Antibacterial activity	66

2013	1,2,3-benzotriazolederivatives synthesized by ultrasonic andsolvent-free conditions	M. S. Sudhir *et al.*	Antifungal activities	67
2014	Benzotriazolo-thiadiazolyl-imidazole derivative	V. K. Singh *et al*.	Anticonvulsant, Antimicrobial activity	68
2015	1H-benzotriazol-1-yl(2-hydroxy -5- [(e) phenyldiazenyl] phenyl) methanone derivatives	C. M. Jamkhandi *et al.*	Anti-inflammatory activity	69

CONCLUSION: The present review of benzotriazole derivatives is focussed on screening of biological activities such as antibacterial, antifungal, antiviral, antiprotozoal, anthelmentic, anti-inflammatory, anticonvulsant etc. in which benzotriazole is act as a tagging molecule to deliver other pharmacologically active heterocyclic nuclei. Now it can be reasonable to expect that benzotriazole as tagging molecule will definitely play a remarkable role in medicinal chemistry. The investigated reports in this review definitely suggests the possibility to develop a lead compound in which benzotriazole is used as a tagging molecule to emerge new chemical entities (NCE's) of benzotriazole having potential pharmacological activity.

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