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An Overview on Medicinal Perspective and Biological Behavior of Benzotriazole; Synthetic Study on Its Multifaceted Biological Activities

V. S. Anjana[1], P. Manoj Kumar[2]

[1,2]Department of Pharmaceutical Chemistry, The Dale View College of Pharmacy and Research Centre, Punalal, Thiruvananthapuram, Kerala

Corresponding Author: V. S. Anjana

ABSTRACT

Benzotriazole (BTA) is a nitrogen containing heterocyclic derivative containing three nitrogen atoms at 1st, 2nd and 3rd positions with chemical formula $C_6H_5N_3$. Benzotriazole and its derivatives have great significance in medicinal chemistry and these derivatives were used by several chemists for therapeutic conditions because it possessing a wide spectrum of pharmacological activities including anti bacterial, anti fungal, anti viral, anti inflammatory, anti hyperglycemic, anti hypertensive, anti cancer and analgesic activity. In this review, different synthetic methods for the preparation of benzotriazole, importance of benzotriazole derivatives in biomedical research, highlighting its biological behavior, versatile activities and Structure Activity Relationship (SAR) studies are described. This review will help the researchers to understand the structure activity relationships and improvise the concepts in their research field.

Keywords: Benzotriazole, Anti microbial, Anthelmintic, Analgesic, Anti mycobacterial, Anti viral, Anti oxidative, Anti tumor, Anti inflammatory, Anti hyperglycemia, Anti fungal, Anticonvulsant activity.

1. INTRODUCTION

Benzo-fused azoles are heterocyclic organic compounds which have a ring system containing three nitrogen atoms and fused benzene ring showing a variety of biological activities (Fig 1). Benzotriazoles derivatives are used as corrosion inhibitors, radioprotectors and photo stabilizers in the production of plastic, rubber and chemical fiber. Benzotriazole derivatives are important as a precursor in the synthesis of peptides, acid azides, in the synthesis of 3-hydroxymethyl-2,3-dihydrobenzofurans and 3-hydroxymethylbenzofurans. It also acts as an electron-donor and as precursor of radicals which is easily insertable into different chemical structures through various reactions, such as condensation, addition reactions and benzotriazolyl-alkylation. [1-2]

The biological activities of benzotriazole is of immense use in the pharmaceutical field, choleretic, anti bacterial, anti fungal, anti protozoal , anti viral, anti oxidant, analgesic, anti inflammatory, anti hyperglycemia and anti proliferative agents. [2,3]

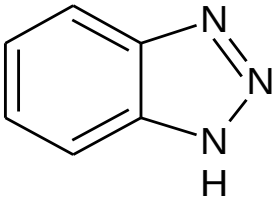


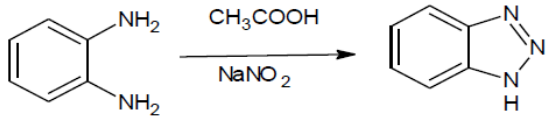
Fig 1; Benzotriazole

2. SYNTHESIS OF BENZOTRAZOLE

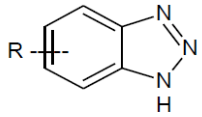
The methods used for the synthesis of benzotriazole and their derivatives depend on the nature of benzotriazole.

2.1. By Diazotization[4]

Benzotriazole is synthesized by diazotization process employing benzene-1,2-diamine, sodium nitrite and acetic acid.



2.2. 1, 3-Dipolar Cylcoaddition Of Azides And Arynes[6]

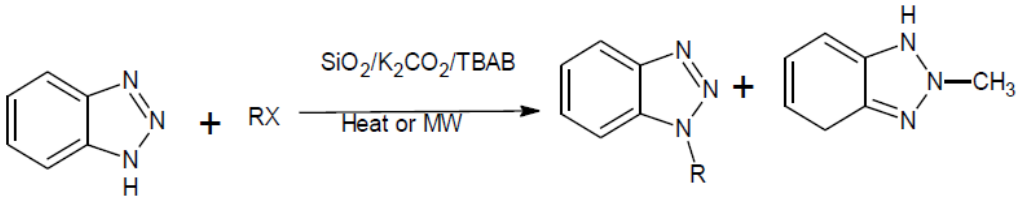


R	R^1
EtO_2CCH_2	H
Cinnamyl	H
p-Fluorobenzyl	H

Arynes formed through fluoride-promoted ortho-elimination of *o*-(trimethylsilyl) aryl triflates can undergo cycloaddition with various azides to form substituted benzotriazoles.

2.3. N-Alkylation Of Benzotriazole Under Solvent-Free Conditions[5]

An efficient and solvent-free method for highly regioselective N-alkylation of benzotriazole in the presence of SiO_2, K_2CO_3 and tetrabutylammonium bromide (TBAB) under thermal and microwave conditions has been described in which 1-alkyl benzotriazoles are obtained regioselectively. These are formed by cooling and stirring of benzene-1,2-diamine with carboxylic acid and this moiety possess anti fungal activity.



R= alkyl, aryl

3. PROPERTIES OF BENZOTRIAZOLE [6,9]

MOLECULAR FORMULA: $C_6H_5N_3$
MOLECULAR WEIGHT: 119.124
COMPOSITION: C(60.50%) H(4.23%)N(35.27%)
MELTING POINT: 98.5-100^{0}C
BOILING POINT: 350 °C
NATURE: White to brown crystalline powder
DENSITY: 1.36 g/cm^3
SOLUBILITY IN WATER: Soluble in water

4. PHARMACOLOGICAL ACTIVITIES OF BENZOTRIAZOLE

4.1 vAnti microbial activity

Sparatore and co-workers studied various nitrogen rings and reported that benzotriazole is part of heterocyclic systems. It possess biological activities, especially anti bacterial activity.[7-8]

In 1989 Sanna and co-workers reported the importance of benzotriazole moiety in triazolo[4,5-f]-quinolinone carboxylic acids (Fig 2), which is related to oxolinic acid. These compounds showed *in vitro* antimicrobial activity against *Escherichia coli*, with a *Minimum Inhibitory Concentration* (MIC) value. [9]

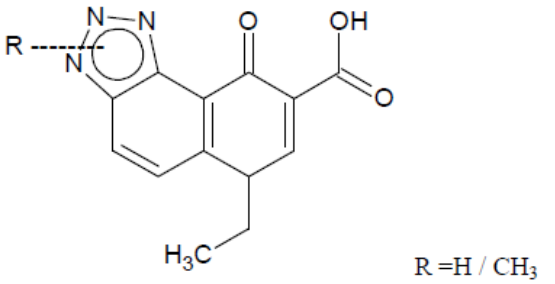


Fig 2; General formula of triazolo[4,5-f]-quinolinone carboxylic acids derivatives.

Purohit and Srivastava synthesized a series of chlorosubstituted, phenoxyacetyl benzotriazoles (3a-e)(Fig 3) and all the compounds were screened for their anti-inflammatory, analgesic, anti bacterial and anti fungal property. The compound 3c exerted analgesic effect and simple

benzotriazole nucleus possessed anti bacterial activity.[10]

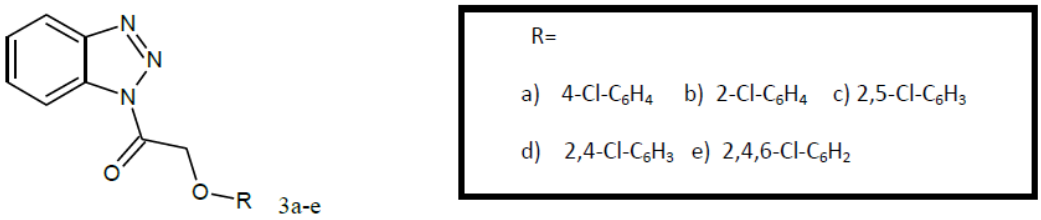


Fig 3; N-acyl-1H-benzotriazole derivatives

Similar anti microbial profile was reported for a series of 1-(1H-benzotriazol-1-yl)-2-(heterocyclyl)ethanones (4a-f)(Fig. 4).[11]

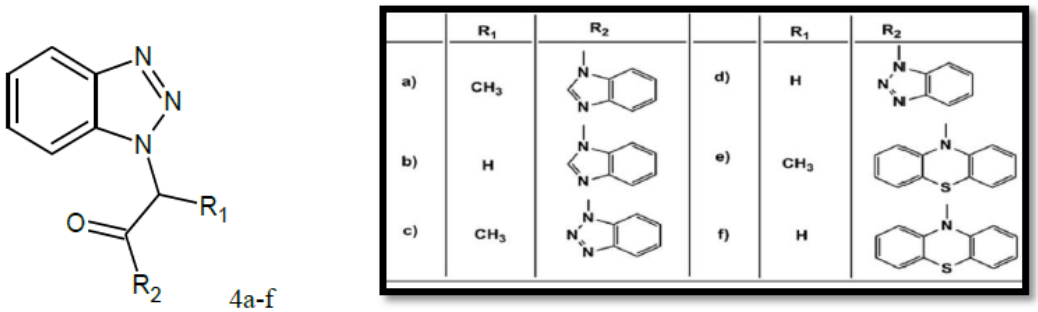


Fig 4; N-substituted 1H-benzotriazole derivatives endowed with antibacterial activity

Jamkhandi and coworkers prepared 1*H*-Benzotriazol-1-yl (2-hydroxy-5-[(E) phenyldiazenyl] phenyl) methanone derivatives through diazonium coupling reaction and these derivatives showed good anti bacterial and anti fungal activity(5a-e) (Fig 5).[12]

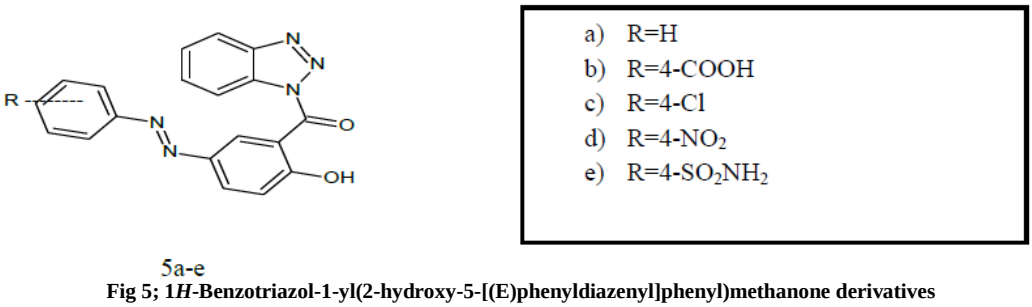


Fig 5; 1*H*-Benzotriazol-1-yl(2-hydroxy-5-[(E)phenyldiazenyl]phenyl)methanone derivatives

In vitro anti bacterial activity of 5-halogenomethylsulfonylbenzotriazoles and benzimidazole ((Fig. 6) were reported by Ochal et al. These compounds were tested against a series of reference (*Gram-positive and Gram-negative bacteria*) and clinical strains (including *methicillin-resistant* (MRSA) and *methicillin-sensitive* (MSSA) *Staphylococcus aureus strains*). All the compounds showed significant anti bacterial activity, whereas benzimidazole derivatives possessing triflurometh substitution at C_2 position were potent and able to inhibit *Staphylococci strains* (MRSA) with MIC values 12.5-25 mg/mL.[13]

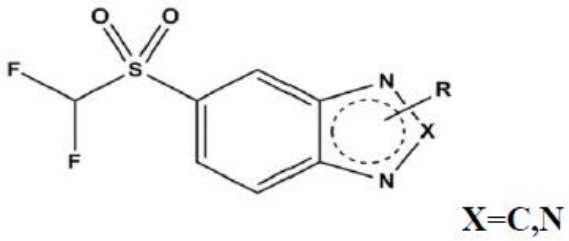


Fig 6; General formula of difluoromethylsulfonyl-benzotriazole and benzimidazole derivatives

In 2006, Swamy et al. prepared a series of N-alkylated benzotriazole derivatives(7a-e) through microwave-assisted synthesis (Fig.7) and the anti bacterial activity of all compounds was tested against bacterial strains like *Bacillus subtilis, Escherichia coli, Pseudomonas fluorescens, Xanthomonas campestris and Xanthomonas oryzae*. They found that the anti bacterial behavior was probably due to the presence of bulky hydrophobic groups (cyano-biphenyl and benzodioxole) present in the compounds.[14]

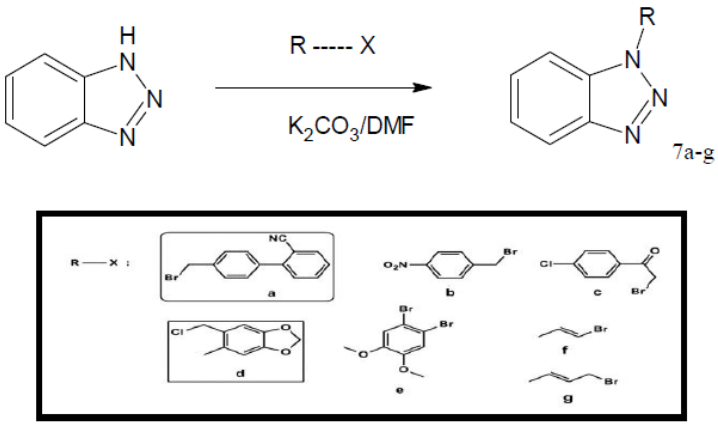


Fig 7; Microwave-assisted synthesis of N-substituted benzotriazole derivatives

Suma et al synthesized (un)substituted-benzotriazoles containing N-1 linked to substituted pyrazilidin-3,5dione moiety which showed anti microbial properties. All the synthesized compounds (8a-i)(Fig.8) were characterized and biologically evaluated by the cup plate diffusion method. Among this, the compound (8h) showed similar potency as that of Ciprofloxacin against *Staphylococcus aureus*, while limited activity was reported against *Candida albicans*.[15]

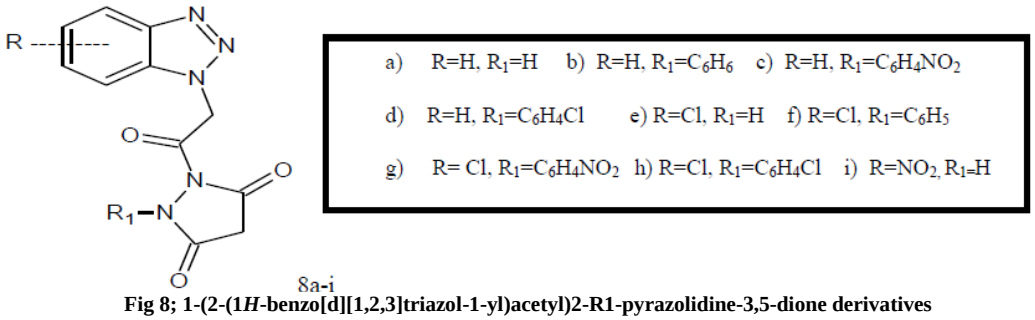
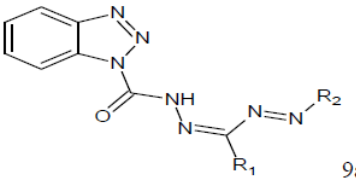


Fig 8; 1-(2-(1*H*-benzo[d][1,2,3]triazol-1-yl)acetyl)2-R1-pyrazolidine-3,5-dione derivatives

Anthelmintic activity

Sudhir and co-workers synthesized a series of benzotriazole-1-carbonyl-3,5-arylformazans (9a-p) (Fig.9) under ultrasonic and solvent free conditions, all the compounds were tested for activity against adult earthworm *Pheretima posthuma* using mebendazole and albendazole as reference drugs. [16]



	R_1	R_2		R_1	R_2
a)	C_6H_5	C_6H_5	i)	$C_6H_4NO_2$	C_6H_5
b)	C_6H_5	$C_6H_4NO_2$	j)	$C_6H_4NO_2$	$C_6H_4NO_2$
c)	C_6H_5	C_6H_4Cl	k)	$C_6H_4NO_2$	C_6H_4Cl
d)	C_6H_5	C_6H_4Br	l)	$C_6H_4NO_2$	C_6H_4Br
e)	C_4H_3O	C_6H_5	m)	C_6H_4Cl	C_6H_5
f)	C_4H_3O	$C_6H_4NO_2$	n)	C_6H_4Cl	$C_6H_4NO_2$
g)	C_4H_3O	C_6H_4Cl	o)	C_6H_4Cl	C_6H_4Cl
h)	C_4H_3O	C_6H_4Br	p)	C_6H_4Cl	C_6H_4Br

Fig 9; Benzotriazole derivatives

Although none of the tested compounds were effective than the reference drugs, derivatives (9b,f,j,n) showed dose-dependent anthelmintic activity because this behavior was attributed to the p-nitrophenyl substituent attached to azo group of benzotriazole moiety. The methyl 6-benzoyl-1*H*-benzo[d][1,2,3]triazole1-carboxylate (10) was designed to be active against *Necatur americanus* infections but were totally inactive in newborn hamsters. N_1alkyl/aryl (11a-e) and alkoxy/aryloxy (12a-e) arylaminomethylene benzotriazole proved to be (Fig.10) good anthelmintic agents against *Pheretima posthuma*.[17]

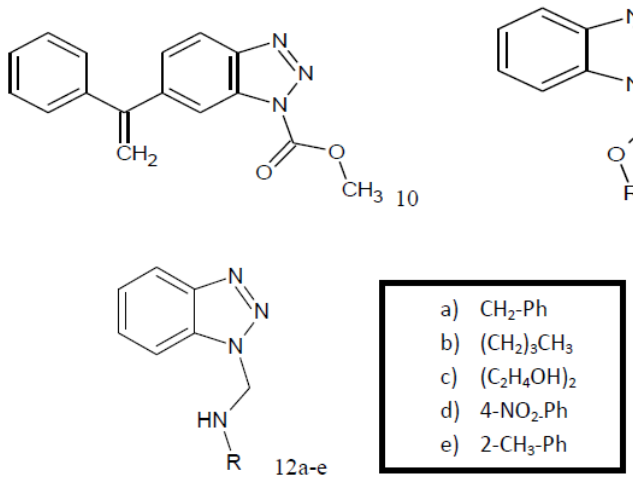


Fig 10; Benzotriazole derivatives endowed with anthelmintic activity

4.3. Analgesic activity

A series of chlorosubstituted phenoxyacetyl and propionylbenzotriazoles were synthesised and evaluated for their analgesic activity. The 2,5-dichlorophenoxy acetyl benzotriazole (13) (**Fig. 11**) exhibited moderately better analgesic activity among the series.[18]

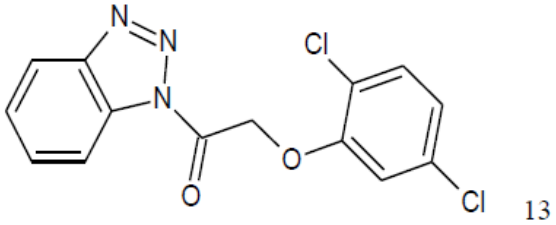


Fig 11; 2,5-dichlorophenoxy acetyl benzotriazole

5-Arylidene-2- aryl-3-(benzotriazoloacetamidyl)-1,3-thiazolidin-4-ones derivatives were prepared from ethyl acetoacetate and evaluated for its analgesic activity by Eddy and Leimbach method. Compound 14h, 14i and 14j were found to be better analgesic activity and acetylsalicylic acid was employed as reference drug(**Fig.12)**.[18]

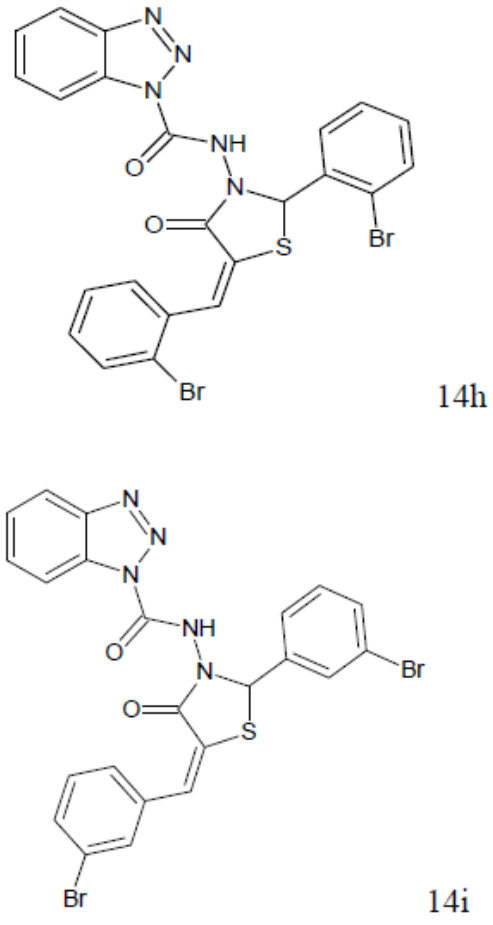


Fig.12; Compound 14h and 14i

4.4. Anti mycobacterial Activity

Carta and co-workers synthesized a series of 3-aryl substituted-2-(1*H(*2*H*)benzotriazol-1(2)-yl)acrylonitriles with the aim to identify the good substituents on the aryl moiety. 1-substituted benzotriazole derivatives were more active than 2-benzotriazolyl isomers, while the unsubstituted phenyl moiety exhibiting the highest anti mycobacterial activity *in vitro* and also against *Mycobacterium avium*. The only exception is represented by 4-bromophenyl derivative, although its activity was lower than that of compound 15a shown in Fig 13.[19]

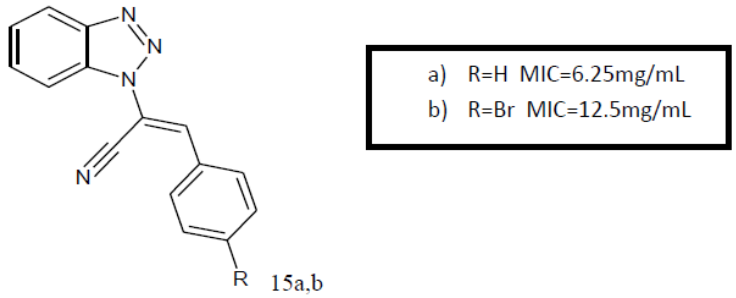


Fig13; 3-Aryl substituted-2-[1*H*(2*H)*benzotriazol-1(2)-yl]acrylonitriles and MIC values for compounds 15a,b

3-aryl, 3-cyclohexyl and 3-heteroaryl substituted-2-(1*H*(2*H*)-benzotriazol-1(2)-yl)prop-2- enenitriles, prop-2-enamides and propenoic acids showed less activity because of their increased lipophilic character. This indicates that the steric hindrance and the nature of the substituents play an important role in the inhibition of *Mycobacterium tuberculosis* proliferation.[20]

Dubey et al. coupled benzotriazole nuclei with b-lactums and 2-azetidinones and checked for their antimicrobial activity. The 2-oxo-4-substituted aryl-azetidinone derivatives of benzotriazole were prepared by both conventional and microwave irradiation method and all the prepared compounds were tested against *Mycobacterium tuberculosis* and other microorganisms. Ewa and co workers synthesized a series of benzotriazoles derivatives and their work was based on the anti mycobacterial activity of benzimidazole derivatives modified both in the heterocyclic core and in exocyclic constituents. The biological activity was enhanced by the introduction of a nitrobenzylsulfenyl group at second position and a substitution on the heterocycles benzene moiety with a halogen atom. [21,9]

Several new *o*-nitrobenzylated derivatives of halogenosubstituted 1-hydroxybenzotriazoles (16a-p) where synthesized and their activity was tested against four *Mycobacterium strains.*[22]

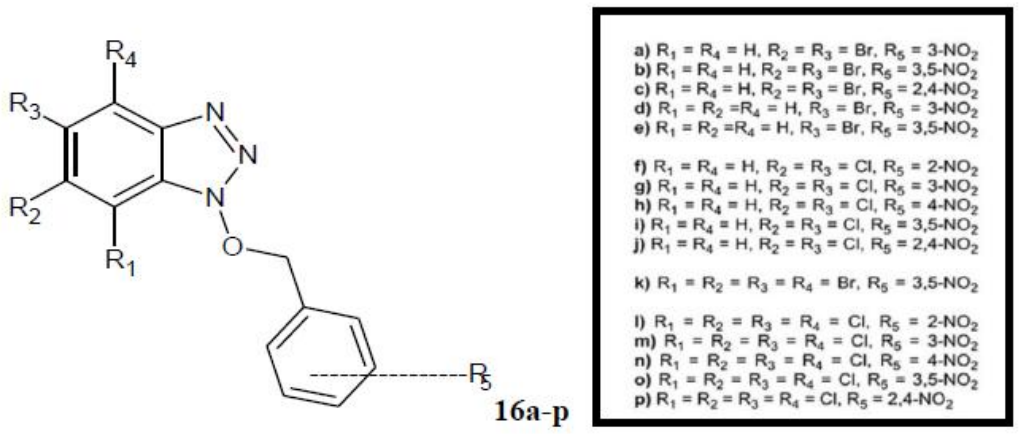


Fig 14; *o*-nitrobenzylated derivatives of halogenosubstituted 1-hydroxybenzotriazoles

Carta et al. prepared a new series of [1,2,3]Triazolo[4h,5h] and [4,5-f]quinolones with the purpose of synthesizing more potent and selective agents against *Mycobacterium tuberculosis* sensitive and resistant strains. They could synthesized triazolo[4,5-h]quinolone carboxylic acids which exhibited low MIC_{90} and the activity depended on the length and position of the substituent at triazole-nitrogen. Compounds bearing methyl group at N_3 showed higher activity and they designed a series of 3-methyl-9- substituted-6-oxo-6,9-dihydro-3H-[1,2,3]-triazolo[4,5-h]quinolone-carboxylic acids (compound17). A variety of substituents on the quinolone nitrogen were introduced with the aim to improve the biological activity of the compound.[23]

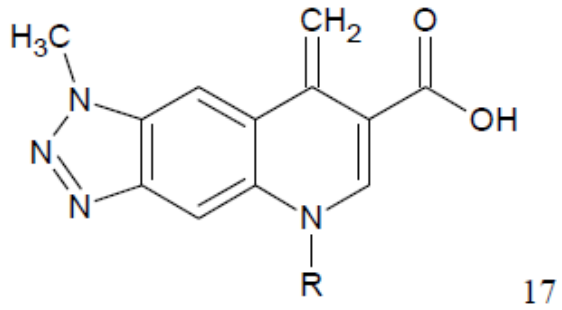


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Fig.15; Chemical structure of 3,9-dimethyl-6-oxo-6,9-dihydro-3H-[1,2,3]triazolo[4,5- h]quinoline-7-carboxylic acid.

4.5. Anti viral Activity

Sakthi et al. reported derivatives of 4-(3*H*)-quinazoline having potential anti viral activity, especially against HIV-1 (IIIB) and HIV-2 (ROD) in MT-4 cells. The benzotriazole-substituted quinazoline derivative showed anti viral activity against IIIB by comparison with the standard drug azidothymidine compound 18 (Fig 16).[24]

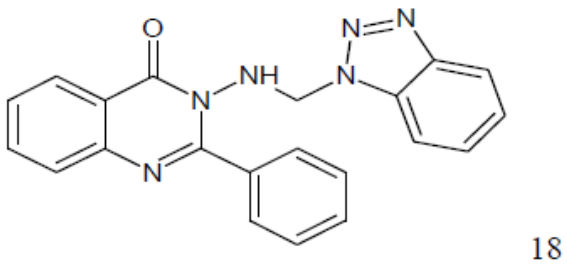

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Fig 16; Quinazolinone benzotriazole derivative as HIV inhibitor

Benzimidazole-substituted benzotriazole showed a significant anti viral effect on Respiratory Syncytial Virus (RSV) and it was more effective than azauridine (Fig. 17). This compound 19 was proved to be a potent RSV inhibitor.[25]

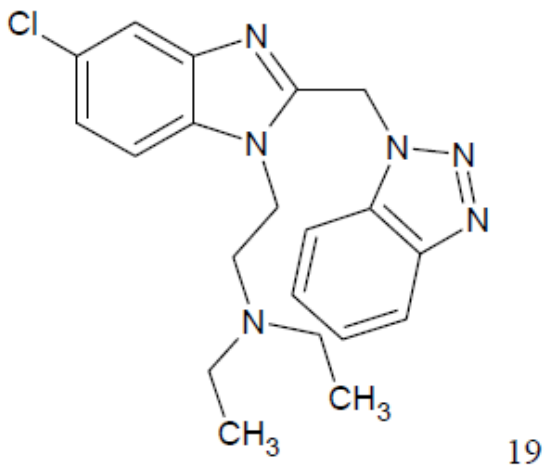

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Fig 17; Benzimidazole-derivatized benzotriazole as RSV inhibitor

4.6. Antioxidants

Reducing agents that stabilize the free radicals produced by cellular metabolism or the compounds that inhibit oxidation are termed as antioxidants.

Benzotriazole-substituted primaquine compound 21 showed a higher antioxidative interaction (73.8%) than parent compound primaquine (31%) which exhibited a good Lipoxygenase Inhibitory (LOX) activity (Fig 19).[27]

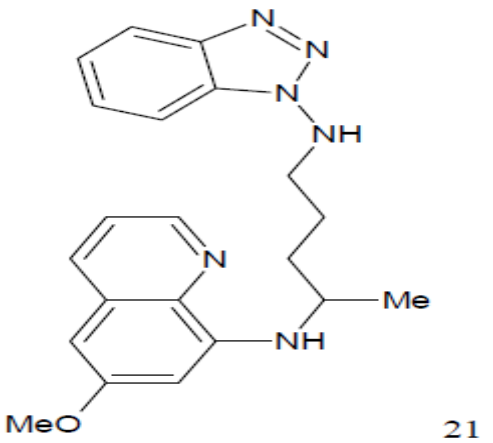

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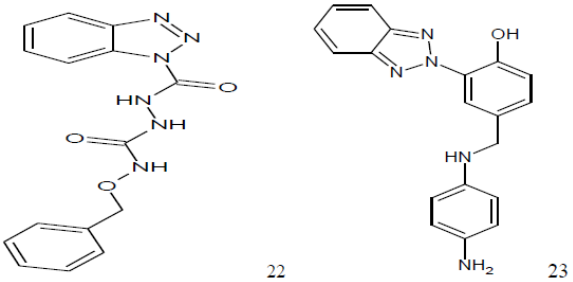
Fig 19; Benzotriazole derivatized drugs as antioxidants

Non-steroidal anti-inflammatory drug (NSAID) Ketoprofen, has an analgesic

and antipyretic activities. Ketoprofen benzotriazole derivative exhibited a good interaction with 1,1-dipheny-l,2-picrylhydrazyl (DPPH), which is a stable free radical with spared electron delocalization. The interaction between this derivative and DPPH indicated its radical scavenging ability in an iron free system, as well as its reductant character it also showed a high soybean lipoxygenase inhibition activity (95%).[28]

N_1-Carbonyl-substituted benzotriazole derivative (22) has good DPPH interaction value of 85% as compared to the reference compound nordihydroguaiaretic acid which showed an interaction value of 91% at the same concentration (Fig. 20). So this derivative showed a good lipid peroxidation (LP) inhibition activity (31%). Benzotriazole derivatives bearing a free phenolic and amine groups such as compound 23 were reported with a pronounced anti oxidant and anti ozonant activity.[29]



22 23

Fig 20; Benzotriazole-based antioxidants

4.7.Anti tumor activity

The therapeutic approach for the treatment of cancer diseases are different which includes surgical treatment, radiation therapy, immunotherapy or chemotherapy. Nowadays, a variety of anticancer drugs are in use such as alkylating agents, platinum complexes, porphyrin drugs, azole agents etc. Benzotriazole derivatives possess potent anticancer activity, vorozole(24), 4,5,6,7- tetrabromobenzotriazole (TBB) (25)(Fig. 21) are selective inhibitor of protein kinase CK2 and act as a potent anti cancer agent. [31]

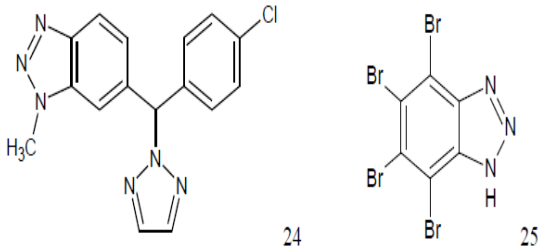


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Fig 21; Benzotriazole-based cancer drugs

Al-Soud et al. combined several alkylated benzotriazoles with 1,2,4 triazole nuclei and they performed its activity on several human tumor cell lines. Compound (27) showed micro molar activity against leukemic, ovarian and renal tumor cells.[30]

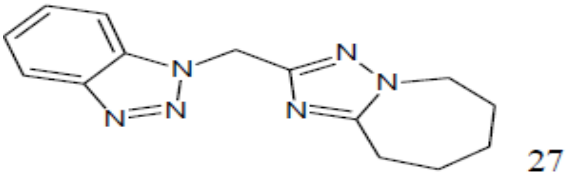

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Fig 22; Benzotriazol-1(2)-yl)-tetrahydro-triazoloazepine.

Wan and co-workers synthesized 3-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1-(4-methoxyphenyl)-1-oxopropan-2-benzoate (BmOB) showed anti proliferative activity on cell lines derived from different tumor types and its analyses carried out on BEL-7402 hepatocellular carcinoma cells. They also found (E)-2-(1*H*-benzo[d][1,2,3]triazol-1-yl)-3-(4-methoxyphenyl) acrylonitrile (Fig.23) showed activity 100 times more than 6-mercaptopurine.[32]

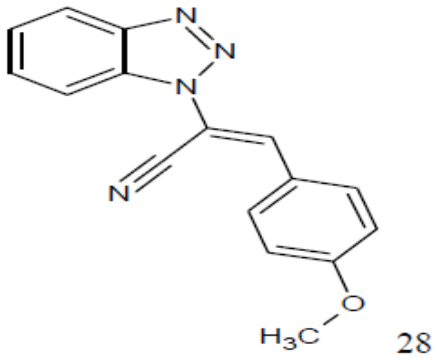

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Fig 23

Zhang and colleagues synthesized 1,3,4-oxadiazole derivatives containing benzotriazole moiety showed potent anti tumor activity and their biological target

was identified in the Focal Adhesion Kinase (FAK), a non-receptor tyrosine kinase that plays an important role in cell proliferation process. Compound 29 displayed good anti proliferative activity against MCF-7 cells and showed FAK inhibitory activity (comparable to the reference drug cisplatin).[9]

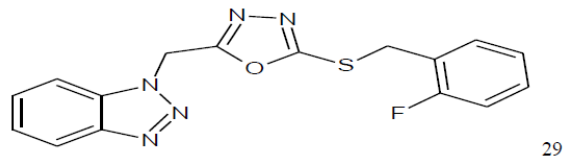

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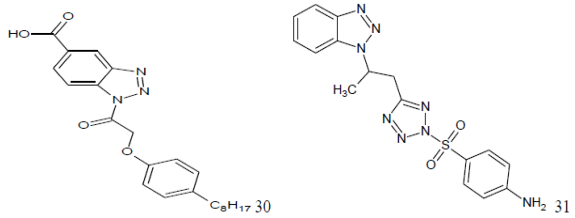
Fig24; 2-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-5-((2-fluorobenzyl)thio)-1,3,4-oxadiazole

4.8. Anti-inflammatory Activity

Anti-inflammatory is the property of a substance to reduces the inflammation or swelling. Benzotriazole-6-carboxylicacid (30) displayed good cPLA2α inhibition and potent anti-inflammatory activity (Fig.25). The replacement of the carboxyl benzotriazole scaffold by a carboxyl indole or a carboxyl benzimidazole moiety resulted in decreased anti-inflammatory activity. [33]

Tetrazole-linked sulfanilamide benzotriazole derivative (31) displayed superior anti-inflammatory activity as compared to the standard drug paracetamol. The introduction of substituted sulfonyl moiety and benzotriazole increases the anti-inflammatory activity of the compound.[34]



30 31

Fig 25; Benzotriazole-based anti-inflammatory agents

4.9. Anti hyperglycemic Activity

Benzotriazole-based PTP1B inhibitor showed anti hyperglycemic effects in animal models, along with oral bioavailability. Series of benzotriazole derivatives containing difluoromethyl-phoshonate (DFMP) moiety (compounds 32 and 33) showed PTP1B inhibitory activity at nanomolar level (Fig.26). [35]

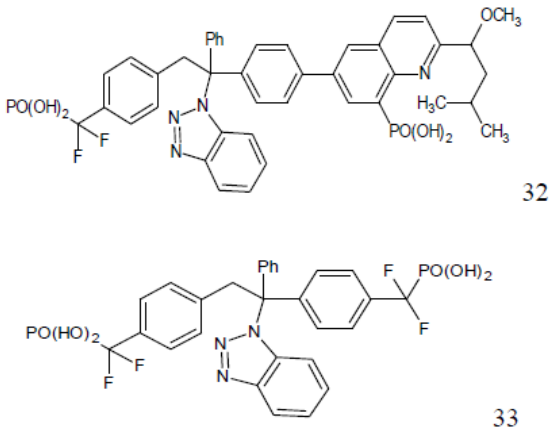


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Fig26; Benzotriazole derivatives containing a difluoromethylphoshonates moiety as PTP1B inhibitors

Patel et al. synthesized tetrasubstituted benzotrazole-based PTP1B inhibitors containing difluoromethyl-phoshonate (DFMP) substituted naphthyl moiety (compound 34). All the synthesized compounds contained a benzotriazole ring, acetophenone and benzyl, naphthyl, or quinolinyl ring systems, substituted with difluoromethylsulfonamide (DFMS) which improve lipophilicity and oral efficacy of the compound. Compound 35 showed excellent anti-hyperglycemic effects in animal models and improved oral bioavailability, along with excellent selectivity over T-Cell Protein Tyrosine Phosphatase (TCPTP).[36]

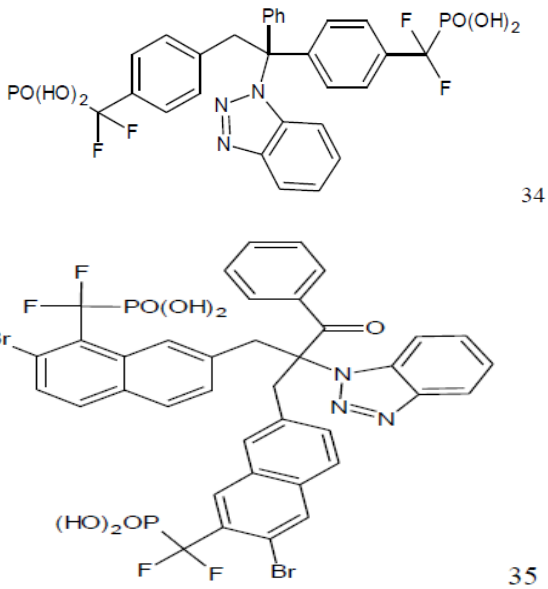

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Fig 27; Benzotriazole derivatives containing a difluoromethylphoshonates moiety as PTP1B inhibitors.

4.10. Anti fungal activity

Substituted 1,2,3-benzotriazole derivatives(36a-b) were synthesized from benzimidazoles with 1-chloromethyl benzotriazoles and evaluated its antifungal activity against *Aspergillus niger* and *Candida albicans* by solidified agar method. Compound 36 b and e showed excellent anti fungal activity and its inhibitory activity was compared with griseofulvin (standard drug) (**Fig. 28**). [37]

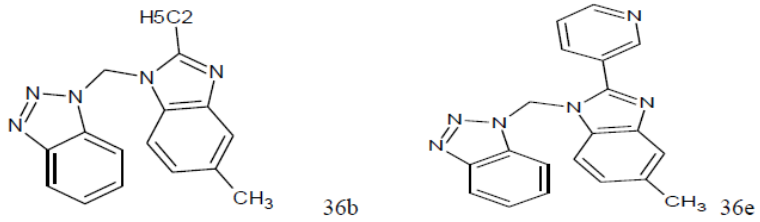

FIG. 28; Compound 36b and 36e

Benzotriazole derivatives containing pyrazolidinedione moiety (8a- i) were synthesized and their anti fungal activity was tested against *Aspergillus niger* and *Candida albicans* by cup plate diffusion method. Compounds 37e, 37h and 37i (**Fig. 29**) were found to have potent activity against *Aspergillus niger* while compound 8c showed activity against *Candida albicans*. Drugs like Ketoconazole and Clotrimazole were used as standard drugs.[15,37]

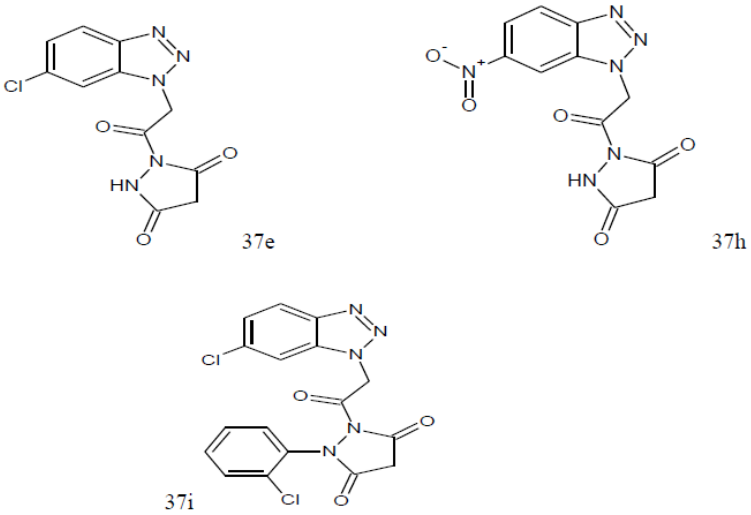

Fig.29; Compound 37e, 37h and 37i

A series of 1*H*-1,2,3-benzotriazole derivatives were synthesized and evaluated for anti fungal activity against species of *Candida*. Compound 38a and 38c (**Fig. 30**) showed desirable anti fungal activity.

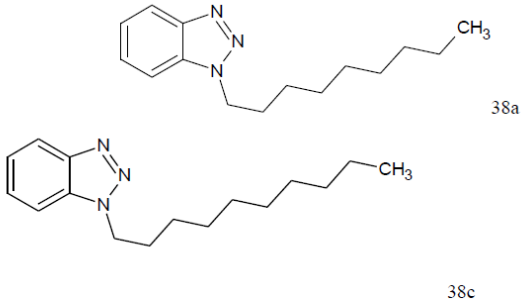

FIG. 30: Compound 38a and 38c

4.11. Anti convulsant activity

A series of benzotriazole containing 1,3,4-thiadiazole derivatives (39a-f) were synthesized and evaluated for the anti convulsant activity in Maximal Electroshock Seizure(MES) and Subcutaneous Metrazole Test (ScMet). Compounds 39a and 39d were found to be active in ScMet only, whereas the compounds 39c (**Fig. 31**) was active in MES. Activity of compound 39c was similar to the activity of Phenytoin and Valproic acid.[39]

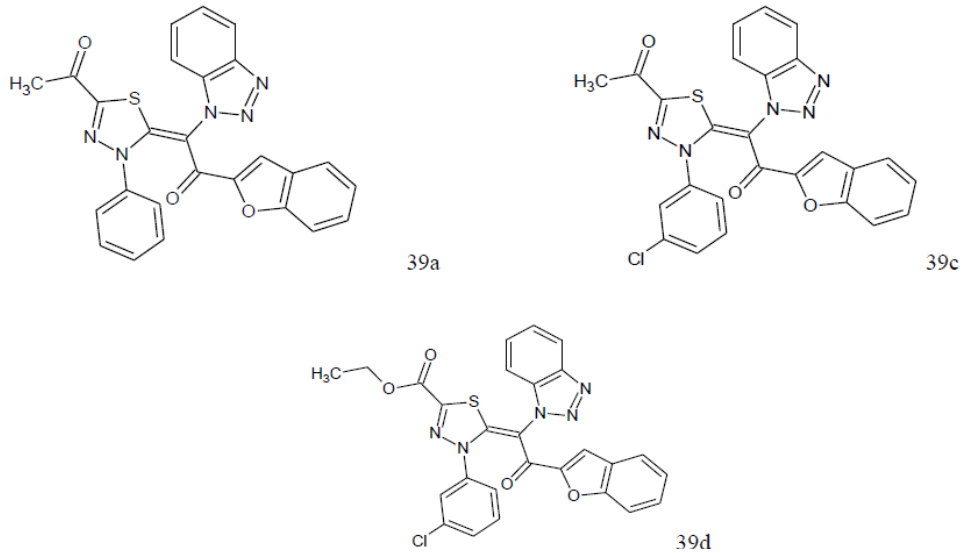

FIG 31; Compound 39a, 39c and 39d

4.12. Miscellaneous Uses

Benzotriazole derivatives are used as ink components in oil-based marking pen. Water-soluble benzotriazole derivatives such as compounds 41, 42 were employed as components for water-thinned ink (Fig. 32) and benzotriazole-based azo dyes were used as dye stuff for hair (Fig. 33). [40]

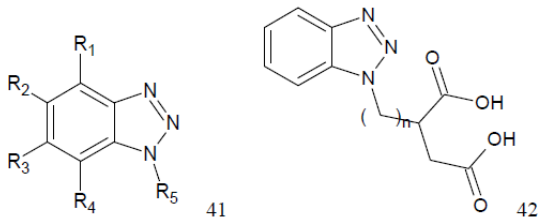

Fig 32; Benzotriazole derivatives used as ink components

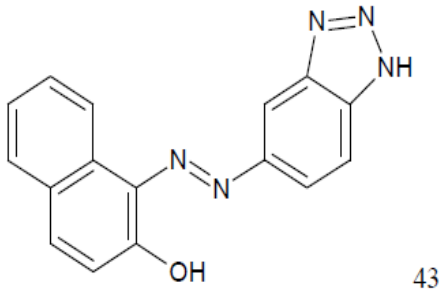

Fig 33; Benzotriazole-based azo dye

5. CONCLUSION

Benzotriazoles are a class of bioactive heterocyclic compounds displayed a wide range of biological activities therefore; this nucleus appears a very interesting scaffold in the drug discovery and development processes. The biological profiles of new derivatives of benzotriazole would represent further development of better medicinal agents. Benzotriazole derivatives showed good biological activities such as anti bacterial, anti fungal, anti viral, anti cancer, anti mycobacterial, anti inflammatory, anti convulsant, analgesic, anti oxidant etc. The present review is about the benzotriazole derivatives and focused on its biological activities such as anti microbial, anthelmintic, analgesic, anti mycobacterial, anti viral, anti oxidative, anti tumor, anti inflammatory, anti hyperglycemia, anti fungal and anticonvulsant activity. This review suggests the possibility to synthesis a lead compound in which benzotriazole is used as a tagging molecule to produce new chemical entities of benzotriazole having good biological activities.

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Ethical Approval: Not Applicable

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