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RECENT ADVANCEMENT IN BIOLOGICAL APPLICATIONS OF BENZOTHIAZOLE DERIVATIVES: A SHORT REVIEW

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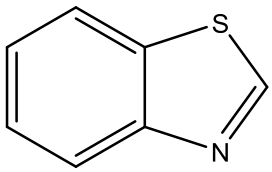
ABSTRACT
Heterocyclic compounds plays very important role in medicinal chemistry or synthesis of new drugs because the most of drug molecules possesses therapeutic activity due to heterocyclic scaffold. Benzothiazole moiety has unique and versatile properties for the development of new drug. The benzothiazole and its derivatives attracted so much interest in biomedical field due to their biological and pharmacological properties. The benzothiazole nucleus and its derivatives process various type of biological actives such as antitumor, antimicrobial, anti-inflammatory, anticonvulsant, and antidiabetic. In present review we tried to summarize the scientific roadmap with special focus on biomedical applications of benzothiazole and its derivatives in detail.

KEYWORDS: Heterocyclic, antidiabetic, benzothiazole, derivatives.

INTRODUCTION
Pharmaceutical chemistry, a discipline firmly rooted in synthetic organic chemistry, has increasingly close links to structural chemistry, computational chemistry, and molecular biology at the discovery interface, to toxicology and pharmacology at the development interface and also to medicine at clinical interface. Thus, pharmaceutical chemistry has occupied the central position and will continue to play a very important role in the new drug development processes.[1, 2] During the later decades traditional dividing lines between biological, chemical and physical sciences were erased and in the present millennium, new border line of investigations such as molecular biology, molecular pharmacology, biomedicine, cellular biology, genetics and other began to capture the interest of medicinal scientist.[3, 4] Since the ancient times, the mankind was under misery and suffering as his life was associated with many physiological and pathological disorders like cancer, AIDS, inflammation, hypertension, diabetes and analgesia, the diseases caused by several bacterial and fungal infections.[5] For the therapy, it was proven in the research that the benzothiazole nucleus found to play an important role as antimicrobial, anti-inflammatory, anticancer and antidiabetic agent. We report herein the new and unreported yet the synthesis of fluoro-benzothiazole derivatives and then followed by screening for antibacterial, antifungal and anti-inflammatory activity.

Benzothiazole is a heterocyclic compound containing benzene ring fused with thiazole ring. It is a colorless liquid, with boiling point 227 °C, and soluble in water. Benzothiazole derivatives have attracted sustained interest over the years because of its varied biological activities. Benzothiazole and its derivatives are the most important heterocyclic compounds, which are mutual and vital feature of a diversity of natural products and pharmaceutical agents.[6] The broad spectrum of pharmacological activity in individual benzothiazole derivative indicates that, this series of compounds is of an undisputed interest. The related research and developments in benzothiazole-based medicinal chemistry have become a rapidly developing and increasingly active topic. In bioorganic and medicinal chemistry, 2-aminobenzothiazole derivatives are broadly found with applications in drug discovery and development for the treatment of diabetes, epilepsy, inflammation, ulcer, analgesia, tuberculosis, viral, bacterial infections.[4]



Benzothiazole

Fig. 1: Structure of benzothiazole.

Benzothiazoles are one of the most important class of organic compounds of medicinal importance due to their documented biological and therapeutic activities.[7]

Benzothiazole moieties are part of compounds showing numerous biological activities such as shown in Figure 2.

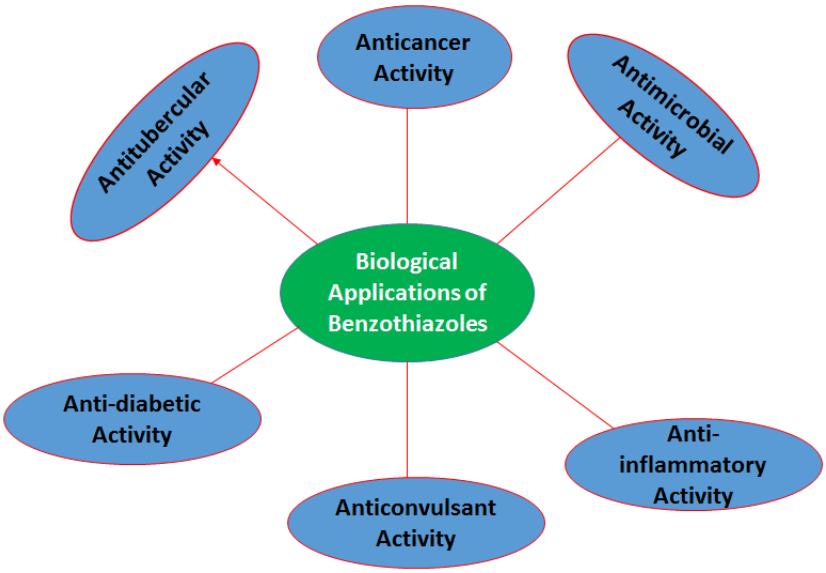


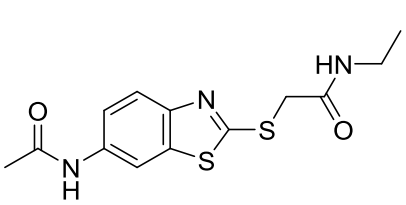
Fig 2: Application spectrum of benzothiazole and its derivatives.

In this review we discussed the chemistry of benzothiazole and the biological applications of benzothiazole and its derivatives in detail.

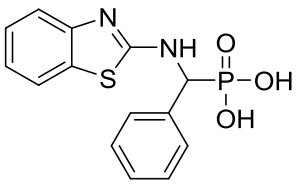
Biological applications of Benzothiazole Derivative

In drug discovery and new chemo-therapeutics program heterocyclic frameworks provide enormous potential. They form the nucleus basis of natural bio-component and are also present in commercial drugs. Heterocyclic compounds have well known essential properties which are necessary for drug discovery such as lipophilicity, polarity and solubility. Benzothiazole is one of the most important classes of honored heterocycles found in various marine and terrestrial bioactive natural components.

Benzothiozole are exploring to more potent for the treatment/cure for cancer. It is a serious health problem with a large scale research going on for developing novel potential antitumor moieties. Benzothiazole-2-thiol derivatives (2-((6-acetamidobenzo[d] thiazol-2-yl) thio) -N-ethyl acetamide) (**1**) were evaluated effective against cancer causing cell and have also shown anti-proliferative activities on *HepG2* and *MCF-7* cell line. Some newly synthesized moieties γ- amino-phosphonates consisting fluorine and benzothiazole units (((benzo[d]thiaole-2-yi amino) (phenyl-methyl) phosphonic acid) (**2**) were found to be active against cancer causing cells which have been synthesized in ionic media with high yield and short reaction time.[8]

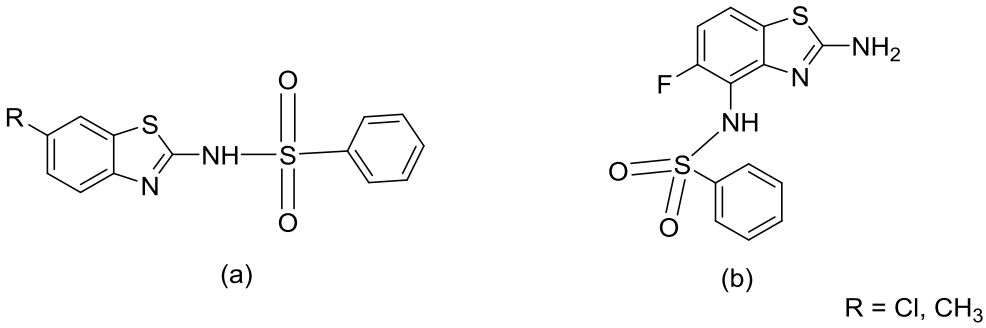


1



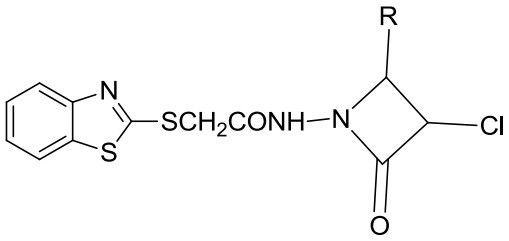
2

Benzothiazoles show a biological activity and a considerable amount of work has been done on the synthesis of new potent antibacterial and antifungal benzothiazoles. 2- (substitutedarylsulfonamido)-6-substituted (**3**) have reported for their anti-bacterial activity against *Bacillus subtilis*, *Salmonella typhi* and *S. dysentery*.[9]



(3)

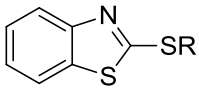
Trivedi et al., were successfully synthesised 2-(substituted benzal hydrazino carbomyl methyl thio) benzothiazoles **(4)** for antimicrobial activity.[10]



R = $C_6H_4Cl_2$, $C_6H_4NO_2$, C_6H_4OH

(4)

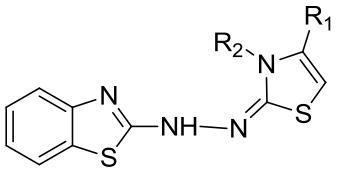
Mohrram et al., were synthesised some benzothiazole derivatives (5) and evaluate their potential as antibacterial agent.[11]



R = H, NO_2

(5)

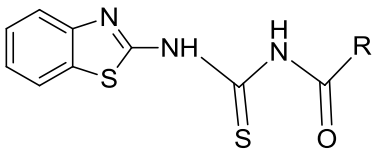
It has been reported that the new benzothiazole derivatives **(6)** as potential antimicrobial and antiparasitic agents as well as antimicrobial activity was evaluated against *Staphylococcus aeurus, Escherichia coli and Candida albicans*.[12]



R1 = 4-C_6H_5(Cl), -CH_2
R2 = 4-$C_6H_5(NO_2)$

(6)

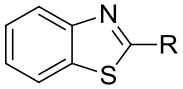
Saeed et al., have been reported the synthesis, characterization and biological evaluation of thiourea derivatives based on benzothiazole moiety **(7)** as potential antimicrobial agents. Antimicrobial activity evaluate against various gram positive and gram negative bacterial and various strains of fungus.[13]



R = 4-nitrophenyl, n-butyl, phenyl

(7)

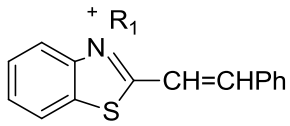
It has been reported that the newly synthesized benzimidazole and benzothiazole derivatives (8) as potential antibacterial agents against Gram-positive bacteria *Staphylococcus aureus*, *Bacilluscereus*, and Gram-negative bacteria *Vibrio cholerae*, *Shigella dysenteriae* and *Escherichia coli*.[14]



Where R = 2-EtCH4, 4-NO2C6H4, 4-OHC6H4

(8)

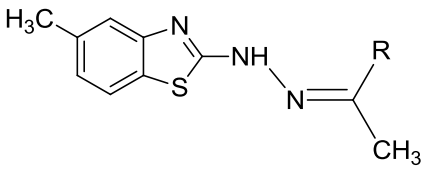
Charlecek et al., studied the antibacterial and fungicidal activity of 2-styryl benzothiazolinium salts **(9).**[15]



R_1 = Me, $PhCH_2$, CH_2COOH

(9)

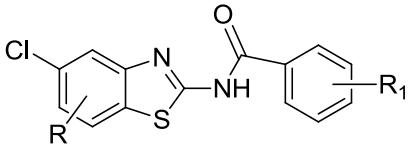
Gaurav et al., observed the antibacterial activity of novel 2{4"-chlorophenyl)-1'-ethylhydrazinyl}-6-methyl benzothiazole **(10).**[16]



R = NO_2, Cl, F, OH

(10)

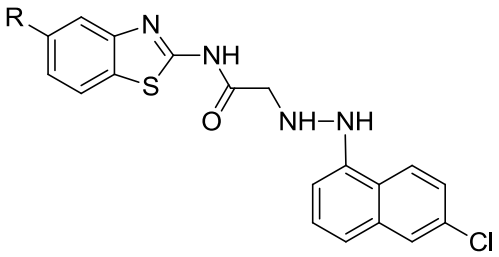
Armenise et al., successfully synthesized the new series of *N*-1,3-benzothiazol-2-ylbenzamides **(11)** and evaluation their antimicrobial against *Enterococcus faecalis*, *Escherichia coli*, *Staphylococcus aureus*.[17]



R = 4-F, 5-F
R1 = 2,3-F2, 2,5-F2

(11)

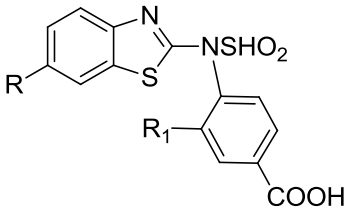
It has been reported that the novel N-(benzo[d]thiazol-2-yl)-2-(2-(6-chloroquinolin-4-yl)hydrazinyl)acetamide derivatives **(12)** containing quinoline linkage as potent antibacterial activity against *Escherichia coli*, *Micrococcus luteus*, *Bacillus cereus*.[18]



R= H, CH3, OCH3, NO2, F

(12)

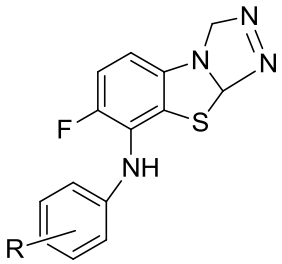
Bhusari et al., found preliminary screening of antibacterial activity of some new 2-(substituted phenylsulfonamido)-6-substituted benzothiazoles **(13).**[19]



R = Br, Cl, CH_3, OCH_3
R_1 = CH_3, NH_2

(13)

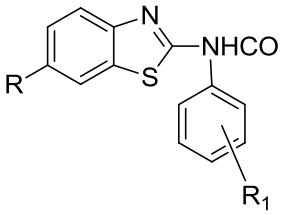
Sreenivasa et al., reported synthesis of fluoro-benzothiazole **(14)** derivatives which found to possess good activity against S. aureus, E. coli and C. ablicans.[20]



R = o-NO_2, p-NO_2, m-NO_2, H, o-Cl

(14)

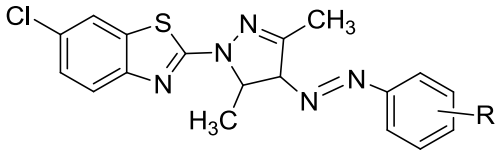
Ghoneim et al., synthesized 2-[(4-amino/2, 4-diaminophenyl) sulfonyl derivatives of benzothiazoles **(15)** and found to possess good activity against E. coli.[21]



R = 5-Cl, 2-F, 5 , 6, di-Cl
R_1 =H, 2-F, 3-F, 4-F, 2-CF_3

(15)

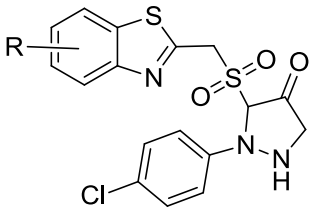
A novel class of 4-arylhydrazono-1-benzothiazolyl-3- methylpyrazolin-5-ones and 4-arylazo-1-benzothiazolyl-3,5-dimethylpyrazoles **(16)** were designed as pharmacophore hybrids between pyrazolinone/pyrazole and benzothiazole moiety and screened for antimicrobial activity.[22]



R = o-OH, p-oCH_3 , o-COOH, p-COOH

(16)

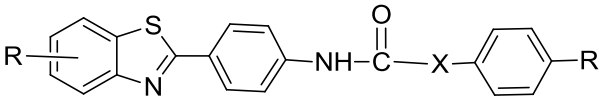
Asundaria et al., synthesis the sydnone sulfonamides bearing thiazole, benzothiazole **(17),** and pyrimidine heterocycles and evaluated for their antibacterial activity against some important Gram-positive and Gram-negative bacterial strains.[23]



R = 4-Cl, 4-Br, 4-F, 4-CH_3, 4-OCH_3

(17)

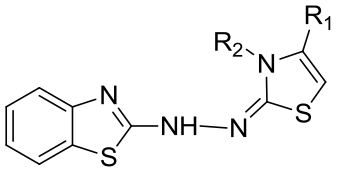
A novel series of 2-[4-(4- substitutedbenzamido/phenylacetamido)phenyl] benzothiazole derivatives **(18)** were synthesized and evaluated for antibacterial and antifungal activities against Staphylococcus aureus, Bacillus subtilis, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Escherichia coli with their drug-resistant isolates and a yeast Candida albicans.[11]



X = -CH_2
R = Cl, Br, F, CH_3, C_2H_5

(18)

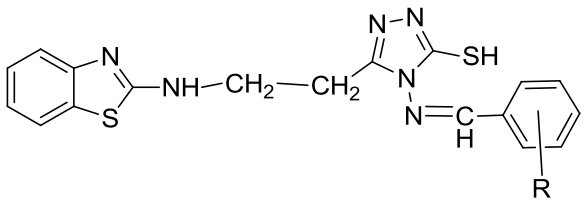
It has been reported that the new benzothiazole derivatives **(19)** as potential antimicrobial and antiparasitic agents as well as antimicrobial activity was evaluated against *Staphylococcus aeurus, Escherichia coli and Candida albicans*.[6]



R1 = 4-C_6H_5(Cl), -CH_2
R2 = 4-$C_6H_5(NO_2)$

(19)

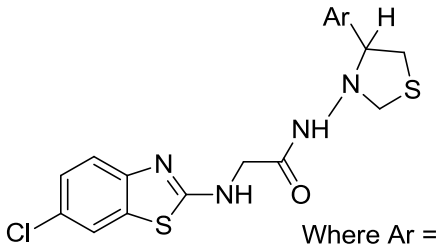
This is reported that the new benzothiazole derivatives **(20)** as potential antimicrobial agents against fungus strains *Candida albicans* and *Aspergillus niger* and bacterial strains *Streptomyces griseus, Escherichia coli, Bacillus subtilis*.[24]



Where R = H, 2-NO2, 3-NO2, 2-Cl

(20)

Saarangi et al., successfully synthesized new novel derivatives of 2-amino-6-chlorobenzothiazole and evaluated their antimicrobial studies **(21)** against *Klebsiella pneumoniae, Proteus vulgaris, Bacillus subtilis.*



Where Ar = -C6H4-Cl, -C6H4-3-NO2, -C6H4

(21)

CONCLUSION

The present review highlights the heterocyclic system resemblances and derivatives have attracted so much attention due to their valuable biological and pharmacological properties. Biological properties of the basic heterocyclic nucleus include anticancer, antidiabetic, analgesic, anti-inflammatory, and antimicrobial. Benzothiazole prospective compounds can be designed and synthesized for a variety of biological activities.

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