Review Article

A Comprehensive Review on Synthetic Strategy of Benzothiazole Lead and Pharmacological Importance

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ABSTRACT

Background: In recent years heterocyclic compounds analogues and derivatives have attracted wide attention due to their useful biological and pharmacological properties. Benzothiazole is among the usually occurring heterocyclic nuclei in many marines as well as natural plant products. Benzothiazole is a privileged bicyclic ring system with multiple applications. **Objective:** To review and explore the synthetic strategy of lead and pharmacological importance of Benzthiazole Derivatives. **Materials and Methods:** A literature search was conducted on various database sources (like PubMed, Science Direct) with the help of a combination of different keywords: Benzothiazole, thiazole, antitumor, anti-inflammatory activity and anti-convulsant, antioxidant, antimutagenic, anti-diabetic, anti-hyperplasia, and antimicrobial. The search was customized by applying the appropriate filter to get the most relevant articles to meet the objective of this review. **Conclusion:** It is known to exhibit a wide range of biological properties including anticancer, antimicrobial, and anti-diabetic, anticonvulsant, anti-inflammatory, and anti-viral, anti-tubercular activities. A large number of therapeutic agents are synthesized with the help of benzothiazole nucleus. During recent years there have been some interesting developments in the biological activities of benzothiazole derivatives. These compounds have special significance in the field of medicinal chemistry due to their remarkable pharmacological potentialities. This review is mainly an attempt to present the research work reported in the recent scientific literature on different biological activities of benzothiazole compounds.

Key words: Benzthiazole, Anticancer, anticonvulsant, anti-inflammatory, antimicrobial etc.

Hantzsch and Waber first described Thiazolein 1887 and its structure confirmed by Popp in 1889. In thiazole, moiety numbering starts from the sulfur atom. The basic structure of benzothiazole is the combination of a benzene ring fused with 4, 5 positions of thiazole. Benzothiazole is one of the most important aromatic heterocyclic compounds having a chemical formula C7H5NS.It plays a very important role in medicinal chemistry as well as in organic chemistry. Today`s most of the drug molecule contains a benzothiazole as an important scaffold and because of this scaffold, it has therapeutic activity. Benzothiazole and its derivatives have tremendous applications in synthetic chemistry as well as in pharmaceutical chemistry because of its unique structure, potent and significant pharmacological activities. Benzothiazole is a combination of two rings six-member mono atomic and five-member hetero atomic and both rings are responsible for the therapeutic activity.[1] (**Fig.1)**

Benzothiazole analogues have also been screened as potential therapeutical applications which include anti- viral, anti-microbial, anti-diabetic, anti-cancer, antiinflammatory, anti-oxidant, anti-fungal, anti-psychotic, anti-leishmanial etc [2]. Because of amyloid-binding property derivatives of 2-aryl benzothiazoles are screened for radioactive imaging moieties in neurodegenerative disorders [3, 4].

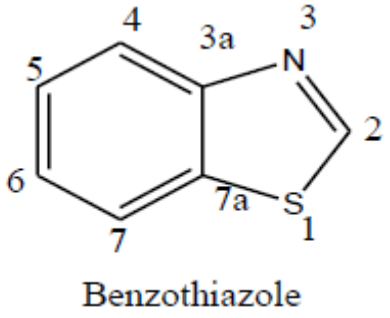

Fig.1 Structure of Benzothiazole

MATERIAL AND METHODS

A literature search was conducted on various database sources (like PubMed, Science Direct) with the help of a combination

of different keywords: Benzothiazole, thiazole, antitumor, anti-inflammatory activity, and anticonvulsant, anti-oxidant, anti-mutagenic, anti-diabetic, anti-hyperplasia, and anti-microbial. The search was customized by applying the appropriate filter to get the most relevant articles to meet the objective of this review

Synthetic and Biological Active Strategy of Benzothiazole Derivatives

Many researchers are using various methodologies. Benzothiazole derivative can be synthesized by using conventional, microwave method or by other green chemistry method. In this review article we are focusing on recent methods which are available for the synthesis of benzothiazole derivatives and their biological activities.

Hebishy synthesized a bis- and poly (benzimidazoles) and Benzothiazoles derivatives by using corresponding bis- and poly (aldehyde) with ophenylenediamine or 2-aminothiophenol, respectively, in ethanol at boiling temperature in presence of sodium hydrogen sulphate, further these synthesized derivatives were screened for anticancer activities against human breast adeno carcinoma cell line (MCF-7), liver cancer cell line (HepG-2), and epithelial colorectal adeno carcinoma cells (CaCO-2). But among all derivatives Hexakis (benzothiazole) showed a highest activity against HepG-2 cell lines with IC50 values of 21.16 and MCF-7 cell lines with IC50 values of 13.25 µM [5].

Racanéa et al., reported about a synthetic method for the synthesis of benzothiazole based derivative and most of the derivatives showed cytotoxic activity which performed using the MTT assay method. Compounds **2a, 2b, 2c,** and **2d (Fig. 2)** were then selected for examining their in vitro enzyme inhibitory activities against EGFR, HER2 and TS enzymes using lapatinib and 5FU as standards. Furthermore, cell cycle analysis and apoptosis induction detection were also evaluated [6].

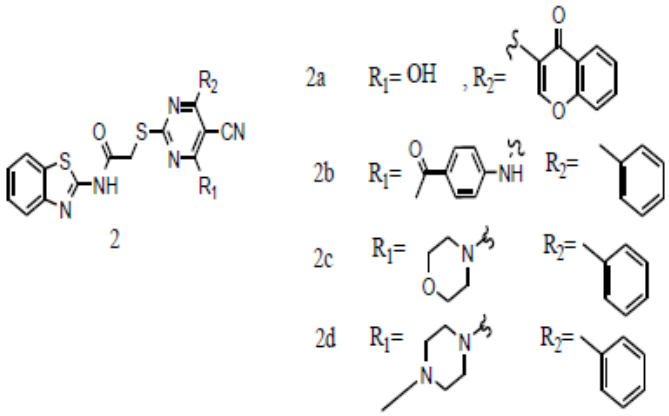

Fig.2 Compounds chosen for MTT assay

Asatkar et al., reported that the aqueous extracts of rice husk derived chemically activated carbon acts as a catalyzed for the synthesis of benzothiazole, benzoxazole and N-benzimidazole in room temperature by converting 2-aminothiophenol, 2amino phenol and ortho-phenylene di-amine with aromatic aldehydes with 98%yeild [7] (**Fig. 3)**

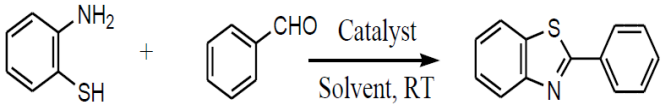

Fig. 3 Synthesis of benzothiazole, benzoxazole and N-benzimidazole from rice husk

A series of novel pyrido [2, 1-b] benzothiazole and pyrido [2, 1-b] benzoimidazole derivatives were synthesized by reacting with N-aryl-2-cyano-3,3-bis (methylthio) acrylamide with benzothiazole acetonitrile and benzoimidazole acetonitrile, respectively, while Nsubstituted 2-pyridyl-benzothiazole derivatives were synthesized by reacting 2- benzo [d] thiazol-2-yl) -3-(dimethylamino) acrylo nitrile with either cyanoacetamide, aryl cyanoacetamides or 2-cyano-N'- (4-substitutedbenzylidene) acetohydrazide (Azzam et al).

Furthermore, synthesized compound tested for fluorescence measurements, the compound N-substituted 2-pyridylbenzothiazole derivatives shows fluorescence properties with high quantum yields upto 0.29. The antimicrobial study of synthesized compound revealed that triazolo-pyridone had the highest potency among all tested compounds against Escherichia coli, Klebsiella pneumonia and Staphylococcus aureus while pyrido [2, 1-b] benzoimidazole derivatives 4a and 4b had the highest potency over other compounds against Candida albicans [8] (**Fig.4).**

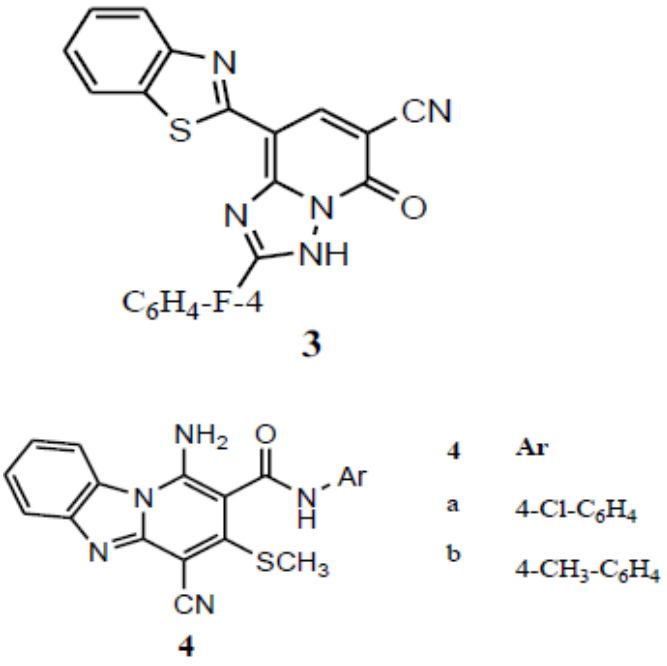

Fig.4 (3) triazolo-pyridone, (4) Benzoimidazole derivatives 4a and 4b with more efficacy against Candida albicans

Ermis et al described the synthesis of a series of thiophene-benzothiazole derivative amine compounds in good yields by

reduction of corresponding imine derivative which is obtain from aromatic aldehyde and 2aminobenzothiazole by microwave reaction. The characterizations of all compounds were performed by FTIR, 1H and 13C NMR and single crystal X-ray diffraction method [9] (**Fig.5**). Azzam et al. prepared a series of N-sulfonamide-2-pyridone derivatives which contains benzothiazole moiety via the reaction of benzothiazole sulfonyl hydrazide with sodium salts of both (hydroxymethylene) cycloalkanones and unsaturated ketones, as well as)

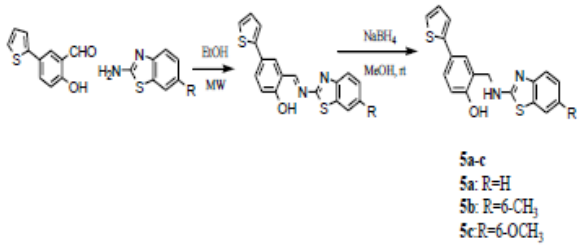

Fig. 5 Derivatives of thiophene-benzothiazole

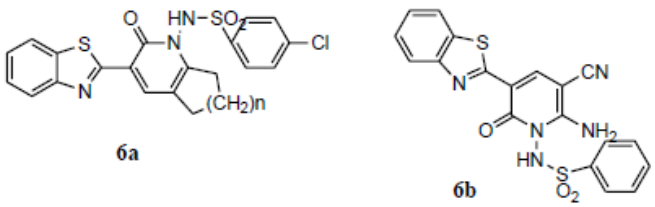

Fig. 6 N-sulfonamide-2-pyridone derivatives

Hethoxymethylene derivatives. The prepared compounds were screened for in vitro for their antiviral activities against the HSV-1, HAVHM175, HCVcc genotype 4, CBV4, and HAdV7 viruses. Among prepared compound, five compounds were found to possess viral reduction of 50% or more against CBV4 with significant IC50, CC50, and SI values. In the case of HSV-1 and HAV HM175 viruses, three compounds have shown more than 50% reduction, while in the case of HCVcc genotype 4 and HAdV7 viruses, only two compounds demonstrated more than 50% reduction. The two most potent compounds against HSV-1 virus, 6a and 6b, were evaluated for their inhibitory activity against USP7 [10] (**Fig. 6).**

A series of 2-pyrimidylbenzothiazoles derivatives containing amino or sulfonamide moieties at the C2 position of the pyrimidine ring were synthesized by Azzam et al. by subsequent reaction of guanidine or Naryl sulfonated guanidine with different derivatives of ylidene benzothiazole. The newly synthesized compounds were evaluated for their antiviral activity against HSV-1, COB4, HAV HM 175, ED-43/SG-Feo (VYG) replicon of HCV genotype 4a, and HAdV7. Nine derivatives were shows high cytotoxicity concentration and more than 50% viral reduction. Another five compounds against HSV-1 have been also evaluated against Hsp90α with their activities compared to that of the reference drug acyclovir. The five potent compounds 7a, 7b, 14b, 14g, and 14h against HSV-1 have also presented inhibitory activity against the Hsp90α protein with IC50 in the range of 4.87−10.47 µg/mL[11] (Fig.7).

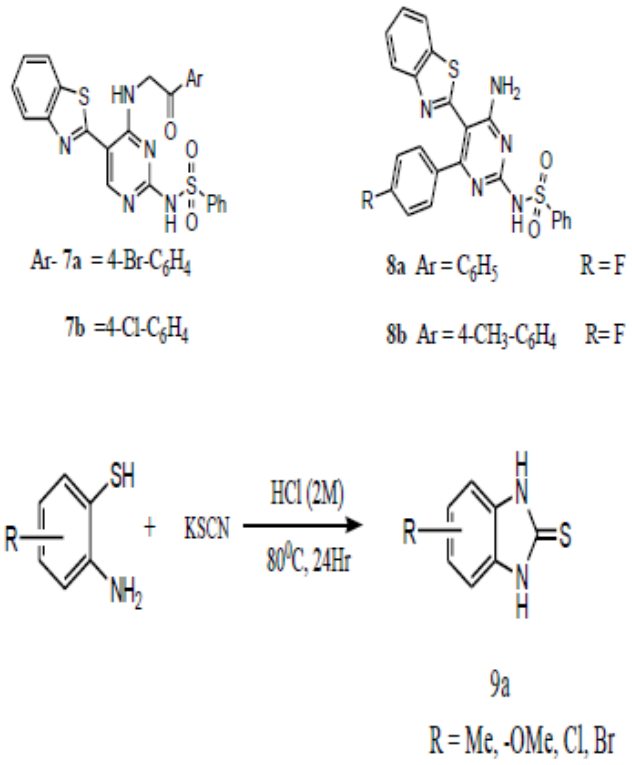

Fig. 7 Synthesis of 2-mercapto -benzazole derivatives

A green protocol given by Vessally et al. for the synthesis of 2-mercapto-benzazole derivatives 9a by using low-cost and nontoxic potassium thiocyanate in water. The reactions proceeded smoothly under catalyst- and ligandfree conditions to give the corresponding products in good to excellent yields [12] (**Fig.7**).

Abdelgawad et al. reported a synthesis of new series of benzothiazole/benzoxazole and/or benzoimidazole substituted pyrazole derivatives 10, 11 and 12 and it were evaluated for anti-proliferative agents. This work revealed that substituting pyrazole ring with an acetyl or phenyl moiety at N-2 of the pyrazo linone nucleus as shown in the target candidates 11 and 12 increased the anti-proliferative activity of these compounds comparing with unsubstituted derivatives 10. Moreover, 2-acetyl-4[(3-(1H-benzimidazol-yl) phenyl] hydrazono-5-methyl2,4-dihydropyrazol-3-one (11) was the most active compound against both MCF-7 and A549 cell lines with half maximal inhibitory concentrations (IC50) = 6.42 and 8.46 lM, respectively [13]

Almehmadi et al. synthesized a novel macromolecule encompassing benzothiazole- 1, 2, 3-triazole containing hydrazone. The synthesized compounds were evaluated for anticancer activities with A549 and H1299 lung cancer cell

lines. The anticancer activities ranged from 55 to 90%. DNA binding study was also carried out to see the mechanism of action and the DNA binding constants were of good value ranging from of 2.0 ×10 5 and 14.7 ×10 5 M −1; indicating good interactions of the reported molecules with DNA. It was observed that compound 13, 14, 15 and 16, 17 &18 were quite good active as anticancer drugs [14] (**Fig.9**)

Asgarshamsi et al. were performed a reaction between para hydroxyl benzaldehyde and amino benzothiazole derivatives. The synthesized derivative was further evaluated for scavenging activity. Various electronic and energetic descriptors such as high occupied molecular orbital and low unoccupied molecular orbital energy gaps, bonding dissociation enthalpy of OH bond, ionization potential, electron affinity, hardness, softness, and spin density of the radical and neutral species were calculated. FT calculations with B3LYP hybrid functional and 6-311++ G** basis set in the polarizable continuum model were utilized to obtain these descriptors. Ascorbic acid showed the best DPPH scavenging activity. But 19th band showed a promising anti-oxidant activity. The values of EHOMO for 19a and 19b were closer to zero, thus, they showed the best scavenging activities. Dadmal et al. reported the synthesis of a series of new triazole and isoxazole linked benzothiazole derivatives were synthesized. Anticancer evaluation against two different cell lines revealed that all these derivatives showed significant anticancer activity against HeLa and A549 cell lines.

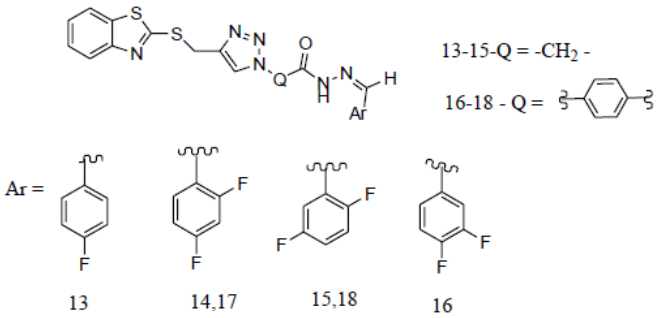

Fig. 8 Novel macromolecules encompassing benzothiazole

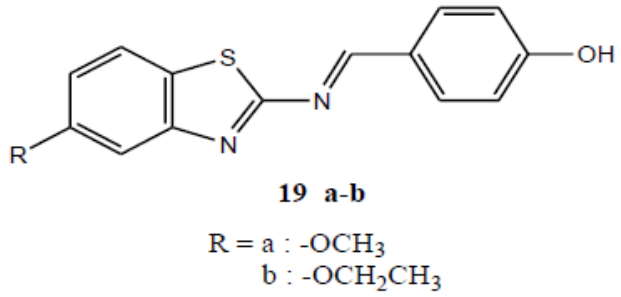

Fig. 9 Para hydroxyl benzaldehyde and amino benzothiazole derivative showing antoxidant activity

Reviewing these recent advances in benzothiazole derivative we will go for synthesis of some novel benzothiazole derivatives and synthesized compound will be evaluated for possible biological activities such as anti-fungal, anti-bacterial, anti-viral, anti-microbial, anti-diabetic, anticancer, anti-inflammatory, antioxidant etc.

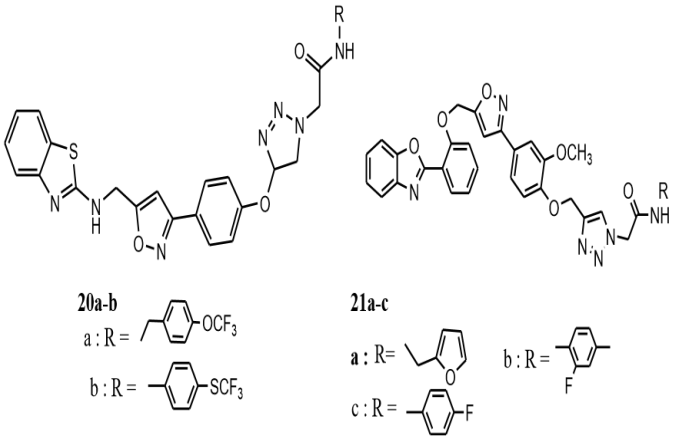

Fig. 10 New triazole and isoxazole linked benzothiazole derivatives

Highly effective compounds (20a-b and 21a-c) have shown less than 4.5 µM concentration in their IC50 values on human cervical (HeLa) and lung (A549) cancer cell line and these compounds inducing apoptosis to cancerous cells through caspase dependent apoptotic process via the mitochondrial pathway. From these study compounds 21a-chas identified as most promising compounds which show higher cytotoxicity in human cervical and lung cancer cell line than the other compounds and can be taken up for further in vivo cancer studies that may be of interest in cancer chemoprevention [16] (**Fig.10**).

CONCLUSION

The present review highlights the use of benzothiazole moiety as a template for development of newer therapeutic agents. Biological properties of the nucleus include anti-cancer, anti-diabetic, analgesic, anti-inflammatory and antimicrobial. With proper designing and structure activity relationship studies of known benzothiazole, prospective compounds can be designed and synthesized for a variety of biological activities. Benzothiazole scaffold is a versatile and multifunctional molecule which possess therapeutic effect in various disease like cancer, diabetes.

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