Review Article

Review on Benzothiazoles: Synthesis and Diverse Biological Activities

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Abstract

Benzothiazole is a class of heterocyclic compound having two hetero atoms namely sulphur and nitrogen. It is a two membered ring heterocyclic moiety, weak base. The analogues of benzothiazole and its derivatives have a significant role in research area especially in synthetic, medicinal and pharmaceutical chemistry because of its biological and pharmacological properties. So, in present the researchers are interested to work in this field.

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Introduction

From the literature survey it clearly knows that the Benzoheterocycles are very widely distributed in various terrestrial and marine compounds and are essential to life in various ways. Among the all Benzoheterocycles, benzothiazole has considerable biological activities including anti-inflammatory, antimicrobial [1-5], anticancer [6-8], anticonvulsant, antidiabetic [9], antitumor, antibiotic, antiviral, antidepressant, anthelmintic, antitubercular, analgesic, antifungal, and diuretic activities etc. Thiazole which is a five membered ring fused with benzene gives the benzothiazole moieties. It's a colorless and slightly viscous in nature with a boiling point of 227-228°C, the density and molar mass of benzothiazole is 1.644 gm/ml and 139.19 g/mol respectively. The numbering is starting from sulphur atom.

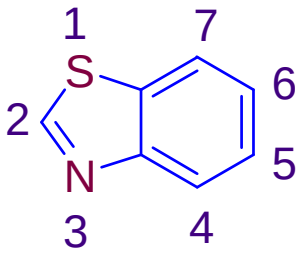


Fig. 1. Structure of Benzothiazole.

Some of the benzothiazoles like 2-aryl benzothiazoles were used as anticancer agents [10] and radioactive amyloid imaging agents [11]. In the 1950s different persons did cytotoxic studies by using new drugs which were designed with the combination of 2-aminobenzothiazole moieties with other heterocyclic moieties and it shows good pharmacological action, toxicity lowering and anticancer activity [12-13].

Higher amounts of substituted benzothiazoles were used in industries as vulcanization accelerators, for example in paper production the 2-Mercaptobenzothiazole used as corrosion inhibitor and are also added to antifreeze [14] and cooling liquids. In rubber industries the 2-morpholinothiobenzothiazole are added in amounts of up to 1% for rubber production [15] and the 2-thiocyanomethylthiobenzothiazole is used as a substitute for chlorophenols in wood preservation [16-18] and leather production [19].

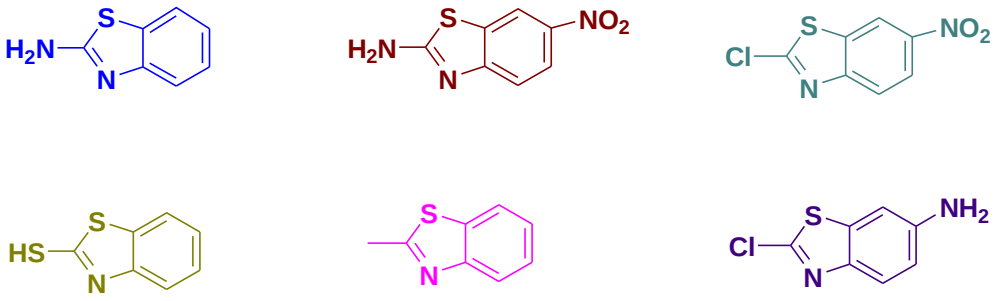


Fig. 2 Substituted benzothiazole.

Synthesis of various benzothiazoles and its derivatives

From isothiocyanates

Tweit et al., in 1970, reported the synthesis of 2-aminobenzothiazole (Fig.3) from isothiocyanates using benzene as a catalyst [20].

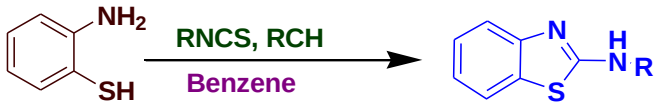


Fig. 3. Synthesis of 2-aminobenzothiazole.

From substituted aniline

Dogreur et al., in 1998, was successfully synthesized various 6-substituted-2-aminobenzothiazoles (fig.4) by the reaction of 4-substituted anilines with potassium thiocyanate in presence of bromine [21].

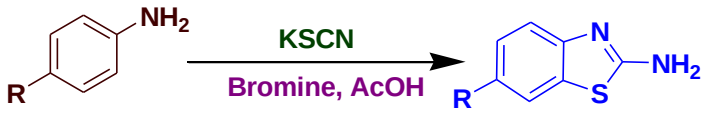


Fig.4: Synthesis of 6-substituted-2-aminobenzothiazole.

Intramolecular C-S bond formation by using Cu & Pd catalyst

Evindar et al., in 2003 successfully reported the synthesis of 2-aminobenzoyhiazoles (Fig.5) through intramolecular C-S bond formation by cross-coupling between aryl halide and thiourea in presence of copper and palladium-catalyzed medium [22].

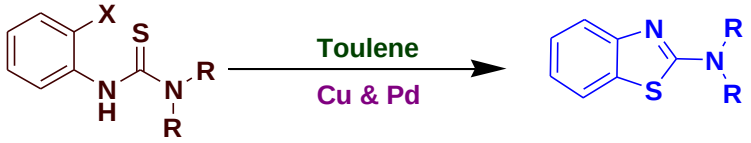


Fig. 5. Synthesis of 2-aminobenzothiazole from Intramolecular C-S bond formation.

One-pot synthesis of 2-aminobenzothiazoles

Jordan et al., in 2003, was directly synthesized 2-aminobenzothiazoles (fig.6) from substituted arylthioureas using Benzyltrimethylammonium tribromide as a catalyst, which is an electrophilic bromine source for the conversion of tetrabutylammonium thiocyanate, isothiocyanates and anilines into 2-aminobenzothiazoles under mild conditions in a variety of solvents with good yields and also the key benefits for $PhCH_2NMe_3Br_3$ when compared with molecular bromine in ease of addition and handling, which minimizes the risk of forming brominated side products [23].

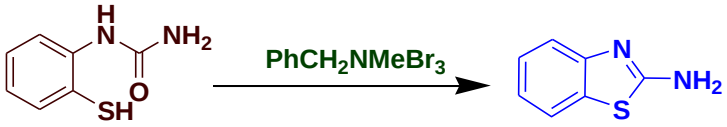


Fig. 6. One-pot synthesis of 2-aminobenzothiazoles

Synthesis of fused benzothiazoles

Dong et al., in 2002 reported the synthesis of 5-methyl-3- substituted-1,2,4-triazolo[3,4-b] benzothiazoles (Fig.7). For this he treated 2-hydrazino-4-methylbenzothiazole with various aromatic carbonic acids in presence of $POCl_3$ under reflux for half day. The reaction mixture war poured into crushed ice and the solution was basified with NaOH solution, the formed solids was filtered and recrystallized with ethanol to get expected one with good yield [24].

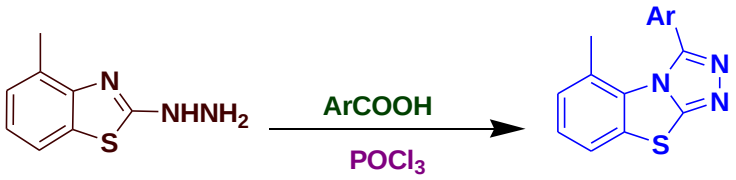


Fig. 7. Synthesis of 5-methyl-3- substituted-1,2,4-triazolo[3,4-b] benzothiazoles

Zaki et al., in 2003, successfully synthesized 1-amino-3H-pyrido[2,1-*b*]- [1,3]benzothiazole- 2,4-dicarbonitrile(a), 1-amino-4-cyano-3Hpyrido[2,1-*b*][1,3] benzothiazole-2-carboxamide(b), and1-amino-4-cyano-3Hpyrido[2,1-*b*][1,3] benzothiazole-2-carbothioamide(c) (Fig.8). These are synthesized by treating the equimolar amounts of formaldehyde, active methylene reagents and 2-cynomethylbenzothiazole in presence of strong base like triethylamine in ethanol [25].

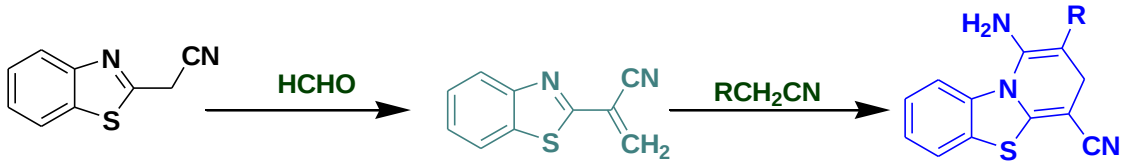


Fig. 8. Synthesis of pyrido benzothiazoles

Trapani et al., in 2001, reported a protocol for synthesis of substituted 2-ethoxycarbonylimidazo [2,1-*b*] benzothiazoles (Fig.9) derivatives using potassium thiocyanate and substituted aniline in presence of Br_2/ CH_3COOH and DMF having characteristic properties against cancer [26].

Biological aspects

Nowadays, health is one of the most important domains which we human beings have focused on in our society. Because of the presence of number of biological properties researchers are aimed to synthesize the benzothiazole nucleus contained products.

Anticancer activity

However, cancer is the biggest killer of lives in worldwide; millions of people were losing their lives due to cancer and is challenging issue to medical science and so there has been steadily focusing research in the field of anticancer therapy.

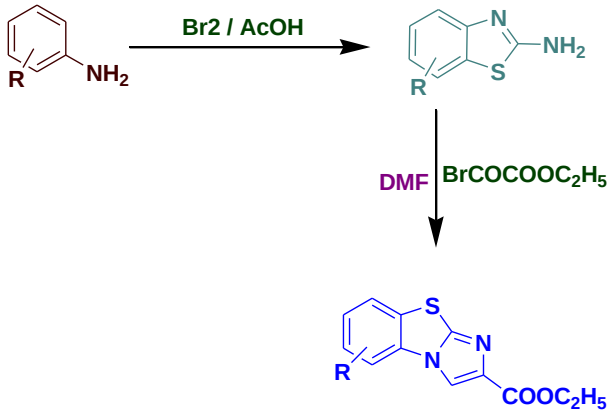
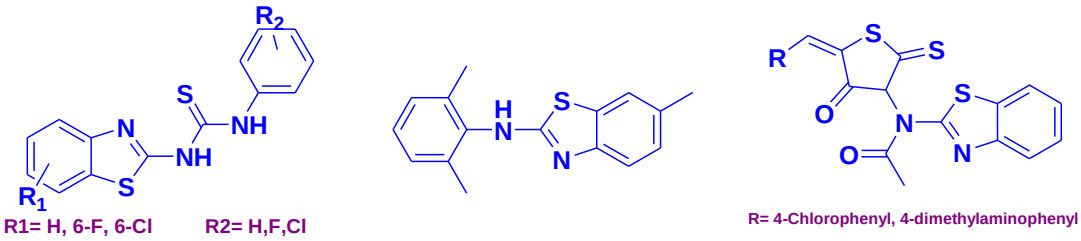


Fig. 9. Synthesis of substituted 2-ethoxycarbonylimidazo [2,1-*b*] benzothiazoles.

Kumbhare et al., in 2012, reported the synthesis of benzothiazolylthiocarbamides **(I)** from catalytic amounts of 4-dimethylaminopyridine followed by its chemo selective oxidative cyclization with 1,3-di-n-butylimidazoliumtribromide which afford the N-bis-benzothiazole derivatives. The synthesized compounds were tested against the two human monocytic cell lines and a mouse melanoma cell line and interestingly the all the compound shows more or less anticancer activity [27].

Havrylyuk et al., in 2010, prepared several novel 4-thiazoloidinones **(II)** using benzothiazole nucleus and performed the in vitro anticancer activity for all synthesized compounds by the help of National Center Institute. In his studies he noticed that two of the synthesized compounds having activity against the lung, ovarian, melanoma, Central nervous system, leukemia, prostate, breast and Colon cancers cell lines [28].

Malleshappa et al., 2012, has performed anticancer screening for 7-chloro-N-(2,6-dichlorophenyl)benzothiazol- 2-amine **(III)** it reveals that compound shows good results against Non-Small Cell Lung Cancer causing cell lines [29].



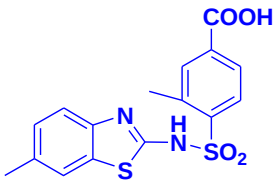
(I) **(II)** **(III)**

Antimicrobial activity

Nowadays one of the most challenging aspects for pharmacist and chemist is to discover the novel and potent antimicrobial drugs. Because microbes are the main causative agents for various types of diseases like tuberculosis, ameobiasis, syphilis, common cough and cold, pneumonia, AIDS, typhoid and influenza etc. Researchers were made number of trails to check the role of benzothiazole nucleus as antimicrobial agent.

Hutchinson I et al., in 2001, successfully made an attempt to prepare 2-(substituted phenylsulfonamido-6-substituted benzothiazoles **(IV)** and screened them for their anti bacterial activity and found to possess good antibacterial activity against *B.subtilis, S.dysentery* and *S.typhi* [30].

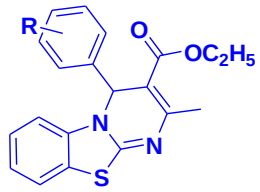
Sahu et al., in 2012, the 4H-pyrimido [2,1-b][1,3]benzothiazole derivatives **(V)** prepared and screened for their antibacterial activities against gram-positive and gram-negative bacteria, viz., *P.aeruginosa*, *B.cereus*, *S.typhi, S.aureus, P.rettegeri* and *E. coli* [31].



R=Cl,Br,CH3, OCH3

R1= I, CH3, NH2

(**4**)



R= phenyl, 4-hydroxyphenyl, 4-methoxyphenyl

(**5**)

Other than anticancer and antimicrobial activities, benzothiazole nucleus is also found to possess other biological properties such as antidiabetic, anti-inflammatory, anthelmintic, antiviral, anthelmintic, antileishmanial, antioxidant, antiviral and Cyclooxygenase inhibitor activity etc**.**

Conclusion

This review highlights the wide spectrum of biological activities of benzothiazole nucleus includes antimicrobial and anticancer etc., with proper design and also synthesis, structure activity relationship studies of known benzothiazole moieties.

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