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Review Article

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Benzothiazole: Unique and versatile scaffold in the field of cancer

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ABSTRACT

Benzoheterocycles such as benzothiazoles can serve as unique and versatile scaffolds for experimental drug design. Among the all benzoheterocycles, benzothiazole has considerable place in research area especially in synthetic as well as in pharmaceutical chemistry because of its potent and significant pharmacological activities. Cancer is a disease characterized by uncontrollable, irreversible, independent, autonomous, uncoordinated and relatively unlimited and abnormal over growth of tissues. The drugs containing benzothiazole groups were the first effective chemotherapeutic agents which were systematically proved for the prevention and cure of bacterial infection in human beings. Literature revealed that benzothiazole derivatives may serve as an important model on as potent anti-cancer agent. When one biological active molecule is linked to another, resultant molecule generally has increased potency. Most of the derivatives showed enhanced anti-cancer activity. So, benzothiazole derivatives can serve as future therapeutic leads for the discovery of anti-cancer drugs. This review was focused on the benzothiazole and its different derivatives that posses different biological activities.

Keywords: Benzothiazole, Cancer, Cytotoxic Activity, Antiproliferative Activity.

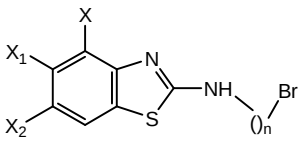
INTRODUCTION

A heterocyclic compound is one which possesses a cyclic structure with at least two different kinds of hetero atoms in the ring. Heterocyclic compounds are very widely distributed in nature and are essential to life in various ways. The chemistry and biological study of heterocyclic compounds has been an interesting field for a long time in medicinal chemistry. A number of heterocyclic derivatives containing nitrogen and sulphur atom serve as a unique and versatile scaffolds for experimental drug design.

Benzothiazole is one of the most important heterocyclic compound, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery.

Benzothiazole possess interesting biological activities like anti-tumor [1], anti-microbial [2], anti-tubercular [3], anti-convulsant [4], anthelmintic [5], anti-oxidant [6], analgesic [7], anti-inflammatory [8], antifungal [9], antileishmanial [10], antipsychotic [11], anti-ulcer [12], local anesthetic[13], schistosomicidal [14] and diuretic [15] activities.
In the 1950s, a number of Benzothiazole derivatives were intensively studied, as the benzothiazole scaffold is one of privileged structure in medicinal chemistry and reported cytotoxic on cancer cells.

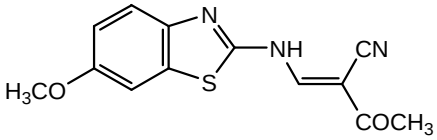
Anticancer activity of benzothiazole derivatives:
Rupinder Kaur Gill and Dr. P. M. S. Bedi, Synthesized 2-aminobenzothiazole derivatives and evaluate *in vitro* cytotoxic activity against four different human cancer cell lines namely Lung: A-549, Prostate: PC-3, Leukemia: THP-1 and Colon: Caco-2 at 10, 50 and 100 μM concentrations [16].



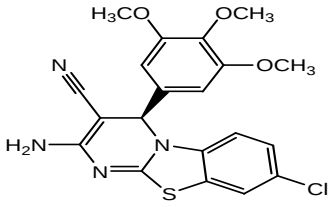
$X_2 = OCH_3$, X = X_1 = H, n = 3

X_2 = F, X = X_1 = H, n = 3 and X = Cl, X_1 = X_2 = H, n = 3)

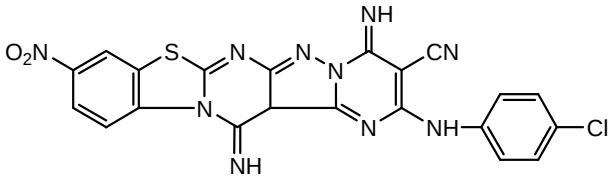
A. Repicky et al, examined the cytotoxic / antiproliferative effect of 2-acetyl-3-(6-methoxybenzothiazo)-2-ylamino-acrylonitril and induction of apoptosis on murine leukemia L1210 cells [17].



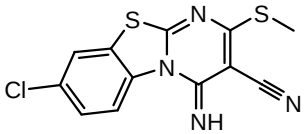
Deshmukh Vinayak K et al, synthesized Microwave Assisted Substituted Pyrimido [2,1-*b*] [1,3] benzothiazole Derivatives, the results showed that a change in the substitution pattern in pyrimido[2,1-*b*][1,3]benzothiazole derivatives may cause a marked effect on their anticancer activity[18].



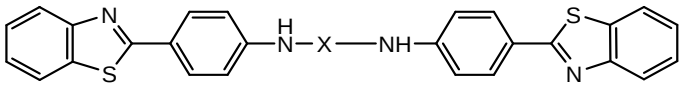
Anil B. Chidrawar et al, Synthesized the novel 3-Cyano-4,14-Diimino-2-Methylthio-10-Nitropyrimido[2,3-b] Pyrazolo[3,4-e] Pyrimido [2,3-b][1,3]Benzothiazole and Its 2-Substituted Derivatives. All these newly synthesized compounds were screened for anticancer activity. Exhibits remarkable anticancer activity against CCRF-CEM (Leukemia) and other cell lines NCI-H522(Non-Small Cell Lung Cancer), SK-MEL-5 (Melanoma cancer), OVCAR-3 (Ovarian Cancer), UO-31(Renal Cancer), MCF7 (Breast Cancer) [19].



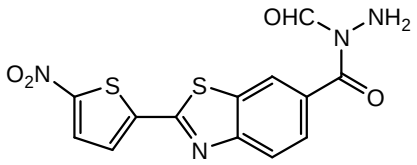
Leena B. Labhsetwar, Giridhar R. Shendarkar, Sharad V. Kuberkar, 8-chloro-3-cyano-4-imino-2-methylthio-4h-pyrimido [2, 1-*b*] [1, 3] benzothiazole and its 2-substituted derivatives and evaluated at National Cancer Institute, Maryland, USA for their *in vitro* anticancer activity towards 60 Human Cancer cell lines, Results revealed that all these compounds displayed remarkable anticancer action across human cancer cell lines [20].



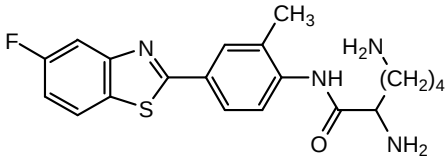
A series of benzothiazole derivatives were synthesized and evaluated for *in vitro* cytotoxic activity against HL-60 and U-937 cell lines and antimicrobial activity against bacterial and fungal strains by Sayan Dutta Gupta et al. The biological evaluation result shows that the dimer exhibits better activity against cancer cell lines [21].



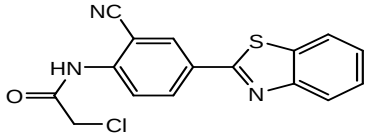
Juan R. Rodrigues et al, studied the Cytotoxic Effects of *N*'-Formyl-2-(5-nitrothiophen-2-yl) benzothiazole-6-carbohydrazide in Human Breast Tumor Cells by Induction of Oxidative Stress [22].



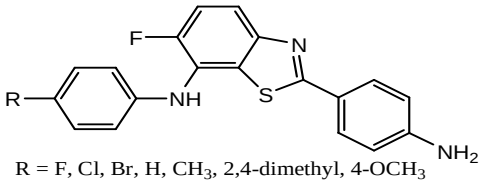
Valentina Trapani et al, synthesized Fluorinated 2-(4-amino-3-methylphenyl) benzothiazoles and they found to possess potent antiproliferative activity against certain cancer cells, similar to the unfluorinated 2-(4-amino-3-methylphenyl)benzothiazole (DF 203,NSC 674495) [23].



A series of benzothiazole and benzoxazole derivatives were synthesized by John N. Philoppes *et al.* Some of the newly formed compounds were evaluated, *in vitro*, for their antitumor activity against MCF-7 [24].

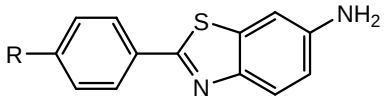


Girish Bolakatti et al, Synthesized 2-(4-Aminophenyl)-6-fluoro-N-(substituted phenyl) benzo[d]thiazol-7-amine Derivatives. These newly synthesized compounds were screened for *in vitro* cytotoxicity against mouse Ehrlich Ascites Carcinoma (EAC) and two human cancer cell lines (MCF-7 and HeLa) [25].



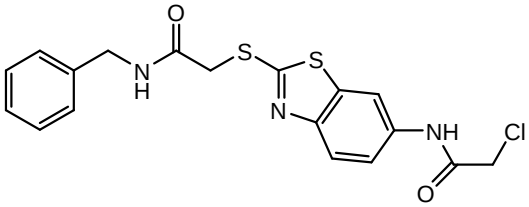
R = F, Cl, Br, H, CH_3, 2,4-dimethyl, 4-OCH_3

Grace Karminski-Zamola et al, synthesized water soluble hydrochloride salts of 6-amino-2-(substituted-phenyl)benzothiazole, and found to exert cytostatic activities against malignant human cell lines: cervical (HeLa), breast (MCF-7), colon (CaCo-2), laryngeal carcinoma (Hep-2), and normal human fibroblast cell lines (WI-38) [26].

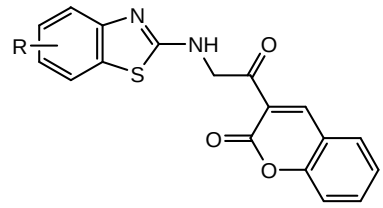


R = amino, dimethylamino or fluoro

X Peng *et al*, developed some new benzothiazole-2-thiol derivatives via computer-aided drug design and de novo synthesis. MTT assay showed it had potent anti-proliferative activity on various human cancer cells [27].

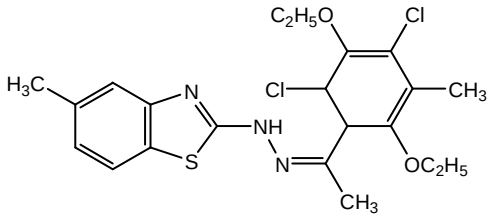


Bolakatti *et al*, Synthesized and studied the pharmacological evaluation of novel series of Benzothiazolyl-coumarin conjugates as anti-inflammatory and anticancer agents [28].

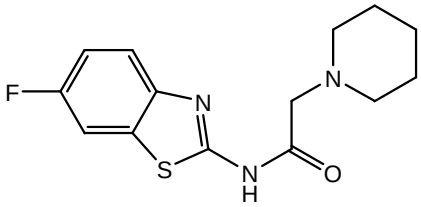


R = 6F, 6Cl, 6Br, 6NO2, 6H, 6,7 dichloro, 6-F-7-Cl

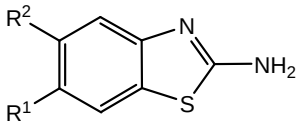
Gaurav Alang *et al,* carried out Antifungal activity of Certain (E)-1-(1-(substitutedphenyl) ethylidene) - 2 - (6-methylbenzo[d]thiazol-2-yl) hydrazine analogues against four fungal strains *Candida albicans (MTCC 183), Aspergillus niger (MTCC 228), Candida tropicalis (MTCC 6192), and Fusarium oxysporium (MTCC 3656)* and justifies the therapeutic application of the benzothiazole moiety in the present era [29].



S. Baluja *et al,* studied the Antifungal activity of Fluoro Substituted Benzothiazole Derivatives and found all the synthesized compounds exhibited inhibition against fungal strain *A. niger* and morpholine substituent is most effective [30].

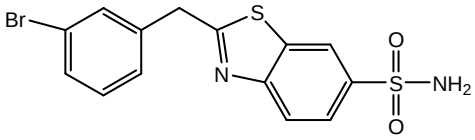


M. Himaja et al, studied the discovery of Anthelmintic activity of 2-Amino-6-substituted Benzothiazoles [31].

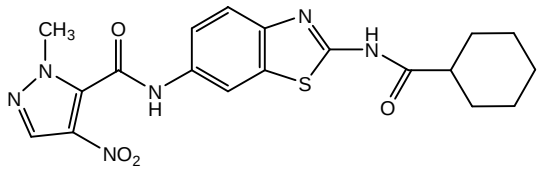


R^1 = Cl, Br, NO_2, CH_3, C_2H_5, OCH_3, OC_2H_5
R^2 = H, H, H, H, H, H, H, CH_3

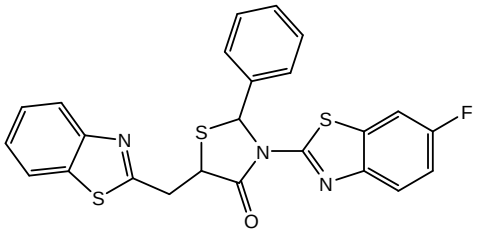
Reena Mahtab *et al,* Synthesized the novel 2-benzylbenzo[d] thiazole-6-sulfonamide derivatives. These compounds were screened for anti-inflammatory activity by carrageenan induced paw oedema method in rats at a dose of 100 mg/kg body weight. All the newly synthesized benzothiazole derivatives have shown considerable anti-inflammatory activity [32].



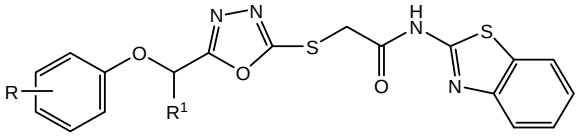
Shailja Sachan *et al,* studied the Structure-Based Optimization of Benzothiazole Derivatives as Potent Anticancer Agents and observed the QSAR of a series of benzothiazole derivative showing a potent and selective cytotoxicity against tumorigenic cell line has been studied by regression analysis which is done firstly with topological indices, later inhibitory activity is correlated with physico-chemical properties [33].



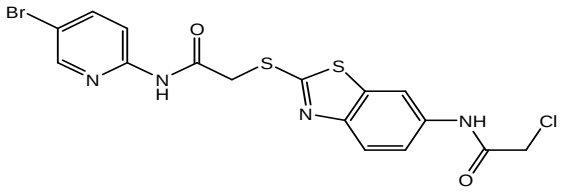
Sekar V *et al*, Synthesized some of the novel bis-benzothiazole derivatives, All the compounds synthesized were screened for *in-vitro* anticancer activity against HeLa (Human Epithelial cervix cancer cell line) cell lines by MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrasolium bromide] assay method along with control. All the newly synthesized compounds were screened for anticancer activity at a concentration of 100, 10, 1, and 0.1µM. All compounds showed good anticancer activity against HeLa cell lines [34].



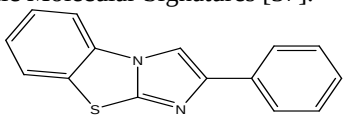
T. Akhtar *et al.*: A series of new benzothiazole derivatives have been synthesized, in five steps, from substituted phenols *via* the 1,3,4-oxadiazole-2-thiones The *in vitro* antitumor activity of the compounds obtained was investigated and the benzothiazol derivatives 6d and 6e showed strong effects on leukaemia cell lines CCRF-CEM (*CC*50 =12±2 µmol L^{-1}, 8±1 µmol L^{-1}, respectively). The title compounds were tested against representatives of several virus families containing single stranded RNA genomes, either positive-sense (ssRNA+), or negative- sense (RNA-), and against double-stranded RNA genomes (dsRNA), as well as some *Flaviviridae* viruses [35].



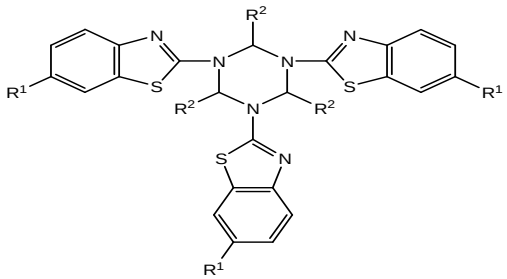
Luo-Ting Yu *et al.* synthesized a series of novel benzothiazole-2-thiol derivatives, and they were evaluated for anticancer activity. Among them, pyridinyl-2-amine linked benzothiazole-2-thiol compounds 7d, 7e, 7f and 7i exhibited potent and broad-spectrum inhibitory activities. Compound 7e displayed the most potent anticancer activity on SKRB-3 (IC50 = 1.2 nM), SW620 (IC50 = 4.3 nM), A549 (IC50 = 44 nM) and HepG2 (IC50 = 48 nM) and was found to induce apoptosis in HepG2 cancer cells [36].



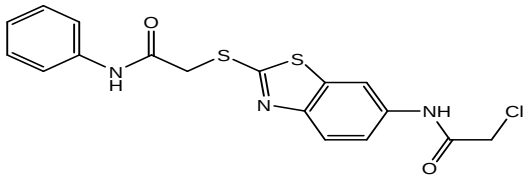
Flavio Maina *et al*, carried out the Combined Drug Action of 2-Phenylimidazo[2,1-b]Benzothiazole Derivatives on Cancer Cells According to Their Oncogenic Molecular Signatures [37].



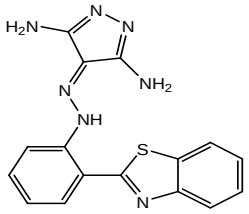
Kishan G. Ojha *et al*, carried out the Rapid synthesis of some medicinally important hexahydrostriazine derivatives incorporating benzothiazole and Anti-proliferative activity was carried out by MTT assay method against Human hepatoma cell line (hepatic cancer) and Human breast adino carcinoma cell line (breast cancer) and observed the marked Anti-proliferative activity [38].



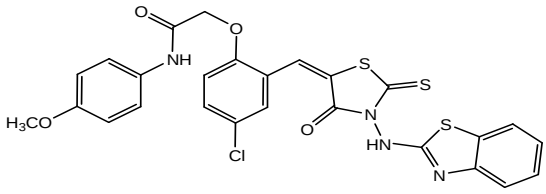
X Peng *et al,* novel benzothiazole-2-thiol derivative, was developed via computer-aided drug design and de novo synthesis. MTT assay showed it had potent anti-proliferative activity on various human cancer cells [39].



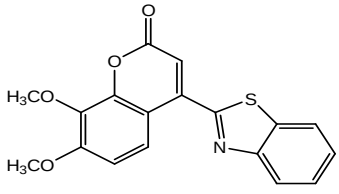
Khaled RA Abdellatif *et al,* carried out the Design and Synthesis of Novel Pyrazole Derivatives Linking to Benzimidazole, Benzoxazole and Benzothiazole and found the anti-tumor cytotoxicity [40].



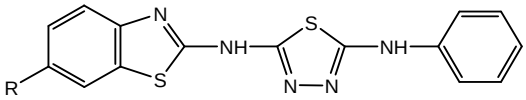
Roman Lesyk *et al,* Synthesized the novel 2-thioxo-4-thiazolidinones with benzothiazole moieties, which were tested for *in vitro* anticancer activity in the National Cancer Institute. Synthesized compounds displayed antitumor activity on renal cancer, non-small cell lung cancer, and ovarian cancer cell lines [41].



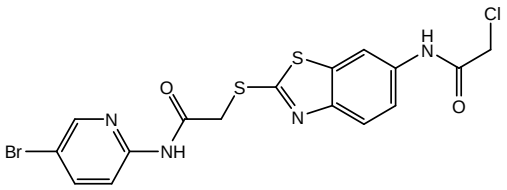
Suvarna G. Kini *et al,* a series of Coumarin substituted benzothiazoles were synthesized by refluxing Coumarin-4-carboxaldehyde and o-aminothiophenol in acetic acid. All the compounds were tested for their anticancer activity against MCF-7 breast cancer cell line with MTT assay. Most of the compounds showed moderate to good anti-breast cancer activity [42].



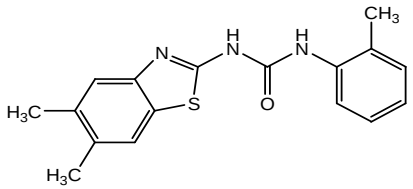
V. Sekar *et al,* worked on the Screening of anticancer activity in newly synthesized benzothiazole derivatives. The compounds were found to exhibit anti cancer activity in cell line. Among the synthesized six compounds, S2 showed significant activity in cell line [43].



A series of novel benzothiazole-2-thiol derivatives were synthesized by Luo-Ting Yu *et al,* they displayed potent and broad-spectrum anti-proliferative activities against other human cancer cell lines [44].



A series of amide and urea derivatives of benzothiazole have been synthesized and evaluated for their antiproliferative profile in human SK-Hep-1 (liver), MDA-MB-231 (breast), and NUGC-3 (gastric) cell lines by Kyeong Lee *et al.* Among them, compounds 1e2, 16e18, 23, and 25e26 had potent to moderate anti-proliferative activities [45].



CONCLUSION

Benzothiazole exhibits a wide range of biological properties due to its potent biological activities. It is a versatile tool in the field of cancer amongst all activities. It produces anticancer activities not only by interacting with heterocyclic ring but also through various inorganic complexes. It can be concluded that this class of compounds certainly holds great promise towards good active leads in medicinal chemistry. A further study to acquire more information concerning pharmacological activity is in progress. The biological profiles of these new generations of benzothiazoles represent much progress with regard to the older compounds. Hence this unique molecule must act like a boon in the field of developing various synthetic anticancer agents.

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