The Substituted Benzothiazole derivatives as promising Antineoplastic Agent: A Review

[1]Zinat I. Mulla, [2]Azad N. Dhage, [3]Rita D. Chakole & [4]Manoj S. Charde.

[1]Research student, [2]Assistant professor, [1]Associate professor, [1]Assistant professor.

[1]Department of Pharmaceutical Chemistry,
Government College of Pharmacy, Vidyanagar, Karad, Dist: Satara,
Pin – 415124, Maharashtra

[2]Ashokrao Mane Institute of Pharmaceutical Science and Research,
Save Tal-Shahuwadi, Dist-Kolhapur-416213

***Abstract*: Benzothiazole is heterocyclic class of bicyclic compound containing mercapto group play an important role in synthetic chemistry due to their wide range of biological and pharmacological activities. Derivatives possesses wild range of biological properties including anticancer, antimicrobial, and antidiabetic, anticonvulsant, anti-inflammatory, antiviral, antitubercularactivities. Due to wide range of pharmacological activity benzothiazole are prominent in medicinal chemistry. In this review study on literature survey over the last decade discloses the role various benzothiazole derivatives mainly as anticancer agents. Such benzothiazole derivative activity against various types of cancer cell lines compare with standard drug available in market.**

***Keywords*: Benzothiazole, Anti-neoplastic, Cancer cell line, pharmacological activities.**

INTRODUCTION:

Heterocyclic compounds have become popular in medicine chemistry research probably because of their crucial and diversity biological functions. Examples include benzothiazole derivatives and its isosteres benzoxazole and benzimidazole derivatives with recorded antitumor. [1] Benzothiazoles arean important class of heterocycles, which can serve as unique and versatile scaffolds for experimental drug design. [2] Benzothiazole and its derivatives (especially 2-aryl benzothiazoles) are radioactive imaging neurodegenerative disorders due to their amyloid binding property. Their comprehensive listof properties associated with nature and the positions of different substitution. Various review include derivative substituted at 2nd, 4th, 5th & 6th position is very important to obtaining effective activity against cancer. [3] The Benzothiazole scaffold possesses a wide spectrum of pharmacological activities such as anti-inflammatory [4], fungicidal [5], anti-diabetic [6], analgesic [7], anti-microbial [8], antitumor [9], antileishmanial [10], anthelmintic [11] and CNS depressant [12] etc.

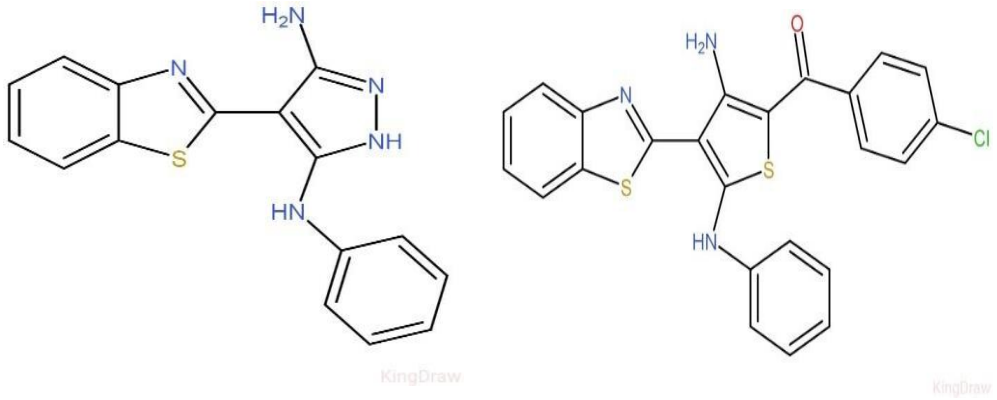
Benzothiazole derivatives exhibit remarkable and prevalent biological and pharmacological activitiesagainst different types of tumors and cancer cell lines such as HeLa (human cervical cancer cell line), SW480 (human colon adenocarcinoma cell line), HepG2 (human liver carcinoma cells)16, mammary and ovarian tumor cell lines17, colon, non-small -cell lung and breast subpanels cell lines18, and HCC (hepatocellular carcinoma)19 etc.[13] Healthy cell are under strict biochemical control for growth and differentiation .In cancer these cell not able to adequately differentiate because of cycle of growth and division get disturb, divide uncontrollably, consuming energy and losing both structure and function .More deaths occur worldwide as a result of infectious diseases One of the world's most dangerous diseases is cancer and despite all medical advances, cancer remains the second leading cause of death in both developing and developed countries. [14]

Although surgical resection may be curative, the risk of recurrence remains very high. In addition to surgical resection, treatment strategies for high-risk patients are still largely based on the use of adjuvant or neoadjuvant of chemotherapeutic agents single or in combination with radiotherapy. Unfortunately, the use of these standard therapies only results in a significant reduction in mortality and the risk of recurrence of the disease remains high. Therefore, it is urgent to develop chemotherapeutic agents fornovel cancer treatment. In a recent lead generation study of an anti-cancer agent. [15]

BENZOTHIAZOLE DERIVATIVES AS AN ANTINEOPLASTIC AGENT:

1.1: Heterocyclic based benzothiazole derivatives as an antineoplastic agent

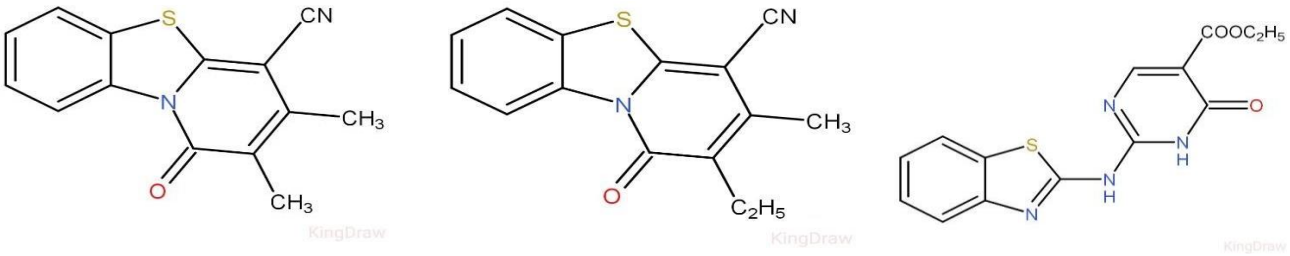
Aisha Y. Hassan et. al. synthesized different heterocyclic substituted derivatives of benzothiazole are prepared by different chemical reactions. Thirteen newly synthesized compound were selected by theNational Cancer Institute, Bethesda, Maryland, USA, and tested for in vitro antitumor activity against 60 tumor cell lines in a one dose screening panel out of 60 two compounds 1 and 2 most potent and was selected for further testing in a five-dose full panel assay, where compound 1 exhibit potent inhibiting growth against all cell line via GI50 from 0.683up to 4.66 µM / L over excellent lethal activity against multiple cell lines.[16]



1. **2.**

Figure 1: Heterocycle fused with benzothiazole as an anti-neoplastic agent

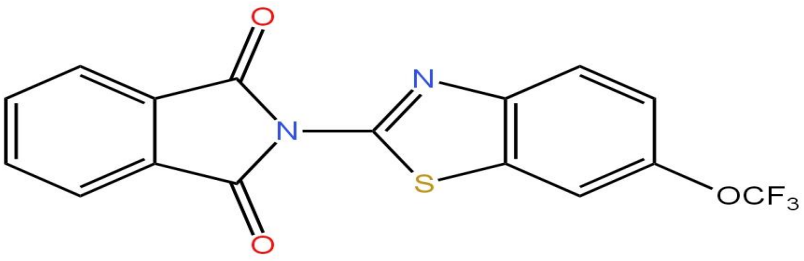
Amal M. Youssef et. al. reported synthesis of novel series of pyrido[2,1-b] benzo[d]thiazole and 2-(benzo [d]thiazol-2-ylamino)pyrimidine derivatives was synthesized. The synthesized compoundswere evaluated for their anticancer activity. while compounds 3 and 4 induced high cytotoxic action with IC50 values of 50.15 µg/ml and 50.45 µg/ml, respective l Compounds 3, 4, showed more cytotoxic effects than the control drug doxorubicin (IC50 52). Compound 5 was the most potent cytotoxic, with IC50 42.55 µg/ml, while compounds 3a and 3b induced high cytotoxicaction with IC50 50.15 and 50.45, respectively. [17]



3. **4.** **5.**

Figure 2: Pyrimidine based benzothiazole derivatives

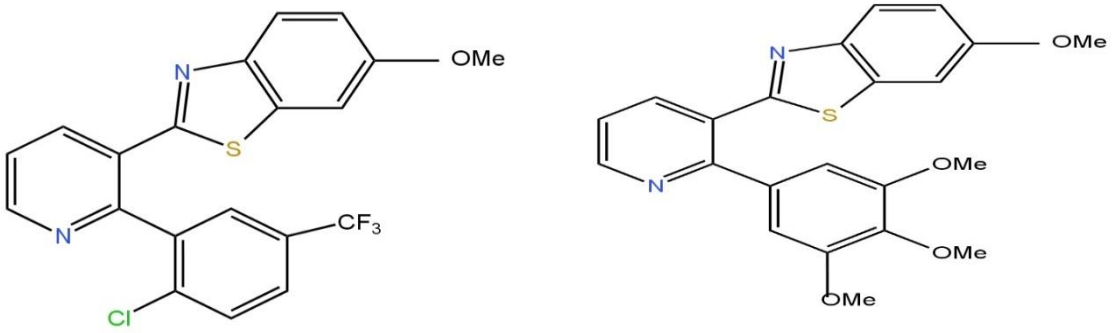
Stanton Hon Lung Kok et. al. synthesized benzothiazole containing phthalimide anticancer compound which shows potent cytotoxic activity towards three human cancer cell lines tested such as Human Burkitt's lymphoma cell line (B cell type) CA46, chronic myelogenous leukemia (CML) K562 and hepatoma cell line SKHep1 were used for preliminary anti-cancer screening of the novel synthesized compound. Synthesized compound also shows anti-microbial activity including inhibition of Beta-lactamase. Study involve Caspase-dependent and -independent pathways are involved in benzothiazole containing phthalimide induced apoptosis on human cancer cells.[18]



6.

Figure 3: Phthalimide based benzothiazole derivatives

Kamal et. al. reported on a new series of benzothiazole-pyrrole-based conjugates for their cytotoxic efficacy against the MCF-7 cell line. MCF-7 cells behaved well to the apoptosis-inducing effects of compounds7 and 8. Compound7 shows carcinogenic expression of Ras and its downstream effector molecules, including MEK1, ERK1/2, p38MAPK, and VEGF. [19]

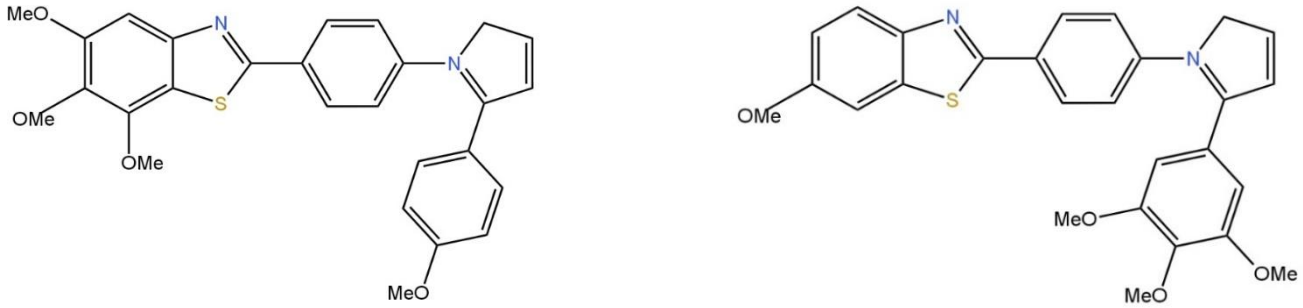


7. **8.**

Figure 4: Pyrrole based benzothiazole derivatives

1.2 Phenyl substituted based benzothiazole derivatives as an antineoplasticagent:

Ashraf et. al. developed and produced a series of colchicine site binding tubulin inhibitors. By modifying the combretastatin A-4 (CA4) pharmacophore utilizing benzothiazole scaffolds. These substances were tested for their ability to inhibit the proliferation of particular cancer cell lines. The two most effective compounds 9 and 10 showed an antiproliferative activity against HeLa cells(human cervical cancer cell line) that was comparable to and superior to that of CA4 (GI50 = 0.06 0.001 M and 0.04 0.001 M, respectively) . According to molecular docking experiments, these drugs attach to the tubulin colchicine site similarly to combretastatin A-4. SAR indicate methoxy group on the benzothiazole moiety at C-6 position was found to be crucial for the antiproliferative effect. [20]



9. **10.**

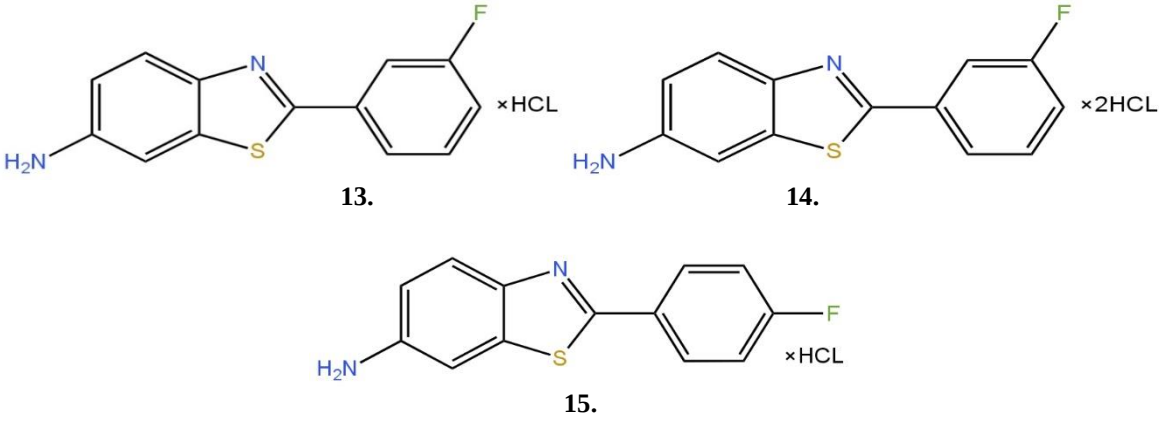
Figure 5: Phenyl substituted pyrrole based benzothiazole derivatives

Leyla Yurtta et. al. synthesized Twenty-five new N-[4-(benzothiazole-2-yl) phenyl] acetamide derivatives. All synthesized compound screened for their cytotoxic activity in vitro against 60 human tumor cell line. Out off twenty-five compound 11, namely N-[4-(benzothiazole2-yl)-3-chlorophenyl]-2-[(benzimidazole-2-yl)thio]acetamide and compound 12, namely N-[4- (benzothiazole-2-yl) phenyl]-2-[(1,5-diphenyl-1H-imidazole-2-yl)thio]acetamide, it shows potent anticancer activity against some cancer cell lines. Those selected for NCI's in vitro disease-oriented human tumor cell lines for compounds 11 and 12 on nine cancer disease at five concentrations gives mean log10 GI50 Values from which activity of compound higher than melphalan and lower than cisplatin. [21]

11. **12.**

Figure 6: Phenyl substituted acetamide linkage benzothiazole derivatives

Livio Racane et. al. reported synthesis of hydrochloride salts of 6-amino-2-phenylbenzothiazole bearing different substituents (amino, diethylamino or fluoro) on the phenyl ring. compound 13 -19exert cytostatic activities [Inhibitory effect] against various cell line malignant human cell lines: cervical (HeLa), breast (MCF-7), colon (CaCo-2), laryngeal carcinoma (Hep-2), and normal human fibroblast cell lines (WI38) against. All derivatives show moderate antitumor activity with IC_{50} values ranging from 9×10-6 to 4×10-3 M. from result it is concluded that activity order from ortho- meta- to para- position get decreased. Fluoro substituted derivatives 13, 14, 15 being more active. [22]

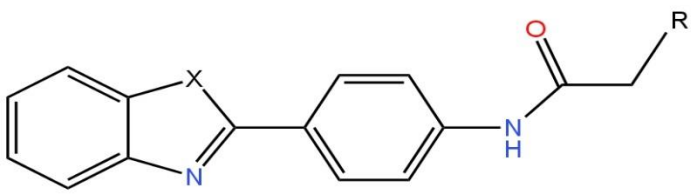


13. **14.**

15.

Figure 7: Phenyl substituted fluoro based benzothiazole derivatives

Mohamed A. Abdelgawad et. al. synthesized derivatives of benzothiazoles and benzoxazoles Preparedcompounds were evaluated for their antitumor activities against human breast cancer cell lines, MCF-7 and MDA-231 231, using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cellviability analysis. Result indicates that all tested compounds having potent antitumor activity, especially the N-methyl piperazinyl substituted derivative 16 and 17, which displayed the most potent inhibitory activity with IC50 values ranging from 8 to 17 nM. Docking study of all synthesized compound performed s into the epidermal growth factor receptor (EGFR), which is highly expressed in breast cancer.to gives an idea related to all possible interaction with EGFR. [23]

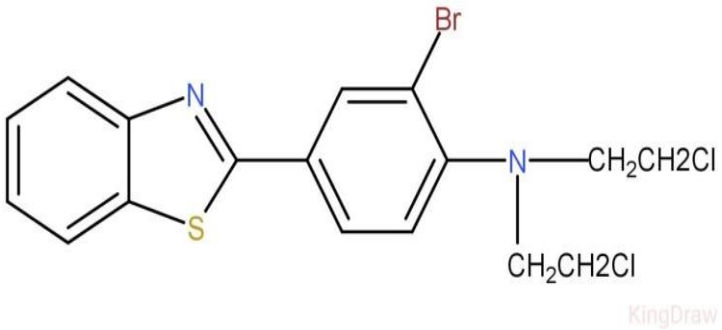


16: X=O,R=methylpiperazin
17: X=S,R=methylpiperazin

Figure 8: Phenyl substituted benzothiazole

Suvarna kini et. al. synthesis derivatives of 2-arylsubstituted benzothiazole, those compounds were confirmed by physical and

spectral data such as MP, Rf, IR, NMR. Compound SBCF, SBNCB, SBSNH (18) were found to be potent cytotoxic activity compared to the other derivatives selected forin vivo study using Swiss mice. Screening for antitumor activity included measuring EAC cell mortality with the Tryphan blue exclusion assay**.** Compound 18 showed good activity on cell growthinhibition of cervical cancer cell lines. comparison with standard cisplatin, SBSNH and SBCF showed moderate cytotoxicity Were SBNCB showed good activity, other show poor activity. [24]



18.

Figure 9: Phenyl substituted benzothiazole derivatives

CONCLUSION:

There is great challenges in medicinal chemistry because Cancer is one of the dangerous disease, killing almost seven million people a year. Various benzothiazole derivatives used in medicinal chemistry. This review gives an idea about how different type of substituted benzothiazole scaffolds in management of different type of cancer for example, breast, ovarian, renal, lung, colon cancer, gastric, liver, pancreatic cancers. This review gives short summary of research on antineoplastic activity of benzothiazole derivative synthesized and evaluated for various cell line by comparing withstandard marketed drugs, which may be useful for the further development of new such derivatives.

ACKNOWLEGMENT:

The authors are thankful to Principal, Government College of Pharmacy, Karad & also to AICTE for providing financial assistance in the form of stipend during my M. Pharm tenure.

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