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Review Article

# SIGNIFICANCE OF BENZOTHIAZOLE MOIETY IN THE FIELD OF CANCER

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**ABSTARCT**

Benzothiazole, the bicyclic ring system consists of thiazole ring fused with benzene ring. The literature study of benzothiazoles reveals that the presence of this bicyclic ring system in various amine or terrestrial natural compounds possess different biological properties. Thus benzothiazole moiety is continuously drawing interest for development of newer drug moiety due to its wide range of activities like antitumor, antimicrobial, schictosomicidal, anti-inflammatory, anticonvulsants, Antidiabetic, antipsychotic and diuretic. Benzothiazole moiety is found to be very important in the field of pharmacy as well as to develop newer anticancer agent in recent year due to the good response as an anticancer agent. In the present review our main interest is to emphasize the various synthetic molecules developed to promote the benzothiazole moiety in the modern era of anticancer agent.

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

## INTRODUCTION

The discipline of medicinal chemistry is devoted to the discovery and development of new agents for treating various diseases. The process of establishing a new pharmaceutical drug is exceedingly complex and involves talent of people from variety of disciplines including chemistry, biochemistry, molecular biology, physiology, pharmacology, pharmaceutics, and medicine [1]. Medicinal chemistry occupies an important position to establish a relationship between chemical structure and pharmacological activity [2]. Heterocyclic compounds are those cyclic compounds whose ring contain besides, carbon, one or more atoms of other elements.

The non-carbon atoms such rings are referred to as hetero atoms. The most common hetero atoms are nitrogen, sulphur and oxygen. Heterocyclic compounds are very widely distributed in nature and are particularly important because of the wide variety of physiological activities associated with this class of substances. Few of the basics rings of the heterocyclic compounds are listed below [3]. Benzothiazole is a 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 [4]. Benzothiazole consists of thiazole ring fused with benzene ring and possess multiple applications. The survey of literature related to benzothiazoles reveals the presence of this bicyclic ring system in various amine or terrestrial natural compounds, which have useful biological properties. In recent years heterocyclic compounds analogues and derivatives have attracted strong interest due to their biological and pharmacological properties. Benzothiazole derivatives possess a wide spectrum of biological applications such as antitumor, antimicrobial, schictosomicidal, anti-inflammatory, anticonvulsants, Antidiabetic, antipsychotic and diuretic etc [5].

## BENZOTHIAZOLE MOIETY USED IN CANCER

Kini S, *et al* synthesized 2- aryl substituted benzothiazoles derivatives by refluxed o-aminothiophenol with substituted benzoic acids in presence of polyphosphoric acid at $220^0$ and evaluated them against Human Cervical Cancer cell lines as anticancer drugs[6]

Gupta S *et al* synthesized a series of benzothiazole derivatives and evaluated for *in vitro* cytotoxic activity against HL-60 and U- 937 cell lines by MTT assay techniques using 5-flurouracil, BCNU, hydroxyurea and cisplatin as standard drug. *In silico* pharmacokinetic toxicity studies showed that benzothiazole dimers were free from teratoginicity, irritation and sensitivity properties than monomers. The QSAR study revealed that presence of hydrophobic moieties in the molecules is conductive for the cytotoxic activity of the benzothiazole derivatives against U-937 cell lines whereas increase in hydrogen donor count is conductive for cytotoxic activity of benzothiazole derivatives against HL-60 cell lines [7].

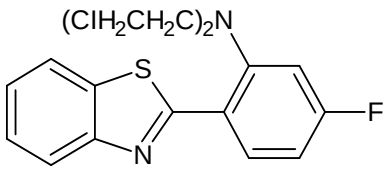



Figure no. 1

**Fig. 1**

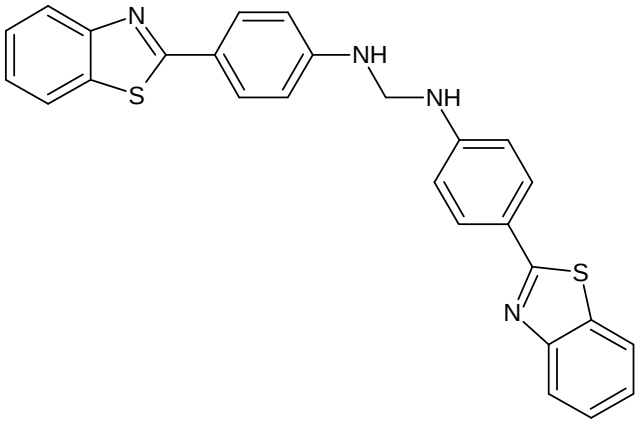



**Fig. 2**

Stanton HLK, *et al* synthesized benzothiazole containing phthalimide and studied their anti-cancer activity on human carcinoma cell lines [8].

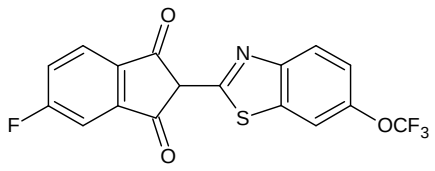


**Fig. 3**

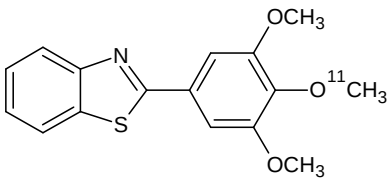
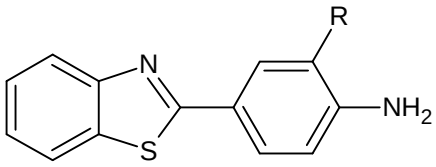


**Fig. 4**

Wang M *et al* synthesized carbon 11 labeled 4-, 5-, and 6-fluorinated 2-aryl benzothiazoles and used as novel potential protein emission tomography (PET) to image tyrosine kinase in cancer [9]. Different substituted benzothiazoles showed antitumor activity. Mainly the 2-(4-aminophenyl) derivatives are especially potent. Stevens *et al* and TD Bradshaw *et al* reported the *in-vitro* antitumor activity of a new series of alkyl-, halo-, cyano-, alkoxy- and hydroxy- substituted 2-(4-aminophenyl) benzothiazoles (**1.A-1.D**). Compound (**1.A**) showed the most potent growth inhibition against the ER+ (MCF-7 and BO) and ER- (MT-1 and MT-3) tumors [10-12].



1.A - 1.D

**Fig. 5a**

| Structure no. | R group |
|---|---|
| 1.A | -CH 3 |
| 1.B | -Br |
| 1.C | -I |
| 1.D | -Cl |

**Fig. 5b**

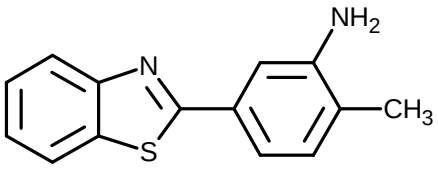


**Fig. 6**

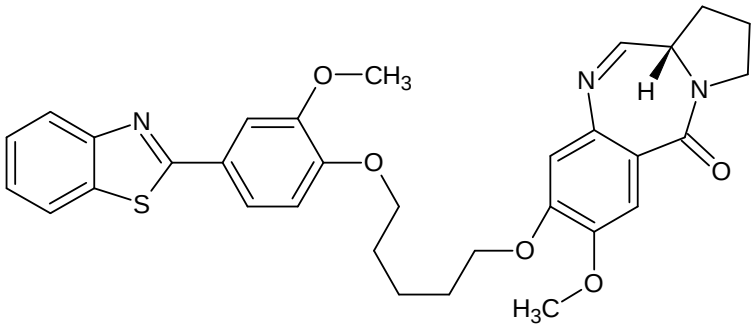


**Fig. 7**

S.-J. Choi *et al* synthesized 2-(substituted phenyl) benzothiazoles and the result showed that most of the compounds synthesized exhibited topoisomerase II inhibitory activity at 100 μM. But the 2-(3-Amino-4-methylphenyl) benzothiazole showed highest activity comparable to etoposide (IC50 = 71.7 μM) [13]. A Kamal *et al* synthesized a series of benzothiazole linked pyrrolobenzodiazepine conjugates attached through different alkane or alkylamide spacers and the compounds were investigated their anticancer activity, DNA thermal denaturation studies, restriction endonuclease digestion assay and flow cytometric analysis in human melanoma cell line (A375). One of the compounds of the series showed significant anticancer activity with promising DNA-binding ability and apoptosis caused G0/G1 phase arrest at sub-micromolar concentrations [14]. Similarly Akhtar *et al* synthesized 1, 3, 4-oxadiazole-2-thione conjugates compounds which showed significant effects on leukaemial cell lines [15].

Shawinski *et al* were prepared a series of novel N-(benzothiazol-2-yl) derivatives of 2-benzylthio-4- chloro-5-$R^1$-benzenesulfonamides by reacting N-(2-benzylthio-4-chloro-5-$R^1$-benzenesulfonyl) cyanamide potassium salts with 2-aminothiophenol and evaluated for activity and selectivity towards non-small cell lung cancer and melanoma cell lines. This Compound serve as a useful lead for more potent due to high lipophilicity of $CH_3$ group as compared to CN or $CONH_2$ group [16].

Luzina *et al* synthesized a number of N-bis-(triflouromethyl)-alkyl-$N^1$- benzothiazolyl ureas and derivatives with an electron withdrawing substituent which showed greater activity towards the tumor cell lines. These two compounds showed significant action on CNS, renal and leukaemial cancer cell lines [17]. Beneteau *et al* synthesized some novel benzothiazoles and dioxinobenzothiazoles among which the 2-cyano derivatives exhibit interesting in vitro antitumour activity [18]. Havrylyuk et al also prepared several novel 4-thiazolidinones with benzothiazole moiety for antitumor screening on leukaemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancer cell lines. Amongest all compounds, the 2-{2-[3-(benzothiazol-2-ylamino)-4-oxo-2-thioxothiazolidin-5-ylidenemethyl]-4-chlorophenoxy}-N-(4-methoxyphenyl)-acetamide was the most active one [19].

Hutchinson I *et al* have been synthesized Fluorinated analogues of 2-(4-aminophenyl) benzothiazoles which successfully block C-oxidation and exhibit selective and potent anticancer activity in sensitive human breast MCF-7 (ER+) and MDA 468 (ER-) cell lines but inactive against PC 3 prostate, nonmalignant HBL 100 breast, and 116 colon cells [20].

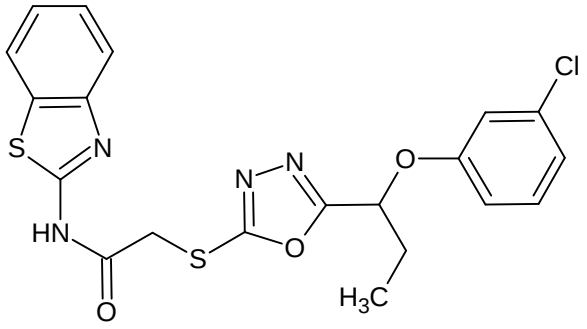


**Fig. 8a**

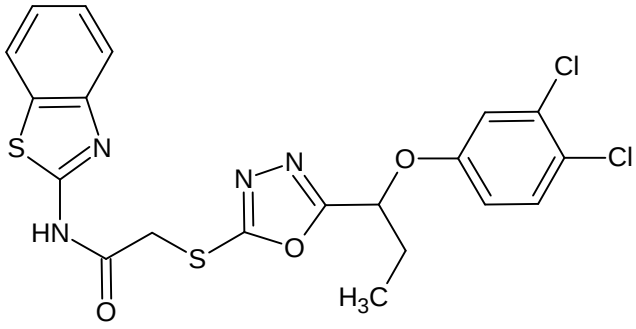


**Fig. 8b**

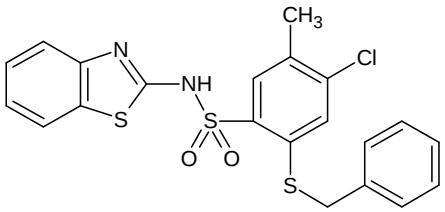


**Fig. 9**

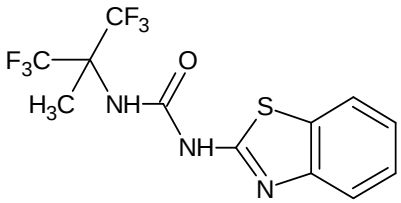


**Fig. 10a**

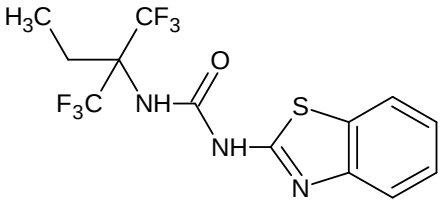


**Fig. 10b**

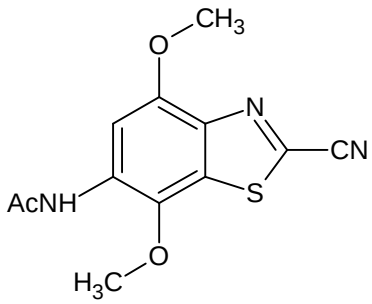


**Fig. 11**

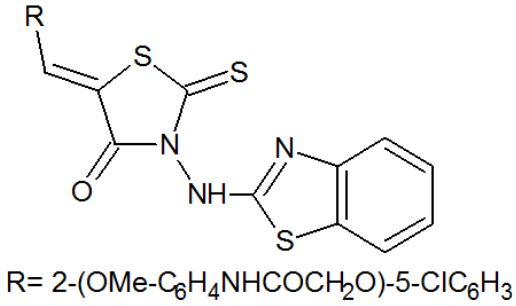



**Fig. 12**

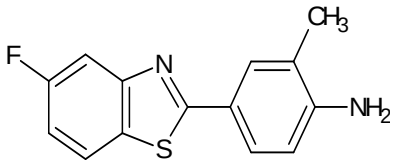


**Fig. 13**

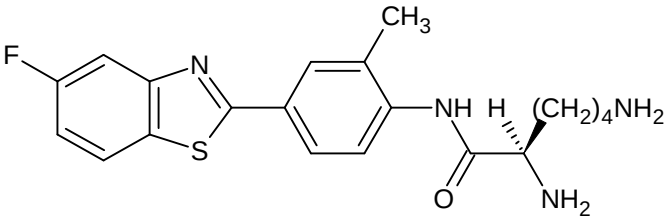


**Fig. 14**

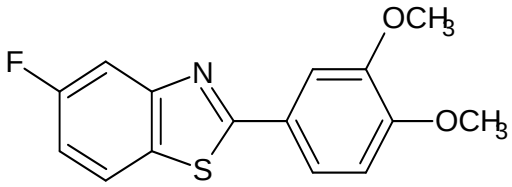


**Fig. 15**

Hutchinson I *et al* also synthesized a series of water soluble L-Lysyl- and L-alanyl-amide prodrugs of the lipophilic antitumor 2-(4-aminophenyl) benzothiazoles and the lysyl-amide of 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole has been selected for phase I clinical trials [21].

Mortimer *et al* has been synthesized a new series of 2-phenylbenzothiazoles and evaluated in Vitro in four human cancer cells lines. The compound 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole possess exquisitely potent antiproliferative activity [22]. Maria Pelecanou *et al* synthesized conjugated complexes of Rhenium and Technetium-99m with the antitumor agent 2-(4$^1$-aminophenyl) benzothiazole. The complexes are evaluated in both in Vitro and in Vivo biological evaluation as breast cancer radiopharmaceuticals. The results provide the 2-(4$^1$-aminophenyl) benzothiazole complexes potential candidates for imaging ($^{99m}$Tc) and targeted radiotherapy ($^{188}$Re) of breast cancer [23].

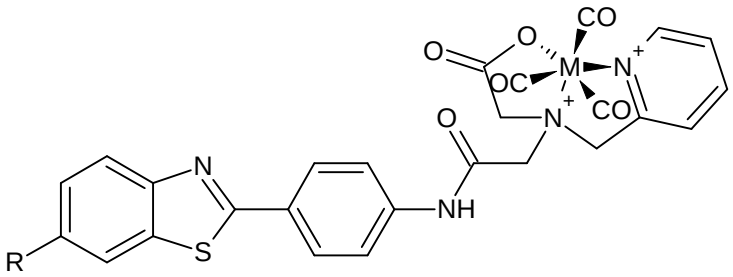


**Fig. 16a**

| Structure no. | R group | M |
|---|---|---|
| 1.7a | -H | -Re |
| 1.7b | -H | $^{99m}$Tc |
| 1.8a | -$CH_3$ | -Re |
| 1.8b | -$CH_3$ | $^{99m}$Tc |

**Fig. 16b**

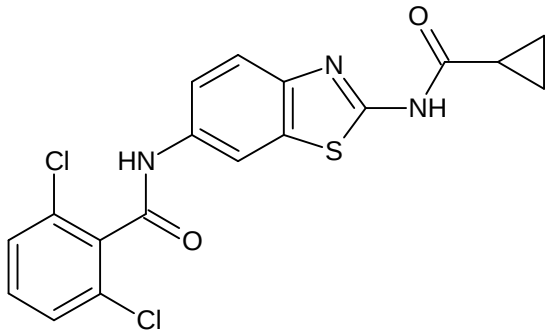


**Fig. 17**

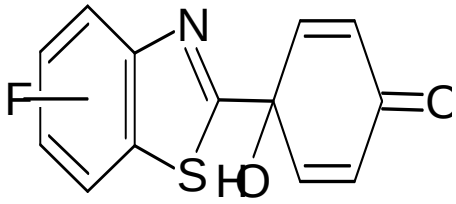


**Fig. 18**

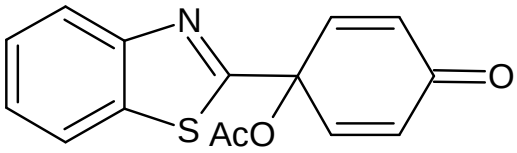


**Fig. 19**

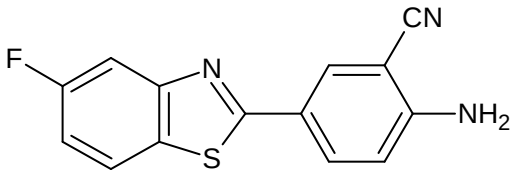


**Fig. 20**

M. Yoshida *et al* prepared a new series of 2,6-dichloro-*N*-[2-(cyclopropanecarbonylamino) benzothiazol-6-yl] benzamide based on 2-methyl-4-nitro-2*H*-pyrazole-3-carboxilic acid[2-(cyclohexanecarbonylamino)benzothiazole-6-yl]amide and the compound possess good antitumor activity [24].

C J Lion *et al* synthesized the fluorinated benzothiazole-substituted-4- hydroxycyclohexa- 2, 5- dienones (quinols) and evaluated for in Vitro antitumor activity [25].

G Wells *et al* synthesized a novel series of antitumour quinol derivatives substituted with benzothiazole and possess good activity against human colon and breast cancer cell lines [26].

I. Hutchinson *et al* synthesized a new series of 2-(4-aminophenyl) benzothiazole antitumor derivatives with a cyano or alkynyl group at 3' position and evaluated for antitumor activity. Amongst all analogues the 5-flourorinated derivative possesses potent *in-vitro* activity against MCF-7 and MDA-468 human cancer cell lines [27].

A. Kamal *et al* synthesized benzothiazolo-4β-anilino-podophyllotoxin and benzothiazolo-4β- aniline-4-*O*-demethylepipodophyllotoxin cogeners by one-pot iodination methodology using zirconium tetrachloride or sodium iodide and some compounds were evaluated for cytotoxicity studies against human cancer cell lines and DNA Topoisomerase-II inhibitory activity [28].

B. Kamal *et al* also synthesized a series of chalcone-amidobenzothiazole conjugates and evaluated for their anticancer activity. Amongst all these compounds these two compounds exhibited potent anticancer activity [29].

Kralj et al synthesized a series of novel cyano and amidino benzothiazole derivatives. Almost all amidino derivatives showed noticeable anti-proliferative effect on several tumor cell lines while the cyano derivatives showed considerably less pronounced activity due to their poor solubility in aqueous cell culture medium [30].

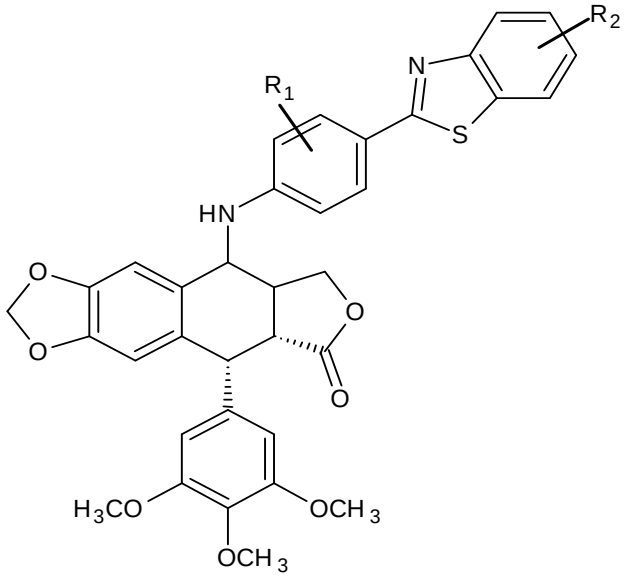
Devmurari V. P. *et al.* synthesized a series of seven substituted 2-phenyl benzothiazole by condensing substituted benzoic acid with 2-amino thiophenol in the presence of phosphoric acid and substituted 1, 3-benzothiazole-2-yl-4-carbothioate derivatives by condensing 2-mercaptobenzothiazole with substituted acid chloride. The result revealed that compounds with more than one halogen showed cytotoxicity towards cancer cell lines. As compared to nitrosubtitued derivatives the amino substituted derivatives are more cytotoxic [31].

Stevens *et al* prepared a series of 2-(4-acylaminophenyl) benzothiazoles derivatives and the in Vitro studies revealed that *N*-Acetylation of compounds exerts a drastic dyschemotherapeutic effect but acetylation of the halogen congers were substantially retain selective antitumor activity [32].

Stevens *et al* also synthesized a series of polyhydroxylated 2-phenylbenzothiazoles for anticancer activity and found to be very active against breast MCF-7 and MDA 468 cells [33].

Labhsetwar *et al* synthesized and evaluated the 8-Chloro-3-cyano-4-imino-2-methylthio-4H-pyrimido [2, 1-*B*] [1, 3] benzothiazole and its 2-substituted derivatives for their *in vitro* anticancer activity towards 60 Human Cancer cell lines [34].

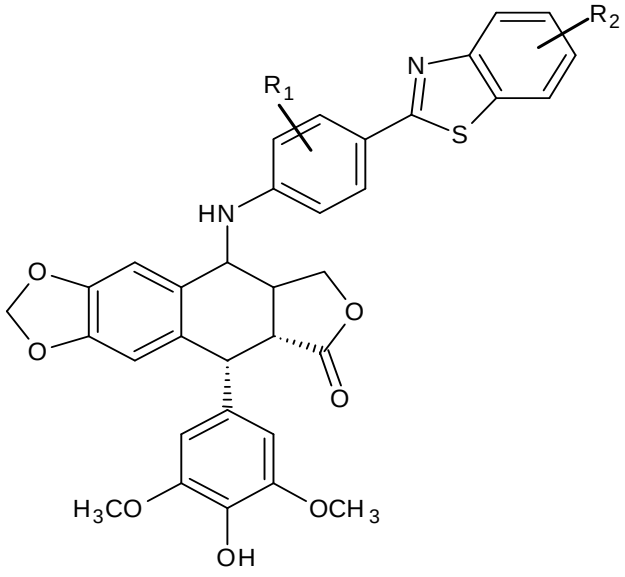
Arun Pareek *et al* synthesized the *N*-(4,5-dihydro-1*H*-imidazol-2-yl)-6-substituted-1,3-benzothiazol-2-amines (3a-c) and *N*-(1*H*benzimidazol-2-yl)-6-substituted-1,3-benzothiazol-2-amines (4a-c) and evaluated for their biological activities [35].



$R_1$=H, 2'-Cl, 3'-$CH_3$, 3'-Br

$R_2$=6-$OCH_3$, 6-F, 4-Cl, 4,6-dichloro

**Fig. 21a**



$R_1$=H, 2'-Cl, 3'-$CH_3$, 3'-Br

$R_2$=6-$OCH_3$, 6-F, 4-Cl, 4,6-dichloro

**Fig. 21b**

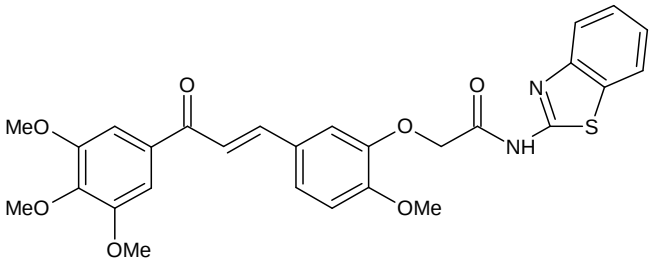


**Fig. 22a**

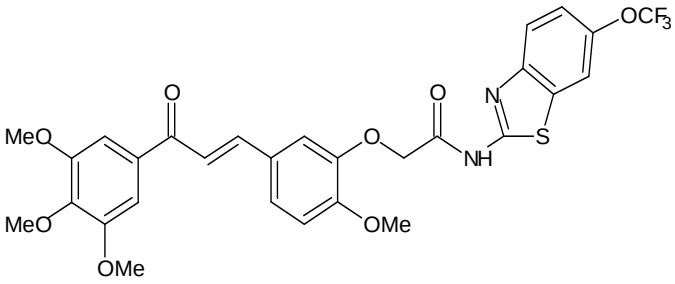


**Fig. 22b**

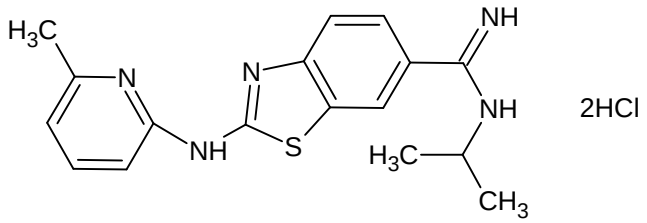


**Fig. 23a**

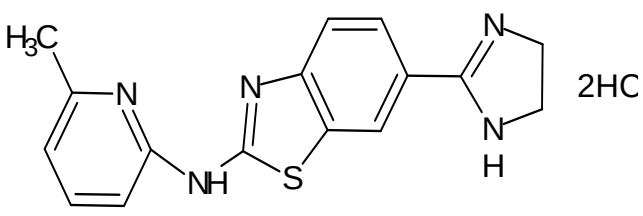


**Fig. 23b**

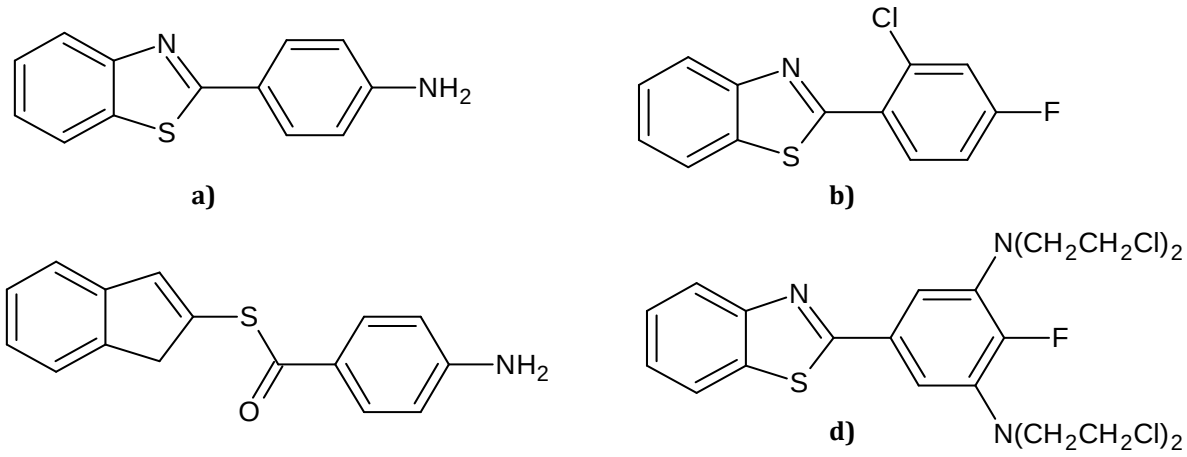



**Fig. 24**

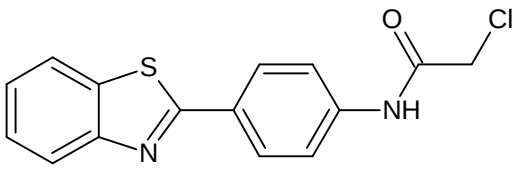



**Fig. 25**

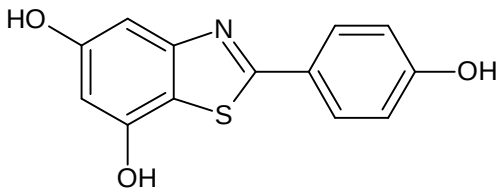
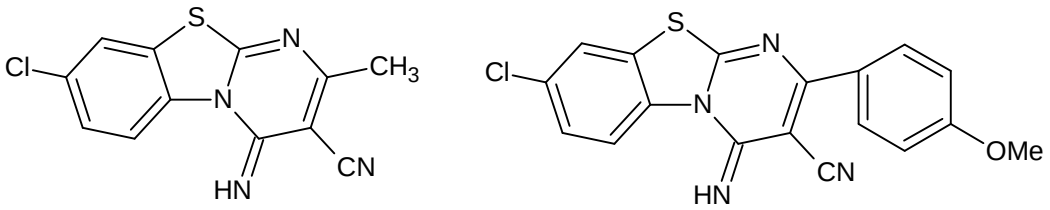



**Fig. 26**



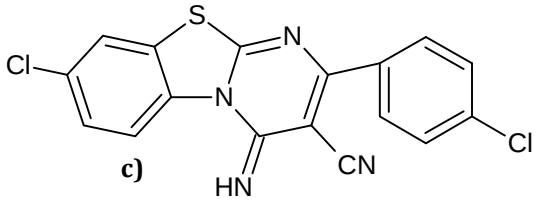
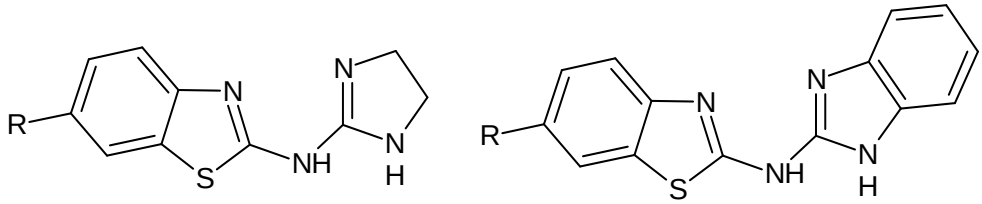




**Fig. 27**




R(3a-c and 4a-c)=( a=Cl, b=$OCH_3$, c= $NO_2$)

**Fig. 28**

**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.

Hence this unique molecule must act like a boon in the field of developing various synthetic anticancer agents

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