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BENZOTHIAZOLE-BASED HYBRID MOLECULES AS PROMISING ANTICANCER AGENTS: RECENT ADVANCES AND THERAPEUTIC POTENTIAL

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ABSTRACT
Benzothiazole derivatives have a broad range of biological properties. This review provides a thorough examination of the literature from the past ten years (March 2015–January 2026), highlighting the main uses of benzothiazole derivatives in cancer treatment. These compounds are efficient against several cancer cell lines and they act through multiple molecular pathways, although some mechanisms are still not completely understood or require further investigation. In contrast, the inhibition of tumor-associated carbonic anhydrases (CAs) by benzothiazole derivatives has been more extensively explored. Furthermore, structure–activity relationship studies and IC50 values indicate promising potency and selectivity of hybrid benzothiazole derivatives. These compounds might potentially serve as lead molecules for developing effective anticancer agents, particularly targeting hypoxic tumor environments.

KEYWORDS: Benzothiazole, Hybrid, Heterocyclics, Cell line, Anticancer agents.

INTRODUCTION

Cancer remains one of the most significant global health challenges, representing a leading cause of morbidity and mortality worldwide [1]. Recent studies estimate that nearly 20 million new cancer cases occur each year across the globe, while the disease causes approximately 10 million deaths annually [2]. The next two decades will see an increase in this burden, according to epidemiological projections that forecast population growth and aging demographics, as well as environmental exposures and lifestyle-related risk factors such as tobacco use, dietary habits, obesity, and reduced physical activity [3]. The growing cancer cases create a dual challenge for healthcare systems, which must develop new treatment methods that enhance patient survival while reducing negative treatment results[4], [5]. The standard treatment methods for cancer, which include surgery, radiotherapy, and chemotherapy, have led to significant improvements in patient outcomes across multiple cancer types. The introduction of targeted therapies together with immunotherapies has created new treatment options that focus on biological pathways and immune system modulation[6]. The existing advancements still present multiple limitations. Chemotherapeutic agents demonstrate poor selectivity because they cause systemic toxicity, which damages healthy tissues[7], [8]. The actual effectiveness of targeted therapies is restricted by three main issues, which include acquired resistance, limited bioavailability, and suboptimal pharmacokinetic properties[9], [10]. Tumor heterogeneity further complicates treatment outcomes, as different subpopulations of cancer cells may respond variably to therapy[11], [12]. The existing limitations demand the development of new chemical scaffolds, which will improve drug-like properties and molecular tarI abilities, together with the capacity to implement multiple treatment methods[13], [14].

Heterocyclic compounds are essential in modern medicinal chemistry research. More than 50% of approved medications contain at least one heterocyclic ring because these compounds play a vital role in shaping their physiological and chemical characteristics[15], [16]. Nitrogen-containing heterocycles are highly valued because these compounds enable scientists to study protein binding through hydrogen bonding, ionic interactions, and dipole–dipole interactions[17], [18].

Benzothiazole (BTA) is a fused benzoheterocycle found in numerous naturally occurring substances, giving to the pharmaceutical and medicinal applications of these natural products[19], [20]. Benzothiazole is present in both terrestrial and marine compounds that exhibit several biological activities. The pharmacological properties of Riluzole[21] (**Figure 1**), which is used to treat amyotrophic lateral sclerosis, have led medicinal chemists to study biologically active benzothiazoles. The BTA structure shows a vast variety of biological activities, including anti-inflammatory [22], fungicidal [23], anti-diabetic [24], analgesic[25], anti-microbial[26], antitumor[22], antileishmanial[27] and anthelmintic[28] etc. HeLa, SW480, HepG2, mammary, and ovarian tumor cell lines, in addition to colon, non-small-cell lung, and breast cancer subpanels, hepatocellular carcinoma, and other tumors and

cancer cell lines are all significantly and extensively pharmacologically and biologically affected by benzothiazole derivatives [29]. The therapeutic adaptability of benzothiazole derivatives is shown by various clinically licensed drugs, such as pramipexole[30], riluzole, ethoxazolamide, zopolrestat, and Pramipexole (**Table 1**), which together illustrate the scaffold's translational potential[31]. Derivatives containing benzothiazole have shown significant anticancer efficacy with advantageous therapeutic indices, making them appealing candidates for cancer medication development[32]. The concurrent integration of computational calculations and molecular docking with ADME studies has transformed the drug development pipeline, yielding accurate predictions of compound behavior and protein-ligand interactions[33], [34]. This approach minimizes the necessity for extensive preliminary laboratory screening, expedites the drug discovery process by identifying promising lead compounds, and offers detailed atomic-level insights into binding mechanisms and structure-activity relationships, thereby significantly reducing drug development costs and enhancing success rates in pharmaceutical research[35], [36].

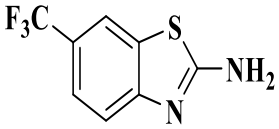


Figure 1: Riluzole.

Benzothiazole derivatives have gained significant attention due to their ability to target multiple pathways involved in cancer progression. They inhibit key enzymes such as kinases, topoisomerases, and tubulin, leading to cell cycle arrest and apoptosis. Additionally, these compounds modulate critical signaling pathways, including PI3K/Akt, MAPK, and NF-κB, which regulate tumor growth and survival. The presence of nitrogen and sulfur atoms enhances their binding with biological targets, making them promising candidates for overcoming drug resistance in cancer therapy[37], [38].

Several benzothiazole compounds are under preclinical and clinical research for medical use. 5F 203 (NSC 703786) showed strong antitumor activity in preclinical testing via activating the AhR pathway. To improve its pharmacological properties, the water-soluble prodrug Phortress (5F-DF-203-L-lysylamide) was studied in Phase I clinical trials for advanced solid tumors. Riluzole, a benzothiazole-based pharmaceutical approved for amyotrophic lateral sclerosis, is being explored for cancer therapy via medication repurposing (**Table 2**).

Recent investigations show that structurally varied benzothiazole hybrids have high cytotoxic action and IC_{50} values against several cancer cell line. Recent findings from the 2025 study demonstrate that benzothiazole–1,2,3-triazole hybrids exhibit significant cytotoxic activity, particularly against T47-D breast cancer cells (IC_{50} = 13–19 μM), with minimal toxicity toward normal fibroblasts (>500 μM)[39],[15].

Benzothiazole-based hybrid molecules possess significant anticancer potential due to their strong cytotoxic effects against multiple cancer cell lines and their ability to interact with important cancer-related molecular targets. These findings emphasize the importance of benzothiazole hybrid scaffolds in medicinal chemistry and support their potential role in the development of new and more effective anticancer agents.[40]

Recent studies have highlighted benzothiazole-based hybrid molecules as promising anticancer agents due to their potent cytotoxic activity against various cancer cell lines and their ability to modulate important signaling pathways involved in tumor progression. However, the available research remains scattered across different hybrid scaffolds, biological targets, and experimental models. Therefore, a concise review summarizing recent developments and therapeutic potential of benzothiazole hybrids is essential to guide future anticancer drug discovery efforts. [22], [41], [42]

Functional Roles of Benzothiazole Derivatives in Anticancer Drug Design

Benzothiazole derivatives represent an important class of heterocyclic compounds in anticancer drug discovery owing to their diverse mechanisms of action and favorable pharmacological properties[43], [44]. These compounds exhibit anticancer activity through DNA interaction, inhibition of key enzymes such as topoisomerases, HDACs, and kinases, disruption of tubulin polymerization, induction of apoptosis, and modulation of oxidative stress pathways. Furthermore, benzothiazole-based molecules have demonstrated anti-angiogenic effects and selective cytotoxicity toward cancer cells[45]. The structural versatility of the benzothiazole scaffold enables the development of hybrid and multi-target-directed agents, making it a valuable pharmacophore for designing novel anticancer therapeutics with improved efficacy and reduced resistance[46], [47].

Table 1: Marketed drug having benzothiazole derivatives.

Drug/Structure	Therapeutic Use	Primary Molecular Target	Benzothiazole Type

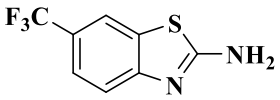
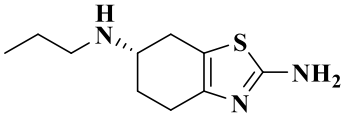
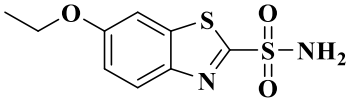
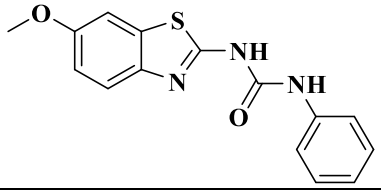
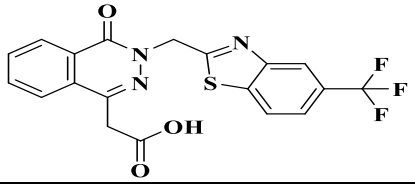
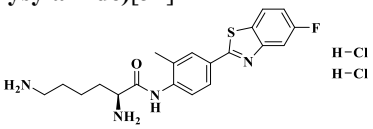
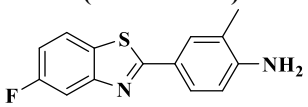
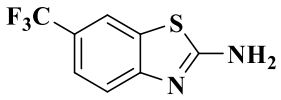
Riluzole[48] 	Amyotrophic Lateral Sclerosis (ALS)	Voltage-gated sodium channels; glutamate neurotransmission pathways	2-Aminobenzothiazole derivative
Pramipexole[49] 	Parkinson's disease, Restless Leg Syndrome	Dopamine D2 and D3 receptors (especially D3)	Benzothiazole-containing dopamine agonist
Ethoxzolamide[50] 	Glaucoma, altitude sickness	Carbonic anhydrase (CA II, CA IV and related isoforms)	Benzothiazole sulfonamide
Frentizole[51] 	Immunosuppressive/anti-inflammatory agent	T-lymphocyte proliferation and immune-response pathways (exact target not fully defined)	Benzothiazole derivative
Zopolrestat[51] 	Diabetic complications (investigational)	Aldose reductase (AKR1B1)	Benzothiazole derivative

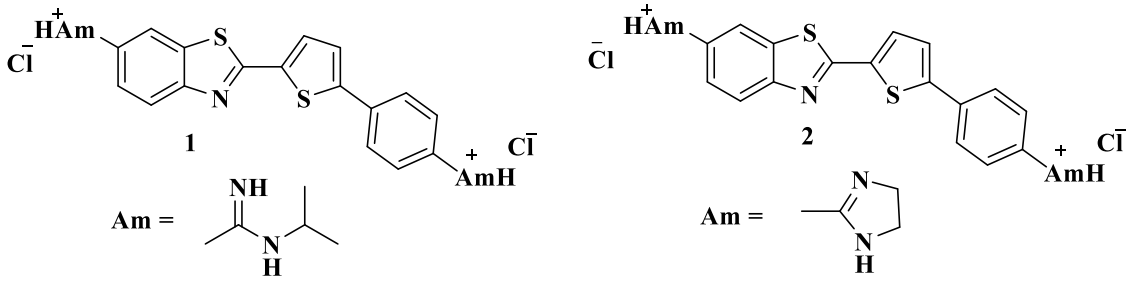
Table 2: Benzothiazole derivatives under clinical trial/preclinical development

Compound/ Structure / CT number	Clinical Status	Indication	Primary Target	Mechanism of Action
Phortress (5F-DF-203-L-lysylamide)[52]  Trial code- PH1/090 UK trial no.- CRUKD/04/036	Phase I clinical trial (prodrug of 5F 203).	Advanced solid tumors	**Aryl Hydrocarbon Receptor (AhR)**; CYP1A1/CYP1B1 enzymes	Prodrug that is converted to active benzothiazole metabolites after AhR activation. Induces CYP1A1/CYP1B1 expression, leading to bioactivation, DNA adduct formation, DNA damage, cell-cycle arrest, and apoptosis in sensitive tumor cells.
5F 203 (NSC 703786)  CT number - not applicable.	Preclinical development	Breast, ovarian, renal, and lung cancers	**AhR**, CYP1A1, CYP1B1	Binds and activates AhR, causing nuclear translocation and induction of CYP1A1/CYP1B1. The compound is metabolically activated into reactive electrophilic species that form DNA adducts and trigger apoptosis.
Riluzole[53]  CT number **- (NCT00866840)**	Repurposing clinical trials in oncology	Melanoma, glioblastoma, and other cancers	**Metabotropic Glutamate Receptor 1 (mGluR1)** signaling pathway; voltage-gated sodium channels	Inhibits glutamate release and glutamate-dependent signaling. Suppresses MAPK/ERK and PI3K/AKT pathways, reducing tumor-cell proliferation and promoting apoptosis.

BENZOTHIAZOLE DERIVATIVES AS ANTICANCER AGENTS

Benzothiazole-Thiophene Hybrids

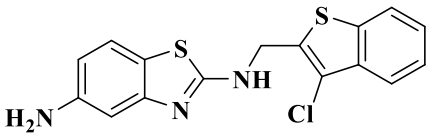
The antiproliferative effects of benzothiazole derivatives with thiophene and imidazole substitutions were demonstrated experimentally. Using *in vitro* testing against several tumor cell lines, Irfan et al. synthesized phenyl benzothiazole derivatives based on furyl and thienyl-based diamidino groups. Derivatives 1 and 2 shown in **figure 2**, which were respectively substituted with diamidino and imidazole, showed little cytotoxicity towards normal human fibroblasts but showed strong anti-cancer against MiaPaCa 2 and MCF-7 cell lines [54].



IC_{50} = 3.0 & 4.1µM
Cell line = MiaPaCa, MCF-7

Figure 2: Imidazolinyl thiophene-based benzothiazoles derivatives.

Cindric et al. synthesized a benzothiazole carboxamide scaffold by combining substituted amino-BTAs with substituted thiophenes. Apart from these synthesized derivatives SAR study shows compound 3 shown in **Figure 3** produce higher activity against cancer cell line due to presence of electron withdrawing group (Cl). They tested it against the MCF-7 with an IC_{50} of 40 µM to see whether it might fight cancer, the benzothiophene-derived carboxylic acid chloro aminobenzothiazole 3 showed substantial antitumor activity [55].



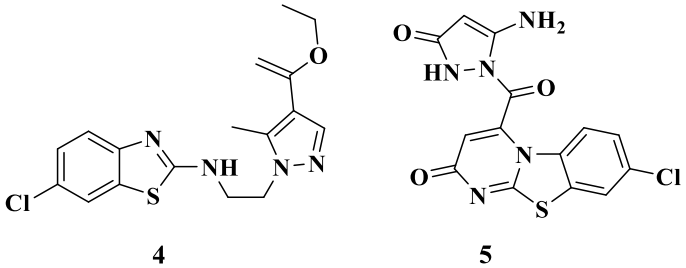
3

IC_{50} = 40 µM.
Cell line = MCF-7

Figure 3: Benzothiophene carboxamide chloro-amino-benzothiazole derivative.

Benzothiazole-Pyrazole Hybrids

Gabr *et al.* synthesized and evaluated novel benzothiazole derivatives against the NCI panel of 60 human tumor cell lines at 10 µM. Following five-dose screening, compounds 4 and 5 (Figure 4) exhibited the most promising antiproliferative activity, with GI_{50} values in the low micromolar to submicromolar range. The enhanced activity was attributed to the incorporation of pyrazole, 2-hydroxy ester, and 3-oxopyrazole moieties. Additionally, the synthesized derivatives showed potent cytotoxicity against HepG2 and HeLa cell lines, with IC_{50} values ranging from 4.5 to 6.1 µM and 5.92 to 8.8 µM, respectively, while compounds 4 and 5 were identified as the most active derivatives.[56].



IC_{50} = 3.97 & 4.31µM
Cell line = HepG2 & HeLA

Figure 2: Pyrazole based benzothiazoles derivatives.

Benzothiazole–Imidazole Hybrids

Yurttas et al. evaluated the anticancer effectiveness of 2-(4-aminophenyl) benzothiazole derivatives produced with different heterocyclic ring substitutions against 60 cancer cell lines. Antitumor activity against several cell lines was shown by BTA derivatives 7 (*N*- (4-(benzo[d]thiazol-2-yl) phenyl)- 2-(1-phenyl-1*H*-benzo[d]imidazol-2-yl-thio)-acetamide) and 1-(2-(1H-benzo[d]imidazol-2-ylthio)-*N* -(4-(benzo[d]thiazol-2-yl)-3-chlorophenyl)acetamide). Derivative 7 of these BTA compounds show anticancer potential on par with conventional pharmaceuticals due to the heterocyclic substitutions, however derivative 6 shows lower activity compared to compound 7 [57].

The anticancer effects of benzothiazole derivatives based on imidazoles were investigated by Singh et al., who reported the synthesis of these compounds by reacting modified anilines with KSCN. In comparison to the standard drug **doxorubicin**, Compound 8 (R=Br) (**Figure 5**) demonstrated exceptional anticancer effectiveness, with an IC_{50} of 10 µM against the cancer cell line HepG2, MCF-7 and HeLA [58].

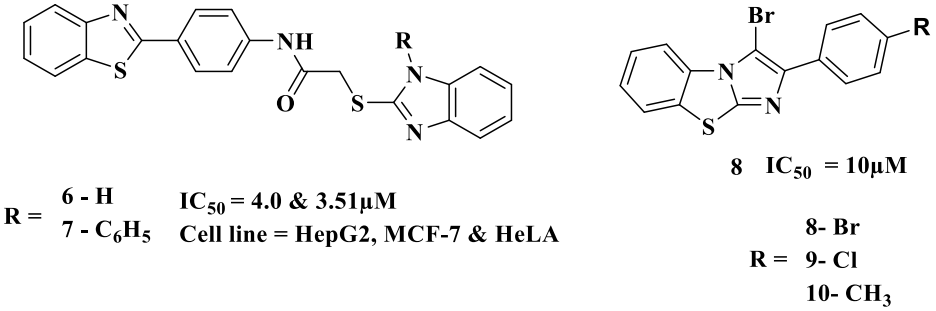


Figure 5: Substituted phenyl imidazole-based benzothiazole derivatives.

Benzothiazole -Thiazolidine Hybrids

Abusharkh et al. synthesized a series of benzothiazole-based thiazolidinone derivatives by reacting aminobenzoic acid with suitably substituted aniline derivatives. The resulting compounds were assessed for their antiproliferative efficacy against MCF-7 (breast cancer) and HepG2 (liver cancer) cell lines. Structure–activity relationship (SAR) analysis indicated that compound 11 (**Figure 6**), featuring a nitrobenzylidene substituent, exhibited the highest anticancer activity in the series, with IC_{50} values of 36 µM against MCF-7 and 48 µM against HepG2 cells. In contrast, compounds 12–15 displayed reduced potency, with IC_{50} values of 53, 49.9, 57, and 62 µM, respectively, suggesting that the nitrobenzylidene moiety positively influenced anticancer activity. [59].

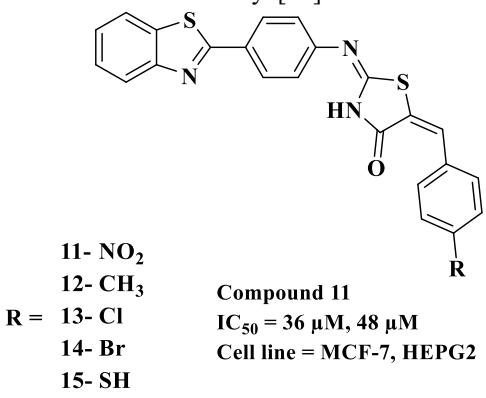
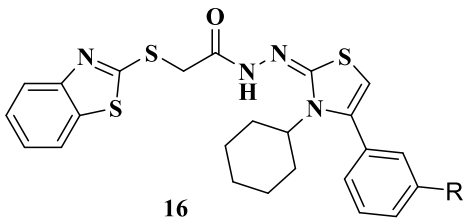


Figure 6: Thiazolidine benzothiazole derivative.

Osmaniye et al. produced a variety of benzothiazole–thiazolidine compounds and assessed their cytotoxic activity against C6 glioma cells, while NIH3T3 fibroblast cells were used to investigate their effects on normal cells. Among the produced compounds, 16 and 17 (**Figure 7**), featuring substituted phenylthiazolidene and substituted nitrophenylthiazolidene moieties, respectively, had the highest anticancer efficacy, with IC_{50} values of 0.03 µM against C6 cells. In contrast, compounds 18–21 exhibited diminished cytotoxic efficacy, with IC_{50} values of 4.0, 4.7, 3.09, and 3.31 µM, respectively. Structure–activity relationship (SAR) research revealed that incorporating a phenyl ring into the thiazolidine moiety improved selectivity, but both electron-donating and electron-withdrawing substituents on the phenyl ring diminished the selectivity of the compounds [60].

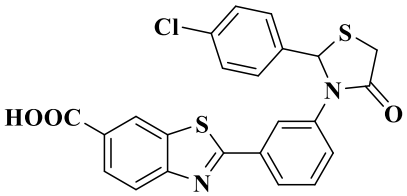


Compound 16
IC_{50} = 0.03 µM
Cell line = C6

R=
16- H
17- NO_2
18- Br
19-Cl
20- NH_2
21- COOH
22- CH_3

Figure 7: Substituted phenylthizolidene based benzothiazole derivative.

Prabhu et al. synthesized benzothiazole molecules from oxothiazolidine and investigated how well they worked against cancer. **Figure 8** shows that associated to the reference cisplatin, the BTA 23 produced from substituted chlorophenyl oxothiazolidine had the utmost anticancer effectiveness against the HeLa, with an inhibition rate of 96.8% and an IC_{50} 9.76 µM [61].



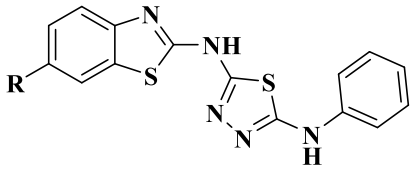
23

IC_{50} = 9.76 µM
Cell line = HeLa

Figure 8: Oxothiazolidine based benzothiazole derivative.

Benzothiazole-Thiadiazole Hybrids

Aazzam et al. developed and assessed a series of new benzothiazole derivatives (24–28) for their anticancer efficacy against the MCF-7 breast cancer cell line. All synthesized compounds shown moderate to substantial antiproliferative efficacy. Compounds 24 and 25 exhibited the greatest efficacy, with IC_{50} values of 7.4 µM and 9.01 µM, respectively. Structure–activity relationship (SAR) research indicated that the increased activity of these derivatives correlated with the presence of electron-donating (methoxy) and highly electronegative (fluorine) substituents. The thiadiazole–fluorobenzothiazole derivative (24) and the methoxy-substituted benzothiazole derivative (25) had the highest antitumor efficacy in the series (**figure 9**) [62].

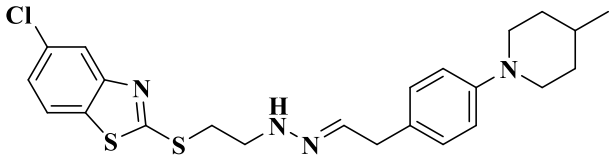


R=
24- F
25- OCH_3
25- COOH
26- CH_3
27- NO_2
28- C_2H_5

Figure 9: Thiadiazole based benzothiazole derivatives.

Benzothiazole-Piperidine Hybrids

Osmaniye et al. studied the anticancer effects of benzothiazole acylhydrazone derivatives on a number of cell lines, such as rat brain glioma (C6), MCF-7, HT-29, lung adenocarcinoma epithelial (A549), and mouse embryo fibroblast (NIH3T3). Additionally, the desired derivatives were synthesized by refluxing 4-fluoro benzaldehyde through substituted amines. In contrast to the reference medication cisplatin, the compound 29 piperidine-derived acetohydrazide (**figure 10**) showed sensible activity against the MCF-7, C6, and NIH3T3 cell lines, with IC_{50} 0.1µM, 0.3µM, and 1.0µM, respectively [63].



29

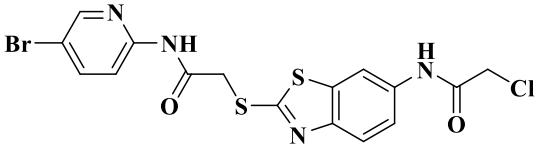
IC_{50} = 0.1µM, 0.3µM, and 1.0µM
Cell line = MCF 7, C6, and NIH3T3

Figure 10: Piperidine based acetohydrazide benzothiazole derivative.

Benzothiazole-Pyridine Hybrids

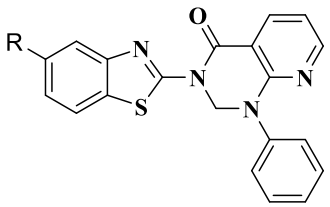
Elgemeie et al. synthesized twenty benzothiazole -2-thiol derivatives and examined their antitumor activity transversely many cell lines, including HeLa, SW480, A549, HCT-116, HepG2, and SKBR-3 cells. **Figure 11** shows that the 9-bromopyridine acetamide benzothiazole derivative had notable anti-tumor effects on the SW620, HepG2, and A549 cell lines, through IC_{50} 4.3µM, 48µM, and 44µM, all in that order. The process by which HepaG2 cells died was concentration-dependent apoptosis. The SAR findings suggest that benzothiazole-2-thiols demonstrate a wide-ranging anti-cancer activity that warrants further investigation[64].

Zhou *et al.* designed and synthesized a series of phenylpyridopyrimidinone-based benzothiazole (BTA) derivatives and evaluated their antiproliferative activity against ME-180, DU145, MCF-7, and B16 cancer cell lines. Among the synthesized compounds, compound 31, containing pyridine, pyrimidine, and benzothiazole moieties, exhibited the highest cytotoxic activity, with an IC_{50} value of 4.01 µM against the ME-180 cell line. The remaining derivatives showed comparatively lower potency, with IC_{50} values of 6.1, 9.3, 11.1, and 8.01 µM, respectively. These findings indicate that the combination of pyridine, pyrimidine, and benzothiazole pharmacophores contributed to the enhanced anticancer activity of compound 31 [65].



30

IC_{50} = 4.3µM, 48µM, and 44µM
Cell line = SW620, HepG2, and A549



Compound 31
IC_{50} = 4.01 µM
Cell line = ME-180

R=
31- OC_2H_5
32- OCH_3
33- CH_3
34- NO_2
35- Cl

Figure 11: pyridine-based benzothiazole derivatives.

Benzothiazole-Secondary pyrimidine Hybrids

Azzam et al. synthesized isoxazole pyrimidine-based benzothiazole and then studied their anticancer effects. They used the MTT assay to test these compounds against numerous cell lines, together with A-549, Colo-205, MCF 7, and U-937. These results were associated to the standard drug, etoposide. Compound 36 (**Figure 12**) exhibited potent anti-cancer effects; it was synthesized from pyridine. The medication's IC_{50} were far lower than those of the well-established drug etoposide, measuring 5.0µM against Colo205, 30.6µM against MCF-7, and 30.4µM against A-549 cell lines. In order to regulate the ratio of programmed cell death to cell growth, scaffold 34 activates the p53 or TP53 pathways [66].

Mohamed et al. synthesized a substituted pyrimidine derivative, compound 37 (**Figure 12**) which incorporated benzothiazole. To achieve this, bis-methylthio methylene malononitrile was refluxed with benzothiazole. Subsequently, they assessed its anticancer activity across eighteen different cell lines. Scaffold 37 displayed considerable anticancer efficacy, as evidenced by a substantial degree of progress inhibition observed in breast and lung cancer cell lines [67].

Juthiga et al. synthesized cyano and amidino BTA-substituted anilines, then reacted with 2-bromo-6-cyano BTA under controlled environments. These derivatives were then tested for their ability to fight cancer in six different cancer cell lines: Hep 2, MCF7, HeLa, MiaPaCa 2, SW-620, H-460, and WI-38. Compound 38 (**Figure 12**), SAR study reveal a benzothiazole derivative with a pyrimidine and carbonitrile group, demonstrated substantial efficacy against all the cancer cell types studied [68].

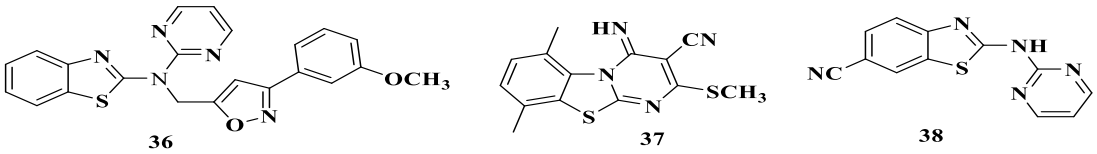


Figure 123: Pyrimidine based benzothiazole derivatives.

Benzothiazole-Quinolone Hybrids

Abdelgawad et al. synthesized quinolone-derived benzothiazole compounds by reacting substituted BTA with aromatic aldehydes. The MCF-7 tumor was inhibited by quinolone derivative 39, which included nitrobenzylidene, and derivative 40, which contained hydroxybenzylidine (**Figure 13**). The IC_{50} for these 2 compounds were 0.058µM and 0.052µM, respectively where as the another synthesized has lesser IC_{50} in comparison to compound 39 & 40 IC_{50} [69].

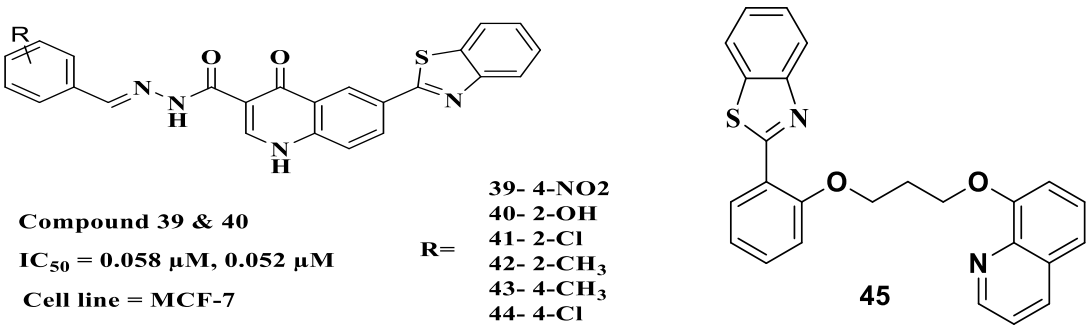


Figure 13: Quinoline based benzothiazole derivative.

Sarkar et al. synthesized benzothiazolyl quinoline derivatives by combining 2-aminobenzothiol with 2-hydroxybenzaldehyde. They then studied how these derivatives interacted with all adenosine receptors (A1, A2A, A2B, and A3). Increased levels of the A3 receptor are seen in many diverse cell lines. Compound 45, a quinolone imitative shown in **Figure 13**, displayed the greatest activity against the human A3 adenosine receptor[70].

Benzothiazole-Benzamide Hybrids

Ma et al. synthesized and assessed 24 derivatives of benzothiazole-2-thiol for their anti-tumor activities against numerous cell lines, including A549, SKRB-3, HCT-116, SW480, SW620, MDA-MB-468, HeLa, SKOV-3, PC-3, and A375. Some compounds exhibited enhanced antitumor activity associated to the standard cisplatin. *In vitro*, the modified methoxy benzamide benzothiazole 46 and chloromethyl benzothiazole 47 (**Figure 14**), showed considerable antitumor activity, with IC_{50} from 1.1µM to 8µM. SAR study shows the addition of methoxy and chloromethyl groups in compounds 46 and 47 improved their antineoplastic activity associated to further synthesized derivatives [71].

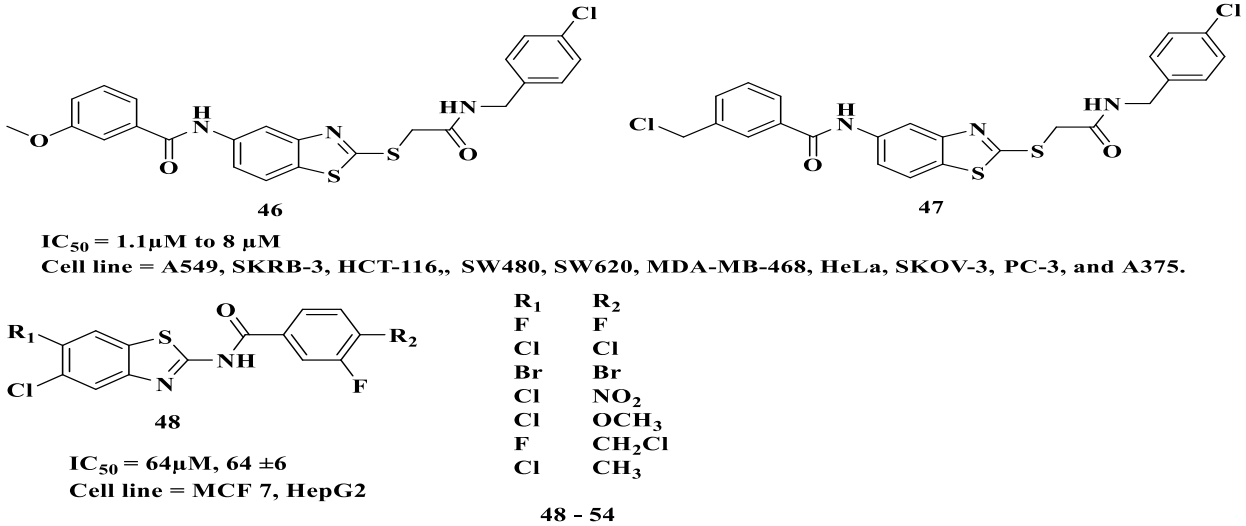


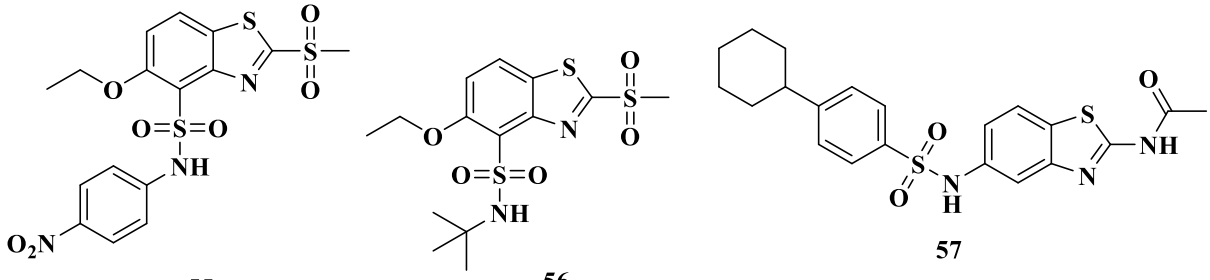
Figure 14: Benzamide based benzothiazole derivatives.

Corbo et al. synthesized thirteen benzamide-derived BTAs. They did this by reacting potassium thiocyanate with bromine and substituted aniline. The resulting compounds were then tested to see how well they stopped the progress of MCF-7 and HepG-2. Substituted difluorobenzamide, when combined with benzothiazole 48 (**Figure 14**), showed considerable anti-proliferative action. This was shown by a 64μM percentage inhibition in the MCF 7 cell line and a 64 ±6μM inhibition in the HepG2 cell line.[72].

Benzothiazole-Secondary sulphonamide Hybrids

Lad *et al.* synthesized a series of methylsulfonyl-substituted benzothiazole derivatives from 5-ethoxybenzothiazole-2-amine and evaluated their anticancer activity against the HeLa cervical cancer cell line. Among the synthesized compounds, compound 55, bearing a nitrophenyl sulfonamide moiety, and compound 56, containing a tert-butyl sulfonamide group (Figure 15), exhibited the highest cytotoxic activity, with GI_{50} values of 0.22 μM and 0.60 μM, respectively. Structure–activity relationship (SAR) analysis indicated that the superior potency of compound 55 was associated with the presence of the nitrophenyl substituent, suggesting that this electron-withdrawing group enhanced the anticancer activity of the methylsulfonyl benzothiazole scaffold [73].

Pathak et al. synthesized the 2,6-disubstituted benzothiazole by mixing 2-amino-6-nitro BTA and acetic anhydride to combat cancer. They then examined its effectiveness against MCF-7, MG63, and HeLa cell lines. The anti-cancer activity of the sulphonamide scaffold-based BTA 57 is modest, as shown in **Figure 15**, with IC_{50} 34.5μM for MCF 7, 44.1μM for HeLa, and 36.1μM for MG-63[74].



55

IC_{50} = 0.22 μM

Cell line = HeLa

56

IC_{50} = 0.6 μM

Cell line = HeLa

57

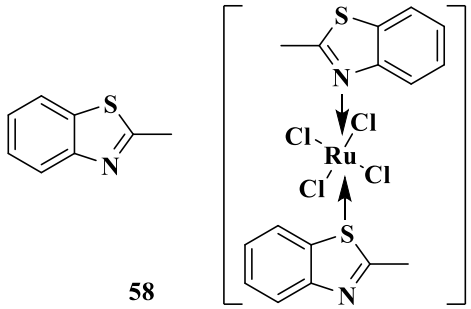
IC_{50} = 34.5 μM, 44.15 μM and 36.1μM

Cell line = MCF-7, HeLa, MG63

Figure15: Secondary sulphonamide based benzothiazole derivatives.

Miscellaneous benzothiazole derivatives as anticancer agents

Kotte et al. evaluated the anticancer efficacy of Ru(III) in conjunction with benzothiazole derivatives against KE-37 and K-562. **Figure 16** shows that out of all the compounds, the Ru(III) combination with methylbenzothiazole 58 had the most cytotoxic effect on K-562 and KE-37, associated to the reference cisplatin, with IC_{50} 7.74 ± 2.50 for KE- 37 and 16.21 ± 2.33 for K-562 [42].



58

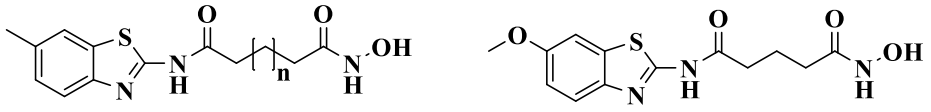
IC_{50} = 16.21 ± 2.33 μM, 7.74 ± 2.50μM

Cell line = K-562 and KE-37

Figure 46: Ru(III) containing methylbenzothiazole derivative.

Cao et al. elucidated the methodology for synthesizing hydroxamic acids containing benzothiazoles. 2-Aminobenzothiazole and adipic acid were first reacted to form esters. The target benzothiazole hydroxamates were then produced from these esters. Scientists examined the anticancer effects of these hydroxamates on five distinct cell lines: MCF-7, AsPC- 1, SW- 620, PC- 3, and NCI- H460. Out of all the compounds that were produced, hydroxamic

acids 59 and 60 (**Figure 17**) showed outstanding anticancer activity. Hydroxamic acid 59 had an normal IC_{50} 0.81 mg/mL and hydroxamic acid 30 1.28 mg/mL [75].



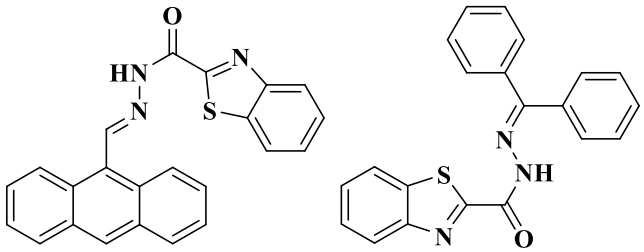
59 **60**

IC_{50} = 0.81 mg/mL and 1.28 mg/mL
Cell line = MCF-7, AsPC-1, SW620, PC3, and NCI-H460

Figure 57: Hydroxamic acid containing methyl/methoxy BTA derivatives.

Benzothiazole derivatives as EGFR inhibitors

A hydrophobic glycoprotein belonging to the tyrosine kinase family, the epidermal growth factor receptor (EGFR) goes under many names, including HER1 and ErbB1. Additionally, ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4) are members of this family [76]. EGFR is involved in many intracellular processes, such as controlling cell survival, growth, movement, the formation of new blood vessels, invasion, attachment, and specialization [77],[78]. Acid hydrazones 61 and 62 (**Figure 18**) showed strong inhibition of EGFR kinase, with IC_{50} values of 24.58 and 30.42 μM, respectively. Gefitinib exhibits potent EGFR kinase inhibition with an IC_{50} value in the nanomolar range (~20–40 nM), whereas the synthesized acid hydrazones 61 and 62 (**Figure 18**) showed comparatively weaker inhibition with IC_{50} values of 24.58 μM and 30.42 μM, respectively. They also inhibited HeLa cells (IC_{50} = 6.12 μM and 7.80 μM for 61 and 62), MCF-7 cells (IC_{50} = 6.95 μM and 8.16 μM for 61 and 62), HCT-116 cells (IC_{50} = 3.26 μM and 4.56 μM for 61 and 62), PC-3 cells (IC_{50} = 5.97 μM and 12.30 μM for 61 and 62), and HepG2 cells (IC_{50} = 7.08 μM and 8.59 μM for 61 and 62). These results were similar to those of the reference drug Lapatinib (HeLa IC_{50} = 3.39 μM, MCF-7 IC_{50} = 5.71 μM, HCT-116 IC_{50} = 6.34 μM, PC-3 IC_{50} = 4.29 μM, HepG2 IC_{50} = 5.13 μM[79].

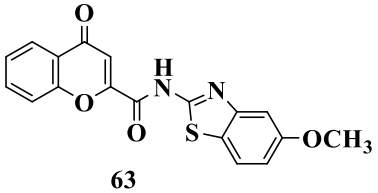


61 **62**

Figure 68: EGFR inhibitors BTA derivatives.

Benzothiazole derivatives as CK2 inhibitors

The protein kinase CK2 is a perpetually active tetrameric enzyme. A regulatory CK2β-dimer and two catalytic α-subunits make it up [80], [81]. A extensive variety of communication pathways, cellular compartments, survival strategies, and metabolic activities have been linked with CK2, which is ubiquitous in eukaryotic creatures [82]. In cancer, CK2 controls cellular activities linked to cancerous transformation, including cell cycle advancement, tumor development, and resistance to cell death [83]. Compound 63 (**Figure 19**) had the highest activity in inhibiting CK2 (IC50 = 0.08 μM) and significantly slowed the development of HL- 60 cell line (IC_{50} = 0.25μM) in comparison of Silmitasertib (CX-4945) is a highly potent CK2 inhibitor with an IC_{50} of approximately 1 nM [84]



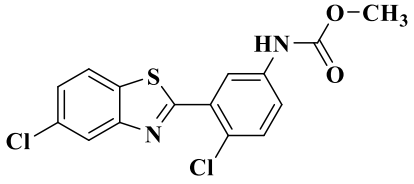
63

Figure 197: Kinase 2 (CK2) inhibitors BTA derivative.

Benzothiazole derivatives as lysophosphatidic acid acyltransferase (LPAAT) inhibitors

Triglyceride synthesis is aided by a class of membrane proteins known as acylglycerol -3-phosphate acyl transferases (AGPATs), which referred as LPAATs. They aid in the conversion of phosphatidic acid (PA) into lysoPA. Overexpression of LPAAT-β is common in several malignancies, such as leukemia, lymphoma, myeloma, ovarian,

melanoma, colorectal, leukemia, mesothelioma, osteosarcoma, and myeloma [85], [86], [87]. The most effective compound against LPAAT-β was compound 64 (**Figure 20**). In the lab, it was examined to see whether it could block the development of MCF7 and DU145 cell lines. The IC_{50} was 50 μM.[88].



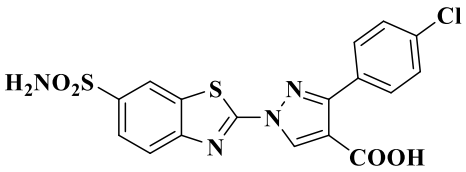
64

Figure 80: Lysophosphatidic acid acyltransferase BTA derivative.

Benzothiazole derivatives as CA inhibitors

There are eight classes of carbonic anhydrases (CA), which are metalloenzymes present in prokaryotes and eukaryotic organisms. The families are α, β, γ, δ, ζ, η, θ, and ι [89], [90], [91]. The alpha family of enzymes known as human carbonic anhydrases (hCAs) has fifteen different variants. Catalytic activity, localization in the body, and cellular location are three ways in which these isoforms vary. They are secreted (hCA VI), located in the cytosol (hCA I, II, III, VII, and XIII), connected to membranes (hCA VA and VB), and in the mitochondria (hCA VA and XII) [92], [93]. CAs facilitate the bicarbonate ion and proton reversible conversion of CO_2. Within the majority of carbonic anhydrases (CAs), you may find a zinc ion (Zn2+), which is absolutely necessary for catalytic activity. Many physiological and pathological systems rely on this response [94]. These activities include the movement of CO_2 and bicarbonate between the body's tissues and lungs, regulating CO_2 and pH levels, the release of electrolytes in diverse tissues and organs, and metabolic responses such as lipogenesis, gluconeogenesis, and ureagenesis [95], [96].

The 6-sulfamoyl-benzothiazole nucleus was introduced to 4-functionalized pyrazoles derivative in four different series of compounds produced in 2014. These derivatives were studied for their potential as carbonic anhydrase inhibitors (CAIs)[69]. Each series showed a significant reduction in the cancer-related isoforms hCA IX and hCA XII. The most effective compound, 65 (**Figure 21**), with a Ki value of 2.8μM for hCA IX and 5.5μM for hCA XII [97].



65

Figure 91: carbonic anhydrase (CA) inhibitors BTA derivative.

CONCLUSION

Molecular hybridization based on benzothiazoles has developed into a platform of critical importance in medicinal chemistry driven by cancer. The most recent research shows that in therapeutically relevant cancer models, BTA hybrids that are rationally developed have better cytotoxic efficacy, ligand efficiency, and multi-target modulation. To target specific kinase-binding interactions, such as those with EGFR, CK2, LPAAT, and hypoxia-associated CA IX/XII isoforms, structural diversity via heterocyclic conjugation allows for fine-tuning of electronic distribution and hydrophobic balance. In order to overcome resistance and increase therapeutic indices, thorough ADMET profiling, system-level mechanistic validation, and structure-guided optimization are necessary for translational success. The development of anticancer medicines derived from benzothiazoles is anticipated to be expedited via the ongoing integration of computational modeling, target-based screening, and hybrid pharmacophore design.

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