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1 Review

2-Aminobenzothiazole: A Privileged Scaffold for Tyrosine Kinase–Targeted Anticancer Agents

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Abstract 2-Aminobenzothiazole's planar structure and tendency to bind to a diverse set of oncogenic targets have made 2-aminobenzothiazole a highly sought heterocyclic in research for anticancer agents. In the past 10 years, intense research in medicinal chemistry has clarified that carefully planned substitution for benzothiazole can yield highly efficient and specific anticancer agents. In this critical assessment, we will specifically evaluate both research and efforts related to 2-aminobenzothiazole-based anticancer agents between 2015 and 2024 for their anticancer targets, SAR relationship, and mechanism of action. In particular, we highlight 2-aminobenzothiazole-based compounds targeting CDKs, Aurora kinase, RAF kinase, and various receptor and non-receptor tyrosine kinases such as EGFR, VEGFR-2, CSF1R, MET, FAK, and DYRK2. Besides inhibition of kinase activity, other non-kinase targets are systematically analysed and introduced in this patent review. These include BCL-2 family members, HDACs, epigenetic modifiers (LSD1, NSD1, FTO), HSP90, mutant p53, and DNA topoisomerases. Substitutions at the C-2, C-5, C-6, and C-7 positions of the benzothiazole ring are examined thoroughly about their anticancer properties and target engagement. Also underscored are the existence of commercially available drugs and patented compounds, as well as translational candidates featuring the 2-aminobenzothiazole pharmacophore. The paper emphasises the dual mechanistic targetability of 2-aminobenzothiazole derivatives as valuable lead compounds targeting both kinases and other targets in an innovative manner aimed at future development of targeted anti-cancer therapies.

Keywords 2-Aminobenzothiazole; Anticancer agents; Tyrosine kinase inhibitors; Structure–activity relationship (SAR); Targeted cancer therapy; VEGFR-2/EGFR inhibition; Kinase signalling; Drug design; Heterocyclic scaffolds

1. Introduction

Cancer encompasses a variety of diseases, which originate in almost all body organs. The condition arises due to the unregulated growth and development of abnormal cells, which also extend beyond their expected boundaries and invade other body organs. The final stage, which is commonly referred to as metastasis, is one of the major reasons for deaths associated with this disease. Cancer is also referred to

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as a malignant tumour and/or neoplasm[1].

The chemical molecule $C_6H_4S(N)CNH_2$ is an aminobenzothiazole. Despite having an amino group at the unique methylene location of the thiazole ring, it is still connected to the parent benzothiazole. It is a planar molecule that occurs as an amine tautomer, as shown by X-ray crystallography[2].

Benzothiazole, a heterocyclic compound, has various physiological properties making it very valuable in pharmacology as well as inorganic chemistry. There have been investigations regarding the possible biological properties of benzothiazole and/or its derivatives. There were studies conducted in the 1950s about the effectiveness of 2-aminobenzothiazole as a muscle relaxer. Since then, various derivatives of benzothiazole have been found to exhibit diverse pharmacological properties such as antibacterial, anti-inflammatory, analgesic, anticonvulsant, antiviral, anti-helmintic, antioxidant, and anticancer activities[3].

The fused benzoheterocycle benzothiazole (BTA) is present in several naturally occurring ring compounds and imparts pharmacological, medicinal, and medical properties to them. Both terrestrial and marine substances contain BTA and serve various biological activities. In BTA, the Thiazole and benzene rings are joined to form the nucleus. BTA compounds are known to possess significant biological and pharmacological effects on various types of cancer cell lines, including HeLa (human cervical carcinoma)[4].

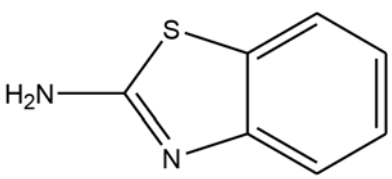
Hepatocellular carcinoma (HCC), SW480 (Human colon adenocarcinoma), HepG2 (Human liver carcinoma cells), Ovarian and Mammary Tumour cell lines, Colon, Non-small cell lung, and Breast subpanel, among others[5].

Although several reviews have addressed benzothiazole derivatives broadly, a focused and updated analysis of 2-aminobenzothiazole derivatives, particularly emphasising molecular targets, SAR trends, and translational relevance from 2015 onward, is lacking. This review aims to fill this gap. Regarding recent developments on 2-aminobenzothiazole derivatives as new antineoplastic agents based on their targets in proteins, such as the mutant p53 proteins[6], tyrosine kinase (CSF1R, EGFR, VEGFR-2, FAK, and DYRK2)[7], HDAC[8], NSD1, LSD1, FTO, DNA topoisomerases, mPGES1, SCD, hCA IX/XII, and CXCR receptor. In addition, the anti-cancer properties of the chelates[7].

2. 2-Aminobenzothiazole Derivatives as Promising Anticancer Scaffolds

2.1 Inhibition of tyrosine kinases

PTKs phosphorylate the γ-phosphate group of ATP and add it to the hydroxyl groups of tyrosyl residues in target proteins. Once again, they are divided into two subclasses. These include non-receptor tyrosine kinases and receptor tyrosine kinases.



2 aminobenzothiazole

Structure 1: Structure of 2-aminobenzothiazole

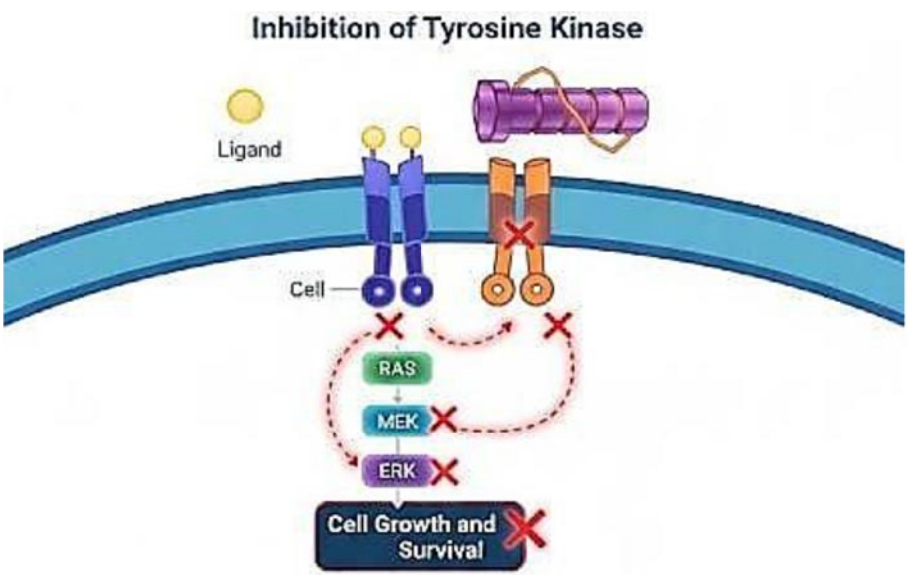


Figure 1: Schematic representation of tyrosine kinase inhibition and downstream signalling blockade.

Several important cellular processes, like the cell cycle, metabolism, migration, and proliferation, are dependent on RTK. The general structure of the RTK protein comprises an extracellular portion that binds the ligand, a single transmembrane domain, and a catalytic part termed the intracellular kinase domain. Uncontrolled activity and mutations in RTKs are implicated in human cancers and resistance to several anticancer agents[6].

2.2 Inhibition of CSF1R kinase

Colony-stimulating factor 1 receptor (CSF1R or c-FMS) is a class III RTK receptor kinase, together with the stem cell factor receptor (c-KIT), FMS-like tyrosine kinase 3 (FLT3), and the alpha and/or beta forms of the platelet-derived growth factor receptor (PDGFR). The CSF1R undergoes transphosphorylation of its cytoplasmic domain in response to its association with IL-34 or the macrophage colony-stimulating factor (CSF1), triggering autophosphorylation for activation. Tumour-associated macrophages (TAMs) play a crucial role as regulatory immune cells that have the potential to negatively impact the prognosis of various malignancies by promoting tumour progression[9]. The M1 and M2 phenotypes of TAMs have both tumour-supporting and tumour-targeting properties. Both M1 and M2. In cancer immunotherapy, the blockade of CSF-1R signal transduction in macrophages has appeared promising. The compound 2-Aminobenzothiazole 3 exhibited potent inhibition of CSF1R kinase (IC50=1.4nM) and a very good selectivity profile against 468 kinases. Moreover, three compounds demonstrated good in vivo PK profiles. The treatment of PANC02 tumours with 3 resulted in the reduction of tumour macrophages and CSF1R protein to an equal extent as that of BLZ945. The MC38 xenograft model treated with 3 resulted in the reduction of tumour development by 62% at a dose of 200 mg/kg[10].

2.3 Suppression of EGFR

Along with ErbB2 (HER2/neu), ErbB3 (HER3), and ErbB4 (HER4), the transmembrane glycoprotein EGFR (HER1/ErbB1) is also a part of the tyrosine kinase family. It has a crucial role as a mediator in the activation of a multitude of biological processes like angiogenesis, migration, cell death, survival, and proliferation. Dysregulation in the biological processes mediated by the EGFR may be caused by either the overexpression/or the mutation in the EGFR and may give rise to diverse solid cancers like non-small-cell lung carcinoma (NSCLC), prostate carcinoma, breast carcinoma, gastric carcinoma, ovarian carcinoma, and cervical carcinoma[11].

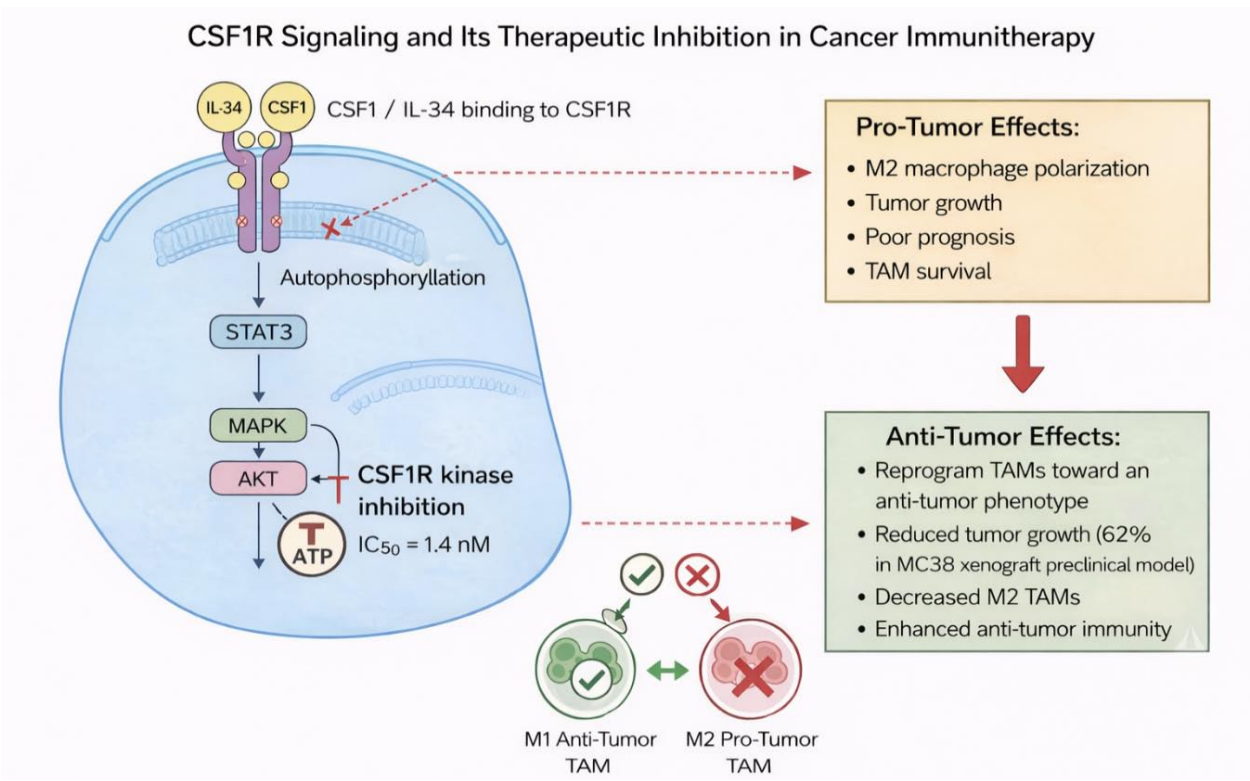
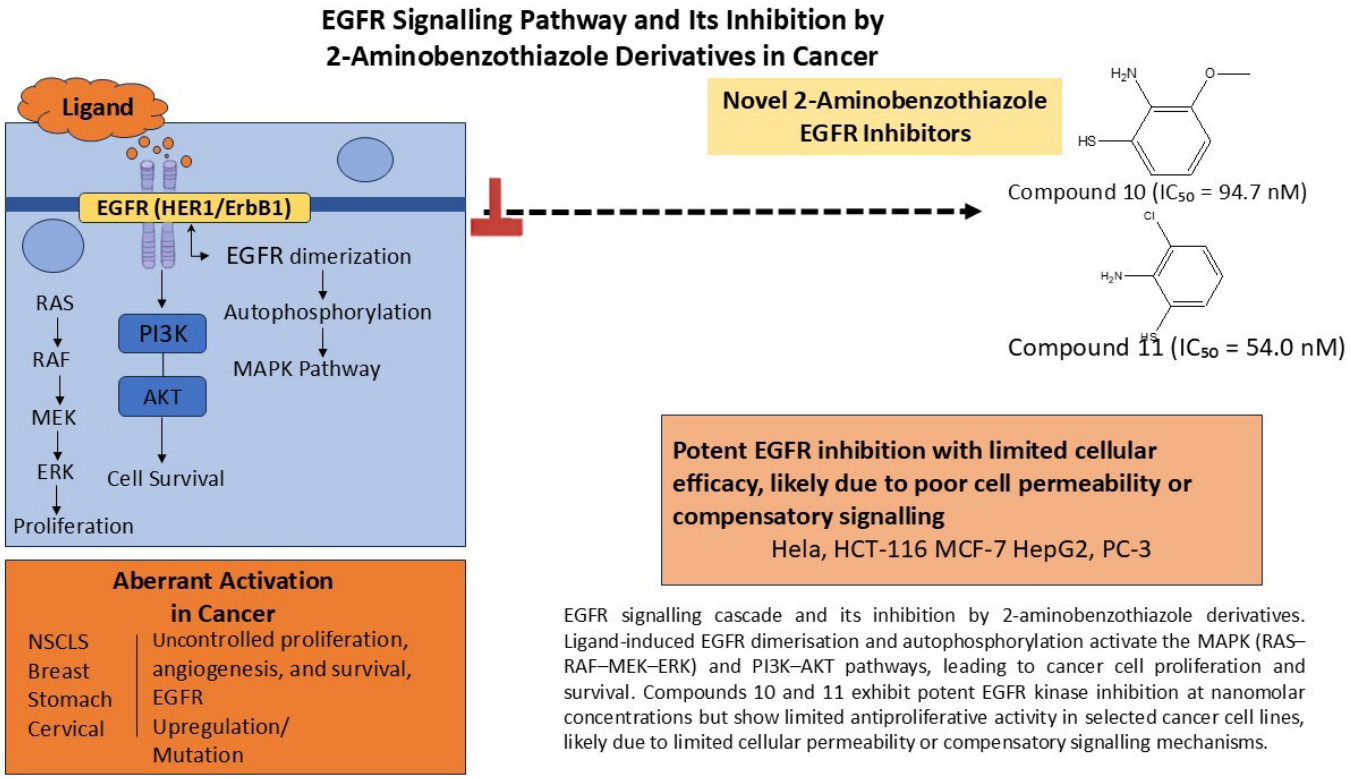


Figure 2: CSF1R signalling pathway and its inhibition by 2-aminobenzothiazole leading to suppression of tumour-associated macrophage–mediated tumour progression.



EGFR signalling cascade and its inhibition by 2-aminobenzothiazole derivatives. Ligand-induced EGFR dimerisation and autophosphorylation activate the MAPK (RAS–RAF–MEK–ERK) and PI3K–AKT pathways, leading to cancer cell proliferation and survival. Compounds 10 and 11 exhibit potent EGFR kinase inhibition at nanomolar concentrations but show limited antiproliferative activity in selected cancer cell lines, likely due to limited cellular permeability or compensatory signalling mechanisms.

Figure 3: EGFR signalling pathway and its inhibition by 2-aminobenzothiazole derivatives in cancer.

Due to the vast effort made by scientists in the application of EGFR as a target, several potential compounds have come forward as EGFR inhibitors. The study team applied structure-based design to develop a novel set of EGFR inhibitors. The 2-aminobenzothiazoles, compounds 10 and 11, display potent inhibition activity against the EGFR kinase with IC50 values of 94.7 and 54.0 nM, respectively. The two compounds did not display significant inhibition in HeLa, HCT-116, MCF-7, HepG2, and PC-3 cells. The antiproliferative activity of compound 11 was demonstrated to be diminished when the 2,5-dimethoxyphenyl moiety was replaced by the 2-thienyl, 5-bromo-2-thienyl, and 9-anthracenyl groups[12].

2.4 Inhibition of VEGFR-2 Kinase

On further testing, 2-aminobenzothiazoles 10 and 11 were found to strongly inhibit EGFR kinase activity with IC50 values of 94.7 and 54.0 nM, respectively. Unfortunately, chemical entities against HeLa, HCT-116, MCF-7, HepG2, and PC-3 cell lines exhibited only minor inhibitions. No inhibition in cell growth was caused by chemical 11 due to replacement by 2-thienyl, 5-bromo-2-thienyl, and 9-anthracen[13]. The strategy of structure-based drug design enabled the scientists to discover that compound 19, which is the 2-aminobenzothiazole analogue, inhibits VEGFR-2 with an IC50 of 0.5 μM. In addition, Analogue 19 exhibited potent suppression of chorioallantoic membrane formation and the growth of vasculogenic arteries on chick embryos[14].

SAR studies revealed that the introduction of a methyl group on the benzothiazole scaffold led to a reduction in activity, while substitution with alternative scaffolds significantly influenced anti-angiogenic efficacy. As indicated by molecular docking studies, compound 19's benzothiazole ring seems to occupy the hydrophobic pocket created by the DFG loop within the kinase domain of VEGFR-2. Hydrogen bonds are observed between the nitrogen atom of the benzothiazole ring and the backbone nitrogen atom of Asp1044, and between the amide nitrogen atom and the side chain carbonyl oxygen atom of Glu883[15].

3. Structure-activity relationship in benzothiazole derivatives concerning anticancer activity

The importance of the ring structure in anticancer drugs has already been proven on the basis of the structural units that make up benzothiazole. The role of the substituted benzothiazole molecules, that is,

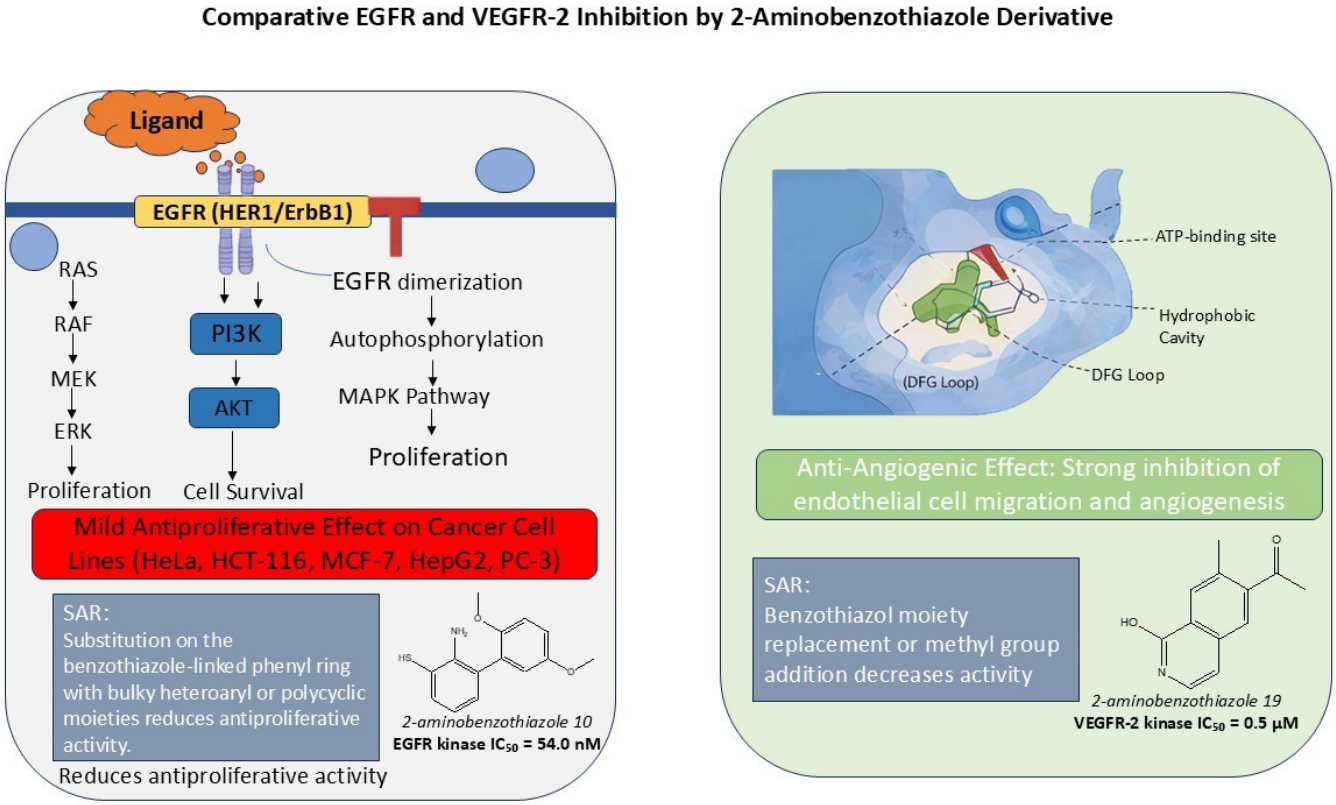


Figure 4: Dual inhibition of EGFR and VEGFR-2 by 2-aminobenzothiazole derivatives and associated structure–activity relationships.

substitution at the 2nd position along with the C-5, C-6, and C-7 positions, has been responsible for its biological properties[5,12].

1. The N-atom needs to be free and unblocked for anticancer effects to occur in the rings of the benzothiazole structure (Compound 4)[16].

2. It should be a plane because the linkages between the DNA molecules of benzothiazoles are essential[16].

3. The aryl group on the C-2 position in the benzothiazole ring plays an important role in the anticancer activity, as studies on structure-activity relationships (compound 5) have found[16].

4. The effect of various substitutions, including the influence of the electron-donating group (OCH3), the electron-withdrawing group (F), and the influence of H, CH3 at the C-30 position in the benzothiazole portion, was investigated. It was found that the presence of the methyl group at C-30 increased the activity of the compound (compound 6)[16].

5. The -NH, -and-Cl groups on the C-40 position in the phenyl ring play a crucial role in the anticancer activity of the benzothiazole compound (compound 6). The data indicate that the 1,2,4-triazole ring is more crucial for activity than the 1,2,3-triazole and 1,2,3,4-tetrazole ring systems[17].

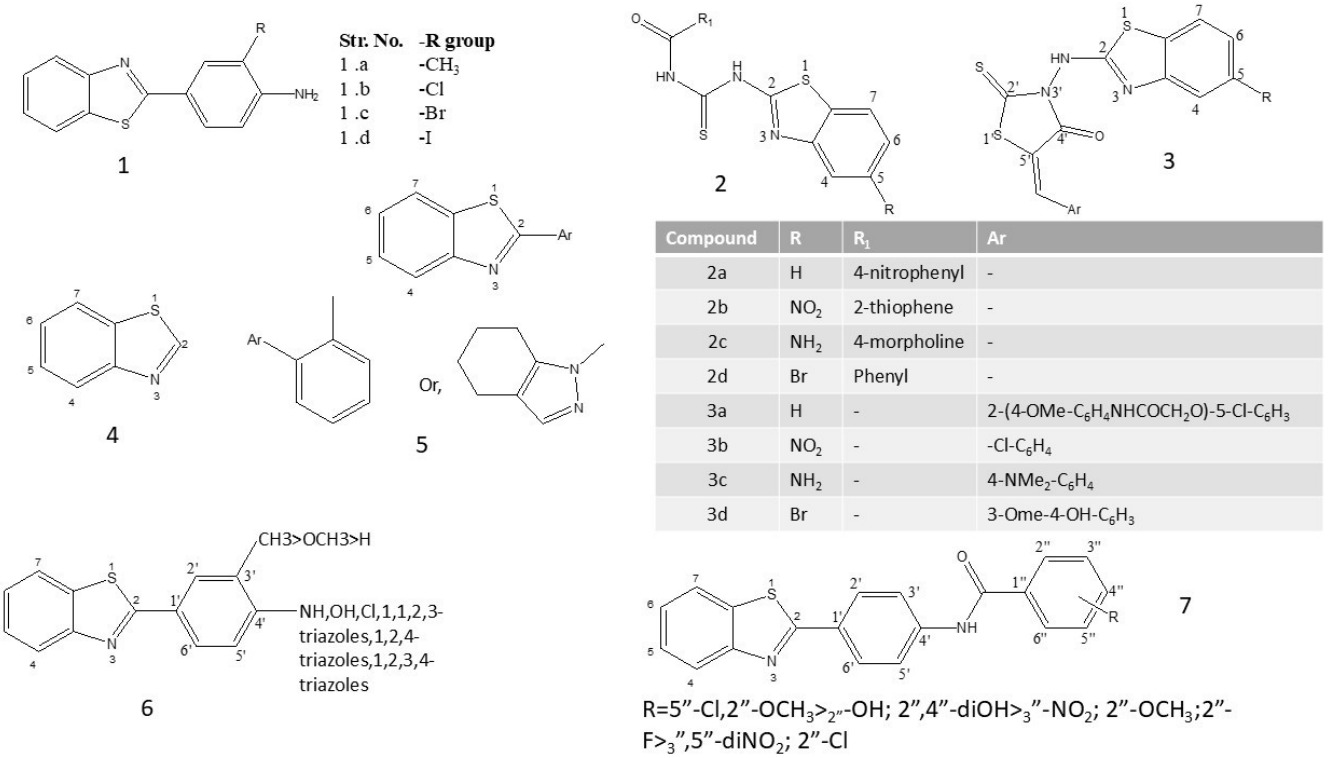
6. Amide derivatives of the 2-phenyl benzothiazoles demonstrate high anticancerous properties against various forms of cancer, such as cervical cancer, as well as human leukaemia cells. Primarily, the principal activity of the drug is dependent on the substitution pattern within the moiety, where the amide bonds are changed with phenyl groups. This is referred to as compound 7[17].

7. The evaluation of the efficacy of several substituents in the C-5, C-6, and C-7 regions of the benzo thiazole ring system: Activity was significantly increased by adding an electron-withdrawing group (most notably F) at position C-5 and a methoxy/methyl group at position C-6. However, the addition of methoxy groups at the C-5 and C-7 positions (i.e., ring series of tri-substituted benzothiazoles) significantly decreased the antiproliferative characteristics of this chemical (compound 7)[17].

4. BTA compound as an anticancer agent

4.1 Fluorinated derivatives of benzothiazole as anticancer agents

Antitumor effects of fluorinated 2-aryl benzothiazole derivatives were tested by Aiello et al. on various types of cancer cell lines, like MCF-7 (breast



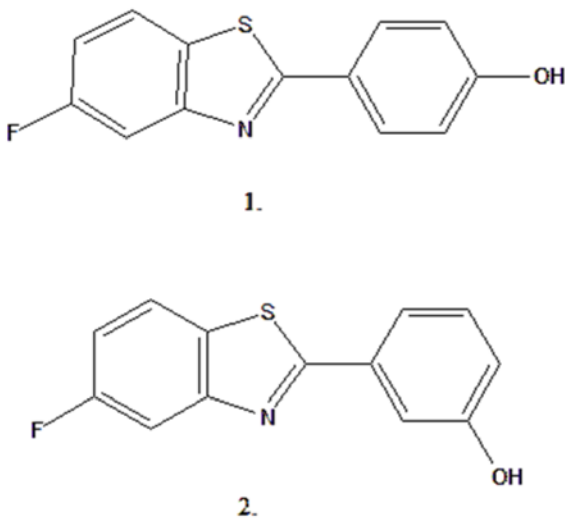
Compound	R	R_1	Ar
2a	H	4-nitrophenyl	-
2b	NO_2	2-thiophene	-
2c	NH_2	4-morpholine	-
2d	Br	Phenyl	-
3a	H	-	2-(4-OMe-$C_6H_4NHCOCH_2O$)-5-Cl-C_6H_3
3b	NO_2	-	-Cl-C_6H_4
3c	NH_2	-	4-NMe_2-C_6H_4
3d	Br	-	3-Ome-4-OH-C_6H_3

Structure 2: Compounds with anticancer activity (1–7)

adenocarcinoma), MDA-MB-468 human breast cancers, which originated from the metastatic site—mammary gland/breast[18]. Various fluorinated BTA derivatives 1 [(3-5fluoro benzo[d]thiazol-2-yl)phenol], 2 [(4-5fluorobenzo[d]thiazol-2yl)phenol], where the phenyl has hydroxyl groups on the third and fourth positions, showed the highest activity on MCF cell lines compared with BTA derivatives containing alkoxy[19].

4.2 Anticancer Activity of Imidazole-Based Benzothiazole Derivatives

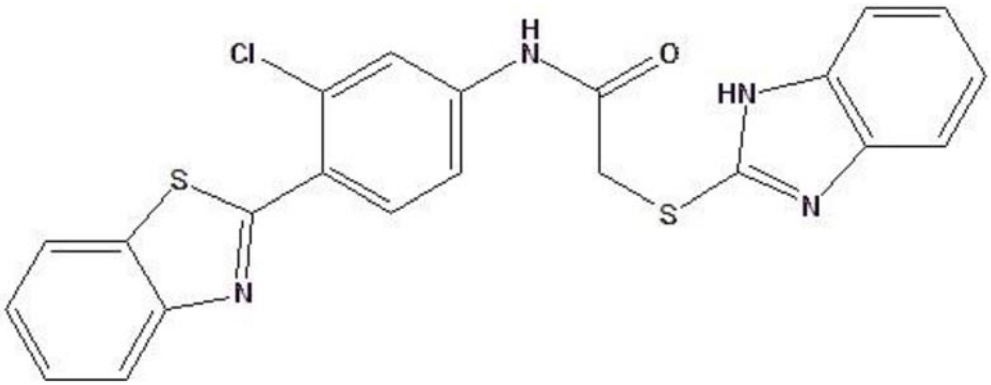
Yurttas et al. have used 60 human tumour cell lines for the anticancer potential evaluation of 2-(4-aminophenyl) BTA derivatives substituted with various heterocyclic rings. BTA derivative 14: N-(4-(benzo[d] thiazol-2-yl) phenyl)-2-(1-phenyl-1Hbenzo[d]imidazol-2-yl-thio)-acetamide and 13: 2– (1H-benzo[d]imidazol-2-ylthio)-N-(4-(benzo[d]thiazol-2-yl)-3 chlorophenyl) acetamide. The heterocylic substitutions change the anticancer potential and activities of these BTA derivatives, while the derivative 13 is less active than the derivative 14, this derivative 14 showed potential comparable to that of standard medicines. Thus, based on the heterocyclic substitution, the overall anticancer potential of 2-(4-aminophenyl) benzo thiazole



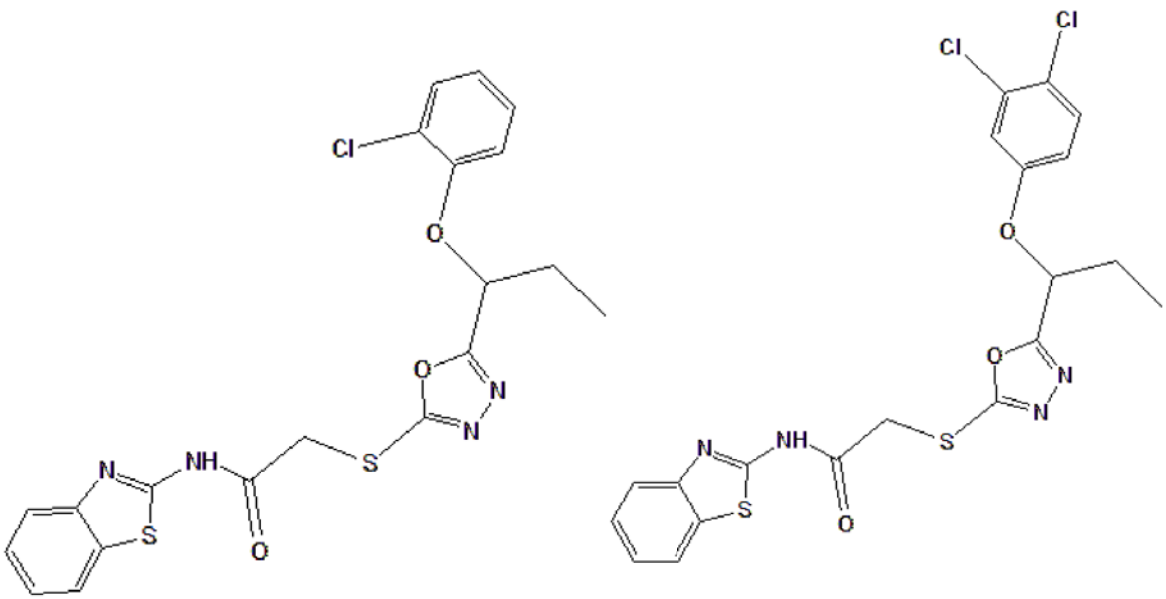
Structure 3: Chemical structures of fluorinated 2-aryl benzothiazole derivatives (1–2)

derivatives was worked out as benzimidazole, imidazole >benzothiazole >benzoxazole[18]. Singh et al. synthesized imidazole-based benzothiazoles by treating modified anilines with KSCN to get the required benzothiazole derivatives and tested their anticancer potential[20].

4.3 Oxadiazole-Substituted Benzothiazole Derivatives with Anticancer Potential



Structure 4: Substituted phenyl imidazole-based benzothiazoles.



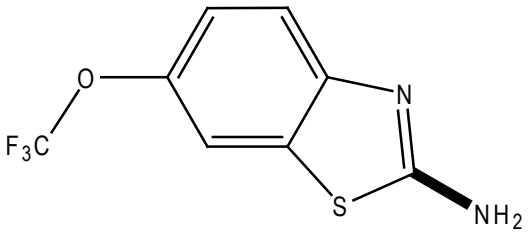
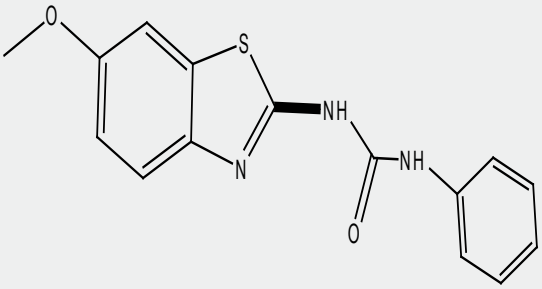
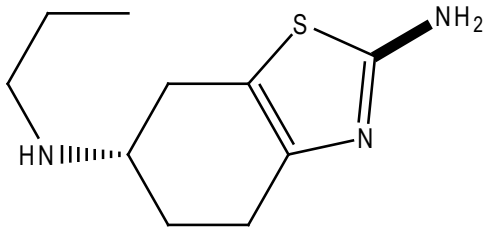
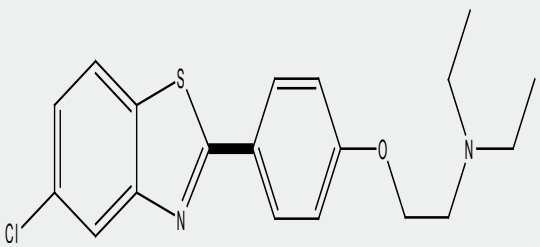
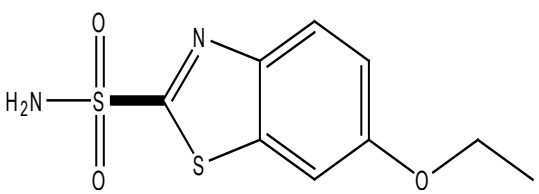
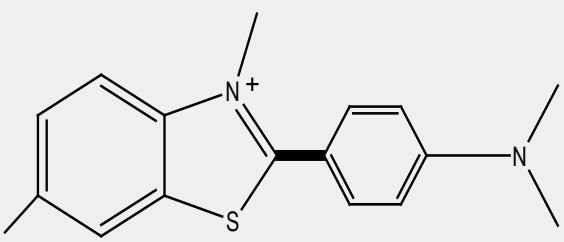
Structure 5: Oxadiazole-based acetamide benzothiazole derivatives.

In the current study, Akhtar et al. synthesised BTA and 1,3,4-oxadiazole-2-thione derivatives and showed their in vitro anticancer activity against a number of tumour cell lines. 20 (N-(benzo[d]thiazol-2-yl)-2–(5-(1–(3,4-dichlorophenoxy)ethyl) and 19-2–(5-(1–(2-chlorophenoxy)propyl)BTA derivatives-1,3,4-oxadiazol-2-ylthio)ace tamide)-1,3,4-oxadiazol 2-ylthio) acetamide) shown remarkable effectiveness against leukaemia cell lines. Compounds 19 and 20 have CCRF-CEM CC50 values that were within the range of doxorubicin, a common medication. However, the hybrid structures of 19 and 20 lost some of their anti-tumour effectiveness when a bromo moiety was swapped out for a chloro moiety[21].

5. Marketed drug 2- Aminobenzothiazole examples

Various SAR studies of benzothiazole analogs have demonstrated that the aminobenzothiazole ring system represents one of the most versatile heterocyclic frameworks in the development of anticancer drugs[22], and the nature and position of the substituent significantly influence anticancer activity. Such a scaffold is known to yield compounds that exhibit potent antiproliferative activity against a wide range of cancer cell lines[18]. Clinically useful drugs such as riluzole, an FDA-approved benzothiazole derivative for amyotrophic lateral sclerosis, and frentizole, a benzothiazole-based immunosuppressive agent, illustrate the wide medicinal utility of this theme. The potential therapeutic applications of compounds containing the benzothiazole backbone extend beyond anticancer agents[23]. To explore new therapeutic applications, much medicinal chemistry effort has focused on diversifying the 2-aminobenzothiazole skeleton[24].

Table 1: Approved and clinically used benzothiazole-containing drugs and their therapeutic applications.

Drug	Structure	Description
Riluzole		A derivative of trifluoromethoxybenzothiazole with neuroprotective qualities is riluzole (6-(trifluoromethoxy) benzothiazol-2-amine). For the treatment of amyotrophic lateral sclerosis (ALS), riluzole is advised[25].
Fretizole		A benzthiazole derivative with a phenyl urea tail, frentizole (1-(6-methoxy benzothiazol-2-yl)-3-phenylurea) is used as an immunosuppressive and antiviral medication. Frentizole is used to treat lupus erythematosus and rheumatoid arthritis[26].
Pramipexole		N-propyl-4,5,6,7-tetrahydro-benzothiazole-2,5-diamine, or pramipexole, is a selective dopamine D2 agonist. It can be used as a monotherapy for Parkinson's disease and has a neuroprotective effect. Additionally, it is used to treat advanced forms of Parkinson's disease in combination with levodopa[27].
Halethazole		Halethazole (2-(4-(5-chlorobenzo thiazol-2-yl)phenoxy)-N,N-diethyl ethan-1-amine) exhibits antibacterial and antifungal activities[28].
Ethoxzolamide		5-ethoxy benzothiazole-2-sulfonamide is the chemical name of ethoxzolamide, a specific carbonic anhydrase inhibitor. Both carbon dioxide and carbonate absorption are restricted by ethoxzolamide. One potent diuretic is ethoxzolamide[29].
Thioflavin-T		Thioflavin-T is used as a fluorescent probe and is chemically 4-(3,6-dimethyl-benzothiazol-2-yl)-N, N-dimethylaniline. It is used as an amyloid imaging agent to identify amyloid fibrils[30].

6. Patents on Aminobenzothiazole-based kinase inhibitors for anticancer activity

Table 2: Selected patents on Aminobenzothiazole-based kinase inhibitors for anticancer activity

Publication No.	Title	International application	International Filing Date	Publication Date	Inventor	Abstract
US 9,345,700 B2	Compositions and Methods Useful for Treating Diseases	PCT/US2012/028263	08 March 2012	24 May 2016	Michael H. Cardone et al.	Describes novel small-molecule compounds (BH3 mimetics) and methods for treating cancers, particularly haematological malignancies, by inhibiting anti-apoptotic Bcl-2 family proteins (especially Mcl-1). The invention also includes combination therapies with proteasome inhibitors to enhance anticancer efficacy[31].
US 8,318,735 B2	2-Aminothiazole-4-Carboxylic Amides as Protein Kinase Inhibitors	PCT/US2007/022928	29 Oct 2007	27 Nov 2012	Gerald W. Shipps Jr. et al.	Reports novel aminothiazole derivatives acting as protein kinase inhibitors. These compounds target cyclin-dependent kinases and tyrosine kinases involved in cancer, inflammatory disorders, and proliferative diseases, providing a broad therapeutic application[32].
US 11,866,426 B2	Substituted Heterocyclic Compounds as Kinase Inhibitors	Not specified in snippet	Not specified	09 Jan 2024	Not specified	Discloses substituted heterocyclic compounds designed as kinase inhibitors with potential applications in oncology. These compounds interfere with aberrant kinase-mediated signalling pathways responsible for tumour growth and survival[33].
US 2024/0287098 A1	Novel Kinase Inhibitor Compounds and Therapeutic Uses	Not specified	Not specified	29Aug 2024	Not specified	Describes newly developed kinase inhibitor molecules targeting receptor and non-receptor tyrosine kinases. The invention focuses on blocking oncogenic signalling pathways, reducing cancer cell proliferation, and improving targeted cancer therapy outcomes[34].

The increasing number of recent patents underscores renewed industrial interest in 2-aminobenzothiazole-based kinase inhibitors, particularly for haematological and solid malignancies.

7. Conclusion

2-Aminobenzothiazole has emerged as a privileged heterocyclic scaffold in anticancer drug discovery due to its rigid, planar structure and strong ability to interact with diverse oncogenic targets. Studies reported between 2015 and 2024 demonstrate that rational modification of the benzothiazole core significantly influences biological activity. In particular, substitution at the C-2 position with aryl groups and the presence of a free amino nitrogen are essential for anticancer efficacy, while electron-withdrawing groups at C-5 and methyl or methoxy substituents at C-6 generally enhance potency. In contrast, excessive or bulky substitutions often reduce antiproliferative activity.

Beyond their well-established role as inhibitors of receptor and non-receptor tyrosine kinases such as EGFR, VEGFR-2, and CSF1R, 2-aminobenzothiazole derivatives have shown promising activity against non-kinase targets including BCL-2 family proteins, HDACs, epigenetic regulators, and DNA topoisomerases. The presence of marketed drugs and patented compounds containing this scaffold further highlights its translational relevance. Collectively, these findings support 2-aminobenzothiazole derivatives as valuable lead structures for the future development of targeted anticancer therapies.

Author contribution

Rani D. Navle performed the literature survey and prepared the initial draft. Nirmala V. Shinde supervised the review and critically evaluated the content. Arshad S. Shaikh coordinated the review process, revised the manuscript, and served as the corresponding author. All authors contributed to the literature analysis and approved the final manuscript.

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Conflict of Interest

The authors gratefully declare that they have no conflicts of interest.

Statements and Declarations

No financial or non-financial competing interests exist. No human or animal subjects were involved in this study.

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3 H. Singh et al., "Insight into the Synthesis, Biological Activity, and Structure-activity Relationship of Benzothiazole and Benzothiazole-hydrazone Derivatives: A Comprehensive Review," Mini-Reviews in Medicinal Chemistry, vol. 23, no. 5, pp. 537–575, May 2022, doi: 10.2174/1389557522666220523110521/CITE/REFWORKS.

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