Benzothiazole derivatives as anticancer agents

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ABSTRACT
Benzothiazole (BTA) belongs to the heterocyclic class of bicyclic compounds. BTA derivatives possess a broad spectrum of biological activities such as anticancer, antioxidant, anti-inflammatory, anti-tumour, antiviral, antibacterial, anti-proliferative, anti-diabetic, anti-convulsant, analgesic, anti-tubercular, antimalarial, anti-arthritic, anti-histaminic and anti-fungal among others. The BTA scaffolds showed a crucial role in the inhibition of the metalloenzyme carbonic anhydrase (CA). In this review an extensive literature survey over the last decade discloses the role of BTA derivatives mainly as anticancer agents. Such compounds are effective against various types of cancer cell lines through a multitude of mechanisms, some of which are poorly studied or understood. The inhibition of tumour associated CAs by BTA derivatives is on the other hand better investigated and such compounds may serve as anticancer leads for the development of agents effective against hypoxic tumours.

1. Introduction
Heterocycles are important pharmacophores and have significance to create privileged chemical structures possessing pharmacological activities. Five membered heterocyclic which incorporate oxygen, nitrogen and sulphur are found in broad spectrum therapeutic agents which have an enormous significance in drug discovery and drug development processes. Benzothiazole (BTA) is a fused benzo-heterocycle which is present in many naturally occurring products and is responsible for the medicinal, pharmacological and pharmaceutical applications of such natural products. BTA is present in terrestrial as well as marine compounds which exhibit various biological activities. The BTA nucleus is formed by the fusion of the thiazole ring with a benzene ring.

The pharmacological profile of the drug used for the management of amyotrophic lateral sclerosis Riluzole (Figure 1) attracted the attention of medicinal chemists towards biologically active benzothiazole.

The BTA scaffold possesses a wide spectrum of biological activities such as anti-inflammatory, fungicidal, anti-diabetic, analgesic, anti-microbial, antitumor, antileishmanial, antithrombinic, anti-histaminic, anti-fungal and anti-tumour activities. These neoplasm malignant tumours, have potential to invade or spread to other parts of body through blood stream and lymphatic system. The plethora of research mentioned in the present review of last decade on anticancer potential of BTA derivatives will be helpful in future drug discovery and drug development for the treatment of lethal cancer disease.

Cancer is the most prominent, notably complex and lethal disease which became a serious concern of today’s medical science. It poses a great challenge to medical scientific community for development of drugs, medicines and procedures for safer treatment and cure of cancer disease. These neoplasm tumour cells are diversified, heterogeneous cells with rapid proliferative properties. These neoplasm malignant tumours, have potential to invade or spread to other parts of body through blood stream and lymphatic system. The plethora of research mentioned in the present review of last decade on anticancer potential of BTA derivatives will be helpful in future drug discovery and drug development for the treatment of lethal cancer disease.

2. BTA derivatives as anticancer agents
2.1. Fluorinated derivatives of benzothiazole as anticancer agents
Aiello et al. synthesised fluorinated 2-aryl benzothiazole derivatives and evaluate them for anti-tumour activities against cancer cell lines such as MDA-MB-468 (mammary gland/breast tissues derived from metastatic site) and MCF-7 cell line (human breast adenocarcinoma). The fluorinated BTA derivatives 1 (3-(5-fluorobenzo[d]thiazol-2-yl)phenol) and 2 (4-(5-fluorobenzo[d]thiazol-2-yl)phenol) having hydroxyl substituents on the third and fourth position of phenyl exhibited the best activity having Gl0 values of 0.57 and 0.4 µM respectively against MCF-cell line as compared to BTA derivatives containing alkoxyl, methyl sulphonyl and ethyl substituents on the benzothiazole (Figure 2). Kumbhare et al.

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afforded the N-bis-benzothiazole and benzothiazoyl thiocarbamide derivatives and screened for cytotoxic activities against two human cell lines U-937 (human macrophage cell line), THP-1 (human leukaemia monocytic cell line) and B16-F10 (mouse melanoma cell line). The thiourea containing benzothiazole derivative 3 (Figure 3) demonstrated the best antiproliferative activity against the U-937 cell line as compared to standard drug Etoposide. The IC₅₀ values of compound 3 were higher (16.23 ± 0.81 μM), (484.73 ± 2.39 μM)) and (34.58 ± 1.73 μM)) as compared to standard compound etoposide IC₅₀ values (17.94 ± 0.89), (18.69 ± 0.94) and (2.16 ± 0.11 μM)) against U-937, B16-F10 and THP-1 cell lines respectively22.

Kumbhare et al. reported the synthesis of mannich base arylidimazo derivatives containing benzothiazole moiety and screened for their anticancer activities against HepG2, MCF-7 and HeLa cell lines. All these synthesised mannich bases BTA scaffolds showed cytotoxicity against all tested cell lines but the pyrrolidine based imidazo benzothiazole derivative 4 (Figure 3) demonstrated specific features of apoptosis as enhancement in the levels of caspase-3. The compound 4 exhibited anti cancer activity and proved to be the best antiproliferative agent as compared to other derivatives against HepG2, MCF-7 and HeLa cell line when screened at 4.0 μM concentrations. The SAR studies revealed that the incorporation of fluorine atom at the 7th position of derivative 4 enhanced the cytotoxicity. The compound 4 have potential to lead in the treatment of cancer especially against hepatocarcinoma. The anticancer activity potential of BTA scaffold 4 is encouraging for the development of new anti-cancer therapeutic agents and this will be good addition in armamentarium that consists of paclitaxel, cisplatin and doxorubicin drugs23.

Caputo et al. afforded two types of five derivatives on the basis of an aryl amide and an aryl urea functionalities attached at C-2 of benzothiazole core and these scaffolds were screened against 60 human cancer cell lines. The urea moiety based fluorophenyl containing benzothiazole derivative 4 (Figure 3) and cyanophenyl containing benzothiazole derivative 5 (Figure 4) demonstrated remarkable anticancer activities. The BTA derivative 4 exhibited the anticancer activity at 10⁻³M against different cell lines such as leukaemia cell lines (log GI₅₀ value -5.48), non-small cell lung cell lines (log GI₅₀ value -5.48), colon cancer cell lines (log GI₅₀ value -5.51), central nervous system cancer cell lines (log GI₅₀ value -5.49), melanoma cell lines (log GI₅₀ value -5.48), ovarian cancer cell lines (log GI₅₀ value -5.49), renal cancer cell lines (log GI₅₀ value -5.53), prostate cancer cell lines (log GI₅₀ value -5.50) and breast cancer cell lines (log GI₅₀ value -5.56) in comparison with reference drug 5-fluorouracil NSC 19893. The BTA scaffold 5 showed remarkable growth inhibitory activities against different human tumour cell lines such as leukaemia cell lines (log GI₅₀ value -5.93), non-small cell lung cell lines (log GI₅₀ value -6.0), colon cancer cell lines (log GI₅₀ value -5.89), central nervous system cancer cell lines (log GI₅₀ value -5.73), melanoma cell lines (log GI₅₀ value -5.89), ovarian cancer cell lines (log GI₅₀ value -5.74), renal cancer cell lines (log GI₅₀ value -5.90), prostate cancer cell lines (log GI₅₀ value -5.72) and breast cancer cell lines
(log GI50 value −6.0) as compared with reference drug 5-fluorouracil (NSC 19893). The scaffolds 4 and 5 showed the best anticancer therapeutic potential due to presence of electron with drawing groups on para position of phenyl ring.

El-Damasy et al. synthesised the novel amide and urea based BTA series of 20 sorafenib analogues in which the pyridylamide privileged functionality was attached with an ether linkage at 6-position of the BTA ring. A selected group of 12 potent scaffolds were evaluated and appraised for anti-proliferative activities against sixty human cancer cell lines. These chlorotrifluoromethyl phenyl ureido picolinamide benzothiazoles showed good inhibitory activities against ACHN (renal cancer cells line) and A-498 (human kidney carcinoma cell line) with GI50 values of 0.542 μM and 1.02 μM respectively. This compound also possess efficacy against UO-31 and RXF 393 cell lines.

Ma et al. reported BTA derivatives containing an ortho-hydroxy-N-acyl hydrazide moiety for antiproliferative activities and procaspase-3 kinase activation activities against five different cell lines, namely MDA-MB-231 (human breast adenocarcinoma cell line), MNK-45 (gastric cancer cell line), NCI-H226 (human lung cancer cell line), HT-29 (human colorectal adenocarcinoma cell line) and SK-N-SH (neuroblastoma cell line). The substituted 2-hydroxybenzylidene containing semicarbazide (Figure 6) showed inhibitory activities against all cell lines with IC50 and EC50 values ranging from 0.24 to 0.92 μM and 0.31 μM respectively. The SAR studies revealed the paaharmacological activities of BTA scaffold (Figure 6) in vitro is due to introduction of phenyl and benzoxyl substitutions.

Gabr et al. obtained hydrazine derivatives by treating 2-amino-6-fluorobenzothiazole with hydrazine hydrate which was further treated with the suitable aldehydes to afford 27 different BTA Schiff base derivatives. These derivatives were screened for antitumour potential against Hela (cervical cancer) and COS-7 (kidney fibroblast cancer) cell lines. The hydrazine based benzothiazole (Figure 6) exhibited IC50 of 2.41 μM and 4.31 μM against Hela and COS-7 cell lines as compared to reference doxorubicin having IC50 20.5 μM and 3.04 μM respectively. The SAR studies explained the effect of various substitutions on activities of all the synthesised derivatives.

Junjie et al. reported the synthesis of semicarbazone containing BTA derivatives by the reaction of 4-nitrobenzyl bromide with substituted amines under different reaction conditions and evaluated their anticancer activity against four different cancer cell line such as human colon cancer cells (HT29), human lung cancer cell (H460), non-small cell lung cancer (A549) and human breast cancer (MDA-MB-231). Among these derivatives, the indole based hydrazine carboxamide scaffold (Figure 7) showed potent antitumor activity with IC50 values of 0.015 μM for HT29, 0.28 μM for H460, 1.53 μM for A549 and 0.68 μM for MDA-MB-231. The structure – activity relationship explained that compound (Figure 7) exhibited the highest antitumor activity due to the presence of electron withdrawing groups in the 4-position of benzyl ring.

2.2. Imidazole based benzothiazole derivatives as anticancer agents

Yurttas et al. obtained 2-((4-amino phenyl)BTA derivatives substituted with different heterocyclic rings and tested their antitumor potential against 60 human tumour cell lines. The BTA derivatives 13 (2-((1H-benzo[d]imidazol-2-ylthio)-N-4-(benzo[d]thiazol-2-yl)-3-chlorophenyl) acetamide) (Figure 8) and 14 (N-4-(benzo[d]thiazol-2-yl)phenyl)-2-(1-phenyl-1H-benzo[d]imidazol-2-yl-thio)-acetamide) (Figure 8) showed remarkable antitumor potential against different cancer cell lines.
cancer cell lines. The heterocyclic substitutions affect the activity and antitumor potential of these BTA derivatives, with derivative 14 having comparable antitumor potential with the standard drugs whereas derivative 13 being less active compared to 14. The order overall antitumor potential of 2-(4-aminophenyl) benzothiazole derivatives with reference to the heterocyclic substitution was benzimidazole > imidazole > benzothiazole > benzoxazole.

Singh et al. reported the synthesis of imidazole based benzothiazoles by treatment of substituted anilines with KSCN which afforded the desired benzothiazole derivatives, and studied their anticancer activities. Compound 15 (Figure 9) showed excellent anticancer activity possessing IC_{50} value 10μM when compared with the standard drug doxorubicin.

### 2.3. Piperazine based benzothiazole derivatives as anticancer agents

Al-Soud et al. reported the synthesis of BTA derivatives incorporating sulphonamide, piperazino-arylsulfonamide and arylthiol scaffolds and determined their anti-proliferative potential against different cell lines, such as CCRF-CEM (Human acute B-lymphoblastic leukaemia), DU-145 (human prostate cancer cell lines express androgen receptor), HepG-2 cell line (human liver cancer), WIL-2NS (Human splenic B-lymphoblastoid cells), MRC-5 (human lung fibroblast cell line), MCF-7 cell line (human breast adenocarcinoma), MT-4 (human T-cells containing an integrated HTLV-1 genome), SK-MES-1 cell line (human lung cancer) and SK-SC cell line (skin melanoma). Derivative 16 (N-(2-(4-(benzo[d]thiazol-2-yl)piperazin-1-yl)-2-oxoethyl)-4-chlorobenzenesulfonodithioamide) showed antiproliferative activity (CC_{50} = 8 ± 3 μM) against human derived DU-145 cell line (Figure 10) whereas derivative 17 (N-(2-(4-(benzo[d]thiazol-2-yl)piperazin-1-yl)-2-oxoethyl)-2,5-dichlorobenzenesulfonodithioamide) demonstrated remarkable activities against several human derived cell lines such as HepG2 and DU-145 (with CC_{50} of 8 ± 2 μM, and 9 ± 2 μM, respectively) (Figure 10). Derivatives 16 and 17 exhibited antiproliferative potential due to the introduction of chloro and dichloro phenyl groups while their replacement of with hydrogen, methoxy, nitro, trifluoromethyl and methyl groups lead to a decrease in the antiproliferative potential of BTA derivatives.

Gurdal et al. synthesised BTA derivatives which incorporate piperazine moieties and evaluated their cytotoxicity against different cancer cell lines such as HUH-7 (Heptacellular), MCF-7 (Breast) and HCT-116 (Colorectal). GI_{50} values of these derivatives indicated that all compounds exhibited good potential against the aforementioned cell lines but the pyridine containing derivative 18 (Figure 11) had a remarkable cytotoxic activity with GI_{50} value 7.9 μM, 9.2 μM and 3.1 μM for HCT-116, MCF-7 and HUH-7 respectively. Apoptosis caused by this derivative during cell cycle arrest at subG1 phase was confirmed by Hoechst staining and fluorescence activated cell sorting analysis.

### 2.4. Oxadiazole based benzothiazole derivatives as anticancer agents

Akhtar et al. synthesised BTA and 1,3,4-oxadiazole-2-thione derivatives and determined their antitumor potential in in-vitro against different tumour cell lines. BTA derivatives 19 (N-(benzo[d]thiazol-2-yl)-2-(5-(1-(2-chlorophenoxy)propyl)-1,3,4-oxadiazol-2-ylthio)acetamide) and 20 (N-(benzo[d]thiazol-2-yl)-2-(5-(1-(3,4-dichloro-phenoxy)ethyl)-1,3,4-oxadiazol-2-ylthio)acetamide) exhibited remarkable activities against CCRF-CEM (leukaemia) cell lines. The CC_{50} values of compounds 19 and 20 (CC_{50} = 12 ± 2 μM and 8 ± 1 μM respectively) were comparable to the standard drug Doxorubicin. The replacement of the chloro moiety with bromo in the hybrid structures of 19 and 20 decreased their anti-tumour potential (Figure 12).

### 2.5. Morpholine-thiourea based benzothiazole derivatives as anticancer agents

Saeed et al. reported the synthesis of imidazole moiety based thiourea derivatives. These novel derivatives were tested for anticancer potential against cancer cell lines MCF-7 and HeLa cells. The MTT assay (colorimetric assessment of cell metabolic activity) indicated that the thiophene based acetamide benzothiazole derivatives 21 (Figure 13), morpholine based thiourea aminobenzothiazole derivative 22 (Figure 13) and morpholine based thiourea bromobenzothiazole derivative 23 (Figures 13) were potent anticancer agents having IC_{50} values of 24.15, 26.43 and 18.10 μM against MCF-7 cell line, and of 46.46, 45.29 and 38.85 μM against HeLa cells respectively.

Lei et al. obtained the morpholine based acetamide benzothiazole derivative 24 (Figure 14) by the treatment of morpholine with 2-chloroacetyl chloride and studied its anticancer activity against HCC (human hepatocellular carcinoma) cell lines HepG2 and Bel7402, reporting IC_{50} value for HepG2 and Bel7402 in the millimolar range.

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**Figure 9.** Imidazole based benzothiazole derivative 15.

**Figure 10.** Di-/monochlorobenzenesulfonamide based piperazine benzothiazoles derivative 16 and 17.

**Figure 11.** Pyridine containing piperazine benzothiazole derivative 18.
2.6. Thiophene based benzothiazole derivatives as anticancer agents

Racane et al. obtained the furyl and thiophenyl based diamidino substituted derivatives of phenyl-BTA and screened them for antiproliferative activities against different tumour cell line in vitro. Derivative 25 (diamidino-substituted thiophene based BTA; Figure 15) and 26 (imidazolinyl-substituted thiophene based BTA; Figure 15) exhibited low cytotoxic effects on normal human fibroblasts and strong antiproliferative effects on MiaPaCa-2 and MCF-7 cancer cell lines. The experimental data indicated that the benzothiazole derivatives having thiophene and imidazole substitutions possessed interesting antiproliferative activities.

2.7. Thiadiazole based benzothiazole derivatives as anticancer agents

Sekar et al. reported the synthesis and anticancer activities of six novel BTA derivatives. All derivatives exhibited anticancer activities of different tumour cell lines in vitro. Derivative 27 (diamidino-substituted thiophene based BTA, Figure 16) and 28 (imidazolinyl-substituted thiophene based BTA; Figure 15) exhibited low cytotoxic effects on normal human fibroblasts and strong antiproliferative effects on MiaPaCa-2 and MCF-7 cancer cell lines. The experimental data indicated that the benzothiazole derivatives having thiophene and imidazole substitutions possessed interesting antiproliferative activities.

2.8. Substituted pyridine based benzothiazole derivatives as anticancer agents

Shi et al. synthesised 20 BTA-2-thiol derivatives and investigated their anti-tumour potential against different cell lines such as SW480 (colon adenocarcinoma), HeLa, A549, HCT-116, HepG2 and SKRB-3 breast cancer cell line. The substituted bromopyridine acetamide benzothiazole derivative 29 (Figure 17) showed potent antitumor activity against SKRB-3, SW620, A549 and HepG2 cell lines with IC₅₀ values of 1.2 nM, 4.3 nM, 44 nM and 48 nM, respectively. Apoptosis was the mechanism of cell death and was concentration dependent in HepaG2 cells. These results indicated that BTA-2-thiols exhibit broad spectrum anti-cancer activities which are worth to be further investigated.

Xuejiao et al. reported the synthesis of a substituted pyridine based acetamide BTA derivative 30 (Figure 18) and screened its anti-cancer activity both in vitro and in vivo. Derivative 30 demonstrated anti-proliferative activities against a wide spectrum of normal human cell lines and induced the mitochondrial apoptotic pathway in HepaG2 cell lines. The BTA scaffold 30 proved to be a promising candidate for cancer chemotherapy.

Kamal et al. reported the synthesis of novel phenyl pyridopyrimidinones based BTA derivatives which were examined against four different cancer cell lines such as ME-180, DU-145, MCF-7 and B-16. The pyridine containing pyrimidine benzothiazole 31 (Figure 18) exhibited interesting cytotoxicity with IC₅₀ value of 4.01 μM against ME-180 (human cervical cancer cell lines).

2.9. Pyrazole based benzothiazole derivatives as anticancer agents

Gabr et al. reported the synthesis and evaluation of novel BTA scaffolds against 60 tumour cell lines at a single dose of 10 μM. The best derivatives were 32 (Figure 19) and 33 (Figure 19), which were further screened at 5 doses. These derivatives demonstrated interesting anticancer activity at micro molar and sub micro molar concentrations, against all sixty tumour cell lines with GI₅₀ in the low micro molar or submicromolar range. The SAR study revealed that introduction of the pyrazole moiety significantly enhanced the antitumor activity of both derivatives. Furthermore the presence of 2-hydroxy ester and 3-oxopyrazole within the pyrimidine moiety increased the anti-tumour activities of both derivatives. The simple BTA scaffolds having pyrazole functionalities were more potent against different cell lines as compared to derivatives having the pyrazole ring within a pyrimidine moiety.

2.10. Pyrimidine based benzothiazole derivatives as anticancer agents

Kambhare et al. synthesised the isoxazole pyrimidine based BTAs and evaluated them for anticancer activity by the MTT assay against different cell lines such as A549, Colo205, MCF-7 and U937.
cell lines, in comparison with the standard drug etoposide. The pyridine containing pyrimidine derivative 34 (Figure 20) demonstrated good anti-cancer potential with IC50 value 5.04 mM against colo205, 13.9 mM against U937, 30.67 mM against MCF-7 and 30.45 mM against A549 cell lines when compared with standard drug etoposide. The scaffold 34 activated p53 or TP53 (tumour protein) pathways, which regulate the equilibrium between apoptosis and cell proliferation. The SAR explained that the maximum cytotoxicity of derivative 34 against colon cancer cell line was due to the presence of methoxy group (–OCH3) in the phenyl40.

Waghmare et al. reported the synthesis of substituted pyrimidine containing benzothiazole derivative 35 (Figure 21) by refluxing BTAs with bis-methylthio methylene malononitrile, and tested their anticancer activity against 18 different cell lines. The scaffold 35 possessed excellent anticancer activity with a good percentage of growth inhibition against lung cancer, breast cancer and renal cancer cell lines. The good anticancer activity of derivative 35 is due to the presence of two methyl and one SCH3 groups in its structure41.

Caleta et al. synthesised cyano and amidinobenzothiazole substituted anilins which were treated with 2-bromo-6-cyanobenzothiazole under specific reaction conditions to afford compounds which have been studied for their anticancer activity against 6 cancer cell lines such as laryngeal carcinoma (Hep-2), breast carcinoma (MCF-7), cervical carcinoma (HeLa), pancreatic carcinoma (MiaPaCa-2), colon carcinoma (SW 620), lung carcinoma (H 460), and diploid fibroblasts (WI 38). Among them, the pyrimidine based carbonitrile benzothiazole derivative 36 (Figure 21) showed potent activity against all cancer cell lines used in the study42.

2.11. Piperidine based benzothiazole derivatives as anticancer agents

Osmaniye et al. prepared BTA acylhydrazone using 4-fluorobenzaldehyde refluxed with substituted amines, to afford the desired derivatives and studied their anticancer activities against rat brain glioma (carcinogenic C6) cell line, human lung adenocarcinoma epithelial (A549) cell line, human breast adenocarcinoma (MCF-7) cell line, human colorectal adenocarcinoma (HT-29) cell line and mouse embryo fibroblast (NIH3T3) cell line. The piperidine based acetohydrazide derivative 37 (Figure 22) showed modest activity having IC50 value 1 < mM, 0.03 mM, 0.10 mM, 0.30 mM and 1 < mM for A549, HT-29, MCF-7, C6, and NIH3T3 cell lines respectively against reference drug cisplatin43.

2.12. Secondary sulphonamide benzothiazole derivatives as anticancer agents

Lad et al. reported the synthesis of a series of methylsulfonyl benzothiazoles, obtained from 5-ethoxybenzothiazol-2-amine which were tested their anticancer activities. Among these derivatives, the nitrophenyl sulphonamide based methylsulfonyl benzothiazole 38 (Figure 23) and ter-butyl sulphonamide based methylsulfonyl benzothiazole 39 (Figure 23) exhibited the best anticancer activities against HeLa cell line with the IG50 value of 0.22 mM and 0.6 mM respectively44.

Sadhasivam et al. reported the synthesis of 2, 6-disubstituted-BTA by reaction of 2-amino-6-nitrobenzothiazole and acetic anhydride and studied their anticancer activity against three cancer cell lines MCF-7, HeLa and MG63 (human osteosarcoma) The sulphonamide scaffold based BTA 40 (Figure 24) exhibited modest anti-cancer activity with IC50 of 34.5 µM for MCF-7, 44.15 µM for HeLa and 36.1 µM for the MG6345.

2.13. Benzamide based benzothiazole derivatives as anticancer agents

Wang et al. synthesised and evaluated 24 benzothiazole-2-thiol derivatives for antiproliferative activities against different human cancer cell lines such as A549, HCT-116, SW620, SW480, MDA-MB-468, SKBR-3, HeLa, SKOV-3, PC-3, BxPC-3, A431 and A375.
derivatives exhibited better anticancer activities as compared to the standard drug cisplatin. The substituted methoxybenzamide benzothiazole 41 and the substituted chloromethylbenzamide benzothiazole 42 (Figure 25) showed good anti-tumour potential in vitro, with IC$_{50}$ values ranging from 1.1 μM to 8.8 μM. The introduction of chloromethyl and methoxy functionalities in compounds 41 and 42 increased their anticancer activity compared to other synthesised analogs 46.

Bolelli et al. synthesised 2-substituted benzothiazoles by the reaction of carboxylic acid with thionyl chloride which afforded acyl chlorides, further treated with substituted benzothiazole to give 2-substituted benzothiazoles, which were studied for their inhibitory activities against human glutathione transferases (hGSTP1-1). The benzamide benzothiazole derivative 43 and benzamide methylbenzothiazole 44 (Figure 26) showed potent hGSTP1-1 inhibitory activities, useful in cancer chemotherapy. The SAR studies pinpointed that both these scaffold showed effective inhibition due to the presence of para-substitutions on the phenyl ring of the benzamide group 47.

Corbo et al. reported 19 derivatives of benzamide based BTAs by the reaction of substituted aniline, potassium thiocyante and bromine, which afforded substituted compounds which were tested for anti-proliferative activity against MCF-7 and HepG2 cell lines. The substituted difluorobenzamide containing benzothiazole 45 (Figure 27) proved to be a potent anti-proliferative compound with the percentual inhibition of 64 ± 2 μM for MCF-7 cell line and of 64 ± 6 μM for HepG2 cell line 48.

2.14. Quinolone based benzothiazole derivatives

Abdelgawad et al. synthesised quinolone based benzothiazole derivatives by the treatment of substituted benzothiazoles with aromatic aldehydes. The nitrobenzylidene containing quinolone derivative 46 (Figure 28) and the hydroxybenzylidene containing derivative 47 (Figure 28) showed antitumor activities against the MCF-7 cell line, having IC$_{50}$ values of 0.058 μM and 0.052 μM, respectively 49.

Sarkar et al. prepared benzothiazolyl quinoline derivatives by treatment of 2-aminobenzothiol with 2-hydroxy-benzaldehyde and studied their activities for the A1, A2A, A2B and A3 adenosine
receptors. The A3 receptor is overexpressed in different cancer cell lines. The quinolone based derivative (Figure 29) showed the maximum potency for the hA3 adenosine receptor50.

2.15. Miscellaneous benzothiazole derivatives as anticancer agents

Tay et al. synthesised and evaluated N-[4-(benzothiazole-2-yl) phenyl]-2-aryloxyacetamide derivatives for cytotoxicity and anticancer activity against sixty human cancer cell lines derived from 9 neoplastic diseases, among which L (leukaemia), M (melanoma), RC (renal cancer) NSCLC (non-small cell lung cancer) CC (colon cancer), OC (ovar ian cancer), BC (breast cancer), CNSC (central nervous system cancer) and PC (prostate cancer). Derivatives 49 (N-(4-(benzo[d]thiazol-2-yl)-3-methoxyphenyl)-3-(4-chlorophenyl)propanamide) and 50 (N-(4-(benzo[d]thiazol-2-yl)-2-chlorophenyl)-2-(4-chlorophenylthio)acetamide) (Figure 30) exhibited interesting anti-cancer activities. The SAR studies investigated that anticancer activities of these compounds were due to the substitutions (methoxy and chloro groups) present in their molecules51.

Noolvi et al. reported the synthesis of chloro substituted benzothiazole amines in order to produce isothiocyanates and thiouracils. These BTA derivatives were tested for their anticancer activities. The dichlorophenyl containing chlorobenzothiazole 51 (Figure 31) showed good anticancer activity against 9 different cancer cell lines having GI50 values in the range of 1.60µM–71.8 nM. The derivative 51 exhibited GI50 = 7.18 × 10–8 M against non-small cell lung cancer (HOP-92). The SAR studies showed that the highest activity of compound 51 was due to the presence of three chlorine atoms in the compound as compared to other derivatives52.

Havrylyuk et al. screened novel 4-thiazolidinone benzothiazole derivatives against ovarian, renal, prostate, leukaemia, melanoma, lung, colon, CNS and breast cancer cell lines. The thioxothiazolidine acetamide benzothiazole 52 (Figure 32) showed the most
promising anti-cancer activity. The SAR studies pinpointed that the introduction of 4-chloro-phenoxy-N-(4-methoxyphenyl)-acetamide substitutions on position 5 of the 4-thiazolidinones ring enhanced the anti-cancer potential. 

Prabhu et al. synthesised and studied the anticaner activities of oxothiazolidine based BTA derivatives. The substituted chlorophenyl oxothiazolidine based benzothiazole showed the most effective anticaner activity against HeLa cell line, inducing 96.8% inhibition and IC50 value of 9.76 μM, when compared with the reference drug cisplatin.

Abdelgawad et al. synthesised thiazolidine containing benzoxazole derivatives by the treatment of aminobenzoic acid with substituted aniline that further reacted in different steps under specific conditions to afford final product and studied their anticaner activities against breast cancer (MCF7) and liver cancer (HEPG2) cell lines. Among all these derivatives, nitrobenzylidene containing thiazolidine derivative exhibited some anticaner activity, with an IC50 value of 36 nM and 48 nM against MCF7 and HEPG2, respectively.

Ma et al. reported indole based BTA derivatives and studied their anticaner activities. Among all these derivatives, the chlorobenzyl indole semicarbazide benzothiazole (Figure 34) exhibited anticaner activity against four cancer cell lines such as HT-29, H460, A549 and MDA-MB-231. Derivative showed IC50 values of 0.024 μM for HT-29, 0.29 μM for H460, 0.84 μM for A549 and 0.88 μM for MDA-MB-231, respectively.

Xie et al. prepared substituted BTA derivatives and studied their anticaner activities. Among all derivatives, the urea benzothiazole (Figure 34) exhibited interesting antitumor activity against 60 cancer cell lines. The average GI50 value for derivative was 0.38 μM.

Uremis et al. synthesised BTA derivatives using substituted aldehyde with bicyclo[3.2.0]hept-2-en-6-one. The nitro-styryl containing benzothiazole derivative and the fluorostyril benzothiazole derivative (Figure 35) were reported for their anticancer activity against pancreatic cancer cells having IC50 values of 27 ± 0.24 μM for and of 35 ± 0.51 μM for derivative.

Cindric et al. obtained carboxamide containing benzothiazole by the condensation of substituted thiophenes and substituted amino-BTAs to prepare the desired product and studied their anticancer activity against MCF-7 cell line. The benzothiazole derivative exhibited potent anticancer activity with an IC50 of 40 nM.

Nikolova et al. obtained Ru(III) complexes containing benzothiazole derivatives and tested their anticaner activity against K-562 and KE-37 (human leukemic) cell lines. Among all these derivatives, the Ru(III) containing methylbenzothiazole (Figure 37) exhibited the highest cytotoxic activity against K-562 and KE-37, having IC50 values of 7.74 ± 2.50 μM for KE-37 and of 16.21 ± 2.33 μM for K-562 when compared with the standard drug cisplatin.

Yurttas et al. obtained benzothiazole derivatives by acetylation of substituted benzothiazole with chloroacetyl chloride that was further treated in series of reactions to obtain specific derivatives which were tested for their anticancer activities against lung carcinoma (A549) cell line. Derivatives and derivative (Figure 38) exhibited good anticancer activities against A549 with IC50 values of 10.67 ± 2.02 μg/mL and 9.0 ± 1.0 μg/mL respectively as compared to the reference compound cisplatin.

Oanh et al. reported the synthesis of hydroxamic acids containing benzothiazole by the reaction of 2-aminothiazole with adipic acid to produce esters that were converted into the desired BTA hydroxamates, and tested for their anticaner activities against five different cell lines such as MCF-7, AsPC-1, SW620, PC3 and NCI-H460. Among the synthesised derivatives, hydroxamic acids and (Figure 39) exhibited good anticancer activities, with the average IC50 value of 0.81 μg/mL and 1.28 μg/mL respectively.

Rodrigues et al. synthesised carbohydrazide containing BTA derivatives and studied their antitumor activities against human prostate cancer cell lines. N'-formyl-2-(5-nitrothiophen-2-yl)benzothiazole-6-carbohydrazide (Figure 40) exhibited potent anticaner activity against PC-3 and LNCaP having IC50 values 19.9 ± 1.17 and 11.2 ± 0.79 μg/mL respectively.

Rao et al. reported DNA-intercalating naphthalimide-benzothiazole derivatives and evaluated their cytotoxicities against three different cancer cell lines such as HT29, A549 and MCF-7. Among all tested derivatives, the naphthalimide derivative (Figure 40) possessed good antitumor activity against HT-29, A549 and MCF-7 cell lines having IC50 values of 3.72 ± 0.3 μM, 4.074 ± 0.3 μM and 0.791 ± 0.4 μM respectively. The naphthalimide (Figure 40) showed antitumor activity with IC50 values of 0.47 ± 0.2 μM for HT-29, 0.389 ± 0.3 μM for A549 and 0.058 ± 0.3 μM for MCF-7 cell lines.

Rao et al. reported the synthesis of 2-arylaminothiazole-arylpropeonones and studied their cytotoxic activities against different human cancer cell lines. Among all synthesised derivatives, substituted phenylamino based methoxybenzothiazole.
Osmaniye et al. synthesised benzothiazole-thiazolidine derivatives and studied their anticancer activities against C6 and healthy NIH3T3 cell lines. Among the synthesised derivatives, substituted phenylthiazolidene based benzothiazole and substituted nitrophenylthiazolidene benzothiazole (Figure 42) exhibited some cytotoxic activities against C6 cell line showing IC50 value 0.03 mM. The SAR studies showed that the presence of a phenyl group on the thiazolidine part of the structure increased the selectivity while substitution with an electron withdrawing or donating groups decreased the selectivity.

Benzothiazole derivatives with carbonic anhydrase inhibitory and antitumor action
Carbonic anhydrases (CAs, EC 4.2.1.1) are zinc enzymes which catalyse the reversible interconversion between CO2 and bicarbonate. CO2 is efficiently hydrated through a zinc hydroxide intermediate from the enzyme active site with generation of the weak base bicarbonate and the strong acid H+. As a consequence, CAs are involved in pH regulation, electrolyte secretion and metabolism, in normal and tumour tissues. Fifteen α-CA isoforms are present in humans, with at least two of them overexpressed in hypoxic tumours (CA IX and XII), as a consequence of the hypoxia inducible factor (HIF-1α) transcription factor cascade activation. CAs are efficiently inhibited by a range of compounds, such as the sulphonamides and their isosteres, and inorganic anions, which constitute the main zinc-binding CA inhibitor (CAI) classes. Some of the CAIs belonging to the sulphonamide, sulfocoumarin, saccharin or other structurally related chemotypes, were shown to possess significant antitumor effects, with one such derivative (SLC-0111) in Phase I/IIb clinical trials for the management of hypoxic metastatic tumours. Indeed, by inhibiting the tumour-associated isoforms CA IX and XII, such CAIs interfere with the pH regulation and metabolism of
tumours, leading to the inhibition of growth of the primary tumour, metastases and reducing the population of cancer stem cells\textsuperscript{78}. As a consequence, many CAIs belonging to various classes are nowadays investigated for their antitumor/antimetastatic effects, including many BTA derivatives (Figure 43)\textsuperscript{84–91}. Indeed, using the ethoxzolamide \textsuperscript{72}, a CAI in clinical use for decades as lead molecule, a multitude of primary sulphonamides (e.g. compounds \textsuperscript{73–75}) as well as the secondary sulfonamide \textsuperscript{76} were reported to act as highly efficient, frequently low nanomolar inhibitors against the tumour-associated isoforms CA IX and XII\textsuperscript{84–91}. No \textit{ex vivo} or \textit{in vivo} studies are available so far with these potent CA IX/XII inhibitors, but compounds belonging to other classes of sulphonamides were proved to possess significant anti-tumor effects in vivo when they act as potent inhibitors of these two CA isoforms\textsuperscript{78,92–98}. Thus future studies may address this issue.

Figure 37. Ru(III) containing methylbenzothiazole derivative \textsuperscript{60}.

Figure 38. Benzimidazole based acetamide methoxybenzothiazole derivative \textsuperscript{61} and acetamide ethoxybenzothiazole derivative \textsuperscript{62}.

Figure 39. Hydroxamic acid containing methyl/methoxy benzothiazole scaffolds \textsuperscript{63} and \textsuperscript{64}.

Figure 40. Derivative \textsuperscript{65–67} discussed in the article.

Figure 41. Substituted phenylamino based methoxy benzothiazoles \textsuperscript{68} and \textsuperscript{69}.

Figure 42. Substituted phenylthizolidene based benzothiazole derivative \textsuperscript{70} and \textsuperscript{71}. 
considering the fact that the BTA scaffold present in these compounds may induce interesting phisico-chemical and pharmacologic properties to the CA IX/XII inhibitors, of which many chemical families are already reported.

4. Conclusions

Benzothiazole is a pharmacophore widely used in medicinal chemistry. This review points out to a growing interest in the development of lead or hybrid structures bearing the BTA moiety as antiproliferative and anticancer agents. The present work describes the potential of BTA scaffolds in the management of various types of cancers such as ovarian, prostate, central nervous system, renal, gastric, pancreatic, liver, breast and colon cancers. SAR studies revealed that the anticancer activity of BTA scaffolds depends upon the nature of substituents present in these molecules, being multifactorial and not always easy to rationalise. The plethora of research on the anticancer profile of BTA derivatives mentioned in this review and their rationalisation based on the drug targets of these derivatives, when this was possible, may be useful for the development of novel such agents.

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