International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1007-1013 www.ijprajournal.com ISSN: 2456-4494

Benzothiazole Analogues as Potent Anticancer in Modern Pharmaceutical Research

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Date of Submission: 15-05-2024 Date of Acceptance: 25-05-2024

ABSTRACT: Cancer is a broad category of disorders that can originate in nearly any organ or tissue in the body when aberrant cells proliferate out of control, cross normal boundaries to infect other body parts, or spread to other organs. The latter process, known as metastasizing, is a primary contributor to cancer-related deaths. Other frequent names for cancer are neoplasm and malignant tumor.

Approximately 9.6 million deaths, or 1 in 6 deaths, were attributed to cancer in 2018, making it the second most common cause of death worldwide. Benzothiazole is an important class of pharmaceutical drug that possesses many attractive biological activities. It has antibacterial [189], anticonvulsant [190], anticancer [191], antifungal [192], antimitotic [193], and antitumor [194] properties. The benzothiazole and its isosteres like the indole ring have proved to exhibit promising antitumor activity. The structure–activity relationship for the various derivatives revealed an excellent understanding of the behavior of benzothiazole moiety in the field of cancer therapy against different cancer cell line.

KEYWORDS: Benzothiazole antibacterial, anticonvulsant, anticancer, antifungal, antimitotic, and antitumor

I. INTRODUCTION

Malignant tumors can metastasize, or spread into, neighboring tissues, and can also generate new tumors by travelling to far-off regions of the body. Malignant tumors are another term for cancerous tumors. Blood cancers, including leukemia's, typically do not develop into solid tumors, although many malignancies can.

Benign tumors do not penetrate or spread to neighboring tissues. Benign tumors seldom grow back after removal, while cancerous tumors occasionally do. However, benign tumors can occasionally grow to be rather enormous. Some, like benign brain tumors, are potentially fatal or cause severe symptoms.

Cancer is a broad category of disorders that can originate in nearly any organ or tissue in the body when aberrant cells proliferate out of control, cross normal boundaries to infect other body parts, or spread to other organs. The latter process, known as metastasizing, is a primary contributor to cancer-related deaths. Other frequent names for cancer are neoplasm and malignant tumor.

Approximately 9.6 million deaths, or 1 in 6 deaths, were attributed to cancer in 2018, making it the second most common cause of death worldwide. Men are most likely to develop lung, prostate, colorectal, stomach, and liver cancers, whereas women are more likely to develop breast, colorectal, lung, cervical, and thyroid cancers.

Globally, the cancer burden is still rising, placing a great deal of physical, psychological, and financial pressure on people, families, communities, and health systems. Many low- and middle-income nations' health systems are ill-equipped to handle this load, and many cancer patients worldwide lack access to prompt, high-quality diagnosis and treatment. Strong health systems in nations have increased the survival rates of many cancer kinds through early detection that is easily accessible, high-quality treatment, and survivorship care.

II. LUNG CANCER

Early medical attention is crucial to preventing major health consequences. The course of treatment is determined by the patient's medical history and the disease's stage. Small cell carcinoma (SCLC) and non-small cell carcinoma (NSCLC) are the two most prevalent forms of lung cancer. While SCLC is less prevalent yet frequently grows swiftly, NSCLC is more common and grows slowly. Lung cancer is a major cause of death worldwide and a major public health

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problem. Lung cancer continues to be the most common cause of cancer-related death, accounting for 1.8 million deaths (18%) in 2020, according to the International Agency for Research on Cancer's (IARC) GLOBOCAN 2020 estimates of cancer incidence and mortality.

The main cause of lung cancer is tobacco use, which includes using pipes, cigars, and cigarettes, although it can also infect non-smokers. Additional risk factors include prior chronic lung disorders, air pollution, hereditary cancer syndromes, exposure to secondhand smoke, and occupational dangers such as asbestos, radon, and certain chemicals.

III. BREAST CANCER

The illness known as breast cancer is caused by aberrant breast cells that proliferate and develop into tumors. Tumors have the potential to spread throughout the body and become lethal if ignored. The milk ducts and/or the breast's milk-producing lobules are where breast cancer cells first proliferate. The first kind, known as "in situ," can be identified early on and is not life-threatening. It is possible for cancer cells to invade neighboring breast tissue. Tumors produced by this result in thickening or lumps. Metastasis is the process by which invasive tumors move to neighboring lymph nodes or other organs. Metastasis can be lethal and perhaps fatal.

2.3 million women worldwide had a breast cancer diagnosis in 2022, and 670,000 people died from the disease. All across the world, breast cancer affects women at any age after adolescence, however its prevalence rises with age.

Global estimations show stark differences in the incidence of breast cancer based on human development. For example, in nations with a very high Human Development Index (HDI), 1 in 12 women may receive a breast cancer diagnosis during their lifetime, and 1 in 71 will pass away from the disease. In comparison, 1 in 48 women will pass away from breast cancer in nations with a low HDI, even though only 1 in 27 women will receive a diagnosis of the disease during their lifetime.

IV. CERVICAL CANCER

Cervical cancer is the fourth most frequent malignancy in women worldwide; in 2022, there will be over 660 000 new cases. Approximately 94% of the 350 000 cervical cancer-related fatalities that year happened in low- and middle-income nations. South-East Asia, Central America, and sub-Saharan Africa (SSA) have the greatest incidence and fatality rates of cervical cancer. The disparities in access to immunization, screening, and treatment facilities, risk factors like HIV prevalence, and social and economic determinants including sex, gender bias, and poverty are all linked to regional variations in the incidence of cervical cancer. Compared to the general population, women living with HIV are six times more likely to acquire cervical cancer, and an estimated 5% of all incidences of cervical cancer are related to HIV. 20% of children whose mothers die from cancer do so as a result of cervical cancer, which disproportionately affects younger women.

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 GI50 values of 0.57 and 0.4 μM respectively against MCF-cell line as compared to BTA derivatives containing alkoxy, methyl sulphonyl and ethyl substituents on the benzothiazole (Figure 2). Kumbhare et al. afforded the N-bis-benzothiazole and benzothiazolyl 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)), (4847.73 ± 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 respectively

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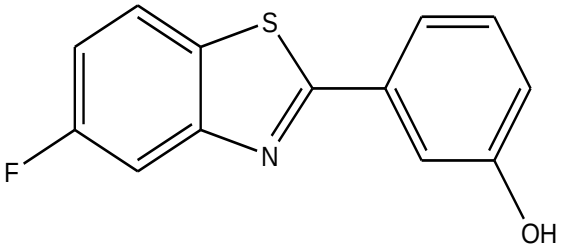

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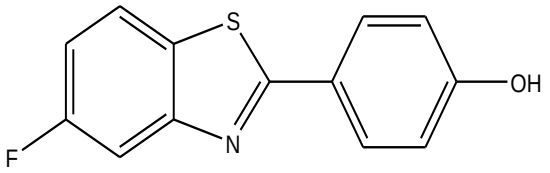

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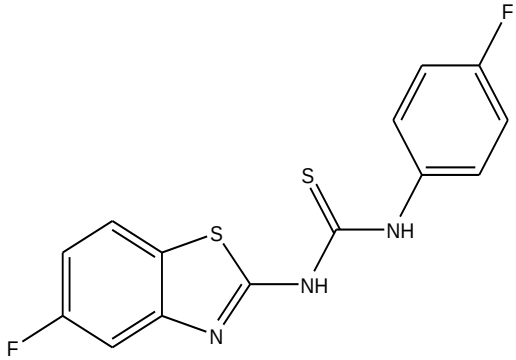
Kumbhare et al. reported the synthesis of mannich base arylimidazo derivatives containing benzothiazole moiety and screened for their anticancer activities against HepG2, MCF -7 and HeLa cell lines. All these synthesised mannich bases BTA scaffolds showed cytotoxicity against all tested cell lines but 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 7^{th} position of derivative **4** enhanced the cytotoxicity. The compound **4** have potential to lead in the treatment of cancer especially against hepatocaricinoma. The anticancer activity potential of BTA scaffold **4** is encourging for the development of new anti-cancer therapeutic agents and this will be good addition in armamentarium that consists of paclitaxel, cisplatin and doxorubicin drugs.



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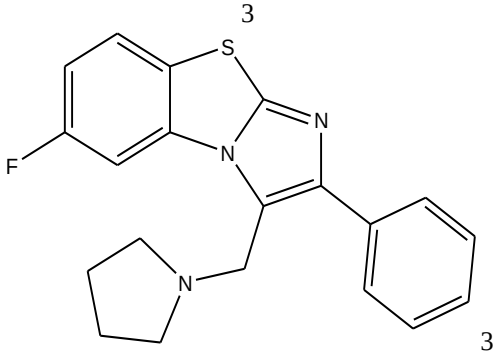

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Caputo et al. afforded two types of five derivatives on the basis of an aryl amide and an aryl urea functionalities attached at C-2 of benzothiazole core and these scaffolds were screened against 60 human cancer cell lines. The urea moiety based fluorophenyl 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^{-5} M against different cell lines such as leukaemia cell lines (log GI_{50} value −5.48), non-small cell lung cell lines (log GI_{50} value −5.48), colon cancer cell lines (log GI_{50} value −5.51), central nervous system cancer cell lines (log GI_{50} value −5.49), melanoma cell lines (log GI_{50} value −5.48), ovarian cancer cell lines (log GI_{50} value −5.49), renal cancer cell lines (log GI_{50} value −5.53), prostate cancer cell lines (log GI_{50} value −5.50) and breast cancer cell lines (log GI_{50} 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 GI_{50} value −5.93), non-small cell lung cell lines (log GI_{50} value −6.0), colon cancer cell lines (log GI_{50} value −5.89), central nervous system cancer cell lines (log GI_{50} value −5.73), melanoma cell lines (log GI_{50} value −5.89), ovarian cancer cell lines (log GI_{50} value −5.74), renal cancer cell lines (log GI_{50} value −5.90), prostate cancer cell lines (log GI_{50} value −5.72) and breast cancer cell lines (log GI_{50} 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.

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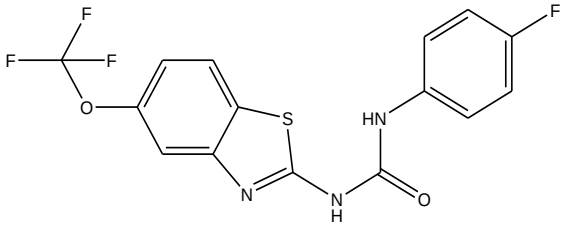

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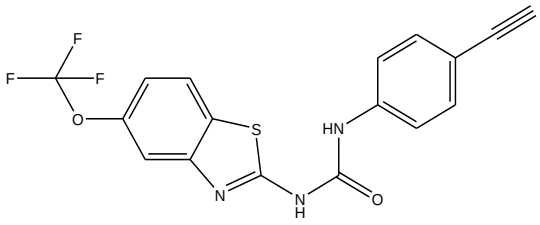

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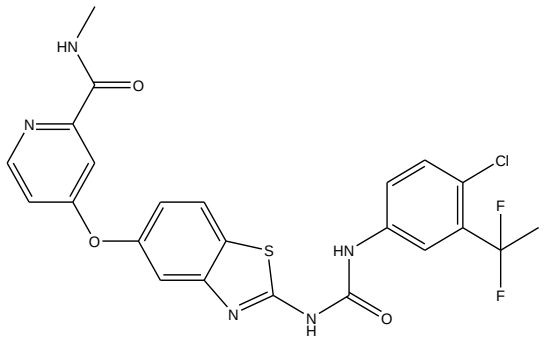
El-Damasy et al. synthesised the novel amide and urea based BTA series of 20 sorafenib analogues in which the pyridylamide privileged functionality was attached with an ether linkage at 6-position of the BTA ring. A selected group of 12 potent scaffolds were evaluated and appraised for anti-proliferative activities against sixty human cancer cell lines. These chlorotrifluoromethyl phenyl ureido picolinamide benzothiazoles **7**, bis-trifluoromethyl phenyl ureido based picolinamide benzothiazole derivative **8** and dichlorophenyl ureido based picolinamide benzothiazoles **9** were more potent in the treatment of renal cell carcinoma than the standard drug sorafenib, used for the treatment of such tumours. The 3,5-bis-trifluoromethylphenylurea **8** showed good inhibitory activities against ACHN (renal cancer cells lines) and A-498 (human kidney carcinoma cell line) with GI_{50} values of 0.542 µM and 1.02 µM respectively. This compound also possess efficacy against UO-31 and RXF 393 cell lines. The derivatives **7** and **9** because of 3,4-disubstitutedphenyl moiety, exhibited excellent anti-proliferative activities with low IG_{50} values of 1.85, 2.10 µM against RCC and ACHN cell lines respectively. The SAR study revealed the fact that sorafenib analogues possesses anti proliferative activity due to the presence of both urea spacer and phenyl disubstitution. Compound **8** demonstrated the highest CLogP value being the most lipophilic and potent derivative, in the low µM range.



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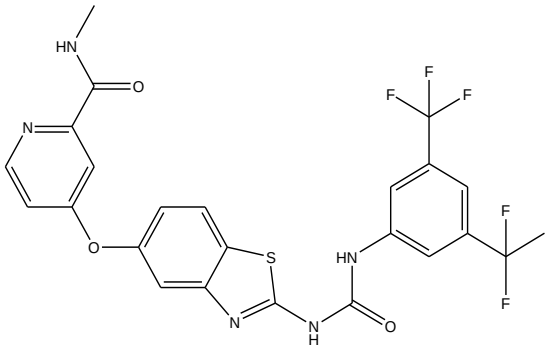

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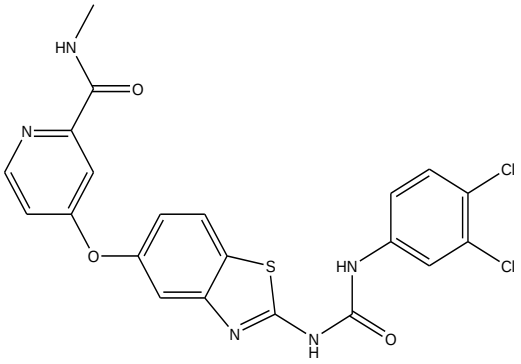

9

Ma et al. reported BTA derivatives containing an ortho-hydroxy-N-acyl hydrazone 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 **10** (Figure 6) showed inhibitory activities against all cell lines with IC_{50} and EC_{50} values ranging from 0.24 to 0.92 µM and 0.31 µM respectively. The SAR studies revealed the paharmacological activities of BTA

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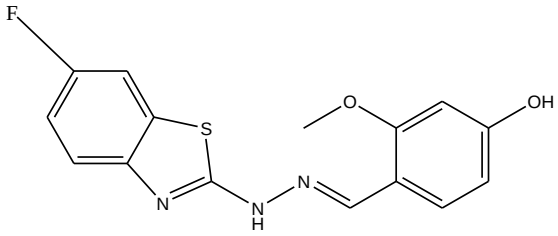
scaffold **10** in in-vitro is due to introduction of phenyl and benzyloxyl substitutions



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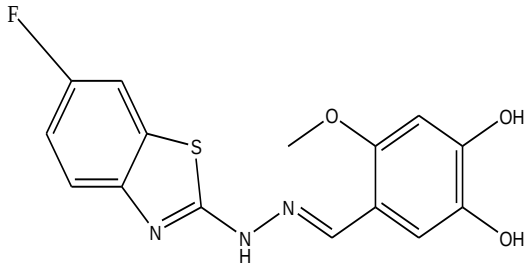
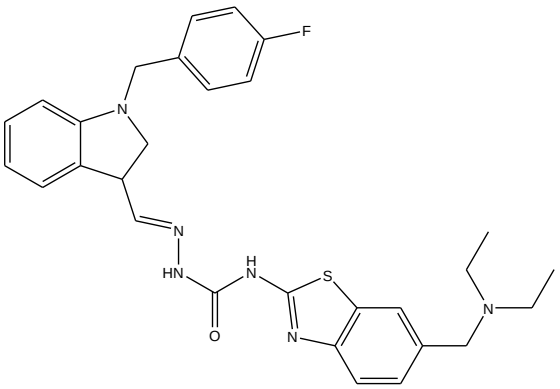
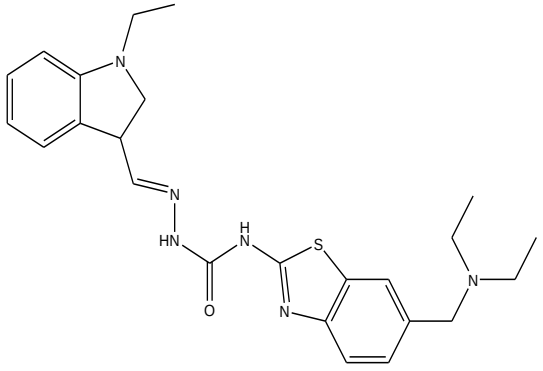


11.

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 anti-tumour potential against Hela (cervical cancer) and COS-7 (kidney fibroblast cancer) cell lines. The hydrazine based benzothiazole **11** (Figure 6) exhibited IC_{50} of 2.41 µM and 4.31 µM against Hela and COS-7 cell lines as compared to reference doxorubicin having IC_{50} 2.05 µM and 3.04 µM respectively. The SAR studies explained the effect of various substitutions on activities of all the synthesised derivatives. The scaffold present in **11** has the 2–(4-hydroxy-methoxy benzylidene)-hydrazino moiety at the C-2 position which remarkably enhances the anti-tumour potential, whereas replacing the 4-hydroxy moiety with 4-methoxy decreased the activities against both cell lines.



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 **12** (Figure 7) showed potent antitumor activity with IC_{50} 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 **12** exhibited the highest antitumor activity due to the presence of electron withdrawing groups in the 4 position of benzyl ring



.13

Yurttas et al. obtained 2–(4-aminophenyl)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-

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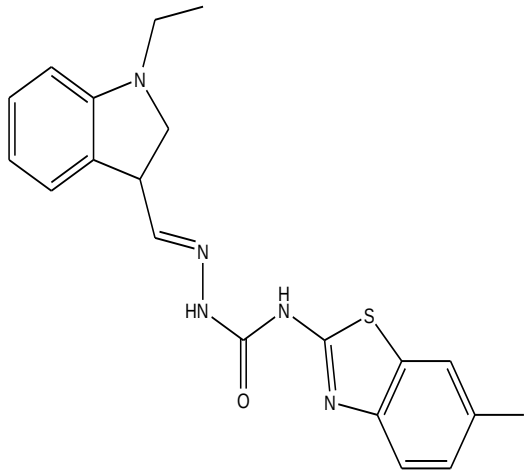
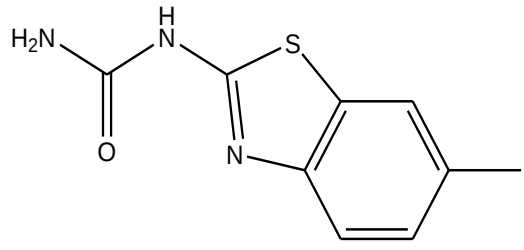
phenyl-1H-benzo[d]imidazol-2-yl-thio)-acetamide) (Figure 8) showed remarkable antitumor potential against different cancer cell lines. The heterocylic substitutions affect the activity and antitumor potential of these BTA derivatives, with derivative **14** having comparable antitumor potential with 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 > benz oxazole.



14

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 10 µM when compared with the standard drug doxorubicin.



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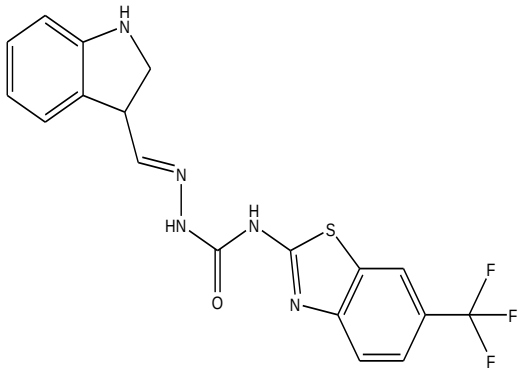
Al-Soud. et al. reported the synthesis of BTA derivatives incorporating sulphonamide, piperazino-arylsulfonamide and arylthiol scaffolds and determined their anti-proliferative potential against different cell lines, such as CCRF-SB (Human acute B-lymphoblastic leukaemia), DU-145 (human prostate cancer 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-28 cell line (skin melanoma). Derivative **16** (N-(2–(4-(benzo[d]thiazol-2-yl)piperazin-1-yl)-2-oxoethyl)-4-chloro-benzenesulfonodithioamide) showed antiproliferative activity ($CC_{50} = 8 \pm 3$ 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-dichloro benzenesulfonodithio-amide) 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** exhibited atiproliferative potential due to the introduction of chloro and dichloro phenyl groups while their replacement of with hydrogen, methoxy, nitro, triflouromethyl and methyl groups lead to a decrease in the antiproliferative potential of BTA derivatives.



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V. CONCLUSION

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 reaveled that the anticancer activity of BTA scaffolds depends upon the nature of substituents present in these molecules, being

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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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