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Exploring the potential of Benzoxazole Derivatives as Anti-cancer Agents: A Comprehensive Review

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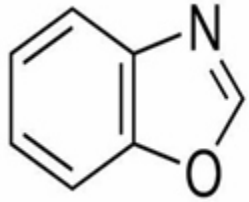
ABSTRACT

One of the primary health issues affecting people and having the highest fatality rate is cancer. The agents that cause cancer can be biological, synthetic, or chemical. It is treated with a variety of medications, but they all have harmful side effects. As a result, extensive research is being done to create new, efficient, and cost-effective anticancer medications with greater selectivity, smaller dosages, and less side effects. Due to their enormous success rate in creating active pharmaceutical intermediates, heterocyclic chemistry has received increased attention in drug discovery throughout the years. One of the most significant heterocyclic compounds with outstanding pharmacological properties is benzoxazole, which belongs to the class of heterocyclic compounds. There have been several reports of both synthetic and naturally occurring substances having a very strong anti-cancer action in the benzoxazole backbone. Designing benzoxazole-containing compounds, synthesising them, and gathering data on their anticancer effectiveness against diverse human cancer cell lines have all advanced significantly in various research groups. The anticancer activity of diverse benzoxazole compounds synthesised by different groups has been examined in an effort to determine how varied heterocyclic moiety coupled with benzoxazole have an effect on it. A summary of all these recent articles aids in pointing the way for additional research.

INTRODUCTION

Benzoxazole is an aromatic organic compound with a molecular formula C_7H_5NO, a benzene-fused oxazole ring structure. It is found within the chemical structures of pharmaceutical drugs such as flunoxaprofen and tafamidis. Benzoxazole derivatives are also of interest for optical brighteners in laundry detergents. Benzoxazoles belong to the group of well-known antifungal agents with antioxidant, antiallergic, antitumoral and antiparasitic activity.



STRUCTURE OF BENZOXAZOLE

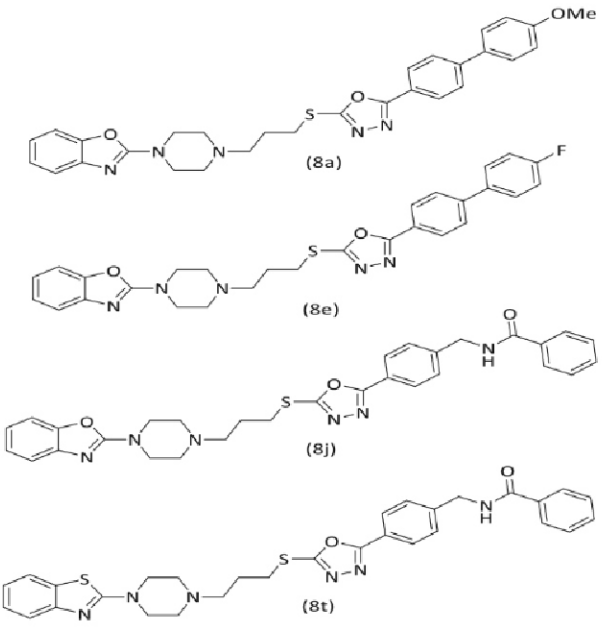
Cancer is a condition when a group of cells divide improperly and uncontrollably to the point where they invade and even kill other tissues. Through the blood and lymph, these cells dispersed throughout the body, causing satellite lesions elsewhere that ultimately resulted in death. One of the most prevalent and dreaded diseases in the western world today is cancer, which is feared in large part due to the fact that it is known to be difficult to treat. The primary cause of this challenge is that cancer is caused by the unchecked division of normally occurring human cells that have undergone subtle modifications. Drug therapy is one of the primary approaches used in contemporary cancer treatment. (chemotherapy). One in four people may develop cancer at some point in their lifetime, making it a serious condition. Currently,

cancer is responsible for around one in five deaths worldwide. (1)

Benzoxazole attached with various heterocyclic moiety and their anticancer activity

Benzoxazole-piperazine moiety

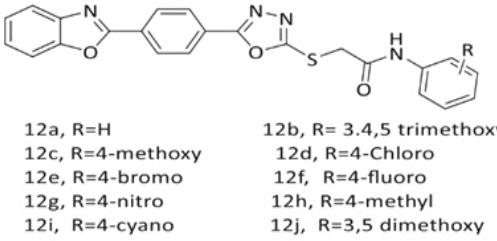
Few benzoxazole linked to piperazine compounds were created by Al-Harthy et al. (2) and tested on human A-549 lung cancer cells. The low solubility of the aryl piperazine compounds, which precipitated in the cell culture conditions, is what caused the initial results to be less than ideal. By substituting N-methyl piperazine for aryl piperazine at position-6 of the benzoxazole and replacing the methyl group at position-2 with a carbamate functional group, it is possible to increase the solubility of the compounds. The number of stages was decreased with the one-pot reductive cyclization using indium, and large yields of compounds were produced. Below is also provided the general compound structure. According to Murty et al. (3), the long chain piperazine Oxadiazoles and benzoxazoles linked together have demonstrated an anticancer impact. Simple procedures were used to synthesise the various oxadiazoles, and they were then combined with the aryl piperazine derivatives utilising KF-Al2O3 and acetonitrile as the solvent at 80 °C heating. Five different human cancer cell lines were used to test the cytotoxicity of the chemical that was synthesised. On cancer cell lines of various origin, including MCF-7 (breast), HeLa (cervical), HepG2 (liver), A431 (skin), and A549, the IC50 values were calculated. (lung). In the MCF-7 cell line, all of the compounds displayed an IC50 value less than 100, however 8a, 8e, 8j, and 8t stood out as being particularly cytotoxic. A few substances that had benzothiazole backbones instead of benzoxazoles had excellent effects on MCF-7 in a cell. The amide-linked substances have a strong cytotoxic effect on the A431 cell line. When compared to other cell lines, all of the synthesised chemicals had positive effects on the A431 cell line.



Benzoxazole - piperazine compounds

Benzoxazole-1,3,4-oxadiazole moiety :

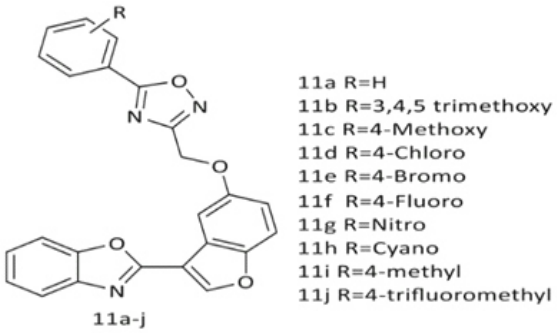
The powerful moiety 1,3,4-oxadiazole (4) exhibits a wide range of biological action. More amide benzoxazole-1,3,4-oxadiazole compounds **(5)** were created, and their anti-cancer activity was examined using CA-4 as a positive control against the four human cancer cell lines A549 (lung cancer), MCF-7 (breast cancer), A-375 (melanoma cancer), and HT-29 (colon cancer). Compounds 12b, 12c, and 12g from these synthesised compounds have been found to exhibit anticancer activity against the HT-29 cancer cell line, and the results are superior to those of the standard medication. Several additional substances, including 12b, 12f, 12 g, and 12 i, were found to have high activity against MCF-7 cancer cell lines. It was discovered that 12b and 12i were active against A-549 cell lines. Compound 12b has displayed excellent activity against the cell lines HT-29, MCF-7, and A-549.



Benzoxazole-1, 3, 4-oxadiazole

Benzoxazole-1,2,4-oxadiazole moiety :

Derivatives of 1,2,4-oxadiazole (6-7) with anti-proliferative properties have been thoroughly documented in the literature. With combretastatin-A4 serving as a positive control, the cytotoxicity activity of benzoxazole fused with benzofuran and 1,2,4-oxadiazole (8) was assessed against human breast cancer (MCF-7), lung (A549), melanoma (A375), and colon (HT-29) cell lines. Compared to the positive control, compounds 11b, 11c, 11d, 11g, 11h, and 11i displayed more powerful action.

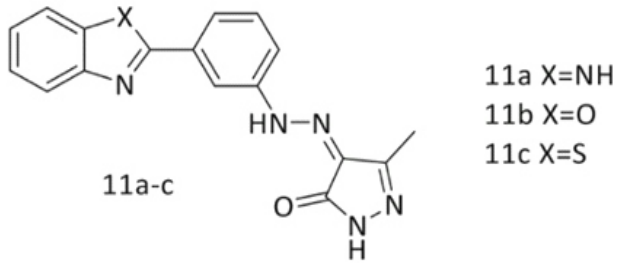


Benzoxazole-1, 2, 4-oxadiazole

Benzoxazole-pyrazolinone moiety :

It was created new compounds of benzoxazole, benzothiazole, and benzimidazole (9). It has been found that when pyrazolinone's N-2 is substituted, the compounds' anti-proliferative action is significantly improved. The N-2 of pyrazolinone was subjected to phenyl and acetyl substitution, which boosts the compounds' antiproliferative action. According to their IC50 value, the acetylated compounds were grouped in

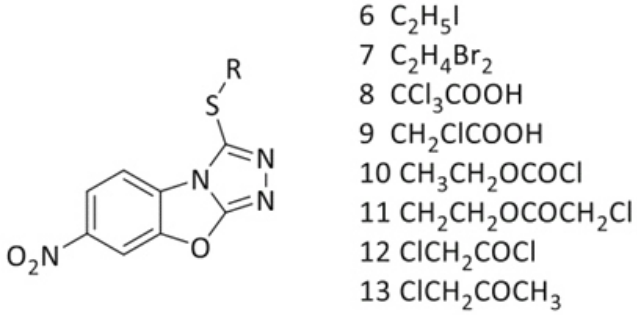
order of activity 12a > 12b > 12c. According to their IC50 value, if the substitution was changed from acetyl to phenyl, then 13b > 13a > 13c. The MCF-7 and A-549 cell lines were found to be extremely responsive to these N-2 substituted pyrazolinone derivatives.



Benzoxazole-pyrazolinone

Benzoxazole-triazole moiety :

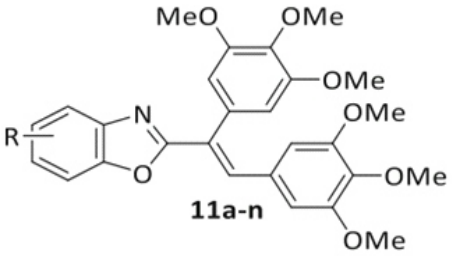
To test the anticancer efficacy, various additional heterocycles were joined with the benzoxazole molecule. Since it was discovered that benzoxazole and triazole have a broad range of activities, Srivastava and colleagues (10) created a one-pot multicomponent reaction to create benzoxazole-triazole scaffolds, which, when tested for anticancer activity against the cancer cell lines HeLa, SKBr3, and HepG2, demonstrated very intriguing activity. Two sequential stages carried out in a single pot were rationalised for the synthesis of benzoxazole-linked triazoles. This included the C-H activation of benzoxazole at the C-2 position, resulting in the in-situ synthesis of alkyne from the appropriate dibromo-olefin precursor. The triazole ring was then created by 1, 3-dipolar cycloaddition between the alkyne and benzyl azide. The base used in the process is lithium tert-butoxide, which is mediated by copper iodide and heating at 120 °C in the first step, then adding the benzyl azide and continuing to heat at 150 °C for a further 12 hours. With HeLa, SKBr3, and HepG2 cancer cells, these chemicals were tested, and it was found that they may have anticancer potential. Compound 42,2,2 has been found to have a comparable cytotoxic impact to the standard daunomycin against the cancer cell lines HeLa, SKBr3, and HepG2. Similar to this, a new series of fused benzoxazole and triazole compounds were created, and their anticancer efficacy against PBMC cell lines was assessed (11). To create a number of compounds, the substitution was done at the thiol. Few of the compounds in the series were having an active state, and compound 12 was discovered to have the best activity and excellent antibacterial effectiveness. Since receptor tyrosine kinase is involved in cell proliferation and differentiation, it is seen as a key therapeutic target for treating cancer. A549, MCF-7, HepG2, and MDA-MB-231 cell lines were used to test the anticancer efficacy of benzoxazole/benzimidazole linked triazolo triazines (12). With compound 8e's IC50 value being very near to that of the reference chemical crizotinib, these compounds were very potently selective towards HepG2 cell lines. A few 1,2,3 triazole-fused benzoxazole compounds were also created and tested for their antibacterial, antifungal, and anticancer properties by Dadashpour and group (13) along similar lines.



Benzoxazole - triazole

Benzoxazole-combretastatin moiety :

Compound 8d was found to be more potent than the standard compound against MCF-7 and A549 cell lines after a series of ten benzoxazole derivatives of combretastatin A4 (14) were synthesised and tested against various cancer cell lines, including Coco-205 (colon), A-549 (lung), and MCF-7 (breast). In 1989, the South African willow tree Combretum caffrum yielded combretastatin A-4, a natural substance that exhibits anticancer action against several cancer cell lines in nanomolar concentration. The natural substance Combretastatin served as a model for the structure of these novel compounds, and cytotoxicity activity was investigated. Starting with substituted phenyl acetic acid and substituted benzaldehyde, the synthesis of these compounds was completed by cyclizing the amino phenol to produce benzoxazole. By employing the SRB assay, the synthesised compounds were tested against a number of different cell lines, including the colon cancer Colo-205, lung cancer A541, and breast cancer MCF-7. The results show that compound 8d shown greater activity than expected in 2 of the cell lines. (MCF7 and A-549). The structural similarity of the newly synthesised benzoxazole-linked combretastatin compounds (15) was tested against three human cancer lines, including melanoma, lung, and breast (MCF-7). (A375). However, compounds 11g, 11h, 11l, 11m, and 11n have demonstrated extremely powerful activity. The majority of these compounds had considerable anti-cancer efficacy. These compounds were the subject of a molecular docking investigation, and 11g and 11l were found to have a potent binding contact with the receptor.

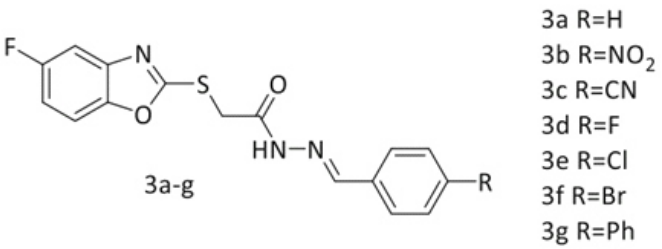


a R=H
b R=4-Me
c R=5-Me
d R=6-Me
e R=5,6-DiMe
f R=7-Me
g R=5-OMe
h R=6-OMe
i R=5-Br
j R=6-Br
k R=6-Cl
l R=5-NO_2
m R=5-Cl-6-NO_2
n R=5,7-diNO_2

Benzoxazole-combretastatin

Benzoxazole-hydrazone moiety

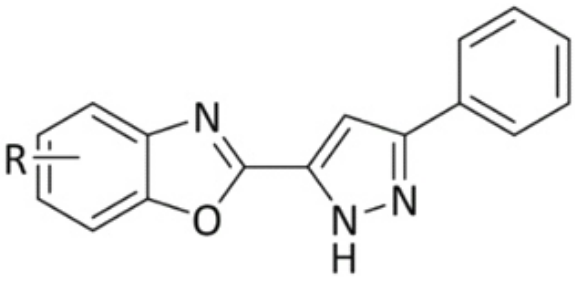
By condensation with various substituted isatin compounds, a number of benzoxazole-5-carbohydrazide derivatives (16) were created. These compounds were then tested using the MTT method on various in vitro anticancer cell lines, including the HeLa, IMR-32, and MCF-7 cancer cell lines. All three cell lines were shown to be responsive to these chemicals. It was found from the initial investigation that compounds containing an electron-withdrawing group have better biological activity than compounds without a replacement. Another finding regarding biological activity was that compounds with C-5 isatin moiety substitutions, particularly with various halides as opposed to C7, have superior biological activity. This knowledge might aid in the future creation of anticancer drugs. The compound's general structure is included after. The hydrazone moiety is crucial in the creation of anticancer medications. New hydrazine compounds based on benzoxazole were created (17). On the C6 rat glioma and NIH/3 T3 mouse embryonic fibroblast cell lines, synthetic and in vitro cytotoxic effects were identified, followed by flow cytometry-based apoptosis detection in the C6 cell line. The chemical 3g appears to be a good subject for additional research.



Benzoxazole-hydrazone

Benzoxazole-pyrazole moiety :

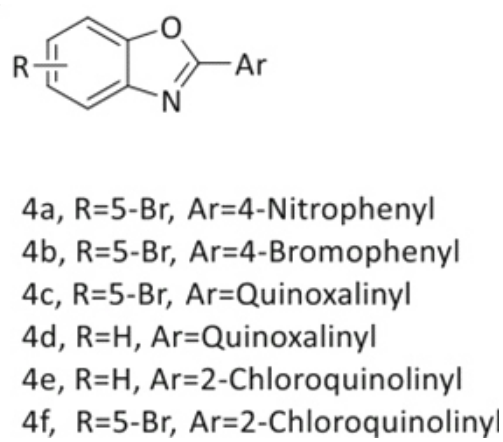
A549, MCF-7, KB, Hop62, and novel substituted pyrazolo-benzoxazole (18) compounds were created and tested for cytotoxicity against these cancer cell lines. It was discovered that the compounds with methoxy substitution at positions 5 and 6 have excellent anticancer action. The MCF-7 and A-549 cell lines were shown to be extremely responsive to the compounds with nitro substitution at position 6. It was also shown that compounds with nitro disubstitution at positions 5 and 7 have excellent anticancer efficacy against A549 cell lines. The anticancer efficacy of a few additional compounds, where the benzoxazole moiety was switched for the benzofuran backbone, was also examined.



Benzoxazole-pyrazole

Benzoxazole-quinoline moiety :

To prepare certain potent anticancer drugs, a single-pot synthetic technique was used to combine benzoxazole with quinoline and quinoxaline molecules (19). In the synthesis, substituted 2-aminophenols and the appropriate aldehyde are heated for 34 hours at 120 °C without the use of a solvent. These chemicals' molecular docking analysis found that they inhibit the enzyme protein tyrosine kinase. The cytotoxicity investigation of these compounds (4a-f) revealed that they are more powerful against the lung and oral cancer cell lines KB and A-549 than the breast cancer cell lines MCF-7 and MDA-MB-231. The enzyme tyrosine kinase was shown to be most effectively inhibited by compound 4c, which was discovered to be extremely active. According to molecular docking, the molecule 4c, two hydrogen bonds have been established, one with the nitrogen of benzoxazole at Thr-766 and the other with the nitrogen of quinoxaline at Met769, which is the location of the enzyme's active site.

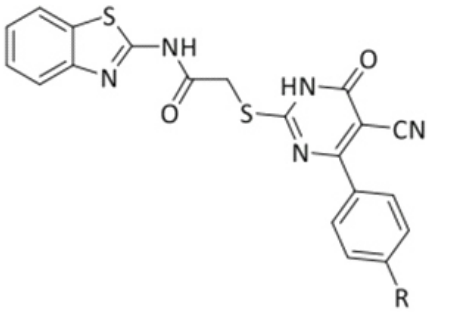


Benzoxazole-quinoline

Benzoxazole moiety and VEGFR-2 inhibition :

When determining tumour angiogenesis, the VEGF signalling pathway is crucial. (20) Numerous studies have demonstrated a connection between tumour growth and migration and aberrant VEGFR-2 expression in tumour cells. (21) As a result, VEGF and VEGFR-2 signalling pathway suppression is a crucial therapeutic target for preventing tumour angiogenesis and subsequent tumour progression. Sorafenib has already received approval as an antiangiogenic medication (22). Based on the structure, it was discovered that the primary VEGFR-2 inhibitory compound has four main characteristics, leading to the synthesis of three series of compounds with a benzoxazole/benzothiazole backbone (23). All three cell lines were shown to be particularly sensitive to compound 4b. All three-compound series were assessed for their ability to inhibit VEGFR-2, and compounds 4b and 4c were discovered to have very similar values to the typical sorafenib molecule. Based on the active site of VEGFR-2, a few more 6-amide-2-aryl benzoxazole and benzimidazole compounds (24) were created, and in vitro activity was tested. In comparison to A549 and MDA-MB-231 cancer cell lines, these chemicals were found to be more effective against HUVEC and HepG2 cancer cell lines. By using the chick chorioallantoic membrane (CAM) assay, the antiangiogenesis potential of these 37 newly synthesised compounds was assessed. The most effective anti-angiogenesis activity was displayed by compound 9d. The 37

freshly synthesised compounds' general structures are now added. When these compounds' molecular docking was examined, it was discovered that compound 9d is a type-II inhibitor of VEGFR kinase. These results showed great promise and could be applied to future anti-angiogenesis treatments.

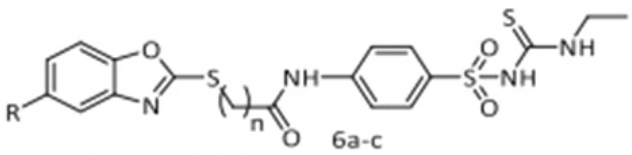


11a R=H, 11b R=F 11c R=CH_3
11d R=OH 11e R=OCH_3

VEGFR-2 inhibition

Benzoxazole-sulphamide moiety :

A few more benzoxazole-sulphamide side chain hybrid compounds were created by El-Helby et al. (25) and evaluated on the HepG2, HCT-116, and MCF-7 cell lines. All of these substances exhibit excellent anti-HCT-116 cell line activity. The most effective molecule, compound 5e, displayed excellent effectiveness against all three cell lines. Compounds 5c, 5e, and 5f have demonstrated excellent activity when tested against VEGFR-2 inhibition using the series' most powerful molecule. Compound 5f has demonstrated an IC50 value as low as 0.10 0.02 M, the same as the common medication sorafenib. All of the compounds had the same position and orientation side as the VEGFR-2 binding site, according to the docking study. The idea was made that excessive the primary cause of the anticancer drug's resistance to hGST P1-1 is human tumour cells (26). Oksuzoglu and colleagues (27) produced a small number of benzoxazole-sulphamide compounds that inhibited the hGST P1-1 enzyme. To comprehend how substitution affected the compounds' behavior, a few structural alterations were also made. The HL-60 cancer cell lines were tested with these chemicals. The IC50 values of compounds 1b, 1c, and 1d were higher than those of the reference medication etoposide. Topo II is a crucial component of the chemotherapy used to treat cancer. Therefore, the ability of each of these synthetic drugs to inhibit Topo II was examined. In order to comprehend the anticancer effects, molecular docking was performed onto the DNA Topo II enzyme active site (PDB: 3QX3) the activity of these substances.

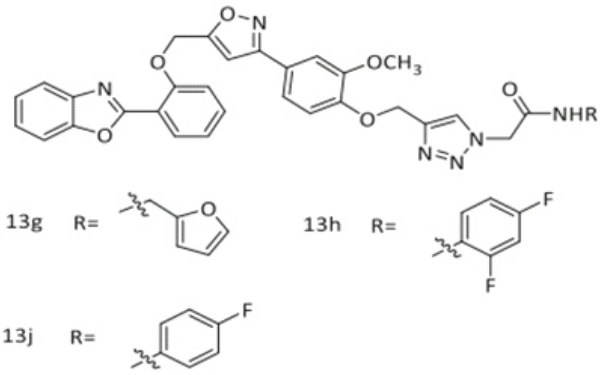


6a n=1, R=CH_3
6b n=2, R=H
6c n=2, R=CH_3

Benzoxazole-sulphamide

Benzoxazole-isoxazole-1,2,3-triazole moiety :

Prior reports have indicated that the 1,2,3-triazole (28,29) and oxazole (29,30) exhibit cytotoxic action. This 1,2,3-triazole and oxazole moiety was combined with benzothiazole and benzoxazole moiety by Dadmal (31) and team, and its cytotoxic impact was tested against the human cancer cell lines Hela (cervical) and A549 (lungs). The effectiveness of compounds 13g, 13h, and 13j when compared to the reference medications GW610 and TAK-165 is particularly excellent. It was also known that these substances cause cancer cells to undergo a caspase-dependent apoptotic pathway, which results in apoptosis.



Benzoxazole-isoxazole-1,2,3-triazole

DISCUSSION

The review discusses heterocyclic compounds that have demonstrated anti-cancer properties, with a particular focus on benzoxazole derivatives. These compounds have been widely employed as treatments for various types of infections and cancers due to their potential therapeutic applications. The review specifically examines the anti-cancer activity of benzoxazole derivatives across different forms of cancer, which makes it a crucial resource for researchers and healthcare professionals seeking to develop novel cancer treatments. The benzoxazole derivatives are especially interesting due to their broad-spectrum activity against various types of pathogens and diseases, which suggests that they may have a wide range of applications in healthcare.

The review focuses on benzoxazole derivatives that exhibit anti-cancer activity, which is a significant area of interest for pharmaceutical research, as the prevalence of cancer is on the rise globally, and there is a critical need for new, effective, and safe treatments. The review provides an in-depth analysis of the mechanisms by which benzoxazole derivatives exert their anti-cancer effects, as well as their efficacy against different types of cancer. This information is vital for developing targeted cancer treatments that can selectively target cancer cells without damaging healthy cells, reducing the risk of side effects.

I. LEUKEMIA:

1) 4-(Benzo[d]oxazol-2-yl)-1-(4-nitrophenyl) pyrrolidin-2-one.
2) N-(4-(N-(Cyclohexylcarbamoyl)sulfamoyl) phenyl) -3-((5- methylbenzoxazole-2-yl) thio) propenamide.

II. LUNG CANCER:

1) 5 (Benzo[d]oxazole 2 carbonyl) 3 [1 (4 bromophenyl)

ethylidene amino] 2 thioxoimidazolidin 4 one.

2) 3-(Benzoxazol-2-ylthio) -N-(5-phenyl-1,3,4-thiadiazol-2-yl) propenamide.

III. COLON CANCER:

1) 2-(4-Fluorophenyl)-4-methyl-7-isopropyl-1,3-benzoxazole-5-ol.

2) 2-[4-(Benzo[d]oxazol-2-yl)-2-methylphenyl] isoindoline-1,3-dione.

IV. CNS CANCER:

1) 2-(2,2-Bis(3,4,5-trimethoxyphenyl)vinyl)-5-methoxybenzoxazole.

2) 2-[4-(Benzo[d]oxazol-2-yl)-2-methylphenyl]isoindoline-1,3-dione.

V. MELANOMA:

1) 2-[b- (4-Hydroxyphenyl)-a-(benzoylamino) vinyl]-benzoxazole.

2) 4-[(4-Benzoxazol-ylphenyl)hyrazono]-5-[(4-nitrobenzylidine)amino]-2,4-dihydro pyrazol-3-one.

The activity of these compounds possess similar (or) more action compared with the conventional standard anti cancer drugs like 5-flurouracil, sorafenib, doxorubicin, erlotinib, etc., Every person in the world is continuously and repeatedly threatened for their health by cancer. To develop a more effective solution to this issue, numerous scholars from all over the world are focusing in this area. Due to its wide range of pharmacological activity, benzoxazole has been a crucial component in the drug discovery process. The current review investigates the impact of several benzoxazole functionalizations and substitutions on its anticancer efficacy. The paper also discusses many target regions such VEGF, VEGFR2, Topo-II, and MEK1. Additional research in this area may result in the creation of benzoxazole compounds with improved activity, selectivity, and reduced toxicity.

CONCLUSION

In conclusion, the review article highlights the importance of benzoxazole in drug discovery and its potential as an effective anticancer agent. Further research in this area may result in the development of more potent and selective benzoxazole compounds with reduced toxicity. The findings of this study have significant implications for the development of novel drugs that can effectively treat cancer and improve the quality of life for cancer patients.

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