Anticancer activity of benzoxazole derivative (2015 onwards): a review

Tanay Ghoshal and Tarun M. Patel*

Abstract

Background: According to the report published recently by the World Health Organization, the number of cancer cases in the world will increase to 22 million by 2030. So the anticancer drug research and development is taking place in the direction where the new entities are developed which are low in toxicity and are with improved activity. Benzoxazole and its derivative represent a very important class of heterocyclic compounds, which have a diverse therapeutic area. Recently, many active compounds synthesized are very effective; natural products isolated with benzoxazole moiety have also shown to be potent towards cancer.

Main text: In the last few years, many research groups have designed and developed many novel compounds with benzoxazole as their backbone and checked their anticancer activity. In the review article, the recent developments (mostly after 2015) made in the direction of design and synthesis of new scaffolds with very potent anticancer activity are briefly described. The effect of various heterocycles attached to the benzoxazole and their effect on the anticancer activity are thoroughly studied and recorded in the review.

Conclusion: These compiled data in the article will surely update the scientific community with the recent development in this area and will provide direction for further research in this area.

Keywords: Benzoxazole, Anticancer activity, Cytotoxicity, Cell lines, Antitumor activity, Anti-proliferative activity

Background

Cancer is one of the major health problems for human beings with the leading mortality rate [1]. Natural, synthetic, or biological and chemical substances are the cancer-causing agents [2]. Many drugs are used to cure it, but they have their own toxic side effects [3]. Hence, there are lots of research carried out to synthesize new [4–6], effective, and affordable anticancer drugs with more selectivity, minimum dosage, and lesser side effects.

Drug discovery over the years have focussed more on the heterocyclic chemistry due to their huge success rate in forming active pharmaceutical intermediate. Among the heterocyclic compounds, benzoxazole is one of the most important heterocyclic compound which exhibit remarkable pharmacological activities [7–11]. There are many reportation of synthetic compounds and naturally occurring compounds with benzoxazole backbone showing a very active anti-cancer activity. Different research groups have done much progress in designing compounds with benzoxazole, synthesizing them, and collecting anticancer activity data of those against various human cancer cell lines. An attempt has been made to see how various heterocyclic moiety attached with benzoxazole have an effect on the anticancer activity of the various benzoxazole compounds synthesized by different groups. A compiled data of all these recent articles helps in providing a direction towards further research.

Benzoxazole attached with various heterocyclic moiety and their anticancer activity

Benzoxazole-piperazine moiety

Al-Harthy et al. [12] have designed few benzoxazole attached to piperazine derivatives and tested it over human A-549 lung carcinoma cells. The initial results were
not that satisfactory, and the results were low which was due to the low solubility of the aryl piperazine compounds, and these compounds precipitated in the cell culture media. The solubility of the compounds can be improved by using N-methylpiperazine instead of aryl piperazine at position-6 of the benzoxazole, and the methyl group at position-2 can be replaced with a carbamate functional group. The one pot reductive cyclization with indium reduced the number of steps, and compounds were synthesized with high yield. The general compound structure is added below (Fig. 1).

Murty et al. [13] reported that the long chain piperazine attached to benzoxazoles coupled with oxadiazoles have shown anticancer effect. The various oxadiazoles were prepared in simple steps and were coupled with the aryl piperazine derivatives using KF-Al₂O₃ with acetonitrile as a solvent at 80°C heating. The cytotoxicity of the compound synthesized was checked on five human cancer cell lines. The IC₅₀ values were determined on cancer cell lines of different origin like MCF-7 (breast), HeLa (cervical), HepG2 (liver), A431 (skin), and A549 (lung). All the compounds showed IC₅₀ value less than 100 in MCF-7 cell line out of which 8a, 8e, 8j, and 8t were observed to be more cytotoxic as compared to others. Few of the compounds which were having benzothiazole backbone instead of benzoxazole have a very good effect on MCF-7 cell line.

The compounds which have an amide linkage have a high cytotoxic effect over the A431 cell line (Fig. 2). All the compounds synthesized showed good results towards the A431 cell line as compared to other cell lines.

**Benzoxazole-1,3,4-oxadiazole moiety**

1,3,4-Oxadiazole [14] are a potent moiety to show a variety of biological activity. A few more amide compounds benzoxazole-1,3,4-oxadiazole compounds [15] were prepared (Fig. 3), and their anti-cancer activity was screened against 4 human cancer cell lines involving A549 (lung cancer), MCF-7 (breast cancer), A-375 (melanoma cancer), and HT-29 (colon cancer) using CA-4 as a positive control. Off these synthesized compounds, it was observed that compounds 12b, 12c, and 12g are showing anticancer activity against HT-29 cancer cell line, and the results are better than the standard drug. Few other compounds 12b, 12f, 12g and 12i were observed to be very active towards MCF-7 cancer cell lines. 12b and 12i were observed to be active against A-549 cell lines. Compound 12b has shown very good activity against HT-29, MCF-7, and A-549 cell lines.

**Benzoxazole-1,2,4-oxadiazole moiety**

1,2,4-Oxadiazole [16, 17] derivatives are well reported in literature to show anti-proliferative activity. Benzoxazole fused with benzofuran and 1,2,4-oxadiazole [18] (Fig. 4) was synthesized in minimum steps and high yields, and cytotoxicity activity was determined against human breast cancer (MCF-7), lung (A549), melanoma (A375), and colon (HT-29) cell lines with combretastatin-A4 as a positive control. Compounds 11b, 11c, 11d, 11g, 11h, and 11i were having more potent activity as compared to the positive control.

**Benzoxazole-pyrazolinone derivative**

New derivatives of benzoxazole, benzothiazole, and benzimidazole derivatives [19] (Fig. 5) were prepared. It was observed that without substitution at N-2, the compounds show very poor anti-proliferative activity as compared to substitution at N-2 of pyrazolinone.

Phenyl and acetyl substitution was done on the N-2 of pyrazolinone, and it increases the antiproliferative activity of the compounds. The acetylated compound (Fig. 6) was arranged as per their activity 12a > 12b > 12c.
according to their IC₅₀ value. Now if the substitution was changed from acetyl to phenyl, then 13b > 13a > 13c according to their IC₅₀ value.

These N-2-substituted pyrazolinone derivatives were found to be very active towards MCF-7 and A-549 cell lines. Compound 12a was found to be the most active compound against MCF-7 and A-549 cell lines with half maximal inhibitory concentrations (IC₅₀) = 6.42 and 8.46 μM.

The docking study of these compounds explains very well the interaction of the structural features and binding patterns of the compounds inside the active sites with the residual amino acids.

**Benzoxazole-triazole derivative**

Various other heterocycles were attached with the benzoxazole moiety to evaluate the anticancer activity. It was observed that benzoxazole and triazole have a wide activity spectrum, and, hence, Srivastava and team [20] (Fig. 7) have developed a one pot multi-component reaction to prepare benzoxazole-triazole scaffolds which when evaluated for anticancer activity against HeLa, SKBr3, and HepG2 cancer cell lines have shown very interesting activity. The synthesis of benzoxazole-linked triazoles was rationalized in two sequential steps in one pot. This involved an in situ generation of alkyne from the corresponding dibromo-olefin precursor through C–H activation of benzoxazole at C-2 position. This was followed by 1, 3-dipolar cycloaddition between the alkyne and benzyl azide to form the triazole ring. The reaction are copper iodide-mediated involving lithium tert-butoxide as a base and heating at 120°C in the first step followed by addition of benzyl azide and heating at 150°C for another 12 h. These series of compounds were screened with HeLa, SKBr3, and HepG2 cancer cells, and they were observed to have potential anticancer activity. Compound 4{2,2,2} has been identified to have potent cytotoxic effect against cancer cell lines: HeLa, SKBr3, and HepG2, and is comparable to the control daunomycin.

Similarly, new series of fused benzoxazole and triazole compounds (Fig. 8) were synthesized, and anticancer activity [21] was evaluated against PBMC cell lines. The substitution was carried out at the thiol to prepare a series of compounds. Compound 12 was found to have...
the best activity; few of the compounds in the series were having a very good antibacterial activity.

Receptor tyrosine kinase is considered as an important therapeutic area of cancer as it is responsible for the cell growth and differentiation. Benzoxazole/benzimidazole-linked triazolotriazines [22] were synthesized, and anticancer activity was evaluated against A549, MCF-7, HepG2, and MDA-MB-231 cell lines. These compounds were selectively very potent towards HepG2 cell lines with compound 8e (Fig. 9) IC50 value very close to standard compound crizotinib.

On similar lines, Dadashpour and group [23] also made some 1,2,3 triazole-fused benzoxazole compounds, and antimicrobial, antifungal, and anticancer activities were evaluated. Though these series of compounds showed very good antibacterial and antifungal activity, these compounds were unable to show relatively good anticancer activity.

**Benzoxazole-combretastatin derivative**

Series of ten benzoxazole derivaties of combretastatin A-4 [24] (Fig. 10) were synthesized and were evaluated against various cancer cell lines like Colo-205 (colon), A-549 (lung), and MCF-7 (breast) cell line, and interestingly, it was observed that compound 8d was more potent than the standard compound against MCF-7 and A549 cell lines. Combretastatin A-4 is a natural product and was isolated from South African willow tree Combretum caffrum in 1989, and it shows anticancer activity against various cancer cell lines in nanomolar concentration. The structure of these new compounds was based on the structure of Combretastatin natural product, and cytotoxicity activity was studied.

The synthesis of these compounds was started from substituted phenyl acetic acid and substituted benzaldehyde followed by cyclization with amino phenol to get benzoxazole. The synthesized compounds were evaluated against selected cell lines like Colo-205 (colon), A-549 (lung cancer), and MCF-7 (breast) by using SRB assay, and results show that compound 8d has shown better activity than standard in 2 of the cell lines (MCF-7 and A-549).

Few more benzoxazole-linked combretastatin compounds (Fig. 11) were synthesized [25] which were not structurally very different from the previous compounds and were tested against three human cancer lines breast (MCF-7), lung (A549), and melanoma (A375). Most of these compounds showed moderate anti-cancer activity, but compounds 11g, 11h, 11l, 11m, and 11n have shown very potent activity. Molecular docking study was carried out for these compounds, and 11g and 11l were observed to have strong binding interaction with the receptor.

**Bisbenzoxazole derivative**

Few other natural-occurring substances also show cytotoxicity activity. Bis(benzoxazole) natural products UK-1 and AJI9561 (Fig. 12) have already been reported to have cytotoxic activity [26, 27]. Kumar et al. [28] subsequently reported the activity of UK-1 against a wide range of human cancer cell lines.

Both UK-1 and AJI9561 were reported to possess growth inhibitory activity against the murine cancer cell line P388. UK-1 though has a very strong antiproliferative activity but does not inhibit the growth of gram-positive and gram-negative bacteria, fungi, or yeast. UK-1 exhibits a wide spectrum of potent anticancer activity against leukemia, lymphoma, and certain solid tumor-derived cell lines, with IC50 values of as low as 20 nM. The natural product of bis(benzoxazole), UK-
1, has potential for use against cancer cell lines. The analog of UK-1 in which the carbomethoxy-substituted benzoxazole ring was replaced with a carbomethoxy-substituted benzimidazole ring was inactive against human cancer cell lines and the two strains of *S. aureus*. In contrast, a simplified analog in which the carbomethoxy-substituted benzoxazole ring of the UK-1 was replaced with a carbomethoxy group was almost as active as UK-1 against the four cancer cell lines examined but lacked activity against *S. aureus*. The metal-binding affinity of these synthesized compounds was studied, and it was observed that they demonstrate good binding towards Zn$^{2+}$ and Ca$^{2+}$ ions. The non-cytotoxic benzimidazole UK-1 analog binds Mg$^{2+}$ ions 50-fold weaker than UK-1, whereas the simple benzoxazole analog binds Mg$^{2+}$ ions nearly as well as UK-1. These results support a role of Mg$^{2+}$ ion binding in the selective cytotoxicity of UK-1 and provide a minimal pharmacophore for the selective cytotoxic activity of the natural product.

Structurally similar bis(benzimidazole) [29] derivatives (Fig. 13) were synthesized and it was observed that compounds 17 and 18 exhibit potent anticancer activity. Interestingly, compound 16 which is the synthetic precursor of compounds 17–19 was found to be more potent than UK-1 against human lung (A-549) and epithelial (HeLa) carcinoma cell lines. Therefore, further work with UK-1, compounds 15–18, and their analogs must be conducted to determine whether such targeting is involved in the selective cytotoxicity of UK-1 and compounds 15–18, and whether the promising spectrum of the in vitro anticancer activity of UK-1 and 15–18 reported herein is also reflected in vivo.

Bis(benzoxazole) natural product (UK-1) shows activity against a wide range of human cancer cell lines, therefore, a very similar compound 4-carbomethoxy-2-(2'-hydroxyphenyl) benzoxazole [30] has comparative activity similar to the natural product UK-1 and also formed complexes with a variety of metal ions such as Mg$^{2+}$, Cu$^{2+}$, Zn$^{2+}$. Analogs of 4-carbomethoxy-2-(2'-hydroxyphenyl)benzoxazole that were prepared whose structure remain very similar to UK-1 were synthesised, and anticancer activity of these compounds were examined against breast and lung cancer cell lines. To check the ability of these synthesized analogs and UK-1 to coordinate with Mg$^{2+}$, Cu$^{2+}$, and Zn$^{2+}$, spectrophotometric titrations were carried out in methanol.
Although none of the new analogs were more cytotoxic than 4-carbomethoxy-2-(2'-hydroxyphenyl)benzoxazole, some analogs were identified that display similar cytotoxicity to this simplified UK-1 analog with improved water solubility. It was found that UK-1 and all of these new analogs (Fig. 14) bind Cu$^{2+}$ ions better than Mg$^{2+}$ ions, and the nature of the 4-substituent is important for the Mg$^{2+}$ ion-binding ability of these 2-(2'-hydroxyphenyl)benzoxazoles. Previous studies of a limited number of UK-1 analogs demonstrated a correlation between Mg$^{2+}$ ion binding ability and cytotoxicity; however, within this series of 4-substituted-2-(2'-hydroxyphenyl)benzoxazoles, the variations in cytotoxicity do not correlate with either Mg$^{2+}$ or Cu$^{2+}$ ion-binding ability. These results, together with recent ESI-MS studies of Cu$^{2+}$-mediated DNA binding by UK-1 and analogs, indicate that UK-1 and analogs may exert their cytotoxic effects by interaction with Cu$^{2+}$ or other transition metal ions, rather than Mg$^{2+}$, and that metal ion-mediated DNA binding, rather than metal ion-binding affinity, is important for the cytotoxic effect of these compounds. The potential role of Cu$^{2+}$ ions in the cytotoxic action of UK-1 is further supported by the observation that UK-1 in the presence of Cu$^{2+}$ displays enhanced cytotoxicity to MCF-7 and A549 cells when compared to UK-1 alone. This result is very promising in the future research activity. Few more structurally similar compounds to that of UK-1 were synthesised, and their anti-proliferative activity were studied.

A new benzoxazole derivative [31] which has a very similar structure to UK-1 was isolated from the
Streptomyces species (strain Tü 6176) that was found to be having very strong growth inhibitory action against various human tumor cell lines. This Streptomyces species was collected from the soil sample from Brazil. This is called as nataxazole (Fig. 15), and it was prepared through batch fermentation of strain Tü 6176, the process engaging for 72 h before extraction with ethyl acetate and column purification over Sephadex LH-20 and Toyopearl HW-40 using MeOH/MDC as mobile phase. The structure of this compound was elucidated by various NMR experiments. The inhibitory action of nataxazole (1) on the growth of tumor cells was compared with UK-1 and tested with various human tumor cell lines AGS (gastric adenocarcinoma), MCF7 (breast adenocarcinoma), and HepG2 (hepatocellular carcinoma). From the resulting concentration-activity curves, the GI50 (concentration at which half of the cells were inhibited in their growth) and TGI values (concentration at which a total inhibition of cell growth was observed) were obtained. The cytotoxic activity of 1 is somewhat better than UK-1 against AGS cells (GI50 0.4 mg/ml vs. 0.8 mg/ml for UK-1) and equal against MCF-7 and HepG2 cells. The cell-cycle analysis revealed that nataxazole (1) and UK-1 produce an accumulation of cells in S phase and reduce the ratio of cells in the G2/M phase. These findings indicate that nataxazole and UK-1 may exert their inhibitory effect on cell growth by a similar mechanism of action.

A new series of bisbenzoxazole [32, 33] derivatives were prepared by heating 2 equivalents of 4-chloro 2-aminophenol with substituted dicarboxylic acids in PPA. These bisbenzoxazole derivatives (Fig. 16) were then evaluated against human prostate (DU145) and breast cancer cell lines (MCF-7). The cell viability results indicated that both of these compounds have a significant effect on human prostate (DU145) and breast cancer (MCF-7) cell lines. To confirm the side effects of these compounds, these compounds were tested against mouse fibroblast cells L929, and they have shown anti-proliferative effect on fibroblast cells in time- and dose-dependent manner.

2-Aryl-benzoxazole derivative
In 2015, Sun and co-workers [34] isolated a new series of compounds from the halophilic bacterial strain Nocardiopsis lucentensis DSM 44048 and tested their cytotoxicity against a panel of human tumor cell lines, and these compounds were known as nocarbenzoxazoles, and structures of these compounds were based on 2-aryl benzoxazole. Of these compound, isolated nocarbenzoxazoles-F (1) and nocarbenzoxazole G (2)
(Fig. 17) were observed to have selective activities of HepG2 and HeLa cell lines.

Later, Kim and team [35] have come up with a coupling process on benzoxazoles to prepare nocarbenzoxazole and observed that analytical data of synthetically prepared nocarbenzoxazole was not matching with the naturally isolated product, and revised structure of nocarbenzoxazole was validated by the total synthesis. A series of 2-aryl benzoxazole (Fig. 18) was prepared and activity checked with HeLa cells and compound observed to be selective activity against HeLa cell lines and did not have any remarkable effect on other cell lines.

A series of imidazolinone and benzoxazole derivatives [36] were synthesized by the condensation of oxazolidinone derivatives with aniline and 2-hydroxyaniline. These compounds were further acetylated with acetic anhydride and chloroacetyl chloride to prepare acetyl derivative of the parent compounds. The compound synthesized was tested against various human cell lines, and the results revealed that imidazolinone and benzoxazole derivatives are potent against the cancer cell lines. In particular, it was found that the benzoxazole derivatives were more potent than imidazolinone derivatives. The biological results obtained for these compounds confirm that they are most potent against the human breast tumor cells (MCF-7) and human hepatocellular cancer cells (HepG2).

A new series involving benzothiazoles and benzoxazoles [37] was synthesized using 4-benzothiazol-2-ylphenylamine and 4-benzoxazol-2-yl-phenylamine (Fig. 19) as starting materials. The first series of compounds involve Schiff base formation with various aldehydes, and the second series involves the condensation of 4-benzothiazol-2-ylphenylamine and 4-benzoxazol-2-yl-phenylamine with chloroacetyl chloride followed by displacement of chloro with various amines. All these compounds which were synthesized were evaluated for their antitumor activities against various human breast cancer cell lines mainly MCF-7 and MDA-231. All the compounds synthesized showed antitumor activity especially the N-methylpiperazine-substituted compounds mainly compound 6c and 6f. The docking results of the

![Fig. 14 Analogs of UK-1](image)

![Fig. 15 Structure of nataxazole and UK-1](image)
synthesized compounds were seen against epidermal growth factor receptor, and these compounds show very good interaction against them.

Further, a new series of hybrid compound [38] of benzothiazole-pyrazole and benzoxazole-pyrazole compounds (Fig. 20) were synthesized, and their anticancer activity were evaluated. In comparison to celecoxib, the pyrazole moiety was replaced with pyrazolinone, linked to benzothiazole or benzoxazole at C4 with different substituents at C3 aiming to obtain new hybrids useful as anticancer active agents. The synthesis of these compounds was started through very simple precursors like 2-aminophenol and 2-amino thiol which were condensed with 4-substituted benzoic acid.

The new hybrids were screened against lung, breast, and liver cancer cell lines (A549, MCF7, and Hep3B), in addition to normal fibroblast cells. Compound 13a was the most active and selective one on the lung cancer cell line (A549); its IC$_{50}$ and SI values were 2.4 μM and 83.2, respectively. Compound 14b was active on MCF-7 with the best selectivity towards this cell line. The new derivatives were screened for their inhibitory activity against COX enzymes; the obtained results revealed that compounds 13a and 14b were more active inhibitors for COX-2 than celecoxib.

**Benzoxazole-hydrazone derivative**

A series of benzoxazole-5-carbohydrazide derivatives [39] (Fig. 21) were prepared by condensation with different substituted isatin compounds. These derivatives were further checked with various in vitro anticancer cell lines like HeLa, IMR-32, and MCF-7 cancer cell lines using MTT method. These compounds were observed to be active against all the three cell lines. From the initial study, it was observed that the compounds having electron-withdrawing group have a better biological activity as compared to the compounds which are not...
substituted. Other observation in the biological activity was, those compounds which have a substitution at C-5 on isatin moiety especially with different halides rather than C7 have a better biological activity. This information might help in the development of anticancer in future. The general structure of the compound is added below.

Hydrazone moiety plays a very important role in the anticancer drug development. New benzoxazole-based hydrazine derivatives were designed [40] (Fig. 22). Synthesized and in vitro cytotoxic effects were diagnosed on C6 rat glioma and NIH/3 T3 mouse embryonic fibroblast cell lines followed by flow cytometry-based apoptosis detection in C6 cell line. The compound 3g looks out to be a promising candidate for further studies.

2-Thiobenzoxazole derivative
It was previously reported [41] that benzothiazole derivative compounds have shown very impressive anticancer in vitro activities, and based on that, some compounds were synthesized by Wang et al. Compounds 1a and 1b (Fig. 23) show very poor solubility and show moderate inhibition against HepG2 and MCF-7 cell lines, and hence, the lead optimization of compound 1a and 1b were done.

To increase the solubility of these compounds, N-methylpiperazine was introduced in position 2 and position 6 (Fig. 24) [42]. The results were impressive; the modified compounds have shown very comparative results as compared to compound 1a with better solubility. It was also noticed that in compound 1e where the benzyl group was replaced with N-methylpiperazine group leads to the total loss of activity of the compound. The introduction of N-methylpiperazine substituent at the 6-position (1e) had a detrimental effect on the potency, that is, about 20–50-fold decrease in potency, compared with that of 1a. These results gave indication that the N-methylpiperazine was well tolerated in 2-position so benzothiazole moiety was replaced with benzoxazole and benzimidazole, and it was to the delight that these new series of novel compounds still retain their anticancer activity.
In the preliminary in vitro biological evaluation, the immunofluorescence staining of HCT116 cells indicated that 1d, 1f, and 1g led to cytosolic vacuolization which was not induced by 1a at low micromolecular concentrations. These results were impressive and suggest that these optimized compounds might potentially constitute a novel class of anticancer agents, which could fuel further studies.

A new series of compounds [43] were prepared by linking benzothiazole, benzoxazole, and pyridine to a hydrophilic moiety like a glycoside. This presence of hydrophilic moiety increases the solubility of these heterocycles and an improved selectivity toward cancer cells which are known to be specifically enriched in carbohydrate receptors such as lectins. The structure of these compounds was well confirmed through ROESY, DFQ-COSY, HMBC, and HMQC NMR spectra. The biological activity of these compounds confirms that these compounds were not that effective against anticancer cell lines.

The synthesis of a range of 2-phenyl-benzothiazoles, -benzoxazoles, and -chromen-4-ones [44] related to the potent antitumor lead compound 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole has been accomplished. Evaluation against the MCF-7 and MDA 468 breast cancer cell lines revealed compounds within the new series with potent (submicromolar Gl50) activity in both cell lines (e.g., 9a, b and 12a, d). Although none of the new series was able to recapitulate the potent antitumor properties of 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole, the new compounds were significantly more active than the structurally related benzimidazoles. Antitumor potency appeared to correlate with the emergence of a G2/M cell cycle block. For lead compound 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole, binding to the aryl hydrocarbon receptor appeared to play an important role in growth inhibition.

**Benzoxazole-pyrazole derivative**

Novel substituted pyrazolo-benzoxazole [45] compounds (Fig. 25) were synthesized, and the cytotoxicity activity was checked against MCF-7, KB, Hop62, and A549 cancer cell lines. The compounds with methoxy substitution at positions 5 and 6 were observed to have an excellent...
anticancer activity. The compounds having nitro substitution at 6 position was observed to have very good anti-tumor activity against MCF-7 and A-549 cell lines. Compounds having nitro disubstitution at 5 and 7 was also found have very good anticancer activity against A-549 cell lines. Few other compounds were also prepared where benzoxazole moiety was exchanged with benzo-furan backbone, and anticancer activity was tested.

**Benzoxazole-quinoline derivative**

A one pot synthetic strategy for the synthesis of hybrid of benzoxazole with quinoline and quinoxaline compounds (Fig. 26) was employed to prepare some active anticancer compounds [46]. The synthesis involves heating substituted 2-aminophenols and corresponding aldehyde with equal equivalents of silica chloride for 3–4 h at 120 °C without any solvent. Molecular docking of these compounds revealed that these compounds inhibit enzyme protein tyrosine kinase. The cytotoxicity study of these compounds (4a-f) showed that these compounds are more potent towards breast cancer cell lines MCF-7 and MDA-MB-231 as compared to oral and lung cancer cell lines KB and A-549. The compound 4c was found to be very active and showed the maximum inhibition in the activity of enzyme tyrosine kinase. Molecular docking revealed that the compound 4c has formed 2 hydrogen bond interaction, one taking place with the nitrogen of benzoxazole with Thr-766 while the other through the nitrogen of quinoxaline with Met769 which corresponds to the active site of the enzyme.

**Benzoxazole derivative and VEGFR-2 inhibition**

The VEGF signaling pathway plays an important role in determining tumor angiogenesis [47]. Many studies have shown that the abnormal expression of VEGFR-2 in tumor cells is related to tumor growth and migration [48]. Therefore, inhibition of VEGF and VEGFR-2 signaling pathways plays a very important therapeutic target for tumor angiogenesis and subsequent tumor growth. Sorafenib is already approved as antiangiogenic drug [49, 50], and based on the structure, it was found out that major VEGFR-2 inhibitory compound has 4 main features, and 3 series of compounds with benzoxazole/benzothiazole backbone were synthesized [51] (Fig. 27), and

![Fig. 26 Benzoxazole fused with quinoxalin](image1)

![Fig. 27 VEGFR-2 inhibition compounds](image2)
cytotoxicity was checked against various cancer cell lines HepG2, HCT-116, and MCF-7. Compound 4b was found to be very active against all the 3 cell lines. All the 3 series of compound were evaluated against VEGFR-2 inhibition, and compounds 4b and 4c were found to have a very close value against standard Sorafenib compound.

Few more 6-amide-2-aryl benzoazole and benzimidazole compounds [52] were synthesized based on the active site of VEGFR-2, and in vitro activity was checked. These compounds were seen to be more potent against HUVEC and HepG2 cancer cell lines as compared to A549 and MDA-MB-231 cancer cell lines. These 37 newly synthesized compounds were evaluated for anti-angiogenesis capability by chick chorioallantoic membrane (CAM) assay. Compound 9d showed the most potent anti-angiogenesis activity. General structure of the 37 newly synthesized compound is added in Fig. 28.

The molecular docking of these compounds was studied, and it was found that compound 9d is a type-II inhibitor of VEGFR kinase. These results were very promising and can be utilized in future for potential treatment of anti-angiogenesis.

Benzoxazole-sulphamide derivative

El-Helby et al. [53] developed few more hybrid compounds of benzoxazole-sulphamide side chains (Fig. 29), and they were tested against HepG2, HCT-116, and MCF-7 cell lines. All these compounds have shown very good activity against HCT-116 cell line. Compound 5e was the most potent compound which showed very good activity against all the 3 cell lines. The most potent compound of the series was tested against VEGFR-2 inhibition, and compounds 5c, 5e, and 5f have shown very good activity. Compound 5f has shown IC50 value as low as 0.10 ± 0.02 μM which is the same to the standard drug sorafenib. The docking study revealed that all the compounds have the similar position and orientation side as the binding site of VEGFR-2.

It was suggested that overexpression of hGST P1-1 by human tumor cells is the main reason for the resistance of the anticancer drug [54]. So few compounds of benzoxazole-sulphamide (Fig. 30) were synthesized by Oksuzoglu and team [55] which showed hGST P1-1 enzyme inhibition. A few modifications to the structure were also done to understand the effect of substitution on the activity of the compounds. These compounds were screened against HL-60 cancer cell lines. Compounds 1b, 1c, and 1d were having better IC50 values than standard drug etoposide. Topo II plays a very important role in the cancer chemotherapy treatment. So all these compounds synthesized were checked if they could inhibit Topo II. Hence, molecular docking was done onto the active site of DNA Topo II enzyme (PDB: 3QX3) to understand the antitumor activity of these compounds.
Benzoxazole-isoxazole-1,2,3-triazole derivative

1,2,3-Triazole [56, 57] and oxazole [57, 58] are previously reported to have shown cytotoxic activity. Dadmal [59] and team have coupled this 1,2,3-triazole and oxazole moiety with benzothiazole and benzoxazole moiety (Fig. 31), and cytotoxic effect was evaluated against human cancer cell lines Hela (cervical) and A549 (lungs). Compounds 13g, 13h, and 13j have shown very impressive results against standard drugs TAK-165 and GW-610. It was also understood that these compounds induces apoptosis to cancer cell through caspase-dependent apoptotic process.

Benzoxazole-tetrazole derivative

A new series of compound involving tetrazole coupled with benzoxazole [60] (Fig. 32) was synthesized, and anticancer activity was evaluated against MCF-7, Hop62, and A549 cell lines. The activity of these synthesized compounds was not that promising as compared to the standard Adriamycin, but compounds 9b and 9g were having the best anticancer activity in the lot.

Benzoxazole-pyrimidine derivative

Pyrimidine moiety has shown anticancer activity previously, so new series of Benzoxazole azo-pyrimidine [61] and benzimidazole azo-pyrimidine were synthesized by using very simple steps. Firstly, the 3-aminophenyl benzoxazole and benzimidazole were synthesized, and then, they were made into diazonium salt and coupled with diethyl malonate further this intermediate was cyclised with urea to prepare new variety of pyrimidine benzoxazole and benzimidazole hybrids (Fig. 33). The cytotoxic activity was evaluated against breast carcinoma (MCF-7), lung cancer (A549), human prostate cancer (PC-3), human pancreatic cancer (PaCa2), and colorectal adenocarcinoma (HT-29) cell lines. From the results, it was observed that benzoxazole compound 7a showed lower activity than benzimidazole compound 7b in all cell lines. Docking study was done with COX-2 enzyme (PDB-1CX2) to explain the lower activity of compound 7b as compared to compound 7a, and it was curtailed that compound 7a gets fitted well in the cavity and has better interaction therefore forms 3 hydrogen bonds whereas compound 7b forms 2 hydrogen bond.

Fig. 31 Benzoxazole triazole compounds

Fig. 32 Benzoxazole-tetrazole compounds

Fig. 33 Benzoxazole-pyrimidine hybrids

| Compound | Substitution |
|----------|-------------|
| 13g      | R = $\text{OCH}_3$ |
| 13h      | R = $\text{F}$ |
| 13j      | R = $\text{F}$ |

**Fig. 31** Benzoxazole triazole compounds

**Fig. 32** Benzoxazole-tetrazole compounds

**Fig. 33** Benzoxazole-pyrimidine hybrids

**Table:**

| Compound | Substitution |
|----------|-------------|
| 9a, 9j   | R = H       |
| 9b       | R = 3,4,5-trimethoxy |
| 9c       | R = 4-methoxy |
| 9d       | R = 4-chloro |
| 9e       | R = 4-bromo |
| 9f       | R = 4-fluoro |
| 9g       | R = 4-nitro |
| 9h       | R = 3-nitro |
| 9i       | R = 4-trifluoromethyl |
| 9j       | R = 4-methyl |
Another series of pyrimidine-based compounds developed by Seenaiah and team [62] were hybrid compounds by coupling pyrimidine with benzimidazole, benzothiazole and benzoxazole (Fig. 34). These were linked to the pyrimidine moieties by thio, methylthio, and amine moieties. These synthesized compounds were studied for their antimicrobial activities and anticancer activity. From the series of 27 synthesized compounds, compound-22 was the most active compound, and compound-24 was most active against A549 cell lines with the IC$_{50}$ value of 10.5 $\mu$M.

**Benzoxazole-phthalimide derivative**

Phthalimide core was coupled with benzoxazole/benzothiazole (Fig. 35) to prepare a new set of compounds. Though in previous occasion it was observed that phthalimide core compounds have shown teratogenic disorders, variation in the phthalimide structure could eliminate the side-effects and show promising anticancer activity [63]. These synthesized hybrid compounds [64] were evaluated through IC$_{50}$ values against two human cancer cell lines HepG2 and MCF7. To check its effect against healthy cells, these compounds were screened against WI-38 cell lines. 5-Fluorouracil and erlotinib were used as the standard against HepG2 and MCF7 cell lines respectively. It was observed that none of the compounds have shown cytotoxic activity against WI-38 cell lines and have shown potent anticancer activity against HepG2 and MCF7 cell lines in nanomolar to micromolar range. Both benzoxazole and benzothiazole derivatives 5a, 5b, and 5k exhibited 1.7 to 3 times more potent anticancer activity against HepG2 cell line than 5-fluorouracil, which is a very promising result. Compounds 5c and 5g were the most potent derivatives between the tested compounds. They showed IC$_{50}$ values 9 and 6 nM with 79 and 118 times more potent anticancer activity than erlotinib against MCF7 cell line.
Benzoxazole-naphthalimide derivative
The flat structure of the naphthalimide has an advantage of inserting into the DNA and thus compounds like amonafide and mitonafide had shown previously very promising results against various cancer cell lines. But these active compounds could not move ahead because of their toxicity [65], but it was reported that by modifying the N,N-dimethyl chain of mitonafide, the toxicity can be reduced [66]. Hence, some novel compounds were synthesized by condensing benzoxazole at C4 position of naphthalimide [67] (Fig. 36), and it was observed that the cytotoxicity of these compounds largely depends on the side chain. Compounds 9 and 10 were able to exhibit better cytotoxic activity against B16F10 cells as compared to compounds 5–8, and the reason behind is largely due to the side chain. Compounds 9 and 10 show the same degree of cytotoxicity as that of amonafide.

Benzoxazole-quinolone derivative
Derivatives of quinolones [68] are confirmed to have anticancer effect. So new series was developed by condensing the quinolones with benzoxazole and benzothiazole moiety [69] (Fig. 37); after that, these compounds were screened for cytotoxicity activity against breast cancer cell lines. Compounds with thiazole connected to quinolones have shown better results as compared to compounds with benzoxazole associated with quinolones. Compounds 5h and 5l were found to be showing the best activity as compared to the other compounds in the series. Hybrid compounds of benzoxazole with...
quinolones were observed to be better antioxidant as compared to thiazole derivative.

**Benxoxazole-pyridine derivative**

Novel benxoxazole derivatives were prepared which were having improved selectivity towards mouse ACC1 against ACC2 [70]. ACC1 is overexpressed in human cancer cells; a number of mammalian ACC inhibitor were reported as dual ACC1 and ACC2 inhibitor or sometimes only ACC2 inhibitor but rarely ACC1 inhibitor. The current set of targets (Fig. 38) is reported to be only ACC1 inhibitor. Slight modifications in the structure of the compound have reduced the side effect of weight loss observed in compound 1a. Unsubstituted ureido compound 1b has a better selectivity towards mouse ACC1 as compared to compound 1c and 1d.

Three novel pyridine-benxoxazole [71] derivatives (Fig. 39) were prepared, and anticancer activity was evaluated against HepG2 cell line. The 2-methyl benxoxazole derivative was coupled with pyridine-2,3 and 4 aldehyde to get the 2-pyridyl, 3-pyridyl, and 4-pyridyl benxoxazole derivative. The crystal structure was studied, and antitumor activity was evaluated. The IC₅₀ values of these compounds were 87.7, 9.6, and 33.5 μmol/l respectively.

**Benxoxazole-metal complexes**

A new ligand 2-((2-((benzo[d]oxazol-2-yl)methoxy)phenoxymethyl)benxoxazole [72] (L) (Fig. 40) and its four transition metal complexes M(NO₃)²L (M = Cu, Co, Ni, Zn) were synthesized, and their characters were investigated. The single crystal structures of these complexes show that all of them have similar molecular structure, and the ligand exhibits good coplanarity after coordination with the metal ions. Further investigation of DNA binding indicates that both the ligand L and the complexes can bond to DNA by intercalation mode, and the latter possesses much stronger binding affinity. The cytotoxicity assays of all the compounds against four different tumor cell lines (A549, HepG2, K562, K562/ADM) were evaluated by MTT assay. It was notable that the ligand was almost inactive against all the cell lines. However, all of the complexes exhibited considerable antitumor activity and cytotoxic specificity toward the tested cancer cell lines. Cu-L showed much higher antitumor activity than other complexes did on all the cell lines.

Novel metal [Zn(II), Cu(II), Mg(II), Ni(II), Pd(II), and Ag(I)] complexes of 2-trifluoroacetyl-benzoxazole [73] (Fig. 41) were synthesized, and multidrug reversing
activity was tested. Multidrug resistance [74, 75] of cancer means the cancer cells become resistant to the various cytotoxic drugs. The cytotoxic activity of these ligands and complexes were measured through MTT assay, and it was observed that as compared to the free ligand the Cu(II) and Zn(II) complexes were more potent, and there was 29- and 5-fold increase in activity of Cu(II) and Zn(II) complexes as compared to free ligands. Verapamil was used as a positive control in this case.

The DNA has several binding site on which the small molecules are bonded through covalent and non-covalent bonds. The binding of Ru(II) complexes to DNA was reported to be the main factor in the anticancer effects of these complexes. Two Ru(II) complexes, NAMI-A and KP1019, are under advanced clinical evaluation as anticancer drugs [76]. A number of Ru(II) complexes bearing π-bonded arene ligands exhibit promising anticancer activities [77]. De and team [78] have prepared 4 Ru(II)-arene-2-pyridinylbenzoxazole complexes (Fig. 42) and characterized. MTT assay results indicate that all complexes exhibit highly selective cytotoxicity for two cancer cell lines (Caco-2 and HeLa) with respect to normal HEK-293 cells. Among the complexes, 4’ and 5 show the highest cytoselectivities for the Caco-2 and HeLa cell lines, respectively.

Bioactive compounds are observed to exhibit improved biological activity upon coordination with transitional metal ions [79, 80]. Paira and team [81] have synthesized few Ru(II)-arene complexes of benzimidazole, benzoxazole, and benzothiazole (Fig. 43) using Amberlite IR-120(H) as the catalyst. This method is environment friendly and gives a scope to prepare a series of ruthenium compounds for anticancer screening. All the compounds synthesized have shown great cytotoxicity activity against HeLa, MCF-7, and A2780 cell lines as compared to cisplatin standard drug. Compound 4g was found to possess the most potent cytotoxic activity and selectivity in the cancer cell lines.

Two new mononuclear mixed ligand copper (II) complexes [82] (Fig. 44) were prepared, and their interaction with the DNA was investigated. Previously, copper(II) complexes are reported to show a variety of biochemical activity in different areas like anticancer [83]. The dipeptides utilized in these compounds are (Gly-gly and Gly-L-leu) glycylglycine anion and glycyl-L-leucine anion respectively for compounds 1 and 2. Both these compounds were found to bind to calf thymus DNA through an intercalative mode. The anticancer activity of these two compounds were investigated against three cell lines HeLa (cervical), PC-3 (prostatic), and A549 (pulmonary). Cisplatin was used as a positive control. It was observed that compound 2 has more cytotoxic effect as compared to compound-1. These could be due to longer hydrocarbon chain associated with compound-2 and making it more permeable in the cell membrane.

Similarly, 3 more Cu(II) dipeptide complexes (Fig. 45) [Cu(Gly-L-Val)(HPMB)H2O].ClO4.H2O (1), [Cu(Gly-L-Val)(TBZ)H2O].ClO4 (2), and [Cu(Gly-L-Val)(PBO)H2O].ClO4 (3) (Gly-L-Val = glycyl-L-valine anion, HPBM = 5-methyl-2-(2’-pyridyl)benzimidazole, TBZ = 2-(4‘-thiazolyl) benzimidazole, PBO = 2-(2’-pyridyl) benzoxazole) were prepared [84], and their interaction with the DNA was studied using UV-visible, fluorescence, viscosity, thermal denaturation and docking study (PDB ID: 454D). The results showed that all these three compounds bind to DNA through an intercalative mode as like the previous compounds. The anticancer activity of these complexes were also studied against A549, PC-3, HeLa, and 3T3 cell lines with cisplatin as a standard.
and the results suggested that compound 1 is more potent than compound-2 which was more potent than compound-3.

5-Hydroxybenzoxazole derivative
Thymoquinone is a natural product which is reported to exhibit antitumor activity [85]. Amination at C3 of thymoquinone also improved the antitumor activity of ATQ (Fig. 46) A series of benzoxazole compounds were synthesized by using thymoquinone [86] (TQ/ARQ) as the starting material. These compounds were observed to have better cytotoxicity values as compared to TQ and ATQ when they were evaluated against 4 cancer cell lines (SW620, CFPAC-1, HepG2, and HeLa). Human lung fibroblast (WI38) was used as healthy control cell lines which help in finding the effect of these chemicals over healthy and normal cells. Compound 1f was observed to have potent activity against cancer cell lines while compound 1e was less toxic against the WI38 cell lines.

2-Aryl 5-hydroxy benzo[d]oxazoles [87] (Fig. 47) were synthesized in a one pot starting from ortho-disubstituted precursor and amino phenols with toluene as a solvent and manganese dioxide as the oxidant. The series of these compounds were evaluated against 5 cancer cell lines as well as noncancerous cells and most of them showed good anticancer activity.

It was observed that the chlorine on the aryl at meta position (TDNSS-10) showed the best activity against the halogen substitution at the ortho-position of the aryl group.

5-Aminobenzoxazole derivative
AZD6244 (selumetinib) was discovered by Array BioPharma, and it is a highly selective MEK1 inhibitor [88], but it was having some limitations, so novel benzoxazole compound (KZ-001, Fig. 48) was developed which was prepared to overcome the limitations of AZD6244. KZ-001 [89] was highly potent and was selective against selective MEK1 and 2 inhibitors. KZ-001 was observed to have 30 times greater inhibition BRAF and KRAS mutant tumor cells as compared to AZD6244. To determine its potential clinical application, the synergistic effect of KZ-001 with other agents was investigated both in vitro and in vivo (xenograft models). KZ-001 exhibited synergistic anticancer effect in combination with BRAF inhibitor vemurafenib and a microtubule-stabilizing chemotherapeutic agent docetaxel.
2-Aminobenzoxazole derivative
An and team [90] have developed a novel series of benzoxazole compounds (Fig. 49) which inhibit the Aurora kinase [91]. Aurora kinases are of 3 types A, B, and C, and all these kinases are associated with human cancer [92]. It was understood that regiochemistry, linker length, and halogen substitution plays an important role in the activity of these compounds. All the compounds were more effective in inhibiting the Aurora-B kinase, and molecular docking was done of these compounds to understand the selectivity of Aurora-A and B kinase. Further, compound 13l and 13q have shown very good cytotoxicity activity. Compound 13q has shown very good activity against prostate cancer PC-3 tumor xenograft model.

Benzoxazole-steroid derivative
Abiraterone and galeterone are commonly used drugs for prostate cancer [93, 94]. So eight noble oxazoline, benzoxazole, and benzimidazole compounds [95] (Fig. 50) were prepared from 3 β-acetoxyandrosta-5,16-dien-17-carboxylic, 3 β-acetoxyandrost-5-en-17β-carboxylic, and 3 β-acetoxypregn-5-en-21-oic acids. The molecular docking of these compounds (PDB code 3RUK) suggests that they form stable complexes with the enzyme. The new compounds (steroid moiety) are positioned in the similar fashion as that of abiraterone and galeterone. These compounds were able to inhibit growth of prostate carcinoma LNCaP and PC-3 cells in 96 h incubation, but compounds 4 and 6 were more potent than abiraterone and galeterone in LNCaP cell lines.

Pyrrolobenzodiazepine-benzoxazole derivative
The benzoxazole, benzimidazole, and benzothiazole backbone which is very common for anticancer compounds [96] was reported to prepare through ligand-free cobalt nanoparticles. These nanoparticles of cobalt oxide promoted cyclization cross-coupling reaction without the use of ligands or additives. These compounds synthesized were further docked (PDB ID: 1NFK) with estrogen receptors to investigate their antibreast cancer activity.

Pyrrolobenzodiazepine moieties were previously evaluated for anticancer activities [97]. So new hybrid compounds were synthesized by attaching benzothiazole and benzoxazole with pyrrolobenzodiazepine moiety 94 (Fig. 51) which was further attached through different alkane or alkylamide spacers. Anticancer activity of these compounds was evaluated against A375 cell lines. One of the compounds of the series compound-17d showed potent anticancer activity with significant DNA-binding ability, and apoptosis caused G0/G1 phase arrest at sub-micromolar concentrations. To confirm the DNA-binding capacity of these series of compounds, molecular docking of these compounds was done, and compound 17d was checked for in vivo activity in human colon cancer HT29 xenograft mice.

Fig. 48 Benzoxazole compounds as MEK1 inhibitor

Fig. 49 Benzoxazole compounds as Aurora-B kinase inhibitor

Fig. 49 Benzoxazole compounds as Aurora-B kinase inhibitor
Conclusion
Cancer possesses a continuous and series threat to the health of every individual in this world. Many researchers across the world are working on this direction to find a better treatment to this problem. Benzoxazole has been a very important moiety in drug discovery due to its diverse pharmacological activity. Present review explores the effect of various functionalization and substitution on benzoxazole and their effect on the anticancer activity. Various target areas like VEGF, VEGFR2, Topo-II, and MEK1 are discussed in the review as well. Further investigation in this direction may lead to development of new derivatives of benzoxazole with better activity, selectivity, and less toxic effect. These compiled data in the article will surely update the scientific community with the recent development in this area and will provide direction for further research in this area.

Abbreviations
KF: Potassium fluoride; PBMC: Peripheral blood mononuclear cells; HepG2: Human hepatocellular carcinoma cell line; MCF-7: Human mammary carcinoma cell line; IC: Inhibitory concentration; Sp: Species; NMR: Nuclear magnetic resonance; AGS: American Geriatrics Society; GI: Growth inhibitory; PPA: Polyphosphoric acid; S.I.: Système International; CA-4: Combretastatin-A4; COX-2: Cyclooxygenase-2; MT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyldiazole bromide; ROESY: Rotating Frame Overhauser Effect Spectroscopy; DFQ-COSY: Double quantum-filtered correlation spectroscopy; HMQC: Heteronuclear multiple quantum correlation spectroscopy; HMBC: Heteronuclear multiple bond correlation spectroscopy; VEGER: Vascular endothelial growth factor; PDB: Protein Data Bank; DNA: Deoxyribonucleic acid; ACC: Acetyl-CoA carboxylase; Cu: Copper; Co: Cobalt; Ni: Nickel; Mg: Magnesium; Zn: Zinc; Ru: Ruthenium; MEK: Mitogen-activated protein kinase

Acknowledgements
We would like to thank Shri MM Patel College of Science and Research, Department of Chemistry, Kadi Sarvavishwavidlaya, for providing their intellectual, technical, and logistical support throughout the review work.

Authors’ contributions
TG is the main author and he has collected, analyzed, conceived, and wrote the first draft. TP reviewed the draft and gave additional inputs to improve the scientific rigor required. Both authors read and approved the final draft for publication.

Funding
Not applicable

Availability of data and materials
Data and materials are available upon request.

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Competing interests
There are no competing interests to declare for all authors.
References
1. American Society of Clinical Oncology (2014) The state of cancer care in America, 2014. A report by the American Society of Clinical Oncology. J. Oncol. Pract. 10:119–142.
2. Blackadar CB (2016) Historical view of the causes of cancer. World J Clin Oncol 7(1):54. https://doi.org/10.5301/wjco.v7.i1.54
3. Zajiczkowska R, Kocot-Kępka M, Leppard W, Wrożek A, Mika J, Wordliczek J (2019) Mechanisms of Chemotherapy-Induced Peripheral Neuropathy. Int J Molecular Sci 20(6):1451. https://doi.org/10.3390/ijms20061451
4. Hitchcock J, White AL, Honow N, Hughes TA, Dupont H, Biggs S, Cayre OJ (2019) Metal-shell nanocapsules for the delivery of cancer drugs. J Colloid Interface Science. https://doi.org/10.1016/j.jcis.2019.12.018
5. Koga Y, Ochiai A (2019) Synthesis, molecular modeling, and biological evaluation of some novel benzothiazole/benzoxazole and/or benzimidazole derivatives incorporating a pyrazole scaffold as antiproliferative agents. Bioorganic Chemistry 748–92. https://doi.org/10.1016/j.bioorg.2017.07.007
6. Srivastava A, Arganwal L, Jain N (2014) One-Pot Sequential Alkylation and Cyclodaddition: Regioselective Construction and Biological Evaluation of Novel Benzoazole–Triazole Derivatives. ACS Combistrial Science 17(1):39–48. https://doi.org/10.1021/acs.combchem.9b00352
7. Kakkar, S, Kumar, S, Narasimhan, B, Lim, S, Ramasamy, K, Mani, V, & Shah, S. A. A. (2018). Design, synthesis and biological potential of heterocyclic benzazole scaffolds as promising antimicrobial and anticancer agents. Chem J2018, 12(1),96. doi: https://doi.org/10.1186/s13053-018-0464-8.
8. Shree dhara, S. H., Vagdevi, H. M., Jayanna, N. D., Raghavendra, R., Kiranmaya, P., Das, Prabhu; Mohamed, Shalefulla, The in vitro Cytoxicity and Molecular Docking Studies of Newly Synthesized Fused Benzodiazole–Triazole Derivatives. J Chem Pharmaceutical Research (2017, 9), 108-119.
9. Dadashpour, Sakineh; Kucukkilic, Tuba; Taran, Ayse; Hosseinimehr, Seyed J, Naderi, Nima; Irannejad, Hamid. Synthesis and Anticancer Activity of Benznidazole: Benzazole Substituted Triazolyltriazines in Hepatocellular Carcinoma (2019), Anti-Cancer Agents in Medicinal Chemistry, 19(17), 2120-2129. doi: https://doi.org/10.1017/s1742168819001521
10. Murty MSR, Ramalingeswara Rao B, Katiki MR, Nath LR, Anto RJ (2013) Recent Advances in the Development of Pharmacologically Active Compounds of Imidazolinone and Benzoxazole derivatives. Arab J Chem 6(7):1361–959. https://doi.org/10.1016/j.arabjc.2013.03.023
11. Singh S, Veenasawmy G, Bhattachar D, Goo JJ, Lee K, Choi Y (2015) Recent Advances in the Development of Pharmacologically Active Compounds that Contain a Benzoxazole Scaffold. Asian Journal of Organic Chemistry 4(1):1338–1361. https://doi.org/10.1002/ajoc.201500235
12. Al-Harthy T, Zoghaib W, Pflüger M, Schöpel M, Önder K, Reitsammer M, Abdel-Jalil R (2016) Design, Synthesis, and Cytotoxicity of 5-Fluoro-2-methyl-4(12):1338-1341. https://doi.org/10.1016/j.shpc.2016.06.007
13. Alexey Lukin, Ruben Karapetian, Yan Ivanenkov, Mikhail Krasavin, Privileged Bis-benzoxazoles, Exert Anti-proliferative Effect on Human Prostate and Breast Cancer Cells. J. Turkish Chem Soc, Section A: Chemistry 5(3):1145-1152. https://doi.org/10.18596/jtcsa.429504
14. Ayaz F, Khereere R, Issa QA, Ersan RH, Algul O (2019) DNA Base Biocisosteres, Bis-benzoxazoles, Evert Anti-proliferative Effect on Human Prostate and Breast Cancer Cells. J. Turkish Chem Soc, Section A: Chemistry 5(3):1145-1152. https://doi.org/10.18596/jtcsa.429504
15. Sun M, Zhang X, Hao H, Li W, Lu C (2015) (2019) Nocarbenzoxazoles A–G, Benzoxazoles Produced by Halophilic Nocardiopsis lucentesis DSM 44048. J Natural Products 78(8):2123–2127. https://doi.org/10.1021/acs.jnatprod.9b00031
16. Kim T, Lee S-A, Noh T, Choi P, Choi S-J, Song BG, Ham J (2019) Synthesis, Structure Revision, and Cytotoxicity of Nocarbenzoxazole G. J Natural Products 82(5):1325–1330. https://doi.org/10.1021/acs.jnatprod.9b00072
17. El-Hady HA (2014) Samar A. Abushatt, Synthesis and anticancer evaluation of imidazolone and benzoxazole derivatives. Arab J Chem 7(5):3731. https://doi.org/10.1016/j.arabjc.2014.05.006
18. Abdelgawad MA, Belal A, Omar HA, Hegazy L, Rabat ME (2013) Synthesis, Anti-Breast Cancer Activity, and Molecular Modeling of Some Benzoazao
and Benzoxazole Derivatives. Archiv Der Pharmaze 346(7):534–541. https://doi.org/10.1002/ardp.201300044

38. Belal A, Abdelgawad MA (2017) New benzothiazole/benzoxazole-pyrazole hybrids with potential as COX inhibitors: design, synthesis and anticancer activity evaluation. Research on Chemical Intermediates 43(7):3859–3872. https://doi.org/10.1007/s11146-016-2851-x

39. Rajalakshmi G, Rama Narsimha Reddy A, Sarangapani M (2012) Synthesis and Biological Activities of Some Novel 2-Amino-1-S or 7-Substituted-2- Oxindolin-3-ylidene) Benzoxazole-5-Carboxyhydrazide Derivatives. Letters in Drug Design & Discovery 9(6):625–632. https://doi.org/10.2174/157012860630702290

40. Allintipati MD, Akalin Cifçi G, Temel HE (2018) Synthesis and evaluation of new benzoxazole derivatives as potential angioma agents. Marmara Pharm J 24(4):547–555. https://doi.org/10.1299/jp.fp.2018.87

41. Wang, Z.; Shi, X.-H.; Wang, J.; Yuan, T.-T.; Xu, Y.-Z.; Huang, T.-T.; Li, Y.-F.; Zhao, Y.-L.; Yang, L.; Yang, S.-Y.; et al. Synthesis, structure-activity relationships and preliminary antitumor evaluation of benzothiazole-2-thiol derivatives as novel apoptosis inducers. Biopharm Drug Dispos. 2011, 32, 1107–1110.doi.org/10.1002/bdd.512

42. Xiang P, Zhou T, Wang L, Sun C-Y, Hu J, Zhao Y-L, Yang L (2012) Novel Benzothiazole, Benzimidazole and Benzoxazole Derivatives as Potential Antitumor Agents: Synthesis and Preliminary in Vivo Biological Evaluation. Molecules 17(1):873–883. https://doi.org/10.3390/molecules17010873

43. Khodair AM, Al-Masoudi NA, Gesson JP (2003) A New Approach to the Synthesis of Benzothiazole, Benzoxazole, and Pyridine Nucleosides as Potential Antitumor Agents. Nucleosides, Nucleotides and Nucleic Acids 22(11):2061–2076. https://doi.org/10.1080/1525777039021266047

44. Aiello S, Wells G, Stone EL, Kadri H, Bazzi R, Bell DR, Westwell AD (2008) Potent Tyrosine Kinase Inhibitors. Bioorganic Chemistry:103382. https://doi.org/10.1016/j.bmcl.2010.12.124.

45. Thiriveedhi, Arunkumar; Nadh, Ratnakaram Venkata; Srinivasu, Navuluri; Balasubramaniam, Narayanan; Prasad, P. Roaji; GSB, Venkata Saty; Kalidasa, S.; Ballaraju T (2018) Design, Synthesis, and Anticancer Evaluation of Tetrazole-Fused Benzoxazole Derivatives as Tubulin Binding Agents. Russ J Gen Chem 2019;103:2189

46. Desai S, Desai V, Shingade S (2019) In-vitro Anti-cancer Assay and Apoptotic Cell Pathway of Newly Synthesized Benzoxazole-N-Heterocyclic Hybrids as Potent Tyrosine Kinase Inhibitors. Bioorganic Chemistry:103382. https://doi.org/10.1016/j.bioorg.2019.103382

47. Niu G, Chen X (2010) Curr. Vascular endothelial growth factor as an angiogenic target for cancer therapy. Drug Targets 11:1000. https://doi.org/10.2174/138945010791591395

48. Holmes K, Roberts OL, Thomas AM, Cross MJ (2007) Vascular endothelial growth factor receptor-2: Structure, function, intracellular signalling and therapeutic inhibition. Cellular Signalling 19(10):2003

49. Sk UH, Prakasha Gowda AS, Crampsie MA, Yun JK, Spratt TE, Amin S, Sharma S., Prokopenko, V. M. Brovarets, V. S. (2019). Dependence of the anticancer activity of 1,3-oxazoles on the donor/acceptor nature of his substitutes. J Heterocyclic Chem. 2019;1–13. doi: https://doi.org/10.1002/jhet.2049

50. Dadmal, T. L., Appalanaidu, killari, Kumbhare, R. M., Mondal, T., Ramiah M., J. & bhadra, manika pal. (2018). Synthesis and biological evaluation of triazole and isoxazole tagged Benzothiazole/Benzoxazole derivatives as potent cytotoxic agents. New J Chem, 2018, 42, 15546-15551. DOIhttps://doi.org/10.1039/c8nj01249k.

51. Madhavilatha B, Fatima N, Sabitha G, Reddy BVS, Yadav JS, Bhattacharjee D, Jain N (2017) Synthesis of 1,2,3-triazole and isoxazole-linked pyrazole hybrids and their cytotoxic activity. Medicinal Chemistry Research 26(8): 1753–1763

52. Petrova KT, Potewar TM, Correia-da-Silva P, Barros MT, Calhelha RC, Cinc A et al (2015) Antimicrobial and cytotoxic activities of 1,2,3-triazole-succinie derivatives. Carbohydrate Research 417:66–71. https://doi.org/10.1016/j.carres.2015.09.003

53. Kachaeva, M. V., Hodyna, D. M., Obernikhina, N. V., Piyo, S. G., Kovalenko, Y. S., Prokopenko, V. M. Brovarets, V. S. (2019). Dependence of the anticancer activity of 1,3-oxazoles on the donor/acceptor nature of his substitutes. J Heterocyclic Chem. 2019;1–13. doi: https://doi.org/10.1002/jhet.3711

54. Rahma Reddy P, Mallikarjuna Reddy G, Padmaja A, Padmavathi V, Siva Krishna N (2014) Synthesis, antimicrobial and cytotoxic activities of pyrimidinyl benzothiazole benzoxazole and benzimidazoles. Euro J Med Chem 77:1–7. https://doi.org/10.1016/j.ejmech.2014.02.050

55. Prieto, M., & Lamur K. F. (2016). Design and Synthesis of New Benzimidazoles as Antioxidant, Artificial Cells, Nanomedicine, and Biotechnology 45(7):1388–1396. https://doi.org/10.1080/10916401.2016.1241796

56. Xing G-X, Tao J-Y, Wang X-Y, Li Z-Z, Fang X-Y, Guo Y-X, Bo F, Xu H-J (2019) Synthesis, crystal structures and biological studies of three new benzoxazole...
