An-Najah National University

Faculty of Graduate Studies

BIOLOGICAL EVALUATION OF 2-OXO-BENZOXAZOLE DERIVATIVES

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Dedication

This thesis is dedicated to everyone who never gave up on me.

To my spouse, who has always stood by me

To my family, who are an authentic source of happiness

To the people at work who helped me and stood by me

Thank you so much for sticking with me, mentor, from the bottom of my heart.

To all of my mates

I commit this effort to you.

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Declaration

I, the undersigned, declare that I submitted the thesis entitled:

BIOLOGICAL EVALUATION OF 2-OXO-BENZOXAZOLE DERIVATIVES

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

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Signature: 

Date: 7/9/2023

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BIOLOGICAL EVALUATION OF 2-OXO-BENZOXAZOLE DERIVATIVES

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Abstract

Benzoxazole derivatives are essential building blocks for innovative drugs due to their wide range of biological activities in medicinal chemistry, particularly their pharmacological effects (such as analgesic, antibacterial, antifungal, anti-inflammatory, and anticancer properties). The importance of benzoxazole derivatives in drug development is emphasized by this work, which also highlights their potential as therapeutic targets with a variety of pharmacological actions and structural flexibility. This study investigates the 1,3-oxazole nucleus, which is a very effective molecule with antibacterial, anticancer, analgesic, and anti-inflammatory characteristics. These substances are created both naturally and artificially by several organisms, including bacteria and marine life. Pharmaceutical compounds belonging to the 1,3-oxazole family can be used to synthesize a wide range of molecules with various therapeutic applications, such as antiviral and anticancer effects. The fascinating possibility of benzoxazole derivatives inhibiting anaerobic choline metabolism and their possible anticancer effects is examined in this work. Certain compounds based on benzoxazoles exhibit enhanced cytotoxicity, especially towards particular cancer cell lines, suggesting that they may be useful in stopping the spread of cancer cells. The promise of benzoxazole derivatives in pharmaceutical research is highly praised, and more investigation into the benzoxazole scaffold and its functionalization is encouraged to find more powerful and selective molecules with enhanced activity and decreased toxicity. The study's findings on sixteen artificial chemicals tested against seven cancer cell lines are presented in the article. The compounds BNZ-2, BNZ-4, BNZ-7, BNZ-9, and BNZ-10 show promise as anticancer agents. Key moieties, such as chlorobenzoyl, piperazine, piperidine, morpholinomethyl, and 4-methylpiperidin-1-yl, that are responsible for their actions against different cell lines are identified by a structural analysis using Structure-Activity Relationship (SAR) study.

BNZ-10 has a lower IC_{50} value than other well-known anticancer medications, which suggests that it may be a more effective treatment against particular cancer cell types. It's important to remember, nevertheless, that doxorubicin (DOX) has far lower IC_{50} values than the majority of BNZ-1-16 drugs and is nonetheless a powerful anticancer agent.

The study concludes by highlighting the tremendous promise of benzoxazole derivatives in drug development, particularly in the treatment of cancer, and the significance of particular structural motifs in controlling their biological activity. Novel treatment approaches in hepG2-associated malignancies require further research on molecular interactions and processes, especially those that affect hepG2 cells. The research advances the hunt for new medicines and helps to rationally develop anticancer drugs.

Keyword: Benzoxazole Derivatives; Anticancer Efficacy; Structure-Activity Relationship (SAR); IC_{50} Values

Chapter One
Introduction

1.1 Introduction

Cancer is responsible for a considerable number of deaths all over the world. It has been reported that multi-drug-resistant diseases are on the rise lately, resulting in a slew of public health issues. One of the most dangerous diseases in the world, cancer continues to be the second most significant cause of death in both industrialized and developing nations despite numerous medical advancements. The incapacity of current chemotherapeutics to treat cancer highlights the need for the development of novel chemical entities, even though chemotherapy is primarily employed to treat malignant sickness. Human colorectal cancer (CRC), the third most often diagnosed malignancy, has a dire prognosis. Therapy has to be more effective, have fewer adverse effects, and have improved survival rates [1]. Cancer, characterized by uncontrolled cell growth, remains a formidable global health challenge. Its prevalence varies across types, regions, and populations. Breast cancer stands as the most commonly diagnosed cancer in females, constituting a significant portion of new cancer cases and deaths. Colorectal cancer ranks high in both male and female diagnoses, with disparities in incidence rates among regions. Lung cancer, a significant cause of mortality, displays gender differences in prevalence, with elevated rates among males. Prostate cancer holds prominence among male diagnoses, especially in developed regions, due to PSA testing, while Caribbean males of African descent exhibit elevated mortality rates. Oral cavity cancers pose a considerable burden worldwide, affected by smoking, alcohol, and other risk factors [1] .

Efforts to mitigate this challenge are underway. The World Health Organization (WHO) recognizes cancer as a leading global threat alongside other non-communicable diseases. Strategies encompass prevention, early detection, and effective patient management. The United Nations General Assembly convened a high-level meeting to address non-communicable diseases, spotlighting the need for global action against cancer. This initiative signals a turning point in the fight against cancer internationally. Innovative techniques like gene therapy, targeted therapy, immunotherapy, and photodynamic therapy are advancing cancer treatment possibilities. Surgical interventions, chemotherapy, radiation therapy, and stem cell transplants are also critical components.

Understanding cancer's prevalence, risk factors and the importance of early detection and treatment are pivotal in reducing its impact [2].

Cancer poses a multifaceted challenge with variations across types, regions, and populations. Efforts to combat cancer involve a multi-pronged approach, encompassing prevention, early detection, advanced treatments, and international collaboration. As the global population grows and ages, the urgency to address cancer's impact becomes more pronounced, making concerted efforts to tackle this challenge essential for the health and well-being of individuals and societies worldwide [3].

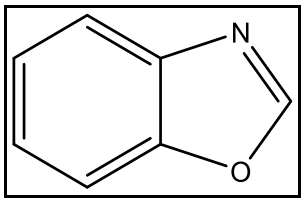
A significant concern, colorectal cancer results in several patient deaths each year. As a result, ongoing efforts are focused on developing cutting-edge chemotherapeutic treatments. Although 5-fluorouracil (5-FU), one of the more well-known medications, is frequently used to treat colorectal cancer, its adverse effects also affect normal cells. It is imperative to overcome these limitations, which calls for creating new and improved chemotherapeutic drugs. Similar to how the prevalence of multidrug-resistant bacterial illnesses has increased reliance on vancomycin, new antimicrobial medicines with distinct characteristics are urgently needed to overcome resistance. The versatile heterocyclic molecule benzoxazole has shown a variety of biological functions, making it an essential component in medical applications [4].

As their application as intermediates to manufacture novel biological materials, Benzoxazole derivatives have attracted much attention in recent years. Antibacterial, antifungal, anticancer, anti-inflammatory, antimycobacterial, antihistamine, antiparkinsonian, and hepatitis C virus, 5-HT3 antagonistic effect, melatonin receptor antagonism, amyloidogenesis inhibition, and Rho-kinase inhibition are just a few of the pharmacological activities of Benzoxazole in medicinal chemistry. Several commercial medications with Benzoxazole as the active component include NSAIDs (flunoxaprofen, benoxaprofen), antibiotics (calcimycin antibacterial—boxazomycin B), and muscle relaxants (chlorzoxazone) [5].

"Isosteres of natural nucleotides" are oxyazole derivatives. Several researchers have focused on them to create synthetic analogs with significant chemotherapeutic effects. Many bioactive compounds containing the benzoxazole scaffold have been discovered to have a wide range of biological effects, including antimalarial, antileishmanial, antiviral,

and antimicrobial properties, as well as inhibiting the activity of the eukaryotic topoisomerase II enzyme and activity against multidrug-resistant cancer cells [6].

Figure 1
Benzoxazole structure



The chemical and biological sciences both rely heavily on heterocyclic molecules. More than 75% of the top 200 drugs are from heterocyclic families, according to the pharmaceutical industry. Since the discovery of organic chemistry in the middle of the nineteenth century, heterocyclic compounds have a lengthy history. An orderly sequence of simple and subordinate heterocyclic carrying nitrogen, oxazole moieties, and oxygen forms the fundamental structure of many physiologically active chemicals. Most medicines and naturally active agrochemicals are composed of heterocyclic molecules. Compounds formed from the heterocyclic moiety play a significant part in improving medication disclosure, which is extensively employed in therapeutic research due to their diverse biological actions, such as antiviral, anticancer, antibacterial, antitubercular, and antimalarial [7].

In recent decades, much study has been done on benzoxazole derivatives' biological potential and manufacture. However, there is an accessible study that only offers sporadic details on their activity. Given this, the current work seeks to offer a thorough. Review of natural and synthetic Benzoxazole compounds and their biological potentials and prospects [8].

Due to its varied and fascinating effects in various domains, benzoxazole, a heterocyclic organic molecule made up of a benzene ring fused with an oxazole ring, has received much attention in scientific study. Benzoxazole derivatives have demonstrated positive pharmacological characteristics in medicinal chemistry, such as antibacterial, anticancer, anti-inflammatory, and antioxidant activity. These substances frequently interact with specific biological targets, including enzymes or receptors, which modify essential cellular functions and may have potential therapeutic uses. Additionally, the unique structural characteristics of benzoxazole make it a crucial component in producing new

pharmacological drugs. Adding benzoxazole moieties enhances these technologies' functionality, stability, and effectiveness. In general, benzoxazole's multiple effects emphasize its relevance in improving medical and materials sciences, highlighting its function as a versatile and influential substance with various possible uses [4].

Novel substituted five-membered heterocycle derivatives comprising 2-oxo-3H-benzoxazole have been successfully synthesized using an environmentally friendly approach using ultrasonic irradiation and conventional heating techniques. The results of this experiment showed that the ultrasound technique is superior when comparing the ultrasound-assisted synthesis approach to the conventional method. Furthermore, it is a desirable and valuable technique in organic synthesis due to the high product yields, quick reaction times, and excellent purity of the final isolated molecules. This strategy may thus be used to synthesize a wide range of diverse heterocyclic substrates that are structurally comparable and have therapeutic potential. This research study also contributed significantly to developing novel medications and their discovery. It may be used to identify physiologically active substances, which can pave the way for developing brand-new, more vital synthetic substances. However, we feel these results will add to our understanding and provide a solid basis for further investigation into the creation of novel antimicrobial medicine bioactive chemicals [9].

The synthesis, structures, and biological activities of benzoxazole derivatives have long been the subject of interest in medical studies because of the transparent potential activities displayed by these compounds. Compared to earlier compounds, the biological properties of new generations of benzoxazole have greatly improved. Modifications to the Benzoxazole nucleus have led to the emergence of several molecules with a variety of pharmacological properties. It will be essential to synthesize and test several novel Benzoxazole derivatives to understand better the pharmacological importance of the Benzoxazole moiety [10].

The benzoxazole moiety has a growing pharmacological significance and is linked to various biological functions. The Benzoxazole derivative improves mycobacterial infection, inflammatory diseases, COX-2 mediatory reactions, and DNA topoisomerase activity. These chemicals' extensive antibacterial and antifungal activity may create a new class of antimicrobials. This study describes the biological effects of the Benzoxazole scaffold. Creating a novel medication using this scaffold might result in more research.

The synthesis, structures, and biological activities of benzoxazole derivatives have long been the focus of interest in medical studies because of the potential activities displayed by these compounds [11].

The physical features of these new generations of Benzoxazole indicate a significant advancement over previous compounds. As a result, a contemporary method is to investigate the QSAR of Benzoxazole derivatives, improve the structure, synthesize newer Benzoxazole derivatives using reaction schemes that produce greater yields, and screen them for biological activity. The inspection guided the creation of the Benzoxazole nucleus, which results in a lead molecule for the future development of new medications to treat various illnesses. As the medicinal importance of benzoxazole moiety grows, it will become an important class of therapeutic compounds [8].

Simple novel analogs of the naturally happening antibiotic Benzoxazole were examined for antileishmanial, antimicrobial, antimalarial, antitrypanosomal, and activities. The chloroacetic amidation of 3-benzoxazole aniline resulted in promising antimalarial and antifungal characteristics and moderate inhibitory action against Trypanosoma and Leishmania spp. However, substituting alternative substituents for the amino group decreased inhibitory effects, which have good antitrypanosomal activity. The work highlights the role of Benzoxazole aniline's chloroacetyl functionalization and provides a good starting point for developing new antibacterial and antiprotozoal medications [12].

Cancer is a constant and recurring threat to everyone's health worldwide. Researchers from all across the world are attempting to develop a more effective treatment for this illness. Due to benzoxazole's wide range of pharmacological activity, it has been crucial in creating several medications. This review investigates the effects of different functionalizations and substitutions on benzoxazole and its anticancer potential. Research in this field may thus create new benzoxazole compounds with enhanced activity, selectivity, and toxicity. The data acquired by the research will undoubtedly educate the scientific world on recent advancements in this sector and pave the path for more investigation [13].

PCSK9 is critical in regulating low-density lipoprotein (LDL) receptor regulation, indirectly regulating LDL-cholesterol levels. PCSK9 interacts with the LDL receptor to facilitate endocytosis and lysosome degradation, both occurring in the liver. The level of

LDL cholesterol in the blood increases as a result. New medications that might be used to prevent or treat illnesses, including hypercholesterolemia, dyslipidemia, atherosclerosis, cardiovascular disease, and coronary heart disease, have been created as a result of the development of PCSK9 inhibitors. Shifa Biomedical Corporation then looked into the ability of compounds based on benzoxazoles to inhibit PCSK9. Benzoxazole 73 is the most potent of the synthetically produced compounds, with an IC_{50} value of 0.6 M. After four days of treatment, it was found that mice given a high-fat diet had significantly lower LDL cholesterol levels after receiving a small dose of 3 mg/kg, a reduction of 20 to 25%. The chemical structure of benzoxazole 73 exhibits less potent activity when compared to other patented substances with a less potent effect [14].

When the chemical structure's benzoxazole moiety was switched out for other functional groups, such as the amide, N-methyl amide, methoxy, tert-butyl, oxazole 4,5-dihydro oxazole, or Nmethylphthalimide group, the efficacy was reduced. The Benzoxazole moiety is necessary for delivering potent PCSK9 inhibitory activity and a wonderful LDL-cholesterol lowering effect [15].

Cancer is brought on by alterations in vital genes that regulate cell division, survival, and proliferation. The uncontrolled growth of cells causes cancer. In cell population dynamics, cancer and apoptosis are prevalent. Cancer is considered one of the most significant factors for death globally. There have been considerable advancements in diagnosis and patient treatment during the previous decade. Some tumors, however, have a terrible prognosis. Angiogenesis and apoptosis are critical for tumor development, differentiation, invasion, and metastasis. It is important in angiogenesis and apoptosis mechanisms [16].

Apoptosis is a controlled and deliberate cell death triggered by intracellular and extracellular signals and controlled by several proteins. Some tumors, however, have an inferior prognosis. Angiogenesis and apoptosis are critical for tumor development, differentiation, invasion, and metastasis. It has been clarified that apoptosis is essential in angiogenesis pathways and apoptosis. Apoptosis is a controlled apoptosis and intentional cell death triggered by intracellular and extracellular signals and regulated by various proteins [17].

It discovered that apoptosis was linked to eliminating possible cancer cells and tumor formation in the early 1970s. Adams and Cory clarified the strong connection between

cancer pathogenesis and apoptosis irregularity [18]. It has been proven that tumor cells may proliferate and avoid dying from apoptosis. According to its findings, Bcl-2 is helpful for the early detection and treatment of breast cancer. According to the study, many therapies that control the caspase cascade might be responsible for apoptotic activity in breast cancer [19].

Where NF-kB is most active is in the nucleus. Due to the continual activation of the IKK pathway, the IkB genes may become changed and damaged in several malignancies, including Hodgkins, and diffuse large B-cell lymphoma cells. Additionally, transcription of Rel/NF-kB results in activation of NF-kB. Constant Rel/NF-kB activity protects cancer cells against apoptosis and, in some circumstances, permits their growth. As a result, NF-kB activity is suppressed by many currents in various anticancer medications. Analogs and benzoxazoles of heterocyclic arms, such as benzothiazoles, benzimidazoles, and benzoxazines, have recently been found to have antifungal, antibacterial, antiviral, anticancer, and topoisomerase inhibitory properties. In addition to human cell lines, the novel benzothiazoles claim to have a potent inhibitory effect. mammary cancer [20].

Some benzoxazole compounds have been identified in earlier investigations. The chemical 5-methylsulfonyl-2-(p-nitrophenyl) benzoxazole was extremely effective in inhibiting tumor growth. Create a particular benzoxazole compound in light of the findings. the levels of the apoptosis-inducing proteins caspase-9, APAF-1, and cytochrome-c, as well as the anti-apoptotic protein bcl-2, on breast cancer lines. Therefore, the impact of the novel benzoxazole compounds on NF-B, bcl-2, cytochrome-c, APAF-1, and caspase-9 stages in breast cancer cell culture indicators of apoptosis [21].

A new series of benzoxazole derivatives was created based on the reaction of 2-mercapto benzoxazole with chloroacetamide derivatives and hydrazine as a critical ingredient. IR, 1H NMR, MS, and elemental analyses confirmed the structural features of the newly synthesized compounds. Four human cancer cell lines were used to investigate the cytotoxic effects of the benzoxazole compounds. The examined cancer cell lines were cytotoxic to a moderate to substantial extent. They had moderate to significant cytotoxic effects on the evaluated cancer cell lines [22].

The five-membered oxyazole derivatives are well-known nitrogen-containing heterocyclic compoundsThese adaptable intermediates may produce various organic

chemicals, including amino acids, peptides, antibacterial or anticancer drugs, immunomodulators, heterocyclic precursors for biosensor coupling, and photosensitive protein composition devices. Benzoxazole and its derivatives have been shown to have antibacterial, antifungal, anticancer, antitubercular, anti-inflammatory, and HIV-1 reverse transcriptase-inhibiting effects [22].

Due to their therapeutic potential, mercaptobenzoxazoles have become an effective medicinal scaffold and have remained at the forefront of drug research. We outline the synthesis of novel benzoxazole derivatives, spectral data characterization (IR, 1H NMR, and MS), and cytotoxicity against several human cancer cell lines[23]. Effective cancer treatment is severely hampered by multidrug resistance (MDR). In this work, MDR-reversing activity of novel metal [Zn(II), Cu(II), Mg(II), Ni(II), Pd(II), and Ag(I)] complexes of In L5178Y mouse T lymphoma (MDR) cells transfected with human ATP-binding cassette sub-family B member 1 (ABCB1; P-g) the effects of 2 trifluoroacetonyl-benzoxazole were examined. The thiazolyl blue tetrazolium bromide (MTT) method was used to assess the complexes' cytotoxic and antiproliferative properties. The modification of ABCB1 activity was identified by flow cytometry utilizing a rhodamine 123 accumulation assay. The annexin V/propidium iodide test was used to examine the ability of specific complexes to cause apoptosis in multidrug-resistant L5178Y mouse T lymphoma cells. Compared to the free ligand, the MDR reversal and cytotoxic activity of the Zn(II) and Cu(II) complexes was much higher. As a positive control, the complexes' activity was 29 and 5 times greater than the ligands and the ABCB1 inhibitor verapamil, respectively. Surprisingly, the complexes were able to trigger the death of MDR cells [24].

Piperazine-benzoxazole moiety developed a few piperazine-related benzoxazoles and tested them against human A-549 lung cancer cells. As a result of the limited solubility of the aryl piperazine compounds, the first results were disappointing, and the results were poor. These substances precipitated in the medium for cell culture. By substituting a carbamate functional group for the methyl group at position two and using N-methyl piperazine at position 6 of the benzoxazole instead of aryl piperazine, it is possible to increase the solubility of the compounds. Indium-based one-pot reductive cyclization produced fewer high-yielding products than other catalysts. The compound's general structure is displayed below [25].

Figure 2

Benzoxazole-piperazine-1,3,4 oxadiazole compounds

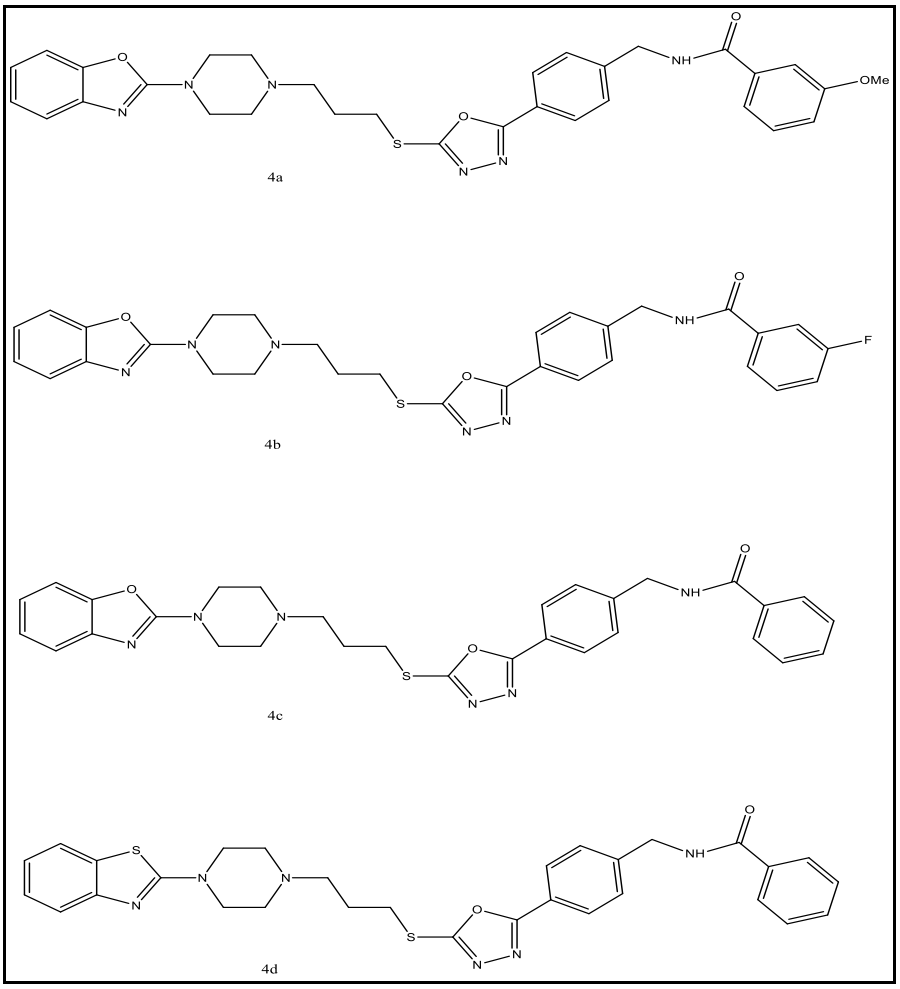
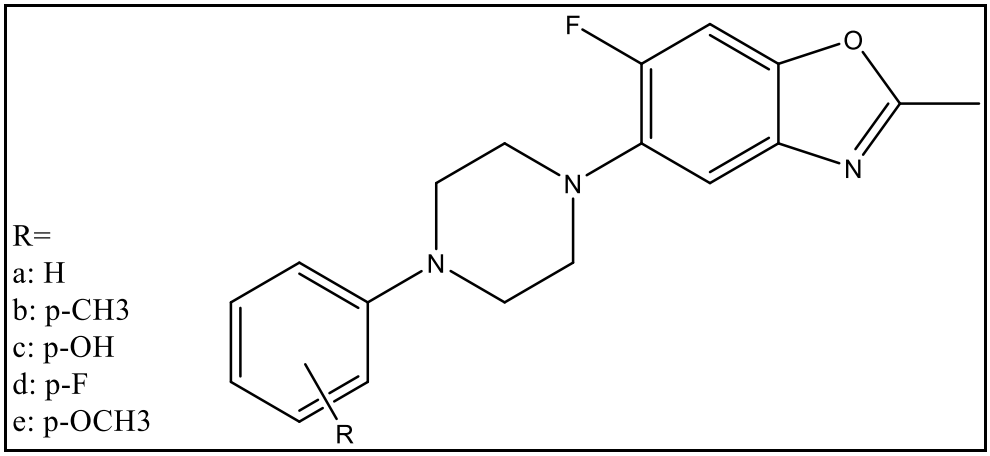


Figure 3

Benzoxazole-piperizine derivatives



Benzoxazoles connected with oxadiazoles to long-chain piperazines (Figure 4.4) were said to have an anticancer effect. The various oxadiazoles were coupled with the aryl piperazine derivatives utilizing KF-Al2O3, acetonitrile, and an 80 °C heating temperature

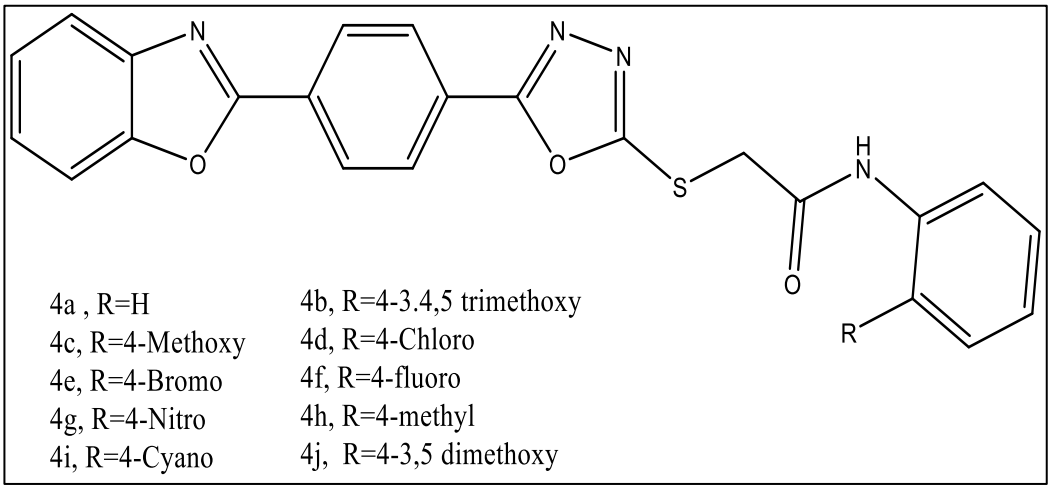
in a few simple steps. Five human cancer cell lines were used to test the chemical's cytotoxicity. The IC_{50} values (lung) were determined using the MCF-7 (breast), HepG2 (liver), HepG2 (liver), HeLa (cervical), A431 (skin), and A549 (skin) cancer cell lines. All substances exhibited an IC_{50} value lower than 100 in the MCF-7 cell line, with compounds 4a, 4e, 4j, and 3t being the most cytotoxic. Few compounds with a benzothiazole backbone than benzoxazole backbone ultimately affected MCF-7 cells. The A431 cell line is very susceptible to the cytotoxic effects of the amide linkage chemicals. Compared to other cell lines, all synthetic chemicals gave the A431 cell line good results [26].

The moiety of 1,3,4-benzoxazole-1,3,4-oxadiazole Oxadiazole is a powerful moiety that exhibits a variety of biological actions. The A549 (lung cancer), A-375 (melanoma cancer), MCF-7 (breast cancer), and HT-29 (colon cancer) cell lines were used to assess the anticancer activity of the amide compounds. Benzoxazole-1,3,4-oxadiazole-containing compounds [27]. The HT-29 cancer cell line was exposed to the produced chemicals 6b, 6c, and 6g, which demonstrated anticancer activity. The outcomes were superior to those of the accepted standard of treatment [28]. Substances such as 4b, 4f, 4g, and 4i were also very effective against MCF-7 cancer cell lines. A-549 cell lines were susceptible to compounds 4i and 4b; compound 4b was remarkably efficient against HT-29, MCF-7, and A-549. 1,2,4-Oxadiazole derivatives with the benzoxazole-1,2,4-oxadiazole moiety have a well-established anti-proliferative effect [29].

It was possible to manufacture benzoxazole coupled with benzofuran and 1,2,4-oxadiazole in a few stages with high yields [30]. Using combretastatin-A4 as a positive control, the cytotoxicity activity was assessed against the human breast cancer (MCF-7), melanoma (A375), lung (A549), and colon (HT-29) cell lines. Compounds 4b, 4c, 4d, 4g, 4h, and 4i had more potent activity when compared to the positive control [31].

Figure 4

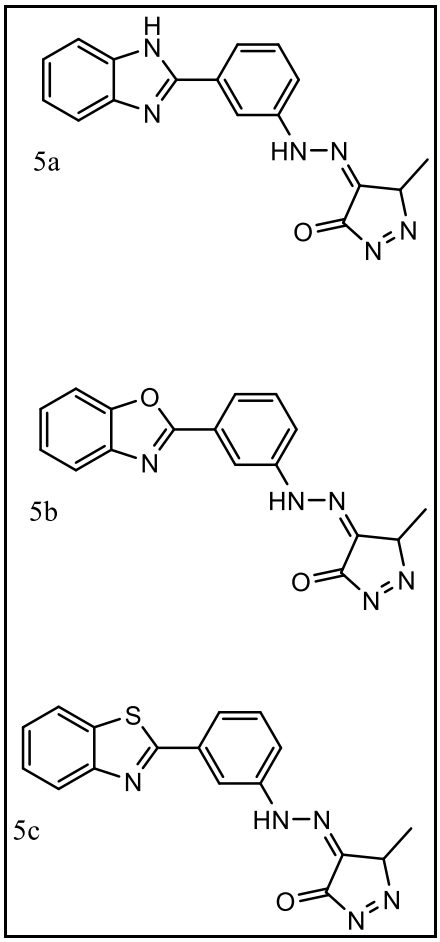
Benzoxazole-1,3,4 oxadiazole derivatives



Deriving from benzoxazole and pyrazolinone, the scientists created new benzothiazole, benzoxazole, and benzimidazole compounds [32]. Compared to pyrazolone substitution at N-2, the compounds with no N-2 substitution have shallow antiproliferative action. Acetyl and Phenyl substitution was done on the N 2 of pyrazolone, increasing the antiproliferative compounds' activity. The acetylated compounds were organized according to their IC_{50} values in the following order: 4a > 4b > 4c. These N-2 substituted pyrazolone substances significantly increased the sensitivity of the MCF-7 and A-549 cell lines. Compound 6a's IC_{50} values were discovered to be 6.42 and 8.46 M for the MCF-7 and A-549 cell lines, respectively. The docking study of these compounds explains the patterns and structural characteristics of the binding compounds' interactions with the remaining amino acids in the active sites [33].

Figure 5

Benzoxazole-pyrazolinone derivatives



To test the anticancer efficacy of the triazole-benzoxazole derivative (Figure 13), several heterocycles were added to the benzoxazole moiety [33]. It was discovered that benzoxazole and triazole had a broad range of activities, and a one-pot multicomponent procedure was to make benzoxazole-triazole scaffolds that have shown positive anticancer activity when tested against groups of HeLa, SKBr3, and HepG2 cancer cell lines. Two successive methods in one pot were used to synthesize benzoxazole-linked triazoles. Through C–H benzoxazole activation in the C-2 position, alkyne was generated in situ from the appropriate dibromo olefin precursor. These compounds were tested for potential anticancer action using HeLa, SKBr3, and HepG2 cancer cells. Compound 42,2,2 has been observed to have a more significant cytotoxic impact on the cancer cell lines HeLa, HepG2, and SKBr3 than regular daunomycin. These compounds were tested for potential anticancer action using HeLa, SKBr3, and HepG2 cancer cells. Compound 42,2,2 has been observed to have a more significant cytotoxic impact on the cancer cell lines HeLa, HepG2, and SKBr3 than regular daunomycin. Because receptor tyrosine kinase is

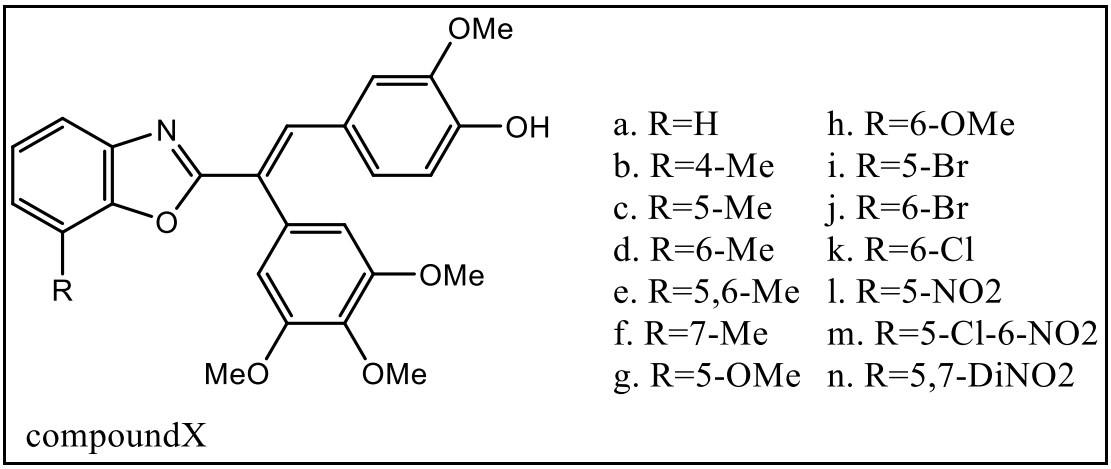
necessary for cell proliferation and differentiation, it is a significant therapeutic target in cancer. A unique series of benzoxazole and triazole compounds that had been joined was generated like this (Figure 15), and its anticancer potency was assessed utilizing PBMC cell lines [5].

The thiol was substituted to create several compounds. Few compounds in the series exhibited perfect antibacterial activity; compound 12 was the best activity. A549, MCF-7, HepG2, and MDA MB-231 cell lines were used to investigate the anticancer activity of benzoxazole/benzimidazole-linked triazolotriazines [34]. Compound 8e was very selective for HepG2 cell lines and had an IC_{50} value similar to crizotinib. Similar to this, Dadashpour and associates [35]. These compounds had good antibacterial and antifungal properties but could not demonstrate anticancer action. The compounds of benzoxazole and combretastatin Combretastatin A- 4 benzoxazole derivatives were produced in ten series [36]. After being tested on cancer cell lines such as Coco-205 (colon), A-549 (lung), and MCF-7 (breast), Compound X was shown to be more potent than conventional compounds against MCF-7 and A549 cell lines [35].

The Combretum caffrum willow tree in South Africa yielded the naturally occurring compound known as combretastatin A-4 in 1989. At nanomolar concentrations, it displayed antitumor efficacy against several cancer cell lines. These novel substances, whose structures were based on the natural molecule combretastatin, were investigated for their cytotoxicity [37].

Figure 6

Benzoxazole-Combretastation Derivatives



Colo-205 (colon), A-549 (lung cancer), and MCF-7 (breast cancer) cell lines were used in investigations on these chemicals. The results revealed compound 6d worked better than anticipated in two cell lines (MCF-7 and A-549) [38].

The effectiveness of a few novel combretastatin compounds linked to benzoxazoles was investigated against the human cancer cell lines MCF-7, A549) and melanoma (A375). Most compounds only revealed weak anticancer action, whereas 6g, 6h, 6l, 6m, and 6n had potent activity. To establish a reliable binding connection with the receptor, 6g and 6l performed a molecular docking examination in addition to being experimental compounds [37].

Synthesis and evaluation of ten innovative benzoxazole analogs of combretastatin A-4 were undertaken to investigate their potential as anticancer agents against three distinct human cancer cell lines. Within this series, four synthesized compounds exhibited remarkable efficacy against diverse tumor cell lines, with one compound outperforming the control drug, particularly in A549 and MCF-7 cell lines. The global significance of cancer as a leading cause of death, prevalent in developed nations, can be attributed to a multitude of external and internal factors, including genetic mutations [37].

Chemotherapy remains a pivotal strategy in cancer treatment, aiming to eradicate cancerous cells while sparing normal cells. Substantial progress has been made through the discovery of novel drugs, and diverse therapeutic approaches have been explored, including drugs that disrupt microtubule/tubulin dynamics—a widely used method in cancer chemotherapy. Nevertheless, the quest for the most potent anticancer agents poses a significant challenge for the future of cancer treatment. The natural product Combretastatin-A4 (CA-4, Fig. 1.7) was first isolated from the bark of the South African willow tree *Combretum caffrum* in 1989. CA-4 has demonstrated nanomolar activity against numerous cancer cell lines, inducing cell cycle arrest in the G2/M phase. Its mechanism of action involves high-affinity reversible binding to the colchicine site of tubulin. Studies on derivatives of CA-4 have revealed that a critical structural element for tubulin binding is the cis-orientation of two ethenyl-bridged aromatic rings, one of which bears 3,4,5-trimethoxy substituents. Notably, the water-soluble prodrug CA-4P (2) is currently undergoing phase II/III clinical evaluation in the USA for its potential use in combination treatments for multidrug-resistant solid tumors [39].

CA-4 and its phosphate form, combretastatin-A4 phosphate (CA-4P, 2), exhibit selective cytotoxicity against rapidly proliferating tumor vasculature compared to normal blood vessels, resulting in reduced blood flow to tumors and eventual hemorrhagic necrosis. Given its properties, combretastatin-A4 is a promising lead compound for developing innovative anticancer agents. Likewise, the benzoxazole ring is found in Various natural products like salvianen and pseudosalvianen. Derivatives of benzoxazole have garnered significant attention due to their extensive applications in the field of medicine. These compounds play a crucial role in medicinal chemistry, displaying various biological activities, including anticancer, topoisomerase-I inhibition, antibacterial, antifungal, antimicrobial, and anti-measles virus effects. Both combretastatin-A4 and benzoxazole exhibit anticancer properties. A strategic approach was devised to create new benzoxazole derivatives of combretastatin-A4 to enhance the synthesis of potent anticancer drugs. These novel compounds were systematically evaluated for their anticancer activity across various human cancer cell lines, including A549, MCF-7, and Colo-205 [39].

Figure 7

Combretastatin A-4

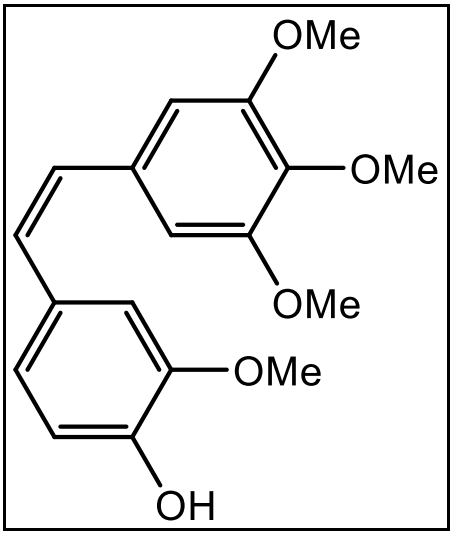
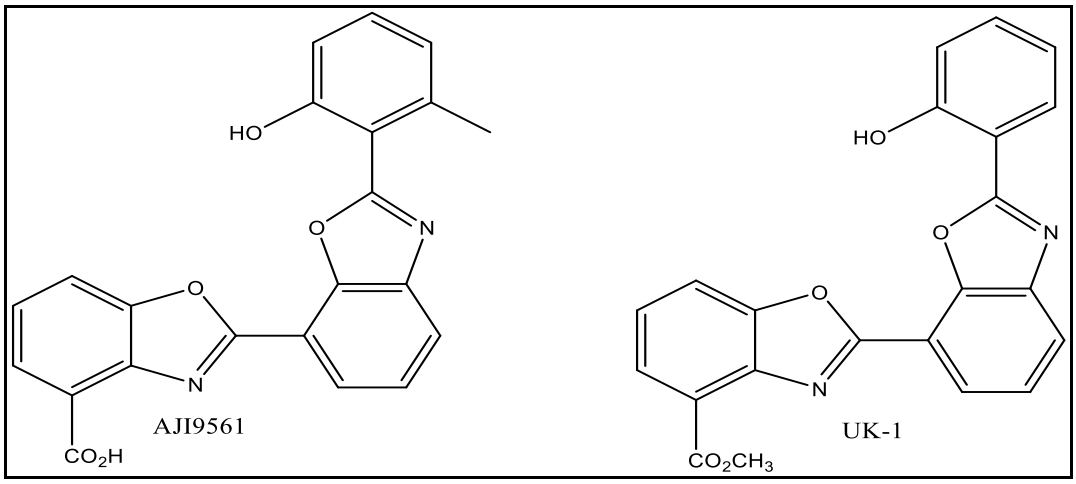


Figure 8

Structure of nataxazole and UK-1



None of the new analogs were proven to have more cytotoxicity than 4-carbomethoxy-2-(2' hydroxyphenyl) benzoxazole, which was also shown to have more excellent water solubility and exhibit comparable cytotoxicity to this more straightforward UK-1 equivalent. Cu2+ ions bind to UK-1, and all of these novel analogs more strongly than Mg2+ ions. The four substituents in these 2-(2' hydroxyphenyl) benzoxazoles must be of a certain kind for them to bind Mg2+ ions. The cytotoxicity of this family of 4-substituted-2-(2' hydroxyphenyl) benzoxazoles is independent of either Mg2+ or Cu2+ nonbinding ability, according to a previous study on several UK-1 analogs. When joined with previous ESIMS studies of Cu2+-induced DNA binding by UK-1 and analogs, these findings imply that interactions with the transition metal ions Cu2+ or others may underlie the cytotoxic effects of UK-1 and analogs rather than the magnesium ion. Metal ion-mediated DNA binding, not metal ion binding affinity, is required for these medicines to be deadly. The discovery adds to the growing research showing that Cu2+ ions contribute to UK-1 cytotoxicity. Compared to UK-1 alone, Cu2+ boosts UK-1's cytotoxicity in MCF-7 and A549 cells. Future research holds much promise, thanks to this discovery. A few structurally similar compounds to UK-1 were also created, and their anti-proliferative properties were investigated [40].

Streptomyces species (strain Tü 6176) produced a new benzoxazole derivative that has shown excellent development inhibitory effects against various human tumor cell lines. This Streptomyces species was identified in a soil sample from Brazil. This drug is known as nataxazole. Batch fermentation using the Tü 6176 strain was used to make it. Before ethyl acetate extraction and column purification on Sephadex LH-20 and Toyopearl HW-

40 with MeOH/MDC as the mobile phase, the procedure was conducted for 72 hours. This chemical structure was identified through NMR analyses [41]. Using the human tumor cell lines AGS (gastric adenocarcinoma), HepG2 (hepatocellular carcinoma), and MCF7 (breast adenocarcinoma), the effects of nataxazole (1) on tumor cell proliferation were compared to UK-1 [42].

The GI50 (concentration at which half of the cells are inhibited in their growth) and TGI values (concentration at which a 100% inhibition of growing cells is found) were calculated using the resultant concentration-activity curves. One showed similar cytotoxic activity to UK-1 against HepG2 and MCF-7 cells but somewhat more significant cytotoxic activity than UK-1 against AGS cells (GI50 0.4 mg/ml vs. 0.8 mg/ml for UK 1). According to the cell-cycle analysis, UK-1 and nataxazole (1) raised the proportion of cells in the S phase while decreasing the proportion of cells in the G2/M phase. These results imply that nataxazole and UK-1 could work together to inhibit cell proliferation [43].

The pharmaceutical landscape is heavily influenced by heterocyclic compounds, with more than 80% of currently prescribed small molecule drugs containing a heterocyclic ring. These unique molecules, known for their rigid structures, can engage in hydrogen bonding and hydrophobic interactions. Moreover, they can be tailored to adjust crucial properties such as lipophilicity, polarity, aqueous solubility, and selectivity. Among the diverse array of heterocycles, oxazoles and oxazolines hold a significant place, often appearing as isolated entities or conjugating with aromatic rings like benzene, giving rise to benzoxazoles. The wide prevalence of benzoxazoles is evident not only in pharmaceutically active compounds but also in various natural sources such as plants (neosalvianen, salvianen, salvia an), marine sponges (nitinol, pseudopteroxazole, ileabethoxazole), and bacteria (UK-1, caboxamycin, A33853, calcimycin, nataxazole, AJI956) [43].

Delving into the synthesis of these heterocyclic structures reveals fascinating pathways. Unconjugated oxazoles, in particular, are predominantly produced through ribosomally synthesized and post-translationally modified peptides (RiPPs) synthesis and non-ribosomal peptides (NRPs) synthesis. In both of these mechanisms, the formation of oxazoles stems from a nucleophilic attack initiated by the hydroxyl group of Ser(Thr) on amide bonds. This reaction occurs through a common hemiorthoamide intermediate,

albeit via distinct enzymatic routes. Surprisingly, the synthesis of benzoxazoles presents intriguing challenges. Notably, despite the well-documented mechanisms for oxazole formation, none of the enzymes identified in RiPPs or NRPs pathways, or even the N-type ATP pyrophosphohydrolase, seem to catalyze the formation of benzoxazole. This peculiarity led to the investigation of biosynthetic gene clusters associated with benzoxazole-containing natural products like calcimycin, nataxazole, A33853, and caboxamycin. Despite thorough sequence analysis, no homologous enzymes were found, raising questions about the elusive biosynthetic pathway. To shed light on this enigma, research has explored potential enzymes involved in benzoxazole formation. Proposed mechanisms involve intricate steps, such as dimerization of 3-hydroxyanthranilic acid (3-HAA) through amide formation catalyzed by BomJ (putative phenylacetate CoA ligase), followed by intramolecular attack and ring closure facilitated by BomN (putative amidohydrolase).

Interestingly, the bomb amidohydrolase homolog in gene clusters related to nataxazole and caboxamycin indicates a standard benzoxazole synthesis route. An essential group of enzymes, acyl-CoA ligases, has been extensively studied due to their role in CoA thioester derivative formation. While phenylacetate-coenzyme A ligase (PaaK) is a structurally characterized member responsible for adenylation and subsequent thioesterification, non-thioesterifying acyl-CoA ligases are rare and predominantly found in fatty acyl-AMP ligases (FAAL) and PtmA1. BomJ stands out as a potentially unprecedented amide-forming enzyme of the PaaK type. Furthermore, BomN, although typically associated with hydrolysis, is of interest due to its role in the proposed benzoxazole biosynthesis pathway [44].

A significant breakthrough in unraveling the mysteries of benzoxazole synthesis emerges from the determination of NatL2 (homolog of BomJ) and NatAM (homolog of BomN) structures from the nataxazole biosynthetic pathway. Contrary to previous assumptions, NatL2 catalyzes ester formation rather than amide formation, with the latter identified as a shunt product. NatAM, on the other hand, is demonstrated to catalyze benzoxazole formation from an ester substrate, implicating a proton shuttle mechanism to control the fate of a hemiorthoamide intermediate. Armed with these newfound insights, the potential of these enzymes is harnessed for innovative applications. The synthesis of novel halogenated benzoxazoles becomes feasible, opening the door to drug discovery and

development possibilities. Through intricate biochemical analyses and structural elucidation, this research paves the way for a deeper understanding of benzoxazole biosynthesis and its implications across various scientific and medical fields [44].

The halophilic bacterial strain generated a brand-new group of compounds that were 2-arylbenzoxazole derivatives. Using No-cardiopsis lucentensis, a panel of human tumor cell lines will be examined in 2015 for cytotoxicity. DSM 44048 [45]. The structures of these compounds, designated as nocarbenzoxazoles, were derived from the 2-aryl benzoxazole. Isolated nocarbenzoxazole G and nocarbenzoxazole F showed selective activity in the HeLa and HepG2 cell lines (Figure 4.6). Following that, Kim and his colleagues created a coupling technique on benzoxazoles to create nocarbenzoxazole. When it was discovered that the analytical data of the synthetically generated nocarbenzoxazole did not match the naturally separated products, total synthesis confirmed the nocarbenzoxazole's revised structure (Figure 17) in appendix (a) [1].

Several 2-aryl benzoxazoles were synthesized, and the chemical's effects were then examined in HeLa cells. HeLa cell lines were discovered to be the drug's exclusive target. It made no appreciable difference to the other cell lines. By combining oxazolidinone compounds with aniline and 2-hydroxyaniline, benzoxazole and imidazolinone derivatives were created in a sequence [46]. The acetyl derivative is produced by acetylating the compounds using acetic anhydride and chloroacetyl chloride. When the substance was tested against several human cell lines, it was discovered that benzoxazole and imidazolinone derivatives were efficient against cancer cell lines. In particular, benzoxazole compounds are shown to be more efficient than imidazolinone derivatives. The chemical's biological results show that human hepatocellular carcinoma cells and MCF-7 breast tumor cells (HepG2) may be defeated more quickly by them [47].

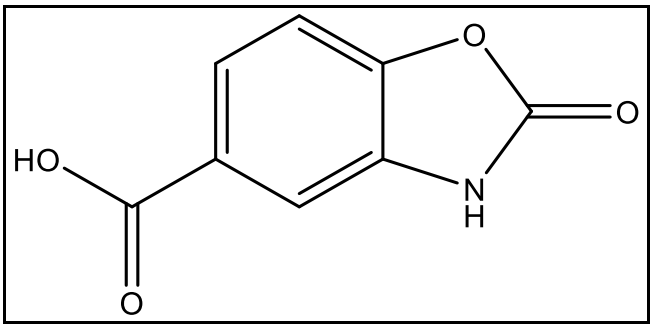
Coumarin (Figure 18) in appendix (a) is a unique scaffold in medicinal chemistry since it exists naturally and is simple to produce. Due to the broad spectrum of biological effects it demonstrates, it continues to catch the interest of medicinal chemists. Numerous coumarin compounds exhibit anti-inflammatory, anti-cancer, antibacterial, antioxidant, anti-Alzheimer's, and anti-hyperlipidemic qualities. Existing coumarin derivatives have the potential to produce new antioxidants since they naturally have excellent antioxidant activity. Scopoletin, umbelliferone, and esculetin are natural coumarin analogs with antioxidant and anti-inflammatory activities. Another heterocycle is benzoxazole, which

has biological effects, including anti-HIV, anti-TB, anti-tumor, anti-proliferative, anti-allergic, and antibacterial in its derivatives. Kinase inhibitory, analgesic, and anti-inflammatory activities are present in this nucleus. In 1982, Benoxaprofen (Figure 18) became widely available. It is a potent non-steroidal anti-inflammatory drug (NSAID) whose main constituent is benzoxazole. The drug's in vivo-generated free radical decarboxylated derivative was removed from clinics due to its phototoxicity. NSAIDs for the treatment of inflammation can have several prominent general side effects that are worth mentioning, in addition to gastrointestinal pain and renal impairment. Because of this, medicinal chemists have been searching for novel anti-inflammatory drugs free of such side effects. The ulcerogenic potential of an NSAID has been successfully decreased or eliminated by combining it with an antioxidant molecule [48].

2-Oxo-Benzoxazole plays a crucial part in medicinal chemistry, contains heterocyclic compounds, and demonstrates a variety of biological functions. Many physiologically active chemical compounds include analogs and derivatives of heterocyclics that contain nitrogen, oxygen, and oxazole moieties as part of their fundamental structure. Numerous pharmacological properties, including antidepressant, antibacterial, antifungal, anti-inflammatory, analgesic, and anticancer, have been linked to the benzoxazole nucleus [49].

Figure 9

2-Oxo-Benzoxazole



The goal of medicinal chemistry is to identify and develop novel disease-treating compounds. Establishing a link between chemical structure and pharmacological action has been a critical medicinal chemistry component. The most crucial aspect of finding novel medications is the chemistry of heterocyclic molecules. Both from a theoretical and practical standpoint, research into these substances is quite interesting. Heterocyclic ring systems are found in many different substances, including alkaloids, vital amino acids,

vitamins, hemoglobin, hormones, numerous synthetic medications, and colors. Several synthetic heterocyclic compounds, such as pyrrole, pyrrolidine, furan, benzoxazole, piperidine, pyridine, and benzimidazole, have significant applications. Many of these compounds are also essential steps in the synthesis process. Benzoxazole is an essential heterocycle with exceptional pharmacological characteristics among all heterocyclic chemicals. The chemical compound known as benzoxazole is created by joining an oxazole ring with a benzene ring. The term "oxazole" refers to a family of 1, 3 azoles with a nitrogen atom of the pyridine type and an oxygen atom in position 3 of a five-member ring. When the substitution pattern of the benzoxazole nucleus is significantly changed, their pharmacological actions diverge noticeably [49].

Compounds utilized in research to assess novel products with fascinating biological features, such as antibacterial, CNS, antihyperglycemic potentiating, analgesic, and anti-inflammatory capabilities, have the compact and straightforward benzoxazole nucleus (Figure 15). Benzoxazole has no home usage; it is mainly employed in business and research. Since it is a heterocyclic molecule, Benzoxazole is commonly employed in research as a building block for synthesizing larger, frequently bioactive chemicals. The naturally occurring nucleic bases adenine and guanine must be considered structural isosteres of benzoxazoles for them to interact with the polymers of biological systems [50]. Numerous heterocyclic compounds are essential in medical chemistry because they exhibit various unusual pharmacological activities and are utilized as active components in producing many potent drugs. The synthetic heterocycles with a 1,3 oxazole nucleus exhibit a wide range of biological activities, including antimicrobial activity (sulfamoxole, a chemotherapeutic agent from the sulfonamides group), anticancer activity (ibrutinib, a tyrosine kinase inhibitor), analgesic, antipyretic, anti-inflammatory activity (oxaprozin), and anti-diabetic [51]. The architectures of the typical bioactive compounds all share the 1,3-oxazole scaffold. Biologically active heterocyclic compounds with 1,3-oxazole rings are produced by a variety of marine invertebrates and microorganisms, including muscoride A (virginiamycin M2, an antibiotic from the group A streptogramin family), ulapualide A (which has antifungal properties), diazonamide A (which inhibits tubulin polymerization), and hennoxazole A (an antimycobacterial alkaloid). Several saturated 1,3 oxazole-5(4H)-ones have also been demonstrated to possess antiviral and antibacterial (jadomycin B) properties [51].

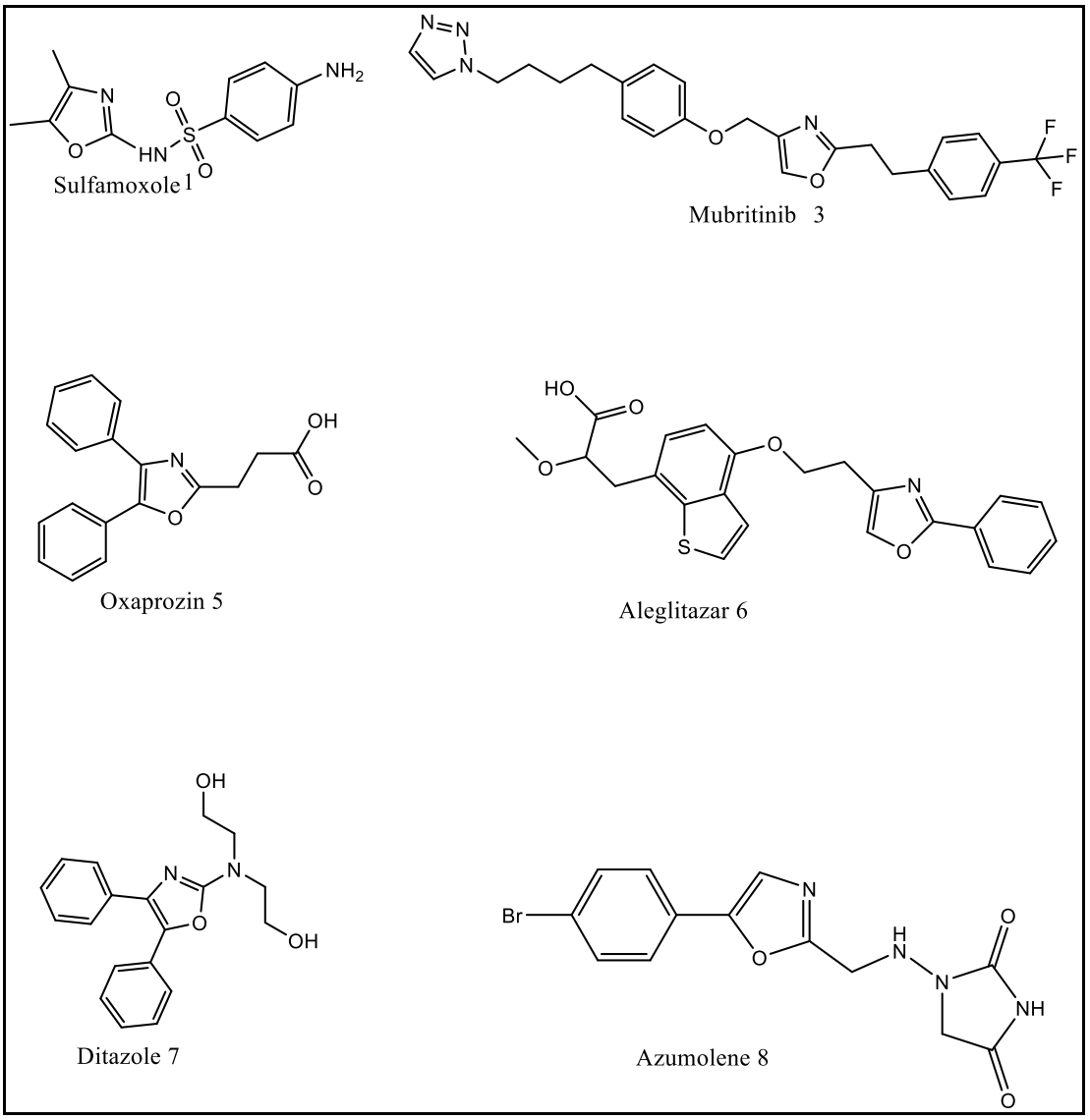
The N-acyl-amino acid and N-acyl-amino ketone derivatives, which are the intermediates used in the synthesis of heterocycles from the 1,3-oxazoles family, are also endowed with a broad spectrum of therapeutic effects, according to a literature survey on the subject. In addition to having specific antidotes for acute intoxications, several N-acyl-amino acid derivatives also have anticancer (methotrexate), mucolytic (N-acetyl cysteine), antihypertensive (ACE inhibitors: captopril, enalapril, lisinopril), antianemic (folic acid), and antiulcer (benzotript) qualities. Rupintrivir has the antiviral, anti-inflammatory, and antithrombotic characteristics of N-acyl-amino ketones [52].

1.2 Biological potential of benzoxazole derivatives

The origin of heterocyclic compounds dates back to the mid-19th century, coinciding with the advancements in organic chemistry. These compounds hold immense importance in the realms of both chemical and life sciences. Remarkably, over 75% of the top 200 pharmaceutical drugs stem from the heterocyclic family, underscoring their significance in the pharmaceutical sector [53]. The foundational structure of many biologically active compounds is built upon simple and derivative heterocyclic molecules containing nitrogen, oxygen, and oxazole moieties. These compounds play a pivotal role in modern drug discovery due to their diverse biological activities, including antiviral, anticancer, antimicrobial, antitubercular, antimalarial, and antioxidant properties. One such instance is benzoxazole, a heterocyclic substance with an oxazole ring structure that has been fused with benzene [54].

Figure 10

the heterocyclic compounds that are essential in medicinal chemistry



Hantzsch first described this substance in 1887. Its chemical formula is C7H5NO; its melting and boiling temperatures are 27–30 °C and 182 °C, respectively. Numerous biological properties, such as anticancer, antifungal, antitubercular, antiviral, and anti-HIV-1, are displayed by benzoxazoles. In addition, they act as a framework for fluorescence probes and sensors, advancing uses outside of medicinal chemistry [7]. Benzoxazole derivatives' production and biological potential have been extensively studied, opening the door for their application in various industries. This in-depth analysis explores the biological activities and potential uses of natural and synthetic benzoxazole derivatives. A thorough literature study that included a wide range of scientific databases and resources and covered topics including pharmacology, pharmaceutical chemistry, and

biomedicine was part of the process. This detailed study was produced after carefully reviewing the literature from January 1947 to March 2020. Fourteen naturally produced benzoxazole derivatives were discovered due to the inquiry, and they were shown to have promise against cancer, microbial infections, and TB. The review also investigated synthesized benzoxazole derivatives, emphasizing their anticancer potential against various cell types. Noteworthy studies revealed the efficacy of specific benzoxazole derivatives in inhibiting the proliferation of cancer cells, indicating their promising role in oncology research. This review aims to bridge the gap in existing knowledge, providing extensive and consolidated insight into benzoxazole derivatives and their manifold biological potentials while offering a glimpse into future research directions [54].

This work effectively prepared novel substituted five-membered heterocycle derivatives containing 2-oxo-3H-benzoxazole to employ an ecologically friendly synthetic process that combined conventional heating and ultrasonic irradiation. The results of this inquiry showed that the ultrasound methodology is better when comparing the ultrasound-assisted synthesis method to the conventional method. It is a desirable and valuable approach in organic synthesis because of the high yields of isolated molecules, quick reaction times, and excellent purity. As a result, this approach may be used and expanded to generate various structurally similar heterocyclic substrates of substantial pharmacological potential. Additionally, this research study was critical to hastening the discovery and development of new drugs. It can be used to find physiologically active substances that might lead to the discovery of brand-new, more powerful synthetic substances. However, these findings are believed to contribute and offer a strong foundation for further research on creating innovative pharmacological bioactive chemicals [55].

1.3 Anticancer activity of benzoxazole derivatives

Due to the limited solubility of aryl piperazine compounds, this study generated a few benzoxazoles coupled to piperazine derivatives and tested them on human A-549 lung cancer cells. These substances precipitated in the cell culture media [56]. The molecule's solubility can be improved by substituting N-methyl piperazine for aryl piperazine at position 6 of the benzoxazole and adding a carbamate functional group instead of the methyl group at position 2. The compound's solubility can be improved by using N-methyl piperazine instead of aryl piperazine at position 6 of the benzoxazole and a carbamate practical group instead of the methyl group at position 2. The indium-based one-pot

reductive cyclization reduced the molecules produced with high yields. A general structure is given to the chemical. It has been suggested that the long-chain piperazine found in benzoxazoles and oxadiazoles may have anticancer properties [57]. The substance's cytotoxicity was investigated utilizing five cancer cell lines from humans. Cancer cell lines such as MCF-7, HeLa, HepG2, A431, and A54 were used to determine the IC_{50} values. Since all of the compounds' IC_{50} values were below 100 in the MCF-7 cell line, they were more cytotoxic than the others. Several drugs work against the MCF-7 cell line that has a benzothiazole backbone rather than a benzoxazole backbone. The A431 cell line is sensitive to the amide linkage agents' cytotoxicity. Compared to other cell lines, the produced compounds had good outcomes in the A431 cell line [13].

Everybody's health is constantly and repeatedly threatened by cancer. Several researchers worldwide are working on this issue to discover a better answer. Benzoxazole has been crucial in creating several drugs because of its broad spectrum of pharmacological activities [58]. The efficiency of benzoxazole in combating cancer is examined in this study, along with the impact of various functionalizations and substitutions. Several target regions include VEGF, VEGFR2, Topo-II, and MEK1. With more studies in this area, new benzoxazole molecules with enhanced activity, selectivity, and toxicity could be created. The data acquired for this publication will enlighten the scientific community about current developments in this field and open the door for more study [13].

1.4 The chemical benzoxazole, which has a variety of medicinal applications

The goal of medicinal chemistry is to find and create novel medications that can be used to cure illness. Establishing a link between chemical structure and pharmacological action has been a critical medicinal chemistry component. The creation of novel medications depends heavily on the chemistry of heterocyclic molecules. Both from a theoretical and practical standpoint, research into these substances is quite interesting. Heterocyclic ring systems are found in many different substances, including alkaloids, vital amino acids, vitamins, hemoglobin, hormones, numerous synthetic medications, and colors [49]. Numerous synthetic heterocyclic compounds, such as pyrrole, pyrrolidine, furan, benzoxazole, piperidine, pyridine, and benzimidazole, have critical applications and function as essential synthesis intermediates in a wide range of other chemicals. Among all the heterocyclic compounds, benzoxazole is one of the essential heterocycles having exceptional pharmacological effects. A benzene and an oxazole ring are fused to form the

chemical molecule known as benzoxazole. Oxazole is a class of 1, 3, and 5-membered azoles with oxygen and nitrogen atoms of the pyridine type at each of the three positions. Their pharmacological effects differ noticeably when the substitution pattern of the benzoxazole nucleus is slightly altered. The pharmacological significance of the benzoxazole moiety increases, and it is linked to several biological functions. The benzoxazole derivative ameliorates the COX-2 mediatory reactions, inflammation, DNA topoisomerase activity, and mycobacterial infection. These compounds' broad-spectrum and antifungal properties might lead to the emergence of a new class of antimicrobials. The biological functions of the benzoxazole scaffold have been described in this article. The development of a novel medicine that can treat various ailments may be aided by further research into this scaffold [59].

1.5 Investigating VEGFR-2 Inhibitors: From Benzoxazole Hybridization to Potential Antitumor Agents via Molecular Design Rationale.

An essential function of the Vascular Endothelial Growth Factor (VEGF) signaling pathway is to control tumor angiogenesis. Its importance as a target for therapy has been demonstrated in several human malignancies [60]. Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2) is a prominent target among angiogenesis-related kinases and the key transducer in VEGF-dependent angiogenesis [61]. As a result, blocking the VEGF/VEGFR signaling pathway becomes a tempting treatment approach to prevent tumor angiogenesis and, in turn, limit tumor development [62]. Strong VEGFR-2 inhibitor sorafenib (Nexavar®) has been approved as an antiangiogenic medication. Examining the structure-activity correlations (SAR) and common pharmacophoric characteristics between sorafenib and other VEGFR-2 inhibitors demonstrates that the majority of VEGFR-2 inhibitors have four essential characteristics: (a) The catalytic ATP-binding domain is occupied by a flat heteroaromatic ring system that has at least one N-atom. (b) A central aryl ring fills the linker area between the enzyme's ATP-binding and DFG domains, functioning as a hydrophobic spacer. (c) An H-bond acceptor and donor, a linker with a functional group acting as a pharmacophore (such as an amino or urea) facilitates binding with critical residues (Glu883 and Asp1044) in the DFG (Asp–Phe–Gly) motif—a tripeptide sequence that is essential to the active kinase domain. The urea or amide moiety's NH motifs typically establish one hydrogen bond with Glu883, and Asp1044 and the C⅐O motif make another hydrogen link. (d) When the phenylalanine residue of the

DFG loop flips out of its lipophilic pocket, defining the DFG-out or inactive conformation, the inhibitors' terminal hydrophobic moiety fills the newly formed allosteric hydrophobic pocket. Thus, this allosteric binding area is usually the site of hydrophobic interactions [63]. Furthermore, examining the X-ray structures of several inhibitors attached to VEGFR-2 confirms that there is plenty of room for different substituents surrounding the terminal heteroaromatic ring. The heterocyclic scaffold benzoxazole in many synthesized molecules has attracted attention because of its wide range of biological and pharmacological properties. Several synthesized compounds with diverse biological activity, including anti-inflammatory and anticancer effects, have the benzoxazole nucleus as their major structural component [64]. Against some solid tumors, leukemia, and lymphoma, the natural substance UK-1, a bis(benzoxazole), has demonstrated anticancer solid activity with an IC_{50} value of 20 nM. Additionally, benzoxazole has been shown to have VEGFR-2 inhibitory action, functioning as a competitive inhibitor at the tyrosine kinase ATP-binding site [65]. Benzoxazole nuclei are regarded as unique scaffolds, belonging to the most promising class of heterocycles with anticancer activity and good human tolerance [66]. Furthermore, benzoxazoles are the structural basis of many bioactive compounds exhibiting potential VEGFR inhibitory properties. Additionally, it has been claimed that several moieties have anticancer properties, including sulfonamide, sulfonylurea, sulfonylthiourea, thiosemicarbazone, hydrazone, oxime, and pyrazoline. It has been attempted to create new compounds with promising antitumor activities by utilizing ligand-based drug design, precisely a molecular hybridization approach that involves coupling benzoxazole with other effective antitumor moieties and incorporating the primary pharmacophoric features of VEGFR-2 inhibitors [66]. We aimed to synthesize novel medicines with the same fundamental pharmacophoric characteristics as established and therapeutically utilized VEGFR-2 inhibitors, such as sorafenib. Our molecular design reasoning was centered around the bioisosteric modification techniques of four distinct locations of VEGFR-2 inhibitors [66].

1.6 As a liver cirrhosis therapy and an inhibitor of anaerobic choline metabolism, a benzoxazole derivative

The human gastrointestinal tract is home to a dynamic community of bacteria known as the gut microbiota, which is crucial for developing a robust immune system, effective nutrient utilization, and direct pathogen control [59]. Additionally, the gut-brain axis—

the mechanism through which the human stomach and brain communicate in both directions—is mediated by gut microbes (GBA). Clinical studies demonstrate direct connections between gut bacteria, intestinal cells, and the central nervous system via neuroendocrine and metabolic pathways [67]. Recent research has shown a link between gut microbiota and several human illnesses, including gastrointestinal disorders, CKD, liver cirrhosis, and neurological problems [68]. A correlation exists between the amount of metabolites generated by gut bacteria in human serum and the pathophysiology of different human illnesses [69]. One well-established gut microbial activity linked to sickness is gut bacteria's anaerobic choline metabolism [70]. The gut microbiota produces trimethylamine (TMA) from choline, glycine betaine, and carnitine, among other sources [70]. The gut microbiota uses the primary source of choline, which provides gut bacteria with carbon and energy, to produce TMA, which is then further oxidized to produce trimethylamine N-oxide (TMAO) in the human body [71]. Elevated TMAO levels have been linked to an increased in vivo risk of atherosclerosis. Sixteen Moreover, several illnesses, including type 2 diabetes, fatty liver disease, and chronic kidney disease, have been connected to increased TMAO levels [72]. One possible treatment approach to lower the amounts of TMAO synthesis linked to CKD and atherosclerosis is to target TMA-lyase (CutC) and FMO3 [73]. In this case, circulating TMAO levels and atherosclerosis decreased in mice with FMO3 knocked out using an antisense oligonucleotide [74]. Decreased levels of hepatic lipids, plasma lipids, ketone bodies, glucose, and insulin indicated that metabolic interactions complicate in vivo FMO3 suppression [74]. These findings validated the dose-dependent regulatory role of FMO3 on lipid and glucose metabolism [74].

Furthermore, mice's cholesterol balance is improved by FMO3 knockdown through the promotion of basal and liver X receptor (LXR)--stimulated macrophage reverse cholesterol transport [75]. Nonetheless, research efforts have shifted to focus on CutC as a potential therapeutic target due to the adverse effects of FMO3 inhibition, including hepatic inflammation and TMA buildup. Research to find CutC inhibitors began with studies of the catalytic activity of CutC and its substrate selectivity utilizing homology modeling and mutagenesis experiments. Thirty S-adenosylmethionine (SAM) activating protein (CutD) stimulates anaerobic choline metabolism mediated by CutC [76]. It is critical to design small-molecule CutC inhibitors that remain active in the diverse gut

microbiota environment to find potential candidates for additional in vivo screening. The human gut microbiota expresses a variety of metabolizing enzymes, many of which have carbohydrates as their usual substrate [77].

Moreover, based on their chemical makeup, monosaccharide profile, and glycosidic linkage, carbohydrate-based prebiotics have shown a capacity to modify the gut flora. Hence, future progress in precisely modulating the microbiome by modification of the structure of carbohydrate-based therapies appears promising (PMMP) [78]. Glycomimetics are analogs of carbohydrates with changed structures that can replicate how they interact with target proteins. Owing to the intricate structure and unstable metabolism of carbohydrates, glycomimetics has become a viable tool for finding leads that might be used as possible treatments for various illnesses. Nevertheless, the use of glycomimetic-based strategies to target bacterial TMA-lyase (CutC) has not been investigated. In this work, we report on a benzoxazole-based ligand that was found by screening a glycomimetic library for in vitro CutC inhibitory action and that can lower TMA levels in whole cell tests [79].

1.7 Pharmacological and Pharmaceutical Importance of Benzoxazole derivatives

Active heterocyclic agrochemicals, such as those used in cosmetics, reprography, information storage, and polymers, are also frequently used in industrial applications. The active moiety and pharmacophore are both centered on the heterocyclic ring. Numerous bicyclic ring systems with benz-fused heteros, including indole, benzothiazole, benzimidazole, and Benzoxazole, have been investigated and shown to have intriguing pharmacological properties. Since benzoxazole derivatives are isosteres of cyclic nucleotides, which occur naturally, they have long been physiologically active. They might readily interact with the biopolymers of the organisms. According to the study, Benzoxazole has the most impressive and wide-ranging biological actions. It has been shown that substituted Benzoxazole has a variety of beneficial properties, including those that are anti-tumor, anti-parasitic, herbicidal, anti-allergic, anti-histaminic, anti-helminthic, COX-2inhibitory, anti-fungal, anti-tubercular, anti-cancer, anticonvulsant, diarrhea-predominant irritable bowel syndrome, hypoglycemic, HIV-1 reverse transcriptase Its propensity for binding to fibrils has been established. Recent research suggests that when employed as chemotherapeutic drugs on humans, substituted benzoxazoles and related heterocycles may display activity while offering a lower risk of

harm. The carboxylic polyether antibiotic calcimycin, a benzoxazole derivative, was created from the Streptomyces chartreuse strain (NRRL 3882). Gram-positive bacteria and several Bacillus and Micrococcus strains both responded favorably to it. It is revealed that the calcimycin analogs Routiennocin and Cezomycin are effective against the bacteria *Bacillus cereus, Bacillus megatherium, Micrococcus luteus, and Streptomyces rimosus*. They are their respective 3-hydroxy-11, 15-desmethyl, and 3-dimethylamino derivatives. Additionally, *Bacillus subtilis, Staphylococcus aureus, Enterococcus faecalis*, and other plant pathogenic fungal species were moderately susceptible to the mild activity of franamide, 11 dimethyl neomycin. Their varied biological properties continue to pique scientists' interest even though their biological activity has long been known. Numerous changes have been made to the biological characteristics of benzoxazole rings [80].

Derivatives of benzoxazole have a wide range of pharmacological actions [81]. Consequently, benzoxazole has taken up a unique position in medicinal chemistry. There are sporadic benzoxazole ring systems in nature. In research, benzoxazole is used as a building block to synthesize bigger, often bioactive molecules [82]. It is thought to interact with biopolymers in living systems and exhibit a variety of biological activities, including antimicrobial, anti-inflammatory, analgesic, antifungal, anticonvulsant, antitumor, anticancer, CNS activities, antihyperglycemic, anti-tubercular, and anti-HIV agents, because of its structural similarity to nucleic bases and the isosteres of naturally occurring cyclic nucleotides like adenine and guanine [65].anthelmintic and further planned actions [83].

1.8 Developments of Benzoxazoles in Drug Discovery

In finding and developing new drugs, heterocyclic molecules are crucial. Heterocyclic scaffolds are the source of many modern medications and intriguing therapeutic prospects. The United States Food and Drug Administration (FDA) has approved about 75% of unique small-molecule drugs that contain nitrogen heterocyclic moieties. Examples of these drugs include atorvastatin, a derivative of pyrrole; flubendazole, a derivative of benzimidazole; and chloroquine, a quinolone derivative. Benzoxazole is one of the often occurring heterocyclic nitrogen-containing moieties that is the primary active component in pharmacological compounds. Key components that make up medication compounds key components that make up medication compounds [84]. Numerous natural substances,

including marine sponges, have the oxazole skeleton, which has been shown to have various pharmacological effects.

In contrast, benzoxazole is a heterocyclic aromatic system in which the oxazole's 4,5-positions have a fused benzene ring. Similarly, medicinal chemistry and drug development have emphasized benzoxazole derivatives. Because it can display the desired pharmacological properties, benzoxazole is a valuable building block for producing biologically active therapeutic compounds [85]. Several studies have demonstrated the biological activity of synthesized and naturally occurring compounds containing a benzoxazole moiety against various illnesses. Much progress has been achieved recently in developing benzoxazole derivatives into potential therapeutic prospects [86]. The compounds with the benzoxazole moiety have demonstrated advantageous structural properties with high selectivity towards specific biological targets and increased bioactivities. The expanding significance of benzoxazole derivatives as therapeutic agents has fueled the creation of medications based on benzoxazoles. Consequently, it is essential to study current patents covering this significant class of chemicals. This review compares the pharmacological importance of patented benzoxazoles between 2015 and 2020. These patent searches look for novel, promising medication candidates and offer a succinct structural analysis of the patented compounds that consider their potential uses [84]. The efficacy and selectivity of benzoxazole derivatives may change depending on the changes performed on the benzoxazole scaffold. Because heterocyclic medicinal compounds have a variety of electronic structures and geometrical configurations, interactions between the drug molecules and biological targets might result in advantageous physicochemical and pharmacological effects [84]. The benzoxazole scaffold contains nitrogen and oxygen atoms that function as hydrogen acceptors. As a result, this chemical entity displays a variety of noncovalent interactions that are significant in medicinal chemistry [87].

Because of these intermolecular interactions, benzoxazole derivatives have better solubility and exhibit affinity and selectivity for various biological targets. Moreover, the geometry of the benzoxazole scaffold is planar. Because of the π-π stacking, π-cation, and hydrophobic interactions with biomacromolecules caused by the planar benzene ring present in the benzoxazole scaffold, this scaffold has been identified as a crucial component for the synthesis of a variety of bioactive molecules [87]. Adenine and guanine nucleobases' structural bioisosteres are frequently thought to be represented by the

benzoxazole ring. Important heterocyclic substances known as nucleobases give nucleic acid structures their structure. The interaction between benzoxazole derivatives and biopolymers of a biological system benefits from this crucial feature of the benzoxazole scaffold [88]. It is hypothesized that benzoxazole derivatives may display microbiological activity by inhibiting the production of nucleic acids because of their structural similarities. This compound might provide an additional explanation for the wide range of biological activity exhibited by derivatives of benzoxazole [89]. There are several strategies to link and create new benzoxazole entities naturally, as they are heterocyclic compounds. These architectures will diversify the resulting molecules, making them suitable for eliciting various pharmacological reactions. Many attempts have been made to develop novel techniques for synthesizing benzoxazole derivatives with diverse substituents, notably those with substituents at the 2- and 5-positions, due to the growing significance of benzoxazole derivatives in medicinal chemistry research. While 5-substituted benzoxazoles are known to affect the intensity of specific biological activities, 2-substituted benzoxazoles have been shown to significantly affect the biological activities of the benzoxazole moiety [90]. In addition to the traditional methods for creating benzoxazole derivatives, additional ways have been developed recently. These include multicomponent reactions, green and solid phase chemistry, solution phase synthetic approach, and more [91]. In several investigations, Benzoxazole-containing compounds are often used as imaging probes for identifying various disorders, particularly neurodegenerative diseases. Since theranostics development aims to achieve specific delivery of both therapeutic and imaging agents in a single package material to the site of interest, overcoming undesired variations in biodistribution and therapeutic efficacy, these studies provide some insight into the potential of developing theranostics from benzoxazole derivatives [92]. According to recent research, compounds containing a benzoxazole moiety exhibit a variety of pharmacological actions with good affinity and selectivity, which are influenced by the substituents on the benzoxazole scaffold. As a result, these derivatives may provide great candidates for creating thermodynamics [93].

1.9 Discovering Novel Antineoplastic Agents: Compound H1 as a Promising Inhibitor of Cervical Cancer Development

Cervical cancer is known to be primarily caused by the human papillomavirus (HPV), and the production of the oncogenic protein E7 is essential for the development of cancer. In this case, 2-(2-aminobenzo[d]thiazol-6-yl)benzo[d]oxazol-5-amine derivatives were created, manufactured, and assessed for their anti-tumor properties as antineoplastic drugs. Virtual screening was also carried out. The most promising compound, H1(Figure 15), demonstrated good tumor growth suppression in the HeLa xenograft model and specific anti-proliferation capacity against HeLa cells (IC_{50} = 380 nM) without evident adverse effects. Compounding H1 inhibited HPV18-positive cervical cell lines (HeLa) but not HPV16-positive cell lines (SiHa), which is an intriguing finding. Subsequent research revealed that a modest dose of compound H1 may marginally (8.77%) increase cell apoptosis and cause a cell cycle obstruction during the G1 phase. Compound H1 also showed transcriptional suppression, particularly for genes linked to the E7 cellular pathway oncoprotein, such as E7/Rb/E2F-1/DNMTI, which were critical for the development of tumors. Proteomics research suggested that E3 ubiquitin ligases may be responsible for E7 degradation, consistent with E7 expression declining after compound H1 therapy. When combined, they suggested that compound H1 could be a viable therapeutic option for cervical cancer [94]. In terms of both incidence and mortality, cervical cancer is the fourth most common malignancy among women and the fourth most common cause of cancer-related deaths [95]. The prognosis for people with malignant or metastatic cervical cancer is still dismal despite significant advancements in surgery, radiation, chemotherapy, and vaccinations [96]. Cervical cancer is mainly caused by high-risk strains of the human papillomavirus (HPV), as has been demonstrated [97]. The cellular genome is integrated by HPV, which also encodes oncoproteins [98]. These oncoproteins alter host cell gene expression patterns, facilitating viral replication [99], controlling viral transcription, and fostering immune evasion and persistence [100]. The host tumor suppressor retinoblastoma protein (Rb) may be influenced and inhibited by the encoded E7 proteins of viruses, which are primarily responsible for their oncogenicity. It has long been known that the E2 factor (E2F) family of transcription factors plays a significant role in controlling S-phase entrance. The E2F family of transcription factors is the downstream target of hyperphosphorylated Rb [100]. When E7 attaches to the combination of Rb and E2F, E2F is released, which causes Rb to separate from E2F

transcription factors—followed by the cell cycle being stopped in the G1 phase [101]. Moreover, cell cycle checkpoints are being canceled. This caused cells that were continuously infected with HPV to gradually accumulate genetic mutations, which eventually led to the development of cancer.

Furthermore, it has been found that epigenetic changes contribute to the development of cancer by causing unchecked cell proliferation [102]. DNA methylation, a reversible event mediated by DNA methyltransferase (DNMT), is one of the most extensively researched epigenetic mechanisms [103]. Every time a cell divides, the maintenance methyltransferase DNMT1 maintains the methylation pattern. DNMTs, especially DNMT1, are expressed and activated more when the E7 oncoproteins are present [100]. A conformal change in DNMT1 is induced by the binding of E7 to DNMT1 (E7/DNMT1), which exposes the latter's DNA binding site and facilitates DNA binding. DNMT1 then closes on the DNA to preserve a stable DNMT1/DNA connection. E7 moves on to the next loop and separates from the complex in the interim [104].

To find novel antineoplastic drugs for cervical cancer, we disclose here a series of structures derived using substructure virtual searching and the investigations of structure-activity relationships (SARs) driven by multi-stage activity evaluation. The intriguing lead chemical H1 was described for its anticancer properties and safety. Additionally, mechanistic experiments were conducted to explore this drug further. Drug H1 was the only known anticancer drug to have a particular anti-proliferation potential in the treatment of HPV18-positive cervical cancer. According to additional studies on the cell cycle and apoptosis, compound H1 can suppress cellular signaling pathways linked to cancer and cell proliferation [94]. HR-HPV infection has been unequivocally shown in epidemiological studies to be the primary cause of invasive cervical cancer. The HPV oncoprotein E7 is necessary for the typical viral life cycle and contributes to the cervical cancer development pathway [105]. The Rb-E2F route, which impacts the transcriptional process and DNMT1 expression, is the most well-known method by which E7 regulates gene expression. Here, we have found that chemical H1 has modest efficacy and selectivity as an inhibitor against cervical cancer. To find more accessible molecules, a structure-activity investigation was conducted, beginning with virtual screening. Compound H1 was ultimately shown to be the most effective inhibitor, exhibiting both in vivo and in vitro first-rate inhibitory efficacy against cervical cancer (IC_{50} = 380 nM). The

anti-cervical action of compound H1 was linked to the suppression of oncoprotein E7. H1 was particularly active in the DNMT1-relevant cellular pathway and the E7-Rb-E2F transcriptional process, both critical for cell cycle and proliferation [106]. We made use of proteomics analysis as well. It was discovered that compound H1 may function as a multi-target inhibitor, influencing a complicated network of pathways linked to cancer development. In our research, we are still investigating the biochemical mechanism behind the inhibition of cervical cancer [94].

In summary, the chemical structure was derivatized to analyze the SARs after the virtual screening. Ultimately, we identified the chemical H1, which has a unique inhibitory effect on cervical cancer. According to our findings, compound H1 exhibited potent in vivo and in vitro antiproliferative properties against cervical cancer. Additionally, our research shows that compound H1 suppresses cervical cancer, indicating that future development and structural optimization are worthwhile in the search for biological causes [94].

1.10 New therapeutic targets and possible treatments for non-alcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD), the most common chronic liver disease, is defined by an accumulation of liver fat unrelated to excessive drinking and can proceed to cirrhosis. Nonalcoholic steatohepatitis and nonalcoholic fatty liver (NASH) are the two manifestations of NAFLD. Insulin resistance, oxidative stress, inflammation, type 2 diabetes, and elevated levels of free fatty acids in the liver all play a role in the pathophysiology of NAFLD. The FDA has not yet approved any medications to treat NAFLD. However, the fact that numerous potential drugs have entered clinical trials and are expected to treat NAFLD is optimistic. The investigation revealed specific possible therapeutic targets in metabolism, inflammation, and fibrosis, as well as various NAFLD signal pathways and pathogenic processes. This study will enhance pertinent investigations by offering a platform for designing and developing future medications. The design and optimization process, pharmacological characteristics, and assessment of the structure-activity connection are other subjects covered regarding similar compounds. In Japan, fenofibrate was utilized in a clinical study for NAFLD/NASH, and it is anticipated that it will one day be used to treat NASH. Benzoxazole, phenoxy alkyl side chains, and carboxylic groups are thought to be responsible for their action. Pemafibrate

has been shown in preclinical research to decrease cholesterol, have anti-atherosclerotic properties, and ameliorate dietary-induced NASH in animal models [107].

1.11 The Impact of Small Molecule AU14022 in Enhancing Colorectal Cancer Cell Death through p53-Mediated G2/M-Phase Arrest and Mitochondria-Mediated Apoptosis

Colorectal cancer (CRC) ranks as the third most prevalent cancer diagnosed in both men and women. It stands as the third principal cause of cancer-associated fatalities in the United States. Its incidence and mortality rates are on a steady upward trajectory globally, including within Asian nations [108]. The primary course of action for CRC involves surgical removal alongside radiotherapy, either individually or combined with chemotherapy, to optimize therapeutic outcomes for patients pre- and post-operation. The p53 tumor-suppressor protein, pivotal in many stress responses, including those driven by the microenvironment and carcinogens, contributes significantly to various signaling pathways related to DNA repair, cell cycle progression, inflammation, apoptosis, and metabolism. While its wild-type form acts as a sentinel for cellular defense against tumor-promoting signals, it can also trigger apoptosis based on cellular context determined by signaling balance, involving factors like nuclear factor (NF)-κB or B-cell lymphoma 2 (Bcl-2) family members. Despite the prevalence of p53 mutations or inactivity in half of all human cancers, its activation remains a target for developing therapeutic agents due to its capacity to enhance apoptosis, induce cell cycle arrest, and heighten 7chemosensitivity or radiosensitivity [109].

Apoptosis manifests through two main avenues: the extrinsic death receptor pathway and the intrinsic mitochondrial pathway. The former is instigated by the binding of death receptors to their cognate ligands or agonistic antibodies, transmitting death signals from the cell surface to intracellular signaling cascades. The latter, regulated by the balance between anti- and pro-apoptotic Bcl-2 family members, p53, and p53-regulated genes, culminates in mitochondrial dysfunction following permeabilization of the outer mitochondrial membrane [110].

To find molecules that drive apoptotic cell death by enhancing p53's transcriptional activity, we undertook a cell-based screening using a luciferase-reporter assay system responsive to p53. During our research, we came across AU14022, a brand-new

benzoxazole derivative that showed a notable dose-dependent increase in p53's transcriptional activity. Additionally, AU14022 induced the phosphorylation of p53 and increased the amounts of mRNA and protein in p53-target genes, such as the CDK inhibitor p21 and the pro-apoptotic mediator PUMA. Cell cycle arrest and apoptosis induction resulted from this interaction of effects. Notably, AU14022 affected colorectal cancer cells that still had the p53 gene intact, highlighting the drug's potential as a potent anti-tumor agent [111]. Illuminate AU14022's capacity to promote p53-mediated apoptosis through mitochondrial malfunction and cell cycle arrest, offering valuable insights into the processes behind its actions. This ground-breaking method has the potential to improve the effectiveness of radiation in the treatment of colon cancer. These findings establish the foundation for further research into AU14022 as a potentially revolutionary cancer treatment [110].

Our findings demonstrated that AU14022 administration enhanced p53-target genes' mRNA and protein amounts while also inducing p53 phosphorylation (Fig. 1C and D). By preventing either CDK activity or the formation of the cyclin B1-CDK1 complex, the CDK inhibitor p21 can reduce the production of cyclin B1 and CDK1, leading to cell cycle arrest and maintaining G2/M arrest after DNA damage (Bunz et al., 1998). The critical regulator of p53-mediated apoptotic cell death, PUMA, was also expressed more often (Taylor et al., 2008). We postulated that p53 activation caused by AU14022 and the increased expression of its target genes, namely p21 and PUMA, contribute to the maintenance of G2/M arrest and the start of apoptosis [111].

Our results showed that AU14022 treatment inhibited cell proliferation and induced apoptotic cell death in HCT116 and RKO colon cancer cells expressing wild-type p53, in contrast with results observed in HT29 colon cancer cells harboring a p53 missense mutation (R273H) and p53−/− HCT116 colon cancer cells. Moreover, mitochondrial-membrane dysfunction induced by AU14022 treatment is a marker of early-stage apoptosis; however, the compound's potential as an inducer of mitochondrial damage requires further study. Importantly, we did not observe AU14022 cytotoxicity following the administration of 20 μM AU14022 to CCD-18Co colon cells or CCD-18Lu lung cells, suggesting that AU14022 might constitute a pharmacologically safe compound suitable for further evaluation as a potential anticancer drug [112].

The p53 tumor suppressor protein is crucial in controlling cell cycle progression and orchestrating programmed cell death, known as apoptosis. Its activation can heighten cancer cells' vulnerability to radiation therapy or chemotherapy treatments. To identify small molecules that amplify apoptosis by enhancing p53's transcriptional activity, we embarked on an investigation using our unique collection of 96 small-molecule compounds. Employing a method that screens cells and involves a luciferase-reporter assay responsive to p53, we focused on benzoxazole derivatives. We discovered that the administration of AU14022 exhibited a notable concentration-dependent elevation in p53's transcriptional activity. Coupled with increased p53 protein expression, phosphorylation at Serine 15, upregulated expression of downstream genes regulated by p53, and a surge in apoptotic activity within p53-intact HCT116 human colon cancer cells [113].

In contrast, p53-knockout HCT116 cells displayed no such response. Remarkably, the AU14022-treated p53-intact HCT116 cells displayed signs of mitochondrial dysfunction, involving alterations in the expression of B-cell lymphoma-2 family proteins and the release of cytochrome c. The combined treatment of AU14022 and ionizing radiation exhibited a synergistic effect, driving increased apoptosis compared to treatments involving either ionizing radiation or AU14022 in isolation. Further analysis revealed that AU14022 impeded cell cycle progression at the G2/M phase after treatment. Remarkably, in a mouse model of colon cancer xenografts featuring p53-intact HCT116 cells, the combined treatment of AU14022 and ionizing radiation proved superior in inhibiting tumor growth compared to radiation therapy alone. These findings underscore the ability of AU14022 to provoke apoptosis through p53-mediated cell cycle arrest linked to mitochondrial dysfunction, ultimately enhancing the sensitivity of colon cancer cells to radiation therapy. These outcomes lay the foundation for exploring AU14022 as a promising agent in the fight against cancer [113].

Chapter Two
Methodology

2.1 Methods

The research sought to assess the anticancer potential of synthetic chemicals against different cancer cell lines. The cell lines used in this experiment included hepatocellular carcinoma (Hep3B and HepG2), cervical adenocarcinoma (HeLa), breast cancer (MCF7), and a standard cell line (hek293T). A clearly defined experimental design was used to achieve accurate and consistent results. The cells were grown in RPMI-1640 medium with 10% fetal bovine serum, 1% penicillin/streptomycin, and 1% l-glutamine as dietary supplements. The cells were kept alive in a regulated setting, including a humidified atmosphere with 5% CO_2 at 37°C [114].

2.2 Cell Seeding and Maintenance

The cultivated cells were seeded in 96-well plates at a density of 2.6 x 10^4 cells per well. After being sown, the cells were given 72 hours to mature till confluence. They were constantly monitored to ensure the cells prosper and stick to the culture surface. The cells' optimal environment was maintained whenever the medium needed to be replaced [114].

2.3 Compound Treatment

The synthesized compounds were administered to the cells after cell seeding and confluence were reached to assess their potential anticancer properties. The chemicals were introduced to the wells at varying doses after being previously synthesized by recognized processes and made it possible to determine how they affected cell viability and proliferation in a dose-dependent manner. The 24-hour treatment period was chosen to give the chemicals enough time to interact with the cells and potentially exert their anticancer effects [114].

2.4 Cell Viability Assessment

The cells' vitality was evaluated using the widely used CellTiter 96® Aqueous One Solution Cell Proliferation (MTS) Assay, which counts viable cells. As long as the manufacturer's instructions (Promega Corporation, Madison, WI) were followed, this test provided a consistent and reliable measure of cell viability. After the 24-hour treatment,

each well got 20 L of MTS solution for every 100 L of media, ensuring uniform distribution. After that, the plate was kept at 37°C in a controlled environment for two hours [114].

2.5 Absorbance Measurement and Data Analysis

Using a microplate reader, such as the SpectraMax® Microplate Reader, the absorbance of the wells was assessed at 490 nm following the incubation time and made it possible to measure the formazan product produced by live cells, which is directly related to cell growth and viability. Absorbance measurements were taken to ascertain how the produced chemicals affected cell viability, and the obtained data were subjected to extensive statistical analysis [114].

2.6 Statistical Analysis

In the context of cancer research, this statistical study aims to investigate the connection between IC_{50} values and the Structure-Activity Relationship (SAR) of substances. The IC_{50} value is the substance needed to block 50% of cellular development or a specific biological function. SAR research examines how changes to a compound's structural makeup affect its activity against cancer cell lines. This study aims to find meaningful connections and patterns that might shed light on the effectiveness of these chemicals. Data collection and preprocessing IC_{50} values for several substances tested against various cancer cell lines were obtained. These chemicals' structural characteristics were included in the SAR data. The statistical examination of the IC_{50} values included measures of central tendency (mean, median) and dispersion (standard deviation). Compounds were categorized using SAR data according to their structural characteristics. Analysis of Correlation: Pearson correlation coefficients were computed to see whether there were any appreciable relationships between structural characteristics and IC_{50} values for particular cell lines. Regression Analysis: Linear regression models were built to forecast IC_{50} values using SAR data. The collected data were evaluated using the appropriate statistical techniques to ascertain the significance of the observed results. By ensuring the results' accuracy, correctness, and robustness, the methodological approach utilized in this study hopes to further scientific knowledge in cancer research [114].

Chapter Three
Result and Discussion

3.1 Results

In the current study, 16 compounds in (figure 20) that were synthesized based on a reference publication employing a panel of 7 cancer cell lines were used to assess the anticancer efficacy of several synthetic compounds [115]. These substances were examined on seven distinct cell types, as well as 5-fluorouracil and doxorubicin, two well-known anticancer medications. The results emphasize the significance of chemical alterations in tailoring drugs' biological reactions. The reported SAR patterns need to be confirmed and further explored, which includes molecular modeling and experimental confirmation. Ultimately, the knowledge gathered from this research aids in the logical design of substances with improved cellular functions and prospective therapeutic uses. As a result, this work gave important new understandings of the anticancer activity of synthetic chemicals against various cancer cell lines. The effectiveness of the compounds varied, but BNZ-2, BNZ-4, BNZ-7, BNZ-9 and BNZ-10, emerged as highly promising agents. These substances produced notable effects on particular cancer cell lines, demonstrating their promise as tailored therapeutics for treating various cancer types.

Table 1

the IC_{50} of the evaluated compounds against various kinds of cancer cell lines in μM

	COLO205	Hep3B	HepG2	HeLa	MCF7	B16F1	Caco2
BNZ1	131.41±1.37	77.02±1.39	80.16±1.33	129.03±2.37	131.59±3.21	>200	106.98
BNZ2	57.38±1.40	60.00±1.41	21.74±1.47	62.43±1.72	39.89±1.75	61.18±2.74	68.537
BNZ4	75.54±1.49	64.50±1.43	28.78±1.61	63.84±1.09	67.01±1.87	31.26±1.47	53.851
BNZ6	>200	>200	>200	>200	>200	115.13±1.76	>200
BNZ7	63.142±1.30	26.75±1.35	54.5±2.10	35.73±1.25	41.32±1.05	76.01±0.78	53.186
BNZ8	89.69±1.51	99.30±1.77	71.58±1.35	91.50±2.64	193.62±2.78	99.30±3.07	63.208
BNZ9	75.75±1.68	64.18±1.75	22.40±0.58	55.70±1.64	111.38±2.04	>200	62.584
BNZ10	25.70±1.41	72.19±1.42	71.69±2.04	78.72±1.08	53.49±1.57	113.08±1.80	54.557
BNZ12	101.90±2.1	166.54±2.01	89.83±1.85	>200	160.58±1.78	115.38±3.01	71.017
BNZ13	69.41±0.78	115.18±2.75	54.08±1.47	80.74±2.89	87.83±2.07	97.22±1.24	84.067
BNZ14	187.05±1.98	154.63±1.78	121.77±2.71	175.79±1.99	138.7±2.41	119.64±2.82	>200
BNZ15	111.06±1.40	147.62±2.57	81.34±2.01	168.34±2.04	189.37±1.89	165.03±2.90	83.549
BNZ16	71.39±1.21	76.40±1.74	51.02±1.21	79.79±3.01	82.22±1.80	164.95±1.74	66.562
DOX	<<0.05	2.23±1.21	2.94±0.89	1.55±1.35	0.57±1.21	0.056±0.03	
5-FU	3.20±1.38	13.28±2.15	5.23±2.20	1.20±1.02	17.73±1.66	>200	

For 16 distinct compounds (BNZ-1 to BNZ-16), the absorbance findings (abs1 and abs2) employing CaCO-2 cells are shown in the table (table 3). On October 28, 2021, absorbance was measured at six different concentrations (300 M, 100 M, 50 M, 10 M, 1 M, and a blank sample) (Table 2) in appendix (b). According to the analysis, absorbance values gradually drop as compound concentrations rise. Suggests that decreased absorption occurs at greater compound concentrations. Given that the 1 M negative control often displays more excellent absorption rates than the 10 M negative control, it is clear that the harmful control concentration significantly influences the outcomes. A comparison of several chemicals also reveals variances in absorption. For instance, whereas certain compounds, like BNZ-4 and BNZ-12, display lesser absorption, others, like BNZ-6 and BNZ-7, often exhibit greater absorption values. Overall, these findings aid in comprehending variances among various chemicals and evaluate compounds' effect on absorption using CaCO-2 cells. This knowledge may help formulate fresh study plans and clarify the link between chemical concentration and biological results. "The table presents absorbance results (abs1 and abs2) for 16 different compounds (BNZ-1 to BNZ-16) using CaCO-2 cells."

- The data table is introduced in this section, which also notes that it comprises absorbance measurements (abs1 and abs2) for 16 different compounds (Table3) in appendix (b), each identified by the numbers BNZ-1 through BNZ-16. These observations were made with CaCO-2 cells, a cell culture probably utilized in biomedical research. "Absorbance was measured at six different concentrations (300µM, 100µM, 50µM, 10µM, 1µM, and a blank sample) on October 28, 2021."
- Information on the experimental setup is provided in this section. In addition to a blank sample, the absorbance—a measure of how much light a substance absorbs—was evaluated at six concentration levels (300 M, 100 M, 50 M, 10 M, and 1 M). The experiment's start date, October 28, 2021, was used as the date of this evaluation. "The analysis demonstrates a gradual decrease in absorbance values as the compound concentrations increase."
- Discussion of the analyses' findings may be found here. As the concentration of the tested substances rises, the findings show a recurrent pattern of declining absorbance. In other words, the amount of light absorbed decreases from lower to greater concentrations of the substances. "This implies that higher compound concentrations lead to reduced absorption."
- This statement derives a conclusion from the collected information. It implies that the decrease in absorbance with rising compound concentrations shows that lower incoming light absorption occurs at greater compound concentrations. Understanding how the concentration of these substances impacts their interaction with the CaCO-2 cells and their capacity to absorb light depends critically on this realization.

Experimental circumstances and the crucial finding that reduced absorbance is correlated with increased compound concentrations indicate a declining potential for light absorption as compound concentrations rise. Understanding the connection between chemical concentration and its effect on cellular absorption depends on knowing this information. The line in Table 2 in appendix (b). that reads, "The significance of the negative control concentration is evident," highlights the significance of the concentration utilized for the negative control. A negative control is employed in scientific research as a benchmark to determine whether the experimental circumstances result in unintended effects. It acts as a benchmark

measurement. "the 1µM negative control typically exhibits higher absorption rates compared to the 10µM negative control."

- Here, we contrast the 1M and 10M concentrations of two separate negative controls. The data consistently reveals that the 10M negative and 1M negative control exhibit more excellent absorption rates. Suggests that the measured absorption rates are significantly affected by the concentration of the negative control. "indicating a notable impact of negative control concentration on the results."
- The emphasis in this section is on the fact that the observed difference in absorption rates between the two harmful control concentrations (1 M and 10 M) is not a chance occurrence but rather a significant influence. In order to assure the correctness and dependability of the experimental data, it is crucial to choose an adequate harmful control concentration since it is suggested that the concentration chosen for the negative control may affect and maybe skew the experimental results.

3.2 Discussion

The investigation, which employed seven distinct types of cancer cells, provided valuable data on the possible efficacy of these compounds. The investigation showed that the compounds on the test exhibited unique activity patterns. BNZ-6, had a little impact on the cells under study, as evidenced by a measured effect value of over 200. This shows that (BNZ-6)'s usefulness in treating cancer is limited. On the other hand, BNZ-2 showed substantial activity against hepG2 cells, a finding that calls for more research into the mechanisms behind its particular impact on this cell line. Similarly, BNZ-10, showed activity only against hepG2 cells, suggesting a possible targeted therapeutic use for malignancies linked to hepG2.

Particularly intriguing was the finding that BNZ-7, significantly influenced hep3B cells, BNZ-9, had an impact on hepG2 cells, and BNZ-4, significantly affected colo205 cells. These substances showed distinct and focused effectiveness on their target cell lines, indicating the possibility of them being used as targeted treatments for treating particular cancer types. The Structure-Activity Relationship (SAR) research findings shed essential light on potential structural factors that may influence a compound's activity against various cell lines. The discovery of comparable activity patterns and shared structural characteristics emphasizes the importance of specific chemical motifs in regulating

biological responses. The observed predominance of the piperazine/piperidine and chlorobenzoyl groups among compounds with comparable activity implies that these groups may play a role in regulating interactions with cellular targets. The constant action of compounds that share morpholinomethyl and 4-methylpiperidin-1-yl moieties is notable and emphasizes the importance of these structural components in determining cellular outcomes. Furthermore, including a benzylpiperazine moiety and a modified benzodioxole group in several compounds underscores the structural variety contributing to activity. However, the complexity of biological systems necessitates further research, such as molecular docking and mechanistic studies, to corroborate the anticipated correlations between structural characteristics and activity, even though SAR analysis offers critical insights. Notably, most substances showed their most significant effects on hepG2 cells, indicating a possible specialization in focusing on this cancer cell line. Most drugs work preferentially on hepG2 cells, necessitating a better comprehension of the underlying mechanisms of action and molecular interactions. Future research should identify the precise targets and signaling pathways connected to the anticancer effects shown in hepG2 cells since this information may help create fresh treatment approaches for hepG2-associated tumors.

To examine the connections between chemical structures and activity patterns across distinct cell lines, this study used a SAR technique. The observed common structural elements, such as the piperazine/piperidine moiety, the chlorobenzoyl group, and specific functional groups, serve as useful building blocks for developing more powerful compounds with targeted action against particular cell types. The link between chemical structures and their effectiveness against cancer cell lines can be better understood by statistical analysis of IC_{50} values and SAR in cancer research. Our understanding of how structural changes affect medication potency is improved by locating meaningful connections and creating prediction models. These results support attempts to discover new drugs and aid in the rational design of anticancer agents. The Structure-Activity Relationship (SAR) analysis of the IC_{50} values for a set of drugs against different cell lines reveals key structural characteristics that may be responsible for their reported activities BNZ-1, BNZ-4, BNZ-8, BNZ-7 and BNZ-4 are examples of compounds that share a chlorobenzoyl group, this group is thought to affect how some cell lines behave; the presence of chlorine can change molecular structure and chemical processes, which can

lead to particular responses against particular cells. BNZ-2, BNZ-4, BNZ-13, BNZ-14, and BNZ-16 are examples of compounds with piperazine or piperidine moieties that may have an impact on the way the drug interacts with cellular components or change its three-dimensional structure, which might influence the substance's effect on cell lines. Notably, common structural components like the 4-methylpiperidin-1-yl and morpholinomethyl groups in BNZ-1, BNZ-13 and BNZ-7 may be responsible for their effects on particular cell lines. In addition, the presence of a benzylpiperazine moiety in BNZ-6 and a substituted benzodioxole group in BNZ-12 may contribute to their respective actions. These results highlight the potential significance of these structural characteristics in controlling the biological activity of the drugs across various cell lines. It is important to note that a thorough investigation of chemical interactions and computational techniques may reveal more exact processes behind the reported SAR patterns. These structural characteristics could influence the action against particular cell lines. Based on their IC_{50} values, the findings are compared between BNZ1-16, 5-Fluorouracil (5-FU), and Doxorubicin (DOX). The differences between these chemicals' impact on the proliferation of cancer cells may be more clearly seen in this comparison. Here is an explanation: 5-FU vs. BNZ1-16:* Compared to 5-FU, BNZ-4 has a much lower IC_{50} (25.701.41 vs. 3.201.38, respectively). BNZ-10 may be more potent than 5-FU at preventing cell proliferation. Some substances, like BNZ8 and BNZ-15, appear to have cellular effects superior to 5-FU.

DOX vs. BNZ1-16: DOX is a solid and successful chemical against cancer cells. It can be shown that all BNZ1-16 compounds have IC_{50} values that are significantly greater than DOX. In contrast, the majority of BNZ1-16 chemicals have a significant impact on cancer cells. Within BNZ1-16, there is much diversity in the IC_{50} values of the individual BNZ1-16 compounds. The fact that (BNZ-10)'s IC_{50} value is substantially lower than that of BNZ-2 or BNZ-4 suggests that it may be more effective against these cancer cells. The findings indicate that BNZ1-16 compounds have a wide range of impacts on the proliferation of cancer cells, some of which are more effective than others. The chemical DOX seems to be the most efficient of them. This information makes it easier to discover substances that might be used as filters in cancer treatment.

The impact of many substances on cell viability, including BNZ-8, BNZ-12, BNZ-15, and 5-FU, was investigated in (figure11). LX-2 cells, a particular kind of cell line used in

research, were employed in these tests. The chemicals were allowed to interact with the cells for 72 hours, which allowed for the evaluation of long-term effects. No matter the quantity, it was found that DMSO (dimethyl sulfoxide) had no appreciable effect on cell survival. Conversely, the compounds BNZ-2, BNZ-13, and BNZ-12 demonstrated a dose-dependent reduction in cell viability, suggesting a detrimental impact as their concentrations escalated. Especially notable was that, at higher doses, 5-FU significantly reduced cell viability more than the other chemicals did. These results shed light on these substances' various effects on LX-2 cells and may help determine the toxicity or therapeutic potential (Figure 11).

In conclusion, the compounds under discussion display a range of structural characteristics that impact their effectiveness against particular cancer cell lines. Specifically, the residues of piperazine or piperidine in SNB2, SNB10, SNB13, SNB14, and SNB16, as well as the chlorobenzoyl group in SNB1, SNB4, SNB7, SNB8, and SNB15, are important. Modifying interactions with cellular targets is facilitated by shared structures such as the Substituted Benzodioxole group in SNB12 and the morpholinomethyl and 4-Methylpiperidin-1-yl groups in SNB7, SNB13, and SNB15. The benzylpiperazine class of SNB6 and the structural diversity of SNB12 both influence their actions. However, accurate insights into the significance of these structural traits need a thorough understanding of chemical processes and biological implications. In summary, the research shows that BNZ1-16 compounds have varying degrees of activity against various cancer cell lines, with some of them demonstrating potential performance in comparison to well-established treatments like 5-FU. Particularly noteworthy is 5-chloro-7-(2-chlorobenzoyl)-3-((4-(4-fluorophenyl)piperazin-1-yl)methyl)benzo[d]oxazol-2(3H)-one. The study emphasizes how crucial structural elements are in affecting biological reactions, particularly the piperazine/piperidine moiety and the chlorobenzoyl group. It is recommended that future research concentrate on clarifying certain targets and signaling pathways, especially in hepG2 cells, to improve comprehension and customize treatment approaches. These findings provide important new information for the development of more precise and potent cancer therapy medications.

Reference

1. Kim, T., et al., *Synthesis, structure revision, and cytotoxicity of nocarbenzoxazole G.* Journal of natural products, 2019. 82(5): p. 1325-1330.
2. Ghoshal, T. and T.M. Patel, *Anticancer activity of benzoxazole derivative (2015 onwards): a review.* Future Journal of Pharmaceutical Sciences, 2020. 6: p. 1-24.
3. Correa, P., *Gastric cancer: overview.* Gastroenterology Clinics, 2013. 42(2): p. 211-217.
4. Kakkar, S., Kumar, S., Narasimhan, B., Lim, S. M., Ramasamy, K., Mani, V, *Design, synthesis and biological potential of heterocyclic benzoxazole scaffolds as promising antimicrobial and anticancer agents.* 2018: Chem Central.
5. Kakkar, S., et al., *Design, synthesis and biological potential of heterocyclic benzoxazole scaffolds as promising antimicrobial and anticancer agents.* Chemistry Central Journal, 2018. 12(1): p. 1-11.
6. Hirao, I. and M. Kimoto, *Unnatural base pair systems toward the expansion of the genetic alphabet in the central dogma.* Proceedings of the Japan Academy, Series B, 2012. 88(7): p. 345-367.
7. Parvathi, J., et al., *Synthesis and pharmacological screening of novel substituted benzoxazole derivatives as an anti-inflammatory agents.* Int J Curr Pharm Res, 2013. 6: p. 4-7.
8. Laeeq, S., A.K. Sirbaiya, and H.H. Siddiqui, *Benzoxazole: progress report on chemistry, synthesis and biological activities.* Indo American journal of Pharmaceutical Research, 2013. 3(12): p. 8550-8562.
9. BENTOUMI, H., et al., *SONOCHEMICAL SYNTHESIS OF SOME NOVEL 6-IMINOBENZOXAZOLINONES WITH POTENTIAL ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES.*
10. Yuan, X., et al., *Design, synthesis and in vitro evaluation of 6-amide-2-aryl benzoxazole/benzimidazole derivatives against tumor cells by inhibiting VEGFR-2 kinase.* European Journal of Medicinal Chemistry, 2019. 179: p. 147-165.

11. Khodair, A.I., N.A. Al-Masoudi, and J.-P. Gesson, *A new approach to the synthesis of benzothiazole, benzoxazole, and pyridine nucleosides as potential antitumor agents.* Nucleosides, Nucleotides and Nucleic Acids, 2003. 22(11): p. 2061-2076.

12. Abdelgawad, M.A., et al., *New Benzoxazole Derivatives as Antiprotozoal Agents: In Silico Studies, Synthesis, and Biological Evaluation.* Journal of Chemistry, 2021. 2021.

13. Ghoshal, T. and T.M. Patel, *Anticancer activity of benzoxazole derivative (2015 onwards): a review.* Future Journal of Pharmaceutical Sciences, 2020. 6(1): p. 1-24.

14. Lagace, T.A., *PCSK9 and LDLR degradation: regulatory mechanisms in circulation and in cells.* Current opinion in lipidology, 2014. 25(5): p. 387.

15. Wong, X.K. and K.Y. Yeong, *A patent review on the current developments of benzoxazoles in drug discovery.* ChemMedChem, 2021. 16(21): p. 3237-3262.

16. Rivlin, N., et al., *Mutations in the p53 tumor suppressor gene: important milestones at the various steps of tumorigenesis.* Genes & cancer, 2011. 2(4): p. 466-474.

17. Kerr, J.F., A.H. Wyllie, and A.R. Currie, *Apoptosis: a basic biological phenomenon with wideranging implications in tissue kinetics.* British journal of cancer, 1972. 26(4): p. 239-257.

18. Takayama, S., J.C. Reed, and S. Homma, *Heat-shock proteins as regulators of apoptosis.* Oncogene, 2003. 22(56): p. 9041-9047.

19. Ohta, T., et al., *Propolis suppresses tumor angiogenesis by inducing apoptosis in tube-forming endothelial cells.* Bioscience, biotechnology, and biochemistry, 2008: p. 0808011016-0808011016.

20. KOSOVA, F., et al., *Synthesis and the effect of a novel benzoxazole compound on breast cancer cell line.* Medicine Science, 2019. 8(1): p. 186-191.

21. Temiz-Arpacı, Ö., et al., *Synthesis and biological activity of some new benzoxazoles.* European journal of medicinal chemistry, 2008. 43(7): p. 1423-1431.

22. Fadda, A.A., et al., *Synthesis Some New Benzoxazole Derivatives and Their Cytotoxicity to Human Cancer Cell Lines.* RESEARCH JOURNAL OF PHARMACEUTICAL BIOLOGICAL AND CHEMICAL SCIENCES, 2016. 7(1): p. 1820-1826.

23. Fadda, A.A., et al., *Synthesis some new benzoxazole derivatives and their cytotoxicity to human cancer cell lines.* Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2016. 7(1): p. 1820-1826.

24. Spengler, G., et al., *Benzoxazole-based Zn (II) and Cu (II) complexes overcome multidrug-resistance in cancer.* Anticancer Research, 2018. 38(11): p. 6181-6187.

25. Murty, M., et al., *Synthesis of piperazinyl benzothiazole/benzoxazole derivatives coupled with 1, 3, 4-oxadiazole-2-thiol: novel hybrid heterocycles as anticancer agents.* Medicinal Chemistry Research, 2013. 22(10): p. 4980-4991.

26. Glomb, T., K. Szymankiewicz, and P. Świątek, *Anticanceractivity of derivatives of 1, 3, 4-oxadiazole.* Molecules, 2018. 23(12): p. 3361.

27. Ravinaik, B., D. Ramachandran, and M. Rao, *Synthesis and anticancer evaluation of amide derivatives of 1, 3, 4-oxadiazole linked with benzoxazole.* Russian Journal of General Chemistry, 2019. 89(5): p. 1003-1008.

28. B, R.R., *benzoxazole derivatives coupled with*. 2013: Medicinal Chemistry Research.

29. Cascioferro, S., et al., *New 1, 2, 4-oxadiazole nortopsentin derivatives with cytotoxic activity.* Marine drugs, 2019. 17(1): p. 35.

30. Pervaram, S., et al., *Synthesis and Anticancer Activity of 1, 2, 4-Oxadiazole Fused Benzofuran Derivatives.* Russian Journal of General Chemistry, 2018. 88(6): p. 1219-1223.

31. Lukin, A., et al., *Privileged 1, 2, 4-oxadiazoles in anticancer drug design: Novel 5-aryloxymethyl-1, 2, 4-oxadiazole leads for prostate cancer therapy.* Letters in Drug Design & Discovery, 2016. 13(3): p. 198-204.

32. Abdelgawad, M.A., R.B. Bakr, and H.A. Omar, *Design, synthesis and biological evaluation of some novel benzothiazole/benzoxazole and/or benzimidazole derivatives incorporating a pyrazole scaffold as antiproliferative agents.* Bioorganic Chemistry, 2017. 74: p. 82-90.

33. Srivastava, A., L. Aggarwal, and N. Jain, *One-pot sequential alkynylation and cycloaddition: regioselective construction and biological evaluation of novel*

benzoxazole–triazole derivatives. ACS Combinatorial Science, 2015. 17(1): p. 39-48.

34. Shreedhara, S., et al., *The in vitro Cytotoxic and Molecular Docking Studies of Newly Synthesized Fused Benzoxazole-Triazole Derivatives. R.* J Chem Pharmaceutical Research, 2017. 9(5): p. 108-119.

35. Dadashpour, S., et al., *Synthesis and anticancer activity of benzimidazole/benzoxazole substituted triazolotriazines in hepatocellular carcinoma.* AnticancerAgents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-AnticancerAgents), 2019. 19(17): p. 2120-2129.

36. Bramhananda Reddy, N., et al., *Synthesis and biological evaluation of benzoxazole fused combretastatin derivatives as anticancer agents.* Monatshefte Für Chemie-Chemical Monthly, 2016. 147(3): p. 593-598.

37. Kumar, V.K., et al., *Synthesis, anticancer evaluation, and molecular docking studies of benzoxazole linked combretastatin analogues.* Medicinal Chemistry Research, 2020. 29: p. 528-537.

38. Kumar, V.K., et al., *Synthesis, anticancer evaluation, and molecular docking studies of benzoxazole linked combretastatin analogues.* Medicinal Chemistry Research, 2020. 29(3): p. 528-537.

39. Bramhananda Reddy, N., et al., *Synthesis and biological evaluation of benzoxazole fused combretastatin derivatives as anticancer agents.* Monatshefte Für Chemie-Chemical Monthly, 2016. 147: p. 593-598.

40. Ayaz, F., R.H. Ersan, and O. Algul, *Symmetric bis-benzoxazole-based chemicals exerted anti-inflammatory effect on danger signal LPS-stimulated macrophages.* Monatshefte Für Chemie-Chemical Monthly, 2019. 150: p. 1137-1146.

41. Furkan, A., et al., *DNA base bioisosteres, bis-benzoxazoles, exert anti-proliferative effect on human prostate and breast cancer cells.* Journal of the Turkish Chemical Society Section A: Chemistry, 2018. 5(3): p. 1145-1152.

42. Sommer, P.S., et al., *Nataxazole, a new benzoxazole derivative with antitumor activity produced by Streptomyces sp. Tü 6176.* The Journal of antibiotics, 2008. 61(11): p. 683-686.

43. Ayaz, F., R.H. Ersan, and O. Algul, *Symmetric bis-benzoxazole-based chemicals exerted anti-inflammatory effect on danger signal LPS-stimulated macrophages.* Monatshefte Für Chemie-Chemical Monthly, 2019. 150(6): p. 1137-1146.

44. Song, H., et al., *The biosynthesis of the benzoxazole in nataxazole proceeds via an unstable ester and has synthetic utility.* Angewandte Chemie International Edition, 2020. 59(15): p. 6054-6061.

45. Sun, M., et al., *Nocarbenzoxazoles A–G, benzoxazoles produced by halophilic Nocardiopsis lucentensis DSM 44048.* Journal of Natural Products, 2015. 78(8): p. 2123-2127.

46. El-Hady, H.A. and S.A. Abubshait, *Synthesis and anticancer evaluation of imidazolinone and benzoxazole derivatives.* Arabian Journal of Chemistry, 2017. 10: p. S3725-S3731.

47. Abdelgawad, M.A., et al., *Synthesis, Anti-B reast Cancer Activity, and Molecular Modeling of Some Benzothiazole and Benzoxazole Derivatives.* Archiv der Pharmazie, 2013. 346(7): p. 534-541.

48. Madhukar, M., S. Sawraj, and P.D. Sharma, *Design, synthesis and evaluation of mutual prodrug of 4-biphenylacetic acid and quercetin tetramethyl ether (BPA–QTME) as gastrosparing NSAID.* European journal of medicinal chemistry, 2010. 45(6): p. 2591-2596.

49. Kaur, A., S. Wakode, and D.P. Pathak, *Benzoxazole: The molecule of diverse pharmacological importance.* International Journal of Pharmacy and Pharmaceutical Sciences, ISSN-0975-1491, 2015: p. 17-23.

50. Lokwani, P., et al., *Benzoxazole: The molecule of diverse biological activities.* J. Chem. Pharm. Res, 2011. 3(3): p. 302-311.

51. Apostol, T.-V., et al., *Synthesis and Biological Evaluation of New N-Acyl-α-amino Ketones and 1, 3-Oxazoles Derivatives.* Molecules, 2021. 26(16): p. 5019.

52. Li, Q., et al., *Synthesis and mechanism of action of group A streptogramin antibiotics that overcome resistance.* 2019.

53. Kaur, A., S. Wakode, and D.P. Pathak, *Benzoxazole: The molecule of diverse pharmacological importance.* Inter. J. Pharm. and Pharm. Sci, 2015. 7(1): p. 16-23.

54. Kamal, U., N.M. Javed, and K. Arun, *Biological potential of benzoxazole derivatives: an updated review.* Asian J. Pharm. Clin. Res, 2020. 13(8): p. 28-41.

55. Kamal, U., N.M. Javed, and K. Arun, *Biological potential of benzoxazole derivatives: an updated review.* Asian J Pharm Clin Res, 2020. 13(8): p. 1-14.

56. Al-Harthy, T., et al., *Design, Synthesis, and Cytotoxicity of 5-Fluoro-2-methyl-6-(4-aryl-piperazin-1-yl) Benzoxazoles.* Molecules, 2016. 21(10): p. 1290.

57. Xiang, P., et al., *Novel benzothiazole, benzimidazole and benzoxazole derivatives as potential antitumor agents: synthesis and preliminary in vitro biological evaluation.* Molecules, 2012. 17(1): p. 873-883.

58. McKee, M.L. and S.M. Kerwin, *Synthesis, metal ion binding, and biological evaluation of new anticancer 2-(2'-hydroxyphenyl) benzoxazole analogs of UK-1*. Bioorganic & medicinal chemistry, 2008. 16(4): p. 1775-1783.

59. Ranjith, R., *The chemistry and biological significance of imidazole, benzimidazole, benzoxazole, tetrazole and quinazolinone nucleus.* Journal of Chemical and pharmaceutical Research, 2016. 8(5): p. 505-526.

60. Niu, G. and X. Chen, *Vascular endothelial growth factor as an anti-angiogenic target for cancer therapy.* Current drug targets, 2010. 11(8): p. 1000-1017.

61. Holmes, K., et al., *Vascular endothelial growth factor receptor-2: structure, function, intracellular signalling and therapeutic inhibition.* Cellular signalling, 2007. 19(10): p. 2003-2012.

62. Eldehna, W.M., et al., *Increasing the binding affinity of VEGFR-2 inhibitors by extending their hydrophobic interaction with the active site: Design, synthesis and biological evaluation of 1-substituted-4-(4-methoxybenzyl) phthalazine derivatives.* European Journal of Medicinal Chemistry, 2016. 113: p. 50-62.

63. Machado, V.A., et al., *Synthesis, antiangiogenesis evaluation and molecular docking studies of 1-aryl-3-[(thieno [3, 2-b] pyridin-7-ylthio) phenyl] ureas: Discovery of a new substitution pattern for type II VEGFR-2 Tyr kinase inhibitors.* Bioorganic & medicinal chemistry, 2015. 23(19): p. 6497-6509.

64. Kakkar, S., et al., *Benzoxazole derivatives: design, synthesis and biological evaluation.* Chemistry central journal, 2018. 12(1): p. 1-16.

65. Oksuzoglu, E., et al., *Some benzoxazoles and benzimidazoles as DNA topoisomerase I and II inhibitors.* Journal of enzyme inhibition and medicinal chemistry, 2008. 23(1): p. 37-42.

66. Viegas-Junior, C., et al., *Molecular hybridization: a useful tool in the design of new drug prototypes.* Current medicinal chemistry, 2007. 14(17): p. 1829-1852.

67. Carabotti, M., et al., *The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems.* Annals of gastroenterology: quarterly publication of the Hellenic Society of Gastroenterology, 2015. 28(2): p. 203.

68. Shreiner, A.B., J.Y. Kao, and V.B. Young, *The gut microbiome in health and in disease.* Current opinion in gastroenterology, 2015. 31(1): p. 69.

69. Sharon, G., et al., *Specialized metabolites from the microbiome in health and disease.* Cell metabolism, 2014. 20(5): p. 719-730.

70. Zeisel, S.H. and M. Warrier, *Trimethylamine N-oxide, the microbiome, and heart and kidney disease.* Annual review of nutrition, 2017. 37: p. 157-181.

71. Gabr, M.T., et al., *A benzoxazole derivative as an inhibitor of anaerobic choline metabolism by human gut microbiota.* RSC Medicinal Chemistry, 2020. 11(12): p. 1402-1412.

72. Kamal, A., et al., *Synthesis, DNA-binding ability and anticancer activity of benzothiazole/benzoxazole–pyrrolo [2, 1-c][1, 4] benzodiazepine conjugates.* Bioorganic & medicinal chemistry, 2010. 18(13): p. 4747-4761.

73. Wang, Z., et al., *Non-lethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis.* Cell, 2015. 163(7): p. 1585-1595.

74. Shih, D.M., et al., *Flavin containing monooxygenase 3 exerts broad effects on glucose and lipid metabolism and atherosclerosis [S].* Journal of lipid research, 2015. 56(1): p. 22-37.

75. Warrier, M., et al., *The TMAO-generating enzyme flavin monooxygenase 3 is a central regulator of cholesterol balance.* Cell reports, 2015. 10(3): p. 326-338.

76. Craciun, S., J.A. Marks, and E.P. Balskus, *Characterization of choline trimethylamine-lyase expands the chemistry of glycyl radical enzymes.* ACS chemical biology, 2014. 9(7): p. 1408-1413.

77. Owolabi, I.O., et al., *Gut microbiota metabolism of functional carbohydrates and phenolic compounds from soaked and germinated purple rice.* Journal of Functional Foods, 2020. 66: p. 103787.

78. Lam, K.-L. and P.C.-K. Cheung, *Carbohydrate-based prebiotics in targeted modulation of gut microbiome.* Journal of agricultural and food chemistry, 2019. 67(45): p. 12335-12340.

79. Pratesi, D., et al., *Glycomimetic based approach toward selective carbonic anhydrase inhibitors.* ACS Medicinal Chemistry Letters, 2020. 11(5): p. 727-731.

80. Chunkhare, M., et al., *Paper Code: P-53 Designing and developing a computerized biomedical equipment's inventory management system.* RECENT ADVANCES IN SCIENCE AND THE CORONAVIRUS PA: p. 91.

81. Asif, M., *Chemical properties and pharmacological potential of various benzoxazole derivatives.* Annals of Pharma Research. ISSN, 2015: p. 2347-1956.

82. Beale, J.M. and J.H. Block, *Organic medicinal and pharmaceutical chemistry*. 2011.

83. Martin, Y.C., *Modern Drug Research: Path to Better and Safer Drugs*. Vol. 12. 1989: Informa Health Care.

84. Kerru, N., et al., *A review on recent advances in nitrogen-containing molecules and their biological applications.* Molecules, 2020. 25(8): p. 1909.

85. Glamočlija, U., et al., *Synthesis, biological evaluation and docking studies of benzoxazoles derived from thymoquinone.* Molecules, 2018. 23(12): p. 3297.

86. Voss, M.H., et al., *Phase 1 study of mTORC1/2 inhibitor sapanisertib (TAK-228) in advanced solid tumours, with an expansion phase in renal, endometrial or bladder cancer.* British journal of cancer, 2020. 123(11): p. 1590-1598.

87. Thakur, A., et al., *Oxazole and isoxazole: From one-pot synthesis to medical applications.* Tetrahedron, 2022. 119: p. 132813.

88. Imramovsky, A., et al., *Synthesis and antimycobacterial and photosynthesis-inhibiting evaluation of 2-[(E)-2-substituted-ethenyl]-1, 3-benzoxazoles.* The Scientific World Journal, 2014. 2014.

89. Erol, M., et al., *Design, synthesis, molecular docking, density functional theory and antimicrobial studies of some novel benzoxazole derivatives as structural bioisosteres of nucleotides.* Journal of Biomolecular Structure and Dynamics, 2021. 39(9): p. 3080-3091.

90. Sattar, R., et al., *Synthetic transformations and biological screening of benzoxazole derivatives: A review.* Journal of Heterocyclic Chemistry, 2020. 57(5): p. 2079-2107.

91. Rajasekhar, S., B. Maiti, and K. Chanda, *A decade update on benzoxazoles, a privileged scaffold in synthetic organic chemistry.* Synlett, 2017. 28(05): p. 521-541.

92. Filippi, L., et al., *Theranostic approaches in nuclear medicine: Current status and future prospects.* Expert review of medical devices, 2020. 17(4): p. 331-343.

93. Franco Machado, J., et al., *Less exploited GPCRs in precision medicine: targets for molecular imaging and theranostics.* Molecules, 2018. 24(1): p. 49.

94. Abdelgawad MA, B.A., Omar HA, Hegazy L, Rateb ME, *Anti-Breast Cancer Activity, and Molecular Modeling of Some Benzothiazole*. 2013.

95. Bray, F., et al., *Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.* CA: a cancer journal for clinicians, 2018. 68(6): p. 394-424.

96. Vora, C. and S. Gupta, *Targeted therapy in cervical cancer.* ESMO open, 2018. 3: p. e000462.

97. Songock, W.K., S.-m. Kim, and J.M. Bodily, *The human papillomavirus E7 oncoprotein as a regulator of transcription.* Virus research, 2017. 231: p. 56-75.

98. Zhao, J., et al., *HPV infection associated DNA damage correlated with cervical precancerous lesions and cancer in the highest area of cervical cancer mortality, Longnan, China.* Cancer Management and Research, 2019: p. 7197-7210.

99. Brant, A.C., et al., *Characterization of HPV integration, viral gene expression and E6E7 alternative transcripts by RNA-Seq: A descriptive study in invasive cervical cancer.* Genomics, 2019. 111(6): p. 1853-1861.

100. Liu, X., et al., *Structure of the human Papillomavirus E7 oncoprotein and its mechanism for inactivation of the retinoblastoma tumor suppressor*. Journal of Biological Chemistry, 2006. 281(1): p. 578-586.

101. Duensing, S. and K. Münger, *Mechanisms of genomic instability in human cancer: insights from studies with human papillomavirus oncoproteins.* International Journal of Cancer, 2004. 109(2): p. 157-162.

102. Pang, B., et al., *Upregulation of DLEU1 expression by epigenetic modification promotes tumorigenesis in human cancer*. Journal of Cellular Physiology, 2019. 234(10): p. 17420-17432.

103. Gupta, S.M. and J. Mania-Pramanik, *RETRACTED ARTICLE: Molecular mechanisms in progression of HPV-associated cervical carcinogenesis.* Journal of biomedical science, 2019. 26: p. 1-19.

104. Jiménez-Wences, H., O. Peralta-Zaragoza, and G. Fernández-Tilapa, *Human papilloma virus, DNA methylation and microRNA expression in cervical cancer*. Oncology reports, 2014. 31(6): p. 2467-2476.

105. Clifford, G.M., et al., *Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis.* British journal of cancer, 2003. 88(1): p. 63-73.

106. McCabe, M.T., J.N. Davis, and M.L. Day, *Regulation of DNA methyltransferase 1 by the pRb/E2F1 pathway*. Cancer research, 2005. 65(9): p. 3624-3632.

107. Yang, Y., et al., *Emerging targets and potential therapeutic agents in non-alcoholic fatty liver disease treatment.* European Journal of Medicinal Chemistry, 2020. 197: p. 112311.

108. Hermann, B., K. Matthias, and P.C. Peter, *Colorectal cancer*. lancet, 2014. 383(9927): p. 1490-1502.

109. El-Deiry, W.S. *Regulation ofp53downstream genes*. in *Seminars in cancer biology*. 1998. Elsevier.

110. Ryu, H., et al., *The small molecule AU14022 promotes colorectal cancer cell death via p53-mediated G2/M-phase arrest and mitochondria-mediated apoptosis.* Journal of cellular physiology, 2018. 233(6): p. 4666-4676.

111. Thanasoula, M., et al., *p53 prevents entry into mitosis with uncapped telomeres.* Current biology, 2010. 20(6): p. 521-526.

112. Toshiyuki, M. and J.C. Reed, *Tumor suppressor p53 is a direct transcriptional activator of the human bax gene.* Cell, 1995. 80(2): p. 293-299.

113. Nigg, E.A., *Mitotic kinases as regulators of cell division and its checkpoints.* Nature reviews Molecular cell biology, 2001. 2(1): p. 21-32.

114. Jaradat, N., M. Hawash, and G. Dass, *Phytochemical analysis, in-vitro anti-proliferative, anti-oxidant, anti-diabetic, and anti-obesity activities of Rumex rothschildianus Aarons. extracts.* BMC Complementary Medicine and Therapies, 2021. 21(1): p. 1-11.

115. Nacak, S., et al., *Synthesis and antimicrobial activity of some new mannich bases of 7-acyl-5-chloro-2-oxo-3H-benzoxazole derivatives.* Turkish J. Pharm. Sci, 2005. 2(1): p. 25-33.

Appendices

Appendix A

Figures

Figure 11

The relationship between cell viability% and the concentration in micro Molar of BNZs compounds after 72hr

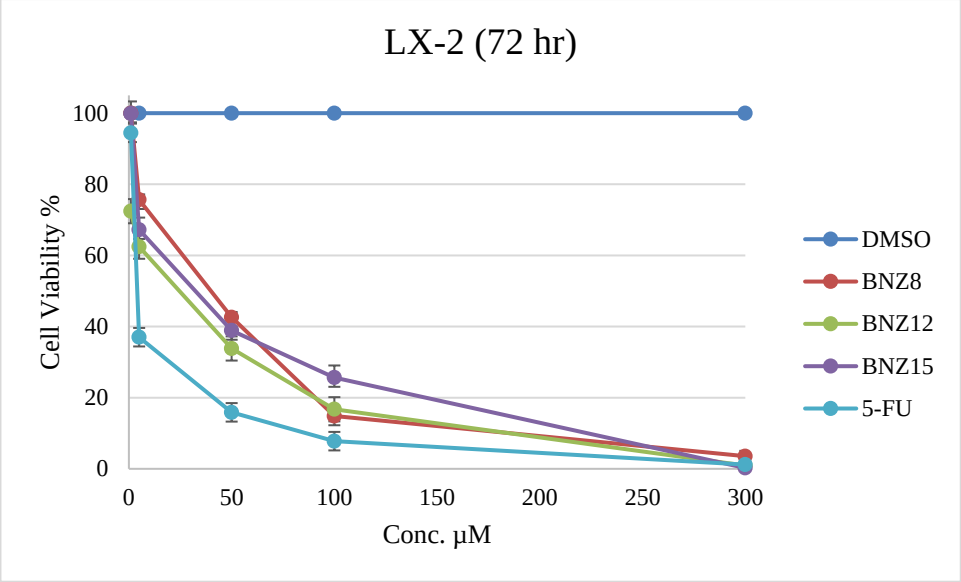


Figure 12

Benzoxazole compound

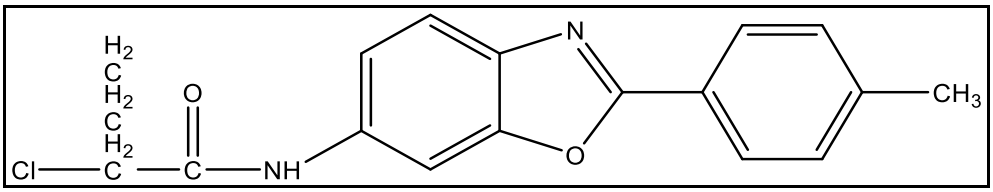


Figure 13

Triazole-benzoxazole derivative

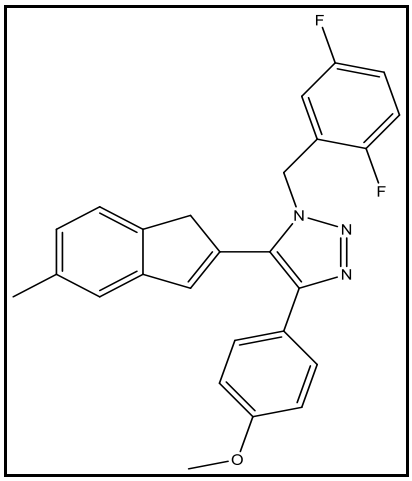


Figure 14

5-Ethylsulfonyl-2-(p-nitrophenyl) benzoxazole

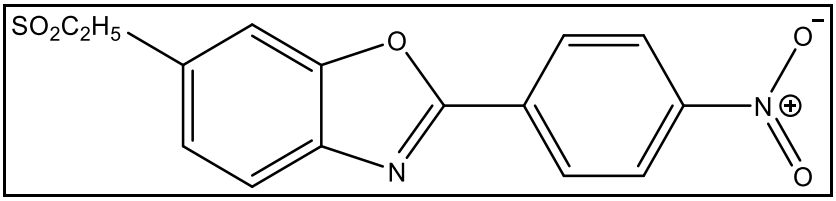


Figure 15

Benzoxazole-fused triazole compounds

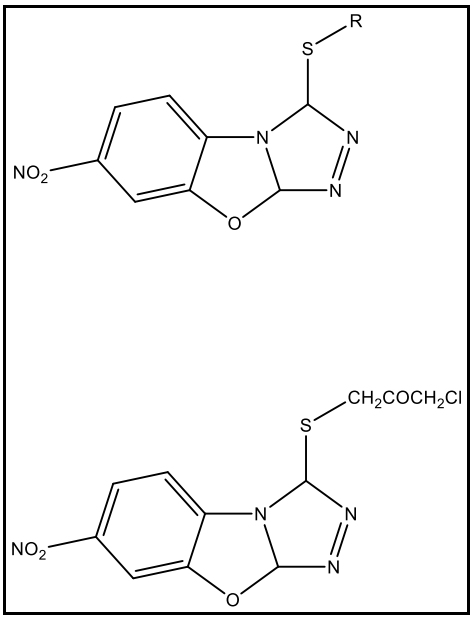


Figure 16

2-(2-aminobenzo[d]thiazol-6-yl)benzo[d]oxazol-5-amine(H1)

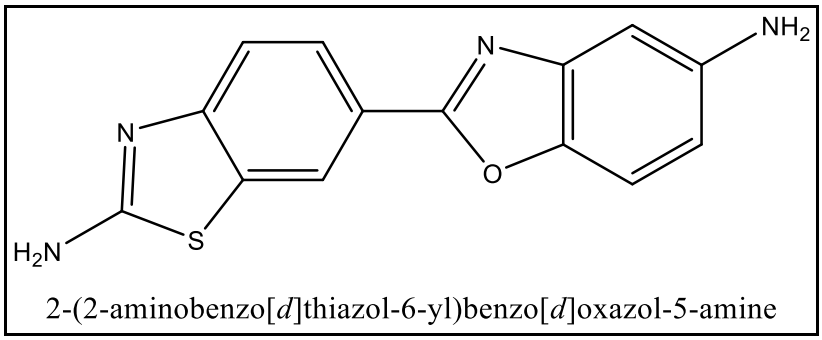


Figure 17

Actual and reported nocarbenoxazole G

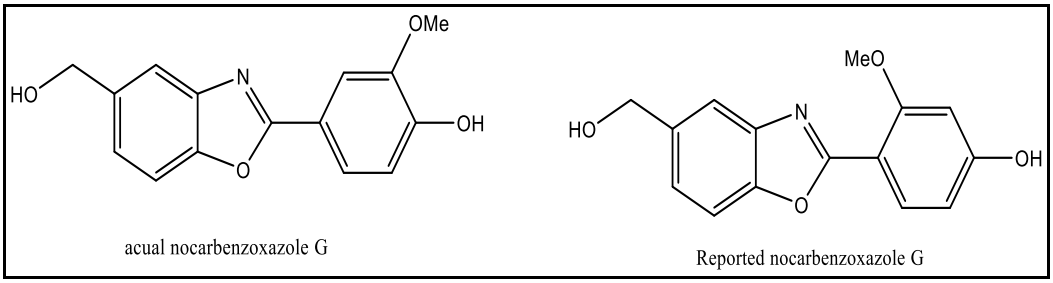


Figure 18

Coumarin structure

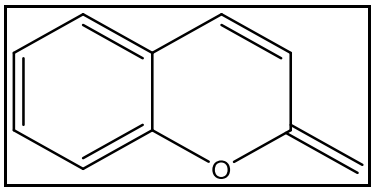


Figure 19

Benoxaprofen

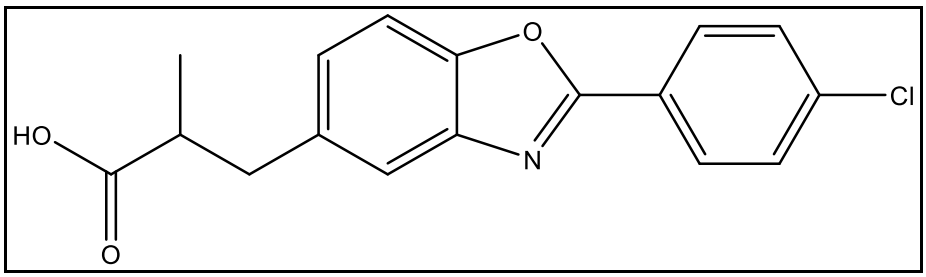


Figure 20

2-oxo-3H-benzoxazole

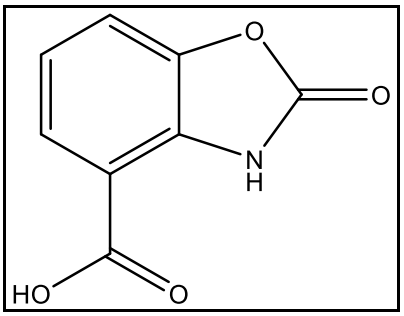
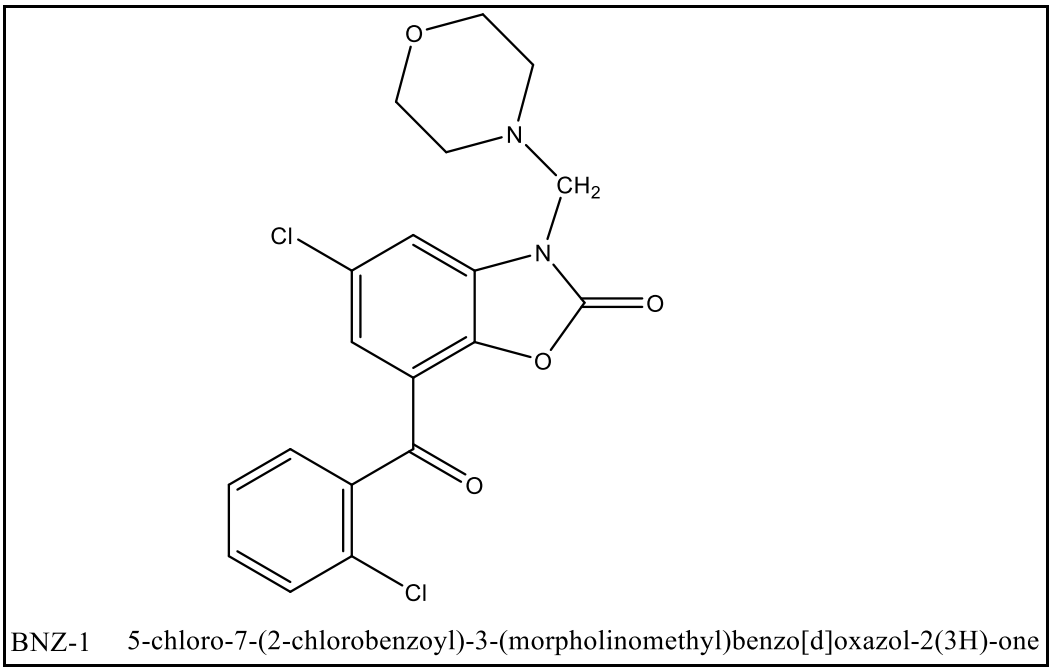
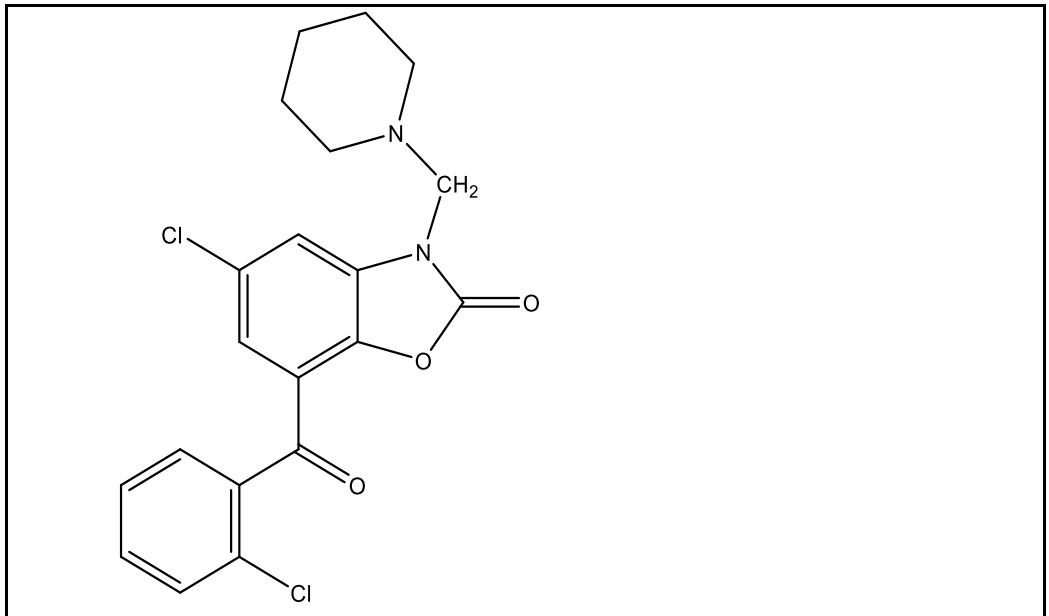


Figure 21

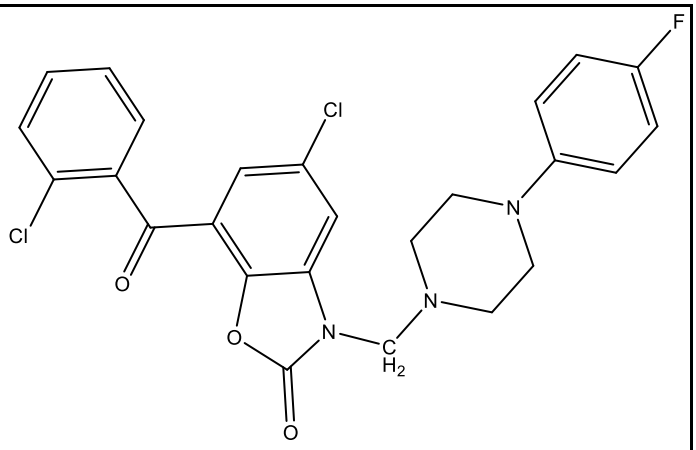
BNZ 1-16



BNZ-1 5-chloro-7-(2-chlorobenzoyl)-3-(morpholinomethyl)benzo[d]oxazol-2(3H)-one

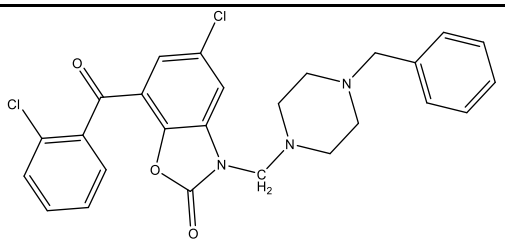


BNZ-2 5-chloro-7-(2-chlorobenzoyl)-3-(piperidin-1-ylmethyl)benzo[*d*]oxazol-2(3*H*)-one

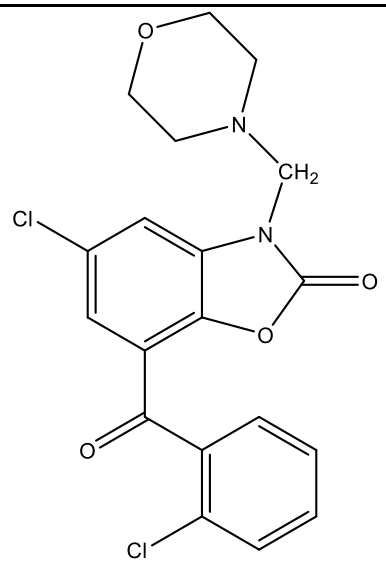


BNZ-4

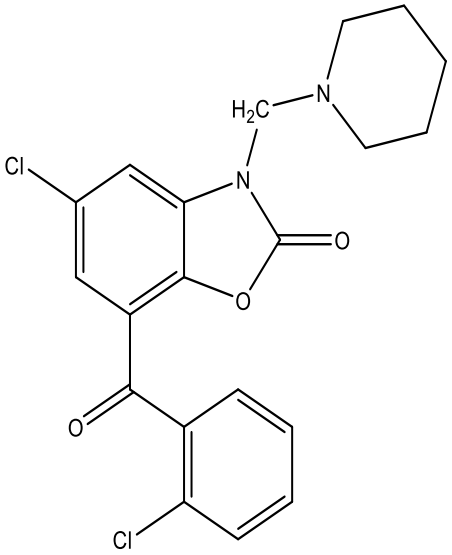
5-chloro-7-(2-chlorobenzoyl)-3-((4-(4-fluorophenyl)piperazin-1-yl)methyl)benzo[*d*]oxazol-2(3*H*)-one



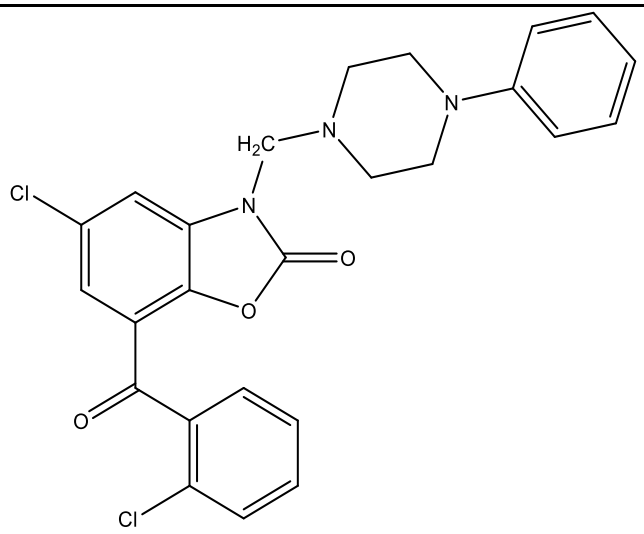
BNZ-6 3-((4-benzylpiperazin-1-yl)methyl)-5-chloro-7-(2-chlorobenzoyl)benzo[*d*]oxazol-2(3*H*)-one



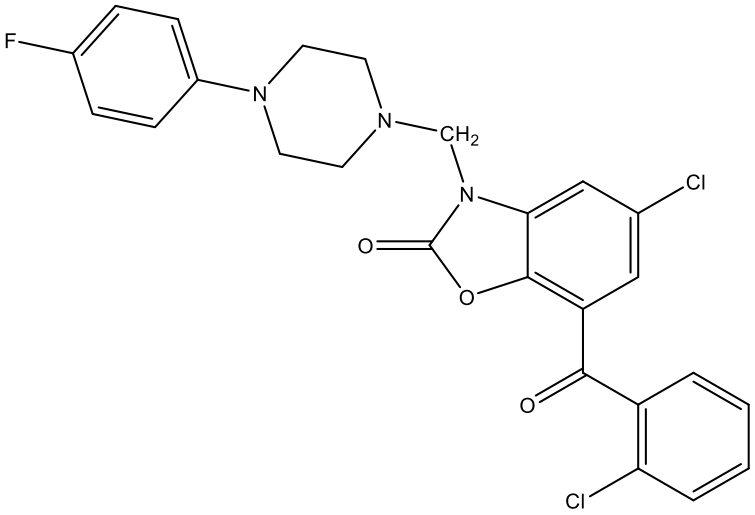
BNZ-7 5-chloro-7-(2-chlorobenzoyl)-3-(morpholinomethyl)benzo[*d*]oxazol-2(3*H*)-one



BNZ-8 5-chloro-7-(2-chlorobenzoyl)-3-(piperidin-1-ylmethyl)benzo[*d*]oxazol-2(3*H*)-one

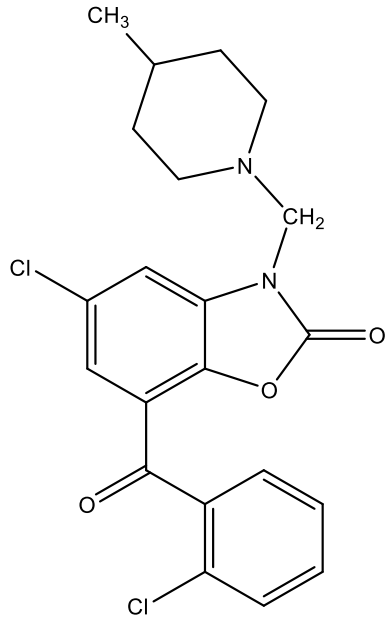


BNZ-9 5-chloro-7-(2-chlorobenzoyl)-3-((4-phenylpiperazin-1-yl)methyl)benzo[*d*]oxazol-2(3*H*)-one



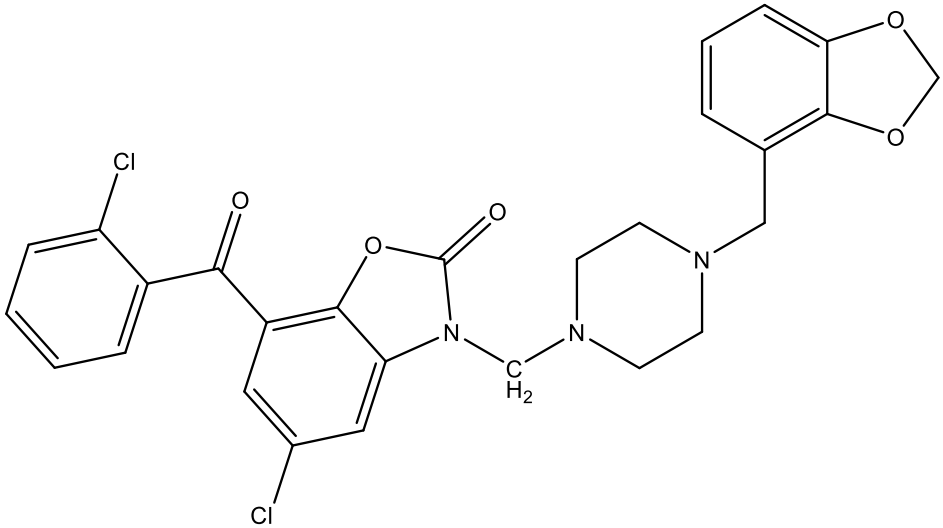
BNZ-10

5-chloro-7-(2-chlorobenzoyl)-3-((4-(4-fluorophenyl)piperazin-1-yl)methyl)benzo[*d*]oxazol-2(3*H*)-one



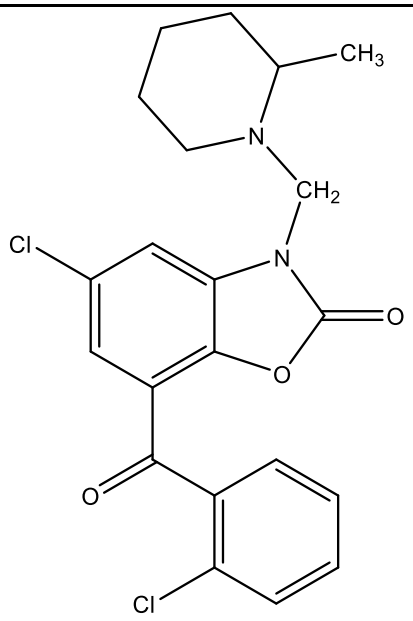
BNZ-13

5-chloro-7-(2-chlorobenzoyl)-3-((4-methylpiperidin-1-yl)methyl)benzo[*d*]oxazol-2(3*H*)-one



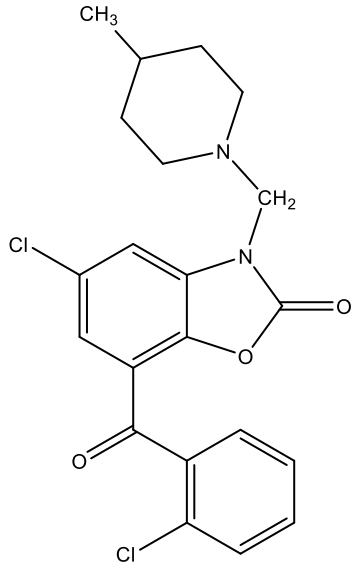
3-((4-(benzo[*d*][1,3]dioxol-4-ylmethyl)piperazin-1-yl)methyl)-5-chloro-7-(2-chlorobenzoyl)benzo[*d*]oxazol-2(3*H*)-one

BNZ-12



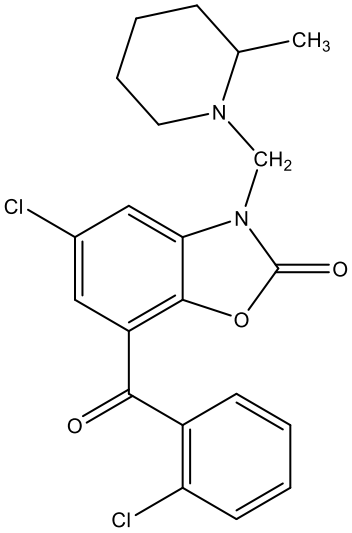
BNZ-14

5-chloro-7-(2-chlorobenzoyl)-3-((2-methylpiperidin-1-yl)methyl)benzo[*d*]oxazol-2(3*H*)-one



5-chloro-7-(2-chlorobenzoyl)-3-((4-methylpiperidin-1-yl)methyl)benzo[*d*]oxazol-2(3*H*)-one

BNZ-15



5-chloro-7-(2-chlorobenzoyl)-3-((2-methylpiperidin-1-yl)methyl)benzo[*d*]oxazol-2(3*H*)-one

BNZ-16

Appendix B

Tables

Table 2

SDs for Caco2

		Statistics						
		Negative Control	uM300	uM100	uM50	uM10	uM1	Blank
N	Valid	6	6	6	6	6	6	6
	Missing	0	0	0	0	0	0	0
Mean		1.08050	0.11400	0.13283	0.71583	1.02567	1.05217	0.11350
Std. Deviation		0.024648	0.005586	0.010496	0.045035	0.051161	0.027426	0.000548
Minimum		1.058	0.109	0.124	0.648	0.954	1.013	0.113
Maximum		1.103	0.121	0.150	0.786	1.091	1.079	0.114

Table 3

Absorbance Measurements for Various Compounds Using CaCO-2 Cells

Type of cell: CaCO-2							
name of compound :BNZ-1	negative control	300µM	100µM	50µM	10µM	1µM	blank
abs1	1.103	0.154	0.606	0.975	0.934	1.072	0.113
abs2	1.058	0.14	0.673	0.978	1.01	1.022	0.114
name of compound :BNZ-2	negative control	300µM	100µM	50µM	10µM	1µM	blank
abs1	1.103	0.122	0.228	0.895	1.004	1.008	0.113
abs2	1.058	0.136	0.234	0.974	1.053	1.033	0.114
name of compound :BNZ-4	negative control	300µM	100µM	50µM	10µM	1µM	blank
abs1	1.103	0.121	0.125	0.786	1.041	1.034	0.113
abs2	1.058	0.121	0.126	0.704	1.013	1.079	0.114
name of compound :BNZ-6	negative control	300µM	100µM	50µM	10µM	1µM	blank
abs1	1.103	0.176	1.001	1.057	1.018	1.1	0.113
abs2	1.058	0.191	1.047	1.014	1.078	1.077	0.114
name of compound :BNZ-7	negative control	300µM	100µM	50µM	10µM	1µM	blank

abs1	1.103	0.109	0.131	0.648	1.068	1.013	0.113
abs2	1.058	0.112	0.15	0.708	1.091	1.069	0.114
name of compound :BNZ-8	negative control	300μM	100μM	50μM	10μM	1μM	blank
abs1	1.103	0.108	0.151	0.843	1.033	1.028	0.113
abs2	1.058	0.111	0.164	0.97	1.043	1.065	0.114
name of compound :BNZ-9	negative control	300μM	100μM	50μM	10μM	1μM	blank
abs1	1.103	0.120	0.142	0.854	1.06	1.068	0.113
abs2	1.058	0.116	0.17	0.96	1.069	1.08	0.114
name of compound :BNZ-10	negative control	300μM	100μM	50μM	10μM	1μM	blank
abs1	1.103	0.109	0.124	0.736	0.954	1.079	0.113
abs2	1.058	0.112	0.141	0.713	0.987	1.039	0.114
name of compound :BNZ-12	negative control	300μM	100μM	50μM	10μM	1μM	blank
abs1	1.103	0.112	0.41	0.823	0.897	0.963	0.113
abs2	1.058	0.112	0.419	0.783	0.885	0.944	0.114
name of compound :BNZ-13	negative control	300μM	100μM	50μM	10μM	1μM	blank
abs1	1.103	0.191	0.453	0.936	0.985	1.019	0.113
abs2	1.058	0.194	0.477	0.953	1.006	1.084	0.114
name of compound :BNZ-14	negative control	300μM	100μM	50μM	10μM	1μM	blank
abs1	1.103	0.134	0.773	0.986	1.007	1.071	0.113
abs2	1.058	0.127	0.76	1.004	0.968	1.058	0.114
name of compound :BNZ-15	negative control	300μM	100μM	50μM	10μM	1μM	blank
abs1	1.103	0.110	0.499	0.907	0.91	0.97	0.113
abs2	1.058	0.114	0.433	0.919	0.984	0.961	0.114
name of compound :BNZ-16	negative control	300μM	100μM	50μM	10μM	1μM	blank
abs1	1.103	0.118	0.254	0.802	0.986	1.075	0.113
abs2	1.058	0.114	0.288	0.894	0.971	1.027	0.114

جـامعـــة النجاح الوطنية

كليـــة الدراســـات العليـــا

التقييم البيولوجي لمشتقات 2-أوكسو بينزوكسازول

إعداد

حنين مروان ابو كتب

إشراف

د. نضال جرادات

محمد هواش

قدمت هذه الرسالة استكمالا لمتطلبات الحصول على درجة الماجستير في العلوم الصيدلانية، من كلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس- فلسطين.

2023

التقييم البيولوجي لمشتقات 2-أوكسو بينزوكسازول

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الملخص

تعتبر مشتقات البنزوكسازول من الكتل الأساسية الضرورية للأدوية المبتكرة بفضل نطاقها الواسع من الأنشطة البيولوجية في الكيمياء الدوائية، خاصة تأثيراتها الدوائية مثل الألم القاص، ومكافحة البكتيريا، ومكافحة الفطريات، ومكافحة الالتهابات، ومكافحة السرطان. يؤكد هذا العمل على أهمية مشتقات البنزوكسازول في تطوير الأدوية، حيث يسلط الضوء أيضًا على إمكانياتها كأهداف علاجية بتنوع في التأثيرات الدوائية والمرونة الهيكلية.

تقوم هذه الدراسة بفحص نواة الأوكسازول 1،3، والتي تعتبر جزيء فعّال للغاية بخصائص مضادة للبكتيريا ومضادة للسرطان ومخففة للألم ومضادة للالتهابات. يتم إنتاج هذه المواد بشكل طبيعي وصناعي من قبل العديد من الكائنات، بما في ذلك البكتيريا والكائنات البحرية. يمكن استخدام المركبات الصيدلانية التابعة لعائلة الأوكسازول 1،3 لتخليق مجموعة واسعة من الجزيئات ذات التطبيقات العلاجية المتنوعة، مثل التأثيرات المضادة للفيروسات والمضادة للسرطان. يتم فحص إمكانية مشتقات البنزوكسازول لتثبيط استقلاب الكولين اللاهوائي وتأثيراتها المحتملة على السرطان في هذا العمل. تظهر بعض المركبات القائمة على مشتقات البنزوكسازول فاعلية مكثفة خاصة تجاه خطوط خلايا سرطانية محددة، مما يشير إلى إمكانية فعالة في وقف انتشار خلايا السرطان. تُشيد مشتقات البنزوكسازول بإمكانياتها الكبيرة في البحث الصيدلاني، ويُشجع على إجراء المزيد من البحث في هيكل مشتقات البنزوكسازول وتفعيلها للعثور على جزيئات أكثر قوة وانتقائية مع نشاط محسن وسمية أقل. يتم تقديم نتائج الدراسة حول ستة عشر مركبًا اصطناعيًا تم اختبارها ضد سبعة خطوط خلايا سرطانية في المقالة. تُظهر المركبات2-BNZ ، 4-BNZ، 7-BNZ، 9-BNZ، و 10-BNZ فاعلية كوكلاء مضادين للسرطان. يُحدد تحليل الهيكل باستخدام دراسة العلاقة بين الهيكل والنشاط (SAR) العناصر الهيكلية الرئيسية المسؤولة عن أفعالها ضد خلايا مختلفة.

يتميز BNZ−10 بقيمة IC_{50} أقل من أدوية السرطان المعروفة، مما يشير إلى إمكانيته كعلاج فعّال ضد أنواع معينة من خلايا السرطان. مع ذلك، يجب أن يُذكر أن دوكسوروبيسين (DOX) لا يزال لديه قيم IC_{50} أقل بكثير من معظم مركبات BNZ−1−16 وهو ما يجعله علاجًا مضادًا للسرطان قويًا. تُختتم الدراسة بتسليط الضوء على الوعد الكبير لمشتقات البنزوكسازول في تطوير الأدوية، خاصة في معالجة السرطان، وأهمية السمات الهيكلية الخاصة في التحكم في نشاطها البيولوجي. يتطلب البحث المستقبلي عن استراتيجيات علاجية جديدة للأورام المرتبطة بخلية hepG2 مزيدًا من البحث حول التفاعلات والعمليات الجزيئية، خاصة تلك التي تؤثر على خلايا hepG2. تُسهم الأبحاث في تقدم البحث عن الأدوية الجديدة وتساعد في تطوير عقاقير مضادة للسرطان بشكل منطقي.

الكلمات المفتاحية: مشتقات البنزوكسازول؛ فعالية مضادة للسرطان؛ العلاقة بين الهيكل والنشاط (SAR)؛ قيم IC_{50}