OPEN ACCESS

Greenfort International Journal of Applied Medical Science
Abbreviated Key Title: Grn Int J Apl Med Sci
ISSN 3048-6904(P) | ISSN 2584-2420(O)
Journal homepage: https://gijams.in

Research Article DOI: 10.62046/gijams.2026.v04i06.006

Synthesis of a Novel Benzoxazole Compound and Its Effect on Breast Cancer Cell Lines

Funda KOSOVA[1], Özlem TEMİZ-ARPACI[2], Feyzan ÖZDAL KURT[3]

[1]Celal Bayar University, School of Health Services, Department of Medical Biochemistry, Manisa, Turkey. https://orcid.org/0000-0001-8070-5067
[2]Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, 06100, Tandoğan, Ankara, Turkey
[3]Celal Bayar University, Faculty of Arts and Sciences, Department of Biology, Manisa, Turkey

*Corresponding Author: Funda KOSOVA Email: fundakosova@gmail.com

Received: 13.07.2026 | Revised: 29.08.2026 | **Accepted:** 15.10.2026 | **Published:** 19.11.2026

Abstract: Background/Aim: Cancer remains one of the leading causes of mortality worldwide. Although significant advancements have been achieved in cancer diagnosis and treatment over the past decade, the prognosis for certain cancer types remains poor. Apoptosis and angiogenesis play critical roles in cell growth and differentiation, as well as tumor dissemination and metastasis. Therefore, this study aimed to investigate the effects of a newly synthesized benzoxazole compound on the levels of apoptotic markers—including NF-κB, Bcl-2, cytochrome c, caspase-9, and APAF-1—in breast cancer cell cultures. **Materials and Methods:** The newly synthesized benzoxazole compound was applied to breast cancer cell lines (MDA-MB, MCF-7), and its cytotoxicity was quantitatively evaluated using the MTT assay. Subsequently, the effects of the compound exhibiting the most favorable bioactivity were analyzed on different breast cancer cell lines by determining the gene expression levels of NF-κB and apoptosis-related proteins (APAF-1, cytochrome c, caspase-3, and Bcl-2) via Quantitative Real-Time PCR (RT-qPCR). **Results:** Upon treatment of the MDA cancer cell line with the benzoxazole compound, NF-κB, caspase, APAF-1, and cytochrome c levels were undetectable in both the control and treatment groups. However, a statistically significant increase in Bcl-2 expression was observed in the treated MDA cells compared to the control group. In the MCF-7 cancer cell line, treatment with the benzoxazole compound resulted in elevated levels of cytochrome c, Bcl-2, and NF-κB compared to controls. Furthermore, APAF-1 expression was reduced, while caspase levels remained comparable to the control group in MCF-7 cells. **Conclusion:** Our findings suggest that the novel benzoxazole compound exhibits higher efficacy in the MCF-7 breast cancer cell line, demonstrating a tendency to induce apoptosis. Consequently, we propose that this compound holds potential for inhibiting tumor growth in cancer therapeutics. Further validation of these findings in animal tumor models will be essential.

Keywords: Benzoxazole compounds, NF-κB, APAF-1, cytochrome c, caspase-3, Bcl-2.

Citation: Funda KOSOVA *et al.* Synthesis of a Novel Benzoxazole Compound and Its Effect on Breast Cancer Cell Lines. Grn Int J Apl Med Sci, 2026 Nov-Dec 4(6):566-571.

INTRODUCTİON

Cancer and apoptosis represent opposing regulatory mechanisms within cell population dynamics [1]. Cancer ranks among the primary causes of death globally. Despite major breakthroughs in diagnostic and therapeutic strategies over the last decade, the clinical prognosis for several malignancies remains dismal. Apoptosis and angiogenesis serve as fundamental drivers not only for cell proliferation and differentiation but also for tumor invasion and metastasis. Nuclear Factor kappa B (NF-κB) has been shown to play a pivotal role in regulating both apoptotic and angiogenic cascades.

In recent years, benzoxazoles and their heterocyclic ring analogs—such as benzimidazoles, benzothiazoles, and benzoxazines—have demonstrated diverse biological activities, including antibacterial, antifungal [2,3], antiviral [4], topoisomerase inhibitory, and antitumor properties [5]. Notably, novel series of benzothiazoles have been reported to exert potent inhibitory activity against human breast cancer cell lines both *in vitro* and *in vivo* [5].

Previous studies have indicated that specific heterocyclic benzoxazole derivatives possess robust anticancer properties. Furthermore, among the benzoxazole derivatives previously synthesized by our chemistry research group [6], 5-ethylsulfonyl-2-(p-nitrophenyl)benzoxazole was identified as a compound of notable interest due to its striking antitumor efficacy [7].

Cytochrome c represents one of the key mediator proteins involved in intrinsic apoptotic pathways. Upon

©The Author(s): This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0) that ensures authors retain full ownership of their published work. This license permits any non-commercial use, sharing, adaptation, distribution, and reproduction in any medium or format, as long as appropriate credit is given to the original authors and the source.

release from the mitochondria into the cytoplasm, cytochrome c forms the apoptosome complex together with APAF-1 and procaspase-9. This complex subsequently activates caspase-9, which sequentially triggers caspase-3 and caspase-7 to initiate programmed cell death.

Conversely, the anti-apoptotic protein Bcl-2 exerts its protective function by preventing mitochondrial cytochrome c release. A reduction in Bcl-2 expression accelerates the apoptotic cascade, whereas its upregulation suppresses cell death. In addition, NF-κB acts as a crucial transcription factor regulating angiogenesis and apoptotic resistance in carcinogenesis.

Accordingly, the present study aimed to evaluate the impact of a novel benzoxazole derivative on the expression profiles of key apoptotic markers—specifically NF-κB, Bcl-2, cytochrome c, caspase-9, and APAF-1—in breast cancer cell culture models.

MATERİALS AND METHODS

Synthesis of the Benzoxazole Compound

All chemicals and solvents were purchased from Sigma-Aldrich Co. (Taufkirchen, Munich, Germany) and Fisher Scientific (Pittsburgh, PA, USA) and used without further purification. Thin-layer chromatography (TLC) was performed on silica gel HF_{254} plates (0.3 mm thickness) using chloroform as the mobile phase. Melting points were determined using a Stuart Scientific SMP 1 melting point apparatus (Bibby Scientific Limited, Stone, Staffordshire, UK) and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian Mercury 400 MHz NMR spectrometer (Palo Alto, CA, USA) with tetramethylsilane (TMS) as the internal standard. Mass spectra were acquired via electrospray ionization in positive mode [ESI(+)] on a Waters ZQ Micromass LC-MS spectrometer (Milford, MA, USA). Elemental analysis was conducted using a LECO 932 CHNS elemental analyzer (St. Joseph, MI, USA), and experimental values were within acceptable limits of the calculated theoretical values.

Synthetic procedures were carried out by researchers at Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry [1,2]. Briefly, 0.02 mol of 2,4-diaminophenol dihydrochloride ($2,4\text{-diaminophenol} \cdot 2HCl$) and 0.02 mol of p-methylbenzoic acid were mixed and heated in 25 g of polyphosphoric acid (PPA) at 180--200 °C for approximately 1 h to yield 5-amino-2-(p-methylphenyl)benzoxazole . The resulting mixture was poured onto crushed ice, and the solution was neutralized with a 10% aqueous sodium hydroxide (NaOH) solution. The observed precipitate was filtered and recrystallized from ethanol.

Subsequently, 3-chlorobutyryl chloride (0.02 mol) was added dropwise over 1 h into an ice-cooled, stirred suspension containing 5-amino-2-(p-methylphenyl)benzoxazole (0.02 mol), sodium bicarbonate ($NaHCO_3$, 0.02 mol), diethyl ether (40 mL), and water (20 mL). The reaction mixture was stirred overnight at room temperature. The formed precipitate was isolated by filtration, washed with distilled water, and dissolved in ethanol. Recrystallization was induced by adding distilled water, and drying the collected residue at ambient temperature yielded the crude target compound. Finally, the compound was obtained as a pure final product. The chemical structure was confirmed by spectral analysis; ^{1}H-NMR, mass spectra, and elemental analysis data were fully consistent with the proposed structure. Physical and spectroscopic characteristics of the synthesized compound are detailed below:

Cell Culture

Cell culture experiments were performed at Celal Bayar University, Faculty of Medicine, Department of Histology and Embryology. Human breast cancer cell lines (MCF-7 and MDA-MB) were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). Cells were maintained in Dulbecco's Modified Eagle Medium/Nutrient Mixture F-12 (DMEM/F-12) supplemented with fetal bovine serum (FBS), L-glutamine, and 1% penicillin-streptomycin in a humidified incubator containing 5% CO_2 at 37 °C. Cellular morphology was monitored and photographed every other day using an inverted phase-contrast microscope (CK40-F200; Olympus, Tokyo, Japan). All experimental setups were performed in triplicate ($n = 3$).

Administration of the Benzoxazole Compound

Stock solutions of the compound were prepared and diluted in dimethyl sulfoxide (DMSO) for experimental applications. In all heterocyclic compound treatment groups, a vehicle control group received an equivalent concentration of DMSO (final concentration $\leq$ 0.1% v/v) to rule out solvent toxicity [3].

Gene Expression Analysis of Apoptotic Proteins via Real-Time PCR

RNA Isolation Protocol

Total RNA extraction was performed using the High Pure RNA Isolation Kit according to the manufacturer's instructions. Prior to first-time usage, working reagents with yellow labels were prepared. Lyophilized DNase I was dissolved in Elution Buffer (colorless cap) and stored in 1.5 mL Eppendorf tubes as aliquots at −20 °C (stable for up to 12 months). Wash Buffer I and Wash Buffer II were prepared by adding absolute ethanol as indicated.

For RNA isolation, Red Blood Cell Lysis Buffer was added to Eppendorf tubes containing blood or cell

Copyright: © Author(s), 2026. Published by Greenfort International Journal of Applied Medical Science | This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC 4.0) License.

samples, vortexed on an automated shaker, and centrifuged. The supernatant was discarded, Red Blood Cell Lysis Buffer was added once more, centrifuged, and the cell pellet was washed with phosphate-buffered saline (PBS). Subsequently, Lysis/Binding Buffer (green cap) was added to lyse the cells, mixed thoroughly, and transferred onto filter spin columns followed by centrifugation.

For on-column genomic DNA digestion, a mixture of DNase Incubation Buffer (white cap) and DNase I enzyme was added to each column and incubated at room temperature (20--25 °C). The columns were sequentially washed with Wash Buffer I (black cap) and Wash Buffer II (blue cap), incubating for 15 s prior to centrifugation at $12{,}000 \times g$. Purified total RNA was eluted into sterile Eppendorf tubes and preserved at -80 °C.

The yield and purity of the isolated RNA were quantified spectrophotometrically by measuring light absorption at wavelengths of 260 nm and 280 nm (A_{260}/A_{280}). An A_{260}/A_{280} ratio of approximately 1.8--2.0 was considered indicative of pure, high-quality RNA. In addition to spectrophotometric analysis, RNA integrity was confirmed via agarose gel electrophoresis. To accurately measure mean mRNA expression levels, the starting input of total RNA was adjusted between 10 ng and 1μg per reaction, depending on the sample characteristics [4].

Complementary DNA (cDNA) Synthesis

Reverse transcription was performed using the Transcriptor First Strand cDNA Synthesis Kit. For each sample, total RNA, nuclease-free water, and random hexamer primers (Vial 6) were combined. When sufficient RNA yield was obtained, cDNA synthesis was performed in triplicate series per sample. Reaction tubes were placed in a thermal cycler, and RNA denaturation was carried out at 65 °C for 10 min prior to reverse transcription.

Real-Time Quantitative PCR (RT-qPCR)

Target gene expression levels were evaluated by reacting the synthesized cDNA with specific primers and probes using a LightCycler® 480 system. Each reaction mixture was prepared to a final volume of $20\,\mu$L containing PCR-Grade Water, LightCycler® 480 Probes Master Mix, specific primer/probe sets, and template cDNA. After careful pipetting, $20\,\mu$L aliquots of the reaction mixture were distributed into individual wells of a 96-well optical plate. The plate was placed into the LightCycler® 480 Instrument, and standard thermal cycling conditions were executed [5].

Statistical Analysis

Statistical analysis was conducted using SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA). Differences between experimental groups were analyzed using the non-parametric Mann-Whitney U test. A p-value < 0.05 was considered statistically significant.

RESULTS

Quantitative Real-Time PCR (RT-qPCR) Analysis of Apoptotic Target Genes

The threshold cycle (C_T) values representing the gene expression levels of target apoptotic markers (NFKB-1, CASPASE-9, BCL-2, APAF-1, and CYCS) normalized against the reference housekeeping gene (β-actin / ACTB) in MDA-MB and MCF-7 human breast cancer cell lines are presented in Table 1.

Table 1. Real-time PCR cycle threshold (C_T) values for target genes in MDA-MB and MCF-7 breast cancer cell lines

Cell Line / Group	Target Gene	Control Group (C_T)	Treatment Group (P/22-X1) (C_T)
Group 1: MDA-MB	ACTB	37.05 ± 0.12	37.15 ± 0.15
	NFKB-1	Undetected	Undetected
	CASPASE-9	Undetected	Undetected
	BCL-2	27.82 ± 0.21	$31.76 \pm 0.18^{*}$
	APAF-1	Undetected	Undetected
	CYCS	Undetected	Undetected
Group 2: MCF-7	ACTB	29.57 ± 0.11	31.22 ± 0.14
	NFKB-1	33.78 ± 0.16	$35.31 \pm 0.19^{*}$
	CASPASE-9	36.64 ± 0.22	36.88 ± 0.20
	BCL-2	34.16 ± 0.14	$35.44 \pm 0.17^{*}$
	APAF-1	37.83 ± 0.25	$36.98 \pm 0.21^{*}$
	CYCS	33.69 ± 0.18	$35.65 \pm 0.23^{*}$

Values are expressed as mean $C_T \pm$ SD. $^{*}p < 0.05$compared to control (Mann-Whitney U test).

Synthesis, Cytotoxicity, and Bioactivity Assessment

In the present study, a novel benzoxazole derivative was successfully synthesized. The chemical purity of the compound was routinely verified by thin-layer chromatography (TLC) and melting point determination. The structural identification and molecular configuration

Copyright: © Author(s), 2026. Published by Greenfort International Journal of Applied Medical Science | This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC 4.0) License.

of the synthesized derivative were unambiguously confirmed by elemental analysis and mass spectrometry (ESI-MS).

To assess the biological profile, the cytotoxicity of the compound was quantitatively measured using the colorimetric MTT assay, which evaluates cellular mitochondrial activity and overall cell density. Derivatives exhibiting high anticancer potential in cell viability screening were prioritized for further mechanistic assays. Subsequently, the derivative exhibiting optimal bioactivity was evaluated via Real-Time Quantitative PCR (RT-qPCR) to measure its regulatory effects on the expression of key apoptosis-related genes—namely NF-κB (NFKB-1), APAF-1, cytochrome c (CYCS), caspase-3/9 (CASPASE-9), and Bcl-2 (BCL-2)—across distinct human breast cancer cell lines.

Effects of Benzoxazole Treatment on MDA-MB Cell Line

In the MDA-MB breast cancer cell line, mRNA expression of NFKB-1, CASPASE-9, APAF-1, and CYCS remained below detectable limits in both the untreated control and the compound-treated (MDA-MB-P/22-X1) groups. However, treatment with the novel benzoxazole compound resulted in a statistically significant increase in the C_T value for BCL-2 relative to the control (31.76 vs. 27.82, $p < 0.05$), indicating a altered transcription level compared to baseline control levels.

Effects of Benzoxazole Treatment on MCF-7 Cell Line

In the MCF-7 breast cancer cell line, exposure to the novel benzoxazole compound altered the expression profiles of several key apoptotic markers:

Cytochrome c (CYCS), BCL-2, and NF-κB (NFKB-1): Treatment led to higher C_T values compared to the control group (35.65 vs. 33.69 for CYCS; 35.44 vs. 34.16 for BCL-2; 35.31 vs. 33.78 for NFKB-1; $p < 0.05$).

APAF-1: A decrease in the C_T value was observed in the treated group compared to the control (36.98 vs. 37.83, $p < 0.05$), reflecting upregulation of APAF-1 gene expression.

Caspase-9 (CASPASE-9): Expression levels remained comparable between the treatment and control groups (36.88 vs. 36.64, $p > 0.05$).

DISCUSSİON

Cancer is a disease characterized by uncontrolled cellular proliferation that often leads to fatal outcomes and has shown an increasing incidence rate in recent years. Today, breast cancer represents the most frequently diagnosed malignancy among women and stands as the second leading cause of cancer-related mortality globally. Certain subtypes of breast cancer exhibit marked resistance to conventional pharmacotherapies. Excess endogenous estrogen is considered to play a critical role in the pathogenesis of this disease [8]. Elevated endogenous estrogen levels have been demonstrated to accelerate the progression of postmenopausal breast carcinoma [9,10].

In the present study, a novel benzoxazole derivative was synthesized, screened for cytotoxic activity using the MTT assay, and administered to different breast cancer cell lines exhibiting anticancer potential. We evaluated its effects on the gene expression profiles of NF-κB and key apoptosis-related proteins (APAF-1, cytochrome c, caspase-3, and Bcl-2) using Real-Time Quantitative PCR (RT-qPCR).

The antitumor properties of the benzoxazole ring system were first identified in 1958 [11]. Subsequent discoveries demonstrated that benzoxazole derivatives harboring a bis(2-hydroxyethyl)amino group, an *N*-((*p*-bis(2-hydroxyethyl)amino)phenyl)formimidoyl structure [12], or a methyl substituent [13] possess potent antitumor activity, prompting researchers to focus heavily on this heterocyclic scaffold. In another study, 7-substituted-2-phenylbenzoxazole and 4-substituted-2-phenylbenzoxazole derivatives along with benzimidazole analogs were synthesized, displaying cytotoxicity in mammalian cells accompanied by lower DNA-binding affinity in *Salmonella typhimurium* [14,15]. Sato *et al*. reported that the compound AJI9561, isolated from *Streptomyces* sp. AC9561, exhibits strong antitumor activity [16]. Furthermore, the novel compound UK-1 was shown to exert broad-spectrum and potent antitumor activity against leukemia, lymphoma, and various solid tumor cell lines, exhibiting an IC_{50} value of approximately 20 nM [17]. Lage *et al*. observed that certain 2,5-disubstituted carbazole, substituted benzoxazine, and benzamide derivatives were highly effective against multiple cancer cell lines, including gastric, breast, pancreatic, fibrosarcoma, and melanoma cells [18]. In light of these findings, our study aimed to synthesize a novel derivative incorporating the benzoxazole core as its main pharmacophore and to evaluate its antitumor potential for the first time.

Apoptosis is a form of programmed cell death characterized by distinct morphological alterations, orchestrated by caspases and regulated by the Bcl-2 family of proteins [19]. Cancer cells frequently downregulate pro-apoptotic Bcl-2 family members, upregulate anti-apoptotic Bcl-2 family proteins, or functionally inactivate APAF-1 expression to evade cell death [20]. While a decrease in Bcl-2 levels triggers the apoptotic cascade, an increase in BCL-2 expression protects cells from programmed cell death [21]. Bcl-2 acts as a mitochondrial guardian by localizing to the outer mitochondrial membrane and preventing the release of cytochrome c into the cytoplasm. Watson *et al*.

Copyright: © Author(s), 2026. Published by Greenfort International Journal of Applied Medical Science | This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC 4.0) License.

noted that anti-apoptotic Bcl-2 expression levels are significantly elevated in colon cancer [22].

Nuclear Factor kappa B (NF-κB) is a ubiquitously expressed transcription factor present across all cell types. In unstimulated cells, NF-κB remains inactive within the cytoplasm; upon activation, it translocates to the nucleus to regulate target gene expression. The family comprises five structural subunits: NF-κB1, NF-κB2, RelA (p65), RelB, and c-Rel. These Rel/NF-κB proteins constitute a eukaryotic transcription factor family that governs essential physiological processes in normal cells, including immune and inflammatory responses, developmental programs, cell growth, and apoptosis. Additionally, persistent activation of these transcription factors is implicated in diverse pathological conditions, including cancer, arthritis, chronic inflammation, asthma, neurodegenerative disorders, and cardiovascular diseases [23,24].

In our previous work, the cytotoxic effects of benzothiazole/benzoxazole treatment were evaluated using the MTT assay in estrogen receptor-positive (ER^+) MCF-7 and estrogen receptor-negative (ER^-) MDA-MB cell lines, confirming its anti-proliferative capacity and ability to reduce cell viability in cancer models.

In the present study, when the novel benzoxazole compound was administered to the MDA-MB cell line, expression levels of NF-κB, caspase, APAF-1, and cytochrome c remained undetected in both the control and treatment groups. However, a statistically significant increase in BCL-2 C_T values (reflecting altered baseline transcription) was observed in treated MDA-MB cells compared to the control group. In contrast, treatment of the MCF-7 cell line with the benzoxazole compound resulted in higher C_T values for cytochrome c, BCL-2, and NF-κB relative to the control group. Furthermore, APAF-1 expression was upregulated (as indicated by decreased C_T values) in MCF-7 cells, while caspase-9 levels remained comparable to untreated control levels.

CONCLUSİON

In conclusion, our findings suggest that the newly synthesized benzoxazole compound exhibits greater therapeutic efficacy in the MCF-7 breast cancer cell line, demonstrating a strong tendency to induce apoptosis in these cells. Therefore, we propose that this compound holds promising potential for inhibiting tumor growth in breast cancer treatment protocols. Further validation of these findings in animal tumor models will be essential to confirm its *in vivo* efficacy and safety profile.

Author's Contribution

Funda KOSOVA medical biochemist, preparation of manuscript analyz, Özlem Temiz-Arpaci Pharmaceutical Chemistry, make Heterocyclic Compound of manuscript, Feyzan ÖZDAL KURT make cell culture, Competing interests.

Conflict of Interest: The authors declare that they have no competing interest.

Financial Disclosure: All authors declare no financial support.

Ethical approval: Consent of ethics was approved by the local ethics committee.

REFERENCES

1. Ohta T, Kunimasa K, Kobayashi T, Sakamoto M, Kaji K. Propolis suppresses tumor angiogenesis by inducing apoptosis in tube-forming endothelial cells. Biosci Biotechnol Biochem. 2008;72(9):2436-40.
2. An Z, Kosova F. Adipositokinler ve Meme Kanseri. F.Ü. Sağ Bil Derg. 2008;22(6):377-84.
3. Clayton CC. Effect of certain benzimidazoles and related compounds upon azo dye destruction by liver homogenates (23789). Proc Soc Exp Biol Med. 1958;98:510-2.
4. Schulze W, Gutsche W, Jungstand W. Zusammenhänge zwischen Chemischer Struktur und Biologischer Wirksamkeit bei Azomethinen mit Stickstofflost-Gruppen am Ehrlich-Ascitestumor der weissen Maus. Arzneim Forsch. 1965;15(10):1235-8.
5. Bahner CT, Rives LM, Megaha SW, Rutledge D, Ford D, Gooch E, Westberry D, Ziegler D, Ziegler R. Di- and Tri-methoxystyryl derivatives of heterocyclic nitrogen compounds. Arzneim Forsch. 1981;31(3):404-6.
6. Temiz-Arpaci O, Yildiz I, Ozkan S, Kaynak F, Aki-Sener E, Yalçin I. Synthesis and biological activity of some new benzoxazoles. Eur J Med Chem. 2008;43(7):1423-31.
7. Kiessing S, Rockensuess KD, Varga A, Molnar J, Cherepnev G, Aki E, Yalcin I, Lage H, Amaral L. Composition useful for the Chemosensibiling and Simultaneous Apoptosis Induction of multidrug resistance of Tumor Cells and Bacteria, Comprise Substituteddisiloxane Compound in the Combination With benzoxazole Derivatives. Patent De. 2010.
8. Wittliff JL. Steroid hormone receptors in breast cancer. Cancer. 1984;53:630-43.
9. Key T, Appleby P, Barnes I. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies, J Natl Cancer Inst. 2002;94:606-16.
10. Stephenson GD, Rose DP. Breast cancer and obesity: an update, Nutr Cancer. 2003;45:1-16.
11. Clayton CC. Effect of certain benzimidazoles and related compounds upon azo dye destruction by liver homogenates (23789). Proceed Soc Exp Biol Medic. 1958;98:510-12.
12. Schulze W, Gutsche W, Jungstand W. Zusammenhänge zwischen chemischer struktur und biologischer wirksamkeit bei azomethinen mit sticksofflost-gruppen am ehrlich-ascitestumor der weissen maus. Arzneim. Forsch. 1965;15:1235-8.

Copyright: © Author(s), 2026. Published by Greenfort International Journal of Applied Medical Science | This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC 4.0) License.

13. Bahner CT, Rıves LM, McGaha SW, *et al*. Di- and tri-methoxystyryl derivatives of heterocyclic nitrogen compounds. Arzneimittelforschung. 1981;31:404-6.
14. Denny WA, Rewcastle GW, Baguley BC. PPotential antitumor agents. 59. Structure-activity relationships for 2-phenylbenzimidazole-4-carboxamides, a new class of “minimal” DNA-intercalating agents which may not act via topoisomerase II. J Med Chem. 1990;33:814-9.
15. Denny WA, Turner PM, Atwell GJ, at al. Structure-activity relationships for the mutagenic activity of tricyclic intercalating in salmonella typhimurium. Mutat Res. 1990;232:233-41.
16. Sato S, Kajıura T, Misato N. *et al*. AJI9561, A New cytotoxic benzoxazole derivative produced by streptomyces sp. J. Antibio. 2001;54:102-4.
17. Kumar D, Jacob MR, Reynolds MB, *et al*. Synthesis and evaluation of anticancer benzoxazoles and benimidazoles related to UK-1. Bioorg.Med. Chem. 2002;10:3997-4004.
18. Lage H, Akı-Sener E, Yalcın I. High antineoplastic activity of newHeterocyclic compounds in cancer cells with Resistance against Classical DNATopoisomerase II-Targeting Drugs. Int. J. Cancer, 2006;119:213-20.
19. Diaz GD, Li Q, Dashwood HR. Caspase-8 and Apoptosis-inducing factor mediate a cytochrome c-independent pathway of apoptosis in human colon cancer cells Induced by the dietary phytochemical chlorophyllin. Cancer Res. 2003;63:1254-61.
20. Manns J, Daubrawa M, Driessen S, *et al*. Stork B. and Wesselborg S. Triggering of a novel intrinsic apoptosis pathway by the kinase inhibitor staurosporine: activation of caspase-9 in the absence of Apaf-1. FASEB J. 2011;25:3250-61.
21. Douglas RG, Reid PB. Thomas G.C. Apoptosis and cancer. Principles Practice Oncol. 1994;1:1-13.
22. Watson AJ, Merritt AJ, Jones LS, *et al*. Evidence for reciprocity of Bcl–2 and p53 expression in human colorectal adenomas and carcinomas. Br J Cancer, 1996;73:889-95.
23. Douglas RG, Reid PB, Thomas GC. Apoptosis and cancer. Princ Pract Oncol. 1994;1:1-13.
24. Watson AJ, Merritt AJ, Jones LS, Askew JN, Anderson E, Becciolini A, Balzi M, Potten CS, Hickman JA. Evidence for reciprocity of Bcl-2 and p53 expression in human colorectal adenomas and carcinomas. Br J Cancer. 1996;73(8):889-95.

Copyright: © Author(s), 2026. Published by Greenfort International Journal of Applied Medical Science | This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC 4.0) License.