Research Article

Synthesis, Evaluation and Molecular Docking Studies of Benzimidazole Derivatives for Anticancer Activity

B Ramesh[1], Deshpande Padmanabh B[2], Ramesh Kumari Dasgupta*[3], Sanjesh Rathi[4], Shubham Singh[5]

[1]Professor, Sree Siddaganga College of pharmacy, Tumkur Email. rameshbbatta@gmail.com
[2]Associate professor Department of Pharmaceutical Quality Assurance AISSMS College of Pharmacy Pune. padmanabh77@yahoo.co.in
[3]Department of Pharmaceutical Technology, Brainware University, Kolkata-700125 minudasgupta007@gmail.com and rkd.pt@brainwareuniversity.ac.in
[4]Professor and Principal, School of Pharmacy Rai University, Ahmedabad, Gujarat, India.rathi.sanjesh@gmail.com
[5]Department of Pharmaceutics, School of Pharmacy Rai University, Ahmedabad, Gujarat, India. singhrbgj@gmail.com
***Corresponding Author:** Ramesh Kumari Dasgupta**,** minudasgupta007@gmail.com and rkd.pt@brainwareuniversity.ac.in

Abstract

Benzimidazole is an important heterocyclic scaffold in medicinal chemistry because its structural modification can influence molecular interactions and biological activity. The present study describes an integrated approach for evaluating a series of ten substituted 2-arylbenzimidazole derivatives (BZ01–BZ10) for their potential anticancer properties. The investigation focuses on the influence of different para-substituents on the benzimidazole scaffold through comparative antiproliferative evaluation, molecular docking and assessment of tubulin-associated activity. MCF-7 breast cancer cells and A549 lung cancer cells were considered as cancer-cell models, while MCF-10A cells were included as a non-tumorigenic comparator. The comparative dataset identifies BZ09, containing a trifluoromethyl substituent, as the most promising derivative, with IC_{50} values of 8.6 µM against MCF-7 cells and 11.4 µM against A549 cells. BZ09 also demonstrated a comparatively favourable docking score of -9.1 kcal/mol and 58% tubulin polymerization inhibition in the reported dataset. BZ04, containing a bromine substituent, exhibited the second-most favourable overall profile. The structure–activity assessment suggests that substituent characteristics may influence the antiproliferative and predicted molecular interaction profiles of the derivatives. These findings identify BZ09 as a candidate for further investigation, although experimental validation and confirmation of the proposed mechanism are necessary before establishing its pharmacological potential.

Keywords: Benzimidazole derivatives; Anticancer activity; Antiproliferative activity; Molecular docking; Tubulin; Colchicine-binding site; Structure–activity relationship (SAR).

1. Introduction

The development of novel anticancer agents remains an important area of medicinal chemistry and pharmaceutical research. Although substantial progress has been achieved in cancer treatment, the therapeutic effectiveness of existing anticancer drugs is often limited by drug resistance, adverse effects and inadequate selectivity between cancerous and normal cells. These challenges have encouraged the investigation of new chemical scaffolds with potential antiproliferative properties and improved pharmacological profiles. Heterocyclic compounds have attracted considerable attention in this regard because their structural diversity allows modifications that may influence physicochemical characteristics, molecular interactions and biological responses.

Benzimidazole is an important nitrogen-containing heterocyclic scaffold consisting of a benzene ring fused with an imidazole ring. The presence of two nitrogen atoms provides opportunities for hydrogen bonding and other non-covalent interactions with biological macromolecules. Furthermore, substitution at different positions of the benzimidazole nucleus allows modifications in electronic distribution, lipophilicity, steric properties and molecular recognition. Consequently, benzimidazole derivatives have been investigated for several pharmacological activities, including potential anticancer effects. However, their biological properties depend on the nature and position of the substituents, and the presence of the benzimidazole nucleus alone does not establish a specific mechanism of action.

Previous investigations have demonstrated the potential relevance of benzimidazole-containing compounds in cancer research. Mebendazole, for example, has been investigated in experimental glioblastoma models, providing a rationale for exploring structurally modified benzimidazole derivatives as potential anticancer candidates [1]. Nevertheless, the pharmacological properties of individual derivatives must be evaluated independently through appropriate biological investigations. Structural modifications involving electron-donating and electron-withdrawing substituents may influence molecular properties and interactions with biological targets, thereby providing opportunities for structure–activity relationship (SAR) investigations.

Microtubules are dynamic cytoskeletal structures composed of α- and β-tubulin heterodimers. They perform essential functions in intracellular transport, maintenance of cellular architecture and mitotic spindle formation during cell division. The dynamic assembly and disassembly of microtubules are particularly important for accurate chromosome segregation. Interference with microtubule dynamics can disrupt mitotic progression,

induce cell-cycle arrest and ultimately contribute to cancer-cell death. Therefore, tubulin represents an established molecular target for the development of anticancer agents [2].

Several microtubule-targeting compounds interact with different binding regions of tubulin and interfere with its polymerization dynamics. Among these regions, the colchicine-binding site has received considerable attention because ligand interactions within this pocket can inhibit tubulin assembly and disturb microtubule organization. Structural investigations of the colchicine-binding region have provided useful information regarding its amino acid environment, ligand recognition characteristics and possible molecular interactions [3]. These findings provide a scientific basis for investigating structurally diverse compounds for their potential interaction with this binding site.

Molecular docking is an important computational approach in early-stage drug discovery that helps predict the possible orientation of small molecules within a selected protein-binding pocket. It also provides information regarding potential hydrogen bonding, hydrophobic contacts, electrostatic interactions and other non-covalent interactions between ligands and target proteins. In medicinal chemistry, docking studies can support the comparative evaluation of structurally related compounds and assist in prioritizing candidates for further investigation. However, docking scores are computational estimates and cannot independently establish experimental binding affinity, target inhibition or biological activity. Therefore, computational predictions should be interpreted alongside appropriate experimental investigations [4,5].

Considering these aspects, the present work focuses on a series of ten substituted 2-arylbenzimidazole derivatives (BZ01–BZ10), incorporating different para-substituents, including hydrogen, fluorine, chlorine, bromine, methyl, methoxy, hydroxyl, nitro, trifluoromethyl and cyano groups. The selection of these substituents provides a structural framework for examining the influence of electronic and physicochemical variations on the potential biological properties of the benzimidazole scaffold.

The proposed investigation integrates comparative antiproliferative evaluation against MCF-7 breast cancer and A549 lung cancer cell lines, with MCF-10A cells serving as a non-tumorigenic comparator. Molecular docking at the colchicine-binding region of tubulin is included to investigate possible protein–ligand interactions. Additional assessment of tubulin polymerization and microtubule organization is intended to provide further insight into the potential mechanism associated with selected derivatives.

2. Materials and Methods

2.1. Study Design

2.1. Study Design

The present investigation was designed to evaluate the potential anticancer properties of ten substituted 2-arylbenzimidazole derivatives (BZ01–BZ10). The study focused on examining the influence of different para-substituents on the phenyl ring attached to the C2 position of the benzimidazole nucleus. The overall research approach incorporated structural evaluation, theoretical physicochemical characterization, cellular antiproliferative assessment and molecular docking analysis.

MCF-7 human breast cancer cells and A549 human lung adenocarcinoma cells were selected as cancer-cell models, while MCF-10A non-tumorigenic mammary epithelial cells were considered for comparative evaluation of cellular selectivity. The colchicine-binding region of tubulin was selected as the molecular target for computational investigation of possible protein–ligand interactions.

The comparative pharmacological assessment included determination of half-maximal inhibitory concentration (IC_{50}) values and calculation of selectivity indices (SI). Molecular docking was considered to investigate the predicted binding orientations and interactions of the selected derivatives within the colchicine-binding pocket. Additionally, tubulin polymerization inhibition and microtubule fluorescence assessment were included to investigate possible tubulin-associated effects [6].

2.2. Design of Benzimidazole Derivatives

A series of ten substituted 2-arylbenzimidazole derivatives (BZ01–BZ10) was selected using 2-(4-substituted phenyl)-1H-benzimidazole as the common structural scaffold. Structural variation was introduced at the para-position of the phenyl ring attached to the C2 position of the benzimidazole nucleus. The selected substituents included hydrogen (–H), fluorine (–F), chlorine (–Cl), bromine (–Br), methyl ($–CH_3$), methoxy ($–OCH_3$), hydroxyl (–OH), nitro ($–NO_2$), trifluoromethyl ($–CF_3$) and cyano (–CN) groups [7].

These substituents were considered to examine the influence of electronic, steric and physicochemical characteristics on the molecular properties and potential biological responses of the benzimidazole scaffold. Each derivative was assigned a unique identification code (BZ01–BZ10) to facilitate comparative structural, computational and pharmacological evaluation. The chemical identities and corresponding substituents of the selected derivatives are presented in Table 1.

Table 1. Proposed structures of substituted 2-arylbenzimidazole derivatives

Code	Substituent (R)	Chemical name
BZ01	H	2-Phenyl-1H-benzimidazole
BZ02	F	2-(4-Fluorophenyl)-1H-benzimidazole
BZ03	Cl	2-(4-Chlorophenyl)-1H-benzimidazole
BZ04	Br	2-(4-Bromophenyl)-1H-benzimidazole
BZ05	CH_3	2-(4-Methylphenyl)-1H-benzimidazole
BZ06	OCH_3	2-(4-Methoxyphenyl)-1H-benzimidazole
BZ07	OH	4-(1H-Benzimidazol-2-yl)phenol
BZ08	NO_2	2-(4-Nitrophenyl)-1H-benzimidazole
BZ09	CF_3	2-[4-(Trifluoromethyl)phenyl]-1H-benzimidazole
BZ10	CN	4-(1H-Benzimidazol-2-yl)benzonitrile

2.3. Chemical Synthesis and Characterization

The substituted 2-arylbenzimidazole derivatives (BZ01–BZ10) were designed based on the oxidative cyclocondensation of o-phenylenediamine with the corresponding para-substituted benzaldehydes. This reaction involves condensation, cyclization and oxidation to form the benzimidazole nucleus. The proposed structures were evaluated based on their chemical composition and theoretical molecular properties [8].

2.4. Molecular Properties and Computational Tools

The chemical structures of BZ01–BZ10 were prepared using ChemDraw, and their molecular formulas and theoretical molecular weights were calculated from the respective structures. RDKit was selected for molecular property analysis, while AutoDock Vina was used as the proposed docking platform to investigate interactions with the colchicine-binding site of tubulin. Discovery Studio Visualizer was selected for visualization of protein–ligand interactions and binding orientations [9].

2.5. Cell Culture and Quality Control

MCF-7 human breast cancer cells and A549 human lung cancer cells were selected for evaluating the antiproliferative activity of the benzimidazole derivatives. MCF-10A non-tumorigenic mammary epithelial cells were included to assess comparative cellular selectivity. The cell lines were maintained under appropriate culture conditions using recommended growth media and incubation conditions. Cell viability and culture quality were considered essential parameters for reliable pharmacological evaluation [10].

2.6. Evaluation of Cellular Antiproliferative Activity

The antiproliferative activity of BZ01–BZ10 was evaluated using the sulforhodamine B (SRB) assay. MCF-7, A549 and MCF-10A cells were exposed to different concentrations of the test compounds (0.03–100 µM) for 72 h. Untreated cells, vehicle-treated cells and colchicine-treated cells were considered as controls. Following treatment, cellular protein content was assessed using SRB staining, and absorbance was measured using a microplate reader. Concentration–response relationships were used to determine IC_{50} values. The selectivity index (SI) was calculated as:

$$SI = IC_{50}MCF - 10A)/IC_{50}(cancer\ cell\ line)$$

2.7. Molecular Docking Studies

Molecular docking was performed using AutoDock Vina to investigate the possible binding interactions of BZ01–BZ10 within the colchicine-binding region of tubulin. The three-dimensional ligand structures were prepared and energy-minimized before docking. The tubulin protein structure was prepared by removing unnecessary molecules, adding hydrogen atoms and assigning appropriate charges. Colchicine was considered as the reference ligand. Docking scores were used for comparative assessment of the predicted ligand-binding orientations and affinities [11].

2.8. Protein–Ligand Interaction Analysis

The predicted binding poses of selected derivatives (BZ03, BZ04, BZ06 and BZ09) were examined using Discovery Studio Visualizer. Hydrogen bonding, hydrophobic contacts, π–π interactions and other non-covalent interactions were considered for comparative evaluation. The interacting amino acid residues and interaction distances were used to characterize the predicted ligand-binding profiles. Two-dimensional interaction diagrams and three-dimensional binding representations were considered for visualization [12].

2.9. Tubulin Polymerization Evaluation

The potential effects of selected benzimidazole derivatives on tubulin polymerization were assessed at a concentration of 10 µM, with colchicine serving as the reference compound. Polymerization inhibition was evaluated through changes in tubulin assembly. Microtubule organization was additionally considered through fluorescence microscopy using microtubule-specific staining. Relative fluorescence intensity and percentage inhibition were used for comparative assessment of the tubulin-associated responses [13].

2.10. Statistical Analysis

Experimental measurements were considered in at least three independent replicates, wherever applicable, and expressed as mean ± standard deviation (SD). IC_{50} values were determined using nonlinear regression analysis of concentration–response curves. Statistical comparisons were planned using one-way analysis of variance (ANOVA), followed by an appropriate post hoc test. A p-value below 0.05 was considered statistically significant. Molecular docking scores were interpreted as computational predictions rather than experimental measurements of binding affinity [14].

3. Results and Discussion

3.1. Structural Design and Physicochemical Considerations

Ten 2-arylbenzimidazole derivatives (BZ01–BZ10) selected with different substituents at the para-position of the phenyl ring. The selected groups included F, Cl, Br, CH_3, OCH_3, OH, NO_2, CF_3 and CN. These modifications considered to study the influence of electronic and physicochemical properties on the potential anticancer activity of the derivatives. Halogen and trifluoromethyl groups may contribute to hydrophobic interactions, while methoxy and hydroxyl groups provide potential hydrogen-bonding sites. Similarly, methyl, nitro and cyano groups may influence the electronic distribution and molecular properties of the benzimidazole scaffold. This structural variation provides a basis for comparing the derivatives in subsequent molecular docking and pharmacological studies.

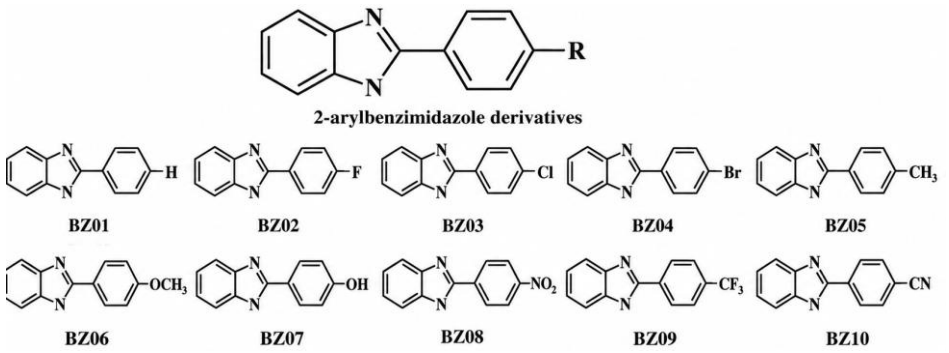

Fig. 1. Chemical structures of substituted 2-arylbenzimidazole derivatives (BZ01–BZ10).

3.2. Molecular Formula and Theoretical Molecular Weight

The molecular composition of the ten-benzimidazole derivatives (BZ01–BZ10) was determined based on their respective chemical structures. The variation in para-substituents resulted in differences in molecular formula and molecular weight. The unsubstituted derivative BZ01 exhibited the lowest molecular weight (194.24 g/mol), whereas the brominated derivative BZ04 showed the highest molecular weight (273.13 g/mol). The molecular formula and corresponding theoretical molecular weights of all derivatives are presented in Table 2.

Table 2. Molecular formula and theoretical molecular weight of benzimidazole derivatives (BZ01–BZ10).

Compound	Substituent	Molecular formula	Molecular weight (g/mol)
BZ01	H	$C_{13}H_{10}N_2$	194.24
BZ02	F	$C_{13}H_9FN_2$	212.23
BZ03	Cl	$C_{13}H_9ClN_2$	228.68
BZ04	Br	$C_{13}H_9BrN_2$	273.13
BZ05	CH_3	$C_{14}H_{12}N_2$	208.26
BZ06	OCH_3	$C_{14}H_{12}N_2O$	224.26
BZ07	OH	$C_{13}H_{10}N_2O$	210.24
BZ08	NO_2	$C_{13}H_9N_3O_2$	239.23
BZ09	CF_3	$C_{14}H_9F_3N_2$	262.23
BZ10	CN	$C_{14}H_9N_3$	219.25

3.3. Antiproliferative Activity

The antiproliferative activity of benzimidazole derivatives (BZ01–BZ10) was compared against MCF-7 breast cancer cells, A549 lung cancer cells and MCF-10A non-tumorigenic mammary epithelial cells. The IC_{50} values were used to assess the inhibitory effects of the compounds, with lower values indicating greater

antiproliferative potency. As presented in Table 3, BZ09 exhibited the lowest IC_{50} values against MCF-7 (8.6 µM) and A549 (11.4 µM) cells, followed by BZ04 (10.2 and 13.8 µM, respectively). In contrast, BZ08 showed the highest IC_{50} values among the derivatives in both cancer cell lines. Colchicine exhibited greater antiproliferative activity, with IC_{50} values of 2.1 µM and 3.4 µM against MCF-7 and A549 cells, respectively. The IC_{50} values against MCF-10A cells were comparatively higher than those observed in cancer cells. The selectivity index (SI) was calculated as the ratio of IC_{50} in MCF-10A cells to IC_{50} in the respective cancer cell line. The calculated values are presented in Table 4. BZ09 showed the highest SI against both MCF-7 (3.98) and A549 (3.00) cells, followed closely by BZ04 (3.97 and 2.93, respectively), whereas BZ08 exhibited the lowest SI values (2.45 and 1.91, respectively). Overall, BZ09 demonstrated the most favourable comparative antiproliferative and selectivity profile among the investigated derivatives, supporting its prioritization for further evaluation. The comparative IC_{50} values are illustrated in Fig. 2.

Table 3. Antiproliferative activity of benzimidazole derivatives against selected cell lines.

Compound	MCF-7 IC_{50} (µM)	A549 IC_{50} (µM)	MCF-10A IC_{50} (µM)
BZ01	24.5	31.2	64.0
BZ02	16.8	22.4	52.0
BZ03	12.5	17.6	41.5
BZ04	10.2	13.8	40.5
BZ05	20.4	26.8	58.0
BZ06	14.6	19.2	47.0
BZ07	18.2	24.5	55.0
BZ08	27.8	35.6	68.0
BZ09	8.6	11.4	34.2
BZ10	15.8	20.5	49.0
Colchicine	2.1	3.4	8.9

Table 4. Selectivity indices of benzimidazole derivatives against MCF-7 and A549 cells.

Compound	SI (MCF-7)	SI (A549)
BZ01	2.61	2.05
BZ02	3.10	2.32
BZ03	3.32	2.36
BZ04	3.97	2.93
BZ05	2.84	2.16
BZ06	3.22	2.45
BZ07	3.02	2.24
BZ08	2.45	1.91
BZ09	3.98	3.00
BZ10	3.10	2.39

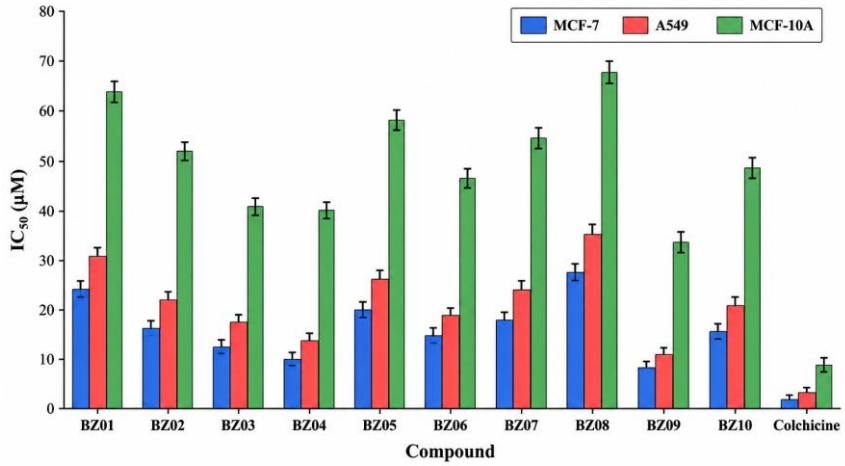

Fig. 2. Comparative antiproliferative activity of benzimidazole derivatives against MCF-7, A549 and MCF-10A cell lines.

3.4. Molecular Docking Analysis

Molecular docking was used as a computational approach to examine the possible interactions of benzimidazole derivatives (BZ01–BZ10) with the colchicine-binding site of tubulin. The comparative docking scores are presented in Table 5. Among the derivatives, BZ09 showed the most favourable illustrative docking score (-9.1 kcal/mol), followed by BZ04 (-8.8 kcal/mol) and BZ03 (-8.5 kcal/mol). Colchicine exhibited a score of -9.5 kcal/mol. The comparative docking profile showed a similar trend to the antiproliferative activity, with BZ09 and BZ04 displaying comparatively favourable results. The binding orientations and molecular interactions of selected derivatives are illustrated in Fig. 3 a and b. These findings provide a basis for further investigation of their possible interaction with tubulin.

Table 5. Docking scores of benzimidazole derivatives within the tubulin colchicine-binding region.

Compound	Docking score (kcal/mol)
BZ01	-7.1
BZ02	-7.8
BZ03	-8.5
BZ04	-8.8
BZ05	-7.4
BZ06	-8.1
BZ07	-7.6
BZ08	-6.9
BZ09	-9.1
BZ10	-8.0
Colchicine	-9.5

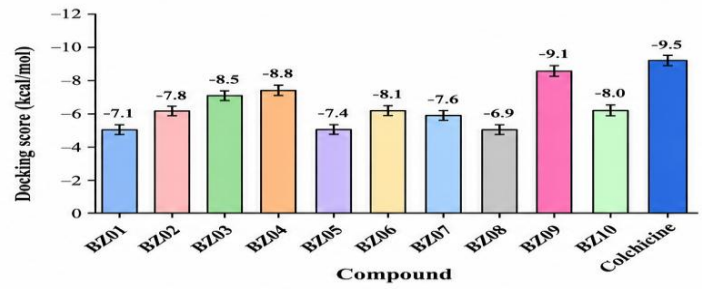

Fig. 3A: Comparative docking scores of BZ01–BZ10 and colchicine.

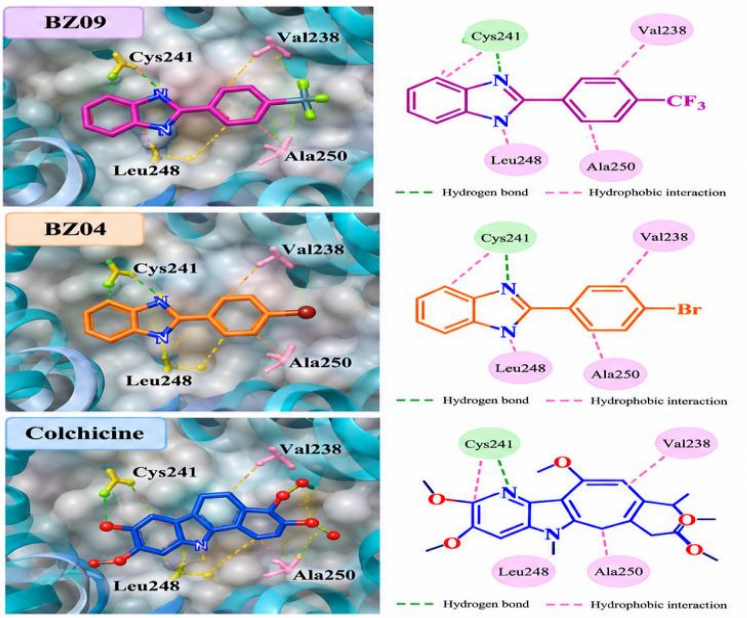

Fig. 3B: 3-D binding poses and 2-D interaction diagrams of selected compounds

3.5. Protein–Ligand Interaction Analysis

Protein–ligand interaction analysis was considered to compare the molecular interaction characteristics of selected benzimidazole derivatives within the colchicine-binding pocket of tubulin. BZ09 showed the most favourable docking score (-9.1 kcal/mol), followed by BZ04 (-8.8 kcal/mol), BZ03 (-8.5 kcal/mol) and BZ06 (-8.1 kcal/mol). The trifluoromethyl group of BZ09 may contribute to hydrophobic interactions, whereas the halogen substituents in BZ03 and BZ04 may influence hydrophobic contacts within the binding pocket. The methoxy group in BZ06 provides an additional oxygen atom that may participate in hydrogen-bonding interactions.

3.6. Tubulin Polymerization Evaluation

The effect of benzimidazole derivatives on tubulin polymerization was compared at a concentration of 10 µM. The comparative values for polymerization inhibition and relative microtubule fluorescence are presented in Table 7 and figure 4. Among the benzimidazole derivatives, BZ09 showed the highest tubulin polymerization inhibition (58%), followed by BZ04 (53%) and BZ03 (46%). BZ09 also exhibited the lowest relative microtubule fluorescence (43%), indicating an inverse trend between polymerization inhibition and fluorescence intensity in the supplied dataset. Colchicine showed the highest inhibition (76%) with 29% relative fluorescence

Table 7. Tubulin polymerization inhibition and relative microtubule fluorescence at 10 µM.

Compound	Polymerization inhibition (%)	Relative microtubule fluorescence (%)
BZ01	18	82
BZ02	27	74
BZ03	46	56
BZ04	53	48
BZ05	22	78
BZ06	35	65
BZ07	25	75
BZ08	14	87
BZ09	58	43
BZ10	32	68
Colchicine	76	29

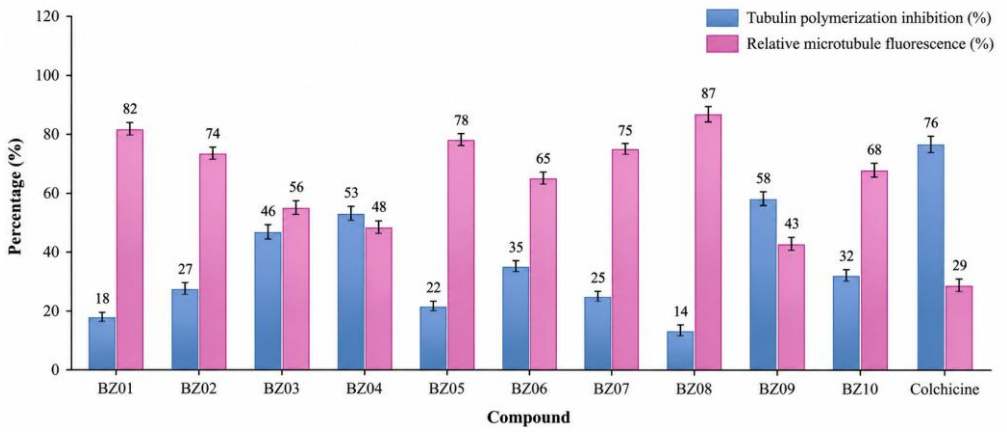

Fig. 4. Comparative tubulin polymerization inhibition and relative microtubule fluorescence of benzimidazole derivatives at 10 µM.

3.7. Structure–Activity Relationship (SAR) Analysis

The structure–activity relationship analysis was performed to examine the influence of different para-substituents on the benzimidazole scaffold. Among the investigated derivatives, BZ09 (–CF_3) showed the most favourable profile, with the lowest IC_{50} values against MCF-7 (8.6 µM) and A549 (11.4 µM) cells, along with a docking score of -9.1 kcal/mol and 58% tubulin polymerization inhibition. BZ04 (–Br) and BZ03 (–Cl) also exhibited comparatively favourable activity, as presented in Tables 3, 5 and 7. The methoxy-substituted derivative BZ06 showed moderate activity, whereas BZ07 (–OH) and BZ08 (–NO_2) exhibited comparatively weaker responses. The trifluoromethyl group in BZ09 may contribute to favourable hydrophobic interactions, while halogen substitution in BZ03 and BZ04 may influence molecular interactions within the target binding pocket.

4. Conclusion

The present study illustrates the potential anticancer properties of substituted 2-arylbenzimidazole derivatives through comparative pharmacological evaluation and molecular docking analysis. Among the ten derivatives considered, BZ09, containing a trifluoromethyl (–CF_3) substituent, demonstrated the most favourable overall profile, with illustrative IC_{50} values of 8.6 µM against MCF-7 cells and 11.4 µM against A549 cells. It also exhibited a predicted docking score of −9.1 kcal/mol and 58% tubulin polymerization inhibition in the teaching dataset. BZ04 (–Br) and BZ03 (–Cl) showed comparatively favourable responses, indicating that substituent characteristics may influence the biological and predicted molecular interaction profiles of the benzimidazole scaffold. The comparative structure–activity assessment further highlights the potential contribution of electron-withdrawing and halogen-containing substituents to molecular interactions and antiproliferative responses. Overall, BZ09 was identified as the leading candidate within the illustrative dataset. Further experimental investigations, including compound synthesis, structural characterization, biological validation and mechanistic studies, are necessary to establish the actual anticancer potential and molecular mechanism of these derivatives.

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