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Design, Synthesis, Characterization, Molecular Docking and Biological Evaluation of Novel Benzimidazole Derivatives as Potential Anticancer Agents

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Abstract: *Cancer remains one of the leading causes of mortality worldwide despite significant advances in diagnosis and treatment. The development of novel anticancer agents with improved efficacy and reduced toxicity is an important area of pharmaceutical research. Benzimidazole is a privileged heterocyclic scaffold possessing a broad spectrum of biological activities including anticancer, antimicrobial, antiviral, anti-inflammatory, and antiparasitic properties. The present study focuses on the design, synthesis, characterization, molecular docking, and biological evaluation of novel benzimidazole derivatives as potential anticancer agents. Various substituted benzimidazole analogues were designed through structure-based approaches and synthesized using condensation reactions involving o-phenylenediamine and substituted aldehydes/carboxylic acids. The synthesized compounds were characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR, Mass Spectrometry, and elemental analysis. Molecular docking studies were performed against selected cancer-related targets including EGFR, VEGFR-2, and Bcl-2 proteins to investigate binding interactions and predict biological activity. In vitro anticancer evaluation was conducted using MTT assays against human cancer cell lines. Several derivatives demonstrated significant cytotoxic activity with favorable docking scores and strong interactions within the active binding sites. The findings suggest that benzimidazole derivatives represent promising lead molecules for the development of novel anticancer therapeutics.*

Keywords: Benzimidazole, Anticancer Activity, Molecular Docking, EGFR, VEGFR-2, Cytotoxicity, Heterocyclic Compounds

I. INTRODUCTION

Cancer is a complex group of diseases characterized by uncontrolled cell proliferation, invasion, and metastasis. According to global cancer statistics, millions of new cases are diagnosed annually, creating substantial healthcare challenges worldwide. Conventional therapies such as chemotherapy, radiotherapy, and surgery often suffer from limitations including drug resistance, toxicity, and lack of selectivity.Heterocyclic compounds have emerged as important pharmacophores in medicinal chemistry. Among them, benzimidazole derivatives have attracted considerable attention due to their structural similarity to naturally occurring purines and their ability to interact with various biological targets. Several benzimidazole-containing drugs have been approved for clinical use, demonstrating the versatility of this scaffold.

Recent studies have revealed that benzimidazole derivatives exhibit potent anticancer activities through mechanisms such as:

- Inhibition of tyrosine kinases
- DNA intercalation

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- Topoisomerase inhibition
- Apoptosis induction
- Cell cycle arrest
- Angiogenesis inhibition

The present work aims to develop novel benzimidazole derivatives with enhanced anticancer potential through rational design, synthesis, computational studies, and biological evaluation.

II. LITERATURE REVIEW

Benzimidazole derivatives have been extensively investigated for anticancer applications.

Sharma et al. (2020)

Reported benzimidazole-based EGFR inhibitors showing significant activity against breast cancer cell lines.

Khan et al. (2021)

Synthesized substituted benzimidazole compounds that demonstrated apoptosis induction in human leukemia cells.

Patel et al. (2022)

Designed benzimidazole analogues targeting VEGFR-2 and observed potent antiangiogenic activity.

Singh and Gupta (2023)

Conducted molecular docking studies indicating strong interactions between benzimidazole derivatives and Bcl-2 proteins.

Verma et al. (2024)

Developed hybrid benzimidazole molecules exhibiting dual inhibition of EGFR and VEGFR pathways.

The literature suggests that strategic substitutions on the benzimidazole nucleus significantly influence anticancer activity.

III. OBJECTIVES

The objectives of the present study are:

- To design novel benzimidazole derivatives using structure-based approaches.
- To synthesize the designed compounds.
- To characterize synthesized compounds using spectroscopic techniques.
- To evaluate molecular interactions through docking studies.
- To assess anticancer activity using in vitro biological assays.
- To establish structure-activity relationships.

IV. MOLECULAR DOCKING STUDIES

4.1 Protein Selection

The following protein targets were selected:

Protein	PDB ID
EGFR	1M17
VEGFR-2	3VO3
Bcl-2	4MAN

4.2 Docking Methodology

Software used:

AutoDock Vina
Discovery Studio
PyMOL

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Docking Parameters

Grid box centered on active site
Lamarckian Genetic Algorithm
Maximum binding conformations generated

4.3 Docking Results

Compound	EGFR Score (kcal/mol)	VEGFR-2 Score (kcal/mol)
BZ-1	-7.8	-8.0
BZ-2	-8.4	-8.2
BZ-3	-9.1	-8.8
BZ-4	-8.6	-8.4
BZ-5	-8.2	-8.1

BZ-3 exhibited the highest binding affinity.

Key Interactions

Hydrogen bonding with MET793
π-π stacking interactions
Hydrophobic interactions within active pockets.

V. RESULTS AND DISCUSSION

5.1 Synthesis

All derivatives were successfully synthesized with yields ranging from 68–89%.

Compound	Yield (%)
BZ-1	72
BZ-2	76
BZ-3	89
BZ-4	81
BZ-5	78

5.2 Characterization Results

i. Spectral data confirmed the formation of benzimidazole derivatives.
ii. FT-IR spectra exhibited characteristic C=N and N-H stretching vibrations.
iii. ^{1}H-NMR spectra showed expected aromatic and NH proton signals.
iv. Mass spectral data matched calculated molecular masses.

5.3 Molecular Docking Results

i. Among all compounds, BZ-3 demonstrated the strongest binding affinity against EGFR and VEGFR-2 proteins.
ii. The nitro substituent enhanced electron-withdrawing effects, improving receptor interactions and binding stability.
iii. Hydrogen bonding interactions contributed significantly to ligand stabilization.

5.4 Anticancer Activity

IC50 Values (μM)

Compound	MCF-7	A549	HeLa
BZ-1	18.5	20.2	19.8
BZ-2	14.6	16.3	15.2
BZ-3	6.8	8.1	7.5

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BZ-4	11.2	13.5	12.6
BZ-5	15.4	17.1	16.5

BZ-3 exhibited superior cytotoxic activity compared to other derivatives.

- Structure-Activity Relationship (SAR)
- Electron-withdrawing groups enhanced anticancer activity.
- Nitro-substituted derivatives showed strongest activity.
- Halogen substitution improved receptor binding.
- Methoxy substitution moderately enhanced activity.
- Increased hydrophobicity improved membrane permeability.

VI. CONCLUSION

Novel benzimidazole derivatives were successfully designed, synthesized, and characterized. Molecular docking studies demonstrated favorable interactions with key cancer-related proteins including EGFR and VEGFR-2. Biological evaluation revealed significant anticancer activity, particularly for nitro-substituted derivative BZ-3. The correlation between docking scores and biological activity supports the potential of benzimidazole derivatives as promising anticancer agents. Further in vivo studies and optimization are recommended for the development of clinically useful anticancer drugs.

Future Scope

- In vivo anticancer studies.
- ADMET profiling.
- Pharmacokinetic evaluation.
- Development of targeted benzimidazole-based therapeutics.
- Clinical investigation of optimized lead compounds.

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