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2-Substituted Benzimidazole–Quinazolinone Hybrids: Design, Synthesis, Spectral Characterization, and Anticancer Evaluation

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Abstract: *Heterocyclic hybrids containing benzimidazole and quinazolinone frameworks represent a promising class of bioactive molecules with diverse pharmacological potential. In this study, a novel series of 2-substituted benzimidazole–quinazolinone hybrids were rationally designed and synthesized through a condensation–cyclization route, employing 2-substituted benzimidazole carboxylic acids and anthranilic acid derivatives. The synthesized hybrids were characterized using FT-IR, ^{1}H NMR, ^{13}C NMR, HRMS, and elemental analysis, confirming the expected structures. Selected compounds were further confirmed by single-crystal X-ray diffraction. Molecular docking studies were performed against EGFR tyrosine kinase and topoisomerase II enzymes to predict the binding interactions responsible for anticancer activity. The MTT assay on HeLa, MCF-7, and HepG2 cancer cell lines revealed that several hybrids exhibited significant cytotoxicity (IC□□ = 5–20 μM) compared with standard drug doxorubicin. SAR analysis indicated that electron-withdrawing substituents at the 2-position of benzimidazole and N-aryl substitution in the quinazolinone ring enhanced potency. The hybridization of benzimidazole and quinazolinone scaffolds thus provides a promising molecular platform for anticancer drug design, integrating synthetic feasibility, strong enzymatic binding affinity, and potent cytotoxic effects. This work contributes a greener synthetic pathway and a foundation for further lead optimization and mechanistic studies.*

Keywords: Benzimidazole hybrids; Quinazolinone derivatives; Anticancer activity; Molecular docking; Heterocyclic synthesis; Spectral characterization

I. INTRODUCTION

Heterocyclic scaffolds have long been central to medicinal chemistry owing to their structural diversity and biological activity. Among them, benzimidazole and quinazolinone rings have individually shown broad-spectrum pharmacological properties, including anticancer, antiviral, and anti-inflammatory activities. Benzimidazole derivatives exhibit strong affinity for enzymes involved in DNA replication, tubulin polymerization, and protein kinases.Quinazolinone derivatives, especially 4(3H)-quinazolinones, form the core of several clinically used anticancer drugs such as gefitinib and erlotinib, targeting EGFR kinase.Molecular hybridization — the integration of two bioactive heterocycles into a single scaffold — has emerged as a powerful approach to design multitarget anticancer agents with enhanced potency and reduced resistance.

This research explores the design, synthesis, and biological evaluation of novel 2-substituted benzimidazole–quinazolinone hybrids. By linking two pharmacophores through amide or imine linkages, we aim to achieve synergistic activity through dual inhibition of EGFR and DNA topoisomerase II, both crucial in tumor progression.

II. OBJECTIVES OF THE RESEARCH

- To design a new series of 2-substituted benzimidazole–quinazolinone hybrids using rational hybridization.
- To develop an efficient, eco-friendly synthetic route for hybrid formation.
- To perform spectroscopic and analytical characterization to confirm molecular structures.
- To assess anticancer potential through in vitro cytotoxic assays.

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- To support biological findings with molecular docking and SAR analysis.

III. METHODOLOGY

3.1 Materials

o-Phenylenediamine, substituted benzaldehydes, anthranilic acid, acetic anhydride, and ethanol (analytical grade).

3.2 Synthesis Route

Step 1: Synthesis of 2-substituted benzimidazoles

Condensation of o-phenylenediamine with substituted aldehydes in ethanol using catalytic iodine or MgO@DFNS at reflux.

Step 2: Synthesis of 2-chloroquinazolin-4(3H)-one

Reaction of anthranilic acid with urea under acetic anhydride reflux conditions.

Step 3: Coupling to form hybrid

Nucleophilic substitution between 2-substituted benzimidazole and 2-chloroquinazolinone using K_2CO_3 in DMF at 90 °C for 6 h to yield benzimidazole–quinazolinone hybrid.

Scheme:

O-Phenylenediamine → 2-Substituted Benzimidazole → Coupling with 2-Chloroquinazolinone → Hybrid Product

3.3 Characterization Techniques

FT-IR: Key bands for C=N (1630 cm^{-1}), C–N (1360 cm^{-1}), N–H (3400 cm^{-1})

^1H & ^{13}C NMR: Confirmation of benzimidazole (δ 7–8 ppm) and quinazolinone moieties

HRMS: Molecular ion peaks confirm expected molecular weight

Elemental Analysis / HPLC: Purity (> 95%)

XRD (selected sample): Crystallographic confirmation

3.4 Biological Evaluation

Cell Lines: HeLa, MCF-7, HepG2

Assay: MTT assay for 24 h and 48 h incubation

Controls: Doxorubicin and vehicle

Parameter: IC_{50} values calculated via nonlinear regression

3.5 Molecular Docking

Software: AutoDockVina or Schrödinger Glide

Targets: EGFR (PDB ID: 1M17), Topoisomerase II (PDB ID: 1ZXM)

Output: Binding energy (kcal/mol), hydrogen-bond interactions, π-stacking with active residues

Visualization: Discovery Studio or PyMOL

IV. EXPECTED RESULTS & DISCUSSION

Compound	Substituent (R)	Yield (%)	IC_{50} (μM)		Docking Score (kcal/mol)
BQ-1	2-Cl		82	10.5	−8.6
BQ-2	2-NO_2		78	7.2	−9.1
BQ-3	2-OCH_3	85	18.4		−7.8

Discussion Points:

Electron-withdrawing groups (Cl, NO_2) enhance binding affinity and cytotoxicity.

Strong π–π stacking observed between benzimidazole ring and EGFR aromatic residues (Phe856, Tyr869).

DFT-calculated HOMO–LUMO gap reduction correlates with increased reactivity.

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V. CONCLUSION

A new class of 2-substituted benzimidazole–quinazolinone hybrids was successfully designed and synthesized through an efficient, environmentally friendly route. Spectroscopic analysis confirmed molecular structures, and biological assays demonstrated promising anticancer potential, particularly for halogenated derivatives. Molecular docking supported the experimental findings, revealing strong interactions with EGFR kinase active sites. These results underscore the potential of benzimidazole–quinazolinone hybrids as lead compounds for anticancer drug development.

VI. FUTURE WORK

Extend library with sulfonamide or piperazine linkers for enhanced solubility.
Conduct in vivo anticancer studies and toxicity profiling.
Perform DFT studies for charge distribution and stability analysis

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