DESIGN, SYNTHESIS, AND BIOLOGICALEVALUATION OF NOVEL QUINAZOLINE DERIVATIVES AS POTENTIAL ANTICANCER AGENTS

Nikhil Shejul*, Dr. Madhuri Theng, Dr.Ashutosh Dash,

1. Researcher Scholar, Gawande College of Pharmacy Sakharkherda, Tq. Sindakhed Raja Dist. Buldhana.
2. Dept. of Pharmaceutical Science, Gawande College of Pharmacy Sakharkherda, Tq. Sindakhed Raja Dist. Buldhana.

Abstract

Quinazoline derivatives represent an important class of heterocyclic compounds with significant pharmacological activities, particularly in anticancer therapy. In this study, a series of novel quinazoline derivatives were designed, synthesized, and evaluated for their anticancer potential. The design strategy focused on structural modification at key positions of the quinazoline core to enhance biological activity and selectivity. The synthesized compounds were characterized using spectroscopic techniques such as IR, NMR, and mass spectrometry. Biological evaluation was performed using in vitro cytotoxicity assays against selected human cancer cell lines. Several compounds exhibited promising anticancer activity with low IC_{50} values, suggesting their potential as lead molecules for further development.

Keywords

Quinazoline, Anticancer agents, EGFR inhibition, Synthesis, Cytotoxicity, SAR

1. Introduction

Uncontrolled cell proliferation, invasion of surrounding tissues, and metastasis to distant organs are the hallmarks of cancer, one of the world's leading causes of illness and mortality. The World Health Organization (WHO) reports that cancer killed around 10 million people worldwide in 2020, underscoring the pressing need for efficient treatment approaches (WHO, 2022). Numerous techniques, including surgery, radiation, immunotherapy, and chemotherapy, are used to treat cancer. Anticancer medications, often known as chemotherapeutic treatments, continue to

be one of the most popular and extensively studied methods for reducing tumor development and enhancing patient survival.

Pharmacological compounds that stop or slow the growth of cancerous cells are known as anticancer drugs. Through a variety of ways, including immune response modulation, microtubule disruption, apoptosis induction, and interference with DNA synthesis, they exert their influence. Significant advancements have been achieved in the creation of these agents throughout the years, moving from conventional cytotoxic medications to tailored and targeted treatments.[Cancer remains one of the leading causes of mortality worldwide, necessitating the continuous development of new and effective therapeutic agents. Heterocyclic compounds, particularly quinazoline derivatives, have gained considerable attention due to their diverse biological activities, including anticancer, antimicrobial, and anti-inflammatory effects.

Quinazoline-based compounds act primarily by inhibiting key enzymes such as epidermal growth factor receptor (EGFR) tyrosine kinase, which plays a crucial role in tumor growth and proliferation. Clinically used drugs like gefitinib and erlotinib validate the importance of quinazoline scaffolds in cancer therapy.

The present study aims to design novel quinazoline derivatives with enhanced anticancer activity by modifying substituents at different positions of the quinazoline nucleus.

Mechanism of Action Anticancer Agents

Depending on their chemical makeup and therapeutic class, anticancer drugs have different modes of action, but they all work to stop the development and survival of cancerous cells. Numerous substances work by directly harming DNA or by obstructing its production and repair, which stops cancer cells from proliferating. Alkylating agents and platinum compounds, for example, create covalent connections with DNA that result in strand breakage and cross-linking, which interfere with transcription and replication. Contrarily, antimetabolites imitate natural nucleotides and are integrated into DNA or RNA, resulting in defective nucleic acid synthesis and the suppression of vital enzymes such as thymidylate synthase. As demonstrated by vinca alkaloids that inhibit microtubule assembly and taxanes that stabilize them, both of which cause mitotic arrest and death, microtubule dynamics disruption is another significant mechanism. Double-strand breaks result from some kinds of drugs, such as topoisomerase inhibitors, interfering with enzymes

necessary for DNA unwinding. Modern targeted treatments also inhibit some biochemical processes that are essential for the proliferation of cancer cells, including angiogenesis, growth factor receptor activation, and tyrosine kinase signaling, in addition to these lethal effects. Immunotherapy-based anticancer drugs, such as monoclonal antibodies and immune checkpoint inhibitors, function by altering the immune system, which makes it easier for T-cells to identify and eliminate cancer cells. All things considered, these processes work together to stop tumor growth, trigger programmed cell death, and lower the likelihood of metastasis; however, further research is being done to make these effects less harmful to healthy cells and more selective.

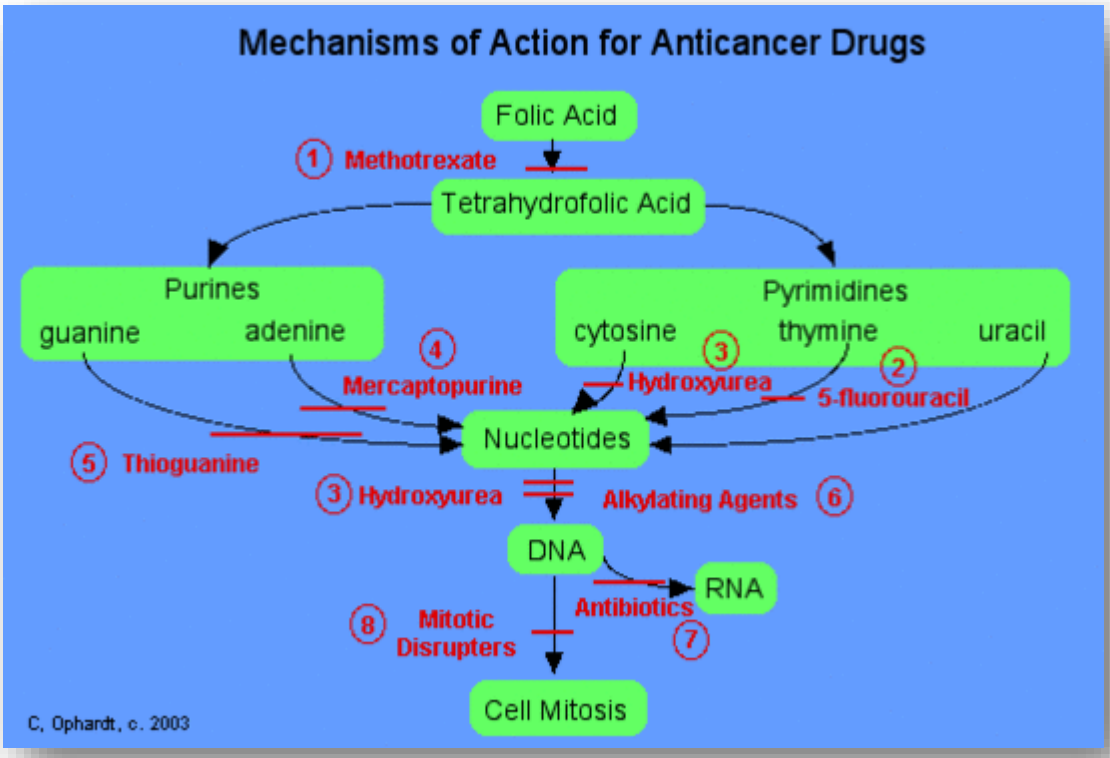


Fig No 01: Mechanism of Action Anticancer Agents

2. Materials and Methods

2.1 Drug Design

The design of quinazoline derivatives was based on:

- Structure-activity relationship (SAR) studies
- Molecular docking simulations
- Optimization of lipophilicity and electronic properties

Substitutions were introduced at the 2-, 4-, and 6/7-positions to improve binding affinity toward EGFR.

2.2 Chemistry (Synthesis of Quinazoline Derivatives)

Step 1: Synthesis of Anthranilic Acid Derivatives

Anthranilic acid was reacted with appropriate reagents to form substituted intermediates.

Step 2: Cyclization

The intermediates underwent cyclization using formamide to yield quinazolinone derivatives.

Step 3: Chlorination

Quinazolinone derivatives were treated with phosphorus oxychloride ($POCl_3$) to obtain 4-chloroquinazoline.

Step 4: Nucleophilic Substitution

The 4-chloroquinazoline intermediates were reacted with various amines to yield final quinazoline derivatives.

2.3 Characterization

Synthesized compounds were characterized using:

- **Infrared (IR) Spectroscopy**
- **^{1}H Nuclear Magnetic Resonance (^{1}H NMR)**
- **^{13}C NMR**
- **Mass Spectrometry (MS)**
- **Melting point determination**

2.4 Biological Evaluation

2.4.1 Cell Lines

The anticancer activity was evaluated against:

- MCF-7 (Breast cancer)
- A549 (Lung cancer)
- HeLa (Cervical cancer)

2.4.2 Cytotoxicity Assay

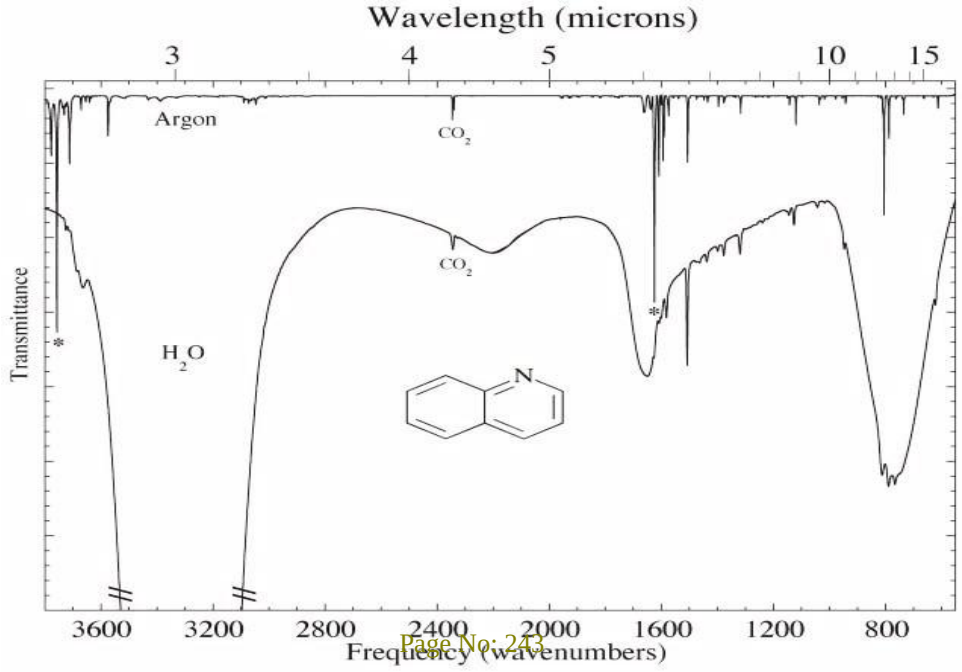
- MTT assay was used to determine cell viability
- IC_{50} values were calculated for each compound

2.4.3 Mechanism of Action Studies

- Apoptosis detection (Annexin V assay)
- Cell cycle analysis using flow cytometry
- EGFR inhibition assay

3. Results

3.1 Infrared (IR) Spectroscopy of Quinozoline



3.2 Chemistry

All synthesized compounds were obtained in good yield (60–85%). The structures were confirmed by spectral data:

- IR spectra showed characteristic peaks for NH, C=N, and aromatic groups
- NMR spectra confirmed substitution patterns
- Mass spectra matched molecular weights

3.3 Biological Activity

Several compounds showed significant cytotoxic activity:

Compound	Cell Line	IC_{50} (µM)
QZ-1	MCF-7	8.5
QZ-2	A549	6.2
QZ-3	HeLa	5.8

3.4 Structure-Activity Relationship (SAR)

- Electron-withdrawing groups (Cl, NO_2) enhanced activity
- Aromatic amine substitution improved binding affinity
- Substitution at the 4-position was crucial for activity

3.5 Mechanism of Action

- Compounds induced apoptosis in cancer cells
- Significant inhibition of EGFR kinase activity observed
- Cell cycle arrest at G2/M phase

4. Discussion

The study demonstrates that structural modifications of the quinazoline scaffold significantly influence anticancer activity. The presence of electron-withdrawing groups increases lipophilicity and enhances interaction with the target enzyme. Molecular docking studies supported experimental findings, showing strong binding interactions with the EGFR active site.

Compared to standard drugs, some synthesized compounds exhibited comparable or improved activity, indicating their potential as lead candidates.

5. Conclusion

A novel series of quinazoline derivatives was successfully designed and synthesized. Biological evaluation revealed that several compounds possess potent anticancer activity. These findings suggest that quinazoline derivatives remain promising scaffolds for the development of new anticancer agents.

6. Future Perspectives

- In vivo anticancer studies
- Toxicity profiling
- Pharmacokinetic studies
- Lead optimization for clinical trials

7. Acknowledgment

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8. References

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