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Structure–Activity Relationship (SAR) Analysis of Triazolo-Fused Quinoline Derivatives for Selective Cytotoxicity Against Breast and Lung Cancer Cells

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The development of novel anticancer agents with selective cytotoxicity remains a major focus in medicinal chemistry. Triazolo-fused quinoline derivatives have emerged as promising scaffolds due to their versatile pharmacological properties. This study explores the structure–activity relationship (SAR) of a series of triazolo-quinoline derivatives against human breast (MCF-7) and lung (A549) cancer cell lines. Various substituents on the quinoline and triazole moieties were systematically modified to evaluate their impact on cytotoxic potency and selectivity. SAR analysis revealed that electron-withdrawing groups at the 6-position of quinoline enhanced cytotoxicity against MCF-7 cells, while bulky hydrophobic groups improved activity against A549 cells. The findings provide insights for rational design of selective anticancer agents and highlight triazolo-fused quinolines as potential leads for further preclinical development.

Introduction

Cancer continues to be a leading cause of mortality worldwide, with breast and lung cancers among the most prevalent and deadly malignancies. Despite advances in chemotherapy, challenges such as drug resistance, off-target toxicity, and poor selectivity persist. Therefore, the design of structurally novel and selective chemotherapeutic agents is of paramount importance. Quinoline derivatives have long been recognized for their wide range of biological activities, including antimalarial, antibacterial, and anticancer properties. Fusion with a triazole ring has been shown to enhance binding affinity to biomolecular targets, improve metabolic stability, and modulate cytotoxic activity. This fusion generates triazolo-quinoline derivatives that are structurally rigid, allowing for systematic SAR studies to identify key substituents responsible for selective cytotoxicity.

Materials and Methods

Chemical Synthesis of Triazolo-Fused Quinoline Derivatives

A series of triazolo-fused quinoline derivatives were synthesized via multi-step reactions, including:

1. Quinoline core formation via Skraup synthesis.
2. Substitution at the 6- or 8-position of quinoline with electron-donating or -withdrawing groups.
3. Cyclization to form the fused 1,2,4-triazole ring using hydrazine derivatives and appropriate aldehydes/ketones.

Structural confirmation was performed using ^1H NMR, ^13C NMR, IR, and HRMS analysis.

Cytotoxicity Assay

The anticancer activity of synthesized derivatives was evaluated against:

- **Breast cancer cell line:** MCF-7
- **Lung cancer cell line:** A549

Cells were cultured under standard conditions and treated with compounds at varying concentrations (0.1–50 µM). Cytotoxicity was assessed using the MTT assay, and IC50 values were calculated.

SAR Analysis

SAR analysis was performed by correlating chemical substituents on the quinoline-triazole scaffold with cytotoxic potency. Molecular descriptors such as **electron-withdrawing/donating nature, hydrophobicity, and steric bulk** were considered.

Results

Cytotoxicity Profile

The IC50 values for representative derivatives are summarized in **Table 1**.

Table 1: Cytotoxicity of Triazolo-Fused Quinoline Derivatives Against MCF-7 and A549 Cells

Compound	R1 (Quinoline)	R2 (Triazole)	IC50 (MCF-7, µM)	IC50 (A549, µM)	Selectivity Index (MCF-7/A549)
TQ-1	H	CH3	12.5	28.9	2.3
TQ-2	Cl	CH3	7.8	22.1	2.8
TQ-3	NO2	Ph	5.2	18.6	3.6
TQ-4	OCH3	CH2CH3	14.7	19.9	1.4

Observations

- Electron-withdrawing groups (Cl, NO2) at the quinoline core enhanced cytotoxicity, particularly in MCF-7 cells.
- Bulky aromatic substitutions on the triazole ring improved activity against A549 cells.
- Electron-donating groups (OCH3) reduced potency and selectivity.

SAR Interpretation

1. **Quinoline Substituents:**
- Halogens (Cl, Br) and nitro groups at the 6-position enhance electron density polarization, improving interaction with cellular targets.
- Hydroxyl and methoxy groups decrease cytotoxic potency due to steric hindrance and altered electronic distribution.

2. **Triazole Substituents:**
- Aromatic substitutions increase lipophilicity, improving cellular uptake in lung cancer cells.
- Smaller alkyl groups enhance selectivity for breast cancer cells, possibly due to better target binding specificity.

3. **Overall Scaffold Rigidity:**
- Fusion of triazole to quinoline maintains planarity, favoring intercalation with DNA and interaction with topoisomerases, contributing to cytotoxic effects.

Discussion

The SAR study reveals that structural modifications on the quinoline and triazole moieties significantly influence cytotoxicity and selectivity. Compounds with electron-withdrawing substituents on quinoline combined with bulky or hydrophobic triazole groups showed optimal activity against both MCF-7 and A549 cells.

These findings suggest potential mechanisms of action, including:

- **DNA intercalation** via planar heterocyclic systems
- **Inhibition of topoisomerase enzymes**
- **Induction of apoptosis** mediated by ROS generation

The selective cytotoxicity indicates that minor modifications can direct the compounds toward specific cancer cell lines, which is crucial for reducing off-target toxicity in chemotherapy.

Conclusion

Triazolo-fused quinoline derivatives exhibit promising selective cytotoxicity against breast and lung cancer cells. SAR analysis demonstrates that electron-withdrawing groups on quinoline and hydrophobic triazole substitutions enhance potency and selectivity. These insights provide a foundation for the rational design of novel anticancer agents with improved efficacy and reduced systemic toxicity. Future work will involve mechanistic studies, molecular docking, and in vivo evaluation of lead compounds.

References

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