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Journal of Developing Drugs

ISSN: 2329-6631

Commentary

Novel Anticancer Agents: Design, Synthesis and *in Vitro* Evaluation of Quinoline-Based Hybrids

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ABOUT THE STUDY

The pursuit of more effective and selective anticancer agents continues to be a high priority in drug development, particularly in the context of chemoresistance and non-specific cytotoxicity associated with current therapies. Quinoline-based compounds have shown promising anticancer potential due to their versatile structure and ability to interact with key biological targets such as DNA, topoisomerases, and kinases. In this study, a series of novel quinoline-based hybrid molecules were designed and synthesized with the objective of enhancing anticancer efficacy while minimizing off-target effects. The hybrids were structurally modified by introducing various pharmacophores such as aryl sulfonamides, thiosemicarbazones, and azoles at the positions of the quinoline nucleus. The synthesis pathway involved multi-step reactions starting from 2-chloroquinoline intermediates, followed by nucleophilic substitution, condensation, and cyclization techniques. All compounds were structurally confirmed by NMR, IR, and mass spectrometry.

To evaluate their biological activity, the synthesized compounds were subjected to a panel of in vitro anticancer assays using human cancer cell lines including MCF-7 (breast cancer), A549 (lung cancer), and HeLa (cervical cancer). The cytotoxicity was measured using the MTT assay, and the IC50 values were calculated to determine potency. Several derivatives showed IC50 values below 10 µM, indicating strong antiproliferative activity, especially in MCF-7 cells. The most potent compound, QH-17, exhibited an IC50 of 2.6 µM in MCF-7 and demonstrated significant induction of apoptosis as evidenced by annexin V-FITC staining and caspase-3 activation. Cell cycle analysis further revealed G2/M phase arrest in treated cells, suggesting disruption of microtubule dynamics or interference with mitotic checkpoint regulators.

Mechanistic studies were conducted to explore the interaction of selected compounds with molecular targets. Molecular docking simulations indicated that the quinoline hybrids had strong binding affinity toward topoisomerase II and PI3K, both of which are crucial targets in cancer therapy. The presence of electron-donating substituents on the phenyl rings enhanced hydrogen bonding and hydrophobic interactions within the active sites of these enzymes. In addition, Reactive Oxygen Species (ROS) levels were elevated in cells treated with QH-17, implying a potential mitochondrial pathway in mediating apoptosis. Normal human fibroblasts were also treated with the active compounds to assess selectivity, and minimal toxicity was observed in non-cancerous cells, indicating a favorable therapeutic window. The physicochemical properties of the quinoline hybrids were analyzed to determine drug-likeness using Lipinski's rule of five and ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) profiling. Most of the compounds met the drug-likeness criteria, with good oral bioavailability predictions and moderate plasma protein binding. Stability studies under physiological conditions showed that the compounds were stable at pH 7.4 for up to 48 hours, making them viable candidates for *in vivo* studies.

The development of these quinoline-based hybrids represents a significant advancement in the search for selective and potent anticancer agents. Their dual mechanism of action targeting both DNA-interacting enzymes and signaling pathways suggests that they could overcome resistance mechanisms encountered in monotherapy. The promising results obtained *in vitro* provide a compelling rationale for proceeding to *in vivo* efficacy and toxicity studies using xenograft models. Furthermore, the molecular framework of these compounds offers a versatile platform for further optimization, including the addition of tumor-targeting moieties or conjugation with nanocarriers for site-specific drug delivery.

In conclusion, this study demonstrates the successful design and synthesis of a new class of quinoline-based hybrids with potent and selective anticancer activity. The compounds, particularly QH-17, exhibit desirable pharmacological properties and promising *in vitro* efficacy against multiple cancer cell lines, including evidence of apoptotic induction and cell cycle arrest. Their ability to selectively target cancer cells while sparing normal cells underscores their therapeutic potential. Future work will involve *in vivo* validation and structural refinement to improve pharmacokinetics and minimize toxicity, aiming to develop clinically viable anticancer drugs derived from the quinoline scaffold.

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Received: 03-Feb-2025, Manuscript No. EOED-25-37621; **Editor assigned:** 05-Feb-2025, PreQC No. EOED-25-37621 (PQ); **Reviewed:** 19-Feb-2025, QC No. EOED-25-37621; **Revised:** 26-Feb-2025, Manuscript No. EOED-25-37621 (R); **Published:** 04-Mar-2025. DOI: 10.35841/2329-6631.25.14.224

Citation: Meier A (2025). Novel Anticancer Agents: Design, Synthesis and *in Vitro* Evaluation of Quinoline-Based Hybrids. J Develop Drugs. 14:224.