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Review Article

Unlocking The Therapeutic Potential Of Quinoline Hybrids In Cancer Treatment

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ABSTRACT

Cancer is a leading global health challenge, ranking as the second major cause of death after cardiovascular diseases. This complex group of diseases involves uncontrolled cellular proliferation, driven by genetic mutations and epigenetic factors. Although numerous anticancer drugs exist, they often have significant side effects. Heterocyclic compounds, especially nitrogen-containing ones like quinolines, have shown broad biological activities, including anticancer properties. Quinoline scaffolds are integral to many FDA-approved drugs due to their ability to form hydrogen bonds and their favourable polarity, enhancing drug solubility and absorption. Molecular hybridization, which combines pharmacophoric subunits from different bioactive compounds, has yielded promising anticancer hybrids. Examples include quinoline-chalcone, quinoline-oxazole, quinoline-imidazopyridine, quinoline-triazole, and quinoline-imidazole/benzimidazole hybrids. These hybrids demonstrate potent anticancer activities through mechanisms like cell cycle arrest, apoptosis induction, and inhibition of angiogenesis. Recent studies highlight the therapeutic potential of these hybrids in treating various cancers. Ongoing research and synthesis of these compounds offer new avenues for overcoming drug resistance and improving therapeutic specificity, making them promising candidates for future anticancer drug development.

INTRODUCTION

Cancer stands as one of the most daunting illnesses globally. Indeed, if there's a condition humanity still dreads the most, it's cancer. It isn't singular but rather a cluster of diseases impacting various organs and bodily systems. Its onset arises from irregular and unrestrained cellular proliferation, often surpassing the typical division rate of healthy

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cells [1]. In recent decades, cancer has emerged as the second most significant life-threatening ailment, contributing to substantial mortality rates following cardiovascular diseases [2]. Carcinogens, substances that raise cancer risk, come in many forms. They can be natural, synthetic, biological, or chemical substances [3]. A DNA mutation can cause cancer, arising from either acquired or hereditary origins. Both genetic and epigenetic factors are involved, with co-carcinogenic responses, hormonal impacts, and other epigenetic variables promoting tumors. Cancer is driven by the conversion of proto-oncogenes to oncogenes and the inactivation of tumor-suppressor genes. Cancer cells can divide quickly, as seen in plasma tumors, or slowly, as in Burkitt's lymphoma. Rapid proliferation of cancer cells leads to changes in proteins, growth factors, telomerase expression, angiogenesis, and intracellular signalling pathways controlling apoptosis and cell cycles. Sulfur mustards, used in WWI, caused marrow aplasia and were later used in chemoprevention. In recent decades, anti-cancer drugs like folate analogs, pyrimidine inhibitors, and purine inhibitors have been developed, with treatment choices depending on cancer type. Surgery can effectively remove benign, non-malignant tumors [4]. While many drugs effectively combat cancer, they can also have negative side effects [5]. Many bioactive compounds, essential for medicinal purposes, come in the form of heterocyclic molecules. These molecules can be either created in a lab setting or found naturally [6]. Rich with potential, heterocyclic compounds possess biological activity due to their inherent ability to form hydrogen bonds. This stems from the presence of nitrogen, oxygen, or sulfur atoms within their structure. These heteroatoms act as both hydrogen bond donors and acceptors, allowing them to readily interact with various therapeutic receptors, ultimately leading to diverse biological effects [7].Nitrogen-containing heterocycles are abundant in nature and are the most frequently found scaffold in approved drugs. A review of small molecule therapeutics approved by the FDA over the past five years indicates that more than half of these drugs include aromatic N-heterocycles. Additionally, N-heterocycles are a significant part of many small molecules recently approved by the FDA for cancer treatment [8]. Quinoline scaffolds are a versatile and significant structure in medicinal chemistry, prominently used for the development of various therapeutic agents. The nitrogen in the quinoline structure can participate in hydrogen bonding with target enzymes. Polarity is another crucial property that can be leveraged to decrease lipophilicity, enhance water solubility, and consequently improve oral absorption in drug design strategies [9]. These compounds exhibit a broad spectrum of biological activities, including antimicrobial, antiproliferative, antineoplastic, antimalarial, anticonvulsant, and anti-inflammatory properties.

Key Therapeutic Applications of Quinoline Scaffolds:

1. Antimicrobial Activity:

Quinoline derivatives have been synthesized and tested for their efficacy against various microbial strains. They have shown potential in combating bacterial, fungal, and protozoal infections.

2. Antiproliferative and Antineoplastic Activities:

a. Quinoline-based compounds have demonstrated significant anticancer properties. They act through multiple mechanisms such as:

- **Apoptosis Induction:**

Triggering programmed cell death in cancer cells.

- **Cell Cycle Arrest:**

Halting the progression of cancer cells through different phases of the cell cycle.

- **Inhibition of Angiogenesis:**

Preventing the formation of new blood vessels that supply nutrients to tumors.

- **Disruption of Cell Migration:**

Inhibiting the movement and invasion of cancer cells to other parts of the body.

3. Antimalarial Activity:

- Quinoline derivatives, such as chloroquine and mefloquine, have been widely used in the treatment and prevention of malaria. They work by interfering with the parasite's ability to detoxify heme, which is toxic to it.

4. Anticonvulsant Activity:

Certain quinoline compounds have been found effective in managing seizures and epilepsy by modulating neurotransmitter release and neuronal excitability.

5. Anti-inflammatory Activity:

Quinoline derivatives possess anti-inflammatory properties, making them useful in treating conditions associated with chronic inflammation [10]. The quinoline scaffold is indeed present in several well-documented anticancer drugs, contributing to their effectiveness in targeting cancer cells through various mechanisms. Here are examples of such drugs: Camptothecin, Exatecan, Bosutinib, Lenvatinib and Pelitinib.

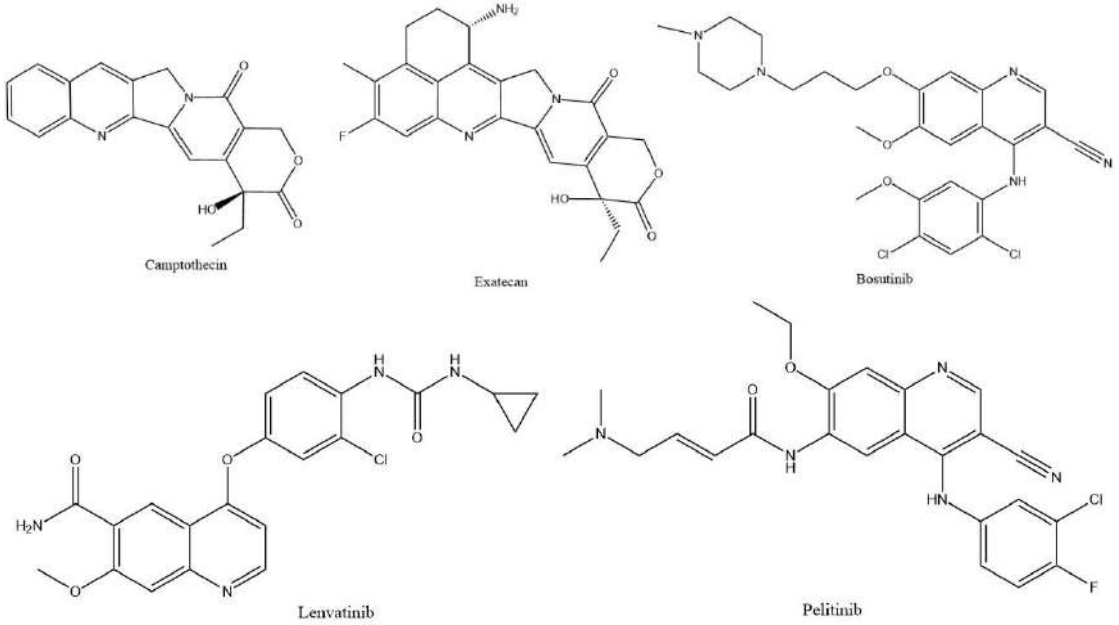


Fig. 1: The structures of some approved quinoline-containing anticancer drugs.

Molecular hybridization (MH) is a strategy for the rational design of new ligands or prototypes. It involves identifying pharmacophoric subunits in the molecular structures of two or more known bioactive compounds. By appropriately combining these subunits, new hybrid molecules are created that retain selected characteristics of the original compounds [11].

1. Quinoline- Chalcone hybrid

Found throughout nature, chalcones are a basic chemical structure present in many plant products. From vegetables and fruits to teas and beyond, these natural compounds are widely distributed [12]. The term "chalcone" originates from the Greek word "chalcos," which means "bronze," reflecting the typical cAolors of most natural chalcones [13]. Chalcone, with other names like benzylidene acetophenone, is a key building block found in many natural pigments called flavonoids. It's both easy to make in a lab and widely available in nature. Interestingly, chalcones have a surprising range of effects on living organisms. [14]. Chalcone compounds possess a chemical scaffold of 1,3-diaryl-2-propen-1-one that can be easily modified to change their biological activities. By incorporating various functional groups such as aryls, halogens, hydroxyls, carboxyls, and phenyls, chalcones can bind with

different molecular targets and interact with other molecules, displaying a wide range of biological activities. Consequently, chalcones serve as valuable templates for developing new anticancer agents. Additionally, combining the chalcone moiety with other anticancer pharmacophores can produce hybrids that may overcome drug resistance and enhance therapeutic specificity, making it a promising approach for creating novel anticancer treatments [15]. Samar H Abbas et al., synthesized novel quinoline chalcone hybrids and their subsequent biological evaluation has highlighted compounds 1a and 1b as promising candidates for cancer therapy, particularly for NSCLC and CML. Their dual ability to induce cell cycle arrest and inhibit PI3K isoforms underscores their therapeutic potential. Nonetheless, further in vivo assessments and optimization are necessary to fully realize their clinical benefits and develop them into effective PI3K inhibitors [16].

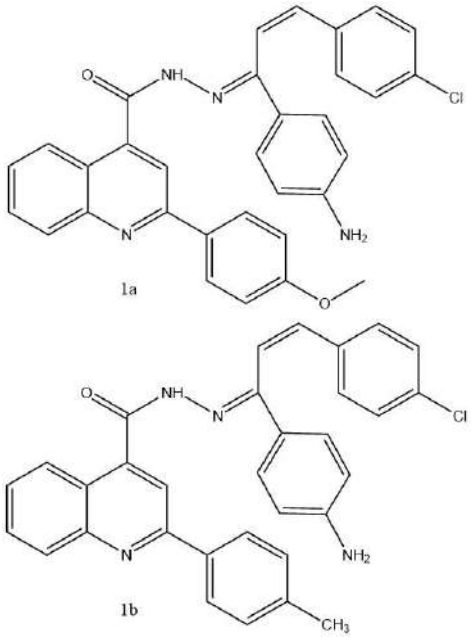


Fig 2: Structure of compound 1a and 1b

2. Quinoline – Imidazopyridine hybrid

Oxazoles are heterocycles featuring nitrogen and oxygen atoms within their five-member aromatic ring. In medicinal chemistry, oxazole compounds can easily bind to a variety of enzymes and receptors in biological systems, demonstrating a wide range of biological activities [17].The quest for potent anticancer agents has led to the synthesis of various heterocyclic hybrids with significant therapeutic potential. Among these, quinoline-based compounds have shown remarkable activity. Shailesh R. Shah et al., synthesized a novel series of quinoline-1,3-oxazole hybrids and evaluated for their anticancer properties. The synthesis of the quinoline-1,3-oxazole hybrids involved a condensation reaction between 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes (10a-f) and 6-bromo/6-chloro-2-methyl-quinolin-4-yl-hydrazines (14a/b). This reaction proceeded in good yield, resulting in twelve distinct compounds. Out of the twelve synthesized hybrids, ten were selected by the National Cancer Institute (NCI), USA, for screening against 60 different human cancer cell lines, representing nine types of cancer. The screening conducted by the NCI highlighted several compounds with potent antiproliferative activities, particularly compound 2d. The molecular docking studies further elucidated the binding interactions with topoisomerase I, reinforcing the potential of these hybrids as effective anticancer agents [18].

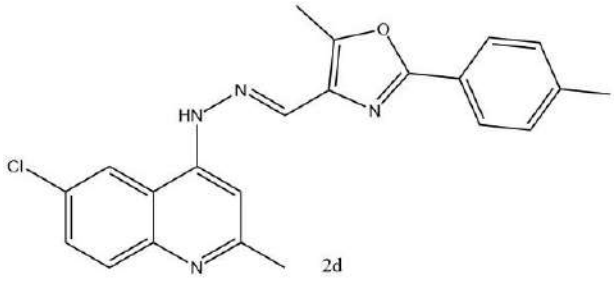


Fig 3: Structure of compound 2d

3. Quinoline – Imidazopyridine hybrid

The development of hybrid molecules combining different pharmacophores has become a promising strategy in the search for potent anticancer agents. Recently, Venkateswaran Vinayagam et al., designed and synthesized novel hybrids of imidazopyridine with quinoline to evaluate their anticancer potential. The design strategy focused on merging the imidazopyridine

core with quinoline. These hybrids were synthesized through a series of chemical reactions, optimizing the yield and purity of the final compounds. The structures of the synthesized molecules were confirmed using spectroscopic techniques such as NMR and MS. The synthesized imidazopyridine-quinoline hybrids were evaluated for their anticancer activity against four human cancer cell lines: Cervical cancer (HeLa), Breast cancer (MDA-MB231), renal cancer (ACHN), Colon cancer (HCT-15). The study highlights the potential of imidazopyridine-quinoline hybrids as potent anticancer agents. Compounds 3a and 3b, particularly compound 3b, demonstrated significant anticancer activity across various human cancer cell lines, making them promising candidates for further development [19].

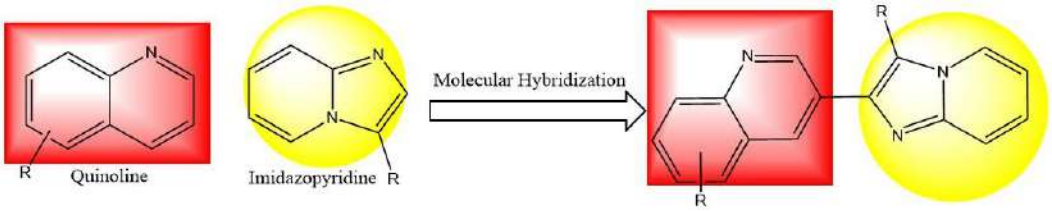


Fig 4: Design of novel hybrid compounds of Imidazopyridine with Quinoline

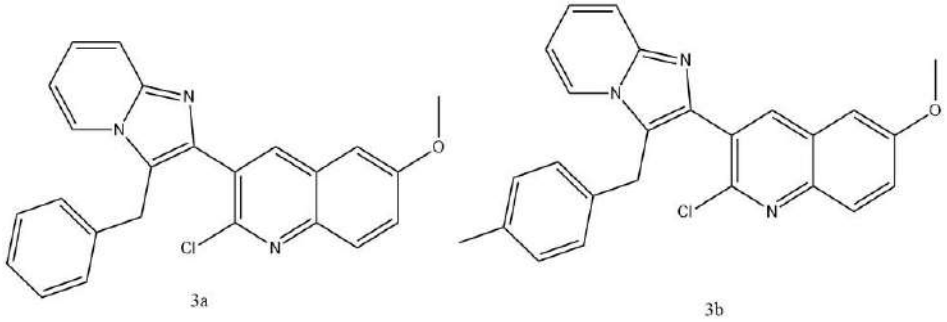


Fig 5: Structure of compound 3a and 3b

4. Quinoline-Triazole hybrid

The continuous search for novel anticancer agents has led to the exploration of various heterocyclic compounds. A recent study of Sivarami Reddy Gangireddy Venkata et al., focused on synthesizing 8-bromo-1H-1,2,3-triazol-4-yl-2-methylquinoline derivatives and their Suzuki coupling products. The aim was to develop a new series of anticancer agents with potent activity against specific cancer cell lines. The synthesis of these derivatives was achieved through a Copper-catalyzed azide-alkyne cycloaddition (CuAAC) strategy, followed by microwave-assisted Suzuki coupling. This approach allowed for efficient construction of the target molecules with good yields. The synthesized compounds were screened for their anticancer activity against two cancer cell lines: Human breast cancer (MDA-MB-231), Melanoma (B16F10). The novel 8-bromo-1H-1,2,3-triazol-4-yl-2-methylquinoline derivatives synthesized via CuAAC and microwave-assisted Suzuki coupling exhibit potent anticancer activity against breast cancer and melanoma cell lines. The compounds, particularly 4a, 4b, 4c, 4d, 4e, 4f and 4g, demonstrated significant inhibition of cancer cell growth with minimal toxicity to normal cells [20].

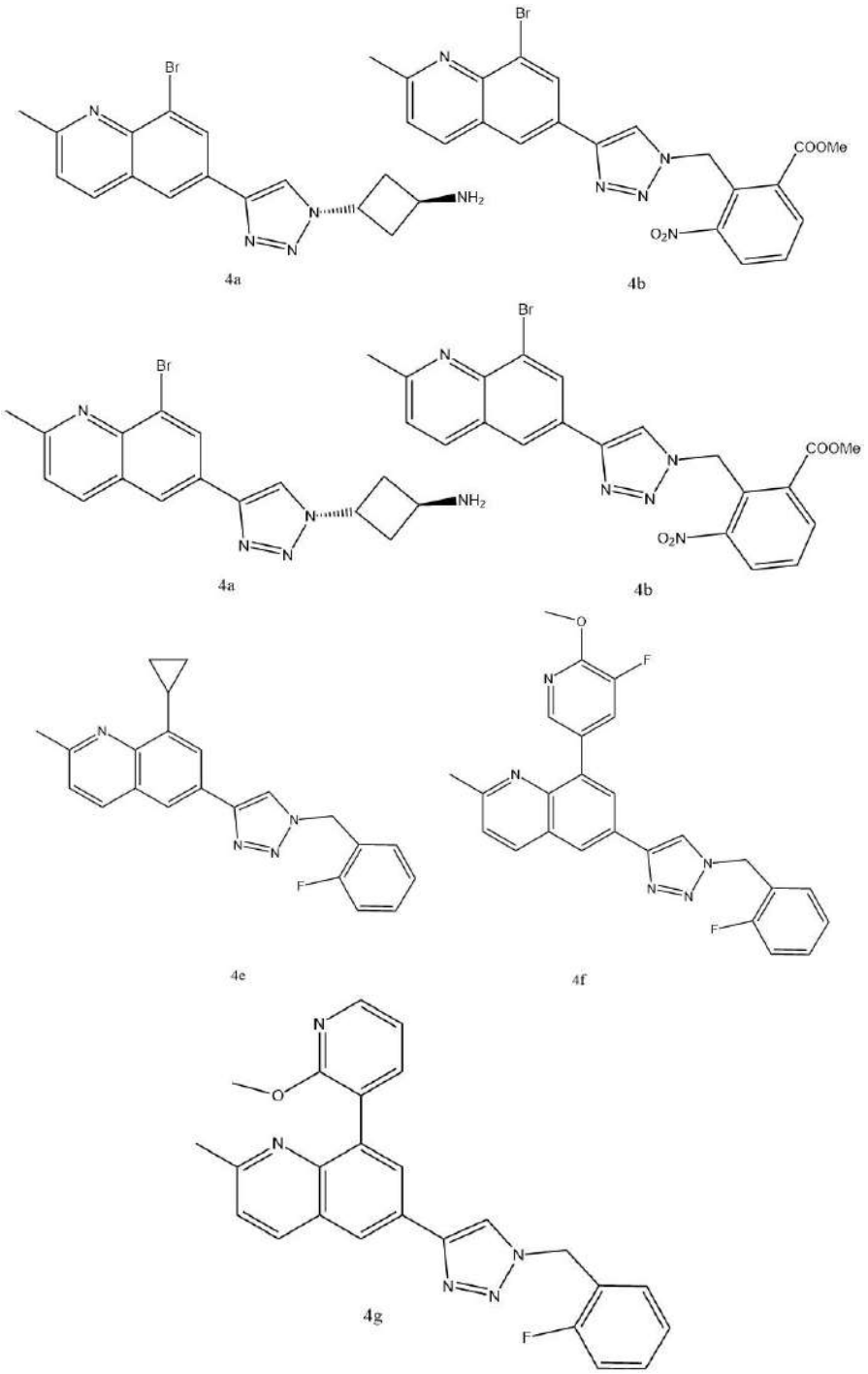
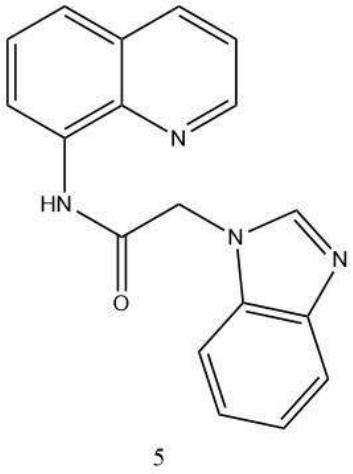


Fig 6: Structure of compound 4a, 4b, 4c, 4d, 4e, 4f, 4g

5. Quinoline- imidazole /Benzimidazole hybrid

The study of Dorina Mantu et al., highlights the potential of new hybrid imidazole/Benzimidazole –Quinoline derivatives in pharmacology, particularly as anticancer agents. The compounds were synthesized using a straightforward three-step procedure involving N-acylation, N-alkylation, and quaternization of nitrogen heterocycles. The anticancer properties of the synthesized compounds were evaluated against various cancer cell lines. Among the compounds, one hybrid derivative, referred to as compound 5, demonstrated significant and selective antitumor activity. Renal Cancer A498: Compound 5 exhibited very good activity against this cell line,

suggesting a specific affinity.Breast Cancer MDA-MB-468: Similar selective activity was observed, indicating the potential of this compound in targeting specific cancer types.The structure-activity relationship (SAR) analysis revealed that the presence of the benzimidazole and 8-aminoquinoline skeleton in compound 9 is crucial for its selective anticancer activity. These findings underscore the importance of continued SAR studies and optimization of these hybrid structures for therapeutic applications [21]



5

Fig 7: Structure of compound 5

CONCLUSION:

The exploration of quinoline hybrids in cancer treatment represents a promising frontier in medicinal chemistry. These compounds, with their diverse biological activities and ability to form hydrogen bonds, offer unique opportunities for overcoming the challenges of traditional anticancer therapies. Through molecular hybridization, novel quinoline-based compounds have been developed, demonstrating potent anticancer effects across various cancer types. The synthesis and evaluation of these hybrids continue to unveil new possibilities for targeted and effective cancer treatment strategies. As research in this field progresses, quinoline hybrids hold immense potential for revolutionizing cancer therapy, offering hope for improved outcomes and enhanced patient care in the fight against cancer.

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