Progress on quinoline-based antitumour agents: Mechanistic insights and optimization strategies (Review)

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Abstract. Quinoline derivatives are a class of heterocycles featuring a fused benzene-pyridine scaffold that have attracted notable interest in anticancer drug discovery owing to their favourable physicochemical properties, structural versatility and broad biological activities. Accumulating evidence indicates that quinoline-based compounds exert antitumour effects through several targets and pathways, including via epigenetic regulation, interference with DNA topology, inhibition of signalling pathways, immune modulation, induction of autophagy and targeting of the cytoskeleton. Structure-activity relationship (SAR) analyses demonstrate that the electronic effects and steric configurations of substituents on the quinoline ring critically determine potency, selectivity and metabolic stability. In particular, oxygenated, halogenated and strongly electron-withdrawing groups, as well as nitrogen-containing heterocyclic substituents, enhance hydrophobic interactions or hydrogen bonding with biological targets, thereby improving inhibitory efficacy. Consequently, the quinoline scaffold has emerged as a rated structural motif in anticancer lead compound discovery. Multidimensional optimisation strategies have been proposed to improve the pharmacokinetic profiles and clinical applicability of quinoline derivatives. Nanocarriers and smart stimuli-responsive delivery systems markedly enhance solubility, circulation time and tumour targeting, whereas prodrug approaches employing enzyme-sensitive, pH-responsive or redox-activated linkers enable selective activation at tumour sites. Combination therapies also exploit the multi-pathway activity of quinoline derivatives, enhancing antitumour responses and delaying resistance when combined with immunotherapy, chemotherapy or radiotherapy. Furthermore, artificial intelligence and machine learning approaches have shown increasing utility in virtual screening, quantitative structure-activity relationship modelling and multi-objective optimisation, accelerating the identification of potent, low toxicity and synthetically accessible candidates. Overall, quinoline derivatives offer systemic advantages as multi-target anticancer agents. The present review summarises recent advances in molecular mechanisms, SAR insights and drug design strategies, providing a comprehensive framework for advancing quinoline-based agents towards next-generation precision anticancer therapies.

Contents

1. Introduction

Quinoline derivatives are nitrogen-containing aromatic heterocycles consisting of fused benzene and pyridine rings. Since they were first synthesized in the 19th century, quinolines have attracted considerable attention in medicinal chemistry, materials science and biocatalysis given their distinctive electronic properties, namely an extended and polarisable π-conjugated aromatic system formed by fusion of an electron-deficient pyridine ring to a benzene ring, which confers a substantial dipole moment, weak basicity (pKa of the conjugate acid, ~4.9) and a ring nitrogen lone pair available for coordination, hydrogen bonding and π-π stacking, and favourable biocompatibility (1,2). The quinoline scaffold (Fig. 1) confers high molecular stability and lipophilicity, while the coordination

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capacity of its ring nitrogen facilitates interactions with various biomacromolecules, including DNA, RNA, enzymes and receptors, thereby producing diverse pharmacological activities (1,3-6).

In drug discovery and development, quinoline compounds constitute a structurally diverse and functionally versatile class of privileged scaffolds. Their derivatives exhibit notable antibacterial, antimalarial, antiviral, anti-inflammatory and anticancer activities (7). Early representative drugs, such as chloroquine and hydroxychloroquine, exert antimalarial effects by disrupting parasite metabolism (8). Structural modification and expansion of the quinoline scaffold have subsequently led to the development of several anticancer candidates, including ametantrone and lenvatinib, as well as various novel histone deacetylase (HDAC), topoisomerase and EGFR inhibitors (9-11).

Compared with conventional single-target anticancer agents, quinoline derivatives often exhibit synergistic effects across multiple targets. They can directly interfere with key tumour-associated signalling pathways, including PI3K/AKT/mTOR, MAPK/ERK and p53-murine double minute 2 (MDM2), thereby blocking cell-cycle progression and inducing tumour cell apoptosis (12-15). Quinoline scaffolds can also modulate immune responses and autophagy within the tumour microenvironment, indirectly enhancing antitumour immunity (12,16,17). This multilayered pharmacological profile provides quinoline-based compounds with distinct advantages in overcoming drug resistance, improving selectivity and facilitating combination therapies.

The quinoline core is amenable to structural modification. Substituents such as -OCH_3, -F, -CF_3, -NH_2 and -$CONH_2$, together with fused heterocyclic motifs including indoloquinoline, thienoquinoline and quinazoline frameworks, can markedly alter physicochemical properties and target affinity through electronic and steric effects (18). Advances in molecular design and high-throughput screening (HTS) have enabled the generation of extensive quinoline derivative libraries through pharmacophore hybridisation, structure-guided synthesis and artificial intelligence (AI)-assisted design. Several candidates with greater anticancer potential than conventional drugs have subsequently been identified in preclinical studies, including quinoline-indole hybrids that are more potent than 5-fluorouracil in gastric, oesophageal and colon cancer cells (19), quinoline-based EGFR/HER-2 dual inhibitors with nanomolar activity against breast and lung cancer cells (20), 4-phenoxyquinoline c-Met inhibitors that are more cytotoxic than foretinib (21) and combretastatin A-4 quinoline analogues with sub-micromolar antiproliferative activity (22).

Targeted optimisation strategies have also been proposed to address limitations such as poor solubility and relatively high toxicity. For example, constructing dual-responsive quinolinium-based prodrugs through N-methylation enables selective activation by tumour-associated β-glucosidase and H_2O_2, resulting in tumour-specific drug release, enhanced solubility, increased mitochondrial targeting and reduced systemic toxicity. Similarly, incorporating the quinoline motif into lipid nanoparticles exploits the proton-sponge effect and specific interactions with the lysosomal protein saposin B to improve endosomal escape. This design markedly increases accumulation and the maximum tolerated dose compared with free quinoline compounds (23,24). Concurrently, structural optimisation and activity prediction facilitated by AI and molecular simulation provide powerful tools for the rational design and accelerated screening of quinoline-based agents (25,26).

Collectively, the distinctive structural properties and multi-target regulatory capabilities of quinoline derivatives have established them as a focus of anticancer drug development. Based on a systematic overview of quinoline derivatives structural features and antitumour mechanisms, the present review highlights recent advances in epigenetic regulation, topoisomerase inhibition, signalling pathway modulation, immune and autophagic regulation, structure-activity relationships (SAR), drug-delivery strategies and AI-assisted design. The present review thereby provides insights into the structural optimisation and development of next-generation quinoline-based anticancer agents.

2. Major antitumour mechanisms of quinoline derivatives

Quinoline derivatives exhibit considerable multitarget and multilayered anticancer properties. Their molecular mechanisms span nuclear-level epigenetic regulation and topoisomerase inhibition, as well as modulation of signalling pathways, immune and autophagy regulation and cytoskeletal targeting (Fig. 1). This integrative regulatory capacity, operating across the nucleus, cytoplasm and signalling networks, confers unique advantages in overcoming tumour heterogeneity, drug resistance and immunosuppression within the tumour microenvironment.

HDAC inhibition. HDAC inhibitors play a critical role in cancer therapy. These compounds directly induce apoptosis in tumour cells and enhance tumour sensitivity to tumour necrosis factor-related apoptosis-inducing ligand, thereby activating apoptotic pathways and producing synergistic anticancer effects (27). HDAC inhibitors can modulate cell-cycle regulation by altering the acetylation of key regulatory elements, including the p21 wild-type p53-activated fragment 1/CDK-interacting protein 1 promoter (28). Several HDAC inhibitors have entered clinical development. For example, vorinostat and romidepsin are used clinically to treat cutaneous T cell lymphoma. These agents exhibit improved pharmacodynamic and pharmacokinetic properties, effectively inhibiting tumour growth, promoting apoptosis and enhancing antiangiogenic activity through regulation of the Janus kinase 2/STAT3/VEGFA signalling axis (29).

To enhance the selectivity and anticancer potency of existing HDAC inhibitors, a range of structural modifications have been introduced into the quinoline scaffold to improve the inhibition of specific HDAC isoforms. A series of newly designed quinoline-indole hybrid compounds have exhibited potent antiproliferative activity against several human cancer cell lines. Among these, 2-chloro-4-(5-methoxy-1H-indol-3-yl) quinoline (compound 1; Fig. 2A) displayed greater antiproliferative activity against MGC-803 gastric cancer, KYSE450 oesophageal cancer and HCT-116 colon cancer cells than the positive control 5-fluorouracil, as indicated by the lower IC50 values of compound 1 (19), although inhibition of individual HDAC isoforms was not assessed in that study. These

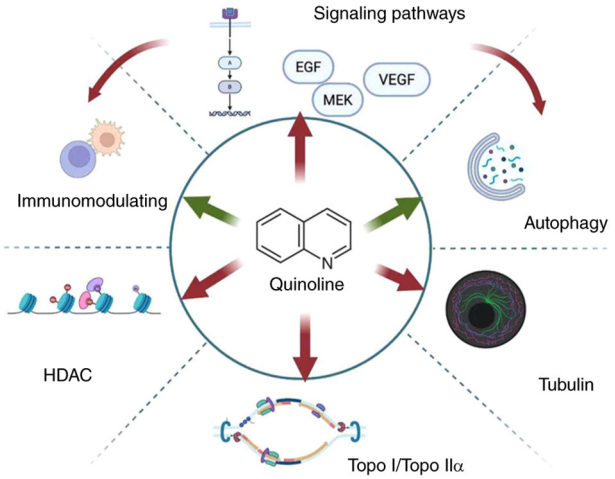

Figure 1. Integrated molecular mechanisms underlying the anticancer activity of quinoline derivatives. Green arrows indicate activating or stimulatory effects, whereas red arrows indicate inhibitory or suppressive effects. Parts of the figure were created Created in BioRender. (BioRender.com/c248457). HDAC, histone deacetylase; Topo, topoisomerase.

findings highlight the importance of rational substituent incorporation into the quinoline core for enhancing antitumour potency. In another study, a series of novel 3,4,5-trimethoxyphenyl-quinoline hybrids were designed and synthesised, and several compounds exhibited potent antiproliferative effects against various tumour cell lines. N-[3-(chloromethyl) benzyl]-3,4,5-trimethoxy-N-(quinolin-8-yl) benzamide (compound 2; Fig. 2B) demonstrated strong activity against PC-3 prostate cancer cells, with an IC50 value of 9.23 μmol/l, and induced apoptosis by activating apoptosis-related signalling pathways (30), although its activity against individual HDAC isoforms was not reported.

HDAC inhibitors can also exert antitumour effects by modulating immune responses, and the incorporation of quinoline scaffolds further enhances immune-cell activity within the tumour microenvironment, thereby strengthening antitumour immune responses. Combining HDAC inhibitors with immune checkpoint inhibitors markedly increases the abundance of CD8+ T cells and natural killer (NK) cells within the tumour microenvironment, thereby improving therapeutic responses (31). Certain quinoline derivatives can also upregulate transcription factors such as B-cell lymphoma 6 (Bcl-6), eomesodermin (EOMES), hypoxia-inducible factor 1-α (HIF-1α) and T-box expressed in T cells (T-bet) while activating the AKT/mTOR or NF-κB signalling pathways, ultimately enhancing the cytotoxic activity of CD8+ cytotoxic T lymphocytes (12,32).

Quinoline-based HDAC inhibitors developed through pharmacophore-guided modelling have also demonstrated potent *in vitro* activity. For example, compound 3 (Fig. 2C) exhibits greater selectivity for HDAC8; it inhibits HDAC8 with an IC_{50} of 442 nM, substantially lower than that of vorinostat at 7,468 nM, and effectively induces apoptosis, indicating considerable potential for anticancer applications (33).

Future research should focus on developing selective HDAC inhibitors through strategies such as isoform-specific binding pocket-based design, thereby enabling more precise targeting and reducing off-target toxicity (34). Combination strategies integrating HDAC inhibitors with immunotherapy or chemotherapy may also produce synergistic anticancer effects.

Topoisomerase inhibition. Topoisomerase inhibitors play a pivotal role in cancer therapy by disrupting DNA replication and transcription. Their principal therapeutic targets are topoisomerase IIα (Topo IIα) and topoisomerase I (Topo I). Topo IIα is frequently upregulated in tumour cells and represents a key target of several anticancer agents. Drugs such as etoposide and doxorubicin stabilise the covalent Topo IIα-DNA complex, resulting in DNA double-strand breaks and subsequent apoptosis (35,36). Similarly, camptothecin (CPT) and its derivatives, including topotecan and irinotecan, act as Topo I inhibitors by inducing DNA single-strand breaks and exhibit potent clinical antitumour activity against metastatic colorectal and ovarian cancer types (37-39).

As topoisomerases perform essential physiological functions in normal cells, their non-selective inhibition can cause substantial toxicity. Although topoisomerase inhibitors are widely used in cancer therapy, their clinical application is often limited by severe adverse effects and drug resistance. Common toxicities include bone marrow suppression, gastrointestinal toxicity and cardiotoxicity. Such off-target damage can markedly impair patients' quality of life and treatment adherence, thereby restricting the broader clinical application of these agents (40).

Quinoline scaffolds have been investigated for the development of novel topoisomerase inhibitors with improved properties, such as greater aqueous solubility, increased tumour-cell selectivity and reduced toxicity towards non-malignant cells (41). In a previous study, a series of quinoline derivatives bearing phosphorus-containing substituents was synthesised. These compounds exhibited Topo I inhibitory activity comparable to that of the natural inhibitor CPT. Compounds 3, 4 and 5 (Fig. 3A-C) demonstrated pronounced antiproliferative activity against A549 human lung cancer cells and favourable selectivity towards non-malignant MRC5 lung fibroblasts, with no observable toxicity (42). Given the acidic pH of the tumour microenvironment, which typically ranges from 5.7-7.2, tumour-targeting nanocarriers based on poly(2-ethyl-2-oxazoline) have been developed due to their pH sensitivity and versatile terminal structure. This design enables efficient drug release under acidic conditions, enhances cellular uptake and reduces systemic toxicity (43). These strategies may facilitate the clinical translation of quinoline-based topoisomerase inhibitors.

Collectively, quinoline derivatives that act as topoisomerase inhibitors induce DNA damage-mediated cytotoxicity and offer potential for synergistic multi-target anticancer therapy.

Regulation of protein kinases and signalling pathways. Aberrant activation of protein kinases is a hallmark of dysregulated tumour signalling networks. Quinoline derivatives can interact with the ATP-binding pocket of kinases, thereby blocking key cancer-related signalling pathways such as EGFR/HER, VEGFR/cellular mesenchymal-epithelial transition factor (c-Met), PI3K/AKT/mTOR, MAPK/ERK and key regulatory axes such as the p53-MDM2 interaction, ultimately exerting potent antitumour effects.

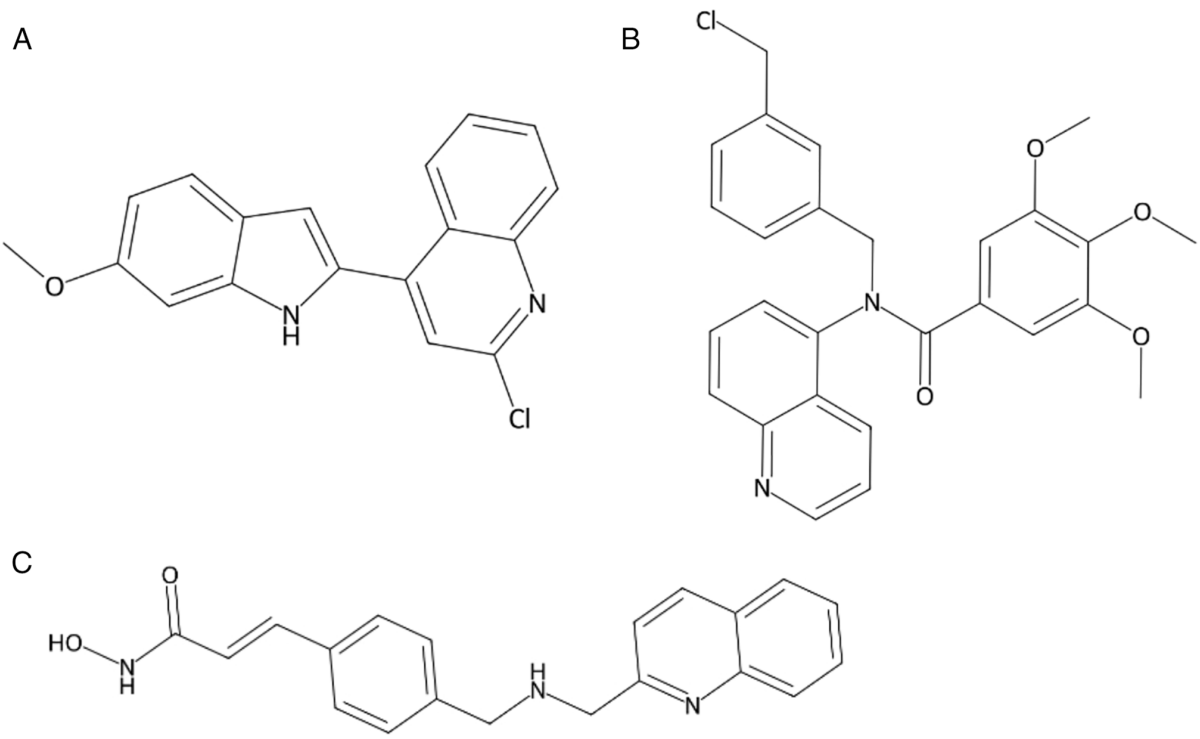

Figure 2. Structures of (A) Compound 1 [2-chloro-4-(5-methoxy-1H-indol-3-yl) quinoline], (B) Compound 2 [N-(3-(chloromethyl) benzyl)-3,4,5-trimethoxy-N-(quinolin-8-yl) benzamide] and (C) Compound 3[(E)-N-hydroxy-3-(4-(((quinolin-2-ylmethyl)amino)methyl)phenyl)acrylamide].

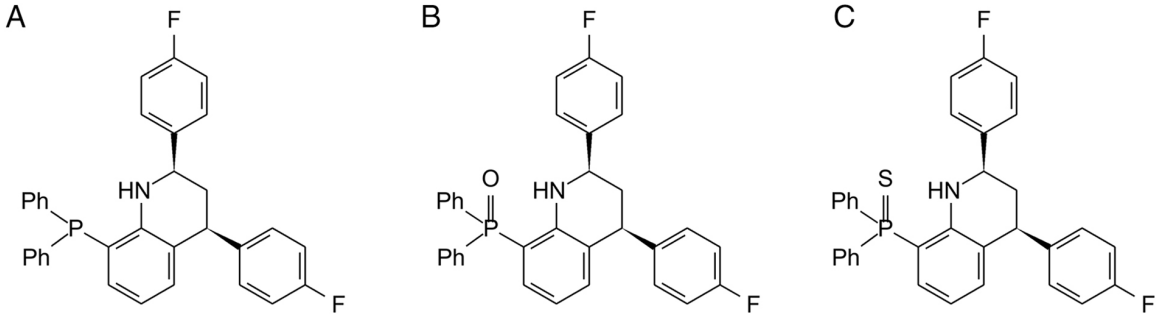

Figure 3. Structures of (A) Compound 4 [(2,4-Bis(4-fluorophenyl)-1,2,3,4-tetrahydroquinolin-8-yl) diphenylphosphine oxide], (B) Compound 5 [(2,4-Bis-(4-fluorophenyl)-1,2,3,4-tetrahydroquinolin-8-yl) diphenylphosphane] and (C) Compound 6 [(2,4-Bis(4-fluorophenyl)-1,2,3,4-tetrahydroquinolin-8-yl) diphenylphosphine sulfide].

Protein tyrosine kinases (PTKs) and their regulation. PTKs play essential regulatory roles in cellular signalling. By catalysing the transfer of the γ-phosphate group from ATP to tyrosine residues on substrate proteins, PTKs regulate a range of biological processes, including cell proliferation, differentiation, migration and apoptosis (44). Dysregulated PTK activity can aberrantly activate downstream signalling pathways, promote uncontrolled cell proliferation and drive malignant transformation, thereby contributing to cancer development (45). Consequently, PTKs have emerged as major molecular targets in anticancer drug development.

Regulation of the p53/MDM2 pathway. p53 is a central tumour suppressor protein essential for maintaining genomic stability, whereas MDM2 is its principal negative regulator, promoting p53 ubiquitination and degradation (13). Owing to their adaptable molecular recognition scaffold, quinoline derivatives have been widely investigated as potential inhibitors of the p53-MDM2 interaction to restore p53 activity and suppress tumour cell proliferation.

Structure-based virtual screening of a quinoline derivative library identified lead compound 7 (Fig. 4A). Molecular docking indicated that compound 7 occupies the MDM2-binding pocket effectively and has a higher predicted binding affinity than the established inhibitor Nutlin-3, primarily due to strong hydrophobic stacking interactions within the pocket (13). Compound 7 effectively disrupts the p53-MDM2 interaction, with IC50 values of 1.3-9.0 μM, thereby preventing MDM2-mediated p53 degradation and restoring p53 stability and transcriptional activity (14). Reactivation of the p53 pathway subsequently induces cell-cycle arrest and apoptosis in cancer cells. A preclinical study has demonstrated notable *in vitro* antitumour activity by compound 7, and further investigation is ongoing (14).

Modulation of the MAPK/ERK signalling pathway. The MAPK/ERK cascade is a central driver of tumour progression

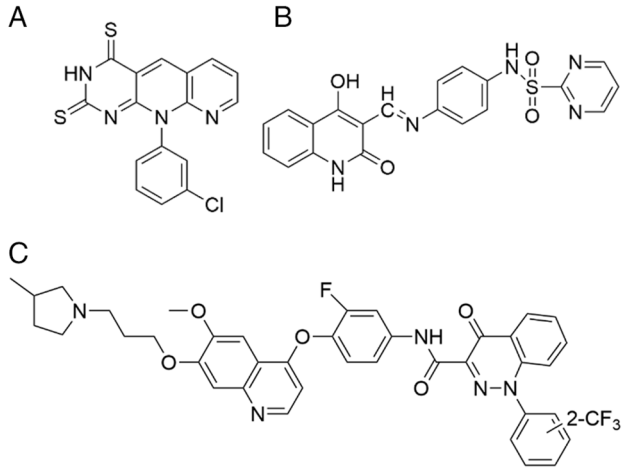

Figure 4. Structures of (A) Compound 7 [10-(3-Chlorophenyl)pyrimido [4,5-b][1,8]naphthyridine-2,4(3H,10H)-dithione], (B) Compound 8 [N-(4-(((4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl) methylene) amino) phenyl) pyrimidine-2-sulfonamide] and (C) Compound 9 [N-(3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy) phenyl)-4-oxo-1-(2-(trifluoromethyl) phenyl)-1,4-dihydrocinnoline-3-carboxamide].

in hepatocellular carcinoma (HCC) and several other malignancies, such as melanoma, non-small cell lung cancer, colorectal cancer and pancreatic ductal adenocarcinoma. Aberrant activation of the MAPK/ERK cascade accelerates tumour cell proliferation by regulating the AP-1 transcription factor subunits c-JUN (Jun proto-oncogene) and c-FOS (Fos proto-oncogene); it also reduces the expression levels of pro-apoptotic proteins, such as BIM, BAX and BAK, and increases the expression levels of anti-apoptotic genes, such as BCL-2, BCL-xL and MCL-1, thereby enhancing tumour cell survival (46,47). In addition, MAPK/ERK signalling promotes tumour invasion and metastasis by upregulating genes involved in these processes, including matrix metalloproteinase 2 (MMP2), MMP9 and epithelial-mesenchymal transition transcription factors such as SNAIL, SLUG and TWIST (48), stimulating angiogenesis to support nutrient supply and facilitating senescence evasion, allowing tumour cells to maintain sustained proliferative capacity (49). Notably, MAPK/ERK activation in HCC is less commonly driven by RAS or RAF mutations and is instead frequently sustained by alternative mechanisms, including dysregulated upstream receptor activity and reduced expression levels of negative regulators of the pathway, such as the dual-specificity phosphatases DUSP1, DUSP5 and DUSP6 and the Sprouty proteins. Persistent pathway activation is closely associated with tumour progression and poor clinical prognosis (50,51).

Singh *et al* (15) evaluated a series of quinoline derivatives as potential allosteric MEK1 inhibitors using molecular docking, long-timescale molecular dynamics simulations and molecular mechanics Poisson-Boltzmann surface area free-energy analysis. Absorption, distribution, metabolism, excretion and toxicity profiling and computer-aided toxicity prediction using Toxicity Prediction by Komputer Assisted Technology were also performed to assess drug-likeness and safety. These quinoline derivatives exhibited improved binding stability, stronger predicted affinities and lower predicted toxicity than the reference inhibitors, providing insights into the rational design of low-toxicity anticancer agents.

EGFR inhibitors. Several types of cancer cell, including non-small cell lung cancer, colorectal cancer, glioblastoma and breast cancer cells, depend heavily on EGFR signalling for tumour initiation and progression. EGFR upregulation activates RAS and PI3K pathways, thereby promoting tumour cell proliferation, migration and angiogenesis (52). The first-generation EGFR inhibitors gefitinib and erlotinib inhibit protein tyrosine kinase autophosphorylation and the downstream RAS/RAF/MEK/ERK and PI3K/AKT signalling cascades in EGFR-mutant non-small cell lung cancer cells, resulting in reduced tumour cell proliferation (53).

A series of quinoline-based dual EGFR/HER inhibitors were recently designed and synthesised (20). Among these, compound 8 (Fig. 4B) exhibited particularly potent biological activity. Compound 8 activated caspase-3, caspase-8 and the pro-apoptotic protein Bax while suppressing the expression level of the anti-apoptotic protein Bcl-2, thereby inducing apoptosis in MCF-7 breast cancer and A549 lung cancer cells. Compound 8 demonstrated potent antiproliferative activity against MCF-7 breast cancer and A549 lung cancer cells, with IC_{50} values of 71 and 31 nM, respectively. These values were lower than that of erlotinib (IC_{50}=80 nM) and comparable to that of lapatinib (IC_{50}=26 nM) (20).

c-Met signalling pathway. c-Met, a receptor tyrosine kinase, is frequently upregulated and aberrantly activated in several types of cancer, including non-small cell lung cancer, gastric cancer, hepatocellular carcinoma and renal cell carcinoma, where it promotes tumour cell proliferation, motility and invasion (21). Two series of 4-phenoxyquinoline-based small-molecule c-Met inhibitors were developed to target this oncogenic pathway. *In vitro* evaluation demonstrated that most compounds exhibited antiproliferative activity comparable to that of the reference drug foretinib. Among these, lead compound 9 (Fig. 4C) displayed the most promising profile, with greater cytotoxic activity and c-Met inhibition than foretinib (21).

VEGFR-related pathways. VEGFR-2 is frequently upregulated in a range of tumour types, including HCC, colorectal cancer, non-small cell lung cancer and renal cell carcinoma, and represents a key target in antiangiogenic drug development (54). A series of 4(3H)-quinazolinone-derived VEGFR-2 inhibitors were designed and synthesised. Among these, compounds 10, 11 and 12 (Fig. 5A-C) exhibited potent inhibitory activity, with IC_{50} values of 3.1, 3.4 and 3.7 μM, respectively. Compound 10 markedly suppressed tumour cell proliferation by inducing G2/M-phase arrest and promoting apoptosis. Molecular docking indicated that these compounds had stronger predicted binding affinities for VEGFR-2 than sorafenib. Consistent with these predictions, compounds 10, 11 and 12 exhibited potent antitumour activity in both *in vitro* assays and animal models (54).

Several quinoline-based compounds have also entered clinical trials to assess their safety and efficacy in cancer treatment. For example, tivozanib, a potent VEGFR kinase inhibitor, has demonstrated greater therapeutic efficacy than sorafenib in previously treated metastatic renal cell carcinoma in the phase III TIVO-3 trial (ClinicalTrials.gov identifier, NCT02627963) (55).

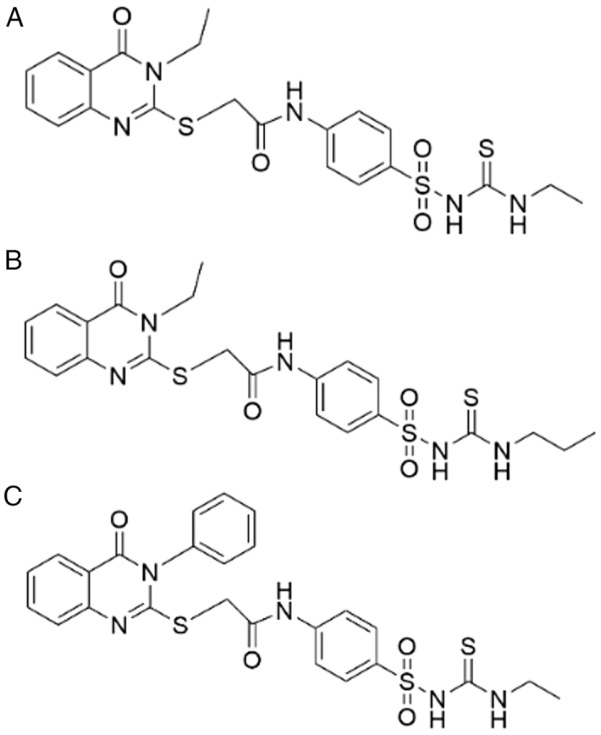

Figure 5. Structures of (A) Compound 10 [2-9(3-Ethyl-4-oxo-3,4-dihydroqu inazolin-2-yl)thio0-N-(4-(N-(ethylcarbamothioyl) sulfamoyl-)phenyl) acetamide], (B) Compound 11 [2-((3-Ethyl-4-oxo-3,4-dihydroquinazolin-2-yl) thio)-N-(4-(N-(propylcarbamothioyl) sulfamoyl) phenyl) acetamide] and (C) Compound 12 [N-(4-(N-(Ethylcarbamothioyl) sulfamoyl) phenyl)-2-((4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl) thio) acetamide].

Coordinated targeting of multiple signalling pathways. Traditional single-target tyrosine kinase inhibitors are a widely used class of cancer treatment; however, their clinical benefits are often limited by poor durability and the rapid emergence of resistance (44). Consequently, increasing attention has focused on multitarget quinoline-based kinase inhibitors that simultaneously modulate several signalling pathways, thereby enhancing antitumour efficacy and reducing compensatory resistance.

Multitarget quinoline-based pathway inhibitors have demonstrated potent antiproliferative and pro-apoptotic activity in diverse cancer models *in vitro* and *in vivo*, including glioblastoma and breast cancer cell lines and the corresponding mouse xenograft models. By simultaneously targeting proteins such as EGFR, HER2, mTOR and MDM2, multitarget quinoline-based pathway inhibitors disrupt compensatory signalling mechanisms and may overcome resistance to single-pathway inhibitors. Their therapeutic efficacy may be further enhanced by combination with cytotoxic chemotherapeutic agents. For example, co-administration of an mTOR inhibitor and a G1 to S phase transition 1 (GSPT1) degrader produced synergistic antitumour effects in glioma models, and the dual-target inhibitor YB-3-17, which simultaneously inhibits mTOR and degrades GSPT1, exhibited greater antitumour activity than single-target inhibitors in cellular assays and animal models (56).

Immunomodulatory properties. Beyond their direct effects on tumour cells, quinoline-based compounds can modulate immune function within the tumour microenvironment, thereby enhancing antitumour immune responses (17,32). This immunoregulatory capacity broadens the therapeutic scope of quinoline derivatives and provides new conceptual and mechanistic directions for their use in cancer treatment.

The PI3K/AKT/mTOR signalling cascade is widely activated in multiple malignancies, including breast, colorectal, endometrial, glioblastoma and non-small cell lung cancer, and plays a pivotal role in regulating tumour cell proliferation, metabolism, apoptosis and metastatic behaviour (32). PI3K, an upstream lipid kinase, converts phosphatidylinositol-4,5-bisphosphate into phosphatidylinositol-3,4,5-trisphosphate (PIP3). AKT, the principal downstream effector of PI3K, modulates cell survival, proliferation and metabolism through the phosphorylation of numerous substrates, including glycogen synthase kinase 3β (GSK3β), forkhead box O (FOXO) transcription factors, BCL-2-associated agonist of cell death (BAD), MDM2 and tuberous sclerosis complex 2 (TSC2). mTOR, the mammalian target of rapamycin and a key downstream node of AKT, regulates protein synthesis, cell proliferation and autophagy (57). Genomic alterations, such as mutations or amplifications in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α, AKT1 and PTEN, frequently result in aberrant activation of this pathway (32). Dysregulation can also arise from mutations or amplifications in upstream receptor tyrosine kinases, including EGFR, HER2, MET and fibroblast growth factor receptors. By targeting these critical upstream components, quinoline derivatives can reduce the production of tumour-derived immunosuppressive factors and enhance the cytotoxic functions of $CD8^+$ T cells and NK cells. Furthermore, combining these compounds with dendritic cell vaccines, immune checkpoint inhibitors or chimeric antigen receptor-T cell therapies can markedly potentiate antitumour immune responses (32). The immunomodulatory mechanisms of quinoline-based inhibitors acting on different targets are summarised in Table I (58-62).

Certain quinoline derivatives can also function as DNA intercalators or alkylating agents, disrupting DNA structure and function, inducing tumour-cell apoptosis and promoting antigen release. This release facilitates immune activation and indirectly strengthens antitumour immunity (63). Collectively, these findings highlight the dual capacity of quinoline-based compounds to exert immunomodulatory and direct antitumour effects, thereby providing multifaceted support for cancer immunotherapy.

The immunomodulatory potential of quinoline derivatives is not limited to inhibition of the PI3K/AKT/mTOR axis. Several compounds can directly engage immune receptors or metabolic checkpoints. Pan *et al* (64) developed SMUL11R, a chiral toll-like receptor 7 (TLR7) agonist based on an imidazoquinoline scaffold. In HEK Blue hTLR7 cells, SMU-L11-R activated TLR7 with an EC_{50} of 0.012±0.003 μM. Mechanistic experiments demonstrated that SMUL11R recruits myeloid differentiation primary response 88 (MyD88) and activates MAPK and NF-κB signalling, resulting in the production of TNFα, IL1β and IL6. Treatment with SMU-L11-R also affected macrophage polarisation, increasing the proportion of M1like macrophages from 26.3 to 61.1%. In the MC38 colorectal cancer model, SMUL11R inhibited tumour growth and exerted an additive effect with programmed death-ligand 1

Table I. Immunomodulatory mechanisms of quinoline-based inhibitors across different molecular targets.

First author/s, year	Inhibitor class	Primary target(s)	Potential immunomodulatory mechanisms	(Refs.)
Arteaga and Engelman, 2014	EGFR inhibitors	EGFR and HER2	EGFR/HER2 signalling plays a central role in tumour cell proliferation and survival. Inhibition of these receptors not only suppresses tumour growth directly but also modifies cytokine and chemokine expression within the tumour microenvironment, thereby affecting immune-cell infiltration and function. EGFR inhibitors may enhance antitumour immunity by reducing tumour-derived immunosuppressive mediators.	(58)
Martorana *et al*, 2020	MAPK inhibitors	MEK	The MAPK pathway is essential for immune-cell activation and function. MEK inhibition can influence immune-cell proliferation and differentiation, ultimately shaping the immune response. Additionally, suppression of MAPK signalling may reduce inflammatory cytokine production and improve the immune status of the tumour microenvironment.	(59)
Zarin *et al*, 2023	ALK5 inhibitors	ALK5 (TGF-β receptor I)	TGF-β is an immunosuppressive cytokine that inhibits T cell and NK cell activity while promoting the differentiation of regulatory T cells and myeloid-derived suppressor cells. ALK5 inhibition diminishes TGF-β signalling and can enhance antitumour immunity by increasing $CD8^+$ T cell and NK cell infiltration and activity.	(60)
Zhang *et al*, 2018	PDGFR inhibitors	PDGFR	PDGFR signalling contributes to tumour angiogenesis and microenvironmental remodelling. Inhibition of PDGFR can reduce angiogenesis, improve oxygen and nutrient delivery and promote immune cell infiltration. Moreover, PDGFR blockade may decrease the recruitment of immunosuppressive cell populations, thereby strengthening antitumour immune responses.	(61)
Byeon *et al*, 2012	Src inhibitors	Src	Src signalling regulates multiple aspects of immune cell activation, differentiation and function. Src inhibition may modulate immune responses through effects on immune cell proliferation and cytokine production. Reduced Src signalling can also reduce the product of inflammatory cytokines and promote a more favourable immune microenvironment.	(62)

PDGFR, platelet-derived growth factor receptor; NK, natural killer; EGFR, epidermal growth factor receptor; HER2, human EGFR 2; MAPK, mitogen-activated protein kinase; MEK, MAPK/ERK kinase; ALK5, activin receptor-like kinase 5; TGF-β, transforming growth factor-β; Src, proto-oncogene tyrosine-protein kinase Src.

(PD-L1) blockade, which was attributed to enhanced $CD8^+$ T cell infiltration.

He *et al* (65) identified compound 30, an 8-methoxy-3-cyanoquinoline derivative, as a potent ectonucleotide pyrophosphatase/phosphodiesterase family member 1 (ENPP1) inhibitor. The compound displayed IC_{50} values of 8.05 nM against ENPP1 and 1.53 nM in MDA-MB-231 triple-negative breast cancer cells, while showing negligible activity against the human ether-à-go-go-related gene potassium channel and a panel of 97 kinases. By blocking cyclic GMP-AMP degradation, compound 30 activated the stimulator of interferon genes pathway. In the same study, compound 30 slowed tumour progression in CT26 colorectal tumour-bearing mice, promoted immune-cell infiltration, increased type I interferon responses and enhanced the efficacy of anti-PD-L1 therapy.

Autophagy-modulating properties. Autophagy is an evolutionarily conserved self-degradative process in which damaged organelles, misfolded proteins and other intracellular components are sequestered within double-membrane autophagosomes and subsequently degraded following fusion with lysosomes. Increasing evidence highlights the dual roles of autophagy in tumour biology and therapeutic response (66,67). Moderate autophagy removes damaged cellular components, maintains cellular homeostasis and protects cells against stress-induced injury. However, excessive autophagy can

induce autophagic cell death, which has potential applications in tumour therapy (68).

Certain quinoline derivatives trigger autophagy by suppressing the PI3K/AKT/mTOR signalling pathway, thereby relieving its inhibition of autophagy initiation. Mechanistically, these compounds inhibit PI3K activity and reduce PIP3 generation, resulting in diminished AKT phosphorylation and activation. Subsequent AKT inactivation suppresses mTOR, removes the blockade on autophagy and initiates the autophagic process (66). A notable example is berberine, an isoquinoline alkaloid isolated from *Coptis chinensis* that has been widely investigated for its anti-inflammatory and anticancer properties. One study demonstrated that berberine induces autophagy and apoptosis by modulating the PI3K/AKT/mTOR axis and regulating reactive oxygen species (ROS) levels, thereby exerting substantial antiproliferative activity across multiple tumour types, including anaplastic thyroid carcinoma, breast cancer, colorectal cancer, lung cancer and hepatocellular carcinoma. Furthermore, berberine exerts strong synergistic effects with doxorubicin in anaplastic thyroid carcinoma cells, markedly enhancing antitumour efficacy without increasing toxicity (67).

Future research should prioritise the development of multi-target quinoline-based autophagy modulators to improve the therapeutic outcomes of patients with cancer and reduce the likelihood of drug resistance.

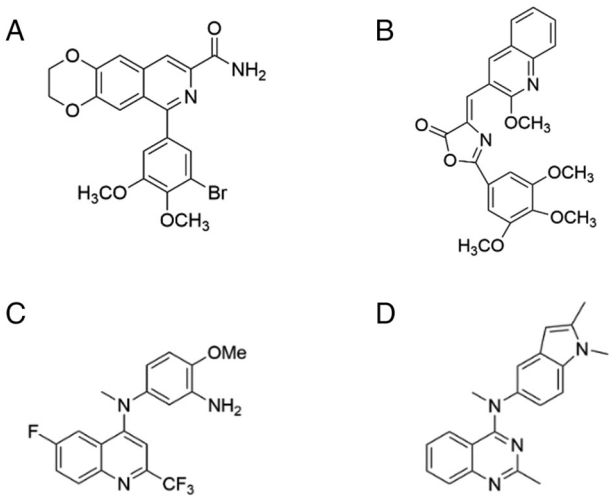

Figure 6. Structures of (A) Compound 13 [5-bromo-3,6-dimethoxybenzo[1,3] dioxol-4-yl quinazolin-4(3H)-carboxamide], (B) Compound 14 [4-[(2-Methoxy-7-methylquinolin-3-yl)methylene]-2-(3,4,5-trimethoxyphenyl) oxazol-5(4H)-one], (C) Compound 15 [N-(4-aminophenyl)-6-methoxy-N-methyl-2-(trifluoromethyl)-quinoline-4-amine] and (D) Compound 16 [N,N-Dimethyl-3-(3-(dimethylamino)-4-phenylpyrrolo[3,4-b]quinolin-1-yl)-1,2-dihydroquinolin-2-yl) methanamine].

Microtubule inhibition. Microtubules are essential cytoskeletal components assembled from α- and β-tubulin heterodimers. They participate in numerous cellular processes, including mitotic spindle formation, maintenance of cell morphology, intracellular transport and cell migration. In tumour cells, disruption of microtubule dynamics causes aberrant mitosis, thereby promoting proliferation and metastasis. Microtubule-targeting agents are broadly classified into two categories: i) Microtubule-destabilising agents, such as colchicine microtubulederivatives and vinca alkaloids, which inhibit tubulin polymerisation and promote microtubule depolymerisation; and ii) microtubule-stabilising agents, such as paclitaxel and its analogues, which enhance tubulin polymerisation and stabilise microtubule structures (69).

Previous studies have shown that numerous quinoline-based compounds possess marked microtubule-inhibitory activity and exert antitumour effects by disrupting microtubule dynamics. For example, isoquinoline derivatives inspired by the natural products podophyllotoxin and diphyllin, such as compound 13 (F10; Fig. 6A), effectively inhibit tubulin polymerisation and V-ATPase and induce immunogenic cell death. These compounds exhibit strong antiproliferative activity across four human cancer cell lines and notable tumour-suppressive effects in an RM-1 homograft mouse model (70). A series of novel combretastatin A-4 (CA-4) quinoline derivatives, represented by compound 14 (Fig. 6B), also block tubulin polymerisation, induce G2/M cell-cycle arrest and activate mitochondria-dependent apoptotic pathways, resulting in notable anticancer activity (22). Trifluoromethyl-substituted quinoline derivatives, such as compound 15 (Fig. 6C), target the colchicine-binding site on tubulin, suppress tubulin polymerisation and induce apoptosis, further highlighting the structural advantages of the quinoline scaffold in the design of microtubule-targeting anticancer agents (71).

Conventional microtubule-targeting agents, such as paclitaxel, vincristine and vinblastine, are widely used in clinical oncology. However, emerging drug resistance increasingly limits their long-term efficacy (72,73). By contrast, quinoline-based microtubule inhibitors may help overcome resistance owing to their unique electronic structures and multitarget binding properties. Several quinoline derivatives have also been designed to inhibit the aryl hydrocarbon receptor, thereby enhancing their anticancer efficacy. For example, compound 16 (Fig. 6D) remains effective against multidrug-resistant tumour cells and paclitaxel-resistant cell lines, providing a promising strategy for addressing resistance commonly encountered in clinical practice (74). Such multi-target therapeutic approaches can enhance antitumour effects through several mechanisms, including inducing cell-cycle arrest, amplifying apoptotic signalling and strengthening antitumour immune responses.

Despite the promising activity and relatively low toxicity of novel quinoline-based microtubule inhibitors *in vitro* and in animal models, their safety and potential adverse effects require further evaluation before clinical application. Most quinoline-derived microtubule inhibitors remain at the preclinical stage, and further structural optimisation is required to improve their aqueous solubility and bioavailability.

In summary, quinoline-based compounds exert antitumour effects through multilayered regulatory mechanisms encompassing nuclear processes and cytoskeletal dynamics. These mechanisms include reactivating tumour-suppressor gene expression through HDAC inhibition, disrupting DNA replication and repair by targeting topoisomerases, modulating oncogenic signalling pathways to suppress proliferation and promote apoptosis, improving the tumour microenvironment and enhancing antitumour immunity as well as disrupting cell division by interfering with microtubule dynamics, either by inhibiting tubulin polymerisation at the colchicine-binding

site or by promoting microtubule depolymerisation, which leads to G2/M-phase arrest and apoptosis. This multitarget, multipathway and multilevel mode of action distinguishes quinoline derivatives from traditional single-target agents and provides a strong conceptual and mechanistic foundation for their continued optimisation in precision anticancer drug design and combination therapies.

3. SAR and molecular modification strategies of quinoline derivatives

Quinoline is one of the most distinctive heterocyclic scaffolds and has attracted considerable attention in medicinal chemistry. The quinoline core is an effective anticancer pharmacophore and growing insight into its multitarget antitumour mechanisms has made SAR studies essential for characterising activity profiles and guiding rational optimisation. The type and position of substituents on the quinoline ring, together with the mode of heterocyclic fusion, can notably affect electronic distribution, spatial conformation and target-binding behaviour, thereby determining pharmacological potency and selectivity. Current evidence indicates that the SAR of quinoline derivatives encompasses five principal structural dimensions.

Oxygen-containing substituents: Modulation of activity and selectivity

Methoxy group (-OCH3). In EGFR/HER2 dual inhibitors, a methoxy group at the 6-position of the quinoline ring is a key structural feature. Replacing this group with a hydroxyl group (-OH) markedly reduces EGFR inhibitory activity, increasing the IC_{50} from 0.12 to 2.3 μmol/l (20). Similarly, in tubulin inhibitors derived from colchicine-inspired CA-4 analogues, introducing a methoxy group at the 4-position of the quinoline ring decreases the IC_{50} from 1.5 to 0.8 μmol/l (22). In HDAC inhibitors containing a 2-aminoquinoline scaffold, ortho-substitution of the aryl moiety with a methoxy group enhances isoform selectivity and reduces off-target inhibition (33).

3,4,5-Trimethoxyphenyl (3,4,5-$(OCH_3)_3$). In HDAC inhibitors derived from an 8-aminoquinoline core, incorporation of a 3,4,5-trimethoxyphenyl group markedly increases lipophilicity and membrane permeability, thereby facilitating cellular uptake. Deletion of any single methoxy group results in an ~40% loss of activity, indicating that the intact trimethoxy motif is indispensable for biological efficacy (30).

Hydroxyl group (-OH). In colchicine-like tubulin inhibitors, a hydroxyl at the 7-position of the quinoline ring is essential for activity. Loss of this group completely abolishes inhibitory potency, suggesting a critical hydrogen bond with the tubulin binding pocket (71). By contrast, in EGFR inhibitors, replacing the 6-hydroxyl with a methoxy group markedly reduces activity, highlighting the strong target specificity of hydroxyl-mediated interactions (20).

Halogen-containing substituents: Improving stability and metabolic properties

Chlorine (-Cl). In HDAC inhibitors featuring a 2-aminoquinoline scaffold, a chlorine atom at the 5-position markedly enhances HDAC1 inhibitory activity. For VEGFR-targeted inhibitors, synergistic effects between a 6-chloro group and a 4-piperazinyl substituent exhibit synergistic effects on molecular stability (33).

Fluorine (-F). Fluorination is commonly associated with enhanced metabolic stability and selectivity in certain quinoline-based series. In EGFR/HER2 dual inhibitors, introducing a fluorine atom ortho to the anilino group improves HER2 selectivity and metabolic stability (20). During the development of c-Met inhibitors, incorporation of a 2-fluorophenoxy group at the 4-position of the quinoline ring decreases the IC_{50} from 156 to 28 nmol/l, markedly enhancing inhibitory potency (21). However, fluorine substitution has a negligible effect in some tubulin inhibitors, further demonstrating the target-dependent nature of its effects (22,71).

Strong electron-withdrawing groups: Enhancing binding energy and conformational fit

Cyano group (-CN). In EGFR/VEGFR-2 dual inhibitors, introduction of a cyano group at the 7-position decreases binding energy from -7.2 to -9.5 kcal/mol, substantially increasing target affinity. As a strong electron-withdrawing group, the cyano group modulates the electron distribution of the quinoline core, improving spatial complementarity and electronic matching with the binding pocket, thereby stabilizing target engagement (75).

Trifluoromethyl group (-CF_3). In the development of colchicine-derived tubulin inhibitors, substitution with a CF_3 group at the 2-position increases lipophilicity and intracellular accumulation, yielding an IC_{50} of 11.2 μmol/l against MCF-7 cells and improving antiproliferative activity (71). Trifluoromethyl groups also enhance the potency and selectivity of Topo I inhibitors through their electron-withdrawing effects (42,76).

Nitrogen-containing substituents: Constructing critical pharmacophores

Anilino group (-NH-Ar). Anilide fragments can fit into the kinase hinge region. In EGFR/HER2 dual inhibitors, introduction of an anilide at the 4-position of the quinoline core forms a key pharmacophore for hinge-binding in both EGFR and HER2. Additional ortho-substitution (such as fluorine) fine-tunes steric and electronic properties, thereby enhancing target selectivity (20). In c-Met inhibitors, nitrogenous fragments derived from phenoxy motifs exert similar hinge-binding interactions, enabling high-affinity engagement with the c-Met kinase pocket (21).

Carboxamide (-$CONH_2$). Carboxamide substitution contributes to active-site construction and stabilises protein interactions. In c-Met inhibitors, a 3-position carboxamide on the quinoline core is essential for bioactivity. However, its marked susceptibility to hydrolysis can rapidly abolish antitumour activity, necessitating structural protection strategies such as steric shielding or electronic modulation (21).

Phosphoryl ester groups [-O-$PO(OR)_2$/-N-$PO(OR)_2$]. Phosphoesters improve aqueous solubility and selectivity. In Topo I inhibitors, phosphoester incorporation at the 4-oxygen or 8-nitrogen of quinoline markedly increases solubility (42). Furthermore, the alkoxy chain length on the phosphoester group is positively associated with Topo I inhibitory activity and methyl esters display three-fold higher potency than ethyl

analogues. Substitution at the 8-position yields a selectivity index of 8.3 toward HCT116 cells. Specific binding of the phosphoester to Lys48 of Topo I is critical for potent Topo I inhibition and selectivity (42,76).

Heterocyclic substituents: Spatial adaptation and target specificity

Thiophene-carboxamide (-CONH-thiophene). In studies of HDAC inhibitors based on a quinolin-2-one scaffold, the introduction of a thiophene-carboxamide group at the 3-position revealed a strong negative association between the size of the heterocycle and HDAC8 inhibitory activity. Compared with furan- or pyridine-based analogues, thiophene-substituted derivatives exhibit superior spatial accommodation within the HDAC8 active pocket and demonstrate markedly enhanced inhibitory potency (34,76).

Indole-fused scaffold. As a fused heterocycle system, the indole can be regarded as a 'large substituent'. When fused to quinoline in a 1:1 ratio, the resulting system fits precisely into the hydrophobic pocket of p53-MDM2, reducing the IC_{50} against A549 cells from 23.1 to 7.8 μmol/l and markedly improving potency and selectivity (19).

SAR studies collectively highlight the central role of the quinoline core in shaping antitumour activity and offer mechanistic insights for rational design of novel derivatives. These structure-activity associations provide a systematic knowledge base that informs the rational design priorities discussed in the following section.

4. Optimization and application strategies for quinoline-based anticancer agents

Building on the aforementioned SAR trends, particularly substituent effects on target affinity, metabolic stability and solubility, this section shifts focus from individual structural determinants to strategic approaches for overcoming pharmacokinetic and formulation barriers, including delivery platforms, prodrug engineering and combination regimens. Despite advances in elucidating the antitumour mechanisms of quinoline derivatives, their clinical translation remains constrained by poor aqueous solubility, low metabolic stability and substantial systemic toxicity. To overcome these limitations, researchers have proposed a comprehensive set of optimization strategies spanning molecular structural design, drug delivery system (DDS) engineering, combination therapy development and AI-assisted screening. These strategies not only improve the pharmacokinetic profiles and target specificity of quinoline derivatives but also provide new avenues for multi-target and individualized precision therapies.

Optimization of DDSs. Although quinoline derivatives exhibit favourable cell membrane permeability, they generally have poor solubility, heterogeneous biodistribution and insufficient target selectivity. Accordingly, DDSs have been widely used to improve the *in vivo* distribution and controlled release of quinoline derivatives. Nanocarriers typically achieve passive tumour targeting through the enhanced permeability and retention (EPR) effect. Active targeting can also be achieved by modifying the surfaces of quinoline derivative with peptides, antibodies or polysaccharide ligands, such as folic acid, RGD (Arg-Gly-Asp) peptides and anti-HER2 antibodies.

Nanocarrier-based delivery systems. Compared with conventional small-molecule formulations, nanocarrier-based delivery platforms offer notable advantages. Nanocarriers enable passive or active targeting through the physical encapsulation of therapeutic agents, protecting drugs from premature degradation and enhancing their selective accumulation at tumour sites. Quinoline derivatives can be incorporated into nanoparticle cores through hydrophobic interactions, thereby preventing crystallisation and metabolic degradation while enhancing tumour accumulation through the EPR effect (24,77). Liposomes encapsulate quinoline compounds within a phospholipid bilayer, markedly improving their plasma stability and solubility. Polyethylene glycolylated liposomes further reduce non-specific binding to plasma proteins and prolong systemic circulation, making them suitable for long-term treatment regimens (78).

Metallic nanoparticles are also promising carriers for quinoline-based drugs due to their high surface-to-volume ratios, facile surface modification and photothermal properties. For example, keratin-modified biomimetic gold nanoparticles (Ker-AuNPs) can load quinoline derivatives through hydrophobic interactions. The keratin coating improves biocompatibility and strengthens specific interactions with tumour cells. Under near-infrared irradiation, Ker-AuNPs generate heat through surface plasmon resonance, disrupting tumour cell membranes, facilitating drug uptake and enhancing drug-induced ROS production. These effects collectively induce notable tumour cell apoptosis. *In vitro* studies have shown that this keratin-modified biomimetic gold nanoparticle system exhibits greater tumour cytotoxicity and lower toxicity towards normal cells than free quinoline drugs, indicating its potential for tumour-targeted therapy (79).

A tumour-targeted nanoscale coordination polymer, abbreviated as OX/GC/CQ, has been engineered to co-deliver three therapeutic agents: Oxaliplatin, gemcitabine prodrugs and the quinoline compound, 5-carboxy-8-hydroxyquinoline. Its pH-responsive structure enables selective release of the encapsulated agents within acidic tumour tissues. This nanosystem exerts synergistic antitumour effects by inducing immunogenic cell death in cancer cells and inhibiting PD-L1 expression, thereby alleviating immunosuppression. *In vivo* experiments using colorectal and triple-negative breast cancer xenograft models demonstrated marked tumour growth inhibition and prolonged animal survival compared with the corresponding control treatments (80).

Receptor-mediated targeted delivery. Targeted delivery to specific cells or tissues can be achieved by introducing functional groups or targeting ligands into the quinoline scaffold. These moieties bind to cell-surface receptors or molecular markers, thereby increasing drug concentrations at the target site. Targeting ligands can selectively bind to receptors upregulated on tumour cells, such as EGFR or HER2. For example, certain quinoline derivatives exert antiproliferative effects on prostate cancer and glioma cells by targeting EGFR (81). Incorporating such ligands promotes drug accumulation within tumour tissues, enhancing therapeutic efficacy while limiting off-target distribution; therefore, receptor-mediated

delivery may reduce damage to normal tissues and reduce the incidence of systemic adverse effects.

Prodrug design strategies. Prodrug design represents another key approach to optimising the pharmacokinetic profiles of quinoline derivatives. This strategy involves incorporating ester, amide or disulphide linkages that are cleaved by tumour-specific enzymes or microenvironmental conditions, enabling controlled drug activation and targeted release (82).

Enzyme-responsive prodrugs. The expression or activity of certain enzymes differs markedly between tumour and normal tissues. For example, fibroblast activation protein-α (FAPα) is highly expressed in several types of tumour, including pancreatic, breast, lung and colorectal carcinomas, but expressed at low levels in normal tissues (83). Therefore, enzyme-responsive prodrugs have been developed which remain inactive until they reach the tumour microenvironment, where they are selectively recognised and hydrolysed by FAPα, releasing active quinoline-based drugs for targeted tumour therapy (83).

pH-responsive prodrugs. Tumour tissues typically exhibit an acidic microenvironment, with a lower pH than normal tissues. This feature can be exploited by engineering prodrugs that release active compounds under acidic conditions. Incorporating pH-sensitive chemical bonds into the quinoline scaffold enables bond cleavage within the acidic tumour microenvironment, thereby releasing active quinoline derivatives for targeted tumour treatment (84).

ROS-responsive prodrugs. The redox state of tumour cells differs from that of normal cells and is typically characterised by elevated levels of ROS (85). This difference can be exploited to design prodrugs that are activated under oxidative conditions. For example, incorporating ROS-cleavable groups, such as thioketal linkages, into quinoline derivatives enables prodrug activation within the ROS-rich tumour microenvironment (86).

Structural modification and controlled release optimization. Conjugation of quinoline derivatives can increase molecular polarity and improve water solubility, promoting more uniform *in vivo* distribution and greater bioavailability (87). Combining the active pharmaceutical ingredient with co-crystal formers can also produce new solid-state forms with improved physicochemical properties. Co-crystals may provide a more stable chemical environment for quinoline derivatives, reducing degradation and preserving their therapeutic performance (88).

Certain quinoline derivatives can enhance intracellular drug uptake by interacting with cell membranes and increasing membrane permeability. Cationic quinoline derivatives interact electrostatically with negatively charged membrane components, promoting endocytosis and intracellular accumulation (89). Similarly, introducing cationic groups into the quinoline scaffold strengthens interactions with cell membranes, thereby improving uptake efficiency and intracellular drug concentrations (90). This strategy may support the development of more effective therapeutic agents.

Prodrug strategies can promote the selective delivery of quinoline derivatives to tumour tissues while limiting their distribution and toxicity in normal tissues, thereby improving overall drug safety. This approach, based on chemical modification, targeted activation and controlled release, may support the clinical translation of quinoline-based therapeutics.

Combination therapy and synergistic treatment strategies. Quinoline derivatives act on multiple signalling pathways and cellular processes, making them suitable for combination therapeutic approaches. Combination therapy not only enhances antitumour efficacy but also helps delay the onset of drug resistance and remodels the tumour microenvironment from an immunosuppressive towards an immune-permissive state.

Synergy with immunotherapy. Owing to their structural flexibility and precise target-binding properties, quinoline derivatives show considerable potential for use in combination with immunotherapy, with well-defined mechanisms of action and broad therapeutic applicability.

Aberrant activation of the PI3K/mTOR pathway in tumour cells frequently contributes to an immunosuppressive microenvironment by restricting cytotoxic T cell infiltration into the tumour core and enhancing the immunosuppressive activity of regulatory T cells, thereby reducing the efficacy of immunotherapy. Quinoline-based PI3K/mTOR inhibitors can selectively block this signalling pathway, suppressing tumour cell proliferation and reversing immunosuppression. These inhibitors promote $CD8^+$ T cell accumulation within the tumour core and restore the activity of suppressed T cells, thereby increasing responsiveness to programmed cell death protein 1/PD-L1 antibodies and enhancing antitumour immunity (66). This strategy has shown potential in several tumour models, including lung cancer and melanoma, by converting immunologically 'cold' tumours into 'hot' tumours. For example, the quinoline selenocarbamate derivative EI201 inhibits AKT and mTOR phosphorylation and suppresses tumour growth in mouse xenograft models, suggesting potential therapeutic value in immunotherapy-resistant tumours (66,91).

HDACs promote immune evasion by epigenetically masking tumour antigens and impairing immune recognition. Quinoline-derived HDAC inhibitors can reverse this phenotype by upregulating major histocompatibility complex class I (MHC-I) and MHC-II expression on tumour cell surfaces. This effect facilitates antigen uptake and presentation by dendritic cells and enhances T cell-mediated antitumour responses, providing a mechanistic basis for combining quinoline-based HDAC inhibitors with immunotherapy (92).

Synergy with chemotherapy. Quinoline derivatives can be combined with agents acting through distinct mechanisms to achieve synergistic multitarget effects. For example, co-administration with topoisomerase inhibitors enhances the disruption of tumour DNA replication, thereby suppressing tumour cell proliferation (93). Combining drugs that act at different phases of the cell cycle may provide broader inhibition of tumour growth. Co-treatment with quinoline derivatives and CDK inhibitors synergistically induces cell-cycle arrest and inhibits tumour cell proliferation (94).

Combining agents that modulate different signalling pathways may also broaden antitumour activity. For example, combining quinoline derivatives with PI3K/AKT/mTOR pathway inhibitors further suppresses tumour cell proliferation and enhances therapeutic efficacy (12,95). In a phase II clinical trial involving patients with anthracycline-refractory advanced breast cancer, chloroquine combined with taxane-based

chemotherapy achieved an objective response rate of 45.16% and a median progression-free survival time of 12.4 months, exceeding the expected response rate of 30% (96).

The recent phase I REVOLUTION platform trial (NCT04787991) evaluated hydroxychloroquine combined with gemcitabine/nab-paclitaxel and ipilimumab in untreated metastatic pancreatic ductal adenocarcinoma. In cohort B, the combination achieved an objective response rate of 40% and a 12-month overall survival rate of 53.9%. Pharmacodynamic analyses demonstrated delayed but sustained increases in activated $CD4^+$ T cells and evidence of autophagy inhibition, suggesting that quinoline-based agents may modulate the tumour immune microenvironment and enhance immune checkpoint inhibitor activity. However, toxicity remained a major concern. Hydroxychloroquine-related adverse effects frequently required dose reductions, resulting in a median relative dose intensity of 60%. Only 2 patients (13%) received >90% of the intended total dose. Grade 3-4 treatment-emergent adverse events occurred in 53% of patients and one grade 5 event involving multiple organ dysfunction syndrome was reported. Consequently, the cohort was not expanded. These findings indicate that quinoline derivatives show promise in combination immunotherapy, although their toxicity and pharmacokinetic properties require improved management in future studies (97).

AI-assisted drug screening and design. In recent years, rapid advances in AI have created new opportunities for drug development and markedly improved the efficiency of quinoline-based compound discovery. Machine learning, deep learning and molecular dynamics simulations can support multiple stages of drug design, including structural optimisation and activity prediction. Advances in AI algorithms, together with improvements in automated HTS platforms, have produced notable synergistic benefits. Studies have shown that AI can process complex drug development datasets to predict compound activity and simulate target binding (25,98).

AI can efficiently analyse large chemical and biological databases containing structural, activity and pharmacokinetic data for tens of thousands of quinoline derivatives, a task that would be impractical to perform manually. Clinical databases, including The Cancer Genome Atlas (TCGA; https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga) and the Clinical Proteomic Tumor Analysis Consortium (CPTAC; https://proteomics.cancer.gov/programs/cptac), provide clinically relevant information on quinoline derivative targets, such as cell division cycle 25 (CDC25) and p53-MDM2, supporting the clinical association and validation of AI models. The fused benzene-pyridine scaffold of quinoline is amenable to structural modification. Oxygen-, nitrogen- or halogen-containing substituents can be introduced at positions 6, 7 and 8 to optimise activity. This structural diversity makes quinoline derivatives well suited to AI-driven QSAR modelling and molecular docking, facilitating high-throughput virtual screening and molecular refinement (99).

Compared with conventional discovery pipelines, AI-assisted HTS offers notable gains in efficiency, accuracy and success rates. Conventional workflows depend on the physical synthesis of compound libraries and *in vitro* validation, which are costly and time-consuming. By contrast, AI-driven virtual screening uses computational simulations for initial compound selection, thereby shortening the discovery cycle. Using Monte Carlo tree search and property-prediction models, researchers evaluated 452 million molecular building blocks within 8.5 h, generated 24,000 complete molecules, selected 58 for synthesis and identified six novel antibacterial compounds with growth-inhibitory activity against the multidrug-resistant Gram-negative pathogen *Acinetobacter baumannii*, several of which also displayed activity against *Escherichia coli*, *Klebsiella pneumoniae* and meticillin-resistant *Staphylococcus aureus*, corresponding to a hit rate of ~10% (26).

AI-based prediction of patient-specific therapeutic responses may also support personalised cancer treatment by guiding the selection of more precise and effective therapies; therefore, AI has become a practical tool in modern drug development (98). AI-assisted HTS and molecular dynamics simulations are hypothesised to accelerate the development and clinical translation of quinoline-based anticancer agents, advancing data-driven medicinal chemistry.

Overall, optimisation strategies for quinoline derivatives have evolved from simple structural modification towards an integrated framework encompassing prodrug design, targeted delivery platforms and multitarget synergy. The application of AI to molecular generation and activity prediction is accelerating the translation of quinoline compounds from laboratory research to clinical application. These advances provide promising directions and technical support for future clinical development. For comparison, the representative quinoline-based compounds discussed in the present review are summarised in Table II according to their molecular targets, biological activities and clinical development status.

5. Challenges in the clinical translation of quinoline-based anticancer agents

Although numerous quinoline derivatives have demonstrated potent antitumour activity in preclinical studies, few have progressed to clinical evaluation. Beyond toxicity, clinical translation is hindered by suboptimal pharmacokinetic properties, rapid metabolic clearance, limited tumour selectivity, inadequate biomarker-guided patient stratification and the complexity of designing combination therapies. These challenges highlight the gap between promising preclinical efficacy and successful clinical application.

SGX523 provides an instructive example of the clinical failure of a quinoline derivative. This c-MET receptor tyrosine kinase inhibitor entered clinical development for solid tumours but was discontinued due to unexpected renal toxicity. A mechanistic study revealed that aldehyde oxidase (AO) metabolises SGX523 to 2-quinolinone-SGX523, whose urinary solubility is ~3% that of the parent compound. Urinary concentrations of this metabolite were ~70-fold higher than those of SGX523, supporting the hypothesis that its precipitation within renal tubules causes obstructive nephropathy (100). This toxicity exhibits marked species dependence. The 2-quinolinone metabolite was generated by monkey and human liver S-9 fractions, to a lesser extent by rat S-9 fractions, but not by dog S-9 fractions (100). An inhibition study using raloxifene and hydralazine confirmed

Table II. Summary of quinoline-based compounds included in the present review: Mechanisms, IC_{50} values and clinical status.

First author/s, year	Compound	Mechanism of action	IC_{50} values	Clinical status	(Refs.)
Wang *et al*, 2021	1	HDAC inhibition (quinoline-indole hybrid)	1.38 μM (MGC-803); 5.34 μM (HCT-116); 5.21 μM (MCF-7)	Preclinical	(19)
Wu *et al*, 2020	2	HDAC inhibition (trimethoxyphenyl-quinoline hybrid)	9.23 μmol/l (PC-3)	Preclinical	(30)
Chen *et al*, 2017	3	HDAC8-selective inhibition	442 nM (HDAC8); 72.5 nM (HDAC1); 0.51 μM (K562)	Preclinical	(33)
Alonso *et al*, 2018	4	Topoisomerase I inhibition	0.25 μM (A549)	Preclinical	(42)
Alonso *et al*, 2018	5	Topoisomerase I inhibition	0.08 μM (A549)	Preclinical	(42)
Alonso *et al*, 2018	6	Topoisomerase I inhibition	0.03 μM (A549)	Preclinical	(42)
Dou *et al*, 2013	7	p53-MDM2 interaction inhibitor	1.3-9.0 μM (binding assay)	Preclinical	(14)
Al-Wahaibi *et al*, 2024	8	EGFR/HER2 dual inhibitor	71 nM (MCF-7); 31 nM (A549)	Preclinical	(20)
Li *et al*, 2013	9	c-Met inhibitor	0.59 nM (c-Met); 0.035 μM (A549); 0.022 μM (MKN-45)	Preclinical	(21)
Eissa *et al*, 2021	10	VEGFR-2 inhibitor	3.1 μM (VEGFR-2); 4.33 μg/ml (HepG-2)	Preclinical	(54)
Eissa *et al*, 2021	11	VEGFR-2 inhibitor	3.4 μM (VEGFR-2)	Preclinical	(54)
Eissa *et al*, 2021	12	VEGFR-2 inhibitor	3.7 μM (VEGFR-2)	Preclinical	(54)
Leng *et al*, 2024	13	Microtubule polymerization inhibitor	Not reported	Preclinical	(70)
Ibrahim *et al*, 2021	14	Microtubule polymerization inhibitor (CA-4 analogue)	0.010 μM (MCF-7); 0.019 μM (HL-60); 0.022 μM (HCT-116); 0.042 μM (HeLa)	Preclinical	(22)
Zhang *et al*, 2023	15	Microtubule polymerization inhibitor	11.2 μmol/l (MCF-7)	Preclinical	(71)
Wang *et al*, 2021	16	Microtubule polymerization inhibitor/AhR antagonist	Not reported (active against MDR cells)	Preclinical	(74)
Pan *et al*, 2025	SMUL11R	TLR7 agonist (immunomodulatory)	0.012 μM (EC50, HEK Blue hTLR7 cells)	Preclinical	(64)
He *et al*, 2025	Compound 30	ENPP1 inhibitor (STING pathway activator)	8.05 nM (ENPP1); 1.53 nM (MDA-MB-231)	Preclinical	(65)
Anand *et al*, 2021	Chloroquine	Autophagy modulator (combination with taxanes)	Not applicable (ORR, 45.16%; median PFS, 12.4 months)	Phase II	(96)
O'Reilly *et al*, 2026	Hydroxy-chloroquine	Autophagy modulator (combination with chemoimmunotherapy)	Not applicable (ORR, 40%; 12-month OS, 53.9%)	Phase I	(97)
Rini *et al*, 2020	Tivozanib	VEGFR-1/-2/-3 selective inhibitor	Not applicable (median PFS, 5.6 months vs. 3.9 months for sorafenib; HR=0.73; P=0.016)	Phase III (approved)	(55)

HDAC, histone deacetylase; MDM2, murine double minute 2; c-MET, mesenchymal-epithelial transition factor; CA-4, combretastatin A-4; MDR, multidrug resistance; AhR, aryl hydrocarbon receptor; EC50, half-maximal effective concentration; TLR7, toll-like receptor 7; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase family member 1; STING, stimulator of interferon genes; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; HR, hazard ratio.

that this species-specific metabolism is mediated by AO rather than xanthine oxidase. Humanised-liver chimeric mice have been used to model this toxicity, showing elevated serum creatinine and blood urea nitrogen levels following SGX523

administration, together with tubular accumulation of amorphous material and inflammatory cell infiltration (101). This case illustrates how metabolic liability, rather than intrinsic target toxicity, can determine clinical failure; therefore, early metabolite profiling and species-specific toxicological assessment should be incorporated into the development of future quinoline derivatives.

Cardiotoxicity represents another major concern for quinoline-based compounds. Halofantrine, a quinoline antimalarial, causes marked QT-interval prolongation at therapeutic concentrations and has been associated with sudden death, presumably resulting from malignant ventricular tachyarrhythmias (102). A systematic review of 177 trials involving 35,448 participants receiving quinoline antimalarials recorded no fatal cardiac events in clinical trial settings, although the extent of QT prolongation underscores the need for continued pharmacovigilance (102). Parenteral quinoline formulations, including chloroquine, quinine and quinidine, predictably cause hypotension when administered rapidly and transiently high plasma concentrations may result in cardiovascular collapse; therefore, cardiovascular safety should be addressed during lead optimisation rather than only during late-stage preclinical evaluation, particularly for quinoline derivatives intended for long-term administration.

Quinoline-associated neurotoxicity has been recognised since the early 1970s. Chloroquine and quinine intoxication may cause neuropsychiatric manifestations, including confusion, coma and convulsions (103). In rats, subacute exposure to diiodohydroxyquinoline induces motor and sensory abnormalities, with histopathological examination revealing degeneration and demyelination in the cerebral cortex, striatum, spinal cord and sciatic nerve. Young female rats demonstrate greater susceptibility, indicating that age and sex may be predisposing factors (103). At the neuromuscular junction, quinine, quinidine and chloroquine reduce the quantal content of end-plate potentials by 37-45% at clinically relevant concentrations ($5x10^{-5}$ M). These compounds affect presynaptic and postsynaptic transmission through open- and closed-channel blockade of acetylcholine receptors (104); therefore, neurological safety should be considered when optimising quinoline-based therapeutics, particularly compounds capable of penetrating the central nervous system.

Genotoxicity and carcinogenic risk also warrant attention. Quinoline is a well-established hepatocarcinogen in rats and mice; it exhibits mutagenic activity in *Salmonella typhimurium* TA100 following metabolic activation and induces placental glutathione S-transferase-positive foci in rat liver (105). However, structure-activity studies have identified opportunities to reduce these risks through structural modification (105,106). For example, 3-fluoroquinoline is neither mutagenic in bacterial tester strains nor carcinogenic in newborn mice; however, 5-fluoroquinoline retains both properties (106). This positional specificity suggests that fluorination at the 3-position may provide an antimutagenic and anticarcinogenic modification, presumably by inhibiting enzymatic epoxidation of the 2,3-double bond, which generates the ultimate mutagenic enamine epoxide intermediate (105). Studies in newborn mice have further shown that quinoline induces HCC, whereas certain benzoquinoline isomers lack carcinogenic activity under the same conditions (106,107). These findings provide a rational basis for designing safer quinoline derivatives and demonstrate that scaffold modification can reduce toxicological liabilities while preserving therapeutic activity.

Despite these challenges, quinoline derivatives retain considerable therapeutic potential. The identification of 3-fluoroquinoline as a non-genotoxic and non-carcinogenic analogue demonstrates that carefully designed structural modifications can eliminate specific toxicological liabilities. The SGX523 case also highlights the importance of early AO metabolism assessment and species-appropriate toxicological modelling. Together with continued structural optimisation and formulation development, these insights offer viable approaches to mitigating the remaining barriers to clinical translation. The development of quinoline-based anticancer therapeutics should consider antitumour potency alongside metabolic stability, safety, pharmacokinetic behaviour and patient stratification. Integrating these factors into medicinal chemistry optimisation will be essential for translating the promising biological activity of quinoline scaffolds into clinically successful anticancer therapies.

6. Conclusions and future perspectives

As an essential scaffold in anticancer drug research, quinoline combines a fused-ring architecture with an intramolecular nitrogen atom, conferring structural stability and strong target-binding affinity. Structural modification and functionalisation enable quinoline derivatives to modulate several hallmarks of tumour development, including DNA topology, signalling pathways, autophagy and immune remodelling. This multitarget activity may enhance the antitumour efficacy of these derivatives relative to traditional single-target agents. Nanodelivery systems and prodrug strategies can improve the pharmacokinetic properties of quinoline derivatives and reduce toxicity, while combination therapies offer potential to enhance efficacy and limit drug resistance. AI technologies and computational modelling also provide valuable tools for screening, optimising and designing new quinoline derivatives.

However, several challenges remain. The metabolic stability, solubility and toxicity of the quinoline core require further optimisation; its intrinsic multitarget activity also demands careful balancing of therapeutic selectivity and toxicity. Most newly developed candidates remain at the preclinical stage, with limited clinical translation and insufficient systematic evaluation of safety and long-term efficacy. Future research should systematically validate multitarget mechanisms, optimise the safety and controllability of prodrug and delivery systems as well as establish closed-loop drug-design pipelines integrating AI with experimental validation.

In summary, quinoline derivatives constitute a valuable and versatile structural class in medicinal chemistry with broad development potential. Research has progressed from fundamental structural studies towards intelligent drug-design paradigms. The potential applications of quinoline derivatives in precision medicine and personalised therapy may support further innovation in anticancer drug development and improve clinical outcomes.

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Authors' contributions

YZe and YY contributed equally to the conception and design of the review, performed the literature search, screened the articles, extracted and synthesized the data and drafted the initial manuscript. SW, WW and KC participated in the literature search and assisted with figure and table preparation, and reviewed and edited the manuscript. YL, QY and NZ critically revised and proofread the manuscript. YZh secured the funding, supervised the study, resolved discrepancies in study selection and data interpretation and provided critical revision of the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools (ChatGPT 5.2; https://chatgpt.com) were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

1. Zhou J, Chen Q, Ren R, Yang J, Liu B, Horton JR, Chang C, Li C, Maksoud L, Yang Y, *et al*: Quinoline-based compounds can inhibit diverse enzymes that act on DNA. Cell Chem Biol 31: 2112-2127.e6, 2024.
2. Pakhariya RP, Bhatnagar A and Pemawat G: Quinoline analogs: Multifaceted heterocyclic compounds with varied synthetic strategies and potent antitubercular properties. RSC Adv 15: 3646-3663, 2025.
3. Kadela-Tomanek M, Jastrzębska M, Chrobak E and Bębenek E: Lipophilicity and ADMET analysis of quinoline-1,4-quinone hybrids. Pharmaceutics 15: 34, 2022.
4. Lauria A, La Monica G, Bono A and Martorana A: Quinoline anticancer agents active on DNA and DNA-interacting proteins: From classical to emerging therapeutic targets. Eur J Med Chem 220: 113555, 2021.
5. Zhao M, Janda L, Nguyen J, Strekowski L and Wilson WD: The interaction of substituted 2-phenylquinoline intercalators with poly(A).poly(U): Classical and threading intercalation modes with RNA. Biopolymers 34: 61-73, 1994.
6. Graves PR, Kwiek JJ, Fadden P, Ray R, Hardeman K, Coley AM, Foley M and Haystead TA: Discovery of novel targets of quinoline drugs in the human purine binding proteome. Mol Pharmacol 62: 1364-1372, 2002.
7. Ferreira LM, García-García P, García PA and Castro MÁ: A review on quinolines: New green synthetic methods and bioactive potential. Eur J Pharm Sci 209: 107097, 2025.
8. Schrezenmeier E and Dörner T: Mechanisms of action of hydroxychloroquine and chloroquine: Implications for rheumatology. Nat Rev Rheumatol 16: 155-166, 2020.
9. Yao K, Li Y, Wei W, Liu S, Wang X, Xu J, Zhang R, Wu Z, Guo C, Yang L and Hu L: Synthesis and biological evaluation of novel 4-Arylaminoquinolines derivatives as EGFR/HDAC inhibitors. Bioorg Med Chem Lett 122: 130214, 2025.
10. Nasr EE, Mostafa AS, El-Sayed MAA and Massoud MAM: Design, synthesis, and docking study of new quinoline derivatives as antitumor agents. Arch Pharm (Weinheim) 352: e1800355, 2019.
11. Yadav P and Shah K: Quinolines, a perpetual, multipurpose scaffold in medicinal chemistry. Bioorg Chem 109: 104639, 2021.
12. Ibáñez E, Agliano A, Prior C, Nguewa P, Redrado M, González-Zubeldia I, Plano D, Palop JA, Sanmartín C and Calvo A: The quinoline imidoselenocarbamate EI201 blocks the AKT/mTOR pathway and targets cancer stem cells leading to a strong antitumor activity. Curr Med Chem 19: 3031-3043, 2012.
13. Ding H, Hu F and Hu M: Virtual screening of quinoline antitumor small molecular compounds targeting the p53-MDM2 interaction. Pharm Inf 12: 434-442, 2023.
14. Dou X, Li X, Tao L, Hu C, Zhang L, He Q, Yang B and Hu Y: Synthesis and biological evaluation of novel pyrimido[4,5-b] quinoline-2,4-dione derivatives as MDM2 ubiquitin ligase inhibitors. Med Chem 9: 581-587, 2013.
15. Singh R, Bhardwaj VK and Purohit R: Computational targeting of allosteric site of MEK1 by quinoline-based molecules. Cell Biochem Funct 40: 481-490, 2022.
16. Sun Z, Li L, Zhai B, Hu M, Huang L, Huang S, Ye L, Kong X, Xu J, Bai J, *et al*: Rational design of PARP1/c-Met dual inhibitors for overcoming PARP1 inhibitor resistance induced by c-Met overexpression. J Med Chem 67: 4916-4935, 2024.
17. Olsson A, Nakhlé J, Sundstedt A, Plas P, Bauchet AL, Pierron V, Bruetschy L, Deronic A, Törngren M, Liberg D, *et al*: Tasquinimod triggers an early change in the polarization of tumor associated macrophages in the tumor microenvironment. J Immunother Cancer 3: 53, 2015.
18. Yadav V, Reang J, Sharma V, Majeed J, Sharma PC, Sharma K, Giri N, Kumar A and Tonk RK: Quinoline-derivatives as privileged scaffolds for medicinal and pharmaceutical chemists: A comprehensive review. Chem Biol Drug Des 100: 389-418, 2022.
19. Wang S, Guan Y, Liu X, Yuan X, Yu G, Li Y, Zhang Y, Song J, Li W and Zhang S: Design, synthesis and anticancer activity studies of novel quinoline-indole derivatives. Chin J Org Chem 41: 3617-3624, 2021.
20. Al-Wahaibi LH, El-Sheref EM, Tawfeek HN, Abou-Zied HA, Rabea SM, Bräse S and Youssif BGM: Design, synthesis, and biological evaluation of novel quinoline-based EGFR/HER-2 dual-target inhibitors as potential anti-tumor agents. RSC Adv 14: 32978-32991, 2024.
21. Li S, Zhao Y, Wang K, Gao Y, Han J, Cui B and Gong P: Discovery of novel 4-(2-fluorophenoxy)quinoline derivatives bearing 4-oxo-1,4-dihydrocinnoline-3-carboxamide moiety as c-Met kinase inhibitors. Bioorg Med Chem 21: 2843-2855, 2013.
22. Ibrahim TS, Hawwas MM, Malebari AM, Taher ES, Omar AM, Neamatallah T, Abdel-Samii ZK, Safo MK and Elshaier YAMM: Discovery of novel quinoline-based analogues of combretastatin A-4 as tubulin polymerisation inhibitors with apoptosis inducing activity and potent anticancer effect. J Enzyme Inhib Med Chem 36: 802-818, 2021.
23. Yao X, Wang J, Liu J, Yu C, Hu J, Wang X, Fu J and Yin J: Developing dual-responsive quinolinium prodrugs of 8-hydroxyquinoline by harnessing the dual chelating sites. Eur J Med Chem 284: 117196, 2025.

24. Liu Z, Wu J, Wang N, Lin Y, Song R, Zhang M and Li B: Structure-guided design of endosomolytic chloroquine-like lipid nanoparticles for mRNA delivery and genome editing. Nat Commun 16: 4241, 2025.
25. Tran NL, Kim H, Shin CH, Ko E and Oh SJ: Artificial intelligence-driven new drug discovery targeting serine/threonine kinase 33 for cancer treatment. Cancer Cell Int 23: 321, 2023.
26. Swanson K, Liu G, Catacutan DB, Arnold A, Zou J and Stokes JM: Generative AI for designing and validating easily synthesizable and structurally novel antibiotics. Nat Mach Intell 6: 338-353, 2024.
27. Al-Yacoub N, Fecker LF, Möbs M, Plötz M, Braun FK, Sterry W and Eberle J: Apoptosis induction by SAHA in cutaneous T-cell lymphoma cells is related to downregulation of c-FLIP and enhanced TRAIL signaling. J Invest Dermatol 132: 2263-2274, 2012.
28. Ocker M and Schneider-Stock R: Histone deacetylase inhibitors: Signalling towards p21cip1/waf1. Int J Biochem Cell Biol 39: 1367-1374, 2007.
29. West AC and Johnstone RW: New and emerging HDAC inhibitors for cancer treatment. J Clin Invest 124: 30-39, 2014.
30. Wu B, Cui X, Zhu T, Wang S, Lu C, Wang J, Dang H, Zhang SY, Ding L and Jin C: Design, synthesis and anticancer activity studies of novel trimethoxyphenyl-quinoline derivatives. Chin J Org Chem 40: 978, 2020.
31. Fang C, Wang Y and Li Y: Research progress of histone deacetylase inhibitor combined with immune checkpoint inhibitor in the treatment of tumor. Zhongguo Fei Ai Za Zhi 24: 204-211, 2021 (In Chinese).
32. Quan Z, Yang Y, Zheng H, Zhan Y, Luo J, Ning Y and Fan S: Clinical implications of the interaction between PD-1/PD-L1 and PI3K/AKT/mTOR pathway in progression and treatment of non-small cell lung cancer. J Cancer 13: 3434-3443, 2022.
33. Chen C, Hou X, Wang G, Pan W, Yang X, Zhang Y and Fang H: Design, synthesis and biological evaluation of quinoline derivatives as HDAC class I inhibitors. Eur J Med Chem 133: 11-23, 2017.
34. Banerjee S, Adhikari N, Amin SA and Jha T: Histone deacetylase 8 (HDAC8) and its inhibitors with selectivity to other isoforms: An overview. Eur J Med Chem 164: 214-240, 2019.
35. Chen GL, Yang L, Rowe TC, Halligan BD, Tewey KM and Liu LF: Nonintercalative antitumor drugs interfere with the breakage-reunion reaction of mammalian DNA topoisomerase II. J Biol Chem 259: 13560-13566, 1984.
36. Tewey KM, Rowe TC, Yang L, Halligan BD and Liu LF: Adriamycin-induced DNA damage mediated by mammalian DNA topoisomerase II. Science 226: 466-468, 1984.
37. Hsiang YH, Hertzberg R, Hecht S and Liu LF: Camptothecin induces protein-linked DNA breaks via mammalian DNA topoisomerase I. J Biol Chem 260: 14873-14878, 1985.
38. ten Bokkel Huinink W, Gore M, Carmichael J, Gordon A, Malfetano J, Hudson I, Broom C, Scarabelli C, Davidson N, Spanczynski M, *et al*: Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. J Clin Oncol 15: 2183-2193, 1997.
39. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, *et al*: Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan study group. N Engl J Med 343: 905-914, 2000.
40. Yang X, Wang ZP, Xiang S, Wang D, Zhao Y, Luo D, Qiu Y, Huang C, Guo J, Dai Y, *et al*: Optimization of the natural product calothrixin A to discover novel dual topoisomerase I and II inhibitors with improved anticancer activity. J Med Chem 65: 8040-8061, 2022.
41. Talukdar A, Kundu B, Sarkar D, Goon S and Mondal MA: Topoisomerase I inhibitors: Challenges, progress and the road ahead. Eur J Med Chem 236: 114304, 2022.
42. Alonso C, Fuertes M, Martín-Encinas E, Selas A, Rubiales G, Tesauro C, Knudssen BK and Palacios F: Novel topoisomerase I inhibitors. Syntheses and biological evaluation of phosphorus substituted quinoline derivates with antiproliferative activity. Eur J Med Chem 149: 225-237, 2018.
43. Mao J, Li JM and Ding JS: The application of poly (2-ethyl-2-oxazoline) in drug delivery system. Acta Pharm Sin 52: 1235-1240, 2017.
44. Santoni M, Iacovelli R, Colonna V, Klinz S, Mauri G and Nuti M: Antitumor effects of the multi-target tyrosine kinase inhibitor cabozantinib: A comprehensive review of the preclinical evidence. Expert Rev Anticancer Ther 21: 1029-1054, 2021.
45. Liu D, Luan T, Kong J, Zhang Y and Wang HF: Synthesis and anti-tumor activities of 4-anilinoquinoline derivatives. Molecules 21: E21, 2016.
46. Yue J and López JM: Understanding MAPK signaling pathways in apoptosis. Int J Mol Sci 21: 2346, 2020.
47. Lavoie H, Gagnon J and Therrien M: ERK signalling: A master regulator of cell behaviour, life and fate. Nat Rev Mol Cell Biol 21: 607-632, 2020.
48. Neuzillet C, Tijeras-Raballand A, de Mestier L, Cros J, Faivre S and Raymond E: MEK in cancer and cancer therapy. Pharmacol Ther 141: 160-171, 2014.
49. Maurer G, Tarkowski B and Baccarini M: Raf kinases in cancer-roles and therapeutic opportunities. Oncogene 30: 3477-3488, 2011.
50. Delire B and Stärkel P: The Ras/MAPK pathway and hepatocarcinoma: pathogenesis and therapeutic implications. Eur J Clin Invest 45: 609-623, 2015.
51. Li L, Zhao GD, Shi Z, Qi LL, Zhou LY and Fu ZX: The Ras/Raf/MEK/ERK signaling pathway and its role in the occurrence and development of HCC. Oncol Lett 12: 3045-3050, 2016.
52. Raggi C, Mousa HS, Correnti M, Sica A and Invernizzi P: Cancer stem cells and tumor-associated macrophages: A roadmap for multitargeting strategies. Oncogene 35: 671-682, 2016.
53. Formisano L, D'Amato V, Servetto A, Brillante S, Raimondo L, Di Mauro C, Marciano R, Orsini RC, Cosconati S, Randazzo A, *et al*: Src inhibitors act through different mechanisms in non-small cell lung cancer models depending on EGFR and RAS mutational status. Oncotarget 6: 26090-26103, 2015.
54. Eissa IH, Ibrahim MK, Metwaly AM, Belal A, Mehany ABM, Abdelhady AA, Elhendawy MA, Radwan MM, ElSohly MA and Mahdy HA: Design, molecular docking, in vitro, and in vivo studies of new quinazolin-4(3H)-ones as VEGFR-2 inhibitors with potential activity against hepatocellular carcinoma. Bioorg Chem 107: 104532, 2021.
55. Rini BI, Pal SK, Escudier BJ, Atkins MB, Hutson TE, Porta C, Verzoni E, Needle MN and McDermott DF: Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): A phase 3, multicentre, randomised, controlled, open-label study. Lancet Oncol 21: 95-104, 2020.
56. Liu Y, Sun X, Liu Q, Han C and Rao Y: A dual-target and dual-mechanism design strategy by combining inhibition and degradation together. J Am Chem Soc 147: 3110-3118, 2025.
57. Li Petri G, Di Martino S and De Rosa M: Peptidomimetics: An overview of recent medicinal chemistry efforts toward the discovery of novel small molecule inhibitors. J Med Chem 65: 7438-7475, 2022.
58. Arteaga CL and Engelman JA: ERBB receptors: From oncogene discovery to basic science to mechanism-based cancer therapeutics. Cancer Cell 25: 282-303, 2014.
59. Martorana A, La Monica G and Lauria A: Quinoline-based molecules targeting c-Met, EGF, and VEGF receptors and the proteins involved in related carcinogenic pathways. Molecules 25: 4279, 2020.
60. Zarin B, Nedaeinia R, Laher I, Manian M and Javanmard SH: The effects of ALK5 inhibition and simultaneous inhibition or activation of HIF-1α in melanoma tumor growth and angiogenesis. Tumour Biol 45: 111-126, 2023.
61. Zhang N, Hu H, Fu Y, He F, Wang L, Zhuang S and Ding M: The overexpression of PDGF-BB and its receptor is correlated with lymphatic metastasis in patients with non-small cell lung cancer. Int J Clin Exp Pathol 11: 6010-6017, 2018.
62. Byeon SE, Yi YS, Oh J, Yoo BC, Hong S and Cho JY: The role of Src kinase in macrophage-mediated inflammatory responses. Mediators Inflamm 2012: 512926, 2012.
63. Chen TL, Lin YW, Chen YB, Lin JJ, Su TL, Shen CN and Lee TC: A low-toxicity DNA-alkylating N-mustard-quinoline conjugate with preferential sequence specificity exerts potent antitumor activity against colorectal cancer. Neoplasia 20: 119-130, 2018.
64. Pan Y, Fu Q, Yang M, Chen Z and Cheng K: Imidazoloquinoline optical isomers as TLR7 selective agonists promote macrophage activation for cancer immunotherapy. Bioorg Chem 166: 109041, 2025.
65. He J, Ma X, Sun J, Chen M, Xu L, Song Z, Ding C, Meng L and Zhang A: Design, synthesis, and pharmacological evaluation of quinazoline and quinoline derivatives as potent ENPP1 inhibitors for cancer immunotherapy. J Med Chem 68: 5856-5873, 2025.

66. Nishimura N, Siegmund A, Liu L, Yang K, Bryan MC, Andrews KL, Bo Y, Booker SK, Caenepeel S, Freeman D, *et al*: Phospshoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) dual inhibitors: discovery and structure-activity relationships of a series of quinoline and quinoxaline derivatives. J Med Chem 54: 4735-4751, 2011.
67. Shi XZ, Zhao S, Wang Y, Wang MY, Su SW, Wu YZ and Xiong C: Antitumor activity of berberine by activating autophagy and apoptosis in CAL-62 and BHT-101 anaplastic thyroid carcinoma cell lines. Drug Des Devel Ther 17: 1889-1906, 2023.
68. Zhou Z, Liu J, Fu T, Wu P, Peng C, Gong X, Wang Y, Zhang M, Li Y, Wang Y, *et al*: Phosphorylation regulates the binding of autophagy receptors to FIP200 Claw domain for selective autophagy initiation. Nat Commun 12: 1570, 2021.
69. Shuai W, Wang G, Zhang Y, Bu F, Zhang S, Miller DD, Li W, Ouyang L and Wang Y: Recent progress on tubulin inhibitors with dual targeting capabilities for cancer therapy. J Med Chem 64: 7963-7990, 2021.
70. Leng J, Zhao Y, Zhao S, Xie S, Sheng P, Zhu L, Zhang M, Chen T, Kong L and Yin Y: Discovery of novel isoquinoline analogues as dual tubulin polymerization/V-ATPase inhibitors with immunogenic cell death induction. J Med Chem 67: 3144-3166, 2024.
71. Zhang S, Mo M, Lv M, Xia W, Liu K, Yu G, Yu J, Xu G, Zeng X, Cheng S, *et al*: Design, synthesis and bioevaluation of novel trifluoromethylquinoline derivatives as tubulin polymerization inhibitors. Future Med Chem 15: 1967-1986, 2023.
72. Yang J, Song D, Li B, Gao X, Wang Y, Li X, Bao C, Wu C, Bao Y, Waxman S, *et al*: Replacing the tropolonic methoxyl group of colchicine with methylamino increases tubulin binding affinity with improved therapeutic index and overcomes paclitaxel cross-resistance. Drug Resist Updat 68: 100951, 2023.
73. Jiang F, Yu M, Liang Y, Ding K and Wang Y: Discovery of novel diaryl-substituted fused heterocycles targeting katanin and tubulin with potent antitumor and antimultidrug resistance efficacy. J Med Chem 67: 12118-12142, 2024.
74. Wang K, Zhong H, Li N, Yu N, Wang Y, Chen L and Sun J: Discovery of novel anti-breast-cancer inhibitors by synergistically antagonizing microtubule polymerization and aryl hydrocarbon receptor expression. J Med Chem 64: 12964-12977, 2021.
75. Fayyazi N, Fassihi A, Esmaeili S, Taheri S, Ghasemi JB and Saghaie L: Molecular dynamics simulation and 3D-pharmacophore analysis of new quinoline-based analogues with dual potential against EGFR and VEGFR-2. Int J Biol Macromol 142: 94-113, 2020.
76. Musiol R: An overview of quinoline as a privileged scaffold in cancer drug discovery. Expert Opin Drug Discov 12: 583-597, 2017.
77. Zhang X, Ma G and Wei W: Simulation of nanoparticles interacting with a cell membrane: Probing the structural basis and potential biomedical application. NPG Asia Mater 13: 52, 2021.
78. Grabarnick Portnoy E, Andriyanov AV, Han H, Eyal S and Barenholz Y: PEGylated liposomes remotely loaded with the combination of doxorubicin, quinine, and indocyanine green enable successful treatment of multidrug-resistant tumors. Pharmaceutics 13: 2181, 2021.
79. Guglielmelli A, Rosa P, Contardi M, Prato M, Mangino G, Miglietta S, Petrozza V, Pani R, Calogero A, Athanassiou A, *et al*: Biomimetic keratin gold nanoparticle-mediated in vitro photothermal therapy on glioblastoma multiforme. Nanomedicine (Lond) 16: 121-138, 2021.
80. Liu J, Jiang X, Feng X, Lee MJ, Li Y, Mao J, Weichselbaum RR and Lin W: A three-in-one nanoscale coordination polymer for potent chemo-immunotherapy. Small Methods 7: e2201437, 2023.
81. Mohassab AM, Hassan HA, Abou-Zied HA, Fujita M, Otsuka M, Gomaa HAM, Youssif BGM and Abdel-Aziz M: Design and synthesis of new quinoline-ester/-amide derivatives as potent antiproliferative agent targeting EGFR and $BRAF^{V600E}$ kinases. J Mol Struct 1297: 136953, 2024.
82. Wankhede S, Badule A, Chaure S, Damahe A, Damahe M and Porwal O: Challenges and strategies in prodrug design: A comprehensive review. J Adv Sci Res 16: 1-20, 2025.
83. Luo Y, Zeng Z, Shan T, Xu X, Chen J, He Y, Zhang T, Huang Z, Chai G, Huang Y, *et al*: Fibroblast activation protein α activatable theranostic pro-photosensitizer for accurate tumor imaging and highly-specific photodynamic therapy. Theranostics 12: 3610-3627, 2022.
84. Monastyrskyi A, Brockmeyer F, LaCrue AN, Zhao Y, Maher SP, Maignan JR, Padin-Irizarry V, Sakhno YI, Parvatkar PT, Asakawa AH, *et al*: Aminoalkoxycarbonyloxymethyl ether prodrugs with a pH-triggered release mechanism: A case study improving the solubility, bioavailability, and efficacy of antimalarial 4 (1 H)-quinolones with single dose cures. J Med Chem 64: 6581-6595, 2021.
85. Han HH, Wang HM, Jangili P, Li M, Wu L, Zang Y, Sedgwick AC, Li J, He XP, James TD and Kim JS: The design of small-molecule prodrugs and activatable phototherapeutics for cancer therapy. Chem Soc Rev 52: 879-920, 2023.
86. Jangili P, Kong N, Kim JH, Zhou J, Liu H, Zhang X, Tao W and Kim JS: DNA-damage-response-targeting mitochondria-activated multifunctional prodrug strategy for self-defensive tumor therapy. Angew Chem Int Ed Engl 61: e202117075, 2022.
87. Medeiros R, Valverde C, Faizi MSH, Jamal A and Osório FAP: A first principles study of nonlinear optical properties of a quinoline derivative. Int J Quantum Chem 123: e27066, 2023.
88. Guan D, Xuan B, Wang C, Long R, Jiang Y, Mao L, Kang J, Wang Z, Chow SF and Zhou Q: Improving the physicochemical and biopharmaceutical properties of active pharmaceutical ingredients derived from traditional Chinese medicine through cocrystal engineering. Pharmaceutics 13: 2160, 2021.
89. Li W, Xu W, Zhang S, Li J, Zhou J, Tian D, Cheng J and Li H: Supramolecular biopharmaceutical carriers based on host-guest interactions. J Agric Food Chem 70: 12746-12759, 2022.
90. Luo M, Wang YM, Zhao FK and Luo Y: Recent advances in Nanomaterial-mediated cell death for cancer therapy. Adv Healthc Mater 14: e2402697, 2025.
91. Lv X, Ying H, Ma X, Qiu N, Wu P, Yang B and Hu Y: Design, synthesis and biological evaluation of novel 4-alkynyl-quinoline derivatives as PI3K/mTOR dual inhibitors. Eur J Med Chem 99: 36-50, 2015.
92. Wang L, Hou X, Fu H, Pan X, Xu W, Tang W and Fang H: Design, synthesis and preliminary bioactivity evaluations of substituted quinoline hydroxamic acid derivatives as novel histone deacetylase (HDAC) inhibitors. Bioorg Med Chem 23: 4364-4374, 2015.
93. Ammar YA, Micky JA, Aboul-Magd DS, Abd El-Hafez SMA, Hessein SA, Ali AM and Ragab A: Development and radiosterilization of new hydrazono-quinoline hybrids as DNA gyrase and topoisomerase IV inhibitors: Antimicrobial and hemolytic activities against uropathogenic isolates with molecular docking study. Chem Biol Drug Des 101: 245-270, 2023.
94. Cheng S, Yang GJ, Wang W, Ma DL and Leung CH: Discovery of a tetrahydroisoquinoline-based CDK9-cyclin T1 protein-protein interaction inhibitor as an anti-proliferative and anti-migration agent against triple-negative breast cancer cells. Genes Dis 9: 1674-1688, 2021.
95. Ha HA, Chiang JH, Tsai FJ, Bau DT, Juan YN, Lo YH, Hour MJ and Yang JS: Novel quinazolinone MJ-33 induces AKT/mTOR-mediated autophagy-associated apoptosis in 5FU-resistant colorectal cancer cells. Oncol Rep 45: 680-692, 2021.
96. Anand K, Niravath P, Patel T, Ensor J, Rodriguez A, Boone T, Wong ST and Chang JC: A phase II study of the efficacy and safety of chloroquine in combination with taxanes in the treatment of patients with advanced or metastatic anthracycline-refractory breast cancer. Clin Breast Cancer 21: 199-204, 2021.
97. O'Reilly EM, Cabanski CR, Lyman JP, Wainberg ZA, Fisher GA, Wolff RA, Ko AH, O'Hara MH, Spencer CN, Yu JX, *et al*: Clinical and translational results from a phase 1 trial of gemcitabine/nab-paclitaxel with nivolumab/ipilimumab or hydroxychloroquine/ipilimumab in untreated metastatic pancreatic adenocarcinoma. J Immunother Cancerr 14: e012864, 2026.
98. Garg P, Singhal G, Kulkarni P, Horne D, Salgia R and Singhal SS: Artificial intelligence-driven computational approaches in the development of anticancer drugs. Cancers (Basel) 16: 3884, 2024.
99. Lin H, Zheng W, Yuan Z, Li L, Tan Y, Huang W, Liu J, Qiu Z, Li Q, Chu B and Jiang Y: Design, synthesis, and biological evaluation of quinoline-based hydroxamic acid derivatives as dual DNMT and HDAC inhibitors with potent anti-breast cancer activity. J Med Chem 68: 19022-19040, 2025.
100. Diamond S, Boer J, Maduskuie TP Jr, Falahatpisheh N, Li Y and Yeleswaram S: Species-specific metabolism of SGX523 by aldehyde oxidase and the toxicological implications. Drug Metab Dispos 38: 1277-1285, 2010.
101. Uehara S, Yasuda M, Higuchi Y, Yoneda N, Kawai K, Suzuki M, Yamazaki H and Suemizu H: SGX523 causes renal toxicity through aldehyde oxidase-mediated less-soluble metabolite formation in chimeric mice with humanized livers. Toxicol Lett 388: 48-55, 2023.

102. Haeusler IL, Chan XHS, Guérin PJ and White NJ: The arrhythmogenic cardiotoxicity of the quinoline and structurally related antimalarial drugs: A systematic review. BMC Med 16: 200, 2018.
103. Kamel AS, Mohamed AF, Rabie MA, Elsherbiny ME, Ahmed KA, Khattab MM and Abdelkader NF: Experimental evidence for diiodohydroxyquinoline-induced neurotoxicity: characterization of age and gender as predisposing factors. Pharmaceuticals (Basel) 15: 251, 2022.
104. Sieb JP, Milone M and Engel AG: Effects of the quinoline derivatives quinine, quinidine, and chloroquine on neuromuscular transmission. Brain Res 712: 179-189, 1996.
105. Saeki K: Anti-carcinogenic structural modification by fluorine-substitution in aza-polycyclic aromatic hydrocarbons. Yakugaku Zasshi 120: 1373-1385, 2000 (In Japanese).
106. Weyand EH, Defauw J, McQueen CA, Meschter CL, Meegalla SK and LaVoie EJ: Bioassay of quinoline, 5-fluoroquinoline, carbazole, 9-methylcarbazole and 9-ethylcarbazole in newborn mice. Food Chem Toxicol 31: 707-715, 1993.
107. LaVoie EJ, Shigematsu A and Rivenson A: The carcinogenicity of quinoline and benzoquinolines in newborn CD-1 mice. Jpn J Cancer Res 78: 139-143, 1987.