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Molecular targets and anticancer activity of quinoline–chalcone hybrids: literature review†

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α,β -Unsaturated chalcone moieties and quinoline scaffolds play an important role in medicinal chemistry, especially in the identification and development of potential anticancer agents. The multi-target approach or hybridization is considered as a promising strategy in drug design and discovery. Hybridization may improve the affinity and potency while simultaneously decreasing the resistance and/or side effects. The conjugation of quinolines with chalcones has been a promising approach to the identification of potential anticancer agents. Most of these hybrids showed anticancer activities through the inhibition of tubulin polymerization, different kinases, topoisomerases, or by affecting DNA cleavage activity. Accordingly, this class of compounds can be classified based on their molecular modes of action. In this article, the quinolone–chalcone hybrids with potential anticancer activity have been reviewed. This class of compounds might be helpful for the design, discovery and development of new and potential multi-target anticancer agents or drugs.

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1 Introduction

Cancer is an abnormal uncontrollable cell cycle disease characterized by the rapid proliferation of normal cells. Cancer has been ranked as the second leading cause of death all over the world, preceded only by cardiovascular diseases.^{1,2} The cancer rates increase annually, and it is expected that cancer rates will increase by about 60% over the next 20 years. According to



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WHO, there are 600 types of cancer, most of which require unique diagnoses and management protocols [file:///C:/Users/compu soft/Downloads/9789240001299-eng.pdf]. In a recent statistic from WHO, about 14 million diagnosed cases and at least 9 million cancer-related deaths occur annually with a ratio of one from every six deaths being due to cancer. The problem of cancer is not only a global health problem but is also a social and economic one. The estimated annual economic cost of cancer was about \$1.16 trillion in 2010.^{3,4} The total cost of cancer in 2020 is estimated to be about \$173 billion in the USA [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3107566/]. For the different cancer types, lung, colorectal, skin, stomach, prostate, breast and liver cancers are the most common, and most deaths are caused by colorectal, stomach, liver and breast cancers.⁵ Although there has been continuous pharmacological progress in the effectiveness of anticancer drugs, there is a continuing urgent need for diverse, novel, targeted molecules to solve the problem of drug resistance and/increase the

potency or decrease the side effects of the currently used drugs.⁶ Consequently, in the literature and clinical trials, large numbers of molecules targeting different sites are under investigation for development as promising anticancer agents.^{7,8}

The α,β -unsaturated chalcones are precursors of flavonoid and isoflavonoid-based compounds.⁹ Chalcones serve as the precursors for the synthesis of various heterocyclic compounds like pyrimidines, pyrazoles,¹⁰ 2-pyrazolines,^{11,12} imidazoles,¹³ and flavonoids.¹⁴ The natural or synthetic chalcones exhibit various biological activities, such as anti-inflammatory,^{15–17} analgesic,¹⁸ antioxidant,^{19–22} antibacterial,^{22,23} antifungal,^{24–27} anti-tuberculosis,²⁸ antimalarial,^{29–32} antiviral,³³ parasitic protease inhibitors,³⁴ antioxidant, anti-human immunodeficiency virus (HIV),³⁵ antitumor activities,^{36–41} HDAC inhibitors,⁴² and as insulin mimetics in 3T3-L1 adipocytes.⁴³ Moreover, chalcones have been identified as privileged structures in the development process of chalcone-based compounds.^{44–48} Many



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

chalcone-based compounds have been reported in the last decade as tubulin inhibitors,^{49–58} in addition to several other possible molecular targets that chalcones directly interact with⁵⁹ (see ESI†).

On the other hand, quinoline stands out among the most essential N-based biologically active heterocyclic compounds. The presence of nitrogen atoms significantly increases the basic character of quinoline-containing compounds. Moreover, the quinoline nitrogen may engage in hydrogen bonding with the target enzymes. Polarity is an additional significant property that can be used as a method for reducing the lipophilic character, increasing water solubility and thus oral absorption in drug design strategies.⁶⁰ The quinoline scaffold possesses a variety of biological activities, including anti-HIV,⁶¹ antipsychotic,⁶² antibiotic,⁶³ anti-inflammatory,^{64–66} PDE4B inhibitors⁶⁷ and antihypertensive activities.⁶⁸ Drugs containing the quinoline ring motif, such as mefloquine, chloroquine, quinine, and amodiaquine, are used as effective drugs for the treatment of malaria.⁶⁹ Moreover, the quinoline nucleus is the milestone structural motif for some important anticancer drugs that are available on the market,^{8,70,71} Fig. 1.

Several molecules containing the quinoline framework are in clinical trials as anticancer agents,^{8,72,73} Fig. 2.

Quinoline derivatives also display excellent anticancer activities *via* different mechanisms of action, such as the inhibition of tyrosine kinase, alkylating agents, cell cycle arrest, angiogenesis inhibition, apoptosis induction, cell migration disruption, targeting Bcl-2, and inhibition of antimetabolic tubulin polymerization^{74–88} (see ESI†).

Chalcones and quinoline have been researched extensively, with many published review articles.^{8,89–106} Nonetheless, the precise modes of action for the broad-spectrum biological

activities of chalcones and quinoline are still not well known. Hybridization has emerged as one of the most promising approaches in the innovation of new candidates with the potential to enhance the affinity and effectiveness and also to overcome cross-resistance when compared with the parent drugs. In addition to the antineoplastic CX-3543 (quarflorin), there are numerous quinoline hybrids under clinical trials, such as the antibacterial agents Ro 23-9424, and MCB3837 (ref. 107 and 108) (see ESI†).

The molecular hybridization of quinoline with other pharmacophoric anti-cancer moieties, such as chalcones, is a promising strategy that can lead to new high-potential anti-cancer agents for drug-sensitive cancers and also for drug-resistant cancers. In the last three decades, substantial efforts have been carried out to innovate novel hybrids of quinoline as anti-cancer candidates with greater safety profiles and better anti-cancer activity. It is obvious from the literature survey that drug molecules binding to more than one target have many advantages in cancer therapy, including synergistic activity, reduced side effects and/or avoiding the problem of drug resistance. There is great interest in multi-target drugs and the combination therapy strategy in cancer drug discovery. Consequently, the aim of this article to review the recent advances of anti-cancer quinolone-chalcone hybrids, discussing their modes of action and structure-activity relationships at the molecular level over the last ten years.

2 Naturally occurring chalcones

Notably, at present, two chalcones are used in clinical practice (see ESI†). Sofalcone is an anti-ulcer agent that increases the amount of mucosal prostaglandins and provides a gastro-protective effect against *Helicobacter pylori*;¹⁰⁹ Metochalcone



Fig. 2 The structures of some quinoline-containing anticancer agents under clinical trials.



Fig. 3 Chemical structures of naturally occurring anticancer chalcones.

was approved as a choleric drug.⁸⁹ Moreover, hesperidin methylchalcone and hesperidin trimethylchalcone showed promising results in clinical trials in chronic venous lymphatic insufficiency and trunk or branch varicosis, respectively.¹¹⁰

Chalcones represent the core of numerous biologically interesting, naturally occurring compounds and have gained considerable research attention.¹¹¹ There are a large number of natural chalcones such as isoliquiritigenin **16** (anti-cancer, cancer chemopreventive, anti-oxidant and anti-inflammation),^{112–114} butein **17** (anti-cancer and anti-inflammation),^{115–117} cardamonin **18** (ATP diphosphohydrolase),¹¹⁸ sappanchalcone **19** (anti-inflammation),^{119,120} licochalcone A **20** (anti-inflammation and anti-cancer),^{121,122} and millepachine **21** (anticancer).¹²³ Many other conventional chalcones, dihydrochalcones, chalcone mimics, bichalcones, and fused chalcones have been isolated from natural sources and have potentially promising biological activities,^{111,124} Fig. 3.

3 Synthesis of chalcones

The simple chemistry and the ease of chalcone synthesis allow a diversity of substitutions, which conducted using base- or acid-catalyzed condensation reactions. Despite the ease of chalcone synthesis, currently, diverse new methods and novel procedures have been described due to their various biological activities and also due to the development of different catalysts or reaction conditions. Among all, condensation using the Claisen–Schmidt reaction is the most widely used for chalcone synthesis.¹²⁵ This reaction is catalyzed by either strong bases or acids in a liquid solvent at 50–100 °C for several hours.^{95,102,126} Using a base as a catalyst, the chalcone is generated *via* the dehydration of the produced aldol intermediate in an enolate mechanism; whereas, on using acid as the catalyst, chalcone formation proceeded *via* an enol mechanism.¹²⁷ Typically, the conventional Claisen–Schmidt reaction is performed in the liquid phase, but some reactions can be performed in the solid phase or solvent-free phase.¹²⁸ Additionally, the use of microwaves in liquid and solvent-free Claisen–Schmidt reactions decreases synthesis time and improves chalcone yield (Table 1).^{129,130}

Table 1 Reported chalcone synthesis conditions using the Claisen–Schmidt condensation

Catalyst	Solvent	Ref.
NaOH	Ethanol	131
NaOH	Methanol	134–136
KOH	Ethanol	
Piperazine	Methanol	138
	Ethanol	
Ca(OH) ₂	Aprotic solvent	140
Ba(OH) ₂		
Sr(OH) ₂		
LiHDMS	THF	142
NaNO ₃	Methanol	144 and 145
(LiNO ₃)/natural phosphates		
HCl	Ethanol	147
AlCl ₃	Carbon disulfide	147
BF ₃ –Et ₂ O	Dioxane	132 and 133
SOCl ₂	Ethanol	137
<i>p</i> -TsOH	Acetic acid	139
NaOH/grind	—	141
KF–Al ₂ O ₃ /grind	—	143
CaO/MW	—	146
TBAB	Inorganic alkaline solution	148
TFAA/H ₃ PO ₄	—	149

Because the Claisen–Schmidt condensation has some drawbacks such as the long reaction time, the reaction completion may require several days. The reaction may also give a mixture of products containing the required chalcone, byproducts, and possibly starting materials. Therefore, both the reactants and catalyst have a dramatic effect on the yield with conversion ranging from less than 10% up to nearly 100%.^{127,150} Thus, for the synthesis of chalcone, more well-recognized reactions such as the photo-Fries rearrangement, cross-coupling, one-pot synthesis from alcohols and Friedel–Crafts acylation were utilized.^{151–186}

4 Chalcone as Michael acceptors

The chemical nature of the structure of chalcones impacts or affects its biological activity.^{187–190} It is known that Michael





Fig. 4 Chalcones as Michael acceptors with cysteine.

acceptors have an electrophile that is involved in many biological processes and regulates important signaling pathways. The α,β -unsaturated carbonyl functional moiety in chalcones is considered a Michael acceptor; it participates in covalent bond formation with thiols or other similar nucleophiles through Michael addition (Fig. 4). For instance, chalcones can modulate Keap1-Nrf2-ARE through covalent bond formation with cysteine. In the design of new drug molecules, it is worth considering the substituents of chalcone aromatic rings, which affect the electron density on the ring and consequently the electrophilicity of the α,β -unsaturated ketone system, and can affect the binding ability and the biological activity of chalcones.¹⁹⁰

5 Quinoline–chalcone hybrids

Tubulin polymerization inhibitors

Microtubules, components of the cytoskeleton, are hollow tubes consisting of α - and β -tubulin. Polymerization of tubulin is necessary to form microtubules that have essential roles in cellular functions, including the maintenance of cell structure, intracellular transport, polarity and mitosis.¹⁹¹ Notably, tubulin also plays a crucial role in non-mitotic cells, which is likely to underlie the overall effectiveness of the tubulin-targeting agents in cancer therapy.^{192,193}

It has been documented that hundreds of compounds kill cancer cells by disrupting tubulin polymerization and are known as microtubule-targeting agents (MTAs).^{194–196} Hence, tubulin polymerization inhibitors are among the most effective targeted anticancer agents. Most tubulin-targeting agents are composed of diverse and sometimes complex structural molecules.¹⁹⁷

Recently, Tseng *et al.* synthesized and investigated the anticancer activity of a series of 3-phenylquinolinyl-chalcones using the XTT assay on three different types of breast cancer cell lines, namely, MCF-7, MDA-MB-231 and SKBR-3, and a non-cancer normal epithelial cell line (H184B5F5/M10).^{46,198} The results showed that the 3,4,5-trimethoxy analog **22** (Fig. 5) is the most potent compound against the three different types of breast cancer cells growth, showing IC_{50} values less than 1.05 μ M without remarkable cytotoxicity on the normal cell line (IC_{50} value more than 10 μ M). Further studies revealed that compound **22** could induce cell cycle arrest in a time- and concentration-dependent manner. Compound **22**, in a dose-dependent manner, caused microtubule disruption with

a decrease in the polymer form of tubulins. Also, compound **22** induced apoptosis *via* the regulation of Bcl-2 and the activation of caspase in MDA-MB-231 cells.

Li *et al.*¹⁹⁹ discovered some novel quinoline–chalcone derivatives and screened their anticancer activities; the results revealed that compound **23** displayed the highest potency (IC_{50} values 0.009 to 0.016 μ M against cancer cell lines panel). Compound **23** also displayed an improved safety profile by intravenous injection, with an LD_{50} value of 665.62 mg kg^{-1} . The hydrochloride salt 50-HCl was more potent than CA-4 in inhibiting tumor growth in H22 xenograft models without noticeable toxicity. Mechanistically, compound **23** was found to be an inhibitor of tubulin polymerization by binding to the colchicine site of tubulin. Moreover, compound **23** induced cell cycle arrest in the G2/M phase, and induced apoptosis, depolarized mitochondria and induced the generation of reactive oxidative stress in the K562 cell line. Furthermore, compound **23** exhibited potent antimetastasis activity *in vitro*, as well as antivascular activities *in vitro* and *in vivo*. These results revealed that compound **23** is a safe and potent anticancer candidate for cancer therapy, which merits further screening.

Mirzaei *et al.*²⁰⁰ synthesized and investigated the cytotoxic activity of a new series of quinoline–chalcone hybrids against four human cancer cell lines including A2780, A2780/RCIS, MCF-7, MCF-7/MX and normal HUVEC cells. Compounds **24**, **25** and **26** with the benzoyl group displayed notable anticancer activity against resistant cancer cells as well as their parents. Compounds **25** and **26**, with IC_{50} values ranging from 2.32 to 22.4 μ M, showed the highest potent anticancer activity. Further studies on the mechanism of action revealed that compounds **25** and **26** were also recognized as tubulin inhibitors, inducing cell cycle arrest at the G2/M phase and also apoptosis. Compound **26** provoked greater arrest in four cancer cell lines at the G2/M phase as compared to compound **25**. Finally, the examination of the molecular docking of compound **26** into the colchicine-binding site of tubulin indicated the possibility of this compound interacting in the tubulin active site.

It was established that the quinoline–chalcones **27** and **28** can act as potent anticancer agents. These compounds are capable of binding nicely to the colchicine binding site of tubulin. Moreover, they were found to kill multi-drug resistant cancer cells. Combining these compounds with paclitaxel had a synergistic effect on multi-drug resistant cancer cells. Furthermore, the analogues **29** and **30** disrupted the



Fig. 5 Quinoline–chalcone hybrids as tubulin polymerization inhibitors.

microtubule dynamics and killed MCF10A breast cancer cells and multi-drug resistant cancer cells,²⁰¹ Fig. 5.

Quinoline–chalcone hybrids as kinase inhibitors

Protein tyrosine kinases (PTKs) play pivotal roles in signal transduction involving the regulation of many cellular functions such as the cell cycle, cell proliferation, differentiation, cell survival, and angiogenesis. Overexpression or kinase activity mutation is related to the development of different cancer types.²⁰² Therefore, tyrosine kinases are promising targets for the treatment of cancer. Many FDA-approved small

molecule inhibitors target different types of tyrosine kinases, such as the vascular endothelial growth factor receptor (VEGFR) and the epidermal growth factor receptor (EGFR), and many others are now at different stages of preclinical and/or clinical development.^{203,204}

Rizvi *et al.* synthesized a series of quinolyl-thienyl chalcones as possible inhibitors of VEGFR-2 kinase, using structure-based virtual screening protocols.²⁰⁵ The *in vitro* inhibitory activity assay revealed that compound 31 is the most potent, with an IC₅₀ value of 73.41 nM. Moreover, all compounds displayed



significant inhibition of the proliferation of human umbilical vein endothelial cells (HUVEC) (compound **31**, IC_{50} : 21.78 nM).

The 2-quinolone-benzimidazole hybrid **32** is a potent inhibitor of two important anticancer targets, protein kinase B (α , β and γ) and I κ B kinase (α and β), with IC_{50} of 1.64–44.46 μ M.²⁰⁶ SAR revealed that incorporation of the N1-methyl group has a deleterious effect on biological activity. On the other hand, methyl, chloro or bromo substituents retain activity, while halogen substituents on benzimidazole enhance the activity. The hybrid **32** showed the highest activity among this series against protein kinase B (α , β and γ) and I κ B kinase (α and β). It also displayed favorable plasma and microsomal stability and acquired potent tumor growth inhibition at dose levels of 10 and 25 mg kg⁻¹ in the xenograft mice model, UACC903 melanoma cells.

George *et al.*²⁰⁷ synthesized and screened derivatives of quinoline–chalcone for their anti-proliferative activity against cancer cell lines MCF-7, HeLa and DLD1, as well as normal fibroblast WI-38. In addition to good safety towards the normal cell line, the compounds tested showed promising anticancer activity. Compounds **33** and **34** have been screened for their effectiveness as EGFR inhibitors. In comparison to Gefitinib (IC_{50} = 29.16 nM), they revealed inhibitory activity at the nanomolar level, in particular, compounds **33** with IC_{50} (37.07 nM).

Novel thienoquinoline carboxamide-chalcone derivatives have been prepared and their anticancer activities were investigated. Thienoquinolines **35** and **36** revealed remarkable broad-spectrum antiproliferative activity. They also showed significant inhibition of EGFR TK with IC_{50} values ranging between 0.5 and 3.2 μ M. Compounds **35** and **36** demonstrated the highest activities among the synthesized series, with better activity than the reference Erlotinib on the melanoma cancer cell line A375. Compound **36** induced pre-G1 apoptosis and cell cycle arrest at the G2/M phase. Docking studies revealed that compound **35** was nicely bound in the active site of EGFR and the thienoquinoline moiety occupied the ATP-binding site, whereas the chalcone moiety was located in the allosteric site; this explains the enhanced activity of these compounds,²⁰⁸ Fig. 6.

Ibrahim *et al.*²⁰⁹ utilized molecular modeling and pharmacophore modeling, docking and binding energy calculations for the design of 4-anilinoquinoline-3-carboxamides. The target-synthesized derivatives were tested as potential anticancer agents with EGFR inhibitory activity. The most promising compound, **37**, showed potent anticancer activity (IC_{50} = 3.46 μ M.) and 67% inhibition of EGFR TK.

Aly *et al.*²¹⁰ designed compound **38** through molecular modeling techniques as a potential EGFR inhibitor anticancer agent, where some analogues experienced more potent activity. The quinoline-3-carboxamide furan-derivative showed potent EGFR inhibition (IC_{50} = 2.61 μ M) with promising anticancer activity against the MCF-7 cell line (IC_{50} = 3.35).

Abbas *et al.*²¹¹ synthesized a series of quinoline–chalcone hybrids as potential anti-cancer agents for NSCLC and CML, *via* inhibiting the PI3K/Akt/mTOR pathway. Cytotoxicity assays revealed that among the synthesized compounds, compounds

39 and **40** were the most active against all cell lines tested, with IC_{50} values of 1.91 and 5.29 μ M against A549 and K-562 cancer cell lines, respectively. Mechanism studies demonstrated that **39** and **40** induced apoptosis and arrested cell cycles at G2/M in both A549 and K562 cells. Moreover, compounds **39** and **40** non-selectively inhibited all PI3K isoforms with IC_{50} values ranging from 52 to 473 nM, with **39** being the most active against PI3K- γ (IC_{50} = 52 nM). Analysis of the docking results showed the possible formation of hydrogen bonds with the essential valine residues in the active sites of PI3K- γ isoforms. Furthermore, western blot analysis showed that **39** and **40** inhibited the phosphorylation of PI3K, Akt, mTOR as well as GSK-3 β in both A549 and K562 cells, indicating a link between blocking the PI3K/Akt/mTOR pathway and the anticancer activities.

Quinoline–chalcone hybrids affecting DNA cleavage activity

DNA has been recognized as a primary target for anticancer drugs, which can change the DNA conformation and inhibit duplication or transcription.²¹² DNA is among the most important biological targets for chemotherapeutic agent development.²¹³ There are two broad categories of non-covalent DNA-binding agents, namely, the intercalators and the groove binders. Groove binders fit into the DNA minor groove causing little perturbation of the DNA structure, whereas intercalators bind by inserting a planar aromatic chromophore between adjacent DNA base pairs.^{213,214}

Conjugates of α,β -unsaturated ketones, phenyl-butenone, and diaryl-propenones with planar pyrroloquinoline scaffolds were synthesized and evaluated for their anticancer activity toward three lines of human cancer cells. Moreover, their capacity to bind, forming molecular complexes with DNA by linear flow dichroism (LD), and their effects on nuclear enzyme DNA topoisomerase II, were investigated. Potent cytotoxic activity was noticed in the target pyrroloquinolines **41–43**, especially against melanoma cell line JR8 (IC_{50} 1.2–3.3 μ M). LD experiments confirmed that the pyrroloquinoline scaffold achieved promising results as a carrier for intercalative complexation with DNA. Their ability to intercalate between DNA base pairs appeared to inhibit the relaxation of supercoiled DNA by the topoisomerase II enzyme without remarkable induction of DNA cleavage.²¹⁵

A series of pyrrolo[2,1-*c*][1,4]benzodiazepines linked to chalcone hybrids were synthesized by Kamal *et al.*^{216,217} Investigation of the potential anticancer activity of hybrid compounds against different lines of human cancer cells, such as leukemia, non-small cell lung, renal, colon, CNS, melanoma, ovarian, breast and prostate cancer, indicated that benzodiazepine-5-one **44** was the most active and demonstrated selective and effective growth inhibition on various cancer cell lines. Further, studies of the thermal denaturation of pyrrolo [2,1-*c*][1,4]benzodiazepine linked to chalcone hybrids using calf thymus DNA (CT-DNA) exhibited that compound **44** has good DNA binding affinity.

A series of simple quinoline–chalcone hybrids were synthesized by Bindu *et al.*²¹⁸ and screened for their nucleolytic activity. Most of the synthesized compounds displayed





Fig. 6 Quinoline–chalcone hybrids as kinase inhibitors.

significant DNA binding and photocleavage activities. However, compounds 45 and 46 showed promising DNA photocleavage against pUC 19 DNA with 85% inhibition at 100 mM concentration and could be potential candidates for future drug discovery and development. The structure–activity relationship analysis of these compounds revealed that the incorporation of an electron-donating group into ring A caused a moderate increase in the DNA binding and photocleavage activities. A series of 4,5-dihydroisoxazoles was prepared from quinoline–chalcones and evaluated for their nucleolytic activities by agarose gel electrophoresis. The results revealed that compound 47 experienced high concentration-dependent DNA cleavage activity. This activity is believed to be enhanced by

iminyl and carboxy radicals of 2-chloro-3-(5-aryl-4,5-dihydroisoxazol-3-yl)quinolines,²¹⁹ Fig. 7.

Quinoline–chalcone hybrids as topoisomerase inhibitors

DNA topoisomerases can be categorized into two classes, namely, type I and type II. They allow DNA strands or double helices to pass through each other, they can solve all of the topological problems of DNA in replication, transcription and other cellular transactions. Over the past three decades, extensive biochemical and structural studies have provided molecular models of how the different sub-families of DNA topoisomerase manipulate DNA. Topoisomerases are considered as important molecular targets of many antimicrobial and





Fig. 7 Quinoline-chalcone hybrids affecting DNA cleavage activity.

anticancer agents. Most drugs targeting topoisomerases, which are currently in clinical use, act through trapping the covalent DNA-enzyme intermediates to convert a normal cellular enzyme to a DNA-damaging agent. Numerous recent reviews of DNA topoisomerases have been published.²²⁰⁻²²³

Abdel-Aziz *et al.* synthesized a new series of *N*-4-piperazinyliciprofloxacin-chalcone hybrids (Fig. 8) with antitumor and topoisomerase I and II inhibitory activities.²²⁴ Compound 48 displayed wide-spectrum anticancer activity without distinct selectivity, whereas compound 49 exhibited significant selectivity against the leukemia subpanel with a selectivity ratio of 6.71 at the GI_{50} level. Moreover, compounds 50 and 51, compared to etoposide and camptothecin, respectively, exhibited significant topoisomerase I and topoisomerase II inhibitory activities.

Quinoline-chalcone hybrids as inducers of cell cycle arrest and apoptosis (Fig. 9)

There are intrinsic and extrinsic pathways for the induction of apoptosis in cancer cells, which are involved in the regulation of the caspase-dependent proteolysis of thousands of cellular proteins, membrane blebbing and endonucleolytic cleavage of chromosomal DNA. Targeting apoptotic pathways in tumor cells is considered a promising anticancer approach because dead tumor cells can contribute to clinical responses but not to tumor relapse. Some of the approved therapeutic drugs, such as venetoclax, directly target the intrinsic apoptosis pathway but most of them indirectly target the apoptosis pathways, such as the proteasome inhibitors, oncogenic signaling pathways inhibitors, and HDAC inhibitors. Novel agents directly targeting



Fig. 8 Quinoline-chalcone hybrids as topoisomerase inhibitors.

the apoptotic pathways are under development and some have promising potential due to high levels of tumor selectivity.²²⁵

Tseng *et al.*²²⁶ synthesized certain 3-phenylquinolinyl-chalcone derivatives (Fig. 9) and evaluated their anticancer activity against a panel of six cancer cell lines. Among them, two compounds, 52 and 53, were the most potent anticancer agents. Compound 53 was more active against the growth of H1299 (IC₅₀ 1.41 μ M) and SKBR-3 (IC₅₀ 0.70 μ M) than the reference topotecan (IC₅₀ values of 6.02 and 8.91 μ M, respectively). Compound 53 displayed an IC₅₀ value of less than 0.10 mM against the growth of MDA-MB231, and was non-cytotoxic toward the normal mammary epithelial cells (H184B5F5/M10). Studying the mechanism of action revealed that compound 53 can induce cell cycle arrest at the G2/M phase, followed by the activation of caspase-3, cleavage of PARP and consequently, cell death.²²⁶

Raghavan *et al.*²²⁷ have reported the synthesis of a series of novel curcumin–quinolone hybrids starting with substituted 3-formyl-2-quinolones and vanillin. The *in vitro* cytotoxicity was determined on four cancer cell lines (A549, MCF7, SKOV3 and H460) using MTT assay. Compound 54, the most potent compound, was analyzed for its mechanism of action using various cell biology experiments. The treatment of SKOV3 cells with compound 54 exhibited distorted cell morphology under phase-contrast imaging and apoptosis induction was confirmed by Annexin V/PE assay. Further experiments on the generation of reactive oxygen species (ROS) and cell cycle analysis revealed that compound 54 induced ROS generation and arrested cell cycle progression in the S and G2/M phases.

The hybridization of quinolines with chloroquine has been recently documented as among the most promising apoptosis-inducing agents used against MCF-7 human breast cancer cells.^{228,229} All differentiation-inducing quinolines caused growth suppression in MCF-7 and MCF10A cells by the strong suppression of E2F1, which resulted in cell cycle arrest.

Very recently, Jernei *et al.*²³⁰ synthesized some novel hybrids containing chalcone and cinchona fragments linked with triazole linkers and investigated their antitumor/cytotoxic activity

against human malignant cell lines PANC-1, COLO-205, A2058 and EBC-1. Among these, compound 55 was recognized as the most potent, exhibiting significant cytotoxicity against all the cancer cell lines used, and characterized by IC₅₀ values in the low-to-submicromolar range. Mechanistically, the most potent compound 55, as well as a compound with markedly low activity, was approached by comparative cell-cycle analyses in PANC-1 cells. These studies revealed that compound 55, with improved antiproliferative activity, exhibited significantly pronounced inhibitory effects in subG1, S and G2/M phases as compared to the less cytotoxic compounds. Additionally, based on the IC₅₀ values, the structure–activity relationships (SAR) could be exploited in rational structure-refinement in the innovation of more potent anticancer candidates with high selectivity, improved activity and well-known mechanisms of action.

Miscellaneous anticancer quinoline–chalcone hybrids

Tavares *et al.* synthesized novel 6-quinoline–chalcones, 56, 57, quinoline–chalcone salts, 58, and quinoline-*N*-oxide chalcones, 59–61. All the prepared chalcones were tested against UACC-62 (melanoma), TK-10 (renal), MCF-7 (breast) and leukemic cells, Jurkat and HL60. The results exhibited that compounds 57 and 59 were the most active against MCF-7 and TK-10, while compounds 57, 58, 60 and 61 showed the best activity against leukemic cell lines.²³¹

More recently, Kamal *et al.* synthesized and screened various podophyllotoxin–chalcone conjugates^{90,232} against A-549 (lung), A375 (melanoma), MCF-7 (breast), HT-29 (colon) and ACHN (renal) cancer cell lines using MTT assay. The results revealed that improvement in the anticancer activity was noticed in quinolone–chalcone-linked podophyllotoxins 62 with IC₅₀ ranging from 2.2 and 15.4 μ M in the cell lines screened.

Aly *et al.* synthesized novel derivatives of quinoline–chalcone hybrids. The target compounds were screened for their anticancer and synergistic anticancer effect with doxorubicin, using



Fig. 9 Quinoline–chalcone hybrids that induce cell cycle arrest and apoptosis.





Fig. 10 Miscellaneous anticancer quinoline-chalcone hybrids.

a colon cancer cell line (Caco-2). Two compounds, **63** and **64**, showed significant anticancer activity with IC₅₀ values of 5.0 and 2.5 μM, respectively.²³³

Kotra *et al.*²³⁴ synthesized a series of quinoline-chalcone derivatives by reacting quinolinyl and chloroquinolinyl acetophenones with substituted aromatic aldehydes; the compounds

were found to exhibit anticancer activity. Among all compounds tested for anticancer activity on RAW cell lines using MTT assay, compound **65** (3-(4-chlorophenyl)-1-(3-methyl-1-phenyl-2-naphthyl)-2-propen-1-one) showed a percentage of inhibition up to 103%.

Kumar *et al.*²³⁵ designed and synthesized a new series of chalcone-fused quinoline derivatives. The results of anticancer activity against three human cancer cell lines, namely, MCF-7 (breast), A-549 (lung), and A375 (melanoma), indicated that all these newly prepared compounds had moderate to good activity on cell lines. In particular, compounds **66a–f**, exhibited more potent activity than the positive control doxorubicin.

Ferrer *et al.*²³⁶ synthesized a series of novel [[7-chloroquinolin-4-yl]amino]chalcone derivatives and evaluated their antiproliferative activity against human prostate cancer cell lines (LNCaP). Compounds **67–70** displayed the highest cytotoxic results against human prostate cancer cell proliferation with IC₅₀ values of 7.93 ± 2.05 , 7.11 ± 2.06 and 6.95 ± 1.62 $\mu\text{g mL}^{-1}$, respectively. The effects of these compounds were dose-dependent, showing a lower viable cell number as the drug concentration increased; this effect was also time-dependent, which was evident from 24 hours to 96 hours after drug exposure. Notably, the results showed that the presence of a hydrogen or a halogen on position 3 or 4 as the substituent groups in the aromatic ring improved the antiproliferative activity of these compounds. The antitumor activity of these compounds in human prostate cancer cells confirmed the diverse biological response of these 4-aminoquinolines.

Azad *et al.*²³⁷ synthesized a series of quinolinyl chalcones by the condensation of *N*-substituted-3-acetyl-4-hydroxyquinolin-2(1*H*)-ones with different aromatic aldehydes using conventional heating and ultrasound-assisted methods. The synthesized chalcone derivatives were assayed for cytotoxicity and among them, three quinoline chalcone derivatives, **71a**, **71b** and **71c**, were found to possess significantly high cytotoxicity.

Recently, Abonia *et al.* reported the synthesis and anticancer screening of a new quinoline-2-one-based chalcone series on an NCI panel of 60 different human tumor cell lines. Compounds **72–75** displayed good antiproliferative activity. In particular, compound **72** exhibited remarkable activity and inhibited the proliferation of most of the used human cancer cell lines at sub-micromolar concentrations. Studying the acute toxicity showed that compound **72** was well tolerated intraperitoneally (150 mg per kg per dose) by athymic nude mice (Fig. 10).²³⁸

6 Conclusion

The simple structures and ease of synthesis of chalcone derivatives, in addition to the characteristic behavior of chalcones in binding with receptors as Michael acceptors, have a great impact on their biological activity. The basic properties and extra-binding ability of the quinoline scaffold play an important role in optimizing the physicochemical properties in the drug design and development strategy. Combining quinoline with chalcone in one molecule revealed the targeted binding to the colchicine binding site of tubulin with synergistic effects and high activity against multi-drug-resistant cancer cells. Such

hybrids gave potent EGFR kinase inhibitors with high potency and a good safety profile regarding normal cells. Moreover, hybridization of quinolines with chalcone analogues introduced molecules with potent anticancer activities acting through the apoptosis-inducing effect, intercalation of DNA and/or inhibition of topoisomerase I and II. Quinoline–chalcone hybrids have a prominent place in the medicinal chemistry of anticancer agents. Compounds containing the quinoline scaffold have been broadly and successfully explored, and have resulted in many drug candidates. To date, there have been no quinoline–chalcone candidates in clinical trials but in the near future, continuous efforts will provide further important discoveries in this field.

Conflicts of interest

There are no conflicts to declare.

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