AN OVERVIEW OF QUINOLINE DERIVATIVES AS ANTI-CANCER AGENTS

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ABSTRACT:

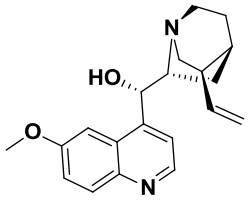
One of the most significant pharmacophoric cores in drug discovery in recent decades, notably in anticancer research, has been the quinoline scaffold. Many lead compounds with promising selective cytotoxic and immunomodulatory properties are discovered using quinoline derivatives. The review of the literature found that quinoline derivatives have the ability to inhibit protein kinases and other molecular targets. It was also designed to be involved in the disruption of tubulin assembly. The purpose of this review is to highlight findings from studies on quinoline compounds that demonstrate several anticancer pathways. Overall, the design, discovery, and development of novel and potential multi-target anticancer agents or drugs may benefit from this class of quinoline molecules.

Keywords*:* Quinoline, Tyrosine kinase, Immunomodulators, Tubulin inhibitors, VEGFR, BCR-Abl, HSP90, Topoisomerases.

1. Introduction

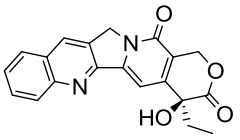
The cancer develops from a single cell in which the normal mechanisms for control of growth and proliferation are altered. There are substances known to have carcinogenic risks, including chemicals, environmental factors, and viruses. Environmental factors, such as excessive sun exposure, can result in skin cancer, and smoking is widely known as a cause of lung cancer. Viruses, including human papilloma virus (HPV), Epstein-Barr virus, and hepatitis B virus, have been linked to cervical cancers, lymphomas, and liver cancers, respectively (**Chisholm-Burns *et al*., 2013**). There are two major classes of genes involved in carcinogenesis (oncogenes) as Ras gene and tumor suppressor genes (anti-oncogene) as p53. If they are mutated, this disrupts the normal cellular function and the cell can become cancerous (**Patrick, 2005**).

Quinoline is a versatile pharmacophore, a privileged scaffold, and an outstanding fused heterocyclic molecule with numerous activities, including anticancer, anti-inflammatory, antibacterial, and antiviral compounds. Quinoline hybrids have already demonstrated outstanding results as an inhibitor of cell proliferation via many modes of actions including cell cycle arrest, death, angiogenesis, disruption of cell migration, and modulation (**Yadav & Shah, 2021**). The study of natural molecules is what sparked interest in quinoline derivatives as bioactive compounds (**Marciniec *et al*., 2023**).

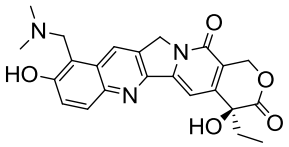


Quinine (1)

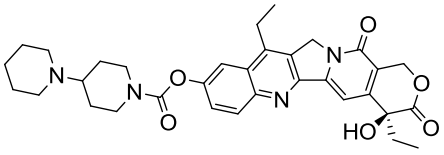
Quinine **(1)** is an antimalarial alkaloid which is extracted from the bark of the *cinchona tree*. Interestingly, the reports in the contemporary literature describe the anti-cancer activity of Quinine in relation to breast cancer cells MCF-7 (**Martirosyan *et al*., 2004**).



Camptothecin (2)



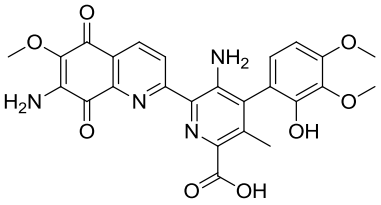
Topotecan (3)



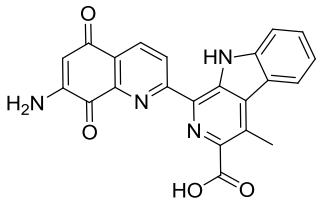
Irinotecan (4)

Many natural and semisynthetic compounds of quinoline core revealed antiproliferative activities. For example, camptothecin **(2)** is a natural topoisomerase I inhibitor was discovered in 1966 after isolation from the bark and stem of *Camptotheca acuminata* (**Khaiwa *et al*., 2021**). Moreover, topotecan (Hycamtin®**) (3)** and irinotecan

(Camptosar®) **(4)** were synthetized from camptothecin to be analogues with enhanced water solubility and to increase the cytotoxicity (**Ulukan *et al*., 2002**).



Streptonigrin (5)



Lavendamycin (6)

Streptonigrin **(5)** is an aminoquinone alkaloid isolated from *Streptomyces locculus* and is gaining attention as a drug molecule owing to its potential antitumor and antibiotic effects. It was previously used as an anticancer drug but has been discontinued because of its toxic effects (**Nasir *et al*., 2023**). Furthermore, lavendamycin **(6)** is a naturally occurring chemical compound with anti-proliferative effects against several cancer cell lines. It was discovered in fermentation broth of the soil bacterium *Streptomyces lavendulae* (**Hassani *et al*., 2008**).

2. Anticancer activity and molecular targets of quinolines:

Quinoline hybrids have already demonstrated outstanding results as an inhibitor of cell proliferation via many modes of actions including cell cycle arrest, death, angiogenesis, disruption of cell migration, and modulation through targeting a variety of receptors and enzymes.

2.1. Protein Kinase inhibitors:

The protein kinase inhibitors have been among the most successful of the targeted anticancer drugs. Protein Kinases are a group of enzymes that are responsible for protein phosphorylation. These kinases' activity is crucial for fundamental processes, including cell cycle regulation, proliferation, differentiation, motility, and apoptosis. In tumor cells, it is frequently observed that key protein kinases are not appropriately regulated, leading to excessive phosphorylation and prolonged activation of signal transduction pathways (**Dancey *et al*., 2003**).

In mammalian signaling systems there are distinct classes of kinases that are classified by their substrate preferences:

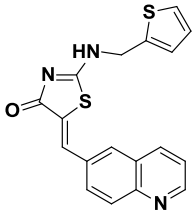
2.1.1. Serine-Threonine Kinases Inhibitors:

Serine-threonine kinases are responsible for phosphorylating the hydroxyl group present in the side chain of serine and threonine amino acids. Examples of such kinases include Cyclin-dependent kinases (CDKs), phosphoinositide-3-kinases (PI3Ks), Aurora

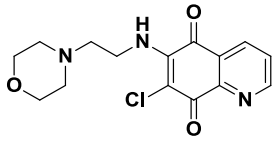
kinases (AURKs), Mitogen-activated protein kinases (MAPKs) and Rapidly Accelerated Fibrosarcoma kinases (RAF Kinases).

2.1.1.1. Quinolines as Cyclin-Dependent Kinases (CDKs) inhibitors:

Cyclin-dependent kinases (CDKs) are critical regulators of cell cycle progression and RNA transcription. CDKs are activated by complexation with a group of associated proteins called cyclins. A variety of genetic and epigenetic events cause universal over activity of the cell cycle CDKs in human cancer, and their inhibition can lead to both cell cycle arrest and apoptosis. Apoptosis is a normal process that ensures equilibrium between cell proliferation and cell death and plays a regulatory role in controlling the size of cell populations as well as in tissues homeostasis. Inadequate or abnormal inhibition of apoptosis leads to unchecked cell proliferation resulting in cell accumulation and is considered as a hallmark of cancer (Shapiro *et al*., 2006).



RO-3306 (7)

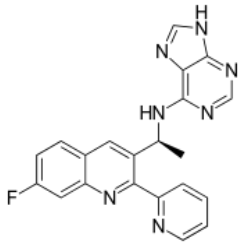


(8)

RO-3306 (7) is a quinolinyl thiazolinone derivative, showed good potency, *in vitro* selectivity, and a cell cycle profile (G2/M arrest) consistent with CDK1 inhibition (**Vassilev *et al*., 2006**). In 2023, a series of quinones derivatives with morpholin alkylamino side chains was designed, synthesized and screened for the cytotoxic activity. The 6-isomer of 5,8-quinolinedione derivatives compound **8** possessed a potent antiproliferative activity, with IC_{50} values of 0.59 μM (DLD1) and 0.44 μM (HCT116). It also resulted in a remarkable effect on cell cycle progression, blocking S-phase progression in DLD1 cells straight away while slowing S-phase progression and accumulated cells in the G2/M phase in HCT116 cells (**Narwanti *et al*., 2023**).

2.1.1.2. Quinolines as Phosphoinositide 3-kinases (PI3Ks) inhibitors:

The family of Phosphoinositide 3-kinases (PI3Ks) has been discovered to have crucial regulatory functions in various cellular processes including growth and proliferation, differentiation, survival, metabolism, and migration (**Liu *et al.*, 2009**). The activation of the serine/threonine kinase Akt, also known as protein kinase B, occurs when PI3Ks translate signals from different growth factors and cytokines into intracellular messages. The PI3K signaling pathway, which is regulated by the tumor suppressor phosphatase and tensin homologue (PTEN), is crucially involved in this process (**Song *et al.*, 2012**).

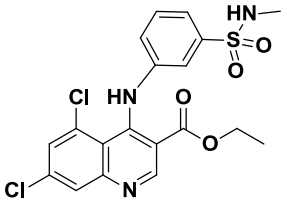


AMG-319 (9)

AMG-319 (**9**) was developed by Amgen as an anti-inflammatory drug with potential applications in the treatment of autoimmune conditions, but subsequent research revealed that it inhibits cell proliferation with promising anti-cancer effects with inhibition activity on the phosphoinositide 3-kinase enzyme subtype PI3Kδ (**Cushing *et al.,* 2015**).

2.1.1.3. Quinolines as Aurora Kinase (AURK) inhibitors:

Aurora kinases (AURKs) were identified as promising targets for targeted cancer therapy. Overexpression of aurora kinases can cause disruption in the process of mitosis, resulting in genetic instability and the potential growth of tumors (**Goldenson *et al.,* 2015**).

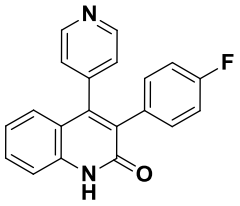


(**10**)

In 2020, Al-Sanea *et al.* designed and synthesized three series of 4-anilinoquinoline derivatives bearing a sulfonamide moiety. The assay of AURKA/B inhibition was determined for all target quinolines showed more than fifty percent inhibition on either of the enzymes, were evaluated further for their IC_{50} on the corresponding enzyme. In particular, compound **10** displayed potent AURKA/B inhibitory activities with IC_{50} of 0.93 and 0.09 µM, respectively (**Al-Sanea *et al.,* 2020**).

2.1.1.4. Quinolines as Mitogen-activated protein kinases (MAPKs) inhibitors:

The MAPKs are vital components of serine/threonine protein kinase signaling pathways in cells that are responsible for responding to extracellular stimuli and regulating important cellular functions like proliferation, differentiation, and programmed cell death (apoptosis). The MAPK family can be divided into three main groups: a) p38 protein kinase b) c-jun N-terminal kinase (JNK) c) extracellular signal-regulated protein kinase (ERK) (**Ravez *et al.,* 2015**).



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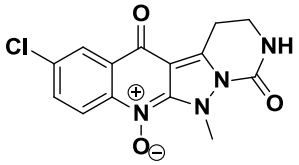
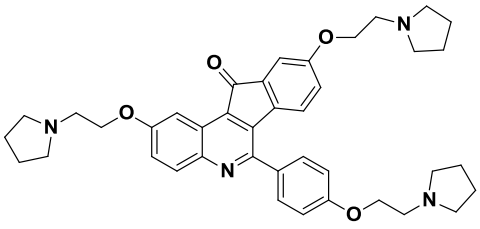


(**12**)

The lead compound **11** with 3,4-diarylquinolinone scaffold showed an inhibitory activity against MAPK with a p38αMAPK IC_{50} of 1.8 μM (**Peifer *et al.*, 2007**). Furthermore, a set of 1,9-dihydro-9-hydroxypyrazolo[3,4-b]quinolin-4-one derivatives were reported as c-jun N-terminal kinase (JNK) inhibitors. Compound **12** was identified as a potent JNK inhibitor with good cellular activity (**Liu *et al.*, 2006**).

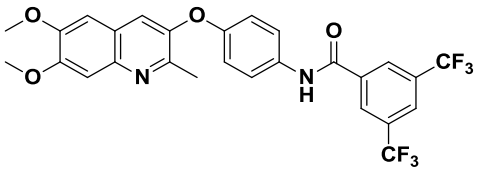


BPIQ (**13**)

A synthetic quinoline analogue 2,9-bis[2-(pyrrolidin-1-yl)ethoxy]-6-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}-11*H*-indeno[1,2-c]quinoline11-one (BPIQ) **13** showed mitochondrial-mediated apoptosis. Moreover, the sub-lethal dose of BPIQ attenuates cellular migration of NSCLC cells through inhibiting extracellular signal-regulated protein kinase (ERK) activity, suggesting the dual roles of ERK in BPIQ-induced apoptosis and anti-migration of NSCLC cells (**Fong *et al.*, 2017**).

2.1.1.5. Quinolines as RAF Kinase inhibitors:

Rapidly Accelerated Fibrosarcoma kinases (RAF kinases) participate in the RAS-RAF-MEK-ERK signal transduction cascade. This cascade participates in the regulation of a large variety of processes including apoptosis, cell cycle progression, differentiation, proliferation, and transformation to the cancerous state. RAS mutations occur in 15–30% of all human cancers, and B-RAF mutations occur in 30–60% of melanomas, 30–50% of thyroid cancers, and 5–20% of colorectal cancers. The three RAF kinase family members are A-RAF, B-RAF, and C-Raf (**Roskoski *et al.*, 2010**).



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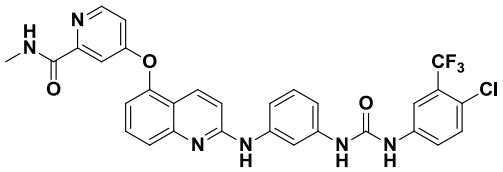
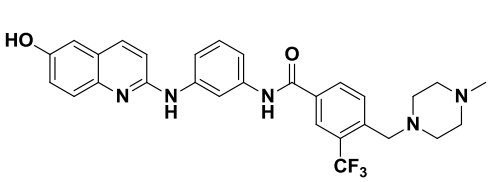


(**14**)

In 2014, El-Gamal *et al.* reported a series of diarylamides possessing 6,7-dimethoxy(dihydroxy)quinoline scaffold that showed antiproliferative activities against NCI-58 human cancer cell lines of nine different cancer types were tested. Compounds **13** showed the highest potencies. It revealed inhibitory effect against C-RAF kinase (76.65% at 10 μM) (**El-Gamal *et al.*, 2014**). Moreover, El-Damasy *et al.* designed and synthesized a series of 2-amido and ureido quinoline derivatives substituted with 2-N-methylamido-pyridin-4-yloxy group at the 5-position of quinoline as anticancer sorafenib congeners. Compound **14** was screened over a panel of 41 oncogenic kinases at a single dose concentration of 10 mM to profile its kinase inhibitory activity. Interestingly, this compound showed highly selective inhibitory activities (81.8% and 96.3%) against B-RAF^{V600E} and C-RAF kinases with IC_{50} values of 316 nM and 61 nM, respectively (**El-Damasy *et al.*, 2015**).



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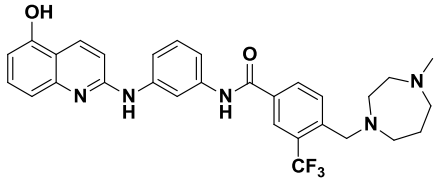


(**16**)

In 2023, Kim *et al.* reported a study revealed that 5/6-hydroxyquinolines **15** and **16** stood out as the most potent RAF Kinase inhibitors, with IC_{50} values of 0.128 μM, 0.114 μM against B-RAF^{V600E}, and 0.0653 μM, 0.0676 μM against C-RAF. Most importantly, compound **15** elicited remarkable inhibitory potency against the clinically resistant B-RAF^{V600K} mutant with an IC_{50} value of 0.0616 μM (**Kim *et al.*, 2023**).

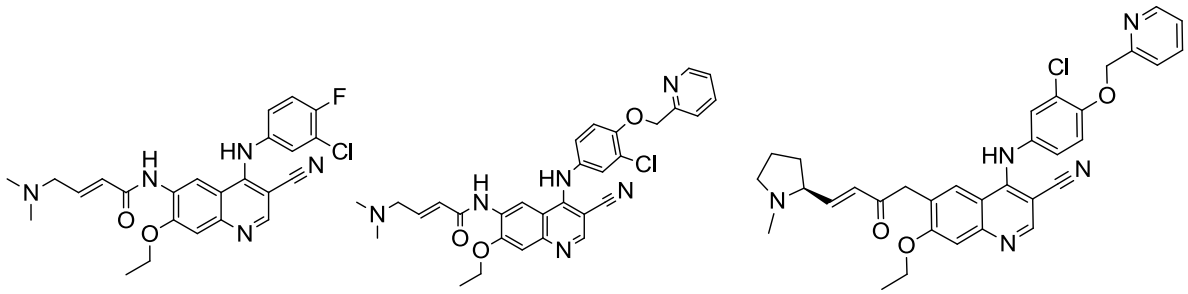
2.1.2. Tyrosine specific kinases:

Tyrosine kinases (TKs) catalyze selective phosphorylation of tyrosine residues in target proteins. This covalent post-translational modification is a significant component of signal transduction process, leading to cell proliferation, differentiation, migration, metabolism and apoptosis (**Hunter *et al.*, 2000**). Tyrosine kinases are primarily classified as**:**

2.1.2.1. Receptor tyrosine kinases (RTKs):

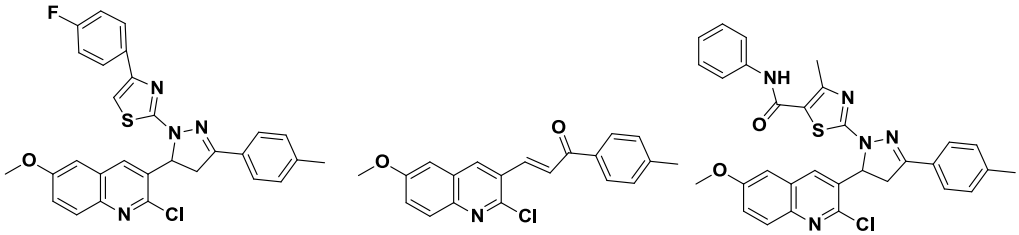
2.1.2.1.1. Quinolines as EGFR inhibitors

The EGFRs are responsible for overgrowth and proliferation of epidermal cells. The abnormal signaling of these pathways results in deregulated cell proliferation, evasion from apoptosis, angiogenesis, migration, and metastasis of cancer cells (**Abhold *et al.*, 2012**). There are four categories of transmembrane receptors called EGFR receptors (also known as HER): HER-1, HER-2, HER-3, and HER-4]. They are recognized as significant biological targets in different types of cancer tumors (**Maennling *et al.*, 2019**).



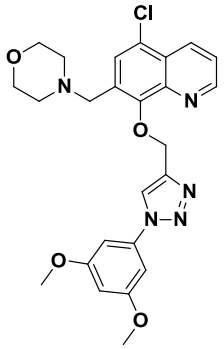
Pelitinib (17) **Neratinib (18)** **Pyrotinib (19)**

Pelitinib (EKB-569) (**17**) is an irreversible epidermal growth factor receptor tyrosine kinase inhibitor that is used in clinical trials for colorectal and lung cancers (**Lee *et al.*, 2023**). Furthermore, in 2011, neratinib (Nerlynx®) (**18**) was discovered and initially developed by Wyeth Pfizer as an orally available irreversible inhibitor of both the receptor tyrosine kinases (RTKs) human epidermal growth factor receptor 2 (HER2; ERBB2) and human epidermal growth factor receptor (EGFR), with potential antineoplastic activity (**Blair *et al.*, 2018**). Pyrotinib (**19**) is an irreversible dual pan-ErbB receptor tyrosine kinase inhibitor developed for the treatment of HER2-positive advanced solid tumours. (**Ayala-Aguilera *et al.*, 2022**).



(20) **(21)** **(22)**

In 2019, George *et al.* reported quinoline derivatives quinolinyl based pyrazolines and quinolinyl pyrazolinyl thiazole hybrids which were synthesized and screened for their anti-proliferative activity against three cell lines. Three of tested of potent compounds revealed inhibitory activity at nanomolar level especially compounds **20**, **21** and **22** with IC_{50} (31.80, 37.07 and 42.52 nM) compared to Gefitinib (IC_{50} = 29.16 nM) (**George *et al.*, 2019**).



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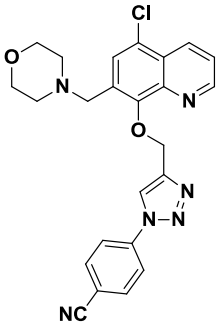

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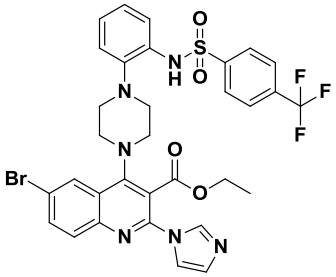
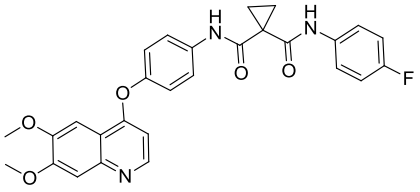


(25)

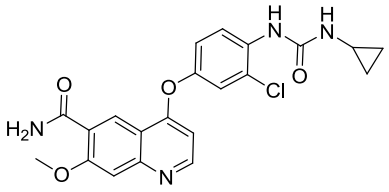
Some of reported 5-chloroquinolin-8-ol derivatives were synthesized and screened for their *in vitro* cytotoxicity towards three human cancer cell lines including MCF-7, A549 and HepG2. They were more potent than the reference erlotinib. Moreover, tyrosine kinase EGFR inhibition assay for the compounds revealed that compound **23** has triple inhibiting power with IC_{50} value of 0.14 μM and compound **24** has nearly double inhibiting power with IC_{50} value of 0.22 μM compared to erlotinib (**Mamidala *et al.*, 2022**). Other quinoline analogues of substituted amide and sulphonamide derivatives were designed synthesized and were evaluated against five cell lines. Compound **25** exhibited promising inhibitory enzymatic activity against the EGFR L858R/T790M with IC_{50} value of 138 nM, compared to Osimertinib's 110 nM (**Kardile *et al.*, 2023**).

2.1.2.1.2. Quinolines as VEGFR inhibitors:

The over-activity of VEGFR-2 receptors was reported in the cancer cells versus the normal cells. This fact enabled researchers to target them therapeutically to produce safe and selective drugs that tackle angiogenesis in tumor cells with no activity on normal cells. The strategy to hinder the VEGF pathway is carried out by blocking the VEGFR-2 receptors activation using VEGFR-2 inhibitors (**Elkaeed *et al.*, 2022**).

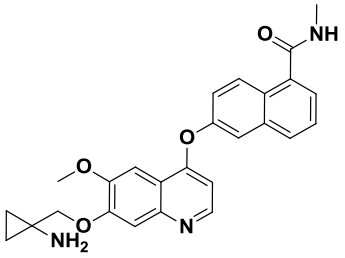


Cabozantinib (**26**)

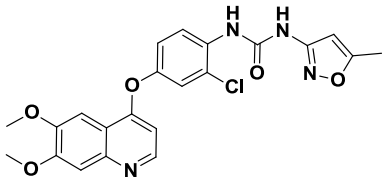


Lenvatinib (**27**)

Cabozantinib **26** (Cometriq® and Cabometyx®) is a multi-targeted TKI that targets a range of receptor kinases involved in tumor pathogenesis, including VEGFR-1, -2 and -3, KIT, TRKB, FLT-3, AXL, RET, MET, and TIE-2 (Atkins *et al.*, 2018). Lenvatinib **27** (Lenvima®) acts as a multiple kinase inhibitor. It inhibits the three main vascular endothelial growth factor receptors VEGFR1, 2 and 3, as well as fibroblast growth factor receptors (FGFR) 1, 2, 3 and 4, platelet-derived growth factor receptor (PDGFR) alpha, c-Kit, and the RET proto-oncogene. In 2016, Lenvatinib **27** was approved by FDA for the treatment of advanced renal cell carcinoma (in combination with everolimus) (**Zschäbitz *et al.*, 2018**).

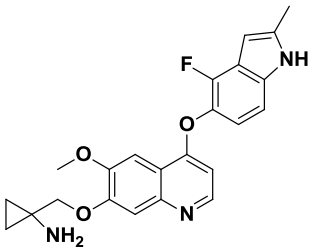


Lucitanib (**28**)



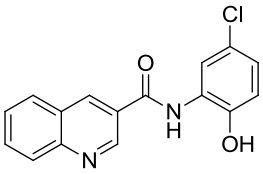
Tivozanib (**29**)

Lucitanib **28,** which is naphthalene-1-carboxamide derivative of quinoline, revealed potent activity inhibiting human vascular endothelial growth factor receptors (VEGFRs) and fibroblast growth factor receptors (FGFRs) with antiangiogenic activity nanomolar range, which may result in the inhibition of tumor angiogenesis and tumor cell proliferation, and the induction of tumor cell death (**Soria *et al.*, 2014**). Additionally, tivozanib **29** (Fotivda®), a quinoline urea derivative, is a potent VEGFR inhibitor and received FDA approval in 2021 as a kinase inhibitor recommended for adult patients with relapsed or refractory advanced renal cell carcinoma (**Caquelin *et al.*, 2022**).

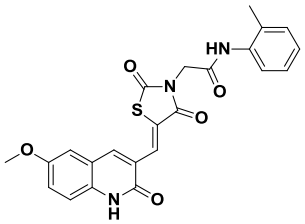


Anlotinib (30)

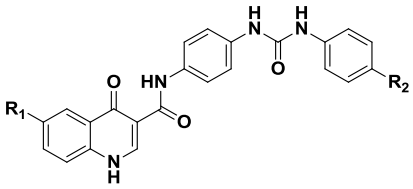
Anlotinib **30** (AL3818) is an oral multitarget tyrosine kinase inhibitor that exerts its inhibitory effects on tumor growth and angiogenesis by targeting VEGFR-2, −3, FGFR1-4, PDGFR-α and -β, c-Kit and Ret. It was approved and launched in China in 2018 as a third-line treatment for patients with refractory advanced NSCLC after more than 2 lines of systemic chemotherapy (**Gao *et al.*, 2020**).



(**31**)



(**32**)



(**33a,b**)

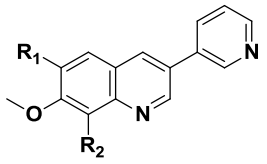
33a: R_1=C1, R_2=4-isopropyl,33b: R_1=F, R_2=3-CF_3

A series of quinoline amide derivatives were designed and prepared to be inhibitors of VEGFR-2. The inhibitory activities were investigated against VEGFR-2 kinase and human umbilical vein endothelial cells (HUVEC) *in vitro*. Compound **31** (5-chloro-2-hydroxy-N-(quinolin-8-yl)benzamide) exhibited the most potent inhibitory activity (IC_{50} = 3.8 and 5.5 nM for VEGFR-2 kinase and HUVEC, respectively) (**Yang *et al.*, 2010**). Furthermore, Elkaeed *et al.* reported that compound **32** showed moderate VEGFR-2 inhibitory activity with an IC_{50} value of 98.53 nM sorafenib (IC_{50} = 53.65 nM) (**Elkaeed *et al.*, 2022**). A novel series of quinoline compounds were designed, synthesized and screened for VEGFR-2 inhibitory activity and cytotoxic activity against HepG2 cancer cell line. Two compounds **33a** and **33b** exhibited potent VEGFR-2 with IC_{50} = 36nM and 38 nM, respectively, compared to sorafenib (IC_{50} = 45 nM) (**El-Fakharany *et al.*, 2023**).

2.1.2.1.3. Quinolines as PDGFR inhibitors

Platelet-derived growth factor receptor (PDGFR) is a specific type of receptor found on the cell surface. It plays a crucial role in regulating cell proliferation, growth, and differentiation. However, when PDGFR becomes hyperactive, it can lead to uncontrolled

cellular growth, ultimately contributing to various diseases such as pulmonary fibrosis, restenosis, and cancer. (**Andrae *et al.,* 2008**).

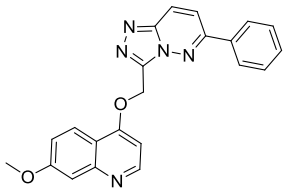


(**34a,b**) **34a:** R_1=OCH_3, R_2=H, **34b:** R_1=H, R_2= OCH_3,

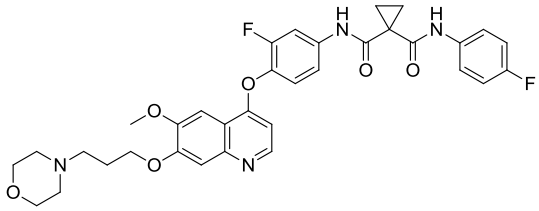
In 1994, Maguire *et al*. reported that the quinoline compound **34a** showed a good inhibition of PDGFR (IC% = 0.1 - 0.8pM) and excellent selectivity against EGFR (IC_{50} > 25 pM) while compound **34b** showed poor inhibition of both EGFR (IC_{50}> 25 pM) and PDGFR (IC_{50} > 50 pM) (**Maguire *et al.,* 1994**).

2.1.2.1.4. Quinolines as C-Met inhibitors:

C-Met protein is a transmembrane tyrosine kinase that binds the hepatic growth factor (HGF) and plays an important role in the ability to activate a wide range of different cellular signaling pathways, including those involved in proliferation, motility, migration and invasion. (**Organ *et al.,* 2011**).

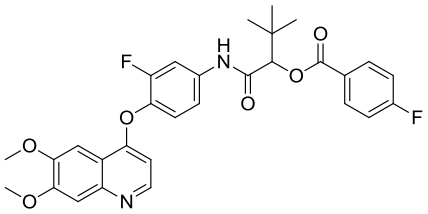


AMG-208 (35)



Foretinib (36)

AMG-208 (**35**) is a small-molecule MET inhibitor with IC_{50} against wild type MET of 5.2 nM. At higher concentrations, AMG 208 inhibited other kinases, such as VEGFR2 with IC_{50} = 112 nM. It suppressed proliferation and induced apoptosis in human tumor xenograft models (**Hong *et al.,* 2015**). Foretinib **36** (GSK1363089) is an experimental c-Met and VEGFR-2 inhibitor. It is a drug candidate for the treatment of cancer was discovered by Exelixis and is under development by GlaxoSmithKline (**Kim *et al.,* 2022**).



(**37**)

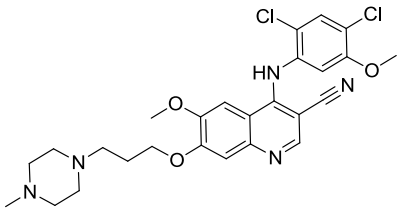
A study reported two novel series of 6,7-disubstitued-4-(2- fluorophenoxy)quinoline derivatives containing a-acyloxycarboxamide or a-acylaminoamide scaffolds were designed, synthesized, and evaluated for their *in vitro* biological activities against c-Met kinase and four cancer cell lines Most of the target compounds showed moderate to potent and possessed selectivity for H460 and HT-29 cancer cell lines. Among these compounds, compound **37** (c-Met IC_{50} = 2.43 nM) exhibited the most potent inhibitory activities against H460, HT-29 and MDA-MB-231 cell lines with IC_{50} values of about 1.7-, 1.3- and 1.6-fold more active than foretinib, respectively (**Nan *et al.*, 2020**).

2.1.2.2. Non-receptor tyrosine kinases (NRTKs):

Non receptor tyrosine kinases are categorized into 9 subfamilies based on sequence similarities, primarily within the kinase domains. These include Abl, Src, FES, JAK, ACK, SYK, TEC, FAK, and CSK family of kinases (**Siveen *et al.*, 2018**).

2.1.2.2.1. BCR-Abl TK as a target for cancer treatment:

Chronic myeloid leukaemia (CML) is associated with the exchange of genetic material between the chromosomes 9 and 22, whereby the latter is altered and becomes the so-called Philadelphia chromosome. This transfer leads to a hybrid gene (bcr-abl), formed by transfer of one of the normal genes. This hybrid has deregulated and high ABL kinase activity, resulting in a high leukocyte count (**Manley *et al.*, 2005**).



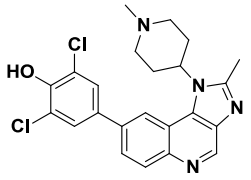
Bosutinib (**38**)

Bosutinib **38** (Bosulif®) is a Bcr-Abl kinase inhibitor. It is also an inhibitor of Src-family kinases including Src, Lyn, and Hck. The FDA approved the use of Bosutinib to treat patients with chronic, accelerated, or blast-phase Philadelphia chromosome-positive

chronic myelogenous leukemia (CML) who are resistant to or cannot tolerate other therapies, such as imatinib (**Cortes *et al.,* 2018**).

2.1.2.2.2. Quinolines as JAK inhibitors:

Janus kinase (JAK) is a family of intracellular that transduces cytokine-mediated signals *via* the JAK-STAT pathway which is a chain of interactions between proteins in a cell, and is involved in processes such as immunity, cell division, cell death, and tumor formation. The pathway communicates information from chemical signals outside of a cell to the cell nucleus, resulting in the activation of genes through the process of transcription (**Kiu *et al.,* 2012**).

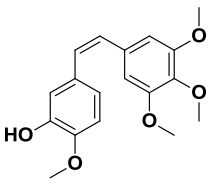


(**39**)

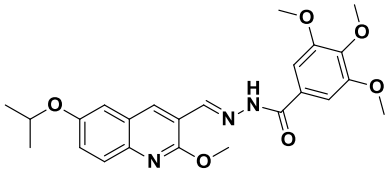
A series of imidazo[4,5-c]quinoline derivatives showed a potent and simultaneous inhibition of two primary proinflammatory signaling pathways JAK/STAT and NF-κB. Especially, lead compound **39** showed potent inhibitory activities against interferon-stimulated genes (IC_{50}=3.3 nM) and NF-κB pathways (IC_{50}=150.7 nM) and decreased the release of various proinflammatory factors at the nanomolar level (**Liang *et al.,* 2022**).

2.2. Quinolines as tubulin inhibitors:

Microtubules have key roles in essential cellular processes such as mitosis, cell motion, and intracellular organelle transport. Microtubule inhibitors work by stopping or slowing down cell division and movement, and then it can stop or slow down the spread of cancer cells. The colchicine binding site is one of the most important pockets for potential tubulin polymerization destabilizers. Colchicine binding site inhibitors (CBSI) exert their biological effects by inhibiting tubulin assembly and suppressing microtubule formation (**Lu *et al.,* 2012**).

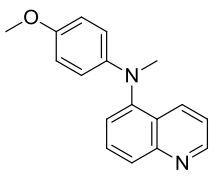


Combretastatin A-4 (**40**)

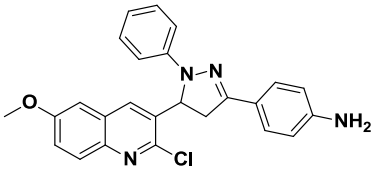


(**41**)

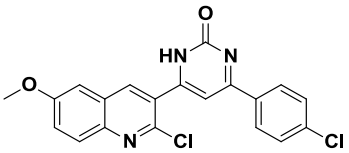
Based on the structure of combretastatin A-4 (**40**), a series of quinoline derivatives incorporating rigid hydrazone and cyclic oxadiazole linkers were designed and synthesized. They demonstrated potent tubulin polymerization inhibitory properties and many of the novel derivatives showed significant antiproliferative activities in the submicromolar range. The most potent compound **(41**) demonstrated superior with IC_{50} values range (0.02-0.04 µM) against four cancer cell lines while maintaining low cytotoxicity in non-cancer cells as well as it inhibited tubulin polymerization (**Ibrahim *et al.*, 2020**).



(**42**)



(**43**)

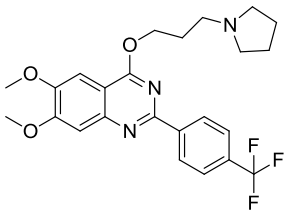


(**44**)

A series of quinoline derivatives were designed and synthesized as novel tubulin inhibitors targeting the colchicine binding site. Among them, compound **42** exhibited the highest antiproliferative activity with an IC_{50} of 261 nM against HepG-2 cells. Mechanism studies revealed that compound **42** effectively inhibited tubulin polymerization *in vitro* and disrupted microtubule dynamics in HepG-2 cells (**Ren *et al.*, 2021**). Furthermore, based on the pharmacophoric features of the colchicine binding site, a number of novel quinoline derivatives were designed to possess tubulin inhibitory activity. The most potent tubulin polymerization inhibitory affect was demonstrated by compounds **43** and **44**, with IC_{50} values of 9.11 and 10.5 nM, respectively compared to those of CA-4 (IC_{50}= 13.2 nM) and colchicine (IC_{50}= 10.6 nM) (**Hagras *et al.*, 2021**).

***2.3. Quinolines as topoisomerase inhibitors*:**

Topoisomerases (TOPs) are nuclear enzymes that play crucial roles in DNA replication, transcription, chromosome segregation, and recombination. All cells have two major forms (topoisomerase I and topoisomerase II). DNA topoisomerases are important targets of approved and experimental anti-cancer agents (**Nitiss *et al.*, 2012**). The camptothecins including camptothecin (**2**), topotecan (**3**) and irinotecan (**4**) are examples of approved quinoline anticancer drugs and drug candidates with topoisomerases I inhibitory activity (**Venditto *et al.*, 2010**).

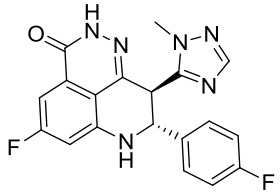


(**45**)

Two series of 4-alkoxy-2-arylquinolines were designed and synthesized as an attempt to develop potential anticancer agents targeting topoisomerase I. The compounds were screened for *in vitro* cytotoxic activity and the Compound **45** the most potent against colon cancer, leukemia and melanoma with GI_{50} MG-MID 0.875, 0.904 and 0.926 μM, respectively (**Elbadawi *et al.*, 2021**).

2.4. Quinolines as PARP inhibitors:

PARP (poly (ADP-ribose) polymerase) (PARP) inhibitors are a novel type of medications that works by preventing cancer cells from repairing their DNA once they have been damaged by other chemotherapy agents (**Wiggans *et al.*, 2015**).

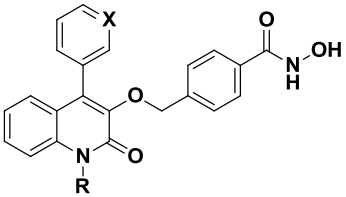


Talazoparib (46)

Talazoparib **46** (Talzenna®) is an orally available PARP inhibitor developed by Pfizer for the treatment of advanced breast cancer with germline BRCA mutations. It was approved in 2018, in the United States and 2019, in the EU for germline BRCA-mutated, HER2-negative locally advanced or metastatic breast cancer (**Hoy *et al.*, 2018**).

2.5. Quinolines as HDAC6 inhibitors

Histone deacetylase 6 (HDAC6) is an enzyme that in humans is encoded by the HDAC6 gene. HDAC6 has emerged as a highly promising candidate to selectively inhibit as a therapeutic strategy to combat several types of cancer and neurodegenerative disorders. HDAC6 is a unique member of the HDAC family that not only participates in histone acetylation and deacetylation but also targets several nonhistone substrates, such as α-tubulin, cortactin, and heat shock protein 90 (HSP90), to regulate cell proliferation, metastasis, invasion, and mitosis in tumors (**Li *et al.*, 2018**).

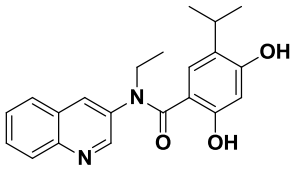


(47a,b) 47a: R=H, X=CH, **47b:** R=CH_3, X=N

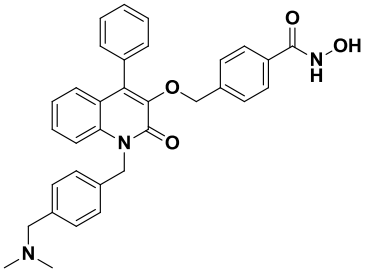
A set of quinolone compounds were investigated in cellular studies to evaluate their anticancer effect against colon (HCT-116) and histiocytic lymphoma (U9347) cancer cells, showing good to excellent potency, leading to tumor cell death by apoptosis induction. The small molecules **47a, b** were able to strongly inhibit the cytoplasmic and slightly the nuclear HDAC enzymes, increasing the acetylation of tubulin and of the lysine 9 and 14 of histone 3, respectively (**Relitti *et al.,* 2021**).

***2.6. Quinolines as HSP90 inhibitors*:**

The mammalian heat shock protein (HSP90) family of proteins is a group of highly conserved molecules that are involved in myriad cellular processes. HSP90 contributes in crucial physiological processes such as cell survival, cell cycle control, hormone signaling, and apoptosis. Conversely, HSP90, and its secreted forms, are included in the development and progress of serious pathologies, including cancer and neurodegenerative diseases. Therefore, targeting HSP90 is an attractive strategy for the treatment of neoplasms and other diseases (**Hoter *et al.,* 2018**).



(**48**)



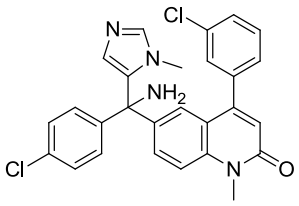
(**49**)

In 2019, Nepali *et al.* reported a study including the design and synthesis of amide tethered quinoline-resorcinol hybrid constructs as a new class of HSP90 inhibitor. *In vitro* studies of the synthetic compounds led to the identification of compound **48**, which possesses potent cell growth inhibitory effects against HCT116, Hep3B and PC-3 cell lines, exerted through HSP90 inhibition. It triggers degradation of HSP90 client proteins along with concomitant induction of HSP70, demonstrates apoptosis inducing ability and causes G2M phase cell cycle arrest in PC-3 cells (**Nepali *et al.,* 2019**). Additionally, a recent study reported that the quinolone derivative **49** was also able to increase Hsp90 acetylation levels in HCT-116 cells. (**Relitti *et al.,* 2021**).

2.7. Quinolines as FTase inhibitors:

Farnesyltransferase (FTase) is a cytosolic metalloenzyme that catalyzes the transfer of a 15-carbon farnesyl lipid moiety to a group of cellular proteins characterized by a C-terminal CAAX motif. FTase inhibitors block the activity of the FTase enzyme by inhibiting prenylation of the CAAX tail motif, which ultimately prevents Ras from binding to the membrane, rendering it inactive which is critical to cell cycle progression. For this

reason, several FTase inhibitors are undergoing testing as anti-cancer agents (**Sebti *et al.*, 2005**).

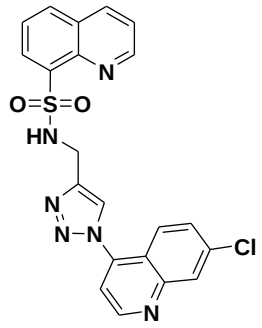


Tipifarnib (50)

Tipifarnib **50** (R115777, Zarnestra®) is a phase II potent and highly selective inhibitor of FTase. The inhibitor was investigated in patients with head and neck cancers, peripheral T-cell lymphoma (PTCL), myelodysplastic syndromes (MDS), and chronic myelomonocytic leukemia (CMML) (**Witzig *et al.*, 2011**).

2.8. Quinolines as PKM inhibitors:

Pyruvate kinase muscle isozyme (PKM), is an enzyme that in humans is encoded by the PKM2 gene. PKM2 can be aggregated into tetrameric and dimeric forms, PKM2 in the dimer state can enter the nuclear to regulate gene expression, and the transformation between them, so it can play an important role in tumor cell energy supply, epithelial–mesenchymal transition (EMT), invasion and metastasis and cell proliferation (**Zhang *et al.*, 2019**).

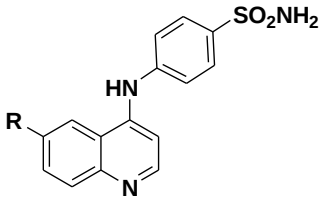


(51)

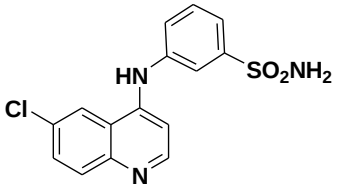
In 2023, Marciniec *et al* reported that a series of 8-quinolinesulfonamide derivatives of PKM2 modulators were designed using molecular docking and molecular dynamics techniques. The results obtained from *in vitro* experiments confirmed the ability of compound **51** to reduce the intracellular pyruvate level in A549 lung cancer cells with simultaneous impact on cancer cell viability and cell-cycle phase distribution (**Marciniec *et al.*, 2023**).

2.9. Quinolines as Carbonic anhydrase inhibitors:

Human carbonic anhydrases (EC 4.2.1.1) IX (*h*CA IX) and XII (*h*CA XII) are two tumor-associated proteins, being overexpressed in many tumors and involved in critical processes associated with cancer progression and response to therapy (**Monti *et al.*, 2013**).



(52a-c) 52a: R=CH_3, **52b**: R=OCH_3, **52c**: R=Cl

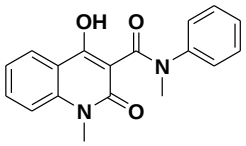


(53)

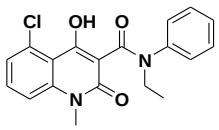
A series of quinoline-based benzenesulfonamides were developed to be potential carbonic anhydrase inhibitors (CAIs). Moreover, the described have been synthesized and investigated for their CA inhibitory action against *h*CA I, II, IX and XII. In general, *para*-sulphonamide derivatives **52a-c** demonstrated the best inhibitory activity against both cancer-related isoforms *h*CA IX (*K*Is = 25.8, 5.5 and 18.6 nM, respectively) and *h*CA XII (*K*Is = 9.8, 13.2 and 8.7 nM, respectively), beside the excellent *h*CA IX inhibitory activity exerted by *meta*-sulphonamide derivative **53** (*K*I = 8.4 nM) (**Shaldam *et al.*, 2021**).

2.10. Immunomodulating quinolines:

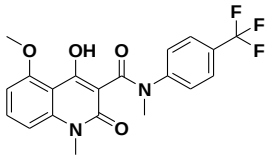
The immunomodulatory activity of targeted anticancer agents originates from the interaction of the drug with cancer cells, as well as from the ability of the drug to interact with, and alter the function of, immune cells. Both these general mechanisms of immunomodulation by targeted anticancer therapy can involve direct or indirect pathways. As an example, targeted anticancer agents can mediate net immunostimulatory effects by promoting the secretion of pro-inflammatory cytokines, or by limiting the release or activity of immunosuppressive factors (**Petroni *et al.*, 2021**).



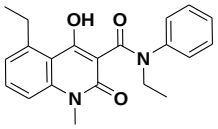
Roquinimex (54)



Laquinimod (55)



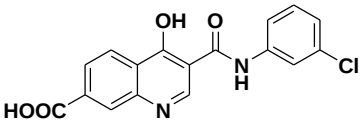
Tasquinimod (56)



Paquinimod (57)

Roquinimex **54** (linomide®) is the first generation immunomodulatory quinoline-3-carboxamide derivative used as anticancer agent. It has an immunostimulant activity as well as it inhibits angiogenesis and reduces the secretion of Tumour Necrosis Factor alpha (TNF alpha). Roquinimex **54** passed phase I, phase II and failed in phase III of clinical trials due to unanticipated serious cardiopulmonary toxicities (Isaacs *et al.*, 2010).

Laquinimod **55** (ABR-215062, Nerventra®) is an experimental second-generation immunomodulator quinoline-3-carboxamide. Besides, other quinoline-3-carboxamide derivatives such as tasquinimod **56** or paquinimod **57** have shown immunomodulatory, anti-tumor, and anti-angiogenic effects in pre-clinical animal models. Moreover, the modulation of myeloid cells was primarily held responsible for their immunomodulatory and anti-tumor effects (**Ott *et al.,* 2019**).



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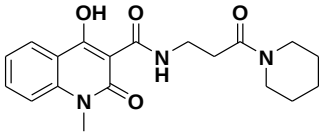
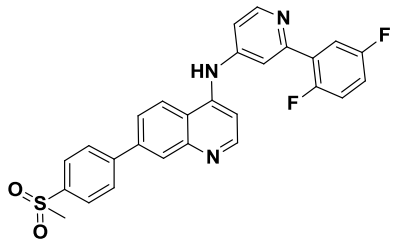


(59)

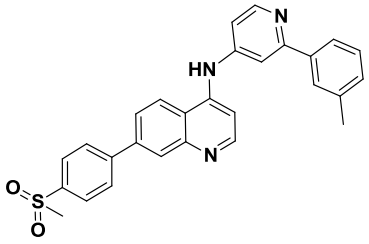
He *et al*. reported a series of novel quinoline-3-carboxamide derivatives showed an immunomodulatory activity on spleen lymphocyte proliferation and Tumour Necrosis Factor alpha (TNF alpha) production by macrophage. Compound **58** showed immunomodulatory profiles more potent than those of roquinimex (linomide®) (**He *et al.,* 2005**). Based on roquinimex scaffold, a new series of 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxamide was designed and synthesized using peptide coupling agents. The synthesized compounds were evaluated for their *in vitro* anti-proliferative activities against PANC 1, HeLa and MDA-MB-231. Compound **59** was the most potent anti-proliferative agent with GI_{50} values ranging from 0.15 μM to 1.4 μM (**Banu *et al.,* 2017**).

2.11. Quinolines as transforming growth factor β inhibitors:

Transforming growth factor β (TGF-β) is a highly pleiotropic cytokine that plays an important role in wound healing, angiogenesis, immunoregulation and cancer. The cells of the immune system produce the TGF-β1 isoform, which exerts powerful anti-inflammatory functions, and is a master regulator of the immune response. The tumor microenvironment contains high concentrations of TGF-β, a crucial immunosuppressive cytokine. TGF-β stimulates immune escape by promoting peripheral immune tolerance to avoid tumoricidal attack. (Prud'homme *et al.,* 2007) (**Kharbanda *et al.,* 2021**).



(60)



(61)

A group of selective 4-aminoquinoline-based compounds was identified as inhibitors of TGFbR1 through structural and rational-based design strategies. This led to the identification of compound **60**, which was found to be selective for TGFbR1 with the exception of MAP4K4 in the kinase profiling assay. The compound was then further optimized to remove MAP4K4 activity, since MAP4K4 is vital for proper T-cell function and its inhibition could exacerbate tumor immunosuppression. Optimization efforts led to compound **61** that inhibited TGFbR1 at an IC_{50} of 0.79 ± 0.19 nM with 2000-fold selectivity against MAP4K4 (**Kharbanda *et al.*, 2021**).

Conclusion:

In the end, numerous studies have established the ability of quinoline derivatives to limit cancer cell growth, induce apoptosis, and block angiogenesis, hence inhibiting tumor progression, through considerable research and experimentation. Quinolines' varied modes of action, such as targeting distinct signaling pathways and signaling molecules, make them appealing candidates for further investigation and development as anticancer drugs. However, additional preclinical and clinical trials are required to assess these substances' full therapeutic potential, optimal dose, and potential side effects. Overall, the data reported in this study highlight the importance of quinoline derivatives in cancer research, necessitating more investigation to realize their full potential in the pursuit of better cancer treatments.

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مقالة عامة عن مشتقات الكينولين كمركبات مضادة للسرطان

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تعد مشتقات الكينولين من أهم العناصر الأساسية في اكتشاف الأدوية في العقود الأخيرة، لا سيما في الأبحاث المضادة للسرطان. مؤخرا تم اكتشاف العديد من مركبات الكينولين ذات الخصائص الانتقائية المثبطة للخلايا السرطانية وأخرى ذات خصائص مؤثرة على الصفات المناعية للخلايا. من خلال مراجعة الأبحاث الصادرة حديثا، وجد أن مشتقات الكينولين لديها القدرة على تثبيط كينازات البروتين والأهداف الجزيئية الأخرى مثل تعطيل تجميع التوبولين.

إن الغرض من هذه المقالة هو تسليط الضوء على نتائج الدراسات التي أجريت على مركبات الكينولين والتي توضح العديد من المسارات المضادة للسرطان بما يفيد في تصميم واكتشاف وتطوير مركبات أو أدوية جديدة ومحتملة مضادة للسرطان متعددة الأهداف من هذه الفئة من جزيئات الكينولين.

الكلمات المفتاحية: الكينولين، مثبطات أنزيمات التايروزين ، مثبطات انزيمات الثيرين والثريونين، المعدلات المناعية، مثبطات التيوبيولين، VEGFR، BCR-Abl، HSP90، توبويزوميراز.