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Review Article

Anticancer Mechanism of Quinoline Based Compounds for Cancer Therapy

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ABSTRACT

Recently quinoline based anticancer agents have gained popularity for anticancer therapy. Numerous quinoline derivatives have been designed, developed and screened for varieties of cancers. Few of them have cleared the clinical trials and now available in the market for sale. Numbers of marketed anticancer agents possess quinoline scaffold. Donorubicin, doxorubicin, actinomiycin etc are few of them possess quinoline nucleous. These agents have well developed anticancer mechanism. Majority of them work through topoisomerase-2 inhibition, however recently other mechanism through which these developed quinoline based anticancer agents works are also reported. Now a days other mechanism though which these agents works are also developed. These includes tubulin polymerization inhibition, PiM kinase inhibition, PAK inhibition, mitotic kinesin spindle protein (KSP) inhibition, vascular endothelial growth factor receptors (VEGFR) inhibition, activin receptor-like kinase-2 (ALK) inhibition, ataxia telangiectasia and Rad3-related protein inhibition, breakpoint cluster region abelson kinase inhibition, casein kinase (CK) inhibition, c-Src kinase and Src-Abl nonreceptor tyrosine kinases inhibition and epidermal growth factor receptor inhibition.

INTRODUCTION

In the search new anticancer agents, millions of heterocyclic compounds have been designed, synthesized and reported till date. Majority of reported compounds are either inactive or showed potent activities against different cancer cell lines [1,2]. Quinoline is a heterocyclic aromatic compound with the molecular formula C9H7N. Its double-ring structure includes a benzene ring bonded to pyridine at two neighboring carbon atoms. Quinoline is sometimes referred to as benzopyridine, benzo[b]pyridine, 1-benzazine, or benzazine. This yellowish oily liquid is hygroscopic and mildly soluble in water, but also in alcohol, ether, and other organic solvents. Isoquinoline, a congener of quinoline, varies from quinoline in nitrogen position (at the second position) [3].

Natural quinoline and isoquinoline alkaloids have piqued the curiosity of scientists, particularly those studying natural product chemistry, due to their amazing biological activity and simple structure. Quinoline and its congeners have also paved the interest of synthetic organic chemists due to the necessity to obtain larger amounts for further biological investigation. Quinoline alkaloids produced from flowering

plants, animals, and microbes demonstrated a wide range of biological activity.

A number of quinolines and their derivatives are known to have antibacterial, antifungal, analgesic, anti-inflammatory, hypotensive, anti-HIV and anticancer properties. Quinoline derivatives are finding applications in practically every domain of medical chemistry, including anticancer medicines. Quinoline derivatives act as antiproliferative agents by intercalating DNA and interfering with replication [4]. Actinomycin D, doxorubicin, mitoxantrone, and streptomycinigrin are quinoline analogues that have antibacterial or anti-cancer action via DNA intercalation. The majority of these medications are now utilized to treat human cancers and target topoisomerase (type II) enzymes [5]. Numerous compounds have been designed and synthesized by various researchers, reflecting quinoline based anticancer activities [6].

Anticancer medicines, including those in development, target numerous enzymes. Quinoline-based anticancer medicines, including new ones in development, target varieties of molecular targets for cancer therapy, these includes: tubulin polymerization, Pim kinase, PAK, mitotic kinesin spindle protein (ksp/eg5 atpase), vascular endothelial growth factor (VEGF), activin receptor-like kinase-2 (alk-2), ataxia telangiectasia and rad3-related protein, breakpoint cluster or abelson kinase, casein kinase (ck), c-src kinase and src-abl nonreceptor tyrosine kinases and epidermal growth factor. In the present manuscript we reported quinoline based anticancer agents. These compounds act through various mechanism as described above.

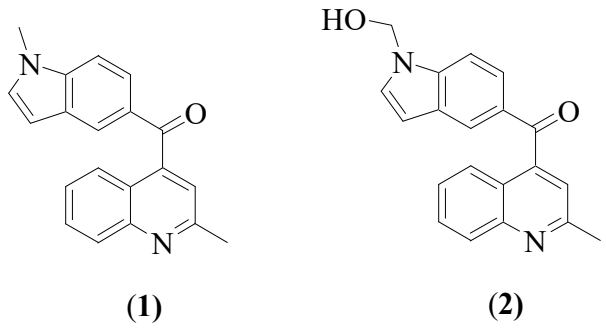
TUBULIN POLYMERIZATION INHIBITORS

Tubulin is a macromolecule (protein) that is commonly found in the protozoan class Kinetolastid. Tubulin is classified into five forms: alpha (α), beta (β), gamma (γ), delta (δ), epsilon (ε), and zeta (ζ). α and β assist create microtubules by polymerizing into protofilament. A microtubule is made up of 10-15 protofilaments arranged laterally. Like other processes, the polymerization process requires critical dimmer concentrations, and the rate can be increased by adding dimer units. To create specific polarity in microtubules, carefully arrange the α and β units. To do this, expose one end of each tubulin unit, known as the α and β ends, respectively [7].

Microtubules are dimmers of tubulin that are hollow and long. These dimmers are generally stable due to complex formation, but the presence of two GTP binding sites makes them susceptible to hydrolysis. The GTP binding site of α-tubulin at the interface of two monomers does not hydrolyze irreversibly with GTP, while the GTP binding site of β-tubulin at the surface hydrolyzes reversibly into GDP. The α-tubulin site with GTP serves a structural function, while β-tubulin with GTP and hydrolysis aids in the attachment of new dimmers. The kinetics of GTP- and GDP-bound tubulins differ. GDP ones are more prone to depolymerization in general and are found at the tip of microtubules, whilst those in the middle do not depolymerize immediately. Disassembly can be protected by GTP tubulins when they are at the tip of microtubule (rescue). Microtubule continuously undergoes growing and shrinking (catastrophe) [8].

Microtubules exist and play an important role in the structure of cells and cytoskeletons. Along with micro- and intermediate filaments, these contribute to the structure of mobile microorganism components such as cilia and flagella. In addition, they aid in intracellular transport (for example, organelles and other intracellular molecules). Their broad significance in cell division makes them the ideal target for cancer treatment [9].

Li et al. reported synthesis, anticancer and anti-tubulin activity of indole quinoline hybrid derivatives against KB, HepG2, MDA-MB-231, H22, HCT-8, and LO2 cancer cell lines [10]. Among the synthesized compounds, compounds (**1**) and (**2**) were more potent against all cell lines (IC_{50} values 5-11 μM), particularly against K562 cell line (Figure 1). Compounds (**1**) and compound (**2**) showed best tubulin polymerization inhibition with IC_{50} values of 2.54 and 2.09 μM respectively, as compared to Combretastatin A-4 (CA-4) with IC_{50} value of 2.12 μM. Compound (**2**) showed arrests of G2/M phase of cell cycle, and also induced apoptosis of K562 cell lines in a dose-dependent manner.



(1) **(2)**

Fig. 1. Structure of compounds (**1**) and (**2**).

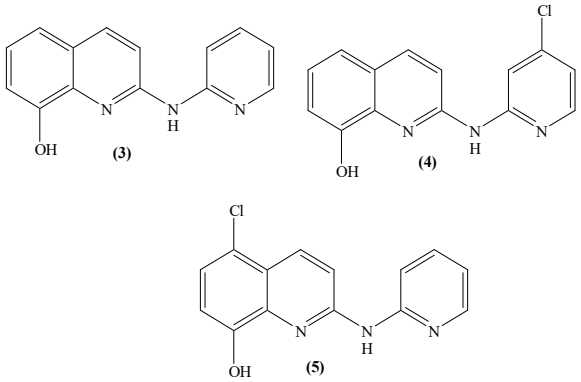


Fig. 2. Structure of compounds **(3-5)**

Pim-1 KINASE INHIBITORS

Pim-1 kinase, a serine/threonine cytoplasmic kinase, controls programmed cell death or apoptosis and cellular metabolism. Pim-1 is upregulated in numerous human malignancies. Pim-1 kinase phosphorylate numerous cellular substrates, including Myc, p21Cip1/WAF1, and p27KIP1. Both Pim-1 and c-Myc promotes cell development and alteration. Numerous Pim-1 inhibitors have been reported as potential therapeutics cancer treatments [11].

Quinoline derivatives have been well reported as Pi-1 inhibiters for cancer therapy. Sliman et al. reported a series of quinoline-2-carboxamides and 2-styrylquinolines that may act as Pim-1 kinase inhibitors [12]. 8-hydroxyquinoline 7-carboxylic acid moiety was reported as an important pharmacophore for action. The interaction of 8-hydroxyquinoline 7-carboxylic acid moiety with Asp186 and Lys67 residues in the ATP-binding site was responsible for kinase inhibitory potency in molecular modelling study outcomes.

Many quinoline derivatives have been reported for anti-tumour efficacy in prostate cancer PC-3 cell line. The Pim-1 kinase inhibitory activity measured via the Ser/Thr KinEase assay kit (CisBio). Compounds **(3-5)** showed with GI_{50} values of 2.60 µM, 2.81 µM, and 1.29 M, respectively, and potential activity against the Pim-1 kinase (Figure 2). The presence of secondary amine with pyridine and a quinoline ring is responsible for their anti-proliferative effect. Compound **(5)** effectively inhibited the PIM-1 kinase, cause apoptosis and halt the cell cycle. All the synthesized compounds showed effective against prostate cancer [13].

Furthermore, Mohareb et al. reported the reaction of cyclohexan-1,3-dione with trichloroacetonitrile and dimeric cyanomethylene to produce numerous fused ring analogs like isoquinoline, dihydrothieno-isoquinoline, 2,3,6,7-tetrahydro quinazoline [14]. These reported compounds were examined for five tyrosine kinases namely: Flt-3, c-Kit, EGFR, VEGFR-2, PDGFR, and Pim-1 kinase. Compounds **(6-10)** showed most potent Pim-1 kinase inhibitory activities (Figure 3).

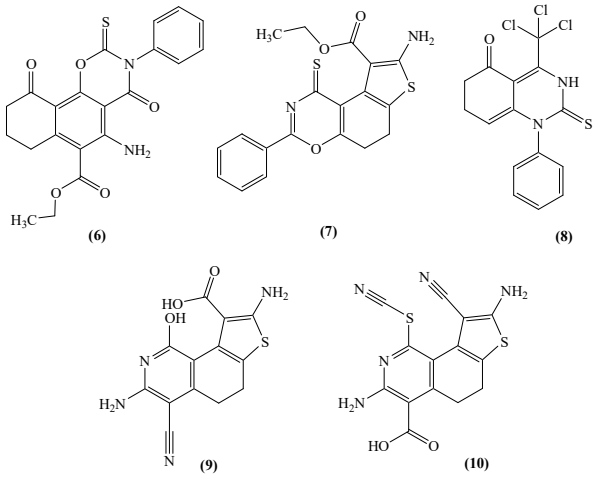


Fig. 3. Structure of compounds (**6-10**).

Quinoline derivatives **(11-13)** showed potent Pim-1 kinase inhibitory activity on par with quercetin (Figure 4). Quercetin and the synthesized compounds **(11-13)** acted as potent inhibitors of Pim-1 kinase, in a kinetic experiment using the Lineweaver-Burk double-reciprocal plot. Compound **(12)** inhibited the Pim-1 kinase enzyme in a competitive and non-competitive manner. The molecular modelling studies

demonstrated that the synthesized compounds met the requirements for hydrophobic and ligand effectiveness to be lead-like compounds [15].

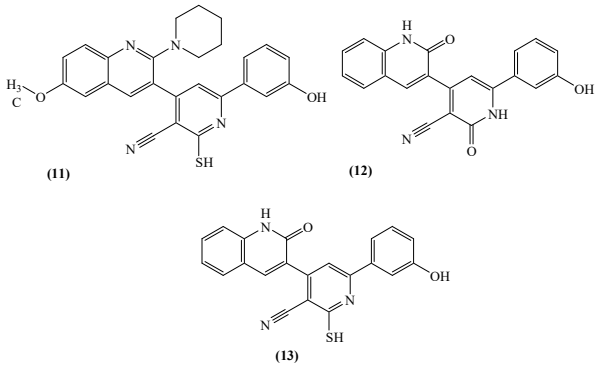


Fig. 4. Structure of compounds **(11-13)**

In a different study, isoxazolo-quinoline-3,4-diones were reported as effective inhibitors of Pim-1/2 kinases. The presence of hydroxyl group on benzene ring is showed to be essential in the HB interaction in the hinge expanse of Pim kinases. The most active compound **(14)**, showed Ki values of 2.5 nM and 43.5 nM against Pim-1 and 2, respectively (Figure 5). The ligand and protein interaction was observed due to formation of hydrogen binding of carbonyl group of the isoxazolone and the charged amino group of Lys67 at a distance of around 3.0 Å. Furthermore, oxygen on the quinolinone ring linked to Lys67 [16].

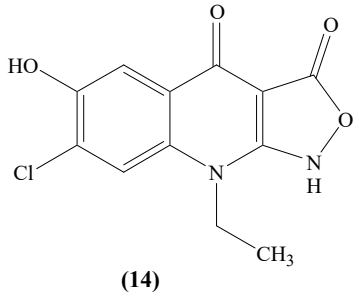


Fig. 5. Structure of compound **(14).**

PAK INHIBITORS

PAK1 is another serine/threonine-protein kinase, typically overexpressed and is particularly pronounced in malignancies. PAK1 signaling regulates the expression, function, and angiogenesis of vascular endothelial growth factors (VEGF) and also regulates endothelial cell migration. Comparative genomic hybridization array and tumor tissue microarrays showed increase DNA copies as on increasing PAK1 numbers. In ovarian carcinomas 30% PAK1 gene copy increases, while PAK1 protein was expressed in 85% of the tumors [17]. Increased PAK1 expression enhanced cyclin D1 promoter activity, cyclin D1 mRNA and protein levels, and cyclin D1 nuclear accumulation in breast cancer cells [18]. By upregulating VEGFs, Heregulin promotes PAK1 and controls angiogenesis [19].

Many PAK1-targeting agents, including ATP-competitive inhibitors, peptide inhibitors, and allosteric inhibitors, have been developed as preclinical medicines or even been tested in a clinical trial. These PAK1 inhibitors' different biochemical and pharmacokinetic features could lead to interesting therapeutic medicines.

Wang et al. designed and reported CP734 (**15**) as strong inhibitor of PAK1 by using a structure- based virtual screening technique. N-[3-(benzylmethylamino) propyl] - 8-methyl- 4- oxo- 5H- thieno[4,5- c] CP734 is a quinoline- 2-carboxamide derivative (Figure 6) [20]. The *in vitro* studies showed PAK1 kinase inhibitory activity with an IC_{50} value of 15.27 mol/L, however showed no inhibitory effects on PAK2, PAK3, and PAK6, but only weak inhibitory effects on PAK4 and PAK7. Authors also found thet CP734 stimulation significantly reduced intracellular PAK1 activity (in 20 mol/L) in BxPC- 3 cells. A dose- and time- dependent cell proliferation was claimed by CP734.

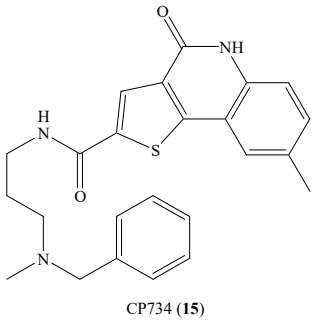


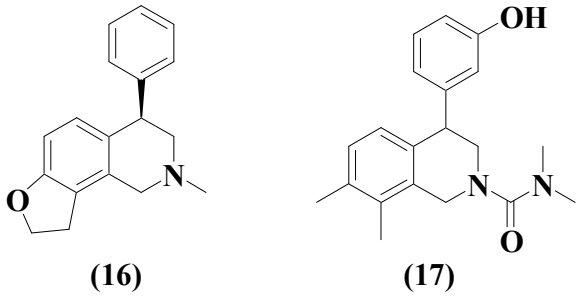
Fig. 6. Structure of compound CP734 (15).

Furthermore, Kim et al. reported compounds comprising 1,4-naphthohydroquinone and 1,4- naphthoquinone, PAK1 and PAK3 selective inhibitory *in vitro* anticancer activity in live cells [21].

MITOTIC KINESIN SPINDLE PROTEIN (KSP/Eg5 ATPase) INHIBITORS

A mitotic kinesin termed KSP, also known as Hs (Homo sapiens) Eg5, is located in the mitotic spindle and is required for the early phases of mitosis to create a bipolar mitotic spindle [22]. As a homotetramer, this protein can bind to microtubules that are oppositely polarized and originate from different spindle poles. Following ATP hydrolysis, KSP can move processivity along with microtubules thanks to the coordinated activity of corresponding motor domains located at either end of the homotetramer. KSP is coupled to two microtubules to produce a bipolar mitotic spindle, causing spindle poles to separate in the opposite direction of the centrosome [23]. Inhibiting KSP causes mitotic arrest, which results in monopolar mitotic spindles generated when centrosomes fail to split. Medications that target KSP, rather than the microtubule cytoskeleton, may avoid peripheral neuropathies associated with antimicrotubule medicines [24]. Small molecule inhibitors have been found to produce mitotic arrest in a variety of tumor cell lines both in vitro and in vivo, and this, together with the expected reduction in brain toxicity, has contributed in the development of multiple ongoing antimitotic drug research programs [25].

A new family of tetrahydroisoquinolines was found utilizing high-throughput screening. Compound (**16**) had an IC_{50} of 9.7 mM in an ATPase experiment and 2.4 mM in a proliferation analysis using A2780 human ovarian cancer cells (Figure 7). An NMR experiment demonstrated that compound (**16**) binds to the same allosteric location as Monastrol. Based on NMR and crystallographic data from KSP Monastrol and KSP-HR2216 co-crystal structures, a binding model was created to guide the structure-activity relationships (SAR) for the series. An optimization research found that 7,8-dimethyl groups might substitute the fused dihydrofuran ring (**16**) without reducing efficacy. Analogues with amino groups added to chains of 2-4 carbon atoms had activity comparable to compound (**16**) when N was replaced with alkyl groups larger than methyl. As a result, the charged side chain may point in the direction of a solvent, which is facilitated by N-acylation products such as amides, sulphonamides, carbamates, and primary urea. The compound (**17**) (racemic) having an N, N-dimethyl urea exhibited a significantly higher ATPase IC50 (IC_{50} 2.75 mM) than the compound (**16**). To summarize the H-bond between the carbonyl group in KSP's backbone amide Glu118 and the phenol-OH group in Monastrol, a hydroxyl group was added to the compound's 3-position (**17**). As a result, the efficacy of the ATPase assay increased by eightfold (IC_{50} 306 nM) and thrice in the cellular assay (IC_{50} 376 nM). Tarby et al. found that the 4-OH counterpart had no action [26]. Compound (**17**)'s (R)-antipode co-crystalized with KSP as expected, and it is likely to bind to KSP at the allosteric site identified. It was obvious that the phenol's oxygen formed an H-bond with the carbonyl oxygen of Arg119 and Glu118. Tetrahydroisoquinoline, dimethyl urea, and the phenyl ring were also discovered to interact with the protein through Van der Waals interactions [27].



(16) **(17)**

Fig. 7. Structure of compounds (**16**) and (**17**).

VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTORS (VEGFR/PDGFR) INHIBITORS

The vascular endothelial growth factor receptor (VEGFR) is the most well-known regulator of tumor angiogenesis, metastasis, and growth of all known angiogenic agents. Inhibiting VEGF/VEGFR signaling appears to be a promising therapeutic option for solid tumor therapy. Despite their great safety and selectivity, monoclonal antibodies have limitations that preclude them from being employed in therapeutic settings. The highly conserved glycoprotein VEGF is a potent multifunctional cytokine that has a significant effect on the vascular endothelium and is most likely required for tumor-induced novo vascularization. As a result, tumor growth can be reduced with angiogenesis inhibitors that target the vascular compartment [28]. Targeting tumor angiogenesis is an essential anticancer approach.

Lenvatinib is manufactured in nine steps using the original strategy. First, 4-amino-2-chlorobenzonitrile (V-i) undergoes

a SNAr with sodium methoxide. The 1,4-dihydroquinoline ring (V-iii) is formed by combining Meldrum acid ethoxy methylene derivative with thermally induced cyclo-condensation. Under basic conditions, the nitrile group is changed to the corresponding carboxylic acid, followed by the formation of acyl chloride derivatives, with the quinolone core altered into a 4-chloroquinoline derivative via thionyl chlorid. In aqueous ammonia, the acyl chloride functionality is changed to a carboxamide, resulting in an intermediate (V-IV) (Figure 8). A SNAr reacts with 4-amino-3-chlorophenol to create the matching carbamate in the presence of phenyl chloroformate, creating another connection with the anilino group. Finally, cyclopropylamine treatment yields lenvatinib [29].

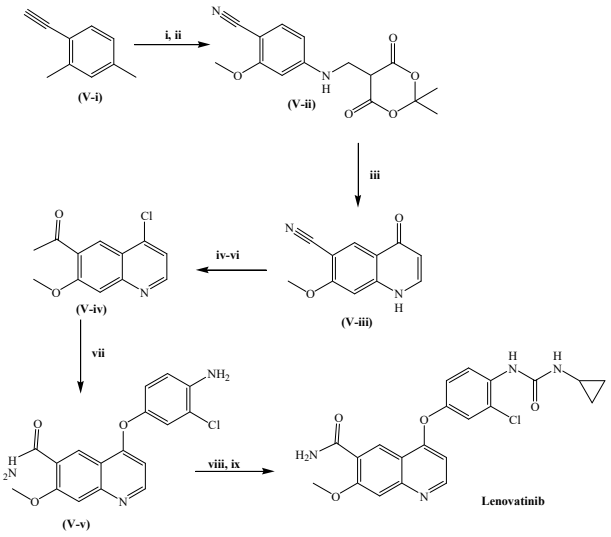


Fig. 8. Synthetic pathway for synthesis of Lenvatinib.

ACTIVIN RECEPTOR-LIKE KINASE-2 (ALK) INHIBITORS

Activin receptor-like kinase 2 (ALK2) is a type I bone morphogenetic protein (BMP) receptor that belongs to the TGFb family subgroup. It participates in the classical SMAD1/5/8 BMP signaling pathway by building tetrameric complexes with BMPRII and ACVRIIA (activin receptor type-2A) as well as noncanonical signaling via p38MAPK [30]. It is essential for the development and differentiation of the bone, heart, neurological, and reproductive systems. Single point mutations (gain of function) in ALK2 are frequently seen in two untreatable uncommon disorders, fibrodysplasia ossificans progressiva (FOP) and diffuse intrinsic pontine glioma (DIPG). Both disorders require the identification of ALK2-targeted medicines. Some effective drug discovery efforts resulted in the development of dorsomorphin, LDN193189, K02288, and LDN214117 [31].

In 2020, Engers et al. discovered 7-aryl-imidazo[1,2-a]pyridine-3-pylquinolines as ALK inhibitors [32]. They studied the heterocyclic cores reported for ALK2 inhibitory activity and chose the imidazo[1,2-a]pyridine scaffold to investigate its ALK2 inhibitory potential. To identify strong inhibitors, they investigated several positions of the imidazo[1,2-a]pyridine core. Overall, lead optimization and SAR analysis revealed three compounds (**18–20**) containing a piperazine moiety and 2-methyl-fluorinated quinoline (Figure 9). These drugs had high ALK2 inhibitory potency and selectivity against other similar receptors. continued profiling revealed that these drugs have a balanced in vivo pharmacokinetic profile, allowing for continued advancement into IND-enabling trials.

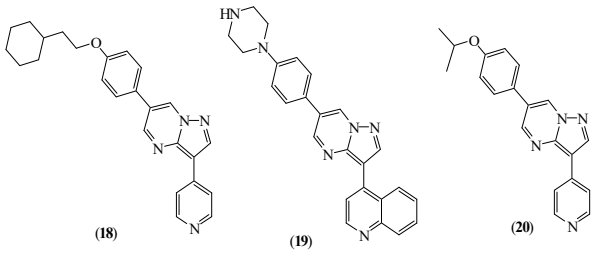


Fig. 9. Structure of compounds (**18-20**) with selective ALK2 inhibitory activity.

Hudson et al. revealed the structure-activity relationship and kinase profiling of new quinazolinone inhibitors of ALK2 [33]. The chemical (**21**), derived from 6-pyrazole quinazolinone, was found to inhibit ALK2 (IC_{50} = 8.2 mM). Following the alteration of the pyrazole ring in the sixth position of quinazoline, further substitutions in the third position of quinazolinone were investigated, as well as the introduction of solvent channel groups. SAR study found that replacing the 6-pyrazole in (**21**) with bicyclic groups increases potency. Furthermore, using a 4-morpholinophenyl as a solvent channel produced the most powerful molecule, (**22**) (Figure 10). The binding mode study of (**22**) revealed that quinazolinone N-1 forms an H-bond with His 286.

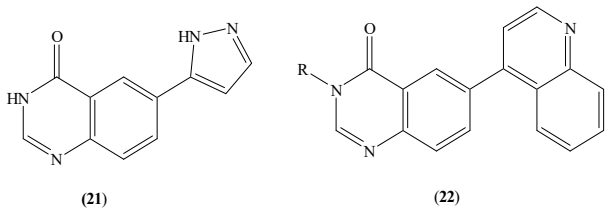


Fig. 10. Novel quinazolinone-based inhibitors (**21-22**) of ALK2.

Mohedas et al. reported the discovery of selective ALK2 inhibitors [34]. The researchers found dorsomorphin and LDN-193189 to be highly effective BMP inhibitors, building on their prior findings. The current study describes the identification of LDN-212854 (**19**), a specific BMP and ALK2 inhibitor. They generated and tested quinoline-coupled pyrazolo[1,5-a]pyrimidine derivatives. SAR analysis revealed that quinoline substitutions at the third, ninth, and sixth positions of the core resulted in a decrease of activity against BMP receptors. However, quinoline substitution at the fifth position produced a strong and selective BMP inhibitor. Adding the phenylpiperazine group to the 5-quinoline moiety resulted in a more powerful and selective molecule, LDN-212854. Finally, a compound between ALK2 and LDN-212,854 revealed that the 5-quinoline group forms an H-bond with K235 in the catalytic domain.

ATAXIA TELANGIECTASIA AND Rad3-RELATED PROTEIN INHIBITORS

Ataxia telangiectasia (AT), commonly known as LouiseBar Syndrome, is a rare autosomal recessive genetic illness marked by progressive neurologic issues that cause ataxia or trouble walking, as well as a higher chance of acquiring several types of cancer [35]. In addition, tiny clusters of swollen blood vessels, known as telangiectasia, form in the eye or on the skin's surface. AT is a disease with an early onset. AT mutations (ATM) are linked to the prognosis of serious clinical malfunctions such AT and tissue-specific processes like apoptosis, CNS development, immunology, and angiogenesis. ATR is primarily crucial for maintaining replication S-phase fork integrity, regulating cell cycle progression, and initiating cell cycle checkpoints in the event of genotoxic shocks. Associating with centromeres, ATR promotes efficient chromosomal segregation during mitosis. Most crucially, Rad3-related ataxia telangiectasia (ATR) detects damaged or stopped DNA replication by identifying replication protein-acoated single-stranded DNA (ssDNA). NVP-BEZ235 and ETP-46464 are ATM/ATR/mTOR inhibitors that work at nanomolar concentrations. The IC_{50} of ETP-46,464 was found to be 25 nM, while that of NVPBEZ235 was 100 nM [36]. The molecular structures of NVP-BEZ235 and ETP-46464 are depicted in Figure 11. NVP-BEZ235 was produced on the basis of an imidazo[4,5c]quinolone core, whereas ETP-46464 was created with a quinoline core [37]. Furthermore, while ETP-46464 was a novel chemical, NVP-BEZ235 was already in phase I/II clinical studies for advanced solid tumors (NCT00620594; NCT01508104; NCT01658436: NCT01756118; NCT01658436) when it was identified as a powerful ATR inhibitor. NVP-BEZ235 has strong activity against DNA-PK (IC50 ¼ 5 nM), making it a DDR inhibitor rather than only an ATR inhibitor [38].

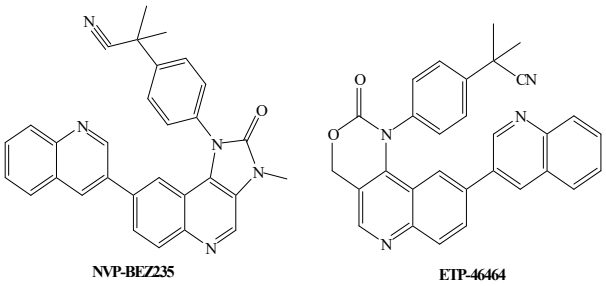


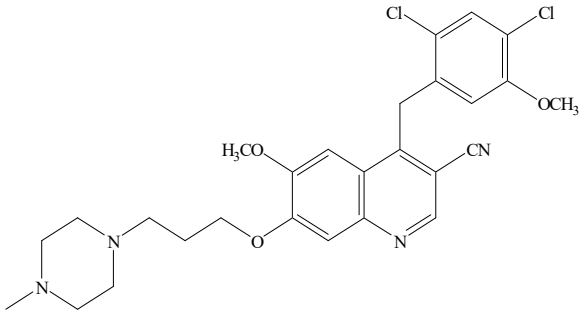
Fig. 11. Structure of NVP-BEZ235 and ETP-46464.

BREAKPOINT CLUSTER REGION ABELSON KINASE INHIBITORS

Breakpoint cluster region-Abelson (BCR-AbL) is a fusion protein that causes CML and ALL. Leukemia can be efficiently treated with BCR-AbL inhibitors; however, a gatekeeper mutation (T315I) in BCR-AbL develops resistance to these inhibitors, reducing their efficiency dramatically. The BCR-AbL protein's resistance to pharmacotherapy is mostly caused by point mutations and gene amplification, as well as a variety of BCR-AbL-independent mechanisms [39].

It is a dual kinase inhibitor and synthetic quinolone derivative that may have anticancer properties. It targets both the Abl and Src kinases. Bosutinib (Figure 12), unlike imatinib, blocks both Abl and Src kinases from autophosphorylating,

hence reducing cell proliferation and death. This drug's two modes of action suggest that it could be useful against solid tumors, other myeloid malignancies, and resistant CML. The abnormal Bcr-abl fusion protein, which is usually associated with chronic myeloid leukemia, increases the activity of the enzyme abl kinase (CML). The phenotype of imatinib-resistant CML is also connected to the overexpression of certain Src kinases [40].



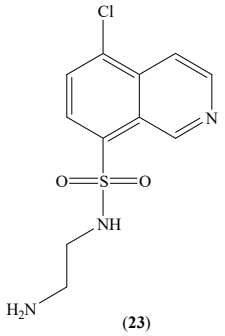
Bosutinib

Fig. 12. Structure of quinolone derivative: bosutinib.

CASEIN KINASE (CK) INHIBITORS

Casein kinase (CK) is a key member of the protein kinases family, phosphorylating numerous essential proteins in a variety of signaling pathways [41]. Casein kinase refers to three types of kinases: protein kinase CK1, protein kinase CK2, and Golgi CK (also known as Fam20C). Overexpression of CK1 has been linked to several cancers, including leukemia (CK1ε) [42], B-cell lymphomas (CK1d) [43], kidney cancer (CK1g3) [44], pancreatic cancer (CK1d/ε) [45], lung cancer (CK1ε), breast cancer (CK1ε) [46], and ovarian cancer (CK1ε) [47]. Upregulated CK1 phosphorylates tumor suppressor p53, resulting in uncontrolled cancer cell proliferation [48]. CK1 has also been linked to various signaling pathways that control cell proliferation and survival, including Wnt/b-catenin [49], Hedgehog [50], and Hippo pathways [51]. Furthermore, CK1-mediated activation of the p75 tumor necrosis factor receptor and caspase 8 inhibits apoptosis [52]. As a result, targeting CK1 offers a viable technique for cancer treatment.

Chijiwa et al. described the first CK1 inhibitor [53]. The ATP-competitive isoquinoline derivative1 (CKI-7) had moderate inhibitory action against CK1 (Ki ¼ 8.5 mM) and poor selectivity between CK1 isoforms (Fig. 4.2). The co-crystal structure of CK1 in association with compound (**23**) (PDB ID: 2CSN) revealed that the isoquinoline core occupied the adenine region, while the 2-nitrogen atom formed a hydrogen bond with residue Leu88 (Figure 13) [54]. Additionally, the 5-Cl substituent and 8-ethylamine sulfonamide chain of 1 had multiple polar interactions with Tyr59, Ser91, and Asp94. Despite its inadequate activity and selectivity, compound (**23**) was a useful tool in the identification of CK1 family members [55].



(23)

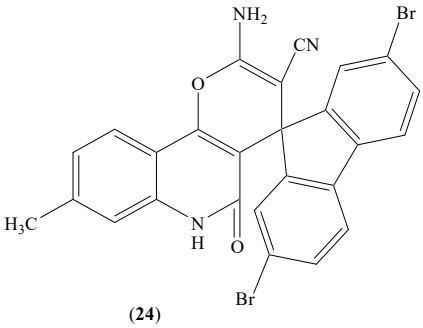
Fig. 13. Structure of compound (**23**).

c-Src KINASE AND Src-Abl NONRECEPTOR TYROSINE KINASES INHIBITORS

c-Src kinase and Src-Abl are two nonreceptor tyrosine kinases in the Src family. They have a conserved domain structure and are essential in signal transduction [56]. Src-Abl is a fusion protein that is linked to certain kinds of leukemia and results from a chromosomal translocation event. This fusion occurs between the BCR (Breakpoint Cluster Region) and ABL1 (Abelson) genes, leading in the development of a hybrid gene known as BCR-ABL1 [57]. The fusion of the BCR and ABL1 genes produces the Src-Abl fusion protein, which has distinct features from its individual components, c-Src kinase and c-Abl. Src-Abl has constitutive activity, which means it is active regardless of external signals or regulatory systems. This constitutive activation is mostly related to the deletion of the C-terminal regulatory region, and the presence of the BCR coiled-coil domain is required for the activation and signaling of the Src-Abl fusion protein [58]. This domain, derived from the BCR gene, enables dimerization and transphosphorylation, both of which are critical processes in Src-Abl activation. This signaling pathway contributes to the development of leukemia, notably chronic myeloid leukemia

(CML) and a subset of acute lymphoblastic leukemia [59]. Src-Abl's continuous kinase activity promotes aberrant leukemic cell growth and survival, disrupts normal hematopoiesis, and inhibits apoptosis. Furthermore, the presence of Src-Abl in leukemia cells imparts resistance to various inhibitors of c-Src kinase or c-Abl, including imatinib. This resistance creates considerable hurdles in the treatment of leukemia, highlighting the need for alternative therapeutic techniques and the development of innovative medicines particularly tailored to target Src-Abl [60].

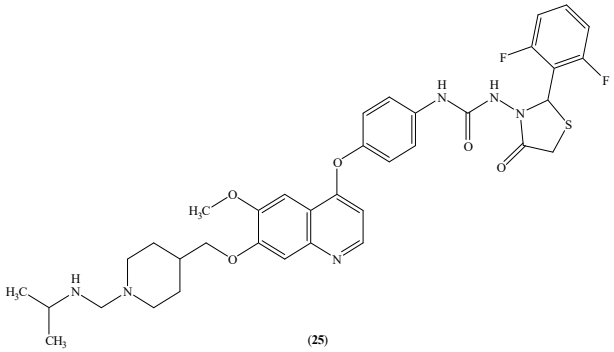
Ramadan et al. synthesized and developed novel 20-aminospiro[pyrano[3,2ec]quinoline]-30-carbonitrile derivatives as non-ATP competitive Src kinase inhibitors to inhibit breast cancer cell migration and proliferation [61]. The chemicals inhibited Src kinase activity strongly, targeting it specifically while having little effect on other kinases. The lead drug (**24**) effectively inhibited Src (IC_{50} ¼ 0.87 mM), Fak, and paxillin phosphorylation in breast cancer cell lines, leading to cell growth inhibition and apoptosis induction (Figure 14). These findings highlight the possibility of these compounds as targeted treatment agents for breast cancer, especially decreasing Src kinase activity.



(**24**)

Fig. 14. Structure of compound (**24**).

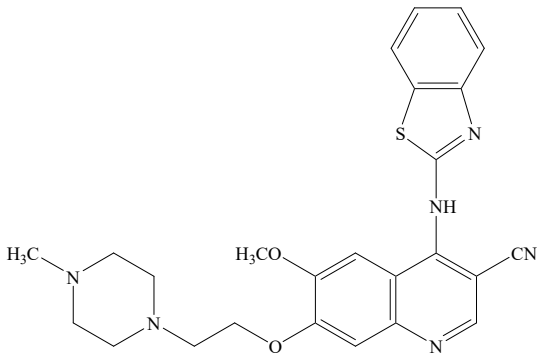
Zhou et al. identified powerful kinase inhibitors for the treatment of colorectal cancer [62]. Based on their prior study, they devised and synthesized a new family of quinoline analogs that contained thiazolidinones. The most promising chemical (4) showed strong inhibitory effect against the c-Met and Ron kinases. It also had mild inhibitory effects on the PDGFRa, c-Src, and AXL kinases. In vitro anticancer studies revealed that compound (**25**) had substantial cytotoxic and antiproliferative effects on HT-29 colorectal cancer cells, outperforming Regorafenib and Cabozantinib. Cellular studies revealed its potential to produce apoptosis and a minor cell cycle arrest in HT-29 cells. Notably, chemical (**25**) demonstrated selectivity for cancer cells while sparing normal colorectal cells (Figure 15). These data imply that compound (**25**) offers promise as a lead chemical for the creation of effective anticancer medicines targeting colorectal cancer, calling for additional structural optimization.



(**25**)

Fig. 15. Structure of compound (**25**).

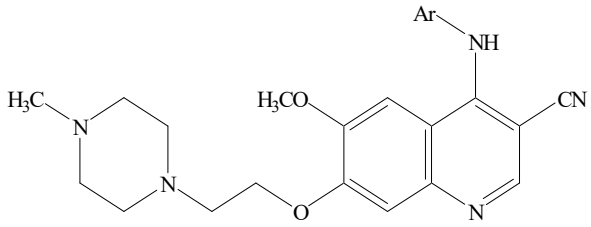
Cao et al. developed and synthesized 7-alkoxy-4-heteroarylamino-3-quinolinecarbonitriles as dual inhibitors of c-Src kinase and nitric oxide synthase (iNOS) in carcinogenesis [63]. The chemicals were tested for their capacity to inhibit both enzymes and cancer-related signaling pathways. Most drugs demonstrated strong dual inhibition and considerable efficacy against a variety of cancer cell lines. Compound (**26**) (CPUeY020) was particularly effective, with IC_{50} values of 6.58 and 7.61 mM against the HT-29 (colon cancer) and HepG2 (liver cancer) cell lines, respectively (Figure 16). This work demonstrates the potential of these chemicals for targeted cancer therapy.



(**26**)

Fig. 16. Structure of compound (**26**).

Cao et al. developed and synthesized 7-alkoxy-4-heteroarylamino-3-quinolinecarbonitriles as dual inhibitors of c-Src kinase and nitric oxide synthase (iNOS) [64]. Both c-Src and iNOS are important regulatory enzymes in carcinogenesis, giving them promising targets for cancer treatment. The researchers developed and synthesized a series of chemicals, then tested their inhibitory effects on both enzymes in vitro using enzyme inhibition and antiproliferation tests. The results showed that the majority of the drugs inhibited c-Src and iNOS, with some having substantial action against various cancer cell lines. Compound (**27**) (CPUeY020) stood out as the most promising contender, with IC_{50} values of 6.58 and 7.61 mM against colon cancer (HT-29) and liver cancer (HepG2) cell lines, respectively (Figure 17). These findings show that these dual inhibitors have the ability to target cancer therapy.



(**27**)

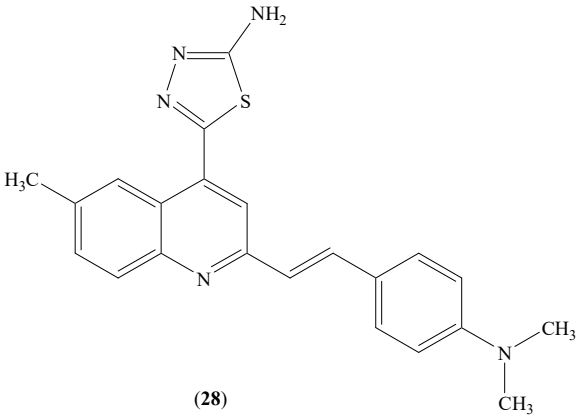
Fig. 17. Structure of compound (**27**).

EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS

Many carcinoma types rely heavily on the epidermal growth factor receptor (EGFR) for development and progression. These receptors are also involved in early embryonic development and the regeneration of stem cells in the liver and skin [65]. EGFR belongs to a receptor family that contains three other proteins: ErbB-2, ErbB-3, and ErbB-4 [66]. These proteins form a system in which a signal attaches to one receptor and is commonly sent to another [67]. This method increased and diversified the initial signal, which is required for cell growth [68]. As a result, analyzing the impact of EGFR signaling requires taking into account the complex interactions that occur between ErbB and growth factors [69]. Such interactions may be required for the development of more effective therapy strategies to inhibit EGFR signaling in cancer patients. All EGFR receptors belong to the ErbB family of receptor tyrosine kinases (RTK) (HER4) [70]. EGFR has a hydrophobic transmembrane, a ligand binding site, and a cytoplasmic TK site [71]. The intracellular TK-site of ErbB receptors is highly conserved, although ErbB-3's kinase domain contains considerable amino acid variations [72]. This receptor reactivates metalloproteinase and promotes tyrosine kinase crossphosphorylation [73]. This activates two pathways, RAS and PI3K. RAS triggers the RAF, which activates the MEK. The signaling molecules that bind to this TK include PLCg, Eps15, and Cbl [74]. It activates MEK, which stimulates cell growth. PI3K activation phosphorylates and activates AKT, causing it to localize in the plasma membrane [75]. This enzyme belongs to the AKT subfamily of serine/threonine kinases that contains an SH2 (Src homology 2-like) protein domain [76]. Then, mTOR increases Akt signaling, promoting cell motility and survival while also causing angiogenesis. When cells are overexpressed and the number of cells grows in the body's organs and other areas, EGFR inhibitors are utilized. These are the chemicals that inhibit the activity of the EGF protein, reducing cell development. Gefitinib and erlotinib (first generation EGFR inhibitors) are the first-line EGFR inhibitors utilized in lung cancer. Gefitinib works by inhibiting TK phosphorylation and thereby preventing the downstream process. It reduces cell proliferation, which produces angiogenesis [77].

El-Sayed and colleagues developed and synthesized 4,6-disubstituted 2-(4-(dimethylamino) styryl)quinolone derivatives and tested them for anticancer efficacy [78]. The anticancer activity of all produced compounds was assessed using the MTT assay on two cancer cell lines, HepG2 and HCT116, which are hepatocellular and colon cancer cell lines, respectively. Furthermore, 5-fluorouracil and afatinib were used as reference medicines. Compound (**28**) was found to be the most powerful against the HepG2 and HCT116 cell lines, with IC_{50} values of 7.7±0.1 mg/mL and 8.8±0.26 mg/mL, respectively (Figure 18). High inhibitory action was observed with IC50 values ranging from 1 to 10 mg/mL. The activity of the EGFR kinase was determined using an enzyme-linked immunosorbent assay. They used the MOE 2008.10 program to perform docking tests on compound (**28**). Docking experiments revealed that compound 1's quinoline ring was hydrophobically surrounded by the amino acids Val702,

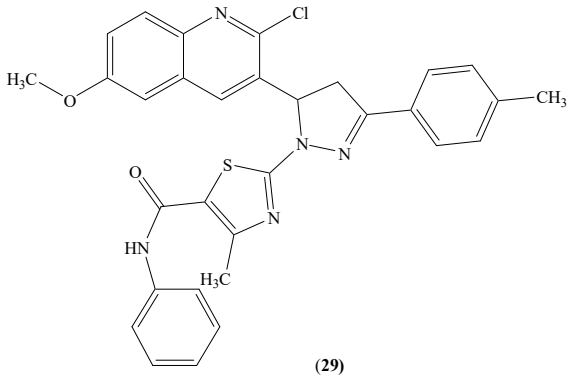
Leu694, and Leu820. The 2-styryl moiety of molecule (**28**) works as a backbone, similar to the 6,7-dialkoxy seen in erlotinib. The docking interaction energy of chemical 1 was determined to be 20.89 kcal/mol. It was discovered that compound (**28**) was properly docked in the presumed EGFR binding site, which was identical to erlotinib. SAR investigations demonstrated that the methyl group on the quinoline ring was required for action. It was also shown that introducing the bromine group at this location somewhat reduced antitumor activity. Furthermore, the 1,3,4-thiadiazol-2-amine moiety on the quinoline ring activated the molecule. The carboxylate group was replaced at this location, which reduced the anticancer efficacy by 100 times compared to compound (**28**).



(**28**)

Fig. 18. Structure of compound (**28**).

In 2019, George et al. performed in vitro cytotoxic screening against MCF-7, HeLa, DLD1, and WI38 cell lines and presented a SAR investigation of quinoline-based 4,5-dihydropyrazoles and their thiazole hybrids as EGFR inhibitors [79]. Of all the substances, (**29**) was shown to be a powerful EGFR inhibitor (Figure 19). The IC_{50} for compound (**29**) was 0.064 mM against the DLD1 cell line. As a positive control, CHS 828 was used. The EGFR inhibitory activity was assessed using gefitinib as a reference medication. The IC_{50} for chemical (**29**) was 42.52 nM. SAR analysis confirmed that quinolinyl pyrazoline hybrids resulted in enhanced activity with great efficiency. Electronegative groups on quinolinyl, such as F and Cl, shown optimal EGFR inhibitory activity than electropositive groups. To build a binding model, compound (**29**) underwent molecular docking at the EGFR binding site. It established hydrogen bonding connections with Met769 and had cationep interactions with Lys721. The docking score of compound (**29**) was discovered to be 12.94 kcal/mol. Other connections were created hydrophobically with Leu694. The hydrophobic contact with the 4,5-dihydropyrazole moiety at the other end of the ATP binding sites increased the stability of the 2D structure.



(**29**)

Fig. 19. Structure of compound (**29**).

SUMMARY and CONCLUSION

In the present article we have reported numerous quinoline based anticancer compounds possess different anticancer mechanism. We have discussed SARs and biological activities of reported compounds. The different anticancer mechanism of these compounds has been discussed vastly.

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None

CONFLICT of INTEREST

NIL

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