Review Article

Anticancer Activity of Quinoline Derivatives: An Overview

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ABSTRACT

Quinoline, 1-aza naphthalene/benzo pyridine, is nitrogen containing heterocyclic nucleus which is one of the major building blocks of many synthetic drugs. Quinoline derivatives have attracted many scholars' attention because of their wide range of pharmacological activities such as antimalarial, anticancer, anti-inflammatory, antimicrobial etc. There are so many quinoline derivatives with anticancer activities were reported in various renowned journals. In this review, an attempt is made to compile the latest updates on anticancer activity of quinoline derivatives. Quinoline derivatives plays an important role in anticancer drug development through different mechanism of action like topoisomerase I and II inhibition, proteasome inhibition, antimitotic and tubulin polymerization inhibition *etc.*

Keywords: Quinoline, anticancer, topoisomerase I and II inhibition, proteasome inhibition, antimitotic inhibition, tubulin polymerization inhibition.

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INTRODUCTION

Quinoline **figure 1** is a nitrogen containing heterocyclic aromatic compound which has a molecular formula of C_9H_7N and molecular weight of 129.[1] Dewar, a well-known scientist noticed the chemical similarity of quinoline with pyridine, divulged its rigid heterocycle core of benzene ortho fused with a pyridine ring in 1871 and shows both electrophilic and nucleophilic substitution reactions.[2] Benzopyridine (Quinoline) is a colorless oily hygroscopic liquid with Pka 4.85 in water at 20^0 C. It is very stable and is usually used as high boiling solvent with a b.p of 237^0 C. Since quinoline has an acidic Pka of 4.85, it can form salts with acids whose log P value is 2.04[1]. Quinoline scaffold is identified as a prominent existence in various biologically active plants (Cinchona), agrochemicals, dyes, pharmaceuticals. Quinoline is a well-known chelating agent in coordination chemistry to chelate metallic ions and are applied as N-donor ligands.[2] Synthesis of quinoline derivatives is done through various synthetic routes. Some of them are Gould-Jacobs, Friedlander, Pfitzner, Skraup synthesis etc.

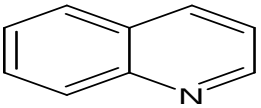
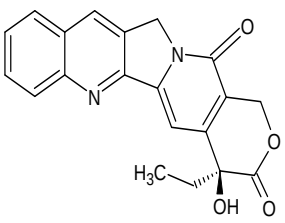


Figure 1

The recently released statistical analytical data by WHO reveals the fact that 14 million diagnosed cancer cases and 9 million cancer related deaths occurs annually. Cancer is the second leading cause of death after cardiovascular disease. Cancer is a rapid abnormal uncontrollable proliferation of normal cells. The anticancer agents currently used are less effective due to the increasing threat of drug resistance.[3] Quinoline derivatives exhibits a promising anticancer strategy that they can lead to new high potential anticancer agents with better safety profile. Quinoline scaffold have been examined for their modes of action in the inhibition of topoisomerase I and II, antimitotic and tubulin polymerization, proteasome *etc.* [4] The demonstration of quinoline derivatives have been conducted on several cancer cell lines to determine anticancer potential. Some of the available anticancer drugs are Camptothecin **figure 2**, Topotecan **figure 3**, Irinotecan **figure 4**, Exatecan **figure 5** (topoisomerase I and II inhibitor), Anlotinib **figure 6**, Lenvatinib **figure 7** (multi-kinase inhibitor), Bosutinib **figure 8** (Src-Abl inhibitor). This review focused on serving medicinal chemists to create a platform to design better anticancer drug by discussing and compiling the anticancer potential of quinoline derivatives in target-oriented basis.[5]



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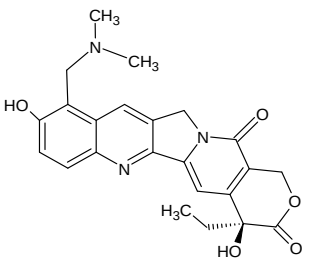

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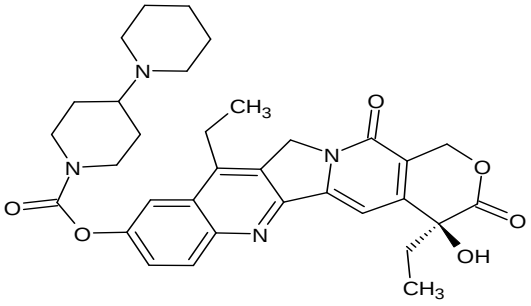

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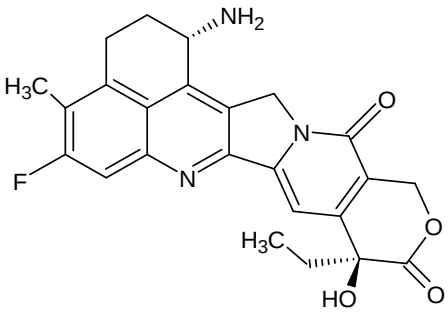

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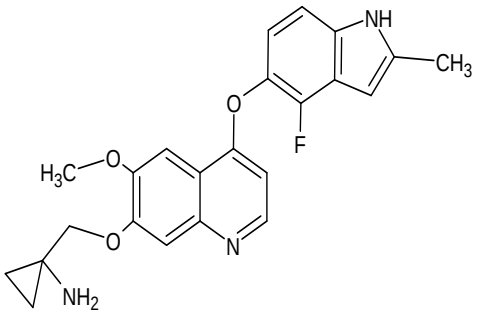

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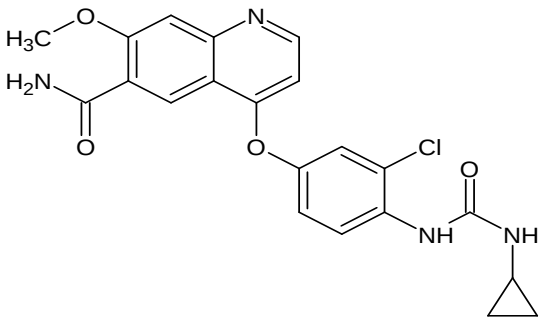

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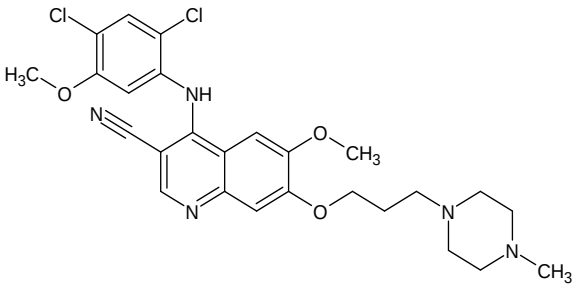


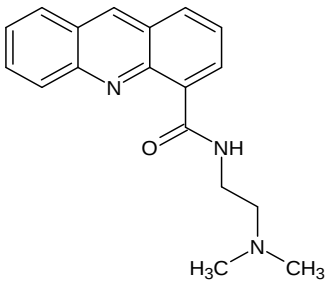
Figure 8

ANTICANCER ACTIVITY OF QUINOLINE DERIVATIVES

1.Topoisomerase I and II Inhibitors

Camptothecin (CPT) **figure 2**, a cytotoxic alkaloid was used as anticancer drug in traditional Chinese medicine and was isolated from the stem wood of Chinese tree, *Camptotheca acuminata.*[6] CPT is a topoisomerase I inhibitor by stabilizing the covalent topoisomerase I -DNA complex. It consists of planar pentacyclic ring structure which includes pyrrolo [3,4-β]-quinoline moiety (rings, A, B and C) with pyridone moiety (ring D) and one chiral center at position 20 with a α-hydroxy lactone ring with (S) configuration (E ring). Essential structural features of CPT for anticancer activity are 20 (S) hydroxyl pyridone moiety of the D ring, the lactone moiety of the E ring and the planarity of the 5 membered ring system, therefore C, D, E ring cannot be altered. In order to increase the potency of CPT derivatives, modification to 9,10,11 position of A ring and 7th position of B ring are generally tolerated. E ring in the structure with the enzyme topoisomerase from three different positions and hydroxyl group in 20th position form a hydrogen bond with Asp533 and the amino group on Arg364 is bonded with 2 hydrogen bonds to the lactone ring. By forming hydrogen bond with the amino group on the pyrimidine ring of cytosine interact with the carbonyl group of D ring, thus stabilizes the topoisomerase I-DNA covalent complex, so it will prevent DNA re-ligation and therefore causes DNA damage which results in apoptosis. Because of the low solubility and high adverse drug reactions of CPT, medicinal chemists have developed analogues of CPT like topotecan **figure 3**, irinotecan **figure 4**, exatecan **figure 5** which have been approved and used in cancer chemotherapy nowadays.[7]

Deady et al. prepared series of tetracyclic quinoline carboxamides and their cytotoxicities were evaluated in a wide range of human tumor cell lines. Quinoline analogues showed cytotoxicities broadly similar to those of known tricyclic acridine-4-carboxamide (DACA) **figure 9** mixed topoisomerase I/II inhibitor with thieno **figure 10** and indeno figure **11** analogues being the most active. The new class of compounds appear to be mixed topoisomerase I/II inhibitors found to be 3-fold more cytotoxic than DACA. [8]



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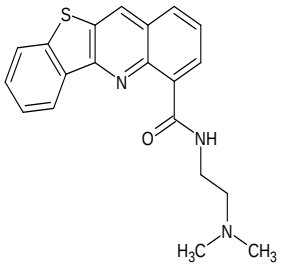

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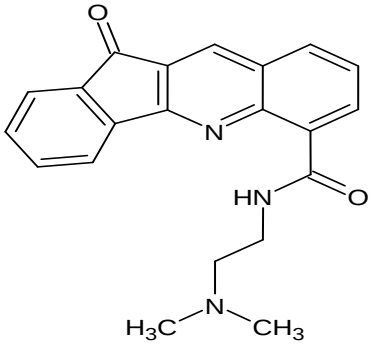
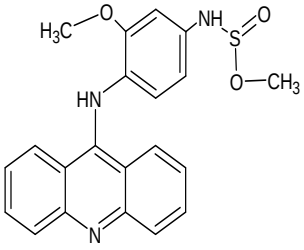


Figure 11

Gonzalez-Sanchez et al., prepared thiazolo [5,4-b] quinoline derivatives, which are compounds structurally related to m-Amsacrine (m-Amsa) **figure 12**, a potent antileukemic drug intercalates to DNA and inhibits topoisomerase II invitro inducing cell death. Thiazolo[5,4-b] quinoline derivative, D_3CLP **figure 13**, considered isosteric with 9-anilioacridines, in order to determine its relative cytotoxic activity in tumoral versus non tumoral cells. The compound D_3CLP found to be four times more cytotoxic to tumor cells than Peripheral Blood Monocyte Cells (PBMCs).[7]



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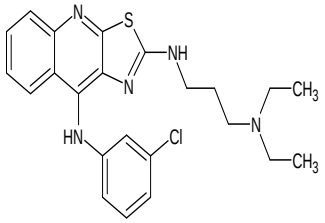
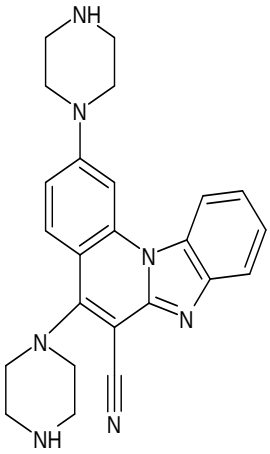


Figure 13

Perin et al. synthesized series of 2-amino, 5-amino and 2,5-diamino substituted benzimidazo [1,2-a] quinolines by uncatalyzed microwave assisted amination. Due to the presence of 4-methyl and 3,5 dimethyl-1-piperazyl groups, these compounds were assessed *in vitro* against colon, lung and breast carcinoma cell lines for antiproliferative activities. Among the compounds tested, 2-amino substituted analogues showed the strongest antiproliferative activity whereas 5-amino and 2,5-diamino substituted derivatives showed much lesser activity. These compounds were prepared and evaluated for 3D QSAR analysis, anticancer property, DNA binding abilities. Substituted benzimidazo[1,2-a] quinolines whose DNA binding properties and mode of interaction were studied using melting temperature studies, a series of spectroscopic studies and biochemical experiments (topoisomerase I- mediated DNA relaxation and DNAase I footprinting experiments). The adjacent base pairs of the DNA helix intercalate between the both compound **figure 14** and bis quaternary iodide salt **figure 15** while compound **figure 16** exhibited less topoisomerase I poisoning activity.[9]



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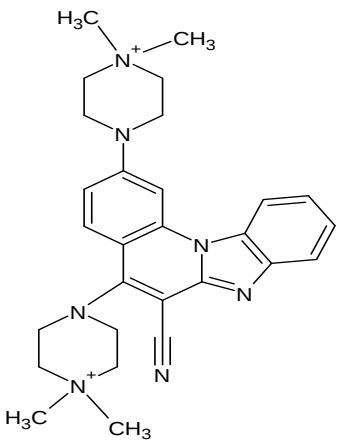

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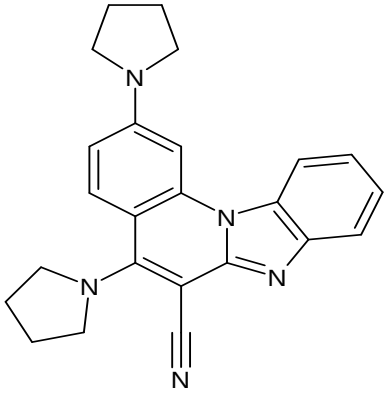
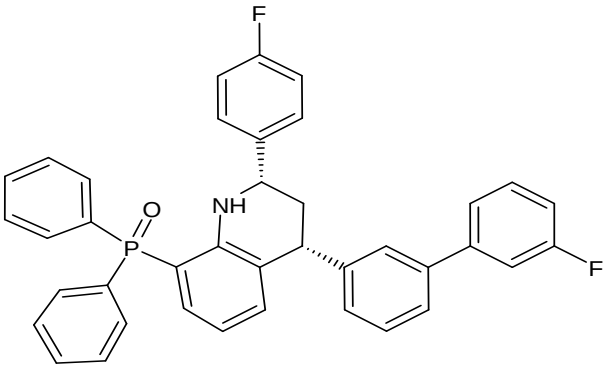


Figure 16

The research of **Alonso et al.** describes the synthesis of 1,2,3,4-tetrahydroquinolinyl phosphine oxides, phosphanes and phosphine sulfides as well as that of quinolinyl phosphine oxides and phosphine sulfides. Among the compounds were tested some of them showed excellent activity as topoisomerase I inhibitors. Even after 3 minutes of the beginning of the enzymatic reaction, prolonged effect of the most potent compounds is maintained. Human lung adenocarcinoma(A549), human embryonic kidney (HEK293), human ovarian carcinoma (SKOVO3) was also screened for the cytotoxic effect on cell lines. Against the lung cancer cell line compound **figure 16** showed potent activity with IC_{50} value of 0.25±0.23 µm whereas compounds **figure 17** and **figure 18** showed better activity against lung cancer cell line with IC_{50} value of 0.08±0.01 µm and 0.03± 0.04 µm.[10]



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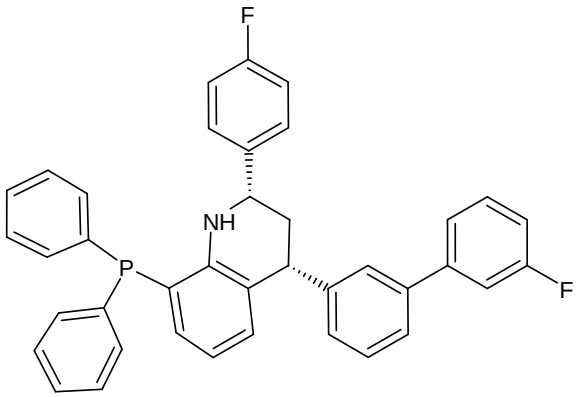

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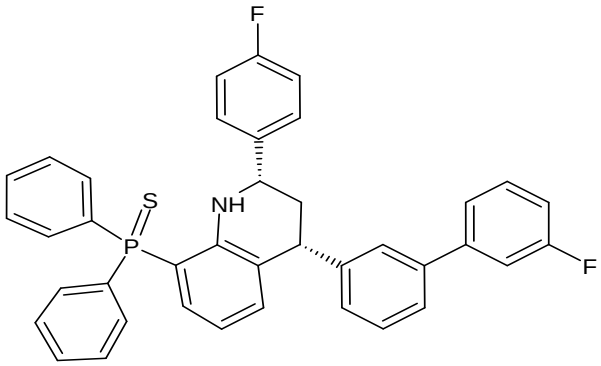


Figure 18

Othman et al. reported the preparation of a series of new isoxazolyl, triazolyl and phenyl based 3-thiophen-2-yl-quinoline derivatives using click chemistry approach. All the synthesized compounds overpowered to *in vitro* MTT cytotoxicity screening against liver (HEPG-2), colon (HCT-110), human cervical cancer (HeLa) and breast (MCF-7) human cancer cells. Out of a pack of 17 compounds, 2 compounds have been identified as potent cytotoxic agents against HeLa and MCF-7 cell lines. Compounds **figure 19** and **figure 20** showed potent antiproliferative activity against breast cancer with IC_{50} 38.14 and 28.36 µm. Furthermore, compounds bearing a halogen group at the 4-position on the phenyl ring showed improvement in antiproliferative activity. Cell death test and cell growth study were also performed. These compounds inhibited breast cancer cells in the 2nd growth phase before mitosis. On top of that, the prominent compounds were found to have a potent inhibitory effect against epidermal growth factor receptor tyrosine kinase enzyme and topoisomerase II.[11]

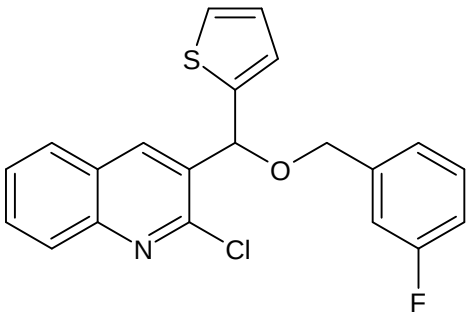


Figure 19

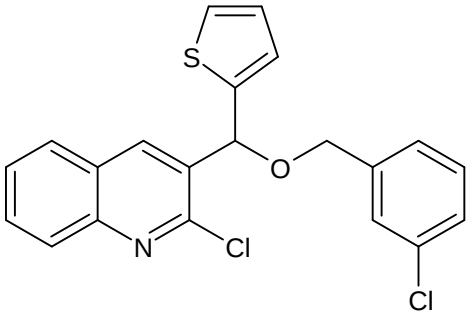


Figure 20

Riberio et al. described that a novel-4-quinoline thiosemicarbazone variant from hydrazine and substituted isothiocyanate at 250C. the derivatives of thiosemicarbazone hydrazine carbothioamide was highlighted because it had a higher Kb and Ksv value for DNA and BSA binding, stipulating a possible method of DNA intercalation which was confirmed by absorption methods, CD, molecular docking. Compound **figure 21** had a lower IC_{50} value of 0.82 µm for MCF-7 lines so it inhibits topoisomerase II partially, giving it a role of an interfacial anticancer inhibitor.[12]

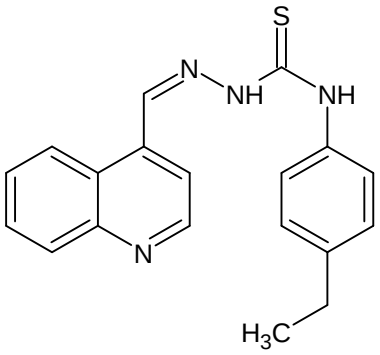
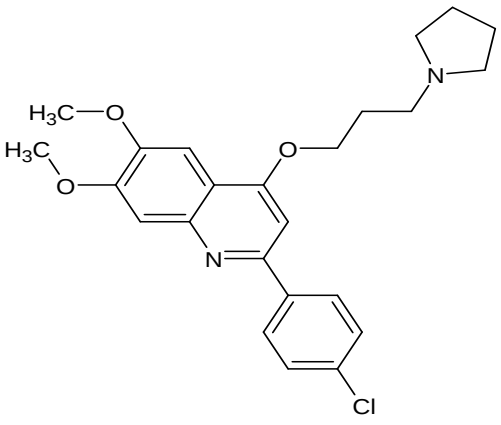


Figure 21

Elbadawai et al. designed and synthesized 2 novel series of 4-alkoxy-2-aryl quinoline derivatives based on SAR of the reported topoisomerase I inhibitors and structural characteristics required for topoisomerase I deoxyribonucleic acid cleavage complex stabilization. To investigate the antitumor properties of these 2 series of compounds *in vitro* at single treatment stage, the NCI 60 cancer cell lines panel was used. Compounds **figure 22** and **figure 23** showed potent anticancer activity at sub micromolar level vs various cancer cell lines because para substituted phenyl at C2 and propyl linker at C4 and they were selected for assay at 5 doses level. Cancer cell death occur when compounds **figure 22** and **figure 23** were assayed using topoisomerase I mediated DNA cleavage assay to evaluate their ability to stabilize topoisomerase I-DNA cleavage complexes. When compared to camptothecin compounds **figure 24** and **figure 25** exhibited moderate topoisomerase I inhibitory activity with IC50 value of 1 µm. Thus, these compounds **figure 24** and **figure 25** were considered to be promising lead compounds for the investigation of more active anticancer drugs with topoisomerase I inhibitory action.[13]



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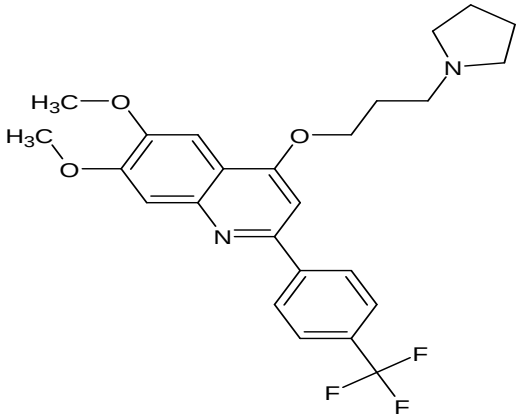

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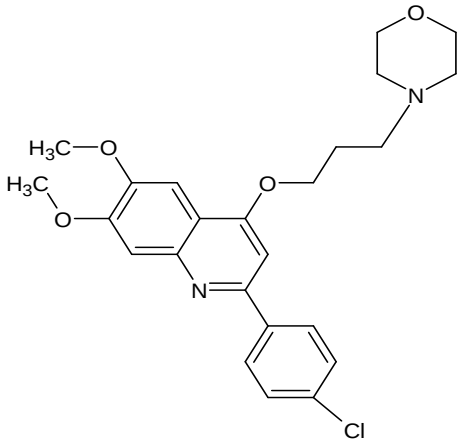

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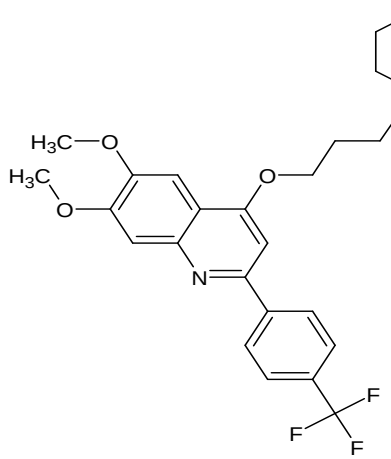

Figure 25

2. An Antimitotic Agents and Tubulin Polymerization Inhibitors

For the development of anticancer chemotherapeutic agents, microtubules are an important subcellular target and it is important for all eukaryotic organisms. The structure is organized in the form of a slender filamentous tube which is made up of α and βtubulin heterodimers. Cell cycle arrest is in the G2-M phase and the development of deviant mitotic spindles can both occur from microtubule disruption. This characteristic makes microtubules a subcellular target for the development of anticancer agents because it plays an important role in mitosis and cell division. Vinca alkaloids (Vincristine), taxoids (paclitaxel), colchicine **figure 26** are the well-known anticancer agents that inhibits microtubular assembly.

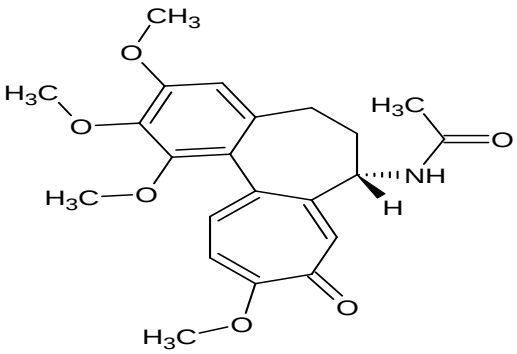

Figure 26

Xia et al. appraised that fluorinated 2-phenyl-4-quinolone derivative in NCI 60 human tumor cell lines. From the results, it was conjectured that the ketone moiety plays an important role in anticancer activity. 2'-fluoro-6-pyrrol-2-phenyl-4-quinolone **figure 27** flaunted the most potent cytotoxic activities (log GI_{50} < -8.00) against renal and melanoma tumor cell lines. When compared to the activities to those of potent antimitotic natural products like Colchicine **figure 26**, Podophyllotoxin and Combretastatin A-4 **figure 28**, the compound **figure 27** was also a potent inhibitor of tubulin polymerization (IC_{50}=0.46 µM) and of radiolabelled colchicine binding to tubulin.[14]

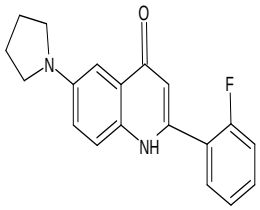

Figure 27

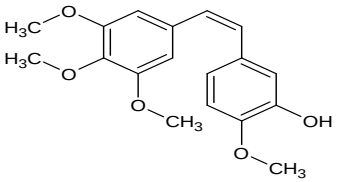

Figure 28

Chen et al. prepared and evaluated 6,7-methylenedioxy (or 5-hydroxy-6-methoxy)-2-(substituted selenophenyl) quinoline-4-ones and their isosteric compounds for anticancer activity. 6,7-methylenedioxy-2-(5-methylselenophen-2-yl) quinoline -4-ones **figure 29** found to be most promising anticancer agent. Compound **figure 29** showed highly selective and potent inhibitory activity against MDA-MB-435 melanoma on screening against NCI's 60 human tumor cell line panel. Results of COMPARE analysis intimated that compound **figure 29** is an antimitotic agent with a different mechanism of action from the prevailing antimitotic agents namely Colchicine **figure 26**, Vincristine, Paclitaxel. [15]

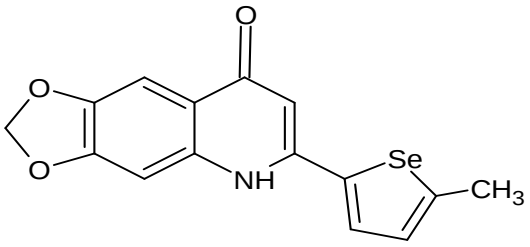

Figure 29

Lai et al. synthesized and evaluated a novel series of the biheterocycles based compounds with core structure distinguished from combretastatin A-4 **figure 28** and colchicine **figure 26** as potent antimitotic agents. Compound 1-(6'quinolinyl)-4,5,6 trimethoxy indoles **figure 30** exhibited significant anti-proliferative activity against several human cancer cell lines, nevertheless to the tissue origin and the expression of MDR_1 with a mean IC_{50} value of 24 nM respectively. [16]

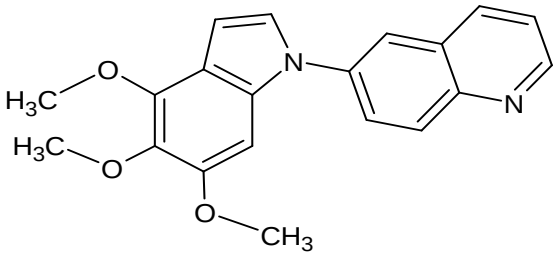

Figure 30

Shobeir at al. designed and synthesized a new series of 2-aryl-trimethoxy quinoline derivatives as tubulin inhibitors using methoxyl flavones as the lead compounds. Four human being tumor cells lines namely breast, resistant breast ovarian and ovarian carcinoma cells have been subjected to the testing of their cytotoxicity activity. Compound **figure 31** exhibited vigorous antiproliferative activity toward breast and ovarian cancer with IC_{50} value of 16.28 and 11.44 µm. The presence of methoxy group gave them high cytotoxicity effect and it had equal cytotoxic potency against both the original and receptor cell lines. Compound **figure 31** causes cell growth arrest in the 2nd growth phase process and apoptosis thus discover it is a high active tubulin inhibitor. The studies relating interaction of compound **figure 31** and colchicine binding site of tubulin is by molecular docking.[17]

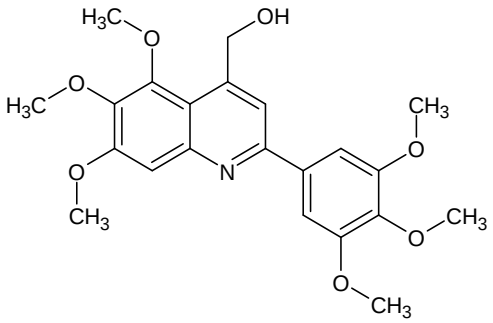

Figure 31

Khelifi et al. synthesized and evaluate a new series of isocombreta quinolines with a 2-subsituted quinoline derivatives. By means of docking experiments compound **figure 32** binds to the colchicine binding sets of tubulins. Compound **figure 32** displayed a potent cytotoxicity activity of IC_{50} value 10 nm against a panel of 5 human cancer cell lines namely malignant gliomas, chronic myeloid leukemia, bone marrow lung and colon. The presence of hydroxyl and methoxy ring system led to cell cycle arrest in G2/M phases makes this compound anticancer agent.[18]

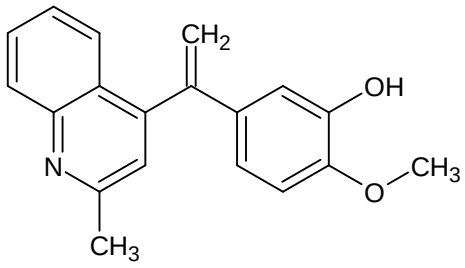

Figure 32

Schmitt et al. synthesized and explored a series of new 4-aryl-pyrano quinoline derivatives with a focus on m-nitro and m-halophenyl derivatives were tested against the six human cancer cell lines for antiproliferative activity. The compounds were tremendously cogent with nanomolar IC_{50} values. By not affecting non-malignant fibroblast, compounds **figures 33,34,35** was promising inhibitor for cancer cell development. Due to an increase of reactive oxygen species in cancer cells, these compounds have a vascular disrupting property by inhibiting tubulin polymerization and that was assessed *in vivo* studies by chorioallantoic membrane assays.[19]

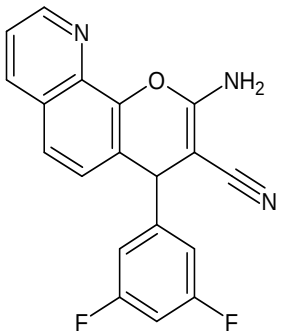

Figure 33

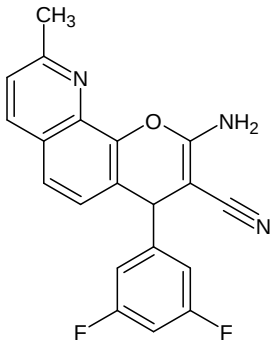

Figure 34

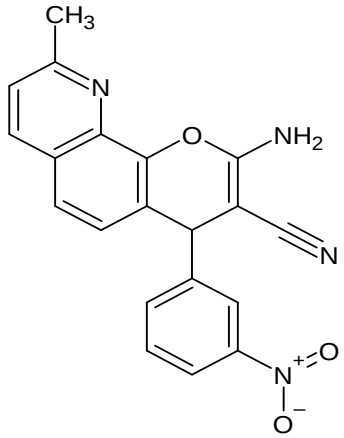

Figure 35

In 2020, a new series of arylamides incorporating the privileged 2- anilio quinoline scaffold has been designed, synthesized and biologically evaluated by **Damsay et al.** A panel of 60 clinically important cancer cell lines representing 9 cancer types has been used to extensively evaluate the target compounds potency and spectrum. Compounds **figures 36 and 37** with piperazine substituted phenyl ring have a potent anticancer activity even more than FDA approved drug imatinib. By analysing data from

SAR report, it can be assumed that the amide binding to the met position of the n-phenyl quinoline-2-amine framework activity. Compounds **figures 36 and 37** had extremely efficacious antitumor properties toward colon cancer with IC_{50} value 0.88 and 0.229 µm. *In vitro* mechanistic analysis, both compounds found to initiate morphological alteration, apoptosis and cell cycle arrest in HCT-116 colon cancer cells. Compound **figure 36** changed microtubule polymerization sequence in an identical way of paclitaxel. Kinase screening of compound **figure 36** revealed its inhibitory activity against proto-oncogene B-Raf 600 E and C-Rapidly accelerated fibrosarcoma kinases.[20]

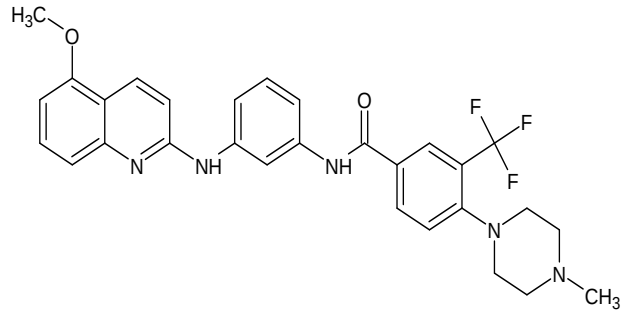

Figure 36

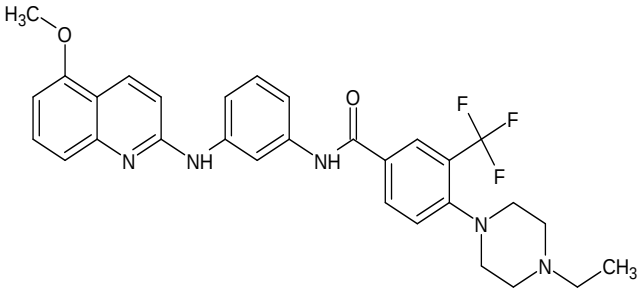

Figure 37

Fang et al. synthesized and designed a series of novel 2-oxoquinoline derivatives containing arylaminothiazole as potential antiproliferative agents. With the help of MTT assay, the synthesized compounds were tested for *in vitro* cytotoxicity toward the cervical, hypotriploid, urinary bladder, ovarian tumor cell cultures. Compound **figure 38** showed most potent activity against tumor cell lines with the half inhibitory concentration ranged from 4.4 to 8.7 µm. Compound **figure 38** could inhibit the tubulin polymerization in vitro according to consequences of the tubulin polymerization assay. In the meantime, docking study illustrated that compound **figure 38** may bind to the colchicine site of tubulin and formed H- bonds with key amino acids in the active site. The study on further mechanism exemplified that compound **figure 38** block cell cycle arrest at G2/M phase, inducing cell apoptosis and depolarized mitochondria of HeLa cells. For the development of highly efficient microtubule polymerization inhibitors for cancer therapy, compound **figure 38** serve as prominent lead. [21]

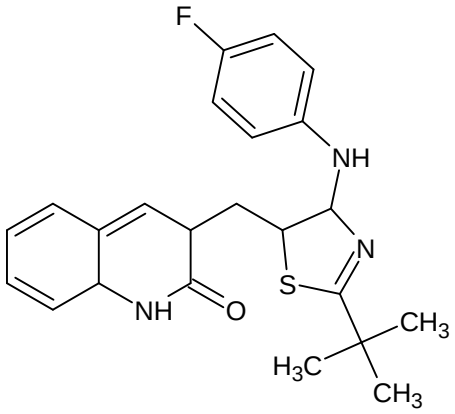

Figure 38

3. Proteasome Inhibitors

For the degradation of cellular proteins, the ubiquitin-proteasome pathway plays a significant role. Ubiquitination and degradation are the 2 essential steps in the proteolytic pathway. In regulating cell proliferation and cell death ubiquitin proteasome pathway is vital.[22] Due to loss of balance between cell growth inducers and inhibitors that leads to deregulation of cell growth, proliferation, and survival, thus result in the premature cell death, uncontrolled cell proliferation and, eventually, tumor development and progress. For controlling tumor, the inhibition of proteasome pathway is potentially efficacious. Proteasome inhibitors have following distinctive features;

a) They show greater apoptosis-inducing potency than current anticancer drug with respective of the results from testing various human tumor cell lines.

b) They can induce cell death rapidly and selectively in oncogene-transformed cells, but not in normal or untransformed cells.

c) They have the ability to overcome tumor cell resistance to cytotoxic therapies.[23]

The report of Daniel et al. studies pointed out that several organic copper compounds except Zn and Ni such as bis-8-hydroxy quinoline copper (II) can inhibit chymotrypsin like activity of purified 20S proteasome in human tumor cells. By the treatment of organic copper compounds, the inhibition of proteasome activity occurs within 15 min, followed by the induction of apoptosis in human leukemia cells. Following the same method of treatment cause neither proteasome inhibition nor apoptosis in non-transformed, immortalized human natural killer cells.[24] In addition, Daniel et al. stated that several quinoline compounds like 8-hydroxy quinoline **figure 39**, clioquinol **figure 40**, 5,7-dichloro-8-hydroxy quinoline **figure 41** serve as potential tumor compounds by binding to endogenous copper in breast and prostate cancer cells. The authors proposed that elevated levels of copper can be tumor-specific, the use of copper chelators might be an effective strategy for cancer therapies. [25]

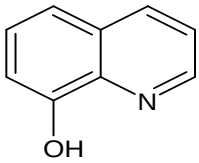

Figure 39

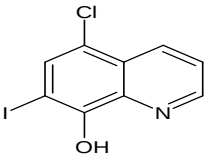

Figure 40

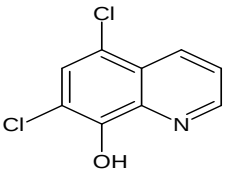

Figure 41

4. Protein kinase inhibitors

Protein kinases are the group of enzymes that regulates the biological activity of protein by phosphorylation of amino acids like serine, threonine and tyrosine with ATP as the source of protein, inducing a conformational change from inactive to an active form of protein. Mitogen activated protein kinases are a group of protein kinases which are the intermediates in signal transduction pathway that are initiated by surface receptors and they provide a physical link in the signal transduction pathway from the cytoplasm to the nucleus. There are at least 11 members of MAPK superfamily in humans, which can be divided into 6 groups: extracellular signal-regulated protein kinases (ERK1 and ERK2); c-Jun-N- terminal kinases (JNK1, JNK2, JNK3); p38s (p38-α, p38-β, p38γ, p38-δ); ERK5 (ERK5); ERK3s (ERK3, p97-MAPK, ERK4); and ERK7s (ERK7, ERK8). Among the family of MAPKs, promising targets for drug development p38-α MAPK and JNK3.[26]

Peifer et al. delineate the design, synthesis and evaluation of 3-(4-fluorophenyl)-4-pyrindin-4-ylquinoline-2(1H)-one **figure 42** as a new inhibitor of MAPK with a p38-α MAPK IC_{50} of 1.8 µM.[27]

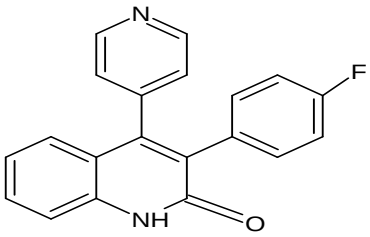

Figure 42

Gunby et al. divulged that 4-phenylamino quinoline compounds especially SKI-606 may have the ability to act as templates for kinase inhibitors. Bosutinib **figure 8** (SKI-606) is an oral Src/Abl tyrosin kinase inhibitor. On September 4 2012, Bosutinib completed phase III clinical trials and received US FDA approval for the treatment of patients who are adults with chronic, accelerated or blast phase Philadelphia chromosome +ve (Ph +) chronic myelogenous leukemia with resistance to prior therapy. It is metabolized by CYP3A4 hepatic enzyme which is safe and well tolerated upto 200-600 mg.[28]

Boschelli et al. study identified that in a yeast-based assay, 4-[(2,4-dichorophenyl) amino]-6,7-dimethoxy-3-quinoline carbonitrile **figure 43** acts as a Src inhibitor. Compound **figure 43** was an ATP-competitive inhibitor of kinase activity of Src, which was established by an enzymatic assay. SAR of compound **figure 43** shows that aniline group at C-4, the carbonitrile group at C-3, and the alkoxy group at C-6 and C-7 of the quinoline are vital for optimal activity. In order the increase Src inhibition the size of C-2 substituent of the aniline at C-4 of compound **figure 43** from chloro to bromo to iodo should be increased. Moreover, to increase both Src enzymatic and cellular activity inhibition 7-methoxy group of compound **figure 43** with various 3-heteroalkyl aminopropoxy groups should be replaced [29].

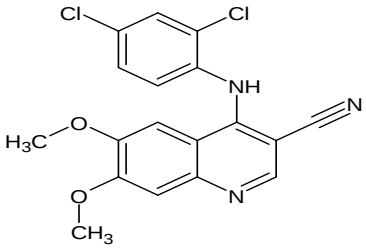

Figure 43

CONCLUSION

The quinoline scaffold is generally used in medicinal chemistry for drug design. It is especially usual in areas such as antibacterial, antifungal, antiviral and anticancer drugs. As presented in this review, quinolines are more important in the area of the anticancer agents. Focusing at the small differences between normal and malignant cells is the foundation of higher refinement and ensuing more robust and safer therapeutic strategies. Enlarging interest in quinoline based anticancer agents will indubitably open new targets and interactions for effectively design novel potent structures.

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