Egypt. J. Chem. **Vol. 66**, No. 7 pp. 527- 551 (2023)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Recent Developments of Quinoline-Heterocyclic Conjugates as Anticancer Agents

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Abstract

Cancer is considered as one of the serious public health problems, and globally it was reported to be the second largest cause of death. The development of novel therapeutic anticancer agents is still in serious need. In this regard quinoline conjugated heterocyclic derivatives remain one of the most attractive class of compounds for anticancer development. Numerous recent reports evidenced that quinoline-heterocyclic hybrids displayed antiproliferative effect against different kinds of cancer cells via different mechanisms including the inhibition of a wide range of protein kinases such as PDK1, CDK2, topoisomerase, APE-1F, GFR3, HDM2, PI3K and others. The present review highlighted the anticancer potential of quinoline conjugated with different heterocycles such as azetidinone, benzimidazole, benzofuran, benzothiazole, coumarin, imidazole, indole, morpholine, oxadiazole, piperazine, pyrazole, pyrimidine, tetrazole, thiazole, triazole and others fused to or substituted directly to the quinoline nucleus or via intermediate chain or linker the in the twenty first century which could serve as a platform for pharmaceutical chemists to design and develop better anticancer candidates.

Keywords: Quinoline Scaffold; Heterocycle; Anticancer.

1. Introduction

Cancer, a large group of diseases, involving abnormal and uncontrolled cell growth, division and differentiation mechanisms that might has the potential to invade and/or spread to other tissues in the human body [1]. For many years, cancer worldwide is count as one of the serious public health problems, and globally it was reported to be, after cardiovascular diseases, the second largest cause of death [2, 3]. Most of the available drugs for cancer management are targeting the cell replication machinery [4, 5] and/or DNA synthesis [6-8] and thus have limited therapeutic usage due to serious side effects and lack of specificity [9]. Therefore, the development of novel therapeutic anticancer agents with increased selectivity and minimized side effects is still ongoing active search [10, 11].

Quinoline (molecular formula of C9H7N and molecular weight is 129.16) is one of the most pervasive nitrogen containing heterocyclic moieties in pharmaceutical chemistry. It is a fundamental scaffold in numerous natural and synthetic compounds that possess different pharmacological activities such as antimalarial [12, 13], antileishmanial [14], antimicrobial [15], antitubercular [16], antifungal [17], anti-inflammatory [18, 19] and anti-HIV [20] properties (Figure 1). Furthermore, one the most distinguished biological effect for the quinoline derivatives and quinoline-heterocyclic conjugates in drug development relate to their anticancer activity, [21] accounting for a numerous bioactive quinoline based drugs known to date (Figure 2). In this review, we have gathered and specifically discussed the anticancer potential of quinoline-heterocyclic conjugates in the twenty first century which could serve as a platform for pharmaceutical chemists to design and develop better anticancer candidates.

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EJCHEM use only: Received date 09 October 2022; revised date 17 October 2022; accepted date 31 October 2022
DOI: 0.21608/EJCHEM.2022.167867.7074

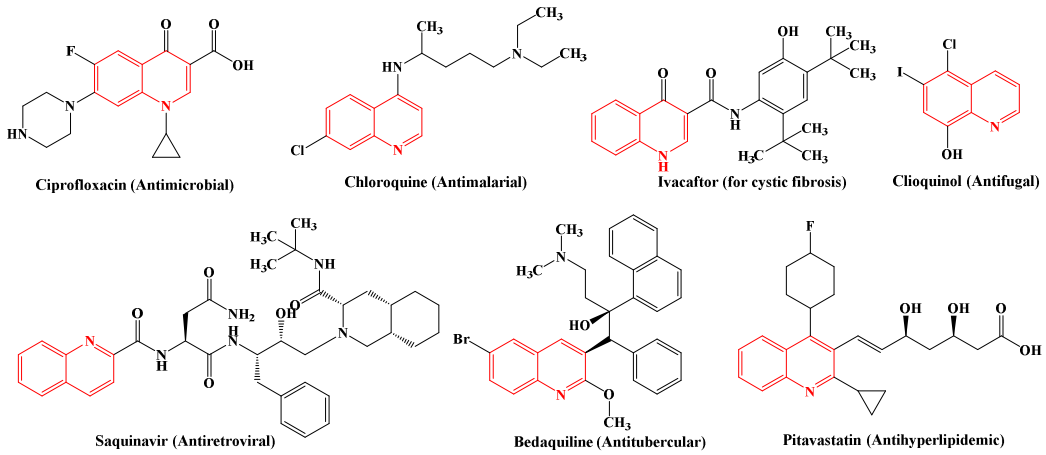

Figure 1: Examples of medically used drugs containing quinoline scaffold

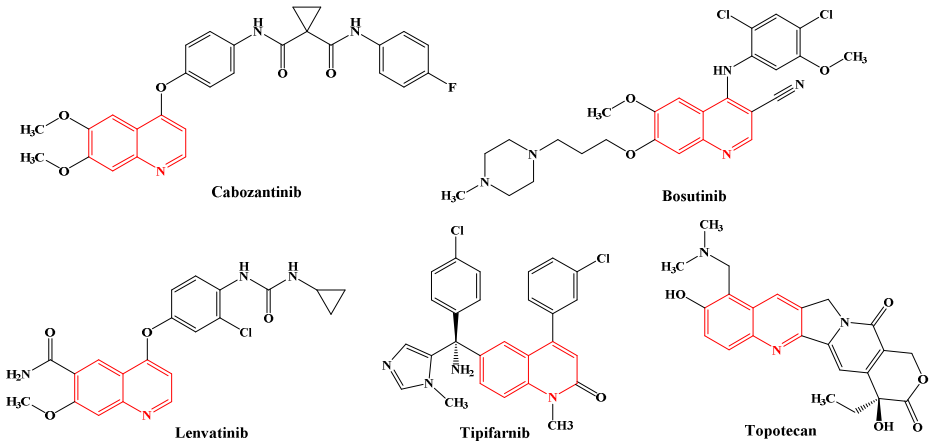

Figure 2: Examples medically used quinoline containing anticancer drugs

2. Quinoline synthesis

Classically, there are several synthetic routes were widely used for the synthesis of quinoline nucleus starting from aniline,as a common reactant, including Gould-Jacobs reaction [22], Skraup reaction [23], Doebner reaction [24, 25], Doebner-Miller reaction [26], Combes quinoline synthesis [27, 28], [29]Riehm synthesis, Conrad- Limpach synthesis [30, 31] and Povarov reaction [32, 33] (Figure 3).

In addition, there are numerous modified synthetic routes which required special substituted anilines or other substituted reactants to afford quinoline nucleus. These include Meth-Cohn reaction [34], Friedlander reaction [35], Knorr reaction [36, 37], Camps reaction [38, 39], Niementowski reaction [40, 41] and Pfitzinger reaction that utilized isatin as starting material [42, 43], (Figure 4).

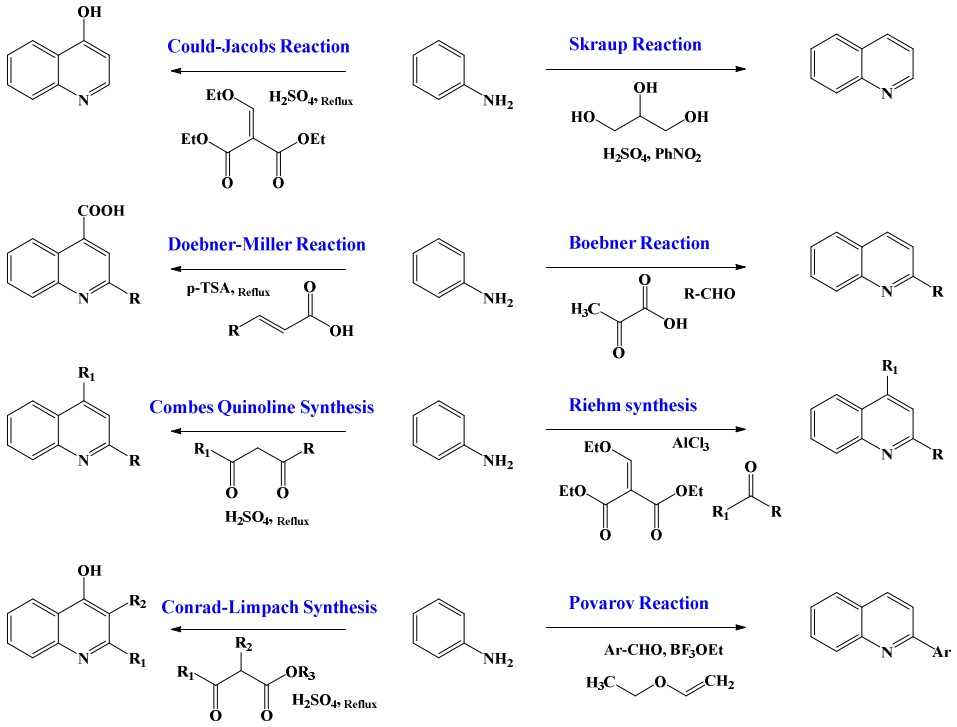

Figure 3: Aniline based classical methods of quinoline scaffold synthesis

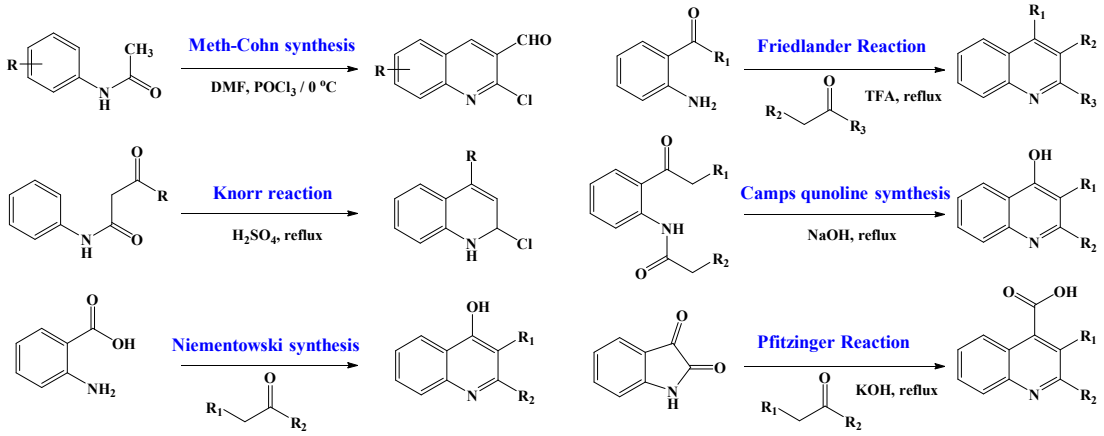

Figure 4: Modified classical methods of quinoline scaffold synthesis

Recently, there are several non-classical methods for the synthesis of quinoline derivatives using different techniques such as electrocyclization [44], microwave irradiation [45] and solvent free reaction conditions [46-48].

3. Quinoline-Heterocyclic Conjugates as Potential Anticancer Agents

Due to its presence in well-affirmed anticancer drugs as Cabozantinib, Bosutinib, Lenvatinib, Tipifarnib and Topotecan (Figure 2), the quinoline nucleus has been exceedingly scrutinized and recognized as a potential chemical foundation in anticancer research. In scientific research papers, the number of quinoline-heterocyclic conjugates with potential anticancer activity has increased throughout the last two decades.

3.1. Quinoline-Azetidinone Conjugates

Govindarao et al., [49] reported the synthesis of two series of quinoline conjugated 2-azetidinones 1 and 2 with potential anticancer activity against breast cancers cell lines (MCF7 and MDA-MB-231) and possessed inhibitory activity against epidermal

growth factor receptor (EGFR) tyrosine kinase with mean inhibition of 89.5-97.1%. Also, Kayarmar et al., [50] reported the development of 2-azetidinones condensed with imidazo-quinoline 3 as good anticancer agents with potential inhibition of β-tubulin. In addition, Alegaon and team, [51] reported the design, synthesis and anticancer evaluation of quinoline-azetidinone hybrids including compound 4 that exhibited potent antiproliferative activity against two hepatic cancer cell lines with IC50 value 0.4-1.7 µM (Figure 5).

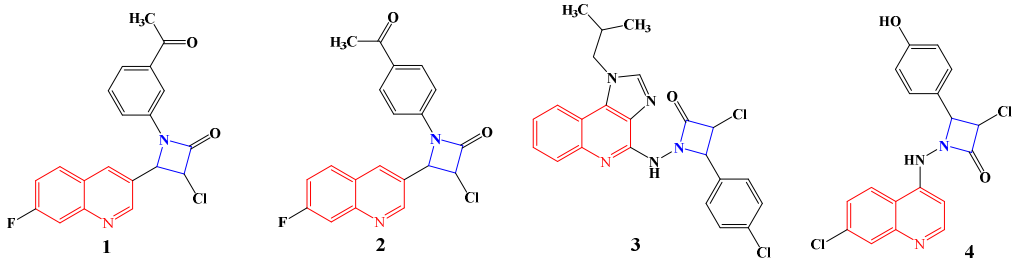

Figure 5: Examples of quinoline-azetidinone conjugates of potential Anticancer activity

3.2. Quinoline-Benzimidazole Conjugates

Li et al., [52] develop a novel series of quinoline derivatives for the treatment of liver cancer among which benzimidazole conjugate 5 which showed moderate activity. Recently, Hu and co-worker, [53, 54] synthesized and characterized two benzimidazole-quinoline-based copper complexes 6 and 7 that showed selective antiproliferative activity against the colon cancer cell line (HCT116) with low cytotoxicity against the normal cell line (L-02). Also, Kuang et al., [55] reported the design and synthesis novel (1H-benzo[d]imidazole-2-yl)quinoline conjugates as potential anticancer agents among which compound 8 which was found to be the most promising cytotoxic derivative with IC50 value of 7.54-15.40 µM against four different cancer cell lines (Figure 6).

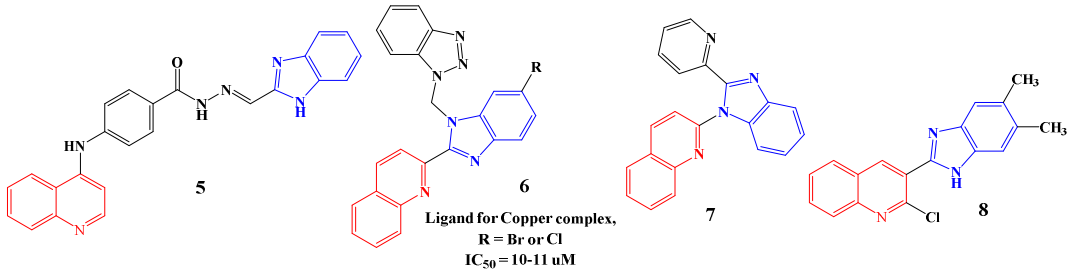

Figure 6: Examples of quinoline-benzimidazole conjugates of potential anticancer activity

1.1. Quinoline-Benzodioxole Conjugates

Vennila et al., [56] designed and synthesized a series of potential anticancer 4-substituted quinolines that target pyruvate dehydrogenase kinase-1 (PDK1) among which quinoline-benzodioxole conjugate **9** that showed excellent anticancer activity. Also, Abonia et al., [57] reported the synthesis of novel quinoline-2-one based chalcones of potential Anticancer activity among which quinoline-benzodioxole conjugate **10** which displayed remarkable anti proliferative activity against fifty human tumor cell lines, among them thirteen exhibited GI_{50} values less than 1.0 µM (Figure 7).

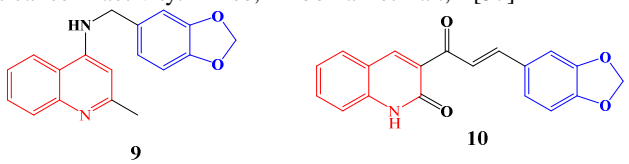

Figure 7: Examples of quinoline-benzodioxole conjugates of potential Anticancer activity

3.4. Quinoline-Benzofuran Conjugates

Quinoline based derivatives that bearing benzofuran nucleus either fused or substituted directly to the quinoline nucleus were frequently report. For instance, Anantacharya et al., [58] develop a novel series of substituted 2-(1-benzofuran-2-yl) quinoline-4-carboxylic acid and its esters among which compound 11 which showed moderate antiproliferative activity against five different human cancer cell lines. Also, Chang and coworkers, [59] designed and synthesized quinoline-benzofuran conjugates and analogs as antitumor agents that inhibit tubulin assembly including compound 12 that exhibited significant Anticancer activity. On the other hand, Huang et al., [60] reported the activity of fused quinoline-benzofuran derivatives 13 and discovered a series of novel benzofuro[3,2-b]quinoline derivatives as dual cyclin dependent kinase-2 (CDK2)/ topoisomerase I inhibitors (Figure 8).

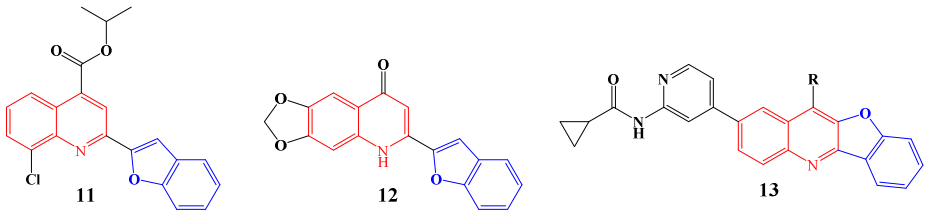

Figure 8: Examples of quinoline-benzofuran conjugates of potential anticancer activity

3.5. Quinoline-Benzothiazole Conjugates

There are few reports regarding the quinoline-benzothiazole conjugates. Bindu et al., [61] reported the synthesis and evaluation of N-(benzo[d]thiazol-2-yl)-2-hydroxyquinoline-4-carboxamides 14 and 15 as potential anti-prostate cancer agents which showed moderate activity. Also, Chen and coworkers, [62] Designed and synthesized and a novel series of 8-hydroxyquinoline derivatives as matrix metalloproteinase (MMP) inhibitors substituted at different positions of the quinoline nucleus. The preliminary evaluations revealed that almost all 5-substituted quinolin-8-ols including the benzothiazole derivatives 16 were proved inactive as inhibitors of MMP-2 and MMP-9 (Figure 9).

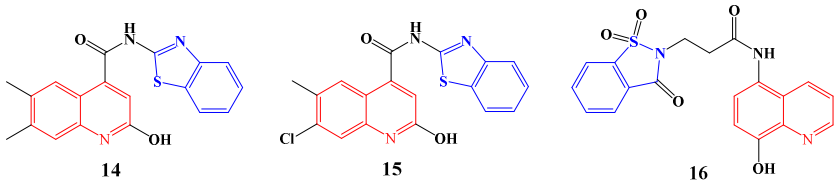

Figure 9: Examples of quinoline-benzothiazole conjugates of potential anticancer activity

3.6. Quinoline-Benzotriazole Conjugates

The synthesis and anticancer evaluation of novel quinoline bearing a benzotriazole moiety 17 and 18 was reported by Korcz et al., [63]. These novel compounds revealed pronounced cancer cell growth inhibitory activity with IC50 values ranged from 1.23–7.39 µM. Wang et al., [64] reported further optimization of previously examined 8-hydroxyquinoline lead compound as potential inhibitor of survivin, (a member of the inhibitor apoptosis proteins (IAP) family. The new series including compound 19 which accommodating benzotriazole moiety demonstrated reduced activities compared to the initial inhibitor (Figure 10).

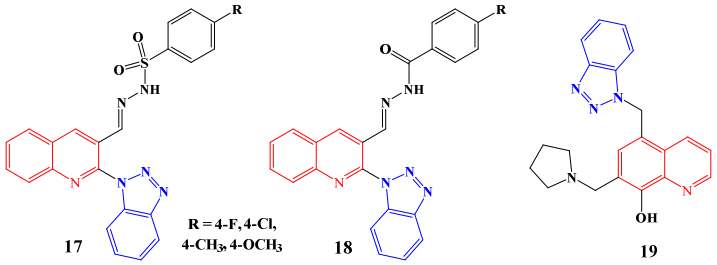

Figure 10: Examples of quinoline-benzotriazole conjugates of potential anticancer activity

3.7. Quinoline-Coumarin Conjugates

Regarding quinoline-coumarin conjugates, Vennila et al., [56] designed and synthesized a series of potential anticancer 4-substituted quinolines that target PDK1 among which quinoline-coumarin conjugate 20. Also, conjugation between quinoline and coumarin via a dicarboxamide linker 21 was reported by Prashanth et al., [65] to produce a series of compounds that possessed moderate apoptogenic effect against murine ascitic carcinoma. On the hand, Mulakayala et al., [66] reported the catalyst free ultrasound mediated synthesis and the potential Anticancer of fused quinoline-coumarin conjugates including compound 22 that was evaluated for its potential anticancer activity against four different human cancer cell lines. In addition, Nasr and coworkers, [67] conjugated the coumarin with quinoline scaffold via a hydrazide-hydrazone linker into conjugate structures among which compound 23 that was the most active compounds against three different cell lines and was significantly inhibited and/or stimulated different genes in the treated cell lines, control cell cycle, apoptosis, and tumor growth and suppression (Figure 11).

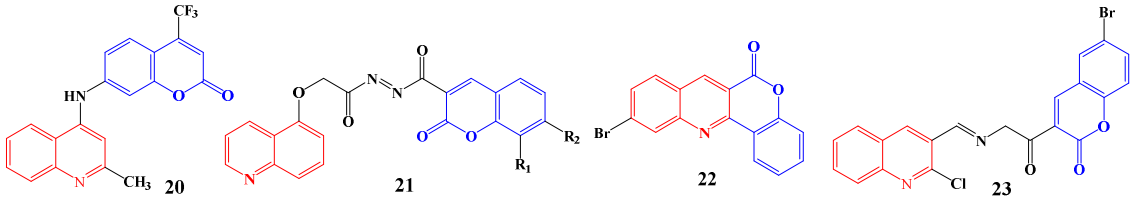

Figure 11: Examples of quinoline-coumarin conjugates of potential anticancer activity

3.8. Quinoline-Dioxane Conjugates

Malayeri et al., [68] designed and synthesized fused[1,4]dioxino[2,3-g]quinoline derivatives 23a and 23b that showed significant cytotoxic activity on MCF-7 cells and significant human epidermal growth factor receptor-2 (Her2) protein degradation and heat shock protein-70 (Hsp70) protein induction (Figure 12).

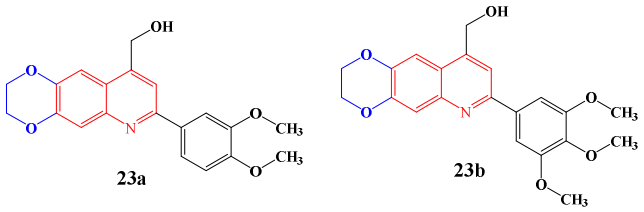

Figure 12: Examples of quinoline-dioxole conjugates of potential anticancer activity

1.2. Quinoline-Dioxole Conjugates

Chang et al., [59] designed and synthesized quinoline derivatives among which (1-Naphthalenyl)-6,7-methylenedioxyquinolin-4-one **24** that exhibited broad cytotoxic effect against seven different cancer cell lines, with IC_{50} values ranged from 0.07–0.19 µM. Also, it was reported by Jin et al., [69] the antitumor as well as antibacterial activity of novel fused quaternary quinoline iodide-dioxole derivatives **25**. In addition, Gold et al. [70] filed a patent for the synthesis of novel quinoline derivatives as AP endonuclease-1 (APE-1) enzyme inhibitors that can be used as potential anticancer agents, compounds **26** with dioxolo- ring was found to be potent APE-1 inhibitor. Furthermore, Schaus et al. [71] filed a patent for [1,3]Dioxolo[4,5-G]quinoline derivatives **27** as Late SV40 factor (LSF) inhibitor that showed significant activity against hepatocellular carcinoma (Figure 13).

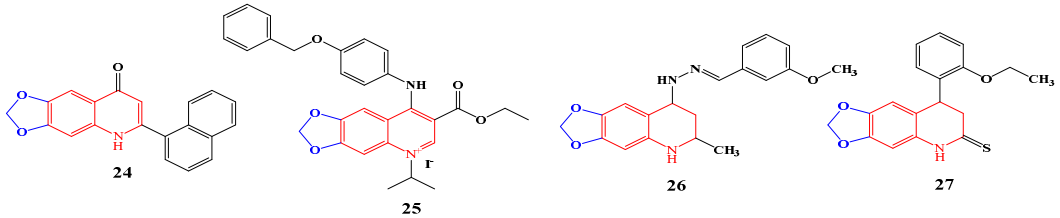

Figure 13: Examples of quinoline-dioxole conjugates of potential anticancer activity

3.10. Quinoline-Furan Conjugates

Aly et al., [72] designed and synthesized a novel series of quinoline-3-carboxamide bearing furan nucleus 28 as EGFR inhibitors with potent anticancer activity. In addition, Bernzweig and his team [73] reported the antiproliferative activity of quinoline-furan conjugate 29 that targeting gap function and exert promising anticancer activity in human breast cancer. On the other hand, fused furo-quinoline derivatives were reported to exert anticancer activity. Chung et al., [74] reported that using optimized conditions, a hexahydrofuro[3,2-c] quinoline derivative 30 (a martinelline type analogue), was synthesized and biologically evaluated that showed potential anticancer activity against breast cancer cells (MDAMB-231). In addition, Tzeng and team, [75] patented the synthesis of a novel series of 4-Anilinofuro[2,3-b]quinoline derivatives as potential anticancer compounds and the results revealed that compounds 31 displayed substantial cell growth inhibitory effect (Figure 14).

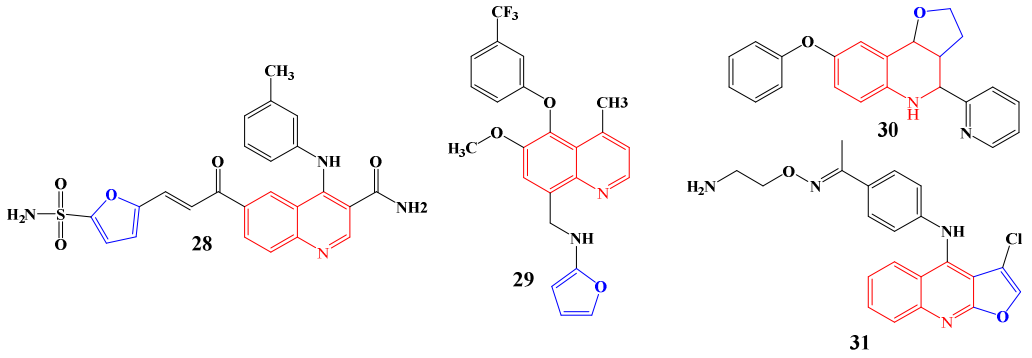

Figure 14: Examples of quinoline-furan conjugates of potential anticancer activity

3.11. Quinoline-Imidazole Conjugates

Quinoline based derivatives that bearing imidazole nucleus either fused or substituted directly to the quinoline nucleus or through intermediate chain or linker were report. Li et al., [52] develop a novel series of quinoline derivatives for the treatment of liver cancer among which benzimidazole conjugate 32 which showed moderate activity. Also, Kardile et al., [76] designed and synthesized a novel series conformationally constrained quinoline derivatives bearing imidazole 33 as potential anticancer agents with potent topoisomerase I inhibitory activity. Singh et al., [77] reported the design and regioselective synthesis of 2-aminoimidazole-quinoline hybrids 34 that revealed a selective antiproliferative activity against human colon cancer cell line. Furthermore, Ibrahim et al., [78] reported the development of novel quinoline-imidazole derivatives 35 as tubulin polymerization inhibitors with potent anticancer effect and apoptosis inducing activity. In addition, Furet and team [79] filed a patent of a novel series quinoline derivatives as Fibroblast growth factor receptor-3 (FGFR-3) inhibitor including compound 36 bearing imidazole ring that was found to be the most potent with IC50 = 9 nM. On the other hand, fused imidazo-quinoline derivatives were reported to possess potential anticancer candidates. For instance, Kumar and coworkers [80], had a patent for the novel Imidazo[4,5-c]quinoline derivatives as anticancer agents among them compound 37 was endowed with excellent cell growth inhibitory effects with IC50 less than 1 µM and exerted an inhibition more than 50% against phosphoinositide 3-kinase-α (PI3K-α) and The mammalian target of rapamycin (mTOR) kinase enzymes. Also, Fuchss and his associates [81], filed a patent on Imidazo[4,5-c]quinoline derivatives as DNA-protein kinase (DNA-PK) inhibitor among which compound 38 was found to possess potential anticancer effect and showed significant DNA-PK inhibitory activity with IC50 value less than 0.1µM (Figure 15).

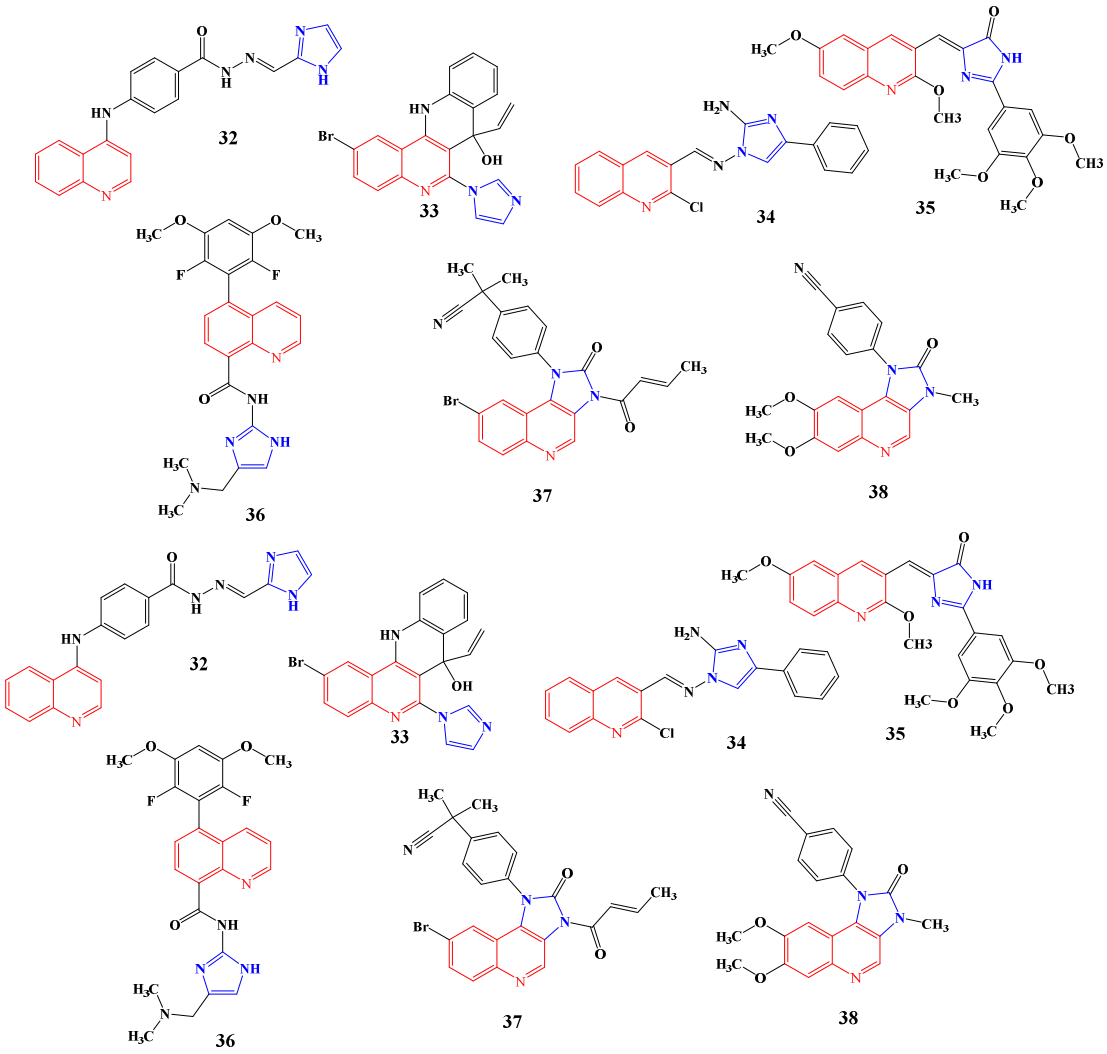

Figure 15: Examples of quinoline-imidazole conjugates of potential anticancer activity

3.12. Quinoline-Indole Conjugates

Numerous quinoline-indole conjugates, either substituted or fused, as potential anticancer agents were reported by many research groups. Karnik et al., [82] designed and synthesized novel substituted quinoline derivatives **39** that showed significant inhibitory effect against mutant EGFR kinase with IC_{50} value of 0.91 µM. Also, Li and co-workers [83] reported the design and synthesis of quinoline-indole hybrids as anti-tubulin agents **40** that targeting the colchicine binding site. In addition, it was reported that compound **41**, a quniloine-indole hybrid [84], possessed a significant inhibitory activity against vascular endothelial growth factor receptor (VEGFR) with potential anticancer activity. On the other hands, fused indolo-quinoline derivatives as potential anticancer candidates were frequently reported in the last two decades. For instance, Chen et al., [85] described the synthesis and antiproliferative assessment of novel indolo[2,3-b]quinoline derivatives among which compound **42** was the most cytotoxic one with a mean GI_{50} value of 0.78µM. Also, Sidoryk et al., [86] reported the synthesis of indolo[2,3-b]quinoline guanidine hybrids including **43** with potential anticancer activity. In addition, Boddupally and associates [87] reported the synthesis of a novel series of indolo[3,2-b]quinolin analogs as c-MYC G-quadruplex–stabilizing compounds including compound **44** that showed IC_{50s} of 0.97 µM in HCT-116 cell line and 2.33 µM in Raji cell line. On the other hand, Wang et al., [88] reported the synthesis and cytotoxic effect of indolo[3,2-c]quinoline derivatives with different substituents on the quinoline ring including

compound **45** which was the most potent with IC_{50} value of 0.052 µM against human leukemia MV4-11 cell line (Figure 16).

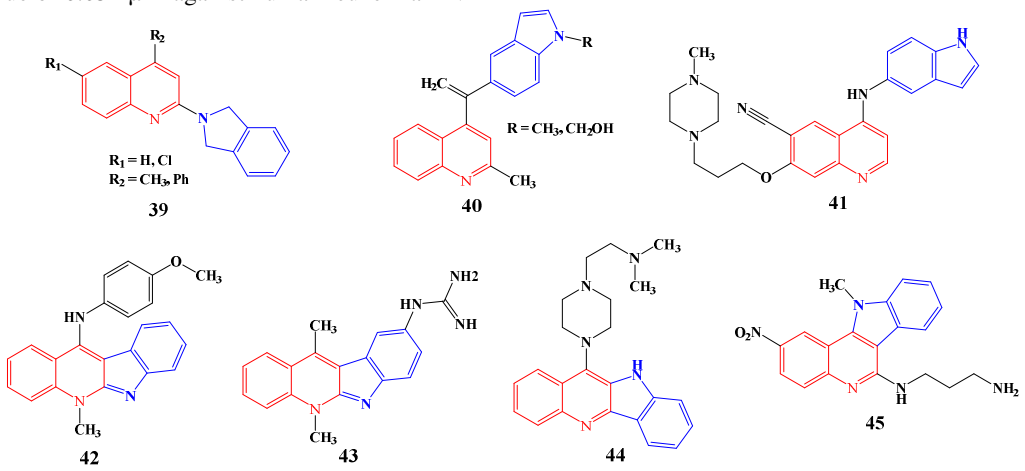

Figure 16: Examples of quinoline-indole conjugates of potential anticancer activity

3.13. Quinoline-Morpholine Conjugates

Zaraei et al., [89] designed and synthesized of a novel series quinoline derivatives among which a derivative bearing morpholine ring 46 that revealed a more potent effect than sorafenib against fifty three of tested cancer cell lines and showed a high selectivity for rapidly accelerated fibrosarcoma (C-RAF) kinase. Also, Cheng et al., [90] developed a series of 2-(hydroxyl substituted phenyl)quinolin-4-one derivatives including a morpholine hybrid 47 that possessed a potential anticancer activity. Haiba and coworkers [91] reported the synthesis novel benzo[h]quinoline derivatives including the morpholine conjugate 48 that was found to exert potential anticancer activity against two human cancer cell lines, HepG-2 and MCF-7. In addition, Wu and his team [92] filed a patent on quinoline derivatives as G protein coupled receptors (GPCRs) like receptors oncogene smoothened (SMO) inhibitors among which compound 49 bearing morpholine ring showed IC50 value less than 50 nM. Furthermore, Liu et al. [93] designed a novel series of quinoline derivatives as potent human methionine aminopeptidase enzyme (hMetAP) inhibitors including the morpholine analog 50 that displayed higher selectivity towards hMetAP2 isoform of enzyme as compared to hMetAP1 (Figure 17).

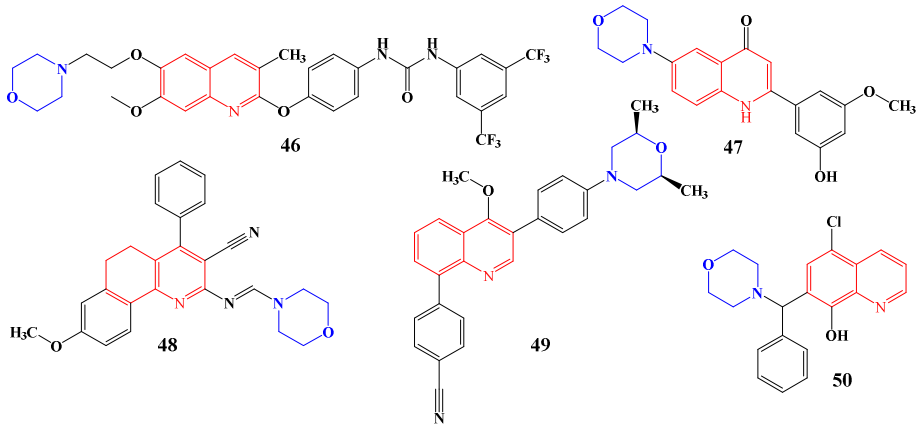

Figure 17: Examples of quinoline-morpholine conjugates of potential anticancer activity

3.14. Quinoline-Oxadiazole Conjugates

Sun et al., [94] reported the synthesis of a series of quinoline derivatives among which compound 51 that displayed the most potent anticancer activity. Also, Hamdy et al., [95] described the synthesis of some novel quinoline-based oxadiazole analogs among which compound 52 showed sub-micromolar anticancer activity in Bcl-2-expressing cancer cell

lines. In addition, Kundu et al., [96] developed a new series of quinoline derivatives including compound 53 that confirmed to be a Topoisomerase I poison and displayed significant anticancer effects against different cancer cell lines IC50 values of 2.34 - 2.74 µM (Figure 18).

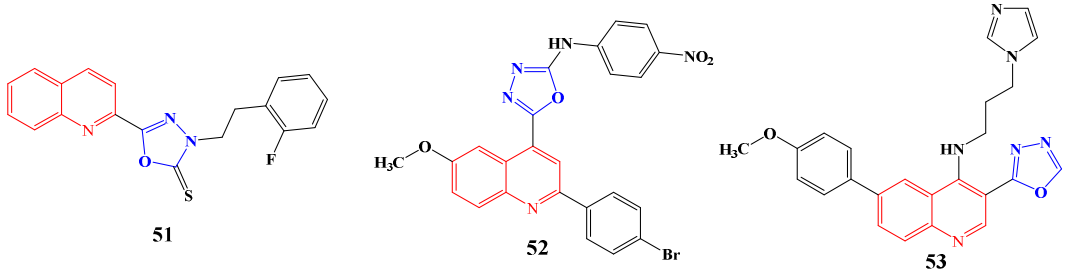

Figure 18: Examples of quinoline-oxadiazole conjugates of potential anticancer activity

3.15. Quinoline-Oxazole Conjugates

Regarding quinoline-oxazole conjugates as potential antiproliferative agents, Ibrahim et al., [78] reported the discovery of novel quinoline-based analogs as tubulin polymerization inhibitors among which compound 54 that showed potent anticancer effect with IC50 value of 10-42 nM against different cancer cell lines. Also, Kumar et al., [97] synthesized and evaluated a new series of oxazole-quinoline hybrids as anticancer drug including compound 55 that demonstrated potential cytotoxic effect and significant tubulin inhibitory activity (Figure 19).

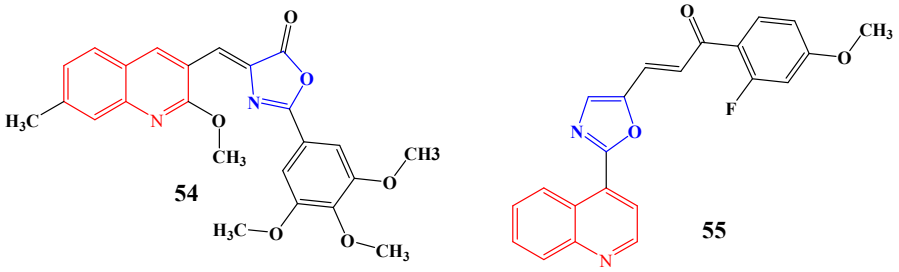

Figure 19: Examples of quinoline-oxazole conjugates of potential anticancer activity

3.16. Quinoline-Piperazine Conjugates

Using hybrid pharmacophore approach, Solomon et al., [98] reported the design and synthesis of a novel series of 4-piperazinyl quinoline as anti-breast cancer agents among which compound **56** that displayed antiproliferative activity in 7–11 fold higher on cancer than noncancer cells. Also, Li and team [99] reported the synthesis of a new series of novel quinolone derivatives including compound **57** that bearing piperazinyl group which was found to be 5-times more potent than the positive control irinotecan or cisplatin, with IC_{50} value of 8-10 nM against the tested cancer cell lines. Furthermore, Lee et al., [100] developed a novel series of quinoline sulfonyl derivatives including compound **58** that possessed a piperazine nucleus and showed potential cell growth inhibitory effects against breast cancer cell lines (MDA-MB468, MCF7 and MDA-MB231). On the other hand, quinoline derivatives bearing piperazine nucleus through intermediate chain or linker was reported. Yang and others, [101] designed and synthesized a new series of quinoline-based aldehyde dehydrogenase-1A1 (ALDH1A1) inhibitors in particular, compound **59** showed potential anticancer activity against HT-29 and OV-90 cell lines IC_{50} value of 0.012 and 0.033 µM, respectively. Also, Li and coworkers, [102] synthesized quinolines derivatives as Pim-1 kinase inhibitors with potential anti-prostate cancer activity and compound **60** bearing piperazine nucleus through aniline intermediate linker, was used as the lead compound. In addition, Mrozek-Wilczkiewicz et al., [103] showed that a novel series of piperazine substituted quinolines via thiosemicarbazone linker possessed a significant anticancer activity with the most potent derivative compound **61**, that displayed IC_{50} value of 0.07-0.22 µM against five different cancer cell lines (Figure 20).

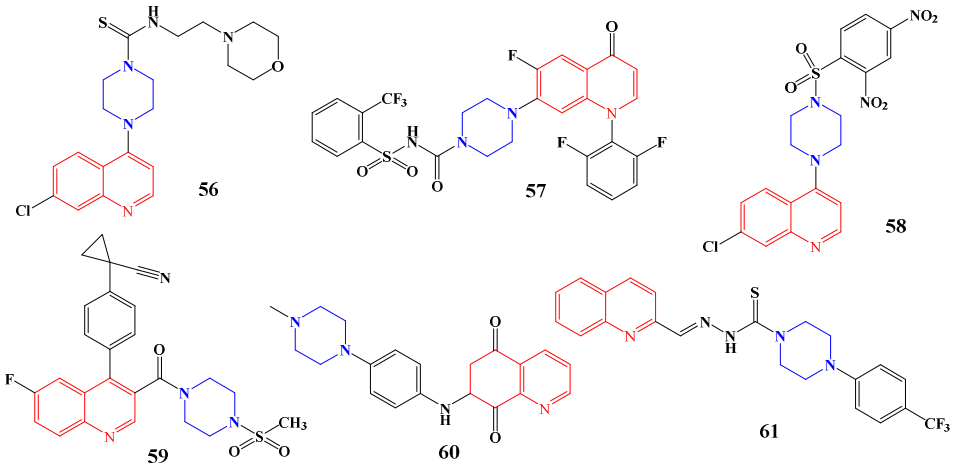

Figure 20: Examples of quinoline-piperazine conjugates of potential anticancer activity

3.17. Quinoline-Piperidine Conjugates

Ramesh et al., [104] reported the synthesis of new rhodanine analogues as anticancer agents among which the piperidinyl quinoline **62** that showed potent anticancer activity against MNK-74 gastric cancer cell lines. Also, Yadav et al., [105] reported the synthesis of novel arylated benzo[h]quinolines with potential Anticancer activity including the 4-piperidinyl analog **63** that displayed potential cytotoxicity against several human cancer cell lines, in addition to significant CDK-2 inhibitory activity. Yang and team, [101] designed and synthesized a new series of quinoline-based aldehyde dehydrogenase-1A1 (ALDH1A1) inhibitors in particular, compound **64** that displayed a remarkable enzyme inhibitory activity with IC_{50} value of 7 nM. In addition, Sonia et al., [106] filed a patent on novel quinoline derivatives among which compound **65** that was screened against three different cancer cell lines and showed cell viability percentage of less than 20%. Berdini and team [107] patented a new series of quinoline derivatives as Fibroblast growth factor receptor (FGFR) inhibitors including compound **66** bearing piperidine nucleus (Figure 21).

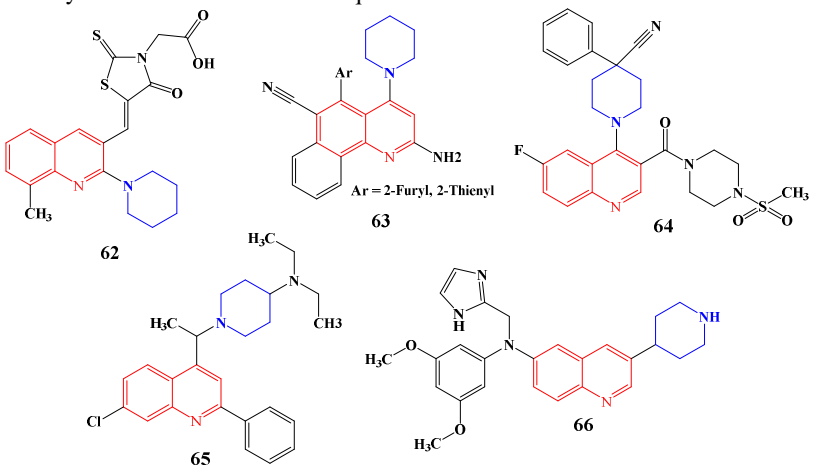

Figure 21: Examples of quinoline-piperidine conjugates of potential anticancer activity

3.18. Quinoline-Pyran Conjugates

The anticancer activity of pyrano[3,2-c]quinoline was frequently reported. Upadhyayand team [108] reported the synthesis of pyrano[3,2-c]quinoline analogues as antiproliferative agents and the screening results revealed that compound 67 was found as most active candidates. Also, Ibrahim et al., [109] synthesized a pyrano[3,2- c]quinoline-3-carboxaldehyde 68 as a ligand and subject to chelate with Cu(II) ion. Ligand 68 and its Cu (II) complexes showed potential antitumor activity against Ehrlich Ascites Carcinoma cell line (Figure 22).

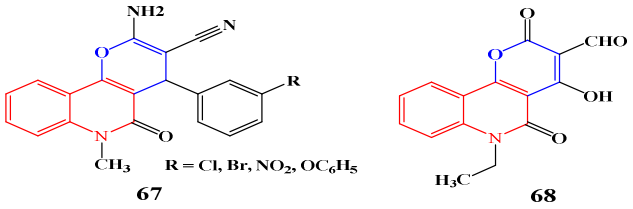

Figure 22: Examples of quinoline-pyran conjugates of potential anticancer activity

3.19. Quinoline-Pyrazole Conjugates

Quinoline based derivatives that bearing pyrazole nucleus either fused or substituted directly to the quinoline nucleus or through intermediate chain or linker were frequently report. George and his team [110] reported the synthesis and anticancer evaluation of some novel quinoline based 4,5-dihydropyrazoles and related thiazole hybrids including compound 69 which showed significant cytotoxic effect with EGFR inhibitory effect with IC50 value of 32 nM. Hagras et al., [111] designed and synthesized a novel series quinoline-heterocyclic conjugates as potent colchicine binding site inhibitors including the most promising pyrazole substituted one 70 that arrest the cell cycle at G2/M phase and induce apoptosis on HepG-2 cancer cells thirteen times more than the control cells. Also, Berdini and team [107] patented a new series of quinoline derivatives as Fibroblast growth factor receptor (FGFR) inhibitor including compound 71 with directly attached pyrazole nucleus. On the other hand, pyrazole could be conjugated with quinoline through linker. Ramírez-Prada et al., [112] synthesized novel quinoline-based pyrazoles as promising anticancer agents including compound 72 that showed prominent values of GI50 against different cancer cell lines, some of them less than 1.00 µM. Li et al., [52] develop a novel series of quinoline derivatives for the treatment of liver cancer among which pyrazole conjugate 73 that showed moderate activity. Also, Xi files a patent on a novel series of substituted quinolines as kinase inhibitors targeted against Kinase insert domain receptor (KDR), c-Met kinase and AxL receptor [113] including compound 74 that revealed significant IC50 value of 5 nM in cellular AxL phosphorylation assay. On the other hand, at different position of quinoline nucleus, fused pyrazolo-quinoline derivatives as potential anticancer agents targeting different targets were reported many times [114-119]. For instance, Fathy et al., [115] reported the synthesis of a new series of tetrahydroquinoline including pyrazolo derivative 75 that showed the highest potential IC50 and a significant apoptotic effect on three different cancer cell lines. Also, Opoku-Temeng and co-workers [118] reported the synthesis of a novel series of 3H-pyrazolo[4,3-f]quinoline including compound 76 inhibitors and anticancer properties was the most potent haspin kinase inhibitor with 14 nM IC50 value. In addition, Kasaboina et al., [117] reported the synthesis of new pyrazolo[4,3-f]quinoline based potential anticancer agents including compounds 77 that showed IC50 values of 2.43 µM, against A549 and MCF7 cancer cell lines. Spano and team [119] reported the synthesis of pyrazolo[3,4-h]quinolines as photosensitizing agents among which compounds 78 that showed potential activity against different cancer cell lines (Figure 23).

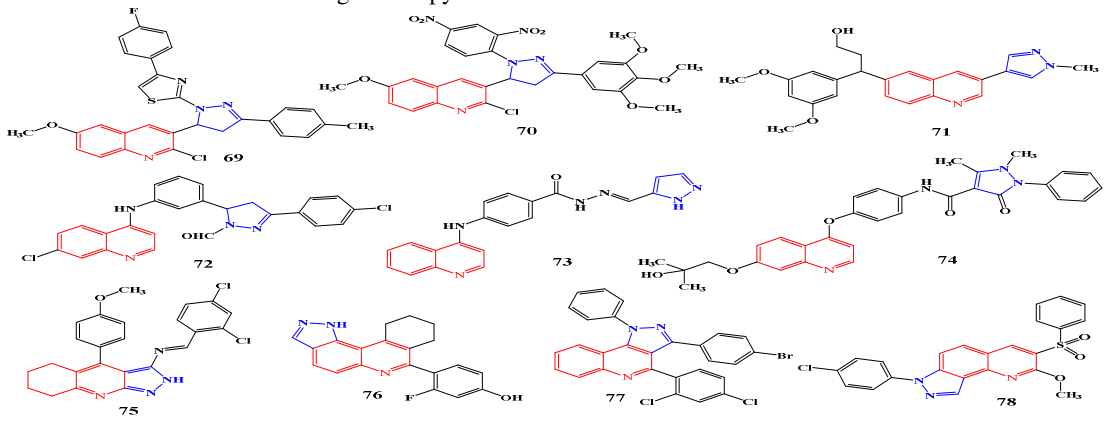

Figure 23: Examples of quinoline-pyrazole conjugates of potential anticancer activity

3.20. Quinoline-Pyridine Conjugates

El-Damasy and team [120] reported the design, synthesis, in-vitro anticancer activity and kinase profile of novel ureido quinoline derivatives including compound 79 bearing pyridine ring that was the most active analog with significant activity and superior potency than sorafenib in different cancer cell lines. Li et al., [102] reported the synthesis and biological evaluation of quinoline-pyridine conjugates as potential anti-prostate cancer agents. Mechanistic studies showed conjugate 80 was a potential Pim-1 kinase inhibitor with abilities of induce apoptosis and cell cycle arrest. Also, Vennila et al., [56] designed and synthesized a series of potential anticancer 4-substituted quinolines that target PDK1 among which quinoline-pyridine conjugate 81. On the other hand, several patents were published on quinoline based pyridine derivatives with potential anticancer and enzyme inhibition activities. Knight et al., [80] filed a patent on the synthesis of novel quinoline derivatives as PI3 kinase alpha enzyme inhibitors including compound 82 bearing two pyridine rings which was found to be potent PI3 kinase alpha enzyme inhibitor and was endowed with IC50 values of 0.8 nM. Also, Furet and coworkers [79] patented the synthesis of novel quinoline carboxamide derivatives as Fibroblast growth factor receptor-3 (FGFR3) inhibitor. Compound 83 bearing pyridine ring through carboxamide linker showed a significant inhibitory potential with IC50 value of 16 nM. In addition, Inukai and team [121] filed a patent on the synthesis of quinoline derivatives as AxL inhibitors among which compound 84 displayed a significant potency with IC50 value of 2.2 nM (Figure 24).

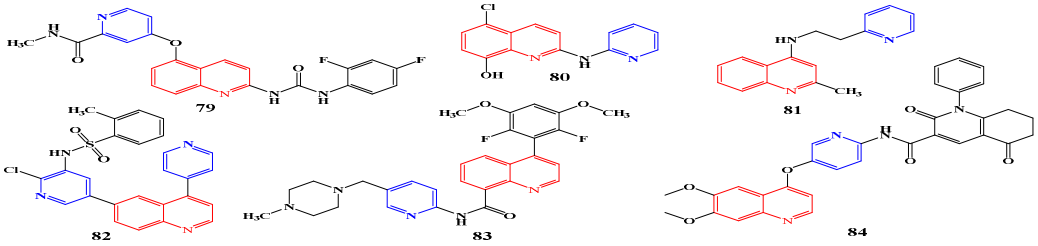

Figure 24: Examples of quinoline-pyridine conjugates of potential anticancer activity

3.21. Quinoline-Pyrimidine Conjugates

Toan et al., [122] reported the synthesis of a novel series of quinoline-pyrimidine hybrids, some of which showed remarkable inhibitory activity against the different tested cancer cell lines including compound 85 with MIC values of 1.32 µM. Ghorab and coworkers [123] reported the design, synthesis and anticancer evaluation of some novel 4-aminoquinoline derivatives including the pyrimidine-2,4-dione derivative 86 that displayed moderate activities. Also, Hagras et al., [111] designed and synthesized a novel series of quinoline-heterocyclic conjugates as potent colchicine binding site inhibitors including compound 87 that displayed moderate anticancer activity. On the other hands, fused pyrimido-quinoline as potential anticancer agents were reported. For instance, Mekheimer and coworkers [124] reported the development of a new series of pyrimido[5,4-c]quinoline derivatives as potential antiproliferative agents among which compound 88 that was found to be a potential anticancer agent and one of the most potent analogs against EGFR. Weissman et al., [125] filed a patent on selective human double minute-2 protein (HDM2) inhibitors pyrimidodione-quinoline derivatives among which the most potent compound 89 that showed significant anticancer activity with selective HDM2 inhibitory effect. In addition, Ghorab et al., [126] reported the synthesis, radiosensitizing evaluation and in-vitro anticancer screening of some new pyrimido[4,5-b]quinolines bearing a sulfonamide moiety including compound 90 that displayed moderate activities (Figure 25).

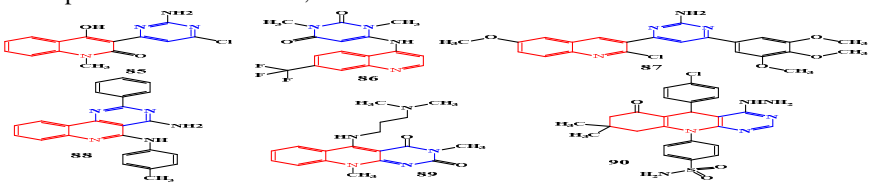

Figure 25: Examples of quinoline-pyrimidine conjugates of potential anticancer activity

3.22. Quinoline-Tetrazole Conjugates

Regarding quinoline-tetrazole conjugates as potential anticancer agents, Shaikh et al., [127] reported the design, synthesis, docking studies, and anticancer evaluation of a new series of tetrazolylmethyl quinoline. Among the tested compounds, tetrazolylmethyl quinoline **91** displayed 99.28% of GI against Melanoma (SK-MEL-5) while its methoxy analog **92** showed 97.56% of GI against Breast Cancer (T-47D). Also, Nippu and coworkers, [128] reported the design and synthesis of a new series of tetrazolo-quinoline derivatives as potential anticancer agents including compound **93** that displayed potential anti-proliferative activity with IC_{50} value of 60.17 µM against the MIA PaCa-2 human pancreatic cancer cell line (Figure 26).

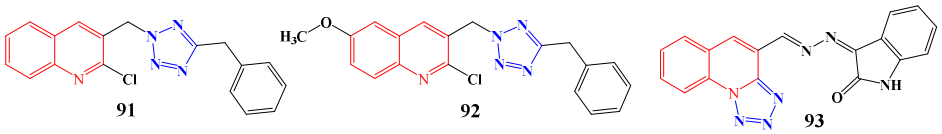

Figure 26: Examples of quinoline-tetrazole conjugates of potential anticancer activity

3.23. Quinoline-Thiazole Conjugates

Regarding the quinoline-thiazole conjugates as potential anticancer agents, Aly et al., [72] designed and synthesized a new series of quinoline based derivatives as EGFR inhibitors with potential anticancer activity including thaizole analogues **94** that showed moderate inhibition effect. Li et al., [52] develop a novel series of quinoline derivatives for the treatment of liver cancer including 1,2-thiazole derivative **95** which showed moderate activity. Also, the synthesis of new rhodanine analogues as anticancer agents was reported [104] among which the piperidinyl quinoline **96** that showed potent anticancer activity against MNK-74 gastric cancer cell lines. In addition, Taghour and team [129] reported the design and synthesis of quinolone-thiazolidine-2,4-diones hybrids as potential VEGFR-2 inhibitors among which compound **97** that potential anticancer activity. Aly et al., [130] reported the synthesis of some novel thiazole-quinolone derivatives including compound **98** that revealed remarkable activity against colon carcinoma HCT-15 and lung cancer NCI-H322 M (Figure 27).

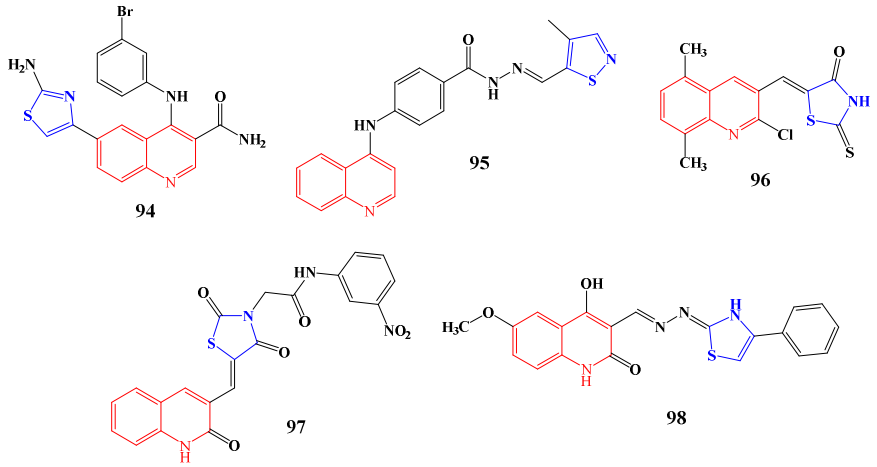

Figure 27: Examples of quinoline-thiazole conjugates of potential anticancer activity

3.24. Quinoline-Thiophene Conjugates

Quinoline based derivatives that bearing thiophene nucleus substituted directly to the quinoline nucleus or through intermediate chain or linker were frequently report. Aly et al., [72] designed and synthesized a novel series of quinoline-3-carboxamide bearing thiophene nucleus **99** that directly attached to the quinoline nucleus as potential anticancer agent with EGFR inhibitors activity with IC_{50} value of 0.49 µM. Lee and coworkers, [100] developed quinoline sulfonyl derivatives including compound **100**, that possessed a thiophene nucleus attached to quinoline nucleus via aminopropyl sulphonamide intermediate chain and showed potential cell growth inhibitory effects against different breast cancer cell lines. Also, Othman et al., [131] designed and synthesized a novel series of thiophene-quinoline hybrids that were evaluated for *in-vitro* cytotoxicity against four

different human cancer cell lines and the most promising compound **101** displayed the most potent anticancer activity against MCF-7, with IC_{50} value of 28.36µM. Vanjare and coworkers, [132] synthesized a new series of quinoline based schiff base derivatives with potential anticancer and elastase inhibitory activities including compound **102** that displayed moderate activity (Figure 28).

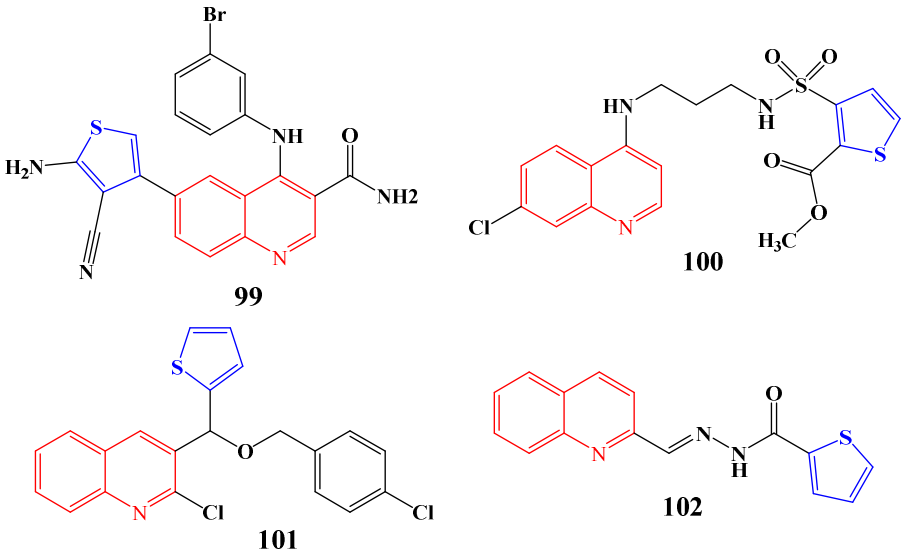

Figure 28: Examples of quinoline-thiophene conjugates of potential anticancer activity

3.25. Quinoline-Triazole Conjugates

Quinoline based derivatives that bearing triazole nucleus either fused or substituted directly to the quinoline nucleus or through intermediate chain or linker were frequently report. Regarding the directly attached pyrazol-quinoline derivatives, Mohassab et al., [133] reported the design and synthesis of a new series of quinoline-triazole hybrids **103** as potential anticancer agent targeting EGFR and $BRAFV^{600E}$ kinases including. Macan and coworkers, [134] reported the synthesis triazolyl-substituted quinolines as potential antiproliferative agents including compound **104** that was the most promising candidate and displayed the highest potency and showed some selectivity against the non-cancer aneuploid immortal keratinocyte (HaCaT) cells. In addition, Hamdy et al., [95] developed a new series of quinoline-based heterocycles hybrids as antiproliferative agents targeting Bcl-2 among which compound **105** bearing triazole nucleus that displayed weak activity against different cancer cell lines. Also, Rajulu and team, [135] designed and synthesized a series of new hydroxamic acid derivatives of fluoroquinolones including compound **106** bearing triazole nucleus that showed good activity against HCT-116 colon carcinoma and A549 lung adenocarcinoma cancer cell lines. On the other hand, quinoline derivatives conjugated with triazole either fused or via linker were also reported. Praveena et al., [136] reported the design and synthesis of a series of new conjugated compounds by linking quinoline, triazole and dihydroquinoline pharmacophores including compound **107** that showed potential cytotoxic effects with IC_{50} values of 10.8 and 11.1 µM against MCF-7 and A549 cancer cell lines, respectively. Also, Dominska and team, [137] reported the synthesis and preliminary anticancer evaluation of potential metabolites of quinoline glycoconjugates linked by an aliphatic chain of different lengths to a 1,2,3-triazole ring including compound **108** that displayed a potential anticancer activity. Reddy et al., [138] reported the synthesis of some novel fused 1,2,3-triazoles hybrids of Clioquinol including compound **109** that was found to exhibit a comparable anticancer activity to the standard drug etoposide against four different human cancer cell lines (Figure 29).

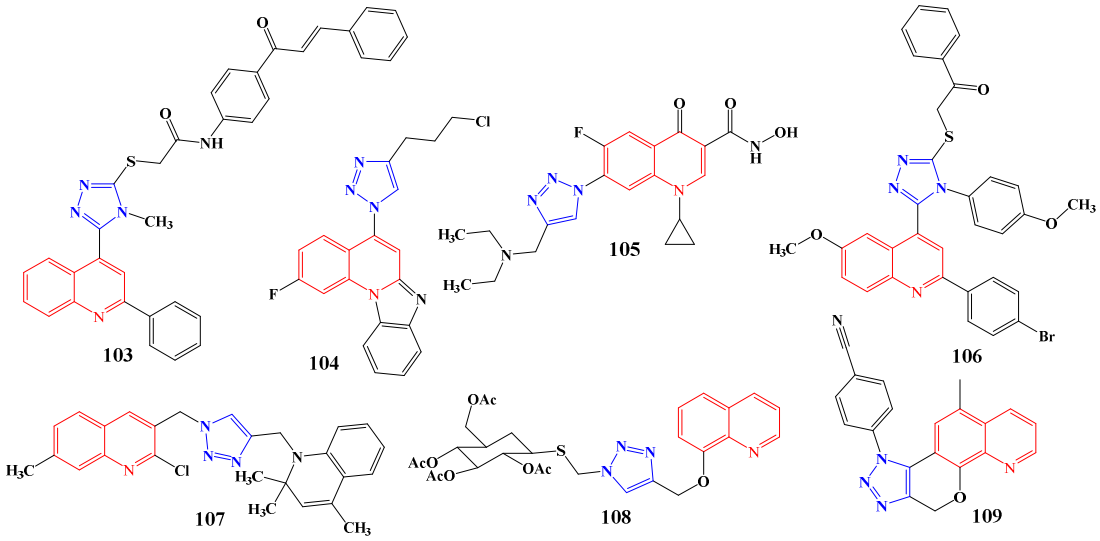

Figure 29: Examples of quinoline-triazole conjugates of potential anticancer activity

3.26.Quinoline-Miscellaneous Heterocycles Conjugates

Quinoline based derivatives containing uncommon heterocycles either fused or substituted directly to the quinoline nucleus or through intermediate chain or linker were frequently report. Castro et al., [139] filled a patent on a new series of trisubstituted quinoline derivatives as kinase inhibitors and compound **110** bearing pyrazolo-pyrimidine nucleus showed significant phosphoionositol-3-kinase-γ(PI3K-γ) inhibitory activity at 0.1 - 0.5µM concentration. Karthikeyan et al. [140] developed a novel series of fused pyrimido [1 ″, 2 ″: 1, 5] pyrazolo [3,4-b] quinolines derivatives as ABCG2 inhibitors among which compound **111** displayed the highest inhibitory activity of ABCG2 and showed high binding affinity to ABCG2 cavity and was involved in key interactions as revealed by docking studies. Vennila et al., [56] designed and synthesized a series of potential anticancer 4-substituted quinolines that target PDK1 among which quinoline-benzodioxan conjugate **112** that exhibited significant antiproliferative activity. Chen et al., [141] patented the synthesis of imidazo[2,1:2,3]imidazol fused quinoline compounds as potential inhibitors of mammalian target of rapamycin (mTOR) and among the synthesized compounds, **113** was found to be the most potent with −5% MTOR activity at 0.03 µM concentration. Shahabuddin and team [142] studied the interaction of a novel pyrimido [4`,5`:4,5]thieno(2,3-b)quinolin-4(3H)-one derivatives with DNA by hydrodynamic methods, circular dichroism, absorbance and fluorescence titrations. The anticancer activity of compound **114** was found to be significant against K-562, HL-60, Colo-205 and B16F10 melanoma with IC_{50} values in the range of 1.1-8 µM. Inukai and coworkers, [143] filled a patent on the synthesis of a novel series of quinoline derivatives as Axl receptor tyrosine kinase(Axl) inhibitor including compound **115** bearing pyrido-azepine nucleus that displayed an excellent Axl inhibitory activity with IC_{50} value of 15 nM. On the other hand, in their search for novel bromodomain-containing protein 4 (BRD4) inhibitors, Xing and coworkers, [144] reported the computational-assisted rational design for the development of a library of various 5-substituted 8-hydroxyquinoline including compound **116** bearing pyrido-diazepine nucleus that revealed significant BRD4 inhibitory activity with IC_{50} value below 300 nM. Martínez- Gonzalez et al. [145] reported the synthesis of a novel series of triazolo[4,3-b]pyridazine-based quinoline derivatives as inhibitors of Proviral Insertion site on Moloney murine leukemia virus (PIM) kinase among which compound **117** bearing triazolo-pyridazine-morpholine nucleus showed significant anticancer activity against broad range of cancer cell lines and was found to be the most potent inhibitor of PIM-1 and PIM-3. Tegley et al., [146] designed and synthesized a new series 1,2-dihydrochromeno[3,4-f]quinoline derivatives as nonsteroidal progestin analogs, among which compound **118** that displayed highly potent progestin agonistic activity with more than 100-fold progestin receptor selectivity over other steroid hormone receptors. Cui et al., [147] reported the discovery triazolo[4,5-b]pyrazin quinoline analog **119** with was found to be an highly potent and selective mesenchymal-epithelial

transition factor (c-MET) protein kinase inhibitor and displayed effective tumor growth inhibition in c-MET dependent tumor models with significant oral pharmacokinetic properties and an accepted safety profile in preclinical studies. Zhang et al., [148] reported development of a series of quinoline-based [1,2,4]triazolo[3,4-b][1,3,4]-thiadiazoles as potential anticancer agents and selective c-Met kinase inhibitors Among which compound **120** that was found to be the most promising c-Met kinase inhibitors analog with IC_{50} value of 2.02 nM. Zhan et al., [149] reported the synthesis of quinoline-based triazolo-pyridazine **121** that a significant antiproliferative activity and a promising c-Met kinase inhibitory effect with IC_{50} value of 2.02 nM. El-Sayed et al., [150] reported the synthesis of a series of 2-styrylquinolines as potent EGFR kinase inhibitors, among which compound **122** that bearing thiadiazoles ring was found to be the best EGFR inhibitors with IC_{50} value of 1.11 µM that was slightly less active or comparable to reference EGFR inhibitors sorafenib (IC_{50}= 1.14 mM). in addition, Khelifi et al., [151] synthesized and tested the potency of a series of quinoline derivatives with various amino-substituted heterocycles, including the dibenzo-pyrrole analog **123** that displayed excellent sub-nanomolar *in-vitro* cytotoxic activity against colon carcinoma cell line HCT-116 (IC_{50} = 0.070 nM) in addition to significant inhibitory activity against tubulin polymerization (Figure 30).

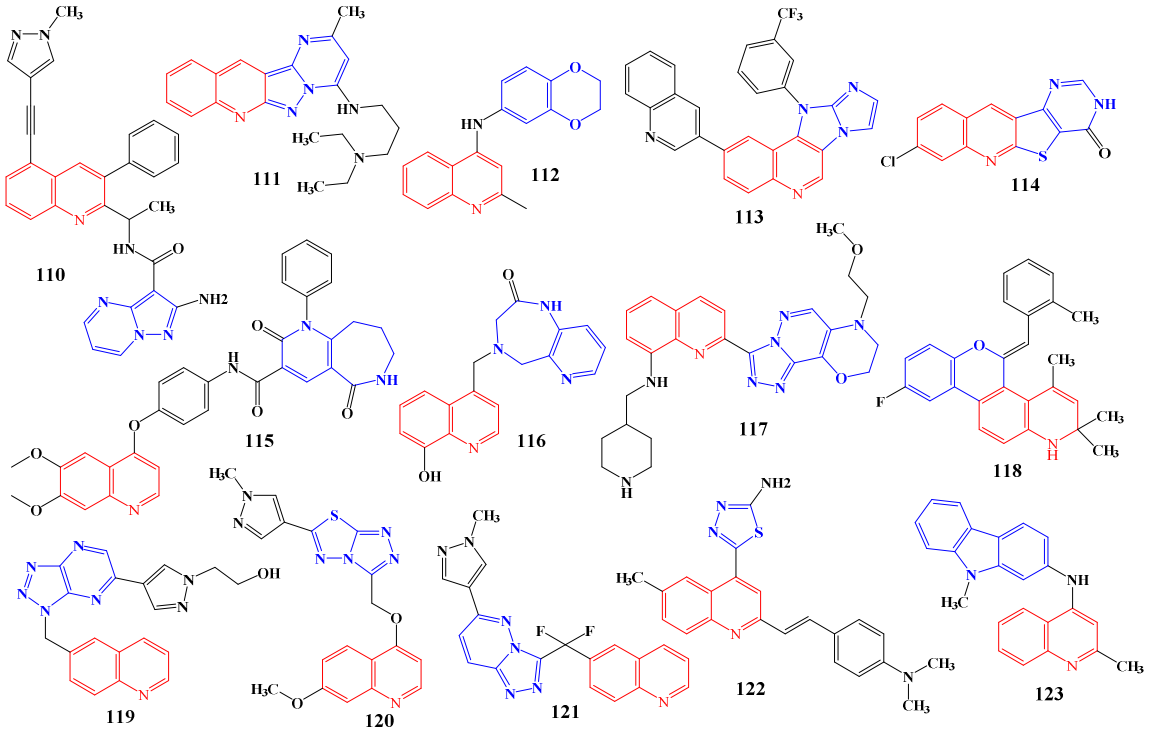

Figure 30: Examples of quinoline-miscellaneous heterocycles conjugates of potential anticancer activity

4. Conclusion

Quinoline conjugated heterocyclic derivatives are a wide class of natural and synthetic compounds that displayed versatile biological and pharmacological effects. Despite the diversified effects of quinoline-heterocyclic hybrids in the search for bioactive compounds, they remain one of the most attractive class of compounds for anticancer drug discovery, design and development. In this regard, heterocycles such as azetidinone, benzimidazole, benzofuran, benzothiazole, coumarin, imidazole, indole, morpholine, oxadiazole, piperazine, pyrazole, pyrimidine, tetrazole, thiazole, triazole and others fused to or substituted directly to the quinoline nucleus or via intermediate chain or linker were frequently reported. Also, the quinoline-heterocyclic hybrids exhibited their antiproliferative effect via different mechanisms including the inhibition of a wide range of protein kinases such as PDK1, CDK2, topoisomerase, APE-1F, GFR3, HDM2, PI3K and others. The present review is expected to highlight the anticancer potential of quinoline conjugated

with different heterocycles in the twenty first century covering approximately 150 references which could serve as a platform for pharmaceutical chemists to design and develop better anticancer candidates.

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