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Mini Review

Recent Advances in Quinolone based Derivatives as Potential Anticancer Agents

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ABSTRACT

As a result of the great annual increase in patients suffering from cancer, there is urgent need for designing new small molecule chemotherapeutic agents that selectively target cancer cells without or with minimal effect on normal cells. Quinolone derivatives are fused heterocyclic ring systems that are explored for their diverse biological activities with the potential for treatment of many diseases such as antimalarial, antibacterial, antifungal, antiviral, antibacterial, antioxidant and their role as broad spectrum anticancer agents. The present mini review is to represent the most recent pharmaceutical aspects and synthetic approaches of different substituted quinolones as anticancer agents reported to date.

Also, Displaying the recent quinolone derivatives recommended or present in preclinical and clinical studies. In addition to showing the importance of the structure activity relationship in designing new lead compounds with potential antitumor activity. Moreover, exploring the effect of different hybridizations with quinolone analogues for designing potent anticancer agents.

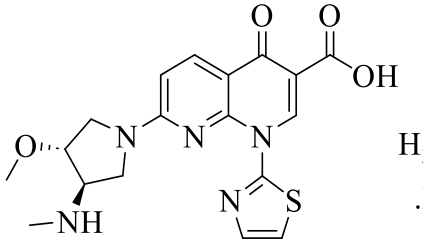
Keywords: Quinolone derivatives, Antitumor, Hybrids.

1. Introduction

Cancer can be identified as a disease that causes uncontrolled increase and abnormal cell proliferation. These cells tend to overcome their biological barriers to give rise to invasive or metastatic cancer. (1) According to the WHO, there were about 10 million deaths cases in 2020. (2) Quinolones and their derivatives showed potent anticancer activity against most of tumor cell lines with different mechanisms of action (3). Moreover, quinolone derivatives are proven to be an antiproliferative pharmacophores along with the ability to enhance their activity using various functional groups. Quinolone substitutions with electron-withdrawing groups as amino, nitro, choro, fluoro, and carbonyl groups revealed activity more potent than substitutions with electron-donating moieties as methoxy or methyl groups (4).

For example, induction of apoptosis through inhibition of topoisomerase type II (5), (6), cell cycle arrest (7), (8), disruption of mitochondrial membrane potential and inhibition of signal stimulated protein kinases that affect growth regulators and angiogenesis (9, 10).

Many quinolones, such as voreloxin **1** (the first-class anticancer quinolone derivative) (11), AT-3639, **2,** and quarfloxin **3**, are being used in clinics or clinical trials at the moment (12). A number of hybridization approaches of the quinolone scaffold with small anticancer molecules improved the affinity and the potency as well as overcoming the cross-resistance compared to the parent drug, for example, Ro 23-9424, **4** (13) and MCB3837, **5** (14).



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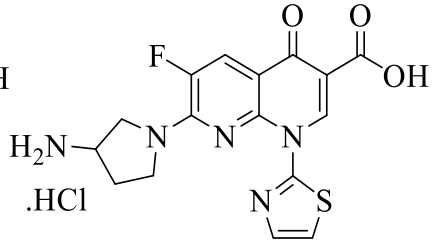
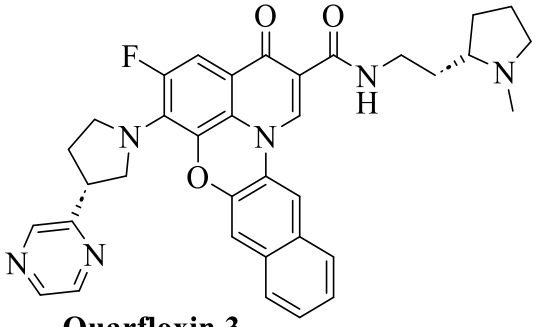
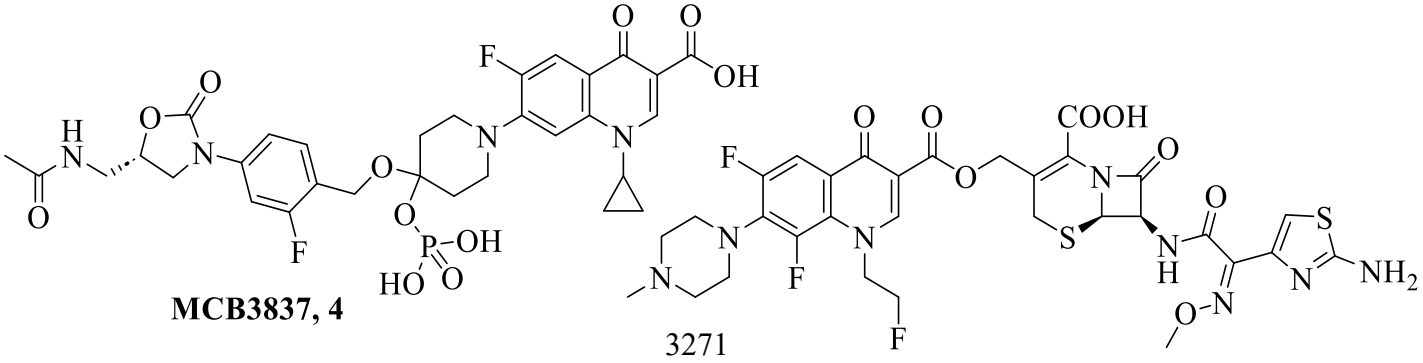


AT-3639, 2



Quarfloxin 3

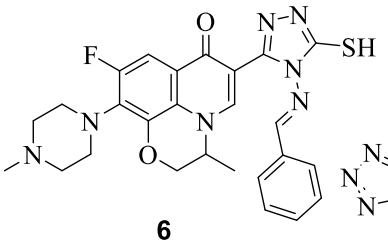


MCB3837, 4

Ro 23-9424, 5

2. Quinolone hybrids having potential as antiproliferative agents

The reported hybridizations include quinolone with nitrogen containing 5 and 6 membered rings hybrids such as **5**, **6** and **7** (15). Quinolone-chalcone hybrids as compound **8** (16, 17), Quinolone-thiazole/ pyrrole/furan/thiophene hybrids **9-12** (18-21), Quinolone-guanidine/oxime hybrids **13** and **14** (22-26), Quinolone-quinolone hybrids **15** (27-29).



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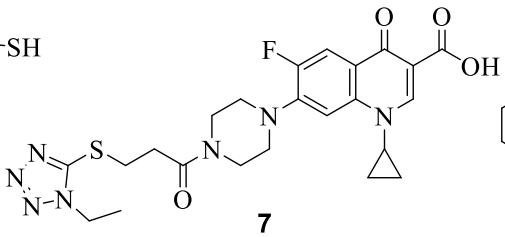

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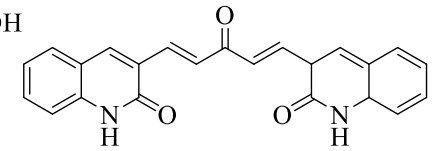

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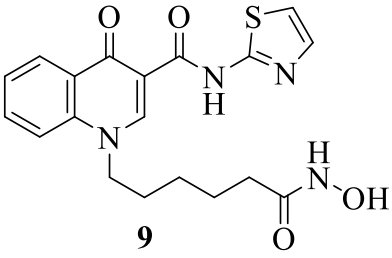

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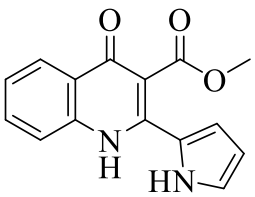

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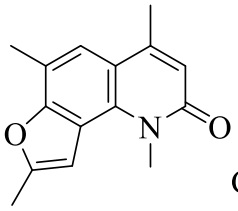

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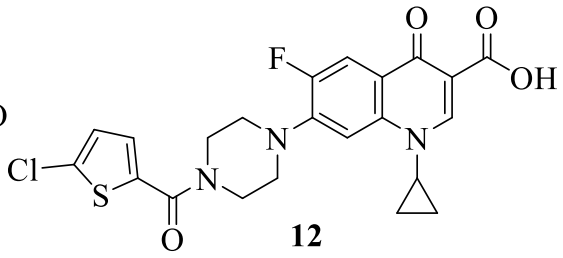

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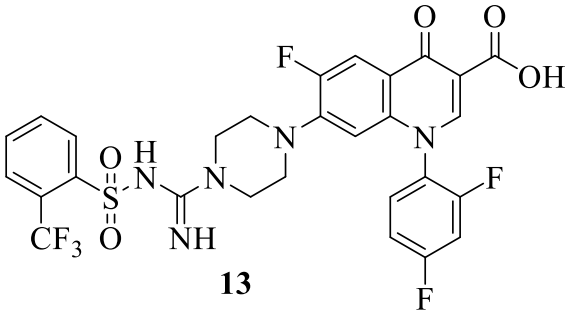

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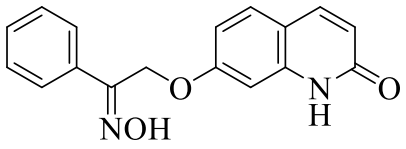

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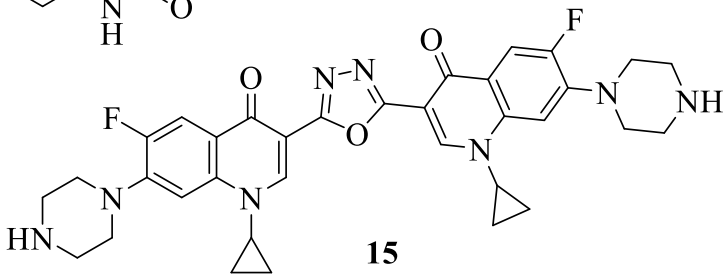

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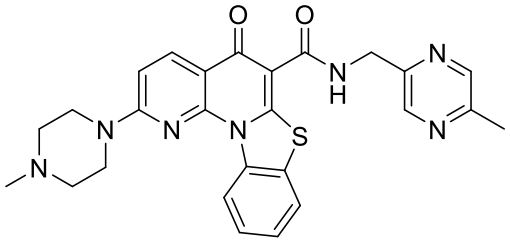
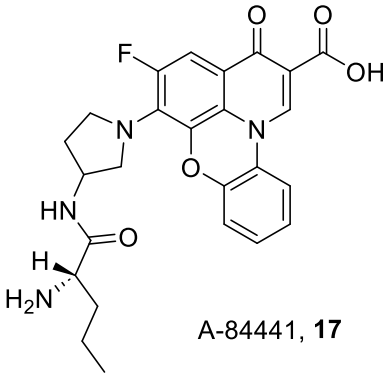
3. Anticancer quinolone hybrids in preclinical and clinical studies

Compound (CX-5461, **16)** is drug under investigation for cancer treatment. It induces the DNA damage response through inhibition of RNA polymerase I. CX-5461 is in clinical trial phase I for treatment of solid tumors (30).



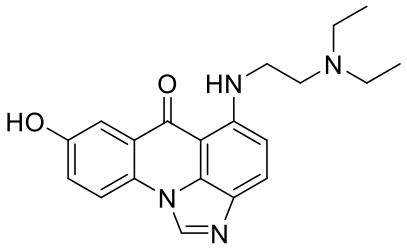
CX-5461, **16**

Quinolone-benzoxazine hybrid (A-84441, **17)** is a prodrug that showed remarkable inhibition activity (IC_{50} = 0.03-0.49 μM) against 7-9 human and murine cancer cell lines. Moreover, an *in vivo* investigation showed that compound **17** exhibited 10 times more potent anti-leukemic activity against cancer cells than normal bone marrow murine cells (31, 32).



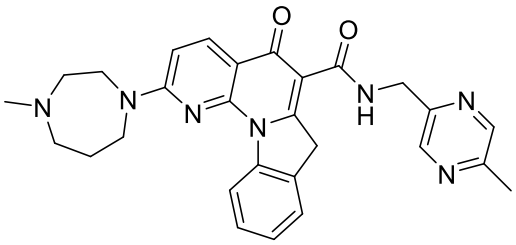
A-84441, **17**

Compound (C-1305, symadex, **18**) is a quinolone-azole hybrid that act as antitumor agent by inhibiting Topoisomerase II, it is subjected to Phase II clinical trials for treatment of metastatic Colorectal Cancer (33, 34).



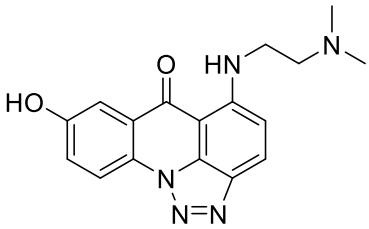
Symadex, C-1311, **18**

Quinolone-pyrazine hybrid (CX-5461, Pidnarulex, **19**) showed inhibition activity against both Topoisomerase II and G-quadruplex, compound **19** exhibited *in vivo* tumor growth inhibition of 84% at intraperitoneal administration of 25 mg/kg dose (35). It was entered Phase I clinical trial in Canada for treatment of patients with ovarian and breast cancer (36).



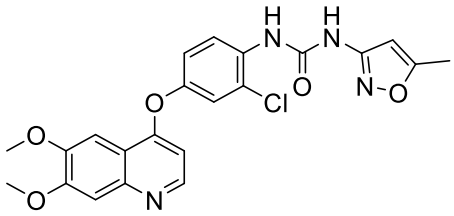
CX-5461, **19**

Quinolone derivative (C-1305, **20)** displayed potent anticancer activity against A549 lung cancer cells. Moreover, combination therapy with paclitaxel showed remarkable antitumor effect against HCT116 colon cancer cells with the improvement of blood perfusion in the tested tumor models (37, 38).



C-1305, **20**

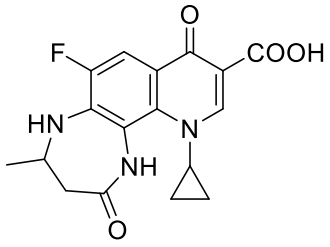
Also, clinically approved drug Tivozanib **21** which is FDA approved quinoline bi-aryl urea derivative for treatment of renal cancer and solid tumors. It is selective pan VEGFR (1,2,3) tyrosine kinase inhibitor (39), (40) with IC_{50} values 30 nM, 6.5 nM and 15 nM, respectively. (41)



Tivozanib, 21

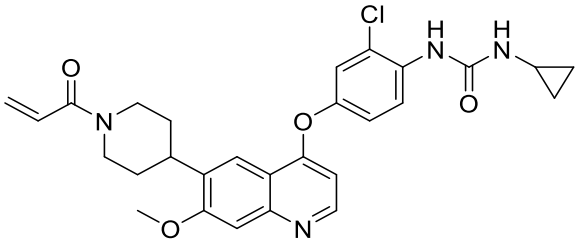
4.Recent developments in quinolone as antiproliferative agents

Hybridization between quinolone scaffold and hetero-tricyclic diazepine nucleus produced a potent GSK-3β enzyme inhibitor **22** with 100 % inhibition and IC_{50} 0.114 μM, while it showed anti-proliferative activity with IC_{50} value 37 μM against U-87 glioma cell cell line (42).



22

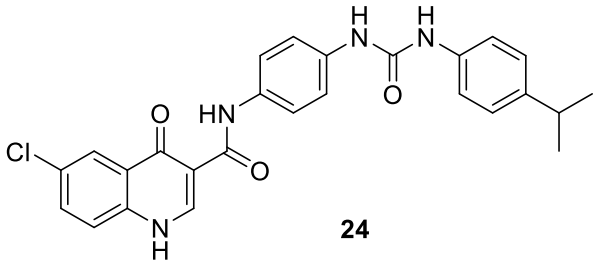
A novel quinolone-based compound **23** was synthesized and evaluated for its antiproliferative activity. it demonstrated a potent irreversible covalent pan-FGFR inhibitory activity at a low nanomolar concentration as well as effective antiproliferative activity against Huh7 and Hep3B HCC cancer cell lines (43).



23

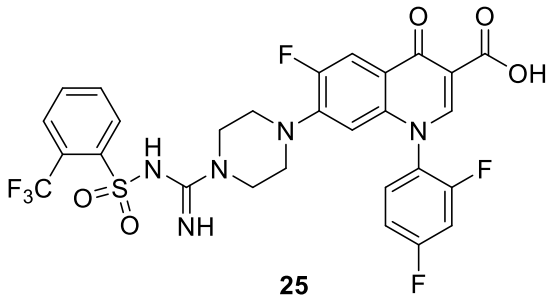
FGFR1 IC_{50}=9.9 nM FGFR4 IC_{50}= 1.8 nM
FGFR2 IC_{50}= 3.1 nM Huh-7 IC_{50}= 12.6 nM
FGFR3 IC_{50}= 16 nM HepB IC_{50}= 52.6 nM

Quinolone-3- carboxamide based VEGFR2 inhibitors were designed, synthesized and tested for their antiproliferative activity. Compound **24** displayed potent VEGFR2 inhibition with IC_{50} 36 nM compared to reference compound sorafenib (45 nM), while it showed better cytotoxic effect (IC_{50} =1.6 µM) than sorafenib (IC_{50} =1.6 µM) against HepG2 cancer cell line along with the induction of caspase mediated apoptosis of human hepatocarcinoma cell (44).



24

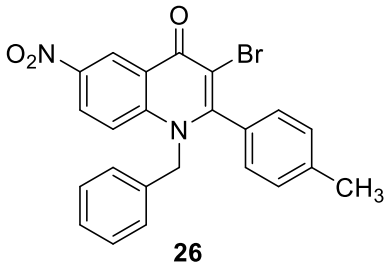
N-1 aryl substituted 4-quinolone compound **25** was designed, synthesized and evaluated for its antiproliferative activity. It showed 5-times more cytotoxic potency against A549, HL-60, and Hela cell lines compared to the reference compound irinotecan or cisplatin (IC_{50} values =0.009, 0.008 and 0.010 µM, respectively) (26).



25

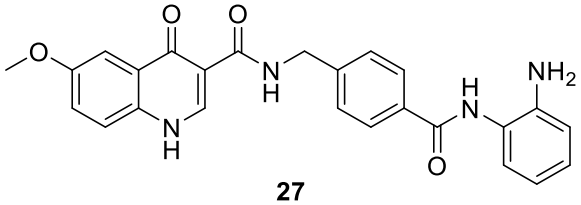
N1 substituted-4-quinolone derivative **26** was synthesized and evaluated against MCF-7, K562, Hela and BHK-21 cell lines. it displayed potent cytotoxic activity with % inhibition 57.1, 97.4, 62.8 and 24.7 %, respectively, compared to carboplatin reference compound with inhibition

90.7, 82.8, 85.2 and 18.4% and IC_{50} values 6.22, 7.91 and 7.65 µM, respectively (carboplatin IC_{50} values 3.91, 4.11 and 5.13 µM, respectively) against MCF-7, K562, Hela, respectively (45).



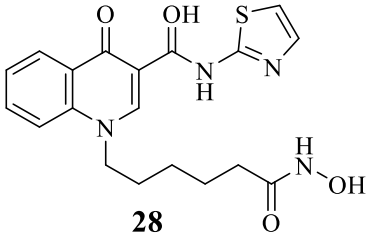
26

Electron withdrawing group was attached to 4-quinolone scaffold at 6-position in compound **27** and evaluated for its activity as anticancer agent. It exhibited superior antiproliferative IC_{50} values of 2.51, 1.90, 1.86, and 0.91 µM against A549, MCF-7, HT29 and HCT116, respectively), apoptosis induction as well as HDAC inhibition (than Entinostat reference compound (IC_{50} 2.11, 2.52, 3.86 and 4.33 µM in HCT116, HT29, MCF7 and A549, respectively) (46).



27

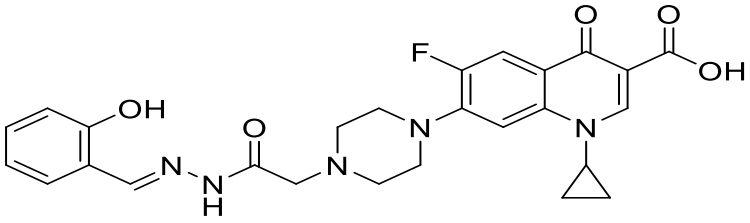
Hybrdization with thiazolyl moiety proved to enhance the antiproliferative activity as tyrosine kinase inhibitor. (47, 48) Moreover, the quinolone-thiazole derivative **28** showed considerable anti-proliferative activities against NCIH460, HCT116 and U251 cell with IC_{50} values of 2.43-2.9 µM. (49)



28

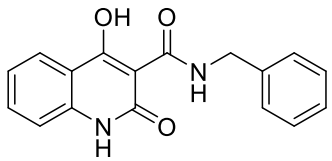
5.Structure activity relationship of most quinolones' anticancer agents

Literature review revealed some important key point suggestions for quinolones SAR (structure activity relationship) as anticancer agents (9, 50), (32, 51-60). Nitrogen in position one is essential for avtivity, moreover, the introduction of a halogen, fluoro-substituted phenyl, or cyclo-propyl moieties at N-1 position of the quinolone scaffold give rise to a potent cytotoxic activity (53). That can be observed in compounds **25**, **28** which demonstrated cytotoxic activity with IC_{50} values of 0.009 μM against A549 cell line and 0.58 μM against the UO-31 kidney cancer cell lines, respectively (26, 60).



IC_{50}=0.58 μM (UO-31 kidney cancer cell lines)

Substitution at C-2 is only permitted upon keeping the coplanar orientation of the quinolone core with substitution at C-3 (53). Remarkable cytotoxic activity is showed when the carboxylic acid group at C-3 position, that is present in most quinolone antibiotics, is substituted with a carboxamide moiety as in compound **29** which has a PI3Kα inhibition activity against both the wild type (IC_{50} = 1.1 μM) and mutant-type $PI3K\alpha_{H1047R}$ (IC_{50} = 0.73 μM) (54).



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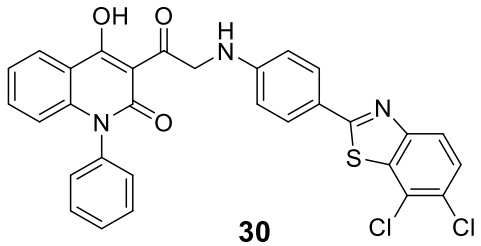
Another modification at C-3 through heterocyclic substitution with benzothiazole through linker (compound **30**) (9) or 1,3,4-thiadiazole substitution (compound **31**) (55) results in a potent activity with IC_{50} values 2.22, 0.954 and 0.398 μM (MCF-7 at 24 h, 48 h and 72 h, respectively)

for compound **30** and IC_{50} values 3.26 µM (MCF-7), 10.53µM (A549) and 5.08 µM (SKOV-3), respectively for compound **31** (9, 55).



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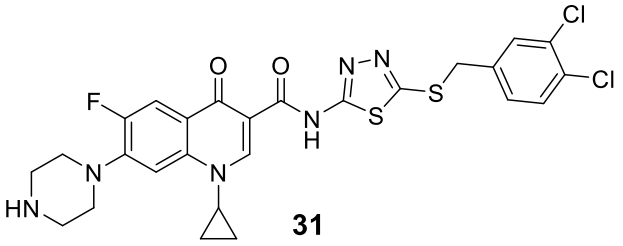
IC_{50}= 2.22, 0.954 and 0.398 µM
(MCF-7 at at 24 h, 48 h and 72 h, respectively)



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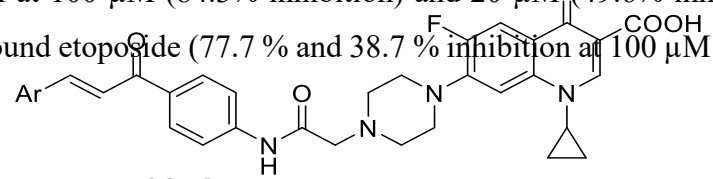
IC_{50}=3.26 µM (MCF-7)
IC_{50}=10.53µM (A549)
IC_{50}=5.08 µM (SKOV-3)

Carbonyl group at C-4 increased the anticancer potency of quinolone compounds due to its ability to chelate metal ions or form H-bonding with the target macromolecules, while carbonyl group substitution diminished this activity (58).

Furthermore, the presence of a halogen atom as fluorine at C-6 enhanced the antiproliferative activity of quinolones (56). New reports have demonstrated the importance of fluoroquinolones as antiproliferative agents (61) via inhibition of DNA topoisomerase II as primary target as revealed in compound **32** that showed a significant cell growth inhibition activity against HCT-116 colon cancer cell line and showed more potent inhibitory activity against topoisomerase II at 100 µM (84.3% inhibition) and 20 µM (49.6% inhibition) corresponding to reference compound etoposide (77.7 % and 38.7 % inhibition at 100 µM and 20 µM, respectively) (50).



32, Ar = 4-OCH_3-C_6H_4
84.3% inhibition of topo II at 100 µM
49.6% inhibition of topo II at 20 µM

Moreover, substitution at C-7 with a basic group or aromatic moieties improved the anticancer activity (50). Modification with a substituted heterocycles such as piperazine, or amino-substitutions at C-7 was significant for the anticancer activity (compounds **25, 28**) (50, 59, 62).

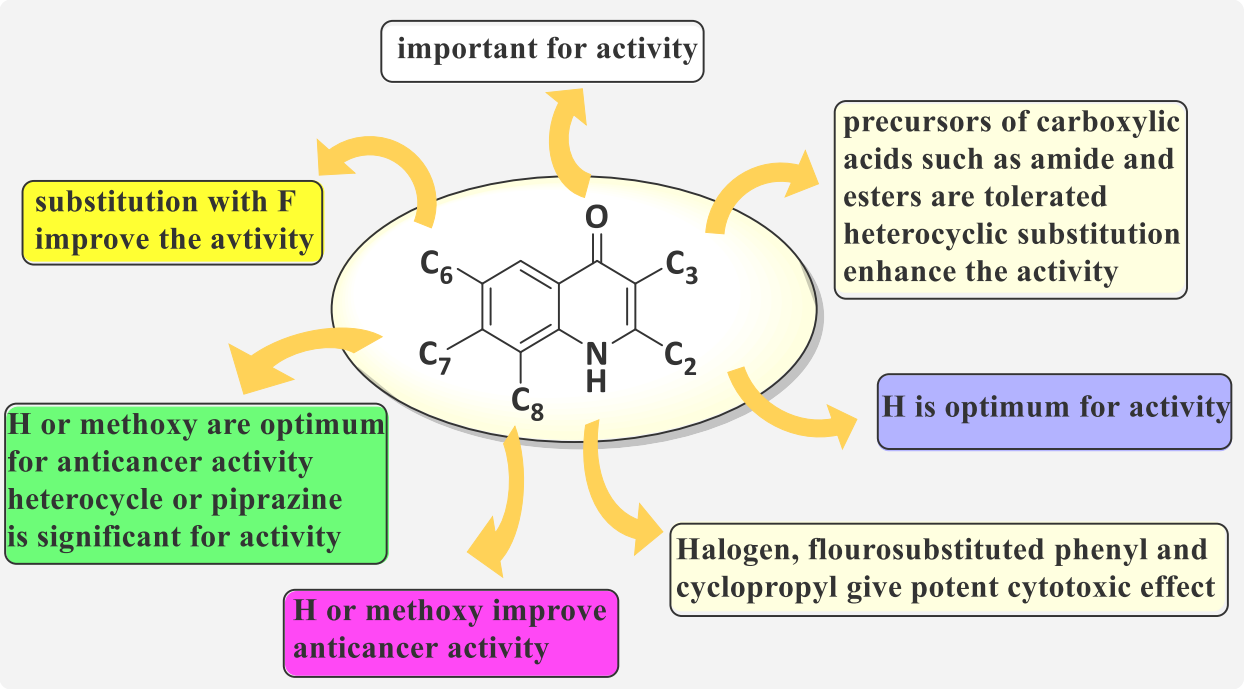


Figure 1. SAR of quinolones as anticancer agents

6. Conclusion

These results provide evidence that exploring the potential of quinolone hybrids could produce a promising lead for further development of potent antitumor agents by manipulating the characteristic chemical features of the attached groups and adjusting the key factors for their anticancer effects. In addition, highlighting the important role in revealing the different mechanisms of action related to the known compounds that help research programs in the future.

- **Conflict of Interest**

The author confirms that there are no conflicts of interest.

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