

Recent Strategies in Design of Antitumor and Antibacterial Fluoroquinolones

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Abstract

Fluoroquinolones are known widely used synthetic antibacterial agents. Generally, there were some obstacles associated with their therapeutic use. Moreover, many research studies all over the world proved the variable biological effects of fluoroquinolones such as antituberculosis, anticancer, or even antiviral activities. The current review is focused on modifications that occurred in the fluoroquinolone scaffold for their repositioning from antibacterial into anticancer agents especially modifications at C-7 or at the carboxylic C-3 groups. In addition, it includes the recent research studies carried out to improve the potency, spectrum of activity, or pharmacokinetics of antibacterial fluoroquinolones. Hence, this review may be useful for researchers in the design and synthesis of new fluoroquinolones with improved biological activities.

Key words

Fluoroquinolones; Antitumor; Antibacterial; Design

1. Introduction

Quinolones (oxo-quinolines) are a member of quinoline family, and they represent one of the most essential classes of antimicrobial agents in the field of medicinal chemistry. The first antimicrobial quinolone **1** was discovered in the early 1960s [1], as a side reaction during the synthesizing of the antimalarial compound, chloroquine, possessing anti-Gram-negative bacterial activity. But due to its narrow spectrum antimicrobial activity and unfavorable pharmacokinetic, it is not significant enough to be useful in therapy [2]. Nalidixic acid **2** is the first developed quinolone. Since this time, many derivatives with different properties have been synthesized and evaluated for their activities [3]. Several quinolone derivatives based on naphthyridine nucleus were synthesized and estimated for their antibacterial activities leading to appearing of the first generation of quinolone antibiotics which characterized by Lack of broad activity and rapid developing bacterial resistance (Figure 1)[4].

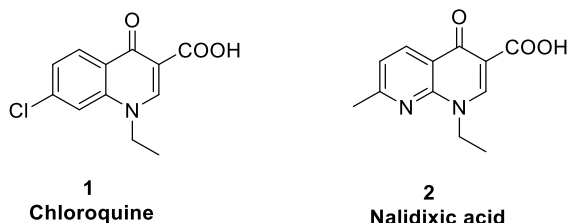


Figure 1: chloroquine and Nalidixic acid

Consequently, considerable work has been performed to develop new quinolone derivatives with high potency, wide spectrum of activity, and long half-life, besides, good physicochemical properties. Certain modification such as,

substitution with (F) atom at C-6 site of quinolones gives fluoroquinolones (FQ)[5], which facilitated penetration into the bacterial cell with a broad spectrum of antibacterial activities. Other modification includes the substitution of quinolone at C7 with piperazinyl, piperidinyl and pyrrolidinyl moieties that participated in an increasing spectrum of antibacterial activities, especially against *Pseudomonas aeruginosa*[6]. Recent fluoroquinolones have a broad spectrum of antibacterial activities. These activities include Gram-negative, Gram-positive, aerobic, and anaerobic bacteria. Moreover, fluoroquinolones are characterized by a short period of treatment, a low rate of developing bacterial resistance[7,8], and a good pharmacokinetic profile[9]. Fluoroquinolones, also acquired other biological activities such as antifungal[10,11], antitubercular [12], antitumor[13-15], anti-HIV-1 integrase, anti- HCV-NS3 helicase[16], antimalarial[17], and anti-Alzheimer activities[18].

Due to high costs and higher failure rates for discovering new anticancer agents for clinical treatment, the most convenient approach is repositioning existing drugs and reevaluating them for new biological activities as it requires less time and money. Different fluoroquinolone derivatives have been used as antimicrobial agents for a long period, so, repositioning of fluoroquinolones as antitumor agents seems to be acceptable due to their apoptotic potential, anti-proliferative activity, and induction of cell cycle arrest [19]. Fluoroquinolones display their antibacterial activities by inhibiting the vital cellular processes such as replication and transcription of bacterial DNA through targeting the essential Topoisomerase enzymes, gyrase, and/or topo IV enzyme. These enzymes are present in prokaryotic bacterial cells, other similar subtypes are present in the eukaryotic mammalian cell. Fluoroquinolones are highly selective and sensitive towards bacteria subtypes, for repurposing to anticancer, modifications based on increasing its selectivity toward mammalian subtypes [20].

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2. Generations of quinolones

Quinolones have been categorized into four generations, based on their spectrum of activity and pharmacokinetic features [21-23]. The first generation of quinolones displayed antibacterial activities only toward the species of Gram-negative bacteria, but they have restricted uses due to short duration of action and rapid renal clearance [24]. Also, they are suffering from minimum serum level, narrow spectrum of activity, and rapid development of bacterial resistance. So, they are only used as therapy for Gram-negative bacteria caused urinary tract disease but are seldom used nowadays (**Figure 2**) [24-26].

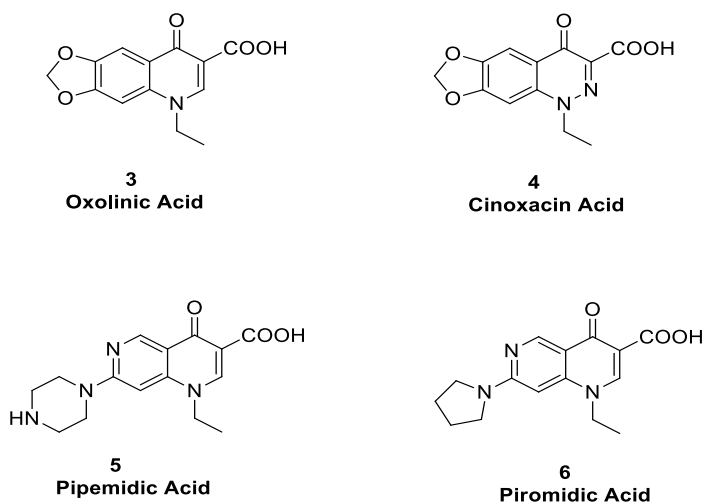


Figure 2; First generation of antibacterial quinolones

Second-generation of quinolones (**Figure 3**) were obtained by substitution with a fluorine atom at C-6, lead to an increase in the spectrum of the activity in comparison with the first generation. So, they showed good antibacterial activities toward Gram-negative bacteria, *P. aeruginosa*, in addition to, Gram-positive species with longer duration of action [21,24]. These agents are used in the treatment of several diseases caused by a bacterial infection such as pyelonephritis, urinary tract infections, pneumonia, bladder infections, and sexually transmitted diseases as well as, skin infections [27].

Ciprofloxacin **7** is the most important example of this class due to its excellent pharmacokinetic properties and ease of oral and intravenous administration, high potency, broad antimicrobial activities toward different bacterial organisms such as Gram-positive, Gram-negative, and atypical bacterial species. Also, it exhibited activity against *Mycobacterium tuberculosis* and short period of treatment in addition, reduced frequency of bacterial resistance particularly against the recent derivatives (**Figure 3**)[28].

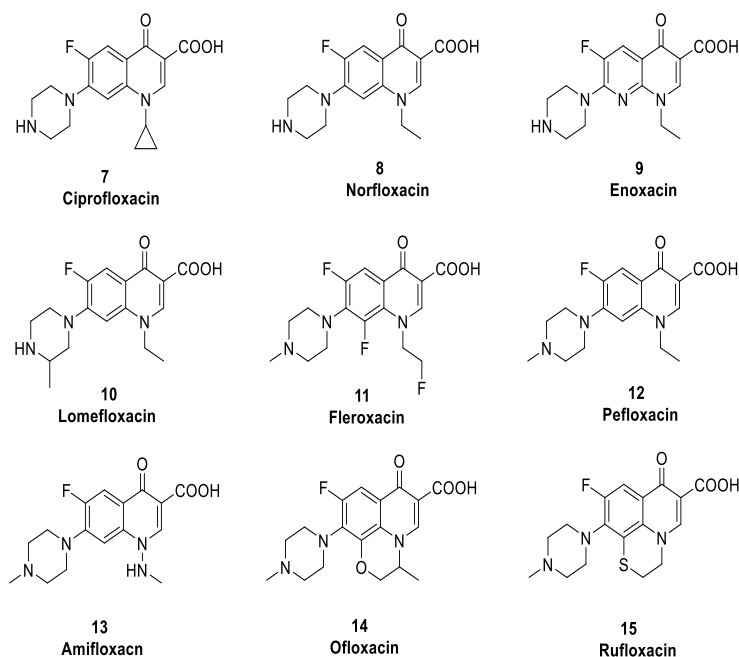


Figure 3: Second generation of antibacterial quinolones

Third-generation quinolones are characterized by long serum half-lives and a wide spectrum of activity than first and second generations. The drugs belonging to this generation showed a good spectrum of activities against different bacterial species, Gram-negative, *P. aeruginosa*, Gram-positive, *M. tuberculosis*, atypical and anaerobic bacteria (**Figure 4**) [29,31].

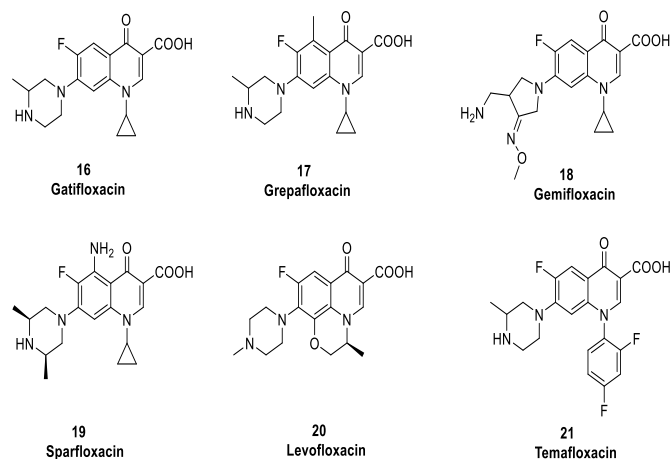


Figure 4: Third generation of antibacterial quinolones

Moreover, the fourth generation of quinolones exhibited higher activity against Gram-positive bacteria especially, *Streptococcus pneumonia*, atypical and anaerobic bacteria as well as, *Mycobacterium tuberculosis*. Moreover, these drugs are characterized by a long serum half-life, excellent tissue penetration, lack of unexpected toxicity, and limited bacterial resistance. Also, they act by inhibition of both DNA gyrase and topo IV enzymes (**Figure 5**) [29,32,33].

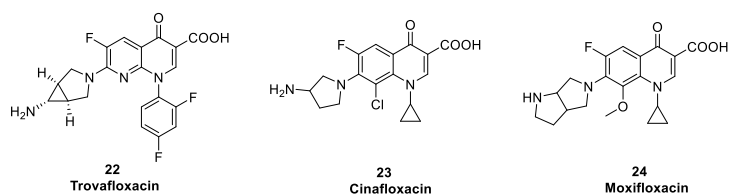
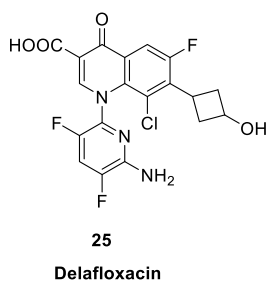


Figure 5: Fourth generation of antibacterial quinolones.

Delafloxacin drug **25** is a new member of the antibacterial fluoroquinolone family that received approval in the USA and become available in sixty eight countries located in Europe, Asia, Australia, and America [34]. The drug Delafloxacin was approved by FDA as medication for different pathogenic bacterial diseases such as acute bacterial skin, and skin structure infections (ABSSSI), Gram-positive and Gram-negative bacterial species, including (MRSA) subtype [35,36].



3. Chemistry of quinolones

The basic structure of quinolone is based on a bicyclic system of pyridine-4-one-3-carboxylic acid merged at 5 and 6 positions with another six-membered aromatic or heteroaromatic system. Two major groups have been developed from this basic structure, quinolones **26** and naphthyridones **27**. Quinolone **26** has a carbon atom at position 8, otherwise, bioisosteric replacement with (N) atom at this site gives naphthyridones **27**. Moreover, some derivatives have belonged to different ring systems, namely cinnoline **28** and pyridopyrimidine nucleus **29** [20,37,38]. Generally termed "quinolones" is a common name for this drug family based on these four ring systems (**Figure 6**).

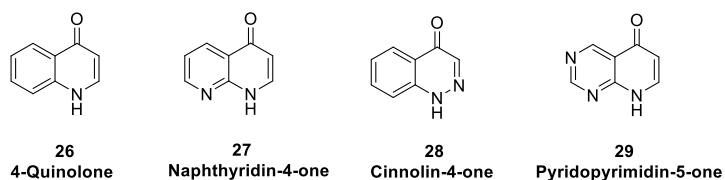


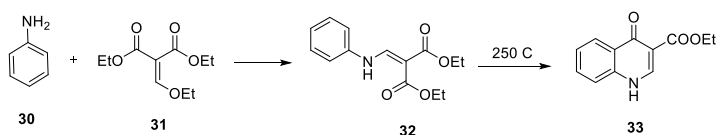
Figure 6: Common ring systems in quinolone drugs

In general, the medicinal importance of quinolone derivatives encouraged many researchers to prepare numerous and different chemical quinolone compounds. Several procedures in literature were described for the synthesis of quinolones.

3.1. Methods for quinolones synthesis

Gould-Jacobs synthesis of quinolones

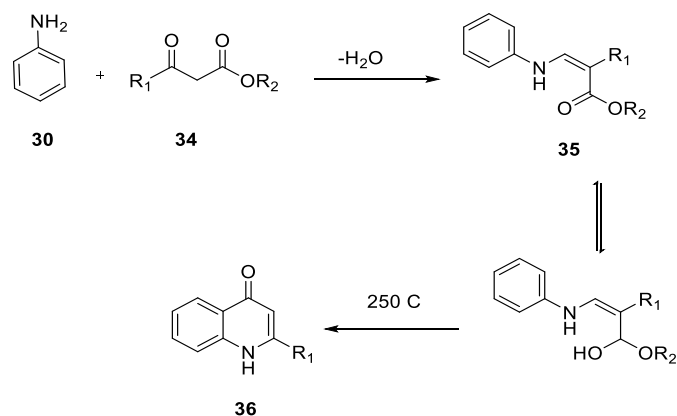
One of the most common synthetic methods of quinolone ring is Gould-Jacobs method [39]. This reaction was performed through an addition-elimination reaction between aniline **30** and ethylethoxymethylmalonate **31** to give intermediate **32**, followed by cyclization at high temperatures to give the quinolone compound **33** as shown in (**Scheme 1**).



Scheme 1: Gould-Jacobs reaction

Conrad-Limpach synthesis

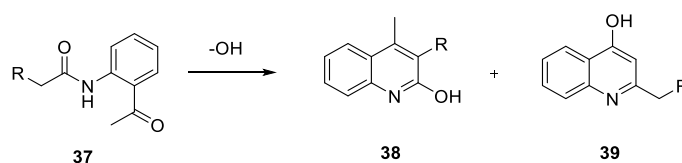
The condensation reactions of aniline **30** with different acetoacetic ester derivatives **34** gave intermediate **35**. The intermediate was tautomerized followed by cyclization at high temperature to yield 4-quinolone derivative **36** (**Scheme 2**) [40].



Scheme 2: Conrad-Limpach quinolone synthesis

Camps quinoline synthesis

In this reaction [41], 2-acetamidoacetophenone derivative **37** undergoes intramolecular condensation in the presence of a hydroxide ion to give quinolin-2-ol **38** and quinolin-4-ol **39** in the percentage of 70%, 20%, respectively (**Scheme 3**).

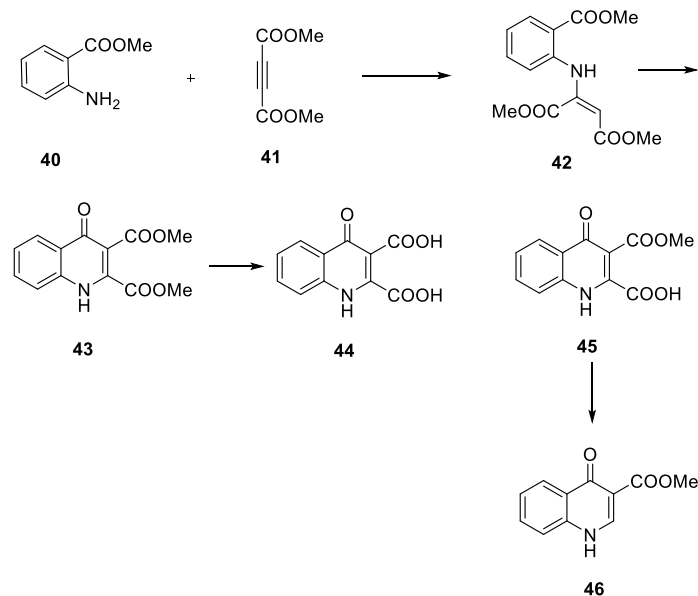


Scheme 3: Camps quinoline synthesis

Biere-Seelen synthesis

This approach of quinolone synthesis [3] was developed through a Michael addition of *o*-aminobenzoate ester **40** to

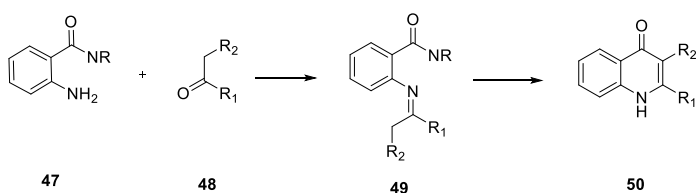
acetylene dicarboxylate ester **41** that gives rise enaminoester **42**. The ester then undergoes cyclization to quinolone dicarboxylic acid ester **43** in the presence of a strong base. The dicarboxylic acid **44** or ester acid **45** are obtained after regioselective or complete alkaline hydrolysis of **43**. Compound **45** undergoes decarboxylation of the acid moiety to yield the corresponding quinolone ester **46** (Scheme 4).



Scheme 4: Biere-Seelen synthesis

Snieckus synthesis

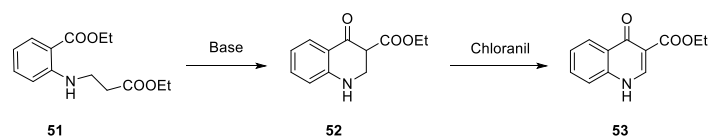
3-Alkyl-substituted 4-quinolones **50** can be synthesized by the Snieckus group [42], through the condensation reaction of an ortho-substituted aniline **47** with a ketone **48** to give intermediate **49**. This intermediate undergoes deprotonation and intramolecular cyclization to yield quinolone **50** in the presence of a base (Scheme 5).



Scheme 5: Snieckus synthesis of 4-quinolones

Dieckmann cyclization

Compound **51** is a diester derivative of anthranilic acid which undergoes intramolecular cyclization using a catalytic amount of alkali to give the dihydroquinolone derivative **52**, followed by oxidation to afford the 4-quinolone-3-carboxylate derivative **53** (Scheme 6) [43].



Scheme 6: Dieckmann cyclization approach to 4-quinolones

4. Mechanism of action of fluoroquinolones

Quinolones act by interfering with the normal process of DNA topo I and II enzymes (especially, II) leading to inhibit the DNA synthesis [44,45]. Topoisomerase enzymes have been performed essential functions during cell life by keeping the proper DNA topology intact[46]. They manage the DNA supercoiling levels during the process of unwinding and rewinding of DNA double helix that's happened throughout the process of replication, recombination, repairing, and cell division [47-49]. Topoisomerase enzymes have induced the formation of DNA breaks followed by religation after the passage of the other DNA strands through these breaks [44,46]. Quinolones drugs can affect the activity of topoisomerase enzymes either by inducing the formation of DNA breaks [50] or stabilization of a transient DNA break that formed by a covalent adduct with the enzyme, through which strand passage can occur and keep it from going back to the original DNA[51] or through intercalation of DNA[52] leading to inhibit the cell division and induce apoptosis. Topoisomerase II enzyme represents the target for quinolone derivatives as antimicrobial and anticancer agents [14,53]. Moreover, certain quinolones exhibited anticancer activity by targeting Topoisomerases I and II enzymes [14]. In addition, some quinolones exhibited antiproliferative activities through different mechanisms such as protein kinases CK2 inhibition [54,55]. or antimitotic activity [56] or different cell cycle arrest pathways [57].

Several anticancer drugs, known as Topoisomerase I & II inhibitors, for example, camptothecin **54** [58] and its silicon-including analog, Karenitecin **55** [58] as topo I inhibitors. Also, etoposide **56** [59,60] and doxorubicin **57** [61] are topo II inhibitors (Figure 7).

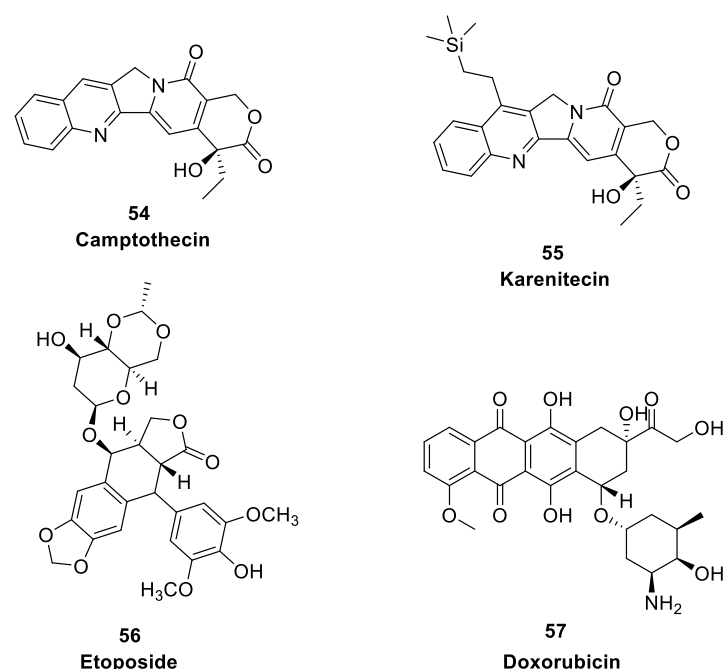


Figure 7: Structure of Topoisomerase I and II inhibitors

5. Structure activity relationships (SAR) of cytotoxic quinolones

Several studies based on structural modifications of antibacterial fluoroquinolones were performed to identify the cytotoxic structural features of fluoroquinolones against eucaryotic cells. These modifications directed the activity of fluoroquinolones from antibacterial to anticancer agents [62]. At the same time, the Topo II inhibitory activity and pharmacokinetic features of fluoroquinolones are significantly influenced by the modification types that occurred at the piperazinyl N-4 and or C-3 position of the fluoroquinolone system [63]. Hence, new fluoroquinolone analogs can be developed by structural modifications at 7 and/or 3 positions of fluoroquinolones which diminished the zwitter ion effect and greatly influenced the lipophilicity nature as well as cytotoxic activity of fluoroquinolones. Also, the other modifications at the different sites of quinolone structure were reported (**Figure 8**).

Position 1: The N atom at this is necessary for activity, the changing of N-1 substituent ethyl group to cyclopropyl group at this position was found to increase the antiproliferative activity and produce better quinolones interference with Topo II than with Gyrase. Also, phenyl and thiazolyl moieties at this site were found to be valuable [64,67].

Position 2 and 3: Substitution at these positions should be coplanar with the main quinolone nucleus and does not disturb the coplanarity of the quinolone nucleus [68]. The isothiazole ring fused at position 2 and 3 with the quinolone ring was reported to increase the activity [65].

The C3-COOH or its isosteric groups are an essential requirement for quinolone's antibacterial activity. The acidic moiety can participate with the ketone at position 4 in metal ions chelation or hydrogen bonding with the targeting enzymes. However, these groups can be replaced with H and still cytotoxic for the eukaryotic Topo II enzyme. Although in 3-H derivatives small substituents can be useful at C-2. If the carboxylate group remaining at this position, no such modification can be performed, it will destabilize the planarity of the ring system [68].

Also, the introduction of a phenyl moiety or a related heteroaromatic ring at C-2 through a methylene linker can enhance the Topo II poisoning activities. Furthermore, increasing in antitumor activity was achieved upon the addition of the hydroxyl group into the phenyl moiety. For example, the 2,6-dihydroxybenzyl compound was exhibited potent *in vitro* cytotoxic activity, as well as, murine antitumor activity [69].

Position 4 carbonyl group was essential for quinolones antibacterial activity, substitution at this position abolish the activity [56]. However, other studies revealed that substitution with alkoxy and amino groups at this position gave potent anticancer agents [70,71].

Position 5: Substitutions at this position have a great influence on the planarity and structural configuration of quinolones, as well as, cell permeability and affinity of the drug to bind with the target [72]. Further, the cytotoxic activity will be improved upon the introduction of an amino group at this position [62,71]. Also, position 5 could be occupied with aromatic or heteroaromatic moieties [73].

Position 6: Substitutions at this position with different substituents especially, fluorine and chlorine atoms have been reported. The fluorine substituted derivatives were found to be potent antitumor compounds. Furthermore, the substituted analogs with fluorine at both 6 and 8 positions provided better inhibitory activities against eukaryotic Topo enzymes [56].

However, some studies reported that the un substitution at this position may be better for antitumor activity [64]. On the other hand, other studies reported that C6 carbon substituted with methoxy group may improve the antitumor activity [71].

Position 7: Different substitutions at this site have been reported by several studies, these substitutions have a great effect on the quinolones interaction with the Topo enzyme-DNA complex [74].

Additionally, modifications at this position are strongly directing the inhibitory activities of quinolones selectively, against bacterial Topoisomerases, gyrase, and Topo IV enzymes [74] or mammalian Topoisomerases, I and II enzymes [75]. Furthermore, some studies reported that increasing the aromatic system at this site improved the antitumor activities [76,77]. For example, 4'-hydroxyphenyl moiety attached to the piperazine group increased the anticancer activity [78]. Besides, the nature of the attached substituents at this site has great effects on the physicochemical and pharmacokinetic features of the quinolone scaffold [14,63].

Position 8: Similarly to position 5, Substitution at position 8 has a significant effect on the quinolones configuration and its affinity to the target site [72]. The activity of quinolones against mammalian Topo II enzymes was increased by fluorine substitution at this site [79]. Certain studies reported that some quinolones derivatives with a fused ring at positions of C7 and C8 have potent anticancer activities (**Figure 8**) [73].

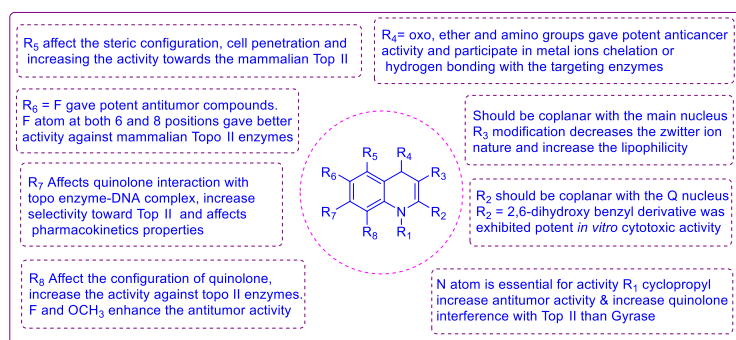


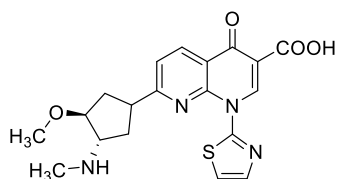
Figure 8: Structure-activity relationship of fluoroquinolones as anticancer agents.

6. Fluoroquinolone derivatives with anticancer activity

In the fact, that type II Topoisomerase enzymes are essential for the formation of required DNA during the cellular processes such as replication, transcription, folding, and unfolding of DNA.[48, 80, 81] The existence of DNA Topoisomerases in both mammalian and bacterial cells makes them a good target for antibacterial and antitumor developing drugs [20,82] Mammalian Topoisomerases represent a potential target for antitumor drug design. For example, camptothecin and doxorubicin are anticancer drugs that target Topo I and Topo II enzymes, respectively [83,84]. The quinolone drugs act by inhibition of Topoisomerases II in both prokaryotic and eukaryotic cell, due to these similarities of the prokaryotic and eukaryotic type; many studies were performed to selectively shifting of quinolones from an antibacterial to an antitumor activity [13, 20, 85].

Quinolones having many required characteristic properties as cancer therapy such as less toxic, low frequency of developing tumor resistance, and a fewer possibility for the development of

drug-caused secondary tumors, as well as favorable physicochemical and pharmacokinetic properties [86]. Voreloxin **58**, was the first quinolones derivative approved by the FDA as therapy for acute myeloid leukemia [87,88].



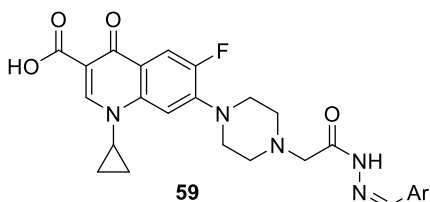
58
Voreloxin

Also, ciprofloxacin was reported as a Topo II inhibitor and antitumor activities⁸⁹ against different human cancer cell lines such as colorectal [90], leukemia [91], and osteosarcoma [92] human cancer cell lines.

Moreover, the Topoisomerase inhibition and the tissue penetration of quinolones are greatly affected by the modification at C3 and C-7 positions, which transforms its selectivity from bacterial to human Topoisomerase II [93]. Hence, new cytotoxic fluoroquinolone analogs can be developed through different modifications at 7 and/or 3 positions of quinolones scaffold leading to decreases zwitterion characters, hydrophilicity nature and subsequently enhance the quinolones cytotoxic activity.

6.1. Modifications of fluoroquinolones at 7-position

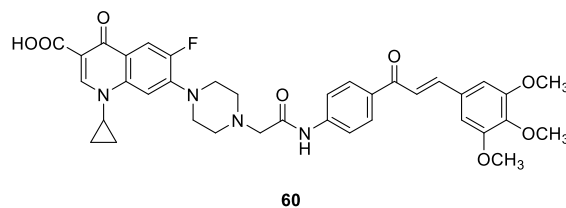
Several studies primarily discussed the structural modification of fluoroquinolone derivatives belong to *N*-4 of piperazinyl moiety. Compound **59** is a hydrazone derivative attached to ciprofloxacin. The ciprofloxacin derivative bearing hydrazone moiety at 7-position **59a** and **59b** [94] showed significant *in vitro* antitumor activities with IC₅₀ values 0.75 μM and 0.72 μM against UO-31 cancer cell line, respectively. Similarly, compound **59b** displayed IC₅₀ of 1.02 and 0.75 μM against NCI-H226 and IGROV1 cancer cell line, respectively. The hydrazones **59a** and **59b** showed inhibitory activities against Topo II with IC₅₀ of 0.75 and 0.72 μM, respectively. Moreover, they revealed a potent pro-apoptotic effect through induction of apoptosis and increasing the level of active caspase-3 compared to control and cell cycle arrest at G₂/M phase.



59a, Ar = 2-OH-phenyl
59b, Ar = 2-indolyl

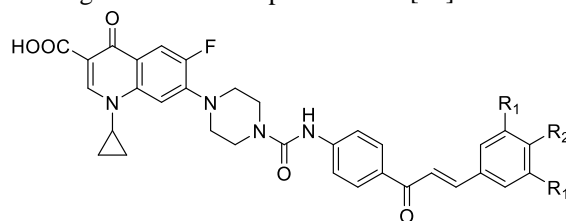
The ciprofloxacin-chalcone hybrids were investigated for their *in vitro* antitumor activities. Some of these derivatives showed a wide range of anticancer activities and induction of cell death against many of the investigated cancer cell lines. Similarly, it showed strong Topo I and II enzymes inhibitory activity very close to reference drugs, camptothecin, and etoposide.

Trimethoxy derivative **60** was the most potent one in this series (IC₅₀ = 2.82 μM). Also, compound **60** revealed high selectivity toward the leukemia cancer cell line [14].



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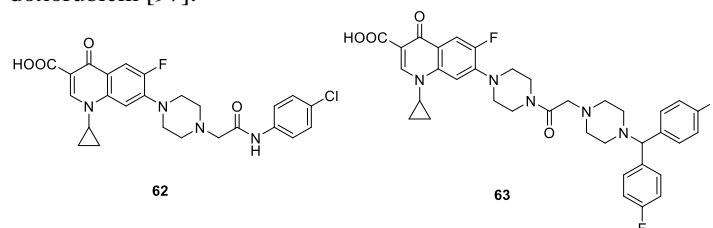
New urea-linked hybrids of ciprofloxacin with chalcone derivatives have been synthesized and investigated for antiproliferative activities, the compounds **61a** and **61b** exhibited significant anticancer activities toward colon HCT-116 and leukemia SR cancer cell lines with IC₅₀ = 2.53, 0.73, 2.01 and 0.64 μM, respectively, compared to camptothecin (IC₅₀, 17.36 and 3.32 μM), topotecan (IC₅₀, 12.23 and 13.72 μM) and staurosporine (IC₅₀, 3.1 and 1.17 μM) according to MTT assay method. Furthermore, the compounds **61a** and **61b** showed Topo I inhibitory activities with inhibition percentage, 51.19% and 56.72%, respectively, compared to camptothecin (inhibition % = 60.05%), as well as Topo IIβ inhibitory activities with inhibition percentage = 60.81% and 60.06%, respectively, compared to topotecan (inhibition % = 71.09%). Furthermore, the compound **61b** display cell cycle arrested against leukemia SR cell line at G₂/M phase, apoptosis induction *via* activation of proteolytic caspases cascade (caspases-3, 8, and 9) and cytochrome C releasing from mitochondria, in addition to upregulation of proapoptotic Bax and down-regulation of Bcl-2 protein level [95].



61

61a, R₁=H, R₂=Cl
61b, R₁, R₂ = OCH₃

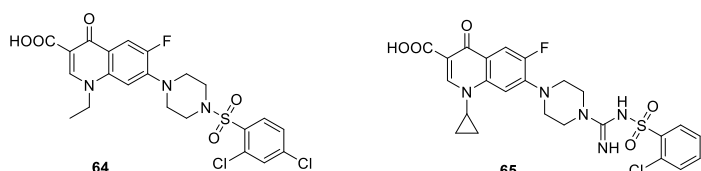
Compound **62** is a hybrid of ciprofloxacin with aryl acetamide at the piperazine *N*-7 site. This hybrid exhibited potent anticancer activities toward non-small cell lung cancer A549, in comparison with the reference drug doxorubicin with IC₅₀ = 14.8 and 1.0 μM, respectively. Besides, cell cycle arrest at the G₂/M phase leading to overexpression of p53/21 and downexpression of Cdc2/B1 proteins [96]. In a similar manner, ciprofloxacin was hybridized with 4-(substituted)piperazin-1-yl acetamide, this analog **63** exhibited antiproliferative activity against (CCRF-CEM) leukemia cancer cell line, (MDA-MB-468) breast adenocarcinoma cell line, and (HCT-116) human colon cancer cell line with activity comparable to stander drug, doxorubicin [97].



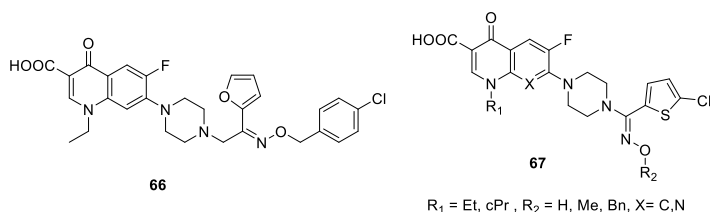
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63

Also, compounds **64**, **65** are hybrids of norfloxacin and ciprofloxacin respectively, with different arylsulfonyl moieties at the N-7 position of quinolones. These analogs exhibited potent anti-proliferative activities; some of these analogs gave activities higher than standard drugs, erlotinib, and 5-fluorouracil. Compound **64** achieved the highest potency in this series with GI₅₀ of 2.30–3.15 μM [98]. Moreover, the ciprofloxacin hybrid **65** exerts potent antitumor activities comparable to the stander drug irinotecan against all the tested cancer cell lines with IC₅₀ ranges: 0.032–0.071 and 0.032–0.044 μM, respectively, in addition to Topo I inhibitory activity [99].



Hybridization of oximes and substituted oximes with norfloxacin and ciprofloxacin has been reported, where the norfloxacin and ciprofloxacin have been linked with oximes derivatives, 2-(furan-2-yl)-2-oxyiminoethyl and 2-(thiophen-2-yl)-2-oxyiminoethyl at N-7 of piperazine group. The synthesized analogs have cytotoxic activities close to or higher than the reference drug, etoposide. Compound **66** is the most active analog in this series where it was showed cytotoxic activities more than etoposide with IC₅₀ range: 1.4– 6.4 and 0.17–19.8 μM, respectively, when investigated against many different cancer cell lines using the MTT assay method [100]. The compounds **67** are also hybrids of quinolone drugs, ciprofloxacin, norfloxacin, and enoxacin with *N*-[2-(5-chlorothiophen-2-yl)-2-oxyiminoethyl] moieties linked at *N*-7 of the quinolone ring. The derivatives **67** exhibited antiproliferative activities higher than the quinolones, ciprofloxacin, norfloxacin, and enoxacin and comparable to Etoposide when the activity was evaluated against six different cancer cell lines using the MTT assay method. The results revealed that this type of hybridization enhanced the cytotoxic activity of the antibacterial quinolones [101].

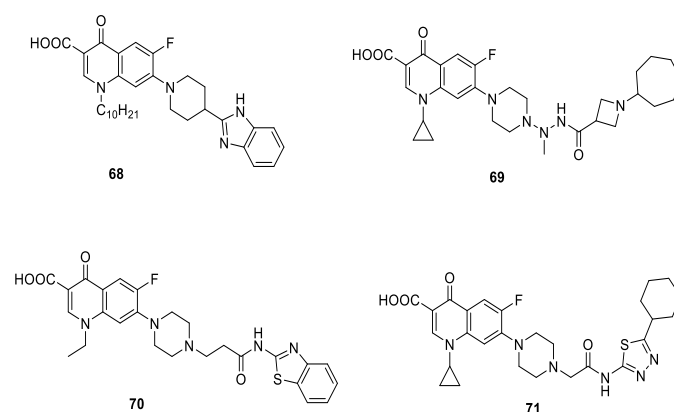


Moreover, the *N*-1-decyl fluoroquinolone derivatives substituted with benzimidazolyl moiety at C-7 position were exhibited *in vitro* antiproliferative activity against human cervical carcinoma (HeLa), human breast carcinoma (MDA-MB-231), human pancreatic carcinoma (MIA PaCa), and human neuroblastoma cell (IMR32). Compound **68** was the most potent one in this series with activity higher than the reference drugs, doxorubicin, and paclitaxel with IC₅₀ 0.01, 0.034, and 0.062 μM, respectively against neuroblastoma IMR-32 cell line [102]. The fluoroquinolone series, substituted with *N*-(substituted azetidino-3-carbonyl)-*N*-methylhydrazino derivatives showed cytotoxic activity toward Breast cancer cell line, MCF-7, Colon cancer cell line, HCT-116, and Lung adenocarcinoma cell line, A549, and some of them exhibited higher activity than

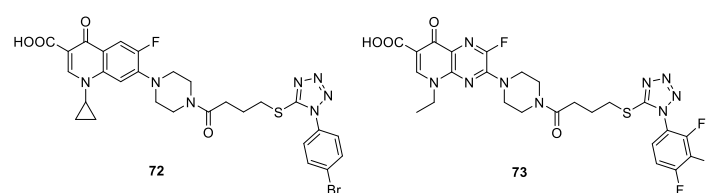
ciprofloxacin and the positive control drug SAHA. Compound **69** exhibited the highest activity among this series against MCF-7 breast cancer cell line with GI% range, 23–56 % at a concentration range 1–50 μM [103].

The norfloxacin analogs substituted at N-7 with benzo[d]thiazolyl moiety through butyramide linker were evaluated for the cytotoxic activities against A549, lung cancer cell line. Compound **70** exhibited the highest activity among these derivatives with GI₅₀ of 28.8 μg/ml [104].

Otherwise, the ciprofloxacin derivatives substituted at the N-7 site with 1,3,4-thiadiazol moiety through acetamide linker does not give the expected cytotoxic activities. Where, compound **71** provides the lowest growth percent, (81 %) against A579, lung cancer cell line [105].

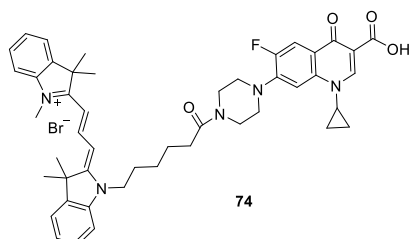


Two series of quinolone analogs were synthesized by the hybridization of ciprofloxacin and pipemidic acid at N-7 position with different tetrazol-5-thiol derivatives. These hybrids exhibited promising *in vitro* antiproliferative activities when investigated against SiHA human cervical cancer cell line, MDA-MB-235 human adenocarcinoma, and PANC-1 pancreatic cancer cell line using the sulforhodamine B (SRB) assay method. Compounds **72** and **73** gave the highest activities among these analogs and higher than the reference, tamoxifen against SiHA and MDA-MB-231 cell lines with GI₅₀ values, 0.07, 0.09, 0.06, 0.08, 0.12, and 0.24 μM, respectively [106].

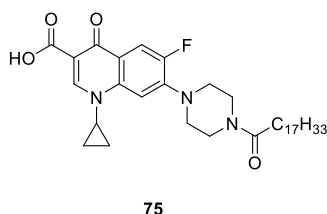


Mitochondria are essential cellular organelle to produce energy in mammalian cells. Generally, the molecules containing hydrophobic and cationic moieties may provide the possibility of mitochondrial targeting due to the negative membrane potential in the mitochondrial matrix. Cy3 is a cationic cyanine dye, commonly used to label molecules for cell fluorescence studies. This dye is relatively small, hydrophobic in nature, and highly delocalized cations. However, Cy3 is a mitochondrion targeting as a single molecule or hybrid and can carry a variety of compounds, such as a peptide, heterocycle, and metal-complex to mitochondria to perform cellular effects. Ciprofloxacin-cyanine dye conjugate was designed and synthesized to increase the uptake of ciprofloxacin to mitochondria in cancer cells, that is meaning, the Cy3 dye acts

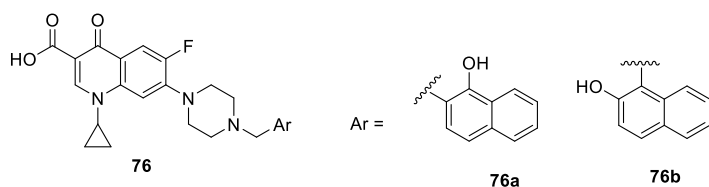
as a carrier for the ciprofloxacin. Moreover, Cy3 hybrids have higher cytotoxic activity against cancer cells than non-cancer cells, due to the higher negative mitochondrial membrane potential in cancer cells than non-cancer cells. The results showed that Cy3-ciprofloxacin hybrid **74** exhibited cytotoxic activities against cancer cell, HeLa, and less activity against the normal cell, HEK with (EC_{50} , 3.9–6.7) mM, respectively, higher than the ciprofloxacin drug (EC_{50} , 1101, 1036 mM) and cyanine dye (EC_{50} , 25.8, 55.3) mM against the same cells [107].



Hybrids of fatty acid with ciprofloxacin derivatives have been designed to increase cellular uptake by cancer cells and improve its bioavailability so, the new hybrid was investigated as anticancer agents. The results of the investigation revealed that the oleic acid conjugate **75** was the most potent one in this series. Hybrid **75** showed antitumor activity (IC_{50} , 7.7 μ M) 12 times higher than for CP alone (IC_{50} , 101.4 μ M) against prostate cancer PC3 and potent apoptosis inducer with high percentage against PC3 cells line in late apoptosis (81.5% \pm 3.9). Besides, compound **75** achieved significant apoptotic activities toward SW480 colon cancer cell line using the MTT assay method [108].

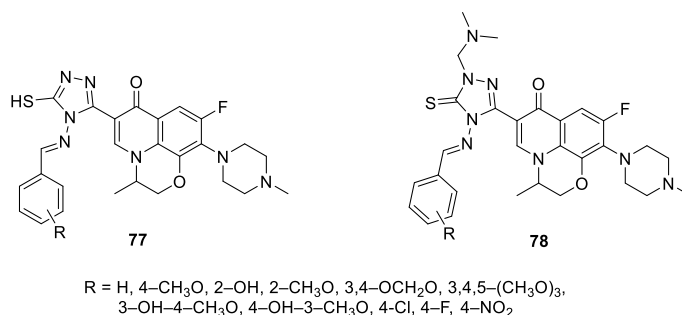


Novel hybrids of ciprofloxacin with a series of different phenolic compounds through Mannich reaction at C-7 of piperazine were synthesized and evaluated for antiproliferative activities. The hybrids **76a** and **76b** among this series exhibited the highest potent antitumor activities. The compound **76a** exhibited a wide range of cytotoxic activities with GI_{50} range, 2.5–6.79 μ M with high selectivity toward renal and prostate cancer cell lines with selectivity range, 0.17 to 6.79. Furthermore, the compound **76a** exhibited anticancer activities against HOP-92 cancer cell line (IC_{50} , 6.66 μ M) while compound **76b** displayed potent activity toward OVCAR-3 ovarian cancer cell line (IC_{50} of 0.97 μ M) using MTT assay method and the reference drug, Doxorubicin with IC_{50} , 0.36 and 0.34 μ M respectively. In addition, the compound **76b** exhibited induction of cell cycle arrest at G2/M phase and apoptosis, as well as, over-expression of caspase-3 protein level (449.2 \pm 7.95) compared to doxorubicin (578.7 \pm 14.4 pg/mL) [109].

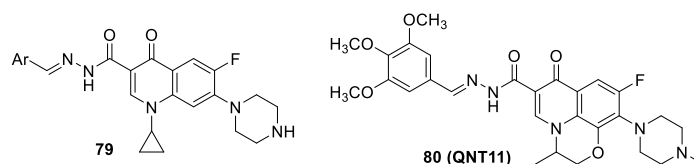


6.2. Modifications of fluoroquinolones at 3-position

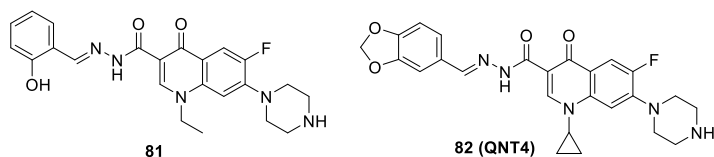
Replacement of the C-3 carboxylic group of fluoroquinolones antibacterial analogs with bioisosteric triazolyl heterocyclic ring is possible for developing novel antitumor analogs [13]. Schiff bases and Schiff–Mannich bases are two series of s-triazole analogs, which were investigated *in vitro* for antitumor activities against L1210 murine leukemia cell line, HL60 human leukemia cell line, and CHO Chinese hamster ovary cell line using the MTT assay methods. The results revealed that compounds **78** exhibited higher anticancer activities (IC_{50} range, 0.14–17.6 μ M) than hydrazone derivatives **77** (IC_{50} range, 10.5–50.2 μ M). Additionally, phenolic moiety-bearing derivatives exhibited the highest activities than the other. Furthermore, the results revealed that the substitution of quinolone carboxylate group with another pharmacophore, hydrazones, or Mannich bases is a promising approach for developing novel anticancer agents.



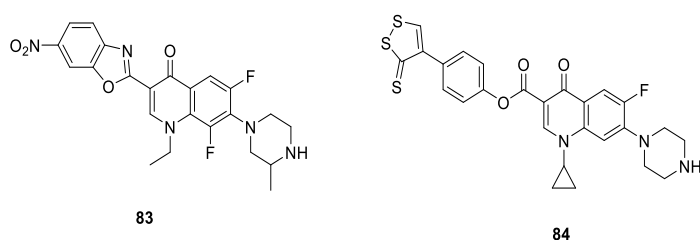
The ciprofloxacin hydrazone derivatives **79** exhibited *in vitro* antitumor activities [110] against Chinese hamster ovary cancer cell line, CHO, human leukemia cancer cell line, HL60, and murine leukemia cell line, L1210 with IC_{50} value within 25.0 mM concentration more active than ciprofloxacin (IC_{50} > 150 mM) using standard MTT assay method. Also, compound **80** QNT11 [111] displayed potent cytotoxic activities toward cancer cell lines, Hep3B, SMMC-7721, MCF-7, and HCT-8 with IC_{50} range, 2.17 - 2.79 mM. Additionally, it showed apoptotic activity associated with mitochondrial dysfunction and regulation of Bcl-2 signaling against Hep3B hepatic cell cancer cell line, as well as QNT11 inhibited topoisomerase II enzyme, regulate of cleaved DNA strands, and induced cell cycle arrest at G2/M phase.



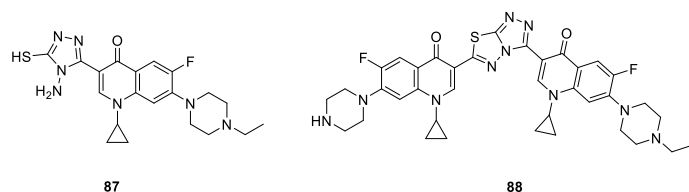
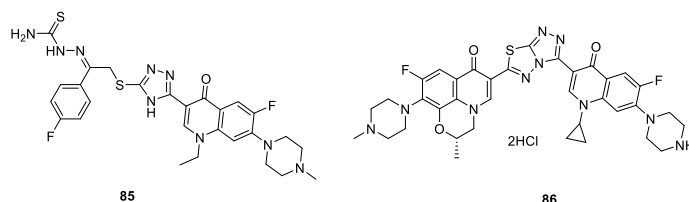
Compound **81** [112] is norfloxacin C3 hydrazone derivatives of Salicylaldehyde that showed the highest anticancer activity with IC_{50} range 8.6–10.3 μ M against human leukemia HL60 cell line, murine L1210 cancer cell line, and CHO tumor cells. That is indicated the ability of such carboxylic modification to improve antitumor activity. In a similar manner to QNT11, compound **82** (QNT4) [113] is a C-3 hydrazone derivative of ciprofloxacin instead of levofloxacin. QNT4 showed antiproliferative activity against SMMC-7721, MCF-7, and HCT-8 cell lines with IC_{50} values 2.956, 3.710, and 3.69 μ mol/L, respectively. QNT4 exhibited apoptotic activity against SMMC-7721 cancer cell line through Topo II inhibiting activity and interfering with mitochondrial-dependent pathways.



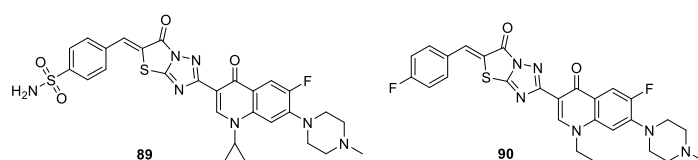
Also, the modification of the carboxyl group of some quinolones derivatives have been reported, many of these analogs gave good cytotoxic activities when investigated against a variety of cancer cell lines, such as (HeLa) cervical adenocarcinoma, (HT-29) colorectal adenocarcinoma, (AGS) gastric adenocarcinoma, (MCF-7 and MDA-MB-261) breast adenocarcinoma, (A549) lung carcinoma, (HepG2 and Hep3B) hepatocarcinoma, (PC-3) prostate adenocarcinoma, (THP-1) acute monocytic leukemia cells, (K562) chronic myelogenous leukemia cells and (U937) acute myeloid leukemia cells. Compound **83** exhibited the highest anticancer activities with IC_{50} range 0.2–0.6 μ M against the used cancer cell lines. This compound exerts its activity through inhibition of Topo I, induction of apoptosis, and stimulation of DNA breaks formation [114]. However, the fluoroquinolones ester analog of 4-(1,2-dithiol-3-thione)-phenol moieties did not give the expected anticancer activity. Only ciprofloxacin analog **84** exhibited moderate activity toward renal cancer cell line 786-0 [115].



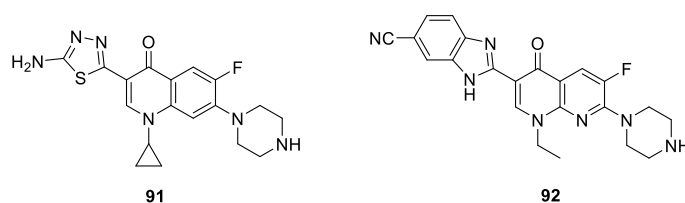
The C-3 group of pefloxacin was modified and replaced by bioisosteric moiety, s-triazole Schiff-base carboxylic acid derivatives. The antiproliferative activities of these derivatives were investigated against (SMMC-7721) hepatocellular carcinoma, (L1210) murine leukemia cancer cell line, and (HL60) human leukemia cell line. The results revealed that the tested compounds possessed anti-proliferative activity more than the parent quinolone, pefloxacin with comparable activity to the control drug, doxorubicin. Compound **85** exhibited the most potent activities among these derivatives against SMMC-7721 cells with IC_{50} ranges 2.7–5.2 μ M. This indicates that using bioisosteric S-triazole moieties as a replacement for the carboxylic moiety is beneficial to improve the anti-proliferative activities of quinolones [116]. Moreover, a series of the fused bis-fluoroquinolones at the C-3 site through [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole was reported and investigated for their antitumor activities against different tumor cell lines, HL60, L1210, and CHO cell lines. The results revealed that the tested compounds showed significant anticancer activities with GI_{50} range, 0.12–26.2 μ M. Compound **86** exhibited the highest activity with GI_{50} range, 0.12–3.4 μ M).¹¹⁷ Similarly, the fused C-3 bis-fluoroquinolones **88** and the parent triazole quinolone **87** were investigated for antitumor activities. Derivatives **87** exhibited moderate activity against L1210 cell line (IC_{50} rang, 0.2–2.5 μ M), whereas the quinolone derivative **88** showed significant antitumor activity with IC_{50} , 0.2 μ M [117].



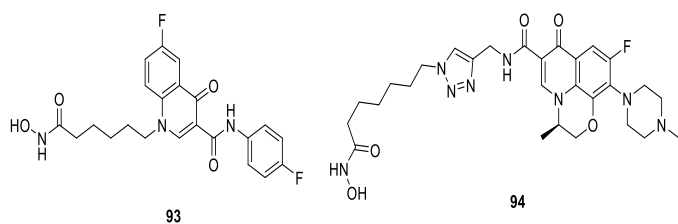
Also, certain a bioisosteric replacement of ciprofloxacin carboxylate moiety with thiazolo-triazolone derivatives have been reported and the antitumor activities have been revealed against leukemia HL60, hepatoma Hep-3B, and pancreatic ductal adenocarcinoma Capan-1 cancer cell lines using MTT assay method. Compound **89** exhibited higher antitumor activities than the reference antitumor drug, doxorubicin with IC_{50} ranges 0.3–1.5 and 1.7–3.5 μ M, respectively) [118]. Meanwhile, the carboxylic group of pefloxacin was replaced with fused thiazolo[2,3-b][1,2,4]triazolone moiety. The *in vitro* antiproliferative activity was achieved when investigated against leukemia HL60 cell line, pancreatic ductal adenocarcinoma Capan-1, and murine (SMMC-7721 and L1210) cell lines. Compound **90** showed the highest activity among these analogs, particularly toward cancer cell lines, Capan-1 (IC_{50} , 2.6 μ M) and SMMC-7721 (IC_{50} , 3.4 μ M) compared to doxorubicin (IC_{50} , 4.8 μ M and 2.8 μ M) respectively [119].



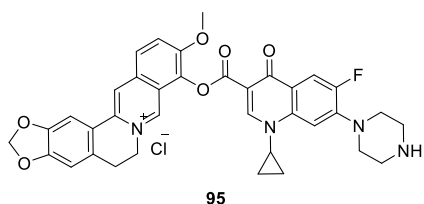
The derivatives with a 5-amino-1,3,4-thiadiazole ring instead of the ciprofloxacin carboxylate group revealed that the compound **91** was exhibited potent anticancer activities against the human hepatocellular carcinoma, Huh-7 with IC_{50} , 25.7 μ M using the MTT assay method [120]. Enoxacin derivatives (LZ-106), **92** were exhibited significant anticancer activities against non-small-cell lung cancer A549 and large cell lung cancer NCI-H460 with IC_{50} , 7.59, and 6.97 μ M, respectively, comparable to, etoposide, with high safety profile. compound **92** mediates a reactive oxygen species leading to DNA damage and apoptosis induction at low concentrations [121].



Histone deacetylase (HDAC) enzymes play an essential role in the proliferation of cancer cells. So, HDAC inhibitors are an attractive approach to developing new antitumor agents against several types of tumor. The promising drugs, vorinostat (SAHA) and romidepsin were approved by FDA as HDAC inhibitors [122,123]. The quinolone analogs **93** are designed as HDAC inhibitors by substitution at N-1 with hydroxamic acid as a zinc-binding group (ZBG) and C-3 position with amide derivatives. The compound **93** showed inhibition activity of HDAC enzyme and antitumor activities against colon cancer cell lines HCT-116, lung cancer cell lines NCI-H460 and glioblastoma cancer cell lines U25 higher than the reference drug, SAHA with IC_{50} 40 and 110 nM, respectively [124]. Also, Levofloxacin was conjugated with HDAC inhibitory acting moiety at C-3 position as a strategy for targeting both HDAC and tubulin polymerization enzymes. These analogs showed potent inhibitory activities of both enzymes when investigated against four different cancer cells, A549, HepG2, PC-3, HeLa, and selective anticancer activity especially against MCF-7 with lower toxicity toward normal cells. Compound **94** showed potent anticancer activities (IC_{50} range, 0.3–4.9 μ M) higher than SAHA drug with (IC_{50} range, 2.9–6.4 μ M). Additionally, it showed HDAC inhibitory activity (IC_{50} range, 0.021–0.041 μ M) comparable to the reference (IC_{50} range, 0.012–0.044 μ M) and tubulin polymerization inhibition activity with (IC_{50} , 1.79 μ M) comparable to the reference drug, colchicine with (IC_{50} , 1.77 μ M) [125].

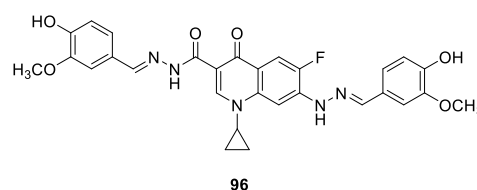


Berberine is a natural isoquinoline alkaloid that possesses antitumor activity against several tumor cell lines with poor bioavailability and moderate therapeutic activity. Therefore, a novel berberine-ciprofloxacin hybrid was designed to improve antiproliferative and apoptosis-inducing activities of the quinolones scaffold. The results revealed that berberine-ciprofloxacin hybrid **95** showed growth inhibitory and apoptosis-inducing activities against different cancer cell lines. The designed compound exhibited significant anticancer activity against leukemia cancer cell line HL-60 with IC_{50} values for 24 and 48 h, are 19.3 and 15.7 μ M, respectively, more potent than references, berberine, and ciprofloxacin with IC_{50} values, (43.7 and 27.1 μ M), and (200 and 142 μ M), respectively for the same experimental periods using MTT assay method. Additionally, it displayed cell cycle arrest at G2/M and S phases [126].

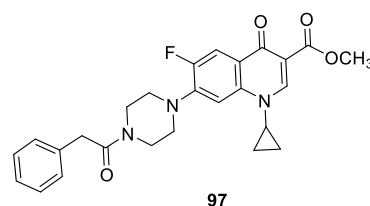


6.3. Modifications of fluoroquinolones at 3 and 7-position

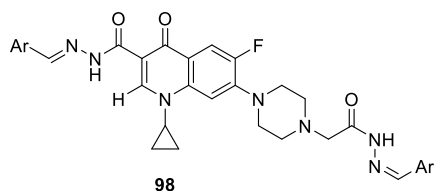
Consequently, some modification includes both C-3 and C-7 sites of the fluoroquinolone, such as compound **96** was functionalized at these positions with hydrazone moieties. Such modifications are greatly improved antitumor activity, where the ciprofloxacin analog **96** exhibited antineoplastic activities toward murine leukemia, L1210, Chinese hamster ovary, CHO, and human leukemia, HL60 cell lines with IC_{50} range of 1.5–2.8 μ M using MTT assay method [110, 127]. These activities were higher potency than that of parent ciprofloxacin, indicating that antitumor activity of fluoroquinolone doesn't have to retain a C-3 carboxyl and a C-7 piperazine ring.



The human tumor cells are different from normal healthy cells by over-expression of thymidine phosphorylase (TP) associated with progression and proliferation of cancer as well as, accumulation of 2-deoxy-D-ribose compound catalyzed by the reaction of thymidine phosphorylase (TP). Both thymidine phosphorylase (TP) and 2-deoxy-D-ribose are responsible for promoting tumor cell angiogenesis. Therefore, developing new thymidine phosphorylase (TP) inhibitors represent a promising method for tumor therapy. New ciprofloxacin derivatives have been synthesized and investigated for inhibitory activity against the thymidine phosphorylase enzyme. Most of the new ciprofloxacin analogs showed good inhibitory activity against thymidine phosphorylase with IC_{50} range, 39.71–161.89 μ M, compared to the reference, 7-deazaxanthine with IC_{50} , 37.82 μ M. Additionally, ciprofloxacin-based inhibitor **97** is the most potent derivative among this series with IC_{50} , 39.71 μ M [128].



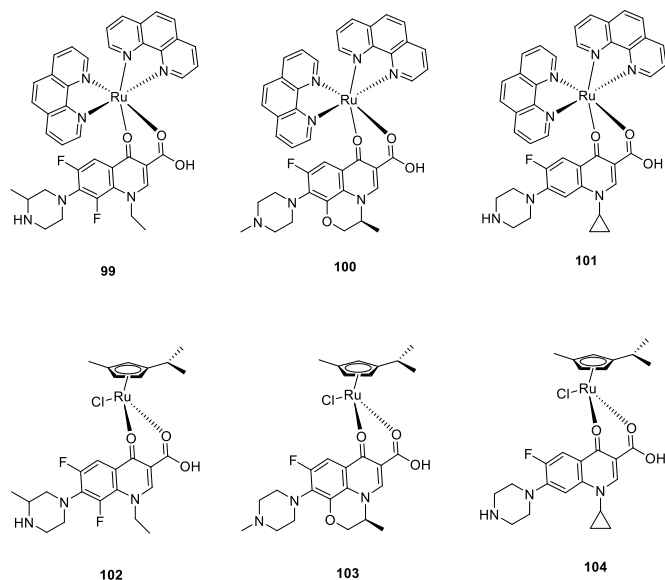
New series of 3,7-bis-benzylidenes derivatives of ciprofloxacin have been synthesized and evaluated for their antitumor activities. The results revealed that most of these compounds exhibited significant antiproliferative activity. Additionally, compounds **98a** and **98c** displayed potent and wide spectrum anticancer activities compared to doxorubicin with IC_{50} of 1.21, 0.87, 1.21; 0.41, 0.57, 1.31 and 1.26, 1.79, 0.63 μ M, respectively against leukemia cancer cell line HL-60 (TB); colon cancer cell line HCT-116 and breast cancer cell line MCF7, respectively using MTT assay method. Moreover, the derivative **98c** induced cell apoptosis at the G2/M phase. In addition to, compounds **98a**, **98b**, and **98c** exhibited promising dual Topo I and II inhibitory activities with IC_{50} , (16.6, 12.1 and 15.1 μ M for Topo I α) and (120.9, 97.3 and 86.5 pg/ml for Topo IIB) comparable to Camptothecin IC_{50} , 10.5 μ M, and Etoposide IC_{50} , 90.6 pg/ml, respectively [129].



- 98a**, Ar = 2-OH-phenyl
98b, Ar = 3,4-di-OCH₃-phenyl
98c, Ar = 3,4,5-tri-OCH₃-phenyl.

6.4. Other strategies of fluoroquinolones modifications

Ruthenium metal complex of 1,10-phenanthroline and *p*-cymene with fluoroquinolone, lomefloxacin, levofloxacin, and ciprofloxacin have been synthesized, characterized, and evaluated for their anticancer activities. The binding studies showed that the complexes have a good binding affinity toward the DNA and BSA due to the planarity phenanthroline rings attached to the metal center capable of intercalating within the DNA base pairs and their hydrophobic nature of (*p*-cymene) moiety that increases the affinities toward BSA. The compounds **99**, **100**, and **101** (phenanthroline) type exhibited cytotoxic activities toward A549 non-small cell lung cancer with IC₅₀, 304, 71.5, 308 μM respectively. Furthermore, the compounds **102**, **103**, and **104** (*p*-cymene) type showed cytotoxic activities against MCF7 cancer cells with IC₅₀, 185, and 222 μM, respectively higher than references NAMI-A and RAPTA, IC₅₀, >1600, 750 μM. The gene expression studies on BAX and BCL-2 genes and FACS analysis presented important evidence on the role of the complexes in triggering apoptosis in cancer cells and revealed the merits of the Ru(II) metal complexes containing fluoroquinolones as potent anticancer agents [130].

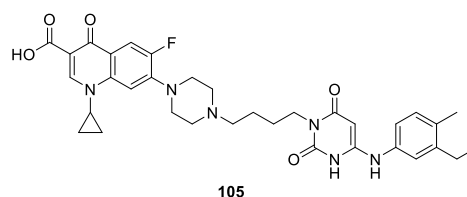


7. Antimicrobial activity

Antibacterial fluoroquinolones are one of the most important antibiotic families and are widely used for the treatment of various infectious diseases. The main problems associated with the therapeutic applications of these drugs are resistance developed by bacterial strains through the development of mutant DNA-binding proteins or efflux pump mechanisms [131]. So, it is necessary for designing and developing new fluoroquinolone derivatives based on some modification of the

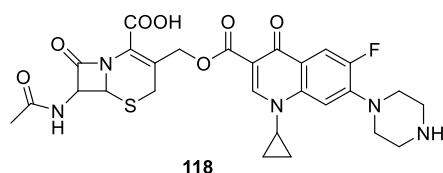
structures at different sites, such as modification at C3-carboxylate moiety, replacing with isosteric groups, and modification of the structures at piperazine moiety. Besides, hybridization of fluoroquinolones with different synthetic or natural molecules having antibacterial activities can enhance the antibacterial activities through increasing the affinity of fluoroquinolones to their binding sites or improving the physicochemical and pharmacokinetic properties to overcome the different mechanisms of bacterial resistance. A multitargeting antibiotic approach is a novel strategy for developing more potent fluoroquinolones antibiotics with a broad spectrum of activity. This new tactic is based on the conjugation of fluoroquinolones with other antibiotic drugs acting through different mechanisms leading to the production of new hybrids characterized by a broad spectrum of activity and low incidence of developing bacterial resistance. For example, hybridization of ciprofloxacin with fidaxomicin antibiotic, the antibacterial activities of the new hybrid were greatly improved against Gram-positive bacteria, as well as the solubility and pharmacokinetic properties of fidaxomicin are greatly enhanced [132]. Another example is the cephalosporin-ciprofloxacin prodrug, this prodrug was selectively activated by β-lactamase producing bacteria and only showed bactericidal activity after activation by a β-lactamase enzyme. This is a new strategy for selective targeting of drug-resistant pathogens without disrupting the host bacteria, reducing the rate of secondary infections and drug side effect, besides, a broad spectrum of activity [133].

It is known that EMAU, 6-(3-ethyl-4-methylanilino) uracil derivatives are a new class of antibacterial agents that exhibited bactericidal activities toward a variety of Gram-positive bacterial species, because of their ability to inhibit polymerase III C enzyme and DNA synthesis. Hence, fluoroquinolones are efficient antibacterial agents against both Gram-positive and Gram-negative bacteria through inhibiting bacterial enzymes, Topo IV, and gyrase. Developing of anilino-uracil-fluoroquinolone (AU-FQ) hybrid, **105** maintained the inhibition activities against DNA polymerase III C in addition to Topoisomerase enzymes. The results indicated that this hybrid exhibited potent activities against *B. subtilis* and DNA polymerase III C (K_i: 0.024 and 0.019 μM) in addition to drug-resistant bacteria with MIC of 0.313–2.5 μg/mL. Additionally, the AU-FQ hybrid displayed antibacterial activity against both anilino-uracil- and fluoroquinolone-resistant strains, such as VREF F118 and MRSA species. Therefore, these hybrids provide a promising approach of multi-targeting drug pharmacophore with a dual-acting mechanism and highly effective antibacterial activities against a variety of species especially, antibiotic-resistant pathogens [134-136].

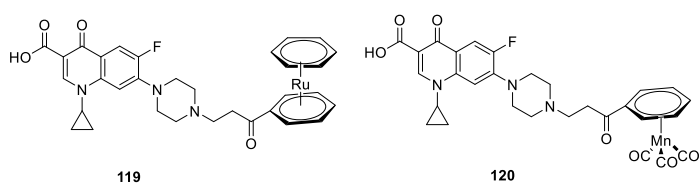


The quinolone-triazole hybrids substituted with different aryl groups were synthesized via microwave-assisted click chemistry technique. The compounds **106**, **107**, and **108** exhibited good antibacterial activities against Gram-positive bacteria, *S. aureus*, and *St. pyogenes* higher than parent drugs, ciprofloxacin, norfloxacin, and pipemidic acid with MIC range, 0.2–0.5 μg/mL. In addition to, antibacterial activities against the Gram-

Novel cephalosporin-ciprofloxacin derivatives have been designed as antibacterial prodrug selectively targeting and activated by β -lactamase producing bacteria. This prodrug **118** showed its antibacterial activities just after hydrolysis occurred by the action of the β -lactamase enzyme therefore it's not observed in strains without β -lactamase. This represents a way for selectively targeting a special type of drug-resistant pathogens without disturbing the host bacteria, reducing the rate of bacterial resistance and subsequent antibiotic use. Prodrug **118** shows growth inhibitory activity similar to ciprofloxacin against uropathogenic *E. coli* expressing the diverse ESBLs CTX-M-1, NDM-1, and KPC but little activity against strains that did not express β -lactamases. The activity of prodrug **118** may be due to an increase in permeability to pathogenic Gram-negative bacteria; β -lactamase mediated intracellular release of ciprofloxacin upon cleavage of the cephalosporin and activation of the prodrug by a broad range of β -lactamases. For example, uropathogenic *E. coli* (UPEC) is a major cause of UTIs and frequently expresses β -lactamase. The prodrug is expected to result in high concentrations of active ciprofloxacin at the site of infection (bladder and kidneys), without disrupting the host microbiota [133].

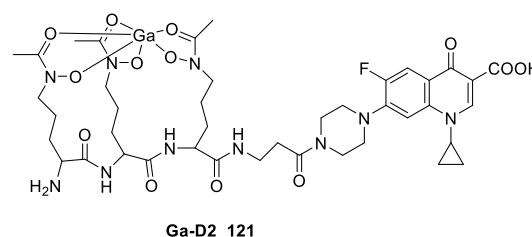


The ciprofloxacin-organometallic conjugates were synthesized and characterized for their biological activity. The antimicrobial results showed that conjugates can significantly enhance the antimicrobial activity through two independent mod of actions; the first mod through inhibition of Topoisomerase enzymes, caused by the action of ciprofloxacin; the second mod, through the initiation of oxygen-reactive molecules produced by the action of the organometallic group. Generally, compounds **119** and **120** exhibited potent antibacterial activities against Gram-negative bacteria, *E. coli* ATCC 25922 (MIC, 0.0006 and 0.0001 μ M) higher than ciprofloxacin (MIC, 0.01 μ M). additionally, compound **120** displayed antibacterial activity against *S. aureus* ATCC 6538 and *K. pneumoniae* ATCC 13883 (MIC, 0.4 and 0.001 μ M respectively), while ciprofloxacin MICs, 0.8, 0.05 μ M, respectively [146].

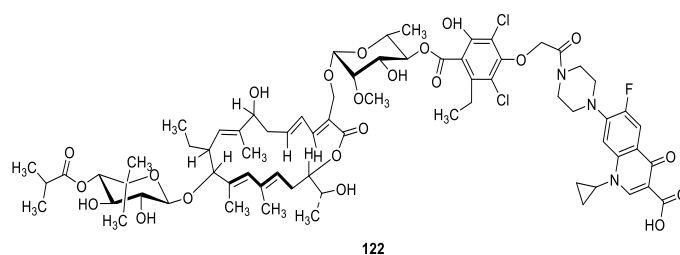


Novel gallium (III) complex of ciprofloxacin-functionalized desferrichrome (D2) as siderophore-mediated transport was designed and developed as a potential therapeutic for bacterial infection as an effective strategy for targeting the bacterial perior cytoplasm and improving the transportation of wide-spectrum antibiotics to their targets and subsequently, enhancing the antimicrobial activity. The results showed that Ga-D2 **121** exhibited antibacterial activities against *Escherichia coli* with MIC, 0.23 μ M while ciprofloxacin MIC, 0.23 μ M. Also, the Ga-D2 exhibited potent antibacterial activities against other bacterial strains, *S. aureus*, *P. aeruginosa*, and *K. pneumoniae* with MIC, 1.9, 3.8, and 12.5 μ M, respectively using

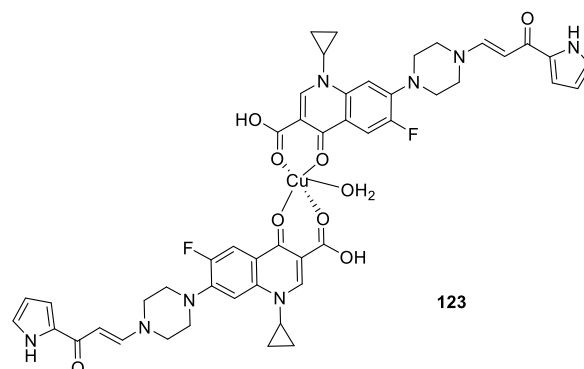
ciprofloxacin as reference drug with MIC, 1.9, 0.94, and 3.12 respectively [147].



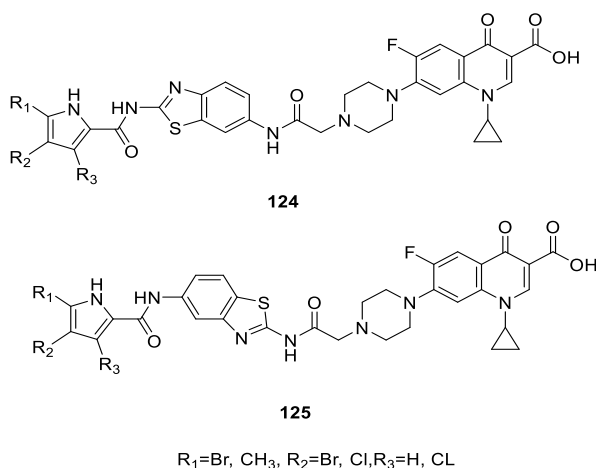
The glycosylated macrocyclic antibiotic fidaxomicin displayed good to excellent *in vitro* antibacterial activity against many Gram-positive bacteria with MIC range, 0.012 - 0.25 μ g/mL and especially against *Clostridium difficile* strain, otherwise not used for the treatment of systemic infections due to the low water solubility and its poor systemic absorption. The semisynthetic fidaxomicin-ciprofloxacin hybrid was developed to improved antibiotic activities of ciprofloxacin against Gram-positive bacteria and pharmacokinetic proprieties of fidaxomicin and subsequent availability for systemic treatment. The hybrid **122** exhibited excellent activity against all *C. difficile* strains with MIC range, 0.015 - 0.12 μ g/mL more than ciprofloxacin itself (MIC, 16 μ g/mL) [132].



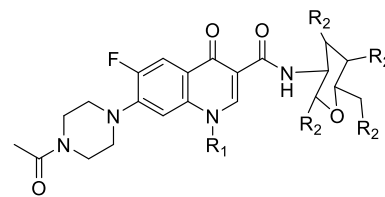
Copper (II) complexes of the ciprofloxacin-Enaminones hybrid were synthesized and investigated for their antibacterial activities against a series of *S. aureus*, *E. coli*, *K. pneumoniae*, and ESBL positive *K. pneumoniae*, species. The copper complex of modified quinolones was expected to enhance the antibacterial activity of the quinolone due to six transition metal complexes. The results showed that all synthesized hybrids are sensitive against the tested organism, and some of them are exhibited activity higher than the parent drug, ciprofloxacin. The compound **123** was the potent compound in this series and displayed antimicrobial activities against *S. aureus*, *E. coli*, and *K. pneumoniae* with inhibition zone, 37, 40, and 11mm respectively higher than ciprofloxacin with inhibition zone, 21mm for all organism using Kirby-Bauer disk diffusion method [148].



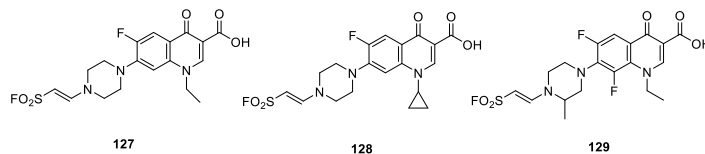
Fluoroquinolones exert their antibacterial activities through targeting the GyrA subunit of a heterodimeric A2B2 enzyme and are widely used as a therapy against several types of Gram-positive and Gram-negative infections. DNA gyrase B inhibitor-ciprofloxacin hybrids were developed as an antibacterial agent against *Escherichia coli* through binding to both site of the *E. coli* GyrA and GyrB subunits, that facilitating the entry of nonpermeating GyrB inhibitors into bacteria by conjugation with ciprofloxacin, a highly permeable GyrA inhibitor, leading to a strong antibacterial activity and slowly development of bacterial resistance. The DNA gyrase supercoiling assay results showed weak inhibitory activity of the hybrids **124** and **125** against *E. coli* DNA gyrase with IC₅₀ range, 0.17 - 6.2 μM than by the GyrB inhibitors, IC₅₀ range, 9 - 66 nM and very close to the GyrA inhibitor, ciprofloxacin IC₅₀, 0.2μM. Also, the two hybrids **124** and **125** exhibited antibacterial activity against the *E. coli* strains ATCC 25922 and K-12 MG1655 in the presence of the efflux pump inhibitor PaβN with MIC range, 130-439 ng/mL (Ciprofloxacin MIC, 4.4 ng/mL) and MIC range, 1481 - 3333 ng/mL in the absence of PaβN, (Ciprofloxacin, MIC, 6.6 ng/mL) for the same strains, which indicated that the hybrids **124** and **125** are not intensively effluxed in *E. coli* strains [149].



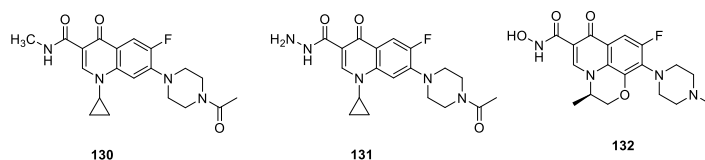
Novel glycosylated-fluoroquinolones, hybrids of ciprofloxacin, norfloxacin, and moxifloxacin coupled with a glucosamine moiety at the C-3 position of fluoroquinolones were developed and evaluated for antimicrobial activity. Glucosamine moiety is a carbohydrate analog of N-Acetyl Glucosamine (NAG), one of the bacterial cell-wall constituents which act as a carrier of the fluoroquinolones in this prodrug conjugate, to enhance the selective uptake of fluoroquinolones into the microbial cells, hence enhancing the selectivity, potency and lowering cytotoxicity of the fluoroquinolone drugs. The results of the *In vitro* antimicrobial activities showed that the hybrids **126a**, **126b**, and **126c** exhibited potential antimicrobial activity against fluoroquinolone-resistant *Escherichia coli* with MIC values, 0.2668, 0.1358, and 0.0898 μM, respectively, compared to ciprofloxacin (MIC 0.5098 μM) and norfloxacin (MIC 0.2937 μM) standard drugs. Furthermore, the compound **126b** also exerted a potential antifungal activity against *Candida albicans* and *Penicillium chrysogenum* with MIC values, 0.0056 and 0.0453 μM respectively compared to the stander drug, Fluconazole (MICs, 0.4081 and 0.2041 μM respectively) [150].

**126****126a**, R₁ = Cyclopropyl, R₂ = OAc**126b**, R₁ = Ethyl, R₂ = OAc**126c**, R₁ = Ethyl, R₂ = OH

The fluoroquinolones, norfloxacin, ciprofloxacin, and lomefloxacin have been functionally coupled at C-7 position with fluorosulfonylvinyl (enaminy sulfonyl fluorides) moiety. The new hybrids have been investigated for their antibacterial activities against Gram-positive and Gram-negative bacteria in addition to, fungi. The compound **127** exhibited potent antibacterial activities against many different bacterial organisms including *S. aureus*, *MRSA*, *P. aeruginosa* and *E. coli* species with (MIC = 1.56, 0.78, 0.39 and 6.25 μM), while compound **128** (MIC = 0.39, 0.39, 0.19 and 6.25 μM) and compound **129** (MIC = 0.78, 0.78, 0.78 and 50.00 μM) against the same organisms, using reference drugs, norfloxacin (MIC = 3.12, 3.12, 0.78 and 3.12μM), ciprofloxacin (MIC = 1.56, 0.78, 0.19 and 0.78 μM) and lomefloxacin (MIC = 3.12, 3.12, 0.39 and 6.25 μM) respectively [151].



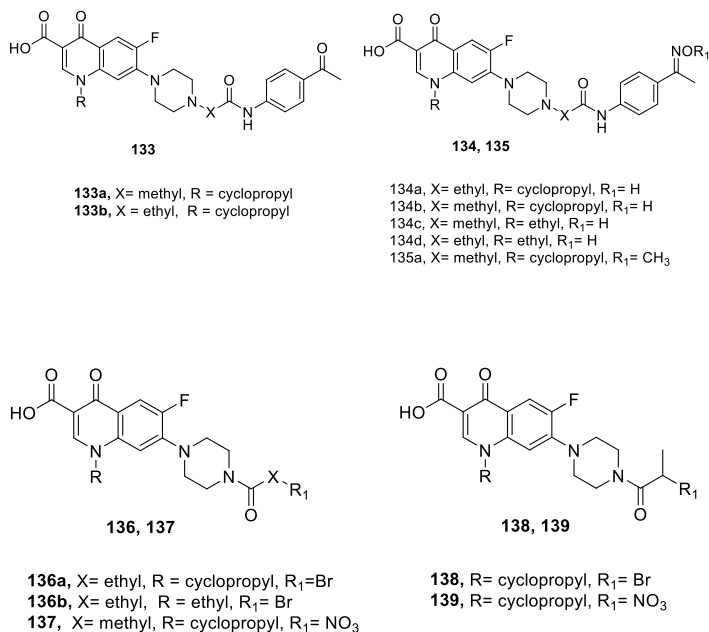
New fluoroquinolone hybrids, ciprofloxacin, and levofloxacin with hydroxamic acid, hydrazide, and amide at C3, carboxylic moiety, were synthesized and evaluated for antibacterial activities against urease splitting bacteria, *Proteus mirabilis*. The urease inhibitory activities were estimated using the indophenol method. The results revealed that the compounds **130**, **131**, and **132** showed significant inhibitory activities against *Proteus mirabilis* species with IC₅₀, 1.29, 1.22, and 2.20 μM, respectively higher than the reference *N*-acetyl ciprofloxacin (IC₅₀, 2.26 μM) [152].



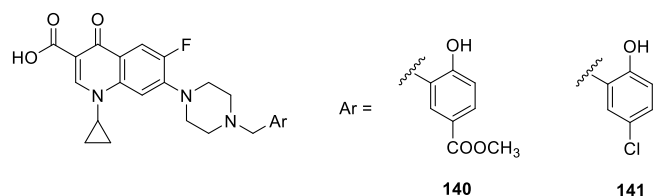
The drugs, ciprofloxacin, and norfloxacin were hybridized with some derivatives of ketones and its nitric oxide-releasing oximes, as well as evaluated for antibacterial activities against a variety of different species of bacterial organisms includes *M. tuberculosis H37Rv*, *S. aureus*, *E. coli* (ATCC 8739), *B. cereus* (AUMC No B-52), *M. luteus* (AUMC No B-112), *K. pneumoniae* (AUMC No B-77), *P. aeruginosa* (AUMC No B-73), and *S. marcescens* (AUMC No B-54) using standard agar cup diffusion method. The results showed that the hybrids, **133a** and **134a**

exhibited antibacterial activities against *M. tuberculosis* species with MIC, 1.5 μM higher than the reference fluoroquinolones, ciprofloxacin, and norfloxacin MIC, 2.4, 9.8 μM respectively. Besides, the compounds **134b-d** showed activities against *Klebsiella pneumonia* (MIC, 0.06, 0.08, and 0.034 μM , respectively) more potent than norfloxacin, MIC, 0.5 μM . Furthermore, the compounds, **133b**, and **135a** exhibited antibacterial activities against Gram-positive species, *Staphylococcus aureus* (MIC, 0.7 and 0.38, respectively), higher than ciprofloxacin MIC, 1.6 μM [153].

The new hybrids of fluoroquinolones-nitrate esters have been synthesized and investigated for (NO) releasing activities using the modified Griess colorimetric method and antibacterial activities against *M. tuberculosis H37Rv* strain. The results revealed that the compounds **136a**, **136b**, **137**, **138**, and **139** exhibited antitubercular activities with (MIC, 1.7, 1.4, 1.8, 1.7, and 1.7 mM respectively) higher than the parent drug, ciprofloxacin (MIC, 2.4 mM). As well as these compounds display DNA cleavage stimulation activities against mycobacteria species but less than parent ciprofloxacin. The growth inhibitory activities of these hybrids may be due to gyrase poisoning activities or NO-releasing effect [154].



New Mannich base hybrids of ciprofloxacin with a series of phenolic compounds have been synthesized and investigated for antibacterial activities against different species of bacterial strains, *MRSA (reference strain)*, *MRSA (clinical strain)*, *S. aureus*, *K. pneumonia*, *E. coli*, and *P. aeruginosa* using standard agar plates method. The hybrids, **140** exhibited high antibacterial activities against *E. coli* and *P. aeruginosa* species with MIC, 0.036 and 0.043 $\mu\text{g/mL}$, respectively. While compound **141** displays potent activities against *S. aureus* and *MRSA (reference strain)* with MIC, 0.061 and 0.066 $\mu\text{g/mL}$, respectively, higher than reference drug, ciprofloxacin with MIC, 1.6 and 1.5 $\mu\text{g/mL}$, respectively [109].



8. Conclusion

Drug repositioning is the redirection of the drug from its original medical indication to another, based on two approaches “On-Target” meaning that a known drug target is involved in other diseases and “Off-Target” meaning that the drug target differs from the known target [19,155]. These studies have two possibilities, the drug targeting a protein, that could be participated in the manifestation of more than one disease or a drug binds to many proteins. The first one can be more useful since a single drug can be used for treating multiple diseases this known as a multitargeting drug. While the second is not useful due to severe side effects [156]. The current review summarizes the new strategies of multitargeting and repositioning of fluoroquinolones from antibacterial to antitumor activities as well as the new strategies for developing new antibacterial fluoroquinolones with improved properties. Fluoroquinolones exert their anticancer activities *via* inhibition of mammalian DNA Topoisomerases type II. Different Fluoroquinolones structural modifications and hybridization have been reported to convert the antibacterial Fluoroquinolones to antitumor analogs. Most of these modification strategies were at position 7 related to piperazine moiety, carboxylate group at position 3, or modification at both sites as well as other strategies may be involved such as metal complexation. These modifications were greatly affecting the inhibition of Topoisomerase enzymes, physicochemical properties, and pharmacokinetics of the newly developed analogs, in addition to decreasing the zwitter ion nature and increasing the lipophilicity that participates in the improvement of fluoroquinolone properties. For example, compounds **61a, b** are linked urea-hybrids of ciprofloxacin with chalcone derivatives at position-7. These hybrids displayed antiproliferative activities against colon HCT-116, leukemia SR cancer cell lines, Topo I and Topo II β inhibitory activities higher than reference drugs, camptothecin, topotecan, and staurosporine. As well as cell cycle arrested against leukemia SR cell line at G2/M phase and apoptosis induction [95]. Another multitarget Fluoroquinolones is compound **94**, a levofloxacin hybrid with HDAC inhibitory acting moiety at C-3 position as a strategy for targeting both histone deacetylase (HDAC) and tubulin polymerization, in addition to Topoisomerase enzymes. Compound **94** showed anticancer activities higher than the reference drug, SAHA against MCF-7, HDAC inhibitory activity, and inhibitory activity against tubulin polymerization comparable to a drug, colchicine [125]. Compounds **98a-c** are 3,7-bis-benzylidenes hybrids of ciprofloxacin. These hybrids exhibited potent antiproliferative activity comparable to Doxorubicin against leukemia cancer cell line HL-60 (TB) colon cancer cell line HCT-116, breast cancer cell line MCF7, and induced apoptosis at G2/M phase, as well as exhibited promising dual Topo I α and Topo IIB inhibition activities comparable to reference drugs Camptothecin and Etoposide [129].

New strategies for developing new antibacterial fluoroquinolones analogs are necessary to improve the antibacterial activities of fluoroquinolones against different species of organism, including Gram-positive, Gram-negative, aerobic, and anaerobic bacteria. Besides, these modifications can overcome the developed bacterial resistance and enhance the pharmacokinetic properties of new fluoroquinolones analogs. Multi targets fluoroquinolones, compound **105** is a hybrid of fluoroquinolone with uracil derivatives and it was designed to targeting DNA polymerase IIIc, Topoisomerase IV,

and gyrase enzymes. It was showed potent antibacterial against *B. subtilis* and DNA polymerase III C inhibitory activities. In addition to excellent activity against various drug-resistant bacteria, such as, VREF F118 (linezolid-resistant) and MRSA B42876 [134-136]. Compounds **119** and **120** are ciprofloxacin-organometallic conjugates, the antimicrobial activities were significantly enhanced due to two independent antibacterial mechanisms of action, bacterial Topoisomerase inhibitory activity and generation of reactive oxygen species caused by the organometallic moiety. The antibacterial activities of these hybrids were greatly enhanced against the *E. coli* ATCC 25922, *S. aureus* ATCC 6538, and *K. pneumonia* ATCC 13883 than the parent drug, ciprofloxacin [146]. Glycosylated-fluoroquinolones, hybrids **126a-c** were designed as a prodrug by coupling with a sugar part, glucosamine moiety at fluoroquinolones C-3 position to increase the uptake of fluoroquinolones into the microbial cells, hence enhancing the selectivity, potency and lowering fluoroquinolones side effects. So, significant antimicrobial activities against fluoroquinolone-resistant *Escherichia coli*, *Candida albicans*, and *Penicillium chrysogenum* have been reported [150]. From all previously discussed data, the researchers become more interested in developing new more safe anticancer agents and look for optimal antibiotics based on fluoroquinolones scaffold.

References

- [1] M. I. Andersson and A. P. MacGowan, *J. Antimicrob. Chemother.*, 2003, **51**, 1.
- [2] G. S. Bisacchi, *J. Med. Chem.*, 2015, **58**, 4874.
- [3] K. Grohe, in *Quinolone antibacterials*, Springer, 1998, pp. 13.
- [4] V. T. Andriole, *Clin. Infect. Dis.*, 2005, **41**, S113.
- [5] T. D. Pham, Z. M. Ziora and M. A. Blaskovich, *Medchemcomm*, 2019, **10**, 1719.
- [6] X. Guo, M. L. Liu, H. Y. Guo, Y. C. Wang and J. X. Wang, *Molecules*, 2011, **16**, 2626.
- [7] M. Asif, *Int. J. Pharm. Chem.*, 2013, **2**, 110.
- [8] R. J. O'Brien, Nunn, Paul P, *Am. J. Respir. Crit. Care Med*, 2001, **163**, 1055.
- [9] K. Soni, *Indo glob. j. pharm. sci.*, 2012, **2**, 43.
- [10] S. C. Ozdek, D. Miller, P. M. Flynn and H. W. Flynn Jr, *Ocul Immunol Inflamm.*, 2006, **14**, 347.
- [11] S. Srinivasan, R. M. B. Shafreen, P. Nithyanand, P. Manisankar and S. K. Pandian, *Eur. J. Med. Chem.*, 2010, **45**, 6101.
- [12] M. V. de Almeida, M. F. Saraiva, M. V. de Souza, C. F. da Costa, F. R. Vicente and M. C. Lourenço, *Bioorganic Med. Chem. Lett.*, 2007, **17**, 5661.
- [13] G. Hu, G. Wang, N. Duan, X. Wen, T. Cao, S. Xie and W. Huang, *Acta Pharm. Sin. B*, 2012, **2**, 312.
- [14] M. Abdel-Aziz, S.-E. Park, G. E.-D. A. Abu-Rahma, M. A. Sayed and Y. Kwon, *Eur. J. Med. Chem.*, 2013, **69**, 427.
- [15] R. H. Advani, H. I. Hurwitz, M. S. Gordon, S. W. Ebbinghaus, D. S. Mendelson, H. A. Wakelee, U. Hoch, J. A. Silverman, N. A. Havrilla and C. J. Berman, *Clin. Cancer Res.*, 2010, **16**, 2167.
- [16] M. Daneshmand and A. Ahmed, *J. Pharm. Pharm.*, 2012, **15**, 52.
- [17] J. Li, S. Li, C. Bai, H. Liu and P. Gramatica, *J. Mol. Graph.*, 2013, **44**, 266.
- [18] M. Pudlo, V. Luzet, L. Ismaïli, I. Tomassoli, A. Iutzeler and B. Refouvelet, *Bioorg Med Chem*, 2014, **22**, 2496.
- [19] V. Yadav and P. Talwar, *Biomed. Pharmacother.*, 2019, **111**, 934.
- [20] S. Emami, A. Shafiei and A. Foroumadi, *IJPR.*, 2005, **3**, 123.
- [21] F. Van Bambeke, J.-M. Michot, J. Van Eldere and P. M. Tulkens, *Clin. Microbiol. Infect.*, 2005, **11**, 256.
- [22] P. Ball, *Int. J. Clin. Pract.*, 2000, **54**, 329.
- [23] Y.-L. Fan, J.-B. Wu, X.-W. Cheng, F.-Z. Zhang and L.-S. Feng, *Eur. J. Med. Chem.*, 2018, **146**, 554.
- [24] M. Koba, T. Bączek, K. Macur, L. Bober, T. Frąckowiak, A. Bucziński, D. Rystok-Grabska, J. Stasiak and K. Koba, *J. Mol. Model*, 2010, **16**, 327.
- [25] J. M. Blondeau, *Surv. Ophthalmol.*, 2004, **49**, S73.
- [26] G. Sarkozy, *Vet Med (Praha)*, 2001, **46**, 257.
- [27] P. Ball, *J. Antimicrob. Chemother.*, 2000, **46**, 17.
- [28] S.-H. Choi, E. Y. Kim and Y.-J. Kim, *Clin Exp Pediatr*, 2013, **56**, 196.
- [29] L. M. Pallo-Zimmerman, J. K. Byron and T. K. Graves, *Compend Contin Educ Vet*, 2010, **32**, E1.
- [30] K. Naber and D. Adam, *Int. J. Antimicrob. Agents*, 1998, **10**, 255.
- [31] S. V. Scoper, *Adv. Ther.*, 2008, **25**, 979.
- [32] G.-F. Zhang, S. Zhang, B. Pan, X. Liu and L.-S. Feng, *Eur. J. Med. Chem.*, 2018, **143**, 710.
- [33] W. M. Scheld, *Emerg. Infect. Dis.*, 2003, **9**, 1.
- [34] A. Markham, *J. Drug*, 2017, **77**, 1481.
- [35] E. R. Ocheretyaner and T. E. Park, *Expert Rev Anti Infect Ther*, 2018, **16**, 523.
- [36] R. Tirupathi, S. Areti, S. A. Salim, V. Palabindala and N. Jonnalagadda, *J. Community Hosp. Intern. Med. Perspect.*, 2019, **9**, 310.
- [37] K. E. Brighty and T. D. Gootz, in *The quinolones*, Elsevier, 2000, pp. 33.
- [38] P. Lucia, in *Antimicrobial Agents*, IntechOpen, 2012.
- [39] R. G. Gould and W. A. Jacobs, *J. Am. Chem. Soc.*, 1939, **61**, 2890.
- [40] J.-C. Brouet, S. Gu, N. P. Peet and J. D. Williams, *Synth. Commun*, 2009, **39**, 1563.
- [41] J. J. Li, in *Name Reactions*, Springer, 2014, pp. 104.
- [42] E. M. Sales and J. D. Figueroa-Villar, *World J Pharm Pharm Sci*, 2016, **5**, 253.
- [43] M. Pesson, *Eur. J. Med. Chem*, 1974, **9**, 585.
- [44] P. Forterre, in *DNA Topoisomerases and Cancer*, Springer, 2012, pp. 1.
- [45] C. R. Barker, A. V. McNamara, S. A. Rackstraw, D. E. Nelson, M. R. White, A. J. Watson and J. R. Jenkins, *Nucleic Acids Res.*, 2006, **34**, 1148.
- [46] V. Visone, A. Vettore, M. Serpe, A. Valenti, G. Perugino, M. Rossi and M. Ciaramella, *Int. J. Mol. Sci*, 2014, **15**, 17162.
- [47] S. H. Chen, N.-L. Chan and T.-s. Hsieh, *Annu. Rev. Biochem.*, 2013, **82**, 139.
- [48] J. C. Wang, *Nat. Rev. Mol. Cell Biol.*, 2002, **3**, 430.
- [49] J. J. Champoux, *Annu. Rev. Biochem.*, 2001, **70**, 369.
- [50] Y. Yamashita, T. Ashizawa, M. Morimoto, J. Hosomi and H. Nakano, *Cancer Res.*, 1992, **52**, 2818.
- [51] J. J. Clement, N. Burren, K. Jarvis, D. T. Chu, J. Swinarski and J. Alder, *Cancer Res.*, 1995, **55**, 830.
- [52] A. Ryckebusch, D. Garcin, A. Lansiaux, J.-F. Goossens, B. Baldeyrou, R. Houssin, C. Bailly and J.-P. Hélichart, *J. Med. Chem.*, 2008, **51**, 3617.
- [53] M. Asif, *Ann Med Chem Res*, 2014, **1**, 1.
- [54] A. G. Golub, O. Y. Yakovenko, V. G. Bdzholia, V. M. Sapelkin, P. Zien and S. M. Yarmoluk, *J. Med. Chem.*, 2006, **49**, 6443.
- [55] S. Sha, H.-W. Han, F. Gao, T.-B. Liu, Z. Li, C. Xu, W.-Q. Zhong and H.-L. Zhu, *Medchemcomm*, 2015, **6**, 2029.
- [56] Q. Shi, K. Chen, S. L. Morris-Natschke and K.-H. Lee, *Curr. Pharm. Des*, 1998, **4**, 219.
- [57] O. Aranha, R. Grignon, N. Fernandes, T. J. McDonnell, D. P. Wood and F. H. Sarkar, *Int. J. Oncol.*, 2003, **22**, 787.
- [58] L. F. Liu, S. D. Desai, T. K. Li, Y. Mao, M. Sun and S. P. SIM, *Ann. N. Y. Acad. Sci.*, 2000, **922**, 1.
- [59] W. Endo, C. Wrzosek, K. Haridas, P. Seetharamulu, F. Hausheer and Y. Rustum, *Eur. J. Cancer*, 1999, **35**, 984.
- [60] S. Alper, Ö. T. Arpacı, E. Ş. Aki and I. Yalçın, *FARMACO*, 2003, **58**, 497.
- [61] H. Mizutani, S. Tada-Oikawa, Y. Hiraku, M. Kojima and S. Kawanishi, *Life Sci.*, 2005, **76**, 1439.
- [62] C. Sissi and M. Palumbo, *Curr Med Chem Anticancer Agents*, 2003, **3**, 439.
- [63] J. M. Domagala, L. D. Hanna, C. L. Heifetz, M. P. Hutt, T. F. Mich, J. P. Sanchez and M. Solomon, *J. Med. Chem.*, 1986, **29**, 394.
- [64] M. Atanasova, S. Ilieva and B. Galabov, *Eur J Med Chem*, 2007, **42**, 1184.
- [65] W. E. Kohlbrenner, N. Wideburg, D. Weigl, A. Saldivar and D. T. Chu, *Antimicrob Agents Chemother*, 1992, **36**, 81.
- [66] E. Benfenati, A. A. Toropov, A. P. Toropova, A. Manganaro and R. Gonella Diaza, *Chem Biol Drug Des*, 2011, **77**, 471.
- [67] M. J. Robinson, B. A. Martin, T. D. Gootz, P. R. McGuirk, M. Moynihan, J. A. Sutcliffe and N. Osheroff, *J Biol Chem*, 1991, **266**, 14585.
- [68] M. P. Wentland, G. Y. Leshner, M. Reuman, M. D. Gruett, B. Singh, S. C. Aldous, P. H. Dorff, J. B. Rake and S. A. Coughlin, *J Med Chem*, 1993, **36**, 2801.
- [69] M. A. Eissenstat, G.-H. Kuo, J. D. Weaver III, M. P. Wentland, R. G. Robinson, K. M. Klingbeil, D. W. Danz, T. H. Corbett and S. A. Coughlin, *Bioorganic Med. Chem. Lett.*, 1995, **5**, 1021.
- [70] M.-C. Fan, G.-Y. Han, X.-J. Zhang and H.-F. Xi, *Bangladesh J. Pharmacol.*, 2015, **10**, 308.
- [71] H. Arakawa, E. Mano, N. Hakoda, T. Yoshinari, S. Nakagawa and A. Okura, *Anticancer Drug Des*, 1996, **11**, 221.
- [72] B. Llorente, F. Leclerc and R. Cedergren, *Bioorg. Med. Chem*, 1996, **4**, 61.
- [73] D. K. Yadav, R. Rai, N. Kumar, S. Singh, S. Misra, P. Sharma, P. Shaw, H. Pérez-Sánchez, R. L. Mancera and E. H. Choi, *Sci. Rep.*, 2016, **6**, 1.
- [74] F. L. Allovero, X.-S. Pan, J. E. Morris, R. H. Manzo and L. M. Fisher, *Antimicrob Agents Chemother*, 2000, **44**, 320.
- [75] T. Gootz, P. McGuirk, M. Moynihan and S. Haskell, *Antimicrob Agents Chemother*, 1994, **38**, 130.
- [76] L. L. Shen, J. Baranowski and A. G. Pernet, *J. Biochem.*, 1989, **28**, 3879.

- [77] C. H. Freudenreich and K. N. Kreuzer, *Proc Natl Acad Sci U S A*, 1994, **91**, 11007.
- [78] S. H. Elsea, P. R. McGuirk, T. D. Gootz, M. Moynihan and N. Osheroff, *Antimicrob Agents Chemother*, 1993, **37**, 2179.
- [79] M. J. Robinson, B. A. Martin, T. D. Gootz, P. R. McGuirk and N. Osheroff, *Antimicrob Agents Chemother*, 1992, **36**, 751.
- [80] D. C. Hooper, *Emerg. Infect. Dis.*, 2001, **7**, 337.
- [81] M. Nagarajan, A. Morrell, B. C. Fort, M. R. Meckley, S. Antony, G. Kohlhagen, Y. Pommier and M. Cushman, *J. Med. Chem.*, 2004, **47**, 5651.
- [82] J. A. Spicer, G. J. Finlay, B. C. Baguley, L. Veale, D. E. Graves and W. A. Denny, *Anticancer Drug Des*, 1999, **14**, 37.
- [83] H. Hentze, M. Latta, G. Künstle, S. Dhakshinamoorthy, P. Y. Ng, A. G. Porter and A. Wendel, *Hepatology*, 2004, **39**, 1311.
- [84] N. Lebedeva, N. Rechkunova, S. Boiteux and O. Lavrik, *IUBMB Life*, 2008, **60**, 130.
- [85] D. Chu, R. Hallas, S. Tanaka, J. Alder, D. Balli and J. Plattner, *Drugs Exp Clin Res*, 1994, **20**, 177.
- [86] G. S. Bisacchi and M. R. Hale, *Curr. Med. Chem*, 2016, **23**, 520.
- [87] X.-D. Jia, S. Wang, M.-H. Wang, M.-L. Liu, G.-M. Xia, X.-J. Liu, Y. Chai and H.-W. He, *Chin Chem Lett*, 2017, **28**, 235.
- [88] G. C. Jamieson, J. A. Fox, M. Poi and S. A. Strickland, *J. Drug*, 2016, **76**, 1245.
- [89] T. Kloskowski, N. Gurtowska, M. Nowak, R. Joachimski, A. Bajek, J. Olkowska and T. Drewna, *Acta Pol Pharm*, 2011, **68**, 859.
- [90] C. Herold, M. Ocker, M. Ganslmayer, H. Gerauer, E. Hahn and D. Schuppan, *Br. J. Cancer*, 2002, **86**, 443.
- [91] E. Somekh, D. Douer, N. Shaked and E. Rubinstein, *JPET*, 1989, **248**, 415.
- [92] T. Miclau, M. L. Edin, G. E. Lester, R. W. Lindsey and L. E. Dahners, *J. Orthop. Res.*, 1998, **16**, 509.
- [93] S. Emami, A. Shafiee and A. Foroumadi, *Mini Rev Med Chem.*, 2006, **6**, 375.
- [94] A. E. Kassab and E. M. Gedawy, *Eur. J. Med. Chem.*, 2018, **150**, 403.
- [95] H. H. Mohammed, S. H. Abbas, A. M. Hayallah, G. E.-D. A. Abuo-Rahma and Y. A. Mostafa, *Bioorg. Chem.*, 2020, 104422.
- [96] H. H. H. Mohammed, A. A. Abd El-Hafeez, S. H. Abbas, E. M. N. Abdelhafez and G. E. A. Abuo-Rahma, *Bioorg Med Chem*, 2016, **24**, 4636.
- [97] N. Suresh, H. N. Nagesh, K. V. Sekhar, A. Kumar, A. N. Shirazi and K. Parang, *Bioorg Med Chem Lett*, 2013, **23**, 6292.
- [98] A. A. Abdel-Aziz, A. S. El-Azab, A. M. Alanazi, Y. A. Asiri, I. A. Al-Suwaidan, A. R. Maarouf, R. R. Ayyad and T. Z. Shawer, *J Enzyme Inhib Med Chem*, 2016, **31**, 796.
- [99] K. J. Shou, J. Li, Y. Jin and Y. W. Lv, *Chem Pharm Bull (Tokyo)*, 2013, **61**, 631.
- [100] S. Rajabalian, A. Foroumadi, A. Shafiee and S. Emami, *J Pharm Pharm Sci*, 2007, **10**, 153.
- [101] A. Foroumadi, S. Emami, S. Rajabalian, M. Badinloo, N. Mohammadhosseini and A. Shafiee, *Biomed Pharmacother*, 2009, **63**, 216.
- [102] A. R. Kumar, B. Lingaiah, P. S. Rao, B. Narsaiah, D. Sriram and P. Sowjanya, *Indian J. Chem. Sect. B*, 2015, **54B**, 1495.
- [103] G. G. Rajulu, H. S. B. Naik, G. C. Kumar, S. Ramaraj, G. Sambasivam and K. P. Koppolu, *Med Chem Res*, 2014, **23**, 2856.
- [104] M. Piplani, H. Rajak and P. C. Sharma, *J. Adv. Res.*, 2017, **8**, 463.
- [105] A. Demirci, K. G. Karayel, E. Tatar, S. Ö. Okullu, N. Ütüböl, P. N. Taşlı, Z. T. Kocagöz, F. Şahin and İ. Küçükgülzel, *Turk. J. Chem*, 2018, **42**, 839.
- [106] K. Dileep, S. Polepalli, N. Jain, S. K. Buddana, R. Prakasham and M. Murty, *Mol. Divers*, 2018, **22**, 83.
- [107] A. R. Nödling, E. M. Mills, X. Li, D. Cardella, E. J. Sayers, S.-H. Wu, A. T. Jones, L. Y. Luk and Y.-H. Tsai, *CHEM COMMUN*, 2020, **56**, 4672.
- [108] A. Chrzanowska, P. Roszkowski, A. Bielenica, W. Olejarz, K. Stępień and M. Struga, *Eur. J. Med. Chem.*, 2020, **185**, 111810.
- [109] I. M. Abdel-Rahman, M. Mustafa, S. A. Mohamed, R. Yahia, M. Abdel-Aziz, G. E.-D. A. Abuo-Rahma and A. M. Hayallah, *Bioorg. Chem.*, 2021, **107**, 104629.
- [110] G. Q. Hu, X. K. Wu, G. Q. Wang, N. N. Duan, X. Y. Wen, T. Y. Cao, Y. Jun, W. Wei, S. Q. Xie and W. L. Huang, *Chin Chem Lett*, 2012, **23**, 515.
- [111] J.-p. Sun, Z.-y. Shi, S.-m. Liu, Y.-h. Kang, G.-q. Hu, C.-s. Huangfu, J.-b. Deng and B. Liu, *Cancer Cell Int.*, 2013, **13**, 67.
- [112] M. A. Abdel-Aal, S. A. Abdel-Aziz, M. S. A. Shaykoon and G. E. D. A. Abuo-Rahma, *Arch. Pharm. (Weinheim)*, 2019, **352**, 1800376.
- [113] Z.-y. Shi, Y.-q. Li, Y.-h. Kang, G.-q. Hu, C.-s. Huang-Fu, J.-b. Deng and B. Liu, *Acta Pharmacol. Sin.*, 2012, **33**, 271.
- [114] Q.-D. You, Z.-Y. Li, C.-H. Huang, Q. Yang, X.-J. Wang, Q.-L. Guo, X.-G. Chen, X.-G. He, T.-K. Li and J.-W. Chern, *J. Med. Chem.*, 2009, **52**, 5649.
- [115] B. Saeed, M. Al-Iraqi and F. Abachi, *Iraqi J. Vet. Sci*, 2012, **26**, 115.
- [116] H. Zhang, L. Ke, H. Zhao, H. Guoqiang and W. Huang, *J. China Pharm. Univ.*, 2017, **48**, 167.
- [117] G. Q. Hu, Z. Q. Zhang, S. Q. Xie and W. L. Huang, *Chin Chem Lett*, 2010, **21**, 661.
- [118] T. Li, Z. Gao Liu, Y. S. Xie, Y. F. Feng, Q. Yan, S. M. Wu, L. L. Ni, H. Zhao, W. L. Huang and G. Q. Hu, *Yao Xue Xue Bao*, 2015, **50**, 569.
- [119] Q. Yan, W. Shumin, N. Lili, Y. Xie, L. Gao, W. Huang, Y. Liu and H. Guoqiang, *J. China Pharm. Univ.*, 2015, **5**, 548.
- [120] S. I. Farooqi, N. Arshad, P. A. Channar, F. Perveen, A. Saeed, F. A. Larik and A. Javeed, *J. Photochem. Photobiol. B.*, 2018, **189**, 104.
- [121] L. Yang, Y. Yuan, C. Fu, X. Xu, J. Zhou, S. Wang, L. Kong, Z. Li, Q. Guo and L. Wei, *Free Radic. Biol. Med*, 2016, **95**, 155.
- [122] S. Bayat, M. Shekari Khaniani, J. Choupani, M. R. Alivand and S. Mansoori Derakhshan, *Biomed Pharmacother*, 2018, **97**, 1445.
- [123] A. C. West and R. W. Johnstone, *J Clin Invest*, 2014, **124**, 30.
- [124] G. Balasubramanian, N. Kilambi, S. Rathinasamy, P. Rajendran, S. Narayanan and S. Rajagopal, *J Enzyme Inhib Med Chem*, 2014, **29**, 555.
- [125] X. Wang, X. Jiang, S. Sun and Y. Liu, *RSC Adv.*, 2018, **8**, 16494.
- [126] V. Milata, A. Svedova, Z. Barbierikova, E. Holubkova, I. Cipakova, D. Cholujova, J. Jakubikova, M. Panik, S. Jantova and V. Brezova, *Int. J. Mol. Sci*, 2019, **20**, 2169.
- [127] Q. Xu, L. Huo and X. Wu, *J. China Pharm. Univ.*, 2013, **44**, 35.
- [128] S. A. Shahzad, A. Sarfraz, M. Yar, Z. A. Khan, S. A. R. Naqvi, S. Naz, N. A. Khan, U. Farooq, R. Batool and M. Ali, *Bioorg. Chem.*, 2020, **100**, 103876.
- [129] M. Samir, M. Ramadan, P. A. Abdelrahman, M. S. Abdelbaset, M. A. Abourehab, M. Abdel-Aziz and G. E.-D. A. Abuo-Rahma, *Bioorg. Chem.*, 2021, **110**, 104698.
- [130] R. Pulipaka, S. R. Dash, P. Khanvilkar, S. S. Jana, R. V. Devkar and D. Chakraborty, *Transit. Met. Chem.*, 2019, **44**, 721.
- [131] K. Poole, *Antimicrob Agents Chemother*, 2000, **44**, 2233.
- [132] A. Dorst, R. Berg, C. G. Gertzen, D. Schäfle, K. Zerbe, M. Gwerder, S. D. Schnell, P. Sander, H. Gohlke and K. Gademann, *ACS Med. Chem. Lett*, 2020, **11**, 2414.
- [133] L. E. Evans, A. Krishna, Y. Ma, T. E. Webb, D. C. Marshall, C. L. Tooke, J. Spencer, T. B. Clarke, A. Armstrong and A. M. Edwards, *J. Med. Chem.*, 2019, **62**, 4411.
- [134] M. M. Butler, W. A. LaMarr, K. A. Foster, M. H. Barnes, D. J. Skow, P. T. Lyden, L. M. Kustigian, C. Zhi, N. C. Brown and G. E. Wright, *Antimicrob Agents Chemother*, 2007, **51**, 119.
- [135] K. M. O'Connell, J. T. Hodgkinson, H. F. Sore, M. Welch, G. P. Salmond and D. R. Spring, *Angew. Chem. Int. Ed.*, 2013, **52**, 10706.
- [136] C. Zhi, Z.-y. Long, A. Manikowski, J. Comstock, W.-C. Xu, N. C. Brown, P. M. Tarantino, K. A. Holm, E. J. Dix and G. E. Wright, *J. Med. Chem.*, 2006, **49**, 1455.
- [137] H. M. Faidallah, A. S. Girgis, A. D. Tiwari, H. H. Honkanadavar, S. J. Thomas, A. Samir, A. Kalmouch, K. A. Alamry, K. A. Khan and T. S. Ibrahim, *Eur. J. Med. Chem.*, 2018, **143**, 1524.
- [138] S. F. Cui, Y. Ren, S. L. Zhang, X. M. Peng, G. L. Damu, R. X. Geng and C. H. Zhou, *Bioorg Med Chem Lett*, 2013, **23**, 3267.
- [139] X.-D. Wang, W. Wei, P.-F. Wang, Y.-T. Tang, R.-C. Deng, B. Li, S.-S. Zhou, J.-W. Zhang, L. Zhang and Z.-P. Xiao, *Bioorg Med Chem*, 2014, **22**, 3620.
- [140] R. V. Patel and S. W. Park, *Chem Biol Drug Des*, 2014, **84**, 123.
- [141] M. F. Gordeev, C. Hackbarth, M. R. Barbachyn, L. S. Banitt, J. R. Gage, G. W. Luehr, M. Gomez, J. Trias, S. E. Morin and G. E. Zurenko, *Bioorganic Med. Chem. Lett.*, 2003, **13**, 4213.
- [142] G. Zhao, M. J. Miller, S. Franzblau, B. Wan and U. Möllmann, *Bioorganic Med. Chem. Lett.*, 2006, **16**, 5534.
- [143] Y.-L. Zhao, Y.-L. Chen, J.-Y. Sheu, I.-L. Chen, T.-C. Wang and C.-C. Tzeng, *Bioorg Med Chem*, 2005, **13**, 3921.
- [144] H. Bayrak, Y. U. Cebeci and Ş. A. Karaoğlu, *ChemistrySelect*, 2019, **4**, 12906.
- [145] D. Ammeter, T. Idowu, G. G. Zhanal and F. Schweizer, *J. Antibiot. Res*, 2019, **72**, 816.
- [146] Ł. Szczupak, A. Kowalczyk, D. Trzybiński, K. Woźniak, G. Mendoza, M. Arruebo, D. Steverding, P. Stączek and K. Kowalski, *Dalton Trans.*, 2020, **49**, 1403.
- [147] A. Pandey, C. Savino, S. H. Ahn, Z. Yang, S. G. Van Lanen and E. Boros, *J. Med. Chem.*, 2019, **62**, 9947.
- [148] T. E. Khalil, A. El-Dissouky, D. Al-Wahaib, N. M. Abrar and D. S. El-Sayed, *Appl. Organomet. Chem.*, 2020, **34**, 5998.
- [149] B. Fois, Ž. Skok, T. Tomašič, J. Ilaš, N. Zidar, A. Zega, L. Peterlin Mašič, P. Szili, G. Draskovits and Á. Nyerges, *ChemMedChem*, 2020, **15**, 265.
- [150] A. A. Mohammed, G. A. Suaifan, M. B. Shehadeh and P. N. Okechukwu, *Eur. J. Med. Chem.*, 2020, **202**, 112513.
- [151] J. Leng, W. Tang, W.-Y. Fang, C. Zhao and H.-L. Qin, *Org. Lett.*, 2020, **11**, 4316.
- [152] M. A. Abdullah, G. E.-D. A. Abuo-Rahma, E.-S. M. Abdelhafez, H. A. Hassan and R. M. Abd El-Baky, *Bioorg. Chem.*, 2017, **70**, 1.

- [153] H. A. Aziz, G. A. Moustafa, G. E. D. A. Abuo-Rahma, S. M. Rabea, G. Hauk, V. S. Krishna, D. Sriram, J. M. Berger and S. H. Abbas, *Arch. Pharm. (Weinheim)*, 2021, **354**, 2000180.
- [154] H. A. Aziz, G. A. Moustafa, S. H. Abbas, G. Hauk, V. S. Krishna, D. Sriram, J. M. Berger and G. E.-D. A. Abuo-Rahma, *Med Chem Res*, 2019, **28**, 1272.
- [155] B. S. Sekhon, *Am. J. Pharm. Educ.*, 2013, **4**.
- [156] C. Tesseromatis and A. Alevizou, *EUR J DRUG METAB PH*, 2008, **33**, 225.