

Biological Activity of the 3-Heteroaryl Fluoroquinolone Hybrids

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Contributor: Halyna Hryhoriv , Sergiy M. Kovalenko , Marine Georgiyants , Lyudmila Sidorenko , Victoriya Georgiyants

There are promising studies in the area of 3-heteroaryl hybrids. The latter can be synthesized via different convenient methods with the formation of new derivatives with five-membered and fused heterocycles or creation of bis-fluoroquinolones with variable linking moieties. These novel compounds revealed not only good antimicrobial properties compared to the parent molecules but were also widely investigated as anticancer agents with promising activity.

fluoroquinolones

synthesis

3-heteroaryl hybrids

biological activity

1. Novel FQ Hybrids as Antimicrobials and Antiviral Medicines

Among the core fluoroquinolones (FQs) molecules that served for the development and research of new potent antimicrobials, the first place is taken by norfloxacin. The carboxylic group of the initial compound was modified mainly with five-membered heterocycles with further investigation of antibacterial, antifungal and antiviral activities.

For example, a series of 1,3,4-oxadiazoles containing FQ derivatives was synthesized and screened for antibacterial and antimycobacterial properties in ref. ^[1] (**Figure 1**). The disk diffusion method revealed potent antibacterial activities against *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus pneumoniae*, *Escherichia coli* and *Klebsiella pneumoniae*. In addition, the obtained norfloxacin derivatives showed antimycobacterial activity against *Mycobacterium smegmatis* H37Rv with minimal inhibitory concentrations (MICs) of 22.35, 16.20 and 20.28 µg/mL. The scholars also studied absorption, distribution, metabolism and excretion (ADME) properties and proved the promising pharmacokinetic properties and drug-likeness for the obtained compounds.

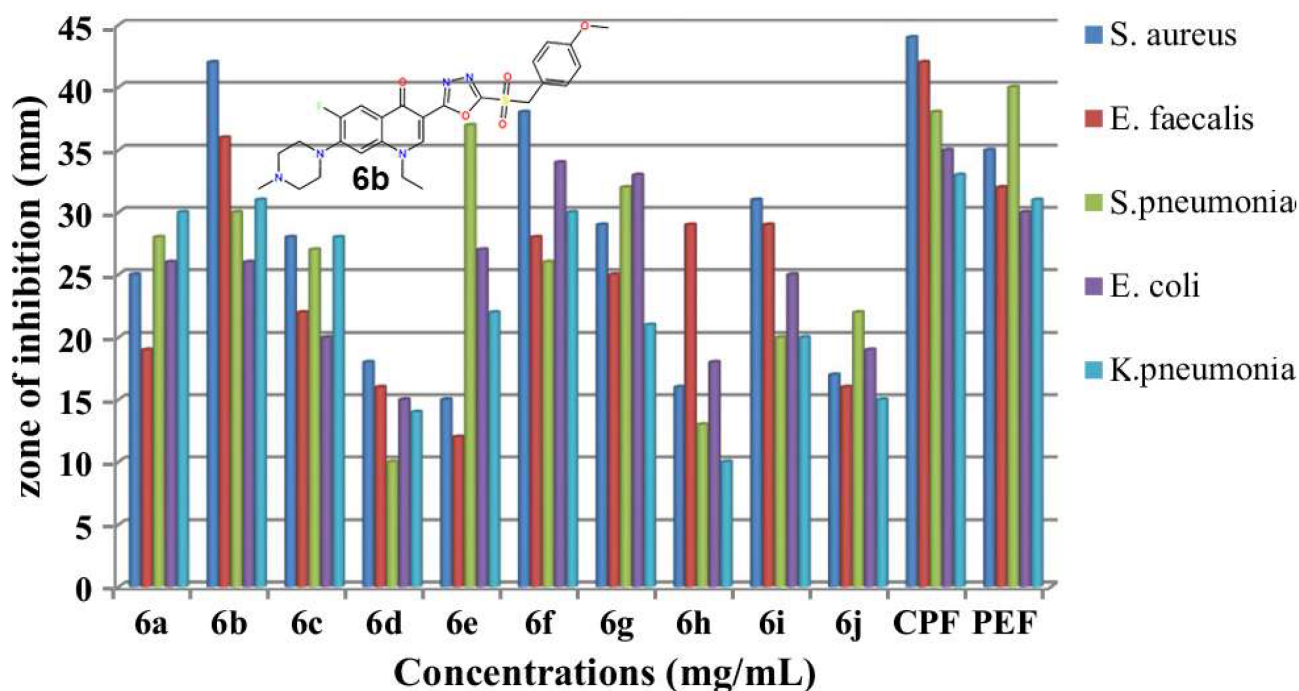


Figure 1. Antibacterial activity of new 1,3,4-oxadiazole hybrids of norfloxacin [1].

It is worth noting that most of the investigations in this area are based on *in silico* studies of drug-likeness and binding properties. Thus, the scholars of [2] described molecular docking investigations (AutoDock Tools-1.5.6) against the receptor GlcN-6P (2VF5) that revealed good binding affinities for synthesized norfloxacin derivatives. In the work, the core molecule was modified with 1,3,4-oxadiazole, thiazolidin-4-one, 1,3,4-oxadiazoline, 1,2,4-triazole and 1,3,4-thiadiazole rings. The antimicrobial assessment via disk diffusion and serial dilution methods showed higher activity than for norfloxacin against *S. aureus*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Micrococcus luteus*, *K. pneumoniae*, *Pseudomonas aeruginosa*, *E. coli* and *Proteus mirabilis*.

1,2,4-Triazole and 1,3,4-oxadiazole norfloxacin hybrids with suitable druglike, antibacterial and antifungal properties were successfully obtained by researches [3]. Especially pronounced was the activity against *S. pneumoniae*, with minimum inhibitory concentrations of 0.89 and 0.96 mg/mL and minimal bactericidal concentrations of 2.95 and 2.80 mg/mL. Combined with simple synthetic approaches, such results are promising for further investigations.

Interestingly, similar oxadiazole norfloxacin and ciprofloxacin derivatives showed good antibacterial activity against both Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) strains, combined with promising antifungal activity against fungi (*Saccharomyces cerevisiae*) in comparison with reference drugs ciprofloxacin and fluconazole in the study [4].

A few interesting works were devoted to an exploration of the antimicrobial potential of aminothiazolyl hybrids of norfloxacin. It was proved that the 2-aminothiazole fragment at the 3-position of the quinolone core plays an important role in exerting antibacterial activity. For instance, in this case, the antibacterial activity investigation revealed higher values in comparison with the reference drugs against methicillin-resistant *Staphylococcus aureus*

(MRSA) and *S. aureus* 25923, with MIC values of 0.009 and 0.017 mM [5]. **Figure 2** shows the detailed activity and concentrations of the synthesized compounds.

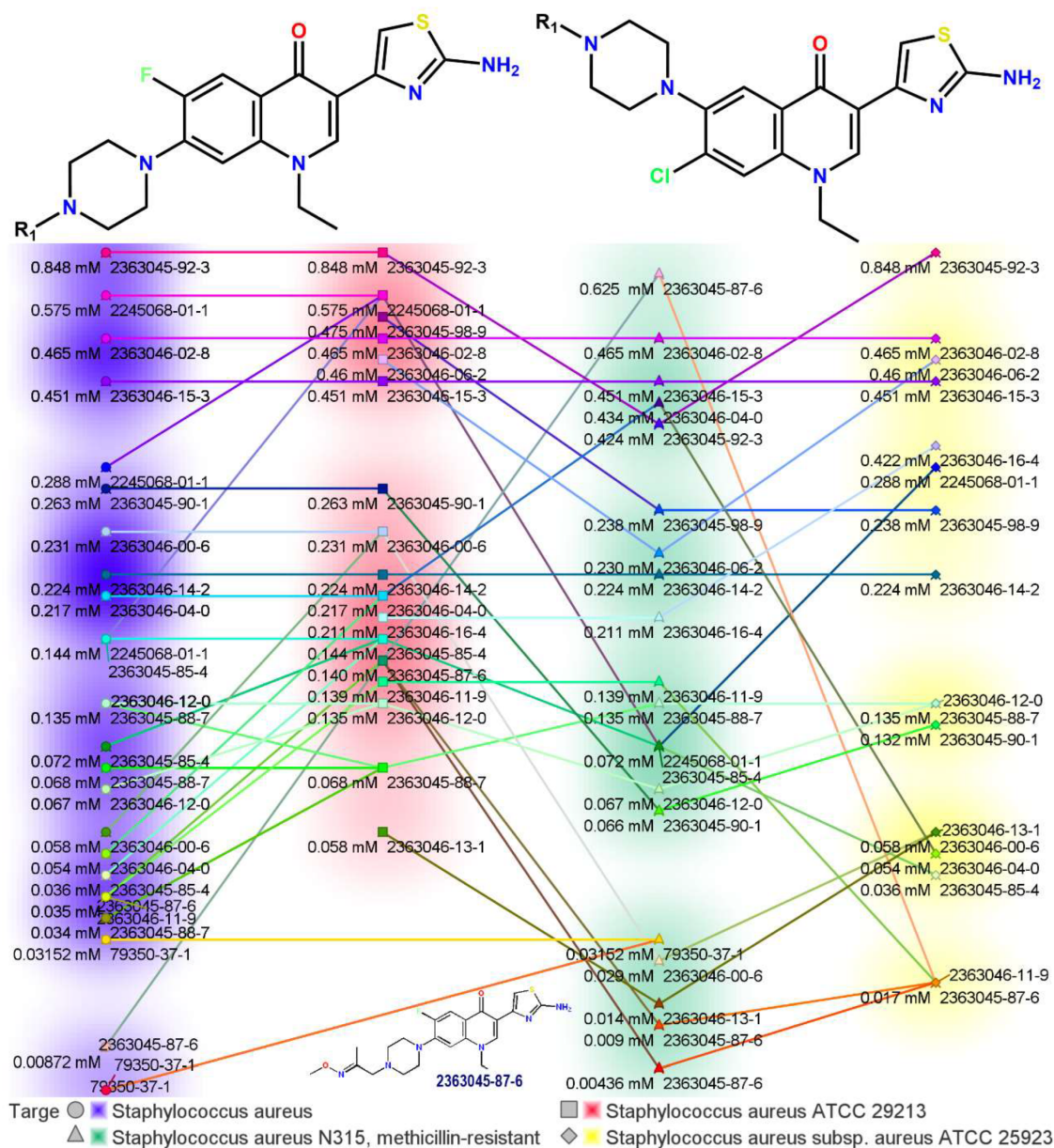


Figure 2. Antimicrobial potency of novel aminothiazolyl hybrids of norfloxacin [5].

Another series of aminothiazolyl norfloxacin analogs was synthesized by the scholars of [6] and was screened for antimicrobial properties. Most of the compounds synthesized were superior to reference drug inhibitory efficiencies against *K. pneumoniae* and *Candida albicans*, with MIC values of 0.005 and 0.010 mM. Furthermore, these compounds revealed better antibacterial activity against *S. aureus* ATCC 29213 and methicillin-resistant strains (Figure 3).

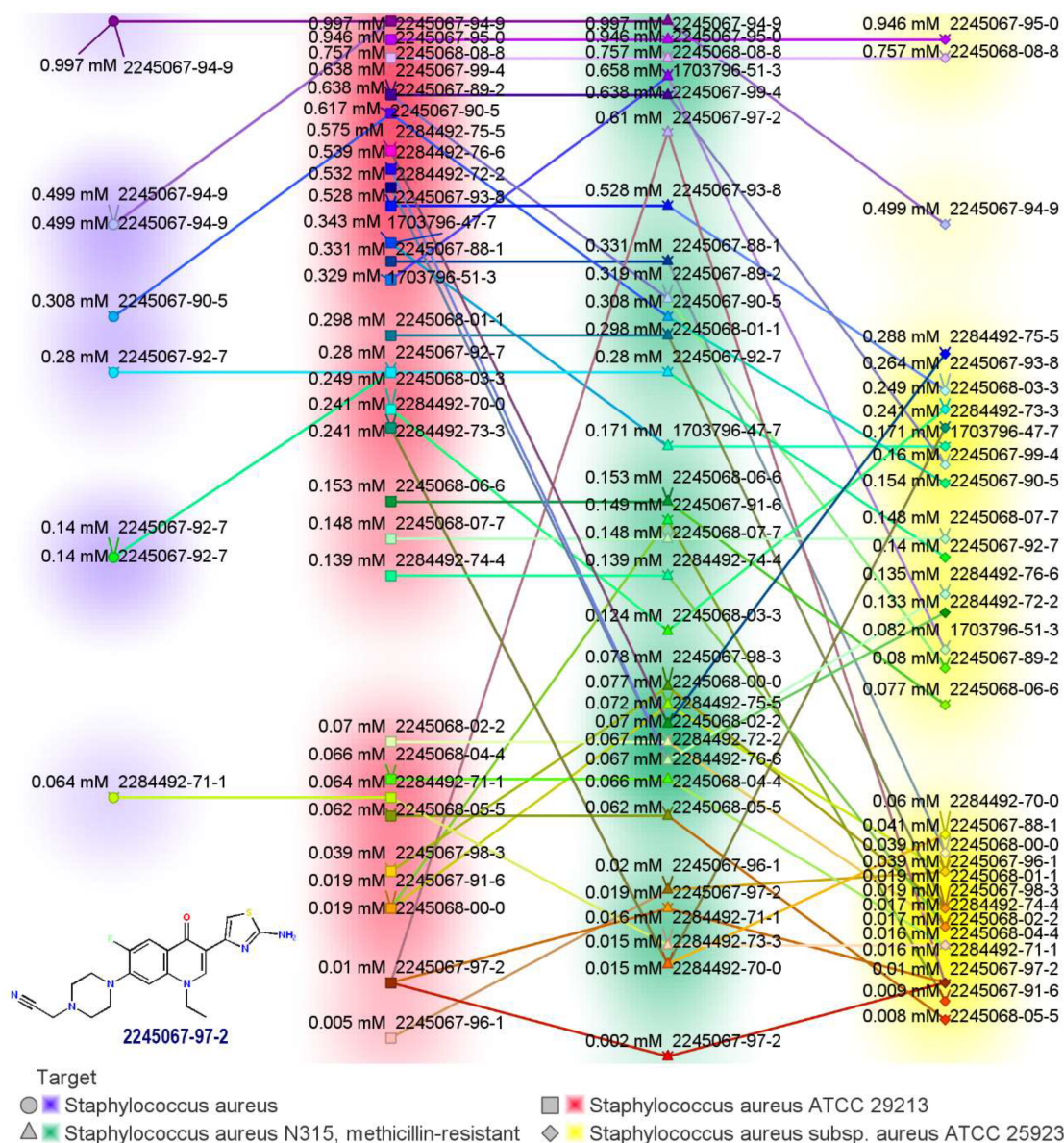


Figure 3. Antimicrobial activity of aminothiazolyl hybrids of norfloxacin [6].

In addition, investigations of the inhibitory activity against the DNA gyrase from *E. coli* showed that aminothiazolyl norfloxacin analogs have good inhibitory potency for DNA gyrase (IC_{50} $\frac{1}{4}$ 16.7 mM), which was more effective than the reference drug norfloxacin (IC_{50} $\frac{1}{4}$ 18.6 mM). Altogether, the scholars concluded that the replacement of the carboxyl group with the weak basic 2-aminothiazole moiety provides a similar antibacterial mechanism to norfloxacin by targeting DNA gyrase.

They additionally proved their hypothesis via docking studies with the topoisomerase IV-DNA complex and gyrase-DNA complex. Among the found interactions, the sulfur atom in the 2-aminothiazole moiety participated in the non-covalent coordination with ARG-136 residue via hydrogen bond formation that is favorable for stabilizing the compound-enzyme-DNA supramolecular complex, which further accounted for the good inhibitory efficiency against the tested strains.

The investigation in ref [7] also describes a series of novel 2-aminothiazol-4-yl norfloxacin analogs created to combat quinolone resistance. Among them, 3-(2-aminothiazol-4-yl)-7-chloro-6-(pyrrolidin-1-yl)quinolone exhibited potent antibacterial activity, strong inhibitory potency to DNA gyrase and a broad antimicrobial spectrum, including against multidrug-resistant strains. Moreover, this molecule induced bacterial resistance more slowly than initial norfloxacin. The docking evaluation gave good total scores (5.68 and 6.46) for aminothiazolquinolones against topoisomerase IV-DNA and gyrase-DNA complexes.

A tetrazolyl moiety appeared to be one more promising bioisostere that was introduced in the C-3 of norfloxacin and ciprofloxacin [8]. The scholars conducted docking studies using a Molegro Virtual Docker (MVD) to prove their idea. The tested compounds showed a very similar binding mode with DNA gyrase compared to the co-crystallized ciprofloxacin. The tetrazole formed three hydrogen bonds with Ser1084 instead of one, which is formed by ciprofloxacin. The bond lengths of the three hydrogen bonds were 1.9, 2.1 and 3.1 Å. The nitrogen of the piperazine formed a hydrogen bond with base pair DNA backbone DT4. The MolDock score (kcal mol^{-1}) and the Rerank Score were -123.54 and -74.67 , respectively. Overall, the tested compound revealed a similar manner to ciprofloxacin, with additional hydrogen bonds related to the 3-tetrazole scaffold, supporting the molecular design.

In addition, this modification led to optimization of the solubility profile of the initial molecules. As for the antibacterial activity, the inhibition zones for *S. aureus* and MRSA were from 12.5 to 25 mM. Several derivatives revealed activity at 12.5 and 25 mM, respectively, against *Salmonella typhi*, while reference drugs were active at 100 mM. Moreover, high activity against *Vibrio cholerae* and *E. coli* was observed.

A few more investigations described modifications of ciprofloxacin. Thus, ref. [9] evidenced the synthesis and evaluation of antibacterial activity of ciprofloxacin C3 hybrids with isatins, phthalimides and oxadiazoles. In vitro antibacterial evaluation was made using disk diffusion and serial dilution methods, and antitubercular activity was measured using the Lowenstein–Jensen (LJ) method. All the obtained compounds were highly effective against *E. coli*, *K. pneumonia* (Gram-negative) and *S. aureus* (Gram-positive) at concentrations of 75 and 100 $\mu\text{g/mL}$. In addition, they possessed antitubercular activity against normal, multidrug-resistant and extensively drug-resistant strains of *Mycobacterium tuberculosis*. Therefore, they are more potent antimicrobial agents than ciprofloxacin.

Similar research was conducted by scientists [10] who successfully obtained 1,3,4-oxadiazole hybrids of ciprofloxacin and tested them against the standard group of Gram-positive and Gram-negative microorganisms. Here, again, promising activity was observed for both groups that exceeded the reference drug ciprofloxacin.

More pronounced activity against Gram-negative strains is described in ref. [11] for new C3 triazole ciprofloxacin derivatives. Antibacterial activity against Gram-positive strains, in this case, remained at the ciprofloxacin level. In addition, molecular docking studies using topoisomerase (3ILW) protein revealed correlation between the antibacterial activity and binding free energy of the molecules. The tested compound showed high affinity with low energy of -6.2 kcal/mol with the employed protein (for ciprofloxacin, it was -6.7 kcal/mol).

Furthermore, a series of new ofloxacin analogs was synthesized by modifying it by triazoles [12]. In the first stage of the research, in silico docking studies using Autodock vina 4.0 program were performed. Almost all the compounds used for docking showed a best-fit Root Mean Square Difference (RMSD) value of 0.000 with topoisomerase II (3ILW), and good inhibition, with an affinity range between -7.4 and -6.4 kcal/mol. The obtained data were verified via in vitro antimicrobial screening, where the obtained compounds showed promising activity against *S. aureus*, *S. epidermidis* and *Bacillus subtilis* (MIC 0.125 µg/mL).

Several patents on FQs hybridized via five-membered heterocycles at C3 were obtained by Chinese scientists. They claim antibacterial (against Gram-positive and Gram-negative strains), antifungal and DNA intercalating properties in the obtained thiazole [13] and aminothiazole derivatives [14][15]. In addition, they describe a simple and affordable preparation technique based on available raw materials. Another patent [16][17] describes the preparation of novel hybrids with rhodamine as promising antibacterial agents.

Among fused hybrids, the scholars of [18] describe novel benzimidazole–quinolinone derivatives of ciprofloxacin and levofloxacin. All the synthesized compounds revealed promising antifungal activity when compared with the reference drug griseofulvin.

A series of new triazolothiadiazole derivatives of ciprofloxacin was obtained and tested against *S. aureus* and *E. coli* [19]. They showed stronger inhibitory activity against *E. coli* than that of *S. aureus* compared to ciprofloxacin. Therefore, the fused heterocycle-based substituted FQs are valuable for further investigations.

Lastly, a novel class of FQ oxadiazole derivatives that inhibit NS5B polymerase, a key enzyme of the Hepacivirus viral life cycle, is described in ref. [20] that may be the first step toward exploration of this dimension of FQs.

Altogether, the published studies definitely prove the logic and efficiency of these investigations. Even if they are now underestimated, their continuation gives a perfect chance to obtain fruitful results, namely, new potent antimicrobials to combat the problem of resistance to antibiotics.

2. Novel FQ Hybrids as Promising Antitumor Agents

Surprisingly, literature data revealed that many research groups searched for antitumor agents among new FQ hybrids. This approach is based on the concept of bioisosters that gained popularity in medicinal chemistry in recent years. Namely, the bioisosteric replacement of the carboxylic group with different heterocyclic moieties and synthesis of bis-fluoroquinolones linked via a heterocycle at C3 are two main strategies that are widely presented.

Another valuable point is the variety of cancer types against which the compounds synthesized were tested in the above-mentioned investigations.

Thus, new 1,3,4-thiadiazole derivatives of ciprofloxacin were synthesized and investigated via thorough in silico and in vitro studies (Figure 4). Theoretical and experimental DNA binding research revealed good correlation with

human hepatocellular carcinoma (Huh-7) cell line activity. IC_{50} values from Huh-7 cell line studies (25.75 μ M) revealed synthesized compounds as potent anticancer agents, promising for further investigations [21].

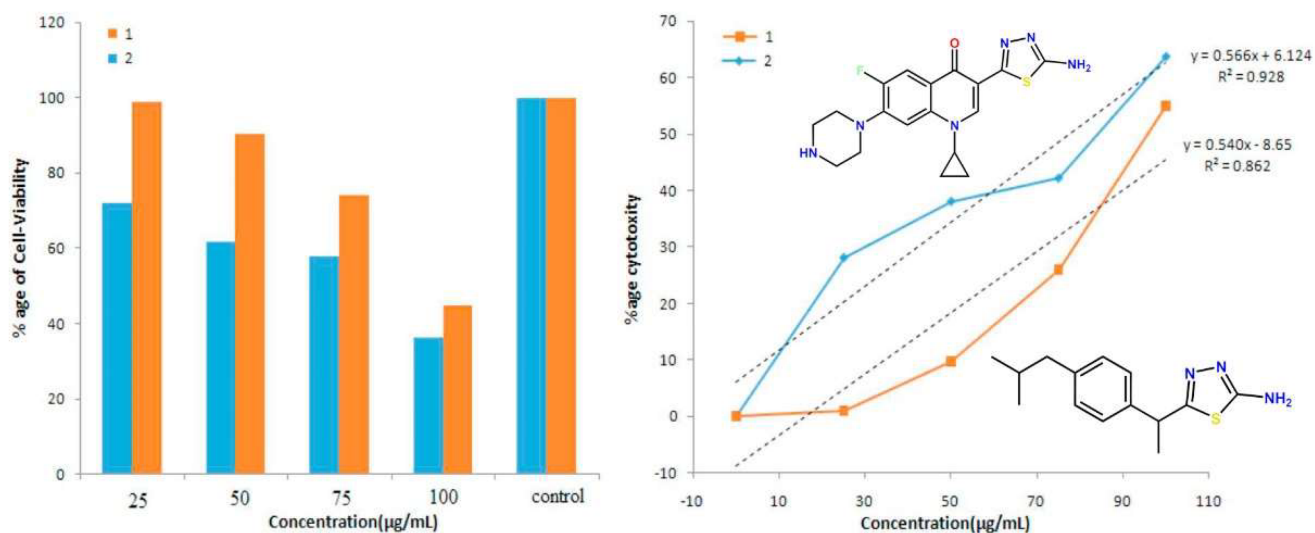


Figure 4. New 1,3,4-thiadiazole ciprofloxacin derivatives and their antitumor activity [21].

Other isosteres of the C-3 carboxylic group for the pefloxacin 1,3,4-oxadiazole-thione ring and oxadiazole thione Mannich bases were suggested by the scholars of [1]. The obtained compounds were tested in vitro against a liver cancer (Hep-3B) cell line and, according to the results, all the title compounds showed more significant potency than parent compounds. In addition, derivatives of aliphatic amines appeared to be more active than the derivatives of aromatic amines. Furthermore, similar derivatives were reported in patent [22], and it was shown that molecules with an electron-withdrawing group attached on the aryl ring had more potency than compounds with an electron-donating group.

The scholars of [23] patented similar oxadiazole norfloxacin derivatives that were screened in vitro against the same liver cancer (Hep-3B) cell line. Evaluation was performed via an MTT assay. The results revealed higher cytotoxicity compared to norfloxacin for fifteen title compounds. Correspondent quaternary ammonium salts exhibited promising anticancer activity with IC_{50} values below 25.0 μ mol/L.

Another search for agents against the human hepatoma (Hep-3B) cancer cell line and human pancreatic (Capan-1) cell line was made based on comparative molecular field analysis techniques [24]. Three-dimensional quantitative structure–activity relationship (3D-QSAR) investigations on the antitumor activity of s-triazole sulfide-ketone derivatives of ciprofloxacin and levofloxacin gave the possibility to design four novel molecules with promising anti-tumor activity and to plan further in vitro research.

A series of ciprofloxacin and norfloxacin oxadiazole derivatives was evaluated for their antiproliferative activities against human lung tumor (A549) cell lines. Among them, the most active compound, 1-cyclopropyl-6-fluoro-3-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]-7-piperazinyl-1,4-dihydro-quinolin-4-one, was found, with a half-maximal inhibitory concentration (IC_{50}) of 9.0 μ g/mL [25].

Furthermore, the scope of cancer cell lines expands via other organs. For instance, the scholars of [12] patented novel ofloxacin 1,3,4-triazole derivatives as antitumor agents for treating bladder, stomach or pancreatic cancer (Figure 5).

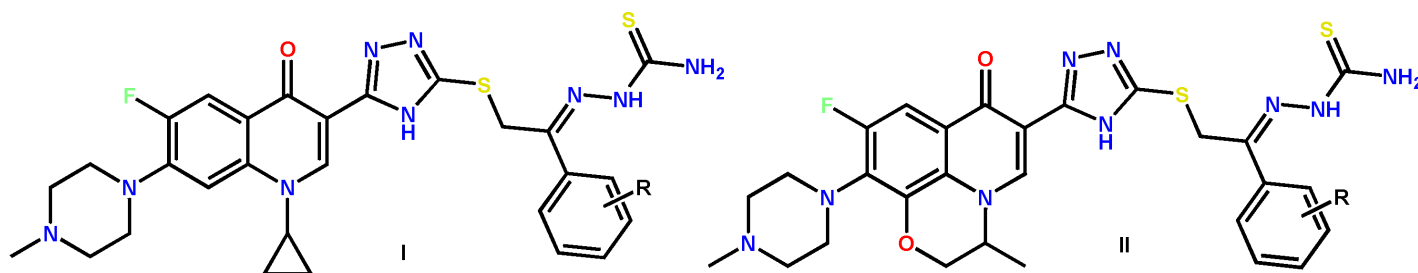


Figure 5. Novel ofloxacin 1,3,4-triazole derivatives as antitumor agents [12].

Research related to bladder tumors is also patented [26] and describes similar triazole derivatives for which an IC_{50} value of 0.6 μM against a bladder tumor was detected.

The series of C-3 s-triazole thioether ketone semicarbazone ciprofloxacin hybrids was synthesized via multi-step synthesis and patented as promising antitumor agents for treating stomach, pancreatic or bladder cancer [27]. Inhibitory activity with an IC_{50} of 6.4, 10.5, 9.7, 3.8, 3.6 and 48.6 μM against bladder cancer (T24), gastric cancer (HGC823, HGC27), pancreatic cancer (Panc-1, Capan-1) and VERO cancer cell lines, respectively, was revealed.

A simple synthetic approach led to the development of novel citrate-triazole-oxadiazole norfloxacin hybrids that exhibited remarkable anticancer activity against cervical cancer (HeLa) cell lines with an IC_{50} value 11.3 ± 0.41 , comparable to the standard drug [3]. The compounds also revealed suitable druglike properties and are expected to present a good bioavailability profile.

Bis-lomefloxacin derivatives linked via an oxadiazole-carbazide bridge showed high activity against the human non-small-cell lung cancer (A549) cell line, human pancreatic cancer (Capan-1) cell line and human skin melanoma (A375) cell line, exceeding the parent compound, as well as isomerase inhibitor hydroxycamptothecin (HC) and tyrosine kinase inhibitors Ragofini (RRF) and cabozantinib (CZT) [28][29].

Similar bis-fluoroquinolone oxadiazole carbazide N-methyl-ciprofloxacin derivatives were synthesized, tested against human A549, Capan-I and A375 cell lines; they showed promising activity and were patented [30][31]. In addition, they reduced toxic side effects on normal cells.

As anti-lung cancer and antihepatoma drugs, bis-fluoroquinolone oxadiazole urea N-acetyl norfloxacin derivatives were also patented [32]. In addition, rufloxacin bis-fluoroquinolone oxadiazole urea derivatives revealed inhibiting activities on the human non-small-cell lung cancer (A549) cell line, human liver cancer (SMCC-7722) cell line, human gastric cancer (HGC27) cell line, human pancreatic cancer (Capan-I) cell line, human skin melanoma (A375) cell line and human leukemia (HL60) cell line [33].

Bis-acetylciprofloxacin linked via thiadiazole and urea pharmacophore showed higher antitumor activity and selectivity as well as a reduction in toxic side effects on normal cells [34]. The compounds synthesized were checked on lung cancer (A549), human papillomavirus-related endocervical adenocarcinoma (SMCC-7721), human gastric cancer (HGC27), human pancreatic cancer Capan-1, melanoma (A375), human leukemia (HL60) and myelogenous leukemia (K562G) cell lines, with promising results. N-acetylnorfloxacin thiadiazole norfloxacin derivatives exhibited IC_{50} values in a range of 0.36 μ M to 4.66 μ M toward cancer cell lines [35].

Many published papers are devoted to the search for potential antileukemic agents among 3-heteroaryl FQ hybrids. For instance, a series of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine and pyrazolo[5,1-*c*][1,2,4]triazole derivatives of norfloxacin, ciprofloxacin and levofloxacin was successfully obtained [36]. Their in vitro antitumor activity was tested against murine leukemia (L1210) and Chinese hamster ovary (CHO) cell lines via the standard MTT assay. The results showed poor inhibitory activity for parent fluoroquinolones ($IC_{50} > 150$ mmol/L), while isolated fused compounds had a potential activity with an IC_{50} value within 10.0 mmol/L.

Several in silico studies prove this idea. Thus, for the therapy of T-cell lymphoma, a molecular electronegativity distance vector of levofloxacin-thiadiazole histone deacetylase (HDAC) inhibitor was measured [37] and the compounds were described as promising.

Quantitative structure–activity relationship (QSAR) and molecular docking study of levofloxacin and thiadiazole as antitumor agents with HDAC1, HDAC2 and HDAC6 also revealed that the main factors affecting their biological activity are hydrogen bonding and hydrophobic interactions [38]. From the docking results, it can be seen that the active part of the molecule formed a hydrogen bond with the active part of the macromolecule, while the hydrophobic part of the small molecule had a hydrophobic interaction with non-polar amino acid residues in the active part of the macromolecule.

Novel C-3 s-triazole-oxadiazole sulfide Mannich base pefloxacin derivatives were also screened against SMMC-7721, L1210 and HL60 cell lines and were evaluated by an MTT assay. The investigation revealed that the sulfides and their corresponding Mannich base compounds are more potent inhibitors than the starting compounds, especially against SMMC-7721 [39][40].

New s-triazole ofloxacin derivatives with functionalized side chains of Schiff bases and Schiff–Mannich bases are described in ref. [41]. Their in vitro antitumor activity against L1210, Chinese hamster ovary (CHO) and HL60 cell lines was evaluated in the MTT assay. Higher inhibitory activity was detected for compounds possessing a free phenol group. Other novel s-triazole-thiosemicarbazone ofloxacin derivatives were also evaluated by the MTT assay and revealed more significant antiproliferative activity than parent ofloxacin. Thiosemicarbazones, especially those containing a nitro group or fluorine atom, showed activity comparable to doxorubicin. Therefore, an azole ring modified with a functional side chain is a favorable bioisosteric replacement of the C-3 carboxylic group for an improvement in antitumor activity [42].

Aminothiadiazole ciprofloxacin derivatives and their Schiff bases were screened against SMMC-7721, HL60 and L1210 cell lines via MTT assay [43]. They showed potential cytotoxicity with IC_{50} values that reached micro-molar concentration and were patented.

Another patent was obtained for the invention of floxacin diazole derivatives that exhibited IC_{50} values of approximately 2, 5 and 2.5 μM against CHO, HL60 and L1210 cell lines, respectively [44].

Several papers describe screening of anticancer activities against CHO, HL60 and L1210 cancer cell lines of fused FQ hybrids. Thus, s-triazolothiadiazole ciprofloxacin derivatives revealed significant antitumor activity against HL60, with IC_{50} values from 50.0 to 8.0 $\mu mol/L$ [19][45], s-triazolothiadiazine ciprofloxacin derivatives showed more significant inhibitory activity ($IC_{50} < 25.0 \mu mol/L$) than parent ciprofloxacin ($IC_{50} > 150.0 \mu mol/L$), s-triazolothiadiazinone enrofloxacin derivatives exhibited significant antitumor activity, with a range of micromole concentrations for IC_{50} value [46], and C-3 thiazolo[3,2-*b*][1,2,4]triazole ofloxacin derivatives exhibited more significant antiproliferative activity than parent ofloxacin [47]. Novel C-3 thiazolotriazole levofloxacin derivatives showed more significant activity than levofloxacin [48]. The compounds with fluorophenyl or o-methoxyphenyl displayed comparable activity to doxorubicin. Antitumor agents, prepared by cyclization of norfloxacin with o-phenylenediamine, 2-aminophenol or 2-aminobenzenethiol in the presence of polyphosphoric acid (PPA), showed strong antitumor activity in cows [49]. Therefore, a fused heterocyclic moiety as an isostere of the C-3 carboxylic acid group appears to be an alternative approach for further design of active antitumor FQs.

Moreover, four different bis-fluoroquinolones investigations in this direction were also made. For example, a series of C3/C3 bis-fluoroquinolones tethered with an 1,3,4-oxadiazole ring was screened against L1210, CHO and HL60 cell lines, showed promising inhibitory activity and was patented [50]. 1,3,4-Oxadiazole-linked norfloxacin showed antitumor activity with IC_{50} values of 15.6, 20.5 and 7.6 μM against CHO, HL-60 and L1210 cell lines, respectively [51]. Bis-oxadiazole methylsulfide derivatives derived from ciprofloxacin [52] and levofloxacin [53] were tested against CHO, HL60 and L1210 cancer cells and evaluated by MTT assay. The preliminary results showed that piperazinium compounds possess more potent activity than that of corresponding free bases.

Furthermore, ciprofloxacin cross-linked with a [1,2,4]-triazolo[3,4-*b*][1,3,4]-thiadiazole core as a common bioisostere of two carboxylic acid groups appeared to be highly potent against the HL60 cell line [54]. In vitro antitumor activity of norfloxacin dimers linked with a s-triazolo[2,1-*b*][1,3,4]thiadiazole moiety against L1210 and CHO cell lines was evaluated and appeared to be promising [55]. 1,2,4-Triazolo[3,4-*b*][1,3,4]thiadiazole-linked ciprofloxacin and levofloxacin dimers were prepared in a multi-step synthesis and revealed inhibitory activities with IC_{50} values of 1.1, 0.25 and 0.15 μM against CHO, HL60 and mouse lymphocytic leukemia (L1210) cell lines, respectively [56].

In addition, there are papers devoted to the hybridization of ofloxacin at C-3 with an s-triazole ring [5], oxadiazole-5-sulfanylacetylhydrazone moiety [57], triazole-oxadiazole methylsulfide [58] and oxadiazole ring [10]. All of them state higher antitumor activity than for the parent ofloxacin in the MTT assay. Similar derivatives patented by the scholars of [6] gave a CHO IC_{50} value of 1.3 μM . A patent for bis-oxadiazolyl methylsulfides derived from ofloxacin

describes in vitro antitumor activity evaluation against three cancer cell lines by the MTT method. The compounds synthesized showed potential anticancer activity ($IC_{50} < 25\mu\text{mol/L}$). The activity of the quaternary ammonium salts was higher than that of the corresponding free bases [24].

Further, there are many inventions on bis-fluoroquinolones as antitumor agents that were patented. Namely, levofloxacin-containing bis-fluoroquinolone oxadiazole carbamide derivative is described as useful in the treatment of cancer [59]. A novel bis-fluoroquinolone thiadiazole urea-series fleroxacin derivative was developed by the scholars of [60] to increase the antitumor activity and selectivity of fluoroquinolones and reduce the toxic side effects on normal cells. Novel thiadiazole urea rifloxacin derivatives exhibited IC_{50} values in a range of 0.46 μM to 2.36 μM [61]. A series of bis-fluoroquinolone thiadiazole urea N-Me lomefloxacin derivatives is described in patent [62], similar bis-fluoroquinolone thiadiazole urea-based N-Me moxifloxacin derivatives designed as promising antitumor agents were patented [63] and the scholars continued this project with thiadiazole urea-based pefloxacin [64], ofloxacin [65], levofloxacin [66] and gatifloxacin [67] derivatives. Furthermore, N-Me moxifloxacin-containing bis-fluoroquinolone oxadiazole urea derivatives for cancer treatment are proposed in the patent [68], N-Me gatifloxacin-containing bis-fluoroquinolone oxadiazole urea derivative in [69], oxadiazole urea fleroxacin derivatives with IC_{50} values from 0.14 μM to 1.36 μM in [70] and oxadiazole urea pefloxacin bis-derivatives in [71].

At last, there are two unusual papers that are unique according to their research strategy. Thus, a novel series of topoisomerase I (Top I) inhibitors was designed via condensation of FQs with *o*-phenylenediamine, *o*-aminophenol or *o*-aminobenzenethiol in polyphosphoric acid (PPA). The most potent compound 1-ethyl-3-(6-nitrobenzoxazol-2-yl)-6,8-difluoro-7-(3-methylpiperazin-1-yl)-4(1*H*)-quinolone revealed a significant inhibitory effect on Top I, leading to Top I-mediated cleavage and influencing Top I expression at the cellular level. Moreover, it induced cell death via apoptosis and accelerated DNA strand breaks without significant alteration in cell cycle populations. The in vivo evaluation on the growth of HT-29 tumor xenografts in nude mice showed its therapeutic potential for further development [72].

The scholars of [73] searched for P-glycoprotein ABCB1 inhibitors among fused FQ derivatives. The ABCB1 is involved in multidrug resistance of tumor cells by preventing intracellular accumulation of cytotoxic drugs. In addition, its overexpression limits drug oral bioavailability. To find new potent ABCB1 inhibitors, a 3D pharmacophore model was created based on known inhibitors. The inhibitory activities of the best hits were evaluated by several biological assays, such as rhodamine 123 accumulation assay, chemosensitization assay and multidrug resistance 1-Madin-Darby canine kidney cell/Madin-Darby canine kidney cell permeability assay. The most promising compounds were identified and taken for further development.

3. Other Types of Biological Activity

Apart from antimicrobial and anticancer potency of FQs, it should emphasize the possibility to broaden the horizons of their utilization as biologically active molecules.

First of all, in line with the problem of combating infectious diseases, the scholars of [74] searched for potent molecules to cure protozoal infections. It was already known that N-benzylamide derivative of norfloxacin is promising so they synthesized thiosemicarbazide of 1-butyl-6-fluoro-7-morpholino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and its heterocyclic derivatives—1,3,4-thiadiazole and 1,2,4-triazole. Furthermore, modification of the 1,2,4-triazole ring with maleimides was also described. For the obtained compounds, antitrypanosomal activity was also typical but lower than for N-benzylamide derivative. Still, the C3 substitution plays a key role in this type of activity.

Triazole derivatives of norfloxacin and their Schiff bases were successfully obtained and described in the paper [35]. The Schiff bases (**Figure 6**) that were screened for analgesic and anti-inflammatory activity on the carrageenan-induced rat paw edema model revealed encouraging results and exceeded the reference drug ibuprofen. At the same time, unsubstituted triazoles revealed antibacterial and antifungal activity. Therefore, further investigations in this area may result in compounds with a versatile pharmacological profile.

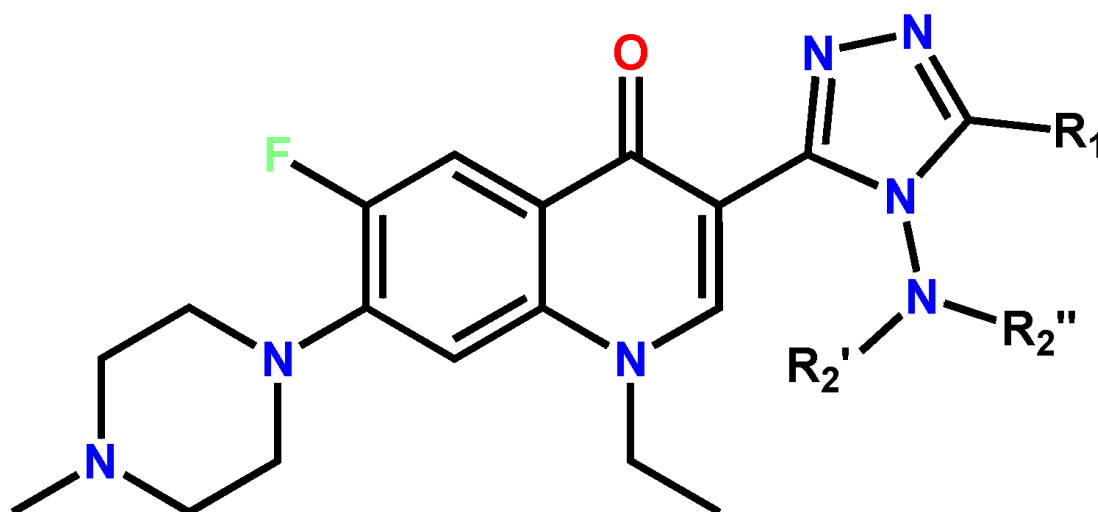


Figure 6. Triazole derivatives of norfloxacin as analgesic and anti-inflammatory agents [35].

The synthesized levofloxacin triazole-3-thiol, oxazole, oxadiazole and thiadiazol derivatives revealed antioxidant activity equivalent to ascorbic acid ($IC_{50} = 31.95 \text{ g/mL}$) in the investigation [75].

A series of novel benzimidazole-quinolinone derivatives of ciprofloxacin and levofloxacin was screened for in vitro antidiabetic activity by α -glucosidase inhibitory action and appeared to be promising at a $200 \text{ }\mu\text{g/mL}$ concentration compared to acarbose [18].

Novel 5-amino-1,3,4-thiazidazole hybrids of norfloxacin and levofloxacin were synthesized, characterized and assessed for their acetyl cholinesterase enzyme (AChE) inhibitory activity [76]. The obtained derivatives showed promising results, especially levofloxacin derivative ($IC_{50} 18.1 \pm 0.9 \text{ nM}$), which substantially exceeded the reference drug neostigmine ($IC_{50} 2186.5 \pm 98.0 \text{ nM}$). In addition, the scholars evaluated the ADMET parameters, and values of the hybrids showed appropriate correlation with the binding energy values (Kcal/mol). Combined with

high drug-likeness scores and the results of molecular docking studies, this research can be a promising background for finding a treatment for Alzheimer's disease.

Altogether, it can assume that the scope of the probable biological activity of FQ hybrids is wide. That makes this area of investigation even more versatile and attractive for medicinal chemists.

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