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# Synthesis of Hybridized Fluoroquinolones and Evaluation of Their Biological Properties †

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**Abstract:** Hybridization of the well-known biologically active molecules is a promising way for the creation of new medicines. Four generations of fluoroquinolones can be taken as an example of this trend. Moreover, it is still in progress due to the appearance of resistant strains and the persistent need for new powerful antibiotics. Current research was devoted to the development of a synthetic route towards hybridized ciprofloxacin and norfloxacin derivatives. The structure and purity of the obtained compounds were confirmed by modern instrumental methods. In vitro research against a range of Gram-positive and Gram-negative microorganisms and fungi was performed and revealed compounds with activity that exceeded the starting molecules.

**Keywords:** fluoroquinolones; synthesis; hybrids; antimicrobial activity

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## 1. Introduction

The problem of resistance to antibiotics is still persistent and requires special attention. While overuse and misuse of these medicines have been in progress for many years, numerous resistant strains have appeared. Even novel active molecules are not always able to cure the infections they cause. Still, it is possible to design new potential antibiotics based on the known pharmacophores. Our investigation was aimed at the synthesis and studies of the antibacterial properties of hybridized fluoroquinolones (FQ).

These medicines have been successfully utilized in clinical practice and are attractive from the chemical point of view due to the several possible ways of modification [1–4]. The most promising pathways are associated with the substitution of the piperazine ring with small heterocycles. Furthermore, other options, like C-3 hybridization, are not studied sufficiently and pose interest for the synthesis of novel compounds and searching for active and safe antimicrobials among them.

## 2. Methods

Through the stages of the investigation, methods of organic synthesis were used. The structures of the obtained compounds were determined using $^{1}$H NMR, $^{13}$C NMR, LC/MS spectroscopy and X-ray diffraction studies.

The antimicrobial activity of the compounds synthesized was measured using the macro method of double serial dilutions against *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Bacillus subtilis* ATCC 6633, *Pseudomonas aeruginosa* ATCC 27853, *Candida albicans* NCTC 885-653 and by the method of diffusion into agar against

*Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922 and culture of yeast-like fungi *Candida albicans* ATCC 885-653. Clinical strains of *Staphylococcus aureus*, *Escherichia coli,* and *Candida albicans* were also utilized in the research.

## 3. Results and Discussion

The first stage of our investigation was related to docking studies, which revealed the promising molecules among C-7 and C-3 FQ derivatives. The initial starting molecules were ciprofloxacin and norfloxacin and their C-7 position was modified with 1,2,3-triazole moiety. A convenient synthetic procedure was developed based on the previous research [5] (Figure 1).

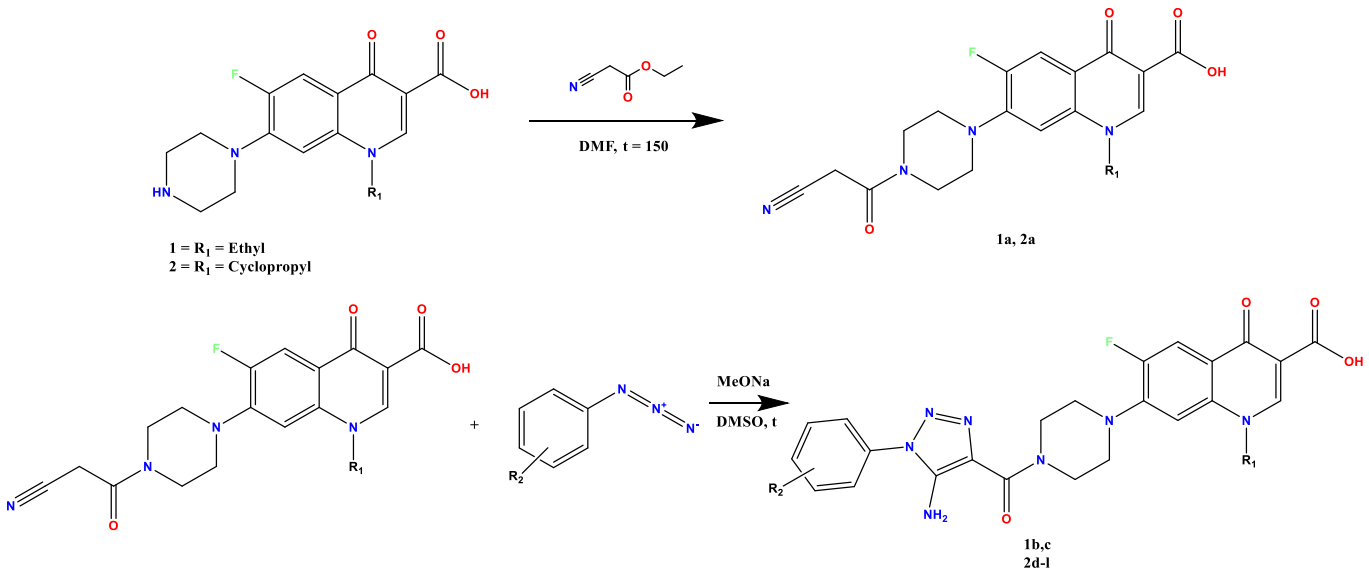


**Figure 1.** Synthesis of target compounds.

The antibacterial activity of the new compounds was evaluated by the method of double serial dilution. For this, DMF solutions were prepared at a concentration of 1 mg/mL. According to the obtained results, a wide range of bactericidal activity against all tested test strains (MIC = 15.6 μg/mL) was shown for 7-(4-(5-amino-1-phenyl-1*H*-1,2,3-triazole-4-carbonyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid. As for the diffusion in the agar method and hospital strains, the growth retardation zone exceeded 25 mm. This reveals the high sensitivity of microorganisms towards the tested compounds.

As the continuation of our investigation, we studied modifications of the C-3 position of initial molecules with arylsulfonyl moiety with subsequent hybridization of C-7 and N-1. This led to the series of new compounds, which were also tested in vitro but revealed moderate activity compared to the previous series.

## 4. Conclusions

New hybridized derivatives of ciprofloxacin and norfloxacin were synthesized and their antibacterial activity was investigated in silico and in vitro. The structure and purity of the obtained compounds were confirmed by modern instrumental methods.

Modification of starting compounds with 1,2,3-triazole moiety led to novel molecules with moderate antimicrobial and antifungal activities. As for C-3 substituted arylsulfonyl derivatives, they appeared to be less soluble and, therefore, their activity was a bit smaller than for the first group. For now, these investigations are still in progress.

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