Search for Novel Fluoroquinolone Hybrids and Assessment of their Antimicrobial Activity

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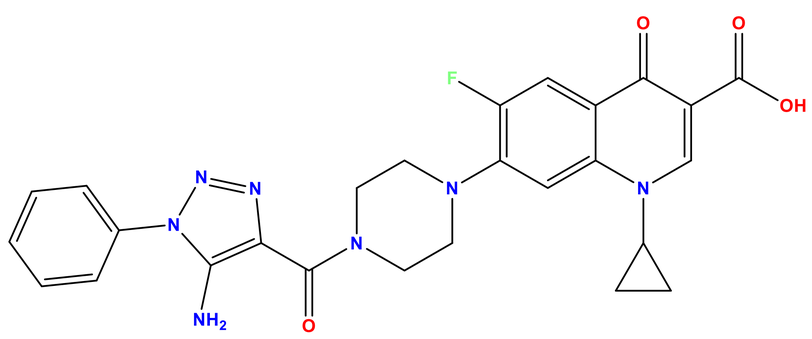
Introduction. Four generations of fluoroquinolones (FQs) are utilized in modern clinical practice due to their wide spectrum of action, high bioavailability and tolerability. Still, their misuse and overuse are leading to the appearance of resistant strains and this issue becomes more and more pressing. Therefore, medicinal chemists design new molecules based on the known core structures to increase activity and combat resistance. Thus, our research was aimed at synthesis and study of antibacterial properties of hybridized fluoroquinolones. Such modifications may proceed in different directions and combination with small heterocycles is a promising way for the creation of new antimicrobials.

Materials and methods. Methods of organic synthesis and docking studies were used. The structures of the compounds synthesized were determined using ^{1}H NMR, ^{13}C NMR, LC/MS spectroscopy and X-Ray diffraction studies. Antibacterial activity was testes against Staphylococcus aureus ATCC 25923, Escherichia coli ATCC 25922, Bacillus subtilis ATCC 6633, Pseudomonas aeruginosa ATCC 27853, Candida albicans NCTC 885-653.

Results and discussion. At first, the molecular docking studies were performed for hybrid compounds based on ciprofloxacin and norfloxacin. The obtained data revealed the important role of quinoline core and a fluorine atom in position 6, as well as carbonyl and carboxyl fragments in the third and fourth positions, which stabilize the structures and their interaction with bacterial targets. At the same time, substitution in C-7 by triazole, piperazine, and phenyl fragments appeared to be a promising way. Therefore, novel ciprofloxacin and norfloxacin hybrids with triazoles were synthesized and purified. Their structure was confirmed and the antibacterial activity investigation showed antimicrobial and antifungal properties that exceeded control for the agar well diffusion method. Then, a range of C-3 substituted with heterocycles hybrids were synthesized. It was of interest to compare both synthetic routes and the activity. The latter, in this case, appeared to be lower, probably because of lower solubility.



7-(4-(5-Amino-1-phenyl-1H-1,2,3-triazole-4-carbonyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid: compound with the highest level of antibacterial activity

Conclusions. Based on the results of the preliminary docking studies, a few series of novel FQs hybrids were synthesized and convenient synthetic procedures were developed. Their structures were determined using modern methods. The C-7 modified molecules revealed moderate antimicrobial and antifungal activities, and a smaller acidity was determined for C-3 substituted arylsulfonyl derivatives. A few hit compounds were selected for further research.