Combination of fluoroquinolones and 1,2,3-triazole moieties as a pathway towards new effective antimicrobials

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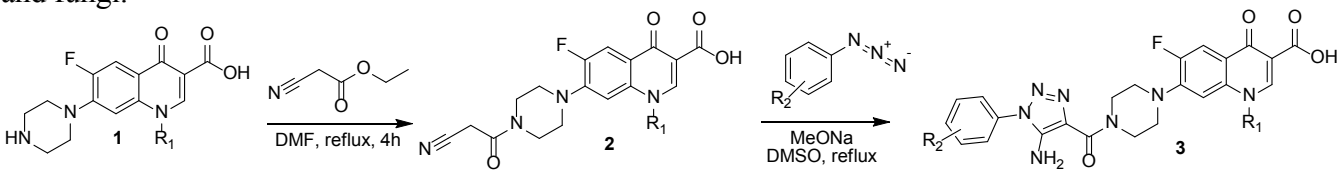
Introduction. Despite the fact that nowadays four generations of highly efficient fluoroquinolones already exist medicinal chemists all over the world are struggling to modify these molecules in order to combat the problem of resistance to them, change pharmacodynamics and pharmacokinetics. Especially important this issue appears to become through the last two years because of COVID-19 pandemic. Fluoroquinolones are used in prescribing practices for this disease treatment as they reveal both antibacterial and antiviral properties. Structural modifications of their core with heterocycles open a pathway to create more effective and safe antimicrobials.

Materials and methods. Standard methods of organic synthesis were used in the investigation. Structures of the obtained compounds were determined using ^{1}H NMR, ^{13}C NMR, LC/MS spectroscopy. Norfloxacin and Ciprofloxacin, ethyl cyanoacetate, substituted azides were used as starting materials.

Results and discussion. At the first stage the two-step procedure to substituted fluoroquinolones **3** was worked out. For this purpose Norfloxacin or Ciprofloxacin **1** was refluxed in DMF with ethyl cyanoacetate excess. The solid products **2** were obtained after cooling the reaction mixture, adding water, filtration and recrystallization from methanol. Then they were utilized in reactions with substituted azides in DMSO in the presence of sodium methoxide giving the target compounds **3** with 37-68 % yield. At the second stage of the investigation the antimicrobial activity of the synthesized molecules was measured by double serial dilutions method. The study revealed bactericidal activity against Gram-positive, Gram-negative strains and fungi.



R_1 = Ethyl, Cyclopropyl

R_2 = H, *o*-Methyl, *p*-Methyl, *p*-Ethyl, *p*-Methoxy, *m*-Thiomethyl, *p*-Thiomethyl, *p*-Br, *p*-F, 2-Methyl-5-Fluoro, *p*-Trifluoromethyl

Conclusions. The research describes synthesis of novel fluoroquinolones modified with 1,2,3-triazole ring, among which biologically attractive molecules were found.

References

1. Suaifan, G.A.R.Y., Mohammed A.A.M. Fluoroquinolones structural and medicinal developments (2013–2018): Where are we now? Bioorganic & Medicinal Chemistry. 2019;27(14):3005-3060.
2. Agalave, S., Maujan S., Pore V. ChemInform Abstract: Click Chemistry: 1,2,3-Triazoles as Pharmacophores. Chemistry, an Asian journal. 2011;6:2696-718.
3. Zhang, G.-F., et al. Ciprofloxacin derivatives and their antibacterial activities. European Journal of Medicinal Chemistry. 2018;146:599-612.