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Assessment of antimicrobial activity of new derivatives of ciprofloxacin

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Introduction

One of the main causes of death in the world is bacterial infections, which after the discovery of antibiotics in the past decades, infectious diseases have decreased significantly. After that, due to misuse and evolution of bacterial resistance, this group of drugs generally lost their effectiveness in clinical settings.

Antibiotic resistance has been a known fact almost since the discovery of antibiotics, but in the last twenty years, the frequency and speed of the emergence of resistant species have been increasing. The increase in bacterial resistance and on the other hand the decrease in the production and development of antibiotics is a frightening and worrying prospect, so the World Health Organization considers the problem of antibiotic resistance as one of the great threats to humans, animals and the environment. Hence, the discovery of new antibacterial agents plays a key role in solving the problem of antibiotic resistance crisis.

Quinolones are one of the most commonly prescribed antibiotics in the world, used to treat a wide range of bacterial infections. The second generation of quinolones, called fluoroquinolones, such as norfloxacin, ciprofloxacin, and ofloxacin, are structurally characterized by the presence of a fluorine atom in the 6-position and a piperazine ring in the 7-position. In this study, instead of the costly and time-consuming process of producing new antibiotics, a more cost-effective way of modifying existing antibiotics was chosen. Considering the importance of the C-7 position, we set out to design and synthesize new substitutes for C-7 in order to increase antimicrobial activity.

Materials & Methods

In this study, a new series of thiourea and thiocarbamate derivatives of ciprofloxacin were synthesized, in compounds S1, S2, S3, derivatives of thiourea and in compounds S4, S5, S6, derivatives of thiocarbamate were attached to the piperazine ring of ciprofloxacin. After synthesis, the compounds were structure determined by C NMR, H NMR and IR. All reactions and obtained compounds were controlled by thin layer chromatography (TLC).

The antimicrobial activity of the synthesized compounds was investigated by disk diffusion methods and determination of minimum inhibitory concentration (MIC) and minimum lethal concentration (MBC) on clinical strains resistant to ciprofloxacin as well as standard strains. In this study, ciprofloxacin was used as a positive control and DMSO was used as a negative control. The Broth microdilution method was chosen to determine the minimum inhibitory concentration of compounds. All experiments were performed in triplicate. Data analysis was performed using one-way analysis of variance (ANOVA) in IBM SPSS Statistics 26 with a significance level of $P \leq 0.05$.

Results & discussion

The results showed that all compounds S1-6 had antibacterial activity, and compound S4 was the most effective compound with an inhibition zone of 38 mm on P. aeruginosa ATCC 27853.

The minimum inhibitory concentration of ciprofloxacin on E. coli ATCC 25922 is 50 µg/ml, while all the synthesized compounds have a minimum inhibitory concentration of less than 50 µg/ml, which indicates the high antibacterial activity of the synthetic compounds. Also, the Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) of compound S4 on P. aeruginosa ATCC 27853 is low and close to each other, which indicates the high antibacterial activity of this compound. Despite the relative resistance of most strains, compound S1 has the best antimicrobial effect with a minimum inhibitory concentrate on of 0.78 mg/ml and a Minimum Bactericidal Concentration of 1.56 mg/ml. The results of this research showed that attaching derivatives of thiourea and thiocarbamate groups to the piperazine ring of ciprofloxacin can show a higher antibacterial effect than pure ciprofloxacin.

In general, based on the obtained results, by adding different substituents and functional groups to ciprofloxacin, it is possible to synthesize new derivatives that are effective on resistant bacteria.

Conclusion

In general, changing the structure of existing antibiotics is an efficient strategy to discover new antibacterial drugs. In this study, the aim of this study was to develop and synthesize new derivatives of ciprofloxacin. The synthesized compounds had a significant antibacterial effect against resistant bacteria, especially Gram-negative bacteria. The combination of S4 with the ethyl carbonothioyl thioacetate group had the largest inhibition zone in the disc diffusion method. The results of this research show that attaching derivatives of thiourea and thiocyanate

groups to the piperazine ring of ciprofloxacin can show a higher antibacterial effect than ciprofloxacin (control).

Keywords: Antibiotic Resistance, Antimicrobial, Ciprofloxacin, Resistant Bacteria, Thiocyanat

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