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# Fund “Nauka” Project № 19026 Resume – Competition-Based Session 2019:

“Determination of antimicrobial activity of novel nitroimidazole derivatives with potential application in transplantation medicine”

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The growing resistance of pathogens to drugs has become one of the most serious problem for medicine and public health.

Discussions about the global risk to life of millions of patients are increasing tremendously. Infections are one of the main reason for implant removal, although after an excellent invasive procedure/ operation.

The problem of “resistance” affects the individual patient and is the cause of failure therapy, rejection of the implant, extension of hospital stay and even lethal outcome for some cases.

In the last few years, the emergence of new types of resistance to clinically important antibiotics has made it even more difficult to manage with infectious agents.

Current data shows that if the rate continues to rise, through 2050 is possible the number of victims of infections to be 10,000,000 yearly-more than the number of neoplasms victim worldwide.

Searching for new biologically active compounds that have stronger antibacterial activity and a wider spectrum of action is necessary.

In most cases, the scientists rely on well-known compounds with proven therapeutic potential. Their purpose is to modify the molecules by replacing, removing or adding radicals to develop the desired new biological effects.

The synthesis and characterization of new substances with potential anti-infective and anti-tumor activity have a central role in modern medicine.

The scientists constantly looking for ways to decrease the toxicity of compounds by means of new mechanisms of action.

The project “Determination of antimicrobial activity of novel nitroimidazole derivatives with potential application in transplantation medicine” is a sequel of a project from Fund “Nauka” session 2018 – “Synthesis and characterization of novel nitroimidazole derivatives with potential biological effect. The main hypothesis of the project is that the novel nitroimidazole derivatives are going to demonstrate extended antimicrobial spectrum of activity compared to the most common nitroimidazole drugs spectrum.

It is provided to be determined and analyzed the activity of novel compounds against anaerobic and facultative anaerobic bacterial strains and fungi.

The **aim** of the project is to investigate the microbial sensitivity to novel nitroimidazoles with potential inhibitory activity on microbial growth of anaerobes, facultative anaerobes and fungi.

The scientific contribution of the project is modification of the basic chemical structures of nitroimidazoles, synthesis and analyzes of new nitroimidazole derivatives, determination of their microbial sensitivity as new drug molecules with potential application in the treatment of neoplasms and infections.

The **expected results** of this scientific project are related to synthesis of new potential drug analogues and determination of their activity. The novel nitroimidazole derivatives should possess higher spectrum of antimicrobial activity than existing nitroimidazoles. This could lead to future explorations of their biological activity, their safety, pharmacological effects and potential application in the therapy of significant diseases and transplantation medicine.

**Achieved results:**

The antimicrobial test aimed to search for and study potential antimicrobial activity of new metronidazole derivatives against clinical isolates of *St.aureus, B. subtilis, E. coli* and *Candida albicans* and referent bacterial strains *B. fragilisATCC25285.*

A total of six different concentration (6,25-200 μg/ml) of two newly synthesized metronidazole derivatives (MT2 and MT3) were tested by diffusion methods: disc diffusion method of Kirby-Bauer (with sterile 8 mm filter paper discs) and cup plate technique on Mueller Hinton Agar (MHA). The selection of solvents was very precise, according to the solubility of new compounds. Therefore, we have used the following solvents: NaCl 0,9%, Phosphate buffer pH 7,2, methanol and ethanol.

We observed weak antimicrobial activity of samples in methanolic and ethanolic solutions against *S. aureus* and *C. albicans.* The zone of inhibition for samples with concentration 100 μg/ml against S. aureus are 12 mm and 14 mm against *C. albicans* for MT2 and 12 mm against and 13 mm against C. albicans for MT3. For samples with concentration 200 μg/ml, the zone of inhibition against *S. aureus* is 13 mm, 14 mm against *C. albicans* for MT2, respectively 12 mm against *S. aureus* and 14 mm against *C. albicans* for MT3. For each sample in NaCl 0,9% and Phosphate buffer there was no detected antimicrobial activity more than controls. The tested derivatives did not show antibacterial activity against E. coli and B. subtilis strains. According to the obtained data, the tested compounds show potential antimicrobial activity.

A total of five different concentrations (2-100 μg/ml) of two newly synthesized metronidazole derivatives (MT2 and MT3) were tested by diffusion methods and Minimal Inhibitory Concentration (MIC) methods. We have used the following solvents: NaCl 0,9% and methanol. The obtained data show that at three of the MT2 concentrations – 25, 50 and 100 μg/ml are detected inhibition zones – 9.7 mm, 11 mm and 11.4 mm, respectively. In MT3, zones of inhibition are also observed, but their diameter is too small and, therefore, the antimicrobial efficiency in agar. We observed antimicrobial activity in samples in both methanolic and sodium chloride 0.9% solutions against *B.fragilis*. The MIC for sodium

chloride solution of MT2 is 25 μg/ml and for MT3 is 100 μg/ml. The MIC in methanolic solutions is as follows: Metronidazole – 25 μg/ml, MT2 - 2 μg/ml, MT3 – 2 μg/ml.

We can conclude that the introduction of an amide group in the structure of metronidazole derivatives leads to the stronger antimicrobial activity compared against tested clinical isolates and reference strain compared to metronidazole.