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Fund “Nauka” Project № 20008 Resume – Competition-Based Session 2020:

“Study of the toxicity of hydrazones of bexarotene using *in vitro* and *in vivo* models”

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The aim of this research project is to study the toxicity of hydrazones of bexarotene. To achieve this goal, phase II of the preclinical stage will be conducted in the development of new drugs. This includes tentative pharmacological screening of newly synthesized bexarotene retinoids in experiments with Wistar rats to establish their pharmacological and toxicological effects on individual systems (nervous, cardiovascular, respiratory, etc.). In the second phase, the mean lethal dose (LD50) and acute toxic dose (LD90) will also be determined by oral administration of the newly synthesized compounds.

The expected results of the research project are related to the determination of the potential activity of bexarotene analogues and the determination of their pharmacological and toxicological profile. This would support future studies to clarify the safety profile and the action of other groups of drug structures with similar chemical structure, in order to refine the therapy and safety profile of socially significant diseases.

Achieved results:

Within the framework of the current project, seven new hydrazones of bexarotene and four bexarotene esters were synthesized and characterized. The synthesis of hydrazones involved the in situ preparation of an acyl chloride, followed by the subsequent formation of a bexarotene ester. This is followed by hydrazinolysis and subsequent reaction with an aldehyde or ketone to yield the corresponding hydrazones. The esters are obtained by optimizing the esterification reaction, and instead of using thionyl chloride, oxalyl chloride was employed to produce the acyl chloride of bexarotene, resulting in a reduced number of side products.

The newly synthesized compounds underwent characterization through the application of fundamental instrumental methods for pharmaceutical analysis, including ultraviolet-visible and infrared spectrophotometry, as well as thin-layer and high-performance liquid chromatography.

To further explore the biological activity of the compounds, an in vitro assay was conducted using liver, liver S9 fraction, and skin metabolic models. This analysis aimed to determine the potential metabolic activity and toxicity of the investigated compounds. The results indicate varying metabolic activity for all analyzed compounds, as well as the capability to bind to proteins and DNA. During the analysis, the potential of esters for use as prodrugs, with the ability to penetrate the blood-brain barrier, providing a potential treatment

option for various diseases related to the central nervous system was also established. This approach could be particularly significant in addressing diseases such as Alzheimer's, Parkinson's, and schizophrenia.

For in vivo analysis, an attempt was made to determine the acute oral toxicity of different doses of bexarotene, some hydrazones of bexarotene, and the ethyl ester of bexarotene on experimental Wistar rats. The doses studied ranged from 500 to 2000 mg/m2. When the experimental animals were treated with the lowest dose of the two hydrazones, mortality was observed in the entire experimental group. Although no signs of acute oral toxicity of bexarotene and its ethyl ester were found after a single administration at doses exceeding therapeutic levels, significant differences were observed in some basic biochemical parameters (AST, ALT, CRP) and in the hemolytic profile. The obtained results justify the need for future long-term studies to explore potential toxic effects in a larger number of groups.