

# STANDPOINT

from

prof. Maya Boyanova Georgieva, Ph.D., Faculty of Pharmacy, MU - Sofia, appointed as a member of the scientific jury on the basis of Art. 4, paras 1 and 2, ZRASRB, Decision of the Faculty Council of the Faculty of "Pharmacy" at the MU - Varna and order of the Rector No. R-109-114/09.02.2023.

for the acquisition of an educational and scientific degree "**doctor**" in the *Higher Education Region: 7. Health care and sports: Professional direction: 7.3. Pharmacy; Doctoral program: Pharmaceutical Chemistry.*

from mag.-pharm. Ivelin Rosenov Iliev, full-time doctoral student in the "Pharmaceutical Chemistry" doctoral program, enrolled by order No. R-109-53/31.01.2020 at the Department of Pharmaceutical Chemistry at the Faculty of Pharmacy, MU - Varna with the topic: "**Synthesis, characterization and toxicity study of bexarotene esters**" with scientific supervisors assoc. prof. Svetlana Georgieva, Ph.D. and assoc. prof. Yana Koleva, Ph.D.

## **Biographical data:**

Ivelin Rosenov Iliev was born on 11.11.1994. In 2019, he completed his higher education in the specialty "Pharmacy" with a Master's degree in the Faculty of Pharmacy at the Medical University of Varna. By Order No. P-P-109-53/31.01.2020, he was enrolled as a full-time doctoral student at the Department of Pharmaceutical Chemistry of the Faculty of Pharmacy at MU-Varna in the Higher Education area "7. Health care and sports", professional direction: "7.3. Pharmacy", doctoral program: "Pharmaceutical Chemistry" with scientific supervisors assoc. prof. Svetlana Georgieva, Ph.D. and assoc. prof. Yana Koleva, Ph.D. By Order No. R-109-114/09.02.2023, he was dismissed with the right of defense for up to one year, starting from 09.02.2023.

The presented dissertation covers research in an up-to-date scientific field related to the evaluation of the possibilities for deriving guidelines for optimizing demand in the development of new synthetic retinoids. Scientific research is aimed at the application of optimized synthetic approaches for the preparation and characterization of ester derivatives from the retionide group, as well as their subsequent study on the *in vivo* general toxic effects and analysis, along with preliminary assessment and prediction of their metabolic activity.

**The dissertation** is written in 171 standard pages and includes the following main elements: Introduction, Theoretical part, Aims and objectives, Experimental part, Results and discussion; Conclusions, Contributions, List of publications related to the dissertation and References. The work contains 63 figures and 37 tables, 1 appendix with 5 figures, as well as 1 page of used abbreviations. 213 literary sources are cited.

**The aim of the dissertation submitted to me for opinion** is the synthesis, structural characterization and investigation of a group of new, not described in the literature ester derivatives of bexarotene and the preparation of a multicomponent toxicological profile of the retinoid analogs. To achieve this, 6 specific **tasks** have been set, formulated precisely and in a logical sequence.

In fulfillment of the set tasks, a suitable methodology was formulated and implemented for the preparation of a series of ester derivatives of the antineoplastic drug bexarotene. In addition, a correct structural characterization of the synthesized compounds was performed using modern instrumental methods, and the presented interpretation of the obtained FTIR spectra fully confirms the proposed structures. A suitable TLC method was modified and developed to evaluate the course of the reaction. The purity of the newly synthesized compounds was confirmed by appropriate physicochemical characterization, including melting point determination. In addition, a modified and validated suitable UV/Vis method was developed. To confirm the purity of the newly obtained derivatives and create the possibility of analyzing them in a mixture, a literature HPLC method was modified and applied.

At the next stage, modern *in silico* approaches were applied to predict the biological activity of the newly synthesized ester derivatives of bexarotene through two approaches: assessment of potential metabolic activity using the QSAR ToolBox software and assessment of drug similarity and probability of manifestation of receptor and/or enzyme activity using the Molinspiration cheminformatics web-based server. In addition, an attempt was made to predict the pharmacokinetic characteristics by determining the ADMET properties of the newly obtained molecules using PreADME/Tox software. An evaluation of the general toxic effects *in vivo* of bexarotene and its ethyl ester was also carried out, and some biochemical parameters were also evaluated.

The results of the conducted research are summarized in 7 **conclusions**. It is noteworthy that the conclusions thus presented do not mention the developed and validated UV/Vis spectral method, but emphasize the modified but not validated HPLC method. In its remaining part, the conclusions are well defined and reflect the results of the conducted research.

**The abstract** is prepared on 108 pages in accordance with the established requirements and correctly reflects the main applications and scientific-applied contributions of the dissertation work.

**The dissertation** complies with the requirements laid down in the Regulations for the conditions and procedures for acquiring scientific degrees and for holding academic positions at the Medical University of Varna in its part concerning the conditions for acquiring the educational and scientific degree "doctor" and its essence corresponds to a professional direction 7.3. Pharmacy ("Pharmaceutical Chemistry").

**The results of the scientific research** in the scientific work of the dissertation student are reflected in 4 scientific publications, in two of which the doctoral student is the first/last author. Parts of the dissertation have been presented at 14 national and international scientific forums. The works presented logically reflect the results obtained by the dissertation student.

### **Questions:**

After getting acquainted with the dissertation, I would like to ask the doctoral student the following questions:

1. Why the modified liquid chromatography method is not validated?
2. Why, in modifying the chromatographic method, 260 nm was adopted as the appropriate detector wavelength?



I would like to point out that the observed inaccuracies do not reduce the achievements of the doctoral student and the scientific value of the research carried out.

### **Conclusion**

The dissertation is devoted to a current problem. The research was conducted at a scientific level and the results are of a scientific and applied orientation. In terms of volume, overall design and scientific publications in connection with it, the dissertation meets the requirements for obtaining the educational and scientific degree "doctor". The scientific parameters are in accordance with the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its implementation and the Regulations of the MU - Varna.

This gives me the reason to give a **positive assessment** of the dissertation work on the topic: "Synthesis, characterization and toxicity study of bexarotene esters" and to recommend the respected members of the Scientific Jury to vote positively for the award of M.Sc. Pharm. **Ivelin Rosenov Iliev** of the educational and scientific degree "**doctor**" in *Professional direction: 7.3. Pharmacy in the Doctoral Program: Pharmaceutical Chemistry*, according to the Law on the Development of the Academic Staff in the Republic of Bulgaria.

Sofia  
10.04.2023

  
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/prof. Maya Georgieva, Ph.D./