STANDPOINT

By Assoc. Prof. Anna Hristova Todorova, Ph.D.
Medical University – 'Prof. Dr. Paraskev Stoyanov' – Varna

Regarding: Dissertation on a topic:
‚SYNTHESIS, CHARACTERIZATION AND STUDY OF THE TOXICITY OF BEXAROTEN ESTERS'

for awarding the educational and scientific degree
‚Doctor'
in a doctoral program ***‚Pharmaceutical chemistry'***
in the professional direction ***7.3. ‚Pharmacy'***,
field of higher education ***7. ‚Health and sports'***

Doctoral student: Ivelin Rosenov Iliev
Scientific supervisors:
Assoc. Prof. Svetlana Georgieva Ph.D and Assoc. Prof. Yana Koleva Ph.D

According to order No. R-109-114/09.02.23 of the Rector of the MU - Varna, I am included in the scientific jury for the procedure for acquiring the ESD "Doctor" of master pharmacist **Ivelin Rosenov Iliev**, a full-time doctoral student at the department of ‚Pharmaceutical Chemistry' of the Faculty of Pharmacy of the MU - Varna, doctoral program in ‚**Pharmaceutical chemistry**', professional direction **7.3. ‚Pharmacy**', field of higher education **7. ‚Health and Sports**', and I have been assigned to submit an opinion on his dissertation work on the topic: ‚Synthesis, characterization and toxicity study of bexarotene esters'.

Brief biographical data of the PhD student

Ivelin Rosenov Iliev obtained his higher education in Pharmacy at the Faculty of Pharmacy at the Medical University ‚Prof. Dr. Paraskev Stoyanov' - Varna in 2019. After graduation, he worked in pharmacies serving the population as a master pharmacist.

His academic development begins in 2021, starting in January as an Assistant Professor in the department of ‚Pharmaceutical Chemistry' at the Faculty of Pharmacy of the Medical University of Varna, where he is currently working. Conducts seminars and laboratory exercises in the disciplines ‚Pharmaceutical Chemistry' and 'Pharmaceutical Analysis', carries out scientific and research activities in the same field. Excellent command of the English language, written and spoken. Ivelin Iliev was enrolled in 2020 as a full-time doctoral student in the Ph.D. program ‚Pharmaceutical Chemistry' in the 'Pharmaceutical Chemistry' department of the Faculty of Pharmacy of the Medical University of Varna. The doctoral student successfully passes the courses and exams set during the training, which is evident from the submitted documents. He was

dismissed with the right of defense by order of the Rector of the MU - Varna No. R-109-114/09.02.23.

Characterization and evaluation of the dissertation work

The dissertation of master pharmacist Ivelin Iliev has a total volume of 192 pages. The main text is presented in the VII section of 165 pages with the following distribution: Introduction (2 pages), Literature review (68 pages), Aim and objectives (1 page), Experimental part including Materials (2 pages) and Methods (13 pages), Results and Discussion (64 pages), Conclusions (2 pages) and Contributions (1 page). The individual parts are connected meaningfully and in a logical sequence. The standards and requirements for the content, structure and proportion between the sections of the development are respected.

The dissertation is illustrated with 63 figures and 37 tables. The bibliography contains 213 sources.

Relevance of the topic of the dissertation

Retinoids are used to treat skin conditions such as acne and psoriasis and some types of cancer. Despite established therapeutic results, their application is limited due to their toxicological profile. The retinoid bexarotene has potential antineoplastic properties. It is approved for the treatment of cutaneous T-cell lymphoma (CTCL), and therapeutic effects have been observed in the treatment of breast and lung cancer. A number of studies have described the potential of bexarotene in the treatment of neurological diseases such as Alzheimer's disease, Parkinson's disease and schizophrenia. All this directs the interest of scientists to explored new applications. The structure of bexarotene enables the application of the pro-drug design strategy. Its potential application in oncology and its ability to modulate a number of physiological effects provides grounds for the synthesis of new, undescribed in the literature analogues of Bexarotene, their characterization, determination of toxicological profile and investigation of the possibilities for therapeutic application. In this sense, the topic of the dissertation work of master pharmacist Ivelin Iliev is markedly current.

The ***introduction*** presents the relevance of the problem to be investigated and its significance for the scientific field.

The ***literature review*** is based on contemporary literary sources and demonstrates very good awareness and theoretical knowledge of the dissertation student on the topic of the dissertation work. The following areas are analyzed in detail: mechanism of action, structure and function of retinoids, therapeutic application, methods of preparation of bexarotene and its derivatives, pharmacodynamics, pharmacokinetics, metabolism, toxicological profile and drug interactions of bexarotene. The limited information in the literature regarding the possibilities of changing the structure of Bexarotene and the synthesis of its new derivatives has been reported, which determines the research interest in the direction of developing a methodology for the synthesis of Bexarotene ester derivatives, their subsequent characterization and determination of the toxicological profile.

The ***objective*** is formulated clearly and precisely based on the outlined scientific problems from the literature review. Six research **tasks** are set, which represent the stages of the research in sequence.

The ***materials and methods*** are adequately selected and described in detail. The individual methods are tailored to the goal and tasks, and lead to their successful implementation.

The obtained ***results*** are comprehensive, correspond to each of the set tasks and follow logically from them.

The preparation of four new esters of the antineoplastic drug Bexarotene using a developed synthetic method for obtaining ester derivatives is described. A method for monitoring the esterification reaction based on thin-layer chromatography has also been developed. The obtained bexarotene derivatives were structurally characterized using melting point, IR spectroscopy, UV-VIS spectroscopy and HPLC. A new HPLC method has been developed for the determination of Bexarotene and its derivatives alone and in mixtures. Using a theoretical approach, the possibilities for metabolic activation of Bexarotene, its metabolites and derivatives have been identified. It was established that the studied Bexarotene derivatives show a potential for binding to DNA and proteins, which is a possible cause of toxic effects. A theoretical model was applied to evaluate the pharmacokinetic characteristics of Bexarotene and the newly synthesized esters and their bioactivity. The resulting esters are characterized with good ADME/Tox properties. Their ability to cross the blood-brain barrier makes it possible to treat CNS-related diseases. By means of an *in vivo* model, the total liver toxicity of bexarotene and ethyl ester of bexarotene was determined. The results show no liver toxicity of ethyl ester of bexarotene at a dose of 750 mg/m^2.

The dissertation ends with the formulation of 7 conclusions, which adequately reflect the obtained results and summarize the most essential of the conducted studies. In the development process, the dissertation student demonstrates the acquired abilities for independent scientific research.

The defined contributions are of an original nature and represent the merits of the work.

I recommend that the contributions be divided into scientific-theoretical and scientific-applied.

Popularization of the results of the dissertation work and scientometric indicators

In connection with the dissertation, the author presents 4 scientific publications. In 3 of the publications he is a second and subsequent author. 1 article is presented in a Bulgarian journal, referenced with a global database, with IF, in which Ivelin Iliev is the first author. The results of the studies were presented in 4 scientific forums with poster presentations, published in full text and corresponding to the titles in the presented list of publications. The doctoral student is participating in a scientific project on the subject of the dissertation work, financed by the ‚Science' Fund of the MU-Varna. The abstract is prepared according to the requirements and reflects the content of the dissertation in a synthesized form. I recommend that the specific participations in scientific forums related to the topic of the dissertation work be added to the attached list of publications and participations.

Conclusion:

Ivelin Iliev's dissertation shows that the author has in-depth theoretical knowledge and practical training in the doctoral program and demonstrates skills for independent research.

I believe that the development in terms of volume, structure, content, contribution results for pharmaceutical science and practice, as well as in accordance with its originality and relevance, and the published scientific production, fully satisfies the qualitative and quantitative criteria for acquiring the ESD ‚Doctor' according to the Law on the Development of the academic staff in the Republic of Bulgaria, the Regulations for its application and the Regulations for the development of the academic staff of the University of Varna, which gives me the reason to give a positive assessment and to propose to the respected members of the Scientific Jury to award the Master Pharmacist Ivelin Rosenov Iliev ESD ‚Doctor' in the doctoral program ‚Pharmaceutical Chemistry', in professional direction 7.3. ‚Pharmacy', field of higher education 7. ‚Health and sports'.

Assoc. Prof. Anna Hristova Todorova, Ph.D

Signature: .....

Varna, 24.03.2023