

**"VICTOR BABEȘ" UNIVERSITY OF  
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DOCTORAL SCHOOL  
PHARMACY**



**IN SILICO AND CHEMICAL SYNTHESIS METHODS  
USED FOR THE DEVELOPMENT AND  
FORMULATION OF PHARMACOLOGICALLY ACTIVE  
COMPOUNDS**

**ABSTRACT**

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The habilitation thesis " IN SILICO AND CHEMICAL SYNTHESIS METHODS USED FOR THE DEVELOPMENT AND FORMULATION OF PHARMACOLOGICALLY ACTIVE COMPOUNDS" summarizes the candidate's postdoctoral achievements.

Chemical synthesis is a critical component and, in many cases, the starting point for the development of a new compound with potential therapeutic effects. Even though there is a vast plethora of chemical molecules that appear daily and are researched for their pharmacological effect, and even though the vast majority of them are effective from a pharmacological standpoint, the same majority has toxicological or pharmacokinetic drawbacks that make them unsuitable for development as future drug-like compounds. Computational methods play an important role in this process because they allow for the rational development of a series of compounds with a high probability of being active against a specific biological target.

The current work is divided into four major chapters. The first chapter summarizes the candidate's postdoctoral scientific activity. It is divided into three major sections. The first section discusses the chemical and computational methods, as well as the biological effects of various 1,2,4-triazole-3-thiol derivatives. This activity is a continuation of the doctoral work, focusing on the expansion of the series of triazole derivatives as well as their formulation in polyurethane nanostructures. On different cancer cell lines, the compounds discussed exhibit varying degrees of cytotoxicity.

The following subchapter focuses on nanoformulations of various bioactive natural compounds from the pentacyclic triterpene class. Thus, metallic bioconjugates like silver nanoparticles conjugated with betulin, gold nanoparticles conjugated with betulin, betulinic acid, and semi-synthetic triterpene derivatives, magnetoliposomes with betulinic acid, co-crystals of betulinic acid with vitamin C, inclusion complexes of some triterpenes in cyclodextrins, and many others are discussed. All of these formulations were created with the goal of increasing the cytotoxic effect of the formulated active substance and improving its bioavailability. This subchapter also compares the biological effects of the formulated compounds to those of the structures tested as such.

The first part's final subchapter focuses on the synthesis and evaluation of a diverse range of triterpene derivatives derived from various basic chemical scaffolds. A series of derivatizations appear in various positions of the triterpene core as a result of these chemical changes. Thus, the compounds under discussion are chemical classes such as lupane, ursane, oleanane, and dammarane and other derivatives. The majority are heterocyclic derivatives with having different structures grafted in various positions, such as piperidine, piperazine, pyridine, 1,2,4-triazole, benzotriazole, or azepane, but compounds such as esters or amides of some triterpenes are also studied for their various biological effects. This section is divided into subsections based on the pharmacological effects of the tested derivatives. The majority of this subchapter is devoted to antitumor derivatives, as pentacyclic triterpenes are known to have an antiproliferative effect against various types of cancer. However, derivatives with antimycobacterial or antichlamydia activity are treated concurrently.

Because of the presence of different research sub-directions, the first chapter that deals with scientific activity in the current work does not necessarily have a chronological division, but is divided according to the obvious two sub-directions, respectively formulations of active compounds, and synthesis of active chemical compounds, and the sub-chapter dedicated to triazole derivatives is treated separately because it represents an extension of the research completed within the doctoral studies, and the other two sub-chapters have pentacyclic triterpenes as a common element. My entire scientific activity has resulted in the publication of 55 articles in ISI journals with a total impact factor of more than 200, two book chapters, and fifteen conference papers. I am the primary author of more than half of these articles. 64.81% of articles published in journals ranked in the Q1/Q2 area. According to the Web of Science Citation Report (Clarivate Analytics), the Hirsch index is 16, based on 778 citations (695 without self-citation) and an average of 11.67% citations per publication (without self-citation). During my research, I was a member of four national research grant teams and the project director of a national and a local grant funded by UMFVBT.

The second chapter is devoted to academic accomplishments. My academic career began in 2014 when I was hired as a University Assistant in the Department of Pharmaceutical Chemistry. I was promoted to lecturer in 2018, and to associate professor in 2021. In the meantime, from 2018 to 2020, I was a resident in the field of Pharmacy, specializing in pharmaceutical laboratory seconded to the Emergency County Clinical Hospital "Pius Brînzeu", Timișoara, Romania, and since 2021 until present, I am a resident in the same institute specializing in general pharmacy. During these years, I achieved an improvement in teaching quality by taking psycho-pedagogy courses, interacting with students, and actively participating in the continuous modification and modernization of course materials. I was also actively involved in our university's tutoring program "Volunteering in Academic Development" (VADA), which allows students to broaden their knowledge and acquire a variety of skills by participating in a teaching or scientific activity.

The third chapter describes my professional activities and is divided into two sub-chapters that show my professional career and the certificates I've received. In October 2013, I graduated from the "Victor Babeș" University of Medicine and Pharmacy, Faculty of Pharmacy, and began doctoral studies at the "Coriolan Drăgulescu" Institute of Chemistry, coordinated by Prof. Dr. Ludovic Kurunczi. In August 2017, I successfully defended my doctoral thesis, "Design, synthesis, and assessment of new bioactive compounds, potential drugs for signalling pathways in colon cancer," and received the grade "Very good." Following the completion of my doctoral studies, I was awarded an internal project funded by UMFVBT, with the assistance of which I was able to continue to some extent the research I began during my doctorate. The following year, I was awarded a national post-doctoral fellowship. The funding allowed us to lay the groundwork for a stable research infrastructure, which has been very productive up to this point. The National Alliance of Student Organizations in Romania (ANOSR) awarded me the "Bologna Professor" award at the end of 2019.

The final chapter discusses future academic, scientific, and professional development opportunities. Academic skills will be improved through the use of modern teaching techniques and the continuous modernization of materials and their exposure, resulting in a more appealing learning environment. From a research standpoint, I will continue in the current direction, but I will try to redirect a portion of this research field to studies related to longevity, a field that appears to be experiencing exponential growth in terms of popularity and results appearing in the literature. To boost both the institutional and personal prestige, I propose maintaining the same high standards in terms of the quality and quantity of scientific results dissemination.