ACADEMIA ROMÂNĂ
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Anexa nr.6

SUMMARY OF THE HABILITATION THESIS

INTEGRATING *IN SILICO* APPROACHES IN DRUG DESIGN AND GREEN CHEMISTRY: SUSTAINABLE SOLUTIONS FOR HEALTH AND THE ENVIRONMENT

Habilitation Domain: *CHEMISTRY*

Author: Dr. CRIȘAN Elena-Luminița

The present habilitation thesis presents the candidate's scientific, academic, and professional research conducted after the award of the PhD degree, titled "*Comparison of Different QSAR Methods for the Same Biological Receptor*", submitted on May 20, 2011, at the Romanian Academy, Institute of Chemistry, Timisoara, in the field of Chemistry, under the supervision of Prof. Dr. Ludovic Kurunczi. The thesis was officially validated by Ministerial Order No. 6468 / 07.12.2011.

The present work is structured into three main chapters, with a chapter dedicated to the candidate's own contributions based on 10 representative papers from a total of 55 personal Web of Science articles, of which the candidate is first author on 21, corresponding author on 19, and co-author on 15. *Chapter I* provides a detailed overview of the candidate's scientific, professional, and academic achievements, emphasizing original contributions in the field of computational chemistry. It highlights the candidate's research on the application of *in silico* methods in drug design, the development of eco-friendly anticorrosive materials, and the identification of non-toxic herbicides, focusing on optimizing molecular properties, reducing environmental impact, and increasing the efficiency of chemical processes. The chapter includes an analysis of the current state of knowledge, the presentation of major results obtained during 2020-2025, and the candidate's complementary activities, such as coordinating research projects, project management, and involvement in the evaluation of scientific publications. *Chapter II* is dedicated to presenting future development directions, both from a scientific and academic perspective. Research objectives for the short, medium, and long term are outlined, in line with the candidate's expertise and emerging trends in computational chemistry, green chemistry, and drug design. The intention to strengthen interdisciplinary collaborations, secure funding for innovative projects, and expand involvement in human resource training is highlighted. *Chapter III* compiles the bibliography used throughout the work, including both relevant sources from the specialized literature and the candidate's own scientific publications, which underpin the contributions and research directions presented in the thesis.

The present habilitation thesis reflects the candidate's scientific and academic trajectory, highlighting her original contributions in promoting and applying *in silico* methods in key areas such as green chemistry and drug design. The work aims at developing sustainable solutions with a positive impact on human health and environmental protection. The thesis also emphasizes the interdisciplinary nature of the research, situated at the intersection of experimental chemistry, theoretical/computational chemistry, biology, and environmental science.

Chapter I of the thesis is dedicated to a detailed characterization of the *in silico methods* used in the candidate's research activities, with a focus on their applicability in green chemistry and rational drug design. The theoretical principles and technological evolution of the main computational methods are presented, including pharmacophore simulations, molecular docking, QSAR analyses, virtual screening, machine learning techniques, pharmacokinetic predictions, as well as multi-target modeling approaches and quantum calculations, highlighting the advantages and limitations of each within the context of interdisciplinary research. The chapter illustrates how these tools were integrated into the studies conducted by the candidate, contributing to the identification and optimization of compounds with pharmacological potential and favorable ecotoxicological profiles. The subchapters are organized according to the main research application areas, each highlighting how *in silico* methods were employed to address specific questions and optimize compound design or material characterization. The first section of original contributions (*subchapter 1.3.2*), dedicated to the study of biologically active inhibitors with therapeutic potential, includes research on molecules active in neurodegenerative, metabolic, and oncological diseases, as well as in addressing human immunodeficiency virus (HIV) infection. This research integrates techniques such as molecular docking, QSAR analyses, pharmacokinetic predictions, machine learning, and deep learning for the evaluation of compound activity and selectivity. The studies revealed relationships between the structural features of molecules and their biological activity, providing a detailed understanding of ligand-target interactions for three main targets: GSK-3 (Glycogen Synthase Kinase-3), MAO-B (monoamine oxidase B), and HIV-1 (human immunodeficiency virus), as well as the molecular mechanisms involved. Hybrid workflows combining molecular modeling, DFT studies, and pharmacokinetic and toxicological assessments (ADMETox) enabled not only the rational selection of relevant natural and synthetic compounds but also the exploration of opportunities for drug repositioning. The results demonstrated that computational methods can predict pharmacological effects and inhibitor selectivity, reducing the chemical space required for experimental testing and accelerating the identification of promising candidates for experimental validation and clinical applicability. Overall, the section emphasizes the significant impact of *in silico* strategies in rational drug design, demonstrating their applicability to multiple therapeutic targets and strengthening the theoretical foundation for the development of new inhibitors with enhanced efficacy and safety. The second section (*subchapter 1.3.3*) focuses on eco-friendly anticorrosive materials, presenting the structural and electronic characterization of metal phosphonates and polymers with graphene oxide nanoparticles, as well as correlating these properties

with their anticorrosive performance. In this part, computational methods enable a synergistic analysis of structures and interactions at the molecular level, providing valuable information for optimizing the properties of environmentally friendly anticorrosive materials. The results show that the metal phosphonates CoPA and NiPA provide superior corrosion protection in saline solutions, both in the short and long term, through the formation of stable protective layers and optimal interactions with the metal surface. Quantum chemical analyses of PU-GON revealed that the reduced forms of graphene oxide have a high capacity to donate and accept electrons, and the distribution of electrostatic potential along with Fukui functions allowed the identification of reactive centers essential for adsorption on the polymer surface. Computational studies confirmed the molecular mechanisms involved in corrosion inhibition, highlighting the direct relationship between structural and electronic properties and anticorrosive efficiency. Overall, this section emphasizes the combined applicability of experimental and *in silico* methods in the development of eco-friendly anticorrosive materials, demonstrating how molecular-electronic information can guide the optimization of material properties and performance. The third section (*subchapter 1.3.4*) addresses non-toxic and environmentally friendly herbicides, including the prediction of insecticidal activity and the identification of natural compounds with minimal risk to human health and bees. The *in silico* methods used combine QSAR approaches, virtual screening, molecular homology, molecular docking, quantum chemical calculations, etc., for the rapid and efficient selection of safe and effective compounds. The results showed that these approaches allow the simultaneous evaluation of biological efficacy and ecological safety, facilitating the identification of compounds that combine high activity with a favorable toxicological profile. The studies identified molecules with herbicidal potential comparable or superior to reference substances (imidacloprid and fluroxypyr), but with minimal risk to bees and human health, demonstrating that integrated computational methods can guide the selection and prioritization of promising candidates. Overall, this section highlights the value of *in silico* strategies as rapid and efficient tools for designing safer and more sustainable herbicides, thus contributing to environmental protection and the development of responsible agricultural practices.

Chapter II explores the professional and scientific development opportunities that have emerged for the candidate in the context of her future academic and research plans. The section highlights prospects for advancement, as well as the main stages and experiences that have strengthened her professional trajectory within the scientific community. Research directions with already significant results will serve as the foundation for future activities, alongside the initiation of

new areas aimed at generating innovative and relevant outcomes. The expansion of the research scope is planned to address emerging challenges and to reinforce the candidate's contribution to scientific progress.

Chapter III of the habilitation thesis consists of the complete list of the 251 bibliographic references consulted during the preparation of the work.

In conclusion, all the research presented in this thesis is focused on the integration of *in silico* methods in green chemistry and drug design, aiming at the development of sustainable solutions for the environment and human health. This thesis aligns with the principles of sustainable development and global efforts to protect the environment, highlighting the role of *in silico* methods in rational drug design and in promoting responsible and efficient chemistry.