STATEMENT

from Prof. Dr. Pavletta Stoyanova Shestakova

Institute of Organic Chemistry with Centre of Phytochemistry, BAS

Member of the Scientific Jury according to order № RD-09-291/28.09.2020 of the Director of IOCCP-BAS

Subject: PhD thesis for awarding the educational and scientific degree "Doctor", professional field 4.2. "Chemical Sciences", scientific specialty "Organic Chemistry".
PhD Candidate: Assistant Zhanina Stoyanova Petkova
Topic: Synthetic approaches towards chiral and biologically active compounds
Supervisors: Prof. DSc Vladimir Dimitrov
Senior assistant dr. Malinka Stoyanova

The PhD thesis and the set of documents presented by Assistant Zhanina Petkova are in accordance with the requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria, The Regulations of BAS for the Implementation of this Law and the Rules of IOCCP-BAS.

General presentation of the Candidate

Zhanina Petkova received a bachelor's degree (2009) and a master's degree (2011) in Chemistry, with a professional qualification in "Modern methods for synthesis and analysis of organic compounds" at the Faculty of Chemistry and Pharmacy, Sofia University "St. Kliment Ohridski ". During the period 2011 - 2014 she was a doctoral student in the laboratory "Organic Synthesis and Stereochemistry" at IOCCP, BAS, and in 2014 she was appointed as an assistant in the same laboratory.

Aims of the PhD Thesis and timeliness of the research topic

The investigations in the Thesis are in the field of asymmetric organic synthesis and aim at the development of effective approaches for synthesis of chiral compounds with applications as ligands and catalysts for achieving high stereoselectivity in various chemical transformations, as well as at the synthesis of a series of compounds with potential biological activity. The dissertation presents studies in a topical, important and promising scientific field; the specific tasks to achieve the research objectives are clearly formulated, based on an in-depth review of current trends and achievements in the field of asymmetric organic synthesis. In particular, the studies in the dissertation are focused on two main directions: i) development of synthetic approaches for the synthesis of chiral sulfonamide compounds modified with a phosphine substituents and their application as ligands in palladium-catalyzed allylic substitution reactions; and (ii) developing a series of chiral amino alcohols, based on natural sources and modified with appropriate substituents, with potential application as new and effective drugs against multidrug-resistant tuberculosis strains.

Main results and contributions of the Thesis

The results obtained in the dissertation have fundamental and applied aspects, and represent an enrichment of existing knowledge in the field of asymmetric organic synthesis, contributing to the development of new chiral catalytic and biologically active systems. The scientific results and contributions can be summarized as follows:

- An effective approach for the synthesis of chiral phenylsulfonamides with diphenylphosphine substituents has been developed, based on the introduction of chirality within the sulfonamide group via Directed ortho Metalation.
- The diphenylphosphine sulfonamides have been shown to be suitable catalysts in the palladium-catalyzed allylic substitution reaction. The results demonstrate that the compounds show high efficiency as P,O-ligands and an enantioselectivity of up to 83% *ee* was achieved under suitable conditions.

- A series of chiral β-amino alcohols with a camphene skeleton were synthesized and their *in vitro* antituberculous activity was studied. For some of the compounds, the cytotoxic activity against a 293T human embryonic kidney cell line was determined. Some of the newly synthesized structures show high efficiency and low cytotoxicity, which makes them suitable candidates for the development of drugs with potential antituberculous activity.
- The contribution of the different structural fragments to the antimycobacterial activity of the compounds was evaluated using an appropriate QSAR model. Based on the obtained results, promising structures have been identified for the synthesis of new compounds with optimized biological activity and improved pharmacological parameters.
- 64 new compounds were synthesized and their structure was characterized in detail by 1D and 2D NMR techniques, mass spectrometry, specific rotation, melting point and elemental analysis.

Research metrics

The results from the investigations conducted in the Thesis are summarized in 3 research papers, published in Tetrahedron Letters (IF = 2.27, Q2), European Journal of Medicinal Chemistry (IF = 5.57, Q1) and Monatshefte für Chemie (IF = 1.35, Q3). A total of 16 citations were noticed, with relatively large number of citations (12) for the publication in the European Journal of Medicinal Chemistry which is indicative of the importance of the results. The results are presented at 13 scientific forums (7 international and 6 national) through 11 posters and 2 oral presentations. Recognition for the high level of studies are the two awards for Young Scientist received by Assistant Zhanina Petkova at the Annual Scientific Sessions of IOCCP in 2013 and 2019, as well as the funding from the Operational Program "Development of Human Resources 2014" for promotion of a research paper. Assistant Zhanina Petkova participated in seven research projects funded by the National Science Fund and the Ministry of Education and Science, as well as in 2 projects funded by companies.

Critical remarks and recommendations

I have no critical remarks on the PhD Thesis of Assistant Zhanina Petkova and on the presented materials.

CONCLUSION

My overall impression is that the dissertation represents a high quality synthetic and analytical work, conducted with great precision. The dissertation presents Assistant Zhanina Petkova as a serious and promising young researcher with in-depth knowledge and experimental skills in the field of synthetic organic chemistry, which she skillfully combines with modern spectral methods for structura l analysis. The dissertation is written clearly and logically, demonstrating excellent general background in synthetic chemistry and in-depth knowledge of the scientific field of the Thesis. The dissertation abstract accurately and correctly reflects the content and main contributions of the Thesis.

The results presented in the dissertation of Assistant Zhanina Petkova cover and exceed the requirements for awarding the scientific and educational degree "Doctor", according to requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria, The Regulations of BAS for the Implementation of this Law and the Rules of IOCCP-BAS.

Based on the above, I give my positive assessment of the PhD Thesis and I am pleased to recommend to the Honored Scientific Jury to award to Assistant Zhanina Petkova the educational and scientific degree "Doctor" in the professional field 4.2. "Chemical Sciences", scientific specialty "Organic Chemistry".

13.11.2020 Prof. Pavletta Shestakova