

## STATEMENT

from prof. Lily Plamenova Peikova, PhD

for the acquisition of the educational and scientific degree "Doctor" of MPharm Ivalina Valerieva Vassileva, PhD student in full-time study, doctorate program "Pharmaceutical Chemistry", field of higher education 7. "Health and Sport" and professional field 7.3. "Pharmacy", "New aspects in pharmaceutical analysis of Quinine and some of its oxidation products", Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Medical University (MU) – Varna.

MPharm Vassileva acquired the educational and qualification degree "Master of Pharmacy" at the Faculty of Pharmacy of MU - Varna in 2015. In 2020 she was enrolled as a full-time PhD student in the Department of Pharmaceutical Chemistry at the Faculty of Pharmacy of MU - Varna. In 2021, MPharm Vassileva acquired a specialization in "Analysis of medicinal products" at MU-Sofia.

The dissertation thesis contains 94 pages, 4 tables, 41 figures and 48 diagrams. 159 literature sources are cited.

The scope and the scientific hypothesis of the work are in the field of pharmaceutical analysis, which together with pharmaceutical chemistry build the PhD program in Pharmaceutical Chemistry. The research focuses on the pharmaco-analytical characterization of the alkaloid Quinine and some of its oxidation products, which are structurally derivatives of Quinoline (benzo[b]pyridine). Quinoline is the basic chemical structure of various drugs and compounds with biological activity. The medicinal product Quinine sulphate (hydrochloride) finds therapeutic application in various forms of malaria, the S-isomer of quinine, quinidine. It has antiarrhythmic activity, and Quinotoxin has been administered mainly as a vasodilator. The topic of the PhD thesis is dissertationable and useful in terms of developing approaches for qualitative analysis of Quinine and its oxidized products. In addition to the development of analytical methods, attention is given to the importance of relevant analytical characteristics.

The detailed literature review sets the objectives of the PhD thesis, which are precise and specific.

Quinine is an R-stereoisomer and Quinidine is an S-stereoisomer and the PhD student developed an efficient analysis of the secondary alcohol group in their structure. An oxidation-reduction reaction between the alkaloids used and elemental S8 and consideration of the reactivity of the separated hydrogen sulfide towards lead acetate was used, with the limit of detection (LOD) of the alkaloids studied being  $\sim 0.006$  mg. The developed method is accurate and reproducible.

An analytical assay was developed for the qualitative analysis of Quinotoxin, which contains a secondary, cyclic amino group in the piperidine fragment of the molecule. By introducing the Quinotoxin to a solution of Bromophenothiazine, an analytical response was immediately obtained at a detection limit of  $\sim 0.0075$  mg.

The PhD student optimized the classical Herapathite test by successfully using potassium iodide instead of iodine.

The developed chemiluminescent method is economical and easy to perform. The methodology allows the use of small quantities of commonly available reagents, which reduces not only the cost of the analysis but also its environmental impact. High repeatability and low detection limit are achieved. This method is particularly suitable for routine analysis of 4-aminophenol, a potential impurity in the synthesis of Paracetamol.

The Ph.D. student analyzed the quartz-crystal microbalance QCM technique and a Quinine-imprinted polymer layer on the QCM wafer surface was realized. Two Carvone enantiomers, R-Carvone and S-Carvone, were used for this study. The sorption capacity of the (S)-enantiomer exceeded that of the (R)-enantiomer approximately 7 to 10-fold.

The optimized and developed analytical methods have scientific and applied contributions. The PhD student has conducted a sufficient number of experiments varying the ratios of reagents, reaction conditions and has mastered various analytical methods. There are some inaccuracies in the work, but they do not impair the scientific study.

The scientific metrics of the thesis meet the requirements of the Regulations for the Development of Academic Staff at MU-Varna. Two scientific publications are presented in Bulgarian Chemical Communications - refereed and indexed in world-known databases with

scientific information and Scripta Scientifica Pharmaceutica - non-refereed publication with scientific peer review.

The Abstract book completely covers the thesis.

#### Conclusion

This is a PhD thesis with a clear goal, a precisely executed experiment and convincing results. I propose that the esteemed scientific jury to award the educational and scientific degree "Doctor" MPharm Ivalina Valeriyeva Vassileva.

My assessment is POSITIVE.

20.01.2024

Reviewer:

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(prof. Peikova, PhD)