OPINION FOR DISSERTATION PAPER

by assoc.prof. Lily Plamenova Peikova, PhD

Regarding for the award of educational and scientific degree "Doctor of Philosophy" to MPharm Sonya Yordanova Ivanova - PhD student in full-time form of study in a doctoral program "Pharmaceutical Chemistry", in the field of higher education 7. "Healthcare and Sport" and professional field 7.3. "Pharmacy" on the topic "New strategy for qualitative and quantitative analysis of Nitrofural and its new derivatives", in the Department of "Pharmaceutical Chemistry" of the Pharmaceutical Faculty, Medical University – Varna.

MPharm Sonya Yordanova Ivanova is born in 1992. She acquires the educational and qualification degree "Master Pharmacist" from the Pharmaceutical Faculty of Medical University – Varna in 2017. She has a working experience in Community pharmacy and from 2019 she is a PhD student in the Department of "Pharmaceutical Chemistry" of the Pharmaceutical Faculty, Medical University – Varna.

The Dissertation consists of 110 pages, 6 tables and 72 figures, 10 schemes and 3 spectral applications. It also consists of 240 references (13 of whom from the past 5 years).

It is multidisciplinary work: synthesis of polymorphic forms and 2-(5-nitrofuran-2-yl)-1,3,4-oxadiazoles; pharmaco-analytical characterization; demonstration of chemical structures; pharmacology and toxicology. The PhD student focuses on the anti-infective medicinal product *Nitrofural* (described in the European Pharmacopeia) - nitrofuran derivative, effective against gram-negative and gram-positive bacteria. The literature review argues the purpose and objectives of the doctoral thesis, which are set very precisely.

Research in recent years has proven the importance of polymorphism in terms of biological activity and the therapeutic effect of medicinal products and newly synthesized molecules with biological activity. The pharmaco-analytical characterization of *Nitrofural*, according to the European Pharmacopoeia, uses the methods: ultraviolet and visible absorption spectrophotometry; infrared absorption spectrophotometry; thin layer chromatography and liquid chromatography without polymorphism. The contribution of scientific research is the analysis of the possibility of the emergence and detection of polymorphic forms of *Nitrofural*. All

polymorphic forms are synthesized by the "solvent / co-solvent evaporation" approach. The results of DSC, XRD and FTIR analyzes convincingly show the presence of a new polymorphic form of the drug molecule, without being synthesized individually.

There are no data in the literature on the use of Gibbs reagent (2,6-dichloroquinone-4-chloroimide) for qualitative analysis of semicarbazones, a structural element of *Nitrofural*. The results of the PhD dissertation clearly show the possibility of using this reagent for qualitative analysis of such structures. A significant contribution of the PhD student is the supposed mechanism of the reaction between the drug molecule and the Gibbs reagent.

Using the structure of *Nitrofural*, the PhD student focuses on its modification in order to obtain structures with potential anti-infective activity. By varying and optimizing synthetic methods, two new 1,3,4-oxadiazoles not described in the literature were obtained: 2-iodo-5-(5-nitrofuran-2-yl)-1,3,4-oxadiazole and 2-isopropyl-5-methyl-4-((5-(5-nitrofuran-2-yl)-1,3,4-oxadiazol-2-yl)diazenyl)phenol. The structure of the compounds is proved by spectral methods. Their antibacterial activity is comparable to the reference *Nitrofural* against *E. coli* and *S. aureus*.

The contribution of the PhD dissertation of MPharm Sonya Ivanova is of scientific-theoretical and potential applied nature.

Scientometrics

The PhD student Ivanova fully meets the requirements of the Law on the development of the academic composition in the Republic of Bulgaria and the Regulations for the development of the academic staff of Medical University – Varna.

The scientific papers related with the PhD thesis are four and are published in reviewed scientific journals. Research on new approaches based on IR spectroscopy, XRD and DSC in Nitrofural polymorphic analysis are published in the Journal of Molecular Structure with IF=3.196.

The abstract completely covers the dissertation.

The dissertational thesis is very well structured, written and illustrated. The written bibliography is scattered, without order and does not follow any pattern of writing. This remark does not question the positive work done by the PhD student.

Conclusion

The work shows a serious development in the field of pharmaco-analytical characterization of synthesized polymorphic forms of *Nitrofural*, optimization of synthetic methods, preparation of new chemical structures - 1,3,4-oxadiazoles, testing for antibacterial activity and proposing a mechanism for using the reagent of Gibbs for qualitative analysis of semicarbazones. The positive contribution of the thesis is its openness to future research at the next higher levels in analysis, synthesis, and pharmacology.

The nature of scientific contributions is the enrichment of existing knowledge and the potential application of these scientific achievements in practice.

My proposition is to award the educational and scientific degree "Doctor of Philosophy" to MPharm Sonya Ivanova.

I give my POSITIVE assessment.

29.05.2022 Reviewer:

(assoc. prof. Peikova, PhD)