

REVIEW

by prof. Alexander Borisov Zlatkov, DSci,
lecturer in the Department of Pharmaceutical Chemistry, Faculty of Pharmacy,
Medical University - Sofia, appointed a member of the scientific jury on the basis of
Art. 4, para 1 and 2, ZRASRB, Decision of the Faculty Council of the Faculty of
Pharmacy at MU - Varna and order of the Rector № № P-109-120/21.03.2022 г.

Subject: dissertation for the acquisition of ONS "Doctor" in the field of higher
education 7. *Health and sports*, professional field: 7.3. *Pharmacy* and doctoral
program: *Pharmaceutical Chemistry*

Topic: "New strategies for quantitative and qualitative analysis of Nitrofural
and its new derivatives"

Author: master pharmacist Sonya Yordanova Ivanova, full-time doctoral student in
the doctoral program "Pharmaceutical Chemistry", enrolled by order № P-
109-62/01.02.2019 at the Department of Pharmaceutical Chemistry at the
Faculty of Pharmacy, MU - Varna.

Scientific supervisor: assoc. prof. Svetlana Georgieva, PhD.

I. General presentation of the procedure and the doctoral student

The presented set of materials on paper and electronic media is in accordance
with Art. 69 of the Regulations for development of the academic staff in MU - Varna
from 15.09.2020 and includes the following documents:

- ✓ Application to the Rector for opening a protection procedure;
- ✓ Curriculum vitae with the signature of the doctoral student;
- ✓ Copy of the diploma for completed higher education, educational-
qualification degree Master's degree with the appendix to it;
- ✓ Enrollment order;
- ✓ Protocol of the doctoral minimum exam;
- ✓ Protocol of Department's council with positive decision on the readiness for
defense;
- ✓ Order for deduction with the right to protection;
- ✓ Declaration of originality;
- ✓ List of publications related to the field of the dissertation (not less than 3
publications) signed by the doctoral student;
- ✓ Copy of the publications related to the topic of the dissertation

- ✓ Declaration of authenticity of the submitted documents
- ✓ Declaration for registration of profiles in scientific databases

The doctoral student has attached 4 (four) scientific publications, of which 1 (one) in a journal with IF and 3 (three) in refereed scientific journals, all related to the topic of the developed dissertation.

Бележки и коментар по документите нямам.

Sonya Yordanova Ivanova was born on August 24, 1992 in the city of Varna. She completed her higher education in pharmacy with a master's degree in June 2017 at the Faculty of Pharmacy at MU-Varna. By Order № P-109-62 / 01.02.2019 she was enrolled as a full-time doctoral student in the field of Higher Education “7. Healthcare and sports”, professional field: “7.3. Pharmacy”, doctoral program: “Pharmaceutical Chemistry” with research supervisor Assoc. Prof. Svetlana Georgieva, Ph.D. at the Department of Pharmaceutical Chemistry of the Faculty of Pharmacy at MU-Varna. With Order № P-109-120 / 21.03.2022. was expelled with the right to protection for up to one year.

II. Brief description of the structure of the dissertation

The presented dissertation is written on 110 pages, of which 1 page introduction, 32 pages literature review, 1 page goals and objectives, 10 pages experimental part, 42 pages results and discussion, 1 page conclusions, 1 page contributions, 15 pages literature. The work includes 6 tables and 72 figures.

III. Relevance and dissertability of the development

The topic of the dissertation developed by the doctoral student S. Ivanova is contemporary and dissertable, given the significant influence of polymorphism on some physical and physicochemical properties of a number of drug molecules and hence on their bioavailability. Often spontaneous polymorphic transitions can lead to a sharp decrease or even loss of pharmacological activity, as examples are given by the dissertation.

On the other hand, the targeted preparation of a particular polymorphic form may be one of the approaches to increase the bioavailability of the respective preparations under equal other conditions.

In this sense, the search for new derivatives with improved pharmacokinetic properties and reduced side effects by targeted production of stable polymorphic forms is fully justified.

IV. Critical analysis of the dissertation

The literature review (32 pages in total) is based on 240 Latin literature sources. The literature review shows the doctoral student's good awareness of the

problem, is written concisely and with understanding, but at the same time is thorough and reflects the theoretical foundations of analysis and proof of polymorphism in general. Due attention is paid to the chemistry of nitrofuran derivatives, their chemical stability and their characteristic pharmacological effects. However, the question arises why the choice of object for research is focused on nitrofuran derivatives, given that they are not widely used in recent years, and specifically Niflural is used mainly for the treatment of tropical diseases not found in Bulgaria.

The aim of the dissertation, correctly determined by the literature review, is set clearly and precisely, although divided into three parts. For its implementation, 9 specific **goals** have been identified, formulated accurately and in a logical sequence.

Research methodology

In the section **Experimental part**, the dissertation student has presented a detailed description of the methods used in this scientific paper. Their way of presentation shows that the dissertation is developed through appropriately and correctly selected methods, allowing to achieve the set goal and obtain an adequate response to the tasks solved in the dissertation. Methodologically well-constructed synthetic, analytical (mainly spectral), microbiological methods and in vitro experiments on cultured specific cell lines have been developed and applied. The methodology is not in doubt and is a prerequisite for obtaining the correct results discussed below.

Characteristics and evaluation of own research and contributions

In the part "**Results and discussion**" Ivanova describes in detail the obtained experimental results and at the same time presents their critical discussion. Four parts are clearly outlined in the work. The first is devoted to the synthesis and spectral characterization of various polymorphic forms of Niflural. The oscillations of the functional groups are considered in great detail. Mathematical deconvolution of the spectra and statistical processing of the results were applied to more fully identify the oscillations. In addition, a computational analysis was performed to find the energy minimum of the available conformations.

The structural characterization of the newly obtained compounds was performed correctly using modern instrumental methods. A detailed interpretation of the FTIR spectra is presented, which fully confirms the proposed structures. Modern methods have been used to study the obtained crystal modifications. I agree with the conclusions made about the position of amide protons in the spectra and interpretations of the differences in wave numbers recorded for some groups. However, I believe that these conclusions are better supported by theoretical calculations, given the low values of these deviations. The recorded UV-vis spectra prove the activity of the compounds in the UV spectrum and the presence of absorption maxima having analytical value.

This finds application in the next part of the dissertation's work, which I will tentatively call "analytical". It presents the analytical methods developed by Ivanova:

- Qualitative photolorimetric method based on the interaction of Niflural with Gibbs reagent (2,6-dichloroquinone-4-chloroimide);
- Electrochemical microanalysis of Niflural in the presence of trisodium aminopentacyanoferrate (II);

Both methods are mostly theoretical in nature, especially the second, and despite the thesis of the dissertation student for easy adaptability and applicability in qualitative and quantitative analysis, they are far from the same. At least due to objective difficulties in their eventual validation.

The third part of the dissertation's research is devoted to the synthesis and characterization of Niflural derivatives. Various approaches for their synthesis are applied, incl. Zandmeier's reaction. The compounds are correctly characterized by instrumental methods. The skillful use of various synthetic approaches in the research work of the doctoral student is impressive.

The last, fourth, part of the dissertation's works reflects the results of the conducted research on the potential antimicrobial activity of the newly obtained compounds against strains of *St. aureus* and *E. coli*. The results show the presence of antimicrobial activity almost comparable to that of Niflural. Experiments were also performed to determine the photo- and cytotoxicity of the newly obtained compounds, and the results show the absence of such.

Conclusions (7 in number) are adequate and correctly reflect the results of the research.

V. Assessment of the publications and personal contribution of the doctoral student

In relation to the dissertation, 4 scientific articles have been published, and in one of the publications Mag.-Pharm. Ivanova is a leading author. There are no data that parts of the dissertation have been presented at national and international scientific forums..

Regarding these scientometric indicators, the dissertation fully meets the requirements for awarding the educational and scientific degree "Doctor", laid down in the Regulations of MU - Varna. The doctoral student does not present a reference for citation of the presented scientific publications. A reference in Scopus showed that the article published in the Journal of Molecular Structure has already been cited once in 2021.

VI. Extended abstract

The extended abstract (total volume of 53 pages) is made according to the requirements and accurately and sufficiently reflects the content of the dissertation.

VII. Critical remarks and recommendations

As noted above, the claim of ease of adaptability and applicability in the qualitative and quantitative analysis of the proposed analytical methods at this stage is too bold. However, I agree that in theoretical terms there is rationality in them.

The dissertation presented a plan for future research, which is a logical continuation of her creative pursuits. This shows her visions for future development, which I sincerely admire.

CONCLUSION

The work is written in good scientific language, there are almost no typographical and grammatical errors in the text. In general, the dissertation deals with a topical issue from a theoretical point of view. The set goals and tasks have been successfully fulfilled, and the doctoral student has mastered and used a number of modern synthetic, analytical and microbiological methods.

The dissertation contains mainly scientific and theoretical results, which represent an original contribution to the research on polymorphism in medicinal products and meet the requirements of the Academic Staff Development Act in the Republic of Bulgaria (ZRASRB), The presented materials and dissertation results correspond to the specific requirements adopted in connection with the Regulations of MU - Varna for application of ZRASRB.

The dissertation shows that the doctoral student Mag.-Pharm. Sonya Yordanova Ivanova has the necessary theoretical knowledge and professional skills and demonstrates qualities and skills for independent research.

Given the above, I give my *positive assessment* of the study presented by the above reviewed dissertation, extended abstract, results and contributions, and I *invite the esteemed scientific jury to award the educational and scientific degree "Doctor"* of Mag.-Pharm. Sonya Yordanova Ivanova in a doctoral program in Pharmaceutical Chemistry.

Sofia

25 May 2022

Reviewer:

(prof. Al. Zlatkov, DSci)