REVIEW

By Assoc. Prof. Velichka Yordanova Andonova, Ph.D.

Head of the Department of Pharmaceutical Technologies, Vice Dean "Educational Affairs, Accreditation and Quality" at the Faculty of Pharmacy, Medical University "Prof. Dr. Paraskev Stoyanov" - Varna

Appointed as an internal member of the Scientific Jury by order № P-109-120 / 21.03.2022 of the Rector of the Medical University "Prof. Dr. Paraskev Stoyanov "- Varna

Subject: *Ph.D. dissertation to acquire the educational and scientific degree "Doctor."*

Field of higher education: *7. Health and sports*

Professional field: *7.3. Pharmacy*

Doctoral program: *Pharmaceutical Chemistry*

Title: *New strategies for the qualitative and quantitative analysis of Nitrofural and its new derivatives*

Author: *Sonya Yordanova Ivanova*

Form of doctoral studies: *Full-time Ph.D. student, enrolled by order № P-109- 62 / 01.02.2019 of the Rector of the Medical University" Prof. Dr. Paraskev Stoyanov "- Varna*

Scientific supervisor: *Assoc. Prof. Svetlana Georgieva, Ph.D.*

Department: *"Pharmaceutical Chemistry" at the Faculty of Pharmacy of the Medical University "Prof. Dr. Paraskev Stoyanov "- Varna*

General presentation of the procedure

The set of materials presented by the doctoral student Sonya Yordanova Ivanova is under Art. 69 of the Regulations on academic staff development at Medical University Prof. Dr. Paraskev Stoyanov - Varna (MU-Varna).

She is a full-time Ph.D. student in the Department of Pharmaceutical Chemistry at the Faculty of Pharmacy at MU-Varna with scientific supervisor Assoc. Prof. Svetlana Georgieva, PhD (Order № P-109-62 / 01.02.2019). During her preparation, she strictly followed the procedure regarding the requirements of full-time doctoral studies, as evident from the submitted documents. Therefore,

Sonya Yordanova Ivanova has the right to defend the dissertation by Order № P-109-120 / 21.03.2022.

The Ph.D. student has submitted 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.

Brief biographical data about the Ph.D. student

Sonya Yordanova Ivanova was born on August 24, 1992, in 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 Ph.D. student in the Field of higher education 7. Health and sports, Professional field 7.3. Pharmacy in the doctoral program: "Pharmaceutical Chemistry" with scientific supervisor Assoc. Prof. Svetlana Georgieva, Ph.D. at the Department of Pharmaceutical Chemistry of the Faculty of Pharmacy at MU-Varna. She is deducted with Order № P-109-120 / 21.03.2022 with the right to dissertation defend. She is currently working as a master pharmacist in Sopharmacy at Varna.

Structure and sections of the dissertation

The presented dissertation is 110 pages long, illustrated with 6 tables and 72 figures. The scientific work includes the following sections: 1-page introduction; 32 pages of literature review, entitled "Theoretical part"; 1 page of goals and objectives; 10 pages of experimental part; 42 pages of results and discussion; 1 page of conclusions; 1-page contributions; 15 pages of used literature and appendix. The dissertation structure follows the procedure for acquiring the educational and scientific degree "Doctor" and the Regulations at MU-Varna.

Relevance of the topic

The polymorphism of drug molecules is the factor that largely determines their biological effect, their ultimate therapeutic efficacy, and the target structures of a drug interaction. It can be a factor in reducing or eliminating some side effects. Targeted preparation of a particular polymorphic form, such as that of Nitrofural, may be one of the approaches to increase the bioavailability of the respective preparation. Last but not least, polymorphic analysis is included as part of the general analytical approach in the content of the modern Pharmacopoeia.

Everything so far shows that the topic of the dissertation is relevant and dissertable. Therefore, the search for strategies in the qualitative and quantitative analysis of Nitrofural and its new derivatives is fully justified.

Knowledge of the issue

Two hundred forty literary sources in Latin were used in the preparation of the literature review. The literature review is written concisely. The nitrofuran group of drugs has been studied in detail, focusing mainly on the Nitrofural molecule. All significant problems in the discussed topic are presented consistently and argumentatively and reflect the theoretical foundations of the analysis and proof of polymorphism as the primary attention is paid to thermo- and spectroanalytical techniques and crystallographic methods. Exhaustive, clear, and understandable writing style and analytical and logical connection between the sections of the literary review are demonstrated.

Purpose and tasks of the research

Based on the literature review, the dissertation formulates the main objectives of this dissertation, namely:

- to study, mainly with the help of an infrared spectrometer, the polymorphic features of the pharmacopoeial representative Nitrofural and to analyze the possibilities for the simultaneous growth of several of its polymorphs over As_2Se_3.
- To explore the possibilities for introducing new and specific qualitative reactions in the Nitrofural identification analysis.
- To synthesize new Nitrofural derivatives with the precursor Nitrofural itself.

Nine specific tasks are defined, which are formulated precisely and in a logical sequence.

Research methodology

The selected methods allow for a thorough, analytical, and logical solution to the tasks in connection with the stated objectives of the dissertation.

In the Experimental part, the Ph.D. student presented a detailed description of the methods used for synthesis and the applied instrumental methods for analyzing the new polymorphic forms of Nitrofural obtained by her. In addition, microbiological methods, in vitro experiments on cultured specific cell lines, and photobiological studies have been developed and applied. All of them are described in detail, clearly, and precisely.

The methodology is not in doubt and is a prerequisite for obtaining the correct results discussed below.

Results analysis

The conducted own research is presented on 42 pages and includes 4 tables and 26 figures, which are clear and concise.

In the section "Results and Discussion," Sonya Ivanova describes in detail the different polymorphic forms of Niflural and, in particular, the oscillations of the functional groups. For

complete identification of the oscillations, mathematical deconvolution of the spectra and statistical processing of the results was applied. In addition, 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, confirming the proposed structures. Modern techniques have been used to study the obtained crystal modifications.

Ivanova develops the following two analytical methods:

• Qualitative photocolorimetric 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 primarily theoretical and would be challenging to validate.

The dissertation describes and applies various approaches to the synthesis of Nitrofural derivatives. The obtained new products are correctly characterized by the instrumental methods selected by the Ph.D. student. Furthermore, the skillful use of various synthetic approaches in the research work of Ph.D. student is impressive.

A study of the antimicrobial activity of the newly obtained compounds against strains of *St. aureus* and *E. coli* was performed. The results show the presence of close and comparable antimicrobial activity of Niflural derivatives compared to the activity of the parent molecule. Experiments have also been conducted to determine the photo- and cytotoxicity of the newly obtained compounds, and the results show a lack of such.

Conclusions

In a synthesized form, 7 conclusions are made, which follow logically, adequately, and correctly from the results obtained from each task.

Contributions and significance of development for science and practice

My detailed acquaintance with the dissertation of Sonya Ivanova showed that there are both scientific-theoretical and scientific-applied contributions (5 contributions are formulated), which are original and are defended in the presented work.

Evaluation of the publications on the dissertation

In connection with the dissertation, 4 scientific articles have been published, and in one of the publications, Sonya Ivanova is a leading author.

Concerning these scientometric indicators, the dissertation fully meets the requirements for awarding the educational and scientific degree "Doctor," laid down in the Regulations at MU-Varna. The total number of points of the Ph.D. student by a group of indicators D is 47. The minimum required points by a group of indicators D for obtaining the scientific degree "Doctor" in field 7. Health and Sports, according to the Act on Development of the Academic Staff in the Republic of Bulgaria, are 30. I am convinced that the participation of Sonya Ivanova in the experimental part is essential and indisputable. The Ph.D. student does not present a reference for citation of the presented scientific publications. The reference in Scopus showed that the article published in the *Journal of Molecular Structure* was already cited in 2021. There are no data that parts of the dissertation have been presented at national and international scientific forums.

Personal participation of the Ph.D. student in the dissertation research

The personal participation of the Ph.D. student in the review of the problem, formulation of the goals and tasks, conducting the experimental research, analysis of the results, and the derived contributions is available. An in-depth understanding of the specific subject and free terminology in the dissertation is evident. In addition, there is the ability to present and describe the scientific results and the supervisor's support.

Extended abstract

The extended abstract is prepared according to the requirements. It includes an introduction, a brief theoretical part, goals and objectives, and a description of the materials and methods used. The presented research and discussion fully reflect the main results achieved in the dissertation. The obtained results are illustrated with a sufficient number of figures and tables. The conclusions coincide with those in the dissertation. Scientific contributions and a list of publications in connection with the dissertation are included. Being acquainted with the abstract allows one to understand the developed problem, the research conducted, and the interpretation of the results.

Critical remarks and recommendations

I have no significant critical remarks on the presented dissertation.

CONCLUSION

The dissertation of Sonya Yordanova Ivanova contains original scientific and applied results, which are a contribution to science and meet all the requirements of the Higher Education Act, the Act on Development of the Academic Staff in the Republic of Bulgaria, Regulations on the implementation of the Development of Academic Staff in the Republic of Bulgaria Act (DASRBA),

and the Regulations on Academic Staff Development at Medical University Prof. Dr. P. Stoyanov - Varna.

Due to the above, **I confidently give my positive assessment of the research presented by the above peer-reviewed dissertation, extended abstract, results, and contributions. Therefore, I invite the esteemed Scientific Jury to award the educational and scientific degree "Doctor" of Sonya Yordanova Ivanova in the doctoral program in "Pharmaceutical Chemistry," Professional field 7.3 "Pharmacy," field of higher education 7. Health and sports.**

10.06. 2022

Varna

Reviewer: .....

(Assoc. Prof. Velichka Andonova, Ph.D.)