

OPINION

by **Dr. Stela Mironova Statkova-Abeghe,**

Associate Professor in Faculty of Chemistry, University of Plovdiv, Department of Organic Chemistry

on the Thesis for awarding the educational and scientific degree "Doctor"

in: higher education field 4. Natural Sciences, Mathematics and Informatics;

Professional field 4.2. Chemical sciences, Doctor Program: Organic Chemistry

Author: Maria Andreeva Argirova

Title: Synthesis of 1H-benzimidazole-2-yl hydrazones and investigation of their anthelmintic, antineoplastic and radical scavenging effects

Scientific Advisor: Assoc. Prof. Dr. Denitsa Pantaleeva, Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences - BAS

1. General description of the procedure and the PhD student

According to order № ПД-09-189/09.12.2022 of the Director of IOCCP (BAS), I have been approved as a member of the scientific jury for the procedure for promotion of a PhD Thesis on topic "Synthesis of 1H-benzimidazole-2-yl hydrazones and investigation of their anthelmintic, antineoplastic and radical scavenging effects" for awarding the educational and academic degree "Doctor". Author of the Thesis is assistant Maria Argirova – laboratory of "Structural organic analysis" - IOCCP (BAS). For the period of 01.08 2018 – 31.07.2021, Maria is studying in full-time doctoral program, and deducted with the right of Thesis defence. The topic of PhD thesis is actualized at 11.07.2022.

The presented by Maria Argirova set of documents is in accordance with the Regulations for development of the academic staff of the IOCCP (BAS) meets the criteria and includes documents as follows: CV, protocol form with passed exam of the discipline, PhD thesis, abstract of the PhD thesis, list of the scientific publications according the topic of the thesis, two copies of the scientific publications, certificates, training courses and participation in scientific forums, reference for fulfillment of the doctoral program criteria etc. The documents are correctly formatted and arrange according to the specific requirements and any reduction regarding content overlap, absence of documents certifying the publication is not required.

2. Relevance of the topic

The topic of the thesis is relevant due to the increasing importance for the discovering of

pharmacologically active molecules with both antioxidant and antineoplastic effects as promising and innovative approach toward new effective therapy for cancer diseases. Identifying different targets for effective cancer treatment including protein tubulin force the development and testing of new drug candidates. The design and synthesis of new benzimidazole derivatives with both antioxidant and antineoplastic/anthelmintic activities is of considerable interest from a synthetic and pharmacological point of view. The aim and the tasks are formulated clearly, correctly, expediently and fully correspond to the topic of the Thesis. The synthetic methods are adequately selected and lead to products with high yields. Instrumental and theoretical methods for structural analysis are completely contemporary.

3. Knowledge of the problem

The literature review is detailed and well structured – covers 293 references absolutely related to the Thesis topic. About 15 % of the cited publications are from the last five years. As. Argirova has knowledge for systematization and critical analysis acquiring the specific pharmacological terminology from several scientific fields such as organic synthesis, organic analysis, medicinal chemistry, pharmacology etc.

4. Research methodology

The introduction of functional groups is carried out by multi-step synthesis, hydrazine chains with aromatic fragments contain combinations of hydroxyl and other groups. Possibilities for varying the lipophilicity of target compounds are explored. The methodology adapted by the authors does not require specific reagents or catalysts and leads to the preparation of the compounds in good yields. As a result 40 1H-benzimidazole-2-yl hydrazones are synthesized of which 37 are newly obtained and at the same time undescribed in the literature.

5. Characteristics and evaluation of the thesis and its contributions

The doctoral thesis is written on 219 standard pages, contains 20 tables, 56 figures and 69 schemes. In this regard 293 references are cited (all in Latin). The experimental part of the thesis is conducted at laboratory of “Structural organic analysis” - IOCCP (BAS), but also in the Department of chemistry at New Lisbon University - Portugal, Faculty of Pharmacy and Medicine at Medical University - Sofia; Department of Infectious Diseases, Parasitology and Tropical Medicine and Medical University - Plovdiv.

A new class of benzimidazole derivatives that exhibit combined antioxidant, antineoplastic and/or anthelmintic activity have been developed. In addition synthetic agents suppressing tumor

cell proliferation at very low micromolar concentrations are selected. Selective concentration-dependent cytotoxicity of the obtained compounds in two cancer cell lines is established. It is found that hydrazones exhibit more significant larvicidal effect in comparison with known drugs such as Albendazole and Ivermectin which further confirms the contributions of the thesis.

The structure of the complexes of the studied benzimidazolyl hydrazone ligands with Cu(II) and Fe(II) and their activity is established. The theoretical studies of 1H-benzimidazole-2-yl hydrazones show the highest stability for the conformers with E configuration of the azomethine double bond and s-trans conformation of the simple N-N bond, which represents a fundamental contribution. Theoretical methods for determination of molecular characteristics related to the mechanisms of antioxidant action, tubulin interaction, drug similarity, bioavailability, ability to pass through physiological barriers and toxicity are applied. The radical-scavenging activity of hydroxy-substituted 1H-benzimidazole-2-yl hydrazones is similar to that of catechins and flavonols and better than that of melatonin derivatives.

6. Assessment of the publications and personal participation of the PhD student

The results achieved in the dissertation, their analysis and discussion fully confirm the authenticity of the research and support the formulated contributions of the dissertation. There is no doubt about the personal contribution of the doctoral student Maria Argirova in obtaining the experimental results.

The results achieved in the dissertation are summarized in two articles from 2021 which are in leading scientific journals. First of them is published in *Chemico-biological interactions*, JCR-IF (Web of Science): 5.194; **Q1** and the second is in *Journal of Royal Society of Chemistry - RSC Advances*, JCR-IF (Web of Science): 3.361; **Q1**. As well as five citations on first publication are noticed in reputable journals. There is no overlap or coincidence of the publication content (total of 60 scientometric points, 50 from publications and 10 from citations).

7. Abstract

The abstract is written according to the requirements and reflects the main results achieved in the dissertation. It is written concisely and analytically in correct chemical language. The accompanying diagrams, figures and tables correctly reflect the published data. The abstract is prepared in accordance with the requirements.

CONCLUSION

The PhD thesis contains scientific and scientific-applied results, which represent an original contribution to science and meet all the requirements of the Law for Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the Regulations for application of LDASRB and the respective Regulations (LDASRB) of Bulgarian Academy of Sciences (BAS).

The presented materials and dissertation results fully comply with the specific requirements of the Regulations of IOCCP (BAS) for the application of LDASRB.

The PhD thesis indicates that the doctoral student Maria Andreeva Argirova has theoretical knowledge and professional skills in the scientific field of Organic Chemistry by demonstrating qualities and skills for independent research.

Based on the above, I give my positive assessment of the research presented by the above reviewed PhD thesis, abstract, achieved results and contributions, and propose to the esteemed academic board to award the educational and academic degree "Doctor" to Maria Andreeva Argirova in higher education field 4. Natural Sciences, Mathematics and Informatics; Professional field 4.2. Chemical sciences, Doctor Program: Organic Chemistry.

21.02.2023

Plovdiv

Reviewer:

Assoc. Prof. Stela Statkova-Abeghe