

## OPINION

by **Petko Denev, PhD, professor at the  
Institute of Organic Chemistry with Centre of Phytochemistry (IOCCP–BAS)**

on a dissertation for awarding the scientific degree "**Doctor of Sciences**" (DSc) in the field of  
Higher education 4. *Natural Sciences, Mathematics and Informatics*,  
Professional field 4.2 *Chemical sciences*, scientific specialty "*Organic chemistry*"

**Author: Assoc. prof. Georgi Milchev Dobrikov, PhD**

**Title: New compounds as perspective antitubercular and antiviral agents**

### **1. General presentation of the procedure and the candidate**

By order № RD-09-102/04.07.2023 of the Director of IOCCP-BAS, I have been appointed as a member of the scientific jury in the procedure for the defense of a dissertation work on the topic "New compounds with promising anti-tuberculosis and antiviral activity" with author assoc. prof. Georgi Milchev Dobrikov, PhD from the Laboratory "Organic Synthesis and Stereochemistry" of IOCCP-BAS. The set of materials presented by assoc. prof. Dobikov is in accordance with the Regulations for the Development of the Academic Staff of IOCCP and meets the criteria of IOCCP-BAS for the acquisition of the scientific degree "Doctor of Sciences". The candidate has submitted a dissertation in English, abstracts in Bulgarian and English, eight scientific publications in refereed journals and a list of 303 citations, which are not included in the procedure for obtaining the educational and scientific degree "doctor".

### **2. Brief biographical data**

Assoc. Prof. Dobikov obtained a master's degree from the Faculty of Chemistry and Pharmacy of Sofia University "St. Kliment Ohridski" in 1998. In the period 1999-2001, he worked as a "chemist" at the Institute of Polymers - BAS and as an assistant professor at the National Center for Public Health and Analysis. In the period 2001-2004, he worked on his doctoral dissertation at IOCCP-BAS on the topic "Preparation of chiral ferrocene derivatives - absolute configuration and application in asymmetric synthesis". After that, he successively held the academic positions of "assistant professor" and "chief assistant professor" at IOCCP-BAS until his habilitation as an associate professor in 2016. And currently, Dr. Dobikov holds the academic position "associate professor" in laboratory OSS of IOCCP-BAS. Assoc. Prof. Dobrikov's scientific interests can be attributed to organic and enantioselective synthesis, and the results of his scientific activity have been published in 41 scientific publications referenced in the Scopus database, cited a total of 289 times with an H-index of 10. He participated in the implementation of 15 scientific research projects, including as the head of five projects from the contests for funding fundamental research and bilateral cooperation of the BNSF. He also participated in projects with Janssen, Johnson&Johnson, 2005-2008 and IPSEN.

### **3. Relevance of the topic**

The presented dissertation is an in-depth study on the synthesis and characterization of new chemical compounds with potential application as anti-tuberculosis and antiviral agents. Tuberculosis is a chronic airborne infectious disease that is transmitted by droplets and mainly affects respiratory organs. It is among the oldest known deadly diseases and still affects millions of people worldwide every year. On the other hand, enteroviruses are a large family of viruses that cause severe and sometimes life-threatening diseases such as meningitis, encephalitis, myocarditis, poliomyelitis, etc. Given the frequent mutations of these viruses, effective chemotherapeutics used in clinical practice are very few, and the demand for new compounds with *in vivo* antiviral activity aimed at inhibiting cell replication is one approach to address viral resistance. Therefore, finding

new synthetic, semi-synthetic or natural antituberculosis and antiviral agents is a problem of great social importance. All this determines the topic of the dissertation as timely, significant and interesting.

#### **4. Familiarity with the problem**

In the introduction to his dissertation, assoc. prof. Dobikov managed to briefly and clearly introduce the reader to the meaning and spread of tuberculosis and to present the classic approaches and modern trends in the development of anti-tuberculosis and anti-enterovirus drugs. Also presents the main classes of anti-enteroviral drugs and methods for the synthesis of diaryl ethers. It makes a good impression that the Dr. Dobrikov manages to justify very well the need to develop new anti-tuberculosis and anti-enteroviral agents, and thus the need to research the problems posed. All this shows excellent knowledge of the issue. Also a good impression is made by the fact that the goal is short and clearly formulated, although the word "мощен" does not sound good and should be replaced by e.g. with "effective", not only in the objective, but also in the entire abstract in Bulgarian.

#### **5. Research methodology**

The selected methodology includes the use of multiple methods for the synthesis of new analogs of ethambutol, (-)-fenchone, as well as new arylmethylidene ketones and pyrimidines with a camphane skeleton and diaryl ethers, using a variety of modern spectral methods for their identification and characterization. To determine the biological activity of the compounds, classical microbiological methods for *in vitro* antibacterial and antifungal activity, as well as *in vitro* and *in vivo* methods for antiviral activity, are relied upon. The methods used are well chosen and allow the fulfillment of the tasks and the achievement of the goal of the dissertation work.

#### **6. Characterization and evaluation of the dissertation and contributions**

The dissertation work is written in English on 175 pages and includes 34 figures, 28 tables, 29 schemes and 340 references. The topic of the dissertation corresponds very well both to the scientific specialty and to the topic that is being worked on in the "Organic Synthesis and Stereochemistry" laboratory of IOCCP-BAS. The contributions of the dissertation can be conditionally divided into two directions: synthesis, characterization and biological activity of new compounds with anti-tuberculosis activity and of those with anti-enteroviral activity. The most important contributions in the first direction can be summarized as follows: a series of 50 new derivatives of ethambutol with low cytotoxicity, some with comparable and others with higher anti-tuberculosis activity, were synthesized. A series of 22 new ureas, thioureas and acylthioureas derived from ethambutol were also synthesized, one of them being a promising anti-tuberculosis agent due to its high activity and low cytotoxicity. 33 new analogs of cinnamamides with a fenchane skeleton were also synthesized, and only one of them demonstrated moderate activity and low cytotoxicity. A series of 20 arylmethylidene ketones (16 of which are new) and 15 new pyrimidines with camphane skeletons were synthesized. Two compounds have excellent antituberculosis activity, and one is a promising broad-spectrum antibiotic against bacteria and fungi. New nitrofuranyl compounds were also synthesized, and the mechanism of their antituberculosis action was investigated by means of *in vitro* induced mutagenesis. In the second direction, new analogs of the well-known diaryl ether MDL-860 were synthesized, which demonstrated better activity against 6 viruses. The contributions thus described are mostly of a fundamental nature, but have great applied potential in clinical practice. As the author himself concludes, some of the newly synthesized structures are suitable for drug development in preclinical phases.

## **7. Evaluation of the publications and personal contribution of the candidate**

The results of the dissertation have been published in 8 publications for the period 2015-2022. Four of them are in quartile 1 (Q1) and the remaining four in quartile 2 (Q2). In five of them, assoc. prof. Georgi Dobrikov is the first and/or corresponding author, which testifies to his personal contribution in the implementation of the experimental work on these publications, the analysis and the interpretation of the results. The results were obtained as a result of the implementation of five projects financed by the Bulgarian National Research Foundation including participation in one COST action and were presented at scientific conferences in Bulgaria and abroad with 26 oral or poster presentations.

## **8. Summary of the dissertation**

The summary reflects well the essence of the dissertation work, the achieved results and the most important conclusions and contributions.

## **9. Recommendations for future use of dissertation contributions and results**

Considering the accumulated huge number of compounds from the various series, I recommend to assoc. prof. Dobrikov to look for opportunities for collaborations to conduct preclinical and clinical studies with these molecules.

## **CONCLUSION**

As a result of the research carried out in the dissertation work of assoc. prof. Georgi Dobrikov, PhD significant results were achieved, which represent an original contribution in the fields of organic chemistry and chemistry of medicinal products. These contributions meet all the requirements of the Act for the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its implementation, as well as the requirements in the specific regulations of the BAS and IOCCP-BAS.

Due to the above, I give my positive assessment of the dissertation work and propose to the honorable scientific jury to award the scientific degree "Doctor of Sciences" to assoc. prof. Georgi Milchev Dobikov, PhD in the field of higher education 4. Natural sciences, mathematics and informatics, professional direction 4.2. Chemical Sciences, scientific specialty "Organic Chemistry".

26.09.2023

Opinion prepared by:

Prof. Petko Denev, PhD