

# REVIEW

by

Prof. Ivaylo Dimitrov, PhD

Institute of Polymers, Bulgarian Academy of Sciences (IP-BAS)

Member of the Academic Jury set to render a decision  
on the competition for filling the academic position of an Associate Professor  
in the Professional Field 4.2. Chemical Sciences according to the Classifier of the Areas of Higher  
Education and the Professional Fields (Scientific Specialty “Polymers and Polymer Materials”)  
for the needs of “Polymers for alternative energy and environmental protection” Department of  
IP-BAS, announced in the State Gazette, no.102 from 23.12.2022

This Peer Review is prepared in response to Order № ПД-09-28/21.02.2023, issued by the  
Director of the Institute of Polymers, Bulgarian Academy of Sciences, following the decision  
made by the Academic Jury that was held on 02.03.2023.

The Review is in compliance with *Development of Academic Staff in the Republic of Bulgaria Act (DASRB)*, *the Rules for the Application of the Development of Academic Staff in the Republic of Bulgaria Act*, *the Rules of BAS* and with the *Rules set at the Institute of Polymers, Bulgarian Academy of Sciences, for applying the Act aforementioned*.

## **1. Biographical information about the candidate.**

The only candidate in the competition is Assist. Prof. Dr. Ivelina Tsankova Tsacheva. Dr. Tsacheva graduated from the Higher Institute of Food and Flavour Industries – Plovdiv (currently University of Food Technologies) in 2002 with a master's degree in biotechnology. During the period 2002-2003, she worked as a teacher in microbiology at the "Marie Curie" Professional High School for Chemical Technologies and Biotechnology in Razgrad. In 2004, she became a PhD student at IP-BAS supervised by Prof. Kolio Troev, DSc and Assoc. Prof. Ivan Gitsov. In 2008, Ivelina Tsacheva acquired educational and scientific degree "Doctor" after successfully defending her PhD thesis on the topic: "Polymeric radioprotective complexes: Design, characterization and performance". Dr. Tsacheva worked for a short period of time as a biotechnologist at the Institute of Chemical Engineering - BAS, and since 2009 she has been appointed to the IP-BAS, holding the academic position of Assistant Professor (from 2011 - until now). During the period 2006 - 2012, Ivelina Tsacheva specialized successively at the Laboratory

of Biotechnology of the Department of Pharmacy of the Ludwig-Maximilian University of Munich (Germany), at the Training Center for Microwave Synthesis in Sorisole (Italy) and at the Institute of Medical Radiation Biology of the University Hospital in Essen (Germany). Dr. Tsacheva has presented the results of her research at 8 international and 10 national scientific forums.

## 2. Assessment of the scientific and research accomplishments of the candidate

According to Art. 24 (1), items 3 and 4 of the DASRB, Art. 53 (1), items 3 and 4 of the Rules for the Application of DASRB, Art. 2, item 4.3 of the Rules of BAS and Art. 70, item 2 of the Rules for Acquisition of Scientific Degrees and for Occupying Academic Positions in IP-BAS, the candidates for filling the academic position of "Associate Professor" must meet the minimum requirements concerning their scientific activities. Dr. Ivelina Tsacheva participates in the competition with 19 scientific publications and one book chapter, which are different from those presented for obtaining the educational and scientific degree "Doctor". All 19 publications presented are assigned to a corresponding quartile (Q1-Q4) according to the metrics of Scopus and/or Web of Science. In addition, a list of 192 citations of the candidate's scientific works in publications that are referred and indexed in the world-renowned databases of scientific information Web of Science and Scopus is presented. From the data provided it is clear that the candidate meets and even exceeds the minimum requirements – her total score in the mandatory for the occupation of Academic position "Associate Professor" groups of indicators is 789 with a minimum required 430 points.

The requirements for *indicator A* are fulfilled, as the candidate holds the educational and scientific degree "Doctor" since 2008.

Concerning the *group of indicators C* Dr. Tsacheva has presented 5 publications. The total score is 107 whereas the minimum required points are 100. The publications referred to this group of indicators are related to the optimisation of synthetic approaches for obtaining new low- and high-molecular weight aminophosphonates. Two of the publications (in the journals *Bioorganic and Medicinal Chemistry* (Q1) and *Phosphorus, Sulfur and Silicon and the Related Elements* (Q4)) are dedicated to the development of synthetic strategies for the preparation of novel low molecular weight aminophosphonates with potential application for antitumor therapy. The remaining three publications (in the journals *European Journal of Medicinal Chemistry* (Q1), *Bioorganic and Medicinal Chemistry* (Q1) and *Advances in Materials Science and Engineering* (Q2)) are devoted to the preparation and characterization of novel poly(oxyethylene aminophosphonate)s with inherent biological activity.

Dr. Tsacheva has presented 14 scientific publications for participation in the competition that are relevant to *the group of indicators D*. They are grouped by the journals' rank as follows: 3 publications with Q1, 1 publication with Q1, 6 publications with Q3 and 4 publications with Q4. Additionally, a co-authored book chapter published by the prestigious publishing house *Elsevier*, and giving 15 points, is also presented. Thus, the total score for the *group of indicators D* is 248 with a minimum required 220 points.

The *indicator E* of the minimum requirements for the candidate's research activities reflects the citations of her publications in scientific journals, referred and indexed in the world-renowned databases with scientific information Web of Science and/or Scopus. The citations list presented by Dr. Tsacheva at the time of submitting the documents reveals a total number of 192 citations (excluding self-citations) in scientific journals, referred and indexed in Web of Science and/or in Scopus. Thus, the score for *indicator E* is 384, which is much more than the required minimum of 60 points.

The group of *indicators F* is not obligatory in the competitions for filling the academic position "Associate Professor", but as some of them correspond to the recommended requirements of the Regulations for Acquisition of Scientific Degrees and for Occupation of Academic Positions at IP-BAS (Art. 70, item 4) Dr. Tsacheva has presented a list of 12 research and applied projects in which she has participated or is still participating. Another recommended requirement is that at least 6 of the candidate's publications have been published in the last 5 years. From the 19 publications and 1 book chapter presented for participation in the competition by Dr. Tsacheva it is evident that 6 of them have been published in the last 5 years deducting the time of the candidate's absence due to a long-term (more than 3 months) leave.

The candidate's scientific contributions include the development and optimization of synthetic procedures for obtaining new biologically active low molecular weight and polymeric aminophosphonates with potential antitumor activity and their detailed characterization, as well as the surface modification of mesoporous silica nanocarriers of active substances by layer-by-layer deposition of oppositely charged natural polymers.

- ***Contributions to the preparation and characterization of novel biologically active aminophosphonates.*** A significant number of Dr. Tsacheva's publications presented for the competition are in this field. A synthetic strategy for the preparation of  $\alpha$ -aminophosphonic acid diesters exhibiting *in vitro* anti-tumor activity was developed. The reaction conditions for the addition of dimethyl or diethyl phosphite to Schiff bases in the presence of various catalysts or without a catalyst were optimized. Novel anthracene-containing Schiff bases and the corresponding aminophosphonates in the presence or absence of catalyst were also

obtained and characterized. Furthermore, the synthetic procedure for the preparation of aminophosphonates was significantly optimized *via* microwave-assisted synthesis. It has been established that the compounds containing both an anthracene residue and a furan ring in their molecule exhibit selective *in vitro* antitumor activity on certain human epithelial cancer cells. Anthracene-containing bisaminophosphonates were also obtained and evaluated. The *in vitro* and *in vivo* studies revealed that they exhibit a strong antitumor activity against a colon carcinoma cell line, while being characterized by moderate clastogenic and antiproliferative effects on normal cells.

- ***Contributions to the synthesis and characterization of poly(oxyethylene aminophosphonate)s with inherent biological activity.*** The accumulated experience from the synthesis and evaluation of low molecular weight aminophosphonates was cleverly applied by Dr. Tsacheva in the development of polyaminophosphonates based on biodegradable and biocompatible poly(oxyethylene H-phosphonate)s, bearing reactive P-H groups along their chains. The synthetic procedures (conventional and microwave assisted synthesis) for the chemical coupling of various Schiff bases to the polymer chains have been investigated and optimized. Thus, fully or partially functionalized poly(oxyethylene aminophosphonate)s were obtained. The *in vitro* studies performed on a panel of human tumor cell lines revealed that selected polymers exhibit cytotoxic effects comparable to or exceeding those of commercial chemotherapeutic drugs. Further *in vitro* and *in vivo* safety studies were also performed, showing lower cytotoxicity and clastogenicity of the polymer conjugates on normal cells compared to the corresponding low molecular weight aminophosphonates. The preparation and radioprotective efficiency evaluation of a polymeric complex of the radioprotector WR 2721 with poly(hydroxyoxyethylene phosphate) can also be attributed to this group of contributions. The polymeric carrier was obtained by a two-step modification of poly(oxyethylene H-phosphonate).
- ***Contributions related to the modification of mesoporous nanocarriers of biologically active substances.*** A surface modification of mesoporous silica nanoparticles preloaded with the biologically active substances curcumin or quercetin was performed. Initially, the surface of the particles was modified with primary amino groups. Then, they were loaded with the corresponding active substance followed by layer-by-layer deposition of three surface layers of the natural polymers  $\kappa$ -carrageenan/chitosan/ $\kappa$ -carrageenan through electrostatic interactions. Thus, control over the release profiles of the active substances from the nanocarriers was achieved. It was found that the encapsulation of curcumin or quercetin in the modified mesoporous nanocarriers did not significantly decrease their cytotoxic potential.

The research carried out by Dr. Tsacheva is in an up to date and rapidly developing field of organic synthesis and polymer science, as the obtained and characterized low-molecular-weight

and polymeric biologically active substances possess a great potential for biomedical applications. The results obtained so far are promising and provide good opportunities for further and in-depth research.

### **3. Opinions, notes and recommendations**

I have no major critical remarks regarding the preparation of the habilitation report and the other documents presented by the candidate for participation in the competition.

The research conducted by Dr. Tsacheva is interdisciplinary in nature, which predetermines the participation of a larger number of scientists with relevant expertise, and hence a larger number of co-authors in her publications. However, I would recommend that in her future research and publications she strives to be a leading (first or corresponding) co-author.

### **4. Conclusion**

The documents presented for the competition and the evaluation of Dr. Ivelina Tsacheva's contributions to the scientific publications show that her scientific indicators meet and exceed the requirements for filling the academic position of "Associate Professor" as defined in the Development of Academic Staff in the Republic of Bulgaria Act and the Rules for its implementation, as well as those specified in the Rules for Acquisition of Academic Degrees and Occupation of Academic Positions at BAS and IP-BAS. Therefore, I give my overall *positive assessment* and I would like to recommend to the Distinguished Members of the Scientific Council of IP-BAS to support the election of Assist. Prof. Ivelina Tsankova Tsacheva, PhD at the academic position of "Associate Professor" in the professional field 4.2. Chemical Sciences ("Polymers and Polymer Materials") for the needs of "Polymers for alternative energy and environmental protection" Department of IP-BAS.

**Date:**

20.04.2023

**Reviewer:**

Prof. Ivaylo Dimitrov, PhD