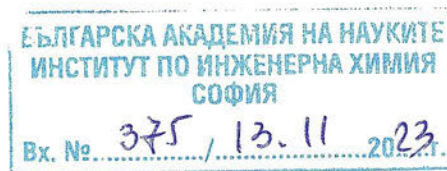


## REVIEW



**Competition:** for the occupation of the academic position "professor" in professional field 4.2. Chemical Sciences (Processes and Apparatus in Chemical and Biochemical Technology), announced in the "State Gazette", no. 67, page 95 of 04.08.2023

**Candidate:** Dr. Daniela Ilieva Batovska, associate professor

**Reviewer:** Ivanka Borisova Stoineva, DSc, prof.

### *Biographical data*

Daniela Batovska is a graduate of the elite NMG "Acad. L. Chakalov". She continued her education at the University of St. Kliment Ohridski, Faculty of Chemistry, Sofia, where she graduated as a master's degree in "Organic and Analytical Chemistry" in 1992. Dr. Batovska developed her professional career mainly at IOCCF-BAS, where she successively grew up from the position of chemist to Ch. assistant and associate professor. She started her career in the atmosphere of erudite and successful scientists such as Prof. Simeon Popov and Prof. Tsenka Milkova. The candidate's scientific interests and basic research are mainly in the field of chemistry of natural compounds. Naturally, the results were not too late, and in 2001, Dr. Daniela Batovska, under the supervision of Prof. Ts. Milkova, successfully defended her doctoral dissertation in the scientific specialty "Bioorganic Chemistry and Chemistry of Natural and Physiologically Active Substances" on the topic "Synthesis and Biological Activity of sterol derivatives".

In the period 2009-2010, Dr. Batovska was invited to give a lectures at the Department of Chemistry at Faculty of Mathematics and Natural Sciences, SWU Neophyt Rilski" as a lecturer in Steroid Chemistry and Bioorganic Chemistry.

During specializations in Japan, Dr. Batovska was honored with a number of awards for her scientific results - FY2002 JSPS postdoctoral scholarship for foreign researchers, an award from the Research Center for Biotechnology, Toyama Prefectural University, Japan - 2002-2003 and from Hokkaido University, Sapporo, Japan -2003—2004.

Dr. Batovska is not afraid of challenges and in the period 2017-2023 she decided to gain some experience in the field of biotechnology by developing food and cosmetic products in a private company.

The documents for participation in the competition of the candidate meet the requirements of the Regulations of IEC-BAS for the application of the Law on the Development of the Academic Staff in the Republic of Bulgaria (ZRASRB), and her scientific

and educational profile is in accordance with the requirements for a "professor" by professional field 4.2. Chemical Sciences

***Evaluation of the presented materials (number and characteristics of the presented works - scientific publications, monographs, research projects, patents, textbooks, etc.).***

Dr. Daniela Batovska participated in the competition for the academic position of "professor" with 20 scientific articles, 19 of which are in publications with an impact factor. The profile of publications by quartiles according to the World scientific databases Web of Science and/or Scopus is as follows: 3 items in a journal with Q1; 9 pcs. – Q2, 5 pcs. – Q3 and 2 pcs. – Q4. According to indicator B, 6 articles are indicated (2 with Q1, 2 with Q2 and 2 with Q3), and according to indicator D - 14 articles (1 with Q1, 7 with Q2, 3 with Q3, 2 with Q4 and 1 without SJR).

Dr. Daniela Batovska is co-author of 1 published book chapter and co-author of 1 patent - US 2019/0390408 A1, WO2020044343, 2020.

A list of the citations of the 383 scientific papers in the competition from a total of 1461 citations (38 publications) and Hirsch Index  $h = 14$  according to Scopus is also presented.

Dr. Daniela Batovska was the head of 2 international projects and 1 doctoral student.

The submitted certificate of fulfillment of minimum requirements for the academic position "professor" in the professional field "4.2. Chemical Sciences" according to the Regulations for the Implementation of the ŽRASRB and the Regulations of the BAS of Dr. Daniela Batovska is in accordance with and even significantly exceeds the requirements.

Indicator	Minimum requirements for BAS	Points declared by the applicant
A	50	50
B	0	0
V	100	120
G	100	274
D	120	766
E	150	160
<b>Total number of points</b>	<b>520</b>	<b>1370</b>



### ***Basic scientific and scientific-applied contributions***

I will consider the scientific contributions of Dr. Daniela Batovska as a development of her knowledge, skills and competences in the light of synthetic design and research of natural products with potential biological properties.

Contributions related to the design and synthesis of pharmacologically active substituted chalcones - (1,3-diaryl-2-propen-1-ones)

- Design and synthesis of 16 chalcones with hydroxycinnamic substitution motifs was carried out (paper 2) and their antioxidant activity was investigated. It was found that the compounds with a catechol structure and chalcones with a p-hydroxyl group in the same ring and two adjacent methoxyl groups showed the best scavenging capacity against the stable DPPH radical. This result would contribute to the design of other chalcones with DPPH radical scavenging activity.

- By applying a chemiluminescence method, the capture of peroxide radicals of 6 of the synthesized aryl chalcones was investigated. It was found that the highest antioxidant activity ( $k_7 \approx 107 \text{ l mol}^{-1} \text{ s}^{-1}$ ) was shown by substituted chalcones that have a catechol structure. The activity of 3,4-dihydroxy chalcone is 2.5 times higher than that of caffeic acid.

- Contributions related to the synthesis of chalcones with antimalarial activity (paper 4, 5, 6, 14, 19)

24 chalcones with different substitution patterns in rings A and B were synthesized, purified and structurally characterized by Claisen-Schmidt condensation between equimolar amounts of appropriately substituted acetophenones and arylaldehydes (or indole-3-carboxaldehyde). They were tested for antimalarial activity by the WHO Mark III method for inhibition of schizont maturation. 10 of the synthesized chalcones were found to show inhibition of schizont maturation with IC<sub>50</sub> in the range 0.10-0.55 µg/mL for two strains of *P. falciparum*, one sensitive and the other resistant to chloroquine (Paper 4). The compound 3,4,3',4',5'-pentamethoxychalcone with IC<sub>50</sub> 0.11 mg/ml shows 13 times higher activity than the standard licochalcone A and has a high selectivity index (85.05), which is a contribution to the search for new antimalarial agents.

- Synthesis of 15 chalcones with structural analogy to curcumin was carried out and multidrug resistance (MDR) was evaluated in mouse lymphoma cells (paper 8). The experimental results obtained in combination with the quantum chemical calculations show

the importance of the substituents in the p-position of the two rings and determine that they must have a hydrophobic nature. Inhibition of glycoprotein Gp170 expression in multidrug-resistant human bladder cancer cell lines was investigated, and a concentration-dependent cytotoxic effect was found. In a model system of combined chemotherapy, it was shown that 2,3,4-trimethoxy- and 2,5-dimethoxy units were the highest antiproliferative activity of chalcones on human MDR1 gene-transfected mouse lymphoma cells. These two chalcones were found to inhibit 50% of cell proliferation at a concentration of about 0.4  $\mu\text{g/mL}$  and were 2 to 100 times more active than the other chalcones. These results would contribute to the design of chalcone-like P-gp modulators and drugs aimed at treating resistant cancers.

- Another contribution to the synthesis of substituted chalcones is the application of the so-called "green synthesis". For the first time, in a reaction catalyzed by enzymes (lipase from porcine pancreas or acylase from *Aspergillus melleus*) by Claisen-Schmidt condensation between benzaldehyde and acetophenone, E-chalcone was synthesized with high stereoselectivity and proved by NMR studies (paper 3).

#### ***Contributions related to the study of natural compounds and the demonstration of pharmacological properties***

- An analysis of methanolic extracts of aerial and root parts of in vitro cultivated *Artemisia alba* and aerial parts of in vitro cultivated *Clinopodium vulgare*, *Hypericum tetrapterum*, *H. richeri* and the endemic *H. rumeliacum* was carried out and their capacity to trap nitric oxide radical was evaluated. The results showed that the extracts of *H. rumeliacum*, *H. richeri* and *H. tetrapterum* had remarkably higher activity (0.18, 0.17 and 0.97  $\text{mg.mL}^{-1}$ , respectively) compared to *C. vulgare* and *A. alba* ( $\text{SC}_{50} = 3.45$ , 2.93 and 2.62  $\text{mg.mL}^{-1}$ , respectively), and the reference compound vitamin C had an activity of 0.26  $\text{mg.mL}^{-1}$ . The contribution of these studies shows the high therapeutic potential of extracts obtained from in vitro cultivated plants and is a good basis for further research (paper 9).

Spectrophotometric methods with an Elisa reader were adapted to determine the antiradical activity in living systems of highly reactive oxygen- and nitrogen-containing particles, as well as synthetic compounds to determine the activity of analogues of polyhydroxylated trans-blocked 2-aryl cinnamic acids towards  $\text{OH}\bullet$  and  $\text{O}_2\bullet^-$  (paper 11) and to determine the activity and study the mechanism of thiazolo- and isoxazolo-hydrazinylidene-chroman-2,4-diones towards  $\text{O}_2\bullet^-$  and  $\text{NO}\bullet$  (paper 12).



- Research was conducted to determine the chemical composition of fresh juice obtained from the leaves of the succulent plant *xGraptopveria* (Crassulaceae) (paper 10), used in folk medicine for the treatment of conjunctivitis. Through GC/MS analysis, the main groups of organic compounds were determined: alkylamines, hydroxycarboxylic acids, aliphatic and aromatic carboxylic acids, amino acids, alcohols, aromatic and aliphatic hydrocarbons. It is suggested that *xGraptopveria* exhibits activity against conjunctivitis through a synergistic effect of different chemical compounds

- An alcoholic extract of *Potentilla reptans* (*Potentilla reptans*) was studied (paper 13), as it is known that aerial parts of the plant are used to treat diarrhea, hemorrhoids, bleeding gums and mastitis. Antibacterial activity was determined against 3 strains of *Staphylococcus aureus*, and it was found that the hexane fraction was the most active with an MIC of 0.313 mg/ml against *S. aureus* ATCC 6538 P.

- Using gas chromatography and mass spectral analysis, 44 components were identified in *Lavandula angustifolia*-lavender oil (paper 17), the main components being linalool (24.1%) and linalyl acetate (27.5%), which serve to assess the quality of the oil. The importance of these studies is based on the fact that lavender oil has numerous pharmacological applications exhibiting, sedative, antioxidant, anti-inflammatory, anti-tumor and antimicrobial activity.

- Information from data in the scientific literature on gentians (*Gentianaceae*) as a means of pain control (paper 15) and wound treatment (paper 16) has been systematized. In paper 18, data were collected on the secondary metabolites of cinquefoil species from 5 sections growing in the Bulgarian mountains. The most abundant secondary metabolites in *Gentiana* (iridoids, flavonoids and xanthenes) were found to be disproportionately investigated across sections. The conclusions drawn may be useful in finding compounds responsible for the field-observed susceptibility of some of the inkwell species to certain insect invaders. The contribution of these studies is an enrichment of knowledge in creating the methods of cultivation and micro-propagation of disappearing gentian species necessary for the development of new medicines based on gentian extracts.

The achieved results convincingly prove the competence and broad research experience of Dr. Batovska. A huge number of complex chemical compounds derived from chalcones have been synthesized, which have been proven by modern instrumental methods.

Their biological properties and potential applications have been investigated. Some of

the obtained results are in a modern and up-to-date field such as the analysis of medicinal plants and their products. Proof of the high quality of scientific research is the large number of citations that found international recognition - over 380 presented for participation in the competition and over 1400 for her entire career.

### ***Critical notes and recommendations***

In general, I have no critical remarks, as the presented documents are convincing enough. I would note that information about participation in national projects, which probably exists, is not presented. Participation in national and international scientific events is also not documented.

### ***Personal impressions of the candidate***

My personal impressions are that Dr. Batovska is a serious and ambitious researcher with creative thinking in planning and solving current scientific challenges. She always shows goodwill, criticism and objectivity when communicating with his colleagues.

### ***Conclusion***

The analysis of the presented documents, the quality of the scientific works and the scientific contributions define Dr. Daniela Batovska as an established researcher with consistency in the search for new solutions to current scientific problems. In terms of volume and quality, all presented scientometric indicators meet, but also significantly exceed, the recommended requirements for occupying the academic position of "professor" according to the Law on the Development of the Academic Staff in the Republic of Bulgaria (ZRASRB), the Regulations for the Implementation of ZRASRB, the Rules of the BAS and the Regulations of IEC-BAS.

With conviction, I give my positive assessment and recommend to the esteemed members of the Scientific Jury to vote for Dr. Daniela Batovska to be elected to the academic position of "Professor" at IEC -BAS in professional direction 4.2. "Chemical Sciences".

10.11.2023

Reviewer

  
/Ivanka Stoineva/