Review

of the materials submitted for participation in the competition for the occupation of the academic position "**Professor**", in Higher Education Area 4. "Natural Sciences, Mathematics and Informatics", Professional field 4.2. "Chemical Sciences" (Organic Chemistry - Organic Synthesis), announced in the State Gazette no. 52 of 02.07.2019 for the needs of the Faculty of Chemistry and Pharmacy at Sofia University "St. Cl. Ohridski "

by Prof. Dr. Natasha Trendafilova, Institute of General and Inorganic Chemistry at BAS

The only candidate in the competition for occupation of the academic position (AP) "Professor", in Higher Education Area 4. "Natural Sciences, Mathematics and Informatics", Professional field 4.2. "Chemical Sciences" (Organic Chemistry - Organic Synthesis), announced in issue 52 of the State Gazette of 02 July 2019 for the needs of the Faculty of Chemistry and Pharmacy at Sofia University "St. Cl. Ohridski, **is Assoc. Prof. Dr. Rositsa Dimitrova Nikolova** (Researcher ID: L-1107-2016 Web of Science, Author ID: 7004236832 Scopus, ORCID: 0000-0003-0671-0532).

1. General presentation of the received materials. Assoc. Prof. Dr. Nikolova has presented a set of materials that is in full compliance with the requirements of the ZRASRB (ЗРАСРБ) and the Regulations for its implementation as well as with the Rules for the conditions and procedure for acquiring academic degrees and occupying academic positions at Sofia University "St. Cl. Ohridski" (July 17, 2019). *The report on the implementation of the minimum national requirements under Art. 2b of ZRASRB for occupation of the AP "Professor" in the Scientific area 4. "Natural sciences, mathematics and informatics", Professional field 4.2. "Chemical Sciences", indicates that the candidate fulfills and exceeds the required minimum by all indicators.*

2. Biographical data, education and professional experience. Assoc. Prof. Dr. Rositsa Nikolova was born on 18.12.1962 in Varna. She graduated from the Faculty of Chemistry at the University of Sofia in 1990 with qualification in "Chemistry" and a Specialization in "Organic and analytical chemistry". After successfully defending her thesis on the topic: "Synthesis and Chemical Transformations of Phosphorus-Coumarin Derivatives", in 2000, the Higher Attestation Commission awarded her the PhD degree in Organic Chemistry. In the period 2000-2009, she was consecutively selected as an "Assistant", "Senior assistant" and "Chief assistant" in the Faculty of Chemistry at Sofia University. In 2009, she was selected as "Associated Professor" in Organic Chemistry at Faculty of Chemistry at the Sofia University, where she has worked until now. Since 2009, Assoc. Prof. Dr. Rositsa Nikolova is the Head of the Organic Synthesis and NMR Spectroscopy Laboratory. In the period 2011-2015, she is the Vice-Chairman of the General Assembly of the Faculty of Chemistry. Since 2012 until now the candidate is the Head of the Department of Organic Chemistry and Pharmacognosy of the Faculty of Chemistry and Pharmacy and since 2017 she is a member of the Faculty Board. Assoc. Prof. Dr. Nikolova has held a number of short-term specializations at the Technical University of Munich (2011, 2012, 2013, 2014, 2018) and at the University of Caen (CNRS), France (2008, 2012, 2013), which have enriched her scientific interests and contributed to her professional development.

The report on the participation of Assoc. Prof. Dr. Nikolova in the implementation of scientific projects showed that she was the manager of 13 successfully accomplished projects, funded by the Scientific Research Fund of Sofia University, and the manager of an ongoing contract. She was a member of the working groups of 9 contracts and the head of two contracts funded by the Ministry of Education and Science – Scientific Research Fund. The candidate is a member of the Management Council of two contracts funded under FP7, Everest and BeyondEverest and one under H2020 MaterialsNetworking.

Assoc. Prof. Dr. Nikolova possesses a wide and deep expertise in the field of Organic Chemistry and Organic Synthesis, which is why she has been repeatedly invited and selected as a reviewer of international scientific publications in the field of organic synthesis, diploma works and dissertations, has participated in scientific juries for the award of academic degrees and occupation of academic positions. She is a member of the Expert Council of the Doctoral School of Sofia University. The applicant's expertise should also be supplemented by her participation in expert groups for accreditation of the Standing Committee on Technical Sciences and Military Affairs and the Standing Committee on Natural Sciences, Mathematics and Informatics. Since 2011, she has been invited and selected as Chairman of the Standing Scientific Expert Committee on Chemical Sciences at the National Scientific Research Fund, which function has been very successful so far.

Assoc. Prof. Dr. Nikolova has participated in the organization of a number of scientific events. She has chaired and co-chaired three international symposiums on organic chemistry, two international conferences and 8 workshops on advanced functional materials. Assoc. Prof. Dr. Nikolova is a member of the Union of Scientists, Union of Chemists, European Association for Chemical and Molecular Science, American Chemical Society.

3. Evaluation of scientific activity

Scientific publications. Assoc. Prof. Dr. Rositsa Nikolova is an author and co-author of a total of 44 scientific papers, 33 of which (75%) have been published in international scientific journals, 2 are publications in Bulgarian journals, 4 are publications in proceedings of scientific conferences, and 5 are study aids. Her publications obtained 219 citations, of which 121 in Scopus. The results of the candidate's research were presented at 57 scientific conferences in the country and abroad with 28 scientific reports and 62 posters.

For participation in the present competition for AP "Professor", Assoc. Prof. Dr. Nikolova presented 22 original scientific papers that were not included in her dissertation for "Doctor" degree and in the list publications for participation in the "Assoc. Professor" competition. Of these, 16 scientific papers have been published in renowned international scientific journals, 2 are in proceedings of scientific conferences, 4 are teaching aids. The distribution of the 16 scientific papers by quartile of the journals in which they are published is as follows: 6 publications are in journals falling in category Q1, 7 publications are in journals of category Q2, 2 are in journals of category Q3, and 1 publication is in a Q4 journal.

Habilitation work. The Habilitation work of Assoc. Prof. Dr. Nikolova is on the topic: "3-Substituted coumarins and 1,2-benzoxaphosphorins as precursors of bioactive compounds". It describes the candidate's studies included in 4 scientific publications, published in journals,

which are referenced and indexed in world-renowned scientific information databases (Web of Science and Scopus). All papers on the subject of the Habilitation work have been published in scientific journals of category Q1, which fulfilled the minimum requirements for the indicators in Group B. The published papers present studies devoted to the development of novel methods for directed synthesis of coumarin derivatives containing various pharmacophore-, chromophore- and complexing groups. The main idea of the studies was to accumulate a sufficient number of results to carry out a comparative examination of the reactivity of the newly obtained substances with respect to nucleophilic reagents, as well as to identify the factors responsible for some differences. The results of the systematic studies have shown that, as an analogue of the coumarin-3-carboxylic acid esters, the diethyl ester of 2-oxo-2H-benzopyranphosphonic acid exhibits similar properties in reactions with nucleophilic reagents. Its behavior is found to be similar to that of other 3-substituted coumarins with electron-acceptor substitutes. In the reactions studied, it reacts more readily, in a shorter time and with higher yields.

The other 12 scientific publications presented in the competition for the academic position “Professor" (according to the indicators of "Group D") have brought to the candidate 232 points with a required minimum of 200 points, which fulfilled and exceeded the minimum requirements. The distribution of these publications by quartile of the journals in which they are published is as follows: 2 publications are in journals of category Q1, 7 - in Q2, 2 - in Q3 and 1 in Q4 journals. Assoc. Prof. Dr. Nikolova has one single publication and the distribution of the remaining papers by authors number is as follows: 1 publication is with 2 authors, 2 publications with 3 authors, 1 publication with 4 authors, 1 - with 5 authors, 3 publications with 6 authors, 2 with 7 authors and 1 with 8 authors.

The scientific publications presented by Assoc. Prof. Dr. Nikolova for participation in this competition have obtained 79 citations (158 points), which met and exceeded the minimum requirements for Indicator 11 of Group D (100 points). All citations of the scientific publications for the competition are in publications that are referenced and indexed in the Scopus database.

Scientific contributions. The research described in the candidate's publications is mainly in the field of *organic chemistry* and in particular in the field of *organic synthesis*. Particularly noteworthy are her studies on the synthesis, modification and study of substituted coumarins and their phosphorus-containing analogs, which include the synthesis of phosphorus-containing coumarins with potential biological activity, the study of the reactions of 3-substituted coumarins with nucleophilic reagents, cycloaddition reactions, tandem reactions, quantum-chemical studies of the mechanisms of the reactions studied. The research carried out is characterized by depth and precision and has led to the accumulation of a large number of valuable scientific results and fundamental conclusions that may be a very good starting point for future developments on the topic.

Assoc. Prof. Nikolova's scientific contributions include the development of original methods for synthesis, isolation of new coumarin derivatives, finding the conditions for a number of reactions, identification of the factors responsible for the type and yield of the target reaction products. The development of new methods for the synthesis of heterocyclic compounds is an

extremely complex task, requiring broad and specific knowledge, resourcefulness and very precise experimental work, which Assoc. Prof. Dr. Nikolova has successfully completed in the process of her scientific research. For this reason, its scientific contributions are not limited to the synthesis and characterization of previously unknown compounds and data, they also have a significant methodological character. To characterize the new compounds and their salts and complexes (including metals), numerous spectroscopic and structural studies were performed with X-ray photoelectron spectroscopy, absorption- and fluorescence spectroscopy, X-ray diffraction. In order to study the mechanisms of ongoing interactions and the role of the various factors affecting them, as well as to study a number of molecular properties of the compounds studied, accurate quantum-chemical calculations were performed at different levels of theory that confirmed and explained the experimental results or predicted molecular properties that could not be obtained from the experiment. The specific scientific contributions, some of the more important results and their conclusions are summarized below.

1. Synthesis and prove of novel compounds

• *Comprehensive experimental studies have clarified the interaction of 2-oxo-2H-1-benzopyran-3-phosphonic acid diethyl ester with nitromethane under various reaction conditions.* The products obtained in the absence and presence of solvent (ethanol) and various bases (potassium fluoride, propylamine, piperidine and triethylamine) have been proven. A mechanism for the formation of pyrrolidinedione is proposed, which involves the sequential Michael type addition reaction, the migration of an oxygen atom (rearrangement of Nef), and the molecular rearrangement leading to the opening of the lactone ring and the formation of a new pyrrolidine ring.

• *A new, effective method for the synthesis of 3,4-disubstituted pyrrolidine-2,5-dione from 3-substituted coumarins is proposed.* The interaction of nitromethane with coumarins with electron acceptor and electron donor substituents and those without substituents has been studied. The interaction of 3-ethoxycarbonyl-1,2-benzoxaphosphorine with nitromethane has been found to produce a Michael addition product in the form of a diastereoisomeric mixture. *Reliable quantum-chemical calculations have been performed at DFT/B3LYP/6-31G** level of theory at all stages of the synthesis of pyrrolidinedione from nitromethane and coumarin, which are not often present in the literature and therefore are in many respects pioneering.* The most likely reaction pathway for the newly discovered rearrangement is predicted, involving sequential addition of nitromethane by Michael reaction, oxygen atom migration, and cyclization of the newly formed pyrrolidine ring.

• *The interaction of 3-phosphonocoumarin with organometallic compounds upon heating and ultrasound irradiation has been studied.* The influence of temperature and irradiation on the reproducibility of the results, the yield and the type of products obtained has been established. Within this topic, a new and effective method for the dimerization of 3-substituted coumarins using ultrasonic radiation has been developed, which achieves an increase in the rate and yield of the reaction compared to those described in the literature. The reaction of homodimerization under ultrasound conditions in the presence of zinc and chloroacetanhydride has been studied. It was found applicable only to coumarins with

electron-acceptor group in the 3rd position, while unsubstituted coumarin and coumarins with electron-donor substitutes in the 3rd position do not change. It was found that under the method conditions no heterodimerization occurs, a homodimer of the more reactive coumarin starting material was obtained. A mechanism of the dimerization reaction is proposed - radical coupling rather than Michael addition, with ultrasound irradiation favoring the coupling of the resulting homoradicals.

• *Decarboxylation reactions of diethyl 3-acyl-2-oxochroman-3-ylphosphonates have been studied, yielding two new product types - β-ketophosphonates and propionic acids.* These studies have shown that decarboxylation proceeds readily when boiled in water in the presence or absence of acids. Reactions occurring in the presence of acids as catalysts have been found to result in leaving the acyl group and subsequently opening the lactone ring, and that the formation of β-ketophosphonates is only facilitated by thermal decarboxylation in water, which occurs with the initial opening of the lactone ring. It has also been found that the length of the acyl group in the third position is crucial for the stability of the starting acylated chromanes, and that the yields of β-ketophosphonates increase with the extension of the acyl group by one methylene group.

• *The interaction of seven new substituted merocyanine dyes with α-CD, γ-CD and a functionalized γ-cyclodextrin phosphate sodium salt has been studied in detail.* The reaction products are characterized by powder X-ray diffraction, spectroscopic and thermal methods. The experiments showed that the interaction resulted in the formation of 1D and 2D nanoscale "supramolecular polymers" and that the dyes adsorbed on the surface of cyclodextrins and formed hexagonal microcrystalline substructures. Solid state γ-CD/dye systems exhibit fluorescence properties that are not observed in pure dyes or cyclodextrin in solution and solid state.

• *The 2-oxo-2H-chromen-3-yl)phosphonic acid monoethyl ester trihydrate is synthesized, isolated, spectral and structurally characterized.* Quantum-chemical calculations have been carried out in the framework of density functional theory, which have studied its electronic structure, vibrational (DFT/B3LYP/6-311++G(2d, 2p)) and electronic spectra in gas phase and aqueous solution (TD-DFT/CIS/6-311++G(2d, 2p)). Correlation between structure and spectroscopic characteristics has been established.

• *Pt (II) and Pd (II) complexes and salts of 3-substituted coumarins and 1,10-phenanthroline were obtained and their structure was proved by X-ray diffraction analysis, TGA, DSC, DTA and spectral methods (NMR, UV, conventional and linearly polarized IR) as well as quantum-chemical calculations performed at DFT/B3LYP/6-311++G**, MP2, CIS levels of theory.*

2. Structural and quantum-chemical studies

• *In order to evaluate the applicability of C1s and O1s binding energies as an experimental descriptor of the reactivity of organic compounds, combined experimental (X-ray photoelectron spectroscopy) and theoretical studies (DFT) of the binding energies of 1s levels of C and O were performed and the results were correlated with the atomic electrostatic potential.* Using DFT/B3LYP/6-311+G* and MP2/6-311+G* methods, local reactivity descriptors were calculated: atomic charges, atomic electrostatic potentials, and Fukui atomic

functions for a series of 3-substituted coumarin (2-oxo -2H-1-benzopyran) derivatives and the influence of the substituents is estimated. According to the calculated atomic electrostatic potentials, the electrophilicity of the reaction centers in the coumarin system is increased in the presence of a phosphonic group, especially with coumarin-3-phosphonic acid. It has also been found that the presence of an electron donor group at C-7 leads to increased electrophilicity of C-7, but the C-3 and O-2 lactone ring atoms increase their nucleophilicity. Calculations of the phosphonocoumarin structures showed that C-3 carbon atoms are soft centers and that phosphorus-containing substituents do not affect the electron localization at C-3. The theoretical results predicted a lower nucleophilicity of the O-2 atom compared to the C-3, indicating that it would be the preferred reaction center upon nucleophilic attachment. According to the calculations, the substituted coumarins will react with soft nucleophiles in position 2 and with hard nucleophiles in position 4.

- *Dissolution processes and dynamics of the H-bonds in 3-phosphono-7-aminocoumarin and 7-aminobenzoxaphosphorin were investigated in the excited state using time-resolved fluorescence spectroscopy and accurate excited-state quantum chemical calculations (DFT/TD-DFT/CAM-B3LYP XC/6-31+G**/PCM).* The absorption and fluorescence spectra of the coumarins investigated in different solvents were analyzed and the attenuation of the H bonds between the solvent and the solute was detected upon optical excitation. The quantum-chemical simulations performed demonstrated the breaking of the H-bond at the amino group of coumarin and the stabilization of the H-bonds at the carbonyl and phosphonic groups. A partial transfer of electron density to the first solvation shell where the phosphonic group is involved is reliably predicted. Fluorescence spectroscopy investigated the dynamics of the dissolution and determined the time of relaxation of the H bonds in the excited state for different solvents.

• *Using X-ray diffraction, 3-iso-nicotinoylcoumarin and the co-crystal of N-(pyridin-3-yl) benzamide benzoic acid are structurally characterized.*

• *Self-association of 2- and 3-(acetylamino) pyridines in the condensed phase was investigated using conventional and linearly polarized IR spectroscopy.* Quantum-chemical calculations of the electronic structure and vibration characteristics of the two compounds were performed and correlations were established.

4. Assessment of teaching activity. The teaching activity of Assoc. Prof. Dr. Nikolova during the last five academic years was very high. The Candidate has provided data for 6 courses on Organic Chemistry I and II, two of which were developed by the Candidate for various specialties and forms of training at the Faculty of Chemistry and Pharmacy. She is the author and lecturer of three new courses: "Active Ingredients in Perfumery and Cosmetics", "Organic Materials in Cosmetic Products" and "Cosmetic Products and Care". Data on the conducted exercises and seminars on "Organic Chemistry" for undergraduate students of the Faculty of Chemistry and Pharmacy and Faculty of Biology of Sofia University, are presented.

Assoc. Prof. Dr. Nikolova was a co-supervisor of a PhD student successfully defended the thesis in 2012 and at present she is a supervisor of another PhD student. Data on the supervision of 12 graduates of the Department of Organic Chemistry and Pharmacognosy of

the Faculty of Chemistry and Pharmacy (1993-2019), as well as the research practice of eight students (2000-2019) are also presented. From 2016 until now, Assoc. Prof. Dr. Nikolova is the Chairman of the Examination Committee for the State Examination for the Bachelor's Degree and for the Master's Degree Examination. She participated in the preparation of tests for State Examination for Bachelor's Degree in the Faculty of Chemistry in 2003 and 2008 and the Entrance examination for the Master's Degree in 2008.

5. Personal impressions and a concluding standpoint. Assoc. Prof. Dr. Rositsa Nikolova is an in-depth researcher and recognized expert in the field of organic synthesis and the study of the structure and properties of a number of new compounds. With motivated and comprehensive experiments, she develops original methods for the synthesis of new compounds, knows and cleverly uses different techniques for their characterization (X-ray diffraction analysis, X-ray photoelectron-, absorption- and fluorescence spectroscopies, NMR, conventional spectroscopy and linear spectroscopy. A number of the experiments carried out are supported by quantum-chemical calculations, which substantially enrich the scientific contributions and extend the meaning of the results obtained, giving them explanatory and predictive character. In the competition for the AP "Professor", Assoc. Prof. Dr. Rositsa Nikolova presented a sufficient number of scientific papers published after obtaining "Doctor" degree and AP "Associate Professor". The results achieved by the candidate are fully in line with the specific requirements for AP “Professor” in the Sofia University for “Chemical sciences”. Assoc. Prof. Dr. Nikolova has unquestionable scientific qualifications and potential to conduct and lead valuable scientific research in the future. **After analyzing the materials presented in the competition: scientific papers, Habilitation work, data on teaching, expert and organizational activity, participation in scientific projects and scientific forums, I find it justified to give my positive assessment by voting "yes" for Assoc. Prof. Dr. Rositsa Nikolova to take the academic position "Professor" at the Faculty of Chemistry and Pharmacy at Sofia University "St. Cl. Ohridski" in Professional Field 4.2. “Chemical Sciences”, Organic Chemistry - Organic Synthesis.**

October 16, 2019, Sofia

Reviewer:

(Natasha Trendafilova, Prof. Dr.)