

REVIEW

in competition for the academic position of Associate Professor
in the professional field 4.2 Chemical Sciences (Structural analysis and physicochemical
characterization of small organic molecules)
for the needs of the department “Structural crystallography and materials science”
at the Institute of Mineralogy and Crystallography “Acad. I. Kostov” (IMC) - BAS,
Announced in the State Gazette, 95/14.11.2023.

Reviewer. Prof. *Vilma Petkova Stoyanova*, IMC-BAS,
member of the scientific jury under Order No. 26 RD-09/10.01.2024.

Candidate: Principal Asst. Dr. Rusi Ivanov Rusew, IMC-BAS

In the competition for the academic position (AD) “Associate Professor” in the professional field 4.2. Chemical Sciences (Structural analysis and physicochemical characterization of small organic molecules) (“State Gazette” issue 95/14.11.2023) participated one candidate - Senior Assistant Dr. Rusi Ivanov Rusew from the department “Structural Crystallography and Materials Science” at the Institute of Mineralogy and Crystallography “Acad. Iv. Kostov” (IMC) - BAS.

1. Brief biographical details of the applicant

Principal asst. Dr. Rusi Ivanov Rusew graduated in 2017 at the Chemical Technological and Metallurgical University - Sofia (CMTU), Sofia, Bulgaria. Diploma, Series HTMU-2017, Registration number 002746/2017) as a Master in the specialty “Fine Organic Synthesis” with professional qualification “Chemical Engineer” and excellent grade. In 2021 he received the educational and scientific degree (DSc) "Doctor" in the scientific specialty “Mineralogy and Crystallography” (Diploma No. 001392/15.09.2021) after successful defense of the dissertation thesis entitled: “Synthesis, structural characterization and antimicrobial activity of quaternary ammonium compounds” as a full-time PhD student at the Institute of Mineralogy and Crystallography “Acad. I. Kostov” (IMC) - BAS, Sofia, Bulgaria. Prof. B. Shivachev. In the same year he was appointed at IMC-BAS as an assistant professor. In 2022, after a successful competition, he was appointed to the academic position of “Senior Assistant Professor” at IMC-BAS, department “Structural Crystallography and Materials Science”, which he holds until the present moment.

2. Compliance of the submitted documents for the academic position of Associate Professor

By Protocol No. 41PD-16/17.01.2024 the Commission for examination of the documents of the candidate for participation in the competition certifies the regularity and conformity of the documents. They were also examined by the scientific jury (appointed by Order 26 RD-09/10.01.2024) at the first meeting on 25.01.2024 (by Order 41 RD-09/22.01.2024), which decided that the candidate Asst. Dr. Rusi Ivanov Rusew to be admitted to the evaluation for the academic position of “Associate Professor” at IMC-BAS.

The review of the documents with which Dr. Rusew participated in the competition for the post of Associate Professor, it was found that:

1. Chief asst. Dr. R. Rusew has provided all the required documents for holding the academic position “Associate Professor” in accordance with Article 24, items 1-5 of the Law on the

Development of Academic Staff in the Republic of Bulgaria (Law on the Development of Academic Staff in the Republic of Bulgaria) (in force from 23.12.2022) and Article 53, par. 18 (4) of the IMC-BAS Regulations (in force from 21.10.2021).

2. Chief asst. Dr. R. 001392/15.09.2021, issued by the Bulgarian Academy of Sciences, Burgas. The title of the study is.
3. According to the submitted Certificate of Work Experience No. 13LS05/08.01.2024, issued by IMC-BAS, the candidate has held the academic position of “Senior Assistant Professor” for 3 years. This satisfies the requirement for more than 2 years of experience in the academic position of “Assistant Professor” according to the requirements of Article 18(2)(2) of the PPPRAS of the IMC-BAS.
4. The publications submitted for the competition are not duplicated with the publications for obtaining the Ph.D. degree and for holding the position of Assistant Professor.
5. There is no evidence of plagiarism in the scientific works of Dr. R. Rusew for participation in this competition.
6. The applicant has enclosed a statement of fulfilment of the minimum national requirements under Art. (1) and (2) of the Mineralogy and Crystallography Act , as well as the enhanced criteria under Article 11(6) of the Mineralogy and Crystallography Act and Article 18(2) of the Mineralogy and Crystallography Act of the Institute of Mineralogy and Crystallography, BAS.
7. The analysis of the provided data shows that Dr. Rusew meets, and in some indicators exceeds, the national requirements (ZRASRB*), as well as the increased criteria of the Bulgarian Academy of Sciences and the Institute of Mineralogy and Crystallography (BAS/IMC**) for holding the position of Associate Professor in the professional field 4.2 Chemical Sciences. The performance of the indicators by points is presented in the following table.

Group by groups	Indicators	Doctor		Required points for AD “Associate Professor” by group		Candidate's points
		Min. Requirements	Achieved points	HIPC*	BAS/IMC**	BAS/IMC**
A	1. Dissertation for the award of the degree of Doctor of Education and Science	50	50	50	50	50
B	3. Habilitation work - scientific publications in publications that are refereed and indexed in WoS and Scopus	-	-	100	100	100
G	7. Scientific publications in journals that are refereed and indexed in WoS and Scopus, outside the habilitation thesis	30	34.66	200	220	273

D	11. Citations in scientific publications, monographs, collective volumes and patents, refereed and indexed in WoS and Scopus			50	60	129
	Total	80	84.66	400	430	552

* The Law on the Development of Academic Staff in the Republic of Bulgaria

** Regulations for the conditions and procedure for the acquisition of scientific degrees and for the occupation of academic positions in the Bulgarian Academy of Sciences / Regulations for the conditions and procedure for the acquisition of scientific degrees and for the occupation of academic positions in the IMC-BAS

3. Description and analysis of the submitted materials

The total number of the publications of prof. as. Dr. R. Rusew is 25 according to the reference in NACID (<https://ras.nacid.bg/dissertation-preview/69320>). To participate in the competition for the AD “Associate Professor” Dr. R. Rusew has included 21 of them, which I will take into account when preparing the review. The detailed scientometric reference shows that 15 (71%) of the candidate's publications are in international journals and 6 (29%) in national journals. According to the list of publications for participation in the competition, all 21 scientific works (100%) of Asst. Dr. Rusew are visible in the WoS and Scopus world databases of scientific information, 16 (76%) of them are published in journals with impact factor and 5 (24%) - in journals with impact rank without impact factor. The distribution of articles by quartiles for WoS and Scopus journals is as follows: 7 articles (B4.1, B4.2, B4.3, B4.4, G7.6, G7.7, G7.8) in Q1 journals; 5 (G7.5, G7.9, G7.10, G7.11, G7.12) in Q2 journals; 4 (G7.17, G7.18, G7.19, G7.21) in Q4 journals and 5 (G7.13, G7.14, G7.15, G7.16, G7.20) in SJR journals. Among the high ranking journals are *Pharmaceuticals*, (*Q1*), *New Journal of Chemistry* (*Q1*), *Water* (*Q1*), *Molecules* (*Q1*), *Crystals* (*Q2*), *Molbank* (*Q2*) and *Bulgarian Chemical Communications* (*Q4*).

In the current competition, head. Dr. R. Rusew participates with one publication, in which he is the first author (in group “G” - №15), in another part of publications - 8 pcs. (B4.4, G7.7, G7.8, G7.9, G7.10, G7.17, G7.18, G7.19) he is the second author, and in the remaining 12 chief asst. R. Rusew is the 3rd and subsequent co-author. Most of the articles were published in 2022 (7 issues) and 2023 (5 issues).

The number of citations noted on the publications of Dr. Rusew, presented in a separate list, is 66 according to the provided reference. Of these, 63 are in scientific journals referenced and indexed in world-renowned databases of scientific information Scopus and WoS and 3 are citations in other journals, dissertations or abstracts abroad. The Hirsch index (h) is 4, excluding self-citations according to Scopus. In the citation record provided by the candidate, it was calculated with a lower score, which I have corrected according to the present data. Thus, the total number of citation points in scientific journals referenced and indexed in world-renowned databases of scientific information Scopus and WoS, presented in the Reference for fulfilment of minimum criteria, is 129. This result exceeds the required 60 points according to the increased requirements under the BAS and IMC-BAS PPPRAWS.

In the period 2018-2023 she is a principal asst. R. rdRusew has participated in 6 scientific forums. Varna, Bulgaria, as well as the National Conference “Personalized Innovative Medicine” (PERIMED) in Varna, Bulgaria. In 2023, the International Conference “PERIMED” will be held in Plovdiv, Bulgaria. Dr. Rusew's participation in all scientific forums is through poster presentations and papers related to the topic of this competition.

Dr. R. R. Rusew actively participates in 6 scientific projects, being the head of one of them, funded by the National Research Fund, with a scientific topic close to that of the announced competition for the post of Associate Professor. The candidate's package of documents does not provide evidence of his participation in the projects, but only a list with the names of the projects and information on the amount of funds involved.

4. Main scientific and/or applied contributions

The contributory nature of the publications with which the candidate participates in the competition has been considered in the two main categories of materials according to the requirements under Article 2b(2) and (3) of the RRADB Act and under Article 18(2)(4) and (4)(10). category "B" - Habilitation Author's Reference for the Contribution of the Publications, which are included in the Habilitation thesis and category "G" - Author's Reference for the Contribution of the Publications by Indicator. The candidate prof. as. R. Rusew has not presented his contributions on the publications separately for each of the categories "B" - group of articles 1-4 and "G" - group of articles 5-21, but in one general reference. By following the subject matter of the publications, it is found that the publications in the two categories are grouped formally rather than thematically.

4.1. Summary of publications

The scientific results of Dr. Rusew's research fall into a specific and interesting area of scientific knowledge - the study of the structural and phase characteristics of small organic molecules. Obtaining reliable data on these specific objects of organic chemistry has become possible in recent decades with the use of modern, high quality and resolution scientific infrastructure, such as is available at the IMC-BAS. This determines both the complexity of the research and the interest in the results obtained, which is evident from the results of its publications and the scientific metrics achieved.

Dr. Rusew's research activity is related to the synthesis, modification and physicochemical characterization of small organic molecules with various applications in medicine. Experimental activity follows the implementation of a defined approach and adherence to a methodology of synthetic protocols, including reaction conditions and methods of product isolation. The physicochemical characterisation of the properties of these products involves the application of single crystal X-ray structure analysis, NMR (in solution), IR, UV-Vis and Mass spectroscopies and Powder X-ray phase analysis to determine the molecular structures, crystalline/röntgen amorphous phases and purity of the substances. An important emphasis in characterization is the application of X-ray structural analysis as an indispensable part of physicochemical characterization, thanks to which the exact location of atoms, the bonds between them and the spatial orientation (conformation, etc.) of molecules (substances, materials) in the solid state are unambiguously proved, which I consider to be a certain personal contribution of Dr. R. Rusew in his research work.

According to the materials submitted to the competition, 2 areas of research can be distinguished in his research:

1. Structural analysis and physicochemical characterization of organic molecules with potential application in medicinal chemistry - №№ B4.1, B4.4, G7.5, G7.6, G7.7, G7.10 and G7.16.
2. Fundamental research containing detailed structural analysis and physicochemical characterization - №№ B4.3, B4.4, G7.1-G7.4, G7.8-G7.15, D17

Two of the publications in the first group discuss (B4.1 and B4.4) the protocol of synthesis (FHF at SU), physicochemical characterization (FHF at SU and IMB-BAS) and study of antitumor activity (IMB-BAS team) of a new class of CA-4 derivatives obtained by bioisosteric substitution of the 2-methoxyphenol fragment of CA-4 with the biologically active benzoxazolone (publication No. B4.1) or benzothiazolone (publication No. B4.4) heterocycles is applied. This type of compounds have potential application as novel antitumor compounds to provide effective and less toxic methods of cancer treatment. They appear to be analogues of the potent tubulin polymerization inhibitor, the natural cis-stilbene, Combretastatin A-4 (CA4) with reduced disadvantages and side effects, the most important of which are marked cardiotoxicity, low water solubility and chemical instability (propensity to transform into the inactive trans isomer) of the natural analogue.

As a result of the applied synthetic protocol, 28 new cis/trans (E/Z) styrylbenzoxazolones (according to Publication No. B4.1) and 26 new cis/trans (E/Z) styrylbenzothiazolones (according to Publication No. B4.4) were obtained. To accurately establish the stable configuration (E or Z) of 12 of the resulting compounds (4 by Publication No. B4.1 and 8 by Publication No. B4.4), their crystal structures were solved and refined by single crystal X-ray structure analysis. The X-ray structure analysis revealed that the investigated substances crystallize mainly in orthorhombic, monoclinic and triclinic crystal systems.

To establish the antitumor activity of the obtained compounds, a series of studies on cytotoxicity and antiproliferative properties against different cell lines were conducted (IMB-BAS team). Among the investigated substances with better or comparable antitumor activity against CA-4, the styrylbenzoxazolone analogue of CA-4 - designated 16Z (publication № B4.1) and the styrylbenzothiazolone analogue - designated 26Z (№ B 4.4) stand out.

Publications G7.5, G7.6, G7.7, G7.10 and G7.16 are aimed at solving problems of preparative medicine related to current and particularly sensitive diseases of our time. Publication G7.5 explores new derivatives of Thioflavin T, which is related to the search for more specific markers for the early diagnosis of Alzheimer's disease. The main contributions are related to the realization of synthesis, isolation, purification and structural characterization of the Thioflavin T homologous molecule- abbreviated XRB. The structural analysis of XRB was carried out to establish the crystal system of the molecule, in the form of iodate and its stabilization by halogen interactions (X...I) of the molecule with the iodide anion. Publication G7.6 reports the synthesis, physicochemical characterization and structural analysis of a hybrid organic molecule derived from 2-methyl cinnamic acid and amantadine, which was studied in a model experiment of Parkinson's disease in mice. The hybrid molecule was found to have positive effects on memory and neuromuscular coordination in mice. The results of X-ray structure analysis confirmed the successful synthesis as well as the significant flexibility of the molecule. In addition, the crystal structure is stabilized by intermolecular hydrogen interactions of the N-H...O type. Publication G7.7 deals with a current topic related to the development of molecules with anticoronaviral activity, such as synthetic derivatives of Rimantadine and Amantadine. The synthesized rimantadine and amantadine derivatives have been studied in detail by X-ray structure analysis, drawing conclusions about their ability to participate in a combination of hydrogen, halogen and close contact interactions. A new polymorphic modification of bisacodyl, (pyridin-2-ylmethylene)bis(4,1-phenylene)diacetate, a drug widely used as a laxative, is reported in Publication G7.10. Crystal structure analysis proves that the compound crystallizes in a non-centrosymmetric manner in the orthorhombic space group P212121. The main contribution of the work is in the discovery of a new polymorphic modification with better pharmacopoeial characteristics.

Publication G7.16 relates to the preparation of casein-like nanoparticles to be used as potential carriers of the model molecule, tolfenamic acid, with a view to improving its antitumour properties. The main contributions of Dr. Rusi Rusew are expressed in the study of the thermal behavior of unloaded and loaded with tolfenamic acid casein-like nanoparticles with the method of low-temperature differential scanning calorimetry to track the phase transitions depending on temperature. Fourier-transform-attenuated total reflection infrared spectroscopy (FTIR-ATR), commonly applied to organic compounds, was used to establish the crosslinking process between casein and CaCl_2 .

The papers in the second group of publications also focus on the application of structural analysis methods to characterize the physicochemical and crystal-chemical properties of a range of new or modified materials with applications in medicinal chemistry and materials science. In publications B4.2 and B4.3, the phenomenon of photochromism in new 5,5'-dimethyl hydantoin (B4.2) and 5,5'-diphenyl hydantoin (B4.3) Schiff bases under the influence of irradiation of the material with electromagnetic waves, mostly from the ultraviolet and visible spectrum, is investigated. Hydantoin derivatives are an important class of organic substances which are used as the basis for the development of drugs for the control and treatment of epilepsy (anticonvulsants, Phenytoin), of antibacterial preparations (Nitrofurantoin), as crosslinkers in the polymer industry, etc. The advantage in these publications is that the photoisomerization properties of compounds containing a hydantoin fragment are investigated. Such measurements are fewer and therefore the results obtained have important implications for the crystal chemistry of these substances. As a result of the proposed synthesis methodology, a total of 9 new hydantoin derivatives (5 by B4.2 and 4 by B4.3) were isolated in high yields (>85%). The X-ray structure analysis of 7 (out of 9) of them proved that they crystallize mostly in triclinic (space group P-1), monoclinic (space groups - P21/c, I2/a and C2/c) and orthorhombic (space groups Pbca and Fdd2) crystal systems with between 2 and 16 molecules in their elementary cage. All the resulting compounds were found to crystallize in the stable trans(E) form.

Publication G7.1 discusses the synthesis of a series of new acylpyrazolones containing methylene-linked heterocycles in the acyl fragment. By X-ray structure analysis, it was found that in the solid state, the products exist as intra- and intermolecular zwitterions between the tautomeric pyrazolone hydroxyl groups and the nitrogen atom of the acyl substituents. It was also found that the products coordinated spontaneously with caesium carbonate used as a base during the syntheses, and that the complexes formed were not stable on silica gel and decomposed, during chromatographic separation, to the free ligands. The materials of publications G7.2 and G7.3 have been characterised by a combination of electron microscopy, powder X-ray phase analysis, infrared spectroscopy and their chemical composition has been analysed by wavelength-dispersive X-ray fluorescence analysis. Publication G7.2 investigates the preparation and physicochemical characterization of titanosilicates ETS-4 and GTS-1, as well as the possibility of using them for contaminated water treatment. They were found to be effective adsorbents of Pb^{2+} . The highest adsorption capacity to Pb^{2+} was found for the GTS-1 material. Publication G7.3 emphasizes the modification of the titanosilicate ETS-10 with zirconium (Zr) and the use of the materials as a catalyst for the photodegradation of the organic dyes Methylene Blue and Crystal Violet. An attempt was made to elucidate the mechanism of photodegradation by using molecules neutralizing OH^- and O_2 radicals (scavengers), and NMR spectroscopy of the spent/final solutions was used as an additional method to establish the photodegradation results. Publications G7.4, G7.8 and G7.17 are purely synthetic in nature/direction. Publication G7.4 relates to the synthesis of polydentate N,O-ligands possessing unsymmetrical urea fragments attached to a p-cresol core. In G7.8, results from the synthesis of enantiomerically pure bis-dihydro naphthoxazines and imidazole derivatives

are presented, the latter being used as catalysts in a model reaction for the enantioselective addition of diethyl zinc to aldehydes. G7.17 deals with the preparation of ligands containing 13-membered cyclic benzodioxatetraaza nuclei. From the analysis of the results of the X-ray structure analysis in G7.4, G7.8 and G7.17, conclusions are drawn concerning the role of the various substituents and functional groups in the molecules studied contributing to the appearance or absence of conformational flexibility, the possibility of intermolecular or intramolecular interactions (hydrogen interactions, electrostatic attractions/repulsions, etc.). Publications G7.13-G7.15 concentrate on a detailed description of the synthesis and physicochemical characterisation of compounds of the class of coumarins (G7.13), perimidines (G7.14) and acylpyrazolones (G7.15), which are widely used in medicine as antibacterial, antitumour and antioxidant substances (G7.13 and G7.14), but also as ligands in coordination chemistry (G7.15). X-ray structure analysis was used to confirm the structure expected from the syntheses and to elucidate the interactions between functional groups inherent to the molecules studied (hydrogen bonds, weak contacts, π - π interactions, etc.). The combination of NMR and X-ray structure analysis established that the perimidine derivative (G7.14) forms a 1:1 solvate with a methanol molecule that is stable both in solution and in the solid state. By differential scanning calorimetry, the methanol molecule was found to leave the crystal structure without inducing a phase transition in the temperature range of 60-110° C. In G7.9, the results of the synthesis of two conformational polymorphs (3-acetamidophenyl) of boric acid are presented. After solving their crystal structures, it is found that the two polymorphs possess a different pattern/scheme of hydrogen interactions (different packing of molecules in the crystal structure) while maintaining the type and number of interactions. In work G7.11, the crystal structures of five magnesium complexes are studied, where the influence of different anions, such as Cl^- , NO_3^- , BF_4^- on the coordination of Mg is considered. The structures reveal that the traditional octahedral coordination of Mg does not change under the influence of the studied anions. It is found that when a complex is formed between MgCl_2 and six urea molecules, additional urea molecules are incorporated into the crystal structure to stabilize the structure due to larger size of the coordinated cation $[\text{U}_6\text{Mg}]^{2+}$. Publication G7.12 describes single crystals of natural habasite that is ion-exchanged with ammonium cations. Subsequent ion exchange of the ammonium habasite (NH_4 -CHA) with 1M solutions of ZnCl_2 and NiCl_2 leads to the formation of the zinc and nickel forms Zn-CHA and Ni-CHA.

4.2 Scientific contributions

The scientific contributions of Dr. R. Rusev are the result of his scientific research and publication activities and can be formulated as the application of a complex approach to the structural and crystal chemical properties of many interesting organic molecules with applications in medicine, natural and synthetic materials, with applications in water purification, etc. Noteworthy is the application of a rich variety of analytical techniques to scientific problems and the large amount of experimental work with emphasis on X-ray structural analysis. This is evidenced by the detailed analysis of more than 50 new crystal structures of various organic materials, the structures of which have been deposited in the international database for organic crystalline substances - the Cambridge structural database (CSD)

5. Critical comments and recommendations

I have no critical remarks to the work of Asst. Dr. R. Rusev and to the competition materials.

I would recommend to Dr. Rusev that when presenting his future research, his individual contributions be better expressed in publications. The materials submitted for the position of Associate Professor demonstrate his theoretical and experimental background. I believe he can

define and solve complex problems, plan and implement projects, and train young researchers. I wish him every success in his further career, of which I am fully convinced.

6. Conclusion

Presented by the head. as. Dr. Rusi Ivanov Rusew documentation for participation in the competition meets the requirements of the Law on the Protection of Human Rights and Fundamental Freedoms of the Institute of Medical Sciences and corresponds to the topic of the announced competition for AD “Associate Professor”. The evidence meets 552 points and exceeds the minimum requirements of the regulations.

I positively evaluate the materials presented in the competition and recommend the Scientific Jury to propose to the Scientific Council of IMC-BAS the candidate Assoc. Dr. Rusi Ivanov Rusew to be elected to the academic position of Associate Professor at IMC-BAS in the professional field 4.2. Chemical sciences (Structural analysis and physicochemical characterization of small organic molecules) for the needs of the department “Structural crystallography and materials science” at IMC-BAS.

24.03.2024

Sofia

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(Prof. V. Petkova, PhD)