REVIEW

of the materials submitted for the competition for the academic position "Associate Professor" in the professional field 4.2 Chemical Sciences (Bioorganic Chemistry, Chemistry of Natural and Physiologically Active Substances), announced in State Gazette, issue. 43 of May 31, 2019

The only candidate is **Senior Assistant Dr. Miroslav Angelov Rangelov**

Reviewer: Professor Dr. Nikolay Georgiev Vassilev, Institute of Organic Chemistry with Centre of Phytochemistry, BAS

1. Biographical information and eligibility

Senior Assistant Dr. Miroslav Rangelov is currently working in the Laboratory “Chemistry and Biophysics of Proteins and Enzymes” of the Institute of Organic Chemistry with Centre of Phytochemistry (IOCCP) at the Bulgarian Academy of Sciences, where his entire career has been ongoing. He graduated as a Master of Science in Organic and Analytical Chemistry at the Faculty of Chemistry, Sofia University "St. Kl. Ohridski” in 1997. In 2008, he defended his doctoral thesis on "Participation of a Vicinal Hydroxyl Group in the Peptide Bond Biosynthesis in the Ribosome - Model Studies" at IOCCP-BAS under the supervision of Prof. DSc Dimitar Petkov.

The documents for participation in the competition of the applicant fulfill the requirements of the IOCCP-BAS Regulations for the implementation of the Law on the Development of the Academic Staff in the Republic of Bulgaria, and the scientific and educational profile of the applicant is in accordance with the requirements for associate professor in the professional field 4.2. Chemical Sciences (Bioorganic Chemistry, Chemistry of Natural and Physiologically Active Substances).

2. General characteristics of the applicant's activities

Senior Assistant Dr. Miroslav Rangelov fulfills the minimum required points of IOCCP-BAS by groups of indicators for the academic position "Associate Professor", as can be seen from the attached information. The applicant participates in the competition with a list of 16 scientific papers and 1 published book chapter. In this list, 5 scientific publications are equated to habilitation thesis (group of indicators "B", indicator "4") and the other scientific publications

are in group of indicators "D", indicator "7". All publications are related to the competition, all of them are published in specialized international journals referenced in the ISI Web of Knowledge and/or SCOPUS and with Impact Factor (IF). The distribution of the 5 scientific publications equated to habilitation thesis according to the rank of scientific journals is as follows: three are in scientific publications with Q1, two are in scientific publications with Q2. The distribution of the other scientific publications with which the applicant participates in the competition for the academic position of Associate Professor according to the rank of scientific journals is as follows: six are in scientific publications with Q1, two are in scientific publications with Q2, three are in scientific publications with Q4 and one is a book chapter. According to the attached information, the total number of citations is 54. According to the Scopus database, the applicant's h-index is 8. This value is indicative of high scientific productivity combined with a wide response in the literature and covers the required minimum (≥5) of the regulations of IOCCP-BAS.

Senior Assistant Dr. Miroslav Rangelov has included in his documents an extended habilitation report, summarizing on 28 pages his own scientific research in the following four directions:

- Studies on the molecular aspects of the ribosome catalytic mechanism.
- Modelling ribosome catalytic activity on ammonolysis of diols.
- Functional study of the mechanism of acyl group migration between vicinal OH groups in monoformylated cis-tetrahydrofuran-3,4-diol as a model system for acyl group migration in amino acylated tRNA.
- Other model studies on ribosomal catalytic activity and application of developed methodologies to other systems.

The habilitation report includes also plans for the future, where scientific plans are in the fields of computational chemistry and drug design; development of a complete working molecular model of the prokaryotic and human ribosomes; application of HPLC in archeology and phytochemistry; continuing development of new software for solving difficult chemical tasks.

The habilitation report cites 65 literature sources, with 5 of them being scientific publications equated to habilitation thesis, and 7 of them being part of the scientific publications with which the candidate participates in the competition for the academic position of Associate Professor.

3. Publications submitted for participation in this competition

The scientific studies of Senior Assistant Dr. Miroslav Rangelov are in the field of bioorganic chemistry and is strongly influenced by his work in the laboratory "Biocalysis" under the leadership of Prof. D. D. Petkov. Under his supervision is the candidate's PhD thesis. Senior Assistant Dr. Miroslav Rangelov applies and develops various computational approaches and models for in silico studies on the mechanism of ribosome-catalyzed reactions.

The scientific contributions of Senior Assistant Dr. Miroslav Rangelov can be grouped in the following areas:

A. Elaboration of methodologies in the theoretical study of systems with conformationally diverse reaction pathways;

B. Development of MolRan software package for visualization and generation of molecular geometries, as well as for analysis of chemical properties and electronic structure of structures;

C. Modeling of ribosomal catalytic activity;

D. Application of developed methodologies to other systems.

I would like to review the scientific contributions of Senior Assistant Dr. Miroslav Rangelov as development of his knowledge, skills and competences for *in silico* research in the field of Bioorganic chemistry, chemistry of natural and physiologically active substances:

A. The first step in computational modeling is to choose a computational method and a basic set that are appropriate for the chemical system under study. As an example, Dr. Miroslav Rangelov modeled the structure of formic acid and its dimer, as well as the ammonolysis of formic acid at different theoretical levels. The statistical analysis of the obtained structural and energy results leads to the conclusion that B3LYP/6-31G** is the fastest, but still reliable method for correctly describing the geometry of the modeled structures and reaction energies (Publication 1 of Indicator B). The next step is the development of automated procedure for conformational search for transition state structures and stable structures of a given conformational family (Publication 1 of Indicator B). The automated procedure developed by Dr. Miroslav Rangelov includes:

- Generation of different structures through a developed algorithm based on the representation of molecules through graph theory;

- partial relaxation of the structures of large pools of generated structures such that during the geometric optimization of structures at the MM level, the atoms from the cleaving/forming bonds are automatically kept fixed with respect to each other;

- determining and eliminating conformationally equivalent structures, the geometric similarity of the structures being evaluated by numerically optimizing the position of one molecule with respect to the other;

- logical connection of structures from different conformational pools according to their geometry similarities, with each couple of intermediate and transition state structures are positioned over each other as the structure of the intermediate is translated into the centre of the coordination system and the position of the transition state structure is set via translation and rotation;

- generation of unknown geometry of the transition states, based on pre-defined connectivity of the atoms involved in the reaction and, as a result, the lowest energy point corresponding to the global minimum is identified, subject to user-imposed constraints.

The next step is the development of a methodology for analyzing the catalysis capabilities of a proton-donor or proton-acceptor group according to its position relative to the reaction center (Publication 3 of Indicator B). The algorithm leads to the construction of graphic maps representing the catalytic effect of the probe molecule in its different positions around atoms at which the main components of the transition vector are placed. The methodology was demonstrated on the influence of proton donor group adjacent to the reaction center during ester ammonolysis of an acylated diol as a model reaction for peptide bond formation in the ribosome.

B. All methodologies listed in point A have been implemented in the MolRan software package developed by Dr. Miroslav Rangel (publ. 1 and 3 of indicator B), which is designed for visualization and generation of molecular geometries, as well as for the analysis of the chemical properties and electronic structure of structures obtained by quantum-chemical calculations. The software package supports various input file formats. Various graphical representation tools are implemented. The program also includes a set of tools for generating, loading, and displaying meshes generated on the base of different data. A system of tools is available for constructing job files for conformational analysis and for analysis of the results obtained.

B. On the Modeling of Ribosomal Catalytic Activity by Ammonolysis of Diols [publ. 1 and 2 of Indicator B] a model reaction is used - the ammonolysis of 1-O-formyl 1,2-ethanediol, the choice of reagents is determined by the presence in the formylethanediol molecule of a vicinal hydroxyl next to the reaction center analogously to the ribose ring in tRNA. The main result is a catalytic acceleration of ester ammonolysis by hydrogen bonding of the vicinal hydroxyl group in tetragonal transition states. In investigating the mechanism of acyl group migration between vincinal OH groups in monoformylated cis-tetrahydrofuran-3,4-diol as a model system for acyl group migration into amino-acylated tRNA [publ. 4 of indicator B], the

results of the calculations suggest that the stepwise mechanism via an orthoester intermediate is preferred over the concerted mechanism.

G. Senior Assistant Dr. Miroslav Rangelov has applied the developed methodologies to other systems such as:

- DFT modeling of different hydrogen bonded, methanol complexes, with different proton acceptor and proton donor molecules containing Cl, F, NH_2, OH, OR and COOH [publ. 1 of indicator D];
- Molecular dynamics study of the interactions between sodium or magnesium ions and phosphate groups of RNA backbone modeled as dinucleotide fragments in aqueous solution using *ab initio* Born Oppenheimer [pub. 2 of indicator D];
- Testing of a set of ligands against the inner pocket formed by the activating segment and the P-loop of the V599E mutant of B-Raf and identifying ligands that, when binding to the V599E B-Raf, promotes an inactive conformation of the enzyme and are promising candidates in the fight with B-Raf-dependent carcinomas [publ. 3 of indicator D];
- Molecular docking study to clarify the interactions between drug-like ligands and xanthine oxidase (XO). The morpholinedione derivatives studied exerting XO inhibitory properties and are promising candidates in the treatment of gout and other conditions related to excessive uric acid production as well as anti-inflammatory drugs [publ. 4 of indicator D];
- Molecular docking study shows that binding of C-amide analogs based on the structure of VV-Hemorphin-5 to kappa opioid receptors could be the mechanism of their anticonvulsant activity [publ. 5 of indicator D];
- *in silico* modeling was performed to characterize the regions of the C1q globular “heads” that are crucial to its recognition and binding [pub. 6 of indicator D].

In these studies, there is a significant shift from fundamental to more practical applications of the methodologies developed. In this sense, the applicant's scientific research has not only scientific but also applied scientific contributions.

4. Project activity and dissemination of results

Senior Assistant Dr. Miroslav Rangelov has managed a national project, has been a team leader in an international project and has worked on the implementation of 16 national and 5 international projects. This shows that he is a sought-after partner because of his skills and competences for *in silico* research in the field of Bioorganic Chemistry, Chemistry of Natural and Physiologically Active Substances.

The results of his scientific work are presented as 17 lectures and 29 posters at various national and international conferences.

5. Assessment of the applicant's personal contribution

I personally know the candidate since his appointment to the IOCCП-BAS, we have discussed various aspects of molecular modeling and I have witnessed his scientific development. Therefore, his personal contribution to the research presented to me is indisputable.

CONCLUSION: Senior Assistant Dr. Miroslav Rangelov fulfills all the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria and the Rules for the Conditions and Procedures for Acquiring the Academic Position "Associate Professor" at the Institute of Organic Chemistry with the Center of Phytochemistry, BAS. The valuable scientific production presented for participation in the competition is sufficient in volume, has been published in renowned scientific journals with high IF and has found wide echo in the literature.

Based on the above, I am convinced of my positive assessment and suggest Senior Assistant Dr. Miroslav Rangelov to be elected to the academic position of "Associate Professor" in the professional field 4.2. Chemical Sciences (Bioorganic Chemistry, Chemistry of Natural and Physiologically Active Substances) at the Institute of Organic Chemistry with the Center of Phytochemistry, BAS.

16.09.2019 Reviewer: .....

Prof. Dr. Nikolay Vassilev