

ASSESSMENT

from Prof. Dr. Ivanka Georgieva Stankova, SWU "Neofit Rilski", Department of Chemistry, a member of the scientific jury in the contest for academic position "ASSOCIATE-PROFESSOR", in 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", Institute of Mineralogy and Crystallography "Acad. Ivan Kostov" at the BAS - Sofia
announced in the "State Gazette", no. 95 /14.11.2023

Candidate: Dr. Rusi Ivanov Rusev - Institute of Mineralogy and Crystallography "Acad. Ivan Kostov" at the BAS - Sofia

In the announced competition, Dr. Rusi Ivanov Rusev participated with 21 scientific publications (6 in Bulgarian scientific journals and 15 in foreign scientific journals indexed in WoS and Scopus). Of them in Q1 – 7, in Q2 – 5, Q4 – 4 and in publications with SJR in Scopus, but without IF – 5. In these publications, Chief Assoc. Dr. Rusi Rusev is the lead author in one publication, and in the remaining 20 he is the second and subsequent author. Total number of citations of the Chief Assistant Dr. Rusi Rusev without self-citations is 66, and the Hirsch Index (H-index) is 4.

From the submitted reference, it can be seen that the candidate is a participant in a total of 6 scientific research projects financed by the National Research Institute - four completed and two ongoing.

The publications of the chief assistant Dr. Rusi Ivanov Rusev are categorized into two main topics:

Structural analysis and physicochemical characterization of organic molecules with a view to application in medicinal chemistry and basic scientific research involving structural analysis and physicochemical characterization.

Structural analysis and physicochemical characterization of organic molecules with a view to application in medicinal chemistry:

□ antitumor action

One of the known inhibitors of tubulin polymerization is Combretastatin A-4 (KA-4). In addition to antitumor properties, KA-4 also has a number of side effects, the most important of which are expressed (cardiotoxicity, low water solubility and chemical instability).

In order to overcome these effects, the antitumor activity (IMB-BAN) of a new class of KA-4 derivatives obtained by bioisosteric substitution of the 2-methoxyphenolic fragment of KA-4 with the biologically active benzoxazolone or benzothiazolone heterocycles was synthesized and investigated. 28 new cis/trans (E/Z) styrylbenzoxazolones and 26 new cis/trans (E/Z) styrylbenzothiazolones were obtained, the crystal structures of which were proved by single crystal X-ray structural analysis.

Cytotoxicity and antiproliferative properties against different cell lines were investigated (IMB-BAS team) and it was shown that the styrylbenzoxazolone and styrylbenzothiazolone analogues of KA-4 possess antitumor activity comparable to KA-4. Through molecular docking, the mechanism of action of styrylbenzoxazolones and styrylbenzothiazolones was clarified and it was found that the degree of antitumor activity depends mainly on the number of methoxy groups in the phenyl ring, and also on the position of the styryl fragment relative to the free positions 4-, 5-, 6- and 7- from the benzoxazolone and benzothiazolone heterocycles.

□ Neurodegenerative diseases

New thioflavin derivatives have been developed in connection with the search for more specific markers for the early diagnosis of Alzheimer's Disease (AD). The main contributions are related to the determination of the molecular structure of the substance by one-dimensional and two-dimensional NMR spectroscopic techniques in solution, and its thermal stability by differential scanning calorimetry.

The physicochemical characterization and structural analysis of a hybrid organic molecule of 2-methylcinnamic acid and amantadine, which was studied in a model experiment of Parkinson's disease (PD) in mice, was performed. The results of the X-ray structural analysis confirm the successful synthesis, as well as the considerable flexibility of the molecule established by measuring the angles between the planes of the individual fragments. In addition, the crystal structure is stabilized by intermolecular hydrogen interactions of the N-H...O type. Molecular docking was performed in four protein molecules related to BP. The best affinity of the studied molecule was found for monoamine oxidase B (MAO-B) and catechol-methyltransferase (COMT).

□ Antiviral studies

Other research is related to the development of molecules with antiviral activity (against the human coronavirus). Synthetic derivatives of Rimantadine and Amantadine have been studied and show limited effect. X-ray structural analysis was performed, inferring their ability to engage in a combination of hydrogen, halogen interactions and close contacts, and the ligand-

viral protein relationship was demonstrated by molecular docking. Fundamental scientific studies containing detailed structural analysis and physicochemical characterization. The candidate is investigating the photochromic and molecular switching properties of novel 5,5'-dimethyl hydantoin and 5,5'-diphenyl hydantoin Schiff bases. 9 new hydantoin derivatives were synthesized and X-ray structural analysis was performed, which showed that they crystallize most often in triclinic (space group P-1), monoclinic (space groups – P21/c, I2/a and C2/c) and orthorhombic (space groups Pbc_a and Fdd₂) crystal systems between 2 and 16 molecules in their unit cell. All the obtained compounds were found to crystallize in the stable trans (E) form. A series of new acylpyrazolones containing methylene linked heterocycles in the acyl fragment were synthesized and X-ray structural analysis revealed 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.

The preparation and physicochemical characterization of titanosilicates ETS-4 and GTS-1 was investigated and the possibility of their use for the purification of polluted waters. They were found to be effective adsorbents of Pb²⁺.

The synthesis of enantiomerically pure bis-dihydro naphthoxazines and imidazole derivatives were investigated, the latter being used as catalysts in a model reaction for the enantioselective addition of diethyl zinc to aldehydes.

Based on the X-ray structural analysis, conclusions have been drawn regarding the role of the various substituents and functional groups in molecules contributing to the appearance or absence of conformational flexibility, the possibility of forming intermolecular or intramolecular interactions (hydrogen interactions, electrostatic attractions/repulsions, etc.).

The synthesis and physicochemical characterization of compounds from the class of coumarins, pyrimidines and acylpyrazolones, which are widely used in medicine and as ligands in coordination chemistry, are described. The X-ray structural analysis was mainly used to confirm the structure expected from the syntheses and to clarify the interactions between the functional groups inherent in the studied molecules (hydrogen bonds, weak contacts, π - π interactions, etc.). The combination of NMR and X-ray structural analysis found that the pyrimidine derivative forms a 1:1 solvate with a methanol molecule that is stable in both solution and solid state.

The original scientific contributions of the candidate, Dr. Rusi Rusev, are related to the structural analysis and physicochemical characteristics of organic molecules used in the

treatment of cancer, in neurodegenerative diseases (Alzheimer's disease, Parkinson's disease), as well as with antiviral activity, and the study of the crystal structure-properties relationship. The candidate has gained experience in the use of X-ray structural analysis as an indispensable part of the physicochemical characterization of organic molecules applied in medicinal chemistry, as well as the relationship between structural studies and molecular docking. The described more than 50 new crystal structures of various organic materials, which have been deposited in the international database for organic crystalline substances - Cambridge structural database (CSD), are an indicator of the enormous work done reflected in the scientific publications.

Conclusion

On the basis of everything stated above in this opinion, I believe that Ch. Assistant Professor Rusi Ivanov Rusev meets the requirements of the Regulations of the Institute of Medical Sciences of the Republic of Bulgaria, PPZRAS of the Republic of Bulgaria for holding the academic position of "associate professor" and I vote with a positive assessment for his overall scientific work.

25.03.2024

Signature

Prof. Dr. Ivanka Stankova