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REVIEW

by Assoc. Prof. Ivanka Petkova Pencheva - El Tibi, Faculty of Pharmacy at the Medical University - Sofia, Department of Pharmaceutical Chemistry, external member of the Scientific jury, according to Order № RD-28 / 05.02.2021 of the Rector of the University "Prof. Dr. Asen Zlatarov", Burgas and Protokol № 2 / 02.04.2021 of the Scientific jury

SUBJECT: Competition for the academic position of ASSOCIATE PROFESSOR in the field of higher education 7. "Health and Sports", professional field 7.3. Pharmacy, scientific specialty "Pharmaceutical Chemistry and Pharmacognosy" for the needs of training in the specialty "Assistant Pharmacist", Department of Pharmacy, Medical College at the University "Prof. Dr. Asen Zlatarov", Burgas (announced in SG, No. 105 / 11.12.2020).

The only candidate allowed to participate in the competition is Stefan Vanev Harkov, Ph.D.

General data:

Assist. Prof. Stefan Vanev Harkov was born in Burgas in 1986. In 2005 he graduated from the Vasil Levski High School for Foreign Languages in Burgas, and graduated with a master's degree in pharmacy from the Danilo Galitsky National Medical University in Lviv, Lviv, Ukraine. From 2010 to 2014 he was a doctoral student at the Department of Pharmaceutical, Organic and Bioorganic Chemistry of the same university. On April 11, 2014, after defending, he acquired the scientific degree "Doctor", specialty "Pharmaceutical Chemistry and Pharmacognosy". The career development of the candidate is as follows - from 26.09.2016 - 13.02.2018 he is an assistant at the Medical College of the University "Prof. Dr. Asen Zlatarov", Burgas, and from 14.02.2018 until now – Assist. Prof. At present, Dr. Harkov holds an administrative position - Deputy director of the Medical College. Fluent in written and spoken English (excellent), Polish (excellent) and Russian (excellent). The total work experience of Stefan Harkov as a lecturer to date is a little over 4 years and 6 months.

Teaching activity:

Assist. Prof. Stefan Vanev Harkov participates in lectures and exercises in the disciplines of Pharmaceutical Chemistry, Pharmacognosy and Technology of Drugs with Biopharmacy, as well as in training practices for full-time students, specialty "Assistant Pharmacist", "Professional Bachelor". The total study load, according to the information provided for the previous 4 academic years, is 2589 hours for training at a normative minimum of 1440 hours (179.79%).

Undisputed methodological contribution of Assist. Prof. Stefan Harkov is also the development of programs for full-time students majoring in "Assistant Pharmacist", "Professional Bachelor" and majoring in "Chemistry of cosmetics and surfactants", 4.2. Chemical Sciences, Bachelor's Degree at the Medical College of the University "Prof. Dr. Asen Zlatarov". There are five presented programs - "Pharmaceutical Chemistry", "Chemistry of Medicines", "Phytotherapy and Cosmetology", a program for internships and undergraduate internships. Личното ми становище е, че кандидатът има широк потенциал в това направление и трябва да продължи с разработването на съвременни учебни програми както за лекции, така и за практически упражнения.

For the short term as a lecturer, Assist. Prof. Stefan Harkov has had classes in a number of disciplines - Pharmaceutical Chemistry, Pharmacognosy, Technology of Biopharmaceuticals, as well as internships and undergraduate internships. This leads to gaining experience as a teacher and validation as such. There is no scientific guidance of students and graduates. I recommend to Assist. Prof. Stefan Harkov to intensify extracurricular activities, which would improve the level of training in the discipline.

With Dr. Harkov, the field of scientific interests and achievements coincides with the profile of the competition - he is a lecturer with modern theoretical and practical knowledge in the field of pharmaceutical chemistry. The reason for this statement is given by his experience gained from scientific activity, which helps the teaching work, namely - mastering methods for synthesis and characterization of substances with potential biological activity.

Research activity:

To evaluate his research activity, Assist. Prof. Stefan Harkov presented 24 publications,

divided by him into two groups - publications on Pharmacognosy (4 copies) and publications on Pharmaceutical Chemistry (20 copies). The articles are also distributed, according to the Regulations for application of the law for development of the academic staff in the Republic of Bulgaria of the University "Prof. Dr. Asen Zlatarov" (Table 2, Number of points by indicators) to indicators B.4. Scientific publications that are referenced and indexed in world-famous databases with scientific information - 11 copies, D.7. Publications and reports published in scientific journals, referenced and indexed in world-famous databases with scientific information (Scopus, Web of Science) - 4 copies. and D.8. Publications and reports published in non-refereed journals with scientific review or published in edited collective volumes - 9 copies. According to the reference from the candidate (Scopus database), 4 citations were presented in specialized editions, but really they are many times more, the *h*-index is 7. I recommend noting all the citations, because they are a good response to the significance of the results.

According to the Regulations for application of the law for development of the academic staff in the Republic of Bulgaria, the candidate Dr. Harkov fulfills the minimum requirements for holding the academic position "Associate Professor" as a total number of points of the indicators - 433 points (Table 1), and also meets the relevant indicators A (50 points), C.4. (101 points), G (222 points) and D (60 points).

The great activity of Assist. Prof. Stefan Harkov regarding the research contracts cannot be missed. He has a participation in 5 completed internal institutional contracts at the research sector / institute of the University "Prof. Dr. Asen Zlatarov".

The main contributions of Assist. Prof. Stefan Harkov can be summarized in two main areas:

1. Pharmaceutical chemistry with subgroups:
 - Synthesis of substances with potential biological activity,
 - Characterization of the synthesized substances,
 - Determination of pharmacological activity of newly synthesized compounds.
2. Pharmacognosy.

The first direction is where Dr. Harkov concentrates his research and works the most, with the largest share of published scientific results. Also, this is the direction for which the main

scientific and applied contributions are declared, with which I agree. The candidate has synthesized a number of new compounds containing thiazolidine, pyrazoline and isatin - (5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-acetic acid hydrazides, N3 substituted derivatives of 4-iminothiazolidin-2-one, N3 substituted 5,7-dimethyl-6-phenylazo-3H-thiazolo[4,5-b]pyridin-2-one, isatin-pyrazoline hybrids and isatin-based conjugates with a thiazolidine residue. The synthesis used effectively sequentially selected organic reactions, which led to the development of optimal conditions for the construction of new compounds with fused heterocyclic systems in good yields, as well as the preparation of compounds with a certain pharmacological profile on predetermined fragments.

The new compounds were characterized by NMR spectroscopy, elemental analysis and by determining the melting point. The spectral data are interpreted correctly, the methods are described accurately, in the elemental analysis there is an excellent comparability between calculated and found values.

My main recommendation is the need for a more thorough study of the purity of the newly obtained compounds and the detection of related substances and impurities from starting and intermediate products by high-resolution methods, namely TLC and HPLC. These are not used in the presented publications.

Analytical method - IR spectrometry, is used to study changes in the mineral and organic matrix of hard dental tissues. The method has a high degree of specificity, is adequate, correctly applied and for me its use can be described as a practical contribution.

In the field of Pharmaceutical Chemistry, several review articles have been published, in which basic synthetic approaches for the preparation of pharmacologically promising derivatives of 1,3,4-thiadiazole and 1,3,4-oxadiazole are discussed; Theoretical and experimental data on the methods for condensed synthesis of thiazoloquinazolines and thiazolopyrimidines, outlined as pharmacophores with diverse biological activity, are systematized, as well as a study for a hybrid approach - preparation of biologically active compounds composed of several pharmacophores with synergistic effect (4-thiazolidinones with pyrazoline or benzothiazole fragment with antitumor potential). The research in the review articles is related to the strategy of synthetic research and outlining the goals and is undoubtedly a contribution from the scientific production

of the candidate, but its definition as fundamental, in my opinion, is incorrect, they are rather a theoretical contribution.

To the field of Pharmaceutical chemistry I would refer two of the research contracts - № 2 and 4, where Dr. Harkov continues his research to obtain low-toxic newly synthesized compounds (hydrazide and hydrazone derivatives) and limit the toxic effects of antibiotics by immobilization in the structure of chitosan. I evaluate the participation and work of the candidate in these contracts positively, as the high toxicity of the drugs often leads to side effects, limitation or cessation of therapy.

Literature studies suggest an increased interest in the biological activity of fused heterocyclic systems containing thiazolidine and isatin. This determines the study of the pharmacological activity of the newly obtained compounds and complements the synthetic studies. For this purpose, Assist. Prof. Stefan Harkov uses:

- DPPH method for determination of antioxidant activity of new N3 substituted derivatives of 4-iminothiazolidin-2-one in vitro (higher antioxidant activity of some of the synthesized compounds is reported), as well as a series of N3 substituted 5,7-dimethyl-6-Phenylazo-3H-thiazolo[4,5-b]pyridin-2-one newly synthesized derivatives;
- Determination of anti-inflammatory activity of new thiazolo[4,5-b]pyridine derivatives by testing on carrageenan-induced rat edema (strong anti-inflammatory effect of some derivatives, exceeding that of diclofenac was reported);
- Determination of antitumor activity of newly synthesized isatin-containing compounds by testing on NCI60 cell lines. One of the derivatives of isatin conjugates with pyrazoline showed a selective effect on the leukemia cell line, and conjugates of isatin with thiazolidine - inhibitory effect with average values on the SR leukemia cell line;
- Determination of antitumor activity by in vitro screening method of 4-thiazolidine derivatives (5-arylidene-2-amino-4-thiazolidinone derivatives; unfused systems with thiazolidine and pyrazoline; fused derivatives with thiazolothiohyran fragment). The selectivity of the effects of the test compounds on certain types of cancer cells was

studied and the antitumor activity of the compounds was compared with known antitumor agents by COMPARE analysis.

I evaluate the synthesis of new compounds containing thiazolidine, pyrazoline and isatin and the studies to determine their biological activity as a novelty in science and a starting point for the development of new drugs.

All this strengthened my personal conviction that Assist. Prof. Stefan Harkov is a graduate researcher at a good level in the field of Pharmaceutical chemistry. The candidate has a wide range of modern synthetic approaches, ability to analyze and interpret data, as well as precision in research.

In direction 2 - Pharmacognosy, the candidate Assist. Prof. Stefan Harkov has presented 4 publications, which occupy a small share of scientific research - 16.6%. They concern the studies of the anatomical structure of the rhizomes and roots of *Geum urbanum* L., phytochemical study of various extracts of the genus *Geum*, the study of antimicrobial activity of phytopreparation - infusion obtained from the roots and rhizomes of the *Geum urbanum* L. and morphological, anatomical and phytochemical study of *Punica granatum* L.

My personal opinion is that the research is incomplete, clearer structuring in the description is needed and more solid scientific evidence to meet the stated goals based on more complete literature research. In the phytochemical study of biologically active substances from different extracts of the genus *Geum* no description of the experimental part is presented, the methods used are TLC for identity and titrimetric and UV-spectrophotometric for quantification. The methods are not well described, have very low specificity and are not supported by validation and suitability test for TLC, there are terminological inaccuracies and errors. My sincere recommendation is that the candidate expand and refine his research in this direction in order to better differentiate the contributions.

My acquaintance with the previous research work of Assist. Prof. Stefan Harkov allows me to make some recommendations, namely - the publication of scientific results in journals with impact factor, which would be of great importance for the level of his future works, as well as to work with students, graduates and PhD students on topics from its area. Not to be overlooked is the leadership of some institutional and even international research projects.

CONCLUSION

In the current competition for the academic position of "Associate Professor" is the only candidate Assist. Prof. Dr. Stefan Harkov with scientific production that meets the criteria of the Regulations for application of the law for development of the academic staff in the Republic of Bulgaria of the University "Prof. Dr. Asen Zlatarov". It is important to emphasize that the candidate has acquired a high qualification as a specialist in the field of Pharmaceutical chemistry, namely - masters the methods of synthesis of substances with potential biological activity, their characterization and study of pharmacological activity. For this reason, the participation of Dr. Stefan Harkov is convincing enough and I suggest to the respected members of the Scientific jury to vote "for" the award of the academic position of "Associate Professor" to Assist. Prof. Dr. Stefan Vanev Harkov.

Sofia

Member of Scientific jury:

20.04.2021

/Assoc. Prof. Ivanka Pencheva – El Tibi, Ph.D/