

REVIEW REPORT

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regarding the competition for filling the academic position "associate professor" in "Chemistry", field of higher education 4. Natural sciences, mathematics and informatics, professional area 4.2. Chemical sciences for the needs of Medical College, Trakia University - Stara Zagora, published in the State Gazette issue 13/15.02.2022.

The terms and conditions of the procedure for acquiring the academic position of "Associate Professor" and the procedure for its holding are observed and are based on the Law for the Development of the Academic Staff in the Republic of Bulgaria, Regulation for the implementation of the Law for the Development of the Academic Staff in the Republic of Bulgaria and the Rules for the Development of the Academic Staff of Trakia University - Stara Zagora. Mag. Dr. Hristo Plamenov Varbanov is the only candidate who has applied for the announced position. I received in due order the required documents and materials, in agreement with Order №1030 / 12.14.2022 from the Rector of Trakia University. The set of materials presented by the candidate is in accordance with the Regulations for the development of the academic staff in the Republic of Bulgaria and the criteria for holding the academic position "Associate Professor" in professional field 4.2. Chemical sciences.

1. Brief biographical and professional information about the applicant

Dr. Hristo Plamenov Varbanov was born on February 12, 1984, in Sofia. In 2003 he graduated with honors from the National High School of Mathematics and Natural Sciences "Acad. L. Chakalov", Sofia. He obtained his university degree at the Faculty of Pharmacy, Medical University - Sofia, Bulgaria. He graduated in 2009 as a Master of Pharmacy (MPharm) with honors. From October 2009 to April 2013 he was a PhD student in Medicinal Inorganic Chemistry at the Institute of Inorganic Chemistry, University of Vienna, Austria. He defended his dissertation on "New antineoplastic platinum (IV) complexes: Synthesis, characterization, biological investigations and structure-activity relationships" with honors on 25.04.2013, and graduated as a doctor of natural sciences (Dr.rer.nat.).

Dr. Hristo Varbanov started his scientific career as a Research Fellow at the Institute of Inorganic Chemistry, University of Vienna, Austria (2009-2013), and Guest lecturer within the European project FP 7 'Beyond Everest' for the period December 2013 - January 2014. Afterwards, he is consequently Postdoc (FWF Schrödinger Research Fellow) at the Institute of Chemical Sciences, EPFL, Switzerland (September 2014 - September 2016) and Senior Postdoc (FWF's Schrödinger Research Fellowship-return phase) at the Institute of Inorganic Chemistry, University of Vienna, Austria (October 2016 - January 2018). From February 2018 to January 2021 he is a Research Scientist at the Institute of Chemistry, Karl-Franzens-Universität Graz, Austria where he worked closely with Bayer AG, Germany. Since February 2022, he is a part-time lecturer in Analytical Chemistry at the Medical College of Trakia University - Stara Zagora.

During the period of his professional development, Hristo Varbanov has been constantly improving his qualification. He has conducted specializations in universities and laboratories worldwide such as: European Project Management Training at FH Joanneum, Graz, Austria (02/2021-05/2021); Separation of biologically active chiral substances by HPLC, Institute of Pharmaceutical Sciences, Karl-Franzens-Universität Graz, Austria (06/2007–08/2007); Theoretical investigations of antineoplastic platinum complexes and development of QSAR models, Institute of Chemistry, Aarhus University, Denmark (09/2011–11/2011).

The research interests of Dr. Hristo Varbanov are in the field of medicinal, bioinorganic and bioanalytical chemistry. His scientific work is at high quality, as evidenced by the prestigious scientific awards he has been awarded: Three-time winner of “Acad. Rostislav Kaishev” scholarship for Chemistry, awarded by “Evrika” Foundation; Best master thesis in chemistry award, granted by the “Union of Chemists in Bulgaria” and “Schimadzu”; Inorganics Best paper award. As a result of his professional competences, he has been acting as a reviewer in a number of prestigious scientific journals: Chemical Science, Current Pharmaceutical Analysis, Dalton Transactions, Journal of Biological Inorganic Chemistry, Journal of Molecular Structure, Inorganic Chemistry, Inorganica Chimica Acta, Medicinal Chemistry, New Journal of Chemistry, RSC Advances. His computer skills include: MS Windows / Mac OS / Linux; MS Office and iWork office suites, ChemBio Office, Mestre Nova, Gauss View, Graph Pad Prism, Mercury, CompuSyn. He speaks English, German and Russian.

2. Assessment of the scientific activity of the candidate

Dr. Hristo Plamenov Varbanov has applied for the announced position of "Associate Professor" with the following scientific works: PhD dissertation on "New antineoplastic

platinum(IV) complexes: Synthesis, characterization, biological investigations and structure-activity relationships"; 27 scientific publications in specialized scientific journals; 13 participations in international scientific symposia and conferences (7 oral presentations and 6 posters). All works are in the scientific field of the announced position.

I give a high assessment of the publication activity of Hristo Varbanov, which is characterized by very high scientometric indicators. A reference issued by the Central University Library of Trakia University shows that all publications are in journals with Impact Factor / Journal Citation Report / and Impact Rank / SCOPUS / (Total Impact Factor - 77,491; Individual - 11,62), distributed by quartiles according to SJR. The candidate is the first author in **9** publications (numbers 2, 6, 7, 14, 16, 17, 18, 20, and 22 from the attached list). The publications in which the candidate is a corresponding author are **6** (numbers 1, 2, 6, 7, 8, and 22 from the attached list). It is important to note that the original scientific work of the candidate in the period after completing his PhD Thesis (respectively after 2013) has been published in 15 scientific publications in some of the most prestigious international peer-reviewed journals in the field such as:

1. Journal of Inorganic Biochemistry (IF 3.348) (4 publications)
2. Dalton Transactions (IF 4.39) (3 publications)
3. Plos One (IF 2.740) (2 publications)
4. Chemical Science (IF 8.668) (1 publication)
5. Journal of Medicinal Chemistry (IF 5.447) (1 publication)
6. Journal of Biological Inorganic Chemistry (IF 2.495) (1 publication)
7. Inorganics (IF 0.495) (1 publication)
8. Inorganica Chimica Acta (IF 2.046) (1 publication)
9. Metallomics (IF 3.540) (1 publication)

The results of Hristo Varbanov's research work have received a serious international response and recognition, which is evident from the number of citations of his papers. The attached reference issued by the Central University Library, TRU shows that the number of citations of the scientific publications of Hristo Plamenov Varbanov in Web of Sciences and SCOPUS is 454 (without self citations).

The research activity of Hristo Varbanov is mainly focused on the design, synthesis and characterization of metal complexes with biological activity as potential drug candidates. His work is in line with the priority areas of the Innovation Strategy for Smart Specialization 2014-2020 (ISIS), therefore I consider it relevant and important. As a proof of this, in 2014 the candidate was awarded the FWF Erwin Schrödinger fellowship for his project "Novel metal-

based therapeutics against problematic tumors". The focus of the project (conducted at EPFL, Switzerland and the University of Vienna, Austria) was on the development of new strategies to improve the chemotherapy of malignancies with poor prognosis. In this regard, screening-based methods have been developed and validated to identify:

- A) new potential chemotherapeutics for the treatment of pancreatic and lung cancers, based on drugs already approved for other applications (an approach known as drug repurposing).
- B) drugs and drug-like molecules that enhance the activity of clinically used platinum cytostatics (potentiating effect or synergistic effect) against pancreatic and lung neoplasms.

To accomplish this research work Hristo Varbanov has gained substantial knowledge, skills and competencies to use different instrumental methods for chemical and biochemical analysis (HPLC, NMR, ESI-MS, etc.); He has also gained experience in work with cell cultures and screening of drug libraries; Development of QSAR and QSPR models, etc.

3. Assessment of the Scientific contributions

The scientific contributions of Hristo Varbanov have a fundamental and applied character and have been correctly summarized by the candidate in the following 4 categories:

- I. Development of new approaches for improving the chemotherapy of cancers with poor prognosis. Design of multifunctional Pt(IV) prodrugs.
- II. Investigations on the impact of the coordination sphere on the physicochemical properties and biological activity of cytotoxic Pt(IV) complexes.
- III. Development of methods for determination and models for prediction of the lipophilicity of metal complexes with biological activity. Relationships between lipophilicity, cellular accumulation, and cytotoxicity.
- IV. Design and development of tungsten-based radiocontrast agents for advancing X-ray diagnostics of neoplastic and pulmonary diseases.

The work on **the first objective** was realized within the frame of the candidate's project "Novel metal-based chemotherapeutics against problematic tumors" which was funded by the Austrian Science Fund (FWF), Erwin Schrodinger program. The studies were conducted at EPFL, Switzerland, and at the University of Vienna, Austria with a focus on the development of new strategies to improve the chemotherapy of cancers with poor prognosis. In this regard, screening-based methods have been developed and validated that identify:

- A) new potential chemotherapeutics for the treatment of lung and pancreatic cancers, based on drugs already approved for other applications (approach referred as drug repurposing).

B) drugs and drug-like molecules that potentiate the activity of clinically used platinum drugs (enhancing effect or synergistic activity) against pancreatic and lung carcinoma.

During the studies, several combinations with a strong synergistic effect against cell models of the above-mentioned resistant carcinomas were found, which include carboplatin and hycanthone, cisplatin and vorinostat, and carboplatin and deferoxamine. The developed methodology has considerable potential for optimizing platinum-based chemotherapy, including the possibility of discovering new combination treatments for resistant malignancies. Furthermore, the synergistic combinations identified in the study provide a rational base for the design of novel multifunctional Pt(IV) prodrugs that have the potential to overcome resistance in some types of malignancies.

The main focus of the work in the **second research category** is to find an appropriate coordination sphere (set of ligands) for the design of a successful antineoplastic Pt(IV) prodrug. In this regard, the candidate has initiated and conducted a number of theoretical, analytical, and biological investigations on the impact of the type of axial and equatorial ligands on the redox behavior, cell accumulation, and cytotoxic activity of a selected series of platinum complexes. The studies have conclusively demonstrated that the above-mentioned properties are strongly dependent on the entire coordination sphere, while complexes featuring axial carboxylate ligands and equatorial halides have significantly faster redox kinetics and higher cellular accumulation than analogues that do not contain halido ligands. For the first time, it has been demonstrated that the cellular accumulation of Pt(IV) complexes with equatorial chlorido ligands cannot only be attributed to passive diffusion and facilitated and/or active transport mechanisms also have to be involved in the cellular transport of these complexes.

The contributions in the **third research category** are related to lipophilicity, an important physicochemical parameter with a key role in the pharmacokinetic properties of drugs. In this regard, the candidate has initiated a collaboration with Dr. I. Tetko (Helmholtz Zentrum Munchen) to develop and optimize convenient and reliable chromatographic methods for determining the lipophilicity of platinum-based drug candidates and to establish models for the prediction of pharmacologically relevant physicochemical properties of metal complexes. As a result, the first publicly available model for the prediction of lipophilicity (in the form of logP) of Pt(IV) and Pt(II) complexes has been developed. The model can be used to screen virtual libraries with platinum-based drug candidates and thus improve the rational design of new metal-based drugs.

The work on the **fourth research category** was conducted at the University of Graz, Austria, where the candidate has worked during the last 3 years as a researcher, on a joint

project in collaboration with Bayer AG. Within the project, new synthetic and analytical methods for the preparation and investigation of W(V) dimeric complexes with suitable properties for potential application as radiocontrast agents have been developed. For the first time, microwave-assisted chemistry with ion pair reverse phase high-performance liquid chromatography (RP-HPLC) reaction monitoring was implemented for the synthesis of tungsten dinuclear complexes. The most promising compounds are currently under preclinical development in the laboratories of the industry partner (Bayer AG).

4. Assessment of compliance with the minimum national scientometric indicators for the acquisition of the academic position "Associate Professor", in the professional field

4.2. Chemical sciences

Dr. Hristo Plamenov Varbanov has presented documents and references that show the following distribution of his scientific output by groups of indicators according to Regulations for implementation of the law on the development of the academic position "Associate Professor" in Professional Field 4.2. Chemical Sciences.

Group of **indicators A** in relation with obtaining a PhD: a link to the dissertation on "New antineoplastic platinum(IV) complexes: Synthesis, characterization, biological investigations and structure-activity relationships" based on 3 first author publications, that brings him **50 points**.

Group of **indicators C**. Habilitation work - scientific publications in journals that are referenced and indexed in international databases with scientific information: 8 publications are presented (Q1 - 5 publications, Q2 - 2 publications and Q3 - 1 publication), which bring him **180 points**.

Group of **indicators D**: 16 publications are submitted for the competition (Q1 – 7 publications, Q2 - 7 publications, and Q3 - 2 publications), which bring him **345 points**.

Group of **indicators E**: "List of citations" 454 citations (without self citations) x 2 points per citation in Scopus brings him **908 points**.

As evident from the documents and references presented by Dr. Hristo Varbanov, his scientific output significantly exceeds the criteria and scientometric indicators for holding the academic position of "Associate Professor" in direction 4.2. Chemical sciences, according to Regulations for implementation of the law on the development of the academic position "Associate Professor" in Professional Field 4.2. Chemical Sciences.

CONCLUSION

The documents and materials submitted by the only candidate for the announced academic position, Dr. Hristo Plamenov Varbanov, meet all the requirements of the Regulations for implementation of the law on the development of the academic position "Associate Professor" in Professional Field 4.2. Chemical Sciences.

A sufficient number of scientific papers, which were published after the materials used for the Doctoral Thesis have been presented. The presented publications, as well as the number of citations, exceed the national requirements, showing that the results from the author's research are highly appreciated and recognized on an international level.

In the work of the candidate, there are original scientific contributions, which have received international recognition, and a representative part of them have been published in some of the most prestigious international peer-reviewed journals in the field. Regarding professional development, Dr. Hristo Varbanov has impressive professional experience and scientific qualifications. He is an established scientist, using modern analytical techniques, and actively collaborating with researchers from various institutions and universities in Bulgaria and abroad.

After getting acquainted with the materials and scientific papers presented for the announced position, analyzing their significance and the scientific contributions contained in them, I give my positive assessment and recommend to the Scientific Jury to prepare a report proposal for the appointment of Hristo Plamenov Varbanov, PhD, in the academic position of "Associate Professor", field of higher education 4. Natural Sciences, Mathematics and Informatics, professional field 4.2. Chemical Sciences for the needs of the Medical College, Trakia University - Stara Zagora,



25.05. 2022

Reviewer:

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