REVIEW

Prof. Dr. Rositca Dimitrova Nikolova,

Faculty of Chemistry and Pharmacy, Sofia University “St. Kliment Ohridski ”

regarding the submitted documents of Assistant Professor Dr. Nikola Tomov Burdzhiev

in a competition for an **Associate professor** in a professional field 4.2. Chemical Sciences, scientific specialty Organic Chemistry (Chemistry of Heterocyclic Compounds) for the needs of the Department of Organic Chemistry and Pharmacognosy of the Faculty of Chemistry and Pharmacy, Sofia University “St. Kliment Ohridski ”

announced in the State Gazette, issue 105 / 11.12.2020

The only candidate who applied and was admitted to the competition is Assistant Professor Dr. Nikola Tomov Burdzhiev, who works in the group of "Organic Synthesis and NMR Spectroscopy" at the Department of Organic Chemistry and Pharmacognosy of the Faculty of Chemistry and Pharmacy.

Personal data of the candidate

Nikola Burdzhiev graduated with a bachelor's degree in Chemistry from the Faculty of Chemistry at Sofia University in 2002 with honors. Since 2003 he has been a full-time doctoral student at the Department of Organic Chemistry at Sofia University with research supervisor Assoc. Prof. Dr. Elena Stanoeva. His doctoral dissertation on "Polyfunctional piperidinones and pyrrolidinones - synthetic and chromatographic studies" was successfully defended in 2007. In the same year he was appointed as a specialist, and in 2008 after a competition as senior assistant. Since 2010 he has been a senior assistant in the Department of Organic Chemistry and Pharmacognosy.

Dr. Burdzhiev has attended three short-term specializations at University of Oxford, Oxford, UK (January-February 2015), Max-Planck-Institut für Polymerforschung, Mainz, Germany (September 2018) and Universitat de Barcelona, Barcelona, Spain (June 2019).

General characteristics of the received materials and admissibility

Dr. Nikola Burdzhiev has submitted all required documents on electronic media, which are in accordance with the Law on the Protection of the Rights of Persons with Disabilities, its regulations, the Regulations on the terms and conditions for acquiring the Supervisory Board and borrowing AD at Sofia University “St. Kliment Ohridski ”and the Recommendations for the criteria for acquiring scientific

degrees and holding academic positions at Sofia University for the professional field “ Chemical Sciences”, related to the procedure for holding the academic position“ Associate Professor ”. The presented documentation is prepared correctly, clearly and in accordance with all requirements and recommendations.

- Attached are:

- **According to indicator A1.** 50 points

Candidate Nikola Burdzhiev defended his dissertation on "Polyfunctional piperidinones and pyrrolidinones - synthetic and chromatographic studies" in 2007, developed in the Department of Organic Chemistry of Faculty of Chemistry at Sofia University.

- **According to indicator C4.** 109 points

A habilitation thesis on the topic "Polyfunctional heterocyclic compounds - synthetic and spectral studies" in a volume of 33 pages is presented.

The habilitation thesis is based on the most significant part of the candidate's research, published in 6 scientific publications in international journals. The importance of the topic is emphasized in terms of the possibilities of application of the synthesized polyfunctional heterocyclic nitrogen-containing compounds as substances with potential biological activity. Analytically and in-depth are presented the literature data for synthesis and structural characterization of mono-ring and polycondensed heterocyclic compounds, as well as the own results. Eighty literature sources are included.

All publications are in accordance to the topic of the competition, published in specialized international journals, referred to in SCOPUS and ISI Web of Science have an impact factor, of which one with Q1 (17%), three with Q2 (50%) and two with Q3 (33 %). According to this indicator, the candidate exceeds the minimum requirements of 100 points.

- **According to indicator D7.** 224 points

The candidate Assistant Professor Dr. Nikola Burdzhiev is a co-author of 27 scientific publications, of which 24 are with impact factor or SJR and referenced in Scopus and ISI Web of Science - 8 with Q1 (33%), 8 with Q2 (33%), 1 with Q3 (13%) and 7 with Q4 (29%), as well as 3 textbooks.

Under this competition are presented 13 scientific publications, 3 of which are published in specialized international journals with Q1 (23%), 4 - in journals with Q2 (31%), 1 in a journal with Q3 (8%), 2 in journals with Q4 (15%) and 3 in journals with SJR but without IF (23%). According to this

indicator, the candidate exceeds the minimum requirements under the Law of 200 points and meets the requirements of the FCP Rules of 220 points.

- **According to indicator E7.** 108 points

Until the submission of the documents, 97 citations registered in Scopus were noticed. The minimum requirements for this indicator for FHF are 70 points, the candidate has submitted 54 citations, which is almost twice the requirements.

- **According to indicator G** 125 points

Includes additional requirements of the Faculty of Chemistry and Pharmacy.

The scientific results of the research are presented at national and international forums with 15 oral presentations and poster presentations. Dr. Burdzhiev is the leader of 1 and participant in 7 research projects at the University Research Fund. Dr. Burdzhiev's H-index in Scopus is 7. Dr. Burdzhiev again exceeds the required minimum of 70 points.

- Author's reference for main scientific contributions in a volume of 8 pages;

The report on scientific contributions emphasizes the personal contributions of the candidate in the synthesis of heterocyclic compounds from cyclic anhydrides and their modification to compounds with potential biological activity, as well as the synthesis of spectral characterization of heterocyclic compounds with application in practice.

- Summaries of scientific publications
- Reference for teaching activity (included in the CV);

The analysis of the presented results shows that Dr. Burdjiev not only meets, but also exceeds the minimum requirements on most indicators for the competition.

The presented scientific communications of the candidate are in the scientific field in which the competition has been announced. The scientific research of Ch. Assistant Professor Dr. Nikola Burdjiev are in the field of synthesis of heterocyclic compounds and are mainly related to:

- Preparation of compounds with potential biological activity by synthesis of heterocyclic compounds from cyclic anhydrides and subsequent modifications

Oxopyrrolidine, oxopiperidine and oxomorpholine carboxylic acids were synthesized in the reactions of N-benzylidenebenzylamine with succinic [3], glutaric [6,12] and diglycol [8] anhydride. The reaction conditions are optimized and high diastereospecificity with respect to the *trans*-diastereomers is achieved. The carboxyl group is transformed to a carboxamide [3,6,8], a substituted aminomethyl [3,12] or a substituted amino group [6]. The configuration of the starting acid and its

derivatives, as well as the preferred conformation in solution, were determined by NMR spectroscopy. Some of the newly obtained compounds were provided to an international pharmaceutical company for biological activity testing.

Two approaches have been used to convert the carboxyl group of (±) -trans-1-benzyl-6-oxo-2-phenylpiperidine-3-carboxylic acid to a peptide [6] - direct acylation with various amino acids or conversion to an amino group and subsequent replacement.

Aminomethylpiperidinones were obtained by the Mitsunobu reaction [12]. The amino group is acylated with different amino acids to give different pseudo-di- and tri-peptides with potential ACE inhibitory activity. Optimal conditions have been found for deprotection of pseudodipeptides. Two of the compounds were found to exhibit weak ACE inhibitory activity. All test compounds showed antihistaminic activity, most pronounced in the pseudopeptide derived from L-tryptophan [7]. Piperazine derivatives exhibit concentration-dependent activity, which indicates their specific interaction with histamine receptors.

The reaction of diglycolic anhydride with imines was carried out to form a morpholine ring [8]. The carboxyl group of one of the newly synthesized trans acids is amidated with the methyl esters of tryptophan and proline. The possibility of its conversion into an aminomethyl derivative by the Mitsunobu reaction has also been studied. The configuration of all newly synthesized compounds was determined by NMR and, for some compounds, by single crystal X-ray diffraction.

A one-step synthesis has been proposed to prepare the benzo [a] quinolizidine system and its bioisosteric O and S analogs by reacting cyclic imines with monocyclic anhydrides [23]. NMR techniques have shown that the reaction of 3,4-dihydroisoquinoline with amber, glutaral, diglycol and thiodioacetic anhydrides proceeds without marked diastereoselectivity. The reaction of 1-methyl and 1-ethyl substituted 3,4-dihydroisoquinolines is a shortcut to the 11b-angularly substituted [1,4] thiazino-[3,4-a] isoquinoline ring system and runs with extreme trans diastereospecificity. A mechanism for the preparation of the test compounds has been hypothesized.

The reactivity of 1-(ω-(N-acylated amino)alkyl)-3,4-dihydroisoquinolines to homophthalic anhydride was tested and 13α-alkylamino-substituted dibenzo [a,g] quinolizidine derivatives with potential biological activity were obtained. Reaction of dibenzo[a,g]quinolysic acid with a Z-protected aminomethyl group with diazomethane produced for the first time the product dibenzo [a,g] pyrrolo[3,4-i]quinolizidinedione.

Tetrahydroisoquinolines containing an indole, phthalimide and imidazole moiety have been synthesized to study their antiaromatase activity [21]. The indole fragment was introduced by reaction of N- (indol-3-yl) methyleneamines with homophthalic anhydride, and the Mitsunobu reaction was used to introduce the phthalimide fragment. Initial evaluation of antiaromatase activity shows the ability of one of the phthalimides to inhibit the enzyme.

- Synthesis and spectral characterization of heterocyclic compounds with potential application in practice

Derivatives of 2-acetyl-1,3-indandione with 4-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl) benzaldehyde [5] and 4-hydroxy-1-naphthaldehyde with 4-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl) aniline [4] as potential new optical sensors and metal ion extraction reagents have been synthesized. In the course of the research, deacetylation of 2-acetylindanedione was observed for the first time, which took place instead of the condensation reaction with aldehydes in an acidic medium. A reaction mechanism is also proposed. The influence of metal ions (K^+, Na^+, Mg^{2+}, Sr^{2+} and Ba^{2+}) on the optical properties of the newly synthesized indandione with a condensed crouneter fragment was studied. The observed changes are mild and are best seen in the presence of strontium and barium ions.

The behavior of tautomeric Schiff bases containing a crown crater fragment in the presence of alkali and alkaline earth metals has also been studied [4]. The newly synthesized ligands complex with alkali metal ions, which causes a hypsochromic shift in the positions of the tautomeric bands. In the presence of Ca^{2+}, Sr^{2+} and Ba^{2+}, a complex is initially formed, but when an excess of salt is added, the tautomeric equilibrium is shifted in the direction of the keto-tautomeric complex. Such a change in the addition of metal ions to imines containing crown fragments was observed for the first time. The structure of the newly synthesized compound was confirmed by IR and NMR spectroscopy, and for indandione derivatives by X-ray diffraction analysis.

A new "green" approach has been developed for the preparation of squarin dye from square acid and two equivalents of 1,3,3-trimethyl-2-methyleneindoline in a solvent of ethyl L-lactate [15]. The target dye is obtained with a very good yield and in a much shorter time compared to known methods. The conditions for the preparation of (3-bromopropyl) triphenylphosphonium bromide have also been modified [14], as well as for the quaternization of 2-methylbenzothiazole with 2-bromoethanol in an ethoxyethanol solvent [11].

3'-Amino-4-thio-1H-tetrahydropyranspiro-5'-hydantoin and its complexes with Pd (II) and Pd (IV) were synthesized and studied [13]. The geometry of the ligand and its palladium complexes was studied using a hybrid DFT method. The complexes were tested in vitro and found to show concentration-dependent cytotoxicity on the five human tumor cell lines studied.

- Spectral properties of heterocyclic compounds used in practice

The solubility of Itraconazole in colloidal aggregates of 16 surfactants and 3 mixtures of surfactants and phospholipids was studied [22]. The solubility was found to be due to the electrostatic attraction of the positively charged drug molecules and the negatively charged surfactant molecules. 1H NMR spectroscopy showed that Itraconazole was protonated at the N-atom of the piperazine ring attached to the phenoxide portion of the molecule and a second time at the N-atom of the triazole moiety, which explains the strong interaction with the surfactant. It was found that the solubility of the drug increases with increasing length of the aliphatic tail of single-chain surfactants, but with the use of double-chain surfactants such as phosphatidylglycerols - decreases. The obtained results could be used in other sparingly soluble drug systems with similar physicochemical properties.

Plant mixtures containing the synthetic cannabinoid 5F-ADB (methyl (S)-3,3-dimethyl-2-[1-(5-fluoropentyl)-1H-indazole-3-carboxamido]butanoate) were studied [18]. The presence of 5F-ADB was detected by gas chromatography-mass spectrometry (GC-MS) and confirmed by proton NMR spectroscopy. Two synthetic cannabinoids 5F-ADB and FUB-AMB (methyl (S)-3-methyl-2-[1-(4-fluorobenzyl)-1H-indazole-3-carboxamido] butanoate) [19] were detected in the drug by GC-MS analysis. Their presence was also confirmed by 1H and 19F NMR spectra and the relative content (1: 1) of the two components in the dry drug was determined. Studies show that combining GC-MS with MRI is an effective tool for identifying known and unknown, illegal substances, the structure of which is often changed, in order to avoid legal consequences.

Two review publications have been prepared: on the synthesis of benzo [a] quinolizidine derivatives [10] and on the properties and application of the five radioisotopes of copper for medical use [16] with emphasis on the synthesis, design and development of various heterocyclic chelators and nanomaterials with potential application in the diagnosis and treatment of cancer.

Teaching activity

Since entering the Faculty of Chemistry in 2007, Dr. Nikola Burdzhiev has been actively involved in the educational activities of the Department of Organic Chemistry and Pharmacognosy. As

an assistant he leads exercises and seminars in Organic Chemistry - Part I and II for bachelor's degree students from FCP and BF at Sofia University, seminars and exercises in Chemistry of heterocyclic compounds for all chemical specialties of FCP, full-time training and seminars. in Construction and biological activity of organic compounds - for all chemical specialties, full-time and part-time education. He is a co-author in the published in 2020 Manual for laboratory exercises with a collection of tasks in Organic Chemistry for students majoring in Pharmacy.

In 2012 he was assigned to give lectures on Construction and biological activity of organic compounds for the specialty Chemistry, full-time and part-time education, compulsory, as well as elective for all chemical specialties. In the same year he started reading the course in Chemistry of heterocyclic compounds for all chemical specialties, regular training, elective. Since 2016 he has been a lecturer at the course in Organic Chemistry II for the specialty Chemistry, part-time education, compulsory. The course programs have been reviewed and updated.

In 2018 he developed the exercises for two new courses for the Faculty of Chemistry and Pharmacy NMR-spectroscopy and Modern techniques in NMR-spectroscopy for all specialties of FCP, regular training.

Dr. Burdjiev actively participates in teaching and is being a supervisor of graduates - he was the head of 5 successfully defended graduates of master's programs and 4 of bachelor's.

Dr. Burdzhiev's teaching activity should include his participation since 2011 in the National Commission for Organizing and Conducting the National Olympiads in Chemistry and Environmental Protection, as well as in the National Commission for Organizing and Conducting the National Competition in Chemistry and Environmental Protection. chemistry and environmental protection, and since 2019 he has benn the chairman of the second commission. He is also a co-author of two collections of tasks for Olympiads. Dr. Burdzhiev is a holder of an honorary badge of Sofia University "St. Cl. Ohridski ”II degree, which is an expression of the high appreciation given by the academic community for his work with outstanding students.

Assistant Professor Dr. Burdzhiev is distinguished by his good theoretical training in the field of organic chemistry, organic synthesis and NMR spectroscopy, creative approach to solving scientific and educational problems. The high requirements for the students and the serious attitude to the educational process are the basis of the respect he has earned as a teacher of organic chemistry. The high evaluation of the students is also reflected in the selection for the best assistant in the period 2012-2016.

I would not like to miss the fact that Dr. Burdzhiev and Dr. Petkova-Yankova have invested a lot of energy, enthusiasm and personal time in the creation and development of the Laboratory of NMR Spectroscopy since 2015 until now. A fact that is highly valued not only by me, but also by the entire faculty community.

In conclusion, I believe that Assistant Professor Dr. Nikola Burdzhiev meets all the requirements of the Law for the academic position of Associate Professor of Organic Chemistry - scientific achievements and teaching, and has fulfilled all additional recommended criteria adopted by the Faculty of Chemistry and Pharmacy of Sofia University. "St. Kliment Ohridski ”.

Based on the attached documents and my long-term direct impressions, I strongly suggest to the esteemed Scientific Jury and the Scientific Council of the Faculty of Chemistry and Pharmacy to award the scientific title "Associate Professor" to Dr. Nikola Tomov Burdzhiev in professional field 4.2. Chemical sciences, scientific specialty Organic chemistry (Chemistry of heterocyclic compounds).

Sofia, 14.04.2021 Signature: