

REVIEW

on the DSc dissertation for awarding the scientific degree “Doctor of Science” in the higher education area 4. Natural Sciences, Mathematics and Informatics, professional field 4.2. Chemical Sciences (Analytical Chemistry)

DSc candidate: Prof. Dr. Ivayla Nedialkova Pantcheva-Kadreva, Faculty of Chemistry and Pharmacy, Sofia University “St. Kliment Ohridski”

Dissertation title: **“Metal complexes of carboxylic polyethers monensin and salinomycin: structure, properties and biological activity”**

Member of the scientific jury, appointed by order № RD-38-608/13.11.2023, of the Rector of Sofia University “St. Kliment Ohridski”: Assoc. Prof. Dr. Silvia Emilova Angelova, Institute of Optical Materials and Technologies “Acad. J. Malinowski”, Bulgarian Academy of Sciences

I. Biographical information

Prof. Dr. Ivayla Nedyalkova Pancheva-Kadreva graduated in 1987 from National Gymnasium of Natural Sciences and Mathematics “Acad. Lyubomir Chakalov” in Sofia. In 1992 she graduated from the Faculty of Chemistry (FC) of Sofia University (SU) “St. Kliment Ohridski” with the qualification “Master of Chemistry” and specialization “Inorganic and Analytical Chemistry”. In 2001, she obtained the educational and scientific degree “Doctor” after successfully defending her dissertation on “Complexes of copper /II/ with antihypertensive drugs”. In the period 1997 - 2011, holding the positions of assistant and chief assistant in the FC of SU, she was actively engaged in research and teaching activities. In the period 2002-2010, she specialized abroad, with two of the specializations being long-term. Since 2011, she has held the position of “Associate Professor”, and since 2020 - the position of “Professor” in the Department of Analytical Chemistry of the Faculty of Chemistry and Pharmacy (FCP), SU. In the period 2011–2019, Dr. Pancheva was the deputy dean of the FCP and was responsible for doctoral studies, international activities, research, project funding and accreditation. She is a very active researcher and erudite lecturer in analytical, coordination and bioinorganic chemistry, supervisor of successfully defended graduate and doctoral students. She has established successful international collaborations and after her habilitation, she made numerous short-term research visits to universities abroad. She has extensive experience in the preparation, participation and management of projects with national and European funding.

II. General description of the dissertation

The dissertation submitted for review on the topic “Metal complexes of carboxylic polyethers monensin and salinomycin: structure, properties and biological activity” is traditionally structured - it consists of an introduction, a brief literature review, purpose of the dissertation, materials and methods, results and discussion, conclusions, contributions, cited literature, list of publications on the topic of the dissertation, list of independent citations of the publications included in the dissertation work, and appendices (1-5).

The literature cited is focused on the research problem. The exposition in the dissertation is accurate, precise, supported by illustrative material and tables of results. The abstract in Bulgarian is 94 pages long (88 pages in English), it is formatted as required, contains all sections of the dissertation except the literature review, and adequately presents the dissertation.

The dissertation includes the research of Dr. Ivayla Pancheva in the field of coordination chemistry of polyether ionophores monensin and salinomycin, conducted in the period 2008-2023. The aim of the dissertation is to present the specificity of the complexation processes involving the polyether ionophore antibiotics monensin and salinomycin and the properties of their complexes with metal cations. Modification (including by complexation with metal ions) of drugs already proven is a successful approach for the development of new therapies. The topic is extremely hot in view not only of the acute need to develop new antibiotic agents for human and veterinary medicine, but also of the need to study in detail the effect of veterinary antibiotics on microorganisms and animal species, as well as the possible influence of their residues on the human organism when consuming food of animal origin.

III. Main scientific results

In the Results and Discussion section of the dissertation, there are 3 sections devoted to three different aspects of the research:

1) *Monensin and salinomycin complexes - structure and spectral properties*

This section describes the isolation and characterization of new neutral “classical” (32) and “non-classical” (7) complexes of the natural polyether ionophores monensin and salinomycin with metal cations. It was found that in the “classical” complexes the antibiotics act bidentate via carboxylate and hydroxyl functions, forming mononuclear bis- and tris-complexes with metal ions in the second and fourth oxidation states (bis-) and with triply charged rare-earth ions (tris-). In the “non-classical” complexes, the ionophores act as polydentate ligands, with binding specific to each individual coordination species depending on the nature of the metal ion and the form of the antibiotic.

2) *Complexation of monensin and salinomycin in solution – experimental and theoretical studies*

In this section, results of the study of the complexation ability of monensin and salinomycin in solution by the circular dichroism method and theoretical models are presented. It is found that monensin can exist as positively charged complex species in the presence of doubly and triply charged metal cations. Theoretical modeling of the competition processes of singly charged metal ions for binding to monensin confirms the experimentally observed phenomena, providing a rationale for applying this approach to systems containing salinomycin. Quantum-chemical calculations have outlined the main factors responsible for the selectivity of monensin and salinomycin towards the singly charged metal cations of groups IA and IB - the radius of the metal ion, the charge acceptance ability of the metal cation, the dielectric properties of the medium, and the size of the internal cavity/flexibility of the polyether chain.

3) *Biological activity of polyether ionophores and their metal complexes*

A particularly interesting part of the study is the investigation of the influence of the metal ion in the composition of the coordination compounds of monensin and salinomycin on

the antibacterial activity and cytotoxicity of the uncoordinated ligands - it was determined whether the metal cation preserved, potentiated or reduced the effectiveness of the polyether ionophores. The dissertation also presents the results of the initial evaluation of the toxicity of complexes of monensin and salinomycin with native ions on laboratory animals and their influence on the clinical and laboratory parameters of individuals surviving after 72-h treatment.

The divergent results on the biological activity of the metal complexes indicate that any candidate therapeutic should be subjected to the fullest possible characterization of properties under *in vitro* and *in vivo* (laboratory model) conditions before the clinical trial phase is reached.

IV. Contributions and significance of research

The dissertation contains scientific results that are primarily of a fundamental nature and contribute to the understanding of the properties of matter and some specific phenomena. The results in the dissertation are presented in an excellently organized and clear manner. The main contributions formulated in the dissertation accurately reflect the scientific results:

1. The monovalent polyether ionophores monensin and salinomycin interact with metal cations in a higher oxidation state to form neutral coordination compounds. The coordination compounds have been characterized by a wide range of experimental techniques (X-ray structural analysis where possible, spectral studies, elemental analysis) and modeled theoretically;

2. The range of experimental techniques used has been extended by circular-dichroic spectroscopy to study the behavior of the chiral ligand monensin in solution. Thanks to this method, the presence of a series of positively charged complex species has been demonstrated. It was found that the method in the ultraviolet region allows the differentiation of "colorless" metal ions (Mg^{2+} , Ca^{2+} , Zn^{2+} , Cd^{2+}), and its application in the visible spectrum allows the study of both "colored systems" (Co^{2+} , Ni^{2+}) and "colorless" metal cation competition processes;

3. The study of the biological activity of monensin, salinomycin and their metal complexes contributes to the understanding of the complex interactions of therapeutics under *in vivo* conditions. The data obtained are promising and reveal the potential of polyether ionophores (alone or as coordination compounds) for *in vivo* therapeutic use.

V. Assessment of publications and personal contribution of the candidate

The research on the topic of the dissertation has been published in full or in part in 27 full-text scientific papers, including 21 articles in refereed and indexed journals and 4 chapters of collective monographs. 63 citations of the publications related to the dissertation were submitted for the procedure for obtaining the scientific degree "Doctor of Science", and a total of 204 independent citations were noted (122 of them in the Scopus database). Of the publications included in the dissertation, 6 are in Q1 journals, 6 in Q2, 6 in Q3, 3 in Q4, 2 are in non-impact factor/impact rank journals and 4 are chapters of collective monographs. Dr. Ivayla Pancheva-Kadreva is a corresponding author in 22 publications, which is a clear indicator of her leading role.

VI. Critical remarks and recommendations

I have no critical remarks and recommendations on the dissertation. The presentation is excellent, illustrated with aesthetically pleasing and informative figures and tables.

VII. Conclusion

The dissertation of Prof. Dr. Ivayla Pancheva-Kadreva represents a focused, well-planned (and qualitatively executed) systematic study of the complexation processes involving the polyether ionophore antibiotics monensin and salinomycin and the properties of their complexes with metal cations. The achieved results and the way of their presentation in the publications and in the dissertation give me a reason to give an extremely high evaluation. A large amount of high level research work has been carried out, using a rich toolkit of experimental and theoretical methods. The dissertation, summarizing many years of research, is written clearly and in a logical sequence.

The materials presented in the procedure for the award of the scientific degree “Doctor of Science” meet the requirements of the Development of Academic Staff in the Republic of Bulgaria Act (DASRBA), the Rules on the conditions and procedure for acquiring science degrees and holding academic positions in Sofia University “St. Kliment Ohridski” and the minimum national requirements in the professional field. I express my positive opinion on the dissertation and support the award of the scientific degree “Doctor of Science” in the professional field “4.2. Chemical Sciences” to Prof. Dr. Ivayla Nedyalkova Pancheva-Kadreva.

Sofia

05.02.2024 г.

/Assoc. Prof. Dr. Silvia Angelova/