UNIVERSITY OF MEDICINE AND PHARMACY OF TÎRGU MUREŞ

Summary of the thesis

*New biologically active complexes prepared by coordination of platinum and palladium cations to lacunary polyoxotungstate compounds*

Scientific supervisor: Prof. Dr. Muntean Daniela Lucia

PhD Student: Grama Lavinia Anda

**The main objective** of this thesis is the synthesis of new polyoxotungstate compounds with biological activity, thus contributing to the development of scientific knowledge in the medical field. In this regard, the first objective was to obtain a trilacunary polyoxotungstate and clusters coordinated with palladium and platinum ions, while the second objective was to demonstrate the biological activity of the synthesised complexes, through *in vitro* studies on bacterial strains and several fungi.

**The theoretical part**, chapters 1-6, summarizes the data from the literature, dealing with general issues regarding: class of polyoxometalate compounds, current state of knowledge of these compounds, structure types, synthesis methods, analytical methods, properties and biological applications.

Polyoxometalates (POM) are a new class of inorganic complexes of theoretical and practical interest. Due to their remarkable properties (high ionic load, massive structures, high solubility, ion-exchange capacity, strong oxidising nature, etc.), we are witnessing a spectacular involvement of polyoxometalates in various fields of practical interest, and with great prospects: chemical analysis, catalysis, biochemistry, medicine, etc. In recent years there has been a growing interest for the use of polyoxometalates in medicine as antiviral, antiretroviral, antitumoral, anti-enzymatic, coagulant and anticoagulant agents. The advantage of polyoxometalates consists in the possibility of changing the molecular properties involved in a targeted molecular action, with biological implications and application in microbiology, pharmacology, toxicology etc., namely the polarity, redox potential, surface charge distribution, shape and acidity.

**The experimental part** is organized in three main chapters.

Chapter I describes the synthesis methods of the $Na_8[HAsW_9O_{33}]*xH_2O$ ligand, $Na_{27}[NaAs_4W_{40}O_{140}]*xH_2O$ cryptand, and of the palladium and platinum complexes. The obtaining of polyoxometalates involves their preparation and isolation in solid form. The substances concerned have been obtained from aqueous solutions at the pH required by each compound. At first, the $Na_8[HAsW_9O_{33}]*xH_2O$ ligand, then the $Na_{27}[NaAs_4W_{40}O_{140}]*xH_2O$ cryptand has been synthesised. The cryptand has been synthesised directly and indirectly from the ligand. These compounds have been coordinated with palladium and platinum ions, by direct reaction of the compounds with the aqueous solutions of the cationic polyoxotungstates.

Chapter II describes the methods used for the characterisation of the compounds obtained previously. These methods have been used for the study of polyoxometalates in solid phase (IR spectroscopy, thermogravimetric analysis, X-ray diffraction) and in liquid

phase (UV spectroscopy, conductometry, thin layer chromatography, capillary electrophoresis). The recording of **UV spectra** was a preliminary stage to confirm that the compounds synthesised belong to the polyoxometalate class. The combination ratio between ligands and cations has been determined by **conductometry.** The **thermogravimetric curves** were necessary to determine the number of water molecules, crystallisation water and coordinated water, in these massive structures. The IR spectroscopy highlighted the bonds in the compounds, based on the recorded vibration bands, which confirmed the data from the literature. **X-ray diffraction** analyses have been conducted on crystals and powder to determine the lattice constants and elucidate the structure of the synthesised compounds. **Thin layer chromatography** and **capillary electrophoresis** determinations have not led to quantifiable results.

The compounds obtained are: $Na_8[HAsW_9O_{33}]*17H_2O$ ligand, and its complexes (Hervè structures): $Na_{12}[(AsW_9O_{33})_2Pd_3]*24H_2O$, $Na_6[(AsW_9O_{33})_2Pt_3]*46H_2O$; $Na_{27}[NaAs_4W_{40}O_{140}]*71H_2O$(direct), $Na_{27}[NaAs_4W_{40}O_{140}]*70H_2O$(indirect) cryptands, and their complexes (Leyrie structures) $Na_{19}[NaAs_4W_{40}O_{140}Pd_4]*34H_2O$(d), $Na_{19}[NaAs_4W_{40}O_{140}Pd_4]*32H_2O$(ind), $Na_{19}[NaAs_4W_{40}O_{140}Pt_2]*45H_2O$(d), $Na_{19}[NaAs_4W_{40}O_{140}Pt_2]*48H_2O$ (ind). The six synthesised complexes constitute new structures.

Chapter III describes the *in vitro* studies regarding the antibacterial and antifungal activity of the synthesised complexes. These studies have been performed on gram-positive and gram-negative bacterial strains, levuriform fungi, inferior, hyaline, non-septate, filamentous fungi, and superior, hyaline, septate fungi. Representatives that may cause severe pathologies or even death in all age groups have been chosen from each category.

**Antibacterial activity:** The most effective compound (lowest value of MIC recorded) proved to be $Na_{19}[NaAs_4W_{40}O_{140}Pt_2]*xH_2O$ on *Enterococcus faecalis* strains. *Staphylococcus aureus MRSA* strains were also sensitive to polyoxotungstates, low inhibitory and bactericidal concentrations being recorded; the polyanions proved to be more active than the coordination complexes. Resistance developed quickly (up to 10x difference between MIC and MBC) in *Escherichia coli*, especially for the ligand and cryptand. Highest resistance has been observed in *Klebsiella* and *Pseudomonas aeruginosa* species, where only the coordinated compounds presented inhibitory activity. In all studied strains, the platinum and palladium complexes have been found to be more active than their ligands, and the platinum complexes proved to have a superior action compared to palladium complexes.

**Antifungal activity:** Only compounds with Hervè structures, in concentrated solutions, proved effective against fungi.

Because the activity on *Enterococcus faecalis* and *Staphylococcus aureus MRSA* strains has been more pronounced than on other strains, it can be affirmed, that these polyoxotungstate compounds have a stronger activity on gram-positive bacteria, than on gram-negative bacteria, and that the **antimicrobial activity is more pronounced than the antifungal activity**.

Keywords: polyoxotungstate, palladium, platinum, antibacterial activity, antifungal activity.