ABSTRACT OF THE PHD THESIS

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Synthesis, physicochemical characterisation and applications of ruthenium complexes in different oxidation states

The chemistry of ruthenium complexes is currently receiving a lot of attention, primarily because of their applications in industry and medicine. Ruthenium compounds are usable as effective catalysts in organic chemistry and chemical technology. Some of Ru(II) complexes are applicable as molecular switches and wires. Additionally, it is worth noting that compounds of ruthenium(II) and ruthenium(III) possess biological properties. It is considered that ruthenium complexes can be the most promising alternatives to platinum antitumor drugs. Furthermore, they can be used as antibiotics and other pharmaceuticals in treatment of many infectious diseases caused by bacteria, fungi and parasites.

In recent years, the search for new compounds with bacteriostatic and/or bactericidal activity has become one of the priority research directions in many scientific fields. The reason is a rapidly increasing resistance of microorganisms to currently used antibiotics, which consequently leads to limitation of the number of effective pharmaceuticals in the treatment. What is very important, the majority of bacteria have an ability to form biofilms which are responsible for bacterial infections and which are difficult to eradicate with a conventional antimicrobial therapy. At present, the problem of antibiotic resistance among bacteria is global and has been recognized by WHO as one of the greatest threats to public life in the 21st century.

Given the above facts, the aim of this dissertation is synthesis, structural and physicochemical characterisation of ruthenium complexes in different oxidation states with heteroaromatic ligands, as well as estimation of potential biomedical applications of these compounds. In particular, it investigates the possibility to utilise ruthenium complexes as effective inhibitors for planktonic cells and bacterial biofilms.

The results have demonstrated that the reactions of $[(\eta^6\text{-}p\text{-cymen})Ru(\mu\text{-}Cl)Cl]_2$ as well as $RuCl_3 \cdot xH_2O$ with benzimidazole, pyridine and quinoxaline derivatives gave 9 new ruthenium complexes in different oxidation states. The isolated ruthenium compounds were characterised by various standard analytical techniques, including an elemental analysis, ultraviolet-visible (UV-Vis), infrared (IR) and nuclear magnetic resonance (^1H and ^{13}C NMR) spectroscopies, as well as an X-ray single crystal analysis. Magnetic measurements and electrochemical experiments were also performed. Additionally, the ruthenium complexes were tested for their antibacterial and antibiofilm activity against pathogenic bacteria: *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* PAO1, *Pseudomonas aeruginosa* LES B58 using microdilution assays, bacteria staining methods and spectrophotometric measurements.

Experimental data revealed that the obtained complexes are in II (complexes **1** – **3**), III (complexes **4** and **5**), IV (complexes **7** – **9**) and mixed III/IV (complex **6**) oxidation states (Table 1). The coordination sphere of all ruthenium complexes is an octahedral. Among these

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compounds, Ru(II) complexes exhibit a pseudo-octahedral three-legged piano-stool geometry. Moreover, X-ray studies confirmed the chelated coordination mode of organic ligands in complexes **1**, **2**, **4**, **5**, **8** and monodentate coordination of ligand in complex **3**. In the case of compounds **6**, **7** and **9**, heteroaromatic ligands: 2,2'-PyBIm, $BImCH_2OH$ and 3-OH-2-COOHBPz do not form coordinate bonds to the ruthenium ion but are present in the crystal lattice. The data obtained from spectroscopy and X-ray crystallography also revealed that benzimidazole (BIm) (in the complex **3**) was formed by decarboxylation of the BImCOOH. In turn, the 3-hydroxy-2-quinoxalinecarboxylic acid used for the synthesis of complex **9** in the reaction medium was changed: in the first step the enol-ketone tautomers were formed, in the second step ligand into 1,4-dihydro-quinoxaline-2,3-dione was transformed (2,3-COBPz). Packing analysis of complexes revealed that the compounds have very interesting coordination networks and remarkable supramolecular architectures generated by hydrogen bonds of N-H···O, N-H···Cl, N-H···F, O-H···O, O-H···Cl types and C-H···O, C-H···Cl, C-H···π, anion···π, π···π *stacking* interactions.

Table 1. The obtained ruthenium complexes in different oxidation states

	Ruthenium compounds
Ru(II)	$[(\eta^6\text{-}p\text{-cymen})Ru^{II}Cl(2,2'\text{-PyBIm})]PF_6$ **(1)**
	$[(\eta^6\text{-}p\text{-cymen})Ru^{II}Cl(BImCOO)]$ **(2)**
	$[(\eta^6\text{-}p\text{-cymen})Ru^{II}Cl_2(BIm)]$ **(3)**
Ru(III)	*mer*-$[Ru^{III}Cl_3(2,2'\text{-PyBIm})(CH_3CN)]\cdot 2,2'\text{-PyBIm}\cdot 3H_2O$ **(4)**
	mer-$[Ru^{III}(BImCOO)_3]\cdot H_2O$ **(5)**
	$(H_2\text{-}2,2'\text{-PyBIm})_2[Ru^{III}Cl_4(CH_3CN)_2]_2[Ru^{IV}Cl_4(CH_3CN)_2]\cdot 2Cl\cdot 6H_2O$ **(6)**
Ru(IV)	$(H\text{-}BImCH_2OH)_4[Ru^{IV}Cl_6]\cdot 2Cl\cdot 4H_2O$ **(7)**
	$[Ru^{IV}Cl_2(2,3\text{-}pydcH)_2]\cdot 4H_2O$ **(8)**
	$(2,3\text{-COBPz})[Ru^{IV}Cl_4(CH_3CN)_2]\cdot H_2O$ **(9)**

2,2'-PyBIm – 2-(2'-pyridyl)benzimidazole, BImCOOH – 1H-benzimidazole-2-carboxylic acid, BIm – 1H-benzimidazole, $BImCH_2OH$ – 2-hydroxymethylbenzimidazole, 2,3-$pydcH_2$ – pyridine-2,3-dicarboxylic acid, 2,3-COBPz – 1,4-dihydro-quinoxaline-2,3-dione

Interestingly, biological studies of the investigated ruthenium complexes have proved their bacteriostatic and antibiofilm activities, where the ruthenium complexes have exhibited a higher activity than ligands in tests with each strain. Among the tested strains, ruthenium compounds have a significant selectivity against *P. aeruginosa* PAO1 strain. The most active complexes against planktonic bacteria of *P. aeruginosa* PAO1 are compounds **4**, **5** and **7** with MIC values 0.5 mM. The data obtained from biofilm assays have showed that the composition of the coordination sphere and the type of heteroaromatic ligand impact on biological properties of ruthenium compounds. The best results of reducing the *P. aeruginosa* PAO1 biofilm have been obtained for ruthenium complexes with 2-(2'-pyridyl)benzimidazole (complexes **2**, **4** and **6**) and 2-hydroxy-methylbenzimidazole (complex **7**). These compounds inhibit biofilm in about 80%. Considering the importance of biofilm in microbial resistance to antibiotics and disinfectants, the new ruthenium complexes seem to be good candidates for the development of new antimicrobial agents.

In conclusion, the objectives stated in the PhD dissertation have been achieved.

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