

November 8<sup>th</sup> 2016

**Report on M. Michal Pawel LOMZIK**  
**PhD Thesis**  
(2 pages)

Find below my report and formal recommendation on the thesis entitled « *Synthesis and characterization of hybrid drugs based on ruthenium complex moiety and biologically active organic compound* » submitted by M. Michal Pawel LOMZIK for the degree of Doctor of “Université de Lorraine” (Supervisors: Dr. Philippe C. GROS, CNRS-research director, *Université de Lorraine*, in international co-direction with professor dr. hab. Grazyna STOCHEL, Jagiellonian University in Krakow).

The manuscript composed of 123 pages (concluded with 18 pages of the CV), describes the synthesis and preliminary characterizations of novel polypyridyl- based Ru(II) complexes bearing “biologically active molecules” (divided in two main groups) as potential theranostic agents. The document is divided in 6 main parts, beginning with an **introduction** (p. 13-62) which concerns the use of metallic complexes, and especially Ru(II) ones and semicarbazones (such as Triapine®, acting as a quencher of the Ribonucleotide Reductase –RNR- involved in the DNA synthesis and hence, cell proliferation), and thiosemicarbazones moieties in medicine.

In the **2<sup>nd</sup> part** (p. 35-36), M. LOMZIK briefly describes the aim and scope of his thesis; the synthesis and characterizations of the photophysical properties of novel polypyridyl-based Ru(II) complexes which general structure is given. Preliminary evaluation of the interaction between those complexes and Human Serum Albumin (HSA), and potential structure-biological activity correlations were planned.

**Part 3** (p. 37-39) concerns the description of the methods used.

In **Chapter 4**, the description of the results is given together with several elements of discussion. The first part (p. 40-53) is related to the presentations (and comments) of the strategy used for the polypyridyl-based ligand (Wittig, Sonogashira reactions), and related Ru(II) complexes synthesis. Microwave irradiation was especially efficiently used in order to improve the synthesis of the intermediate dichlororuthenium(II) complexes. A second part (p. 54-58) is devoted to the photophysical properties (absorption and emission) of the Ru(II) complexes. Pages 59 to 71 is described a computational study (TD-DFT) related to the obtained Ru(II) complexes (geometry

optimization, correlation with calculated HOMO-LUMO energies, and simulation of the absorption spectra). Another part of this chapter (p. 72-76) is related to the interactions of the Ru(II) complexes with HSA, the major extracellular protein of the circulatory system. In this perspective, luminescence spectra of HAS is recorded in the presence of various concentrations of ruthenium complexes, and the results were analysed using the classical Stern-Volmer equation. Kinetic quenching ( $k_q$ ), and binding constants were extracted for several Ru(II) complexes. Could this study be also performed, recording the change in luminescence of the Ru(II) complexes themselves? Same result?

In a summary given as a **conclusion** (p. 77-80), M. LOMZIK describes the main results obtained and several perspectives especially in the evaluation of the biological activity of the ruthenium(II) complexes. It is also claimed, for example, that the luminescence properties of the negatively charged Ru(II) complexes are much more sensitive to the presence of dioxygen; this could have been studied more in details; is there any possibility to evidence correlations with the calculations?

**Synthetic procedures** and compounds main characterizations are given in the **6<sup>th</sup> part** (p. 81-106) of the manuscript, which is concluded by the bibliography (179 references, p. 107-123).

**To conclude**, the presented work is interesting and pertinent. The manuscript is well written, and led to 2 publications (*Inorg. Chim. Acta*, **2016**, and *Chemik*, **2013**) with M. LOMZIK as co-author. Preliminary results are presented and quite well commented. A rigorous study of the synthesis and characterization of the obtained compounds are given. I support the defence of M. Michal LOMZIK in order to obtain the Doctorate Degree in chemistry from "Université de Lorraine" (France) and Jagiellonian University in Krakow (Poland).

With Best Regards



Gilles LEMERCIER, Professor