1. PHD PROJECT DESCRIPTION (4000 characters max., including the aims and work plan, all in English)

Project title:

Tuning the activity of ruthenium complexes of biological relevance.

1.1. Project goals

Many ruthenium complexes, representing a variety of different structural types, have shown activity against tumour cells and have been investigated as efficient metallopharmaceuticals that may be used in antitumour therapy. In contrast to the well-known mechanism of action of platinum compounds in antitumour therapy, the mechanism of anticancer activity of other transition metals, e.g. ruthenium compounds is still unknown. A complete structural and mechanistic understanding at the molecular level opens the opportunity to tune the design of new compoundsand the reactivity of chemical species in a systematic way, to optimize their structure, reactivity and ability to action under biologically relevant conditions, and biological activity in order to enable efficient inorganic pharmaceuticals, suitable for medicinal applications.

1.2. Outline

Compounds of almost all metals of the periodic table have been investigated, in therms of their potential anticancer activity.[1-11] Many metals have shown activity against toumor cells. However, most often their anticancer activity in vitro has not been paralleled by their therapeutic afficiency, and only a few of the many metal compounds have shown similar biological activity in clinical trials. Among them, the ruthenium compounds are the most promising and potent chemotherapeutics that competitive against cisplatin, the first inorganic anticancer drug. A possible explanation for the success of ruthenium compounds derived from the rate of reaction. Similarly to cisplatin, ruthenium is a relatively nonreactive metal, and is transformed into more reactive form of drug typically within the same timescale as cellular division processes. Therefore ruthenium provide an attractive alternative to cisplatin and other platinum compounds due to their similar reactivity, which result in fewer side effects and leads to higher biological activity. From a chemical point of view, the effective transition metal chemotherapeutic agents should be sufficiently inert to reach the cytoplasm and then be transformed into more labile species, which should then react effectively with DNA and other cell components. In general, it is known that platinum drugs may bind to guanine or adenine in a DNA helix, via intra- and inter-strand crosslinking, and act as

antitumour agents by inhibiting replication and transcription of DNA in cancer cells. In opposite of the well-known mechanism of action of platinum compounds in antitumor therapy, the mechanism of anticancer activity of other transition metals including ruthenium compounds is still unknown. Ruthenium complexes have shown significant ability to binding many biological molecules, including serum proteins (e.g. transferrin and albumin). The project focuses on tuning the reactivity of selected ruthenium compounds, and factors that can affect and modulate biological activity of these potential anticancer drugs in their binding processes to certain DNA fragments or other biologically important molecules and their reduction with vitamin C or glutathione. The key point is to understand whether ruthenium interacts with DNA or other active sites of some biomolecules (e.g. enzymes, cell wall components) in tumour cells. What is the correlation between their structure, various oxidation states and biological activity of these potential cytotoxic drugs. It is important also to determine whether in the cell environment or extracellular fluids ruthenium can be reduced by natural reducing agents, which essentially modifies its reactivity and modulates its transformation into the active form of the drug. It is necessary in this case to check whether the level of antioxidant concentrations (vitamin C or glutathione) and the rate of redox processes are the relevant and effective for such a process to actually take place in the cell environment. The answer to this and the above questions will allow us to better understand the mechanism of action of potential ruthenium pharmaceuticals and will in the future better plan the synthesis of new compounds with potential anticancer activity, determining the relevance and signifity of the research presented in the project.

1.3. Work plan

1. Preparation and identification of a selected series of ruthenium complexes

2. Biological study on cytotoxic activity of ruthenium complexes against particular cancer cell lines

3. Detailed studies on interaction with transporting proteins and DNA

4. DFT calculations to support the interpretation of the experimental data

5. Determination of structure-citotoxicity correlations for all the series of complexes

1.4. Literature

[1] C.J. Jones, J.R. Thornback, Medicinal Application of Coordination Chemistry, RSCPublishing, Cambridge, 2007, pp. 324 – 339.

[2] B. Lippert Cisplatin, Chemistry and Biochemistry of a Leading Anticancer Drug, Wiley-VCH, Weinheim, 1999.

[3] J. Reedijk Platinum Met. Rev. 52 (2008) 2–11.

[4] J. Reedijk Eur. J. Inorg. Chem. 10 (2009) 1303–1312.

[5] C.V. Christodoulou, A.G. Eliopoulos, L.S. Young, L. Hodgkins, D.R. Ferry, D.J. Kerr, Br. J. Cancer 77 (1998) 2088–2097.

[6] M. Guo, P.J. Sadler, J. Chem. Soc., Dalton Trans. (2000) 7–9.

[7] C.H.S. Ruxton, P.C. Calder, C.S. Reed, M.J.A. Simpson, Nutr. Res. Rev. 18 (2005) 113–129.

[8] S.H. van Rijt, A.F.A. Peacock, R.D. Johnstone, S. Parsons, P.J. Sadler, Inorg. Chem. 48 (2009) 1753–1762.

[9] S.H. van Rijt, A. Mukherjee, A.M. Pizarro, P.J. Sadler, J. Med. Chem. 53 (2010) 840–849.

[10] H. Faneca, V.A. Figueiredo, I. Tomaz, G. Gonçalves, F. Avecilla, M.C. Pedroso de Lima, C.F.G.C. Geraldes, J.C. Pessoa, M.M.C.A. Castro, J. Inorg. Biochem. 103 (2009) 601–608.

[11] I. Kostova, Anticancer Agents Med. Chem. 9 (2009) 827–842.

1.5. Required initial knowledge and skills of the PhD candidate

- Knowledge of the principles and techniques of the subject disciplines.
- Knowledge of the design, synthesis and spectroscopic studies on transition metal coordination compounds
- Knowledge of the selected spectroscopic methods, NMR, IR, MS.

• Organizational and project management skills.

• English written and oral communication skills.

1.6. Expected development of the PhD candidate's knowledge and skills

• Advanced knowledge of the principles and techniques of the subject disciplines.

• Advanced knowledge of the design, synthesis and spectroscopic studies on transition metal coordination compounds

• Knowledge of the spectroscopic methods, 1H, 13C, 14N NMR, IR, CV, MS.

• Knowledge of the kinetics of slow and fast reactions.

• Knowledge of the fluorescence methods and fluorescence imaging methods.

• Organizational and project management skills.

• Advanced English written and oral communication skills.