FACULDADE DE CIÊNCIAS E TECNOLOGIA
UNIVERSIDADE NOVA DE LISBOA

MSc in Bioorganic Chemistry
Dissertation Project – 2nd Cycle

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Lab/Institution: Carlos Romão Lab (ITQB) and Teresa Santos-Silva (FCT)
TITLE: New CO Releasing Molecules (CORM) as anti-inflammatory agents for rheumatoid arthritis

BACKGROUND

The beneficial biological effects of carbon monoxide (CO) are now well established and overturn its once dark profile as a "silent killer". In fact, CO is continuously produced in living organisms when the enzyme heme oxygenase (HO-1) breaks down toxic free heme from dead cells. Together, CO and HO-1 form a cytoprotective tandem as anti-inflammatory, anti-thrombotic and innate immune system modulators, which have a tremendous therapeutic potential. Administration of CO, which enhances the CO/HO-1 action, is best done through CO Releasing Molecules (CORMs) of general formula $M(CO)_xLy$ (M = metal). Since 2011 the labs of Teresa Santos-Silva at FCT/UNL and Carlos Romão at ITQB, have been studying the behavior of some Ruthenium and Molybdenum based CORMs, which have a remarkable therapeutic activity in a broad range of diseases tested in animal models. These studies have revealed important properties of the CORMs in terms of their interaction with plasma proteins, which is a fundamental interaction for drugs administered in vivo.
Rheumatoid arthritis (RA) is a serious, widespread autoimmune disease with a very destructive action on the tissues of joints, which can lead to severe pain and incapacitation. Both Ru and Mo based CORMs have shown strong anti-arthritic activity in in vivo rodent models of RA, resulting in a clear protection of the joints comparing favorably to the standard of care drug, methotrexate. Therefore, CORMs with improved ability to deliver CO to RA affected tissues are then a real option for a better treatment of this disease.

OBJECTIVES

The ultimate objective of this MSc Thesis is:
Design and assemblage of CORMs on gold nanoparticles (AuNP) with improved targeting, and CO delivery capacity to RA tissues.

Specific, intermediate objectives are:

Synthesis of CORMs ligands ready for conjugation to AuNP.
Conjugation of the synthesized CORMs to gold nanoparticles.
Characterization of the conjugates and preliminary biological assays.

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PROJECT DESCRIPTION

The CORM are based on $[Ru(CO)_3]^{2+}$, $[M(CO)_3]^{+}$(M = Mn, Re) and $[Mo(CO)_4]$ fragments. According to existing knowledge, these fragments will be stabilized with bidentate ligands of the diimine type, namely bipyridine and analogues. These ligands will have to be equipped with linkers bearing a distal Sulfidryl (SH) function In order to bind the AuNPs. At the other end, the linkers will have an amine function that can readily react with a $–CO_2Cl$ function generated at the appropriate position on the diimine or other ancillary ligand on CORM. The resulting complexes will be isolated, purified (HPLC) and characterized by the usual spectroscopic (FTIR, NMR) and analytical (Elemental Analysis, MS) methods.
Once purified the compounds will be used to conjugate to gold nanoparticles, freshly synthesized. Structural characterization of the conjugates will be achieved using dynamic light scattering (DLS) and small angle X-ray scattering (bioSAXS).
Preliminary biological assays will be carried out using the new CORMs and the nanoconjugates to attend cell toxicity.

After these tests, the results will be evaluated globally in order to identify problems and flaws and propose feasible approaches to their resolution, which will be included in the Thesis.

The Project will be organized in the following tasks.
Task 1
Learn vacuum line and inert atmosphere techniques for organometallic synthesis.
Preparation of three non-commercial reactive carbonyl fragments as CORM precursors of Mo, Mn and Ru. Learn FTIR and NMR spectral collection.
Task 2
Synthesis of the ligands and linkers designed to bind CORMs to AuNP.

Task 3 Synthesis and characterization of CORMs equipped with linkers to AuNP
Task 4 Synthesis of gold nanoparticles and conjugation with CORMs
Task 5 Structural characterization of the conjugates
Task 6 Biological assays using normal and cancer cell lines.

Critical evaluation of results, and Thesis writing.

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TIMELINE (use fill tool for the cells)

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10
Task 1										
Task 2										
Task 3										
Task 4										
Task 5										
Task 6										
Thesis										