

## Research Project for Master Students

### Synthetic and Mechanistic Studies on Metal Carbonyls for therapeutic delivery of CO

Carbon monoxide (CO) is an endogenous mediator that plays important roles in mammalian physiology. Inhalation of CO doses well below toxic levels has been shown to prevent inflammation, thrombosis, oxidative stress and apoptosis and has been shown to have therapeutic, curative effects on a wide variety of diseases like rheumatoid arthritis, multiple sclerosis, cerebral malaria and many, many others. (see Ryter and Otterbein, 2004)

To circumvent the fact that inhaled CO - despite its obvious potential - is difficult to use in the clinical setting (because it is a gas and because it binds strongly to hemoglobin after inhalation), several efforts have been undertaken in recent years to generate molecules which deliver CO in a more specific way to diseased tissues. A plethora of CO-Releasing Molecules (CO-RMs) has been produced by various groups and used in animal proof-of-concept studies (see Alberto & Motterlini, 2007). Although various CO-RMs have been shown to reproduce and/or improve on the therapeutic effects of CO seen in inflammatory and other diseases there is still a need to prepare new CO-RM which possess improved physical-chemical and “drug-like” properties that make them more biocompatible and more efficient for pharmaceutical, clinically-acceptable test and use.

The work will be coordinated with that currently taking place in the laboratories of the company Alfama Lda which possesses the world leading technology, expertise and intellectual property in the CO-RM field.

The proposed research plan will contemplate:

- synthesis and chemical characterization (IR, NMR, MS) of some transition metal carbonyl complexes bearing pharmacologically acceptable ligands involving inert atmosphere techniques;
- characterization of the pharmacologically relevant parameters for the new compounds (solubility, stability water and to biological media, lipophilicity (logP), distribution (log D7.4))
- characterization of the CO releasing profile in vitro in chemical and biological media.
- mechanistic investigation of the CO releasing mechanisms promoted by chemicals and proteins necessary to establish structure-activity relationships.

**Supervisor:** Carlos C. Romão

**Area:** Chemistry, Pharmacology

**Location:** ITQB, Laboratory of Organometallic Chemistry

Alberto and Motterlini. Chemistry and biological activities of CO-releasing molecules (CORMs) and transition metal complexes. Dalton Transactions 2007, 17, 1651

Ryter and Otterbein. Carbon monoxide in biology and medicine. Bioessays 2004, 26, 270-280