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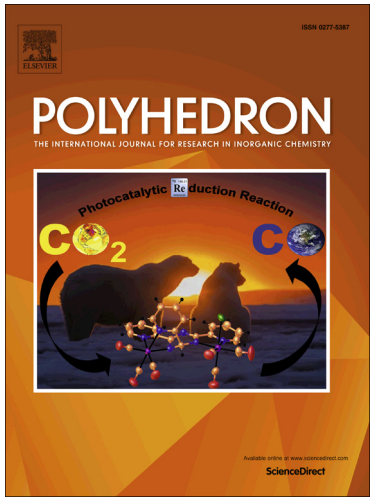

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In vitro Studies of Dermally Absorbed Cu(II) Tripeptide Complexes as Potential Anti-inflammatory Drugs

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Abstract

Copper complexes have been reported to alleviation the inflammation associated with rheumatoid arthritis (RA). The aim of this research was to design and test new ligands that are able to promote the percutaneous absorption of copper and/or mobilise endogenous copper reserves, with the ultimate aim of testing these as anti-inflammatory agents. Formation constants of H^+ and Cu(II) with the tripeptides sarcosyl-L-histidyl-L-histidine (Sar-HH) and sarcosyl-L-glycyl-L-histidine (Sar-GH) were measured at 25±0.01°C and at an ionic strength of 0.15M (NaCl) using glass electrode potentiometry. In the pH range 2-11, four species; CuLH, CuL, $CuLH_{-1}$, and $CuLH_{-2}$ were observed. The two tripeptides showed significantly different coordination behaviour at physiological pH, Sar-HH forming a $CuLH_{-1}$ species while Sar-GH formed a $CuLH_{-2}$ species. The solution structures of the different Cu(II) species formed with these ligands were investigated using visible spectroscopy (Uv-vis), electron paramagnetic resonance (EPR) and nuclear magnetic resonance (NMR) spectroscopy. The $CuLH_{-2}$ species involved coordination of two deprotonated amide groups to give a neutral complex. ^{1}H NMR identified the binding sites to be the imidazole nitrogen, the two-amide nitrogens and the terminal amino group. Uv-vis and EPR spectroscopy confirmed this mode of coordination. Speciation calculations using a blood plasma model were used to estimate the complexing ability of the ligands *in silico*. Octanol/water partition coefficients and Franz cell permeation studies were used to evaluate percutaneous skin absorption. The results showed that the Cu(II) complexes are hydrophilic but that Sar-GH caused a 2 fold increase in membrane permeability of Cu(II).

Keywords: Rheumatoid arthritis; Copper tripeptides; Copper partition coefficients; Copper membrane permeability; Speciation calculations; Anti-inflammatory Drugs.

1. Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic, debilitating disease that leads to the destructions of diarthrodial joints [1],[2]. It is considered to be an autoimmune