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Study of hybrid peptide phenanthroline-based ligands for the therapy by chelation in the context of Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disease and the major cause of dementia throughout the world. This pathology is still incurable since no therapies have so far reach the objective to prevent or even stop its progression. It is characterized by the presence of senile plaques in the synapses and neurofibrillary tangles in the neurons. A broad consensus attributes the early development of AD to the development of senile plaques, composed of aggregated amyloid-β peptides. These plaques are enriched in metal ions, especially Cu and Zn, and this phenomenon is linked to a dysregulation of metal ions in an AD brain.

Strong evidences have associated the high toxicity of Cu-containing aggregates to their ability to promote the oxidative stress observed in AD *via* the catalytic production of toxic reactive oxygen species (*Redox Biol., 2017, DOI: 10.1016/j.redox.2017.10.014*). Development of new therapeutic tools and approaches focusing on the molecular mechanisms responsible for the progression of AD is an appealing concept. For the reasons given above, Cu is considered as the therapeutic target. Its removal from Aβ with ligands (L) is a particularly promising approach since it combines the advantages to have an impact on both (i) ROS production and (ii) formation of toxic Aβ aggregates, but it is still in its infancy and requires basic research *(Inorg. Chem., 2019, DOI: 10.1021/acs.inorgchem.9b00995)*.

A new family of hybrid histidine-phenanthroline based ligands has shown promising properties for the chelation of copper and inhibition of ROS production. However, these ligands display a surprising behavior: when added in excess (against Cu), they catalyze the production of ROS. This is attributed to the formation of CuL_2 complexes in the presence of Cu(I) and an excess of ligand *(Inorg. Chem., 2022, DOI: 10.1021/acs.inorgchem.0c03407 ; Molecules, 2022, DOI: 10.3390/molecules26247630)*. To avoid this phenomenon, a new set of derived ligands will be synthesized and studied.

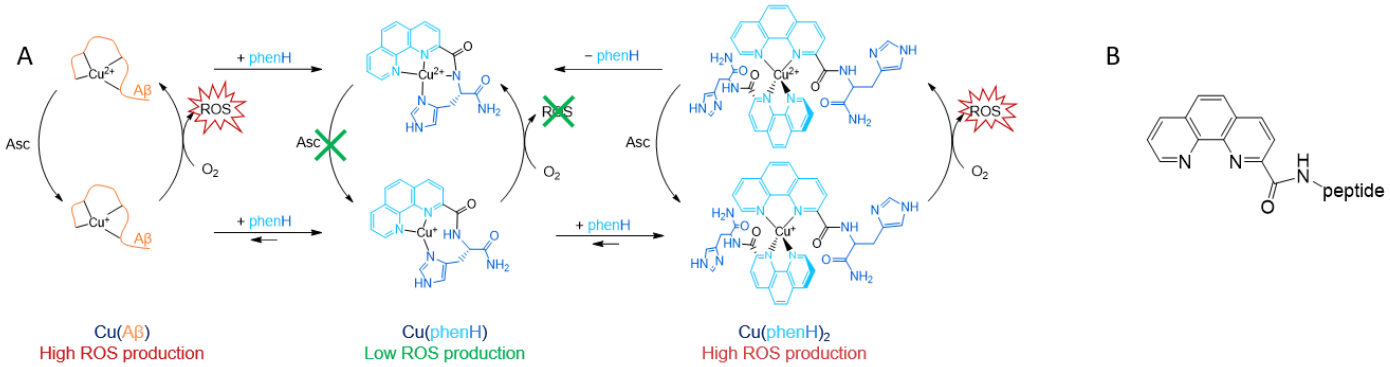

Figure 1 : (A) Simplified mechanism of CuAß, Cu(phenH) and Cu(phenH)$_2$ redox cycling reactions, with structure of Cu(II)(phenH) and proposed structures of Cu(I)(phenH) and Cu(I/II)(phenH)$_2$and (B) structure of the ligands

The present work aims at synthesizing new hybrid peptide phenanthroline-based ligands and study their potential therapeutic effects, investigated by spectroscopies and electrochemistry. Organic and peptidic synthesis will be employed in order to obtain the desired ligands. The properties of the Cu complexes will be studied by EPR and UV-visible spectroscopy, as well as by electrochemical techniques. Their ability to stop ROS production will be studied by UV-visible spectroscopy.

The candidate should be a motivated and perseverant person, willing to work on the interface synthesis chemistry / analytical chemistry in a multidisciplinary environment. The candidates should have a background in organic synthesis and analytical chemistry, and be open-minded to inorganic chemistry and electrochemistry.