Reducing ROS and Chelating Metal Ions in Neuronal Cells Using Novel Compounds

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Abstract

It is estimated that 45% of people over the age of 85 in the U.S. suffer from Alzheimer's disease. Patients with Alzheimer's disease, which is characterized by cognitive deficiencies and memory loss, have higher concentrations of amyloid plaques in brain tissue than patients without the disease. Abnormal levels of transition metal ions Fe, Zn, and Cu in brain tissue are associated with amyloid beta plaques and also have been shown to catalyze the generation of excess reactive oxygen species (ROS) and cause oxidative stress. The combination of the ROS generation and the amyloid plaque formation results in neurodegeneration, which ultimately causes the memory loss and ultimate death associated with Alzheimer's. We have synthesized the compounds **L2** and **L4** which are designed to be chelating agents of metal ions and also scavengers of ROS. We hypothesize that due to their chelating properties and pyridol groups, **L2** and **L4** should reduce oxidative damage in neuronal cells by chelating metal ions and scavenging radicals. Furthermore, we hypothesize that due to its extra pyridol group, **L4** will be a stronger antioxidant than **L2.** The cytotoxicity of the compounds was tested on HT-22 neuronal cells. Neuronal cells will be treated with BSO, a compound that induces formation of ROS, in the presence and absence of **L2** and **L4.** If our hypothesis is correct, our compounds should reduce the oxidative damage induced by BSO, and **L4** should be more effective at doing so than **L2**.

L2 and L4

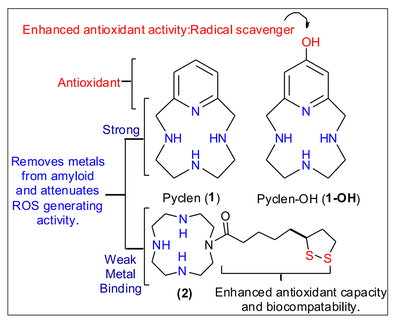
The drugs **L2** and **L4** have recently been synthesized and have shown antioxidant and chelating properties. The N atoms act as chelators of metal ions and the pyridol groups are designed to quench radicals. **L2** is the parent drug and **L4** was designed with an extra pyridol group.

Hypothesis

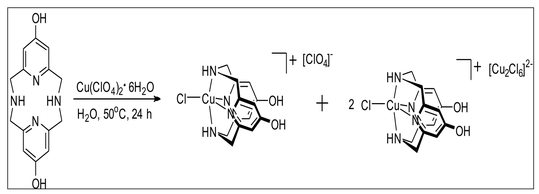
Neuronal cells under oxidative stress treated with **L2** and **L4** are expected to show an increase in viability and a decrease in ROS. Additionally, **L4** is hypothesized to be a more effective scavenger of ROS due to its extra pyridol group,.

Compounds

L2



L4

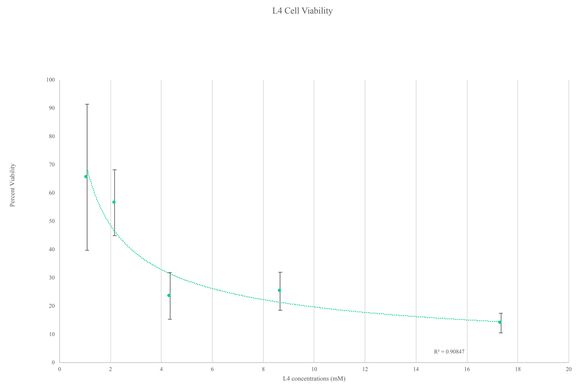


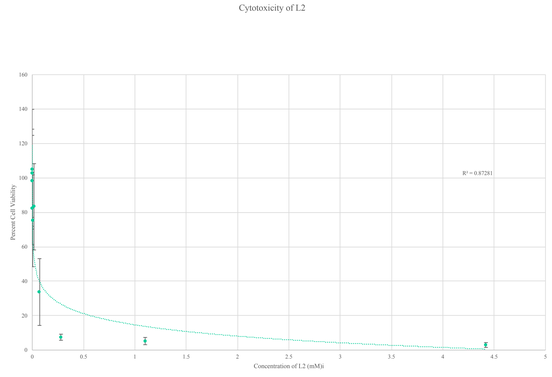
HeLa

HeLa + SV

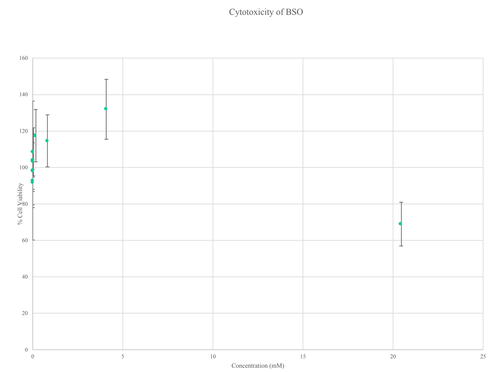
HeLa: NS5A + SV

Cytotoxicities of L2 and L4 in HT-22 Cells





Inducing Oxidative Stress with BSO



Buthionine Sulphoximine (BSO) induces oxidative stress by inhibiting the synthesis of the natural antioxidant glutathione. BSO was used to induce stress and increase ROS in HT-22 cells. However, no decrease in cell viability in cells treated with BSO was observed. Next, a DCFH-DA assay will be performed to quantify the ROS levels in cells treated with BSO.

Conclusions

The cytoxicites of **L2** and **L4** were tested and it was determined **L2** more cytotoxic in HT-22 cells. BSO was determined to not be cytotoxic in HT-22 cells.

References

Lincoln, K., et al. *ChemComm* (2014) **49,** 2712-2714

Gonzalez, P., et al. *Metallomics* (2014) **6,** 2072