Towards the bioavailability of a super vitamin E derivative

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Introduction

Lipid peroxidation and Ferroptosis:

Lipid rich regions in the cell (plasma membrane, mitochondria, nuclear membrane), undergo lipid peroxidation since their components, polyunsaturated fatty-acids, are vulnerable to autoxidation (a free radical chain reaction).

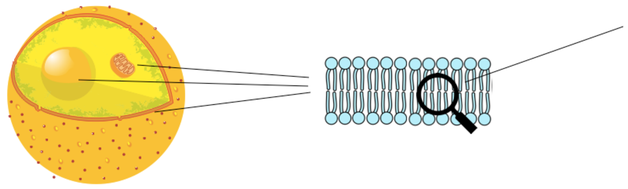
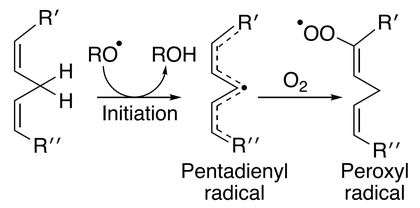
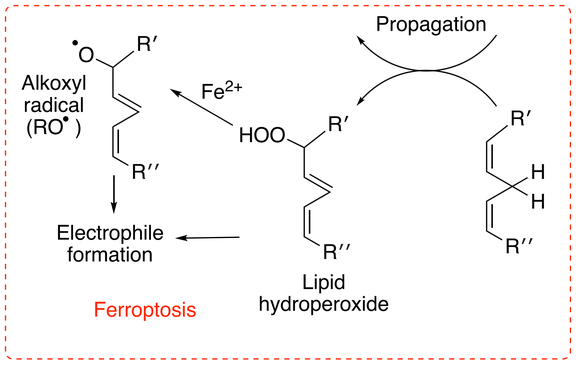
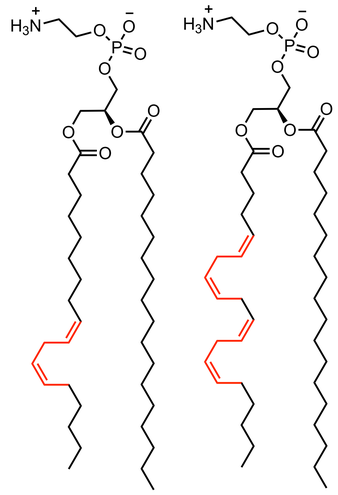


Figure 1. Polyunsaturated fatty-acids found in the cell.







Ferroptosis is a recently characterized form of regulated cell death associated with the accumulation of lipid oxidation products. Since lipid oxidation products have been implicated in diseases such as atherosclerosis[1] and neurodegeneration[2], such as Alzheimer's disease[3], ferroptosis may play a significant role in their development. Therefore, inhibition of ferroptosis by slowing lipid oxidation is a potential preventive and/or therapeutic strategy for degenerative disease.

Figure 2. Molecular pathway of lipid peroxidation leading to ferroptosis.

Inhibition of autoxidation:

Radical trapping antioxidants (RTAs) can inhibit the propagation of autoxidation by reacting with chain-carrying peroxyl radicals. α-tocopherol (α-TOH) the most biologically active constituent of Vitamin E, is the most potent naturally-occurring RTA.

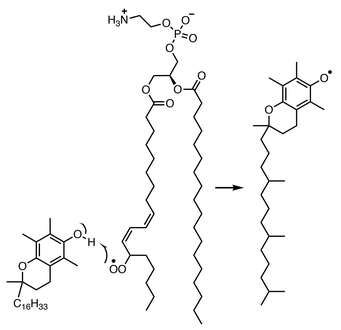


Figure 3. α-TOH reacts with a peroxyl radical.

α-TOH vs THN:

Recently, the Pratt Research group at the University of Ottawa has reported the most potent inhibitors of lipid oxidation yet (more effective then α-TOH) . These compounds, are known as tetrahydronaphthyridinols (THN) have been demonstrated to be among the most effective inhibitors of ferroptosis in cell culture[4].

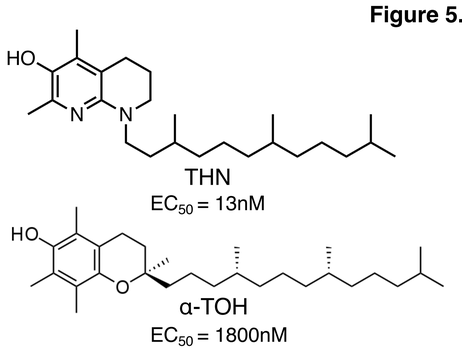
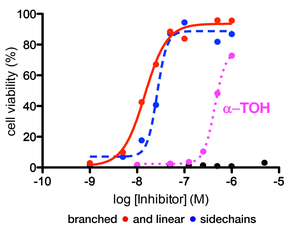


Figure 4. α-TOH and the Pratt Group's 'super vitamin E'.

Figure 5. THNs are 100 fold more effective at protecting mammalian cells then α-TOH[5].



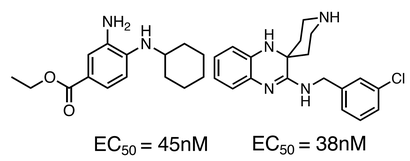


Figure 6. THN has comparable EC_{50} values to ferrostatin-1 and lipproxstatin-1, the gold standards for ferroptosis inhibition.

Objective & Methodology

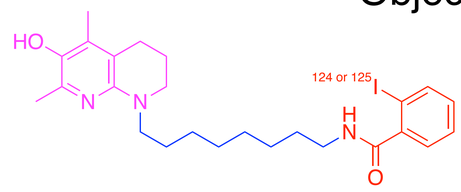
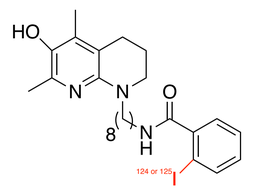


Figure 7. Radio-labelled THN. Crucial structural elements are coloured: tetrahydronaphthyridinol core structure (pink), lipophilic side-chain (blue), and a radioactive moiety (red).

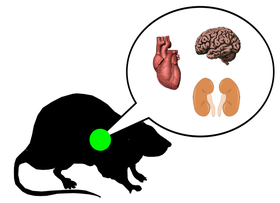
The objective of this research project is to synthesize a radio-labelled THN -labelled with either ^{124}I ($t_{1/2}$ =4.18 days) or ^{125}I ($t_{1/2}$ =59.49 days. This compound can be used to study the uptake of THN in animals, since its systemic distribution can be determined by positron emission tomography (PET).

Future steps:



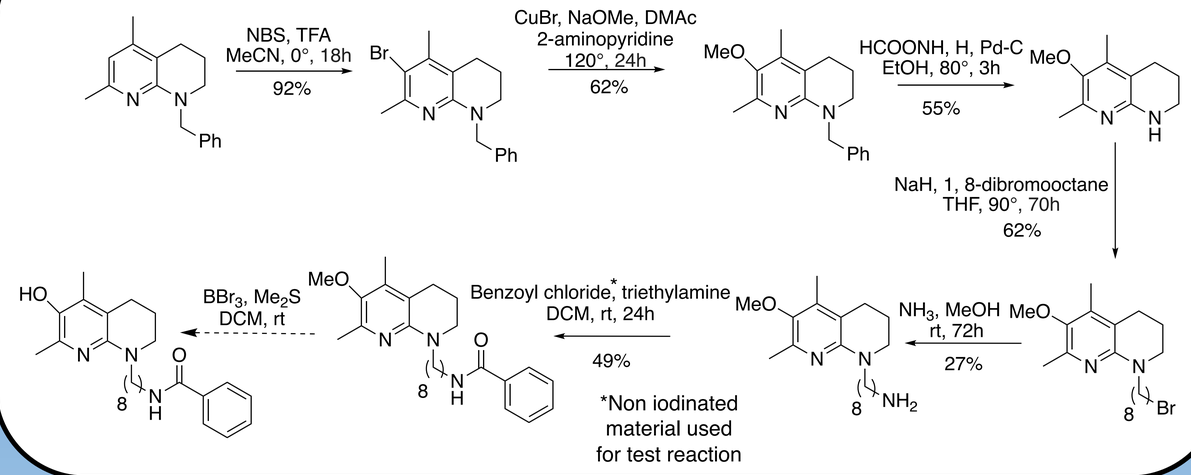
1. Synthesis of radio-labelled THN

2. Injection of live mice with THN



3. Analysis of distribution of THN in mice using PET.

Synthesis



Discussion, Conclusion & Future Studies

A non-radio-labelled model compound was successfully synthesized paving the way for the synthesis of an analogous related compound. The first four steps of the synthesis were executed as previously described by a former group member[4], albeit with lower yields. The subsequent substitution has presented some challenges. During this reaction, a yield of 27% was obtained. Efforts to improve this key step are underway and may include carrying out the reaction at elevated pressure. Upon optimizing this step, synthesis of the radio-labelled substrate will be carried out.

Since this project has demonstrated the apparent feasibility of the synthesis of the radio-labelled THN, future studies will have to be conducted to demonstrate its synthesis on a large scale. The radio-labelled compound will be administered to Balb/C or C57BL mice in order to demonstrate its systemic distribution and bioavailability *in vivo*. The results of those studies may provide a better understanding of ferroptosis and its role in the development of degenerative diseases, which could lead to the development of new therapeutic techniques for their treatment.

References

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