Flow synthesis of nature-derived MITO-phenolic compounds as potential neuroprotective agents

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Among all systems and organs, the central nervous system (CNS) is particularly exposed to oxidative stress because of the high oxygen consumption (20% of the total oxygen) and the large amount of ATP produced [1]. Oxidative stress, together with aging and genetic factors, plays an important role in the occurrence of neurodegenerative diseases, like Alzheimer's, Parkinson's and Huntington's diseases.
It is known that, during the oxidative phosphorylation in mitochondria, byproducts known as reactive oxygen species (ROS) are generated. ROS are beneficial at low concentration, but at higher concentration they can cause oxidative stress damaging DNA, proteins and lipids and causing cell death. Therefore, researchers have been focused on the development of mitochondria-targeted antioxidant molecules.
In this context, we designed and synthetize nature-derived phenolic esters to target mitochondria by covalently linking a lipophilic cation to some selected natural antioxidant (i.e., coumaric acid, sinapic acid, syringic acid, ferulic acid, gallic acid, caffeic acid and rosmarinic acid). The synthesis was optimized under flow conditions, using Cyrene, also known as dihydrolevoglucosenone, as the solvent. Cyrene is produced in two steps from cellulose, which makes it an eco-friendly bio-available solvent useful to replace dipolar aprotic solvents, like DMF and NMP, which are in the REACH restricted substances list [2]. A two-step flow protocol was developed and the desired compounds were isolated in moderate to good yields (Scheme 1). For the evaluation of the biological effects, the obtained compounds were tested on in vitro neuronal cells (SH-SY5Y cells). By MTS assay, we determined cytocompatibility and neuroprotection activity under oxidative stress stimulation of the compounds.

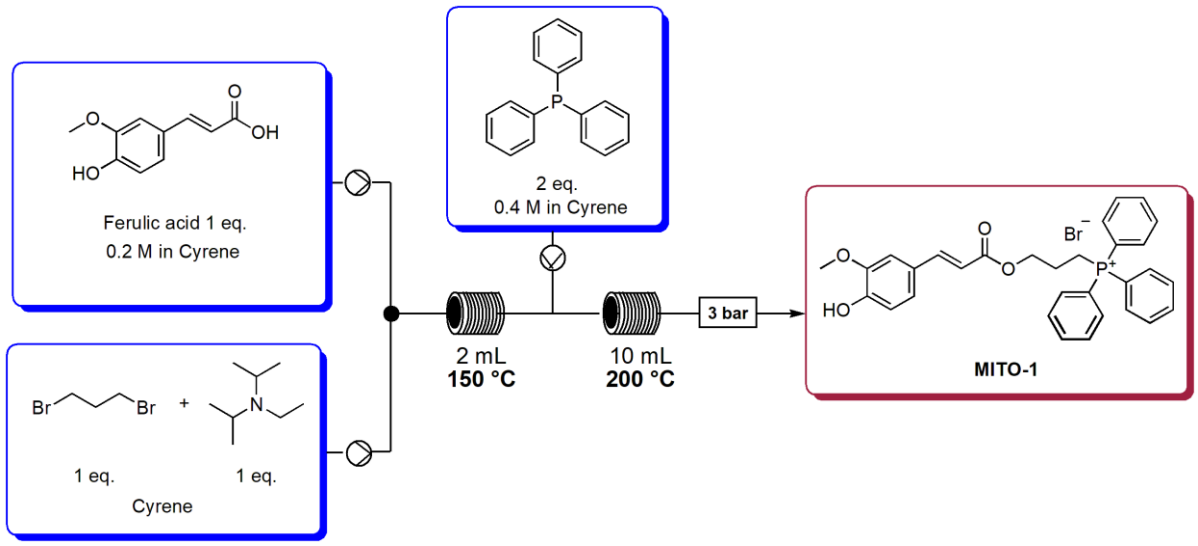

Figure 1. Schematic representation of the two-step flow protocol for the synthesis of compound **MITO-1**

[1] P. Sailaja Rao, S. Kalva, A. Yerramilli, S. Mamidi, *Free Radicals and Antioxidants*, 2011, **1**, 2–7.
[2] J. E. Camp, *ChemSusChem*, 2018, **11**, 3048–3055.