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

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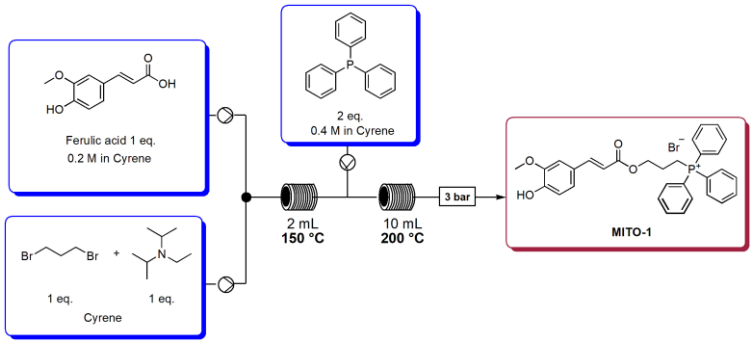
Among all systems and organs, the central nervous system (CNS) is particularly exposed to oxidative stress because of the high oxygen consumption and the large amount of ATP produced [1]. Oxidative stress plays an important role in the occurrence of neurodegenerative diseases.

It is known that, during the oxidative phosphorylation in mitochondria, byproducts known as reactive oxygen species (ROS) are generated. ROS 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 synthesized nature-derived phenolic esters to target mitochondria by covalently linking a lipophilic cation to some selected natural antioxidants (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 (*i.e.*, dihydrolevoglucosenone) as the solvent. Cyrene is an eco-friendly bio-available solvent useful to replace dipolar aprotic solvents 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.



Scheme 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.