New low-cytotoxic P-containing nitrones targeting mitochondria

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Reactive oxygen species, including free radicals, play a crucial role in cell signaling but also contribute to the initiation and progression of a variety of chronic diseases such as cancer, neurodegenerative diseases, diabetes or ischemia/reperfusion [1]. Cyclic diethoxyphosphoryl-substituted nitrones are enhanced spin trapping agents for investigating free radical processes in whole biological systems by electron paramagnetic resonance (EPR) spectroscopy [2]. Besides, therapeutic properties of nitrones have also been reported on numerous disorders, by mechanisms not only relevant to free radical scavenging [2,3]. Thus, the linear α-phenyl-*N*-tert-butyl nitrone (PBN) and derivatives could act through nitric oxide release, enzymes induction and suppression of mitochondria-dependent signaling [4]. Recently, increased therapeutic property of a new generation of hybrid phosphorylated PBN derivatives (PPNs) including antioxidant moieties found in natural phenolic acids was established [5]. Since mitochondrial diseases are an emerging public health concern, a new challenge consists to control cell distribution of drugs to finely target mitochondria [6]. Here we report the synthesis of a series of PPNs derivatives targeting mitochondria (mito-PPNs, Figure 1). Compared to previous mitochondria targeting agents, these more biocompatible mito-PPNs showed less cytotoxicity due to improvements in the nature of the lipophilic cation acting as a mitochondrial vector.

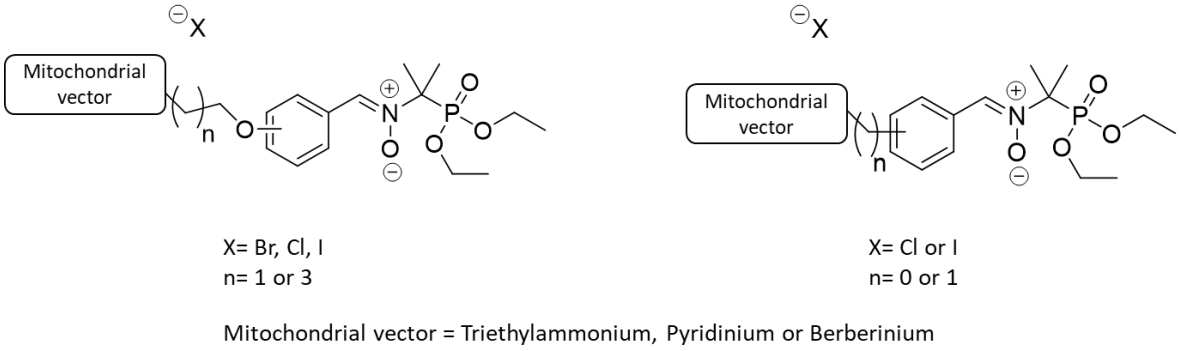

Figure 1: Structure of new low-cytotoxic nitrones targeting mitochondria

New mito-PPNs were good EPR probes for biologically-relevant carbon- and oxygen-derived free radicals, efficiently inhibited superoxide in vitro and showed low toxicity on cultured fibroblasts. Their mitochondrial permeation was assessed by ^{31}P NMR spectroscopy on isolated rat livers. Altogether, mito-PPNs could be promising tools to elucidate radical mechanisms impacting mitochondria, as well as low toxic mitochondria targeted antioxidants.

[1] Jones DP, *Antioxid. Redox Signal.* **2015**, *23*, 734; [2] Pietri S *et al. Eur J Biochem.* **1998**, *254*, 256; [3] Floyd RA *et al. Free Radic. Biol. Med.* **2008**, *45*, 1361; [4] Das A *et al. Biochem. Pharmacol* **2012**, *84*, 486; [5] Cassien M. *et al. Eur. J. Med. Chem*. **2016**, *119*, 197; [6] Murphy MP *et al. J. Biol. Chem.* **2003**, *278*, 48534.