# Modulating Cytotoxicity with Lego-like Chemistry: Upgrading Mitochondriotropic Antioxidants with Prototypical Cationic Carrier Bricks


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## Abstract

Although the lipophilic triphenylphosphonium ($TPP^+$) cation is widely used to target antioxidants to mitochondria, $TPP^+$-based derivatives have shown cytotoxicity in several biological in vitro models. We confirmed that Mito.TPP is cytotoxic to both human neuronal (SH-SY5Y) and hepatic (HepG2) cells, decreasing intracellular adenosine triphosphate (ATP) levels, leading to mitochondrial membrane depolarization and reduced mitochondrial mass after 24 h. We surpassed this concern using nitrogen-derived cationic carriers (Mito.PICO, Mito.ISOQ, and Mito.IMIDZ). As opposed to Mito.TPP, these novel compounds were not cytotoxic to SH-SY5Y and HepG2 cells up to 50 μM and after 24 h of incubation. All of the cationic derivatives accumulated inside the mitochondrial matrix and acted as neuroprotective agents against iron(III), hydrogen peroxide, and tert-butyl hydroperoxide insults. The overall data showed that nitrogen-based cationic carriers can modulate the biological performance of mitochondria-directed antioxidants and are an alternative to the TPP cation.