Neuroprotective Effect of a New 7,8-Dihydroxycoumarin-Based Fe2+/Cu2+ Chelator in Cell and Animal Models of Parkinson?s Disease

Aguirre, Pabla

García-Beltrán, Olimpo

Tapia, Victoria

Muñoz, Yorka

Cassels, Bruce K.

Núñez, Marco T.

Disturbed iron homeostasis, often coupled to mitochondrial dysfunction, plays an important role in the progression of common neurodegenerative diseases such as Parkinson?s disease (PD). Recent studies have underlined the relevance of iron chelation therapy for the treatment of these diseases. Here we describe the synthesis, chemical, and biological characterization of the multifunctional chelator 7,8-dihydroxy-4-((methylamino)methyl)-2H-chromen-2-one (DHC12). Metal selectivity of DHC12 was Cu2+ ? Fe2+ > Zn2+ > Fe3+. No binding capacity was detected for Hg2+, Co2+, Ca2+, Mn2+, Mg2+, Ni2+, Pb2+, or Cd2+. DHC12 accessed cells colocalizing with Mitotracker Orange, an indication of mitochondrial targeting. In addition, DHC12 chelated mitochondrial and cytoplasmic labile iron. Upon mitochondrial complex I inhibition, DHC12 protected plasma membrane and mitochondria against lipid peroxidation, as detected by the reduced formation of 4-hydroxynonenal adducts an