Hydroxybenzoic acid derivatives as dual-target ligands: Mitochondriotropic antioxidants and cholinesterase inhibitors

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Alzheimer's disease (AD) is a multifactorial age-related disease associated with oxidative stress (OS) and impaired cholinergic transmission. Accordingly, targeting mitochondrial OS and restoring cholinergic transmission can be an effective therapeutic strategy toward AD. Herein, we report for the first time dual-target hydroxybenzoic acid (HBAc) derivatives acting as mitochondriotropic antioxidants and cholinesterase (ChE) inhibitors. The studies were performed with two mitochondriotropic antioxidants AntiOxBEN1 (catechol derivative), and AntiOxBEN2 (pyrogallol derivative) and compounds 15-18, which have longer spacers. Compounds AntiOxBEN1 and 15, with a shorter carbon chain spacer (six- and eight-carbon) were shown to be potent antioxidants and BChE inhibitors (IC50 = 85 ± 5 and 106 ± 5 nM, respectively), while compounds 17 and 18 with a 10-carbon chain were more effective AChE inhibitors (IC50 = 7.7 ± 0.4 and 7.2 ± 0.5 ?M, respectively). Interestingly, molecular modeling data pointed toward bifunctional ChEs inhibitors.

The most promising ChE inhibitors acted by a non-competitive mechanism. In general, with exception of compounds 15 and 17, no cytotoxic effects were observed in differentiated human neuroblastoma (SH-SY5Y) and human hepatocarcinoma (HepG2) cells, while A?-induced cytotoxicity was significantly prevented by the new dual-target HBAc derivatives. Overall, due to its BChE selectivity, favorable toxicological profile, neuroprotective activity and drug-like properties, which suggested blood-brain barrier (BBB) permeability, the mitochondriotropic antioxidant AntiOxBEN1 is considered a valid lead candidate for the development of dual acting drugs for AD and other mitochondrial OS-related diseases.

Acetyl and butyrylcholinesterase

Cholinesterase inhibitors

Hydroxybenzoic acids

Mitochondria-targeted antioxidants

Oxidative stress