Fine-tuning the neuroprotective and blood-brain barrier permeability profile of multi-target agents designed to prevent progressive mitochondrial dysfunction

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Alzheimer's disease is an irreversible, complex and progressive neurodegenerative disorder associated with oxidative stress and mitochondrial dysfunction. Exogenous antioxidants can be beneficial for decreasing oxidative stress, as they are able to reward the lack of efficacy of the endogenous defense systems and raise the overall antioxidant response in a pathological condition. Along our overarching project related with the design and development of potent and safe multi-target mitochondriotropic antioxidants, based on dietary antioxidants, novel derivatives were obtained. Overall, mitochondriotropic antioxidants showed remarkable antioxidant and chelating properties, presenting low cytotoxic effects on human differentiated neuronal (SH-SY5Y) and hepatocarcinoma (HepG2) cells and exhibited neuroprotective properties on SH-SY5Y cells against 6-hydroxydopamine (6-OHDA) or hydrogen peroxide (H2O2) oxidative insults. Moreover,

compounds 58, 59, 62, 63, 66 and 67 were able to permeate a layer of hCMEC/D3 cells in a time-dependent manner. Mitochondriotropic antioxidant 67 stands out by its remarkable iron chelating and neuroprotective properties toward both H2O2 and 6-OHDA-induced oxidative damage, drug-like properties and BBB permeability. © 2019 Elsevier Masson SAS

Alzheimer's disease

Blood-brain barrier

Mitochondriotropic antioxidants

Neuroprotection

2 (3,4,5 trihydroxyphenyl)acetic acid

3 (3,4 dihydroxyphenyl)propanoic acid

3 (3,4,5trihydroxyphenyl)propanoic acid

3,4 dihydroxyphenylacetic acid

3,4,5 trihydroxycinnamic acid

acetic acid derivative

antioxidant

bromide

caffeic acid

gallic acid

hydrocinnamic acid derivative

hydrogen peroxide

neuroprotective agent

oxidopamine

propionic acid derivative

protocatechuic acid

pyrogallol

reactive oxygen metabolite

triton x 100

trolox C

unclassified drug

[10 [2 (3,4 dihydroxyphenyl)acetamide]decyl]triphenylphosphonium methanesulfonate

[10 [2 (3,4,5 trihydroxyphenyl)acetamide]decyl]triphenylphosphonium methanesulfonate

[10 [3 (3,4 dihydroxyphenyl)propanamide]decyl]triphenylphosphonium methanesulfonate

[10 [3 (3,4,5 trihydroxyphenyl)propanamide]decyl]triphenylphosphonium methanesulfonate

[6 [2 (3,4 dihydroxyphenyl)acetamide]hexyl]triphenylphosphonium methanesulfonate

[6 [2 (3,4,5 trihydroxyphenyl)acetamide]hexyl]triphenylphosphonium methanesulfonate

[6 [3 (3,4 dihydroxyphenyl)propanamide]hexyl]triphenylphosphonium methanesulfonate

[6 [3 (3,4,5 trihydroxyphenyl)propanamide]hexyl]triphenylphosphonium methanesulfonate

antioxidant

neuroprotective agent

ABTS radical scavenging assay

antioxidant activity

Article

blood brain barrier

cell viability

concentration response

controlled study

disorders of mitochondrial functions

DPPH radical scavenging assay

drug cytotoxicity

drug design

drug targeting

EC50

hCMEC/D3 cell line

Hep-G2 cell line

human

human cell

IC50

iron chelation

lipophilicity

mitochondrion

MTT assay

neuropharmacology

neuroprotection

neurotoxicity

nucleophilicity

oxidation reduction potential

oxidative stress

partition coefficient

resazurin assay

SH-SY5Y cell line

substitution reaction

Alzheimer disease

antagonists and inhibitors

blood brain barrier

cell line

disorders of mitochondrial functions

drug effect

metabolism

pathology

pathophysiology

synthesis

tumor cell line

Alzheimer Disease

Antioxidants

Blood-Brain Barrier

Cell Line

Cell Line, Tumor

Humans

Hydrogen Peroxide

Mitochondrial Diseases

Neuroprotective Agents

Oxidative Stress

Oxidopamine