Discovery and optimization of 3-thiophenylcoumarins as novel agents against Parkinson's disease: Synthesis, in vitro and in vivo studies

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Monoamine oxidase B (MAO-B) inhibitors are still receiving great attention as promising therapeutic agents for central nervous system disorders. This study explores, for the first time, the potential of 3-thiophenylcoumarins as in vitro and in vivo agents against Parkinso?s disease. Twelve compounds were synthesized via Perkin-Oglialoro reaction, and in vitro evaluation of six hydroxylated molecules was performed. MAO-A and MAO-B inhibition, DPPH scavenging and inhibition of ROS formation, neurotoxicity on motor cortex neurons and neuroprotection against H2O2, were studied. In vivo effect on locomotor activity using the open field test was also evaluated for the best candidate [3-(4?-bromothiophen-2?-yl)-7-hydroxycoumarin, 5], a potent, selective and reversible MAO-B inhibitor (IC50 = 140 nM). This compound proved to have a slightly better in vivo profile than selegiline, one of the currently treatments for Parkinson's disease, in reserpinized mice pretreated with levodopa and benserazide. Results suggested that, comparing positions 7 and 8, substitution at position 7 of the coumarin scaffold is better for the enzymatic inhibition. However, the presence of a catechol at positions 7 and 8 exponentially increases the antioxidant potential and the neuroprotective properties. Finally, all the molecules present good theoretical physicochemical properties that make them excellent candidates for the optimization of a lead compound. © 2020 Elsevier Inc.

3-Thiophenylcoumarins

DPPH scavengers

monoamine oxidase B inhibitors

Neuroprotectors

Open field test

Parkinson's disease

3 (4' bromothiophen 2' yl) 7 hydroxycoumarin

3 (4' bromothiophen 2' yl) 7,8 dihydroxycoumarin

3 (4' bromothiophen 2' yl) 8 hydroxycoumarin

3 thiophenylcoumarin derivative

7 hydroxy 3 (thiophen 3' yl)coumarin

7,8 dihydroxy 3 (thiophen 3' yl)coumarin

8 hydroxy 3 (thiophen 3' yl)coumarin

amine oxidase (flavin containing) isoenzyme A

amine oxidase (flavin containing) isoenzyme B

coumarin derivative

hydrogen peroxide

levodopa

selegiline

unclassified drug

animal cell

animal experiment

animal model

antioxidant activity

Article

controlled study

DPPH radical scavenging assay

drug potency

drug selectivity

drug synthesis

embryo

enzyme inhibition

female

IC50

in vitro study

in vivo study

locomotion

male

motor cortex

mouse

neuroprotection

neurotoxicity

nonhuman

open field test

Parkinson disease

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structure activity relation