Publication

Design and Synthesis of CNS-targeted Flavones and Analogues with Neuroprotective Potential Against H; 2; O; 2; - and Aβ; 1-42; -Induced Toxicity in SH-SY5Y Human Neuroblastoma Cells

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With the lack of available drugs able to prevent the progression of Alzheimer's disease (AD), the discovery of new neuroprotective treatments able to rescue neurons from cell injury is presently a matter of extreme importance and urgency. Here, we were inspired by the widely reported potential of natural flavonoids to build a library of novel flavones, chromen-4-ones and their; C; -glucosyl derivatives, and to explore their ability as neuroprotective agents with suitable pharmacokinetic profiles. All compounds were firstly evaluated in a parallel artificial membrane permeability assay (PAMPA) to assess their effective permeability across biological membranes, namely the blood-brain barrier (BBB). With this test, we aimed not only at assessing if our candidates would be well-distributed, but also at rationalizing the influence of the sugar moiety on the physicochemical properties. To complement our analysis, log; D; 7.4; was determined. From all screened compounds, the; p; -morpholinyl flavones stood out for their ability to fully rescue SH-SY5Y human neuroblastoma cells against both H; 2; O; 2; - and Aβ; 1-42; -induced cell death. Cholinesterase inhibition was also evaluated, and modest inhibitory activities were found. This work highlights the potential of; C; -glucosylflavones as neuroprotective agents, and presents the; p; -morpholinyl; C; -glucosylflavone; 37; , which did not show any cytotoxicity towards HepG2 and Caco-2 cells at 100 μM, as a new lead structure for further development against AD.
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