NEUROGENIC INDUCERS BASED ON THE CHROMONE SCAFFOLD, A NEW FAMILY OF MULTITARGET DIRECTED LIGANDS FOR ALZHEIMER'S DISEASE

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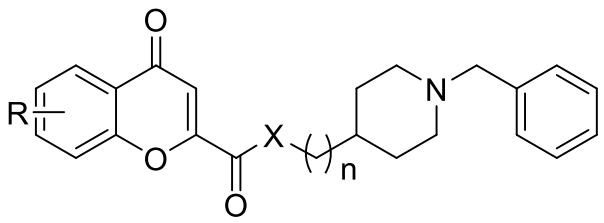
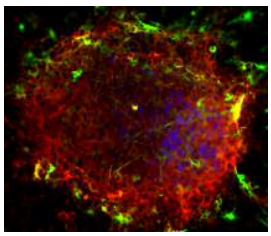
The highly complex pathophysiology of Alzheimer's disease (AD) and other neurodegenerative illnesses have led to replace the traditional one-drug – one-target by the multi-target-directed ligands (MTDLs) paradigm, in which a single molecule is designed to be active against several pharmacological targets [1]. Continuing with our interest in neuroprotective and neurogenic compounds [2,3], in this work we describe a new family of donepezil – flavonoid hybrids exhibiting nanomolar affinities for the sigma-1 receptor and a combined inhibition of key enzymes in AD, such as 5-lipoxygenase, acetylcholinesterase, and monoaminoxidases. In general, they scavenge free radical species and are predicted to be brain-permeable. In phenotypic assays, new hybrids protect neuronal cells against mitochondrial oxidative stress and promote maturation of neural stem cells into a neuronal phenotype. Therefore, new donepezil - flavonoid hybrids could contribute to the protection and even, the reparation of neuronal tissues, of great therapeutic interest in AD and neurodegenerative diseases.





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