

Novel Coumarin-Quinoline Hybrids: Design of Multitarget Compounds for Alzheimer's Disease

Duarte Y.

Fonseca A.

Gutiérrez M.

Adasme-Carreño F.

Muñoz-Gutierrez C.

Alzate-Morales J.

Santana L.

Uriarte E.

Álvarez R.

Matos M.J.

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease, presenting the most devastating consequences on human health and life quality. Coumarin-quinoline hybrids were synthesized following a very efficient and versatile strategy. Small structural variations contributed to dual acetyl/butrylcholinesterases (AChE/BuChE) activity or selectivity towards one of these enzymes. In addition, some of the studied compounds are interesting iron chelators, presenting a tendency to be neuroprotective. Moreover, the compounds are not cytotoxic for SH-SY5Y neuroblastoma cells. Compound 9c proved to be the most interesting compound of the studied series. This compound is selective against AChE and proved to be an excellent iron chelating agent (iron chelation at 100 μ M=72.87%). Molecular docking studies were performed to establish the nature of the interaction between the studied compounds and the binding pockets, leading to a rationalization of structure-activity relationships. Compound 9c forms a well-defined π -stacking interaction with Phe330 and interacts with Tyr121 residue via a hydrogen bond, while the inactive compounds cannot establish these interactions. Important preliminary results against different targets, as well as some structure-activity relationships, were concluded from the experimental

results. © 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Acetyl/butyrylcholinesterases? inhibitors

Coumarin-quinoline hybrids

Drug design

Iron chelating agents

Neuroprotective agents.