Imidazole-Linked Heterocycles with anti-Alzheimer properties

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Alzheimer’s disease (AD) is the most dominant neurodegenerative diseases, without efficacious drugs, and with only a few therapeutic targets identified. In this scenario, we aim to find molecular entities that modulate imidazoline I2 receptors (I2-IRs) that have been pointed out as relevant targets in AD.1,2 In this work, we explored structural modifications of well-established I2-IR ligands, giving access to derivatives with an imidazole-linked heterocycle as a common key feature that showed good brain permeation and affinity/selectivity upon I2-IR. It permitted the proposal of a pharmacophore after 3D-QSAR, and the theoretical ADME and physicochemical parameters were calculated to rule out warnings to continue with the medicinal chemistry program. Selected compounds showed neuroprotective properties and beneficial effects in an in vitro model of Parkinson’s disease and showed crucial anti-inflammatory effects in a cellular model of neuroinflammation. After a preliminary pharmacokinetic study, we explored the action of our representative 2-(benzo[b]thiophen-2-yl)-1H-imidazole LSL33 in a mouse model of AD (5xFAD). Oral administration of LSL33 at 2 mg/Kg for 4 weeks ameliorated 5XFAD cognitive impairment and synaptic plasticity, as well as reduced neuroinflammation markers. In summary, this new I2-IR ligand that promoted beneficial effects in a well-established AD mouse model should be considered a promising therapeutic strategy for neurodegeneration.

References:

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