Adenosine receptor ligands: Coumarin–Chalcone hybrids as modulating agents on the activity of hARs

Vazquez-Rodriguez, S.
Vilar, S.
Kachler, S.
Klotz, K.-N.
Uriarte, E.
Borges, F.
Matos, M.J.

Abstract
Adenosine receptors (ARs) play an important role in neurological and psychiatric disorders such as Alzheimer's disease, Parkinson's disease, epilepsy and schizophrenia. The different subtypes of ARs and the knowledge on their densities and status are important for understanding the mechanisms underlying the pathogenesis of diseases and for developing new therapeutics. Looking for new scaffolds for selective AR ligands, coumarin–chalcone hybrids were synthesized (compounds 1–8) and screened in radioligand binding (hA_1, hA_{2A} and hA_3) and adenylyl cyclase (hA_{2B}) assays in order to evaluate their affinity for the four human AR subtypes (hARs). Coumarin–chalcone hybrid has been established as a new scaffold suitable for the development of potent and selective ligands for hA_1 or hA_3 subtypes. In general, hydroxy-substituted hybrids showed some affinity for the hA_1, while the methoxy counterparts were selective for the hA_3. The most potent hA_1 ligand was compound 7 (K_i = 17.7 μM), whereas compound 4 was the most potent ligand for hA_3 (K_i = 2.49 μM). In addition, docking studies with hA_1 and hA_3 homology models were established to analyze the structure–function relationships. Results showed that the different residues located on the protein binding pocket could play an important role in ligand selectivity.

Author keywords
Adenosine receptors
Binding affinity
Chalcone
Coumarin
Docking
Neurodegenerative diseases