Coumarins and adenosine receptors: New perceptions in structure?affinity relationships

Fonseca A.

Matos M.J.

Vilar S.

Kachler S.

Klotz K.-N.

Uriarte E.

Borges F.

Adenosine receptor (AR) subtypes are involved in several physiological and pharmacological processes. Ligands that are able to selectively modulate one receptor subtype can delay or slow down the progression of diverse diseases. In this context, our research group focused its investigation into the discovery and development of novel, potent and selective AR ligands based on coumarin scaffold. Therefore, a series of 3-phenylcarboxamidocoumarins were synthesized and their affinity for the human AR subtypes was screened by radioligand binding assays for A 1 , A 2A and A 3 receptors and for A 2B by adenylyl cyclase assay. Compound 26 was found to be the most remarkable, with a hA 1 /hA 3 and hA 2A /hA 3 selectivity of 42, for the A 3 AR (K i = 2.4 ?m). Receptor-driven molecular modelling studies have provided valuable information on the binding/selectivity data of compound 26 and for the following optimization process. Moreover, compound 26 presents drug-like properties according to the general guidelines linked to the concept.

adenosine receptors

carboxamidocoumarin

coumarins

3 phenylcarboxamidocoumarin derivative

adenosine receptor

adenylate cyclase

coumarin derivative

n (2 bromophenyl) 6 methoxycoumarin 3 carboxamide

n (2 bromophenyl)coumarin 3 carboxamide

n (2 chlorophenyl) 6 methoxycoumarin 3 carboxamide

n (2 chlorophenyl) 6 methylcoumarin 3 carboxamide

n (2 chlorophenyl)coumarin 3 carboxamide

n (2 hydroxyphenyl) 6 methoxycoumarin 3 carboxamide

n (2 hydroxyphenyl)coumarin 3 carboxamide

n (2 methoxyphenyl) 6 methoxycoumarin 3 carboxamide

n (2 methoxyphenyl)coumarin 3 carboxamide

n (2 methylphenyl) 6 methoxycoumarin 3 carboxamide

n (2 methylphenyl)coumarin 3 carboxamide

n (3 bromophenyl) 6 methoxycoumarin 3 carboxamide

n (3 bromophenyl)coumarin 3 carboxamide

n (3 chlorophenyl) 6 methoxycoumarin 3 carboxamide

n (3 chlorophenyl) 6 methylcoumarin 3 carboxamide

n (3 chlorophenyl)coumarin 3 carboxamide

n (3 hydroxyphenyl) 6 methoxycoumarin 3 carboxamide

n (3 hydroxyphenyl)coumarin 3 carboxamide

n (3 methoxyphenyl) 6 methoxycoumarin 3 carboxamide

n (3 methoxyphenyl)coumarin 3 carboxamide

n (3 methylphenyl) 6 methoxycoumarin 3 carboxamide

n (3 methylphenyl)coumarin 3 carboxamide

n (4 hydroxyphenyl) 6 methoxycoumarin 3 carboxamide

n (4 hydroxyphenyl)coumarin 3 carboxamide

n (4 methylphenyl)coumarin 3 carboxamide

unclassified drug

unindexed drug

adenosine receptor

coumarin derivative

isoprotein

ligand

Article

binding affinity

drug receptor binding

drug structure

drug synthesis

human

molecular docking

molecular model

priority journal

process optimization

structure analysis

binding site

chemistry

drug design

metabolism

protein tertiary structure

radioassay

structure activity relation

Binding Sites

Coumarins

Drug Design

Humans

Ligands

Molecular Docking Simulation

Protein Isoforms

Protein Structure, Tertiary

Radioligand Assay

Receptors, Purinergic P1

Structure-Activity Relationship