Structure-Based Optimization of Coumarin hA3 Adenosine Receptor Antagonists

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Adenosine receptors participate in many physiological functions. Molecules that may selectively interact with one of the receptors are favorable multifunctional chemical entities to treat or decelerate the evolution of different diseases. 3-Arylcoumarins have already been studied as neuroprotective agents by our group. Here, differently 8-substituted 3-arylcoumarins are complementarily studied as ligands of adenosine receptors, performing radioligand binding assays. Among the synthesized compounds, selective A3 receptor antagonists were found. 3-(4-Bromophenyl)-8-hydroxycoumarin (compound 4) displayed the highest potency and selectivity as A3 receptor antagonist (Ki = 258 nM). An analysis of its X-ray diffraction provided detailed information on its structure. Further evaluation of a selected series of compounds indicated that it is the nature and position of the substituents that determine their activity and selectivity. Theoretical modeling calculations corroborate and explain the experimental data, suggesting this novel scaffold can be involved in the generation of candidates as multitarget drugs.