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2-Aminopyrimidine derivatives as selective A_1 adenosine receptor antagonists

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The purinic nucleoside adenosine[1] modulates a variety of physiological functions within the central nervous system, peripheral nervous system, and tissues through interaction with various receptors located on the cell. Adenosine mediates their effects by activation of a family of four G-protein coupled receptors: A_1, A_{2A}, A_{2B}, and A_3[2].

Different therapeutic applications have been identified in preclinical and clinical studies for A_1 adenosine receptor antagonists, which are effective as potassium-sparing diuretic agents with kidney-protecting properties[3]. This type of compound is also being tested in the treatment of bradyarrhythmias associated with inferior myocardial infarction, cardiac arrest and cardiac transplant rejection, and could be useful in the treatment of chronic heart diseases[4]. A_1 adenosine receptor antagonists may also offer a therapeutic opportunity for chronic lung diseases such as asthma, chronic obstructive pulmonary disease and pulmonary fibrosis[5]

Here we describe the identification of 2-Aminopyrimidines as a new family of potent adenosine ligands. Affinities of the new compounds toward human A_1, A_{2A}, A_{2B} and A_3 adenosine receptors were evaluated by competition experiments assessing their respective abilities to displace [^{3}H]8-cyclopentyl-1,3-dipropylxanthine ([^{3}H]DPCPX) for for A_{1A}R and A_{2B}AR, [^{3}H]4-(2-[7-amino-2-(2-furyl)[1,2,4]triazolo[2,3-a][1,3,5]triazin-5-ylamino]ethyl)phenol ([^{3}H]-ZM241,385) for A_{2A}AR and [^{3}H]adenosine-5'-N-ethylcarboxamide, ([^{3}H]NECA) for A_3AR binding. Human adenosine receptors expressed in transfected CHO (A_1AR), HeLa (A_{2A}AR and A_3AR), and HEK-293 (A_{2B}AR) cells were employed.

From these results we have established a preliminary SAR requirement for activity and selectivity. We obtained some examples of potent ligands (Ki in the low nanomolar range) with variable selectivity profiles in relation to the nature of substituents introduced at C^4, C^6 and/or amine moiety. We identified compound 2-(ethylamino)-4,6-diphenylpyrimidine-5-carbonitrile as the most active (Ki of 5.82 ± 0.76nM (Ki ± SEM, n=3) in A_1 receptor) showing high selectivity over A_{2A}, A_{2B} and A_3ARs (21±1, 17±5 and 16±5, %± SEM (percentage displacement of specific binding at 0.1µM (n=2)). It becomes a promising starting point in order to obtain useful hits for the treatment of chronic heart diseases.

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