Substituted pyrazolo[3,4-*b*]pyridines as potent A_1 adenosine antagonists

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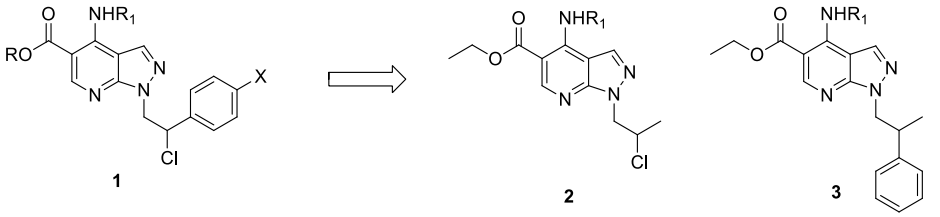
Adenosine is an endogenous neuromodulator which mediates its effects by interacting with four G-protein-coupled receptor subtypes named A_1, A_{2A}, A_{2B} and A_3. These receptors are distributed in a wide variety of tissues, including the central nervous system (CNS), cardiovascular system and airways, where they play key roles in the regulation of several biological functions. Many studies showed that some pathophysiological states are associated with changes of adenosine levels, making the search for adenosine receptor agonist or antagonist an interesting target in medicinal chemistry (1). In particular, an excessive stimulation of A_1 adenosine receptors (A_1ARs) is related to different pathologies, such as various forms of dementia, including Alzheimer's disease, depression, congestive heart failure, bradyarrhythmias and asystolic arrest. For these reasons, many A_1ARs antagonist have been developed in the last decades (2).

In this context, our group synthesized a wide library of 4-aminopyrazolo[3,4-*b*]pyridine-5-carboxylic acid esters **1** active as A_1AR antagonists both on bovine and human receptors; some of these compounds are characterized by high affinity and selectivity towards A_1AR, with the most active compounds having a bovine A_1AR affinity in the low nanomolar range (3). Starting from these promising results, we decided to synthesize a second generation of compounds **2**, with the aim of obtaining more potent and selective agents for human A_1AR. Since previous studies indicated that human A_1ARs contain a binding pocket smaller than that of bovine receptors, we substituted the N1 2-cloro-2-phenylethyl chain with the less bulky 2-cloropropyl chain. Furthermore, to extend SAR evaluations, we synthesized compounds **3** bearing in N1 the 2-phenylpropyl chain. Assays performed on bovine cortical membranes and human A_1AR CHO transfected cells show that compounds **2** are endowed with an improved activity on human A_1AR compared with the first generation derivatives **1**. Derivatives **3**, as expected, show good affinity for bovine A_1ARs, but are less active on human A_1ARs. Biological data will be reported in the poster section.



General structures of first generation (**1**) and second generation (**2** and **3**) of pyrazolo[3,4-*b*]pyrimidines.

References: 1. Chen, J. F. *et al*. Nat. Rev. Drug Discov. 2013, 12, 265-286. 2. Schenone, S. *et al*. Curr. Top. Med. Chem. 2010, 10, 878-901. 3. Tuccinardi, T. *et al*. Chem. Med. Chem. 2008, 3, 898-913.