STRUCTURE-AFFINITY RELATIONSHIPS OF 5'-CARBAMOYL- AND 5'-THIOCARBAMOYL DERIVATIVES OF THE A_1 SELECTIVE ADENOSINE RECEPTOR AGONIST 2'-ME-CCPA AS PARTIAL A_1 AGONISTS

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The A_1 adenosine receptor (A_1AR) agonists have many potential therapeutic applications. The receptor subtype is widely distributed in the body and in the heart is found in higher density in supraventricular tissues than in the ventricles. Many agonists with high affinity and efficacy for the A_1 receptor subtype have been investigated and selective agonists for the A_1AR have been developed for their potential use for the treatment of cardiovascular diseases. However, the ubiquitous distribution and wide range of physiological actions mediated by A_1AR are obstacles to development of A_1 agonists as therapeutic agents. In this respect, partial agonists that may produce less receptor desensitisation and exhibit fewer side effects may be advantageous for certain indications.

It is known that the substitution of the 5'-hydroxyl group of adenosine with different groups, such as ethoxy, phenyloxy, alkylthio, phenylthio, alkylamino, carbamate or thionocarbamate, induces partial agonism at A_1AR. In this communication we describe a series of 5'-carbamates and 5'-thionocarbamates of 2-chloro-2'-*C*-methyl-N^6-cyclopentyl-adenosine (2'-Me-CCPA), a potent and highly selective A_1 agonist at the bovine and human receptors [1]. The new compounds were tested in radioligand binding assays at bovine and pig receptors and compared with similar derivatives of the CVT-510 (N^6-[(*R*)-3-tetrahydrofuranyl]adenosine, Tecadenoson) an A_1 agonist that is currently being developed for the potential control of rapid heart rate during atrial arrhythmias. Some compounds proved to be partial agonists with good affinity and selectivity for pig A_1AR. Interestingly, N^6-[(*R*)-3-tetrahydrofuranyl]-derivatives of adenosine such as Tecadenoson and its 2-chloro- and 2'-*C*-methyl-analogues showed species selectivity having high affinity for pig A_1AR and low affinity for bovine receptor. This selectivity is the opposite of the selectivity displayed by 2'-Me-CCPA. Preliminary molecular modeling studies to explain the species selectivity will be reported.

[1] (a) Franchetti, P.; Cappellacci, L.; Marchetti, S.; Trincavelli, L.; Martini, C.; Mazzoni, M. R.; Lucacchini, A.; Grifantini, M. 2'-*C*-Methyl Analogues of Selective Adenosine Receptor Agonists: Synthesis and Binding Studies. *J. Med. Chem.* **1998**, *41*, 1708-1715. (b) Cappellacci, L.; Franchetti, P.; Pasqualini, M.; Petrelli, R.; Vita, P., Lavecchia, A.; Novellino, E.; Costa, B.; Martini, C.; Klotz, K.-N.; Grifantini, M. Synthesis, Biological Evaluation and Molecular Modeling of Ribose-modified Adenosine Analogues as Adenosine Receptor Agonists. *J. Med. Chem.* **2005**, in press.