TRICYCLIC TRIAZINO- AND TRIAZEPINO[3,4-*f*] PURINEDIONES: NEW ADENOSINE A_1 AND A_{2A} RECEPTOR LIGANDS

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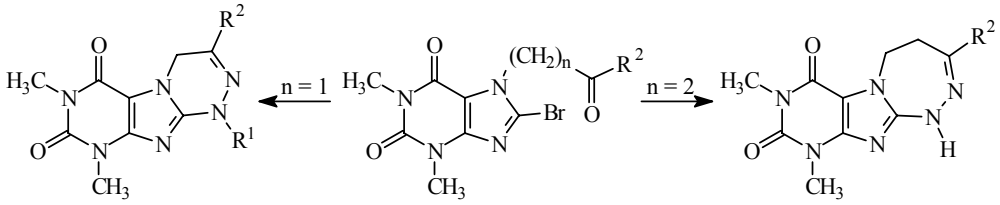
Extracellular adenosine regulates several physiological functions by activation of specific cell membrane receptors. There are adenosine receptor subclasses defined A_1, A_{2A}, A_{2B} and A_3ARs. The most intensively studied subtypes are the high-affinity A_1AR and A_{2A}AR which adenosine activates in nano- to sub-micromolar concentrations. Since the first reports on the adenosine A_1 and A_{2A} receptors appeared, efforts have been made to identify ligands for these receptors and xanthine derivatives have been described to posses high antagonistic activity [1]. As a continuation of our research [2, 3] a series of [1,2,4]triazino- (**I–VIII**) and [1,2,4]triazepino[3,4-*f*]purinediones (**IX, X**) has been synthesised.

Tricyclic theophylline derivatives (**I–X**) were obtained as a result of cyclocondensation of 8-bromotheopylline derivatives (**A**) bearing a keto group at the 7-alkyl substituent and hydrazine, or phenylhydrazine, respectively.



I - VIII **A** **IX , X**

№	R^1	R^2	№	R^1	R^2
I	H	C_6H_5	**VI**	C_6H_5	p-Cl–C_6H_4
II	H	p-Cl–C_6H_4	**VII**	$C(O)CH_3$	C_6H_5
III	H	m-OCH_3–C_6H_4	**VIII**	H	p-F–C_6H_4
IV	H	CH_3	**IX**		CH_3
V	C_6H_5	m-OCH_3–C_6H_4	**X**		C_2H_5

The prepared compounds (**I-X**) were evaluated *in vitro* for adenosine A_1 and A_{2A} receptor binding affinities. Adenosine A_1 and A_{2A} receptors binding was measured in rat cortical membranes using [^{3}H]CCPA and in rat striatal membranes using [^{3}H]MSX-2 respectively. Amongst them, compounds **I, III, VII** were found to be adenosine A_1 receptor ligands; **I, IV, X** showed adenosine A_{2A} receptor affinity.

Molecular modelling and SAR studies of **I–X** were performed to investigate structure–activity relationships using programs CAChe 6.1, HyperChem 7.5 and Alchemy2000.

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