# 2-PHENYL[1,2,3]TRIAZOLO[1,2-*a*][1,2,4]BENZOTRIAZIN-1-ONE DERIVATIVES AS A NEW CLASS OF ADENOSINE RECEPTOR ANTAGONISTS.

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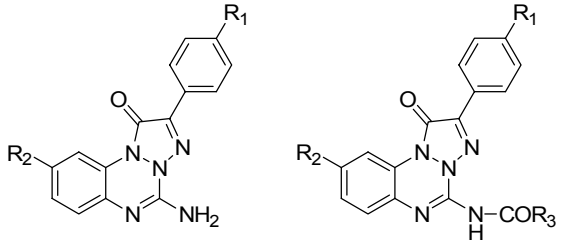
A wide variety of physiological functions on central nervous, cardiovascular, immune, and hormonal systems are modulated by adenosine. This ubiquitary molecule also inhibits lipolysis, platelet aggregation, and neurotransmitter release from nerve endings and potentiates histamine release from mast cells. Adenosine modulates these physiological functions acting via at least four specific cell surface receptors (ARs), classified as $A_1$, $A_{2A}$, $A_{2B}$, and $A_3$.

Selective antagonists at $A_1$ receptors have demonstrated promising therapeutic potential for the treatment of cognitive disease, renal failure, Alzheimer's disease, and cardiac arrhythmias; $A_{2A}$ antagonists could find applications in Parkinson's disease, Huntington's chorea, and myasthenic syndromes. $A_{2B}$ selective antagonists may prove useful in the treatment of asthma, and $A_3$ selective antagonists could act as antiasthmatic, cerebroprotective, and antiinflammatory agents [1-4].

In the present study a number of 2-(4-substituted-phenyl)-[1,2,3]triazolo[1,2-*a*][1,2,4]benzotriazin-1-one derivatives **1** and **2** were synthesized and tested for their affinity at $A_1$, $A_{2A}$ and $A_3$ adenosine receptors.




**1** **2**

The preparation of compounds **1** was accomplished by cyclization with cianogen bromide in absolute methanol of the appropriate 1-(2-amino-5-substituted-phenyl)-4-(4-substituted-phenyl)-[1,2,3]triazol-5-ones [5]. The reaction of the 5-amino group of compounds **1** with the appropriately substituted phenylisocyanates or benzoyl chlorides gave the uretane or the amide derivatives **2**, respectively. Careful examination of the binding data for the triazole derivatives **1** and **2** revealed that the effects of the $R_1$, $R_2$, and $R_3$ substituents on affinity and selectivity for the adenosine receptor subtypes were not constant but interdependent.

[1] Poulsen S.A., Quinn R.J. *Bioorg. Med. Chem*. **6**, 619 (1998). [2] Fredholm B.B. et al. *Pharmacol. Rev*. **53**, 527 (2001). [3] Baraldi P.G. et al. *Eur J. Med. Chem*. **38**, 367 (2003). [4] Ribeiro J.A. et al. *Progress in Neurobiology* **68**, 377 (2003). [5] Primofiore G. et al. *J. Med. Chem*., in press.