Nucleotide derivatives as new ligands of the purinergic P2 Receptors

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The purinergic P2 receptors respond to extracellular nucleotides and include two different families of receptors: the metabotropic G protein coupled receptors P2Y(1,2,4,6,11-14) and ionotropic receptors P2X(1-7). They are widely express in various organs and tissues and are involved in the regulation of numerous functions in the central and peripheral nervous system, as well as in the immune, muscular, renal, pulmonary, digestive, and cardiovascular apparatus.1

While the P2X receptor family is activated mainly by ATP, the P2Y receptors respond to different nucleotides like ATP, ADP, UTP, UDP and some nucleotide sugar. Recently, a P2Y-like dual receptor, the GPR17, has been deorphanized and seems to respond to two unrelated families of endogenous ligands: extracellular nucleotides and cysteinyl-leukotrienes.

In the last years many efforts have been directed toward the discovery of potent and selective ligands of P2 receptors and many of them have been obtained by structural modification of ATP. In particular, the 2-phenylethynylATP has been reported to antagonize the P2Y1-mediated platelet aggregation induced by ADP. Moreover, it behaves as strong agonist (EC50 = 0.036 nM) of the P2Y-like receptor GPR17.2 On the other hand, the ATP analogue 2',3'-O-(2,4,6-trinitrophenyl)adenosine-5'-triphosphate (TNP-ATP), resulted a very potent antagonist of the P2X1, P2X3, and heteromeric P2X2/3 receptors.

Based on these observations and in the search of new ligands, new ATP derivatives substituted at the 2- and N6-positions, including stable analogues, have been designed and synthesized together to novel ATP analogues bearing cycloalkyl or arylalkyl substituents replacing the trinitrophenyl moiety of TNP-ATP.3

Biological assays demonstrated that the 2 substituted ATP behave as potent ligand of GPR17, while the TNP-ATP analogues result potent (nanomolar range) antagonists of the P2X3 receptors.

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