

## **ANTI-NOCICEPTIVE EFFECTS OF NOVEL HIGHLY POTENT A2A ADENOSINE RECEPTOR INVERSE AGONISTS**

1)Vincenzi F. 2)Varano F. 3)Ravani A. 4)Pasquini S. 5)Merighi S. 6)Gessi S. 7)Catarzi D. 8)Colotta V. 9)Borea PA. 10)Varani K.

*University of Ferrara*

Despite opioids remain the most effective drugs for the treatment of pain, their use is often associated with numerous side effects highlighting a need for the development of new analgesics (Passik and Webster, 2014). The study of A2A adenosine receptor and its pharmacological modulation is a growing area of research where A2A antagonists and inverse agonists open new therapeutic frontiers for the treatment of neurodegenerative diseases and pain (Borea et al., 2016; Varano et al., 2016). In this study, we describe the synthesis of novel N5-arylmethyl-2-(furan-2-yl)-thiazolo[5,4-d]pyrimidine-5,7-diamines and their pharmacological characterization by using in vitro and in vivo assays. In competition binding experiments the new compounds emerged as outstanding ligands showing two affinity values for the A2A receptor with the high affinity  $K_i$  value (nM) in the femtomolar range. The in vitro functional activity assays, performed by using cyclic AMP experiments, assessed that they behaved as potent inverse agonists at the A2A receptor, but not at the other adenosine receptor subtypes. The novel compounds were evaluated for their anti-nociceptive activity in acute experimental models of pain such as writhing and hot water tail immersion tests. The acetic acid-induced writhing response was performed after intraperitoneal injection of 10 ml/kg of 0.6% acetic acid solution where a writhing is indicated by stretching of the abdomen followed by the extension of the hind limbs (Vincenzi et al., 2014). The warm-water tail immersion assay was performed using a water bath with the temperature maintained at 52°C. Interestingly, the novel A2A inverse agonists showed an anti-nociceptive effect equal to or major than morphine in the writhing test as well as in the hot water tail immersion test. Moreover they revealed a more evident analgesic effect than the typical A2A antagonist/inverse agonist ZM 241385. Overall, these novel inverse agonists might represent potential drug candidates for an alternative approach to the management of pain.

Passik & Webster (2014). *J Opioid Manag.* 10, 263-275.

Borea et al. (2016). *Trends Pharmacol Sci.* 37, 419-434.

Varano et al. (2016). *J Med Chem.* 59, 10564-10576.

Vincenzi et al. (2014). *Neuropharmacology* 81, 6-14.