

## Accepted Manuscript

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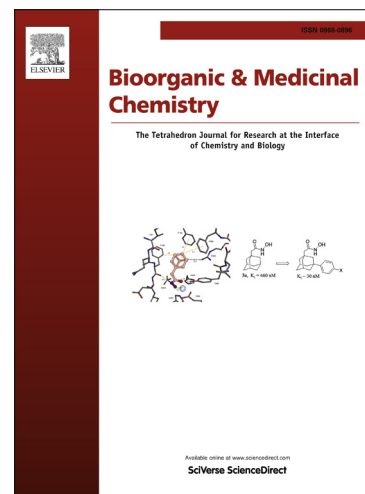
PII: S0968-0896(13)00823-7  
DOI: <http://dx.doi.org/10.1016/j.bmc.2013.09.043>  
Reference: BMC 11127

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 31 July 2013  
Revised Date: 9 September 2013  
Accepted Date: 17 September 2013

Please cite this article as: Thomas, R., Lee, J., Chevalier, V., Sadler, S., Selesniemi, K., Hatfield, S., Sitkovsky, M., Ondrechen, M.J., Jones, G.B., Design and Evaluation of Xanthine Based Adenosine Receptor Antagonists: Potential Hypoxia Targeted Immunotherapies, *Bioorganic & Medicinal Chemistry* (2013), doi: <http://dx.doi.org/10.1016/j.bmc.2013.09.043>

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## Design and Evaluation of Xanthine Based Adenosine Receptor Antagonists: Potential Hypoxia Targeted Immunotherapies

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**Abstract:** Molecular modeling techniques were applied to the design, synthesis and optimization of a new series of xanthine based adenosine A<sub>2A</sub> receptor antagonists. The optimized lead compound was converted to a PEG derivative and a functional *in vitro* bioassay used to confirm efficacy. Additionally, the PEGylated version showed enhanced aqueous solubility and was inert to photoisomerization, a known limitation of existing antagonists of this class.

### Introduction

The adenosine receptors are a class of GPCR's divided into four subtypes, A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, and A<sub>3</sub>, differentiated based on their pathways of signal transduction.<sup>1</sup> Activation of A<sub>1</sub>R and A<sub>3</sub>R induces coupling to G<sub>i</sub> pertussis-toxin sensitive proteins causing downregulation of adenylate cyclase while activation of the A<sub>2A</sub>R and the A<sub>2B</sub>R results in G<sub>s</sub> protein coupling and subsequent upregulation of adenylate cyclase.<sup>1</sup> These mechanisms result in control of intracellular cAMP levels. Additionally, adenosine receptors, when bound to other G proteins, play a role in the control of ion channels via protein kinases and phospholipase C (PLC) activity.<sup>1a,1c</sup> Until recently, homology models of the four AR subtypes (based on the X-ray structure of rhodopsin)

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