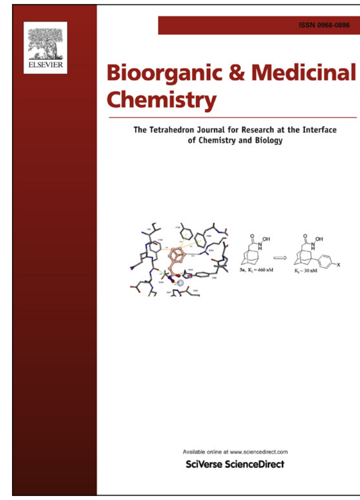

Design and Evaluation of Xanthine Based Adenosine Receptor Antagonists: Potential Hypoxia Targeted Immunotherapies

Rhiannon Thomas, Joslynn Lee, Vincent Chevalier, Sara Sadler, Kaisa Selesniemi, Stephen Hatfield, Michail Sitkovsky, Mary Jo Ondrechen, Graham B. Jones

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

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

Rhiannon Thomas,[1] Joslynn Lee,[1] Vincent Chevalier,[1] Sara Sadler,[1] Kaisa Selesniemi,[2] Stephen Hatfield,[2] Michail Sitkovsky,[2] Mary Jo Ondrechen,[1] and Graham B. Jones[1] *

[1]Bioorganic and Medicinal Chemistry Laboratories, Department of Chemistry and Chemical Biology, Northeastern University, 360 Huntington Avenue, Boston, MA, 02115 Fax: 617-373-8795 Email: gr.jones@neu.edu [2]New England Tissue Protection Institute, Northeastern University, 360 Huntington Avenue, Boston, MA, 02115

Abstract: Molecular modeling techniques were applied to the design, synthesis and optimization of a new series of xanthine based adenosine A2A 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_1, A_{2A}, A_{2B}, and A_3, differentiated based on their pathways of signal transduction.[1] Activation of A_1R and A_3R induces coupling to G_i pertussis-toxin sensitive proteins causing downregulation of adenylate cyclase while activation of the A_{2A}R and the A_{2B}R results in G_s protein coupling and subsequent upregulation of adenylate cyclase.[1] 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.[1a,1c] Until recently, homology models of the four AR subtypes (based on the X-ray structure of rhodopsin)