

Accepted Manuscript

Discovery and synthetic optimization of a novel scaffold for hydrophobic tunnel-targeted autotaxin inhibition

Lauren E. Ragle, Dilip J. Palanisamy, Margaux J. Joe, Rachel S. Stein, Derek D. Norman, Gabor Tigyi, Daniel L. Baker, Abby L. Parrill

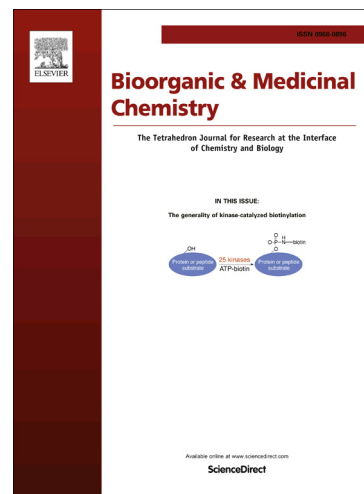
PII: S0968-0896(16)30597-1
DOI: <http://dx.doi.org/10.1016/j.bmc.2016.08.004>
Reference: BMC 13187

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 2 May 2016
Revised Date: 1 August 2016
Accepted Date: 3 August 2016

Please cite this article as: Ragle, L.E., Palanisamy, D.J., Joe, M.J., Stein, R.S., Norman, D.D., Tigyi, G., Baker, D.L., Parrill, A.L., Discovery and synthetic optimization of a novel scaffold for hydrophobic tunnel-targeted autotaxin inhibition, *Bioorganic & Medicinal Chemistry* (2016), doi: <http://dx.doi.org/10.1016/j.bmc.2016.08.004>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Discovery and synthetic optimization of a novel scaffold for hydrophobic tunnel-targeted autotaxin inhibition

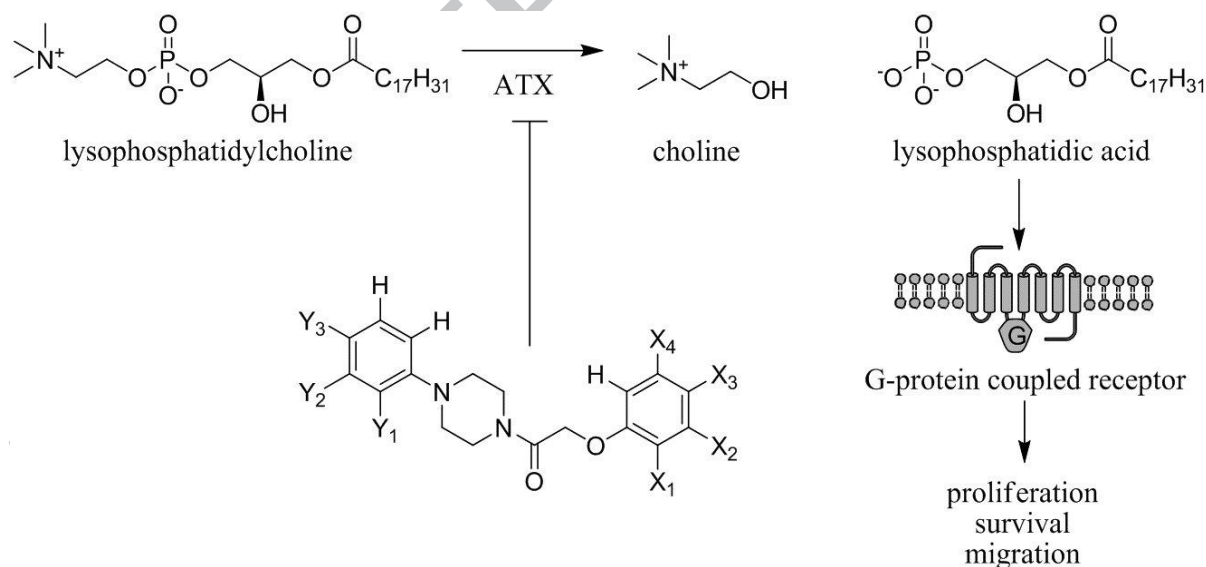
Lauren E. Ragle¹, Dilip J. Palanisamy¹, Margaux J. Joe¹, Rachel S. Stein¹, Derek D. Norman², Gabor Tigyi², Daniel L. Baker¹, Abby L. Parrill¹

¹Department of Chemistry, University of Memphis, 3744 Walker Avenue, Memphis, TN 38152

²Department of Physiology, University of Tennessee Health Sciences Center, 894 Union Avenue, Memphis, TN 38163

Abstract

Autotaxin (ATX) is a ubiquitous ectoenzyme that hydrolyzes lysophosphatidylcholine (LPC) to form the bioactive lipid mediator lysophosphatidic acid (LPA). LPA activates specific G-protein coupled receptors to elicit downstream effects leading to cellular motility, survival, and invasion. Through these pathways, upregulation of ATX is linked to diseases such as cancer and cardiovascular disease. Recent crystal structures confirm that the catalytic domain of ATX contains multiple binding regions including a polar active site, hydrophobic tunnel, and a hydrophobic pocket. This finding is consistent with the promiscuous nature of ATX hydrolysis of multiple and diverse substrates and prior investigations of inhibitor impacts on ATX enzyme kinetics. The current study used virtual screening methods to guide experimental identification and characterization of inhibitors targeting the hydrophobic region of ATX. An initially discovered inhibitor, GRI392104 (IC₅₀ 4 μM) was used as a lead for synthetic optimization. In total twelve newly synthesized inhibitors of ATX were more potent than GRI392104 and were selective for ATX as they had no effect on other LPC-specific NPP family members or on LPA₁₋₅ GPCR.



Keywords: autotaxin; structure-activity relationship; pharmacophore

Download English Version:

<https://daneshyari.com/en/article/7777797>

Download Persian Version:

<https://daneshyari.com/article/7777797>

[Daneshyari.com](https://daneshyari.com)