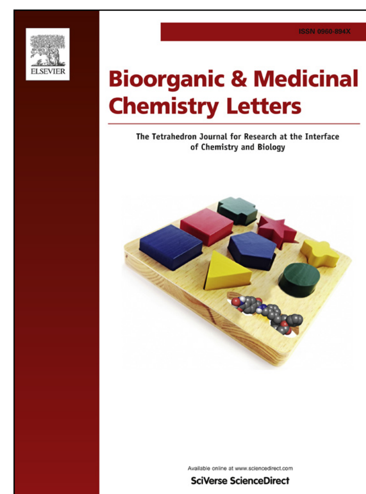
Accepted Manuscript



Novel bivalent inhibitors with sub-nanomolar affinities towards human glyoxalase I

Yankui Sang, Qing Shi, Mingguang Mo, Caixia Ni, Zonghe Li, Bichong Liu, Qishan Deng, Donald J. Creighton, Zhe-Bin Zheng

PII: S0960-894X(15)30007-X
DOI: http://dx.doi.org/10.1016/j.bmcl.2015.08.055
Reference: BMCL 23049

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 30 June 2015
Revised Date: 14 August 2015
Accepted Date: 20 August 2015

Please cite this article as: Sang, Y., Shi, Q., Mo, M., Ni, C., Li, Z., Liu, B., Deng, Q., Creighton, D.J., Zheng, Z-B., Novel bivalent inhibitors with sub-nanomolar affinities towards human glyoxalase I, *Bioorganic & Medicinal Chemistry Letters* (2015), doi: http://dx.doi.org/10.1016/j.bmcl.2015.08.055

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.

ACCEPTED MANUSCRIPT

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

Novel bivalent inhibitors with sub-nanomolar affinities towards human glyoxalase I

Yankui Sang[a], Qing Shi[a], Mingguang Mo[a], Caixia Ni[a], Zonghe Li[a], Bichong Liu[a], Qishan Deng[a], Donald J. Creighton[b*], Zhe-Bin Zheng[a*]

[a]*Department of Antibiotic Research & Re-evaluation, Key Laboratory of Sichuan Province, Sichuan Industrial Institute of Antibiotics, Chengdu University, Huaguan Road 168, Chengdu City, Sichuan Province 610052, P.R. China*
[b]*Department of Chemistry & Biochemistry, University of Maryland Baltimore County, 1000 Hilltop Circle, Baltimore, MD, 21250, USA*

ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
Glyoxalase I
Bivalent inhibitor
linker
Methylglyoxal

ABSTRACT

The zinc metalloenzyme glyoxalase I (GlxI) catalyzes the glutathione-dependent inactivation of cytotoxic methylglyoxal. Two competitive bivalent GlxI inhibitors, polyBHG2-62 (K_i = 1.0 nM) and polyBHG2-54 (K_i = 0.3 nM), were synthesized based on the transition-state analog *S*-(*N*-bromophenyl-*N*-hydroxycarbamoyl) glutathione (BHG). The most effective inhibitor, polyBHG2-54, is the first subnanomolar inhibitor of GlxI, and is over 50-fold more potent than BHG itself.

Human glyoxalase I (GlxI) is a 42 kDa[1] dimeric Zn^{2+} metalloenzyme that detoxifies methylglyoxal *in vivo* by converting it into *S*-D-lactoylglutathione, which is then converted to D-lactate by glyoxalase II.[2,3] Since high activities of GlxI are present in tumor tissues, inhibitors of GlxI increase the accumulation of cytotoxic methylglyoxal, which results in significant anti-tumor activity both *in vitro* and *in vivo*.[4] A potent and selective GlxI inhibitor could therefore potentially result in an adjuvant to restore chemotherapy sensitivity in tumor cells.[5,6]

Linking two identical binding groups by a spacer unit has been proposed[7] to improve both the selectivity and the activity of inhibitors compared with the corresponding univalent ligands, and this approach has been verified experimentally.[8-10] However, optimization of the spacer unit between the binding groups remains a challenge, and is crucial in fragment-based drug design.[11] In this paper, we extend our previous work on bivalent transition-state analog inhibitors of human glyoxalase I (hGlxI)[10] to include two new competitive bivalent GlxI inhibitors in which symmetric ligands are linked by linkers that differ in flexibility, length, and water solubility.

We previously developed a new class of competitive inhibitors of homodimeric human glyoxalase I by cross-linking two molecules of the transition state analog *S*-(*N*-chlorophenyl-*N*-hydroxycarbamoyl)glutathione (CHG) through their γ-glutamyl-NH_2 groups with poly-β-alanyl tethers of different length: $[CHG(\beta\text{-ala})_n]$ suberate diamide (n = 1−7). The strongest inhibitors of this antitumor target enzyme likely bind simultaneously to the active site on each subunit, and give K_i values as low as 0.96 nM (n = 6), a 50-fold tighter binding than the monomer inhibitor CHG (K_i = 46 nM).[5,12] Cross-linking not only improves the binding affinity, but also improves the selectivity by almost 100-fold for human GlxI (hGlxI) relative to yeast GlxI (yGlxI). In the X-ray crystal structure of the hGlxI complex with CHG, the γ-glutamyl-NH_2 groups are exposed to solvent, and are about 30 Å apart. However, a 70–80 Å tether length was found to give the best inhibition.

Nevertheless, these inhibitors have two drawbacks that need to be addressed: amidation of the γ-glutamyl-NH_2 groups decreases the binding affinity by 7 to 13-fold, and the bivalent inhibitors have low solubility, making them unable to cross the cell membrane. In this work, we modify the linker by replacing the amide groups with ethylcarbonyl groups, which do not affect the binding affinity of CHG. Two new inhibitors based on *S*-(*N*-bromophenyl-*N*-hydroxycarbamoyl) glutathione (BHG)[5,12] exhibit inhibition constants of 1 nM or less, and one of these

∗ Corresponding author Tel.: +86-28-8421-5041(Z-B. ZH);
E-mail: zhebinzheng@hotmail.com

Download English Version:

https://daneshyari.com/en/article/10593604

Download Persian Version:

https://daneshyari.com/article/10593604

Daneshyari.com