Accepted Manuscript

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PII: S0003-9861(18)30347-3

DOI: 10.1016/j.abb.2018.07.001

Reference: YABBI 7764

To appear in: *Archives of Biochemistry and Biophysics*

Received Date: 2 May 2018

Revised Date: 5 June 2018

Accepted Date: 2 July 2018

Please cite this article as: A. Tramonti, A. Paiardini, A. Paone, A. Bouzidi, G. Giardina, G. Guiducci, M.C. Magnifico, S. Rinaldo, L. McDermott, J.A. Menendez, R. Contestabile, F. Cutruzzolà, Differential inhibitory effect of a pyrazolopyran compound on human serine hydroxymethyltransferase-amino acid complexes, *Archives of Biochemistry and Biophysics* (2018), doi: 10.1016/j.abb.2018.07.001.

Differential inhibitory effect of a pyrazolopyran compound on human serine hydroxymethyltransferase-amino acid complexes.

Angela Tramonti[a,b] , Alessandro Paiardini[b], Alessio Paone[b], Amani Bouzidi[b], Giorgio Giardina[b], Giulia Guiducci[b], Maria Chiara Magnifico[b], Serena Rinaldo[b], Lee McDermott[c], Javier A. Menendez[d,e] Roberto Contestabile[b*], Francesca Cutruzzolà[b*]

[a]Istituto di Biologia e Patologia Molecolari, Consiglio Nazionale delle Ricerche, Piazzale Aldo Moro 5, 00185 Roma, Italy.

[b]Dipartimento di Scienze Biochimiche "A. Rossi Fanelli", Sapienza Università di Roma, Piazzale Aldo Moro 5, 00185 Roma, Italy.

[c]Department of Pharmaceutical Sciences and Drug Discovery Institute, University of Pittsburgh, Pittsburgh, PA 15261, USA

[d]Program Against Cancer Therapeutic Resistance (ProCURE), Metabolism and Cancer Group, Catalan Institute of Oncology, Girona, Catalonia, Spain

[e]Molecular Oncology Group, Girona Biomedical Research Institute (IDIBGI), Girona, Spain

* Corresponding authors. Dipartimento di Scienze Biochimiche "A. Rossi Fanelli", Sapienza Università di Roma, Piazzale Aldo Moro 5, 00185 Roma, Italy. E-mail address: roberto.contestabile@uniroma1.it; francesca.cutruzzola@uniroma1.it

Abstract

Serine hydroxymethyltransferase (SHMT) is a pivotal enzyme in one-carbon metabolism that catalyses the reversible conversion of serine and tetrahydrofolate into glycine and methylenetetrahydrofolate. It exists in cytosolic (SHMT1) and mitochondrial (SHMT2) isoforms. Research on one-carbon metabolism in cancer cell lines has shown that SHMT1 preferentially catalyses serine synthesis, whereas in mitochondria SHMT2 is involved in serine breakdown. Recent research has focused on the identification of inhibitors that bind at the folate pocket. We have previously found that a representative derivative of the pyrazolopyran scaffold, namely 2.12, inhibits both SHMT isoforms, with a preference for SHMT1, causing apoptosis in lung cancer cell lines. Here we show that the affinity of 2.12 for SHMT depends on the identity of the amino acid substrate bound to the enzyme. The dissociation constant of 2.12 is 50-fold lower when it binds to SHMT1 enzyme-serine complex, as compared to the enzyme-glycine complex. Evidence is