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Design and synthesis of inhibitors of cysteine protease γ-glutamyl hydrolase

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Abstract

Folic acid and its derivatives are important for metabolic processes crucial to human health. Intracellular polyglutamylation of folates and antifolates is performed in a reaction catalyzed by an ATP-dependent enzyme folylpolyglutamate synthetase (FPGS, EC 6.3.2.17), whereas the reverse process, hydrolysis of folylpolyglutamates to monoglutamyl derivatives occurs in a reaction catalyzed by a cysteine protease, γ-glutamyl hydrolase (GH, EC 3.4.22.17). GH is a lysosomal and secreted glycoprotein that is very selective for γ -glutamyl peptide bonds. GH is overexpressed in cancerous hepatic and breast tissue. Tumor cells having high levels of GH are inherently resistant to classical antifolates. Proper function of γ-glutamyl hydrolase is very important for the homeostasis of folylpolyglutamate and antifolate pharmacology. The mechanism of GH-catalyzed amide bond hydrolysis is similar to that of the cysteine protease, papain. Earlier it was shown that the natural peptidyl epoxide E-64 can function as an inhibitor for cysteine proteases, e.g., cathepsin, papain, ficin, etc. In an effort to understand the detailed function of GH, we have synthesized novel internal γ-glutamyl peptidyl epoxides, **1** and **2**, as inhibitors for GH (Figure 1). In these molecules, the scissile amide bonds have been replaced by an internal epoxide functionality so that they will be devoid of substrate type activity. At the same time, the epoxide functionality will act as an electrophile in the active site which, in the presence of a general acid, will allow nucleophilic attack by the cysteine thiol on the epoxide functionality thus leading to irreversible inhibition of GH.

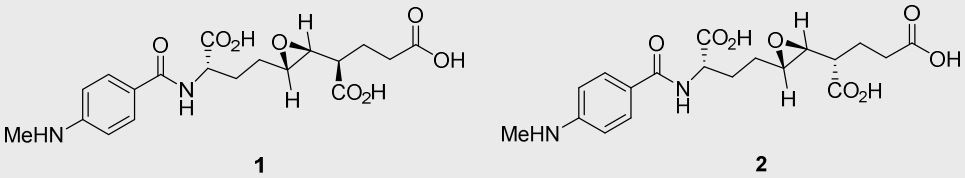


Figure 1: Peptidyl epoxides as inhibitors for γ -glutamyl hydrolase

Biography

Debatosh Majumdar has completed his PhD from the Complex Carbohydrate Research Center at the University of Georgia. He worked on the design and synthesis of biologically important carbohydrates and glycopeptides. He was a research fellow at the University of Michigan Ann Arbor, where he worked on the design and synthesis of cysteine protease inhibitors. Then he worked on cancer therapy and cancer nanomedicine at Emory Winship Cancer Institute. Now, Debatosh is a scientist at Glycosyn LLC, a premier biopharmaceutical company. He has published many papers and book chapters, and has been serving as an editorial board member of the World Journal of Organic Chemistry, and reviewers of Frontiers in Bioscience, PLoS ONE, the World Journal of Organic Chemistry, and others.