DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION OF A SMALL-MOLECULE INHIBITOR OF THE HISTONE ACETYLTRANSFERASE GCN5

Jana Fischer[a], Markus Biel[a], Athanassios Giannis[a,*], A. Kretsovali[b], E. Karatzali[b], J. Papamatheakis[b]

[a]Institute of Organic Chemistry, University of Leipzig, 04103 Leipzig, Germany
[b]Institute of Molecular Biology and Biotechnology, FORTH, 71110 Heraklion, Greece

Histone proteins are basic components of the eukaryotic chromatin [1]. They contain a DNA-interacting globular domain and a more flexible N-terminal region, which is a target for several posttranslational modifications. These include the acetylation of lysine residues and the methylation of lysine and arginine residues as well as the phosphorylation of serine hydroxyl functions and the attachment of an ubiquitin group [2]. The "histone-code hypothesis" is based on the assumption that these modifications create a specific substitution pattern on the histone tails. This pattern is readable by regulatory proteins, which connect the histone code with fundamental cellular processes like activation or repression of transcription. To date, acetylation is the best studied histone modification. It has been shown that the adjustment of a specific acetylation balance on the histone *N*-termini within a particular gene region is the result of a highly regulated interplay of selective histone acetyltransferases (HATs) and histone deacetylases (HDACs) [1].
For decoding the histone code a carefully directed influence on fine-tuning these processes through the development of low-molecular-weight and cell-permeable inhibitors is of extraordinary importance. Furthermore new inhibitors may open up new possibilities for treatment of pathological diseases like cancer [1]. In contrast to the HATs, several small molecule inhibitors of the HDACs are known, and some of them are in clinical trials [3]. Recently, anacardic acid was identified in a broad screening of plant extracts with antitumor activity as the first small-molecule inhibitor of the HAT p300 [4].
Here, we describe the development and biological evaluation of the first small-molecule inhibitor, structurally based on the α-methylene-γ-butyrolactone motif, of the human histone acetyltransferase Gcn5, a prominent member of the GNAT family with high preference for histone H3 as a substrate. The affinity of this inhibitor to the Gcn5 enzyme is comparable to that of the natural substrate H3 and provides an excellent starting point for the study of structure–activity relationships [5].

[1] M. Biel, V. Wascholowski, A. Giannis, *Angew. Chem.Int. Ed.* **2005**, in press.
[2] M. Biel, V. Wascholowski, A. Giannis, *Angew. Chem.Int. Ed.* **2004**, *43*, 6414-6416.
[3] T. A. Miller, D . J. Witter, S. Belvedere, *J. Med. Chem.* **2003**, *46*, 5097 – 5116.
[4] K. Balasubramanyam, V. Swaminathan, A. Ranganathan, T. K. Kundu, *J. Biol. Chem.* **2003**, *278*, 19134 – 19140.
[5] M. Biel, A. Kretsovali, E. Karatzali, J. Papamatheakis, A. Giannis, *Angew. Chem. Int. Ed.* **2004**, *43*, 3974 –3976.