

## DELINEATING MECHANISMS OF PROCESSING MANNOSIDASES USING NOVEL SYNTHETIC INHIBITORS

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The mode-of-action of the two processing mannosidases, ER Mannosidase I and human Golgi mannoside II (HGMII), are probed using various synthetic inhibitors.<sup>1-5</sup> Rapid syntheses of these chemical probes is described as well as their inhibitory activity against a number of human glycosidases. Amongst the molecules touched upon is a family of polyhydroxylated sulfonium salts, one of which inhibits a cloned, human lysosomal mannosidase with a  $K_i$  of 800 nM and is thus seen to be the most potent synthetic sulfonium salt described to date.<sup>1,2</sup> Also described is a pyrrolopyrimidinone that shows a marked inhibition of HGMII in preference to its lysosomal counterpart.<sup>3</sup> This remarkable selectivity provides hope that an  $\alpha$ -mannosidase inhibitor might be developed which does not manifest the severe complications which invariably accompany the use of swainsonine or mannostatin as a putative cancer therapeutic.<sup>4</sup> The possible modes-of-inhibition of a number of the inhibitor classes will be discussed in the light of their thermodynamics of binding (ITC studies) as well as their structures in solution and when enzyme-bound.

- [1] A. Siriwardena, et al, *ChemBiochem*, **2005**, *in press*
- [2] J. Gonzalez-Outereirino, et al, *J. Am. Chem. Soc.*, **2004**, *126*, 6866
- [3] B. Li et al., *ChemBiochem*, **2005**, *in press*
- [4] J. Glushka et al, *Angew. Chem. Int. Ed.*, *submitted*
- [5] K. Karaveg et al, *J. Biol. Chem.*, **2005**, *in Press*