New Class of Proteasome 20S Inhibitors: a Crystallographic and Molecular Modelling Study

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26S proteasome represents the multicatalytic proteinase of the ubiquitin/adenosine triphosphate-dependent proteolytic pathaway. This large enzymatic complex is found in the cytosol and nucleus of eukaryotic cells, and plays a central role in the selective degradation of intracellular proteins. The 20S proteasome is a kind of proteolytic chamber formed by four stacked rings, where each of the two inner rings is made up of seven different β subunits. Proteasomes remove abnormal proteins and play a role in cell-cycle progression and apoptosis, representing thus a potential target for the development of therapeutic agents for the treatment of pathologies such as cancer, inflammation, immune diseases.

Very recently the synthesis and biological characterization of a new series of vinyl ester tripeptides acting as proteasome inhibitors have been reported [1]. In this communication we present the crystallographic structures of two of them, together with a conformational study of the molecules in the solid state, *in vacuum* and in a polar environment which is in turn the basis for a docking study of such inhibitors to the crystallographic structure of the 20S proteasome[2] in order to define the inhibitor-enzyme interaction subsite pockets.

[1] Marastoni M., et al., *J. Med. Chem*., 2005, *in press*. [2] Groll M., Koguchi Y., Huber R., Kohno J., *J. Mol. Biol*., 2001, **311**, 543.

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