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Macrophagic Metalloelastase (MMP-12): determinants of ligand binding

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The interaction of 10 high affinity ligands with the catalytic domain of MMP-12 has been investigated by using an integrated approach were the structural data have been correlated with the thermodynamic parameters. Therefore crystals of MMP-12 have been soaked with the different ligands and the structures solved by x-ray.
The Ki obtained by enzymatic assay have been compared with the dissociation constant provided by isothermal titration microcalorimetry measurements. For each ligand the values of ΔH^0 and ΔS^0 have been qualitatively correlated with the structural features of the complex with the protein.
The analysis has provided an accurate value of the contribution of the hydroxamic moiety to the overall affinity, that for many of the molecules, seems to be of the same order of the lipophilic group interacting with the $S1^{'}$ cavity.
Through the use of this extensive set of data of data it has been possible to qualitatively relate the ΔG^0 values to the structural features by visual inspection of Van der Waals and electrostatic contacts.

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dSNAP: Applications of cluster analysis to real chemical and structural problems

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The amount of structural and chemical information available within the Cambridge Structural Database (CSD) is reaching enormous proportions. Despite efficient and user-friendly searching and visualisation algorithms, it can still be daunting for the structural analyst to process the many hundreds or even thousands of structural fragments obtained from a simple search. We have recently established the use of highly automated, highly visual cluster analysis methods as a tool for analysing these large datasets [1]. Cluster analysis using dendrograms, metric multidimensional scaling and suitable visualization tools can reduce the workload of analysing a large (few thousand fragment) dataset to a few hours with minimal user intervention, and thus minimal user bias. The real beauty of the method is in its interactivity and scalability, allowing the user to go from an overview of the entire dataset and easily spot any outliers or errors, to the ability to 'drill down' within a cluster, looking at progressively more detailed differences between different fragments. The methods are implemented in the computer program *d*SNAP [1].
In this poster we show how these methods can be applied to real chemical problems - from simple organic conformational questions to intermolecular interactions, and including studies of ligand-metal interactions. The examples range from small datasets of around 50 fragments to large datasets containing many thousands of geometries. The examples include many recently published or in the process of being published [1-3], as well as current problems being investigated. If you are interested in seeing in greater detail how the methods work after visiting this poster, then we will be very happy to demonstrate on the datasets above or on fragments of particular interest to you.
The dSNAP software is available free of charge to all interested researchers from the Bruker-AXS website at http://www.bruker-axs.de.

[1] G. Barr, W. Dong, C. J. Gilmore, A. Parkin and C. C. Wilson,. *J. Appl. Cryst*,. 2005, 38, 833-841.
[2] A. Parkin, G. Barr, W. Dong, C.J. Gilmore and C. C. Wilson,. *Cryst. Eng. Comm.*, 2006, 8, 257-264.
[3] A. Parkin, G. Barr, W. Dong, C.J. Gilmore, P. A. Tasker and C. C. Wilson,. *Dalton Trans.*, 2006, Submitted for publication.