

and other beta-pore-forming toxins. This homology and its trimeric form will allow us to make some conclusions regarding the formation of complexes with Claudin at tight junctions.

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**Keywords:** toxin, food, hairpin

## MS.17.1

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### Designer enzymes

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Protein design is a challenging problem. We do not fully understand the rules of protein folding, and our knowledge of structure-function relationships in these macromolecules is at best incomplete. Nature has solved the problem of protein design through the mechanism of Darwinian evolution. From primitive precursors, recursive cycles of mutation, selection and amplification of molecules with favorable traits have given rise to all of the many thousands of gene products in every one of our cells. An analogous process of natural selection can be profitably exploited in silico and in the laboratory on a human time scale to create, characterize and optimize artificial catalysts for tasks unimagined by Nature. Recent progress in combining computational and evolutionary approaches for enzyme design will be discussed, together with insights into enzyme function gained from studies of the engineered catalysts.

**Keywords:** enzyme, computational design, evolution

## MS.17.2

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### Molecular probes as starting point for structure-based lead development

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In addition to high-throughput screening and structure-based drug design, fragment-based approaches have recently become increasingly popular for lead development in pharmaceutical drug research. Here, a small but well selected library of low molecular weight compounds (< 300 Da) is screened by biophysical methods such as surface plasmon resonance (SPR), nuclear magnetic resonance (NMR) or X-ray crystallography.

In this study, we started with even smaller, highly-soluble probe molecules, such as aniline, urea, N-methylurea, propanediol, bromophenol and phenol. These probe molecules were selected to experimentally map out protein binding pockets by detecting hot spots of binding with respect to hydrophobic and hydrophilic properties. Furthermore, they should be applicable to a wide range of target proteins. As model protein the zinc protease thermolysin

was selected. Subsequently, our studies were extended to additional proteins such as protein kinase A (PKA), D-xylose isomerase (DXI), 4-diphosphocytidyl-2C-methyl-D-erythritol synthase (IspD) and the aspartyl protease endothiapepsin (ETP). The obtained crystal structures clearly show that the probe molecules could be located in these protein binding pockets. These probe molecules form similar interactions as larger ligands containing analogical chemical features and therefore are deemed suitable for hotspot detection.

Next, the structure of PKA in complex with phenol was used as template for docking of a virtual in-house fragment library of about 4000 entries. With one promising candidate a crystal structure was subsequently determined. Using the structural information and the experimental hot spot analysis, a putative lead skeleton was obtained that was translated into a synthetically accessible compound class. Of the synthesized compound series, one first representative showed an affinity of 70  $\mu$ M. Based on this complex structure further lead optimization is in progress.

**Keywords:** probe molecules, fragments, drug design

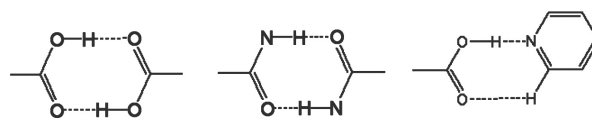
## MS.17.3

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### Supramolecular synthons in crystal engineering

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Crystal engineering deals with creation of novel materials using controlled arrangements of molecules in the crystal lattice using intermolecular interactions.[1], [2] Various common functional groups such as carboxylic acids, amides, phenols and other weak hydrogen bonding functional groups known to form certain recognition motifs in a repetitive manner (Scheme 1). These motifs were termed as supramolecular synthons signifying the importance of such motifs in the aggregation of molecules in the crystal lattice. Supramolecular synthons are defined by Desiraju as “structural units within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interaction” [1]. In this talk the utility of synthons and robustness and interference effects of popular synthons will be discussed in detail by using some of our recent results [3-11]. Further the discovery of new synthons and transfer of supramolecular synthons observed in organic molecules into coordination polymers will also be discussed.



Scheme 1: Popular strong hydrogen bonding synthons

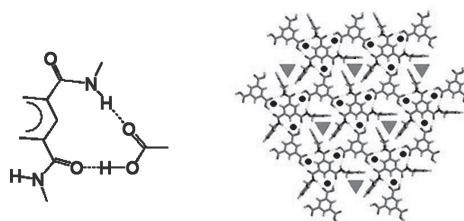


Figure 1: A new robust synthon in the generation of two-dimensional layer between two chemical components.

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**Keywords:** hydrogen bonding, supramolecular synthons, coordination networks

## MS.17.4

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### Cocrystallization of amino acids

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Cocrystals are multi-component systems where intermolecular interactions are used to form supramolecular networks containing more than one molecular entity. Cocrystals offer potential benefits in manufacturing of Active Pharmaceutical Ingredients in solid state with improved pharmaceutical properties like solubility, stability, manufacturability and bioavailability.

A series of hydrophobic amino acids L- Leucine, L- Isoleucine and L- Valine were selected to develop cocrystals by employing different crystallization strategies under various conditions of temperature and pressure. Crystals suitable for single crystal X-Ray diffraction were grown and the structures of these novel forms were resolved. Raman spectroscopy was also used to aid in the identification of these new forms. The final structures were compared to the pure forms of the amino acids so that structural similarities could be drawn.

**Keywords:** amino acids, cocrystallization, X-ray diffraction

## MS.17.5

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### The XPac dissimilarity index as a quantitative descriptor of isostructurality

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We investigate the crystal structures formed by closely related organic molecules. In this way, it should be possible to examine the effects of incremental changes in molecular shape, van der Waals interactions and other, more directed intermolecular forces on the crystal packing. A  $9 \times 8$  matrix of 4,4'-benzenesulfonamido-2-pyridines was obtained by the systematic variation of the substituents  $R^1$  at the benzene and  $R^2$  at the pyridine ring.  $R^1$  and  $R^2$  can be CN, CF<sub>3</sub>, I, Br, Cl, F, Me or H (and  $R^1$  additionally OMe). 103 crystal structures were determined in total, at least one for each of the 72 compounds investigated. The computer program XPac [1] was used to establish the packing relationships between individual crystal structures.

One particular 1D stack of N-H...N bonded dimers was identified as the common building block of 37 crystals. These in turn belong to eight distinct 3D packing types. The most frequent of these fundamental structure types comprises all compounds with  $R^1 = \text{CF}_3, \text{I}, \text{Br}, \text{Cl}, \text{F}$ ,

Me, H and  $R^2 = \text{CF}_3$  or I. Thus, this fundamental 3D crystal packing arrangement is maintained even if  $R^1 = \text{H}$  is exchanged against  $R^1 = \text{I}$ , which leads to an approximate doubling of the effective distance at  $R^1$  and increases the molecular volume by 11 %.

A detailed picture of the incremental changes in geometry that occur within this series of 14 isostructures was obtained from matrix maps. These are collections of XPac dissimilarity indices  $x$  which have been calculated for individual crystal structure pairs. An inspection of XPac  $\delta$ -plots provides additional information. It was found that the structural change in this series is predominantly translational and occurs in the direction of the crystallographic  $c$ -axes, which lies approximately parallel to the C-R<sup>1</sup> bond. Within the common 1D stack of N-H...N bonded dimers, the relative orientation of the molecules varies with the volume of  $R^1$ .

The analogous geometrical analysis of another series from the same compound class showed that in this case a common basic 3D packing arrangement is maintained only approximately and with substantial geometrical alterations. Therefore, the relationship between these crystals is homeostructural rather than isostructural.

This systematic investigation of 4,4'-benzenesulfonamido-2-pyridines provides a set of universal reference values for the study of packing similarity in molecular crystals.

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**Keywords:** packing, isostructurality, polymorphism

## MS.18.1

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### Structure of nanosized crystals by total x-ray diffraction

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Nanosized crystals show diffraction patterns with a few, if any, Bragg-like peaks and a pronounced diffuse component that are difficult to be analyzed in the traditional way. The problem has a solution based on an approach involving high-energy x-ray diffraction coupled to atomic pair distribution functions analysis [1]. In the talk, the foundations of the approach will be introduced and its great potential in characterizing the atomic scale structure, size and shape of nanosized crystals illustrated with examples from several recent studies [2-6].

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**Keywords:** nano, WAXS, structure

## MS.18.2

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### Contrasting $p$ and $T$ -induced amorphization using ZrW<sub>2</sub>O<sub>8</sub> and ZIF-4 as case studies

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