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Monoamine oxidases (MAOs) and the histone demthylase LSD1 are evolutionarily related enzymes that catalyze the oxidative deamination of their substrates. They represent a spectacular example of how similarities in the chemistry of the catalyzed reaction can constrain evolution, despite different biological functions and cellular localizations. MAOs bind the outer mitochondrial membrane and play a central role in the metabolism of neurotransmitters such as dopamine and serotonin. MAO's rise to prominence in the biomedical community originated in the early fifties from Zeller's finding that MAO was the target for hydrazine inhibition which could function in treating depression. Since then, a huge number of MAO inhibitors have been developed and several of them have been used for the treatment of Parkinson's disease and depression. Our structural studies have shown that most of the known MAO inhibitors function through a mechanism-based mode that generates a covalent adduct with the FAD cofactor. LSD1 is a more recently discovered enzyme. It is responsible for the demethylation of Lys4 of histone H3. LSD1 is implicated in tumorigenesis and there are increasing efforts to identify LSD1 inhibitors. The crystal structure of LSD1 reveals a different substrate-binding site but similar catalytic machinery compared to those exhibited by MAO structures. This similarity is proving to be particularly insightful, prompting researchers to exploit the knowledge gained from MAO inhibition studies to develop effective LSD1 inhibitors. We shall present a comparative analysis of LSD1 and MAOs with a focus on the relevance of the structural investigations for understanding the mechanisms drug action and for the design of new inhibitor molecules targeting these amine oxidase enzymes.

Keywords: enzyme inhibitor design, enzymatic catalysis, chromatin

MS.16.4

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CPADD(Closest Packing Approach for denovo Drug Design) to inhibit VEGF/R and Notch/RBP/MAM systems

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CPADD generates almost all possible ligand structures that fit with a binding pocket of target protein(s), by extracting chemical structures among closest packing putative atom network. It has succeeded in finding active compounds for all projects so far both on enzymes and on PPI (Protein-Protein Interaction) systems. In this presentation, results on VEGF/VEGFR and Notch/RPB/MAM systems are shown. As the first screening, inhibition of HUVEC-proliferation by VEGF inhibitors and inhibition of Notch reporter gene expression by Notch inhibitors were evaluated. As the second screening, the abilities of selected compounds to suppress the LS174T-tumor growth were estimated using the xenograft model. Several promising compounds significantly suppressed the tumor growth in their single use without the loss of body weight. Combined use with Avastin or chemotherapeutic agents showed stronger tumor growth inhibitory effects than Avastin or chemotherapeutic agents alone.

Keywords: inhibitor, VEGF, notch

MS.16.5

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A family wide approach to structure-based inhibitor design for protein tyrosine phosphatases

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The protein tyrosine phosphatase (PTP) family is a large and diverse group of enzymes that together with protein tyrosine kinases control signaling pathways in the cell. Deregulation of PTPs has been linked to a range of human diseases, including cancer, diabetes, obesity and arthritis, and certain members of the family are recognised drug targets. PTPs exhibit high similarity in their overall fold but changes in the region surrounding the active site pocket can be exploited to achieve inhibitors through structure based rational design. We have screened a focused compound library and identified several small molecule inhibitors of PTPs many of which are selective against certain members of the family. In a biochemical assay these compounds inhibit phosphatase activity with IC50 values in the low micro molar range. At the Structural Genomics Consortium (SGC) PTPs have been studied for several years and 22 structures have been deposited in the protein data bank. With successful protocols for producing well diffracting crystals in place we are now developing a family based method for soaking crystals with the established inhibitors. The aim is to produce chemical probes specific for particular PTPs but to find means of taking advantage of the similarities between members of the family to reach this goal. Results with PTPs have so far identified crystal forms where the active site is in the open conformation due to crystal contacts between neighbouring molecules. This conformation is not optimal for binding compounds that inhibit activity, thus new crystal forms are being sought. By August, the latest results will be presented together with the evolved methodology for high-throughput generation of complex structures.

Keywords: ligand binding of proteins, structural genomics, cellular signaling

MS.17.1

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Time-resolved diffraction at atomic resolution: What's here now and what's next?*

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Monochromatic time-resolved diffraction experiments of excited-state geometry are flux limited even at third generation sources. For sub-microsecond experiments polychromatic techniques are needed. To avoid the known complexities of the Laue method we use a 'raw intensity' technique in which the intensity response to laser irradiation is directly extracted from dark-light pairs of frames,

thus bypassing the wavelength dependence of the Laue intensities. A monochromatic reference structure is then used to recover the 'light-on' intensities. Using polychromatic radiation time-resolution becomes limited only by the larger of the width of the synchrotron and laser pulses. In addition to allowing studies of much shorter-lived excited states, this should make it possible to monitor the initial steps of chemical reactions in solids. The suitability for this purpose of a number of solid-state reactions have been explored by steady state methods [1-3]. We find that trans-cis, cis-trans isomerizations and [2+2] cycloadditions in solids are highly stereospecific and activation-energy-controlled, so that their rate can be manipulated by adjustment of the temperature. A number of examples will be presented. Research supported by the US Department of Energy.

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Keywords: time-resolved diffraction, solid-state reaction, excited state geometry

MS.17.2

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Reactive crystalline molecular assemblies

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Effects of long-range molecular packing on solid-state structure are a nemesis of the crystal engineer. One way to circumvent effects of long-range packing so as to control the properties of organic solids is to centralize molecules within zero-dimensional (0D), or discrete, structures. A discrete assembly of molecules possesses a structure that is largely independent of crystal packing. This means that properties introduced by the components of a discrete system can, in principle, be modified in the wake of unpredictable effects of packing. In this presentation, we will describe an approach to engineer the formation of discrete molecular assemblies in the solid state. The components of the 0D structures undergo reactions in the solid state. The reactions of the components are accompanied by a number of movements (e.g. tilting, flipping) that, in some cases, proceed via single-crystal processes.

Keywords: crystal engineering, hydrogen bonds, reactivity

MS.17.3

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Vapor-induced transformation followed by luminescence switching for a dinuclear platinum(II) complex

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Vapochromism is one of the recent interesting topics for luminescent metal complexes. We have found that the crystalline sample of a dinuclear platinum(II) complex, syn-$[Pt_2(pyt)_2(bpy)_2](PF_6)_2$ (pyt = pyridine-2-thiolate ion, bpy = 2,2'-bipyridine) exhibits a remarkable change in its luminescence by sensing organic vapors [1]. The light-red form with red luminescence converts to the "dark" dark-red form on exposure to acetonitrile and ethanol vapors, while the reverse change occurs in the presence of chloroform vapor. We have elucidated that the dynamic transformation of the molecular arrangement as the mechanism of the vapochromism. For the dark-red form including vapor molecules, the dinuclear complex units are arranged in a head-to-head manner with a short Pt···Pt distance. However, the arrangement is shifted drastically by the release of vapor molecules to form a $\pi\pi$ stack of bipyridine ligands for the light-red form. Thus it is concluded that the luminescence switching occurs by the change in the electronic Pt···Pt interaction between the dinuclear complexes.

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Keywords: platinum coordination compounds, luninescence, transformation

MS.17.4

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Photochromism and thermochromism of crystalline salicylideneanilines

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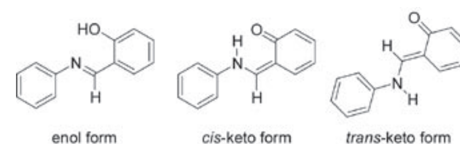
Salicylideneaniline (SA) is one of the most well known families of photochromic and thermochromic compounds. The reversible color changes of the compounds take place in crystals and have been a subject of substantial interest. For the past 10 years we have studied the photo- and thermochromism of SAs in the solid state using X-ray diffraction analysis and variable-temperature diffuse reflectance spectroscopy. We have succeeded in providing a new framework of understanding the chromic phenomenon of crystalline SAs: The photochromism is due to the transformation between the enol and *trans*-keto forms. The thermochromism is mainly due to the temperature-induced change of fluorescence.



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Keywords: photochromism, tautomerism, fluorescence

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