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combinatorial chemistry library and first principles based alchemical calculations for accurate free energy estimates appears to be a powerful approach for ligand optimization.

1332-Pos Board B62

Probing the Ligand Binding Mechanism of Mnk Inhibitors by Docking and Molecular Dynamics Simulations

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Mitogen-activated protein kinases-interacting kinases 1 and 2 (MNK1 and MNK2) are Ser/Thr kinases belongs to the group of Ca^{2+}/calmodulin-dependent kinases (CaMK) that phosphorylate Eukaryotic initiation factor 4E (eIF4E) [Luc Furic.,et. al., PNAS, 2010, 107 (32):14134-14139] on Ser-209. Overexpression of eIF4E has been associated with tumoregenicity and studies have indicated that eIF4E phosphorylation is oncogenic [Jinqiang Hou. et. al., Oncotarget, 2012, 3:118-131]. Therefore, Mnk1/2 inhibitors could be effective therapeutic agents for the treatment of cancers driven by an overexpression of phosphorylated eIF4E. In the current study we have carried out molecular docking combined with molecular dynamics simulations to study the interaction between ligand and Mnk1/2 kinase catalytic domains. Three dimensional structures of both Mnk1 and Mnk2 were built using comparative modeling methods. A series of Mnk kinase inhibitors were docked to the ensemble of representative structures extracted from a clustering analysis of the MD simulations. The predicted bound conformations were further studied in explicit solvent by MD simulations. Our combined computation approach identified key residues that are important for the protein - inhibitor interactions, provides detailed understanding of the mechanism of these kinds of inhibitors and will be useful for the rational design of Mnk inhibitors.

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Development of Novel Xanthine Oxidase Inhibitors with Radical Scavenging Properties for the Prevention of Reperfusion Injuries

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Reperfusion injuries can cause severe damage in hypoxic tissue after the blockage of oxygen supply has been relieved. The condition frequently occurs after ischemic events or surgery and is caused by a combination of inflammation and the generation of harmful reactive oxygen species (ROS). In an effort to gain access to agents capable of combating the damaging effects of ROS, we developed compounds with dual properties capable of preventing the generation of ROS and of absorbing ROS already formed. By combining two beneficial properties in a single molecule, we expected these compounds to be more flexible and effective than those that feature only one of the two activities. Based on the scaffolds of the natural products chalcone and caffeic acid phenethyl ester (CAPE), we synthesized and tested a selection of compounds capable of inhibiting the enzyme xanthine oxidase (XO), a major source of ROS production, and of absorbing radicals. Assays employed in this study measured inhibitory potency against XO activity, radical scavenging ability, and the capacity to increase cell viability under oxidative stress. In addition, computational docking was performed to elucidate XO/inhibitor interactions at the molecular level. Structure-activity relationships were established that identified correlations between molecular structure and the two bioactivities under investigation and that can guide the future synthesis of materials with improved properties.

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Data Mining the Pdb: Phosphorylation Can Directly Interfere with Drug Binding

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As many as 30% of all proteins are phosphorylated. Protein kinases play a central role in controlling cell proliferation, differentiation, cell cycle progression, and angiogenesis - processes which frequently become dysregulated during carcinogenic transformation. Many experimental therapeutics are developed using purified protein and may be less effective against targets that are post-translationally modified in vivo. To test whether protein phosphorylation may decrease drug binding and increase resistance, we examined 310 unique drug-bound protein structures mapped from the DrugBank database to the Protein Data Bank. We cross-referenced the sites with recorded phosphorylation sites found in the PhosphoSitePlus database. "Hits" are defined as target proteins that have phosphorylated residues within 12 Å of their drug binding sites. For these proteins, phosphorylation could directly interfere with drug binding *in vivo*. The hits fell into two classes. Class I hits are targets for which the drug compound competes with natural substrate in the active site. The phosphorylation site is also in the active site, and phosphorylation results in inactivation of the protein. One would not expect a large reduction in drug efficacy for these proteins, as phosphorylation simultaneously causes drug resistance and inactivates the protein target. For Class II hits, the drug compounds bind to allosteric sites outside the active site of the target protein, and the documented phosphorylation either activates the target or only moderately decreases its activity. We hypothesize that Class II compounds are more likely to encounter resistance when used as therapy, especially in cancer where there are larger populations of aberrantly phosphorylated proteins.

1335-Pos Board B65

Effect of Natural Product Extracts on Lipoxygenase, Cyclooxygenase, and Protein Tyrosine Phosphatase 1β

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The purpose of this research project is to examine the inhibition of enzymes linked to inflammation and associated diseases by plants traditionally as anti-inflammatory medicines: *Tussilago farfara, Grindelia squarrosa,* and *Uritca dioica.*
Arachidonic acid is metabolized in the body through two main metabolic pathways with the enzymes: cyclooxygenases (COX) and lipoxygenases (LOX). Elevated levels of prostanoids and leukotrienes, products of the two respective pathways, have been linked to inflammatory diseases. Finding a dual inhibitor of COX and LOX is promising in preventing the inflammation and diseases that are linked to the overproduction of both pathways while minimizing the side effects associated with inhibition of individual pathways.
Furthermore, the enzyme protein tyrosine phosphatase 1β (PTP1β) is linked between inflammation and metabolic disease through the leptin receptor-associated Janus Kinase (JAK). PTP1β is a negative regulator of insulin and leptin receptors thus being explored as a possible therapeutic for type II diabetes and obesity.
Crude methanolic extracts of *Tussilago farfara, Grindelia squarrosa,* and *Urtica dioica* were taken to approximate the plants' components released in the body upon consumption. The bioactivities of the standardized extracts were then determined using enzymatic assay kits for COX I and II, LOX, and PTP1β. *T. farfara* is the strongest LOX inhibitor at 60% inhibition of 15-LOX, followed by *U. dioica* and *G. squarrosa* at 45% and 39%, respectively. Studies for COX I and II as well as PTP1β inhibition are ongoing, and the results will be presented.

1336-Pos Board B66

Structure-Thermodynamics Correlations of Fluorinated Benzensulfonamides as Inhibitors of Human Carbonic Anhydrases

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The carbonic anhydrases (CA) are established as therapeutic targets [1]. There are 12 catalytically active CA isozymes in human body. At least 30 CA sulfonamide inhibitors have been used as drugs to treat glaucoma, epileptic seizures, altitude sickness, and as diuretics. However, most of them exhibit poor selectivity towards target isozymes and result in various side effects.
In this work, a class of 4-substituted-2,3,5,6-tetrafluorobenzensulfonamides as inhibitors of CA is reported. Crystal structures of CAII, CAXII and CAXIII bound with the fluorinated compounds were solved and provided structural details of inhibitor binding. The binding affinity to carbonic anhydrases I, II, VII, XII and XIII was measured by isothermal titration calorimetry and the fluorescent thermal shift assay, and inhibition was determined by stopped-flow CO2 hydration assay. The combined use of these methods has provided a detailed picture of protein-ligand interactions. Experimentally obtained binding data usually depends on various factors including temperature, pH, buffer, etc. In this study, we present intrinsic parameters of binding that are independent of experimental conditions. Structure-thermodynamics correlations were studied using intrinsic parameters. All used biophysical methods have confirmed that fluorinated sulfonamides bound stronger to CA than non-fluorinated, because of the presence of electronegative substituents that decrease the pKa of sulfonamide group and this correlates with an increase in the CA inhibitory properties [2]. A large group of fluorinated compounds possessed nanomolar affinity for selected CAs and several of them were selective towards CAI.

1337-Pos Board B67

An Asymmetric Pattern in Binding of Prostaglandin Endoperoxide H Synthases to their Inhibitors and its Implications for Enzyme Catalysis and Allosteric Regulation

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Proteins experience some conformational changes upon ligand bindings and their effects on protein functions are displayed in various ways. Crystallographic data of