screening methods, considers the protein conformation change upon binding by using two different protein conformations and also takes into account the solvation effect by including conserved water molecules in the active site. The top ranked molecules from each pharmacophore hypothesis are further analyzed according to their interactions with AKT-2 and the ultimate docking results from Glide are compared with previously identified inhibitors based on structure and chemistry.

307-Pos Board B93
Stable Complexes of LYN Kinase and Druglike Small Molecules
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Glioblastoma multiforme (GBM) is a very aggressive brain cancer in humans. Even with improvements in surgical, radiation, and chemotherapy treatments, current prognosis is bleak, with only a 14-month median survival time. LYN, an important kinase involved in cell regulation, is often overexpressed in GBM. This work addresses computational design of druglike small molecules that could potentially inhibit LYN and thus hinder GBM progression. New putative LYN inhibitors were obtained by atomic substitutions and structural alterations of bafetinib, a small molecule previously found to bind LYN. Druglike properties and toxicities of the designed molecules were evaluated using the Osiris Property Explorer program. Molecules with no implied toxicities and most favorable druglike properties were used for docking studies in the ArgusLab program. Designed molecules that made the most stable docking configurations with LYN, but no stable configurations with other kinases, were identified as LYN-specific. Binding energies of the stable complexes formed by these molecules and LYN were calculated. Possible utilization of the designed molecules in drug research against GBM is discussed.

308-Pos Board B94
Crystal Structure of the Kinase Domain of ABL in Complex with a Potent Rationally-Designed Derivative of the PP1 Inhibitor, AB129
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As part of our effort to understand the determinants of drug binding to the Abl tyrosine kinase, we determined the crystal structure of the Abl kinase domain bound to a derivative of the PP1 nucleoside analog. Just as the cancer drug imatinib selectively inhibits the tyrosine kinase activity of c-Abl, c-Kit, and the PDGF receptor, but is a poor inhibitor of the closely related Src kinases (1), PP1 is a selective inhibitor of the Src family (2), c-Kit (3), and PDGFR kinases but not of Abl tyrosine kinase activity (3, 4). In fact, PP1 is 1000X less effective at inhibiting Abl and Bcr-Abl kinases than at inhibiting the Src kinases (3, 4). We rationally designed a derivative of the PP1 compound to introduce hydrogen bonding between it and a strictly conserved lysine residue that coordinates the alpha and beta phosphate groups of ATP in protein kinases (5). By expanding the interactions between the inhibitor and Abl kinase, we sought to make the PP1 derivative, AB129, less selective. Our crystal structure of the Abl kinase domain bound to the AB129 inhibitor shows three important features. First, the compound binds to the kinase domain in the active conformation: alpha C helix is rotated inward facilitating a salt bridge between Lys271 and Glu286 and the conserved Asp-Phe-Gly (DFG) motif is oriented Asp-In. In contrast, the structure of PP1 bound to the Src family kinase Hck is in the inactive conformation (6). Second, the strictly conserved Glu286 residue, not Lys271, hydrogen bonds to the hydroxyl group of AB129. Third, the conformation of the phosphate binding loop (P-loop) is extended. We provide kinetic and calorimetric data to support our rationale for the observed conformational changes.

309-Pos Board B95
Crystallization of the Abl Kinase Domain with Combi-Inhibitors, ZRF1 and ZRF2
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The uncontrolled kinase activity of the oncogenic protein Bcr-Abl is a hallmark of Chronic myelogenous leukemia (CML). Although the drug imtanib is highly effective at shutting down aberrant Abl kinase activity, some CML patients harbor additional mutations in their bcr-abl gene that renders their gene product, the Bcr-Abl protein, resistant to this drug. Since second generation Abl kinase inhibitors such as dasatinib are effective only against particular resistant mutant proteins, new targeted agents are needed to combat drug resistance. Two combi-inhibitors ZRF1 and ZRF2, which block Bcr-Abl activity and damage DNA in the cell, have been shown to be more potent than imatinib in cellular assays. Since both ZRF1 is hydrolyzed in the cell to ZRF0, an imatinib analog in which only the mono-substituted benzamide piperazinyl moiety is replaced with bi-substituted amino and trifluoromethyl groups, we wondered why these two changes had such a profound effect on the potency of the drug. To determine whether ZRF1/2's increased potency was due to the DNA damaging agent attached to the parent compounds, we sought to co-crystallize the Abl kinase domain with these two inhibitors at room temperature and 4°C using commercially available sparse-matrix screens. We screened over 400 crystallization conditions, with Abl and ZRF1, ZRF2, or dasatinib inhibitors but were unable to obtain crystals of either the Abl-ZRF1 or Abl-ZRF2 drug complex. Protein crystals in wells containing the Abl kinase domain and dasatinib, however, were evident in every tray. Since ZRF1 and ZRF2 are hydrolyzed in the cell, future co-crystallization studies of Abl and its mutant proteins will employ the hydrolyzed inhibitor analogs as the ligand.

310-Pos Board B96
BindingDB: A Protein-Ligand Database for Drug Discovery
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The large and growing body of experimental data on biomolecular binding is of enormous value in developing a deeper understanding of molecular biology, in developing new therapeutics, and in various molecular design applications. However, most of these data are found only in the published literature and are therefore difficult to access and use. BindingDB is a public web-accessible database of measured binding affinities for various molecular types. The BindingDB allows queries based upon a range of criteria, including chemical similarity or substructure, sequence homology, numerical criteria and reactant names. The data specification includes significant experimental detail. The time and expense required to extracting data from the literature, for this and many other databases, highlight the importance of moving toward machine-readable components of publications.

311-Pos Board B97
GALAXYDock: Docking Ligands to Receptor Proteins with Selected Flexible Side-Chains
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Protein-ligand docking techniques are one of the essential tools for structure-based drug design. Although conformational changes of protein receptor frequently occur in the binding process, a large fraction of contemporary docking programs ignore receptor flexibility. Consideration of protein flexibility efficiently and accurately in docking studies is challenging due to difficulties in finding accurate scoring function and in sampling conformations efficiently. Previously we developed a docking program called LigDockCSA which incorporates LigDock scoring function that combines AutoDock3 and PLP scoring function and conformational space annealing (CSA) as a sampling method. However, the program treats protein rigid. Here, we present GALAXYDock, an extension of LigDockCSA that accounts flexibility of pre-selected side-chains of receptor protein in the binding site. To test the performance of the new docking method, 3 sets of protein-ligand complexes that share similar backbone structures but have different side chain conformations were selected as test sets: HIV-PR, LXRβ and cAPK. The cross-docking results show that the accuracy of binding pose prediction is increased about 20% when compared with our previous rigid-receptor results.

312-Pos Board B98
Docking Simulations of Perylene-HSA Binding
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The study of the binding and effects of polyaromatic hydrocarbons (PAH) to proteins remains one of the fundamental aspects of research in biophysics. Among other processes, ligand binding can regulate the function of proteins including inhibiting their action. Binding to small ligands remains a very important aspect in the study of the function of many proteins. We studied a new class of 3,9-substituted perylene derivatives designed to optimize