a bacterial DNA replication enzyme beginning with a fragment based lead generation approach will be presented. In this approach, biochemical, biophysical and structural tools were employed to screen fragment libraries against the target enzyme and progress initial hits to drug-like leads. The availability of high-resolution target structure provided valuable chemistry guidance in designing such leads.

1178-Pos Board B88
ROSETTAEPR: An Integrated Tool for Protein Structure Determination From Sparse EPR Data
Stephanie Hirst, Nathan Alexander, Hassane S. Mchaourab, Jens Meiler.
Membrane proteins remain a particular challenge in structural biology. Only about 1.5% of reported tertiary structures and 60 unique membrane protein topologies consisting of more than one transmembrane span are represented in the PDB. However, these proteins make up an estimated 30-40% of the entire proteome, and over half of all therapeutics target this group. Site-directed spin labeling electron paramagnetic resonance (SDSL-EPR) is often used for the structural characterization of proteins that elude other techniques, such as X-ray crystallography and NMR. However, high-resolution structures are difficult to obtain due to uncertainty in the spin label location and sparseness of experimental data. ROSETTAEPR has been designed to improve high-resolution protein structure prediction using sparse SDSL-EPR distance data. The ''motion-on-a-cone'' spin label model is converted into a knowledge-based potential, which was implemented as a scoring term in ROSETTA. We have demonstrated the feasibility of using ROSETTAEPR with soluble proteins by benchmarking the method on T4-lysozyme. ROSETTAEPR increased the fractions of correctly folded models ($RMSD_C < 7.5Å$) and models accurate at medium resolution ($RMSD_C < 3.5Å$) by 25%. After full-atom refinement, ROSETTAEPR yielded a 1.7Å model of T4-lysozyme, thus indicating that atomic detail models can be achieved by combining sparse EPR data with ROSETTA. ROSETTAEPR was also benchmarked on a set of membrane proteins of known structure. If EPR experimental data were not available, simulated data were derived from the existing structures. It was generally observed that *de novo* folding in the presence of EPR restraints enriched the recovery of the proteins' correct topology compared to when folding with no restraints.

1179-Pos Board B89
Incorporating the Effects of pH in Protein-Protein Docking
Krishna Praneeth Kilambi, Jeffrey J. Gray.
Highly charged interfaces often frustrate protein-protein docking methods. Current approaches do not account for changes in the ionization states which may play a crucial role in binding. Predicting the charges on the residues would be the first step towards understanding the dependence of docking on pH. We developed a method to predict the pKa values of the common ionizable residues in proteins (Asp, Glu, Lys, His and Tyr) . It incorporates conformational flexibility through extensive amino-acid side-chain rotamer sampling and is based on the Rosetta energy function with an explicit term to account for the protonation state probabilities of the amino-acids. In approximately 80% of the cases, the method predicts the pKa value of a residue to an accuracy of 1 pH unit from the experimental value and 95% of the time it predicts a value within 2 units of pH. The method is comparable in accuracy to the other published computational pKa prediction methods and is fast enough to be used to dynamically predict and alter the ionization states of the amino-acid side chains during protein-protein docking. We expect the new protocol to lead to improvements in conformational sampling during docking as well as help in the discrimination and ranking of the generated ensemble of tentative protein complexes.

1180-Pos Board B90
Mechanism and Action of Flufirvitide, a Peptide Inhibitor of Influenza Virus Infection
Hussain Badani, Robert F. Garry, Russell B. Wilson, William C. Wimley.
Influenza is an infectious disease typically transmitted through the air. It is responsible for seasonal epidemics affecting millions of people, and sporadic global pandemics. Influenza infection is a membrane fusion-dependant process, occurring in the endosome of the host cell after viral binding and endocytosis. The virus-host membrane fusion process is mediated by hemagglutinin (HA), a viral surface glycoprotein. Studies show that when the virus is subjected to low pH in the endosome, the HA protein partially unfolds and changes conformation, exposing the fusion initiation region (FIR). A 16 amino acid peptide sequence (Flufirvitide) derived from the fusion initiation region of the HA protein has shown effective inhibition of influenza virus infection. It is hypothesized that there is an interaction between the peptide and the FIR which inhibits fusion of the virus to the host cell. Plaque inhibition assays and animal studies show high efficacy of the peptide against the virus. We are currently developing biochemical and biophysical assays to study the interaction between Flufirvitide and HA. Circular Dichroism studies show that the peptide has a random coil conformation at pH 7 and higher. To elucidate the mechanism of fusion inhibition, the interaction between peptide and HA is being investigated with immunodetection, immunoprecipitation, and florescence techniques. Additionally, binding and interaction of the peptide with the intact virus is being studied by using Cryo-electron microscopy.

1181-Pos Board B91
Computational Design of Small Molecules with Druglike Properties
D.S. Dalafave, K.S. Jani.
Many cancers overexpress antiapoptotic proteins, which can lead to poor chemotherapy response. This work reports on computational design of druglike small molecules that could potentially facilitate apoptosis by forming complexes with antiapoptotic proteins. Drugs based on small molecules that target a single protein can lead to drug resistance. On the other hand, a drug that operates too broadly may harm healthy tissue. An alternative is a drug that can bind two or more of the proteins. A single drug would be more economical and lead to fewer side effects than a combination of drugs with each one targeting a single protein. In this work, structures of experimentally known small molecules were used as templates to design new molecules. Common structural features of the experimental molecules were identified. The Osiris Property Explorer program was employed to study how the features influenced molecular druglike properties. Atomic substitutions and structural modifications were done to design new small molecules. Drug-related properties and potential toxicities of the molecules were determined and compared to those of commercial drugs. Molecules with no indicated toxic risks and optimal values of drug-related properties were used for docking studies in the ArgusLab program. Binding energies of stable configurations of the designed molecules and antiapoptotic proteins were calculated. Designed molecules that made the most stable complexes with two or more antiapoptotic proteins were identified. The potential to use the designed molecules in anticancer drug design is discussed.

1182-Pos Board B92
Total Synthesis of Moscatilines and Wedelolactones as Potential Inhibitors of Anti-Metastic Agents in MDA-MB-231 Cells
Yean-Jang Lee, Wen-Shing Tsau, Chia-Fu Cheng, Tsui-Hwa Tseng, Pei-Yun Huang, Shien-Kai Chuang.
Combretastatins, which are an important group of anticancer drugs, were isolated by Pettit et al. from the African tree Combretum caffrum in 1989. Additionally, Liang et al. have reported that ten coumestans were isolated from the roots of *Hedysarum multijugum*, which is a plant in *Hedysarum* Linn. of the family *Leguminosae* used as a folk herbal drug in northwest China. Coumestans comprise a class of naturally occurring products with a variety of biological activities including phytoestrogenic, antibacterial, antifungal, antimyotoxic, and phytoalexine effects. Due to their biological activities, the synthesis of Hedysarimcoumestan **B** is achieved in which the longest linear sequence is only eight steps in 50% overall yield from commercially available phloroglucinol. The key transformations in the synthesis are Stille coupling and DDQ oxidative-cyclization reactions. This synthetic strategy can be applied to give access to the demethylwedelolactone and wedelolactone, which were afforded from α-bromocoumarin in high 55% and 47% yields, respectively. In addition, CA-4 analogues are also synthesized by Pd-catalyzed coupling in overall yield 20~28%. Furthmore, the molecular model was examined the interactions of proteins and ligands as well. Finally, the bioassay results show that the anti-invasion and anti-metastsis activity of wedelolactones in breast cancer are associated with inhibition of signaling pathway and promotion of chromatin remodeling. Camphorataimide B reduced the size and weigth of lung as well as lung colonization of MDA-MB-231 cells.

1183-Pos Board B93
In Silico Approach to Identify Substrates and Inhibitors of Malaria Proteases
Lauren E. Boucher, Jenny Lundqvist, Holly L. Hammond, Jürgen Bosch.
Malaria affects over 500 million people and causes 1.3 million deaths annually. The parasite, *Plasmodium falciparum*, is responsible for the most deadly variant of malaria in humans. Due to evolving resistance to current treatments, it is necessary to develop new drugs targeting the parasite. Potential drug targets are the malaria proteases; several proteases are critical in both the liver and blood stages of the parasite's life cycle, essential for both invasion and egress of cells. Proteases have been effective drug targets for the treatment of several diseases evidenced by the development of HIV protease inhibitors, ACE inhibitors treating hypertension, and anticoagulants treating thrombosis.
In developing new therapies, we are taking a structure-based drug design approach to design inhibitors of proteases key to parasite survival. While several vital proteases have been identified, relatively little else is known and substrates for many proteases have yet to be identified. To identify these substrates, we are using an *in silico* approach to screen for peptides that bind to the protease active