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TRACK 5(III)

PHARMACOPROTEOMICS

TRACK 5(IV)

BIOINFORMATICS IN PHARMACEUTICAL STUDIES

02 November 2010 (Tuesday)

SESSION CHAIR : **DR. JEOVANIS GIL**
Division of Physical Chemistry, Center for Genetic Engineering and Biotechnology Cuba

SESSION CO-CHAIR: DR. BASAVARAJ K. NANJWADE
KLE University's College of Pharmacy, India

SESSION INTRODUCTION

TITLE: INTERACTION OF SYNTHETIC GLYCOCONJUGATES WITH GLYCOSIDASES AND LECTINS

DR. C. P. RAO, Department of Chemistry, Indian Institute of Technology Bombay, India

TITLE: IDENTIFICATION AND CHARACTERIZATION OF A CALCIUM OXALATE CRYSTAL GROWTH PROTEIN INHIBITOR FROM HUMAN RENAL STONE MATRIX

DR. CHANDERDEEP TANDON, Biotechnology & Bioinformatics Jaypee University of Information Technology Distt, India

TITLE:

DR. BASAVARAJ K. NANJWADE, KLE University's College of Pharmacy, India

COFFEE BREAK & POSTER SESSION

TITLE: IN DEEP PROTEOMIC CHARACTERIZATION OF AN OMV BASED VACCINE AGAINST N. MENINGITIDIS

DR. JEOVANIS GIL, Division of Physical Chemistry, Center for Genetic Engineering and Biotechnology Cuba

TITLE: DIVERSITY ORIENTED PRIVILEGED STRUCTURES AS DRUG MOLECULES

DR. M. VIJJULATHA, Department of Chemistry, Nizam College, Hyderabad, India

TITLE: DRUG DESIGN AND DEVELOPMENT USING PHARMACOPHORE MODELING AND VIRTUAL SCREENING

DR. MADHU CHOPRA, B. R. Ambedkar Center for Biomedical Research, University of Delhi, India

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Interaction of Synthetic Glycoconjugates with Glycosidases and Lectins

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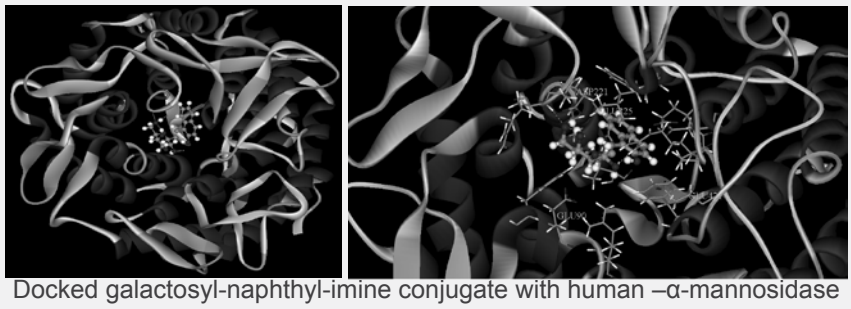
Inhibition of the glycosidases as well as alteration of lectin properties by chemically modified glycoconjugates can have profound effect in biology. Several C_1-imino conjugates of D-galactose, D-lactose and D-ribose and C_2-imino conjugates of D-glucose, where the nitrogen center was substituted by the salicylidene or naphthylidene, were synthesized and characterized. Those glyco-imino-aromatic conjugates, which are transition state analogues, exhibited 100% inhibition of glycosidases extracted from soybean and jack bean meal. Some of these conjugates exhibited IC_{50} values in the range of 20 to 50 μM and hence are potent inhibitors of glycosidases. The kinetic studies suggested non-competitive inhibition. Similar studies have been carried out by treating the lectins of both glucose/mannose specific (DLL-I, pea lectin, lentil lectin), galactose specific (DLL-II, PNA, SBA, moringa lectin) as well as lactose specific (unio lectin) with these glycoconjugates. Those conjugates which exhibit highest glycosidase inhibition also inhibit the agglutination of lectins and thereby modify the property of lectin accordingly. Both the experimental and computational docking studies revealed differences in the binding strengths of naphthylidene *vs.* salicylidene as well as galactosyl *vs.* lactosyl moieties present in these conjugates. The differential interactions of these glyco-conjugates have been addressed by computational docking studies to quantify the same exists between the enzyme (Figure) or lectin and the corresponding glycoconjugate. The present studies clearly supported the binding mainly through polar interactions in addition to exhibiting some nonpolar/hydrophobic ones.



Docked galactosyl-naphthyl-imine conjugate with human –α-mannosidase

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Identification and Characterization of a Calcium Oxalate Crystal Growth Protein Inhibitor from Human Renal Stone Matrix

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A relatively small number of well-characterized inhibitors of kidney stone formation have been identified from the previous research involved in its formation. In this study conventional biochemical methods have been combined with recent advances in mass spectrometry (MS) to identify a novel calcium oxalate (CaOx) crystal growth inhibitor in human renal stone matrix. Proteins were isolated from the matrix of human CaOx containing kidney stones. Proteins having MW>10 kDa were subjected to anion exchange and molecular-sieve chromatography. Protein fractions were tested for their effects on CaOx crystal growth. Most potent fraction was excised, in-gel tryptic digested and identified by matrix assisted laser desorption/ionization-time of flight (MALDI-TOF) MS. An anionic protein (MW~42 kDa) with potent inhibitory activity against CaOx crystal growth was purified. Its homogeneity was confirmed by RP-HPLC. It was identified by MALDI-TOF-MS followed by database search on MASCOT server as human phosphate cytidylyltransferase 1, beta. Molecular weight of this novel CaOx crystal growth inhibitor from human renal stone matrix is also the same as that of human phosphate cytidylyltransferase 1, choline, beta.

Human phosphate cytidylyltransferase 1, choline, beta is a novel CaOx crystal growth inhibitor. It is involved in the biosynthesis of phosphatidylcholine which happens to be an important constituent of human renal stones and is also reported to have an antilithiatic effect.

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Bioinformatics for Drug Formulations and Delivery System

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Drug companies spend more than $5 billion per year on IT. So what does this mean for drug delivery and formulation development as we know? An injectable or solid oral immediate or sustained released are "no brainers" for pharma in terms of dosage form selection. Now go have fun with solubility and stability, and its headache time or cocktail time, depending where you are in the world and your choice of vice. To combine the right chemical ingredients in the right proportions, driving the right reactions under the right conditions to achieve the right end product with the right properties requires an incredible amount of information and an incredible amount of knowledge. All this information and knowledge has to be available at the point of formulation. Managing the formulation process without iteration is the secret to reducing development time. Having software to provide the right information at the right place at the right time and you avoid costly, embarrassing mistakes and eliminate duplicate work. Today, a formulator could even identify promising formulation leads, store, and manage a pharma company's formulation portfolio or library. To quickly discard all about the leading options and eliminating time wasted on low probability routes while identifying the best and least expensive ingredient mix can save money and time. In the final analysis, this will allow drug delivery companies to be in a greater position of strength. Drug delivery companies can improve their odds of solidifying licensing and development deals on better terms.

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In Deep Proteomic Characterization of an OMV Based Vaccine Against *N. meningitidis*

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At present one of the efforts devoted to the development of an effective vaccine against *Neisseria meningitidis* serogroup B have been focused in the proteomic studies of outer membrane vesicles (OMV). This work presents the results from a detailed study of the protein composition of OMV from VA-MENGOC-BC™ (Finlay Institute, Cuba). The characterization of this protein preparation is a challenge because of it is enriched in lipids and membrane proteins and only a few number of proteins represent about 70 % of the total protein mass. Proteins were identified by, combining two-dimensional gel electrophoresis of proteins and peptides and mass spectrometry, and the application of non-gel based approaches starting form the tryptic digest of the OMV preparation followed by (1) the Selective Capture of Peptides (SCAPE-nHnR), and (2) equalization of the peptide mixture by using peptide libraries and fractionation by reverse phase liquid chromatography at basic pH before LC-MS/MS analysis. Most of the applied methods have been developed in our group. This study resulted in the identification of more than three hundred proteins. Bioinformatics analysis of the identified components allowed the selection of potential antigens for cloning, expression, purification and immunological studies, which were part of a wider project aimed to the development of a new vaccine based on a defined protein composition.

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Diversity Oriented Privileged Structures as Drug Molecules

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The Exploration of privileged structures in drug discovery is a rapid emerging theme in Medicinal Chemistry. Privileged structures/substructures, is a single molecule frame work able to provide ligands for diverse receptors. Privileged structures represented as ideal source of lead compounds. These structures must display key physicochemical characteristics that facilitate their ability to bind with multiple receptors. The main objective was to design inhibitors for Dihydrofolate Reductase (DHFR) and Thymidylate Synthase (TS) enzymes. The blocking of the enzymatic activity is a key element in the treatment of many diseases including cancer, bacterial, protozoal and also opportunistic infections associated with AIDS like Pneumonia and Toxoplasmosis. Our computationally designed privileged structures having characteristic requirements like low Molecular weight, cyclic structure in scaffolds, since they provide molecular rigidity, allowing less entropy to be lost upon binding to the receptors and also providing better bioavailability. In addition to the above characteristics of privileged structures medicinal chemist favorite suite of descriptors like rotatable bonds, polar surface area and Lipinski's drug like characteristics have been applied. The designed molecules along with existing ligands with known activity, when docked into the multiple receptors of DHFR (1OHJ, 1MVS, 1S3V, 1KMS, 1KMV, 1DHF, 1MVT, 3GHC and 3GHW) extracted from protein data bank have shown greater binding affinity with these receptors. In order to further evaluate these results homology modeling of bovine and rat liver DHFR were established based on the template structures of mouse DHFR (PDB entry 1FZJ and 3D80) respectively using MODELLER 8v2 program. These results were assessed as reliable structures by PROCHECK, Verify 3D and PROSA 2003. These structurally diverse ligands were docked into the active site of modeled 3D structures of rat liver, bovine and also into the template structure of mouse DHFR using Glide 4.0 to identify important protein ligand interactions. Interestingly all these molecules showed greater affinity towards the active site showing 7-9 hydrogen bond interactions. When docked into the active site of pneumocystis carnii (1DYR) and modeled bifunctional protein Toxoplasma gondii (Tg) having 610 amino acids. Tg model was generated taking the modeled TS having 290 amino acids that was build using 1HVY template and DHFR having 248 amino acids was modeled using 1J3K and 2BL9 as templates. The linker region between these two proteins consisting of 72 amino acids was modeled using 1ON3 as a template. This bifunctional protein modeled by this process was very much refined compared to the conventional modeling scenario. The docking results were impressing by showing designed molecules to be top ranked compared to the existing molecules. Several classical and non- classical inhibitors of Thymidylate synthase with wide range of inhibition constants were taken and QSAR model was generated using multiple linear regression (MLR) method, this gave a good predictive model with r^2 = 0.959 and r^2_{loo} = 0.871 with leave-one-out method with cross validation r^2_{cv} = 0.587. All the existing and designed molecules were docked into the TS (Human and E.coli) active site and existing molecules showed maximum 1-2 hydrogen bond interactions. The designed molecules had 6-8 hydrogen bonds with the active site. In the current docking studies on multiple receptors with 75 diverse structures, it is established that the designed molecules showed better binding affinity in terms of estimated dock scores. Hence, suggesting that these diversity oriented privileged molecules can be considered as most potent anti cancer agents.

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Drug Design And Development Using Pharmacophore Modeling And Virtual Screening

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A drug discovery cycle, to identify, to optimize and eventually take a compound to the market is generally along process (approx 12–15 years) and is very expensive (approx $500million R&D expense). The enormous pressure that pharmaceutical and biotech companies are facing, has created the need to apply all available techniques to decrease attrition rates, costs and the time to market. Pharmacophore identification is one such technique. As case study example of drug design against Cycloxygenase (COX) enzyme is being discussed here using Catalyst Software. COX enzyme catalyze the biosynthesis of prostaglandins and thromboxane from arachidonic acid (AA). In the present paper we summarize, the development of hypotheses of a dataset comprising six chemically diverse series of known inhibitors for COX-2, by using the Catalyst/ Hypogen module. The most predictive pharmacophore model, consisting of four features, namely, one hydrogen bond donors, one hydrogen bond acceptor, one hydrophobic aliphatic and one ring aromatic feature, had a correlation (r) of 0.954 and a root mean square deviation of 0.894. The model was validated on a test set consisting of six different series of structurally diverse 27 compounds and performed well in correctly classifying active and inactive molecules correctly. The resultant best hypothesis was used to screen databases viz. NCI and maybridge to produce hit compounds. 264 hits were obtained which were arranged according to their fit value in 8 categories and subjected to secondary screening using Lipnski's rule of five. The resultant compounds were then docked into the COX-2 binding site to study the ligand – protein interaction and binding energies were evaluated in terms of LUDI scores. Several new structural scaffolds have been obtained as a result of the virtual screening. The Compounds were screened in in-vitro assay and novel scaffolds were identified as lead compounds for development of COX-2 inhibitors.

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Natural History of Isoprostanes as Biomarkers of Oxidative Stress

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A large body of evidences implies that the measurement of isoprostanes is reliable biomarkers of oxidative stress. Isoprostanes are families of PGF-like compounds derived by non-enzymatic oxidation of fatty acids with two double-bonds or more. Of these, PGF2-like compounds specifically derived from arachidonic acid have received the most attention because of their availability at major research laboratories with long lasting interest in prostaglanding metabolism in the United States. Recent advancement in the analytical field has led to discovery of an array of other PGF-like compounds derived from linoleic acid, linolenic acid, eicosapentaenoic acid and docosahexaenoic acid. The aim of this presentation is to shed a light on the natural history of PGF-like compounds since their discovery by Nugteren in 1975, discuss recent achievement and address new directions in the filed.