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An Insight on Insilico Softwares

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Abstract

Discovery of a drug which involves time that causes a downside consequence in the development of new drugs. In this present decade computers provide support in the design, identification and optimisation of both targets and lead pharmacophores. They are various softwares both offline-online, free and purchasable available that assist in our research work for developing lead molecules. In my presentation I will be focussing on various such free easily accessible softwares that help us to provide a basic idea in our research. These soft wares gives a detailed idea in improving the pharmacokinetic parameters in the designing of molecules.
They include:

Chemicalize chemaxon online software: The physiochemical parameters such as pKa, solubility mg/ml, isoelctric point and Log P values for the compounds were determined by online computational method using chemicalize chemaxon software. These properties provided a detailed insight of solubility and ionisation. The software focused on change in the aqueous solubility of the compound with pH. As solubility has impact on ADME related properties like drug uptake, distribution and oral bioavailability that are relevant descriptors for property-based computational screening methods in drug discovery process. Hence this method served as a fast, reliable, structure-based method for predicting solubility in water for promising drug candidate.The pKa prediction program was based on the calculation of partial charge distribution of atoms in the molecule that uses a fragment-based method to identify different structural fragments in the molecule (micro and macro species) that alter the pKa of a molecule. The pKa graph was plotted against pH and micro species that alter the pKa value of the compound.

Molinspiration cheminformatics :Molinspiration cheminformatics was developed by Bratislava University, Slovak Republic. Molecule structures were imported by the JSME molecule editor written in java script. Important molecular properties such as MiLogP, total polar surface area, number of hydrogen bond donors and acceptors and others were assessed along with bioactivity score for the most important drug targets such as GPCR ligands, kinase inhibitors, ion channel modulators, nuclear receptors, protease and enzyme inhibitors. A good descriptor to predict oral bioavailability of drugs depends on the number of rotatable bonds, a topological parameter that measures molecular flexibility. The greater the number of rotatable bonds the more is the oral bioavailability.

DataWarrior,: offline downloadable software Datawarrior developed at Actelion Pharmaceuticals Ltd. It was specialized in data visualization and analysis tool for chemical and biological data. After the software was downloaded, window of datawarrior opens and analysis of data was carried as follows: From the File menu, Open... was selected and the dialog window to import the selected SD-file(s) (the file extension is .sdf). The entire content of the SD-File was read by datawarrior and data was displayed as rows in the table view, where defaults 2D- and 3D-views were developed. Structure view was created which generates a structure index with fragment descriptor needed internally for some structure related tasks. It was used to assess the toxicity risk within one of five major toxicity classes (tumorigenic, mutagenic, irritant, reproductive effective, nasty functionality). It was also used to assess a compounds drug likeness partially based on topological descriptors, properties as cLogP and molecular weights.

OCHEM: The cytochrome P450 (P450 or CYP) isoenzymes are a group of heme-containing enzymes embedded primarily in the lipid bilayer of the endoplasmic reticulum of hepatocytes, it takes part in the metabolism of many drugs, steroids and carcinogens. Drug-drug interactions have become an important issue in health care. It is now realized that many drug-drug interactions can be explained by alterations in the metabolic enzymes that are present in the liver and other extra-hepatic tissues. Many of the major pharmacokinetic interactions between drugs are due to hepatic cytochrome P450 (P450 or CYP) enzymes being affected by previous administration of other drugs. After co-administration, some drugs act as potent enzyme inducers, whereas others are inhibitors. OCHEM an Online chemical modeling software used to predict the inhibition designed compounds against CYPP450 and its isotypes such that we can predict its metabolism and interactions.

Swiss ADME: the website was accessed using http://www.swissadme.ch/ in a web browser that displayed directly the submission page of Swiss ADME. Molecules were directly pasted or typed in SMILES format or drawn in the Molecular Sketcher and were transferred into the list of smiles by clicking on “double arrow button”. When the list of compounds was ready to be submitted click the “Run” button and the calculations appear as one-panel-per molecule Output. The output results in two sections: The first section, including the two-dimensional chemical structure and canonical SMILES and the second section, includes Bioavailability Radar displayed for a rapid appraisal of drug-likeness After all calculations completed, the “Show BOILED-Egg” red button appears below the sketcher to display the graphical output on the same page. This consists primarily in the BOILED-Egg with WLogp *vs.* TPSA on x and y axis respectively, an intuitive method to predict simultaneously two key ADME parameters, i.e. the passive gastrointestinal absorption (HIA) and brain access (BBB). The knowledge about compounds being

substrate or non-substrate of the permeability glycoprotein (PgP) plays an important to estimate active efflux through biological membranes. BOILED-Egg was used to predict gastrointestinal absorption and brain penetration of molecules that contribute in the cell permeability and bioavailability to a substantial extent.

Pharmagist: A pharmacophore mapping tool.
Source: www.pharmagist.com
The method consists of four major stages: (i) ligand representation (ii) pairwise alignment (iii) multiple alignments and (iv) solution clustering and output. In the first stage, each input ligand was processed separately. The method detects the rotatable bonds of the ligand and divided it into rigid groups accordingly. In addition, the ligand was assigned with a set of physiochemical features (hydrogen bond donor/acceptor, anion/cation, aromatic ring, hydrophobic group and other features defined by the user). In the second stage, were given a pivot (treated as rigid) and one target ligand (treated as flexible), pairwise alignments were computed. First, for each rigid group of the target ligand, the method generated a set of transformations for superimposing the target rigid group onto the pivot. The result for each target rigid group was a set of candidate new poses on the pivot. Then, these poses were reassembled into new conformations of the target ligand aligned on the pivot. The score of a resulting pairwise alignment was a weighted sum of the matched pivot features. Two features, one from the pivot and one from a confirmation of the target ligand were matched if they were of the same type and the distance between them were predefined by various thresholds represented as $1A^0$ by default. The output of the stage was a large number of high-scoring pairwise alignments between the pivot and the target ligand. The third stage also worked with a selected pivot. Pair wise alignments between the pivot and the target ligand which were combined into multiple alignments. The goal was to find significant subsets of pivot features that were matched by as many pair wise alignments for different target ligands as possible. However, maximizing the number of aligned ligands was done contradictory to maximize the score of the matched features. Thus, the method produced multiple alignments for each subset size of input ligands. Due to efficiency considerations, this was achieved by enumerating all the possible subsets of pivot features and the ones selected can be aligned by as many ligands as possible. Subsets of pivot features with a significant score for pharmacophores will be reported to the user.
I will be able to deal with these softwares with a few examples and I will be focussing on my research highlighting these softwares.

Our research work:
In the study two subclasses of coumarin derivatives were selected 14 coumarin sulphonamides and 14 coumarin schiff bases *i.e.*, totally 28 compounds from our earlier research work. A comparative study for two subclasses of coumarins by using various CADD (online and offline) softwares. Computational calculations and predictions of important molecular properties suggest that among the two sub classes of coumarin derivatives, coumarin Schiff bases could be further improved to provide biologically active agents. These results and insights drawn from the computational calculations and predictions offers an opportunity to further modify the coumarin Schiff bases accordingly as potential biological agents. The insights drawn from these theoretical studies would be harnessed to further improve their pharmacokinetic properties.