MedChem Sample Application

To maximize productivity at the bench, medicinal chemists spend a considerable amount of time collecting, exploring and evaluating different sets of molecules related to their therapeutic project. These might be lists of active molecules within that project, compounds currently considered for synthesis, or lists gathered from the literature or patents.

Due to the complexity of the procedures and software that must be used, the process of gathering information from across the organization, performing a variety of calculations, organizing the resultant data and sharing results can be inherently slow and difficult. Time is wasted by chemists wrestling with data and applications, and computational chemists are burdened with performing routine calculations which the medicinal chemist could perform for themselves if they only had a simple means to do so. As projects rapidly evolve, medicinal chemists need access to computational tools that will rapidly deliver the information they need, such as:

- What are the molecular properties of a given set of molecules?
- What are the trends in structure-activity relationship?
- What are the latest biological screening results?
- What is known in the literature about their molecules and those of their competitors
- What reagents are available to synthesize the compounds they need

"The Medicinal Chemists Sample Application"

The MedChem Sample Application demonstrates a straightforward method of managing lists of compounds, gathering information about them and performing routine processing tasks, all presented in a simple, easy-to-use web interface. Powered by Pipeline Pilot Enterprise Server (PPES), the MedChem Sample Application allows domain experts within an organization, such as research IT, computational chemists, or expert medicinal chemists to capture their best practices encoded as protocols (or workflows) and have those protocols deployed through a web application to bench chemists. Using the Pipeline Pilot client, tasks can be encoded using an intuitive graphical interface that doesn't require programming expertise. The wide range of scientifically aware components for chemistry, bioinformatics, statistics, data mining, image and text processing available within PPES ensures that a host of tasks relevant to medicinal chemists can be built and deployed across an

organization. Furthermore, PPES allows existing validated in-house or 3rd party programs to be incorporated, meaning that underlying results can remain consistent and best value can be obtained from those programs.

Real Results in the Real World

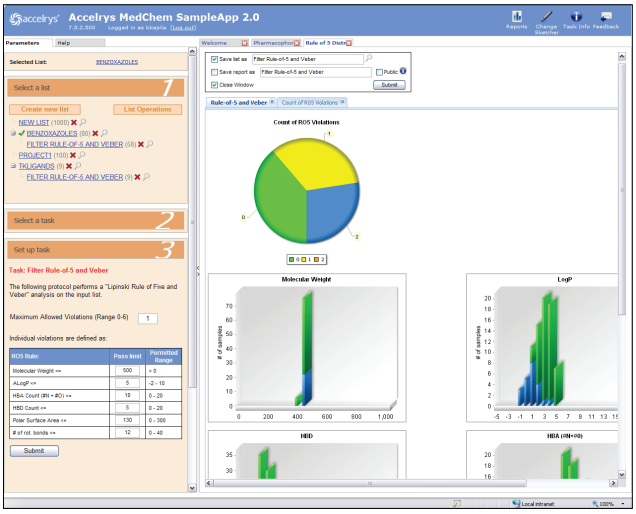
Applications similar to the Medicinal Chemists' Sample Application have already been developed by a number of pharma and biotech customers and a previous version of the Sample Application has been deployed in many organizations. They have all deployed a web application built on top of Pipeline Pilot Enterprise Server and published protocols built using the scientific collections. At user forums, a number of these companies have discussed the need to have a simple one-stop-shop to present routine tasks to the chemistry community that doesn't require the mastery of multiple programs and the manipulation of files to achieve results. Typical tasks they have deployed include Rule of 5 property calculations, identification and elimination of molecules with reactive fragments, learning and elimination of promiscuous hitters, inventory and screening status reporting. In many cases, protocols are built that capture the collective

wisdom of experts within the company and make it available to all scientists. Implementing an application like the Medicinal Chemists' Sample Application has been shown to provide a significant return on investment (ROI). Before implementation, two companies we studied had to have computational chemists run property calculations for chemists, due to the complexity of the various software packages that had to be used. After implementation, chemists could run calculations for themselves. Balancing the savings in cost of the time of the computational chemists in the prior process vs the expenditure on software and implementation of workflows, a large pharma customer found a 3:1 ROI, a mid-size biotech found a 4:1 ROI. In both cases, after implementation they found an additional intangible benefit that many more jobs could be run without the bottleneck of the computational chemist's availability—turnaround time went from days to minutes. In other words, chemists started asking more "what-if" questions and more fully exploring their compounds. Full details of the ROI studies are available from your Accelrys account manager.

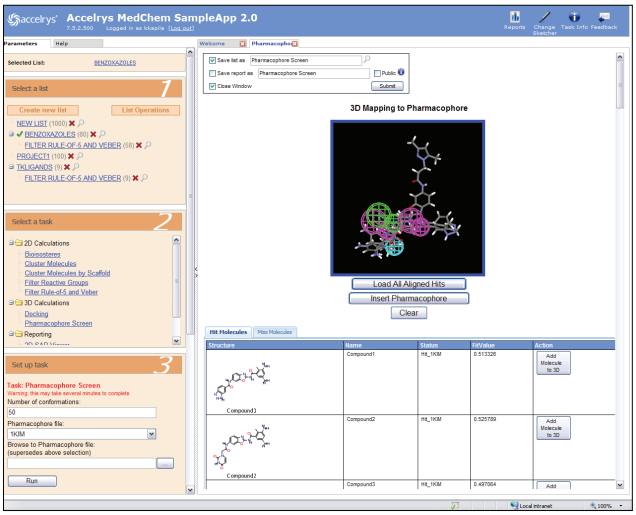
Typical Sample Application Tasks

A wide range of tasks are available within the Sample Application including:

- **List creation** – generates lists by loading a file, sketching molecules, providing a list of corporate IDs, Accelrys List Management Query Services (LMQS), or by structure based search against a corporate database
- **Cluster molecules** – organizes molecules into clusters by structural similarity and allows browsing of the clusters or select of a single molecule representative of the cluster as a whole.
- **Filter Rule-of-5** – Applies the Lipinski Rule-of -5 and Veber calculations. Six molecular properties are calculated and a molecule passes the filter if it does not violate more than a given number of the upper bound rules.
- **Reactive Group Filtering** - Identify and annotate molecules with undesirable functional groups.
- **2D SAR Viewer** – generates a 2D SAR table with cells colored by activity (or other selected) value.
- **Bioisosteres** – Enumerates bioisosteres of incoming list molecules using three different methods.
- **Pharmacophore profiler** – allows a prebuilt 3D pharmacophore model to be applied to a set of input molecules, ranking the molecules by their fit to the model.



Rule of 5 filter – calculates molecular weight, logP, number of donors and acceptors and then filters out compounds that exceed acceptable ranges in one or more of those properties. Default limits are set by the computational chemists and can be overridden during a run



Pharmacophore filter – applies a pre-computed pharmacophore model to a list of molecules. Separate tables are produced for those that fit the pharmacophore and those that dont. For those that match the matching conformation is shown supperimposed on the pharmacophore in the 3D viewer and a fit score is given.

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