A web-based Glide Docking Interface for the Bench Chemist

-A good tool for communicating structure-based ligand design

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Introduction

Our objective:

- Build a Web-based docking interface using java applets and Schrödinger's Glide as a docking engine.

- The Interface should be easy to use and tools for evaluating the docked poses should be readily accessible.

- The user should be able to access the results by a hyperlink, making it easy to present and communicate structure-based design within SBIO.

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Infrastructure

The infrastructure is built in Perl/CGI.

The docking result viewer & Page for submitting jobs are written in HTML and Java script.

The docking result viewer use the Astex Viewer 2.0 Applet.

The Page for submitting jobs use the JME viewer.

Schrodinger products Glide & LigPrep running in batch mode.

We use an Apache web-server running on an Linux Red Hat machine. However, most web-servers running on any Linux flavor should be compatible with our setup.

Very robust:
Change from SGI to Linux: Only Perl dir had to be changed.

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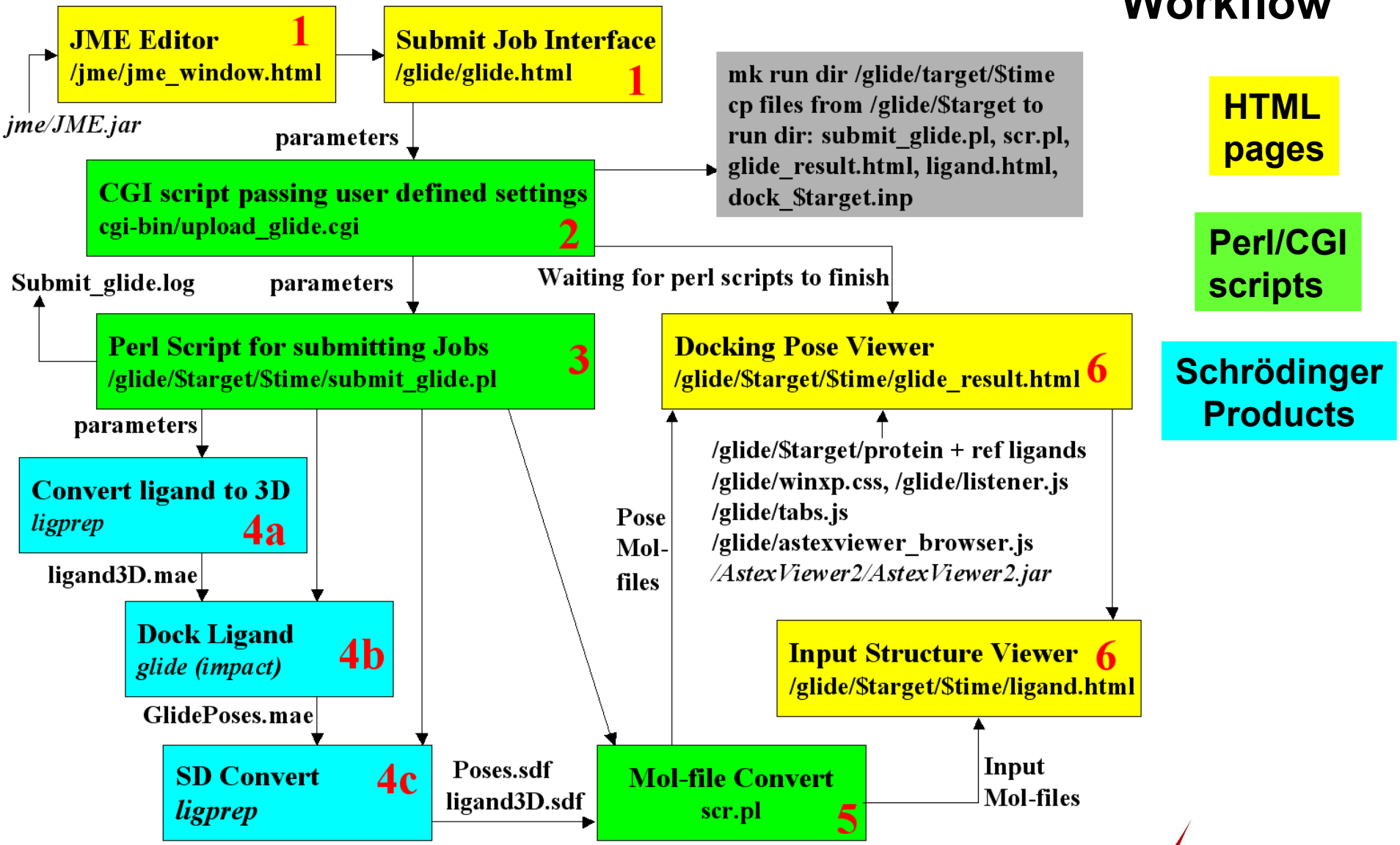
Workflow



HTML pages

Perl/CGI scripts

Schrödinger Products

Paths are relative to the htdocs root directory.

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Setting up Targets

Each target is set up by a computational chemist.

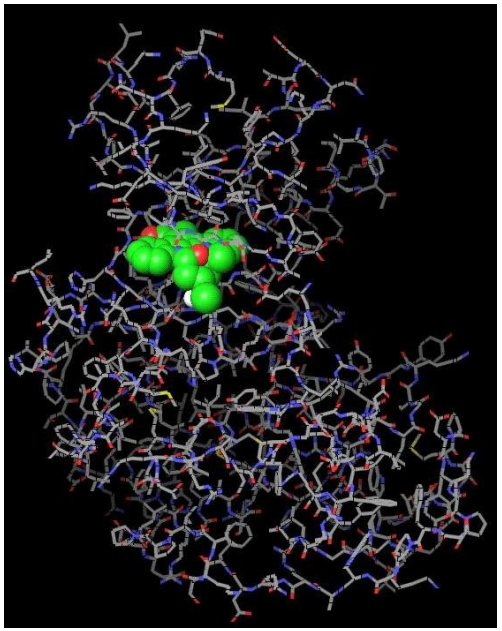
The X-ray structure is first superimposed on a template for the relevant protein family.

Protein structures are prepared as recommended by Schrödinger.

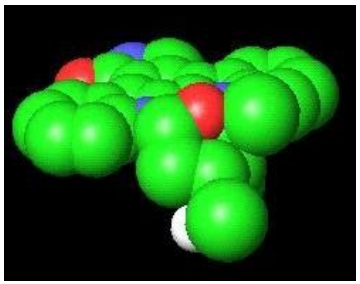
Grid files are calculated including proper constraints like essential hydrogen bonds or metal interactions. The user will not be able to switch the constraints off, and the docking will fail if the constraints are not fulfilled.

Reference ligands are selected: Reference ligand(s) used in the enzymatic assay, lead structures & and co-crystallised ligands from publicly available protein structures.

Superimpose target on template



Reference ligand



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Submitting Docking Jobs

Tautomerizer & Ionizer default on

Glide Docking - Web Mode

You can submit 1 compound in a MOL file (SDF file) or draw the compound in the editor. The results will be displayed in the Astex Viewer, which will automatically load once the docking calculation have finished. Maximum 20 poses will be shown. If you want to dock up to 10 compounds use Glide Batch docking. If you wish to dock more than 10 compound use Glide on a SGI workstation.

For more information see the FAQ page

Options: Make sure you select the right target. Otherwise dont change the default if you dont know the implications.

Ligand Preparation

Force input geometry of double bonds: OFF

Neutraliser & Ioniser: ON & ON

Tautomeriser: ON

Chirality: Ignore input Chirality

Max number of Ring Conformers: 1

Glide Docking

Target: CDK2 ..... X-ray

Penalise Cis Amide: ON

van der Waal Scaling: ON

Select a target and supply a valid structure. All other controls are optional

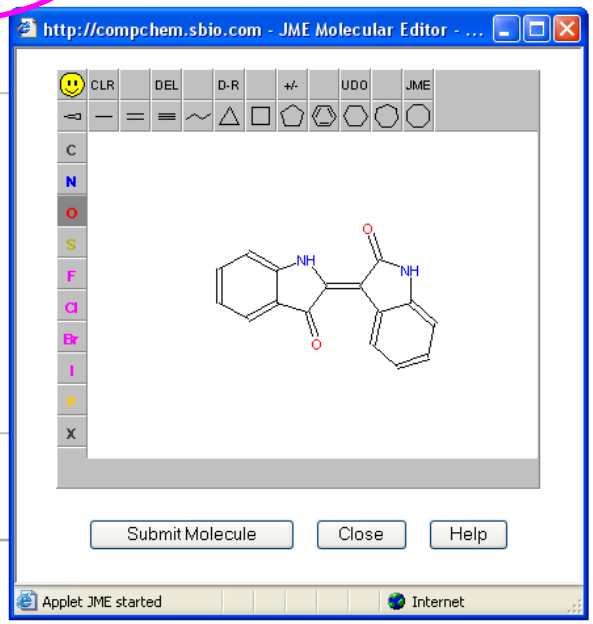
Press the Draw Molecule button, draw molecule and then press Submit Molecule button in the editor window. Alternatively paste a MDL MOL File into the text area

Clear | Draw Molecule

Process Molecule

A new page will load when your job has finished. Count on 1-5 min. for a druglike compound.

Do not refresh or go back once you have submitted the file!



The interface was designed to be as simple as possible while still enabling the user to maintain some control of the docking and ligand preparation.

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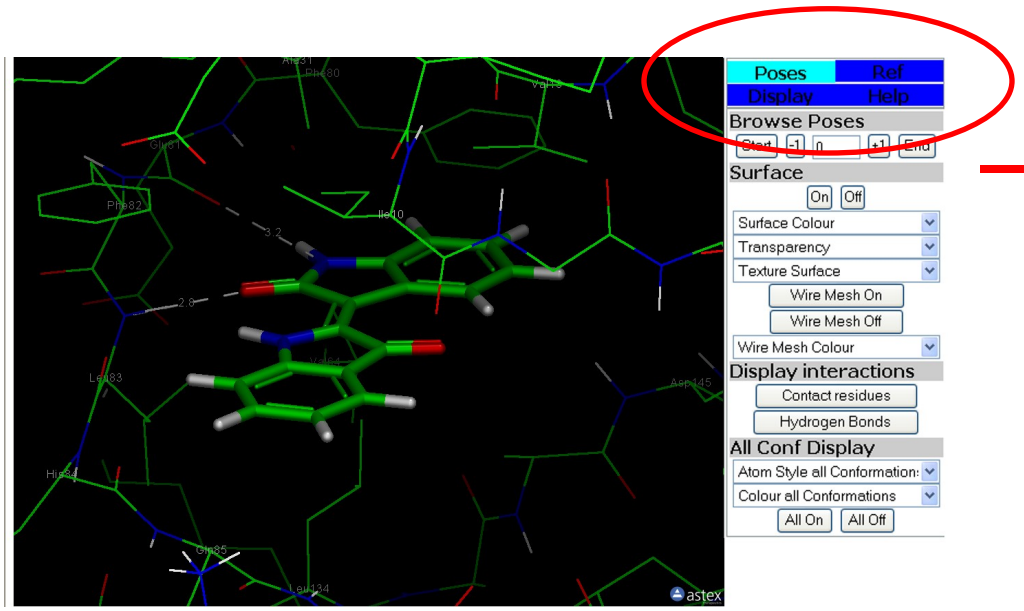
Viewing the Docking Results

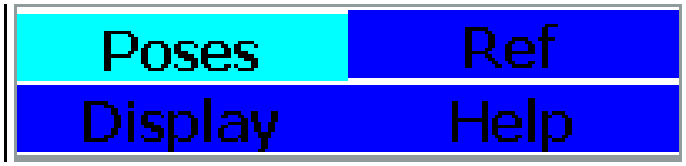
The docking result viewer is an HTML page displaying the AstexViewer 2.0 Java applet.

This page loads automatically when the docking job is finished.

The user can manipulate the viewer through controls on 4 separate tabs.

Poses: Browse through docked poses.
Ref: Target protein as well as reference ligands.
Display: More advanced graphics controls
Help: Information on shortcut keys and links to help files, log files.





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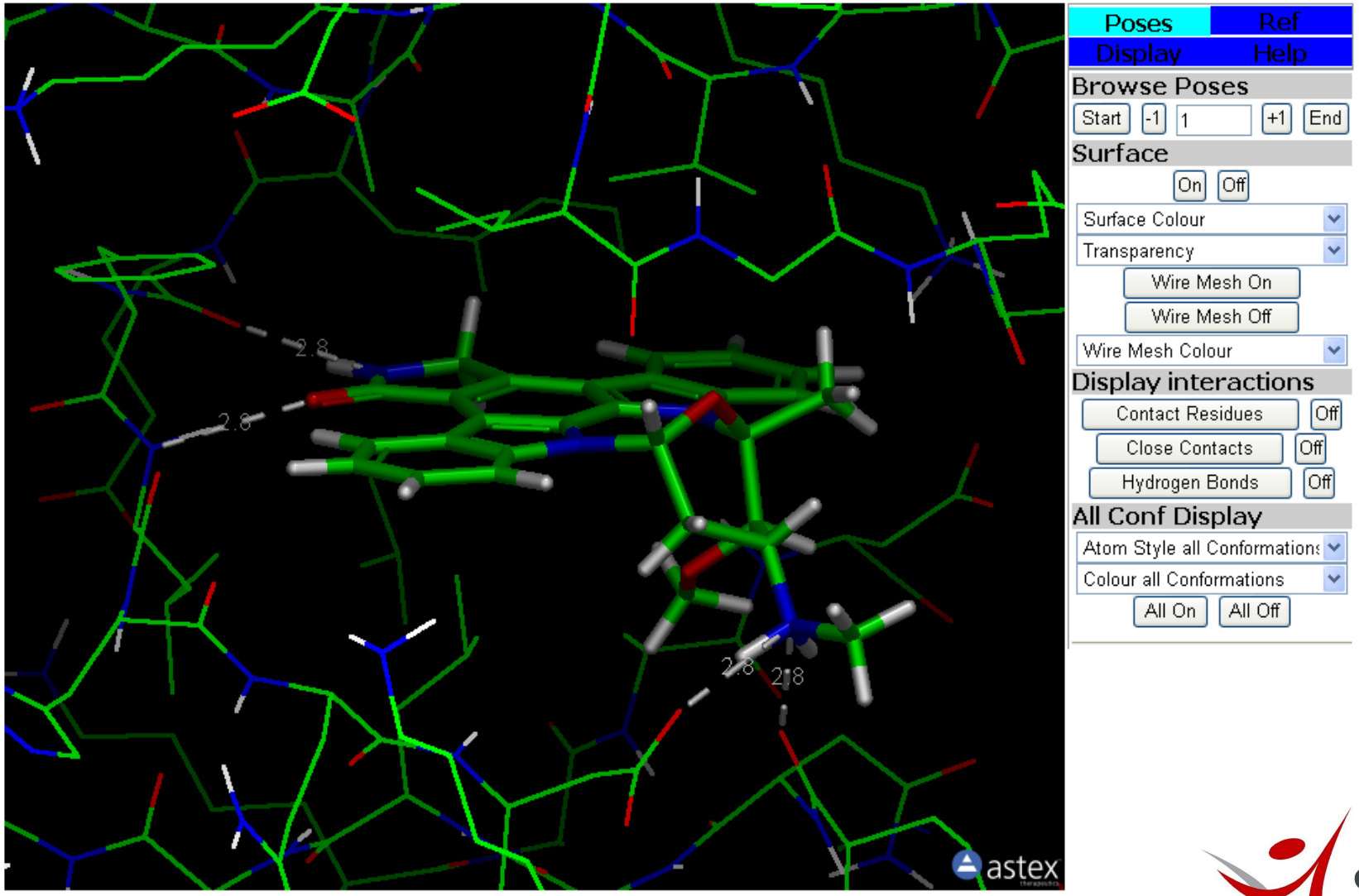
Viewing the Docking Results

Hydrogen bonds, distances and contact residues may be displayed for the active pose.



The docking result viewer displaying the “Poses” tab.

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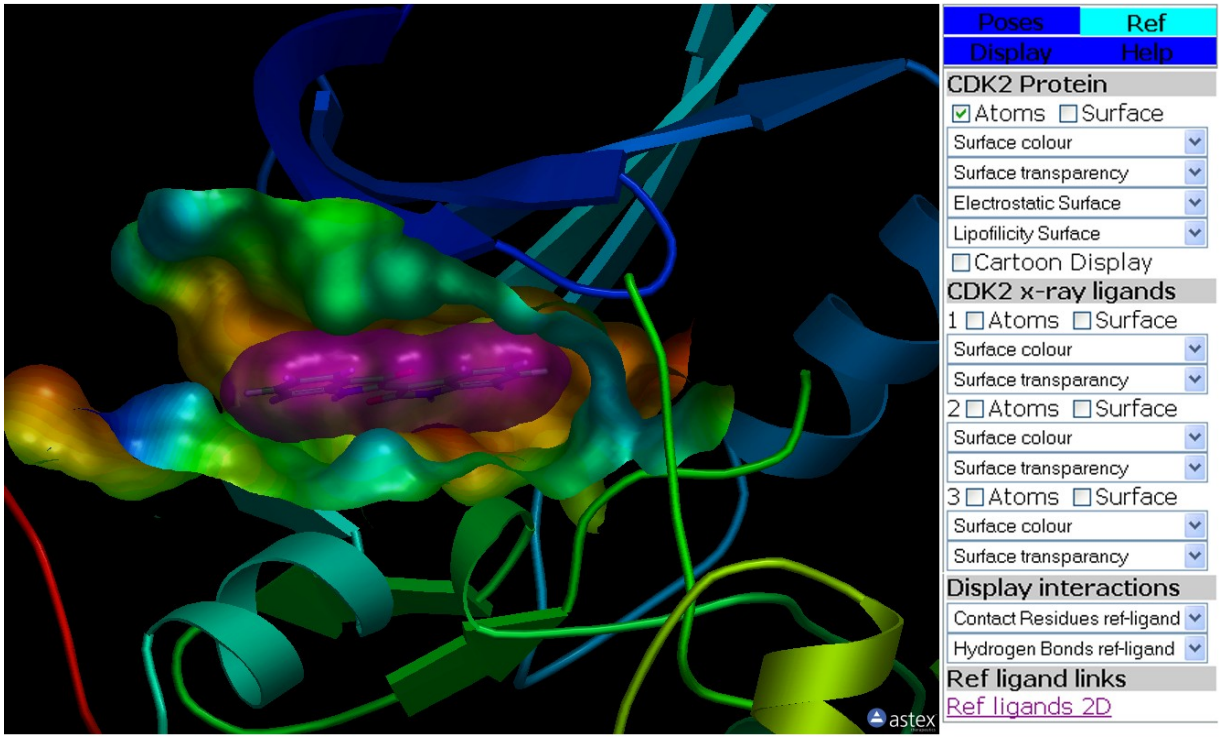
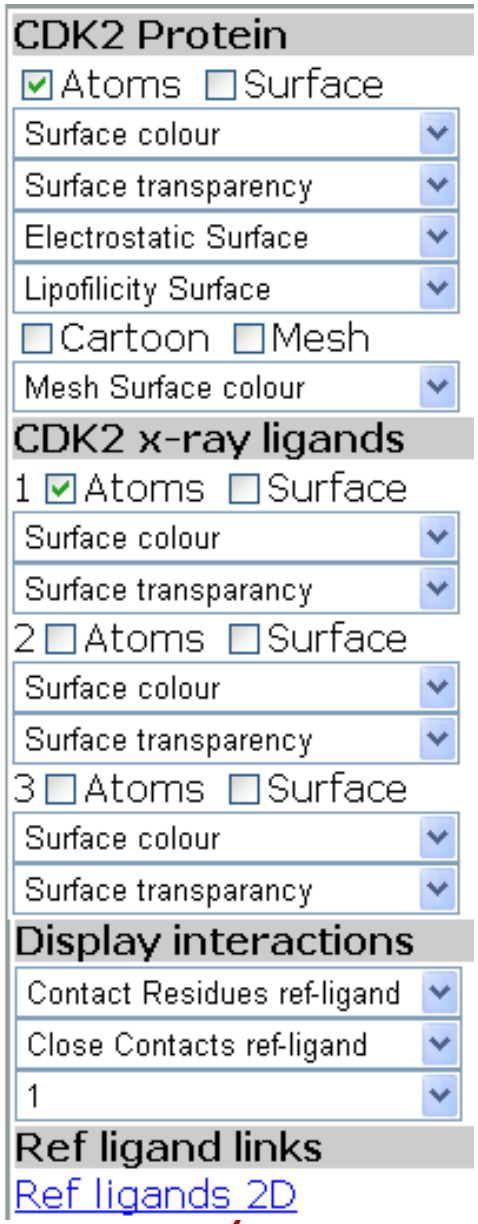
Evaluating Docked Poses

Displaying surfaces on the protein binding site as well as the pose is helpful in determining how complementary the ligand is to the receptor and how well it fills out the binding site The surfaces can be displayed as solid, transparent or mesh.



The docking result viewer displaying the "Ref" tab.



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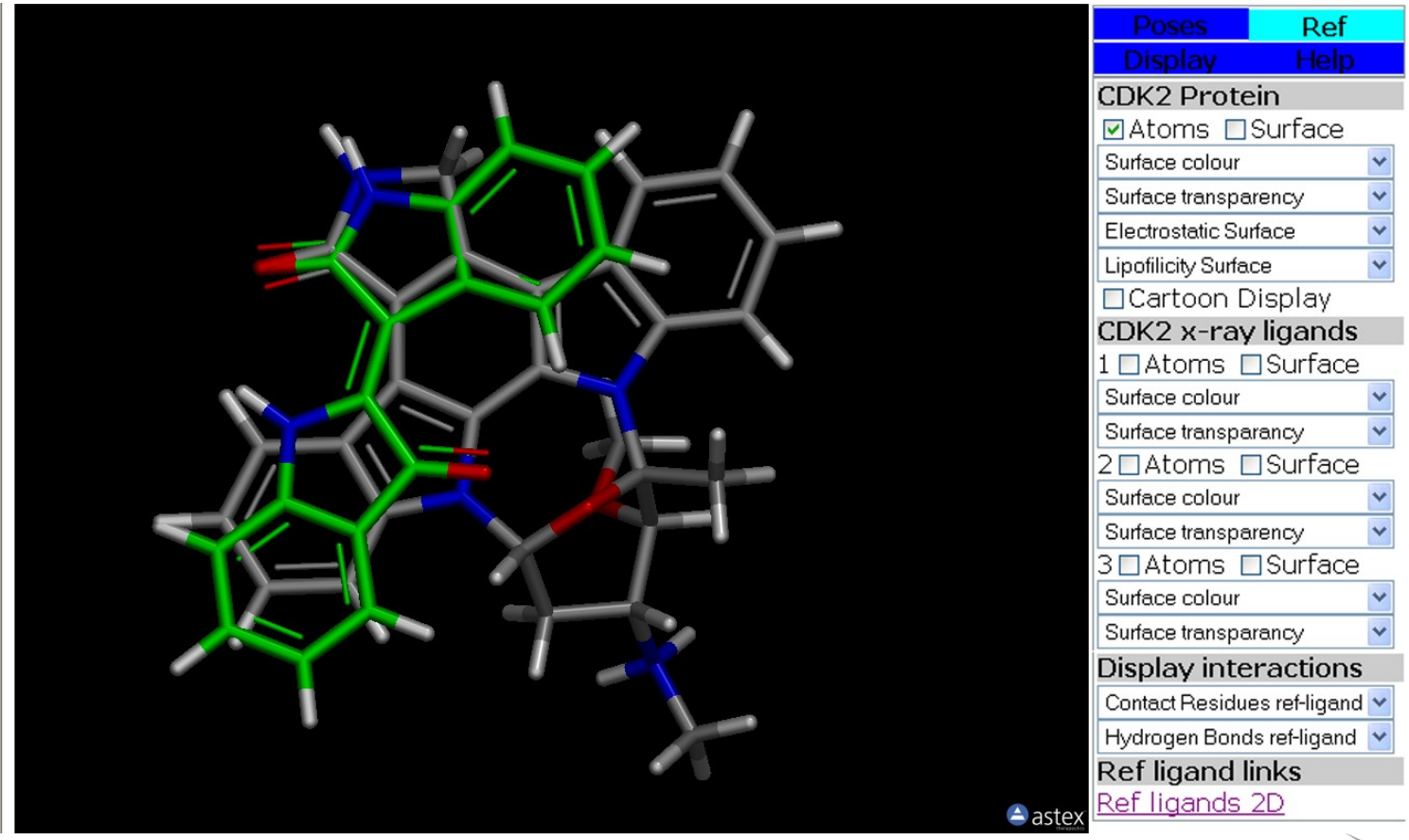
Evaluating Docked Poses

Medicinal chemists often think of protein-ligand interactions in terms of pharmacophores. Reference ligands containing these pharmacophore elements may be displayed to compare the binding mode to that of the docked poses.



The docking result viewer displaying the "Ref" tab.

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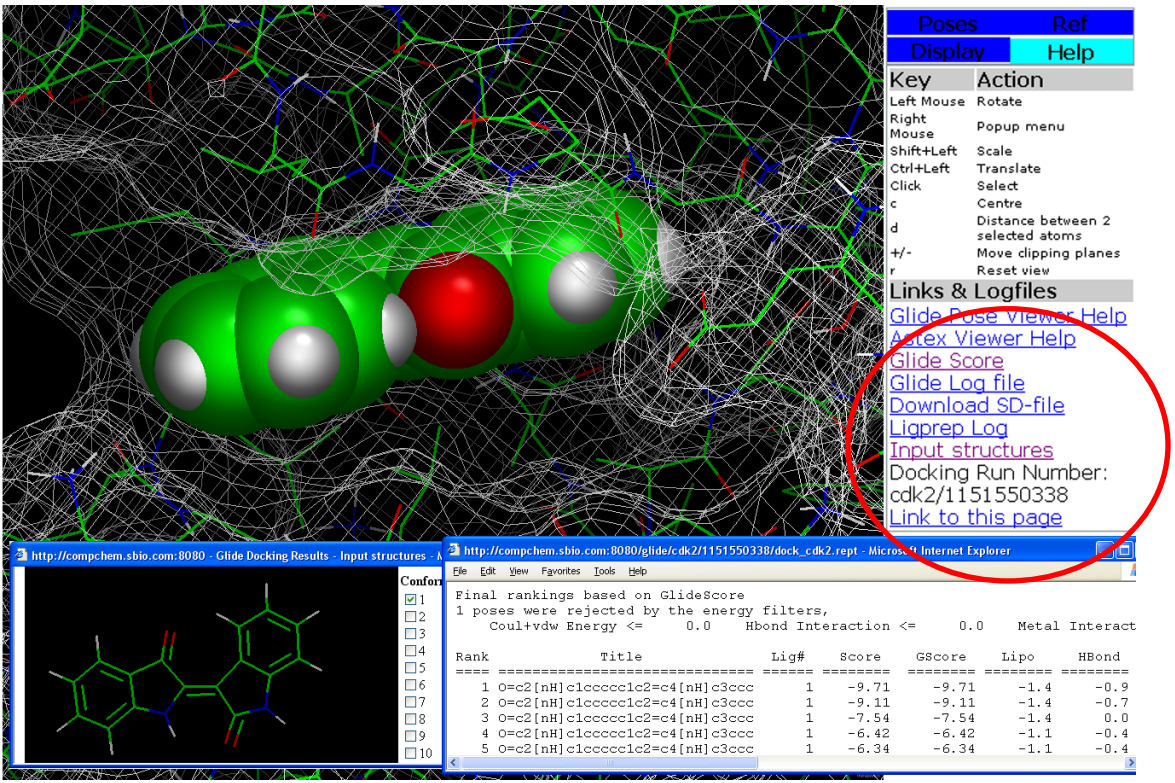
The Display & Help Tabs

The “Display” tab contains controls for the AstexViewer applet as well as for more advanced graphics controls for the protein, docked poses and reference ligands. Since the graphics rendering of the applet is excellent, these are useful for displaying fancy graphics for screen-dumps.

In the “Help” tab information on shortcut keys and links to help files, log files and the Glide score are found. The output structures from Ligprep can also be opened in a separate window and displayed in the AstexViewer applet.



Glide Pose Viewer Help
Astex Viewer Help
Glide Score
Glide Log-file
Download SD-file
Ligprep Log-file
Input Structures

The “Help” tab with the Glide score and input structures open

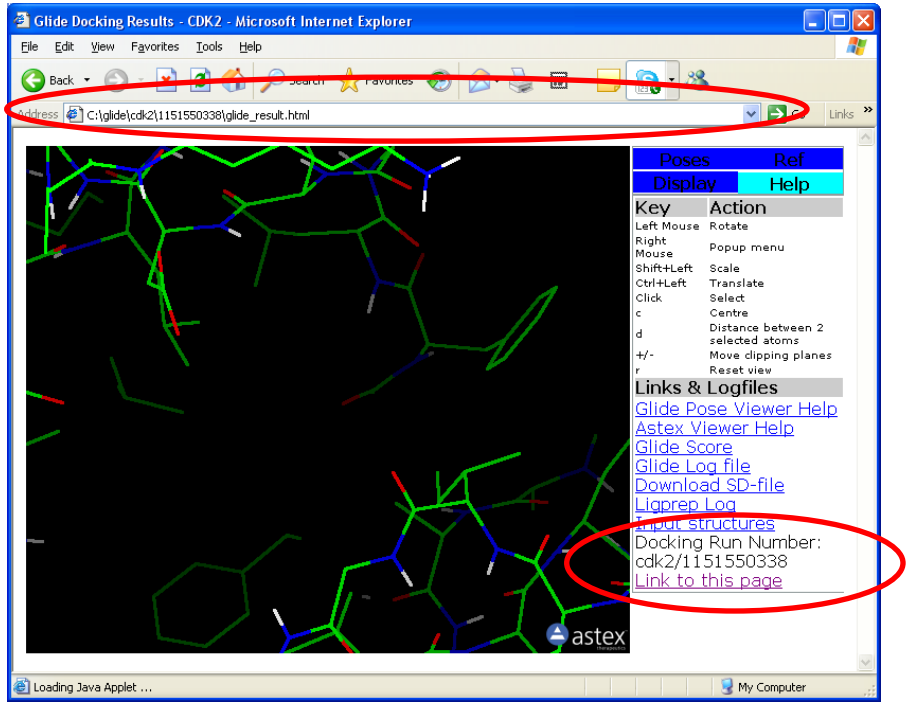
Communicating Structure-Based Design

The docking viewer interface resides in the unique job directory on the intranet server.

The link to the docking viewer interface can be copied and pasted into any document such as a PowerPoint presentation or an e-mail.

This makes it easy to share docking results with colleagues and present structure-based design at project meetings.

The only requirement is access to S*BIO's intranet.



Docking Run Number:
cdk2/1151550338
Link to this page

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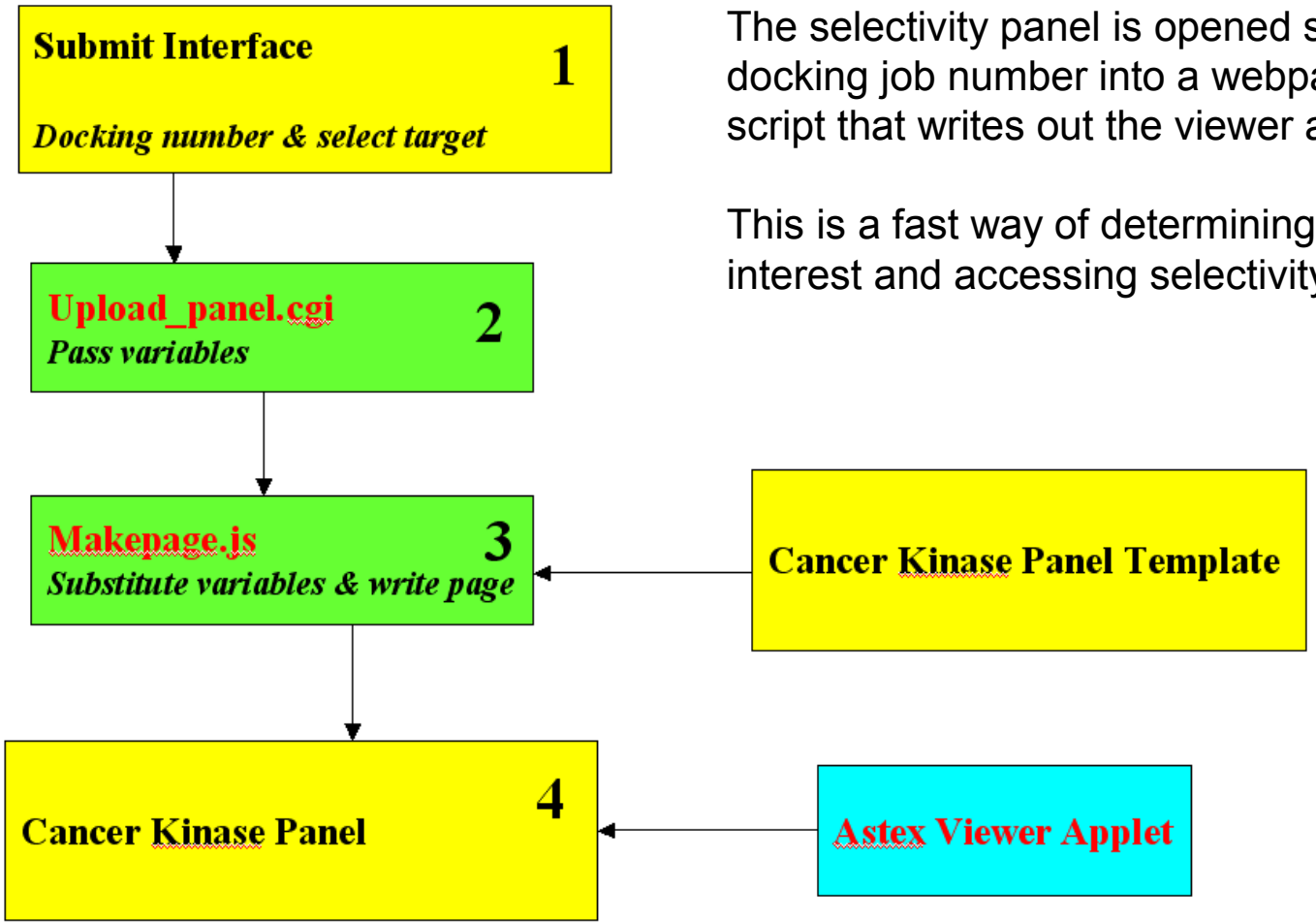
Cancer Target Viewer

The docking job number, i.e. the job directory, may be used to access the docking results from other viewers.

Cancer target panel: All cancer related kinase targets available from the Protein Data Bank were superimposed.

The selectivity panel is opened simply by pasting the docking job number into a webpage which calls a perl script that writes out the viewer as a new webpage.

This is a fast way of determining potential targets of interest and accessing selectivity.



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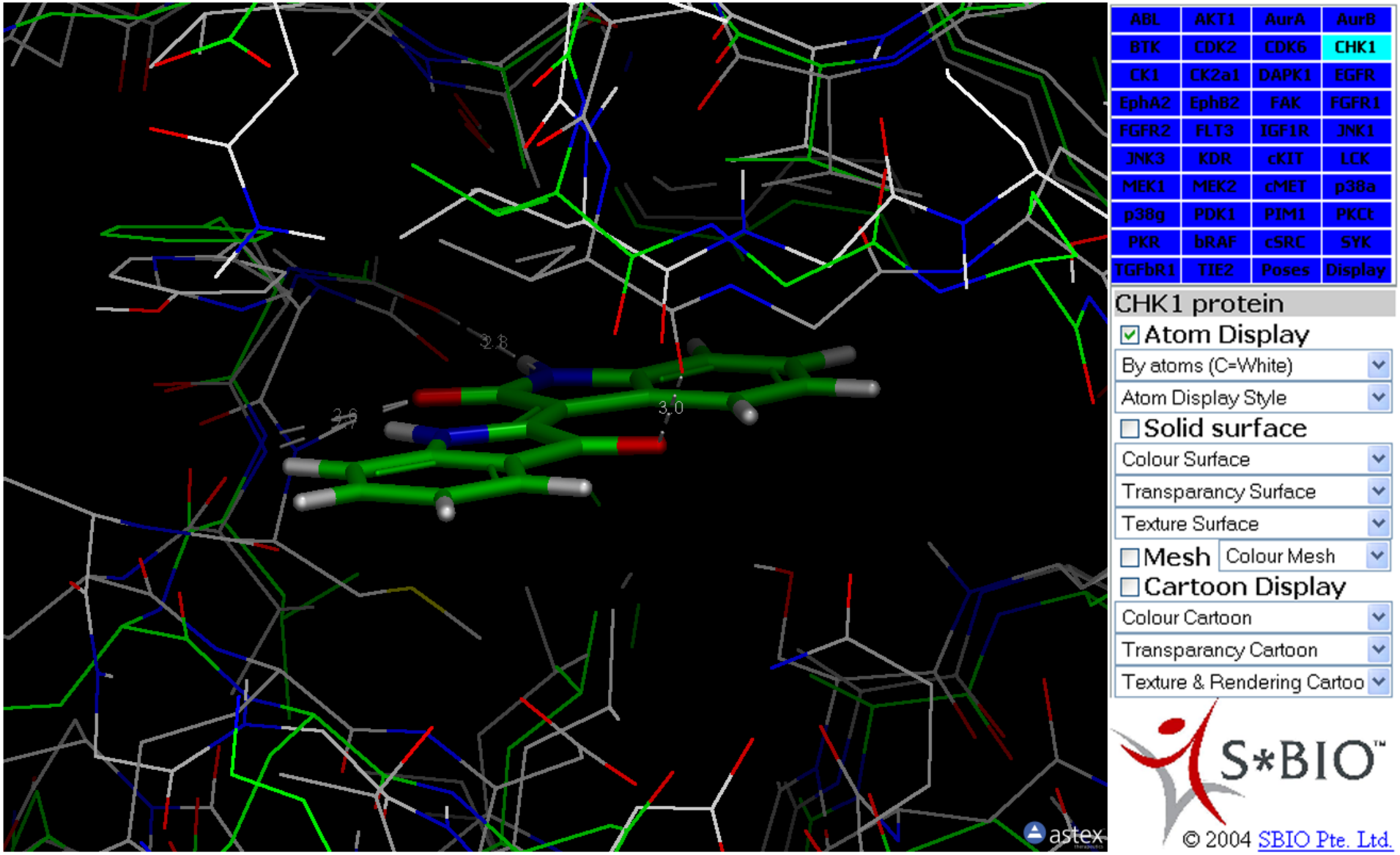
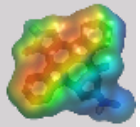
Cancer Target Viewer



The kinase cancer target panel. The binding mode of one target may quickly be compared to other targets.

Docking multiple ligands in multiple targets

View Glide Docking Results



This is only available for kinase targets. More targets can be added at your request

Select your target and key in the Docking Run Numbers (excluding target and slash, ie. only the numbers) shown on the bottom of the Docking Results page

For more information see the FAQ page

Target: CDK2 ..... X-ray
Docking Run Number 1:

Target: CDK2 ..... X-ray
Docking Run Number 2:

Target: CDK2 ..... X-ray
Docking Run Number 3: Submit Form Reset Form

View Glide Docking Results

The user may compare docking results from several targets just by pasting in the docking job numbers & selecting the targets. Similar set-up as cancer target panel.

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Conclusion

- We have built a Web-based docking interface that is intuitive and simple to use.

- The docking viewer contains tools that lets the user evaluate the docking results visually simply by the push of a button.

- The use of a target family template allows for building virtual selectivity panels.

- We use the docking viewer as a tool for communicating structure-based design within the company. Docking results may be shared with anyone who has access to our intranet or integrated into PowerPoint presentations.

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References

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