

A web-based docking interface for the bench chemist

- A good tool for communicating structure-based ligand design

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Introduction

As the number of x-ray structures of drugable targets increases, more bench chemists are venturing into the area of structure-based design. However, interpreting docking requires expertise in molecular modeling which is not always available to the scientist. Often the docking score alone is useless as a measure of how well a potential inhibitor will bind to the target protein, and a visual inspection of the docked poses is essential.

Our objective was to build a Web-based docking interface using java applets and Schrödinger's Glide [1] 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.

Work Flow

Each target protein is set up by a computational chemist. Appropriate docking constraints (e.g. hydrogen bonds or metal interactions) are included in the setup. If these are not fulfilled the docking will fail. The use of constraints ensures that many irrelevant poses are eliminated thereby making it easier for the user to evaluate the docking results.

The input structure may be drawn in the JME Editor [2], which is embedded in the webpage, before submitting the docking job. The input structure is sent to the server, where it is converted to 3D and possible tautomer and ionisation-states are enumerated with Ligprep [1]. The compound(s) are docked in the selected target using Glide. Finally the docked poses are converted to SD-files and the docking pose viewer loads on the user PC. This page uses the AstexViewer2 applet [3] for displaying and manipulating the protein target and the docked poses.

Figure 1 gives an overview of the workflow, programs and applets used in the docking. Yellow boxes: HTML pages. Cyan boxes: Programs running on server performing the actual docking job. Red text: Programs and applets. Each step is described by the text in italics.

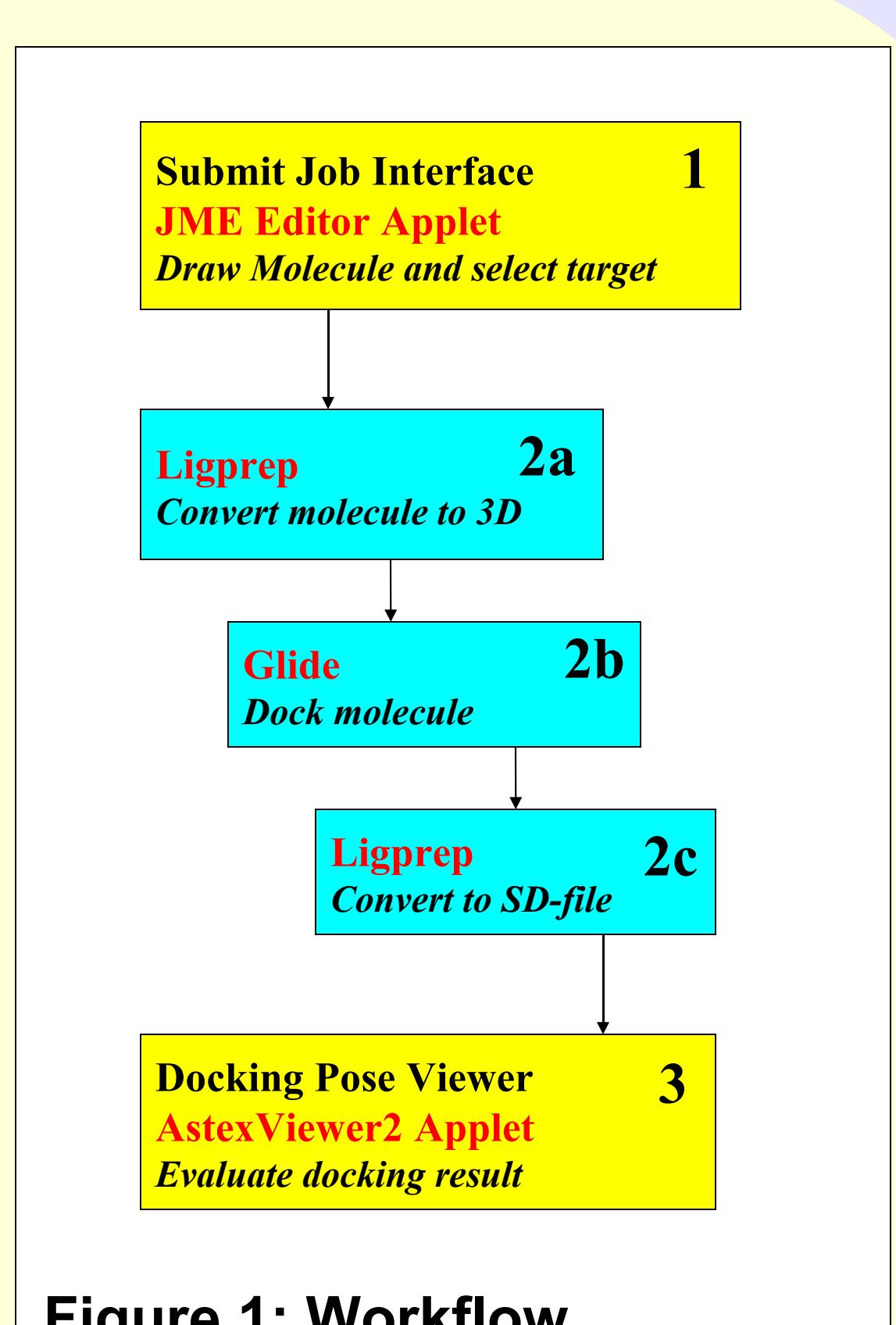


Figure 1: Workflow

Submitting Docking Jobs

The interface was designed to be as simple as possible while still enabling the user to maintain some control over docking and ligand preparation. Using pull-down menus, the user selects a target and supplies a valid structure. All other controls are optional.

The structure can be submitted as a mol-file or the user can draw the structure with the freely available JME Java applet [2]. As default, the tautomerizer and ionizer functions of Ligprep are run to produce physiologically relevant tautomer and ionization states of the ligand, but the user has the option to switch these off, thereby decreasing the docking time (**Figure 2**).

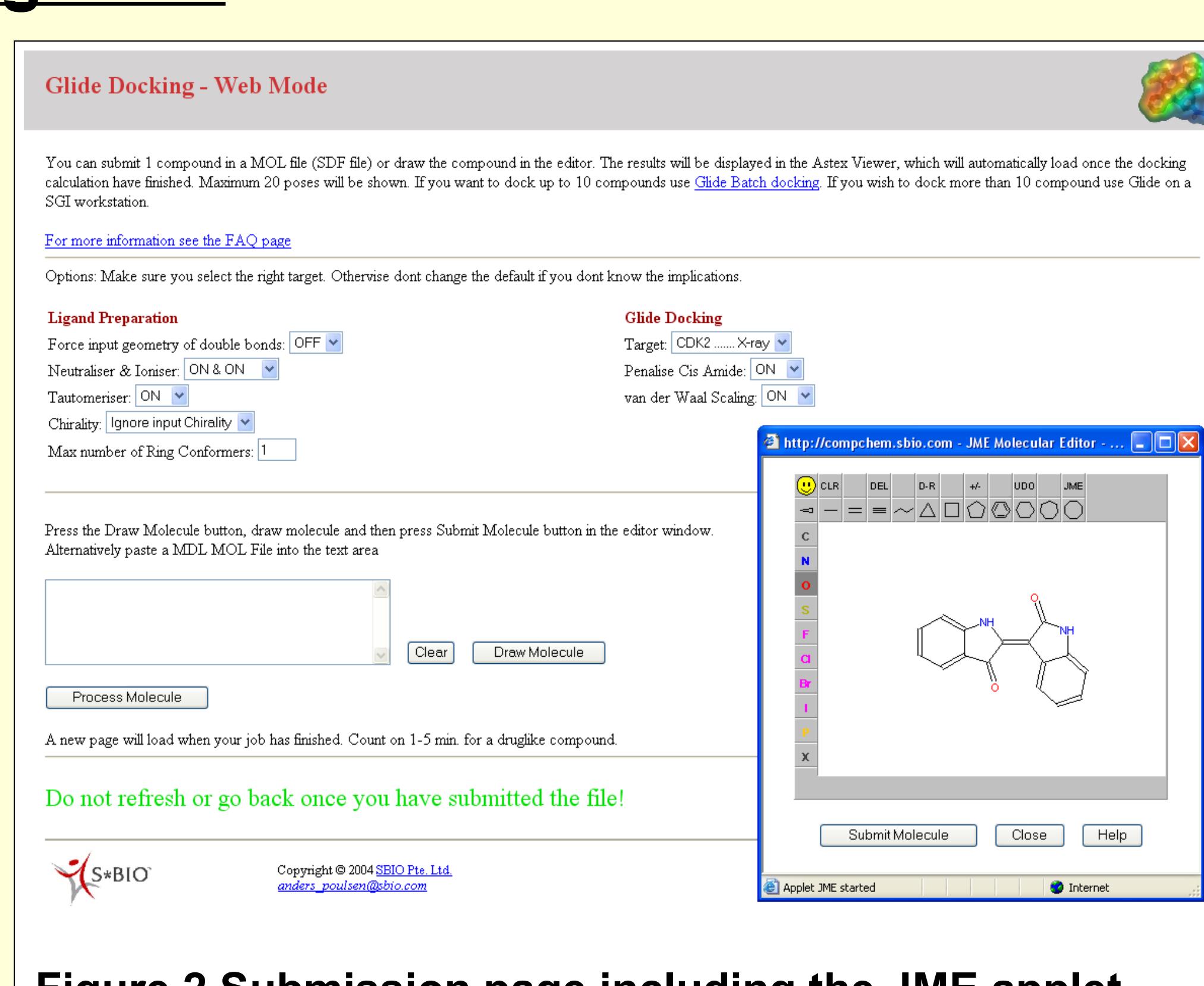


Figure 2 Submission page including the JME applet.

Viewing the Docking Results

The docking result viewer is an HTML page displaying the AstexViewer [3] Java applet. The user can manipulate the viewer through controls on 4 separate tabs. Each control executes a function written in Java script. This page loads automatically when the docking job is finished with the "Poses" tab displayed as default.

On this tab the controls for browsing through the docked poses is located on top. Below are other controls relating to the docked poses (**Figure 3**).

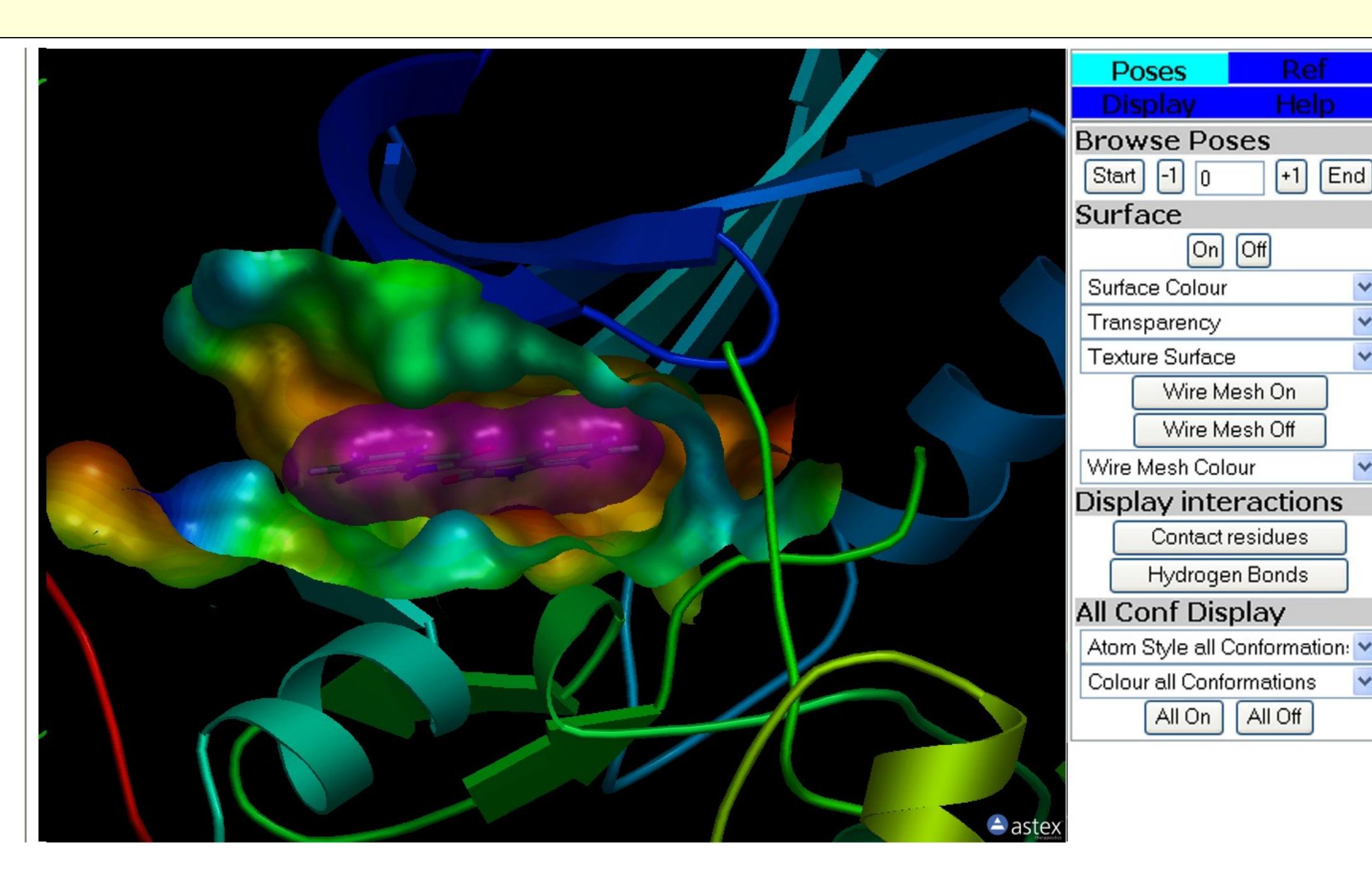


Figure 3: The docking result viewer displaying the "Poses" tab. Hydrogen bonds, contact residues and surfaces may be displayed at the push of a button

Evaluating Docked Poses

Our main objective was to write an interface which makes it easy to evaluate docking results. These controls are located on the "Poses" and "Ref" tabs. Hydrogen bonds and distances can be displayed for the active pose, as well as, for contact residues. Displaying surfaces on the binding site is helpful in determining how complementary the ligand is to the receptor and how well it fills out the binding site (**Figure 3**).

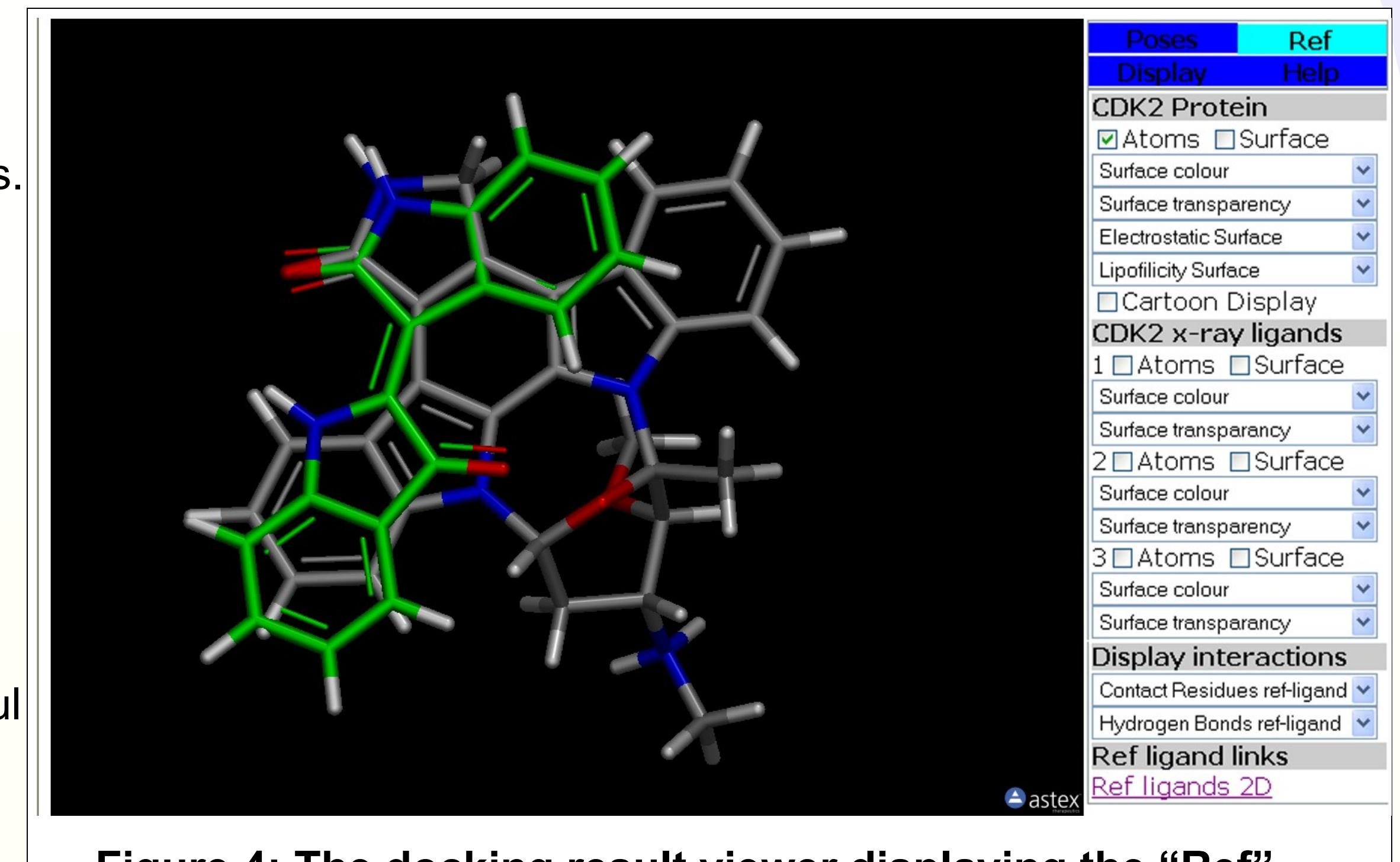


Figure 4: The docking result viewer displaying the "Ref" tab. The docked poses can be compared to the binding mode of reference ligands at the push of a button

Medicinal chemists often think of protein-ligand interactions in terms of pharmacophores. A very useful feature of our docking viewer interface is that the user can display reference ligands containing these pharmacophore elements and compare the binding mode to that of the docked poses. This is shown in **Figure 4** with the protein turned off. Displaying all reference ligands simultaneously is like superimposing the docked pose on a pharmacophore model.

Communicating Structure-Based Design

The docking results are saved in a unique job directory on the intranet server. The directory path is part of the link to the docking pose viewer interface, so the docking results can always be reloaded at a later date. The link 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 project team members. The link to the docking pose viewer interface can also be inserted directly into a PowerPoint presentation. This is an easy and interactive way of presenting structure-based design at project meetings. The only requirement is access to S*BIO's intranet.

Cancer Target Viewer

The hyperlink may be used to load the docked poses into other viewers. In the cancer target panel (**Figure 5**) all cancer related kinase targets available from the Protein Data Bank were superimposed. This is a fast way of determining potential targets of interest and accessing selectivity.

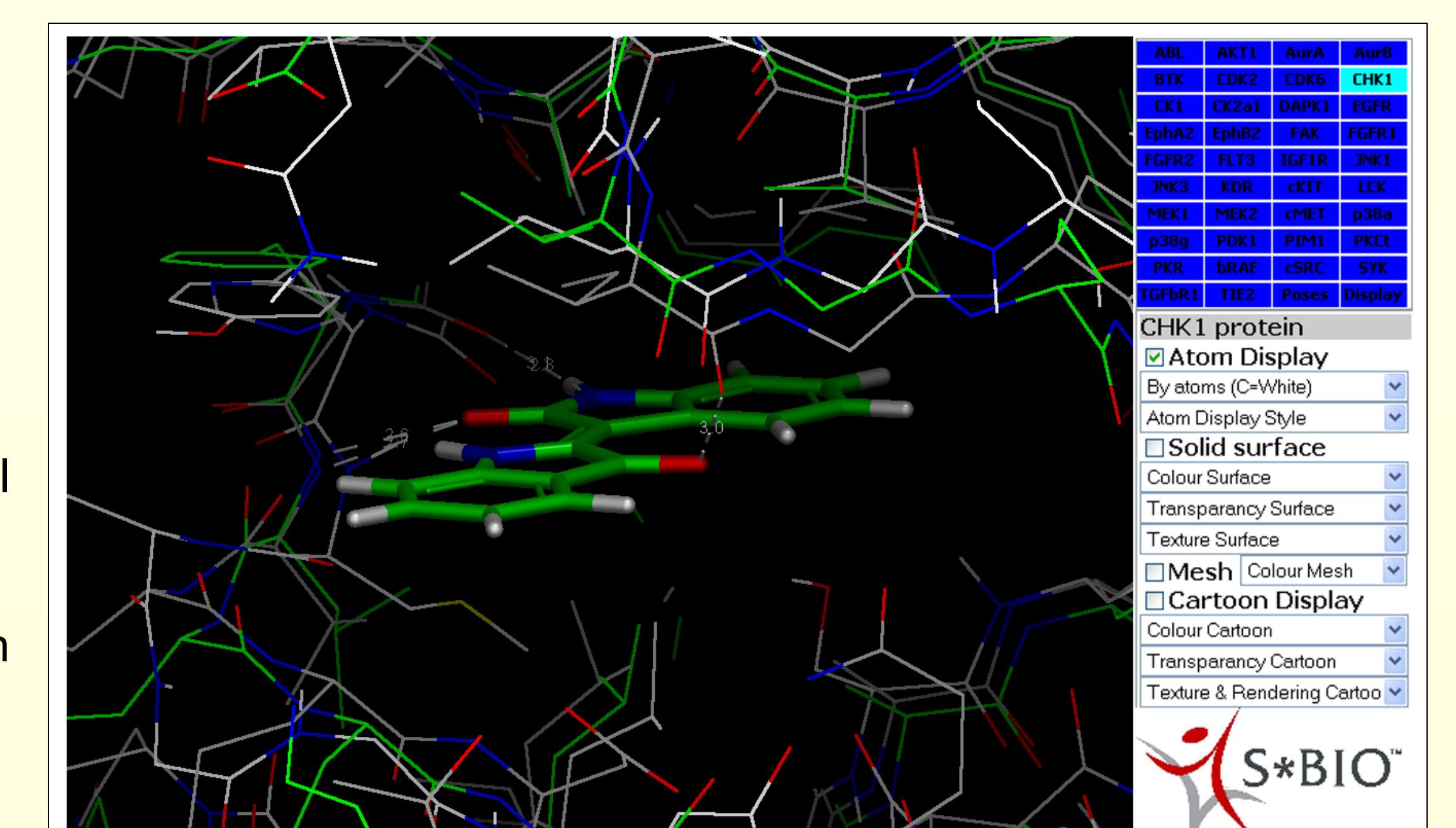


Figure 5: The kinase cancer target panel. The binding mode on one target may quickly be compared to other targets.

Conclusions

We have built a Web-based docking interface that is intuitive and simple to use. The docking pose viewer contains tools that let the user evaluate the docking results visually simply by pressing a button. We use the docking viewer as a tool for communicating structure-based design within the company. Docking results can be shared with anyone who has access to our intranet or integrated into PowerPoint presentations.

References

- [1] Schrödinger, 101 SW Main Street, Suite 1300, Portland, OR 97204, www.schrodinger.com.
- [2] Peter Ertl, Novartis Institutes for BioMedical Research, Basel, Switzerland, peter.ertl@pharma.novartis.com.
- [3] Astex Therapeutics Limited, 436 Cambridge Science Park, Milton Road, Cambridge CB4 0QA, United Kingdom, www.astex-therapeutics.com.