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Ligand preparation using Discovery Studio



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Ligand preparation

- Three-dimensional (3D) coordinates were generated for all ligands with LigPrep. Ionization/tautomeric states were generated with either a pair of fast rule-based programs (called the ionizer and tautomerizer) or with Epik, which is based on the more accurate Hammett and Taft methodologies.
- In addition to calculating reasonable ligand states, Epik also estimates a penalty to quantify the energetic cost it takes to generate each state in solution. The Epik state penalty is computed in units of kcal/mol, thereby making it directly compatible with the GlideScore used for docking and allowing us to explore the impact of adding the Epik state penalty to the GlideScore.
- The sum of the GlideScore and the Epik state penalty is referred to as the DockingScore in Glide. The DockingScore is used for the final ranking and enrichment calculations. Epik also has a mode to treat metal binding states, which involves increasing the pH range for the state generation step and then reducing the penalty in the docking stage for states where a negative charge is satisfied when binding to a metal ion.



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H-bond optimization (ProtAssign)

The H-bond optimization step (called ProtAssign) creates the best network of hydrogen bonds by placing/rotating hydrogens and functional groups that do not impact the electron density (Asn, Gln, and His). The optimized state was then subjected to force field minimization of only hydrogen atoms while keeping all other atoms fixed.

Analysis of DUD screening results

To simplify the analysis of all of the settings explored here, we compressed the 36 possible combinations of settings into 4 general levels of preparation: Minimal, Intermediate, Full, and Full ? Ligand. Minimal preparation involves only minimizing hydrogen atoms. Intermediate adds ProtAssign H-bond optimization. Full preparation adds Impref minimization of the protein with RMSD of 0.3 Å after H-bond optimization. Finally, Full ? Ligand adds Epik ligand preparation with metal binding states to the Full protocol. The enrichment results for these 4 protocols run on the Glide validation set and DUD exploratory sets with the HTVS mode of Glide.



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The role of water

Up to this point, all systems were prepared with water molecules removed prior to any preparation steps. However, it is interesting to consider the implications of preparing the targets with binding site waters present and then removing them before docking. Doing this, we found very little change in average enrichments if water molecules were retained or eliminated prior to the protein preparation process. For example, with the Full ? Ligand preparatio the average EF(1 %) enrichment for Glide SP on the Glide exploratory set changes from 27.0 without water molecules to 26.9 with water molecules in the preparation. Similar small changes are observed for Glide HTVS.



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➤ This application starts by clicking on the icon on the Desktop.

Discovery Studio Visualizer

File Edit View Chemistry Structure Sequence Chart Scripts Tools Window Help

Macromolecules Simulation Receptor-Ligand Interactions Pharmacophores Small Molecules X-ray My Tools

Search product features

Tools x DS Welcome x

BIOVIA | Discovery Studio 2017R2

What's new

Actions

My Recent Actions

- ▶ Open URL...
- ▶ Open...

My Recent Tool Panels

As you access different tools, the most recently used tool panels will be listed here.

Data

My Recent Files

- ▶ 3rze receptor.dsv
- ▶ 3rze.pdb
- ▶ Famotidine 1.dsv
- ▶ 6icg ALXR.dsv
- ▶ Aspirin.dsv
- ▶ 6icg.pdb
- ▶ 5u09 Cannabinoid.dsv
- ▶ 5u09.pdb
- ▶ 5xr8.pdb
- ▶ Paracetamol.dsv
- ▶ 4orrH2 receptor.dsv
- ▶ 4orr.pdb
- ▶ Famotidine.dsv
- ▶ 3bbb.pdb
- ▶ 5tgz Cannabinoid.dsv

Upgrade

▶ Upgrade now

Want more Discovery Studio? Unleash the power of the complete Discovery Studio with the BIOVIA Foundation:

- Homology Modeling
- Model Antibodies
- Create Pharmacophores
- Search and Build Databases
- Docking
- Fragment Based Design
- Scoring and Analysis
- Dynamics
- Electrostatics
- QM-MM
- ADMET
- Conformations
- Library Analysis and Design
- QSAR/SAR
- And more!

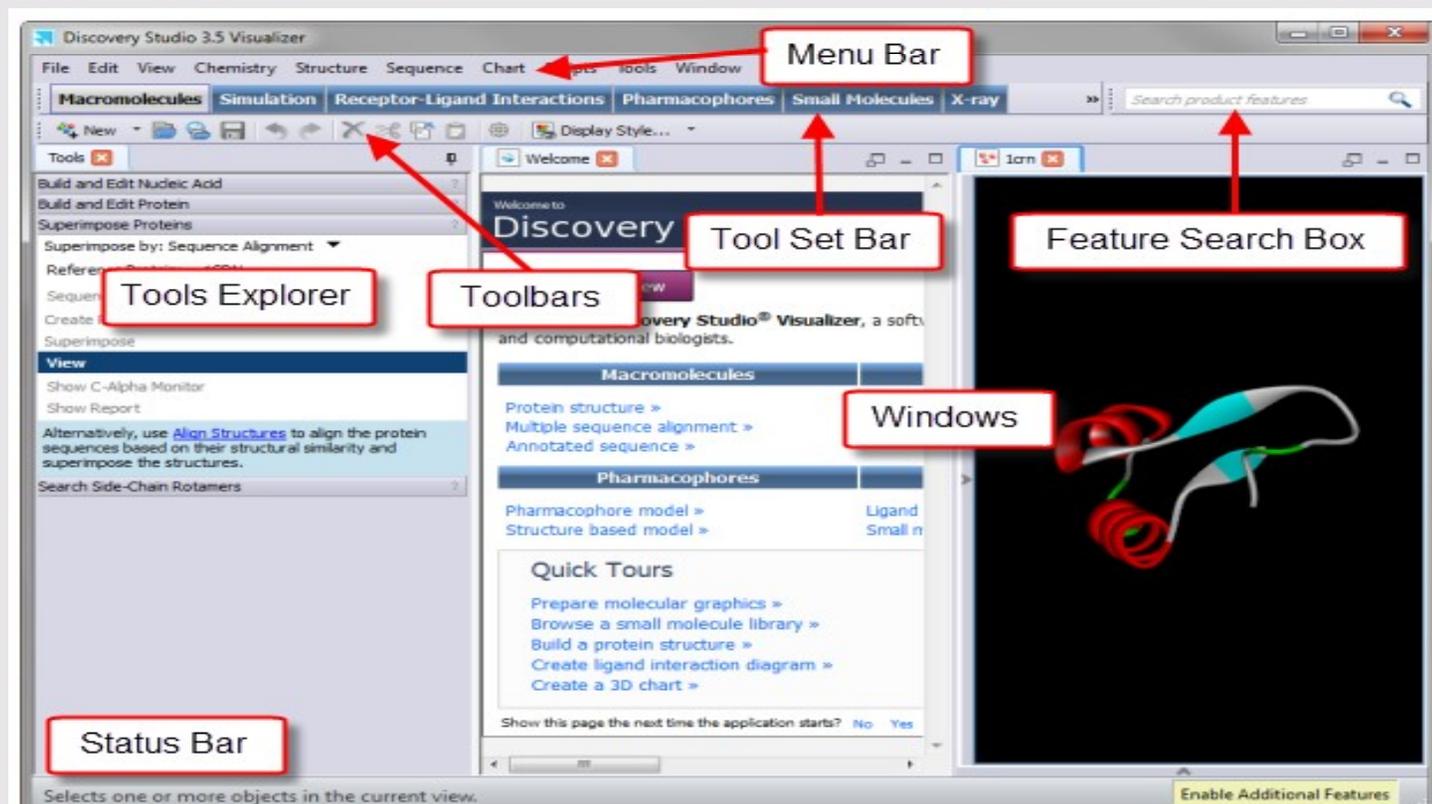
Enable Additional Features



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Application Workspace

- The application workspace occupies the main screen area when the application is opened.
- By default, a Welcome page is displayed in this space when the application is first started.
- As 2 subsequent windows are opened they can be easily arranged to either tile them or arrange them on top of each other.





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Discovery Studio Visualizer features

FEATURE	DESCRIPTION
Feature Search Box	Use this to search and open functionality.
Menu Bar	Select menu items to access commonly used tools, such as file access, editing, and viewing commands.
Toolbars	Click buttons to gain access to commonly used tools for viewing and editing data.
Tool Set Bar	Click buttons in the tool set bar to display different groups of related analysis tools in the Tools Explorer.



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Windows

The Discovery Studio Visualizer allows you to work with data in a variety of windows, including:

- Molecule Window: Edit and view molecular structures and property data.
- Sequence Window: Edit and view sequences and sequence alignments.
- Script Window: Create, edit, and execute Perl scripts within the Visualizer.

Status Bar

Displays information about the current application activity.

Files Explorer

Explore the file system to locate and open data files.



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- The application offers several ways of organizing and switching between windows.
- You can move a Window by clicking and dragging its tab to the desired position.
- In this way you can arrange windows on top of each other or organize them to view them simultaneously.

Tools

- Discovery Studio offers a wide variety of tools for working with and visualizing data.
- Tools can be accessed from menus, toolbars and tool panels. In addition you can create you own tools using scripting and expose them anywhere in the application. Of all of the methods for accessing the tools, tool panels are the most flexible.



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- Tool panels group tools based on specific tasks you want to perform. Furthermore, tool panels are groups into large sets for working in areas such as Pharmacophores and Receptor-Ligand Interactions.
- A useful feature for most buttons and menu items is the tool tip.
- Hover your cursor over a feature to display a small note that offers basic information about it. In many cases, the tool tip includes a link to more detailed help or related functionality such as preferences.
- Another valuable resource for finding information about the application is the Feature Search Box in the toolbar. To locate a feature, begin typing its name, or some term that relates to its functionality.
- A list of associated features appears in a dropdown list. The Feature Search Box matches text in the short descriptions of features so matches are obtained even if you do not specify the precise name of a tool. Click on it in the list to present the corresponding menu item, toolbar button, or tool panel.