

Creating pharmacophore queries

Required functionality and modules: Discovery Studio Client.

Required data files: 1aq1_lig.mol.

Time: 10 minutes.

Introduction

Discovery Studio provides several methods for creating pharmacophore models. You can:

- Automatically create a model from a set of ligands using the 3D QSAR Pharmacophore Generation or Common Feature Pharmacophore Generation protocol.
- Enumerate a collection of pharmacophore features from ligand(s) using the Feature Mapping protocol and then manually generate a pharmacophore from a subset of features.
- Use the Interaction Generation protocol to generate a collection of pharmacophore features in an active site of a protein.

Additionally, you can use the Edit and Cluster Pharmacophores tool to selectively display, cluster, and edit a set of pharmacophore features.

In this tutorial, you will learn how to build a basic pharmacophore starting from a single conformation of a ligand. The following tasks are covered:

- [Opening and viewing a ligand](#)
- [Adding pharmacophore features using ligand atoms](#)
- [Adding location constraints to the pharmacophore features](#)
- [Adding a shape constraint](#)

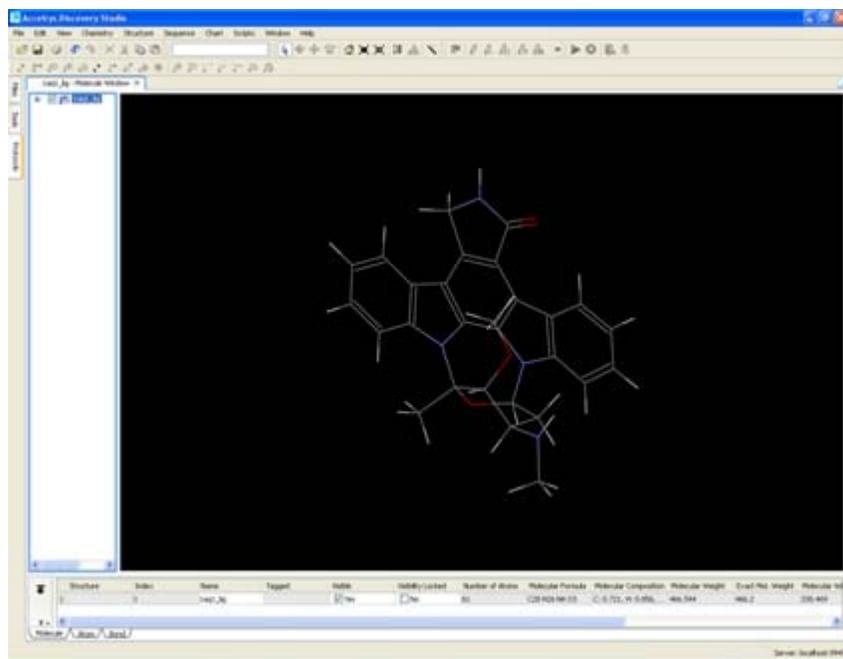
Opening and viewing a ligand

In this lesson you will build a pharmacophore starting with the X-ray structure of staurosporine complexed with Cyclin-Dependent Protein Kinase 2 (CDK2). The PDB code for this ligand-protein complex is 1AQ1. The file was downloaded from the PDB web site and the ligand was extracted and exported to 1aq1_lig.mol.

From the **Files Explorer**, open **Samples | Tutorials | Pharmacophore | 1aq1_lig.mol**.

This opens 1aq1_lig.mol in a Molecule Window. Typically, only the Data Table View is displayed when opening small molecules. Since interaction with the molecule is required for adding pharmacophore features, you will need to ensure the Graphics View and Hierarchy View are displayed.

From the menu bar, choose **View | Graphics**, and then *View | Hierarchy*. Click the Visible column in the Data Table View to make the ligand visible.



Adding pharmacophore features using ligand atoms

You can add pharmacophore features based on selected atoms in the ligand in one of two ways:

- Choose *Structure | Query Feature...* from the menu bar.
- Use the *Query* toolbar.

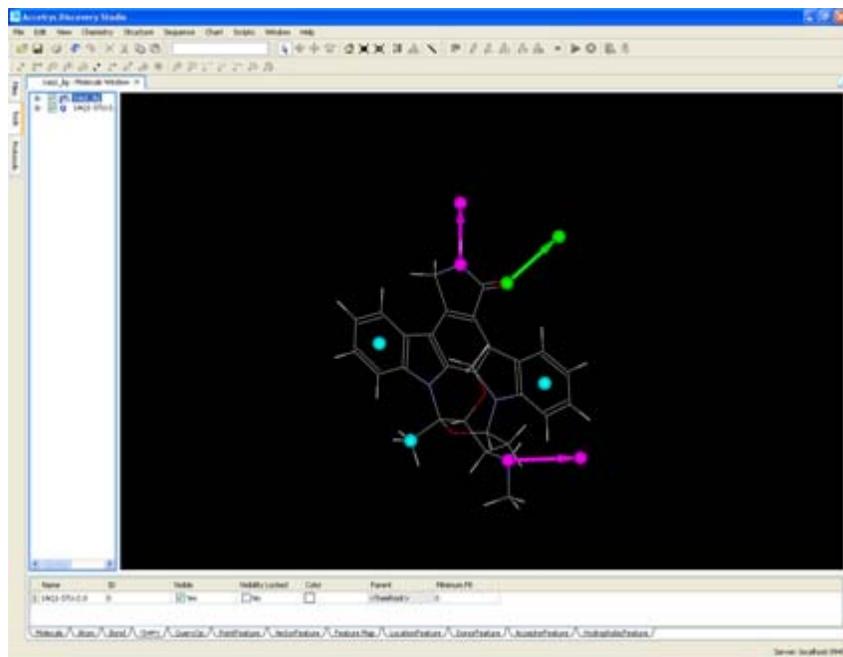
Both enable appropriate options based on the type of atom(s) selected. This tutorial demonstrates the Query toolbar.

From the menu bar, choose **View | Toolbars | Query**.

This displays the Query toolbar:



You will use several buttons from this toolbar to add hydrogen bond acceptor, donor, and hydrophobic features based on atoms in Stauroporine. The following illustrates the desired pharmacophore features:



First, add the hydrophobic features.

In the **Graphics View**, select the methyl carbon (atom C7).

In the **Query toolbar**, click the **Point Feature** button .

This places a selected hydrophobic feature at the methyl carbon.

Tip. It is easy to change the type of this feature if desired. With the feature still selected, right-click in the Graphics View and choose *Attributes of Point...* Select an appropriate *Type* to change it. For example, you could choose [Hydrophobe_Aliphatic](#) to change this feature to a Hydrophobic Aliphatic feature.

In the **Graphics View**, select all the heavy atoms in one of the aromatic rings (atoms C25, C26, C27, C28, C29, C30).

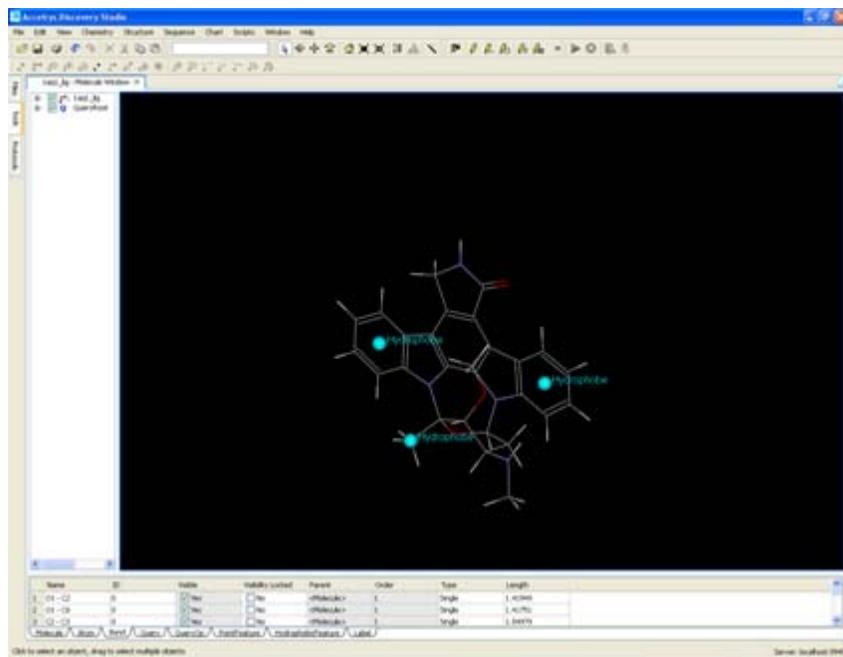
Click the **Point Feature** button  to add a hydrophobic feature.

Notice that the type is automatically set to Hydrophobic Aromatic. Change this to a generic Hydrophobic group.

Right-click in the **Graphics View**, and choose **Attributes of Point...**

Set the **Type** to [Hydrophobe](#).

Repeat the previous step for the other aromatic ring (atoms C15, C16, C17, C18, C19, C20).



Add the hydrogen bond acceptor features.

In the **Graphics View**, select the double bonded Oxygen (atom O24).

Click the **Acceptor Feature** button  on the **Query** toolbar.

With the feature selected, right-click in the **Graphics View** and choose *Attributes*.

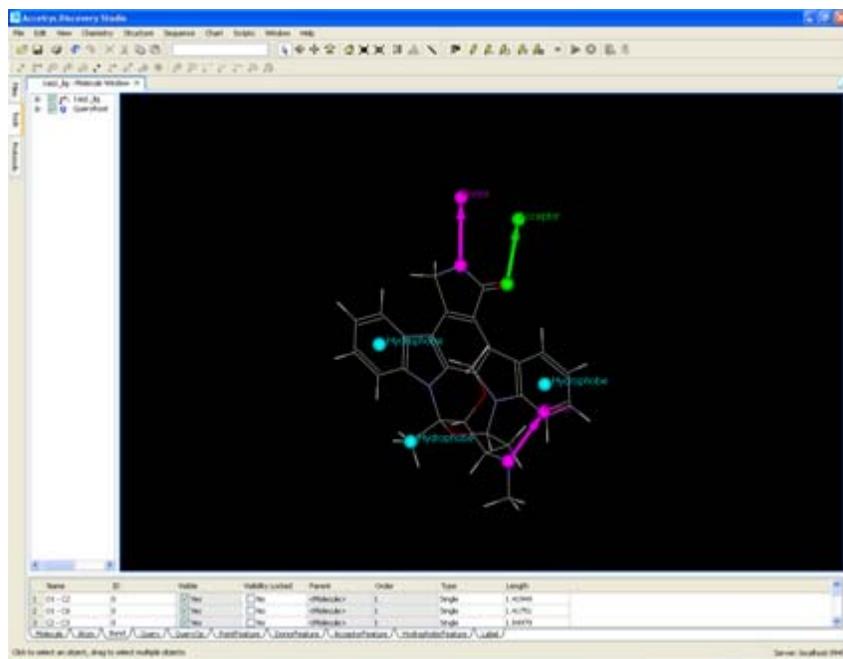
Set the **Orientation** to **First Lone Pair**. **Tip.** If none of the choices give you the right location for the projection point, you can change the projection point to free and put the point wherever you want by selecting it and dragging it.

Add the hydrogen bond donor features.

In the **Graphics View**, select the Nitrogen atom N22

Click the **Donor Feature** button .

Repeat the previous step for the Nitrogen atom N34.

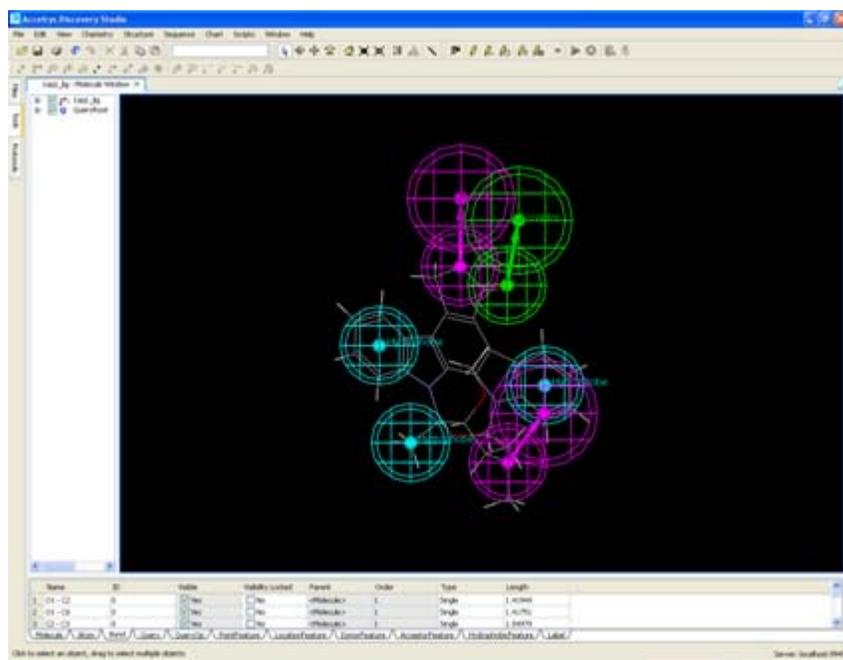


Adding location constraints to the pharmacophore features

So far in this tutorial, pharmacophore features have been added based on the atoms of a ligand. However, you must add some type of constraints to define the relative location of the features. Without constraints of some kind, this query will map any ligand that has three hydrophobic, one acceptor, and two donor groups no matter where they are in space. Typically, location constraints are used to define pharmacophore features. Roughly speaking, a location constraint ensures that a matching atom will be in the tolerance sphere of the corresponding feature. You can add location constraints to individual features or to all features.

In the **Hierarchy View**, select the **QueryRoot** node to select all of the pharmacophore features.

From the **Query toolbar**, click the **Location Constraint** button .



Note. You can also set location constraints for selected features by choosing *Structure | Query Feature...* from the

menu bar, and then choosing [Location](#) from the *Feature* list.

Adding a shape constraint

The pharmacophore you created in the previous steps is a valid pharmacophore and can be used, as is, in several of the Pharmacophore protocols that use a pharmacophore as input. However, you may want to add steric information to the pharmacophore to make it more selective. You can do this using two different methods:

- Select atoms that are regions that ligands atoms are forbidden to go and add excluded volumes using the *Exclusion Constraint* button . For example, you could import the PDB code, select atoms on the protein that are within a certain distance of the ligand, and add excluded volumes.
- Convert the ligand molecule to a shape using the *Shape Feature* button  on the Query toolbar.

In the **Hierarchy View**, select the **1aq1_lig node** to select all of the atoms in the ligand.

From the **Query toolbar**, click the **Shape Feature** button .

This adds a shape to the pharmacophore. A ligand will match all features of the pharmacophore if a matching atom is found in the right location for the hydrophobic, acceptor, and donor features and if the overall shape of the molecule after being aligned is similar to the staurosporine shape:

