

Creating customized pharmacophore features

Required functionality and modules: Discovery Studio Client.

Required data files: None.

Time: 10 minutes.

Introduction

Discovery Studio provides several default pharmacophore feature definitions that are used during pharmacophore modeling. These pharmacophore features are essentially a collection of complex substructure mappings. When one of the substructures is found on a ligand, it is a potential mapping for that feature. The language that describes these pharmacophore features in Discovery Studio is rich and powerful. It is possible to assign several attributes to each atom (e.g., hydrogen count, multiple-elements, possible formal charges) and each bond in a substructure. It is also possible to define exclusions for each substructure. In addition, it is possible to define the atom or the region (such as a centroid of atoms), where the actual feature mapping on the ligand will occur.

The 11 default pharmacophore features are sufficient for most projects. However, occasionally it may be desirable to modify a default feature definition to address a specific need. For example, you may want to allow a particular functional group in a molecule to be recognized as a pharmacophore feature. Discovery Studio provides an interactive environment for modifying and creating pharmacophore features. You can extend or modify an existing pharmacophore feature or you can create an entirely new feature definition.

In this tutorial, you will learn how to customize pharmacophore features using the Customize Pharmacophore Features tool panel by modifying an pharmacophore feature. The following tasks are covered:

- [Modifying the default positive ionizable feature](#)
- [Mapping the feature to the fragment](#)
- [Adding custom features](#)

Modifying the default positive ionizable feature

The following 11 feature definitions are available in Discovery Studio:

- hydrophobic
- hydrophobic aliphatic
- hydrophobic aromatic
- hydrogen bond donor
- hydrogen bond acceptor
- hydrogen bond acceptor lipid
- negative charge
- positive charge
- negative ionizable
- positive ionizable
- ring aromatic

A detailed description of these feature definitions is available in the [Discovery Studio help](#).

The Customize Pharmacophore Features tool panel allows you to modify existing feature definitions as well as to create new feature types. In this tutorial, you will customize the positive ionizable feature to map pyridyl and imidazolyl groups (the default positive ionizable feature does not map pyridyl or imidazolyl groups).

From the menu bar, choose **File | New | Molecule Window**.

This opens a new Molecule Window.

From the top of the **Tools Explorer**, choose **Pharmacophore** from the list.

This opens the Pharmacophore tool panels.

Open the **Customize Pharmacophore Features** tool panel.

In the **Feature Dictionary** tools group, click **Add Feature From Dictionary...**

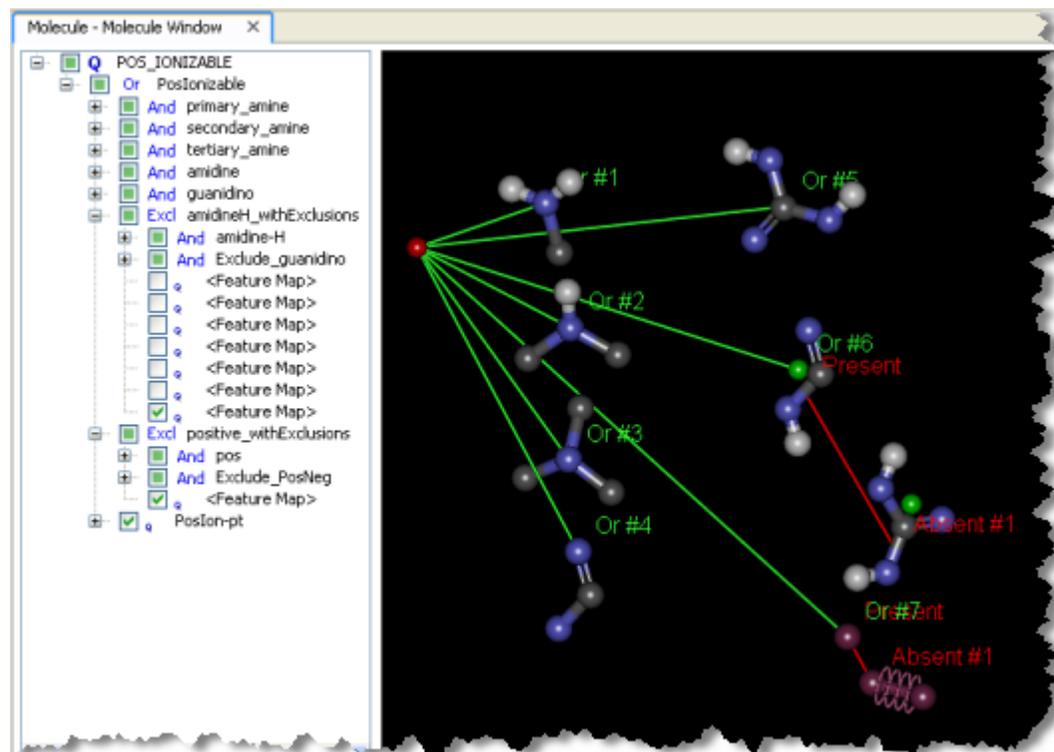
This opens the Add Feature From Dictionary dialog.

On the dialog, click **POS_IONIZABLE** to select it.

Click **OK**.

A single red sphere appears that defines the positive ionizable group. It is possible to see more details of the definitions using the Hierarchy View and some of the tool buttons. See the tip below for more information.

Tip. You can use the *Hierarchy View* to turn on the display of substructure definitions associated with this feature. You can also use the *Show Mappings* button to identify which atoms or collection of atoms are used for the mapping. The *Simplify Customized Feature View* button will improve the visualization of the substructures. To view only the red sphere again, click on the check box of the top node in the Hierarchy labelled POS_IONIZABLE to turn off the display of everything, then click the check box again. Only the red sphere will be displayed.



Now add the new fragments to be included in the definition

From the top of the **Tools Explorer**, select **Visualization** from the list.

This opens the Visualization tool panels.

Open the **Build Fragment** tool panel and expand **Aromatics** in the listbox.

Select **2-Imidazolyl** and click **Add Fragment**.

Select **2-Pyridyl** and click **Add Fragment**.

Press **CTRL+A**.

This adds the fragments to the same Molecule Window and selects all the objects in the Molecule Window.

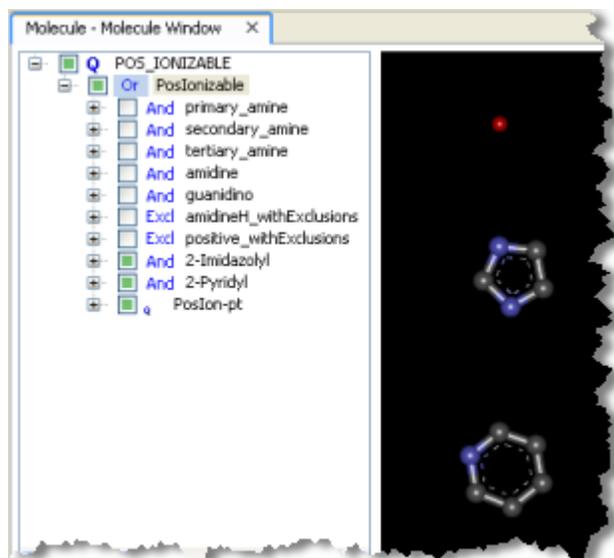
From the top of the **Tools Explorer**, choose **Pharmacophore** from the list.

This opens the Pharmacophore tool panels.

Open the **Customize Pharmacophore Features** tool panel.

Click **Map ANY Selected**.

This adds the two new substructures to the definition. Notice that the bond types are conveniently set to aromatic by default and the hydrogen counts are reset:



Mapping the feature to the fragment

With the substructures added to the positive ionizable definition, you can now choose the atoms or region of the new substructures that will be responsible for the mapping. In this case, the most appropriate mapping location is the centroid of the ring.

In the **Graphics View**, select the **2-Imidazolyl** fragment by double-clicking any atom in the molecule.

From the menu bar, choose **Structure | Query Features....**

This opens the Create Feature dialog.

On the dialog, choose **Centroid** from the list.

Click **OK**.

This creates the required association for the point at which the feature mapping will take place.

Repeat these steps for the **2-Pyridyl** fragment.

The two centroids are displayed in the Graphics View. The mapping can now be created.

In the **Graphics View**, select **both centroids** and the **red positively ionizable feature** object.

In the **Customize Pharmacophore Features** tool panel, click **Create Mapping**.

The modified positive ionizable feature is complete and you can save it as a new [CHM](#) file or add it to the dictionary using *Add Feature To Dictionary...* in the Customize Pharmacophore Features tool panel. Customized pharmacophore features that are added to the dictionary can be used in many of the pharmacophore protocols.

Adding custom features

In the **Customize Pharmacophore Features** tool panel, click **Add Feature To Dictionary**.

This opens the Add Feature To Dictionary dialog.

On the dialog, enter `POS_IONIZABLE_MOD` in the **Function name** textbox.

Click **OK**.

This adds the feature to the dictionary and makes it available for use with many of the pharmacophore protocols.

In the **Protocols Explorer**, expand the **Pharmacophore** folder and double-click **Common Feature Pharmacophore Generation**.

In the **Parameters Explorer**, click the **Features** parameter, then click

This opens the Select Features dialog. The dialog contains the added feature `POS_IONIZABLE_MOD`, which is now available as one of the possible features for building pharmacophore models.