Phase Pharmacophore Modeling in Maestro

This document summarizes the procedure for developing a pharmacophore model using the Develop Pharmacophore Model panel in Maestro, which you open from the Phase submenu of the Applications menu. Full details are given in the *Phase User Manual*.

To select and prepare the ligands (Prepare Ligands step):

1. Import the ligands into the Phase run, by clicking From File, From Run, or From Project.
2. Separate stereoisomers if necessary by selecting the relevant ligands in the table and choosing Separate stereoisomers from the shortcut (right-click) menu.
3. If you want to build a QSAR model or do activity scoring, enter activity data for the ligands if it is not already present.
4. Clean up the ligand structures and generate variations on stereochemistry or ionization state by clicking Clean Ligands, if necessary.
5. Generate sets of conformers for each ligand by clicking Generate Conformers, if necessary.
6. Define the pharm (active) set and the inactive set, either by setting the activity thresholds (click Activity Thresholds), or by selecting ligands in the Ligands table.
7. Assign actives to groups if desired, and specify any required matches for partial matching.
8. Click Next.

To create site points for each ligand (Create Sites step):

1. Set options as required:
   - Add to the existing features, create custom features, and exclude or ignore patterns by clicking Edit Features.
   - Select the use of projected points for acceptors and donors rather than treating them as vector features.
   - Define the active and inactive ligands by clicking Activity Threshold or clicking in the Pharm Set column of the Ligands table.
   - Select features to exclude from the search for common pharmacophores.
2. Click Create Sites.
3. Click Next.

To find common pharmacophores (Find Common Pharmacophores step):

1. Choose the number of sites from the Number of sites option menu.
2. Specify the number of actives to match in the Must match section.
3. Set limits on the minimum and maximum number of features of each type in the Feature frequencies table.
4. Select variants from the Variant list.
5. (Optional) Set search parameters by clicking Options and entering values in the Find Common Pharmacophores - Options dialog box.
6. Start the search by clicking Find.
7. Click Next.

To score hypotheses (Score Hypotheses step):

1. Click Score Actives.

2. Set scoring options in the Score Actives dialog box.
3. Score the hypotheses by clicking OK.

Optional tasks:

- Score inactives to generate an adjusted scoring function by clicking Score Inactives.
- Rescore the hypotheses with an adjusted scoring function by clicking Rescore.
- Export the selected hypothesis to a file, by clicking Export.
- Cluster the hypotheses, by clicking Cluster, and restrict the hypotheses shown to ta representative of each cluster, by clicking View Clusters.
- Add excluded volumes to the selected hypothesis, by clicking Excluded Volumes.
- View hypotheses and alignments in the Workspace, using the toolbar buttons and the Alignments table.

To proceed to building QSAR models:

1. Select the desired hypotheses in the Hypotheses table.
2. Click Next.

To proceed to searching for matches:

1. Select the desired hypotheses in the Hypotheses table.
2. Click Search for Matches.

To build QSAR models (Build QSAR step):

1. Display the ligands in the Alignments table.
2. Select the training set and the test set.
3. (Optional) Choose a model and set parameters in the Build QSAR Model - Options dialog box.
4. Click Build Models.

To proceed to searching for matches:

1. Select the desired hypotheses in the Hypotheses table.
2. Click Search for Matches.