Aldrich Market Select® Phase Database

This document provides an overview of the Aldrich Market Select Screening Collection Phase database distributed by Schrödinger. Aldrich Market Select provides structure files for the screening deck in compressed SDF format. The SDF input is processed to generate structures suitable for property calculations and for the generation of the Phase database, as well as for the generation of the GPU shape screening bin file.

The structures are run through LigPrep in order to generate stereoisomers, as well as tautomers and charged states using Epik, including the calculation of metal-binding states. The LigPrep output is then imported into a Phase database to generate pharmacophore sites, conformers and fingerprints. Database subsets are provided for drug-like, lead-like, near-drug, and fragment structures. The LigPrep output is also used to generate the bin datafile for GPU shape screening. Updates to the distribution are provided on a quarterly basis.

Table 1. Structure counts. Some structures are problematic and will not make it through the entire workflow.

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source SMI</td>
<td>10,467,062</td>
</tr>
<tr>
<td>2D Properties</td>
<td>10,466,884</td>
</tr>
<tr>
<td>3D variants</td>
<td>22,474,609</td>
</tr>
</tbody>
</table>
Classifications

Schrödinger classifies screening compounds based on properties calculated on a single, neutralized and desalted representation. Near drug-like compounds are those that fall close, but not quite into the drug-like property space. Drug-like compounds are expected to have properties similar to known marketed drugs. Lead-like compounds typically have a more restrictive set of properties that align with the goals of finding a hit and expanding that hit into a more drug-like compound. Fragments are compounds that are typically very small and are used to probe a target in order to determine the functionalities expressed by compounds that bind to a particular site. All other molecular structures are not given a classification.

Several rubrics are used in a hierarchical funnel to associate a molecular entity to a specific class. Note that even though a molecule may fit into several classifications, in practice, compounds are allowed to match and get assigned to categories further down the funnel in the order: near drug-like, drug-like, lead-like, to fragment. The count of structures in each class is summarized in table below.

Table 2. Classification criteria. These properties are discussed below. Note that NCC, NR, and HAC correspond to Num chiral centers, Num rings, and Num heavy atoms as calculated by ligfilter. Structures are assigned to a class by the last successful match on all criteria proceeding from right to left.

<table>
<thead>
<tr>
<th>Near drug-like</th>
<th>Drug-like</th>
<th>Lead-like</th>
<th>Fragment</th>
</tr>
</thead>
<tbody>
<tr>
<td>−1.5 ≤ AlogP ≤ 5.5</td>
<td>−1 ≤ AlogP ≤ 4</td>
<td>0 ≤ AlogP ≤ 3</td>
<td>AlogP ≤ 3</td>
</tr>
<tr>
<td>150 ≤ MW ≤ 575</td>
<td>250 ≤ MW ≤ 500</td>
<td>250 ≤ MW ≤ 375</td>
<td>MW &gt; 110</td>
</tr>
<tr>
<td>30 &lt; PSA &lt; 150</td>
<td>50 &lt; PSA &lt; 130</td>
<td>PSA &lt; 110</td>
<td>PSA ≤ 110</td>
</tr>
<tr>
<td>HBD ≤ 5</td>
<td>HBD ≤ 5</td>
<td>HBD ≤ 2</td>
<td>HBD ≤ 3</td>
</tr>
<tr>
<td>HBA ≤ 12</td>
<td>HBA ≤ 10</td>
<td>HBA ≤ 5</td>
<td>HBA ≤ 5</td>
</tr>
<tr>
<td>RB ≤ 10</td>
<td>RB ≤ 10</td>
<td>RB ≤ 10</td>
<td>RB ≤ 3</td>
</tr>
<tr>
<td>NCC ≤ 3</td>
<td>NCC ≤ 3</td>
<td>NCC ≤ 1</td>
<td></td>
</tr>
<tr>
<td>NR ≥ 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAC ≤ 18</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Screening classification

<table>
<thead>
<tr>
<th></th>
<th>Drug-like</th>
<th>Lead-like</th>
<th>Near drug-like</th>
<th>Fragment</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td>4,445,621</td>
<td>1,214,647</td>
<td>2,661,125</td>
<td>959,377</td>
<td>1,186,114</td>
</tr>
<tr>
<td>Percentage</td>
<td>42.5%</td>
<td>11.6%</td>
<td>25.4%</td>
<td>9.2%</td>
<td>11.3%</td>
</tr>
</tbody>
</table>
Property Description

A brief description of each property is provided below.

**HBD:**
Number of hydrogen bond donors

**HBA:**
Number of hydrogen bond acceptors

**RB:**
Number of rotatable bonds

**Total Rings:**
Number of rings

**Stereo Centers:**
Number of stereogenic centers

**N+O:**
Sum of nitrogen and oxygen atoms

**AlogP:**
Logarithm of the atomistic partition coefficient

**PSA:**
Fragment-based topological polar surface area

**MW:**
Molecular weight

**Frac. CSP3:**
Frequency of sp3-hybridized carbon atoms with respect to total carbon atom count
Schrödinger commands for creating the database

LIGPREP STRUCTURE PREPARATION
$SCHRODINGER/ligprep -epik -bff 16 -s 16 -pht 1.0 -emb -imae Sigma_input.maegz -omae ligprep.mae.gz

SHAPE BIN FILE CREATION
$SCHRODINGER/shape_screen_gpu generate -shape_data_treatment remote
-shape_data_dir /path/2023q3_shape -source /path/ligprep.mae.gz -flex -shape_type pharm
-sample thorough -limit 10 -conformer_format compact

PHASE DATABASE CREATION

Add records to the database
$SCHRODINGER/phase_database /path/2023q3_millipore_sigma.phdb splice ligprep.mae.gz
-new -fmt int -title s_lp_Variant -JOB 2023q3_millipore_sigma_splice

Generate sites, conformers, fingerprints
$SCHRODINGER/phase_database //2023q3_millipore_sigma.phdb revise -sites -confs all -fp
-add dendritic,fdendritic,maccs,radial,ecfp4 -props -JOB 2023q3_millipore_sigma_revise

Extract properties
$SCHRODINGER/phase_database /path/2023q3_millipore_sigma.phdb extract -map

Generate subsets

-- Drug-like:
$SCHRODINGER/phase_database /path/2023q3_millipore_sigma.phdb query
subset_drug_like -where "r_canvas_AlogP >= -1.0 AND r_canvas_AlogP <= 4.0 AND
r_canvas_MW >= 250.0 AND r_canvas_MW <= 500.0 AND r_canvas_PSA > 50.0 AND
r_canvas_PSA < 130.0 AND i_canvas_HBD <= 5 AND i_canvas_HBA <= 10 AND
i_canvas_RB <= 10 AND i_canvas_ChiralCenterCount <= 3"

-- Near-drug:
$SCHRODINGER/phase_database /path/2023q3_millipore_sigma.phdb query
subset_near_drug -where "r_canvas_AlogP >= -1.5 AND r_canvas_AlogP <= 5.5 AND
r_canvas_MW >= 150.0 AND r_canvas_MW <= 575.0 AND r_canvas_PSA > 30.0 AND
r_canvas_PSA < 150.0 AND i_canvas_HBD <= 5 AND i_canvas_HBA <= 12 AND
i_canvas_RB <= 10 AND i_canvas_ChiralCenterCount <= 3"

-- Lead-like:
$SCHRODINGER/phase_database /path/2023q3_millipore_sigma.phdb query subset_lead_like -where "r_canvas_AlogP >= 0.0 AND r_canvas_AlogP <= 3.0 AND r_canvas_MW >= 250.0 AND r_canvas_MW <= 375.0 AND r_canvas_PSA <= 110.0 AND i_canvas_HBD <= 2 AND i_canvas_HBA <= 5 AND i_canvas_RB <= 5 AND i_canvas_ChiralCenterCount <= 1"

-- Fragment-like: $SCHRODINGER/phase_database /path/2023q3_millipore_sigma.phdb query subset_fragment -where "r_canvas_AlogP <= 3.0 AND r_canvas_MW > 110.0 AND r_canvas_PSA <= 110.0 AND i_canvas_HBD <= 3 AND i_canvas_HBA <= 5 AND i_canvas_RB <= 3 AND i_canvas_RingCount >= 1 AND i_canvas_HeavyAtomCount <= 18"

-- Epik metal state $SCHRODINGER/phase_database /path/2023q3_millipore_sigma.phdb query subset_epik_metal_only -where "b_epik_Metal_Only == 0"