Design and Linkage of Compound Filters to HTS Assay Promiscuity

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BMS Screening Deck Flags / Filters

- *Property flags: Compounds flagged ≥ 2
  - MW > 639 & absolute cutoff if MW ≤ 130 or ≥ 900
  - cLogP < -3 or > 5.5
  - HBD > 5
  - HBA > 9
  - RTB > 14

- Functional group queries
  - Annotation flags
  - Exclusion filters
  - Daylight SMARTS-based

- How effective are these flags / filters?

Linkage of Property and Functional Group Filters to Promiscuous HTS Data

- Used verified primary HTS data
  - Unfiltered – No HTS triage biases
  - 12 Years of data
  - Greater than 61 million data points
  - Annotated by screeners – Inactive 0, Active 1

- Definitions:
  - \textit{Inactive} = Inactive and have seen > 15 assays
  - \textit{Active} = Active in \geq 1 and < 7 assays
  - \textit{Promiscuous} = Active in \geq 7 assays
Active Primary HTS Data

48% Active
12% Promiscuous
0.8%
Evaluation of Property and Functional Group Filters Using HTS Data

<table>
<thead>
<tr>
<th>HTS Classification</th>
<th>% Property Fails</th>
<th>% Functional Group Fails</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive</td>
<td>3.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Active</td>
<td>4.8</td>
<td>5.5</td>
</tr>
<tr>
<td>Promiscuous</td>
<td>4.4</td>
<td>10.9</td>
</tr>
</tbody>
</table>

- Compound Promiscuity
  - Weak correlation to property filters
  - Strong correlation to functional group filters
Active Primary HTS Data
Functional Group Filter Impact

Promiscuity strongly associated with functional group flagged compounds
Functional Group Filter Analysis

  - Any two med chemists agree only 28% of the time!
  - The same med chemist is only 50% consistent!
- Filter design is highly dependent on personal biases
- Reduce subjectivity by relying on empirical data
  - In-depth analysis of primary HTS data and FG filters
  - Linkage of compound screening promiscuity to FG filter
    - Expected percentage of actives relative to HTS
    - How the actives translate across multiple assays
- For this analysis we used the entire set of annotation and exclusion-based SMARTS
Promiscuity Ratio Index (PRI) Calculation & Statistical Method

The PRI is a measure of how strongly compounds grouped or flagged by a particular functional group filter are active in assays versus background HTS (HTS)

- PRI = mean FG filter % actives / 1.925
- Statistical analysis
  - 95% Confidence intervals constructed for a ratio
- Rule classifications:
  - Less is where confidence bounds < 1
  - Same is where confidence bounds contain 1
  - Greater is where confidence bounds > 1
Promiscuity Strength Index (PSI)
Calculation & Statistical Method

The PSI is a measure of how strongly active compounds grouped or flagged by a particular functional group filter express that activity across an increasing number of assays.

- Weighted mean of the number of actives for each compound flagged by a particular functional group filter
- \( \text{PSI} = 3.29 \pm 0.004 \text{ SE for HTS benchmark} \)
- Standard t-statistics applied
- Rule classifications:
  - *Less* is where \( \text{PSI} < 3.29 \) and \( p\)-value < 0.05
  - *Same* is where \( p\)-value > 0.05
  - *Greater* is where \( \text{PSI} > 3.29 \) and \( p\)-value < 0.05
HTS Filter Promiscuity Linkage

Linkage Rating Based on Statistical Rule Classes:

- **LOW (9%)**
  - PRI & PSI both less or one same one less

- **MEDIUM (18%)**
  - PRI & PSI both same or one greater one less

- **HIGH (64%)**
  - PRI & PSI both greater or one same one greater
Structural Integrity (SI) Data

- Connectivity between functional group filter flag and screening data depend on compound SI
- Coupled LC/MS: compound identity and integrity
- SI passes where purity > 75% with expected MW
- Limited set of historic SI data on deck compounds
- Non or under-represented flagged compounds supplemented by additional SI analyses
- Current data does not necessarily link to past conditions
- General guide to suspected reactivity patterns
# Functional Group Filter Linkage to HTS Data – Some LOW Examples

<table>
<thead>
<tr>
<th>Functional Group Filter</th>
<th>Distinct Cmpds</th>
<th>Query Structure</th>
<th>PRI</th>
<th>PRI Class</th>
<th>PSI</th>
<th>PSI Class</th>
<th>% Pass SI</th>
<th>Linkage</th>
</tr>
</thead>
<tbody>
<tr>
<td>2halo pyrazine 5EWG</td>
<td>78</td>
<td><img src="image" alt="Query Structure" /></td>
<td>0.11</td>
<td>Less</td>
<td>1</td>
<td>Same</td>
<td>0</td>
<td>LOW</td>
</tr>
<tr>
<td>2halo pyridazine 3EWG</td>
<td>40</td>
<td><img src="image" alt="Query Structure" /></td>
<td>2.08</td>
<td>Same</td>
<td>1.09</td>
<td>Less</td>
<td>30</td>
<td>LOW</td>
</tr>
<tr>
<td>2halo pyridine 3EWG</td>
<td>890</td>
<td><img src="image" alt="Query Structure" /></td>
<td>0.82</td>
<td>Less</td>
<td>2.72</td>
<td>Less</td>
<td>56</td>
<td>LOW</td>
</tr>
<tr>
<td>Activated 4mem ring</td>
<td>28</td>
<td><img src="image" alt="Query Structure" /></td>
<td>0.15</td>
<td>Less</td>
<td>5</td>
<td>Same</td>
<td>0</td>
<td>LOW</td>
</tr>
</tbody>
</table>
## Functional Group Filter Linkage to HTS Data – Some HIGH Examples

<table>
<thead>
<tr>
<th>Functional Group Filter</th>
<th>Distinct Cmpds</th>
<th>Query Structure</th>
<th>PRI</th>
<th>PRI Class</th>
<th>PSI</th>
<th>PSI Class</th>
<th>% Pass SI</th>
<th>Linkage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branched polycyclic aromatic</td>
<td>729</td>
<td><img src="image" alt="Query Structure" /></td>
<td>3.73</td>
<td>Greater</td>
<td>9.49</td>
<td>Greater</td>
<td>50</td>
<td>HIGH</td>
</tr>
<tr>
<td>Polyhalo phenol d</td>
<td>40</td>
<td><img src="image" alt="Query Structure" /></td>
<td>9.84</td>
<td>Greater</td>
<td>23.3</td>
<td>Greater</td>
<td>25</td>
<td>HIGH</td>
</tr>
<tr>
<td>Quinone methide</td>
<td>160</td>
<td><img src="image" alt="Query Structure" /></td>
<td>6.91</td>
<td>Greater</td>
<td>9.1</td>
<td>Greater</td>
<td>29</td>
<td>HIGH</td>
</tr>
<tr>
<td>Thio xanthate</td>
<td>52</td>
<td><img src="image" alt="Query Structure" /></td>
<td>4.68</td>
<td>Greater</td>
<td>14.78</td>
<td>Greater</td>
<td>33</td>
<td>HIGH</td>
</tr>
<tr>
<td>thiosulfoxide</td>
<td>6</td>
<td><img src="image" alt="Query Structure" /></td>
<td>4.92</td>
<td>Greater</td>
<td>11</td>
<td>Greater</td>
<td>0</td>
<td>HIGH</td>
</tr>
</tbody>
</table>
### Functional Group Filter Linkage to HTS Data – Controls

<table>
<thead>
<tr>
<th>Functional Group Filter</th>
<th>PRI</th>
<th>PRI Class</th>
<th>PSI</th>
<th>PSI Class</th>
<th>% Pass SI</th>
<th>Linkage</th>
</tr>
</thead>
<tbody>
<tr>
<td>All HTS Data</td>
<td>1</td>
<td>NA</td>
<td>3.29</td>
<td>NA</td>
<td>73</td>
<td>NA</td>
</tr>
<tr>
<td>diphenylmethane</td>
<td>1.23</td>
<td>Greater</td>
<td>3.75</td>
<td>Greater</td>
<td>74</td>
<td>HIGH</td>
</tr>
<tr>
<td>ethylcarbamate</td>
<td>0.83</td>
<td>Less</td>
<td>3.81</td>
<td>Greater</td>
<td>79</td>
<td>MED</td>
</tr>
<tr>
<td>hydantoin</td>
<td>0.91</td>
<td>Less</td>
<td>4.18</td>
<td>Greater</td>
<td>83</td>
<td>MED</td>
</tr>
<tr>
<td>indole</td>
<td>0.83</td>
<td>Less</td>
<td>3.88</td>
<td>Greater</td>
<td>80</td>
<td>MED</td>
</tr>
<tr>
<td>isoquinoline</td>
<td>0.74</td>
<td>Less</td>
<td>3.52</td>
<td>Same</td>
<td>92</td>
<td>LOW</td>
</tr>
<tr>
<td>phenethylamine</td>
<td>1.43</td>
<td>Greater</td>
<td>3.20</td>
<td>Less</td>
<td>86</td>
<td>MED</td>
</tr>
<tr>
<td>SI &gt; 75% purity</td>
<td>1.47</td>
<td>Greater</td>
<td>4.50</td>
<td>Greater</td>
<td>100</td>
<td>HIGH</td>
</tr>
<tr>
<td>SI &lt; 50% purity</td>
<td>2.05</td>
<td>Greater</td>
<td>5.10</td>
<td>Greater</td>
<td>0</td>
<td>HIGH</td>
</tr>
</tbody>
</table>

- **Indole & phenethylamine** ⇒ Considered GPCR privileged structures
  - Levels of promiscuity similar to HTS background
- **Diphenylmethane** ⇒ Prevalent substructure in many drug databases
  - Higher level of promiscuity but still on low end of high class
- **Ethylcarbamate, hydantoin, isoquinoline** ⇒ no particular bias
  - None of these differ strongly from HTS
- **Structural Integrity Flags**
  - Modest trend of highly impure compounds being more promiscuous
Functional Group Filter Implementation

- **Example of LOW**: 2-Halo Pyridine 3-EWG
  - Low PRI and PSI values
  - In general, these halo-substituted \( \pi \)-deficient systems are not showing high linkages to promiscuity
  Action \( \Rightarrow \) filter removal

- **Example of MED**: Trichloromethyl Ketone
  - Similar to HTS means with respect PRI and PSI
  - Typical of other reversible electrophiles
  Action \( \Rightarrow \) compound annotation flag

- **Example of HIGH**: Polyhalo Phenol D
  - Excessively high PRI and PSI values
  Action \( \Rightarrow \) compound exclusion from screening
Future Directions

- Only 15% of the promiscuous HTS hits are flagged by current FG filters
  - Other mechanisms of compound promiscuity
    - Compound aggregation

- Cheminformatic approaches:
  - New SMARTS functional group queries
  - Bayesian modeling (SciTegic)
  - Other software such as LeadScope
  - Understanding new descriptor linkages using statistical mapping to HTS data
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