BACKGROUND

Fragment-based drug discovery (FBDD) has become an efficient methodology toward identification of small-molecule leads [1-2], and therefore fragment libraries are of great interest in both industry and academia. The majority of commercially available fragment libraries are predominantly populated with flat (hetero)aromatic chemotypes [3-5]; this can be explained by two factors. Initially, fragment libraries were designed to be well detectable in NMR screening. Since (hetero)aromatic compounds usually exhibit well resolved chemical shifts, they are NMR friendly for high identification rates [6]. In addition, a large number of fragments hits have been reported against kinase ATP-binding pocket [7]. The number of fragment hits against kinase ATP-binding pocket was reported in a large series of three-dimensional fragments [8]. Fsp3 parameter has become one of the most important criterion of HTS libraries [9,10] and therefore complexity for libraries members. According to their biological activity observations, scaffold/molecule saturation may benefit:

- More diversity;
- More complexity;
- Access to greater chemical space;
- Improved polar (hetero)aromatic chemotypes;
- 1,2-Di (bulky)substituted (hetero)cycles;
- Spiro-structures;
- Bridged structures;
- More opportunity for further scaffold modification;
- Improved phys-chem parameters (logP; PSA; water solubility etc.);
- More complexity;
- More than 200 bridged fragments;
- More than 1100 compounds meet strict Astex Rule of Three criteria [12] (MW ≤ 400, cLogP ≤ 3.5, HBA ≤ 8, HBD ≤ 5; cLogSW (pH 7.4) ≤ 5.4, NRB ≤ 4); Fsp3 ≥ 0.4, preferably due to higher saturation of (hetero)cycle but not side chains; Fsp3 ≥ 0.4. Distribution of fragments by Fsp3 parameter for both libraries is represented in Fig. 1.

We have compared the main characteristics of both libraries and found that the 3D-library is more attractive in terms of both, 2D- and 3D-diversity. Thus, diversity coefficient (1) for 3D-library is 0.96, compared to 0.91 for conventional library (Fig. 2).

STRATEGY OF LIBRARY MEMBERS SELECTION

The library candidates should meet at least one of the following criteria:

- Fsp3 ≥ 0.4, preferably due to higher saturation of (hetero)cycle (Fig. 2);
- One or more chiral center in structure;
- Bridged structures;
- Spiro-structures;
- 1,2-Di (bulky)substituted (hetero)cycles;
- More than 200 bridged fragments;
- More than 450 sp2-fragments.

Table 1. Phys-Chem Parameters for Beyond the Flatland 3D-Fragment Library

<table>
<thead>
<tr>
<th>Phys-Chem Parameter</th>
<th>Range for BF-3DF</th>
<th>Average for BF-3DF</th>
</tr>
</thead>
<tbody>
<tr>
<td>cLogP</td>
<td>0.6...3.0</td>
<td>1.82</td>
</tr>
<tr>
<td>MW</td>
<td>98...338</td>
<td>146</td>
</tr>
<tr>
<td>HBA</td>
<td>0...4</td>
<td>0.84</td>
</tr>
<tr>
<td>HBD</td>
<td>0...5</td>
<td>0.9</td>
</tr>
<tr>
<td>PSA</td>
<td>32...100</td>
<td>96.5</td>
</tr>
<tr>
<td>cLogSW (pH 7.4)</td>
<td>−8.3...5.4</td>
<td>−2.1</td>
</tr>
<tr>
<td>NRB</td>
<td>0...4</td>
<td>2.64</td>
</tr>
<tr>
<td>HBA</td>
<td>0...8</td>
<td>4.5</td>
</tr>
<tr>
<td>Fsp3</td>
<td>0.06...1.0</td>
<td>0.58</td>
</tr>
<tr>
<td>Chiral centers</td>
<td>0...5</td>
<td>1</td>
</tr>
<tr>
<td>cLogP (pKa)</td>
<td>0.6...3.0</td>
<td>1.5</td>
</tr>
</tbody>
</table>

REDINESS FOR HIT TO LEAD FOLLOW-UP

The key feature of our BF-3D-fragment library is that more than 50% of the library members have arisen from ChemDiv’s DDS program. This means:

- Majority of scaffolds having some specific skeletons, so these scaffolds are represented in a 3D-fragment library by small sets of fragments that are seeds for preliminary SAR studies;
- Usually these scaffolds are registered also in our stock-available HTS-structures libraries on reactive functionalities, toxicophores, instability polytopes etc.

SELECTED EXAMPLES OF 3D-FRAGMENTS

Examples of sp2-fragments (approx. 400 library members)

Beckman et al. [11] have previously identified a set of “ideal” scaffolds for fragment-based lead discovery with the aim to combine scaffold efficiency with 3D-shape diversity for hit expansion. Some research groups have made first practical contribution on this direction [8,11]. Nevertheless, the authors of this paper use a fragment-based approach to identify small-molecule lead candidates. In order to find suitable molecules for further lead optimization, a novel fragment-based lead discovery approach has been developed. Some researchers have tried to overcome the limitations of FBDD technology by expanding fragment-based libraries to include scaffolds that are significantly more complex [12]. In contrast to predominantly “flat” ChemDiv conventional fragment library (14.3K members), the library candidates should meet at least one of the following criteria:

- Fsp3 ≥ 0.4, preferably due to higher saturation of (hetero)cycle but not side chains;
- One or more chiral center in structure;
- Bridged structures;
- Spiro-structures;
- 1,2-Di (bulky)substituted (hetero)cycles;
- More than 200 bridged fragments;
- More than 450 sp2-fragments.

Finally, 3D-library is more “water soluble” almost 70% of its members have cLogP > 3.5 whereas there are only 50% of conventional library in the range 2.5...3.5.

REFERENCES