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ChemDiv "Beyond the Flatland" 3D-Fragment Library for Fragment-Based Drug Discovery (FBDD)

CHEMDIV "BEYOND THE FLATLAND" 3D-FRAGMENT LIBRARY

BACKGROUND

Fragment-based drug discovery (FBDD) has become an efficient methodology toward identification of small-molecule leads [1 - 3], 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 [4, 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 fragments for hit identification [6]. In addition, a large number of fragment hits have been reported against kinase ATP-binding pocket. Since such fragment hits should mimic the adenine base of ATP, almost all of them can be characterized as flat sp^2-rich structures.

On the other hand, nature is three-dimensional and therefore recognizes small molecules in a complementary 3D-fashion, and so drugs are likely to be more selective for their targets if they are three-dimensional too [7, 8]. Not coincidentally, compounds with diverse and well-developed 3D-shapes have become the most attractive ones on the market of screening compounds for HTS for last several years. Furthermore, Fsp^3 parameter has become one of the most important criterion of HTS libraries value since it was introduced in 2009 by Frank Lovering et.al [9] as a measure of three-dimensionality and therefore complexity for libraries members. According to their findings and our further observations, scaffold/molecule saturation may benefit:

> ➢ More diversity;
> ➢ More complexity;
> ➢ Access to greater chemical space;
> ➢ Improved phys-chem parameters (logP; PSA; water solubility etc.);
> ➢ More opportunity to reduce scaffold MW;
> ➢ More opportunity for further scaffold modification;
> ➢ Natural product-likeness;
> ➢ Better affinity to target proteins and greater selectivity;
> ➢ Easy access to IP-clean field.

Noteworthy, this trend retained almost unnoticed on FBDD field until recently perhaps because complexity of such compounds contradicts main principle of FBDD "from simplest fragments toward complex ligands". Nevertheless, the authors of numerous recent discussion papers are convinced that chemical space and quality of current fragment libraries will be improved significantly if their 3D-diversity is enriched. In their opinion, this can expand the horizons of FBDD enabling new opportunities in most challenging target classes such as PPI, β-secretase etc [3-6,10]. Some research groups have made first practical contribution on this direction [8,11]. Furthermore, several UK-based non-profit drug discovery institutions, spanning a range of therapeutic foci, have come together to form the 3D Fragment Consortium (http://www.3DFrag.org) aiming to build a shared fragment library with enhanced three-dimensional characteristics and subsequently evaluate them in a range of fragment screens using a variety of screening methodologies.

Taking into account this trend on FBDD field we at ChemDiv have built our own "Beyond the Flatland" 3D-Fragment Library.

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 but not side chains;
- ➢ One and more chiral center in structures;
- ➢ Bridged structures;
- ➢ Spiro-structures;
- ➢ 1,2-Di (bulky)substituted (hetero)cycles

The following filters have been applied for final library population:

- ➢ MW ≤ 300;
- ➢ cLogP ≤ 3.0;
- ➢ HBD ≤ 5;
- ➢ HBA ≤ 8;
- ➢ NRB ≤ 4;
- ➢ No Med-Chem restrictions (widely used and proprietary ChemDiv substructure filters on reactive functionalities, toxicophores, instability suspicions etc.)

LIBRARY SUMMARY

- ➢ *The library consists of more than 4,400 fragments;*
- ➢ *Assured chemical diversity (diversity coefficient 0.9);*
- ➢ *More than 1100 compounds meet strict Astex Rule of Three criteria [12] (MW ≤ 300, cLogP ≤ 3, H-bond donors ≤ 3, H-bond acceptors ≤ 3);*
- ➢ *More than 2850 library members contain at least one chiral center in the structure;*
- ➢ *More than 200 bridged fragmens;*
- ➢ *More than 450 spiro-fragments.*

Key Phys-Chem Parameters for Beyond the Flatland 3D-Fragment Library are represented in Table 1.

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

Phys-Chem Parameter	Range for 3D-FL	Average for 3D-FL
MW	111…300	264
cLogP	-2.8…3.0	1.22
NRB	0…4	2.64
HBA	0…8	4.5
HBD	0…5	0.9
PSA	3.2…108.3	56.4
Fsp^3	0.06…1.0	0.58
Chiral centers	0…5	1
cLogD (pH 7.4)	-6.8…5.5	1.0
cLogSW (pH 7.4)	-8.3…5.4	-2.1

READINESS FOR HIT TO LEAD FOLLOW-UP

The key feature of our BF-3D-fragment library is that more than 90% of the library members have arisen from ChemDiv's DOS program. This means:

➢ Majority of fragments belong some specific scaffolds, so each of these scaffolds is represented in BF-3D-fragment library by small sets of fragments that are ready for preliminary SAR;
➢ Usually these scaffolds are represented also in our stock-available HTS-library that can be used for further advanced SAR;
➢ Based on these scaffolds additional sub-libraries can be designed and synthesized upon request;
➢ These scaffolds contain at least two points of variability and very often they can be modified into another chemotypes.

All listed above make our fragments ready for easy hit to lead follow-up if some hits are found.

STEREOCHEMISTRY NOTES

We track carefully stereochemistry of the library members, so we provide stereochemical information for all of them.

For compounds with one and more chiral centers in structure we usually deliver racemates. However, in some cases (e.g. compounds arisen from nature products) we provide pure enantiomers. Their absolute configuration is as drawn with up/down wedges, and structures are marked with chirality flag in db/sdf.

For compounds with two and more chiral centers we deliver pure diastereomer as a racemic mixture (if chirality flag is not applied). Relative configurations are shown with up/down wedges. The relative configuration for scaffolds or singletons has been assigned by at least one of the following:
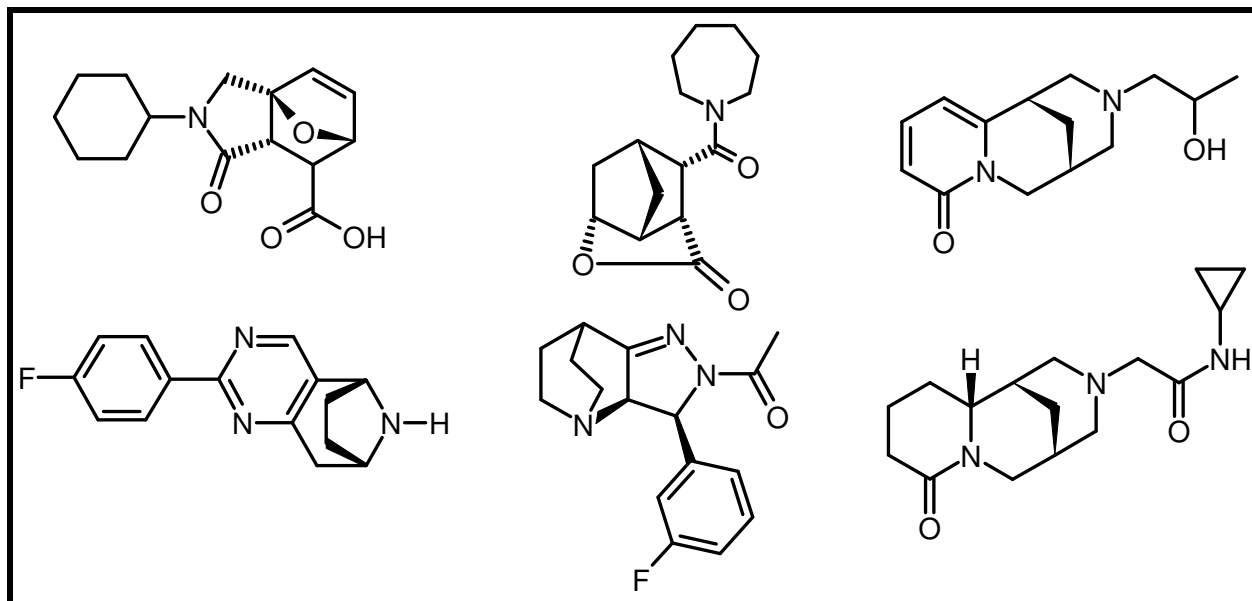
- Literature data for reported compounds
- Reported reaction mechanisms and/or stereochemical outcome for stereo-controlled reactions
- Spectral data (2D-NMR, X-Ray).

SELECTED EXAMPLES OF 3D-FRAGMENTS

Examples of spiro-fragments (approx. 450 library members):
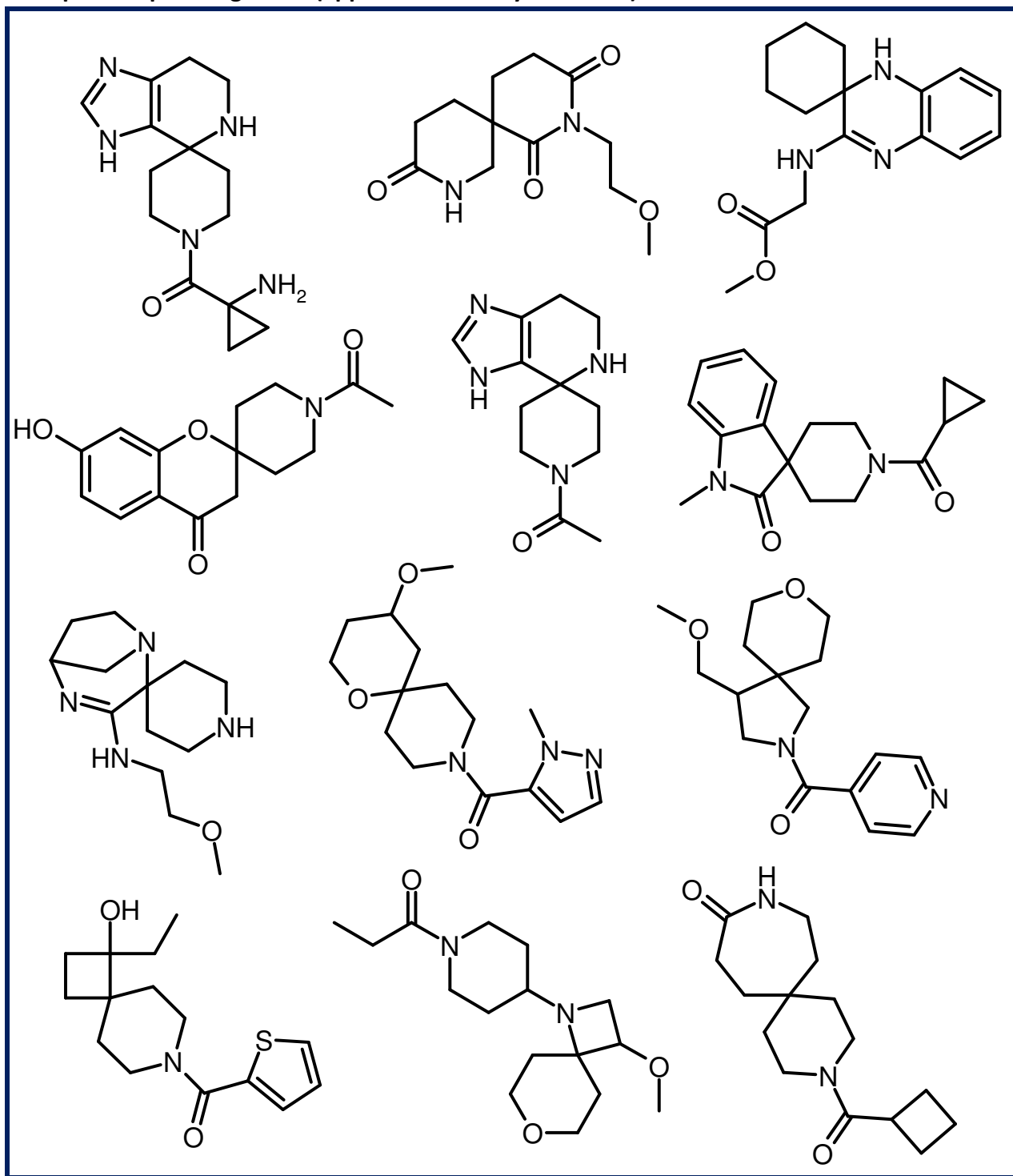
Examples of bridged fragments (approx. 200 library members):

BEYOND THE FLATLAND 3D-FRAGMENT LIBRARY vs CHEMDIV CONVENTIONAL FRAGMENT LIBRARY

In contrast to predominantly "flat" ChemDiv conventional fragment library (14.3K members, see separate description), more than 80% of 3D-library members have Fsp3≥0.4. Distribution of fragments by Fsp^3 parameter for both libraries is represented in Fig. 1.
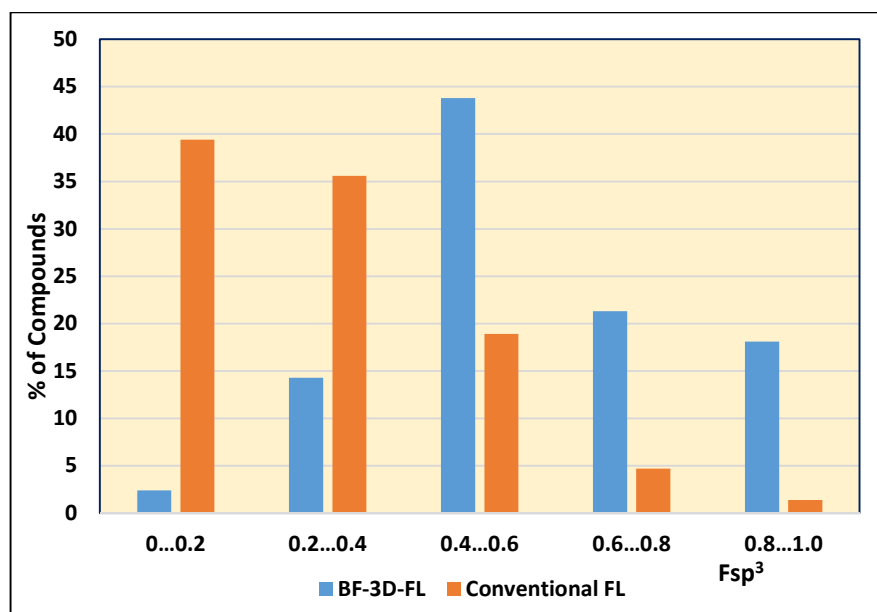

Fig. 1.

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 [13] for 3D-library is 0.90 vs 0.87 for conventional one. For distribution of the libraries members by diversity see Fig.2.
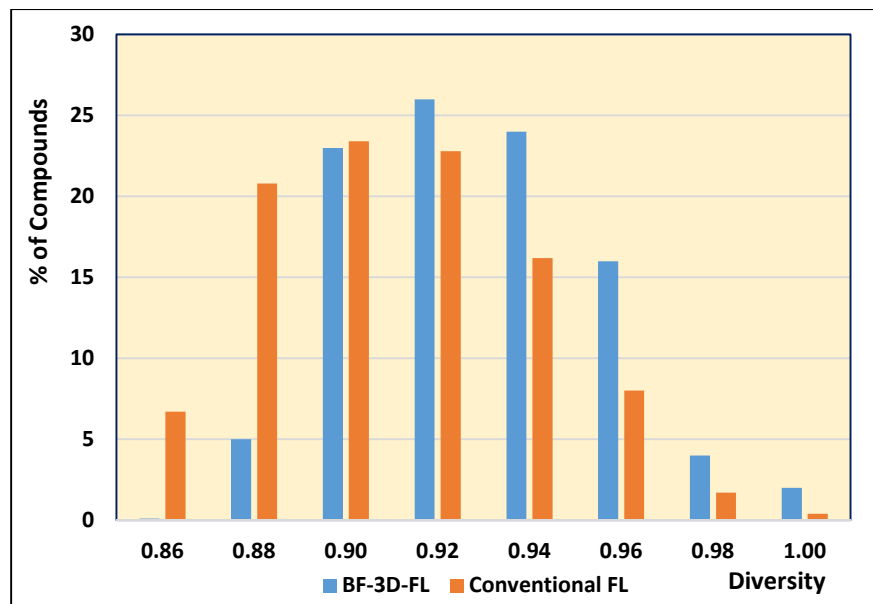

Fig. 2.

Plots of Principal Moments of Inertia (PMI) [14] clearly illustrate significantly increased three-dimensionality and 3D-shape diversity for 3D-library members (Fig 3a) if compare to conventional library (Fig. 3b).
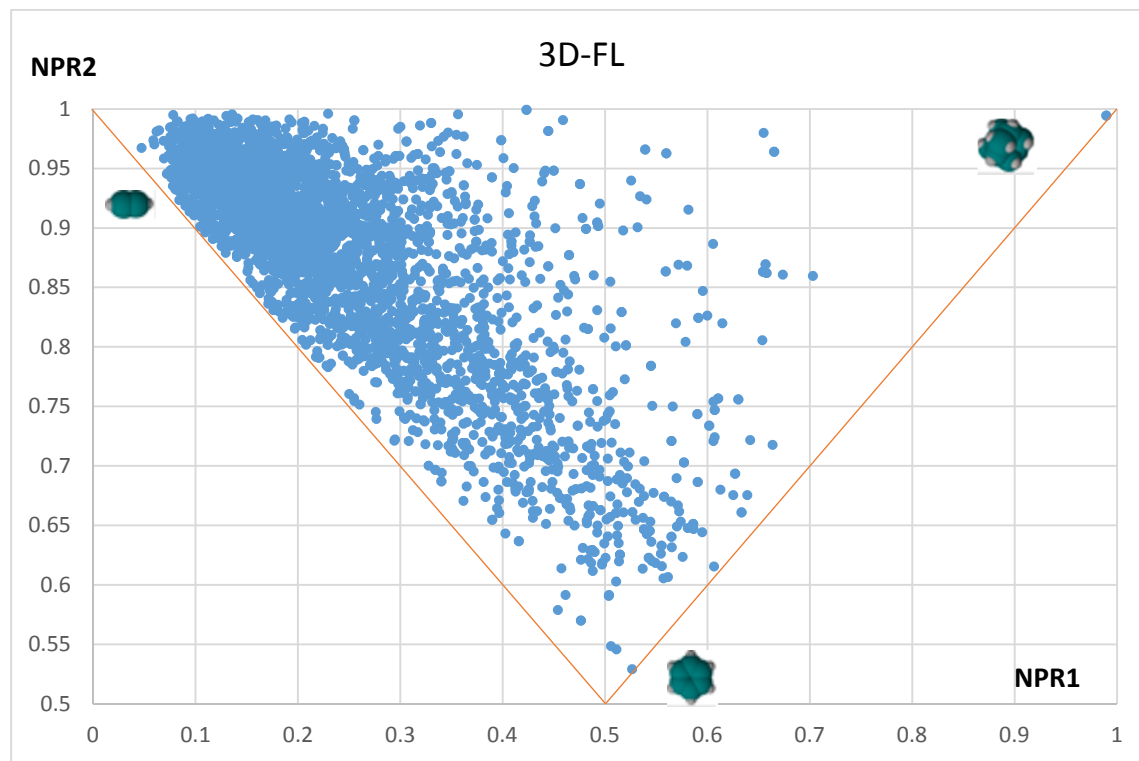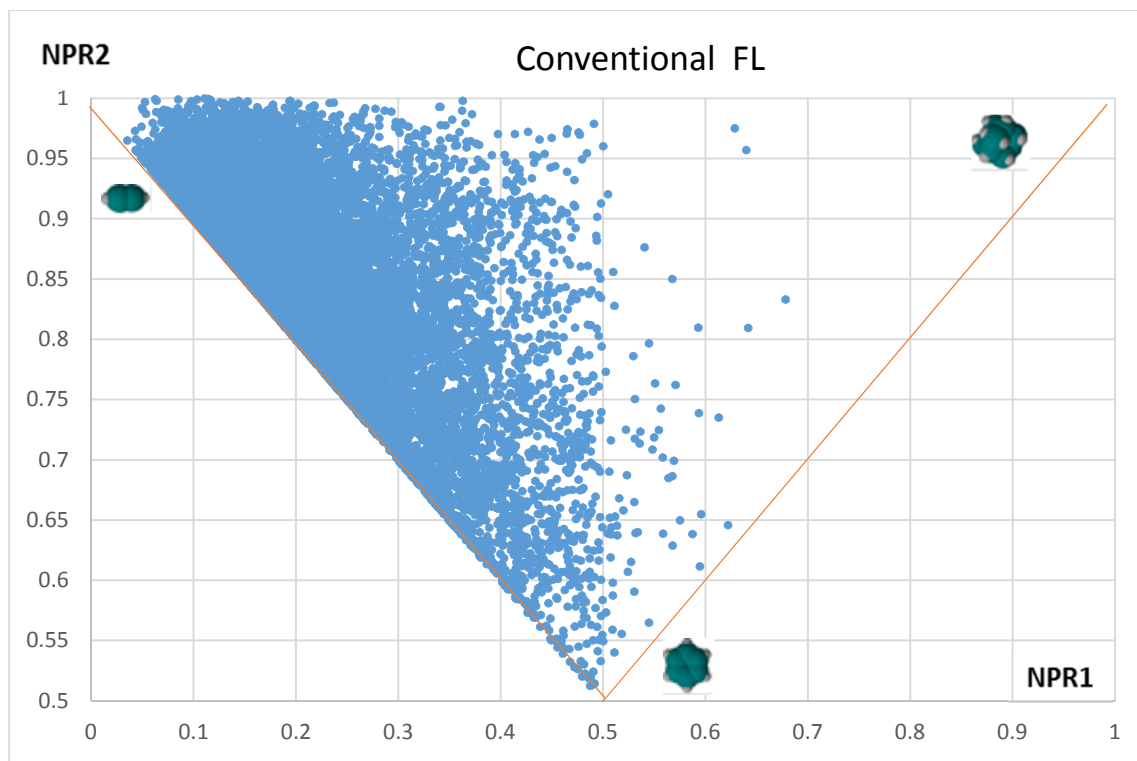

Fig. 3a.

Fig. 3b.

Higher degree of saturation (Fsp^3) affects favorably on the physico-chemical parameters of 3D-library. Thus, 16% of conventional library lie in pharmacologically unfavorable range of PSA (≥ 80), whereas 3D-library contains only 9.5% of such fragments. For distribution the libraries member by PSA see Fig. 4.
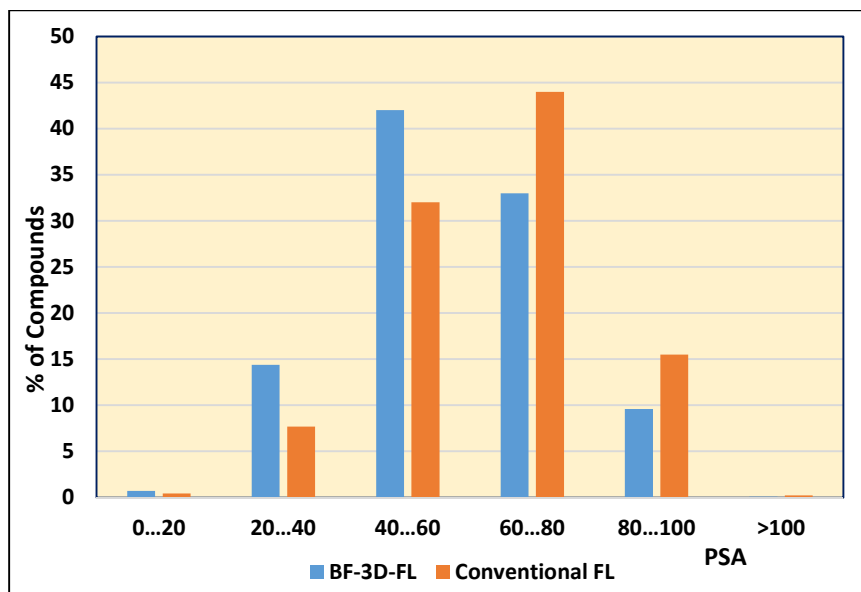

Fig. 4.

Represented below charts demonstrate clearly the improvement in important parameters such as cLogP (Fig. 5), cLogD (Fig. 6), and, the most importantly, water solubility cLogSW (Fig. 7).
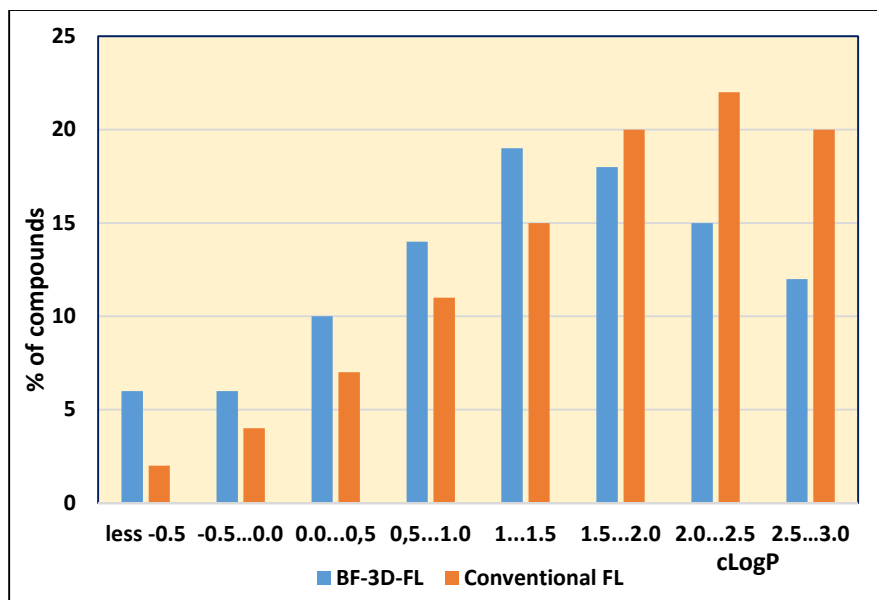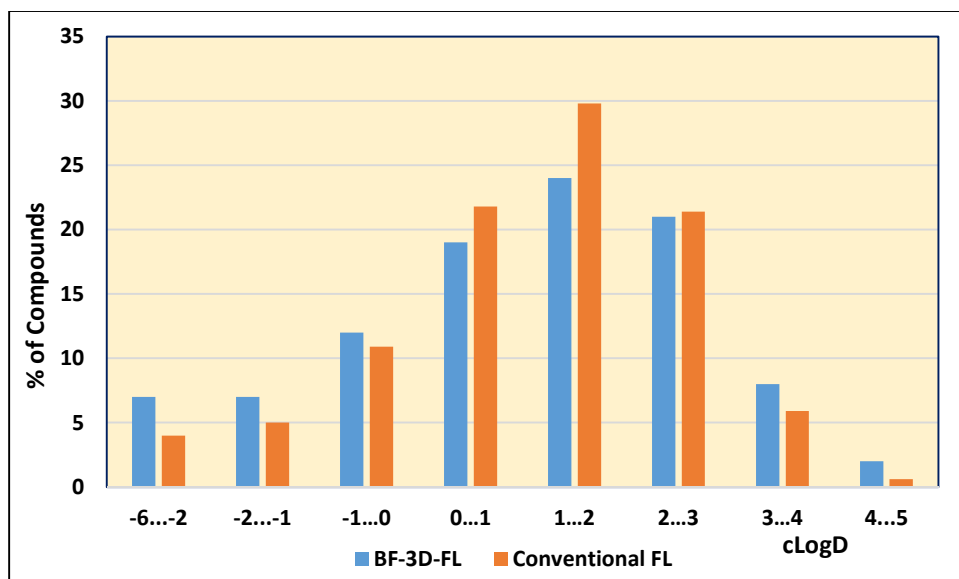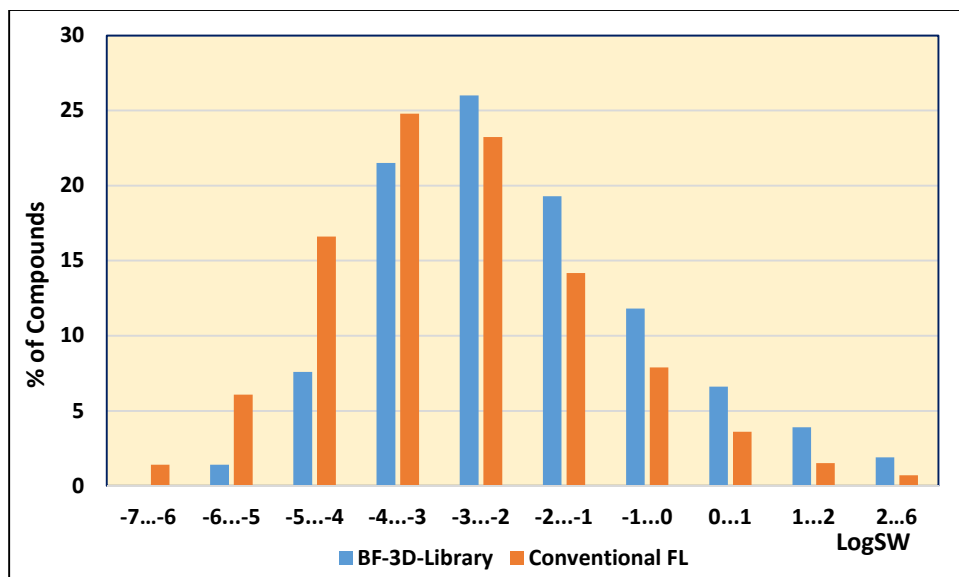
Fig. 5.

Fig. 6.

Finally, 3D-library is more "water soluble": almost 70% of its members have cLogSW≥ 3.0 whereas there are only 50% of conventional library lie in this range.

FURTHER INFORMATION

➢ *We provide structure data file (MDL sdf or db) or SMILE upon request;*

➢ *You can choose entire library or set of selected fragments; we will be happy to assist you with selection (e.g. by applying custom filters, by core diversity etc,);*

➢ *All fragments are available in ≥ 1 mg quantities and can be delivered as custom weighted dry powders or as solutions in DMSO. Custom formatting is available;*

➢ *We provide analytical data with all orders.*

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