3D Compound Libraries for HTS

The 3D-shape of a free ligand is a crucial feature for its molecular recognition by the desired biomolecule and affinity to the binding site [1]. In order to bind strongly to a protein target, the drug ligand should first adopt the right conformation and spatial complementarity to fit efficiently into the binding site. If a dramatic change of the molecular shape is necessary, it would require a lot of activation energy, making such a compound unsuitable as a drug. In contrast, if the molecule is already in "bioactive conformation" (suitable shape for binding), it is more likely to bind strongly and be a good drug.

Non-planar screening compounds with diverse and well-developed 3D shapes have become the most attractive ones on the market for HTS in the last few years. Higher three-dimensionality (3D) of hit compounds has been shown to correlate with their successful passage of various clinical development stages [2].

The use of more complex, more 3D-like sp^3-rich screening compounds can undoubtedly enrich chemical space that might, in turn, be advantageous in exploring more demanding biological targets.

At present readily accessible for your selection are the following proprietary collections of 3D-shaped drug-like screening compounds (Fig. 1-2):

- 3D-shaped Diversity Compound Library (**23,000** compounds)
- 3D-Pharmacophore-based Screening Library (**8,700** compounds)

The compound selection can be customized based on your requirements, cherry-picking is available.

Please, contact us at orders@lifechemicals.com for any additional information and price quotations.

For a **pre plated set** based on this Screening Library, please, explore our Pre-plated Focused Libraries.

Further exploring our related products will make your search even more rewarding:

- 3D-shaped Fragment Library
- Fsp³-enriched Screening Compound Library
- Fsp³-enriched Fragment Library

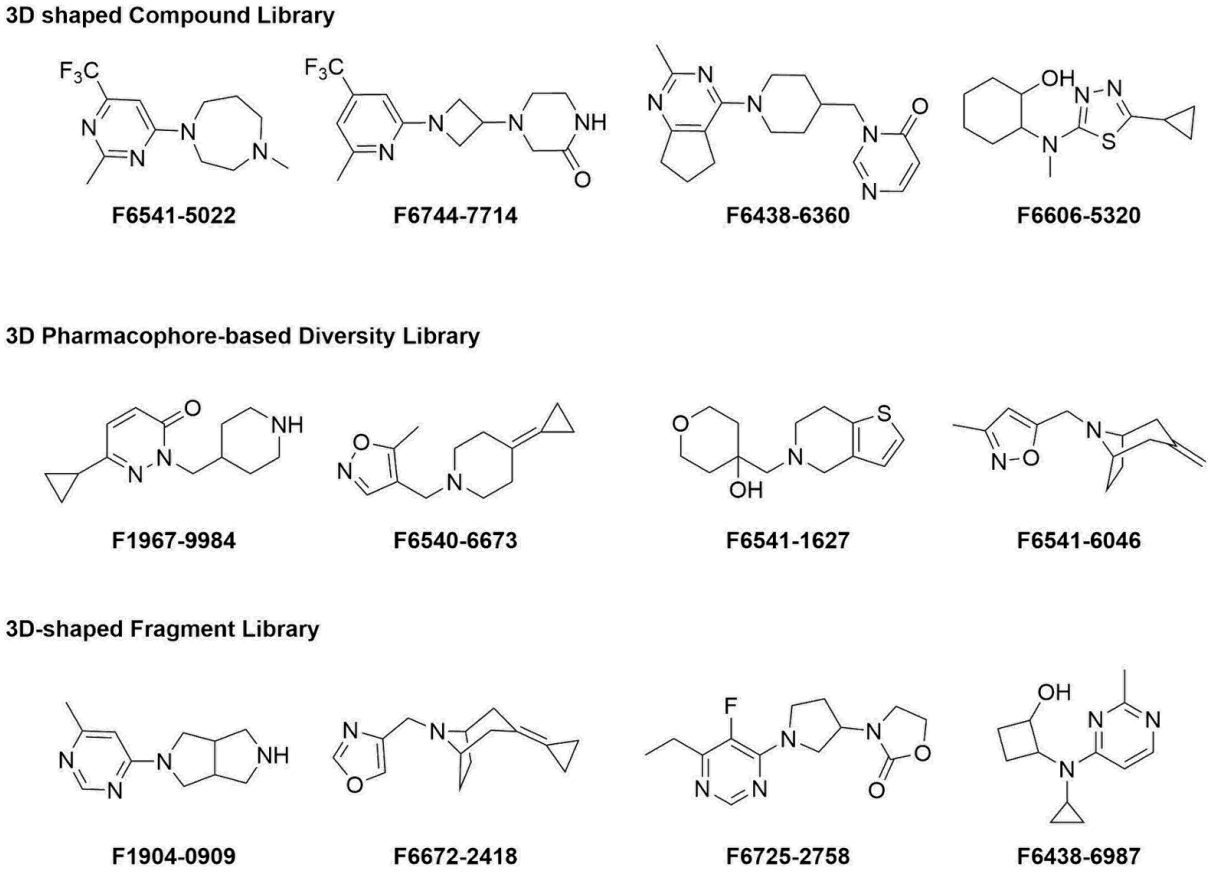

Figure 1. Representative screening molecules from 3D-shaped Diversity Compound and 3D-Pharmacophore-based Diversity Libraries.

3D-shaped Compound Library

The so-called "3D-shapeness" is defined by the plane of best fit (PBF) or principal moments of inertia (PMI) parameters thresholds, which at the moment are the best metrics that describe the shape of the molecule. Detailed analysis of publications on this subject [2-5] enabled us to establish a set of criteria that allow evaluating the 3D diversity of the molecules. These cut-offs with respect to physicochemical parameters (Table 1) were applied to the Life Chemicals HTS Compound Collection to result in a selection of over **23,000** drug-like screening compounds.

3D-pharmacophore-based Diversity Library

First, PAINS filters together with Life Chemicals toxicophore and undesired functionalities filters, developed in-house, were applied to the Life Chemicals HTS Compound Collection. A 3D-conformation was generated for each molecule, after that three of the most different 3-centered pharmacophore hypotheses were constructed, focusing on physicochemical parameters (HBA, HBD, etc. points). The most diverse virtual hits were then selected from each pharmacophore pool, which covered a broad chemical space. In total, over **8,700** structurally-diverse screening compounds based on privileged 3D scaffolds were selected in accordance with these pharmacophore hypotheses.

Table 1. Physicochemical parameters for 3D-shaped Diversity Compound Library

Physicochemical parameter	Range	Average Value
MW	250-500	365.60
FSP³	≥0.35	0.48
ClogP	≤10	2.37
TPSA	≤140	77.92
H-acceptors	≤10	4.06
H-donors	≤5	1.41
Rotatable Bonds	≤10	4.99
Molecular Flexibility	≥0.35	0.47
Molecular Complexity	≥0.53	0.81
Rings	≥ 1	3.36
npr1	≥ 0.15	0.25
npr2	≥ 0.85	0.86
Structure in-house filters	all	

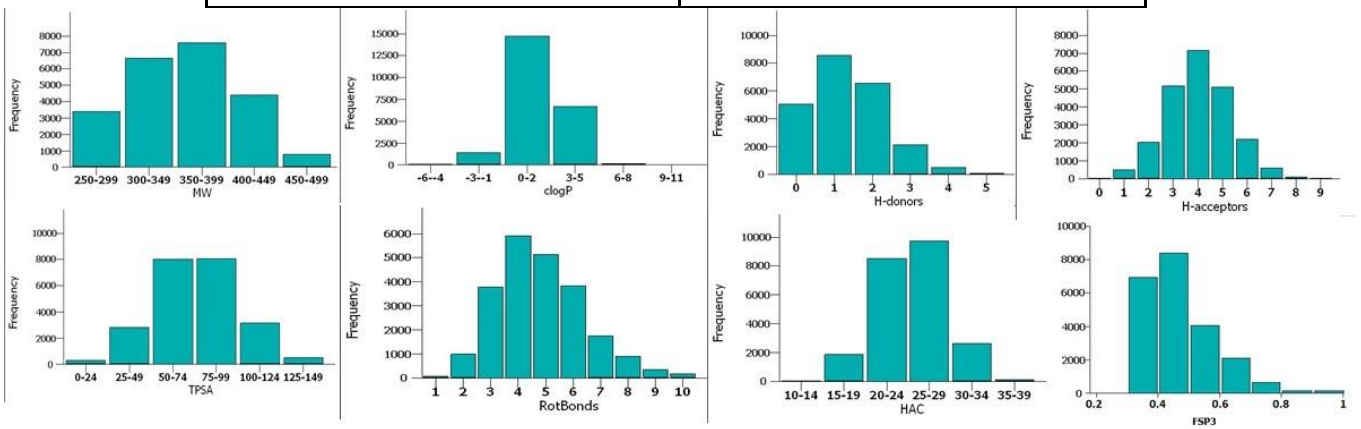

Figure 2. Physicochemical value distributions of the screening compounds in the 3D-shaped Compound Library.

References

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