3D-shaped Fragment Library

The molecular shape is one of the essential factors in molecular recognition by a biomolecule and its affinity to the binding site [1]. Nonetheless, the vast majority of existing drugs have been centered on the sp^2-rich aromatic core [2,3]. Moreover, often the same core moiety can be found in several drugs with different targeted diseases, which leads to a low specificity (selectivity) and the rise of side effects [4]. Although most fragment libraries provide a high level of diversity, having been refined to contain the right balance of properties, they all tend to have a limited shape diversity [5,6].

In this context, it has been established that a higher three-dimensionality (3D) of molecules is a desirable feature of drug candidates and is correlated with the successful passage of molecules at various stages of clinical development [7]. The use of more complex, more 3D-like sp^3-rich fragments would undoubtedly build up the drug-like fragment chemical space that might, in turn, be advantageous in exploring more demanding biological targets.

In view of the above, we have carefully designed a proprietary **3D-shaped Fragment Library** of **4,700** non-flat fragment-like molecules for efficient fragment-based drug discovery (FBDD). The selection was focused on physicochemical properties and descriptors that allow evaluating 3D-dimensionality and structural diversity of the fragment-like screening compounds. This screening set covers various molecule shapes: rod-like, disk-like, and spherical with sufficient diversity shown in triangle 2D normalized PMI plot (Fig.1).

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.

Compound selection

First, the Rule of Three with several filtering criteria was applied to the Life Chemicals General Fragment Collection. **Principal moments of inertia (PMI)** [1,7] calculation was used as an efficient method to calculate and evaluate 3D-dimensionality. Then, appropriate diversity levels of the Library were proved by applying the max Tanimoto coefficient of diversity of 85 % (linear fingerprints were used). Finally, undesirable functionalities were eliminated by applying PAINS and our exclusive in-house medicinal chemistry filters. In total, around **4,700** readily available fragments, representing a variety of 3D shaped molecules, were selected for the Screening Library.

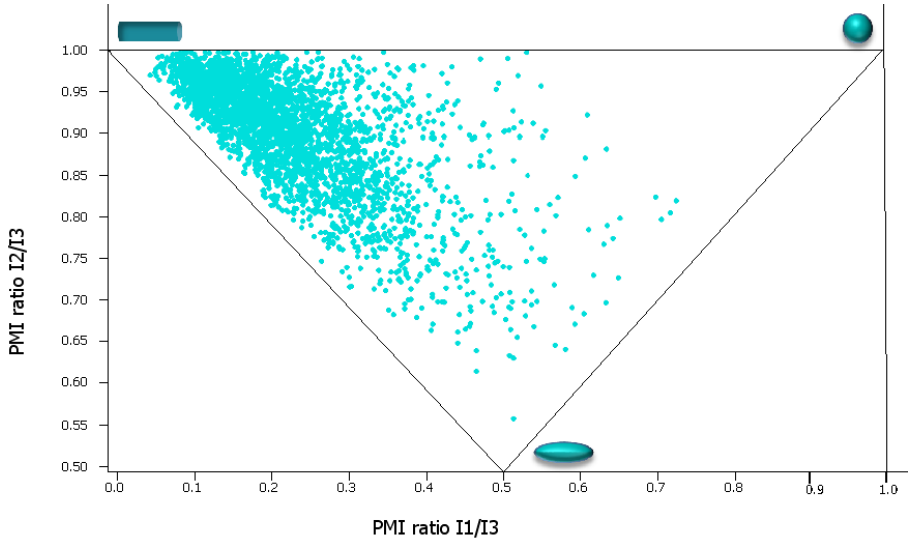


Figure 1. The 2D-normalized PMI plot indicates high compound 3D diversity in Life Chemicals 3D Fragments Library.

The following basic criteria were used to improve the functionality of 3D scaffolds in our Library:

Parameter	Range
MW	100 - 300
Fsp^3	> 0.47
TPSA	< 100 $Å^2$
Rotatable bonds	≤ 3.0
H-donors	≤ 3.0
H-acceptors	≤ 4.0
Chiral centers	≥ 1
Functionalization points	2
-CN, -NO2, Br count	≤ 1
S, Cl count	≤ 2
Ring count	1 - 4

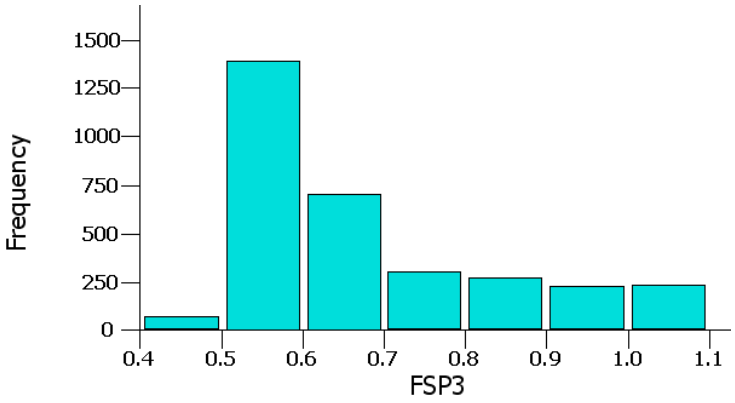
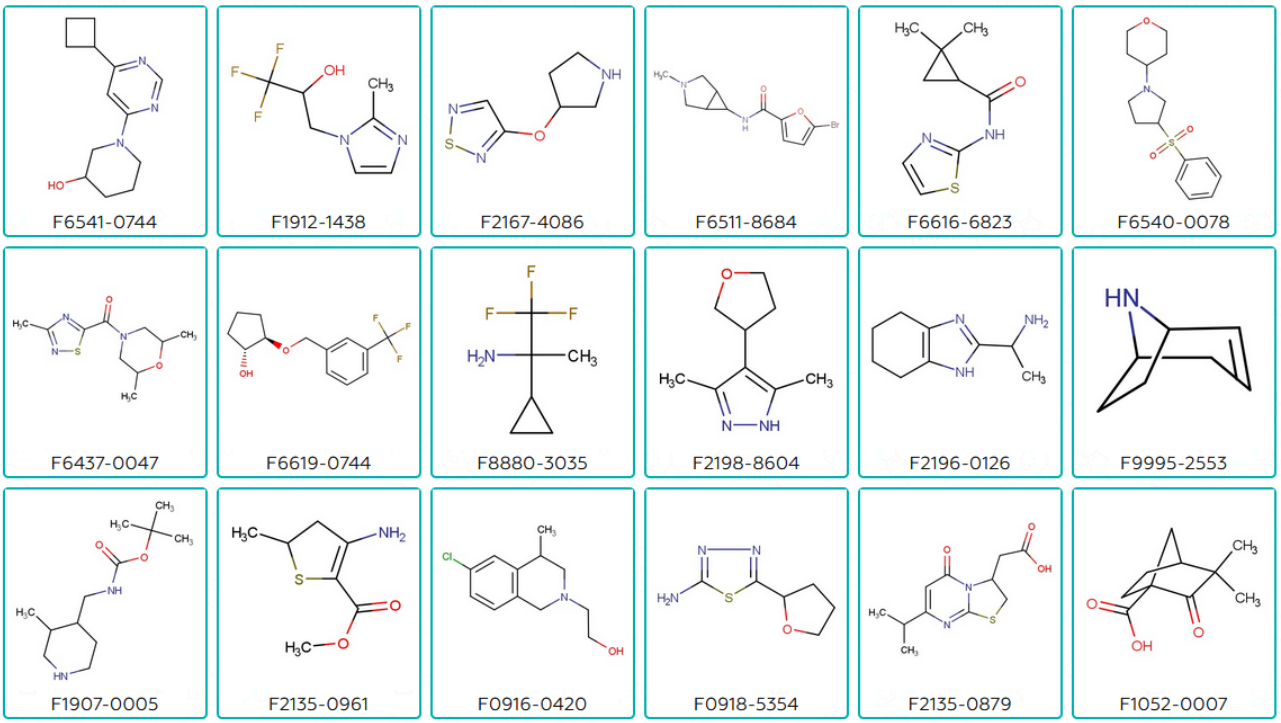


Figure 2. Distribution of Life Chemicals 3D Fragments by Fsp3 values.

Representative compounds from the 3D Fragment Library



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