Fragment Libraries Working in Harmony: A Comparative Study of LCC Fragment Library and Eurofins Fragment Library

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Fragment-based drug design (FBDD) is an approach used in drug discovery to develop biologically potent compounds starting from a single or multiple fragment hit(s).[1] Of the currently available libraries, it has been noted that there is an overrepresentation of flat, sp^2-rich molecules, and a lack of commercially available sp^3-rich 3-dimensional (3D) molecules with suitable growth vectors required for hit development.[2] 3D character can offer many advantages, such as increased solubility, pharmacophore coverage, and receptor/ligand complementarity which in turn can reduce off-target activity, resulting in better starting points for lead generation.[3–5] However, increased 3D character can result in reduced screening hits,[6,7] so use of sp^3-rich libraries in tandem with complementary sp^2-rich libraries would yield the highest possible hit success across the widest range of parameters.

At LCC we have developed our own sp^3-rich, rule of three (Ro3)-compliant fragment library containing suitable growth vectors. Eurofins have also developed the Eurofins Fragment Library, a novel fragment library which closely mirrors current published fragment characteristics. Both libraries offer excellent diversity across a number of different key parameters which we will discuss below.

The LCC and Eurofins fragment libraries were compared with each other, as well as a dataset of published hits extracted from the literature (Table 1).

Table 1: Comparison of LCC and Eurofins fragment libraries with published hits

Database	EID Fragments	LCC Fragments	Published Hits
EID Fragments	1366	3	98
LCC Fragments	3	1017	4
Published Hits	98	4	1651

There is very little overlap between the LCC and Eurofins fragment collections and whilst the Eurofins collection does contain some of the published fragments, these represent only a small fraction (6 %). This highlights the novelty and diversity of both libraries, and their ability to cover a wider array of chemical space.

A range of physicochemical properties were then calculated for the three collections. Both the Eurofins and LCC libraries are within the desired molecular weight range with Eurofins having a slightly lower mean. The Eurofins library looks to have some fragments with a higher HBA count and the LCC collection has more non-aromatic fragments.

The most notable physiochemical properties are displayed below (Figure 1) and include the ionisation state (ABZN), fraction of aromatic atoms, plane of best fit (PBF), and molecular shape (npr).

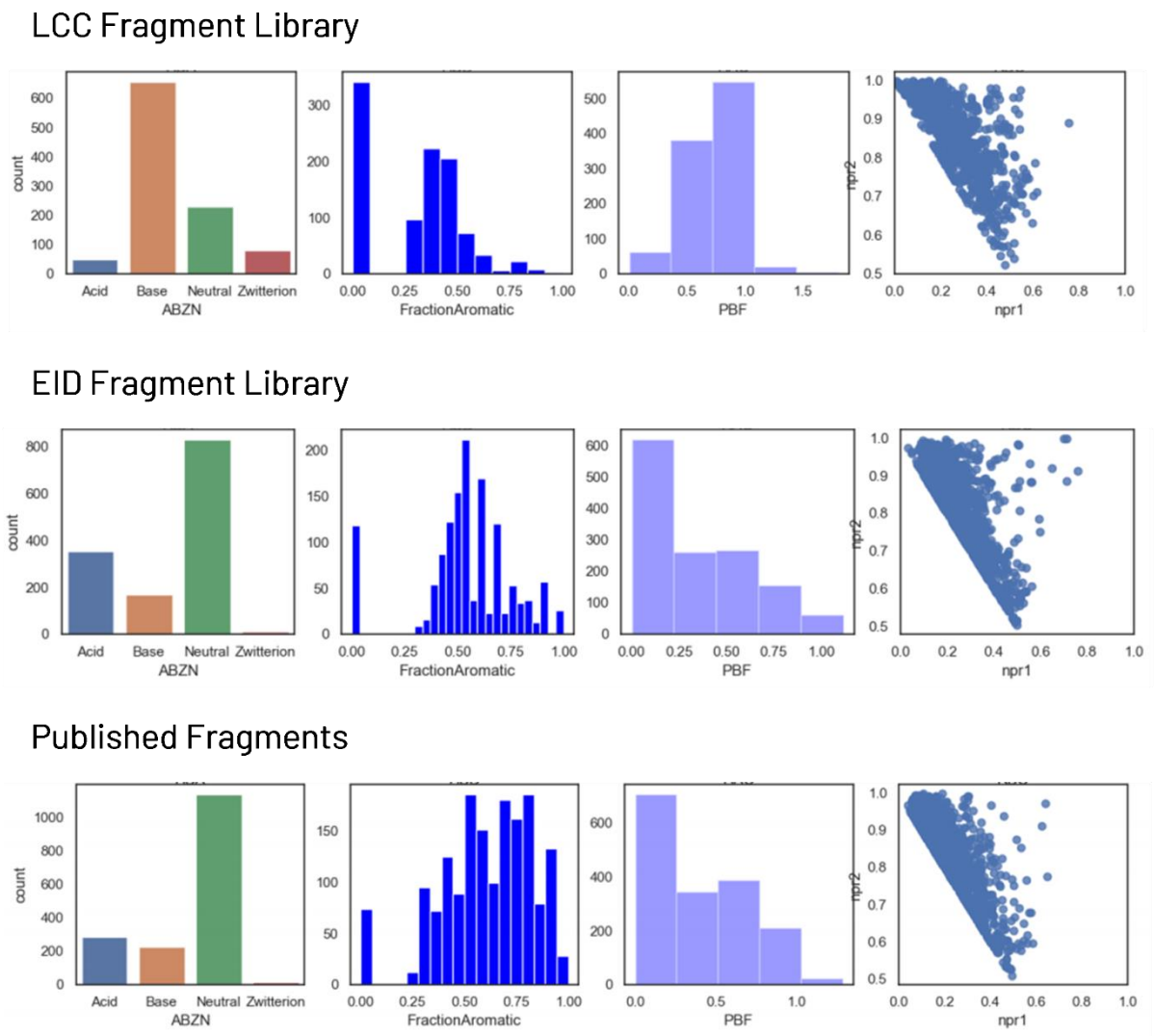

Figure 1: Comparison of most notable physiochemical properties of LCC and EID libraries with published hits

Both the LCC and Eurofins libraries contain many compounds with ionisable groups; interestingly, while LCC contains mainly bases, Eurofins has more acids. These ionisable groups are critical for ensuring good solubility at the high test concentrations required in fragment screening. The LCC collection also includes a number of zwitterions and has more non-aromatic fragments. Comparison of 3D shape is difficult since only single conformations are considered; however, based on the plane of best fit (PBF) data, the LCC library explores more 3D space. Finally, the LCC library contains a greater proportion of sphere-like fragments and fewer disk like fragments as displayed by the normalised PMI ratio (npr) data. Sphere-like, rod-like, and disk-like molecules can be found towards the upper right, upper left, and bottom points of the triangular graph, respectively. The EID fragment library more closely mirrors the published fragments on the npr plot.

Finally, PCA of the libraries was carried out using circular fingerprint relative to molecular size (Figure 2). The data shown below appears to indicate that the bottom half of the graph consists of planer aromatic systems whilst the top half consists of 3D non-aromatic systems.

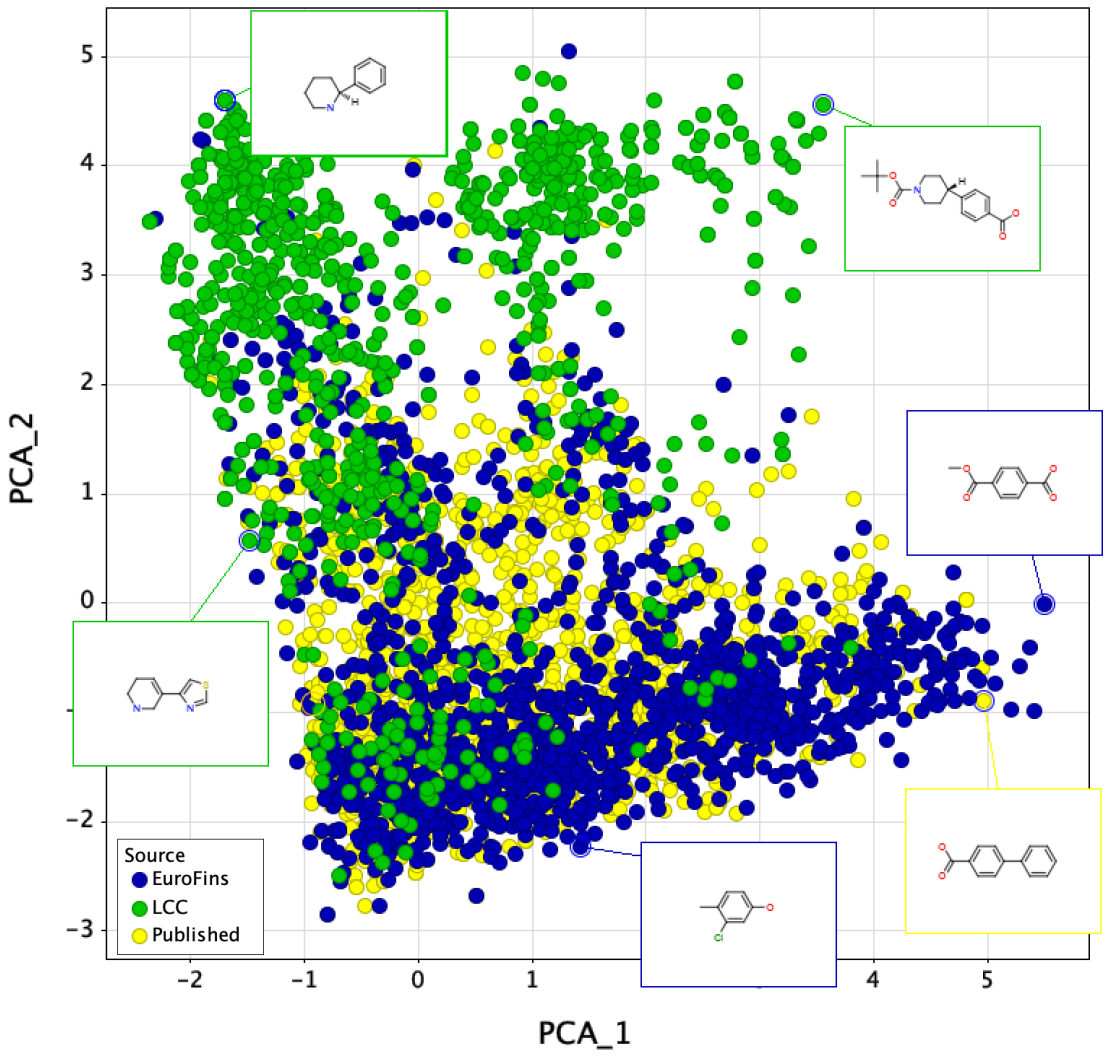

Figure 2: PCA of LCC and EID libraries with published hits

Analysis of the data appears to highlight the greater 3D character of the LCC library which has the largest collection of compounds residing in the top half of the graph, whilst the majority of the EID/published hits reside in the bottom half/middle of the graph.

In conclusion, the LCC and EID libraries were compared with a selection of published hit fragments, highlighting the novelty and diversity of both the LCC and EID fragment collections. The EID library contains a greater proportion of acidic fragments where the LCC library contains a greater proportion of basic fragments, which, together with optimal physicochemical properties, can lead to improved developability. PCA analysis revealed that LCC fragments expand into novel chemical space, complementing the EID fragments which more closely mirror the published chemical space.

Thus, the LCC and EID fragment libraries could be used in tandem to gain access to a wider chemical space and potential increased hit success, all while bringing novelty and diversity to the current fragment chemical space.

References

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