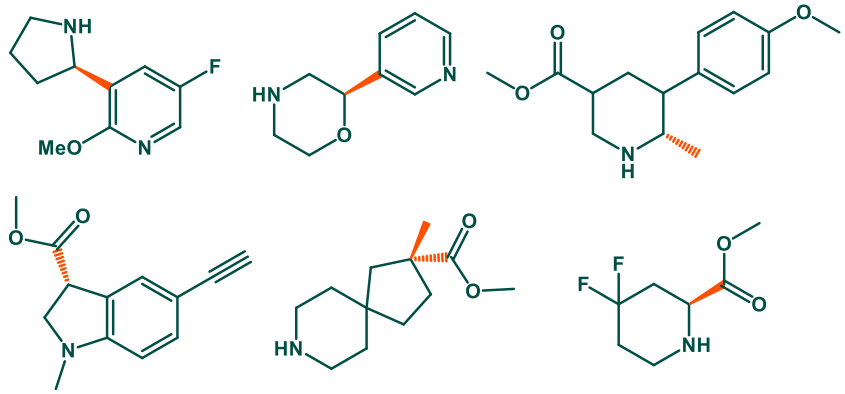
June. 2021

LCC'S MOLECULES OF THE MONTH

Exploring New Fragment Chemical Space
A Comparative Study

Fragment Based Drug Design (FBDD) is a method used in drug discovery which utilises and identifies single or multiple fragment hits to bind to biological targets. As the current available fragment libraries contain a large proportion of planar, sp2 -rich molecules, it is becoming **increasingly important to delve into 3D chemical space.**

At LCC, we have designed and synthesized a library of Ro3 compliant fragments, which are **novel/patentable, diverse, and stereo defined.** Their 3D-rich character allows for improved physicochemical properties, with increased solubility, and high binding specificity, which should give hits with better developability.



We have compared our fragment library to well-established libraries from Maybridge and Key Organics, as well as published fragment hits from the literature. The analysis of the fragment libraries showed a small overlap between LCC's fragments with the other libraries, highlighting the ability of LCC's fragments to **complement existing libraries through unlocking access to new chemical space.**

LCC's fragments also contain a higher proportion of basic and zwitterionic groups, with the ionisable groups offering a **higher predicted aqueous solubility,** as well as potentially acting as the **key binding motifs in the molecule.** This, along with the higher proportion of fragments with 3D character, displays the novel chemical space reached by LCC's fragments, and their potential to boost the drug-like properties needed to enhance the FBDD approach to small molecule drug discovery.

Please see our white paper below for the full analysis results, and if you would like to discuss any of this further, please reach out at **sales@liverpoolchirochem.com.**

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Exploring New Fragment Chemical Space: A Comparative Study of LCC's Fragment Library with Established Libraries and Published Hits

Matthew Pye, Chris Swain

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 available libraries it has been noted that there is an overrepresentation of flat, sp^2-rich molecules and a lack of representation of commercially available sp^3-rich 3-dimensional (3D) molecules containing suitable growth vectors required for hit development.[2] Thus, there are calls for fragment libraries to incorporate novel 3D molecules which also contain suitable synthetic handles to complement existing flat libraries in order to facilitate the development of hit compounds.[2] Indeed, there are pros and cons to adding 3D character to fragment libraries, for example, there are concerns that increased 3D character will result in reduced screening hits.[3,4] On the other hand, 3D character can increase solubility and may offer advantages in terms of pharmacophore coverage, and receptor/ligand complementarity which in turn can reduce off-target activity, resulting in better starting points for lead generation.[5–7]

At Liverpool ChiroChem (LCC) we have developed our own sp^3-rich, rule of three (Ro3)-compliant fragment library containing a diverse array of heterocyclic compounds containing suitable growth vectors (Figure 1).

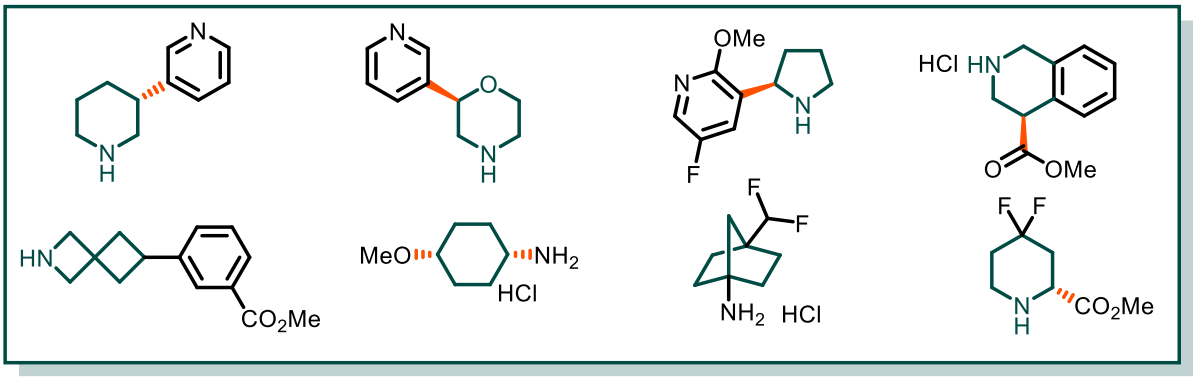

Figure 1: Examples of 3D-rich fragments from LCC fragment library

We compared our library with other well-established libraries from Maybridge (MB) and Key Organics (KO) along with published fragment hits from the literature. The number of identical molecules between each of the fragment libraries is shown below (Table 1). As expected the well-established libraries yielded multiple published hits and have a small overlap, whilst the LCC library has minor overlap with the established libraries.

Table 1: Comparison of LCC library with well-established libraries and published fragments.

Database	MB Fragments	KO Fragments	LCC Fragments	Pub. Fragments
MBFragments	958	60	8	77
KO Fragments	60	1163	9	56
LCC Fragments	8	9	1015	4
Pub. Fragments	77	56	4	1480

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Fragment ionisation state was compared next and the data is shown in Figure 2.

A significant proportion of the published fragments (red) contain an ionisable group. In contrast to the MB and KO libraries which are mainly neutral, the LCC library (green) contains a greater proportion of basic and zwitterionic compounds. Ionisable groups provide two potential benefits: 1) they tend to have higher aqueous solubility allowing for fragment screens to be carried out at high concentrations. 2) they may be key motifs required for hit binding. As the LCC library contains more ionisable groups, it may yield more desirable hit fragments in future screens.

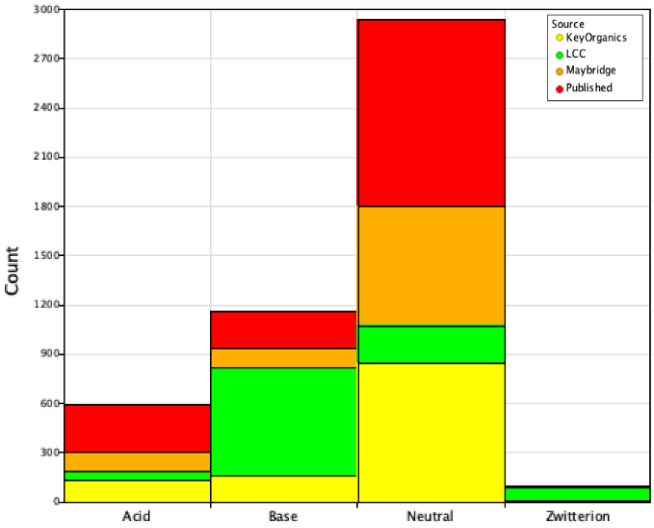

Figure 2: Comparison of published fragments, LCC, MB, and KO libraries ionisation states

Next we compared 3D shape of the libraries and the published fragments. In order to estimate 3D shape, the plane of best fit was calculated for all fragments (Figure 3).

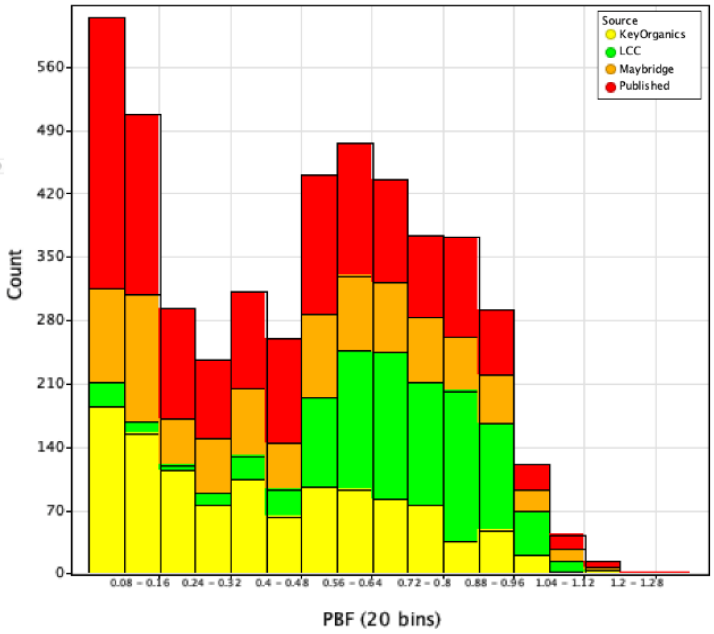

Figure 3: Comparison of published fragments, LCC, MB, and KO libraries plane of best fit

As expected, there are a large amount of published hit fragments in the flatland region, yet it should be noted there is a moderate proportion of published fragments with 3D character. It is clear that the LCC library shows a larger proportion of fragments with 3D character in comparison to the well-established libraries. This highlights the 3D novelty of the LCC library and its ability to complement existing libraries.

Finally, the first two principal components from a principal component analysis (PCA) using circular fingerprints were calculated for all of the libraries and the data is visualised below (Figure 4).

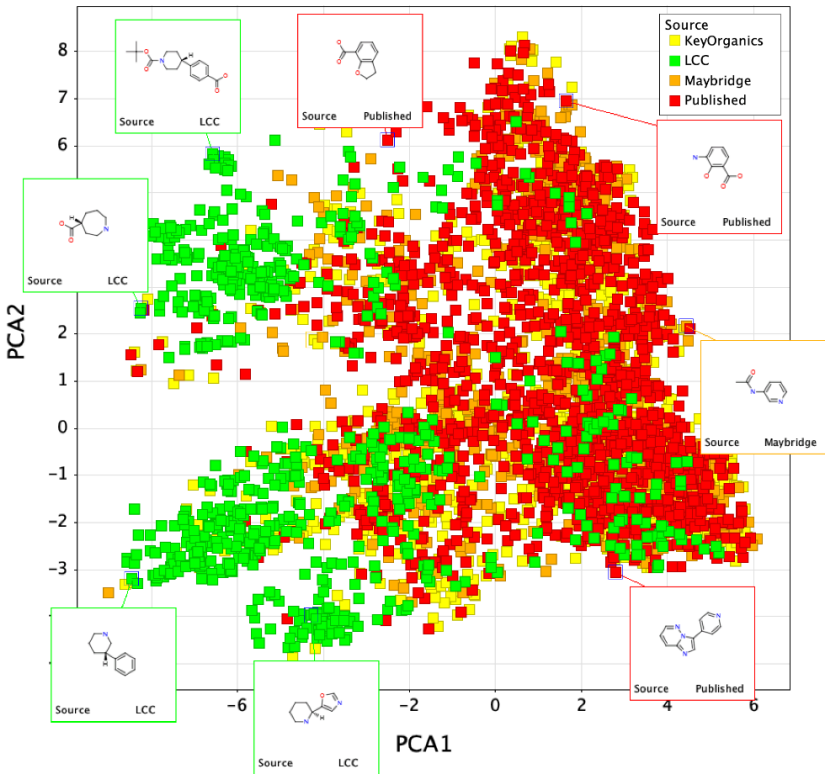

Figure 4: PCA of LCC, MB, KO libraries, and published hit fragments

As might be expected, the published fragments are similar to the two commonly used fragment libraries. In contrast, the LCC fragment library extends into novel fragment space which provides opportunities to develop novel druglike molecules using LCC fragments as building blocks to explore this new chemical space.

In conclusion, the LCC library has been compared with well-established libraries from MB and KO along with published hit fragments. The LCC library contains a significant amount of ionisable groups and a larger proportion of fragments with 3D character, which can offer an advantage for fragment screening. In contrast, the MB and KO libraries are closer to published fragments in terms of chemical space and 2D character. PCA analysis revealed LCC fragments expand into novel chemical space which may aid future development of novel druglike molecules. Ultimately the LCC fragment library could complement existing flatter libraries to facilitate development of hit compounds.

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