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The Frag4Lead 3D Pharmacophore-Diverse Fragment Library and Following Up on Crystallographic Fragment Hits

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The key idea of fragment screening is that a small selection of appropriate fragments covers a much larger proportion of the overall chemical fragment space than a typical high-throughput screening collection with respect to the drug-sized chemical space. Fragments may bypass strict steric requirements for binding, leading to high hit rates. They often efficiently bind in anchor positions making them excellent starting points for ligand design. However, to make the most out of a fragment screen it should adequately cover chemical space allowing to easily follow up on hits by available compounds and feasible chemistry.

Our Frag2Xtal fragment library was designed to cover 3D-diverse yet representative pharmacophores intended for crystallographic screening against generic targets. This representativity allows easily following up on hits by available analogues and superstructures or by synthesis started from reactive synthons. We present a clustering- and docking-based strategy to select tailored fragment subsets and promising follow-up compounds from available candidates. Application to natural compound-derived fragment hits from AnalytiCon´s FRGx library resulted in multiple superstructure ligands with improved affinity.

The presented libraries and methods are part of the Frag2Xtal and Frag4Lead service facility for crystallographic fragment screening currently made available at the automated crystallographic BL14.2 at the BESSY II storage ring of the Helmholtz-Zentrum Berlin.

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