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"Exhaustive X-ray Crystallographic Screening of a Hit-Enriched 96 Fragment Library Against Diverse Targets"

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Modern automated beamlines are well suited for crystallographic screening of 100-500 entry fragment libraries or diverse subsets at no higher effort than alternative biochemical or biophysical pre-screening assays.

As an entry point for a direct crystallographic fragment screening and drug discovery, we compiled 96 well-suited fragments based on experience from prior fragment screening campaigns and PDB entries. For evaluation, we crystallographically screened this library against seven diverse targets (endothiapepsin, protein kinase A, tRNA-guanine transglycosylase, carbonic anhydrase II, thrombin, 17-β-hydroxysteroid-dehydrogenase 14 and thermolysin) at different conditions. Crystallographic hits were obtained for each target at hit rates up to 31%.

We compare the fragment-bound structures of each target. Fragments bound to multiple targets are compared with respect to their binding mode and local interaction pattern. We also show the potential to follow up on these fragments based on feasible growing vectors in the fragment-bound structures.

The presented library is available in collaboration with Jena Bioscience as a ready-to-soak 96-well plate (Frag Xtal Screen). Complementary fragment libraries and methods are part of the Frag2Xtal and Frag4Lead service facility for crystallographic fragment screening currently made available and extended at the automated crystallographic BL14.2 at the BESSY II storage ring of the Helmholtz-Zentrum Berlin.

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