Fragment-based drug discovery truly unlocks synergy of parts by finding highly diverse and rather small ligands that ever increase their binding efficiency and maximize bioavailability once joined in a new molecule.

FBDD is also great compliment to any HTS campaign for enzyme targets as it aids early hit discovery and optimization when data from both screening approaches is compared. Fragment library screen is always target specific in fit being comprised of minimum pharmacophores. FBDD “combines the empiricism of random screening with the rationality of structure-based design”. If available, any structural parts match between HST and FBDD hits is good foundation for preliminary SAR.

TimTec Fragment-Based Library, FBL gathers structurally diverse ligands with low molecular weight and high solubility.

TimTec Fragment-Based Library, FBL, Criteria:

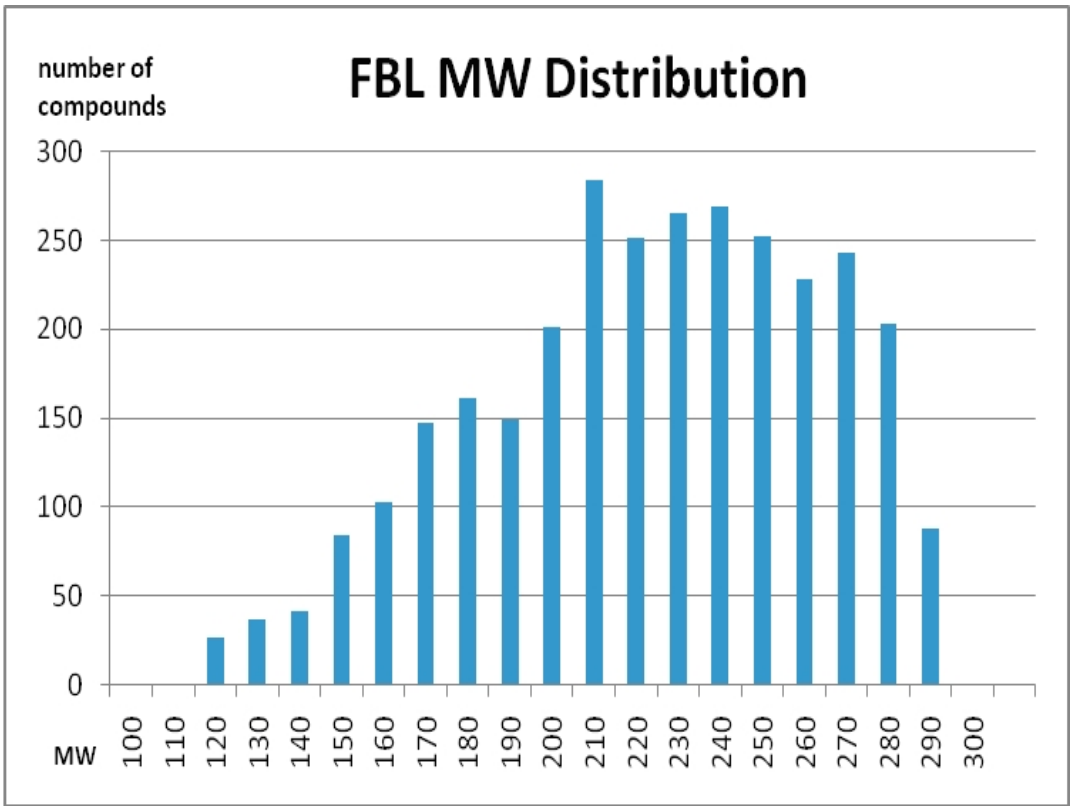
MW	**110-290**
ClogP	**≤ 2.5**
HBA	**≤ 5**
HBD	**≤ 3**
Rotatable bond	**≤ 5**
Heavy Atoms (non-Hydrogen)	**≤ 20**
Rings	**0 – 3**
Polar Surface Area	**Not defined**
LogS calculated	**>10** $^{-3}$
Concentration	**1.5mM**

Potential IC50's number target

0.1 to 1.0mM Ki/K

*All calculations are performed using TimTec proprietary software ChemDBsoft

Compounds can be delivered in dry form in custom milligram or micromolar amounts and as fre shly prepared DMSO solution aliquots.



Screening Results

Meiby E, Knapp S, et.al. Fragment screening of cyclin G-associated kinase by weak affinity chromatography. Anal Bioanal Chem. 2012 Nov;404(8):2417-25. doi: 10.1007/s00216-012-6335-6

TimTec FBL was used in fragment screening of a kinase target-cyclin G-associated kinase (GAK) using new method, weak affinity chromatography (WAC), in combination with mass spectrometry (MS). GAK is a potential drug target for Parkinson's disease. Eight fragment-hits that were identified and the reference compound are shown below. ST088036 is "one of the highest ranked fragments".

- ST014664
- ST034758
- ST048901
- ST057236
- ST057640
- ST081058 *(ST059935)*
- ST088036
- ST009496

Screening results against GAK were used to assemble a small collection of drug-like

compounds that possess the same fragments.

Duong-Thi M-D, Bergstrom M, et al. High-Throughput Fragment Screening by Affinity LC-MS. J Biomol Screen. Feb 2013. 18(2), p 160-171. Pub online: Sept 13, 2012. doi:1087057112459271

Weak affinity LC/MS is identified as a viable and productive method to screen fragments under high-throughput conditions. It is valuable tool to add to already widely used methods for the identification, structural analysis, and optimization of fragment leads. The article provides compelling evidence in favor of weak affinity LC/MS as well as recognizes its very few limitations. TimTec FBL subset was screened to identify the selective hit, ST036785 , at the active site of thrombin, Human alfa-thrombin.

Download subset of compounds that possess benzamidine and 3-hydroisoindolylamine (ST036785) moieties.

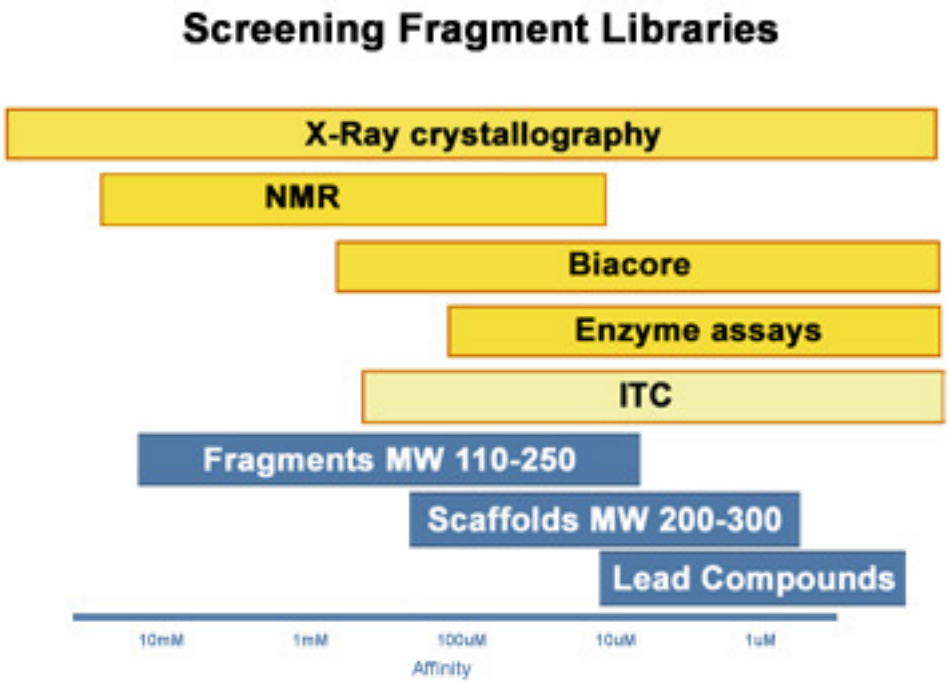
Please read more about Weak Affinity Chromatography for fragment screening:

Duong-Thi M-D, Bergstrom M, et al. Weak Affinity Chromatography for Evaluation of Stereoisomers in Early Drug Discovery. J Biomol Screen. March 11, 2013, doi: 10.1177/1087057113480391

Contact TimTec today to discover your “powerful” weak inhibitors!

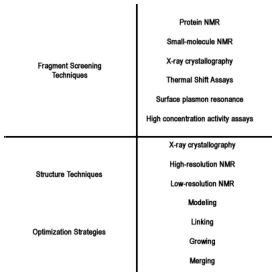
Fragment-Based Drug Discovery has been gaining more and more attention since mid 1990s, the year when the SAR-by-MNMR technology is developed at Abbott. Number of most recent technological advancements makes FBDD approachable part of HTS campaigns.

Comparison Chart



Vernalis classification: the strength and limitations of various experimental approaches. *GEN. March 2009, Vol 29, 5, 22-24*

Small in size FBDD libraries furnish vast chemical space design combinations in building drugs from small molecular pieces. Structure-based approach can be applied very early in fragments optimization to decrease and/or eliminate undesirable structural characteristics to boost in vivo safety and minimize number of synthesized lead candidates.



Various methods for the identification, structural analysis, and optimization of fragment leads. Am Drug Disc. Feb/March 2008, Vol 3, 2, pp 56-60

FBDD complementary benefits to HTS:

-

Oftentimes HTS falls short of generating leads for selected challenging targets

-

Combinations of fragments cover greater chemical diversity space multiplying optimization options

-

FBDD is an economical precursor to HTS being able to identify compound-analogs with desirable “active” fragments

-

Faster aggregation of SAR data for hit-to-lead development

FBDD credibility is also backed up by clinical candidates: Chessari, G. and Woodhead, A.J. (2009) From fragment to clinical candidate – a historical perspective. Drug Discov. Today 14, 668–675

Reference:

Jahnke, W., Erlanson, D. A. (Eds.), (2006). *Fragment-based approaches in drug discovery*. Weinheim, Germany: Wiley-VCH.

Barker J., et. al. Integrating HTS and fragment-based drug discovery. Drug Discovery World. Summer 2008; Vol 9, 3, pp.69-75

Sun C., Hajduk P.J. How Then Shall We Screen? American Drug Discovery. Feb/March 2008, Vol 3, 2, pp 56-60

Gitig D. Revitalizig Surface Plasmon Resonance. Resurgence is Drivenby SPR's Aptitude for Fragment-Based Lead Discovery. GEN. March 2009, Vol 29, 5, 22-24

Liszewski K. Capitalizing on Fragment-Based Discovery. Computational and Medicinal Chemists are Joining Forces to Turn Hits into Leads. GEN. April, 2009, Vol. 29, 8, 18-22

Boettcher A., et.al. Fragment-Based Screening by Biochemical Assays Systematic Feasibility Studies with Trypsin and MMP12. Sept 20, 2010, vol. 15 no. 9, p 1029-1041

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