THE CFL: MAXIMIZING FRAGMENT-TARGET INTERACTION SPACE WITH A MINIMAL SCREENING SET

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BioBlocks — A CHEMISTRY PARTNER IN DRUG DISCOVERY

Cayman Chemical · Visionary Pharmaceuticals

FBLD AT BIOBLOCKS

Many fragment library compounds are unique but not designed to enable follow-up. BioBlocks's Comprehensive Fragment Library (CFL) is a next-generation set of small, rigid, medicinally interesting fragments designed to address this common problem in fragment SAR. Extensive clustering analysis allows broad coverage of chemistry space and ensures that an immediate follow-up strategy is available from every screening hit.

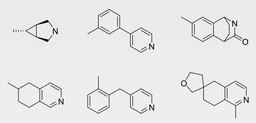
DESIGNING THE CFL

The CFL originates from a set of >3 million potentially synthesizable virtual fragments designed from first principles and 3D enabled to maximize exploration of target interactions. An exhaustive virtual set of ring structures containing ≤18 heavy atoms and 1 handle atom was generated.

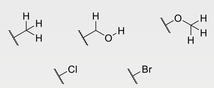
Key inclusion criteria:

- ≥ 1 ring, including bridged, spiro and fused ring connections
- ≤ 3 unique rings
- ≤ 2 ring assemblies
- ≤ 2 rotatable bonds
- 1 atom has all rotatable bonds
- C,N,S,O atoms only
- ≤ 1 S

Example CFL Fragments

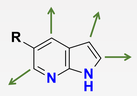


Example CFL Handles



FRAGMENT ANALOGS FROM A CFL HIT

Analog Category	CFL000025	10 Fragment Hits	Plate 1
Handle Analogs	**10**	100	550
Handle Vectors	4	47	257
Same 2D Scaffold	37	343	3308
Same HBond Pattern	274	12857	42667
Same 3D Cluster	47	573	6371
Total CFL Compounds	873	13676	50669
% Unique to Compound	100%	74%	26%
CFL Analogs	>30,000	>1 M	>25 M



Five categories give access to orthogonal analog sets from a hit

- Handle – variable synthesis options
- Vector – handle position options
- Scaffold – heavy atom options
- HBond Pattern – core options
- 3D Cluster – similarity options

L2L also uses an analog generator to explore sp3 ring variations

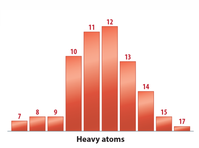
CURRENT FRAGMENT SET

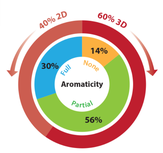
Available screening collection:

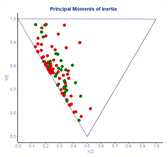
120 Fragments for initial screen
- Soluble at 200 mM in DMSO
- Well behaved at 2 mM in multiple assay formats

>100 Analogs for follow up
- Soluble at ≥100 mM in DMSO
- Alternative handles for multiple expansion chemistries

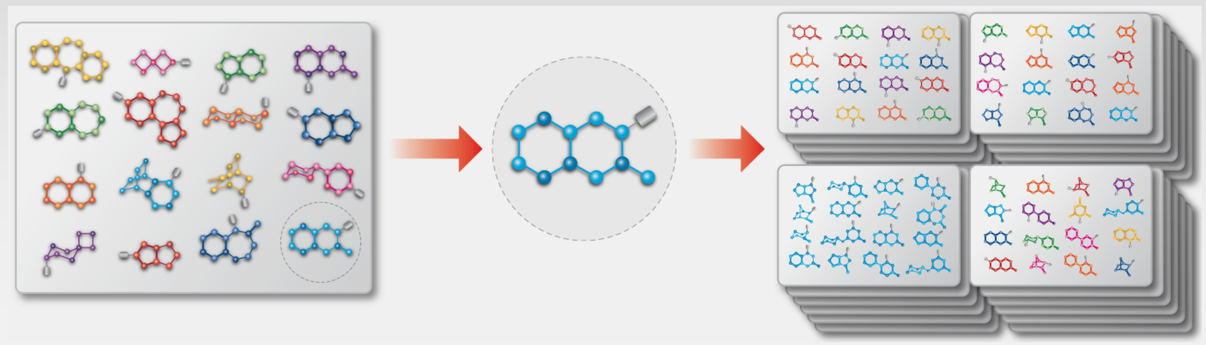
Plate Summary:







THE LEAP-TO-LEAD™ PLATFORM REVEALS IMPROVED PATHS FORWARD



Each compound in a CFL plate represents a different 3D cluster

Each screening hit is connected by multiple paths to related analogs in the CFL

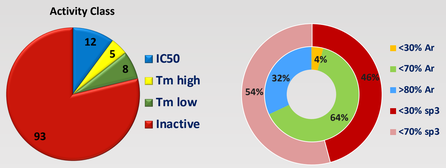
>1,000 Related CFL compounds arise from each hit via different analog pathways

TARGET CASE STUDY 1

Cayman Chemical

Prostaglandin D synthase (HPGDS) mediates inflammatory signaling in asthma
The CFL library set was screened against HPGDS in a thermal shift assay (TSA)
Followed by a competitive FP assay with a known active site inhibitor

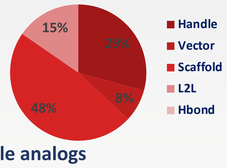
Screening Summary:



Hit fragments are more flat and more aromatic than the overall plates
Published inhibitors for this target have high % aromatic character
The majority of the CFL fragment hits are only partially aromatic

ANALOG GENERATION

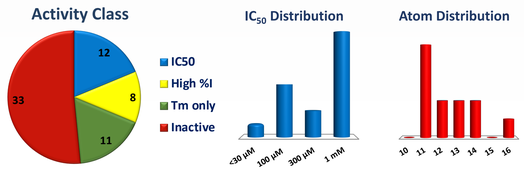
4/6 Analog Categories Assayed
- Handle
- Vector
- Scaffold
- L2L analoger
- 3D reserved for next round



17/25 Fragments had readily accessible analogs
- <1% of possible analogs were commercially available
- Supplemented with 1 step synthesis

64 Analogs tested in follow up activity assays

ANALOG ACTIVITY

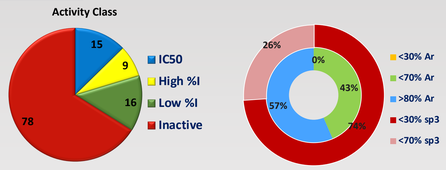


TARGET CASE STUDY 2

Visionary Pharmaceuticals

SGK1 is an emerging kinase target in oncology and inflammation
Amenable to high concentration biochemical assays
The CFL library set was screened for %inhibition at 2 mM against active SGK1

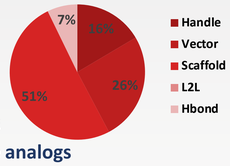
Screening Summary:



Hit fragments with IC_{50} values are predominantly aromatic
Published inhibitors for this target are also predominantly aromatic
Some hits identified from CFL with higher Fsp^3
Most hits biased towards typical hinge-binding HBond pattern DA-2

ANALOG GENERATION

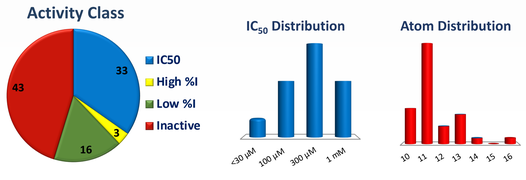
4/6 Analog Categories Assayed
- Handle
- Scaffold
- Vector
- HBond pattern – varied core with DA-2



12/15 Fragments had readily accessible analogs
- <1% of possible analogs were available commercially
- >95% of available analogs were predominantly aromatic

95 Analogs tested in follow up activity assays

ANALOG ACTIVITY

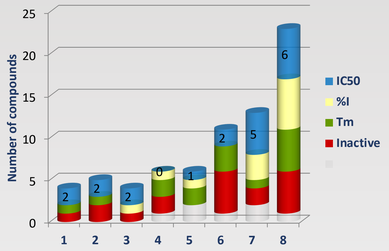


ANALOG FAMLIES FOR LEAD FINDING

Analysis pathways designed to distribute analogs into families
Focus on ligand efficient families to start with desirable properties
Tactical med chem allows improved potency while maintaining properties
L2L strategy provides superior entry points to lead optimization

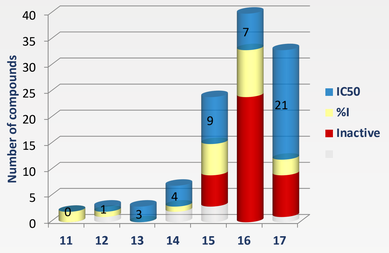
HPGDS analogs distribute into 8 structural families

- Remaining singletons had no available analogs
- Partially aromatic families had limited availability
- Next phase requires synthesis of related analogs



SGK1 analogs distribute into 7 structural families

- Remaining singletons had no available analogs
- Predominantly aromatic families had high availability
- Next phase requires expansion of nonaromatic regions



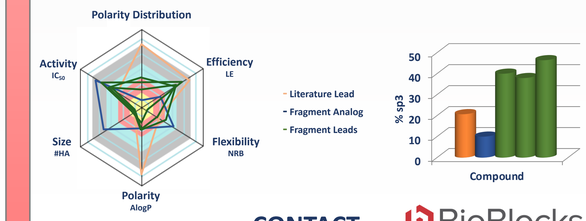
% hit overlap between targets in initial screens
Only minor activity overlap between targets (0-3 compounds/family)
Each target had 3-4 families for next phase of fragment evolution

NOVEL LEAD SERIES IDENTIFIED

One SGK1 analog family was progressed to medicinal chemistry
Superior drug-like properties compared to literature leads
Novel series is now in early lead optimization for oncology indications

ProperType Optimization Plot

A good lead hits the bull's eye



CONTACT

BioBlocks — A CHEMISTRY PARTNER IN DRUG DISCOVERY

BioBlocks is developing Leap-to-Lead™ for use in Lead Discovery Collaborations. While the CFL is not available for independent purchase, we welcome new collaborators. For additional information or to discuss using the CFL and the Leap-to-Lead™ platform in a drug discovery effort, please contact wwade@bioblocks.com or visit our website: www.bioblocks.com