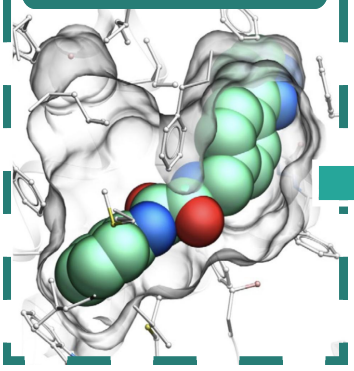
Exploration of the ultra-large chemical spaces

CHEM SPACE
Delivering Discovery Solutions®

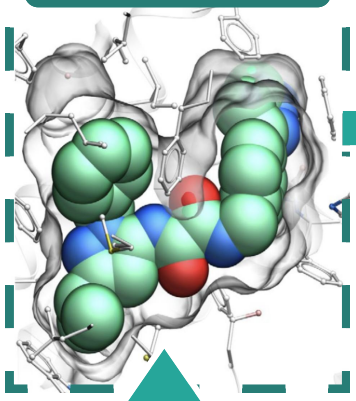
V-SYNTHES Approach

Enamine xREAL 173B molecules

Docking the Minimal Enumeration Library (MEL)

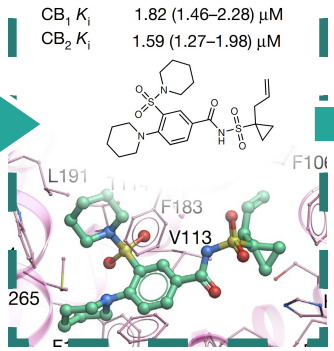


Ligand-Receptor Docking

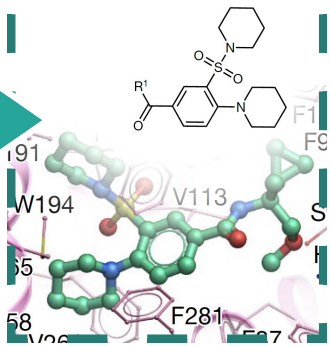


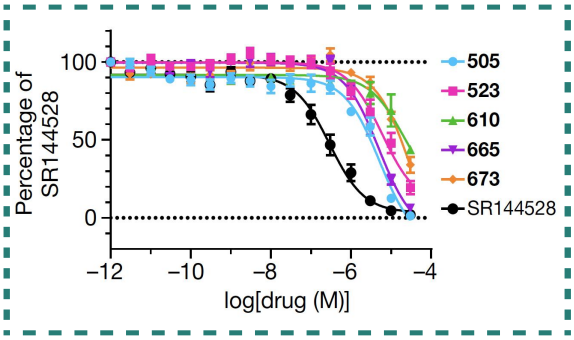
Focused set based on the best scoring fragments from MEL

Hit Compounds



SAR from Enamine REAL



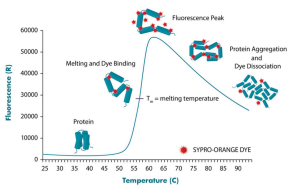


Concentration–response curves for the top antagonists in β-arrestin recruitment Tango assays at the CB2 receptors.

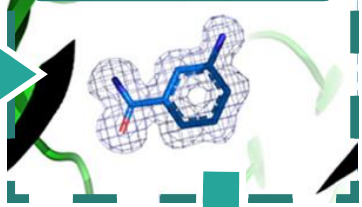
Nature 601, (2022) 452

"Crystal Structure First" Approach

TSA Fragment Pre-Screen



X-Ray Fragment Hits Protein Kinase A

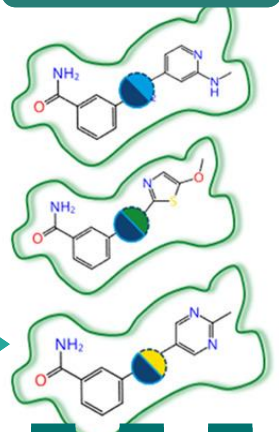


Bioorg. Med. Chem., 2018, 26(12), 3399-3405

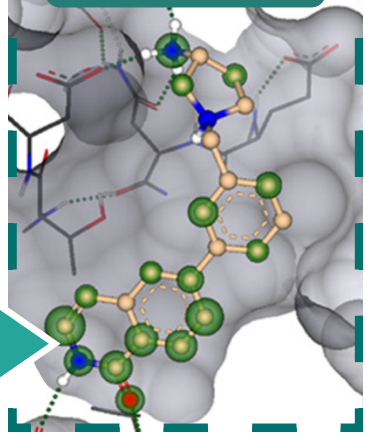
cluster	compound	K_i in μM	crystal structure	# analogues
c1	**Frag1**	n/a	yes	n/a
	EN064	~5,000	empty	3,190
c2	**Frag2**	~10,000	yes	n/a
	EN093	5.6/3.1/ 0.744	yes	190
	EN078	154.7	no	329
c3	**Frag3**	~20,000	yes	n/a
	EN090	139.3	empty	359
	EN089	354.3	no	95
c4	**Frag4**	~5,000	yes	n/a
	EN088	85.8	yes	15
	EN086	390.2	yes	34
	EN081	174.4	yes	837

Focused Subset of Enamine REAL

Chemical Space Docking



13,500-Fold Affinity Gain



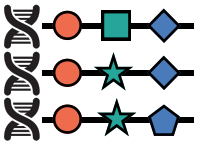
J. Med. Chem. 2022, 65 (23), 15663-15678

contact us at cs_sales@chem-space.com

DEL-ML-CS Approach

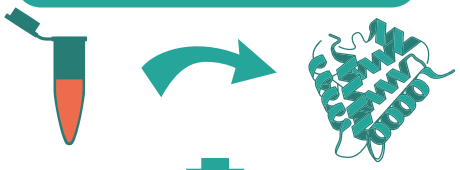
Classical Approach

DNA-Encoded Library



up to **3B** compounds

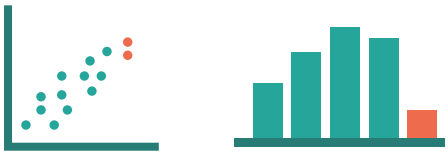
Target Selection and DEL Screening



PCR and DNA Sequencing

CTAAAGATGATCTTTAGAT
GATCTTGTTCGAATCTTTA
GTCCCGGTTGATAACACC
AACCTGATGATCTTGATGA
TCTTATAACACCAGT

Data Analysis and Hit Proposal



Off-DNA Synthesis

Possible Cons:

- Not all compounds can be synthesized off-DNA
- Custom synthesis is rather expensive
- This is a time consuming process

ML-Assisted Approach

Synthesis of hits

3-4 weeks
80% success rate

Filtering compounds by properties of interest

- ✓ MolWeight
- ✓ LogP
- ✓ PAINS
- ✓ Bad Groups
- ✓ Custom filters

Application to Commercial Spaces

Enamine REAL **33B+** compounds

In-Stock Collections

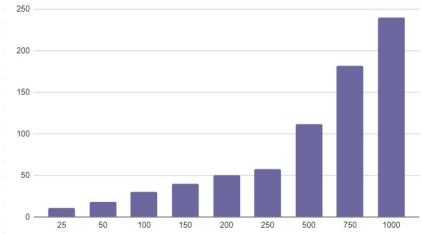
Train a Machine Learning Model

DEL Data

Results:

- Disynthon aggregation helps determine substructures responsible for binding
- Regression model successfully identifies CAIX actives from ChEMBL

Number of actives in top N compounds from ChEMBL by prediction



"Hit rate" of top 100 - 30%

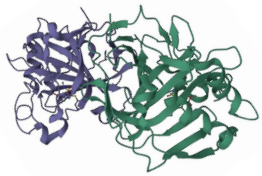
- Application to Enamine REAL results in 25% experimentally confirmed hit rate

33B+	150	130	33	25.4%
Enamine REAL Space	Compounds for testing	Successfully synthesized	Confirmed hits	Hit rate

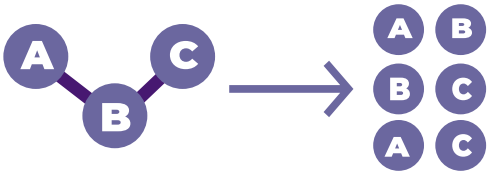
* Most hits with IC50 in low micromolar-high nanomolar range

ML-assisted Approach - Case Study

Target: CAIX
108K open-source DEL datapoints



Strategy:
disynthon aggregation for noise reduction



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