Unveiling Hidden Treasures: Exploring Large Chemical Spaces with Machine Learning Models Trained on DNA-Encoded Libraries Selection Results

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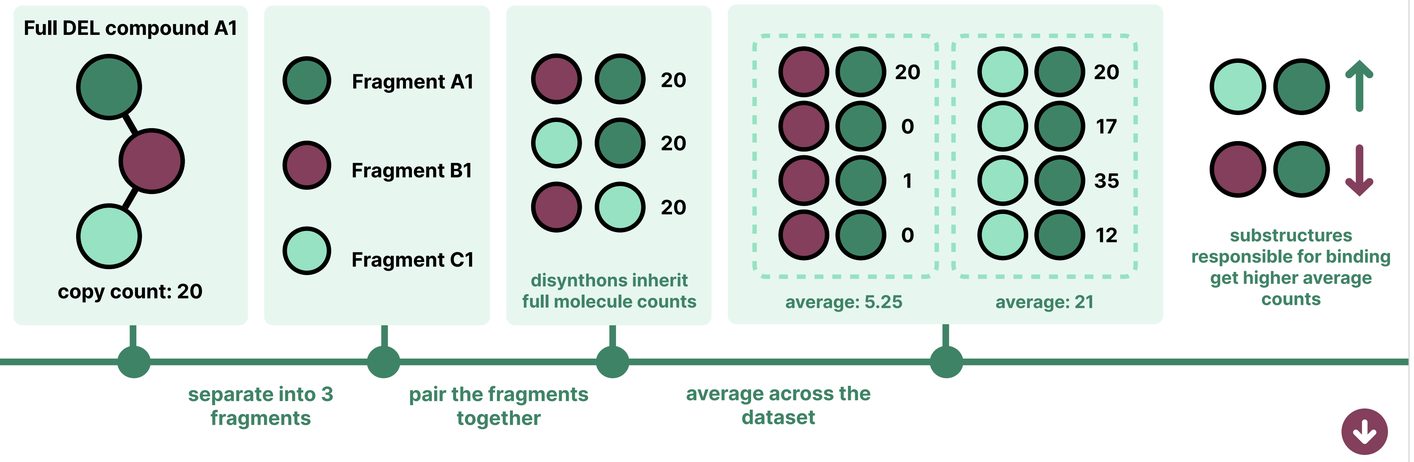
DEL Screening Data

DEL screening results:

- 4 experiment selections
- 2 control selections
- 108.5k datapoints

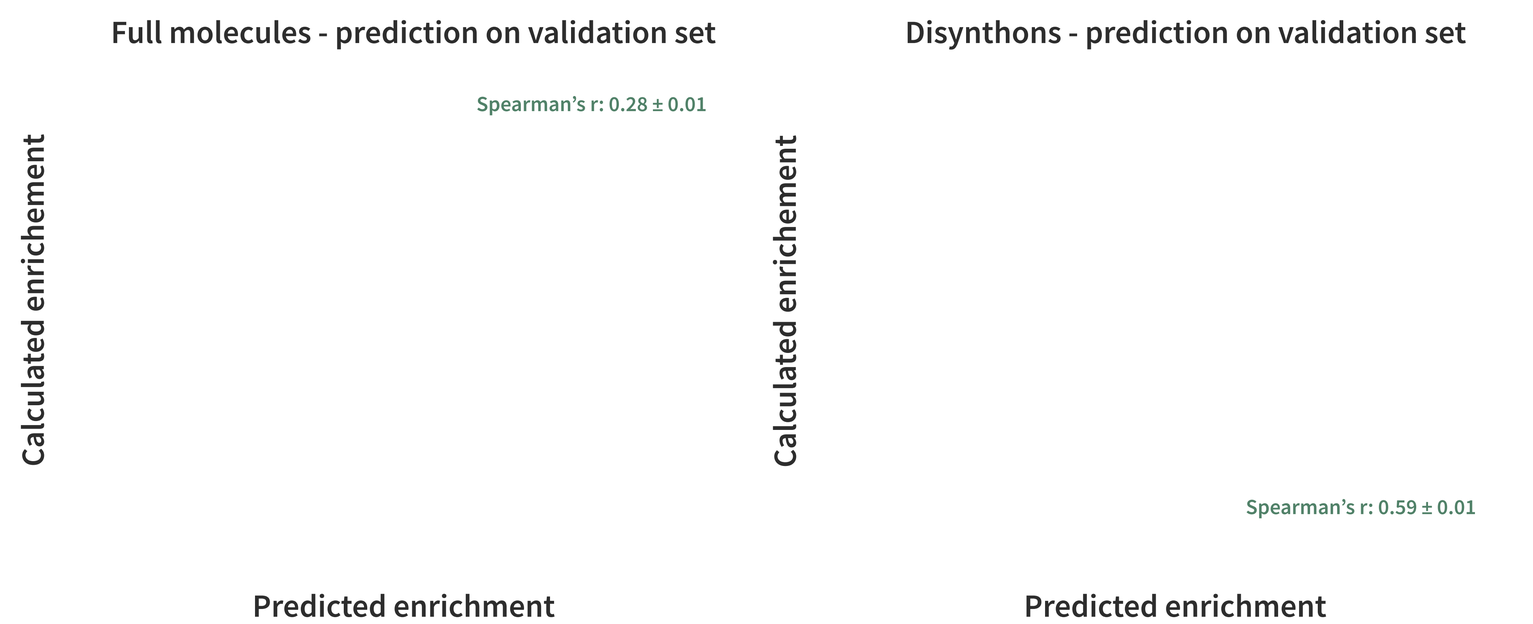
CAIX

Noise Reduction

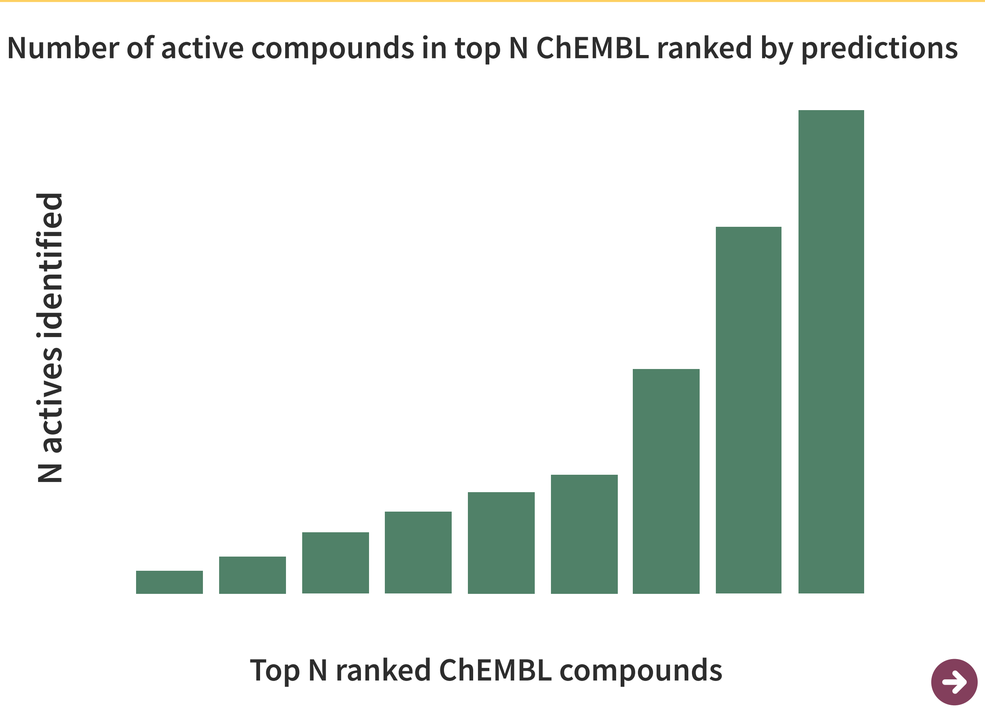


Regression Model Performance

Model	Spearman Ki (full)	Spearman Ki (subset)
Molecular weight Benzenesulfonamide presence	-0.121 -0.199	0.074 -0.063
Top Vina docking score Top GNINA docking score	-0.068 -0.279 ± 0.044	0.119 -0.091 ± 0.061
RF trained on enrichment scores from Gerry et al.	-0.231 ± 0.007	-0.091 ± 0.012
GNN (Lim et al.)	-0.298 ± 0.005	-0.075 ± 0.011
DEL-Dock (Shmilovich et al.)	-0.328 ± 0.01	-0.186 ± 0.01
Our model	-0.309 ± 0.007	-0.214 ± 0.014



Selecting active compounds from ChEMBL



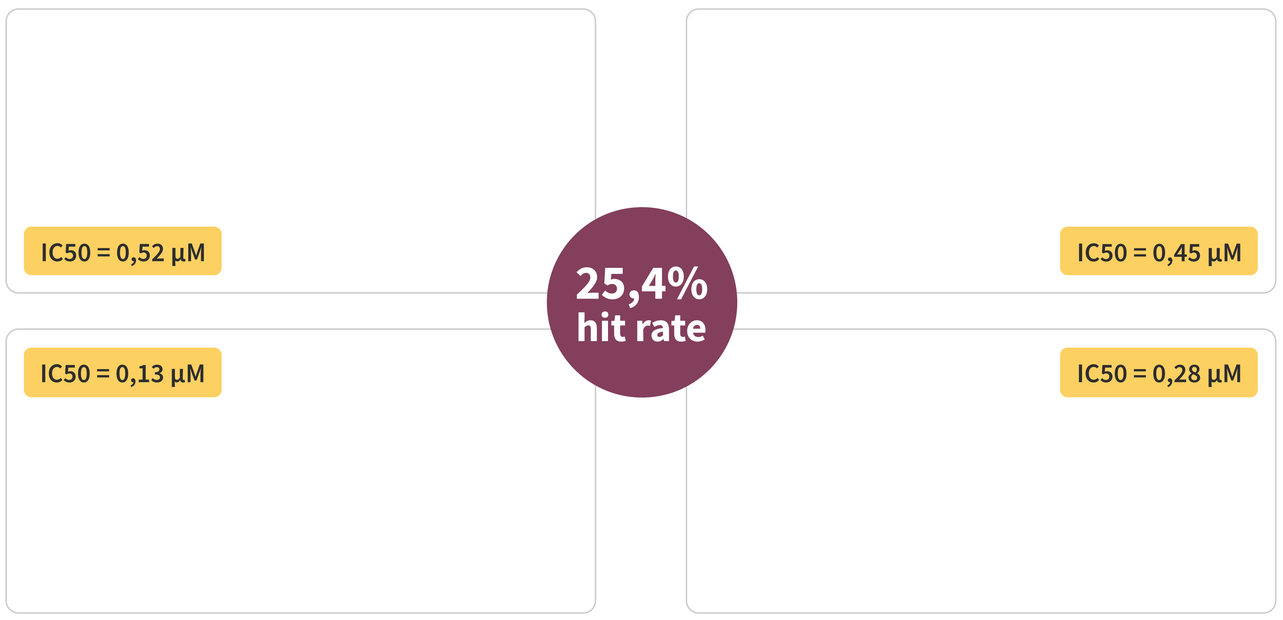
Exploration of Enamine REAL

33B+ Enamine REAL Space → **1M** Top compounds by prediction → Sphere exclusion clustering → Visual inspection → **150** Selected for synthesis → **130** Successfully synthesized

- Regression model with best performance used for prediction
- Selected diverse compounds with the best predicted enrichment in the cluster
- Compounds are dissimilar from known actives
- Synthesis success rate 87% by Enamine

Results

- Disynthon aggregation helps to identify substructures important for binding and de-noise DEL datasets
- Regression models trained on DEL data can efficiently rank compounds from large compound databases.
- Exploration on Enamine REAL by ML model leads to identification of 33 novel hits with 25.4% hit rate.



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