10× HIGHER HIT RATES AT 3–10× LOWER COSTS: ACCELERATING LIGAND DISCOVERY WITH ML-GUIDED SYNTHESIS & SCREENING

Greta Klejborowska[1], Łukasz Szczupak[1], Jan Kulczycki[1], Łukasz Sztukiewicz[1], Piotr Setny[2], Michał Michalski[2], Karolina Zakrzewska[2], Jarosław Walczak[2], Michał Komorowski[2], Michał Mońka[1], Jan Rzymkowski[1], Paulina Wach[1], Paweł Włodarczyk-Pruszyński[1], Stanisław Jastrzębski[1], Piotr Byrski[1]

[1]Molecule.one, Warsaw, Poland, g.klejborowska@molecule.one
[2]Inventro.co, Białystok, Poland

Rapid & reliable hit generation with Direct-to-biology-SpaceM1

- Unique & highly novel molecular space of ~100M compounds and still growing
- **First chemical space built using deep learning models trained on proprietary HTE lab data of over 300,000 reactions**
- Rapid turnaround (fastest subset from order to measured biological activity in **4 weeks**)
- Compounds starting from <$10

In comparative virtual screening[#] on 12 protein targets with ~395 randomly selected compounds from commercial reference space and D2B-SpaceM1; D2B-SpaceM1 showed on average higher hit rates:

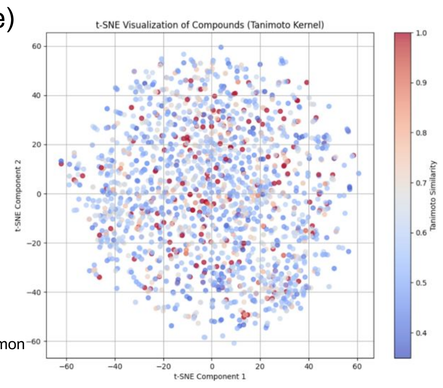
Target (examples)	**D2B-SpaceM1 docking hit rate****	**C-Ref* docking hit rate****	**Novel to C-Ref** (Tanimoto < 0.75)	**Highly novel to C-Ref** (Tanimoto < 0.5 & Different Scaffold)
PRMT5	**10.4%**	1.0%	60.0%	10.8%
KRAS(G12C)	**6.6%**	0.0%	48.6%	18.9%
LRRK2	**4.3%**	0.3%	54.5%	21.2%
mGluR5-5M	**8.1%**	0.5%	43.5%	10.1%
BTK	**24.3%**	3.6%	46.7%	15.6%

[#]Based on ligand efficiency; *C-Ref - commercial reference, **Hit rates calculated using ligand efficiency with threshold of activity was set dynamically as at max(0.4, thr_chembl), where thr_chembl is median ligand efficiency of top 10% most active compounds stored in ChEMBL. Compounds were randomly sampled from each space.

Hit identification & confirmation from virtual screen in 5 weeks

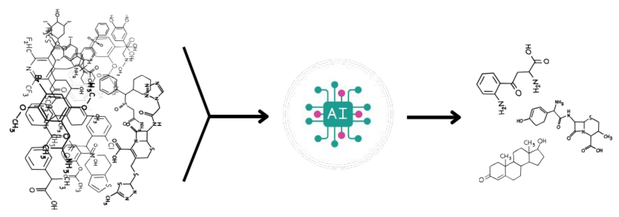
D2B-SpaceM1: designed with generative deep models & 300k+ reaction data points

- The biggest D2B space available on the market
- Highly novel comparing to commercial ref.
- HTE data-driven feasibility prediction (~80% success rate)



Only 4% of SpaceM1 compounds exhibit >0.7 Tanimoto similarity to common commercial ref.

Hit candidates selection based on INVENTRO AI Predictive Models



DTB-SpaceM1 — **Proprietary Algorithm** — **Filtered Hits**

- Efficient exploration of 10^{12} cmpd spaces
- On-target activity hit rate for up to 30%
- Cost (AI model & biological assay): ~$100 per one active
- Time: hours/days
- Multiple activities

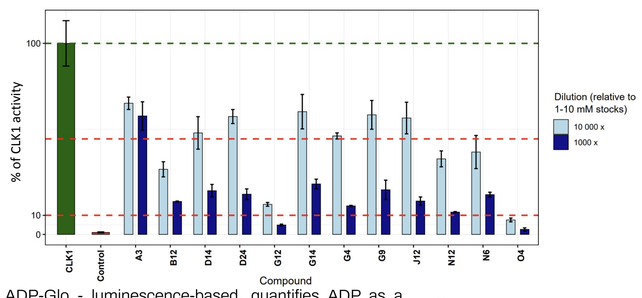
INVENTRO EXPLORING CELL COMPLEXITY

Direct-to-biology (D2B) plate synthesis

- D2B: parallel micro-scale synthesis in well plates followed by minimal work-up
- Molecule's one HTE lab: on average 13,000 reactions/weekly
- Synthesis success rate ~92% (84/92)
- Feasibility based on proprietary experimental data
- Cmpds delivered in 384-well plates (1–10 mM)

Rapid biological screening

- Initial 100× dilution screen in ADP-Glo → 12 compounds with CLK1 activity <10%
- 2nd run at 1,000× and 10,000× dilutions
- Outcome: 11 compounds inhibited CLK1 activity >50%; hit rate: 18% (AI-prioritized), 12% (full grid)

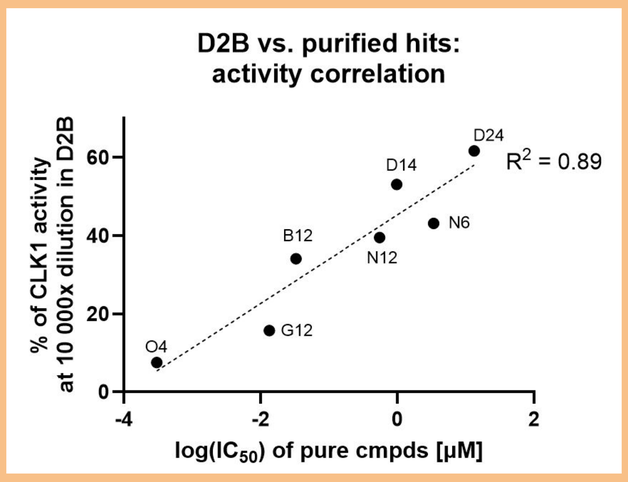


ADP-Glo - luminescence-based, quantifies ADP as a readout of enzymatic activity; 100% activity is defined in the absence of inhibitor, control CLK-IN-T3 at 1 µM

INVENTRO EXPLORING CELL COMPLEXITY

Hit resynthesis & confirmatory assay

- Fast turnaround: hits resynthesized, purified and delivered within 1 week of D2B assay results
- All purified hits confirmed active at Inventro
- Potent hits* down to sub-nM level (IC_{50} distribution: 2 at µM, 2 at sub-µM, 2 at nM, 1 at sub-nM)



*No prior literature reports for these structures; for O4, SciFinder similarity 85 to the closest known

Summary:

- **Largest & most novel D2B space**, built on extensive HTE reaction data
- **Strong (0.89 R^2) correlation between D2B crude activity and purified IC_{50} ranking**
- Hit activity up to **sub-nM level**, hit rate 18%
- End-to-end workflow is **very rapid**, enabling experimental hitID and confirmation within **weeks, not months**
- Workflow applicable also to hit expansion and hit2lead

Discover Molecule.one's offer — scan here

molecule.one

Scan to schedule a meeting with us!