Delivering High-Quality Hits through Novalix DEL Platform & Generative AI

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DNA-encoded libraries (DELs) are a powerful hit-finding approach enabling the rapid screening of millions to billions of compounds. However, library size alone does not guarantee success. Productive screening campaigns require libraries that combine broad chemotype diversity with drug-like physicochemical properties.

Here, we present a case study demonstrating how the proprietary DEL platform of Novalix applies advanced cheminformatics workflows to guide DEL design and maximize screening performance. By prioritizing diverse druglike chemical space, the NovaDEL collection enabled the identification of high-quality hit series for PI4KIIIβ with promising properties for medicinal chemistry optimization. Furthermore, we show that combining DEL with generative AI can successfully identify novel chemotypes distinct from the known binders.

Together, these results demonstrate that quality-driven library design and synthesis, combined with computational approaches, can enhance DEL screening outcomes and accelerate the discovery of novel chemical matter for relevant therapeutic targets.

Bibliography :

[1] Fischer, Y.; Cedeno, R.; Triki, D.; Vivet, B.; Schambel, P. Evaluating the Diversity and Target Addressability of DELs Using Scaffold Analysis and Machine Learning. ACS Med. Chem. Lett. 2025, 16 (2), 263–270. https://doi.org/10.1021/acsmedchemlett.4c00505.

[2] Loeffler, H. H.; He, J.; Tibo, A.; Janet, J. P.; Voronov, A.; Mervin, L. H.; Engkvist, O. Reinvent 4: Modern AI–Driven Generative Molecule Design. J Cheminform 2024, 16 (1), 20. https://doi.org/10.1186/s13321-024-00812-5.

[3] Mejdrová, I.; Chalupská, D.; Kögler, M.; Šála, M.; Plačková, P.; Baumlová, A.; Hřebabecký, H.; Procházková, E.; Dejmek, M.; Guillon, R.; Strunin, D.; Weber, J.; Lee, G.; Birkus, G.; Mertlíková-Kaiserová, H.; Boura, E.; Nencka, R. Highly Selective Phosphatidylinositol 4-Kinase IIIβ Inhibitors and Structural Insight into Their Mode of Action. J. Med. Chem. 2015, 58 (9), 3767–3793. https://doi.org/10.1021/acs.jmedchem.5b00499.

[4] Probst, D.; Reymond, J.-L. Visualization of Very Large High-Dimensional Data Sets as Minimum Spanning Trees. J Cheminform 2020, 12 (1), 12. https://doi.org/10.1186/s13321-020-0416-x.

[5] Swanson, K.; Walther, P.; Leitz, J.; Mukherjee, S.; Wu, J. C.; Shivnaraine, R. V.; Zou, J. ADMET-AI: A Machine Learning ADMET Platform for Evaluation of Large-Scale Chemical Libraries. Bioinformatics 2024, 40 (7), btae416. https://doi.org/10.1093/bioinformatics/btae416.