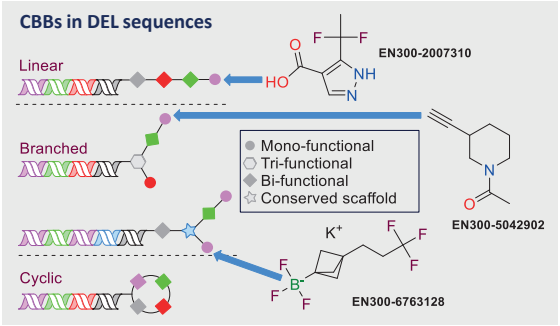
Chemical Landscape of Capping Agents for DNA-Encoded Technologies (DELT) from Enamine Perspective

A. Pashenko, R. Smaliy, I. Kos, Dmytro M. Volochnyuk, Serhiy V. Ryabukhin

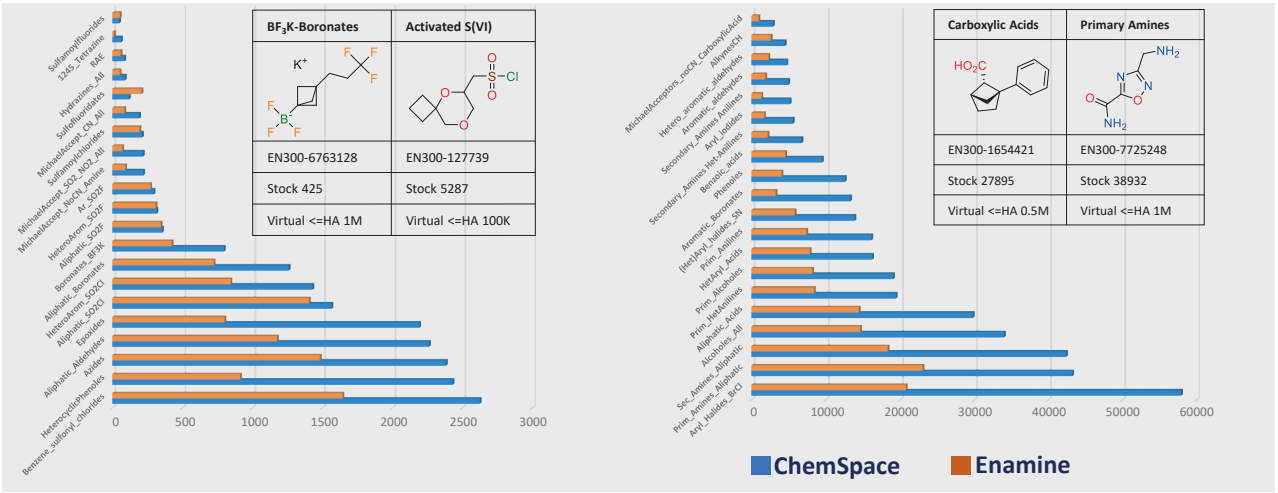
Introduction to the Problem

DNA-encoded libraries (DELs) rely heavily on the diversity of mono-functional "capping" building block (CBBs), to ensure broad chemical coverage. However, selecting these building blocks is complex, as they must balance chemical diversity, reactivity, and compatibility with DNA tagging[1]. This work examines the chemical space of these building blocks, offered by prominent vendor, - Enamine and global chemical aggregator ChemSpace.

Aim: ***to identify trends and gaps, ultimately guiding the future expansion and success of DELs in drug discovery.***



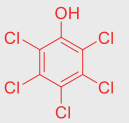
DEL-Viable CBBs globally (according to ChemSpace)

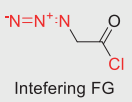


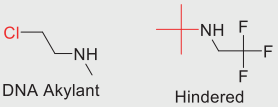
Selection Criteria

The selection criteria for DEL-relevant CBBs are crucial for ensuring library diversity, reactivity, and biological compatibility. Despite the vast chemical space of world stock BBs, only a small fraction meet these stringent criteria, which are applied through computational screening[2], expert curation, and empirical testing. We can categorize those into two subgroups: **"Essential"** for the non-negotiable criteria, and **"Preferred"** for the less crucial ones.

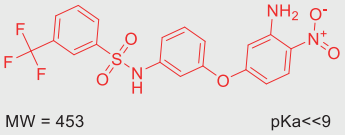
Essential:
- No interfering functional groups;
- Molecular weight <125 Da;
- No DNA-alkylating potential;
- Defined stereochemistry;
- No toxicophores;
- Limited steric hindrance;
- Chemical stability.


Toxicophore

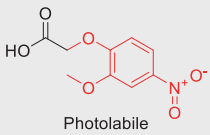

Intefering FG

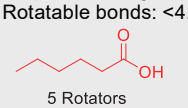

DNA Akylant

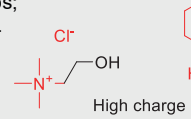
Hindered

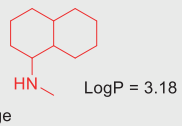

MW = 453 pKa<<9

Preferred:
- LogP < 3 (representing lipophilicity);
- Basicity: pKa between 9-11 (amines);
- Limited charge under physiological conditions;
- No photolabile groups;
- Rotatable bonds: <4.


Photolabile


5 Rotators

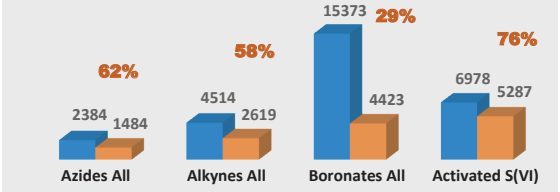

High charge


LogP = 3.18

Summary and Outlook

In DEL chemistry, prioritized CBBs like **click-reactive compounds (azides, alkynes), boronates, and activated sulfur compounds (sulfonyl chlorides, sulfonamides)** have consistently shown promise. They offer diverse on-DNA reactions, distinguishing from common functionalities.

Notable: ***Enamine often outpaces other global vendors in this domain***



Contact

Dmitriy M. Volochnyuk, Prof. Dr. Sci., d.volochnyuk@gmail.com;
Sergey V. Ryabukhin, Prof. Dr. Sci., s.v.ryabukhin@gmail.com

References

1. Satz, A. L.; *et al., Bioconjug. Chem.* **2015**, 26 (8), 1623-32;
2. Oksiuta, O. V.; *et al., J. Org. Pharm. Chem.* **2023**, 21 (1), 3-19.