Polyfunctional Core Building Blocks for DNA-Encoded Technologies (DELT): the Definitive Factor for Libraries Diversity

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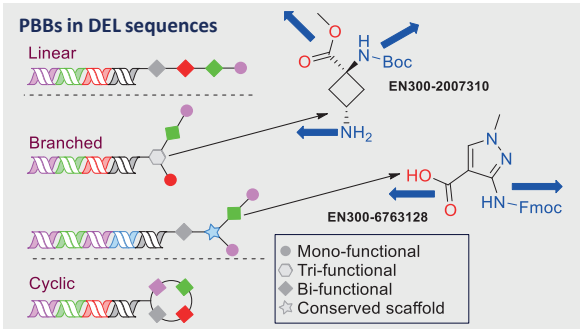
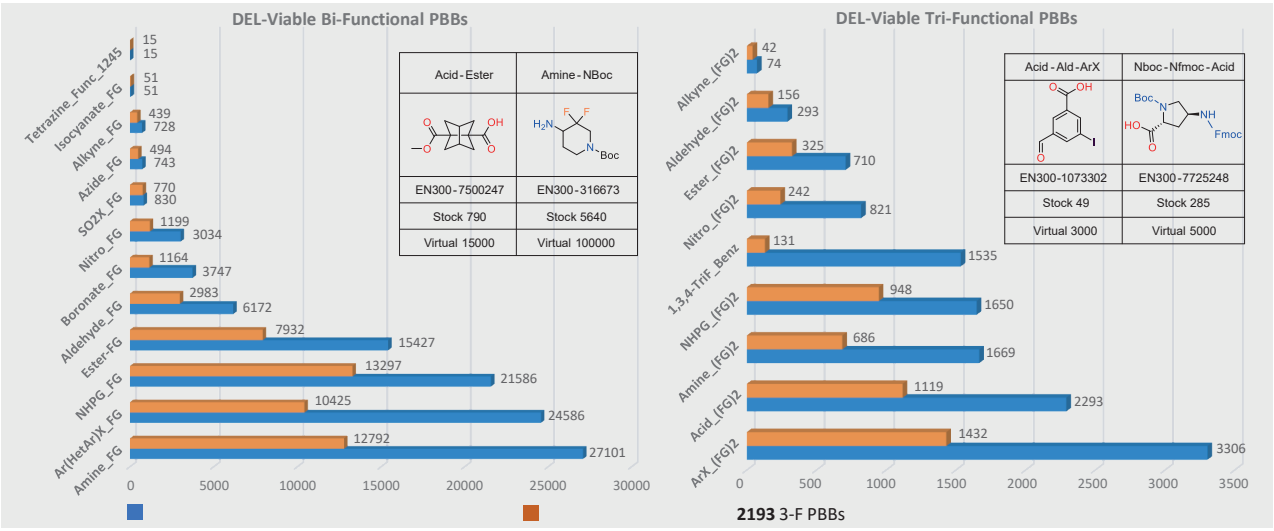
Introduction to the Problem

DNA-encoded libraries (DELs) hinge on the diverse array of polyfunctional building blocks (PBBs) to achieve comprehensive chemical representation. The challenge lies in judiciously choosing these PBBs, ensuring they harmonize chemical variety, reactivity, and affinity for DNA tagging[1]. This study delves into the chemical breadth of such building blocks, spotlighting offerings from leading vendor Enamine and the world-stock aggregator, ChemSpace.

Aim: ***to discern patterns and voids in PBBs, directing their strategic development for enhancing DELs' efficacy in drug discovery.***



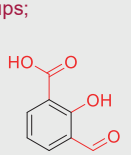
DEL-Viable PBBs globally (according to ChemSpace)



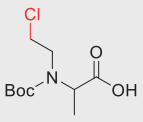
Selection Criteria for PBBs

The selection criteria for DEL-suited PBBs are pivotal in guaranteeing on-DNA reactivity library chemical diversity, and further biological relevance. Even with the expansive chemical reservoir of global BBs, only a minor subset satisfies these rigorous standards, determined via computational analysis[2], visual inspection, and hands-on evaluation. Some of the risk factors **elevate** in case of polyfunctional molecules.

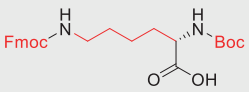
Elevated Risk Criteria ("Essential" Marked Red):
- No interfering functional groups;
- No DNA-alkylating potential;
- Defined stereochemistry;
- Molecular weight <125 Da;
- Limited steric hindrance;
- Rotatable bonds: <4.



Interfering FG
Hindered

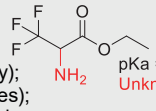


6 Rotatating Bonds;
Alkylates DNA

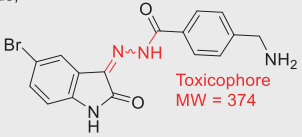


6 Rotating Bonds

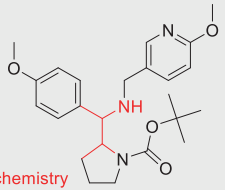
Average Risk Criteria:
No toxicophores;
Chemical stability;
LogP < 3 (representing lipophilicity);
Basicity: pKa between 9-11 (amines);
Limited charge under physiological conditions;
No photolabile groups.



pKa = 3.47;
Unknown Stereochemistry



Toxicophore
MW = 374

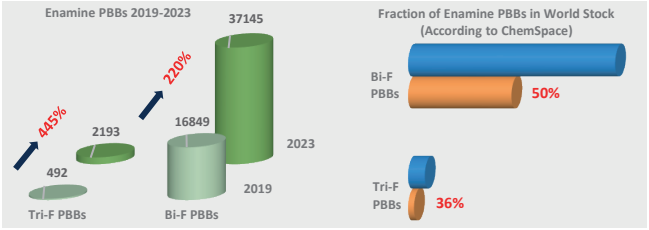


MW = 428
Unknown Stereochemistry

Summary and Outlook

While the **chemical space of polyfunctional BBs** is much smaller compared to mono-functional ones, they **significantly amplify DEL diversity** and are **rapidly expanding.**

Note: ***Enamine efforts in PBBs synthesis gave multiplicative growth of the collection***



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References:

1. Huang, Y.; Savych, O.; Moroz, Y.; Chen, Y.; Goodnow, R. A., Jr., **2019**, 75-87., 1623-32;
2. Oksiuta, O. V.; *et al., J. Org. Pharm. Chem.* **2023**, 21 (1), 3-19.