ANALYSIS OF COMMERCIALLY AVAILABLE BUILDING BLOCKS FOR THE NEEDS OF DNA-ENCODED LIBRARIES (DEL)

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DNA-encoded library (DEL) technology occupies a prominent position in the early drug discovery toolkit as a rapid and inexpensive approach to generate large collections of compounds using combinatorial chemistry techniques. It is notable, that the size of libraries created using DEL technology sometimes exceeds the size of conventional HTS combinatorial libraries by several orders of magnitude [1]. Because of the increased size, creating a DEL requires a significant number of suitable, available mono-, bi- and tri-functional building blocks (BBs). (Fig. 1)

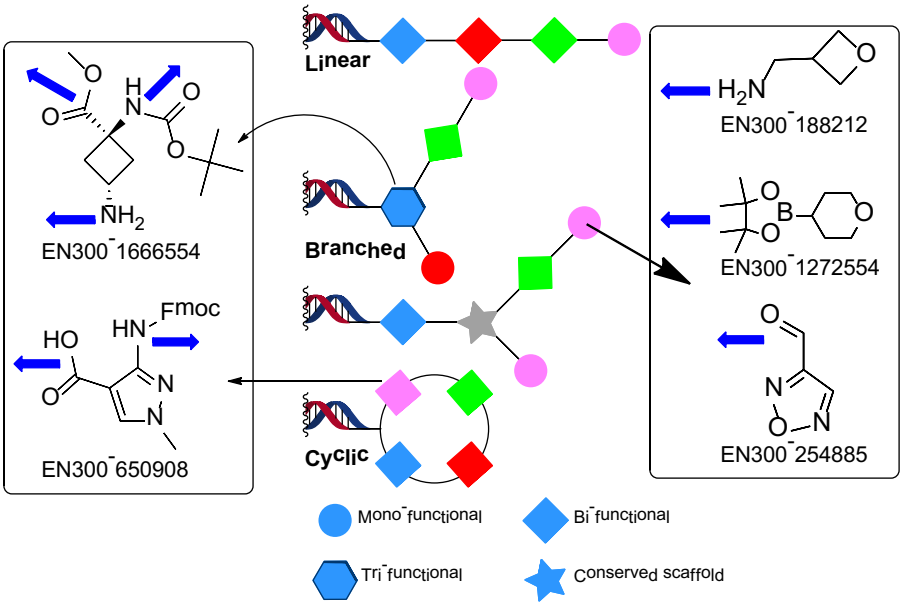


Fig. 1. Typical DEL sequence for a 4-step cycle with examples of mono-, bi-, tri-functional BBs

Despite the popular belief that most HTS building blocks can be used for DEL technology, there are selection criteria that limit the number of actual DEL compatible building blocks. Reactivity in aqueous, non-acidic conditions at temperatures below 90°C with a high degree of conversion and selectivity are characteristics of DEL-compatible building blocks [2].

We report a chemoinformatic selection algorithm that allows pre-screening of constraints for building blocks. General exclusion criteria for modifying and polyfunctional BBs considering are interfering functional groups, racemic compounds or compounds with unidentified chirality,

functional groups with reactivity significantly decreased within the given class (for instance deactivated by neighboring EWG), molecular weight above 125 Da (when targeting 500 Da and less screening compounds) [3], steric hindrance molecular weight, compatibility of substituents, steric hindrance, and chirality. Custom exclusion filters allow to select building blocks based on lipophilicity, the number of rotatable bonds, fraction of saturated carbons (Fsp3) or the basicity of the molecule.

A statistical analysis of the proportion of "likely compatible with DEL technology" modifying agents compared to the total array of commercially available building blocks in the eMolecules [4], Chemspace [5] and Enamine [6] data sets is given. (Fig. 2)

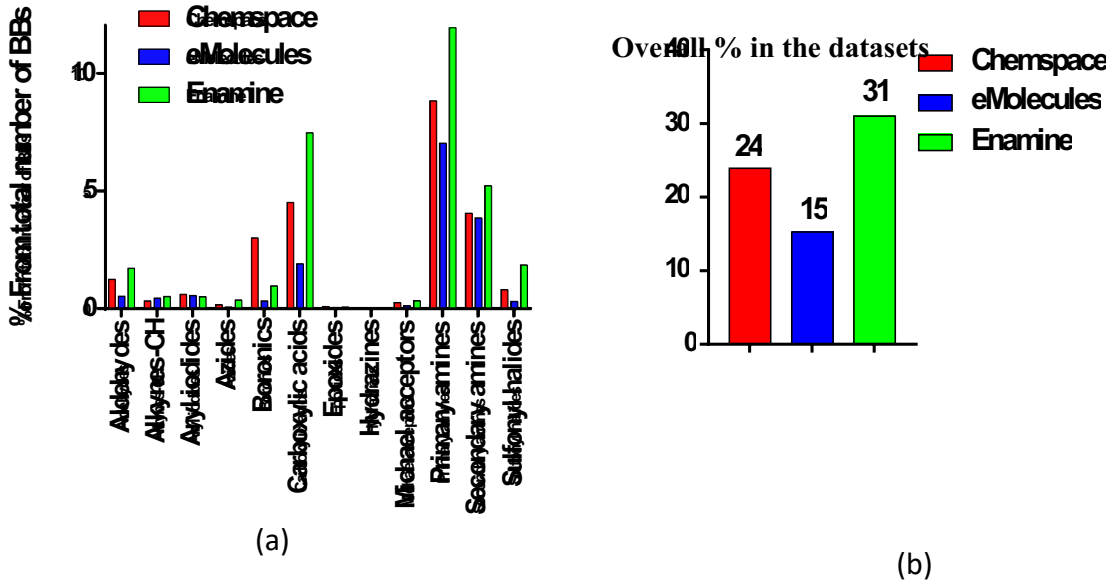
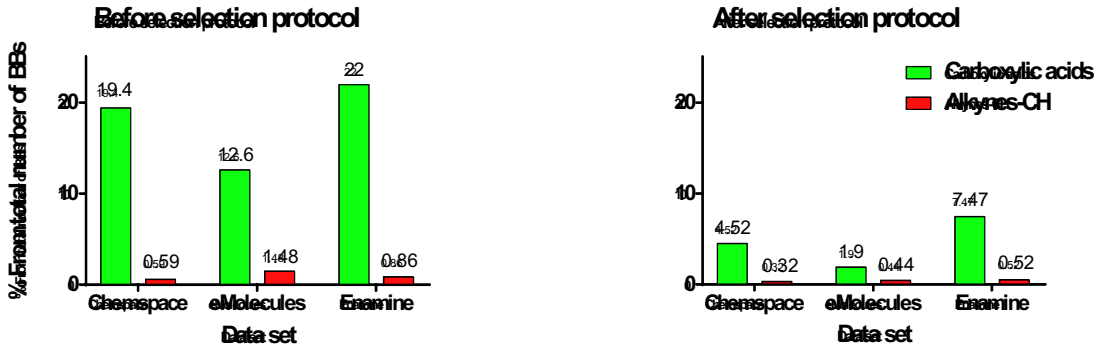


Fig. 2. (a) Availability of DEL-compatible modifying agents and (b) overall percentage in the datasets

The results of applying selection protocols of DEL-compatibility criteria to the most populated and underpopulated classes of modifying agents shows significant attrition comparing with initial quantity. (Fig. 3)



	Chemspace	eMolecules	Enamine
Total BBs count	468 061	6 908 533	156 927
Carboxylic acids (unsorted)	90 908	871 856	34 511
Alkynes-CH (unsorted)	2 748	102 296	1 348

Fig. 3. Database analysis for widespread class of modifying agents and one in low supply

The in-depth statistical analysis of the current state of the commercially available bi- and tri-functional BBs shows similar pattern of chemotypes distribution as the datasets of modifying agents. Extracted with the help of in-house selection protocols pool of bi-functional BBs was

classified in 29 subclasses and tri-functional cores were divided in 20 subclasses. (Fig. 4)

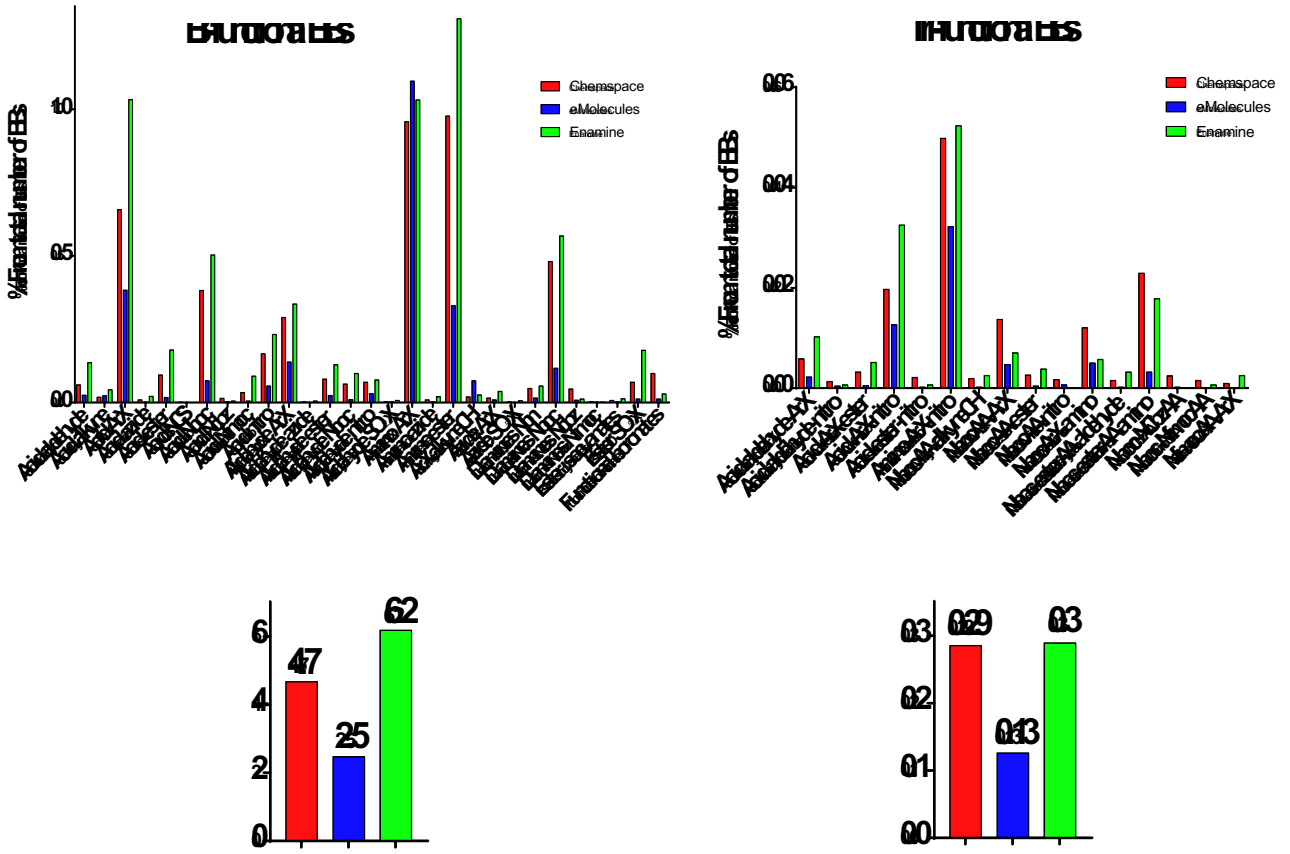


Fig. 4. Statistical analysis of DEL-compatible poly-functional BBs availability

1. Goodnow R. A., Dumelin C. E., Keefe A. D. DNA-encoded chemistry: Enabling the deeper sampling of chemical space. *Nature Reviews Drug Discovery*. 2017. Vol. 16, No. 2. P. 131–147.

2. Satz A. L., Cai J., Chen Y., Goodnow R., Gruber F., Kowalczyk A., Petersen A., Naderi-Oboodi G., Orzechowski L., Strebel Q. DNA Compatible Multistep Synthesis and Applications to DNA Encoded Libraries. *Bioconjugate Chemistry*. 2015. Vol. 26, No. 8. P. 1623–1632.

3. Huang Y., Savych O., Moroz Y., Chen Y., Goodnow R. A. DNA-Encoded Library Chemistry: Amplification of Chemical Reaction Diversity for the Exploration of Chemical Space. *Aldrichimica Acta*. 2019. Vol. 52, No. 3. P. 75-87.

4. https://www.emolecules.com/info/plus/download-database.

5. https://chem-space.com/compounds#building-blocks.

6. https://enamine.net/building-blocks.