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PHARMARON

New DEL Design Strategies with Innovative Linkers

The Linker Strategic Advantages

Pharmaron is a premier R&D service provider for the life sciences industry that offers a broad spectrum of research, development and manufacturing service capabilities throughout the entire drug discovery, preclinical and clinical development process across multiple therapeutic modalities, including small molecules, biologics and CGT products.

Introduction

In conventional DEL synthesis, during which building blocks or cores are sequentially and linearly inserted, the chemical diversity brought by the first cycle of synthesis could be physically screened by the building blocks introduced in subsequent cycles. This results in reduced interactions of the first cycle building blocks to the target proteins during the DEL selection. Consequently, cycle 1 chemical diversity plays a negligible role in most reported DEL selections outcomes.[1] Nonetheless, Pharmaron has envisioned alternative DEL design strategies, using a new form of linker, routinely amenable in any DEL syntheses. It provides a variety of valuable advantages such as larger exposure of diversities produced from all cycles to the protein binding interface, higher lipophilicity, improved chemical stability and solubility, and inherently unveils unexplored chemical space.[2]

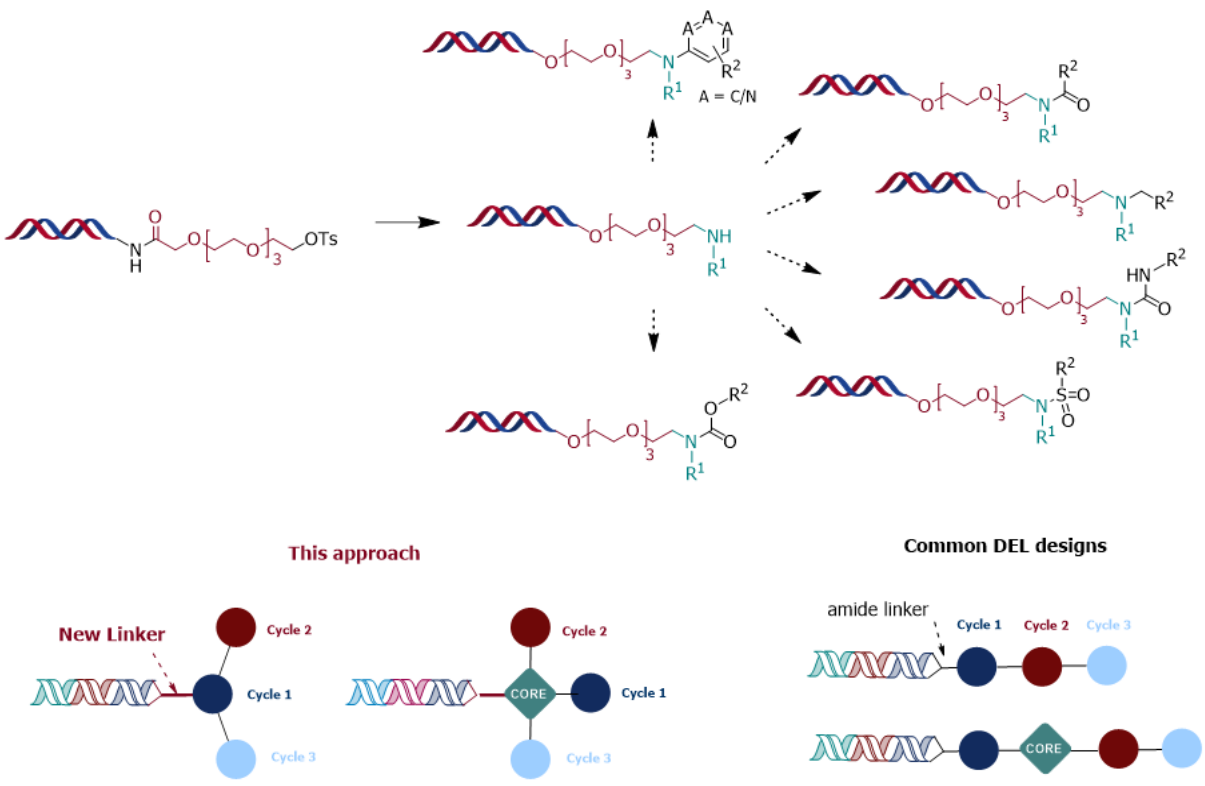

Fig. 1: Innovative linkers for DEL synthesissynthesis.

Synthesis of the New DEL Linker

The new linker, composed of a polyglycol chain and a terminal tosylate, is prepared in 3 simple steps (>70% over 3 steps) before conjugation to the DNA headpiece as shown in Fig. 2.

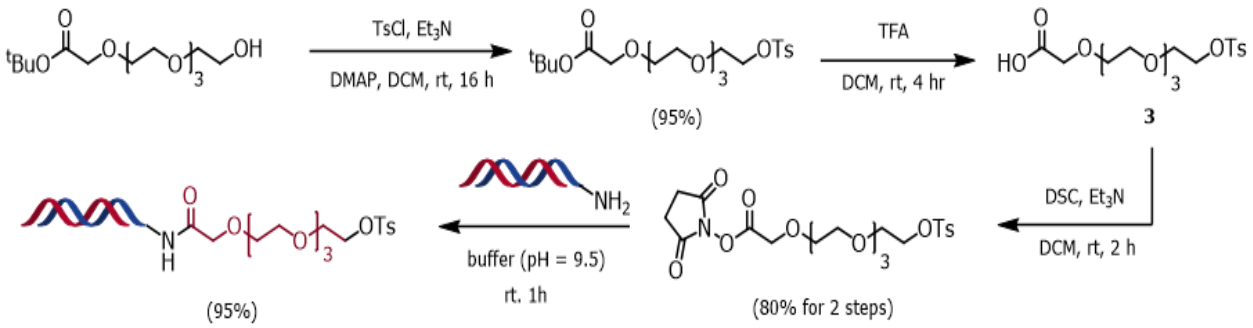

Fig. 2: Synthesis of the tosylated linker.

Exemplification of the New DEL Linker Use

To demonstrate the amenability of this new strategy in routine DEL synthesis, a variety of cycle 1 building blocks are tested in a typical conjugation new linker-equipped DNA tags. Examples of conjugation are showed in Fig. 3 and all desired products can be obtained in high yields. Most importantly, these compounds strike by their synthetic relevance:

- Secondary amine products yielded by conjugation of primary amines can be considered as versatile cycle 1 products and are directly ready for subsequent cycle 2.
- For secondary amines and unprotected amino acids starting building blocks and cores, they can also be used directly for cycle 2 or DEL core installation, whereas conventional linkers may need to include a protecting group to be cleaved off.

> **Considering that certain DNA compatible reactions can modify the DNA tags and cause irreversible damage to their decodability,[4] we envision that the fewer chemical reactions are involved, the higher the DNA encoding capability is.**

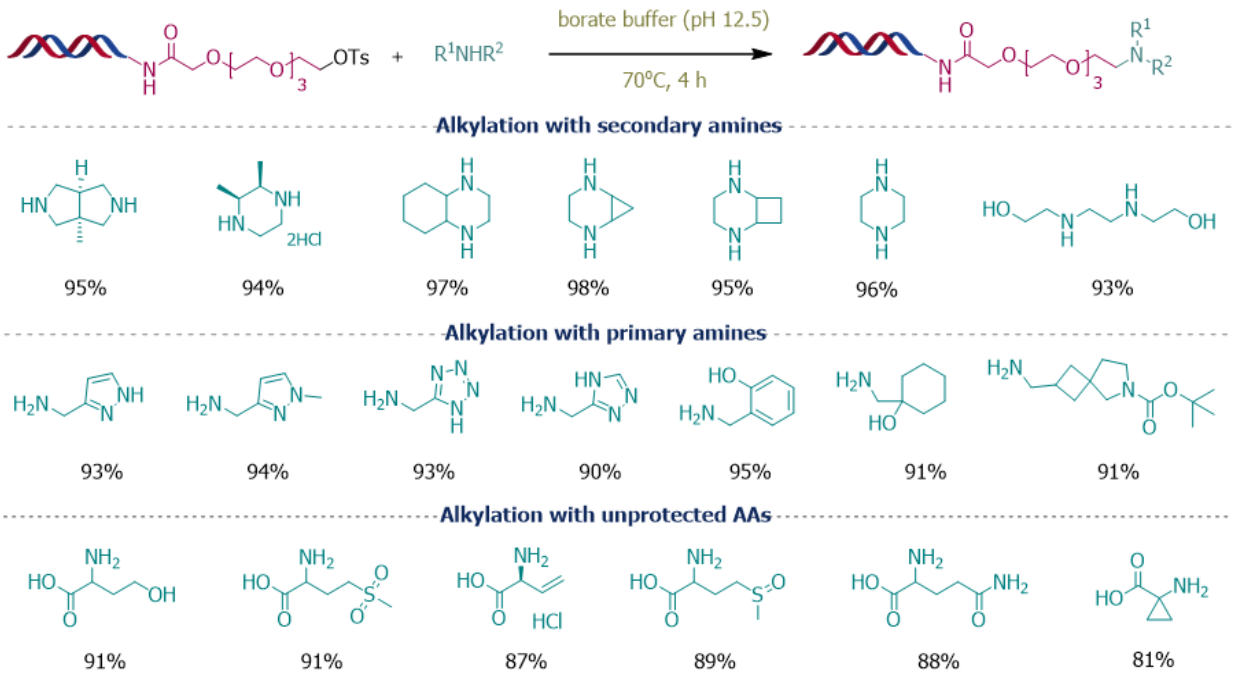

Fig. 3: *N*-Alkylation with secondary, primary amines and amino acids on new linker.

Application to DNA-encoded Libraries Synthesis

As shown in Figures 4 and 5, a series of conceptual syntheses of three cycle-DELs, lead to the on-DNA syntheses of various compounds.

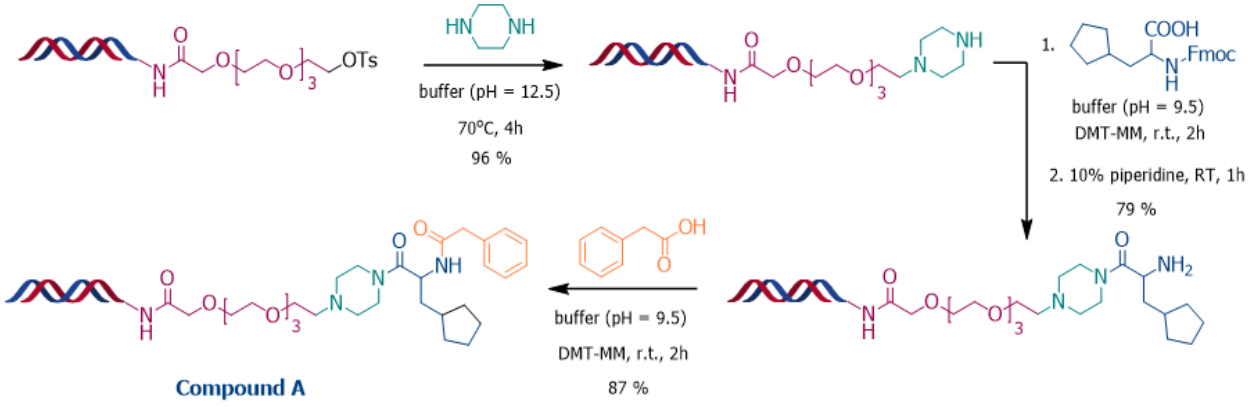

Fig. 4: 3-cycle conceptual DEL synthesis of compound A.

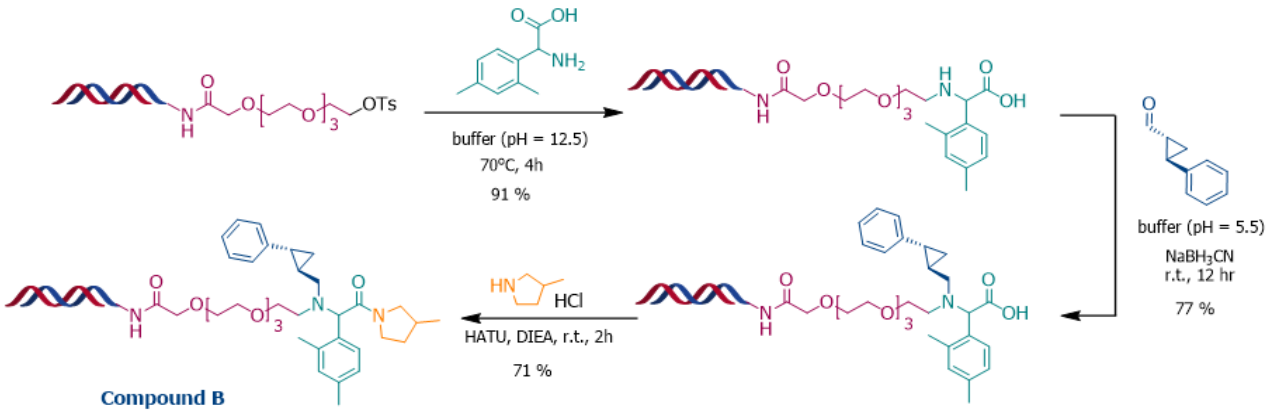

Fig. 5: 3-cycle conceptual DEL synthesis of compound B.

Key Takeaways

Pharmaron can now routinely use a new tosylate linker,[4] with the following advantages:

1. Smooth reaction with unprotected primary or secondary amines, including free amino acids and leads to products directly ready for Cycle-2 DEL synthesis
2. Higher synthesis efficiency can be achieved if conventional linkers are used
3. Multi-functional building blocks can be used as cores for complex DELs
4. Equivalent proximity of each cycle's building blocks to the biding site of the target protein and the polyglycol backbone of the DNA tag (for more information regarding this statement, please consult the original publication[4])
5. Reduced bias derived from standard DEL designs

References:

1. Arico-Muendel, C. C., 2016. From haystack to needle: finding value with DNA encoded library technology library at GSK. MedChemComm, 7, pp. 1898–1909.
2. Martín, A., Nicolaou, C. A., Toledo, M. A., 2020. Navigating the DNA encoded libraries chemical space. Communications Chemistry, 3, 127–136.
3. Malone, M. L., Paegel, B. M., 2016. What is a “DNA-Compatible” Reaction? ACS Combinatorial Science, 18, pp. 182–187.
4. Sun, Z. M.; Yang, S. G.; Xue, L. J.; Zhang, J.; Yang, K. X.; Hu, Y., 2022. N-Alkyl Linkers for DNA-Encoded Chemical Libraries. Chemistry, An Asian Journal, e202200016

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Pharmaron is a leading, fully integrated pharmaceutical R&D services platform with global operations and has a well-established team of over 19,000 employees working in 20 different sites located in China, United States and United Kingdom. Founded in 2004, Pharmaron provides a broad spectrum of research, development and manufacturing service capabilities throughout the entire drug discovery, preclinical and clinical development process across multiple therapeutic modalities, including small molecules, biologics and CGT products. It has an excellent track record in the delivery of R&D solutions to its partners in North America, Europe, Japan and China.