High-Efficiency Solid Phase Synthesis of Peptides and Peptidomimetics

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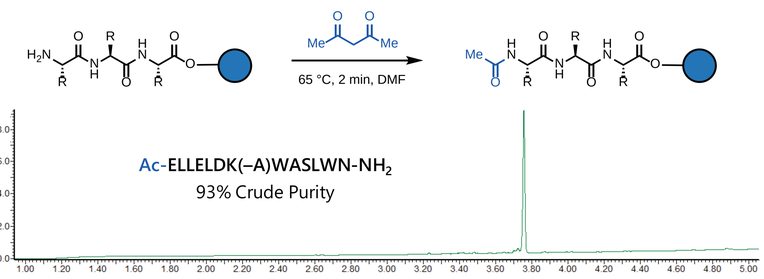
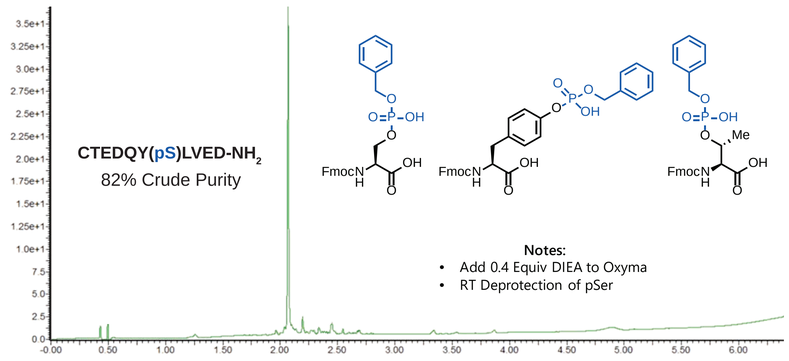
PEPTIDE THERAPEUTICS SYMPOSIUM

Peptide Modifications

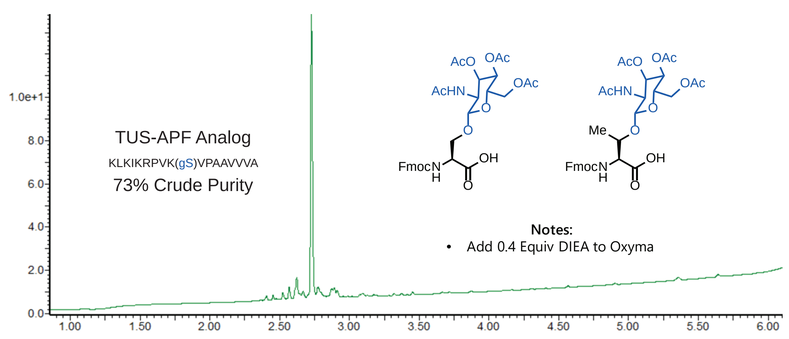
N-Terminal Acetylation



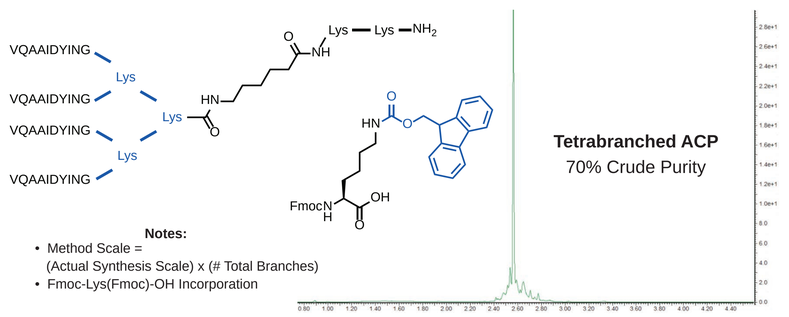
Phosphoamino Acid Incorporation



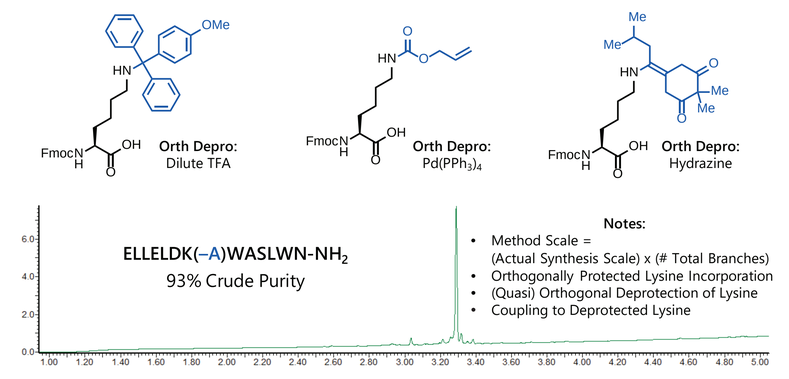
Glycoamino Acid Incorporation



Symmetric Branching



Asymmetric Branching



Abstract

The development of peptide-based therapeutics and drug delivery systems is continually increasing, due in part to the high selectivity of peptide-receptor interactions.[1] In addition, peptides typically exhibit low tissue accumulation and, therefore, reduced toxicity.[2] While these traits are advantageous, they are not without shortcomings; peptides can exhibit low oral bioavailability and are subject to ready proteolytic degradation.

To combat these limitations, new peptide modifications and peptidomimetic systems are being developed and tested in order to increase bioavailability and resist proteolytic degradation.[3] Highly efficient synthetic strategies are paramount for the development and application of these systems; increased production capabilities, while limiting waste generation and minimizing time requirements, are necessary. The Liberty Blue automated microwave peptide synthesizer offers all of these advantages, plus the flexibility to readily incorporate a multitude of peptide modifications and peptidomimetic systems, including cyclic peptides, peptoids, and glycosylated motifs.

[1] Gallo, R. L.; Murakami, M.; Ohtake, T.; Zaiou, M. J. Allergy Clin. Immunol. 2002, 110, 823–831.
[2] Lopez-Otin, C. Matrisian, L. M. Nat. Rev. Cancer. 2007, 7, 800–808.
[3] Gunnoo, S. B.; Madder, A. Org. Biomol. Chem. 2014, 14, 8002–8013.

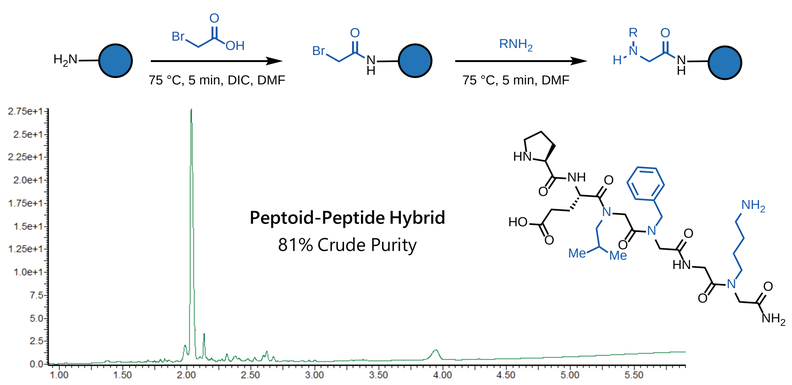
High-Efficiency Solid Phase Synthesis

In 2013, we developed an improved methodology for microwave SPPS, based on the use of higher temperature carbodiimide based coupling at 90 °C, along with the elimination of all washing after each coupling step.[4] These insights led to significant time and solvent savings, while providing peptides of incredibly high purity. The more acidic coupling environment with carbodiimide chemistry overcomes coupling issues for cysteine (epimerization) and arginine (γ-lactam formation), which were previously an issue under more basic coupling conditions (ex. HCTU/DIEA). The instrumentation design used on CEM's Liberty Blue™ peptide synthesizer is also a critical component of HE-SPPS to eliminate inefficient internal fluidic and reagent path cleaning that increases waste generated. HE-SPPS used on the Liberty Blue is now used in hundreds of laboratories worldwide and provides very fast, high purity peptides with incredibly low waste generated.

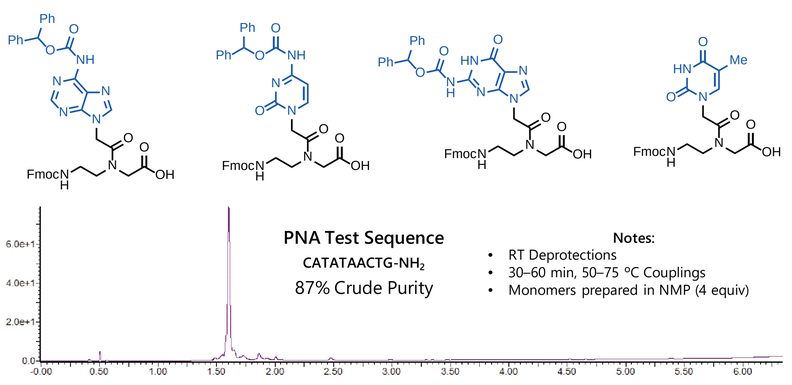
[4] J. Collins, K. Porter, S. Singh and G. Vanier, "High-Efficiency Solid Phase Peptide Synthesis (HE-SPPS)," Org. Lett., vol. 16, pp. 940-943, 2014.

Peptidomimetic Synthesis

Peptoid Synthesis

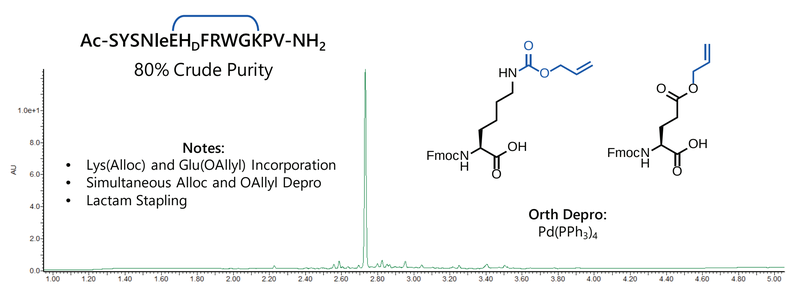


PNA Synthesis

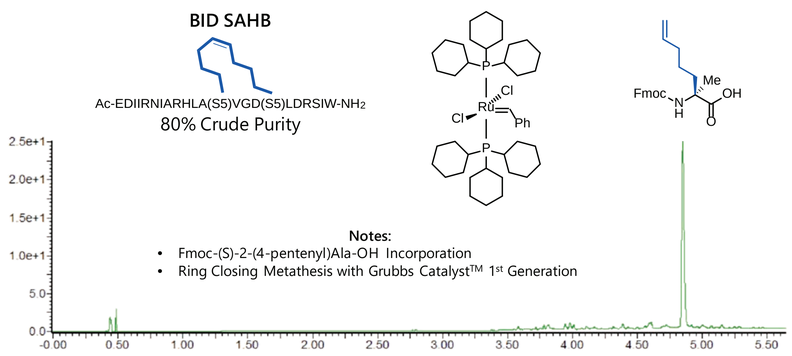


Peptide Cyclizations

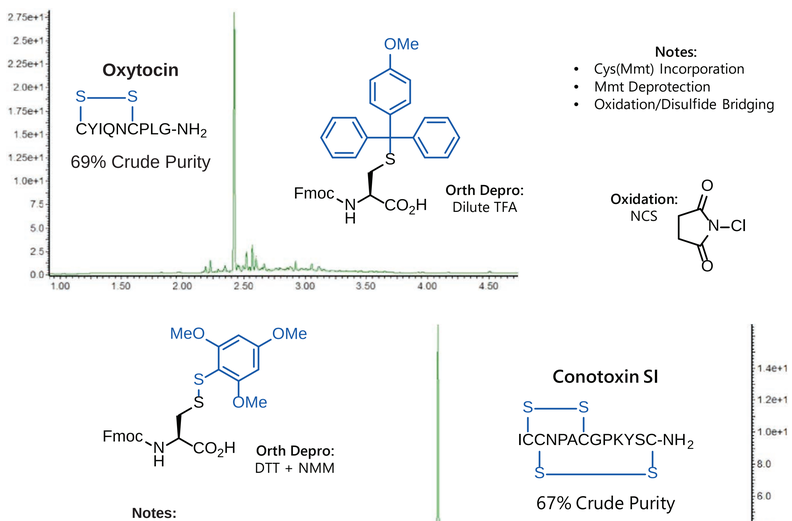
Lactam Stapling



Hydrocarbon Stapling



Disulfide Bridging



Head-To-Tail Cyclization