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Scalable Cyclic Peptide Synthesis Featuring Copper-Catalyzed Aldehyde–Alkyne–Amine Chemistry

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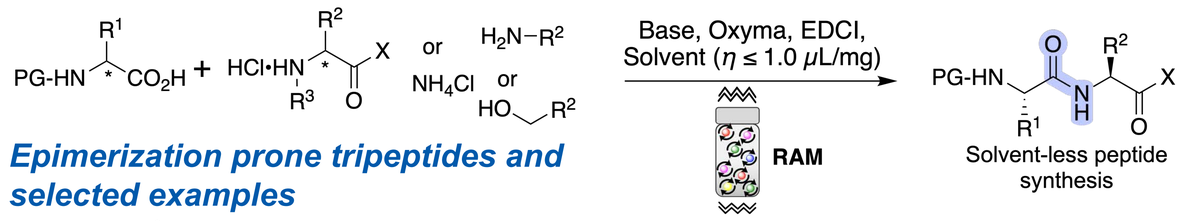
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Abstract

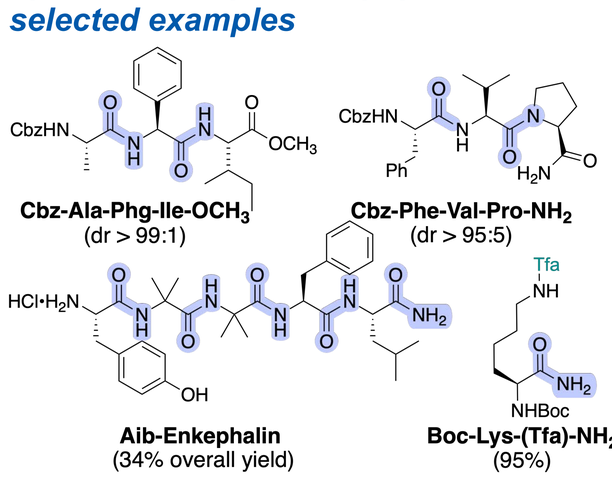
The solution-phase synthesis and applications of a macrocyclic peptidomimetic are presented. Solvent-less syntheses are demonstrated using environmentally benign, high-concentration methods enabled by resonant acoustic mixing (RAM). For example, RAM-assisted azapeptide synthesis was achieved through solvent-less peptide synthesis and phosgene-free semicarbazide construction. Using inter- and intramolecular copper-catalyzed aldehyde–alkyne–amine reactions, convergent solution-phase routes to the antiatherosclerotic agent cyclic azapeptide **298** were developed, with RAM employed for peptide and semicarbazide construction.

Green Aolvent-less Peptide Synthesis

First, we introduced the use of RAM for solution-phase peptide synthesis, successfully preparing amides, dipeptides, epimerization-prone tripeptides, and Aib-enkephalin [4].



Epimerization prone tripeptides and selected examples



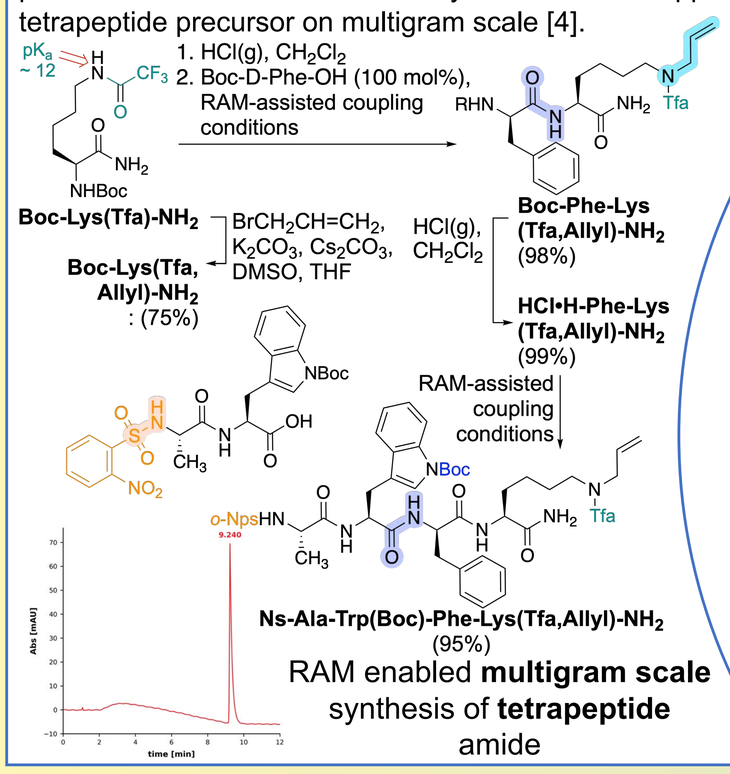
Resonant acoustic mixing (RAM)



20-gram slurry — Exceptional blending by vibrational and acoustic mixing energies — >99% conversion

Dipeptides, esters and amide

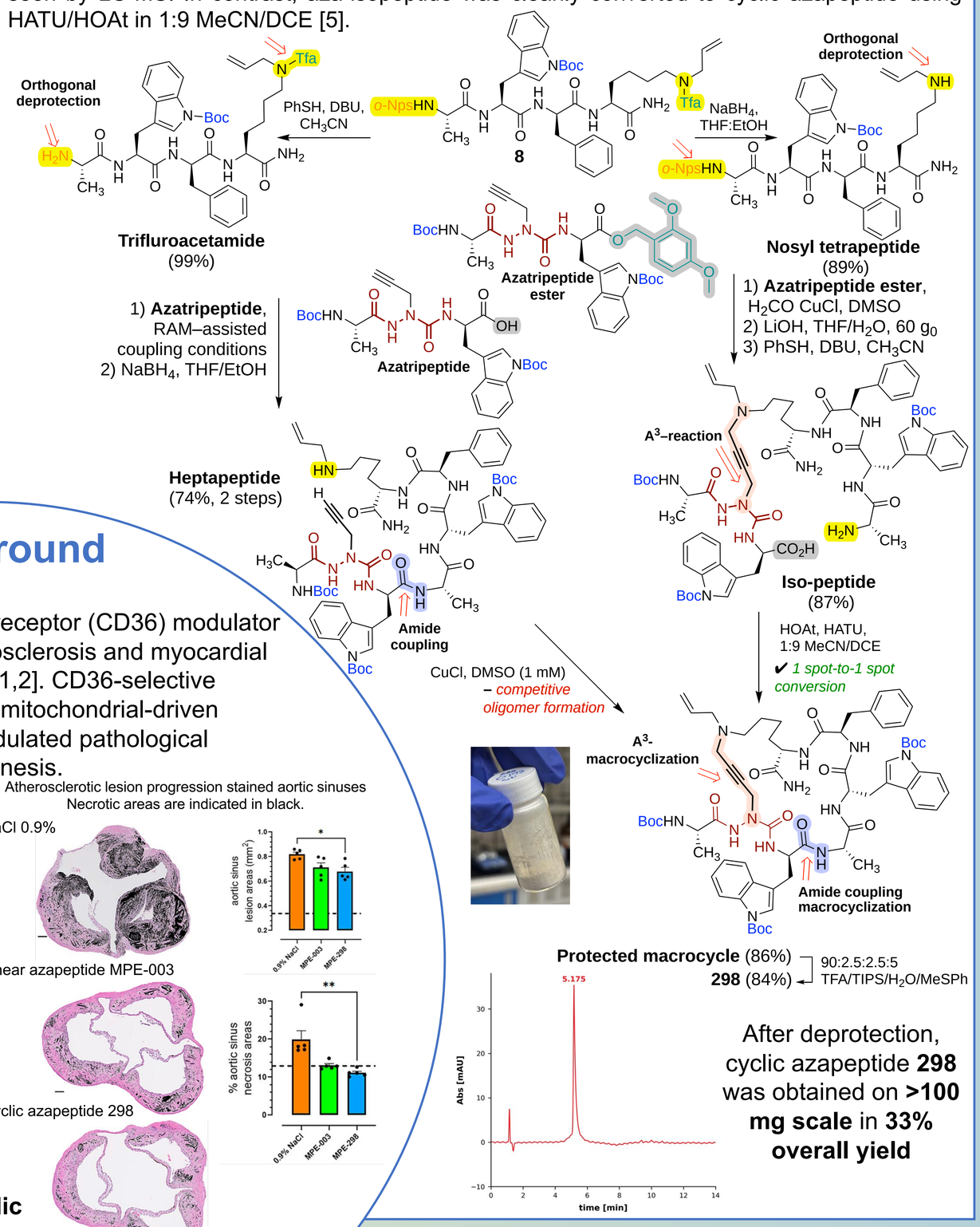
Orthogonal *o*-nitrophenylsulfonamide - trifluoroacetamide protection enabled effective synthesis and application of tetrapeptide precursor on multigram scale [4].



RAM enabled **multigram scale** synthesis of **tetrapeptide** amide

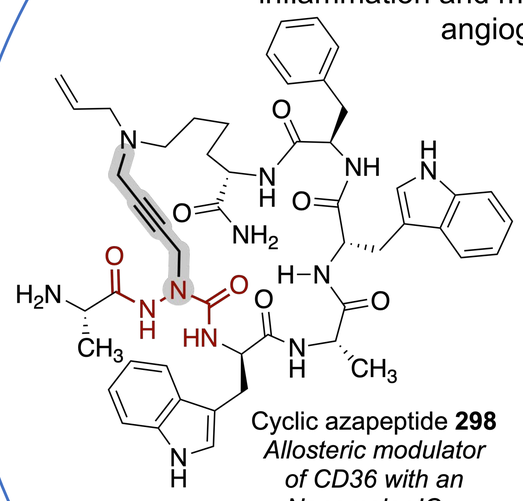
Macrocyclization Pathways

RAM [3+4] amide coupling to linear azapeptide and inter A^3-reaction to linear iso-peptide proceeded smoothly. In contrast, A^3-macrocyclization gave dimer and oligomer formation as seen by LC-MS. In contrast, aza-isopeptide was cleanly converted to cyclic azapeptide using HATU/HOAt in 1:9 MeCN/DCE [5].



Background

Cluster of differentiation 36 receptor (CD36) modulator **298** protects against atherosclerosis and myocardial ischemia reperfusion [1,2]. CD36-selective azapeptides mitigated mitochondrial-driven inflammation and modulated pathological angiogenesis.



Cyclic azapeptide **298**
Allosteric modulator of CD36 with an Nanomolar IC_{50}

Atherosclerotic lesion progression stained aortic sinuses
Necrotic areas are indicated in black.

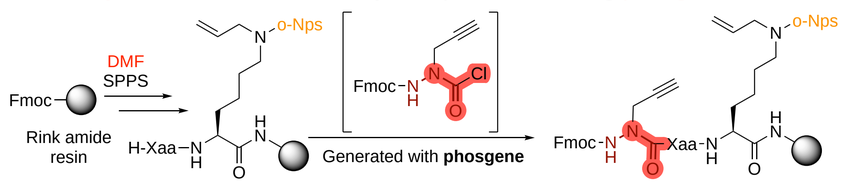
Previously [3], cyclic azapeptide 298 was made by a diversity oriented solid-phase synthesis with issues. A greener more scalable synthesis is needed.

✗ DMF
✗ Phosgene
✗ mg scale
✗ 1% overall yield

Solvent-less Azapeptide Aynthesis

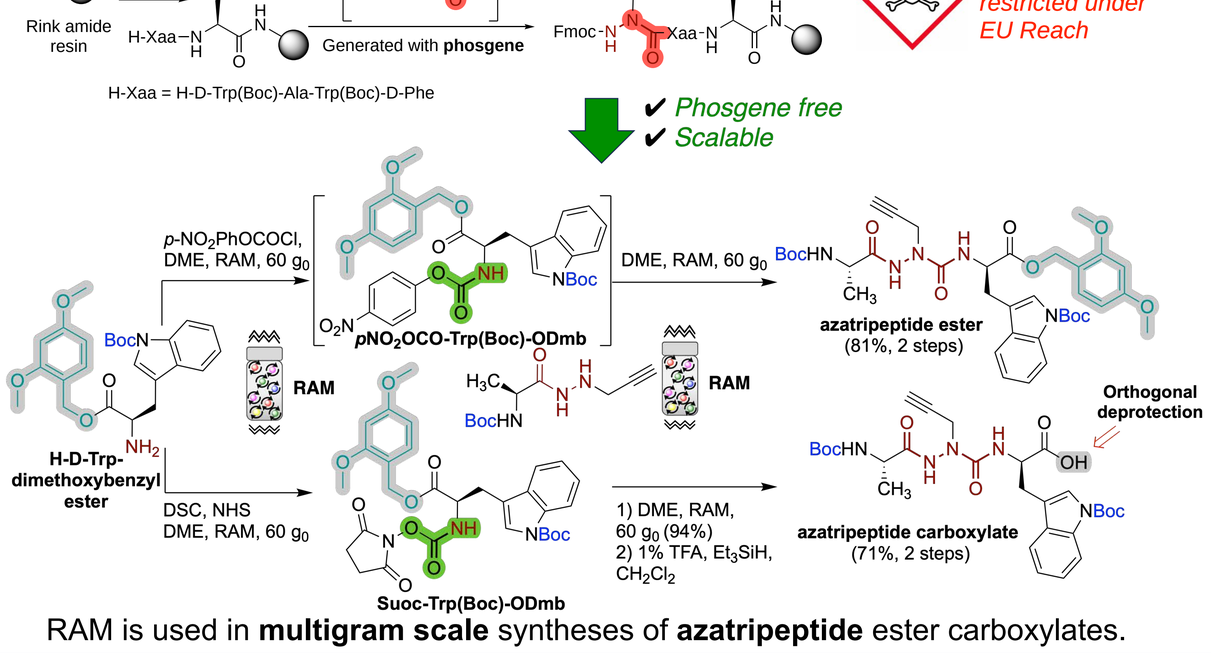
Second, a scalable phosgene-free approach to azatripeptide was developed using RAM-based strategies featuring amine activation nitrophenyl carbamate and succcinyloxy carbamate [5,6].

Previously semicarbazide assembly was performed using phosgene and DMF.



– *Phosgene is deadly*
– *DMF is toxic and restricted under EU Reach*

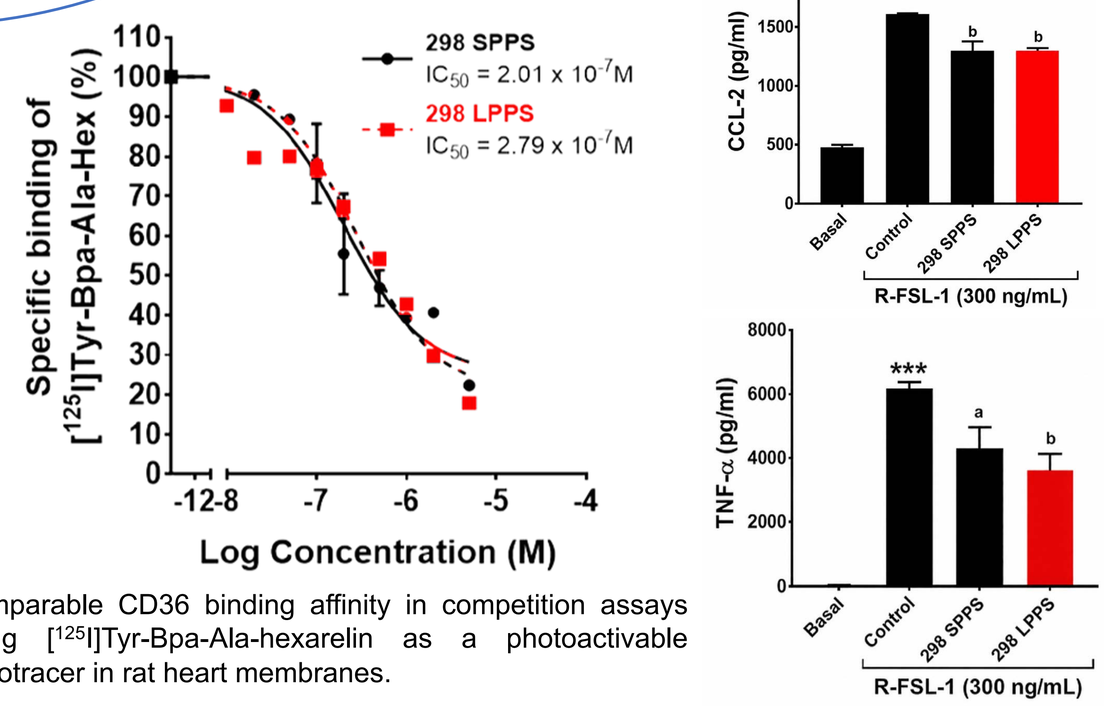
✔ *Phosgene free*
✔ *Scalable*



RAM is used in **multigram scale** syntheses of **azatripeptide** ester carboxylates.

Biological Application

Effects of **298** (0.1 μM) on RFSL-1-induced proinflammatory cytokine (TNF-α) and chemokine (CCL2) secretion on murine RAW264.7 macrophages.



Comparable CD36 binding affinity in competition assays using [^{125}I]Tyr-Bpa-Ala-hexarelin as a photoactivable radiotracer in rat heart membranes.

Batches made in solution **exhibit identical properties** as that made on solid-phase [5,7], expediting the batch for broader preclinical evaluation.

Conclusions

A 33-fold increase in overall yield was achieved using RAM-assisted peptide and azapeptide synthesis, intermolecular A³ chemistry, and lactam macrocyclization. RAM enabled the rapid, high-concentration synthesis of amides and structurally diverse peptides, including epimerization-prone sequences and azapeptides, in environmentally preferred solvents. These advances culminated in a scalable, optimized synthetic route to cyclic azapeptide 298, providing sufficient material for broader preclinical applications.

References

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