Convergent Solution-Phase Synthesis of a Cyclic Azapeptide CD36 Modulator

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Cyclic azapeptide cluster of differentiation-36 receptor (CD36) modulator **298** has exhibited biomedical potential for treating diseases implicating macrophage-driven inflammation.[1,2] Previously, azapeptide **298** was prepared in mg amounts using a linear solid-phase peptide synthesis approach featuring an A^3-macrocyclization on resin prior to cleavage and deprotection.[3,4] Towards scale-up, a solution-phase synthesis of azapeptide **298** has now been achieved using a fragment coupling strategy. Employing phosgene-free semicarbazide synthesis, orthogonal protection, and A^3 macrocyclization in solution, the convergent approach minimizes chromatographic purification to effectively afford the cyclic azapeptide. Our presentation discloses the features of this promising means for delivering the potent CD36 modulator for preclinical investigations.

References

1. Gauvin, J.; Frégeau, G.; Elimam, H.; Ménard, L.; Huynh, D.; Lê, C.; Ahsanullah, A.; Lubell, W. D.; Ong, H.; Marleau, S., A cyclic azapeptide ligand of the scavenger receptor CD36/SR-B2 reduces the atherosclerotic lesion progression and enhances plaque stability in apolipoprotein E-deficient mice. *Frontiers in Pharmacology* **2023,** *14*, 1204905.
2. Ohm, R. G.; Mulumba, M.; Chingle, R. M.; Ahsanullah; Zhang, J.; Chemtob, S.; Ong, H.; Lubell, W. D., Diversity-oriented A3-macrocyclization for studying influences of ring-size and shape of cyclic peptides: CD36 receptor modulators. *Journal of Medicinal Chemistry* **2021,** *64* (13), 9365-9380.
3. Ahsanullah; Chingle, R.; Ohm, R. G.; Chauhan, P. S.; Lubell, W. D., Aza-propargylglycine installation by aza-amino acylation: Synthesis and Ala-scan of an azacyclopeptide CD36 modulator. *Peptide Science* **2019,** *111* (1), e24102.
4. Zhang, J.; Mulumba, M.; Ong, H.; Lubell, W. D., Diversity-oriented synthesis of cyclic azapeptides by A3-macrocyclization provides high-affinity CD36-modulating peptidomimetics. *Angewandte Chemie International Edition* **2017,** *56* (22), 6284-6288.