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Chemical Synthesis of Cyclotide from the Medicinal Plant

Clitoria ternatea

Wang Yingqi, Nguyen Thi Kim Ngan, and James P Tam

Introduction

Cyclotides are a special class of ultrastable peptides which possess a cyclized backbone and three disulfide bridges. They display many bioactivities and are attractive targets for drug discovery. The medicinal plant Clitoria ternatea contains a high abundance cyclotides, named as clotides (cT), which have been shown to constitute the active ingredients of C. ternatea. cT19 is one of the clotides that showed strong antibacterial and immunomodulatory activities. Native cT19 yield from conventional extracting methods is relatively low and it is difficult to separate cT19 from its deaminated form cT19a. With the recent understanding of cT19’s structure and amino acid sequence, chemical synthesis of cT19 is made possible.

Methodology

1. Cyclization
   - cT19-hydrazone
   - Cyclized cT19 4mM
   - Cyclized cT19 1mM (Adjusted concentration)
   - After PREP-HPLC purification
   - Cyclized cT19 was obtained for further folding.

2. Folding: Test Conditions: 0.1mg/ml cT19, cT19:GSH:GSG=1:150:5, RT with different co-solvent
   - 50% PrOH
   - H20
   - 50% TFE (24hr)
   - 50% TFE (46hr)
   - Thus, 50% TFE was chosen as the co-solvent, the incubation time was 46hr.

3. Co-elution & Yield
   - 0.1mg/ml cT19 Co-Elution with Native cT19
   - The sample co-eluted with native cT19.

Calculating Yield:

- Starting material: cyclized cT19 0.1mg/ml
- Folded cT19
- Area = 2330444
- Area = 488035
- Yield = \( \frac{488035}{2330444} = 20.9\% \)

Conclusion

The peptide cT19 was successfully synthesized. The folding condition provides information for further study on cyclotide folding. Further studies can be done on better folding conditions to achieve a higher yield.

Acknowledgement

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Reference