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Programmable Chemical Synthesis & in-situ Modifications of Peptides

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digital chemistry
programming matter

Introduction

In this work, we **fully automated** all stages of solid-phase peptide synthesis (SPPS) including peptide assembly, cleavage, precipitation, and further **chemical modifictions**. Syntheses were carried out on the **Chemputer** platform, a modular batch synthesiser, operated via the standardised chemical programming language **χDL**.

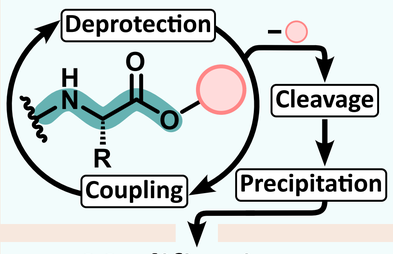
Workflow

Chemical

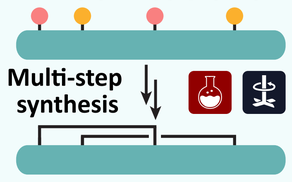
Reagents

Fmoc-AA$_n$-OH, HATU, DIPEA, Piperidine, Ac_2O, TIPS, TFA, ..., H_2O, DMF, DCM, Et_2O, MeCN

SPPS



Modifications



Physical

Procedure

- Deprotection and coupling
- Cleavage and precipitation
- Chemical modifications

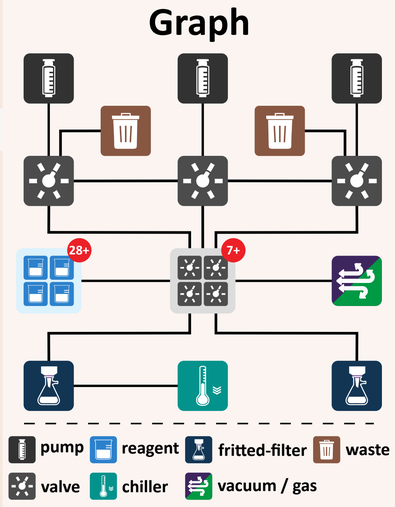
Chemputer hardware

Digital

χDL

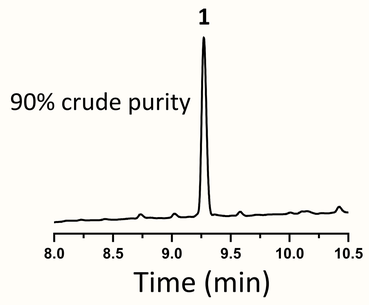
```
<Add
  vessel="spps_reactor"
  reagent="amino_acid"
  amount="2 mL"/>
...
```

Graph

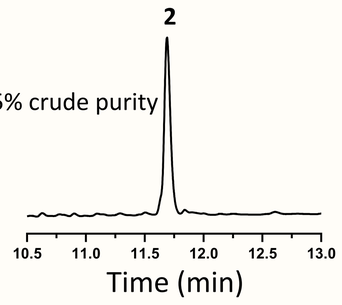


Benchmark results

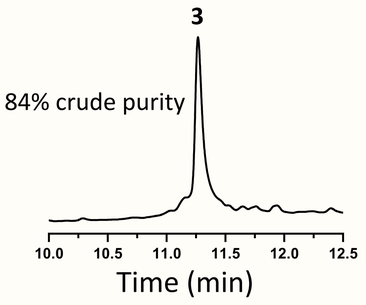
ACP(65-74)
H-VQAAIDYING-OH



18A
Ac-DWLKAFYDKVAEKLKEA-NH_2



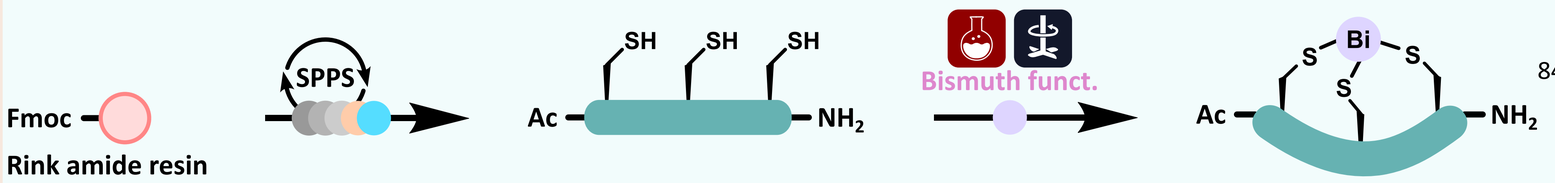
GHRH(1-29)
H-YADAIFTNSYRKVLGQLSARKLLQDILSA-NH_2

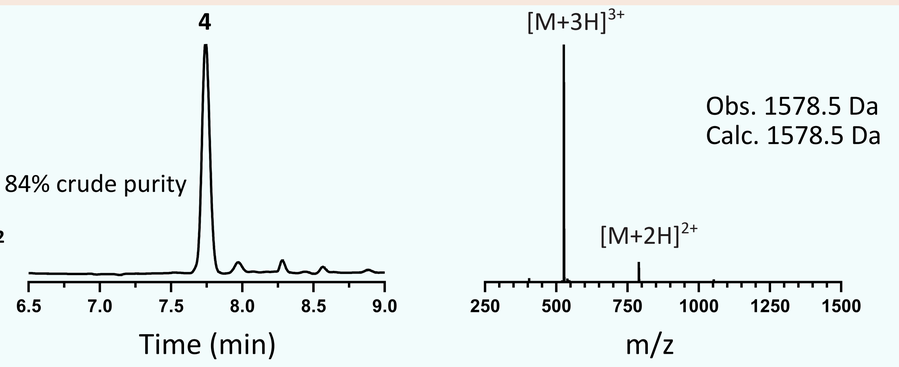


Fully automated peptide assembly, cleavage, precipitation, and chemical modifications

Bismuth mediated bicycle formation

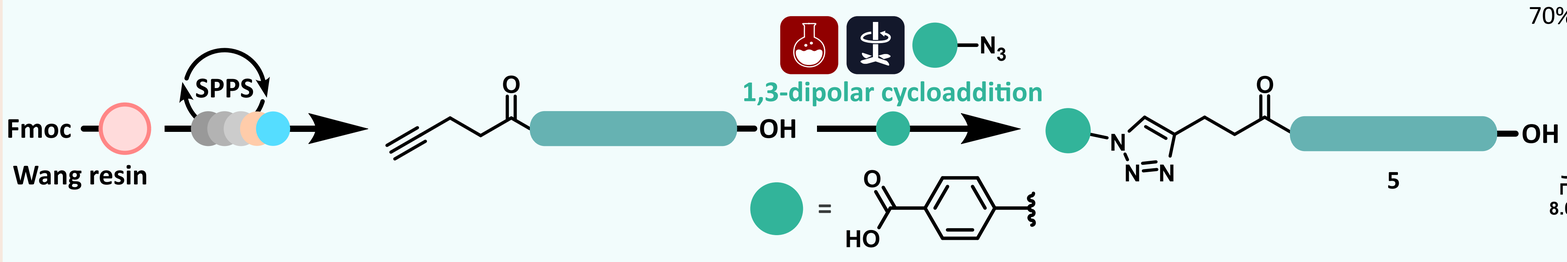
= CHGFKCDGFKCS

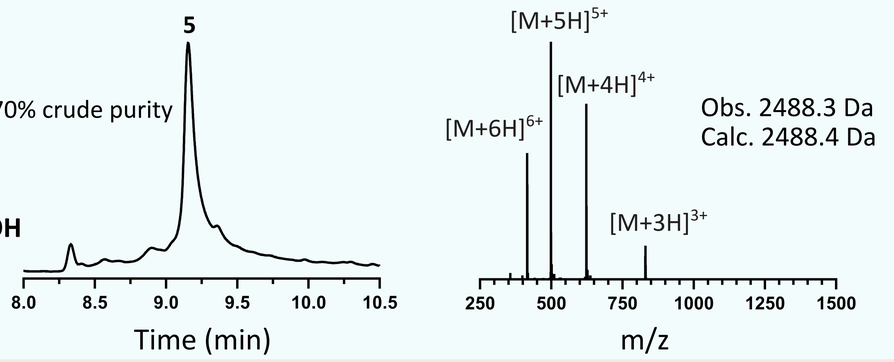




1,3-Dipolar cycloaddition "click" reaction

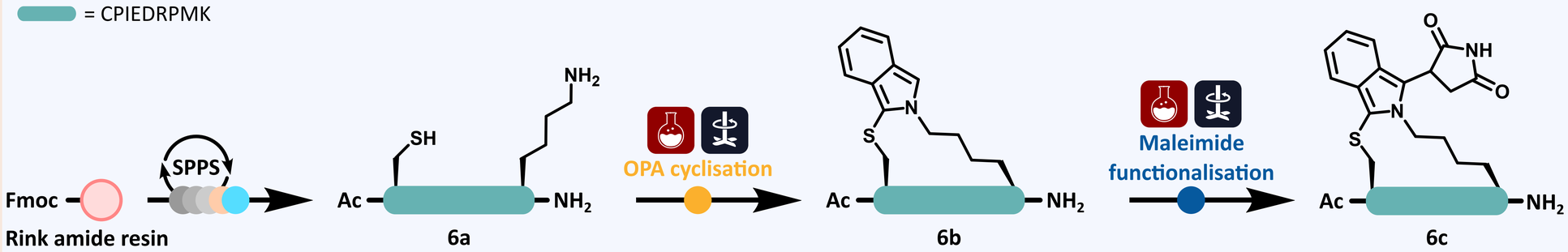
= RQIKIWFQNRRMKWKK

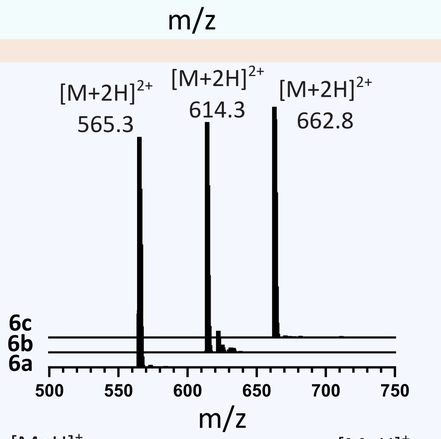




Chemoselective cyclisation and one-pot functionalisation

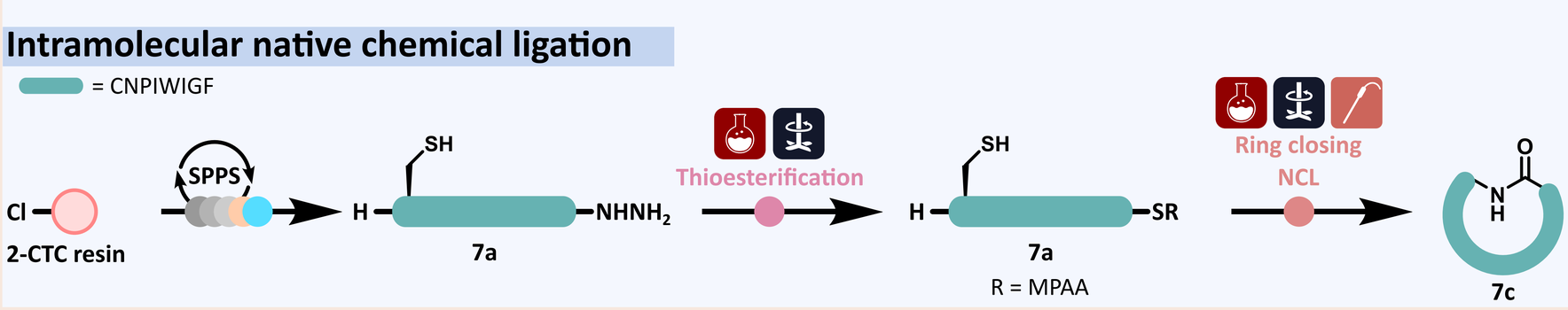
= CPIEDRPMK

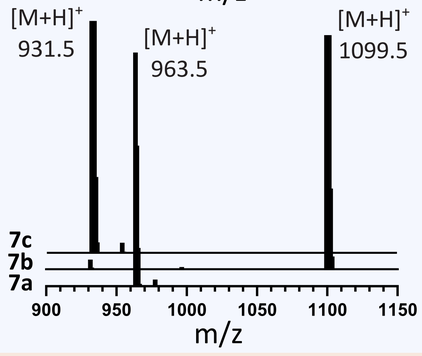




Intramolecular native chemical ligation

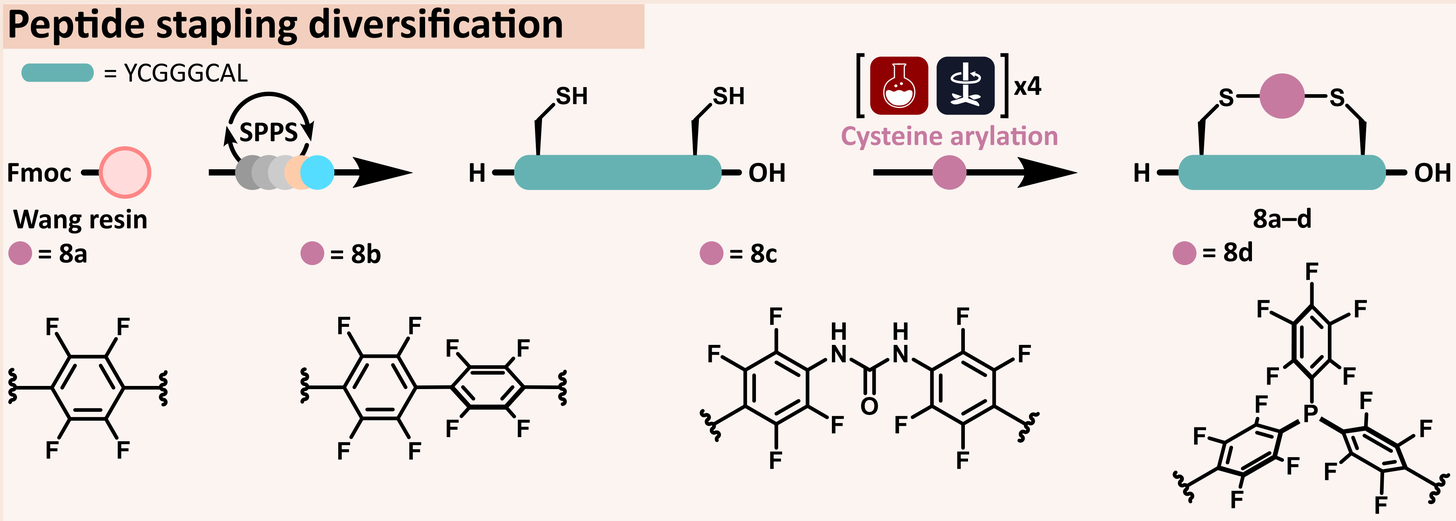
= CNPIWIGF

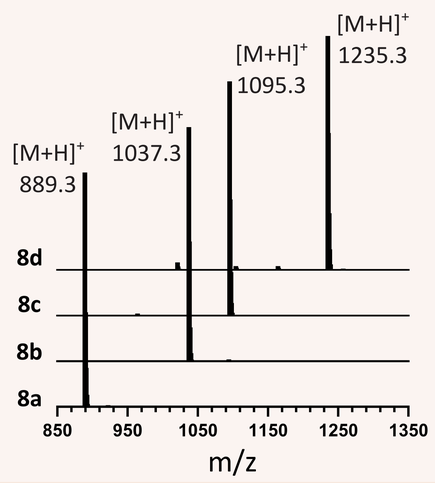




Peptide stapling diversification

= YCGGGCAL





Conclusion

A universal workflow using **χDL** on the **Chemputer** platform was established to synthesise increasingly complex peptides from commercially available building blocks.

EPSRC Pioneering research and skills
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