Accelerating peptide discovery via high throughput plate-based synthesis

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https://doi.org/10.17952/38EPS.2026.P027

Introduction

In early peptide discovery, peptides are often synthesised, purified and characterised one at a time, creating a bottleneck that limits throughput and slows hit validation. To address this, we established a high-throughput, plate-based synthesis workflow that enables parallel production of diverse linear and cyclic peptides in a 96-well format. The workflow is fully optimised for the synthesis of both linear and disulfide-containing peptides. This miniaturised approach increases throughput, reduces solvent and reagent consumption, and supports broader sequence exploration. Plate-based peptide samples can be tested directly in multiple assay formats, accelerating progression through the hit-to-lead stage. Benchmarking against individually purified peptides showed strong concordance in activity, supporting the suitability of this workflow for direct-to-biology evaluation.

Methods

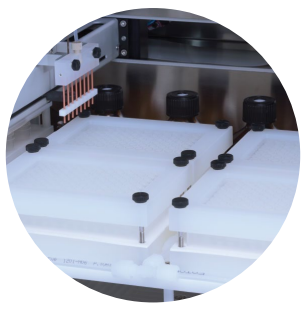
Synthesis → **Analysis** → **Purification** → **Concentration determination** → **Direct to Biology assays**



Results

Capacity

Parallel synthesis capacity increased by **16 times** from **6** to **96-384 compounds** per run

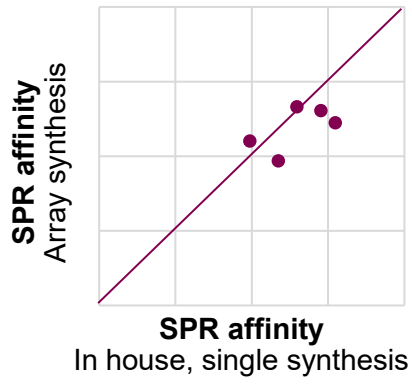


Workflow validation

Productivity

Validating and optimising hits faster to accelerate targeting projects

Figure 2. SPR affinity trends were concordant between array-derived and individually synthesised reference compounds



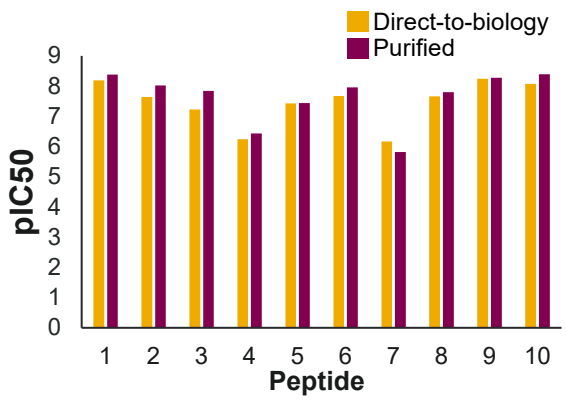




Sustainability

Reaction scale decreased from **10-100 mg** to **1-10 mg**, reducing reagent consumption and solvent use by approximately **10 L per plate**.

Figure 1. 96 disulfide-cyclised peptides were tested by HTRF, showing nanomolar binding for project A. Strong data correlation shown for HT workflow and direct-to-biology profiling of the same peptide sequences individually synthesised & purified to >95% purity.



Project impact

Hit Validation Stage

Typical Workflow — 6 months

Project B — 6 weeks → Progressed to patent filing

In project B, hit-validation timeline was reduced from a typical 6 months to 6 weeks, supporting rapid project progression.

Conclusions

- In-house array synthesis increased hit-validation capacity, expanding parallel synthesis from 6 to 96-384 compounds per run.
- The workflow improved project productivity and sustainability, reducing one hit-validation timeline from 6 months to 6 weeks and decreasing reaction scale from 10-100 mg to 1-10 mg, with approximately 10 L less solvent used per plate.
- Workflow validity was supported by concordant SPR and HTRF affinity trends versus reference compounds, indicating that higher-throughput, lower-scale synthesis was suitable for hit validation.
- This platform is now routinely applied to all AZ peptide projects.

Future work

- Expand throughput to 384-peptide parallel synthesis, targeting a 64-fold increase in capacity.
- Broaden chemistry scope by exploring cyclisation chemistries and conjugation to oligonucleotides and radioligands.
- Develop an AI/ML workflow to enable concentration measurement of peptides containing non-natural amino acids.
- Implement the HT workflow routinely across all peptide projects.
- Evaluate alternative green solvents systematically within the HT workflow to improve sustainability and enable process optimisation.

References

1. Wang et al., Sig. Transduct. Target Ther., **2022**, 7, 48.

Supported by AstraZeneca

Presented at the 38th European Peptide Symposium, Vienna, Austria,6-11th September 2026