Full Circle Chemistry: Expanding Macrocyclic Peptidomimetics

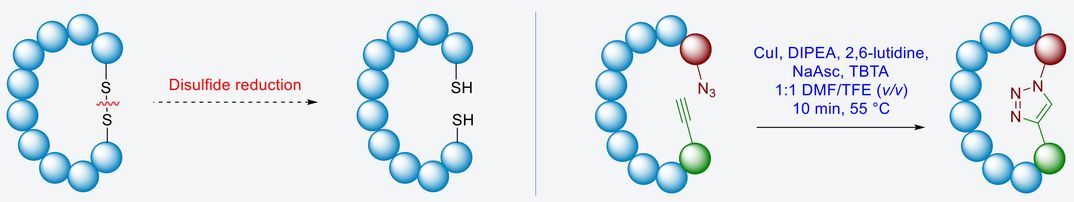
Jacob E. Simms[a], Oscar A. Shepperson[a], Michael A. Malone[a], Andrew J. Reid[a], Maxime Rouah[b], David J. Battersby[b] and Andrew G. Jamieson[a].

[a]*Advanced Research Centre, School of Chemistry, University of Glasgow, Glasgow, G11 6EW, UK.*
[b]*GSK Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK.*

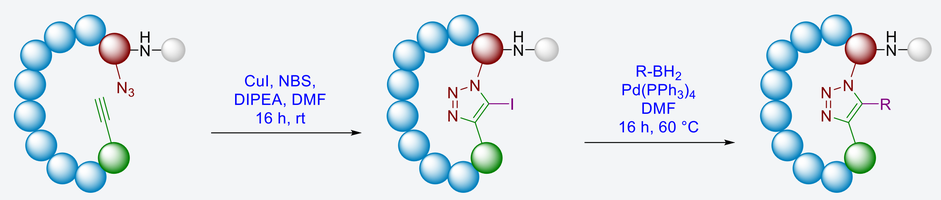
https://doi.org/10.17952/38EPS.2026.P156 j.simms.1@research.gla.ac.uk Jacob Simms

1. Background and Aims

- **Disulfide bridge mimetics** are synthetic replacements of native disulfide bridges which **preserve peptide structure** and **biological activity** while **enhancing stability**. Previously, the Jamieson group has focused on developing **triazole-based** disulfide bridge mimetics.
- This approach has been successfully applied to **α-Conotoxins**, **Urotensin-II**, **Oxytocin**, and **RGD** peptides.[1,2]



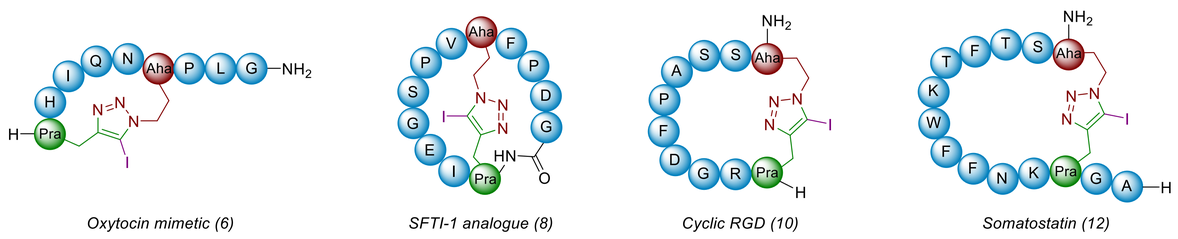
- Recent work in the Jamieson group has developed **novel on-resin chemistry** to access **5-iodo-1,4-triazole** cyclised peptides.[3]
- The 5-iodo-1,4-triazole is a **bifunctional** mimetic, as it acts as a **conformational constraint**, while also providing a **reactive handle** for further functionalisation.



- This work aims to expand the **scope** of this novel on-resin chemistry.

2. Variable Ring Size Investigations

- To probe the **versatility** of the 5-iodo-1,4-triazole chemistry, four **diverse** model peptides were selected, encompassing a range of amino acid functionalities and macrocyclic ring sizes.
- 5-iodo-1,4-triazole analogues of all model peptides were **efficiently** formed **on-resin** with good conversion from their linear precursors.

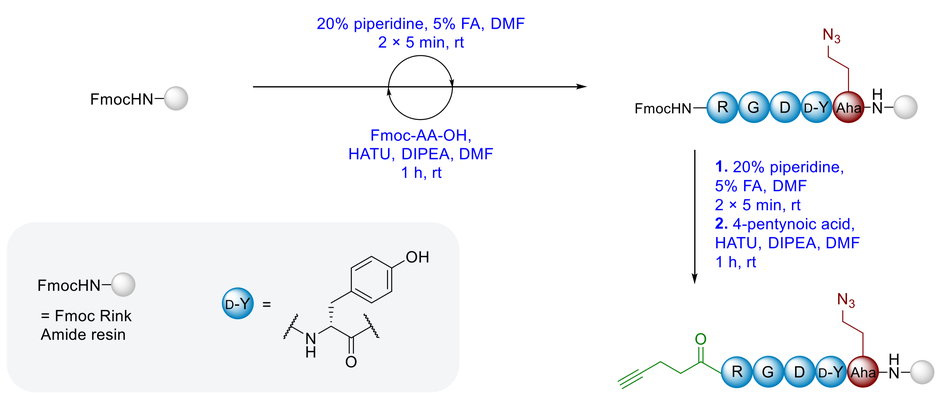


Oxytocin mimetic (6) | *SFTI-1 analogue (8)* | *Cyclic RGD (10)* | *Somatostatin (12)*

- Subsequent **Suzuki-Miyaura** and **Sonogashira** cross-coupling reactions were successful on all 5-iodo-1,4-triazole substrates, except for the histidine-containing oxytocin mimetic (suspected palladium poisoning).[4]

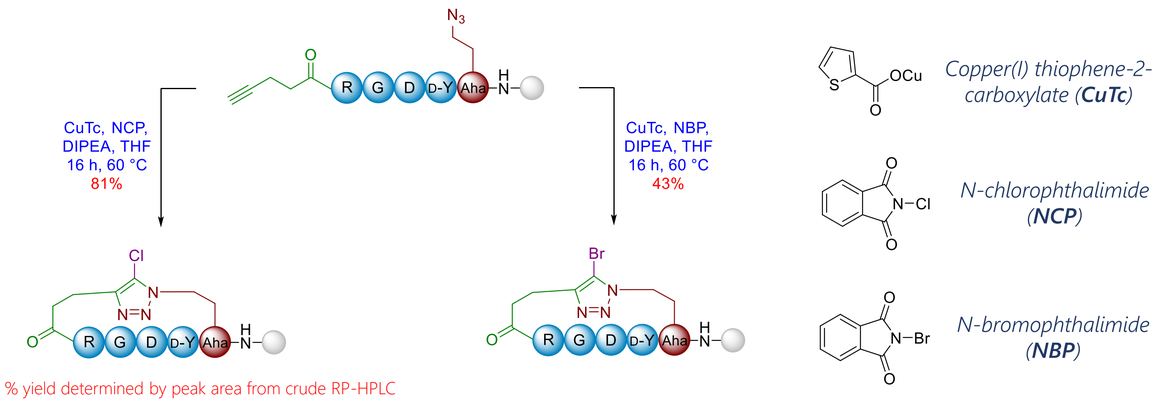
3. Peptide Synthesis

- Reaction scope studies were performed on a model peptide containing the biologically relevant **RGD** motif, synthesised by Fmoc solid-phase peptide synthesis.



4. Development of 5-Halo-1,4-Triazoles

- Optimised conditions were developed to efficiently access **5-chloro-1,4-triazole** and **5-bromo-1,4-triazole** cyclised peptides **on-resin**.



*Copper(I) thiophene-2-carboxylate (**CuTc**)*

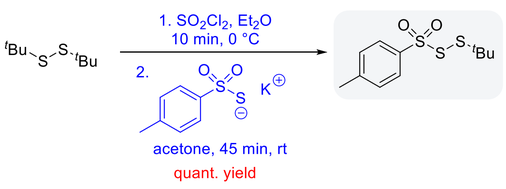
*N-chlorophthalimide (**NCP**)*

*N-bromophthalimide (**NBP**)*

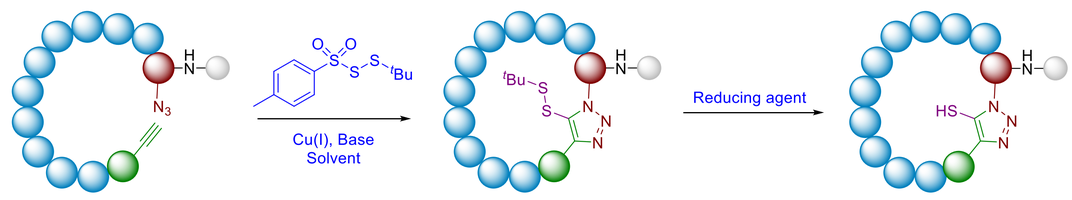
% yield determined by peak area from crude RP-HPLC

5. 5-Thio-1,4-Triazole

- The scope of 5-substituted triazoles amenable to on-resin peptides was expanded by developing a **5-thio-1,4-triazole**.
- Facile synthesis under mild conditions gave an **electrophilic persulfur reagent**, with previous literature precedent in modified CuAAC reactions.[5]

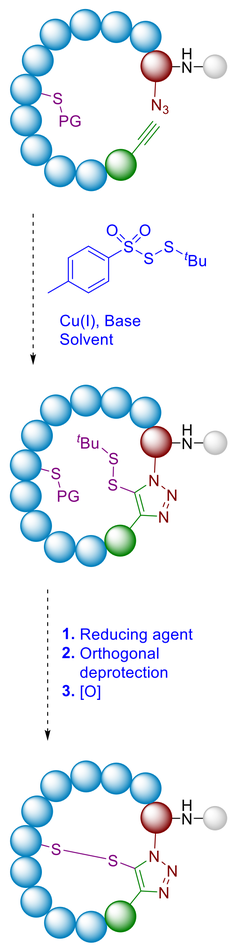


- This reagent enabled formation of a **triazole disulfide**, which could be reduced **on-resin** to access the free thiol.



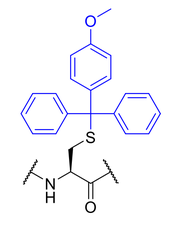
Current Work:

- This chemistry may be used to access **bicyclic** peptides.
- Bicyclic peptides are **privileged medicinal chemistry scaffolds** due to their advantageous **stability** and **specificity** profiles over monocyclic peptides.

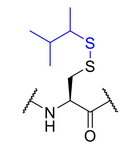


- Inclusion of an **orthogonally protected cysteine** in the peptide sequence allows for a short route to the desired bicycle.
- The proposed synthesis route involves an **interrupted CuAAC** to yield the monocyclic peptide, followed by **disulfide cleavage**, **orthogonal deprotection**, and **thiol oxidation**.
- The choice of a suitable orthogonal protecting group for the cysteine residue could shorten the synthesis *via* **simultaneous** disulfide cleavage and thiol deprotection:

***S-PG**:*



Cys(Mmt)
Deprotected with weak acid (1-5% TFA in DCM)



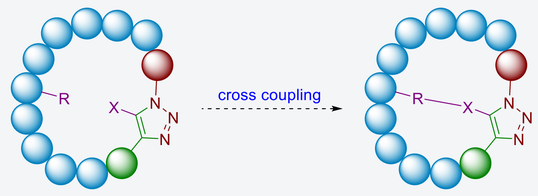
Cys(SIT)
Deprotected under reducing conditions (3 equiv. Dithiothreitol in DMF)

6. Conclusions and Future Work

- A **5-chloro-1,4-triazole** bridged peptide was successfully utilised in an **on-resin** Suzuki-Miyaura cross-coupling reaction.
- Further optimisation is required for the **5-bromo-1,4-triazole**, to enhance conversion.



- The feasibility of the 5-thio-1,4-triazole chemistry will be assessed in a **bioactive** model peptide as an alternative methodology for macrocyclization, incorporating the **redox stable** triazole chemistry.
- Metal-catalysed cross couplings with **halo-triazoles** and **non-natural amino acids** could afford increased stability in the bicycles, removing disulfide bridges.



References

1. S. Pacifico, A. Kerckhoffs, A. J. Fallow, R. E. Foreman, R. Guerrini, J. McDonald, D. G. Lambert and A. G. Jamieson, *Org. Biomol. Chem.*, 2017, **15**, 4704–4710.
2. A. Knuhtsen, C. Whitmore, F. S. McWhinnie, L. McDougall, R. Whiting, B. O. Smith, C. M. Timperley, A. C. Green, K. I. Kinnear and A. G. Jamieson, *Chem. Sci.*, 2019, **10**, 1671–1676.
3. O. A. Shepperson, M. A. Malone, K. I. M. Arnott, R. J. Brown and A. G. Jamieson, *Org. Lett.*, 2025, **27**, 11249–11253.
4. M. A. Malone, O. A. Shepperson, J. E. Simms, A. J. Reid and A. G. Jamieson, *J. Org. Chem.*, 2026, **91**, 22, 7416–7422.
5. W. Wang, Y. Lin, Y. Ma, C-H. Tung and Z. Xu, *Org. Lett.*, 2018, **20**, 10, 2956–2959.

Acknowledgements

Financial support from the JMS PhD scholarship and GSK is gratefully acknowledged.

Jamieson Lab