THIOL-ENE CLICK LIGATION AS AN EFFICIENT APPROACH FOR PEPTIDE MACROCYCLIZATION

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Interest in developing stable peptide analogues as therapeutics has grown tremendously in the pharmaceutical sector over the last decade. To date, peptide stapling has been demonstrated to be an efficient synthetic approach in addressing the limitations of linear peptides resulting in more stable molecules.[1] Peptide stapling techniques are based on different macrocyclazation chemistries, such as disulfide and thioester formation, lactamization, ring-closing metathesis and cycloadditions, which were extensively investigated and applied to the synthesis of several cyclic peptides.[2,3] With the aim of promoting rapid and efficient synthesis of peptide macrocycles, a number of "click reactions" were also taken into account.[4] Thiol-ene 'click' (TEC) chemistry is a radical mediated addition of a thiol to an alkene.[5] Herein we report a novel, fast and high-yielding synthetic method based on radical TEC ligation to generate Oxytocin thio-ether analogues of the natural substrate.

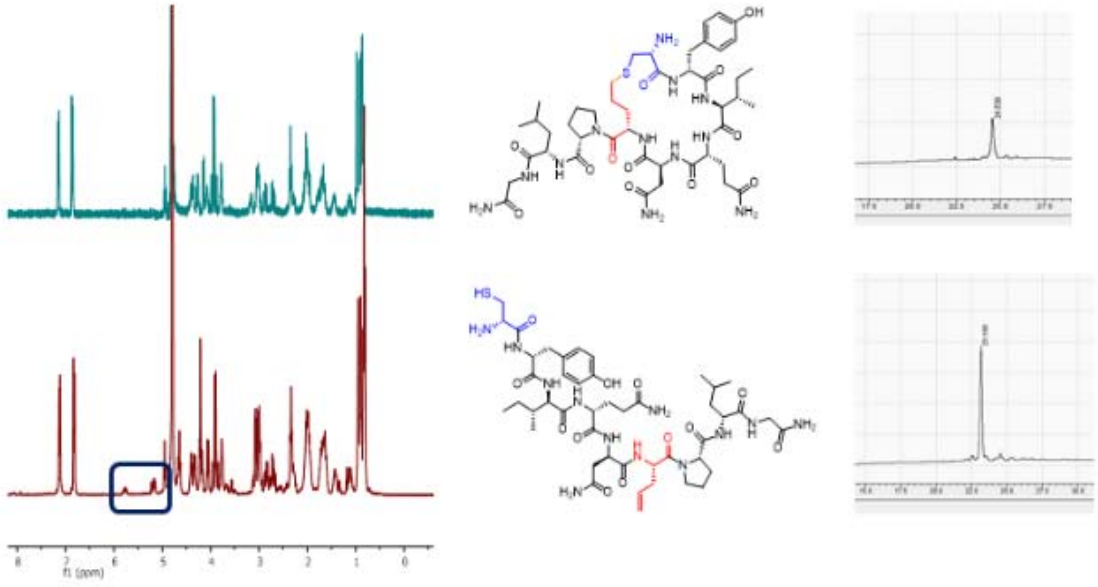

Figure 1. Schematic overview of Oxytocin macrocyclazation.

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[2] Y. H. Lau et al. *Chem. Soc. Rev*. **2015**, 44, 91-102

[3] C. J. White et al. *Nat. Chem*. **2011**, 3, 509-24

[4] A. A. Aimetti et al. *Chem. Comm.* **2010**, 46, 4061-3

[5] R. O. McCourt et al. *Org Lett.* **2018**, 20, 2948-51.