Site-selective labeling of biomolecules *via* disulfide rebridging

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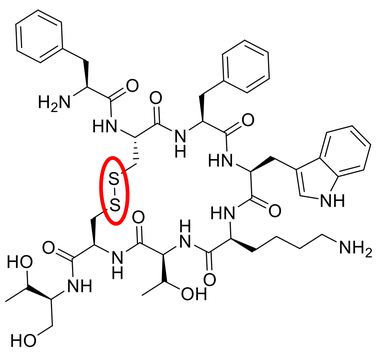
INTRODUCTION

Disulfide Rebridging

- **Site-selective modification**
- **Biocompatible** (mild conditions)
- **Tertiary structure maintained**
- **Homogeneous bioconjugate**

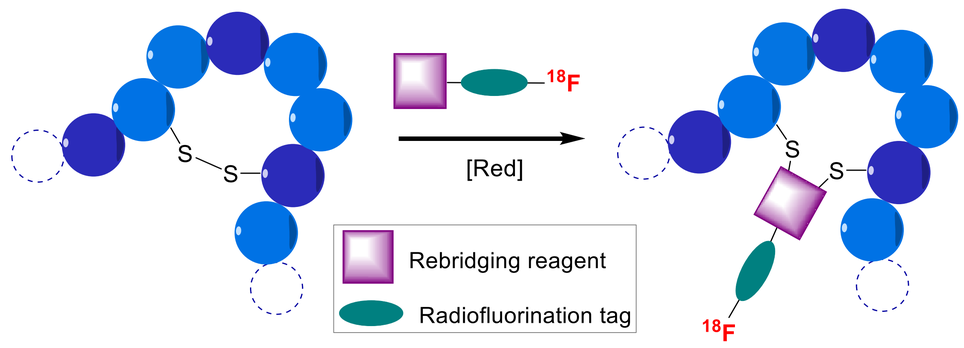
Octreotide

- Analogue of somatostatine - Ligand of **SST2**
- **Imaging of neuroendocrine tumours**
- Contains a disulfide bridge



Good candidate for labeling by rebridging

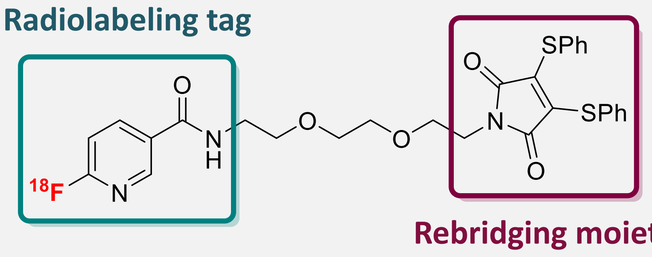
Labeling of biomolecules *via* disulfide rebridging



Objectives

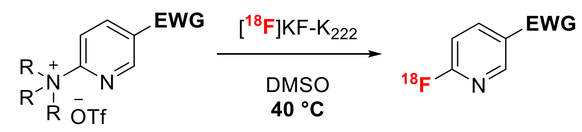
➢ **Synthesis and radiolabeling** of rebridging prosthetic group

Radiolabeling tag



➢ **Proof of concept** of radiolabeling by rebridging on model peptide octreotide

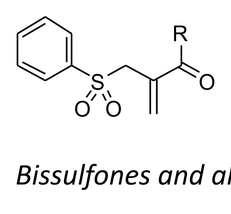
Radiofluorination tag[1]



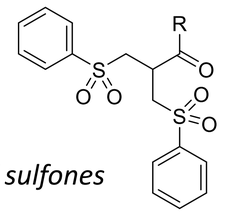
Activated pyridines:

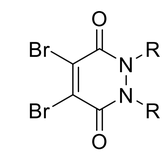
- Accessible synthesis of precursors
- Radiolabeling in mild conditions

Disulfide rebridging reagents[2,3]

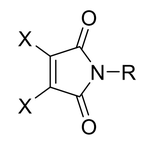


Bissulfones and allyl sulfones



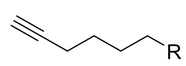


pyridazinediones



X = Br, Cl, PhS, ...

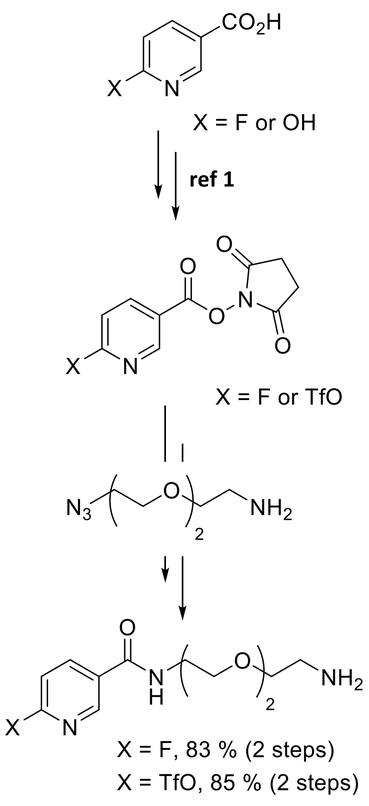
Mono or disubstituted maleimides

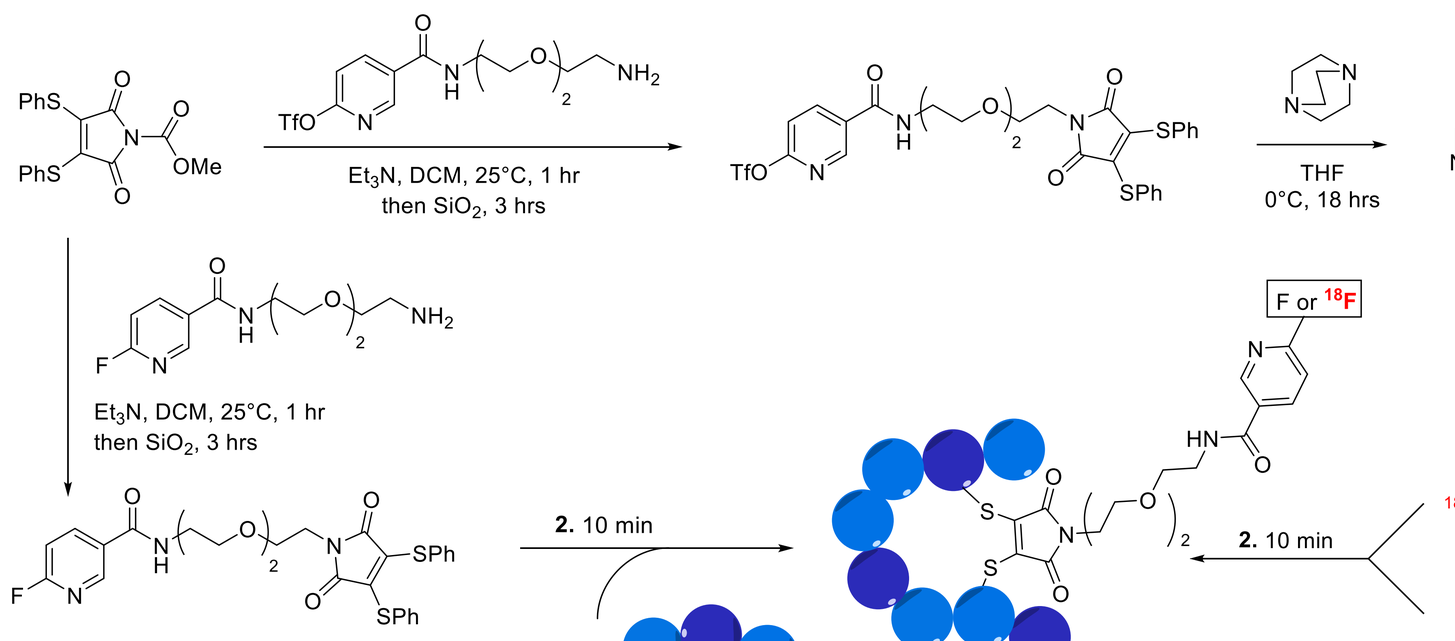


Alkynes

PREPARATION OF PRECURSORS & COLD REFERENCES

Radiofluorination tag





Labeling precursor 2 steps – 41 %

Prosthetic group reference – 77 %

Rebridged octreotide reference

2 steps – quantitative

Preliminary radiosyntheses

➢ **Prosthetic group**

RCY: 13 % d.c.

Formulation: AttractSPE HLB

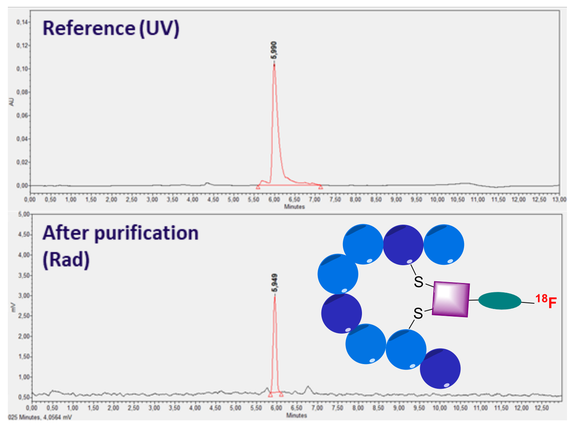
Reaction time: 80 min E.O.B.

➢ **Rebridged radiofluorinated octreotide**

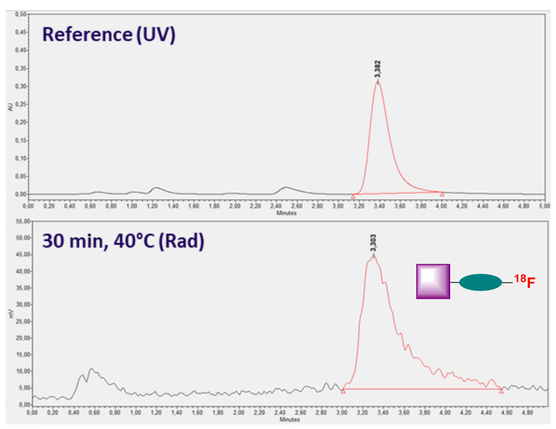
RCY: 25% d.c. after purification

Purification: Minitrap G10, PBS

Reaction done after 10 min at 25 °C



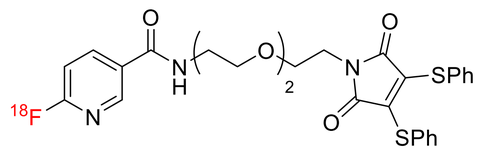
Chromatograms of rebridged fluorinated octreotide



Chromatograms of prosthetic group

CONCLUSION & PERSPECTIVES

➡ Design and synthesis of an **original radiolabeling rebridging reagent**



➡ Radiolabeling of **octreotide**

⇨ **Automation** of radiosynthesis

⇨ Determination of rebridged octreotide **affinity for SST2**

⇨ **Biodistribution** of rebridged octreotide

⇨ **Labeling of FAb** *via* rebridging

[1] M. Richard, S. Specklin, M. Roche, F. Hinnen and B. Kuhnast, *Chem Commun.* **2020**, DOI: 10.1039/C9CC09434B **[2]**. S. L. Kuan, T. Wang and T. Weil, *Chem. Eur. J.* **2016**, *22*, 17112 – 17129 **[3]** L. Castañeda *et al.*, *Tetrahedron Letters* **2013**, *54*, 3493–3495

Supported by ANR PeptOpain (ANR-17-CE-18-0019-03)