Amino Acids and Peptides –

Current Projects and Future Perspectives

Group Seminar

08.11.2019

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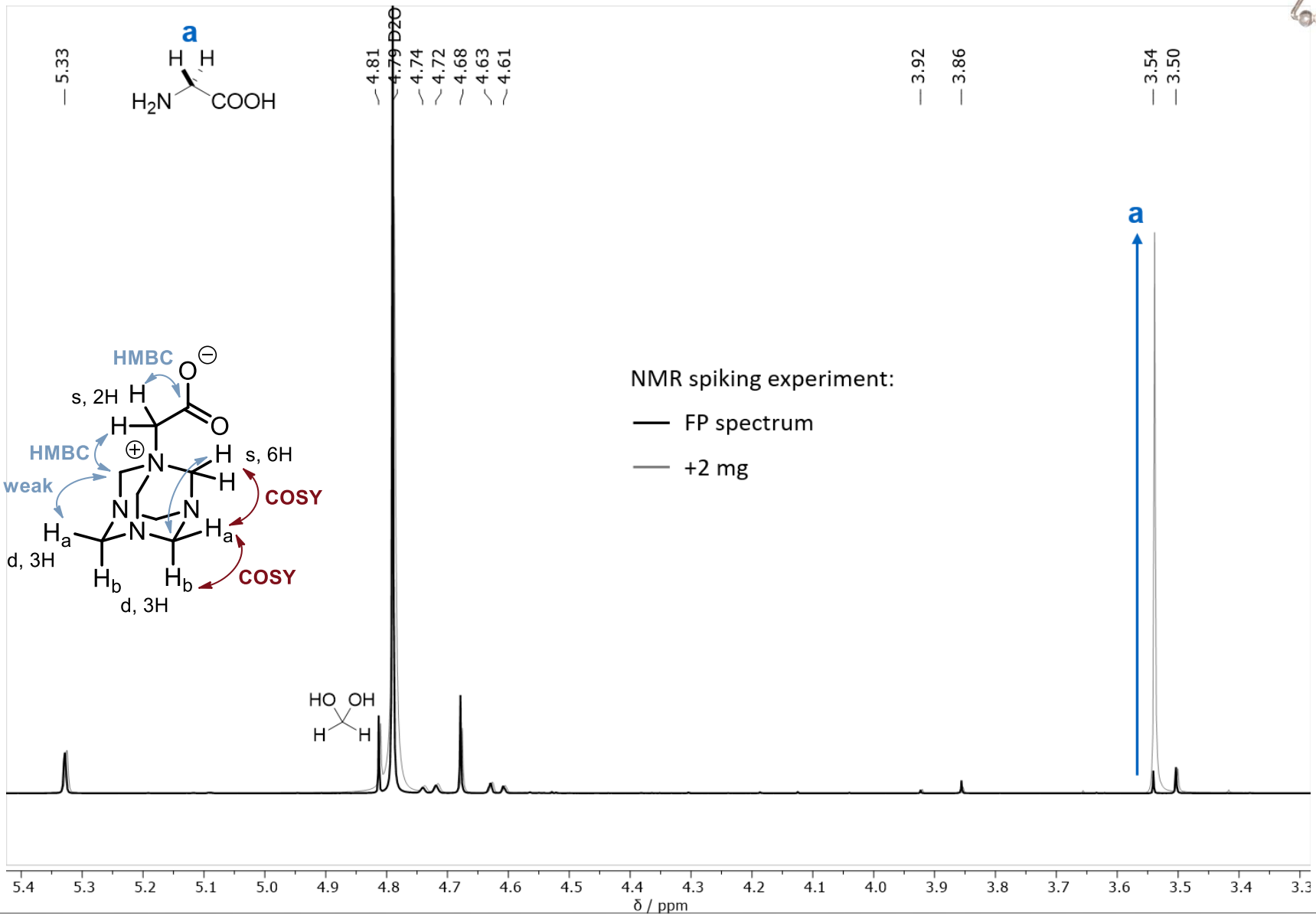
A Convenient Synthesis of 2,3-Diaminopropanoic Acid Derivatives(?)

An “Unknown” Compound from Flow Pyrolysis



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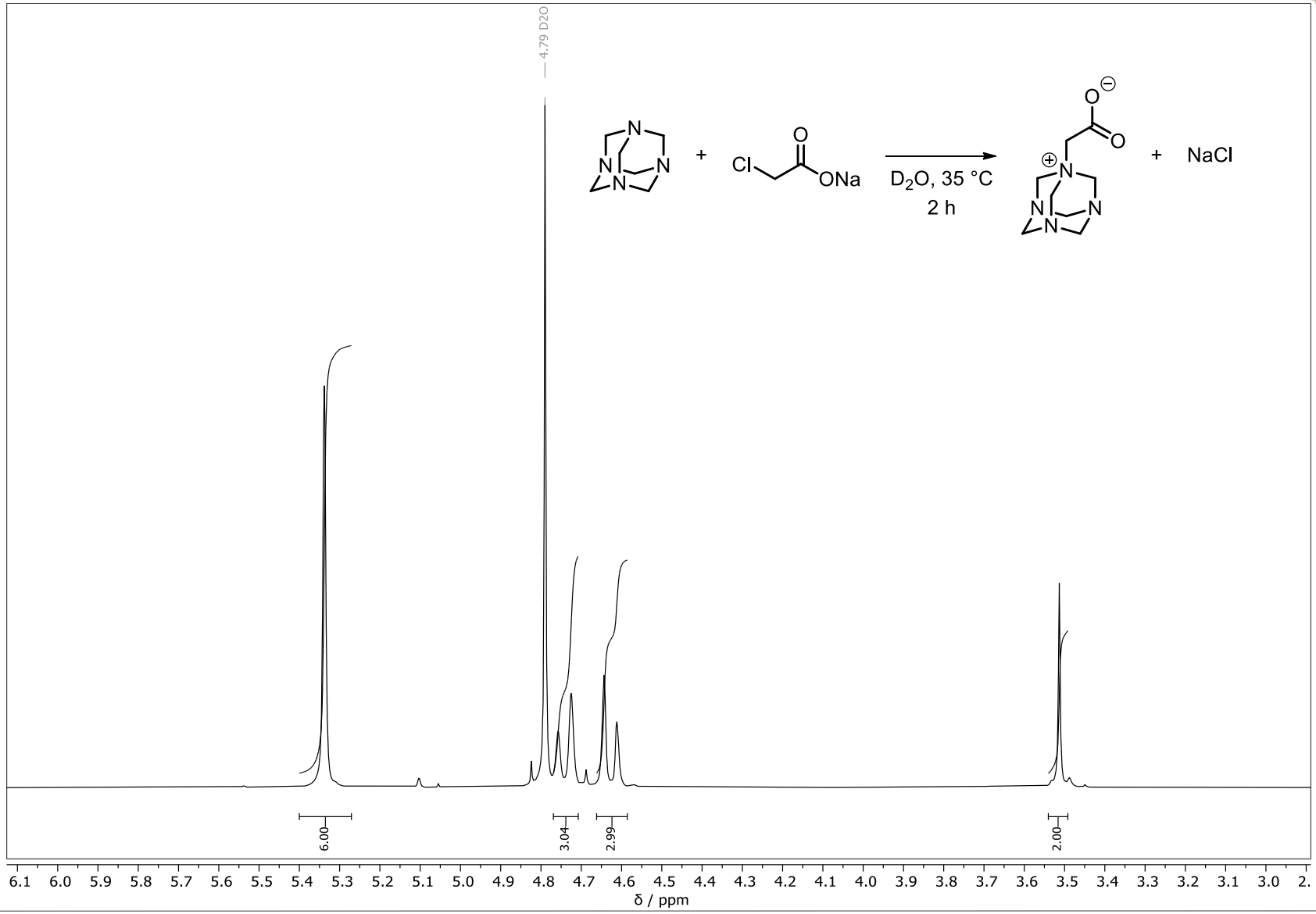

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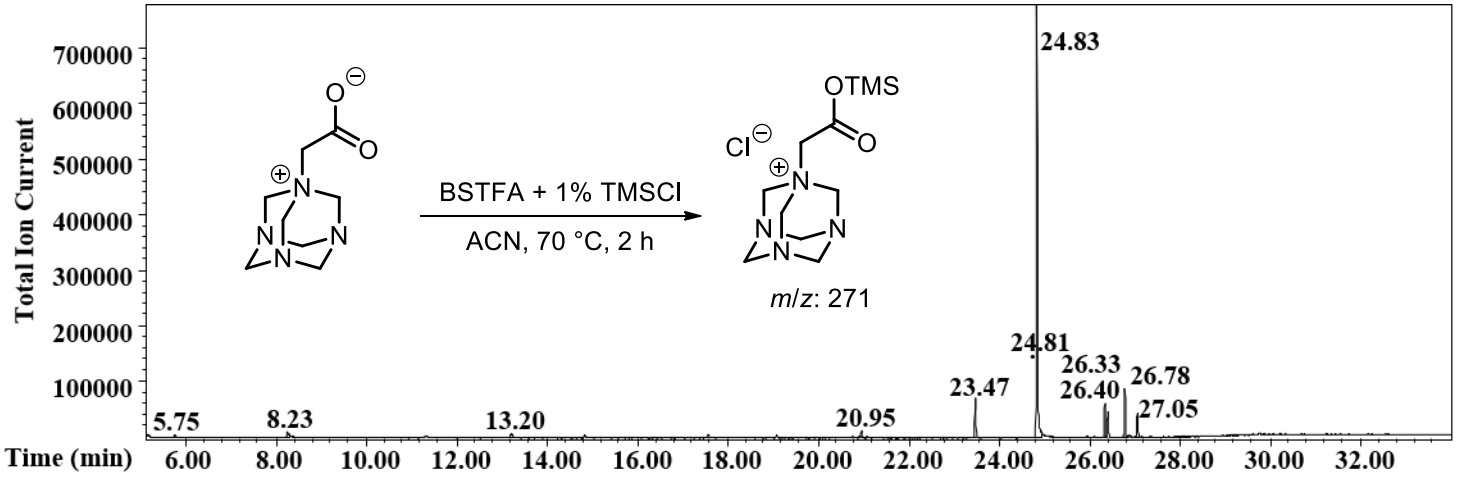
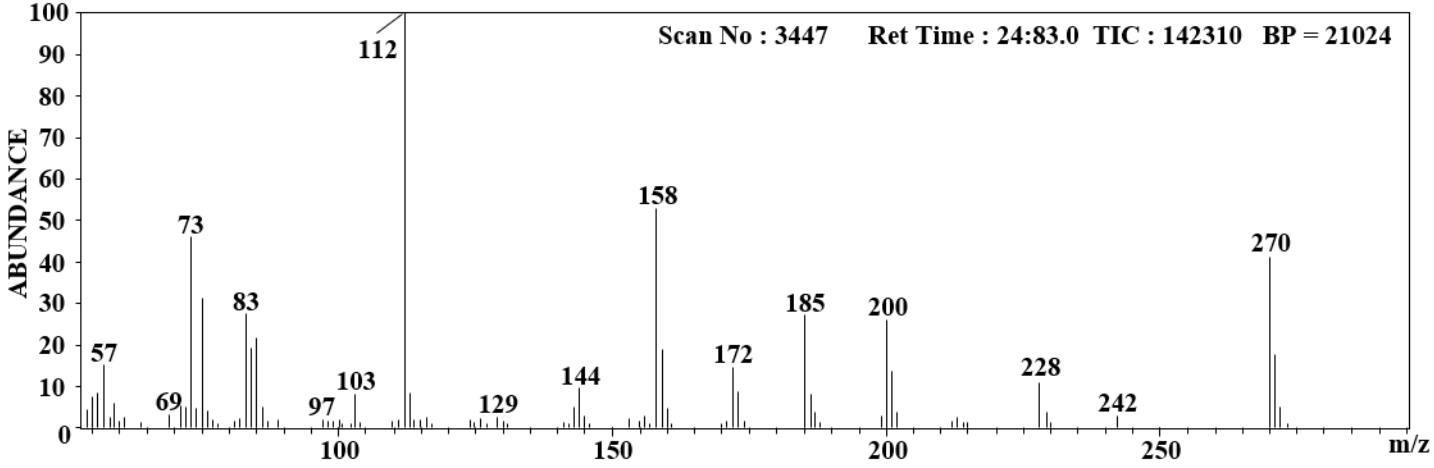
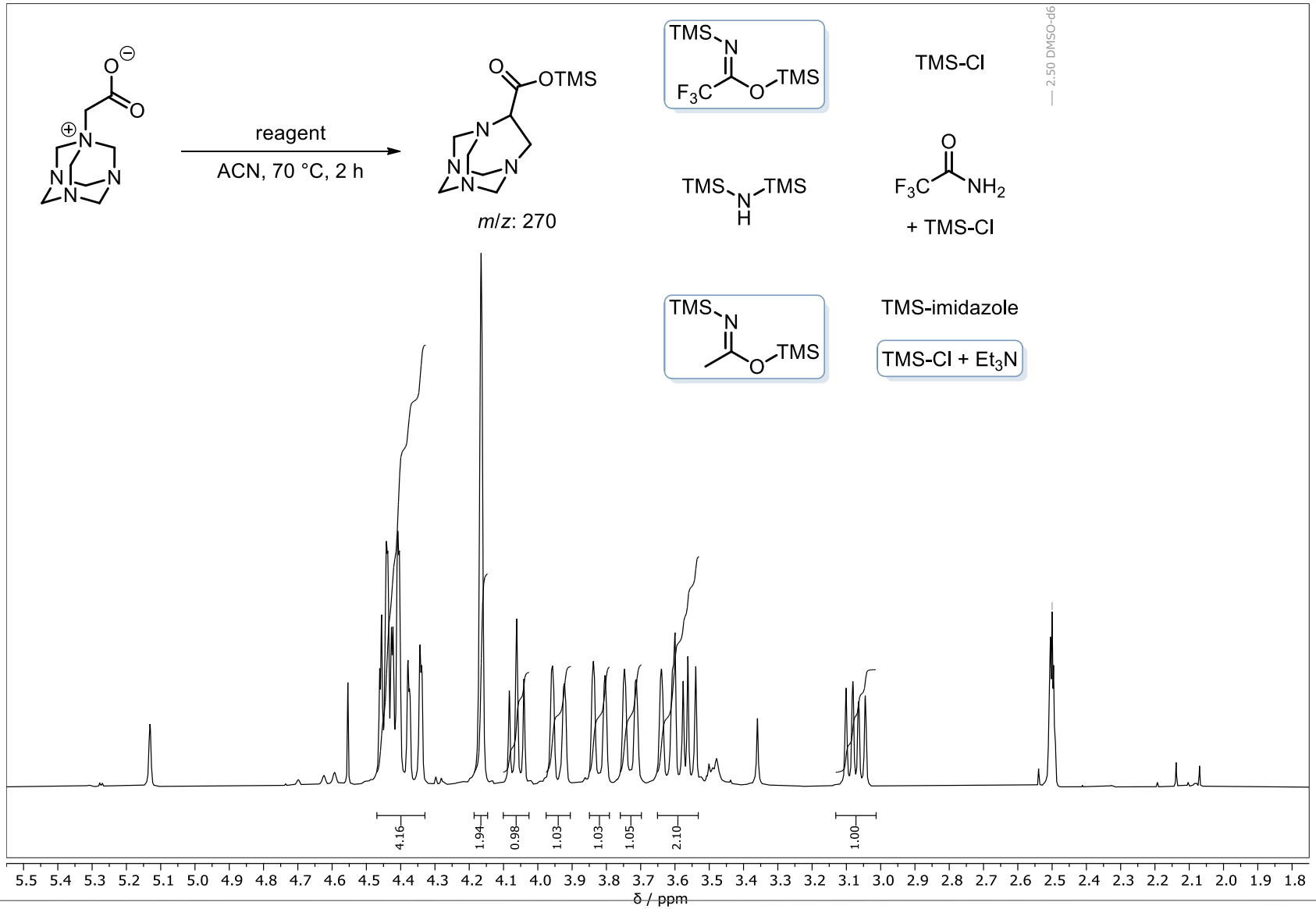
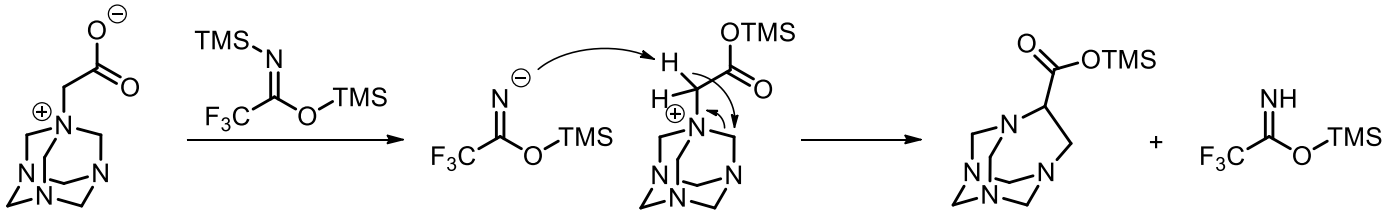




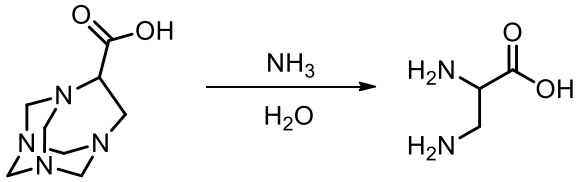
Identification

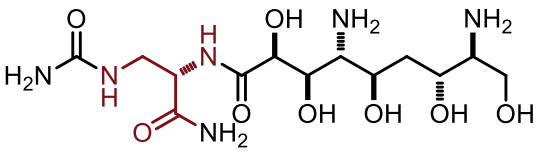


Proposed Mechanism

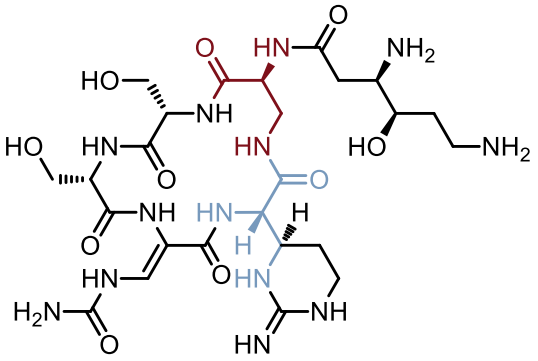


Stevens-type rearrangement



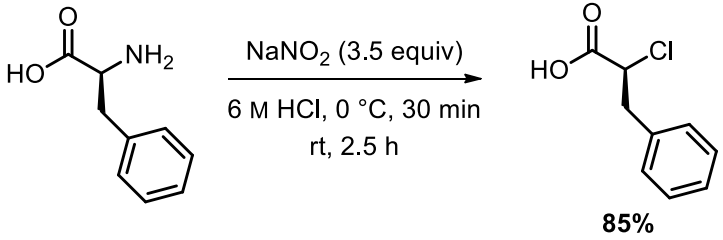


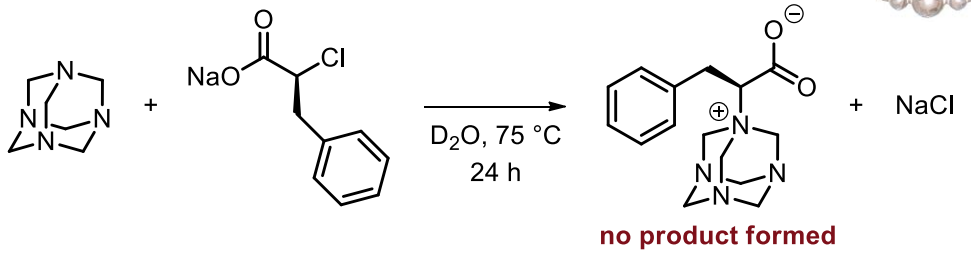
Zwittermicin A

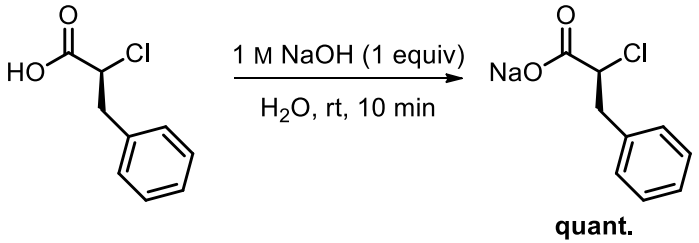


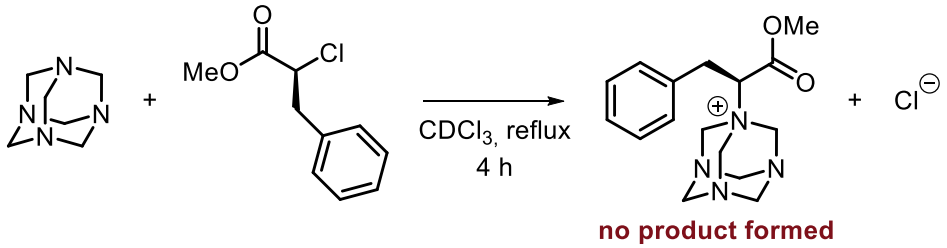
Enviomycin

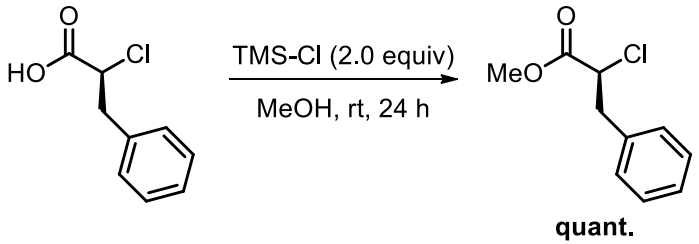
Synthesis of Quaternary Diamino Acids



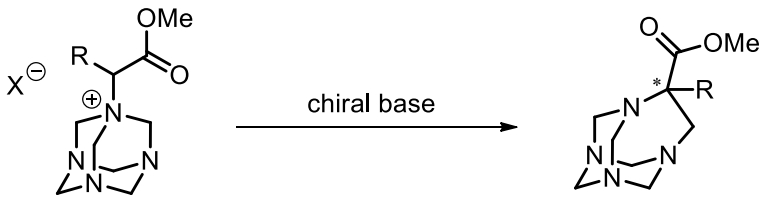








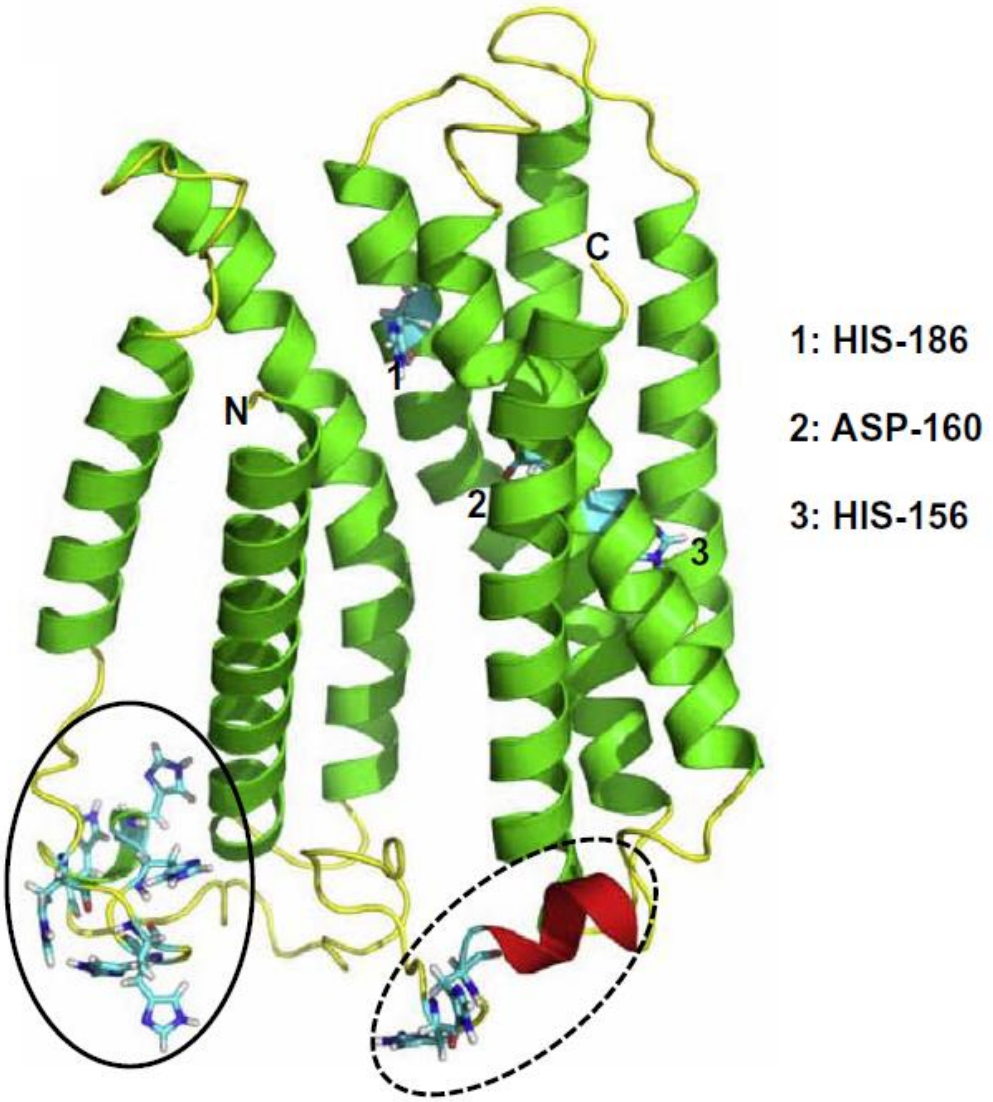
- Use of different leaving groups
- Variation of amino acid side-chains
- Stereoselective rearrangement
- Hydrolysis



Targeting the Testosterone Binding Site of ZIP9 with Andromimetic Peptides

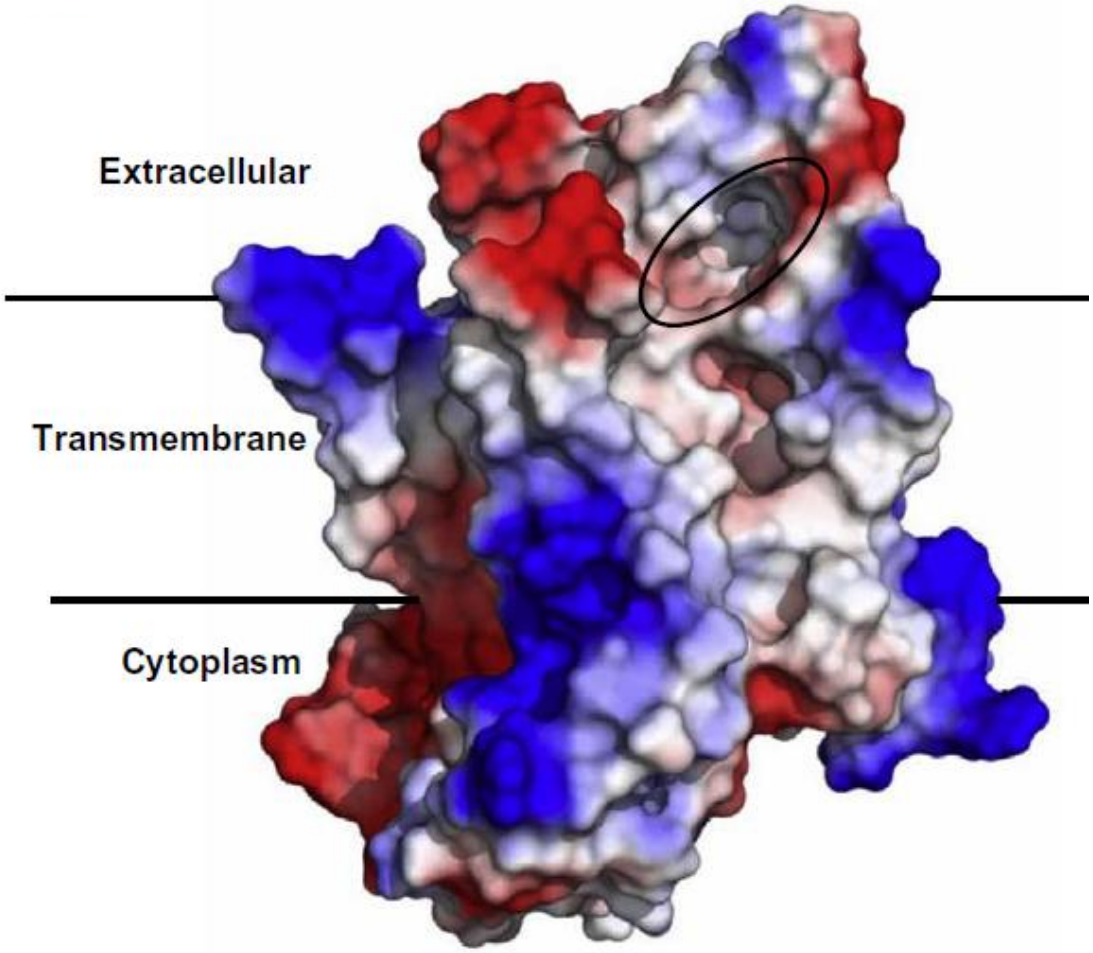
The Zinc Transporter ZIP9

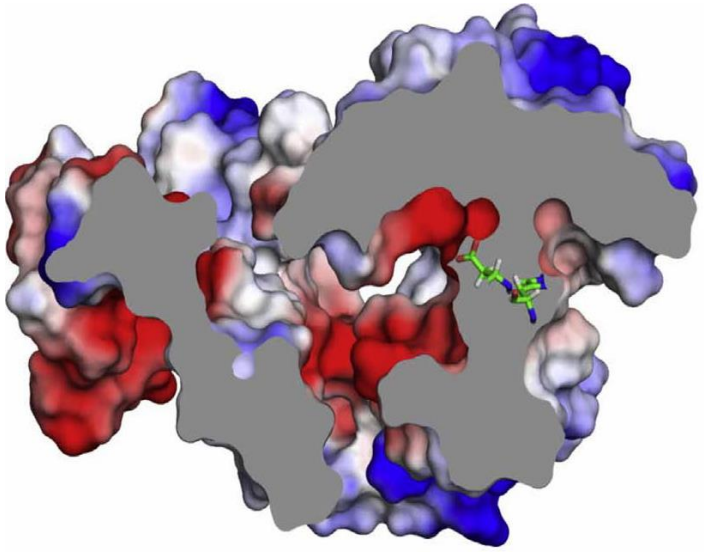
- Membrane-bound protein originally identified as a Zn^{2+} transporter
- It can also bind testosterone
- Trigger the activation of the Src, Ras, Raf, Erk1/2, CREB, and ATF-1 signaling cascade
- Cascade is mediated through the interaction of ZIP9 with G-proteins
- Represents an interesting pharmacological target



M. Shihan, A. Bulldan, G. Scheiner-Bobis, *Biochim. Biophysi. Acta* **2014**, *1843*, 1172-1181; A. Bulldan, V. N. Malviya, N. Upmanyu, L. Konrad, G. Scheiner-Bobis, *BBA – Mol. Cell Res.* **2017**, *1864*, 2402-2414.

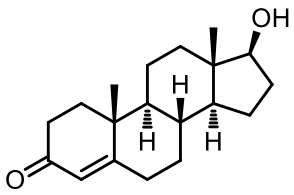
The Zinc Transporter ZIP9

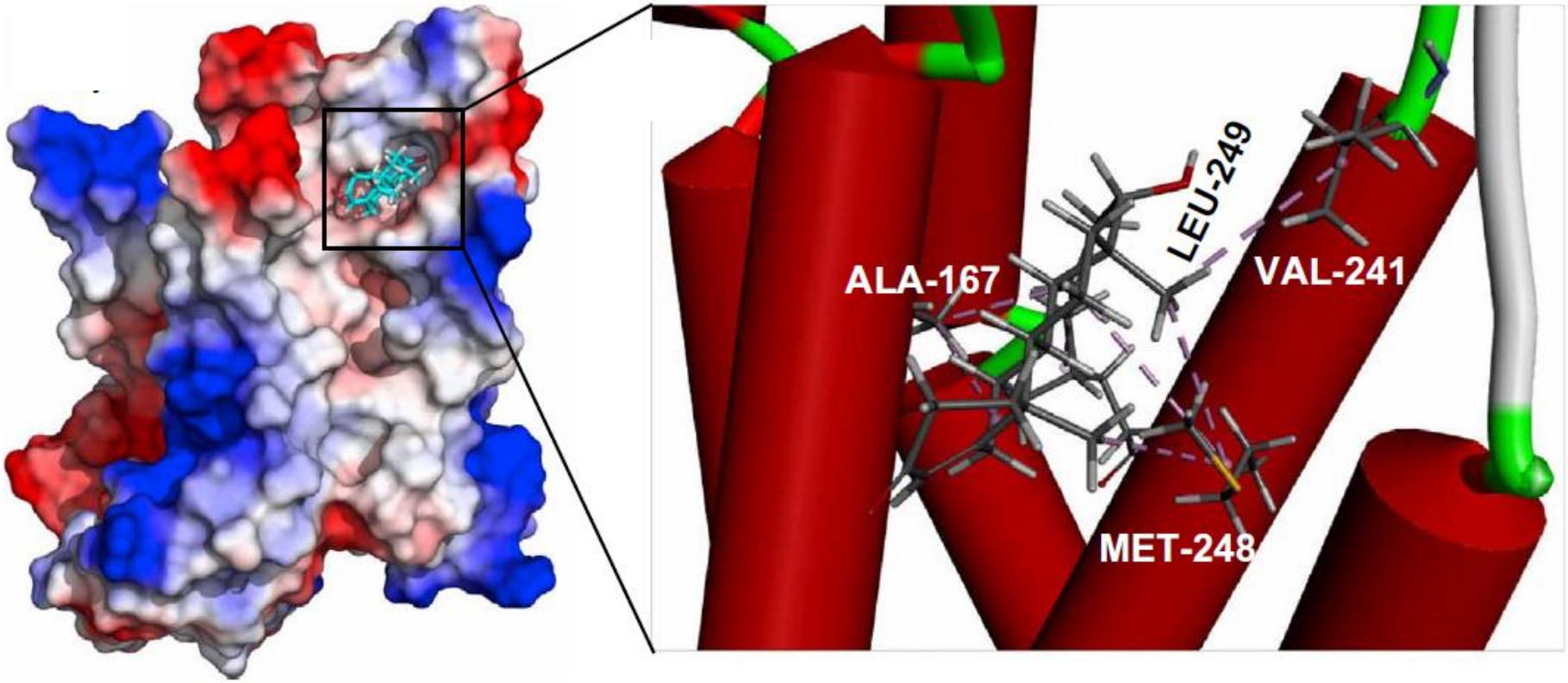




A. Bulldan, V. N. Malviya, N. Upmanyu, L. Konrad, G. Scheiner-Bobis, *BBA – Mol. Cell Res.* **2017**, *1864*, 2402-2414.

Binding of Testosterone





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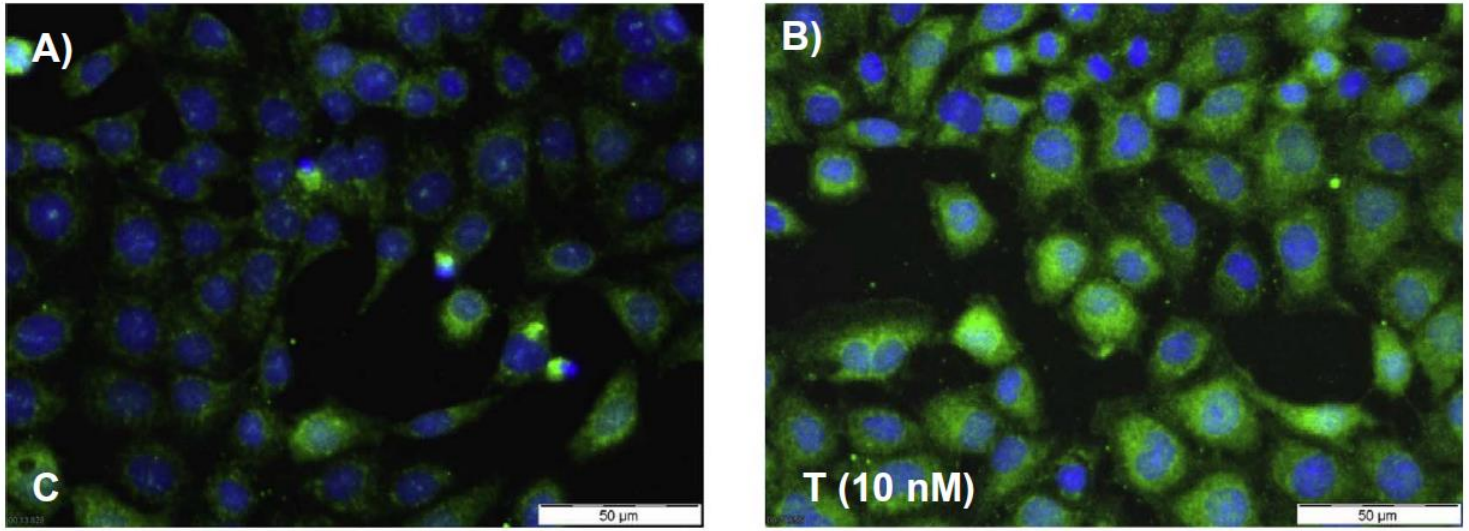
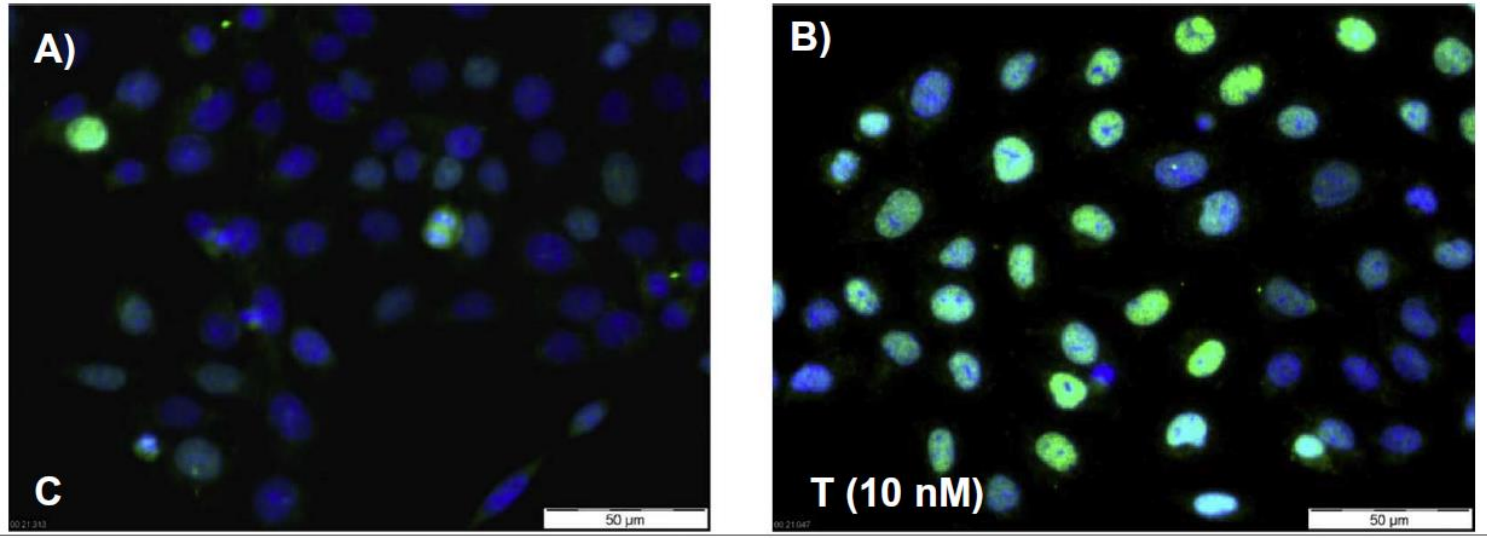
Immunofluorescence Assays

p-Erk1/2



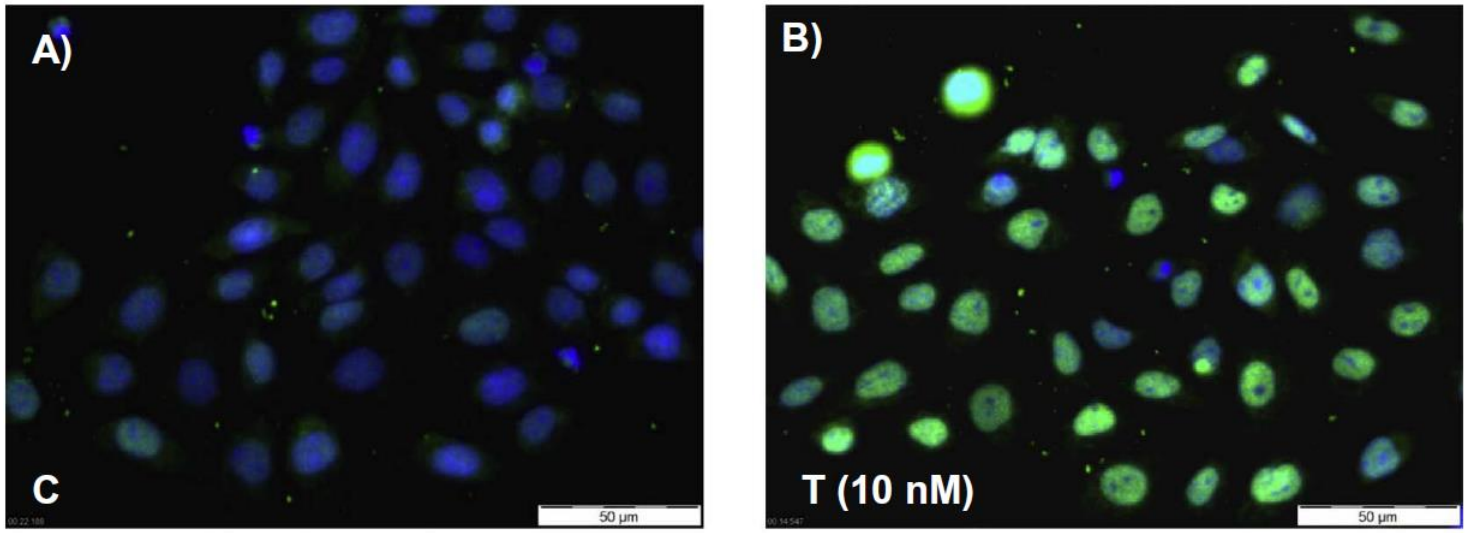
p-CREB



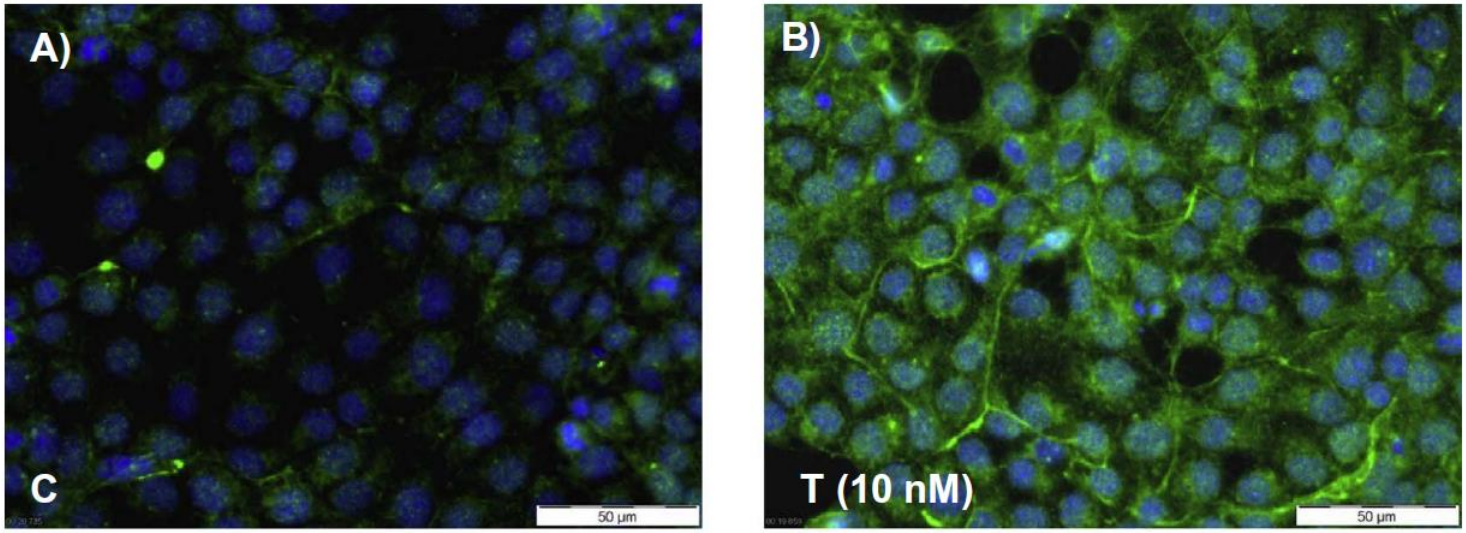
A. Bulldan, V. N. Malviya, N. Upmanyu, L. Konrad, G. Scheiner-Bobis, *BBA – Mol. Cell Res.* **2017**, *1864*, 2402-2414.

Immunofluorescence Assays

p-ATF-1

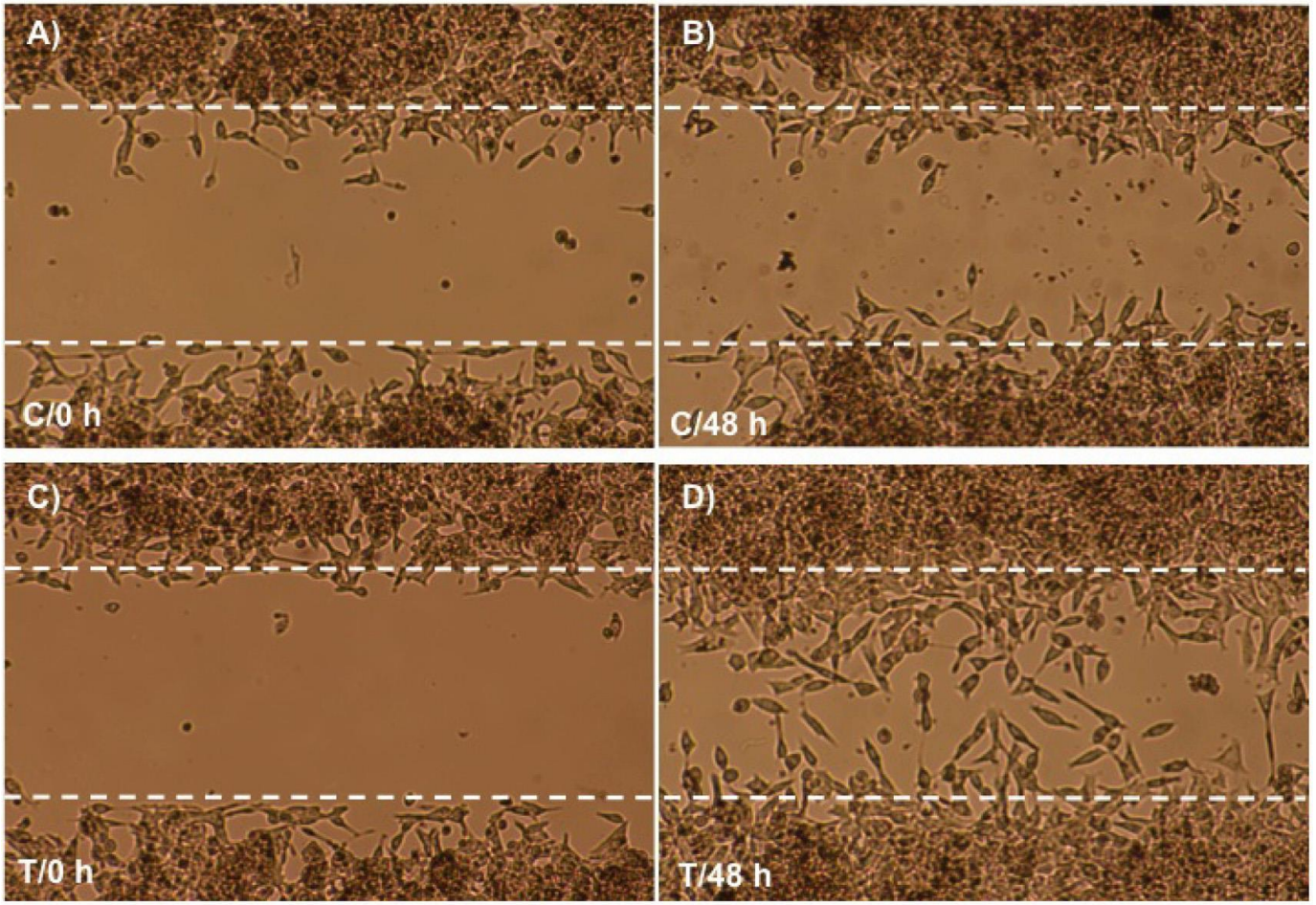


Claudin-5



A. Bulldan, V. N. Malviya, N. Upmanyu, L. Konrad, G. Scheiner-Bobis, *BBA – Mol. Cell Res.* **2017**, *1864*, 2402-2414.

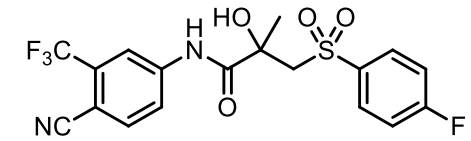
Cell Migration Assay



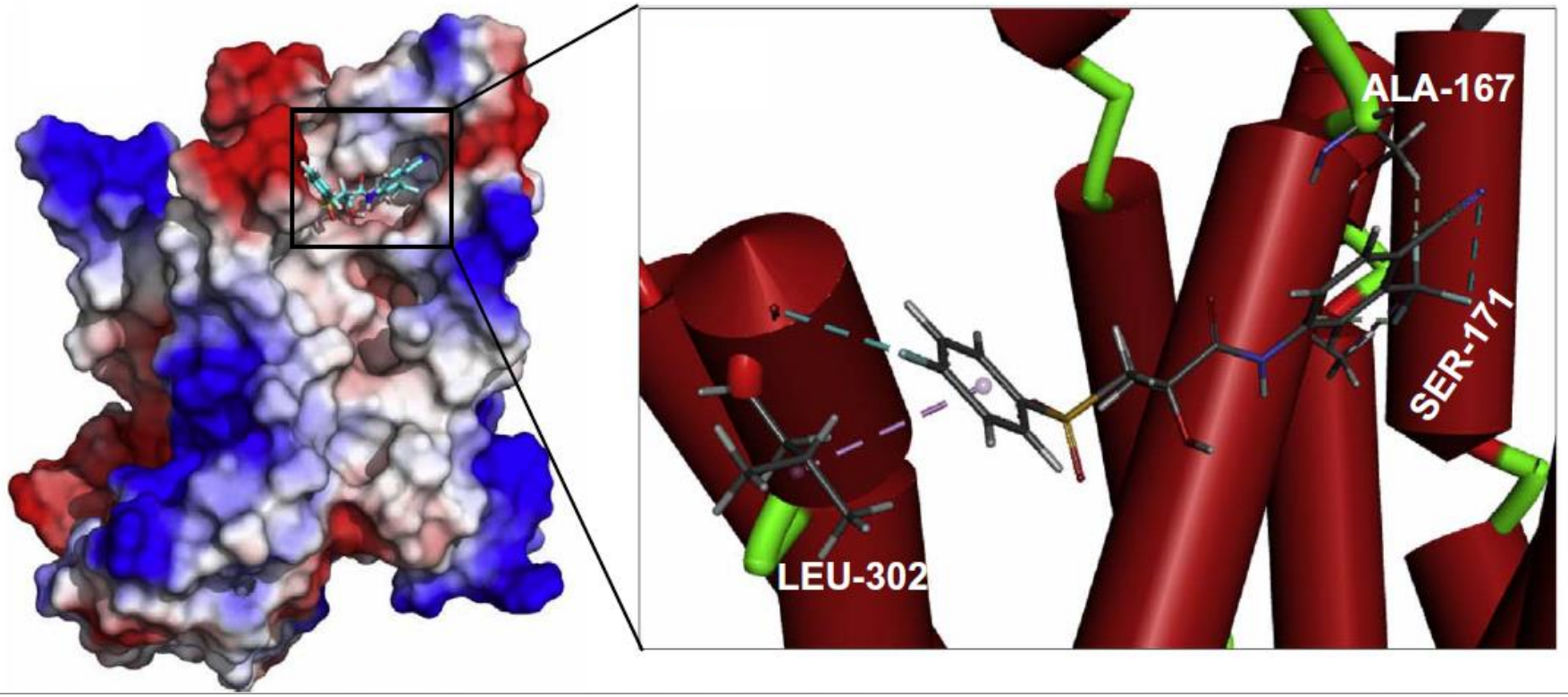
M. Shihan, A. Bulldan, G. Scheiner-Bobis, *Biochim. Biophysi. Acta* **2014**, *1843*, 1172-1181.

The Antiandrogen Bicalutamide

- Significant clinic impact
- Severe side-effects
- Accommodates same binding pocket as testosterone



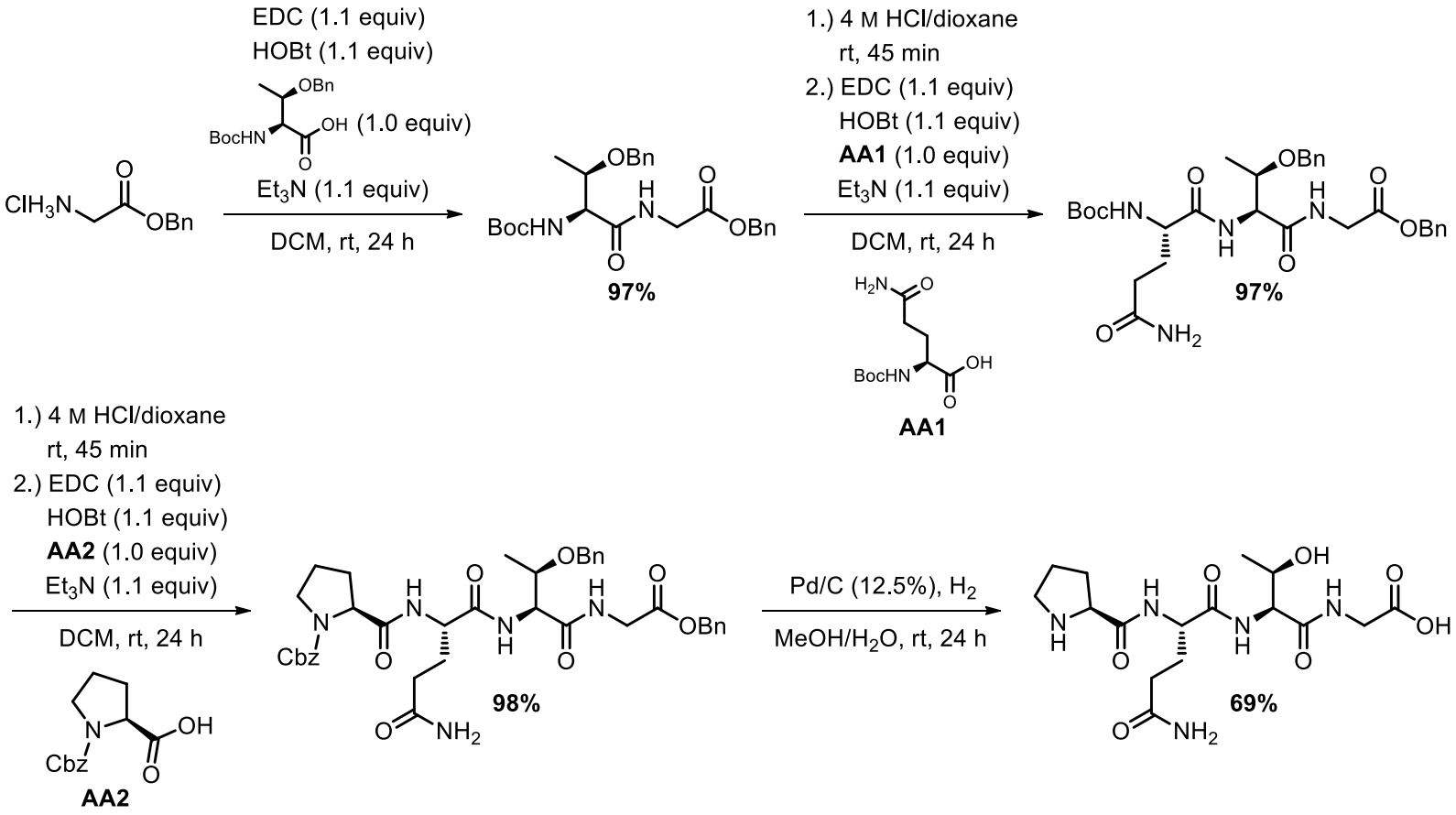
1.3 billion US$ world wide sales in 2007
13.4 billion as of the end of 2018



A. Bulldan, V. N. Malviya, N. Upmanyu, L. Konrad, G. Scheiner-Bobis, *BBA – Mol. Cell Res.* **2017**, *1864*, 2402-2414.

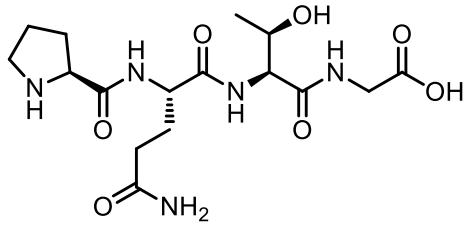
Design and Synthesis of Andromimetic Peptides

- In silico design of potential andromimetic peptides
- Six candidates identified that may bind to proposed binding site of ZIP9

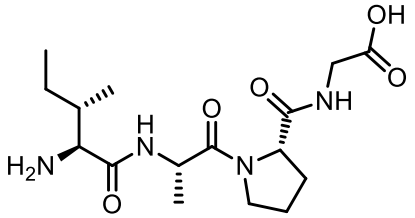


M.-L. Möller, A. Bulldan, V. N. Malviya, Raffael C. Wende, P. R. Schreiner, G. Scheiner-Bobis, *J. Med. Chem.*, *manuscript in preparation*.

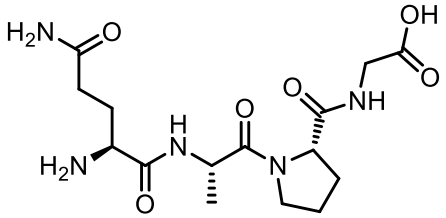
Design and Synthesis of Andromimetic Peptides



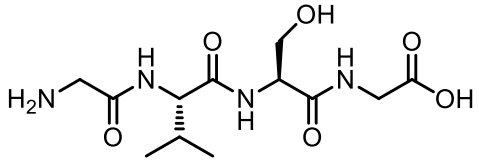
64%, 27.5 mg



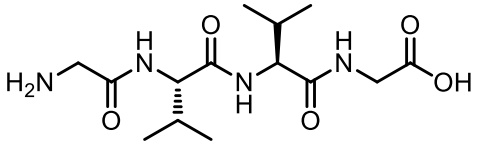
53%, 55.0 mg



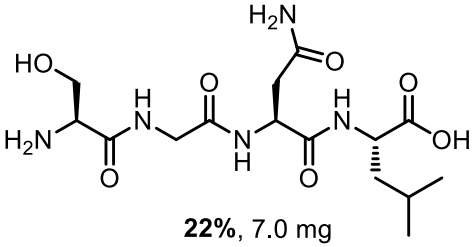
33%, 28.2 mg



60%, 27.4 mg

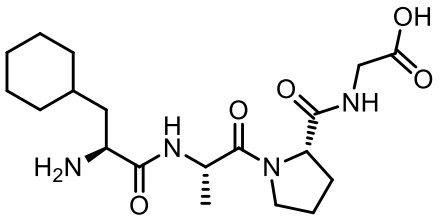


54%, 16.4 mg



22%, 7.0 mg

- All peptides showed activity comparable to bicalutamide
- Activation of osteoblasts
- Synthesis of modified peptides in progress



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Acknowledgement

Urotropin-betaine project:

Prof. Dr. Peter R. Schreiner
Dr. André K. Eckhardt

Peptide project:

Prof. Dr. Georgios Scheiner-Bobis
Marie-Louise Möller
Dr. Viveka Nand Maliya

Synthesis of 2-Deoxy-*C*-Glycosyl α-Amino Acids