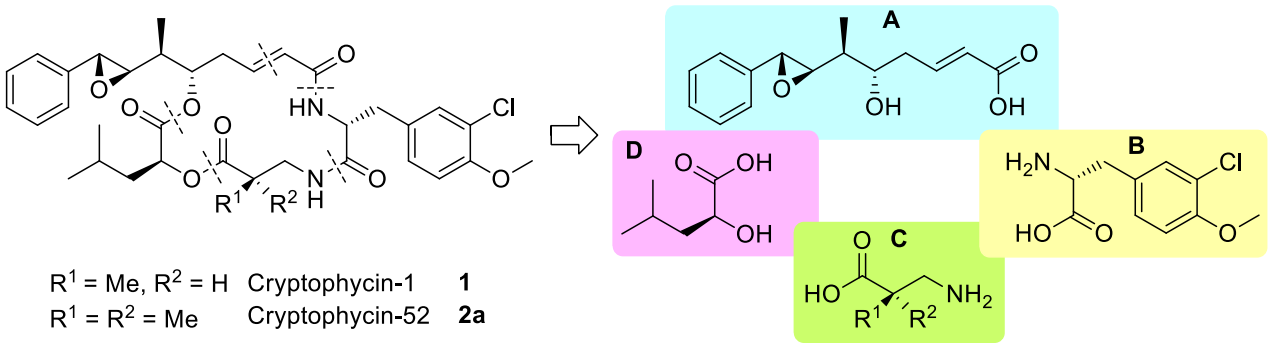
# Cryptophycins and conjugates

Norbert Sewald, Eduard Figueras, Adina N. Borbély, Cedric Dessin, Thomas Schachtsiek

Department of Chemistry, Bielefeld University, PO Box 100131, 33501 Bielefeld, Germany
norbert.sewald@uni-bielefeld.de

Cryptophycins, natural occurring cyclic depsipeptides, show high cytotoxicity against several cancer cell lines, even towards multi-drug resistant (MDR) cancer cell lines [1,2]. The biological activity is based on their ability to interact with tubulin. Strong antiproliferative activities with 100- to 1000-fold potency compared to paclitaxel and vinblastine have been observed. Cryptophycins are highly promising drug candidates, since their biological activity is not compromised by P-glycoprotein, a drug efflux system commonly found in multdrug resistant cancer cell lines and solid tumors [1]. These characteristics made the synthetic analog cryptophycin-52 (LY355703) a promising drug for cancer treatment. However, the clinical trials had to be discontinued because of neurotoxic side effects and lacking efficacy in vivo.




Selectivity issues may be tackled with in a directed therapy approach. The lack of an addressable functional group in cryptophycin-52 hampers the conjugation to a homing device. We developed efficient strategies for the total synthesis of cryptophycins and their analogues. New functionalities have been introduced in different positions for SAR studies and bioconjugation while maintaining the high biological activity. Cryptophycin conjugates with peptide hormones [3] and integrin ligands [4,5] as homing devices have been developed.

[1] C. Weiss, B. Sammet, N. Sewald, *Nat. Prod. Rep.* **2013**, *30*, 924.
[2] C. Weiss, E. Figueras, A.N. Borbely, N. Sewald, *J. Pept. Sci.,* **2017**, 23, 514.
[3] E. Figueras, A. Martins, A. N. Borbély, V. Le Joncour, P. Cordella, R. Perego, D. Modena, P. Pagani, S. Esposito, G. Auciello, M. Frese, et al. Octreotide Conjugates for Tumor Targeting and Imaging. *Pharmaceutics* **2019**, *11*, 220.
[4] M. Nahrwold, C. Weiß, T. Bogner, F. Mertink, J. Conradi, B. Sammet, R. Palmisano, S. R. Gracia, T. Preuße, N. Sewald, *J. Med. Chem.* **2013**, *56*, 1853.
[5] A. N. Borbély, F. Thoreau, E. Figueras, M. Kadri, J.L. Coll, D. Boturyn, N. Sewald. Synthesis and Biological Characterization of Monomeric and Tetrameric RGD-Cryptophycin Conjugates. *Chem. Eur. J.* **2020**, *26*, 2602.