**Chemistry and Biology of Freak Electrophiles and Hybrid Ionophores**

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Molecular outcasts. If such things exist, then prime candidates - at least within the realm of medicinal chemistry - would be electrophiles and ionophores. Typical labels associated with the use of both electrophiles and ionophores in cellular systems are ‘pleiotropic’ and/or ‘unspecific’ and most drug discovery campaigns filter these compounds out if possible. No doubt, electrophilic compounds have been taken to grace in recent years and are finding numerous interesting applications in chemical biology and in drug discovery. Ionophores are still pretty much in bad standing. My lab has taken an interest in structurally unusual protein reactive electrophiles[[1]](#endnote-1),[[2]](#endnote-2),[[3]](#endnote-3),[[4]](#endnote-4),[[5]](#endnote-5) and their applications for protein functionalization or as molecular probes. In my talk, I will discuss mainly unpublished examples from our work on such compounds. Also, I will present our initial efforts[[6]](#endnote-6) to develop strategies to access structural diversity within the class of polyether ionophore antibiotics and discuss how new cellular profiling techniques might be used in the search for compounds with an increased therapeutic potential.

1. Tsakos, M. *et al.* Total Synthesis and Biological Evaluation of Rakicidin A and Discovery of a Simplified Bioactive Analogue. *Angew. Chem. Int. Ed.* **55,** 1030–1035 (2016). [↑](#endnote-ref-1)
2. Villadsen, N. L. *et al.* Synthesis of ent-BE-43547A1 reveals a potent hypoxia-selective anticancer agent and uncovers the biosynthetic origin of the APD-CLD natural products. *Nat. Chem.* **9,** 264–272 (2017). [↑](#endnote-ref-2)
3. Jacobsen, K. M. *et al.* APD-Containing Cyclolipodepsipeptides Target Mitochondrial Function in Hypoxic Cancer Cells. *Cell Chem. Biol.* **25,** 1337–1349.e12 (2018). [↑](#endnote-ref-3)
4. Hansen, B. K. *et al.* STEFs: Activated Vinylogous Protein-Reactive Electrophiles. *Angew. Chem. Int. Ed.* **58,** 3533–3537 (2019). [↑](#endnote-ref-4)
5. Wørmer, G. J., Hansen, B. K., Palmfeldt, J. & Poulsen, T. B. A Cyclopropene Electrophile that Targets Glutathione S-Transferase Omega-1 in Cells. *Angew. Chem. Int. Ed.* **58,** 11918–11922 (2019). [↑](#endnote-ref-5)
6. Lin, S., Liu, H., Svenningsen, E. B., Pedersen, C. N., Nørby, P., Tørring, T. Poulsen, T. B. Diversity Focused Semi-syntheses of Tetronate Polyether Ionophores**,** *ChemRxiv*, (2019), DOI: 10.26434/chemrxiv.8299715.v1 [↑](#endnote-ref-6)