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Arsenic and other Geogenic Contaminants in Groundwater – a Global Challenge

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Groundwater is the main drinking and irrigation water resource in many regions around the world. Natural contamination of groundwater with geogenic contaminants (e.g., arsenic, manganese, fluoride, uranium, thallium) poses a major health threat to hundreds of millions of people worldwide. Especially problematic is arsenic due to its abundance and toxicity. To find solutions to this global challenge, it is essential to not only understand the biogeochemical mechanisms that control the release of geogenic contaminants and their fate in soils and aquifers, but also to predict areas at risk of contamination and to design strategies for water treatment and for minimizing contaminant transfer into the food chain. Our team addresses these challenges by combining fundamental and applied research as well as experimental and modeling approaches, thereby contributing to the mitigation and prevention of public health hazards related to geogenic contaminants.

20 Years of Medicinal Chemistry – Always look at the bright side (of life)

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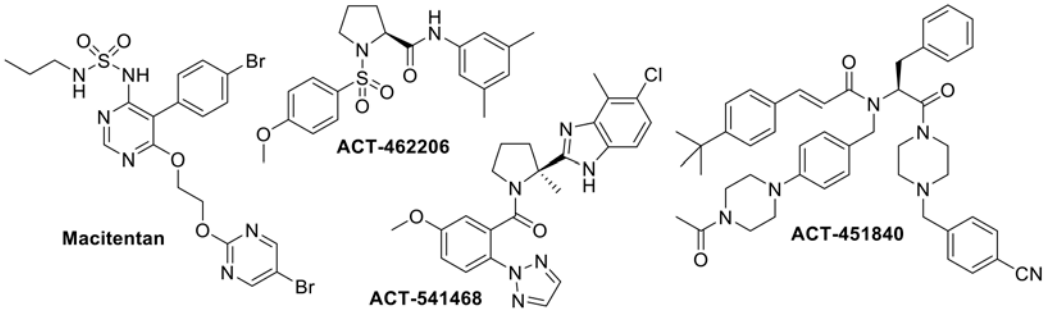
This lecture will summarize a personal perspective of key learnings from projects the author was involved in over the last 20 years, e.g. the discovery of **macitentan**, the most successful molecule to date from this personal collection, marketed by J&J for the treatment of pulmonary arterial hypertension (PAH) [1] or the discovery of **ACT-462206**, a dual orexin receptor antagonist for the treatment of insomnia with the shortest story from the screening hit to the drug [2] or the identification of **ACT-541468**, another dual orexin receptor antagonist in phase 3 clinical trials by Idorsia for the treatment of insomnia disorders [3] (*"Good things come to those who wait"*), and finally the selection of**ACT-451840**, an antimalarial drug with a novel mechanism of action, representing the most collaborative project in the authors experience resulting in a compound in phase 2 clinical development [4].



In addition, there will be a brief discussion on the importance of the screening compound collection, as a key asset for drug discovery, and the measures Idorsia implemented to obtain optimal hits from high-throughput screening (HTS) campaigns [5]. Drug discovery is a multi-disciplinary business with unlimited exciting challenges asking for excessive optimism when tackling them in a playful manner.

[1] M.H. Bolli, C. Boss, C. Binkert, et al; J. Med. Chem, 2012, 55, 7849-7864.
[2] C. Boss, C. Brisbare-Roch, M.A. Steiner, et al; ChemMedChem, 2014, 9, 2486-2496.
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Photochemical Dearomatization of Nonactivated Arenes

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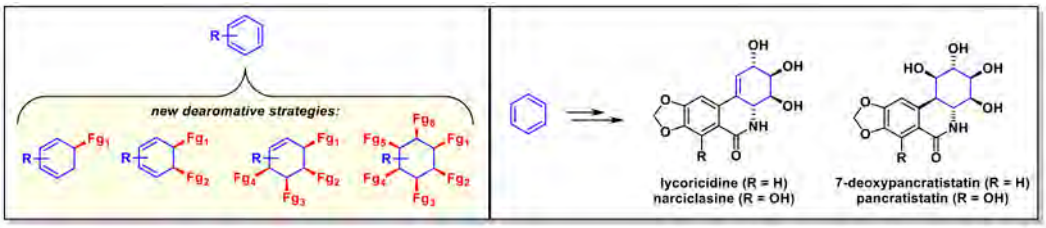
Small, heteroatom-containing complex molecules are highly desired in all areas of chemistry, but they are also often difficult to access. Selective transformations of aromatic compounds could provide a more direct route to such desirable targets; however, the many challenges associated with dearomative functionalization have left these types of reactions widely underdeveloped. Our group has been developing new strategies that bridge the gap between dearomatization and alkene chemistry. In pursuit of this goal, we have established dearomative functionalizations using small molecules–arenophiles. Arenophiles photochemically reacts with arenes in [4+2] fashion, enabling reactions of formally isolated alkenes in aromatic substrates. Thus, well-established olefin reactions, such as dihydroxylation and reduction [1], can now be more directly applied to arenes. Additionally, arenophiles in combination with transition metal catalysis provide unique platform [2, 3] and enable the rapid access to a diverse range of products that are both challenging to synthesize via existing methods and complementary to those acquired through biological or chemical dearomative processes. Finally, using this methodology we have recently completed the synthesis of several complex anticancer natural products, including pancratistatins, lycoricidine, and narciclasine [4, 5].



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[4] E. H. Southgate, D. R. Holycross, D. Sarlah, *Angew. Chem. Int. Ed.*,**2017**,*56*, 15049–15052.
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Alternative solvents: from a compliance-driven activity to a trigger for innovation

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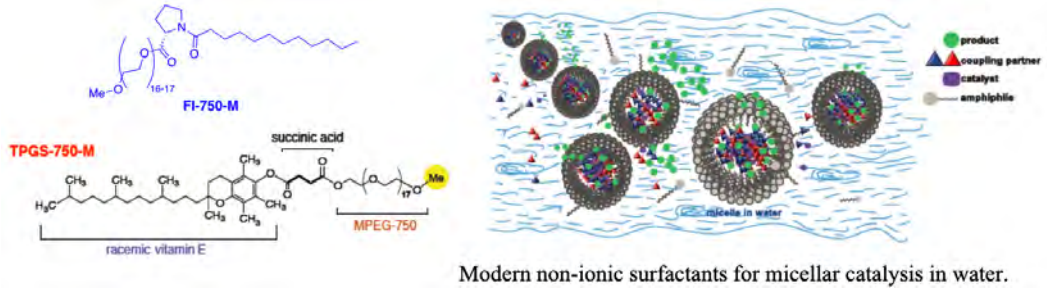
During our evaluation of the potential of surfactant technology in collaboration with Professors Lipshutz and Handa,[1,2,3] we have identified a variety of straightforward and highly advantageous transformationsand applied them successfully on-scale on various chemo and biocatalytic transformations.[4] Implementation of the technology typically results into significant benefits across our entire portfolio, not just from an environmental standpoint but also from an economic and productivity perspective. To name a few: reduction of organic solvent consumption, water use and cycle time, milder reaction conditions, improved yields and selectivities, which all contribute to improved process performance and lower manufacturing costs.[5]



Modern non-ionic surfactants for micellar catalysis in water.

These surfactant mediated reactions can be up-scaled in the already existing multi-purpose facilities of pharmaceutical or chemical organizations, using a catalytic amount of a combination of a non-ionic designer surfactant (*e.g*. TPGS-750-M, FI-750-M) in water, and a well-chosen organic co-solvent instead of traditional and undesirable organic solvents.[6] We now start gaining insight onto the physical phenomena involved and the role of the various components of the system and utilize this know-how to design even better catalytic systems.[7]

[1] See for example: *Science***2015**, *349*, 1087; *Ang. Chem. Int. Ed. **2016**, 55, 8979; Ang. Chem. Int. Ed. **2016**, 55, 4914.*
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