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Molecular capsule catalysis: Ready to address current challenges in synthetic organic chemistry?

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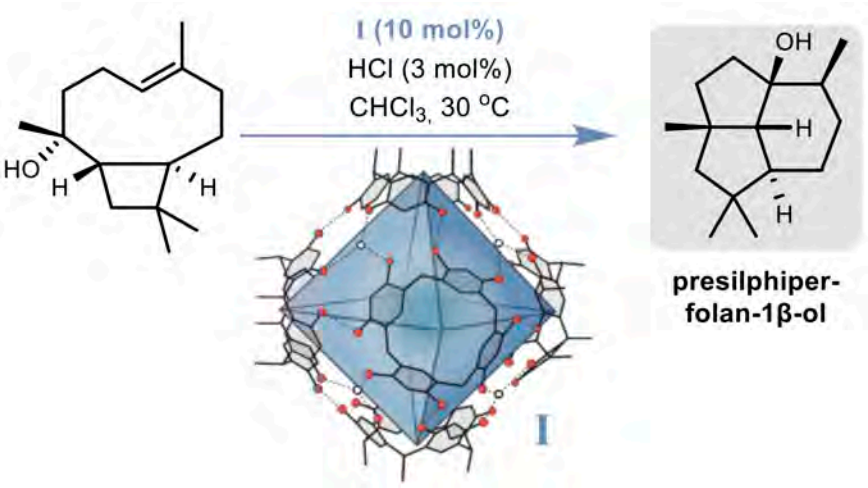
Self-assembled molecular capsules are closed host structures that form spontaneously when their building blocks are mixed in a suitable solvent.[1] As they feature a defined binding pocket suitable for substrate uptake, they are regarded as simple enzyme pocket mimics. Although their potential as catalysts has been explored since their discovery, applications that solve current challenges in synthetic organic chemistry have remained limited.

In this presentation, I will present some of our recently published and unpublished solutions for current synthetic challenges that are difficult to address with alternative tools. For instance, we were able to synthesize the tricyclic sesquiterpene natural product presilphiperfolan-1β-ol in only four steps, with the key cyclization (see below) taking place inside the supramolecular catalyst **I**.[2] This natural product was previously only available via a long synthetic sequence (13 linear steps),[3] demonstrating the potential of molecular capsule catalysis for natural product synthesis. Interestingly, extensive control experiments in solution indicated that the key step is not possible in solution utilizing regular Lewis or Brønsted acid catalysis. Several further examples of catalysis inside capsule **I**, which was reported already more than 20 years ago by the Atwood group,[4] will be presented.



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Development of the Commercial Manufacturing Process for Ipatasertib

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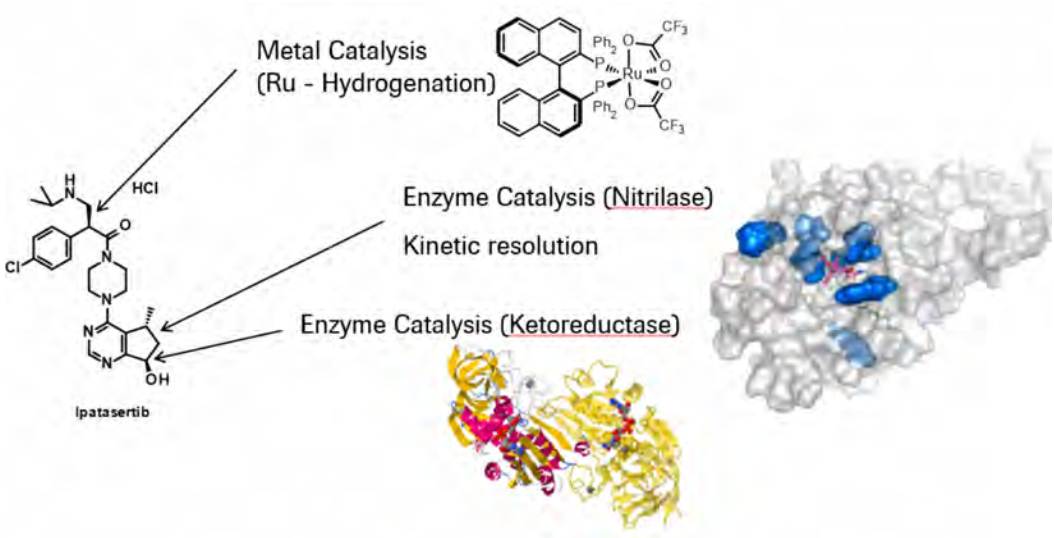
Ipatasertib is a potent small molecule Akt kinase inhibitor currently tested in Phase III clinical trials for the treatment of metastatic castration-resistant prostate cancer and triple negative metastatic breast cancer. In this presentation an overview of the development activities towards the commercial manufacturing process is given. The convergent synthesis comprises ten steps with eight isolated intermediates and utilizes a wide range of chemical techniques and technologies to build this complex drug. All three stereocenters are introduced using enzyme as well as metal catalysis.



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Tailored Catalysis for the F&F Industry

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F&F industry implements a wide variety of fascinating chemical transformations towards the manufacture of prestigious iconic ingredients such as Ambrox® Super, Hedione®, Damascone Delta, Muscenone®, Dartanol®…

Over the past decades, scientists at Firmenich have focused their efforts on continuously improving these chemical transformations in order to make them safer, cleaner, more efficient and consequently more cost effective, through the implementation of green Chemistry principles, more specifically the principle 9 concerning catalysis [1] [2].

Among the F&F companies, Firmenich has always been a pioneer in developing innovative catalytic technologies, often relying on in-house manufactured sophisticated catalysts. Even though the technological edge was clearly demonstrated in the field of homogeneous and heterogeneous catalytic hydrogenations towards the reduction of almost all types of functionalities [3], this presentation will provide a rare insight into the industrial application of highly atom economic Carbon-Carbon bond forming reaction such as Aldol, Michael condensations or C allylation.

Albeit well documented in the traditional literature, these C-C coupling reactions are often particularly unsuitable towards industrialization, due to unreactive substrates, use of large amounts of strong base (alkyl magnesium or metal amides) or use of protective groups and high dilution in toxic solvents. The talk will outline how going industrial in these challenging coupling reactions has resulted in the development of effective catalytic methodologies, now used on multi tons processes at industrial scale. Interestingly, these catalytic methodologies do not require the use of expensive precious metals, but are essentially based on the use of the widely available nonprecious metals of the periodic table such as Titanium, Zirconium, Iron, Nickel, Copper…

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Natural Product Sciences in Modern Drug Discovery and Paths to the Future

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Natural products with their specific structural features deliver chemical starting points in drug discovery to develop innovative therapies for diseases for which no or only unsatisfactory treatments exist. The evolved function of natural products in regulating physiological pathways in nature makes them to a biologically biased and complementary source of chemical probes to decipher novel modes of molecular interactions. As there is a high need for specific modulators of new targets, the access to novel natural product chemotypes and the understanding of their modulatory activities are gaining increasing attraction in today's drug research. The fragmentation of natural products to generate new sp^3-enriched chemicals expands the research toolbox in chemistry and chemical biology. Selected examples will illustrate how new natural products scaffolds and natural products-inspired synthetics are shuttles to a new biological space of therapeutic relevance.

The technological driving forces of Synthetic Biology, genome sequencing and DNA-synthesis, are changing the face of modern natural products research. Whole genome data of microorganisms reveals that encoding genes for natural products biosynthesis pathways, their corresponding resistance factors, and for nearby positioned metabolite pathways can form cooperative functional entities. These "co-localization signatures" prompt the investigation of potential biological synergisms of encoded metabolites or enable natural product-target pair analyses by comparative genomics.

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Discovery of a new medicine Risdiplam, a Survival of Motor Neuron-2 (SMN2) gene splicing modifier for the treatment of Spinal Muscular Atrophy (SMA)

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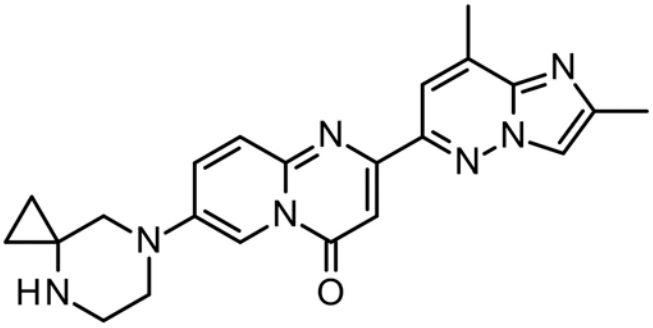
Targeting RNA drastically expand our target space to therapeutically modulate numerous cellular processes implicated in human diseases. Of particular interest, drugging pre-mRNA splicing appears a very viable strategy, to control levels of splicing product by promoting the inclusion or exclusion of exons.[1] The outstanding progress achieved in this field, will be by highlighted by discussing the breakthrough accomplished recently for the treatment of spinal muscular atrophy (SMA).

SMA is an inherited disease that leads to loss of motor function and ambulation, and a reduced life expectancy. We have been working to develop orally-administrated, systemically-distributed small molecules to increase levels of functional SMN protein. Our initial development candidate RG7800 was the first SMN2 gene splicing modifier tested in clinical trials in healthy volunteers and SMA patients.[2] It was safe and well tolerated, and increased SMN protein levels up to 2-fold in patients. Nevertheless, its development was stopped as a precautionary measure because retinal toxicity was observed in cynomolgus monkeys after chronic daily oral dosing (39 weeks), at exposures in large excess of those investigated in patients. Herein, we describe the discovery risdiplam (RG7916, RO7034067) that focused on thorough pharmacology, DMPK and safety characterization and optimization.[3] This compound has demonstrated efficacy and safety for the treatment of patients in all ages and stages with SMA, and is now awaiting FDA approval by August 2020.



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Discovery and Optimization of Enantioselective Catalysts through Chemoinformatics

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The development of synthetic methods in organic chemistry has historically been driven by Edisonian empiricism. Catalyst design is no exception wherein experimentalists attempt to qualitatively recognize patterns in catalyst structures to improve catalyst selectivity and efficiency. However, this approach is hindered by the inherent limitations of the human brain to find patterns in large collections of data, and the lack of quantitative guidelines to aid catalyst selection. Chemoinformatics provides an attractive alternative for several reasons: no mechanistic information is needed; catalyst structures can be characterized by 3D-descriptors which quantify the steric and electronic properties of thousands of candidate molecules; and the suitability of a given catalyst candidate can be quantified by comparing its properties to a computationally derived model on the basis of experimental data. The ability to accurately predict a selective catalyst using a set of non-optimal data remains a Grand Challenge of machine learning with respect to asymmetric catalysis.

This lecture will describe a newly developed, chemoinformatic workflow that consists of the following components: (i) construction of an *in silico* library of a large collection of conceivable, synthetically accessible catalysts of a particular scaffold; (ii) calculation of robust chemical descriptors for each scaffold (iii) selection of a representative subset of the catalysts in this space. This subset is termed the Universal Training Set (UTS), so named because it is agnostic to reaction or mechanism. (iv) Collection of the training data, and (v) application of modern machine learning methods to generate models that predict the enantioselectivity of each member of the *in silico* library. These models are evaluated with an external test set of catalysts. The validated models can then be used to select the optimal catalyst for a given reaction.