



Swiss Science Concentrates

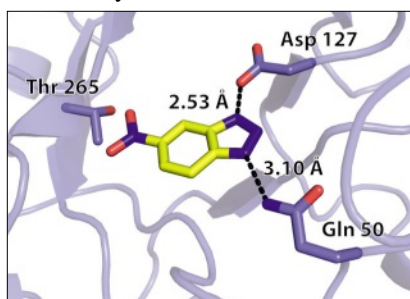
A CHIMIA Column

Short Abstracts of Interesting Recent Publications of Swiss Origin

Precision is Essential for Efficient Catalysis in an Evolved Kemp Eliminate

R. Blomberg, H. Kries, D. M. Pinkas, P. R. E. Mittl, M. G. Grütter, H. K. Privett, S. L. Mayo, D. Hilvert*, *Nature* **2013**, doi:10.1038/nature12623. Caltech (USA) and ETHZ

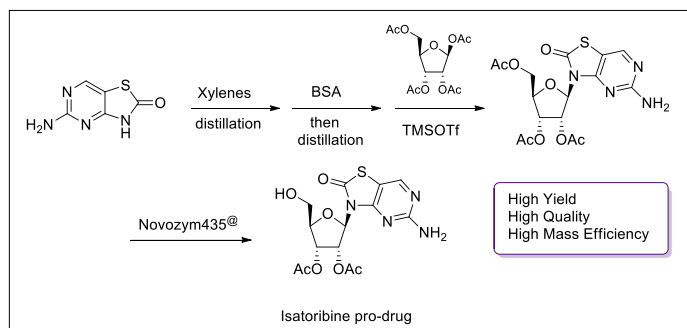
The *ex nihilo* creation of artificial enzymes remains a formidable challenge. Upon combining computational design and directed evolution, Hilvert and coworkers report on a Kemp eliminate that displays an excellent kinetic profile. In the spirit of the Lock-and-Key principle, a host protein was designed to stabilize the transition state of the proton transfer step. However, the resulting enzyme displayed only modest activity. Seventeen rounds of evolution were used to evolve the activity and thermostability, eventually yielding an artificial enzyme that accelerates the reaction more than 10^8 fold with high turnover numbers. In contrast to previous design strategies, including the production of catalytic antibodies, the rates achieved here compare favorably with those of natural enzymes.



Development of a Robust and Sustainable Process for Nucleoside Formation

F. Gallou*, M. Seeger-Weibel, P. Chassagne, *Org. Process Res. Dev.* **2013**, *17*, 390. Novartis Pharma AG, Basel

The process mass intensity (PMI) is a well-accepted indicator of the 'greenness' of a process. Gallou *et al.* developed an improved process to manufacture Isatoribine pro-drug, used in the treatment of chronic hepatitis C. Challenges included the final two steps, due to poor solubility of the precursor and the low throughput and yield. The solubility issues were circumvented by solvent substitution to xylene and distillation of the various side-products generated in the course of the persilylation. Furthermore, a portionwise addition of the components resulted in less by-product formation and a simplified work-up. This led to a four-fold improvement in the PMI. For the final mono deacetylation of the pro-drug, a semibatch set-up over an immobilized enzyme was

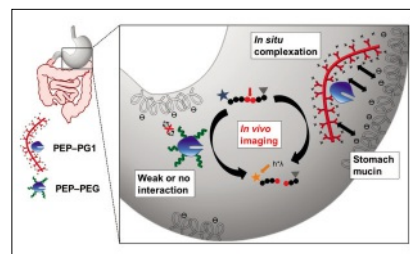


implemented. This increased the throughput, the overall quality of the drug substance and the yield and resulted in a >six-fold increase of the PMI. In conclusion, a practical and robust synthesis of an Isatoribine pro-drug was developed with a significantly improved environmental footprint.

Sustained Gastrointestinal Activity of Dendronized Polymer-Enzyme Conjugates

G. Fuhrmann, A. Grotzky, R. Lukić, S. Matoori, P. Luciani, H. Yu, B. Zhang, P. Walde, A. D. Schlüter, M. A. Gauthier, J. C. Leroux*, *Nat. Chem.* **2013**, *5*, 582. ETHZ

The stabilization and retention of therapeutic proteins for oral administration is rarely investigated due to the inherent difficulties associated with the digestive environment of the gastrointestinal (GI) tract. As a relevant example, proline-specific endopeptidases (PEPs) were conjugated to neutral or charged polymers and administered to rats. Modification of a bacterial PEP with a single poly-cationic dendronized polymer chain led to high retention in the stomach through interaction with mucin. The conjugate showed little or no loss of activity within 3 h. In contrast, the enzyme modified with multiple methoxy poly(ethylene glycol) chains showed little mucoadhesion and was active in the small intestine. This work highlights that functional polymer modification enables improvement and control of oral enzyme activity in the GI tract.



Specific Chemical Reactivities of Spatially Separated 3-Aminophenol Conformers with Cold Ca⁺ Ions

Y-P. Chang, K. Długołęcki, J. Küpper*, D. Rösch, D. Wild, S. Willitsch*, *Science* **2013**, *342*, 98. University of Basel, CFEL, DESY and University of Hamburg

The study of the reactivity of conformers is very challenging as rotational isomers typically rapidly interconvert. Küpper, Willitsch and coworkers developed a new method to probe the reactivities of individual structural isomers. 3-Aminophenol exhibits two conformers (rotational isomers) with different dipole moments. These were separated by an inhomogeneous electrostatic field. The reactivity of both conformers towards laser-cooled Ca⁺ ions was then investigated. The *cis*-conformer, which possesses the larger dipole moment, was shown to react fastest with the cation. This proof-of-principle method can be applied to more complex chemical reactions, thus allowing reaction mechanisms to be scrutinized with unprecedented precision.

