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Swiss Science Concentrates

A CHIMIA Column

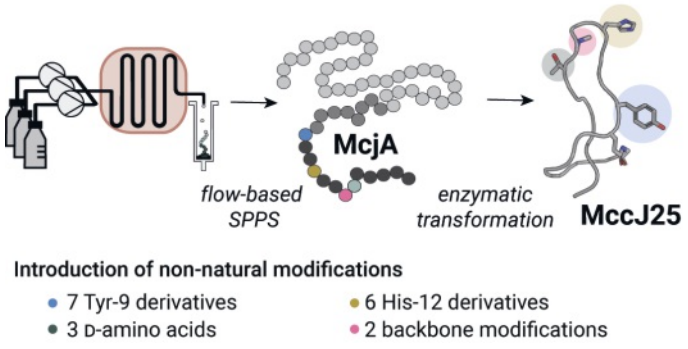
Short Abstracts of Interesting Recent Publications of Swiss Origin

Merging Flow Synthesis and Enzymatic Maturation to Expand the Chemical Space of Lasso Peptides

Kevin Schiefelbein, Jakob Lang, Matthias Schuster, Claire E. Grigglestone, Robin Striga, Laurent Bigler, Meredith C. Schuman, Oliver Zerbe, Yanyan Li, and Nina Hartrampf*
J. Am. Chem. Soc. **2024**, *146*, 17261.
https://doi.org/10.1021/jacs.4c03898
University of Zurich

Peptides are commonly thought of as biopolymers with a simple linear sequential structure. However, nature also produces intricately constrained structures such as cyclic peptides, cyclotides, and lasso peptides. Chemical methods for the synthesis of both linear and cyclic constructs are generally considered robust and well-established, but synthetic access to knot-like lasso peptides remains elusive. Here, the authors disclose a hybrid approach consisting of flow-based chemical synthesis of precursor peptides followed by *in vitro* enzymatic maturation to produce a diverse range of lasso peptides. To achieve this, reproducible access to the lasso maturation enzymes McjB and McjC was first established. Using this workflow, single-point mutations such as non-canonical tyrosine and histidine derivatives, as well as three simultaneous D-amino acids and backbone modifications could be introduced. This method gives access to chemically modified lasso peptides for applications in the investigation of structure-activity relationships, epitope grafting, or improvements of therapeutic properties.

Authors' comments:
"Lasso peptides are attractive scaffolds for therapeutic applications. We hope that our chemoenzymatic approach, which enables the synthesis of backbone- and sidechain-modified derivatives, will help to unlock their potential."

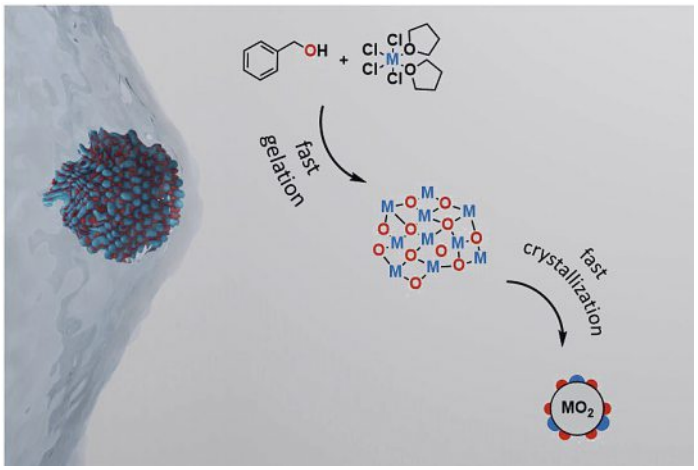


From Gel to Crystal: Mechanism of HfO_2 and ZrO_2 Nanocrystal Synthesis in Benzyl Alcohol

Eline Goossens[a,b], Olivia Aalling-Frederiksen[c], Pieter Tack[a], Dietger Van den Eynden[a,b], Zarah Walsh-Korb[b], Kirsten M. Ø. Jensen[c], Klaartje De Buysser[a], and Jonathan De Roo[*b]
J. Am. Chem. Soc. **2024**, *146*, 10723.
https://doi.org/10.1021/jacs.4c00678
[a]Department of Chemistry, Ghent University, Belgium; [b]Department of Chemistry, University of Basel, Switzerland; [c]Department of Chemistry, University of Copenhagen, Denmark

The authors used nonaqueous sol-gel synthesis to produce hafnium and zirconium oxide nanocrystals from metal chlorides in benzyl alcohol. The current paradigm is that these reactions have slow kinetics, which favor the thermodynamic product. In this study, the transformation of the precursor into nanocrystals was investigated using rheology, EXAFS, NMR, TEM, and X-ray total scattering (PDF analysis). Upon dissolution of the metal chloride starting material, benzyl alcohol displaced the halides and formed HCl as a side product, which then catalyzed benzyl alcohol etherification. The reaction mixture was heated up to 220 °C, which released enough water to form a macroscopic gel. The first crystalline particles appeared within a few minutes, while the nucleation and growth were completed after 30 minutes. The findings challenge the paradigm that nonaqueous sol-gel synthesis directly yields crystalline products without an amorphous intermediate.

Authors' comments:
"While nanocrystals are widespread, their crystallization mechanism is still under debate. Our new insights question the existing theories of nucleation and growth and with this work we thus hope to initiate a discussion among chemists."



Prepared by Cesare Berton, Patrick A. Cieslik, Eda Nisli, Fan Liu, Stanislav Prytuliak, Simon Klinger, Jonas Genz, Dominik Roth, Samy Kichou, Perle Hermant, Ben Boback, and Jason P. Holland*
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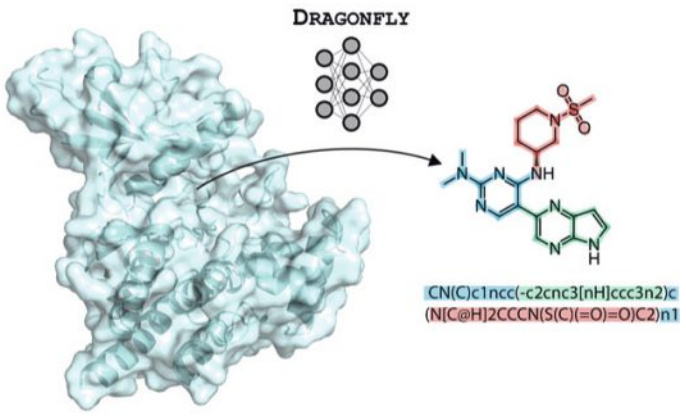
Please contact jason.holland@chem.uzh.ch

Prospective *de novo* Drug Design with Deep Interactome Learning

Kenneth Atz, Leandro Cotos, Clemens Isert, Maria Håkansson, Dorota Focht, Mattis Hilleke, David F. Nippa, Michael Iff, Jann Ledergerber, Carl C. G. Schiebroek, Valentina Romeo, Jan A. Hiss, Daniel Merk, Petra Schneider, Bernd Kuhn, Uwe Grether and Gisbert Schneider
Nat. Comm. **2024**, *15*, 3408.
https://doi.org/10.1038/s41467-024-47613-w
ETH Zurich, Roche, and SARomics

This article explores a novel computational method called DRAGONFLY for designing drug-like molecules from scratch. Unlike traditional approaches that consider potential ligands as isolated molecules, the underlying deep learning model leverages interactome data–a network of interactions between ligands and their macromolecular targets. This approach facilitates the generation of bespoke ligands by starting from a 3D structural model of the target protein. DRAGONFLY combines graph neural networks and chemical language models, enabling the 'zero-shot' construction of compound libraries tailored for specific properties, bioactivity, and synthesizability, without the need for transfer or reinforcement learning. The researchers tested their software by designing molecules to activate the protein PPAR gamma, which is involved in human metabolism. Selected molecules were synthesized successfully and demonstrated desired activity and selectivity on PPAR family proteins, showcasing DRAGONFLY's potential for drug discovery. Overall, this article presents a promising new approach for *de novo* drug design that could lead to more effective and selective drugs.

Authors' comments:
"*De novo* drug design generates molecules with specific properties. Deep interactome learning enables 'zero-shot' construction of bioactive, synthesizable ligands based solely on the drug target's 3D structure."



Light in a Heartbeat: Bond Scission by a Single Photon above 800 nm

Marina Russo, Hana Janekovà, Deobra Meier, Melanie Generali, and Peter Štacko*
J. Am. Chem. Soc. **2024**, *146*, 8417,
https://doi.org/10.1021/jacs.3c14197
University of Zurich

Photocages offer precise control over molecular activity through light, ideal for photoactivated therapies. Effective use in the near-infrared (NIR) window, however, remains a challenge. This study introduces synthetically accessible cyanine photocages that release alcohol, phenol, amine, and thiol payloads upon NIR light irradiation up to 820 nm in water. These photocages exhibit unique chameleon-like behavior, operating *via* two distinct uncaging mechanisms: photooxidation and heterolytic bond cleavage. Notably, the latter represents the first instance of direct bond scission by a single photon in cyanine dyes or wavelengths beyond 800 nm. Demonstrating their potential, these photocages enabled modulation of human cardiomyocytes' beating rates by releasing adrenergic agonist etilefrine at sub micromolar concentrations and low NIR light doses (~12 J cm^{-2}). This highlights their promising applications in biology and medicine, providing a significant advancement in the field of light-activated molecular control.

Authors' comments:
"Photocages present exciting opportunities to seize control over molecular processes and activities using light, but achieving this with tissue-penetrating light has been notoriously difficult. We are thrilled to lay the groundwork for enabling the adoption of this technology in biological and medical fields, and ultimately industry."