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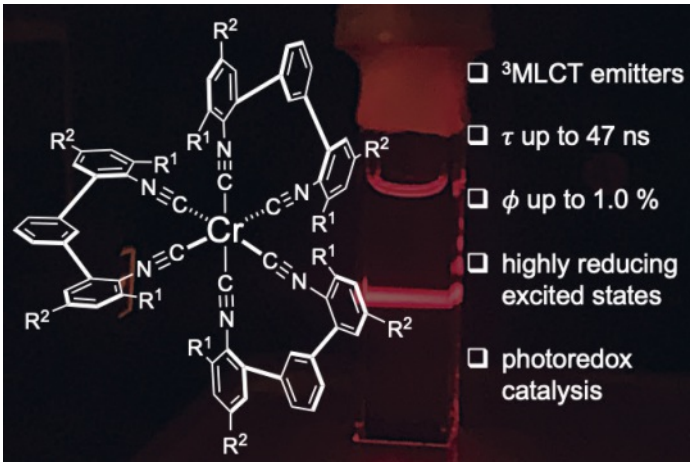
Short Abstracts of Interesting Recent Publications of Swiss Origin

Photoredox-active Cr(0) luminophores featuring photophysical properties competitive with Ru(II) and Os(II) complexes

Narayan Sinha, Christina Wegeberg, Daniel Häussinger, Alessandro Prescimone, and Oliver S. Wenger*, *Nat. Chem.* **2023**
https://doi.org/10.1038/s41557-023-01297-9
University of Basel

Coordination complexes featuring precious metals with the d^6 valence electron configuration, such as Ru(II), Os(II), and Ir(III), find applications in lighting, solar energy conversion, and photocatalysis. Until now, the creation of d^6 complexes using more readily available first-row transition metals with competitive photophysical and photochemical properties has proven challenging. While previous research predominantly focused on Fe(II), the authors present evidence that the isoelectronic Cr(0) offers enhanced photoluminescence quantum yields and longer excited-state lifetimes compared with other first-row d^6 metal complexes reported thus far. The luminescent properties of the metal-to-ligand charge transfer excited states in these Cr(0) complexes rival those of Os(II) polypyridines. These Cr(0) complexes enable the exploitation of metal-to-ligand charge transfer states in first-row d^6 metal complexes for photoredox catalysis, facilitating efficient chemical reductions under low-energy red illumination. Their findings demonstrate that strategic molecular design opens up new avenues for exploring photophysics and photochemistry using abundant first-row d^6 metals.

Authors' comments:
"Research in this field traditionally focuses on iron(II). Our work suggests that isoelectronic alternatives such as chromium(0), manganese(I), and cobalt(III) would perhaps deserve more attention."



Peptide-Hypervalent Iodine Reagent Chimeras: Enabling Peptide Functionalization and Macrocyclization

Xing-Yu Liu, Xinjian Ji, Christian Heinis, and Jerome Waser*
Angew. Chem. Int. Ed. **2023**, *62*, e202306036
https://doi.org/10.1002/anie.202306036
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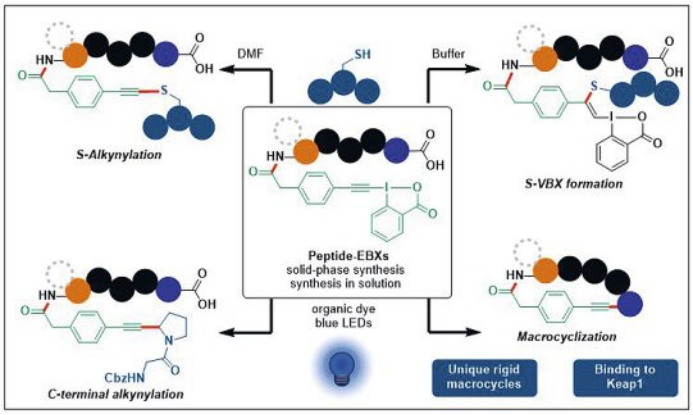
This work presents a novel method involving the use of highly reactive hypervalent iodine reagents called ethynyl-benziodoxolones (EBXs) for modifying peptides. These modified peptide-EBXs compounds can be easily synthesized through both solution- and solid-phase peptide synthesis (SPPS). They facilitate the coupling of peptides to other peptides or proteins by reacting with cysteine residues, resulting in thioalkynes in organic solvents and hypervalent iodine adducts in water buffer. Additionally, a photocatalytic decarboxylative coupling technique is introduced for attaching peptides to their C-terminus, even in an intramolecular fashion, to create macrocyclic peptides with unique crosslinking properties. The authors also investigated the possibility of using the obtained macrocyclic peptides as Keap1-Nrf2 protein-protein interactions (PPIs) inhibitors, which have a critical role in biological pathways connected to inflammation and neurodegenerative diseases. The inclusion of a rigid linear aryl alkyne linker is crucial for achieving a high affinity for Keap1 at the Nrf2 binding site.

Authors' comments:
"We expanded the toolbox of peptide modifications by installing EBX reagents onto peptides, which react with thiols or via photocatalytic decarboxylation. We are happy to send reagents on demand!"



Prepared by Cesare Berton, Patrick A. Cieslik, Fan Liu, Eda Nisli, Stanislav Prytuliak, Simon Klinger, Jonas Genz, Samy Kichou, Dominik Roth, and Jason P. Holland*

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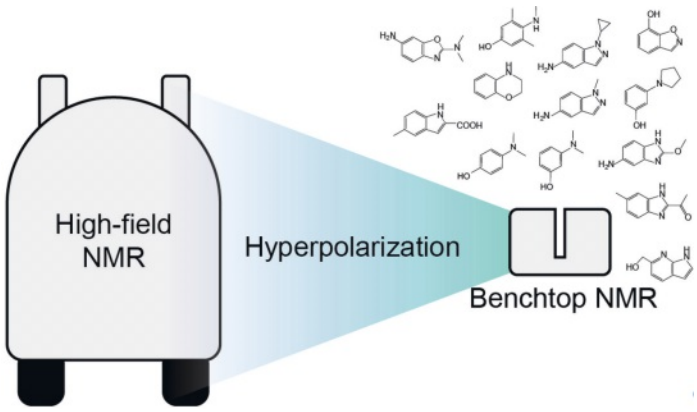
Fragment Screening and Fast Micromolar Detection on a Benchtop NMR Spectrometer Boosted by Photo-induced Hyperpolarization

Gabriela R. Stadler[a], Takuya F. Segawa[a], Matthias Bütikofer[a], Venita Decker[b], Sandra Loss[b], Barbara Czarniecki[b], Felix Torres*[ad], and Roland Riek*[a]
Angew. Chem. Int. Ed. **2023**, e202308692
https://doi.org/10.1002/anie.202308692
[a]ETH Zürich; [b]Bruker BioSpin GmbH; [c]Bruker Switzerland AG; [d]NexMR AG

Fragment-based drug design is a cornerstone of pharmaceutical research, traditionally relying on high-field nuclear magnetic resonance (NMR) spectrometers for screening and validation. However, these machines are costly, require specialized maintenance, dedicated facilities, and rely on liquid helium cooling which is susceptible to economic pressures and global shortages. An innovative alternative approach employs fragment screening *via* photoinduced hyperpolarized NMR on an 80 MHz benchtop NMR spectrometer, eliminating cryogenic needs. This method offers significant signal amplification, sometimes exceeding three orders of magnitude. It accelerates screening compared to conventional high-field NMR, achieving a nanomolar-level detection limit. This method aligns with benchtop NMR's cost-effectiveness and simplicity, promising a new era in drug design and broader life science applications. Experiments confirmed the feasibility of using this benchtop NMR for discovering drug candidates using only micromolar concentrations of both the target protein and ligand. This approach enhances accessibility and efficiency in pharmaceutical research, opening doors to broader applications in near-physiological conditions.

Authors' comments:
"Benchtop NMR as a screening tool will bring the agility and orthogonality that are so critical to fragment-based drug discovery platforms. We hope to see this method widely adopted across the molecular biology field."



Development of a New Class of CXCR4-Targeting Radioligands Based on the Endogenous Antagonist EPI-X4 for Oncological Applications

Raghuvir Haridas Gaonkar, Yannik Tim Schmidt, Rosalba Mansi, Yasser Almeida-Hernandez, Elsa Sanchez-Garcia, Mirja Harms, Jan Münch, and Melpomeni Fani*
J. Med. Chem. **2023**, *66*, 13, 8484–8497
https://doi.org/10.1021/acs.jmedchem.3c00131
University Hospital Basel

C-X-C Chemokine Receptor 4 (CXCR4) is an important target for radiotheranostics, as it is overexpressed by cells of numerous cancer types. Various peptide inhibitors of CXCR4 were developed in the past. The authors identified the first endogenous peptide antagonist of CXCR4, termed EPI-X4, derived from human serum albumin. However, its low metabolic stability drove them to develop a series of truncated ^{177}Lu-radiolabeled EPI-X4 derivatives and explored their suitability for peptide receptor imaging and therapeutic applications. Initial studies showed that one derivative possesses favorable CXCR4 binding and is suitable for further optimization.

Authors' comments:
"The discovery paves the way for the development of new effective diagnosis and treatment in nuclear oncology *via* CXCR4 targeting."