UNIVERSITÄT LEIPZIG

Institute of Organic Chemistry
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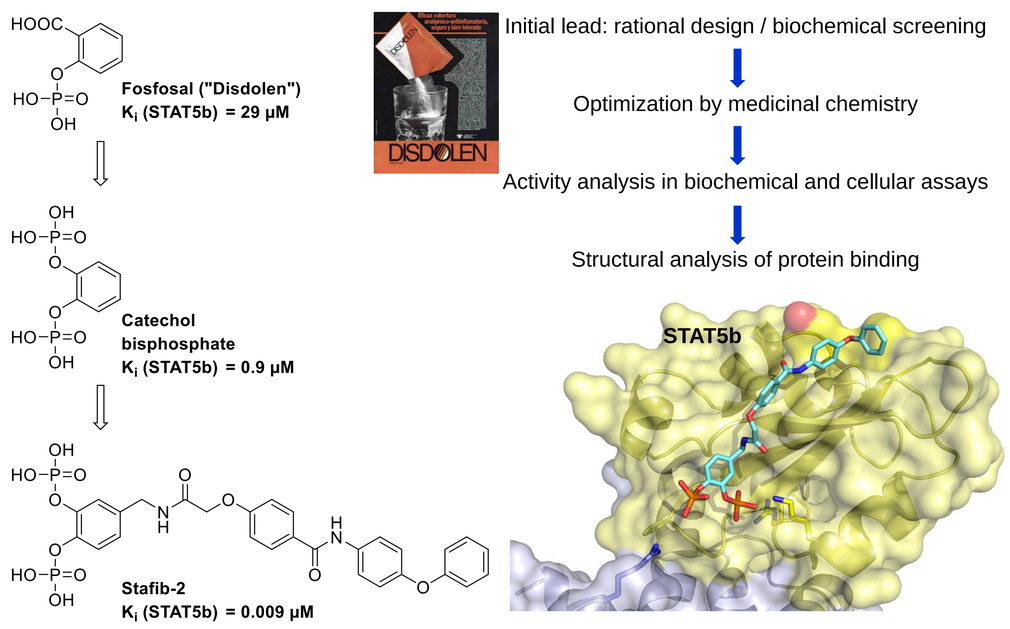
Chemical Biology

Small-molecule inhibitors of protein-protein interactions

Current small-molecule drugs target only 10-15 % of the human proteome. The remaining 85-90 % of human proteins are commonly considered to be “undruggable”. A powerful approach by which to expand the proportion of human proteins as potential targets for drug development is the modulation of protein-protein interactions using small organic molecules. The focus of our research is to develop innovative methods for the efficient design of small organic inhibitors of protein-protein interactions. These methods are used to guide the synthesis and functional characterization of highly potent inhibitors of pre-selected protein-protein interactions. The resulting small organic molecules can be used as chemical probes to investigate biological questions, and may serve as lead structures for drug development. Using an interdisciplinary combination of chemical and biological methods, our current research includes the following topics:

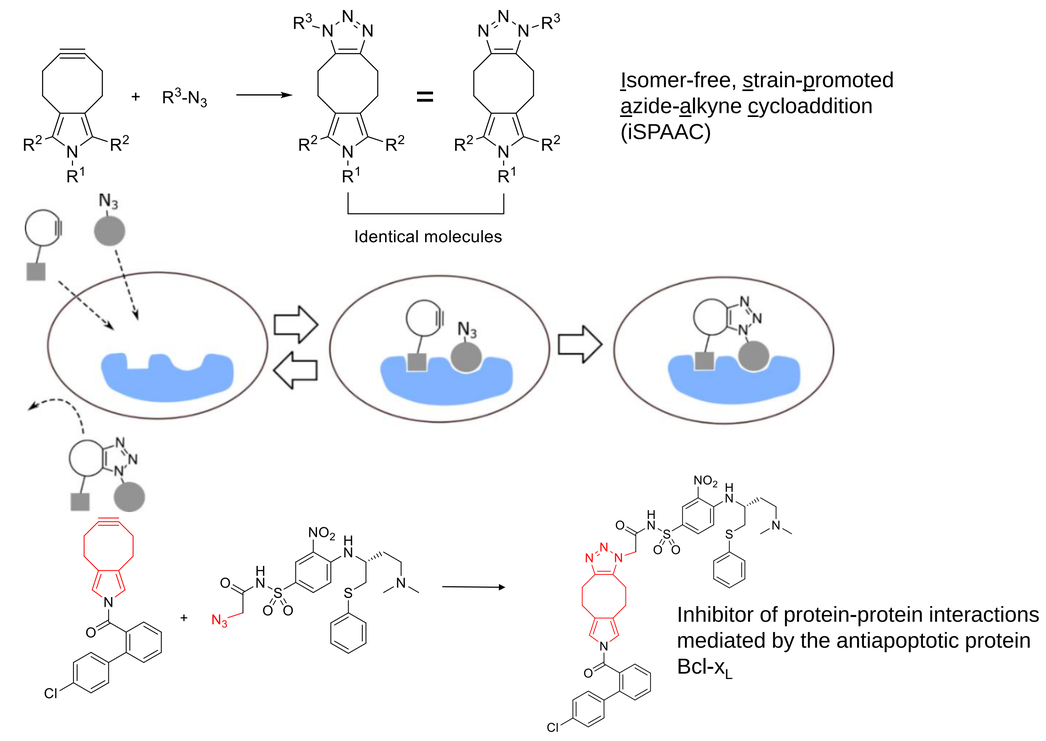
Inhibitors of phosphorylation-dependent protein-protein interactions

We have developed a novel design concept for inhibitors of phosphorylation-dependent protein-protein interaction domains based on *O*-phosphorylation of suitable precursor molecules.[1] Application of this concept facilitated the development of catechol bisphosphates as the first chemical entities that inhibit the tumor-relevant transcription factor STAT5b with high selectivity over the highly homologous family member STAT5a, with activities in the nanomolar concentration range.[2-4] We also developed *m*-terphenyl phosphates as the first small molecules which inhibit STAT5a with selectivity over STAT5b.[5] Comparative analysis of point mutant proteins and wild-type proteins allowed us to understand the molecular origin of the unprecedented selectivity and led to a deeper understanding of STAT5 biology.[6]



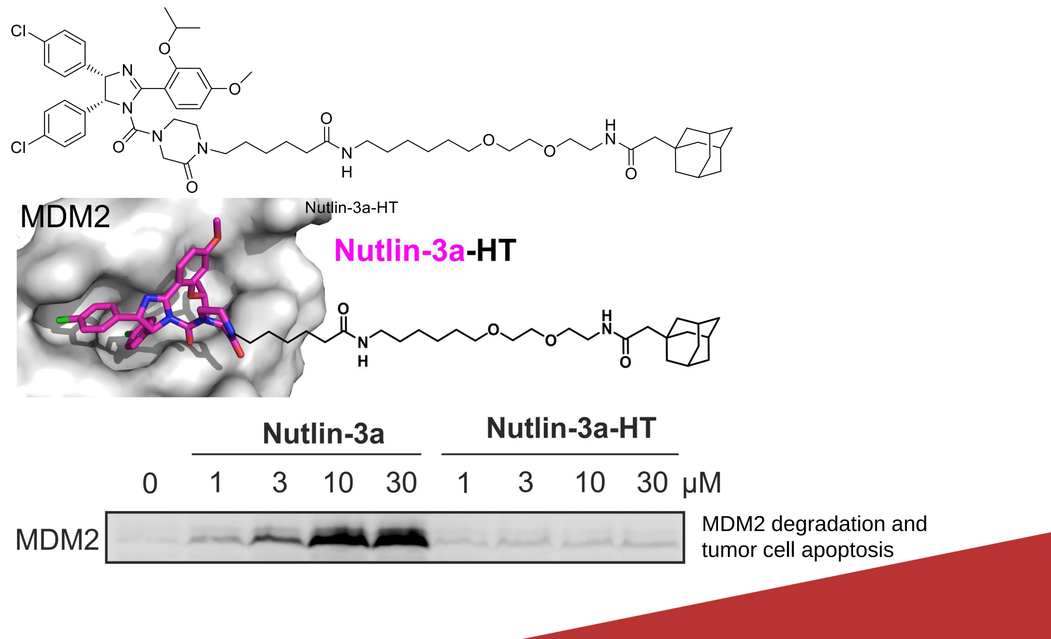
Intracellular synthesis of large bioactive compounds via isomer-free strain-promoted azide-alkyne cycloaddition (iSPAAC)

High-affinity inhibitors of large protein-protein interactions often have a high molecular weight, compromising cell permeability and oral bioavailability. We developed isomer-free, strain-promoted azide-alkyne cycloaddition (iSPAAC) as a method by which to generate large, chemically uniform bioactive molecules inside living cells from two smaller, and thus more cell-permeable, components. Key to the development of iSPAAC was the design and synthesis of the symmetrically substituted pyrrolocyclooctynes PYRROC,[7] SYPCO,[8] and TRIPCO,[9] and the azacyclononyne Fmoc-ACN.[10] The SYPCO study provided the first demonstration that bioactive molecules can be formed by iSPAAC, both in vitro and in living cells.[8] We see iSPAAC as a broadly applicable method for generating large bioactive molecules directed against intracellular targets inside living cells from smaller, more cell-permeable building blocks.



Protein degradation-inducing inhibitors of protein-protein interactions

Most inhibitors cause functional inhibition of their protein targets via reversible binding. Stronger and longer-lasting effects can be achieved by molecules that not only bind, but also induce the degradation of their target proteins. This can be achieved by fusing a ligand of the target protein with a hydrophobic tag, which the cellular machinery erroneously recognizes as an incorrectly folded protein. We fused Poloxin-2, an inhibitor of the protein-protein interaction domain of the kinase Plk1, to a hydrophobic tag. The fusion molecule Poloxin-2-HT induced degradation of Plk1 and apoptosis in cultured human tumor cells.[11] By fusing Nutlin-3a, an inhibitor of the protein-protein interaction between the tumor target MDM2 and the tumor suppressor p53, with a hydrophobic tag, we were able to induce degradation of MDM2 and induce apoptosis in cultured human tumor cells.[12] These data validate hydrophobic tagging of existing inhibitors of protein-protein interactions as a novel strategy for targeting and degrading disease-related proteins.



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