Jetze J. Tepe

Synthetic and Medicinal Chemistry

Associate Professor

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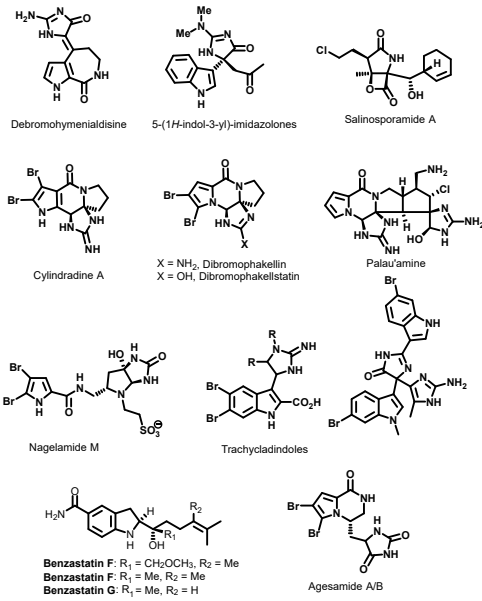
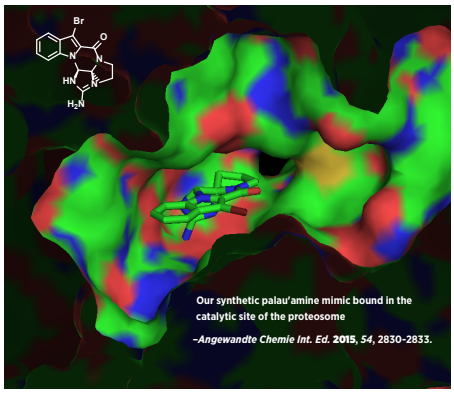
Our research program provides an interdisciplinary blend of synthetic and medicinal chemistry that includes the total synthesis of natural products, the discovery of new reactions, as well as the evaluation for their cellular mechanism and medicinal properties.

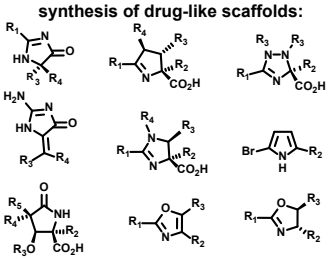
Natural product synthesis: Natural products are still the primary source for medicines, and marine sponge metabolites represent a highly diverse and complex class of natural products with remarkable biological activities. Members of our lab will develop new heterocyclic methodologies to efficiently access these natural products.[1,4,5] Cellular studies in our lab will subsequently be performed to identify the biological target responsible for the exciting biological properties these compounds elicit.[2,6,7]



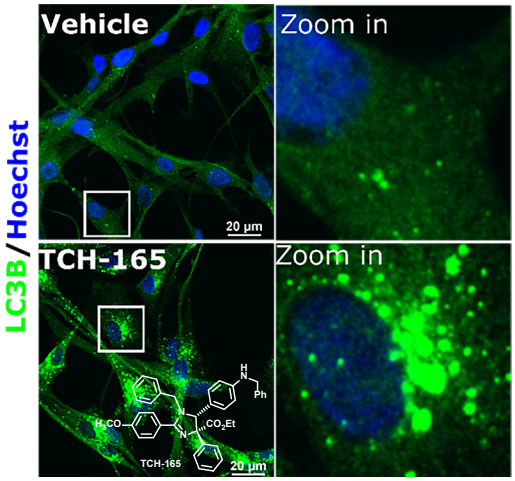


Medicinal chemistry: Our medicinal chemistry program is aimed at the development of more drug-like scaffolds containing a skeletal diversity inspired by natural products. One of our biological targets includes the human proteasome.

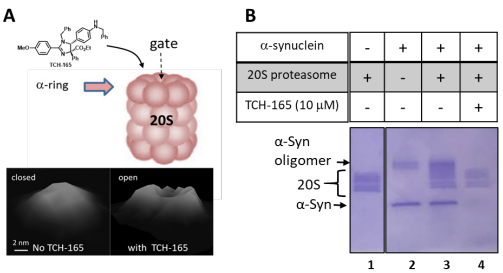
Development of new reactions for the synthesis of drug-like scaffolds:



Cancer research: Inhibition of the proteasome is clinically validated for the treatment of multiple myeloma, however nearly all patients relapse after some time. Our natural product-inspired scaffolds elicit a unique mechanism of inhibition of this large protease that overcomes resistance to current cancer therapies.[2, 6]



Alzheimer's and related research: In Alzheimer's disease and related dementias, amyloid oligomers inhibit the activity of the proteasome, resulting in the accumulation, oligomerization and aggregation of disordered proteins such as Aβ, tau and α-synuclein.[3] Our research team is exploring the use of small heterocyclic scaffolds to activate a specific sub-complex of the proteasome, the 20S proteasome, to treat these neurodegenerative diseases.[7]



TCH-165 opens the gate of the 20S proteasome and enhances α-synuclein degradation. A. AFM images of 20S α-ring showing TCH-165 opening the gate of the 20S, rendering an activated 20S proteasome. B. Coomassie stain of TCH-165 enhanced degradation of α-syn (and oligomers) by the 20S in vitro.

Selected Publications

1. *Regulation of Autophagic Flux by the 20S proteasome. Cell*, Njomen, Evert and Tepe, Jetze, *Cell Chemical Biology* **2019**, *in print, CCBIO3321.*
2. *Proteasome activation as a new therapeutic approach to target proteotoxic disorders*, Njomen, Evert and Tepe, Jetze J., *J. Med. Chem.* **2019**, in print, DOI:10.1021/ acs.jmedchem.9b00101.
3. *Diastereoselective one-pot synthesis of oxazolines using sulfur ylides and acyl imines*, Mehedi, Md Shafaat Al and Tepe, Jetze J., *J. Organic Chemistry* **2019**, *84*, 7219-7226.
4. *Pipecolic esters as new templates for proteasome inhibition*, Giletto, Matthew B; Osmulski, Pawel A.; Jones, Corey L.; Gaczynska Marie E. and Tepe, Jetze J., *Org. & Biomol. Chem.* **2019**, *17*, 2734-2746.
5. *Substrate Controlled Regioselective Bromination of 2-Acyl Pyrroles Using Tetrabutyl Ammonium Tribromide (TBABr$_3$)*, Gao, Shuang, Bethel, Travis K. Kakeshpour T.; Hubbell, Grace E., Jackson, James, E. and Tepe, Jetze J., *J. Org. Chem.* **2018**, *83*, 9250-9255. PMID: 29969032
6. *Small Molecule Modulation of Proteasome Assembly*, Njomen, Evert; Osmulski, Pawel A.; Jones, Corey L; Lansdell, Theresa A. Gaczynska, Maria E. and Tepe, Jetze J., *Biochem.* **2018**, *57*, 4214-4224. PMID: 29897236
7. *Small molecule enhancement of 20S proteasome activity targets intrinsically disordered proteins*, Jones, Corey L.; Njomen, Evert; Sjogren B.; Dexheimer, Thomas S. and Tepe, Jetze J. *ACS Chem. Biol.* **2017**, *15;12(9)*, 2240-2247. PMID: 28719185.