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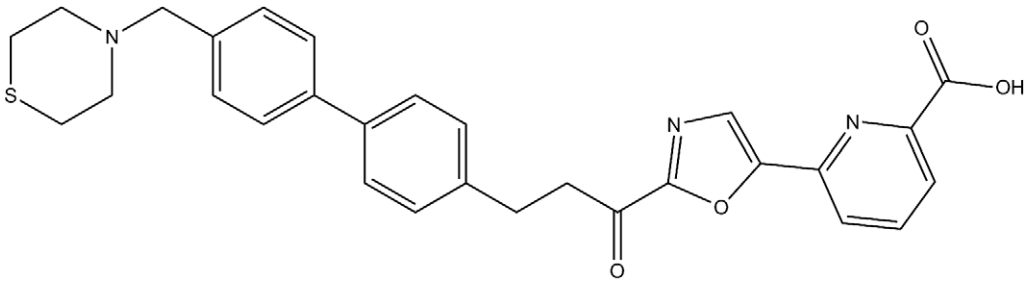
Symposium-in-Print

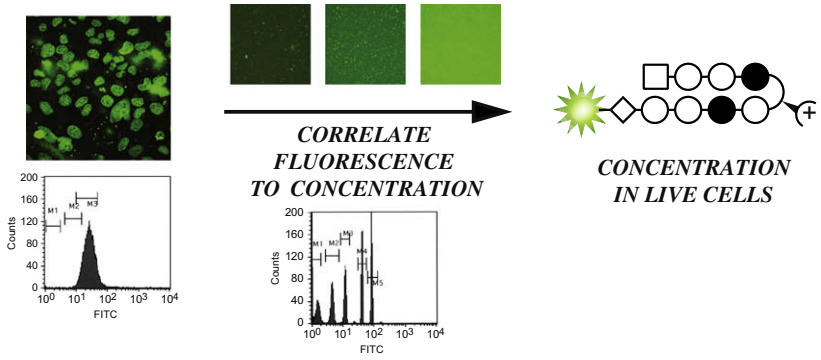
Tetrahedron Young Investigator Award 2008

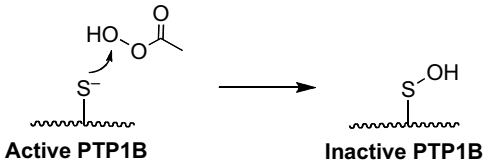
Benjamin F. Cravatt

Edited by: Dale L. Boger

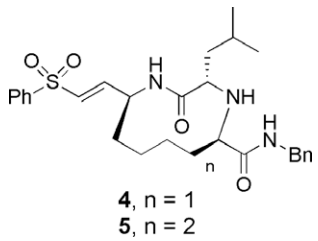
Contents



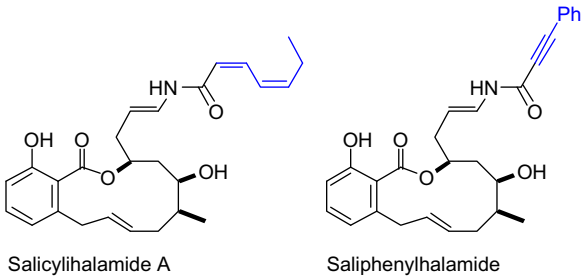


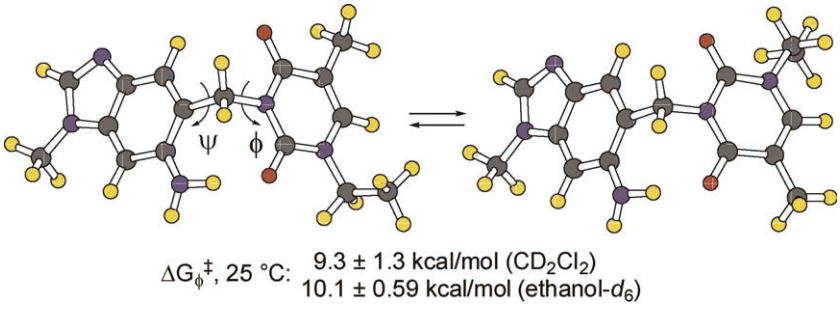


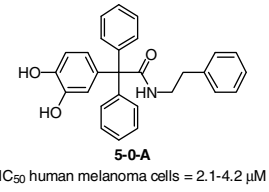
Protein tyrosine phosphatases (PTPs) are cysteine-dependent enzymes that play a central role in cell signaling. Organic hydroperoxides cause thiol-reversible, oxidative inactivation of PTP1B in a manner that mirrors the endogenous signaling agent hydrogen peroxide.



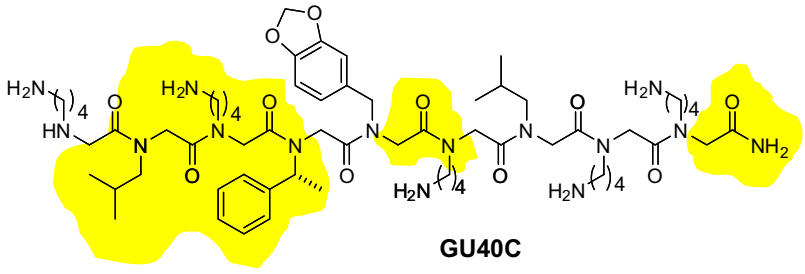
4, n = 1
5, n = 2

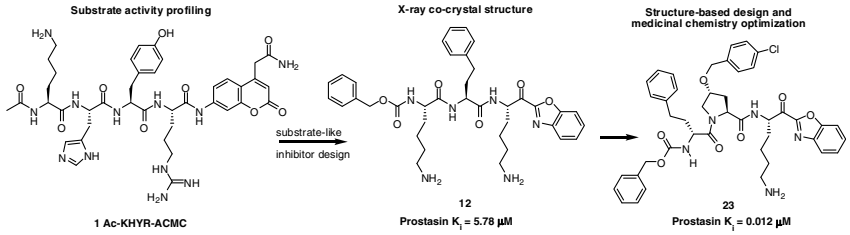




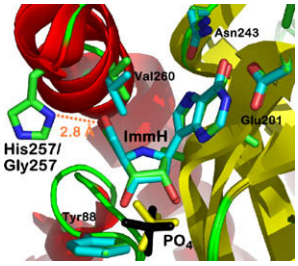


The optimization of triphenylmethylamides (TPMAs) as anticancer agents is reported.



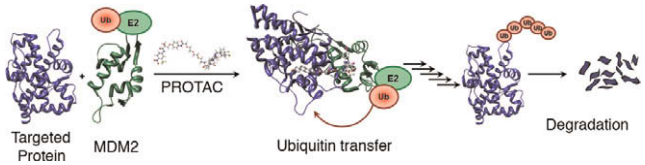


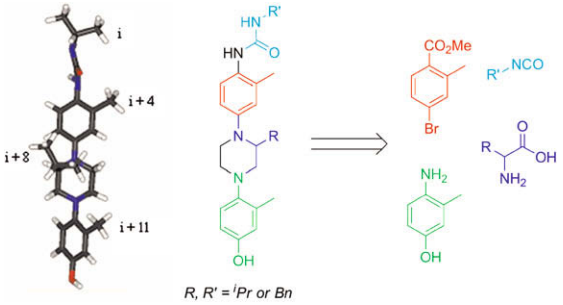
Structure-based design was utilized to guide the early stage optimization of a substrate-like inhibitor to afford potent peptidomimetic inhibitors of the channel-activating protease prostasin. The first X-ray structure of a small molecule inhibitor bound to the active site of prostasin is also reported.

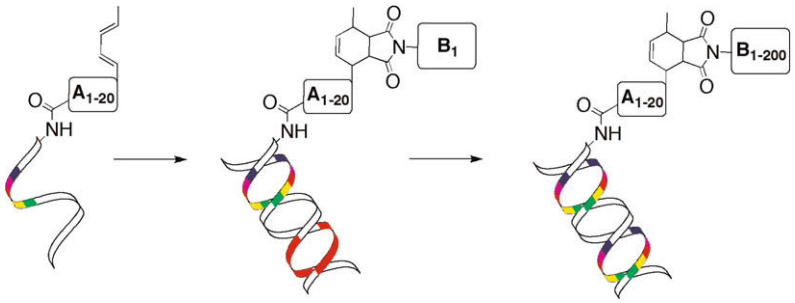


	ImmH	PhS-ImmH
K_d (His257)	58 pM	160 nM
K_d (Gly257)	11,000 pM	6 nM

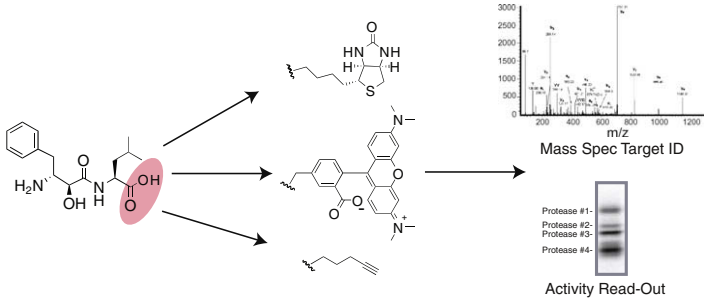
Neighboring-group participation in the reaction catalyzed by purine nucleoside phosphorylase involves His257-facilitated compression of the 5′- and 4′-ribosyl oxygens. The His257Gly mutant opens a space for preferential binding of 5′-substituted Immucillins, transition-state analogues of this reaction.

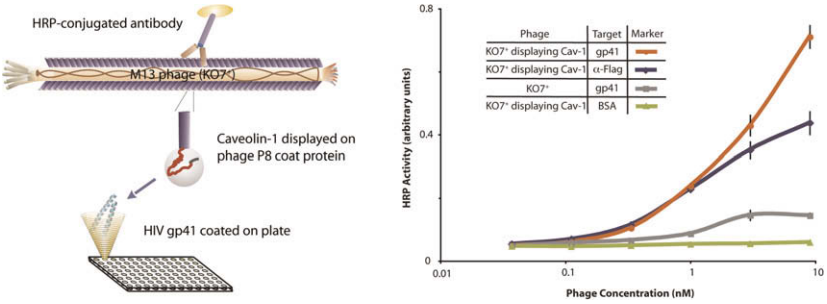


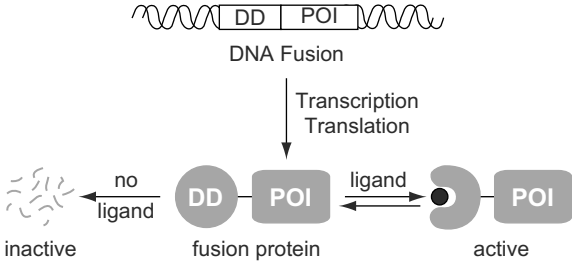




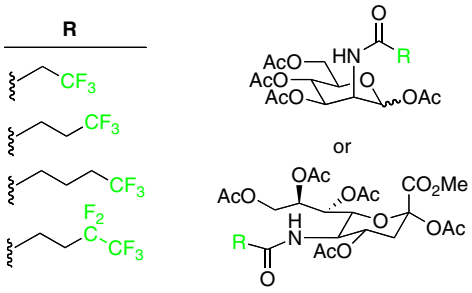
Synthesis and characterization of a novel 4000 compound DNA-encoded chemical library based on the Diels-Alder cycloaddition reaction.



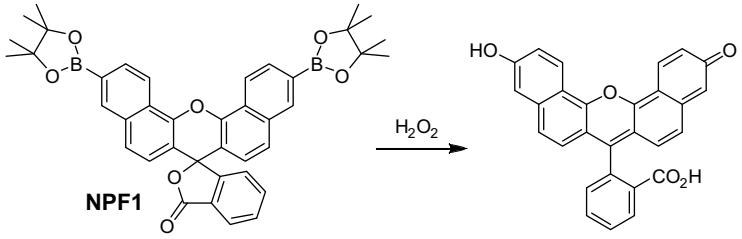




We recently engineered mutants of the FKBP12 protein that are rapidly degraded when expressed in cells. Recent results expand the utility of this general technology to provide small molecule control over protein stability.

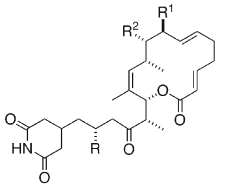


The surfaces of living cells have been fluorinated by incubation with *N*-fluoroacyl mannosamines or *N*-fluoroacyl neuraminic acids. Fluorinated cells showed reduced adhesion to extracellular matrix biomolecules.

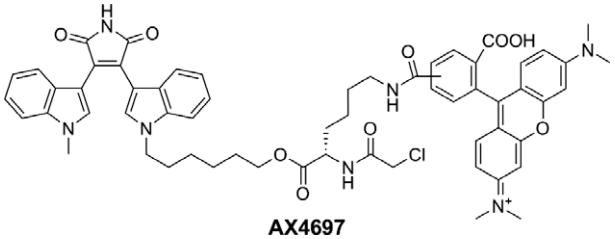


The synthesis, spectroscopy, and live-cell evaluation of a red-emitting fluorescent probe for cellular hydrogen peroxide are reported.

Biological evaluation of new cell migration inhibitors bearing migrastatin (MGS)-derived scaffolds is reported unveiling structural elements crucial to activity and two new MGS analogs with superior activity.

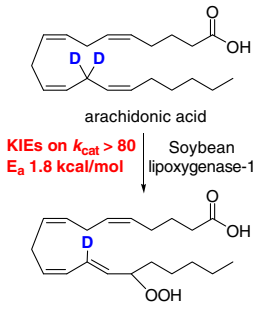


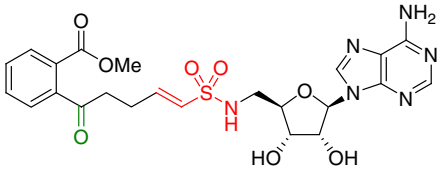
MGS: R = H, R^1 = OCH_3, R^2 = OH
14: R = OH, R^1 = OCH_3, R^2 = OH
17: R = OH, R^1 = R^2 = H
Cell migration inhibitor potency:
17 >> **14** > **MGS**



AX4697

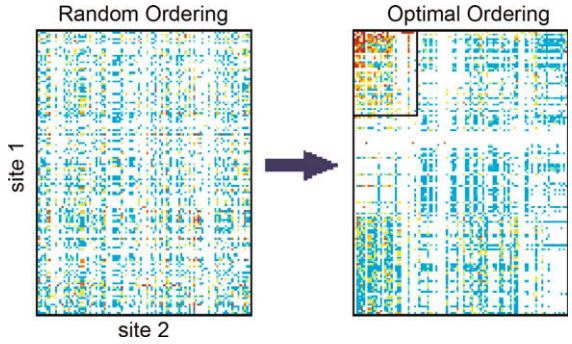
The synthesis and biochemical characterization of **AX4697**, bisindolylmaleimide-derived, exo-affinity probe for PKCα and β, is described.



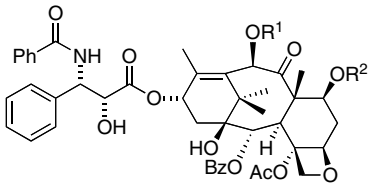


OSB-AVSN
MenE IC_{50} = 5.7 μM

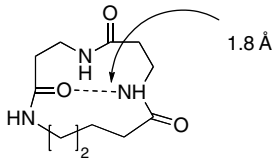
The design, synthesis, and biochemical evaluation of mechanism-based OSB-CoA synthetase inhibitors is reported.

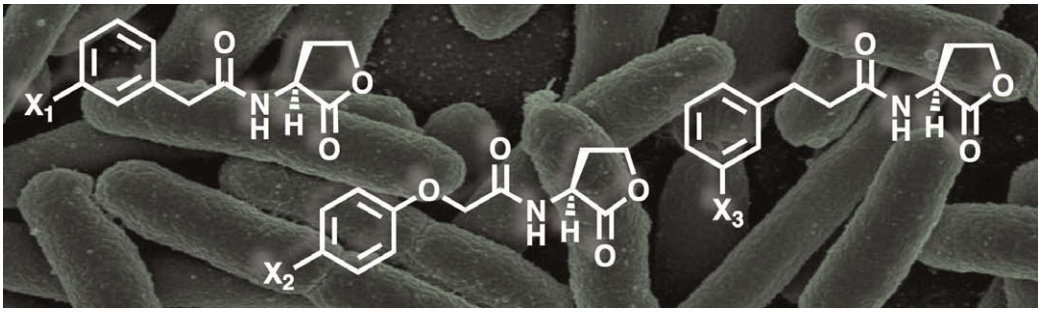


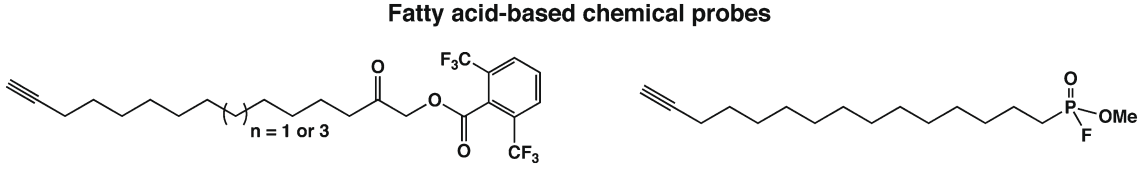
TX-67 (C10 hemi-succinate) analogs were investigated, including C7 regioisomers, esters, amides, and one-carbon homologs for tubulin stabilization, cytotoxicity, and Pgp interactions. All carboxylic acid analogs and several of the amides had no apparent interactions with Pgp, whereas the ester variants displayed characteristics of Pgp substrates. Furthermore, it was demonstrated that hydrogen-bonding properties were significant with respect to Pgp interactions.

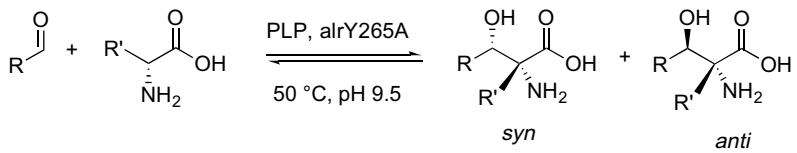


Series A: R^1 = hemi-succinate and glutarate, methyl ester, amides; R^2 = H
Series B: R^1 = Ac; R^2 = hemi-succinate and glutarate, methyl ester, amides

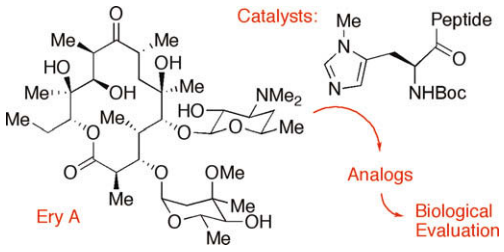


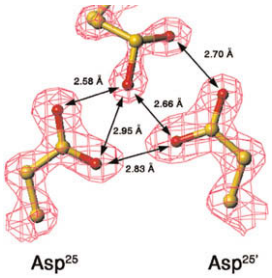






The Y265A mutant of alanine racemase catalyzes the stereoselective condensation of glycine or alanine with a range of aromatic aldehydes.





Crystal structure of HIV-1 protease with its ketomethylene isostere inhibitor is reported.

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

The Cravatt lab develops advanced synthetic and analytical chemistry technologies for the proteome-wide analysis of enzyme function. Shown are exemplary activity-based chemical probes (stick diagram), enzyme activity proteomic profiles (red bands in backdrop), and metabolomic signatures arising from enzyme inhibition (blue heat diagram) that collectively represent several of the core technologies introduced by the Cravatt group. [Hoover, H. S., Blankman, J. L., Niessen, S., Cravatt, B. F. *Bioorg. Med. Chem. Lett.* **2008,** *18,* 5838.]

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