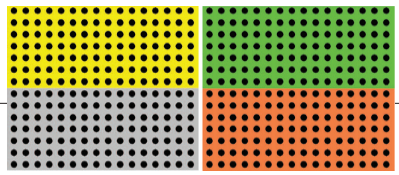
In this ISSUE

acs chemical biology



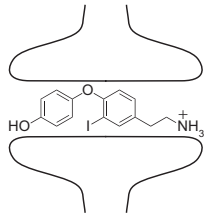
Unnaturally Natural

Natural products arise from collaboration among multienzyme pathways within an organism, pathways that scientists have begun to exploit to create additional "natural-product-like" compounds for biological and medicinal purposes. However, the complexity of the biological systems required to generate the compounds has confounded the development of this approach as a drug discovery method. Kwon *et al.* (p 419) now describe an *in vitro*, microarray-based approach based on biosynthetic pathways for the synthesis of natural-product-like libraries.

Using three type III polyketide synthase (PKS) enzymes, 16 acyl-coenzyme A (CoA) ester precursors, a malonyl-CoA extender substrate, and three oxidative post-PKS tailoring enzymes, the authors generated a biosynthetic, combinatorial library of >400 polyketides on a microarray platform. The library was then screened for inhibitors of a human tyrosine kinase. This clever strategy combines the benefits of biosynthetic machinery in natural product production with high-throughput screening methods needed for drug discovery efforts.

Figuring Out Farnesylation

The addition of a farnesyl group is an important post-translational modification for dozens of proteins, serving to guide them to the cell membrane for participation in cell signaling events. Farnesyltransferase (FTase) uses farnesyl diphosphate (FPP) to transfer the 15-carbon isoprenoid to various protein substrates. Current FTase inhibitors, some of which are in clinical trials as anticancer agents, block farnesylation of all FTase substrate proteins, precluding their utility in the investigation of individual farnesylated proteins. Krzysiak *et al.* (p 385) now describe several FPP analogues designed to explore farnesylation of specific proteins.



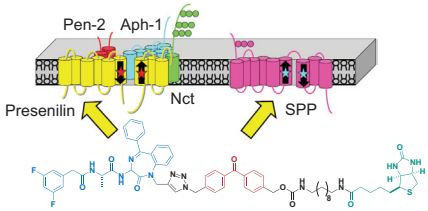
Guidance from the crystal structure of FTase inspired the design of 11 FPP analogues. The authors screened the compounds against seven peptides based on the recognition sequences of key FTase protein substrates. The analogues exhibited surprisingly distinct reactivity profiles with the substrates in an *in vitro* assay and in cells, an indication of their usefulness in deciphering the role of farnesylation of individual proteins.

Death by DMC

10-Decarbamoyl mitomycin C (DMC) is a derivative of the anticancer agent mitomycin C (MC). Both DMC and MC induce apoptosis *via* a mechanism dependent on the tumor suppressor protein p53. However, DMC can also lead cells to their death in a p53-independent mechanism. Boamah *et al.* (p 399) investigate how these two compounds kill cells that either contain or lack p53.

It is known that both MC and DMC cross-link DNA, but DMC produces 1′-β-interstrand cross-links not generated by MC. The authors found evidence that DMC–DNA adducts activate distinct targets, triggering cell signaling events that lead to programmed necrosis, not apoptosis. This provides insight into alternative cell death pathways used by cytotoxic agents, impacting therapeutic strategies for cancer treatment and the design of future drugs.

Deciphering the Dipeptidics



The devastating consequences of Alzheimer's disease (AD) have stimulated much research into the molecular basis of the disorder and therapeutic strategies to combat it. Inhibitors against γ-secretase, a key multiprotein complex involved in the pathogenesis of AD, are promising future drugs. However, the complexity surrounding γ-secretase function in both physiological and pathological processes necessitates deciphering the mechanism of action of its inhibitors. Fuwa *et al.* (p 408) now describe a synthetic strategy for generating multifunctional probes of prominent γ-secretase inhibitors.

The authors employed copper(I)-catalyzed azide/alkyne fusion reactions to generate derivatives of two dipeptidic γ-secretase inhibitors, each containing a photoactivatable group for target cross-linking, a linker region, and a biotin moiety for detection purposes. This clever synthetic strategy provides valuable tools for dissecting the mechanism of action of various γ-secretase inhibitors and helping to evaluate their therapeutic potential.

Tracing Thyronamine Activity

Thyronamines, which are metabolites of thyroid hormone, are ligands for the G-protein-coupled receptor trace-amine-associated receptor 1 (TAAR1) and possess potent biological activity distinct from thyroid hormone. The endogenous presence of thyronamines, such as 3-iodothyronamine (T_1AM), in tissues suggested that they may also have uncharacterized physiological roles. Snead *et al.* (p 390 and Point of View p 377) report that thyronamines act as neuromodulators by inhibiting neurotransmitter transport across plasma and vesicle membranes.

Using membrane preparations, the authors determined that T_1AM prevents transport of dopamine, norepinephrine, and serotonin across plasma and vesicle membranes. In addition, experiments with heterologous expression of various neurotransmitter transporters revealed that T_1AM inhibits the activity of the dopamine and norepinephrine transporters. The authors propose that the effects of thyronamine on monoamine transport and its activity with TAAR1 may synergistically lead to its profound pharmacological effects.

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