Total Synthesis and Chemical Biology of Pederin, Mycalamide A, and Related Natural Products

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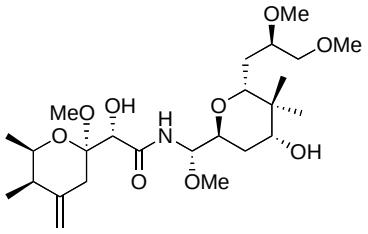
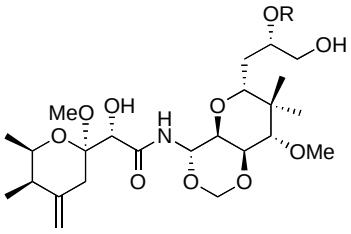
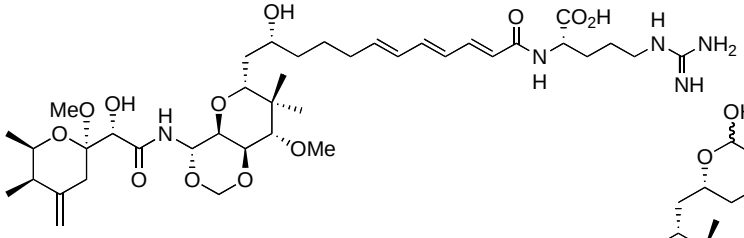
Pederin, mycalamides A-D, onnamides A-F, and theopederins A-L belong to a class of structurally related natural products with both highly potent biological activity and structural appeal. Whereas pederin, a potent blistering agent, was isolated from a terrestrial beetle, *Paederus fuscipes* the remaining members were isolated from marine sponges of the genera *Mycale* and *Theonella*, collected from New Zealand and Okinawan waters. Although the biological properties of every member has not been fully evaluated, several of these compounds exhibit potent cytotoxicity—sub-nanomolar in many cases—against various tumor cell lines. Mycalamide A (**1**), in particular, has been evaluated as an anti-tumor agent based on its in vivo activity against P388 murine leukemia and a variety of solid tumor model systems, including Lewis lung, M5076, Burkitt's lymphoma, and MX-1 and CX-1 human tumor xenografts. Mycalamide A not only displays significant anti-viral activity but also exhibits immunosuppressive action by blocking T-cell activation in mice, and is significantly more potent than FK-506 and cyclosporine A in this assay. In this presentation I will present the results of our convergent syntheses of pederin and mycalamide A, as well as our efforts to define the cellular target of these natural products.



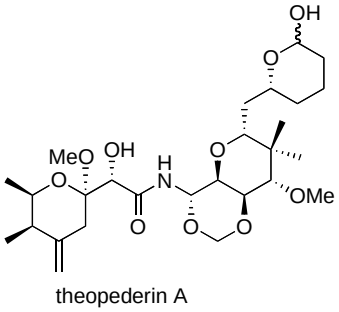
pederin



mycalamide A, R = H (**1**)
mycalamide B, R = Me (**2**)



onnamide A



theopederin A