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Tunicamycins: translocase-I inhibitors that target bacterial cell wall and mammalian N-glycoproteins. The potential for selective inhibitors

Tunicamycins are a heterologous family of nucleoside antibiotics that target the biosynthesis of bacterial peptidoglycan and eukaryotic N-glycoproteins. The mechanism of action is known, with the tunicamycin-Mg²⁺ complex established as a transition state analog for hexosamine-1-phosphate:pre-nol phosphate translocases. Hence, this inhibits the formation of N-acetylmuramyl-undecanol pyrophosphate in bacteria or N-acetylglucosamine-dolichol pyrophosphate in eukaryotes, which are essential intermediates in these organisms. We have investigated the biosynthesis of the tunicamycins by certain streptomyces species, and have proposed a pathway in which the 11-carbon dialdose sugar, tunicamine, is derived from uridine and N-acetylglucosamine. Once formed the uridyl-tunicaminy intermediate is α,β -1,11-glycosylated and N-acylated to form the bioactive compounds prior to secretion. Heterologous expression identified twelve *tun* genes (*tunA* – *tunL*) responsible for tunicamycin biosynthesis in the producing organisms *Streptomyces chartreusis* and *S. clavuligerus*. Amongst these is a putative radical SAM enzyme (TunB) with a potentially unique role in biosynthetic carbon-carbon bond formation, and an unusual glycosyltransferase (TunD) involved in the formation of the anomeric-to-anomeric α,β -1,11-glycosidic bond. Hence, a biosynthetic pathway is proposed for tunicamycin biosynthesis which may be useful for the design of new tunicamycin analogs with selective/enhanced translocase specificity.

Biography

Neil P.J. Price has a PhD from the University of London and has Postdoctoral experience at the University of Geneva in Switzerland, Paul-Sabatier University in Toulouse and the Complex Carbohydrate Research Center in Athens. He held a Faculty Position the University of Rochester, NY before moving to the NCAUR, Peoria. His research includes carbohydrate chemistry and biochemistry, mass spectrometry and microbial metabolism. He currently serves on the ARS National Chemical Patent committee and has over 90 peer-reviewed research publications.

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