Insights into the substrate specificity and mechanism of the macrolide sugar O-methyltransferase, MycF

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Natural products represent a significant source of pharmacologically active compounds. Heteroatoms are frequently methylated in natural product biosynthesis pathways. Methylation can increase the membrane permeability and slow oxidation of the natural product. Mycinamicin is a potent macrolide antibiotic produced by the soil bacterium Micromonospora griseorubida. In the biosynthesis of mycinamicin, a 6-deoxyallose sugar is appended to the macrolactone core and subsequently methylated first at the 2’ and then at the 3’ hydroxyl group. MycF is the SAM and metal-dependent methyltransferase responsible for the 3’ methylation. The structure of MycF in complex with S-adenosyl homocysteine, Mg2+ and the substrate mycinamicin III reveals that the catalytic base is most likely to be Asp 191 based on proximity to the substrate hydroxyl. In the absence of substrate, Asp 191 is a Mg2+ ligand. The structure supports a mechanism where Mg2+ plays a critical role in substrate binding and stabilization of the hydroxalate intermediate. The enzyme forms no specific interactions with the macrolide core, suggesting that MycF may accept a variety of substrates bearing the javose moiety.

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