SL06 **PKS Enzymes From Fungi: Protein Machines that Build Complex Natural Products**

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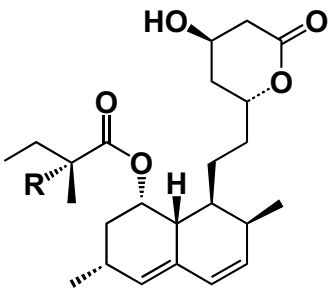
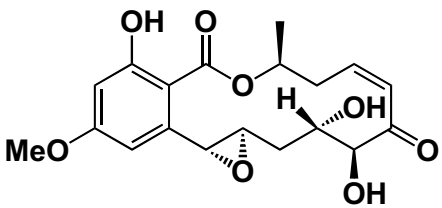
Polyketides represent a class of over 7000 known naturally-occurring structures, of which more than 20 are commercial drugs. Among these are cholesterol-lowering agents such as lovastatin (Mevacor™), which is produced by the fungus *Aspergillus terreus*. Its semi-synthetic derivative, simvastatin (Zocor™), had US $4.3 billion sales in 2005 prior to patent expiration, and it is one of the most widely prescribed generic drugs today.

Lovastatin is produced by a fungal type I iterative polyketide synthases (PKS). These are large multifunctional enzymes that resemble mammalian fatty acid synthases in arrangement of their catalytic domains. However, they assemble complex functionalized metabolites through a highly ordered sequence of catalytic steps with great precision. In the case of lovastatin, the LovB PKS and LovC enoyl reductase constitute a molecular machine that makes a functionalized nonaketide in ca 35 chemical steps. Recent advances in understanding the biosynthesis of secondary metabolites by PKS and structures of some of their domains will be described, including for example, for fungal resorcylic macrolide lactones such as hypothemycin and radicicol.

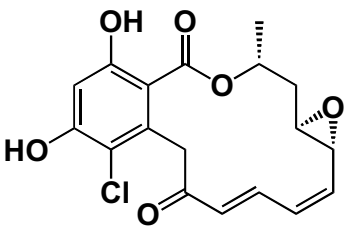


R = H Lovastatin

R = Me Simvatstatin



Hypothemycin



Radicicol