Synopsis of Original Research Paper

Engineered biosynthesis of Aloe chromones

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Octaketide synthase (OKS) from *Aloe arborescens* is a plant-specific type III polyketide synthase (PKS) that catalyzes iterative condensations of eight molecules of malonyl-CoA to produce the C_{16} aromatic octaketides SEK4 and SEK4b. On the basis of the crystal structures of OKS, the F66L/N222G double mutant was constructed and shown to produce an unnatural dodecaketide TW95a by sequential condensations of twelve molecules of malonyl-CoA. The C_{24} naphthophenone TW95a is a product of the minimal type II PKS, and is structurally related to the C_{20} decaketide benzophenone SEK15, the product of the OKS N222G point mutant. The C_{24} dodecaketide naphthophenone TW95a is the first and the longest polyketide scaffold generated by a structurally simple type III PKS. A homology model predicted that the active-site cavity volume of the F66L/N222G mutant is increased to 748 $Å^3$, from 652 $Å^3$ of the wild-type OKS. The structure-based engineering thus greatly expanded the catalytic repertoire of the simple type III PKS to further produce larger and more complex polyketide molecules.