Drug Discovery & Development

Type 1 Polyketide Synthase Extender Units

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The Wisconsin Alumni Research Foundation (WARF) is seeking commercial partners interested in developing two novel extender units that can be used in the creation of new polyketide derivatives.

Overview

Microorganisms produce a variety of biologically active secondary metabolites, which display a range of useful antibiotic and immunosuppressant activities. One class of secondary metabolites, known as polyketides, possess antimicrobial, antifungal, antiparasitic, antitumor and agrochemical properties and have been found in organisms from bacteria to insects to sponges. Genetic manipulation of polyketide biosynthesis has generally been very successful in generating novel products, such as the broad spectrum antibiotic Erythromycin A.

Polyketides are synthesized by sequential reactions catalyzed by polyketide synthases (PKSs), which are large, multi-enzyme protein complexes. Each Type I PKS module consists of several domains with defined functions. The flexibility of these domains has been exploited to create metabolically engineered “natural” products through combinatorial biosynthesis. For example, a catalytic domain from one PKS may be replaced with a domain from a different PKS to create a hybrid enzyme that generates a novel polyketide. This combinatorial approach was used to create a library of nearly 60 erythromycin derivatives.

To create additional derivatives, different extender unit(s) can be incorporated by a PKS into a polyketide backbone to alter the polyketide’s interaction with its biological target. However, this approach is limited because only four Type I PKS extender units are currently known. Additionally, all four lack simple chemical reactivity for further downstream modification by semisynthetic chemistry.

The Invention

UW-Madison researchers have discovered two novel extender units that can be used in the creation of new polyketide derivatives. This invention also includes the enzymes needed to form the extender units and the PKSs needed to incorporate the units into the polyketide backbone.

One or both of the extender units can be introduced into a desired polyketide to create new structural derivatives. For example, the PKSs involved in the production of polyketides such as erythromycin, rifamycin, rapamycin, FK520 or zwittermicin can be engineered to incorporate these units. The resulting polyketide derivatives can then be used as bioactive molecules or as lead compounds for further modification.

Applications

- Generating collections of potentially useful polyketides for drug development

Key Benefits

- Provides a novel means of generating potentially useful polyketides
- Enhances structural diversification by combinatorial biosynthesis
- Enables the introduction of hydroxyl or amino groups into a polyketide backbone
- Expands the metabolic engineering potential of Type I PKSs
- Provides additional opportunities for downstream modification by semisynthetic chemistry

Additional Information

For More Information About the Inventors

- Jo Handelsman

Tech Fields

- Drug Discovery & Development : Compound libraries
- Drug Discovery & Development : Drug production & design

For current licensing status, please contact Rafael Diaz at rdiaz@warf.org or 608-960-9847