TODAY'S HEADLINES

August 19, 2002
Volume 80, Number 33
CENEAR 80 33 p. 12
ISSN 0009-2347

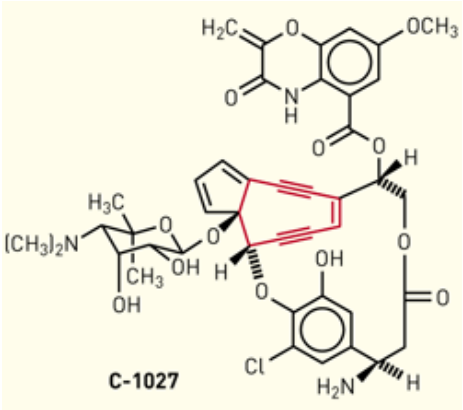
SCIENCE

PATH TO ENEDIYNES

Engineering of biosynthetic route could lead to better anticancer drugs

AMANDA YARNELL

Highly complex synthetic schemes have been devised for a number of members of the enediyne class of potent anticancer agents. But relatively little has been known about how these bacterial natural products are synthesized in nature.



Not anymore. Two teams of researchers from the University of Wisconsin, Madison, have shown that the enediyne cores of both C-1027 and calicheamicin are synthesized via a common polyketide pathway, suggesting that all enediynes are biosynthesized in the same manner [*Science,* **297,** 1170 and 1173 (2002)].

Enediynes are characterized by a nine- or 10-membered ring containing two triple bonds separated by a double bond. The enediyne group readily cyclizes via a diradical intermediate that cleaves DNA, giving rise to enediynes' powerful antitumor activity.

But just how bacteria create the enediyne core--and whether they all use the same method--has long been controversial. Hypotheses have included a polyketide pathway in which the enediyne core is built up sequentially from two-carbon units and a pathway in which the enediyne core is created by degrading an unsaturated fatty acid precursor.

Related Stories

Alternate Route For Enediyne Cyclization [C&EN, Apr. 16, 2001]

Enediyne Research Continues Apace [C&EN, Mar. 13, 2000]

'Molecular Break Lights' Detect DNA-Cleaving Agents [C&EN, Dec. 11, 2000]

Related People

Ben Shen

Jon S. Thorson

E-mail this article to a friend

Print this article

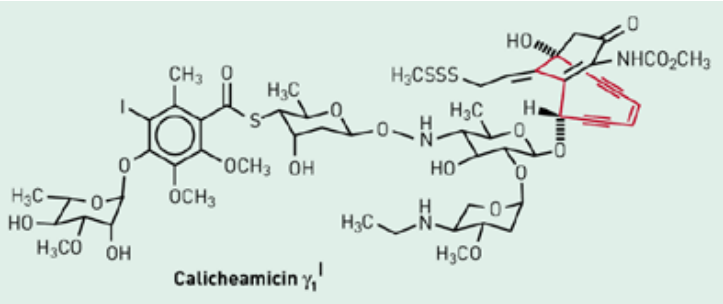
E-mail the editor

Ben Shen, associate professor of pharmaceutical sciences and chemistry, and coworkers cloned and characterized the stretch of the *Streptomyces globisporus* genome necessary for biosynthesis of the nine-membered enediyne C-1027. Disruption of the single polyketide synthase (PKS) gene in this region stops C-1027 production, they find.

Working in *Micromonospora echinospora* ssp. *calichensis*, pharmaceutical sciences associate professor Jon S. Thorson, Chris M. Farnet of Ecopia Biosciences, and coworkers found that a homologous PKS gene in the calicheamicin gene cluster is required for production of this 10-membered enediyne.

In both sequence and organization, the C-1027 and calicheamicin PKSs are remarkably similar. "Taken together, our findings suggest that all enediynes share a common polyketide biosynthetic pathway," Thorson says.

Despite their potency, the enediynes' reactivity and toxicity have limited their usefulness as drugs. But by disrupting a hydroxylase gene in the C-1027 cluster, Shen's team created a novel C-1027 analog with improved chemical stability. "The work opens the door to genetic manipulation of these biosynthetic pathways to develop new drug candidates," Shen says.



Top
