Volume 93 Issue 25 | p. 32 | Concentrates
Issue Date: June 22, 2015

Natural Product Precursor Could Hit Cancer Selectively

Drug Discovery: Leinamycin E1's cytotoxic mechanism is selective for cancer cells

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Department: Science & Technology
News Channels: Biological SCENE, Organic SCENE
Keywords: leinamycin, cancer, reactive oxygen species, ROS

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Researchers have isolated and characterized a precursor of the anticancer agent leinamycin that could have more highly selective anticancer activity and fewer side effects than leinamycin itself. Leinamycin is a natural product that, in the presence of cellular thiols, forms an episulfonium ion that alkylates DNA, causing DNA cleavage and cell death. But it can kill cancer cells and normal cells, likely contributing to its substantial toxicity. Ben Shen of Scripps Research Institute Florida and coworkers have now manipulated the leinamycin biosynthetic pathway to make engineered bacteria produce a precursor, leinamycin E1 (*Proc. Natl. Acad. Sci. USA* 2015, DOI: 10.1073/pnas.1506761112). E1 also forms an episulfonium ion that alkylates DNA, but it does so in the presence of reactive oxygen species (ROS) instead of thiols. Cancer cells are under higher oxidative stress and have higher levels of ROS than normal cells do, so E1 acts as an ROS-activated prodrug that would likely be selective for cancer cells. Shen and his coworkers are currently looking for analogs of leinamycin E1 with the same mechanism for potential development as anticancer agents.

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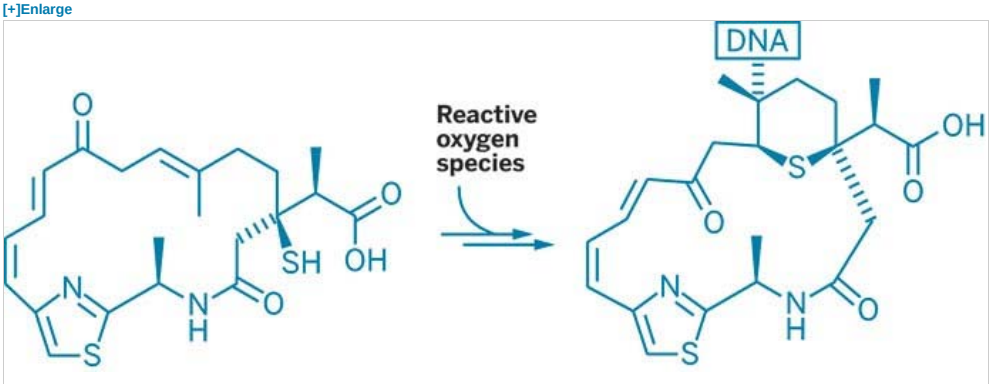

Leinamycin E1 (left) kills cancer cells by alkylating DNA in the presence of reactive oxygen species.

Chemical & Engineering News
ISSN 0009-2347

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