Novel Inhibitors of Farnesyl Diphosphate Synthase and Undecaprenyl Pyrophosphate Synthase Used as Treatments for African Sleeping Sickness and Bacterial Infections

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Technology description

Summary

Isoprenoids, natural compounds critical to the survival of organisms ranging from bacteria to parasitic protists to human cancer cells, have diverse functions, including endocrine signaling, signal transduction, and cell membrane/cell wall biosynthesis. Consequently, isoprenoid biosynthesis has been the target of several FDA-approved drugs, including treatments for high cholesterol (statins), cancer (taxol), and bone diseases (bisphosphonates). Inhibitors of the isoprenoid biosynthesis pathways are also effective against trypanosomes, includingTrypanosoma bruceiandTrypanosoma cruzi,the organisms responsible for African sleeping sickness and Chagas' disease, as well as against bacteria, such as drug-resistantStaphylococcus aureus, an ever increasing public-health threat. Two anti-infective targets involved in isoprenoid biosynthesis are farnesyl diphosphate synthase (FPPS) and undecaprenyl diphosphate synthase (UPPS). Both enzymes are essential for bacterial and trypanosomal cell growth, and UPPS is of particular interest because it is absent in humans.

Description

Scientists at the UC San Diego used a virtual-screening approach to identify selective, micro-molar, nonbisphosphonate FPPS/UPPS inhibitors. Bisphosphonate compounds are subject to rapid removal from the circulatory system via bone-mineral binding; consequently, nonbisphosphonate compounds may have enhanced efficacy. Additionally, the polypharmacophoric combined inhibition of both FPPS/UPPS, each an excellent drug target in its own right, is likely to be synergistic. The simultaneous inhibition of these two key enzymes may also reduce the chances that a resistance-conferring mutation will render future derivative therapeutics ineffective.

Institution

University of California, San Diego

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com