Synthesis of Novel Δ 12 -Prostaglandin J2/3 Analogues

Published date: Sept. 7, 2018

Technology description

Challenge

The presence of cancer stem cells presents particular challenges to treatment in all cases. Certain cancerous stem cells are notoriously refractory to conventionaldrugs. Consequently, eradicating these cells is an important, unrealized therapeutic goal.

Solution

D ^{12} -prostaglandin J $_{2/3}$ (D ^{12} -PGJ $_{3}$), a naturally formed metabolite of eicosapentaenoic acid (EPA), has been reported to selectively target and induce apoptosis of leukemia stem cells (LSC), but not normal hematopoietic stem cells in mouse spleen and bone marrow leukemic models. Treatment with D ^{12} -PGJ $_{3}$ induces unmitigated apoptosis of the LSCs in vivo—shown by the inability of donor cells from treated mice to cause leukemia in secondary transplants. Given the potent activities of D ^{12} -PGJ $_{3}$, this invention describes procedures and new synthetic strategies for the synthesis of D ^{12} -PGJ $_{3}$ and D ^{12} -PGJ $_{3}$ analogs.

Technology Relevant Papers

K.C. Nicolaou et al, "Total Synthesis of D ^{12} -Prostaglandin J $_{3}$, a Highly Potent and Selective Antileukemic Agent", Angew. Chem. Int. ed. 2014, 53: 10443-10447.
K.C. Nicolaou et al, "Synthesis and Biological Investigation of D ^{12} -Prostaglandin J $_{3}$ Analogues and Related Compounds", J. Am. Chem. Soc. 2016, 138: 6550-6560.
K.C. Nicolaou et al, "Total Synthesis of D ^{12} -Prostaglandin J $_{3}$: Evolution of Synthetic Strategies to a Streamlined Process", Chem. Eur. J. 2016, 22: 8559-8570.
Hegde et al, "D ^{12} -prostaglandin J3, an omega-3 fatty acid–derived metabolite, selectively ablates leukemia stem cells in mice", Blood J. 2013, 118: 6909-6919.
Kudva et al, "Evaluation of the stability, bioavailability, and hypersensitivity of the omega-3 derived anti-leukemic prostaglandin: D ^{12} -PGJ $_{3}$ ", PLoS ONE 2013, 8(12): e80622.

Application area

According to the International Agency for Research on Cancer, there were 14.1 million new cancer cases, 8.2 million cancer deaths, and 32.6 million people living with cancer in 2012 worldwide. The global market for therapeutics was $120 billion in 2017, and therapeutics for cancer stem cells will comprise $1.9 billion of that total market by 2022.

Advantages

· Series of D^{12}-PGJ_3 analogues have been synthesized and evaluated for their cytotoxicity against a variety of cancer cell lines, such as non-small cell lung, colon, CNS, melanoma, sarcoma, ovarian, renal, breast, and prostate, in addition to leukemia.
· Lead compounds identified with nanomolar potencies.
· Analogs demonstrating ~ 30-130 fold increase in cytotoxicity over other prostaglandins in a cytotoxicity screen of various human cell cancer lines.
· D^{12}-PGJ_3, among other derivatives, have the potential to exhibit reduced side effects, with enhanced potency and pharmacokinetic profile (e.g., higher bioavailability and/or lower clearance) over compounds known in the prior art.
· D^{12}-PGJ_3 and analogues developed here have the potential to be used in combination therapies.

Institution

Rice University

Inventors

Nicolaou
Olga K. Wiess Professor

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com