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Phenstatins

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Inventors

George Pettit, PhD
Regents Professor
Department of Chemistry and Biochemistry
Arizona State University

Matthew Grealish

Brian Toki

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Contact

Yash Vaishnav, PhD, MBA

Vice President

Business Development, Life Sciences

Arizona Technology Enterprises, LLC (AzTE)

P: 480.884.1648

F: 847.971.2871

YASH@AZTE.COM

HEALTHSCIENCES@AZTE.CO

Invention Description

The Combretastatin A-4 (CA-4) Prodrug is a very promising compound now in phase II clinical trials against cancer. CA-4 is acting as a tubulin polymerization inhibitor, preventing cancerous cells from dividing.

While performing a structural activity relationship (SAR) study of the antineoplastic compound CA-4, ASU researchers discovered the Phenstatins family. Phenstatins are Combretastatins analogs with a modification of the double bond, which is replaced by a carbonyl group.

The first compound, Phenstatin, showed strong cytotoxicity and an antitubulin activity similar to that of CA-4. Phenstatin was also found to be as effective as CA-4 in competing with colchicine for binding site.

Phenstatin and its Prodrug were found to be essentially indistinguishable in potency (e.g. mean panel GI50 values) and differential cytotoxicity. Both were also quite similar to the CA-4 Prodrug both in terms of both potency and differential cytotoxicity, suggesting that their mechanism of action is similar to that of CA-4.

ASU researchers also investigated Hydroxyphenstatin, a compound possessing an additional hydroxy group, as found in Combretastatin A-1 (CA-1). Hydroxyphenstatin inhibition of tubulin polymerization appeared greater than that of both CA-4 and CA-1. A comparative testing of Hydroxyphenstatin and its Prodrug in the NCI 60-cell screen revealed a differential cytotoxicity profile and potency (mean-panel GI50 value of 1.7 x 10-7 M) that were essentially indistinguishable from each other or from those of CA-4.

In general, new discovered compounds disclose a potency and a differential cytotoxicity profile comparable to CA-4.

Potential Applications

Since these novel compounds have comparable results to their previously known structural analogs they have applications as:

- **Anti-neoplasic and anti-cancer therapeutic agents**

Benefits and Advantages

- **Diversity** – The new compounds are analogs of confirmed very potent candidates for anti-cancer drugs.
- **Synthesis** – The syntheses for the new compounds are well described. A multigram scale synthesis of Hydroxyphenstatin is available.
- **Efficacy** – New compounds are quite similar to Combretastatin A-4 or its prodrug in terms of both potency and differential cytotoxicity.