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Case ID:M18-001LC^
Published: 2/26/2020

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Anticancer Betulastatin Compositions

Natural compounds are a productive and promising source of new anticancer and antiproliferative drugs. Dr. Pettit and his team have been at the forefront of discovering, isolating and synthesizing such compounds with anticancer and antimicrobial activities for a long time. Current developments in the antibody-drug conjugate (ADC) space have sparked a renewed interest in natural products as a source of potent payloads for ADCs. Dr. Pettit is one of the key players that helped advance the ADC space and continues to contribute greatly to the field.

The widely studied plant pentacyclic triterpene, betulin, and its C-28 carboxylic acid derivative, Betulinic acid, come primarily from the bark of birch trees and are the subject of several clinical cancer studies. Betulinic acid is more potent than betulin and is a cancer cell growth inhibitor with a mitochondrial mechanism of action.

Dr. Pettit and his team at Arizona State University have developed novel betulastatin compounds which demonstrate considerable cancer cell growth inhibition. These compounds are analogues (chimeras) that were developed after studying betulin bonded to the Dov-Val-Dil-Dap unit of dolastatin 10, itself a potent anticancer compound. The Dov-Val-Dil-Dap sequence was added to betulin structural modifications to create unique compounds that show greater cancer inhibition than the parent compounds. Evaluation for inhibition of human cancer cell growth was performed in a variety of cancer cell lines using the standard sulforhodamine B assay of the U.S. National Cancer Institute with calculation of a growth inhibition of 50% (GI50).

These betulastatins show great promise as anticancer compounds, particularly since they are chimeras which provide multiple anticancer mechanisms of action.

Potential Applications

- Anticancer compounds
  - Melanoma
  - Pancreatic cancer
  - Breast cancer

- Brain cancer
- Lung cancer
- Colon cancer
- Prostate cancer

Benefits and Advantages

- Betulastatin 3 had a GI50 value of 0.01 µg/mL
- 10-fold increase in cancer cell growth inhibition for three of the compounds and a hundred-fold increase in inhibition in one compound
- Could be conjugated to antibodies through a linker for more targeted therapeutics
- Total synthesis achieved

In Vitro and/or In Vivo Data

Human Cancer Cell Lines (GI50 µg/mL in DMSO) Growth Inhibition Results:

State of Development

Total synthesis achieved. Compounds with particularly good GI50 values could be considered for linkage to monoclonal antibodies and further development.

Lead Structures

For more information about the inventor(s) and their research, please see Dr. Pettit's departmental webpage

For more information about this opportunity, please see Pettit et al – J Nat Prod - 2018