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Emetine Auristatin Compounds

Natural compounds are a productive and promising source of novel anticancer and antiproliferative drugs. Dr. Pettit and his team have been at the forefront of discovering, isolating and synthesizing such compounds having anticancer and antimicrobial activities for many years. 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 was a key player in helping to advance the ADC space and continues to contribute greatly to the field.

Emetine is a tetrahydroisoquinoline alkaloid found mostly in the roots of the plant species, Psychotria ipecacuanha (Brot.) Stokes, and was commonly used as an anti-protozoal and emetic. However, more recently, it has been shown that emetine inhibits protein, DNA and RNA synthesis and could be useful in cancer treatments.

Dr. Pettit and his team at Arizona State University have developed novel emetine auristatin compounds which demonstrate considerable cell growth inhibition. These compounds are analogues (chimeras) that were developed after initially bonding emetine to the auristatin peptide side chain Dov-Val-Dil-Dap. Additional chimeras have been creating by bonding the Dov-Val-Dil-Dap-β-Ala and Dov-Val-Dil-Dap-Ethylamine sequences to emetine, to create three chimeras in total.

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).

Potential Applications

- Anticancer compounds
  - Pancreatic cancer
  - Breast cancer
  - Brain cancer
  - Lung cancer

- Colon cancer
- Prostate cancer
- And more

Benefits and Advantages

- Compound 5 showed cytotoxicity comparable to that of emetine in four of the 6 cell lines, with a 10-fold decrease in the BXPC-3 cell line
- Only a 10-fold decrease in cytotoxicity for the other two compounds compared to the parent emetine compound
- Total synthesis achieved
- Compound 5 could be the key to advancing the syntheses of structural modifications of emetine with increasing activity
- These compounds may sensitize tumor cells to secondary therapeutic agents

In Vitro and/or In Vivo Data

State of Development

Total synthesis has been achieved for all three compounds. Compound 5 showed cytotoxicity comparable to that of emetine in four of the 6 cell lines, with a 10-fold decrease in the BXPC-3 cell line. Only a 10-fold decrease in biological activity was observed for compounds 9 & 10 in four cell lines compared to both emetine and compound 5. Compounds could also be considered for linkage to monoclonal antibodies for further development.

Lead Structures

For more information about this opportunity, please see

Pettit et al - J. Nat. Prod. - 2020

For more information about the inventor(s) and their research, please see

Dr. Pettit's departmental webpage