Ellipticine Analogs as Anti-Cancer Therapeutics

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Technology description

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Ellipticine is an established anticancer chemotherapeutic, however, its current method of synthesis requires many steps and has an unfavorable toxicity profile. MUSC researchers have developed a method to obtain ellipticine analogs in one step by utilizing radiation and acid catalysis. These analogs have unique characteristics that may improve the toxicity profile, such as the prevention of bioactive 9-hydroxyellipticine formation which is critical for the cytotoxicity of ellipticine. Further, these analogs have the potential to treat triple negative breast cancer (TNBC) as a stand-alone or combination therapy. Studies on many of the 17 analogs were done by the National Cancer Institute NCI60 screening program (one-dose studies with 10 uM and multi-dose for aza-15), as well as SUM lines at MUSC demonstrating powerful inhibition of TNBC cells (example of analog aza-8; Table 1).

Further, MCF7 and HepG2 response to Aza-8 showcases the cellular specificity of these analogs (Figure 1). While clinically proven drugs such as ellipticine and doxorubicin are known to inhibit cell growth in HepG2 cells, exposure to Aza-8 does not inhibit cell growth. Additional data has been gathered across multiple analogs in various cancer lines, and is available to be shared. Taken together, these data suggest that these ellipticine analogs have potent anti-tumour activity in TNBC lines, which may representeffective and safer topoisomerase based chemotherapy.

Overview

Ellipticine is a member of the pyrido[4,3-b] carbazole alkaloids that were first isolated in 1959. The ellipticine family represents a class of natural products that have been used to develop potential treatments for cancer, HIV, and malarial infection. Two of the mechanisms of action affiliated with ellipticine are inhibition of DNA topoisomerase II activity and DNA intercalation. Clinically used compounds Etoposide, Doxorubicin, Mitoxantrone, and Benzophenanthridine all act on topoisomerase II to produce an antitumour effect. Developing an entirely new topoisomerase II poison related to the ellipticine family but with refined activity and structure could provide resurgence to this family of natural products and offer solutions against multidrug resistance especially when used in conjunction with other clinically validated therapies.

Key Words:Ellipticine, cancer, chemotherapy, topoisomerase, breast cancer, triple negative, SUM, MCF7

Application area

Applications:Drug development, cancer therapeutics, chemotherapy, breast cancer

Simple synthesis, potent activity, Effective against TNBC lines, cell line specificity, unique characteristics

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