The Synthesis of Melampomagnolide B Derivatives and Their Anti-leukemic Activity

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Purpose
Melampomagnolide B (MMB) is a new sesquiterpene that has anti-leukemic properties similar to the structurally related parthenolide molecule. Carbamoyl analogs of MMB have been designed to enhance antileukemic activity and improved bioavailability when compared to the parent compound. A series of novel carbamoyl analogs of MMB have been synthesized and screened for anti-leukemic activity against three primary human AML cell lines, and their cytotoxicity compared to that of MMB.

Methods
To obtain a small sub-library of [20 compounds] carbamoyl derivatives of MMB, the drug was treated with 4-nitrophenyl chloroformate to afford the key nitrophenyl ester intermediate [4-nitrophenyl MMB carbonate] which was then reacted with a variety of nitrogen-containing heterocyclic amines such as imidazole, morpholine, piperidine, pyrrolidine, triazole and pyridine, etc., to generate a series of water-soluble carbamate analogs. A thiocarbamate analog of MMB was prepared by the reaction of MMB with thiocarbonyldiimidazole.

Results
All 20 MMB derivatives were screened for anti-leukemic activity against primary cultures of AML 052308, AML 123009 and M9ENL cells. Several compounds LC50 values were in the range of 2-7 µM. Furthermore, these active compounds were tested against normal CD34+ bone marrow and cord blood cells, but no significant cytotoxicity was observed in these cell lines. Moreover, 4 of these newly synthesized compounds were more potent than the parent compound, MMB.

Conclusion
A series of novel MMB derivatives were synthesized and evaluated for anti-leukemic activity against primary AML cell lines and normal CD34+ bone marrow and cord blood cell lines. Several analogs showed improved and selective cytotoxicity against AML cells when compared to the parent compound MMB, and had no effect on normal cells.