Heterocyclic Esters of Melampomagnolide B as Potent Anti-Cancer Agents
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Purpose
Melampomagnolide B (MMB), isolated from Magnolia glandiflora, is a naturally occurring sesquiterpene lactone (SL) belonging to the Melampolide sesquiterpene of germacrolides family of natural products. MMB is structurally related to parthenolide (PTL). In streptavidin pull-down studies the biotin conjugate of MMB targets the NFκB and glutathione pathways in acute myelogenous leukemia stem cells. As an extension of our previous SAR studies on indole-carboxylate esters of MMB, the present study focuses on the synthesis and anti-cancer activities of various substituted heterocyclic/aliphatic carboxylic acid ester analogues of MMB.

Methods
A variety of commercially available heterocyclic/aliphatic carboxylic acids were reacted with MMB using standard Steglich esterification conditions in DCM at room temperature for 8 h to afford the corresponding MMB-heterocyclic/aliphatic carboxylic ester.

Results
All the synthesized compounds were screened for antileukemic activity against M9-ENL1 AML cells in culture and some of them were also evaluated against primary AML cell lines from AML patients. Generally, the heterocyclic ester analogs were more potent than parthenolide (PTL), whereas aliphatic esters were less potent than PTL. The heterocyclic analog BS-2-66 was the most potent analog in the series with EC50 values of 720 nM and 1.15 μM against two types of primary AML cells from AML patients. Analogs BS-2-65 and BS-3-18 were screened against a panel of 60 human tumor cell lines. BS-2-65 exhibited GI50 values in the range 200 nM to 980 nM against 12 human cancer cell lines in the panel. Of all the esters of MMB synthesized, BS-1-28 was demonstrated to be the most promising analog against the panel of 60 human cancer cell lines. Against rat 9L-SF gliosarcoma cells in culture, BS-1-28 exhibited anticancer activity that was >10,000-fold more potent than DMAPT, a sequiterpene drug currently in clinical trials for AML. To improve the drug-likeness of BS-1-28, we synthesized BS-3-18, a water-soluble analog, which exhibited GI50 values in the range 174 nM to 677 nM against 11 human cancer cell lines in the 60-cell panel, and retained the anticancer potency exhibited by the parent compound, BS-1-28, against rat 9L-SF gliosarcoma cells.

Conclusion
Ten novel MMB-heterocyclic/aliphatic carboxylic ester analogues have been synthesized and evaluated for their antileukemic activity against the M9-ENL1 cell lines and against primary AML cell lines from AML patients. Analogs were also evaluated against a panel of 60 human cancer cell lines. Among all the analogs investigated, BS-1-28 and BS-3-18 were found to be very promising anticancer agents with the potential as treatments for both solid and hematological cancers.