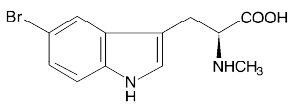
B143 Cytotoxic bromoindole derivatives and terpenes from a marine *Smenospongia* sp.

D. Tasdemir [a,b], T.S. Bugni [b], G.C. Mangalindan [c], G.P. Concepción [c], M.K. Harper [b] and C.M. Ireland [b]
[a] Hacettepe University, Faculty of Pharmacy, Department of Pharmacognosy, TR-06100 Ankara, Turkey. [b] University of Utah, Department of Medicinal Chemistry, Salt Lake City, Utah 84112, U.S.A. [c] Marine Science Institute, University of the Philippines, Quezon City 1101, Philippines.

In the continuation of our investigations into the chemistry of marine organisms, we investigated a *Smenospongia* sp. collected from the Philippines. Detailed examination of this sponge resulted in the isolation of a variety of simple indole alkaloids, 5-bromo-*L*-tryptophan (**1**), 5-bromo-*L*-abrine (**2**), 5,6-dibromo-*L*-abrine (**3**) and 5-bromoindole-3-acetic acid (**4**). The pyrroloiminoquinone alkaloid makaluvamine O (**5**), 5,6-dibromotryptamine (**6**), aureol (**7**) and furospinulosin 1 (**8**) were also isolated and characterized. The structures of **1-8** were established by spectroscopic methods (UV, IR, 1D and 2D NMR, MS, $[\alpha]_D$). 5-bromo-*L*-abrine (**2**) and 5,6-dibromo-*L*-abrine (**3**) are new compounds. 5-Bromo-*L*-tryptophan (**1**) and 5-bromoindole-3-acetic acid (**4**) have been synthesized previously, but this is the first report on the isolation of these compounds from a natural source. All compounds were screened in HCT-116 colon carcinoma cell lines using an MTT assay. Compounds that showed at least moderate cytotoxicity were further examined in a set of isogenic HCT-116 cell lines consisting of p53 and p21 knockouts ($p53^{-/-}$ and $p21^{-/-}$) as well as the parental cell line of each ($p53^{+/+}$ and $p21^{+/+}$). Makaluvamine O (**5**), 5,6-dibromotryptamine (**6**), aureol (**7**), and furospinulosin 1 (**8**) all displayed significant activity in HCT-116 cell lines. With the exception of makaluvamine O (**5**), all compounds showed decreased activity against the $p53^{-/-}$ cell line indicative of a p53 dependant mechanism. Makaluvamine O (**5**) showed a promising activity profile showing very little differential between the p53 cell lines while showing an order of magnitude lower IC_{50} (2.3 µg/ml) against the $p21^{-/-}$cell line.



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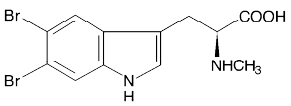

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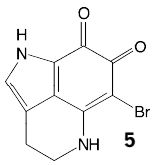

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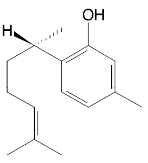
B144 Cytotoxic bisabolane type sesquiterpenes from a marine sponge, *Didiscus* sp.

D. Tasdemir [a,b], T.S. Bugni [b], G.C. Mangalindan [c], G.P. Concepción [c], M.K. Harper [b] and C.M. Ireland [b]
[a] Hacettepe University, Faculty of Pharmacy, Department of Pharmacognosy, TR-06100 Ankara, Turkey. [b] University of Utah, Department of Medicinal Chemistry, Salt Lake City, Utah 84112, U.S.A. [c] Marine Science Institute, University of the Philippines, Quezon City 1101, Philippines.

The p53 tumor suppressor gene is the most frequently mutated gene in human cancers. In response to DNA damage, p53 induces the expression of several genes, including p21 ($p21^{Waf1/Cip1}$), the key mediator of p53. In our continuing search for bioactive natural products from marine organisms, we screened marine invertebrate extracts in a set of isogenic colorectal cancer cells: wild type human colon tumor [HCT-116, $p53^{+/+}$ and $p21^{+/+}$], p53-deficient ($p53^{-/-}$) or p21-deficient ($p21^{-/-}$) HCT-116 cell lines in which the p53 and p21 genes were individually disrupted through homologous recombination. The crude MeOH extract of a Philippine marine sponge, *Didiscus* sp. showed some differential between the $p53^{+/+}$ and $p53^{-/-}$ HCT cell lines. Bioactivity-guided isolation carried out on the hexanes, $CHCl_3$ and aqueous MeOH extracts yielded two known bisabolane type sesquiterpenes, (+)-curcuphenol (**1**) and (+)-curcudiol (**2**), as well as β-sitosterol and phenethylamine. (+)-Curcuphenol (**1**) showed moderate activity against our panel of HCT-116 cells while (+)-curcudiol (**2**) was practically inactive at concentrations tested. Interestingly, **1** does not show a pattern indicative of a p53 dependant mechanism [IC50: 27 µg/ml ($p53^{+/+}$); 33 µg/ml ($p53^{-/-}$ and $p21^{+/+}$); 35 µg/ml ($p21^{-/-}$)], whereas the etoposide control clearly shows a dependence on p53 [IC_{50}: 2 µg/ml ($p53^{+/+}$); 10 µg/ml ($p53^{-/-}$), 2 µg/ml ($p21^{+/+}$) and 15 µg/ml ($p21^{-/-}$)].



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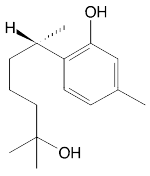

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