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Total synthesis and biological evaluation of tambjamine K and a library of unnatural analogs

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ABSTRACT

Herein we disclose the first total synthesis of tambjamine K and a library of unnatural analogs. Unnatural analogs were shown to be more potent in viability, proliferation, and invasion assays than the natural product in multiple cancer cell lines, with minimal to no cytotoxicity on non-transformed cell lines.

The tambjamines A–J (**1**–**10**) are a 2,2′-bipyrrolic class of cytotoxic alkaloids with diverse aliphatic termini isolated from bacteria and marine invertebrates and related to the tripyrolic prodigiosin **11** family (Fig. 1).[1–8] Members of this class have demonstrated a wide range of biological activities including antitumor, antimicrobial, and immunosuppressive properties. For tambjamines D (**4**) and E (**5**), the antitumor properties have been correlated with DNA intercalation and oxidative cleavage of single-strand DNA.[9] In a recent Letter in this journal, Gavagnin and co-workers described the isolation and characterization of a new member of the tambjamine family, tambjamine K (**13**), isolated from the Azorean nudibranch *Tambja ceutae*.[10] Like other members of this family, **12** displayed antiproliferative and cytotoxicity against tumor (CaCo-2, IC_{50} = 3.5 nM, HeLa IC_{50} = 14.6 μM, C6 IC_{50} = 14 μM, H9c2 IC_{50} = 2.7 μM, and 3T3-L1 IC_{50} = 19 μM) and non-tumor cell lines. Interestingly, **12** displayed differential effects across these tumor cell lines with a variance of >5000-fold (CaCo-2 vs 3T3-L1).[10] Based on these data and our own efforts in related areas, we initiated an effort for the total synthesis and biological evaluation of **12** along with a library of unnatural analogs with unprecedented diversity in the eastern C7 position to survey moieties other than aliphatic alkyl chains.

Interest in the tambjamine family originated in our evaluation[11] of Fenical's biosynthetic proposal[12] for synthesis of marineosin A (**14**) via an intramolecular inverse-electron demand Diels–Alder reaction with prodigiosin analog **13** (Fig. 2). Like **1**–**12**, marineosin A displayed potent cytotoxic activity against HCT116 cells (IC_{50} = 500 nM).[11,12]

Our synthetic approach to access **12** was similar to that we employed for the synthesis of **13**.[11] As shown in Scheme 1, a Vilsmeier–Haack haloformylation was performed on 4-methoxy-3-pyrrolin-2-one **15** to provide bromoenamine **16** in 59% yield. Suzuki coupling with Boc-1*H*-pyrrol-2yl boronic acid **17** delivered the Boc protected analog **18** in 48% yield. Finally, an acid mediated condensation between **18** and isopentyl amine **18** afforded tambjamine K (**12**) in 65% yield and 18% overall yield for the three step sequence. Synthetic **12** was identical in all aspects to the natural product.[13]

While **12** was studied in a number of tumor cell lines, it was not evaluated in cell viability assays with HCT116 colorectal carcinoma or MB231 breast carcinoma cell lines—tumor lines of interest to our lab.[14] Moreover, we had not yet evaluated **13** or another related prodigiosin analog **19** we employed as a template for an intermolecular inverse-electron demand Diels–Alder (IEDDA) reaction to access the marineosin A core.[11] As shown in Table 1, tambjamine K (**12**) displayed weak cytotoxicity against HCT116 (IC_{50} = 13.7 μM) and MB231 (IC_{50} = 15.3 μM). In contrast, the intramolecular IEDDA prodigiosin analog **13** was more potent with IC_{50} values of 3.5 μM for both tumor lines. The intermolecular IEDDA prodigiosin analog **19** was found to be extremely potent, with IC_{50} values of 146 nM and 362 nM, for HCT116 and MB231 cell lines, respectively.

These data prompted us to synthesize and evaluate a library of unnatural tambjamine analogs[15] to capitalize on the SAR observed for this class of natural products akin to our earlier work developing unnatural analogs with activities beyond the natural product.[16–18]

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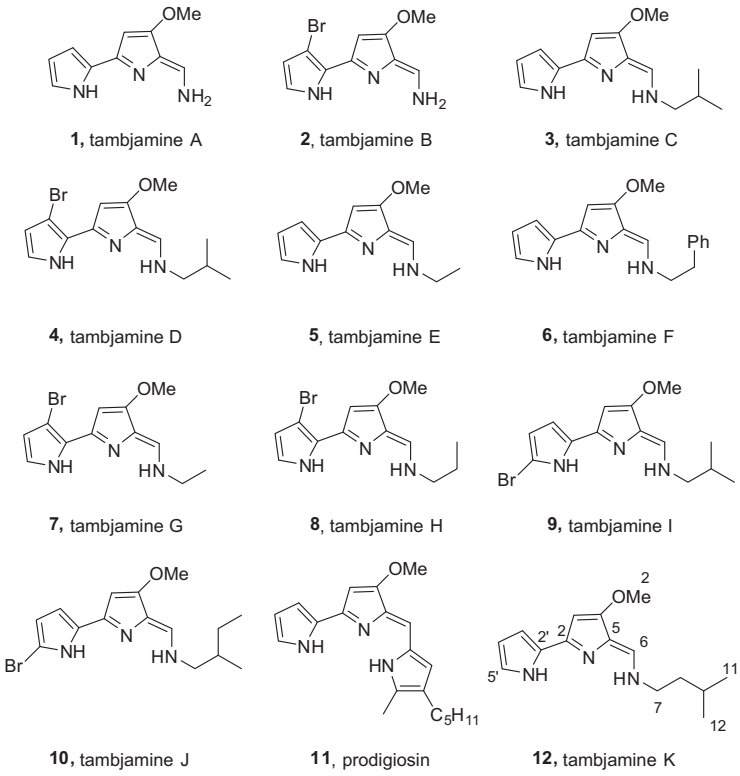


Figure 1. Structures of the tambjamines A–J (**1**–**10**), prodigiosin (**11**) and the newly discovered tambjamine K (**12**).

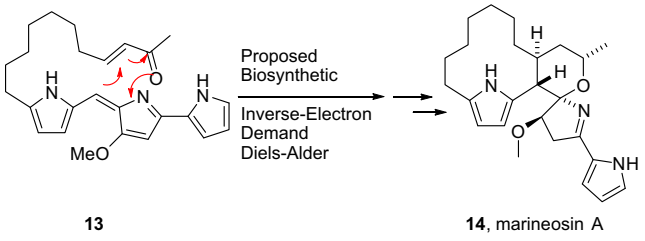
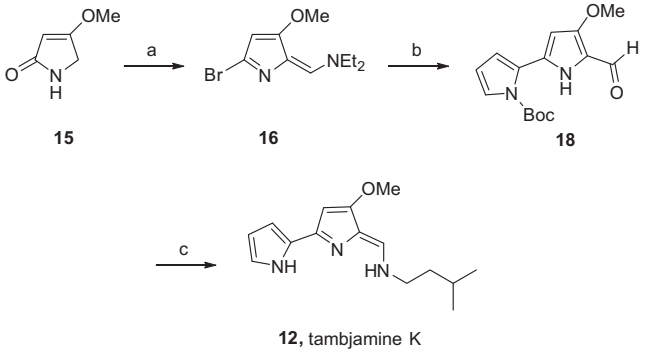


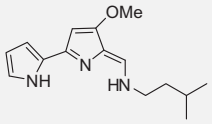
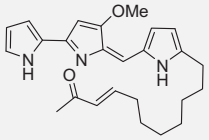
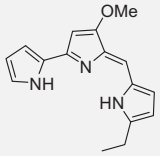
Figure 2. Proposed biosynthesis of marineosin A (**14**) via an inverse-electron demand Diels–Alder reaction with prodigiosin analog **13**.



Scheme 1. Reagents and conditions: (a) (i) $POBr_3$, $HCONEt_2$, CH_2Cl_2, 0–40 °C, 3.5 h; (ii) 15% NaOH until pH ~7, 59%; (b) (i) $Pd(OAc)_2$, PPh_3, toluene, 70 °C, 20 min; (ii) Boc-1*H*-pyrrol-2yl boronic acid (**17**), 9:1 dioxane/H_2O, Na_2CO_3, 85 °C, 3 h, 48%; (c) isopentyl amine, 0.87 M HCl, MeOH, rt, 6 h, 65%.

Importantly, Quinn and co-workers[19] previously prepared a combinatorial library of 10 unnatural tambjamine analogs, but all possessed limited diversity with respect to R^2 and aliphatic side chains dominated.

Table 1
Structures and activities of tambjamine K and unnatural analogs

Compd	Structure	HCT116 IC_{50}[a] (μM)	MBA231 IC_{50}[a] (μM)
12		13.7	15.3
13		3.6	3.5
14		0.14	0.36

[a] 8000 cells/well in 96-well plate followed by 24 h for attachment. Added vehicle or compounds in RPMI 1640 plus 10% FBS + penicillin–streptomycin. Cells allowed to grow for 48 h, then viability was assessed.

Our library was designed to incorporate functionalized benzyl, heteroaryl moieties and other previously undescribed analogs with varying degrees of lipophilicity and basicity to further develop SAR. The library was prepared as shown in Scheme 2, and differed from the route to access **12** only in extended reaction time, as several amines proved sluggish in their conversion to unnatural tambjamine analogs **20**; however, all analogs were successfully prepared in yields ranging from 35% to 88%.[15]

We triaged the library of analogs **20** by a employing a 10 μM single point screen in the standard 48 h viability assay using both HCT116 and MB231 cells.[14] The majority of analogs, especially the