SYNTHESIS OF MARINE NATURAL PRODUCT ANALOGUES

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2-aminoimidazoles such as naamidine A (Figure 1) show an abundant presence in marine natural product cores, and have motivated the development of methodology to access these nitrogen-rich heterocycles with robust chemistry. Tailoring of the heterocycle to the 2-monoacylaminoimidazole scaffold has yielded a class of pharmacologically privileged compounds that include transforming growth factor β1 receptor (TGFβ1) inhibitors, integrin receptor antagonists, glial inflammation suppressors, XIAF inhibitors, anti-hepatitis C compounds, and p-gp-multidrug resistance reversal agents.

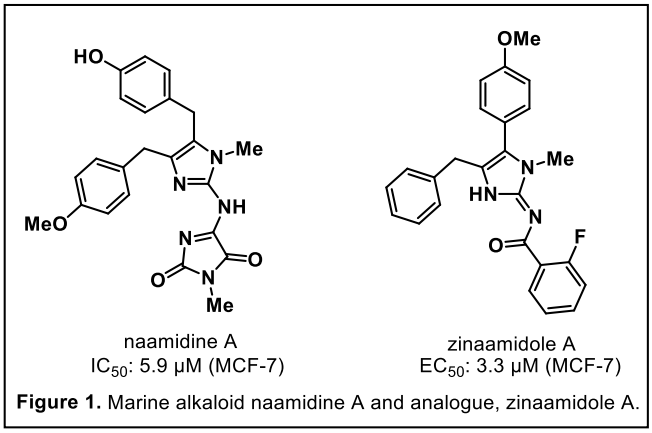


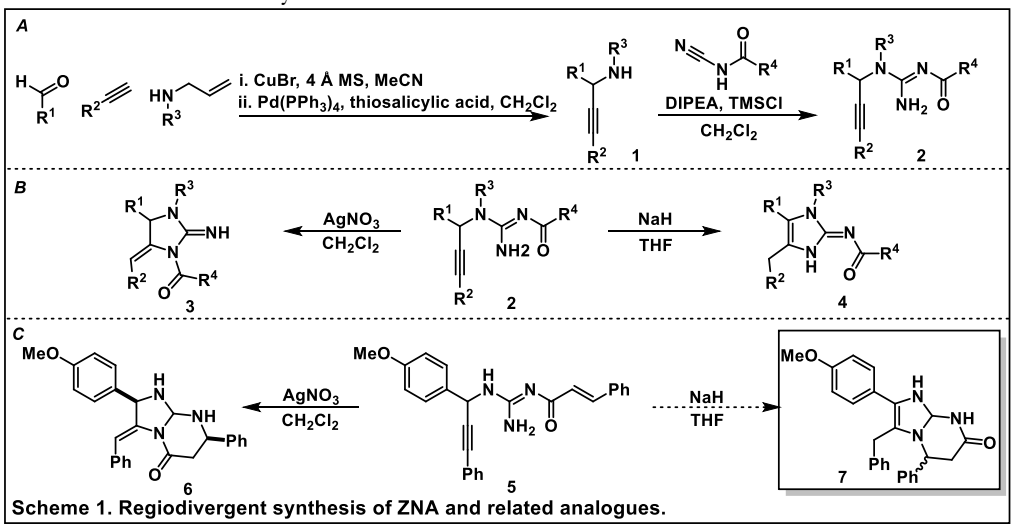
Figure 1. Marine alkaloid naamidine A and analogue, zinaamidole A.

We were particularly inspired by the unique EGF-dependent cytotoxicological profile of naamidine A, a 2-aminoimidazole alkaloid originally isolated from the marine sponge Leucetta chagosensis, and its applications in breast cancer therapy. Extending our methodology for the synthesis of naamidine A, we reported a number of first generation analogues. Initial screening of these compounds identified zinaamidole (ZNA) as a promising lead due to its anti-proliferative activity (EC_{50} =1.4 μM) against drug-resistant pleural effusion cells derived from patients with breast cancer (PE1005339) as well as immortalized, cancerous MCF-7 cells (EC_{50} = 3.3 μM). In additional assays, ZNA showed negligible cytotoxicity against the untransformed breast cancer cell line MCF-10a, unlike its natural product inspiration naamidine A. The demonstrated preferential growth inhibition against cancerous tissue necessitated efforts towards scalable, modular synthesis of ZNA and structurally related compounds.

This work has been focused on developing a base-promoted tandem cyclization-Michael addition of α-β unsaturated *N*-monoacylpropargylguanidines to form bicyclic guanidines analogous to the core ZNA structure. Three-component coupling of an aldehyde, alkyne, and *n*-allylmethylamine yields an allyl-protected propargylamine. Deprotection with $Pd(PPh_3)_4$ and thiosalicylic acid unmasks a propargylamine **1**, which can undergo guanylation with acylcyanamides to yield propargylguanidine **2** (Scheme 1A). Addition of a Lewis acid ($AgNO_3$) or a strong base (NaH) gives divergent regioselectivity (Scheme 1B).

Further studies are being conducted to determine a productive method for the synthesis of the desired bicyclic guanidine **7** (Scheme 1C). While we have obtained the product as shown by NMR spectroscopy, it is present in a 1:1 mixture with the

starting material. Our efforts are currently directed toward the optimization of reaction conditions to yield **7.**



Scheme 1. Regiodivergent synthesis of ZNA and related analogues.