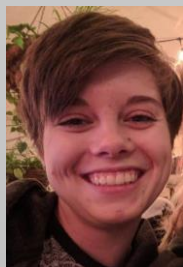


REGIOSELECTIVE CONSTRUCTION OF N²-ACYL-C⁴-ARYLAMINOIMIDAZOLES

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I have worked on developing methodology towards N²-acyl-C⁴-arylaminoimidazoles, a class of compounds inspired by the marine alkaloid naamidine A (NA) (Figure 1). The library of 2-acylaminoimidazoles designed to mimic the zinc-chelating siderophore NA were included in a university-wide small molecule screen against chemoresistant pleural effusion cells. From this library, zinaamidole (ZNA) was identified as a scaffold that induced selective toxicity in transformed cell lines.¹ ZNA analogs were investigated in order to improve ZNA's poor solubility and reduce high clearance rates.

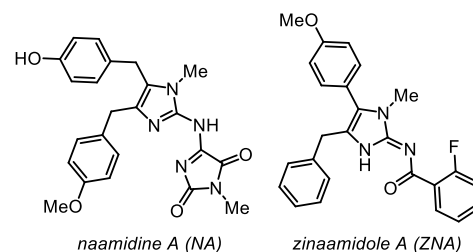
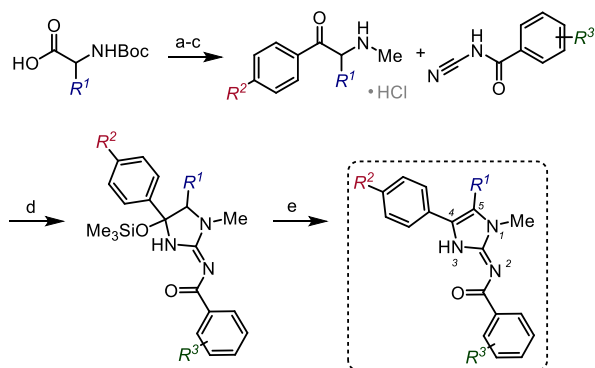


Figure 1. Structures of naamidine A and zinaamidole A.

Previous methods used in the synthesis of ZNA analogs relied on a metal or base-catalyzed hydroamination of propargylguanidines.² The formation of regioisomers of ZNA were explored due to the similar zinc-binding topology. Our previous synthesis did not afford these regioisomers due to the 5-exo-dig cyclization of the propargylguanidines. Our synthesis (Scheme 1) of these ZNA analogs began with the Weinreb amidation of N-methyl Boc-protected amino acids. Nucleophilic addition of Grignard reagents allowed for the formation of the α -amino ketones, which were subsequently deprotected. Guanylation chemistry with cyanobenzamides developed in the Looper lab then allowed for the formation of the monoacylguanidine, which cyclized to



Scheme 1. Synthesis of N²-acyl-C⁴-arylaminoimidazoles. a) HNMeOMe-HCl, CDI, CH₂Cl₂; b) R²MgBr, THF; c) HCl, MeOH; d) TMSCl, iPr₂NEt, CH₂Cl₂; e) TFA (cat.), EtOH.

the silyl hemiaminal (confirmed by x-ray crystallography). Treatment of this intermediate with strong acid then afforded the desired aminoimidazole. This chemistry enabled the construction of a library of 16 analogs, which are currently being evaluated in dose-response assays in MCF-7 (breast cancer) and MCF-10A (untransformed breast tissue) cell lines.

References:

(1) Gligorich, K. M.; Vaden, R. M.; Shelton, D. N.; Wang, G.; Matsen, C. B.; Looper, R. E.; Sigman, M. S.; Welm, B. E., Development of a screen to identify selective small molecules active against patient-derived metastatic and chemoresistant breast cancer cells. *Breast Cancer Res.* **2013**, 15 (4), R58.

(2) Gibbons, J. B.; Salvant, J. M.; Vaden, R. M.; Welm, B. E.; Looper, R. E. "A synthesis of naamidine A and selective access to N²-acyl-2-aminoimidazole analogues." *J. Org. Chem.* **2015**, 80 (20), 10076-10085.

