REGIOSELECTIVE CONSTRUCTION OF N^2-ACYL-C^4-ARYLAMINOIMIDAZOLES

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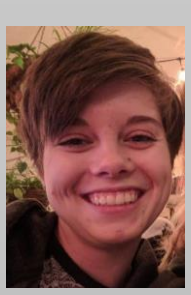

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I have worked on developing methodology towards N^2-acyl-C^4-arylaminoimidazoles, a class of compounds inspired by the marine alkaloid naamidine A (NA) (Figure 1). The library of 2-acylaminoimidazoles designed to mimic the zinc-chelating siderophore 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.

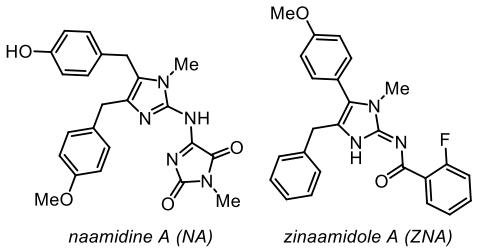
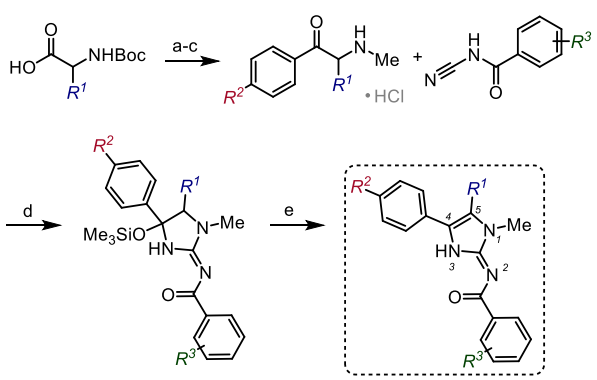


Figure 1. Structures of naamidine A and zinaamidole A.

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 Nmethyl Boc-protected amino acids. Nucleophilic addition of Grignard reagents allowed for the formation of the αamino 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 the silyl hemiaminal (confirmed by x-ray crystallography). Treatment of this intermediate with strong acid then afforded the desired aminoimidzole. 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.



Scheme 1. Synthesis of N^2-acyl-C^4-arylaminoimidazoles. a) HNMeOMe-HCl, CDI, CH_2Cl_2; b) R^2MgBr, THF; c) HCl, MeOH; d) TMSCl, iPr_2NEt, CH_2Cl_2; e) TFA (cat.), EtOH.

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.