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Synthesis and antibacterial activity of novel water-soluble nocathiacin analogs

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ABSTRACT

Semi-synthetic water-soluble analogs were synthesized from nocathiacin I through the formation of a versatile intermediate nocathiacin amine **5**, and subsequent transformation via reductive amination, acylation or urea formation. Several of the novel analogs displayed much improved aqueous solubility over **1**, while retained antibacterial activity. Compound **15** and **16** from the amide series, demonstrated excellent in vitro and in vivo antibacterial activity.

Nocathiacins are a group of thiazolyl peptide antibiotics isolated from the fermentation broth of *Norcadia* sp.[1,2] and fungus *Amicolaptosis* sp.[3] Nocathiacin I (**1**, Fig. 1), the most abundant member of the family, displays potent in vitro antibacterial activity[4] against a variety of Gram-positive bacteria and exhibits in vivo efficacy in a systemic *Staphylococcus aureus* infection mouse model.[5] While poor aqueous solubility of nocathiacin I precludes its potential for development as a hospital iv drug, its novel structure and superior antibacterial activity make it a promising lead for the development of new antibacterial agents with broad spectrum efficacy against resistant pathogens, and it has served both as a lead and starting material for the development of novel semi-synthetic water soluble antibiotics.[6–12]

The presence of several functional groups (hydroxyl, olefin, amide) in nocathiacin I presents multiple opportunities for chemical manipulation. Previous approaches described in the literature to obtain compounds with increased water solubility include derivatization of the pyridyl hydroxyl and/or indole *N*-hydroxyl with structural diverse polar groups,[6,7] Michael addition of amines and thiols to the dehydroalanine side chain,[8] substitution of dehydroalanine with L-alanine amides,[9] and synthesis of amino ethyl amides via Amadori rearrangement.[10] As part of our own efforts in this area, we recently disclosed[11] a facile conversion of nocathiacin I to an important and versatile intermediate nocathiacin acid (**3**, Fig. 1), and subsequent coupling to various amines to yield a variety of water-soluble nocathiacin analogs.[12] In this Letter, we describe an alternate approach to obtain novel water-soluble analogs through a series of transformations involving the generation of an amine versatile intermediate (**5**, Scheme 1).

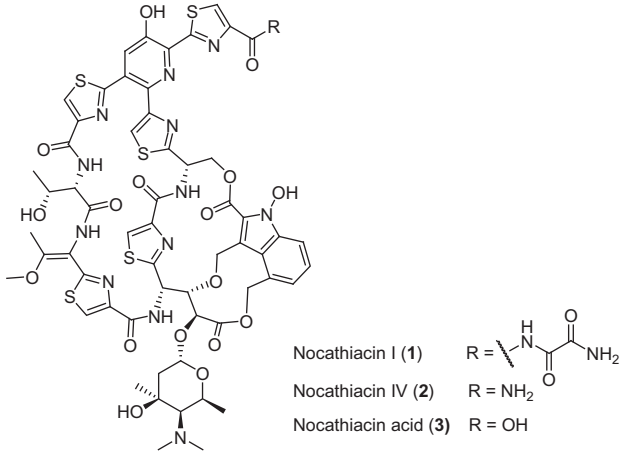

Figure 1. Structures of nocathiacins I, IV and nocathiacin acid.

Amine **5** was readily synthesized in 2 steps from nocathiacin IV (**2**, Scheme 1), prepared from nocathiacin I by a known procedure.[13] Although a very large number of reagents have been reported to dehydrate primary amides to nitriles,[14] the presence of several sensitive motifs and chiral centers in nocathiacins limited our choice of reagents to convert **2 to 4**. After multiple unsuccessful attempts with various reagents and conditions, including Burgess Reagent, cyanuric chloride, and oxalyl chloride, we found that the desired transformation could be accomplished cleanly by

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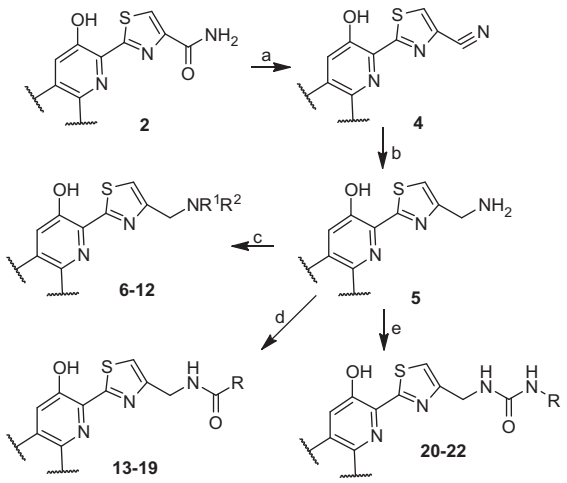


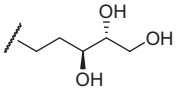
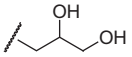
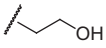
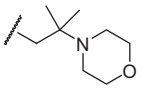
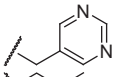
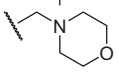
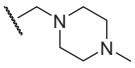
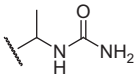
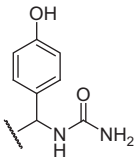
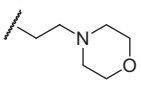
Scheme 1. Reagents and conditions: (a) TFAA, Py, THF, 0 °C; (b) H_2, Rh/Al_2O_3, MeOH, NH_4OAc, 50 psi; (c) RCHO, $NaCNBH_4$, MeOH, AcOH; (d) RCO_2H, EDC, HOBt, DMF; (e) RN = C=O or 4-NO_2Ph carbamate.

the treatment of **2** with trifluoroacetic anhydride and pyridine in THF or acetonitrile at 0 °C. Intermediate nitrile **4** was obtained in moderate yield after purification by silica gel chromatography or reversed-phase HPLC.

The subsequent reduction of **4** to the primary amine **5** was accomplished with catalytic hydrogenation using 5% Rh/Al_2O_3 in methanol.[15] A significant excess of rhodium (up to 100% mol) was needed in order to drive the reaction to moderate product formation, presumably due to the presence of many hetero atoms in **4**. Excess ammonium acetate (20 equiv) was used to suppress the formation of secondary amine side product.[16] Other catalysts were found to be either ineffective (Pd/C, cobalt powder, $Pd/CaCO_3$) or destructive (Raney Ni). Chemical reduction with $NaBH_4/CoCl_2$[17] or $NaBH_4/NiCl_2$, $N_2H_4/HCOOH$[18] and $BH_3/NiCl_2$ all resulted in decomposition of **4** with trace amount of **5**.

Compound **5** was proved to be highly amenable to elaboration. It can be readily transformed into a variety of analogs under mild conditions (Scheme 1). Reductive amination with various aldehydes produced compounds **6**–**12** in quantitative yield. Coupling to different carboxylic acids under standard peptide coupling

Table 1
Antibacterial activity of nocathiacin analogs **5**–**22**

Compound	R or R^1R^2	MIC (μg/mL)			**ED_{99}**[a] (mg/Kg)
		S. aureus MB2865	*S. pneumo.* CL2883	*E. faecalis* C21560	
1	—	0.007	0.002	0.03	
5	—	0.077	0.00047	0.06	>0.5
6	$(CH_3)_2$	0.03	0.00095	0.0075	>0.5
7		0.125	0.015	1	ND[b]
8		0.06	0.0075	0.25	ND
9		0.03	0.00046	0.06	0.32
10		0.06	0.00046	0.03	ND
11	$(CH_2CH_2OH)_2$	0.06	0.0075	0.12	ND
12		0.0225	0.0007	0.03	0.13
13		0.06	0.0075	0.25	> 0.5
14		0.0075	0.00046	0.015	> 0.5
15		0.0375	0.0007	0.09	0.28
16		0.06	0.0038	0.25	0.02
17		>1	ND	>1	ND
18		0.0075	0.00457	0.0075	ND
19		0.06	0.0075	0.12	> 0.5

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