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3-Hydroxy-1,5-dihydro-*2H*-pyrrol-2-ones as novel antibacterial scaffolds against methicillin-resistant *Staphylococcus aureus*

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ABSTRACT

Herein, we report the synthesis and evaluation of 3-hydroxy-1,5-dihydro-*2H*-pyrrol-2-ones as antibacterial agents against methicillin-resistant *S. aureus* (MRSA) and methicillin-resistant *S. epidermidis* (MRSE). Lead compound **38** showed minimum inhibitory concentrations (MICs) of 8 and 4 μg/mL against MRSA and MRSE, respectively. Furthermore, compound **38** displayed a MIC of 8–16 μg/mL against linezolid-resistant MRSA. These molecules, previously underexplored as antibacterial agents, serve as a new scaffold for antimicrobial development.

Arising from the acquisition of staphylococcal cassette chromosome *mec* (SCC*mec*) by *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA) displays an altered penicillin-binding protein (PBP2a) that renders β-lactam antibiotics (BLAs) ineffective as therapeutic agents.[1] As such, MRSA infections can be difficult to treat, and in some cases, life-threatening. While several classes of antibiotics have been developed to combat such infections, including oxazolidinones (linezolid),[2] resistance is becoming an increasing issue in the clinic. Therefore, the development of novel antibiotic scaffolds is crucial to our ability to effectively treat MRSA infections and natural products and their analogs are fruitful starting points for these explorations.[3]

Isolated in 1995 and 2005 from the marine fungus *Chromocleista* sp., phenopyrrozin[4] (**1**) and *p*-hydroxyphenopyrrozin[5] (**2**) are marine natural products containing the 2-hydroxy-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-one core. While the isolation group reported no activity of **1** or **2** against *S. aureus* at tested concentrations,[4] a modest minimum inhibitory concentration (MIC) of 50–100 μg/mL was reported against the Gram-positive pathogen *Bacillus cereus*.[6] Prompted by this initial report, as well as our recent synthesis of the natural products and a series of novel analogs (Scheme 1),[7a-d] we aimed to explore the development of the scaffold as antibacterial agents against methicillin-resistant *S. aureus* and other Gram-positive pathogens.

Starting from the natural products **1** and **2**, we explored functionalization of the aryl side chain while maintaining the [3.3.0] bicyclic core (Fig. 1). Building off of our previously reported cyclization/condensation reaction between cyclic imines and α-oxoesters, a library of phenopyrrozin analogs, along with the natural products, was prepared.[7a] A variety of substitution patterns were investigated, including electron rich aryl (**3**), electron poor aryl (**4**–**6**), heteroaromatic (**7**), alkyl (**8**), and allyl (**9**) substituted derivatives. Initial antimicrobial testing of this series revealed a MIC of 128 μg/mL for compounds **4** and **5** against MRSA (ATCC 33591), while all other analogs showed no activity at the maximum tested concentration (128 μg/mL) (Table 1). Intrigued by the initial hits, several other analogs were prepared to further develop a structure-activity relationship (SAR). To explore whether the origin of the activity of **4** and **5** arises from the electron withdrawing nature of the substituents, or the steric bulk they impart, compounds **10** and **11** were synthesized (Fig. 1). With a 4-fluorophenyl substituent, compound **10** electronically resembles **4** and **5**, yet is an isostere of the inactive natural product **1**. Compound **11**, with a 4-methylphenyl substituent, was designed as an electron-rich isostere of **4**. The 4-chlorophenyl analog **12** was also synthesized to complete the series of 4-haloaryl analogs. Compounds **10** and **12** showed no activity at tested concentrations, while **11** maintained the activity of **4** and **5** with MICs of 128 μg/mL.

We next aimed to investigate effects of varying the ring size of the core. Starting with a six-membered cyclic imine, a similar approach was employed to synthesize analogs with the [4.3.0]

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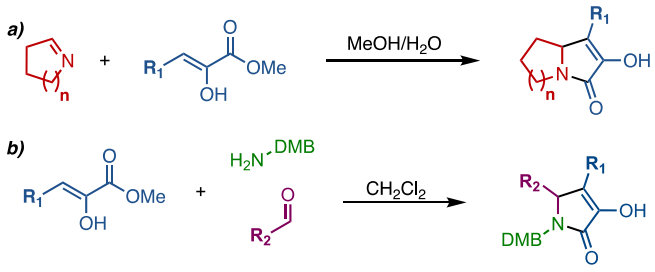

Scheme 1. Our previously reported approaches to 2-hydroxy-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-ones (a) and 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one scaffolds (b).

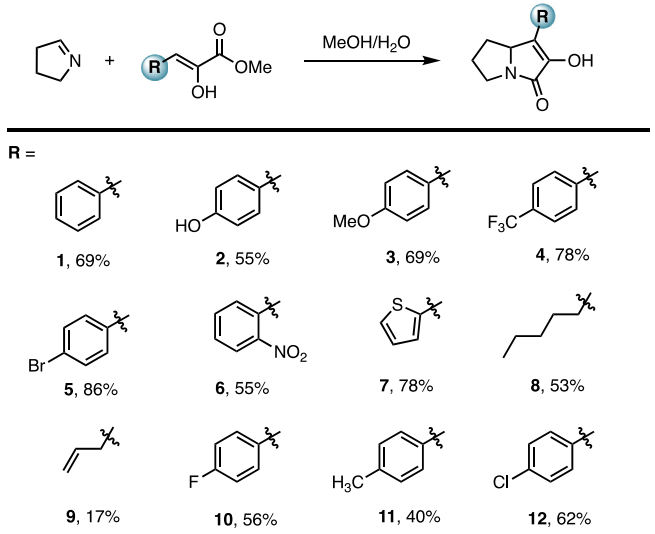

Fig. 1. Synthesis of 2-hydroxy-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-one core analogs.

Table 1
MIC values of compounds against ATCC 33591 (MRSA).

Compound	MIC (μg/mL)	Compound	MIC (μg/mL)
1	>128	**22**	32
2	>128	**23**	128
3	>128	**24**	64
4	128	**25**	128
5	128	**26**	8
6	>128	**27**	2
7	>128	**28**	32
8	>128	**29**	32
9	>128	**30**	64
10	>128	**31**	64
11	128	**32**	32
12	>128	**33**	>128
13	>128	**34**	16
14	16	**35**	32
15	32	**36**	32
16	>128	**37**	8
17	32	**38**	8
18	>128	**39**	32
19	>128	**40**	64
20	>128	**41**	32
21	>128	Linezolid	1

bicyclic core with varying substituents, including aryl, heteroaryl and electronically-varied aryl derivatives (Fig. 2). A general trend of increased activity was observed (Table 1). Compounds **15** and **17**, the six-membered ring analogs of **4** and **5**, showed a 4x increase in activity with MICs of 32 μg/mL. Interestingly, the 2-thienyl substituted analog (**14**) was the most potent with a MIC

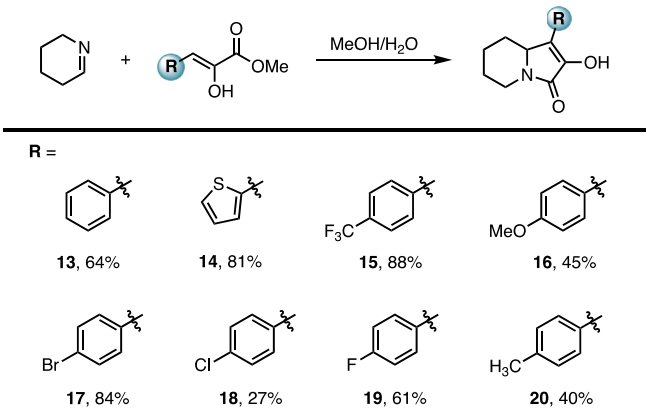

Fig. 2. Synthesis of 2-hydroxy-6,7,8,8a-tetrahydroindolizin-3(5*H*)-one core analogs.

of 16 μg/mL. The ring-expanded version of phenopyrrozin (**13**) remained inactive. Due to the metabolic liability of a thiophene, the 4-(trifluoromethyl)phenyl side chain of **15** was employed in further optimization studies.

At this stage we investigated the role of the enolic proton in the activity of the scaffold by converting **15** to vinyl methyl ether **21** (Fig. 3). Treatment of **15** with K_2CO_3 and iodomethane in acetone yielded the desired compound **21** with only *O*-methylation observed. Interestingly, **21** displayed no activity at tested concentrations. As such, we postulate the ability to hydrogen bond or to tautomerize between the enol- keto- form is critical to the general activity of the scaffold.

Given the importance of ring size in the structure-activity relationship, we next aimed to explore the synthesis of a further ring expanded analog. To achieve the synthesis of the [5.4.0] bicyclic motif with our established methods, a seven-membered imine would be required. The instability of the imine, however, requires an *in-situ* generation, followed by trapping with the corresponding α-oxoester. To accomplish this, hexamethyleneimine was treated with NCS in Et_2O to yield the corresponding *N*-chloramine, which was then subjected to KOH in ethanol to generate the seven-membered cyclic imine.[8] The resulting imine was subsequently trapped with an α-oxoester to provide **22** (Scheme 2). **22** had comparable activity to that of the six-membered analog **15**, with a MIC of 32 μg/mL (Table 1).

The substitution on the six-membered ring of **15** was next explored. The respective *p*-methyl six-membered cyclic imine was prepared and yielded **23** as a 4:1 mixture of diastereomers (Fig. 3). As the diastereomers were inseparable by column chromatography, the 4:1 mixture was tested against MRSA to provide a MIC of 128 μg/mL (Table 1).

In parallel to exploring various ring sizes of cyclic imine substrates, we continued our investigations to include the monocyclic 3-hydroxy-1,5-dihydro-2H-pyrrol-2-one scaffold. Analogous to the preparation of the bicyclic compounds, 3-hydroxy-pyrrol-2-ones were accessed via the condensation of acyclic imines with α-oxoe-

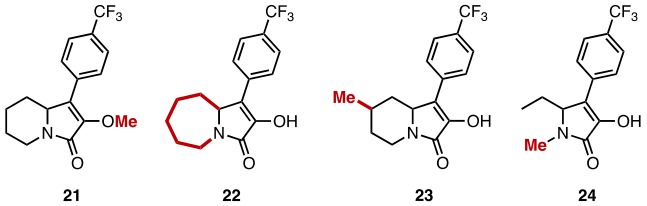

Fig. 3. Expanded SAR via structural modifications to compound **15**.