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Exploration of the structure–activity relationship of 1,2,4-oxadiazole antibiotics

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ABSTRACT

We have recently disclosed the discovery of the class of 1,2,4-oxadiazole antibiotics, which emerged from in silico docking and scoring efforts. This class of antibacterials exhibits Gram-positive activity, particularly against *Staphylococcus aureus*. We define the structure–activity relationship (SAR) of this class of antibiotics with the synthesis and evaluation of a series of 59 derivatives with variations in the C ring or C and D rings. A total of 17 compounds showed activity against *S. aureus*. Four derivatives were evaluated against a panel of 16 Gram-positive strains, inclusive of several methicillin-resistant *S. aureus* strains. These compounds are broadly active against Gram-positive bacteria.

The Gram-positive bacterium *Staphylococcus aureus* is commensal to humans and exists on the skin and mucosa of 30% of the population.[1,2] It is a principal cause of hospital infections, the most frequent and serious of which are bacteremia and endocarditis in hospitalized patients.[3–6] This organism has become resistant to many different classes of antibiotics.[7,8] Of special concern are the strains designated as methicillin-resistant *S. aureus* (MRSA), which are broadly resistant to most -lactam antibiotics, agents of historic choice for treatment of infections by *S. aureus*. There has been recent activity in discovery of novel antibiotics for treatment of *S. aureus* infections,[9] but emergence of antibiotic-resistant variants is inevitable, necessitating search for novel classes of antibiotics effective against these organisms.

We recently reported the discovery of the 1,2,4-oxadiazole class of antibiotics, which emerged from in silico docking and scoring, followed by screening against the ESKAPE panel of bacteria.[10,11] This class of antibiotics targets the cell wall for inhibition, it exhibits good in vitro and in vivo activity and it is orally bioavailable.[10,11]

The 1,2,4-oxadiazoles are generally comprised of four rings, designated as A, B, C and D, as indicated by the representative compound **1a** (Fig. 1). A hydrogen-bond donor in the A ring is necessary for antibacterial activity. The phenol, aniline and some heterocycles with hydrogen-bonding capability, such as pyrazoles, are tolerated. However, some substituents at this site such as sulfonamides, amides and carboxylic acids reduce the antibacterial activity or are inactive.[11] Hydrogen-bond acceptors on the A ring are not favored. As indicated, pyrazoles with halogen substituents are all active, as is the indole at the A ring. Other variants with heteroaromatic systems such as pyridines, triazoles and pyrroles generally lose activity, as do the ones with aliphatic heterocycles.[11]

We outline here our preparation and evaluation of a series of 59 additional oxadiazole analogs. In general, the derivatives have attempted to explore the effect of structural diversity on the antibacterial activity on the right-hand side of the molecule in the perspective depicted in Figure 1. The diverse analogs were selected for variation in rings C or in rings C and D, inclusive of fused-ring variants (Fig. 2). These studies further define the structure–activity relationship (SAR) for this class of antibacterials.

The general synthesis of this library followed the methodology reported earlier, as depicted in Scheme 1.[11] Nitrile intermediates with the C and D rings fused were commercially available (examples **26** and **33**). The nitrile intermediates **2**–**50** were key to the formation of the 1,2,4-oxadiazole derivatives. The biphenyl ether fragment can be formed through Ullmann reaction or aromatic substitution. The former takes place between aryl iodides and phenols in the presence of CuI, Cs_2CO_3 and *N*,*N*-dimethylglycine·HCl at 90 °C. Nucleophilic aromatic substitution between the aryl fluorides and phenols was accomplished using K_2CO_3 as base. With the nitriles **2**–**50** in hand, the amidoximes were easily generated from the reaction between the nitrile and hydroxylamine in ethanol. Under the standard conditions, the acyl chloride was allowed to react with amidoxime in the presence of pyridine under reflux to afford the key 1,2,4-oxadiazole

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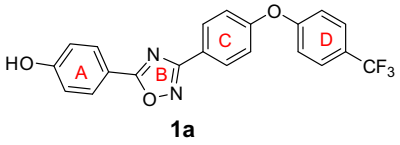

1a

Figure 1. The structure of compound **1a**.

intermediates. Removal of the protective groups furnished the final compounds. For example, the Boc group was removed by exposure to acid and deprotection of the benzyl was performed in the presence of BBr_3.

These compounds were screened for antibacterial activity by determination of minimal-inhibitory concentrations (MICs) against the ESKAPE panel of bacteria, including *S. aureus* ATCC29213. Active compounds were designated as those with MIC values of $\leqslant$8 μg/mL, which encompassed 17 of the synthetic compounds. The MIC data and the corresponding structures are listed in Figure 2. All the active derivatives (**51a–67a)** have the phenol moiety as the A ring. Compounds **51a** and **52a** displayed identical antibacterial potency with an MIC value of 2 μg/mL, which indicated both the electron-withdrawing group chlorine or the electron-donating hydroxyl were well tolerated. Other substituents such as iodine, fluorine and the nitro group at the R^1 and R^2

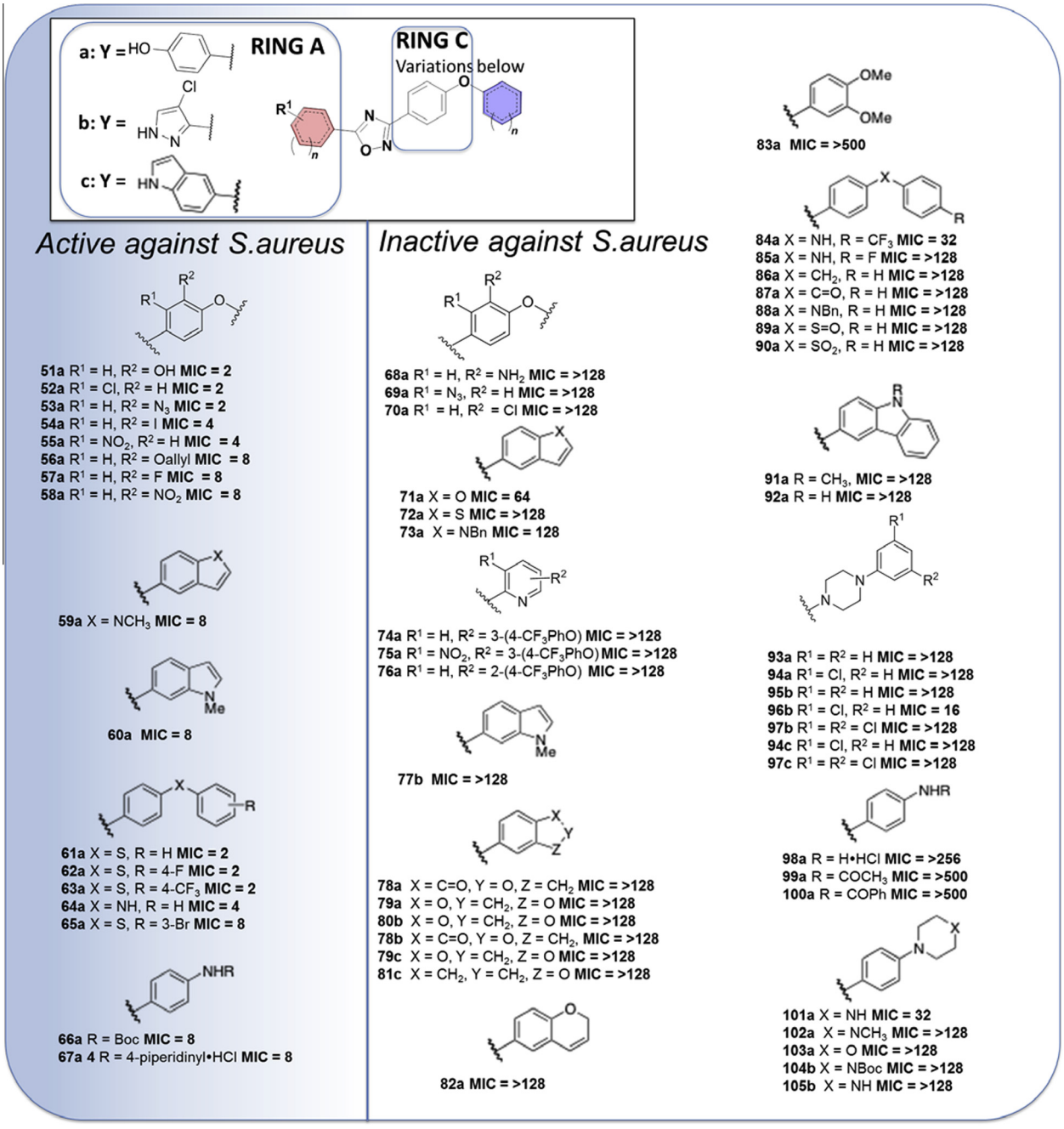

Figure 2. Results of in vitro antibacterial activity against *S. aureus* ATCC29213 of the new 1,2,4-oxadiazole derivatives. The functional groups in ring C were changed to produce all the synthetic compounds in this series and Y was limited to the three indicated entities. MIC values were measured in μg/mL and active compounds have an MIC $\leqslant$ 8 μg/mL.