

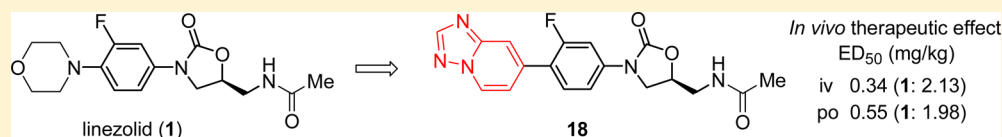
## Potent Oxazolidinone Antibacterials with Heteroaromatic C-Ring Substructure

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### S Supporting Information



**ABSTRACT:** Novel oxazolidinone analogues bearing a condensed heteroaromatic ring as the C-ring substructure were synthesized as candidate antibacterial agents. Analogues **16** and **21** bearing imidazo[1,2-a]pyridine and **18** and **23** bearing [1,2,4]triazolo[1,5-a]pyridine as the C-ring had excellent *in vitro* antibacterial activities against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecalis* (VRE), and penicillin-resistant *Streptococcus pneumoniae* (PRSP). They also showed promising therapeutic effects in a mouse model of lethal infection. Preliminary safety data (inhibitory effects on cytochrome P450 isoforms and monoamine oxidases) were satisfactory. Further evaluation of **18** and **23** is ongoing.

**KEYWORDS:** Antibacterial, oxazolidinone, methicillin-resistant *Staphylococcus aureus*, condensed heteroaromatic ring

Infections caused by multidrug-resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA),<sup>1</sup> vancomycin-resistant *Enterococcus faecalis* (VRE),<sup>2</sup> and penicillin-resistant *Streptococcus pneumoniae* (PRSP),<sup>3</sup> are a major problem in hospitals around the world, and effective antibiotics are urgently needed. Oxazolidinone antibacterials are a class of synthetic antibiotics that have been developed over the last three decades<sup>4,5</sup> and are composed of an A-ring (oxazolidinone), B-ring (phenyl), and C-ring (an appropriate heterocycle, such as morpholine or piperazine), with a C-5 side chain unit on the A-ring substructure. Linezolid (**1**) was the first oxazolidinone antibiotic to be approved by the US Food and Drug Administration (FDA) and has been used for the treatment of serious infections caused by Gram-positive strains such as MRSA and VRE since 2000 (Figure 1).<sup>6</sup> However, linezolid-resistant *Staphylococcus aureus* and *Enterococcus* spp.<sup>7–9</sup> have appeared since **1** was released, and **1** is also an inhibitor of monoamine oxidases (MAOs), which may result in drug–drug interactions with adrenergic and serotonergic agents.<sup>10</sup> Thus, there is considerable interest in new oxazolidinone-type drug candidates (Figure 1). A series of oxazolidinones containing a pyrroloaryl substituent as C-ring unit was developed by J&J Pharmaceutical, and one analogue advanced to phase I clinical trial.<sup>11</sup> Ranbezolid (**2**), which has a furan ring as the terminal unit, was developed by Ranbaxy Laboratories, and a phase I clinical trial was performed in 2003.<sup>12,13</sup> Radezolid (**3**), which has a [1,2,3]triazole framework as the terminal substructure, was developed by Rib-X Pharmaceuticals and has completed a phase II clinical trial.<sup>5</sup> Tedizolid phosphate (**4**, formerly called torezolid phosphate), which contains a tetrazole structure, was developed by Trius

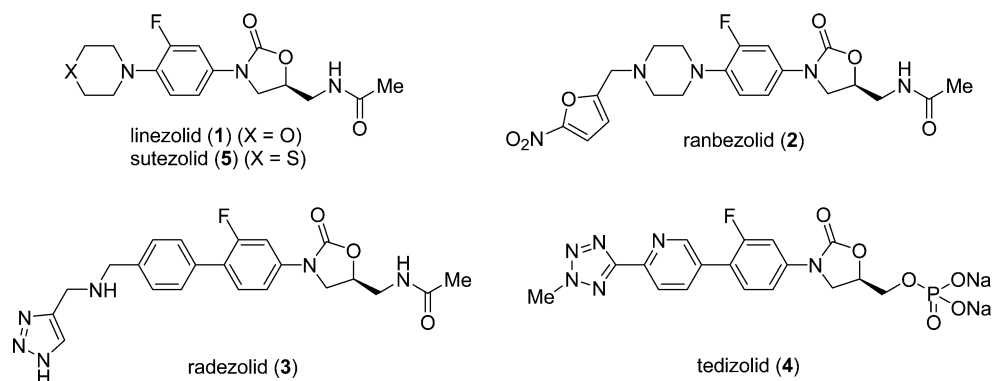
Therapeutics and has recently completed a phase III clinical trial.<sup>14</sup> These candidate compounds all have a heteroaromatic ring as the terminal chemical structure unit. However, Okamoto et al. reported the synthesis and *in vitro* antimycobacterial activity of pyrazolo[1,5-a]pyridine derivatives and suggested that the condensed heteroaromatic ring system was a pharmacophore exhibiting antimycobacterial activity.<sup>15</sup> Although this scaffold has not been investigated for activity against Gram-positive or -negative bacteria, the oxazolidinone antibacterial sutezolid (**5**) is known to exhibit strong *in vitro* activities against both Gram-positive bacteria (such as MRSA) and *Mycobacterium tuberculosis*.<sup>16</sup> Since the above heteroaromatic ring system showed antimycobacterial activity, we suspected that it might also have antibacterial activity potential because antimycobacterial activity is generally correlated with antibacterial activity toward Gram-positive bacteria such as MRSA. Therefore, we expected that introduction of the above pyrazolo[1,5-a]pyridine or a related scaffold into oxazolidinone antibacterials might result in potent antibacterial activity. Herein, we report the synthesis and biological evaluations of novel oxazolidinone derivatives bearing pyrazolo[1,5-a]pyridine or its similar scaffold as the C-ring substructure.

The synthesis of the desired oxazolidinone analogues was performed by Suzuki–Miyaura coupling reaction of the known boronic acid ester (**6**)<sup>17</sup> with 6-bromopyrazolo[1,5-a]pyridine (**7**),<sup>18</sup> 6-bromoimidazo[1,5-a]pyridine (**8**),<sup>19</sup> 6-bromoimidazo-

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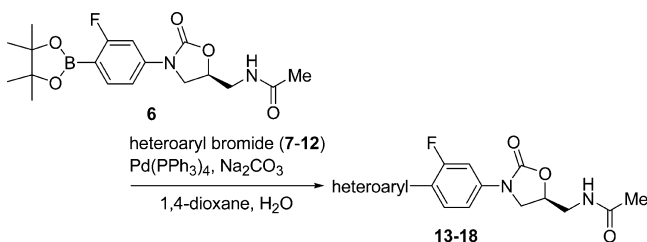
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**Figure 1.** Recently developed potent antibacterials of the oxazolidinone family.

[1,2-*a*]pyridine (9),<sup>20</sup> 7-bromoimidazo[1,2-*a*]pyridine (10),<sup>21</sup> 6-bromo[1,2,4]triazolo[1,5-*a*]pyridine (11),<sup>22</sup> and 7-bromo[1,2,4]triazolo[1,5-*a*]pyridine (12),<sup>23</sup> as shown in Table 1. The products 13–18 were recrystallized from appropriate organic solvents. These compounds 13–18 were then evaluated for *in vitro* antibacterial activity against Gram-positive (*S. aureus*, *E. faecalis*, *E. faecium*, and *S. pneumoniae*) and Gram-negative (*Moraxella catarrhalis* and *Haemophilus influenzae*) bacteria using a conventional broth microdilution method.

**Table 1. Synthesis of Targeted Oxazolidinone Analogues 13–18 Bearing an Acetamide C-5 Side Chain on the Oxazolidinone Ring**



entry	heteroaryl bromide	product	yield (%)
1			71
2			75
3			74
4			77
5			56
6			74

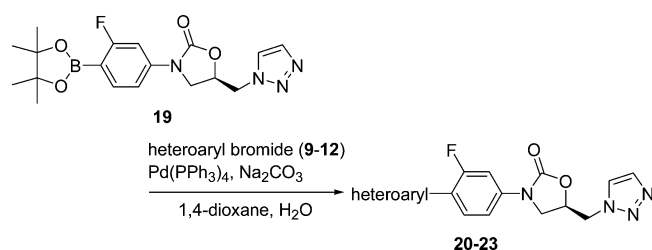
Activity against linezolid-resistant *S. aureus* NRS271, a clinical isolate, was also examined. NRS271 carries G2576T mutation in domain V, the peptidyl transferase center, of 23S rRNA gene (*Escherichia coli* 23S rRNA numbering). As shown in Table 2, the minimum inhibitory concentrations (MICs,  $\mu\text{g/mL}$ ) of 13–18 against *S. aureus* generally indicated 2- to 8-fold greater potency in comparison with linezolid 1. Compounds 13 and 16 showed clinically relevant MIC values against linezolid-resistant *S. aureus* NRS271, as well as Gram-negative *M. catarrhalis*. Compound 16 with an imidazo[1,2-*a*]pyridine ring unit also exhibited good antibacterial activity toward Gram-negative *H. influenzae*. Next, we examined the effect of replacing the conventional acetamide type C-5 side chain unit on the A-ring with a [1,2,3]triazole unit, which has been reported to enhance antibacterial activity and reduce inhibition of monoamine oxidase (MAO).<sup>24</sup> The compounds were synthesized via a similar procedure to that described for compounds 13–18, using boronic acid ester (19)<sup>25</sup> instead of 6, with heteroaryl bromides 9–12 (Table 3). The prepared compounds 20–23 exhibited similar *in vitro* antibacterial activity to the acetamide derivatives 15–18, and compound 21 showed most potent antibacterial activity among all the synthesized compounds (Table 4). We then evaluated the *in vivo* therapeutic effect of selected compounds via intravenous or oral administration in a mouse lethal systemic infection model employing *S. aureus* SR3637 (MRSA). The results are shown in Table 5. Though compound 13 had potent *in vitro* antibacterial activity, it was not effective *in vivo*. This unsuccessful result may suggest that 13 has poor pharmacokinetic (PK) properties or is metabolically unstable. However, other tested compounds showed moderate to excellent *in vivo* therapeutic effect, regardless of administration route. Compound 18 exhibited a 4- to 6-fold greater *in vivo* potency than that of linezolid 1 via both intravenous and oral administration, in line with the *in vitro* results. In addition, compounds 16 and 21, bearing an imidazo[1,2-*a*]pyridine C-ring unit, also showed a good therapeutic effect, superior to that of linezolid, after both intravenous and oral administration. Compound 23 also had a good therapeutic effect via oral administration. The pharmacokinetics (PK) of compound 18 was evaluated after oral administration to mice (Table 6). Compound 18 showed a sufficient AUC even at a 10-fold lower dosage than linezolid (1), used as a reference compound. This excellent PK profile is consistent with the *in vivo* efficacy of 18 regardless of the route of administration. We made a preliminary examination of the safety profile of the *in vivo* active compounds 16, 18, 21, and 23. Specifically, we examined whether these compounds inhibit

Table 2. In Vitro Antibacterial Activity of Compounds 13–18 Bearing an Acetamide C-5 Side Chain on the Oxazolidinone Ring

compd	minimum inhibitory concentration ( $\mu\text{g/mL}$ )									
	S.a. <sup>a</sup>	S.a. <sup>b</sup>	S.a. <sup>c</sup>	S.a. <sup>d</sup>	E.f. <sup>e</sup>	E.f. <sup>f</sup>	M.c. <sup>g</sup>	S.p. <sup>h</sup>	S.p. <sup>i</sup>	H.i. <sup>j</sup>
1	2	2	2	32	4	2	8	1	0.5	16
13	0.25	0.5	0.25	2	0.5	0.25	2	$\leq 0.063$	$\leq 0.063$	8
14	0.25	1	0.5	4	0.5	0.5	4	$\leq 0.063$	$\leq 0.063$	8
15	0.5	1	0.5	8	0.5	0.25	8	$\leq 0.063$	$\leq 0.063$	4
16	0.25	0.25	0.25	2	0.25	0.5	2	$\leq 0.063$	$\leq 0.063$	2
17	0.5	0.5	0.5	8	0.5	0.5	8	$\leq 0.063$	$\leq 0.063$	4
18	0.25	0.5	0.25	4	0.25	0.25	4	$\leq 0.063$	$\leq 0.063$	4

<sup>a</sup>*Staphylococcus aureus* SR20549. <sup>b</sup>*Staphylococcus aureus* Smith. <sup>c</sup>*Staphylococcus aureus* SR3637 (methicillin-resistant). <sup>d</sup>*Staphylococcus aureus* NRS271 (linezolid-resistant). <sup>e</sup>*Enterococcus faecalis* SR1004. <sup>f</sup>*Enterococcus faecium* SR7940 (vancomycin-resistant). <sup>g</sup>*Moraxella catarrhalis* SR26840. <sup>h</sup>*Streptococcus pneumoniae* SR26207. <sup>i</sup>*Streptococcus pneumoniae* SR11031 (penicillin-resistant). <sup>j</sup>*Haemophilus influenzae* SR27914.

Table 3. Synthesis of Targeted Oxazolidinone Analogues 20–23 Bearing a [1,2,3]Triazole C-5 Side Chain on the Oxazolidinone Ring



entry	heteroaryl bromide	product	yield (%)
1			86
2			84
3			59
4			67

four subtypes of cytochrome P450 (CYP) isoforms, as well as MAO-A, and MAO-B. The results are listed in Table 7. Three

Table 4. In Vitro Antibacterial Activity of Compounds 20–23 Bearing a [1,2,3]Triazole C-5 Side Chain on the Oxazolidinone Ring

compd	minimum inhibitory concentration ( $\mu\text{g/mL}$ )									
	S.a. <sup>a</sup>	S.a. <sup>b</sup>	S.a. <sup>c</sup>	S.a. <sup>d</sup>	E.f. <sup>e</sup>	E.f. <sup>f</sup>	M.c. <sup>g</sup>	S.p. <sup>h</sup>	S.p. <sup>i</sup>	H.i. <sup>j</sup>
1	2	2	2	32	4	2	8	1	0.5	16
20	0.25	0.5	0.25	4	0.5	0.5	4	$\leq 0.063$	$\leq 0.063$	4
21	0.125	0.25	0.125	2	0.25	0.25	2	$\leq 0.063$	$\leq 0.063$	2
22	0.25	0.5	0.25	8	0.5	0.25	8	$\leq 0.063$	$\leq 0.063$	4
23	0.125	0.25	0.25	2	0.25	0.25	4	$\leq 0.063$	$\leq 0.063$	2

<sup>a</sup>*Staphylococcus aureus* SR20549. <sup>b</sup>*Staphylococcus aureus* Smith. <sup>c</sup>*Staphylococcus aureus* SR3637 (methicillin-resistant). <sup>d</sup>*Staphylococcus aureus* NRS271 (linezolid-resistant). <sup>e</sup>*Enterococcus faecalis* SR1004. <sup>f</sup>*Enterococcus faecium* SR7940 (vancomycin-resistant). <sup>g</sup>*Moraxella catarrhalis* SR26840. <sup>h</sup>*Streptococcus pneumoniae* SR26207. <sup>i</sup>*Streptococcus pneumoniae* SR11031 (penicillin-resistant). <sup>j</sup>*Haemophilus influenzae* SR27914.

Table 5. In Vivo Therapeutic Effects of Selected Oxazolidinone Analogues in a Mouse Lethal Systemic Infection Model Employing *S. aureus* SR3637

compd	MIC ( $\mu\text{g/mL}$ )	therapeutic effect ED <sub>50</sub> (mg/kg) <sup>a</sup>	
		administration route	
		iv	po
13	0.25	>10 (1: 1.98)	N.T.
14	0.5	3.05 (1: 4.32)	N.T.
15	0.5	3.17 (1: 2.46)	3.05 (1: 2.83)
16	0.25	1.09 (1: 1.73)	1.05 (1: 2.83)
18	0.25	0.34 (1: 2.13)	0.55 (1: 1.98)
21	0.125	0.95 (1: 1.73)	1.02 (1: 2.83)
23	0.25	N.T.	0.95 (1: 3.87)

<sup>a</sup>Compound 1 was used as reference in each test, and its ED<sub>50</sub> value was shown in the parentheses. N.T.: not tested.

Table 6. PK Properties of in Vivo Potent Analogue 18 in Mice

parameter	linezolid (1)	18
dose (mg/kg)	67.7	5.56
T <sub>max</sub> (hr)	0.50	1.00
C <sub>max</sub> ( $\mu\text{g/mL}$ )	37.00	4.78
AUC <sub>∞</sub> ( $\mu\text{g}\cdot\text{h/mL}$ )	161.85	30.93

compounds did not show marked CYP inhibition even at concentrations greatly exceeding the antibacterial minimum inhibitory concentrations, and their inhibition of MAO-A was less than that of linezolid 1, though compound 18 inhibited MAO-B slightly more strongly than 1. Compound 21 with the [1,2,3]triazole C-5 side chain unit on the oxazolidinone ring showed low inhibition rates of MAO-A and MAO-B.

**Table 7. CYP450 Isoform and MAO-A,B Inhibition Indices of in Vivo-Active Analogues 16, 18, 21, and 23**

compd	CYP450 isoform, IC <sub>50</sub> (μM)				MAO inhibition (%) (30 μM of each compound)	
	1A2	2C9	2D6	3A4	A	B
1	>20	>20	>20	>20	61.3	70.4
16	>20	>20	>20	>20	54.8	52.8
18	>20	>20	>20	>20	55.9	78.2
21	>20	>20	>20	15	41.2	26.7
23	>20	>20	>20	>20	33.2	27.9

Furthermore, compound **23** exhibited the lowest inhibition rate toward MAO-A among the four tested compounds. On the basis of these results, we consider that compounds **18** and **23** are promising candidates for more extensive evaluation. In particular, it will be important to evaluate the toxicity of these compounds, particularly myelosuppression and peripheral neuropathy, because this is often an issue with oxazolidinone-type antibiotics. In the present work, we introduced six kinds of basic condensed heteroaromatic ring substructure as the C-ring part and obtained potent compounds **18** and **23**, with promising in vitro and in vivo antibacterial efficacy. We are now examining in more detail the structure–activity relationships around compounds **18** and **23**, which represent both lead compounds and potential clinical candidates.

In summary, we have synthesized several oxazolidinone-type antibacterials bearing a condensed heteroaromatic ring system as the C-ring and evaluated their activity against a panel of multidrug-resistant organisms. Almost all of the synthesized compounds exhibited potent in vitro antibacterial activity and several also showed superior in vivo antibacterial activity in a mouse model of lethal infection. The in vivo-active compounds **16**, **18**, **21**, and **23** also showed similar or improved values of MAO-A inhibition index in comparison with linezolid **1**, along with similar levels of CYP inhibition potential (IC<sub>50</sub> >10 μM for the four selected isoforms) to **1**, and these levels are satisfactory from a safety point of view. More detailed evaluation of the potent compounds **18** and **23** is ongoing, together with synthesis of further analogues for structure–activity relationship studies.

## ■ ASSOCIATED CONTENT

### Supporting Information

Synthetic method, characterization of compounds, and protocols of biological evaluations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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#### ■ NOTE ADDED AFTER ASAP PUBLICATION

This paper posted ASAP on September 24, 2013. A correction was made to Table 7 and the revised version was reposted on September 25, 2013.