Design, Synthesis, and Antibacterial Evaluation of Oxazolidinones with Fused Heterocyclic C-Ring Substructure

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Supporting Information

ABSTRACT: A series of novel oxazolidinone antibacterials with diverse fused heteroaryl C-rings bearing hydrogen bond donor and hydrogen bond acceptor functionalities were designed and synthesized. The compound with benzoxazinone C-ring substructure (**8c**) exhibited superior activity compared to linezolid against a panel of Gram-positive and Gram-negative bacteria. Structural modifications at C5-side chain of **8c** resulted in identification of several potent compounds (**12a**, **12b**, **12g**, and **12h**). Selected compounds **8c** and **12a** showed very good microsomal stability and no CYP₄₅₀ liability, thus clearing preliminary safety hurdles. A docking model of **12a** binding to 23S rRNA suggested that the increased potency of **12a** is due to additional ligand–receptor interaction.

KEYWORDS: Antibacterial, oxazolidinone, linezolid, fused heteroaromatics

Severe bacterial infections caused by multidrug resistant bacteria are posing major health problems across the globe.¹ Unfortunately, the effectiveness of available antibacterial agents is diminishing, as the microorganisms are evolving new mechanisms of resistance and rapidly spreading them via mobile genetic elements such as plasmids and integrons.² The severity of the global health crisis has propelled the Infectious Disease Society of America (IDSA) to issue the challenge of developing ten new antibiotics by 2020.³ While the infections caused by Gram-negative pathogens have witnessed a steady rise, the number of severe infections caused by Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA),⁴ vancomycin-resistant *Enterococcus faecalis* (VRE),⁵ and penicillin-resistant *Streptococcus pneumoniae* (PRSP)⁶ are also significantly increasing. To combat these multidrug-resistant Gram-positive bacteria, oxazolidinones were developed as a new class of totally synthetic antibacterial agents. Oxazolidinones exhibit their antibacterial activity by a unique mode of action. They bind to 23S RNA of the 50S ribosomal subunit and inhibit the bacterial protein synthesis at the initiation step. As shown in Figure 1, linezolid (**1**), the first approved (2000) antibacterial agent of the oxazolidinone family was the leading branded antibiotic for serious Gram-positive infections with reported worldwide sales of \$1.3 billion in 2011.⁷ Soon, emergence of resistance^{8–10} and associated safety issues,¹¹ namely, myelosuppression and monoamine oxidase enzyme inhibition led to restriction on its wide usage. These challenges caught the attention of several pharmaceutical companies and academia to develop superior oxazolidinones.^{2,8,12,13} Extensive efforts in this direction have resulted in identification of several oxazolidinone clinical candidates currently at various stages of drug development. Tedizolid phosphate (**2**) (Sivextro, Trius/Cubist, Figure 1), approved in 2014, is a second-generation oxazolidinone antibacterial to

originate from these efforts.¹⁴ Oxazolidinones such as MRX-1 developed by MicuRx Pharmaceuticals¹⁵ and LCB01-037 developed by LegoChem Biosciences¹⁶ are currently undergoing the phase III and phase II clinical trials, respectively. Of late, research on oxazolidinone antibacterials is focused on overcoming the linezolid-resistance,¹⁷ broadening of antibacterial spectrum against Gram-negative strains,^{18–20} exploring the utility in diseases of central nervous system (CNS),²¹ and reducing the toxic side effects.²² To achieve these objectives, extensive structural modification of oxazolidinone pharmacophore has been done. Modification at C-ring portion with various heterocycles has been the most successful, and many compounds have been recognized as clinical candidates. However, despite the extensive work for several decades on oxazolidinone antibacterials, very limited heterocyclic C-ring systems of the total known heterocyclic space have been explored. Further, reports on fused bicyclic heteroaryls are even rare. A series of oxazolidinones with fused pyrroloheteroaryl C-rings possessing potent activity against Gram-positive pathogens were reported by J&J Pharmaceutical.²³ Recently, Suzuki et al. reported potent oxazolidinone derivatives with fused bicyclic heteroaryl C-rings such as pyrazolopyridine, imidazopyridine, and triazolopyridine (**3**), out of which two compounds exhibited desired *in vivo* efficacy in a lethal mouse infection model.²⁴ Since the reported fused bicyclic heteroaryl C-rings are a small fraction of the available fused heterocyclic chemical space, we thought of exploring diverse fused heteroaryls as a C-ring substructure. Docking studies reported by Trius Therapeutics revealed additional hydrogen bonding interactions between C- and D-rings of tedizolid with

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Figure 1. Approved drugs, active molecule, and our design strategy.

the sugar backbone of ribosome and suggested it to be responsible for improved activity.²⁵ Further, Boyer et al. reported that oxazolidinones with fused pyrazole C-ring with hydrogen bond donor substructure possess potent activity against Gram-positive and moderate activity against fastidious Gram-negative pathogens.²⁶ In light of these literature reports, we hypothesized that the combination of hydrogen-bond donor (HBD) and hydrogen bond-acceptor (HBA) functionalities in the diverse fused C-ring substructures (4) should facilitate stronger ligand–receptor binding; which in turn might lead to superior antibacterial activity compared to linezolid. Herein, we report the design, synthesis, and *in vitro* biological evaluation of novel oxazolidinone antibacterials with heteroaromatic C-ring substructure. An explanation for the observed antibacterial activity has been provided with the help of *in silico* molecular docking studies.

The chemical synthesis was initiated with the preparation of (R)-3-(3-fluoro-4-iodophenyl)-5-(hydroxymethyl)oxazolidin-2-one (5) starting from 3-fluoroaniline using literature reported procedures.¹⁴ The heteroaryl bromides (6a–n) were then subjected to palladium catalyzed borylation to obtain corresponding boronates (7a–n), which was followed by *in situ* Suzuki–Miyaura cross coupling with 5 to obtain the coupled products (8a–n) in moderate to good yields (Table 1). It is noteworthy to mention that reversing the functionalities of coupling partners, i.e., coupling of boronate of 5 with 6c under identical reaction conditions yielded impure product mixture.

All the synthesized compounds (8a–n) were screened for their antibacterial activity against various Gram-positive (*Staphylococcus aureus* including linezolid-resistant strain, *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Staphylococcus epidermidis*) and Gram-negative (*Haemophilus influenzae*) bacteria. The minimum inhibitory concentration (MIC) was determined by the microbroth dilution method, and the results are summarized in Table 2. The marketed antibiotics such as linezolid, levofloxacin, and vancomycin were used as controls in the present study. In general, all compounds (except 8f, 8h, and 8n) showed an activity similar or superior to linezolid. The compounds with [6,5]-fused heteroaryl C-rings such as 2-oxindol-6-yl (8a) and 2-oxobenzoxazol-5-yl (8b) showed superior activity compared to linezolid against most of the strains, while activity against few strains was substantially inferior.

However, the benzoxazinone derivative (8c) showed highly potent activity (MIC < 1 μg/mL) across the panel and was better than other [6,6]-fused derivatives (8d and 8e). These

Table 1. Synthesis of Oxazolidinone Derivatives with Diverse Heteroaryl C-Rings^a

^aReaction conditions: (a) heteroaryl bromide (0.439 mmol), bis(pinacolato)diboron (0.658 mmol), PdCl₂(dppf) (0.044 mmol), KOAc (1.317 mmol), Dioxane, 80–90 °C, 8 h; (b) above reaction mixture, 5 (0.307 mmol), K₂CO₃ (0.921 mmol), EtOH, H₂O, 80–90 °C, 8 h. Yields reported in parentheses are isolated yields.

preliminary results demonstrated the superiority of benzoxazinone over [6,5]- and [6,6]-fused heteroaryl C-rings. To identify the most favorable linkage position of benzoxazinone (C-ring) to the B-ring of oxazolidinone pharmacophore, the other three possible regioisomers (8f–h) of compound 8c were synthesized and screened; however, none of them displayed a better activity. Although the benzoxazinon-7-yl derivative (8g) showed comparable or slightly inferior activity to 8c, other isomers (8f and 8h) were completely inactive. The rationale for loss of activity might be attributed to the steric clashes between compound and receptor due to the L-shaped molecular conformation of 8f and 8h. These results are consistent with the previous reports by Khera et al.²⁷ Since tedizolid with pyridine as a C-ring substructure is known to be more potent than linezolid, 5-azabenzoxazinone derivative (8i) was synthesized as it was expected to display enhanced activity. Surprisingly, however, a 2–4-fold reduction in the activity

Table 2. *In Vitro* Antibacterial Activity of the Compounds with C-Ring Modifications

compd	minimum inhibitory concentration ($\mu\text{g/mL}$)										
	S.a. ^a	S.a. ^b	S.a. ^c	S.a. ^d	S.a. ^e	E.f. ^f	E.f. ^g	S.p. ^h	S.p. ⁱ	S.e. ^j	H.i. ^k
8a	0.25	32	1	32	4	0.25	0.25	0.125	0.125	<0.06	2
8b	0.25	32	1	32	4	0.5	0.25	0.125	0.125	<0.06	4
8c	<0.06	0.5	0.125	0.5	1	<0.06	<0.06	<0.06	<0.06	<0.06	0.5
8d	0.25	0.25	0.5	16	8	0.5	0.125	0.25	0.25	0.25	0.5
8e	0.125	0.5	0.25	0.25	2	0.5	0.25	0.25	0.25	0.125	0.5
8f	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
8g	0.5	0.5	0.5	0.5	16	1	1	2	2	0.5	0.25
8h	8	4	2	8	>32	16	32	8	8	2	1
8i	0.125	0.125	0.5	0.25	4	0.25	0.25	0.25	0.25	<0.06	1
8j	0.125	1	0.25	0.25	16	0.5	0.25	0.25	0.25	<0.06	0.125
8k	<0.06	0.5	0.25	<0.06	2	0.125	<0.06	0.25	0.25	<0.06	0.5
8l	0.06	0.5	0.125	0.125	2	0.25	0.125	0.25	0.25	0.06	0.5
8m	0.25	1	0.5	0.5	4	0.5	0.5	0.5	0.5	0.25	1
8n	1	32	4	32	>32	4	2	0.5	0.5	0.06	8
linezolid	1	1	2	1	16	2	2	0.5	0.5	N.D.	4
levofloxacin	0.125	0.25	0.125	16	>32	0.25	4	0.125	0.06	0.5	0.06
vancomycin	1	1	0.5	0.5	1	2	1	2	2	1	N.D.

^a*Staphylococcus aureus* ATCC 6538P. ^b*Staphylococcus aureus* ATCC 33591. ^c*Staphylococcus aureus* ATCC 29213. ^dMRSA 1201984. ^e*Staphylococcus aureus* (linezolid-resistant). ^f*Enterococcus faecalis* ATCC 29212. ^g*Enterococcus faecium* 19434. ^h*Streptococcus pneumoniae* 55143. ⁱ*Streptococcus pyogenes* ATCC 19615. ^j*Staphylococcus epidermidis* ATCC 14990. ^k*Haemophilus influenzae* ATCC 49247.

was observed in this case. Generally it is seen that compounds with flat aromatic rings suffer from the problem of low aqueous solubility due to increased crystallinity; and one of the strategies to address this issue is by disturbing the planarity of the molecule. With this rationale, we substituted the 2-position of benzoxazinone with *gem*-dimethyl and *spiro*-cyclopropane groups and prepared respective compounds **8j** and **8k**. While **8j** showed 2–4-fold inferior activity against most of the strains and was completely inactive against linezolid resistant *S. aureus*, *spiro*-cyclopropane derivative **8k** showed comparable activity to that of **8c** against all the strains. Our initial results revealed that compounds with a six-membered terminal ring had superior antibacterial activity compared to the five-membered ones (**8c** vs **8b**). In this series, we further investigated compounds with a seven-membered terminal ring such as 1,4-benzoxazepin-4(5*H*)-one derivative (**8l**) and its reverse-lactam isomer (**8m**). Both the compounds showed potent activity (MIC < 1 $\mu\text{g/mL}$) against all strains except linezolid-resistant *S. aureus* for which MIC was 2 and 4 $\mu\text{g/mL}$, respectively. Further, a substantial loss in the activity of the benzodioxine derivative (**8n**) was observed. This may be attributed to the absence of hydrogen bond donor functionality in the benzodioxine C-ring system. These results unequivocally emphasize the importance of hydrogen bond donor groups in the C-ring substructures for a superior antibacterial activity. The exploration of diverse C-ring heteroaryls enabled us to identify several lead compounds such as **8c**, **8e**, **8k**, and **8l** with potent activity against both Gram-positive and Gram-negative pathogens including linezolid resistant *S. aureus*. Each of these lead compounds can be subjected to further structure optimization to balance the activity and drug-like properties. In the next set of structural design for obtaining effective antibacterials, we selected the most potent compound **8c** as a lead for further modifications at the C5-side chain. Previous reports on C5-side chain modification of different oxazolidinone scaffolds involved substitution with aliphatic and heteroaromatic groups.⁸ However, since our molecules already consisted of flat aromatic ring systems as a pharmacophore;

introduction of an additional aromatic ring at the C5-side chain might influence its physicochemical properties negatively; so we decided to focus only on small aliphatic groups for this study.

The crucial intermediate **9**, required for the synthesis of C5-side chain derivatives, was synthesized starting from alcohol **5** (Scheme S1, SI). The palladium catalyzed borylation of 6-bromo-2*H*-1,4-benzoxazin-3(4*H*)-one (**6c**) followed by *in situ* Suzuki–Miyura cross coupling with **9** furnished product **10**. The deprotection of **10** using hydrochloric acid (4 M in dioxane) yielded amine **11** as a hydrochloride salt (Scheme 1).

Scheme 1. Synthesis of 6-{4-[(5*S*)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-2-fluorophenyl}-2*H*-1,4-benzoxazin-3(4*H*)-one Hydrochloride (**11**)^a

^aReaction conditions: (a) **6c**, PdCl₂(dppf), KOAc, bis(pinacolato)diborane, dioxane, 80–90 °C, 7 h; (b) above reaction mixture, **9**, K₂CO₃, EtOH, H₂O, 80–90 °C 18 h; (c) **10**, HCl (4 M) in dioxane, DCM, MeOH, 0 °C to RT, 18 h. Yields reported in parentheses are isolated yields.

Amine **11** was then converted to diverse amides (**12a–f**), carbamate (**12g**), thioamide (**12h**), sulfonamide (**12i**), and guanidine (**12j**) derivatives in good to excellent yields (Scheme 2). All the compounds (**11**, **12a–j**) with diverse C5-side chain were screened for antibacterial activity, and the results are summarized in Table 3. Compound **11**, an amino analogue of potent compound **8c**, displayed highly inferior activity compared to its parent (**8c**), whereas all other compounds with side chain modification (except **12i** and **12j**) showed superior activity compared to linezolid. Especially, compounds **12a**, **12b**, **12g**, and **12h** showed very potent antibacterial activity with MIC < 1 $\mu\text{g/mL}$ against all the strains including

Scheme 2. Modifications at Oxazolidinone C5-Side Chain^a

^aReaction conditions: (a) acyl chloride/anhydride/methyl chloroformate/methyl dithioacetate, Et₃N, DMF, 0 °C to RT, 18 h; (b) methane sulfonyl chloride, Et₃N, DMF, 0 °C to RT, 18 h; (c) (i) *N,N'*-Bis-boc-1-guanylpurazole, pyridine, MeOH, RT, 24 h; (ii) HCl (4 M) in dioxane, DCM, MeOH, 0 °C to RT, 18 h; (d) (i) acetoxyacetyl chloride, Et₃N, DMF, 0 °C to RT, 18 h; (ii) NaOMe, DCM, MeOH, RT, 24 h.

linezolid-resistant *S. aureus* and *H. influenzae*. The compound with an acetamide side chain (12a), typical of linezolid, was found to be 2–16-fold more potent than linezolid and was even active against linezolid-resistant *S. aureus* and *H. influenzae*. Although the propanamide derivative 12b showed activity in the desired range (MIC ≤ 1 μg/mL), other amide derivatives (12c–f) were found to be inferior compared to 12a. The

compounds with methyl carbamate (12g) and thioacetamide (12h) side chains exhibited the highest activity among all the synthesized compounds with MIC < 0.5 and < 0.125 μg/mL, respectively against all pathogens including linezolid-resistant *S. aureus* and fastidious *H. influenzae*. The sulfonamide derivative 12i displayed inferior activity against few strains of *S. aureus*, and it was active against others including *H. influenzae*. Conversely, the guanidine derivative 12j showed complete loss of activity (MIC > 32 μg/mL), which could be attributed to low or no membrane permeability due to its highly polar nature.

To understand the possible receptor interactions of our novel oxazolidinone derivatives, the molecular docking study of selected compounds was performed in the crystal structure of the 50S ribosomal unit of *Haloarcula marismortui* (PDB code 3CPW).²⁸ We found that, in general, the binding mode of our compounds to ribosome was similar to that of linezolid. A major portion of compound 12a and 12g showed very good overlay with linezolid (Figure 2). The bicyclic heteroaryl C-rings of compounds 12a and 12g extend beyond the morpholine ring of linezolid and make hydrogen bond interactions with the sugar moiety of U2541 and A2486, respectively (Figure S1, SI). The N-H of the acetamide side chain of 12a and methyl carbamate side chain of 12g made hydrogen bond interactions with the phosphate group of G2540. The additional hydrogen bond interactions with the receptor seemed to be responsible for the superior activity of these compounds compared to linezolid. Similarly, the inactive compounds 8f and 8h were also examined to understand the reason for loss in their activity. Both the compounds showed a 180° flipped binding mode and led to substantial distortion of the residues adjoining the linezolid binding pocket due to steric clash with the receptor arising out of the L-shaped geometry (Figure S2, SI).

After complete evaluation of antibacterial activity, two of the most potent compounds (8c and 12a) were selected for the ADME and physicochemical profiling, and the results are summarized in Table 4. Both compounds 8c and 12a were found to be metabolically stable in the presence of mice liver

Table 3. *In Vitro* Antibacterial Activity of the Compounds with C5-Side Chain Modifications

compd	minimum inhibitory concentration (μg/mL)										
	S.a. ^a	S.a. ^b	S.a. ^c	S.a. ^d	S.a. ^e	E.f. ^f	E.f. ^g	S.p. ^h	S.p. ⁱ	S.e. ^j	Hi. ^k
8c	<0.06	0.5	0.125	0.5	1	<0.06	<0.06	<0.06	<0.06	<0.06	0.5
11	4	16	8	8	>32	8	4	4	4	4	4
12a	0.125	0.5	0.125	0.5	1	0.03	0.03	0.06	0.06	0.06	0.25
12b	0.125	0.25	0.25	0.5	1	0.25	0.06	0.5	0.25	0.125	0.25
12c	0.25	1	1	1	4	0.25	0.125	0.5	0.5	0.25	1
12d	0.125	0.5	0.5	0.5	2	0.06	0.06	1	1	0.25	1
12e	0.125	0.5	0.5	0.5	4	0.06	0.06	0.25	0.25	0.125	0.5
12f	0.25	1	1	1	4	0.06	0.06	0.125	0.125	0.25	0.5
12g	0.06	0.125	0.125	0.06	0.5	0.06	0.06	0.06	0.06	0.06	0.125
12h	0.06	0.125	0.06	0.06	0.125	0.06	0.06	0.06	0.06	0.06	0.125
12i	0.25	1	8	1	8	0.25	0.125	0.25	0.25	0.5	0.5
12j	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
linezolid	1	1	2	1	16	2	2	0.5	0.5	N.D.	4
levofloxacin	0.125	0.25	0.125	16	>32	0.25	4	0.125	0.06	0.5	0.06
vancomycin	1	1	0.5	0.5	1	2	1	2	2	1	N.D.

^a*Staphylococcus aureus* ATCC 6538P. ^b*Staphylococcus aureus* ATCC 33591. ^c*Staphylococcus aureus* ATCC 29213. ^dMRSA 1201984. ^e*Staphylococcus aureus* (linezolid-resistant). ^f*Enterococcus faecalis* ATCC 29212. ^g*Enterococcus faecium* 19434. ^h*Streptococcus pneumoniae* 55143. ⁱ*Streptococcus pyogenes* ATCC 19615. ^j*Staphylococcus epidermidis* ATCC 14990. ^k*Haemophilus influenzae* ATCC 49247.

Figure 2. Overlay of 12a (cyan) and 12g (yellow) with linezolid (green) in the receptor binding pocket.

Table 4. *In Vitro* Physchem and ADME Results

compd	sol. at pH 1.2/6.8 ($\mu\text{g/mL}$)	LogD (pH 7.4)	CYP ₄₅₀ inhibition at 10 μM (%) 1A2/2C8/2C9/2C19/ 2D6/3A4	metabolic stability (%) remain
8c	4.4/5.2	1.9	4/0/12/29/4/0	113
12a	22/15	1.9	6/12/13/20/10/0	84

microsomes, thus indicating to have low potential to form toxic or pharmacologically inactive metabolites due to phase I metabolism. Further, both compounds did not show significant inhibition of cytochrome P₄₅₀ enzymes at 10 μM concentration, indicating the compounds exhibit low or no potential for drug–drug interaction related toxicities. Further, both compounds showed moderate solubility at the pH relevant to stomach and intestine and displayed distribution coefficients (logD) in the desired range. The solubility of 8c, a hydroxy derivative similar to tedizolid, can be significantly improved by synthesizing its prodrug preferably phosphate prodrug.¹⁴

In summary, we demonstrated the design and synthesis of novel oxazolidinones bearing a condensed heterocyclic C-ring substructure and evaluated their activity against a panel of Gram-positive and Gram-negative pathogens, including multi-drug resistant strains. Most of the compounds displayed highly potent activity across the panel. Specifically, compounds 8c, 12a, 12b, 12g, and 12h showed *in vitro* antibacterial activity superior to the existing drug molecules such as linezolid, levofloxacin, and vancomycin. Further, compounds 8c and 12a were found to be metabolically stable in the presence of mouse liver microsomes and showed no significant inhibition of CYP₄₅₀ enzymes at 10 μM concentration. The activity results have also been explained with the help of *in silico* docking studies. The improved activity of our compounds against Gram-positive and Gram-negative bacteria strengthens our hypothesis that the combination of HBD along with HBA promotes strong ligand–receptor binding, which is responsible for enhanced activity. Our experimental findings along with the *in silico* docking results enable the researchers not only in understanding the high-value interactions available in the binding

pocket but also encourage them to follow the structure based design approach for designing the next generation oxazolidinones. Further evaluation of the potent compounds (8c, 12a, 12g, and 12h) along with extensive structural optimization of other lead compounds (8e, 8k, and 8l) is ongoing in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmmedchemlett.7b00263.

Experimental procedures, compound characterization details, protocols for biological evaluation, and molecular docking studies (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

ADME, absorption distribution metabolism excretion; ATCC, American type culture collection; physchem, physicochemical properties

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