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Synthesis and Antibacterial Activity of Pyrroloaryl-Substituted Oxazolidinones

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Abstract—A novel series of oxazolidinones containing a pyrroloaryl substituent was synthesized and screened against a representative panel of susceptible and resistant Gram-positive bacteria. Several members of this series were found to have antibacterial activity comparable to or better than linezolid.

Antimicrobial resistance among hospital-acquired Gram-positive bacterial pathogens, including vancomycin-resistant enterococci (VRE),[1] has been increasing over the last decade. Especially worrisome is the recent identification of vancomycin-resistance in two clinical isolates of *Staphylococcus aureus*,[2] one of the most common infectious agents in the hospital environment. Because of the emergence of resistance among Gram-positive cocci, vancomycin has become a less reliable therapeutic option.

The introduction of linezolid has provided the healthcare community with a new weapon in the battle against multi-drug resistant Gram-positive bacteria. Its mode of action, inhibiting protein synthesis at an early phase of translation by binding selectively to the 50S ribosomal subunit,[3] is distinct from earlier inhibitors of bacterial protein synthesis. Linezolid has been approved for various indications in man including both hospital-acquired and community-acquired pneumonia, skin infections, including cases due to methicillin-resistant *S. aureus* (MRSA), and infections associated with vancomycin-resistant *Enterococcus faecium* (VREF), including cases with bloodstream infection.[4] Several key properties make this compound an effective antibacterial agent: broad spectrum potency against resistant and susceptible Gram-positive bacteria; high bioavailability, which allows for a facile transition from parenteral to oral dosage forms; and an acceptable therapeutic index.[3] Of note is the activity of linezolid against vancomycin-resistant *S. aureus* clinical isolates.[2] Nevertheless, clinical failures of linezolid due to resistance in VRE,[4] as well as documented safety concerns following long term dosing,[5] argue in favor of the continued development of new agents to treat multi-drug resistant Gram-positive infections.

We have implemented a research program to develop second-generation oxazolidinones with a primary goal of identifying compounds with increased potency against resistant Gram-positive bacteria compared to linezolid. To this end we have explored replacing the morpholine ring of linezolid with a pyrroloaryl substituent (Fig. 1).[6–11] Several pyrroloaryl-substituted oxazolidinones (**8b**, **8c**, **10**, **11a**, **11b**, and **12**) were identified with superior or comparable in vitro antibacterial activity to linezolid against a representative panel of

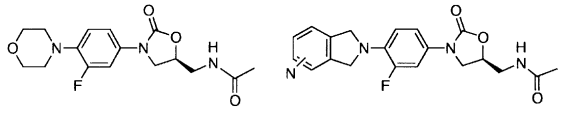

Figure 1. Linezolid and pyrroloaryl oxazolidinone antimicrobial structures.

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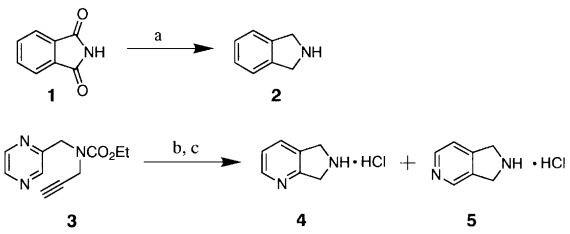
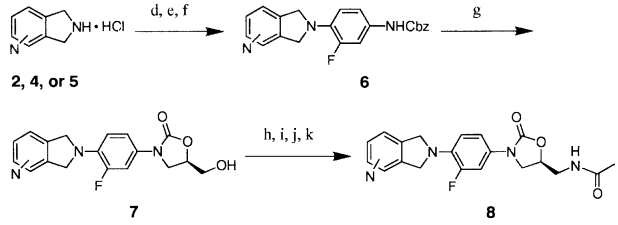


Scheme 1. Reagents and conditions: (a) BH_3–THF, THF; (b) undecane, 180 °C; (c) concd aq HCl, reflux.



Scheme 2. Reagents and conditions: (d) 3,4-difluoronitrobenzene, DIPEA, DMF, 60 °C; (e) 10% Pd/C, $HCOONH_4$, THF, MeOH; (f) CbzCl, $NaHCO_3$, H_2O, acetone; (g) *n*-BuLi, THF then (*R*)-glycidyl butyrate, −78 °C to rt; (h) MsCl, Et_3N, DMF; (i) NaN_3, DMF, 60 °C; (j) H_2, Pd/C, DMF; (k) Ac_2O, pyr, DMF.

clinically relevant Gram-positive bacteria. The SAR of this new series is discussed herein.

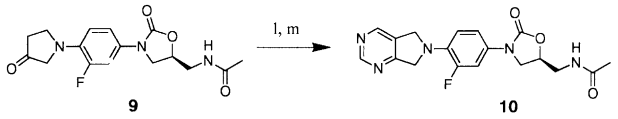
The synthetic routes to various pyrroloaryl-substituted oxazolidinone analogues are outlined in Schemes 1–6.

Following literature procedures, isoindoline (**2**) was produced by borane–THF reduction of phthalimide (**1**).[12] The two isomeric dihydropyrrolopyridines (**4** and **5**) were formed by an inverse electron demand Diels–Alder reaction of acyclic precursor **3** with extrusion of hydrogen cyanide,[13] followed by acid hydrolysis of the carbamate protecting groups (Scheme 1). Scheme 2 depicts the prototypical oxazolidinone synthesis.[14] To begin the sequence, SNAr reaction of 3,4-difluoronitrobenzene with the desired amine (**2**, **4**, or **5**), followed by transfer hydrogenation of the nitro group with palladium on carbon and ammonium formate and carboxybenzylation of the resulting amine furnished the Cbz-protected aniline **6**. Nucleophilic attack of the lithium anion of **6** on (*R*)-glycidyl butyrate provided oxazolidinone carbinol derivative **7**. Following standard procedures[14] **7** was converted to target **8** by the following sequence: (1) mesylation, (2) sodium azide displacement, (3) hydrogenation, and (4) acetylation.

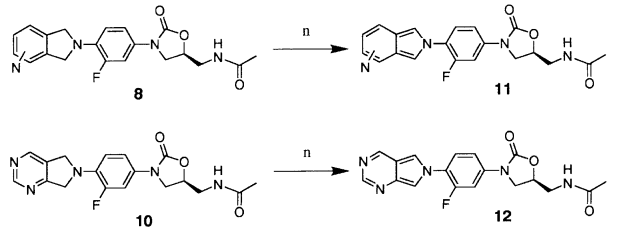
Pyrrolopyrimidine derivative **10** was accessed by treatment of the known compound **9**[15] with a Bredereck-type reagent followed by condensation with formamidine (Scheme 3).[16]

Oxidation of the dihydropyrrolopyridines **8** and **10** with manganese dioxide provided pyrroloaryl oxazolidinones **11** and **12**, respectively (Scheme 4).[17]

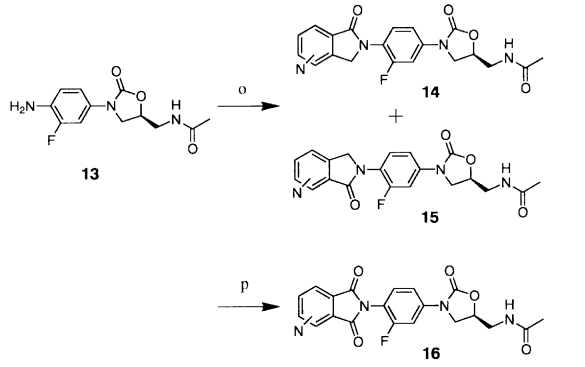
A series of oxo- and dioxo-heterocycles were prepared from the known aniline **13** (Scheme 5).[18] Treatment of **13** with 1,2-aryldicarboxaldehydes under acidic conditions



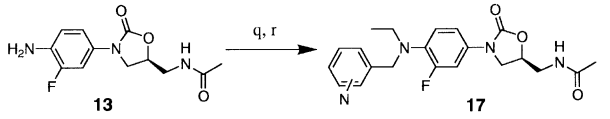
Scheme 3. Reagents and conditions: (l) $MeOCH(NMe_2)_2$, 60 °C; (m) formamidine hydrochloride, DMF, 90 °C.



Scheme 4. Reagents and conditions: (n) MnO_2, CH_2Cl_2.



Scheme 5. Reagents and conditions: (o) 1,2-aryldicarboxaldehydes, acetic acid, acetonitrile; (p) arylanhydrides, acetonitrile, reflux.



Scheme 6. Reagents and conditions: (q) 2- or 3-pyridinecarboxaldehyde, $NaBH_4$, MeOH; (r) acetic acid, $NaBH_4$.

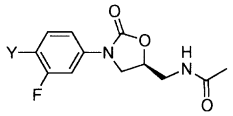
provided the oxo-heterocycles **14** and **15**. The pyrrolidinone ring forms via cyclic imine formation and subsequent 1,3-hydride shift.[19] The dioxo-heterocycles (**16**) were synthesized under standard conditions,[20] via reaction of aniline **13** with the corresponding anhydrides.

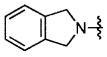
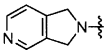
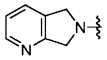
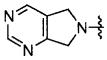
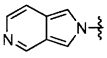
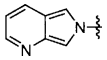
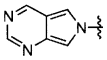
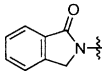
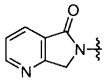
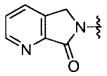
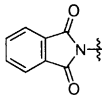
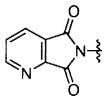
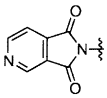
Access to acyclic analogues was achieved by sequential reductive aminations (Scheme 6). Reaction of aniline intermediate **13** with 2- or 3-pyridinecarboxaldehyde in the presence of sodium borohydride followed by treatment with acetic acid and sodium borohydride[21] afforded **17**.

Minimum inhibitory concentrations (MIC) were measured against a group of antibiotic susceptible and resistant strains of Gram-positive bacteria with linezolid as a standard. A set of four strains was used as the screening panel: *S. aureus* OC 4172 (Smith strain) is methicillin-susceptible; *S. aureus* OC 2878 is methicillin-

resistant (MRSA); *Enterococcus faecalis* ATCC 29212 and *E. faecium* OC 3312 are susceptible and resistant to vancomycin, respectively. Compounds were also tested against *S. aureus* OC 4172 in the presence of 50% mouse serum to gauge the extent of protein binding or inactivation due to serum. Broth microdilution MIC (lowest concentration of compound inhibiting visible growth) determinations were performed according to National Committee for Clinical Laboratory Standards methods.[22]

Table 1. Antibacterial activity (MIC[a] values in μg/mL) for pyrroloaryl-substituted oxazolidinones



Compd	Y	*E. faecalis*	VRE	MRSA	*S. aureus* broth	*S. aureus* 50% mouse serum
Linezolid		2	2	1	2	2
8a		4	4	1	4	16
8b		1	1	0.5	1	1
8c		0.5	0.5	0.25	0.5	1
10		2	1	1	1	2
11a		1	0.5	0.5	0.5	1
11b		1	1	0.5	1	2
12		1	0.5	1	1	2
14a		8	8	4	4	16
14b		16	8	4	16	8
15		32	8	8	8	8
16a		64	32	16	32	128
16b		> 128	> 128	> 128	> 128	> 128
16c		> 128	> 128	> 128	> 128	> 128
17a		16	16	8	16	32
17b		> 128	> 128	> 128	> 128	> 128

[a]The variance in the determination of MIC values is 2-fold such that an MIC difference of at least 4-fold is significant.

The initial compound screened, isoindoline analogue **8a**, was equipotent to linezolid versus the MRSA strain and 2-fold less active against the other strains in the testing panel (Table 1). The 4-fold increase in the MIC value in the presence of serum observed for **8a**, however, suggested a high degree of protein binding or inactivation by serum components, possibly due to the hydrophobicity of the molecule. Isoindoline **8a** had an ED_{50} value (effective dose which protects 50% of mice from death) greater than 80 mg/kg/day following oral administration in a murine model of lethal systemic infection due to *S. aureus* OC4172 (Smith).[10] In contrast, linezolid had an oral ED_{50} of 8 mg/kg/day in this model. The lack of oral activity was likely due to insufficient free drug concentration of **8a** in the blood to inhibit bacterial growth. Therefore, the next step conceptually in the design of new analogues was to incorporate nitrogen atoms in the aryl ring of the substituent to increase the overall polarity of the molecule.The heteroaryl compounds (**8b**, **8c**, **10**, **11a**, **11b**, and **12**) in this series exhibited antibacterial profiles comparable to or better than linezolid. Also noteworthy was the attenuated increase in MIC in the presence of serum upon inclusion of nitrogen atoms in the aryl ring. In particular, the pyrrolo[3,4-*b*]pyridinyl analogue (**8c**) was 4-fold more active than linezolid against all strains in the testing panel, including MRSA and VRE. In addition, **8c** was 2-fold more active than linezolid in the presence of serum. Likewise, the antibacterial profile of the isomeric compound, **8b**, was improved compared to linezolid with MIC values consistently 2-fold lower, both in the presence and absence of serum. The diminished effect of serum on the MIC values of **8b** and **8c**, compared to **8a**, translated into improved in vivo efficacy. In particular, **8b** and **8c** had oral ED_{50} values of 13 and 11 mg/kg/day, respectively, in the murine model of systemic infection due to *S. aureus* OC4172 (Smith), which was nearly as efficacious as linezolid (oral ED_{50} of 8 mg/kg/day). Additionally, MIC values for **8b** and **8c** against four linezolid-resistant *S. aureus* clinical isolates[23] were 4–64 μg/mL, with **8c** generally 4-fold more active than linezolid which had MIC values of 8–64 μg/mL.

Adding another ring nitrogen, as in the pyrrolo[3,4-*d*]pyrimidinyl analogue **10**, decreased activity generally 2-fold relative to **8b** and **8c**. Compounds **11a**, **11b**, and **12**, obtained from oxidation of **8b**, **8c**, and **10** respectively, were generally 2- to 4-fold more potent than linezolid against both susceptible and resistant strains. The antibacterial activities of compounds **11a** and **12** were slightly improved relative to their parent compounds, while compound **11b** was equivalent to or 2-fold less potent than parent **8c**.

Introduction of carbonyl groups in the pyrrole ring, as in the lactam and imide derivatives **14a**, **14b**, **15**, **16a**, **16b** and **16c**, raised MIC values against both susceptible and resistant strains. A detrimental effect on antibacterial activity resulted upon incorporation of each carbonyl group. The isoindoline series exemplifies this additive effect, where **8a** is generally 2- to 4-fold more active than lactam **14a**, which is in turn 4- to 8-fold more active than imide **16a**. The position of the carbonyl group made little difference in the pyrrolopyridine series, such that lactam isomer **14b** had similar antibacterial activity to isomer **15**. In contrast to the parent compounds, incorporation of nitrogen atoms in the aryl ring of the lactam and imide derivatives offered no advantage, with pyrrolopyridine isomers **14b** and **15** having slightly less antibacterial activity than the isoindoline compound **14a**. Furthermore, pyrrolopyridine isomers **16b** and **16c** were inactive while the corresponding isoindoline analogue **16a** still retained some antibacterial activity.

The pyrrole ring appeared to be important for optimal activity. Acyclic compound **17a**, in which the pyrrolopyridine heterocycle was replaced with picolyl and ethyl substituents, was much less potent (16- to 32-fold less active than **8b**, **8c**, **11a**, **11b**). In addition, an isomeric analogue, compound **17b**, was inactive. This large difference in activity between the cyclic and conformationally mobile analogues may be reflective of the relative degree of bacterial cell penetration, or may be due to the reduced entropic penalty upon binding of the conformationally constrained compound to the bacterial ribosome.

In summary, replacement of the morpholine ring of linezolid with a pyrroloaryl substituent has afforded a potent series of oxazolidinones with in vitro (**8b**, **8c**, **10**, **11a**, **11b**, and **12**) and in vivo (**8b** and **8c**) activity comparable or superior to linezolid against Gram-positive bacterial pathogens. Compound **8c** exhibited the best in vitro profile in our abbreviated testing panel with MIC values of 0.25–0.5 μg/mL against staphylococci, including MRSA, and 0.5 μg/mL against enterococci, including VRE.

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