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Synthesis and antibacterial activities of novel oxazolidinones having cyclic sulfonamide moieties

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ABSTRACT

The synthesis of a new series of oxazolidinones having cyclic sulfonamide moieties is described. Their in vitro antibacterial activities against both Gram-positive and Gram-negative bacteria were tested and the effect of substituents on the oxazolidinone ring was investigated. A particular compound **15g** having [1,2,5]thiadiazolidin-1,1-dioxide moiety showed the most potent antibacterial activity.

The emergence of bacterial resistance to the antibiotics poses a serious concern for medical professionals during the last decade.[1] In particular, multi-drug-resistant Gram-positive bacteria[2] including methicillin-resistant *Staphylococcus aureus* (MRSA)[3] and *Staphylococcus epidermidis* (MRSE), and vancomycin-resistant *Enterococci* (VRE) are of major concern.[4]

Oxazolidinones, a new class of synthetic antibacterial agents, exhibit activity against a large number of Gram-positive organisms. Linezolid is the first oxazolidinone approved for the treatment of Gram-positive bacterial infections in humans.[5] Since Linezolid, the many attractive traits of oxazolidinone series have encouraged further work in this area, and also the literature reveals extensive chemical programs exist.[6,7] At present, most efforts are focused on substituted phenyl oxazolidinones. Eperezolid and AZD2563 have been extensively used as the structural precursors for modification.[8]

In this letter, we describe the synthesis and structure–activity relationship of oxazolidinones having cyclic sulfonamide moieties instead of morpholine (Fig. 1). In addition, our approach for improvement of antibacterial activity of the oxazolidinones is also discussed.

It is revealed that sulfonamide moieties can enhance largely the activity of antibacterial agents especially against both Gram-positive and Gram-negative bacteria.[9,10] Based on this fact, a positive effect of sulfonamide moieties on the activity of oxazolidinone was anticipated.

The substituted sulfonamides **3a–d**, **3f**, **3g**, and **3i** were easily accessible by the condensation of the corresponding diamines **1a–d**, **1f**, **1g**, and **1i** with sulfamide (**2**) in refluxing pyridine (Scheme 1).[11]

The other cyclic sulfonamides **3e** and **3h** were also synthesized by the improved procedure shown in Scheme 2.[11] The intermediates **Ie** and **Ih** were directly synthesized by reaction of the corresponding mustards with BOC-sulfamoyl chloride. The *N*-BOC cyclosulfamides **3e** and **3h** were obtained in high yields by treatment of **Ie** and **Ih** with K_2CO_3 in DMSO.

The cyclic sulfamidate **3j** ([1,2,3]-oxathiazolidine-2,2-dioxide) is typically prepared as shown in Scheme 3.[11] The sulfamidite **7** was obtained by reaction of *N*-protected aminoethanol with $SOCl_2$ in CH_3CN at low temperature. The oxidation of the sulfamidite **7**

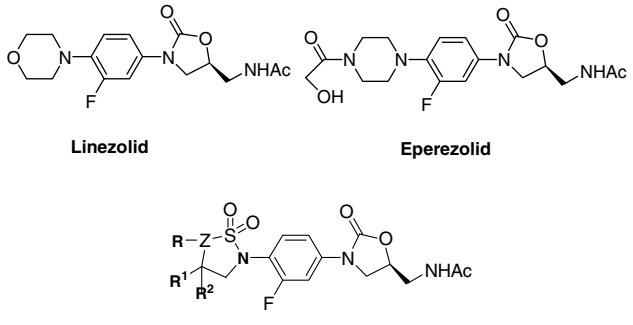

Figure 1. Structure of Linezolid, Eperezolid, and target molecules.

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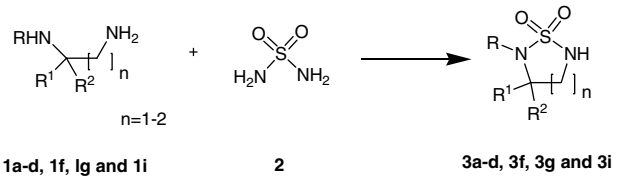


a:n=1, R=Me, R_1=R_2=H
b:n=1, R=Et, R_1=R_2=H
c:n=1, R=H, R_1=Me, R_2=H
d:n=1, R=H, R_1=R_2=Me
f:n=1, R=Bn, R_1=R_2=H
g:n=1, R=H, R_1=R_2=H
i:n=2, R=Me, R_1=R_2=H

Scheme 1. Reagents and condition: (i) pyridine, reflux, 16 h, 46–79% (for **3a**–**d**, **3f**, **3g**, and **3i**).

with RuO_4 in CH_3CN gave sulfamidate **8**, which was successfully converted into the deprotected cyclosulfamidate **3j** using trifluroacetic acid.

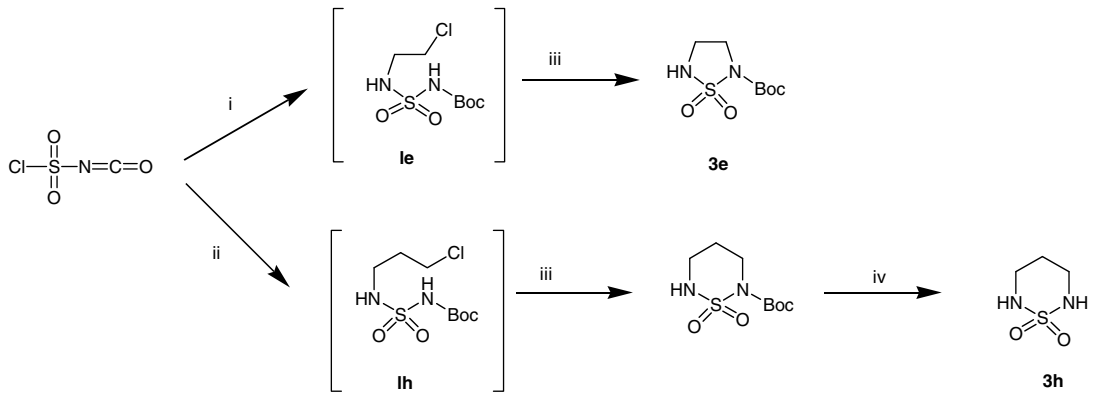
The syntheses of derivatives **15a–j** are outlined in Scheme 4. Cyclic sulfonamide moieties as starting materials on condensation with 3,4-difluoronitro benzene in acetonitrile under reflux yielded the corresponding nitro compounds **9**. Hydrogenation of compound **9** with 10% Pd–C/H_2 followed by condensation with benzyl chloroformate afforded the protected compound **11**. Conversion of compound **11** to oxazolidinone **12** was accomplished by use of *n*-butyllithium and (*R*)-glycidyl butyrate in dry THF at −78 °C. Compound **12** was reacted with methane sulfonyl chloride, subsequently was treated with sodium azide to yield azide **14**. Reduction and acylation of compound **14** gave title compounds **15a–j**.

The MICs were determined by the agar dilution method using test agar. An overnight culture of bacteria in tryptosoy broth was diluted to about 10^6 cells/ml with the same broth and inoculated with an inoculating device onto agar containing serial 2-fold dilutions of the tested compounds. Organisms were incubated at 37 °C for 18–20 h. The MICs of a compound were defined as the lowest concentration that visibly inhibited growth.

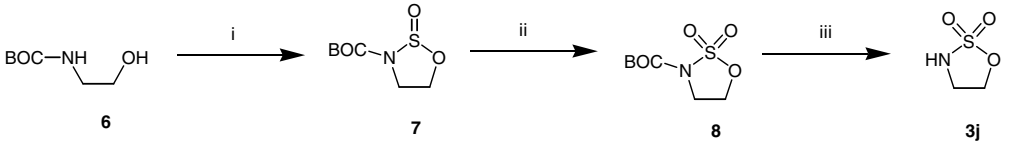
The in vitro antibacterial activities of the new oxazolidinones (**15a–j**) prepared above against both Gram-positive and Gram-negative organism such as *Haemophilus influenzae* are listed in Tables 1 and 2. For comparison, the MIC values of Linezolid are also listed. Among the tested compounds, **15g**, **15h**, **15i**, and **15j** displayed superior or similar antibacterial activities to Linezolid against Gram-positive, methicillin-, and vancomycin-resistant strains, while the analogs **15a–f** showed inferior activity.

In particular, compound **15g**[12] having [1,2,5]thiadiazolidin-1,1-dioxide moiety was 3- to 4-fold superior active against most of the targeted both Gram-positive and Gram-negative strains to Linezolid. As to the substituents on the oxazolidinone chain, compounds **15a** and **15g** having thiadiazolidine moieties were generally more potent than compounds **15h–i** having thiadiazinane moieties against Gram-positive strains (Table 1). The introduction of alkyl group at *N*-position of thiadiazolidine (**15a** and **15b**) led to significantly enhanced antibacterial activity compared to compounds **15c** and **15d** with alkyl substituents at C-3 position. Compound **15g** having [1,2,5]thiadiazolidine moiety was more potent than compound **15j** having [1,2,3]-oxathiazolidine moiety. This can be attributed to the different electronic characters between nitrogen and oxygen. With increasing bulkiness from methyl to ethyl, benzyl, *tert*-butoxy in compounds **15a**, **15b**, **15e**, and **15f**, the activity was found to be decreased in regular sequence. In case of **15e** and **15f**, any bulky substituents also led to significant loss in antibacterial activity. This suggests that bulky substituents are not favorable.

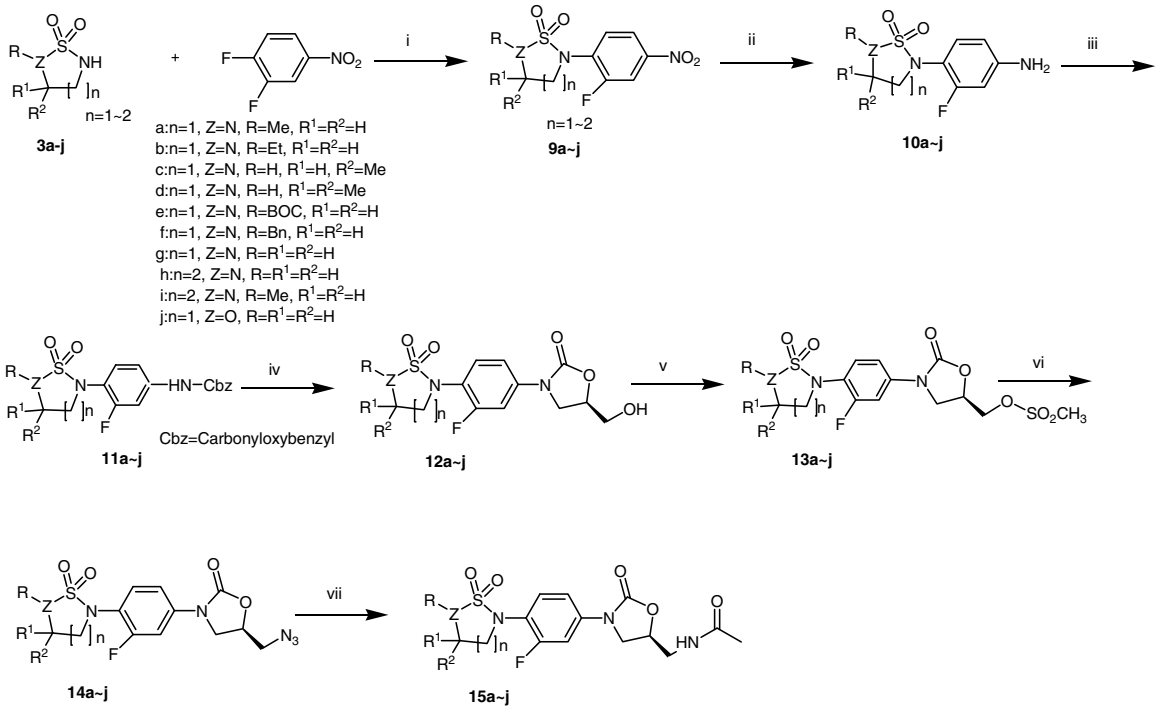
In summary, the introduction of [1,2,5]thiadiazolidine-1,1-dioxide moiety to oxazolidinones afforded potent compounds with in vitro antibacterial activity comparable or superior to Linezolid against Gram-positive, methicillin-, and vancomycin-resistant strains.



Scheme 2. Reagents and conditions: (i) BuOH, 2-chloroethylamine, CH_2Cl_2, 0 °C to rt, 2 h, 71%; (ii) BuOH, 2-chloropropylamine, CH_2Cl_2, 0 °C to rt, 2 h, 57%; (iii) K_2CO_3, DMSO, 80–83%; (iv) TFA, CH_2Cl_2, rt, 1 h, 83%.



Scheme 3. Reagents and conditions: (i) $SOCl_2$, CH_3CN, pyridine, −40 °C to rt, 2 h; (ii) $NaIO_4$, $RuCl_3$, CH_3CN, 5 °C to rt, 1 h, 85%; (iii) TFA, CH_2Cl_2, rt, 1 h, 83%.



Scheme 4. Reagents and conditions: (i) CH_3CN, reflux, 3 h, 74–89% (for **9a–j**); (ii) H_2, Pd/C, THF, 3 h, 81–88% (for **10a–j**); (iii) benzylchloroformate, $NaHCO_3$, acetone–H_2O, 5 °C to rt, 10 h, 58–78% (for **11a–j**); (iv) *n*-BuLi, (*R*)-glycidyl butyrate, −78 °C to rt, 28–51% (for **12a–j**); (v) MsCl, TEA, CH_2Cl_2, 5 °C, 1 h, 78–84% (for **13a–j**); (vi) NaN_3, DMF, 75 °C, 16 h, 74–84% (for **14a–j**); (vii) 1—H_2,Pd/C, ethyl acetate, rt, 20 h; 2—Ac_2O, pyridine, −5 °C to rt, 3 h, 38–62% (for **15a–j**).

Table 1
In vitro antibacterial activity (MIC, μg/ml) of oxazolidinone derivatives against standard strains

Compound	*S. a.*[a]	*C. s.*[b]	*E. f.*[c]	*E. f.*[d]	*S. p.*[e]	*S. p.*[f]	*S. a.*[g]	*H. i.*[h]
15a	3.12	6.25	3.12	3.12	0.78	1.56	1.56	3.12
15b	6.25	6.25	3.12	1.56	0.78	0.78	3.12	3.12
15c	12.5	12.5	6.25	3.12	3.12	1.56	3.12	6.25
15d	12.5	12.5	12.5	25	12.5	6.25	12.5	25.0
15e	12.5	12.5	12.5	25	25	6.25	6.25	6.25
15f	6.25	6.25	6.25	6.25	6.25	6.25	6.25	3.12
15g	0.39	0.20	0.20	0.39	0.20	0.20	0.20	0.20
15h	3.12	1.56	1.56	1.56	0.78	1.56	1.56	1.56
15i	1.56	1.56	1.56	1.56	0.78	0.78	1.56	1.56
15j	3.12	3.12	1.56	1.56	1.56	0.78	0.39	3.12
Linezolid	1.56	1.56	1.56	1.56	0.39	0.39	1.56	1.56

[a] *S. a.*, *Staphylococcus aureus* C463.
[b] *C. s.*, *Coagulase negative staphylococci*.
[c] *E. f.*, *Enterococcus faecalis* C474.
[d] *E. f.*, *Enterococccus faecium* C803.
[e] *S. p.*, *Streptococcus pneumoniae* C402.
[f] *S. p.*, *Streptococcus pyogenes* ATCC8736.
[g] *S. a.*, *Streptococcus agalactiae* ATCC2901.
[h] *H. i.*, *Haemophilus influenzae*.

Table 2
In vitro antibacterial activity (MIC, μg/ml) of oxazolidinone derivatives against MRSA and VRE

Compound	MRSA 1	VRE 1	VRE 2	VRE 3	VRE 4	VRE 5	VRE 6	VRE 7	VRE 8
15a	3.12	3.12	3.12	6.25	6.25	3.12	3.12	3.12	3.12
15b	6.25	6.25	3.12	3.12	6.25	3.12	3.12	6.25	3.12
15c	12.5	6.25	6.25	6.25	12.5	6.25	6.25	12.5	12.5
15d	12.5	12.5	12.5	25	12.5	6.25	12.5	12.5	12.5
15e	12.5	12.5	12.5	25	25	6.25	6.25	12.5	12.5
15f	6.25	6.25	1.56	6.25	6.25	1.56	6.25	6.25	6.25
15g	0.20	0.20	0.20	0.78	0.39	0.78	0.78	0.39	0.78
15h	1.56	3.12	1.56	3.12	1.56	0.78	3.12	3.12	3.12
15i	1.56	0.78	1.56	1.56	1.56	1.56	1.56	1.56	1.56
15j	3.12	1.56	1.56	1.56	1.56	3.12	3.12	1.56	3.12
Linezolid	3.12	1.56	0.78	0.78	1.56	1.56	1.56	1.56	1.56

MRSA 1, methicillin-resistant *Staphylococcus aureus* 1; VRE 1, vancomycin-resistant *Enterococcus faecalis*; VRE 2, vancomycin-resistant *Enterococcccus faecium*; VRE 3: vancomycin-resistant *Enterococci* 1; VRE 4, vancomycin-resistant *Enterococci* 2; VRE 5, vancomycin-resistant *Enterococci* 3; VRE 6, vancomycin-resistant *Enterococci* 4; VRE 7, vancomycin-resistant *Enterococci* 5; VRE 8, vancomycin-resistant *Enterococci* 6.

Acknowledgments

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12. *Compound* ***9g***: ^{1}H NMR ($CDCl_3$): δ 1.97 (s, 9H), 3.96 (s, 4H), 7.12 (t, 1H, J = 7.0 Hz), 7.97–8.04 (m, 2H). HRMS(FAB) Calcd for $C_8H_8FN_3O_4S$ 261.0220. Found 261.0221.
Compound ***11g***: ^{1}H NMR ($CDCl_3$): δ 1.53 (s, 9H), 3.78 (t, 2H, J = 3.3 Hz), 3.97 (t, 2H, J = 3.1 Hz), 5.18 (s, 2H), 7.00 (d, 1H, J = 3.3 Hz), 7.29–7.51 (m, 8H). HRMS(FAB) Calcd for $C_{16}H_{16}FN_3O_4S$ 365.0846. Found 365.0849.
Compound ***12g***: ^{1}H NMR ($CDCl_3$): δ 3.72 (t, 2H, J = 3.5 Hz), 3.91 (t, 2H, J = 3.6 Hz), 4.10–4.17 (m, 6H),4.70–4.74 (m, 1H), 7.21 (d, 1H, J = 4.3 Hz), 7.26–7.66 (m, 2H). HRMS(FAB) Calcd for $C_{12}H_{14}FN_3O_5S$ 331.0638. Found 331.0639.
Compound ***13g***: ^{1}H NMR (MeOD): δ 3.07 (s, 3H), 3.88 (t, 2H, J = 3.7 Hz), 4.03 (t, 2H, J = 5.4 Hz), 4.25–4.29 (m, 2H), 4.30–4.32 (m, 3H), 4.83–4.85 (m, 1H), 7.12 (d, 1H, J = 3.3 Hz), 7.41–7.48 (m, 1H), 7.63–7.68 (m, 1H). HRMS(FAB) Calcd for $C_{12}H_{13}FN_6O_4S$ 356.0703. Found 356.0705.
Compound ***14g***: ^{1}H NMR (MeOD): δ 3.90 (t, 2H, J = 3.3 Hz), 4.01 (t, 2H, J = 6.0 Hz), 4.24–4.27 (m, 2H), 4.31–4.33 (m, 3H), 4.83–4.86 (m, 1H), 7.12 (d, 1H, J = 3.3 Hz), 7.42–7.48 (m, 1H), 7.63–7.68 (m, 1H). HRMS(FAB) Calcd for $C_{13}H_{16}FN_3O_7S_2$ 409.0414. Found 409.0419.
Compound ***15g***: ^{1}H NMR ($CDCl_3$): δ 1.86 (s, 3H), 3.20 (m, 2H), 3.47 (t, 2H, J = 5.7 Hz), 3.70 (t, 2H, J = 6.0 Hz), 4.03 (t, 3H, J = 3.5 Hz), 4.73–4.78 (m, 1H), 5.30 (m, 1H), 7.20 (d, 1H, J = 3.1 Hz), 7.39 (t, 1H, J = 6.6 Hz), 7.58 (dd, 1H, J = 6.2 and 5.9 Hz). HRMS(FAB) Calcd for $C_{14}H_{17}FN_4O_5S$ 372.0904. Found 372.0901.