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A New and Efficient Synthetic Method and Antibacterial Activities of Oxazolidinone Analogues

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Abstract: A series of novel oxazolidinone analogues were prepared by a new and efficient synthetic method and their antibacterial activities were determined. These compounds were characterized by LC-MS and ^{1}H NMR.

Keywords: Oxazolidinones, antibacterial activity, synthesis.

Oxazolidinones, exemplified by Linezolid, are a novel class of totally synthetic antibacterial agents with activity against multi-drug-resistant gram-positive bacteria, such as *methicillin-resistant Staphylococcus aureus* (MRSA), *methicillin-resistant Staphylococcus epidermidis* (MRSE) and *vancomycin-resistant enterococci* (VRE)[1]. Recently, some 4-substituted piperazinyl phenyl oxazolidinone analogues which had wider antibacterial spectrum and stronger activity than Linezolid were reported [2]. So our interest turned to the 4-substituted piperazinyl phenyl oxazolidinone analogues and their activities. In this paper, a series of novel oxazolidinone analogues were prepared by a new and efficient synthetic method, and their antibacterial activities were evaluated.

Chemistry

The general synthetic method of 4-substituted piperazinyl phenyl oxazolidinone analogues has been reported by Brickner *et al.*[3], but in which the sensitive reagents and extreme conditions were needed. We designed a new synthetic method and solved this problem successfully. The method was outlined in the **Scheme 1** and **Scheme 2**.

In the Brickner's method, phenyl oxazolidinone was synthesized by using BuLi at -78℃ under nitrogen atmosphere. In our paper, by starting with (R)-*epi*-chlorohydrin as the chiral source, which was commecially available and cheap. Starting from 3-fluorophenyl isocyanate **1**, which could be transformed into phenyl oxazolidinone **2** in one step in the presence of lithium bromide and tributylphosphine oxide. The reaction mixture was refluxed in toluene for two hours to give 83% yield. Then displacement chlorine with NaN_3 to give **3** by the catalysis of sodium iodide in DMF at 80℃ in 95% yield. Reacting **3** with thioacetic acid gave **4** in 90% yield, which was higher than

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reported[4](61%). **5** was obtained according to the literatured 5. Finally, the bromide **5** with morpholine or **9a-j** in DMF at 80℃ gave linezolid or corresponding **6a-j** in 70%-80% yield by using CuI and L-proline as the ligand[6].

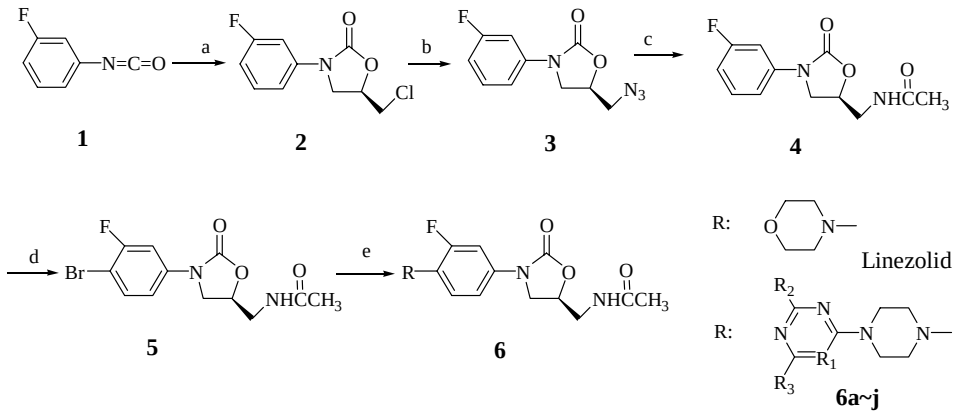
The compounds **8a-j** were prepared by reacting **7a-j** with various substituted compound in the present of Na_2CO_3 in 0-45℃ in 82-90% yield, then **8a-j** were heated with excess piperazine and K_2CO_3 in CH_3CN in 85-95% yield to afford the compound **9a-j**.

In conclusion, we have synthesized ten new target compounds with a new synthetic method, and their structures, LC-MS and ^{1}H NMR data were listed in **Table 1**.

Antibacterial Activity

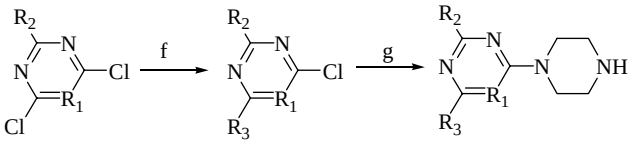
The antibacterial activities *in vitro* of the target compounds against *Straphylococcus aureus* (MA) were tested with Linezolid as a contrast. The results were shown in **Table 2**.

Scheme 1



reagents and conditions: a. (R)-*epi*-chlorohydrin, LiBr, $(n\text{-}Bu)_3PO$, toluene, reflux, 83%; b. NaN_3, NaI, DMF, 80℃, 95% ; c. CH_3COSH, r.t, 90%; d. $NaBO_3$, Na_2WO_4, KBr, 75℃, 86%; e. **9a-j** or morpholine, CuI, K_2CO_3, L-proline, DMF, 80℃, 70%-80%.

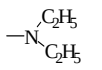
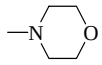
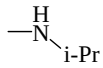
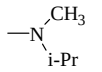
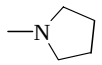
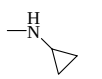
Scheme 2



7a-j **8a-j** **9a-j**

reagents and conditions: f. Na_2CO_3, 0-45℃, R_3H, acetone, 82%-90%; g. piperazine, K_2CO_3, CH_3CN, 45-80℃, 85%-95%;

Table 1 The structures, FAB-MS and ^{1}H NMR data of compound **6a-j**

Compd	R_1	R_2	R_3	LC-MS (*m*/*z*)	^{1}H NMR(δ ppm)*
6a	CH	H-	CH_3O-	445 (M+1)	1.83(s, 3H), 3.02(s, 4H), 3.43(m, 2H), 3.73(dd, 1H, *J*=9Hz, *J*"=6 Hz), 3.83(s, 4H), 3.90(s, 3H), 4.12(t, 1H, *J*=9 Hz), 4.72 (m, 1H), 7.06-7.19 (m, 3H), 7.50(d, 1H), 8.28(dd, 2H)
6b	CH	H-	Cl-	449 (M+1)	1.83(s, 3H), 3.03(s, 4H), 3.41(m, 2H), 3.74(dd, 1H, *J*=9Hz,*J*"=6 Hz), 3.82(s, 4H), 4.12(t, 1H, *J*=9 Hz), 4.72(m, 1H), 7.06-7.20(m, 3H), 7.50(d, 1H), 8.28(t, 1H), 8.37(s, 1H, *J*=9 Hz)
6c	N	CH_3O-	CH_3O-	476 (M+1)	1.83(s, 3H), 3.02(s, 4H), 3.43(m, 2H), 3.73(dd, 1H, *J*=9Hz, *J*"=6 Hz), 3.86(s, 6H), 3.92(s, 4H), 4.12(t, 1H, *J*=9 Hz), 4.72(m, 1H), 7.06-7.20(m, 2H), 7.50(d, 1H), 8.28(t, 1H, *J*=9 Hz)
6d	N	C_2H_5O-	C_2H_5O-	504 (M+1)	1.40(s, 6H), 1.83(s, 3H), 3.02(s, 4H), 3.43(m, 2H), 3.74(dd, 1H, *J*=9Hz,*J*"=6 Hz), 3.94(m, 10H), 4.12(t, 1H, *J*=9 Hz), 4.72(m, 1H), 7.06-7.20(m, 2H), 7.50(d, 1H), 8.28(t, 1H, *J*=9 Hz)
6e	N	CH_3O-		517 (M+1)	1.10(t, 6H), 1.83(s, 3H), 2.99(s, 4H), 3.41(m, 2H), 3.52(dd, 4H), 3.70(m, 1H), 3.78(s, 3H), 3.85(s, 4H),4.08(t, 1H, *J*=9 Hz), 4.72(m, 1H), 7.07-7.19(m, 2H), 7.50(d, 1H), 8.24(t, 1H, *J*=9 Hz)
6f	N	CH_3O-		531 (M+1)	1.83(s, 3H), 2.99(s, 4H), 3.41(m, 2H), 3.61(d, 4H), 3.69(m, 5H), 3.79(s, 3H), 3.86(s, 4H), 4.12(t, 1H, *J*=9 Hz), 4.72 (m, 1H), 7.06-7.20(m, 2H), 7.50(d, 1H), 8.24(t, 1H, *J*=9 Hz)
6g	N	CH_3O-		503 (M+1)	1.36(d, 6H), 1.83(s, 3H), 2.99(s, 4H), 3.41(m, 2H), 3.70(m, 2H), 3.76(s, 3H), 3.84(s, 4H), 4.11(t, 1H, *J*=9 Hz), 4.72(m, 1H), 6.90(d, 1H), 7.06-7.20(m, 2H), 7.50(t, 2H), 8.25(t, 1H, *J*=9 Hz)
6h	N	CH_3O-		517 (M+1)	1.11(d, 6H), 1.83(s, 3H), 2.90(s, 3H), 2.99(s, 4H), 3.41(m, 2H), 3.70(m, 1H, *J*=9Hz, *J*"=6 Hz), 3.73(s, 3H), 3.86(s, 4H), 4.10(t, 1H, *J*=9 Hz), 4.72(m, 1H), 4.93(m, 1H), 7.06-7.20(m, 2H), 7.50(d, 1H), 8.24(t, 1H, *J*=9 Hz)
6i	N	CH_3O-		515 (M+1)	1.83-1.90(m, 7H), 2.98(s, 4H), 3.38-3.46(m, 6H), 3.70(m, 1H, *J*=9Hz,*J*"=6 Hz), 3.78(s, 3H), 3.86(s, 4H), 4.10(t, 1H, *J*=9 Hz), 4.72(m, 1H), 7.06-7.19(m, 2H), 7.50(d, 1H), 8.25(t, 1H, *J*=9 Hz)
6j	N	CH_3O-		501 (M+1)	0.46(s, 2H), 0.63(d, 2H), 1.83(s, 3H), 2.76(s, 1H), 2.98(s, 4H), 3.41(m, 2H), 3.68(m, 2H), 3.75(s, 3H), 3.83(s, 4H), 4.10(t, 1H, *J*=9 Hz), 4.70(m, 1H), 7.06-7.20(m, 2H), 7.50 (t, 2H), 8.24(t, 1H, *J*=9 Hz)

*DMSO-d_6 as solvent

Compound **6a-c** showed good fungicidal activity, antibacterial activity of **6b** was even higher than linezolid. The further experiments and pharmacological evaluations are in progress. These results encourage us to design and synthesize more antibacterial agents.

Table 2 The antibacterial activities of compounds **6a-j**

Compd.	*Straphylococcus aureus* MIC(μg/mL)	Compd.	*Straphylococcus aureus* MIC(μg/mL)
Linezolid	2.5		
6a	2.5	**6f**	10
6b	1.25	**6g**	20
6c	2.5	**6h**	20
6d	40	**6i**	5
6e	10	**6j**	10

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