Synthesis of novel oxazolidinone derivatives for antibacterial investigation

Y. Cui, Y. Dang, Y. Yang* and R. Ji

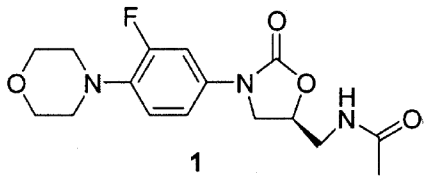
Shanghai Institute of Materia Medica, Shanghai Institute for Biological Science, Chinese Academy of Sciences, Shanghai 201203, China

A series of oxazolidinones were synthesized and evaluated as antibacterial agents. They were screened *in vitro* against a panel of Gram-positive organisms. Compound 9a was found to exhibit activity comparable to linezolid.

Keywords: Antibacterial activity, bacterial resistance, linezolid, oxazolidinones.

THE emergence of bacterial resistance to antibiotics has posed serious concern to medical professionals during the past decade[1]. Oxazolidinones are a new class of totally synthetic antimicrobial agents against multidrug resistant Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermitis* (MRSE), penicillin-resistant *Streptococcus pneunoniae* (PRSP) and vancomycin-resistant *enterococci* (VRE). They have a novel mechanism of action, selectively and uniquely binding to the 50S ribosomal subunit, and inhibiting bacterial translation at the initiation phase of protein synthesis. Consequently, it was supposed[2,3] that the drug would not show cross-resistance with existing antibacterial agents. Linezolid (Zyvox, (**1**)), approved by FDA, is the first agent of this class coming into the market[4]. The unique mechanism of action of oxazolidinones has attracted interest to develop derivatives with potent activity and broad spectrum[5–7].

The combination of two antibacterial agents or substructures into a single entity to achieve drugs has received considerable attention[8]. Sulpha drugs exhibit antibacterial activity. Schiff base as activity component has been linked to antibacterial agents[9]. Aspirin is also an anti-inflammatory agent. Based on these considerations, we have set out to prepare oxazolidinone derivatives bearing sulphonyl, acyl and Schiff base groups in order to investigate their antibacterial activity.



1

The key intermediate, N-[[(5S)-3-(4-amino-3-fluorophenyl)-2-oxo-1, 3-oxazolindin-5-yl]-methyl]acetamide (**2**), was prepared according to the reported method[10]. Reaction of (**2**) with sulphonyl chloride gave products (**3a–g**). Hydrogenation of (**3f, g**) with 10% Pd/C in methanol afforded compounds (**4a, b**). Compounds (**5a, b**) were obtained by acetylation of (**4a, b**) with acetic anhydride (Scheme 1).

The intermediate (**2**) reacted with aldehydes in ethanol at room temperature or refluxing to yield products (**6a–g**) (Scheme 2).

Acid chloride (**8a, b**) (prepared from acid (**7a, b**)) reacted with (**2**) to afford amide (**9a, b**) respectively (Scheme 3).

All prepared compounds were screened for their antibacterial activity *in vitro* against a panel of Gram-positive pathogens isolated clinically. Minimum inhibitory concentration (MIC, μg/ml) values were determined using agar dilution methodology[11] and are shown in Table 1. Linezolid was prepared as described earlier[12].

In all prepared compounds **6a**, **6b**, **6e** and **9a** exhibited antibacterial activities towards Gram-positive strains used. Others are inactive. The activity of compounds **6a, b** and **6e** with Schiff base group is significantly less than the reference compound. Introduction of Schiff base to oxazolidinone could not improve activity. Compound **9a**, resulting from a combination of aspirin and oxazolidinone, exhibited potent bacterial activity comparable to linezolid. Compound **9a**, which was a combination of aspirin structure with oxazolidinone, exhibited antibacterial activity comparable to linezolid. This may be due to strong interaction between the aspirin derivative and the receptor. Compounds **3a–g**, **4a**, **b** and **5a**, **b** with sulphonyl group completely lose antibacterial activity. The hypothesis that the sulphonyl group as a pharmacophore is linked to oxazolidinone, proves no effect.

All melting points were uncorrected. ^{1}H NMR spectra were recorded on Varian Mercury 400 spectrometer. Electron impact mass spectra were obtained on Finnigan MAT-95 spectrometer. Elemental analyses were performed on Vario Elementar analyser.

N-[[(S)-3-(4-substitutedsulfamino-3-fluorophenyl)-2-oxo-1,3-oxazolindin-5-yl]methyl]acetamide (**3a–g**): To a stirred mixture of (**2**) (0.4 mmol) and triethylamine (1.2 mmol) in methylene chloride (10 ml) under ice-bath was added RSO_2Cl (0.78 mmol). The mixture was slowly heated to room temperature overnight. The reaction mixture was washed with 1N HCl, H_2O, saturated $NaHCO_3$ and brine respectively. The organic layer was dried over anhydrous Na_2SO_4 and concentrated, then purified by column chromatography (5% methanol-methylene chloride) to give (**3a–g**).

Hydrogenation of (**3f, g**): A mixture of (**3f**) or (**3g**) (0.44 mmol) and 50 mg of 10% Pd/C in 50 ml methanol was stirred under hydrogen (balloon) overnight. The mixture was then filtered; the filtrate was concentrated and purified by column chromatography (5% methanol-methylene chloride) to give (**4a, b**).

Acetylation of (**4a, b**): To a stirred solution of (**4a, b**) (0.19 mmol) in pyridine (8 ml) under ice-bath, was added acetic anhydride (10.6 mmol). The mixture was slowly

*For correspondence. (e-mail: ysyang@mail.shcnc.ac.cn)

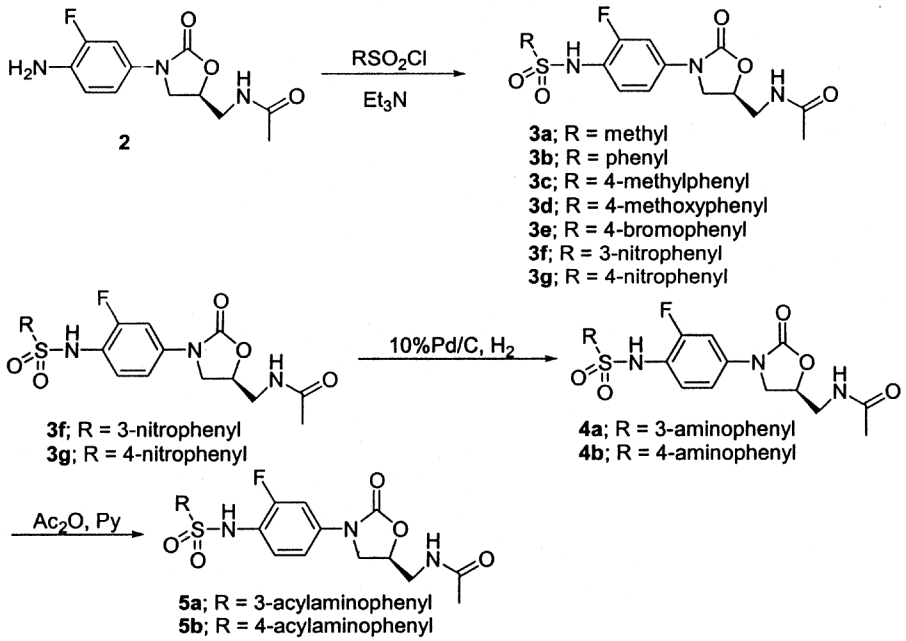
Table 1. Characterization of compounds **3a–g**, **4a, b**, **5a**, **6b–g** and **9a,b**

Compound	Melting point	Yield (%)	Molecular formula	Calculated (%) (Found) C	H	N	^{1}H NMR δ (ppm)
3a	223–224	42	$C_{13}H_{16}FN_3O_5S$	45.22 (45.05	4.64 4.37	12.17 12.05)	2.04 (s, 3H, $COCH_3$), 3.43 (s, 3H, SO_2CH_3), 3.68 (m, 2H, CH_2), 3.80 (q, 1H, CH_2), 4.05 (t, 1H, CH_2), 4.80 (m, 1H, CH), 6.03 (m, 1H, Ar-H), 7.35 (t, 1H, Ar-H), 7.70 (dd, 1H, Ar-H)
3b	>230	55	$C_{18}H_{18}FN_3O_5S$	53.07 (53.45	4.42 4.08	10.32 10.28)	2.04 (s, 3H, $COCH_3$), 3.60–3.80 (m, 3H, 2 × CH_2), 4.05 (t, 1H, CH_2), 4.79 (m, 1H, CH), 6.00 (brs, 1H, NH), 7.20 (d, 2H, Ar-H), 7.09 (t, 1H, Ar-H), 7.20 (m, 1H, Ar-H), 7.95 (dd, 2H, Ar-H), 7.68 (t, 1H, Ar-H), 7.51–7.58 (m, 3H, Ar-H)
3c	202–204	64	$C_{19}H_{20}FN_3O_5S$	54.15 (53.62	4.75 4.59	9.98 9.56)	2.00 (s, 3H, $COCH_3$), 2.37 (s, 3H, CH_3), 3.54–3.74 (m, 3H, 2 × CH_2), 3.98 (t, 1H, CH_2), 4.74 (m, 1H, CH), 6.00 (t, 1H, NH), 6.65 (brs, 1H, NH), 6.99 (m, 1H, Ar-H), 7.20 (d, 2H, Ar-H), 7.47 (dd, 1H, Ar-H), 7.55 (t, 1H, Ar-H), 7.60 (d, 2H, Ar-H)
3d	>230	77	$C_{19}H_{20}FN_3O_6S$	52.17 (52.17	4.57 4.21	9.61 9.57)	2.03 (s, 3H, $COCH_3$), 3.60–3.68 (m, 2H, CH_2), 3.78 (t, 1H, CH_2), 3.88 (s, 3H, OCH_3), 4.04 (t, 1H, CH_2), 4.79 (brs, 1H, CH), 6.03 (brs, 1H, NH), 6.96–7.00 (m, 2H, Ar-H), 7.07 (t, 1H, Ar-H), 7.18 (d, 1H, Ar-H), 7.54 (dd, 1H, Ar-H), 7.83–7.88 (m, 2H, Ar-H)
3e	>230	85	$C_{18}H_{17}BrFN_3O_5S$	44.44 (44.15	3.50 3.29	8.64 8.61)	2.03 (s, 3H, $COCH_3$), 3.60–3.70 (m, 2H, CH_2, 3.79 (t, 1H, CH_2), 4.05 (t, 1H, CH_2), 4.79 (brs, 1H, CH), 6.00 (t, 1H, NH), 7.05 (t, 1H, Ar-H), 7.20 (m, 1H, Ar-H), 7.56 (dd, 1H, Ar-H), 7.68 (dd, 2H, Ar-H), 7.78 (dd, 2H, Ar-H)
3f	210–214	72	$C_{18}H_{17}FN_4O_7S$	47.79 (47.98	3.76 3.94	12.39 12.03)	2.00 (s, 3H, $COCH_3$), 3.60–3.80 (m, 3H, 2 × CH_2), 4.00 (t, 1H, CH_2), 4.79 (m, 1H, CH), 6.00 (brs, 1H, NH), 6.92 (brs, 1H, Ar-H), 7.08 (m, 1H, Ar-H), 7.49 (dd, 1H, Ar-H) 7.58 (t, 1H, Ar-H), 7.67 (q, 1H, Ar-H), 8.03–8.06 (m, 1H, Ar-H), 8.38–8.42 (m, 1H, Ar-H), 8.56 (t, 1H, Ar-H)
3g	218–222	30	$C_{18}H_{17}FN_4O_7S$	47.79 (48.09	3.76 3.86	12.39 12.04)	2.00 (s, 3H, $COCH_3$), 3.60 (m, 1H, CH_2), 3.65–3.80 (m, 2H, CH_2), 4.00 (t, 1H, CH_2), 4.79 (m, 1H, CH), 5.96 (brs, 1H, NH), 6.77 (brs, 1H, Ar-H), 7.10 (d, 1H, Ar-H), 7.50 (dd, 1H, Ar-H), 7.59 (t, 1H, Ar-H), 7.92 (d, 2H, Ar-H), 8.29 (d, 2H, Ar-H)
4a	218–222	20	$C_{18}H_{19}FN_4O_5S$	51.18 (50.85	4.50 4.66	13.27 12.82)	1.80 (s, 3H, $COCH_3$), 3.04 (t, 1H, CH_2), 3.69 (m, 1H, CH_2), 4.68 (brs, 1H, CH), 5.74 (s, 1H, NH), 6.69–6.78 (m, 2H, Ar.H), 6.88 (brs, 1H, Ar.H), 7.10–7.20 (m, 3H, Ar-H), 7.44 (d, 1H, Ar-H), 8.22 (d, 1H, Ar-H)
4b	189–194	60	$C_{18}H_{19}FN_4O_5S$	51.18 (50.79	4.50 4.70	13.27 12.76)	1.80 (1H, $COCH_3$), 3.69 (brs, 1H, CH_2), 3.94 (m, 1H, CH_2), 4.65 (brs, 2H, CH_2+ CH), 7.00 (brs, 1H, Ar-H), 7.20–7.40 (m, 2H, Ar-H), 7.50–8.20 (m, 3H, Ar-H)
5a	>230	42	$C_{20}H_{21}FN_4O_6S$	51.72 (51.52	4.52 4.75	12.07 12.37)	1.83 (s, 3H, $COCH_3$), 2.07 (s, 3H, Ar-$NHCOCH_3$), 3.42 (m, 2H, CH_2), 3.79 (q, 1H, CH_2), 4.05 (q, 1H, CH_2), 4.19 (t, 1H, CH_2), 4.76 (m, 1H, CH), 7.45 (dd, 1H, Ar-H), 7.59 (m, 3H, Ar-H), 7.75 (dd, 1H, Ar-H), 7.90 (dd, 1H, Ar-H), 8.25 (t, 1H, Ar-H), 8.29 (brs, 1H, Ar-H), 10.37 (s, 1H, NH)
6b	228	73	$C_{19}H_{18}FN_3O_4$	61.45 (61.83	4.85 4.78	11.32 11.12)	1.84 (s, 3H, $COCH_3$), 3.42 (m, 2H, CH_2), 4.08–4.18 (m, 2H, CH_2), 4.75 (m, 1H, CH), 7.00 (m, 1H, Ar-H), 7.20–7.30 (m, 1H, Ar-H), 7.35 (dd, 1H, Ar-H), 7.35–7.80 (m, 4H, Ar-H), 8.30 (m, 1H, Ar-H)
6d	214–218	76	$C_{19}H_{17}FN_4O_5$	57.00 (57.09	4.25 4.20	14.00 13.72)	1.84 (s, 3H, $COCH_3$), 3.43 (m, 2H, CH_2), 3.80 (m, 1H, CH_2), 4.16 (t, 1H, CH_2), 4.75 (m, 1H, CH), 7.40 (dd, 1H, Ar-H), 7.55 (t, 1H, Ar-H), 7.66 (dd, 1H, Ar-H), 8.19 (d, 2H, Ar-H), 8.28 (t, 1H, Ar-H), 8.37 (d, 2H, Ar-H), 8.91 (s, 1H, CH=N–)

(*cont...*)

Table 1. (*Cont...*)

Compound	Melting point	Yield (%)	Molecular formula	Calculated (%) (Found) C	H	N	^{1}H NMR δ (ppm)
6e	218–220	52	$C_{19}H_{17}F_2N_3O_3$	61.13 (61.44	4.56 4.72	11.26 11.42)	1.84 (s, 3H, $COCH_3$), 3.43 (m, 2H, CH_2), 3.80 (m, 1H, CH_2), 4.16 (t, 1H, CH_2), 4.75 (m, 1H, CH), 7.40 (dd, 1H, Ar-H), 7.55 (t, 1H, Ar-H), 7.66 (dd, 1H, Ar-H), 8.19 (d, 2H, Ar-H), 8.28 (t, 1H, Ar-H), 8.37 (d, 2H, Ar-H), 8.91 (s, H, CH=N–)
6f	>230	71	$C_{19}H_{17}ClFN_3O_3$	58.53 (58.45	4.36 4.52	10.78 10.73)	1.82 (s, 3H, $COCH_3$), 3.42 (m, 2H, CH_2), 3.73 (q, 1H, CH_2), 4.14 (t, 1H, CH_2), 4.75 (m, 1H, CH), 7.35 (dd, 1H, Ar-H), 7.48 (t, 3H, Ar-H), 7.60 (m, 3H, Ar-H), 7.95 (d, 2H, Ar-H), 8.24 (t, 1H, Ar-H), 8.70 (s, 1H, CH=N–)
6g	191–194	25	$C_{20}H_{17}BrFN_3O_5$	50.21 (50.31	3.56 3.59	8.79 8.54)	1.84 (s, 3H, $COCH_3$), 3.43 (t, 2H, CH_2), 3.78 (q, 1H, CH_2), 4.15 (t, 1H, CH_2), 4.75 (m, 1H, CH), 6.19 (s, 3H, Ar-H), 7.33–7.43 (t, 3H, Ar-H), 7.59–7.65 (m, 2H, Ar-H), 8.26 (t, 1H, Ar-H), 8.76 (s, 1H, CH=N–)
9a	220–222	24	$C_{21}H_{20}FN_3O_6$	58.74 (58.22	4.66 4.94	9.79 9.02)	1.82 (s, 3H, $COCH_3$), 2.20 (s, 3H, Ar-$OCOCH_3$), 3.40 (m, 2H, CH_2), 3.73 (m, 1H, CH_2), 4.10 (t, 1H, CH_2), 4.73 (m, 1H, CH), 7.25 (m, 1H, Ar-H), 7.38 (t, 1H, Ar-H), 7.60 (m, 3H, Ar-H), 7.70 (d, 1H, Ar-H), 10.03 (s, 1H, NH)
9b	181–184	97	$C_{22}H_{19}ClF_2N_4O_5$	52.33 (52.48	3.77 3.55	11.10 11.79)	1.83 (s, 3H, $COCH_3$), 2.72 (s, 3H, Ar-$OCOCH_3$), 3.70 (q, 1H, CH_2), 4.08 (t, 1H, CH_2), 4.70 (m, 1H, CH), 7.25 (d, 1H, Ar-H), 7.38 (m, 1H, Ar-H), 7.48 (d, 3H, Ar-H), 7.50–7.60 (m, 3H, Ar-H), 8.23 (t, 1H, Ar-H)

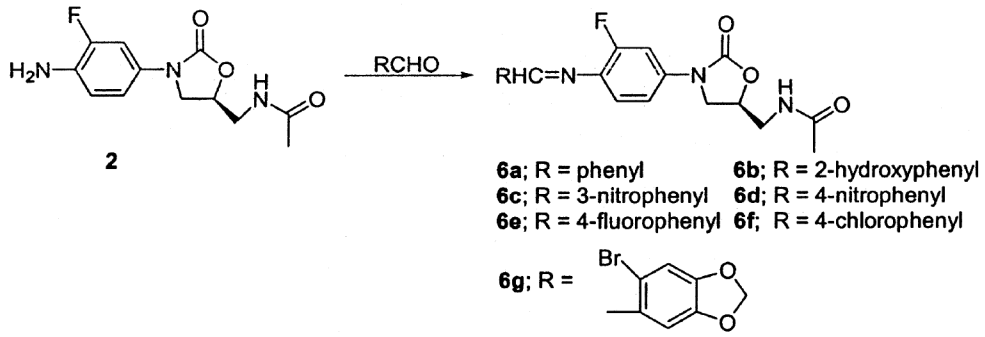


Scheme 1.

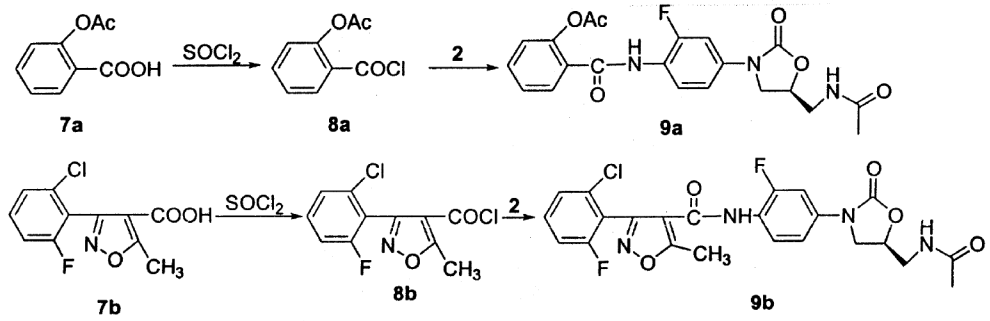
warmed to room temperature overnight. The reaction mixture was washed with 1N HCl, H_2O, saturated $NaHCO_3$ and brine respectively. The organic layer was dried over anhydrous Na_2SO_4 and concentrated, then purified by column chromatography (5% methanol-methylene chloride) to give (**5a, b**).

Synthesis of (**6a–g**): A solution of (**2**) (0.2 mmol) in ethanol (8 ml) was treated with aldehyde (5.6 mol) at room temperature or refluxing overnight. The solid obtained after filtration was air-dried to give (**6a–g**).

Acid chloride (**8a, b**): To a stirred solution of acid (**7a, b**) (1.65 mol) in dry tetrahydrofuran (10 ml) under ice-bath



Scheme 2.



Scheme 3.

Table 2. Antibacterial activity of some synthesized compounds (MIC, μg/ml)

Compound	Microorganism				
	S.a. (8 strains)	S.e. (4 strains)	S.hom. (2 strains)	Str. p. (1 strain)	Str. (3 strains)
6a	0.5–16	0.5–16	8	2	2
6b	16–128	8–16	32	32	32–128
6e	8–64	1–32	4–8	32	16–32
9a	0.5–8	0.25–4	0.25	8	0.5–1
LZ	0.5–2	0.25–0.5	0.25–1	2	1–2

LZ, Linezolid; S.a., *Staphylococcus aureus*; S.e., *Staphylococcus epidermitis*; S.hom, *Staphylococcus hominis*; Str. p., *Streptococcus pneumoniae*; Str., *Streptococcus.*

was added $SOCl_2$ (0.5 ml). After 2 h, the mixture was heated at 50°C for 3 h. Excess $SOCl_2$ was removed under reduced pressure, which resulted in acid chloride.

Synthesis of (**9a, b**): To a stirred solution of (**2**) (0.2 mmol) in pyridine (8 ml) under ice-bath was added dropwise acid chloride (**8a, b**). The mixture was slowly warmed to room temperature overnight. The reaction mixture was washed with 1 N HCl, H_2O, saturated $NaHCO_3$ and brine respectively. The organic layer was dried over anhydrous Na_2SO_4 and concentrated, then purified by column chromatography (5% methanol-methylene chloride) to give (**9a, b**).

1. Service, R. F., *Science*, 1995, **270**, 724–727.
2. Swaney, S. M., Aoki, H. and Ganoza, M. C., *Antimicrob. Agents Chemother.*, 1997, **41**, 2132–2136.
3. Clemett, D. and Markham, A., *Drugs*, 2000, **59**, 815–827.
4. *Scrip*, 2000, **2526**, 18.
5. Woodford, N., *Expert Opin. Invest. Drugs*, 2003, **12**, 117–137.
6. Ryan, B., Ho, H. T. and Wu, P., *Expert Opin, Invest. Drugs*, 2000, **9**, 2945–2972.
7. Karen, B., Mark, M. and Michele, W. W., *Curr. Opin. Microbiol.*, 2004, **7**, 466–476.
8. Hutchinson, D. K., *Expert Opin. Ther. Pat.*, 2004, **14**, 1309–1328.
9. Sridhar, S. K., Saravanan, M. and Ramesh, A., *Eur. J. Med. Chem.*, 2001, **36**, 615–625.
10. Genin, M. J. *et al.*, *J. Med. Chem.*, 2000, **43**, 953–970.
11. National Committee for Clinical Laboratory Standards, NCCLs Document M7-A3 (ISBN 1-56238-209-8), NCCLs, Villanova, PA, 1993.
12. Brickner, S. J. *et al.*, *J. Med. Chem.*, 1996, **39**, 673–679.

Received 20 August 2004; revised accepted 4 January 2005