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Synthesis and Antibacterial Activity of Oxazolidinone Containing Sulphonyl Group

Yingjie Cui,[a] Yushe Yang,[a,*] Kaixian Chen,[a] Ruyun Ji[a] and Shuhua Zhang[b]

[a]*Shanghai Institute of Materia Medica, Shanghai Institute for Biological Science, Chinese Academy of Sciences, Shanghai 200031, China*
[b]*Sichuan Industrial Institute of Antibiotics, Chengdu 610051, China*

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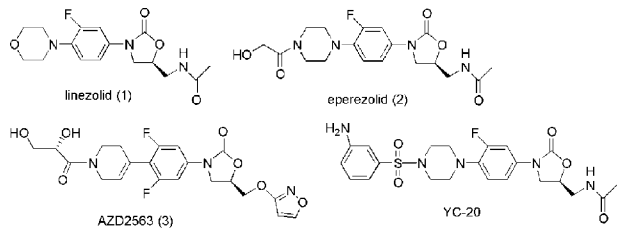
Abstract—A series of oxazolidinone derivatives carrying sulphonyl group was synthesized and their antibacterial activity was evaluated in vitro. Many of such compounds demonstrated potent antibacterial activity. The activity of a novel compound (**YC-20**) was 2–4-fold more potent than that of linezolid.

The incidence of infections caused by Gram-positive bacteria broadly resistant to current treatment is dramatically growing.[1] Thus, the development of new broad spectrum antibacterial agents aimed at methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis* (MRSE), vancomycin-resistant *Enterococci* (VRE), and penicillin-and cephalosporin-resistant *Streptococci* is the subject of current research.

Oxazolidinones, exemplified by linezolid (**1**), eperezolid (**2**) and AZD2563 (**3**), represent an exciting new class of totally synthetic antibacterial agents.[2,3] Linezolid (Zyvox®), approved by FDA, is the first agent of oxazolidinone coming into market.[4] Linezolid is a powerful new tool to deal with described above Gram-positive bacterial infections.[5] It is believed that oxazolidinones lack cross-resistance with any known antibiotics.[6] Many companies such as Pharmacia, Bayer, AstraZeneca et al. are devoting to the development of oxazolidinones with increased activity and expanded spectrum.[7–9] Oxazolidinones have a novel mechanism of action that shows to selectively and uniquely bind to the 50S ribosomal subunit, inhibiting bacterial translation at the initiation phase of protein synthesis[10] They inhibit protein synthesis by binding to the central loop of domain of 23S rRNA of 50S ribosomal subunit, interfering with initiator fMet-tRNA binding to the P-site of the ribosomal peptidyltransferase center.[11,12]



Although resistance to oxazolidinone is difficult to generate, there are already reports in clinical isolates of linezolid-resistance *Enterococci*[13,14] and linezolid-resistance *S. aureus*.[15,16] So it is necessary to develop newer and more effective antimicrobial agents. Eperezolid (**2**) and other compounds possessing alkyl, aryl and acyl on the piperazine of oxazolidinones exhibit potent antibacterial activity, the pipeazine subclass become the principal focus of ongoing chemical modification.[17–19] Considering antibacterial activity of sulfa drugs, we designed to link sulphonyl group to piperazine of oxazolidinones. A new series of oxazolidinone containing sulphonyl group was synthesized. We now report the synthesis and antibacterial activity of these compounds.

Condensation of (*S*)-*N*-[3-[3-Fluoro-4-(*N*-1-piperazinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide[2] with sulfonyl halide gave the product 4-12 after chromatographic purification on silica gel (5%methanol-methylene chloride).[20] Hydrogenation of **9**–**11** with 10% Pd/C in methanol gave compounds **13**, **YC-20**, 14. Compounds 15–17 were obtained by acetylation of **13**, **YC-20**, **14** with acetic anhydride (Scheme 1). The structure of Compounds **4**–**17**, **YC-20** is shown in Table 1.

*Corresponding author. Tel.: +86-21-50806600-3403; fax: +86-21-50806786; e-mail: ysyang@shcnc.ac.cn

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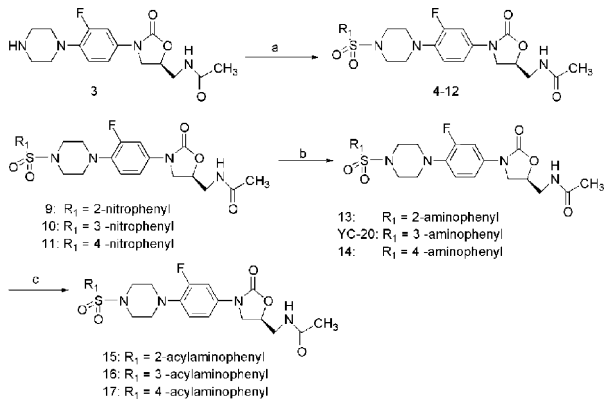

Scheme 1.

Table 1. Prepared compounds **4**–**17** and **YC-20**

No	R_1	M.p. (°C)	Yield (%)
4	Methyl	209.5–211	24.2
5	Phenyl	191–193	82.9
6	4-Methylphenyl	224–227	69.0
7	4-Methoxyphenyl	>230	83.0
8	4-Bromophenyl	203–205	75.7
9	2-Nitrophenyl	158–162	52.4
10	3-Nitrophenyl	175–178	63.0
11	4-Nitrophenyl	188–190	56.6
12	2-Thiophenyl	202–205	85.0
13	2-Aminopheny	>230	43.5
YC-20	3-Aminophenyl	206–210	80.7
14	4-Aminophenyl	>230	91.0
15	2-Acylaminophenyl	156–158	30.0
16	3-Acylaminopheny	222–225	27.7
17	4-Acylaminophenyl	228–230	66.0

Antibacterial activity of compounds **4**–**17**, **YC-20** was tested in vitro against a panel of clinical isolates of Gram-positive pathogenic bacteria. Linezolid was selected as reference compound. Minimum inhibitory concentration (MIC) values were determined using agar dilution or broth microdilution methodology.[21] Compounds were incorporated into MH (Mueller–Hinton) agar medium at concentration of 128, 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.125, 0.06, 0.03 mg/L. The test organism was grown in MH broth medium at 35 °C for 16–18 h, the broths were adjusted to the turbidity of 0.5 McFarland standard; then the bacterial suspensions were inoculated onto the drug-supplemented MH agar plates at 35 °C for 18–20 h. The MIC was defined as the lowest concentration of drug that completely inhibited growth of the organism. The results are shown in Table 2.

Most of analogues exhibited potent antibacterial activity against Gram-positive strains. The activity of compound **YC-20** was 2–4-fold more potent than that of linezolid. By comparing activities of **10** with **9**, **11**, and **YC-20** with **13**, **14**, it could be found that position of substituent had important effect on activity. Meta substituent in phenyl is more favorable for antibacterial activity. The aminophenyl derivatives are more potent than the corresponding nitrophenyl derivatives. On the other hand, acetylation of aminophenyl derivative leads to decrease activity.

Table 2. In vitro antibacterial activity of oxazolidinone derivatives against 18 bacterial strains (MIC, μg/mL)

Compd	Microorganism[a]				
	S.a. (8 strains)	*S.e.* (4 strains)	*S.hom.* (2 strains)	*Str.p.* (1 strain)	*Str.* (3 strains)
4	1–4	0.5	2	2	2–4
5	0.5–4	0.25	0.5–1	2	2–4
6	8–128	2–4	4–64	>128	64–128
7	0.5–16	0.25–0.5	0.5–2	8	2–16
8	>128	128	>128	>128	>128
9	1–8	2–4	N.T.[b]	8	2–8
10	0.25–4	0.25	0.25–0.5	1	0.5–4
11	4–128	4–8	16–32	128	64–128
12	0.25–16	0.25–4	N.T. [b]	4	4
13	1–8	0.125–4	N.T. [b]	2	1–2
YC-20	0.25–0.5	0.25	0.25	1	1
14	0.25–16	0.25	0.25	16	2–16
15	>64	>64	>64	>64	>64
16	>128	>128	>128	>128	>128
17	1–32	0.5–1	1–4	32	8–32
LZ	0.5–2	0.25–0.5	0.25–1	2	1–2

LZ = linezolid
[a]Str.p. = *Streptococcus pneumoniae*, Str. = *Streptococcus*, S.hom. = *Staphylococcus hominis*, S.a. = *Staphylococcus aureus*, S.e. = *Staphylococcus epidermidis*.
[b]N.T. = No Tested.

Based on above facts, potent activity of **YC-20** may be due to strong polarity of amine group. There may be intense 'binding action' at the site of action between **YC-20** and receptor. Conversion of amino of **YC-20** to acylamino results in complete loss of antibacterial activity. This observation may direct existence of hydrogen bond between amino of **YC-20** and receptor. Furthermore, **YC-20** demonstrates potent activity possibly because of hydrophilicity of amino. The position of amino in **YC-20** is similar to that of hydroxyl moiety in Eperezolid and AZD2563, these three compounds may have similar stereoelectronic action with receptor.

In conclusion, we have found that introduction of sulphonyl to oxazolidinones could enhance their antibacterial activity. Compound **YC-20** was 2–4-fold more potent than linezolid and as drug candidate is now in further studies.

Acknowledgements

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20. Representative procedure: to a suspension of (*S*)-*N*-[3-[3-fluoro-4-(*N*-1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide (**3**) (514 mg, 1.5 mmol) in 20 mL pyridine at 0 °C under stirring was added portion wise 3-nitrophehylsulfonyl chloride (533 mg, 2.4 mmol). The mixture was slowly warmed to rt, then overnight. The reaction mixture was washed with 1N HCl, H_2O, saturated $NaHCO_3$, brine, and then dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (5% methanol-methylene chloride) to give the product 511 mg, yield: 63.0%. ^1H NMR (400 MHz, $CDCl_3$): δ 8.63 (m, 1H), 8.50 (m, 1H), 8.15 (m, 1H), 7.80 (t, $J = 8.05$ Hz, 1H), 7.45 (dd, $J = 2.19$ Hz, $J' = 13.91$ Hz, 1H), 7.98–8.04 (m, 2H), 6.10 (t, $J = 6.24$ Hz, 1H), 4.76 (m, 1H), 4.00 (t, $J = 8.79$ Hz, 1H), 3.60–3.85 (m, 3H), 3.30 (brs, 4H), 3.18 (brs, 4H), 2.00 (s, 3H). MS: m/z 521 (M^+). Anal. ($C_{22}H_{24}FN_5O_7S$) C, H, N: Calcd, 50.67, 4.60, 13.43, Found, 50.43, 4.28, 12.95.
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