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Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 16 (2006) 1557–1561

Novel 4-N-substituted aryl pent-2-ene-1,4-dione derivatives of piperazinyloxazolidinones as antibacterials

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Received 19 September 2005; revised 25 November 2005; accepted 9 December 2005
Available online 28 December 2005

Dedicated to Professor Dr. S. Chandrasekaran, Indian Institute of Science, Bangalore, India, on his 60th birthday.

Abstract—A few substituted piperazinylphenyloxazolidinone compounds **6–13** having substitution on the distant nitrogen atom of piperazine ring scaffold have been synthesized and evaluated for their antibacterial activity in Gram-positive bacteria. A few compounds showed superior in vitro antibacterial activity against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, and *Streptococcus pyogenes* than linezolid and eperezolid.

Oxazolidinones are new class of synthetic antibacterial agents with unique mechanism of action [1] and have been explored by a number of research groups.[2]

Pharmacia and Upjohn discovered two lead candidates, linezolid **1** and eperezolid **2** (Fig. 1), belonging to the oxazolidinone class.[3] Linezolid showed favorable activities against Gram-positive pathogens including multidrug-resistant *Staphylococci*, *Enterococci*, and *Pneumococci*.[4] Linezolid (Zyvox®) is the only oxazolidinone in the market after US-FDA approval in 2001.[5] Unfortunately, emergence of resistance to antibacterial agents did not spare linezolid, since a few cases of linezolid resistant pathogens in hospital isolates have been reported.[6]

Eperezolid was not taken for further development due to its shorter half-life in humans[7] as well as due to significant levels of bone marrow toxicity observed in higher animal models when given for a prolonged period.[8] However, due to the structural similarity to linezolid and scope for modification, eperezolid template has been modified by various research groups.[9] Recently, we have reported some of our research findings in this area.[10–14]

Both linezolid and eperezolid (Fig. 1) possess an electron-donating nitrogen atom in the 4-position of the phenyl ring, which may be responsible for their activity and safety.[15] Therefore, without removing the piperazine ring of eperezolid, we attached groups with extended conjugation and a carbonyl group at the 4-position of piperazine. In this communication, we report the synthesis and in vitro antibacterial activities of these new oxazolidinone compounds **6–13** (Table 1) in several Gram-positive organisms (Tables 1 and 2). Recently, we have disclosed compound **3** (Fig. 2) and various modifications of **3**, which have shown very good activity in Gram-positive bacteria.[10]

We further modified **3** by introducing a carbonyl group in between the aryl moiety and the unsaturation. The minimum inhibitory concentration (MIC) for 90% bacterial growth inhibition was determined by the microbroth dilution technique using the National Committee for Clinical and Laboratory Standards (NCCLS) method.[16] Compounds, which showed MIC values in the range of 0.25–1.0 μg/mL in the primary panel of strains (Table 1), were further evaluated against a broader panel of Gram-positive strains (Table 2).

4-N-substituted aryl pent-2-ene-1,4-dione derivatives **6–12** were synthesized by the coupling reaction of 4-oxo-4-aryl-but-2-enoic acid **4** and piperazinylaryloxazolidinone **5** using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1-hydroxy-benzotriazole

Keywords: Piperazinylaryloxazolidinone; In vitro MIC; Linezolid; Eperezolid; Antibacterials; Gram-positive bacteria.
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doi:10.1016/j.bmcl.2005.12.025

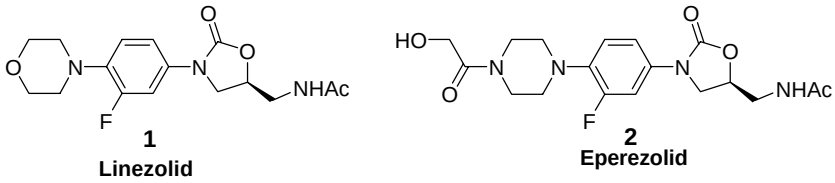
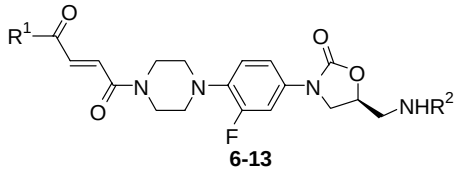


Figure 1.

Table 1. In vitro MIC (minimum inhibitory concentration in μg/mL) values of novel oxazolidinones **6–13** in various Gram-positive bacteria[a]



Compound	R^1	R^2	% yield	B.p.	S.e.	E.f.1	S.a.1
3				0.5–1	1–2	1–2	1–2
6	–Ph	–COMe	51	1–2	0.12–0.25	0.5–1	⩽0.12
7	1-Naphthyl	–COMe	21	1–2	2–4	0.5–1	2–4
8	4-Br Ph–	–COMe	45	0.12–0.25	0.25–0.5	2–4	⩽0.12
9	4-MeOPh–	–COMe	25	0.5–1	0.25–0.5	0.5–1	0.5–1
10	4-NHAcPh–	–COMe	12	0.5–1	⩽0.12	0.25–0.5	0.5–1
11	–Me	–COMe	33	0.5–1	0.25–0.5	1–2	0.25–0.5
12	–ONa	–COMe	80	>16	>16	>16	>16
13	4-MeOPh–	–CSMe	15	0.5–1	0.12–0.25	0.25–0.5	0.25–0.5
Linezolid				2–4	1–2	1–2	1–2
Eperezolid				1–2	ND	2–4	2–4

[a] MIC were determined by the microbroth dilution technique and values reported in the table represent values obtained in triplicate. B.p., *Bacillus pumilus* **ATCC 14348**; S.e., *Staphylococcus epidermidis* **ATCC 155**; E.f.1, *Enterococcus faecalis* **ATCC**; **35550**; S.a.1, *Staphylococcus aureus*, **ATCC 25923**; ND, not done.

Table 2. In vitro antibacterial activity of selected oxazolidinones against a broader panel of susceptible and resistant Gram-positive strains (MIC values in μg/mL)[a]

Compound	S.a.2	S.a.3	S.a.4	S.a.5	S.a.6	E.f.2	E.f.3	S.p. 1	S.p. 2
6	⩽0.12	⩽0.12	0.25–0.5	⩽0.12	4–8	2–4	2–4	0.25–0.5	⩽0.12
7	4–8	4–8	2–4	8–16	>16	1–2	8–16	0.5–1	2–4
8	4–8	2–4	4–8	4–8	>16	2–4	>16	ND	2–4
9	0.5–1	⩽0.12	0.25–0.5	1–2	>16	1–2	2–4	⩽0.12	2–4
10	⩽0.12	⩽0.12	⩽0.12	1–2	>16	1–2	ND	⩽0.12	ND
11	1–2	1-2	ND	1–2	>16	4–8	2–4	ND	0.5–1
13	⩽0.12	0.25–0.5	⩽0.12	0.5–1	>16	1–2	ND	0.25–0.5	1–2
3	2–4	2–4	2–4	1–2	>16	0.5–1	0.5–1	1–2	0.5–1
Eperezolid	2–4	2–4	2–4	1–2	>16	1–2	1–2	0.5–1	0.5–1
Linezolid	2–4	2–4	2–4	1–2	>16	2–4	1–2	0.25–0.5	0.25–0.5

[a] MIC were determined by the microbroth dilution technique and values reported in the table represent values obtained in triplicate. S.a.2, *Staphylococcus aureus* **ATCC 9144**; S.a.3, *Staphylococcus aureus* **ATCC 14154**; S.a.4, *Staphylococcus aureus* **ATCC 29213**; S.a.5, methicillin-resistant *Staphylococcus aureus* **ATCC 700699**; S.a.6, linezolid-resistant *Staphylococcus aureus* **NRS 119**; E.f.2, *Enterococcus faecalis* **ATCC 14506**; E.f.3, vancomycin-resistant *Enterococcus faecalis* **ATCC 700802**; S.p.1, *Streptococcus pyogenes* **ATCC 14289**; S.p.2, penicillin-resistant *Streptococcus pneumoniae* **ATCC 700904**; ND, not done.

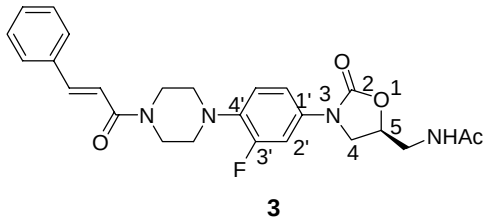
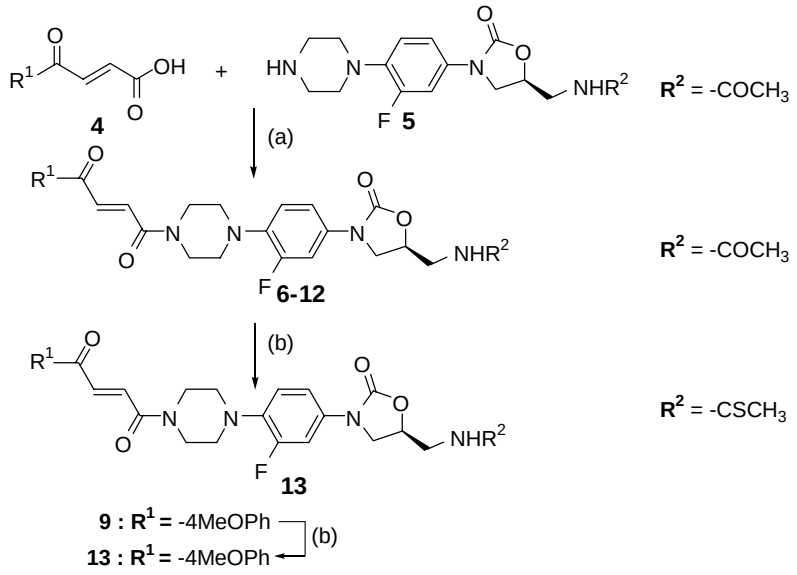


Figure 2.

monohydrate (Scheme 1) and are characterized.[17] The 4-oxo-4-aryl-but-2-enoic acids were synthesized as reported,[18] and the piperazinylaryloxazolidinones were synthesized as described in the literature.[3] The compound **9** was converted to thioacetamide derivative **13** by reacting with Lawesson's reagent.[19]

The 4-N-substituted alkyl and aryl pent-2-ene-1,4-dione derivatives of piperazinylphenyloxazolidinones



Scheme 1. Reagents and conditions: (a) EDC-HCl, HOBt·H_2O, NEt_3, CH_2Cl_2, 27–29 °C, 15–20 min; (b) Lawesson's reagent, THF, 65–70 °C, 1 h.

6–**13** were prepared and screened for their in vitro antibacterial activities against a panel of Gram-positive strains. Our previously reported compound **3**, which has an unsubstituted cinnamoyl group on the distant nitrogen atom of piperazinylphenyloxazolidinone, showed a slightly superior in vitro antibacterial activity than linezolid against sensitive Gram-positive strain *Bacillus pumilus* and comparable activity to that of the linezolid in the other bacteria used (Tables 1 and 2). Interestingly, when an additional carbonyl group was introduced to get further conjugation, the compound **6**, so formed, showed 4–8 times superior activity than compound **3**, linezolid and eperezolid against almost all the Gram-positive strains evaluated. This result prompted us to carry out further subtle structural modification and we synthesized compounds **8**–**10**, with further substitution on the 4-position of the phenyl pent-2-ene-1,4-dione system. Replacing the phenyl ring of compound **6** by a naphthyl ring elicited a moderate in vitro MIC value for the compound **7**, which may be attributed to the bulky nature of the naphthyl ring compared to the phenyl ring. The bromo derivative **8** showed excellent antibacterial activity in the strains mentioned in Table 1 and moderate to inferior activity in several other *Staphyloccocus aureus*, *Enterococcus faecalis*, and *Streptococcus pneumoniae* including the resistant strains mentioned in Table 2. However, substitution of an electron-releasing methoxy group on the 4-position the phenyl group as in **9** proved to be particularly worthwhile as compound **9** showed very good MIC values invariably in all the strains and superior to linezolid, eperezolid, and compound **3** (Tables 1 and 2).

The electron-withdrawing acetamide group (–NHAc) in compound **10** showed significantly good MIC values. Compound **11**, where a methyl group has been introduced in place of aromatic phenyl group of compound **6**, showed a slightly inferior antibacterial activity in strains mentioned in Table 2, although it showed very good activity in a few bacteria (Table 1). Furthermore, we modified the cinnamoyl group of compound **3** by completely removing the phenyl ring by sodium salt of carboxylate to obtain **12**, which led to complete loss of antibacterial activity. This deterioration is possibly due to the polar nature of the carboxylic group. It has been reported that thioacetamide at the 5th position of the oxazolidinone improves the antibacterial activities.[14,19] Thus, we selected compound **9**, which has shown consistent and improved MIC values, and modified at its 5th position by replacing the acetamide group by thioacetamide to get **13**. The replacement of "O" with "S" atom made the compound **13** superior to linezolid, eperezolid, and compound **3**.

In summary, compound **6** bearing a phenyl group showed improved MIC values in the range of 0.25–1.0 μg/mL for Gram-positive strains, which is superior to linezolid **1**. The 4-Br substitution (**8**) imparted better antibacterial activity in a few strains tested. Substitution by the 4-OMe-group (**9**) contributed significantly to the improvement of antibacterial activity, whereas, 4-NHCOMe group on the phenyl ring (**10**) showed improved antibacterial activity against all the entire Gram-positive strains studied. Furthermore, when the 5-acetamide group of the oxazolidinone **9** was transformed to a 5-thioacetamide group as in **13**, very good antibacterial activity was observed.

Acknowledgments

Authors are thankful to NARSA, USA, for providing linezolid resistant strains. We are grateful to Mr. Pankaj R. Patel, CMD, and the management of Zydus Group for encouragement. We thank Mr. Vijay Takale for some experimental contributions and the analytical department for support.

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17. Characterization data for compounds **6**–**13**: Compound **6**: (mp 192–195 °C); ^{1}HNMR (300 MHz, DMSO-d_6), δ 8.22 (d, J = 5.76 Hz, 1H), 8.02 (t, J = 7.14 Hz, 2H), 7.76 (d, J = 15.24 Hz, 1H), 7.57 (t, J = 7.50 Hz, 1H), 7.52 (t, J = 3.93 Hz, 2H), 7.46 (dd, J = 15.30, 4.38 Hz, 2H), 7.16 (dd, J = 6.78, 2.10 Hz, 1H), 7.10 (t, J = 9.42 Hz, 1H), 4.67 (q, J = 6.21 Hz, 1H), 4.07 (t, J = 8.91 Hz, 1H), 3.74–3.66 (m, 4H), 3.38 (t, J = 5.46 Hz, 3H), 3.0 (br s, 4H), 1.81 (s, 3H); IR (KBr) 3303.8, 1747.4, 1672.2, 1637.5, 1554.5, 1521.7 cm^{-1}; ESI-MS (M+H)$^+$ = 495.3.
Compound **7**: (mp 244–246 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.15 (d, J = 8.10 Hz, 1H), 8.12 (d, J = 8.40 Hz, 1H), 7.92 (d, J = 8.10 Hz, 1H), 7.72–7.57 (m, 3H), 7.52–7.46 (m, 4H), 7.13 (d, J = 1.81 Hz, 1H), 7.12 (t, J = 7.20 Hz, 1H), 5.99 (br s, 1H), 4.77 (m, 1H), 4.02 (t, J = 8.94 Hz, 1H), 3.92 (t, J = 5.04 Hz, 2H), 3.80 (t, J = 5.05 Hz, 2H), 3.75–3.60 (m, 3H), 3.09 (t, J = 4.83 Hz, 4H), 2.02 (s, 3H); IR (KBr) 3319.3, 1759.0, 1672.2, 1633.6, 1571.9, 1517.9 cm^{-1}; ESI-MS (M+H)$^+$ = 545.3.
Compound **8**: (mp 238–240 °C), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (*t*, J = 7.02 Hz, 3H), 7.65 (*d*, J = 8.58 Hz, 2H), 7.49 (dd, J = 11.64, 2.52 Hz, 2H); 7.10 (dd, J = 6.96, 1.80 Hz, 1H), 6.92 (t, J = 9.03 Hz, 1H), 5.99 (br s, 1H), 4.77 (m, 1H), 4.02 (t, J = 8.94 Hz, 1H), 3.92 (t, J = 5.04 Hz, 2H), 3.80 (t, J = 5.05 Hz, 2H), 3.75–3.61 (m, 3H), 3.09 (t, J = 4.83 Hz, 4H), 2.02 (s, 3H); IR (KBr) 3301, 1745, 1637, 1521 cm^{-1}; ESI-MS (M+H)$^+$ = 573.
Compound **9**: (mp 212–214 °C); ^{1}H NMR (300 MHz,

$CDCl_3$), δ 8.0 (dd, J = 4.98, 1.98 Hz, 2H), 7.96 (d, J = 14.88 Hz, 1H), 7.82 (t, J = 9.03 Hz, 1H), 7.50 (d, J = 12.0 Hz, 1H), 7.47 (dd, J = 11.40, 2.57 Hz, 1H), 7.03 (dd, J = 6.95, 1.81 Hz, 1H), 6.99–6.90 (m, 3H), 4.97–4.95 (m, 1H), 4.29 (t, J = 9.0 Hz, 1H), 4.11–4.05 (m, 3H), 3.92–3.86 (m, 5H), 3.80–3.77 (m, 3H), 3.09 (t, J = 5.10 Hz, 3H), 2.02 (s, 3H); IR (KBr) 3309, 1747.4, 1635.5, 1595,1521.7 cm^{-1}; ESI-MS $(M+H)^+$ = 525.3.

Compound **10**: (mp 267–270 °C); ^{1}HNMR (300 MHz, DMSO-d_6), δ 10.34 (s, 1H), 8.22 (t, J = 5.76 Hz, 1H), 8.02 (d, J = 8.76 Hz, 2H), 7.76 (t, J = 8.52 Hz, 3H), 7.51 (dd, J = 11.97, 2.52 Hz, 2H), 7.18 (dd, J = 6.78, 2.07 Hz, 1H), 7.07 (t, J=9.33 Hz, 1H), 4.71–4.65 (m, 1H), 4.07 (t, J = 9.06 Hz, 1H), 3.73 (br s, 4H), 3.68 (t, 1H), 3.39 (t, J = 5.49 Hz, 2H), 2.99 (br s, 4H), 2.08 (s, 3H), 1.82 (s, 3H); IR (KBr) 3328.9, 1745.5, 1724.2, 1670.2, 1591.2, 1517 cm^{-1}; ESI-MS $(M+H)^+$ = 552.3.

Compound **11**: (mp 204–206 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 (t, J = 5.75 Hz, 1H), 7.51 (dd, J = 12.54, 2.33 Hz, 1H), 7.40 (d, J = 15.94 Hz, 1H), 7.18 (dd, J = 6.62, 2.18 Hz, 1H), 7.07 (t, J = 9.33 Hz, 1H), 6.67 (d, J = 15.75 Hz, 1H), 4.79–4.67 (m, 1H), 4.04 (t, J = 9.0 Hz, 1H), 3.75–3.66 (m, 4H), 3.38 (t, J = 5.32 Hz, 3H), 2.97 (d, J = 4.21 Hz, 4H), 2.35 (s, 3H),1.81 (s, 3H); IR (KBr) 3421.5, 1735.8, 1647.1, 1618.2, 1517.9 cm^{-1}; ESI-MS $(M+H)^+$ = 433.3.

Compound **12**: (mp 218–220 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 (t, J = 5.75 Hz, 1H), 7.51 (dd, J = 12.54, 2.33 Hz, 1H), 7.40 (d, J = 15.94 Hz, 1H), 7.18 (dd, J = 6.62, 2.18 Hz, 1H), 7.07 (t, J = 9.33 Hz, 1H), 6.67 (d, J = 15.75 Hz, 1H), 4.79–4.67 (m, 1H), 4.04 (t, J = 9.0 Hz, 1H), 3.75–3.66 (m, 4H), 3.38 (t, J = 5.32 Hz, 3H), 2.97 (d, J = 4.21 Hz, 4H), 1.81 (s, 3H); IR (KBr) 3421.6, 1730, 1647.3, 1618.2, 1517.9 cm^{-1}.

Compound **13**: (mp 190–193 °C); ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.06 (dd, J = 4.98, 1.98 Hz, 2H), 7.96 (d, J = 14.88 Hz, 1H), 7.83 (t, J = 9.03 Hz, 1H), 7.50 (d, J = 12.0 Hz, 1H), 7.48 (dd, J = 11.40, 2.58 Hz, 1H), 7.07 (dd, J = 6.96, 1.80 Hz, 1H), 6.99–6.90 (m, 3H), 4.97–4.95 (m, 1H), 4.29 (m, 1H), 4.11–4.05 (m, 2H), 3.93–3.87 (m, 5H), 3.81–3.77 (m, 3H), 3.09 (t, J = 5.01 Hz, 4H), 2.60 (s, 3H); IR (KBr) 3246.0, 1631.7, 1596.9, 1571.9, 1521.7 cm^{-1}; ESI-MS $(M+H)^+$ = 541.3.

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