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Short communication

Novel Mannich ketones of oxazolidinones as antibacterial agents

Brijesh Kumar Srivastava *, Prashant B. Kapadnis, Purvi Pandya, Vidya Bhushan Lohray *

Zydus Research Centre, Sarkhej- Bavla N. H.8A, Moraiya, Ahmedabad 382210, India

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Abstract

A few Mannich ketones of piperazinyl oxazolidinone derivatives have been synthesized and their antibacterial activity in various Gram-positive organisms such as *Bacillus subtilis, Staphylococcus aureus, Staphylococcus epidermidis* and *Enterococcus faecalis* were evaluated by MIC determination. Compound **12** showed comparable activity (MIC) to linezolid and superior to eperezolid.

Keywords: Oxazolidinone; Linezolid; Eperezolid; In-vitro MIC; Mannich ketones; Gram-positive organism; Antibacterial activity

1. Introduction

Oxazolidinones are new class of synthetic antibacterials [1]. Linezolid (Fig. 1) has been the first and the only candidate of oxazolidinone class in the market [2]. However, there are reports that linezolid resistant organisms have started appearing in hospital isolates [3–5]. Eperezolid (Fig. 2) is a follow up molecule of Pharmacia, which has been exploited by several research organizations to get superior molecules [6–8].

We have earlier reported a few rational approaches to get better antibacterial agents [9–12]. Antibacterial activity of several fused Mannich ketones has been reported in literature with significant antibacterial activity against *Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, Staphylococcus saprophyticus, Micrococcus letucs* and *Bacillus subtilis* [13,14].

In the present communication we report for the first time the synthesis and activity of substituted Mannich ketones (**5–12**) of piperazinyl oxazolidinones (**3–4**) and their antibacterial activities in in-vitro MIC assay have been evaluated against selected Gram-positive organisms (Table 1 and Fig. 3).

The Mannich ketones (**5–12**) (Table 1) were synthesized using our earlier reported method [15] and characterized [16], where piperazinyl phenyl oxazolidinone **3** or **4** template were taken in methanol and treated with 37% formaldehyde solution at 0–5 °C. After removal of the solvents under reduced pressure the resulting residue was treated with ethereal HCl at 0–5 °C followed by refluxing with appropriate ketone in methanol (Scheme 1).

The piperazinyl phenyl oxazolidinone derivatives **3** and **4** (Fig. 3) used for the synthesis of Mannich ketones have been synthesized according to literature methods [17,18]. The in-vitro MIC antibacterial activity of the compounds **5–12** against Gram-positive bacteria (*S. aureus, S. epidermidis, B. subtilis, Enterococcus faecalis*) was tested as growth inhibition using microdilution broth method according to NCCLS standards [19]. Compounds were dissolved in concentrated

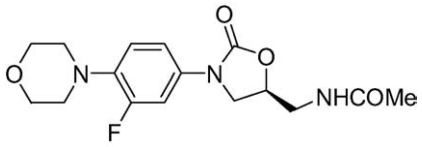

Fig. 1.

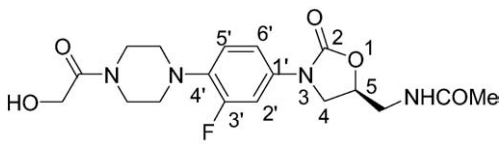

Fig. 2.

* Corresponding authors. Tel.: +91-2717-250801; fax: +91-2717-250606.
E-mail addresses: brijeshsrivastava@zyduscadila.com (B.K. Srivastava), vidya.lohray@zyduscadila.com (V.B. Lohray).

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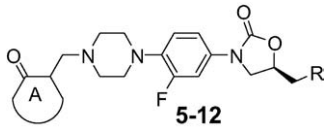
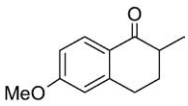
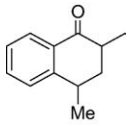
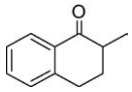
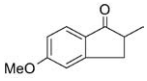
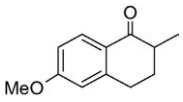
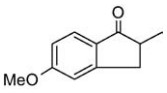
Table 1
Minimum inhibitory concentration (MIC in μg/ml) values of novel Mannich ketones of oxazolidinones in various Gram-positive bacteria [a]



5-12

Compound	A	R	%yield [b]	S.a1	S.a2	S.e	B.s	E.f
5		NHCOMe	29	16	16	8	4	8
6		NHCOMe	22	64	64	32	8	32
7		NHCOMe	12	32	32	ND	4	32
8		NHCOMe	20	32	32	8	4	8
9		NHCOMe	26	32	32	32	4	8
10		NHCSMe	21	4	4	4	ND	1
11		NHCSMe	21	8	4	2	0.5	4
12		$NHCSNH_2$	60	4	ND	2	2	1
Linezolid				4	4	0.5	1	4
Eperezolid				2	4	4	2	2

[a] MIC were determined by microbroth dilution technique and values reported in table represent the highest MIC value obtained in triplicate. S.a1, *Staphylococcus aureus* ZYABL 006; S.a2, *Staphylococcus aureus* ATCC 33591; S.e, *Staphylococcus epidermidis* ATCC 12228, B.s, *Bacillus subtilis* ATCC 6633; E.f, *Enterococcus faecalis* ATCC 29212; ND, not done.

[b] Yield of **5–12** in the Mannich reaction of **3–4**.

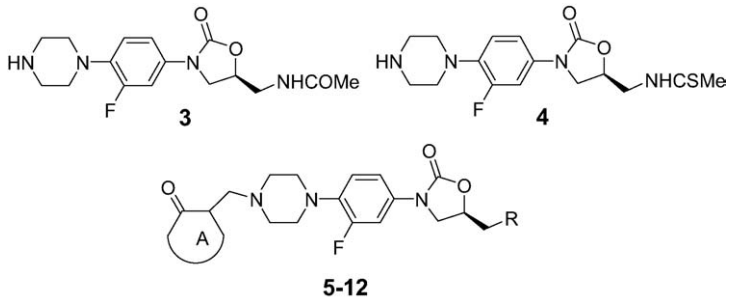
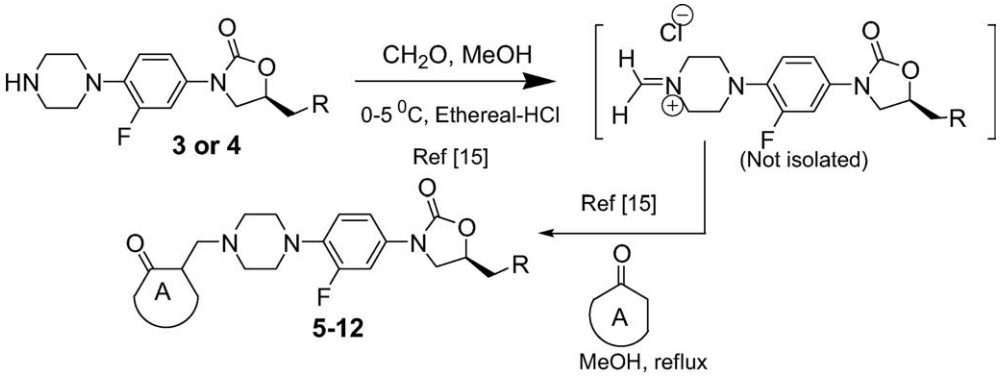


Fig. 3.



Scheme 1.

DMSO and water was added to get stock solution in 80% DMSO. The working solution was prepared by diluting the stock solution 1:10 times in 4–8% DMSO in water or medium and the dissolved compounds were evaluated in the concentrations of 0.25, 0.5, 1, 2, 4, 8, 16, 32 and 64 μg/ml.

2. Results and discussion

The Mannich ketone analogues of oxazolidinones **3** and **4**, were screened for in-vitro activity against a panel of Gram-positive organisms. The analog **5** showed inferior activity than linezolid as well as eperezolid (Table 1). Thus in an attempt to improve potency, we prepared several analogues by modifying the ketone part A (see Fig. 3). However, all such resulting compounds **6–9** lost their in-vitro antibacterial activity. It has been reported that thioacetamide at the 5th position of the oxazolidinone improves the activity [17]. Thus, in order to see the effect of thioacetamide moiety in place of acetamide, we synthesized compounds **10** and **11** using Lawesson's reagent. This replacement of "O" with "S" atom made these compounds (**10** and **11**) nearly as active as linezolid. We further replaced acetamide chain by thiourea, which lead to compound **12**, which showed the in-vitro activity equal to linezolid in the Gram-positive bacteria screened.

3. Conclusion

A moderately active compound **5** has been taken as a lead to get active compounds **10–12**. It has been shown that thio compounds are more potent than their oxygen counterpart.

Acknowledgements

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[16] Characterization data: **5** (mp 158–160 °C), IR 3282, 2931, 1743, 1664, 1598, 1517, 1245, 1128 cm^{-1}, ^{1}HNMR ($CDCl_3$), δ 7.98 (d, 1H, *J* = 9.0 Hz), 7.50 (d, 1H, *J* = 13.4 Hz), 7.02 (m, 2H), 6.85 (d, 1H, *J* = 7.6 Hz), 6.70 (s, 1H), 6.03 (m, 1H), 4.78 (m, 1H), 3.87 (s, 3H), 3.43 (s, 4H), 3.26 (s, 4H), 3.00 (s, 2H), 2.03 (s, 3H), 1.17 (s, 2H); ESI-MS $(M + H)^+$ –HCl = 525.2 **6** (mp 127–131 °C), IR 3404, 2962, 1733, 1637, 1517, 1099, 802 cm^{-1}, ^{1}HNMR ($CDCl_3$), δ 7.54 (d, 1H), 7.03 (m, 2H), 4.76 (m, 1H), 4.03 (m, 1H), 3.71 (m, 8H), 3.10 (m, 2H), 2.51 (s, 3H); ESI-MS $(M + H)^+$ –HCl = 447.2. **7** (mp 154–156 °C), IR 3323, 2941, 1741, 1672, 15159, 1224, 775 cm^{-1}, ^{1}HNMR ($CDCl_3$), δ 8.02 (t, 1H, *J* = 9.2 Hz), 7.50 (m, 1H), 7.43 (dd, 1H, *J* = 2.6 and 11.5 Hz), 7.32 (d, 1H, *J* = 6.7 Hz), 7.09 (dd, 1H, *J* = 2.3 and 6.39 Hz), 6.96 (t, 1H, *J* = 9.0 Hz), 5.96 (s, 1H), 4.89 (m, 1H), 4.02 (t, 1H, *J* = 9.0 Hz), 3.73 (m, 2H), 3.61 (m, 1H), 3.09 (bs, 5H), 2.81(d, 1H), 2.72 (m, 2H), 2.61 (m, 3H), 2.17 (d, 1H), 2.02 (s, 3H), 1.44 (m, 3H); ESI-MS $(M + H)^+$ -HCl = 509.4. **8** (mp 155–157 °C), IR 3325, 2817, 1739, 1647, 1517, 1417, 1224, 804 cm^{-1}, ^{1}HNMR (CD_3OD), δ 7.95 (dd, 1H, *J* = 1.5 and 6.8 Hz), 7.48 (s, 1H), 7.32 (m, 2H), 7.13 (dd, 1H, *J* = 1.8 and 6.2 Hz), 7.08 (t, 1H, *J* = 9.4 Hz), 4.81 (m, 1H), 4.62 (s, 1H), 4.10 (t, 1H), 3.78 (m, 1H), 3.55 (d, 2H, *J* = 5.0 Hz), 3.29 (m, 4H), 3.22 (m, 4H), 2.72 (m, 2H), 2.62 (m, 2H), 2.38 (m, 1H), 1.95 (s, 3H); ESI-MS $(M + H)^+$ –HCl = 495.3. **9** (mp 146–149 °C), IR 3400, 2925, 1751, 1701, 1600, 1517, 1261, 1224, 750 cm^{-1}, ^{1}HNMR ($CDCl_3$), δ 7.69 (d, 1H, *J* = 7.89 Hz), 7.54 (d, 1H, *J* = 12.6 Hz), 6.94 (m, 3H), 6.43 (s, 1H), 4.81 (bs, 1H), 4.02 (bs, 1H), 3.89 (s, 3H), 3.78 (bs, 4H), 3.74 (bs, 4H), 3.60 (m, 4H), 3.34 (m, 2H), 2.03 (s, 3H), 1.17 (bs, 2H); ESI-MS $(M + H)^+$ –HCl =511.4. **10** (mp 156–158 °C), IR 3290, 2925, 2817, 1745, 1666, 1598, 1515, 1251, 1228, 802 cm^{-1}, ^{1}HNMR ($CDCl_3$), δ 8.02 (d, 1H, *J* = 8.7 Hz), 7.70 (s, 1H), 7.42 (dd, 1H, *J* = 2.5 and 11.7 Hz), 7.05 (dd, 1H, *J* = 1.9 and 6.8 Hz), 6.93 (t, 1H, *J* = 9.0 Hz), 6.80 (dd, 1H, *J* = 2.4 and 6.2 Hz), 6.71 (d, 1H, *J* = 2.3 Hz), 4.90 (m, 1H), 4.41 (m, 1H), 4.01 (m, 2H), 3.87 (s, 3H), 3.73 (q, 1H), 3.09 (s, 4H), 2.70 (s, 4H), 2.63 (s, 3H), 2.52 (m, 2H), 1.17 (s, 2H); ESI-MS $(M + H)^+$ –HCl = 541.4. **11** (mp 160–162 °C), IR 3276, 2941, 1745, 1695, 1604, 1517, 1419, 1228, 1193, 1101 cm^{-1}, ^{1}HNMR ($CDCl_3$), δ 7.70 (s, 1H), 7.67 (d, 1H, *J* = 5.4 Hz), 7.42 (dd, 1H, *J* = 2.5 and 11.7 Hz), 7.08 (dd, 1H, *J* = 1.83 and 6.9 Hz), 6.93 (m, 3H), 4.96 (m, 1H), 4.52 (m, 1H), 4.28 (m, 1H), 4.01 (m, 2H), 3.89 (s, 3H), 3.78 (t, 1H), 3.23 (dd, 1H), 3.08 (s, 5H), 3.03 (m, 1H), 2.09 (m, 6H); ESI-MS $(M + H)^+$ –HCl = 527.3. **12** (mp 210 °C), IR 3419, 3355, 3280, 3190, 2829, 1743, 1620, 1566, 1521, 1417, 1328, 1228, 1151, 975, 783 cm^{-1}, ^{1}HNMR ($CDCl_3$), δ 7.44 (dd, 1H, *J* = 2.4 and 11.6 Hz), 7.07 (dd, 1H, *J* = 2.04 and 6.78 Hz), 6.92 (t, 1H, *J* = 9.0 Hz), 4.78 (m, 1H), 4.12 (s, 2H), 4.03, (s, 1H), 3.98 (m, 4H), 3.71 (s, 1H), 3.33 (m, 4H), 3.30 (s, 2H), 3.12 (m, 4H), 2.83 (s, 3H), 1.27 (m, 2H); ESI-MS $(M + H)^+$ –HCl = 464.1.

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