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Oxazolidinone: search for highly potent antibacterial ☆

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Abstract—A number of substituted piperazinyl oxazolidinone derivatives have been synthesized and their antibacterial activities were evaluated by MIC determination. A systematic SAR was carried out to get highly potent oxazolidinone derivatives.

1. Introduction

Oxazolidinone class of antibacterials has attracted considerable interest from various research institutions[1] including pharmaceutical industries[2] especially after the successful launch of linezolid by Upjohn and Pharmacia in 1999. Linezolid **1** (Fig. 1) has been of great interest due to growing resistance of bacteria to a number of antibacterial therapies.[3] Vancomycin and methicillin, which were once considered the ultimate line of therapy for Gram +ve infection, is no more sustainable due to increasing number of reports of VRS, VRE and MRSA organisms isolated from patients. Unfortunately, linezolid has poor efficacy; need multiple dosing and has serious side effects. Therefore, search for superior analogs of this class of antibacterials has been unawaited during the last decade without notable success.[4]

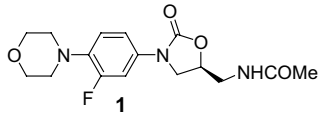

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Figure 1.

Keywords: Oxazolidinone; Antibacterial; Linezolid; Cinnamoyl groups.
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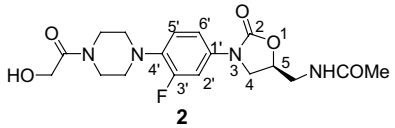


2

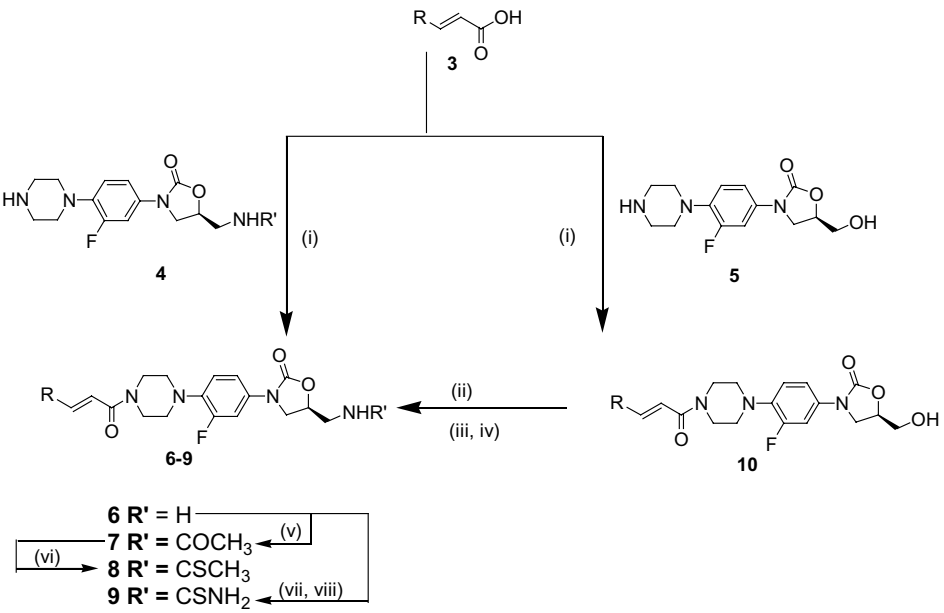
Figure 2.

In the present communication, we wish to report our efforts in search of a novel and superior antibacterial especially for Gram +ve organisms, which may be useful for treating vancomycin and methicillin resistant organisms. Eperezolid **2** (Fig. 2), which is not yet approved for treating antibacterial infection, has been the main structural feature for modification to get superior analogs by a number of research groups.[5] We report here synthesis of several substituted piperazine analogs **7**–**9** and their antibacterial activities (MIC) across several Gram +ve organisms.

2. Chemistry

A number of N-substituted piperazinyl derivatives **7**–**9** were prepared according to the pathways shown in (Scheme 1). 4′ Substituted piperazine derivative **4** or **5** can be prepared by literature method.[6]

The piperazine derivative **4** or **5** were coupled with cinnamic acid derivative **3** using EDC/HOBT in the presence of triethylamine at 27–28 °C (Scheme 1). The



Scheme 1. Reagents and conditions: (i) EDC–HCl, HOBt·H_2O, TEA, CH_2Cl_2, 27–28 °C, 0.5–1 h; (ii) $MeSO_2Cl$, TEA, CH_2Cl, 0.5 °C, 1 h; (iii) NaN_3, DMF, 70–80 °C, 2–3 h; (iv) $P(Ph)_3$, 1,4-dioxane, MeOH, NH_3 (aq), 27–28 °C, 30 min; (v) $(CH_3CO_2)_2O$, pyridine; (vi) Lawesson's reagent, THF, 65–70 °C, 1 h; (vii) CS_2 solution, ethyl chloroformate, TEA, 20–30 min; (viii) methanolic ammonia, 0–5 °C, 5–10 min.

piperazine derivative **4** gave **6**, whereas compound **5** gave oxazolidinone **10**, which was then converted into **6** by standard method (Scheme 1).

A large number of compounds were synthesized (Table 1) and screened for antibacterial activities in a panel of Gram +ve bacteria. Results of MIC assay carried out in triplicate is summarized in Table 2. Some of the selected compounds having MIC comparable to linezolid or eperezolid were further screened in an extended panel of bacteria having several strains of Gram +ve and Gram −ve organisms, some of which are resistant to methicillin and vancomycin (Table 3).

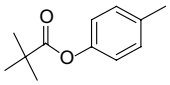
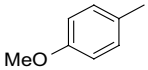
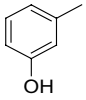
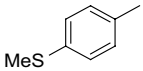
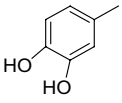
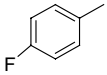
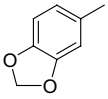
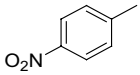
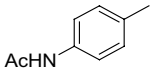
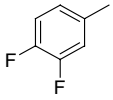
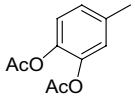
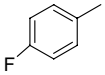
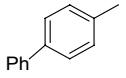
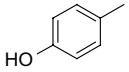
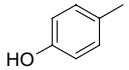
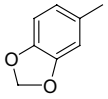
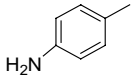
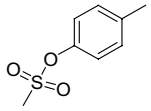
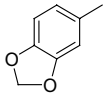
3. Results and discussion

Examination of Table 2 reveals that the parent compound **7a** containing the unsubstituted cinnamoyl group is nearly as active as linezolid in in vitro MIC assay and is superior to eperezolid in all the strains of bacteria. Substitution of phenyl ring of cinnamoyl group showed interesting structure–activity relationship. When 4-position of phenyl ring (in cinnamoyl moiety) is substituted with –OMe group **7b**, there is moderate decrease in the antibacterial activity. Further replacement of –OMe by –SMe (**7c**) led to further decrease in antibacterial activity. This suggests that electron donating group on cinnamoyl moiety is not preferred. Hence, we substituted 4th position of phenyl ring with electron withdrawing groups such as –F (**7d**), $-NO_2$ (**7e**), difluoro (**7f**) and diacetyl (**7g**). From the results, it is clear that even powerful electron withdrawing group is not preferred on phenyl ring of cinnamoyl moiety and none of the compounds showed good antibacterial activities. In fact, when we substituted 4th position by bulky phenyl group (**7h**), it led to the complete loss in antibacterial activities. Thus, we synthesized compounds having 4-OH (**7i**) and 4-NH_2 (**7j**) group on the phenyl group of cinnamoyl moiety. Both the compounds **7i** and **7j** showed much superior antibacterial activities, however, **7i** is found to be slightly superior to its amino counterpart.

Further, we modified 4-OH group into 4-OSO_2CH_3 (**7k**), 4-OCOC $(CH_3)_3$ (**7l**), 3-OH (**7m**), 3,4-dihydroxy (**7n**) and 1,2-methylenedioxy (**7o**). From the results reported in the Table 2, it is clear that any bulky substituent or modification of electronic properties of 4-OH group is not favourable (see **7k**, **7l**). However, replacement of 4-OH group by 3-OH group (**7m**) did not destroy its antibacterial activity but compounds having both 3,4-dihydroxy (**7n**) led to complete loss of antibacterial activity. In contrast, when both –OH group at 3 and 4 position are protected as 1,2-methylenedioxy group (**7o**), there is considerable recovery of antibacterial activity. Similar attempts to modify 4-NH_2 group was made by substituting $-NH_2$ by $-NHCOCH_3$ (**7p**), as expected the compound **7p** was found to be inferior to **7j** (4-NH_2).

Thus, the compounds **7a**, **7d**, **7i**, **7o**, were taken for further modification in order to get better antibacterial compounds. In these compounds acetamide group **7** ($R' = -COCH_3$) is replaced by thioacetamide group **8** ($R' = -CSCH_3$) to yield **8a**, **8d**, **8i**, **8o**, respectively. From the results shown in Table 2 it is clear that the compounds **8a**, **8d** and **8i** showed very potent antibacterial activities. Compound **7a** and **7o** were further modified to furnish **9a** and **9o** ($R' = -CSNH_2$), respectively. Both these analogs showed much superior antibacterial activities than their acetamide analogs (**7a** and **7o**).

Table 1. New oxazolidinones as antibacterial agents

Compd	R	R′	% Yield	Compd	R	R′	% Yield
7a		$COCH_3$	80	**7l**		$COCH_3$	85
7b		$COCH_3$	47	**7m**		$COCH_3$	70
7c		$COCH_3$	88	**7n**		$COCH_3$	25
7d		$COCH_3$	73	**7o**		$COCH_3$	77
7e		$COCH_3$	55	**7p**		$COCH_3$	27
7f		$COCH_3$	64	**8a**		$CSCH_3$	78
7g		$COCH_3$	81	**8d**		$CSCH_3$	31
7h		$COCH_3$	39	**8i**		$CSCH_3$	49
7i		$COCH_3$	52	**8o**		$CSCH_3$	79
7j		$COCH_3$	6.9	**9a**		$CSNH_2$	67
7k		$COCH_3$	47	**9o**		$CSNH_2$	45

Thus, we selected compounds **7a**, **7i**, **7m**, **7o**, **8a**, **8d**, **8i**, **8o**, **9a** and **9o** for further screening in a wider panel of Gram +ve bacteria, some of which are resistant to methicillin and are also particularly resistant to vancomycin and even linezolid and eperezolid. Table 3 summarizes the results of the MIC assay carried out with various strains of Gram +ve organisms.

It is noteworthy that compounds **7a**, **7i**, **7m** and **7o** all of which contain acetamide group ($R' = COCH_3$) showed nearly comparable antibacterial activity with that of linezolid or eperezolid.

However, compounds having thioacetamide group (**8a**, **8d**, **8i** and **8o**) showed superior antibacterial activities even in MRSA, VRS as well as intrinsically resistant Gram negative Klebsiella.

This is remarkable in view of the fact that linezolid resistant organisms have also started appearing in hospital isolates of Gram +ve organisms, although very very few cases have been reported.[8]

4. Conclusion

In summary, a series of *N*-phenyl piperazinyl derivatives of oxazolidinone in which the nitrogen atom at 4-position of piperazinyl ring is substituted by different cinnamoyl groups resulted in a few good antibacterial compounds against several Gram positive organisms. Some groups are well tolerated on the phenyl ring of cinnamoyl group; however, bulky substituents and

Table 2. MIC [minimum inhibitory concentration in μg/mL] values of new oxazolidinones in various Gram positive bacteria[a]

Compd	B.p.	B.c.	S.p.	S.e.	E.f. 1	Sa 1	Compd	B.p.	B.c.	S.p.	S.e.	E.f. 1	Sa 1
7a	1	1	2	0.5	2	4	**7m**	0.5	0.5	2	0.25	1	2
7b	2	2	4	1	4	4	**7n**	8	16	16	4	8	8
7c	2	2	16	1	2	16	**7o**	1	1	2	1	1	2
7d	4	4	8	2	4	16	**7p**	8	4	8	4	4	8
7e	2	1	1	4	4	4	**8a**	0.5	0.5	0.5	0.25	0.5	2
7f	16	4	4	>16	>16	>16	**8d**	0.5	0.5	2	0.5	0.5	1
7g	2	2	4	1	2	4	**8i**	0.25	0.25	0.5	⩽0.12	1	0.25
7h	>16	>16	>16	>16	>16	>16	**8o**	0.25	0.25	4	1	8	1
7i	1	0.5	2	0.25	1	2	**9a**	1	0.25	0.25	1	0.5	1
7j	1	1	2	0.5	1	1	**9o**	1	1	0.5	0.25	0.25	1
7k	4	1	2	8	4	8	Linezolid	1	2	0.5	2	2	4
7l	8	16	>16	4	8	>16	Eperezolid	2	2	4	1	4	ND

[a] MIC were determined by microbroth dilution technology[7] and the values reported in the table represent the highest MIC value obtained in triplicate.

Table 3. MIC [minimum inhibitory concentration in μg/mL] values of selected compounds in several Gram positive and Gram negative bacteria

Compd	B.p.	B.c.	S.p.	S.e.	E.f. 1	E.f. 2	Sa 1	Sa 2	Sa 3	Sa 4	K.p.
7a	1	1	2	0.5	2	1	4	4	2	4	>16
7i	1	0.5	2	0.25	1	2	2	2	1	2	>16
7m	0.5	0.5	2	0.25	1	1	2	4	4	1	>16
7o	1	1	2	1	1	2	2	2	4	4	>16
8a	0.5	0.5	0.5	0.25	0.5	0.5	2	2	1	1	>16
8d	0.5	0.5	2	0.5	0.5	2	1	1	4	4	>16
8i	0.25	0.25	0.5	⩽0.12	1	0.25	0.25	0.5	0.25	0.5	4
8o	0.25	0.25	4	1	8	0.25	1	1	0.5	1	2
9a	1	0.25	0.25	1	0.5	0.5	1	2	2	1	8
9o	1	1	0.5	0.25	0.25	0.5	1	1	2	2	>16
Linezolid	1	2	0.5	2	2	4	4	4	4	4	>16
Eperezolid	2	2	4	1	4	2	ND	4	4	4	>16

B.p. = *Bacillus pumilus* MTCC 1607, B.c. = *Bacillus cereus* MTCC 430, S.p. = *Streptococcus pyogenes* MTCC 442, S.e. = *Staphylococcus epidermidis* MTCC 155, E.f. 1 = *Enterococcus faecalis* MTCC 439, E.f. 2 = *Enterococcus faecalis* ATCC 14506, Sa 1 = *Staphylococcus aureus* MTCC 96, Sa 2 = *Staphylococcus aureus* ATCC 14154, Sa 3 = *Staphylococcus aureus* ATCC 25923, Sa 4 = *Staphylococcus aureus* ATCC 29213, K.p. = *Klebsiella pneumoniae* ATCC 10031, ND = not done.

electron withdrawing groups resulted in loss of activity. One of the most potent compounds **8i** is active against a broader panel of Gram positive bacterial pathogens. Our SAR study has also revealed that the antibacterial activity is greatly affected by the conversion of 5-acetylaminomethyl moiety to thioacetamide as well as 5-thiourea group.

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