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Influence of Ethylene-Oxy Spacer Group on the Activity of Linezolid: Synthesis of Potent Antibacterials Possessing a Thiocarbonyl Group☆

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Abstract—The influence of an ethylene-oxy spacer element between the heterocycle and the aromatic ring in linezolid is reported. The introduction of such spacer group generated compounds with inferior antibacterial activity. However, the conversion of the acetamide group present in the linezolid analogues to either thiocarbamate or thioacetamide functionality restored the activity. The synthesis of linezolid analogues possessing the ethylene-oxy spacer group along with SAR studies with different heterocycles and preparation of some thiocarbonyl compounds possessing potent antibacterial property are presented.

The emergence of bacterial resistance to the antibiotics poses a serious concern for medical professionals during the last decade.[1] In particular, multi-drug-resistant Gram-positive bacteria[2] including methicillin-resistant *Staphylococcus aureus* (MRSA)[3] and *Staphylococcus epidermidis* (MRSE) and vancomycin resistant enterococci (VRE) are of major concern.[4] Oxazolidinones are a new class of synthetic antibacterials with activity against Gram-positive bacteria and anaerobic bacteria.[5,6] They have been shown to selectively bind to the 50S ribosomal subunit and inhibit bacterial translation at the initiation phase of the protein synthesis.[7] Linezolid **1**, developed by Pharmacia and Upjohn, is the first compound commercialised world wide from the oxazolidinone class of antibacterials.[8] This class of compounds is particularly active against Gram-positive organisms such as MRSA, MRSE and VRE. The novel mechanism of action combined with the biological activity against resistant organisms aroused widespread attention and stimulated others to explore chemistry in the oxazolidinone class.[4] In an ongoing project on anti-infectives in our laboratory, we have explored the introduction of an ethylene-oxy spacer group between the heterocycle and the phenyl ring in linezolid **1** (Fig. 1). In this letter, we report our initial results on the influence of this spacer element, as illustrated in structure **2**, on the antibacterial activity of linezolid.[9]

The general method of introducing the spacer element involved the aromatic nucleophilic substitution of ethylene glycol with mono or difluoro nitrobenzenes. Thus, substitution of fluorine by ethylene glycol under basic conditions in 4-fluoronitrobenzene and 3,4-difluoronitrobenzene resulted in the displacement of the fluorine atom leading to the nitro compounds **3** and **4**, respectively (Scheme 1). The nitro alcohol **3** and the fluoro nitro-alcohol **4** were the starting materials for the linezolid analogues possessing no fluorine and fluorine respectively. The nitro compounds **3** and **4** afforded the benzylated compounds **5** under standard conditions. Having obtained the nitro compounds **5**, further steps for the synthesis of **8** were carried out along the lines of established protocol.[8] Thus, compound **5** upon reduction followed by protection afforded the Cbz-protected compound **6**. Deprotonation of compound **6** followed by treatment with (*R*)-glycidyl butyrate yielded the oxazolidinone alcohol **7**, which was converted into the corresponding azide by standard procedures. The treatment of the azide with thioacetic acid produced the target acetamides **8** and **9** that in turn underwent

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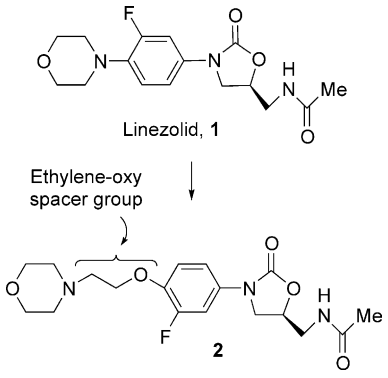
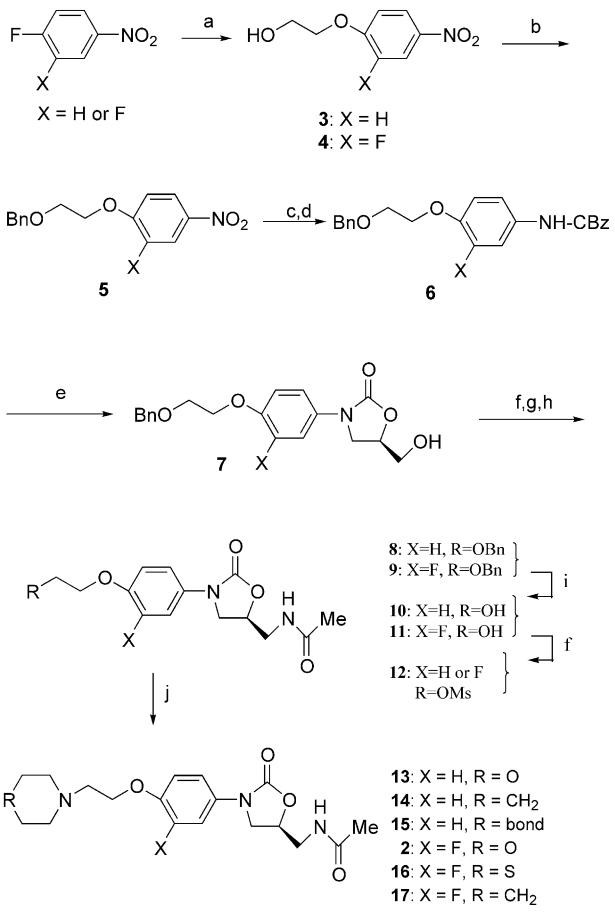


Figure 1.



Scheme 1. Reagents and conditions: (a) ethylene glycol, K_2CO_3, DMF, rt, 48 h; (b) NaH, BnBr, THF, rt, 12 h; (c) Fe, HCl, EtOH, 0 °C–rt, 2 h; (d) Cbz–Cl, aq Na_2CO_3, acetone, 0 °C, 2 h; (e) BuLi, (*R*)-glycidyl butyrate, THF, −78 °C to rt, 14 h; (f) MsCl, Et_3N, CH_2Cl_2, 0 °C, 4 h; (g) NaN_3, DMF, 80 °C, 1 h; (h) CH_3COSH, rt, 14 h; (i) 10% Pd/C, H_2, THF, 14 h; (j) heterocycle, Et_3N, DMF, 80 °C, 12 h.

hydrogenolysis to afford the hydroxy compounds **10** and **11**. The compounds **10** and **11** were converted to their corresponding mesylates **12** by standard methods to facilitate introducing heterocycles. The above mesylates underwent nucleophilic displacement with various heterocycles under basic conditions yielding the target compounds **13**–**17** and **2**.

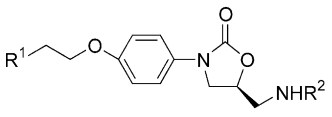
The thiocarbamates **23** and **24** and thioacetamides **25**–**27** were prepared following a route illustrated in Scheme 2. The nitro-alcohol **4** was converted to its mesylate **18**, which was treated with various heterocycles to afford the nitro-compounds **19**. Having obtained the nitro compounds possessing different heterocycles, the rest of the synthesis was carried out following a route discussed in Scheme 1 to afford the azides **21**. These azides were transformed to the corresponding amines **22** by standard procedure. The above amines were converted to the corresponding thiocarbamates **23** and **24** via the respective isothiocyanates using standard experimental procedures.[4] Treatment of the amines with ethyldithioacetate resulted in the thioacetamides **25**–**27** in good yields.

The analogues of linezolid possessing the spacer group were screened for in vitro activity against a panel of Gram-positive organisms and the results are summarized in Table 1. The compounds without a fluorine atom in the aromatic ring **13**–**15** exhibited no antibacterial activity. Consequently, analogues possessing a fluorine atom in the aromatic ring were evaluated. The closest variant of linezolid with ethylene-oxy spacer group **2** exhibited moderate activity having MIC values ranging 4–16 μg/mL. While the activity of its thiomorpholine analogue **16** was similar from MIC values, the piperidine analogue **17** exhibited nearly no activity. Thus, the effort to introduce the ethylene-oxy spacer group generated molecules having inferior activity when compared to linezolid. It is interesting that the benzyl compound **9** containing fluorine atom in the aromatic ring and the corresponding hydroxy compound **11** showed MIC values of 8 μg/mL against MRSA strain ATCC 33591.

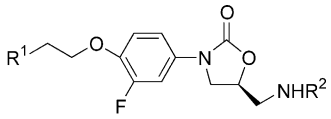
At this juncture, we turned our attention towards modifying the right hand side of the molecule in an effort to restore the activity of the above analogues. We, along with others, have recently established that the conversion of acetamide moiety of the oxazolidinone class of antibacterials into either thioacetamide or thiocarbamate results in significant improvement of activity.[4] Consequently when the above compounds were converted into their thiocarbamate or thioacetamide analogues, there was significant improvement in the in vitro activity. The linezolid analogue **23** having a thiocarbamate group exhibited a one- to three-fold better activity compared to the acetamide analogue **2**. Interestingly, the thiomorpholine analogue **24** showed even better in vitro results possessing excellent MIC values that are comparable to that of linezolid. Similarly, the thioacetamide analogues **25** and **27** showed activities equivalent to their thiocarbamate counterparts and compound **25** appeared to be slightly more potent with respect to the MRSA strain. Once again, the piperidine analogue **26** had poorer antibacterial spectrum compared to its closest variants **25** and **27**.

In conclusion, a study conducted towards understanding the influence of introducing ethylene-oxy spacer group on the activity of linezolid has been accomplished. While, the acetamide analogues resulted

Table 1. In vitro antibacterial activity (MIC, μg/mL)[a] of novel oxazolidinones[b]



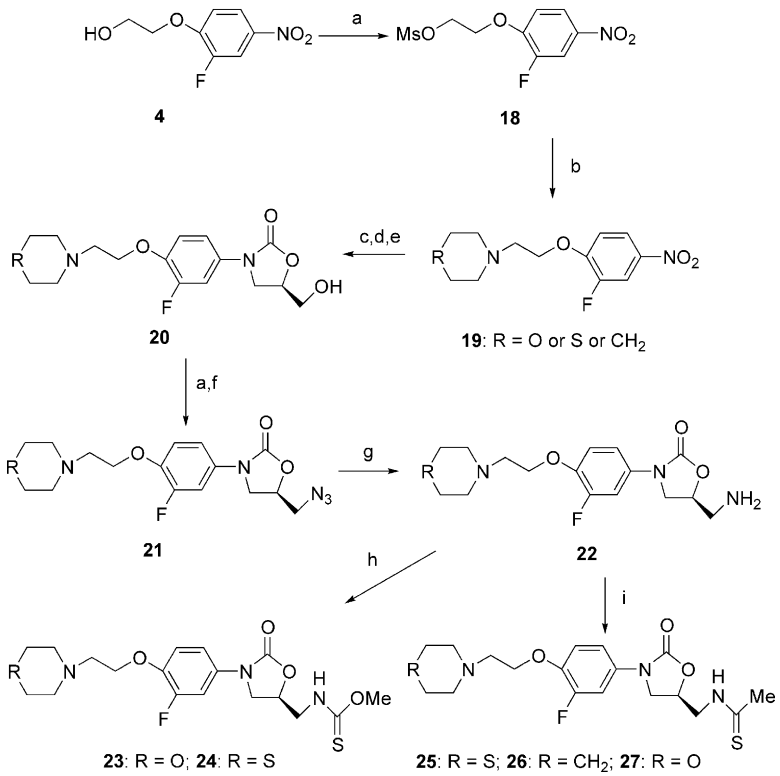
Entries 1-3



Entries 4-13

Entry	Compd	R^1	R^2	S.a 019	S.a 213	S.a 035	E.f 034	E.f 153	E.fm 154
1	**13**		$NHCOCH_3$	> 32	ND[c]	> 32	> 32	> 32	> 32
2	**14**		$NHCOCH_3$	> 32	ND	> 32	> 32	> 32	> 32
3	**15**		$NHCOCH_3$	32	ND	> 32	> 32	> 32	> 32
4	**9**	OCH_2Ph	$NHCOCH_3$	8	ND	16	32	32	32
5	**11**	OH	$NHCOCH_3$	8	ND	8	16	16	16
6	**2**		$NHCOCH_3$	4	16	16	16	16	4
7	**16**		$NHCOCH_3$	4	16	16	16	16	4
8	**17**		$NHCOCH_3$	32	64	64	64	64	64
9	**23**		$NHCSOCH_3$	2	4	4	2	4	2
10	**24**		$NHCSOCH_3$	1	4	4	1	2	2
11	**25**		$NHCSCH_3$	0.5	2	2	1	2	2
12	**26**		$NHCSCH_3$	2	8	8	8	4	4
13	**27**		$NHCSCH_3$	1	2	2	2	2	2
14	Linezolid			1	2	2	2	2	2
15	Vancomycin			2	1	1	2	> 32	> 32

[a]S.a 019 = *Staphylococcus aureus* ATCC 33591 (methicillin-resistant); S.a 213 = *S. aureus* ATCC 49951; S.a 035 = *S. aureus* ATCC 29213; E.f 034 = *Enterococcus faecalis* ATCC 29212 (vancomycin-susceptible); E.f 153 = *E. faecalis* NCTC 12201 (vancomycin-resistant) and E.fm 154 = *Enterococcus faecium* ATCC 12202 (vancomycin-resistant).
[b]The MIC values were obtained as described previously.[4]
[c]ND, not determined.



Scheme 2. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 4 h; (b) heterocycle, Et_3N, DMF, 80 °C, 12 h; (c) 10% Pd/C, H_2, THF, 14 h; (d) Cbz–Cl, aq Na_2CO_3, acetone, 0 °C, 2 h; (e) BuLi, (*R*)-glycidyl butyrate, THF, −78 °C to rt, 14 h; (f) NaN_3, DMF, 80 °C, 1 h; (g) PPh_3, H_2O, THF, rt, 36 h; (h) $CSCl_2$, aq $NaHCO_3$, CH_2Cl_2, 0 °C, 0.5 h; then MeOH, reflux, 12 h; (i) ethyldithioacetate, THF, Et_3N, rt, 12 h.

in compounds possessing inferior antibacterial activity, their corresponding thiocarbamate and thioacetamide analogues produced certain potent compounds such as **24**, **25** and **27**. Further work to vary the length of the spacer group in **2** along with changing the oxygen atom in the spacer element to other heteroatoms is currently underway in our laboratory.

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