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Synthesis and antibacterial activity of dihydro-1,2-oxazine and 2-pyrazoline oxazolidinones: novel analogs of linezolid

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Abstract—The synthesis and antibacterial activity of oxazolidinones containing dihydro-1,2-oxazine and 2-pyrazoline ring systems are described. Linezolid analogs utilizing dihydro-1,2-oxazines as morpholine mimics were prepared utilizing a nitrosoamine/diene 4+2 cycloaddition strategy. Pyrazolidine, hexahydro-pyridazine, and 2-pyrazoline analogs more closely related to eperezolid were also prepared. The most active of these new oxazolidinones were the dihydro-1,2-oxazine **6** and the 2-pyrazoline **20** both of which had potency similar to linezolid against a panel of Gram-positive bacteria.

The oxazolidinone antibacterial linezolid (**1**) discovered and developed by Upjohn/Pharmacia (now marketed by Pfizer as Zyvox™) has been described as the first new class of antibacterial agents to be marketed in the last 30 years. The related eperezolid (**2**) (Fig. 1) was not advanced to Phase 3 studies presumably due to its shorter human $T_{1/2}$.[1]

The urgency of discovering new classes of antibacterial agents was highlighted when the first clinical case of vancomycin-resistant *Staphylococcus aureus* (VRSA) infection was reported in 2002.[2] Clinically, one of linezolid's most valuable characteristics is that it is one of the few orally active agents available to treat MRSA[1] and VRSA[2] infections. Another distinguishing feature of this class of antibacterial agents is its synthetic origin.

Efforts to enhance the spectrum and potency of this class of antibiotics have been ongoing throughout the pharmaceutical industry.[3] It has been argued that the most urgent improvement needed for the oxazolidinone class is an enhanced safety profile.[4] Hematological toxicity (possibly due to myelo-suppression) is a side effect especially during prolonged treatment (>14 days). Based on our analysis of the limited published oxazolidinone toxicity data available at the time, we concluded that the most prudent approach would be to maintain the amine functionality at the 4-position of the phenyl ring.

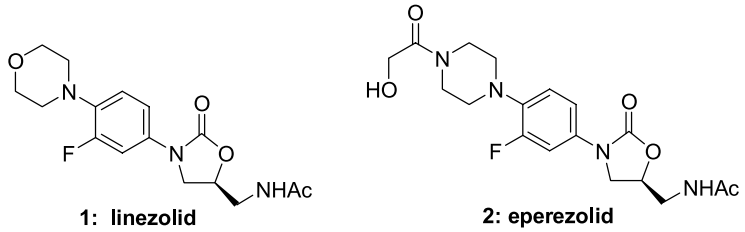

Figure 1. Linezolid and eperezolid.

Keywords: Antibacterial; Oxazolidinones; Linezolid.
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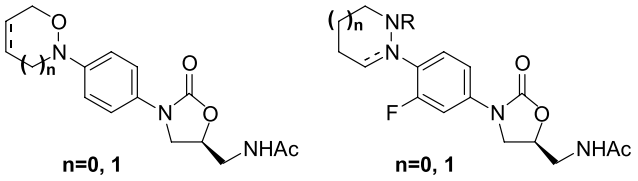
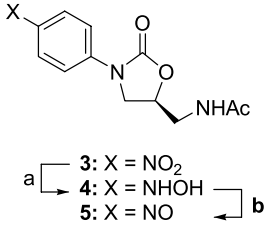


Figure 2. Pseudo-isomers of linezolid and eperezolid.

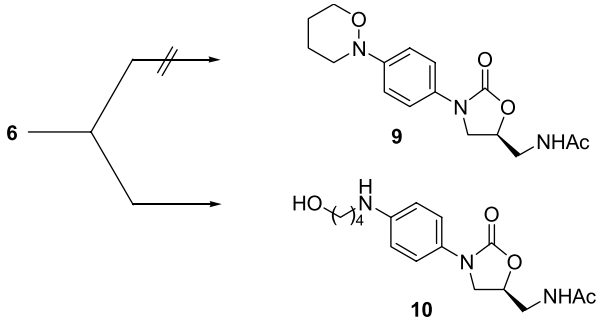


Scheme 1. Synthesis of hydroxylamine and nitroso derivative. Reagents and conditions: (a) Zn, NH_4Cl, 60 °C, 10 min; (b) PCC, rt, 10 min, THF/CH_3CN (5:2).

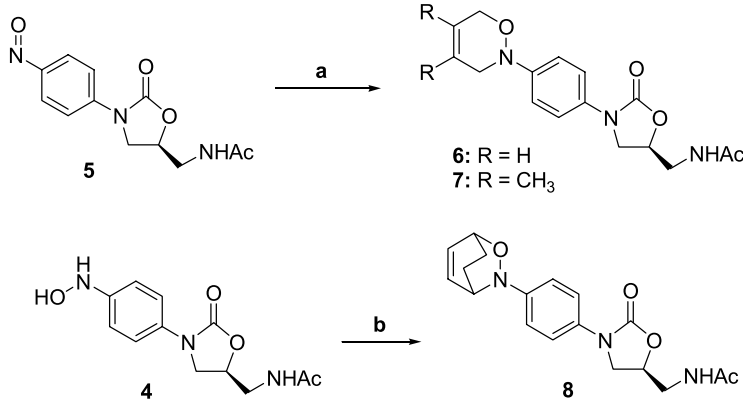
Further, we felt that modulating (either reducing or increasing) the electron-donating ability of the nitrogen in the 4-position of the phenyl ring could have a beneficial effect on the safety profile.[5] It should be emphasized that these presumed structure/toxicity relationships remain unproven to date. The SAR of amines in the 4-position was studied in detail by Upjohn/Pharmacia, but 4-amino groups imparting useful properties continue to emerge.[6–8] In this paper, we will detail our efforts to replace the linezolid morpholine by the pseudo-isomeric dihydro-1,2-oxazine and isoxazolidine ring systems. In addition, we will describe the replacement of the eperezolid piperazine by pyrazolidine, hexahydropyridazine, and 2-pyrazoline rings (Fig. 2).

These morpholine and piperazine replacements were chosen based on their modest structural resemblance, their modified electronic properties,[9] and the fact that they remained unexplored by previous researchers. In general, these cyclic amines containing an N–O or N–N linkage are less basic and less electron donating than the corresponding morpholine, piperazine, and pyrrolidine ring systems.[10] Inspired by a synthetic strategy used to functionalize the 7-position of quinolone antibacterials,[11] the known nitro oxazolidinone **3**[12] was reduced with Zn/NH_4Cl to give the hydroxylamine **4** in 94% yield. Oxidation of **4** with PCC provided the nitroso derivative **5** in 56% isolated yield (Scheme 1). The [4+2] cycloaddition of **5** with butadiene and 2,3-dimethylbuta-1,3-diene gave rise to dihydro-1,2-oxazines **6** and **7** (89% and 57% yield, respectively) (Scheme 2). In some cases, it was possible to carry out this two step sequence in one pot by generating the nitroso derivative **5** in situ in the presence of the appropriate diene. For instance, this in situ oxidation procedure carried out in the presence of cyclohexadiene provided the dihydro-1,2-oxazine **8** (31%) (Scheme 2). Attempted catalytic hydrogenation of the olefinic double bond in **6** did not result in the formation of **9**, instead, the N–O bond was severed and the ring-opened product **10** was formed (Scheme 3). This result was somewhat surprising based on the successful catalytic hydrogenation of similar dihydro-1,2-oxazines.[13] Attempted diimide reduction of **8** resulted in no reaction.

The fluoro analog of **5** was sought as a key intermediate to prepare a fluorinated series of dihydro-1,2-oxazines. Nitration of 3-fluoro-oxazolidinone **11**[14] provided a 1:1 ratio of the 6-nitro oxazolidinone **12** and the desired 4-nitro regioisomer **13** (Scheme 4). Separation by preparative HPLC gave a 20% yield of each pure



Scheme 3. Reduction of dihydro-1,2-oxazine **6** (H_2, 5% Pd/C, EtOAc, Parr shaker, 2 h).



Scheme 2. Nitroso amine/diene 4+2 cycloadditions. Reagents and conditions: (a) butadiene or 2,3-dimethylbuta-1,3-diene, 0 °C to rt, 3 h, CH_2Cl_2; (b) 4.3 equiv Bu_4NIO_4, cyclohexadiene, DMF, rt, 3 h.