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Synthesis and SAR of novel conformationally-restricted oxazolidinones possessing Gram-positive and fastidious Gram-negative antibacterial activity. Part 1: Substituted pyrazoles

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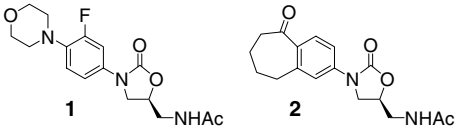
Abstract—A novel series of conformationally-restricted oxazolidinones was synthesized which possess a fused pyrazole ring substituted with various alkyl, aryl and heteroaryl substituents. A number of analogs exhibited potent activity against both Gram-positive and fastidious Gram-negative organisms.

The continual emergence of multi-drug resistant bacteria creates a pressing need for novel antimicrobial agents. Oxazolidinones, as exemplified by linezolid (Zyvox™) **1**, are a novel, completely synthetic class of antibacterial agents that possess potent activity against Gram-positive bacteria.[1] Efforts at our laboratories to identify an oxazolidinone antibacterial agent with an increased spectrum of activity as compared to linezolid led to ketone **2** which displayed activity against Gram-positive (*Staphylococcus aureus* MIC = 1.0 μg/mL, *Streptococcus pneumoniae* MIC = 0.5 μg/mL) but did not display activity against fastidious Gram-negative microorganisms.[2,3]



Genin et al. have reported a series of oxazolidinones possessing 5-membered heterocyclic ring systems (e.g., **3**, Fig. 1), some of which exhibited Gram-negative activity.[4] MIC values for compound **3** against fastidious Gram-negative organisms were in the range of 8–32 μg/mL. Building on these two results, we utilized the principles of 'conformation–restriction' towards the discovery of a novel series of oxazolidinones. Conformation–restriction would provide an entropically

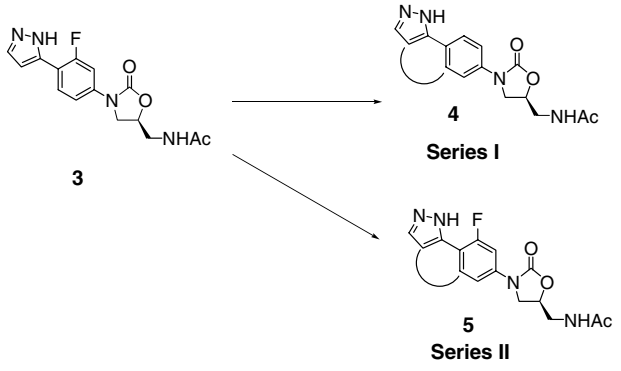


Figure 1.

Keywords: Oxazolidinones; Conformationally-restricted; Gram-positive activity; Fastidious Gram-negative activity.
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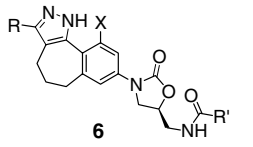
advantageous situation due to the lesser number of degrees of freedom prior to binding with the target ribosome. To design this series of compounds we started with oxazolidinone **3**.[4] Though this compound did not possess fastidious Gram-negative activity, we postulated that conformation–restriction would improve the potencies of the target molecules. Connecting the aromatic ring, either by displacing or retaining the fluorine atom on the phenyl ring, with a pyrazole ring restricts the rotation along the C–C bond. This could lead to two types of structures: one containing a phenyl ring without a fluorine atom (Series I) and the other series with a phenyl ring which possesses a fluorine atom (Series II, Fig. 1). The resulting novel structures would provide entropically favorable states or possibly even mimic 'bioactive conformations'. In order to explore the SAR we synthesized a series of fused pyrazole oxazolidinone analogs which possessed substitution on the 5-position of the pyrazole ring by alkyl, aryl and heteroaryl substituents. In this communication, we describe the synthesis and antibacterial activity of novel conformationally-restricted oxazolidinones of the general structure **6** possessing potent antibacterial activity against Gram-positive as well as Gram-negative and quinolone-resistant microorganisms.[3]



6

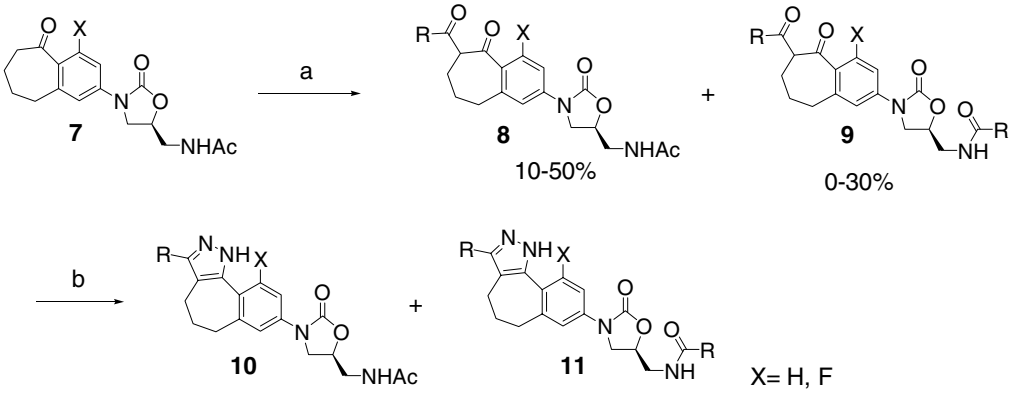
R = H, alkyl, aryl, or heteroaryl
R' = alkyl, aryl, or heteroaryl
X = H, F

The substituted pyrazoles, **10** and **11**, were synthesized from the known ketones **7**[2] as shown in Scheme 1. Treatment of ketone **7** with the appropriate acid chloride or ester in the presence of lithium hexamethyldisilazane, lithium diisopropylamide or lithium *t*-butoxide gave the di-keto compounds **8** in 10–50% yield. In some cases the transamidation products **9** were observed and isolated by flash chromatography. Treatment of **8** or **9** with hydrazine hydrate in ethanol at room temperature gave the desired substituted pyrazoles **10** and **11** (22–75% yield). The unsubstituted pyrazole analogs **10a** and **10w** (R = H) were prepared by treating the appropriate ketone with dimethyl formamide dimethyl acetal in refluxing 1-propanol overnight. The resulting compounds were then subjected to hydrazine hydrate in ethanol at room temperature overnight to yield the desired compounds (38% and 65%, respectively, over two steps).

Alternatively, pyrazoles of the general structure **15** in which R does not equal R′ were obtained as shown in Scheme 2. Ketone **12** was treated with the appropriate acid chloride or ester in the presence of lithium hexamethyldisilazane, lithium diisopropylamide or lithium *t*-butoxide to afford the di-keto compounds **8**. Reaction of **13** with hydrazine hydrate in ethanol at room temperature gave the desired pyrazole intermediates **14**. Boc removal with 4 N HCl in 1,4-dioxane followed by treatment with an acid chloride resulted in compounds **15**.

The pyrazole oxazolidinone analogs were tested against a panel of Gram-positive and fastidious Gram-negative bacteria. Minimum inhibitory concentration (MIC, in μg/mL) values were determined by micro broth methodology.[5] The *Escherichia coli* in vitro transcription and translation (TnT) assay was performed in 96-well micro titer plates using a luciferase reporter system.[6] The activities of the pyrazole analogs are summarized in Table 1. MIC data for linezolid **1** is provided for comparison.

The majority of analogs in this series displayed improved activity against both Gram-positive bacteria as well as fastidious Gram-negative bacteria compared to linezolid **1** (Table 1). The unsubstituted pyrazole **10a** exhibited the lowest IC_{50}, (0.45 μM) in the *E. coli* in vitro transcription and translation (TnT) assay of any compound tested in this series of analogs. The in vitro activity of **10a** displayed a fourfold improvement against Gram-positive pathogens *S. aureus* and *S. pneumoniae* and a two and fourfold improvement against the fastidious Gram-negative bacteria *H. influenzae* and *M. catarrhalis* (MICs = 4 and 2 μg/mL, respectively) as compared to linezolid. Substitution on the 5-position of the pyrazole ring with alkyl substituents (**10b**–**10f**) generally led to analogs with one to twofold decrease in activity against Gram-positive pathogens and similar or somewhat less activity against the fastidious Gram-negative bacteria. Only the ethyl-substituted



Scheme 1. Reagents and condition: (a) R(C═O)Cl or RCO_2Et, LiHMDs or LDA or *t*-BuOLi; (b) hydrazine hydrate, EtOH, rt.[4]