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Bioorganic & Medicinal Chemistry Letters 17 (2007) 4699–4702
Bioorganic & Medicinal Chemistry Letters

Synthesis and SAR of novel conformationally restricted oxazolidinones possessing Gram-positive and fastidious Gram-negative antibacterial activity. Part 2: Amino substitutions on heterocyclic D-ring system

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Received 17 April 2007; revised 23 May 2007; accepted 25 May 2007
Available online 31 May 2007

Abstract—A novel series of conformationally restricted oxazolidinones was synthesized, in which the heterocyclic D ring was substituted with various amino groups. Several analogs exhibited potent activity against both Gram-positive and fastidious Gram-negative organisms. Certain amino-substituted analogs also exhibited improved aqueous solubility compared to the corresponding un-substituted heterocyclic D-ring analogs.

Linezolid (Zyvox™) **1** is the first oxazolidinone to be approved for clinical use against serious Gram-positive bacterial infections (Fig. 1).[1] We have been interested in developing oxazolidinone antibacterial agents with a broader spectrum of antibacterial activity. We recently disclosed a novel series of conformationally restricted oxazolidinones, exemplified by the lead compound **2**.[2,3] Compound **2** has activity against Gram-positive (*Staphylococcus aureus* MIC = 0.5 μg/mL, *Streptococcus pneumoniae* MIC = 0.25 μg/mL) and the fastidious Gram-negative respiratory tract pathogens (*Haemophilus influenzae* and *Moraxella cattarhalis* MICs = 2 μg/mL).[2] However, the poor aqueous solubility of compound **2** (14 μg/mL) was considered a barrier to good oral absorption. In order to improve the aqueous solubility of this series, the 3-position of the pyrazole ring was substituted with hydrophilic functionality to give amino-substituted analogs **3**. The synthesis and SAR of these amino-substituted analogs is presented here.[3]

The amino-substituted pyrazoles **3** were synthesized from the known ketone **4**[4] in two steps as shown in

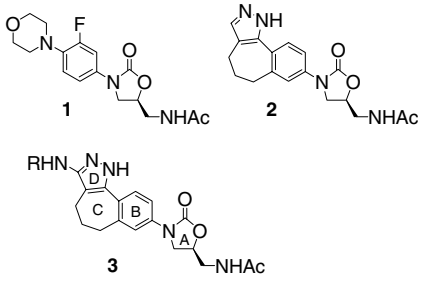

Figure 1.

Scheme 1. Bromination of ketone **4** with pyridinium tribromide and glacial acetic acid gave the bromoketone **5** in quantitative yield. Treatment of bromoketone **5** with the appropriately substituted thiosemicarbazide gave the desired amino-substituted pyrazoles **3**, albeit in low to modest yields (5–50%).[5]

Thiosemicarbazides that were not commercially available were prepared according to literature methods[6] as shown in Scheme 2. The appropriately substituted amines **6a**–**h** were treated with triethylamine and carbon disulfide to give the dithiocarbamates **7a**–**h**. The dithiocarbamates **7a**–**h** were then heated with hydrazine monohydrate to give the thiosemicarbazides **8a**–**h**. In the case

Keywords: Oxazolidinones; Antibacterials; Pyrazoles.
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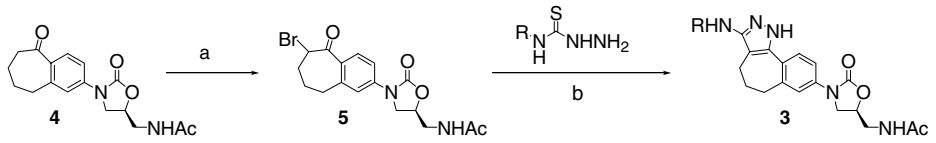
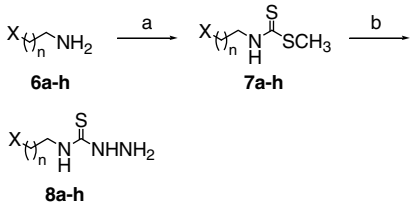
doi:10.1016/j.bmcl.2007.05.085



Scheme 1. Reagents and conditions: (a) pyridinium tribromide, glacial HOAc, CH_2Cl_2, rt, 100%; (b) abs EtOH, 88 °C, 5–50%.



a, n = 1; X = CH_3; **b**, n = 1; X = OCH_3; **c**, n = 2; X = OCH_3; **d**, n = 1; X = $NHCO_2t$-Bu; **e**, n = 2; X = $NHCO_2t$-Bu; **f**, n = 2; X = $N(CH_2CH_3)_2$; **g**, n = 1; X = $OSi(CH_3)_2t$-Bu; **h**, n = 2; X = $OSi(CH_3)_2t$-Bu

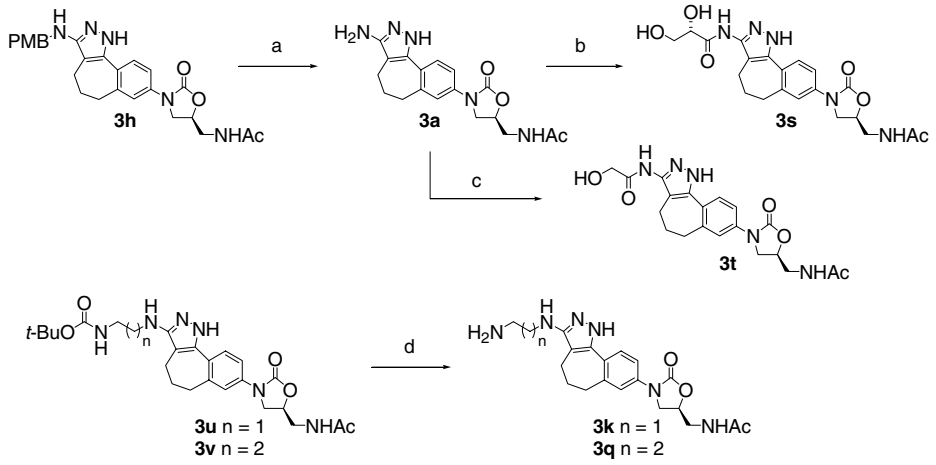
Scheme 2. Reagents and conditions: (a) i—CS_2, NEt_3, CH_3OH, Et_2O, 0 °C–rt; ii—CH_3I, 0 °C–rt; (b) hydrazine monohydrate, 2-methoxymethanol, 80 °C.

of 4-(2-*tert*-butyldimethylsilanyloxyethyl)-3-thiosemicarbazide **8g** and 4-(3-*tert*-butyldimethylsilanyloxypropyl)-3-thiosemicarbazide **8h**, reaction with bromoketone **5** resulted in in situ cleavage of the silyl ethers and isolation of the hydroxy analogs **3i** and **3o**, respectively.

The 3-aminopyrazole analog **3a** (R = H) and the *N*-acyl pyrazoles **3s**–**t** were prepared from the *p*-methoxybenzyl (PMB) amine **3h** as shown in Scheme 3. Treatment of the *p*-methoxybenzylamine **3h** with triethylsilane and trifluoroacetic acid (TFA) gave the free amine **3a** in 87% yield. Coupling of amine **3a** with (*S*)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid, followed by treatment with 1 M hydrochloric acid, gave amide **3s**. Similarly, amine **3a** was coupled with benzyloxyacetic acid, followed by debenzylation with palladium on carbon to give amide **3t**. The amino analogs **3k** and **3q** were prepared in 43–54% yields by removal of the Boc-protecting groups in **3u** and **3v** with acetyl chloride in methanol.

The amino-substituted oxazolidinone analogs were tested against a panel of Gram-positive and fastidious Gram-negative bacteria.[7] Minimum inhibitory concentration (MIC, in μg/mL) values were determined by microbroth methodology.[7] The *Escherichia coli* in vitro transcription and translation (EC TnT) assay was performed in 96-well microtiter plates using a luciferase reporter system.[8] The activities of the amino-substituted analogs are summarized in Table 1. MIC data for linezolid **1** and the lead pyrazole compound **2** are provided for comparison.

The in vitro activity of analogs with small alkylamino substituents at the 3-position of the pyrazole ring (**3a**–**e**) was similar to that of the lead pyrazole compound **2** (Table 1), except that they were somewhat less active against the Gram-positive pathogens *S. aureus* and *Enterococcus faecalis*. The aminopyrazoles **3a**–**c** retained activity against the fastidious Gram-negative bacteria *H. influenzae* and *Moraxella catarrhalis* (MICs = 2–4 μg/mL). Analogs with larger alkylamino substituents (**3d**–**e**) showed a loss of fastidious Gram-negative activity, but maintained Gram-positive antibacterial activity similar to or better than linezolid **1**. In general, analogs with 'R' groups containing polar functionalities showed reduced antibacterial activity. The substituted ethylaminopyrazole analogs **3i**–**m** and the substituted propylaminopyrazole analogs **3o**–**r** exhibited decreased antibacterial activity against both Gram-positive and fastidious Gram-negative organ-



Scheme 3. Reagents and conditions: (a) Et_3SiH, TFA, CH_2Cl_2, 87%; (b) i—*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride, pyridine, (*S*)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid, 25%; ii—1 M HCl, THF, 85%; (c) i—*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride, pyridine, benzyloxyacetic acid, 47%; ii—Pd/C, MeOH, 73%; (d) CH_3COCl, CH_3OH, 0 °C–rt, 43–54%.