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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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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.
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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

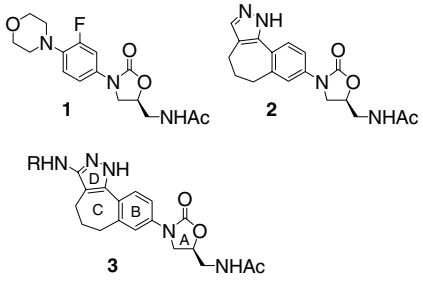

Figure 1.

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

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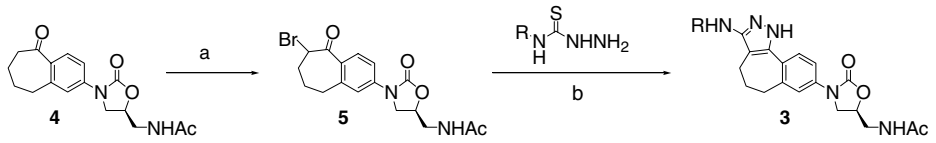
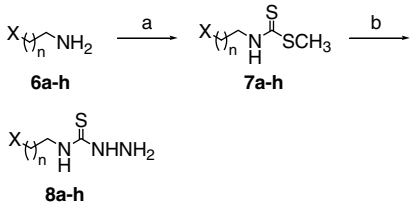


Scheme 1. Reagents and conditions: (a) pyridinium tribromide, glacial HOAc, CH_2Cl_2, rt, 100%; (b) abs EtOH, 88 °C, 5–50%.



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

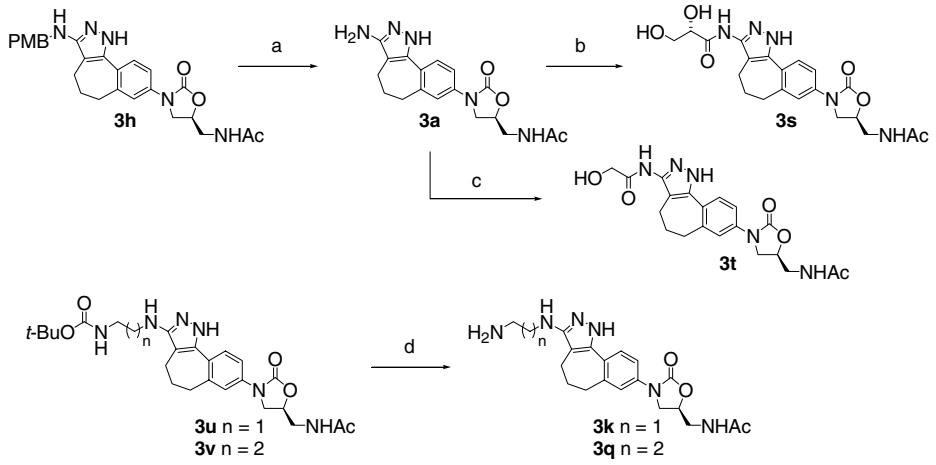
Scheme 2. Reagents and conditions: (a) i—CS_2, NEt_3, CH_3OH, Et_2O, 0 °C–rt; ii—CH_3I, 0 °C–rt; (b) hydrazine monohydrate, 2-methoxymethanol, 80 °C.

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%.

Table 1. *Escherichia coli* in vitro transcription and translation (EC TnT) assay results (IC_{50}, μM) and minimum inhibitory concentrations (MICs, μg/mL) for compounds **1**, **2**, **3a**–**t**

Compound	R	EC TnT IC_{50} (μM)	S.a.	S.p.	E.f.	H.i.	M.c.
1 linezolid	n/a	0.95	2	1	4	8	8
2	n/a	0.45	0.50	0.25	0.25	2	2
3a	–H	1.2	4	0.5	2	4	2
3b	$–CH_3$	1	2	0.5	1	4	2
3c	$–CH_2CH_3$	1.3	1	0.25	1	4	4
3d	$–CH(CH_3)_2$	2.2	4	0.5	2	8	8
3e	$–CH_2CH_2CH_3$	2.5	2	0.25	1	4	8
3f	–Ph	—	1	0.5	0.5	4	2
3g	$–CH_2Ph$	2	2	1	1	8	4
3h	$–CH_2Ph$(4-OMe)	2.2	1	0.5	1	8	4
3i	$–(CH_2)_2OH$	1.2	8	2	8	2	16
3j	$–(CH_2)_2OMe$	2.6	2	1	2	1	8
3k	$–(CH_2)_2NH_2$	0.8	32	4	16	16	4
3l	$–(CH_2)_2$(*N*-Morpholine)	1.9	16	2	8	8	16
3m	$–(CH_2)_2$(2-Pyridyl)	1.7	8	0.5	1	8	8
3n	$–(CH_2)_2Ph$(4-OH)	2.1	2	0.5	1	4	2
3o	$–(CH_2)_3OH$	1.8	8	4	8	16	32
3p	$–(CH_2)_3OMe$	2.9	4	1	4	16	16
3q	$–(CH_2)_3NH_2$	0.45	32	4	8	>64	32
3r	$–(CH_2)_3NEt_2$	13	64	4	32	32	32
3s	$–C(=O)CH(OH)CH_2OH$	0.78	16	2	16	32	32
3t	$–C(=O)CH_2OH$	1.3	16	4	4	16	16

Strains: S.a., *Staphylococcus aureus* UC-76 SA-1; S.p., *Streptococcus pneumoniae* SV1 SP-3; E.f., *Enterococcus faecalis* MGH-2 EF1-1; H.i., *Haemophilus influenzae* HI-3542; M.c., *Moraxella catarrhalis* BC-3531.

isms, when compared to the alkylaminopyrazoles **3a**–**e** and the lead pyrazole compound **2**. The *N*-acyl pyrazoles **3s**–**t** retained activity only against *S. pneumoniae*. Analogs with 'R' groups that contained aryl functionality (**3g**–**h**) maintained activity against the Gram-positive pathogens *S. aureus*, *S. pneumoniae*, and *E. faecalis*, but showed decreased activity against the fastidious Gram-negative bacteria *H. influenzae* and *M. catarrhalis*. However, the aniline derivative **3f** and the tyramine derivative **3n** maintained Gram-negative activity comparable to **2**.

The apparent aqueous solubility[9] was determined for selected oxazolidinone analogs and the results are shown in Table 2. Although the lead pyrazole analog **2** has poor aqueous solubility (14 μg/mL), introduction of amino substituents at the 3-position of the pyrazole ring resulted in significant improvements in the solubility of these compounds. The alkylamino analog **3b**, and the ethylamino and propylamino analogs **3k** and **3q**, had excellent solubility (>70 μg/mL) compared to the un-substituted pyrazole **2**. The *N*-acyl pyrazole **3s** also showed improved solubility (46 μg/mL) over the lead compound **2**.

In summary, a novel series of conformationally restricted oxazolidinones were synthesized in which the heterocyclic ring was substituted with various hydrophilic amino groups as an effort to improve the aqueous solubility of these compounds. Several analogs showed improved aqueous solubility compared to the lead pyrazole compound **2**, while retaining Gram-positive and fastidious Gram-negative antibacterial activity. In particular, analog **3b** had excellent solubility (>70 μg/mL) and showed antibacterial activity similar to the lead pyrazole compound **2**. Further research results with oxazolidinones with an expanded spectrum of activity will be reported in due course.

Table 2. Aqueous solubilities (μg/mL) of selected analogs

Compound	R	Solubility (μg/mL)
2	n/a	14
3b	$–CH_3$	>70
3k	$–(CH_2)_2NH_2$	>70
3i	$–(CH_2)_2OH$	53
3q	$–(CH_2)_3NH_2$	>70
3s	$–C(=O)CH(OH)CH_2OH$	46

References and notes

1. For recent reviews of linezolid, see: (a) Wilcox, M. H. *Expert Opin. Pharmacother.* **2005**, *6*, 2315; (b) Stevens, D. L.; Dotter, B.; Madaras-Kelly, K. *Expert Rev. Anti Infect. Ther.* **2004**, *2*, 51; (c) Nilius, A. M. *Curr. Opin. Investig. Drugs* **2003**, *4*, 149; (d) Moellering, R. C. *Ann. Inter. Med.* **2003**, *138*, 135.
2. Boyer, F. E.; Vara Prasad, J. V. N.; Choy, A. L.; Chupak, L.; Dermyer, M. R.; Ding, Q.; Huband, M. D.; Jiao, W.; Kaneko, T.; Khlebnikov, V.; Kim, J.-Y.; Lall, M. S.; Maiti, S. N.; Romero, K.; Wu, X. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4694.
3. For experimental details and ^1H NMR data, see: Chupak, L. S.; Kaneko, T.; Vara Prasad, J. V. N.; Kim, J.-Y.; Choy, A. L.; Hagen, S. E.; Boyer, F. E. U.S. Patent 0288273 A1, 2005.
4. Vara Prasad, J. V. N.; Boyer, F. E.; Chupak, L.; Dermyer, M.; Ding, Q.; Gavardinas, K.; Hagen, S. E.; Huband, M. D.; Jiao, W.; Kaneko, T.; Maiti, S. N.; Melnick, M.; Romero, K.; Patterson, M.; Wu, X. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5392.
5. For examples of the preparation of pyrazole derivatives from thiosemicarbazides and α-halo ketones, see: (a) Rowley, M.; Collins, I.; Broughton, H. B.; Davey, W. B.; Baker, R.;

Emms, F.; Marwood, R.; Patel, S.; Patel, S.; Ragan, I.; Freedman, S. B.; Ball, R.; Leeson, P. D. *J. Med. Chem.* **1997**, *40*, 2374; (b) Rádl, S. *Collect. Czech. Chem. Commun.* **1992**, *57*, 656; (c) Gulbis, Y. V.; Utinan, M. F.; Karlivan, G. A.; Valter, R. É. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1992**, *28*, 357; (d) Papageorgiou, C.; Albert, R.; Floersheim, P.; Lemaire, M.; Bitch, F.; Weber, H.-P.; Andersen, E.; Hungerford, V.; Schreier, M. H. *J. Med. Chem.* **1988**, *41*, 3530; (e) Kaji, K.; Nagashima, H.; Ohhata, Y.; Tabashi, K.; Oda, H. *J. Heterocycl. Chem.* **1985**, *22*, 161.

6. Ashton, W. T.; Cantone, C. L.; Meurer, L. C.; Tolman, R. L.; Greenlee, W. J.; Patchett, A. A.; Lynch, R. J.; Schorn, T. W.; Strouse, J. F.; Siegl, P. K. S. *J. Med. Chem.* **1992**, *35*, 2103.
7. Clinical and Laboratory Standards Institute (formerly, National Committee for Clinical Laboratory Standards). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria*; Approved Standard-Sixth Edition; NCCLS Document M11-A6; Vol. 24.
8. (a) Murray, R. W.; Melchior, E. P.; Hagadorn, J. C.; Marotti, K. R. *Antimicrob. Agents Chemother.* **2001**, *45*, 1900; (b) Zubay, G. *Annu. Rev. Genet.* **1973**, *7*, 267.
9. Apparent aqueous solubility was determined by laser nephelometry at pH 6.5 (potassium phosphate buffer).