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Synthesis and structure–activity studies of antibacterial oxazolidinones containing dihydrothiopyran or dihydrothiazine C-rings

Adam R. Renslo,[a,*] Gary W. Luehr,[a] Stuart Lam,[a] Neil E. Westlund,[b] Marcela Gómez,[a] Corrine J. Hackbarth,[a] Dinesh V. Patel[a] and Mikhail F. Gordeev[a]

[a]*Pfizer Global Research and Development, 34790 Ardentech Ct. Fremont, CA 94555, USA*
[b]*Pfizer Global Research and Development, 2800 Plymouth Rd. Ann Arbor, MI 48105, USA*

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Abstract—A new series of antimicrobial oxazolidinones bearing unsaturated heterocyclic C-rings is described. Dihydrothiopyran derivatives were prepared from the saturated tetrahydrothiopyran sulfoxides via a Pummerer-rearrangement/elimination sequence. Two new synthetic approaches to the dihydrothiazine ring system were explored, the first involving a novel trifluoroacetylative-detrifluoroacetylative Pummerer-type reaction sequence and the second involving direct dehydrogenation of tetrahydrothiopyran *S*,*S*-dioxide intermediates. Final analogs such as **4** and **13** represent oxidized congeners of recent pre-clinical and clinical oxazolidinones.
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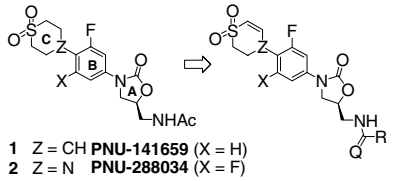
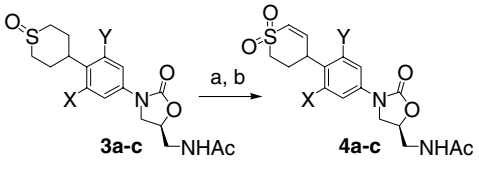
The oxazolidinones, exemplified by linezolid, comprise a promising new class of antibacterial protein synthesis inhibitors with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE).[1] The clinical and commercial success of linezolid has inspired the search for second-generation oxazolidinones with improved antibacterial potency and/or spectrum. Oxazolidinone analogs **1** and **2** exemplify this new generation of oxazolidinones and have been the subject of pre-clinical and clinical studies.[2] These new oxazolidinones substitute sulfur-containing heterocycles for the morpholine ring of linezolid and, in the case of **2**, introduce an additional fluorine atom in the B-ring.



Structure–activity studies of these new C-ring types included the examination of oxidized congeners (i.e., analogs bearing dihydrothiopyran or dihydrothiazine ring systems). We considered that these unsaturated C-ring structures might confer improved activity against fastidious Gram-negative bacteria as is often observed for fully unsaturated (i.e., aromatic and heteroaromatic) C-ring oxazolidinone analogs.[3] Here, we describe the synthesis and antibacterial activity of oxidized congeners of **1** and **2**, including a systematic exploration of B-ring and C-5 SAR. We also report new synthetic methods to access the dihydrothiazine ring system.

We prepared dihydrothiopyran and dihydrothiazine ring systems from the saturated precursors using Pummerer-type reaction sequence (Schemes 1 and 2).[4] The synthesis of dihydrothiopyran analogs **4a**–**c** began from



Scheme 1. Reagents and conditions: (a) $(CF_3CO)_2O$, *N*-methylmorpholine, CH_2Cl_2, rt, 20 h; (b) AcOOH, THF, rt (60–80% overall).

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* Corresponding author. Tel.: +1 415 514 9698; fax: +1 415 514 4507; e-mail: adam.renslo@ucsf.edu

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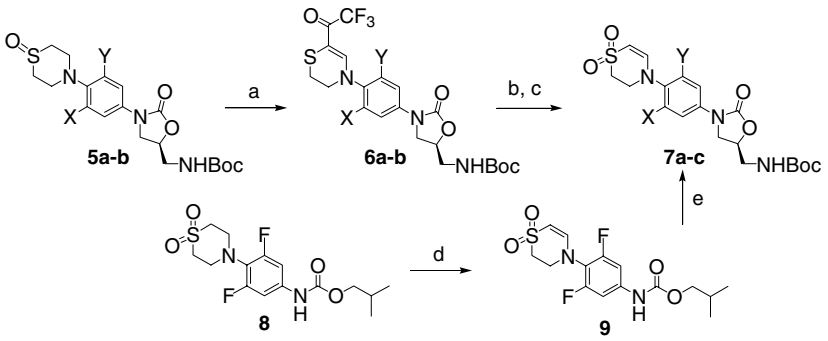


Scheme 2. Reagents and conditions: (a) $(CF_3CO)_2O$, *N*-methylmorpholine, CH_2Cl_2, rt; (b) mCPBA, CH_2Cl_2; (c) K_2CO_3, MeOH, CH_3CN, reflux (30–45% for three steps); (d) DDQ, dioxane, reflux, 22 h (35%); (e) 2.5 equiv Li*O*t-Bu, 1.3 equiv (*S*)-$ClCH_2CH(OH)CH_2NHBoc$, DMF (71%).

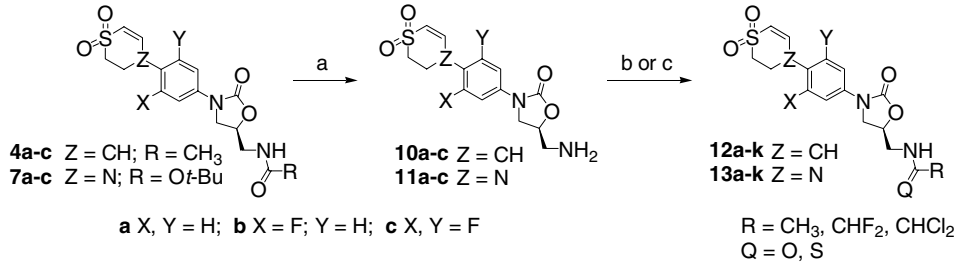
the sulfoxide analogs **3a**–**c**, which were prepared as described elsewhere.[5] Reaction of **3a**–**c** with trifluoroacetic anhydride in the presence of *N*-methylmorpholine produced the dihydrothiopyran ring system in a single step. This conversion presumably proceeds via initial Pummerer rearrangement followed by elimination of trifluoroacetic acid from the α-trifluoroacetoxy sulfide intermediate.[6] Oxidation with peracetic acid in THF then provided sulfone analogs **4a**–**c**. When thiomorpholine sulfoxide analogs **5a**–**b**[5] were subjected to similar reaction conditions, the unexpected trifluoroacetyl-substituted compounds **6a**–**b** were obtained (Scheme 2). In this case, the initially formed dihydrothiazine intermediate reacts with excess trifluoroacetic anhydride in the reaction mixture, thus generating **6a**–**b**. The trifluoroacetyl group in **6a**–**b** could be removed under surprisingly mild conditions (K_2CO_3 in refluxing MeOH–MeCN). A final oxidation step then provided the desired dihydrothiazine *S*,*S*-dioxide intermediates **7a**–**b**. For the bis-fluoro B-ring series (i.e., **7c**) an alternative protocol was employed. Thiomorpholine intermediate **8**[5] was oxidized with DDQ in refluxing dioxane to afford the dihydrothiazine **9** directly in modest yield along with recovered **8**. This protocol was only effective with bis-fluorinated intermediates such as **8**. The desired bis-fluoro oxazolidinone intermediate **7c** was prepared from **9** using established procedures.[7]

The synthesis of analogs of various C-5 side-chain type was accomplished as shown in Scheme 3, starting from compounds **4a**–**c** or **7a**–**c**. The C-5 acetamide in **4a**–**c** was cleaved via acid hydrolysis and the resulting amines **10a**–**c** acylated with anhydride or ester reagents. This two-step protocol provided dihydrothiopyran analogs **12a**–**k** bearing dichloroacetamide, difluoroacetamide, or difluorothioacetamide[8] functionality at C-5.

The synthesis of dihydrothiazine analogs **13a**–**k** proceeded similarly, starting from Boc-protected aminomethyl oxazolidinones **7a**–**c**. Removal of the Boc group in **7a**–**c** was accomplished with TMSOTf in 2,6-lutidine,[9] after we discovered that the dihydrothiazine ring in **7a**–**c** was sensitive to typical acidic Boc cleavage conditions. The resulting amines **11a**–**c** were then converted to dihydrothiazine analogs **13a**–**k** as described above for **12a**–**k** (Scheme 3).

The new 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 using standard broth microdilution methods.[10] The activities of dihydrothiopyran analogs are summarized in Table 1 and those for the dihydrothiazine analogs are presented in Table 2. MIC data for the progenitor analogs **1** and **2** are provided for comparison.

The in vitro activity of dihydrothiopyran analogs was similar to that of the parent tetrahydrothiopyran analog **1**. The acetamides **4a**–**c** had similar Gram-positive activity as **1** but were generally less active against the Gram-negative pathogen *Haemophilus influenzae*. Surprisingly, the degree of B-ring fluorination had little impact on overall potency, although a mono-fluoro B-ring does appear optimal for activity against *H. influenzae* and *Moraxella catarrhalis*. Among the C-5 side chains examined, the dichloroacetamide variant (e.g., **12a**, **12e**, and **12i**) consistently produced the best Gram-negative activity,



Scheme 3. Reagents and conditions: (a) for **4a**–**c**: HCl, MeOH, 75 °C, 20 h; for **7a**–**c**: TMS-OTf, 2,6-lutidine, CH_2Cl_2, rt, 1 h, then MeOH, 30 min; (b) $(RC{=}O)_2O$, Py, CH_2Cl_2 (80% overall); (c) $CHF_2C(O)OEt$ or $Ph_2CHCH_2CH_2OC(S)CHF_2$, Et_3N, MeOH (40–80% overall).

Table 1. Minimum inhibitory concentrations (MICs, μg/mL) for dihydrothiopyran analogs **4a**–**c** and **12a**–**k** against Gram-positive and fastidious Gram-negative bacteria[a]

Compound	X	Y	R	Q	S. a. MIC	S. p. MIC	E. f. MIC	H. i. MIC	M. c. MIC
—			Linezolid		4	1	4	16	8
1			PNU-141659		2–4	0.5	2	4–8	2–4
4a	H	H	CH_3	O	4–8	1–2	4	8–16	8
12a	H	H	$CHCl_2$	O	2–4	0.5	2	4	4
12b	H	H	$CHCF_2$	O	4–8	1	4	8–16	4–8
12c	H	H	$CHCF_2$	S	2–4	0.5–1	2	8–16	4
4b	H	F	CH_3	O	4	1	2	8	2
12e	H	F	$CHCl_2$	O	2–4	0.5	2	4	2–4
12f	H	F	$CHCF_2$	O	2–4	1	2	4–8	4–8
12g	H	F	$CHCF_2$	S	2	0.5	1	8–16	2–4
4c	F	F	CH_3	O	4	1	2	8–16	8
12i	F	F	$CHCl_2$	O	2	0.5–1	2	8	4
12j	F	F	$CHCF_2$	O	2	1	2	8–16	8
12k	F	F	$CHCF_2$	S	1–2	0.5	2	16	4

[a] Strains: S. a. *Staphylococcus aureus* UC12673, UC9213, ATCC29213, and UC9271; S. p. *Streptococcus pneumoniae* ATCC6305 and 31573; E. f. *Enterococcus faecium* UC12712, vancomycin-resistant; H. i. *Haemophilus influenzae* 30063 and ATCC31517; M. c. *Moraxella catarrhalis* 30607 and 30603.

Table 2. Minimum inhibitory concentrations (MICs, μg/mL) for dihydrothiazine analogs **13a**–**k** against Gram-positive and fastidious Gram-negative bacteria[a]

Compound	X	Y	R	Q	S. a. MIC	S. p. MIC	E. f. MIC	H. i. MIC	M. c. MIC
—			Linezolid		4	1	4	16	8
2			PNU-288034		2	1	2	4–8	4
13a	H	H	$CHCl_2$	O	4	0.5–1	2	2–4	2–4
13b	H	H	$CHCF_2$	O	4–8	1	2	8–16	4–8
13c	H	H	$CHCF_2$	S	2	0.5	1	4–8	4–8
13d	H	F	CH_3	O	4	0.5	2	4	2–4
13e	H	F	$CHCl_2$	O	2–4	0.5	1–2	2–4	2–4
13f	H	F	$CHCF_2$	O	4	0.5–1	2	4	4
13g	H	F	$CHCF_2$	S	1–2	0.5	1	4	4–8
13h	F	F	CH_3	O	2–4	0.5–1	1–2	8	4–8
13i	F	F	$CHCl_2$	O	4	0.5–1	1	4–8	4
13j	F	F	$CHCF_2$	O	4	0.5–1	1	4–8	4
13k	F	F	$CHCF_2$	S	1–2	0.25	0.25	4–8	2–4

[a] Strains: see Table 1.

while retaining good activity against the rest of the panel. The novel C-5 difluorothioacetamide analogs **12c**, **12g**, and **12k** exhibited excellent activity against the Gram-positive strains, although *H. influenzae* activity suffered somewhat.

Dihydrothiazine analogs **13a**–**k** displayed antibacterial activity comparable or slightly better than the thiomorpholine progenitor **2** (Table 2). In comparison to dihydrothiopyrans **12a**–**k**, the dihydrothiazine analogs **13a**–**k** were somewhat more potent in general, and in particular against *H. influenzae* strains. The mono-fluoro B-ring type was optimal with respect to both activity and spectrum. As in the dihydrothiopyran series, the dichloroacetamide side chain provided the best Gram-negative activity (**13a**, **13e**, and **13i**), while the difluorothioacetamide C-5 moiety conferred excellent Gram-positive activity. For example, the difluorothioacetamide analog **13k** was 4- to 8-fold more potent than the saturated thiomorpholine analog **2** against *Streptococcus pneumoniae* and *Enterococcus faecium* strains. In total, five dihydrothiazine analogs displayed improved Gram-negative activity as compared to the thiomorpholine oxazolidinone PNU-288034 (**2**).

In summary, novel oxazolidinones featuring dihydrothiopyran and dihydrothiazine heterocyclic C-rings were prepared and evaluated for antimicrobial activity. En route to the dihydrothiazine derivatives, two new synthetic approaches to this unusual heterocyclic ring system were explored. These novel unsaturated C-ring analogs exhibit in vitro antibacterial activity similar and in some cases superior to that of fully saturated progenitors **1** and **2**, and of linezolid. More notable improvements in potency and spectrum can be realized through the introduction of various halogenated amide and thioamide C-5 side-chain moieties.

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