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

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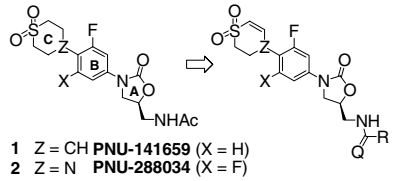
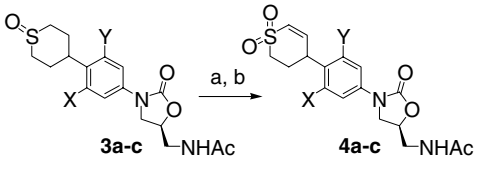
Abstract—A new series of antimicrobial oxazolidinones bearing unsaturated heterocyclic C-rings is described. Dihydrothiopyran derivatives were prepared from the saturated tetrahydrothiopyran sulfoxides via a Pummerer-rearrangement/elimination sequence. Two new synthetic approaches to the dihydrothiazine 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.

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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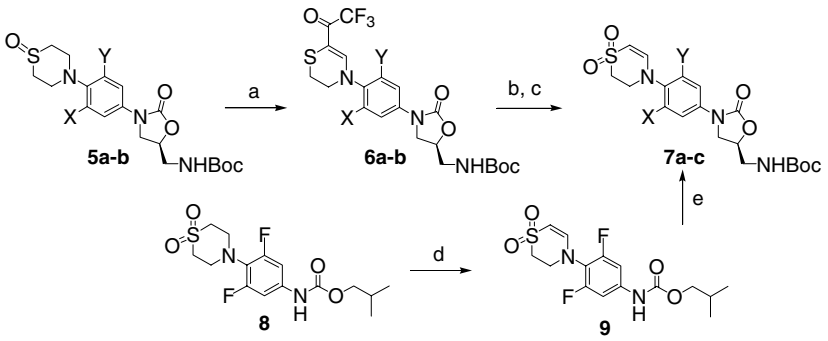


Scheme 2. Reagents and conditions: (a) $(CF_3CO)_2O$, *N*-methylmorpholine, CH_2Cl_2, rt; (b) mCPBA, CH_2Cl_2; (c) K_2CO_3, MeOH, CH_3CN, reflux (30–45% for three steps); (d) DDQ, dioxane, reflux, 22 h (35%); (e) 2.5 equiv Li*O*t-Bu, 1.3 equiv (*S*)-$ClCH_2CH(OH)CH_2NHBoc$, DMF (71%).

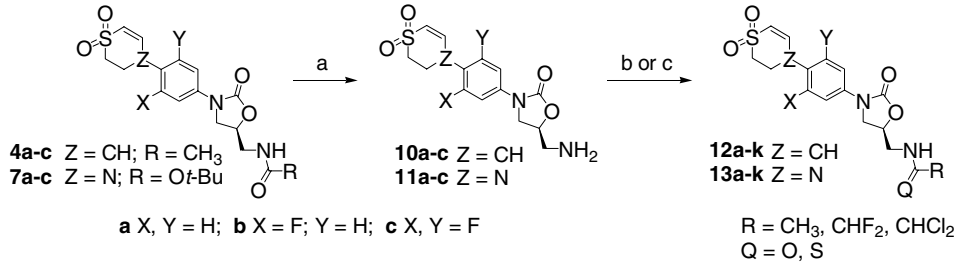
the sulfoxide analogs **3a**–**c**, which were prepared as described elsewhere.[5] Reaction of **3a**–**c** with trifluoroacetic anhydride in the presence of *N*-methylmorpholine produced the dihydrothiopyran ring system in a single step. This conversion presumably proceeds via initial Pummerer rearrangement 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).