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Antibacterial oxazolidinone analogues having a *N*-hydroxyacetyl-substituted seven-membered [1,2,5]triazepane or [1,2,5]oxadiazepane C-ring unit

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ABSTRACT

We synthesized a series of oxazolidinone analogues bearing a *N*-hydroxyacetyl-substituted [1,2,5]triazepane or [1,2,5]oxadiazepane C-ring unit as homologues of an earlier drug candidate, eperezolid. Several of these compounds exhibited potent *in vitro* antibacterial activities towards not only Gram-positive, but also Gram-negative and linezolid-resistant pathogens. Compounds **21a** and **21b**, bearing a thiocarbamate side chain, showed high *in vivo* activity against methicillin-resistant *Staphylococcus aureus* SR3637, together with a promising safety profile in terms of weak inhibition of monoamine oxidase and cytochrome P450 isozymes.

1. Introduction

Linezolid (**1**) is a new, completely synthetic class of antibiotic belonging to the oxazolidinone family, and is used for the treatment of serious infections caused by Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VRE) [1,2]. Though linezolid was the first member of the oxazolidinone family to be approved by the US Food and Drug Administration (FDA), eperezolid (**2**) [3] was also a potent drug candidate, developed in parallel with **1** (Fig. 1). Indeed, **2** exhibited more potent *in vitro* antibacterial activity and a better *in vivo* therapeutic effect than **1**, but concerns about its safety profile and pharmacokinetics in humans led to the selection of **1** as the preferred candidate for clinical application [4]. The oxazolidinone antibacterials **1** and **2** contain a six-membered saturated heterocycle (morpholine or piperazine, respectively) as the C-ring unit. Morpholine or piperazine moieties have been incorporated in a variety of recently reported pharmacologically active compounds [5–40], and their favourable balance of lipophilicity and hydrophilicity has led to their utilization as partial structural units for improvement of bioavailability or water-solubility of various lead compounds in medicinal-chemical research [41]. However, we were interested in developing a novel scaffold with favourable chemical and pharmaceutical properties for drug development. This led us to consider the seven-membered heterocycles [1,2,5]triazepane and [1,2,5]oxadiazepane as possible substitutes for the six-membered heterocycles morpholine in **1** and piperazine in **2**. Little work has been done on the synthesis of derivatives of these seven-membered heterocycles [42], and their potential as pharmacophores remains unexplored. Herein we report the synthesis and evaluation of a series of oxazolidinones in which the piperazine ring of **2** is replaced with [1,2,5]triazepane or [1,2,5]oxadiazepane [43].

2. Results and discussion

2.1. Chemistry

First of all, we planned to synthesize the title oxazolidinone analogues, in which the C-ring unit was changed to [1,2,5]triazepane or [1,2,5]oxadiazepane bearing a hydroxyacetyl functional group. The remaining structure was configured as follows, based

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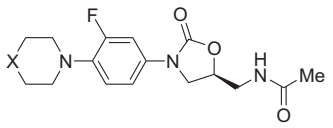
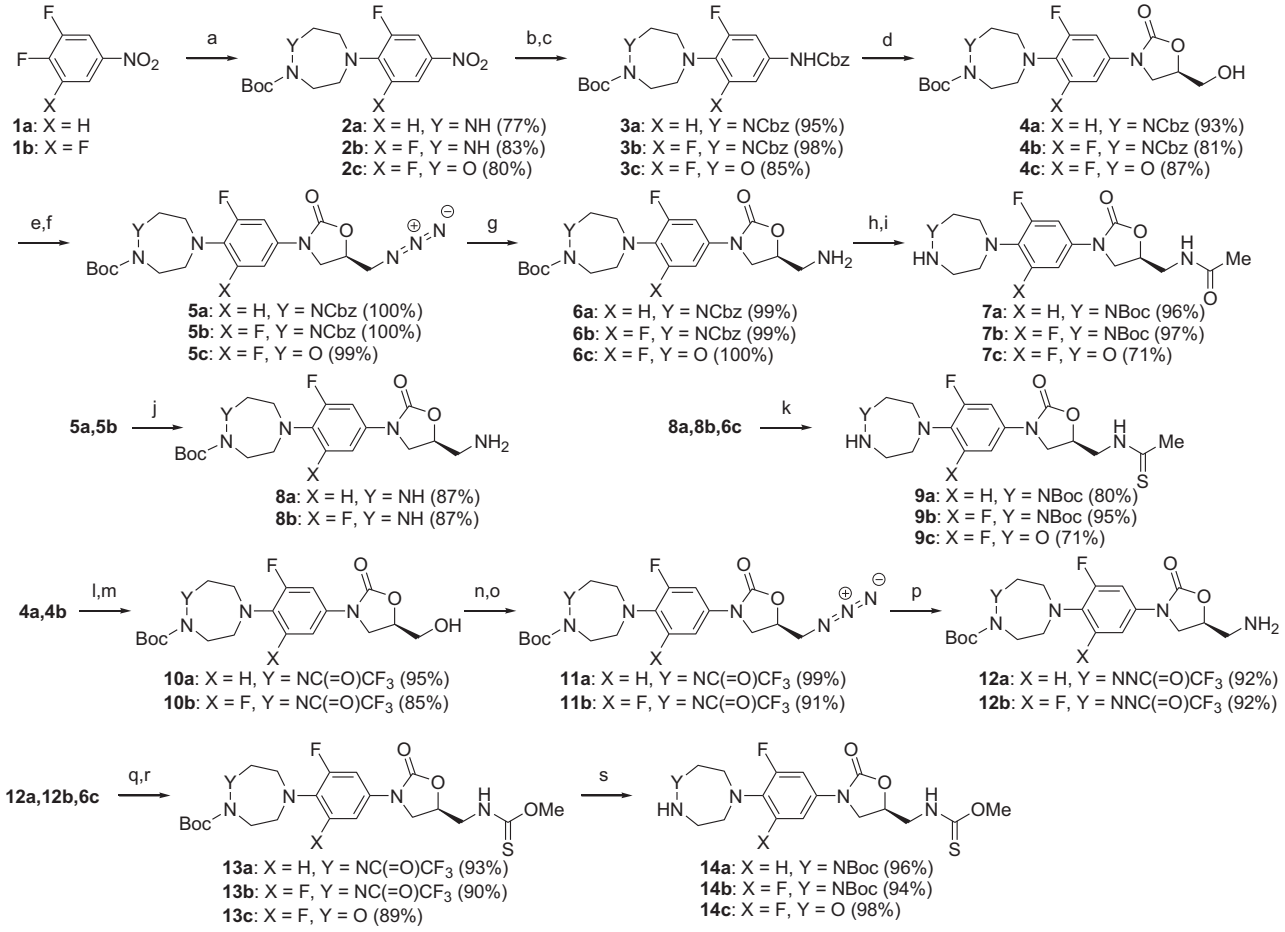


Fig. 1. Representative oxazolidinone antibacterial agents.

upon abundant related research. Two kinds of aromatic structures, 3-fluorophenyl or 3,5-difluorophenyl were selected as the B-ring aromatic unit [44]. As the side chain moiety at the C-5 position on the A-ring, we employed conventional acetamide [45], thioacetamide [46], thiocarbamate [47], [1,2,3]triazole [48], or isoxazolylaminomethyl [49]. The synthesis of our oxazolidinone intermediates is outlined in Schemes 1 and 2. Cyclization reaction to the seven-membered carbocycle was performed at the first stage of the synthetic process. Commercially available 3,4-difluoronitrobenzene (**1a**) or 3,4,5-trifluoronitrobenzene (**1b**) was used as a starting material for all our oxazolidinone analogues. Compound **1a** or **1b** was treated with [1,2,5]triazepane-1-carboxylic acid *tert*-butyl ester [43] or [1,2,5]oxadiazepane-2-car boxylic acid *tert*-butyl ester [43] in the presence of diisopropylethylamine to afford seven-membered heterocycles **2a**–**c**, respectively. Reduction of the nitro group in **2** to an amino group by catalytic hydrogenation, followed by protection of the amino group with benzyloxycarbonyl (Cbz) gave compounds **3a**–**c**. The carbamates **3a**–**c** were then subjected to cyclization to obtain oxazolidinones **4a**–**c**, respectively. The hydroxyl groups in **4a**–**c** were converted to azide using a standard method, and the azide was further transformed to amine, affording **6a**–**c**. The acetamidation of [1,2,5]triazepanes **6a** and **6b**, followed by deprotection of the Cbz group, afforded the oxazolidinone precursors **7a** and **7b** bearing the acetamide side chain unit. Acetamidation of [1,2,5]oxadiazepane **6c**, followed by deprotection of *tert*-butoxycarbonyl (Boc) group, gave oxazolidinone precursor **7c**. Catalytic hydrogenation of **5a** and **5b** afforded amines **8a** and **8b**, which were treated with ethyl dithioacetate in the presence of triethylamine to afford oxazolidinone precursors **9a** and **9b** bearing a thioamide side chain unit. For the synthesis of the oxazolidinone precursor bearing thiocarbamate, we changed the protective Cbz group to a trifluoroacetyl



[a] Reagents: (a) [1,2,5]triazepane-1-carboxylic acid *t*-butylester (for **2a** and **2b**) or [1,2,5]oxadiazepane-2-carboxylic acid *t*-butylester (for **2c**), *i*-Pr_2NEt; (b) 10%Pd/C, H_2; (c) CbzCl, Na_2CO_3; (d) *n*-BuLi, (*R*)-glycidylbutyrate; (e) MsCl, pyridine; (f) NaN_3; (g) Ph_3P, H_2O; (h) Ac_2O, pyridine; (i) 10%Pd/C, H_2 (for **7a** and **7b**) or CF_3CO_2H (for **7c**); (j) 10%Pd/C, H_2; (k) ethyl dithioacetate, Et_3N and CF_3CO_2H (for **9c**); (l) 10%Pd/C, H_2; (m) trichloroacetic acid anhydride, Et_3N, then NH_4OH; (n) MsCl, pyridine; (o) NaN_3; (p) Ph_3P, H_2O; (q) CS_2, Et_3N, $ClCO_2Et$; (r) MeONa; (s) LiOH (for **14a** and **14b**) or CF_3CO_2H (for **14c**).

Scheme 1.