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Research paper

Synthesis and biological evaluation of novel 5-(hydroxamic acid) methyl oxazolidinone derivatives

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ABSTRACT

Research activities on the oxazolidinone antibacterial class of compounds continue to focus on developing newer derivatives with improved potency, broad-spectrum activity and safety profiles superior to linezolid. Among the safety concerns with the oxazolidinone antibacterial agents is inhibition of monoamine oxidases (MAO) resulting from their structural similarity with toloxatone, a known MAO inhibitor. Diverse substitution patterns at the C-5 position of the oxazolidinone ring have been shown to significantly affect both antibacterial activity and MAO inhibition to varying degrees. Also, the antibacterial activity of compounds containing iron-chelating functionalities, such as the hydroxamic acids, 8-hydroxyquinolines and catechols have been correlated to their ability to alter iron intake and/or metabolism. Hence a series of novel 5-(hydroxamic acid)methyl oxazolidinone derivatives were synthesized and evaluated for their antibacterial and MAO-A and -B inhibitory activities. The compounds were devoid of significant antibacterial activity but most demonstrated moderate MAO-A and -B inhibitory activities. Computer modeling studies revealed that the lack of potent antibacterial activity was due to significant steric interaction between the hydroxamic acid N-OH oxygen atom and one of the G2540 5′-phosphate oxygen atoms at the bacterial ribosomal binding site. Therefore, the replacement of the 5-acetamidomethyl group of linezolid with the 5-(*N*-hydroxyacetamido)methyl group present in the hydroxamic acid oxazolidinone derivatives was concluded to be detrimental to antibacterial activity. Furthermore, the 5-(hydroxamic acid)methyl oxazolidinone derivatives were also less active as MAO-A and -B inhibitors compared with linezolid and the selective inhibitors clorgyline and pargyline. In general, the 5-(hydroxamic acid)methyl oxazolidinone derivatives demonstrated moderate but selective MAO-B inhibitory activity.

1. Introduction

The oxazolidinone class of compounds are potent antibacterial agents active against susceptible and resistant Gram-positive bacterial strains including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococci (VRE) and penicillin-resistant *Streptococcus pneumoniae* known to cause serious difficult to treat infections in hospital and community settings [1–4]. Linezolid (**1**; Fig. 1), the first member of this class to be clinically used, has demonstrated clinical success against these bacterial strains. Ongoing efforts have led to the discovery, development, and approval of the newest member of this class of antibacterial agents, tedizolid phosphate, as a second-generation oxazolidinone. Tedizolid phosphate, a pro-drug readily converted to the active tedizolid (**2**; Fig. 1) *in vivo*, has been shown to have significant advantages over linezolid, which include once daily dosing and enhanced effectiveness against linezolid-resistant strains [5,6]. Oxazolidinones inhibit bacterial protein biosynthesis by binding to sites on the bacterial ribosomes and preventing formation of a functional 70S initiation complex [7,8]. In particular, it

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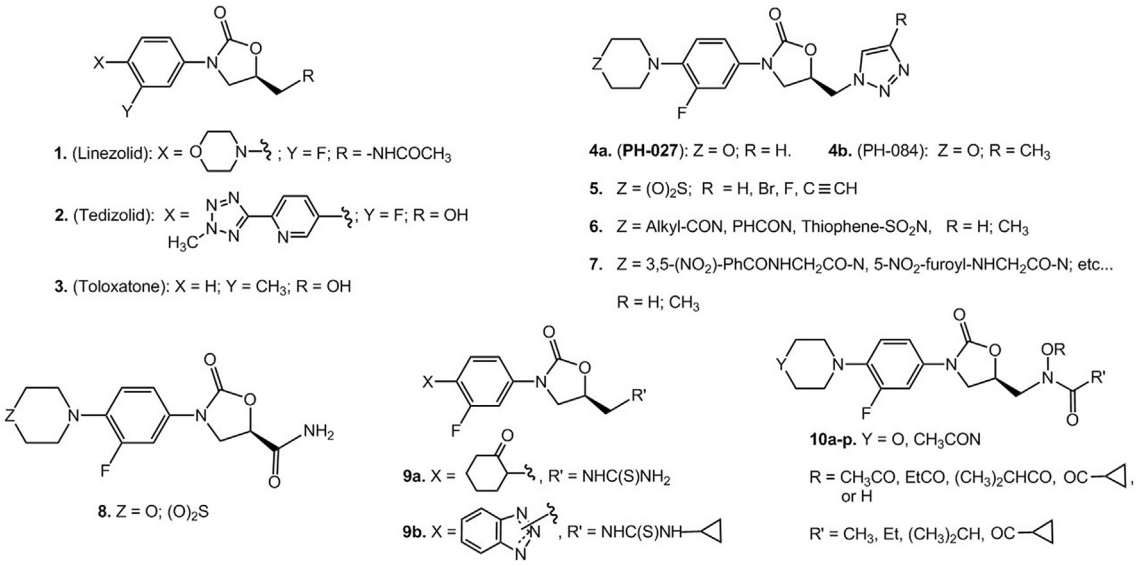

Fig. 1. Chemical structures of oxazolidinone derivatives.

has been demonstrated that linezolid binds to the A-site of the 50S subunit, thus preventing binding of the aminoacyl-tRNA to this site [9]. This class of antibacterial agents are plagued with unwanted side-effects, namely, myelosuppression and inhibition of monoamine oxidases (MAO) [10]. MAO inhibition, which is due to their structural similarity to the MAO inhibitor toloxatone (**3**; Fig. 1), may potentially lead to unfavorable interactions with serotonergic and adrenergic agents causing severe hypertensive crisis in patients [11–13]. *In vitro*, linezolid and tedizolid are reversible, non-selective inhibitors of human MAO-A and MAO-B with 50% inhibitory concentrations of 46.0 and 8.7 μM (MAO-A) and 2.1 and 5.7 μM (MAO-B), respectively [14]. Therefore research efforts involving the development of newer oxazolidinone derivatives continue to focus on overcoming the potential safety issues intrinsic to this class of compounds and on extending the spectrum of antibacterial activity.

Several investigators have carried out extensive structural modifications around the phenyl-oxazolidinone pharmacophoric group with the intention of identifying newer derivatives with extended antibacterial spectrum and improved safety profiles [4,10,15,16]. Studies have revealed that the presence of the fluorophenyl moiety in linezolid is essential for effective binding at the active site, hence modification of this ring could alter binding interaction and decrease activity [10,15,16]. As part of the structure-antibacterial activity relationships, studies have shown that incorporation of optionally diverse substituents such as the 3-aryl or heteroaryl ring at the 4-position of the phenyl-oxazolidinone moiety significantly enhanced antibacterial potency, whether the C-5 position is an acetamidomethyl or hydroxymethyl group [16]. In addition, several other studies have shown tolerance to a wider diversity of substituents at the oxazolidinone C-5 position with retention of antibacterial activity. For example, our group and others have reported that the incorporation of the 1*H*-1,2,3-triazolyl moiety at the oxazolidinone C-5 position resulted in compounds (**4a**–**b**, **5**, **6**, **7**, Fig. 1) with comparable or superior antibacterial activity to linezolid [17–21]. On the other hand, study on the reverse amide of linezolid analogs of general structure **8** (Fig. 1) gave compounds with weak to strong antibacterial activities, lower MAO-A inhibition and reduced myelotoxicity in rodents compared to linezolid [4,22]. Furthermore, thiourea substitution at the oxazolidinone C-5 position gave derivatives **9a**–**b** (Fig. 1) with variable antibacterial and anti-mycobacterium activities [2,4]. The cyclohexan-2-one **9a** and benzotriazolyl **9b** derivatives showed antibacterial activity comparable to linezolid against various Gram-positive bacterial strains. In addition, compound **9a** showed anti-mycobacterial activity against *Mycobacterium tuberculosis* H37RV strain with MIC 0.06 μg/mL [4].

Based on the observed diversity of the substituents around the phenyl-oxazolidinone with retention of antibacterial activity, we are searching for new oxazolidinone derivatives with potent broad-spectrum antibacterial activity. Our laboratory has previously reported synthesis of the 5-(*N*-hydroxyacetamido) methyl oxazolidinone derivative (**10b**, Y = O, R = H, R' = CH_3; (Fig. 1), which demonstrated only weak activity against Gram-positive bacterial strains with MIC value range of 16–>32 [17]. This 5-(*N*-hydroxyacetamido)methyl oxazolidinone derivative also showed anti-mycobacterial activity against *M. tuberculosis* H37RV (ATCC 27294) strain with MIC_{50} and MIC_{90} of 1.38 and 4.6 μg/ml, respectively, and a selectivity index, SI > 35 in the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF), Southern Research Institute, Birmingham, Alabama, USA [data from TAACF screening program]. In addition, studies have shown that compounds containing iron chelating functional groups, such as the hydroxamic acids, 8-hydroxyquinolines and catechols demonstrated antibacterial activities against non-replicating *M. tuberculosis*, *Eschericia coli, Clostridium difficile* and *Propionibacterium acnes*, due to their abilities to alter iron intake and/or metabolism [23,24]. Inspired by the activity of this hydroxamic acid derivative and the diversity of the C-5 side chain substituents reported for antibacterial oxazolidinones, we herein report the synthesis of a series of novel morpholino and piperazino 5-(*N*-hydroxy-alkanamido)methyl oxazolidinone derivatives (**10a**–**p**, Fig. 1), and their effects on bacterial growth and monoamine oxidase activities.

2. Results and discussion

2.1. Chemistry

The morpholino and piperazino oxazolidione-hydroxamic acid derivatives were synthesized as indicated in Scheme 1. The 5-hydroxymethyl oxazolidinone intermediates **18** and **19** were prepared according to published methods starting from readily