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Short communication

Synthesis and structure–antibacterial activity of triazolyl oxazolidinones containing long chain acyl moiety

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Abstract

A series of new piperazinyl 5-triazolylmethyl oxazolidinones containing long chain acyl group at the piperazine N-4-position were synthesized and evaluated against a panel of standard and clinical isolates of Gram-positive and Gram-negative bacteria. Derivatives having long chain acyl groups with nine or more number of carbon atoms showed significant decrease in antibacterial activity. Antibacterial activity correlated positively with heat of formation of the compounds, but correlated negatively with Clog *P* values, surface area, ovality and molecular volume. However, no significant correlation was observed between activity and E_{LUMO}, E_{HOMO} and dipole, respectively.

Keywords: Antibacterial activity; Heat of formation; Linezolid; Molecular descriptors; Oxazolidinones; Structure–activity relationships

1. Introduction

Although the judicious use of antibacterial agents is an important approach in attempts to control the emergence of bacterial resistance, the discovery and development of newer agents are desirable for the successful treatment of infections caused by resistant pathogenic bacteria. Among the new agents under development, only the oxazolidinone, cationic peptide and lipopeptide antibiotics can be truly regarded as novel mechanism agents [1]. A clinically useful member of the oxazolidinone class of antibacterial agents, linezolid (Fig. 1) is highly effective against multi-drug resistant Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci (MR-CNS), penicillin-resistant *Streptococcus pneumoniae* (PRSP) and vancomycin-resistant enterococcus (VRE) [2–4], which have been identified as the most prevalent bacteria species isolated from inpatient specimens in USA [5]. These organisms are also reported to be resistant to at least three classes of antibacterial agents commonly used for therapy. Oxazolidinones, linezolid and eperezolid (Fig. 1) exhibit a unique mechanism of action that involves interference with the binding of mRNA to the ribosomes at the initiation phase of translation. They explicitly inhibit the formation of the initiation complex in bacterial translation system thus preventing formation of the *N*-formylmethionyl-*t*RNA-ribosome-*m*RNA ternary complex ($tRNA^{fMet}$-*m*RNA) [6–8]. Although linezolid has demonstrated clinical success, recent reports on emerging linezolid-resistant *S. aureus* [9] and *Enterococcus* spp. [10–12] in hospital isolates suggest an increasing need for new, more effective and safer antibacterial agents. These situations continue to serve as impetus for the development of novel and more effective antibacterial agents.

Recent developments in the modification of the C-5 position of the oxazolidinones have highlighted the bioisosteric replacement of the acetamide group by a triazole moiety [13–15], which is exemplified by PH-027, and compounds of general structures **1** and **2** (Fig. 1). We have previously

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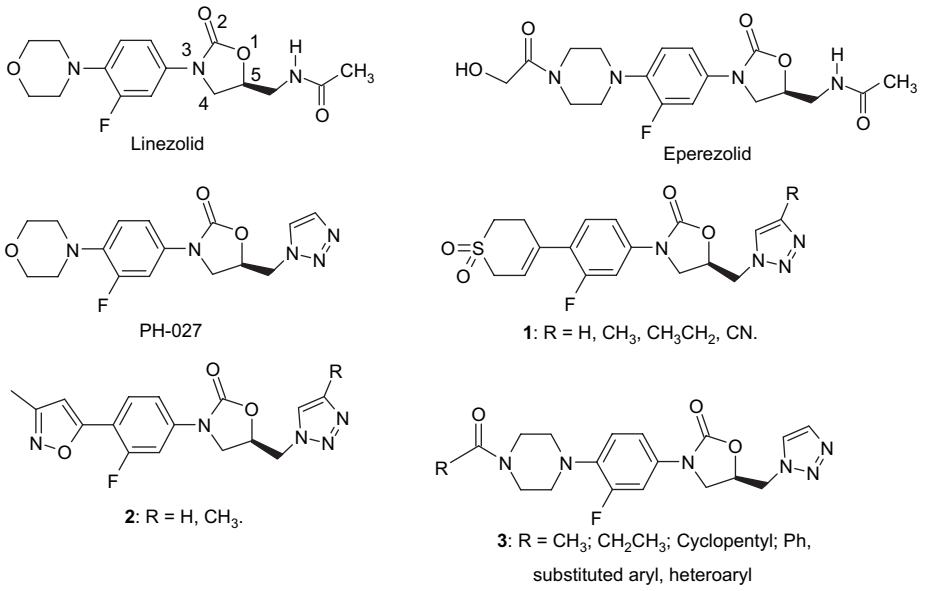

Fig. 1. Structures of antibacterial oxazolidinones.

elaborated on the structure–activity relationships of the piperazine derivatives similar to eperezolid, namely, the novel alkyl-(C_{1-5}) and 4-(phenylcarbonyl)piperazinyl 5-triazolylmethyl oxazolidinones **3** (Fig. 1), with improved antibacterial activity compared to the morpholine derivative PH-027 [16,17]. In addition, we have shown that substitution of the tolylsufonyl groups at the distal piperazine N-4-position resulted in diminished antibacterial activity [17]. In the present communication we investigated the effect of the alkyl group chain length at the distal piperazine N-4-position on the antibacterial activity. The structural variations were selected in order to investigate optimal structure–activity requirements for this novel class of 5-triazolylmethyl oxazolidinone derivatives **8a–o** and potential correlations between selected 3D molecular descriptors with the antibacterial activity. The molecular descriptors used, included lipophilicity reported as calculated log of partition coefficient (Clog *P* values), surface area (SA), molecular volume (MV), ovality, heat of formation (HOF), energies of the lowest unoccupied (E_{LUMO}) and the highest occupied (E_{HOMO}) molecular orbitals, dipole, and net charge on the nitrogen of the amide ($I_{NC=O}$), carbonyl carbon ($I_{NC=O}$), and oxygen atom ($I_{NC=O}$) at the distal piperazine N-4-position. We now report on the synthesis and structure–antibacterial activity of hitherto unreported long chain ($C_{n=5-18}$) alkylcarbonyl-oxazolidinones **8f–o**.

2. Chemistry

Compounds **8a–e** were previously reported [16], while the other derivatives **8f–o** were prepared as follows. The synthesis of the target compounds **8f–o** was carried out as outlined (Scheme 1) from the chiral alcohol derivative **6**, which was obtained in multi-step reactions in good yield according to published procedures [16,18]. Further chemical transformation of **6** to **7** involved the versatile Huisgen's 1,3 dipolar cycloaddition reaction [19] with acetylene in dimethoxyethane (DME) at 90 °C in excellent yield [16]. This was followed by the deprotection of the *tert*-butoxycarbonyl protecting group at the piperazine N-4-position with trifluoroacetic acid in CH_2Cl_2 at 0 °C to room temperature to give the key-intermediate triazole **7a** as a trifluoroacetic acid salt (quantitative). The intermediate triazole **7a** was subsequently reacted with appropriate long chain alkyl chlorides in MeCN, using triethylamine as base to give the respective target compounds **8f–n** in moderate to good yields. The bicyclo[2.2.1]heptan-2-yl acetyl derivative was prepared by reaction of the intermediate triazole **7b** with the activated bicyclo[2.2.1]heptan-2-yl acetic acid, which was obtained by the reaction with 1-hydroxybenzotriazole and dicyclohexylcarbodiimide in a mixture of CH_2Cl_2 and CH_3CN. All the compounds were characterized by their physical, analytical and spectroscopic data (^{1}H NMR, ^{13}C NMR, MS and IR) and melting points and were microanalyzed satisfactorily for C, H and N. Thorough structural verification of a representative compound **8f** was further performed by ^{13}C NMR decoupled, ^{13}C DEPT-135 (Distortionless enhancement by polarization transfer) and ^{13}C APT (Attached proton test) experiments.

3. Results and discussion

The C-5-triazolylmethyl oxazolidinones, exemplified by PH-027 are novel bioisoteres of the C-5-acetamidomethyl oxazolidinones, based on the similarities in the dipole moment and potential of the nitrogen atoms of the triazole and acetamide moieties to function as weak hydrogen bond acceptors [20]. Furthermore, the observed comparable or superior antibacterial activity [15,16] and reduced monoamine oxidase inhibitory activity [4,14,15] of the triazolyl derivatives **1** (Fig. 1) served as impetus for establishing the structure–antibacterial activity relationship of this class of compounds.