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Synthesis and antibacterial activities of novel oxazolidinones having spiro[2,4]heptane moieties

So-Young Kim, Hyeong Beom Park, Jung-Hyuck Cho, Kyung Ho Yoo, Chang-Hyun Oh *

Life Sciences Research Division, Korea Institute of Science and Technology, PO Box 131, Cheongryang, Seoul 130-650, Republic of Korea

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ABSTRACT

The synthesis of a new series of oxazolidinones having spiro[2,4]heptane moieties is described. Their in vitro antibacterial activities against both Gram-positive and Gram-negative bacteria were tested and the effect of substituents on the oxazolidinone ring was investigated. A particular compound **Ih** having fluoro group showed the most potent antibacterial activity.

The emergence of bacterial resistance to the antibiotics poses a serious concern for medical professionals during the last decade.[1] In particular, multi-drug-resistant Gram-positive bacteria[2] including methicillin-resistant *Staphylococcus aureus* (MRSA)[3] and *Staphylococcus epidermidis* (MRSE), and vancomycin resistant enterococci (VRE) are of major concern.[4]

Oxazolidinones, a new class of synthetic antibacterial agents, exhibit activity against a large number of Gram-positive organisms. Linezolid is the first oxazolidinone approved for the treatment of Gram-positive bacterial infections in humans.[5] Since Linezolid, the many attractive traits of oxazolidinone series have encouraged further work in this area, and also the literature reveals extensive chemical programs exist.[6,7] At present, most efforts are focused on substituted phenyl oxazolidinones. Eperezolid and AZD2563 have been extensively used as the structural precursors for modification.[8]

In this Letter, we describe the synthesis and structure–activity relationship of oxazolidinones having spiro[2,4]heptane moieties instead of morpholine (Fig. 1). In addition, our approach for the improvement of antibacterial activity of oxazolidinones is also discussed.

It is revealed[9,10] that a spiro[2,4]heptane substituent could enhance largely the activity of quinolone antibiotics especially against both Gram-positive and Gram-negative bacteria. Based on the facts, a positive effect of a spiro[2,4]heptane moiety on the activity of oxazolidinone was anticipated.

7-Oxo-5-azaspiro[2,4]heptane **8**[11] was prepared via seven steps from diketene and benzylamine as shown in Scheme 1. Aceto compound **2** was obtained from diketene and benzylamine, which was then cyclized to compound **3** using 1,2-dibromoethane. Carbonyl group of **3** was protected by ethylene glycol and subsequently brominated to give **5**, which was converted to spiro[2,4]heptane **6** using sodium hydride. Cyclized compound **6** was reduced with lithium aluminum hydride to give **7**. The key compound **8** was obtained by hydrogenation of **7** in the presence of palladium carbon.

The syntheses of derivatives **Ia–i** are outlined in Schemes 2 and 3. 7-Oxo-5-azaspiro[2,4]heptane as a starting material on condensation with 3,4-difluoronitrobenzene in acetonitrile gave compound **9**.

Hydrogenation of compound **9** with 10% Pd–C/H_2 followed by condensation with benzyl chloroformate afforded the protected

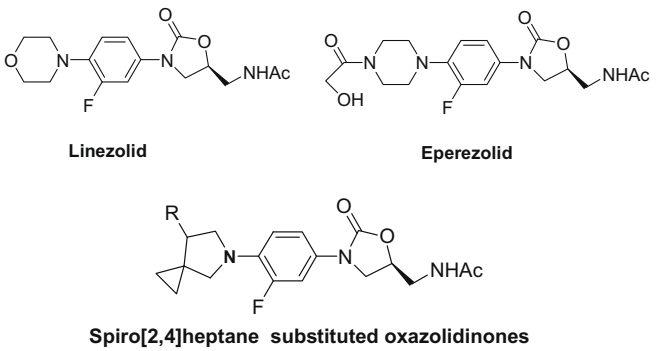

Figure 1. Structures of Linezolid, Eperezolid, and target molecules.

* Corresponding author. Tel.: +82 2 958 5160; fax: +82 2 9585189.
E-mail address: choh@kist.re.kr (C.-H. Oh).

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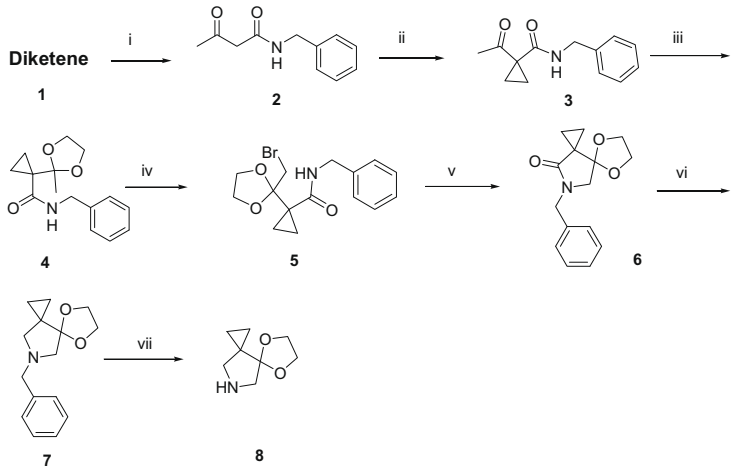
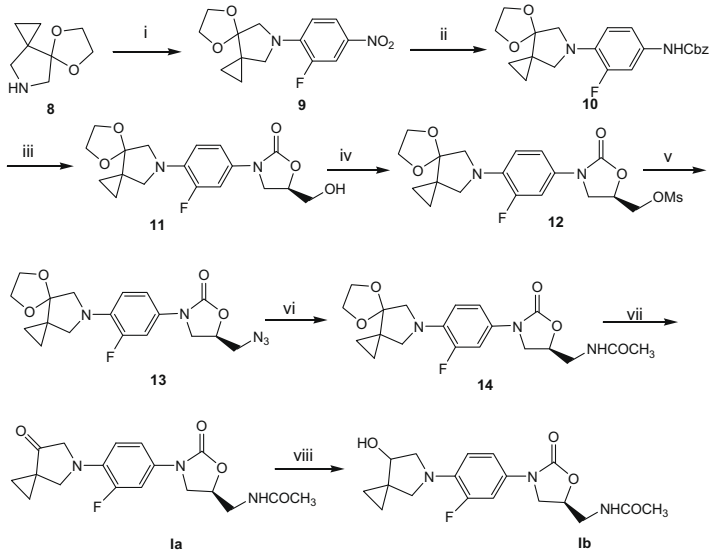
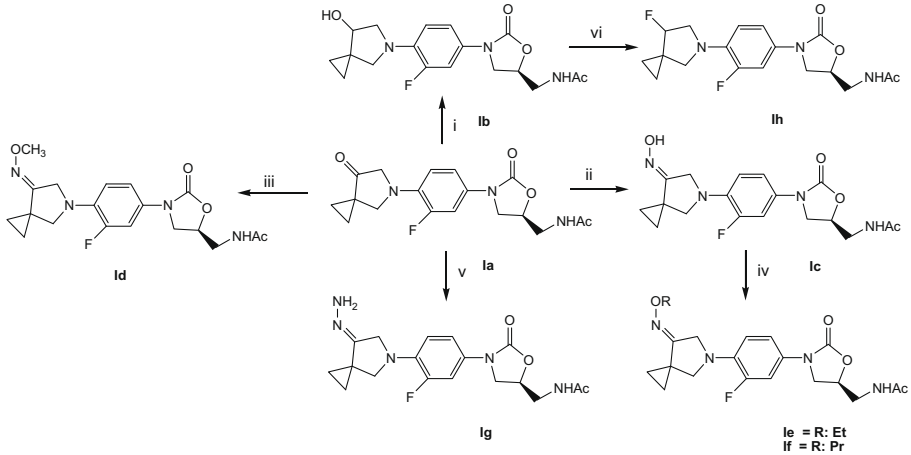


Scheme 1. Reagents and conditions: (i) benzylamine, CH_2Cl_2; (ii) 1,2-dibromoethane, K_2CO_3, DMF; (iii) ethylene glycol, *p*-toluensulfonic acid, benzene; (iv) Br_2, dioxane, ether; (v) NaH, DMF; (vi) $LiAlH_4$, THF; (vii) Pd/C, H_2, EtOH.



Scheme 2. Reagents and condition: (i) 3,4-difluoronitrobenzene, CH_3CN, reflux, 67%; (ii) (1) H_2, Pd/C, THF (2) benzylchloroformate, $NaHCO_3$, acetone–H_2O; (iii) *n*-BuLi, (*R*)-glycidyl butyrate, −78 °C, 65%; (iv) MsCl, TEA, CH_2Cl_2, 5 °C, 79%; (v) NaN_3, DMF, 75 °C, 78%; (vi) (1) H_2, Pd/C, EtOAc (2) Ac_2O, pyridine, 69%; (vii) *p*-toluenesulfonic acid monohydrate, acetone–H_2O; (viii) $NaBH_4$, THF, −5 °C, 75%.



Scheme 3. Reagents and conditions: (i) $NaBH_4$, THF, −5 °C, 75%; (ii) $NH_2OH{\cdot}HCl$, TEA, EtOH, 60 °C, 70%; (iii) $NH_2OCH_3{\cdot}HCl$, TEA, MeOH, rt, 65%; (iv) **Ie**: C_2H_5Br, KOH, DMF, 40 °C, 71%; **If**: C_3H_7Br, KOH, DMF, 40 °C, 73%; (v) N_2H_4, TEA, EtOH, 60 °C, 55%; (vi) DAST, CH_2Cl_2, −75° C to rt, 53%.