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Discovery of novel bis-oxazolidinone compounds as potential potent and selective antitubercular agents

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ABSTRACT

A variety of new mono-oxazolidinone molecules by modifying the C-ring of Linezolid, a marketed antibiotic for MRSA, were synthesized and tested for their *in vitro* antibacterial activities against several *Staphylococcus aureus*, *Mycobacterium smegmatis* and two Gram-negative bacteria strains (*Escherichia coli* and *Pseudomonas aeruginosa*). Among them, compounds **4**–**7** displayed moderate antimicrobial activities. After development of a second oxazolidinone ring in the western part of the mono-oxazolidinone compounds **4**–**7** by a ring closure reaction with *N*,*N*′-carbonyldiimidazole (CDI), we found thus obtained bis-oxazolidinone compounds **22**–**25** possess excellently inhibitory activities against $H_{37}Rv$ but poor or no effects on other test bacteria. Among them, bis-oxazolidinone compound **22** and **24** are the most potent two compounds with a same MIC value of 0.125 μg/mL against $H_{37}Rv$ virulent strain. Compound **22** also exhibited extremely low cytotoxicity on monkey kidney Vero cells with a selective index (IC_{50}/MIC) over 40,000, which suggested bis-oxazolidinone compound **22** is a promising lead compound for subsequent investigation in search of new antitubercular agents.

Tubcerculosis, or TB, is one of the most widespread infectious diseases. The World Health Organization (WHO) has declared that one-third of the world's population is currently infected with TB, while nearly 13.7 million active cases worldwide.[1] The WHO also estimates that 8 million people get TB every year and 3 million people will die yearly if control is not further strengthened.[2] The emergence of multi-drug resistant TB strains (MDR-TB) and extensively drug resistant TB strains (XDR-TB) is a great challenge for the treatment of tuberculosis. Furthermore, the combined epidemics of HIV and tuberculosis have aggravated this situation.

Most of first-line TB drugs were discovered in 1950s and 1960s. For nearly half a century, TB treatment lacks new drug until Bedaquiline was launched in the end of 2012, which was approved to treat multi-drug-resistant tuberculosis.[3] The successful discovery of Bedaquiline is an exciting milestone in TB therapy with a unique mechanism of action targeting adenosine triphosphate (ATP) synthase, which Mycobacterium tuberculosis requires to generate its energy.[4] Nevertheless, case report suggested that its adverse effects such as nausea, joint, pain and headache lead to a risk in clinical use. The drug also has a black-box warning by FDA for arrhythmias, as it may induce long QT syndrome by blocking the hERG channel.[5,6] Consequently it is still desirable to develop new antitubercular drugs to address the unmet demand of anti-tuberculosis medical goals such as fast and long-acting, high potency against MDR-TB and latent infections, minimal drug–drug interactions and low toxicity.[7]

The development of new members of established antibiotics, which already possess desirable pharmacological properties, is one approach to add new drugs to the existing anti-TB armamentarium rapidly. Linezolid (Fig. 1) was approved for the treatment of serious infections caused by Gram-positive bacteria such as *Streptococci*, vancomycin-resistant *enterococci* and methicillin-resistant *Staphylococcus aureus*. And it was once failed in clinical trials for TB as a result of its peripheral and optic nerve toxicity.[8] However, recently research demonstrated that Linezolid is effective with patients who suffering from treatment-refractory extensive drug-resistant (XDR) pulmonary tuberculosis when the

Abbreviations: INH, Isoniazid; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

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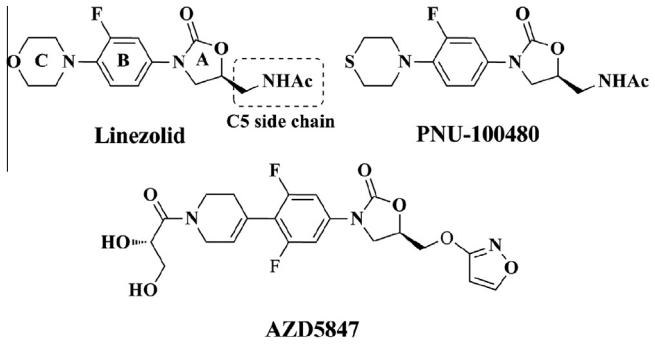


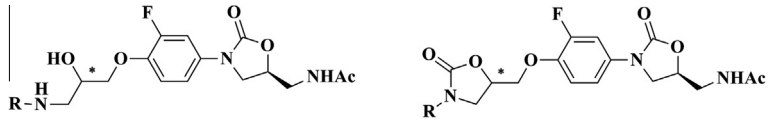
Figure 1. Chemical structures of Linezolid, PNU-100480 and AZD5847.

adverse events can be monitored carefully.[9,10] Besides, great efforts have made to modify the C-ring of Linezolid in order to find some promising candidates with potent antimicrobial activities, which successfully led PNU-100480 (Fig. 1) to phase II clinical trials.[11–13] Combinational modification strategy of C-ring and C-5 side chain of Linezolid brought another phase II clinical candidate AZD5847 (Fig. 1).

Encouraged by the mentioned clinic success and research advancement, we undertook novel structural modification of the western part (C-ring) of Linezolid as a continuing effort of our group to find novel antibacterial agents. At beginning, a variety of mono-oxazolidione Linezolid analogues **4**–**21** (Table 1) with 3-phenyloxazolidin-2-one scaffold remained, were synthesized and tested for their *in vitro* antibacterial activities against several *Staphylococcus aureus*, *Mycobacterium smegmatis* and two Gram-negative bacteria strains (*Escherichia coli* and *Pseudomonas aeruginosa*). Among them, compounds **4**–**7** displayed moderate antimicrobial activities. In order for the enhancement of their antibacterial potencies, we took advantage of the bis-pharmacophore strategy, which has been widely applied in drug design and many inspiring progresses have been achieved with this method. Thus a second pharmacophore oxazolidinone ring was developed in western part of each of the oxazolidinone compounds **4**–**7** by a ring-closure reaction with *N*,*N*′-carbonyldiimidazole (CDI) to obtain bis-oxazolidinone compounds **22**–**25**. Biological assays showed that thus obtained four bis-oxazolidinone compounds possess good antitubercular effects. Such good results prompt us to make subsequent structural modifications aiming at establishment of a preliminary body of structure–activity relationships (SARs) and elucidation of the importance of oxazolidinone ring number within a single molecule. The *in vitro* antitubercular activities of the final compounds were assessed on virulent *Mycobacterium tuberculosis* H_{37}Rv strain and the cytotoxicities were assayed towards monkey kidney Vero cells.

To efficiently achieve the mono-oxazolidinone compounds **4**–**21**, a synthetic route outlined in Scheme 1 was adopted. Firstly, the starting material (*S*)-*N*-((3-(3-fluoro-4-hydroxyphenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide **1**, conveniently prepared in our lab according to a reported procedure,[14] reacted with (*S*)-epichlorohydrin or (*R*)-epichlorohydrin in the presence of potassium carbonate[15] at 50 °C to get the common intermediate **2** (S configuration in western part) or **3** (R-counterpart of compound **2**). Secondly, the terminal epoxide in compound **2** or **3** was opened

Table 1
Structures of the new target compounds **4**–**30** and their calculated Log*P* (*C*Log*P*), Log*P* and aqueous solubility values



Compd	R	*S*/*R*	*C*Log*P*	Log*P*	Solubility (μmol/L)
4	*p*-Methoxyphenyl	*S*	1.56	0.95	56
5	*p*-Methoxyphenyl	*R*	1.56	1.15	1.3
6	Phenyl	*S*	1.64	1.42	124
7	Phenyl	*R*	1.64	0.59	296
8	*p*-Cyanophenyl	*S*	1.07	2.12	47
9	*p*-Cyanophenyl	*R*	1.07	1.29	69
10	3,5-Di(trifluoro-methyl) phenyl	*S*	3.40	3.10	NT[a]
11	3,5-Di(trifluoro-methyl) phenyl	*R*	3.40	3.01	22
12	2-Pyridyl	*S*	0.14	1.37	22,207
13	2-Pyridyl	*R*	0.14	1.60	35,080
14	3-Pyridyl	*S*	0.14	0.02	3042
15	3-Pyridyl	*R*	0.14	-0.18	10,138
16	4-Pyridyl	*S*	0.14	-0.04	17,724
17	4-Pyridyl	*R*	0.14	0.02	24,631
18	Cyclopropyl	*S*	0.89	0.02	96,015
19	Cyclopropyl	*R*	0.89	-0.10	2202
20	3-Methylbutyl	*S*	2.29	1.17	385
21	3-Methylbutyl	*R*	2.29	1.19	7276
22	Phenyl	*S*	1.70	1.78	14
23	Phenyl	*R*	1.70	1.86	164
24	*p*-Methoxyphenyl	*S*	2.14	1.91	132
25	*p*-Methoxyphenyl	*R*	2.14	1.73	211
26	—	—	0.59	0.01	2720
27	—	—	0.78	0.59	81
28	—	—	1.28	0.43	333
29	—	—	2.69	NT[a]	NT[a]
30	—	—	3.13	3.19	441

[a] Not tested.