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Synthesis and Antibacterial Activity of Novel 2-Oxo-pyrrolidinyl Oxazolidinones

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Novel antibacterial oxazolidinones bearing pyrrolidinone ring system at the C-5 side chain were synthesized and their *in vitro* antibacterial activities were evaluated. Most of the synthesized oxazolidinones showed good antibacterial activity against the Gram-positive and Gram-negative bacteria tested.

Key Words : Pyrrolidinone, Oxazolidinone, Antimicrobial activity

Introduction

Because of deficiency in innovative advance in the antibacterial drug development, the increasing incidence and prevalence of bacterial resistance to clinically useful antibiotics is one of the most serious global health threats of the last two decades.[1-4] Oxazolidinones are a new class of antibacterial agents used to overcome the innovation deficiency. Linezolid (Figure 1) is the first oxazolidinone antibiotics approved in 2000 for the treatment of Gram-positive bacterial infections in humans.[5] It exhibits consistent activity against multi-resistant gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE) and penicillin-resistant *Streptococcus pneumouniae*.[6,7] Furthermore, oxazolidinone class antibiotics show good activity against multidrug resistance *Mycobacterium tuberculosis* infections which is one of the most threatening and wide spreading infectious disease.[8-10]

Linezolid is known to inhibit bacterial protein synthesis by binding to 50S ribosomal subunit at the translation step and prevent the formation of 70S complex, and the binding mode was confirmed by X-ray crystallography.[11]

Linezolid is widely used in clinical care as a synthetic unnatural antibiotics and is now prescribed as a last resort antibiotics for the treatment of multi-resistant pathogens like vancomycin, however, clinical emergences of linezolid resistant bacteria including *Staphylococci* and *Enterococci* have been reported.[12-14] The most common mechanism of linezolid resistance is point mutations in the 23S rRNA peptidyl transferase region,[15-18] and recently a new resistance mechanism mediated by *cfr* gene encoding methyltransferase has been reported.[19,20] Thus, there is a significant need for the development of new oxazolidinone series with an improved potency and spectrum of antibacterial activity.

Four types of chemical modifications of linezolid and oxazolidinone-type antibiotics have been reported,[21-24] including modifications on each of the A, B and C-rings as well as the C-5 side chain of the A-ring substructure.[22,25] Among them, recently, torezolid[25] and radezolid[27] as shown in Figure 1 are under clinical development.

Oxazolidinones containing a lactam substituent represented not only antibacterial agents[28,29] but also antithrombotic

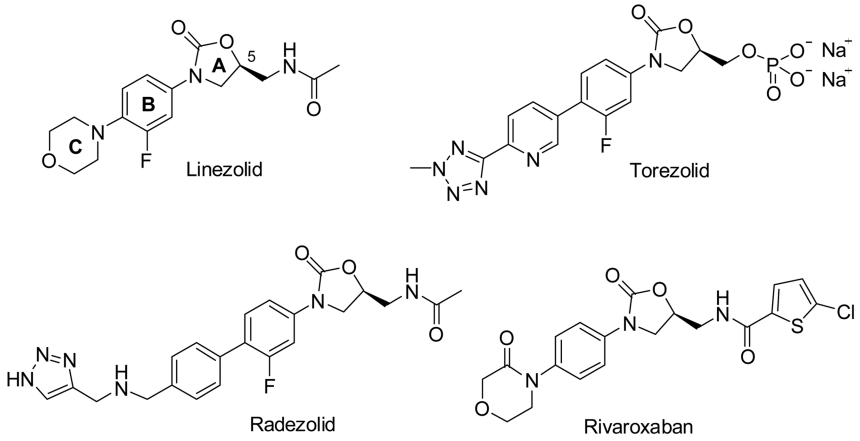


Figure 1

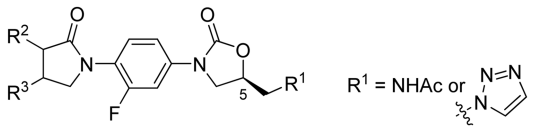


Figure 2

agents. Rivaroxaban, a lactam substituted oxazolidinone marketed as Xarelto, is orally active and highly potent coagulation factor Xa inhibitors and has been approved in United States recently for the prophylaxis of venous thromboembolism (VTE).[30]

Herein we report the synthesis and biological evaluation of a series of oxazolidinone-type antibiotics in which the C-ring has been modified by substituted pyrrolidinone ring as shown in Figure 2. Both acetamide and triazole are used as a C-5 side chain. The resulting compounds were then screened against Gram-positive, Gram-negative bacteria, and also *Mycobacterium tuberculosis* (Mtb) $H_{37}Rv$.

Experimental Section

General. ^{1}H and ^{13}C-NMR spectra were recorded on Bruker DPX 300 MHz spectrophotometer using $CDCl_3$, CD_3OD, DMSO-d_6 as NMR solvent. TMS was used as an internal standard and chemical shift data are reported in parts per million (ppm) and s, d, t, and m are designated as singlet, doublet, triplet and multiplet respectively. Coupling constants (*J*) were reported in hertz (Hz). Mass spectra were recorded on Waters Acquity UPLC/Synapt G2 QTOF MS mass spectrometer. The reaction progress was monitored by thin layer chromatography (TLC).

(*S*)-*N*-(4-(5-(Acetamidomethyl)-2-oxo-oxazolidin-3-yl)-2-fluorophenyl)-4-chlorobutanamide (2a). Sodium carbonate (87 mg, 0.89 mmol) was added to the solution of aniline **1a** (20 mg, 0.74 mmol) in acetone at room temperature. 4-Chlorobutyryl chloride (0.10 mL, 0.89 mmol) was added to the mixture slowly. Reaction mixture was stirred at the same temperature for 5 h and concentrated. Water (5 mL) was added and the mixture was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 10:1) to yield amide **2a** (24 mg, 86%): ^{1}H MMR (DMSO-d_6, 300 MHz) δ 9.52 (s, 1H), 8.02 (t, *J* = 5.5 Hz, 1H), 7.56 (t, *J* = 8.9 Hz, 1H), 7.34 (dd, *J* = 13.3, 2.3 Hz, 1H), 6.98 (m, 1H), 4.50 (m, 1H), 3.88 (t, *J* = 8.9 Hz, 1 H), 3.50 (m, 3H), 3.19 (t, *J* = 5.4 Hz, 2H), 2.39 (t, *J* = 5.4 Hz, 2H), 1.82 (m, 2H), 1.61 (s, 3H).

(*S*)-*N*-((3-(3-Fluoro-4-(2-oxo-pyrrolidin-1-yl)phenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (3a). Amide **2a** (200 mg, 0.54 mmol) was dissolved in ethanol (5 mL) and potassium hydroxide (45.4 mg, 0.81 mmol) was added. Reaction mixture was stirred at room temperature for 3 h. Solvent was concentrated, and the mixture was extracted with chloroform (10 mL × 2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel ($CHCl_3$/MeOH, 10:1) to yield lactam **3a** (110 mg, 63%): ^{1}H MMR (DMSO-d_6, 300 MHz) δ 8.29 (t, *J* = 5.6 Hz, 1H), 7.65-7.36 (m, 3H), 4.81 (m, 1H), 4.19 (t, *J* = 9.3 Hz, 1H), 3.78 (m, 3H), 3.48 (t, *J* = 5.4 Hz, 2H), 2.50 (t, *J* = 8.2 Hz, 2H), 2.22 (m, 2H), 1.89 (s, 3H).

***N*-(4-((*S*)-5-(Acetamidomethyl)-2-oxo-oxazolidin-3-yl)-2-fluorophenyl)-2-(benzyloxy)-4-hydroxybutanamide (6a).** Intermediate **1a** (3.3 g, 12.2 mmol) was dissolved in CH_2Cl_2 (35 mL) at room temperature and 1 M solution of dimethylaluminium chloride in hexane (29.2 mL, 14.4 mmol) was added. The mixture was stirred till the solution was transparent. 3-(Benzyloxy)dihydrofuran-2(3*H*)-one **5** (2.81 g, 14.64 mmol) was added to the reaction mixture and was stirred for 4 h at the same temperature. Phosphate buffer (pH 7, 20 mL) was added to the reaction mixture, and the mixture was extracted with CH_2Cl_2 (20 mL × 2). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 25:1) to afford amide **6a** (4.48 g, 79%) as white solid: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.89 (t, *J* = 8.8 Hz, 1H), 7.68 (dd, *J* = 13.7, 2.7 Hz, 1H), 7.40 (m, 6H), 4.84 (m, 1H), 4.74 (d, *J* = 11.6 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.20 (m, 2H), 3.86 (dd, *J* = 9.0, 6.3 Hz, 1H), 3.77 (t, *J* = 6.3 Hz, 2H), 3.60 (d, *J* = 5.1 Hz, 2H), 2.05 (m, 2H), 1.99 (s, 3H).

***N*-(((5*S*)-3-(4-(3-(Benzyloxy)-2-oxo-pyrrolidin-1-yl)-3-fluorophenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (7a).** Compound **6a** (3.7 g, 8.3 mmol) and triphenyl phosphine (2.6 g, 9.8 mmol) were dissolved in CH_2Cl_2 (100 mL) and diethyl azodicarboxylate (1.7 g, 9.8 mmol) was added slowly for 20 min at ice bath temperature. The reaction mixture was stirred at room temperature for 4 h. Water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (100 mL × 2). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 25:1) to yield lactam **7a** (2.98 g, 84%): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.28 (t, *J* = 5.7 Hz, 1H), 7.61 (dd, *J* = 13.2, 2.1 Hz, 1H), 7.50 (t, *J* = 8.7 Hz, 1H), 7.35 (m, 6H), 4.87 (part A of AB, *J* = 11.9 Hz, 1H), 4.71 (part B of AB, *J* = 11.9 Hz, 1H), 4.76 (m, 1H), 4.33 (t, *J* = 7.6 Hz, 1H), 4.15 (t, *J* = 8.9 Hz, 1H), 3.76 (dd, *J* = 8.7, 6.6 Hz, 1H), 3.70 (dd, *J* = 7.9, 5.3 Hz, 1H), 3.43 (t, *J* = 5.2 Hz, 2H), 2.5 (m, 1H), 2.08 (m, 1H), 1.85 (s, 3H).

***N*-(((5*S*)-3-(3-Fluoro-4-(3-hydroxy-2-oxo-pyrrolidin-1-yl)phenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (8a).** Benzyl ether **7a** (1.0 g, 2.26 mmol) was dissolved in ethyl alcohol (50 mL), and palladium hydroxide in activated charcoal (0.16 g, 5 mol %) and cyclohexene (10 mL) were added. Reaction mixture was refluxed for 3 d, cooled to room temperature and filtered through celite. The filtrate was concentrated and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 10:1) to yield alcohol **8a** (0.73 g, 92%): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.28 (t, *J* = 5.8 Hz, 1H), 7.57 (dd, *J* = 13.3, 2.6 Hz, 1H), 7.48 (t, *J* = 8.7 Hz, 1H), 7.36 (dd, *J* = 8.7, 2.1 Hz, 1H), 4.76 (m, 1H), 4.32 (m, 1H), 4.12 (t, *J* = 9.1 Hz, 1H), 3.76 (dd, *J* = 8.7,

6.6 Hz, 1H), 3.65 (dd, *J* = 10.7, 4.1 Hz, 1H), 3.44 (t, *J* = 5.2 Hz, 2H), 2.43 (m, 1H), 1.92 (m, 1H), 1.85 (s, 3H); HRMS (EI^+) calcd for $C_{16}H_{18}FN_3NaO_5$ (M^+): 374.1128, found: 374.1290.

***N*-(((5*S*)-3-(3-Fluoro-4-(3-fluoro-2-oxo-pyrrolidin-1-yl)-phenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (9a).** A solution of diethylaminosulfur trifluoride (60 μL) in CH_2Cl_2 (2 mL) was added dropwise to a solution of alcohol **8a** (120 mg, 0.34 mmol) in CH_2Cl_2 (12 mL) at −78 °C. The reaction mixture was warmed to room temperature gradually and stirred for 24 h. Saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was extracted with CH_2Cl_2 (12 mL × 2). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 15:1) to yield fluoride **9a** (24 mg, 20%): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.63 (dd, *J* = 13.2, 2.1 Hz, 1H), 7.51 (t, *J* = 8.9 Hz, 1H), 7.38 (dd, *J* = 9.1, 2.0 Hz, 1H), 4.87 (dd, *J* = 7.7, 5.5 Hz, 1H), 4.76 (m, 1H), 4.16 (t, *J* = 8.7 Hz, 1H), 3.77 (m, 3H), 3.43 (d, *J* = 5.1 Hz, 1H), 2.79 (m 1H), 2.30 (m, 1H), 1.85 (s, 1H), 1.83 (s, 3H).

***N*-(((5*S*)-3-(4-(3-Chloro-2-oxo-pyrrolidin-1-yl)-3-fluoro-phenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (10a).** Thionyl chloride (60 μL) was added dropwise to a solution of alcohol **8a** (120 mg, 0.34 mmol) in acetonitrile (8 mL) at room temperature. The reaction mixture was refluxed for 24 h, cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 10:1) to yield chloride **10b** (70.6 mg, 56%): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.71 (dd, *J* = 13.2, 3.0 Hz, 1H), 7.48 (t, *J* = 8.5 Hz, 1H), 7.39 (dd, *J* = 8.9, 1.6 Hz, 1H), 4.84(m, 1H), 4.74 (dd, *J* = 7.7, 5.0 Hz, 1H), 4.20 (t, *J* = 9.0 Hz, 1H), 3.96 (m, 1H), 3.87 (m, 2H), 3.60 (d, *J* = 4.8 Hz, 2H), 2.85 (m, 1H), 2.42 (m, 1H), 2.00 (s, 3H); HRMS (EI^+) calcd for $C_{16}H_{17}ClFN_3NaO_4$ (M^+): 392.0789, found: 392.0781.

***N*-[[(5*S*)-3-[4-(3-Bromo-2-oxo-1-pyrrolidinyl)-3-fluoro-phenyl]-2-oxo-5-oxazolidinyl] methyl] acetamide (11a).** Triphenylphosphine (194 mg, 0.74 mmol) and carbon tetrabromide (245 mg, 0.74 mmol) were added to a solution of alcohol **8a** (120 mg, 0.34 mmol) in acetonitrile (8 mL) at room temperature. The reaction mixture was refluxed for 24 h and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 10:1) to yield bromide **11a** (45 mg, 32%):

^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.27 (t, *J* = 5.7 Hz, 1H), 7.64 (dd, *J* = 16.0, 4.9 Hz, 1H), 7.51 (t, *J* = 8.4 Hz, 1H), 7.39 (dd, *J* = 8.9, 1.6 Hz, 1H), 4.88 (m, 1H), 4.77 (m, 1H), 4.16 (t, *J* = 9.0 Hz, 1H), 3.88 (m, 1H), 3.77 (m, 2H), 3.44 (d, *J* = 5.1 Hz, 2H), 2.83 (m, 1H), 2.38 (m, 1H), 1.85 (s, 3H); HRMS (EI^+) calcd for $C_{16}H_{17}BrFN_3NaO_4$ (M^+): 436.0284, found: 436.0271.

***N*-[[(5*S*)-3-[3-Fluoro-4-(3-methoxy-2-oxo-1-pyrrolidin-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (12a).** Silver oxide (95 mg, 0.4 mmol) and methyl iodide (42 μL, 2.0 equiv) were added to a solution of alcohol **8a** (120 mg, 0.34 mmol) in CH_2Cl_2 (8 mL), and stirred for 1.5 h at room temperature. The reaction mixture was filtered through celite and the filtrate was concentrated. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1) to yield methyl ether **12a** (37 mg, 30%): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.7 (dd, *J* = 13.2, 2.4 Hz, 1H), 7.46 (t, *J* = 8.6 Hz, 1H), 7.37 (dd, *J* = 8.7, 2. 7 Hz, 1H), 4.85 (m, 1H), 4.22 (m, 2H), 3.86 (dd, *J* = 9.3, 6.6 Hz, 1H), 3.79 (dd, *J* = 8.2, 5.0 Hz, 2H), 3.60 (s, 3H), 3.44 (d, *J* = 5.1 Hz, 2H), 2.62 (m, 1H), 2.14 (m, 1H), 2.0 (s, 3H).

***N*-[[(5*S*)-3-[4-(3-Carboxy-2-oxo-1-pyrrolidinyl)-3-Fluoro-phenyl]-2-oxo-5-oxazolidinyl] methyl] acetamide (14a).** To a solution of aniline **1a** (1.0 g, 3.7 mmol) in toluene (20 mL), 6,6-dimethyl-5,7-dioxaspiro [2.5] octane-4,8-dione (0.95 g, 5.6 mmol) was added, and the reaction mixture was refluxed for 24 h. The reaction mixture was cooled and concentrated. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1) to yield carboxylic acid **14a** (1.2 g, 86%): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.68 (dd, *J* = 13.2, 2.7 Hz, 1H), 7.44 (t, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 9.3, 2.7 Hz, 1H), 4.83 (m, 1H), 4.20 (t, *J* = 9.0 Hz, 2H), 3.86 (t, *J* = 7.4 Hz, 2H), 3.60 (d, *J* = 4.8 Hz, 2H), 2.59 (t, *J* = 7.9 Hz, 1H), 2.27 (m, 2H), 2.00 (s, 3H).

***N*-(4-((*S*)-5-(Acetamidomethyl)-2-oxo-oxazolidin-3-yl)-2-fluorophenyl)-3-(benzyloxy)-4-hydroxybutanamide (17a).** Compound **17a** was prepared from **1a** and **16** according to the similar procedure for the preparation of compound **6a** (yield 49%): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.76 (s, 1H), 8.28 (t, *J* = 5.6 Hz, 1H), 7.80 (t, *J* = 8.8 Hz, 1H), 7.59 (dd, *J* = 13.2, 2.7 Hz, 1H), 7.27 (m, 5H), 4.82 (t, *J* = 5.5 Hz, 1H), 4.74 (m, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 3.91 (m, 1H), 3.74 (dd, *J*=8.7, 6.6 Hz, 1H), 3.52 (t, *J* = 5.2 Hz, 2H), 3.43 (t, *J* = 5.2 Hz, 2H), 2.62 (m, 2H), 1.85 (s, 3H).

***N*-(((*S*)-3-(4-((*S*)-4-(Benzyloxy)-2-oxo-pyrrolidin-1-yl)-3-fluorophenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (18a).** Compound **18a** was prepared from **17a** according to the similar procedure for the preparation of compound **7a** (yield 99%): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.25 (t, *J* = 5.6 Hz, 1H), 7.58 (dd, *J* = 13.2, 2.2 Hz, 1H), 7.45 (t, *J* = 8.7 Hz, 1H), 7.33 (m, 6H), 4.74 (m, 1H), 4.56 (s, 2H), 4.35 (m, 1H), 4.12 (t, *J* = 9.1 Hz, 1H), 4.03 (m, 1H), 3.75 (m, 2H), 3.42 (t, *J* = 5.5 Hz, 2H), 2.82 (dd, *J* = 17.3, 6.5 Hz, 1H), 2.49 (m, 1H), 1.83 (s, 3H).

***N*-(((*S*)-3-(3-Fluoro-4-((*S*)-4-hydroxy-2-oxo-pyrrolidin-1-yl)phenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (19a).** Compound **19a** was prepared **18a** according to the similar procedure for the preparation of compound **8a** (yield 73%): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.27 (t, *J* = 5.7 Hz, 1H), 7.59 (dd, *J* = 13.2, 2.4 Hz, 1H), 7.47 (t, *J* = 8.9 Hz, 1H), 7.35 (dd, *J* = 8.7, 2.7 Hz, 1H), 4.76 (m, 1H), 4.44 (m, 1H), 4.15 (t, *J* = 9.0 Hz, 1H), 4.00 (dd, *J* = 9.9, 5.1 Hz, 1H), 3.76 (dd, *J* = 9.0, 6.3 Hz, 1H), 3.50 (dd, *J* = 9.9, 1.8 Hz, 1H), 3.44 (t, *J* = 5.6 Hz, 2H), 2.76 (dd, *J* = 17.1, 6.6 Hz, 1H), 2.25 (dd, *J* = 16.7, 2.5 Hz, 1H), 1.85 (s, 1H), 1.83 (s, 3H); HRMS (EI^+) calcd for C16H18FN3NaO5 (M^+): 374.1128, found: 374.1302.

***N*-(((*S*)-3-(3-Fluoro-4-((*S*)-4-fluoro-2-oxo-pyrrolidin-1-yl)phenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (20a).**

Compound **20a** was prepared **19a** according to the similar procedure for the preparation of compound **9a** (yield 33%): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.61 (dd, *J* = 13.2, 2.4 Hz, 1H), 7.46 (t, *J* = 12.6 Hz, 1H), 7.35 (dd, *J* = 8.9, 2.3 Hz, 1H), 4.81 (m, 1H), 4.42 (dd, *J* = 11.6, 5.0 Hz, 1H), 4.20 (t, *J* = 9.1 Hz, 2H), 3.91 (m, 1H), 3.87 (dd, *J* = 9.0, 6.3 Hz, 1H), 3.50 (d, *J* = 4.8 Hz, 2H), 3.26 (dd, *J* = 17.4, 6.6 Hz, 1H), 2.74 (dd, *J* = 16.4, 3.5 Hz, 1H), 2.0 (s, 3H).

***N*-(((*S*)-3-(4-((*S*)-4-Chloro-2-oxo-pyrrolidin-1-yl)-3-fluorophenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (21a).** Compound **21a** was prepared from **19a** according to the similar procedure for the preparation of compound **10a** (yield 56%): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.71 (dd, *J* = 13.2, 2.4 Hz, 1H), 7.47 (t, *J* = 12.6 Hz, 1H), 7.38 (dd, *J* = 8.9, 2.3 Hz, 1H), 4.86 (m, 1H), 4.42 (dd, *J* = 11.6, 5.0 Hz, 1H), 4.20 (t, *J* = 9.1 Hz, 2H), 3.92 (m, 1H), 3.87 (dd, *J* = 9.0, 6.3 Hz, 1H), 3.60 (d, *J* = 4.8 Hz, 2H), 3.26 (dd, *J* = 17.4, 6.6 Hz, 1H), 2.74 (dd, *J* = 16.4, 3.5 Hz, 1H), 2.0 (s, 3H).

***N*-(((5*S*)-3-(4-(4-Bromo-2-oxo-pyrrolidin-1-yl)-3-fluorophenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (22a).** Compound **22a** was prepared from **19a** according to the similar procedure for the preparation of compound **11a** (yield 80%): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.71 (dd, *J* = 12.9, 2.7 Hz, 1H), 7.48 (t, *J* = 8.5 Hz, 1H), 7.38 (dd, *J* = 9.4, 2.3 Hz, 1H), 4.85 (m, 1H), 4.48 (dd, *J* = 11.8, 5.2 Hz, 1H), 4.20 (t, *J* = 9.1 Hz, 2H), 4.02 (dd, *J* = 11.7, 1.8 Hz, 1H), 3.87 (dd, *J* = 9.0, 6.3 Hz, 1H), 3.63 (d, *J* = 4.8 Hz, 2H), 3.34 (m, 1H), 2.86 (dd, *J* = 17.7, 2.1 Hz, 1H), 2.00 (s, 3H); HRMS (EI^+) calcd for $C_{16}H_{17}BrFN_3NaO_4$ (M^+): 436.0284, found: 436.0397.

***N*-(((5*S*)-3-(3-Fluoro-4-(4-methoxy-2-oxo-pyrrolidin-1-yl)phenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (23a).** Compound **23a** was prepared from **19a** according to the similar procedure for the preparation of compound **12a** (yield 42%): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.68 (dd, *J* = 13.1, 2.6 Hz, 1H), 7.44 (t, *J* = 8.4 Hz, 1H), 7.35 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.53 (s, 1H), 4.82 (m, 1H), 4.22 (m, 1H), 4.12 (m, 2H), 3.82 (m, 2H), 3.59 (d, *J* = 4.8 Hz, 2H), 3.42 (s, 3H), 2.90 (dd, *J* = 17.4, 6.3 Hz, 1H), 2.56 (dd, *J* = 17.6, 2.3 Hz, 1H), 2.00 (s, 3H).

Biological Assay.

MIC (Minimal Inhibitory Concentrations) Determination: Minimal inhibitory concentrations (MICs) were determined by two-fold agar dilution as described by the Clinical and Laboratory Standards Institute.[31] Test strains were grown for 18 h at 37 °C in tryptic soy broth and diluted with the same fresh medium to a density of *ca*. 107 colony forming units (CFU)/mL. Suspensions were applied to Mueller-Hinton agar (MHA) plates containing serial dilutions of antimicrobial agents using a multipoint inoculator to yield 105 CFU/spot. Plates were incubated in air at 37 °C for 18 h and were examined for growth. The MIC was considered to be the lowest concentration that completely inhibited growth on agar plates, disregarding a single colony or a faint haze caused by the inoculum.

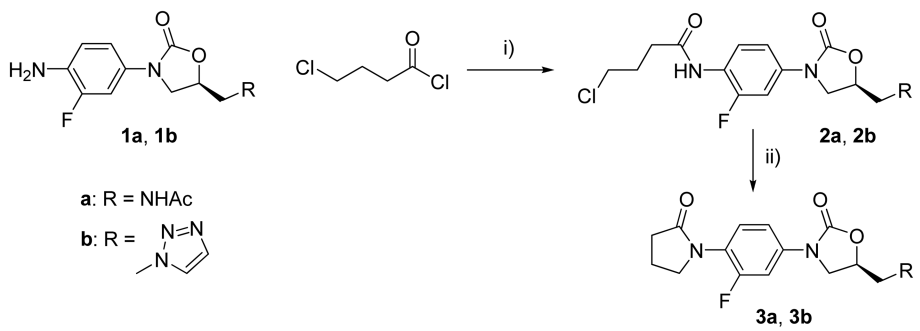
MIC (Minimal Inhibitory Concentrations) Determination of *Mycobacterium tuberculosis*: The MICs of compounds against *Mycobacterium tuberculosis* (Mtb) $H_{37}Rv$ was determined by the Microplate Alamar Blue Assay.[32]

Results and Discussion

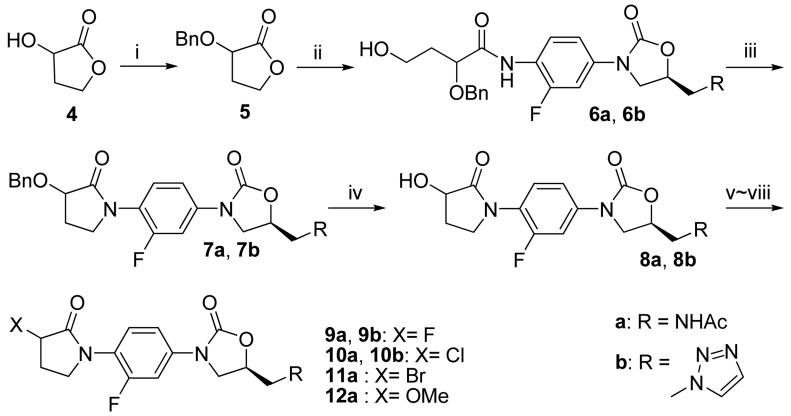
Chemistry. Two types of oxazolidinone starting material, acetamide **1a** and 1,2,3-triazole **1b**, were synthesized by modification of literature method.[33,34] Oxazolidinone derivatives having pyrrolidinone at the C-ring were prepared by coupling of amino group in **1a** and **1b** with 4-chlorobutyryl chloride and the subsequent cyclization to form pyrrolidone in good yields as shown in Scheme 1.

α-Hydroxy pyrrolidinonyl oxazolidinone **8a** and **8b** were also prepared by the condensation of amino group in **1a** and **1b** with 3-(benzyloxy)dihydrofuran-2(3*H*)-one and followed by intramolecular Mitsunobu-type cyclization and subsequent hydrogenation protocol as shown in Scheme 2. α-Hydroxy pyrrolidinone **8a** was obtained as inseparable diastereomeric mixture, and one of its single diastereomer was prepared by using optically active 3(*R*)-3-(benzyloxy)dihydrofuran-2(3*H*)-one. The synthesis of other oxazolidinone derivatives having α-substituted pyrrolidinones at C-ring of linezolid was shown in Scheme 2 too. Halogenation of alcohol **8a** and **8b** gave the fluoride, chloride and bromide compounds **9-11** by using diethylaminosulfur trifluoride (DAST), thionyl chloride and triphenylphosphine with carbon tetrabromide respectively in moderate to good yields. *O*-Methylation of α-hydroxy compound **8a** with methyl iodide in the presence of silver oxide provided α-methoxy compound **12a**.

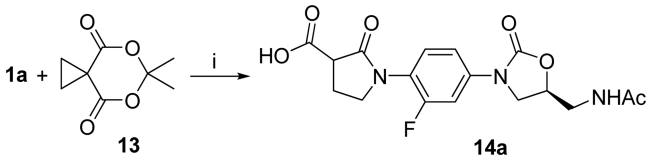
N-Aryl-2-oxo-pyrrolidine-3-carboxylic acid **14a** were synthesized by the reaction of arylamine **1a** and 6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione **13** in toluene at



Scheme 1. i) Na_2CO_3, acetone, rt, 5 h, 86% (**2a**), 85% (**2b**); ii) KOH, EtOH, rt, 3 h, 63% (**3a**), 68% (**3b**).



Scheme 2. (i) Ag_2O, BnBr, MC, rt, 10 h, 60%; (ii) **1a** or **1b**, Me_2AlCl, DCM, rt, 5 h, 79% (**6a**), 70% (**6b**); (iii) PPh_3, DEAD, DCM, rt, 5 h, 84% (**7a**), 85% (**7b**); (iv) $Pd(OH)_2/C$, cyclohexene, EtOH, reflux, 3 d, 92% (**8a**), 75% (**8b**); (v) Et_2NSF_3, DCM, −78 °C to rt, 24 h, 20% (**9a**), 43% (**9b**); (vi) $SOCl_2$, MeCN, rt to reflux, 24 h, 56% (**10a**), 46% (**10b**); (vii) PPh_3, CBr_4, MeCN, reflux, 24 h, 32% (**11a**); (viii) CH_3I, Ag_2O, MC, rt, 1.5 h, 30% (**12a**).



Scheme 3. (i) toluene, reflux, 24 h, 86%.

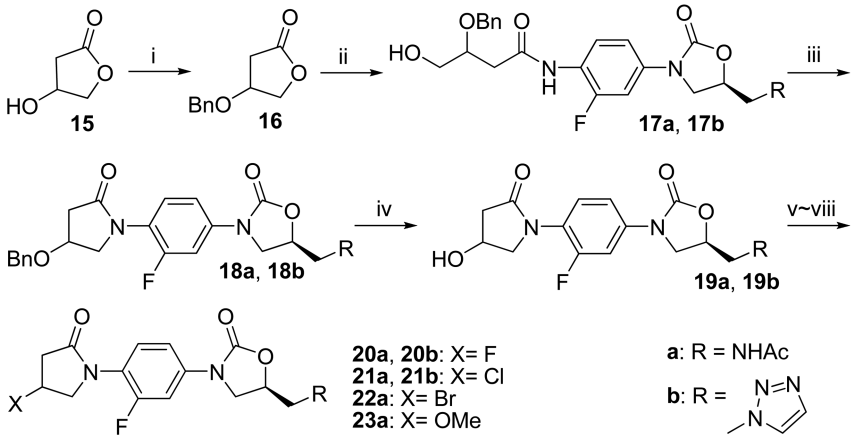
reflux condition in good yield as shown in Scheme 3.

3-Substituted-2-oxo-pyrrolidinyl oxazolidinone derivatives **18-23** were synthesized from 4-hydroxydihydrofuran-2(3*H*)-one **15** following the similar synthetic procedure of the corresponding α-substituted compounds **7-12** as shown in Scheme 4.

Biological Evaluation. This series of oxazolidinone antimicrobial compounds prepared above were screened against panel of susceptible and resistance bacteria. MICs (μg/mL) of these compounds against standard strains were summarized in Table 1 and linezolid was used as a reference compound for comparison. The compounds were also tested against drug-resistant strains such as MRSA, VRE (vancomycin-resistant *Enterococcus faecium*), *Coagulase negative Staphylococi*, *E. faecalis*, and *S. pneumonia*, and the results were shown in Table 2.

Most of the prepared oxazolidinone derivatives having pyrrolidinone moiety exhibited good activity against the tested Gram-positive and Gram-negative bacteria (Table 1 and Table 2). The new pyrrolidone compounds bearing acetamide at position C-5 were more active than those with 1,2,3-triazole at the same position, and the α-substituted pyrrolidinone compounds were more active than the corresponding α-substituted compounds.

Among C-5 acetamide-substituted oxazolidinones, pyrrolidinone compound **3a** had comparable activity with the reference compound linezolid but α-hydroxy substituted pyrrolidinone compound **8a** lost the activity. In case of **8a**, both single isomer and diastereomeric mixture exhibited similar antibacterial activity against most tested strains. However oxazolidinones with halogenated pyrrolidinone moiety at α- or β-position (**9a-11a**, **20a-22a**) showed com-



Scheme 4. (i) Ag_2O, BnBr, DCM, rt, 10 h, 60%; (ii) **1a** or **1b**, Me_2AlCl, DCM, rt, 5 h, 49% (**17a**), 65% (**17b**); (iii) PPh_3, DEAD, DCM, rt, 5 h, 99% (**18a**), 83% (**18b**); (iv) $Pd(OH)_2/C$, cyclohexene, EtOH, reflux, 3 d, 73% (**19a**), 80% (**19b**); (v) Et_2NSF_3, DCM, −78 °C to rt, 24 h, 33% (**20a**), 40% (**20b**); (vi) $SOCl_2$, MeCN, rt to reflux, 24 h, 56% (**21a**), 48% (**21b**); (vii) PPh_3, CBr_4, MeCN, reflux, 24 h, 80% (**22a**); (viii) CH_3I, Ag_2O, DCM, rt, 1.5 h, 42% (**23a**).

Table 1. *In vitro* antibacterial activities of oxazolidinone derivatives against standard strains (MICs in μg/mL)

Compounds	*S. a.*[a]	*C. s.*[b]	*E. f.*[c]	*E. f*[d]	*S. p.*[e]	*S. p*[f]	*S. a.*[g]	*H. i.*[h]
3a	1.56	nd	3.12	3.12	nd	nd	nd	nd
8a	12.5	12.5	12.5	6.25	1.56	1.56	3.12	25
8a[i]	12.5	12.5	12.5	6.25	3.12	3.12	6.25	25
9a	3.12	3.12	3.12	3.12	1.56	1.56	1.56	3.12
10a	3.12	6.25	3.12	3.12	0.78	1.56	1.56	3.12
11a	3.12	3.12	3.12	3.12	1.56	1.56	1.56	3.12
12a	6.25	12.5	6.25	6.25	3.12	3.12	3.12	6.25
14a	6.25	6.25	6.25	6.25	1.56	1.56	3.12	6.25
19a	100	100	100	25	12.5	12.5	25	100
20a	3.12	3.12	3.12	3.12	1.56	1.56	3.12	3.12
21a	3.12	3.12	3.12	3.12	1.56	1.56	1.56	3.12
22a	12.5	12.5	3.12	3.12	1.56	3.12	3.12	6.25
23a	50	50	50	50	12.5	12.5	25	25
3b	12.5	6.25	6.25	nd	3.12	3.12	12.5	12.5
8b	6.25	6.25	6.25	25	1.56	1.56	6.25	6.25
9b	6.25	6.25	3.12	3.12	1.56	1.56	3.12	3.12
10b	6.25	6.25	3.12	6.25	1.56	1.56	6.25	6.25
19b	100	100	50	6.25	12.5	12.5	25	100
20b	25	25	12.5	12.5	6.25	6.25	12.5	25
21b	6.25	6.25	6.25	6.25	1.56	3.12	6.25	6.25
Linezolid	3.12	3.12	1.56	1.56	0.78	0.78	1.56	0.78

[a]methicillin-susceptible *Staphylococcus aureus* C463. [b]methicillin-susceptible *Coagulase negative Staphylococi*. [c]vancomycin-susceptible *Enterococcus faecalis* C474. [d]vancomycin-susceptible *Enterococcus faecium* C803. [e]penicillin-susceptible *Streptococcus pneumonia* C402. [f]*Streptococcus pyogenes* ATCC8736. [g]*Streptococcus agalactiae* ATCC2901. [h]*Hameophilus influenzae.* [i](*R*)-3-hydroxy-2-oxo-pyrrolidine diastereomer of **8a**

Table 2. *In vitro* antibacterial activities of oxazolidinone derivatives against resistant strains and *Mycobacterium tuberculosis* $H_{37}Rv$ (MICs in μg/mL)

Compounds	*S. a.*[a]	*C. s.*[b]	*E. f.*[c]	*E. f*[d]	*S. p*[e]	*M. t.*[f]
3a	3.12	nd	3.12	3.12	nd	nd
8a	12.5	25	12.5	25	1.56	nd
8a[g]	12.5	12.5	12.5	25	1.56	1
9a	3.12	3.12	3.12	3.12	0.78	1
10a	3.12	3.12	3.12	6.25	0.78	1
11a	3.12	3.12	3.12	6.25	0.78	0.5
12a	6.25	6.25	6.25	12.5	0.78	4
14a	12.5	6.25	6.25	6.25	1.56	nd
19a	100	100	100	100	6.25	nd
20a	6.25	6.25	3.12	3.12	1.56	0.5
21a	3.12	3.12	3.12	6.25	0.78	nd
22a	6.25	6.25	6.25	12.5	1.56	2
23a	50	50	50	50	6.25	4
3b	6.25	6.25	6.25	nd	3.12	4
8b	12.5	6.25	6.25	100	1.56	2
9b	3.12	3.12	3.12	3.12	1.56	0.5
10b	3.12	12.5	6.25	6.25	1.56	2
19b	100	100	25	12.5	6.25	2
20b	25	25	12.5	25	3.12	2
21b	6.25	6.25	6.25	6.25	1.56	2
Linezolid	3.12	3.12	3.12	1.56	0.78	1

[a]methicillin-resistant *Staphylococcus aureus.* [b]methicillin-resistant *Coagulase negative Staphylococi.* [c]vancomycin-resistant *Enterococcus faecalis.* [d]penicillin-resistant *Streptococcus pneumoniae*. [e]vancomycin-resistant *Enterococcus faecium.* [f]*Mycobacterium tuberculosis* $H_{37}Rv$. [g](*R*)-3-hydroxy-2-oxo-pyrrolidine diastereomer of **8a**

parable antibacterial activities against most tested bacteria including resistant strains with the linezolid. Substitution of methoxy and carboxylic group at α-position of pyrrolidone (**12a**, **14a**) lost the activity slightly, and β-hydroxy compounds **19a** completely lost the activity.

Among C-5 1,2,3-triazole oxazolidinones, pyrrolidinone compound **3b** was less active than reference compound, and substitution of hydroxyl group at α-position of pyrrolidinone (**8b**) slightly improved the activity. Fluoride and chloride substituted oxazolidinones at α-position of pyrrolidone (**9b** and **10b**) showed good antibacterial activity, and demonstrated similar activities against most resistant strains compared to linezolid. Almost β-substituted compounds at pyrrolidinone part were less active than α-substituted compounds in the 1,2,3-triazole series, and β-hydroxy compound **19b** completely lost the activity. The 2-oxopyrrolidinyl oxazolidinones of both C-5 acetamide and triazole series are less active than linezolid against gram-negative *Hameophilus influenza.*

Notably, the new oxazolidinone derivatives possessing pyrrolidinone moiety showed comparable or higher activity than linezolid against *Mycobacterium tuberculosis* (Mtb) $H_{37}Rv$ as shown in Table 2. Compound **11a**, **20a** and **9b** showed 2-fold higher activity than linezolid against *Mycobacterium tuberculosis*.

Conclusion

A new series of oxazolidinones having 2-oxopyrrolidine moiety have been synthesized, and their *in vitro* antibacterial activities were evaluated against Gram-positive, Gram-negative bacteria including resistant strains of *Staphylococi*, *Streptococci* and *Enterococci.* Some of these analogs exhibited potent in vitro antibacterial activities comparable or superior to linezolid. The compounds exhibited potent antibacterial activity against *Mycobacterium tuberculosis* (Mtb) $H_{37}Rv$, and the compound **11a**, **20a** and **9b** showed 2-fold higher activity than linezolid against *M. tuberculosis.*

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