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Synthesis and *In Vitro* Antibacterial Activity of Novel 3-Azabicyclo[3.3.0]octanyl Oxazolidinones

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We synthesized a series of oxazolidinone-type antibacterials in which morpholine C-ring of linezolid has been modified by substituted 3-azabicyclo[3.3.0]octanyl rings. Acetamide or 1,2,3-triazole heterocycle was used as C-5 side chain of oxazolidinone. The resulting series of compounds was then screened *in vitro* against panel of susceptible and resistant Gram-positive, Gram-negative bacteria, and *Mycobacterium tuberculosis* (Mtb). Several analogs in this series exhibited potent *in vitro* antibacterial activity comparable or superior to linezolid against the tested bacteria. Compounds 10a, 10b, 11a, and 15a displayed highly potent activity against *M. tuberculosis*. Selected compound 10b showed good human microsomal stability and CYP-profile, and showed low activity against hERG channel.

Key words: antibacterial agents, drug design, drug discovery, *Mycobacterium tuberculosis*, oxazolidinone

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Because of innovation gap in the antibacterial drug development, the growing incidence and prevalence of bacterial resistance to clinically useful antibacterials are 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 gap. Linezolid (**1**, Figure 1), marketed under the trade name Zyvox® in 2000, is the first oxazolidinone antibacterials approved for the treatment of Gram-positive bacterial infections in humans (5). It is consistently active against multiresistant Gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE), and penicillin-resistant *Streptococcus pneumouniae* (6,7). In addition, oxazolidinone class antibacterials have good activity against multidrug resistant *Mycobacterium tuberculosis* infections which are one of the most threatening and wide-spreading infectious diseases (8–10).

Linezolid binds to 50S ribosomal subunit at the translation step and inhibits the formation of 70S complex, leading to the inhibition of protein synthesis, and the binding mode was confirmed by X-ray crystallography (11). Although linezolid has demonstrated clinical success as synthetic unnatural antibacterials and is now in the position of a last resort for the treatment of multi-resistant pathogens like vancomycin, 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 (15–17), and recently, a new resistance mechanism mediated by *cfr* gene has been reported (18,19). 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 antibacterials have been reported (20–23), including modifications on each of the A, B, and C-rings as well as the C-5 side chain of the A-ring substructure (20,24). Among them, recently, torezolid (**2**, Figure 1) (25) and radezolid (26) are under clinical development.

We are interested in conformationally constrained azabicyclic isostere of the morpholine ring (C-ring) of linezolid. Some oxazolidinones with

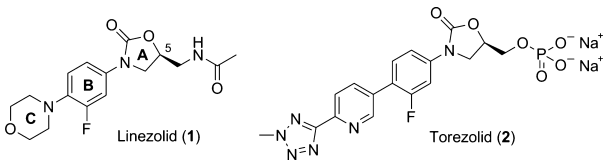


Figure 1: Structures of linezolid and torezolid.

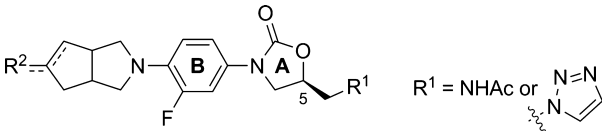


Figure 2: Oxazolidinone analogs with 3-azabicyclo[3.3.0]octanyl C-rings.

bicyclic substituents are reported with good antibacterial activities in panels of bacteria (27,28). In an effort to improve the potency and broaden the spectrum of oxazolidinones as antibacterial agents, we herein described the synthesis and biological evaluation of a series of oxazolidinone-type antibacterials in which C-ring has been modified by 3-azabicyclo[3.3.0]octanyl ring systems with oxime or cyano group substituent at C-7 position. Cyano group was known to drastically enhance the antibacterial activity as a substituent of oxazolidinones (29,30).

Acetamide and 1,2,3-triazole are introduced as C-5 side chain of oxazolidinone rings. The structural skeleton of designed compounds is shown in Figure 2, and the resulting library of compounds was then screened against Gram-positive and Gram-negative bacteria, and also *Mycobacterium tuberculosis* (Mtb) H37Rv.

Experimental

Reagents and analysis

Melting points were measured on MEL-TEMP® 3.0 Laboratory Devices INC, USA. ^{1}H and ^{13}C-NMR spectra were recorded on Bruker DPX 300 MHz spectrophotometer using $CDCl_3$, CD_3OD, and DMSO-*d6* 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). Infrared spectra (IR) were recorded on Perkin Elmer 16F PC FT-IR spectrometer, and frequencies are given in reciprocal centimeters. Mass spectra were recorded on Waters Acquity UPLC/Synapt G2 QTOF MS mass spectrometer. The reaction progress was monitored by thin layer chromatography (TLC).

2-(2-Fluoro-4-nitrophenyl)octahydrocyclopenta [c]pyrrol-5-ol (5)

tert-Butyl 5-oxohexahydrocyclopenta[c]pyrrole-2(1*H*)-carboxylate (10.0 g, 44.4 mmol) was dissolved in methanol, and sodium borohydride (3.36 g, 88.8 mmol) was added at 0 °C. The reaction mixture was stirred at same temperature for 1 h, and then, 15 mL of concentrated hydrochloric acid was added to it. The mixture was stirred for another 1 h at room temperature. The solvent was removed in reduced pressure, and the white solid product was used directly without purification.

The white solid product was dissolved in acetonitrile (100 mL). To the solution, 3, 4-difluoronitrobenzene (4.91 mL, 44.4 mmol) and *N*, *N*-diisopropylethylamine (23.20 mL, 133.2 mmol) were added, and the mixture was refluxed for 6 h. It was cooled to room temperature, and the solvent was removed under reduced pressure. Residue was dissolved in ethyl acetate and washed with water. Organic layer was dried by magnesium sulfate. Solution was filtered, and the solvent was removed under vacuum to provide 8.27 g (70%) of yellow solid product. It was used for next step without further purification: mp 98.4–100.9 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 (m, 2H), 6.66 (t, J = 8.7 Hz, 1H), 4.34 (t, J = 4.8 Hz, 1H), 3.60 (m, 4H), 2.82 (m, 2H), 2.21 (m, 2H), 1.70 (t, J = 4.5 Hz, 1H), 1.65 (t, J = 3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.03, 148.77, 142.78, 142.66, 121.46, 115.25, 115.17, 112.73, 112.38, 74.34, 57.21, 41.99, 41.77, 40.81, 40.68; IR (film): $\bar{\upsilon}$ = 3350, 2952, 1605, 1525, 1491, 1380, 1319/cm; HRMS (EI$^+$) calcd for $C_{13}H_{15}FN_2NaO_3$ (M^+): 289.0964, found: 289.0980.

2-(2-Fluoro-4-nitrophenyl)hexahydro-1H-spiro[cyclopenta[c]pyrrole-5,2′-[1,3]dioxolane] (6)

DMSO (0.8 mL, 11.26 mmol) was dissolved in methylene chloride (13 mL), and the solution was cooled down at −78 °C under argon environment. Oxalyl chloride (0.483 mL, 5.63 mmol) was added to it slowly with stirring at the same temperature, and the mixture was stirred for 1 h. The solution of compound **5** in methylene chloride (1.00 g, 3.75 mmol) was added to reaction mixture slowly, and the reaction mixture was stirred for another 2 h. Triethylamine (2.63 mL, 18.77 mmol) was added to the reaction mixture, and the temperature was allowed to increase up to room temperature. The mixture was stirred for another 2 h at room temperature, water was added to it, and the mixture was extracted with methylene chloride three times. Combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The yellow solid was recrystallized in methanol to provide 0.93 g (94%) pure compound.

The yellow crystal from above reaction was dissolved in benzene (10 mL) with ethylene glycol (0.25 mL, 4.5 mmol) and *p*-toluene sulfonic acid monohydrate (49.9 mg, 0.26 mmol). Solution was refluxed under argon environment for 3 h using Dean-Stark trap. Reaction mixture was cooled down to room temperature and washed with saturated aqueous sodium carbonate solution. Organic layer was dried in magnesium sulfate, and the solvent was removed under reduced pressure to provide yellow solid product. The product was purified by silica gel column using hexane and ethyl acetate (3:1) solution to provide 0.92 g (80%) of pure compound: mp 117.0–118.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 (m, 2H), 6.57 (t, J = 8.9 Hz, 1H), 3.92 (m, 4H), 3.74 (m, 2H), 3.52 (t, J = 4.5 Hz, 2H), 3.48 (t, J = 3.2 Hz, 1H), 2.86 (m, 1H), 2.17 (dd, J = 13.9, 8.7 Hz, 2H), 1.84 (dd, J = 13.9, 5.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.11, 147.86, 142.55, 142.43, 136.87, 136.76, 121.66, 114.10, 114.03, 113.46, 113.39, 112.91, 112.56, 112.44, 112.16, 55.70, 55.62, 54.93, 54.85, 50.09, 48.82, 42.40, 39.82, 39.80, 39.30, 38.88, 38.85; IR (film):$\bar{\upsilon}$ = 2949, 2882, 1741, 1605, 1525, 1490, 1379, 1321/cm; HRMS (EI$^+$) calcd for $C_{15}H_{17}FN_2NaO_4$ (M^+): 331.1070, found: 331.1080.

(5R)-3-(3-Fluoro-4-(tetrahydro-1H-spiro [cyclopenta[c]pyrrole-5,2′-[1,3]dioxolane]-2(3H)-yl)phenyl)-5-(hydroxymethyl)oxazolidin-2-one (7)

Compound **6** (0.80 g, 2.61 mmol) was dissolved in ethyl acetate, and 10% palladium on charcoal (139 mg, 0.13 mmol) was added to it. Reaction mixture was stirred at room temperature for 6 h under hydrogen gas environment. The reaction mixture was filtered through celite, and the solvent was concentrated to provide pure white solid product 0.72 g (95%).

The white solid product (0.69 g, 2.48 mmol) in above reaction was dissolved in tetrahydrofuran, and saturated sodium bicarbonate

solution (2.17 mL) was added. The temperature of reaction mixture was lowered to 0 °C in argon environment. Benzyl chloroformate (0.50 mL, 3.46 mmol) was added to it gradually, and the temperature of reaction mixture was increased gradually to room temperature. Mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated and extracted with ethyl acetate. It was dried over magnesium sulfate, and the solvent was evaporated to yield white solid product. The product was purified by silica gel column using hexane and ethyl acetate (3:1) solution to provide 0.74 g (75%) of pure compound.

The above-prepared pure compound (0.70 g, 1.75 mmol) was dissolved in tetrahydrofuran (7 mL). Temperature of the solution was lowered to −78 °C. *n*-BuLi (1.3 mL, 2.1 mmol) was added to the solution gradually. The mixture was stirred at the same temperature for 1 h. Then, (*R*)-glycidyl butyrate (0.28 mL, 2.1 mmol) was added slowly. Temperature was raised to room temperature slowly, and the reaction mixture was stirred for another 12 h at room temperature. The solvent was concentrated, and the residue was extracted with ethyl acetate. Organic layer was washed with saturated ammonium chloride solution. It was dried over magnesium sulfate, and the solvent was evaporated to provide white solid product. The product was purified by silica gel column chromatography using methylene chloride and methanol (50:1) solution to provide 0.55 g (82%) of pure compound: mp 173.9–175.8 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83 (d, J = 1.2 Hz, 1H), 7.79 (d, J = 1.2 Hz, 1H), 7.23 (dd, J = 15.3, 2.4 Hz, 1H), 6.93 (dd, J = 8.7, 2.7 Hz, 1H), 6.65 (t, J = 9.3 Hz, 1H), 5.07 (m, 1H), 4.81 (dd, J = 4.1, 1.4 Hz, 2H), 4.14 (t, J = 9.0 Hz, 1H), 3.91 (dd, J = 9.5, 6.1 Hz, 1H), 3.61 (m, 2H), 3.31 (m, 2H), 3.07 (m, 2H), 2.60 (dd, J = 19.5, 9.0 Hz, 2H), 2.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.99, 147.86, 134.53, 129.85, 118.55, 117.24, 117.17, 113.46, 107.95, 107.60, 70.57, 64.79, 64.04, 62.91, 56.47, 47.75, 41.02, 39.20; IR (film): $\bar{\upsilon}$ = 3405, 2959, 1741, 1706, 1523, 1479, 1437, 1318/cm; HRMS (EI$^+$) calcd for $C_{19}H_{23}FN_2NaO_5$ (M^+): 401.1489, found: 401.1497.

(5R)-5-(Azidomethyl)-3-(3-fluoro-4-(tetrahydro-1H-spiro[cyclopenta[c]pyrrole-5,2′-[1,3]dioxolane]-2(3H)-yl)phenyl)oxazolidin-2-one (8)

Compound **7** (0.48 g, 1.27 mmol) was dissolved in methylene chloride, and the temperature was lowered to 0 °C. Triethylamine (0.45 mL, 3.17 mmol) was slowly added to the solution of alcohol **7**, and then, methanesulfonyl chloride (0.2 mL, 2.54 mmol) was added to the reaction mixture. Temperature was gradually increased to room temperature, and the mixture was stirred for 4 h. Solvent was removed in reduced pressure and was extracted with ethyl acetate. Organic portion was dried in sodium sulfate and concentrated. The residue was used to next step directly.

The above product was dissolved in dimethylformamide, and sodium azide (1.14 g, 17.5 mmol) was added. The mixture was stirred at 80 °C for 4 h. The solvent was concentrated and then extracted with ethyl acetate. Organic layer was dried over sodium sulfate, and solvent was removed under reduced pressure. The product was purified by silica gel column chromatography using methylene chloride and methanol (50:1) solution to provide 0.46 g (90%) of pure compound as white solid: mp 143.3–150.6 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.37 (dd, J = 15.3, 2.1 Hz, 1H), 7.05 (dd, J = 8.7, 2.7 Hz, 1H), 6.69 (t, J = 9.3 Hz, 1H), 4.77 (m, 1H), 4.03 (t, J = 9.1 Hz, 1H), 3.93 (s, 4H), 3.69 (t, J = 6.6 Hz, 1H), 3.62 (m, 2H), 3.33 (t, J = 7.4 Hz, 2H), 3.23 (d, J = 9.1, 2H), 2.83 (br s, 2H), 2.11 (dd, J = 19.2, 8.1 Hz, 2H), 1.84 (dd, J = 19.5, 3.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.99, 147.86, 134.53, 129.85, 118.55, 117.24, 117.17, 113.46, 107.95, 107.60, 70.57, 64.79, 64.04, 56.47, 53.09, 47.75, 41.02, 39.20; IR (film): $\bar{\upsilon}$ = 2947, 2105, 1729, 1519, 1519, 1478, 1426, 1318/cm; HRMS (EI$^+$) calcd for $C_{19}H_{22}FN_5NaO_4$ (M^+): 426.1554, found: 426.1548.

N-(((5S)-3-(3-Fluoro-4-(tetrahydro-1H-spiro[cyclopenta[c]pyrrole-5,2′-[1,3]dioxolane]-2(3H)-yl)phenyl)-2-oxo-oxazolidin-5-yl)methyl) acetamide (9a)

Compound **8** (1.0 g, 2.48 mmol) was dissolved in ethyl acetate (10 mL), and 10% palladium on charcoal (100 mg, 0.13 mmol), pyridine (0.4 mL, 4.56 mmol), and acetic anhydride (0.35 mL, 3.72 mmol) were added to it. Reaction mixture was stirred at room temperature for 6 h under hydrogen gas environment. The reaction mixture was filtered through celite, and the solvent was concentrated. The white solid compound was purified by silica gel column chromatography using methylene chloride and methanol (30:1) solution to provide 0.62 g (65%) of pure compound as white solid: mp 177.5–178.4 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (dd, J = 15.3, 2.1 Hz, 1H), 7.05 (dd, J = 8.7, 2.7 Hz, 1H), 6.69 (t, J = 9.3 Hz, 1H), 6.24 (t, J = 5.7 Hz, 1H), 4.77 (m, 1H), 4.02 (t, J = 9.1 Hz, 1H), 3.91 (s, 4H), 3.69 (t, J = 6.6 Hz 1H), 3.62 (m, 2H), 3.33 (t, J = 7.4 Hz, 2H), 3.23 (d, J = 9.1, 2H), 2.81 (br s, 2H), 2.11 (dd, J = 19.2, 8.1 Hz, 2H), 2.01 (s, 3H), 1.84 (dd, J = 19.5, 3.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.25, 154.78, 151.54, 134.62, 134.49, 129.97, 129.84, 118.54, 117.21, 117.13, 114.36, 107.95, 107.60, 71.93, 64.75, 64.04, 56.36, 47.83, 41.01, 39.20, 23.09; IR (film): $\bar{\upsilon}$ = 3315, 2963, 1746, 1659, 1519, 1479, 1420, 1360, 1320/cm; HRMS (EI$^+$) calcd for $C_{21}H_{26}FN_3NaO_5$ (M^+): 442.1754, found: 442.1759.

(5R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(tetrahydro-1H-spiro[cyclopenta[c]pyrrole-5,2′-[1,3]dioxolane]-2(3H)-yl)phenyl)oxazolidin-2-one (9b)

Compound **8** (1 g, 2.48 mmol) was dissolved in vinyl acetate (10 mL) and then refluxed for 48 h. Reaction mixture was cooled down to room temperature. Distilled water was added, and then, the mixture was extracted with ethyl acetate. Organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The white solid compound was purified by silica gel column chromatography using methylene chloride and methanol (30:1) solution to provide 0.52 g (55%) of pure compound as white solid: mp 191.1–192.9 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, J = 0.8 Hz), 7.74 (d, J = 0.9 Hz), 7.20 (dd, J = 14.8, 2.5 Hz, 1H), 6.90 (dd, J = 8.8, 2.4 Hz, 1H), 6.68 (t, J = 9.2 Hz, 1H), 5.05 (m, 1H), 4.77 (dd, J = 4.2, 2.1 Hz, 2H), 4.11 (t, J = 9.1 Hz, 1H), 3.94 (s, 4H), 3.88 (t, J = 6.6 Hz 1H), 3.26 (t, J = 7.4 Hz, 2H), 3.19 (d, J = 9.0, 2H), 2.78 (br s, 2H), 2.11 (dd, J = 19.2, 8.1 Hz, 2H), 1.79

(dd, J = 19.5, 3.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.59, 134.99, 134.85, 134.47, 129.14, 129.09, 125.06, 118.52, 117.13, 117.06, 114.86, 108.34, 108.0, 70.39, 64.75, 64.04, 56.36, 52.10, 47.65, 41.01, 39.20; IR (film): $\bar{\upsilon}$ = 3111, 2959, 1733, 1523, 1485, 1420, 1359, 1321/cm; HRMS (EI$^+$) calcd for $C_{21}H_{24}FN_5NaO_4$ (M^+): 452.1710, found: 452.1709.

N-(((5S)-3-(3-Fluoro-4-(5-oxohexahydrocyclopenta[c]pyrrol-2(1H)-yl)phenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (10a)

Compound **9a** (1.0 g) was dissolved in acetone:water (3:1) solution. To the solution, *p*-toluene sulfonic acid was added, and the mixture was refluxed for 6 h. The solution was cooled to room temperature. Acetone was removed under reduced pressure. The aqueous layer was extracted by using saturated aqueous sodium bicarbonate solution and ethyl acetate. Organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The white solid compound was purified by silica gel column chromatography using methylene chloride and methanol (30:1) solution to provide 0.67 g (75%) of pure compound as white solid: mp 154.6–155.7 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.37 (dd, J = 15.3, 2.1 Hz, 1H), 7.05 (dd, J = 8.7, 2.7 Hz, 1H), 6.69 (t, J = 9.3 Hz, 1H), 6.24 (t, J = 5.7 Hz, 1H), 4.77 (m, 1H), 4.03 (t, J = 9.1 Hz, 1H), 3.68 (m, 5H), 3.30 (d, J = 17.4 Hz, 2H), 3.07 (br s, 2H), 2.60 (dd, J = 19.2, 8.1 Hz, 2H), 2.29 (dd, J = 19.5, 3.3 Hz, 2H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.06, 154.48, 153.71, 153.62, 133.91, 133.78, 125.19, 116.00, 115.92, 114.58, 108.19, 107.84, 71.85, 55.96, 55.90, 47.89, 43.33, 42.02, 38.47, 23.08; IR (film): $\bar{\upsilon}$ = 3301, 2826, 1737, 1659, 1520, 1481, 1420, 1363, 1321/cm; HRMS (EI$^+$) calcd for $C_{19}H_{22}FN_3NaO_4$ (M^+): 398.1492, found: 398.1491.

(5R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(5-oxohexahydrocyclopenta[c]pyrrol-2(1H)-yl)phenyl)oxazolidin-2-one (10b)

The compound was prepared according to compound **10a**. Pure compound was white solid, 0.88 g (98%): mp 145.7–146.9 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83 (d, J = 1.2 Hz, 1H), 7.79 (d, J = 1.2 Hz, 1H), 7.23 (dd, J = 15.3, 2.4 Hz, 1H), 6.93 (dd, J = 8.7, 2.7 Hz, 1H), 6.65 (t, J = 9.3 Hz, 1H), 5.07 (m, 1H), 4.81 (dd, J = 4.1, 1.4 Hz, 2H), 4.14 (t, J = 9.0 Hz, 1H), 3.91 (dd, J = 9.5, 6.1 Hz, 1H), 3.61 (m, 2H), 3.31 (m, 2H), 3.07 (m, 2H), 2.60 (dd, J = 19.5, 9.0 Hz, 2H), 2.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.56, 153.71, 153.62, 134.27, 134.15, 134.02, 128.70, 128.57, 125.19, 115.96, 115.88, 115.04, 108.45, 108.10, 70.51, 55.85, 55.78, 52.09, 47.67, 43.29, 38.40; IR (film): $\bar{\upsilon}$ = 3129, 2956, 1740, 1519, 1481, 1421, 1361, 1320/cm; HRMS (EI$^+$) calcd for $C_{19}H_{20}FN_5NaO_3$ (M^+): 408.1448, found: 408.1453.

N-(((5S)-3-(3-Fluoro-4-(5-(hydroxyimino)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)phenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (11a)

Compound **10a** (0.1 g, 0.27 mmol) was dissolved in ethanol and distilled water (2:1). To the solution, sodium bicarbonate (24.6 mg, 0.29 mmol) and hydroxylamine hydrochloride (27.8 mg, 0.4 mmol) were added, and the mixture was stirred at room temperature for 18 h. Ethanol was removed under reduced pressure, and the aqueous layer was extracted with methylene chloride. Organic layer was washed with brine, dried over magnesium sulfate, and filtered. The solvent was concentrated, and the compound was purified by column chromatography using methylene chloride and methanol (20:1) solution to provide 21.2 mg (20%) of pure compound as white solid: mp 180.4–182.0 °C (decomposed); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.40 (dd, J = 15.6, 2.7 Hz, 1H), 7.10 (dd, J = 8.4, 3.0 Hz, 1H), 6.79 (t, J = 9.3 Hz, 1H), 4.79 (m 1H), 4.12 (t, J = 9.0 Hz, 1H) 3.8 (dd, J = 9.0, 6.3 Hz, 1H), 3.58 (d, J = 4.8 Hz, 2H), 3.55 (m, 2H), 3.21 (m, 3H), 3.00–2.70 (m, 4H), 2.44 (m, 2H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.13, 165.62, 155.22, 153.71, 134.05, 125.19, 115.54, 114.88, 108.36, 108.01, 72.09, 55.73, 54.95, 41.95, 40.61, 35.01, 31.92, 22.42; IR (film): $\bar{\upsilon}$ = 3314, 2952, 1736, 1650, 1526, 1417, 1353, 1323/cm; HRMS (EI$^+$) calcd for $C_{19}H_{23}FN_4O_4$ (M^+): 413.1601, found: 413.1604.

(5R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(5-(hydroxyimino)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)phenyl)oxazolidin-2-one (11b)

The compound was prepared according to compound **11a**. Pure compound was white solid, 20 mg (22.8%): mp 186.8–187.7 °C (decomposed); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.36 (s, 1H), 8.18 (s, 1H), 7.78 (s, 1H), 7.32 (dd, J = 16.1, 2.8 Hz, 1H), 7.04 (dd, J = 8.9, 2.3 Hz, 1H), 6.75 (t, J = 9.4 Hz, 1H), 5.10 (m, 1H), 4.83 (d, J = 5.1 Hz, 2H), 4.18 (t, J = 9.0 Hz, 1H), 3.83 (dd, J = 9.3, 5.4 Hz, 1H), 3.47 (m, 2H), 3.10 (m, 2H), 2.83 (m, 2H), 2.63 (m, 2H), 2.27 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.23, 165.46, 154.32, 153.71, 134.43, 133.73, 125.46, 115.34, 108.36, 108.27, 70.61, 55.51, 54.72, 51.98, 49.23, 40.48, 34.76, 31.71; IR (film): $\bar{\upsilon}$ = 3150, 2850, 1738, 1566, 1519, 1483, 1365, 1330/cm; HRMS (EI$^+$) calcd for $C_{19}H_{21}FN_6NaO_3$ (M^+): 423.1557, found: 423.1555.

N-(((5S)-3-(3-Fluoro-4-(5-(methoxyimino)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)phenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (12a)

Compound **12a** was prepared according to compound **11a**. The reaction time was 48 h. Pure compound was white solid, 100 mg (92.8%): mp 153.4–154.4 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.39 (dd, J = 15.5, 2.9 Hz, 1H), 7.09 (dd, J = 8.7, 2.7 Hz, 1H), 6.77 (t, J = 9.3 Hz, 1H), 4.79 (m, 1H), 4.10 (t, J = 8.9 Hz, 1H), 3.83 (s, 3H), 3.78 (m, 1H), 3.57 (d, J = 5.4 Hz, 2H), 3.52 (m, 2H), 3.20 (m, 2H), 2.92 (m, 2H), 2.76 (m, 2H), 2.44 (m, 1H), 2.40 (m, 1H), 2.00 (s, 3H); ^{13}C NMR (CD_3OD, 75 MHz) δ 172.90, 165.95, 155.71, 153.84, 150.64, 134.19, 129.54, 115.95, 115.10, 108.11, 107.76, 72.30, 60.57, 55.97, 55.26, 55.20, 42.03, 40.94, 40.71, 35.14, 32.39, 21.31; IR (film): $\bar{\upsilon}$ = 3296, 2954, 2437, 1731, 1642, 1523, 1479, 1421, 1364, 1323/cm; HRMS (EI$^+$) calcd for $C_{20}H_{25}FN_4NaO_4$ (M^+): 427.1758, found: 427.1759.

(5R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(5-(methoxyimino)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)phenyl)oxazolidin-2-one (12b)

Compound **12b** was prepared according to compound **11a**. The reaction time was 48 h. Pure compound was white solid, 98.2 mg (92%): mp 172.6–174.7 °C; H NMR (DMSO-d_6, 300 MHz) δ 8.18 (d,

J = 0.9 Hz, 1H), 7.78 (d, J = 1.2 Hz, 1H), 7.32 (dd, J = 15.6, 2.4 Hz, 1H), 7.02 (dd, J = 8.7, 2.1 Hz, 1H), 6.75 (t, J = 9.3 Hz, 1H), 5.11 (m, 1H), 4.84 (d, J = 4.8 Hz, 2H), 4.19 (t, J = 9.3 Hz, 1H), 3.84 (dd, J = 9.3, 6.0 Hz, 1H), 3.75 (s, 3H), 3.47 (m, 2H), 3.11 (m, 2H), 2.85 (m, 2H), 2.66 (m, 2H), 2.32 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.15, 154.28, 153.36, 150.18, 134.33, 129.62, 116.70, 115.64, 108.23, 107.90, 71.42, 61.61, 56.61, 56.34, 55.65, 52.50, 48.01, 35.51, 33.13; IR (film): $\bar{\upsilon}$ = 3104, 2955, 2109, 1732, 1524, 1480, 1449, 1422, 1365, 1321/cm; HRMS (EI$^+$) calcd for $C_{20}H_{23}FN_6NaO_3$ (M^+): 437.1713, found: 437.1709.

N-(((5S)-3-(4-(5-(Cyanomethylene) hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-3-fluorophenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (13a)

Potassium *t*-butoxide (29.9 mg, 0.27 mmol) was dissolved in THF. The temperature of the solution was lowered to −78 °C. Diethyl cyanomethyl phosphonate (233.9 mg, 0.33 mmol) was added to the solution slowly, and the mixture was stirred at the same temperature for 1 h. The solution of compound **10a** (0.1 g, 0.27 mmol) in THF was added to the reaction solution slowly. Reaction temperature was increased slowly to room temperature. Solvent was removed under reduced pressure, and the residue was extracted with methylene chloride. Organic layer was washed with brine, dried in magnesium sulfate, and filtered. The solvent was concentrated, and the compound was purified by column chromatography using ethyl acetate and methanol (40:1) solution to provide 88.1 mg (83%) of pure compound as white solid: mp 90.8–91.6 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (dd, J = 15.0, 2.4 Hz, 1H), 7.06 (t, J = 6.0 Hz, 1H), 6.97 (dd, J = 8.9, 2.3 Hz, 1H), 6.61 (t, J = 9.0 Hz, 1H) 5.24 (t, J = 2.0 Hz, 1H), 4.74 (m, 1H), 3.97 (t, J = 9.0 Hz, 1H), 3.72 (dd, J = 8.7, 6.6 Hz, 1H), 3.6 (t, J = 5.3 Hz, 2H), 3.45 (m, 1H), 3.43 (s, 1H), 3.14 (m, 2H), 2.90 (m, 3H). 2.78 (m, 1H), 2.56 (m, 1H), 2.46 (m, 1H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.62, 171.79, 155.01, 154.10, 150.89, 134.12, 133.98, 129.77, 129.63, 117.30, 116.36, 116.29, 114.83, 108.33, 107.99, 91.97, 72.23, 56.11, 56.05, 55.97, 48.12, 42.21, 42.14, 41.86, 39.77, 38.85, 23.19; IR (film): $\bar{\upsilon}$ = 3313, 2955, 2215, 1746, 1659, 1519, 1480, 1420, 1365, 1320/cm; HRMS (EI$^+$) calcd for $C_{21}H_{23}FN_4NaO_3$ (M^+): 421.1652, found: 421.1646.

2-(2-(4-((R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-2-oxo-oxazolidin-3-yl)-2-fluorophenyl) hexahydrocyclopenta[c]pyrrol-5(1H)-ylidene)acetonitrile (13b)

Compound **13b** was prepared according to compound **13a**. Pure compound was white solid, 84.8 mg (80%): mp 72.9–74.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83 (s, 1H), 7.77 (s, 1H), 7.22 (dd, J = 14.9, 1.6 Hz, 1H) 6.92 (dd, J = 8.7, 2.4 Hz, 1H), 6.63 (t, J = 9.3 Hz, 1H), 5.28 (t, 1H), 5.06 (m, 1H), 4.81 (dd, J = 4.0, 1.4 Hz, 2H), 4.13 (t, J = 9.0 Hz, 1H), 3.89 (dd, J = 9.4, 6.1 Hz, 1H), 3.50(m, 2H), 3.19 (m, 2H), 2.80 (m, 2H), 2.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.13, 153.58, 150.89, 134.57, 129.77, 125.08, 117.00, 116.09, 116.01, 115.05, 108.58, 108.23, 91.92, 70.34, 55.68, 52.10, 47.63, 42.06, 41.65, 39.50, 38.58; IR (film): $\bar{\upsilon}$ = 3129, 2955, 2214, 1750, 1519, 1480, 1420, 1362, 1321/cm; HRMS (EI$^+$) calcd for $C_{21}H_{21}FN_6NaO_2$ (M^+): 431.1608, found: 431.1606.

N-(((5S)-3-(4-(5-(Cyanomethyl)-3,3a,6,6a-tetrahydrocyclopenta[c]pyrrol-2(1H)-yl)-3-fluorophenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (14a)

Compound **10a** (0.1 g, 0.27 mmol) and ammonium acetate (2 mg, 0.027 mmol) was dissolved in benzene, and cyanoacetic acid (22.6 mg, 0.27 mmol) was added. The apparatus was fitted with Dean-stark device, and the mixture was refluxed for 20 h. Temperature was cooled down to room temperature, and the solvent was removed under reduced pressure. The residue was extracted with methylene chloride. Organic layer was washed with brine, dried in magnesium sulfate, and filtered. The solvent was concentrated, and the compound was purified by column chromatography using ethyl acetate and methanol (40:1) solution to provide 31 mg (30%) of pure compound as white solid: mp 167.2–168.3 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.10 (d, J = 1.2 Hz, 1H), 7.79 (d, J = 1.2 Hz, 1H), 7.30 (dd, J = 15.0, 2.4 Hz, 1H), 7.02 (dd, J = 9.0, 2.7 Hz, 1H), 6.84 (t, J = 9.0 Hz, 1H), 5.69 (d, J = 2.4 Hz, 1H), 5.14 (m, 1H), 4.89 (m, 2H), 4.25 (t, J = 9.3 Hz, 1H), 3.96 (dd, J = 9.3, 5.4 Hz, 1H), 3.51–3.08 (m, 6H), 2.78 (dd, J = 16.5, 8.1 Hz, 1H), 2.31 (dd, J = 16.8, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.02, 154.39, 153.10, 134.12, 132.85, 131.60, 129.63, 117.23, 114.24, 107.87, 107.52, 71.81, 57.86, 54.95, 49.36, 47.79, 42.03, 41.61, 40.16, 23.19, 19.68; IR (film): $\bar{\upsilon}$ = 3292, 2920, 1746, 1658, 1518, 1478, 1415, 1365, 1319/cm; HRMS (EI$^+$) calcd for $C_{21}H_{23}FN_4NaO_3$ (M^+): 421.1652, found: 421.1647.

2-(2-(4-((R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-2-oxo-oxazolidin-3-yl)-2-fluorophenyl)-1,2,3,3a,4,6a-hexahydrocyclopenta[c]pyrrol-5-yl)acetonitrile (14b)

Compound **14b** was prepared according to compound **14a**. Pure compound was white solid, 37 mg (35%): mp 99.0–100.6 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.10 (d, J = 1.2 Hz, 1H), 7.79 (d, J = 1.2 Hz, 1H), 7.30 (dd, J = 15.0, 2.4 Hz, 1H), 7.02 (dd, J = 9.0, 2.7, 1H), 6.84 (t, J = 9.0 Hz, 1H), 5.69 (d, J = 2.4 Hz, 1H), 5.14 (m, 1H), 4.90 (m, 2H), 4.25 (t, J = 9.3 Hz, 1H), 3.96 (dd, J = 9.3, 5.4 Hz, 1H), 3.49 (m, 1H), 3.39–3.08 (m, 6H), 2.78 (dd, J = 16.5, 8.1 Hz, 1H), 2.32 (d, J = 16.8, 1.5 Hz, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 156.09, 152.88, 135.88, 135.75, 135.23, 134.58, 131.81, 131.68, 131.54, 129.51, 127.25, 118.77, 118.57, 118.50, 116.27, 109.21, 108.86, 72.57, 59.09, 59.03, 56.41, 56.34, 53.47, 50.74, 42.42, 41.46; IR (film): $\bar{\upsilon}$ = 3129, 2921, 1750, 1519, 1478, 1416, 1361, 1319/cm; HRMS (EI$^+$) calcd for $C_{21}H_{21}FN_6NaO_2$ (M^+): 431.1608, found: 431.1601.

N-(((5S)-3-(4-(5-Cyano-3,3a,6,6a-tetrahydrocyclopenta[c]pyrrol-2(1H)-yl)-3-fluorophenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (15a)

Compound **10a** (0.3 mg, 0.80 mmol) and indium bromide (30 mg, 0.085 mmol) was dissolved in methylene chloride. The temperature was lowered to 0 °C. Trimethylsilyl cyanide (0.36 g, 3.6 mmol) was added dropwise to the reaction mixture and stirred for 20 h at room temperature. Mixture was washed with

saturated sodium bicarbonate solution, and the aqueous layer was extracted with methylene chloride. Organic layer was washed with brine, dried over magnesium sulfate, and filtered. The solvent was concentrated, and the compound was purified by column chromatography using ethyl acetate and methanol (40:1) solution.

The solid compound was dissolved in formic acid and was stirred for 24 h at room temperature. Formic acid was removed under reduced pressure. The residue was dissolved in pyridine, and the temperature of the solution was lowered to 0 °C. Phosphorus oxychloride (0.17 g, 1.1 mmol) was added to it slowly, and the reaction mixture was stirred at room temperature for 30 h. The solvent was removed under reduced pressure. Compound was extracted with methylene chloride. Organic layer was washed with brine, dried over magnesium sulfate, and filtered. The solvent was concentrated, and the compound was purified by column chromatography using methylene chloride and methanol (30:1) solution to provide 0.184 g (60%) of pure compound as white solid: mp 156.8–159.1 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (dd, J = 15.1, 2.6 Hz, 1H), 7.05 (dd, J = 8.7, 1.8 Hz, 1H), 6.72 (t, J = 9.3 Hz, 1H), 6.52 (t, J = 9.1 Hz, 1H), 4.77 (m, 1H), 4.02 (t, J = 8.7 Hz, 1H), 3.77 (t, J = 4.3 Hz, 1H), 3.63 (m, 3H), 3.38 (m, 3H), 3.22 (m, 2H), 3.13 (m, 1H), 2.59 (dd, J = 16.2, 1.8 Hz, 1H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.50, 162.31, 155.21, 154.76, 151.96, 149.95, 133.90, 131.15, 117.62, 116.43, 115.10, 114.49, 108.11, 107.77, 72.19, 57.66, 54.25, 54.33, 50.73, 47.99, 42.20, 41.32, 39.63, 23.32; IR (film): $\bar{\upsilon}$ = 3311, 2925, 1738, 1659, 1520, 1481, 1420, 1365, 1321/cm; HRMS (EI^+) calcd for $C_{20}H_{21}FN_4NaO_3$ (M^+): 407.1495, found: 407.1491.

2-(4-((R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-2-oxo-oxazolidin-3-yl)-2-fluorophenyl)-1,2,3,3a,4,6a-hexahydrocyclopenta[c]pyrrole-5-carbonitrile (15b)

Compound **15b** was prepared according to compound **15a**. Pure compound was white solid, 0.156 g (51%): mp 157.1–157.8 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 (d, J = 1.2 Hz, 1H), 7.25 (dd, J = 14.9, 2.2 Hz, 1H), 6.94 (dd, J = 8.9, 2.9 Hz, 1H), 6.69 (t, J = 9.1 Hz, 1H), 5.06 (m, 1H), 4.80 (m, 2H), 4.13 (t, J = 9.0 Hz, 1H), 3.89 (dd, J = 9.4, 6.1 Hz, 1H), 3.39 (m, 1H), 3.21 (m, 3H), 3.21 (m, 2H), 3.12 (m, 1H), 2.58 (dd, J = 16.5, 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.07, 153.78, 151.83, 149.95, 134.73, 130.38, 125.36, 117.61, 117.53, 116.43, 115.09, 114.97, 114.92, 108.48, 108.14, 70.64, 57.65, 57.60, 54.27, 54.19, 52.30, 50.72, 47.76, 41.31, 39.62; IR (film): $\bar{\upsilon}$ = 3138, 2931, 1751, 1570, 1517, 1436, 1361, 1322/cm; HRMS (EI^+) calcd for $C_{20}H_{19}FN_6NaO_2$ (M^+): 417.1451, found: 417.1452.

Biological assay

Minimal inhibitory concentration (MIC) determination

Minimal inhibitory concentrations were determined by twofold 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.

Minimal inhibitory concentration determination of *Mycobacterium tuberculosis*

The MICs of compounds against *Mycobacterium tuberculosis* (Mtb) H_{37}Rv was determined by the microplate Alamar Blue Assay (32).

Determination of CYP, microsomal stability, and hERG profile of the compound 10a

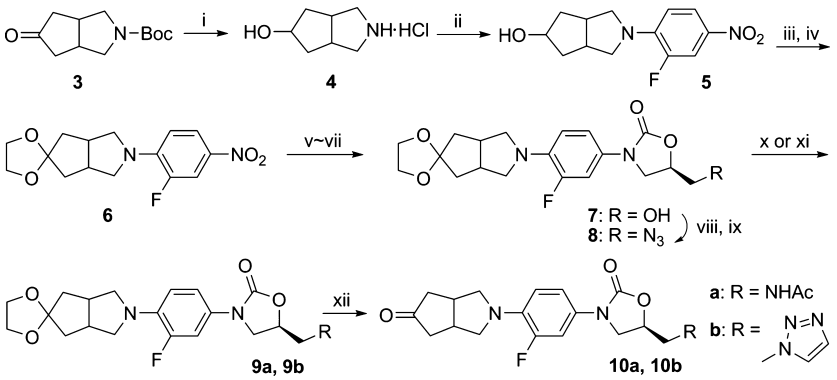
CYP450 remaining test was conducted using Vivid® CYP450 Screening Kits Protocol (Invitrogen, Carlsbad, CA, USA), and hERG (human ether-a-go-go-related gene) potassium channel assay for cardiac toxicity test was conducted using an automated patch-clamp device, NPC-16 Patchliner (Nanion Technologies, Munchen, Germany) (33), and human hepatic microsomal stability test was conducted by automated HPLC/Mass Spectrometry System (34).

Result and Discussion

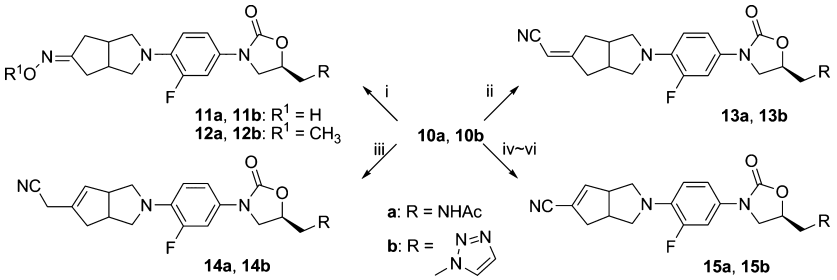
Synthesis

The synthesis of oxazolidinone derivative **10a**, in which morpholine C-ring of linezolid was replaced with azabicyclic ketone, is shown in Scheme 1. Also, the preparation of its triazole analog **10b** additionally replaced acetamide by triazole at the C-5 position of oxazolidinone **10a** is described. Reduction in *tert*-butyl 3-azabicyclo[3.3.0]octane-7-one 3-carboxylate **3**, purchased from Hanchem (Daejeon, South Korea), with sodium borohydride, and subsequent deprotection of *tert*-butyloxycarbonyl (Boc) group by concentrate hydrochloric acid gave 3-azabicyclo[3.3.0]octane-7-one hydrochloride **4**. S_NAr reaction of 3,4-difluoronitrobenzene with **4** gave **5** in good overall yield. Swern oxidation of the alcohol **5** and followed by the protection of the corresponding ketone with ethylene glycol afforded the ketal **6**. On the other hand, attempts to prepare the ketone intermediate without additional reduction and oxidation steps by S_NAr reaction with 3-azabicyclo[3.3.0]octane-7-one, prepared from starting material **3** by *N*-Boc deprotection, were unsuccessful.

The preparation of oxazolidinone **7** from **6** was accomplished by established procedure (35). Carbamate intermediate derived from nitro reduction, and successive Cbz protection was deprotonated with *n*-BuLi and followed by reaction with (*R*)-glycidyl butyrate to give the oxazolidinone alcohol **7**. Alcohol **7** was converted into the corresponding azide **8** by the standard procedure in high yield. Hydrogenation of azide **8** in the presence of acetic anhydride and pyridine to provide the acetamide **9a** in 65% yield. 1,2,3-Triazole derivative **9b** was also prepared by cycloaddition of azide **8** with vinyl acetate and spontaneous elimination. Deprotection of ketal **9a**



Scheme 1: (i) $NaBH_4$, MeOH, 0 °C, 1 h, then conc. HCl, rt, 1 h; (ii) DIEA, 3,4-difluoronitrobenzene, CH_3CN, reflux, 6 h, 70% in two steps; (iii) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, −78 °C, 6 h, 94%; (iv) $HOCH_2CH_2OH$, *p*-TsOH, benzene, reflux, 1 h, 80%; (v) Pd/C, H_2, EtOAc, 10 h, 95%; (vi) CbzCl, sat. $NaHCO_3$, THF, 0 °C to rt, 12 h; (vii) *n*-BuLi, (*R*)-glycidyl butyrate, THF, −78 °C, 12 h, 78% in two steps; (viii) MsCl, TEA, CH_2Cl_2, 0 °C, 4 h; (ix) NaN_3, DMF, 90 °C, 4 h, 90% in two steps; (x) Pd/C, H_2, Ac_2O, pyridine, EtOAc, rt, 6 h, 65% (**9a**); (xi) vinyl acetate, reflux, 48 h, 55% (**9b**); (xii) *p*-TsOH, acetone/water (3:1), 6 h, 75% (**10a**), 98% (**10b**).



Scheme 2: (i) $HONH_2$·HCl or CH_3ONH_2·HCl, $NaHCO_3$, H_2O, rt, 18–48 h, 20% (**11a**), 23% (**11b**), 99% (**12a**), 98% (**12b**); (ii) *t*-BuOK, $PO(OEt)_2CH_2CN$, THF, −78 °C to rt, 83% (**13a**), 80% (**13b**); (iii) NH_4OAc, $CH_2(CN)CO_2H$, benzene, reflux, 20 h, 30% (**14a**), 35% (**14b**); (iv) $InBr_3$, TMSCN, CH_2Cl_2, 0 °C to rt, 20 h; (v) HCO_2H, rt, 24 h; (vi) $POCl_3$, pyridine, 0 °C to rt, 30 h, 60% (**15a**), 51% (**15b**) in three steps.

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

Compound	*S.a.*[a]	*C.s.*[b]	*E.f.*[c]	*E.f.*[d]	*S.p*[e]	*S.p.*[f]	*S.a.*[g]	*H.i.*[h]
10a	1.56	1.56	0.78	0.78	0.39	0.39	0.78	0.39
11a	1.56	1.56	0.78	0.78	0.39	0.39	0.78	0.78
12a	3.12	3.12	1.56	1.56	0.78	0.78	1.56	1.56
13a	3.12	3.12	1.56	0.78	0.78	0.78	1.56	0.78
14a	3.12	3.12	1.56	1.56	0.78	0.78	1.56	1.56
15a	3.12	3.12	3.12	1.56	0.78	0.78	1.56	0.39
10b	3.12	3.12	1.56	1.56	0.78	0.39	1.56	1.56
11b	6.25	6.25	6.25	3.12	1.56	0.78	3.12	3.12
12b	6.25	6.25	1.56	1.56	0.39	0.19	0.78	0.39
13b	1.56	1.56	1.56	1.56	0.78	0.39	0.78	0.39
14b	6.25	6.25	6.25	6.25	3.12	1.56	3.12	1.56
15b	3.12	3.12	3.12	3.12	1.56	0.78	1.56	0.78
Linezolid	3.12	3.12	1.56	1.56	0.78	0.78	1.56	0.78

[a]Methicillin-susceptible *Staphylococcus areus* 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* ATCC 8736.
[g]*Streptococcus agalactiae* ATCC 2901.
[h]*Hameophilus influenza.*

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

Compound	*S.a.*[a]	*C.s.*[b]	*E.f.*[c]	*E.f.*[d]	*S.p.*[e]	*M.t.*[f]
10a	1.56	1.56	0.78	0.78	0.39	0.5
11a	1.56	1.56	0.78	0.78	0.39	0.5
12a	3.12	3.12	1.56	1.56	0.78	1
13a	3.12	3.12	1.56	1.56	0.78	1
14a	1.56	3.12	3.12	1.56	0.78	1
15a	1.56	3.12	3.12	1.56	0.39	0.5
10b	3.12	3.12	1.56	3.12	0.39	0.5
11b	6.25	6.25	6.25	6.25	0.78	–
12b	6.25	6.25	3.12	1.56	0.19	1
13b	0.78	1.56	3.12	1.56	0.39	1
14b	1.56	6.25	6.25	6.25	1.56	2
15b	1.56	3.12	3.12	3.12	0.78	1
Linezolid	3.12	3.12	3.12	1.56	0.78	1

[a]Methicillin-resistant *Staphylococcus areus.*
[b]Methicillin-resistant *Coagulase negative Staphylococi.*
[c]Vancomycin-resistant *Enterococcus faecalis.*
[d]Vancomycin-resistant *Enterococcus faecium.*
[e]Penicillin-resistant *Streptococcus pneumonia.*
[f]*Mycobacterium tuberculosis* $H_{37}Rv$.

Table 3: The inhibitory effect of compound **10b** on specific CYP enzyme in cDNA-expressed CYP microsomes, and its stability in human hepatic microsome, and hERG channel activity

	% Control of CYP-450 (at 10 μM)[a]					
Compound	1A2	2D6	2C9	3A4	Microsomal stability (% remains after 30 min)	hERG (IC_{50}, μM)
10b	94.9 ± 13.4	107.7 ± 1.3	73.7 ± 34.9	105.6 ± 6.0	83.82	80.5 ± 6.0
Positive control	2.3[b]	11.1[c]	−3.5[d]	2.3[e]		

[a]Values are remained % activities and the mean ± SD of triplicate determinations.
[b]α-naphthoflavone.
[c]Quinidine.
[d]Sulfaphenazole.
[e]Ketoconazole.

and **9b** by using *p*-toluene sulfonic acid catalyst in acetone and water mixture (3:1) provided 3-azabicyclo[3.3.0]octane-7-one derivative **10a** and **10b** having acetamide and 1,2,3-triazole moiety at the C-5 position of the oxazolidinone, respectively.

Then, azabicyclic ketone intermediates **10a** and **10b** were converted into a variety of new oxazolidinone derivatives **11**–**15** bearing acetamide or 1,2,3-triazole ring moiety at the A-ring C-5 position as shown in Scheme 2. The preparation of hydroxime (**11a** and **11b**) and methoxime (**12a** and **12b**) analogs was achieved by treating the ketones **10a** and **10b** with hydroxylamine hydrochloride and methoxyamine hydrochloride, respectively, in the presence of saturated aqueous sodium carbonate solution. *Exo*-cyanomethylene compounds **13a** and **13b** were prepared from the ketones by employing Horner–Wadsworth–Emmons reaction with diethyl cyanomethyl phosphonate and *tert*-butoxide. Knoevenagel condensation and decarboxylation of ketones **10a** and **10b** with cyanoacetic acid in the presence of ammonium acetate provided cyanomethyl substituted hexahydrocyclopenta[c]pyrrole compounds **14a** and **14b**. α,β-Unsaturated nitriles **15a** and **15b** with one-carbon homologations were also prepared by $InBr_3$-catalyzed formation of trimethylsilyl cyanohydrin followed by dehydration with $POCl_3$.

Biological activity

This series of oxazolidinone antimicrobial compounds prepared above was screened against panel of susceptible and resistant 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 compounds showed good activity against Gram-positive and Gram-negative bacteria. Among C-5 acetamide oxazolidinones **10a**–**15a**, ketone and oxime analogs of **10a** and **11a** showed twofold higher activity against most of the tested strains compared to linezolid, and particularly fourfold higher activity against VRE as shown in Table 2. The antibacterial activities of *O*-methyloxime **12a** and cyano compounds **13a**–**15a** were similar to linezolid. Acetamide analogs showed potent activity against resistant strains such as *S. areus* and *E. faecalis*.

Among C-5 triazole oxazolidinones **10b**–**15b**, cyanomethylene **13b** demonstrated highest activity. Thus, **13b** resulted in comparable or twofold higher activity against most of the strains, and notably, fourfold higher activity against MRSA than linezolid. Among the C-5 triazole derivatives, ketone **10b** showed similar activity, but oximes, **11b** and **12b**, and cyanomethyl compound **14b** lost the activity slightly. *O*-Methyloxime **12b** especially exhibited highly potent activity against *S. pneumonia* and *S. pyogenes*. In general, the replacement of acetamide with triazole at the C-5 position of 3-azabicyclic oxazolidinone series led to less potent compounds. Ketone **10a** and nitrile **15a** among C-5 acetamide analogs, and *O*-Methyloxime **12b** and cyanomethylene **13b** among triazole analogs showed higher activity against Gram-negative strain *H. influenza* than linezolid.

Furthermore, the new oxazolidinone derivatives possessing 3-azabicyclo[3.3.0]octanyl moiety were evaluated for their antibacterial activity against *Mycobacterium tuberculosis* $H_{37}Rv$. Most of the compounds examined, except **14b**, showed comparable or higher activity than linezolid against *Mycobacterium tuberculosis* as shown in Table 2.

CYP, microsomal stability, and hERG profile of the compound 10b

We selected the compound **10b** from more active compounds than linezolid against *M. tuberculosis* and evaluated for its CYP profile, microsomal stability, and hERG inhibition as shown in Table 3. The compound **10b** was found to be stable in human microsome and to have no-CYP-related liabilities, involved in drug metabolism and drug interaction. The compound exhibits remaining activities of minimum 73.6%, maximum 105.6% in the activity test for four isozymes of CYP450 (1A2, 2D6, 2C9, 3A4), indicating that it is not affected by CYP450 compared to positive control up to 10 μM concentrations. The compound **10b** also showed low activity against hERG channel, which plays a crucial role on cardiac side effects of drugs.

Conclusion

A new series of oxazolidinones having 3-azabicyclo[3.3.0]octanyl moiety have been synthesized, and their *in vitro* antibacterial activities were evaluated against Gram-positive, Gram-negative, and *M. tuber-*

culosis including resistant strains of *Staphylococi, Streptococci,* and *Enterococci*. Some of these analogs exhibited potent *in vitro* antibacterial activities comparable or superior to linezolid.

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