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Structure-Antibacterial Activity Relationships of *N*-Substituted-(D-/L-Alaninyl) 1*H*-1,2,3-Triazolylmethyl Oxazolidinones

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Abstract: Bacterial resistance towards the existing class of antibacterial drugs continues to increase, posing a significant threat to the clinical usefulness of these drugs. These increasing and alarming rates of antibacterial resistance development and the decline in the number of new antibacterial drugs' approval continue to serve as a major impetus for research into the discovery and development of new antibacterial agents. We synthesized a series of D-/L-alaninyl substituted triazolyl oxazolidinone derivatives and evaluated their antibacterial activity against selected standard Gram-positive and Gram-negative bacterial strains. Overall, the compounds showed moderate to strong antibacterial activity. Compounds **9d** and **10d** (D- and L-alaninyl derivatives bearing the 3,5-dinitrobenzoyl substituent), **10e** (L-alaninyl derivative bearing the 5-nitrofurancarbonyl group) and **9f** and **10f** (D- and L-alaninyl derivatives bearing the 5-nitrothiophene carbonyl moiety) demonstrated antibacterial activity (MIC: 2 µg/mL) against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis* and *Moraxella catarrhalis* standard bacterial strains. No significant differences were noticeable between the antibacterial activity of the D- and L-alaninyl derivatives as a result of the stereochemistry of the compounds.

Keywords: antibacterial; linezolid; SARs; alaninyl-oxazolidinone; triazolyl-oxazolidinone

1. Introduction

Antibacterial agents are among the successful class of drugs that are effective in treating human infectious diseases with positive clinical outcomes. However, a persistent and significant clinical problem in the fight against bacterial infections is the ever-increasing emergence of bacterial resistance to major classes of antibacterial agents [1–3]. Multiply-resistant Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), methicillin-resistant *Staphylococcus epidermidis* (MRSE), vancomycin-resistant enterococci (VRE) and multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) are among the troublesome pathogens within the healthcare and some community settings worldwide [4–7]. The emergence of antibacterial resistance continues to serve as the impetus for research into novel antibacterial drug discovery and development of more potent and safer antibacterial agents.

Oxazolidinones exemplified by linezolid (**1**, Figure 1) and more recently tedizolid phosphate (**2a**, Figure 1), which is a pro-drug of the active form tedizolid (**2b**, Figure 1), represent derivatives of this class of compounds with potent activity against multidrug-resistant Gram-positive pathogenic bacterial strains [8–10]. Linezolid is characterized by excellent oral bioavailability, tissue and organ

penetration, with demonstrated effectiveness against multi-drug-resistant Gram-positive bacterial pathogens, including MRSA, PRSP and VRE. Furthermore, it is also active against MDR-TB; hence, it may be useful for treating multi-drug-resistant tuberculosis [8,9,11].

Oxazolidinones inhibit bacterial protein biosynthesis by binding to sites on the bacterial ribosomes, thus preventing the formation of a functional 70S initiation complex [11–13]. More detailed studies have investigated the orientation of the oxazolidinone class of compound on the ribosome [14] and Duffy et al. [15] have shown that linezolid binds to the A-site of the 50S subunit, thus preventing binding of the aminoacyl-tRNA.

Several investigators have engaged in structural modifications around the phenyl-oxazolidinone pharmacophore with the hope of discovering newer derivatives with a broader spectrum of activity, to improve potency and to reduce side-effects compared with linezolid. However, linezolid is plagued with a number of undesirable side effects, such as lactic acidosis, myelosuppression, neuropathies and thrombocytopenia during prolonged administration. Furthermore, treatment with linezolid may lead to unfavorable interactions with adrenergic and serotonergic agents, and this may result in severe hypertensive crisis in patients [12,16,17]. Serotonin toxicity has been associated with its inhibitory effects on monoamine oxidases (MAO), due to the structural similarity to the MAO inhibitor toloxatone, which also contains the oxazolidinone moiety. The triazolyl derivatives (**3**, Figure 1) [18] and the reverse C5 amide derivative of linezolid of a general structure (**4**, Figure 1) have been shown to exhibit strong antibacterial activity and lower monoamine oxidase inhibition [19]. In addition, Compound **4** also exhibited reduced myelotoxicity in rodents compared to linezolid [20].

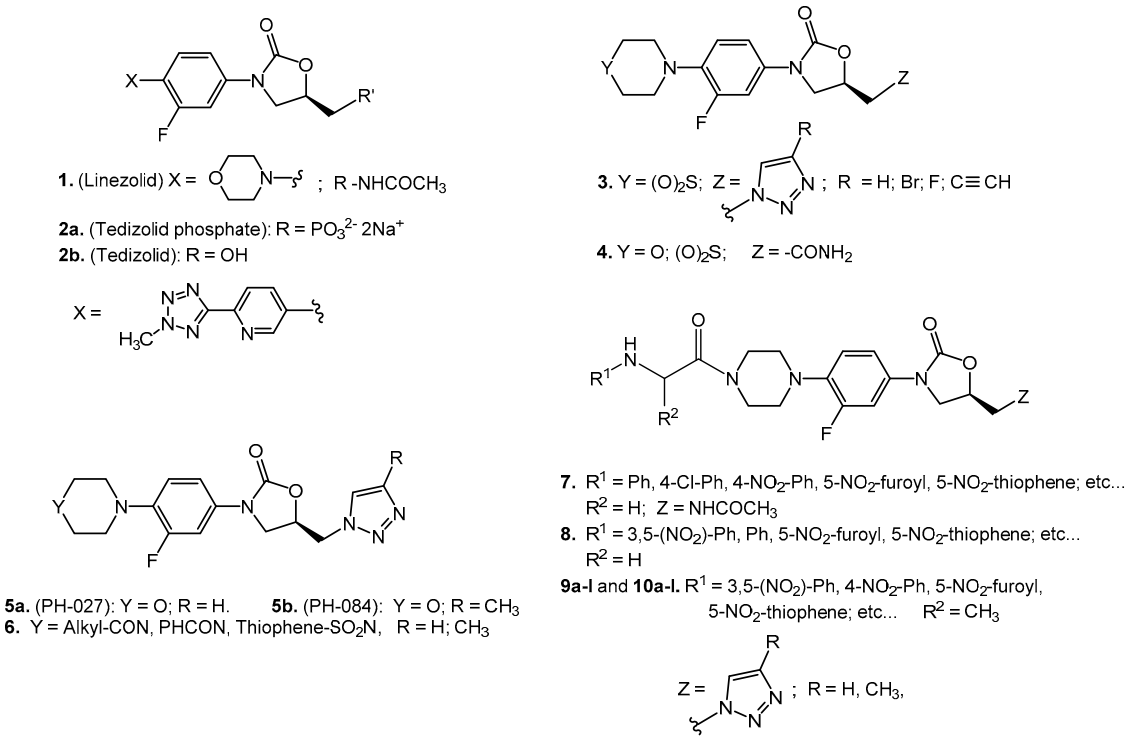


Figure 1. Chemical structure of oxazolidinone antibacterial agents.

Studies from our laboratory and those of others have reported the synthesis of several triazolylmethyl oxazolidinones containing acyl or aroyl-substituted piperazine of the general structures of **5**–**8** (Figure 1) with potent activity that is comparable or superior to linezolid against Gram-positive bacterial strains including MRSA, VRE, PRSP and MDR-TB [18,21–27]. Moreover, other studies have also demonstrated that the incorporation of *N*-substituted-glycinyl moieties on the 4-*N*-piperazine position resulted in oxazolidinone derivatives that would fit a potential pocket identified at the bacterial ribosomal receptor binding site [27]. The most potent oxazolidinones in

the glycinyl series contain the *N*-nitroaroyl substituents on the glycine nitrogen [23]; in particular, the 3,5-dinitrobenzoyl and the 5-nitrofuroyl derivatives demonstrated MIC values in the range of 0.06–16 μg/mL against Gram-positive bacterial clinical isolates. On the basis of the potent antibacterial activities of the *N*-substituted glycinyl-triazolyl oxazolidinones, we decided to investigate the effects of incorporating D- and L-alanine as spacers instead of the glycine on the antibacterial activity with focus on the nitro- and amino-substituted aroyl and heteroaroyl derivatives. We hereby report the synthesis and qualitative structure-antibacterial activity relationships of new *N*-substituted-D- and L-alaninyl-triazolyl oxazolidinone derivatives of the general structures **9a–l** and **10a–l**, respectively.

2. Materials and Methods.

2.1. Characterization

Purification of compounds was performed with silica gel column chromatography using silica gel (Kieselgel 60, 70–230 mesh; Merck, (formerly Sigma-Aldrich), Germany, and TLC was conducted on 0.25-mm pre-coated silica gel plates ($60F_{254}$, Merck). Melting points were determined on a Stuart Scientific melting point apparatus (SMP1) (Stuart, Stone, UK) and were uncorrected. Mass spectra were recorded on a Thermo Scientific DFS Gas Chromatography/Mass Spectrometer (DFS GC-MS) (Thermo Fisher Scientific, Bremen, Germany) and Waters QToF high resolution/Mass Spectrometer (LC MS/MS high resolution) (Waters Corporation, Milford, MA, USA). The ^{1}H-NMR and ^{13}C-NMR spectra in DMSO-d_6 using solvent peaks as reference signals were recorded on Bruker DPX 400 MHz and Bruker Avance II 600 NMR spectrometers. Chemical shifts of protons and carbons were reported in parts per million (ppm) downfield and upfield from solvent DMSO-d_6 (δ = 2.5; 39.7) peaks as references. Infrared (IR) spectra of solids (KBr) were recorded on an FT-IR (Jasco FT/IR-6300) (JASCO, Tokyo, Japan) spectrometer. The Elemental analyses were performed on an Elementar Vario Micro Cube CHN Analyzer (Elementar, Langenselbold, Germany). Elemental analyses (C, H, N) were used to confirm the purity of all newly synthesized compounds (>95%) and indicated by the symbols of the elements within ±0.40% of the theoretical values. Analyses were performed by The General Facilities Science (GF-S), Faculty of Science, Kuwait University, Kuwait.

2.2. Syntheses

2.2.1. Preparation of (*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-3-(4-(4-(*D*-alanyl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one 2,2,2-trifluoroacetate **16a**

A solution of (*tert*-butoxycarbonyl)-*D*-alanine (1.027 gm, 5.430 mmol) in anhydrous DCM (35 mL) was treated with *N*, *N*′-dicyclohexylcarbodiimide (1.40 gm, 6.787 mmol) and 1-hydroxybenzotriazole (0.917 gm, 6.787 mmol), and the mixture was stirred under a nitrogen atmosphere for 2 h. The reaction mixture was filtered directly into a solution of the trifluoro acetate salt, **14** (2.50 gm, 5.430 mmol) and TEA (2.19 mL, 15.747 mmol) in anhydrous CH_3CN (40 mL) at 0 °C. The reaction mixture was stirred overnight and concentrated on a rotavap under vacuum to give a viscous oil, which was dissolved in DCM (40 mL), and the precipitated urea was filtered off. The DCM layer was washed with water, 10% Na_2CO_3 solution, brine, dried (Na_2SO_4), filtered and concentrated under vacuum to give a brown foam, which was triturated with ether to yield a cream-colored crude solid. This solid was recrystallized from ethyl acetate to afford the carbamate **15a** as an off-white solid, 2.07 gm, yield: 74%; mp.: 214–216 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 8.18 (d, 1H, *J* = 0.7 Hz, triazole H), 7.77 (d, 1H, *J* = 0.8 Hz, triazole H), 7.43 (dd, 1H *J* = 2.5 Hz, 14.7 Hz, phenyl H), 7.14 (dd, 1H, *J* = 2.3 Hz, 8.8 Hz, phenyl H), 7.07 (t, 1H, *J* = 9.3 Hz, phenyl H), 6.96 (d, 1H, NH, *J* = 7.9 Hz, exchangeable with D_2O), 5.12-5.14 (m, 1H, oxazolidinone H), 4.83 (d, 2H, *J* = 5.1 Hz, CH_2), 4.45–4.50 (m, 1H, D-alanine CH), 4.21 (t, 1H, *J* = 9.2 Hz, oxazolidione H), 3.87 (q, 1H, *J* = 5.8 Hz, 9.3 Hz, oxazolidinone H), 3.59–3.66 (br. d, 4H, piperazine H), 2.96 (br. d, 4H, piperazine H), 1.36–1.38 (br., 9H, $C(CH_3)_3$), 1.17 (d, 3H, *J* = 6.9 Hz, CH_3)). ^{13}C-NMR (DMSO-d_6): δ 171.2, 155.8, 155.3, 154.2, 153.9, 135.8, 133.9, 133.8, 133.7, 126.3, 120.2, 120.2, 114.8, 114.7, 107.3, 107.1, 78.4, 71.3, 52.2, 51.1, 50.8, 47.6, 46.3, 45.2, 42.0, 28.7, 18.2. IR (KBr pellet, cm^{-1}):

ν 3328, 3185, 3125, 2929, 2792, 1738, 1628, 1574, 1536, 1386, 1311, 1271, 1462, 1244, 1185, 1088, 1047. LRMS (*m*/*z*): 517.3 (M^+), HRMS (*m*/*z*): calcd. for $C_{24}H_{32}FN_7O_5$: 517.2449; found 540.2400 (M^+ + Na). Anal. calcd. for $C_{24}H_{32}FN_7O_5$: C: 55.70, H: 6.23, N: 18.94; found C: 55.75, H: 6.56, N: 18.41.

A solution of **15a** (6.07 g, 11.73 mmol) in DCM (12.0 mL) was treated with trifluoroacetic acid (12.0 mL) and stirred to room temperature overnight. The reaction mixture was concentrated to dryness to give a brown oil, which was digested several times with ether and treated with THF/diethyl ether (1:1 mixture) with stirring to give **16a** as a cream-colored solid, 4.92 g, yield: 79%. This solid was utilized for subsequent reactions without further purification. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 8.17 (d, 1H, *J* = 0.7 Hz, triazole H), 8.13 (br. d, 3H, *J* = 3.8 Hz, $^+NH_3$, exchangeable with D2O), 7.76 (d, 1H, *J* = 0.8 Hz, triazole H), 7.42 (dd, 1H, *J* = 2.5 Hz, 14.7 Hz, phenyl H), 7.12 (dd, 2H, *J* = 2.3 Hz, 8.8 Hz, phenyl H), 7.07 (t, 1H, *J* = 9.3 Hz, phenyl H), 5.10–5.14 (m, 1H, oxazolidinone H), 4.83 (d, 1H, *J* = 5.0 Hz, CH_2), 4.42–4.44 (m, 1H, D-alanine CH), 4.22 (t, 1H, *J* = 9.2 Hz, oxazolidinone H), 3.86 (q, 1H, *J* = 5.8 Hz, 9.3 Hz, oxazolidinone H), 3.56–3.79 (m, 4H, piperazine H), 2.91–3.03 (m, 4H, piperazine H), 1.33 (d, 3H, *J* = 7.0 Hz, CH_3)). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 168.0, 158.5, 158.3, 158.1, 157.9, 155.4, 153.8, 153.5, 135.2, 135.2, 135.2, 133.5, 133.4, 125.9, 119.9, 119.8, 117.5, 115.6, 114.6, 113.6, 106.9, 106.7, 70.8, 51.7, 50.5, 50.1, 47.1, 45.9, 44.8, 41.7, 16.4. LRMS (*m*/*z*): calcd. for $C_{19}H_{24}FN_7O_3$ ($M^+ - CF_3O_2H$): 417.30. HRMS (*m*/*z*): calcd. for $C_{21}H_{25}F_4N_7O_5$: 531.1853; found 530.2300 ($M^+ - H$).

2.2.2. Preparation of (*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-3-(4-(4-(*L*-alanyl)piperazin-1-yl)-3-fluorophenyl) oxazolidin-2-one 2,2,2-trifluoroacetate **16b**

Compound **16b** was prepared via a similar procedure to the *D*-alaninyl isomer **16a** from (*tert*-butoxycarbonyl)-*L*-alanine (0.410 gm, 2.172 mmol), *N*,*N*′-dicyclohexyl carbodiimide (0.560 gm, 2.715 mmol), 1-hydroxy -benzotriazole (0.366 gm, 2.715 mmol), TFA salt (1.00 gm, 2.172 mmol) and TEA (0.877 mL, 6.30 mmol) in a mixture of DCM (40 mL) and acetonitrile (15 mL) and worked up in a similar manner to give the intermediate compound **15b** as an off-white solid, 0.913 g, yield: 82%; recrystallized (EtOAc), mp.: 203–207 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 8.18 (d, 1H, *J* = 0.7 Hz, triazole H), 7.77 (d, 1H, *J* = 0.8 Hz, triazole H), 7.43 (dd, 1H, *J* = 2.5 Hz, 14.4 Hz, phenyl H), 7.28 (dd,1H, *J* = 2.3 Hz, 8.8 Hz, phenyl H), 7.06 (t, 1H, *J* = 9.3 Hz, phenyl H), 7.00 (br. d, 1H, *J* = 7.9 Hz, NH, exchangeable with D_2O), 5.09–5.15 (m, 1H, oxazolidinone H), 4.83 (d, 2H, *J* = 5.1 Hz, CH_2), 4.45–4.50 (m, 1H, L-alanine CH), 4.21 (t, 1H, *J* = 9.2 Hz, oxazolidinone H), 3.87 (q, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H), 3.63–3.65 (br. d, 4H, piperazine H), 2.91–2.98 (br. d, 4H, piperazine H), 1.36 (br d, 9H, $(CH_3)_3$), 1.16 (d, 3H, *J* = 6.9 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 170.7, 155.3, 154.8, 153.7, 153.4, 135.4, 135.3, 133.3, 133.3, 133.2, 125.8, 119.7, 114.2, 106.8, 106.7, 77.9, 70.7, 51.7, 50.6, 50.3, 47.1, 45.8, 44.7, 41.5, 28.2, 17.7. IR (KBr pellet, cm^{-1}): ν 3634, 3500, 3346, 3121, 2980, 2900, 2811, 2722, 1877, 1736, 1653, 1578, 1520, 1447, 1387, 1367, 1280, 1236, 1120, 1061, 1028. LRMS (*m*/*z*): 517.3 (M^+). Calcd. for $C_{24}H_{32}FN_7O_5$: 517.2449; found 540.2500 (M^+ + Na). Anal. calcd. for $C_{24}H_{32}FN_7O_5$: C: 55.70, H: 6.23, N: 18.94; found C: 55.21, H: 6.31, N: 18.55.

Compound **16b** was prepared via a similar procedure to **16a** from a solution of **15b** (8.0 g, 15.46 mmol) in DCM (16.0 mL) in trifluoroacetic acid (16.0 mL) to afford the title compound as a cream solid, 7.36 g, yield: 90%. This solid was utilized for subsequent reactions without further purification. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 8.17 (d, 1H, *J* = 0.7 Hz, triazole H), 8.12 (br. d, 3H, *J* = 4.0 Hz, $^+NH_3$, exchangeable with D2O), 7.76 (d, 1H, *J* = 0.7 Hz, triazole H), 7.42 (dd, 1H, *J* = 2.5 Hz, 14.7 Hz, phenyl H), 7.14 (dd, 2H, *J* = 2.3 Hz, 8.8 Hz, phenyl H), 7.07 (t, 1H, *J* = 9.3 Hz, phenyl H), 5.11–5.14 (m, 1H, oxazolidinone H), 4.83 (d, 1H, *J* = 5.0 Hz, CH_2), 4.41–4.44 (m, 1H, L-alanine CH), 4.21 (t, 1H, *J* = 9.1 Hz, oxazolidinone H), 3.86 (q, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H), 3.59–3.67 (m, 4H, piperazine H, overlaps with DOH signal), 2.90–3.08 (m, 4H, piperazine H), 1.33 (d, 3H, *J* = 7.0 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 167.9, 158.0, 157.8, 155.4, 153.8, 153.5, 135.2, 135.2, 133.4, 133.3, 125.9, 119.8, 119.8, 116.1, 114.3, 114.3, 106.9, 106.7, 70.7, 51.7, 50.4, 50.1, 47.1, 45.9, 44.7, 41.6, 16.4. LRMS (*m*/*z*): calcd. for $C_{19}H_{24}FN_7O_3$ ($M^+ - CF_3O_2H$): 417.3. HRMS (*m*/*z*): calcd. for $C_{21}H_{25}F_4N_7O_5$: 531.1853; found 530.2400 ($M^+ - H$).

2.2.3. Preparation of *N*-((*R*)-1-(4-(4-((*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-1-oxopropan-2-yl)-2-nitrobenzamide **9a**

To an ice-cooled solution of **16a** (0.700 g, 1.317 mmol) in anhyd. CH_3CN (20 mL) was added TEA (0.70 mL) and 2-nitrobenzoyl chloride (0.363 g, 1.97 mmol), and the reaction mixture was stirred overnight. The reaction mixture was diluted with DCM (100 mL), washed with water (3 × 80 mL), 10% $NaHCO_3$ solution (80 mL), water (80 mL) and brine (80 mL), dried (Na_2SO_4), filtered and concentrated to give a yellow solid, which was triturated with ether and filtered to give a yellow solid, 0.580 g, recrystallized (CH_3CN) to give the title Compound **9a** as a yellow solid, 190 mg, yield: 23%; mp.: 124–126 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z):δ 9.03 (d, 1H, NH, *J* = 8.0 Hz), 8.17 (d,1H, *J* = 0.7 Hz, triazole H), 8.03 (dd, 1H, *J* = 0.9 Hz, 8.1 Hz, nitrobenzene H), 7.79 (t, 1H, *J* = 7.1 Hz, nitrobenzene H), 7.76 (d, 1H, *J* = 1.0 Hz, triazole H), 7.66–7.77 (m, 1H, nitrobenzene H), 7.61 (dd, 1H, *J* = 1.3 Hz, 7.6 Hz, nitrobenzene H), 7.42 (dd,1H, *J* = 3.4 Hz, 12.1 Hz, phenyl H), 7.27 (dd, 1H, *J* = 2.3 Hz, 8.8 Hz, phenyl H), 7.06 (t, 1H, *J* = 7.5 Hz, phenyl H), 5.09–5.14 (m, 1H oxazolidinone H), 4.94–4.95 (m, 1H, D-alanine CH), 4.83 (d, 2H, *J* = 5.2 Hz, CH_2), 4.20 (t,1H, *J* = 9.0 Hz, oxazolidinone), 3.87 (dd, 1H, *J* = 5.3 Hz, 8.9 Hz, oxazolidinone CH), 3.74–3.61 (m, 4H, piperazine H), 3.03–2.93 (m, 4H, piperazine H), 1.29 (d, 3H, *J* = 6.8 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 167.9, 163.1, 153.7, 152.1, 151.8, 145.3, 133.8, 133.7, 131.9, 133.7, 131.7, 131.6, 130.5, 129.1, 127.6, 124.2, 122.4, 118.1, 118.1, 112.6, 112.6, 105.2, 105.0, 69.1, 50.1, 49.1, 48.6, 45.4, 43.3, 43.2, 40.0, 15.7. IR (KBr pellet, cm^{-1}): 3305, 3112, 1753, 1645, 1519, 1282, 1228, 1026, 743. LRMS (*m*/*z*) 566.5 (M^+). Anal. calcd. for $C_{26}H_{27}FN_8O_6$: C: 55.12, H: 4.80, N: 19.78; found C: 55.1, H: 5.21, N: 19.65.

2.2.4. Preparation of *N*-((*S*)-1-(4-(4-((*R*)-(5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-1-oxopropan-2-yl)-2-nitrobenzamide **10a**

Compound **10a** was prepared via a similar procedure to **9a** from **16b** (0.90 g, 1.693 mmol) and 2-nitrobenzoyl chloride (0.471 gm, 2.54 mmol) to give **10a** as a yellow solid, 258 mg, yield: 27%; recrystallized (CH_3CN), mp.: 185–190 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 9.05 (d, NH, 1H, J = 8.0 Hz, exchangeable with D_2O), 8.17 (s, 1H, triazole H), 8.05 (dd, 1H, *J* = 0.5 Hz, 8.2 Hz, nitrobenzene H), 7.79–7.82 (m, 1H, nitrobenzene H), 7.77 (s, 1H, triazole H), 7.69–7.72 (m, 1H, nitrobenzene H), 7.62 (dd, 1H, *J* = 1.1 Hz, 7.6 Hz, nitrobenzene H), 7.44 (dd, 1H, *J* = 2.4 Hz, 14.7 Hz, phenyl H), 7.14 (dd, 1H, *J* = 2.3 Hz, 8.8 Hz, phenyl H), 7.07 (t, 1H, *J* = 9.3 Hz, phenyl H), 5.11–5.15 (m, 1H, oxazolidinone H), 4.96–5.01 (m, 1H, L-alanine CH), 4.84 (d, 2H, *J* = 5.1, CH_2), 4.22 (t, 1H, *J* = 9.2 Hz, oxazolidinone H), 3.87 (dd, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H), 3.60–3.80 (m, 4H, piperazine H), 2.90–3.06 (m, 4H, piperazine H), 1.30 (d, 3H, *J* = 6.8 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 175.4, 169.4, 158.9, 158.7, 154.3, 144.8, 140.6, 140.6, 138.6, 134.3, 131.1, 128.7, 125.0, 119.6, 112.1, 111.9, 84.8, 84.5, 84.3, 76.1, 57.0, 55.9, 55.5, 52.4, 50.8, 50.2, 46.9, 22.5. IR (KBr pellet, cm^{-1}): ν 3309, 3122, 2826, 1729, 1635, 1601, 1524, 1442, 1341, 1228, 1160, 1118, 1028. LRMS (*m*/*z*) 566.2 (M^+). Anal. calcd. for $C_{26}H_{27}FN_8O_6$: C: 55.12, H: 4.80, N: 19.78; found C: 54.98, H: 5.22, N: 19.70.

2.2.5. Preparation of *N*-((*R*)-1-(4-(4-((*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-1-oxopropan-2-yl)-3-nitrobenzamide **9b**

Compound **9b** was prepared via a similar procedure to **9a** from **16a** (0.700 g, 1.317 mmol) and 3-nitrobenzoyl chloride (0.363 g, 1.97 mmol) to give a yellow solid, 0.580 g, yield: 68%; recrystallized (CH_3CN), mp.: 208–210 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 9.13 (d, NH, 1H, J = 7.4 Hz, exchangeable with D_2O), 8.75 (t, 1H, *J* = 1.9 Hz, nitrobenzene H), 8.38–8.40 (m, 1H, nitrobenzene H), 8.33–8.35 (m, 1H, nitrobenzene H), 8.17 (d, 1H, *J* = 0.8 Hz, triazole H), 7.79 (t, 1H, *J* = 8.0 Hz, nitrobenzene H), 7.77 (d, 1H, *J* = 0.7 Hz, triazole H), 7.42 (dd, 1H, *J* = 2.5 Hz, 14.7 Hz, phenyl H), 7.12 (dd, 1H, *J* = 3.8 Hz, 9.4 Hz, phenyl H), 7.06 (t, 1H, *J* = 9.3 Hz, phenyl H), 5.11–5.14 (m, 1H, oxazolidinone H), 4.98–5.05 (m, 1H, D-alanine CH), 4.83 (d, 2H, *J* = 5.1 Hz, CH_2), 4.21 (t, 1H, *J* = 9.2 Hz, oxazolidinone H), 3.86 (dd, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H), 3.62–3.70 (m, 4H, piperazine H), 2.95–3.01 (br. d, 4H, piperazine H), 1.35 (d, 3H, *J* = 7.0 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 170.7, 164.2, 155.8, 154.2, 153.9,

148.2, 135.9, 135.8, 135.8, 134.5, 133.9, 133.8, 133.7, 130.6, 126.5, 126.3, 122.7, 120.3, 120.2, 114.7, 114.7, 107.3, 107.1, 71.3, 52.2, 51.1, 50.8, 47.6, 45.9, 45.4, 42.1, 17.7. IR (KBr pellet, cm^{-1}): 3288, 3117, 2823, 1720, 1637, 1517, 1445, 1349, 1285, 1228. LRMS (*m*/*z*): 566.6 (M^+). Anal. calcd. for $C_{26}H_{27}FN_8O_6$: C: 55.12, H: 4.80, N: 19.78; found: C: 54.91, H: 4.71, N: 19.79.

2.2.6. Preparation of *N*-((*S*)-1-(4-(4-((*R*)-(5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-1-oxopropan-2-yl)-3-nitrobenzamide **10b**

Compound **10b** was prepared via a similar procedure to **9a** from **16b** (0.90 g, 1.693 mmol) and 3-nitrobenzoyl chloride (0.471 g, 2.54 mmol) to give a cream-colored solid, 480 mg, yield: 51%; recrystallized (EtOAc), mp.: 138–145 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 9.13 (d, NH, 1H, *J* = 7.4 Hz, exchangeable with D_2O), 8.75 (t, 1H, *J* = 1.9 Hz, nitrobenzene H), 8.38–8.40 (m, 1H, nitrobenzene H), 8.33–8.35 (m, 1H, nitrobenzene H), 8.16 (d, 1H, *J* = 0.7 Hz, triazole H), 7.78 (t, 1H, *J* = 8.0 Hz, nitrobenzenene H), 7.76 (d, 1H, *J* = 0.7 Hz, triazole H), 7.42 (dd, 1H, *J* = 2.5 Hz, 14.7 Hz, phenyl H), 7.13 (dd, 1H, *J* = 3.8 Hz, 9.4 Hz, phenyl H), 7.06 (t, 1H, *J* = 9.3 Hz, phenyl H), 5.10–5.14 (m, 1H, oxazolidinone H), 5.01–5.05 (m, 1H, L-alanine CH), 4.83 (d, 2H, *J* = 5.1 Hz, CH_2), 4.20 (t, 1H, *J* = 11.8 Hz, oxazolidinone H), 3.86 (dd, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H), 3.62–3.70 (m, 4H, piperazine H), 2.95–3.01 (br. d, 4H, piperazine H), 1.35 (d, 3H, *J* = 7.0 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 175.4, 168.9, 160.6, 159, 158.7, 153, 140.7, 140.6, 140.5, 139.2, 138.6, 138.6, 138.5, 135.3, 131.3, 131.1, 127.5, 125.0, 119.5, 112.1, 112.9, 76.0, 56.9, 55.9, 55.6, 52.3, 50.7, 50.2, 46.9, 22.5, 19.3. IR (KBr pellet, cm^{-1}): ν 3442, 3309, 3122, 2826, 1729, 1635, 1600, 1523, 1442, 1419, 1340, 1227, 1200, 1160, 1118, 1028. LRMS (*m*/*z*): 566.4 (M^+). Anal. calcd. for $C_{26}H_{27}FN_8O_6$: C: 55.12, H: 4.80, N: 19.78; found C: 55.16, H: 4.88, N: 19.91.

2.2.7. Preparation of *N*-((*R*)-1-(4-(4-((*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-1-oxopropan-2-yl)-4-nitrobenzamide **9c**

Compound **9c** was prepared via a similar procedure to **9a** from **16a** (0.700 g, 1.317 mmol) and 4-nitrobenzoyl chloride to give a yellow solid, 300 mg, yield: 38%, recrystallized (CH_3CN); mp.: 228–230 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z) δ: 9.04 (d, 1H, *J* = 9 Hz, NH, exchangeable with D_2O), 8.32 (d, 2H, *J* = 8.9 Hz, phenyl H), 8.16 (d, 1H, *J* = 0.8 Hz, triazole H), 8.12 (d, 2H, *J* = 8.9 Hz, phenyl H), 7.76 (d, 1H, *J* = 0.8 Hz, triazole H), 7.42 (dd, 1H, *J* = 2.9 Hz, 15.7 Hz, phenyl H), 7.13 (dd, 1H, *J* = 3.5 Hz, 8.3 Hz, phenyl H), 7.06 (t, 1H, *J* = 9.6 Hz, phenyl H), 5.10–5.15 (m, 1H, oxazolidinone H), 4.99–5.04 (m, 1H, D-alanine CH), 4.83 (d, 2H, *J* = 5.1 Hz, CH_2), 4.20 (t, 1H, *J* = 9.2 Hz, oxazolidinone H), 3.86 (dd, 1H, *J* = 5.5 Hz, 8.3 Hz, oxazolidinone H), 3.58–3.75 (m, 4H, piperazine H), 2.90–3.06 (m, 4H, piperazine H), 1.34 (d, 3H, *J* = 7.0 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 170.6, 164.7, 155.8, 154.2, 153.9, 149.6, 140.0, 135.9, 135.8, 133.9, 133.8, 133.7, 129.5, 126.3, 123.9, 120.3, 120.2, 114.7, 107.3, 107.1, 71.3, 52.2, 51.1, 50.8, 47.6, 45.9, 45.4, 42.1, 17.7. IR (KBr pellet, cm^{-1}): 3373, 2821, 1742, 1640, 1529, 1444, 1341, 1226, 1162, 1110, 1028. LRMS (*m*/*z*): 566.5 (M^+). Anal. calcd. for $C_{26}H_{27}FN_8O_6$: C: 55.12, H: 4.80, N: 19.78; found: C: 54.73, H: 5.00, N: 20.06.

2.2.8. Preparation of *N*-((*S*)-1-(4-(4-((*R*)-(5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-1-oxopropan-2-yl)-4-nitrobenzamide **10c**

Compound **10c** was prepared via a similar procedure to **9a** from **16b** (0.90 g, 1.693 mmol) and 4-nitrobenzoyl chloride (0.471 g, 2.54 mmol) to afford a yellow solid, 450 mg, yield: 47%, recrystallized (CH_3CN), mp.: 245–247 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 9.06 (d, NH, 1H, *J* = 7.4, NH, exchangeable with D_2O), 8.33 (d, 2H, *J* = 8.9 Hz, nitrobenzene H), 8.18 (d, 1H, *J* = 0.7 Hz, triazole H), 8.13 (d, 2H, *J* = 8.9 Hz, nitrobenzene H), 7.77 (s, 1H, triazole H), 7.43 (dd, 1H, *J* = 3.0 Hz, 14.2 Hz, phenyl H), 7.13 (dd, 1H, *J* = 3.5 Hz, 8.3 Hz, phenyl H), 7.07 (t, 1H, *J* = 8.9, phenyl H), 5.10–5.16 (m, 1H, oxazolidinone H), 4.98–5.18 (m, 1H, L-alanine CH), 4.84 (d, 2H, *J* = 5.1 Hz, CH_2), 4.21 (t, 1H, *J* = 8.9, oxazolidinone H), 3.87 (dd, 1H, *J* = 6.2 Hz, 10.1 Hz, oxazolidinone H), 3.58–3.76 (m, 4H, piperazine H), 2.92–3.08 (m, 4H, piperazine H), 1.35 (d, 3H, *J* = 7.0, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 170.6, 164.7, 155.8, 154.2, 154.0, 149.6, 140.1, 135.9, 135.8, 133.9, 133.8, 133.7, 129.5, 126.3, 124.0, 120.3, 120.3,

114.8, 107.3, 107.2, 71.3, 52.2, 51.1, 50.8, 47.6, 45.9, 45.4, 42.1, 17.7. IR (KBr pellet, cm^{-1}): ν 3439, 3309, 3123, 2826, 1728, 1635, 1601, 1525, 1442, 1341, 1282, 1228, 1200, 1161, 1118, 1028. LRMS (*m*/*z*) 566.3 (M^+). Anal. calcd. for $C_{26}H_{27}FN_8O_6$: C: 55.12, H: 4.80, N: 19.78; found C: 54.95, H: 5.20, N: 19.69.

2.2.9. Preparation of *N*-((*R*)-1-(4-(4-((*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-1-oxopropan-2-yl)-3,5-dinitrobenzamide **9d**

Compound **9d** was prepared via a similar procedure to **9a** from **16a** (1.00 g, 1.881 mmol) and 3,5-dinitrobenzoyl chloride (0.65 g, 2.82 mmol) to give a yellow solid, 390 mg, yield: 32%, purified by silica gel column chromatography (EtOAc-Hex 10-1, EtOAc and EtOAc-MeOH 10:1)], mp.: 223–225 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 9.52 (d, 1H, *J* = 8.8 Hz, NH, exchangeable with D_2O), δ 9.13 (d, 2H, *J* = 2.1 Hz, nitrobenzene H), 8.96 (t, 1H, *J* = 2.1 Hz, nitrobenzene H), 8.16 (d, 1H, *J* = 1.0 Hz, triazole H), 7.76 (d, 1H, *J* = 0.8 Hz, triazole H), 7.42 (d, 1H, *J* = 3.0 Hz, 14.2 Hz, phenyl H), 7.13 (d, 1H, *J* = 3.5 Hz, 8.3 Hz, phenyl H), 7.07 (t, 1H, *J* = 11.1Hz, phenyl H), 5.02–5.14 (m, 2H, oxazolidinone H and D-alanine CH), 4.83 (d, 2H, *J* = 5.0 Hz, CH_2), 4.2 (t, 1H, *J* = 10.7 Hz, oxazolidinone H), 3.87 (dd, 1H, *J* = 6.2 Hz, 10.1 Hz, oxazolidinone H), 3.60–3.78 (m, 4H, piperazine H), 2.96–3.08 (m, 4H, piperazine H), 1.38 (d, 3H, *J* = 7.0 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 170.4, 162.2, 155.8, 154.2, 153.9, 148.7, 136.9, 135.9, 135.8, 133.9, 133.8, 133.7, 128.3, 126.3, 121.5, 120.3, 120.3, 114.8, 114.7, 107.3, 107.1, 71.3, 67.5, 65.4, 60.2, 52.2, 51.1, 50.8, 47.6, 46.2, 45.6, 42.1, 17.7. IR (KBr pellet, cm^{-1}): ν 3481, 3276, 3094.23, 1756, 1633, 1542, 1517, 1445, 1346, 1230, 1028. HRMS (*m*/*z*): calcd. for $C_{26}H_{26}FN_9O_8$: 611.1888, found 612.20 (M^+ + H), LRMS (*m*/*z*) 611.5 (M^+). Anal. CHN, calcd.: C: 51.06, H: 4.29, N: 20.61; found: C: 49.95, H: 4.70, N: 20.12.

2.2.10. Preparation of *N*-((*S*)-1-(4-(4-((*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluoro phenyl)piperazin-1-yl)-1-oxopropan-2-yl)-3,5-dinitrobenzamide **10d**

Compound **10d** was prepared via a similar procedure to **9a** from **16b** (0.700 g, 1.317 mmol) and 3,5-dinitro benzoyl chloride (0.455 g, 1.976 mmol) to give a yellow solid, 382 mg, yield: 45%, recrystallization (CH_3CN), mp.: 191–194 °C. ^{1}H-NMR (DMSO-d_6, 400 MH_Z): δ 9.53 (d, 1H, *J* = 7.2 Hz, NH, exchangeable with D_2O), 9.12 (d, 2H, *J* = 2.0 Hz, nitrobenzene H), 8.96 (t, 1H, *J* = 2.0 Hz, nitrobenzene H), 8.16 (s, 1H, triazole H), 7.76 (s, 1H, triazole H), 7.42 (dd, 1H, *J* = 2.2 Hz, 14.7 Hz, phenyl H), 7.06–7.14 (m, 2H, phenyl H), 5.05–5.12 (m, 2H, oxazolidinone H and L-alanine CH), 4.82 (d, 2H, *J* = 5.0 Hz, CH_2), 4.20 (t, 1H, *J* = 9.1 Hz, oxazolidinone H), 3.85 (dd, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H), 3.64–3.72 (m, 4H, piperazine H), 2.95–3.01 (m, 4H, piperazine H), 1.37 (d, 3H, *J* = 6.9 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 400 Hz): δ 170, 161.8, 153.5, 148.2, 136.4, 135.4, 135.3, 133.4, 133.2, 127.8, 125.9, 121.0, 119.8, 114.3, 107.3, 107.1, 70.8, 51.7, 50.7, 50.3, 47.1, 45.7, 45.0, 42.4, 17.2. IR (KBr pellet, cm^{-1}): ν 3425, 3278, 3109, 1752, 1668, 1631, 1541, 1518, 1484, 1446, 1345, 1230, 1028. HRMS (*m*/*z*): calcd. for $C_{26}H_{26}FN_9O_8$: 611.1888, found 612.2090 (M^+ + H), LRMS (*m*/*z*) 611.4 (M^+). Anal. CHN, expected: C: 51.06, H: 4.29, N: 20.61, found C: 50.72, H: 4.25, N: 19.61.

2.2.11. Preparation of *N*-(*R*)-1-(4-(4-((*R*)-(5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-1-oxopropan-2-yl)-5-nitrofuran-2-carboxamide **9e**

To a stirred solution of 5-nitrofuran-2-carboxylic acid (1.77 gm, 11.288 mmol) in anhyd. DCM (30 mL) cooled in an ice bath was added oxalyl chloride (2.46 mL, 28.22 mmol) under nitrogen followed by 2 drops of dry DMF, and effervescence ensued. The ice bath was removed, and the reaction mixture was stirred 2 h. The mixture was evaporated to dryness on a rotavap to give the acid chloride as a yellow semisolid, which was dried under vacuum. The resulting acid chloride was dissolved in anhyd. DCM (30 mL) and added in rapid drops to a solution of the TFA salt **16a** (1.5 g, 2.822 mmol) and TEA (2.14 mL, 11.288 mmol) in CH_3CN (32 mL) with cooling in an ice bath. The reaction mixture was left to stir to room temperature overnight under nitrogen and concentrated to dryness. The residue was dissolved in DCM and washed with water, 10% Na_2CO_3 solution, water, brine and dried with Na_2SO_4, filtered and concentrated to give a brown foam, which was triturated with ether and hexane (1:1) to

afford **9e** as a brown solid, 624 mg, yield: 40%, recrystallized (EtOAc), mp.: 180–185 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 9.08 (d, 1H, *J* = 8.7 Hz, NH, exchangeable with D_2O), 8.18 (d, 1H, *J* = 0.7 Hz, triazole H), 7.77 (d, 1H, *J* = 0.7 Hz, triazole H), 7.76 (d, *J* = 3.9 Hz, nitrofuran H), 7.55 (d, 1H, *J* = 5.3 Hz, nitrofuran H), 7.43 (dd, 1H, *J* = 3.7 Hz, 15.0 Hz, phenyl H), 7.14 (dd, 1H, *J* = 3.7 Hz, 8.0 Hz, phenyl H), 7.08 (t, 1H, *J* = 7.7 Hz, phenyl H), 5.14–5.12 (m, 1H, oxazolidinone H), 4.97–5.01 (m, 1H, D-alanine CH), 4.83 (d, 2H, *J* = 6.7 Hz, CH_2), 4.21 (t, 1H, *J* = 9.2 Hz, oxazolidinone H), 3.85–3.88 (q, 1H, *J* = 4.0 Hz, 8.7 Hz, oxazolidinone H), 3.62–3.71 (m, 4H, piperazine H), 3.00 (m, 4H, piperazine H), 1.34 (d, 3H, *J* = 6.9 Hz, CH_3). IR (KBr pellet, cm^{-1}): ν 3403, 3131, 2929, 2811, 1753, 1642, 1590, 1548, 1521, 1444, 1386, 1350, 1233, 1157, 1113, 1023. LRMS (*m*/*z*): 556.5 (M^+). Anal. calcd. for $C_{24}H_{25}FN_8O_7$: C: 51.80, H: 4.53, N: 20.14; found: C: 51.97, H: 4.26, N: 20.36.

2.2.12. Preparation of *N*-((*S*)-1-(4-(4-((*R*)-(5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxo oxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-1-oxopropan-2-yl)-5-nitrofuran-2-carboxamide **10e**

Compound **10e** was prepared via a similar procedure to **9e** from **16b** (0.700 g, 1.317 mmol) and 5-nitrofuran-2-carboxylic acid (0.827 g, 5.268mmol) to give a yellowish-brown solid, 356 mg, yield 46%, recrystallized (CH_3CN/MeOH), mp.: 218–222 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 9.09 (d, 1H, *J* = 7.5 Hz, NH, exchangeable with D_2O), 8.18 (d, 1H, *J* = 0.7 Hz, triazole H), 7.78 (d, 1H, *J* = 0.7 Hz, triazole H), 7.77 (d, 1H, *J* = 3.8 Hz, nitrofuran H), 7.44 (d, 1H, *J* = 3.8 Hz, nitrofuran H), 7.42 (d, 1H, *J* = 2.5 Hz, phenyl H), 7.13 (d, 1H, *J* = 2.3 Hz, phenyl H), 7.08 (t, 1H, *J* = 9.4 Hz, phenyl H), 5.12–5.14 (m, 1H, oxazolidinone H), 4.98–5.02 (m, 1H, L-alanine CH), 4.84 (d, 1H, *J* = 5.0, CH_2), 4.21 (t, 1H, *J* = 9.3 Hz, oxazolidinone H), 3.85–3.88 (q, 1H, *J* = 4.0 Hz, 8.7 Hz, oxazolidinone H), 3.60–3.74 (m, 4H, piperazine H), 2.93–3.06 (m, 4H, piperazine H), 1.34 (d, 3H, *J* = 7.0 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 400 Hz): δ 169.7, 155.5, 155.3, 153.7, 153.4, 147.7, 135.3, 135.3, 133.3, 133.3, 133.2, 125.8, 119.8, 119.8, 115.9, 114.3, 113.3, 106.8, 106.7, 70.7, 51.7, 50.6, 50.2, 47.1, 45, 44.9, 41.7, 17.3. IR (KBr pellet, cm^{-1}): ν 3396, 3351, 3107, 2917, 2823, 1748, 1637, 1542, 1488, 1445, 1421, 1381, 1342, 1276, 11648, 1105, 1074, 1029. LRMS (*m*/*z*): 556.5 (M^+). HRMS (*m*/*z*): calcd. for $C_{24}H_{25}FN_8O_7$: 556.1830, found 579.1700 (M^+ + Na). Anal. calcd. for $C_{24}H_{25}FN_8O_7$: C: 51.80, H: 4.53, N: 20.14, found: C: 51.41, H: 4.78, N: 20.44.

2.2.13. Preparation of *N*-((*R*)-1-(4-(4-((*R*)-(5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazin-1-yl)-1-oxopropan-2-yl)-5-nitrothiophene-2-carboxamide **9f**

Compound **9f** was prepared via a similar procedure to **9e** from **16a** (1.00 g, 1.881 mmol) and 5-nitrothiophene-2-carboxylic acid (1.302 g (7.524 mmol) to give an off-white solid, 262 mg, yield: 24%, recrystallized (CH_3CN), mp.: 223–227 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): 9.27 (d, NH,1 H, *J* = 7.4 Hz, exchangeable with D_2O), 8.17 (d, 1H, *J* = 0.5 Hz, triazole H), 8.15 (d, nitrothiophene, *J* = 4.3 Hz, 1H, nitrothiophene H), 7.95 (d, 1H, *J* = 4.4 Hz, nitrothiophene H), 7.77 (s, 1H, triazole H), 7.43 (dd, 1H, *J* = 2.4 Hz, 14.7 Hz, phenyl H), 7.27 (dd, 1H, *J* = 8.8 Hz, 2.3 Hz, phenyl H), 7.07 (t, 1H, *J* = 9.4 Hz, phenyl H), 5.12–5.14 (m, 1H, oxazolidinone H), 4.97–5.01 (m, 1H, D-alanine CH), 4.83 (d, 1H, *J* = 5.0 Hz, CH_2), 4.21 (t, 1H, *J* = 9.1 Hz, oxazolidinone H), 3.87 (dd, 1H, *J* = 5.7 Hz, 9.3 Hz, CH), δ 3.58–3.70 (m, 4H, piperazine H), 2.90–3.05 (m, 4H, piperazine H), 1.34 (d, 3H, *J* = 7.0 Hz, CH_3). ^{13}C-NMR (DMSO-d_6): δ 159.5, 155.8, 154.2, 154.0, 153.5, 146.3, 135.8, 133.9, 133.8, 133.7, 130.7, 128.4, 126.3, 120.3, 114.8, 107.3, 107.2, 71.3, 52.2, 51.1, 50.8, 47.6, 46, 45.4, 42.1, 17.7. IR (KBr pellet, cm^{-1}): ν 3396, 3351, 3107, 2917, 2823, 1748, 1637, 1542, 1488, 1445, 1421, 1381, 1342, 1276, 1164, 1105, 1074, 1029. MS: 572.5 (M^+). HRMS (*m*/*z*): calcd. for $C_{24}H_{25}FN_8O_7S$: 572.1602, found 573.1700 (M^+ + H), LRMS (*m*/*z*): 572.5 (M^+). Anal. calcd. for $C_{24}H_{25}FN_8O_6S$: C: 49.91, H: 4.57, N: 19.54.; found C: 50.35, H: 4.40, N: 19.57.

2.2.14. Preparation of *N*-((*S*)-1-(4-(4-((*R*)-(5-((1*H*-1,2,3-triazol-1-yl) methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazin-1-yl)-1-oxopropan-2-yl)-5-nitrothiophene-2-carboxamide **10f**

Compound **10f** was prepared via a similar procedure to **9e** from **16b** (0.700 g, 1.317 mmol) and 5-nitrothiophene-2-carboxylic acid (0.912 g, 5.268 mmol) to give a yellowish-brown solid, 560 mg, yield: 76%, recrystallized (EtOAc), mp.: 211–214 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 9.27 (d, 1H, *J* = 7.4 Hz,

NH, exchangeable with D_2O), 8.18 (d, 1H, *J* = 0.6 Hz, triazole H), 8.16 (d, 1H, *J* = 4.4 Hz, nitrothiophene H), 7.98 (d, 1H, *J* = 4.4 Hz, nitrothiophene H), 7.78 (s, 1H, triazole H), 7.43 (dd, 1H, *J* = 2.4 Hz, 14.7 Hz, phenyl H), 7.27 (dd, 1H, *J* = 2.3 Hz, 8.8 Hz, phenyl H), 7.07 (t, 1H, *J* = 9.4 Hz, phenyl H), 5.11–5.15 (m, 1H, oxazolidinone H), 4.96–5.01 (m, 1H, L-alanine CH), 4.83 (d, 1H, *J* = 5.0 Hz, CH_2), 4.21 (t, 1H, *J* = 9.4 Hz, oxazolidinone H), 3.87 (dd, 1H, *J* = 5.3 Hz, 8.9 Hz, oxazolidinone H), 3.56–3.76 (m, 4H, piperazine H), 2.90–3.06 (m, 4H, piperazine H), 1.34 (d, 3H, *J* = 7.0 Hz, CH_3). ^{13}C-NMR (DMSO-d_6): δ 169.8, 159.1, 155.4, 153.8, 153.5, 153.1, 145.8, 135.4 135.3, 133.4, 133.3, 133.3, 130.2, 128, 125.9, 119.8, 114.3, 106.8, 106.7, 70.8, 51.7, 50.6, 50.3, 47.1, 45.5, 45.0, 41.7, 17.2. IR (KBr pellet, cm^{-1}): 3425, 3296, 3079, 2918, 2843, 1742, 1643, 1553, 1517, 1424, 1336, 1276, 1228, 1030. LRMS (*m*/*z*) 572.5 (M^+). HRMS (*m*/*z*): calcd. for $C_{24}H_{25}FN_8O_6S$ (M^+): 572.1602, found 573.1800 (M^+ + H). Anal. calcd. for $C_{24}H_{25}FN_8O_6S$ C: 50.35, H: 4.40, N: 19.57, found C: 50.36, H: 4.52, N: 19.20.

2.2.15. Preparation of *N*-(*R*)-1-(4-(4-((*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-1-oxopropan-2-yl)-2-nitrobenzenesulfonamide **9g**

Compound **9g** was prepared via a similar procedure to **9a** from **16a** (650 mg, 1.222 mmol), TEA (0.650 mL) and 2-nitrobenzenesulfonyl chloride (406 mg, 1.834 mmol) in anhyd. CH_3CN (15 mL) to give a yellow solid, 200 mg, yield: 20%, recrystallized (CH_3CN), mp.: 128–130 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 8.33 (br. s,1H, NH exchangeable with D_2O), 8.17 (d, 1H, *J* = 0.7 Hz, triazole H), 8.01–8.03 (m, 1H, nitrobenzene H), 7.94–7.96 (m, 1H, nitrobenzene H), 7.83–7.86 (m, 2H, nitrobenzene H), 7.77 (d, 1H, *J* = 0.7 Hz, triazole H), 7.41 (dd, 1H, *J* = 2.6 Hz, 14.7 Hz, phenyl H), 7.13 (dd, 1H, *J* = 2.4 Hz, *J* = 8.4 Hz, phenyl H), 7.02 (t, 1H, *J* = 9.5 Hz, phenyl H), 5.10–5.14 (m, 1H oxazolidinone H), 4.83 (d, 2H, *J* = 5.1 Hz, CH_2), 4.48 (q, 1H, *J* = 6.8 Hz, D-alanine CH), 4.20 (t, 1H, *J* = 8.9 Hz, oxazolidinone H), 3.86 (q, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H), 3.60–3.37 (m, 4H, piperazine H), 2.67–2.97 (m, 4H, piperazine H), 1.22 (d, 3H, *J* = 7.0 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 169.4, 155.8, 154.2, 153.9, 147.8, 135.8, 135.7, 134.5, 133.9, 133.8, 133.6, 133.0, 130.4, 126.3, 124.7, 120.2, 120.2, 114.8, 114.7, 107.3, 107.1, 71.3, 52.2, 50.9, 50.5, 49.1, 47.6, 45.3, 42.0, 19.4. IR (KBr pellet, cm^{-1}): ν 3446, 3303, 3100, 2829, 1752, 1650, 1541, 1518, 1483, 1444, 1417, 1356, 1330, 1233, 1170, 1123, 1028. LRMS (*m*/*z*): 602.5 (M^+). Anal. calcd. for $C_{25}H_{27}FN_8O_7S$: C: 49.83, H: 4.52, N: 18.60; found: C: 49.48, H: 4.73, N: 18.80.

2.2.16. Preparation of *N*-((*S*)-1-(4-(4-((*R*)-(5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazin-1-yl)-1-oxopropan-2-yl)-2-nitrobenzene sulfonamide **10g**

Compound **10g** was prepared via a similar procedure to **9a** from **16b** (700 mg, 1.317 mmol) and 2-nitrobenzenesulfonyl chloride (4–6 mg, 1.834 mmol), to give a yellow solid, 265 mg, yield 30%, recrystallized (CH_3CN), mp.: 78–80 °C. ^{1}H-NMR (DMSO-d_6, 400 MH_Z): δ 8.30 (br., 1H, NH, exchangeable with D_2O), 8.16 (s, 1H, triazole H), 8.00–8.03 (m, 1H, nitrobenzene H), 7.93–7.96 (m, 1H, nitrobenzene H), 7.82–7.85 (m, 2H, nitrobenzene H), 7.76 (s, 1H, triazole H), 7.41 (dd, 1H, *J* = 2.4 Hz, 14.7 Hz, phenyl H), 7.13 (dd, 1H, *J* = 2.0 Hz, 8.7 Hz, phenyl H), 7.02 (t, 1H, *J* = 9.3 Hz, phenyl H), 5.09–5.15 (m, 1H, oxazolidinone H), 4.82 (d, 2H, *J* = 5.0 Hz, CH_2), 4.48 (q, 1H, *J* = 6.8 Hz, L-alanine CH), 4.20 (t, 1H, *J* = 9.2 Hz, oxazolidinone H), 3.85 (dd, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H), 3.45–3.63 (m, 4H, piperazine H), 2.80–2.96 (m, 4H, piperazine H), 1.21 (m, 3H, *J* = 6.9 Hz, CH_3). IR (KBr pellet, cm^{-1}): ν 3446, 3287, 3130, 2984, 2903, 2827, 1756, 1647, 1542, 1517, 1481, 1442, 1417, 1371, 1230, 1169, 1121, 1028. HRMS (*m*/*z*): calcd. for $C_{25}H_{27}FN_8O_7S$: 602.1707, found 603.1812 (M^+ + H), LRMS (*m*/*z*) 602.4 (M^+). Anal. calcd. for $C_{25}H_{27}FN_9O_7S$: C: 49.83, H: 4.52, N: 18.6; found C: 49.36, H: 4.72, N: 18.34

2.2.17. Preparation of *N*-((*R*)-1-(4-(4-((*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazin-1-yl)-1-oxopropan-2-yl)-3-nitrobenzenesulfonamide **9h**

Compound **9h** was prepared via a similar procedure to **9a** from **16a** (660 mg, 1.241 mmol) and 3-nitrobenzenesulfonyl chloride (412 mg, 1.862 mmol) to give a yellow solid, which was triturated with ether and filtered to give a yellow solid, 300 mg, 40% yield, recrystallized (CH_3CN); mp.: 115–118 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 8.45–8.52 (m, 3H, nitrobenzene H and NH, exchangeable with D2O),

8.18–8.20 (m, 1H, nitrobenzene H), 8.17 (s, 1H, triazole H), 7.88 (t, 1H, *J* = 8.01 Hz, phenyl H) 7.76 (s, 1H, triazole H), 7.42 (dd, 1H, *J* = 2.5 Hz, 14.7 Hz, phenyl H), 7.14 (dd, 1H, *J* = 2.3 Hz, 8.8 Hz, phenyl H), 7.00 (t, 1H, *J* = 9.3 Hz, phenyl H), 5.11–5.14 (m, 1H oxazolidinone H), 4.83 (d, 2H, CH_2), 4.44–4.50 (br., 1H, D-alanine CH), 4.20 (t, 1H, *J* = 9.2 Hz, oxazolidinone H), 3.86 (dd, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H), 3.36–3.64 (m, 2H, piperazine H), 3.28–3.38 (m, 2H, piperazine H, overlaps with DOH signal), 2.58–2.96 (m, 4H, piperazine H), 1.12 (d, 3H, *J* = 6.9 Hz, CH_3). ^{13}C-NMR (DMSO-d_6): δ 169.3, 155.8, 154.2, 153.9, 148.1, 143.3, 135.7, 135.7, 133.9, 133.8, 133.3, 131.5, 127.4, 126.3, 122.0, 120.2, 120.2, 114.7, 107.3, 107.1, 71.3, 52.2, 51.1, 50.4, 48.7, 47.6, 45.2, 41.8, 19.2. IR (KBr pellet, cm^{-1}): ν 3149, 3102, 2828, 1756, 1645, 1524, 1422, 1351, 1230, 1167, 1121, 1079, 1027. LRMS (*m*/*z*): 602.5. Anal. calcd. for $C_{25}H_{27}FN_9O_7S$: C: 49.83, H: 4.52, N: 18.6; found C: 49.55, H: 4.85, N: 18.68.

2.2.18. Preparation of *N*-((*S*)-1-(4-(4-((*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazin-1-yl)-1-oxopropan-2-yl)-3-nitrobenzamide **10h**

Compound **10h** was prepared via a similar procedure to **9a** from **16b** (700 mg, 1.317 mmol) and 3-nitrobenzenesulfonyl chloride (437 mg, 1.975 mmol) to give a yellow solid, 180 mg, yield 23%, recrystallized (EtOAc); mp.: 108–110 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 8.52 (t, 1H, *J* = 2.0 Hz, nitrobenzene H), 8.46—8.48 (m, 2H, nitrobenzene H and of NH; the NH broad peak is exchangeable with D_2O), 8.20–8.21 (m, 1H, nitrobenzene H), 8.18 (d, 1H, *J* = 0.8 Hz, triazole H), 7.89 (t, 1H, *J* = 8.0 Hz, nitrobenzene H), 7.78 (d, 1H, *J* = 0.8 Hz, triazole H), 7.43 (dd, 1H, *J* = 2.6 Hz, 14.7 Hz, phenyl H), 7.15 (dd, 1H, *J* = 2.6 Hz, 8.7 Hz, phenyl H), 7.02 (t, 1H, *J* = 9.3 Hz, phenyl H), 5.12–5.15 (m, 1H, oxazolidinone H), 4.84 (d, 2H, *J* = 5.2 Hz, CH_2), 4.47–4.50 (m, 1H, L-alanine CH), 4.22 (t, 1H, *J* = 9.2 Hz, oxazolidinone H), 3.87 (dd, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H), 3.55–3.67 (m, 2H, piperazine H), 3.33–3.403 (m, 2H, piperazine H, overlaps with DOH signal), 2.80–2.98 (m, 3H, piperazine H), 2.62 (br., 1H, piperazine H), 1.13 (d, 3H, *J* = 6.9 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 155.8, 154.0, 148.1, 133.9, 133.3, 131.5, 126.3, 122.0, 120.2, 114.7, 107.3, 107.1, 71.3, 65.4, 52.2, 51.1, 47.6, 45.2, 41.8, 19.2. IR (KBr pellet, cm^{-1}): ν 3449, 3271, 3150, 2895, 1754, 1645, 1518, 1442, 1421, 1352, 1229, 1169, 1124, 1028. LRMS (*m*/*z*) 602.5 (M^+). Anal. calcd. for $C_{25}H_{27}FN_9O_7S$: C: 49.83, H: 4.52, N: 18.60; found: C: 49.38, H: 4.85, N: 18.74.

2.2.19. Preparation of *N*-((*R*)-1-(4-(4-((*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazin-1-yl)-1-oxopropan-2-yl)-4-nitrobenzenesulfonamide **9i**

Compound **10h** was prepared via a similar procedure to **9a** from **16a** (600 mg, 1.128 mmol) and 4-nitrobenzenesulfonyl chloride (374 mg, 1.862 mmol) to give a yellow solid, 200 mg, yield: 29%, recrystallized (CH_3CN); mp.: 190–192 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z):δ 8.49 (br., 1H, NH, exchangeable with D_2O), 8.38–8.40 (m, 2H, nitrobenzene H), 8.17 (d, 1H, *J* = 0.7 Hz, triazole H), 8.00–8.04 (m, 2H, nitrobenzene H), 7.77 (s, 1H, *J* = 0.7 Hz, triazole H), 7.42 (dd, 1H, *J* = 2.5 Hz, 14.7 Hz, phenyl H), 7.13 (dd, 1H, *J* = 2.6 Hz, 8.7 Hz, phenyl H), 7.02 (t, 1H, *J* = 9.5 Hz, phenyl H), 5.11–5.14 (m, 1H, oxazolidinone H), 4.83 (d, 2H, *J* = 5.0 Hz, CH_2), 4.45–4.48 (m, 1H, D-alanine CH), 4.21 (t, 1H, *J* = 9.2 Hz, oxazolidinone H), 3.86 (dd, 1H, *J* = 5.5 Hz, 9.1 Hz, oxazolidinone H), 3.57–3.65 (m, 2H, piperazine H), 3.38–3.41 (m, 2H, piperazine H, overlaps with the DOH signal, 2.83–2.94 (m, 3H, piperazine H), 2.67–2.71 (br., 1H, piperazine H), 1.11(d, 3H, *J* = 6.8 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 169.2, 153.7, 152.1, 151.8, 147.8, 145.1, 133.6, 133.6, 131.7, 131.7, 126.6, 124.2, 122.6, 118.1, 118.1, 112.6, 112.6, 105.2, 105.0, 69.1, 50.1, 48.9, 48.3, 46.5, 45.4, 43.1, 39.7, 17.1. IR (KBr pellet, cm^{-1}): ν 3268, 3102, 2833, 1747, 1643, 1525, 1426, 1347, 1317, 1228, 1165, 1027. LRMS (*m*/*z*) 602.4 (M^+). Anal. calcd. for $C_{25}H_{27}FN_9O_7S$: C: 49.83, H: 4.52, N: 18.6; found: C: 49.47, H: 4.46, N: 18.4

2.2.20. Preparation of *N*-((*S*)-1-(4-(4-((*R*)-(5-((1*H*-1,2,3-triazol-1-yl) methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazin-1-yl)-1-oxopropan-2-yl)-4-nitrobenzene sulfonamide **10i**

Compound **10l** was prepared via a similar procedure to **9a** from **16b** (700 mg, 1.317 mmol) and 4-nitrobenzenesulfonyl chloride (437 mg, 1.975 mmol) to give a yellow solid, 411 mg, yield

52%, recrystallized (EtOAc); mp.: 203–205 °C. ^{1}H-NMR (DMSO-d_6, 400 MH_Z): δ 8.48 (br., 1H, NH, exchangeable with D_2O), 8.39 (d, 2H, *J* = 8.8 Hz, nitrobenzene H), 8.16 (s, 1H, triazole H), 8.02 (d, 2H, *J* = 8.8 Hz, nitrobenzene H), 7.76 (s, 1H, triazole H), 7.41 (dd, 1H, *J* = 2.4 Hz, 14.8 Hz, phenyl H), 7.14 (dd, 1H, *J* = 2.1 Hz, 8.5 Hz, phenyl H), 7.02 (t, 1H, *J* = 9.3 Hz, phenyl H), 5.10–5.14 (m, 1H, oxazolidinone H), 4.82 (d, 2H, *J* = 5.1 Hz, CH_2), 4.40–4.50 (m, 1H, L-alanine CH), 4.20 (t, 1H, *J* = 9.1 Hz, oxazolidinone H), 3.86 (d, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H), 3.54–3.60 (m, 2H, piperazine H), 3.33 (m, 2H, piperazine H overlaps with DOH signal), 2.83–3.04 (br., 4H, piperazine H), 1.10 (d, 3H, *J* = 6.9 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 169.9, 155.3, 153.7, 153.4, 149.4, 146.7, 135.2, 135.2, 133.3, 133.3, 128.2, 125.8, 124.2, 119.7, 119.7, 114.2, 106.8, 106.6, 70.7, 51.7, 50.5, 49.9, 48.1, 47.1, 44.7, 41.3, 18.7. HRMS (*m*/*z*): calcd. for $C_{25}H_{27}FN_8O_7S$: 602.1707, found 603.1912 (M^+ + H), LRMS (*m*/*z*) 602.4 (M^+). IR (KBr pellet, cm^{-1}): ν 3452, 3279, 3102, 1732, 1649, 1520, 1424, 1352, 1310, 1228, 1196, 1168, 1078, 1042, 1026. Anal. calcd. for $C_{25}H_{27}FN_9O_7S$: C: 49.83, H: 4.52, N: 18.6; found C: 49.7, H: 4.704, N: 18.4.

2.2.21. Preparation of *N*-((*R*)-1-(4-(4-((*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-1-oxopropan-2-yl)-2-aminobenzamide 2,2,2-trifluoroacetate **9j**

An ice cooled solution of 2-((*tert*-butoxycarbonyl) amino-benzoic acid (0.446 gm, 1.881 mmol) in anhyd. DCM (40 mL) was treated with *N*, *N*′-dicyclohexylcarbodiimide (485 mg, 2.351 mmol) and 1-hydroxybenzotriazole (318 mg, 6.787 mmol), respectively, and the reaction mixture was stirred for 2 h under nitrogen. The reaction mixture was then filtered into a solution of the TFA salt **16a** (1.00 g, 1.881 mmol) and TEA (0.760 mL, 5.45 mmol) in anhyd. CH_3CN (15 mL) and left stirring at room temperature overnight. The reaction mixture was concentrated to give a crude brown oil, which was dissolved in DCM, washed with water, 10% Na_2CO_3 solution, brine, dried Na_2SO_4, filtered and concentrated to yield a cream-colored solid. The solid was triturated with ether, collected by filtration and recrystallized from ethyl acetate to give the intermediate compound carbamate **17a** as a solid, 507 mg, yield 43%; mp.: 188–191 °C. This product was utilized for subsequent reactions. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 10.45 (s, 1H, NH, exchangeable with D_2O), 8.89 (d, 1H, *J* = 7.3 Hz, NH, exchangeable with D_2O), 8.19 (d, 1H, *J* = 10.1 Hz, phenyl H), 8.17 (d, 1H, *J* = 0.9 Hz, triazole H), 7.81 (dd, 1H, *J* = 1.4 Hz, 7.9 Hz, phenyl H), 7.77 (d, 1H, *J* = 0.8 Hz, triazole H), 7.48 (t, 1H, *J* = 7.1 Hz, phenyl H), 7.43 (dd, 1H, *J* = 2.4 Hz, 15.4 Hz, phenyl H), 7.04–7.15 (m, 3H, phenyl H), 5.11–5.15 (m, 1H, oxazolidinone H), 4.95–5.00 (m, 1H, D-alanine CH), 4.83 (d, 2H, *J* = 5.0 Hz, CH_2), 4.21 (t, 1H, *J* = 8.2 Hz, oxazolidinone H), 3.86 (dd, 1H, *J* = 5.5 Hz, 9.1 Hz, oxazolidinone H), 3.60–3.78 (m, 4H, piperazine H), 2.94–3.04 (m, 4H, piperazine H), 1.45 (s, 9H, $(CH_3)_3$), 1.34 (d, 3H, *J* = 7.0 Hz, CH_3). MS 636.8 (M^+). ^{13}C-NMR (DMSO-d_6, 400 MH_Z): δ 170.2, 167.8, 155.8, 153.5, 153.4, 152.1, 139.4, 135.4, 135.4, 133.4, 133.3, 132.2, 128.6, 125.9, 121.4, 119.8, 119.3, 118.5, 114.3, 106.9, 82.8, 79.8, 70.8, 51.7, 50.3, 47.1, 45.3, 44.9, 41.7, 27.9. IR (KBr pellet, cm^{-1}): ν 3350, 3116, 2978, 2931, 1758, 1718, 1647, 1587, 1520, 1442, 1227, 1159, 1089, 1026. LRMS (*m*/*z*): 536.4 ($M^+ - (CH_3)_2C{=}CH_2 + CO_2$). Anal. calcd. for $C_{31}H_{37}FN_8O_6$: C: 58.48, H: 5.86, N: 17.18, found C: 58.36, H: 6.19, N: 17.18.

Compound **9j** was prepared via a similar procedure to **16a** from the intermediate **17a** (372 mg, 0.70 mmol) to give a white solid, 157 mg, yield 28%; recrystallized (EtOAc); mp.: 106–109 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 8.40 (d, 1H, *J* = 7.4 Hz, NH, exchangeable with D_2O), 8.18 (d, 1H, *J* = 0.7 Hz, triazole H), 7.78 (s, 1H, *J* = 0.6 Hz, triazole H), 7.60 (d, 1H, *J* = 7.0 Hz, aminobenzene H), 7.43 (dd, 1H, *J* = 2.5 Hz, 14.7 Hz, phenyl H), 7.18 (t, 1H, *J* = 14.7 Hz, aminobenzene H), 7.14 (dd, 1H, *J* = 2.3 Hz, 8.8 Hz, phenyl H), 7.07 (t, 1H, *J* = 9.3 Hz, phenyl H), 6.75 (d, 1H, *J* = 8.2 Hz, aminobenzene H), 6.59 (t, 1H, *J* = 7.5 Hz, aminobenzene H), 5.11–5.14 (m, 1H, oxazolidinone H), 4.90–4.97 (m, 1H, D-alanine CH), 4.84 (d, 2H, *J* = 5.0 Hz, CH_2), 4.21 (t, 1H, *J* = 9.2 Hz, oxazolidinone H), 3.87 (dd, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H, overlapping with $^+NH_3$ signal), 3.60–3.71 (br. m, 7H, piperazine H, overlapping with $^+NH_3$ signal, which is exchangeable with D_2O), 2.95–3.01 (br. d, 4H, *J* = 7.0 Hz, piperazine H), 1.31 (s, 3H, *J* = Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 170.6, 168.1, 158.3, 158.0, 155.4, 153.7, 153.5, 135.4, 135.4, 133.4, 133.3, 133.2, 131.8, 128.5, 125.9, 119.8, 119.7, 116.8, 115.4, 115.1, 114.3, 114.3, 106.8, 106.7, 70.8, 64.9, 51.7, 50.7, 50.3, 47.1, 44.9, 44.7, 41.6, 17.4, 15.2. IR (KBr pellet, cm^{-1}): ν 3447, 3354, 2981,

2829, 1755, 1635, 1517, 1446, 1326, 1230, 1200, 1162, 1027. HRMS (*m*/*z*): for $C_{28}H_{30}F_4N_8O_6$: 650.2224, found 650.0167.

2.2.22. Preparation of *N*-(*R*)-1-(4-(4-((*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-1-oxopropan-2-yl)-3-aminobenzamide 2,2,2-trifluoroacetate **9k**

Compound **9k** was prepared via a similar procedure to **9j** from 3-((*tert*-butoxycarbonyl) amino benzoic acid and **16a** (1.00 g, 1.881 mmol) to give the intermediate compound **17b** as a white solid, 314 mg, yield 26%, recrystallized (EtOAc). mp.: 194–197 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 9.48 (s, 1H, NH, exchangeable with D_2O), 8.55 (d, 1H, *J* = 10.0 Hz, NH, exchangeable with D_2O), 8.17 (d, 1H, *J* = 0.5 Hz, triazole H), 7.90 (s, 1H, aminobenzene H), 7.77 (s, 1H, triazole H), 7.54 (d, 1H, *J* = 19.9 Hz, aminobenzene H), 7.47 (d, 1H, *J* = 14.9 Hz, aminobenzene H), 7.41 (dd, 1H, *J* = 2.5 Hz, 14.7 Hz, phenyl H), 7.33 (t, 1H, *J* = 14.9 Hz, aminobenzene H), 7.05–7.15 (m, 2H, phenyl H), 5.10–5.14 (m, 1H, oxazolidinone H), 4.94–4.08 (m, 1H, D-alanine CH), 4.83 (d, 2H, *J* = 5.10, CH_2), 4.21 (t, 1H, *J* = 9.0 Hz, oxazolidinone H), 3.86 (dd, 1H, *J* = 5.5 Hz, 9.1 Hz, oxazolidinone H), 3.58–3.70 (m, 4H, piperazine H), 2.92–3.05 (m, 4H, piperazine H), 1.48 (s, 9H, $(CH_3)_3$), 1.31(d, 3H, *J* = 7.0 Hz, CH_3). IR (KBr pellet, cm^{-1}): ν 3409, 3255, 2979, 2934, 1763, 1639, 1517, 1480, 1443, 1322, 1233, 1159, 1028. HRMS (*m*/*z*): for $C_{31}H_{37}FN_8O_6$: 636.2820, found 637.2976 (M^+ + H).

The intermediate compound **17b** was deprotected via a similar procedure to **16a** to give the title Compound **9k** as a solid, 180 mg, yield 75%, mp.: 129–132 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 8.54 (d, 1H, *J* = 7.4 Hz, NH, exchangeable with D_2O), 8.18 (s,1H, triazole H), 7.78 (d, 1H, *J* = 0.5 Hz, triazole H), 7.35–7.45 (m, 3H, phenyl H), 7.28 (t, 1H, *J* = 7.8 Hz, phenyl H), 7.12–7.46 (m, 1H, phenyl H), 7.07 (t, 1H, *J* = 9.3 Hz, phenyl H), 7.01 (d, 1H, *J* = 7.5 Hz, phenyl H), 5.11–5.15 (m, 1H, oxazolidinone H), 4.94–4.99 (m, 1H, D-alanine CH), 4.84 (d, 2H, *J* = 5.0 Hz, CH_2), 4.20–4.23 (m, 2H, oxazolidinone H), 3.87 (dd, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H, overlapping with $^+NH_3$ signal), 3.50–3.88 (br. m, 7H, piperazine H, overlapping with $^+NH_3$ signal, which is exchangeable with D_2O), 2.95–3.27 (br. d, 4H, piperazine H), 1.31 (d, 3H, *J* = 7.0 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 170.4, 165.7, 158.3, 158.0, 155.4, 153.7, 153.5, 135.4, 135.1, 133.4, 133.3, 133.2, 129.1, 125.9, 125.9, 119.9, 119.8, 117.1, 116.4, 115.1, 114.3, 106.9, 106.7, 70.8, 51.7, 50.6, 50.3, 47.3, 47.1, 45.1, 44.9, 43.0, 41.6, 17.5. IR (KBr pellet, cm^{-1}): ν 3423, 2921, 1753, 1674, 1638, 1518, 1447, 1326, 1231, 1201, 1135, 1028. HRMS (*m*/*z*): for $C_{28}H_{30}F_4N_8O_6$: 650.2224, found 650.0204 (M^+).

2.2.23. Preparation of *N*-(*R*)-1-(4-(4-((*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-1-oxopropan-2-yl)-4-aminobenzamide 2,2,2-trifluoroacetate **9l**

Compound **9l** was prepared via a similar procedure to **9j** from 3-((*tert*-butoxycarbonyl) amino benzoic acid and **16a** (1.00 g, 1.881 mmol) to give the intermediate compound **17c** as a white solid, 352 mg, yield 32%, recrystallized (EtOAc), mp.: 142–145 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 9.62 (s, 1H, NH, exchangeable with D_2O), 8.47 (d, 1H, *J* = 7.6 Hz, NH, exchangeable with D_2O), 8.17 (d, 1H, *J* = 0.9 Hz, triazole H), 7.82 (d, 2H, *J* = 8.8 Hz, aminobenzene H), 7.77 (d, 1H, *J* = 0.7 Hz, triazole H), 7.52 (d, 2H, *J* = 8.8 Hz, aminobenzene H), 7.43 (dd, 1H, *J* = 2.5 Hz, 14.7 Hz, phenyl H), 7.13 (dd, 1H, *J* = 2.3 Hz, 8.8 Hz, phenyl H), 7.06 (t, 1H, *J* = 8.8 Hz, phenyl H), 5.11–5.14 (m, 1H, oxazolidinone H), 4.95–5.00 (m, 1H, D-alanine CH), 4.83 (d, 2H, *J* = 5.1 Hz, CH_2), 4.21 (t, 1H, *J* = 9.2 Hz, oxazolidinone H), 3.86 (dd, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H), 3.61–3.70 (m, 4H, piperazine H), 2.95–2.98 (m, 4H, piperazine H), 1.49 (s, 9H, $(CH_3)_3$), 1.31 (d, 3H, *J* = 7.0 Hz, CH_3). IR (KBr pellet, cm^{-1}): ν 3409, 2979, 2932, 1758, 1730, 1637, 1517, 1446, 1320, 1232, 1159, 1027. HRMS (*m*/*z*): for $C_{31}H_{37}FN_8O_6$: 636.2820, found 637.3028 (M^+ + H).

The intermediate compound **17c** was deprotected via a similar procedure to **16a** to give the title Compound **9l** as a solid, 261 mg, yield 71%, recrystallized (EtOAc); mp.: 139–142 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 8.20 (d, 1H, *J* = 7.6 Hz, NH, exchangeable with D_2O), 8.18 (d,1H, *J* = 0.5 Hz, triazole H), 7.78 (s, 1H, triazole H), 7.67 (d, 1H, *J* = 8.6 Hz, aminobenzene H), 7.43 (dd, 1H, *J* = 2.4 Hz, 14.6 Hz, phenyl H), 7.14 (dd, 1H, *J* = 2.6 Hz, 8.9 Hz, phenyl H), 7.06 (t, 1H, *J* = 9.3 Hz, phenyl H), 6.63

(d, 2H, *J* = 8.5 Hz, phenyl H), 5.11–5.16 (m, 1H, oxazolidinone H), 4.92–4.98 (m, 1H, D-alanine CH), 4.83 (d, 2H, *J* = 5.0 Hz, CH_2), 4.21 (t, 2H, oxazolidinone H overlaps with $^+NH_3$ signal), 3.90–4.50 (br. m, 4H, oxazolidinone H overlaps with $^+NH_3$ signal), 3.68 (dd, 1H, *J* = Hz, oxazolidinone H), 3.60–3.69 (m, 4H, piperazine H), 2.94–3.30 (br. d, 4H, piperazine H), 1.29 (d, 3H, *J* = 6.9 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 170.8, 165.5, 158.3, 158.1, 155.4, 153.7, 153.5, 135.4, 135.4, 133.8, 133.7, 133.4, 133.3, 133.2, 129.2, 129.0, 128.3, 125.9, 125.9, 119.9, 119.7, 114.8, 114.3, 106.8, 106.7, 70.8, 51.7, 51.7, 50.6, 50.3, 47.3, 47.1, 47.1, 44.9, 44.7, 43.0, 41.6, 17.6. IR (KBr pellet, cm^{-1}): ν 3364, 2985, 2835, 1750, 1674, 1635, 1518, 1448, 1231, 1199, 1134, 1027. HRMS (*m*/*z*): for $C_{28}H_{30}F_4N_8O_6$: 650.2224, found 650.0215 (M^+).

2.2.24. Preparation of *N*-((*S*)-1-(4-(4-((*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-1-oxopropan-2-yl)-2-aminobenzamide 2,2,2-trifluoroacetate **10j**

Compound **10j** was prepared via a similar procedure to **9j** starting from 3-((*tert*-butoxycarbonyl) amino benzoic acid and **16b** (1.00 g, 1.881 mmol) to give the intermediate compound **18a** as a white solid, 377 mg, yield 32%, recrystallized (EtOAc), mp.: 129–131 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 10.46 (s, 1H, NH, exchangeable with D_2O), 8.91 (d, 1H, *J* = 7.3 Hz, NH, exchangeable with D_2O), 8.20 (d, 1H, *J* = 8.5 Hz, phenyl H), 8.18 (d, 1H, *J* = 0.5 Hz, triazole H), 7.81 (d,1H, *J* = 7.9 Hz, phenyl H), 7.78 (s, 1H, triazole H), 7.47–7.50 (m, 1H, phenyl H), 7.43 (dd, 1H, *J* = 2.4 Hz, 14.7 Hz, phenyl H), 7.08–7.14 (m, 3H, phenyl H), 5.12–5.14 (m, 1H, oxazolidinone H), 4.95–5.00 (m, 1H, L-alanine CH), 4.84 (d, 2H, *J* = 5.0 Hz, CH_2), 4.21 (t, 1H, *J* = 9.2 Hz, oxazolidinone H), 3.87 (dd, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H), 3.60–3.78 (m, 4H, piperazine H), 2.90–3.06 (m, 4H, piperazine H), 1.45 (s, 9H, $(CH_3)_3$), 1.34 (d, 3H, *J* = 7.0 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 170.2, 167.8, 155.4, 153.8, 153.5, 152.1, 139.4, 135.4, 135.4, 133.4, 133.3, 133.3, 132.2, 128.6, 125.9, 121.4, 119.8, 119.3, 118.5, 114.3, 106.8, 106.7, 79.8, 70.8, 64.9, 51.7, 50.7, 50.2, 47.1, 45.3, 44.9, 41.7, 30.7, 27.9, 17.1. IR (KBr pellet, cm^{-1}): ν 3350, 3114, 2978, 2931, 1757, 1718, 1647, 1589, 1442, 1227, 1160, 1110, 1050, 1026. HRMS (*m*/*z*): for $C_{31}H_{37}FN_8O_6$: 636.2820, found 637.0000 (M^+ + H). LRMS (*m*/*z*): 536.3 ($M^+ - (CH_3)_2C{=}CH_2 + CO_2$). Anal. calcd. for CHN: C: 58.48, H: 5.86, N: 17.6, found C: 58.50, H: 6.38, N: 18.04.

The intermediate compound **18a** was deprotected via a similar procedure to **16b** to give **10j** as a white solid, 240 mg, yield 57%; recrystallized (EtOAc), mp.: 168–173 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 8.40 (d, 1H, *J* = 7.4 Hz, NH, exchangeable with D_2O), 8.18 (d, 1H, *J* = 0.9 Hz, triazole H), 7.78 (d, 1H, *J* = 0.7 Hz, triazole H), 7.60 (dd, 1H, *J* = 1.3 Hz, 7.9 Hz, phenyl H), 7.43 (dd, 1H, *J* = 2.5 Hz, 14.7 Hz, phenyl H), 7.17–7.20 (m, 1H, phenyl H), 7.14 (dd, 1H, *J* = 2.3 Hz, 8.8 Hz, phenyl H), 7.07 (t, 1H, *J* = 9.3 Hz, phenyl H), 6.75 (d, 1H, *J* = 7.9 Hz, phenyl H), 6.60 (t, 1H, *J* = 7.5 Hz, phenyl H), 5.10–5.15 (m, 1H, oxazolidinone H), 4.92–4.96 (m, 1H, L-alanine CH), 4.83 (d, 2H, *J* = 5.1 Hz, CH_2), 4.21 (t, 1H, *J* = 9.2 Hz, oxazolidinone H), 3.87 (dd, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H), 3.40–3.80 (br. m, 7H, piperazine H, overlapping with $^+NH_3$ signal, which is exchangeable with D_2O), 2.95–3.01 (br. d, 4H, piperazine H), 1.31 (s, 3H, *J* = 7.0 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 170.6, 168.0, 158.3, 158.0, 155.4, 153.7, 153.5, 135.4, 135.4, 133.4, 133.3, 133.2, 131.9, 128.5, 125.9, 119.7, 116.8, 115.5, 115.2, 114.3, 106.8, 106.7, 70.8, 51.7, 50.7, 50.3, 47.1, 44.9, 44.7, 41.6, 30.7, 17.4. IR (KBr pellet, cm^{-1}): ν 3427, 2984, 2922, 1755, 1635, 1587, 1517, 1447, 1327, 1230, 1200, 1138, 1028. HRMS (*m*/*z*): for $C_{28}H_{30}F_4N_8O_6$: 650.2224, found 650.0234 (M^+).

2.2.25. Preparation of *N*-((*S*)-1-(4-(4-((*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-1-oxopropan-2-yl)-3-aminobenzamide 2,2,2-trifluoroacetate **10k**

Compound **10k** was prepared via a similar procedure to **9j** starting from 3-((*tert*-butoxycarbonyl) amino benzoic acid and **16b** (1.00 g, 1.881 mmol) to give the intermediate compound **18b** as a white solid, 480 mg, yield 43%, recrystallized (EtOAc); mp.: 171–174 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 9.50 (s, 1H, NH, exchangeable with D_2O), 8.57 (d, 1H, *J* = 7.6 Hz, NH, exchangeable with D_2O), 8.18 (d, 1H, *J* = 0.9 Hz, triazole H), 7.98 (s, 1H, phenyl H), 7.78 (d,1H, *J* = 0.9 Hz, triazole H), 7.55 (d, 1H, *J* = 7.9 Hz, phenyl H), 7.48 (d, 1H, *J* = 7.9 Hz, phenyl H), 7.44 (dd, 1H, *J* = 2.5 Hz, 14.7 Hz, phenyl H), 7.34 (t, 1H, *J* = 9.2 Hz, phenyl H), 7.13 (dd, 1H, *J* = 2.3 Hz, 9.3 Hz, phenyl H), 7.07 (t, 1H, *J* = 9.3 Hz,

phenyl H), 5.12–5.13 (m, 1H, oxazolidinone H), 4.95–4.97 (m, 1H, L-alanine CH), 4.84 (d, 2H, *J* = 5.1 Hz, CH_2), 4.21 (t, 1H, *J* = 9.2 Hz, oxazolidinone H), 3.87 (dd, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H), 3.61–3.70 (br. m, 4H, piperazine H), 2.96–3.00 (br. d, 4H, piperazine H), 1.49 (s, 9H, $(CH_3)_3$), 1.32 (d, 3H, *J* = 7.0 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 170.4, 165.9, 155.4, 153.7, 153.5, 152.8, 139.6, 135.4, 135.4, 134.8, 133.4, 133.3, 133.2, 128.4, 125.8, 120.9, 120.8, 119.8, 119.7, 117.5, 114.3, 106.8, 106.6, 79.2, 70.8, 51.7, 50.6, 50.3, 47.1, 45.1, 44.9, 41.6, 28.1, 17.4. IR (KBr pellet, cm^{-1}): ν 3414, 3256, 2978, 1760, 1730, 1637, 1556, 1519, 1441, 1414, 1237, 1158, 1029. HRMS (*m*/*z*): for $C_{31}H_{37}FN_8O_6$: 636.2820, found 637.0000 (M^+ + H). CHN Anal. calcd.: C: 58.48, H: 5.86, N: 17.60, found C: 58.78, H: 6.29, N: 17.60.

The intermediate compound **18b** was deprotected via a similar procedure to **16b** to give **10k** as a white solid, 323 mg, yield 71%; recrystallized (EtOAc), mp.: 203–208 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 8.80 (d, 1H, *J* = 7.4 Hz, NH, exchangeable with D_2O), 8.17 (d, 1H, *J* = 0.6 Hz, triazole H), 7.87 (d, 1H, *J* = 7.8 Hz, phenyl H), 7.77 (d, 1H, *J* = 6.1 Hz, triazole H and phenyl H), 7.56 (t, 1H, *J* = 7.9 Hz, phenyl H), 7.47 (d, 1H, *J* = 8.0 Hz, phenyl H), 7.43 (dd, 1H, *J* = 2.4 Hz, 14.7 Hz, phenyl H), 7.13 (dd, 1H, *J* = 2.2 Hz, 8.9 Hz, phenyl H), 7.06 (t, 1H, *J* = 9.3 Hz, phenyl H), 5.10–5.14 (m, 1H, oxazolidinone H), 4.96–5.00 (m, 1H, L-alanine CH), 4.82 (d, 2H, *J* = 5.0 Hz, CH_2), 4.20 (t, 1H, *J* = 9.2 Hz, oxazolidinone H), 3.86 (dd, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H, overlapping with $^+NH_3$ signal), 3.50–3.86 (br. m, 7H, piperazine H, overlapping with $^+NH_3$ signal, exchangeable with D_2O), 2.95–3.00 (m, 4H, piperazine H), 1.32 (d, 3H, *J* = 6.9 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 170.4, 165.7, 158.3, 158.0, 155.4, 153.7, 153.5, 135.4, 135.1, 133.4, 133.3, 133.2, 129.1, 125.9, 125.9, 119.9, 119.8, 117.1, 116.4, 115.1, 114.3, 106.9, 106.7, 70.9, 51.7, 50.6, 50.3, 47.3, 47.1, 45.1, 44.9, 43.0, 41.6, 17.5. IR (KBR pellet, cm^{-1}): 3406, 3061, 2921, 2854, 2585, 1758, 1641, 1519, 1482, 1443, 1417, 1336, 1280, 1216, 1167, 1147, 1023. HRMS (*m*/*z*): for $C_{28}H_{30}F_4N_8O_6$: 650.2224, found 650.0000 (M^+).

2.2.26. Preparation of *N*-((*S*)-1-(4-(4-((*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-1-oxopropan-2-yl)-4-aminobenzamide 2,2,2-trifluoroacetate **10l**

Compound **10l** was prepared via a similar procedure to **9j** starting from 3-((*tert*-butoxycarbonyl) amino benzoic acid and **16b** (1.00 g, 1.881 mmol) to give the intermediate compound **18c** as a white solid, 485 mg, yield 43%, recrystallized (EtOAc); mp.: 139–142 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 9.64 (s, 1H, NH, exchangeable with D_2O), 8.49 (d, 1H, *J* = 7.6 Hz, NH, exchangeable with D_2O), 8.18 (d, 1H, *J* = 0.9 Hz, triazole H), 7.83 (d, 2H, *J* = 8.8 Hz, phenyl H), 7.78 (d, 1H, *J* = 0.8 Hz, triazole H), 7.52 (d, 2H, *J* = 8.7 Hz, phenyl H), 7.43 (dd, 1H, *J* = 2.5 Hz, 14.7 Hz, phenyl H), 7.13 (dd, 1H, *J* = 2.3 Hz, 8.8 Hz, phenyl H), 7.05 (t, 1H, *J* = 9.3 Hz, phenyl H), 5.11–5.15 (m, 1H, oxazolidinone H), 4.95–5.00 (m, 1H, D-alanine CH), 4.84 (d, 2H, *J* = 5.1 Hz, CH_2), 4.21 (t, 1H, *J* = 9.2 Hz, oxazolidinone H), 3.87 (dd, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H), 3.61–3.70 (br. m, 4H, piperazine H), 2.95-2.98 (br. m, 4H, piperazine H), 1.49 (s, 9H, $(CH_3)_3$), 1.31 (d, 3H, *J* = 7.0 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 170.6, 165.2, 155.3, 153.7, 153.5, 152.9, 142.4, 135.4, 135.4, 133.4, 133.3, 133.2, 128.3, 127.2, 125.8, 119.8, 119.7, 117.0, 114.3, 114.3, 106.8, 106.7, 79.5, 70.8, 64.9, 51.7, 50.6, 50.3, 47.1, 44.9, 41.6, 28.1, 17.5. IR (KBr pellet, cm^{-1}): ν 3409, 2979, 2932, 1757, 1727, 1637, 1446, 1320, 1232, 1159, 1027. HRMS (*m*/*z*): for $C_{31}H_{37}FN_8O_6$: 636.2820, found 637.0000 (M^+ + H).

The intermediate compound **18c** was deprotected via a similar procedure to **16a** to give **10l** as a white solid, 229 mg, yield 63%; recrystallized (EtOAc), mp.: 239–242 °C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 8.60 (br. d, 1H, *J* = 6.5 Hz, NH, exchangeable with D_2O), 8.17 (d, 1H, *J* = 0.8 Hz, triazole H), 7.89 (d, 2H, *J* = 8.5 Hz, phenyl H), 7.76 (s, 1H, *J* = 0.7 Hz, triazole H), 7.42 (dd, 1H, *J* = 2.5 Hz, 14.7 Hz, phenyl H), 7.21 (d, 2H, *J* = 8.0 Hz, phenyl H), 7.12 (dd, 1H, *J* = 2.3 Hz, 8.8 Hz, phenyl H), 7.06 (t, 1H, *J* = 9.3 Hz, phenyl H), 5.10–5.13 (m, 1H, oxazolidinone H), 4.94–4.99 (m, 1H, L-alanine CH), 4.82 (d, 2H, *J* = 5.1 Hz, CH_2), 4.20 (t, 1H, *J* = 9.2 Hz, oxazolidinone H, partially overlaps with the $^+NH_3$ signal), 3.74–4.30 (br., 3H, $^+NH_3$, exchangeable with D_2O, partially overlaps with oxazolidinone H) 3.86 (dd, 1H, *J* = 5.7 Hz, 9.3 Hz, oxazolidinone H, partially overlaps with the $^+NH_3$ signal), 3.59–3.72 (br. m, 4H, piperazine H), 2.95-2.99 (br. d, 4H, piperazine H), 1.31 (s, 3H, *J* = 7.0 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 600 MH_Z): δ 170.5, 165.0, 155.3, 153.7, 153.4, 135.3, 135.3, 133.3, 133.2, 129.1, 128.9, 125.8, 119.7, 119.4,

114.3, 106.9, 106.7, 70.7, 51.7, 50.6, 50.2, 47.1, 47.1, 45.0, 44.9, 41.9, 17.4. IR (KBr pellet, cm^{-1}): ν 3407, 2833, 2575, 1758, 1640, 1515, 1417, 1234, 1217, 1020. HRMS (*m*/*z*): for $C_{28}H_{30}F_4N_8O_6$: 650.2224, found 649.0000 ($M^+ - H$) and 537.000 ($M^+ - CF_3CO_2H$).

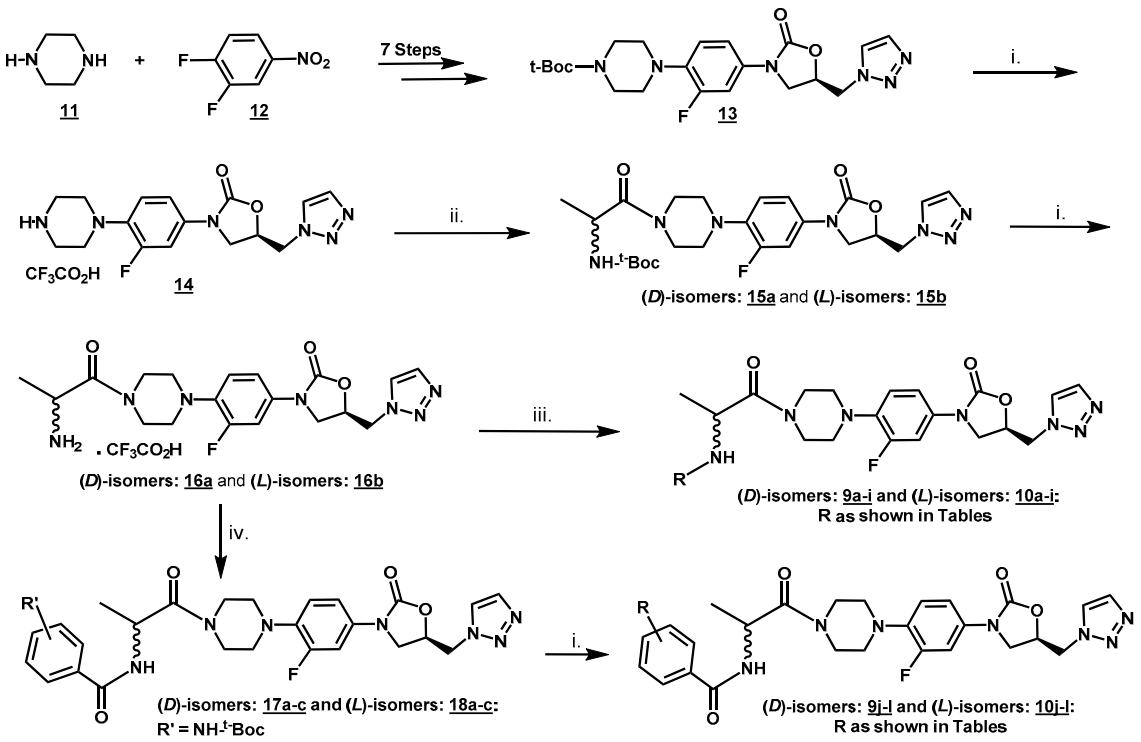
2.3. Antibacterial Susceptibility Testing

Antibacterial susceptibility testing was performed by determining the minimum inhibitory concentrations (MIC, μg/mL), which is defined as the lowest concentration of a compound that inhibits visible bacterial growth. The MIC was determined on Mueller–Hinton (MH) agar with medium containing dilutions of antibacterial agents ranging from 0.12–32 μg/mL. Linezolid [24,28], used as the reference standard antibacterial agent, was dissolved in 60% ethanol in water and test compounds in 80% DMSO in water. The antibacterial activity of the compounds was evaluated against 6 standard reference Gram-positive and Gram-negative bacterial strains available at the MRSA Reference Laboratory, Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait. The Gram-positive standard bacterial strains used in this study consisted of *S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228 and *E. faecalis* ATCC 29212, and the Gram-negative bacterial strains included *E. coli* ATCC 25922, *H. influenzae* ATCC 49247 and *M. catarrhalis* ATCC 8176. MH agar plates were used for all staphylococci and enterococci, while the MH agar plates were supplemented with 5% sheep blood to facilitate the growth of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. For all, the final bacterial concentration for inocula was 10^7 CFU/mL, incubated at 35 °C for 18 h.

3. Results and Discussion

3.1. Chemistry

The final compounds, (D)-alaninyl isomers **9a–l** and the (L)-alaninyl isomers **10a–l**, were synthesized as outlined in Scheme 1 according to reported literature procedures starting from commercially available piperazine **11** and 3,4-difluoronitrobenzene **12** [18,23,28] with minor modifications to the synthetic route and outlined in Scheme 1. Using standard organic transformation, intermediate compound 5-triazolylmethyl derivative **13** was deprotected using TFA (trifluoroacetic acid) in DCM (dichloromethane) to afford the TFA salt **14** in quantitative yield. Compound **14** was coupled with *tert*-(D)- and *tert*-(L)-alanine using dicyclohexylcarbodiimide and 1-hydroxybenzotriaole as coupling reagents under standard derivatization protocols to give the *tert*-(D)-alaninyl **15a** and the *tert*-(L)-alaninyl derivatives **15b**, respectively in very good yields. Deprotection of Compounds **15a** and **15b**, in TFA and DCM, gave the (D)-alaninyl **16a** and the (L)-alaninyl **16b** TFA salts in excellent yields. Further chemical transformation via the reaction of the TFA salts with activated nitro-benzoic and nitro-heteroaroyl acids or the respective acid chlorides and nitrobenzene sulfonyl chlorides yielded the (D)-alaninyl **9a–f** and (L)-alaninyl **10a–f** amide and the (D)-alaninyl **9g–i** and (L)-alaninyl **10g–i** sulfonamide derivatives, respectively. For preparation of the amino benzoyl derivatives **9j–l** and **10j–l**, the TFA salts **16a–b** were reacted with 2-, 3- and 4-((*tert*-butoxycarbonyl) amino benzoic acids to afford the boc-protected (D)-alaninyl **17a–c** and (L)-alaninyl **18a–c** amide derivatives, respectively. The deprotection of Boc from these derivatives using TFA in DCM gave the final 2-, 3- and 4-aminobenzamide (D)-alaninyl **9j–l** and (L)-alaninyl **10j–l** derivatives as TFA salts. All compounds were isolated, purified and characterized as reported in the experimental sections and evaluated for their antibacterial activities as detailed in the Antibacterial Evaluation Section.



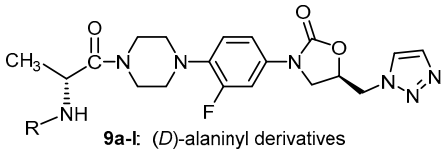
Scheme 1. Synthesis of 5-(1*H*-1,2,3-triazolyl)methyl (*D*)- and (L)-alaninyl-oxazolidinone derivatives. (**i**) TFA/DCM, 0 °C-r.t.; (**ii**) CH_3CN/DCM/*tert*-boc-(*D*)- or (L)-alanine/DCC/1-HOBT/TEA, r.t.; (**iii**) CH_3CN/DCM/nitroaroyl acid/DCC/1-HOBT/TEA, or CH_3CN/DCM/nitroheteroaroyl chloride, or nitroarylsulfonyl chloride/TEA, room temperature.

3.2. Antibacterial Evaluation

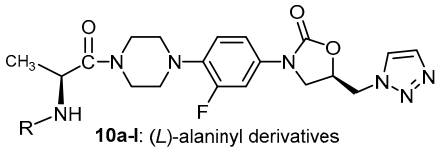
A total of twenty-four final compounds comprised of the (D)-alaninyl **9a–l** and (L)-alaninyl **10a–l** oxazolidinone derivatives containing nitro- and amino-aroyl substitutions and two *tert*-butoxycarbonyl intermediate compounds (**15a** and **15b**) were evaluated for their antibacterial activity against standard Gram-positive and Gram-negative bacterial strains. The Gram-positive standard bacterial strains used in this study consisted of *S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228 and *E. faecalis* ATCC 29212, while the Gram-negative bacterial strains included *Escherichia coli* ATCC 25922, *Haemophilus influenzae* ATCC 49247 and *Moraxella catarrhalis* ATCC 8176. Antibacterial susceptibility testing was carried out using the agar dilution method on Mueller–Hinton (MH) agar according to the Clinical and Laboratory Standard Institute (CSLI) [29], and the data are presented in Table 1. With a minimum inhibitory concentration of >32 μg/mL, none of the compounds demonstrated acceptable antibacterial activity against the Gram-negative bacterial strains, namely *E. coli* ATCC 25922 and *H. influenzae* ATCC 49247. Overall, the novel (D)-alaninyl and (L)-alaninyl oxazolidinones showed moderate to strong antibacterial activity against the Gram-positive bacterial strains tested with a MIC range of 2–>16 μg/mL. In general, there is no identifiable significant difference between the antibacterial activity of the (D)-alaninyl and (L)-alaninyl oxazolidinone derivatives, suggesting similar binding interaction at the ribosomal receptor binding site irrespective of the stereochemistry at the alaninyl side-chain spacer. However, in some of the derivatives, the (L)-alaninyl spacer seemed to have a slightly improved antibacterial activity; for example, the 4-nitrobenzoyl (D)-alaninyl oxazolidinone derivative **9c** (MIC: 8 and 4 μg/mL) was 1–3-fold less active than the corresponding (L)-alaninyl derivative **10c** (MIC: 2 and 2 μg/mL) against *S. epidermidis* ATCC 12228 and *E. faecalis* ATCC 29212, respectively. Similarly, the 5-nitrofuran-2-carbonyl substituted (L)-alaninyl oxazolidinone derivative **10e** (MIC: 2 and 2 μg/mL) demonstrated 1–3-fold superior antibacterial activity to the corresponding (D)-alaninyl oxazolidinone derivative **9e** (MIC: 8 and 4 μg/mL), against *S. aureus* ATCC 25923 and

E. faecalis ATCC 29212, respectively. Overall, aminoaryl, nitroaroyl and nitroheteroaroyl substitutions in the (D/L)-alaninyl oxazolidinone derivatives favored retention of antibacterial activity and showed selective activity against *S. epidermidis* ATCC 12228 and *E. faecalis* ATCC 29212. The precise reasons for this are unknown. However, the presence of these moieties might result in additional interactions at the ribosomal receptor binding sites, due to a combination of H-bond acceptor and/or donor groups coupled with potential van der Waals interactions [15,27]. In addition, the observed selective activity against *S. epidermidis* ATCC 12228 and *E. faecalis* ATCC 29212 could also suggest a subtle difference in the conformation of rRNA nucleotides in these two bacterial strains, which may have some effect on the interaction with the compounds. Conformation changes of rRNA nucleotide had been utilized to explain dramatic differences in the interactions for some antibiotics, namely macrolides and lincosamides, respectively [14,30]. The nitro-substituted derivatives showed improved activity against the Gram-negative respiratory pathogen *M. catarrhalis* ATCC 25922 with an MIC range of 2–8 μg/mL. In addition, previous studies from our laboratory and others have shown that incorporation of 5-nitro-2-furoyl and 3,5-dinitrobenzoyl moieties selectively enhanced antibacterial activity of *N*-substituted-piperazinyl oxazolidinone derivatives [27,31]. However, we anticipated that the incorporation of the alanine spacer group may result in potential hydrogen bond acceptor and donor interactions in addition to hydrophobic interaction due to the presence of the aroyl, heteroaroyl and methyl moieties, whose orientation at the ribosomal receptor binding site may result in favorable stereochemistry that might positively influence the observed antibacterial activity. Moreover, the 5-nitrofuran-2-carbonyl (D/L)-alaninyl oxazolidinone derivatives were less active than the previously reported 5-nitrofuran-2-carbonyl glycinyl oxazolidinone derivatives with demonstrated potent antibacterial activity, with MIC value ranges of 2–8 and 0.06–0.50 μg/mL [23], respectively. The findings from the present study further suggest that the glycinyl spacer probably favors or permits a more effective interaction of the compounds at the bacterial ribosomal receptor binding site [27], which eventually translates into more potent antibacterial activity [23]. Furthermore, previous studies from our laboratory and others have demonstrated that unsubstituted-benzenesulfonyl and tolylsulfonyl groups generally resulted in oxazolidinone derivatives with reduced antibacterial activity compared with the benzoyl and substituted-benzoyl derivatives [26,27,31]. Therefore, data from the present study further elaborate that the introduction of the electron withdrawing nitro group alone does not significantly improve antibacterial activity. This is evident from the fact that the nitrobenzenesulfonyl (D/L)-alaninyl oxazolidinone derivatives were also generally less active than the corresponding nitrobenzoyl derivatives with an MIC value range of 2–>16 μg/mL.

Table 1. Antibacterial activity of *D*- and *L*-alaninyl triazolyl-oxazolidinone derivatives.



9a-l: (*D*)-alaninyl derivatives



10a-l: (*L*)-alaninyl derivatives

Compound	R	MIC (μg/mL) for			
		S. aureus ATCC25923	*S. epidermidis* ATCC12228	*E. faecalis* ATCC29212	*M. catarrhalis*
15a (D)	*tert*-butoxycarbonyl	16	8	8	>16
15b (L)	*tert*-butoxycarbonyl	8	8	8	>16
9a	2-nitrobenzoyl	8	4	2	16
10a	2-nitrobenzoyl	8	2	4	8
9b	3-nitrobenzoyl	2	2	2	4
10b	3-nitrobenzoyl	2	2	2	2
9c	4-nitrobenzoyl	4	8	4	4
10c	4-nitrobenzoyl	4	2	2	4
9d	3,5-dinitrobenzoyl	2	2	2	2
10d	3,5-dinitrobenzoyl	2	2	2	2
9e	5-nitrofuran-2-carbonyl	8	2	4	8
10e	5-nitrofuran-2-carbonyl	2	2	2	2

Table 1. *Cont.*

Compound	R	MIC (μg/mL) for			
		S. aureus ATCC25923	*S. epidermidis* ATCC12228	*E. faecalis* ATCC29212	*M. catarrhalis*
9f	5-nitrothiopehene-2-carbonyl	2	2	2	2
10f	5-nitrothiopehene-2-carbonyl	2	2	2	2
9g	2-nitrobenezesufonyl	16	8	8	>16
10g	2-nitrobenezesufonyl	16	8	8	16
9h	3-nitrobenezesufonyl	>16	4	16	16
10h	3-nitrobenezesufonyl	16	8	8	4
9i	4-nitrobenezesufonyl	>16	4	16	16
10i	4-nitrobenezesufonyl	>16	2	4	4
9j	2-aminobenzoyl .CF_3CO_2H	4	2	2	4
10j	2-aminobenzoyl .CF_3CO_2H	4	2	4	4
9k	3-aminobenzoyl .CF_3CO_2H	8	2	4	8
10k	3-aminobenzoyl .CF_3CO_2H	4	2	2	4
9l	4-aminobenzoyl .CF_3CO_2H	4	2	2	4
10l	4-aminobenzoyl .CF_3CO_2H	2	2	2	4
Linezolid		2	2	2	8

4. Conclusions

In conclusion, all the newly synthesized D- and L-alaninyl oxazolidinone derivatives demonstrated antibacterial activity against all standard Gram-positive bacterial strains and one Gram-negative bacterial strain tested. The compounds were devoid of activity against standard Gram-negative bacterial strains, namely *E. coli* and *H. influenzae*. Moreover, the 3,5-dinitrobenzoyl and 5-nitroheteroaroyl substitution pattern on alanine nitrogen enhanced antibacterial activity, while amino-aroyl substitution seems to selectively favor activity against *S. epidermidis* and *E. faecalis*. The introduction of nitro groups on the benzenesulfonyl derivatives did not improve their antibacterial potency. Finally, the incorporation of the D- and L-alaninyl spacer did not have a significant effect on the activity of this series of compounds.

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Conflicts of Interest: The authors declare no conflict of or secondary interest.

References

1. Butler, M.S.; Blaskovich, M.A.; Cooper, M.A. Antibiotics in the clinical pipeline at the end of 2015. *J. Antibiot.* **2017**, *70*, 3–24. [CrossRef] [PubMed]
2. Fernandes, P.; Martens, E. Antibiotics in late clinical development. *Biochem. Pharmacol.* **2017**, *133*, 152–163. [CrossRef] [PubMed]
3. Torrice, M. Antibaterial boom and bust. *C&EN* **2013**, *91*, 34–37.
4. Frieden, T. *Antibiotic Resistance Threats in the United States*; U.S. Centers for Disease Control and Prevention: Atlanta, GA, USA, 2013; pp. 1–114.
5. Holmes, N.E.; Tong, S.Y.; Davis, J.S.; van Hal, S.J. Treatment of methicillin-resistant Staphylococcus aureus: Vancomycin and beyond. *Semin. Respir. Crit. Care Med.* **2015**, *36*, 17–30. [CrossRef] [PubMed]
6. Poce, G.; Cocozza, M.; Consalvi, S.; Biava, M. SAR analysis of new anti-TB drugs currently in pre-clinical and clinical development. *Eur. J. Med. Chem.* **2014**, *86*, 335–351. [CrossRef] [PubMed]
7. WHO. Global Tuberculosis Report 2016. Available online: http://apps.who.int/iris/bitstream/10665/250441/1/9789241565394-eng.pdf?ua=1 (accessed on 22 April 2018).

8. Bassetti, M.; Righi, E. Development of novel antibacterial drugs to combat multiple resistant organisms. *Langenbeck's Arch. Surg.* **2015**, *400*, 153–165. [CrossRef] [PubMed]
9. Holmes, N.E.; Howden, B.P. What's new in the treatment of serious MRSA infection? *Curr. Opin. Infect. Dis.* **2014**, *27*, 471–478. [CrossRef] [PubMed]
10. Xu, H.B.; Jiang, R.H.; Li, L.; Xiao, H.P. Linezolid in the treatment of MDR-TB: A retrospective clinical study. *Int. J. Tuberc. Lung D* **2012**, *16*, 358–363. [CrossRef] [PubMed]
11. Ager, S.; Gould, K. Clinical update on linezolid in the treatment of Gram-positive bacterial infections. *Infect. Drug Resist.* **2012**, *5*, 87–102. [CrossRef] [PubMed]
12. Shaw, K.J.; Barbachyn, M.R. The oxazolidinones: Past, present, and future. *Ann. N. Y. Acad. Sci.* **2011**, *1241*, 48–70. [CrossRef] [PubMed]
13. Shinabarger, D.L.; Marotti, K.R.; Murray, R.W.; Lin, A.H.; Melchior, E.P.; Swaney, S.M.; Dunyak, D.S.; Demyan, W.F.; Buysse, J.M. Mechanism of action of oxazolidinones: Effects of linezolid and eperezolid on translation reactions. *Antimicrob. Agents chemother.* **1997**, *41*, 2132–2136. [PubMed]
14. Wilson, D.N.; Nierhaus, K.H. The oxazolidinone class of drugs find their orientation on the ribosome. *Mol. Cell* **2007**, *26*, 460–462. [CrossRef] [PubMed]
15. Ippolito, J.A.; Kanyo, Z.F.; Wang, D.; Franceschi, F.J.; Moore, P.B.; Steitz, T.A.; Duffy, E.M. Crystal structure of the oxazolidinone antibiotic linezolid bound to the 50S ribosomal subunit. *J. Med. Chem.* **2008**, *51*, 3353–3356. [CrossRef] [PubMed]
16. Lawrence, K.R.; Adra, M.; Gillman, P.K. Serotonin toxicity associated with the use of linezolid: A review of postmarketing data. *Clin. Infect. Dis.* **2006**, *42*, 1578–1583. [CrossRef] [PubMed]
17. Leach, K.L.; Brickner, S.J.; Noe, M.C.; Miller, P.F. Linezolid, the first oxazolidinone antibacterial agent. *Ann. N. Y. Acad. Sci.* **2011**, *1222*, 49–54. [CrossRef] [PubMed]
18. Reck, F.; Zhou, F.; Girardot, M.; Kern, G.; Eyermann, C.J.; Hales, N.J.; Ramsay, R.R.; Gravestock, M.B. Identification of 4-substituted 1,2,3-triazoles as novel oxazolidinone antibacterial agents with reduced activity against monoamine oxidase A. *J. Med. Chem.* **2005**, *48*, 499–506. [CrossRef] [PubMed]
19. Srivastava, B.K.; Soni, R.; Patel, J.Z.; Jain, M.R.; Patel, P.R. Oxazolidinone antibacterials and our experience. *Anti-Infect. Agents Med. Chem.* **2008**, *7*, 258–280. [CrossRef]
20. Poel, T.J.; Thomas, R.C.; Adams, W.J.; Aristoff, P.A.; Barbachyn, M.R.; Boyer, F.E.; Brieland, J.; Brideau, R.; Brodfuehrer, J.; Brown, A.P.; et al. Antibacterial oxazolidinones possessing a novel C-5 side chain(5R)-trans-3-[3-fluoro-4-(1-oxotetrahydrothiopyran-4-yl-phenyl]-2-oxooxazolidinone-5-carboxylic acid amide (PF-00422602), a new lead compound. *J. Med. Chem.* **2007**, *50*, 5886–5889. [CrossRef] [PubMed]
21. Al-Tannak, N.F.; Phillips, O.A. Antimycobacterial Activities of N-Substituted-Glycinyl 1H-1,2,3-Triazolyl Oxazolidinones and Analytical Method Development and Validation for a Representative Compound. *Sci. Pharm.* **2017**, *85*, 34. [CrossRef] [PubMed]
22. Hauck, S.I.; Cederberg, C.; Doucette, A.; Grosser, L.; Hales, N.J.; Poon, G.; Gravestock, M.B. New carbon-linked azole oxazolidinones with improved potency and pharmacokinetics. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 337–340. [CrossRef] [PubMed]
23. Phillips, O.A.; Udo, E.E.; Abdel-Hamid, M.E.; Varghese, R. Synthesis and antibacterial activities of N-substituted-glycinyl 1H-1,2,3-triazolyl oxazolidinones. *Eur. J. Med. Chem.* **2013**, *66*, 246–257. [CrossRef] [PubMed]
24. Phillips, O.A.; Udo, E.E.; Ali, A.A.; Al-Hassawi, N. Synthesis and antibacterial activity of 5-substituted oxazolidinones. *Bioorg. Med. Chem. Lett.* **2003**, *11*, 35–41. [CrossRef]
25. Phillips, O.A.; Udo, E.E.; Ali, A.A.; Samuel, S.M. Synthesis and antibacterial activity of new N-linked 5-triazolylmethyl oxazolidinones. *Bioorg. Med. Chem.* **2005**, *13*, 4113–4123. [CrossRef] [PubMed]
26. Phillips, O.A.; Udo, E.E.; Ali, A.A.; Samuel, S.M. Structure-antibacterial activity of arylcarbonyl- and arylsulfonyl-piperazine 5-triazolylmethyl oxazolidinones. *Eur. J. Med. Chem.* **2007**, *42*, 214–225. [CrossRef] [PubMed]
27. Wang, X.J.; Wu, N.; Du, G.J.; Zhao, S.Q.; Yan, M.; Gu, L.Q. Synthesis and antibacterial activities of eperezolid analogs with glycinyl substitutions. *Arch. Pharm. (Weinheim)* **2009**, *342*, 377–385. [CrossRef] [PubMed]
28. Brickner, S.J.; Hutchinson, D.K.; Barbachyn, M.R.; Manninen, P.R.; Ulanowicz, D.A.; Garmon, S.A.; Grega, K.C.; Hendges, S.K.; Toops, D.S.; Ford, C.W.; et al. Synthesis and antibacterial activity of U-100592 and U-100766, two oxazolidinone antibacterial agents for the potential treatment of multidrug-resistant gram-positive bacterial infections. *J. Med. Chem.* **1996**, *39*, 673–679. [CrossRef] [PubMed]

29. Clinical and Laboratory Standards Institute (CLSI). *Susceptibility Testing of Mycobacteria, Nocaridae, and Other Aerobic Actinomycetes. Approved Standard*, 2nd ed.; CLSI Document M24-A2; CLSI: Wayne, PA, USA, 2011.
30. Wilson, D.N.; Harms, J.M.; Nierhaus, K.H.; Schlunzen, F.; Fucini, P. Species-specific antibiotic-ribosome interactions: Implications for drug development. *Biol. Chem.* **2005**, *386*, 1239–1252. [CrossRef] [PubMed]
31. Phillips, O.A.; Udo, E.E.; Abdel-Hamid, M.E.; Varghese, R. Effects of varied substituents on the antibacterial activity of triazolylmethyl oxazolidinones. *Arch. Pharm. (Weinheim)* **2012**, *345*, 790–803. [CrossRef] [PubMed]