

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

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Summary

Bacterial resistance towards existing class of antibacterial drugs continues to increase posing significant threat to clinical usefulness of these drugs. This increasing and alarming rates of antibacterial resistance development and the decline in the number of new antibacterial drugs approval continue to serve as major impetus for research into discovery and development of new antibacterial agents. We synthesized a series *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 3,5-dinitrobenzoyl substituent), **10e** (*D*-alaninyl derivative bearing 5-nitrofurancarboxyl group) and **9f** and **10f** (*D*- and *L*-alaninyl derivatives bearing 5-nitrothiophene carbonyl moiety) demonstrated antibacterial activity (MIC:2 µg/mL) against *S. aureus*, *S. epidermidis*, *E. faecalis* and *M. 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.

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 impetus for research for novel antibacterial drug discovery and development of more potent and safer antibacterial agents.

Oxazolidinones exemplified by linezolid (**1**, Fig. 1) and more recently tedizolid phosphate (**2a**, Fig. 1), which is a pro-drug of the active form tedizolid (**2b**, Fig. 1) represent derivatives of this class of compounds with potent activity against multidrug-resistant Gram-positive pathogenic bacterial strains [8-10]. Oxazolidinones inhibit bacterial protein biosynthesis by binding to sites on the bacterial ribosomes, thus preventing formation of a functional 70S initiation complex [11-13]. While more detail 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 broader spectrum of activity, improve potency and to reduce side-effects compared to linezolid. The triazolyl derivatives (**3**, Fig. 1) [16] and the reverse C5 amide derivative of linezolid of general structure (**4**, Fig. 1) have been shown to exhibit strong antibacterial activity and lower monoamine oxidase inhibition, [17]. In addition, compound **4** also exhibited reduced myelotoxicity in rodents compared to linezolid [18].

Studies from our laboratory and those of others have reported the synthesis of several triazolylmethyl oxazolidinones containing acyl or aroyl substituted-piperazine of

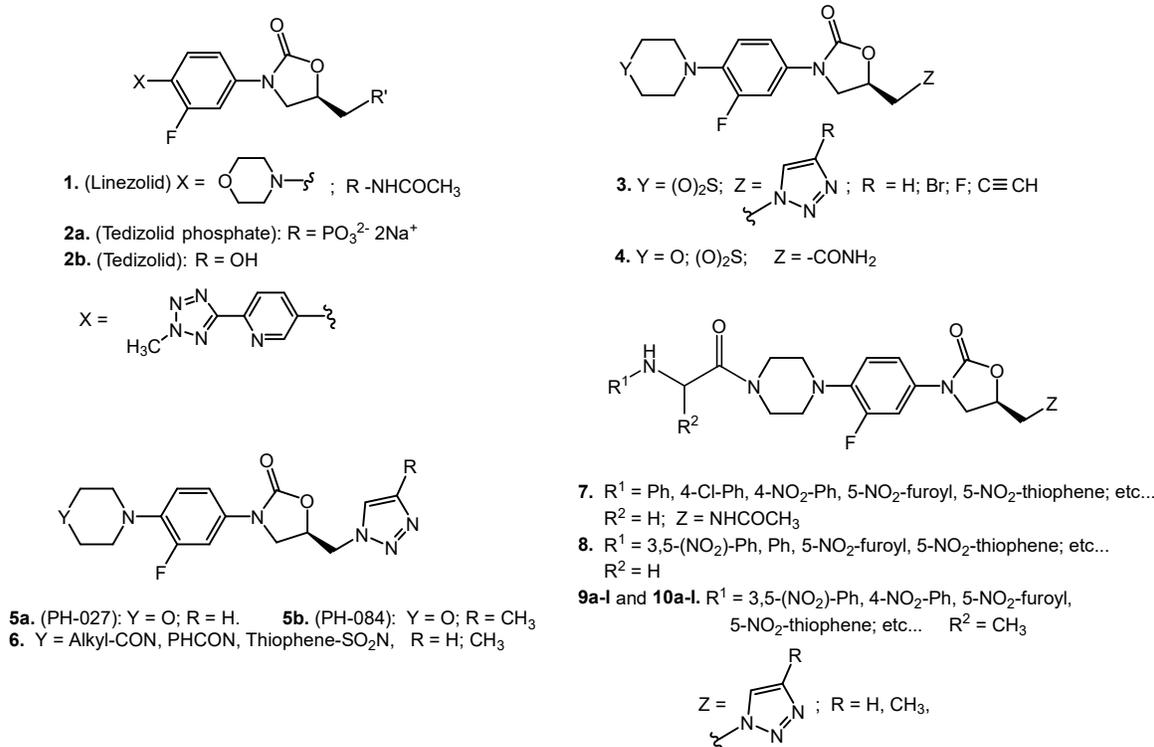


Figure 1. Chemical structure of oxazolidinone antibacterial agents

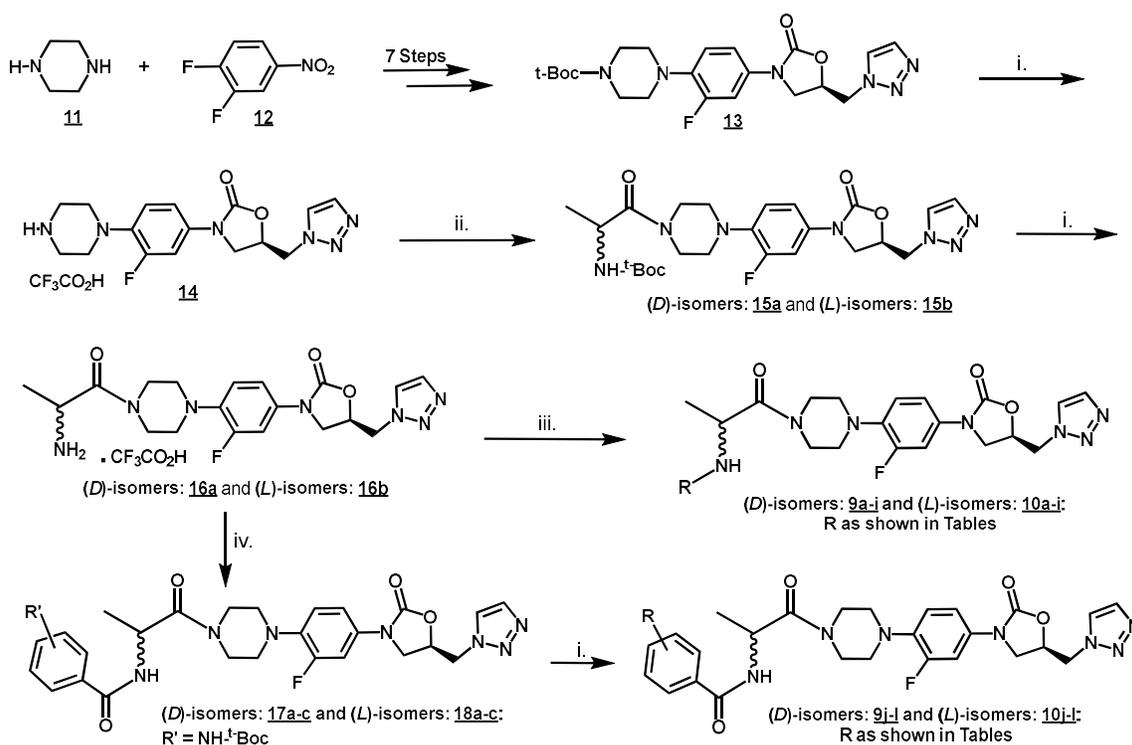
general structures **5**, **6**, **7** and **8** (Fig. 1) with potent activity that is comparable or superior to linezolid against Gram-positive bacterial strains including MRSA, VRE, PRSP and MDR-TB [16, 19-25]. Moreover, other studies have also demonstrated that the incorporation of an *N*-substituted-glycyl moieties on the 4-*N*-piperazine position resulted in oxazolidinone derivatives that would fit a potential pocket identified at the bacterial ribosomal receptor site [25]. The potent oxazolidinones in the glycyl series contain the *N*-nitroaryl substituents on the glycine nitrogen [23, 25], in particular the 3,5-dinitrobenzoyl and the 5-nitrofuroyl derivatives demonstrated MIC values in the range 0.06-16 µg/ml against Gram-positive bacterial clinical isolates. On the basis of the potent antibacterial activities of the *N*-substitutedglycyl-triazolyl oxazolidinones, we decided to investigate the effects of incorporating a *D*- and *L*-alanine as spacers instead of the glycine on the antibacterial activity with focus on the nitro and amino substituted aryl and heteroaryl derivatives. We hereby report the synthesis and qualitative

structure-antibacterial activity relationships of new *N*-substituted-*D*- and *L*-alaninyl-triazolyl oxazolidinone derivatives of general structures **9a-l** and **10a-l**, respectively.

2.0 Results and Discussion

2.1 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** [16, 23, 26] with minor synthetic modifications. Using standard organic transformation, intermediate compound 5-triazolylmethyl derivative **13** was deprotected using TFA in DCM to afford the TFA salt **14** in quantitative yield. Compound **14** was coupled with *tert*-(*D*)- and *tert*-(*L*)-alanine using dicyclohexylcarbodiimide and 1-hydroxybenzotriazole 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 reaction of the TFA salts with activated nitro-benzoic and nitro-heteroaryl acids, 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 activity



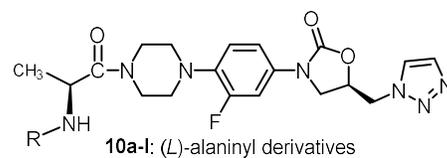
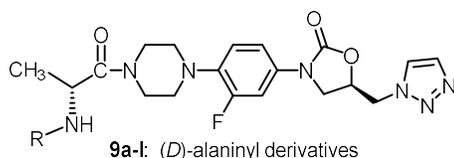
Scheme 1. Synthesis of 5-(1*H*-1,2,3-triazolyl)methyl (*D*)- and (*L*)-alaninyl-oxazolidinone derivatives. i. TFA/DCM, 0 °C-r.t.; ii. CH₃CN/DCM/*tert*-boc-(*D*)- or (*L*)-alanine/DCC/1-HOBT/TEA, r.t.; iii. CH₃CN/DCM/nitroaryl acid/DCC/1-HOBT/TEA,; or CH₃CN/DCM/nitroheteroaryl chloride or nitroarylsulfonyl chloride/TEA, r.t.

2.2 Antibacterial evaluation

A total of twenty four final compounds comprising of the (*D*)-alaninyl **9a-l** and (*L*)-alaninyl **10a-l** oxazolidinone derivatives containing nitro- and amino-aryl 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 *E. coli* ATCC 25922, *H.*

influenzae ATCC 49247 and *M. 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 (CLSI) [27] and the data are presented in Table 1. With a minimum inhibitory concentration of $> 32 \mu\text{g/mL}$, 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 MIC range of $2 - >16 \mu\text{g/mL}$. In general, there is no identifiable significant difference between the antibacterial activity of the (*D*)-alaninyl and (*L*)-alaninyl oxazolidinone derivatives suggesting similar binding 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 seems to impact a slightly improved antibacterial activity, for example the 4-nitrobenzoyl (*D*)-alaninyl oxazolidinone derivative **9c** (MIC: 8 and $4 \mu\text{g/mL}$) was 1-3 fold less active than the corresponding (*L*)-alaninyl derivative **10c** (MIC: 2 and $2 \mu\text{g/mL}$) 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 $2 \mu\text{g/mL}$) demonstrated 1-3 fold superior antibacterial activity to the corresponding (*D*)-alaninyl oxazolidinone derivative **9e** (MIC: 8 and $4 \mu\text{g/mL}$), against *S. aureus* ATCC 25923 and *E. faecalis* ATCC 29212, respectively. Overall, aminoaroyl, 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 is un know. The nitro substituted derivative showed improved activity against the Gram-negative respiratory pathogen *M. catarrhalis* ATCC 25922 with MIC range of $2-8 \mu\text{g/mL}$. 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 [25, 28]. Although we anticipated that the incorporation of the alanine spacer group may

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



Compd	R	MIC ($\mu\text{g/mL}$) for			
		<i>S. aureus</i> ATCC2592 3	<i>S.</i> <i>epidermidis</i> ATCC1222 8	<i>E. faecalis</i> ATCC2921 2	<i>M.</i> <i>cattarrhalis</i> s
15a (<i>D</i>)	<i>tert</i> - butoxycarbonyl	16	8	8	> 16
15b (<i>L</i>)	<i>tert</i> - 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-nitrofurane-2- carbonyl	8	2	4	8
10e	5-nitrofurane-2- carbonyl	2	2	2	2
9f	5-nitrothiophene- 2-carbonyl	2	2	2	2
10f	5-nitrothiophene- 2-carbonyl	2	2	2	2
9g	2- nitrobenzenesulfonyl	16	8	8	> 16
10g	2- nitrobenzenesulfonyl	16	8	8	16
9h	3- nitrobenzenesulfonyl	> 16	4	16	16
10h	3- nitrobenzenesulfonyl	16	8	8	4
9i	4- nitrobenzenesulfonyl	> 16	4	16	16

	1				
10i	4-nitrobenzenesulfonyl	> 16	2	4	4
9j	2-aminobenzoyl .CF ₃ CO ₂ H	4	2	2	4
10j	2-aminobenzoyl .CF ₃ CO ₂ H	4	2	4	4
9k	3-aminobenzoyl .CF ₃ CO ₂ H	8	2	4	8
10k	3-aminobenzoyl .CF ₃ CO ₂ H	4	2	2	4
9l	4-aminobenzoyl .CF ₃ CO ₂ H	4	2	2	4
10l	4-aminobenzoyl .CF ₃ CO ₂ H	2	2	2	4
Linezolid		2	2	2	8

provide potential hydrogen bond acceptor and donor interaction in addition to hydrophobic interaction due to the presence of the methyl moiety whose orientation at the ribosomal receptor binding site may result in favorable stereochemistry that may positively influence the observed antibacterial activity. Moreover, the 5-nitrofuranyl-2-carbonyl (*D/L*)-alaninyl oxazolidinone derivatives were less active than the previously reported 5-nitrofuranyl-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 [25], 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 [21, 25, 28]. In addition, data from the present study further elaborates that the introduction of electron withdrawing nitro groups 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 MIC value range of 2 - >16 $\mu\text{g/mL}$.

3.0 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, 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 significant effect on the activity of this series of compounds.

4.0 Experimental

4.1 Characterization

Purification of compounds were performed on silica gel column chromatography using silica gel (Kieselgel 60, 70-230 mesh; Aldrich) and TLC was conducted on 0.25 mm pre-coated silica gel plates (60F₂₅₄, Merck). Melting points were determined on a Stuart Scientific melting point apparatus (SMP1, UK) and were uncorrected. Mass spectra were recorded on a Thermo Scientific DFS Gas Chromatography/Mass Spectrometer (DFS GC - MS) and Waters QToF high resolution / Mass Spectrometer (LC MS/MS High resolution). The ¹H-NMR and ¹³C-NMR spectra in DMSO-d₆ 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-d₆ ($\delta=2.5$; 39.7) peaks as references. Infrared (IR) spectra of solids (KBr) were recorded on FT-IR (Jasco FT/IR-

6300) (JASCO, Japan Spectrometer. While the Elemental analyses were performed on an Elementar Vario Micro Cube CHN Analyzer (Elementar, Germany). Elemental analyses (C,H,N) were used to confirm purity of all newly synthesized compounds (>95%), and indicated by the symbols of the elements were within $\pm 0.40\%$ of the theoretical values. Analyses were performed by The General Facilities Science (GF-S), Faculty of Science, Kuwait University, Kuwait.

4.2. Syntheses

(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 nitrogen atmosphere for 2 hours. 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 CH₃CN (40 mL) at 0 °C. The reaction mixture was stirred overnight and concentrated on a rotavapor 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% Na₂CO₃ solution, brine, dried (Na₂SO₄), filtered and concentrated under vacuum to give a brown foam, which was triturated with ether to yield a cream colored solid. The crude solid was recrystallized from ethyl acetate to afford tert-Butyl (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)carbamate **15a** as an off-white solid 2.07 gm, yield: 74 %; mp.: 214-216 °C. ¹H-NMR (DMSO-d₆, 600 MHz): 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 D₂O), 5.12-5.14 (m, 1H, oxazolidinone H), 4.83 (d, 2H, J=5.1 Hz, CH₂), 4.45-4.50 (m, 1H, D-alanine CH), 4.21 (t, 1H, J=9.2 Hz, oxazolidinone H), 3.87 (q, 1H, J=5.8 Hz, 9.3 Hz, oxazolidinone H), 3.59-3.66 (br., 4H, piperazine H), 2.96 (br. d, 4H, piperazine H), 1.36-1.38 (br., 9H, C(CH₃)₃), 1.17 (d, 3H, J=6.9 Hz, CH₃). ¹³C-

NMR (DMSO- d_6): δ 171.21, 155.84, 155.34, 154.22, 153.94, 135.84, 133.85, 133.78, 133.71, 126.31, 120.21, 120.19, 114.75, 114.73, 107.31, 107.14, 78.44, 71.25, 52.19, 51.11, 50.77, 47.56, 46.27, 45.24, 42.01, 28.67, 18.15. 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. $^1\text{H-NMR}$ (DMSO- d_6 , 600 MHz): δ 8.17 (d, 1H, $J=0.7$ Hz, triazole H), 8.13 (br. d, 3H, $J=3.8$ Hz, $^+\text{NH}_3$, exchangeable with D_2O), 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). $^{13}\text{C-NMR}$ (DMSO- d_6): δ 167.95, 158.52, 158.30, 158.08, 157.85, 155.39, 153.77, 153.48, 135.24, 135.24, 135.18, 133.45, 133.36, 125.86, 119.85, 119.83, 117.52, 115.56, 114.56, 113.60, 106.89, 106.71, 70.77, 51.70, 50.47, 50.09, 47.09, 45.94, 44.76, 41.66, 16.39. LRMS (m/z): Calcd for $C_{19}H_{24}FN_7O_3$ ($M^+ - \text{CF}_3\text{O}_2\text{H}$): 417.30. HRMS (m/z): Calcd for $C_{21}H_{25}F_4N_7O_5$: 531.1853; found 530.2300 ($M^+ - \text{H}$).

(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 carbodimide (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. ¹H-NMR (DMSO-d₆, 600 MHz): 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 D₂O), 5.09-5.15 (m, 1H, oxazolidinone H), 4.83 (d, 2H, J=5.1 Hz, CH₂), 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, 4H, piperazine H), 2.91-2.98 (br, 4H, piperazine H), 1.36 (br d, 9H, (CH₃)₃), 1.16 (d, 3H, J=6.9 Hz, CH₃). ¹³C-NMR (DMSO-d₆): δ 170.70, 155.33, 154.83, 153.72, 153.43, 135.40, 135.34, 133.33, 133.27, 133.20, 125.80, 119.71, 114.24, 106.82, 106.65, 77.93, 70.74, 51.67, 50.60, 50.26, 47.06, 45.76, 44.74, 41.51, 28.17, 17.65. 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 C₂₄H₃₂FN₇O₅: 517.2449; found 540.2500 (M⁺ + Na). Anal calcd for C₂₄H₃₂FN₇O₅: 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 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. ¹H-NMR (DMSO-d₆, 600 MHz): δ 8.17 (d, 1H, J=0.7 Hz, triazole H), 8.12 (br. d, 3H, J=4.0 Hz, ⁺NH₃, 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, CH₂), 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, CH₃). ¹³C-NMR (DMSO-d₆): δ 167.92, 157.98, 157.77, 155.36, 153.75, 153.45, 135.21, 135.15, 133.44, 133.34, 125.85, 119.84, 119.82, 116.05, 114.30, 114.29, 106.87, 106.70, 70.73, 51.67, 50.44, 50.08, 47.07, 45.93, 44.73, 41.64, 16.38. LRMS (*m/z*): Calcd for C₁₉H₂₄FN₇O₃ (M⁺ - CF₃O₂H): 417.3. HRMS (*m/z*): Calcd for C₂₁H₂₅F₄N₇O₅: 531.1853; found 530.2400 (M⁺ - H).

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

To an ice cooled solution of **16a** (0.700 g, 1.317 mmol) in anhyd. CH₃CN (20 mL) was added TEA (0.70 mL), 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 x 80 mL), 10% NaHCO₃ solution (80 mL), water (80 mL) and brine (80 mL), dried (Na₂SO₄), filtered and concentrated to give a yellow solid, which was triturated with ether and filtered to give a yellow solid 0.580 g, recrystallized (CH₃CN) to give the title compound **9a** as a yellow solid 190 mg, yield: 23 %; mp.: 124-126 °C. ¹H-NMR (DMSO-d₆, 600 MHz): 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, CH₂), 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, CH₃). ¹³C-NMR (DMSO-d₆): δ 167.93, 163.12, 153.71, 152.10, 151.83, 145.25, 133.80, 133.74, 131.93, 133.73, 131.65, 131.58, 130.47, 129.08, 127.64, 124.20, 122.37, 118.10, 118.07, 112.64, 112.62, 105.21, 105.04, 69.13, 50.06, 49.06, 48.56, 45.44, 43.26, 43.17, 39.95, 15.67. IR (KBr pellet, cm⁻¹): 3305, 3112, 1753, 1645, 1519, 1282, 1228, 1026, 743. LRMS (*m/z*) 566.5 (M⁺). Anal calcd for C₂₆H₂₇FN₈O₆: C: 55.12, H: 4.80, N: 19.78; found C: 55.1, H: 5.21, N: 19.65

*Preparation of N-((S)-1-(4-(4-((R)-5-((1H-1,2,3-triazol-1-yl)methyl)oxazolidin-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 yellow solid 258 mg, yield: 27 %; recrystallized (CH₃CN), mp.: 185-190°C. ¹H-NMR (DMSO-d₆, 600

MHz): 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 (br., 4H, piperazine H), 2.90-3.06 (br., 4H, piperazine H), 1.30 (d, 3H, $J=6.8$ Hz, CH_3). ^{13}C -NMR (DMSO- d_6): δ 175.37, 169.44, 158.93, 158.72, 154.27, 144.76, 140.62, 140.56, 138.57, 134.29, 131.13, 128.68, 125.02, 119.57, 112.10, 111.93, 84.75, 84.53, 84.31, 76.05, 56.96, 55.88, 55.49, 52.36, 50.75, 50.18, 46.87, 22.49. 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.

*Preparation of N-((R)-1-(4-(4-((R)-5-((1H-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. 1H -NMR (DMSO- d_6 , 600 MHz): 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 (br., 4H, piperazine H), 2.95-3.01 (br., 4H, piperazine H), 1.35 (d, 3H, $J=7.0$ Hz, CH_3). ^{13}C -NMR (DMSO- d_6): δ 170.66, 164.16, 155.84, 154.22, 153.94, 148.21, 135.89, 135.83, 135.77, 134.45, 133.85, 133.79, 133.71, 130.55, 126.47, 126.32, 122.70, 120.25, 120.23, 114.74, 114.73, 107.31, 107.14, 71.25, 52.19, 51.12, 50.77, 47.57, 45.89,

45.42, 42.12, 17.72. IR (KBr pellet, cm^{-1}): 3288, 3117, 2823, 1720, 1637, 1517, 1445, 1349, 1285, 1228. LRMS (m/z): 566.6 (M^+). Anal calcd for $\text{C}_{26}\text{H}_{27}\text{FN}_8\text{O}_6$: C: 55.12, H: 4.80, N: 19.78; found: C: 54.91, H: 4.71, N: 19.79.

Preparation of N-((S)-1-(4-(4-((R)-5-((1H-1,2,3-triazol-1-yl)methyl)oxazolidin-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. $^1\text{H-NMR}$ (DMSO- d_6 , 600 MHz): 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, nitrobenzene 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 (br., 4H, piperazine H), 2.95-3.01 (br., 4H, piperazine H), 1.35 (d, 3H, $J=7.0$ Hz, CH_3). $^{13}\text{C-NMR}$ (DMSO- d_6): δ 175.42, 168.93, 160.61, 158.98, 158.70, 152.97, 140.67, 140.60, 140.53, 139.24, 138.61, 138.57, 138.48, 135.32, 131.25, 131.08, 127.46, 125.03, 119.50, 112.09, 112.90, 76.01, 56.94, 55.90, 55.55, 52.32, 50.66, 50.16, 46.90, 22.47, 19.32. 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 for calcd $\text{C}_{26}\text{H}_{27}\text{FN}_8\text{O}_6$: C: 55.12, H: 4.80, N: 19.78; found C: 55.16, H: 4.88, N: 19.91.

Preparation of N-((R)-1-(4-(4-((R)-5-((1H-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. $^1\text{H-NMR}$ (DMSO- d_6 , 600 MHz) 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, CH₂), 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, CH₃). ¹³C-NMR (DMSO-d₆): δ 170.61, 164.66, 155.83, 154.21, 153.94, 149.56, 140.04, 135.89, 135.83, 133.85, 133.78, 133.71, 129.47, 126.32, 123.94, 120.26, 120.23, 114.74, 107.32, 107.14, 71.25, 52.18, 51.12, 50.75, 47.56, 45.91, 45.41, 42.12, 17.72. 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 C₂₆H₂₇FN₈O₆: C: 55.12, H: 4.80, N: 19.78; found: C: 54.73, H: 5.00, N: 20.06

Preparation of N-((S)-1-(4-(4-((R)-5-((1H-1,2,3-triazol-1-yl)methyl)oxazolidin-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 (CH₃CN), mp.: 245-247 °C. ¹H-NMR (DMSO-d₆, 600 MHz): δ 9.06 (d, NH, 1H, J=7.4, NH, exchangeable with D₂O), 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, CH₂), 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 (br., 4H, piperazine H), 2.92-3.08 (br., 4H, piperazine H), 1.35 (d, 3H, J=7.0, CH₃). ¹³C-NMR (DMSO-d₆): δ 170.62, 164.67, 155.84, 154.22, 153.96, 149.57, 140.05, 135.89, 135.84, 133.86, 133.79, 133.73, 129.48, 126.33, 123.95, 120.27, 120.25, 114.77, 107.32, 107.15, 71.26, 52.19, 51.13, 50.76, 47.57, 45.92, 45.41, 42.12, 17.73. 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 C₂₆H₂₇FN₈O₆: C: 55.12, H: 4.80, N: 19.78; found C: 54.95, H: 5.20, N: 19.69.

Preparation of N-((R)-1-(4-(4-((R)-5-((1H-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. ¹H-NMR (DMSO-d₆, 600 MHz): δ 9.52 (d, 1H, J=8.8 Hz, NH, exchangeable with D₂O), 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=11.1 Hz, phenyl H), 5.02-5.14 (m, 2H, oxazolidinone H and *D*-alanine CH), 4.83 (d, 2H, J=5.0 Hz, CH₂), 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, CH₃). ¹³C-NMR (DMSO-d₆): δ 170.43, 162.23, 155.83, 154.22, 153.94, 148.66, 136.85, 135.87, 135.81, 133.85, 133.79, 133.73, 128.26, 126.32, 121.48, 120.27, 120.25, 114.75, 114.73, 107.31, 107.14, 71.25, 67.48, 65.37, 60.21, 52.18, 51.14, 50.75, 47.56, 46.20, 45.45, 42.14, 17.65. IR (KBr pellet, cm⁻¹): ν 3481, 3276, 3094.23, 1756, 1633, 1542, 1517, 1445, 1346, 1230, 1028. HRMS (*m/z*): Calcd for C₂₆H₂₆FN₉O₈: 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.

N-((S)-1-(4-(4-((R)-5-((1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)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 (CH₃CN), mp.: 191-194 °C. ¹H-NMR (DMSO-d₆, 400 MHz): δ 9.53 (d, 1H, J=7.2 Hz, NH, exchangeable with D₂O), 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, CH₂), 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 (br., 4H, piperazine H), 2.95-3.01 (br., 4H, piperazine H), 1.37 (d, 3H, $J=6.9$ Hz, CH_3). ^{13}C -NMR (DMSO- d_6 , 400 Hz): δ 169.95, 161.75, 153.46, 148.18, 136.37, 135.42, 135.34, 133.37, 133.24, 127.79, 125.85, 121.02, 119.79, 114.25, 107.31, 107.14, 70.77, 51.70, 50.65, 50.32, 47.09, 45.72, 45.01, 42.41, 17.17. IR (KBr pellet, cm^{-1}): ν 3425, 3278, 3109, 1752, 1668, 1631, 1541, 1518, 1484, 1446, 1345, 1230, 1028. HRMS (m/z): Calcd for $\text{C}_{26}\text{H}_{26}\text{FN}_9\text{O}_8$: 611.1888, found 612.2090 ($\text{M}^+ + \text{H}$), 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

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

To a stirred solution of 5-nitrofur-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 hours. 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 temp 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. ^1H -NMR (DMSO- d_6 , 600 MHz): 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, nitrofur H), 7.55 (d, 1H, $J=5.3$ Hz, nitrofur 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 (br, 4H, piperazine H), 3.00 (br. d, 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.

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

Compound **10e** was prepared *via* a similar procedure to **9e** from **16b** (0.700 g, 1.317 mmol) and 5-nitrofur-2-carboxylic acid (0.827g, 5.268mmol) to give a yellowish-brown solid 356 mg, yield 46 %, recrystallized ($CH_3CN/MeOH$), mp.: 218-222°C. 1H -NMR ($DMSO-d_6$, 600 MHz): 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, nitrofur H), 7.44 (d, 1H, $J=3.8$ Hz, nitrofur 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 (br. d, 4H, piperazine H), 2.93-3.06 (br, 4H, piperazine H), 1.34(d, 3H, $J=7.0$ Hz, CH_3). ^{13}C -NMR ($DMSO-d_6$, 400 Hz): δ 169.68, 155.47, 155.33, 153.72, 153.44, 147.71, 135.36, 135.30, 133.34, 133.30, 133.23, 125.81, 119.77, 119.75, 115.88, 114.25, 113.30, 106.82, 106.65, 70.74, 51.68, 50.59, 50.20, 47.07, 44.99, 44.93, 41.67, 17.30. 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.

Preparation of N-((R)-1-(4-(4-((R)-5-((1H-1,2,3-triazol-1-yl)methyl)oxazolidin-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. 1H -NMR ($DMSO-d_6$, 600 MHz): 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, CH₂), 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 (br. d, 4H, piperazine H), 2.90-3.05 (br., 4H, piperazine H), 1.34 (d, 3H, J=7.0 Hz, CH₃). ¹³C-NMR (DMSO-d₆): δ 159.52, 155.84, 154.22, 153.95, 153.53, 146.25, 135.81, 133.86, 133.81, 133.74, 130.66, 128.42, 126.33, 120.26, 114.75, 107.32, 107.15, 71.26, 52.19, 51.11, 50.75, 47.57, 45.96, 45.44, 42.14, 17.67. 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 C₂₄H₂₅FN₈O₇S: 572.1602, found 573.1700 (M⁺ + H), LRMS (*m/z*): 572.5 (M⁺). Anal calcd for C₂₄H₂₅FN₈O₆S: C: 49.91, H: 4.57, N: 19.54.; found C: 50.35, H: 4.40, N: 19.57.

Preparation of N-((S)-1-(4-(4-((R)-5-((1H-1,2,3-triazol-1-yl)methyl)oxazolidin-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, 5.268mmol) to give a yellowish-brown solid 560 mg, yield: 76 %, recrystallized (EtOAc), mp.: 211-214°C. ¹H-NMR (DMSO-d₆, 600 MHz): δ 9.27 (d, 1H, J=7.4 Hz, NH, exchangeable with D₂O), 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, CH₂), 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 (br. d, 4H, piperazine H), 2.90-3.06 (br., 4H, piperazine H), 1.34 (d, 3H, J=7.0 Hz, CH₃). ¹³C-NMR (DMSO-d₆): δ 169.81, 159.05, 155.36, 153.75, 153.48, 153.07, 145.77, 135.39 135.33, 133.40, 133.33, 133.26, 130.19, 127.95, 125.87, 119.81, 114.29, 106.84, 106.67, 70.79, 51.72, 50.64, 50.26, 47.09, 45.50, 44.96, 41.67, 17.18. 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.

Preparation of N-((R)-1-(4-(4-((R)-5-((1H-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. 1H -NMR (DMSO- d_6 , 600 MHz): 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): δ 169.39, 155.81, 154.20, 153.94, 147.84, 135.75, 135.69, 134.53, 133.85, 133.77, 133.57, 132.96, 130.36, 126.33, 124.69, 120.24, 120.22, 114.75, 114.73, 107.29, 107.12, 71.25, 52.18, 50.88, 50.50, 49.05, 47.56, 45.27, 41.95, 19.38. 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.

Preparation of N-(((S)-1-(4-(4-((R)-5-((1H-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. 1H -NMR (DMSO- d_6 , 400 MHz): 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, CH₂), 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 (br., 4H, piperazine H), 2.80-2.96 (br., 4H, piperazine H), 1.21 (m, 3H, J=6.9 Hz, CH₃). 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 C₂₅H₂₇FN₈O₇S: 602.1707, found 603.1812 (M⁺ + H), LRMS (*m/z*) 602.4 (M⁺). Anal calcd for C₂₅H₂₇FN₉O₇S: C: 49.83, H: 4.52, N: 18.6; found C: 49.36, H: 4.72, N: 18.34

Preparation of N-((R)-1-(4-(4-((R)-5-((1H-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 (CH₃CN); mp.: 115-118°C. ¹H-NMR (DMSO-d₆, 600 MHz): 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, CH₂), 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, CH₃). ¹³C-NMR (DMSO-d₆): δ 169.34, 155.81, 154.20, 153.94, 148.06, 143.26, 135.71, 135.65, 133.85, 133.80, 133.28, 131.51, 127.42, 126.32, 122.00, 120.18, 120.15, 114.71, 107.28, 107.11, 71.25, 52.18, 51.05, 50.44, 48.65, 47.56, 45.22, 41.80, 19.20. 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 C₂₅H₂₇FN₉O₇S: C: 49.83, H: 4.52, N: 18.6; found C: 49.55, H: 4.85, N: 18.68.

Preparation of N-((R)-1-(4-(4-((R)-5-((1H-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. ¹H-NMR (DMSO-d₆, 600 MHz): δ 8.52 (t, 1H, J=2.0 Hz, nitrobenzene H), 8.46-8.48 (m, 2H, nitrobenzene H and of NH, NH broad peak is exchangeable with D₂O), 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, CH₂), 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, CH₃). ¹³C-NMR (DMSO-d₆): δ 155.81, 153.96, 148.07, 133.86, 133.29, 131.51, 126.33, 122.00, 120.19, 114.74, 107.29, 107.12, 71.27, 65.39, 52.19, 51.07, 47.57, 45.23, 41.81, 19.23. 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 C₂₅H₂₇FN₉O₇S: C: 49.83, H: 4.52, N: 18.60; found: C: 49.38, H: 4.85, N: 18.74

Preparation of N-((R)-1-(4-(4-((R)-5-((1H-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 (CH₃CN); mp.: 190-192°C. ¹H-NMR (DMSO-d₆, 600 MHz): δ 8.49 (br., 1H, NH, exchangeable with D₂O), 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, CH₂), 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 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, CH₃). ¹³C-NMR (DMSO-d₆): δ 169.24, 153.69, 152.08, 151.82, 147.79, 145.10, 133.62, 133.56, 131.73, 131.66, 126.60, 124.20, 122.63, 118.09, 118.06, 112.58, 112.57, 105.16, 104.99, 69.13, 50.06, 48.90, 48.30, 46.50, 45.43, 43.11, 39.69, 17.07. 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 C₂₅H₂₇FN₉O₇S: C: 49.83, H: 4.52, N: 18.6; found: C: 49.47, H: 4.46, N: 18.4

Preparation of N-(((R)-1-(4-(4-((R)-5-((1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-1-oxopropan-2-yl)-4-nitrobenzene sulfonamide 101

Compound **101** 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. ¹H-NMR (DMSO-d₆, 400 MHz): δ 8.48 (br., 1H, NH, exchangeable with D₂O), 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, CH₂), 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 (br., 2H, piperazine H), 3.33 (br., 2H, piperazine H overlaps with DOH signal), 2.83-3.04 (br., 4H, piperazine H), 1.10 (d, 3H, J=6.9 Hz, CH₃). ¹³C-NMR (DMSO-d₆): δ 169.87, 155.31, 153.70, 153.43, 149.41, 146.73, 135.24, 135.18, 133.33, 133.27, 128.21, 125.80, 124.23, 119.71, 119.69, 114.23, 106.80, 106.63, 70.73, 51.67, 50.52, 49.91, 48.11, 47.06, 44.73, 41.32, 18.67. HRMS (*m/z*): Calcd for C₂₅H₂₇FN₈O₇S: 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 C₂₅H₂₇FN₉O₇S: C: 49.83, H: 4.52, N: 18.6; found C: 49.7, H: 4.704, N: 18.4.

*Preparation of N-((R)-1-(4-(4-((R)-5-((1H-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), 1-hydroxybenzotriazole (318 mg, 6.787 mmol), respectively, and the reaction mixture was stirred for 2 hrs 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. CH₃CN (15 mL) and left stirring at room temp overnight. The reaction mixture was concentrated to give a crude brown oil, which was dissolved in DCM, washed with water, 10% Na₂CO₃ solution, brine, dried Na₂SO₄, filtered and concentrated to yield 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. ¹H-NMR (DMSO-d₆, 600 MHz): δ 10.45 (s, 1H, NH, exchangeable with D₂O), 8.89 (d, 1H, J=7.3 Hz, NH, exchangeable with D₂O), 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, CH₂), 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 (br, 4H, piperazine H), 2.94-3.04 (br., 4H, piperazine H), 1.45 (s, 9H, (CH₃)₃), 1.34 (d, 3H, J=7.0 Hz, CH₃). MS 636.8 (M⁺). ¹³C-NMR (DMSO-d₆, 400 MHz): δ 170.21, 167.78, 155.78, 153.49, 153.36, 152.11, 139.42, 135.44, 135.36, 133.41, 133.26, 132.21, 128.61, 125.89, 121.44, 119.79, 119.32, 118.52, 114.27, 106.92, 82.80, 79.81, 70.80, 51.73, 50.26, 47.09, 45.29, 44.93, 41.69, 27.94. 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⁺ - (CH₃)₂C=CH₂ + CO₂). Anal calcd for C₃₁H₃₇FN₈O₆: 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. ¹H-NMR (DMSO-d₆, 600 MHz): δ 8.40 (d, 1H, J=7.4 Hz, NH, exchangeable with D₂O), 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, CH₂), 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 ⁺NH₃ signal), 3.60-3.71 (br, 7H, piperazine H, overlapping with ⁺NH₃ signal, which is exchangeable with D₂O), 2.95-3.01 (br d, 4H, J=7.0 Hz, piperazine H), 1.31 (s, 3H, J= Hz, CH₃). ¹³C-NMR (DMSO-d₆, 600 MHz): δ 170.63, 168.05, 158.27, 158.03, 155.35, 153.74, 153.47, 135.43, 135.37, 133.38, 133.30, 133.23, 131.84, 128.50, 125.85, 119.76, 119.74, 116.80, 115.41, 115.11, 114.27, 114.26, 106.84, 106.66, 70.78, 64.90, 51.71, 50.65, 50.27, 47.08, 44.88, 44.73, 41.61, 17.38, 15.15. IR (KBr pellet, cm⁻¹): ν 3447, 3354, 2981, 2829, 1755, 1635, 1517, 1446, 1326, 1230, 1200, 1162, 1027. HRMS (*m/z*): for C₂₈H₃₀F₄N₈O₆: 650.2224, found 650.0167.

Preparation of N-((R)-1-(4-(4-((R)-5-((1H-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. ¹H-NMR (DMSO-d₆, 600 MHz): δ 9.48 (s, 1H, NH, exchangeable with D₂O), 8.55 (d, 1H, J=10.0 Hz, NH, exchangeable with D₂O), 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, CH₂), 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, (CH₃)₃),

1.31(d, 3H, J=7.0 Hz, CH₃). IR (KBr pellet, cm⁻¹): ν 3409, 3255, 2979, 2934, 1763, 1639, 1517, 1480, 1443, 1322, 1233, 1159, 1028. HRMS (*m/z*): for C₃₁H₃₇FN₈O₆: 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. ¹H-NMR (DMSO-d₆, 600 MHz): δ 8.54 (d, 1H, J=7.4 Hz, NH, exchangeable with D₂O), 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, CH₂), 4.20-4.23 (m, 2H, oxazolidinone H), 3.87 (dd, 1H, J=5.7 Hz, 9.3 Hz, oxazolidinone H, overlapping with ⁺NH₃ signal), 3.50-3.88 (br, 7H, piperazine H, overlapping with ⁺NH₃ signal, which is exchangeable with D₂O), 2.95-3.27 (br., 4H, piperazine H), 1.31 (d, 3H, J=7.0 Hz, CH₃). ¹³C-NMR (DMSO-d₆, 600 MHz): δ 170.42, 165.71, 158.25, 158.02, 155.36, 153.74, 153.48, 135.43, 135.09, 133.38, 133.30, 133.23, 129.07, 125.90, 125.86, 119.92, 119.76, 117.06, 116.35, 115.12, 114.28, 106.85, 106.68, 70.78, 51.71, 50.64, 50.26, 47.30, 47.09, 45.08, 44.90, 43.02, 41.62, 17.47. IR (KBr pellet, cm⁻¹): ν 3423, 2921, 1753, 1674, 1638, 1518, 1447, 1326, 1231, 1201, 1135, 1028. HRMS (*m/z*): for C₂₈H₃₀F₄N₈O₆: 650.2224, found 650.0204 (M⁺).

*Preparation of N-((R)-1-(4-(4-((R)-5-((1H-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 the 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. ¹H-NMR (DMSO-d₆, 600 MHz): δ 9.62 (s, 1H, NH, exchangeable with D₂O), 8.47 (d, 1H, J=7.6 Hz, NH, exchangeable with D₂O), 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, CH₂), 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 (br., 4H, piperazine H), 2.95-2.98 (br., 4H, piperazine H), 1.49 (s, 9H, (CH₃)₃), 1.31 (d, 3H, $J=7.0$ Hz, CH₃). IR (KBr pellet, cm⁻¹): ν 3409, 2979, 2932, 1758, 1730, 1637, 1517, 1446, 1320, 1232, 1159, 1027. HRMS (m/z): for C₃₁H₃₇FN₈O₆: 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. ¹H-NMR (DMSO-d₆, 600 MHz): δ 8.20 (d, 1H, $J=7.6$ Hz, NH, exchangeable with D₂O), 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, CH₂), 4.21 (t, 2H, oxazolidinone H overlaps with ⁺NH₃ signal), 3.90-4.50 (br. m, 4H, oxazolidinone H overlaps with ⁺NH₃ signal), 3.68 (dd, 1H, $J=$ Hz, 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, CH₃). ¹³C-NMR (DMSO-d₆, 600 MHz): δ 170.77, 165.52, 158.33, 158.09, 155.35, 153.73, 153.47, 135.44, 135.38, 133.80, 133.73, 133.38, 133.28, 133.21, 129.15, 129.00, 128.32, 125.90, 125.85, 119.92, 119.74, 114.82, 114.25, 106.83, 106.66, 70.78, 51.72, 51.68, 50.63, 50.28, 47.31, 47.08, 47.06, 44.87, 44.74, 43.02, 41.57, 17.62. IR (KBr pellet, cm⁻¹): ν 3364, 2985, 2835, 1750, 1674, 1635, 1518, 1448, 1231, 1199, 1134, 1027. HRMS (m/z): for C₂₈H₃₀F₄N₈O₆: 650.2224, found 650.0215 (M⁺).

*Preparation of N-((R)-1-(4-(4-((R)-5-((1H-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 the 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. ¹H-NMR (DMSO-d₆, 600 MHz): δ 10.46 (s, 1H, NH, exchangeable with D₂O), 8.91 (d, 1H, $J=7.3$ Hz, NH, exchangeable with D₂O), 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, CH₂), 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, (CH₃)₃), 1.34 (d, 3H, J=7.0 Hz, CH₃). ¹³C-NMR (DMSO-d₆, 600 MHz): δ 170.21, 167.78, 155.36, 153.75, 153.46, 152.08, 139.40, 135.41, 135.35, 133.37, 133.32, 133.25, 132.17, 128.57, 125.85, 121.40, 119.75, 119.32, 118.51, 114.26, 106.84, 106.67, 79.77, 70.77, 64.90, 51.70, 50.67, 50.24, 47.08, 45.26, 44.91, 41.67, 30.68, 27.92, 17.12. IR (KBr pellet, cm⁻¹): ν 3350, 3114, 2978, 2931, 1757, 1718, 1647, 1589, 1442, 1227, 1160, 1110, 1050, 1026. HRMS (*m/z*): for C₃₁H₃₇FN₈O₆: 636.2820, found 637.0000 (M⁺ + H). LRMS (*m/z*): 536.3 (M⁺ - (CH₃)₂C=CH₂ + CO₂). 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. ¹H-NMR (DMSO-d₆, 600 MHz): δ 8.40 (d, 1H, J=7.4 Hz, NH, exchangeable with D₂O), 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, CH₂), 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., 7H, piperazine H, overlapping with ⁺NH₃ signal, which is exchangeable with D₂O), 2.95-3.01 (br. d, 4H, piperazine H), 1.31 (s, 3H, J=7.0 Hz, CH₃). ¹³C-NMR (DMSO-d₆, 600 MHz): δ 170.63, 168.04, 158.27, 158.03, 155.35, 153.74, 153.47, 135.44, 135.38, 133.38, 133.30, 133.22, 131.85, 128.50, 125.86, 119.74, 116.84, 115.49, 115.15, 114.26, 106.84, 106.67, 70.77, 51.71, 50.66, 50.27, 47.08, 44.88, 44.74, 41.61, 30.68, 17.38. IR (KBr pellet, cm⁻¹): ν 3427, 2984, 2922, 1755, 1635, 1587, 1517, 1447, 1327, 1230, 1200, 1138, 1028. HRMS (*m/z*): for C₂₈H₃₀F₄N₈O₆: 650.2224, found 650.0234 (M⁺).

*Preparation of N-((S)-1-(4-(4-((R)-5-((1H-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 the 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. ¹H-NMR (DMSO-*d*₆, 600 MHz): δ 9.50 (s, 1H, NH, exchangeable with D₂O), 8.57 (d, 1H, J=7.6 Hz, NH, exchangeable with D₂O), 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, CH₂), 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., 4H, piperazine H), 2.96-3.00 (br., 4H, piperazine H), 1.49 (s, 9H, (CH₃)₃), 1.32 (d, 3H, J=7.0 Hz, CH₃). ¹³C-NMR (DMSO-*d*₆, 600 MHz): δ 170.36, 165.86, 155.35, 153.73, 153.46, 152.77, 139.57, 135.43, 135.37, 134.77, 133.38, 133.29, 133.22, 128.43, 125.84, 120.93, 120.82, 119.76, 119.73, 117.53, 114.26, 106.82, 106.64, 79.19, 70.77, 51.70, 50.61, 50.28, 47.07, 45.11, 44.89, 41.61, 28.09, 17.43. IR (KBr pellet, cm⁻¹): ν 3414, 3256, 2978, 1760, 1730, 1637, 1556, 1519, 1441, 1414, 1237, 1158, 1029. HRMS (*m/z*): for C₃₁H₃₇FN₈O₆: 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. ¹H-NMR (DMSO-*d*₆, 600 MHz): δ 8.80 (d, 1H, J=7.4 Hz, NH, exchangeable with D₂O), 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, CH₂), 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 ⁺NH₃ signal), 3.50-

3.86 (br, 7H, piperazine H, overlapping with $^+NH_3$ signal, exchangeable with D_2O), 2.95-3.00 (br, 4H, piperazine H), 1.32 (d, 3H, $J=6.9$ Hz, CH_3). ^{13}C -NMR (DMSO- d_6 , 600 MHz): δ 170.42, 165.71, 158.25, 158.02, 155.36, 153.74, 153.48, 135.43, 135.09, 133.38, 133.30, 133.23, 129.07, 125.90, 125.86, 119.92, 119.76, 117.06, 116.35, 115.12, 114.28, 106.85, 106.68, 70.78, 51.71, 50.64, 50.26, 47.30, 47.09, 45.08, 44.90, 43.02, 41.62, 17.47. 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^+).

Preparation of N-((R)-1-(4-(4-((R)-5-((1H-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 101

Compound **101** was prepared *via* a similar procedure to **9j** starting from 3-((*tert*-butoxycarbonyl) amino benzoic acid and the 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. 1H -NMR (DMSO- d_6 , 600 MHz): 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., 4H, piperazine H), 2.95-2.98 (br., 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 MHz): δ 170.56, 165.17, 155.34, 153.73, 153.46, 152.58, 142.37, 135.43, 135.37, 133.38, 133.28, 133.21, 128.30, 127.19, 125.84, 119.75, 119.73, 117.02, 114.26, 114.25, 106.82, 106.65, 79.48, 70.78, 64.90, 51.71, 50.63, 50.27, 47.08, 44.93, 41.59, 28.06, 17.48. 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 **101** as a white solid 229 mg, yield 63 %; recrystallized (EtOAc), **mp.**: 239-242 °C. 1H -

NMR (DMSO- d_6 , 600 MHz): 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 $^+NH_3$ 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 $^+NH_3$ signal), 3.59-3.72 (br., 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 MHz): δ 170.46, 165.04, 155.32, 153.70, 153.42, 135.32, 135.26, 133.29, 133.22, 129.06, 128.92, 125.79, 119.74, 119.41, 114.28, 106.86, 106.69, 70.72, 51.67, 50.60, 50.24, 47.14, 47.08, 45.00, 44.93, 41.85, 17.43. 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 ($M^+ - CF_3CO_2H$).

4.3 Antibacterial susceptibility testing.

Antibacterial susceptibility testing was performed by determining the minimum inhibitory concentrations (MIC's, $\mu g/ml$), which is defined as the lowest concentration of a compound that inhibits visible bacterial growth. The MIC's were determined on Mueller-Hinton (MH) agar with medium containing dilutions of antibacterial agents ranging from 0.12 to 32 $\mu g/mL$. Linezolid [19, 26], 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 were 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 and were incubated at 35 °C for 18 h.

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Conflict of Interest

The authors declare no conflict of or secondary interest.

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