Full Paper

Effects of Varied Substituents on the Antibacterial Activity of Triazolylmethyl Oxazolidinones

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A number of 1,2,3-triazolylmethyl piperazino oxzalidinone derivatives with optionally varied substituents at the 4*N*-piperazine position were synthesized and their antibacterial activity evaluated against a panel of susceptible and resistant Gram-positive and selected Gram-negative bacteria. Substitution with 5-membered heteroaroyl and dinitrobenzoyl moieties potentiated activity against staphylococci and enterococci strains. Furthermore, the compounds having dinitrobenzoyl **7n**, **7o**, and 5-nitrofuroyl **7t** substitutions were four- to eightfold more potent than linezolid against *M. catarrahlis*. However, substitution of guanidino and other water-solubilizing functionalities at the 4*N*-piperazine position resulted in compounds that are devoid of antibacterial activity.

Keywords: Antibacterial activity / Gram-positive bacteria / Guanidino-oxazolidinone / Linezolid / Triazolylmethyl-oxazolidinone

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Introduction

The World Health Organization (WHO) regards antibacterial resistance as one of the three greatest threats to human health. In addition, a House of Lords report blatantly considered bacterial resistance a ''major threat to public health''; while the British Society for Antimicrobial Chemotherapy (BSAC), the Infectious Diseases Society of America (IDSA) and the European Union continue to voice their concerns [1]. This growing incidence of bacterial resistance world-wide poses a major threat to the treatment of infectious diseases that were previously readily treated, and serves as impetus for the development of new, more effective, and less toxic antibacterial agents. Although bacterial resistance continues to spread like wildfire with devastating effects, the hope for new agents remains very bleak [1, 2]. Linezolid (**Lzd**, Fig. 1), is a prototypical oxazolidinone with demonstrated activity against Gram-positive bacteria including multidrug-resistant strains namely, methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP) and vancomycin-resistant enteroccoci (VRE) [3]. Oxazolidinones including linezolid inhibit bacterial ribosomal protein biosynthesis and recent studies by Duffy and coworkers [4] revealed that linezolid binds to the A-site of the 50S subunit. The success of linezolid in the clinic and the demonstrated efficacy of the oxazolidinone class of antibacterial agents against Gram-positive resistant bacteria have impelled considerable interest in the pursuit for development of newer broad-spectrum oxazolidinone derivatives.

Consequently, significant efforts have been and continue to be expended by several research groups on the structural modifications around the phenyl-oxazolidinone ring in order to combat bacterial resistance [5]. We and other investigators have demonstrated that the 4-morpholinoaryl (PH027), 4-thiopyranoaryl (**1**, Fig. 1) and 4-substitued-piperazinoaryl (**2**, Fig. 1) oxazolidinones containing 5-triazolyl groups have potent antibacterial activities against Gram-positive bacteria including resistant strains [5–9]. Furthermore, derivatives with 4-substituted-triazolyl moiety have been shown to possess diminished monoamine oxidase (MAO) inhibition [9], identifying these derivatives as having potentially reduced side-effects. Further observations have shown that the antibacterial activities of the 4-substituted-piperazinoaryl oxazolidinones varied significantly depending on the substituent groups at the distal 4*N*-piperazine position. While structure-activity relationships of selected piperazino analogs have

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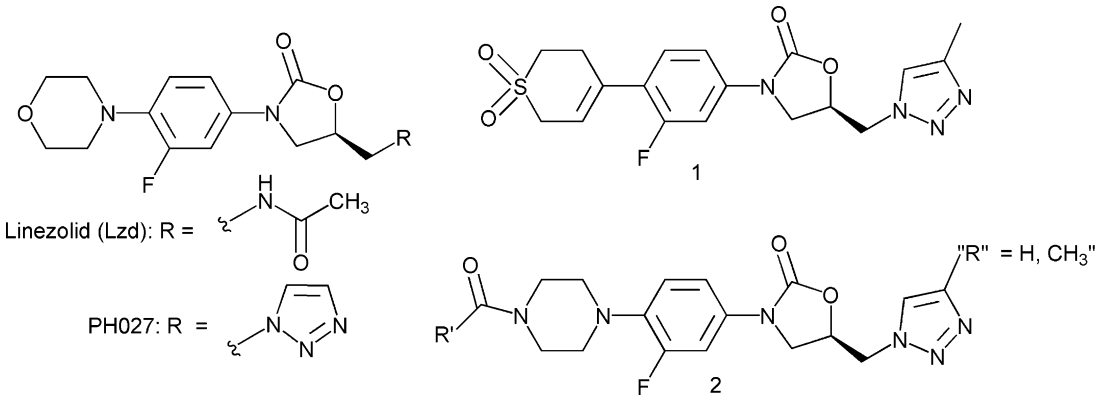


Figure 1. Chemical structure of oxazolidinone antibiotics.

suggested the necessity of an H-bond acceptor group at the 4*N*-position [5, 10]. Hence, appropriate functional group substitutions at the 4*N*-piperazine position are highly significant for predicting the antibacterial activity of 4-substituted-piperazinoaryl oxazolidinones. We herein report the synthesis of new 5-(4-methyl-1*H*-1,2,3-triazol-1-yl)methyl oxazolidinones with optionally varied substituents at the 4*N*-piperazine position, which are anticipated to enhance binding at the active site, and thus improve antibacterial activity against susceptible and multidrug-resistant Gram-positive bacteria. These new derivatives incorporate functionalized groups bearing hydrogen bond acceptor and/or donor moieties at the terminal *N*-piperazine position, which may enhance interactions at the bacterial ribosomal binding sites and may result in extended activity towards Gram-negative bacterial strains, such as *Haemophilus influenzae* and *Moraxella catarrhalis*.

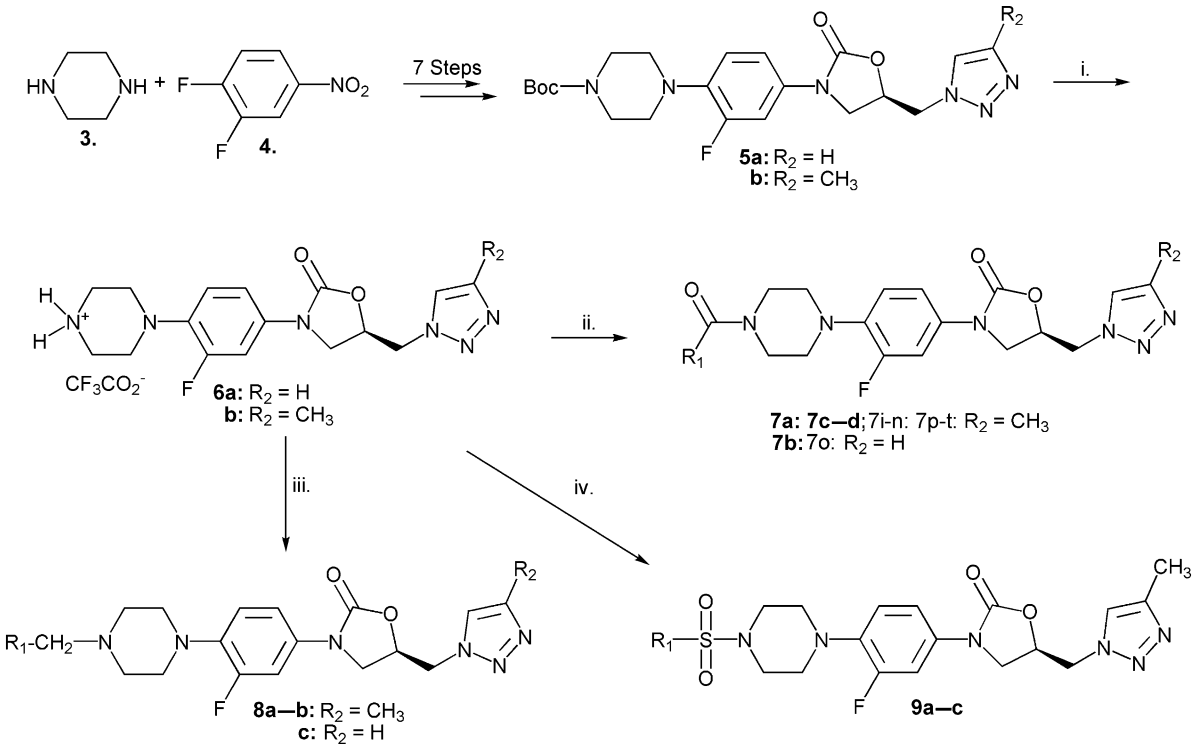
Results and discussion

Chemistry

The syntheses of the target compounds **7a–t**, **8a–c**, **9a–c**, **10a–b**, and **11a–b** are outlined in Schemes 1 and 2. The chiral methyl substituted and unsubstituted triazolylmethyl oxazolidinone intermediates **5a** and **5b** were obtained from the starting piperazine **3** and 3,4-difluoronitrobenzene **4**, respectively, according to established literature procedures [7, 9, 11]. These intermediates **5a** and **5b** were deprotected to give the TFA-salts **6a** [7] and **6b** [8]; and were further reacted with a series of optionally varied aroyl chlorides, substituted acyl chlorides, activated carboxylic acids, and arylsulfonyl chlorides to afford the target compounds **7a–d**, **7f**, **7i–t**, and **9a–c**. Reaction of compound **7a** with 1,2-dibromoethane and CS_2 in the presence of NaH gave the cyclic 1,3-dithian-2-ylidene derivative **7e**. The deprotection of **7f** gave the TFA-salt **7g**, which was further reacted with CS_2 in the presence of DIEA and *p*-toluenesulfonyl chloride to give the isothiocyanate **7h**, according to a literature method [12]. The acetamido **8a** and 3,5-dinitrobenzyl **8b–c** derivatives were prepared by reacting 2-iodoacetamide or 3,5-dinitrobenzyl chloride with **6b** and **6a**, respectively, in DMF or CH_3CN at 90°C. The boc-protected guanidino derivatives **10a–b** were prepared by reacting *N*,*N*-(bis(*tert*-butoxycarbonyl)-*S*-methyl isothiourea [13] with **6b** and **6a**, respectively. The compounds **10a–b** were deprotected in TFA to give the final water-soluble guanidinium derivatives **11a–b**.

Antibacterial evaluation

The antibacterial activities of compound **7a–t**, **8a–c**, **9a–c**, **10a–b**, and **11a–b** were examined against a panel of standard and clinical isolates of Gram-positive and selected Gram-negative bacteria encompassing susceptible and resistant strains ($n = 46$). The Gram-positive clinical isolates tested include MRSA ($n = 9$), methicillin-susceptible *S. aureus* (MSSA, $n = 11$), methicillin-resistant coagulase-negative staphylococci (MR-CNS, $n = 4$), methicillin-sensitive coagulase-negative staphylococci (MS-CNS, $n = 6$), *S. pneumoniae* ($n = 3$), vancomycin-sensitive enterococci (VSE, $n = 7$) and VRE ($n = 3$). Reference Gram-positive strains *S. aureus* ATCC 25923, *Staphylococcus epidermidis* ATCC 12228 and *Enterococcus faecalis* ATCC 29212; and Gram-negative strains, namely, *Escherichia coli* ATCC 25922, *H. influenzae* ATCC 49247, and *M. catarrhalis* ATCC8176 were used. Antibacterial susceptibility testing was performed by the agar dilution method according to the Clinical and Laboratory Standard Institute (CSLI) [14] and reported as minimum inhibitory concentrations (MIC, μg/mL). The experimental results of this *in vitro* antibacterial evaluation using linezolid and vancomycin as positive controls are summarized in Tables 1 and 2. The Clog *P* and MIC values of the compounds against *S. aureus* ATCC25923 in the absence and presence of 50% human plasma are shown in Table 1. From this result all the active compounds with the exception of linezolid, PH027, vancomycin, the monoethyl malonyl (**7b**), and 3,5-dinitrobenzoyl (**7n**) derivatives showed fourfold or higher MIC values in the



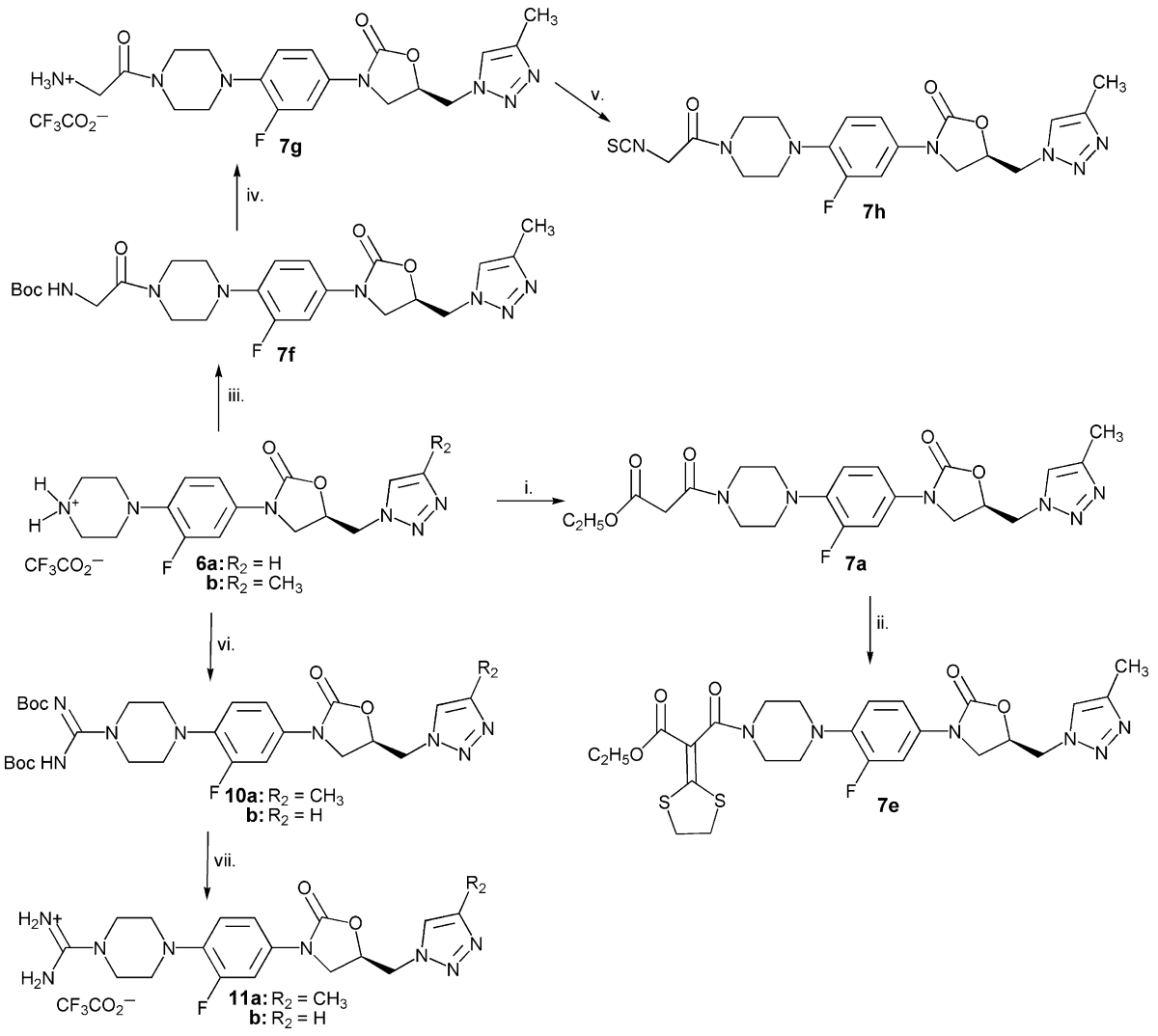
Scheme 1. Synthesis of 5-(4-methyl-1*H*-1,2,3-triazolyl)methyl oxazolidinone derivatives. i. TFA/DCM, 0°C-r.t.; ii. CH_3CN/acid chloride/acid anhydride/TEA, r.t.; iii. DMF or CH_3CN/benzyl halide or substituted alkyl halide/TEA/90°C; (iv) TEA, arylsulfonyl chloride, CH_3CN, 0°C-rt.

presence of 50% human plasma, indicating potentially significant plasma binding. Results from our previous studies of some 4*N*-acyl- and 4*N*-aroyl-substituted piperazinyl analogs have shown that these derivatives are relatively stable in human plasma at the experimental temperature conditions [15]. Generally, compounds with very low and very high Clog *P* values tend to be relatively less active in this series.

The antibacterial activity of the new oxazolidinone derivatives against a panel of susceptible and resistant Gram-positive and selected Gram-negative bacteria are presented on Table 2 as the MICs. Most of the compounds showed potent activity against most Gram-positive organisms tested. Overall, the 5-membered heteroaroyl and heteroarylsulfonyl containing derivatives **7r–7t**, and **9c** had enhanced antibacterial activity against Gram-positive bacteria, especially staphylococci and enterococci. In addition, dinitro group substitutions on the arylcarbonyl moiety as found in **7n** and **7o** also resulted in improved activity against similar Gram-positive bacteria strains including streptococci, while the dinitrobenzyl derivatives **8b** and **8c** were less active against Gram-positive bacteria particularly against streptococci (MIC, 4–8 μg/mL). Worthy of note are the activities of the 3,5-dinitrobenzoyl **7n** and **7o**, and nitrofuroyl **7t** derivatives against the fastidious Gram-negative bacteria *M. catarrahlis* strain with MICs of 1 and 2 μg/mL, respectively. These compounds (**7n**, **7o**, and **7t**) showed potent antibacterial activity against *M. catarrahlis* with MIC values four- to eightfold lower than linezolid, and several-fold lower than other compounds evaluated in this study, thus suggesting the requirement for electron withdrawing groups to enhance antibacterial activity. However, the boc-protected guanidino **10a** and **10b** and their respective water-soluble derivatives **11a** and **11b** were devoid of antibacterial activity against Gram-positive bacteria. Similarly, the 1,3-dithian-2-ylidene **7e** and isothiocyanate **7h** derivatives were also devoid of activity. All the compounds tested were inactive against *H. influenza* and *E. coli* bacterial strains (Table 2).

Conclusions

In conclusion, a series of 5-(1,2,3-triazolylmethyl) containing piperazino oxazolidinones having optionally varied substituent groups at the piperazine 4*N*-position were prepared. Most of the compounds show potent antibacterial activities against Gram-positive bacteria pathogens. The 5-membered heteroaroyl and the dinitrobenzoyl containing derivatives showed comparable activity to linezolid against Gram-positive bacteria, but were four- to eightfold more active than



Scheme 2. Synthesis of 5-(4-methyl-1*H*-1,2,3-triazolyl)methyl oxazolidinone derivatives. i. DCM/CH_3CN/DCC/1-HBT/mono ethyl malonate; ii. DMF/NaH/1,2-dibromoethane/CS_2, 0°C; iii. DCM/CH_3CN/DCC/1-HBT/*N*-*tert*-butoxycarbonylglycine; iv. TFA/DCM, 0°C-r.t.; v. DCM/DIEA/CS_2/4-tolyl SO_2Cl, −7 to 0°C-r.t.; vi. DMF/*N*,*N*-(bis(*tert*-butoxycarbonyl)-*S*-methyl isothiourea/TEA, r.t.; vii. TFA/DCM, 0°C-r.t.

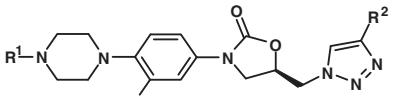
linezolid against the fastidious Gram-negative bacteria *M. catarrahlis*. The highly hydrophilic guanidine derivatives were inactive against the Gram-positive and Gram-negative bacteria strains tested in this study.

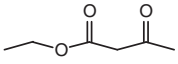
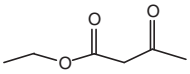
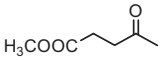
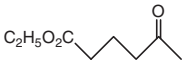
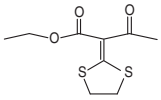
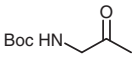
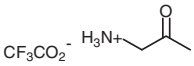
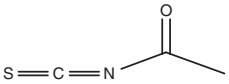
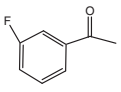
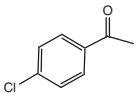
Experimental

Characterization

Column chromatography was carried out with silica gel (Kieselgel 60, 70–230 mesh; Aldrich) and TLC was conducted on 0.25 mm pre-coated silica gel plates ($60F_{254}$, Merck). Melting points were determined on a Stuart Scientific SMP1 melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance II 600 NMR spectrometer. In addition, the ^{13}C NMR spectra of representative compounds, **7t**, **8c**, and **9c**, were recorded on a Bruker Avance II 600 NMR spectrometer. The ^{13}C NMR experiments performed included ^{13}C NMR decoupled, ^{13}C-DEPT-135 (distortionless enhancement by polarization transfer-139) and ^{13}C-APT (attached proton test). Chemical shifts of protons are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal reference or DMSO-d_6 (δ = 2.5; 39.7) as solvent. Mass spectra were recorded on a Finnigan MAT INCOS XL mass spectrometer. Infrared (IR) spectra were recorded on a Perkin Elmer System 2000 FT-IR spectrometer. Elemental analyses were performed on a LECO elemental analyzer CHNS 932 apparatus, and analyses indicated by the symbols of the elements were within ±0.4% of the theoretical values. Analyses were performed by the Science Analytical Facilities (SAF), Faculty of Science, Kuwait University, Kuwait. The structures of the oxazolidinones and their Clog *P* values were sketched and estimated, respectively, using the CambridgeSoft ChemDraw Ultra 8.0 software.

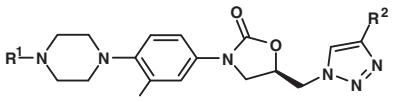
Table 1. Clog *P* values and antibacterial activities of 5-(1*H*-1,2,3-triazolyl)methyl oxazolidinones against *S. aureus* standard strain ATCC25923.



Compd	R^1	R^2	Clog *P* values	MIC against ATCC 25923	
				Without plasma	+50% plasma
7a		CH_3	0.1688	2	16
b		H	−0.1002	4	8
c		CH_3	−0.1342	2	8
d		CH_3	0.6208	2	16
e		CH_3	2.6234	8	32
f		CH_3	0.6456	4	16
g		CH_3	−0.0982	64	>64
h		CH_3	0.0670	16	32
i		CH_3	1.1024	1	16
j		CH_3	1.6724	1	32

continued

Table 1. (*continued*)



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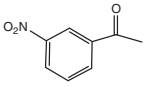
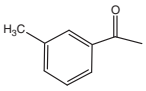
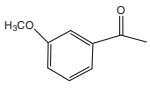
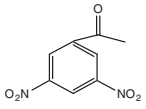
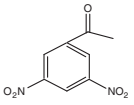
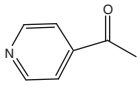
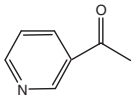
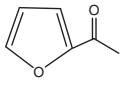
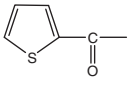
k		CH_3	0.7888	2	>64
l		CH_3	1.3828	2	>64
m		CH_3	1.1037	2	8
n		CH_3	0.5885	4	4
o		H	0.3195	1	8
p		CH_3	−0.2172	1	2
q		CH_3	−0.2172	2	8
r		CH_3	0.0598	0.5	8
s		CH_3	0.8903	0.5	4

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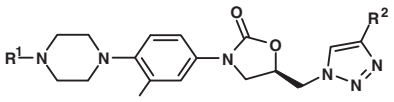
Table 1. (*continued*)



Compd	R^1	R^2	Clog *P* values	MIC against ATCC 25923	
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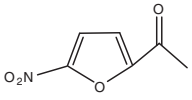
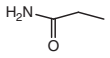
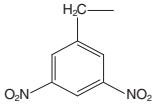
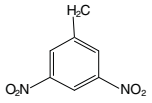
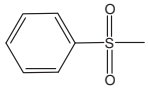
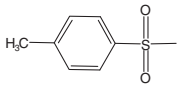
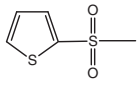
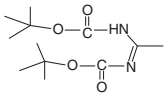
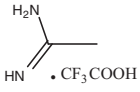
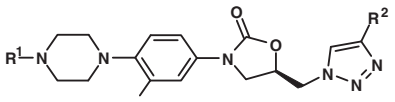
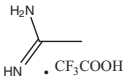
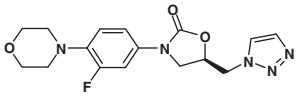
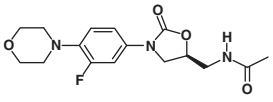
t		CH_3	−0.0352	0.5	4
8a		CH_3	−.06470	2	16
b		CH_3	1.7388	8	16
c		H	1.4698	2	16
9a		CH_3	1.6138	4	16
b		CH_3	1.8438	>64	>64
c		CH_3	1.5648	1	16
10a		CH_3	3.6508	16	>64
b		H	3.3818	16	>64
11a		CH_3	−0.0899	32	64

continued

Table 1. (*continued*)



Compd	R^1	R^2	Clog *P* values	MIC against ATCC 25923	
				Without plasma	+50% plasma
b		H	−0.1791	64	>64
PH027			0.631	1	1
Lzd			0.532	2	2
Van			n/d	2	2

Syntheses

*General procedure for the synthesis of compounds **7a–d**, **7f**, **7i–s**, and **9a–c***

A solution of compound **6a** (700 mg, 1.52 mmol) or **6b** (1.0 g, 2.11 mmol) in CH_3CN (20 mL) and TEA (1.0 mL) was treated with 1.1 equiv. of suitable activated acid (activated by reaction with DCC, 1-hydroxybenzotriazole, or oxalyl chloride) or acid anhydride or acid chloride or the arylsulfonyl chloride under stirring at 0°C. The reaction mixture was stirred to r.t. overnight. The reaction mixture was concentrated on a rotovap to give a crude, which was dissolved in DCM (30 mL), washed successively with water, dilute aq. Na_2CO_3 solution (15 mL), water, dried (anhydrous Na_2SO_4), filtered and concentrated to obtain a crude. The crude was purified either by silica gel column chromatography and/or recrystallized from a suitable organic solvent to give the respective products.

*(R)-Ethyl 3-(4-(2-fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl) phenyl)-piperazin-1-yl)-3-oxopropanoate **7a***

Prepared *via* the general procedure from compound **6b** and mono-ethyl malonic acid (2.31 mmoL) activated by DCC and 1-HOBT. Silica gel column chromatography (EtOAc/MeOH = 9:1) gave a solid, yield: 35%; m.p.: 164–166°C. ^{1}H NMR (DMSO-d_6): δ 7.87 (s, 1H, triazole H), 7.44 (dd 1H, J = 2.4, Hz, 14.9 Hz, phenyl H), 7.15 (dd, 1H J = 2.2 Hz, 9.0 Hz, phenyl H), 7.07 (t, 1H, J = 9.4 Hz, phenyl H), 5.05–5.08 (m, 1H, oxazolidinone H), 4.74 (d, 2H, J = 5.2 Hz, CH_2), 4.18 (t, 1H, J = 9.2 Hz, oxazolidinone H), 4.11 (q, 2H, J = 7.1 Hz, CH_3CH_2), 3.83 (dd, 1H, J = 5.9 Hz, 9.0 Hz, oxazolidinone H), 3.57–3.62 (m, 6H, piperazine H overlapping with the $-CH_2$ signal), 2.93–2.98 (m, 4H, piperazine H), 2.28 (s, 3H, triazole CH_3), 1.19 (t, 3H, J = 7.1 Hz, CH_3). IR (KBr pellet, cm^{-1}): ν 2930, 1744, 1641, 1519, 1446, 1417, 1326, 1219, 1160, 1098, 1054. MS 474.4 (M^+). Anal calcd for $C_{22}H_{27}FN_6O_5$: C: 55.69, H: 5.74, N: 17.71; found C: 55.30, H: 6.00, N: 17.41.

*(R)-Ethyl 3-(4-(4-(5-((1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazin-1-yl)-3-oxopropanoate **7b***

Prepared *via* the general procedure from compound **6a** and mono-ethyl malonate (2.31 mmol) activated by DCC and 1-HOBT. Silica gel column chromatography (EtOAc/MeOH = 9:1) gave a solid, yield: 37%; m.p.: 168–170°C. ^{1}H NMR (DMSO-d_6): δ 8.16 (s, 1H, triazole H), 7.76 (s, 1H, triazole H), 7.42 (dd, 1H, J = 2.5 Hz, 14.7 Hz, phenyl H), 7.13 (dd, 1H, J = 2.0 Hz, 8.4 Hz, phenyl H), 7.06 (t, 1H, J = 9.4 Hz, phenyl H), 5.11–5.13 (m, 1H, oxazolidinone H), 4.82 (d, 2H, J = 5.1 Hz, CH_2), 4.20 (t, 1H, J = 9.3 Hz, oxazolidinone H), 4.10 (q, 2H, J = 7.1, 14.2 Hz, CH_3CH_2), 3.85 (dd, 1H, J = 5.8, 9.4 Hz, oxazolidinone H), 3.54–3.62 (m, 6H, piperazine H overlapping with the $-CH_2$ signal), 2.92–2.98 (m, 4H, piperazine H), 1.20 (t, 3H, J = 7.1 Hz, CH_3). IR (KBr pellet, cm^{-1}): ν 2981, 2906, 1750, 1632, 1518, 1475, 1417, 1327, 1227, 1188, 1164, 1099, 1074, 1032. MS 460.4 (M^+); Anal calcd for $C_{21}H_{25}FN_6O_5$: C: 54.78, H: 5.47, N: 18.25; found C: 54.70, H: 4.99, N: 18.23.

Table 2. Antibacterial activities of 5-(1*H*-1,2,3-triazolyl)methyl oxazolidinones against Gram-positive standard strains and clinical isolates.

Compd	Minimum inhibitory concentrations (MIC's, μg/mL) against									
	S. aureus				*Enterococci*		*E. coli*	*H. influ*	*S. pn* ($n = 3$)	*M. cat*
	MRSA ($n = 9$)	MSSA ($n = 11$)	MRCNS ($n = 4$)	MSCNS ($n = 6$)	VSE ($n = 7$)	VRE ($n = 3$)				
7a	2	1–2	1	1–2	2	2	>64	32	2–4	8
b	2–4	4	2–4	2–4	2–4	4	>64	>64	1	16
c	1–2	1–2	1	1–2	2	2	>64	16–32	2	16
d	2–4	2–4	2–4	2–4	4	4	>64	64->64	4	16
e	4–8	4–8	4–8	4–8	4–8	4–8	>64	>64	4–8	64
f	8	4–8	4–8	4–8	4–8	8	>64	64->64	4–8	16
g	32–64	32–64	32–64	32–64	32–64	32	>64	>64	8–16	>64
h	8–16	8–16	8–16	8–16	8–16	8	>64	>64	8–16	64
i	1–2	1–2	1	1	1–2	1–2	>64	>64	1–2	32
j	1–2	1–2	1–2	1–2	1–2	1–2	>64	>64	4	16
k	1–2	1–2	1–2	1–2	1	1	>64	>64	2	8
l	2	1–2	1–2	1–2	1–2	1	>64	>64	4	>64
m	2	2	1–2	1–2	1–2	1–2	>64	>64	8	64
n	4	0.5–4	0.5	0.5–4	4	1–4	>64	>64	1–2	1
o	1	0.5–1	0.5–1	0.5–1	1	1	>64	>64	0.5–1	2
p	1–2	1–2	1–2	1–2	1–2	2	>64	>64	4	64
q	1–2	1–2	1–2	1–2	1–2	1–2	>64	64	1	8
r	0.5–1	0.5–1	0.5	0.5–1	0.5–1	0.5–1	>64	64	1–2	16
s	0.5–1	0.5–1	0.5–1	0.5–1	0.5	0.5–1	>64	>64	8	64
t	0.5–1	0.5–1	0.5–1	0.5–1	0.5–1	0.5	>64	32	1–2	2
8a	2–4	2–4	2–4	2–4	4	4	>64	32	2	16
b	8	8	1–4	4	1–4	1–4	>64	>64	4–8	32
c	2	2	1–2	1–2	1–2	1	>64	>64	4–8	32
9a	2–4	2–4	4	2–4	4	2–4	>64	>64	4–8	32
b	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
c	1	0.5–1	0.5–1	0.5–1	0.5	0.5	>64	>64	4	>64
10a	16–32	16–32	16	16	16	16	>64	>64	16	64
b	8–16	8–16	8–16	8–16	8–16	8	>64	>64	16	>64
11a	32	16–32	16–32	16	16–32	16	64	>64	2–16	>64
b	16–64	64	16–64	16–64	16–32	16–64	>64	>64	4–16	>64
PH027	0.5–1	0.5–1	0.5–1	0.5–1	0.5–1	1	>64	32	0.5	>16
Lzd	0.5–1	0.5–1	0.5–1	0.5–1	0.5–1	0.5–1	>64	8	0.5	8
Van	0.5–1	1–2	1	1–2	0.25–2	>64	n/d	n/d	0.5	n/d

MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; MR-CNS, methicillin-resistant coagulase-negative *S. aureus*; MS-CNS, methicillin-susceptible coagulase-negative *S. aureus*; VRE, vancomycin-susceptible enteroccoci; VRE, vancomycin-resistance enteroccoci; *E. coli*, *Escherichia coli*; *H. inf*, *H. influenzae*; *S. pn*, *S. pneumoniae*; *M. cat*, *M. catarrhalis*.

(R)-Methyl 4-(4-(2-fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl) phenyl)piperazin-1-yl)-4-oxobutanoate ***7c***

Prepared *via* the general procedure from compound **6b** and methyl chloro-4-oxobutanoate (3.25 mmol). Recrystallization (EtOAc/hexanes) gave a solid, yield: 90%; m.p.: 138–140°C. ^{1}H NMR (DMSO-d_6): δ 7.87 (s, 1H, triazole H), 7.44 (dd, 1H, $J = 2.3$ Hz, 14.7 Hz, phenyl H) 7.13 (dd, 1H, $J = 2.3$ Hz, 9.0 Hz, phenyl H), 7.05 (t, 1H, $J = 9.0$ Hz, phenyl H), 5.06–5.11 (m, 1H, oxazolidinone H), 4.74 (d, 2H, $J = 5.2$ Hz, CH_2) 4.20 (t. 1H, $J = 9.0$ Hz, oxazolidinone H), 3.84 (dd, 1H, $J = 5.9$ Hz, 9.3 Hz, oxazolidinone H), 3.56–3.67 (m, 7H, piperazine H, overlaps with the CH_3 signal), 2.98 (t, 2H, $J = 4.7$ Hz, piperazine H), 2.91 (t, 2H, $J = 4.7$ Hz, piperazine H), 2.64 (t, 2H, $J = 5.8$ Hz, CH_2), 2.54 (t, 2H, $J = 5.8$ Hz, CH_2, overlaps with DMSO signal at 2.51 ppm), 2.23 (s, 3H, triazole CH_3). IR (KBr pellet, cm^{-1}): ν 2998, 2949, 2831, 1744, 1638, 1518, 1439, 1419, 1371, 1325, 1279, 1220, 1167, 1137, 1100, 1054, 1033. MS 474.3 (M^+). Anal calcd for $C_{22}H_{27}FN_6O_5$: C: 55.69, H: 5.74, N: 17.71; found C: 55.69, H: 5.90, N: 17.55.

(R)-Ethyl 5-(4-(2-fluoro-4-(5-((4-methyl-1H-1,2,-3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl) phenyl)-piperazin-1-yl)-5-oxopentanoate ***7d***

Prepared *via* the general procedure from compound **6b** and glutaric acid monoethyl ester chloride (3.25 mmol).

Recrystallization (EtOAc/hexanes) gave a solid, yield: 58%; m.p.: 125–127°C. ^{1}H NMR (DMSO-d_6): δ 7.86 (s, 1H, triazole H), 7.44 (dd, 1H, J = 2.5 Hz, 14.7 Hz, phenyl H), 7.14 (dd, 1H, J = 2.5 Hz, 9.0 Hz, phenyl H), 7.11 (t, 1H, J = 9.0 Hz, phenyl H), 5.06–5.10 (m, 1H, oxazolidinone H), 4.73 (d, 2H, J = 5.2 Hz, CH_2), 4.19 (t, 1H, J = 9.0 Hz, oxazolidinone H), 4.05 (q, 2H, J = 7.1 Hz, CH_3CH_2), 3.83 (dd, 1H, J = 5.9 Hz, 9.0 Hz, oxazolidinone H), 3.59 (m, 4H, piperazine H), 2.96 (t, 2H, J = 4.7 Hz, piperazine H), 2.91 (t, 2H, J = 4.7 Hz, piperazine H), 2.33–2.39 (m, 4H, CH_2CH_2), 2.22 (s, 3H, triazole CH_3), 1.76–1.78 (m, 2H, CH_2), 1.18 (t, 3H, J = 7.1 Hz CH_3CH_2). IR (KBr pellet, cm^{-1}): ν 2958, 2897, 2836, 1743, 1643, 1521, 1450, 1428, 1384, 1340, 1282, 1233, 1179, 1138, 1100, 1048, 1030. MS 502.4 (M^+). Anal calcd for $C_{24}H_{31}FN_6O_5$: C: 57.36, H: 6.22, N: 16.72; found C: 57.00, H: 6.40, N: 16:45.

(R)-Ethyl 2-(1,3-dithiolan-2-ylidene)-3-(4-(2-fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl) methyl)-2-oxooxazolidin-3-yl)phenyl)piperazin-1-yl)-3-oxopropanoate **7e**

A solution of **7a** (200 mg, 0.42 mmol) in DMF (anhyd. 10 mL) at 0°C was treated with 1,2-dibromoethane (50 μL, 0.56 mmol), CS_2 (130 μL, 2.1 mmol), and NaH (60% in mineral oil, 58 mg, 1.42 mmol) and stirred for 1 h. Then diluted with EtOAc (30 mL), washed with water, dried (Na_2SO_4), filtered and concentrated to give a residue. Recrystallization (DCM/Et_2O) gave a white solid, yield: 41%; m.p.: 110–112°C. ^{1}H NMR (DMSO-d_6): δ 7.87 (s, 1H, triazole H), 7.44 (dd, 1H, J = 2.3 Hz, 14.7 Hz, phenyl H), 7.08–7.13 (m, 2H, phenyl H), 5.08–5.1 (m, 1H, oxazolidinone H), 4.74 (d, 2H, J = 5.2 Hz, CH_2), 4.12–4.22 (m, 3H, oxazolidinone H and CH_2), 3.84 (dd, 1H, J = 5.9 Hz, 9.4 Hz, oxazolidinone H), 3.68–3.72 (m, 2H, piperazine H), 3.45–3.51 (br, 2H, thiolane H), 3.37–3.41 (m, 4H, piperazine H), 2.90–3.10 (m, 4H, piperazine H), 2.22 (s, 3H, triazole CH_3). IR (KBr pellet, cm^{-1}): ν 2951, 2921, 2858, 2835, 2071 (S=C=N–), 1753, 1734, 1659, 1520, 1443, 1420, 1387, 1323, 1232, 1226, 1159, 1136, 1101, 1032. MS 576.2 (M^+). Anal calcd for $C_{25}H_{29}FN_6O_5S_2$: C: 52.07, H: 5.07, N: 14.57; found C: 52.10, H: 5.27, N: 14.10.

(R)-2-(4-(2-Fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)-methyl)-2-oxooxazolidin-3-yl)phenyl) piperazin-1-yl)-2-oxoethanaminium 2,2,2-trifluoroacetate **7g**

This compound was prepared from **7f**, which was obtained *via* the general procedure from compound **6b** and *N-tert*-butoxycarbonylglycine (2.62 mmol) activated by DCC/1-HOBT. Silica gel column chromatography (EtOAc/MeOH = 9:1) gave *(R)-tert-butyl (2-(4-(2-fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-phenyl)piperazin-1-yl)-2-oxoethyl) carbamate* **7f** as a solid, yield: 83%; m.p.: 175–177°C. ^{1}H NMR (DMSO-d_6): δ 7.86 (s, 1H, triazole H), 7.43 (dd, 1H, J = 2.5 Hz, 14.7 Hz, phenyl H), 7.13 (dd, 1H J = 2.5 Hz, phenyl H), 7.06 (t, 1H, J = 9.0 Hz, phenyl H), 6.77 (br. t, 1H, NHBoc, exchangeable with D_2O), 5.07–5.10 (m, 1H, oxazolidinone H), 4.74 (d, 2H, J = 5.2 Hz, CH_2), 4.19 (t, 1H, J = 9.0 Hz, oxazolidinone H), 3.82–3.85 (m, 3H, oxazolidinone H and CH_2), 3.55–3.59 (m, 4H, piperazine H), 2.92–2.97 (m, 4H, piperazine H), 2.22 (s, 3H, triazole CH_3), 1.39 (s, 9H, $C(CH_3)_3$). IR (KBr pellet, cm^{-1}): ν 3444, 2977, 2932, 1741, 1708, 1667.79, 1517, 1427, 1440, 1455, 1367, 1339, 1283, 1230, 1165, 1049, 1034. MS 517.4 (M^+). Anal calcd for $C_{24}H_{32}FN_7O_5$: C: 55.70, H: 6.23, N: 18.94; found C: 55.74, H: 6.52, N: 18.74. A solution of **7f** (5.22 mmol) in DCM (6 mL) and TFA (6 mL) at 0°C was stirred to r.t. overnight. The reaction mixture was concentrated and the residue triturated with ether to give **7g** as a solid in quantitative yield. ^{1}H NMR (DMSO-d_6): δ 7.70–7.82 (m, 3H, $^+NH_3$, exchangeable with D_2O), 7.64 (s, 1H, triazole H), 7.21 (dd, 1H, J = 2.6 Hz, 14.7 Hz, phenyl H), 6.93 (dd, 1H, J = 2.1 Hz, 8.6 Hz, phenyl H), 6.84 (t, 1H, J = 9.5 Hz, phenyl H), 4.86–4.88 (m, 1H, oxazolidinone H), 4.52 (d, 2H, J = 5.2 Hz, CH_2), 3.97 (t, 1H, J = 9.2 Hz, oxazolidinone H), 3.71 (q, 2H, J = 5.7 Hz, 11.4 Hz, CH_2), 3.61 (dd, 1H, J = 5.9 Hz, 9.3 Hz, oxazolidinone H), 3.4–3.5 (m, 4H, piperazine H), 2.7–2.8 (m, 4H, piperazine H), 2.00 (s, 3H, triazole CH_3). MS 418.75 (M^++H).

(R)-3-(3-Fluoro-4-(4-(2-isothiocyanatoacetyl)piperazin-1-yl)-phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-oxazolidin-2-one **7h**

To a solution of **7g** (200 mg, 0.38 mmol) in DCM (anhyd. 15 mL), *N*,*N*-diisopropylethylamine (140 μL, 0.803 mmol) and CS_2 (150 μL, 2.55 mmol) were added with stirring. A solution of *p*-toluenesulfonylchloride (75 mg, 1.04 mmol) in anhyd. DCM (10 mL) was added dropwise at −7°C. Slow effervescence was observed and stirring was continued for 30 min at 0°C to r.t. overnight. The solvent was evaporated under vacuum to give a residue, which was purified by column chromatography over silica gel (EtOAc/MeOH = 10:1) to give **7h** as white crystals, yield: 75%; m.p.: 160–161°C. ^{1}H NMR (DMSO-d_6): δ 7.86 (s, 1H, triazole H), 7.43 (dd, 1H, J = 2.5 Hz, 14.7 Hz, phenyl H), 7.13 (dd, 1H, J = 2.4 Hz, 9.0 Hz, phenyl H), 7.05 (t, 1H, J = 9.1 Hz, phenyl H), 5.06–5.1 (m, 1H, oxazolidinone H), 4.77 (s, 2H, CH_2), 4.73 (d, 2H, J = 5.5 Hz, –CH_2), 4.19 (t, 1H, J = 9.5 Hz, oxazolidinone H), 3.83 (dd, 1H, J = 5.9 Hz, 9.4 Hz, oxazolidinone H), 3.62–3.64 (m, 2H, piperazine H), 3.40–3.43 (m, 2H, piperazine H), 2.94–3.05 (m, 4H, piperazine H), 2.22 (s, 3H, triazole CH_3). IR (KBr pellet, cm^{-1}): ν 2951, 2921, 2858, 2835, 2071 (S=C=N–), 1753, 1734, 1659, 1520, 1443, 1420, 1387, 1323, 1232, 1226, 1159, 1136, 1101, 1032. MS 459.2 (M^+). Anal calcd for $C_{20}H_{22}FN_7O_3S$: C: 52.28, H: 4.83, N: 21.34; found C: 51.99, H: 4.87, N: 20.77.

(R)-3-(3-Fluoro-4-(4-(3-fluorobenzoyl)piperazin-1-yl)-phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-oxazolidin-2-one **7i**

Compound **7i** was prepared *via* the general procedure from compound **6b** and fluorobenzoyl chloride (1.50 mmol). Recrystallization (EtOAc/hexanes) to give a solid, yield: 96%; m.p.195–197°C. ^{1}H NMR (DMSO-d_6): δ 7.87 (s, 1H, triazole H), 7.52 (m, 1H, phenyl H), 7.44 (dd, 1H, J = 2.4 Hz, 14.7 Hz, phenyl H), 7.26–7.36 (m, 3H, phenyl H), 7.15 (dd, 1H, J = 2.3 Hz, 8.8 Hz, phenyl H), 7.09 (t, 1H, J = 9.20 Hz, phenyl H), 5.04–5.11 (m, 1H, oxazolidinones H), 4.74 (d, 2H, J = 5.2 Hz, CH_2), 4.19 (t, 1H, J = 9.2 Hz, oxazolidinones H), 3.83 (dd, 1H, J = 5.9 Hz, 9.4 Hz, oxazolidinone H), 3.7–3.8 (m, 2H, piperazine H), 3.45–3.60 (m, 2H, piperazine H), 2.90–3.10 (m, 4H, piperazine H), 2.23 (s, 3H, triazole CH_3). IR (KBr pellet, cm^{-1}): ν 2992, 2907, 2836, 1740, 1629, 1524, 1440, 1417, 1329, 1288, 1217, 1162, 1021. MS 482.1 (M^+). Anal calcd for $C_{24}H_{24}F_2N_6O_3$: C: 59.74, H: 5.01, N: 17.42; found C: 59.85, H: 5.06, N: 17.63.

(R)-3-(4-(4-(4-Chlorobenzoyl)piperazin-1-yl)-3-fluorophenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)-methyl)oxazolidin-2-one **7j**

Compound **7j** was prepared *via* the general procedure from compound **6b** and 4-chlorobenzoyl chloride (1.60 mmol).

Recrystallization (EtOAc/hexanes) to give a solid, yield: 84%; m.p.: 195–197°C. ^{1}H NMR (DMSO-d_6): δ 7.87 (s, 1H, triazole H), 7.54 (m, 1H, phenyl H), 7.49 (dd, 1H, J = 2.0 Hz, 14.7 Hz, phenyl H), 7.44 (dd, 1H, J = 2.4 Hz, 14.7 Hz, phenyl H), 7.14 (dd, 1H, J = 2.3 Hz, 9.0 Hz, phenyl H), 7.08 (t, 1H, J = 9.2 Hz, phenyl H), 5.04–5.08 (m, 1H, oxazolidinone H), 4.74 (d, 2H, J = 5.2 Hz, CH_2), 4.19 (t, 1H, J = 9.2 Hz, oxazolidinone H), 3.84 (dd, 1H, J = 5.9 Hz, 9.4 Hz, oxazolidinone H), 3.72–3.80 (m, 2H, piperazine H), 3.45–3.51 (m, 2H, piperazine H), 2.90–3.10 (m, 4H, piperazine H), 2.23 (s, 3H, triazole CH_3). IR (KBr pellet, cm^{-1}): ν 2912, 2837, 1740, 1627, 1523, 1489, 1438, 1418, 1380, 1329, 1286, 1219, 1159, 1096, 1014. Anal calcd for $C_{24}H_{24}ClFN_6O_3$: C: 57.78, H: 4.85, N: 16.84; found C: 57.91, H: 4.88, N: 17.09.

(R)-3-(3-Fluoro-4-(4-(3-nitrobenzoyl)piperazin-1-yl)-phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-oxazolidin-2-one ***7k***

Compound **7k** was prepared *via* the general procedure from compound **6b** and 3-nitrobenzoyl chloride (1.60 mmol). Recrystallization (EtOAc/hexanes) to give a cream colored solid, yield: 84%; m.p.: 183–185°C. ^{1}H NMR (DMSO-d_6): δ 8.31–8.34 (m, 1H, phenyl H), 8.27 (t, 1H, J = 1.75 Hz, phenyl H), 7.90–7.93 (m, 1H, phenyl H), 7.87 (s, 1H, triazole H), 7.77 (t, 1H, J = 7.9 Hz, phenyl H), 7.44 (dd, 1H, J = 2.4 Hz, 14.7 Hz, phenyl H), 7.15 (dd, 1H, J = 2.5 Hz, 9.0 Hz, phenyl H), 7.09 (t, 1H, J = 9.3 Hz, phenyl H), 5.06–5.10 (m, 1H, oxazolidinone H), 4.74 (d, 2H, J = 5.2 Hz, CH_2), 4.19 (t, 1H, J = 9.3 Hz, oxazolidinone H), 3.84 (dd, 1H, J = 5.9 Hz, 9.5 Hz, oxazolidinone H), 3.49 (m, 2H, piperazine H), 3.08 (m, 2H, piperazine H), 2.97 (m, 2H, piperazine H), 2.22 (m, 2H, piperazine H), 2.23 (s, 3H, triazole CH_3). IR (KBr pellet, cm^{-1}): ν 2900, 2836, 1737, 1637, 1530, 1488, 1421, 1346, 1223, 1162, 1033. MS 509.5 (M^+). Anal calcd for $C_{24}H_{24}FN_7O_5$: C: 56.58, H: 4.75, N: 19.24; found C: 56.66, H: 4.77, N: 19.44.

(R)-3-(3-Fluoro-4-(4-(3-methylbenzoyl)piperazin-1-yl)-phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-oxazolidin-2-one ***7l***

Compound **7l** was prepared *via* the general procedure from compound **6b** and *m*-toluoyl chloride (1.50 mmol). Recrystallization (EtOAc/hexanes) to give a solid, yield: 72%; m.p.: 165–167°C. ^{1}H NMR (DMSO-d_6): δ 7.86 (s, 1H, triazole H), 7.43 (dd, 1H, J = 2.5 Hz, 14.6 Hz, phenyl H), 7.34 (t, 1H, J = 7.6 Hz, phenyl H), 7.28 (d, 1H, J = 7.7 Hz) phenyl H), 7.24 (s, 1H, phenyl H), 7.21 (d, 1H, J = 7.5 Hz, phenyl H), 7.14 (dd, 1H, J = 2.4 Hz, 8.8 Hz, phenyl H), 7.08 (t, 1H J = 9.4 Hz, phenyl H), 5.05–5.09 (m, 1H, oxazolidinone H), 4.73 (d, 2H, J = 5.3 Hz, CH_2), 4.19 (t, 1H, J = 9.2 Hz, oxazolidinone H), 3.83 (dd, 1H, J = 6.0 Hz, 9.3 Hz, oxazolidinone H), 3.77 (m, 2H, piperazine H), 3.48 (m, 2H, piperazine H), 2.94–3.02 (m, 4H, piperazine H), 2.35 (s, 3H, CH_3), 2.22 (s, 3H, triazole CH_3). IR (KBr pellet, cm^{-1}): ν 2915, 2849, 1742, 1631, 1524, 1489, 1440, 1418, 1327, 1288, 1219, 1136, 1101. MS 478.0 (M^+); Anal calcd for $C_{25}H_{27}FN_6O_3$: C: 62.75, H: 5.69, N: 17.56; found C: 62.29, H: 5.4, N: 17.42.

(R)-3-(3-Fluoro-4-(4-(3-methoxybenzoyl)piperazin-1-yl)-phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-oxazolidin-2-one ***7m***

Compound **7m** was prepared *via* the general procedure from compound **6b** and *m*-anisoyl chloride (1.50 mmol). Recrystallization (EtOAc/hexanes) to give a white solid, yield: 62%; m.p.: 155–157°C. ^{1}H NMR (DMSO-d_6): δ 7.87 (s, 1H, triazole H), 7.44 (dd, 1H, J = 2.4 Hz, 14.6 Hz, phenyl H), 7.38 (t, 1H, J = 7.9 Hz, phenyl H), 7.15 (dd, 1H, J = 2.3 Hz, 9.0 Hz, phenyl H), 7.09 (t, 1H, J = 9.2 Hz, phenyl H), 6.96–7.05 (m, 3H, phenyl H), 5.06–5.10 (m, 1H, oxazolidinone H), 4.74 (d, 2H, J = 5.2 Hz, CH_2), 4.19 (t, 1H, J = 9.3 Hz, oxazolidinone H), 3.84 (dd, 1H, J = 5.9 Hz, 9.5 Hz, oxazolidinone H), 3.79–3.84 (s, 5H, OCH_3, and overlapping piperazine H multiplet signal), 3.46–3.54 (m, 2H, piperazine H), 2.90–3.08 (m, 4H, piperazine H), 2.23 (s, 3H, triazole CH_3). IR (KBr pellet, cm^{-1}): ν 2996, 2836, 1741, 1631, 1524, 1422, 1323, 1289, 1230, 1102, 1042, 1021. Anal calcd for $C_{25}H_{27}FN_6O_4$: C: 60.72, H: 5.50, N: 16.99; found C: 61.00, H: 5.57, N: 17.23.

(R)-3-(4-(4-(3,5-Dinitrobenzoyl)piperazin-1-yl)-3-fluorophenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-oxazolidin-2-one ***7n***

Compound **7n** was prepared *via* the general procedure from compound **6b** and 3,5-dinitro-benzoyl chloride (1.58 mmol). Silica gel column chromatography (EtOAc) gave a yellow solid, yield: 39%; m.p.: 105–107°C. ^{1}H NMR (DMSO-d_6): δ 8.88 (t, 1H, J = 2.0 Hz, phenyl H), 8.69 (d, 2H, J = 2.2 Hz, phenyl H), 7.86 (s, 1H, triazole H), 7.43 (dd, 1H, J = 2.5 Hz, 14.7 Hz, phenyl H), 7.15 (dd, 1H, J = 2.2 Hz, 8.7 Hz, phenyl H), 7.08 (t, 1H, J = 9.4 Hz, phenyl H), 5.06–5.09 (m, 1H, oxazolidinone H), 4.73 (d, 2H, J = 5.2 Hz, CH_2), 4.19 (t, 1H, J = 9.1 Hz, oxazolidinone H), 3.83 (m, 3H, oxazolidinone H and piperazine H), 3.45–3.55 (m, 2H, piperazine H), 3.09–3.18 (m, 2H, piperazine H), 2.93–2.99 (m, 2H, piperazine H), 2.22 (s, 3H, triazole H). IR (KBr pellet, cm^{-1}): ν 2919, 2852, 1756, 1641, 1545, 1516, 1478, 1438, 1344, 1282, 1232, 1159, 1028. MS 554.2 (M^+). Anal calcd for $C_{24}H_{23}FN_5O_7$: C: 51.99, H: 4.18, N: 20.21; found C: 51.82, H: 4.53, N: 19.94.

(R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(4-(4-(3,5-dinitrobenzoyl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one ***7o***

Compound **7o** was prepared *via* the general procedure from compound **6a** and 3,5-dinitro-benzoyl chloride (1.63 mmol). Recrystallization (EtOAc/hexanes) to give a solid, yield: 53%; m.p.: 240–242°C. ^{1}H NMR (DMSO-d_6): δ 8.76 (t, 1H J = 2.0 Hz, phenyl), 8.61 (d, 2H, J = 2.1 Hz, phenyl), 8.17 (s, 1H, triazole H), 7.77 (s, 1H, triazole H), 7.40 (dd, 1H, J = 2.5 Hz, 14.5 Hz, phenyl), 7.11 (dd, 1H, J = 2.9 Hz, 8.7 Hz, phemyl), 7.07 (t, 1H, J = 8.7 Hz, phenyl), 5.09–5.15 (m, 1H, oxazoldinone H) 4.82 (d, 2H, J = 5.1 Hz, CH_2), 4.20 (t, 1H, J = 8.6, oxazolidinone H), 3.86 (t, 1H, J = 5.4 Hz) oxazoldinone H), 3.00–3.02 (m, 4H, piperazine H), 2.61–2.63 (m, 4H, piperazine H). IR (KBr pellet, cm^{-1}): ν 2921, 2845, 1746, 1640, 1546, 1516, 1482, 1435, 1342, 1285, 1236, 1192, 1027. MS 540.2 (M^+). Anal calcd for $C_{23}H_{21}FN_8O_7$: C: 51.10, H: 3.92, N: 20.72; found C: 50.86, H: 3.97, N: 20.64.

(R)-3-(3-Fluoro-4-(4-isonicotinoylpiperazin-1-yl)phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one ***7p***

Compound **7p** was prepared *via* the general procedure from compound **6b** and isonicotinoyl chloride (2.10 mmol). Silica gel column chromatography (EtOAc/MeOH = 10:1) gave a white solid, yield: 45%; m.p.: 194–196°C. ^{1}H NMR (DMSO-d_6): δ 8.68–8.70 (m, 2H, pyridyl H), 7.86 (s, 1H, triazole H), 7.41–7.45 (m, 3H, pyridyl and phenyl 1H), 7.15 (dd, 1H, J = 2.4 Hz 9.0 Hz, phenyl

H), 7.08 (t, 1H, J = 9.4 Hz, phenyl H), 5.05–5.11 (m, 1H, oxazolidinone H), 4.74 (d, 2H J = 5.2 Hz, CH_2), 4.19 (t, 1H J = 9.2 Hz, oxazolidinone H), 3.84 (dd, 1H, J = 5.9 Hz, 9.4 Hz, oxazolidinone H), 3.79–3.82 (m, 2H, piperazine H), 3.30–3.45 (m, 2H, piperazine H), 3.05–3.08 (m, 2H, piperazine H), 2.92–2.96 (m, 2H, piperazine H), 2.22 (s, 3H, triazole CH_3). IR (KBr pellet, cm^{-1}): ν 2898, 2851, 1743, 1633, 1517, 1440, 1413, 1334, 1285, 1217, 1160. MS 465.6 (M^+). Anal calcd for $C_{23}H_{24}FN_7O_3$: C: 59.35, H: 5.20, N: 21.06; found C: 58.98, H: 5.21, N: 20.77.

(R)-3-(3-Fluoro-4-(4-nicotinoylpiperazin-1-yl)phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one ***7q***

Compound **7q** was prepared *via* the general procedure from compound **6b** and nicotinoyl chloride (1.58 mmol). Recrystallization (EtOAc/hexanes) gave crystalline needles, yield: 80%; m.p.: 186–188°C. ^{1}H NMR (DMSO-d_6): δ 8.63–8.70 (m, 2H, pyridyl H), 7.85–7.91 (m, 2H, pyridyl and triazole H), 7.49–7.52 (m, 1H, pyridyl H), 7.44 (dd, 1H, J = 2.2 Hz, 14.6 Hz, phenyl H), 7.15 (dd, 1H, J = 2.3 Hz, 9 Hz, phenyl H), 7.11 (t, 1H, J = 9.3 Hz, phenyl H), 5.05–5.10 (m, 1H, oxazolidinone H), 4.74 (dd, 2H, J = 5.2 Hz CH_2), 4.19 (t, 1H, J = 9.3 Hz, oxazolidinone H), 3.81–3.85 (m, 3H, oxazolidinone H overlaps with piperazine H multiplet signals), 3.45–3.54 (m, 2H, piperazine H), 2.97–3.10 (m, 4H, piperazine H), 2.22 (s, 3H, triazole CH_3). IR (KBr pellet, cm^{-1}): ν 2953, 2918, 1740, 1624, 1522, 1438, 1416, 1333, 1218, 1136. MS 464.7 (M^+). Anal calcd for $C_{23}H_{24}FN_7O_3$: C: 59.35, H: 5.20, N: 21.06; found C: 59.10, H: 5.26, N: 21:27.

(R)-3-(3-Fluoro-4-(4-(furan-2-carbonyl)piperazin-1-yl)-phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-oxazolidin-2-one ***7r***

Compound **7r** was prepared *via* the general procedure from compound **6b** and 2-furoyl chloride (1.61 mmol). Silica gel column chromatography (MeOH/EtOAc = 20:0.5 → 10:1) gave a white solid, yield: 25%; m.p.: 191–193°C. ^{1}H NMR (DMSO-d_6): δ 7.87 (br s, 2H, triazole and furan H), 7.45 (dd, 1H, J = 2.8 Hz, 15.3 Hz, furan H), 7.15 (dd, 1H, J = 2.8 Hz, 15.3 Hz, phenyl H), 7.09 (t, 2H, J = 9.0 Hz, phenyl H), 7.04 (d, 1H, J = 3.4 Hz, furan H), 6.60 (dd, 1H, J = 1.8 Hz, 3.5 Hz, furan H), 5.05–5.10 (m, 1H, oxazolidinone H), 4.74 (d, 2H, J = 5.3 Hz, CH_2), 4.19 (t, 1H, J = 9.1 Hz, oxzolidinone), 3.82–3.86 (m, 5H, oxazolidinone and piperazine H), 3.03 (m, 4H, J = 5 Hz, piperazine H), 2.23 (s, 3H, triazole CH_3). IR (KBr pellet, cm^{-1}): ν 2918, 2825, 1740, 1622, 1518, 1481, 1422, 1341, 1281, 1229, 1196, 1155, 1106, 1029. MS 454.7 (M^+). Anal calcd for $C_{22}H_{23}FN_6O_4$: C: 58.14, H: 5.10, N: 18.49; found C: 58.23, H: 5.14, N: 18.46.

(R)-3-(3-Fluoro-4-(4-(thiophene-2-carbonyl)piperazin-1-yl)-phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-oxazolidin-2-one ***7s***

Compound **7s** was prepared *via* the general procedure from compound **6b** and 2-thiophene-carbonyl chloride (1.58 mmol). Recrystallization (EtOAc) gave a white solid, yield: 97%; m.p.: 183–185°C. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 7.87 (s, 1H, triazole H), 7.79 (dd, 1H, J = 0.9 Hz, 5.0 Hz, thiophene H), 7.43–7.47 (m, 2H, thiophene and phenyl H), 7.13–7.16 (m, 2H, thiophene and phenyl H), 7.09 (t, 1H, J = 9.3 Hz, phenyl H), 5.06–5.10 (m, 1H, oxazolidinone H), 4.74 (d, 2H, J = 5.2 Hz, CH_2), 4.19 (t, 1H J = 9.2 Hz, oxazolidinone H), 3.84 (dd, 1H, J = 5.9 Hz, 9.4 Hz, oxazolidinone H), 3.82 (t, 4H, J = 5.5 Hz, piperazine H), 3.03 (t, 4H, J = 5.5 Hz, piperazine H), 2.23 (s, 3H, triazole CH_3). IR (KBr pellet, cm^{-1}): ν 2918, 1741, 1605, 1518, 1441, 1419, 1327, 1274, 1234, 1132, 1004. MS 469.7 (M^+). Anal calcd for $C_{22}H_{23}FN_6O_3S$: C: 56.16, H: 4.93, N: 17.86, S: 6.81; found C: 55.83, H: 4.97, N: 17.64, S: 6.64.

(R)-3-(3-Fluoro-4-(4-(5-nitrofuran-2-carbonyl)piperazin-1-yl)phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-oxazolidin-2-one ***7t***

Compound **7t** was prepared *via* the general procedure from compound **6b** and 5-nitrofuran carboxylic acid (1.08 mmol) activated by oxalyl chloride. Recrystallization (EtOAc/hexanes) gave a yellow crystalline solid, yield: 60%; m.p.: 178–180°C. ^{1}H NMR (DMSO-d_6): δ 7.86 (s, 1H, triazole H), 7.79 (d, 1H, J = 3.8 Hz, furan H), 7.45 (dd, 1H, J = 2.5 Hz, 14.7 Hz, phenyl H), 7.32 (dd, 1H, J = 3.9 Hz, furan H), 7.15 (dd, 1H, J = 2.3 Hz, 8.8 Hz, phenyl, H), 7.08 (t, 1H, J = 9.4 Hz, phenyl H), 5.06–5.1 (m, 1H, oxazolidinone), 4.73 (d, 2H, J = 5.2 Hz, CH_2), 4.19 (t, 1H, J = 9.2 Hz, oxazolidinone), 3.86 (dd, 1H, J = 5.9 Hz, 9.0 Hz, oxazolidinone, overlaps with piperazine signal), 3.82–3.85 (m, 4H, piperazine), 3.02–3.05 (m, 4H, piperazine), 2.22 (s, 3H, triazole CH_3). ^{13}C NMR (DMSO-d_6): δ 157.20, 155.85, 154.23, 153.98, 151.72, 147.95, 142.53, 135.69, 135.63, 133.94, 133.86, 123.69, 120.34, 117.59, 114.76, 113.33, 107.33, 107.16, 71.35, 66.59, 52.16, 47.60, 10.86. IR (KBr pellet, cm^{-1}): ν 2897, 1743, 1643, 1521, 1450, 1428, 1384, 1340, 1282, 1233, 1179, 1138, 1100, 1049, 1030. MS 499 (M^+). Anal calcd for $C_{22}H_{27}FN_7O_6$: C: 52.91, H: 4.44, N: 19.63; found C: 52.50, H: 4.52, N: 19.39.

(R)-2-(4-(2-Fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)-methyl)-2-oxooxazolidin-3-yl)phenyl)piperazin-1-yl)-acetamide ***8a***

A solution of compound **6b** (500 mg, 1.05 mmol) and iodoacetamide (600 mg, 3.24 mmol) in DMF (10 mL) and TEA (0.5 mL) was heated at 90°C overnight. The reaction mixture was diluted with water and extracted with DCM. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated to give a crude mass, which was purified by silica gel column chromatography (EtOAc) to give a solid, which was recrystallized from EtOAc/hexanes to give a solid, yield: 18%; m.p.: 212–215°C. ^{1}H NMR (DMSO-d_6): δ 7.86 (d, 1H, triazole H), 7.40 (dd 1H, J = 2.50, Hz, 14.7 Hz, phenyl H), 7.21 (br, s, 1H, NH, exchangeable with D_2O), 7.13 (br, s, 1H, NH, exchangeable with D_2O), 7.12 (dd, 1H, J = 2.5 Hz, 9.0 Hz, phenyl H overlapping with broad NH signal), 7.05 (t, 1H, J = 9.0 Hz, phenyl H), 5.06–5.09 (m, 1H, oxazolidinone H), 4.73 (d, 2H, J = 5.0 Hz, CH_2), 4.18 (t, 1H, J = 9.0 Hz, oxazolidinone H), 3.83 (dd, 1H, J = 5.9 Hz, 9.0 Hz, oxazolidinone H), 3.01 (t, 4H, J = 4.5 Hz, piperazine H), 2.92 (s, 2H, CH_2), 2.59 (t, 4H, J = 4.5 Hz, piperazine H), 2.22 (s, 3H, triazole CH_3). IR (KBr pellet, cm^{-1}): ν 3431, 3354, 2828, 1744, 1659, 1519, 1450, 1409, 1331, 1240, 1134, 1102, 1053. MS 417.3 (M^+). Anal calcd for $C_{19}H_{24}FN_7O_3$: C: 54.67, H: 5.80, N: 23.49; found C: 54.13, H: 5.94, N: 22.99.

(R)-3-(4-(4-(3,5-Dinitrobenzyl)piperazin-1-yl)-3-fluorophenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-oxazolidin-2-one ***8b***

Compound **8b** was prepared *via* a similar procedure to **8a** from **6b** and 3,5-dinitrobenzyl chloride (340 mg, 1.57 mmol) in CH_3CN

(20 mL); to give a yellow solid, yield: 40%; m.p.: 192–194°C. ^{1}H NMR (DMSO-d_6): δ 8.75 (t, 1H, J = 2.1 Hz phenyl H), 8.60 (d, 2H, J = 2.1 Hz phenyl H), 7.86 (s, 1H, triazole H), 7.40 (dd, 1H, J = 2.5 Hz, 14.8 Hz phenyl H), 7.12 (dd, 1H, J = 2.4 Hz and 8.8 Hz, phenyl H), 7.07 (t, 1H, J = 9.4 Hz, phenyl H), 5.05–5.09 (m, 1H, oxazolidinone H), 4.73 (d, 2H, J = 5.08 Hz, CH_2), 4.18 (t, 1H, J = 9.2 Hz oxazolidinone H), 3.80–3.83 (m, 3H, oxazolidinone H and CH_2), 2.95–3.05 (m, 4H, piperazine H), 2.60–2.68 (m, 4H, piperazine H), 2.22 (s, 3H, triazole CH_3). IR (KBr pellet, cm^{-1}): ν 2938, 2829, 1739, 1541, 1517, 1448, 1410, 1344, 1236, 1128, 1048. MS 540.2 (M^+). Anal calcd for CHFNO: C: 53.33, H: 4.66, N: 20.73; found C: 53.67, H: 4.63, N: 20.96.

(R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(4-(4-(3,5-dinitrobenzyl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one ***8c***

Compound **8c** was prepared *via* a similar procedure to **8a** from **6a** and 3,5-dinitrobenzyl chloride (340 mg, 1.57 mmol) in CH_3CN (20 mL) to give an orange powder, yield: 67%; m.p.: 150–152°C. ^{1}H NMR (DMSO-d_6): δ 8.88 (t, 1H, J = 2.1 Hz, benzyl H), 8.69 (d, 2H, J = 2.1 Hz, benzyl H), 8.17 (s, 1H, triazole H), 7.77 (s, 1H, triazole H), 7.43 (dd, 1H, J = 2.43 Hz, 14.61 Hz, phenyl H), 7.14 (dd, 1H, J = 2.8 Hz, 8.9 Hz, phenyl H), 7.08 (t, 1H, J = 9.4 Hz, phenyl H), 5.09–5.15 (m, 1H, oxazolidinone H), 4.82 (d, 2H, J = 5.04 Hz, CH_2), 4.21 (t, 1H, J = 9.3 Hz, oxazolidinone H), 3.83–3.88 (m, 3H, oxazolidinone and piperazine H), 3.40–3.60 (m, 4H, piperazine H and CH_2), 2.97–3.11 (m, 4H, piperazine H). ^{13}C NMR (DMSO-d_6): δ 164.81, 155.33, 153.71, 153.44, 148.15, 138.77, 135.32, 135.26, 133.35, 133.26, 127.57, 125.83, 119.85, 119.83, 119.15, 114.22, 106.80, 106.63, 70.75, 51.67, 47.05. IR (KBr pellet, cm^{-1}): ν 2927, 2812, 1751, 1625, 1538, 1515, 1447, 1419, 1342, 1226, 1146, 1109, 1078. MS 526.2 (M^+). Anal calcd for $C_{23}H_{23}FN_8O_6$: C: 52.47, H: 4.40, N: 21.28; found C: 52.13, H: 4.58, N:21.18.

(R)-3-(3-Fluoro-4-(4-(phenylsulfonyl)piperazin-1-yl)-phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-oxazolidin-2-one ***9a***

Prepared from compound **6b** and benzenesulfonyl chloride *via* the general procedure. Purification by silica gel column chromatography (EtOAc/MeOH = 9:1) gave a white solid, yield: 67%; m.p.: 208–210°C. ^{1}H NMR (DMSO-d_6): δ 7.85 (s, 1H, triazole H), 7.46–7.79 (m, 3H, phenyl H), 7.69 (t, 2H, J = 7.8 Hz, phenyl H), 7.39 (dd, 1H, J = 2.5 Hz, 14.7 Hz, phenyl H), 7.11 (dd, 1H, J = 2.4 Hz, 8.9 Hz, phenyl H), 7.05 (t, 1H, J = 9.4, phenyl H), 5.04–5.08 (m, 1H, oxazolidinone H), 4.72 (d, 2H, J = 5.0 Hz, –CH_2), 4.16 (t, 1H, J = 9.2 Hz, oxazolidinone H), 3.18 (dd, 1H, J = 6.0 Hz, oxazolidinone H), 3.03 (m, 8H, piperazine H), 2.21 (s, 3H, triazole CH_3). IR (KBr pellet, cm^{-1}): ν 2974, 2916, 2840, 1750, 1519, 1479, 1447, 1424, 1330, 1271, 1234, 1200, 1109, 1067, 1044. MS 500.2 (M^+). Anal calcd for $C_{22}H_{27}FN_6O_5$: C: 55.19, H: 5.03 N: 16.79; found C: 55.31, H: 5.27, N: 16.90.

(R)-3-(3-Fluoro-4-(4-tosylpiperazin-1-yl)phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl) methyl)oxazolidin-2-one ***9b***

Prepared from compound **6b** and *p*-toluenesulfonyl chloride *via* the general procedure. Purification by silica gel column chromatography (EtOAc/MeOH = 9:1) gave a white solid yield: 88%; m.p.: 206–208°C. ^{1}H NMR (DMSO-d_6): δ 7.85 (s, 1H, triazole H), 7.66 (d, 2H, J = 8.3 Hz, phenyl H), 7.49 (d, 2H, J = 8.1 Hz, phenyl H), 7.39 (dd, 1H, J = 2.5 Hz, 14.7 Hz, phenyl H), 7.11 (dd, 1H, J = 2.3 Hz, 8.8 Hz, phenyl H), 7.05 (t, 1H, J = 9.5 Hz, phenyl H), 5.04–5.08 (m, 1H, oxazolidinone H), 4.72 (d, 2H, J = 4.8 Hz, CH_2), 4.17 (t, 1H, J = 9.2 Hz, oxazolidinone H), 3.81 (dd, 1H, J = 5.9 Hz, oxazolidinone H), 3.03 (m, 8H, piperazine H), 2.43 (s, 3H, tolyl CH_3), 2.21 (s, 3H, triazole CH_3). IR (KBr pellet, cm^{-1}): ν 2920, 2855, 1740, 1520, 1448, 1420, 1335, 1225, 1157, 1115, 1050. MS 514.2 (M^+). Anal calcd for $C_{24}H_{27}FN_6O_4S$: C: 56.02, H: 5.29, N: 16.33, S: 6.23; found C: 56.30, H: 5.19, N: 16.19, S: 6.20.

(R)-3-(3-Fluoro-4-(4-(thiophen-2-ylsulfonyl)piperazin-1-yl)-phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-oxazolidin-2-one ***9c***

Prepared from compound **6b** and 2-thiophenesulfonyl chloride *via* the general procedure. Purification by silica gel column chromatography (EtOAc/MeOH = 9:1) afforded a white solid, yield: 81%; m.p.: 183–185°C. ^{1}H NMR (DMSO-d_6): δ 8.11 (dd, 1H, J = 1.3 Hz, 5.0 Hz, thiophene H), 7.86 (s, 1H, triazole H), 7.70 (dd, 1H, J = 1.2 Hz, 3.8 Hz, thiophene H), 7.40 (dd, 1H, J = 2.5 Hz, 14.6 Hz, phenyl), 7.34 (dd, 1H, J = 3.8 Hz, 5.0 Hz, thiophene H), 7.13 (dd, 1H, J = 2.4 Hz, 9.0 Hz, phenyl H), 7.07 (t, 1H, J = 9.3 Hz, phenyl H), 5.04–5.10 (m, 1H, oxazolidinone H), 4.73 (d, 2H, J = 5.2 Hz, CH_2), 4.18 (t, 1H, J = 9.2 Hz, oxazolidinone H), 3.82 (dd, 1H, J = 5.9 Hz, 9.4 Hz, oxazolidinone H), 3.33 (m, 4H, piperazine H), 3.08 (m, 4H, piperazine H), 2.21 (s, 3H, triazole CH_3). ^{13}C NMR (DMSO-d_6): δ 155.28, 153.66, 153.46, 142.01, 134.84, 134.35, 134.10, 133.52, 133.34, 128.42, 123.18, 119.90, 114.20, 106.76, 106.59, 70.85, 51.65, 49.40, 47.08, 45.99, 10.37. IR (KBr pellet, cm^{-1}): ν 3101, 1740, 1519, 1447, 1419, 1347, 1224, 1156, 1052. MS 506.0 (M^+). Anal calcd for $C_{21}H_{23}FN_6O_4S_2$: C: 49.79, H: 4.58, N: 16.59, S: 12.66; found C: 49.89, H: 4.62, N: 16.81, S: 12.38.

(R)-Amino(4-(2-fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)phenyl)piperazin-1-yl)methaniminium 2,2,2-trifluoroacetate ***11a***

To a solution of (*R*)-4-(2-fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)phenyl)piperazin-1-ium 2,2,2-trifluoroacetate **6b** (400 mg, 0.84 mmol) salt in DMF (anhyd. 4 mL), TEA (3 mL) was added *N,N*-(bis(*tert*-butoxy-carbonyl) *S*-methyl isothiourea [13] (370 mg, 1.27 mmol). The mixture was stirred at r.t. for 5 days, treated with water (30 mL) and extracted with EtOAc. The EtOAc layer was separated, washed with water, dried (Na_2SO_4), filtered and concentrated to give a crude mass. Silica gel column chromatography (EtOAc/hexane = 2:1 → EtOAc) afforded *(R)-tert-butyl (((tert-butoxycarbonyl) amino)(4-(2-fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)phenyl)piperazin-1-yl)methylene)carbamate* **10a** as a solid, yield: 63%; m.p.: 170–172°C. ^{1}H NMR (DMSO-d_6): δ 9.67 (s, 1H, NH, exchangeable with D_2O), 7.86 (s, 1H, triazole H), 7.43 (dd, 1H, J = 2.4 Hz, 14.6 Hz, phenyl H), 7.13 (dd, 1H, J = 6.6 Hz, 8.8 Hz, phenyl H), 7.07 (t, 1H, J = 9.3 Hz, phenyl H), 5.06–5.09 (m, 1H, oxazolidinone H), 4.74 (d, 2H, J = 5.2 Hz, CH_2), 4.19 (t, 1H, J = 9.2 Hz, oxazolidonone H), 3.83 (dd, 1H, J = 5.9 Hz, 9.4 Hz, oxazolidinone H), 3.50–3.51 (m, 4H, piperazine H), 2.91–3.0 (m, 4H, piperazine H), 2.22 (s, 3H, triazole CH_3), 1.42 (s, 9H (CH_3)$_3$), 1.36 (s, 9H (CH_3)$_3$). IR (KBr pellet, cm^{-1}): ν 3435, 2977, 2931, 1746, 1615, 1517, 1484, 1427, 1365, 1299, 1231, 1148, 1136, 1051. Anal calcd for $C_{28}H_{39}FN_8O_6$: C: 55.80, H: 6.52, N: 18.59; found C: 55.61, H: 6.56, N: 18.38. A solution of compound **10a** (400 mg, 0.66 mmol) in DCM (1 mL) and TFA (1 mL) was stirred at 0°C to r.t. overnight. The reaction mixture was concentrated on a rotavapor to give a

mass, which was triturated with diethyl ether to afford **11a** as a white solid in quantitative yield; m.p.: 241–243°C. ^{1}H NMR (DMSO-d_6): δ 7.86 (s, 1H, triazole H), 7.44 (m, 5H, phenyl H and guanidine H), 7.15 (dd, 1H, J = 2.3 Hz, 8.9 Hz, phenyl H), 7.08 (t, 1H, J = 9.4 Hz, phenyl H), 5.07–5.15 (m, 1H, oxazolidinone H), 4.74 (d, 2H, J = 6.1 Hz, CH_2), 4.19 (t, 1H, J = 9.2 Hz, oxazolidinone H), 3.83 (dd, 1H, J = 5.7 Hz, 9.4 Hz, oxazolidinone H), 3.57 (t, 4H, J = 4.7 Hz, piperazine H), 3.04 (t, 4H, J = 4.7 Hz, piperazine H), 2.22 (s, 3H, triazole CH_3). IR (KBr pellet, cm^{-1}): ν 3375, 3168, 2923, 1749, 1672, 1615, 1519, 1485, 1447, 1230, 1189. MS 403.75 (M^++H).

(R)-(4-(4-(5-((1H-1,2,3-Triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-(amino)methaniminium 2,2,2-trifluoroacetate ***11b***

Compound **10b** was prepared *via* a similar procedure to **10a** from compound **6a** to afford a white solid, yield: 34%; m.p.: 191–193°C. ^{1}H NMR (DMSO-d_6): δ 9.49 (br s, 1H, NH), 8.00 (s, 1H, triazole H), 7.59 (s, 1H, triazole H), 7.25 (dd, 1H, J = 2.6 Hz, 14.7 Hz, phenyl H), 6.96 (dd, 1H, J = 2.1 Hz, 8.6 Hz, phenyl H), 6.89 (t, 1H, J = 9.5 Hz, phenyl H), 5.08–5.10 (m, 1H, oxazolidinone H), 4.66 (d, 2H, J = 5.1 Hz, CH_2), 4.04 (t, 1H, J = 9.3 Hz, oxazolidonone H), 3.69 (dd, 1H, J = 5.7 Hz, 9.4 Hz, oxazolidinone H), 3.36–3.38 (m, 4H, piperazine H), 2.80–2.81(m, 4H, piperazine H), 1.20–1.25 (2br s, 18H, $[C(CH_3)_3]_2$). IR (KBr pellet, cm^{-1}): ν 3392, 2980, 2821, 1741, 1689, 1619, 1518, 1488, 1453, 1367, 1298, 1223, 1157, 1120. MS 590.21 (M^++H). Anal calcd for $C_{27}H_{37}FN_8O_6$: C: 55.09, H: 6.34, N: 19.04; found C: 55.00, H: 5.99, N: 18.93. Compound **11b** was prepared *via* a similar procedure to **11a** from **10b** (100 mg, 0.17 mmoL) to afford a white solid yield: 88%; m.p.: 253–255°C. ^{1}H NMR (DMSO-d_6): δ 8.16 (s, 1H, triazole H), 7.76 (s, 1H, triazole H), 7.43 (m, 5H, phenyl H and guanidine H), 7.14 (dd, 1H, J = 2.3 Hz, 9.4 Hz, phenyl H), 7.08 (t, 1H, J = 9.4 Hz, phenyl H), 5.07–5.15 (m, 1H, oxazolidinone H), 4.82 (d, 2H, J = 5.0 Hz, CH_2), 4.20 (t, 1H, J = 9.2 Hz, oxazolidinone H), 3.85 (dd, 1H, J = 5.7 Hz, 9.4 Hz, oxazolidinone H), 3.57 (t, 4H, J = 4.8 Hz, piperazine H), 3.03 (t, 4H, J = 4.6 Hz, piperazine H). IR (KBr pellet, cm^{-1}): ν 3347, 3162, 2917, 2849, 1750, 1669, 1595, 1519, 1486, 1447, 1330, 1281, 1240, 1201, 1140, 1111. MS 389.75 (M^++H).

Antibacterial susceptibility testing

The MIC's (μg/mL), defined as the lowest concentration of a drug that inhibits visible bacterial growth were determined on Mueller–Hinton (MH) agar with medium containing dilutions of antibacterial agents ranging from 0.12 to 64 μg/mL. Linezolid and vancomycin were dissolved in 60% ethanol in water and water, respectively, and test compounds in 80% DMSO in water. MH agar plates were used for all staphylococci and enterococci, and on MH agar plates supplemented with 5% sheep blood to facilitate the growth of *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. The Gram-positive clinical isolates at the MRSA Reference Laboratory, Faculty of Medicine, Kuwait University utilized in this study consisted of MRSA (n = 9), methicillin-susceptible *S. aureus* (MSSA, n = 11), methicillin-resistant coagulase-negative staphylococci (MR-CNS, n = 4), methicillin-sensitive coagulase-negative staphylococci (MS-CNS, n = 6), *S. pneumoniae* (n = 3), vancomycin-sensitive (VSE, n = 7) and vancomycin-resistant enterococci (VRE, n = 3). Reference strains *S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228 and *E. faecalis* ATCC 29212, *E. coli* ATCC 25922, *H. influenzae* ATCC 49247, and *M. catarrhalis* ATCC8176 were used. The final bacterial concentration for inocula was 10^7 CFU/mL, and incubation was at 35°C for 18 h. To assess the extent of plasma binding and/or plasma instability, test compounds were evaluated against *S. aureus* ATTC 25923 in MH broth supplemented with 50% human plasma. Linezolid and PH-027 [6, 11] and vancomycin (Sigma–Aldrich, Germany) were used as reference antibacterial agents.

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