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Original article

Synthesis and antibacterial activity of novel 5-(4-methyl-1*H*-1,2,3-triazole) methyl oxazolidinones

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ABSTRACT

A series of 5-(4-methyl-1,2,3-triazole)methyl oxazolidinones were synthesized and tested for their antibacterial activity against a panel of Gram-positive and Gram-negative clinical isolates in comparison with linezolid and vancomycin. Most of the compounds demonstrated strong to moderate in vitro antibacterial activity against susceptible and resistant Gram-positive pathogenic bacteria. Antibacterial activity varied with substitutions at the phenyl C4 position with bulky alkylcarbonyl and alkoxycarbonyl substitutions on the piperazine N4 being detrimental to antibacterial activity. Whereas the presence of the 4-methyl-1,2,3-triazole moiety in the acyl-piperazine containing analogs resulted in increased protein binding, and decreased antibacterial activity particularly against *Streptococcus pneumoniae* strains.

1. Introduction

The alarming rates of emerging and reemerging microbial threats coupled with increasing antibacterial resistance in hospitals are major concerns to the public health and scientific communities worldwide, especially in regard to multidrug-resistant Gram-positive bacteria [1–4]. Among the problematic organisms that have developed multidrug resistance include methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci (MR-CNS), penicillin-resistant *Streptococcus pneumoniae* (PRSP) and vancomycin-resistant enterococcus (VRE) [3,5–7]. These organisms have occurred both in the community and hospital settings and are reported to be resistant to at least three classes of the antibacterial agents commonly used for therapy. These trends have emphasized the pressing need for new, more effective and safe antibacterial agents. Among the attractive ways of achieving this goal include the introduction of structurally new classes of antibacterial agents with novel mechanism of action or by structural modification of existing agents by improving both the binding affinity to the receptor and spectrum of activity while retaining bioavailability and safety profiles.

The oxazolidinones represent a novel class of antibacterials that emerged in the last four decades, having potent activity against multidrug-resistant Gram-positive bacteria [8,9]. Extensive research efforts led to the discovery and introduction of linezolid (Fig. 1) in clinical use against hospital- and community-acquired pneumonia, skin infections and diabetic foot infections caused by Gram-positive bacterial strains [8–10]. Linezolid binds 50S ribosomal subunit thus inhibiting the 70S complex formation resulting in inhibition of protein synthesis. To date, numerous new derivatives with varied structural modifications have been reported in various patent reviews and scientific literature [8,9,11–14] but none of these have led to the development of a new drug belonging to the oxazolidinone class. Many efforts expended on developing new oxazolidinones have been directed to extending the spectrum of activity and reducing or eliminating toxic effects and potential drug–drug interactions associated with monoamine oxidase (MAO) inhibition. We and others have reported the 5-triazolylmethyl oxazolidinones based on the replacement of the 5-acetamido methyl substituents with the *N*-linked triazolyl moiety, exemplified by **PH-027** (Fig. 1) and have also shown that di-substitution and substitution of bulky groups on the triazole resulted in loss of antibacterial activity [15]. In addition, we have further shown that

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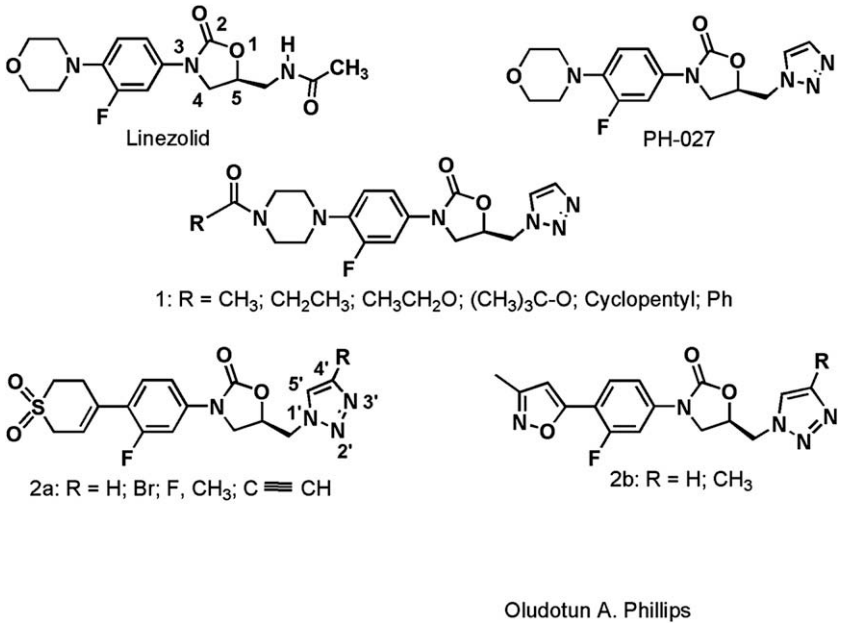


Fig. 1. Structures of antibacterial oxazolidinones.

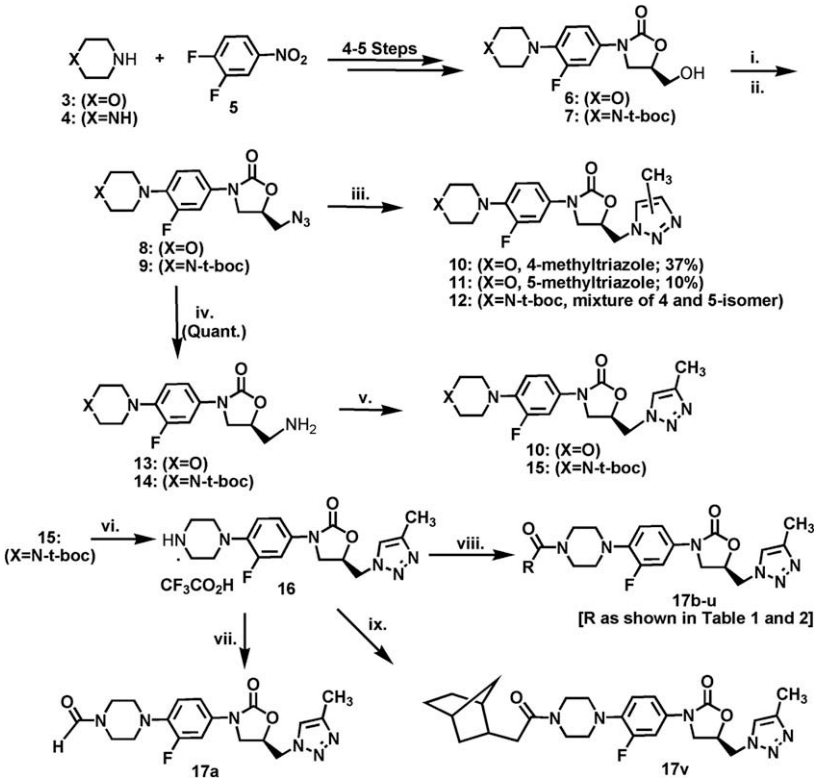
the introduction of the carboalkoxy, alkyl-, aryl- and heteroarylcarbonyl groups to piperazinyl oxazolidinone derivatives **1** [Fig. 1] gave compounds with improved or comparable activity to **PH-027** and linezolid against resistant Gram-positive clinical isolates [16,17]. The potencies of these compounds were comparable or 2- to 8-fold higher than linezolid.

Recent study by Reck et al. reported a series of novel oxazolidinones bearing different 4′-substituted and 5′-substituted 1,2,3-triazoles at the C5 position of the oxazolidinone [18]. This study demonstrated that 1,2,3-triazole oxazolidinones bearing a substituent like methyl, small substituted methyl, bromo or linear (sp-hybridized) group with general structure **2a** (Fig. 1) at the 4-position have good antibacterial activities with reduced or no MAO inhibitory activity. Furthermore, a more recent study by Hauck et al. further disclosed that 4-methyl substituted triazoles can diminish MAO-A inhibition [19] in a series of phenyl-oxazolidinones with carbon-linked azoles of general structure **2b** (Fig. 1).

In the present communication we report the synthesis and antibacterial activity of previously unreported 5-(4-methyl-1,2,3-triazoles) oxazolidinones containing morpholine (**10**) and the piperazine (**15**, **17a**–**v**) basic moieties having varied alkylcarbonyl and arylcarbonyl substitutions at the distal piperazine N4 position in order to identify new derivatives with improved antibacterial and potentially reduced or eliminated MAO inhibitory activity. Since we have previously shown that the incorporation of an alkyl- or arylcarbonyl and alkoxycarbonyl substituents at the distal piperazine N4 position could improve the antibacterial activity of the unsubstituted-1,2,3-triazole oxazolidinone derivatives [16,17]. Attempts would also be made to correlate antibacterial activity to selected physicochemical properties, namely, lipophilicity (calculated as the *C* log *P* values) of the compounds.

2. Chemistry

The syntheses of the final morpholine **10** and piperazine oxazolidinone derivatives **15** and **17a**–**v** were performed as outlined in Scheme 1, starting from the readily available morpholine **3**, piperazine **4** and 3,4-difluoronitrobenzene **5** to give the chiral alcohols **6** and **7**, and the azide derivatives **8** and **9**, respectively; in multi-step reactions and in good yields according to published procedures [15,20]. Further chemical transformation of the morpholine derivative **8** via Huisgen's 1,3 dipolar cycloaddition reaction [21] with propyne in dimethoxyethane (DME) at 100 °C in a steel bomb gave a mixture of the regioisomers **10** and **11** in 37% and 10% yield after recrystallization, respectively. On the other hand, Huisgen's 1,3 dipolar cycloaddition reaction of the piperazine derivative **9** under similar reaction conditions gave an inseparable mixture of the 4-methyl and 5-methyl regioisomers **12**, after several column chromatography and recrystallization attempts. The selective synthesis of the 4-methyltriazole regioisomers **10** and **15** was achieved by reacting the readily obtained amines **13** and **14** with 2-(1,1-dichloropropan-2-ylidene)-1-tosylhydrazine [18,22] in excellent yields of 81 and 91%, respectively. The hydrazone 2-(1,1-dichloropropan-2-ylidene)-1-tosylhydrazine was prepared from *p*-toluene sulfonyl chloride and hydrazine to give 4-methylbenzenesulfonohydrazine, which was reacted with 1,1-dichlorobutan-2-one according to published literature methods [18,22]. Deprotection of the *tert*-butoxycarbonyl protecting group at the piperazine N-4-position of **15** with trifluoroacetic acid in CH_2Cl_2 at 0 °C to room temperature gave the key-intermediate triazole oxazolidinone derivative **16** as a trifluoroacetic acid salt in quantitative yield. A quantity of the trifluoroacetic acid salt **16** was converted to the free amine by stirring with cold saturated solution of $KHCO_3$ to afford an off-white solid, which was collected by filtration, dried and refluxed in acetonitrile in the presence of ammonium formate [23] to give the *N*-formyl derivative **17a** in moderate yield (Scheme 1). Further derivatization of the intermediate triazole **16** was performed by subsequent reactions with an appropriate acid chlorides or anhydrides in CH_2Cl_2/CH_3CN using triethylamine as base to give the respective target compounds **17b**–**u** in moderate to excellent yields. The bicyclo[2.2.1]heptan-2-yl acetyl derivative **17v** was prepared by reacting the intermediate triazole **16** with the activated bicyclo[2.2.1]heptan-2-yl acetic acid (obtained by the reaction with 1-hydroxybenzotriazole and dicyclohexylcarbodiimide) in a mixture of CH_2Cl_2/CH_3CN. All the reported compounds were characterized by analytical spectroscopic methods (^{1}H NMR, ^{13}C NMR, MS and IR), m.p. and were microanalyzed for satisfactory C, H and N. However, due to the complex nature of the compounds thorough structural verification of representative compounds **10** and **15** was further carried out by ^{13}C NMR decoupled,



Scheme 1. Synthesis of 5-(4-methyl-1*H*-1,2,3-triazolyl)methyl oxazolidinone derivatives. (i) MsCl/TEA/DCM; (ii) NaN_3/DMF/H_2O, 75 °C; (iii) DME/propyne, 100 °C; (iv) THF/Ph_3P/H_2O, 75 °C; (v) MeOH/DIEA/2-(1,1-dichloropropan-2-ylidene)-1-tosylhydrazine, r.t.; (vi) TFA/DCM, 0 °C to r.t.; (vii) aq. $KHCO_3$/$^+NH_4{\cdot}HCOO^-$/CH_3CN, 90 °C; (viii) DCM/acid chloride/acid anhydride/TEA, r.t.; (ix) DCM/CH_3CN/DCC/1-HBT, r.t.

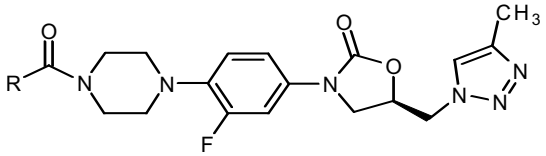
^{13}C-DEPT-135 (Distortionless Enhancement by Polarization Transfer-139) and ^{13}C-APT (Attached Proton Test) experiments.

3. Results and discussion

The in vitro antibacterial activity of the morpholine **10** and piperazine **15** and **17a–v** containing oxazolidinones against a panel of standard reference and clinical isolates of Gram-positive and Gram-negative pathogens was tested and compared with linezolid, **PH-027** and vancomycin as reference antibacterials. Linezolid and **PH-027** were prepared according to literature methods [15,20]. The antibacterial activities of the compounds reported as the minimum inhibitory concentrations (MICs, μg/ml) determined by the agar dilution method on Mueller–Hinton (HM) agar and the calculated lipophilicity reported as the calculated log *P* values (*C* log *P*) are summarized in Tables 1 and 2. Furthermore, the effect of human plasma due to protein binding and/or plasma instability on the antibacterial activity of the compounds against a standard strain of *S. aureus* ATCC 25923 was also investigated and presented in Table 1. As can be seen from the MIC values (Table 1), most of the compounds demonstrated strong to moderate activity against *S. aureus* ATCC 25923 strain in the absence of human plasma with MIC values in the range of 1–16 μg/ml. In contract, most of the compounds showed a 4-fold or greater increase in MIC values in the presence of 50% human plasma, with the exception of linezolid, **PH-027**, the morpholine **10** and trifluoroacetyl piperazine **17c** derivatives. This significant increase in MIC seems to correlate to some extent with the lipophilicity (*C* log *P*) of the compounds, with compounds **15** (R = *tert*-butoxy, *C* log *P*: 1.952), **17g** (R = thioethyl, *C* log *P*: 1.374), **17m** (R = pentyl, *C* log *P*: 1.188), **17n** (R = hexyl, *C* log *P*: 1.710), **17t** (R = benzyl, *C* log *P*: 2.803), **17u** (R = *trans*-cinnamyl, *C* log *P*: 1.978), and **17v** (R = norboranyl, *C* log *P*: 1.990) showing MIC values in the range of 64 and >64 μg/ml, respectively. Generally, the 4-methyl-(1,2,3-triazole) oxazolidinone derivatives reported in this study showed somewhat reduced antibacterial activity in the absence and presence of 50% human plasma compared with the unsubstituted-1,2,3-triazole derivatives in our previous studies [16,17,24]. For instance, our previous reports showed that the acylpiperazinyl-4-desmethyltriazole analogs, having R = *tert*-butoxy ($MIC_{+50\%\ plasma}/MIC_{no\ plasma}$ = 4/0.5 μg/ml), R = H ($MIC_{+50\%\ plasma}/MIC_{no\ plasma}$ = 1/1 μg/ml), R = Ph ($MIC_{+50\%\ plasma}/MIC_{no\ plasma}$ = 1/1 μg/ml) and R = *trans*-cinnamyl ($MIC_{+50\%\ plasma}/MIC_{no\ plasma}$ = >8/0.5 μg/ml) [16,17], were relatively more active than the corresponding 4-methyltriazolyl analogs **15** (R = *tert*-butoxy, $MIC_{+50\%\ plasma}/MIC_{no\ plasma}$ = 64/4 μg/ml), **17a** (R = H, $MIC_{+50\%\ plasma}/MIC_{no\ plasma}$ = 8/2 μg/ml), **17s** (R = Ph, $MIC_{+50\%\ plasma}/MIC_{no\ plasma}$ = 32/2 μg/ml), and **17u** (R = *trans*-cinnamyl, $MIC_{+50\%\ plasma}/MIC_{no\ plasma}$ = 64/16 μg/ml), respectively, against *S. aureus*. Moreover, it appears that the presence of the 4-methyl group on the triazole in these derivatives resulted in somewhat decreased antibacterial activity, which resulted probably from increased binding to human plasma and/or instability. The precise cause of this is a subject of further investigation in our laboratory.

The piperazino oxazolidinones presented in this study were anticipated to show antibacterial activity since it has been shown that the morpholino ring of linezolid does not appear to make significant interactions at the ribosomal binding site, suggesting that a variety of different functional groups can be substituted for the morpholine without significant loss of activity [11]. In addition, linezolid has been shown to use hydrogen bonding and hydrophobic packing interactions to bind within the ribosomal binding site and that the acetamide NH participates in hydrogen bond with a phosphate group at the binding site [25]. However, the similarity

Table 1
C log *P* values and antibacterial activity of 5-[(4-methyl-1,2,3-triazolyl)methyl] oxazolidinones against Gram-positive standard strains and clinical isolates.



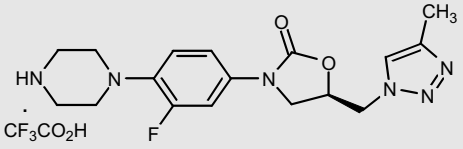
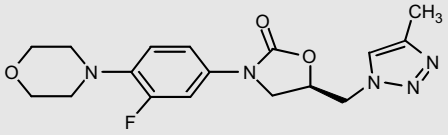
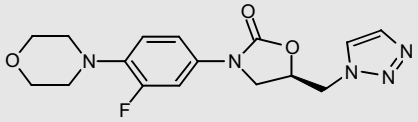
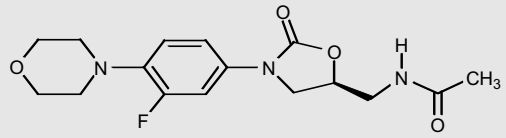
Compound	–R	Minimum inhibitory concentrations (MICs, μg/ml) against								
		C log *P*	*S. aureus*[a] + no plasma[b]	*S. aureus*[a] + 50% plasma	MSSA[c] ($n=10$)	MRSA[d] ($n=10$)	MS-CNS[e] ($n=6$)	MR-CNS[f] ($n=3$)	*S. pn*[g] ($n=4$)	VSE[h] ($n=6$)	VRE[i] ($n=4$)
15	$(CH_3)_3CO$–	1.952	4	64	2–8	4–8	2–8	2–4	8	2–4	2–4
17a	H–	−0.881	2	8	1–2	1–2	1–2	1–2	1–2	1–2	1
17b	CH_3–	−0.935	2	8	1–4	1–4	1–4	1–4	1–2	1–2	1–2
17c	F_3C–	1.552	4	8	1–4	2–4	1–4	1–4	1–4	1–2	1–2
17d	CH_3CH_2–	−0.406	2	8	1–2	1–2	1–2	1–2	1–2	1–4	1
17e	Cl_3C–	1.494	1	16	1–2	1–2	1	1–2	4	1	1
17f	CH_3CH_2O–	1.244	1	32	1	1–2	1	1	4	1	1
17g	CH_3CH_2S–	1.374	2	64	1–2	1–2	1–2	1–2	2–4	1–2	1
17h	Cl_2CH–	1.494	2	8	1–2	1–2	1–2	0.5–2	1–2	1–2	1–2
17i	$(CH_3)_2CH$–	−0.097	1	16	1	0.5–1	0.5–1	0.5–1	2	1	0.5–1
17j	$CH_3(CH_2)_3$–	0.652	2	32	1–2	1–2	1–2	1–2	2–4	1–2	1–2
17k	$(CH_3)_2CHCH_2$–	0.522	4	32	2	2	2–4	2–4	4	2–4	4
17l	$CH_3CH_2CHCH_3$	0.432	2	32	2–4	2–4	2–4	2	4	4	4
17m	$CH_3(CH_2)_4$–	1.188	4	>64	2–4	4	2	2–4	8	2–4	2–4
17n	$CH_3(CH_2)_5$–	1.710	8	>64	8	8	4–8	8	8–16	4	4
17o		−0.581	2	16	2–4	2	1–2	1–4	2	1–2	1–2
17p		0.123	4	16	2–4	2–4	2–4	2–4	4	2–4	2
17q		0.537	4	32	2–4	2	2–4	2–4	4	2–4	2–4
17r		1.096	2	32	1–2	2–4	1–2	1–2	4–8	1–2	1–2
17s	Ph–	0.884	2	32	1–2	1–2	1	1	4	1	1
17t	$PhCH_2$–	2.803	4	>64	2–4	2–4	2–4	2–4	2–4	2–4	1–2
17u		1.978	16	>64	16	8–16	8–16	8–16	8–16	8	8
17v		1.990	4	>64	2–4	4	2–4	2–4	16–32	2–4	2
16		0.019	4	32	4–8	4	4	4–8	2	4–8	8
10		0.900	2	4	1–2	0.5–2	1–2	1–2	1–2	1–2	1
PH-027		0.631	1	1	0.5–1	0.5–1	0.5–1	0.5–1	0.5	0.5–1	1

Table 1 (*continued*).

Compound	–R	Minimum inhibitory concentrations (MICs, μg/ml) against								
		C log *P*	*S. aureus*[a] + no plasma[b]	*S. aureus*[a] + 50% plasma	MSSA[c] ($n=10$)	MRSA[d] ($n=10$)	MS-CNS[e] ($n=6$)	MR-CNS[f] ($n=3$)	*S. pn*[g] ($n=4$)	VSE[h] ($n=6$)	VRE[i] ($n=4$)
Lzd[j]		0.532	2	2	0.5–1	0.5–1	0.5–1	0.5–1	0.5–1	0.5–1	0.5–1
Van[k]		n/c	2	2	1–2	0.5–1	1–2	1	0.5	0.25–2	>64

[a] ATCC 25923.
[b] Human plasma.
[c] Methicillin-susceptible *S. aureus*.
[d] Methicillin-resistant *S. aureus*.
[e] Methicillin-susceptible coagulase-negative staphylococci.
[f] Methicillin-resistant coagulase-negative staphylococci.
[g] *Streptococcus pneumoniae*.
[h] Vancomycin-susceptible enterococci.
[i] Vancomycin-resistant enterococci.
[j] Linezolid.
[k] Vancomycin.

in the dipole moment of the acetamide and triazole moieties is consistent with the believe that both the triazolyl and acetamido moieties are bioisteres, and buttressed by the observed retention of antibacterial activity [15,16,18,19].

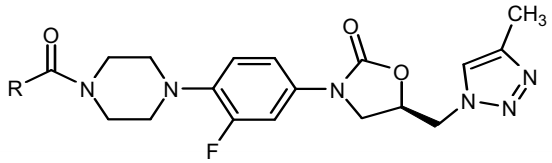
Against the selected Gram-positive clinical isolates most of the compounds showed good antibacterial activity with MIC ranges of 0.5–16 μg/ml (Table 1). However, it was noted that the activity decreased with increased bulkiness of the acyl group at the piperazine N4 position. The most active compound **17i**, having the isopropylcarbonyl group at the piperazine nitrogen showed comparable antibacterial activity to linezolid and **PH-027** with MIC range 0.5–1 μg/ml against all Gram-positive (staphylococci, streptococci and enterococci) pathogens tested. Other derivatives having the formyl **17a**, trichloroacetyl **17e**, ethoxycarbonyl **17f**, thioethoxycarbonyl **17g**, dichloroacetyl **17h**, pentanoyl **17j** and benzoyl **17s** moieties at the piperazine nitrogen also showed good activity with MIC ranges of 1–2 μg/ml, respectively against similar strains. However, branching of the acyl carbon chain also resulted in slight decrease in antibacterial activity as can be seen by comparing with the pentanoyl **17j**, isovaleryl **17k**, and 2-methylbutyryl **17l** derivatives with MIC value ranges of 1–2, 2–4 and 2–4 μg/ml, respectively. In addition, some of the compounds, namely, **15**, **17e**, **17f**, **17k–n**, and **17p–v** showed only moderate antibacterial activity against *S. pneumoniae* strains tested with rather high MIC value in range 4–32 μg/ml. In general, these acylpiperazinyl-4-methyltriazole oxazolidinone derivatives **15** (R = *tert*-butoxy, MIC ranges = 8 μg/ml), **17a** (R = H, MIC ranges = 1–2 μg/ml), **17s** (R = Ph, MIC ranges = 4 μg/ml), and **17u** (R = *trans*-cinnamyl, MIC ranges = 8–16 μg/ml) showed slightly decreased antibacterial activity compared to the previously reported acylpiperazinyl-4-desmethyltriazole analogs with MIC value ranges of 2–4 μg/ml (R = *tert*-butoxy), 0.5–1 μg/ml (R = H), 1–2 μg/ml (R = Ph) and 1 μg/ml (R = *trans*-cinnamyl) [16,17], respectively, against *S. pneumoniae* strains. Moreover, the morpholino derivative **10** also showed good activity against all Gram-positive isolates with MIC value range of 0.5–2 μg/ml. Overall, antibacterial activity was noted to decrease with increased bulk of the acyl group with the least active compounds having the heptanoyl **17n** and cinnamoyl **17u** groups at the distal piperazine nitrogen showing MIC ranges of 4–8 and 8–16 μg/ml, respectively. These results suggest that the effect of the N4 acyl substitution on the piperazine moiety was mostly steric in nature, and may correlate to some extent with the *C* log *P* values of these derivatives. Although the removal of the acyl moiety to give the trifluoroacetic acid salt, compound **16** (MIC range 2–8 μg/ml), did not result in any notable change in the MIC values (Table 1).

In general, substitution of the 4-methyl group on the triazole gave compounds that were inactive against Gram-negative organisms including *Escherichia coli*, *Haemophilus influenzae* and *Moraxella catarrhalis* strains with MIC value ranges of 8 to >64 μg/ml with exception of the trifluoroacetyl derivative **17c** having MIC value of 8 μg/ml against *E. coli*. Four of the compounds namely, the morpholine derivative **10**, and the piperazinyl derivatives, formyl **17a**, acetyl **17b**, and trifluoroacetyl **17l** exhibited comparable but moderate activity (MIC value of 8 μg/ml) to linezolid against the *M. catarrhalis* clinical isolate tested (Table 2).

4. Conclusion

In conclusion, a series of morpholino and piperazino oxazolidinone derivatives bearing 5-[(4-methyl-1,2,3-triazolyl)methyl] at the C5 position of the oxazolidinone ring were synthesized and tested for antibacterial activity. Most of the compounds showed good to moderate antibacterial activity against Gram-positive bacteria and moderate to lack of activity against selected Gram-negative bacterial strains. However, substitution of the isopropylcarbonyl group at the piperazine C4 position gave the most active compound **17i** against all the Gram-positive bacterial strains tested. Although Reck et al. have reported that the 4-methyltriazole and unsubstituted triazole derivatives of (1,1-dioxo-3,6-dihydro-2H-thiopyran-4-yl) and isoxazolyl containing oxazolidinones have comparable antibacterial activity [18,19], with the 4-methyltriazole derivatives showing reduced MAO inhibitory activity. The compounds reported in the present study were found to be relatively less active compared to our previously reported series of 4-desmethyltriazolyl oxazolidinones [16,17,24], suggesting that the methyl substitution on the triazole C4 position may be somewhat detrimental for antibacterial activity in this class of acylpiperazinyl 4-methyltriazolyl oxazolidinone compounds. On the other hand, the morpholino derivative **10** showed somewhat comparable antibacterial activity to linezolid and **PH-027**. However, the MAO

Table 2
Antibacterial activity[a] of 5-[(4-methyl-1,2,3-triazolyl)methyl] oxazolidinones against Gram-negative clinical isolates.



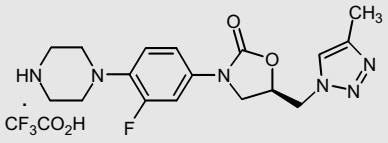
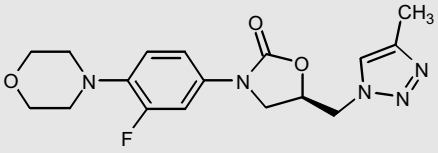
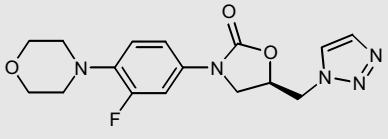
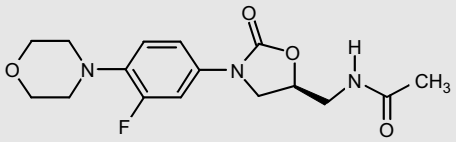
No.	–R	ATCC 49247[b]	*H. inf* 280[c]	*H. inf* 282[c]	*H. inf* 283[c]	*H. inf* 285[c]	*M. cat*[d]
15	$(CH_3)_3CO$–	>64	>64	>64	>64	>64	64
17a	H–	64	64	64	64	64	8
17b	CH_3–	64	64	64	64	64	8
17c	F_3C–	64	64	64	64	64	8
17d	CH_3CH_2–	32	32	32	32	32	16
17e	Cl_3C–	>64	>64	>64	>64	>64	32
17f	CH_3CH_2O–	64	64	64	64	64	16
17g	CH_3CH_2S–	>64	>64	>64	>64	>64	16
17h	Cl_2CH–	64	32	32	64	32	16
17i	$(CH_3)_2CH$–	>64	>64	>64	>64	>64	16
17j	$CH_3(CH_2)_3$–	64	64	64	64	64	16
17k	$(CH_3)_2CHCH_2$–	64	>64	>64	>64	>64	32
17l	$CH_3CH_2CHCH_3$	>64	>64	>64	>64	>64	32
17m	$CH_3(CH_2)_4$–	>64	>64	>64	>64	>64	>64
17n	$CH_3(CH_2)_5$–	>64	>64	>64	>64	>64	64
17o		32	32	32	32	32	16
17p		32	32	32	32	32	32
17q		32	32	32	32	32	32
17r		32	32	32	32	32	32
17s	Ph–	>64	>64	>64	>64	>64	32
17t	$PhCH_2$–	>64	>64	>64	>64	>64	16
17u		>64	>64	>64	>64	>64	64
17v		>64	>64	>64	>64	>64	64
16		32	32	32	32	32	16
10		64	64	64	64	64	8
PH-027		32	32	32	32	32	>16

Table 2 (*continued*).

No.	–R	ATCC 49247[b]	*H. inf* 280[c]	*H. inf* 282[c]	*H. inf* 283[c]	*H. inf* 285[c]	*M. cat*[d]
Lzd[e]		8	8	16	16	8	8
Van[f]		>16	>16	>16	>16	>16	>16

[a] All the compounds were inactive against *E. coli* ATCC 25922 (MIC > 64 μg/ml), except compound **17c** (MIC ranges 8 μg/ml).
[b] *H. inf*: *Haemophilus influenzae*.
[c] *H. influenzae* (clinical isolate).
[d] *M. cat*: *Moraxella catarrhalis* (clinical isolate).
[e] Linezolid.
[f] Vancomycin.

inhibitory activity of these 5-[(4-methyl-1,2,3-triazolyl)methyl] oxazolidinone compounds is yet to be determined. In general, substitution of the 5-methyl group on the triazole was observed to be detrimental to antibacterial activity, and in particular against *S. pneumoniae* strains. We believe that the activity of this class of compounds could be improved by introducing an appropriate moiety at the piperazine C4 position that would enhance affinity at the ribosomal binding site and improve antibacterial activity. Significant efforts are on-going in our laboratory to achieve this and also to investigate their MAO inhibitory activity and the potential reasons for decreased antibacterial activity in the presence of human plasma.

5. Experimental

5.1. Characterization

All common reagents and solvents were obtained from commercial sources and used without further purification. Extracted solvents were dried over anhydrous Na_2SO_4, followed by evaporation in vacuo and column chromatography was carried out with silica gel (Kieselgel 60, 70–230 mesh; Aldrich). 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 are uncorrected. The Science Analytical Facilities (SAF), Faculty of Science, Kuwait University, performed all the instrumental analyses. ^{1}H NMR spectra for all compounds were recorded on Bruker Avance II 600 NMR spectrometer using DMSO-d_6 as solvent and tetramethylsilane (TMS) as an internal reference, and chemical shifts were reported in parts per million. In addition, for further structural elucidation, the ^{13}C NMR spectrum of representative compounds **10** and **15** was recorded on Bruker Avance II 600 NMR spectrometer using DMSO-d_6 as solvent and tetramethylsilane (TMS) as an internal reference, and the chemical shifts were reported in ppm. 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) to enable identification and proper assignment of the carbon types. The mass spectrometry measurements were performed on a Finnigan MAT INCOS XL mass spectrometer. Infrared (IR) spectra were recorded on 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. The structures of the synthesized oxazolidinone derivatives **10**, **15** and **17a–v** were sketched and the *C* log *P* values estimated using ChemDraw Ultra 8.0 [26].

5.2. Syntheses

5.2.1. (R)-3-(3-Fluoro-4-morpholinophenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl) oxazolidin-2-one (*10*)

A solution of (*S*)-5-(azidomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one (**8**, 11 g, 34.23 mmol) in a mixture of THF (135 ml) and water (6 ml) was treated with triphenylphosphine (10.8 g, 41.18 mmol) and was heated at 70 °C overnight. The reaction mixture was treated with 20% aqueous HCl to acidic pH and extracted with ethyl acetate. The ethyl acetate layer was washed once with water and the aqueous layers were pooled. The pooled aqueous layer was basified with 20% NaOH and extracted successively with DCM. The DCM layers were pooled, washed with water and brine, dried (Na_2SO_4) and concentrated to give (*S*)-5-(aminomethyl)-3-(3-fluoro-4-morpholinophenyl) oxazolidin-2-one (**13**) as a white solid (10 g, Quant) after trituration with a mixture of ether and hexane (1:3). This amino compound was used without further purification for the next step in the reaction sequence as follows. A solution of (*S*)-5-(aminomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one (1.0 g, 3.11 mmol) and diisopropylethylamine (2.40 g, 1.75 ml, 13.56 mmol) in anhydrous MeOH (30 ml) at 0 °C under nitrogen gas was treated with 2-(1,1-dichloropropan-2-ylidene)-1-tosylhydrazine [22] (1.30 g, 4.40 mmol) and stirred for 5 h. The reaction mixture was concentrated under vacuum to give a yellow solid, which was dissolved in DCM. The DCM layer was subsequently washed with water and brine, dried (Na_2SO_4), filtered and concentrated to give a yellow solid. Purification by silica gel column chromatography using ethyl acetate:hexane 9:1, followed by ethyl acetate afforded the title compound (**10**) as a white solid (1.00 g, 91% yield), m.p. 170–173 °C. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 7.87 (s, 1H), 7.41 (dd, 1H, J = 2.3 Hz, 14.9 Hz), 7.13 (dd, 1H, J = 2.3 Hz, 9.0 Hz), 7.05 (t, 1H, J = 9.2 Hz), 5.05–5.10 (m, 1H), 4.74 (d, 2H, J = 5.0 Hz), 4.19 (t, 1H, J = 9.2 Hz), 3.92 (dd, 1H, J = 5.6 Hz, 9.2 Hz), 3.84 (dd, 1H, J = 5.4 Hz, 9.2 Hz), 3.72 (t, 4H, J = 4.5 Hz), 2.96 (t, 4H, J = 4.5 Hz), 2.23 (s, 3H). ^{13}C NMR (600 MHz, DMSO-d_6): δ 155.76, 153.99, 142.51, 136.15, 133.43, 123.71, 119.67, 114.73, 107.30, 107.13, 71.35, 66.59, 52.15, 51.12, 47.57, 10.88. IR (KBr pellet, cm^{-1}): ν 2852, 2829, 1741, 1519, 1449, 1414, 1329, 1239. MS 361 (M^+). Anal Calcd for $C_{17}H_{20}FN_5O_3$: C: 56.50, H: 5.58, N: 19.38. Found C: 56.35, H: 5.48, N: 19.19.

5.2.2. tert-Butyl 4-(2-fluoro-4-((R)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)phenyl)piperazine-1-carboxylate (*15*)

This compound was prepared according to the method described for compound **10** from *tert*-butyl 4-(4-((*S*)-5-(aminomethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazine-1-carboxylate (**14**, 20 g, 50.704 mmol) and diisopropylethylamine (26.28 g, 35 ml, 203.33 mmol) in anhydrous MeOH (250 ml) at 0 °C under

nitrogen gas, treated with 2-(1,1-dichloropropan-2-ylidene)-1-tosylhydrazine [22] (19.00 g, 64.37 mmol) and stirred for 5 h. Purification by silica gel column chromatography using ethyl acetate:hexane 9:1, followed by ethyl acetate afforded the title compound (**15**) as a white solid (18.78 g, 81% yield), m.p. 168–170 °C. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 7.87 (s, 1H, triazole H), 7.43 (dd, 1H, J = 2.3 Hz, 14.7 Hz, phenyl H), 7.14 (dd, 1H, J = 2.3 Hz, 9.0 Hz, phenyl H), 7.07 (t, 1H, J = 9.0 Hz, phenyl H), 5.07–5.10 (m, 1H oxazolidinone H), 4.74 (d, 2H, J = 5.1 Hz, triazole-CH_2), 4.19 (t, 1H, J = 9.0 Hz, oxazolidinone H), 3.84 (dd, 1H, J = 5.9 Hz, 9.0 Hz, oxazolidinone H), 3.47 (t, 4H, J = 4.7 Hz), 2.92 (t, 4H, J = 4.7 Hz), 2.23 (s, 3H, triazole-CH_3), 1.42 (s, 9H, $(CH_3)_3$C–O). ^{13}C NMR (600 MHz, DMSO-d_6): δ 155.36, 153.74, 153.46, 142.01, 135.61, 133.25, 123.19, 119.47, 114.23, 106.80, 106.63, 78.96, 70.84, 51.66, 50.27, 47.11, 28.02, 10.37. IR (KBr pellet, cm^{-1}): ν 2980, 2864, 1737, 1693, 1477, 1520, 1451, 1418, 1365, 1332, 1243, 1230. MS 460 (M^+). Anal Calcd for $C_{22}H_{29}FN_6O_4$: C: 57.38, H: 6.35, N: 18.25. Found C: 57.22, H: 6.21, N: 18.22.

5.2.3. (R)-3-(3-Fluoro-4-(piperazinium-1-yl) phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one trifluoroacetic acid salt (**16**)

A solution of *tert*-butyl 4-(2-fluoro-4-((*R*)-5-((4-methyl-1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)phenyl)piperazine-1-carboxylate (**15**, 13 g, 28.23 mmol) in DCM (20 ml) cooled to 0 °C with an ice bath was treated with trifluoroacetic acid (26 ml). The reaction mixture was stirred to room temperature overnight and concentrated on a rotatory evaporator to give an oily residue, which was triturated with a (1:1) mixture of diethyl ether and tetrahydrofuran with stirring to afford the title compound (**15**) as a white solid 12.78 g (96% yield). This solid was used without further purification.

5.2.4. (R)-2-Fluoro-4-((R)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)phenylpiperazine-1-carbaldehyde (**17a**)

An aqueous saturated solution of potassium hydrogen carbonate (2 ml) was added to (*R*)-3-(3-fluoro-4-piperazinium-1-yl-phenyl)-5-[1,2,3] triazol-1-yl methyl oxazolidin-2-one trifluoroacetic acid salt (**16**, 800 mg, 1.69 mmol) and stirred for about 15 min. The precipitated solid (*R*)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-5-((4-methyl-1*H*-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one was collected by filtration and dried. A mixture of the free amine and ammonium formate (370 mg, 5.88 mmol) in acetonitrile (42 ml) was stirred overnight under reflux at 90 °C [23]. The mixture was cooled and concentrated on a rotovap to give a crude solid, which was dissolved in DCM and subsequently washed with water and brine, and the organic layer dried (anhydrous Na_2SO_4). The organic layer was concentrated and dried to give a crude solid 390 mg. Recrystallization (EtOAc–CH_3CN) gave **17a** as crystalline solid (200 mg, 31% yield), m.p. 173–175 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.07 (s, 1H), 7.87 (s, 1H) 7.45 (dd, 1H, J = 2.3 Hz, 14.7 Hz), 7.14 (dd, 1H, J = 2.3 Hz, 9.0 Hz), 7.07 (t, 1H, J = 9.0 Hz), 5.07–5.10 (m, 1H), 4.74 (d, 2H, J = 5.1 Hz), 4.20 (t, 1H, J = 9.0 Hz), 3.84 (dd, 1H, J = 5.9 Hz, 9.0 Hz), 3.53 (overlapping t, 4H), 2.98 (t, 2H, J = 4.7 Hz), 2.92 (t, 2H, J = 4.7 Hz), 2.23 (s, 3H). IR (KBr pellet, cm^{-1}): ν 2927, 2824, 1744, 1734, 1663, 1518, 1442, 1416, 1327, 1276, 1217, 1234. MS 388 (M^+). Anal Calcd for $C_{18}H_{21}FN_6O_3$: C: 55.66, H: 5.45, N: 21.64. Found C: 55. 28, H: 5.49, N: 21.42.

5.2.5. General procedure for the alkylcarbonyl oxazolidinones **17b–u**

A suspension of 3-(3-fluoro-4-piperazinium-1-yl-phenyl)-5-(5-methyl)[1,2,3]triazol-1-yl methyl oxazolidin-2-one trifluoroacetic acid salt (**16**, 800 mg, 1.74 mmol) in a mixture of anhydrous DCM (5 ml) and CH_3CN (5 ml) was treated with triethylamine (1.5 ml) and cooled to 0 °C. The resulting solution was treated with the suitable acid anhydride or acid chloride (3.46 mmol) and the reaction mixture was allowed to stir overnight. The reaction mixture was concentrated on a rotovap to give a crude gum, which was dissolved in DCM (30 ml), washed successively with water and dilute sodium carbonate solution (15 ml each). The DCM layer was separated and washed with water, dried under anhydrous Na_2SO_4, filtered and concentrated to obtain a crude gum, which was triturated with small volumes of diethyl ether to afford a solid. The crude solid was purified using either by silica gel column chromatography and/or recrystallized from a suitable organic solvent to give the respective products.

5.2.6. (R)-3-(4-(4-Acetylpiperazin-1-yl)-3-fluorophenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17b**)

Recrystallization (EtOAc) gave a crystalline solid (0.540 g, 61% yield), m.p. 100–102 °C. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 7.86 (s, 1H), 7.43 (dd, 1H, J = 2.3 Hz, 14.7 Hz), 7.14 (dd, 1H, J = 2.3 Hz, 9.0 Hz), 7.06 (t, 1H, J = 9.0 Hz), 5.07–5.10 (m, 1H), 4.74 (d, 2H, J = 5.0 Hz), 4.19 (t, 1H, J = 9.0 Hz), 3.83 (dd, 1H, J = 5.9 Hz, 9.0 Hz), 3.57–3.59 (overlapping t, 4H), 2.96 (t, 2H, J = 4.7 Hz), 2.90 (t, 2H, J = 4.7 Hz), 2.22 (s, 3H), 2.03 (s, 3H). IR (KBr pellet, cm^{-1}): ν 2911, 2833, 1750, 1616, 1634, 1521, 1442, 1418, 1324, 1234. MS 402 (M^+). Anal Calcd for $C_{19}H_{23}FN_6O_3$: C: 56.71, H: 5.76, N: 20.88. Found C: 56.22, H: 5.63, N: 20.76.

5.2.7. (R)-3-(3-Fluoro-4-(4-(2,2,2-trifluoroacetyl)piperazin-1-yl)phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17c**)

Purification by silica gel column chromatography (EtOAc–MeOH, 9:1) gave a solid (400 mg, 42% yield), m.p. 95–97 °C. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 7.86 (s, 1H), 7.44 (dd, 1H, J = 2.3 Hz, 14.7 Hz), 7.14 (dd, 1H, J = 2.3 Hz, 9.0 Hz), 7.09 (t, 1H, J = 9.0 Hz), 5.06–5.10 (m, 1H), 4.74 (d, 2H, J = 5.0 Hz), 4.19 (t, 1H, J = 9.0 Hz), 3.84 (dd, 1H, J = 5.9 Hz, 9.0 Hz), 3.72–3.75 (m, 4H), 3.05–3.08 (m, 4H), 2.22 (s, 3H). IR (KBr pellet, cm^{-1}): ν 2962, 2835, 1743, 1690, 1518, 1480, 1410, 1449, 1327, 1244, 1221. MS 456 (M^+). Anal Calcd for $C_{19}H_{20}F_4N_6O_3$: C: 50.00, H: 4.42, N: 18.41. Found C: 49.80, H: 4.41, N: 18.12.

5.2.8. (R)-3-(3-Fluoro-4-(4-propionylpiperazin-1-yl)phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17d**)

Recrystallization (EtOAc) afforded a solid (460 mg, 51% yield), m.p. 120–122 °C. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 7.87 (s, 1H), 7.44 (dd, 1H, J = 2.3 Hz, 14.7 Hz), 7.14 (dd, 1H, J = 2.3 Hz, 9.0 Hz), 7.04 (t, 1H, J = 9.0 Hz), 5.06–5.10 (m, 1H), 4.74 (d, 2H, J = 5.0 Hz), 4.19 (t, 1H, J = 9.0 Hz), 3.84 (dd, 1H, J = 5.9 Hz, 9.0 Hz), 3.54–3.60 (m, 4H), 2.96 (t, 2H, J = 4.7 Hz), 2.91 (t, 2H, J = 4.7 Hz), 2.36 (q, 2H, J = 7.3 Hz), 2.23 (s, 3H), 1.01 (t, 3H, J = 7.3 Hz). IR (KBr pellet, cm^{-1}): ν 2824, 2982, 1743, 1757, 1643, 1519, 1439, 1427, 1331, 1227. MS 416 (M^+). Anal Calcd for $C_{20}H_{25}FN_6O_3$: C: 57.68, H: 6.05, N: 20.18. Found C: 56.70, H: 6.09, N: 19.96.

5.2.9. (R)-3-(4-(4-(2,2,2-Trichloroacetyl)piperazin-1-yl)-3-fluorophenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17e**)

Recrystallization (EtOAc–Hex) gave a crystalline solid (576 mg, 46% yield), m.p. 165–167 °C. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 7.85 (s, 1H), 7.44 (dd, 1H, J = 2.5 Hz, 14.7 Hz), 7.15 (dd, 1H, J = 2.5 Hz, 9 Hz), 7.09 (t, 1H, J = 9.4 Hz), 5.07–5.09 (m, 1H), 4.74 (d, 2H, J = 5.0 Hz), 4.19 (t, 1H, J = 9.2 Hz), 3.90–4.05 (br s, 2H), 3.84 (dd, 1H, J = 5.95 Hz, 9.3 Hz, overlaps with broad singlet), 3.75–3.90 (br s, 2H, overlaps with dd), 3.08 (br s, 4H), 2.22 (s, 3H). IR (KBr pellet, cm^{-1}): ν 2925, 2828, 1754, 1680, 1518, 1427, 1329, 1231. MS 505.2 (M^+). Anal Calcd for $C_{19}H_{20}Cl_3FN_6O_3$: C: 45.12, H: 3.99, N: 16.62. Found C: 46.15, H: 4.25, N: 16.91.

*5.2.10. Ethyl 4-(2-fluoro-4-((R)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)phenyl)piperazine-1-carboxylate (**17f**)*

Recrystallization (EtOAc) gave off-white crystals (833 mg, 92% yield), m.p. 143–145 °C. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 7.87 (s, 1H), 7.43 (dd, 1H, J = 2.3 Hz, 14.6 Hz), 7.14 (dd, 1H, J = 2.2 Hz, 10.8 Hz), 7.07 (t, 1H, J = 9.4 Hz), 5.05–5.10 (m, 1H), 4.74 (d, 2H, J = 5.1 Hz), 4.19 (t, 1H, J = 9.3 Hz), 4.07 (dd, 2H, J = 7.06 Hz, 14.1 Hz), 3.84 (dd, 1H, J = 5.9 Hz, 9.2 Hz), 3.48–3.55 (br s, 4H), 2.94 (t, 4H, J = 4.58 Hz), 2.23 (s, 3H), 1.21 (t, 3H, J = 7.0 Hz). IR (KBr pellet, cm^{-1}): ν 2953, 2904, 1700, 1739, 1518, 1427, 1379, 1338, 1327, 1284, 1233. MS 432 (M^+). Anal Calcd for $C_{20}H_{25}FN_6O_4$: C: 55.55, H: 5.83, N: 19.73. Found C: 55.60, H: 6.27, N: 19.55.

*5.2.11. S-Ethyl 4-(2-fluoro-4-((R)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)phenyl)piperazine-1-carbothioate (**17g**)*

Recrystallization (EtOAc) gave a crystalline solid (433 mg, 46% yield), m.p. 180–182 °C. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 7.86 (s, 1H), 7.43 (dd, 1H, J = 2.3 Hz, 14.7 Hz), 7.14 (dd, 1H, J = 2.3 Hz, 9.0 Hz), 7.07 (t, 1H, J = 9.0 Hz), 5.05–5.10 (m, 1H), 4.73 (d, 2H, J = 5.0 Hz), 4.19 (t, 1H, J = 9.0 Hz), 3.84 (dd, 1H, J = 5.9 Hz, 9.0 Hz), 3.54–3.66 (br s, 4H), 2.97 (t, 4H, J = 4.7 Hz), 2.85 (q, 2H, J = 7.3 Hz), 2.22 (s, 3H), 1.21 (t, 3H, J = 7.3 Hz). IR (KBr pellet, cm^{-1}): ν 2864, 2965, 1762, 1661, 1641, 1517, 1440, 1413, 1333, 1223. MS 448 (M^+). Anal Calcd for $C_{20}H_{25}FN_6O_3S$: C: 53.56, H: 5.62, N: 18.74. Found C: 53.20, H: 5.66, N: 18.34.

*5.2.12. (R)-3-(4-(4-(2,2-Dichloroacetyl)piperazin-1-yl)-3-fluorophenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17h**)*

Recrystallization (EtOAc) gave a crystalline solid (643 mg, 65% yield), m.p. 102–104 °C. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 7.86 (s, 1H), 7.42 (dd, 1H, J = 2.5 Hz, 14.7 Hz), 7.31 (s, 1H), 7.13 (dd, 1H, J = 2.5 Hz, 9.0 Hz), 7.08 (t, 1H, J = 9.0 Hz), 5.06–5.09 (m, 1H), 4.73 (d, 2H, J = 5.3 Hz), 4.19 (t, 1H, J = 9.0 Hz), 3.85 (dd, 1H, J = 5.09 Hz, 9.0 Hz), 3.70 (t, 2H, J = 4.7 Hz), 3.67 (t, 2H, J = 4.7 Hz), 3.02 (t, 2H, J = 4.7 Hz), 2.99 (t, 2H, J = 4.7 Hz), 2.22 (s, 3H). IR (KBr pellet, cm^{-1}): ν 2948, 2828, 1755, 1669, 1518, 1445, 1420, 1329, 1231. MS 471.3 (M^+). Anal Calcd for $C_{19}H_{21}Cl_2FN_6O_3$: C: 48.42, H: 4.49, N: 17.83. Found C: 47.72, H: 4.56, N: 16.91.

*5.2.13. (R)-3-(3-Fluoro-4-(4-(isobutyryl)piperazin-1-yl)phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17i**)*

Recrystallization (EtOAc–Hex) gave a crystalline solid (629 mg, 70% yield), m.p. 175–177 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.86 (s, 1H), 7.43 (dd, 1H, J = 2.5 Hz, 14.7 Hz), 7.28 (dd, 1H, J = 2.5 Hz, 9.0 Hz), 7.07 (t, 1H, J = 9.0 Hz), 5.06–5.10 (m, 1H), 4.74 (d, 2H, J = 5.3 Hz), 4.19 (t, 1H, J = 9.0 Hz), 3.83 (br dd, 1H, J = 5.9 Hz, 9.0 Hz), 3.64 (t, 2H, J = 4.7 Hz), 3.61 (t, 2H, J = 4.7 Hz), 2.97 (t, 2H, J = 4.7 Hz), 2.88–2.93 (m, 3H), 2.22 (s, 3H), 1.01 (d, 6H, J = 6.7 Hz). IR (KBr pellet, cm^{-1}): ν 2970, 2832, 1756, 1637, 1518, 1477, 1416, 1438, 1338, 1229. MS 430 (M^+). Anal Calcd for $C_{21}H_{27}FN_6O_3$: C: 58.59, H: 6.32, N: 19.52. Found C: 58.52, H: 6.33, N: 19.26.

*5.2.14. (R)-3-(3-Fluoro-4-(4-pentanoylpiperazin-1-yl)phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17j**)*

Recrystallization (EtOAc–Hex) gave crystalline solid (629 mg, 68% yield), m.p. 189–190 °C. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 7.86 (s, 1H), 7.43 (dd, 1H, J = 2.5 Hz, 14.7 Hz), 7.13 (dd, 1H, J = 2.4 Hz, 9.0 Hz), 7.06 (t, 1H, J = 9.0 Hz), 5.07–5.09 (m, 1H), 4.74 (d, 2H, J = 5.2 Hz), 4.19 (t, 1H, J = 9.0 Hz), 3.83 (dd, 1H, J = 5.9 Hz, 9.0 Hz), 3.59 (d, 4H, J = 4.0 Hz), 2.96 (br t, 2H, J = 4.7 Hz), 2.90 (br t, 2H, J = 4.7 Hz), 2.34 (t, 2H, J = 7.5 Hz), 2.22 (s, 3H), 1.46–1.50 (m, 2H), 1.29–1.33 (m, 2H), 0.89 (t, 3H, J = 7.4 Hz). IR (KBr pellet, cm^{-1}): ν 2927, 2891, 2975, 1747, 1642, 1622, 1518, 1417, 1331, 1230. MS 444 (M^+). Anal Calcd for $C_{22}H_{29}FN_6O_3$: C: 59.45, H: 6.58, N: 18.91. Found C: 59.85, H: 6.92, N: 18.29.

*5.2.15. (R)-3-(4-(4-(3-Methylbutanoyl)piperazin-1-yl)-3-fluorophenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17k**)*

Recrystallization (EtOAc–Hex) gave crystalline solid (671 mg, 72% yield), m.p. 173–175 °C. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 7.86 (s, 1H), 7.43 (dd, 1H, J = 2.5 Hz, 14.7 Hz), 7.13 (dd, 1H, J = 2.5 Hz, 9.0 Hz), 7.06 (t, 1H, J = 9.0 Hz), 5.06–5.10 (m, 1H), 4.74 (d, 2H, J = 5.2 Hz), 4.19 (t, 1H, J = 9.0 Hz), 3.83 (dd, 1H, J = 5.9 Hz, 9.0 Hz), 3.60 (d, 4H, J = 4.0 Hz), 2.95 (t, 2H, J = 4.7 Hz), 2.90 (t, 2H, J = 4.7 Hz), 2.23 (d, 2H, overlaps with singlet at 2.22 ppm), 2.22 (s, 3H, overlaps with CH_2 doublet at 2.23 ppm), 1.98–2.03 (m, 1H), 0.91 (d, 6H, J = 6.7 Hz). IR (KBr pellet, cm^{-1}): ν 2868, 2956, 1741, 1630, 1520, 1442, 1420, 1325, 1223. MS 444 (M^+). Anal Calcd for $C_{22}H_{29}FN_6O_3$: C: 59.45, H: 6.58, N: 18.91. Found C: 59.35, H: 6.43, N: 18.60.

*5.2.16. (R)-3-(4-(4-(2-Methylbutanoyl)piperazin-1-yl)-3-fluorophenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17l**)*

Recrystallization (EtOAc–Hex) gave crystalline solid (670 mg, 72% yield), m.p. 158–160 °C. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 7.86 (s, 1H), 7.44 (dd, 1H, J = 2.5 Hz, 14.7 Hz), 7.13 (dd, 1H, J = 2.4 Hz, 9.0 Hz), 7.07 (t, 1H, J = 9.4 Hz), 5.06–5.09 (m, 1H) 4.74 (d, 2H, J = 5.2 Hz), 4.19 (t, 1H, J = 9.2 Hz), 3.83 (dd, 1H, J = 5.9 Hz, 9.3 Hz), 3.63–3.67 (m, 4H), 2.92–2.96 (m, 4H), 2.70–2.78 (m, 1H), 2.22 (s, 3H), 1.54–1.59 (m, 1H), 1.28–1.36 (m, 1H), 1.00 (d, 3H, J = 6.8 Hz), 0.83 (t, 3H, J = 7.4 Hz). IR (KBr pellet, cm^{-1}): ν 2933, 2970, 2827, 1749, 1639, 1519, 1471, 1444, 1424, 1337, 1225. MS 444.3 (M^+). Anal Calcd for $C_{22}H_{29}FN_6O_3$: C: 59.45, H: 6.58, N: 18.91. Found C: 59.65, H: 6.74, N: 19.03.

*5.2.17. (R)-3-(3-Fluoro-4-(4-hexanoylpiperazin-1-yl)phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17m**)*

Recrystallization (CH_3CN) gave solid (567 mg, 58% yield), m.p. 189–190 °C. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 7.86 (d, 1H), 7.43 (dd, 1H, J = 2.5 Hz, 14.7 Hz), 7.13 (dd, 1H, J = 2.5 Hz, 9.0 Hz), 7.04 (t, 1H, J = 9.0 Hz), 5.07–5.09 (m, 1H), 4.73 (d, 2H, J = 5.0 Hz), 4.19 (t, 1H, J = 9.0 Hz), 3.83 (dd, 1H, J = 5.9 Hz, 9.0 Hz), 3.58 (br s, 4H), 2.96 (t, 2H, J = 4.7 Hz), 2.90 (t, 2H, J = 4.7 Hz), 2.33 (t, 2H, J = 7.6 Hz), 2.22 (s, 3H), 1.26–1.51 (m, 9H). IR (KBr pellet, cm^{-1}): ν 2856, 2953, 1746, 1641, 1624, 1516, 1466, 1438, 1481, 1416, 1328, 1344, 1226. MS 458.3 (M^+). Anal Calcd for $C_{23}H_{31}FN_6O_3$: C: 60.25, H: 6.81, N, 18.33, Found C: 60.16, H: 6.96, N: 18.48.

*5.2.18. (R)-3-(3-Fluoro-4-(4-heptanoylpiperazin-1-yl)phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17n**)*

Recrystallization (EtOAc–Hex) gave crystalline solid (914 mg, 92% yield), m.p. 173–175 °C. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 7.86 (s, 1H), 7.43 (dd, 1H, J = 2.5 Hz, 14.7 Hz), 7.13 (dd, 1H, J = 2.5 Hz, 9.0 Hz), 7.06 (t, 1H, J = 9.5 Hz), 5.07–5.09 (m, 1H), 4.74 (d, 2H, J = 5.2 Hz), 4.19 (t, 1H, J = 9.0 Hz), 3.83 (dd, 1H, J = 5.9 Hz, 9.0 Hz), 3.59 (br s, 4H), 2.95 (t, 2H, J = 4.7 Hz), 2.90 (t, 2H, J = 4.7 Hz), 2.33 (t, 2H, J = 7.4 Hz), 22.2 (s, 3H), 1.48–1.51 (m, 2H), 1.25–1.30 (m, 6H), 0.86 (t, 3H, J = 6.8 Hz). IR (KBr pellet, cm^{-1}): ν 2857, 2925, 1745, 1631, 1517, 1478, 1428, 1417, 1343, 1328, 1226. MS 472.4 (M^+). Anal Calcd for $C_{24}H_{33}FN_6O_3$: C: 61.00, H: 7.04, N: 17.18. Found C: 60.62, H: 7.21, N: 17:73.

*5.2.19. (R)-3-(3-Fluoro-4-(4-cyclopropanecarbonyl-piperazin-1-yl)phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17o**)*

Recrystallization (EtOAc–Hex) gave crystalline solid (729 mg, 81% yield), m.p. 165–167 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.86

(s, 1H), 7.44 (dd, 1H, $J = 2.5$ Hz, 14.7 Hz), 7.14 (dd, 1H, $J = 2.5$ Hz, 9.0 Hz), 7.08 (t, 1H, $J = 9$ Hz), 5.07–5.09 (m, 1H), 4.74 (d, 2H, $J = 5.0$ Hz), 4.19 (t, 1H, $J = 9.0$ Hz), 3.82–3.85 (m, 3H), 3.61 (br s, 2H), 3.00 (br s, 2H), 2.91 (br s, 2H), 2.22 (s, 3H), 2.00–2.05 (m, 1H), 0.73–0.76 (m, 4H). IR (KBr pellet, cm^{-1}): ν 2899, 2829, 1746, 1632, 1520, 1444, 1470, 1415, 1340, 1279, 1237. MS 428.3 (M^+). Anal. Calcd for $C_{21}H_{25}FN_6O_3$: C: 58.87, H: 5.88, N: 19.61. Found C: 58.79, H: 6.18, N: 19.65.

*5.2.20. (R)-3-(3-Fluoro-4-(4-cyclobutanecarbonyl-piperazin-1-yl)phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17p**)*

Recrystallization (EtOAc–Hex) gave crystalline solid (814 mg, 87% yield), m.p. 143–145 °C. ^1H NMR (DMSO-d_6, 600 MHz): δ 7.86 (s, 1H), 7.42 (dd, 1H, $J = 2.5$ Hz, 14.7 Hz), 7.13 (dd, 1H, $J = 2.5$ Hz, 9.0 Hz), 7.05 (t, 1H, $J = 9.0$ Hz), 5.07–5.09 (m, 1H), 4.73 (d, 2H, $J = 5.0$ Hz), 4.19 (t, 1H, $J = 9.0$ Hz), 3.83 (dd, 1H, $J = 5.9$ Hz, 9.0 Hz), 3.59 (t, 2H, $J = 4.7$ Hz), 3.46 (t, 2H, $J = 4.7$ Hz), 3.35–3.39 (m, 1H), 2.89–2.92 (m, 4H), 2.22 (s, 3H), 2.09–2.20 (m, 4H), 1.85–1.94 (m, 1H), 1.70–1.78 (m, 1H). IR (KBr pellet, cm^{-1}): ν 2836, 2947, 1742, 1638, 1520, 1420, 1328, 1224. MS 442 (M^+). Anal Calcd for $C_{22}H_{27}FN_6O_3$: C: 59.72, H: 6.15, N: 18.99. Found C: 59.24, H: 6.20, N: 18.49.

*5.2.21. (R)-3-(3-Fluoro-4-(4-cyclopentanecarbonyl-piperazin-1-yl)phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17q**)*

Recrystallization (EtOAc–Hex) gave crystalline solid (857 mg, 89% yield), m.p. 144–145 °C. ^1H NMR (DMSO-d_6, 600 MHz): δ 7.90 (s, 1H), 7.47 (dd, 1H, $J = 2.5$ Hz, 14.7 Hz), 7.17 (dd, 1H, $J = 2.4$ Hz, 9.0 Hz), 7.11 (t, 1H, $J = 9.0$ Hz), 5.11–5.13 (m, 1H), 4.77 (d, 2H, $J = 5.3$ Hz), 4.23 (t, 1H, $J = 9.0$ Hz), 3.88 (dd, 1H, $J = 5.9$ Hz), 3.69 (t, 2H, $J = 4.7$ Hz), 3.65 (t, 2H, $J = 4.7$ Hz), 3.03–3.05 (m, 1H), 3.00 (t, 2H, $J = 4.7$ Hz), 2.95 (t, 2H, $J = 4.7$ Hz), 2.27 (s, 3H), 1.82–1.56 (m, 8H). IR (KBr pellet, cm^{-1}): ν 2868, 2954, 1749, 1638, 1518, 1441, 1426, 1336, 1228. MS 444 (M^+). Anal Calcd for $C_{23}H_{29}FN_6O_3$: C: 60.51, H: 6.40, N: 18.41. Found C: 60.11, H: 6.36, N: 17.91.

*5.2.22. (R)-3-(3-Fluoro-4-(4-cyclohexanecarbonyl-piperazin-1-yl)phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17r**)*

Recrystallization (EtOAc–Hex) gave crystalline solid (814 mg, 82% yield), m.p. 169–170 °C. ^1H NMR (DMSO-d_6, 400 MHz): δ 7.86 (s, 1H), 7.43 (dd, 1H, $J = 2.5$, 14.7 Hz), 7.12 (dd, 1H, $J = 2.5$ Hz, 9.0 Hz), 7.07 (t, 1H, $J = 9.0$ Hz), 5.01–5.09 (m, 1H), 4.73 (d, 2H, $J = 5.3$ Hz), 4.2 (t, 1H, $J = 9.2$ Hz), 3.83 (dd, 1H, $J = 5.9$ Hz, 9.2 Hz), 3.60 (two br s, 4H), 2.93 (two br s, 4H), 2.60 (m, 1H), 2.22 (s, 3H), 1.69 (m, 4H), 1.32 (m, 6H). IR (KBr pellet, cm^{-1}): ν 2855, 2932, 1753, 1638, 1518, 1448, 1329, 1239, 1222. MS 470.24 (M^+). Anal Calcd for $C_{24}H_{31}FN_6O_3$: C: 61.26, H: 6.64, N: 17.86. Found C: 60.99, H: 6.59, N: 17.64.

*5.2.23. (R)-3-(4-(4-Benzoyl-piperazin-1-yl)-3-fluorophenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17s**)*

Recrystallization (EtOAc) gave crystalline solid (614 mg, 63% yield), m.p. 195–197 °C. ^1H NMR (DMSO-d_6, 600 MHz): δ 7.86 (s, 1H), 7.41–7.47 (m, 6H), 7.13 (dd, 1H, $J = 2.4$ Hz, 14.7 Hz), 7.10 (t, 1H, $J = 9.4$ Hz), 5.07–5.09 (m, 1H), 4.74 (d, 2H, $J = 5.2$ Hz), 4.19 (t, 1H, $J = 9.0$ Hz), 3.84 (dd, 1H, $J = 5.9$ Hz, 9.0 Hz), 3.70–3.80 (br s, 2H), 3.45–3.52 (br s, 2H), 2.90–3.09 (br, 4H), 2.22 (s, 3H). IR (KBr pellet, cm^{-1}): ν 2922, 2839, 1742, 1624, 1524, 1493, 1440, 1417, 1337, 1286, 1238, 1220. MS 464.4 (M^+). Anal Calcd for $C_{24}H_{25}FN_6O_3$: C: 62.06, H: 5.42, N: 18.07. Found C: 61.14, H: 5.80, N: 17.45.

*5.2.24. (R)-3-(3-Fluoro-4-(4-(2-phenylacetyl)piperazin-1-yl)phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17t**)*

Recrystallization (EtOAc–Hex) gave crystalline solid (729 mg, 72% yield), m.p. 197–199 °C. ^1H NMR (DMSO-d_6, 600 MHz): δ 7.85 (s, 1H), 7.42 (dd, 1H, $J = 2.5$ Hz, 14.7 Hz), 7.31–7.33 (m, 2H), 7.23–7.25 (m, 3H), 7.11 (dd, 1H, $J = 2.5$, 9.0 Hz) 7.03 (t, 1H, $J = 9.0$ Hz), 5.07–5.10 (m, 1H), 4.73 (d, 2H, $J = 5.0$ Hz), 4.18 (t, 1H, $J = 9.0$ Hz), 3.83 (dd, 1H, $J = 5.9$ Hz, 9.0 Hz), 3.76 (s, 2H), 3.61–3.65 (m, 4H), 2.91 (t, 2H, $J = 4.7$ Hz), 2.78 (t, 2H, $J = 4.7$ Hz), 2.2 (s, 3H). IR (KBr pellet, cm^{-1}): ν 3063, 1739, 1630, 1520, 1495, 1442, 1420, 1367, 1325, 1238, 1223. MS 478.4 (M^+). Anal Calcd for $C_{25}H_{27}FN_6O_3$: C: 62.75, H: 5.69, N: 17.56. Found C: 62.62, H: 5.73, N: 17.40.

*5.2.25. (R)-3-(3-Fluoro-4-(4-((E)-3-phenylacryloyl) piperazin-1-yl)phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17u**)*

Recrystallization (EtOAc–Hex) gave crystalline solid (643 mg, 62% yield), m.p. 255–257 °C. ^1H NMR (DMSO-d_6, 600 MHz): δ 7.86 (s, 1H), 7.72–7.75 (m, 2H), 7.53 (d, 1H, $J = 15.4$ Hz), 7.36–7.46 (m, 4H), 7.32 (d, 1H, $J = 15.4$ Hz), 7.14 (dd, 1H, $J = 2.4$ Hz, 9.0 Hz), 7.09 (t, 1H, $J = 9.4$ Hz), 5.06–5.10 (m, 1H), 4.73 (d, 2H, $J = 5.2$ Hz), 4.19 (t, 1H, $J = 9.0$ Hz), 3.88 (br s, 2H), 3.84 (dd, 1H), 3.74 (br s, 2H), 3.00 (br d, 4H), 2.22 (s, 3H). IR (KBr pellet, cm^{-1}): ν 2958, 2857, 1738, 1646, 1601, 1517, 1450, 1434, 1420, 1342, 1279, 1229. MS 490.4 (M^+). Anal Calcd for $C_{26}H_{27}FN_6O_3$: C: 63.66, H: 5.55, N: 17.13. Found C: 63.29, H: 5.71, N: 16.84.

*5.2.26. (R)-3-(4-(4-(2-(Bicyclo[2.2.1]heptan-2-yl)acetyl)piperazin-1-yl)-3-fluoro phenyl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**17v**)*

A solution of 2-norboraneacetic acid (170 mg, 1.10 mmol) in anhydrous DCM (20 ml) under nitrogen gas was treated with *N,N*-dicyclohexylcarbodiimide (210 mg, 1.02 mmol) and 1-hydroxybenzotriazole (150 mg, 1.10 mmol) and the mixture stirred for 2 h at room temperature under N_2 gas. This reaction mixture was filtered directly into a round bottom flask containing 3-(3-fluoro-4-piperazinium-1-yl-phenyl)-5-(5-methyl)[1,2,3]triazol-1-yl methyl oxazolidin-2-one trifluoroacetic acid salt (500 mg, 1.05 mmol) and triethylamine (420 μl) in anhydrous CH_3CN (10 ml). The reaction mixture was stirred at room temperature overnight under N_2 gas. The mixture was concentrated under vacuum to give a gum, which was dissolved in ethyl acetate (40 ml), washed with 10% Na_2CO_3, water, and brine, dried (Na_2SO_4) and concentrated on rotovap to afford a solid. Purification by silica gel column chromatography (DCM–MeOH, 9:1) gave a solid (270 mg, 52% yield), m.p. 178–180 °C. ^1H NMR (DMSO-d_6, 600 MHz): δ 7.87 (s, 1H), 7.44 (dd, 1H, $J = 2.38$ Hz, 14.72 Hz), 7.14 (dd, 1H, $J = 2.35$ Hz, 8.83 Hz), 7.06 (t, 1H, $J = 9.41$ Hz), 5.09 (m, 1H), 4.74 (d, 2H, $J = 5.23$ Hz), 4.2 (t, 2H, $J = 9.19$ Hz), 3.84 (dd, 1H, $J = 5.98$ Hz, 9.38 Hz), 3.60 (t, 4H, $J = 4.55$ Hz, 9.88 Hz), 2.91 (t, 4H, $J = 16.17$ Hz), 2.33 (m, 1H), 2.18 (m, 5H), 1.96 (s, 1H), 1.81 (m, 1H), 1.45 (m, 3H), 1.14 (m, 2H), 1.04 (m, 2H). IR (KBr pellet, cm^{-1}): ν 2867, 2949, 1742, 1624, 1523, 1441, 1419, 1325, 1222. MS 496.3 (M^+). Anal Calcd for $C_{26}H_{33}FN_6O_3$: C: 62.89, H: 6.7, N: 16.96. Found C: 63.32, H: 6.99, N: 16.30.

6. Microbiology

6.1. Antibacterial susceptibility testing

The clinical isolates tested in this study were obtained from culture collection maintained at the MRSA Reference Laboratory, Faculty of Medicine, Kuwait University. Antibacterial susceptibility testing was performed by the agar dilution method according to the Clinical and Laboratory Standard Institute (CSLI)

(formerly National Committee for Clinical Laboratory Standards) [27]. Minimum inhibitory concentrations (MICs, μg/ml) were determined on Mueller–Hinton (MH) agar with medium containing dilutions of antibacterial agents ranging from 0.12 to 64 μg/ml. The test compounds were dissolved in 20% water in DMSO, while linezolid and vancomycin were dissolved in 40% water in ethanol and water, respectively. The tests were performed using MH agar plates 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 utilized in this study consisted of methicillin-resistant *S. aureus* (MRSA, $n = 10$), methicillin-susceptible *S. aureus* (MSSA, $n = 10$), methicillin-resistant coagulase-negative staphylococci (MR-CNS, $n = 3$), methicillin-sensitive coagulase-negative staphylococci (MS-CNS, $n = 6$), *S. pneumoniae* ($n = 3$), vancomycin-sensitive (VSE, $n = 6$) and vancomycin-resistant (VRE, $n = 4$) enterococci. The Gram-negative clinical isolates tested included *H. influenzae* ($n = 4$) and *M. catarrhalis* ($n = 1$). The reference strains, *S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228 and *E. faecalis* ATCC 29212, *E. coli* ATCC 25922 and *H. influenzae* ATCC 49247 were used as controls. The final bacterial concentration for inocula was 10^7 CFU/ml, and was incubated at 35 °C for 18 h. The test compounds were also evaluated against *S. aureus* ATTC 25923 in MH broth supplemented with 50% human plasma to assess the extent of plasma binding and/or plasma instability. The MIC was defined as the lowest drug concentration that completely inhibited growth of the bacteria. Linezolid and **PH-027** were prepared according to literature methods [15,20], and vancomycin obtained from a commercial source was used as reference antibacterial agents.

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References

[1] National Nosocomial Infections Surveillance (NNIS) System, Am. J. Infect. Control 32 (2004) 470–485.
[2] H. Goossens, Chemotherapy 51 (4) (2005) 177–181.
[3] D. Styers, D.J. Sheehan, P. Hogan, D.F. Sahn, Ann. Clin. Microbiol. Antimicrob. 5 (2006) 2 [online journal published by Biomed Central].
[4] Antimicrobial Resistance Prevention Initiative, Am. J. Infect. Control 34 (5 Suppl.) (2006) A1-S79.
[5] M. Wiselka, Clin. Med. 4 (6) (2004) 494–498.
[6] A.S. Fauci, N.A. Touchette, G.K. Folkers, Emerg. Infect. Dis. 11 (4) (2005) 519–525.
[7] Infectious Diseases Society of America, Bad Bugs, No Drugs as Antibiotic Discovery Stagnates, a Public Health Crisis Brews (July 2004).
[8] D.K. Hutchinson, Curr. Top. Med. Chem. 3 (2003) 1021–1042.
[9] M.B. Gravestock, Curr. Opin. Drug Discov. Devel. 8 (4) (2005) 469–477.
[10] T.S. Lundstrom, J.D. Sobel, Infect. Dis. Clin. North Am. 18 (2004) 651–658.
[11] M.R. Barbachyn, C.W. Ford, Angew. Chem. Int. Ed. 42 (2003) 2010–2023.
[12] A.R. Renslo, G.W. Luehr, M.F. Gordeev, Bioorg. Med. Chem. 14 (12) (2006) 4227–4240.
[13] J.V.N.V. Prasad, Curr. Opin. Microbiol. 10 (2007) 454–460.
[14] G. Poce, G. Zappia, G.C. Porretta, B. Botta, M. Biava, Exp. Opin. Ther. Patents 18 (2) (2008) 97–121.
[15] O.A. Phillips, E.E. Udo, A.A.M. Ali, N. Al-Hassawi, Bioorg. Med. Chem. 11 (2003) 35–41.
[16] O.A. Phillips, E.E. Udo, A.A.M. Ali, S.M. Samuel, Bioorg. Med. Chem. 13 (2005) 4113–4123.
[17] O.A. Phillips, E.E. Udo, A.A.M. Ali, S.M. Samuel, Eur. J. Med. Chem. 42 (2007) 214–225.
[18] F. Reck, F. Zhou, M. Girardot, G. Kern, C.J. Eyermann, N.J. Hales, R.R. Ramsay, M.B. Gravestock, J. Med. Chem. 48 (2005) 499–506.
[19] S.I. Hauck, C. Cederberg, A. Doucette, L. Grosser, N.J. Hales, G. Poon, M.B. Gravestock, Bioorg. Med. Chem. Lett. 17 (2007) 337–340.
[20] S.J. Brickner, D.K. Hutchinson, M.R. Barbachyn, P.R. Manninen, D.A. Ulanowicz, S.A. Garmon, K.C. Grega, S.K. Hendges, D.S. Toops, C.W. Ford, G.E. Zurenko, J. Med. Chem. 39 (1996) 673–679.
[21] R. Huisgen, 1,3 Dipolar cycloaddition – introduction, survey, mechanism, in: A. Padwa (Ed.), 1,3 Dipolar Cycloaddition Chemistry, vol. 1, Wiley, New York, 1984, pp. 1–176.
[22] K. Sakai, N. Hida, K. Kondo, Bull. Chem. Soc. Jpn. 59 (1986) 179–183.
[23] P.G. Reddy, G.D.K. Kumar, S. Baskaran, Tetrahedron Lett. 41 (47) (2000) 9149–9151.
[24] O.A. Phillips, E.E. Udo, S. Samuel, Eur. J. Med. Chem. 43 (2008) 1095–1104.
[25] J.A. Ippolito, Z.F. Kanyo, D. Wang, F.J. Franceschi, P.B. Moore, T.A. Steitz, E.M. Duffy, J. Med. Chem. 51 (2008) 3353–3356.
[26] Calculated log *P* (*C* log *P*) values were computed by using the CS ChemDraw Ultra ver. 8.0.3, September 24, 2003 by CambridgeSoft.Com, Cambridge, MA, USA.
[27] National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically Approved Standard. NCCLS Document M7-A4, fourth ed. National Committee for Clinical Laboratory Standards, Villanova, PA, 1997.