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Original article

Structure–antibacterial activity of arylcarbonyl- and arylsulfonyl-piperazine 5-triazolylmethyl oxazolidinones

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Abstract

A series of novel arylcarbonyl- and arylsulfonyl-piperazinyl 5-triazolylmethyl oxazolidinones were synthesized and tested against a panel of Gram-positive and Gram-negative bacterial clinical isolates. The arylcarbonyl oxazolidinone derivatives showed strong *in vitro* antibacterial activity against susceptible and resistant Gram-positive pathogenic bacteria and were more active than the arylsufonyl derivatives. Substitution of varied electron-withdrawing and electron-donating groups on the phenyl ring in the arylcarbonyl series did not alter antibacterial activity significantly. However, in the arylsufonyl series, methyl substitution on the phenyl ring resulted in the loss of antibacterial activity. Antibacterial activity could not be directly correlated with the calculated partition coefficient (Clog *P*) values in this series of compounds.

Keywords: Antibacterial; Arylcarbonyl; Arylsulfonyl; Linezolid; PH-027; 5-Triazolylmethyl-oxazolidinone

1. Introduction

Despite the advent of new antibiotics, appallingly high level of antibacterial resistance continues to increase in hospital and community settings, thus reducing therapeutic options for patients, with increased health care costs. The alarming rates of emerging and reemerging microbial threats have continued to challenge the public health and scientific communities worldwide. Furthermore, Gram-positive bacteria continue to surface as important pathogens both in hospital- and community-acquired infections; and *Staphylococcus aureus*, *Enterococcus* spp. and coagulase-negative staphylococci have been identified as the first, third and fourth most prevalent bacterial species isolated from inpatient specimens in the USA, respectively [1]. In addition, the rate of isolation of multiple-resistant Gram-positive cocci including methicillin-resistant *S. aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci (MR-CNS), penicillin-resistant *Streptococcus pneumoniea* (PRSP) and vancomycin-resistant enterococcus (VRE) continued to increase [1–4]. These organisms are reported to be resistant to at least three classes of the antibacterial agents commonly used for therapy. The recent reports of the appearance of *S. aureus* with significantly reduced sensitivity to vancomycin [5–7], and the dissemination of other multi-drug resistant Gram-positive bacteria including *Enterococcus* spp. [8] and *Streptococcus* spp. [9], have highlighted the possibility of emergence of serious bacterial infections that may prove impossible to treat with current antibiotics.

Oxazolidinones are novel class of antibacterial agents. Linezolid (Fig. 1) the first and only member of the oxazolidinone class to be approved for clinical use is highly effective against multi-drug resistant Gram-positive bacteria, including staphylococci, streptococci and enterococci. Linezolid has been approved for treating hospital- and community-acquired

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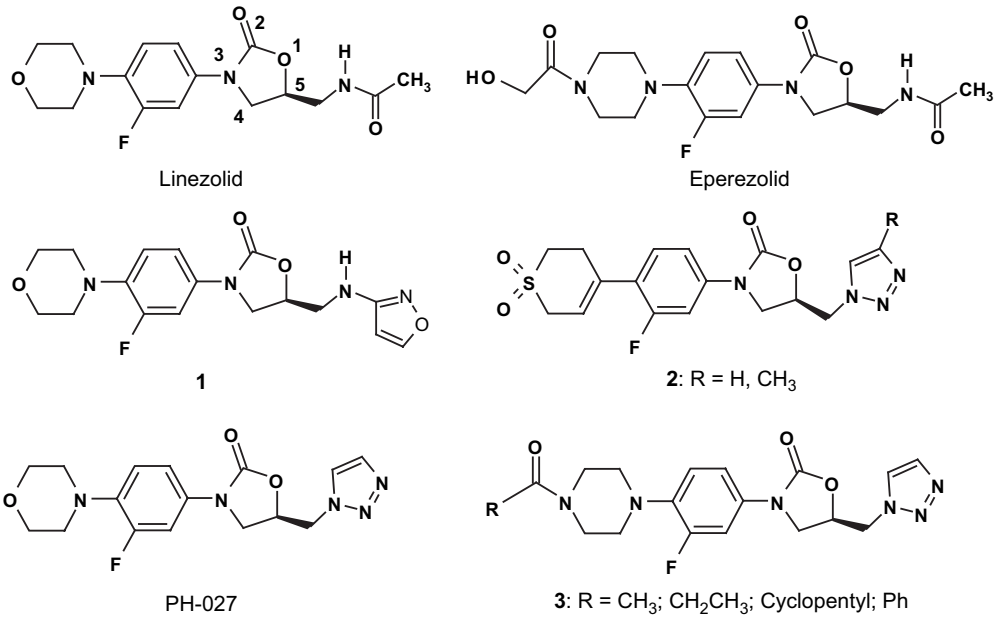


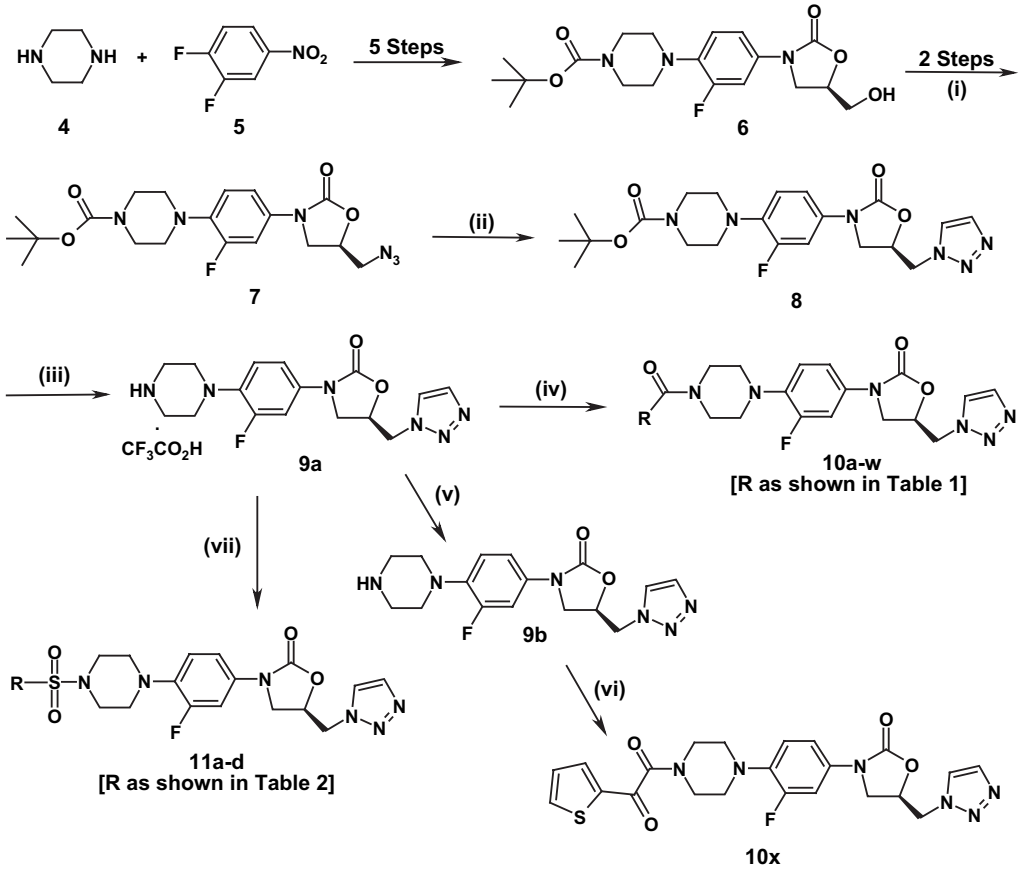
Fig. 1. Structures of antibacterial oxazolidinones.

pneumonia, skin infections and diabetic foot infections caused by Gram-positive bacterial strains [10–12]. It also showed activity against certain Gram-negative pathogens, particularly those associated with community-acquired respiratory tract infections (*Moraxella catarrhalis* and *Haemophilus influenzae*) and some anaerobes [11–13]. Linezolid exhibits a unique mode of action by binding at the P site of the 50S ribosomal subunit without affinity to the 30S subunit [14–16]. The ultimate effect of this binding to 50S is inhibition of the 70S complex formation thus inhibiting protein synthesis. This novel mode of action offers a potential for low cross-resistance with existing antibacterial protein synthesis inhibitors. However, recent reports on emerging linezolid-resistant *S. aureus* [17] and *Enterococcus* spp. [18–20] in hospital isolates are daunting and suggest the pressing need for new, more effective and safer antibacterial agents. These situations continue to serve as impetus for the development of novel and more effective antibacterial agents. Moreover, the suggestion that oxazolidinones impair different ribosomal complexes with varying efficiencies explains the pleiotropic action of this class of compounds and their potent antibacterial action [21], thus making efforts directed at discovery of new and more potent derivatives an attractive undertaking.

Recent reviews of developments in the identification of novel oxazolidinones have highlighted extensive structure–activity relationships that are structurally related to linezolid and eperezolid (Fig. 1). Such modifications include derivatives having the *N*-linked heterocyclic aryl and triazolyl moieties at the C-5 position as in general structures **1** and **2** (Fig. 1) of the oxazolidinone ring [11–13,22]. Furthermore, we recently reported new 5-triazolylmethyl oxazolidinones based on the replacement of the 5-acetamidomethyl substituents with N-linked triazolyl, exemplified by *PH-027* (Fig. 1) [23], and have further shown that the alkyl- and phenylcarbonylpiperazine derivatives **3** (Fig. 1) have improved activity over *PH-027* [24]. In the present communication we report the synthesis and antibacterial activity of hitherto unreported substituted arylcarbonyl- and arylsulfonyl oxazolidinones **10a–x** and **11a–d** having varied aryl-substitutions at the distal piperazine N4 position. The structural variations were selected in order to establish optimal structure–activity requirements for this novel class of 5-triazolylmethyl oxazolidinones and to identify new derivatives with improved antibacterial activity. Attempt was made to correlate antibacterial activity to lipophilicity (calculated as the Clog *P* values) of the compounds.

2. Chemistry

Compounds **10a–x** and **11a–d** were obtained (Scheme 1) from the readily available starting materials piperazine **4** and 3,4-difluoronitrobenzene **5**, from which the alcohol **6** and intermediate azide **7** derivatives were obtained in multi-step reactions in good yield according to published procedures [25]. The azide derivative readily underwent Huisgen's 1,3 dipolar cycloaddition reaction [26] with acetylene in dimethoxyethane (DME) as solvent in a steel bomb at 90 °C, to give the *tert*-butoxycarbonyl protected derivative **8** in excellent yield [24]. This was followed by the deprotection of the *tert*-butoxycarbonyl protecting group on the piperazine nitrogen 4-position using trifluoroacetic acid in CH_2Cl_2 at 0 °C to room temperature to give the key-intermediate triazole **9a** as a trifluoroacetic acid salt (quantitative). Further chemical transformations involving N-acylation and N-sulfonylation of the intermediate salt **9a** with appropriate substituted-aryl acid chlorides or arylsufonyl chlorides in CH_2Cl_2, using triethylamine as an acid scavenger afforded compounds **10a–w** and **11a–d**, respectively (Scheme 1), in moderate to good yields. Treatment of



Scheme 1. Synthesis of arylcarbonyl and arylsulfonyl oxazolidinones (i) TEA, MsCl, CH_2Cl_2/DMF, NaN_3; (ii) acetylene, DME, 90 °C; (iii) TFA, 0 °C–rt, CH_2Cl_2; (iv) TEA, arylcarbonyl chlorides, 0 °C–rt, CH_3CN; (v) $KHCO_3$ aq; (vi) 2-thiophene glyoxalic acid, *N*,*N*-dimethylamino pyridine, Et–N=C=N–$CH_2CH_2CH_2N(CH_3)_2$, pyridine; (vii) TEA, arylsulfonyl chloride, CH_3CN, 0 °C–rt.

salt **9a** with a cold saturated solution of $KHCO_3$ afforded the free base **9b**, which was treated with 2-thiophene glyoxalic acid, *N*,*N*-dimethylamino pyridine and 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride in pyridine to afford compound **10x**. All the compounds were characterized by spectroscopic data (^{1}H NMR, MS and IR), m.p. and CHN analyses.

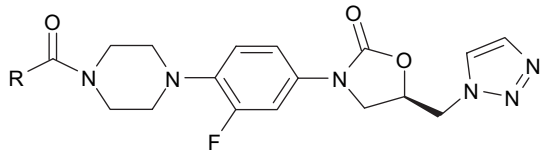
3. Results and discussion

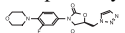
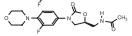
The newly synthesized oxazolidinones were evaluated for antibacterial activity against a panel of standard and clinical isolates of Gram-positive and Gram-negative bacterial strains. In addition, the antibacterial activity of the compounds was also evaluated against standard strain of *S. aureus* ATCC 25923 in the absence and presence of 50% human plasma to estimate potential for both the stability and/or protein binding in plasma. We had previously reported on the activity of the phenyl substituted derivative **10a** and showed that this compound retained activity in the absence and presence of 50% human plasma, suggesting stability and/or lack of protein binding in plasma [24]. In the present study, we investigated the effects of substitution patterns on the phenyl ring and the replacement of the phenyl group with varied heteroaromatic moieties on antibacterial activity. The effect of replacing the arylcarbonyl moiety by arylsulfonyl groups was also investigated. The minimum inhibitory concentrations (MIC's, μg/ml) of the arylcarbonyl and arylsulfonyl oxazolidinones determined by agar dilution method on Mueller–Hinton (MH) agar, and the lipophilicity reported as the calculated apparent partition coefficient (Clog *P*) values are presented in Tables 1 and 2.

In the absence of 50% human plasma, the arylcarbonyl oxazolidinones showed significant antibacterial activity against standard strain of *S. aureus* ATCC 25923 with MIC values in the range of 0.5–2 μg/ml (Table 1). While compounds **10d** (R = 4-ClPh, Clog *P*: 1.40), **10e** (2-FPh, 0.83), **10l** (3-CH_3 Ph, 1.11), **10q** (*E*-cinnamyl, 1.71), **10r** ((*E*)2-chlorocinnamyl, 2.42), **10w** (thiophen-2-yl, 0.39) and **10x** (thiophen-2-ylcarbonyl, 0.21) with MIC's of 0.5 μg/ml, showed a range of 2–4-fold reduction in MIC values in comparison to **10a** (phenyl, 1 μg/ml, Clog *P*: 0.62), PH-027 (1 μg/ml, 0.63), linezolid (2 μg/ml, 0.53) and vancomycin (2 μg/ml). Unfortunately, these derivatives also showed significant increase in MIC values of 4-fold or greater (range of 4 to >16-fold) in the presence of 50% human plasma, which may be attributed to instability or protein binding in plasma [24,27,28].

Furthermore, all the other less active arylcarbonyl oxazolidinones also displayed a range of 2–8-fold increase in MIC values in the presence of 50% plasma, with the exception of

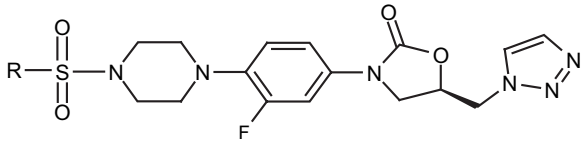
Table 1
Comparative MIC (μg/ml) and Clog *P* values of arylcarbonyl oxazolidinones against Gram-positive standard strains and clinical isolates

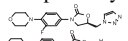
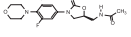


Compound	−R	Minimum inhibitory concentrations (MIC, μg/ml) against[a]									
		Clog *P*	*S. aureus*[b]		MSSA ($n=11$)	MRSA ($n=10$)	MS-CNS ($n=8$)	MR-CNS ($n=3$)	S. pn ($n=6$)	VSE ($n=7$)	VRE ($n=4$)
			No plasma[c]	+50% plasma[c]							
10a	Ph[d]	0.62	1	1	0.25−1	0.25−1	0.25−1	0.25	1−2	0.25−0.5	0.25
10b	$PhCH_2$	2.53	2	4	0.5−2	0.5−2	0.5−2	0.5−2	0.5−1	0.5−1	1−2
10c	2-ClPh	1.40	1	8	0.5−1	0.5−1	0.5−1	0.5−1	4	0.5−1	0.5
10d	4-ClPh	1.40	0.5	8	0.25−1	0.25−0.5	0.12−0.5	0.12−0.5	1−2	0.5	0.5
10e	2-FPh	0.83	0.5	8	0.25−1	0.25−1	0.25−0.5	0.25−0.5	1	0.5	0.5
10f	3-FPh	0.83	1	4	0.25−1	0.25−1	0.5−1	0.5−1	0.5−1	0.5−1	0.5
10g	4-FPh	0.83	1	4	0.5−1	0.5−1	0.5−1	0.5−1	0.5−1	1	0.5−1
10h	2-NO_2Ph	0.52	2	2	1−2	0.5−1	1−2	1−2	0.5−1	2	1−2
10i	3-NO_2Ph	0.52	2	2	0.25−2	0.25−0.5	0.5−2	0.25−1	0.25−0.5	0.5−1	0.5
10j	4-NO_2Ph	0.52	2	4	2	1−2	1−2	1−2	1−2	2	2
10k	2-CH_3Ph	1.11	2	8	0.5−2	0.5−2	0.5−2	0.5−1	1−2	1−2	1
10l	3-CH_3Ph	1.11	0.5	8	0.25−0.5	0.25−0.5	0.25−0.5	0.25−0.5	1	0.5	0.5
10m	4-CH_3Ph	1.11	1	8	0.5−2	0.5−1	0.5−1	0.5−1	2	1−2	0.5
10n	2-CH_3OPh	0.84	1	4	0.5−1	1	0.25−1	0.25−1	1	1	1
10o	3-CH_3OPh	0.84	2	4	0.25−2	0.25−0.5	0.25−2	0.25−1	0.25−0.5	0.5−1	0.5−1
10p	4-CH_3OPh	0.84	2	8	1−2	0.5−1	0.5−2	1−2	0.5−1	1	1
10q	*E*-PhCH═CH−	1.71	0.5	>8	0.25−0.5	0.25−0.5	0.25−0.5	0.25−0.5	1	0.5	0.25−.5
10r	*E*-2-ClPhCH═CH−	2.42	0.5	>8	0.25−0.5	0.25−0.5	0.25−0.5	0.25−0.5	4	0.5	0.25
10s	Pyridin-3-yl	−0.49	1	4	0.5−2	0.5−2	0.5−1	0.5−1	0.5−1	1	0.5−1
10t	Pyridin-4-yl	−0.49	1	8	0.5−1	0.5−1	0.25−1	0.5−1	1	1	0.5−1
10u	2-Cl-Pyridin-3-yl	0.26	2	4	0.5−2	0.5−2	0.5−2	0.5−1	1−2	1	1
10v	Furan-2-yl	−0.21	1	4	0.5−1	0.5−1	0.25−1	0.25−0.5	0.25−0.5	0.5	0.5
10w	Thiophen-2-yl	0.39	0.5	4	0.5−1	0.5−1	0.25−1	0.25−0.5	0.25−0.5	0.5	0.5
10x	Thiophen-2-ylcarbonyl	0.21	0.5	2	0.25−0.5	0.25−0.5	0.25−0.5	0.25−0.5	0.25−0.5	0.5	0.25−0.5
PH-027		0.63	1	1	0.5−1	0.5−1	0.5−1	0.5−1	0.5−1	0.5−1	1
Lzd		0.53 (0.55)[e]	2	2	1−2	0.5−2	0.25−2	1−2	0.5	0.5−2	2
Van		n/d	2	2	1−2	0.5−1	1−2	1	0.5	0.25−2	>64

[a] All compounds showed moderate to lack of activity against *H. influenzae*, *M. catarrhalis* and *E. coli*. (MIC ≥ 8 μg/ml).
[b] ATCC 25923 strain.
[c] Human plasma.
[d] Ref. [24].
[e] Pharmacia UpJohn, Material Safety Data Sheet for Linezolid (2000).

Table 2
Comparative MIC (μg/ml) and Clog *P* values of arylsulfonyl oxazolidinones against Gram-positive standard strains and clinical isolates



Compound	Minimum inhibitory concentrations (MIC's, μg/ml) against[a]										
	−R	Log P_{App}	*S. aureus*[b]		MSSA ($n=11$)	MRSA ($n=10$)	MS-CNS ($n=8$)	MR-CNS ($n=3$)	S. pn ($n=6$)	VSE ($n=7$)	VRE ($n=4$)
			No plasma[c]	+50% plasma[c]							
11a	Ph	1.34	2	8	0.5–2	0.5–2	0.5–2	0.5–1	1–2	2	0.5–2
11b	3-CH_3Ph	1.84	>8	>8	4[a]–>8	2[b]–>8	2[c]–>8	2[d]–>8	2	>8	>8
11c	4-CH_3Ph	1.84	>8	>8	>8	>8	>8	>8	2–8	>8	>8
11d	Thiophen-2-yl	1.07	1	>8	0.5–1	0.5–1	0.5–1	0.5	1–2	0.5–1	0.5–1
PH-027		0.63	1	1	0.5–1	0.5–1	0.5–1	0.5–1	0.5–1	0.5–1	1
Lzd		0.53 (0.55)[d]	2	2	1–2	0.5–2	0.25–2	1–2	0.5	0.5–2	2
Van		n/d	2	2	1–2	0.5–1	1–2	1	0.5	0.25–2	>64

[a] All compounds showed moderate to lack of activity against *H. influenzae*, *M. catarrhalis* and *E. coli* (MIC ≥ 8 μg/ml).
[b] ATCC 25923 strain.
[c] Human plasma.
[d] Pharmacia UpJohn, Material Safety Data Sheet for Linezolid (2000).

the nitrophenyl derivatives **10h** (R = 2-NO_2Ph) and **10i** (3-NO_2Ph) with Clog *P* values of 0.52. These nitro compounds retained antibacterial activity with MIC value of 2 μg/ml in absence and presence of 50% human plasma. In the arylcarbonyl series, the increase in MIC in the presence of human plasma seems to correlate more closely to the lipophilicity (Clog *P* values) rather than the potential for activation or deactivation of the amide carbonyl group of the *N*-4-acylpiperazine moiety by electron-withdrawing or electron-donating substituents on the aryl ring, which may facilitate or decrease amide bond hydrolysis.

In the absence of human plasma, only the arylsulfonyl derivatives **11a** (R = Ph, Clog *P*: 1.34) and **11d** (thiophen-2-yl, 1.07) showed comparable activity to PH-027, linezolid and vancomycin, with MIC values of 1, 2 and 2 μg/ml, respectively. In this series, it became obvious from the data that 3-methyl and 4-methyl substitution patterns on the phenyl ring, respectively, resulted in the loss of antibacterial activity, indicating lack of tolerability of such group at the receptor site. Antibacterial activity of the arylsulfonyl derivatives was consistently reduced in the presence of 50% human plasma with a 4-fold or greater increase in MIC values (Table 2) suggesting a potential lack of *in vivo* activity for such compounds.

The antibacterial activity of the compounds evaluated on a broader panel of susceptible and resistant clinical isolates from hospitals in Kuwait is also presented (Tables 1 and 2). Most of the arylcarbonyl derivatives demonstrated strong antibacterial activity with MIC range of 0.12–4 μg/ml (Table 1) superior to the arylsulfonyl derivative's MIC range from 0.5 to >8 μg/ml (Table 2) against all Gram-positive bacterial strains tested. Against certain MSSA, MRSA, MS-CNS and MR-CNS strains some of the substituted arylcarbonyl oxazolidinones (MIC range 0.12–2 μg/ml) showed somewhat superior antibacterial activity than the previously reported [24] unsubstituted-phenyl derivative **10a** (0.25–1 μg/ml), PH-027 (0.5–1 μg/ml), linezolid (0.5–2 μg/ml) and vancomycin (0.5–2 μg/ml). Interestingly, substitution on the phenyl ring with 2-nitro **10h** and 4-nitro **10j** (MIC range 1–2 μg/ml) substituents elicited slightly inferior antibacterial activity than compound **10a** against all staphylococcal strains tested. However, substitution with the 4-chloro **10d** (MIC range 0.12–0.5 μg/ml) and 3-methyl **10l** (MIC range 0.25–0.5 μg/ml) on the phenyl ring, representing electron-withdrawing and electron-donating groups, respectively, showed superior activity than PH-027, linezolid and vancomycin. In addition, replacing the phenyl group with more lipophilic groups such as (*E*)-cinnamyl **10q** (Clog *P*: 1.71) and (*E*)-2-chlorocinnamyl **10r** (Clog *P*: 2.42) moieties, respectively, resulted in compounds with improved antibacterial activity (MIC range 0.25–0.5 μg/ml) over the reference agents against sensitive and resistant staphylococci. A similar enhancement of antibacterial activity due to the presence of a cinnamoyl group on the distant nitrogen atom of 5-acetamidomethyl piperazinyl phenyloxazolidinone derivatives has been observed [29].

The replacement of the aryl group with furan-2-yl **10v**, thiophen-2-yl **10w**, and thiophen-2-ylcarbonyl **10x**, also resulted in superior activity than PH-027, linezolid and vancomycin against *S. pneumoniae* strains. Furthermore, substitution with 3-nitrophenyl **10i** and 3-methoxyphenyl **10o** also gave compounds with superior activity (MIC range 0.25–0.5 μg/ml) than reference antibacterial agents against similar strains. While some of the arylcarbonyl oxazolidinones including the 2-chlorophenyl **10c**, 4-methylphenyl **10m**, (*E*)-2-chlorocinnamyl **10r** derivatives, resulted in antibacterial activity (MIC range 2–4 μg/ml) inferior to reference agents (MIC range 0.25–2 μg/ml) and other derivatives in this series. Against vancomycin-sensitive (VSE) and -resistant enterococci (VRE) strains, the arylcarbonyl derivatives displayed

antibacterial activity comparable or superior to linezolid and vancomycin (Table 1).

Although only a limited number of compounds were synthesized in the arylsulfonyl series, the phenylsulfonyl **11a** (Clog *P*: 1.34) and thiophen-2-ylsulfonyl **11d** (Clog *P*: 1.07) derivatives showed activity comparable or superior to PH-027, linezolid and vancomycin against all bacterial strains tested (Table 2).

On the other hand, the 3-methylphenylsulfonyl derivative **11b** was active against *S. pneumoniea* (MIC = 2 μg/ml), but showed moderate to lack of activity against staphylococcal strains and was inactive against enterococci (MIC > 8 μg/ml). Similarly, the 4-methylphenyl derivative **11c** was only moderately active against *S. pneumoniae* (MIC range 2–8 μg/ml), and devoid of activity against other strains tested. Moreover, the compounds in this series were generally not active in the presence of 50% human plasma, indicating a potential lack of effectiveness *in vivo*, probably due to inactivation or protein binding in plasma.

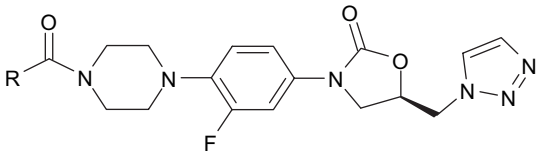
The cumulative percents for specific MIC values of the newly synthesized compounds against a panel of staphylococcal clinical isolates ($n = 32$) are presented in Tables 3 and 4. From these data, the arylcarbonyl oxazolidinones **10d** (R = 4-ClPh), **10e** (2-FPh), **10l** (3-CH_3Ph), **10q** (*E*-cinnamyl), **10r** (*E*-2-chlorocinnamyl) and **10w** (thiophen-2-yl), inhibited between 91 and 100% of the strains at MIC value 0.5 μg/ml. On the contrary, PH-027, linezolid and vancomycin inhibited only 34, 13 and 22% of the staphylococcal strains at the same MIC value. Moreover, most of the compounds in this series inhibited between 66 and 100% of the staphylococcal strains at MIC value 1 μg/ml, with the exception of the nitrophenyl derivatives **10h** (R = 2-NO_2Ph) and **10j** (4-NO_2Ph) with inhibition percentages of only 44 and 13, respectively (Table 3). In general, the 4-nitrophenyl derivative appears to be the least active in this series.

In comparison, the arylsulfonyl oxazolidinones were significantly less active than the arylcarbonyl derivatives, with the exception of the thiophen-2-ylsulfonyl derivative **11d** showing 100% inhibition of staphylococcal growth at MIC value of 1 μg/ml (Table 4). However, the phenylsulfonyl derivative **11a** inhibited 100% of the strains at 2 μg/ml, while the corresponding tolylsulfonyl derivatives were inactive, exhibiting 100% inhibition only at MIC values > 8 μg/ml, which is way above the breakpoint for this class of compounds typified by linezolid (MIC ≤ 4 μg/ml) [30].

4. Conclusion

In conclusion, most of the arylcarbonyl oxazolidinones demonstrated excellent *in vitro* antibacterial activity comparable or superior to reference agents, namely, PH-027, linezolid and vancomycin. Furthermore, substitution with electron-withdrawing or electron-donating groups on varying positions of the phenyl ring did not alter the antibacterial activity significantly. In addition, replacing the phenyl group with heteroaryl moieties such as the furan-2-yl, pyridinyl and thiophen-2yl was shown to be well tolerated with the retention and/or enhancement of antibacterial activity. In general, most of the arylcarbonyl derivatives exhibited a 4-fold or greater increase in MIC values in the presence of 50% human plasma, with the exception of phenyl **10a** [24], benzyl **10b**, 2-nitrophenyl

Table 3
MIC (μg/ml) values of arylcarbonyl oxazolidinones against clinical isolates of staphylococci



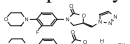
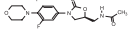
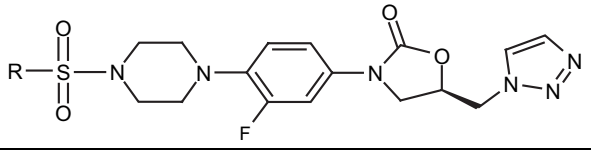
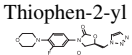
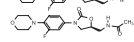
Compound	Cumulative percent of staphylococci isolates ($n = 32$) with specific MIC (μg/ml)					
	−R	0.12	0.25	0.5	1	2
10a	Ph	0	53	88	100	100
10b	$PhCH_2$	0	0	38	75	100
10c	2-ClPh	0	0	44	100	100
10d	4-ClPh	13	44	97	100	100
10e	2-FPh	6	38	91	100	100
10f	3-FPh	0	13	63	100	100
10g	4-FPh	0	0	28	100	100
10h	2-NO_2Ph	0	0	0	44	100
10i	3-NO_2Ph	0	28	41	84	100
10j	4-NO_2Ph	0	0	0	13	100
10k	2-CH_3Ph	0	0	19	66	100
10l	3-CH_3Ph	0	34	100	100	100
10m	4-CH_3Ph	0	0	34	94	100
10n	2-CH_3OPh	0	19	34	94	100
10o	3-CH_3OPh	0	19	28	81	100
10p	4-CH_3OPh	0	0	6	66	100
10q	*E*-PhCH=CH−	0	25	100	100	100
10r	*E*-2-ClPhCH=CH−	0	44	100	100	100
10s	Pyridin-3-yl	0	0	50	94	100
10t	Pyridin-4-yl	0	3	59	100	100
10u	2-Cl-Pyridin-3-yl	0	0	22	66	100
10v	Furan-2-yl	-	13	72	100	100
10w	Thiophen-2-yl	3	16	100	100	100
10x	Thiophen-2-ylcarbonyl	0	22	78	100	100
PH-027		0	0	34	100	100
Lzd		0	6	13	81	100
Van		0	0	22	97	100

Table 4
MIC (μg/ml) values of arylsulfonyl oxazolidinones against clinical isolates of staphylococci



Compound	Cumulative percent of staphylococci ($n = 32$) isolates with specific MIC (μg/ml)							
	−R	0.12	0.25	0.5	1	2	4	>8
11a	Ph	0	0	22	63	100	100	100
11b	3-CH_3−Ph	0	0	0	0	9	22	100
11c	4-CH_3−Ph	0	0	0	0	0	0	100
11d	Thiophen-2-yl	0	0	59	100	100	100	100
PH-027		0	0	34	100	100	100	100
Lzd		0	6	13	81	100	100	100
Van		0	0	22	97	100	100	100

10h, 3-nitrophenyl **10i**, 4-nitrophenyl **10j** and 3-methoxyphenyl **10o**, 2-Cl-pyridin-3-yl **10u**, derivatives with only a 2-fold or less increase. While the arylsulfonyl oxazolidinones demonstrated antibacterial activity inferior to the arylcarbonyl oxazolidinones and reference agents. Compounds in the arylsulfonyl series also elicited significant loss of antibacterial activity in presence of 50% human plasma. Finally, the modification of the distal piperazine nitrogen by substitution with arylcarbonyl and arylsulfonyl resulted in new 5-triazolylmethyl oxazolidinones with strong antibacterial activity against susceptible and resistant Gram-positive pathogenic bacteria. None of the compounds reported in this study displayed any noticeable significant activity against standard and clinical isolates of Gram-negative organisms including *H. influenzae*, *M. catarrhalis* and *E. coli* (MIC values ≥ 8 μg/ml).

5. Experimental

Melting points were determined on a Stuart Scientific SMP1 melting point apparatus and are uncorrected. Science Analytical Facilities (SAF), Faculty of Science, Kuwait University, performed all the instrumental analyses. Elemental analyses were determined on LECO elemental analyzer CHNS 932 apparatus, and were within ±0.4% of the calculated values. The ^{1}H NMR spectra were recorded on Bruker DPX 400 NMR spectrometer using DMSO-d_6 as solvent and tetramethylsilane (TMS) as an internal reference, and chemical shifts were reported in parts per million. Mass spectra were measured on a Finnigan MAT INCOS XL mass spectrometer. Infrared (IR) spectra were recorded on Perkin Elmer System 2000 FT-IR spectrometer. 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). All extracted solvents were dried over Na_2SO_4, followed by evaporation *in vacuo*. The lipophilicity as the calculated partition coefficient (Clog *P*) values (Tables 1 and 2) were estimated by using the CS ChemDraw Ultra version 8.0.3, computer software by CambridgeSoft. Com (www.cambridgesoft.com) [31].

5.1. Syntheses

5.1.1. General procedure for the arylcarbonyl oxazolidinones *10a–w*

A solution of 5-((1*H*-1,2,3-triazol-1-yl)methyl)-3-(3-fluoro-4-(piperazinium-1-yl) phenyl)oxazolidin-2-one trifluoroacetic acid salt **9a** (1.00 g, 2.17 mmol) in acetonitrile (10 ml) cooled to 0 °C was treated with triethylamine (1 ml) and an appropriate arylcarbonyl chloride (3.26 mmol) and stirred to room temperature overnight. Dichloromethane (20 ml) was added to the reaction mixture and the solution was washed with water (3 × 10 ml). The organic layer was washed with brine, dried (anhydrous Na_2SO_4), filtered and concentrated to give a solid, which was triturated in ether to give a solid. The crude solid was recrystallized in appropriate solvent systems to give the products.

5.1.1.1. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(2-phenylacetyl)piperazin-1-yl)phenyl)oxazolidin-2-one *10b*.

Recrystallization (CH_3CN) afforded **10b** as a crystalline solid (397 mg, 39% yield), m.p. 173–174 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.18 (s, 1H, triazole H), 7.77 (s, 1H, triazole H), 7.42 (dd, 1H, $J = 2.0$ Hz, 15.0 Hz, phenyl H), 7.30–7.34 (m, 2H, phenyl H), 7.22–7.26 (m, 3H, phenyl H), 7. 12 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz, phenyl H), 7.03 (t, 1H, $J = 9.0$ Hz, phenyl H), 5.12 (m, 1H, CH_2CHCH_2–N–N=N), 4.83 (d, 2H, $J = 5.0$ Hz, CH_2CHCH_2–N–N=N), 4.20 (t, 1H, $J = 9.0$ Hz, $CHCHCH_2$–N–N=N), 3.86 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz, $CHCHCH_2$–N–N=N), 3.77 (s, 2H), 3. 64 (s, 4H, piperazine H), 2.91–2.87 (m, 4H, piperazine H). IR (KBr pellet, cm^{-1}): ν 2825, 1739, 1629, 1521, 1443, 1420, 1326, 1280, 1223. MS 464 (M^+). Anal calcd for $C_{24}H_{25}FN_6O_4$: C: 62.06, H: 5.42, N: 18.09. Found C: 61.73, H: 5.25, N: 17.88.

5.1.1.2. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(4-(4-(2-chlorobenzoyl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one *10c*.

Recrystallization (CH_3CN) gave a white solid 63% yield, m.p. 207–209 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (s, 1H), 7.77 (s, 1H), 7.40–7.56 (m, 5H), 7.14 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.08 (t, 1H, $J = 9.0$ Hz), 5.12 (m, 1H), 4.83 (d, 2H, $J = 5.0$ Hz), 4.20 (t, 1H, $J = 9.0$ Hz), 3.86 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.80–3.82 (m, 2H), 3.28 (t, 2H, $J = 5.0$ Hz, overlaps partly with D_2O signal at 3.33), 3.05 (m, 2H), 2.93 (d, 2H, $J = 4.0$ Hz). IR (KBr pellet, cm^{-1}): ν 2940, 2678, 1741, 1644, 1574, 1524, 1484, 1422, 1385, 1325, 1284, 1222. Anal calcd for $C_{23}H_{22}ClFN_6O_3$: C: 56.96, H: 4.57, H: 17.33. Found C: 57.21, H: 4.60, N: 17.34.

5.1.1.3. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(4-(4-(4-chlorobenzoyl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one *10d*.

Recrystallization (CH_3CN–CH_2Cl_2–EtOAc) gave **10d** as a beige crystalline solid (371 mg, 44% yield), m.p. 187–188 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.16 (s, 1H), 7.77 (s, 1H), 7.53 (d, 2H, $J = 8.0$ Hz), 7.47 (d, 2H, $J = 8.0$ Hz), 7.41 (dd, 1H, $J = 2.0$ Hz, 15.0 Hz), 7.13 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.07 (t, 1H, $J = 9.0$ Hz), 5.12 (m, 1H), 4.82 (d, 2H, $J = 5.0$ Hz), 4.21 (t, 1H, $J = 9.0$ Hz), 3.86 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.77 (br s, 2H), 3.42 (br s, 2H, overlaps partly with D_2O signal), 2.99 (br d, 4H). IR (KBr pellet, cm^{-1}): ν 2978, 2834, 1746, 1616, 1574, 1414, 1325, 1283, 1264, 1224. Anal calcd for $C_{23}H_{22}ClFN_6O_3$: C: 56.96, H: 4.57, N: 17.33. Found C: 57.22, H: 4.50, N: 17.23.

5.1.1.4. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(2-fluorobenzoyl)piperazin-1-yl)phenyl)oxazolidin-2-one *10e*.

Recrystallization (CH_3CN–EtOAc) gave **10e** as an off-white fluffy solid (617 mg, 61% yield), m.p. 189–191 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.15 (s, 1H), 7.77 (s, 1H), 7.55–7.50 (m, 1H), 7.40–7.47 (m, 2H), 7.29–7.35 (m, 2H), 7.13 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.08 (t, 1H, $J = 9.0$ Hz), 5.12 (m, 1H), 4.83 (d, 2H, $J = 5.0$ Hz), 4.20 (t, 1H, $J = 9.0$ Hz), 3.86 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.80 (t, 4H, $J = 5.0$ Hz), 3.04 (t, 2H, $J = 5.0$ Hz), 2.93 (t, 2H, $J = 5.0$ Hz). IR (KBr pellet, cm^{-1}): ν 3102, 2829, 1741,

1648, 1523, 1490, 1421, 1325, 1223, 1194, 1163, 1105, 1084. MS 468.91 (M+1). Anal calcd for $C_{23}H_{22}F_2N_6O_3$: C: 58.96, H: 4.73, N: 18.10. Found C: 59.05, H: 4.71, N: 17.94.

5.1.1.5. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(3-fluorobenzoyl)piperazin-1-yl)phenyl)oxazolidin-2-one ***10f***. Recrystallization (CH_3CN–EtOAc) afforded **10f** as a crystalline solid (600 mg, 59% yield), m.p. 183–185 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (s, 1H), 7.77 (s, 1H), 7.50–7.55 (m, 1H), 7.42 (dd, 1H, $J = 2.0$ Hz, 15.0 Hz), 7.22–7.34 (m, 3H), 7.13 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.08 (t, 1H, $J = 9.0$ Hz), 5.12 (m, 1H), 4.83 (d, 2H, $J = 5.0$ Hz), 4.21 (t, 1H, $J = 9.0$ Hz), 3.86 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.78 (br s, 2H), 3.51 (br s, 2H), 3.04 (br s, 2H), 2.95 (br s, 2H). IR (KBr pellet, cm^{-1}): ν 2847, 1742, 1622, 1583, 1572, 1416, 1325, 1283, 1225, 1165, 1111, 1071. MS 468.91 (M+1). Anal calcd for $C_{23}H_{22}F_2N_6O_3$: C: 58.97, H: 4.73, N: 18.10. Found C: 59.08, H: 4.64, N: 17.94.

5.1.1.6. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(4-fluorobenzoyl)piperazin-1-yl)phenyl)oxazolidin-2-one ***10g***. Recrystallization (CH_3CN–EtOAc) gave compound **10g** as a crystalline solid (617 mg, 61% yield), m.p. 193–194 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (s, 1H), 7.77 (s, 1H), 7.50–7.53 (m, 2H), 7.42 (dd, 1H, $J = 2.0$ Hz, 15.0 Hz), 7.28–7.30 (t, 2H, $J = 9.0$ Hz), 7.13 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.07 (t, 1H, $J = 9.0$ Hz), 5.12 (m, 1H), 4.83 (d, 2H, $J = 5.0$ Hz), 4.21 (t, 1H, $J = 9.0$ Hz), 3.86 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.76 (br s, 2H), 3.48 (br s, 2H), 2.99 (br s, 4H). IR (KBr pellet, cm^{-1}): ν 2897, 1744, 1634, 1515, 1460, 1439, 1416, 1333, 1285, 1266, 1221, 1200, 1157, 1099. Anal calcd for $C_{23}H_{22}F_2N_6O_3$: C: 58.97, H: 4.73, N: 18.10. Found C: 59.20, H: 4.58, N: 17.99.

5.1.1.7. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(2-nitrobenzoyl)piperazin-1-yl)phenyl)oxazolidin-2-one ***10h***. Recrystallization (CH_3CN) gave compound **10h** as a crystalline solid (409 mg, 38% yield), m.p. 207–208 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.23 (d, 1H, $J = 8.0$ Hz), 8.17 (s, 1H), 7.88 (t, 1H, $J = 7.0$ Hz), 7.77 (s, 1H), 7.87 (t, 1H, $J = 8.0$ Hz), 7.60 (d, 1H, 7.5), 7.43 (dd, 1H, $J = 2.0$ Hz, 15.0 Hz), 7.14 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.09 (t, 1H, $J = 9.0$ Hz), 5.13 (m, 1H), 4.83 (d, 2H, $J = 5.0$ Hz), 4.23 (t, 1H. $J = 9.0$ Hz), 3.86 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.81 (br s, 2H), 3.36 (br s, 2H, overlaps with D_2O signal), 3.08 (br s, 2H), 2.93 (br s, 2H). IR (KBr pellet, cm^{-1}): ν 2905, 2843, 1750, 1633, 1524, 1422, 1349, 1283, 1217. MS 495 (M^+). Anal calcd for $C_{23}H_{22}FN_7O_5$: C: 55.70, H: 4.48, N: 19.79. Found C: 55.39, H: 4.29, N: 19.70.

5.1.1.8. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(3-nitrobenzoyl)piperazin-1-yl)phenyl)oxazolidin-2-one ***10i***. Recrystallization (CH_3CN) gave compound **10i** as a crystalline solid (218 mg, 21% yield), m.p. 171–173 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.34–8.31 (m, 1H), 8.26 (br s, 1H), 8.17 (s, 1H), 7.91 (d, 1H, $J = 8.0$ Hz), 7.77 (s, 2H, overlaps with the aryl hydrogen), 7.75–7.79 (m, 1H, overlaps with triazole hydrogen), 7.43 (dd, 1H, $J = 2.2$ Hz, 15.0 Hz), 7.14 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.08 (t, 1H, $J = 9.0$ Hz), 5.12 (m, 1H), 4.83 (d, 2H, $J = 5.0$ Hz), 4.21 (t, 1H, $J = 9.0$ Hz), 3.86 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.81 (br s, 2H), 3.48 (br s, 2H), 3.02 (br d, 4H). IR (KBr pellet, cm^{-1}): ν 2838, 1737, 1633, 1529, 1488, 1439, 1419, 1349, 1288, 1220. MS 495 (M^+). Anal calcd for $C_{23}H_{22}FN_7O_5$: C: 55.70, H: 4.48, N: 19.79. Found C: 55.49, H: 4.26, N: 19.71.

5.1.1.9. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(4-nitrobenzoyl)piperazin-1-yl) phenyl)oxazolidin-2-one ***10j***. Recrystallization (CH_3CN) gave **10j** as a crystalline solid (472 mg, 46% yield), m.p. 177–178 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.31 (d, 2H, $J = 8.0$ Hz), 8.17 (s, 1H), 7.74 (t, 2H + 1H overlaps with the aryl hydrogen), 7.42 (d, 1H, $J = 2.0$ Hz, 15.0 Hz), 7.14 (d, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.07 (t, 1H, $J = 9.0$ Hz), 5.12 (m, 1H), 4.83 (d, 2H, $J = 5.0$ Hz), 4.21 (t, 1H, $J = 9.0$ Hz), 3.81–3.88 (m, 2H + 1H, 2H from piperazine ring overlaps,), 3.39 (br s, 2H), 2.96–3.08 (br d, 4H). IR (KBr pellet, cm^{-1}): ν 2848, 1755, 1629, 1599, 1518, 1489, 1449, 1435, 1412, 1394, 1351, 1333, 1284, 1239, 1224, 1153, 1132, 1116, 1077, 1041, 1020. MS 480 (M^+). Anal calcd for $C_{23}H_{22}FN_7O_5$: C: 55.70, H: 4.48, N: 19.79. Found C: 55.80, H: 4.77, N: 19.98.

5.1.1.10. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(2-methylbenzoyl) piperazin-1-yl)phenyl)oxazolidin-2-one ***10k***. Recrystallization (CH_3CN–EtOAc) gave **10k** as a crystalline solid (646 mg, 64% yield), m.p. 213–214 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (s, 1H), 7.77 (s, 1H), 7.42 (dd, 1H, $J = 2.0$ Hz, 15.0 Hz), 7.20–7.34 (m, 4H), 7.13 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.08 (t, 1H, $J = 9.0$ Hz), 5.12 (m, 1H), 4.83 (d, 2H, $J = 5.0$ Hz), 4.20 (t, 1H, $J = 9.0$ Hz), 3.86 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.82 (br t, 2H, $J = 5.0$ Hz), 3.28 (br t, 2H, $J = 5.0$ Hz), 3.04 (br s, 2H), 2.89 (br s, 4H), 2.25 (s, 3H). IR (KBr pellet, cm^{-1}): ν 3110, 2847, 1741, 1634, 1522, 1489, 1420, 1324, 1282, 1223, 1162, 1107, 1013. Anal calcd for $C_{24}H_{25}FN_6O_3$: C: 62.06, H: 5.43, N: 18.10. Found C: 62.23, H: 5.26, N: 18.16.

5.1.1.11. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(3-methylbenzoyl) piperazin-1-yl)phenyl)oxazolidin-2-one ***10l***. Recrystallization (CH_3CN–EtOAc) gave **10l** as a crystalline solid (477 mg, 47% yield), m.p. 161–162 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (s, 1H), 7.77 (s, 1H), 7.42 (dd, 1H, $J = 2.0$ Hz, 15.0 Hz), 7.35 (t, 1H, $J = 8.0$ Hz), 7.28 (d, 1H, $J = 8.0$ Hz), 7.22 (t, 2H, $J = 8.0$ Hz), 7.13 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.08 (t, 1H, $J = 9.0$ Hz), 5.12 (m, 1H), 4.83 (d, 2H, $J = 5.0$ Hz), 4.20 (t, 1H, $J = 9.0$ Hz), 3. 86 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.77 (br s, 2H), 3.48 (br s, 2H), 2.98 (br d, 4H), 2.35 (s, 3H). IR (KBr pellet, cm^{-1}): ν 3212, 2843, 1743, 1625, 1527, 1491, 1441, 1417, 1325, 1282, 1220, 1163, 1114, 1078. Anal calcd for $C_{24}H_{25}FN_6O_3$: C: 62.06, H: 5.43, N: 18.10. Found C: 62.20, H: 5.46, N: 18.13.

5.1.1.12. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(4-methylbenzoyl) piperazin-1-yl)phenyl)oxazolidin-2-one ***10m***. Recrystallization (CH_3CN–EtOAc) gave **10m** as

a crystalline solid (535.3 mg, 53% yield), m.p. 189–191 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.16 (s, 1H), 7.77 (s, 1H), 7.41 (dd, 1H, $J = 2.0$ Hz, 15.0 Hz), 7.33 (d, 2H, $J = 8.0$ Hz), 7.27 (d, 2H, $J = 8.0$ Hz), 7.11 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.09 (t, 1H, $J = 9.0$ Hz), 5.12 (m, 1H), 4.82 (d, 2H, $J = 5.0$ Hz), 4.20 (t, 1H, $J = 9.0$ Hz), 3.85 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.74 (br s, 2H), 3.53 (br s, 2H), 2.97 (br s, 4H), 2.34 (s, 3H). IR (KBr pellet, cm^{-1}): ν 3828, 1748, 1612, 1570, 1516, 1435, 1412, 1323, 1284, 1263, 1224, 1193, 1159, 1112, 1075. Anal calcd for $C_{24}H_{25}FN_6O_3$: C: 62.06, H: 5.43, N: 18.10. Found C: 62.24, H: 5.30, N: 18.17.

5.1.1.13. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(2-methoxybenzoyl) piperazin-1-yl)phenyl)oxazolidin-2-one ***10n***. Recrystallization (CH_3CN) gave **10n** as a crystalline solid (434 mg, 42% yield), m.p. 214–215 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (s, 1H), 7.77 (s, 1H), 7.42 (dd, 2H, $J = 7.0$ Hz), 7.22 (dd, 1H, $J = 8.0$ Hz), 7.05–7.14 (m, 3H), 5.12 (m, 1H), 4.83 (d, 2H, $J = 5.0$ Hz), 4.21 (t, 1H, $J = 9.0$ Hz), 3.86 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.75–3.81 (m, 5H), 3.27 (s, 2H), 3.01 (s, 2H), 2.89 (t, 2H, $J = 6.0$ Hz). IR (KBr pellet, cm^{-1}): ν 2844, 1755, 1629, 1598, 1518, 1434, 1412, 1350, 1284, 1238, 1116, 1019. MS 480 (M^+). Anal calcd for $C_{24}H_{25}FN_6O_4$: C: 59.98, H: 5.24, N: 17.49. Found C: 59.58, H: 5.03, N: 17.43.

5.1.1.14. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(3-methoxybenzoyl) piperazin-1-yl)phenyl)oxazolidin-2-one ***10o***. Recrystallization (CH_3CN) gave **10o** as a crystalline solid (473 mg, 45% yield), m.p. 180–182 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (s, 1H), 7.77 (s, 1H), 7.42 (dd, 1H, $J = 2.0$ Hz, 15.0 Hz), 7.37 (t, 1H, $J = 8.0$ Hz), 6.97–7.15 (m, 5H), 5.12 (m, 1H), 4.83 (d, 2H, $J = 5.0$ Hz), 4.21 (t, 1H, $J = 9.0$ Hz), 3.86 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.79 (br s, 5H), 3.48 (br s, 2H), 2.99 (br d, 4H). IR (KBr pellet, cm^{-1}): ν 2839, 1742, 1627, 1589, 1526, 1490, 1467, 1440, 1418, 1325, 1291, 1264, 1238, 1223. MS 480 (M^+). Anal calcd for $C_{24}H_{25}FN_6O_4$: C: 59.98, H: 5.24, N: 17.49. Found C: 59.72, H: 5.08, N: 17.34.

5.1.1.15. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(4-methoxybenzoyl) piperazin-1-yl)phenyl)oxazolidin-2-one ***10p***. Recrystallization (CH_3CN) gave **10p** as a crystalline solid (261 mg, 25% yield), m.p. 163–165 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (s, 1H), 7.77 (s, 1H), 7.42 (dd, 3H, $J = 2.0$ Hz, 15.0 Hz), 7.05–7.14 (dd, 5H), 7.00 (d, 2H, $J = 9.0$ Hz), 5.12 (m, 1H), 4.83 (d, 2H, $J = 5.0$ Hz), 4.20 (t, 1H, $J = 9.0$ Hz), 3.86 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.80 (br s, 3H), 3.45–3.50 (m, 4H), 2.99 (br d, 4H). IR (KBr pellet, cm^{-1}): ν 2835, 1748, 1613, 1517, 1433, 1415, 1321, 1284, 1249, 1224, 1110, 1022. MS 480 (M^+). Anal calcd for $C_{24}H_{25}FN_6O_4$: C: 59.98, H: 5.24, N: 17.49. Found C: 59.70, H: 5.26, N: 17.33.

5.1.1.16. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(4-(4-(E)-cinnamoylpiperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one ***10q***. Purified on silica gel column chromatography (EtOAc) and recrystallization (CH_3CN) gave **10q** as a crystalline solid (158 mg, 15% yield), m.p. 228–230 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.18 (s, 1H), 7.77 (s, 1H), 7.74 (d, 2H, $J = 7.0$ Hz), 7.53 (d, 1 H, $J = 15.0$ Hz), 7.37–7.45 (m, 4H), 7.32 (d, 1H, $J = 15.0$ Hz), 7.14 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.08 (t, 1H, $J = 9.0$ Hz), 5.12 (m, 1H), 4.83 (d, 2H, $J = 5.0$ Hz), 4.21 (t, 1H, $J = 9.0$ Hz), 3.87 (m, 3H), 3.74 (br s, 2H), 3.00 (br s, 4H). IR (KBr pellet, cm^{-1}): ν 1739, 1646, 1603, 1516, 1419, 1341, 1281, 1230, 1163, 1108. Anal calcd for $C_{25}H_{25}FN_6O_3$: C: 63.01, H: 5.29, N: 17.64. Found C: 62.84, H: 5.18, N: 17.49.

5.1.1.17. (R,E)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(4-(4-(3-(2-chlorophenyl)acryloyl)-piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one ***10r***. Recrystallization (CH_3CN–CH_2Cl_2) gave **10r** as a crystalline solid (618 mg, 56% yield), m.p. 213–215 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (s, 1H), 8.04–8.06 (m, 1H), 7.85 (d, 1H, $J = 15.0$ Hz), 7.77 (s, 1H), 7.53–7.55 (m, 1H), 7.37–7.46 (m, 4H), 7.14 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.08 (t, 1H, $J = 9.0$ Hz), 5.13 (m, 1H), 4.83 (d, 2H, $J = 5.0$ Hz), 4.21 (t, 1H, $J = 9.0$ Hz), 3.85–3.88 (m, 3H), 3.75 (br s, 2H), 3.01 (br s, 1H). IR (KBr pellet, cm^{-1}): ν 2858, 1765, 1740, 1713, 1641, 1595, 1519, 1472, 1439, 1325, 1248, 1232. MS 510 (M^+). Anal calcd for $C_{25}H_{24}ClFN_6O_3$: C: 58.76, H: 4.73, N: 16.45. Found C: 59.12, H: 4.46, N: 16.37.

5.1.1.18. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-nicotinoylpiperazin-1-yl) phenyl)oxazolidin-2-one ***10s***. Recrystallization (CH_3CN–EtOAc) gave **10s** as a light brown crystalline solid (412 mg, 53% yield), m.p. 190–191 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.67–8.68 (m, 2H), 8.17 (s, 1H), 7.89 (d, 1H, $J = 8.0$ Hz), 7.77 (s, 1H), 7.51 (dd, 1H, $J = 5.0$ Hz, 8.0 Hz), 7.43 (dd, 1H, $J = 2.0$ Hz, 15.0 Hz), 7.14 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.08 (t, 1H, $J = 9.0$ Hz), 5.13 (m, 1H), 4.83 (d, 2H, $J = 5.0$), 4.21 (t, 1H, $J = 9.0$ Hz), 3.87 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.80 (br s, 2H), 3.50 (br s, 2H), 2.99 and 3.05 (two br s, 4H). IR (KBr pellet, cm−1): ν 2901, 1738, 1633, 1574, 1523, 1418, 1325, 1285, 1222. Anal calcd for $C_{22}H_{22}FN_7O_3$: C: 58.53, H: 4.91, N: 21.72. Found C: 58.74, H: 4.78, N: 21.55.

5.1.1.19. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-isonicotinoylpiperazin-1-yl)phenyl)oxazolidin-2-one ***10t***. Recrystallization (CH_3CN–MeOH) gave a beige crystalline solid (425 mg, 54% yield), m.p. 198–199 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.69 (d, 2H, $J = 6.0$ Hz), 8.17 (s, 1H), 7.77 (s, 1H), 7.44 (d, 2H, $J = 6.0$ Hz), 7.42 (dd, 1H, $J = 2.0$ Hz, 15.0 Hz, partly overlaps with the doublet at 7.44), 7.14 (dd, 2H, $J = 2.0$ Hz, 9.0 Hz), 7.08 (t, 1H, $J = 9.0$ Hz), 5.13 (m, 1H), 4.83 (d, 2H, $J = 5.0$ Hz), 4.21 (t, 1H, $J = 9.0$ Hz), 3.86 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.80 (br s, 2H), 3.43 (br s, 2H), 3.06 (br s, 2H), 2.96 (br s, 2H). IR (KBr pellet, cm^{-1}): ν 3043, 2897, 2361, 1744, 1639, 1601, 1518, 1573, 1440, 1415, 1333, 1283, 1225. Anal calcd for $C_{22}H_{22}FN_7O_3$: C: 58.53, H: 4.91, N: 21.72. Found C: 58.74, H: 4.88, N: 21.58.

5.1.1.20. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(4-(4-(2-chloronicotinoyl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one ***10u***. Recrystallization ($CH_3CN-CH_2Cl_2$) gave a beige crystalline solid (634 mg, 60% yield), m.p. 229–231 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.51 (dd, 1H, $J = 2.0$ Hz, 5.0 Hz), 8.17 (s, 1H), 7.96 (dd, 1H, $J = 2.0$ Hz, 8.0 Hz), 7.77 (s, 1H), 7.55 (dd, 1H, $J = 5.0$ Hz, 8.0 Hz), 7.43 (dd, 1H, $J = 2.0$ Hz, 15.0 Hz), 7.14 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.08 (t, 1H, $J = 9.0$ Hz), 5.12 (m, 1H), 4.83 (d, 2H, $J = 5.0$ Hz), 4.21 (t, 1H, $J = 9.0$ Hz), 3.86 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.79–3.83 (m, 2H), 3.31 (br s, 2H, overlaps with D_2O signal), 3.09–3.04 (m, 2H), 2.96 (br s, 2H). IR (KBr pellet, cm^{-1}): ν 2846, 1738, 1647, 1579, 1523, 1421, 1394, 1324, 1286, 1220. MS 485 (M^+). Anal calcd for $C_{22}H_{21}ClFN_7O_3$: C: 54.38, H: 4.36, N: 20.18. Found C: 54.19, H: 4.23, N: 20.07.

5.1.1.21. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(furan-2-carbonyl) piperazin-1-yl)phenyl)oxazolidin-2-one ***10v***. Recrystallization (CH_3CN) gave crystalline solid (400 mg, 42% yield), m.p. 207–208 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (s, 1H), 7.87 (s, 1H), 7.77 (s, 1H), 7.43 (dd, 1H, $J = 2.0$ Hz, 15.0 Hz), 7.04–7.14 (m, 3H), 6.65 (dd, 1H, $J = 2.0$ Hz, 3.0 Hz), 5.12 (m, 1H), 4.82 (d, 2H, $J = 5.0$ Hz), 4.20 (t, 1H, $J = 9.0$ Hz), 3.82–3.88 (m, 5H), 3.02 (t, 4H, $J = 5.0$ Hz). IR (KBr pellet, cm^{-1}): ν 2834, 1744, 1623, 1568, 1519, 1485, 1438, 1328, 1282, 1244, 1229. MS 440 (M^+). Anal calcd for $C_{21}H_{21}FN_6O_4$: C: 57.27, H: 4.80, N: 19.08. Found C: 57.26, H: 4.81, N: 19.06.

5.1.1.22. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(thiophene-2-carbonyl) piperazin-1-yl)phenyl)oxazolidin-2-one ***10w***. Recrystallization (CH_3CN) gave a crystalline solid (343 mg, 35% yield), m.p. 194–195 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.18 (s, 1H), 7.79 (dd, 1H, $J = 1.0$ Hz, 5.0 Hz), 7.7 (s, 1H), 7.41–7.47 (m, 2H), 7.12–7.16 (m, 2H), 7.08 (t, 1H, $J = 9.0$ Hz), 5.12 (m, 1H), 4.83 (d, 2H, $J = 5.0$ Hz), 4.21 (t, 1H, $J = 9.0$ Hz), 3.86 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.80 (t, 4H, $J = 5.0$ Hz), 3.03 (t, 4H, $J = 5.0$ Hz). IR (KBr pellet, cm^{-1}): ν 2906, 2844, 1748, 1614, 1517, 1442, 1414, 1325, 1282, 1226. MS 456 (M^+). Anal calcd for $C_{21}H_{21}FN_6O_3S$: C: 55.25, H: 4.64, N: 18.41. Found C: 55.27, H: 4.66, N: 18.38.

5.1.1.23. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(2-oxo-2-(thiophen-2-yl) acetyl)piperazin-1-yl)phenyl)oxazolidin-2-one ***10x***. Trifluoroacetic acid salt **9a** (1.00 g, 2.17 mmol) was treated with a saturated solution of $KHCO_3$, filtered and dried to give the free base **9b**. A solution of **9b** in pyridine (5 ml) was treated with 2-thiophene glyoxalic acid (407 mg, 2.61 mmol), *N*,*N*-dimethylamino pyridine (319 mg, 2.61 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (500 mg, 2.61 mmol) and the mixture stirred for 48 h. The reaction mixture was concentrated to give an oil, which was diluted with CH_2Cl_2 (20 ml) and extracted with water (3×20 ml). The CH_2Cl_2 layer was washed with brine, dried (anhydrous Na_2SO_4), filtered and concentrated to give a light yellow solid, which was triturated with ether, filtered and dried to give 654 mg. Purification on silica gel column chromatography (EtOAc) gave the title compound **10x** as a solid (214 mg, 20% yield), m.p. 177–178 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.27 (d, 1H, $J = 4.0$ Hz), 8.17 (s, 1H), 7.93 (d, 1H, $J = 3.0$ Hz), 7.77 (s, 1H), 7.43 (dd, 1H, $J = 2.0$ Hz, 15.0 Hz), 7.35 (t, 1H, $J = 4.0$ Hz), 7.14 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.08 (t, 1H, $J = 9.0$), 5.12 (m, 1H), 4.83 (d, 2H, $J = 5.0$ Hz), 4.20 (t, 1H, $J = 9.0$ Hz), 3.86 (dd, 1H, $J = 6.0$ Hz), 3.79 (t, 2H, $J = 4.0$ Hz), 3.49 (t, 2H, $J = 4.0$ Hz), 3.09 (t, 2H, $J = 4.0$ Hz), 2.96 (t, 2H, $J = 4.0$ Hz). IR (KBr pellet, cm^{-1}): ν 2827, 1741, 1645, 1519, 1446, 1410, 1328, 1279, 1228. MS 484 (M^+). Anal calcd for $C_{22}H_{21}FN_6O_4S$: C: 54.54, H: 4.37, N: 17.35. Found C: 54.31, H: 4.39, N: 17.15.

5.1.2. General procedure for the arylsulfonyl oxazolidinones ***11a–d***

A solution of the trifluoroacetic acid salt **9a** (1.00 g, 2.17 mmol) in acetonitrile (20 ml) at 0 °C, was treated with triethylamine (1 ml) and the suitable arylsulfonyl chloride (575 mg, 3.258 mmol), the cooling bath was removed and stirred overnight. Then CH_2Cl_2 (20 ml) was added and the solution was extracted with water (3×10 ml). The pooled CH_2Cl_2 layers were washed with brine, dried (anhydrous Na_2SO_4), concentrated and triturated with ether to give a solid 945 mg. Recrystallization from acetonitrile afforded the desired compounds as crystalline solid.

5.1.2.1. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(phenylsulfonyl)piperazin-1-yl)phenyl)oxazolidin-2-one ***11a***. Yield 398 mg, 38%, m.p. 194–196 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.16 (s, 1H), 7.68–7.80 (m, 6H), 7.38 (dd, 1H, $J = 2.0$ Hz, 15.0 Hz), 7.11 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.04 (t, 1H, $J = 9.0$ Hz), 5.14 (m, 1H, $J = 5.0$ Hz), 4.81 (d, 2H, $J = 5.0$ Hz), 4.18 (t, 1H, $J = 9.0$ Hz), 3.84 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.03 (s, 8H). IR (KBr pellet, cm^{-1}): ν 2820, 1741, 1519, 1483, 1448, 1421, 1332, 1275, 1226. MS 486 (M^+). Anal calcd for $C_{22}H_{23}FN_6O_4S$: C: 54.31, H: 4.77, N: 17.27. Found C: 54.04, H: 4.60, N: 17.24.

5.1.2.2. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(3-tolylsulfonyl)piperazin-1-yl)phenyl)oxazolidin-2-one ***11b***. Yield 597 mg, 55%, m.p. 201–202 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.16 (s, 1H), 7.76 (s, 1H), 7.58–7.59 (m, 4H), 7.38 (dd, 1H, $J = 2.0$ Hz, 15.0 Hz), 7.11 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.05 (t, 1H, $J = 9.0$ Hz), 5.11 (m, 1H), 4.82 (d, 2H, $J = 5.0$ Hz), 4.19 (t, 1H, $J = 9.0$ Hz), 3.84 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.03 (s, 8H), 2.45 (s, 3H). IR (KBr pellet, cm^{-1}): ν 2893, 2850, 1751, 1519, 1486, 1449, 1418, 1337, 1310, 1274, 1224. MS 500 (M^+). Anal calcd for $C_{23}H_{25}FN_6O_4S$: C: 55.19, H: 5.03, N: 16.79. Found C: 55.07, H: 4.84, N: 16.82.

5.1.2.3. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-tosylpiperazin-1-yl)phenyl) oxazolidin-2-one ***11c***. Yield 646 mg, 59%, m.p. 207–208 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.16 (s, 1H), 7.76 (s, 1H), 7.67 (d, 2H,

$J = 8.0$ Hz), 7.50 (d, 2H, $J = 8.0$ Hz), 7.38 (dd, 1H, $J = 2.0$ Hz, 15.0 Hz), 7.11 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.05 (t, 1H, $J = 9.0$ Hz), 5.11 (m, 1H), 4.82 (d, 2H, $J = 5.0$ Hz), 4.19 (t, 1H, $J = 9.0$ Hz), 3.84 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.03–3.01 (m, 8H), 2.43 (s, 3H). IR (KBr pellet, cm^{-1}): ν 2817, 1740, 1599, 1574, 1519, 1483, 1421, 1391, 1377, 1346, 1332, 1273, 1224. MS 500 (M^+). Anal calcd for $C_{23}H_{25}FN_6O_4S$: C: 55.19, H: 5.03, H: 16.79. Found C: 54.99, H: 4.85, N: 16.82.

5.1.2.4. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(thiophen-2-ylsulfonyl)piperazin-1-yl)phenyl)oxazolidin-2-one ***11d***. Yield 456 mg, 43%, m.p. 205–207 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.16 (s, 1H), 8.11 (d, 1H, $J = 5.0$), 7.76 (s, 1H), 7.70 (d, 1H, $J = 3.0$ Hz), 7.4 (dd, 1H, $J = 2.0$ Hz, 15.0 Hz), 7.33 (t, 1H, $J = 9.0$ Hz), 7.12 (dd, 1H, $J = 2.0$ Hz, 9.0 Hz), 7.06 (t, 1H, $J = 9.0$ Hz), 5.12 (m, 1H), 4.82 (d, 2H, $J = 5.0$ Hz), 4.19 (t, 1H, $J = 9.0$ Hz), 3.86 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 3.08 (s, 8H). IR (KBr pellet, cm^{-1}): ν 2815, 1741, 1519, 1420, 1349, 1224, 1154. MS *m*/*z* 492 (M^+). Anal calcd for $C_{20}H_{21}FN_6O_4S_2$: C: 48.77, H: 4.30, N: 17.06. Found C: 49.10, H: 4.37, N: 17.11.

6. Microbiology

6.1. Antibacterial susceptibility testing

The clinical isolates used in the 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 (CLSI) (formerly National Committee for Clinical Laboratory Standards) [32]. Minimum inhibitory concentrations (MIC's, μg/ml) were determined on Mueller–Hinton (MH) agar with medium containing dilutions of antibacterial agents ranging from 0.12 to 8 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 organisms utilized in this study consisted of methicillin-resistant *S. aureus* (MRSA, $n = 10$), methicillin-susceptible *S. aureus* (MSSA, $n = 11$), methicillin-resistant coagulase-negative staphylococci (MR-CNS, $n = 3$), methicillin-sensitive coagulase-negative staphylococci (MS-CNS, $n = 8$), *S. pneumoniae* ($n = 6$), vancomycin-sensitive (VSE, $n = 7$) and vancomycin-resistant (VRE, $n = 4$) enterococci. The Gram-negative organisms included were *H. influenzae* ($n = 7$) and *M. catarrhalis* ($n = 3$) clinical isolates, and *E. coli* ATCC 25922. The reference strains, *S. aureus* ATCC 25923, *Staphylococcus epidermidis* ATCC 12228 and *Enterococcus 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 Muller–Hinton broth supplemented with 50% human plasma. The MIC was defined as the lowest drug concentration that completely inhibited growth of the bacteria. PH-027, prepared according to literature methods [23,25], and linezolid and vancomycin obtained from commercial sources were used as reference antibacterial agents.

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