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Bioorganic & Medicinal Chemistry 13 (2005) 4113–4123
Bioorganic & Medicinal Chemistry

Synthesis and antibacterial activity of new N-linked 5-triazolylmethyl oxazolidinones

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Received 10 February 2005; revised 20 March 2005; accepted 20 March 2005
Available online 25 April 2005

Abstract—A new series of N-linked 5-triazolylmethyl oxazolidinones with varying substitution at the piperazine nitrogen 4-position were synthesized and tested against a panel of Gram-positive and Gram-negative bacteria including clinical isolates. Most of the compounds showed excellent antibacterial activity against susceptible and resistant Gram-positive organisms. One of the compounds showed enhanced antibacterial activity against *Moraxella catarrhalis*.

1. Introduction

Infectious diseases remain one of the major scourge of human life mainly due to a combination of factors including socio-economic, emerging infectious diseases, and the appallingly high level of antibiotic resistance worldwide. Antibacterial resistance continues to increase in hospital and community settings, reducing treatment options for patients, while increasing hospital stay and health care costs. This situation has prompted active research efforts aimed at developing new antibacterial agents to treat resistant bacterial pathogens. Recently new agents including daptomycin, synercid, and linezolid have been approved for human use.[1] Linezolid (**1**, Fig. 1) is the first and only candidate of the oxazolidinone class of orally active, totally synthetic antibacterial agent in the market.[1–3] Oxazolidinones are highly effective against multi-drug resistant Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and penicillin-resistant *Streptococcus pneumoniae*, which are of clinical concerns with regard to the emergence of resistance. This class of compounds also showed activity against certain anaerobes, including *Bacteroides fragilis*, *Clostridium difficile*, *Peptostreptococcus* spp. *Corynebacterium* spp., *Prevotella bivia*, and *Fusobacterium* spp.[2–6] Oxazolidinones exhibit a unique mode of action by binding at the P site of the 50S ribosomal subunit thus inhibiting protein synthesis.[7,8] This unique mode of action offers a potential for low cross-resistance with existing antimicrobial protein synthesis inhibitors. However, recent reports on emerging linezolid-resistant *S. aureus*[9] and *Enterococcus* spp.[10–12] in hospital isolates are disappointing. Development of linezolid resistance has been suggested to be due to reduced binding to the ribosome, which was associated with 23S rRNA alterations.[7] The development of oxazolidinone resistance coupled with recent isolation of vancomycin intermediate-resistant (VISA) and vancomycin-resistant *Staphylococcus aureus* (VRSA) with vancomycin minimum inhibitory concentration (MIC) values of $\geqslant 32$ μg/mL,[13–15] and the dissemination of other multi-drug resistant Gram-positive bacteria, including *Enterococcus* spp.[16] and *Streptococcus* spp.,[17] continue to serve as impetus for the development of new and more effective treatment options for infectious diseases.

Extensive structure–activity relationships have been established for oxazolidinone derivatives structurally related to linezolid **1** and eperezolid **2a** having the 5-acetamidomethyl, 5-thiourea **3a**, 5-thiocarbamate **3b**, 5-dithiocarbamate **3c**, and oxygen-substituted **2b** (AZD2563) and nitrogen-substituted **3d** heterocyclic aryl moieties at the C5 position of the oxazolidinone

Keywords: Antibacterial activity; Linezolid; PH-027; 5-Triazolylmethyl-oxazolidinone.
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doi:10.1016/j.bmc.2005.03.036

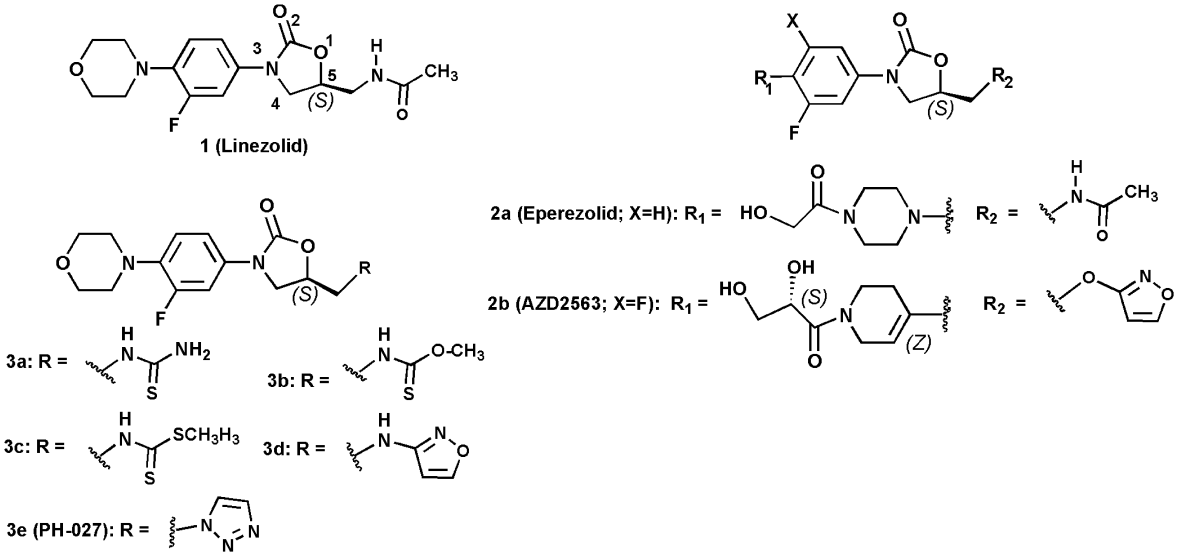
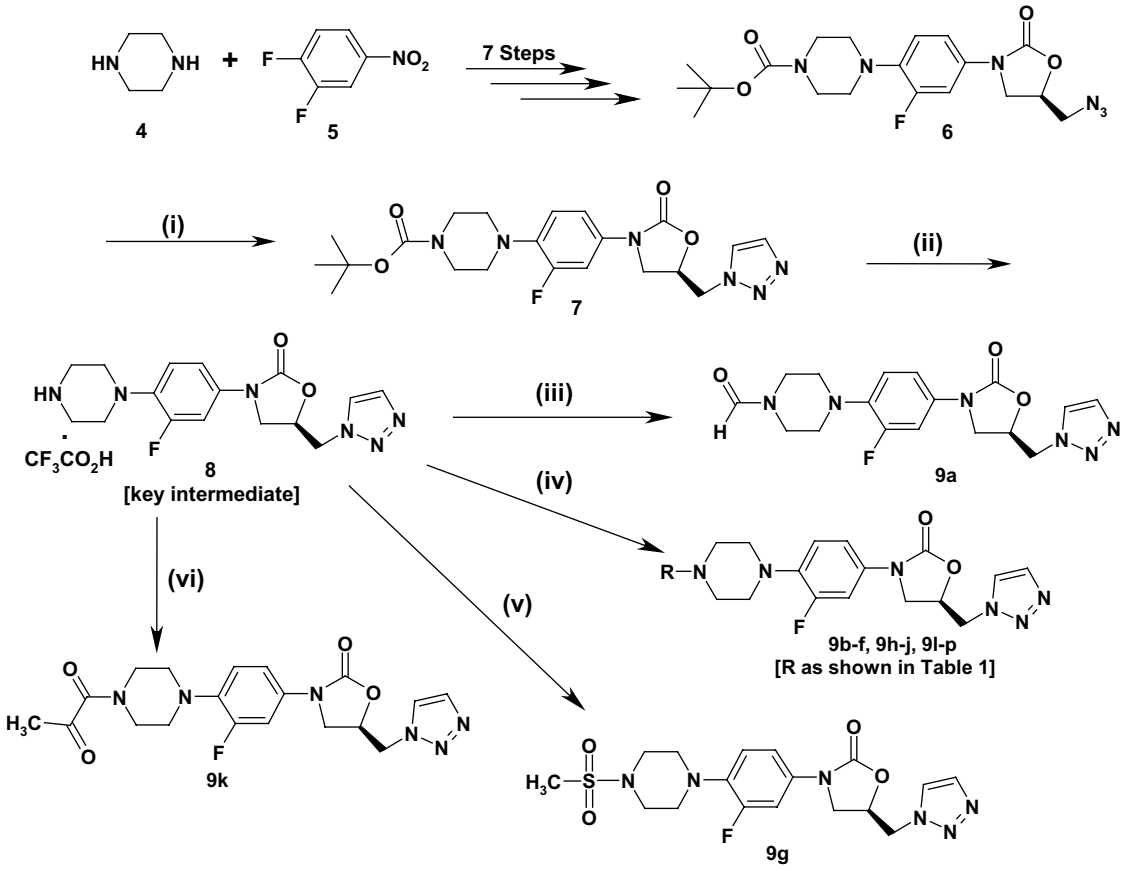


Figure 1. Structures of oxazolidinone antibacterial agents.

ring[2,3] (Fig. 1). In addition, a variety of C4-substituents at the 3-fluorophenyl to give the acetyl, methylsulfonyl, formamide, heteroaryl, morpholine, thiomorpholine, 4-methylpiperidine, and 4-acyl piperazine derivatives have also been investigated. Of the many compounds described, the morpholine and 4-acyl piperazine and 4-acyl tetrahydropyridine derivatives exemplified by **1** (linezolid), **2a** (eperezolid), and **2b** (AZD2563), respectively, showed favorable balance of antibacterial activity, pharmacokinetic profiles, and tolerability that deserved further clinical investigation.[2,3] We recently reported new 5-triazolylmethyl oxazolidinones based on the replacement of the 5-acetamidomethyl substituents with N-heterocyclic (imidazole, triazole, and substituted-triazole) moieties.[18] A representative of this group PH-027 (**3e**, Fig. 1) having an unsubstituted-triazol-1-yl group was identified as having strong antibacterial activity comparable to or better than linezolid and vancomycin against selected standard and clinical isolates of Gram-positive aerobes including MRSA, methicillin-susceptible *S. aureus* (MSSA), methicillin-resistant (MR-CNS), and -susceptible coagulase-negative (MS-CNS) staphylococci and VRE strains.[18] This new oxazolidinone also showed strong activity against Gram-positive anaerobic (*C. difficile* and *Peptostreptococcus* spp.) and Gram-negative anaerobic (*B. fragilis*, *P. bivia*, and *Fusobacterium* spp.) bacterial strains.[5] This strong antibacterial activity further supported the potential bioisosteric substitution of the triazolyl group for acetamido moiety, based on the similarity of their physicochemical properties such as the dipole moment and the potential of the nitrogen atoms at two and three positions to function as weak hydrogen bond acceptors.[19] In the present communication we report the synthesis and antibacterial activity of 4-substituted-piperazinyl N-linked 5-triazolylmethyl oxazolidinones having varied acyl substitutions at the distal piperazine N4 position, since the 4-acyl piperazine and 4-acyl tetrahydropyridine motifs have been established to be well tolerated and essential for strong antibacterial activity as exemplified by **2a** (eperezolid) and **2b** (AZD2563).[2,3] The structural variations were selected to encompass certain physicochemical properties including hydrophobic and steric, in order to identify new oxazolidinones with improved activity, and to establish structure–activity requirements for the 5-triazolylmethyl oxazolidinone class of compounds.

2. Chemistry

Compounds **7** and **9a**–**p** were synthesized in several steps from the readily available starting materials piperazine **4** and 3,4-difluoronitrobenzene **5** to afford good yield of the intermediate azide[20] derivative **6** in seven steps as shown in Scheme 1. The azide derivative readily underwent Huisgen's 1,3 dipolar cycloaddition reaction[21] with acetylene in DME as solvent in a steel bomb at 90 °C, to give the *tert*-butoxycarbonyl protected derivative **7** in 81% yield. The *tert*-butoxycarbonyl protecting group on the piperazine nitrogen 4-position was deprotected by trifluoroacetic acid in CH_2Cl_2 at 0 °C to room temperature to give the key-intermediate triazole **8** as a trifluoroacetic acid salt in quantitative yield. Treatment of the trifluoroacetic acid salt **8** with a cold concentrated $KHCO_3$ solution afforded an off-white solid, which was refluxed in acetonitrile in the presence of ammonium formate[22] to give the N-formyl derivative **9a** in good yield (Scheme 1). Further chemical transformations involving N-acylation of the intermediate **8** with the respective acid chlorides, anhydrides or chloroformates in CH_2Cl_2, using triethylamine as an acid scavenger afforded compounds **9b**–**f**, **9h**–**j**, and **9l**–**p** (Scheme 1) in moderate to good yields. While the methanesulfonyl derivative **9g** was obtained in moderate yield from the reaction of intermediate **8** with methanesulfonyl chloride. Compound **9k** was prepared by reacting 2-oxo-propionyl chloride (prepared in situ by the reaction of 2-oxo-propionic acid with oxalyl chloride in CH_2Cl_2) with **8**. All the compounds were characterized by spectroscopic data (^{1}H NMR, MS, and IR), mp and CHN analyses.



Scheme 1. Synthesis of N-linked 5-triazol-1-ylmethyl oxazolidinones. Reagents and conditions: (i) acetylene/DME/90 °C; (ii) TFA/DCM/0 °C to rt; (iii) $KHCO_3$aq/HCO_2^- $^+NH_4$/CH_3CN; (iv) acid chlorides/NEt_3/DCM; (v) $CH_3S(O)_2Cl/NEt_3$/DCM; (vi) pyruvic acid/$(COCl)_2$/DCM; NEt_3/DCM.

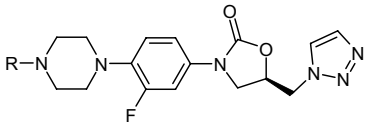
3. Results and discussion

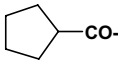
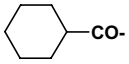
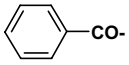
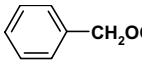
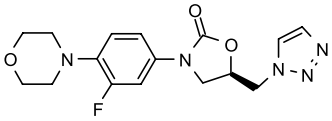
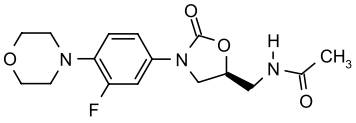
All of the newly synthesized analogues were tested in vitro against a panel of selected standard and clinical isolates of Gram-positive and Gram-negative bacteria strains. The antibacterial activity of the compounds was also evaluated against standard strain of *S. aureus* ATCC 25923 in the absence and presence of 50% human plasma to investigate the potential serum binding or instability of the compounds. The calculated log *P* (Clog *P*) values,[23] which represent a measure of the lipophilicity of the compounds and MIC (μg/mL) values of the newly synthesized N-linked 5-triazolylmethyl oxazolidinones against *S. aureus* ATCC 25923 are presented in Table 1. In this series of compounds, although the replacement of the hydrogen of the formyl (HCO) group on the piperazine N4 position by different substituents significantly altered the Clog *P* values as observed for **9a** (R = HCO, −0.90) and **9p** (R = $PhCH_2OCO$, 3.12), it showed little or no effect on the antibacterial activity with MIC values of 1 and 0.5 μg/mL, respectively. In addition, the progressive increase in lipophilicity of the compounds acquired by replacing the formyl group in compound **9a** with the *tert*-butoxycarbonyl **7**, acetyl **9b**, trifluoroacetyl **9c**, trichloroacetyl **9d**, dichloroacetyl **9e**, ethoxycarbonyl **9i**, thioethoxycarbonyl **9j**, and benzyloxycarbonyl **9p** groups, respectively, had little or no significant effects on the MIC values in the absence of human plasma. However, compounds **7**, **9d**, and **9p** having Clog *P* values of 1.94, 1.48, and 3.12, respectively, were accompanied by significant increase in the MIC values of fourfold or greater in the presence of 50% human plasma. This fourfold or greater increase in MIC values in the presence of plasma may be attributed to strong binding to plasma proteins and/or inactivation by enzymes in the plasma. This may reduce the concentration of the free antibacterial agent available to inhibit the growth of the bacteria effectively in vivo.[24,25]

The benzyloxycarbonyl compound **9p** with highest lipophilicity (Clog *P* = 3.12) was most affected and showed the highest increase in MIC of 16 μg/mL, which is greater than the break-point for linezolid (MIC $\leqslant$ 4 μg/mL).[26] From this study, a Clog *P* value of 1.4 shown by the thioethoxycarbonyl derivative **9j** may be suggested as a cut-off point for strong plasma protein binding for this series of compound. However, since the Clog *P* values for PH-027 and linezolid are less than 1.4, their antibacterial activity was not affected by human plasma, which is in agreement with previously reported activity for linezolid in the presence of 50% rat serum.[24]

To further elaborate on the strong antibacterial activity of this series of compounds, the oxazolidinones were tested against a panel of selected Gram-positive and Gram-negative clinical isolates. The MIC (μg/mL) value

Table 1. Calculated log *P* (Clog *P*) and MIC (μg/mL) values of N-linked-5-triazolylmethyl oxazolidinones



Compd	–R	Clog *P*	*S. aureus* without plasma	*S. aureus*[a] with 50% plasma
7	$(CH_3)_3COCO$–	1.94	0.5	4
9a	HCO–	−0.90	1	1
9b	CH_3CO–	−0.95	1	1
9c	CF_3CO–	0.16	0.5	1
9d	CCl_3CO–	1.48	1	4
9e	$CHCl_2CO$–	0.38	0.5	1
9f	CH_3SCO–	0.83	0.25	0.5
9g	$CH_3S(O)_2$–	−0.35	0.5	1
9h	CH_3CH_2CO–	−0.42	1	1
9i	CH_3CH_2OCO–	1.23	1	1
9j	CH_3CH_2SCO–	1.36	1	1
9k	CH_3COCO–	−0.35	2	2
9l	$(CH_3)_2CHCO$–	−0.11	2	2
9m		0.52	2	4
9n		1.08	4	4
9o		0.87	1	1
9p		3.12	0.5	16
PH-027		0.89	1	1
Lzd		0.76	2	2
Van		n.d.	2	2

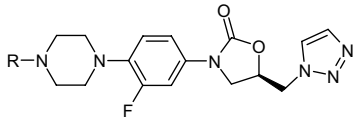
n.d. = not determined.
[a] *S. aureus* ATCC 25923.

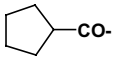
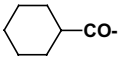
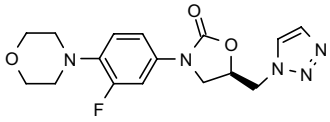
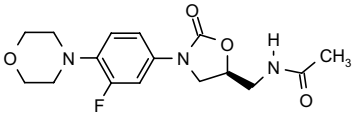
ranges are presented in Table 2. All the newly synthesized compounds showed measurable excellent in vitro antibacterial activity against a range of susceptible (MSSA, MS-CNS, and vancomycin-susceptible enterococci, VSE) as well as resistant Gram-positive clinical isolates, such as MRSA, MR-CNS, and VRE.

Against MSSA ($n = 11$), most of the compounds demonstrated MIC values in the range of 0.5–2 μg/mL, however, compounds **9c** (R = CF_3CO), **9f** (R = CH_3SCO), **9g** (R = $CH_3S(O)_2$), **9o** (R = PhCO), and **9p** (R = $PhCH_2OCO$) showed superior antibacterial activity with MIC value ranges of 0.25–0.5 and 0.25–1 μg/mL. A comparable level of activity was observed for most of the compounds against other panels of staphylococci (MRSA, MS-CNS, and MR-CNS) with MIC range of 0.12–2 μg/mL. However, substitutions with the isobutyryl **9l**, cyclopentanecarbonyl **9m**, and cyclohexanecarbonyl **9n** motifs at the piperazine N4 position were consistently less active against all staphylococci strains tested, with MIC value ranges of 1–2, 1–2, and 1–4 μg/mL, respectively. The demonstrated levels of activity were comparable or inferior to those of linezolid and vancomycin. The MIC distribution of oxazolidinones against clinical isolates of staphylococci ($n = 42$) showing the cumulative percent for specific MIC is presented in Table 3. From this data, compounds **7**, **9c**, **9f**, **9g**, and **9p** inhibited 100% of the strains at MIC value of 0.5 μg/mL, in comparison to PH-027, linezolid and vancomycin, which inhibited 100% of the strains in the MIC's of 1 and 2 μg/mL, respectively. In addition, the thiomethylcarbonyl substituted compound **9f** (R = CH_3SCO) showed the strongest activity against all staphylococci with 10%, 98%, and 100% inhibition of bacterial growth at 0.12, 0.25, and 0.5 μg/mL, respectively.

Most of the compounds showed excellent activity against *S. pneumoniae* with MIC value range of 0.5–1 μg/mL, which is comparable to those of PH-027, vancomycin and linezolid with MIC values of 0.5–1, 0.5,

Table 2. MIC ranges (μg/mL) of new N-linked-5-triazolylmethyl oxazolidinones against Gram-positive and Gram-negative clinical isolates



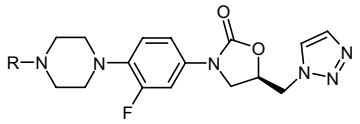
Compd	–R	Minimum inhibitory concentration (MIC, μg/mL) against								
		MSSA[a] (11)	MRSA[b] (20)	MS-CNS[c] (8)	MR-CNS[d] (3)	S.p.[e] (6)	VSE[f] (7)	VRE[g] (4)	H. inf.[h] (7)	M. cat.[i] (3)
7	$(CH_3)_3COCO$–	0.5	0.25–0.5	0.5	0.25–0.5	2–4	0.5	0.5	>8	>8
9a	HCO–	0.5–1	0.12–1	0.12–1	0.25–1	0.5–1	0.12–0.5	0.25–0.5	8–16	8
9b	CH_3CO–	0.5–1	0.25–0.5	0.25–1	0.25–0.5	0.5–1	0.5–1	0.25	>8	>8
9c	CF_3CO–	0.25–0.5	0.25–0.5	0.25–0.5	0.25–0.5	1	0.25–0.5	0.25	>8	>8
9d	CCl_3CO–	0.5–1	0.5–1	0.12–1	0.5–1	2–4	0.5	0.5	>8	>8
9e	$CHCl_2CO$–	0.5–1	0.5	0.5	0.5	0.25	0.5	0.5	>8	2
9f	CH_3SCO–	0.25–0.5	0.12–0.5	0.25	0.25	0.5	0.25	0.25	>8	>8
9g	$CH_3S(O)_2$–	0.25–0.5	0.5	0.12–0.5	0.25–0.5	0.5	0.5	0.5	>8	>8
9h	CH_3CH_2CO–	1	1	012–1	1	1	0.5–1	1	>8	>8
9i	CH_3CH_2OCO–	0.5–1	0.5–1	0.5–1	0.5–1	1	0.5–1	0.5–1	>8	>8
9j	CH_3CH_2SCO–	0.5–1	0.12–1	0.12–1	0.25–0.5	0.5–1	0.12–0.5	0.5–1	>8	>8
9k	CH_3COCO–	0.5–2	0.5–2	0.5–2	0.5–2	0.5–1	0.5–1	0.5	8	8
9l	$(CH_3)_2CHCO$–	1–2	1–2	1–2	1–2	0.5–1	1–2	1–2	>8	>8
6m		1–2	1–2	1–2	1–2	1–2	1–2	1–2	>8	>8
6n		1–4	1–4	1–4	1–4	0.5–1	1–2	1–2	>8	>8
9o	PhCO–	0.25–1	0.25–1	0.25–1	0.25	1–2	0.25–0.5	0.25	>8	>8
9p	$PhCH_2OCO$–	0.25–0.5	0.25–0.5	0.12–0.5	0.25–0.5	2–4	0.5	0.5	>8	>8
PH-027		0.5–1	0.5–1	0.5–1	0.5–1	0.5–1	0.5–1	1	>8	>8
Lzd		1–2	0.5–2	0.25–2	1–2	0.5	0.25–2	2	8	8
Van		1–2	0.5–1	1–2	1	0.5	0.5–2	>64	>8	>8

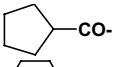
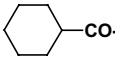
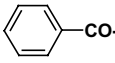
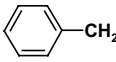
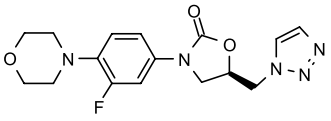
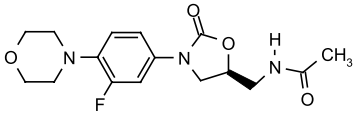
[a] Methicillin-susceptibile *S. aureus*.
[b] Methicillin-resistant *S. aureus*.
[c] Methicillin-susceptibile coagulase-negative staphylococci.
[d] Methicillin-resistant coagulase-negative staphylococci.
[e] *Streptococcus pneumoniae*.
[f] Vancomycin-susceptibile enterococci.
[g] Vancomycin-resistant enterococci.
[h] *Haemophilus influenzae*.
[i] *Moraxella catarrhalis*.

and 0.5 μg/mL, respectively, while compound **9e** (R = Cl_2CHCO) showed superior activity with MIC of 0.25 μg/mL. Furthermore, the most lipophilic compounds **7** (R = $(CH_3)_3COCO$), **9d** (R = Cl_3CCO), and **9p** (R = $PhCH_2OCO$) showed higher MIC values in the range of 2–4 μg/mL. Against VSE and VRE strains, all the compounds showed comparable or superior activity to PH-027 and linezolid. Most importantly the activities of all compounds were several folds higher than vancomycin against VRE. The introduction of the isobutyryl **9l**, cyclopentanecarbonyl **9m**, and cyclohexanecarbonyl **9n** moieties consistently resulted in the reduction of antibacterial activity against all enterococci and staphylococci with MIC ranges of 1–2 and 1–4 μg/mL, respectively. Overall, all the newly synthesized compounds, irrespective of their Clog *P* values, strongly inhibited the growth of all Gram-positive clinical isolates, suggesting that all the acyl substituents at the piperazine C4 nitrogen were well tolerated in terms of the Gram-positive activity, as exemplified by the excellent MIC values in the range of 0.12–4 μg/mL for all compounds tested (Tables 1–3). This range of MIC values shown by most of the compounds is comparable or superior to PH-027, linezolid, and vancomycin with MIC ranges of 0.5–1, 0.5–2, and 0.5–>64 μg/mL, respectively.

Evaluation of the antibacterial activity of these compounds against Gram-negative bacterial strains showed that most of the compounds were inactive (MIC,

Table 3. MIC (μg/mL) distribution of N-linked-5-triazolylmethyl oxazolidinones against clinical isolates of staphylococci ($n = 42$)



Compd	–R	Cumulative percent of isolates with specific MIC (μg/mL)					
		0.12	0.25	0.5	1	2	4
7	$(CH_3)_3COCO–$	0	12	100	—	—	—
9a	HCO–	14	26	60	100	—	—
9b	$CH_3CO–$	0	45	83	100	—	—
9c	$CF_3CO–$	0	43	100	—	—	—
9d	$CCl_3CO–$	2	5	48	100	—	—
9e	$CHCl_2CO–$	0	0	91	100	—	—
9f	$CH_3SCO–$	10	98	100	—	—	—
9g	$CH_3S(O)_2–$	2	14	100	—	—	—
9h	$CH_3CH_2CO–$	5	10	17	100	—	—
9i	$CH_3CH_2OCO–$	0	2	64	100	—	—
9j	$CH_3CH_2SCO–$	7	19	86	100	—	—
9k	$CH_3COCO–$	0	0	26	64	100	—
9l	$(CH_3)_2CHCO–$	0	0	0	36	100	—
9m		0	0	0	19	100	—
9n		0	0	0	33	55	100
9o		0	74	93	100	—	—
9p		2	29	100	—	—	—
PH-027		0	0	45	100	—	—
Lzd		0	5	14	86	100	—
Van		0	0	24	93	100	—

⩾8 μg/mL) against *Haemophilus influenzae*, *Escherichia coli*, and *Moraxella catarrhalis*, with the exception of the dichloroacetyl substituted compound **9e**. Compound **9e** showed improved activity against three clinical isolates of *M. catarrhalis* with MIC value of 2 μg/mL, which is superior to linezolid (MIC, 8 μg/mL and break-point of ⩽4 μg/mL).[26]

In conclusion, a series of N-linked 5-triazolylmethyl oxazolidinone antibacterial agents with in vitro activity against clinically relevant susceptible and resistant Gram-positive bacteria are reported. All the compounds showed excellent antibacterial activity indicating that the diverse functionalities were well tolerated on the piperazine N4-position for proper fit at the potential receptor site. The substitution of the cyclopentanecarbonyl and cyclohexanecarbonyl groups on the piperazine N4 position resulted in compounds with decreased antibacterial activity. In addition, direct correlation of antibacterial activity with Clog*P* values could not be established. However, compounds with higher Clog*P* values >1.4 showed increased MIC values in the presence of 50% human plasma, suggesting high plasma binding or inactivation. The lack of direct correlation between structure–antibacterial activity and Clog*P* values for these N-linked 5-triazoylmethyl oxazolidinones further corroborates our previous report.[18] Although studies from other laboratories have reported a favorable Clog*P* value range of −1 to +2 for strong in vitro MRSA and VRE activity for 5-acetamidomethyl oxazolidinones.[27] Compound **9e** showed activity against the fastidious Gram-negative diplococci, *M. catarrhalis* with MIC value of 2 μg/mL. Further structure–antibacterial activity study of the N-linked 5-triazolyl oxazolidinone series, in vivo evaluation and determination of some important physicochemical parameters of selected compounds are the subjects of further investigation in our laboratories.

4. Experimental

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. Elemental analyses were determined on LECO

elemental analyzer CHNS 932 apparatus, and were within ±0.4% of the calculated values. ^{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. The chemical shifts were reported in parts per million. High-resolution 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 performed on 0.25 mm precoated silica gel plates ($60F_{254}$, Merck). All extracted solvents were dried over Na_2SO_4, followed by evaporation in vacuo. The calculated partition coefficient (Clog *P*) values were determined by using the CS ChemDraw Ultra version 6.01, computer software by CambridgeSoft.Com.[23]

4.1. Syntheses

4.1.1. 4-[2-Fluoro-4-(2-oxo-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester 7. A solution of the azide **6** (10.00 g, 23.79 mmol) in dimethoxyethane (150 mL) was transferred to a steel bomb, cooled to −190 °C with liquid nitrogen; and a stream of acetylene gas was condensed into the bomb over a period of 5 min. The steel bomb was tightly closed and heated in an oil bath at 90 °C for 48 h. The steel bomb was cooled to 0 °C and the pressure was released slowly. TLC (ethyl acetate) indicated complete reaction. The solution was filtered into a round-bottomed flask and concentrated to give a crude solid, which was recrystallized from ethyl acetate to give **7** (8.55 g, 81% yield), mp 167–169 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (s, 1H, triazole H), 7.77 (s, 1H, triazole H), 7.41 (dd, 1H J = 2.3, 14.7 Hz, phenyl H), 7.09 (m, 2H, phenyl H), 5.12 (m, 1H, CHHC*H*CH$_2$–N–N=N), 4.82 (d, 2H, J = 4.4 Hz, CHHCHC*H*$_2$–N–N=N), 4.20 (t, 1H, J = 8.9 Hz, CH*H*CHCH$_2$–N–N=N), 3.85 (dd, 1H, J = 5.7, 9.3 Hz, C*H*HCHCH$_2$–N–N=N), 3.46 (s, 4H, piperazine H), 2.90 (br s, 4H, piperazine H), 1.42 (br s, 9H, (C*H*$_3$)$_3$C). IR (KBr pellet, cm^{-1}): v 3121, 2978, 2896, 2861, 1753, 1693, 1576, 1519, 1482, 1419, 1366, 1331, 1284, 1238. *m*/*z* 446 (M$^+$). Anal. CHN: calcd 56.49, 6.10, 18.8, found 56.61, 5.93, 18.76.

4.1.2. 4-[2-Fluoro-4-(2-oxo-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl]-piperazin-1-ium trifluoroacetate 8. A solution of the *tert*-butoxycarbonyl-protected triazole **7** (3.00 g, 6.72 mmol) in DCM (6 mL) was cooled to 0 °C, and treated with trifluoroacetic acid (6 mL); the ice bath was removed after 10 min and the mixture stirred for 2 1/2 h. The reaction mixture was concentrated to dryness to give a gummy residue, which was triturated with small portions of anhydrous ether, followed by the addition of THF to give **8** as an off-white solid (2.76 g, 89% yield). This product was utilized for reactions without further purifications. ^{1}H NMR: 8.79 (broad s, 2H), 8.16 (s, 1H), 7.76 (s, 1H), 7.42 (dd, 1H, J = 2.3, 14.7 Hz), 7.12 (m, 2H), 5.12 (m, 1H), 4.82 (d, 2H, J = 4.2 Hz), 4.20 (t, 1H, J = 9.2 Hz), 3.85 (dd, 1H, J = 5.7, 9.3 Hz), 3.22 (br s, 4H), 3.15 (br s, 4H). *m*/*z* 457 (M$^+$).

4.1.3. 4-[2-Fluoro-4-(2-oxo-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl]-piperazine-1-carbaldehyde 9a. The trifluoroacetic acid salt **8** (800 mg) was treated with saturated aqueous solution of $KHCO_3$ and the insoluble solid was collected by filtration and dried to give the free base (600 mg, 1.73 mmol). The free base was dissolved in acetonitrile (25 mL), treated with ammonium formate (180 mg, 2.86 mmol) and heated under reflux overnight. The mixture was cooled, concentrated to dryness, treated with water and extracted with DCM. The aqueous layer was re-extracted with DCM (2 × 10 mL) and the combined DCM layers were washed with saturated solution of NaCl, dried (Na_2SO_4), filtered, and concentrated to afford a white solid 390 mg. Recrystallization from ethyl acetate–acetonitrile gave a white solid **9a** (167 mg, 26% yield), mp 139–141 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (s, 1H), 8.07 (s, 1H), 7.77 (s, 1H), 7.43 (dd, 1H, J = 2.3, 14.7 Hz), 7.13 (dd, 1H, J = 2.2, 9.0 Hz), 7.07 (t, 1H, J = 9.0 Hz), 5.13 (m, 1H, J = 5.2 Hz), 4.83 (d, 2H, J = 5.0 Hz), 4.21 (t, 1H, J = 9.2 Hz), 3.86 (dd, 1H, J = 5.7, 9.3 Hz), 3.53 (overlapping t, 4H, J = 7.0, 13.6 Hz), 2.98 (t, 2H, J = 5.0 Hz), 2.92 (t, 2H, J = 5.0 Hz). IR (KBr pellet, cm^{-1}): v 2827, 1745, 1663, 1574, 1520, 1442, 1329, 1279, 1235. Anal. CHN: calcd 54.54, 5.12, 22.45, found 54.90, 5.11, 22.28.

4.1.4. 3-[4-(4-Acetyl-piperazin-1-yl)-3-fluoro-phenyl]-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one 9b. A solution of 3-(3-fluoro-4-piperazinium-1-yl-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one trifluoroacetic acid salt **8** (710 mg, 1.54 mmol) in acetonitrile (8 mL), was treated with triethylamine (2 mL) and acetic anhydride (291 μL, 3.08 mmol) at 0 °C, and the reaction mixture was stirred overnight. The reaction mixture was concentrated to give a gummy residue, which was dissolved in DCM (20 mL), washed with water and brine. The aqueous layer was further re-extracted with DCM (2 × 30 mL). The combined DCM layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated to obtain a crude gum, which was triturated with small volumes of ethyl acetate to afford a white solid. Recrystallization from ethyl acetate gave the title compound **9b** (480 mg, 83% yield), mp 136–138 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.16 (s, 1H), 7.77 (s, 1H), 7.41 (dd, 1H, J = 2.3, 14.7 Hz), 7.12 (dd, 1H, J = 2.2, 9.0 Hz), 7.05 (t, 1H, J = 9.0 Hz), 5.11 (m, 1H, J = 5.2 Hz), 4.82 (d, 2H, J = 4.5 Hz), 4.20 (t, 1H, J = 9.1 Hz), 3.85 (dd, 1H, J = 5.7, 9.3 Hz), 3.57 (overlapping t, 4H, J = 7.0, 13.6 Hz), 2.96 (t, 2H, J = 5.0 Hz), 2.89 (t, 2H, J = 5.0 Hz), 2.03 (s, 3H). IR (KBr pellet, cm^{-1}): v 2815, 1757, 1635, 1575, 1519, 1419, 1330, 1282, 1223. Anal. CHN: calcd 63.57, 5.34, 9.27, found 63.56, 5.42, 9.25.

4.1.5. 3-{3-Fluoro-4-[4-(2,2,2-trifluoro-acetyl)-piperazine-1-yl]-phenyl}-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one 9c. This compound was prepared from the trifluoroacetic acid salt **8** (900 mg, 1.96 mmol), trifluoroacetic anhydride (414 μL, 2.93 mmol), and triethylamine (1 mL), and worked up as described for **9b**. Recrystallization from ethyl acetate gave an off-white fluffy solid **9c** (346 mg, 40% yield), mp 134–135 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.18 (s, 1H), 7.77 (s, 1H),

7.44 (dd, 1H, $J = 2.2$, 14.7 Hz), 7.14 (dd, 1H, $J = 2.2$, 8.9 Hz), 7.09 (t, 1H, $J = 9$ Hz), 5.12 (m, 1H, $J = 5.2$ Hz), 4.83 (d, 2H, $J = 5.0$ Hz), 4.21 (t, 1H, $J = 9.2$ Hz), 3.86 (dd, 1H, $J = 5.7$, 8.9 Hz), 3.73 (br s, 4H), 3.05 (t, 4H, $J = 4.8$ Hz). IR (KBr pellet, cm^{-1}): ν 3143.15, 2833, 1741, 1690, 1518, 1481, 1448, 1408, 1323, 1277, 1242. Anal. CHN: calcd 48.87, 4.10, 19.00, found 49.19, 4.15, 18.70.

4.1.6. 3-{3-Fluoro-4-[4-(2,2,2-trichloro-acetyl)-piperazin-1-yl]-phenyl}-5-[1,2,3]triazol-1-ylmethyl oxazolidin-2-one 9d. This compound was prepared from trifluoroacetic acid salt **8** (800 mg, 1.74 mmol), trichloroacetic anhydride (476 μL, 2.61 mmol), and triethylamine (1 mL), and worked up as described for **9b**. Recrystallization from acetonitrile–ether gave **9d** (182 mg, 21% yield), mp 146–148 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.16 (s, 1H), 7.77 (s, 1H), 7.44 (dd, 1H, $J = 2.0$, 14.8 Hz), 7.15 (dd, 2H, $J = 2.2$, 9.0 Hz), 7.10 (t, 1H, $J = 9.0$ Hz), 5.13 (m, 1H, $J = 5.3$ Hz), 4.83 (d, 2H, $J = 5.0$ Hz), 4.21 (t, 1H, $J = 9.2$ Hz), 3.97 (br s, 2H), 3.87 (dd, 1H, $J = 5.7$, 9.3 Hz, overlaps with the broad signals at 3.97 and 3.74), 3.74 (br s, 2H), 3.09 (br s, 4H). IR (KBr pellet, cm^{-1}): ν 2985, 2826, 1746, 1675, 1633, 1574, 1519, 1479, 1420, 1384, 1336, 1281, 1229. Anal. CHN: calcd 43.96, 3.69, 17.09, found 44.03, 3.75, 17.25.

4.1.7. 3-{4-[4-(2,2-Dichloroacetyl)-piperazin-1-yl]-3-fluoro-phenyl}-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one 9e. Compound **9e** was prepared from reaction of the trifluoroacetic acid salt **8** (1.00 g, 2.17 mmol), dichloroacetyl chloride (313 μL, 3.26 mmol), and triethylamine, and worked up as described for **9b**. Recrystallization from ethyl acetate–acetonitrile gave compound **9e** (381 mg, 38% yield) as a light brown crystalline solid, mp 178–179 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.18 (s, 1H), 7.77 (s, 1H), 7.43 (dd, 1H, $J = 2.3$, 14.8 Hz), 7.31 (s, 1H), 7.14 (dd, 1H, $J = 2.2$, 9.0 Hz), 7.08 (t, 1H, $J = 9.2$ Hz), 5.13 (m, 1H, $J = 5.0$ Hz), 4.83 (d, 2H, $J = 5.0$ Hz), 4.21 (t, 1H, $J = 9.2$ Hz), 3.86 (dd, 1H, $J = 5.8$, 9.3 Hz), 3.72–3.67 (m, 4H), 3.03–2.98 (m, 4H). IR (KBr pellet, cm^{-1}): ν 2918, 2828, 1739, 1663, 1577, 1521, 1483, 1446, 1424, 1386, 1324, 1303, 1225. m/z 457 (M^+). Anal. CHNS: calcd 47.28, 4.19, 18.38 found 47.35, 4.07, 18.33.

4.1.8. 4-[2-Fluoro-4-(2-oxo-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl] piperazine-1-carbothioic acid *S*-methyl ester 9f. Compound **9f** was prepared from the trifluoroacetic acid salt **8** (1.0 g, 2.17 mmol) and methylchloroformate (280 μL, 3.26 mmol) and triethylamine (1 mL) in acetonitrile, as described for **9b** and worked up to give a crude solid 674 mg. Recrystallization from acetonitrile gave **9f** as a crystalline solid (276 mg, 30% yield), mp 168–170 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (s, 1H), 7.77 (s, 1H), 7.43 (dd, 1H, $J = 2.2$, 14.7 Hz), 7.13 (dd, 1H, $J = 2.2$, 9.0 Hz), 7.07 (t, 1H, $J = 9.0$ Hz), 5.12 (m, 1H, $J = 5.2$ Hz), 4.83 (d, 2H, $J = 5.0$ Hz), 4.20 (t, 1H, $J = 9.2$ Hz), 3.86 (dd, 1H, $J = 5.7$, 9.3 Hz), 3.61 (br s, 4H), 2.97 (t, 4H, $J = 4.9$ Hz), 2.27 (s, 3H). IR (KBr pellet, cm^{-1}): ν 3129, 2918, 2831, 1742, 1645, 1518, 1417, 1325, 1281, 1222. Anal. CHNS: calcd 51.42, 5.03, 19.99, 7.31, found 51.68, 5.03, 19.92, 7.11.

4.1.9. 3-[3-Fluoro-4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one 9g. Compound **9g** was prepared from trifluoroacetic acid salt **8** (800 mg, 1.74 mmol), methanesulfonyl chloride (201 μL, 2.61 mmol), and triethylamine (1 mL), as described for **9b**. Work-up and recrystallization from acetonitrile–ethyl acetate gave the title compound **9g** (317 mg, 43% yield), mp 225–226 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (s, 1H), 7.77 (s, 1H), 7.43 (dd, 1H, $J = 2.3$, 14.8 Hz), 7.14 (dd, 1H, $J = 2.2$, 9.0 Hz), 7.09 (t, 1H, $J = 9.0$ Hz), 5.13 (m, 1H, $J = 5.0$ Hz), 4.83 (d, 2H, $J = 4.8$ Hz), 4.21 (t, 1H, $J = 9.1$ Hz), 3.86 (dd, 1H, $J = 5.7$, 9.1 Hz), 3.26 (d, 4H, $J = 4.0$ Hz), 3.07 (t, 4H, $J = 5.0$ Hz), 2.94 (s, 3H). IR (KBr pellet, cm^{-1}): ν 2946, 2741, 2606, 1740, 1574, 1520, 1482, 1449, 1421 1380, 1326, 1276, 1226. Anal. CHNS: calcd 48.10, 4.99, 19.80, 7.55, found 48.34, 4.91, 19.56, 7.42.

4.1.10. 3-[3-Fluoro-4-(4-propionyl-piperazin-1-yl)-phenyl]-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one 9h. Compound **9h** was prepared from the trifluoroacetic acid salt **8** (800 mg, 1.74 mmol), propionic anhydride (334 μL, 2.61 mmol), and triethylamine (1 mL) and worked up as described for **9b**. Recrystallization of the crude solid (657 mg) from ethyl acetate–acetonitrile gave **9h** (436 mg, 62% yield), mp 138–139 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.18 (s, 1H), 7.77 (s, 1H), 7.43 (dd, 1H, $J = 2.2$, 14.8 Hz), 7.13 (dd, 1H, $J = 2.2$, 9.0 Hz), 7.06 (t, 1H, $J = 9.2$ Hz), 5.13 (m, 1H, $J = 5.1$ Hz), 4.83 (d, 2H, $J = 5.0$ Hz), 4.21 (t, 1H, $J = 9.2$ Hz), 3.86 (dd, 1H, $J = 5.8$, 9.3 Hz), 3.59 (s, 4H), 2.96 (t, 2H, $J = 5.0$ Hz), 2.92 (t, 2H, $J = 5.0$ Hz), 2.36 (q, 2H, $J = 7.4$, 14.4 Hz), 1.01 (t, 3H, $J = 7.4$ Hz). IR (KBr pellet, cm^{-1}): ν 3120, 3001, 2833, 2360, 1743, 1640, 1572, 1517, 1477, 1444, 1407, 1361, 1321, 1278, 1230, 1214. Anal. CHN: calcd 56.71, 5.76, 20.88, found 56.98, 5.66, 20.85.

4.1.11. 4-[2-Fluoro-4-(2-oxo-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl]-piperazine-1-carboxylic acid ethyl ester 9i. Compound **9i** was prepared from the trifluoroacetic acid salt **8** (800 mg, 1.74 mmol), ethyl chloroformate (248 μL, 2.61 mmol), and triethylamine (1 mL) as described for **9b**. Work-up and recrystallization from acetonitrile–ether gave **9i** (256 mg, 35% yield), mp 158–159 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (s, 1H), 7.77 (s, 1H), 7.41 (dd, 1H, $J = 2.0$, 14.7 Hz), 7.12 (dd, 1H, $J = 2.0$, 8.9 Hz), 7.06 (t, 1H, $J = 9.1$ Hz), 5.12 (m, 1H, $J = 5.1$ Hz), 4.82 (d, 2H, $J = 5.0$ Hz), 4.20 (t, 1H, $J = 9.2$ Hz), 4.06 (q, 2H, $J = 7.1$Hz, 14.1 Hz), 3.85 (dd, 1H, $J = 5.7$ Hz), 3.51 (t, 4H, $J = 4.4$ Hz), 2.93 (t, 4H, $J = 4.4$ Hz), 1.99 (t, 3H, $J = 7.1$ Hz). IR (KBr pellet, cm^{-1}): ν 2953, 2822, 1748, 1684, 1573, 1519, 1439, 1391, 1330, 1281, 1238. Anal. CHN: calcd 54.54, 5.54, 20.08, found 54.84, 5.40, 20.09.

4.1.12. 4-[2-Fluoro-4-(2-oxo-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl]-piperazine-1-carbothioic acid *S*-ethyl ester 9j. Compound **9j** was prepared from the trifluoroacetic acid salt **8** (800 mg, 1.74 mmol), ethyl

chlorothioformate (326 μL, 3.48 mmol), and triethylamine (1 mL), and worked up as described for **9b**. Recrystallization from acetonitrile gave **9j** (519 mg, 69% yield), mp 188–190 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): 8.16 (s, 1H), 7.76 (s, 1H), 7.42 (dd, 1H, J = 2.0, 14.7 Hz), 7.13 (dd, 1H, J = 2.0, 9.0 Hz), 7.10 (t, 1H, J = 9.0 Hz), 5.12 (m, 1H, J = 5.2 Hz), 4.82 (d, 2H, J = 5.0 Hz), 4.21 (t, 1H, J = 9.2 Hz), 3.86 (q, 1H, J = 5.7, 9.2 Hz), 3.61 (s, 4H), 2.97 (t, 4H, J = 4.6 Hz), 2.85 (q, 2H, J = 7.3, 14.6 Hz), 1.21 (t, 3H, J = 7.3 Hz). IR (KBr pellet, cm^{-1}): ν 3155, 2966, 2917, 2863, 2361, 1762, 1659, 1640, 1571, 1519, 1479, 1408, 1330, 1283, 1223. Anal. CHNS: calcd 52.52, 5.34, 19.34, 7.38 found 52.83, 5.32, 19.26, 6.90.

4.1.13. 1-{4-[2-Fluoro-4-(2-oxo-5-[1,2,3]triazol-1-yl-methyl-oxazolidin-3-yl)-phenyl]-piperazin-1-yl}-propane-1,2-one 9k. To a solution of pyruvic acid (287 mg, 3.26 mmol) in DCM, oxalyl chloride (620 mg, 4.89 mmol) was added with cooling in an ice bath, followed by the addition of one drop of dimethyl formamide. After effervescence evolved, the cooling bath was removed and the mixture stirred at room temperature for 2 h. The mixture was concentrated to dryness to give the pyruvic acid chloride. A solution of the acid chloride in acetonitrile was added to a solution of the trifluoroacetic acid salt (1.0 g, 2.17 mmol) and triethylamine (1 mL) in acetonitrile and the mixture was stirred overnight. The reaction mixture was concentrated to dryness to give a crude mass 675 mg. Purification by silica gel column chromatography (ethyl acetate) gave **9k** as a white solid 214 mg (24% yield), mp 159–161 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): 8.17 (s, 1H), 7.77 (s, 1H), 7.43 (dd, 1H, J = 2.2, 14.7 Hz), 7.14 (dd, 1H, J = 2.3, 9.0 Hz), 7.08 (t, 1H, J = 9 Hz), 5.12 (m, 1H, J = 5.0 Hz), 4.83 (d, 2H, J = 5.0 Hz), 4.21 (t, 1H, J = 9.2 Hz), 3.86 (q, 1H, J = 5.8, 9.2 Hz), 3.64 (br s, 2H), 3.51 (br s, 2H), 2.99 (d, 4H, J = 4.8 Hz), 2.40 (s, 3H). IR (KBr pellet, cm^{-1}): ν 2825, 1743, 1640, 1521, 1422, 1332, 1281, 1231. Anal. CHN: calcd 54.80, 5.08, 20.18, found 54.82, 5.13, 19.88.

4.1.14. 3-[3-Fluoro-4-(4-isobutyryl-piperazin-1-yl)-phenyl]-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one 9l. Compound **9l** was prepared from the trifluoroacetic acid salt **8** (1.00 g, 2.17 mmol), isobutyryl chloride (344 μL, 3.26 mmol), and triethylamine, and worked up as described for **9b**. Recrystallization from acetonitrile gave compound **9l** as a beige crystalline solid (423 mg, 47% yield), mp 184–186 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.18 (s, 1H), 7.77 (s, 1H), 7.43 (dd, 1H, J = 2.3, 14.7 Hz), 7.13 (dd, 1H, J = 2.2, 9.0 Hz), 7.06 (t, 1H, J = 9.2 Hz), 5.13 (m, 1H, J = 5.0 Hz), 4.83 (d, 2H, J = 5.1 Hz), 4.21 (t, 1H, J = 9.0 Hz), 3.86 (dd, 1H, J = 5.7, 9.3 Hz), 3.65–3.61 (mp, 4H), 2.97–2.88 (mp, 4H, 1H), 1.02 (d, 6H, J = 6.8 Hz). IR (KBr pellet, cm^{-1}): ν 2848, 1732, 1641, 1521, 1487, 1467, 1369, 1324, 1279, 1226. m/z 416 (M$^+$). Anal. CHNS: calcd 57.68, 6.05, 20.18 found 57.54, 5.83, 20.04.

4.1.15. 3-[4-(4-Cyclopentanecarbonyl-piperazin-1-yl)-3-fluoro-phenyl]-5-[1,2,3]triazol-1-yl-methyl-oxazolidin-2-one 9m. Compound **9m** was prepared from the trifluoroacetic acid salt **8** (1.0 g, 2.17 mmol), cyclopentanecarbonyl chloride (396 μL, 3.26 mmol), and triethylamine (1 mL) as described for **9b**. Work-up and recrystallization (ethyl acetate–acetonitrile) gave **9m** (638 mg, 66% yield), mp 183–185 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (s, 1H), 7.77 (s, 1H), 7.42 (dd, 1H, J = 2.4, 14.7 Hz), 7.13 (dd, 1H, J = 2.2, 9.0 Hz), 7.06 (t, 1H, J = 9.0 Hz), 5.12 (m, 1H, J = 5.2 Hz), 4.82 (d, 2H, J = 5.0 Hz), 4.21 (t, 1H, J = 9.2 Hz), 3.86 (dd, 1H, J = 5.7, 8.9 Hz), 3.64 (t, 2H, J = 4.8 Hz), 3.61 (t, 2H, J = 4.8 Hz), 3.01 (m, 1H), 2.95 (t, 2H, J = 4.6 Hz), 2.90 (t, 2H, J = 4.8 Hz), 1.54–1.76 (m, 8H). IR (KBr pellet, cm^{-1}): ν 3107, 2957, 2867, 1748, 1627, 1520, 1484, 1443, 1421, 1404, 1325, 1280, 1226. m/z 442 (M$^+$). Anal. CHN: calcd 59.71, 6.15, 18.99, found 59.72, 6.09, 18.90.

4.1.16. 3-[4-(4-Cyclohexanecarbonyl-piperazin-1-yl)-3-fluoro-phenyl]-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one 9n. Compound **9n** was prepared from the trifluoroacetic acid salt **8** (1.0 g, 2.17 mmol) and cyclohexanecarbonyl chloride (436 μL, 3.26 mmol) using triethylamine as acid scavenger in acetonitrile, and worked up as described for **9b**. Recrystallization from acetonitrile gave compound **9n** (620 mg, 63% yield) as a crystalline solid, mp 212–214 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (s, 1H), 7.77 (s, 1H), 7.42 (dd, 1H, J = 2.23, 14.7 Hz), 7.13 (dd, 1H, J = 2.0, 8.9 Hz), 7.06 (t, 1H, J = 9 Hz), 5.12 (m, 1H, J = 5.2 Hz), 4.82 (d, 2H, J = 5.0 Hz), 4.20 (t, 1H, J = 9.2 Hz), 3.86 (dd, 1H, J = 5.7, 9.3 Hz), 3.62 (d, 4H), 2.92 (d, 4H), 2.61 (br s, 1H), 1.64–1.71 (m, 4H), 1.15–1.38 (m, 6H). IR (KBr pellet, cm^{-1}): ν 3140, 3115, 2937, 2856, 1741, 1624, 1517, 1476, 1444, 1423, 1329, 1292, 1206, 1228. m/z 456 (M$^+$). Anal. CHN: calcd 60.51, 6.40, 18.41, found 60.42, 6.21, 18.37.

4.1.17. 3-[4-(4-Benzoyl-piperazin-1-yl)-3-fluoro-phenyl]-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one 9o. Compound **9o** was prepared from 3-(3-fluoro-4-piperazinium-1-yl-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one trifluoroacetic acid salt **8** (500 mg, 1.09 mmol) and benzoyl chloride (189 μL, 1.63 mmol), and worked up as described for **9b**. Recrystallization from ethyl acetate–acetonitrile gave a beige crystalline solid **9o** (157 mg, 32% yield), mp 204–205 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (s, 1H), 7.77 (s, 1H), 7.41 (d, 1H, J = 2.34 Hz), 7.46 (m, 6H), 7.14 (dd, 1H, J = 2.2, 9.0 Hz), 7.08 (t, 1H, J = 9.0 Hz), 5.13 (m, 1H, J = 5.2 Hz), 4.83 (d, 2H, J = 5.0 Hz), 4.21 (t, 1H, J = 9.2 Hz), 3.86 (q, 1H, J = 5.7, 9.3 Hz), 3.78 (br s, 2H), 3.46 (br s, 2H), 2.98 (br s, 4H). IR (KBr pellet, cm^{-1}): ν 2842, 1747, 1620, 1574, 1517, 1442, 1411, 1363, 1324, 1282. Anal. CHN: calcd 61.33, 5.15, 18.66, found 61.71, 5.10, 18.68.

4.1.18. 2-Fluoro-4-[4-(2-oxo-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl]-piperazine-1-carboxylic acid benzyl ester 9p. Compound **9p** was prepared from the trifluoroacetic acid salt **8** (500 mg, 1.09 mmol), benzyl chloroformate (278 mg, 1.63 mmol), and triethylamine (1 mL) and worked up as described for **9b** to give **9p** (351 mg, 67% yield), after recrystallization (ethyl acetate–acetonitrile), mp 186–188 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.16 (s, 1H), 7.77 (s, 1H), 7.33–7.42 (m, 6H), 7.04–7.13 (m, 2H), 5.11 (m, 3H), 4.82 (d, 2H,

J = 5.0 Hz), 4.19 (t, 1H, J = 9.1 Hz), 3.85 (q, 1H, J = 5.8, 9.1 Hz), 3.54 (br d, 4H, J = 11.23 Hz), 2.94 (br s, 4H). IR (KBr pellet, cm^{-1}): v 2835, 2384, 1742, 1700, 1574, 1515, 1482, 1418, 1332, 1250, 1286, 1223. Anal. CHN: calcd 60.00, 5.24, 17.49, found 60.39, 5.24, 17.68.

5. Microbiology

5.1. Antibacterial susceptibility testing

Antibacterial susceptibility testing was performed by the agar dilution methods according to the National Committee for Clinical Laboratory Standards.[28] 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 32 μg/mL. The new compounds were dissolved in 20% water in DMSO, while linezolid and vancomycin were dissolved in 40% water in ethanol and water, respectively. The test compounds were diluted in MH broth for all staphylococci and enterococci, and in MH broth 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 = 20), 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 utilized included *S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228 and *E. faecalis* ATCC 29212, *E. coli* ATCC 25922, and *H. influenzae* ATCC 49247 strains were used as controls. All clinical isolates were identified at the Reference Laboratories, Faculty of Medicine, Kuwait University. 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. The MIC was defined as the lowest drug concentration that completely inhibited growth of the bacteria. Linezolid and PH-027, prepared according to the literature methods,[18,20] and vancomycin obtained from a commercial source were used as reference antibacterial agents.

Acknowledgment

Project was supported by Kuwait University Research Grant PC01/02, and the Instrument Grants GS01/01 and GS03/01 awarded to the Science Analytical Facilities (SAF).

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