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Original article

Synthesis and biological evaluation of new N-linked 5-triazolylmethyl oxazolidinones

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Abstract

A new series of oxazolidinones bearing N-linked 5-triazolylmethyl group have been synthesized and their *in vitro* antibacterial activities (*MIC*) were evaluated against a spectrum of resistant and susceptible Gram-positive organisms. Some of the analogues in this series displayed activity superior to linezolid and vancomycin. Furthermore, *in vivo* efficacies and pharmacokinetic properties of the selected compounds were also disclosed herein; the selected compounds showed reasonable bioavailability as well as *in vivo* efficacy comparable to that of linezolid.

Keywords: Oxazolidinone; Linezolid; Antibacterial agents; Gram-positive organisms

1. Introduction

Infections due to Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (*MRSA*), vancomycin-resistant *Enterococcus faecium* (*VREF*), and penicillin-resistant *Streptococcus pneumoniae* (*PRSP*) are the leading cause of morbidity and mortality in hospital settings and community today [1–5]. Oxazolidinones, typified by linezolid (Zyvox™, Pharmacia/Pfizer, Fig. 1), represent a new class of synthetic antibacterial agents with potent activity against clinically important susceptible and resistant Gram-positive pathogens [6]. Oxazolidinones inhibit the bacterial protein synthesis prior to the chain initiation step, by binding to the 23S rRNA of 50S ribosomal subunit, and interfering with the initiator fMET-tRNA binding to the P-site of the ribosomal peptidyltransferase center [7,8]. Resistance to antibiotics may be unavoidable, some linezolid-resistant clinical isolates of VREF and *S. aureus* have been reported recently [9,10]. This unexpected early development of resistance emphasizes the need for further exploration of features of oxazolidinone series to overcome these issues.

Phillips and co-workers recently reported that new 5-triazolylmethyl oxazolidinones based on the replacement of the 5-acetamidomethyl substituents with N-linked triazolyl, exemplified by **pH-027** (Fig. 2), demonstrated strong *in vitro* activity [11]. Furthermore, we have found that the arylsulfonyl oxazolidinones bearing N-linked 5-triazolylmethyl group such as **YX-10** (Fig. 2) demonstrated potent *in vitro* activities (MIC = 0.25–1 μg/mL against *MSSA*), but their *in vivo* activities ($ED_{50} > 100$ mg/kg) were not desirable, the inferior *in vivo* potency may be due to their poor solubility in the vehicle or suboptimal pharmacokinetic properties [12]. However, **RBx 7644** (Fig. 2), 5-nitro-2-furyl attached to the 'piperazinyl-phenyl-oxazolidinone' core structure of eperezolid (Fig. 1) with a methylene linker, has successfully completed Phase I clinical trial in UK [13]. It showed similar or superior activity to linezolid against common Gram-positive pathogens, but more potent antibacterial activity than linezolid against some

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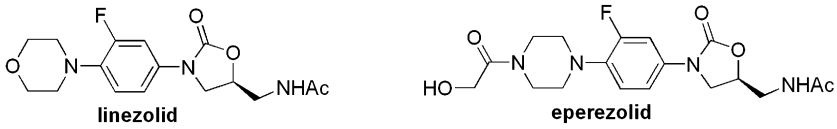


Fig. 1. Structure of linezolid and eperezolid.

fastidious Gram-negative organisms ($MIC_{90} = 2$ μg/mL) [14]. Based on these findings, we designed and synthesized a new series of oxazolidinones bearing N-linked 5-triazolylmethyl group to find more potent oxazolidinone antibacterial agents with greater water solubility and better pharmacokinetic profiles. Here we report our efforts towards the synthesis and biological evaluation (including *in vitro*, *in vivo* and pharmacokinetics) of this series of compounds, resulting in the discovery of a promising drug candidate (compound **4e**) with potent antibacterial activity and reasonable bioavailability.

2. Chemistry

Synthesis of these novel compounds was carried out in a straightforward manner. Compound **1** was synthesized from the readily available starting materials piperazine and 3,4-difluoronitro-benzene according to the known method [12,15,16] in several steps. As shown in Scheme 1, compound **1** readily underwent Leuckart–Wallach reaction with the corresponding substituted formaldehyde in DMF as solvent at 100 °C afforded compounds **2a–2c**, **2e**, **2g**, **3a–3c**, **4a–4d** and **5a–5e** in moderate to good yields. Treatment of compound **1** with 2-chloromethyl-5-nitrofuran [17] and triethylamine in CH_3CN gave **4e** in 71% yield. Further chemical transformations involving treatment of **2c**, **2e** and **2g** with 10% palladium on carbon in CH_2Cl_2 and CH_3OH under hydrogen afforded **2d**, **2f** and **2h**, respectively, in moderate to good yields. All the newly synthesized compounds were characterized by spectroscopic data (^{1}H NMR, IR, EI-MS or ESI-MS), mp and elemental analysis.

3. Result and discussion

The result of *in vitro* antibacterial activities against a spectrum of resistant and susceptible Gram-positive organisms is summarized in Table 1. It clearly showed that most of the compounds in this series displayed good antibacterial activities, especially compound **4e**, the most potent one, exhibited more potent antibacterial activity than linezolid and vancomycin, with MIC values of 0.125 μg/mL against *S. aureus ATCC 25923*, 0.06 μg/mL against *S. aureus ATCC 29213*, 0.06–0.25 μg/mL against MSSA, 0.06–4 μg/mL against MRSA, 0.03–0.125 μg/mL against *Streptococcus pneumoniae*, 0.25–0.5 μg/mL against *Enterococcus faecalis*. It identified the N-linked-5-triazoylmethyl group as structural alternative for strong antibacterial in the oxazolidinone class.

Compounds **2a–2h**, substituted phenyl ring attached to the 'piperazinyl-phenyl-oxazolidinone' core structure with a methylene linker, displayed potent antibacterial activity. Substitution on the phenyl ring with $-NO_2$ or $-CHO$ also showed good antibacterial activity, and the substituted position was relevant to the activity, reducing $-NO_2$ group to electron-donating group $-NH_2$ resulted in enhancement of activity.

The replacement of substituted phenyl ring with 2-pyridyl **3a** and 3-pyridyl **3b** resulted in superior activity to linezolid, while 4-pryidyl derivative **3c** led to inferior activity to linezolid. *In vitro* rank order being 2-pyridyl > 3-pyridyl > 4-pyridyl, the activity decreased with the increment of distance between the nitrogen atom of pyridyl ring and the methylene linker. It may be explained that compound **3a** has a stronger binding affinity with the receptor than that of compounds **3b** and **3c**.

The replacement of substituted phenyl ring with 2-furyl **4a** and 3-furyl **4b** resulted in superior activity to linezolid. Interestingly, compound **4b** displayed more potent activity than **4a**, it suggested that the linked position was relevant to the activity. Replacing 2-furyl with electron-donating group $-CH_3$ (**4c**) or weak electron-withdrawing group $-Cl$ (**4d**) led to a slight decrease in activity, while strong electron-withdrawing group $-NO_2$ (**4e**) led to a great increase in activity.

Substitution with 2-thienyl **5a** and 3-thienyl **5b** also gave compounds with superior activity to the reference compounds, however, similar trend for furyl series was not observed in the thienyl series, 2-thienyl derivative **5a** was more potent than 3-thienyl derivative **5b**. Substitution of 2-thienyl ring with electron-donating group $-CH_3$ (**5d** and **5e**) or weak electron-withdrawing group $-Br$ (**5c**) on the different position resulted in activity inferior to unsubstituted-thienyl derivative **5a**.

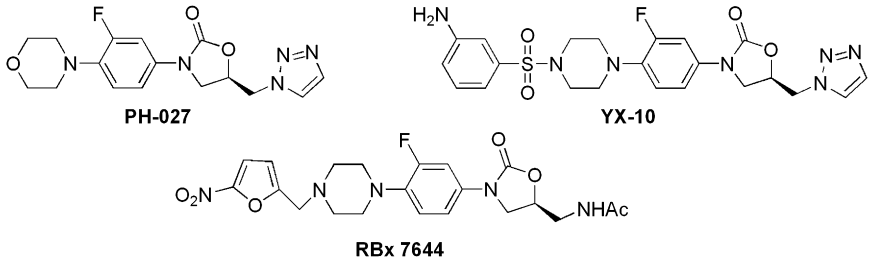
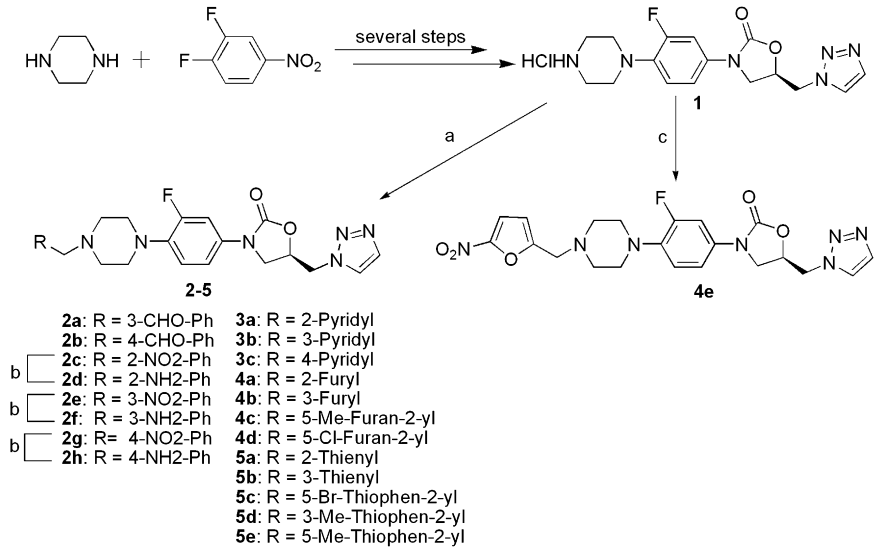


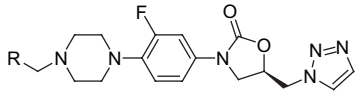
Fig. 2. Structure of **pH-027**, **YX-10** and **RBx 7644**.



Scheme 1. (a) RCHO, HCO_2H, DMF, 100 °C, 2–24 h; (b) 10% Pd/C, H_2, CH_2Cl_2/MeOH, rt, 2 h; (c) 2-chloromethyl-nitrofuran, Et_3N, CH_3CN, 50 °C, 6 h.

The *in vivo* activities of compounds **2e**, **2h**, **4a** and **4b** were tested in mice mode (see Table 2). Compounds **4b** ($ED_{50} = 7.47$ mg/kg) and **2e** ($ED_{50} = 7.87$ mg/kg) displayed oral efficacies slightly superior than that for linezolid ($ED_{50} = 8.45$ mg/kg), while compounds **4b** ($ED_{50} = 6.99$ mg/kg) and **2h** ($ED_{50} = 6.73$ mg/kg) displayed intravenous efficacies slightly superior than that for linezolid ($ED_{50} = 8.45$ mg/kg), whereas compound **4a** was inferior to linezolid and vancomycin.

Table 1
MIC ranges (μg/mL) of new oxazolidinones against Gram-positive clinical isolates



Compounds	R	S.a.[a]	MSSA[b] $n = 5$	MRSA[c] $n = 3$	S.p.[d] [5]	E.f.[e] [5]
2a	3-CHO–Ph	0.25	0.5–1	0.125–1	1	1
2b	4-CHO–Ph	0.008	1–2	0.25–2	1	2
2c	2-NO_2–Ph	0.125	0.125–2	1–4	1–2	2 to >8
2d	2-NH_2–Ph	0.125	0.125–0.5	0.5–4	0.5–1	1–2
2e	3-NO_2–Ph	0.03	0.06–1	0.5–4	0.5	0.5–1
2f	3-NH_2–Ph	0.25	0.25–1	0.5–4	0.5–1	0.5–2
2g	4-NO_2–Ph	0.5	0.5 to >8	>8	4 to >8	8 to >8
2h	4-NH_2–Ph	0.125	0.06–0.5	0.5–4	0.5	0.25–1
3a	2-Pyridyl	0.125	0.125–0.5	0.5–4	0.5–1	0.5–1
3b	3-Pyridyl	0.125	0.125–1	1–4	1	1–4
3c	4-Pyridyl	0.5	0.5–1	1–8	1–2	2–8
4a	2-Furyl	0.06	0.06–0.5	0.5–4	0.5	0.5–1
4b	3-Furyl	0.008	0.008–0.06	0.03–4	0.03–2	0.5–4
4c	5-Me-furan-2-yl	0.125	0.125–1	1–8	2	2 to >8
4d	5-Cl-furan-2-yl	0.125	0.125–1	1–4	1	2–4
4e	5-NO_2-furan-2-yl	0.06	0.06–0.25	0.06–4	0.03–0.125	0.25–0.5
5a	2-Thienyl	0.06	0.06–0.5	0.06–4	0.06–0. 25	2–4
5b	3-Thienyl	0.06	0.06–0.5	1 to >8	0.5	1 to >8
5c	5-Br-thiophen-2-yl	0.06	0.06–0.5	0.5–4	0.5–1	1–8
5d	3-Me-thiophen-2-yl	1	1–4	4 to >8	4	4 to >8
5e	5-Me-thiophen-2-yl	0.125	0.06–8	4–8	2–8	4 to >8
Linezolid		0.5	0.5–2	1–4	1–2	1–2
Vancomycin		0.125	0.125–1	1–4	1–2	1–2

[a] S.a. = *Staphylococcus aureus* ATCC 29213.
[b] MSSA = Methicillin-susceptible *Staphylococcus aureus*.
[c] MRSA = Methicillin-resistant *Staphylococcus aureus*.
[d] S.p. = *Streptococcus pneumoniae*.
[e] E.f = *Enterococcus faecalis*.

Table 2
In vivo efficacies of the selected compounds

Organism	Compound	Route	ED_{50}[a] (mg/kg)
MRSA 05-2	**2e**	p.o.	7.87 (5.24–21.81)
		i.v.	11.21 (7.30–18.99)
	2h	p.o.	14.53 (9.72–34.78)
		i.v.	6.73 (4.47–10.79)
	4a	p.o.	12.28 (8.25–24.67)
		i.v.	12.00 (7.65–27.95)
	4b	p.o.	7.47 (5.21–15.41)
		i.v.	6.99 (4.48–19.90)
	Linezolid	p.o.	8.45 (5.65–14.26)
		i.v.	8.45 (5.65–14.26)
	Vancomycin	s.c.	6.00 (3.83–13.96)
		i.v.	6.54 (3.89–21.87)

[a] The amount of drug required after oral administration (mg/kg/day) to cure 50% of infected mice subjected to a lethal systemic infection. Numbers in parentheses are 95% confidence ranges.

Compounds **2e**, **2h**, **4b** and **4e** were subjected to pharmacokinetic performance assessment (Table 3). All of the selected compounds have reasonable oral bioavailability ($F = 43.8$–102.6%). In a p.o. dose escalation study, a linear increase in drug exposure was observed as indicated by AUC.

4. Conclusion

In conclusion, a new series of N-linked 5-triazolyl-methyl substituted oxazolidinones were synthesized and evaluated for microbiological activity against resistant and susceptible Gram-positive organisms *in vitro* comparable to linezolid and vancomycin. Most of them showed more potent or equivalent activity to that of linezolid and vancomycin. Several compounds from this series exhibited reasonable oral bioavailability as well as *in vivo* efficacies comparable to that of linezolid. The result suggested that this series of oxazolidinones bearing N-linked 5-triazolylmethyl group have potent antibacterial activity and perfect pharmacokinetic profiles. Further development of compound **4e** as a promising drug candidate is on going in preclinical investigations.

5. Experimental

5.1. General

All solvents used were of analytical grade (Sinopharm Chemical Reagent Co., Ltd.). Melting points (uncorrected) were determined on an X-4 melting point apparatus. ^{1}H NMR spectral data were recorded on a Varian Mercury-400 spectrometer, chemical shifts are given in parts per million (δ) values and coupling constants (J) in Hertz. Infrared (IR) spectra were recorded on a Nicolet FTIR-750 spectrometer. EI-MS spectra were obtained on a Finnigan MAT 95 mass spectrometer and ESI-MS spectra were obtained on a Kratos MS 80 mass spectrometer. Elemental analysis was obtained using a vario EL spectrometer. Column chromatography was performed on silica gel H (200–300 mesh, Qingdao Marine Chemical Ltd.), and the solvent proportions were expressed on a volume:volume basis.

5.2. Preparation of compounds *2a–2h*, *3a–3c*, *4a–4e* and *5a–5e*

5.2.1. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(3-formylbenzyl)piperazin-1-yl)phenyl)-oxazolidin-2-one (*2a*)

Compound **1** (383 mg, 1.0 mmol), isophthalaldehyde (201 mg, 1.5 mmol) and formic acid (92 mg, 2.0 mmol)

Table 3
Pharmacokinetic parameters of the selected compounds

Cp[a]	Rt[b]	Dose (mg/kg)	C_{max}[c] (μg/mL)	T_{max}[d] (h)	$t_{1/2\beta}$[e] (h)	$AUC_{0-\infty}$[f] (μg h/mL)	CL[g] (mL/min/kg)	F[h] (%)
2e	p.o.	10	3.24 ± 0.68	1.40 ± 0.80	2.36 ± 0.56	16.10 ± 5.98	11.70 ± 4.99	61.5
	p.o.	50	10.77 ± 2.15	2.30 ± 0.50	5.34 ± 2.56	74.50 ± 21.90	11.30 ± 3.58	n.c.
	i.v.	10	n.c.[i]	n.a.[j]	2.95 ± 0.46	26.16 ± 8.24	6.98 ± 2.73	n.a.
	p.o.	10	1.20 ± 0.47	0.75 ± 0.29	3.40 ± 0.24	3.10 ± 0.46	54.4 ± 8.00	43.8
2h	p.o.	50	2.32 ± 0.77	1.00 ± 0.00	4.67 ± 0.98	18.10 ± 6.50	49.00 ± 17.50	n.c.
	i.v.	10	n.c.	n.a.	3.52 ± 0.52	7.08 ± 1.07	23.90 ± 4.24	n.a.
	p.o.	10	3.04 ± 0.12	0.88 ± 0.25	2.76 ± 0.52	16.40 ± 3.50	10.50 ± 2.50	62.7
4b	p.o.	50	10.70 ± 3.00	1.90 ± 1.00	8.60 ± 3.15	85.80 ± 20.00	8.86 ± 3.03	n.c.
	i.v.	10	n.c.	n.a.	2.95 ± 0.46	26.20 ± 8.20	6.98 ± 2.73	n.a.
	p.o.	10	5.44 ± 1.28	0.25 ± 0.00	1.51 ± 0.55	19.40 ± 10.40	18.00 ± 4.33	102.6
4e	p.o.	50	16.9 ± 2.30	0.50 ± 0.27	1.66 ± 0.48	139.00 ± 48.00	16.80 ± 3.17	n.c.
	i.v.	10	n.c.	n.a.	1.18 ± 0.32	18.9 ± 9.20	16.17 ± 4.83	n.a.

[a] Compound.
[b] Route.
[c] Maximum plasma concentration.
[d] Time at which C_{max} achieved.
[e] Elimination half-life.
[f] Area under the concentration–time curve.
[g] Clearance.
[h] Absolute oral bioavailability assuming linear pharmacokinetics.
[i] n.c. = not calculated.
[j] n.a. = not applicable.

were placed in dry DMF (5 mL) and heated to 100 °C under N_2 for 16 h. The reaction was cooled and partitioned between CH_2Cl_2 (30 mL) and saturated $NaHCO_3$ solution (200 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL) and the combined extracts washed with water (200 mL) and brine (100 mL), and dried over Na_2SO_4. Removal of the solvent gave a residue which was chromatographed with CH_2Cl_2/MeOH (50:1) to afford **2a** (270 mg, 58%) as a white solid, mp 120–121 °C. ^{1}H NMR ($CDCl_3$): δ 10.03 (s, 1H), 7.87 (s, 1H), 7.76–7.82 (m, 2H), 7.74 (s, 1H), 7.64 (d, $J = 7.50$ Hz, 1H), 7.50 (t, $J = 7.59$ Hz, 1H), 7.27 (dd, $J_1 = 2.47$ Hz, $J_2 = 14.18$ Hz, 1H), 6.95 (dd, $J_1 = 2.47$ Hz, $J_2 = 8.88$ Hz, 1H), 6.88 (t, $J = 8.78$ Hz, 1H), 5.03 (m, 1H), 4.78 (m, 2H), 4.12 (t, $J = 9.15$ Hz, 1H), 3.88 (dd, $J_1 = 6.13$ Hz, $J_2 = 9.42$ Hz, 1H), 3.64 (s, 2H), 3.12 (t, $J = 4.76$ Hz, 4H), 2.64 (t, $J = 4.76$ Hz, 4H). IR (KBr pellet, cm^{-1}): 3429, 2947, 2837, 1751, 1703, 1518, 1412, 1225, 1113, 750. MS (EI) *m/z* (%): 464 (M^+, 100). Anal. Calcd for $C_{24}H_{25}FN_6O_3 \cdot 1/2CH_3OH$: C, 61.24; H, 5.66; N, 17.49. Found: C, 61.35; H, 5.37; N, 17.79.

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

The title compound was prepared according to the similar procedure for **2a** utilizing terephthalaldehyde instead of isophthalaldehyde, chromatography using CH_2Cl_2/MeOH (50:1) afforded **2b** (348 mg, 75%) as a white solid, mp 161–162 °C. ^{1}H NMR ($CDCl_3$): δ 10.00 (s, 1H), 7.85 (d, $J = 8.05$ Hz, 2H), 7.78 (s, 1H), 7.74 (s, 1H), 7.53 (d, $J = 8.05$ Hz, 2H), 7.27 (dd, $J_1 = 2.57$ Hz, $J_2 = 14.09$ Hz, 1H), 6.95 (dd, $J_1 = 2.38$ Hz, $J_2 = 8.78$ Hz, 1H), 6.88 (t, $J = 8.78$ Hz, 1H), 5.04 (m, 1H), 4.78 (m, 2H), 4.12 (t, $J = 9.15$ Hz, 1H), 3.88 (dd, $J_1 = 6.22$ Hz, $J_2 = 9.33$ Hz, 1H), 3.64 (s, 2H), 3.08 (t, $J = 4.76$ Hz, 4H), 2.64 (t, $J = 4.76$ Hz, 4H). IR (KBr pellet, cm^{-1}): 3469, 3109, 2933, 2821, 1741, 1691, 1606, 1514, 1417, 1223, 1009, 754. MS (EI) *m/z* (%): 464 (M^+, 91), 420 (100). Anal. Calcd for $C_{24}H_{25}FN_6O_3 \cdot 1/2CH_3OH$: C, 61.24; H, 5.66; N, 17.49. Found: C, 61.51; H, 5.43; N, 17.83.

5.2.3. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(2-nitrobenzyl)piperazin-1-yl)phenyl)-oxazolidin-2-one (**2c**)

The title compound was prepared according to the similar procedure for **2a** utilizing 2-nitrobenzaldehyde instead of isophthalaldehyde, chromatography using CH_2Cl_2/MeOH (50:1) afforded **2c** (240 mg, 50%) as a yellow foam, mp 136–137 °C. ^{1}H NMR ($CDCl_3$): δ 7.82 (d, $J = 7.97$ Hz, 1H), 7.78 (d, $J = 0.96$ Hz, 1H), 7.74 (d, $J = 0.96$ Hz, 1H), 7.56 (m, 2H), 7.42 (m, 1H), 7.27 (dd, $J_1 = 2.33$ Hz, $J_2 = 14.15$ Hz, 1H), 6.94 (dd, $J_1 = 2.40$ Hz, $J_2 = 9.13$ Hz, 1H), 6.87 (t, $J = 8.92$ Hz, 1H), 5.05 (m, 1H), 4.88 (m, 2H), 4.12 (t, $J = 9.13$ Hz, 1H), 3.84–3.90 (m, 3H), 3.06 (br s, 4H), 2.60 (br s, 4H). IR (KBr pellet, cm^{-1}): 3124, 2827, 1736, 1518, 1452, 1336, 1240, 1134, 735. MS (EI) *m/z* (%): 481 (M^+, 25), 304 (100). Anal. Calcd for $C_{23}H_{24}FN_7O_4$: C, 57.37; H, 5.02; N, 20.36. Found: C, 57.05; H, 4.96; N, 20.11.

5.2.4. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(2-aminobenzyl)piperazin-1-yl)phenyl)-oxazolidin-2-one (**2d**)

A mixture of compound **2c** (200 mg, 0.41 mmol) and 10% palladium on carbon (40 mg) in CH_2Cl_2 (15 mL) and MeOH (15 mL) was stirred under hydrogen (balloon) for 2 h. The mixture was then filtered through diatomaceous earth, the filter cake was washed with CH_2Cl_2 (30 mL), and the combined filtrates were concentrated, the residue was purified by silica gel column chromatography eluting with CH_2Cl_2/MeOH (25:1) to afford compound **2d** (146 mg, 78%) as a white solid, mp 201–202 °C. ^{1}H NMR (DMSO-d_6): δ 8.16 (d, $J = 0.78$ Hz, 1H), 7.74 (d, $J = 0.78$ Hz, 1H), 7.36 (dd, $J_1 = 2.40$ Hz, $J_2 = 14.96$ Hz, 1H), 7.08 (dd, $J_1 = 2.25$ Hz, $J_2 = 9.10$ Hz, 1H), 7.02 (t, $J = 9.29$ Hz, 1H), 6.95 (t, $J = 7.34$ Hz, 2H), 6.62 (d, $J = 8.02$ Hz, 1H), 6.49 (t, $J = 6.85$ Hz, 1H), 5.10 (m, 1H), 4.80 (d, $J = 5.09$ Hz, 2H), 4.18 (t, $J = 9.19$ Hz, 1H), 3.83 (dd, $J_1 = 5.77$ Hz, $J_2 = 9.19$ Hz, 1H), 3.44 (br s, 2H), 3.36 (s, 2H), 2.96 (br s, 4H), 2.48 (br s, 4H). IR (KBr pellet, cm^{-1}): 3369, 3288, 2951, 2823, 1743, 1618, 1514, 1423, 1336, 1219, 1070, 748. MS (EI) *m/z* (%): 451 (M^+, 17), 106 (100). Anal. Calcd for $C_{23}H_{26}FN_7O_2$: C, 61.18; H, 5.80; N, 21.72. Found: C, 61.16; H, 5.72; N, 21.92.

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

The title compound was prepared according to the similar procedure for **2a** utilizing 3-nitrobenzaldehyde instead of isophthalaldehyde, chromatography using CH_2Cl_2/MeOH (50:1) afforded **2e** (390 mg, 81%) as a yellow foam, mp 127–128 °C. ^{1}H NMR ($CDCl_3$): δ 8.23 (t, $J = 1.77$ Hz, 1H), 8.12 (m, 1H), 7.80 (d, $J = 0.98$ Hz, 1H), 7.74 (d, $J = 0.98$ Hz, 1H), 7.70 (d, $J = 7.43$ Hz, 1H), 7.48 (t, $J = 7.92$ Hz, 1H), 7.27 (dd, $J_1 = 2.54$ Hz, $J_2 = 14.09$ Hz, 1H), 6.94 (dd, $J_1 = 2.54$ Hz, $J_2 = 9.19$ Hz, 1H), 6.88 (t, $J = 8.90$ Hz, 1H), 5.05 (m, 1H), 4.87 (m, 2H), 4.12 (t, $J = 9.10$ Hz, 1H), 3.88 (dd, $J_1 = 6.06$ Hz, $J_2 = 9.39$ Hz, 1H), 3.66 (s, 2H), 3.06 (t, $J = 4.70$ Hz, 4H), 2.65 (t, $J = 4.30$ Hz, 4H). IR (KBr pellet, cm^{-1}): 3124, 2939, 2818, 1741, 1518, 1421, 1348, 1227, 1194, 1014, 798, 731. MS (EI) *m/z* (%): 481 (M^+, 100). Anal. Calcd for $C_{23}H_{24}FN_7O_4$: C, 57.37; H, 5.02; N, 20.36. Found: C, 57.43; H, 4.98; N, 20.46.

5.2.6. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(3-aminobenzyl)piperazin-1-yl)phenyl)oxazolidin-2-one (**2f**)

The title compound was prepared according to the similar procedure for **2d** utilizing **2e** instead of **2c**, chromatography using CH_2Cl_2/MeOH (25:1) afforded **2f** (120 mg, 64%) as a white solid, mp: 189–191 °C. ^{1}H NMR (DMSO-d_6): δ 8.13 (d, $J = 0.78$ Hz, 1H), 7.72 (d, $J = 0.78$ Hz, 1H), 7.34 (dd, $J_1 = 2.53$ Hz, $J_2 = 14.86$ Hz, 1H), 7.07 (dd, $J_1 = 2.34$ Hz, $J_2 = 8.80$ Hz, 1H), 6.99 (t, $J = 9.29$ Hz, 1H),

6.92 (t, $J = 7.63$ Hz, 1H), 6.54 (d, $J = 1.77$ Hz, 1H), 6.44 (m, 2H), 5.08 (m, 1H), 4.95 (br s, 2H), 4.80 (d, $J = 5.09$ Hz, 2H), 4.17 (t, $J = 9.19$ Hz, 1H), 3.83 (dd, $J_1 = 5.77$ Hz, $J_2 = 9.19$ Hz, 1H), 3.36 (s, 2H), 2.96 (br s, 4H), 2.48 (br s, 4H). IR (KBr pellet, cm^{-1}): 3464, 3363, 2951, 2823, 1747, 1618, 1514, 1423, 1331, 1225, 1101, 775. MS (EI) *m/z* (%): 451 (M^+, 33), 57 (100). Anal. Calcd for $C_{23}H_{26}FN_7O_2$: C, 61.18; H, 5.80; N, 21.72. Found: C, 61.10; H, 5.68; N, 21.72.

*5.2.7. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(4-nitrobenzyl)piperazin-1-yl)phenyl)-oxazolidin-2-one (**2g**)*

The title compound was prepared according to the similar procedure for **2a** utilizing 4-nitrobenzaldehyde instead of isophthalaldehyde, chromatography using CH_2Cl_2/MeOH (50:1) afforded **2g** (294 mg, 61%) as a yellow foam, mp 181–182 °C. ^1H NMR ($CDCl_3$): δ 8.18 (d, $J = 8.60$ Hz, 2H), 7.80 (d, $J = 0.98$ Hz, 1H), 7.75 (d, $J = 0.78$ Hz, 1H), 7.54 (d, $J = 8.61$ Hz, 2H), 7.27 (dd, $J_1 = 2.44$ Hz, $J_2 = 14.18$ Hz, 1H), 6.95 (dd, $J_1 = 2.64$ Hz, $J_2 = 8.90$ Hz, 1H), 6.88 (t, $J = 8.91$ Hz, 1H), 5.05 (m, 1H), 4.78 (m, 2H), 4.13 (t, $J = 9.19$ Hz, 1H), 3.90 (dd, $J_1 = 6.17$ Hz, $J_2 = 9.27$ Hz, 1H), 3.66 (s, 2H), 3.08 (br s, 4H), 2.65 (br s, 4H). IR (KBr pellet, cm^{-1}): 3444, 3111, 2935, 2823, 1741, 1599, 1516, 1483, 1419, 1346, 1222, 1200, 1009, 862, 739. MS (EI) *m/z* (%): 481 (M^+, 99), 304 (100). Anal. Calcd for $C_{23}H_{24}FN_7O_4$: C, 57.37; H, 5.02; N, 20.36. Found: C, 57.52; H, 5.05; N, 20.54.

*5.2.8. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(4-aminobenzyl)piperazin-1-yl)phenyl)-oxazolidin-2-one (**2h**)*

The title compound was prepared according to the similar procedure for **2d** utilizing **2g** instead of **2c**, chromatography using CH_2Cl_2/MeOH (25:1) afforded **2h** (54 mg, 29%) as a white solid, mp: 191–192 °C. ^1H NMR ($CDCl_3$): δ 7.78 (s, 1H), 7.74 (s, 1H), 7.27 (dd, $J_1 = 2.34$ Hz, $J_2 = 14.08$ Hz, 1H), 7.14 (d, $J = 8.05$ Hz, 2H), 6.95 (dd, $J_1 = 2.02$ Hz, $J_2 = 8.96$ Hz, 1H), 6.88 (t, $J = 8.79$ Hz, 1H), 6.68 (d, $J = 8.06$ Hz, 2H), 5.04 (m, 1H), 4.87 (m, 2H), 4.12 (t, $J = 9.03$ Hz, 1H), 3.87 (dd, $J_1 = 6.10$ Hz, $J_2 = 9.27$ Hz, 1H), 3.64 (br s, 2H), 3.52 (s, 2H), 3.10 (br s, 4H), 2.66 (br s, 4H). IR (KBr pellet, cm^{-1}): 3433, 3317, 3211, 2941, 2814, 1736, 1626, 1516, 1421, 1229, 1198, 1080, 793. MS (EI) *m/z* (%): 451 (M^+, 3), 304 (100). Anal. Calcd for $C_{23}H_{26}FN_7O_2$: C, 61.18; H, 5.80; N, 21.72. Found: C, 61.05; H, 5.72; N, 21.74.

*5.2.9. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(pyridin-2-ylmethyl)piperazin-1-yl)phenyl)oxazolidin-2-one (**3a**)*

The title compound was prepared according to the similar procedure for **2a** utilizing 2-pyridinecarboxaldehyde instead of isophthalaldehyde, chromatography using CH_2Cl_2/MeOH (50:1) afforded **3a** (258 mg, 59%) as a white solid, mp 140–142 °C. ^1H NMR ($CDCl_3$): δ 8.58 (m, $J = 1.08$ Hz, 1H), 7.78 (d, $J = 0.95$ Hz, 1H), 7.74 (d, $J = 1.10$ Hz, 1H), 7.66 (t, $J = 7.63$ Hz, 1H), 7.45 (d, $J = 7.70$ Hz, 1H), 7.27 (dd, $J_1 = 2.47$ Hz, $J_2 = 14.16$ Hz, 1H), 7.18 (m, 1H), 6.94 (dd, $J_1 = 2.75$ Hz, $J_2 = 8.94$ Hz, 1H), 6.87 (t, $J = 8.94$ Hz, 1H), 5.04 (m, 1H), 4.77 (m, 2H), 4.12 (t, $J = 9.14$ Hz, 1H), 3.87 (dd, $J_1 = 9.35$ Hz, $J_2 = 6.18$ Hz, 1H), 3.75 (s, 2H), 3.08 (t, $J = 4.54$ Hz, 4H), 2.72 (br s, 4H). IR (KBr pellet, cm^{-1}): 3433, 2953, 2808, 1743, 1518, 1452, 1242, 1134, 760. MS (EI) *m/z* (%): 437 (M^+, 6), 121 (100). Anal. Calcd for $C_{22}H_{24}FN_7O_2$: C, 60.40; H, 5.53; N, 22.41. Found: C, 60.45; H, 5.60; N, 22.28.

*5.2.10. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(pyridin-3-ylmethyl)piperazin-1-yl)phenyl)oxazolidin-2-one (**3b**)*

The title compound was prepared according to the similar procedure for **2a** utilizing 3-pyridinecarboxaldehyde instead of isophthalaldehyde, chromatography using CH_2Cl_2/MeOH (50:1) afforded **3b** (216 mg, 49%) as a white solid, mp 158–159 °C. ^1H NMR ($CDCl_3$): δ 8.57 (d, $J = 2.01$ Hz, 1H), 8.52 (dd, $J_1 = 1.64$ Hz, $J_2 = 4.75$ Hz, 1H), 7.78 (d, $J = 0.92$ Hz, 1H), 7.74 (d, $J = 0.91$ Hz, 1H), 7.71 (d, $J = 8.68$ Hz, 1H), 7.27 (m, 2H), 6.94 (dd, $J_1 = 2.74$ Hz, $J_2 = 8.96$ Hz, 1H), 6.87 (t, $J = 9.06$ Hz, 1H), 5.03 (m, 1H), 4.77 (m, 2H), 4.12 (t, $J = 9.06$ Hz, 1H), 3.87 (dd, $J_1 = 6.22$ Hz, $J_2 = 9.33$ Hz, 1H), 3.58 (s, 2H), 3.07 (t, $J = 4.48$ Hz, 4H), 2.64 (t, $J = 4.21$ Hz, 4H). IR (KBr pellet, cm^{-1}): 3441, 3116, 2816, 1741, 1518, 1404, 1323, 1223, 1122, 1009, 714. MS (EI) *m/z* (%): 437 (M^+, 100). Anal. Calcd for $C_{22}H_{24}FN_7O_2$: C, 60.40; H, 5.53; N, 22.41. Found: C, 60.34; H, 5.53; N, 22.33.

*5.2.11. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(pyridin-4-ylmethyl)piperazin-1-yl)phenyl)oxazolidin-2-one (**3c**)*

The title compound was prepared according to the similar procedure for **2a** utilizing 4-pyridinecarboxaldehyde instead of isophthalaldehyde, chromatography using CH_2Cl_2/MeOH (50:1) afforded **3c** (242 mg, 55%) as a white solid, mp 151–152 °C. ^1H NMR ($CDCl_3$): δ 8.56 (d, $J = 5.50$ Hz, 2H), 7.78 (d, $J = 0.79$ Hz, 1H), 7.74 (d, $J = 0.79$ Hz, 1H), 7.34 (d, $J = 5.36$ Hz, 2H), 7.27 (dd, $J_1 = 2.34$ Hz, $J_2 = 14.16$ Hz, 1H), 6.95 (dd, $J_1 = 2.40$ Hz, $J_2 = 8.87$ Hz, 1H), 6.88 (t, $J = 8.87$ Hz, 1H), 5.04 (m, 1H), 4.77 (m, 2H), 4.12 (t, $J = 9.15$ Hz, 1H), 3.87 (dd, $J_1 = 6.12$ Hz, $J_2 = 9.35$ Hz, 1H), 3.58 (s, 2H), 3.08 (br s, 4H), 2.75 (br s, 4H). IR (KBr pellet, cm^{-1}): 3446, 2935, 2823, 1759, 1738, 1603, 1516, 1423, 1227, 1014, 789. MS (EI) *m/z* (%): 437 (M^+, 43), 393 (100). Anal. Calcd for $C_{22}H_{24}FN_7O_2$: C, 60.40; H, 5.53; N, 22.41. Found: C, 60.20; H, 5.41; N, 22.13.

*5.2.12. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(furan-2-ylmethyl)piperazin-1-yl)phenyl)oxazolidin-2-one (**4a**)*

The title compound was prepared according to the similar procedure for **2a** utilizing 2-furaldehyde instead of isophthalaldehyde, chromatography using CH_2Cl_2/MeOH (50:1) afforded **4a** (346 mg, 81%) as a white solid, mp 148–149 °C. ^1H NMR ($CDCl_3$): δ 7.78 (d, $J = 0.98$ Hz, 1H), 7.73

(d, $J = 0.98$ Hz, 1H), 7.39 (dd, $J_1 = 1.01$ Hz, $J_2 = 8.74$ Hz, 1H), 7.27 (dd, $J_1 = 2.54$ Hz, $J_2 = 14.09$ Hz, 1H), 6.93 (dd, $J_1 = 2.40$ Hz, $J_2 = 8.86$ Hz, 1H), 6.87 (t, $J = 8.86$ Hz, 1H), 6.32 (dd, $J_1 = 1.95$ Hz, $J_2 = 3.13$ Hz, 1H), 6.24 (d, $J = 2.93$ Hz, 1H), 5.05 (m, 1H), 4.77 (m, 2H), 4.11 (t, $J = 9.19$ Hz, 1H), 3.88 (dd, $J_1 = 6.16$ Hz, $J_2 = 9.29$ Hz, 1H), 3.62 (s, 2H), 3.08 (t, $J = 4.79$ Hz, 4H), 2.65 (t, $J = 4.69$ Hz, 4H). IR (KBr pellet, cm^{-1}): 3105, 2953, 2816, 1736, 1518, 1421, 1227, 1202, 1115, 754. MS (EI) *m/z* (%): 426 (M^+, 100). Anal. Calcd for $C_{21}H_{23}FN_6O_3$: C, 59.15; H, 5.44; N, 19.71. Found: C, 59.20; H, 5.52; N, 19.61.

5.2.13. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(furan-3-ylmethyl)piperazin-1-yl)phenyl)-oxazolidin-2-one (**4b**)

The title compound was prepared according to the similar procedure for **2a** utilizing 3-furancarboxaldehyde instead of isophthalaldehyde, chromatography using CH_2Cl_2/MeOH (50:1) afforded **4b** (236 mg, 55%) as a white solid, mp 156–157 °C. ^{1}H NMR ($CDCl_3$): δ 7.78 (d, $J = 1.10$ Hz, 1H), 7.74 (d, $J = 1.10$ Hz, 1H), 7.39 (t, $J = 1.65$ Hz, 1H), 7.35 (t, $J = 0.76$ Hz, 1H), 7.27 (dd, $J_1 = 2.33$ Hz, $J_2 = 14.16$ Hz, 1H), 6.94 (dd, $J = 8.93$ Hz, 2.47 Hz, 1H), 6.87 (t, $J = 8.80$ Hz, 1H), 6.41 (dd, $J_1 = 0.82$ Hz, $J_2 = 1.78$ Hz, 1H), 5.03 (m, 1H), 4.77 (m, 2H), 4.11 (t, $J = 9.08$ Hz, 1H), 3.87 (dd, $J_1 = 6.12$ Hz, $J_2 = 9.42$ Hz, 1H), 3.45 (s, 2H), 3.06 (t, $J = 4.82$ Hz, 4H), 2.63 (t, $J = 4.82$ Hz, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 47.30, 50.32, 51.89, 52.70, 52.76, 70.34, 107.60 (d, $J_{C-F} = 25.9$ Hz), 111.31, 114.21 (d, $J_{C-F} = 2.7$ Hz), 118.90 (d, $J_{C-F} = 4.1$ Hz), 121.06, 125.01, 131.85 (d, $J_{C-F} = 10.7$ Hz), 134.29, 136.95 (d, $J_{C-F} = 9.1$ Hz), 140.84, 142.93, 153.37, 155.18 (d, $J_{C-F} = 245$ Hz). IR (KBr pellet, cm^{-1}): 3440, 3107, 2814, 1745, 1518, 1452, 1240, 1124, 1018, 808. MS (EI) *m/z* (%): 426 (M^+, 100). Anal. Calcd for $C_{21}H_{23}FN_6O_3$: C, 59.15; H, 5.44; N, 19.71. Found: C, 59.03; H, 5.35; N, 19.84.

5.2.14. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-((5-methylfuran-2-yl)methyl)-piperazin-1-yl)phenyl)oxazolidin-2-one (**4c**)

The title compound was prepared according to the similar procedure for **2a** utilizing 5-methyl-2-furaldehyde instead of isophthalaldehyde, chromatography using CH_2Cl_2/MeOH (50:1) afforded **4c** (100 mg, 23%) as a white solid, mp 139–140 °C. ^{1}H NMR ($CDCl_3$): δ 7.78 (d, $J = 0.96$ Hz, 1H), 7.74 (d, $J = 0.97$ Hz, 1H), 7.27 (dd, $J_1 = 2.42$ Hz, $J_2 = 8.98$ Hz, 1H), 6.94 (dd, $J_1 = 2.42$ Hz, $J_2 = 8.89$ Hz, 1H), 6.87 (t, $J = 8.87$ Hz, 1H), 6.10 (d, $J = 2.89$ Hz, 1H), 5.90 (dd, $J_1 = 1.00$ Hz, $J_2 = 3.01$ Hz, 1H), 5.04 (m, 1H), 4.77 (m, 2H), 4.12 (t, $J = 9.15$ Hz, 1H), 3.87 (dd, $J_1 = 6.18$ Hz, $J_2 = 9.34$ Hz, 1H), 3.56 (s, 2H), 3.10 (t, $J = 4.82$ Hz, 4H), 2.65 (t, $J = 4.61$ Hz, 4H), 2.28 (s, 3H). IR (KBr pellet, cm^{-1}): 3435, 3138, 2926, 2818, 1738, 1518, 1421, 1225, 1198, 1113, 806. MS (EI) *m/z* (%): 440 (M^+, 18), 123 (100). Anal. Calcd for $C_{22}H_{25}FN_6O_3$: C, 59.99; H, 5.72; N, 19.08. Found: C, 58.82; H, 5.71; N, 18.98.

5.2.15. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-((5-chlorofuran-2-yl)methyl)piperazin-1-yl)-phenyl)oxazolidin-2-one (**4d**)

The title compound was prepared according to the similar procedure for **2a** utilizing 5-chloro-2-furaldehyde instead of isophthalaldehyde, chromatography using CH_2Cl_2/MeOH (50:1) afforded **4d** (190 mg, 41%) as a white solid, mp 135–137 °C. ^{1}H NMR ($CDCl_3$): δ 7.78 (d, $J = 1.10$ Hz, 1H), 7.74 (d, $J = 0.96$ Hz, 1H), 7.27 (dd, $J_1 = 2.32$ Hz, $J_2 = 14.16$ Hz, 1H), 6.94 (dd, $J_1 = 2.47$ Hz, $J_2 = 8.93$ Hz, 1H), 6.88 (t, $J = 8.72$ Hz, 1H), 6.24 (d, $J = 3.16$ Hz, 1H), 6.10 (d, $J = 3.16$ Hz, 1H), 5.04 (m, 1H), 4.77 (m, 2H), 4.12 (t, $J = 9.14$ Hz, 1H), 3.87 (dd, $J_1 = 6.18$ Hz, $J_2 = 9.34$ Hz, 1H), 3.58 (s, 2H), 3.08 (t, $J = 4.81$ Hz, 4H), 2.66 (t, $J = 4.74$ Hz, 4H). IR (KBr pellet, cm^{-1}): 3460, 3115, 2945, 2821, 1740, 1518, 1421, 1335, 1225, 1198, 1011, 806, 752. MS (EI) *m/z* (%): 460 (M^+, 72), 290 (100). Anal. Calcd for $C_{21}H_{22}ClFN_6O_3$: C, 54.73; H, 4.81; N, 18.23. Found: C, 54.63; H, 4.95; N, 17.96.

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

To a solution of compound **1** (383 mg, 1 mmol) in CH_3CN was added Et_3N (1 mL) followed by 2-(chloromethyl)-5-nitrofuran (293 mg, 1.8 mmol). The mixture was stirred at 50 °C under N_2 for 6 h, then washed with water (200 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and then concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with CH_2Cl_2/MeOH (50:1) to afford compound **4e** (333 mg, 71%) as a yellow solid, mp 128–130 °C. ^{1}H NMR ($CDCl_3$): δ 7.79 (d, $J = 0.96$ Hz, 1H), 7.73 (d, $J = 0.97$ Hz, 1H), 7.27 (m, 2H), 6.95 (dd, $J_1 = 2.55$ Hz, $J_2 = 8.94$ Hz, 1H), 6.88 (t, $J = 8.87$ Hz, 1H), 6.54 (d, $J = 3.58$ Hz, 1H), 5.05 (m, 1H), 4.78 (m, 2H), 4.12 (t, $J = 9.15$ Hz, 1H), 3.89 (dd, $J_1 = 6.19$ Hz, $J_2 = 9.35$ Hz, 1H), 3.71 (s, 2H), 3.09 (t, $J = 4.82$ Hz, 4H), 2.71 (t, $J = 4.82$ Hz, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 47.28, 50.16, 51.90, 52.68, 54.45, 70.36, 107.61 (d, $J_{C-F} = 26$ Hz), 112.23, 112.47, 114.18 (d, $J_{C-F} = 2.7$ Hz), 119.00 (d, $J_{C-F} = 4.1$ Hz), 125.05, 132.16 (d, $J_{C-F} = 10$ Hz), 134.28, 136.54 (d, $J_{C-F} = 9.1$ Hz), 151.78, 153.37, 155.18 (d, $J_{C-F} = 245$ Hz), 155.61. IR (KBr pellet, cm^{-1}): 3440, 3136, 2945, 2825, 1745, 1587, 1518, 1498, 1360, 1236, 1014, 812, 739. MS (ESI) *m/z* (%): 472 $(M + H)^+$. Anal. Calcd for $C_{21}H_{22}FN_7O_5 \cdot 1/2CH_3OH$: C, 52.97; H, 4.96; N, 20.11. Found: C, 53.19; H, 4.86; N, 20.26.

5.2.17. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(thiophen-2-ylmethyl)-piperazin-1-yl)phenyl)oxazolidin-2-one (**5a**)

The title compound was prepared according to the similar procedure for **2a** utilizing 2-thiophenecarboxaldehyde instead of isophthalaldehyde, chromatography using CH_2Cl_2/MeOH (50:1) afforded **5a** (330 mg, 75%) as a white solid, mp 156–157 °C. ^{1}H NMR ($CDCl_3$): δ 7.78 (d, $J = 1.10$ Hz, 1H), 7.74 (d, $J = 0.96$ Hz, 1H), 7.23–7.30 (m, 2H), 6.85–6.97

(m, 4H), 5.05 (m, 1H), 4.77 (m, 2H), 4.11 (t, $J = 9.08$ Hz, 1H), 3.87 (dd, $J_1 = 6.19$ Hz, $J_2 = 9.35$ Hz, 1H), 3.80 (s, 2H), 3.08 (t, $J = 4.82$ Hz, 4H), 2.67 (t, $J = 4.75$ Hz, 4H). IR (KBr pellet, cm^{-1}): 3124, 2941, 2810, 1749, 1518, 1452, 1333, 1242, 1134, 717. MS (EI) *m/z* (%): 442 (M^+, 66), 97 (100). Anal. Calcd for $C_{21}H_{23}FN_6O_2S$: C, 57.00; H, 5.24; N, 18.99. Found: C, 57.06; H, 5.15; N, 18.92.

5.2.18. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(thiophen-3-ylmethyl)piperazin-1-yl)-phenyl)oxazolidin-2-one (**5b**)

The title compound was prepared according to the similar procedure for **2a** utilizing 3-thiophenecarboxaldehyde instead of isophthalaldehyde, chromatography using CH_2Cl_2/MeOH (50:1) afforded **5b** (310 mg, 70%) as a white solid, mp 149–151 °C. ^1H NMR ($CDCl_3$): δ 7.78 (d, $J = 0.96$ Hz, 1H), 7.74 (d, $J = 1.10$ Hz, 1H), 7.24–7.30 (m, 2H), 7.15 (dd, $J_1 = 1.10$ Hz, $J_2 = 3.02$ Hz, 1H), 7.08 (dd, $J_1 = 1.31$ Hz, $J_2 = 4.88$ Hz, 1H), 6.95 (dd, $J_1 = 2.47$ Hz, $J_2 = 9.07$ Hz, 1H), 6.88 (t, $J = 8.80$ Hz, 1H), 5.05 (m, 1H), 4.77 (m, 2H), 4.11 (t, $J = 9.14$ Hz, 1H), 3.88 (dd, $J_1 = 6.19$ Hz, $J_2 = 9.35$ Hz, 1H), 3.61 (s, 2H), 3.07 (t, $J = 4.82$ Hz, 4H), 2.63 (t, $J = 4.82$ Hz, 4H). IR (KBr pellet, cm^{-1}): 3458, 3105, 2935, 2814, 1736, 1518, 1333, 1227, 1200, 797. MS (EI) *m/z* (%): 442 (M^+, 90), 97 (100). Anal. Calcd for $C_{21}H_{23}FN_6O_2S$: C, 57.00; H, 5.24; N, 18.99. Found: C, 57.07; H, 5.22; N, 18.82.

5.2.19. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-((5-bromothiophen-2-yl)methyl)piperazin-1-yl)-phenyl)oxazolidin-2-one (**5c**)

The title compound was prepared according to the similar procedure for **2a** utilizing 5-bromo-2-thiophenecarboxaldehyde instead of isophthalaldehyde, chromatography using CH_2Cl_2/MeOH (50:1) afforded **5c** (260 mg, 50%) as a white solid, mp 151–152 °C. ^1H NMR ($CDCl_3$): δ 7.78 (d, $J = 0.97$ Hz, 1H), 7.74 (d, $J = 1.10$ Hz, 1H), 7.27 (dd, $J_1 = 2.41$ Hz, $J_2 = 14.10$ Hz, 1H), 7.14 (d, $J = 1.37$ Hz, 1H), 6.85–6.97 (m, 3H), 5.04 (m, 1H), 4.77 (m, 2H), 4.11 (t, $J = 9.08$ Hz, 1H), 3.88 (dd, $J_1 = 6.19$ Hz, $J_2 = 9.35$ Hz, 1H), 3.73 (s, 2H), 3.07 (t, $J = 4.82$ Hz, 4H), 2.67 (t, $J = 4.75$ Hz, 4H). IR (KBr pellet, cm^{-1}): 3118, 2945, 2812, 1743, 1520, 1452, 1240, 1136, 837, 746. MS (EI) *m/z* (%): 520 (M^+, 41), 290 (100). Anal. Calcd for $C_{21}H_{22}BrFN_6O_2S$: C, 48.37; H, 4.25; N, 16.12. Found: C, 48.49; H, 4.19; N, 16.01.

5.2.20. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-((3-methylthiophen-2-yl)methyl)piperazin-1-yl)-phenyl)oxazolidin-2-one (**5d**)

The title compound was prepared according to the similar procedure for **2a** utilizing 3-methyl-2-thiophenecarboxaldehyde instead of isophthalaldehyde, chromatography using CH_2Cl_2/MeOH (50:1) afforded **5d** (300 mg, 66%) as a white solid, mp 131–133 °C. ^1H NMR ($CDCl_3$): δ 7.78 (d, $J = 0.96$ Hz, 1H), 7.73 (d, $J = 0.82$ Hz, 1H), 7.27 (dd, $J_1 = 2.27$ Hz, $J_2 = 14.10$ Hz, 1H), 7.14 (d, $J = 5.09$ Hz, 1H), 6.95 (dd, $J_1 = 2.26$ Hz, $J_2 = 8.87$ Hz, 1H), 6.88 (t, $J = 8.80$ Hz, 1H), 6.80 (d, $J = 5.09$ Hz, 1H), 5.05 (m, 1H), 4.77 (m, 2H), 4.11 (t, $J = 9.14$ Hz, 1H), 3.87 (dd, $J_1 = 6.26$ Hz, $J_2 = 9.28$ Hz, 1H), 3.78 (s, 2H), 3.08 (t, $J = 4.54$ Hz, 4H), 2.67 (t, $J = 4.60$ Hz, 4H), 2.12 (s, 3H). IR (KBr pellet, cm^{-1}): 3086, 2951, 2820, 1751, 1514, 1452, 1421, 1331, 1223, 1132, 1011, 785, 737. MS (EI) *m/z* (%): 456 (M^+, 41), 111 (100). Anal. Calcd for $C_{22}H_{25}FN_6O_2S$: C, 57.88; H, 5.52; N, 18.41. Found: C, 58.00; H, 5.24; N, 18.29.

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

The title compound was prepared according to the similar procedure for **2a** utilizing 5-methyl-2-thiophenecarboxaldehyde instead of isophthalaldehyde, chromatography using CH_2Cl_2/MeOH (50:1) afforded **5e** (302 mg, 66%) as a white solid, mp 153–154 °C. ^1H NMR ($CDCl_3$): δ 7.78 (d, $J = 1.10$ Hz, 1H), 7.74 (d, $J = 1.10$ Hz, 1H), 7.27 (dd, $J_1 = 2.34$ Hz, $J_2 = 14.16$ Hz, 1H), 6.95 (dd, $J_1 = 2.40$ Hz, $J_2 = 8.86$ Hz, 1H), 6.88 (t, $J = 8.71$ Hz, 1H), 6.72 (d, $J = 3.30$ Hz, 1H), 6.59 (m, 1H), 5.05 (m, 1H), 4.77 (m, 2H), 4.11 (t, $J = 9.07$ Hz, 1H), 3.87 (dd, $J_1 = 6.16$ Hz, $J_2 = 9.35$ Hz, 1H), 3.71 (s, 2H), 3.08 (t, $J = 4.81$ Hz, 4H), 2.65 (t, $J = 4.61$ Hz, 4H), 2.45 (s, 3H). IR (KBr pellet, cm^{-1}): 3120, 2935, 2812, 1751, 1516, 1452, 1240, 1134, 798. MS (EI) *m/z* (%): 456 (M^+, 77), 139 (100). Anal. Calcd for $C_{22}H_{25}FN_6O_2S$: C, 57.88; H, 5.52; N, 18.41. Found: C, 57.96; H, 5.44; N, 18.36.

5.3. Pharmacology

5.3.1. In vitro

The *in vitro* antibacterial activity of the compounds against Gram-positive bacteria was tested with linezolid and vancomycin as positive controls. Minimum inhibitory concentration (MIC) values were determined using agar dilution method according to NCCLS [18]. Compounds were dissolved in 20% water in DMSO to prepare a stock solution in which the concentration of the compounds is 1920 μg/mL. Serial two-fold dilutions were prepared from the stock solution in sterile water or Mueller–Hinton (MH) agar medium to provide the concentration ranges 8–0.0005 μg/mL. The tested organisms were grown in MH broth medium at 35 °C for 16–18 h, the broths were adjusted to the turbidity of 0.5 McFarland standard and then the bacterial suspensions were inoculated onto the drug-supplemented MH agar plates at 35 °C for 18–20 h.

5.3.2. In vivo

KunMing *SPF* level mice weighing 20 ± 2 g were used in the study with five mice in each group. Lethal systemic infection was caused in the mice by the injection of the *MLD* inoculum of MRSA 05-2 intraperitoneally. Compounds were administered orally or by intravenous injection (dissolved in 0.9% NaCl solution) immediately and 4 h post-infection. The ED_{50} was calculated by the Bliss method [19,20] on day 7 post-infection.

5.3.3. Pharmacokinetics

The selected compounds **2e**, **2h**, **4b** and **4e** were subjected to pharmacokinetic studies on Sprague–Dawley rats weighing 220–280 g with four mice in each group (two male and two female). The tested compounds were administered orally at the dose of 10 mg/kg and 50 mg/kg, while administered intravenously at the dose of 10 mg/kg. Serial specimens (300 μL) were collected via the retrobulbar vein and quantitation was performed by LC–MS, pharmacokinetic parameters were calculated from the mean plasma concentration by non-compartmental analysis.

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