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Short communication

Synthesis and antibacterial activity of oxazolidinones containing triazolyl group

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Abstract

A new series of oxazolidinones containing triazolyl group has been synthesized and tested for *in vitro* antibacterial activity by MIC determination against a panel of resistant and susceptible Gram-positive organisms. Most of the analogs in this series displayed activity superior to linezolid and vancomycin *in vitro*. Further, *in vivo* efficacies of the selected oxazolidinones were also disclosed herein.

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 and, recently, some linezolid-resistant clinical isolates of VREF and *S. aureus* have been reported [9,10]. This unexpected early development of resistance emphasizes the need for further exploration of features of oxazolidinone series to overcome these issues.

We have found that the introduction of sulfonyl group to oxazolidinones, such as **YC-20** (Fig. 1) [11], could enhance their antibacterial activities. In addition, recent studies have shown that the conversion of the acetamide group of linezolid to the triazolyl group to get **PH-027** (Fig. 1) could restore its antibacterial activities and reduce its activity against monoamine oxidase [12,13]. In order to find more potent oxazolidinone antibacterial agents with reduced side effects, we combined the structural properties of **YC-20** and **PH-027** into one molecule. In this paper, we report our efforts towards the synthesis and *in vitro* antibacterial activities of a new series of oxazolidinone derivatives bearing a triazolyl side chain at the C-5 position and a sulfonyl group as well as being linked to piperazine ring. Furthermore, the *in vivo* activity of the selected compounds **7**, **16** and **20** was tested in mice mode.

2. Chemistry

Synthesis of these novel compounds was carried out in a straightforward manner. The intermediate azide derivative

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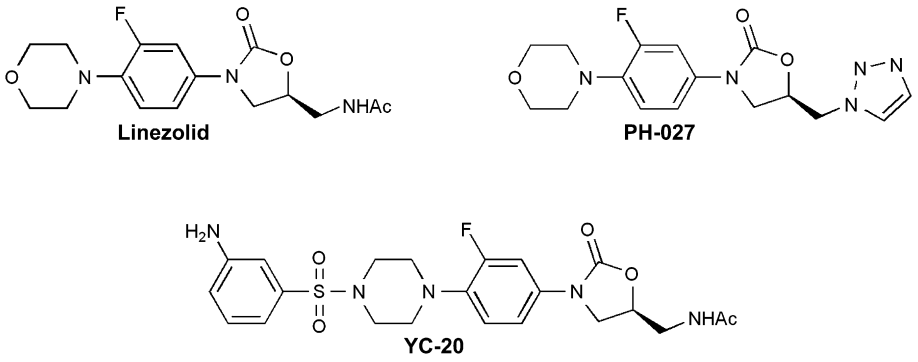


Fig. 1. Structures of **linezolid**, **PH-027** and **YC-20**.

1 was synthesized from the readily available starting materials piperazine and 3,4-difluoronitrobenzene according to the known method [14,15] in several steps. Treatment of compound **1** with acetylene in a steel bomb and dimethoxyethane (DME) as solvent at 90 °C for 16 h afforded compound **2**. Another improved method is treatment of compound **1** with vinyl acetate, sodium carbonate and 4 Å molecular sieves at refluxing temperature for 84 h to get compound **2** with a yield of 82%. This improved method has several advantages over the former such as no use of inflammable gas acetylene or high-pressure proof equipments. Removal of the Cbz protection group of compound **2** under an atmosphere of hydrogen by hydrogenation at room temperature afforded compound **3**. The key intermediate amine compound **3** was condensed with various sulfonyl chloride analogs to afford the desired compounds (Scheme 1). Further chemical transformation involving treatment of compound **16** with 10% palladium on carbon in dichloromethane and methanol under hydrogen afforded compound **20** with good yield. The structure of the target compounds was confirmed by ^{1}H NMR, MS and elemental analysis.

3. Results and discussion

The result of *in vitro* antibacterial activity against a spectrum of resistant and susceptible Gram-positive organisms is summarized in Table 1. It clearly shows that all compounds bearing sulfonyl group have good antibacterial activity. Compounds **5**, **7**, **13**, **16** and **20** showed more potent antibacterial activity than linezolid and vancomycin. Obviously, the introduction of strong electron-withdrawing groups (e.g. $-CF_3$, $-F$ and $-NO_2$) into the oxazolidinones can confer excellent antibacterial activity especially at the 3-position of the phenylsulfonyl group, in addition, electron-donating groups (e.g. $-Cl$ and $-NH_2$), as shown in compounds **5** and **20**, can increase activity too, but $-Br$ and $-CH_3$ lead to a slight decrease in activity. The replacement of the phenyl of compound **4** with 2-thiophenyl (compound **19**) led to an increase in activity, it suggested that the introduction of heteroaryl ring system into the molecule may increase its antibacterial activity.

The *in vivo* activity of compounds **7**, **16** and **20** was tested in mice mode, see Table 2, but the result was not desirable. They were less potent by several-fold than linezolid despite comparable *in vitro* activity against the organism. This difference in *in vivo* potency may be due to their poor water solubility or suboptimal pharmacokinetic properties.

4. Conclusion

In conclusion, a series of new 5-triazole substituted oxazolidinones was synthesized and evaluated for microbiological activity against a panel of resistant and susceptible Gram-positive organisms *in vitro* comparable to linezolid and vancomycin. Most of them were more potent than linezolid and vancomycin. Several analogs from this series also exhibited *in vivo* activity in a lethal murine infection model when administered orally, but were less effective than linezolid. Further optimization of this new class of oxazolidinone analogs is ongoing in our laboratories.

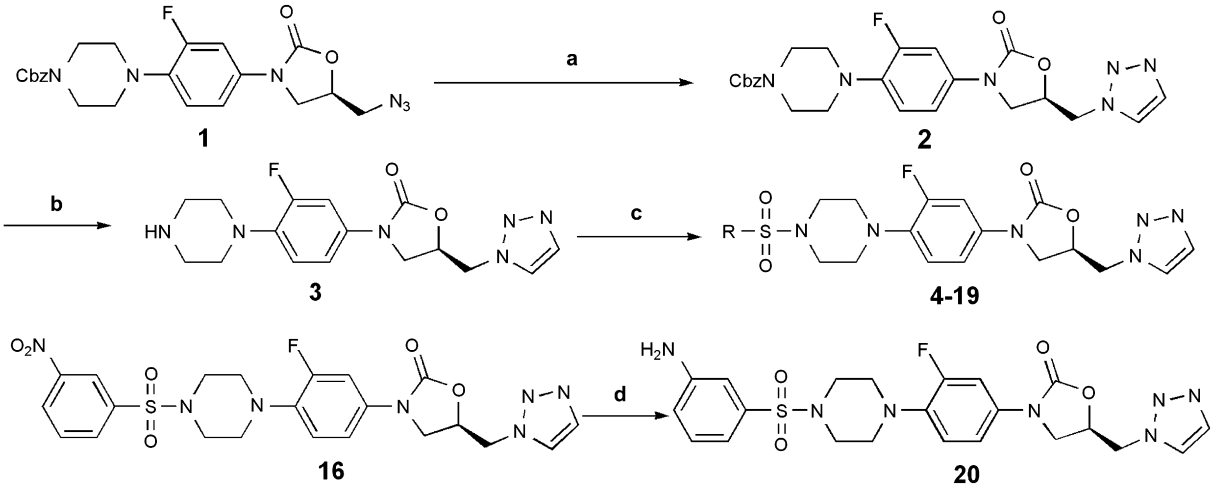
5. Experimental protocols

5.1. General procedures

All solvents used were of analytical grade (Sinopharm Chemical Reagent Co., Ltd.). Melting points (uncorrected) were determined in open capillaries on a MEL-TEMP 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 Hz. EI-MS spectra were obtained on a Finnigan MAT 95 mass spectrometer. Elemental analyses were 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. Procedure for preparation of compound 2

A solution of the 5-azidomethyl **1** (4.34 g, 9.56 mmol) in dimethoxyethane (40 mL) was placed in a steel bomb and cooled to −78 °C in a dry ice–acetone bath. A stream of excess acetylene gas was passed into the bomb to condense over a period of 3 min, the steel bomb was tightly closed and the mixture was heated at 90 °C for 16 h. The bomb was cooled

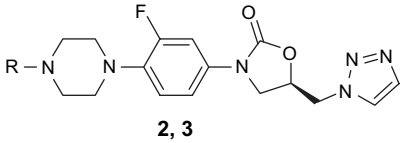


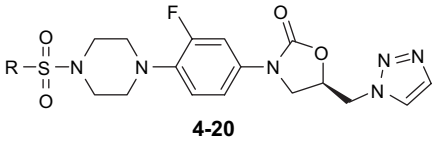
Scheme 1. (a) C_2H_2, DME, 90 °C, 16 h; or vinyl acetate, 4 Å molecular sieves, Na_2CO_3, refluxing, 84 h; (b) 10% Pd/C, H_2, CH_3OH overnight; (c) RSO_2Cl, Et_3N, CH_2Cl_2, 0.5 h; (d) 10% Pd/C, H_2, CH_3OH/CH_2Cl_2, overnight.

to 0 °C and excess acetylene was released carefully and the mixture was concentrated to give a yellow solid, which was recrystallized from ethyl acetate and petroleum ether (1:10) mixture to afford compound **2** (3.37 g, 81%) as a white solid.

Another improved method to get compound **2**. A mixture of compound **1** (17.82 g, 39.25 mmol), anhydrous sodium carbonate (4.16 g, 39.25 mmol) and a small amount of 4 Å molecular sieves in vinyl acetate (350 mL) was stirred under

Table 1
MIC (μg/ml) values of new oxazolidinones in various Gram-positive bacteria





No	R	MSSA[a]	MRSA[b]	MSSE[c]	MRSE[d]	EF[e]	PRSP[f]
2	Cbz	0.25–1	0.5	1	0.5–2	0.5	0.5–1
3	H	1–2	1–2	1–4	1–2	2	1–2
4	Ph	1–2	1–2	0.5–2	2–4	2–4	1–4
5	(*p*)-ClPh	0.125–0.5	0.5–2	0.5–2	0.5–1	0.25–0.5	0.125–0.5
6	(*p*)-BrPh	4–8	8	8	4–8	2–8	2–4
7	(*m*)-FPh	0.001–0.008	0.25–0.5	0.25–1	1–2	0.004–0.015	0.002–0.5
8	(*p*)-FPh	0.5–1	1–2	0.5–1	1	1–2	0.5–1
9	2,4-*di*-FPh	2–4	2–8	1–2	1–4	2–8	2–4
10	(*p*)-CH_3Ph	1–2	1–2	0.5–2	2–4	2–4	1–4
11	(*p*)-CH_3OPh	1–2	0.5–2	2–4	2–4	2–4	0.5–2
12	(*o*)-CF_3Ph	1–2	0.5–2	2–4	2–4	2–4	0.5–2
13	(*m*)-CF_3Ph	0.06–0.125	0.06–1	0.06–0.125	0.5–1	0.03–0.06	0.015–0.06
14	(*p*)-CF_3Ph	0.5–1	1	0.5–1	1	0.5–2	0.5–2
15	(*o*)-NO_2Ph	0.5–1	1	0.5–1	1	0.5–2	0.5–2
16	(*m*)-NO_2Ph	0.06–0.125	0.06–1	0.06–0.5	0.5–1	0.03–0.06	0.015–0.06
17	(*p*)-NO_2Ph	1–2	1–4	1–2	1–2	1–4	0.5–2
18	(*p*)-CNPh	2–4	0.5–4	2–4	2–4	4–8	4–8
19	2-Thiophenyl	1–2	1	1	1	1–2	1–2
20	(*m*)-NH_2Ph	0.125–0.5	0.25–1	0.5–1	1–2	0.25–0.5	0.5–1
Van		0.25–0.5	0.5–1	0.5–1	0.25–1	0.25–1	0.25–0.5
LZ		0.125–1	1–2	1–2	0.5–2	0.25–1	0.25–0.5

Van = Vancomycin; **LZ** = linezolid.
[a] MSSA = Methicillin-susceptible *S. aureus*. $n = 5$ strains.
[b] MRSA = Methicillin-resistant *S. aureus*. $n = 5$ strains.
[c] MSSE = Methicillin-susceptible *Streptococcus epidermidis*. $n = 5$ strains.
[d] MRSE = Methicillin-resistant *S. epidermidis*. $n = 5$ strains.
[e] EF = *Enterococcus faecalis*. $n = 5$ strains.
[f] PRSP = Penicillin-resistant *S. pneumoniae*. $n = 10$ strains.

Table 2
In vivo efficacies (ED_{50}, mg/kg) of selected compounds (route = p.o.)

Compounds	MRSA BAA-42	MSSA 04-5	MRSE 03427
7	>100	55.14	>100
16	>100	55.14	84.30
20	>100	>100	>100
Linezolid	17.88	23.96	84.77

nitrogen at refluxing temperature for 84 h. The mixture was concentrated and the residue was diluted with dichloromethane, the mixture was then filtered through diatomaceous earth, the filter cake was washed with dichloromethane, and the combined filtrates were concentrated to give a slight yellow solid. The solid was triturated with methanol (30 mL) twice to afford compound **2** (15.4 g, 82%) as a white solid.

5.3. Procedure for preparation of compound *3*

A mixture of compound **2** (4.80 g, 10 mmol) and 10% palladium on carbon (0.1 g) in ethyl acetate (50 mL) and methanol (50 mL) was stirred under hydrogen (balloon) overnight. The mixture was then filtered through diatomaceous earth, the filter cake was washed with methanol, and the combined filtrates were concentrated to give a slight yellow solid. Purification by silica gel column chromatography eluting with dichloromethane and methanol (5:1) gave a slight yellow solid. Recrystallization from ethyl acetate and petroleum ether (1:2) afforded compound **3** (1.84 g, 53%) as a white solid.

5.4. General procedure for preparation of compounds *4–19*

To a solution of compound **3** (100 mg, 0.29 mmol) and pyridine (0.2 mL) in anhydrous dichloromethane (15 mL) was added phenylsulfonyl chloride (67 mg, 0.30 mmol) under ice–salt bath. The mixture was stirred at room temperature for 0.5 h, then washed with water and extracted with dichloromethane. The combined organic extract was dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with dichloromethane and methanol (50:1) to afford compound **4** (48 mg, 34%) as a white solid.

5.5. Procedure for preparation of compound *20*

A mixture of compound **16** (100 mg, 0.19 mmol) and 10% palladium on carbon (20 mg) in dichloromethane (10 mL) and methanol (10 mL) was stirred under hydrogen (balloon) overnight. The mixture was then filtered through diatomaceous earth, the filter cake was washed with methanol, and the combined filtrates were concentrated to give a slight yellow solid. The solid was purified by silica gel column chromatography eluting with dichloromethane and methanol (50:1) to get a slight yellow solid, followed by recrystallization from a mixture of ethyl acetate and petroleum ether (1:5) to afford compound **20** (58 mg, 62%) as a white solid.

5.6. Structural data

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

Mp: 184–186 °C. ^{1}H NMR ($CDCl_3$): δ 7.78 (s, 1H), 7.74 (s, 1H), 7.28–7.38 (m, 6H), 6.96 (dd, $J_1 = 2.57$ Hz, $J_2 = 8.91$ Hz, 1H), 6.88 (t, $J = 9.04$ Hz, 1H), 5.15 (s, 2H), 5.04 (m, 1H), 4.78 (d, $J = 4.39$ Hz, 2H), 4.12 (t, $J = 9.16$ Hz, 1H), 3.90 (dd, $J_1 = 6.10$ Hz, $J_2 = 9.28$ Hz, 1H), 3.66 (m, 4H), 3.00 (br s, 4H). MS (EI) *m/z* (%): 480 (M^+, 93), 91 (100). Anal. Calcd for $C_{24}H_{25}FN_6O_4$: C, 59.99; H, 5.24; N, 17.49. Found: C, 60.06; H, 5.25; N, 17.51.

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

Mp: 202–204 °C. ^{1}H NMR ($CDCl_3$): δ 7.79 (s, 1H), 7.75 (s, 1H), 7.28 (dd, $J_1 = 2.48$ Hz, $J_2 = 13.75$ Hz, 1H), 6.97 (dd, $J_1 = 2.20$ Hz, $J_2 = 8.94$ Hz, 1H), 6.89 (t, $J = 8.87$ Hz, 1H), 5.04 (m, 1H), 4.78 (d, $J = 3.90$ Hz, 2H), 4.12 (t, $J = 9.14$ Hz, 1H), 3.89 (dd, $J_1 = 6.12$ Hz, $J_2 = 9.28$ Hz, 1H), 3.02 (m, 8H). MS (EI) *m/z* (%): 346 (M^+, 54), 304 (100).

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

Mp: 182–184 °C. ^{1}H NMR ($CDCl_3$): δ 7.71–7.76 (m, 3H), 7.67 (d, $J = 0.98$ Hz, 1H), 7.56–7.62 (m, 1H), 7.49–7.54 (m, 2H), 7.25 (dd, $J_1 = 2.54$ Hz, $J_2 = 14.08$ Hz, 1H), 6.89 (dd, $J_1 = 2.35$ Hz, $J_2 = 8.81$ Hz, 1H), 6.82 (t, $J = 9.00$ Hz, 1H), 5.01 (m, 1H), 4.74 (m, 2H), 4.07 (t, $J = 9.09$ Hz, 1H), 3.84 (dd, $J_1 = 6.06$ Hz, $J_2 = 9.39$ Hz, 1H), 3.03–3.14 (m, 8H). MS (EI) *m/z* (%): 486 (M^+, 7), 91 (100). Anal. Calcd for: $C_{22}H_{23}FN_6O_4S$: C, 54.31; H, 4.76; N, 17.27. Found: C, 54.38; H, 4.88; N, 16.99.

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

Mp: 232–234 °C. ^{1}H NMR ($CDCl_3$): δ 7.78–7.83 (m, 2H), 7.77 (d, $J = 1.01$ Hz, 1H), 7.74 (d, $J = 1.01$ Hz, 1H), 7.28 (dd, $J_1 = 2.69$ Hz, $J_2 = 13.93$ Hz, 1H), 7.21–7.26 (m, 2H), 6.94 (dd, $J_1 = 2.68$ Hz, $J_2 = 9.40$ Hz, 1H), 6.86 (t, $J = 8.98$ Hz, 1H), 5.05 (m, 1H), 4.79 (d, $J = 4.19$ Hz, 2H), 4.12 (t, $J = 9.15$ Hz, 1H), 3.88 (dd, $J_1 = 6.05$ Hz, $J_2 = 9.40$ Hz, 1H), 3.18 (t, $J = 4.70$ Hz, 4H), 3.10 (t, $J = 4.70$ Hz, 4H). MS (EI) *m/z* (%): 520 (M^+, 3), 460 (100). Anal. Calcd for $C_{22}H_{22}FN_6O_4SCl.1/2CH_3OH$: C, 50.37; H, 4.47; N, 15.67. Found: C, 50.58; H, 4.30; N, 15.55.

5.6.5. *(R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(4-bromophenylsulfonyl)piperazin-1-yl)phenyl)oxazolidin-2-one (**6**)*

Mp: 197–200 °C. ^{1}H NMR ($CDCl_3$): δ 7.78 (d, $J = 1.07$ Hz, 1H), 7.74 (d, $J = 0.92$ Hz, 1H), 7.62–7.72 (m, 4H), 7.28 (dd, $J_1 = 2.44$ Hz, $J_2 = 13.88$ Hz, 1H), 6.93 (dd, $J_1 = 2.30$ Hz, $J_2 = 9.30$ Hz, 1H), 6.86 (t, $J = 8.93$ Hz, 1H),

5.04 (m, 1H), 4.78 (d, $J = 4.71$ Hz, 2H), 4.11 (t, $J = 9.16$ Hz, 1H), 3.89 (dd, $J_1 = 6.11$ Hz, $J_2 = 9.46$ Hz, 1H), 3.08–3.20 (m, 8H). MS (EI) *m/z* (%): 564 (M^+, 12), 566 (12), 56 (100). Anal. Calcd for $C_{22}H_{23}FBrN_6O_4S.1/2CH_3OH$: C, 46.48; H, 4.16; N, 14.45. Found: C, 46.21; H, 4.08; N, 14.14.

*5.6.6. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(3-fluorophenylsulfonyl)piperazin-1-yl)phenyl)oxazolidin-2-one (**7**)*

Mp: 232–234 °C. ^{1}H NMR ($CDCl_3$): δ 7.85 (d, $J = 2.06$ Hz, 1H), 7.82 (d, $J = 2.02$ Hz, 1H), 7.77 (d, $J = 1.10$ Hz, 1H), 7.74 (d, $J = 0.96$ Hz, 1H), 7.38 (d, $J = 8.11$ Hz, 2H), 7.28 (dd, $J_1 = 2.47$ Hz, $J_2 = 13.89$ Hz, 1H), 6.94 (dd, $J_1 = 2.48$ Hz, $J_2 = 9.15$ Hz, 1H), 6.88 (t, $J = 9.06$ Hz, 1H), 5.05 (m, 1H), 4.79 (d, $J = 4.40$ Hz, 2H), 4.12 (t, $J = 9.21$ Hz, 1H), 3.90 (dd, $J_1 = 6.05$ Hz, $J_2 = 9.35$ Hz, 1H), 3.20 (t, $J = 4.74$ Hz, 4H), 3.08 (t, $J = 4.74$ Hz, 4H). MS (EI) *m/z* (%): 504 (M^+, 52), 345 (100). Anal. Calcd for $C_{22}H_{22}F_2N_6O_4S$: C, 52.38; H, 4.40; N, 16.66. Found: C, 52.65; H, 4.73; N, 16.57.

*5.6.7. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(4-fluorophenylsulfonyl)piperazin-1-yl)phenyl)oxazolidin-2-one (**8**)*

Mp: 220–222 °C. ^{1}H NMR ($CDCl_3$): δ 7.78–7.83 (m, 2H), 7.77 (d, $J = 0.96$ Hz, 1H), 7.74 (d, $J = 1.10$ Hz, 1H), 7.30 (dd, $J_1 = 2.26$ Hz, $J_2 = 13.91$ Hz, 1H), 7.22–7.27 (m, 2H), 6.95 (dd, $J_1 = 2.34$ Hz, $J_2 = 8.94$ Hz, 1H), 6.90 (t, $J = 8.74$ Hz, 1H), 5.05 (m, 1H), 4.78 (d, $J = 4.13$ Hz, 2H), 4.12 (t, $J = 9.14$ Hz, 1H), 3.88 (dd, $J_1 = 6.05$ Hz, $J_2 = 9.35$ Hz, 1H), 3.20 (t, $J = 4.40$ Hz, 4H), 3.12 (t, $J = 4.68$ Hz, 4H). MS (EI) *m/z* (%): 504 (M^+, 51), 56 (100). Anal. Calcd for $C_{22}H_{22}F_2N_6O_4S$: C, 52.38; H, 4.40; N, 16.66. Found: C, 52.57; H, 4.59; N, 16.34.

*5.6.8. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(2,4-difluorophenylsulfonyl)piperazin-1-yl)phenyl)-oxazolidin-2-one (**9**)*

Mp: 224–226 °C. ^{1}H NMR ($CDCl_3$): δ 7.88 (m, 1H), 7.78 (d, $J = 0.96$ Hz, 1H), 7.74 (d, $J = 0.96$ Hz, 1H), 7.30 (dd, $J_1 = 2.47$ Hz, $J_2 = 13.75$ Hz, 1H), 7.96–7.06 (m, 2H), 6.94 (dd, $J_1 = 2.06$ Hz, $J_2 = 8.80$ Hz, 1H), 6.87 (t, $J = 8.94$ Hz, 1H), 5.05 (m, 1H), 4.78 (m, 2H), 4.12 (t, $J = 9.07$ Hz, 1H), 3.85 (dd, $J_1 = 6.05$ Hz, $J_2 = 9.34$ Hz, 1H), 3.34 (t, $J = 4.88$ Hz, 4H), 3.10 (t, $J = 4.88$ Hz, 4H). MS (EI) *m/z* (%): 522 (M^+, 55), 345 (100). Anal. Calcd for $C_{22}H_{22}F_2N_6O_4S.CH_3OH$: C, 49.82; H, 4.54; N, 15.15. Found: C, 49.72; H, 4.22; N, 15.39.

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

Mp: 195–198 °C. ^{1}H NMR ($CDCl_3$): δ 7.77 (d, $J = 0.92$ Hz, 1H), 7.76 (d, $J = 1.06$ Hz, 1H), 7.64 (m, 2H), 7.33 (m, 3H), 7.27 (dd, $J_1 = 2.52$ Hz, $J_2 = 13.96$ Hz, 1H), 6.92 (dd, $J_1 = 2.37$ Hz, $J_2 = 8.85$ Hz, 1H), 6.86 (t, $J = 8.85$ Hz, 1H), 5.04 (m, 1H), 4.76 (m, 2H), 4.10 (t, $J = 9.16$ Hz, 1H), 3.86 (dd, $J_1 = 6.03$ Hz, $J_2 = 9.38$ Hz, 1H), 3.05–3.16 (m, 8H), 2.42 (s, 3H). MS (EI) *m/z* (%): 500 (M^+, 52), 345(100). Anal. Calcd for $C_{23}H_{25}FN_6O_4S$: C, 55.19; H, 5.03; N, 16.78. Found: C, 54.92; H, 5.00; N, 16.38.

*5.6.10. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(4-methoxphenylsulfonyl)piperazin-1-yl)phenyl)oxazolidin-2-one (**11**)*

Mp: 203–205 °C. ^{1}H NMR ($CDCl_3$): δ 7.70–7.79 (m, 4H), 7.28 (dd, $J_1 = 2.44$ Hz, $J_2 = 13.89$ Hz, 1H), 7.02 (m, 2H), 6.94 (dd, $J_1 = 2.64$ Hz, $J_2 = 9.29$ Hz, 1H), 6.86 (t, $J = 8.90$ Hz, 1H), 5.05 (m, 1H), 4.78 (dd, $J_1 = 0.88$ Hz, $J_2 = 3.92$ Hz, 2H), 4.10 (t, $J = 9.15$ Hz, 1H), 3.88 (m, 4H), 3.06–3.16 (m, 8H). MS (EI) *m/z* (%): 516 (M^+, 28), 56 (100). Anal. Calcd for $C_{23}H_{25}FN_6O_5S$: C, 53.48; H, 4.88; N, 16.27. Found: C, 16.38; H, 4.83; N, 53.64.

*5.6.11. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(2-trifluoromethylphenylsulfonyl)piperazin-1-yl)phenyl)-oxazolidin-2-one (**12**)*

Mp: 144–146 °C. ^{1}H NMR ($CDCl_3$): δ 8.14 (m, 1H), 7.92 (m, 2H), 7.70–7.80 (m, 3H), 7.30 (dd, $J_1 = 2.47$ Hz, $J_2 = 13.88$ Hz, 1H), 6.95 (dd, $J_1 = 2.88$ Hz, $J_2 = 8.80$ Hz, 1H), 6.87 (t, $J = 8.93$ Hz, 1H), 5.05 (m, 1H), 4.79 (m, 2H), 4.12 (t, $J = 9.21$ Hz, 1H), 3.90 (dd, $J_1 = 6.19$ Hz, $J_2 = 9.49$ Hz, 1H), 3.40 (t, $J = 4.82$ Hz, 4H), 3.09 (t, $J = 4.95$ Hz, 4H). MS (EI) *m/z* (%): 554 (M^+, 1), 256 (100). Anal. Calcd for $C_{23}H_{22}F_4N_6O_4S$: C, 49.82; H, 4.00; N, 15.16. Found: C, 49.92; H, 3.96; N, 15.06.

*5.6.12. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(3-trifluoromethylphenylsulfonyl)piperazin-1-yl)phenyl)-oxazolidin-2-one (**13**)*

Mp: 202–204 °C. ^{1}H NMR ($CDCl_3$): δ 8.03 (s, 1H), 7.98 (d, $J = 8.06$ Hz, 1H), 7.90 (d, $J = 8.06$ Hz, 1H), 7.70–7.80 (m, 4H), 6.94 (dd, $J_1 = 2.36$ Hz, $J_2 = 8.97$ Hz, 1H), 6.86 (t, $J = 8.94$ Hz, 1H), 5.05 (m, 1H), 4.79 (d, $J = 4.20$ Hz, 2H), 4.10 (t, $J = 9.21$ Hz, 1H), 3.89 (dd, $J_1 = 6.21$ Hz, $J_2 = 9.57$ Hz, 1H), 3.10–3.22 (m, 8H). MS (EI) *m/z* (%): 554 (M^+, 49), 345 (100). Anal. Calcd for $C_{23}H_{22}F_4N_6O_4S$: C, 49.82; H, 4.00; N, 15.16. Found: C, 49.86; H, 4.20; N, 14.92.

*5.6.13. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(4-trifluoromethylphenylsulfonyl)piperazin-1-yl)phenyl)-oxazolidin-2-one (**14**)*

Mp: 245–247 °C. ^{1}H NMR ($CDCl_3$): δ 7.92 (d, $J = 8.25$ Hz, 2H), 7.83 (d, $J = 8.39$ Hz, 2H), 7.77 (d, $J = 1.10$ Hz, 1H), 7.74 (d, $J = 1.10$ Hz, 1H), 7.28 (dd, $J_1 = 2.34$ Hz, $J_2 = 13.88$ Hz, 1H), 6.94 (dd, $J_1 = 2.20$ Hz, $J_2 = 9.90$ Hz, 1H), 6.86 (t, $J = 8.95$ Hz, 1H), 5.05 (m, 1H), 4.80 (d, $J = 4.13$ Hz, 2H), 4.10 (t, $J = 9.21$ Hz, 1H), 3.89 (dd, $J_1 = 6.19$ Hz, $J_2 = 9.49$ Hz, 1H), 3.20 (t, $J = 4.75$ Hz, 4H), 3.10 (t, $J = 4.75$ Hz, 4H). MS (EI) *m/z* (%): 554 (M^+, 40), 56 (100). Anal. Calcd for $C_{23}H_{22}F_4N_6O_4S$: C, 49.82; H, 4.00; N, 15.16. Found: C, 49.90; H, 3.99; N, 15.02.

*5.6.14. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(2-nitrophenylsulfonyl)piperazin-1-yl)phenyl)oxazolidin-2-one (**15**)*

Mp: 197–199 °C. ^{1}H NMR ($CDCl_3$): δ 8.63 (t, $J = 2.33$ Hz, 1H), 8.45 (m, 1H), 8.12 (m, 1H), 7.74–7.82 (m, 3H), 7.28 (dd, $J_1 = 2.48$ Hz, $J_2 = 13.98$ Hz, 1H), 6.94 (dd, $J_1 = 2.36$ Hz, $J_2 = 8.97$ Hz, 1H), 6.86 (t, $J = 8.94$ Hz, 1H), 5.05 (m, 1H), 4.78 (d, $J = 4.12$ Hz, 2H), 4.12 (t, $J = 9.08$ Hz, 1H), 3.89 (dd, $J_1 = 6.05$ Hz, $J_2 = 9.48$ Hz, 1H), 3.25 (m, 4H), 3.13 (m, 4H). MS (EI) *m/z* (%): 531 (M^+, 6), 57 (100). Anal. Calcd for $C_{22}H_{22}FN_7O_6S$: C, 49.71; H, 4.17; N, 18.45. Found: C, 49.43; H, 4.46; N, 18.26.

*5.6.15. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(3-nitrophenylsulfonyl)piperazin-1-yl)phenyl)oxazolidin-2-one (**16**)*

Mp: 197–199 °C. ^{1}H NMR ($CDCl_3$): δ 8.63 (t, $J = 1.81$ Hz, 1H), 8.49 (m, 1H), 8.11 (m, 1H), 7.80 (t, $J = 7.97$ Hz, 1H), 7.77 (d, $J = 0.88$ Hz, 1H), 7.73 (d, $J = 0.88$ Hz, 1H), 7.30 (m, 1H), 6.94 (dd, $J_1 = 2.47$ Hz, $J_2 = 8.85$ Hz, 1H), 6.87 (t, $J = 8.91$ Hz, 1H), 5.04 (m, 1H), 4.79 (d, $J = 4.02$ Hz, 2H), 4.10 (t, $J = 9.15$ Hz, 1H), 3.90 (dd, $J_1 = 6.06$ Hz, $J_2 = 9.29$ Hz, 1H), 3.26 (t, $J = 4.45$ Hz, 4H), 3.12 (t, $J = 4.80$ Hz, 4H). MS (EI) *m/z* (%): 531 (M^+, 22), 345 (100). Anal. Calcd for $C_{22}H_{22}FN_7O_6S$: C, 49.71; H, 4.17; N, 18.45. Found: C, 49.87; H, 4.16; N, 18.12.

*5.6.16. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(4-nitrophenylsulfonyl)piperazin-1-yl)phenyl)oxazolidin-2-one (**17**)*

Mp: 222–224 °C. ^{1}H NMR ($CDCl_3$): δ 8.40 (m, 2H), 7.98 (m, 2H), 7.74 (s, 1H), 7.77(s, 1H), 7.28 (dd, $J_1 = 2.55$ Hz, $J_2 = 14.19$ Hz, 1H), 6.94 (dd, $J_1 = 3.03$ Hz, $J_2 = 9.68$ Hz, 1H), 6.86 (t, $J = 9.00$ Hz, 1H), 5.05 (m, 1H), 4.79 (d, $J = 4.21$ Hz, 2H), 4.10 (t, $J = 9.10$ Hz, 1H), 3.90 (dd, $J_1 = 6.16$ Hz, $J_2 = 9.11$ Hz, 1H), 3.24 (t, $J = 4.40$ Hz, 4H), 3.12 (t, $J = 4.75$ Hz, 4H). MS (EI) *m/z* (%): 531 (M^+, 11), 56 (100). Anal. Calcd for $C_{22}H_{22}FN_7O_6S$: C, 49.71; H, 4.17; N, 18.45. Found: C, 49.70; H, 4.23; N, 18.16.

*5.6.17. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(4-cyanophenylsulfonyl)piperazin-1-yl)phenyl)oxazolidin-2-one (**18**)*

Mp: 237–239 °C. ^{1}H NMR ($CDCl_3$): δ 7.90 (m, 4H), 7.78 (s, 1H), 7.74 (s, 1H), 7.28 (dd, $J_1 = 2.34$ Hz, $J_2 = 14.15$ Hz, 1H), 6.94 (m, 1H), 6.86 (t, $J = 8.80$ Hz, 1H), 5.04 (m, 1H), 4.78 (d, $J = 3.85$ Hz, 2H), 4.10 (t, $J = 8.93$ Hz, 1H), 3.90 (dd, $J_1 = 5.77$ Hz, $J_2 = 8.93$ Hz, 1H), 3.20 (m, 4H), 3.10 (m, 4H). MS (EI) *m/z* (%): 511 (M^+, 46), 345 (100). Anal. Calcd for $C_{23}H_{22}FN_7O_6S$: C, 54.00; H, 4.33; N, 19.17. Found: C, 54.06; H, 4.30; N, 19.05.

*5.6.18. (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 (**19**)*

Mp: 202–204 °C. ^{1}H NMR ($CDCl_3$): δ 7.77 (s, 1H), 7.74 (s, 1H), 7.65 (dd, $J_1 = 1.34$ Hz, $J_2 = 5.04$ Hz, 1H), 7.57 (dd, $J_1 = 1.34$ Hz, $J_2 = 3{,}69$ Hz, 1H), 7.30 (dd, $J_1 = 2.52$ Hz, $J_2 = 13.93$ Hz, 1H), 7.17 (dd, $J_1 = 3.86$ Hz, $J_2 = 5.03$ Hz, 1H), 6.95 (dd, $J_1 = 2.43$ Hz, $J_2 = 9.32$ Hz, 1H), 6.88 (t, $J = 8.90$ Hz, 1H), 5.05 (m, 1H), 4.78 (d, $J = 3.86$ Hz, 2H), 4.12 (t, $J = 9.15$ Hz, 1H), 3.90 (dd, $J_1 = 6.21$ Hz, $J_2 = 9.40$ Hz, 1H), 3.24 (t, $J = 4.87$ Hz, 4H), 3.14 (t, $J = 4.87$ Hz, 4H). MS (EI) *m/z* (%): 492 (M^+, 1), 345 (100). Anal. Calcd for $C_{22}H_{21}FN_6O_4S_2$: C, 48.77; H, 4.30; N, 17.06. Found: C, 48.72; H, 4.42; N, 17.39.

*5.6.19. (R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(3-fluoro-4-(4-(3-aminophenylsulfonyl)piperazin-1-yl)phenyl)oxazolidin-2-one (**20**)*

Mp: 165–167 °C. ^{1}H NMR (DMSO-d_6): δ 8.15 (d, $J = 0.96$ Hz, 1H), 7.75 (d, $J = 0.96$ Hz, 1H), 7.37 (dd, $J_1 = 2.41$ Hz, $J_2 = 14.64$ Hz, 1H), 7.28 (t, $J = 7.91$ Hz, 1H), 7.10 (dd, $J_1 = 2.52$ Hz, $J_2 = 8.93$ Hz, 1H), 7.04 (t, $J = 9.26$ Hz, 1H), 6.93 (t, $J = 2.01$ Hz, 1H), 6.84 (m, 2H), 5.10 (m, 1H), 4.81 (d, $J = 5.08$ Hz, 2H), 4.19 (t, $J = 9.21$ Hz, 1H), 3.81 (dd, $J_1 = 5.77$ Hz, $J_2 = 9.42$ Hz, 1H), 3.02 (m, 8H). MS (EI) *m/z* (%): 501 (M^+, 4), 56 (100). Anal. Calcd for $C_{22}H_{24}FN_7O_4S.1/2H_2O$: C, 51.71; H, 4.90; N, 19.19. Found: C, 51.95; H, 4.92; N, 18.87.

5.7. Pharmacology

5.7.1. In vitro

The *in vitro* antibacterial activity (MIC) of the compounds **2–20** against Gram-positive bacteria was tested as growth inhibition with the use of the microdilution broth method according to NCCLS [16]. The 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 twofold dilutions were prepared from the stock solution in sterile water or Mueller-Hinton (MH) agar medium to provide the concentration of 8, 4, 2, 1, 0.5, 0.25, 0.125, 0.06, 0.03, 0.015, 0.008, 0.004, 0.002, 0.001 and 0.0005 μg/mL.

5.7.2. In vivo

KunMing mice weighing 18–20 g were used in the study with five mice in each group. Lethal systemic infection was caused in the mice by injecting intraperitoneally MLD inoculum of MRSA BAA-42, MSSA 04-5 and MRSE 03427, the compounds were administered orally immediately and 4 h post-infection. The ED_{50} was calculated by the Bliss method [17,18] on day 7 post-infection.

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