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Short communication

Syntheses and antibacterial activity of a series of 3-(pyridine-3-yl)-2-oxazolidinone

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Abstract

The syntheses of substituted piperazinyl pyridyl oxazolidinones **8**–**16** are described. Their in vitro activities against Gram-positive organisms such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus* and *enterococcus* were evaluated by minimum inhibitory concentration (MIC) determination. Compound **8** and **10** were found to be superior to linezolid.

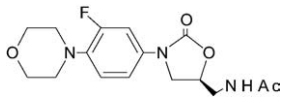
Keywords: Oxazolidinone; Linezolid; Antibacterial activity; Gram-positive organism

1. Introduction

Oxazolidinones, a new class of synthetic antibacterial agents, exhibit activity against a large number of Gram-positive organisms including methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis* (MRSE), penicillin- and cephalosporinresistant *Streptococcus* and vancomycin-resistant *enterococcus* (VRE) [1,2]. Their mode of action has been shown to inhibit protein synthesis at the initial phase by binding to the 50S ribosomal subunit to prevent formation of 70S initiation complex [3]. Due to the unique action mechanism of oxazolidinones, it is believed that oxazolidinones are not cross resistant with other types of antibiotics. Linezolid (Fig. 1), the only oxazolidinone approved by FDA, has already taken it place in the clinic for treatment of Gram-positive infections [4].

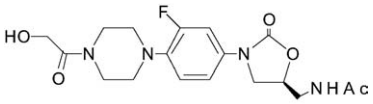
After a few years of introducing linezolid, there are already reports on linezolid-resistance *Enterococci* [5,6] and linezolid-resistance *S. aureus* [7,8].

Therefore, it is necessary to develop more effective oxazolidinones antibacterial agent. At present most efforts are focused on substituted phenyl oxazolidinones. Eperezolid (Fig. 2) and AZD2563 (Fig. 3) have been the main structural feature for modification [9–11]. We consider to link pyridine as isoster of phenyl to oxazolidinone ring in order to study the antibacterial activity. To our knowledge, there are some investigations on pyridyl and pyrryl oxazolidinone [12,13]. In the present communication we wish to report the synthesis



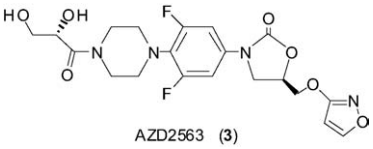
Linezolid (**1**)

Fig. 1.



Eperezolid (**2**)

Fig. 2.



AZD2563 (**3**)

Fig. 3.

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and antibacterial activity of 3-(pyridine-3-yl)-2-oxazolidinones derivatives.

2. Chemistry

The syntheses of derivatives **8–16** are outlined in Scheme 1.

2-Chloro-5-nitropyridine as starting material on condensation with anhydrous piperazine in acetonitrile at room temperature (r.t.) gave 1-(5-nitro-2-pyridinyl) piperazine **4**.

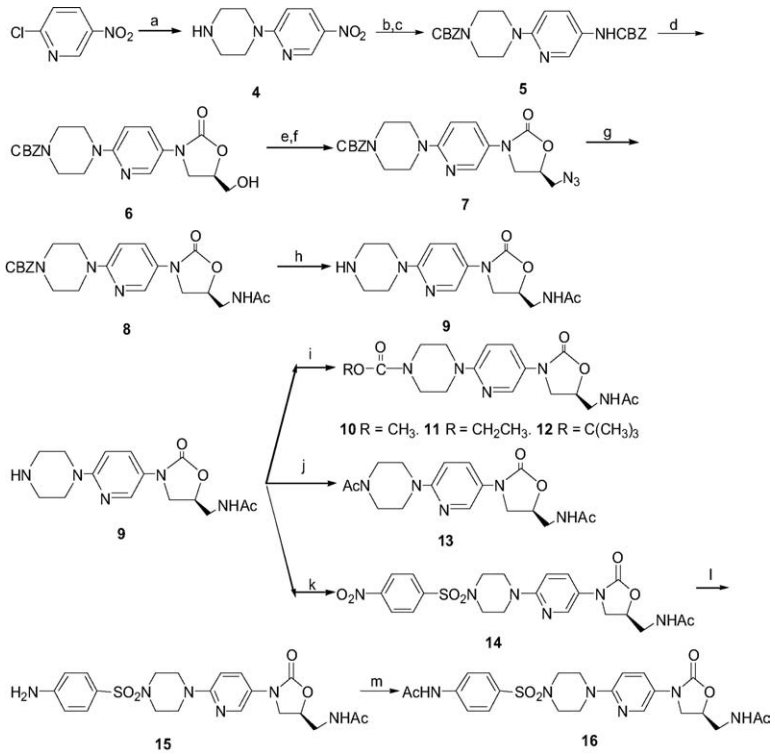
Hydrogenation of compound **4** with 10% Pd–C/H_2 was followed by condensation with benzyl chloroformate to afford protected pyridine **5**. Conversion of compound **5** to oxazolidinone **6** was accomplished by use of *n*-butyl lithium and (*R*)-glycidyl butyrate in dry THF at –78 °C. Compound **6** was reacted with methanesulfonyl chloride, followed by treatment with sodium azide to yield azide **7**. Reduction and acylation of compound **7** by thioacetic acid gave acetamide derivative **8** and subsequent hydrogenation provided piperazine acetamide **9**. Derivatives **10–12** were obtained by condensation of compound **9** with chloroformate. Acylation of compound **9** yielded derivative **13**. The reaction of compound **9** with 4-nitrophenyl sulfonyl chloride furnished derivative **14**. Hydrogenation of compound **14** with 10% Pd–C/H_2 gave derivative **15**. Acylation of compound **15** yielded derivatives **16**.

3. Biological activities

The in vitro antibacterial activity of compounds **8–16** against Gram-positive pathogens clinically isolated was tested with Linezolid as reference compound. Linezolid was prepared according to literature method [1]. Minimum inhibitory concentration (MIC) values were determined using Agar dilution methodology according to NCCLS standards [14]. Compounds were dissolved in 20% water in DMSO to prepare stock solution in which concentration of compound is 1920 μg/ml. Serial two fold dilutions were prepared from stock solution in sterile water or Mueller–Hinton (MH) agar medium to provide the concentration of 128, 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.125, 0.06, 0.03 mg/l. The test organism was grown in MH broth medium at 35 °C for 16–18 h, the broths were adjusted to the turbidity of 0.5McFarland standard; then the bacterial suspensions were inoculated onto the drug-supplemented MH agar plates at 35 °C for 18–20 h. The MIC was defined as the lowest concentration of drug that completely inhibited growth of the organism. At the end of each series of tests, one plate was inoculated without antimicrobial agent; it was used as a control for growth comparison.

4. Results and discussion

Compounds **8**, **9** and **13–16** were firstly synthesized and screened during our work (Table 1). Compound **8** containing



Scheme 1. Reagents and conditions: (a) piperazine, CH_3CN, r.t.; (b) 10% Pd/C, H_2, THF; (c) CBZ-Cl, Na_2CO_3, acetone: H_2O = 2:1, 0 °C to r.t.; (d) (i) *n*-BuLi, dry THF, –78 °C, (ii) (*R*)-glycidyl butyrate, –78 °C to r.t.; (e) MsCl, Et_3N, CH_2Cl_2; (f) NaN_3, DMF, 70–80 °C; (g) CH_3COSH, r.t.; (h) H_2, 10% Pd/C, CH_3OH/CH_2Cl_2; (i) RSO_2Cl, Et_3N, 0 °C to r.t.; (j) Ac_2O, Py, 0 °C to r.t.; (k) ClCOOR, Et_3N, THF, 0 °C to r.t.; (l) H_2, 10% Pd/C, CH_3OH/CH_2Cl_2; (m) Ac_2O, Py, 0 °C to r.t.

Table 1
MIC (μg/ml) values of oxazolidinone derivatives against 20 bacterial strains

Compounds	Microorganism				
	S.a.[a] (five strains)	S.a.[b] (four strains)	S.e.[c] (three strains)	S.e.[d] (five strain)	Str.A (three strains)
8	0.015–0.06	0.06–0.125	<0.004	<0.004–0.015	<0.004–0.008
9	32–64	16–32	16–64	32–128	16
13	>128	>128	>128	>128	>128
14	8–128	16–32	<0.004–0.5	0.5–1	<0.004–1
15	8–16	8–16	1–8	2–4	0.5–2
16	>128	>128	2–128	>128	0.008–4
LZ	1–2	1–2	0.25	0.5–2	0.125–2

LZ = linezolid, Str.A = *Streptococcus* A.
[a] S.a. = MSSA.
[b] S.a. = MRSA.
[c] S.e. = MSSE.
[d] S.e. = MRSE.

Table 2
MIC (μg/ml) values of oxazolidinone derivatives against 40 bacterial strains

Microorganism	Compounds				
	8	**10**	**11**	**12**	LZ
S.a.[a] (one strain)	1	0.5	4	1	0.5
S.a.[b] (eight strains)	<0.008–1	N.T.[f]	0.5–8	2–8	0.25–1
S.a.[c] (six strains)	0.015–0.125	N.T.[f]	4–8	8	1–2
S.e.[d] (14 strains)	0.03–1	0.015–0.25	0.03–2	0.125–4	0.015–1
S.e.[e] (two strains)	<0.008–0.125	N.T.[f]	4	8	1
Str.p. (four strains)	0.5–1	0.25–0.5	2–4	1	0.5
E.f. (five strains)	0.25	0.25–0.5	2–4	1–2	0.25–0.5

LZ = linezolid, Str.p. = *Streptococcus pneumoniae*, E.f. = *enterococcus* sensitive.
[a] S.a. = *Staphylococcus aureus*, ATCC 29213.
[b] S.a. = MSSA.
[c] S.a. = MRSA.
[d] S.e. = MSSE.
[e] S.e. = MRSE.
[f] N.T. = no tested.

carbobenzoxy group exhibits more potent antibacterial activity than linezolid. When removal of carbobenzoxy group from **8** yields compound **9**, it is almost inactive. This suggests that carbobenzoxy group is favorable for antibacterial activity. Derivative **13** resulting from acylation of compound **9** completely loses activity. None of compounds **14**, **15** and **16** containing sulphonyl groups show good activities. From the results, introduction of carboalkoxy group to piperazinyl pyridyl oxazolidinone appears to be the best choice comparing with introduction of acyl and sulphonyl groups. Further, three compounds **10**–**12** containing carboalkoxy group were prepared. We selected compounds **8**, **10**, **11** and **12** for further screening in more Gram-position strains (Table 2). All four compounds show potent antibacterial activity.

Compounds **8** and **10** show more potent antibacterial activity than linezolid. Compounds **11** and **12** were found to be inferior to linezolid. With increasing bulk from methoxy, ethoxy to *tert*-butoxy in compounds **10**, **11** and **12**, their activities decrease. The electron donating effect of phenyl in compound **8** maybe enhances interaction between compound **8** and receptor.

5. Conclusion

A series of substituted piperazinyl pyridyl oxazolidinones was synthesized and evaluated for microbiological activity against Gram-positive organisms in vitro comparable to linezolid. The carboalkoxy piperazinyl pyridyl oxazolidinones exhibits potent antibacterial activity. Compounds **8** and **10** were found to be superior to linezolid and this type of compound is worth further study.

6. Experimental protocol

Melting points (m.p.) were determined on a MEL-TEMP m.p. apparatus and were uncorrected. ^{1}H NMR spectral data were recorded using a Bruker AM-400 spectrometer. Chemical shifts are reported in units (ppm). Coupling contants (*J*) are reported in hertz (Hz). Mass spectra were recorded on a MAT-711. Elemental analysis were recorded on an Elemental vario 1106. Optical rotations were measured with a PERKINELMER 241.

*6.1. 1-(5-Nitro-2-pyridinyl)piperazine (**4**)*

A solution of 2-chloro-5-nitropyridine (1.61 g, 10.0 mmol) in CH_3CN (20 ml) was treated with piperazine (2.61 g, 25.2 mmol) at r.t. After 2.5 h, TLC showed that the reaction completed. The mixture was filtered and filtrate was concentrated in vacuo. The residue was dissolved in AcOEt and it was washed with H_2O, dried over Na_2SO_4, then concentrated in vacuo to afford **4** (1.76 g, 84.6%) as yellow solid; m.p. 124–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 9.02 (d, *J* = 2.57 Hz, 1H), 8.20 (dd, *J* = 9.5 Hz, *J* = 2.6 Hz, 1H), 7.55 (d, *J* = 9.5 Hz, 1H), 3.75 (m, 4H), 3.95 (m, 4H).

*6.2. 2-(*N*-carbobenzoxypiperazinyl)-5-(carbobenzoxyamino)pyridine (**5**)*

A mixture of compound **4** (1.76 g, 8.46 mmol) and 5% Pd/C (0.166 g) in THF (420 ml) was stirred at r.t. under a H_2 atmosphere (1 atm) overnight. The resulting mixture was filtered and concentrated in vacuo to give the amine as red oil, which was used for the next reaction without further purification.

To a cooled solution of crude amine in acetone (60 ml) and H_2O (30 ml) was added Na_2CO_3 (2.12 g, 20.0 mmol) and then benzyl chloroformate (3.0 ml, 90% W/W, 19 mmol) over 10 min via syringe. The mixture was allowed to warm to r.t. and stirred overnight. The mixture was filtered, and precipitate was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH = 50:1) and then recrystallized from DMF and H_2O to give **5** (3.23 g, 86.7%) as pale red solid; m.p. 157-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.10 (s, 1H), 7.82 (brs, 1H), 7.30–7.40 (m, 8H), 6.65 (d, *J* = 9.2 Hz, 1H), 5.19 (s, 2H), 5.16 (s, 2H), 3.62 (m, 4H), 3.50 (m, 4H); EI-MS (*m*/*z*): 446 (M+); Calc. for $C_{25}H_{26}N_4O_4$: C 67.26, H 5.83, N 12.56. Found: C 67.29, H 5.78, N 12.40.

*6.3. (R)-(*N*-3-(4-(*N*-carbobenzoxypiperazinyl)-pyridine-3-yl)-2-oxo-5-oxazolidinyl)methanol (**6**)*

To a stirred solution of compound **5** (2.04 g, 4.57 mmol) in dry THF (30 ml) at –78 °C under Ar was added dropwise 1.6 M *n*-butylithium-hexane (2.90 ml, 4.64 mmol). After 3.5 h, (*R*)-glycidyl butyrate (0.70 ml, 93% W/W, 4.6 mmol) was added and stirred at –78 °C for 2 h. Then the mixture was allowed to warm to r.t. overnight. AcOEt (50 ml) was added to the mixture, the mixture was washed with H_2O and brine, respectively, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH = 25:1) and then recrystallized from AcOEt and petroleum to give **6** (1.30 g, 69.1%) as white solid; m.p. 136–138 °C; $[\alpha]_D^{20}$ –30.53° (*C* 0.83, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$): 8.10 (d, *J* = 2.8 Hz, 1H), 8.00 (dd, *J* = 9.2 Hz, *J* = 2.8 Hz, 1H), 7.30–7.40 (m, 4H), 6.70 (d, *J* = 9.2 Hz, 1H), 5.16 (s, 2H), 4.75–4.80 (m, 1H), 3.95–4.02 (m, 3H), 3.75 (dd, *J* = 12.8 Hz, *J* = 3.9 Hz, 1H), 3.60–3.65 (m, 4H), 3.50–3.58 (m, 4H); EI-MS (*m*/*z*): 412 (M+); Calc. for $C_{21}H_{24}N_4O_5{\cdot}H_2O$: C 58.60, H 6.04, N 13.02. Found: C 58.99, H 6.17, N 13.09.

*6.4. (R)-(*N*-3-(4-(*N*-carbobenzoxypiperazinyl)-pyridine-3-yl)-2-oxo-5-oxazolidinyl)methyl azide (**7**)*

To a cooled (0 °C) solution of compound **6** (0.16 g, 0.39 mmol) and Et_3N (0.16 ml, 1.0 mmol) in CH_2Cl_2 (10 ml) was added dropwise $MeSO_2Cl$ with stirring, the reaction mixture was allowed to warm to r.t. overnight. The mixture was washed with H_2O and extracted with CH_2Cl_2. Combined extract was dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH = 50:1) to give mesylate (0.146 g, 76%) as pale red solid, still contaminated with impurity. The mesylate was used in next reaction. ^{1}H NMR (400 MHz, $CDCl_3$): 8.12 (d, *J* = 2.8 Hz, 1H), 7.95 (dd, *J* = 9.1 Hz, *J* = 2.6 Hz, 1H), 7.30–7.40 (m, 4H), 6.70 (d, *J* = 9.2 Hz, 1H), 5.16 (s, 2H), 4.70–4.85 (m, 1H), 4.50 (dd, *J* = 11.5 Hz, *J* = 3.5 Hz, 1H), 4.45 (dd, *J* = 11.7 Hz, *J* = 4.0 Hz, 1H), 4.12 (t, *J* = 9.2 Hz, 1H), 3.92 (m, 1H), 3.60–3.65 (m, 4H), 3.50–3.60 (m, 4H), 3.10 (s, 3H).

A mixture of mesylate (1.67 g, 3.40 mmol) and NaN3 (0.88 g, 13.5 mmol) in DMF (50 ml) was heated at 70-80 °C for 5 h. The mixture was poured into H_2O and filtered, the precipitate was air dried to give **7** (1.1 g, 73%) as white solid; m.p. 117–119 °C; $[\alpha]_D^{20}$ –100.43° (*C* 0.42, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$): 8.10 (d, *J* = 2.8 Hz, 1H), 8.00 (dd, *J* = 9.1 Hz, *J* = 2.5 Hz, 1H), 7.30–7.40 (m, 4H), 6.70 (d, *J* = 9.2 Hz, 1H), 5.17 (s, 2H), 4.80 (m, 1H), 4.05 (t, *J* = 8.8 Hz, 1H), 4.45 (dd, *J* = 11.7 Hz, *J* = 4.0 Hz, 1H), 3.92 (m, 1H), 3.50–3.85 (m, 10H); EI-MS (*m*/*z*): 437 (M+); Calc. for $C_{21}H_{23}N_7O_4$: C 57.66, H 5.26, N 22.42. Found: C 57.99, H 5.36, N 22.04.

*6.5. (S)-(*N*-3-(4-(*N*-carbobenzoxypiperazinyl)-pyridine-3-yl)-2-oxo-5-oxazolidinyl)acetamide (**8**)*

A solution of compound **7** (1.1 g, 2.5 mmol) in CH_3COSH (10 ml) was stirred at r.t. for 36 h. The mixture was diluted with CH_2Cl_2 (20 ml) and washed with saturated $NaHCO_3$, H_2O and brine, respectively, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH = 25:1) and then recrystallized from AcOEt and petroleum to give **8** (0.70 g, 57%) as white solid; m.p. 151–153 °C; $[\alpha]_D^{20}$ –20.86° (*C* 0.52, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$): 8.12 (d, *J* = 2.5 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.30–7.40 (m, 4H), 6.70 (d, *J* = 9.2 Hz, 1H), 5.17 (s, 2H), 4.80 (m, 1H), 4.02 (t, *J* = 8.7 Hz, 1H), 3.70–3.80 (m, 2H), 3.50–3.70 (m, 10H), 2.03 (s, 3H); EI-MS (*m*/*z*): 453 (M+); Calc. for $C_{23}H_{27}N_5O_5$: C 60.93, H 5.96, N 15.45. Found: C 61.30, H 6.08, N 15.52.

*6.6. (S)-(N-3-(4-(N-piperazinyl)-pyridine-3-yl)-2-oxo-5-oxazolidinyl)acetamide, hydrochloride (**9**)*

A mixture of compound **8** (0.70 g, 1.4 mmol) and 10% Pd/C (0.090 g) in CH_3OH (35 ml) and CH_2Cl_2 (10 ml) was stirred at r.t. under a H_2 atmosphere (1 atm) overnight. The resulting mixture was filtered and filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (CH_3OH) to give **9** (0.425 g, 93.2%) as white solid; m.p. 194–198 °C; $[\alpha]_D^{20}$ –18.17° (*C* 0.125, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$): 8.82 (brs, 1H), 8.22 (d, *J* = 2.9 Hz, 2H), 7.82 (dd, *J* = 9.2 Hz, *J* = 2.7 Hz, 1H), 6.99 (d, *J* = 9.2 Hz, 1H), 4.70 (m, 1H), 4.05 (m, 1H), 3.60–3.70 (m, 5H), 3.15–3.20 (m, 5H), 1.82 (s, 3H). EI-MS (*m*/*z*): 319 (M+); Calc. for $C_{15}H_{21}N_5O_3{\cdot}2HCl$: C 45.92, H 5.87, N 17.86. Found: C 46.27, H 5.74, N 17.60.

*6.7. (S)-(N-3-(4-(N-carbomethoxypiperazinyl)-pyridine-3-yl)-2-oxo-5-oxazolidinyl)acetamide (**10**)*

To a cooled mixture of compound **9** (0.058 g, 0.18 mmol) and Et_3N (0.5 ml) in THF (5 ml) was added dropwise methyl chloroformate with stirring, the reaction mixture was allowed to warm to r.t. overnight. The mixture was diluted with CH_2Cl_2 (20 ml) and washed with H_2O and brine, dried over Na_2SO_4, then concentrated in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH = 10:1) to give **10** (0.053 g, 78%) as white solid; m.p. 130–132 °C; $[\alpha]_D^{20}$ –30.86 (*C* 0.20, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$): 8.14 (d, *J* = 2.6 Hz, 1H), 7.90 (dd, *J* = 9.2 Hz, *J* = 2.8 Hz, 1H), 6.78 (d, *J* = 9.4 Hz, 1H), 6.17 (t, *J* = 6.0 Hz, 1H), 4.78 (m, 1H), 4.03 (t, *J* = 9.0 Hz, 1H), 3.65–3.78 (m, 5H), 3.45–3.62 (m, 9H), 2.02 (s, 3H). EI-MS (*m*/*z*): 377 (M+); Calc. for $C_{17}H_{23}N_5O_5{\cdot}CH_3OH$: C 52.81, H 6.60, N 17.11. Found: C 53.01, H 6.06, N 17.01.

*6.8. (S)-(N-3-(4-(N-carboethoxypiperazinyl)-pyridine-3-yl)-2-oxo-5-oxazolidinyl)acetamide (**11**)*

Compound **9** was treated by the same procedure as for the derivative **10**, giving 11 (0.057 g, 75%) as white solid; m.p. 154–157 °C; $[\alpha]_D^{20}$ –17.72° (*C* 0.345, DMSO): ^{1}H NMR (400 MHz, $CDCl_3$): 8.13 (d, *J* = 2.8 Hz, 1H), 7.89 (dd, *J* = 9.1 Hz, *J* = 2.8 Hz, 1H), 6.68 (d, *J* = 9.2 Hz, 1H), 6.13 (t, *J* = 5.9 Hz, 1H), 4.78 (m, 1H), 4.10–4.20 (m, 2H), 4.02 (t, *J* = 9.0 Hz, 1H), 3.65–3.78 (m, 2H), 3.45–3.62 (m, 9H), 2.02 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H). EI-MS (*m*/*z*): 391 (M+). Calc. for $C_{18}H_{25}N_5O_5$: C 55.24, H 6.39, N 17.90. Found: C 55.19, H 6.40, N 17.10.

*6.9. (S)-(N-3-(4-(N-carbotertbutoxypiperazinyl)pyridine-3-yl)-2-oxo-5-oxazolidinyl)acetamide (**12**)*

Compound **9** was treated by the same procedure as for the derivative **10**, giving **12** (0.071 g, 68%) as white solid; m.p. 184–186 °C; $[\alpha]_D^{20}$ –17.63° (*C* 0.345, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$): 8.12 (d, *J* = 2.7 Hz, 1H), 7.85 (dd, *J* = 9.2 Hz, *J* = 2.9 Hz, 1H), 6.65 (d, *J* = 9.2 Hz, 1H), 6.36 (t, *J* = 6.2 Hz, 1H), 4.78 (m, 1H), 4.02 (t, *J* = 8.9 Hz, 1H), 3.65–3.78 (m, 2H), 3.45–3.55 (m, 9H), 2.02 (s, 3H), 1.47 (s, 9H). EI-MS (*m*/*z*): 419 (M+). Calc. for $C_{20}H_{29}N_5O_5$: C 57.28, H 6.92, N 16.71. Found: C 57.16, H 6.84, N 16.43.

*6.10. (S)-(N-3-(4-(N-acetylpiperazinyl)-pyridine-3-yl)-2-oxo-5-oxazolidinyl)acetamide (**13**)*

To a cooled mixture of compound **9** (0.050 g, 0.18 mmol) in pyridine (5 ml) was added Ac_2O (1 ml) with stirring, the reaction mixture was allowed to warm to r.t. overnight. The mixture was diluted with CH_2Cl_2 (20 ml) and washed with H_2O and brine, dried over Na_2SO_4, then concentrated in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH = 15:1) and then recrystallized from EtOAc to give **13** (0.020 g, 34%) as white solid; m.p. 125–127 °C; $[\alpha]_D^{20}$ –25.14 (*C* 0.125, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$): 8.15 (d, *J* = 2.9 Hz, 1H), 7.88 (m, 1H), 6.69 (d, *J* = 9.2 Hz, 1H), 4.80 (m, 1H), 4.00 (t, *J* = 8.8 Hz, 1H), 3.82–3.85 (m, 1H), 3.60 (m, 4H), 3.45 (m, 2H), 2.14 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.3, 169.3, 156.2, 155.0, 138.7, 129.7, 126.1, 107.2, 72.3, 47.7, 45.8, 45.4, 45.3, 42.0, 40.9, 23.0, 21.4. HRMS Calc. for $C_{17}H_{23}N_5O_4$ (M+) 361.1750. Found: 361.1751.

*6.11. (S)-(N-3-(4-(N-(4-nitrophenylsulfonyl) piperazinyl)-pyridine-3-yl)-2-oxo-5-oxazolidinyl)acetamide (**14**)*

To a cooled solution of compound **9** (0.10 g, 0.31 mmol) and Et_3N (2 ml) in CH_2Cl_2 (35 ml) was added 4-nitrobenzenesulfonyl chloride (0.136 g, 0.614 mmol) with stirring, the reaction mixture was allowed to warm to r.t. overnight. The mixture was washed with H_2O and brine, dried over Na_2SO_4, then concentrated in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH = 10:1) to give **14** (0.15 g, 95%) as yellow solid; m.p. >230 °C; $[\alpha]_D^{20}$ –13.29° (*C* 0.15, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$): 8.40 (d, *J* = 8.8 Hz, 1H), 8.07 (d, *J* = 2.3 Hz, 1H), 7.95 (d, *J* = 8.9 Hz, 1H), 7.90 (d, *J* = 9.1 Hz, 1H), 6.65 (d, *J* = 9.1 Hz, 1H), 5.96 (m, 1H), 4.78 (m, 1H), 4.00 (t, *J* = 8.9 Hz, 1H), 3.55–3.75 (m, 7H), 3.19 (m, 4H), 2.00 (s, 3H). EI-MS (*m*/*z*): 504 (M+). Calc. for $C_{21}H_{24}N_6O_7S{\cdot}0.5H_2O$: C 49.12, H 4.87, N 16.37. Found: C 49.34, H 5.02, N 16.07.

*6.12. (S)-(N-3-(4-(N-(4-aminophenylsulfonyl) piperazinyl)-pyridine-3-yl)-2-oxo-5-oxazolidinyl) acetamide (**15**)*

A mixture of compound **14** (0.15 g, 0.30 mmol) and 10% Pd/C (0.090 g) in CH_3OH (30 ml) and CH_2Cl_2 (20 ml) was stirred at r.t. under a H_2 atmosphere (1 atm) overnight. The resulting mixture was filtered and filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH = 15:1) to give **15** (0.10 g, 70%)

as white solid; m.p. >230 °C; $[\alpha]_D^{20}$ –13.83 (*C* 0.125, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$): 8.08 (d, *J* = 2.8 Hz, 1H), 7.85 (dd, *J* = 9.2 Hz, *J* = 2.9 Hz, 1H), 6.70 (dd, *J* = 6.7 Hz, *J* = 1.9 Hz, 1H), 6.60 (d, *J* = 9.2 Hz, 1H), 5.98 (m, 1H), 4.78 (m, 1H), 4.13 (brs, 2H), 4.00 (t, *J* = 9.1 Hz, 1H), 3.65–3.75 (m, 2H), 3.55–3.62 (m, 5H), 3.05 (m, 4H), 2.00 (s, 3H). EI-MS (*m*/*z*): 474 (M+). Calc. for $C_{21}H_{26}N_6O_5S{\cdot}1.5H_2O$: C 50.30, H 5.79, N 16.77. Found: C 50.43, H 5.67, N 16.46.

*6.13. (*S*)-(*N*-3-(4-(*N*-(4-acetylaminophenylsulfonyl)piperazinyl)-pyridine-3-yl)-2-oxo-5-oxazolidinyl)acetamide (**16**)*

To a cooled mixture of compound **15** (0.10 g, 0.21 mmol) in pyridine (7 ml) was added Ac_2O (1 ml) with stirring, the reaction mixture was allowed to warm to r.t. overnight. The mixture was filtered and filtrate was concentrated in vacuo. The residue was recrystallized from CH_3OH to give **16** (0.75 g, 69%) as white solid; m.p. >230 °C; $[\alpha]_D^{20}$ –15.07° (*C* 0.20, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$): 10.36 (s, 1H), 8.20 (t, *J* = 5.9 Hz, 1H), 8.15 (d, *J* = 2.6 Hz, 1H), 7.70–7.80 (m, 3H), 7.60–7.70 (m, 2H), 6.85 (d, *J* = 9.2 Hz, 1H), 4.60–4.70 (m, 1H), 4.00 (t, *J* = 8.8 Hz, 1H), 3.60–3.65 (m, 1H), 3.50–3.60 (m, 4H), 2.95 (m, 4H), 2.06 (s, 3H), 1.80 (s, 3H). EI-MS (*m*/*z*): 516 (M+). Calc. for $C_{23}H_{28}N_6O_6S$: C 53.49, H 5.43, N 16.28. Found: C 53.58, H 5.53, N 15.88.

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