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Design, synthesis and antibacterial activity of novel 1-oxacephem analogs

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Abstract

A series of 1-oxacephem analogs were synthesized and their antibacterial properties against five strains of Gram-positive and Gram-negative bacteria were evaluated *in vitro* while ceftazidine was selected as control. Some of the tested compounds, compound **12c** in particular, showed more active against three selected strains than the standard.

Keywords: 1-Oxacephem; Synthesis; Antibacterial activity; Ceftazidine

1-Oxacephem is a special group among cephalosporin antibiotics family and a class of new compounds obtained by substituting sulfur atom in the cephalosporin with oxygen according to principles of bioisostere. In the 1970s and 1980s, Narisada *et al*. published the synthesis of several l-oxacephalosporins. The antibacterial potency against sensitive bacterial strains of l-oxa congeners, including l-oxacephalothin and l-oxacefamandole exhibited four to eight more times than the corresponding cephalosporins [1,2]. Nagata *et al*. established a well sophisticated and industrially feasible synthetic route to the nucleus of the 1-oxacephems and achieved in finding latamoxef and flomoxef [3–5] (Fig. 1).

In recent years, a lot of new side chains of cephalosporin are developed and have made significant contribution in promoting the antibacterial activity and spectrum of the cephalosporin, such as the use of the quaternary ammonium group in the 3 position of the cephalosporin. This was demonstrated to be a good strategy to enhance its permeability to the outer membrane of Gram-negative bacteria and results in improved antibacterial activity [6–9]. Oxacephem with substituted thioacetamide at position 7 shows good antibacterial activity against Gram-positive and Gram-negative bacteria, being especially highly active against clinical isolates of *Staphylococcus aureus* resistant to either ampicillin or methicillin [4]. Cephalosporins with the similar group also displayed the similar efficacy [10]. Based on the structure–activity relationships above, a series of new 1-oxacephems were designed, synthesized, and their preliminary efficacy was also evaluated, expecting to get promoted antibacterial activity when the latest side chains of cephalosporins were introduced to the nucleus of 1-oxacephems.

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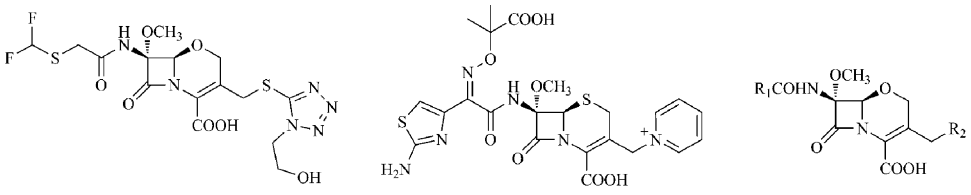


Fig. 1. Structures of flomoxef, ceftazidine and the target compounds **12a**–**12i**.

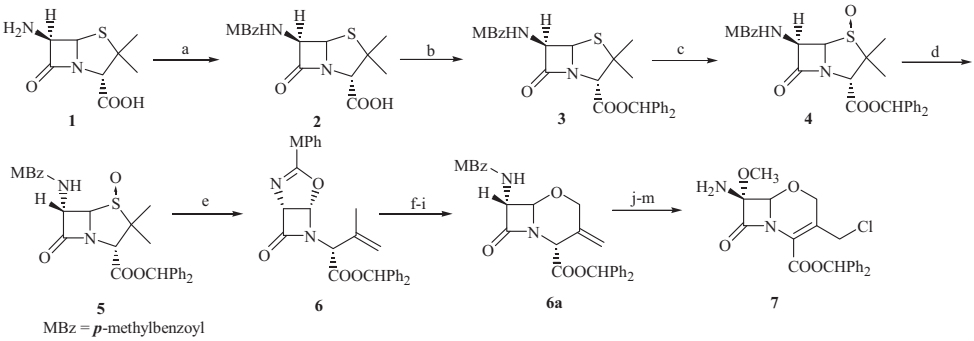
The synthetic route of the key intermediate **7** was illustrated in Scheme 1. The commercially available 6-APA **1** was protected by *p*-methylbenzoyl group to get **2**. Compounds **2**–**4** showed highly crystalline property, which benefits the purification. Furthermore, we can prepare **4** starting from **1** in 3 steps with a higher yield [11]. The epimerization of **4** was achieved by treatment of trimethylchlorosilane and triethylamine in dichloromethane to afford **5** [12]. Thus, epipenicillin sulfoxide **5** was treated with triphenylphosphine to give epioxazoline **6** [13]. Finally, the key intermediate **7** was obtained from **6** according to the known method in 8 steps [14].

With compound **7** in hand, we carried out to synthesize the 1-oxacephem derivatives. The acid **8a** used for 7β side chains was prepared in the reported method [4]. **8b** and **8c** were prepared by coupling of ethyl chloroacetate and substituted thiophenol followed by hydrolysis with sodium hydroxide. Subsequent acylation of **7** with **8a**–**8c** in the presence of phosphorus oxychloride and pyridine to afford **9a**–**9c**, followed by introduction of the heterocycles **10a**–**10c** to the allylic position using sodium iodide as a catalyst in acetone gave **10a**–**10i**. Removal of the protective group *m*-cresol furnished the target compounds **11a**–**11i**. The chemical structures of target compounds were confirmed by ^{1}H NMR, MS spectra and elemental analyses (Scheme 2) [15].

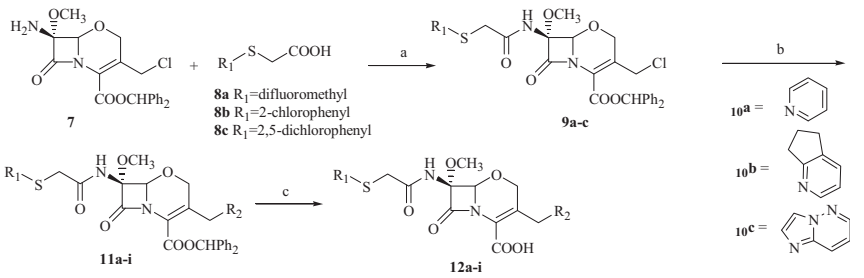
All the new oxacephem derivatives were tested *in vitro* against several strains of Gram-positive and Gram-negative bacteria, and the MIC values are shown in comparison with that of Ceftazidine in Table 1.

As shown in Table 1, some compounds displayed enhanced antibacterial potency over ceftazidine against different strains. However, all compounds are less active than the standard against *Escherichia coli* and *Pseudomonas aeruginosa*. The most promising compound **12c** exhibited antibacterial activity against *S. aureus*, *S. epidermidis* and *Klebsiella pneumoniae* strains with the MIC value of 4, 16, 16 mg/L, respectively.

The reported SARs of cephalosporins showed that the side chain at position 7 had great influence to the antibacterial spectrum while the side chain at position 3 contributed less to its activity and only affected the pharmacokinetics. In order to eliminate the influence of side chain at different position, orthogonal strategy was adopted to synthesis of the target 1-oxacephems. Among **12a**–**12c** which contain a difluoromethylthioacetamido substituent at C-7, **12b** was more active than **12a**, but less than **12c**. The result indicated that a substituent at pyridine ring would increase its activity and a heterocycle was better than an alicycle. In the case of compounds having the same

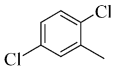
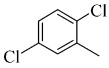
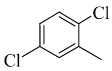


Scheme 1. Synthesis of **7**. Reagents and conditions: (a) *p*-toluene sulfonyl chloride, $NaHCO_3$, 0 °C. (b) benzhydrol, CH_3SO_2Cl, Py, −5 to 10 °C (c), H_2O_2, Na_2WO_4, 0 °C, 80.4% yield over three steps. (d) Et_3N, $(CH_3)_3SiCl$, 10 °C, 77%. (e) Ph_3P, EA, 78 °C, 80.2%. (f) Cl_2, EA, 20–25 °C, aqueous $NaHCO_3$. (g) NaI, THF, 25 °C. (h) Cu_2O, DMSO, H_2O, 55 °C. (i) $BF_3{\cdot}Et_2O$, EA, 25 °C, 38.2% yield over four steps. (j) Cl_2, Py, CH_2Cl_2. (k) diethylamine, −20 °C. (l) *t*-BuOCl, CH_3OLi, CH_3OH, CH_2Cl_2, −45 °C. (m) PCl_5, Py, CH_3OH, CH_2Cl_2, −40 °C, 42.6 yield over four steps.



Scheme 2. Synthesis of compounds **12a**–**12i**. Reagents and conditions: (a) $POCl_3$, Py, CH_3OH, CH_2Cl_2, −40–0 °C, 61–67.8%. (b) NaI, acetone, CH_2Cl_2, 0 °C, 61–69%. (c) *m*-cresol, 40 °C, 81–88%.

Table 1
Structures and antibacterial activity to *E. coli*, *S. aureus*, *P. aeruginosa*, *S. epidermidis*, *K. pneumoniae* strains of target compounds.

Compd.	R_1	R_2	MIC (mg/L)				
			E. coli	*S. aureus*	*P. aeruginosa*	*S. epidermidis*	*K. pneumoniae*
12a			32	32	>64	64	64
12b			8	8	>64	32	32
12c			4	4	>64	16	16
12d			64	128	>64	>64	>64
12e			32	64	>64	>64	>64
12f			32	64	>64	>64	>64
12g			64	>128	>64	>64	>64
12h			128	>128	>64	>64	>64
12i			64	>128	>64	64	>64
Ceftazidine			<0.5	4	4	64	64

side chain at C-3, a difluoromethylthioacetamido substituent at C-7 had more advantages than the others. Compared with 2-chlorophenylthioacetamido, additional substituent at phenyl may cause reduce of its activity.

As the preliminary result shown above, the activities of the target compounds did not seem as a simple combination of each of the three moieties, C-7 side chain, 1-oxacephem nucleus and C-3 side chain. Nonetheless, this unexpected result provides us new guidance for further study.

Acknowledgments

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[14] M. Yoshioka, T. Tsuji, S. Uyeo, et al. Tetrahedron Lett. 21 (1980) 351.
[15] Physical and spectral data of some target compounds. All the target compounds are amorphous powder. **12a**: ^{1}H NMR (400 MHz, CDC1$_3$): δ 3.40 (s, 3H), 3.55–3.69 (m, 2H), 4.43 (s, 1H), 5.17 (s, 1H), 5.42 (d, 1H, J = 14.4 Hz), 5.63 (d, 1H, J = 14.4 Hz), 7.31 (t, 1H, J_{HF} = 56 Hz), 8.17 (t, 2H, J = 6.8 Hz), 8.63 (t, 1H, J = 7.6 Hz), 9.07 (t, 2H, J = 5.6 Hz), 9.33 (s, 1H); ESI-MS m/z: 558 (M+H)$^+$; Anal. Calcd. for $C_{17}H_{18}F_2IN_3O_6S$: C, 36.64; H, 3.26; F, 6.82; I, 22.77; N, 7.54; S, 5.75. Found: C, 36.61; H, 3.29; F, 6.80; I, 22.75; N, 7.52; S, 5.71. **12b**: ^{1}H NMR (400 MHz, CDC1$_3$): δ 2.19–2.27 (m, 2H), 3.11–3.14 (m, 2H), 3.28–3.32 (m, 2H), 3.41 (s, 3H), 3.49–3.70 (m, 2H), 4.20–4.39 (m, 2H), 5.14 (s, 1H), 5.50 (s, 2H), 7.31 (t, 1H, J_{HF} = 56 Hz), 7.89 (t, 1H, J = 6.8 Hz), 8.39 (d, 1H, J = 7.6 Hz), 8.76 (d, 1H, J = 6 Hz), 9.33 (s, 1H); ESI-MS m/z: 598 (M+H)$^+$; Anal. Calcd. for $C_{20}H_{22}F_2IN_3O_6S$: C, 40.21; H, 3.71; F, 6.36; I, 21.24; N, 7.03; S, 5.37. Found: C, 40.18; H, 3.75; F, 6.35; I, 21.20; N, 7.01; S, 5.32. **12c**: ^{1}H NMR (400 MHz, CDC1$_3$): δ 3.39 (s, 3H), 3.50–3.68 (m, 2H), 4.29–4.39 (m, 2H), 5.11 (s, 1H), 5.37 (d, 1H, J = 14.4 Hz), 5.61 (d, 1H, J = 14.4 Hz), 7.30 (t, 1H, J_{HF} = 56 Hz), 8.00–8.03 (m, 1H), 8.49 (s, 1H), 8.83 (s, 1H), 8.92 (d, 1H, J = 9.6 Hz), 9.09 (d, 1H, J = 4.4 Hz), 9.32 (s, 1H); ESI-MS m/z: 598 (M+H)$^+$; Anal. Calcd. for $C_{18}H_{18}F_2IN_5O_6S$: C, 36.19; H, 3.04; F, 6.36; I, 21.25; N, 11.72; S, 5.37. Found: C, 36.15; H, 3.10; F, 6.34; I, 21.22; N, 11.68; S, 5.36. **12d**: ^{1}H NMR (400 MHz, CDC1$_3$): δ 3.38 (s, 3H), 3.77–3.89 (m, 2H), 4.23–4.38 (m, 2H), 5.15 (s, 1H), 5.37 (d, 1H, J = 14.4 Hz), 5.73 (d, 1H, J = 14.4 Hz), 7.12–7.43 (m, 4H), 8.17 (t, 2H, J = 6.8 Hz), 8.63 (t, 1H, J = 7.6 Hz), 9.07 (t, 2H, J = 5.6 Hz), 9.33 (s, 1H); ESI-MS m/z: 618 (M+H)$^+$; Anal. Calcd. for $C_{22}H_{21}ClIN_3O_6S$: C, 42.77; H, 3.43; Cl, 5.74; I, 20.54; N, 6.80; S, 5.19. Found: C, 42.73; H, 3.49; Cl, 5.71; I, 20.53; N, 6.76; S, 5.17. **12e**: ^{1}H NMR (400 MHz, CDC1$_3$): δ 2.19–2.27 (m, 2H), 3.11–3.14 (m, 2H), 3.29–3.31 (m, 2H), 3.39 (s, 3H), 3.80–3.90 (m, 2H), 4.18–4.33 (m, 2H), 5.16 (s, 1H), 5.51 (s, 2H), 7.14–7.45 (m, 4H), 7.87 (t, 1H, J = 6.8 Hz), 8.40 (d, 1H, J = 7.6 Hz), 8.68 (d, 1H, J = 6 Hz), 9.44 (s, 1H); ESI-MS m/z: 658 (M+H)$^+$; Anal. Calcd. for $C_{25}H_{25}ClIN_3O_6S$: C, 45.64; H, 3.83; Cl, 5.39; I, 19.29; N, 6.39; S, 4.87. Found: C, 45.61; H, 3.87; Cl, 5.36; I, 19.27; N, 6.39; S, 4.88. **12f**: ^{1}H NMR (400 MHz, CDC1$_3$): δ 3.33 (s, 3H), 3.81 (d, 1H, J = 15.6 Hz), 3.82 (d, 1H, J = 15.6 Hz), 3.98 (d, 1H, J = 16.8 Hz), 4.38 (m, 1H, J = 16.8 Hz), 4.94 (s, 1H), 5.17 (d, 1H, J = 14.4 Hz), 5.75 (d, 1H, J = 14.4 Hz), 7.11–7.41 (m, 4H), 7.94–7.98 (m, 1H), 8.72 (s, 1H), 8.75 (s, 1H), 9.00 (d, 1H, J = 4.4 Hz), 9.19 (s, 1H), 9.41 (d, 1H, J = 9.6 Hz); ESI-MS m/z: 658 (M+H)$^+$; Anal. Calcd. for $C_{23}H_{21}ClIN_5O_6S$: C, 41.99; H, 3.22; Cl, 5.39; I, 19.29; N, 10.65; S, 4.87; Found: C, 41.92; H, 3.31; Cl, 5.36; I, 19.28; N, 10.67; S, 4.85. **12g**: ^{1}H NMR (400 MHz, CDC1$_3$): δ 3.39 (s, 3H), 3.86–3.97 (m, 2H), 4.09(d, 1H, J = 18.8 Hz), 4.34 (d, 1H, J = 18.8 Hz), 5.13 (1H, s), 5.23 (1d, H, J = 14.4 Hz), 5.73 (d, 1H, J = 14.4 Hz), 7.15–7.45 (m, 3H), 8.18 (t, 2H, J = 6.8 Hz), 8.63 (t, 1H, J = 7.6 Hz), 9.07 (t, 2H, J = 5.6 Hz), 9.33 (s, 1H); ESI-MS m/z: 652 (M+H)$^+$; Anal. Calcd. for $C_{22}H_{20}C_{l2}IN_3O_6S$: C, 40.51; H, 3.09; Cl, 10.87; I, 19.46; N, 6.44; S, 4.92. Found: C, 40.48; H, 3.12; Cl, 10.86; I, 19.45; N, 6.41; S, 4.88. **12h**: ^{1}H NMR (400 MHz, CDC1$_3$): δ 2.18–2.26 (m, 2H), 3.11–3.15 (m, 2H), 3.30 (m, 2H), 3.41 (s, 3H), 3.89–3.98 (m, 2H), 4.24 (s, 2H), 5.17 (s, 1H), 5.47–5.57 (m, 2H), 7.20–7.48 (m, 3H), 7.88 (t, 1H, J = 6.8 Hz), 8.41 (d, 1H, J = 7.6 Hz), 8.71 (d, 1H, J = 6 Hz), 9.44 (s, 1H); ESI-MS m/z: 692 (M+H)$^+$; Anal. Calcd. for $C_{25}H_{24}C_{l2}IN_3O_6S$: C, 43.37; H, 3.49; Cl, 10.24; I, 18.33; N, 6.07; S, 4.63. Found: C, 43.35; H, 3.52; Cl, 10.21; I, 18.32; N, 6.00; S, 4.58. **12i**: ^{1}H NMR (400 MHz, CDC1$_3$): δ 3.38 (s, 3H), 3.81–3.95 (m, 2H), 4.15–4.38 (m, 2H), 5.12 (s, 1H), 5.35 (d, 1H, J = 14.4 Hz), 5.57 (d, 1H, J = 14.4 Hz), 7.15–7.45 (m, 3H), 8.01–8.04 (m, 1H), 8.53 (s, 1H), 8.84 (s, 1H), 9.00 (d, 1H, J = 9.6 Hz), 9.10 (d, 1H, J = 4.4 Hz), 9.41 (s, 1H); ESI-MS m/z: 692 (M+H)$^+$; Anal. Calcd. for $C_{23}H_{20}Cl_2IN_5O_6S$: C, 39.90; H, 2.91; Cl, 10.24; I, 18.33; N, 10.12; S, 4.63. Found: C, 39.87; H, 2.95; Cl, 10.21; I, 18.32; N, 10.14; S, 4.60.