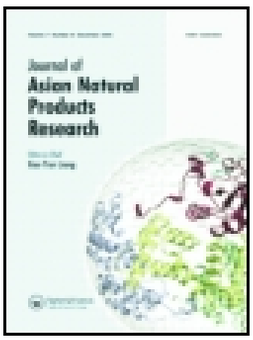

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Synthesis and Antibacterial Activity of Novel 4″-*O*-desosaminyl clarithromycin derivatives with 11, 12-arylalkyl side chains

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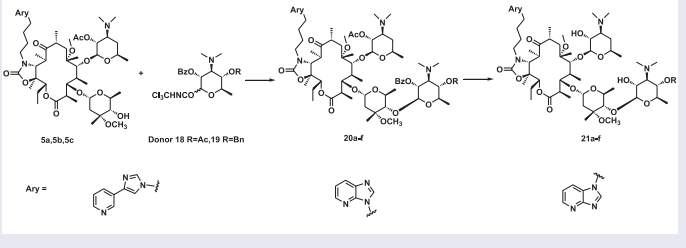
ABSTRACT

A series of novel 4″-*O*-desosaminyl clarithromycin derivatives with 11, 12-arylalkyl side chains was synthesized by coupling 6-deoxy-desosamine donors (**18**, **19**) with 4″-OH of compounds **5a**–**c**. The activities of the target compounds were tested against a series of macrolide-sensitive and macrolide-resistant pathogens. Some of them showed activities against macrolide sensitive and resistant pathogens, and compounds **21d** and **21e** displayed significant improvement of activities against resistant pathogens.



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Clarithromycin; antibacterial activity; desosamine

1. Introduction

With the macrolide antibiotics widely used in clinic since 1950s, the emergence of macrolide-resistant bacteria has been increasingly prevalent. Great efforts have been made to develop novel macrolide structures against resistant pathogens [1]. The most successful improvement of anti-resistant macrolide antibiotics is well known as ketolides, represented by telithromycin [2], cethromycin [3], and solithromycin [4] (Figure 1). The mechanism of anti-resistance of ketolides is through an extra interaction between the side chain, a tethered hetero-aromatic substituent, and A752 in domain II of the 23S rRNA [5].

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[#]Authors contributed equally to this work.

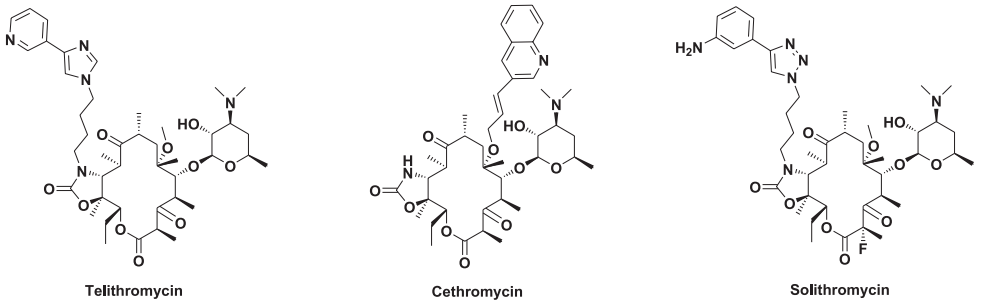


Figure 1. Chemical structures of telithromycin, cethromycin, and solithromycin.

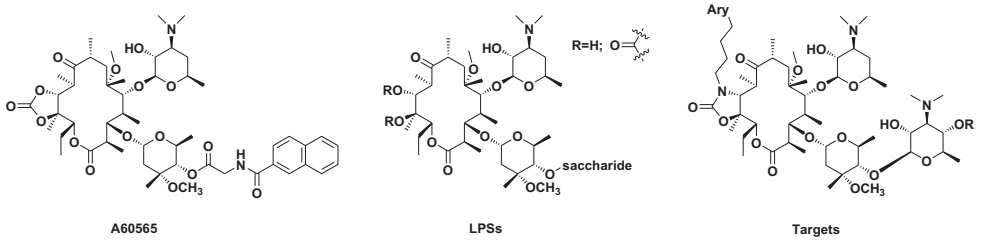
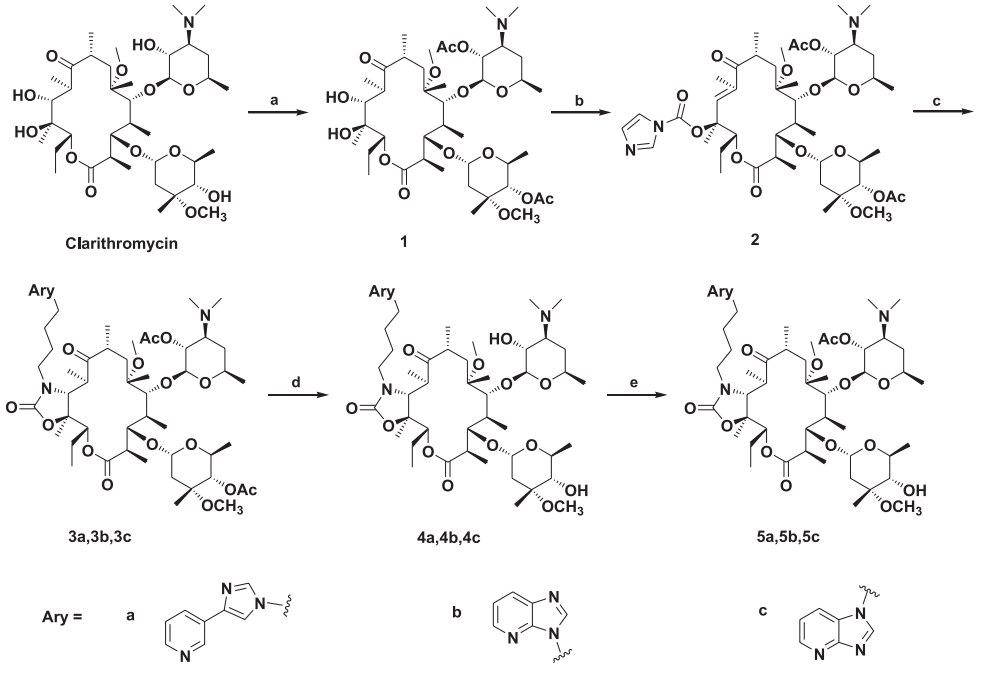


Figure 2. Chemical structures of A60565, LPSs, and targets.

Ketolides, however, are not the only class of macrolides against resistant bacteria. Among the many none ketolides, 4″-*O*-modified macrolide derivatives show a notable potent activity against macrolide-sensitive and macrolide-resistant pathogens. In 1989, Fernandes *et al.* found that compound A-60565 had better activity than erythromycin against some constitutively resistant *Streptococcus pyogenes* [6]. Since then, such 4″-*O*-modified macrolides have been investigated by several research groups. 4″-OH-modified macrolide derivatives, with ether, ester, and carbamate as linkers, have been frequently investigated in recent years [7–12]. A series of clarithromycin derivatives with 4″-*O*-saccharide substituents (Figure 2) using carbohydrate as a linker was reported by our lab [13,14]. Without 11,12-modification, such derivatives showed poor activity against either susceptible or resistant strains [13]. To further delve into the structure–activity relationship of 4″-*O*-modified macrolides and explore for novel macrolide antibiotics, Zhu *et al.* synthesized a series of novel clarithromycin derivatives with 4″-*O*-desosamine substituents (Figure 2) in the next work [14]. Among them, two compounds displayed significant improvement of activities against sensitive pathogens and two strains of MRSE (*S. epidermidis* **12–4**, **12–11**).

It is well known that the 14-membered macrolides carrying the side chain could improve the activities against macrolide sensitive and resistant pathogens and 4″-*O*-modified macrolide derivatives also could improve the activities against macrolide sensitive and some of resistant pathogens. In this research, we focused on whether the new macrolide molecular carrying both 11, 12-arylalkyl side chains and 4″-*O*-desosamine substituent could promote the activities against resistant pathogens at the same time. Herein, we reported an efficient synthetic procedure designed for preparing a series of novel 4″-*O*-desosaminyl clarithromycin derivatives with 11, 12-arylalkyl side chains (Figure 2) and aimed to improve their activities, especially against resistant pathogens.



Scheme 1. Reagents and conditions: (a) Ac_2O, pyridine, CH_2Cl_2, room temperature, overnight, 88%; (b) $NaN(TMS)_2$, CDI, THF, −40 °C to room temperature, 12 h, 69%; (c) 4-arylbutan-1-amine, DBU, THF, room temperature, 24 h, 56% for **3a**, 66% for **3b**, 56% for **3c**; (d) K_2CO_3, MeOH, 40 °C, 24 h, 60% for **4a**, 68% for **4b**, 68% for **4c**; (e) Ac_2O, TEA, CH_2Cl_2, 0 °C to room temperature, 6 h, 74% for **5a**, 71% for **5b**, 71% for **5c**.

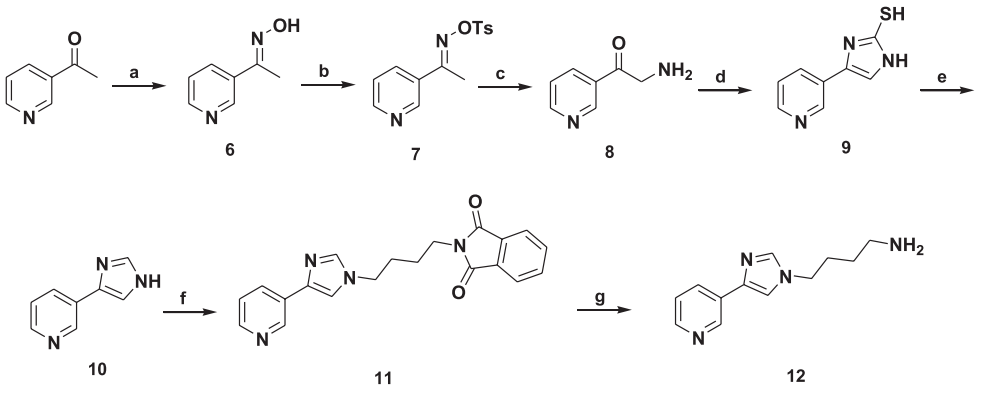
2. Results and discussion

2.1. Chemistry

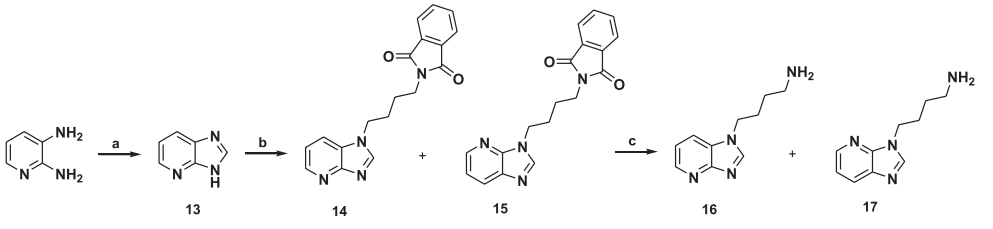
Our approach is to find an efficient route to synthesis of new 14-membered macrolides with 4″-*O*-desosaminyl and 11, 12-arylalkyl side chains. Scheme 1 outlines the syntheses of compounds **5a**–**c**, 4′-*O*-acetyl clarithromycin derivatives with 11, 12-arylalkyl side chains, as acceptors. Clarithromycin was protected by treatment with acetic anhydride in dichloromethane, pyridine as the base, to give compound **1**. The compound **1** was readily reacted with carbonyldiimidazole (CDI) in the presence of sodium bis(trimethylsilyl)amide (NaHMDS) to give compound **2**. The compound **2** was coupled with selected 4-arylbutan-1-amine (**12**, **16**, and **17**) in the presence of DBU to give compounds **3a**–**c**. Deprotection of compounds **3a**–**c** smoothly with K_2CO_3 in the methanol gave the compounds **4a**–**c**. Acceptors **5a**–**c** were prepared by selectively protecting the 2′-OH of compounds **4a**–**c**.

Scheme 2 and Scheme 3 outlines the syntheses of 4-arylbutan-1-amine (**12**, **16**, and **17**). The compound **12** was obtained via seven steps from 3-acetylpiridine. Compounds **16** and **17** were prepared via three steps from 2,3-diamino-pyridin as the way reported in our lab [15]. Two isomers **14** and **15** were distinguished according to the NOESY spectrum (see Table 1).

With the acceptors **5a**–**c** in hand, donors **18** and **19** [14] were successfully glycosylated with acceptors **5a**–**c** to obtain the compounds **20a**–**f**, triethylsilyl trifluoromethanesulfonate (TESOTf) used as a promoter (Scheme 4). Deprotection of compounds **20a**–**f** smoothly

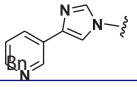
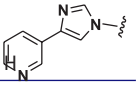


Scheme 2. Reagents and conditions: (a) NH_2OH•HCl, TEA, MeOH, reflux, 5 h, 98%; (b) *p*-toluenesulphonyl chloride, pyridine, 0 °C to room temperature, 16 h, 97%; (c) EtOK, EtOH, 0 °C to room temperature, 9 h, 86%; (d) KSCN, H_2O, *p*-toluenesulfonic acid, 50 °C, 5 h, 58%; (e) HNO_3, 90 °C, 2 h, 85%; (f) *N*-(4-bromobutyl) phthalimide, K_2CO_3, DMF, 90 °C, 10 h, 65%; (g) NH_2NH_2, EtOH, reflux, 5 h.



Scheme 3. Reagents and conditions: (a) trimethyloxymethane, 120 °C, 12 h, 70%; (b) *N*-(4-bromobutyl) phthalimide, K_2CO_3, DMF, 90 °C, 10 h, 45% for **14**, 25% for **15**; (c) NH_2NH_2, EtOH, reflux, 5 h.

Table 1. The structures of compounds **21a**–**f**.

	a	**b**	**c**	**d**	**e**	**f**
Ary						
R						

with the methanol gave the target compounds **21a**–**f**, which were confirmed by HR-MS, ^{1}H NMR, and ^{13}C NMR spectra (Tables 1 and 2).

2.2. Biological activities

The antibacterial activities of the target compounds **21a**–**f** were assessed against some respiratory pathogens, including macrolide drug sensitive and resistant strains. Clarithromycin and telithromycin were chosen as the reference compounds. The *in vitro* antibacterial activity was reported as minimum inhibitory concentrations (MICs), which was determined by the broth microdilution method as recommended by the CLSI [16] (Scheme 4).

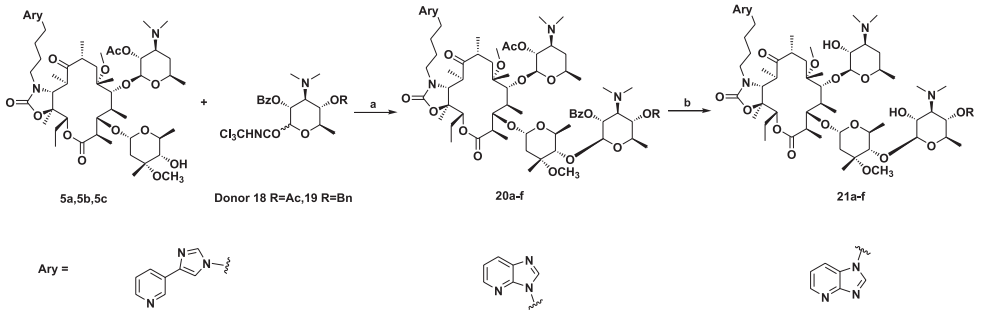
Table 2. The spectral data of compounds **21a**–**f**.

	^{1}H NMR	^{13}C NMR	HR-ESI-MS
21a	^{1}H NMR (300 MHz, $CDCl_3$): δ 8.94 (S, 1H), 8.44 (d, J = 4.5 Hz, 1H), 8.11 (d, J = 7.5 Hz, 1H), 7.44 (s, 1H), 7.31 (s, 1H), 7.29 (dd, J = 4.5, 7.5 Hz, 1H), 5.12 (dd, J = 2.0, 11.5 Hz, 1H), 4.98 (d, J = 4.0 Hz, 1H), 4.77 (d, J = 10.0 Hz, 1H), 4.69 (d, J = 10.5 Hz, 1H), 4.56 (d, J = 11.0 Hz, 1H), 4.47 (d, J = 11.0 Hz, 1H), 4.20 (dd, J = 2.5, 8.0 Hz, 1H), 3.97 (s, 1H), 3.64 (d, J = 6.5 Hz, 1H), 3.20 (s, 3H), 3.02 (s, 6H), 2.89 (s, 6H).	^{13}C NMR (75 MHz, $CDCl_3$): δ 216.7, 203.5, 169.9, 157.8, 147.6, 146.3, 139.1, 137.8, 132.0, 123.6, 109.3, 103.9, 82.9, 79.5, 78.2, 77.2, 70.2, 69.5, 65.8, 61.2, 51.1, 49.7, 47.6, 45.9, 45.0, 42.5, 40.1, 39.5, 38.9, 33.4, 29.6, 29.2, 28.3, 27.0, 22.2, 21.1, 19.7, 18.2, 15.9, 14.3, 13.9, 13.7, 10.4, 8.9.	*m/z* 1235.7379 $[M+H]^+$ (calcd for $C_{66}H_{103}N_6O_{16}$ 1235.7425).
21b	^{1}H NMR (300 MHz, $CDCl_3$): δ 8.94 (S, 1H), 8.42 (d, J = 3.6 Hz, 1H), 8.10 (d, J = 8.1 Hz,1H), 7.43 (s, 1H), 7.32 (s, 1H), 7.28 (dd, J = 3.6, 8.1 Hz, 1H), 5.02 (dd, J = 2.0, 10.0 Hz, 1H), 4.88 (d, J = 4.0 Hz, 1H), 4.61 (d, J = 7.2 Hz, 1H), 4.53 (d, J = 11.0 Hz, 1H), 4.50 (d, J = 6.4 Hz, 1H), 4.19 (t, J = 5.6 Hz, 1H), 3.62 (t, J = 8.8 Hz, 1H), 3.30 (s, 3H), 2.98 (s, 6H), 2.12 (s, 6H).	^{13}C NMR (75 MHz, $CDCl_3$): δ 216.5, 203.5, 169.8, 157.7, 147.6, 146.2, 139.0, 137.8, 132.2, 130.3, 123.5, 109.2, 101.4, 96.4, 84.7, 81.7, 78.5, 77.5, 74.5, 74.4, 73.4, 71.5, 70.4, 69.3, 68.1, 65.8, 65.4, 50.9, 49.6, 45.5, 45.3, 40.5, 39.4, 38.9, 37.5, 35.0, 32.2, 30.6, 30.4, 30.4, 29.9, 22.9, 22.4, 21.8, 21.3, 19.9, 19.4, 18.3, 18.2, 16.4, 14.4, 12.6, 10.9, 9.6.	*m/z* 1145.6904 $[M+H]^+$ (calcd for $C_{59}H_{97}N_6O_{16}$ 1145.6956)
21c	^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (dd, J = 1.2, 4.8 Hz, 1H), 8.11 (s, 1H), 8.04 (dd, J = 1.2, 8.1 Hz, 1H), 7.50–7.47 (m, 1H), 7.39–7.35 (m, 3H), 7.20 (dd, J = 4.8, 8.1 Hz, 1H), 5.54 (s, 1H), 4.96–4.92 (m, 2H), 4.55 (d, J = 7.5 Hz, 1H), 4.47 (d, J = 7.2 Hz, 1H), 4.37–4.32 (m, 3H), 4.19–4.16 (m, 1H), 3.59 (s, 1H), 3.32 (s, 3H), 3.05 (s, 6H), 2.95 (s, 6H).	^{13}C NMR (100 MHz, $CDCl_3$): δ 216.1, 176.1, 157.4, 147.0, 144.2, 144.0, 136.9, 135.4, 129.2, 128.3, 127.7, 126.2, 117.9, 104.1, 102.7, 101.9, 96.1, 84.6, 82.6, 80.7, 80.4, 78.7, 77.8, 76.3, 75.4, 74.0, 73.2, 71.0, 68.6, 68.1, 66.4, 65.4, 65.1, 59.9, 50.3, 49.3, 45.5, 45.0, 43.4, 42.6, 40.1, 38.8, 38.4, 34.9, 29.6, 27.4, 24.4, 22.0, 21.9, 21.5, 19.9, 18.8, 15.9, 14.2, 14.1, 10.4, 9.2.	*m/z* 1209.7235 $[M+H]^+$ (calcd for $C_{63}H_{95}N_5O_{18}$ 1209.6667).
21d	^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (d, J = 4.5 Hz, 1H), 8.11 (s, 1H), 8.04 (d, J = 7.5 Hz, 1H), 7.20 (dd, J = 4.5, 7.5 Hz, 1H), 4.93–4.90 (m, 2H), 4.45 (d, J = 8.1 Hz, 1H), 3.34 (s, 3H), 2.87 (s, 3H), 2.69 (s, 6H), 2.44 (s, 6H).	^{13}C NMR (100 MHz, $CDCl_3$): δ 216.1, 176.4, 157.4, 146.9, 144.2, 144.0, 135.3, 127.7, 118.0, 104.2, 103.0, 96.9, 84.3, 82.5, 81.0, 78.9, 77.2, 76.4, 75.4, 74.3, 73.8, 71.4, 70.7, 68.3, 64.6, 64.4, 62.4, 59.9, 50.3, 49.5, 45.4, 45.2, 43.4, 42.6, 40.9, 40.0, 39.1, 38.9, 35.1, 29.6, 27.4, 24.4, 21.9, 21.7, 21.2, 18.9, 18.7, 16.1, 14.2, 14.0, 10.4, 9.3.	*m/z* 1119.6796 $[M+H]^+$ (calcd for $C_{57}H_{95}N_6O_{16}$ 1119.6799).
21e	^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 (d, J = 4.2 Hz, 1H), 8.14 (s, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.48–7.45 (m, 2H), 7.37–7.33 (m, 3H), 7.19 (dd, J = 4.2, 7.8 Hz, 1H), 5.53 (s, 1H), 4.86 (d, J = 9.3 Hz, 1H), 4.59 (d, J = 6.9 Hz, 1H), 4.54 (d, J = 7.8 Hz, 1H), 4.33–4.13 (m, 4H), 3.38 (s, 3H), 2.90 (s, 3H), 3.72 (s, 6H), 2.56 (s, 6H).	^{13}C NMR (100 MHz, $CDCl_3$): δ 216.1, 176.3, 157.5, 156.1, 145.2, 144.7, 137.0, 129.2, 128.3, 126.3, 126.1, 118.1, 117.9, 104.4, 101.9, 95.9, 84.0, 82.7, 80.7, 80.6, 78.6, 77.6, 76.3, 75.3, 74.3, 73.1, 70.7, 68.6, 67.1, 66.2, 64.7, 64.5, 59.9, 50.3, 49.4, 45.4, 45.2, 45.1, 44.9, 42.4, 39.8, 38.9, 38.7, 35.1, 29.6, 27.6, 24.5, 21.9, 21.5, 21.3, 120.1, 19.0, 18.7, 16.0, 14.2, 14.1, 10.4, 9.5.	*m/z* 1209.7244 $[M+H]^+$ (calcd for $C_{63}H_{95}N_5O_{18}$ 1209.6667).

(*Continued*)

Table 2. (*Continued*).

	^{1}H NMR	^{13}C NMR	HR-ESI-MS
21f	^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (s, 2H), 8.04 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 4.88 (d, J = 4.5 Hz, 1H), 4.51 (d, J = 5.5 Hz, 1H), 4.40 (d, J = 7.5 Hz, 1H), 4.37–4.33 (m, 2H), 4.09–4.06 (m, 1H), 3.86 (d, J = 11.0 Hz, 1H), 3.77–3.74 (m, 1H), 3.70–3.68 (m, 1H), 3.31 (s, 3H), 2.84 (s, 6H), 2.59 (s, 6H).	^{13}C NMR (100 MHz, $CDCl_3$): δ 216.9, 176.6, 158.4, 155.1, 146.2, 144.3, 126.7, 119.7, 118.3, 103.9, 101.8, 96.0, 83.5, 82.9, 80.0, 78.8, 77.4, 76.9, 76.5, 76.1, 75.2, 74.8, 70.9, 69.5, 66.9, 65.3, 64.5, 62.0, 60.5, 49.9, 49.5, 45.5, 45.3, 45.1, 42.9, 38.9, 38.6, 34.7, 29.7, 27.7, 24.7, 21.8, 20.6, 20.4, 19.6, 19.0, 17.7, 17.0, 15.2, 13.2, 9.7, 8.8.	*m/z* 1119.6801 $[M+H]^+$ (calcd for $C_{57}H_{95}N_6O_{16}$ 1119.6799).



Scheme 4. Reagents and conditions: (a) TESOTf, 4A molecular sieves, CH_2Cl_2, –20 °C to room temperature, 72 h, 85–95%, (b) MeOH, room temperature, 12 h, 40–45%.

Table 3. *In vitro* antibacterial activities of the target compounds.

	S. pneumonia		*S. pyogenes*		*S. aureus*		*S. epidermidis*		*H. influenzae*	
	11G364	11J011	11L264	11N369	11B122	11B117	11X315	11C176	11P042	11Q373
21a	0.5	8	0.062	8	2	>64	2	>64	64	64
21b	0.25	16	0.125	16	0.5	>64	0.5	>64	8	16
21c	0.5	16	0.25	8	1	>64	1	>64	32	32
21d	0.062	2	0.031	2	0.25	64	0.25	32	8	16
21e	0.031	4	0.016	0.5	0.5	>64	0.5	>64	16	32
21f	1	32	0.062	32	2	>64	4	>64	32	64
Teli.	0.008	0.031	0.016	0.031	0.031	>64	0.016	0.016	4	4
Clar.	0.031	64	0.016	>64	0.031	>64	0.125	>64	8	8

11G364 is erythromycin-sensitive *Streptococcus pneumonia*. 11J011 is erythromycin-resistant *Streptococcus pneumonia*. 11L264 is erythromycin-sensitive *Streptococcus pyogenes*. 11N369 is erythromycin-resistant *Streptococcus pyogenes*. 11B122 is methicillin-sensitive *Staphylococcus aureus*. 11B117 is methicillin-resistant *Staphylococcus aureus*. 11X315 is methicillin-sensitive *Staphylococcus epidermidis*. 11C176 is methicillin-resistant *Staphylococcus epidermidis*. 11P042 is azithromycin-sensitive *Haemophilus influenzae*. 11Q373 is azithromycin-resistant *Haemophilus influenzae*. All the resistant strains chosen in this test are constitutively resistant strains supplied by the Ministry of Health National Antimicrobial Resistance Investigation Net (MOHNARIN, China).

The antibacterial activities of compounds **21a–f** were shown in Table 3. In reviewing the data of Table 3, all the targets that we synthesized showed some activities against a panel of sensitive and resistant pathogens, but weaker or slightly weaker than that of telithromycin. Compounds **21a–21c**, **21f** showed weaker antibacterial activity than that of clarithromcin against erythromycin-sensitive *S. pneumonia*, while compounds **21d** and **21e** preserved antibacterial activity against erythromycin-sensitive *S. pneumonia*. The activity of compounds **21a–21f** was stronger than that of clarithromycin against erythromycin-resistant *S. pneumonia*. Among them, compound **21d** showed a 32-fold stronger than that of clarithromycin against erythromycin-resistant *S. pneumonia* (2: 64). The activity of compounds **21a–21f** was at same level against erythromycin-sensitive *S. pyogenes* compared that with clarithromycin. The activity of compounds **21a–21f** was stronger than that of clarithromycin against erythromycin-resistant *S. pyogenes*. Among them, compound **21e** showed two orders of magnitude stronger than that of clarithromycin against erythromycin-resistant *S.*

pyogenes (0.5:>64). The activity of compounds **21a**–**21f** was similar or slightly weaker than that of clarithromycin against *S. aureus, S. epidermidis*, and *H. influenzae*. Only compound **21d** showed some activities against methicillin-resistant *S. aureus* (64) and methicillin-resistant *S. epidermidis* (32).

From the data mentioned above, it could be seen that all targets that we synthesized preserved activities against sensitive strains, while improved activities against some resistant strains. It might be concluded that 11, 12-arylalkyl side chains and 4″-*O*-desosamine substituent were favorable for activities against resistant strains. The activities of compounds **21d** and **21e** were stronger than that of **21a** and **21b**, indicated that side chains **16** and **17** were favorable than **12**. The targets containing free 4‴-OH (compounds **21a**, **21c**, **21e**) possessed similar antibacterial activities compared to those with 4‴-OBn (compounds **21b**, **21d**, **21f**), which could indicate that 4‴-OH modified or unmodified derivatives have no influence on the antibacterial activities.

3. Conclusion

In summary, a series of novel 4″-*O*-desosaminyl clarithromycin derivatives with 11, 12-arylalkyl side chains were obtained with efficient synthesis of macrolide acceptors and desosamine donors, proper method of glycosylation, and reasonable strategy of deprotection. Some of them showed comparable activities against macrolide sensitive and resistant pathogens and compounds **21d** and **21e** displayed significant improvement of activities against some resistant pathogens. The result offered us some valuable information of macrolide overcoming the resistant pathogens.

Acknowledgments

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Disclosure statement

No potential conflict of interest was reported by the authors.

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