ORIGINAL ARTICLE

Design, synthesis and antibacterial activity of a novel alkylide: 3-*O*-(3-aryl-propenyl)clarithromycin derivatives

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A series of novel 3-*O*-(3-aryl-propenyl)clarithromycin derivatives were designed, synthesized and evaluated for their *in vitro* antibacterial activities. Regioselective allylation at 3-OH was efficiently achieved in the presence of 9-oxime ether, compared with 9-keto. Most of the side chains were identified as the 3-*O*-(3-aryl-*Z*-prop-1-enyl) group, not the expected 3-*O*-(3-aryl-*E*-prop-2-enyl) group. Some derivatives of this series showed improved activities against erythromycin-resistant *Staphylococcus aureus* and *Staphylococcus pneumoniae* compared with the reference compound, clarithromycin, but weaker activities against susceptible strains.

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INTRODUCTION

Erythromycin, a 14-membered macrolide antibiotic, has been used safely and effectively against respiratory tract infections since 1952. However, owing to its acid-instability, clarithromycin (6-*O*-methylerythromycin) as the second-generation erythromycin was developed to address the problem of ketalization of the C-9 carbonyl group by the 6-OH group.¹ It is noted that regioselective methylation at 6-OH to yield clarithromycin was not achieved until the introduction of oxime ether in the 9-carbonyl group.² Similarly, new emerging cethromycin [3-oxo-6-*O*-(3-(3'-quinolyl)-2-propenyl)erythromycin derivative] as the third-generation erythromycin was synthesized by regioselective allylation at 6-OH^{3–5} to overcome the relatively recent issues associated with the development of bacterial resistance.

Most of the third-generation erythromycin, cethromycin included, shares two distinguishing structural features: first, cladinose is not an essential moiety for the antibacterial activity, and removal of cladinose can prevent the induction of resistance (Figure 1). As a result, modification at 3-OH led to the emergence of ketolide,^{3–6} acylide,⁷ bicyclolide,⁸ anhydrolide,⁹ 2,3-enol-ether,¹⁰ 3-deoxy,¹¹ 3-ether,¹² 3,6-ketal¹³ and 3,6-ether.¹⁴ Second, an aryl side chain tethered to the erythronolide core is believed to be very important for the improvement of activities against erythromycin-resistant bacteria, due to the interaction with a secondary ribosomal binding site.¹⁵

The results published were not ours. In the search for novel erythromycin derivatives against erythromycin-resistant bacteria, the allyl group was a very important one for various further modifications

at 6-OH of erythromycin.^{4,5} To the best of our knowledge, the introduction of the allyl group at 3-OH of 14-membered macrolides was not disclosed yet, in addition to the recent modification of 16-membered macrolides, leucomycin.¹⁶

RESULTS AND DISCUSSION

Initially, we attempted to attach an allyl group to 3-OH of the 2'-*O*-Ac-3-OH-6-*O*-methylerythromycin 11, 12-carbonate with the structure of 9-keto, but unfortunately it failed and the major product in the resulting mixture was identified as 10,11-anhydro-3-OH-6-*O*-methylerythromycin A after methanolysis. Later, we found that the introduction of 9-oxime ether could dramatically improve the selectivity of allylation at 3-OH. Thus, a facile synthesis of 3-*O*-allyl of clarithromycin was conducted as a lead compound. In this study, we report a novel series of macrolides: 3-*O*-(3-aryl-propenyl)clarithromycin derivatives, which we named alkylides.

The synthesis of the targeted alkylide **9** in five steps from the intermediate 3-OH-6-*O*-methylerythromycin 9-*O*-(2-chlorobenzyl) oxime **4** was outlined in Schemes 1 and 2. Compound **4** was obtained by the acidic hydrolysis of 2',4''-*O*-bis(trimethylsilyl) 6-*O*-methylerythromycin 9-*O*-(2-chlorobenzyl)oxime **3**,¹⁷ which was an important intermediate for the synthesis of clarithromycin. Next, acetylation at 2'-OH of **4** was followed by carbonation at 11, 12-OH generated **6**. Consequently, allylation at 3-OH was efficiently achieved in the presence of allyl bromide and KOTBu, and **7** was produced in high yield (95.2%). Thus, various hetero-aryl bromides were used to install

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Figure 1 Structure of erythromycin, clarithromycin and cethromycin.

Scheme 1 Reagents and conditions: (a) 2-chlorobenzyl chloride, KOH, acetonitrile, 98.6%; (b) hexamethyldisilazane (HMDS), pyridine hydrochloride, acetonitrile, 85.8%; (c) CH_3I , KOH, THF/dimethyl sulfoxide (DMSO), 0 °C, 98.6%; (d) $\text{C}_2\text{H}_5\text{OH}/\text{H}_2\text{O}$, HCl, 73.8%.

Scheme 2 Reagents and conditions: (a) Ac_2O , CH_2Cl_2 , 94.5%; (b) bis(trichloromethyl)carbonate (BTC), pyridine, CH_2Cl_2 , 0 °C, 98.7%; (c) allyl bromide, KOtBu, THF/DMSO, 0 °C, 95.2%; (d) $\text{Pd}(\text{OAc})_2$, $\text{P}(\text{O-MePh})_3$, Et₃N, acetonitrile, hetero-aryl bromide, 60 °C 1 h then 90 °C 24 h; (e) MeOH, 60 °C.

Scheme 3 Reagents and conditions: (a) allyl bromide, KOTBu, THF/DMSO, 0 °C, 85.7%; (b) Pd(OAc)₂, P(O-MePh)₃, Et₃N, acetonitrile, hetero-aryl bromide, 60 °C 1 h then 90 °C 24 h; (c) MeOH, 60 °C.

Figure 2 Crystal structure of 9f (4-isoquinolyl).

the aryl side chain by Heck reaction, catalyzed by Pd(OAc)₂/P(*o*-MePh)₃. The major products of Heck reaction and its methanolysis were purified to yield **8** and **9** by column chromatography using CH₂Cl₂/EtOH/NH₃·H₂O (15:0.4:0.1) and petroleum ether/acetone/triethylamine (5:5:0.2) as an eluent, respectively.

To confirm the regioselectivity of 3-OH, compound **12** was synthesized without the protection of 11, 12-OH (Scheme 3). The results proved that the regioselective allylation of **5** was also conducted in good yield (85.7%) and, as indicated, the regioselectivity at 3-OH was mainly influenced by 9-oxime ether.

A combination of ¹H NMR, COSY, ¹³C NMR and HRMS was used to analyze the structure of this series. Surprisingly, the NMR spectrum showed that the aryl side chains of **9b–9g** and **12c–12f** were characterized by predominant *Z* configuration (*J*=6 Hz), such as the 1-phenyl (a mixture of *Z/E*: 10:4), 3-pyridyl, 5-pyrimidyl, 3-quinolyl, 4-isoquinolyl and 5-isoquinolyl groups, whereas the 5-indolyl **9h** side chain had *E* configuration (*J*=16 Hz). This was significantly different from the previous results of allylation at 6-OH.⁴ Further study by X-ray crystallography of **9f** disclosed that the allylic double bond

isomerized from 2-position to 1-position, and the Heck-isomerization to furnish enol concomitantly resulted in *Z* configuration, as shown in Figure 2. Therefore, with the exception of **9h**, the real structure of **9b–9g** and **12c–12f** should be the 3-O-(3-aryl-*Z*-prop-1-enyl)clarithromycin derivatives, not the expected 3-O-(3-aryl-*E*-prop-2-enyl)clarithromycin derivatives.

The *in vitro* antibacterial activity of alkylides **9** and **12** was assessed against erythromycin-susceptible and erythromycin-resistant bacteria, including *Staphylococcus aureus* and *Streptococcus pneumoniae*. Data are represented in Table 1 as the minimal inhibitory concentration, which is determined by the broth microdilution method as recommended by the NCCLS (National Committee of Clinical Laboratory Standard).¹⁸

Some of the alkylides such as **9**, **12** showed improved activities compared with the reference compound, clarithromycin, against resistant pathogens, particularly for *S. aureus*. Among them, **9d** and **12d** (3-pyrimidinyl) were promising candidates. The compounds with the mono-heteroaryl ring (**9c–9d**, **12c–12d**) and the parent compounds **9a** and **12a** (H) possessed better activity against resistant pathogens than did those with fused aryl rings (**9e–9h**, **12e–12f**).

Table 1 Antibacterial effects of alkylides against selected respiratory tract pathogens

			In vitro MIC (μg/ml)								
Compound			Staphylococcus aureus				Staphylococcus pneumoniae				
	Aryl	Config.	ATCC 29213 ^a	D18 ^b	D6 ^b	D9 ^b	ATCC 49619 ^a	SPJ8 ^b	SPJ15 ^b	CP18 ^b	SPM12 ^b
CAM	—	—	0.25	>64	>64	>64	<0.03	>16	>16	>16	>16
9a	H	—	8	16	16	16	4	>16	16	>16	>16
9b	1-phenyl	Z/E	64	64	>64	64	8	>16	16	>16	>16
9c	3-pyridyl	Z	8	32	32	16	1	>16	>16	>16	>16
9d	5-pyrimidyl	Z	4	32	32	4	2	>16	16	>16	>16
9e	3-quinolyl	Z	64	>64	>64	64	8	16	>16	>16	>16
9f	4-isoquinolyl	Z	>64	64	64	>64	4	>16	16	>16	>16
9g	5-isoquinolyl	Z	>64	>64	>64	>64	4	>16	8	>16	>16
9h	5-indolyl	E	>64	>64	>64	>64	8	>16	16	>16	>16
12a	H	—	32	16	64	16	16	>16	>16	>16	>16
12c	3-pyridyl	Z	32	16	32	16	4	>16	>16	>16	>16
12d	5-pyrimidyl	Z	8	16	32	16	1	>16	>16	>16	>16
12e	3-quinolyl	Z	32	64	>64	32	16	16	16	>16	>16
12f	4-isoquinolyl	Z	32	32	64	16	8	16	16	>16	>16

Abbreviations: Config., configuration; MIC, minimal inhibitory concentration.

^aErythromycin-susceptible.^bErythromycin-resistant.

The crystal structure of **9f** (4-isoquinolyl) disclosed that the fused aryl rings, regardless of the location of the nitrogen (**e-g**), may sterically prevent the 3'-dimethylamino group from approaching the binding site, resulting in a decrease in activities. Compounds **9c**, **12c** (3-pyridyl) and **9d**, **12d** (3-pyrimidinyl) showed better activities than did the parent compounds **9a** and **12a** (H) against erythromycin-susceptible pathogens, but unfortunately no significant difference was found between them against erythromycin-resistant pathogens.

In conclusion, the 3-O-allyl clarithromycin derivative was synthesized in high regioselectivity to serve as a template. The introduction of the 3-O-aryl-propenyl group led to the acquisition of activities against erythromycin-resistant pathogens than reference compound, clarithromycin. The further chemical modification to improve activities is ongoing.

EXPERIMENTAL SECTION

All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise noted. Column chromatography was performed on silica gel (200–300 mesh for **8** and 300–400 mesh for **9**). ¹H and ¹³C NMR spectra were recorded in CDCl₃ on a Bruker ARX 400 and 600 MHz (Bruker BioSpin AG Ltd, Beijing, China) with tetramethylsilane (TMS) as an internal standard. The assignments of **4**, **7**, **9c** and **12a** were made on the basis of D₂O exchange and ¹H-¹H COSY. HRMS were obtained with Bruker Apex II ICRMS, or Bruker Apex IV FTMS.

Erythromycin A 9-O-(2-chlorobenzyl)oxime (1)

To a solution of Erythromycin A, 9-O-oxime (10 g, 13.3 mmol) in acetonitrile (120 ml) was added 2-chlorobenzyl chloride (2.1 ml, 16.5 mmol) and KOH (1.3 g, 21 mmol). The reaction mixture was stirred at room temperature for 2 h, and in ice bath for another 1 h. The resulting precipitate was filtrated and dried to yield **1** (11.5 g, 98.6%).

2, 4''-O-bis(trimethylsilyl)erythromycin A 9-O-(2-chlorobenzyl)oxime (2)

To a solution of **1** (23 g, 26.3 mmol) in acetonitrile (200 ml) was added pyridine hydrochloride (8.8 g, 76.1 mmol) and hexamethyldisilazane (HMDS) (20 ml, 94.2 mmol). The reaction mixture was stirred at room temperature for 1 h and

extracted twice with petroleum ether. The organic phase was dried over MgSO₄ and evaporated to yield **2** (23.0 g, 85.8%). ¹³C NMR(100 MHz, CDCl₃) δ : 175.8, 172.0, 135.4, 133.0, 129.5, 129.2, 128.8, 126.8, 102.5, 96.5, 81.4, 80.8, 79.3, 76.9, 75.3, 74.2, 73.2, 73.1, 72.8, 70.4, 67.6, 65.1, 64.9, 49.6, 44.6, 40.9, 40.2, 38.4, 35.8, 33.2, 29.6, 26.8, 26.7, 22.1, 21.7, 21.2, 19.3, 18.5, 16.2, 15.6, 14.3, 10.7, 9.6, 0.9, 0.8.

2', 4''-O-bis(trimethylsilyl)-6-O-methylethylerythromycin A 9-O-(2-chlorobenzyl)oxime (3)

To an ice-cold solution of **2** (23.0 g, 22.6 mmol) in 80 ml THF and 80 ml dimethyl sulfoxide (DMSO) was added CH₃I (2.4 ml, 47.3 mmol) and KOH (2.4 g, 42.8 mmol). The reaction mixture was stirred at 0 °C for 1 h, and then was poured with water and extracted with petroleum ether. The organic layer was concentrated to yield **3** (23.0 g, 98.6%).

3-OH-6-O-methylethylerythromycin A 9-O-(2-chlorobenzyl)oxime (4)

To a solution of **3** (23.0 g, 22.3 mmol) in ethanol (80 ml) was slowly added a solution of diluted HCl (8 ml HCl in 80 ml water) over 10 min. The reaction mixture was stirred at room temperature for 1.5 h and neutralized with NH₃·H₂O (36%, 8 ml). The precipitate was collected by filtration and washed with water to yield **4** (12.0 g, 73.8%). MS(MALDI-TOF) (M+Na⁺) *m/z* 751.5, calcd for C₃₇H₆₁ClN₂O₁₀ 728.4 (M). ¹H NMR(400 MHz, CDCl₃) δ : 7.41–7.22 (m, 4H, benzyl ring), 5.22–5.06 (m, 3H, H-13, –CH₂–PhCl), 4.36–4.35 (m, 2H, H-1', 11-OH), 3.81 (s, 1H, H-11), 3.78–3.71 (m, 1H, H-8), 3.64 (m, 2H, H-5, 2'-OH), 3.54–3.51 (m, 2H, H-3, H-5'), 3.28 (s, 12-OH), 3.23 (dd, 1H, H-2'), 2.82 (s, 3H, 6-OCH₃), 2.66–2.62 (m, 1H, H-2), 2.57 (q, 1H, H-10), 2.49–2.43 (m, 1H, H-3'), 2.24 (s, 6H, –N(CH₃)₂), 2.09 (m, 1H, H-4), 1.97–19.2 (m, 1H, H-14eq), 1.67–1.50 (m, 3H, H-4', H-7ax, H-14ax), 1.38 (s, 3H, 6-CH₃), 1.35–1.22 (m, 8H, H-7eq, H-4'eq, 5'-CH₃, 2-CH₃), 1.18 (s, 3H, 12-CH₃), 1.13 (d, 3H, 10-CH₃), 1.07 (d, 3H, 4-CH₃), 0.97 (d, 3H, 8-CH₃), 0.83 (t, 3H, 15-CH₃). ¹³C NMR(100 MHz, CDCl₃) δ : 174.9, 170.5, 135.7, 133.4, 129.8, 129.2, 128.9, 126.5, 106.7, 87.9, 78.8, 78.3, 76.8, 73.9, 72.6, 70.6, 70.4, 70.1, 65.6, 49.3, 44.5, 40.2, 37.3, 35.9, 33.1, 28.0, 26.4, 21.5, 21.2, 18.7, 18.3, 16.2, 15.3, 15.1, 10.4, 8.1.

2'-O-Ac-3-OH-6-O-methylethylerythromycin A 9-O-(2-chlorobenzyl)oxime (5)

A solution of **4** (5.0 g, 6.9 mmol) in CH₂Cl₂ (50 ml) was treated with acetic anhydride (1.7 ml, 17.9 mmol) at room temperature for 1 h. The reaction mixture was washed with saturated NaHCO₃ and brine. The organic layer was dried over MgSO₄ and evaporated to yield **5** (5.0 g, 94.5%).

**2'-O-Ac-3-OH-6-O-methylerythromycin A
9-O-(2-chlorobenzyl)oxime 11,12-carbonate (6)**

To an ice-cold solution of **5** (4.8 g, 6.3 mmol) in CH₂Cl₂ (120 ml) was added pyridine (5.0 ml, 61.9 mmol) and dropped by a solution of Bis(trichloromethyl)carbonate (3.73 g, 12.5 mmol) in CH₂Cl₂ (60 ml) over 1 h. The reaction mixture was stirred at room temperature for 18 h and then cooled to 0 °C. To the reaction mixture was added dropwise water (100 ml). The organic layer was washed with saturated NaHCO₃ and water, and then dried over MgSO₄ and evaporated to yield **6** (4.9 g, 98.7%).

**2'-O-Ac-3-O-allyl-6-O-methylerythromycin A
9-O-(2-chlorobenzyl)oxime 11,12-carbonate (7)**

To an ice-cold solution of **6** (2.0 g, 2.5 mmol) in 20 ml of DMSO and 20 ml THF was added allyl bromide (0.42 ml, 5.0 mmol) and KOTBu (0.56 g, 5.0 mmol). The reaction mixture was stirred for 30 min, and then poured with water and extracted with ethyl acetate. The organic phase was washed with water and brine. The organic layer was dried over MgSO₄ and concentrated to yield **7** (2.0 g, 95.2%). HRMS (ESI) (M+H⁺) *m/z* 837.42967, calcd for C₄₃H₆₆ClN₂O₁₂ 837.42988. ¹H NMR (400 MHz, CDCl₃) δ: 0.82–0.91 (m, 9H, 15-CH₃, 8-CH₃, 4-CH₃), 1.18–1.30 (m, 13H, 10-CH₃, 5'-CH₃, 2-CH₃, 6-CH₃, H-7), 1.46 (s, 3H, 12-CH₃), 1.51–1.56 (m, 1H, H-14ax), 1.67 (dd, *J*=2.7 Hz, 1H, H-4'), 1.83–1.88 (m, 2H, H-4, H-14eq), 2.02 (s, 3H, 2'-COCH₃), 2.24 (s, 6H, -N(CH₃)₂), 2.44 (q, 1H, H-10), 2.62–2.64 (m, 1H, H-3'), 2.68 (s, 3H, 6-OCH₃), 2.78–2.82 (m, 1H, H-2), 3.19 (d, *J*=10.5 Hz, 1H, H-3), 3.39–3.45 (m, 1H, H-5'), 3.62 (d, *J*=3.2 Hz, 1H, H-5), 3.72 (m, 1H, H-8), 4.05 and 4.27 (dd, *J*=5.1 and 13.2 Hz, 2H, -CH₂-CH=CH₂), 4.41 (d, *J*=7.5 Hz, 1H, H-1'), 4.70 (dd, *J*=7.5 and 10.5 Hz, 1H, H-2'), 4.78 (s, 1H, H-11), 5.08–5.24 (m, 3H, H-13, benzyl-CH₂), 5.34 (dd, *J*=1.6 and 17.2 Hz, 1H, -CH=CH₂), 5.83–5.93 (m, 1H, -CH=CH₂), [7.48–7.50 (m, 1H), 7.30 (d, *J*=1.2 and 7.6 Hz, 1H), 7.15–7.26 (m, 2H), benzyl ring]. ¹³C NMR (100 MHz, CDCl₃) δ: 175.2 (C-1), 169.7 (C-9), 165.3 (-COCH₃), 154.6 (carbonate), 136.1, 134.4, 133.4, 130.8, 128.9, 128.6, 126.4, 116.4, 99.2, 84.9, 84.2, 82.8, 79.0, 78.4, 75.1, 74.4, 72.6, 71.4, 68.5, 49.4, 44.7, 40.6 (-N(CH₃)₂), 36.9, 36.6, 32.8, 31.0, 25.8, 22.1, 21.1, 20.9, 19.3, 18.8, 15.5, 15.2, 12.8, 10.1, 8.5.

**3-O-[3-(3'-Quinolyl)-Z-1-propenyl]-6-O-methylerythromycin A
9-O-(2-chlorobenzyl)oxime 11, 12-carbonate (9e)**

To a solution of **7** (1.0 g, 1.2 mmol), palladium(II) acetate (53.6 mg, 0.24 mmol) and tri(*o*-tolyl) phosphine (145.36 mg, 0.48 mmol), in acetonitrile (8 ml) were added 3-bromoquinoline (0.324 ml, 2.4 mmol) and triethylamine (0.33 ml, 2.4 mmol). The reaction mixture was flushed with nitrogen and sealed in a pressure tube. The reaction mixture was stirred at 60 °C for 1 h and thereafter at 90 °C for 24 h. The reaction mixture was extracted with ethyl acetate, washed with water and brine and the organic phase was concentrated. The crude mixture was purified by column chromatography on silica gel (15:0.4:0.1 CH₂Cl₂/C₂H₅OH/NH₃·H₂O) to yield **9e** (216 mg, 19.4%).

The product obtained above (216 mg, 0.22 mmol) was heated to reflux in MeOH (20 ml) for 3 h. After the solvent was evaporated, the crude product was purified by column chromatography (silica gel, 5:5:0.2 petroleum ether/acetone/triethylamine) to yield **9e** (100 mg, 48.4%): MS(MALDI-TOF) (M+Na⁺) *m/z* 944.7. HRMS (ESI) (M+H⁺) *m/z* 922.46049, calcd for C₅₀H₆₉ClN₃O₁₁ 922.46151. ¹H NMR (400 MHz, CDCl₃) δ: 0.85 (t, 3H, 15-CH₃), 0.93 (d, *J*=6.9 Hz, 3H, 8-CH₃), 1.12–1.20 (m, 9H, 4-CH₃, 2-CH₃, 5'-CH₃), 1.22 (d, *J*=6.8 Hz, 3H, 10-CH₃), 1.28 (s, 3H, 6-CH₃), 1.32–1.35 (m, 1H, H-7), 1.42–1.60 (m, 6H, H-7, 12-CH₃, H-14ax, H-4'), 1.88–1.99 (m, 2H, H-4, H-14eq), 2.14–2.17 (m, 7H, -N(CH₃)₂, H-3'), 2.47 (q, 1H, H-10), 2.71 (s, 3H, 6-OCH₃), 2.89–2.96 (m, 1H, H-2), 3.12 (dd, *J*=7.2 and 10.1 Hz, 1H, H-2') 3.33–3.36 (m, 2H, H-5', 3-O-CH=CH-CH₂-Ar), 3.49–3.55 (m, 2H, -3-O-CH=CH-CH₂-Ar, H-3), 3.66 (d, *J*=2.7 Hz, 1H, H-5), 3.67–3.75 (m, 2H, 2'-OH, H-8), 4.21 (d, *J*=7.3 Hz, 1H, H-1'), 4.62 (q, 1H, 3-O-CH=CH-CH₂-Ar), 4.83 (s, 1H, H-11), 5.09–5.25 (m, 3H, -CH₂-PhCl, H-13), 6.25 (d, *J*=6.5 Hz, 1H, 3-O-CH=CH-CH₂-Ar), [7.19–7.25 (m, 2H), 7.32 (dd, *J*=1.3 and 5.2 Hz, 1H), 7.52–7.54 (m, 1H), benzyl ring], [7.52–7.54 (m, 1H), 7.64 (m, 1H), 7.75 (d, *J*=8.0 Hz, 1H), 7.94 (s, 1H), 8.05 (d, *J*=8.3 Hz, 1H), 8.82 (d, *J*=2.1 Hz, 1H), quinolyl].

**3-O-[3-(4'-Isoquinolyl)-Z-1-propenyl]-6-O-methylerythromycin A
9-O-(2-chlorobenzyl)oxime 11,12-carbonate (9f)**

By a similar procedure to **9e**, **8f** was prepared as a white solid in 17.1% yield according to the general procedure for the preparation of **8e**, and then deacetylated to give **9f** (38.6%). HRMS (ESI) (M+H⁺) *m/z* 922.46301, calcd for C₅₀H₆₉ClN₃O₁₁ 922.46151. ¹H NMR (400 MHz, CDCl₃) δ: 0.85 (t, 3H, 15-CH₃), 0.93 (d, *J*=6.9 Hz, 3H, 8-CH₃), 1.12–1.22 (m, 9H, 4-CH₃, 2-CH₃, 5'-CH₃), 1.23 (d, *J*=6.8 Hz, 3H, 10-CH₃), 1.29 (s, 3H, 6-CH₃), 1.35 (d, 1H, H-7), 1.45 (d, 1H, H-7), 1.51 (s, 3H, 12-CH₃), 1.56 (m, 2H, H-4', H-14ax), 1.87–1.93 (m, 1H, H-14eq), 1.99–2.03 (m, 1H, H-4), 2.23 (s, 6H, -N(CH₃)₂), 2.25–2.26 (m, 1H, H-3'), 2.48 (q, 1H, H-10), 2.71 (s, 3H, 6-OCH₃), 2.95–2.99 (m, 1H, H-2), 3.14 (dd, *J*=7.3 and 10.0 Hz, 1H, H-2'), 3.31–3.35 (m, 2H, H-5', 2'-OH), 3.55 (d, *J*=10.5 Hz, 1H, H-3), 3.66–3.72 (m, 2H, H-5, 3-O-CH=CH-CH₂-Ar), 3.77 (m, 1H, H-8), 3.94 (dd, *J*=7.6 and 15.6 Hz, 1H, 3-O-CH=CH-CH₂-Ar), 4.26 (d, *J*=7.2 Hz, 1H, H-1'), 4.60 (q, 1H, 3-O-CH=CH-CH₂-Ar), 4.85 (s, 1H, H-11), 5.10–5.16 (m, 2H, -CH₂-PhCl, H-13), 5.24 (d, *J*=12.9 Hz, 1H, -CH₂-PhCl), 6.19 (d, *J*=6.1 Hz, 1H, 3-O-CH=CH-CH₂-Ar), [7.12–7.25 (m, 2H), 7.32 (dd, *J*=1.1 and 7.9 Hz, 1H), 7.53 (dd, *J*=1.3 and 7.5 Hz, 1H), benzyl ring], [7.63 (t, 1H), 7.74 (m, 1H), 7.98 (d, *J*=8.1 Hz, 1H), 8.07 (d, *J*=8.4 Hz, 1H), 8.42 (s, 1H), 9.13 (s, 1H), isoquinolyl]. ¹³C NMR (100 MHz, CDCl₃) δ: 174.4 (C-1), 165.1 (C-9), 154.6 (carbonate), 151.4, 148.1, 142.3, 136.0, 134.5, 133.5, 131.0, 130.3, 130.2, 128.9, 128.7, 128.3, 128.1, 126.9, 126.4, 123.1, 102.1, 101.6, 89.5, 84.9, 82.8, 79.7, 78.4, 77.1, 75.4, 72.6, 70.4, 69.2, 65.6, 49.3, 44.5, 40.2 (-N(CH₃)₂), 37.1, 36.5, 32.8, 28.4, 25.9, 25.2, 22.1, 21.1, 19.3, 18.8, 15.6, 15.4, 12.8, 10.0, 8.9.

**3-O-[3-(5'-Isoquinolyl)-Z-1-propenyl]-6-O-methylerythromycin A
9-O-(2-chlorobenzyl)oxime 11,12-carbonate (9g)**

By a similar procedure to **9e**, **8g** was prepared as a white solid in 18.0% yield according to the general procedure for the preparation of **8e**, and then deacetylated to give **9g** (52.3%). HRMS (ESI) (M+H⁺) *m/z* 922.46176, calcd for C₅₀H₆₉ClN₃O₁₁ 922.46151. ¹H NMR (600 MHz, CDCl₃) δ: 0.86 (t, 3H, 15-CH₃), 0.94 (d, *J*=7.6 Hz, 3H, 8-CH₃), 1.13 (d, *J*=6.9 Hz, 3H, 4-CH₃), 1.16–1.18 (m, 9H, 2-CH₃, 4-CH₃, 5'-CH₃), 1.21–1.25 (m, 3H, 10-CH₃), 1.31 (s, 3H, 6-CH₃), 1.35–1.31 (m, 1H, H-7), 1.43–1.48 (m, 1H, H-7), 1.51 (s, 3H, 12-CH₃), 1.54–1.61 (m, 2H, H-14ax, H-4'), 1.89–1.93 (m, 1H, H-14eq), 1.97–2.02 (m, 1H, H-4), 2.18 (m, 7H, H-3', -N(CH₃)₂), 2.48 (q, 1H, H-10), 2.71 (s, 3H, 6-OCH₃), 2.92–2.95 (m, 1H, H-2), 3.14 (dd, *J*=6.9 and 10.3 Hz, 1H, H-2'), 3.28–3.32 (m, 2H, 2'-OH, H-5'), 3.53 (d, *J*=10.9 Hz, 1H, H-3), 3.67–3.71 (m, 2H, H-5, 3-O-CH=CH-CH₂-Ar), 3.76–3.78 (m, 1H, H-8), 3.98 (dd, *J*=7.5 and 15.8 Hz, 1H, 3-O-CH=CH-CH₂-Ar), 4.25 (d, *J*=7.5 Hz, 1H, H-1'), 4.57–4.60 (m, 1H, 3-O-CH=CH-CH₂-Ar), 4.84 (s, 1H, H-11), 5.11–5.29 (m, 2H, H-13, -CH₂-PhCl), 6.20 (d, *J*=6.2 Hz, 1H, 3-O-CH=CH-CH₂-Ar), [7.19–7.25 (m, 2H), 7.32 (d, *J*=7.5 Hz, 1H), 7.51–7.54 (m, 1H), benzyl ring], [7.51–7.54 (m, 1H), 7.59 (d, *J*=6.8 Hz, 1H), 7.84 (d, *J*=8.2 Hz, 1H), 7.89 (d, *J*=6.2 Hz, 1H), 8.56 (d, *J*=5.5 Hz, 1H), 9.24 (s, 1H), isoquinolyl].

**3-O-[3-(5'-Indolyl)-E-2-propenyl]-6-O-methylerythromycin A
9-O-(2-chlorobenzyl)oxime 11,12-carbonate (9h)**

By a similar procedure to **9e**, **8h** was prepared as a white solid in 21.0% yield according to the general procedure for the preparation of **8e**, and then deacetylated to give **9h** (13.9%). HRMS (ESI) (M+H⁺) *m/z* 910.46418, calcd for C₄₉H₆₉ClN₃O₁₁ 910.46151. ¹H NMR (400 MHz, CDCl₃) δ: 0.87 (t, 3H, 15-CH₃), 0.91 (d, *J*=6.9 Hz, 3H, 8-CH₃), 1.09 (d, *J*=7.5 Hz, 3H, 4-CH₃), 1.22–1.19 (m, 6H, 5'-CH₃, 2-CH₃), 1.25–1.34 (m, 6H, 10-CH₃, 6-CH₃), 1.42 (m, 1H, H-7), 1.49 (s, 3H, 12-CH₃), 1.56 (m, 3H, H-7, H-14ax, H-4'), 1.92–1.87 (m, 2H, H-14eq, H-4), 2.10 (s, 6H, -N(CH₃)₂), 2.37 (br, 1H, H-3'), 2.47 (q, 1H, H-10), 2.63 (s, 3H, 6-OCH₃), 2.92–2.87 (m, 1H, H-2), 3.16 (m, 1H, H-2'), 3.28 (s, 1H, 2'-OH), 3.34 (d, *J*=7.8 Hz, 1H, H-3), 3.46 (m, 1H, H-5'), 3.71 (m, 2H, H-8, H-5), 4.23 (dd, *J*=5.3 and 13.2 Hz, 1H, 3-O-CH₂-CH=CH-Ar), 4.48 (d, *J*=5.4 Hz, 1H, H-1'), 4.53 (dd, *J*=9.3 Hz, 1H, 3-O-CH₂-CH=CH-Ar), 4.82 (s, 1H, H-11), 5.08–5.15 (m, 2H, -CH₂-PhCl, H-13), 5.23 (d, *J*=12.9 Hz, 1H, -CH₂-PhCl), 6.29 (dt, *J*=15.6 Hz, 1H, 3-O-CH₂-CH=CH-Ar), 6.78 (d, *J*=15.9 Hz, 1H, 3-O-CH₂-CH=CH-Ar), [6.52 (m, 1H), 7.12 (m, 1H), 7.20–7.31 (m, 4H), 7.34–7.36 (m, 1H), 7.50–7.53 (m, 1H), 7.62 (s, 1H), 8.19 (s, 1H), benzyl ring, indolyl]. ¹³C NMR (100 MHz, CDCl₃) δ: 175.4 (C-1), 165.3 (C-9), 154.8 (carbonate), 136.1,

135.5, 133.5, 133.2, 131.0, 128.9, 128.6, 128.5, 128.1, 126.4, 124.8, 122.6, 120.4, 119.2, 111.1, 102.7, 101.7, 85.0, 83.8, 82.9, 80.2, 78.3, 77.1, 75.0, 74.2, 72.6, 70.5, 69.1, 65.1, 49.3, 44.9, 39.9 (–N(CH₃)₂), 37.2, 36.9, 32.8, 28.6, 25.9, 22.1, 21.3, 19.4, 18.8, 15.6, 15.5, 12.8, 10.1, 8.8.

3-O-[3-(5'-Pyrimidyl)-Z-1-propenyl]-6-O-methylerythromycin A 9-O-(2-chlorobenzyl)oxime 11,12-carbonate (9d)

By a similar procedure to **9e**, **8d** was prepared as a white solid in 9.4% yield according to the general procedure for the preparation of **8e**, except for the addition of 3eq 5-bromopyrimidine, and then deacetylated to give **9d** (32.3%). HRMS (ESI) (M+H⁺) *m/z* 873.44271, calcd for C₄₅H₆₆ClN₄O₁₁ 873.44111. ¹H NMR (400 MHz, CDCl₃) δ: 0.83 (t, 3H, 15-CH₃), 0.91 (d, 3H, 8-CH₃), 1.04–1.11 (m, 6H, 4-CH₃, 2-CH₃), 1.17–1.24 (m, 7H, 10-CH₃, 5'-CH₃, H-4'ax), 1.27 (s, 3H, 6-CH₃), 1.42–1.28 (m, 2H, H-7), 1.48 (s, 3H, 12-CH₃), 1.61 (m, 2H, H-14ax, H-4'eq), 1.86–1.96 (m, 2H, H-14eq, H-4), 2.25 (s, 6H, –N(CH₃)₂), 2.31 (m, 1H, H-3'), 2.46 (q, 1H, H-10), 2.69 (s, 3H, 6-OCH₃), 2.86–2.91 (m, 1H, H-2), 3.14 (dd, *J*=7.3 and 15.9 Hz, 1H, H-2'), 3.25–3.35 (m, 2H, H-5', 3-O-CH=CH-CH₂-Ar), 3.48–3.52 (m, 2H, 3-O-CH=CH-CH₂-Ar, H-3), 3.61 (d, *J*=2.4 Hz, 1H, H-5), 3.75 (m, 1H, H-8), 4.16 (d, *J*=7.2 Hz, 1H, H-1'), 4.52 (q, 1H, 3-O-CH=CH-CH₂-Ar), 4.81 (s, 1H, H-11), 4.78–4.81 (m, 2H, –CH₂-PhCl, H-13), 5.22 (d, *J*=12.9 Hz, 1H, –CH₂-PhCl), 6.22 (d, *J*=6.0 Hz, 1H, 3-O-CH=CH-CH₂-Ar), [7.16–7.23 (m, 2H), 7.29–7.31 (m, 1H), 7.50–7.52 (m, 1H), benzyl ring], [8.60 (s, 2H), 9.04 (s, 1H), pyrimidyl]. ¹³C NMR (100 MHz, CDCl₃) δ: 174.2 (C-1), 165.1 (C-9), 156.6, 154.6 (carbonate), 149.2, 136.0, 134.4, 133.5, 130.9, 128.9, 128.7, 126.4, 101.8, 100.5, 89.8, 84.8, 82.8, 80.1, 78.4, 77.1, 75.5, 72.6, 70.2, 69.2, 65.8, 49.3, 44.4, 40.2 (–N(CH₃)₂), 37.1, 36.4, 32.8, 28.4, 25.8, 25.3, 22.1, 21.1, 19.3, 18.7, 15.6, 15.4, 12.8, 10.0, 8.8.

3-O-[3-(1'-Phenyl)-Z-1-propenyl]-6-O-methylerythromycin A 9-O-(2-chlorobenzyl)oxime 11,12-carbonate (9b)

By a similar procedure to **9e**, **8b** was prepared as a white solid in 51.2% yield according to the general procedure for the preparation of **8e**, and then deacetylated to give **9b** (16.2%). HRMS (ESI) (M+H⁺) *m/z* 871.45056, calcd for C₄₇H₆₈ClN₂O₁₁ 871.45062. ¹H NMR (600 MHz, CDCl₃) δ: 0.83–0.88 (m, 3H, 15-CH₃), 0.91–0.95 (m, 3H, 8-CH₃), 1.09–1.12 (m, 3H, 4-CH₃), 1.18 (d, *J*=2.7 Hz, 3H, 2-CH₃), 1.19–1.22 (m, 3H, 5'-CH₃), 1.22–1.24 (m, 3H, 10-CH₃), 1.28 (s, 3H, 6-CH₃), 1.30–1.34 (m, 1H, H-7), 1.43–1.45 (m, 1H, H-7), 1.50 (s, 3H, 12-CH₃), 1.54–1.58 (m, 1H, H-14eq), 1.90–1.92 (m, 1H, H-14ax), 1.96 (q, 1H, H-4), 2.21 (s, 6H, –N(CH₃)₂), 2.23–2.27 (m, 1H, H-3'), 2.48 (q, 1H, H-10), 2.71 (s, 3H, 6-OCH₃), 2.87–2.94 (m, 1H, H-2), 3.11–3.13 (m, 1H, H-2'), 3.25–3.38 (m, 3H, 2'-OH, H-5', 3-O-CH=CH-CH₂-Ar), 3.48 (d, *J*=10.3 Hz, 1H, H-3), 3.54 (dd, *J*=15.8 and 7.6 Hz, 1H, 3-O-CH=CH-CH₂-Ar), 3.67 (d, *J*=2.7 Hz, H-5), 3.75–3.77 (m, 1H, H-8), 4.23 (d, *J*=7.5 Hz, H-1'), 4.53 (q, 1H, 3-O-CH=CH-CH₂-Ar), 4.83 (s, 1H, H-11), 6.15 (d, *J*=6.2 Hz, 1H, 3-O-CH=CH-CH₂-Ar), [7.16–7.32 (m, 7H), 7.38 (d, 1H, *J*=7.5 Hz), 7.52–7.54 (m, 1H), benzyl ring, phenyl]. Including 41% 3-O-[3-(1'-Phenyl)-E-2-propenyl] isomer, δ: 6.71 (d, *J*=15.8 Hz, 1H, 3-O-CH₂-CH=CH-Ar), 6.24 (dt, 1H, 3-O-CH₂-CH=CH-Ar).

3-O-[3-(3'-Pyridyl)-Z-1-propenyl]-6-O-methylerythromycin A 9-O-(2-chlorobenzyl)oxime 11,12-carbonate (9c)

By a similar procedure to **9e**, **8c** was prepared as a white solid in 25.6% yield according to the general procedure for the preparation of **8e**, and then deacetylated to give **9c** (46.7%). HRMS (ESI) (M+H⁺) *m/z* 872.44808, calcd for C₄₆H₆₇ClN₃O₁₁ 872.44586. ¹H NMR (400 MHz, CDCl₃) δ: 0.84 (t, 3H, 15-CH₃), 0.92 (d, 3H, 8-CH₃), 1.15–1.13 (m, 6H, 4-CH₃, 2-CH₃), 1.16 (d, *J*=6.1 Hz, 3H, 5'-CH₃), 1.21 (d, *J*=6.8 Hz, 3H, 10-CH₃), 1.25 (s, 3H, 6-CH₃), 1.27–1.30 (m, 1H, H-7), 1.41–1.45 (m, 1H, H-7), 1.48 (s, 3H, 12-CH₃), 1.51–1.59 (m, 2H, H-14ax, H-4'), 1.86–1.97 (m, 2H, H-14eq, H-4), 2.23 (s, 6H, –N(CH₃)₂), 2.28 (m, 1H, H-3'), 2.46 (q, 1H, H-10), 2.70 (s, 3H, 6-OCH₃), 2.87–2.94 (m, 1H, H-2), 3.13 (dd, *J*=7.3 and 10.1 Hz, 1H, H-2'), 3.28–3.33 (m, 3H, H-5', 2'-OH, 3-O-CH=CH-CH₂-Ar), 3.47–3.55 (m, 2H, H-3, 3-O-CH=CH-CH₂-Ar), 3.64 (d, *J*=2.7 Hz, 1H, H-5), 3.74–3.82 (m, 1H, H-8), 4.19 (d, *J*=7.2 Hz, 1H, H-1'), 4.48–4.54 (q, 1H, 3-O-CH=CH-CH₂-Ar), 4.82 (s, 1H, H-11), 5.24–5.09 (m, 3H, –CH₂-PhCl, H-13), 6.18 (d, *J*=6.0 Hz, 1H, 3-O-CH=CH-CH₂-Ar), [7.16–7.26 (m, 3H), 7.30 (dd, *J*=1.2 and 7.7 Hz, 1H),

7.50–7.52 (m, 2H), 8.41–8.47 (m, 2H), benzyl ring, pyridyl]. ¹³C NMR (100 MHz, CDCl₃) δ: 174.3 (C-1), 165.1 (C-9), 154.6 (carbonate), 149.7, 148.5, 147.3, 136.6, 136.0, 135.6, 133.5, 130.9, 128.9, 128.6, 126.4, 123.2, 101.9, 101.6, 89.5, 84.8, 82.8, 79.7, 78.4, 75.4, 72.6, 70.3, 69.1, 65.6, 49.3, 44.5, 40.2 (–N(CH₃)₂), 37.1, 36.4, 32.8, 27.7, 25.8, 22.1, 21.1, 19.3, 18.7, 15.6, 15.4, 12.8, 10.0, 8.8.

3-O-allyl-6-O-methylerythromycin A 9-O-(2-chlorobenzyl)oxime 11,12-carbonate (9a)

Compound **7** was heated to reflux in MeOH for 3 h. After the solvent was evaporated, the crude product was purified by column chromatography (silica gel, 15:0.3:0.1 CH₂Cl₂/C₂H₅OH/NH₃·H₂O) to give **9a** in 62.1% yield. HRMS (ESI) (M+H⁺) *m/z* 795.42088, calcd for C₄₁H₆₄ClN₂O₁₁ 795.41932. ¹H NMR (400 MHz, CDCl₃) δ: 0.86 (t, 3H, 15-CH₃), 0.92 (d, *J*=7.0 Hz, 3H, 8-CH₃), 1.03 (d, *J*=7.5 Hz, 3H, 4-CH₃), 1.17–1.23 (m, 6H, 10-CH₃, 5'-CH₃), 1.25–1.29 (m, 6H, 2-CH₃, 6-CH₃), 1.32–1.35 (m, 1H, H-7), 1.41–1.44 (m, 1H, H-7), 1.48 (s, 3H, 12-CH₃), 1.51–1.67 (m, 2-3H, H-14ax, H-4'), 1.86–1.92 (m, 2H, H-4, H-14eq), 2.28 (s, 6H, –N(CH₃)₂), 2.46–2.50 (m, 2H, H-3', H-10), 2.72 (s, 3H, 6-CH₃), 2.80–2.89 (m, 1H, H-2), 3.16 (dd, *J*=7.2 and 10.1 Hz, 1H, H-2'), 3.21–3.24 (m, 2H, H-3, 2'-OH), 3.42–3.46 (m, 1H, H-5'), 3.70 (d, *J*=3.2 Hz, 1H, H-5), 3.74–3.78 (m, 1H, H-8), 4.05–4.30 (m, 2H, –CH₂-CH=CH₂), 4.37 (d, *J*=7.2 Hz, 1H, H-1'), 4.81 (s, 1H, H-11), 5.11–5.26 (m, 5H, H-13, –CH₂-PhCl, –CH=CH₂), 5.35 (dd, *J*=1.6 and 17.2 Hz, 1H, –CH=CH₂) 5.84–5.93 (m, 1H, –CH=CH₂), [7.17–7.26 (m, 2H), 7.32 (dd, *J*=1.2 and 7.8 Hz, 1H), 7.53 (dd, *J*=1.6 and 7.5 Hz, 1H), benzyl ring].

3-O-allyl-6-O-methylerythromycin A 9-O-(2-chlorobenzyl)oxime (12a)

Compound **12a** was synthesized by a similar procedure to **9a** in 70.0% yield. MS(MALDI-TOF) (M+Na⁺) *m/z* 791.2, calcd for C₄₀H₆₅ClN₂O₁₀ 768.4 (M). ¹H NMR (400 MHz, CDCl₃) δ: 0.82 (t, 3H, 15-CH₃), 0.96 (d, 3H, 8-CH₃), 1.05 (d, 3H, 4-CH₃), 1.12 (d, 3H, 10-CH₃), 1.14 (s, 3H, 12-CH₃), 1.20 (d, 3H, 5'-CH₃), 1.25 (d, 3H, 2-CH₃), 1.31 (s, 3H, 6-CH₃), 1.39–1.52 (m, 3H, H-7, H-14ax), 1.62–1.66 (m, 1H, H-4'), 1.92–2.08 (m, 2H, H-4, H-14eq), 2.27 (s, 6H, –N(CH₃)₂), 2.45–2.46 (m, 1H, H-3'), 2.57 (q, 1H, H-10), 2.81–2.84 (m, 1H, H-2), 2.85 (s, 3H, 6-CH₃), 3.14–3.27 (m, 4H, H-2', H-3, 12-OH, 2'-OH), 3.42–3.46 (m, 1H, H-5'), 3.74–3.76 (m, H-5, H-8, H-11), 4.09–4.28 (m, 2H, –CH₂-CH=CH₂), 4.39 (s, 1H, 11-OH), 4.42 (d, 1H, H-1'), 5.07–5.37 (m, 5H, H-13, –CH₂-PhCl, –CH=CH₂), 5.86–5.93 (m, 1H, –CH=CH₂), 7.19–7.40 (m, 4H, benzyl ring). ¹³C NMR (100 MHz, CDCl₃) δ: 175.0, 170.8, 135.8, 134.7, 133.2, 129.6, 129.2, 128.7, 126.5, 116.0, 101.2, 84.4, 79.2, 78.3, 76.8, 74.2, 73.9, 72.6, 70.7, 70.3, 68.9, 65.3, 49.9, 44.6, 40.2, 36.9, 33.0, 28.8, 26.4, 21.3, 21.1, 19.4, 18.5, 16.0, 15.3, 15.2, 10.4, 8.6.

3-O-[3-(3'-Pyridyl)-Z-1-propenyl]-6-O-methylerythromycin A 9-O-(2-chlorobenzyl)oxime (12c)

Compound **12c** was synthesized by a similar procedure to **9c** (26.3% in two steps). HRMS (ESI) (M+H⁺) *m/z* 846.4648, calcd for C₄₅H₆₉ClN₃O₁₀ 846.4666. ¹H NMR (400 MHz, CDCl₃) δ: 0.81 (t, 3H, 15-CH₃), 0.96 (d, 3H, 8-CH₃), 1.11–1.24 (m, 16H, 4-CH₃, 2-CH₃, 10-CH₃, 5'-CH₃, 12-CH₃, H-4'ax), 1.30 (s, 3H, 6-CH₃), 1.30–2.12 (m, 6H, H-7, H-14ax, H-4'eq, H-14eq, H-4), 2.30 (s, 6H, –N(CH₃)₂), 2.31–2.34 (m, 1H, H-3'), 2.56 (q, 1H, H-10), 2.87 (s, 3H, 6-OCH₃), 2.88–2.91 (m, 1H, H-2), 3.31–3.54 (m, 7H, H-5', H-2', 12-OH, 2'-OH, 3-O-CH=CH-CH₂-Ar, H-3), 3.67 (m, 3H, H-5, H-8, H-11), 4.22 (d, *J*=7.3 Hz, 1H, H-1'), 4.42 (s, 1H, 11-OH), 4.50 (q, 1H, 3-O-CH=CH-CH₂-Ar), 5.06–5.21 (m, 3H, –CH₂-PhCl, H-13), 6.20 (d, *J*=6.1 Hz, 1H, 3-O-CH=CH-CH₂-Ar), 7.20–8.49 (m, 8H, benzyl ring, pyridyl).

3-O-[3-(5'-Pyrimidyl)-Z-1-propenyl]-6-O-methylerythromycin A 9-O-(2-chlorobenzyl)oxime (12d)

Compound **12d** was synthesized by a similar procedure to **9d** (12.2% in two steps). HRMS (ESI) (M+H⁺) *m/z* 847.4612, calcd for C₄₄H₆₈ClN₄O₁₀ 847.4618. ¹H NMR (400 MHz, CDCl₃) δ: 0.81 (t, 3H, 15-CH₃), 0.97 (d, 3H, 8-CH₃), 1.11–1.24 (m, 16H, 4-CH₃, 2-CH₃, 10-CH₃, 5'-CH₃, 12-CH₃, H-4'ax), 1.27 (s, 3H, 6-CH₃), 1.30–2.20 (m, 6H, H-7, H-14ax, H-4'eq, H-14eq, H-4), 2.38

(s, 6H, $-N(CH_3)_2$), 2.46 (m, H-3'), 2.56 (q, 1H, H-10), 2.87 (s, 3H, 6-OCH₃), 2.88–2.91 (m, 1H, H-2), 3.23–3.54 (m, 7H, H-5', H-2', 12-OH, 2'-OH, 3-O-CH=CH-CH₂-Ar, H-8), 3.67 (d, $J=2.8$ Hz, 1H, H-5), 3.74–3.76 (m, 2H, H-3, H-11), 4.20 (d, $J=7.2$ Hz, 1H, H-1'), 4.41 (s, 1H, 11-OH), 4.50 (q, 1H, 3-O-CH=CH-CH₂-Ar), 5.07–5.20 (m, 3H, H-13, $-CH_2$ -PhCl), 6.25 (d, $J=6.0$ Hz, 1H, 3-O-CH=CH-CH₂-Ar), 7.19–7.41 (m, 4H, benzyl ring), [8.62 (s, 2H), 9.06 (s, 1H), pyrimidyl].

3-O-[3-(3'-Quinolyl)-Z-1-propenyl]-6-O-methylerythromycin A 9-O-(2-chlorobenzyl)oxime (12e)

Compound 12e was synthesized by a similar procedure to 9e (45.0% in two steps). HRMS (ESI) ($M+H^+$) m/z 896.4802, calcd for C₄₉H₇₁ClN₃O₁₀ 896.4822. ¹H NMR (400 MHz, CDCl₃) δ : 0.82 (t, 3H, 15-CH₃), 0.97 (d, 3H, 8-CH₃), 1.11–1.27 (m, 16H, 4-CH₃, 2-CH₃, 10-CH₃, 5'-CH₃, 12-CH₃, H-4'ax), 1.30 (s, 3H, 6-CH₃), 1.30–2.20 (m, 6H, H-7, H-14ax, H-4'eq, H-14eq, H-4), 2.22–2.32 (m, 7H, $-N(CH_3)_2$, H-3'), 2.57 (q, 1H, H-10), 2.89 (s, 3H, 6-OCH₃), 2.89–2.96 (m, 1H, H-2), 3.17 (dd, 1H, H-2'), 3.26 (s, 1H, 12-OH), 3.28–3.55 (m, 4H, H-5', 3-O-CH=CH-CH₂-Ar, H-3), 3.71–3.78 (m, 3H, H-5, H-11, H-8), 4.24 (d, $J=7.4$ Hz, 1H, H-1'), 4.43 (s, 1H, 11-OH), 4.59 (q, 1H, 3-O-CH=CH-CH₂-Ar), 5.07–5.22 (m, 3H, $-CH_2$ -PhCl, H-13), 6.27 (d, $J=6.1$ Hz, 1H, 3-O-CH=CH-CH₂-Ar), 7.21–7.42 (m, 4H, benzyl ring), 7.53–8.83 (m, 6H, quinolyl).

3-O-[3-(4'-Isoquinolyl)-Z-1-propenyl]-6-O-methylerythromycin A 9-O-(2-chlorobenzyl)oxime (12f)

Compound 12f was synthesized by a similar procedure to 9f (26.2% in two steps). HRMS (ESI) ($M+H^+$) m/z 896.4819, calcd for C₄₉H₇₁ClN₃O₁₀ 896.4822. ¹H NMR (400 MHz, CDCl₃) δ : 0.83 (t, 3H, 15-CH₃), 0.93 (d, $J=6.9$ Hz, 3H, 8-CH₃), 0.97 (d, 3H, 8-CH₃), 1.11–1.27 (m, 16H, 4-CH₃, 2-CH₃, 10-CH₃, 5'-CH₃, 12-CH₃, H-4'ax), 1.32 (s, 3H, 6-CH₃), 1.30–2.20 (m, 6H, H-7, H-14ax, H-4'eq, H-14eq, H-4), 2.23 (s, 6H, $-N(CH_3)_2$), 2.25–2.26 (m, 1H, H-3'), 2.58 (q, 1H, H-10), 2.89 (s, 3H, 6-OCH₃), 2.97–2.99 (m, 1H, H-2), 3.15–3.27 (m, 4H, H-2', H-5', 12-OH, 2'-OH), 3.57 (d, $J=10.2$ Hz, 1H, H-3), 3.58–3.98 (m, 5H, H-11, H-5, H-8, 3-O-CH=CH-CH₂-Ar), 4.29 (d, $J=7.2$ Hz, 1H, H-1'), 4.41 (s, 1H, 11-OH), 4.57 (q, 1H, 3-O-CH=CH-CH₂-Ar), 5.07–5.23 (m, 3H, $-CH_2$ -PhCl, H-13), 6.22 (d, $J=6.1$ Hz, 1H, 3-O-CH=CH-CH₂-Ar), 7.21–7.42 (m, 4H, benzyl ring), 7.61–9.14 (m, 6H, isoquinolyl).

Crystallographic data for the structure of 9f in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 729701. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or E-mail: deposit@ccdc.cam.ac.uk].

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