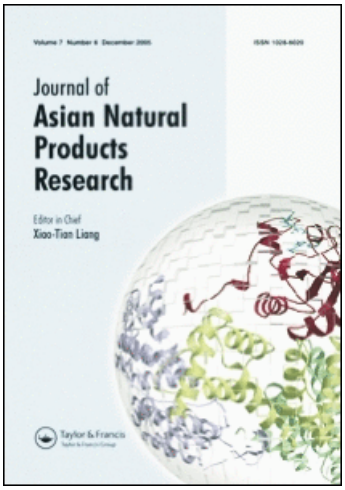

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A novel series of acylide derivatives have been synthesized which exhibit *in vitro* potency against key respiratory pathogens. Modification of position 3 was accomplished by replacing different 3-*O*-substituted acyl groups in the macrolide core via a facile procedure. Compounds **7a**–**7i** were eventually yielded by the conjunction of diverse hetero-aryl side chains with the 11-*N*,12-*O*-carbamate sub-structure.

Keywords: macrolide; acylide; antibacterial activity; resistant strains

1. Introduction

The increasing resistance of community-acquired respiratory tract infection to many antimicrobials has become a serious problem over the past decades [1]. Resistance is most commonly conferred by ribosomal mutation (*erm*) or by efflux (*mef*) mechanism [2]. Many efforts have been made to discover novel 14-membered [3] and 15-membered [4] macrolides to address this status. For example, telithromycin [5] and cethromycin [6], known as ketolide, were investigated.

These compounds possess a 3-keto group and a proper side chain which can interact with nucleotide A752 in domain II of the 23S rRNA, and showed strong activity against major macrolide-resistant strains [7]. It is known that the ketolide series is not the only class of new macrolides for the effective management of respiratory tract infections. Medicinal chemists have synthesized other derivatives of nonketolide families [8–10]. The synthesis and the antibacterial activity of 3-*O*-acyl erythromycin derivatives (acylide) were first reported by Asaka *et al.* [11]. The acylide derivatives showed activity against the erythromycin-susceptible (Ery-S) and -resistant (Ery-R) strains. The study of acylides was mainly focused on the different substitution at position 3 [12], as well as on the modification of the macrolide skeleton [13]. Zhu *et al.* [14] have reported a series of acylide derivatives with 6-*O*-carbamoyl. Some of them showed comparable activity as telithromycin against several Ery-R pathogens. This evokes us to synthesis a class of new acylide derivatives with an aryl-substituted 11,12-carbamate group which could have a secondary interaction with domain II of the 23S rRNA.

In our research, the acyl groups applied at position 3 were proved to have a significant effect for the antibacterial activity, including (3,4-methylenedioxyl)-phenyl acetyl group which had been

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published in our previous report [15]. Four typical side chains selected to attach at 11-*N*,12-*O*-carbamate were also representative. The hetero-arylamines used here were 4-phenylbutylamine (R′1), (4-phenyl-1H-1-imidazoyl)butylamine (R′2), 4-(3H-imidazoyl(4,5-b)pyridin-3-yl)butylamine (R′3), and 4-(1H-imidazoyl(4,5-b)pyridin-1-yl)butylamine (R′4) (Figure 1). We hoped that such conjugation might reasonably improve the antibacterial activity against both macrolide-susceptible and -resistant strains.

2. Results and discussion

Scheme 1 indicated the actual synthesis that started with a well-established intermediate 2′-*O*-acetyl-3-*O*-descladinosyl-6-*O*-methylerythromycin A (**1**) [13]. Formation of 11,12-carbonate (**2**) was carried out with trichloromethyl chloroformate in a mixture of CH_2Cl_2 and pyridine at 0°C. Compound **2** was obtained in a yield of 75%.

The 11,12-carbonate acylides **3a**–**3c** were prepared by condensation of **2** with the corresponding carboxylic acid by using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC·HCl) and 4-dimethylaminopyridine (DMAP) in dichloromethane. The yields were 61–68%. Compounds **3a**–**3c** could be β-eliminated using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base in acetone at room temperature to provide the 10,11-anhydro acylides **4a**–**4c** in yields ranging from 56 to 78%.

Subsequently, **4a**–**4c** were treated with excess 1,1′-carbonyldiimidazole (CDI) and sodium hydride in DMF at −25°C to obtain acylimidazolides **5a**–**5c** in yields of 63–67%. The structures of **3a**–**3c**, **4a**–**4c**, and **5a**–**5c** were confirmed by ^{13}C NMR and MS spectra. The key intermediates **5a**–**5c** could be readily converted to the desired carbamate compounds **6a**–**6i** by treatment with a primary hetero-arylamine in aqueous acetonitrile, following the method originally developed by Baker *et al.* [16] (Scheme 2). Compounds **6a**–**6i** were refluxed overnight in methanol to cleave the 2′-*O*-acetyl group. Compounds **7a**–**7i** were obtained in the yields of 70–94%. The structures of **6a**–**6i** and **7a**–**7i** were confirmed by ^{13}C NMR and MS spectra. Some of them were also confirmed by ^{1}H NMR and HR-MS experiments.

The 11-*N*,12-*O*-carbamate acylides **7a**–**7i** and reference compounds, clarithromycin, telithromycin, and roxithromycin, were tested against different representative pathogens (Tables 1 and 2). Various macrolide- and multidrug-resistant pathogens were tested in order to identify the potence of these acylide analogs. All the methicillin-resistant *Staphylococcus aureus* (MRSA) and Ery-R strains chosen in this test were constitutively resistant strains supplied by the Ministry of Health National Antimicrobial Resistance Investigation Net (MOHNARIN, Beijing, China). *S. aureus*, ATCC29213, 01-430, 01-431, and 01-481 were methicillin-susceptible *S. aureus* (MSSA). *S. aureus* 01-433, 01-429, and

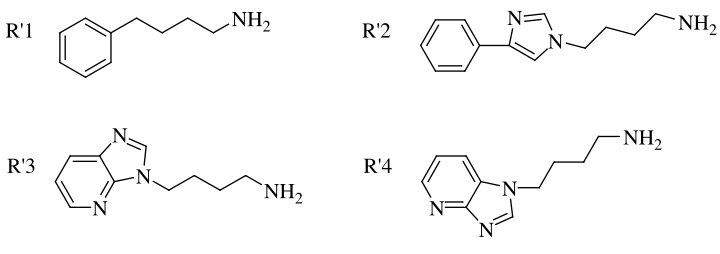
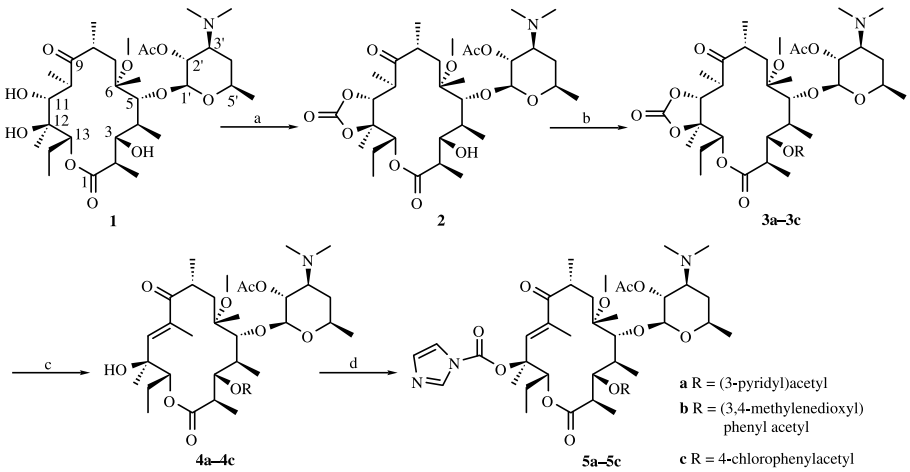
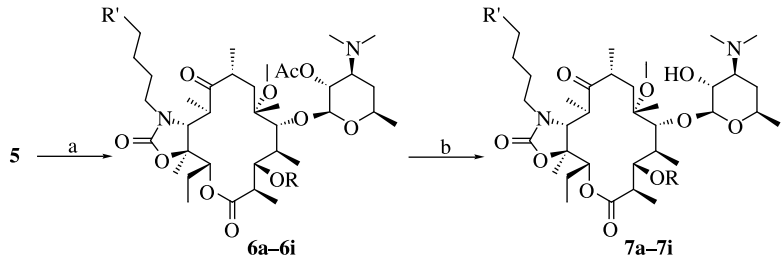


Figure 1. Structures of hetero-arylamine.



Scheme 1. Synthesis of compounds **5a**–**5c**. Reagents and conditions: (a) trichloromethyl chloroformate, CH_2Cl_2/pyridine, rt 75%; (b) EDC·HCl, hetero-arylcarboxylic acid, DMAP, CH_2Cl_2, 61–68%; (c) DBU, acetone, rt 56–78%; and (d) NaH, CDI, DMF, −25°C, 63–67%.

01-483 were MRSA. *Staphylococcus pneumoniae*, ATCC49619, 01-863 and 01-991 were Ery-S strains. *S. pneumoniae* 01-862 and 01-868 were Ery-R strains. *Staphylococcus pyogenes* 03-804 was an Ery-S strain. *S. pyogenes* 03-474, 03-475, 03-476, and 01-781 were Ery-R strains. *S. pyogenes* 03-480 was an Ery-R strain encoded by the *ermB* gene. *Enterococcus faecalis* 03H065 and 03I076 were Ery-S strains. *E. faecalis* 03A056, 03A080, and 03A133 were Ery-R strains. All the strains shown in Table 2 were Ery-R strains. The *in vitro* antibacterial activity was reported



6a,**7a** R = 4-chlorophenylacetyl
R' = 4-phenylbutylamine
6b,**7b** R = 4-chlorophenylacetyl
R' = 4-(3H-imidazoly(4,5-b)pyridin-3-yl) butylamine
6c,**7c** R = 4-chlorophenylacetyl
R' = (4-phenyl-1H-1-imidazoyl)butylamine
6d,**7d** R = (3-pyridyl)acetyl
R' = 4-phenylbutylamine
6e, **7e** R = (3-pyridyl)acetyl
R' = 4-(3H-imidazoly(4,5-b)pyridin-3-yl) butylamine
6f,**7f** R = (3-pyridyl)acetyl
R' = (4-phenyl-1H-1-imidazoyl)butylamine
6g,**7g** R = (3-pyridyl)acetyl
R' = 4-(1H-imidazoyl(4,5-b)pyridin-1-yl) butylamine
6h,**7h** R = (3,4-methylenedioxyl)phenyl acetyl
R' = 4-(1H-imidazoly(4,5-b)pyridin-1-yl) butylamine
6i,**7i** R = (3,4-methylenedioxyl)phenyl acetyl
R' = 4-(3H-imidazoyl(4,5-b)pyridin-3-yl) butylamine

Scheme 2. Synthesis of compounds **7a**–**7i**. Reagents and conditions: (a) primary hetero-arylamine, CH_3CN, 50°C and (b) MeOH, reflux, 70–94%.

Table 1. Antibacterial activity of acylides **7a**–**7f**.

	MIC (μg/ml)						
Pathogens	**7a**	**7b**	**7c**	**7d**	**7e**	**7f**	Clarithromycin
ATCC29213	4	0.25	1	1	0.25	0.25	0.25
01-430 MSSA	4	0.25	1	1	0.125	0.25	0.25
01-431 MSSA	4	0.25	2	1	0.25	0.25	0.25
01-481 MSSA	8	0.5	2	2	1	0.5	0.5
01-433 MRSA	16	16	16	16	16	16	256
01-429 MRSA	8	16	16	16	16	16	256
01-483 MRSA	16	4	8	4	0.5	0.5	256
S. pneumoniae							
ATCC 49619	1	0.125	0.25	0.25	0.031	0.062	0.062
S. pneumoniae							
01-863(Ery-S)	1	0.125	0.5	0.25	0.125	0.062	0.062
01-991(Ery-S)	1	0.25	0.25	0.25	0.016	0.062	0.031
01-862(Ery-R)	16	16	8	16	2	1	256
01-868(Ery-R)	16	16	8	16	2	1	256
S. pyogenes							
03-804(Ery-S)	0.5	0.125	0.5	0.25	0.062	0.125	0.031
03-474(Ery-R)	8	8	16	8	2	2	256
03-475(Ery-R)	8	8	16	8	2	2	256
03-476(Ery-R)	8	8	16	8	2	2	256
03-480(Ery-R)	8	8	16	8	2	2	256
01-781(Ery-R)	8	8	16	8	2	2	256
E. faecalis							
03H065(Ery-S)	1	0.125	1	0.5	0.062	0.125	0.062
03I076(Ery-S)	1	0.125	1	0.5	0.062	0.125	0.062
03A056(Ery-R)	16	16	16	16	4	4	256
03A080(Ery-R)	16	16	16	16	16	8	256
03A133(Ery-R)	16	16	16	16	4	2	256

as minimum inhibitory concentrations (MICs), which were determined by the broth microdilution method as recommended by the National Committee of Clinical Laboratory Standard [17–19].

From Table 1, it appears that all the compounds **7a**–**7f** were active against macrolide-resistant strains. The activity of some compounds against macrolide-susceptible strains was decreased to a certain extent compared with clarithromycin, for example **7a** and **7c**. Compound **7e** almost kept active against macrolide-susceptible strains at the same level as clarithromycin. A comparison of compound **7c** with **7f** indicated that the latter was more potent against all the strains tested. A similar trend can be seen for **7a** versus **7d** and **7b** versus **7e**. This suggested that a 3-pyridylacetyl at position 3 gave better activity. The structure of the aryl group played an important role in SAR. It seemed that compounds with a fused bicyclic aryl group have more potent activity than compounds with a biaryl group or mono-aryl group. This conclusion could be drawn from the comparison of **7e** with **7d** and **7f**.

The best compound in Table 1 (**7e**) was compared with **7g**, **7h**, and the reference compounds telithromycin and roxithromycin in Table 2. All the three compounds exhibited significant improved activity against Ery-R strains compared with roxithromycin but slightly weaker than telithromycin. As **7h** was the

Table 2. Antibacterial activity of acylides **7e**, **7g**, and **7h**.

	MIC (μg/ml)				
Pathogens	**7e**	**7g**	**7h**	Telithromycin	Roxithromycin
S. pneumoniae					
1	0.25	0.25	0.25	0.125	4
2	0.25	0.25	0.25	0.125	4
5	1	1	1	0.25	8
9	1	2	1	0.5	4
S. pyogenes					
11	0.125	0.25	0.125	0.0625	32
14	0.5	1	0.25	0.125	4
15	4	4	2	4	4
16	0.25	1	1	0.125	8
S. aureus					
30	0.125	0.125	0.125	0.0625	8
31	0.25	0.25	0.25	0.125	8
35	0.0625	0.03125	0.03125	0.03125	16
36	0.0625	0.0625	0.03125	0.03125	4
Staphylococcus epidermidis					
41	0.25	0.5	0.125	0.125	>64
43	0.125	0.25	0.0625	0.0625	8
45	0.125	0.25	0.0625	0.0625	8
47	0.125	0.125	0.0625	0.03125	2

one which had the most comparable potency with telithromycin, this confirmed our conclusion that attachment of a (3,4-methylenedioxyl)phenyl acetyl at position 3 could get the best *in vitro* result.

3. Conclusion

In conclusion, a series of novel derivatives of acylide analogs **7a**–**7i** were synthesized and found to have potent activity *in vitro* against macrolide-resistant pathogens. Especially, **7e**, **7g**, and **7h** had an excellent *in vitro* antibacterial potency against resistant strains. The SAR study proved that the combination of the 3-*O*-acyl and 11-*N*-tethered 11-*N*,12-*O*-carbamate substructure possessed potent antibacterial activity against bacteria resistance. This work provides a new insight into the antibacterial activity of macrolides, which will certainly help the researchers in envisioning new antibacterial agents.

4. Experimental

4.1 General experimental procedures

NMR spectra were recorded on Mercury-300 and Mercury-400 spectrometers in $CDCl_3$. The chemical shifts are reported in ppm using TMS as an internal standard. Mass spectra were obtained on a VGZAB-2F mass spectrometer for ESI-MS. HR-MS was recorded on an Aglient 1100 series LC/MSD TOF. Analytical thin layer chromatography (TLC) was carried out on silica gel 60 F_{254} plates precoated by the Branch of Qingdao Haiyang Chemical Plant. Chromatography was performed with silica gel H (HG/T2354-92).

In general, organic layer was dried with anhydrous Na_2SO_4 or K_2CO_3, and evaporation and concentration were carried out under reduced pressure below 40°C, unless otherwise noted.

Clarithromycin for antibacterial testing was purchased from HUAYI Pharmaceutical Co. (Zhejiang, China). Bacterial strains were from the American Type

Culture Collection (ATCC) as indicated in Table 1, or were clinically isolated from the MOHNARIN.

4.2 Synthesis

4.2.1 2′-O-Acetyl-3-O-descladinosyl-6-O-methylerythromycin A 11,12-cyclic carbonate (2)

To a solution of **1** (14.0 g, 22.2 mmol) in CH_2Cl_2 (140 ml), trichloromethyl chloroformate (7.12 ml, 59.0 mmol) and pyridine (29 ml) were added at 0°C. After stirring for 12 h under N_2, the reaction mixture was diluted with CH_2Cl_2 and washed with H_2O. The evaporation of the organic solvent gave 19.0 g of the crude product, which was purified by chromatography on a column of silica gel (acetone/petroleum ether/triethylamine) to afford **2** (10.9 g, 75%). ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.1 (4-CH_3), 9.9 (14-CH_3), 12.7 (10-CH_3), 12.8 (12-CH_3), 15.1 (2-CH_3), 18.2 (8-CH_3), 19.1 (6-CH_3), 20.9 (2′-OAc), 21.3 (5′-CH_3), 21.9 (14-C), 30.8 (4′-C), 35.8 (4-C), 37.2 (10-C), 38.4 (7-C), 40.5 (3′-$N(CH_3)_2$), 44.0 (2-C), 45.1 (8-C), 49.4 (6-OCH_3), 63.0 (3′-C), 68.7 (5′-C), 71.3 (2′-C), 74.9 (3-C), 76.7 (13-C), 77.9 (11-C), 80.8 (12-C), 80.9 (5-C), 84.8 (6-C), 99.6 (1′-C), 154.0 (11-O—CO—O), 169.8 (2′-OAc), 174.9 (1-C), 212.2 (9-C).

4.2.2 2′-O-Acetyl-3-O-(3-pyridyl)acetyl-3-O-descladinosyl-6-O-methylerythromycin A 11,12-cyclic carbonate (3a)

To a solution of **2** (50 mg, 0.076 mmol) in CH_2Cl_2 (0.5 ml), 3-pyridinyl acetic acid (40 mg, 0.23 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (44 mg, 0.23 mmol), and DMAP (9 mg, 0.076 mmol) were added. After stirring for 72 h under N_2, the reaction mixture was diluted with CH_2Cl_2 and washed with sat. aqueous NH_4Cl. The evaporation of the organic solvent gave 70 mg of the crude product, which was purified by chromatography on a column of silica gel (acetone/petroleum ether/triethylamine) to afford **3a** (40 mg, 68%). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.7 (4-CH_3), 10.0 (14-CH_3), 12.7 (10-CH_3), 13.0 (12-CH_3), 15.1 (2-CH_3), 18.2 (8-CH_3), 19.4 (6-CH_3), 20.8 (2′-OAc), 21.4 (5′-CH_3), 21.9 (14-C), 30.2 (4′-C), 36.2 (4-C), 37.4 (10-C), 38.3 (7-C), 40.5 (3′-$N(CH_3)_2$), 40.6 (3-OCO—*C*H_2), 43.1 (2-C), 44.8 (8-C), 49.8 (6-OCH_3), 63.2 (3′-C), 69.1 (5′-C), 71.1 (2′-C), 75.7 (13-C), 78.1 (3-C), 78.5 (11-C), 79.8 (12-C), 80.7 (5-C), 84.6 (6-C), 100.5 (1′-C), 123.5 (3-Py-C), 129.1 (3-Py-C), 136.9 (3-Py-C), 149.0 (3-Py-C), 150.3 (3-Py-C), 153.9 (11-O—*C*O—O), 169.7 (2′-OAc), 169.9 (3-O*C*O—CH_2), 173.7 (1-C), 212.1 (9-C); MS (ESI): *m/z* 776.9 $[M+H]^+$ ($C_{40}H_{61}N_2O_{13}$).

4.2.3 2′-O-Acetyl-3-O-descladinosyl-3-O-(3,4-methylenedioxy)phenylacetyl-6-O-methylerythromycin A 11,12-cyclic carbonate (3b)

To a solution of **2** (300 mg, 0.46 mmol) in CH_2Cl_2 (3 ml), 3,4-(methylenedioxy)phenylacetic acid (247 mg, 1.37 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (263 mg, 1.37 mmol), and DMAP (56 mg, 0.46 mmol) were added. After stirring for 36 h under N_2, the reaction mixture was diluted with CH_2Cl_2 and washed with sat. aqueous NH_4Cl. The evaporation of the organic solvent gave 500 mg of the crude product, which was purified by chromatography on a column of silica gel (CH_2Cl_2/MeOH/Et_3N) to afford **3b** (242 mg, 65%). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.7 (4-CH_3), 10.0 (14-CH_3), 12.7 (10-CH_3), 13.0 (12-CH_3), 15.1 (2-CH_3), 18.2 (8-CH_3), 19.4 (6-CH_3), 20.8 (2′-OAc), 21.3 (5′-CH_3), 21.9 (14-CH_3), 30.3 (4′-C), 36.2 (4-C), 37.4 (10-C), 38.3 (7-C), 40.5 (3′-$N(CH_3)_2$), 41.0 (3-OCO—*C*H_2), 43.1 (2-C), 44.8 (8-C), 49.8 (6-OCH_3), 63.1 (3′-C), 68.8 (5′-C), 71.2 (2′-C), 75.5 (13-C), 77.9 (6-C), 78.1 (3-C), 79.6 (11-C), 80.7 (5-C), 84.6 (12-C), 100.4 (1′-C), 101.1 (O—*C*H_2—O), 108.2 (Ph-C),

109.9 (Ph-C), 122.5 (Ph-C), 126.8 (Ph-C), 146.9 (Ph-C), 147.9 (Ph-C), 153.9 (11-O—*C*O—O), 169.7 (2′-OAc), 170.7 (3-O*C*O—CH_2), 173.8 (1-C), 212.1 (9-C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87 (s, 1H), 6.76 (s, 2H), 5.95 (s, 2H), 5.10 (dd, $J = 2.1$, 11.1 Hz, 1H), 5.03 (d, $J = 11.1$ Hz, 1H), 4.72 (s, 1H), 4.65 (dd, $J = 7.5$, 10.5 Hz, 1H), 3.81 (d, $J = 7.5$ Hz, 1H), 3.68 (d, $J = 3.6$ Hz, 1H), 3.61 (s, 2H), 2.97 (s, 3H, 6-OCH_3), 2.23 (s, 6H, 3′-$N(CH_3)_2$), 2.07 (s, 3H, 2′-OAc); HR-ESI-MS: *m/z* 820.4098 $[M+H]^+$ (calcd for $C_{42}H_{62}NO_{15}$, 820.4113).

*4.2.4 2′-O-Acetyl-3-O-(4-chlorophenyl)acetyl-3-O-descladinosyl-6-O-methylerythromycin A 11,12-cyclic carbonate (**3c**)*

To a solution of **2** (100 mg, 0.152 mmol) in CH_2Cl_2 (1.5 ml), 4-chlorophenylacetic acid (104 mg, 0.61 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (116 mg, 0.61 mmol), and DMAP (18 mg, 0.152 mmol) were added. After stirring for 36 h under N_2, the reaction mixture was diluted with CH_2Cl_2 and washed with sat. aqueous NH_4Cl. The evaporation of the organic solvent gave 150 mg of the crude product, which was purified by chromatography on a column of silica gel (acetone/petroleum ether/triethylamine) to afford **3c** (75 mg, 61%). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.7 (4-CH_3), 10.0 (14-CH_3), 12.7 (10-CH_3), 13.0 (12-CH_3), 15.1 (2-CH_3), 18.2 (8-CH_3), 19.4 (6-CH_3), 20.7 (2′-OAc), 21.5 (5′-CH_3), 21.9 (14-C), 30.2 (4′-C), 36.2 (4-C), 37.4 (10-C), 38.3 (7-C), 40.6 (3′-$N(CH_3)_2$), 40.6 (3-OCO—*C*H_2), 43.1 (2-C), 44.8 (8-C), 49.9 (6-OCH_3), 63.2 (3′-C), 68.7 (5′-C), 75.6 (2′-C), 76.5 (13-C), 78.0 (3-C), 78.2 (11-C), 79.6 (12-C), 80.6 (5-C), 84.6 (6-C), 100.3 (1′-C), 128.8 (3-Ph-C, 2C), 130.8 (3-Ph-C, 2C), 131.7 (3-Ph-C), 133.4 (3-Ph-C), 153.9 (11-O—*C*O—O), 169.8 (2′-OAc), 170.3 (3-O*C*O—CH_2), 173.7 (1-C), 212.1 (9-C); MS (ESI): *m/z* 810.6 $[M+H]^+$ ($C_{41}H_{60}ClNO_{13}$).

*4.2.5 2′-O-Acetyl-11-deoxy-10,11-didehydro-3-O-descladinosyl-3-O-(3-pyridyl)acetyl-6-O-methylerythromycin A (**4a**)*

To a solution of **3a** (170 mg, 0.21 mmol) in 2 ml of acetone,1,8-diazabicyclo[5.4.0]undec-7-ene (320 μg, 2.1 mmol) was added. After stirring for 5 h under N_2, to the reaction mixture, KH_2PO_4 solution and AcOEt were added. The mixture was extracted three times with AcOEt and dried over Na_2SO_4. The evaporation of the organic solvent gave 120 mg of the crude product. After purification on a column of silica gel, a white foam (**4a**) was obtained (110 mg, 72%). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.1 (4-CH_3), 10.6 (14-CH_3), 12.6 (10-CH_3), 13.4 (12-CH_3), 19.7 (2-CH_3), 20.3 (8-CH_3), 20.9 (6-CH_3), 21.3 (2′-OAc), 22.1 (5′-CH_3), 23.0 (14-C), 30.4 (4′-C), 38.3 (4-C, 7-C), 40.5 (7-C), 40.9 (3′-$N(CH_3)_2$, 3-OCO—*C*H_2, 3C), 42.3 (8-C), 49.9 (6-OCH_3), 63.2 (3′-C), 69.1 (5′-C), 71.3 (2′-C), 73.9 (12-C), 75.7 (13-C), 77.5 (3-C), 79.3 (5-C), 82.6 (6-C), 101.8 (1′-C), 123.4 (3-Py-C), 129.1 (3-Py-C), 136.9 (3-Py-C), 139.3 (10-C), 139.7 (11-C), 148.7 (3-Py-C), 150.3 (3-Py-C), 169.8 (2′-OAc), 170.3 (3-O*C*O—CH_2), 173.4 (1-C), 206.9 (9-C); MS (ESI): *m/z* 733.3 $[M+H]^+$ ($C_{39}H_{60}N_2O_{11}$).

*4.2.6 2′-O-Acetyl-11-deoxy-10,11-didehydro-3-O-descladinosyl-3-O-(3,4-methylenedioxy)phenylacetyl-6-O-methylerythromycin A (**4b**)*

To a solution of **3b** (240 mg, 0.29 mmol) in 5 ml of acetone,1,8-diazabicyclo[5.4.0]undec-7-ene (440 μg, 2.93 mmol) was added. After stirring for 5 h under N_2, to the reaction mixture, KH_2PO_4 solution and AcOEt were added. The mixture was extracted three times with AcOEt and dried over Na_2SO_4. The evaporation of the organic solvent gave

192 mg of the crude product. After purification on a column of silica gel, a white foam (**4b**) was obtained (127 mg, 56%). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.9 (4-CH_3), 10.6 (14-CH_3), 13.0 (10-CH_3), 13.5 (12-CH_3), 19.4 (2-CH_3), 20.6 (8-CH_3), 20.9 (6-CH_3), 21.3 (2′-OAc), 22.0 (5′-CH_3), 22.9 (14-C), 30.5 (4′-C), 40.3 (4-C), 40.5 (3C, 3′-$N(CH_3)_2$, 7-C), 40.9 (3-OCO—*C*H_2), 41.6 (8-C), 42.5 (2-C), 50.0 (6-OCH_3), 63.2 (3′-C), 69.0 (5′-C), 71.4 (2′-C), 73.8 (12-C), 75.7 (13-C), 77.9 (3-C), 79.1 (5-C), 82.0 (6-C), 101.0 (O—*C*H_2—O), 101.6 (1′-C), 108.1 (Ph-C), 109.9 (Ph-C), 122.6 (Ph-C), 126.9 (Ph-C), 139.6 (11-C), 139.7 (10-C), 146.8 (Ph-C), 147.7 (Ph-C), 169.7 (2′-OAc), 171.2 (3-O*C*O—CH_2), 173.5 (1-C), 207.0 (9-C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.80 (s, 1H), 6.73 (s, 2H), 6.56 (s, 1H), 5.93 (s, 2H), 5.53 (d, J = 4.5 Hz), 5.07 (dd, J = 2.1, 10.5 Hz, 1H), 4.66 (dd, J = 7.5, 10.5 Hz, 1H), 4.14 (d, J = 7.5 Hz, 1H), 3.55 (s, 2H), 3.48 (d, J = 7.5 Hz, 1H), 2.91 (s, 3H, 6-OCH_3), 2.24 (s, 6H, 3′-$N(CH_3)_2$), 2.05 (s, 3H, 2′-OAc); MS (ESI): *m/z* 776.4 $[M+H]^+$ ($C_{41}H_{61}NO_{13}$).

4.2.7 2′-O-Acetyl-11-deoxy-10,11-didehydro-3-O-descladinosyl-3-O-(4-chlorophenyl)acetyl-6-O-methylerythromycin A (*4c*)

To a solution of **3c** (81 mg, 0.1 mmol) in 1 ml of acetone,1,8-diazabicyclo[5.4.0]undec-7-ene (170 μg, 1.2 mmol) was added. After stirring for 3 h under N_2, to the reaction mixture, KH_2PO_4 solution and AcOEt were added. The mixture was extracted three times with AcOEt and dried over Na_2SO_4. The evaporation of the organic solvent gave 120 mg of the crude product. After purification on a column of silica gel, a white foam (**4c**) was obtained (60 mg, 78%). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.0 (4-CH_3), 10.6 (14-CH_3), 12.7 (10-CH_3), 13.4 (12-CH_3), 19.6 (2-CH_3), 20.3 (8-CH_3), 20.9 (6-CH_3), 21.3 (2′-OAc), 22.0 (5′-CH_3), 23.0 (14-C), 30.4 (4′-C), 40.4 (4-C), 40.5 (7-C), 40.5 (3′-$N(CH_3)_2$, 2C), 40.6 (3-OCO—*C*H_2), 41.9 (2-C), 42.3 (8-C), 49.9 (6-OCH_3), 63.2 (3′-C), 69.0 (5′-C), 71.3 (2′-C), 73.8 (12-C), 75.6 (13-C), 77.5 (3-C), 79.2 (5-C), 82.4 (6-C), 101.7 (1′-C), 128.6 (3-Ph-C, 2C), 130.8 (3-Ph-C, 2C), 131.8 (3-Ph-C), 133.2 (3-Ph-C), 139.4 (10-C), 139.6 (11-C), 169.7 (2′-OAc), 170.7 (3-O*C*O—CH_2), 173.5 (1-C), 206.9 (9-C); MS (ESI): *m/z* 766.3 $[M+H]^+$ ($C_{40}H_{60}ClNO_{11}$).

4.2.8 2′-O-Acetyl-11-deoxy-3-O-descladinosyl-10,11-didehydro-3-O-(3-pyridyl)acetyl-6-O-methyl-12-(1H-imidazole-1-carboxylate)erythromycin A (*5a*)

A solution of sodium hydride (5.2 mg, 0.13 mmol) in 0.5 ml DMF was stirred for 10 min at −20°C under nitrogen atmosphere. The mixture was added dropwise to a solution of compound **4a** (50 mg, 0.068 mmol) in 0.5 ml DMF. After stirring for 30 min, a solution of CDI (33 mg, 0.2 mmol) in 0.5 ml DMF was added dropwise in a flask. The reaction mixture was stirred for 1 h at −20°C. Then, the reaction mixture was extracted with 5% KH_2PO_4 and EtOAc. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness. The crude product was purified by chromatography on a column of silica gel eluted with 1:1:0.5% acetone/petroleum ether/triethylamine. Thirty-five milligrams (62%) of compound **5a** were obtained as a white foam. ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.9 (4-CH_3), 10.2 (14-CH_3), 13.5 (10-CH_3), 15.0 (12-CH_3), 18.5 (2-CH_3), 19.8 (8-CH_3), 20.7 (6-CH_3), 21.5 (2′-OAc), 22.4 (5′-CH_3, 14-C, 2C), 30.4 (4′-C), 37.4 (4-C), 38.5 (7-C, 2-C, 2C), 39.2 (3-OCO—*C*H_2), 40.4 (3′-$N(CH_3)_2$), 42.9 (8-C), 50.5 (6-OCH_3), 63.2 (3′-C), 68.8 (5′-C), 70.5 (2′-C), 75.8 (12-C), 78.0 (13-C), 78.3 (3-C), 79.0 (5-C), 84.3 (6-C), 100.7 (1′-C), 117.0 (12-imidazole-C), 123.6 (3-Py-C), 129.3 (3-Py-C), 130.8 (12-imidazole-C), 136.9 (12-imidazole-C), 137.0 (3-Py-C), 137.6 (10-C), 139.3 (11-C), 145.8 (12-O*C*O—N), 149.0 (3-Py-C), 150.2

(3-Py-C), 169.8 (2′-OAc), 170.1 (3-O*C*O), 172.7 (1-C), 204.5 (9-C); MS (ESI): *m/z* 827.5 $[M+H]^+$ ($C_{43}H_{62}N_4O_{12}$).

*4.2.9 2′-O-Acetyl-11-deoxy-3-O-descladinosyl-10,11-didehydro-3-O-(3,4-methylenedioxy)phenylacetyl-6-O-methyl-12-(1H-imidazole-1-carboxylate) erythromycin A (**5b**)*

A solution of sodium hydride (34 mg, 1.34 mmol) in 1.5 ml DMF was stirred for 10 min at −20°C under nitrogen atmosphere. The mixture was added dropwise to a solution of compound **4b** (550 mg, 0.67 mmol) in 5 ml DMF. After stirring for 30 min, a solution of CDI (345 mg, 2.0 mmol) in 3 ml DMF was added dropwise in a flask. The reaction mixture was stirred for 1 h at −20°C. Then, the reaction mixture was extracted with 5% KH_2PO_4 and EtOAc. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness. The product was purified by chromatography on a column of silica gel eluted with 60:1:0.5% DCM/MeOH/triethylamine to afford compound **5b** (214 mg, 55%) as a white foam. ^{13}C NMR (125 MHz, $CDCl_3$): δ 8.9 (4-CH_3), 10.2 (14-CH_3), 13.5 (10-CH_3), 15.0 (12-CH_3), 18.4 (2-CH_3), 19.8 (8-CH_3), 20.8 (6-CH_3), 21.0 (2′-OAc), 21.3 (5′-CH_3), 22.4 (14-C), 30.3 (4′-C), 37.4 (4-C), 38.4 (7-C), 40.5 (3′-$N(CH_3)_2$), 40.6 (3-OCO—*C*H_2), 41.1 (2-C), 42.9 (8-C), 50.6 (6-OCH_3), 63.2 (3′-C), 68.8 (5′-C), 71.2 (2′-C), 75.6 (12-C), 77.5 (13-C), 78.3 (3-C), 79.0 (5-C), 84.3 (6-C), 100.9 (1′-C), 101.1 (O—*C*H_2—O), 108.2 (Ph-C), 109.9 (Ph-C), 117.0 (imidazole-C), 122.5 (Ph-C), 127.0 (Ph-C), 130.5 (imidazole-C), 136.9 (imidazole-C), 137.2 (11-C), 139.3 (10-C), 145.8 (12-O*C*O—N), 146.9 (Ph-C), 147.9 (Ph-C), 169.7 (2′-OAc), 171.0 (3-O*C*O—CH_2), 172.8 (1-C), 204.5 (9-C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, imidazole-H, 1H), 7.35 (s, imidazole-H, 1H), 7.06 (s, imidazole-H, 1H), 6.86 (s, ph-H, 1H), 6.76 (s, ph-H, 2H), 6.65 (s, 11-H, 1H), 5.95 (s, O—CH_2—O, 2H), 5.86 (dd, J = 2.7, 9.9 Hz, 13-H, 1H), 5.06 (d, J = 9.9 Hz, 1H), 4.63 (dd, J = 7.5, 10.2 Hz, 2′-H, 1H), 3.14 (s, 6-OCH_3, 3H), 2.23 (s, 3′-$N(CH_3)_2$, 6H), 2.04 (s, 2′-OAc, 3H); MS (ESI): *m/z* 870.5 $[M+H]^+$ ($C_{45}H_{63}N_3O_{14}$).

*4.2.10 2′-O-Acetyl-3-O-(4-chlorophenyl)acetyl-11-deoxy-3-O-descladinosyl-10,11-didehydro-6-O-methyl-12-(1H-imidazole-1-carboxylate)erythromycin A (**5c**)*

A solution of sodium hydride (3.8 mg, 0.095 mmol) in 0.5 ml DMF was stirred for 10 min at −20°C under nitrogen atmosphere. The mixture was added dropwise to a solution of compound **4c** (40 mg, 0.05 mmol) in 0.5 ml DMF. After stirring for 30 min, a solution of CDI (24 mg, 0.15 mmol) in 0.5 ml DMF was added dropwise in a flask. The reaction mixture was stirred for 1 h at −20°C. Then, the reaction mixture was extracted with 5% KH_2PO_4 and EtOAc. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness. The product was purified by chromatography on a column of silica gel eluted with 1:1:0.5% acetone/petroleum ether/triethylamine to afford compound **5c** (30 mg, 63%) as a white foam. ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.9 (4-CH_3), 10.2 (14-CH_3), 13.5 (10-CH_3), 15.0 (2-CH_3), 19.8 (12-CH_3), 20.8 (8-CH_3), 21.3 (6-CH_3), 21.8 (2′-OAc), 22.4 (5′-CH_3), 22.6 (14-C), 30.2 (4′-C), 37.4 (4-C), 38.5 (7-C), 39.3 (3-OCO—*C*H_2), 40.5 (3′-$N(CH_3)_2$), 41.7 (2-C), 42.9 (8-C), 50.5 (6-OCH_3), 63.3 (3′-C), 68.8 (5′-C), 71.1 (2′-C), 75.7 (12-C), 77.2 (13-C), 77.7 (3-C), 78.2 (5-C), 84.3 (6-C), 100.9 (1′-C), 117.0 (12-imidazole-C), 128.6 (10-C), 128.8 (3-Ph-C, 2C), 130.7 (12-imidazole-C), 130.8 (3-Ph-C, 2C), 131.9 (3-Ph-C), 133.3 (3-Ph-C), 136.9 (12-imidazole-C), 137.6 (11-C), 145.8 (12-O*C*O—N), 169.7 (2′-OAc), 170.5 (3-O*C*O—CH_2), 172.8 (1-C), 204.5 (9-C); MS (ESI): *m/z* 860.4 $[M+H]^+$ ($C_{44}H_{62}ClN_3O_{12}$).

*4.2.11 2′-O-Acetyl-3-O-(4-chlorophenyl)acetyl-3-O-descladinosyl-11,12-dideoxy-6-O-methyl-12,11-(oxycarbonyl((4-phenylbutyl)imino)) erythromycin A (**6a**)*

To a solution of **5c** (50 mg, 0.058 mmol) in 1 ml CH_3CN:H_2O (10:1), 4-phenylbutylamine (34.6 mg, 0.232 mmol) was added dropwise. After stirring for 5 h at 50°C, the aqueous solution was extracted with 5% KH_2PO_4 and EtOAc. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness. The product was purified by chromatography on a column of silica gel eluted with 1:3:0.5% acetone/petroleum ether/triethylamine to afford compound **6a** (30 mg, 55%) as a white foam. ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.6 (4-CH_3), 10.1 (14-CH_3), 14.2 (10-CH_3), 14.3 (2-CH_3), 15.1 (12-CH_3), 18.8 (8-CH_3), 19.4 (6-CH_3), 20.8 (2′-OAc), 20.4 (5′-CH_3), 22.0 (14-C), 26.9 (11-$NCH_2CH_2CH_2CH_2$-Ph), 30.3 (4′-C), 35.5 (11-$NCH_2CH_2CH_2$-CH_2Ph), 35.9 (11-$NCH_2CH_2CH_2CH_2$Ph), 38.0 (4-C), 38.7 (10-C), 39.3 (C-7), 40.5 (3-OCO—CH_2), 40.7 (3′-$N(CH_3)_2$), 42.9 (2-C), 43.3 (8-C), 45.5 (11-$NCH_2CH_2CH_2$-CH_2Ph), 49.9 (6-OCH_3), 60.2 (C-11), 63.2 (3′-C), 68.9 (5′-C), 71.2 (2′-C), 77.2 (13-C), 78.0 (12-C), 78.3 (3-C), 78.9 (5-C), 82.4 (6-C), 100.4 (1′-C), 125.5 (11,12-Ph-C), 128.1 (11,12-Ph-C, 2C), 128.3 (11,12-Ph-C, 2C), 128.7 (3-Ph-C,2C), 128.8 (3-Ph-C), 130.7 (3-Ph-C), 131.7 (3-Ph-C), 133.5 (3-Ph-C), 142.4 (11,12-Ph-C), 157.2 (12-OCO—N), 169.7 (2′-OAc), 170.4 (3-OCO—CH_2), 173.8 (1-C), 215.5 (9-C); MS (ESI): *m/z* 941.4 $[M+H]^+$ ($C_{51}H_{73}ClN_2O_{12}$).

*4.2.12 2′-O-Acetyl-3-O-(4-chlorophenyl)acetyl-3-O-descladinosyl-11,12-dideoxy-6-O-methyl-12,11-(oxycarbonyl((4-(3H-imidazoly(4,5-b)pyridin-3-yl)butyl)imino))erythromycin A (**6b**)*

To a solution of **5c** (100 mg, 0.116 mmol) in 1.5 ml CH_3CN:H_2O (10:1), 4-(3H-imidazoly(4,5-b)pyridin-3-yl)butylamine (90 mg, 0.464 mmol) was added. After stirring for 36 h at room temperature, the reaction solution was extracted with 5% KH_2PO_4 and EtOAc. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness. The product was purified by chromatography on a column of silica gel eluted with 1:3:0.5% acetone/petroleum ether/triethylamine to afford compound **6b** (80 mg, 77%) as a white foam. ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.6 (4-CH_3), 10.2 (14-CH_3), 14.2 (10-CH_3, 2-CH_3, 2C), 15.0 (12-CH_3), 18.8 (8-CH_3), 19.4 (6-CH_3), 20.7 (2′-OAc), 21.3 (5′-CH_3), 21.9 (14-C), 24.4 (11-$NCH_2CH_2CH_2CH_2$Ar), 27.4 (11-$NCH_2CH_2CH_2CH_2$Ar), 30.3 (4′-C), 36.0 (4-C), 38.0 (10-C), 38.7 (C-7), 40.5 (3-OCO—CH_2), 40.6 (3′-$N(CH_3)_2$), 42.7 (2-C), 42.8 (8-C), 43.3 (11-$NCH_2CH_2CH_2$-CH_2Ar), 45.5 (11-$NCH_2CH_2CH_2CH_2$Ar), 50.0 (6-OCH_3), 60.1 (C-11), 63.2 (3′-C), 68.9 (5′-C), 71.1 (2′-C), 77.2 (13-C), 77.8 (12-C), 78.3 (3-C), 78.8 (5-C), 82.5 (6-C), 100.5 (1′-C), 117.9 (11,12-Ar-C), 127.7 (11,12-Ar-C), 128.8 (3-Ph-C), 130.7 (3-Ph-C, 2C), 131.7 (3-Ph-C, 2C), 133.4 (3-Ph-C), 135.4 (11,12-Ar-C), 144.0 (11,12-Ar-C, 2C), 146.9 (11,12-Ar-C), 157.2 (12-OCO—N), 169.6 (2′-OAc), 170.4 (3-OCO—CH_2), 174.0 (1-C), 215.7 (9-C); MS (ESI): *m/z* 982.4 $[M+H]^+$ ($C_{51}H_{72}ClN_5O_{12}$).

*4.2.13 2′-O-Acetyl-3-O-(4-chlorophenyl)acetyl-3-O-descladinosyl-11,12-dideoxy-6-O-methyl-12,11-(oxycarbonyl((4-phenyl-1H-1-imidazoyl)butyl)imino)erythromycin A (**6c**)*

To a solution of **5c** (50 mg, 0.058 mmol) in 0.5 ml CH_3CN:H_2O (10:1), (4-phenyl-1H-1-imidazoyl)butylamine (50 mg, 0.232 mmol) was added. After stirring for 36 h at room temperature, the reaction solution was extracted with 5% KH_2PO_4 and EtOAc. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness.

The product was purified by chromatography on a column of silica gel eluted with 1:2:0.5% acetone/petroleum ether/triethylamine to afford compound **6c** (40 mg, 69%) as a white foam. ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.6 (4-CH_3), 10.2 (14-CH_3), 14.2 (10-CH_3), 14.3 (2-CH_3), 15.0 (12-CH_3), 18.8 (8-CH_3), 19.4 (6-CH_3), 20.7 (2′-OAc), 21.3 (5′-CH_3), 22.0 (14-C), 24.3 (11-$NCH_2CH_2CH_2CH_2Ar$), 28.7 (11-$NCH_2CH_2CH_2CH_2Ar$), 30.4 (4′-C), 36.1 (4-C), 38.1 (10-C), 38.8 (C-7), 40.5 (3′-$N(CH_3)_2$), 40.7 (3-OCO—CH_2), 42.7 (2-C), 42.9 (8-C), 45.5 (11-$NCH_2CH_2CH_2CH_2Ar$), 46.7 (11-$NCH_2CH_2CH_2CH_2Ar$), 50.0 (6-OCH_3), 60.2 (C-11), 63.3 (3′-C), 68.9 (5′-C), 71.2 (2′-C), 76.6 (13-C), 77.9 (12-C), 78.4 (3-C), 78.9 (5-C), 82.6 (6-C), 100.5 (1′-C), 114.7 (11,12-Ar-C), 124.7 (11,12-Ar-C, 2C), 126.4 (11,12-Ar-C), 128.4 (11,12-Ar-C, 2C), 128.8 (3-Ph-C, 2C), 130.7 (3-Ph-C), 131.7 (3-Ph-C), 133.5 (3-Ph-C, 2C), 134.4 (11,12-Ar-C), 137.2 (11,12-Ar-C), 142.2 (11,12-Ar-C), 157.3 (12-OCO—N), 169.6 (2′-OAc), 170.4 (3-OCO—CH_2), 174.2 (1-C), 215.7 (9-C); MS (ESI): *m/z* 1007.5 $[M+H]^+$ ($C_{54}H_{76}ClN_4O_{12}$).

*4.2.14 2′-O-Acetyl-3-O-descladinosyl-11,12-dideoxy-6-O-methyl-12,11-(oxycarbonyl((4-phenylbutyl)imino))-3-O-(3-pyridyl)acetylerythromycin A (**6d**)*

To a solution of **5a** (50 mg, 0.06 mmol) in 1 ml CH_3CN:H_2O (10:1), 4-phenylbutylamine (36 mg, 0.24 mmol) was added dropwise. After stirring for 5 h at 50°C, the reaction solution was extracted with 5% KH_2PO_4 and EtOAc. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness. The product was purified by chromatography on a column of silica gel eluted with 1:1:0.5% acetone/petroleum ether/triethylamine to afford compound **6d** (48 mg, 87%) as a white foam. ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.7 (4-CH_3), 10.1 (14-CH_3), 14.2 (10-CH_3), 14.3 (2-CH_3), 15.1 (12-CH_3), 18.8 (8-CH_3), 19.5 (6-CH_3), 20.6 (2′-OAc), 21.7 (5′-CH_3), 22.0 (14-C), 26.9 (11-$NCH_2CH_2CH_2CH_2Ph$), 29.0 (11-$NCH_2CH_2CH_2CH_2Ph$), 30.4 (4′-C), 35.5 (4-C), 35.9 (10-C), 37.9 (C-7), 38.4 (3-OCO—CH_2), 38.7 (3′-$N(CH_3)_2$, 2C), 40.2 (2-C), 42.9 (8-C), 43.3 (11-$NCH_2CH_2CH_2CH_2Ph$), 45.4 (11-$NCH_2CH_2CH_2CH_2Ph$), 49.9 (6-OCH_3), 60.2 (C-11), 62.9 (3′-C), 68.4 (5′-C, 2′-C, 2C), 76.6 (13-C), 78.1 (12-C), 78.4 (3-C), 79.2 (5-C), 82.3 (6-C), 100.0 (1′-C), 123.8 (3-Py-C), 125.5 (11,12-Ar-C), 128.1 (11,12-Ar-C, 2C), 128.3 (11,12-Ar-C, 2C), 129.2 (3-Py-C), 137.2 (3-Py-C), 142.4 (11,12-Ar-C), 149.2 (3-Py-C), 150.1 (3-Py-C), 157.2 (12-OCO—N), 170.0 (2′-OAc), 170.1 (3-OCO—CH_2), 173.7 (1-C), 215.4 (9-C); MS (ESI): *m/z* 930.4 $[M+Na]^+$ ($C_{50}H_{73}O_{12}N_3Na$).

*4.2.15 2′-O-Acetyl-3-O-descladinosyl-11,12-dideoxy-6-O-methyl-12,11-(oxycarbonyl((4-(3H-imidazoly(4,5-b)pyridin-3-yl)butyl)imino))-3-O-(3-pyridyl)acetylerythromycin A (**6e**)*

To a solution of **5a** (150 mg, 0.18 mmol) in 2.5 ml CH_3CN:H_2O (10:1), 4-(3H-imidazoly(4,5-b)pyridin-3-yl)butylamine (140 mg, 0.72 mmol) was added. After stirring for 36 h at room temperature, the reaction solution was extracted with 5% KH_2PO_4 and EtOAc. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness. The product was purified by chromatography on a column of silica gel eluted with 1:1:0.5% acetone/petroleum ether/triethylamine to afford compound **6e** (80 mg, 47%) as a white foam. ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.7 (4-CH_3), 10.2 (14-CH_3), 14.2 (10-CH_3), 14.3 (2-CH_3), 15.2 (12-CH_3), 18.8 (8-CH_3), 19.5 (6-CH_3), 20.6 (2′-OAc), 21.8 (5′-CH_3), 21.9 (14-C), 24.4 (11-$NCH_2CH_2CH_2CH_2Ar$), 27.4 (11-$NCH_2CH_2CH_2CH_2Ar$), 30.4 (4′-C), 35.9 (4-C), 37.8 (10-C), 38.4 (C-7), 38.7 (3-OCO—CH_2, 3′-$N(CH_3)_2$), 42.6 (2-C), 42.9

(8-C), 43.3 (11-NCH$_2$CH$_2$CH$_2$*C*H$_2$Ar), 45.4 (11-N*C*H$_2$CH$_2$CH$_2$CH$_2$Ar), 50.0 (6-OCH$_3$), 60.0 (C-11), 62.8 (3′-C), 68.2 (5′-C, 2′-C), 76.6 (13-C), 78.1 (12-C), 78.3 (3-C), 79.1 (5-C), 82.5 (6-C), 99.8 (1′-C), 118.0 (11,12-Ar-C), 123.9 (Py-C), 127.7 (11,12-Ar-C), 129.2 (Py-C), 135.4 (11,12-Ar-C), 137.3 (Py-C), 144.0 (11,12-Ar-C), 146.9 (11,12-Ar-C), 149.4 (Py-C), 150.0 (Py-C), 157.2 (12-OCO—N), 170.1 (2′-OAc), 170.3 (3-O*C*O—CH$_2$), 173.9 (1-C), 215.6 (9-C); ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.58–8.53 (m, Py-H, Ar-H, 3H), 8.14 (s, Ar-H, 1H), 7.79–7.72 (m, Ar-H, Py-H, 2H), 7.31 (dd, $J = 4.8$, 8.1 Hz, Py-H, 1H), 7.19 (dd, $J = 4.8$, 8.1 Hz, Ar-H, 1H), 4.67 (dd, $J = 7.5$, 10.5 Hz, 2′-H, 1H), 3.89 (d, $J = 7.5$ Hz, 1′-H, 1H), 3.73 (s, 3-OCO—C*H*$_2$, 2H), 2.93 (s, 6-OCH$_3$, 3H), 2.26 (s, 3′-N(CH$_3$)$_2$, 6H), 2.09 (s, 2′-OAc, 3H); MS (ESI): *m/z* 949.5 $[M+H]^+$ ($C_{50}H_{72}N_6O_{12}$).

*4.2.16 2′-O-Acetyl-3-O-descladinosyl-11,12-dideoxy-6-O-methyl-12,11-(oxycarbonyl(((4-phenyl-1H-1-imidazoyl)butyl)imino))-3-O-(3-pyridyl)acetylerythromycin A (**6f**)*

To a solution of **5a** (120 mg, 0.14 mmol) in 2 ml CH$_3$CN:H$_2$O (10:1), (4-phenyl-1H-1-imidazoyl)butylamine (156 mg, 0.72 mmol) was added. After stirring for 36 h at room temperature, the reaction solution was extracted with 5% KH$_2$PO$_4$ and EtOAc. The organic phase was washed with brine, dried over anhydrous Na$_2$SO$_4$, and evaporated to dryness. The product was purified by chromatography on a column of silica gel eluted with 1:1:0.5% acetone/petroleum ether/triethylamine to afford compound **6f** (56 mg, 42%) as a white foam. ^{13}C NMR (75 MHz, CDCl$_3$): δ 8.8 (4-CH$_3$), 10.3 (14-CH$_3$), 14.2 (10-CH$_3$), 14.3 (2-CH$_3$), 15.2 (12-CH$_3$), 18.8 (8-CH$_3$), 19.5 (6-CH$_3$), 20.5 (2′-OAc), 21.9 (5′-CH$_3$, 14-C, 2C), 24.2 (11-NCH$_2$CH$_2$*C*H$_2$CH$_2$Ar), 28.5 (11-NCH$_2$*C*H$_2$CH$_2$CH$_2$Ar), 29.6 (4′-C), 35.9 (4-C), 37.8 (10-C), 38.4 (C-7), 38.7 (3-OCO—*C*H$_2$, 3′-N(CH$_3$)$_2$, 3C), 42.6 (2-C), 42.9 (8-C), 45.4 (11-NCH$_2$CH$_2$CH$_2$*C*H$_2$-Ar), 47.0 (11-N*C*H$_2$CH$_2$CH$_2$CH$_2$Ar), 50.0 (6-OCH$_3$), 60.1 (C-11), 62.7 (3′-C), 67.9 (5′-C, 2′-C, 2C), 76.6 (13-C), 78.2 (12-C), 78.3 (3-C), 79.1 (5-C), 82.5 (6-C), 99.5 (1′-C), 114.8 (11,12-Ar-C), 124.0 (3-Py-C), 124.8 (11,12-Ar-C, 3C), 126.9 (11,12-Ar-C), 128.4 (11,12-Ar-C, 3C), 129.2 (3-Py-C), 136.9 (3-Py-C), 137.2 (11,12-Ar-C), 149.9 (3-Py-C), 151.9 (3-Py-C), 157.3 (12-O*C*O—N), 170.2 (2′-OAc), 170.3 (3-O*C*O—CH$_2$), 174.1 (1-C), 215.6 (9-C); MS (ESI): *m/z* 974.8 $[M+H]^+$ ($C_{53}H_{75}N_5O_{12}$).

*4.2.17 2′-O-Acetyl-3-O-descladinosyl-11,12-dideoxy-6-O-methyl-12,11-(oxycarbonyl((4-(1H-imidazoly(4,5-b)pyridin-1-yl)butyl)imino))-3-O-(3-pyridyl)acetylerythromycin A (**6g**)*

To a solution of **5a** (73 mg, 0.088 mmol) in 1.5 ml CH$_3$CN:H$_2$O (10:1), 4-(3H-imidazoyl(4,5-b)pyridin-1-yl)butylamine (67.7 mg, 0.356 mmol) was added. After stirring overnight at 60°C, the reaction solution was extracted with 5% KH$_2$PO$_4$ and EtOAc. The organic phase was washed with brine, dried over anhydrous Na$_2$SO$_4$, and evaporated to dryness. The product was purified by chromatography on a column of silica gel eluted with 30:1:0.5% DCM/MeOH/triethylamine to afford compound **6g** (32 mg, 38%) as a white foam. ^{13}C NMR (75 MHz, CDCl$_3$): δ 8.6 (4-CH$_3$), 10.2 (14-CH$_3$), 14.2 (10-CH$_3$, 12-CH$_3$), 15.0 (2-CH$_3$), 18.8 (8-CH$_3$), 19.4 (6-CH$_3$), 20.7 (2′-OAc), 21.4 (5′-CH$_3$), 21.9 (14-C), 24.4 (11-NCH$_2$CH$_2$*C*H$_2$CH$_2$-Ar), 27.4 (11-NCH$_2$*C*H$_2$CH$_2$CH$_2$Ar), 30.2 (4′-C), 36.0 (4-C), 38.0 (10-C), 38.4 (3-OCO—*C*H$_2$), 38.7 (7-C), 40.5 (3′-N(CH$_3$)$_2$), 42.7 (11-NCH$_2$CH$_2$CH$_2$*C*H$_2$-Ar), 42.8 (2-C), 43.3 (8-C), 45.5 (11-N*C*H$_2$CH$_2$CH$_2$CH$_2$Ar), 49.9 (6-OCH$_3$), 60.1 (11-C), 63.2 (3′-C), 69.1 (5′-C), 71.1 (2′-C), 76.7 (13-C), 78.2 (6-C), 78.3 (3-C),

78.9 (5-C), 82.5 (12-C), 100.6 (1′-C), 118.0 (11,12-Ar-C), 123.5 (Py-C), 127.7 (11,12-Ar-C), 129.0 (Py-C), 135.4 (11,12-Ar-C), 136.9 (Py-C), 144.0 (11,12-Ar-C), 144.0 (11,12-Ar-C), 146.9 (11,12-Ar-C), 148.9 (Py-C), 150.2 (Py-C), 157.2 (12-OCO—N), 169.7 (2′-OAc), 170.0 (3-O*C*O—CH_2), 173.9 (1-C), 215.7 (9-C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57–8.54 (m, Py-H, 2H), 8.35 (dd, $J = 1.2$, 4.8 Hz, Ar-H, 1H), 8.08 (s, Ar-H, 1H), 8.02 (dd, $J = 1.2$, 8.1 Hz, Ar-H, 1H), 7.74 (d, $J = 7.8$ Hz, Py-H, 1H), 7.30 (dd, $J = 4.8$, 7.2 Hz, Py-H, 1H), 7.19 (dd, $J = 4.8$, 8.1 Hz, Ar-H, 1H), 4.66 (dd, $J = 7.5$, 10.5 Hz, 2′-H, 1H), 3.87 (d, $J = 7.5$ Hz, 1′-H, 1H), 3.72 (s, 3-OCO—C*H*$_2$, 2H), 2.91 (s, 6-OCH_3, 3H), 2.24 (s, 3′-$N(CH_3)_2$, 6H), 2.08 (s, 2′-OAc, 3H); HR-ESI-MS: *m/z* 949.5251 $[M+H]^+$ (calcd for $C_{50}H_{73}N_6O_{12}$, 949.5286).

*4.2.18 2′-O-Acetyl-3-O-descladinosyl-11,12-dideoxy-6-O-methyl-3-O-(3,4-methylenedioxy)phenylacetyl-12,11-(oxycarbonyl((4-(1H-imidazoly(4,5-b)pyridin-1-yl)butyl)imino))erythromycin A (**6h**)*

To a solution of **5b** (146 mg, 0.168 mmol) in 4 ml CH_3CN:H_2O (10:1), 4-(1H-imidazoly(4,5-b)pyridin-1-yl)butylamine (128 mg, 0.67 mmol) was added. After stirring overnight at 60°C, the aqueous solution was extracted with 5% KH_2PO_4 and EtOAc. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness. The product was purified by column chromatography eluted with 60:1:0.5% DCM/MeOH/triethylamine to afford compound **6h** (57.9 mg, 35%) as a white foam. ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.6 (4-CH_3), 10.3 (14-CH_3), 14.1 (10-CH_3), 14.2 (10-CH_3), 15.0 (12-CH_3), 18.8 (8-CH_3), 19.5 (6-CH_3), 20.8 (2′-OAc), 21.3 (5′-CH_3), 21.9 (14-C), 24.4 (11-NCH_2CH_2*C*H_2CH_2Ar), 27.6 (11-NCH_2*C*$H_2CH_2CH_2$Ar), 30.3 (4′-C), 36.1 (4-C), 38.0 (10-C), 38.8 (7-C), 40.5 (3′-$N(CH_3)_2$), 41.1 (3-OCO—*C*H_2), 42.4 (2-C), 42.9 (8-C), 45.1 (11-$NCH_2CH_2CH_2$*C*H_2Ar), 45.6 (11-N*C*$H_2CH_2CH_2CH_2$Ar), 50.1 (6-OCH_3), 60.0 (11-C), 63.1 (3′-C), 68.9 (5′-C), 71.2 (2′-C), 76.7 (13-C), 77.6 (6-C), 78.5 (3-C), 78.8 (5-C), 82.7 (12-C), 100.5 (1′-C), 101.1 (O—CH_2—O), 108.3 (Ph-C), 109.8 (Ph-C), 117.9 × 2(11,12-Ar-C), 122.5 (Ph-C), 126.1 (11,12-Ar-C), 126.7 (Ph-C), 144.8 (11,12-Ar-C), 145.0 (11,12-Ar-C), 147.0 (Ph-C), 147.9 (Ph-C), 156.3 (11,12-Ar-C), 157.4 (12-OCO—N), 169.8 (2′-OAc), 171.0 (3-O*C*O—CH_2), 174.4 (1-C), 215.8 (9-C); HR-ESI-MS: *m/z* 992.5266 $[M+H]^+$ (calcd for $C_{52}H_{74}N_5O_{14}$, 992.5232).

*4.2.19 2′-O-Acetyl-3-O-descladinosyl-11,12-dideoxy-6-O-methyl-3-O-(3,4-methylenedioxy)phenylacetyl-12,11-(oxycarbonyl((4-(3H-imidazoly(4,5-b)pyridin-3-yl)butyl)imino))erythromycin A (**6i**)*

To a solution of **5b** (102 mg, 0.117 mmol) in 3 ml CH_3CN:H_2O (10:1), 4-(3H-imidazoyl(4,5-b)pyridin-3-yl)butylamine (90 mg, 0.47 mmol) was added. After stirring overnight at 60°C, the aqueous mixture was extracted with 5% KH_2PO_4 and EtOAc. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness. The product was purified by column chromatography eluted with 60:1:0.5% DCM/MeOH/triethylamine to afford compound **6i** (33.8 mg, 29%) as a white foam. ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.6 (4-CH_3), 10.2 (14-CH_3), 14.2 (10-CH_3), 14.2 (12-CH_3), 15.0 (2-CH_3), 18.8 (8-CH_3), 19.5 (6-CH_3), 20.8 (2′-OAc), 21.3 (5′-CH_3), 21.9 (14-C), 24.4 (11-NCH_2-CH_2*C*H_2CH_2Ar), 27.4 (11-NCH_2*C*H_2-CH_2CH_2Ar), 30.3 (4′-C), 36.0 (4-C), 38.0 (10-C), 38.7 (7-C), 40.5 (3′-$N(CH_3)_2$), 41.1 (3-OCO—*C*H_2), 42.7 (11-$NCH_2CH_2CH_2$*C*H_2Ar), 42.9 (2-C), 43.3 (8-C), 45.5 (11-N*C*$H_2CH_2CH_2CH_2$

Ar), 50.0 (6-OCH_3), 60.1 (11-C), 63.1 (3′-C), 68.9 (5′-C), 71.2 (2′-C), 76.6 (13-C), 77.6 (6-C), 78.3 (3-C), 78.9 (5-C), 82.6 (12-C), 100.5 (1′-C), 101.1 (O—CH_2—O), 108.2 (Ph-C), 109.8 (Ph-C), 118.0 (11,12-Ar-C), 122.5 (Ph-C), 126.7 (Ph-C), 127.7 (11,12-Ar-C), 135.4 (11,12-Ar-C), 144.0 (11,12-Ar-C), 144.1 (11,12-Ar-C), 146.9 (Ph-C), 146.9 (11,12-Ar-C), 147.9 (Ph-C), 157.3 (12-OCO—N), 169.8 (2′-OAc), 170.9 (3-O*C*O—CH_2), 174.1 (1-C), 215.7 (9-C); HR-ESI-MS: *m/z* 992.5234 $[M+H]^+$ (calcd for $C_{52}H_{74}N_5O_{14}$, 992.5232).

*4.2.20 3-O-(4-Chlorophenyl)acetyl-3-O-descladinosyl-11,12-dideoxy-6-O-methyl-12,11-(oxycarbonyl((4-phenylbutyl) imino))erythromycin A (**7a**)*

A solution of compound **6a** (137 mg, 0.148 mmol) in 3 ml MeOH was refluxed for 3 h. After evaporation of the solvent, the residue was purified by column chromatography eluted with 60:1:0.5% DCM/MeOH/triethylamine to afford compound **7a** (100 mg, 76%) as a white foam. ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.8 (4-CH_3), 10.1 (14-CH_3), 14.2 (10-CH_3), 14.3 (2-CH_3), 14.9 (12-CH_3), 18.8 (8-CH_3), 19.5 (6-CH_3), 21.0 (5′-CH_3), 22.0 (14-C), 26.9 (11-$NCH_2CH_2CH_2CH_2Ph$), 29.0 (4′-C), 35.5 (11-$NCH_2CH_2CH_2CH_2Ph$), 36.2 (11-$NCH_2CH_2CH_2CH_2Ph$), 38.4 (4-C), 38.8 (10-C), 40.2 (C-7), 40.6 (3-OCO—CH_2), 40.2 (3′-$N(CH_3)_2$), 42.9 (2-C), 43.3 (8-C), 45.5 (11-$NCH_2CH_2CH_2CH_2Ph$), 50.0 (6-OCH_3), 60.2 (C-11), 65.9 (3′-C), 69.3 (5′-C), 70.3 (2′-C), 76.6 (13-C), 78.2 (3-C), 78.2 (12-C), 80.6 (5-C), 82.5 (6-C), 103.4 (1′-C), 125.5 (11,12-Ph-C, 2C), 128.1 (11,12-Ph-C, 2C), 128.4 (11,12-Ph-C, 2C), 128.7 (3-Ph-C, 2C), 130.8 (3-Ph-C), 131.9 (3-Ph-C), 133.3 (3-Ph-C), 142.5 (11,12-Ph-C), 157.3 (12-O*C*O—N), 170.8 (3-O*C*O—CH_2), 173.9 (1-C), 215.6 (9-C); HR-ESI-MS: *m/z* 899.4794 $[M+H]^+$ (calcd for $C_{49}H_{72}ClN_2O_{11}$, 899.4819).

*4.2.21 3-O-(4-Chlorophenyl)acetyl-3-O-descladinosyl-11,12-dideoxy-6-O-methyl-12,11-(oxycarbonyl((4-(3H-imidazoly (4,5-b)pyridin-3-yl)butyl)imino)) erythromycin A (**7b**)*

The title compound **7b** was prepared from **6b** (60 mg, 0.061 mmol) following the procedure used to prepare **7a** (70% yield). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.8 (4-CH_3), 10.2 (14-CH_3), 14.1 (10-CH_3), 14.2 (2-CH_3), 14.9 (12-CH_3), 18.8 (8-CH_3), 19.5 (6-CH_3), 21.0 (5′-CH_3), 21.9 (14-C), 24.4 (11-$NCH_2CH_2CH_2CH_2CH_2Ar$), 27.4 (11-$NCH_2CH_2CH_2CH_2CH_2Ar$), 28.2 (4′-C), 36.2 (4-C), 38.4 (10-C), 38.7 (C-7), 40.2 (3-OCO—CH_2), 40.6 (3′-$N(CH_3)_2$), 42.7 (2-C), 42.9 (8-C), 43.3 (11-$NCH_2CH_2CH_2CH_2Ar$), 45.5 (11-$NCH_2CH_2CH_2CH_2CH_2Ar$), 50.0 (6-OCH_3), 60.1 (C-11), 66.0 (3′-C), 69.3 (5′-C), 70.3 (2′-C), 76.6 (13-C), 78.0 (12-C), 78.3 (3-C), 80.5 (5-C), 82.6 (6-C), 103.4 (1′-C), 118.0 (11,12-Ar-C), 127.7 (11,12-Ar-C), 128.7 (3-Ph-C), 130.7 (3-Ph-C), 131.9 (3-Ph-C,2C), 133.3 (3-Ph-C, 2C), 135.4 (11,12-Ar-C), 144.0 (11,12-Ar-C), 144.1 (11,12-Ar-C), 146.9 (11,12-Ar-C), 157.3 (12-O*C*O—N), 170.7 (3-O*C*O—CH_2), 174.2 (1-C), 215.7 (9-C); MS (ESI): *m/z* 940.5 $[M+H]^+$ ($C_{49}H_{70}ClN_5O_{11}$).

*4.2.22 3-O-Descladinosyl-3-O-(4-chlorophenyl)acetyl-6-O-methyl-11,12-dideoxy-12,11-(oxycarbonyl(((4-phenyl-1H-1-imidazoyl)butyl)imino)) erythromycin A (**7c**)*

The title compound **7c** was prepared from **6c** (120 mg, 0.12 mmol) following the procedure used to prepare **7a** (70% yield). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.8 (4-CH_3), 10.2 (14-CH_3), 14.2 (10-CH_3), 14.2 (2-CH_3), 14.9 (12-CH_3), 18.8 (8-CH_3), 19.5 (6-CH_3), 21.0 (5′-CH_3), 21.9 (14-C), 24.2 (11-$NCH_2CH_2CH_2CH_2CH_2Ar$), 28.1 (11-$NCH_2CH_2CH_2CH_2CH_2Ar$), 28.6 (4′-C), 36.2 (4-C), 38.4 (10-C), 38.7 (C-7), 40.2 (3′-$N(CH_3)_2$), 40.6

(3-OCO—*C*H_2), 42.7 (2-C), 42.9 (8-C), 45.5 (11-NCH$_2$CH$_2$CH$_2$*C*H_2Ar), 46.7 (11-N*C*H_2CH$_2$CH$_2$CH$_2$Ar), 50.1 (6-OCH_3), 60.1 (C-11), 65.9 (3′-C), 69.4 (5′-C), 70.2 (2′-C), 76.6 (13-C), 77.9 (12-C), 78.3 (3-C), 80.4 (5-C), 82.6 (6-C), 103.4 (1′-C), 114.7 (11,12-Ar-C), 124.6 (11,12-Ar-C, 2C), 126.4 (11,12-Ar-C), 128.4 (11,12-Ar-C, 2C), 128.7 (3-Ph-C, 2C), 130.7 (3-Ph-C), 131.8 (3-Ph-C), 133.3 (3-Ph-C, 2C), 134.2 (11,12-Ar-C), 137.2 (11,12-Ar-C), 142.0 (11,12-Ar-C), 157.3 (12-O*C*O—N), 170.7 (3-O*C*O—CH_2), 174.3 (1-C) 215.8 (9-C); MS (ESI): *m/z* 965.5 $[M+H]^+$ ($C_{52}H_{73}ClN_4O_{11}$).

*4.2.23 3-O-Descladinosyl-11,12-dideoxy-6-O-methyl-12,11-(oxycarbonyl((4-phenylbutyl)imino))-3-O-(3-pyridyl)acetylerythromycin A (**7d**)*

The title compound **7d** was prepared from **6d** (130 mg, 0.15 mmol) following the procedure used to prepare **7a** (94% yield). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.0 (4-CH_3), 10.1 (14-CH_3), 14.2 (10-CH_3), 14.3 (2-CH_3), 15.1 (12-CH_3), 18.8 (8-CH_3), 19.5 (6-CH_3), 20.0 (5′-CH_3), 22.0 (14-C), 26.9 (11-NCH$_2$CH$_2$*C*H$_2$-CH$_2$Ph), 29.0 (11-NCH$_2$*C*H$_2$CH$_2$CH$_2$Ph), 30.5 (4′-C), 35.5 (4-C), 36.2 (10-C), 38.1 (C-7), 38.2 (3-OCO—*C*H_2), 38.8 (3′-N$(CH_3)_2$), 40.3 (2-C), 42.9 (8-C), 43.3 (11-NCH$_2$CH$_2$CH$_2$*C*H$_2$Ph), 45.4 (11-N*C*H$_2$CH$_2$CH$_2$CH$_2$Ph), 49.9 (6-OCH_3), 60.3 (C-11), 66.5 (3′-C), 67.8 (5′-C), 69.4 (2′-C), 76.6 (13-C), 78.1 (12-C), 78.6 (3-C), 81.3 (5-C), 82.4 (6-C), 102.4 (1′-C), 123.6 (3-Py-C), 125.5 (11,12-Ar-C), 128.1 (11,12-Ar-C, 2C), 128.3 (11,12-Ar-C, 2C), 129.7 (3-Py-C), 137.5 (3-Py-C), 142.4 (11,12-Ar-C), 148.6 (3-Py-C), 150.4 (3-Py-C), 157.2 (12-O*C*O—N), 170.7 (3-O*C*O—CH_2), 173.9 (1-C), 215.5 (9-C); HR-ESI-MS: *m/z* 866.5141 $[M+H]^+$ (calcd for $C_{48}H_{72}N_3O_{11}$, 866.5161).

*4.2.24 3-O-Descladinosyl-11,12-dideoxy-3-O-(3-pyridyl)acetyl-6-O-methyl-12,11-(oxycarbonyl((4-(3H-imidazoly(4,5-b)pyridin-3-yl)butyl)imino)) erythromycin A (**7e**)*

The title compound **7e** was prepared from **6e** (80 mg, 0.084 mmol) following the procedure used to prepare **7a** (91% yield). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.9 (4-CH_3), 10.2 (14-CH_3), 14.2 (10-CH_3), 14.2 (2-CH_3), 15.1 (12-CH_3), 18.8 (8-CH_3), 19.5 (6-CH_3), 20.7 (5′-CH_3), 21.9 (14-C), 24.3 (11-NCH$_2$CH$_2$*C*H$_2$-CH$_2$Ar), 27.4 (11-NCH$_2$*C*H$_2$CH$_2$CH$_2$Ar), 30.0 (4′-C), 36.3 (4-C), 38.1 (10-C, C-7), 38.7 (3-OCO—*C*H_2), 40.2 (3′-N$(CH_3)_2$), 42.7 (2-C), 42.9 (8-C), 43.3 (11-NCH$_2$-CH$_2$CH$_2$*C*H$_2$Ar), 45.5 (11-N*C*H$_2$CH$_2$-CH$_2$CH$_2$Ar), 50.0 (6-OCH_3), 60.1 (C-11), 66.3 (3′-C), 68.2 (5′-C), 69.6 (2′-C), 77.7 (13-C), 78.2 (12-C), 78.3 (3-C), 81.0 (5-C), 82.6 (6-C), 102.6 (1′-C), 118.0 (11,12-Ar-C), 123.6 (Py-C), 127.7 (11,12-Ar-C), 129.6 (Py-C), 135.4 (11,12-Ar-C), 137.4 (Py-C), 144.0 (11,12-Ar-C), 146.9 (11,12-Ar-C), 148.7 (Py-C), 150.4 (Py-C), 157.3 (12-OCO—N), 170.7 (3-O*C*O—CH_2), 174.1 (1-C), 215.7 (9-C); MS (ESI): *m/z* 907.7 $[M+H]^+$ ($C_{48}H_{70}N_6O_{11}$).

*4.2.25 3-O-Descladinosyl-11,12-dideoxy-6-O-methyl-12,11-(oxycarbonyl(((4-phenyl-1H-1-imidazoyl)butyl)imino))3-O-(3-pyridyl)acetylerythromycin A (**7f**)*

The title compound **7f** was prepared from **6f** (56 mg, 0.084 mmol) following the procedure used to prepare **7a** (47% yield). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.8 (4-CH_3), 10.2 (14-CH_3), 14.2 (10-CH_3, 2-CH_3, 2C), 15.0 (12-CH_3), 18.8 (8-CH_3), 19.5 (6-CH_3), 20.9 (5′-CH_3), 22.0 (14-C), 24.3 (11-NCH$_2$CH$_2$*C*H$_2$CH$_2$Ar), 28.4 (11-NCH$_2$*C*H$_2$CH$_2$CH$_2$Ar), 28.6 (4′-C), 36.3 (4-C), 38.3 (10-C), 38.4 (C-7), 38.7 (3-OCO—*C*H_2), 40.2 (3′-N$(CH_3)_2$,2C), 42.7 (2-C), 42.9 (8-C), 45.5 (11-NCH$_2$CH$_2$

CH_2CH_2Ar), 46.7 (11-$NCH_2CH_2CH_2CH_2Ar$), 50.0 (6-OCH_3), 60.2 (C-11), 66.0 (3′-C), 69.4 (5′-C), 70.1 (2′-C), 76.7 (13-C), 78.4 (12-C, 3-C, 2C), 80.9 (5-C), 82.6 (6-C), 103.6 (1′-C), 114.7 (11,12-Ar-C), 123.5 (3-Py-C), 124.7 (11,12-Ar-C), 126.4 (11,12-Ar-C), 129.3 (3-Py-C), 131.0 (11,12-Ar-C), 134.3 (11,12-Ar-C), 137.0 (3-Py-C), 137.2 (11,12-Ar-C, 2C), 142.1 (11,12-Ar-C, 2C), 148.8 (3-Py-C), 150.3 (3-Py-C), 157.3 (12-O*C*O—N), 170.4 (3-OCO—CH_2), 174.2 (1-C), 215.7 (9-C); MS (ESI): *m/z* 932.7 $[M+H]^+$ ($C_{51}H_{73}N_5O_{11}$).

*4.2.26 3-O-Descladinosyl-11,12-dideoxy-6-O-methyl-12,11-(oxycarbonyl((4-(1H-imidazoly(4,5-b)pyridin-1-yl)butyl)imino))-3-O-(3-pyridyl)acetylerythromycin A (**7g**)*

The title compound **7g** was prepared from **6g** (32 mg, 0.038 mmol) following the procedure used to prepare **7a** (85% yield). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.8 (4-CH_3), 10.2 (14-CH_3), 14.1 (10-CH_3), 14.2 (12-CH_3), 15.0 (2-CH_3), 18.8 (8-CH_3), 19.5 (6-CH_3), 21.0 (5′-CH_3), 21.9 (14-C), 24.4 (11-$NCH_2CH_2CH_2CH_2Ar$), 27.4 (11-$NCH_2CH_2CH_2CH_2Ar$), 28.2 (4′-C), 36.2 (4-C), 38.3 (10-C), 38.3 (3-OCO—CH_2), 38.7 (7-C), 40.2 (3′-$N(CH_3)_2$), 42.7 (11-$NCH_2CH_2CH_2CH_2Ar$), 42.9 (2-C), 43.3 (8-C), 45.5 (11-$NCH_2CH_2CH_2CH_2Ar$), 50.0 (6-OCH_3), 60.1 (11-C), 66.0 (3′-C), 69.5 (5′-C), 70.2 (2′-C), 76.6 (13-C), 78.3 (3-C), 78.3 (6-C), 81.0 (5-C), 82.6 (12-C), 103.7 (1′-C), 118.0 (11,12-Ar-C), 123.4 (Py-C), 127.7 (11,12-Ar-C), 129.2 (Py-C), 135.4 (11,12-Ar-C), 137.0 (Py-C), 144.0 (11,12-Ar-C), 144.1 (11,12-Ar-C), 146.9 (11,12-Ar-C), 148.8 (Py-C), 150.3 (Py-C), 157.3 (12-OCO—N), 170.4 (3-O*C*O—CH_2), 174.1 (1-C), 215.7 (9-C); ^1H NMR (300 MHz, $CDCl_3$): δ 8.54-8.52 (m, Py-H, 2H), 8.35 (dd, $J = 1.2$, 4.8 Hz, Ar-H, 1H), 8.09 (s, Ar-H, 1H), 8.02 (dd, $J = 1.2$, 8.1 Hz, Ar-H, 1H), 7.73 (m, Py-H, 1H), 7.29 (dd, $J = 4.8$, 7.5 Hz, Py-H, 1H), 7.19 (dd, $J = 4.8$, 8.1 Hz, Ar-H, 1H), 3.86 (d, $J = 7.2$ Hz, 1′-H, 1H), 3.71 (s, 3-OCO—CH_2, 2H), 2.93 (s, 6-OCH_3, 3H), 2.29 (s, 3′-$N(CH_3)_2$, 6H); HR-ESI-MS: *m/z* 907.5203 $[M+H]^+$ (calcd for $C_{48}H_{71}N_6O_{11}$, 907.5175).

*4.2.27 3-O-Descladinosyl-3-O-(3,4-methylenedioxy)phenylacetyl-6-O-methyl-11,12-dideoxy-12,11-(oxycarbonyl((4-(1H-imidazoly(4,5-b)pyridin-1-yl)butyl)imino))erythromycin A (**7h**)*

The title compound **7h** was prepared from **6h** (33.8 mg, 0.039 mmol) following the procedure used to prepare **7a** (86% yield). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.8 (4-CH_3), 10.3 (14-CH_3), 14.1 (10-CH_3), 14.2 (12-CH_3), 14.9 (2-CH_3), 18.8 (8-CH_3), 19.5 (6-CH_3), 21.0 (5′-CH_3), 21.9 (14-C), 24.4 (11-$NCH_2CH_2CH_2CH_2Ar$), 27.6 (11-$NCH_2CH_2CH_2CH_2Ar$), 28.2 (4′-C), 36.3 (4-C), 38.4 (10-C), 38.7 (7-C), 40.2 (3′-$N(CH_3)_2$), 40.9 (3-OCO—CH_2), 42.4 (2-C), 42.9 (8-C), 45.0 (11-$NCH_2CH_2CH_2CH_2Ar$), 45.6 (11-$NCH_2CH_2CH_2CH_2Ar$), 50.1 (6-OCH_3), 60.0 (11-C), 65.8 (3′-C), 69.5 (5′-C), 70.3 (2′-C), 77.1 (13-C), 77.6 (3-C), 78.4 (5-C), 80.2 (6-C), 82.7 (12-C), 101.1 (O—CH_2—O), 103.4 (1′-C), 108.2 (Ph-C), 109.8 (Ph-C), 117.9 × 2(11,12-Ar-C), 122.5 (Ph-C), 126.0 (Ph-C), 126.9 (11,12-Ar-C), 144.8 (11,12-Ar-C), 145.0 (11,12-Ar-C), 146.8 (Ph-C), 147.8 (Ph-C), 156.2 (11,12-Ar-C), 157.4 (12-OCO—N), 171.3 (3-O*C*O—CH_2), 174.6 (1-C), 215.8 (9-C); ^1H NMR (300 MHz, $CDCl_3$): δ 8.54 (d, $J = 4.8$ Hz, Ar-H, 1H), 8.14 (s, Ar-H, 1H), 7.79 (d, $J = 8.1$ Hz, Ar-H, 1H), 7.20 (dd, $J = 4.8$, 8.1 Hz, Ar-H, 1H), 6.84 (s, Ar-H, 1H), 6.75 (s, Ar-H, 2H), 5.94 (s, O—CH_2—O, 2H), 4.97 (m, 2H), 3.88 (d, $J = 7.2$ Hz, C1′-H), 2.97 (s, 6-OCH_3, 3H), 2.26 (s, 3′-$N(CH_3)_2$, 6H);

HR-ESI-MS: *m/z* 950.5170 $[M+H]^+$ (calcd for $C_{50}H_{72}N_5O_{13}$, 950.5126).

*4.2.28 3-O-Descladinosyl-3-O-(3,4-methylenedioxy)phenylacetyl-6-O-methyl-11,12-dideoxy-12,11-(oxycarbonyl((4-(3H-imidazoly(4,5-b)pyridin-3-yl)butyl)imino))erythromycin A (**7i**)*

The title compound **7i** was prepared from **6i** (24.7 mg, 0.025 mmol) following the procedure used to prepare **7a** (84% yield). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.8 (4-CH_3), 10.2 (14-CH_3), 14.1 (10-CH_3), 14.2 (12-CH_3), 14.9 (2-CH_3), 18.8 (8-CH_3), 19.5 (6-CH_3), 21.0 (5′-CH_3), 21.9 (14-C), 24.4 (11-$NCH_2CH_2CH_2CH_2Ar$), 27.4 (11-$NCH_2CH_2CH_2CH_2Ar$), 28.2 (4′-C), 36.2 (4-C), 38.4 (10-C), 38.7 (7-C), 40.2 (3′-$N(CH_3)_2$), 41.0 (3-OCO—CH_2), 42.7 (11-$NCH_2CH_2CH_2CH_2Ar$), 42.9 (2-C), 43.3 (8-C), 45.6 (11-$NCH_2CH_2CH_2CH_2Ar$), 50.1 (6-OCH_3), 60.1 (11-C), 65.8 (3′-C), 69.4 (5′-C), 70.3 (2′-C), 76.6 (13-C), 77.7 (6-C), 78.3 (3-C), 80.3 (5-C), 82.6 (12-C), 101.0 (O—CH_2—O), 103.3 (1′-C), 108.2 (Ph-C), 109.8 (Ph-C), 118.0 (11,12-Ar-C), 122.5 (Ph-C), 126.9 (Ph-C), 127.7 (11,12-Ar-C), 135.4 (11,12-Ar-C), 144.0 (11,12-Ar-C), 144.1 (2C, 11,12-Ar-C), 146.9 (Ph-C), 147.8 (Ph-C), 157.3 (12-OCO—N), 171.2 (3-O*C*O—CH_2), 174.3 (1-C), 215.7 (9-C); ^1H NMR (300 MHz, $CDCl_3$): δ 8.36 (d, $J = 4.5$ Hz, Ar-H, 1H), 8.09 (s, Ar-H, 1H), 8.03 (d, $J = 7.8$ Hz, Ar-H, 1H), 7.20 (dd, $J = 4.5$, 7.8 Hz, Ar-H, 1H), 6.84 (s, Ar-H, 1H), 6.75 (s, Ar-H, 2H), 5.93 (s, O—CH_2—O, 2H), 4.97 (d, $J = 11.1$ Hz, C13-H, 1H), 3.87 (d, $J = 7.2$ Hz, C1′-H), 2.96 (s, 6-OCH_3, 3H), 2.26 (s, 3′-$N(CH_3)_2$, 6H); HR-ESI-MS: *m/z* 950.5117 $[M+H]^+$ (calcd for $C_{50}H_{72}N_5O_{13}$, 950.5126).

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