ORIGINAL ARTICLE

Design, synthesis and antibacterial activity of novel ketolides bearing an aryltetrazolyl-substituted alkyl side chain

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A set of 17 novel ketolides bearing an aryltetrazolyl-substituted alkyl side chain were synthesized and evaluated for their antibacterial activities, which the aryltetrazolyl group was selected to replace the hetero-aryl moiety of the side chain in telithromycin for designing new compounds. The synthesis of aryltetrazolyl alkylamines was reported in detail. The antibacterial activities of new ketolides were evaluated against a number of pathogens including macrolide-resistant organisms by using telithromycin as the reference. Many of the evaluated compounds exhibited remarkable activities against both erythromycin-susceptible and erythromycin-resistant organisms such as *Staphylococcus aureus* (except *S. aureus* AD-08), *Pseudomonas aeruginosa* and *Escherichia coli*. Among these, the compound 11e exhibited excellent antibacterial potency against all the strains in comparison with others.

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INTRODUCTION

The macrolide antibiotic erythromycin A has been widely used to treat respiratory, skin and soft tissue infections for almost 60 years. In order to overcome the problems associated with acid instability of erythromycin A,^{1,2} the second generation of macrolides, including clarithromycin and azithromycin have been developed and used clinically in recent decades.^{3,4} These compounds displayed better pharmacokinetic properties and a broader spectrum of antibacterial activity.

The widespread use of these drugs resulted in macrolide resistance in many pathogenic strains. The primary mechanisms of resistance are mediated by erm-encoded methylation of 23S ribosomal RNA and mef-encoded efflux.^{5–7} To overcome the growing problems of macrolide resistance, great efforts have been made to discover novel macrolides. The ketolides, including telithromycin (Figure 1) and cethromycin (ABT-773),^{8–12} which displayed improved activities against macrolide-resistant pathogens such as *Streptococcus pneumoniae* (*S. pneumoniae*) and *Staphylococcus aureus* (*S. aureus*), were developed. Both telithromycin and cethromycin share the same key structure features, including 3-keto group, 11,12-cyclic carbamate and a proper hetero-arylalkyl side chain, which is responsible for binding to the 23S ribosomal RNA of bacteria.¹³

To develop novel potent ketolides, a variety of structural modifications of the ketolide core skeleton have been carried out. Recently, many ketolide derivatives such as 6-O-alkyl ketolides,^{14–19} 9-oxime

macrolides,^{20–25} 11,12-cyclic carbamate ketolides,^{26–32} 13-substituents ketolides and 6,11-bridged ketolides^{33–35} with excellent activities toward numerous macrolide-resistant pathogens were obtained. Herein, we described the synthesis and *in vitro* biological evaluation of a set of novel ketolides bearing an aryltetrazolyl-substituted alkyl side chain. All new derivatives were tested for their antibacterial activities against a number of strains such as *S. aureus*, *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Escherichia coli* (*E. coli*). The results will be useful for future design and development of other ketolides.

In our previous work, 3D-QSAR studies on a set of ketolides and their antibacterial activities were carried out.³⁶ The structure–activity relationship revealed by CoMFA and CoMSIA models indicated that the hydrophilic group at the first heterocyclic ring of side chain in ketolides would increase the potency (Figure 2). In an effort to find novel ketolides with extended antibacterial spectrum and improved activity, we designed the novel derivatives by replacing the imidazole ring in telithromycin with a more hydrophilic tetrazole ring.

Tetrazole is a very important pharmacophore skeleton, and is regarded as a bio-isostere of carboxylic group,³⁷ or a peptide bond.³⁸ The tetrazole is frequently employed in the lead optimization of ethical drug candidates. The tetrazole-containing compounds were found in various drugs such as matrix metalloproteinase (MMP) inhibitors,³⁹ monoamine oxidase B inhibitors,⁴⁰ antibacterial, antifungal and antiproliferative agents.⁴¹ This evoked us to develop novel

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ketolides containing tetrazole group with the hope that they could improve their potencies against susceptible and resistant pathogens. These designed ketolides were new compounds bearing an aryltetrazolyl-substituted alkyl side chain and with varying alkyl length.

RESULTS

Chemistry

In this study, 5-aryl-tetrazolyl alkylamines were prepared as side chain compounds for the first time (Scheme 1). Starting from aromatic nitriles or aromatic aldehydes, the 5-aryl tetrazoles were prepared by (2+3) cycloaddition of nitriles and azides according to the literature procedure.^{40,42–44} A process similar to Gabriel reaction was applied to achieve 5-aryl-tetrazolyl alkylamines. The *N*-alkylation on tetrazoles **3** were carried out with *N*-(3-bromopropyl) phthalimide, *N*-(4-bromobutyl) phthalimide or *N*-(5-bromopentyl) phthalimide to get **4**, which were then hydrazinolized to produce amines **5**.

It was found that when 5-(pyridin-2-yl) tetrazole (**3a**) was used as a substrate for *N*-alkylation, a mixture of *N*1-substituted compounds (**4a**, **4e** and **4i**) and *N*2-substituted products (**4b**, **4f** and **4j**) were obtained in different molar ratio (Scheme 2). The possible mechanism

was illustrated in Scheme 3. In general, there was equilibrium between 5-pyridinyl-2*H*-tetrazoles and 5-pyridinyl-1*H*-tetrazoles. When the 5-(pyridine-2-yl)-tetrazole acted as a substrate, the yielded 1*H*-tetrazole can be stabilized by forming intramolecular hydrogen bond, therefore, two isomers of 5-(pyridine-2-yl)-tetrazole are present in the same system. Meanwhile, when they reacted with alkylating agents, two *N*-alkylation products were obtained. As there are not intramolecular hydrogen bonds in 5-(pyridine-3-yl)-tetrazole and 5-(pyridine-4-yl)-tetrazole, they mainly yielded 2*H*-tetrazole. The products of *N*-alkylation are predominance in *N*2-substituted compounds.

A series of C-11,12 cyclic carbamate ketolide derivatives (**11a–q**) were prepared via eight steps from clarithromycin by following the similar synthesis procedures of telithromycin.^{45,46} Synthesis route was shown in Scheme 4. Clarithromycin was treated with diluted acid to accomplish cleavage of cladinose, which afforded 3-*O*-decladinosyl-6-*O*-methylerythromycin. Protection of 2'-OH of 3-*O*-decladinosyl-6-*O*-erythromycin was achieved by using benzoic anhydride to provide compound **6**. Formation of 11,12-cyclic carbonate of derivative **7** was carried out with triphosgene in a mixture of CH₂Cl₂ and pyridine at 0 °C. The resulting derivative **7** was oxidized by pyridinium chlorochromate to yield the ketolide **8**. Treatment of **8** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetone allowed formation of **9**. Deprotonation of the C-12 hydroxyl of **9** with sodium hydride and carbonyldiimidazole yielded the C-12 imidazolyl carbamate **10**. Finally, compound **10** on reaction with an excess of side chain 5-aryl-tetrazolyl alkylamine, and then deprotection of the benzonate by refluxing in methanol yielded the final ketolide **11**. The structures of the novel ketolide derivatives (**11a–q**) were displayed in Figure 3.

Antibacterial activity

All of the synthesized ketolides, taking erythromycin, clarithromycin and telithromycin as reference compounds, were tested for *in vitro* antibacterial activity against six strains of *S. aureus*, three strain of *P. aeruginosa* and two strains of *E. coli*. Their MICs were determined by the broth microdilution method recommended by the National Committee for Clinical Laboratory Standards⁴⁷ and listed in Table 1. The strains included three erythromycin-susceptible strains of *S. aureus* ATCC 29213, 6538p and 26001, three erythromycin-resistant clinical isolates of *S. aureus* 5676, 5677 and AD-08, and two strains of *P. aeruginosa* ATCC 27853 and 9027, a clinical isolate of *P. aeruginosa* 1317, as well as *E. coli* ATCC 8739 and 25922.

The tabulated results revealed that erythromycin and clarithromycin were potent against erythromycin-susceptible strains and inactive toward all the resistant strains. Some of the evaluated compounds showed potent or equivalent activities compared with that of telithromycin. The novel ketolides that possessed 4–5 carbon atoms alkyl side chain, such as **11e–k**, exhibited somewhat increased potencies

Figure 1 Structures of erythromycin, clarithromycin, cethromycin (ABT-773) and telithromycin.

Figure 2 Structure–activity relationships of ketolides from 3D-QSAR study.³⁶

Scheme 1 Synthesis of *N*2-substituted 5-aryl-tetrazolyl alkylamines. Reagents and condition: (a) NaN₃, NH₄Cl, DMF 130 °C and (b) (i) I₂, aq. NH₃, r.t.; (ii) NaN₃, ZnBr₂; reflux.; (c) *N*-(3-bromopropyl)phthalimide, *N*-(4-bromobutyl)phthalimide or *N*-(5-bromopentyl)phthalimide, K₂CO₃, DMF, 80 °C; (d) NH₂NH₂•H₂O, EtOH/CH₃CN, reflux.

<i>n</i>	<i>N</i> 1-substituted		<i>N</i> 2-substituted	
	4 (Yield)	5 (Yield)	4 (Yield)	5 (Yield)
1	4a (35%)	5a (86%)	4b (60%)	5b (89%)
2	4e (50%)	5e (87%)	4f (50%)	5f (87%)
3	4i (37%)	5i (86.9%)	4j (52%)	5j (92.3%)

Scheme 2 Synthesis of *N*1-substituted and *N*2-substituted 5-aryl-tetrazolyl alkylamines. Reagents and condition: (a) NaN₃, NH₄Cl, DMF 130 °C; (b) *N*-(3-bromopropyl)phthalimide, *N*-(4-bromobutyl)phthalimide or *N*-(5-bromopentyl)phthalimide, K₂CO₃, DMF, 80 °C; (c) NH₂NH₂•H₂O, EtOH/CH₃CN, reflux.

toward all of the erythromycin-susceptible *S. aureus*; **11n**, **11p** and **11q** showed the equivalent potencies compared with telithromycin against the erythromycin-susceptible *S. aureus*. Compounds **11a**, **11e–i**, **11n** displayed some extent increased potencies against erythromycin-resistant *S. aureus* 5677; **11d**, **11j**, **11k**, **11p**, and **11q** showed the equivalent potencies compared with telithromycin against *S. aureus* 5677. Meanwhile, the compound **11n** bearing a phenyl-tetrazolyl moiety in the side chain was slightly more potent against *S. aureus* AD-08. Furthermore, compared with **11b**, **11c** and **11d**, the compound **11a** exhibited the improved potencies against both erythromycin-susceptible *S. aureus* and erythromycin-resistant *S. aureus*.

Some of the novel ketolides were slightly more potent against *P. aeruginosa* and *E. coli*. Generally compounds **11a**, **11e–h** and **11q** seemed to be more potent than other tetrazole-containing ketolides toward *P. aeruginosa* ATCC 27853. Especially the compounds **11e**, **11p** and **11q** showed the equivalent or improved activities

compared with telithromycin against *P. aeruginosa* ATCC 27853 and 9027, and *P. aeruginosa* 1317. Compounds **11e** and **11q** also showed the same or improved potencies compared with telithromycin against *E. coli* strains.

The results indicated that compound **11e** was one of the most active compounds, which exhibited excellent activity against both the Gram-positive and Gram-negative pathogens. It could be inferred that introducing the 5-(pyridin-2-yl)-1*H*-tetrazol-1-yl group as a heterocyclic moiety in the side chain may enhance the antibacterial activity of ketolide.

Conclusions

Seventeen novel ketolides have been synthesized and evaluated for antibacterial activities against Gram-positive and Gram-negative pathogens. All of the synthesized compounds were found to be potent against both erythromycin-susceptible and erythromycin-resistant

strains. Some of the compounds (for example, **11e-l**, **11n**, **11p** and **11q**, having alkyl length side chains with 4–5 carbon atoms) exhibited better or the same inhibitory potencies compared with telithromycin against erythromycin-susceptible strains. Compound **11e** showed excellent activity against all the strains but *S. aureus* AD-08, which inferred that compounds bearing the 5-(pyridin-2-yl)-1*H*-tetrazol-1-yl group as a heterocyclic moiety in the side chain of ketolides may enhance their antibacterial activities. The results could aid in designing for novel ketolides with desired potencies.

METHODS

General experimental procedures

All reagents and solvents were purchased from commercial sources. Further purification and drying by standard methods were employed when necessary. Clarithromycin and its derivatives were predried azeotropically from benzene. CH₂Cl₂ and EtOAc were distilled from CaH₂. The thin-layer chromatographic analyses were performed on silica gel plates (Qingdao haiyang GF₂₅₄) and

Scheme 3 Equilibrium between 5-pyridinyl-2*H*-tetrazoles and 5-pyridinyl-1*H*-tetrazoles.

visualized under UV light. All NMR spectra were recorded on a Mercury-300 (Agilent Technologies, Inc., Santa Clara, CA, USA), Mercury-400 (Agilent Technologies, Inc.) or Mercury-500 spectrometers (Agilent Technologies, Inc.) in DMSO-*d*₆, CDCl₃ or CD₃OD. The chemical shifts are reported in ppm using tetramethylsilane (TMS) as an internal standard. ESI mass spectra (MS) were obtained on a Finnigan LCQ Advantage MAX mass spectrometer (Applied Biosystems, Carlsbad, CA, USA; 4000 Q TRAP). High-resolution MS (HRMS) were obtained on an Agilent 6210 series LC/MSD TOF mass spectrometer (Agilent Technologies, Inc.).

2-(2*H*-tetrazol-5-yl) pyridine (**3a**), 3-(2*H*-tetrazol-5-yl) pyridine (**3b**), 4-(2*H*-tetrazol-5-yl) pyridine (**3c**), 5-phenyl-2*H*-tetrazole (**3d**), 5-(thiophen-2-yl)-2*H*-tetrazole (**3e**) and 5-(furan-2-yl)-2*H*-tetrazole (**3f**) were prepared according to the literature procedure.

General procedure for the synthesis of compounds **4a–q**

To a solution of aryl-tetrazole (**3a–f**) (5 mmol) in anhydrous *N,N*-dimethylformamide (DMF) (24 ml) was added K₂CO₃ (5 mmol) and *N*-(bromoalk-yl)phthalimide (6 mmol). The mixture was heated to 80 °C for 10 h under nitrogen. Then the mixture was poured into ice water (100 ml), and the resulting precipitation was filtered and washed with ice water. The crude product was purified by column chromatography on silica gel using petroleum-ethyl acetate (1:1) to petroleum-ethyl acetate-dichloromethane (1:1:1), affording compounds **4a–q** as a white solid.

2-(3-(5-(Pyridin-2-yl)-1*H*-tetrazol-1-yl)propyl)isoindoline-1,3-dione (**4a**)

Yield 35%. ¹H NMR (300 MHz, CDCl₃): δ 8.83 (m, 3H), 8.33 (d, *J*=7.8 Hz, 1H), 7.83 (m, 1H), 7.72 (m, 2H), 7.35 (m, 2H), 5.03 (t, *J*=7.8 Hz, 2H), 3.83 (t, *J*=6.9 Hz, 2H), 2.39 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 168.1, 151.5, 149.2, 144.7, 137.4, 134.1, 131.9, 125.2, 123.3, 47.3, 35.0, 28.9. MS (ESI) [*M*+*H*]⁺ *m/z* 335.

2-(3-(5-(Pyridin-2-yl)-2*H*-tetrazol-2-yl)propyl)isoindoline-1,3-dione (**4b**)

Yield 60%. ¹H NMR (300 MHz, CDCl₃): δ 8.67 (d, *J*=4.2 Hz, 3H), 8.12 (d, *J*=7.8 Hz, 1H), 7.77 (m, 3H), 7.64 (m, 2H), 7.31 (m, 1H), 4.73 (t, *J*=7.5 Hz, 2H), 3.80 (t, *J*=6.9 Hz, 2H), 2.46 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 167.9, 164.6, 150.1, 146.9, 136.9, 133.9, 131.6, 124.6, 123.2, 122.2, 51.0, 34.8, 28.2. MS (ESI) [*M*+*H*]⁺ *m/z* 335.

Scheme 4 Synthesis of a set of ketolide derivatives **11**. Reagents and conditions: (a) HCl, EtOH/H₂O; (b) Bz₂O, DMAP, TEA, CH₂Cl₂; (c) (Cl₃CO)₂CO, Py, CH₂Cl₂, –5 °C to r.t.; (d) PCC, CH₂Cl₂; (e) 1,8-diazabicyclo[5.4.0]undec-7-ene, acetone, reflux; (f) CDI, NaH, DMF, –10 °C; (g) RNH₂, CH₃CN, 55 °C; (h) CH₃OH, reflux.

Figure 3 Structures of synthesized ketolides 11a–q.

Table 1 Antibacterial activities of novel ketolides *in vitro*

Compd.	MIC ($\mu\text{g ml}^{-1}$)										
	S. aureus						P. aeruginosa			E. coli	
	ATCC 29213	ATCC 6538p	ATCC 26001	5676	5677	AD-08	ATCC 27853	ATCC 9027	1317	ATCC 8739	ATCC 25922
ERY	0.5	0.5	≤ 0.063	>128	>128	>128	16	128	>128	16	8
CLA	0.25	0.5	≤ 0.063	>128	>128	>128	8	64	128	8	4
TEL	0.125	0.125	0.031	2	16	128	4	32	32	4	4
11a	0.25	0.125	0.125	8	8	>128	8	64	128	8	8
11b	1	0.25	0.125	32	32	>128	16	>128	>128	32	16
11c	1	0.25	0.5	32	32	>128	64	>128	>128	64	64
11d	1	0.125	0.5	16	16	>128	64	>128	>128	32	64
11e	0.063	≤ 0.031	≤ 0.063	4	8	>128	4	8	8	4	2
11f	0.063	≤ 0.031	≤ 0.063	8	8	>128	8	64	128	8	4
11g	≤ 0.031	≤ 0.031	≤ 0.063	8	8	>128	8	64	128	8	16
11h	≤ 0.031	≤ 0.031	≤ 0.063	4	8	>128	8	32	64	8	16
11i	0.063	≤ 0.031	≤ 0.063	8	8	>128	16	64	64	16	8
11j	0.063	≤ 0.031	≤ 0.063	16	16	>128	32	128	>128	16	16
11k	0.063	≤ 0.031	≤ 0.063	16	16	>128	16	64	128	16	16
11l	0.125	≤ 0.031	≤ 0.063	16	32	>128	16	128	128	16	16
11m	1	0.5	0.5	64	64	128	64	>128	>128	64	64
11n	0.125	0.125	≤ 0.063	16	8	64	16	128	64	8	16
11o	1	0.5	0.5	32	64	>128	64	>128	>128	32	64
11p	0.125	0.063	≤ 0.063	32	16	>128	16	32	16	16	16
11q	0.125	0.125	≤ 0.063	16	16	>128	8	32	16	4	4

Abbreviations: CLA, clarithromycin; Compd, compound; *E. coli*, *Escherichia coli*; ERY, erythromycin; *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. aureus*, *Staphylococcus aureus*; TEL, telithromycin.

2-(3-(5-(Pyridin-3-yl)-2H-tetrazol-2-yl)propyl)isoindoline-1,3-dione (4c)

Yield 96%. ^1H NMR (300 MHz, CDCl_3): δ 9.91 (m, 1H), 8.60 (m, 1H), 8.25 (d, $J=7.8$ Hz, 1H), 7.73 (m, 2H), 7.62 (m, 2H), 7.33 (m, 1H), 4.70 (t, $J=6.9$ Hz, 2H), 3.81 (t, $J=6.6$ Hz, 2H), 2.42 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 162.3, 151.0, 147.8, 134.0, 133.8, 131.6, 123.4, 123.3, 50.9, 35.0, 27.9. MS (ESI) $[\text{M}+\text{H}]^+$ m/z 335.

2-(3-(5-(Pyridin-4-yl)-2H-tetrazol-2-yl)propyl)isoindoline-1,3-dione (4d)

Yield 88.6%. ^1H NMR (400 MHz, CDCl_3): δ 8.70 (m, 2H), 7.90 (m, 2H), 7.79 (m, 2H), 7.67 (m, 2H), 4.76 (t, $J=7.1$ Hz, 2H), 3.86 (t, $J=6.7$ Hz, 2H), 2.50 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 167.6, 162.7, 150.1, 134.1, 133.7, 131.4, 122.9, 120.3, 50.8, 34.8, 27.7. MS (ESI) $[\text{M}+\text{H}]^+$ m/z 335.

2-(4-(5-(Pyridin-2-yl)-1H-tetrazol-1-yl)butyl)isoindoline-1,3-dione (4e)

Yield 50%. ¹H NMR (300 MHz, CDCl₃): δ 8.73 (d, *J*=4.5 Hz, 1H), 8.20 (d, *J*=8.1 Hz, 1H), 7.82 (m, 1H), 7.79 (m, 2H), 7.67 (m, 2H), 7.41 (m, 1H), 5.02 (t, *J*=7.2 Hz, 2H), 3.73 (t, *J*=7.2 Hz, 2H), 2.02 (m, 2H), 1.77 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 168.2, 151.6, 149.4, 144.8, 137.4, 133.9, 125.2, 124.5, 123.2, 48.9, 37.1, 27.1, 25.4. MS (ESI) [M+H]⁺ *m/z* 349.

2-(4-(5-(Pyridin-2-yl)-2H-tetrazol-2-yl)butyl)isoindoline-1,3-dione (4f)

Yield 50%. ¹H NMR (300 MHz, CDCl₃): δ 8.73 (d, *J*=4.5 Hz, 1H), 8.20 (d, *J*=8.1 Hz, 1H), 7.82 (m, 1H), 7.79 (m, 2H), 7.67 (m, 2H), 7.36 (m, 1H), 4.74 (t, *J*=7.2 Hz, 2H), 3.73 (t, *J*=7.2 Hz, 2H), 2.11 (m, 2H), 1.75 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 168.2, 164.7, 150.2, 146.7, 137.0, 133.9, 131.9, 124.7, 123.2, 122.3, 52.6, 36.8, 26.5, 25.4. MS (ESI) [M+H]⁺ *m/z* 349.

2-(4-(5-(Pyridin-3-yl)-2H-tetrazol-2-yl)butyl)isoindoline-1,3-dione (4g)

Yield 87%. ¹H NMR (300 MHz, CDCl₃): δ 9.34 (m, 1H), 8.71 (m, 1H), 8.40 (d, *J*=8.1 Hz, 1H), 7.85 (m, 2H), 7.72 (m, 2H), 7.44 (m, 1H), 4.75 (t, *J*=6.9 Hz, 2H), 3.78 (t, *J*=6.9 Hz, 2H), 2.12 (m, 2H), 1.79 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 168.2, 162.7, 151.1, 148.0, 134.0, 133.8, 131.8, 123.2, 123.6, 52.5, 36.8, 26.5, 25.4. MS (ESI) [M+H]⁺ *m/z* 349.

2-(4-(5-(Pyridin-4-yl)-2H-tetrazol-2-yl)butyl) isoindoline-1,3-dione (4h)

Yield 94%. ¹H NMR (300 MHz, CDCl₃): δ 8.76 (d, *J*=4.5 Hz, 2H), 7.99 (d, *J*=4.5 Hz, 2H), 7.84 (d, *J*=5.4 Hz, 2H), 7.73 (d, *J*=5.4 Hz, 2H), 4.76 (t, *J*=6.9 Hz, 2H), 3.78 (t, *J*=6.9 Hz, 2H), 2.13 (m, 2H), 1.79 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 168.2, 163.0, 162.4, 150.5, 134.6, 134.0, 131.8, 123.2, 120.7, 52.6, 36.8, 26.5, 25.4. MS (ESI) [M+H]⁺ *m/z* 349.

2-(5-(5-(Pyridin-2-yl)-1H-tetrazol-1-yl)pentyl)isoindoline-1,3-dione (4i)

Yield 37%. ¹H NMR (400 MHz, CDCl₃): δ 8.74 (d, *J*=4.4 Hz, 1H), 8.36 (d, *J*=7.9 Hz, 1H), 7.92 (m, 1H), 7.84 (m, 2H), 7.73 (m, 2H), 7.46 (m, 1H), 4.99 (t, *J*=7.2 Hz, 2H), 3.68 (t, *J*=7.1 Hz, 2H), 2.04 (m, 2H), 1.75 (m, 2H), 1.43 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 168.2, 151.5, 149.4, 144.8, 137.3, 133.8, 133.7, 131.9, 125.2, 124.4, 123.1, 123.0, 49.2, 37.4, 29.2, 27.8, 23.5. MS (ESI) [M+H]⁺ *m/z* 363.

2-(5-(5-(Pyridin-2-yl)-2H-tetrazol-2-yl)pentyl)isoindoline-1,3-dione (4j)

Yield 52%. ¹H NMR (400 MHz, CDCl₃): δ 8.78 (d, *J*=4.7 Hz, 1H), 8.25 (d, *J*=7.9 Hz, 1H), 7.88 (m, 1H), 7.83 (m, 2H), 7.71 (m, 2H), 7.40 (m, 1H), 4.72 (t, *J*=7.1 Hz, 2H), 3.69 (t, *J*=7.2 Hz, 2H), 2.18 (m, 2H), 1.76 (m, 2H), 1.45 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 168.2, 164.7, 150.2, 146.7, 137.0, 133.8, 131.9, 124.7, 123.1, 122.3, 53.1, 37.3, 28.7, 27.8, 23.5. MS (ESI) [M+H]⁺ *m/z* 363.

2-(5-(5-(Pyridin-3-yl)-2H-tetrazol-2-yl)pentyl)isoindoline-1,3-dione (4k)

Yield 87%. ¹H NMR (400 MHz, CDCl₃): δ 9.36 (s, 1H), 8.71 (m, 1H), 8.41 (m, 1H), 7.83 (m, 2H), 7.70 (m, 2H), 7.43 (m, 1H), 4.69 (t, *J*=7.0 Hz, 2H), 3.70 (m, 2H), 2.14 (m, 2H), 1.77 (m, 2H), 1.44 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 168.3, 162.7, 151.1, 148.0, 134.0, 133.9, 131.9, 123.7, 123.6, 123.2, 53.1, 37.3, 28.7, 27.8, 23.5. MS (ESI) [M+H]⁺ *m/z* 363.

2-(5-(5-(Pyridin-4-yl)-2H-tetrazol-2-yl)pentyl)isoindoline-1,3-dione (4l)

Yield 92%. ¹H NMR (300 Mz, CDCl₃): δ 8.74 (d, *J*=5.9, 2H), 7.98 (m, 2H), 7.80 (d, *J*=5.4, 2H), 7.69 (d, *J*=5.4, 2H), 4.68 (t, *J*=7.1, 2H), 3.68 (m, 2H), 2.13 (m, 2H), 1.78 (m, 2H), 1.41 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 167.9, 162.6,

150.1, 134.4, 133.5, 131.6, 122.8, 120.4, 52.7, 36.9, 28.3, 27.3, 23.1. MS (ESI) [M+H]⁺ *m/z* 363.

2-(3-(5-Phenyl-2H-tetrazol-2-yl)propyl)isoindoline-1,3-dione (4m)

Yield 93%. ¹H NMR (300 MHz, CDCl₃): δ 8.06 (m, 2H), 7.81 (m, 2H), 7.68 (m, 2H), 7.43 (m, 3H), 4.73 (t, *J*=7.1 Hz, 2H), 3.88 (t, *J*=6.8 Hz, 2H), 2.50 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 168.0, 165.1, 133.9, 131.8, 130.2, 128.7, 126.7, 123.3, 123.2, 50.9, 35.2, 28.2. MS (ESI) [M+H]⁺ *m/z* 334.

2-(4-(5-Phenyl-2H-tetrazol-2-yl)butyl)isoindoline-1,3-dione (4n)

Yield 95%. ¹H NMR (400 MHz, CDCl₃): δ 8.12 (m, 2H), 7.83 (m, 2H), 7.70 (m, 2H), 7.46 (m, 3H), 4.72 (t, *J*=7.0 Hz, 2H), 3.75 (m, 2H), 2.13 (m, 2H), 1.78 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 168.3, 165.1, 134.0, 132.0, 130.2, 128.8, 126.8, 123.2, 52.3, 36.9, 26.6, 25.5. MS (ESI) [M+H]⁺ *m/z* 348.

2-(3-(5-(Thiophen-2-yl)-2H-tetrazol-2-yl)propyl)isoindoline-1,3-dione (4o)

Yield 81%. ¹H NMR (400 MHz, CDCl₃): δ 7.83 (m, 2H), 7.70 (m, 3H), 7.42 (m, 1H), 7.11 (m, 1H), 4.70 (m, 2H), 3.83 (m, 2H), 2.48 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 168.2, 168.1, 161.2, 134.1, 133.9, 131.9, 130.2, 129.0, 127.8, 123.4, 123.2, 51.0, 35.2, 28.3. MS (ESI) [M+H]⁺ *m/z* 340.

2-(4-(5-(Thiophen-2-yl)-2H-tetrazol-2-yl)butyl)isoindoline-1,3-dione (4p)

Yield 63%. ¹H NMR (400 MHz, CDCl₃): δ 7.83 (m, 2H), 7.77 (m, 1H), 7.70 (m, 2H), 7.43 (m, 1H), 7.13 (m, 1H), 4.69 (t, *J*=7.0 Hz, 1H), 3.76 (m, 2H), 2.12 (m, 2H), 1.77 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 168.3, 161.2, 134.0, 133.9, 132.0, 127.8, 127.7, 123.3, 52.4, 36.9, 26.5, 25.4. MS (ESI) [M+H]⁺ *m/z* 354.

2-(4-(5-(Furan-2-yl)-2H-tetrazol-2-yl)butyl)isoindoline-1,3-dione (4q)

Yield 85%. ¹H NMR (400 MHz, CDCl₃): δ 7.83 (m, 2H), 7.73 (m, 2H), 7.68 (s, 1H), 7.29 (m, 1H), 6.64 (m, 1H), 4.74 (t, *J*=7.1 Hz, 1H), 3.75 (m, 2H), 2.03 (m, 2H), 1.77 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 168.2, 145.4, 134.0, 133.8, 131.9, 123.2, 123.1, 114.8, 112.3, 48.0, 36.8, 26.9, 25.3. MS (ESI) [M+H]⁺ *m/z* 338.

General procedures for the synthesis of compounds 5a–q

To a solution of compound 4a–q (3 mmol) in ethanol (20 ml) and acetonitrile (15 ml) was added hydrazine monohydrate (85%, 6 mmol). The solution was refluxed for 6 h. After cooling to room temperature, the mixture was filtered and washed with ethanol. The filtrate was concentrated *in vacuo*. To the residue NaOH aqueous solution (2 mol l⁻¹, 30 ml) was added. Then it was extracted with dichloromethane (30 ml × 3), washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using dichloromethane:methanol:triethylamine (9:1:0.1) as eluent to give compounds 5a–q as a yellow oil.

3-(5-(Pyridin-2-yl)-1H-tetrazol-1-yl)propylamine (5a)

Yield 89%. ¹H NMR (300 MHz, CDCl₃): δ 8.65 (d, *J*=4.1 Hz, 1H), 8.11 (d, *J*=4.8 Hz, 1H), 7.75 (m, 1H), 7.28 (m, 1H), 4.72 (t, *J*=6.9 Hz, 2H), 2.67 (t, *J*=6.6 Hz, 2H), 2.11 (m, 2H), 1.80 (s, br, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 165.1, 150.7, 147.1, 137.6, 125.3, 122.8, 51.5, 38.9, 32.9. MS (ESI) [M+H]⁺ *m/z* 205.

3-(5-(Pyridin-2-yl)-2H-tetrazol-2-yl)propylamine (5b)

Yield 86%. ¹H NMR (300 MHz, CDCl₃): δ 8.51 (d, *J*=4.8 Hz, 1H), 8.10 (d, *J*=7.8 Hz, 1H), 7.71 (m, 1H), 7.27 (m, 1H), 4.85 (t, *J*=7.2 Hz, 2H), 2.53 (t, *J*=6.9 Hz, 2H), 1.90 (m, 2H), 1.81 (s, br, 2H, -NH₂). ¹³C NMR (75 MHz, CDCl₃): δ 165.1, 150.7, 147.1, 137.6, 125.3, 122.8, 51.5, 38.9, 32.9. MS (ESI) [M+H]⁺ *m/z* 205.

3-(5-(Pyridin-3-yl)-2H-tetrazol-2-yl)propylamine (5c)

Yield 82%. ¹H NMR (300 MHz, CDCl₃): δ 9.20 (s, 1H), 8.55 (d, *J*=4.8 Hz, 1H), 8.24 (d, *J*=7.8 Hz, 1H), 7.28 (m, 1H), 4.67 (t, *J*=6.9 Hz, 2H), 2.66 (t, *J*=6.6 Hz, 2H), 2.05 (m, 2H), 1.39 (s, br, 2H, -NH₂). ¹³C NMR (75 MHz, CDCl₃): δ 162.3, 150.8, 147.6, 133.7, 123.3, 50.6, 38.3, 32.3. MS (ESI) [M+H]⁺ *m/z* 205.

3-(5-(Pyridin-4-yl)-2H-tetrazol-2-yl)propylamine (5d)

Yield 92%. ¹H NMR (500 MHz, CD₃OD) δ 8.66 (m, 2H), 8.00 (d, *J*=6.5 Hz, 2H), 4.87 (m, 4H), 2.86 (t, *J*=7.5, 2H), 2.29 (m, 2H). ¹³C NMR (125 MHz, CD₃OD): δ 164.1, 151.4, 137.0, 122.4, 53.9, 40.1, 36.3, 31.6. MS (ESI) [M+H]⁺ *m/z* 205.

4-(5-(Pyridin-2-yl)-1H-tetrazol-1-yl)butylamine (5e)

Yield 87%. ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.80 (d, *J*=4.8 Hz, 1H), 8.24 (d, *J*=7.8 Hz, 1H), 8.08 (m, 1H), 7.63 (m, 1H), 4.90 (t, *J*=7.2 Hz, 2H), 2.50 (m, 2H), 1.89 (m, 2H), 1.33 (s, 2H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 151.8, 150.1, 144.4, 138.4, 126.1, 124.6, 49.1, 41.1, 29.9, 27.0. MS (ESI) [M+H]⁺ *m/z* 219.

4-(5-(Pyridin-2-yl)-2H-tetrazol-2-yl)butylamine (5f)

Yield 87%. ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.73 (d, *J*=4.8 Hz, 1H), 8.13 (d, *J*=7.8 Hz, 1H), 7.99 (m, 1H), 7.54 (m, 1H), 4.75 (t, *J*=6.9 Hz, 2H), 2.53 (m, 2H), 1.99 (m, 2H), 1.34 (s, 2H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 164.3, 150.4, 146.5, 137.8, 125.4, 122.6, 53.2, 40.9, 29.8, 26.5. MS (ESI) [M+H]⁺ *m/z* 219.

4-(5-(Pyridin-3-yl)-2H-tetrazol-2-yl)butylamine (5g)

Yield 74%. ¹H NMR (300 MHz, CDCl₃): δ 9.24 (s, 1H), 8.59 (d, *J*=4.8 Hz, 1H), 8.30 (d, *J*=7.8 Hz, 1H), 7.32 (m, 1H), 4.61 (t, *J*=7.2 Hz, 2H), 2.67 (t, *J*=6.9 Hz, 2H), 2.05 (m, 2H), 1.89 (s br, 2H), 1.44 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 162.5, 150.9, 147.8, 147.8, 133.8, 123.5, 53.0, 41.0, 29.8, 26.5. MS (ESI) [M+H]⁺ *m/z* 219.

4-(5-(Pyridin-4-yl)-2H-tetrazol-2-yl)butylamine (5h)

Yield 92%. ¹H NMR (300 MHz, CDCl₃): δ 8.72 (d, *J*=5.4 Hz, 2H), 7.97 (d, *J*=5.1 Hz, 2H), 4.67 (t, *J*=6.9 Hz, 2H), 2.76 (s, 2H), 2.09 (m, 2H), 1.48 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 162.4, 151.0, 134.3, 120.6, 53.3, 40.9, 29.8, 26.5. MS (ESI) [M+H]⁺ *m/z* 219.

5-(5-(Pyridin-2-yl)-1H-tetrazol-1-yl)pentylamine (5i)

Yield 87%. ¹H NMR (400 MHz, CDCl₃): δ 8.64 (d, *J*=2.8 Hz, 1H), 8.22 (m, 1H), 7.82 (m, 1H), 7.36 (m, 1H), 4.88 (m, 2H), 2.61 (t, *J*=7.1 Hz, 2H), 1.45 (m, 2H), 1.32 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 151.5, 149.3, 144.6, 137.3, 125.2, 124.3, 49.2, 41.0, 31.5, 29.3, 23.3. MS (ESI) [M+H]⁺ *m/z* 233.

5-(5-(Pyridin-2-yl)-2H-tetrazol-2-yl)pentylamine (5j)

Yield 92%. ¹H NMR (400 MHz, CDCl₃): δ 8.78 (m, 1H), 8.24 (m, 1H), 7.87 (m, 1H), 7.54 (m, 1H), 4.73 (t, *J*=7.1 Hz, 2H), 2.80 (m, 2H), 2.13 (m, 2H), 1.63 (m, 2H), 1.43 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 164.7, 150.2, 146.7, 137.1, 124.8, 122.4, 53.2, 40.6, 30.3, 28.9, 23.5, 26.5. MS (ESI) [M+H]⁺ *m/z* 233.

5-(5-(Pyridin-3-yl)-2H-tetrazol-2-yl)pentylamine (5k)

Yield 85%. ¹H NMR (400 MHz, CDCl₃): δ 9.26 (s, 1H), 8.60 (d, *J*=4.2 Hz, 1H), 8.33 (d, *J*=7.9 Hz, 1H), 7.36 (m, 1H), 4.61 (t, *J*=7.0 Hz, 2H), 2.62 (t, *J*=7.0 Hz, 2H), 2.01 (m, 2H), 1.46 (m, 2H), 1.32 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 162.4, 150.8, 147.6, 133.9, 123.5, 123.4, 53.0, 41.2, 32.1, 28.8, 23.4. MS (ESI) [M+H]⁺ *m/z* 233.

5-(5-(Pyridin-4-yl)-2H-tetrazol-2-yl)pentylamine (5l)

Yield 84%. ¹H NMR (400 MHz, CDCl₃): δ 8.61 (m, 2H), 7.88 (m, 2H), 4.57 (t, *J*=6.8 Hz, 2H), 2.58 (t, *J*=6.8 Hz, 2H), 1.96 (m, 2H), 1.42 (m, 2H), 1.28 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 162.6, 150.2, 134.6, 120.5, 53.1, 41.1, 31.9, 28.8, 23.3. MS (ESI) [M+H]⁺ *m/z* 233.

3-(5-Phenyl-2H-tetrazol-2-yl)propylamine (5m)

Yield 94%. ¹H NMR (400 MHz, CDCl₃): δ 8.02 (m, 2H), 7.32 (m, 3H), 4.64 (m, 2H), 3.74 (s, br, 2H, -NH₂), 2.70 (t, *J*=6.8 Hz, 2H), 2.09 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 164.6, 129.9, 128.5, 126.9, 126.3, 50.5, 38.0, 31.4. MS (ESI) [M+H]⁺ *m/z* 204.

4-(5-Phenyl-2H-tetrazol-2-yl)butylamine (5n)

Yield 87%. ¹H NMR (400 MHz, CDCl₃): δ 7.99 (m, 2H), 7.30 (m, 3H), 4.50 (m, 2H), 3.05 (s, br, 2H, -NH₂), 2.60 (m, 2H), 1.93 (m, 2H), 1.37 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 164.6, 129.9, 128.5, 126.9, 126.3, 50.5, 38.0, 31.4. MS (ESI) [M+H]⁺ *m/z* 218.

3-(5-(Thiophen-2-yl)-2H-tetrazol-2-yl)propylamine (5o)

Yield 87%. ¹H NMR (400 MHz, CDCl₃): δ 7.69 (m, 1H), 7.35 (m, 1H), 7.04 (m, 1H), 4.61 (m, 2H), 2.70 (m, 2H), 2.07 (m, 2H), 1.77 (s, 2H, -NH₂). ¹³C NMR (100 MHz, CDCl₃): δ 160.9, 128.8, 127.7, 127.6, 127.5, 50.5, 38.3, 32.3. MS (ESI) [M+H]⁺ *m/z* 210.

4-(5-(Thiophen-2-yl)-2H-tetrazol-2-yl)butylamine (5p)

Yield 96%. ¹H NMR (400 MHz, CDCl₃): δ 7.79 (m, 1H), 7.45 (m, 1H), 7.14 (m, 1H), 4.65 (t, *J*=7.1 Hz, 2H), 2.75 (t, *J*=7.1 Hz, 2H), 2.10 (m, 4H), 1.51 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 160.9, 128.8, 127.7, 127.6, 127.5, 52.8, 41.0, 29.8, 26.5. MS (ESI) [M+H]⁺ *m/z* 224.

4-(5-(Furan-2-yl)-2H-tetrazol-2-yl)butylamine (5q)

Yield 95%. ¹H NMR (400 MHz, CDCl₃): δ 7.49 (m, 1H), 7.00 (m, 1H), 6.45 (m, 1H), 4.58 (m, 2H), 2.64 (m, 2H), 2.00 (m, 4H), 1.41 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 157.9, 145.3, 142.6, 111.5, 111.0, 52.8, 40.8, 29.5, 26.4. MS (ESI) [M+H]⁺ *m/z* 208.

3-O-Descladinosyl-6-O-methyl-2'-O-benzoyl erythromycin A (6)

Stage a: to a solution of clarithromycin (9.0 g, 12 mmol) in water (100 ml) and ethanol (500 ml) at 0 °C was added HCl(aq) (2 mol l⁻¹, 21.6 ml) dropwise within 50 min. The solution was stirred at room temperature for 24 h. After 24 h, NaOH(aq) (2 mol l⁻¹, 120 ml) was added to adjust pH of the solution to 10.5~11.0, then the mixture was stirred for 1 h at 0 °C. The resulted precipitation was filtered, washed with a little water and yielded 3-O-descladinosyl-6-O-methyl-erythromycin A as white solid (6.2 g, 87%). ¹H NMR (400 MHz, CDCl₃): δ 5.18 (dd, *J*=11.0, 2.1 Hz, 1H), 4.41 (d, *J*=7.4 Hz, 1H), 3.92 (s, 1H), 3.85 (s, 1H), 3.69 (s, 1H), 3.51~3.58 (m, 2H), 3.37~3.41 (m, 1H), 3.22~3.27 (m, 2H), 3.00~3.02 (m, 1H), 2.97 (s, 3H), 2.64~2.68 (m, 1H), 2.64~2.68 (m, 1H), 2.56~2.60 (m, 2H), 2.32 (s, 6H), 2.17 (s, 3H), 2.11~2.14 (m, 1H), 1.90~1.93 (m, 2H), 1.63 (s, br, -OH), 1.36 (s, 3H), 1.25~1.30 (m, 6H), 1.18 (s, 3H), 1.11~1.14 (m, 9H), 0.84 (t, *J*=7.4 Hz, 3H). MS (ESI) [M+H]⁺ *m/z* 590.

Stage b: to a solution of 3-O-descladinosyl-6-O-methyl-erythromycin A (6 g, 10 mmol) in anhydrous CH₂Cl₂ (25 ml) at 0 °C was added benzoic anhydride (3.8 g, 16 mmol), triethylamine (2.2 ml, 16 mmol) and a sprinkle of 5-dimethylaminopyridine. The solution was stirred for 58 h at room temperature. Cold saturated NaHCO₃ (aq) (20 ml) was added and the mixture was stirred for another 30 min. Then the organic layer was separated and washed with water, brine, dried over Na₂SO₄, filtered, the filtrate was concentrated *in vacuo*, the residue was purified by column chromatography on silica gel using petroleum:acetone:triethylamine (5:1:0.01) as eluent to afford 6 (6.03 g, 86%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 8.06 (d, *J*=7.1 Hz, 2H), 7.57 (d, *J*=7.4 Hz, 1H), 7.45 (d, *J*=7.8 Hz, 2H), 5.12 (dd, *J*=11.1, 2.3 Hz, 1H), 5.04 (m, 1H), 4.75 (d, *J*=7.6 Hz, 1H), 3.94 (s, 1H), 3.73~3.75 (m, 2H), 3.53~3.58 (m, 1H), 3.43~3.57 (m, 1H), 2.93 (s, 3H), 2.86~2.90 (m, 1H), 2.48~2.68 (m, 2H), 2.28 (s, 6H), 1.97~1.99 (m, 1H), 1.87~1.92 (m, 1H), 1.60~1.65 (m, 1H), 1.37~1.47 (m, 3H), 1.19~1.33 (m, 9H), 1.04~1.08 (m, 9H), 0.81 (t, *J*=7.4 Hz, 3H). MS (ESI) [M+H]⁺ *m/z* 694.

3-O-Descladinosyl-6-O-methyl-cyclic 11,12-carbonate-2'-O-benzoyl erythromycin A (7)

To a solution of compound 6 (2 g, 2.89 mmol) in CH₂Cl₂ (27 ml) was added pyridine (1.87 ml, 23.12 mmol), the solution was stirred at 0 °C for 20 min under nitrogen atmosphere. After 20 min, triphosgene (1.03 g, 3.47 mmol) in

CH_2Cl_2 (5 ml) was added to above solution. The solution was stirred at room temperature for another 7 h. After quenching with cold brine (30 ml) at 0°C , the organic layer was separated and the aqueous layer was extracted with dichloromethane (20 ml $\times$ 3). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered, the filtrate was concentrated *in vacuo*, the residue was purified via silica gel column using petroleum:acetone:triethylamine (5:1:0.01) as eluent to afford **7** (1.72 g, 83%) as a white solid. ^1H NMR (400 MHz, CDCl_3): δ 8.06 (d, $J=7.8$ Hz, 2H), 7.56 (t, $J=7.4$ Hz, 1H), 7.45 (t, $J=7.8$ Hz, 2H), 5.02~5.09 (m, 2H), 4.73 (d, $J=7.6$ Hz, 1H), 4.68 (s, 1H), 3.72 (d, $J=2.5$ Hz, 1H), 3.54~3.60 (m, 1H), 3.43~3.48 (m, 2H), 2.91 (s, 3H), 2.80~2.87 (m, 1H), 2.54~2.64 (m, 2H), 2.28 (s, 6H), 1.76~1.89 (m, 3H), 1.43~1.51 (m, 3H), 1.39~1.41 (m, 1H), 1.38 (s, 3H), 1.20~1.32 (m, 9H), 1.10~1.17 (m, 3H), 1.05 (d, $J=7.1$ Hz, 3H), 0.82 (t, $J=7.4$ Hz, 3H), 0.70 (d, $J=7.5$ Hz, 3H). MS (ESI) $[\text{M}+\text{H}]^+$ m/z 720.

3-O-Descladinosyl-6-O-methyl-3-oxo-cyclic 11,12-carbonate-2'-O-benzoyl erythromycin A (8)

To a solution of compound **8** (0.2 g, 0.28 mmol) in anhydrous dichloromethane (3 ml) was added pyridinium chlorochromate (0.18 g, 0.85 mmol), the solution was stirred for 25 h at room temperature. The reaction was diluted with dichloromethane (5 ml) and washed with saturated NaHCO_3 , brine, dried over Na_2SO_4 , filtered, the filtrate was concentrated in vacuum, the residue was purified by column chromatography on silica gel using petroleum:acetone:triethylamine (3:1:0.01) as eluent to afford **8** (0.15 g, 71%) as a white solid. ^1H NMR (400 MHz, CDCl_3): δ 8.03 (d, $J=7.8$ Hz, 2H), 7.57 (t, $J=7.4$ Hz, 1H), 7.44 (t, $J=7.8$ Hz, 2H), 4.95~5.05 (m, 2H), 4.60 (s, 1H), 4.54 (d, $J=7.6$ Hz, 1H), 4.19 (d, $J=7.8$ Hz, 1H), 3.59~3.71 (m, 2H), 2.80~2.93 (m, 3H), 2.64 (s, 3H), 2.26 (s, 6H), 1.78~1.85 (m, 2H), 1.65 (dd, $J=14.5$, 2.7 Hz, 1H), 1.51~1.56 (m, 1H), 1.48 (s, 3H), 1.25~1.34 (m, 9H), 1.17 (d, $J=6.8$ Hz, 3H), 1.13 (d, $J=7.0$ Hz, 3H), 0.96 (d, $J=7.5$ Hz, 3H), 0.86 (t, $J=7.4$ Hz, 3H). MS (ESI) $[\text{M}+\text{H}]^+$ m/z 718.

10,11-Didehydro-11-deoxy-3-O-descladinosyl-6-O-methyl-3-oxo-cyclic 1,12-carbonate-2'-O-benzoyl erythromycin A (9)

To solution of compound **8** (1.86 g, 2.6 mmol) in acetone (30 ml) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.99 g, 6.5 mmol), the solution was stirred at 60°C for 5 h. On concentrating and drying in vacuum, the residue was dissolved in dichloromethane and washed with brine, dried over Na_2SO_4 , filtered, the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using petroleum:acetone:triethylamine (6:1:0.01) as eluent to afford **9** (1.71 g, 98 %) as a white solid. ^1H NMR (400 MHz, CDCl_3): δ 8.01 (d, $J=8.1$ Hz, 2H), 7.55 (t, $J=7.6$ Hz, 1H), 7.43 (t, $J=7.6$ Hz, 2H), 6.55 (s, 1H), 4.99~5.04 (m, 1H), 4.54 (dd, $J=9.6$, 2.7 Hz, 1H), 4.51 (d, $J=7.6$ Hz, 1H), 4.15 (d, $J=8.3$ Hz, 1H), 3.59~3.64 (m, 2H), 3.13~3.16 (m, 1H), 2.92~2.96 (m, 1H), 2.85 (s, 3H), 2.33~2.36 (m, 1H), 2.26 (s, 6H), 1.99 (s, 3H), 1.86~1.95 (m, 2H), 1.77~1.82 (m, 2H), 1.50~1.56 (m, 1H), 1.40~1.48 (m, 3H), 1.36 (s, 3H), 1.26~1.30 (m, 9H), 1.15 (d, $J=6.8$ Hz, 3H), 0.95 (d, $J=7.4$ Hz, 3H), 0.89 (t, $J=7.3$ Hz, 3H). MS (ESI) $[\text{M}+\text{H}]^+$ m/z 674.

10,11-Didehydro-11-deoxy-3-O-descladinosyl-6-O-methyl-3-oxo-12-(1H-imidazole-1-carboxylate)-2'-O-benzoyl erythromycin A (10)

To a solution of compound **9** (2 g, 3 mmol) in DMF (15 ml) was added sodium hydride (60% dispersion in mineral oil 0.25 g, 6 mmol), the solution was stirred at -10°C under nitrogen atmosphere. After stirring for 30 min, a solution of CDI (1.56 g, 9 mmol) in DMF (15 ml) was added and stirred for another 2 h at -5°C to -10°C . Then the mixture was warmed to 0°C , ice water (50 ml) was added cautiously to quench the excess sodium hydride. The precipitation was filtered, washed with a little water twice. The material was diluted with dichloromethane and washed with brine, dried over Na_2SO_4 , filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using petroleum:acetone:triethylamine (6:1:0.01) as eluent to afford **10** (2.05 g, 90%) as a white solid. ^1H NMR (400 MHz, CDCl_3): δ 8.08 (s, 1H), 8.03 (d, $J=7.1$ Hz, 2H), 7.56 (t, $J=7.4$ Hz, 1H), 7.44 (t, $J=7.8$ Hz, 2H), 7.35~7.36 (m, 1H), 7.06~7.07 (m, 1H), 6.76 (s, 1H), 5.66 (dd, $J=9.8$, 3.2 Hz, 1H), 4.99~5.04 (m, 1H), 4.51 (d, $J=7.6$ Hz, 1H), 4.15 (d, $J=8.8$ Hz, 1H), 3.55~3.66 (m, 3H), 3.08~3.23 (m, 3H), 2.90 (s, 1H),

2.80~2.97 (m, 2H), 2.78 (m, 3H), 2.28~2.34 (m, 4H), 2.25 (s, 6H), 2.17 (d, $J=3.1$ Hz, 1H), 1.81 (s, 3H), 1.76 (s, 3H), 1.59~1.68 (m, 4H), 1.40~1.48 (m, 3H), 1.36 (s, 3H), 1.22~1.35 (m, 15H), 1.15 (d, $J=6.7$ Hz, 3H), 0.95 (t, $J=7.3$ Hz, 3H). MS (ESI) $[\text{M}+\text{H}]^+$ m/z 768.

General procedures for the synthesis of compounds 11a–q

To a solution of compound **10** (0.26 mmol) in acetonitrile (1 ml) was added compound (**5a–q**) (0.53 mmol), the solution was heated in a 55°C oil bath and stirred for 24 h. On quenching with ice water (5 ml), the mixture was diluted with ethyl acetate, washed with saturated NaHCO_3 , and brine, dried over Na_2SO_4 . Filtered, the filtrate was concentrated *in vacuo*. After adding methanol (5 ml) to the crude material, the solution was stirred at 60°C for another 25 h. On concentrating, the crude product was purified by column chromatography on silica gel using petroleum:acetone:triethylamine (5:1:0.01) as eluent to afford compounds **11a–q** as a white solid.

Compound 11a

Yield 58%. ^1H NMR (400 MHz, CDCl_3): δ 8.76 (m, 1H), 8.35 (m, 1H), 7.90 (m, 1H), 7.42 (m, 1H), 5.02~5.11 (m, 2H), 4.91 (dd, $J=10.6$, 2.1 Hz, 1H), 4.27 (d, $J=7.3$ Hz, 1H), 4.20 (d, $J=8.7$ Hz, 1H), 3.65~3.82 (m, 3H), 3.52~3.56 (m, 2H), 3.15~3.20 (m, 1H), 3.02~3.09 (m, 2H), 2.51 (s, 3H), 2.41~2.47 (m, 1H), 2.27 (s, 6H), 1.89~1.93 (m, 2H), 1.80 (dd, $J=14.5$, 2.3 Hz, 1H), 1.66~1.69 (m, 1H), 1.52~1.59 (m, 2H), 1.45 (s, 3H), 1.25~1.33 (m, 15H), 1.13 (d, $J=6.9$ Hz, 3H), 0.97 (d, $J=6.9$ Hz, 3H), 0.82 (t, $J=7.3$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 215.8, 203.6, 169.5, 157.1, 151.7, 149.5, 145.1, 137.2, 125.1, 124.5, 103.9, 82.3, 79.6, 78.1, 77.1, 70.3, 69.6, 65.9, 60.9, 51.1, 49.6, 47.6, 47.5, 44.8, 41.5, 40.2, 39.5, 38.9, 28.2, 27.6, 22.2, 21.1, 19.7, 18.2, 15.7, 14.5, 14.3, 13.8, 10.3. MS (ESI) $[\text{M}+\text{H}]^+$ m/z 801.0. HRMS (ESI, m/z) calcd for $\text{C}_{40}\text{H}_{61}\text{N}_7\text{O}_{10}$ 800.4553, found 800.4549.

Compound 11b

Yield 50.2%. ^1H NMR (400 MHz, CDCl_3): δ 8.77 (d, $J=4.7$ Hz, 1H), 8.24 (d, $J=7.9$ Hz, 1H), 7.84 (m, 1H), 7.37 (m, 1H), 4.95 (dd, $J=9.7$, 2.1 Hz, 1H), 4.73~4.86 (m, 2H), 4.27 (d, $J=6.9$ Hz, 1H), 4.20 (d, $J=8.8$ Hz, 1H), 3.78~3.85 (m, 2H), 3.65~3.70 (m, 1H), 3.51~3.57 (m, 2H), 3.15~3.18 (m, 1H), 3.00~3.12 (m, 2H), 2.58 (s, 3H), 2.35~2.54 (m, 1H), 2.27 (s, 6H), 1.93~1.98 (m, 2H), 1.79 (dd, $J=13.4$, 2.2 Hz, 1H), 1.66~1.69 (m, 1H), 1.56~1.59 (m, 2H), 1.46 (s, 3H), 1.34 (d, $J=6.8$ Hz, 3H), 1.24~1.29 (m, 12H), 1.13 (d, $J=6.9$ Hz, 3H), 1.00 (d, $J=6.9$ Hz, 3H), 0.88 (t, $J=7.3$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 215.9, 203.6, 169.6, 164.7, 157.1, 150.2, 147.0, 136.9, 124.5, 122.5, 103.9, 82.3, 79.6, 78.1, 77.2, 70.3, 69.5, 65.9, 60.8, 51.2, 51.1, 49.7, 47.6, 44.8, 40.2, 41.5, 40.2, 39.5, 38.9, 28.2, 27.1, 22.2, 21.1, 19.6, 18.2, 15.7, 14.5, 14.3, 13.8, 10.3. MS (ESI) $[\text{M}+\text{H}]^+$ m/z 801.1. HRMS (ESI, m/z) calcd for $\text{C}_{40}\text{H}_{60}\text{N}_7\text{O}_{10}$ 798.4407, found 798.4407.

Compound 11c

Yield 55.8%. ^1H NMR (400 MHz, CDCl_3): δ 9.38 (s, 1H), 8.69 (d, $J=4.1$ Hz, 1H), 8.43 (d, $J=7.9$ Hz, 1H), 7.40~7.43 (m, 1H), 4.95 (d, $J=8.7$ Hz, 1H), 4.71~4.83 (m, 2H), 4.26 (d, $J=7.3$ Hz, 1H), 4.20 (d, $J=8.8$ Hz, 1H), 3.82~3.87 (m, 2H), 3.67~3.76 (m, 1H), 3.51~3.57 (m, 2H), 3.15~3.19 (m, 1H), 2.99~3.13 (m, 1H), 2.56 (s, 3H), 2.37~2.51 (m, 1H), 2.27 (s, 6H), 1.93~1.97 (m, 1H), 1.78~1.82 (m, 1H), 1.66~1.69 (m, 1H), 1.56~1.61 (m, 2H), 1.47 (s, 3H), 1.35 (d, $J=6.8$ Hz, 3H), 1.21~1.29 (m, 12H), 1.14 (d, $J=6.9$ Hz, 3H), 1.01 (d, $J=6.9$ Hz, 3H), 0.88 (t, $J=7.3$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 216.0, 203.5, 169.7, 162.8, 157.1, 151.0, 148.2, 134.2, 123.9, 123.5, 103.9, 82.3, 79.6, 78.1, 77.2, 70.3, 69.5, 65.8, 60.7, 51.2, 51.1, 49.6, 47.6, 44.8, 41.3, 40.2, 39.5, 38.9, 28.2, 27.1, 22.2, 21.1, 19.5, 18.2, 15.7, 14.5, 14.3, 13.8, 10.3. MS (ESI) $[\text{M}+\text{H}]^+$ m/z 801.0. HRMS (ESI, m/z) calcd for $\text{C}_{40}\text{H}_{61}\text{N}_7\text{O}_{10}$ 800.4553, found 800.4552.

Compound 11d

Yield 49.5%. ^1H NMR (400 MHz, CDCl_3): δ 8.75 (d, $J=4.4$ Hz, 2H), 8.03 (d, $J=5.8$ Hz, 2H), 4.95 (dd, $J=10.6$, 2.3 Hz, 1H), 4.73~4.83 (m, 2H), 4.26 (d, $J=7.3$ Hz, 1H), 4.19 (d, $J=8.9$ Hz, 1H), 3.80~3.85 (m, 2H), 3.64~3.71 (m, 1H), 3.51~3.55 (m, 2H), 3.01~3.20 (m, 3H), 2.55 (s, 3H), 2.37~2.51 (m, 1H), 2.29 (s, 6H), 1.94~1.98 (m, 1H), 1.78~1.81 (m, 1H), 1.67~1.69

(m, 1H), 1.55~1.61 (m, 2H), 1.47 (s, 3H), 1.35 (d, $J=6.8$ Hz, 3H), 1.22~1.29 (m, 12H), 1.14 (d, $J=6.9$ Hz, 3H), 1.01 (d, $J=6.9$ Hz, 3H), 0.87 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 216.0, 203.6, 169.7, 163.1, 157.2, 150.5, 135.0, 120.9, 103.9, 82.4, 79.6, 78.2, 77.3, 70.3, 69.5, 65.9, 60.7, 51.2, 51.1, 49.7, 47.6, 44.8, 41.4, 40.2, 39.5, 38.9, 28.2, 27.1, 22.2, 21.1, 19.6, 18.2, 15.8, 14.5, 14.3, 13.8, 10.4. MS (ESI) $[\text{M}+\text{H}]^+$ m/z 801.0. HRMS (ESI, m/z) calcd for $\text{C}_{40}\text{H}_{61}\text{N}_7\text{O}_{10}$ 800.4553, found 800.4568.

Compound 11e

Yield 60.1%. ^1H NMR (400 MHz, CDCl_3): δ 8.78 (d, $J=4.8$ Hz, 1H), 8.35 (d, $J=7.5$ Hz, 1H), 7.89 (t, $J=7.8$ Hz, 1H), 7.44 (m, 1H), 4.96~5.08 (m, 2H), 4.91 (d, $J=10.5$ Hz, 1H), 4.29 (d, $J=7.3$ Hz, 1H), 4.24 (d, $J=8.7$ Hz, 1H), 3.83~3.88 (m, 1H), 3.64~3.76 (m, 2H), 3.53~3.58 (m, 2H), 3.03~3.21 (m, 3H), 2.61 (s, 3H), 2.43~2.48 (m, 1H), 2.27 (s, 6H), 1.91~2.04 (m, 3H), 1.67~1.84 (m, 4H), 1.52~1.62 (m, 2H), 1.47 (s, 3H), 1.24~1.38 (m, 15H), 1.16 (d, $J=6.8$ Hz, 3H), 1.01 (d, $J=6.8$ Hz, 3H), 0.83 (t, $J=7.3$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 215.9, 203.6, 169.5, 157.1, 151.5, 149.6, 144.9, 137.2, 125.1, 124.4, 103.9, 82.1, 79.5, 78.1, 77.1, 70.3, 69.5, 65.9, 60.3, 51.1, 49.6, 49.1, 47.5, 44.8, 42.7, 40.1, 39.4, 38.9, 28.1, 27.4, 24.0, 22.1, 21.1, 19.6, 18.3, 15.7, 14.5, 14.3, 13.8, 10.3. MS (ESI) $[\text{M}+\text{H}]^+$ m/z 815.0. HRMS (ESI, m/z) calcd for $\text{C}_{41}\text{H}_{63}\text{N}_7\text{O}_{10}$ 814.4709, found 814.4715.

Compound 11f

Yield 51.5%. ^1H NMR (400 MHz, CDCl_3): δ 8.78 (d, $J=4.7$ Hz, 1H), 8.24 (d, $J=7.9$ Hz, 1H), 7.86 (m, 1H), 7.37 (m, 1H), 4.94 (dd, $J=10.6$, 2.1 Hz, 1H), 4.71~4.81 (m, 2H), 4.28 (d, $J=7.3$ Hz, 1H), 4.23 (d, $J=8.3$ Hz, 1H), 3.83 (q, $J=6.8$ Hz, 1H), 3.63~3.77 (m, 2H), 3.51~3.58 (m, 2H), 3.04~3.21 (m, 3H), 2.62 (s, 3H), 2.47 (m, 1H), 2.28 (s, 6H), 2.11~2.17 (m, 2H), 1.83~1.97 (m, 1H), 1.55~1.82 (m, 6H), 1.47 (s, 3H), 1.23~1.34 (m, 15H), 1.16 (d, $J=7.0$ Hz, 3H), 1.01 (d, $J=6.9$ Hz, 3H), 0.87 (t, $J=7.3$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 216.0, 203.6, 169.6, 164.7, 157.2, 150.2, 147.0, 136.9, 124.6, 122.4, 103.9, 82.2, 79.6, 78.1, 77.3, 70.3, 69.5, 65.9, 52.9, 51.2, 49.8, 47.5, 44.8, 42.6, 40.2, 39.5, 39.0, 28.2, 26.8, 24.1, 22.2, 21.1, 19.7, 18.3, 15.6, 14.6, 14.3, 13.8, 10.4. MS (ESI) $[\text{M}+\text{H}]^+$ m/z 815.0. HRMS (ESI, m/z) calcd for $\text{C}_{41}\text{H}_{63}\text{N}_7\text{O}_{10}$ 814.4709, found 814.4717.

Compound 11g

Yield 65.7%. ^1H NMR (400 MHz, CDCl_3): δ 9.36 (s, 1H), 8.69 (d, $J=4.1$ Hz, 1H), 8.41 (dt, $J=7.9$, 1.7 Hz, 1H), 7.40~7.43 (m, 1H), 4.95 (dd, $J=10.5$, 1.8 Hz, 1H), 4.69~4.74 (m, 2H), 4.27 (d, $J=7.3$ Hz, 1H), 4.20 (d, $J=8.8$ Hz, 1H), 3.64~3.85 (m, 3H), 3.49~3.56 (m, 2H), 3.03~3.19 (m, 3H), 2.61 (s, 3H), 2.41~2.47 (m, 1H), 2.26 (s, 6H), 2.07~2.15 (m, 2H), 1.93~1.98 (m, 1H), 1.54~1.83 (m, 7H), 1.46 (s, 3H), 1.23~1.33 (m, 15H), 1.15 (d, $J=6.9$ Hz, 3H), 1.00 (d, $J=6.9$ Hz, 3H), 0.86 (t, $J=7.2$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 216.1, 203.6, 169.6, 162.7, 157.3, 151.0, 148.2, 134.2, 123.9, 123.6, 104.0, 82.2, 79.6, 78.2, 70.4, 69.6, 65.9, 60.4, 52.9, 51.2, 49.8, 47.5, 44.5, 42.6, 40.2, 39.6, 39.0, 28.2, 26.8, 24.2, 22.2, 21.2, 19.7, 18.4, 15.6, 14.6, 14.3, 13.9, 10.4. MS (ESI) $[\text{M}+\text{H}]^+$ m/z 814.9. HRMS (ESI, m/z) calcd for $\text{C}_{41}\text{H}_{63}\text{N}_7\text{O}_{10}$ 814.4709, found 814.4700.

Compound 11h

Yield 74.1%. ^1H NMR (400 MHz, CDCl_3): δ 8.75 (d, $J=5.3$ Hz, 2H), 8.02 (d, $J=5.4$ Hz, 2H), 4.92 (d, $J=9.7$ Hz, 1H), 4.70~4.79 (m, 2H), 4.28 (d, $J=7.3$ Hz, 1H), 4.23 (d, $J=8.7$ Hz, 1H), 3.74~3.86 (m, 2H), 3.63~3.70 (m, 1H), 3.52~3.56 (m, 2H), 3.03~3.20 (m, 3H), 2.61 (s, 3H), 2.44~2.49 (m, 1H), 2.27 (s, 6H), 2.06~2.15 (m, 2H), 1.93~1.98 (m, 1H), 1.80~1.84 (m, 1H), 1.66~1.75 (m, 2H), 1.53~1.62 (m, 2H), 1.47 (s, 3H), 1.24~1.37 (m, 15H), 1.15 (d, $J=6.9$ Hz, 3H), 1.01 (d, $J=6.9$ Hz, 3H), 0.86 (t, $J=7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 216.1, 203.5, 169.6, 162.9, 157.2, 150.5, 135.0, 120.8, 103.9, 82.2, 79.5, 78.2, 70.3, 69.9, 65.9, 60.4, 52.9, 51.1, 49.7, 47.5, 44.8, 42.6, 40.2, 39.5, 38.9, 28.2, 26.7, 24.1, 22.2, 21.1, 19.7, 18.3, 15.6, 14.6, 14.3, 13.8, 10.4. MS (ESI) $[\text{M}+\text{H}]^+$ m/z 814.9. HRMS (ESI, m/z) calcd for $\text{C}_{41}\text{H}_{63}\text{N}_7\text{O}_{10}$ 814.4709, found 814.4711.

Compound 11i

Yield 53.0%. ^1H NMR (400 MHz, CDCl_3): δ 8.77 (d, $J=4.8$ Hz, 1H), 8.35 (d, $J=8.0$ Hz, 1H), 7.89 (dt, $J=1.7$, 7.8 Hz, 1H), 7.44 (m, 1H), 4.91~4.99 (m, 3H), 4.28 (d, $J=7.3$ Hz, 1H), 4.24 (d, $J=8.6$ Hz, 1H), 3.84 (q, $J=6.7$ Hz, 1H), 3.50~3.64 (m, 4H), 3.16~3.20 (m, 1H), 3.05~3.14 (m, 2H), 2.62 (s, 3H), 2.42~2.49 (m, 1H), 2.27 (s, 6H), 1.93~2.00 (m, 3H), 1.82 (dd, $J=14.5$, 2.3 Hz, 1H), 1.55~1.69 (m, 5H), 1.46 (s, 3H), 1.24~1.38 (m, 15H), 1.16 (d, $J=7.0$ Hz, 3H), 1.00 (d, $J=6.9$ Hz, 3H), 0.85 (t, $J=7.3$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 216.0, 203.7, 169.5, 157.1, 151.6, 149.6, 145.0, 137.3, 125.1, 124.5, 103.9, 82.1, 79.5, 78.1, 77.2, 70.3, 69.6, 65.9, 60.5, 51.2, 49.7, 49.6, 47.5, 44.9, 43.3, 40.2, 39.5, 39.0, 29.6, 28.2, 26.5, 23.8, 22.3, 21.2, 19.7, 18.3, 15.7, 14.6, 14.3, 13.9, 10.4. MS (ESI) $[\text{M}+\text{H}]^+$ m/z 829.1. HRMS (ESI, m/z) calcd for $\text{C}_{42}\text{H}_{65}\text{N}_7\text{O}_{10}$ 828.4866, found 828.4859.

Compound 11j

Yield 57.6%. ^1H NMR (400 MHz, CDCl_3): δ 8.78 (d, $J=4.7$ Hz, 1H), 8.24 (d, $J=7.9$ Hz, 1H), 7.86 (m, 1H), 7.38 (m, 1H), 4.94 (dd, $J=10.5$, 2.2 Hz, 1H), 4.68~4.72 (m, 2H), 4.28 (d, $J=7.3$ Hz, 1H), 4.25 (d, $J=8.6$ Hz, 1H), 3.83 (m, 1H), 3.52~3.65 (m, 4H), 3.06~3.21 (m, 3H), 2.65 (s, 3H), 2.44~2.49 (m, 1H), 2.28 (s, 6H), 2.11~2.16 (m, 2H), 1.93~1.96 (m, 1H), 1.81 (dd, $J=14.5$, 2.1 Hz, 1H), 1.54~1.70 (m, 5H), 1.47 (s, 3H), 1.21~1.35 (m, 15H), 1.08 (d, $J=7.0$ Hz, 3H), 1.01 (d, $J=6.9$ Hz, 3H), 0.86 (t, $J=7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 216.0, 203.7, 169.6, 164.7, 157.2, 150.3, 147.0, 137.0, 124.6, 122.4, 103.9, 82.1, 79.6, 78.1, 77.2, 70.3, 69.6, 65.9, 60.5, 53.4, 51.2, 49.8, 47.5, 44.9, 43.2, 40.2, 39.5, 39.0, 29.0, 28.2, 26.5, 23.8, 22.3, 21.2, 19.7, 18.4, 15.6, 14.4, 14.3, 13.9, 10.4. MS (ESI) $[\text{M}+\text{H}]^+$ m/z 829.1. HRMS (ESI, m/z) calcd for $\text{C}_{42}\text{H}_{65}\text{N}_7\text{O}_{10}$ 828.4866, found: 828.4878.

Compound 11k

Yield 50.9%. ^1H NMR (400 MHz, CDCl_3): δ 9.38 (s, 1H), 8.70 (d, $J=4.8$ Hz, 1H), 8.43 (dt, $J=8.0$, 1.9 Hz, 1H), 7.41~7.45 (m, 1H), 4.94 (dd, $J=10.5$, 2.3 Hz, 1H), 4.65~4.72 (m, 2H), 4.28 (d, $J=7.3$ Hz, 1H), 4.24 (d, $J=8.7$ Hz, 1H), 3.85 (q, $J=6.8$ Hz, 1H), 3.50~3.70 (m, 4H), 2.99~3.21 (m, 3H), 2.65 (s, 3H), 2.41~2.47 (m, 1H), 2.28 (s, 6H), 2.08~2.16 (m, 2H), 1.93~1.98 (m, 1H), 1.54~1.83 (m, 6H), 1.46 (s, 3H), 1.23~1.33 (m, 15H), 1.16 (d, $J=7.0$ Hz, 3H), 1.01 (d, $J=6.9$ Hz, 3H), 0.85 (t, $J=7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 216.1, 203.7, 169.6, 162.7, 157.2, 151.0, 148.1, 134.2, 123.8, 123.6, 103.9, 82.2, 79.6, 78.2, 70.3, 69.6, 65.9, 60.5, 53.3, 51.2, 49.8, 47.5, 44.5, 43.2, 40.2, 39.5, 39.0, 28.9, 28.2, 26.4, 23.7, 22.2, 21.2, 19.7, 18.4, 15.7, 14.6, 14.3, 13.9, 10.3. MS (ESI) $[\text{M}+\text{H}]^+$ m/z 829.1. HRMS (ESI, m/z) calcd for $\text{C}_{42}\text{H}_{65}\text{N}_7\text{O}_{10}$ 828.4866, found 828.4874.

Compound 11l

Yield 55.6%. ^1H NMR (400 MHz, CDCl_3): δ 8.76 (d, $J=4.8$ Hz, 2H), 8.02 (d, $J=4.8$ Hz, 2H), 4.93 (d, $J=10.2$ Hz, 1H), 4.66~4.73 (m, 2H), 4.28 (d, $J=7.3$ Hz, 1H), 4.24 (d, $J=8.7$ Hz, 1H), 3.82~3.87 (m, 1H), 3.52~3.69 (m, 4H), 3.05~3.21 (m, 3H), 2.65 (s, 3H), 2.44~2.50 (m, 1H), 2.32 (s, 6H), 2.10~2.18 (m, 2H), 1.92~1.98 (m, 1H), 1.81~1.84 (m, 1H), 1.52~1.72 (m, 5H), 1.47 (s, 3H), 1.24~1.36 (m, 15H), 1.16 (d, $J=7.0$ Hz, 3H), 1.01 (d, $J=6.8$ Hz, 3H), 0.85 (t, $J=7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 216.1, 203.7, 169.6, 162.7, 157.1, 150.5, 134.9, 120.8, 103.9, 82.2, 79.5, 78.1, 77.2, 70.3, 69.5, 65.8, 60.4, 53.3, 51.2, 49.7, 47.5, 44.9, 43.1, 40.2, 39.5, 39.0, 28.8, 28.2, 26.4, 23.7, 22.2, 21.1, 19.7, 18.3, 15.7, 14.6, 14.3, 13.8, 10.4. MS (ESI) $[\text{M}+\text{H}]^+$ m/z 829.1. HRMS (ESI, m/z) calcd for $\text{C}_{42}\text{H}_{65}\text{N}_7\text{O}_{10}$ 828.4866, found 828.4862.

Compound 11m

Yield 45.2%. ^1H NMR (400 MHz, CDCl_3): δ 8.14~8.16 (m, 21H), 7.41~7.49 (m, 3H), 4.95 (dd, $J=10.5$, 2.1 Hz, 1H), 4.70~4.78 (m, 2H), 4.26 (d, $J=7.3$ Hz, 1H), 4.18 (d, $J=8.8$ Hz, 1H), 3.79~3.85 (m, 2H), 3.67~3.72 (m, 1H), 3.57 (s, 1H), 3.51~3.54 (m, 1H), 3.01~3.18 (m, 3H), 2.55 (s, 3H), 2.37~2.46 (m, 2H), 2.26 (s, 6H), 1.93~1.98 (m, 1H), 1.79 (dd, $J=14.5$, 2.2 Hz, 1H), 1.51~1.68 (m, 3H), 1.47 (s, 3H), 1.35 (d, $J=6.8$ Hz, 3H), 1.21~1.31 (m, 12H), 1.13 (d, $J=6.9$ Hz, 3H), 1.01 (d, $J=6.9$ Hz, 3H), 0.87 (t, $J=7.3$ Hz, 3H). ^{13}C

NMR (100 MHz, CDCl₃): δ 215.9, 203.6, 169.6, 165.1, 157.2, 130.0, 128.7, 127.7, 126.0, 103.9, 82.4, 79.6, 78.1, 77.2, 70.3, 69.6, 65.9, 60.8, 51.2, 50.9, 49.7, 47.6, 44.8, 41.5, 40.2, 39.5, 38.9, 29.7, 28.2, 27.1, 22.2, 21.1, 19.5, 18.2, 15.8, 14.5, 14.3, 13.8, 10.3. MS (ESI) [M+H]⁺ *m/z* 799.9. HRMS (ESI, *m/z*) calcd for C₄₁H₆₂N₆O₁₀, 799.4527, found 799.4583.

Compound 11n

Yield 61.4%. ¹H NMR (400 MHz, CDCl₃): δ 8.13~8.15 (d, *J*=7.9 Hz, 2H), 7.42~7.50 (m, 3H), 4.95 (dd, *J*=10.2, 2.2 Hz, 1H), 4.65~4.74 (m, 2H), 4.28 (d, *J*=7.3 Hz, 1H), 4.24 (d, *J*=8.7 Hz, 1H), 3.79~3.90 (m, 1H), 3.73~3.81 (m, 1H), 3.63~3.71 (m, 1H), 3.58 (s, 1H), 3.52~3.54 (m, 1H), 3.03~3.18 (m, 3H), 2.64 (s, 3H), 2.58~2.59 (m, 1H), 2.43~2.49 (m, 1H), 2.27 (s, 6H), 2.08~2.15 (m, 2H), 1.93~1.98 (m, 1H), 1.81 (dd, *J*=14.5, 2.3 Hz, 1H), 1.66~1.76 (m, 3H), 1.53~1.62 (m, 2H), 1.47 (s, 3H), 1.18~1.31 (m, 15H), 1.15 (d, *J*=7.0 Hz, 3H), 1.01 (d, *J*=6.9 Hz, 3H), 0.86 (t, *J*=7.3 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 216.0, 203.6, 169.6, 165.0, 157.2, 130.0, 128.8, 127.7, 126.9, 103.9, 82.2, 79.6, 78.2, 77.2, 70.3, 69.6, 65.9, 60.4, 52.7, 51.2, 49.8, 47.5, 44.9, 42.7, 40.2, 39.6, 39.0, 29.7, 28.2, 26.8, 24.2, 22.2, 21.1, 19.7, 18.4, 15.6, 14.6, 14.4, 13.9, 10.4. MS (ESI) [M+H]⁺ *m/z* 813.8. HRMS (ESI, *m/z*) calcd for C₄₂H₆₄N₆O₁₀, 813.4757, found 813.4759.

Compound 11o

Yield 52.6%. ¹H NMR (400 MHz, CDCl₃): δ 7.79 (d, *J*=3.6 Hz, 1H), 7.43 (d, *J*=5.1 Hz, 1H), 7.13 (d, *J*=4.3 Hz, 1H), 4.95 (dd, *J*=10.6, 2.1 Hz, 1H), 4.69~4.75 (m, 2H), 4.27 (d, *J*=7.3 Hz, 1H), 4.20 (d, *J*=8.8 Hz, 1H), 3.77~3.85 (m, 2H), 3.65~3.70 (m, 1H), 3.52~3.57 (m, 2H), 3.16~3.20 (m, 1H), 3.02~3.10 (m, 2H), 2.57 (s, 3H), 2.34~2.41 (m, 2H), 2.29 (s, 6H), 1.93~1.99 (m, 1H), 1.79 (dd, *J*=14.5, 2.2 Hz, 1H), 1.67~1.70 (m, 1H), 1.52~1.61 (m, 2H), 1.47 (s, 3H), 1.34 (d, *J*=6.8 Hz, 3H), 1.17~1.31 (m, 12H), 1.14 (d, *J*=7.0 Hz, 3H), 1.01 (d, *J*=6.9 Hz, 3H), 0.82 (t, *J*=7.3 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 215.9, 203.6, 169.5, 161.2, 157.2, 129.4, 127.7, 127.6, 127.5, 103.9, 82.4, 79.6, 78.1, 70.3, 69.5, 65.9, 60.8, 51.2, 51.0, 49.7, 47.6, 44.8, 41.5, 40.2, 39.5, 38.9, 28.2, 27.1, 22.2, 21.1, 19.5, 18.2, 15.7, 14.6, 14.4, 13.8, 10.3. MS (ESI) [M+H]⁺ *m/z* 805.9. HRMS (ESI, *m/z*) calcd for C₃₉H₆₀N₆O₁₀S, 805.4164, found: 805.4166.

Compound 11p

Yield 56.4%. ¹H NMR (400 MHz, CDCl₃): δ 7.79 (d, *J*=3.5 Hz, 1H), 7.43 (d, *J*=5.0 Hz, 1H), 7.13 (d, *J*=4.3 Hz, 1H), 4.95 (dd, *J*=10.6, 2.0 Hz, 1H), 4.65~4.70 (m, 2H), 4.28 (d, *J*=7.3 Hz, 1H), 4.20 (d, *J*=8.7 Hz, 1H), 3.54~3.85 (m, 4H), 3.06~3.20 (m, 4H), 2.64 (s, 3H), 2.45 (m, 1H), 2.27 (s, 6H), 2.08~2.11 (m, 2H), 1.95~1.97 (m, 1H), 1.81 (dd, *J*=14.6, 2.3 Hz, 1H), 1.66~1.74 (m, 3H), 1.55~1.62 (m, 2H), 1.47 (s, 3H), 1.21~1.34 (m, 15H), 1.16 (d, *J*=6.9 Hz, 3H), 1.01 (d, *J*=6.9 Hz, 3H), 0.85 (t, *J*=7.3 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 216.0, 203.6, 169.6, 161.1, 157.3, 129.3, 127.8, 127.6, 127.5, 103.9, 82.2, 79.6, 78.1, 77.2, 70.3, 69.6, 65.9, 60.4, 52.7, 51.2, 49.8, 47.5, 44.9, 42.6, 40.2, 39.5, 38.9, 29.7, 28.2, 26.8, 24.1, 22.2, 21.1, 19.7, 18.3, 15.6, 14.6, 14.3, 13.9, 10.4. MS (ESI) [M+H]⁺ *m/z* 820.0. HRMS (ESI, *m/z*) calcd for C₄₀H₆₂N₆O₁₀S, 819.4321, found: 819.4314.

Compound 11q

Yield 57.7%. ¹H NMR (400 MHz, CDCl₃): δ 7.59 (d, *J*=3.5 Hz, 1H), 7.43 (d, *J*=5.0 Hz, 1H), 7.13 (d, *J*=4.3 Hz, 1H), 4.93 (dd, *J*=10.6, 2.2 Hz, 1H), 4.65~4.75 (m, 2H), 4.28 (d, *J*=7.3 Hz, 1H), 4.24 (d, *J*=8.7 Hz, 1H), 3.84 (q, *J*=6.8 Hz, 1H), 3.63~3.78 (m, 3H), 3.57 (s, 1H), 3.51~3.56 (m, 1H), 3.04~3.20 (m, 3H), 2.63 (s, 3H), 2.44~2.47 (m, 1H), 2.27 (s, 6H), 2.09~2.12 (m, 2H), 1.94~1.97 (m, 1H), 1.81 (dd, *J*=14.5, 2.3 Hz, 1H), 1.65~1.74 (m, 3H), 1.55~1.62 (m, 2H), 1.47 (s, 3H), 1.21~1.34 (m, 15H), 1.16 (d, *J*=6.9 Hz, 3H), 1.01 (d, *J*=7.0 Hz, 3H), 0.87 (t, *J*=7.3 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 216.0, 203.6, 169.6, 158.2, 157.2, 144.0, 143.1, 111.6, 111.1, 103.9, 82.2, 79.6, 78.1, 70.3, 69.6, 65.9, 60.4, 52.8, 51.2, 49.8, 47.5, 44.9, 40.2, 39.0, 26.8, 24.1, 21.1, 19.7, 18.3, 15.6, 14.6, 14.3, 13.9, 10.4. MS (ESI) [M+H]⁺ *m/z* 803.7. HRMS (ESI) calcd for C₄₀H₆₂N₆O₁₁, 803.4549, found: 803.4545.

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