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Synthesis and antibacterial activity of novel ketolides with 11,12-quinoylalkyl side chains

Zhe-hui Zhao*, Xiao-xi Zhang, Long-long Jin, Shuang Yang, Ping-sheng Lei*

State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Beijing Key Laboratory of Active Substances Discovery and Drugability Evaluation, Department of Medicinal Chemistry, Institute of Materia Medica, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing 100050, PR China

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ABSTRACT

A series of quinoylalkyl side chains was designed and synthesized, followed by introduction into ketolides by coupling with building block **6** or **32**. The corresponding targets **7a–n**, **33b**, and **33e** were tested for their *in vitro* activities against a series of macrolide-sensitive and macrolide-resistant pathogens. Some of them showed a similar antibacterial spectrum and comparable activity to telithromycin. Among them, two C2-F ketolides, compounds **33b** and **33e**, displayed excellent activities against macrolide-sensitive and macrolide-resistant pathogens.

Because these has been widespread clinic use of macrolide antibiotics since the 1950s, the emergence of macrolide-resistant bacteria has become increasingly prevalent. Great efforts have been made to develop novel macrolide structures against resistant pathogens.[1] The most successful improvement of anti-resistant macrolide antibiotics is the development of the well-known ketolides, which are derived from erythromycin and are represented by telithromycin,[2] cethromycin[3] and solithromycin[4] (Fig. 1). The structural features of ketolides include a 3-keto group, an 11,12-carbamate functionality, and a proper arylalkyl side chain. The aromatic heterocycles of the side chain can offer an extra interaction with nucleotide A752 in domain II of the 23S rRNA.[5] In recent years, many types of aromatic heterocycles have been introduced into ketolides by different linkers in order to find new macrolides with improved activity and low toxicity.[6–8]

During our efforts to develop novel ketolides that would be active against bacteria, we became interested in the quinoline ring as the aromatic heterocycle of the side chain. Many research groups have reported that introducing a quinoline ring into the macrolides could improve the antibacterial activity.[9–14] It is well known that there is a quinoyl group in the side chain of cethromycin at the 6-position, which is introduced by the Heck reaction. In previous works, Nam et al. synthesized a series of 9-*O*-arylpropenyloxime ketolides and evaluated them for their antibacterial activity.[9] Among the targets they synthesized, compound **I** showed the greatest potency against clinical strains of *Streptococcus pneunoniae* and *Streptococcus pyogenes* (Fig. 2). Liang et al. synthesized a series of ketolides bearing a 3-aryl-*E*-prop-2-enyl group at the 9-oxime and evaluated the compounds for their *in vitro* antibacterial activity, in which an aryl group was introduced by the Sonogashira reaction.[11] Compound **II** (Fig. 2) and two isoquinoyl derivatives displayed significant antibacterial activity against inducible MLS_B-resistant and efflux-mediated resistant pathogens, regardless of the methicillin-susceptible or methicillin-resistant phenotypes they carried. In some cases, the quinoyl group was introduced into 16-membered macrolides, which also showed excellent antibacterial activity against resistant pathogens. For instance, compound **III** (Fig. 2) was synthesized by Miura et al., and it showed potent activity against mef- and erm-resistant bacterial strains.[14] Based on that, we deduced that the quinoyl group may be favorable for antibacterial activity, especially against resistant bacteria.

In this research, we focused on how the linker atom between the quinoline ring with the alkyl of the 11,12-position of ketolides influenced the antibiotic activities, and furthermore how the substituent group of the quinoline ring influenced the antibacterial activity of new ketolides, finally to find new ketolides as leader with improved activity and low toxicity. Herein, we report an efficient synthetic procedure designed for preparing a series of arylalkyl side chains with different linker atoms, followed by coupling them with building blocks to give novel ketolides with 11, 12-arylalkyl side chains. A new procedure for the synthesis of C2-F ketolides is also reported.

Our approach was to find an efficient route to synthesize a series of ketolides with 11,12-arylalkyl side chains carrying quinoline heterocycles. Scheme 1 outlines the syntheses of targets **7a–g**. Building block **6** was prepared via 6 steps from clarithromycin.[8] Then, building block **6** was coupled with arylalkyl amines (**a–g**) in acetonitrile/water to give corresponding targets **7a–7g**.

* Corresponding authors.
E-mail address: zhaozh@imm.ac.cn (Z.-h. Zhao).

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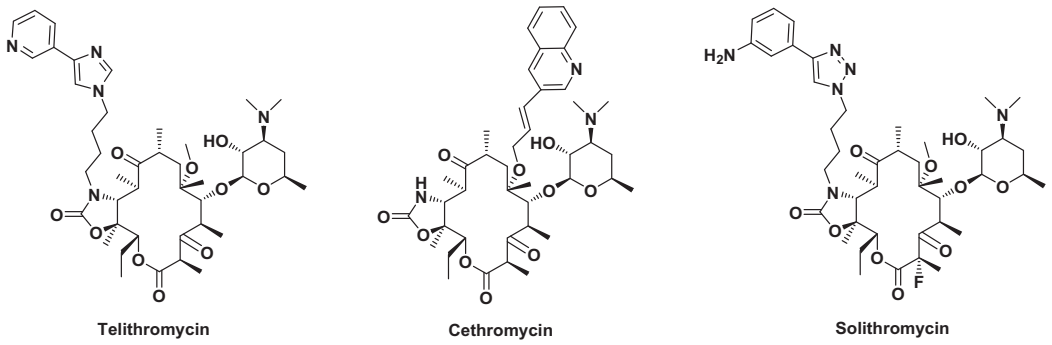


Fig. 1. Chemical structures of telithromycin, cethromycin and solithromycin.

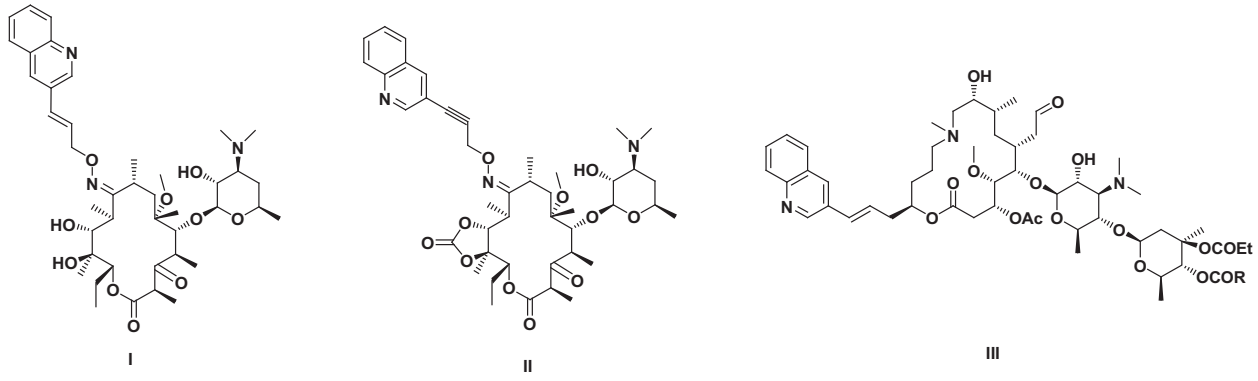
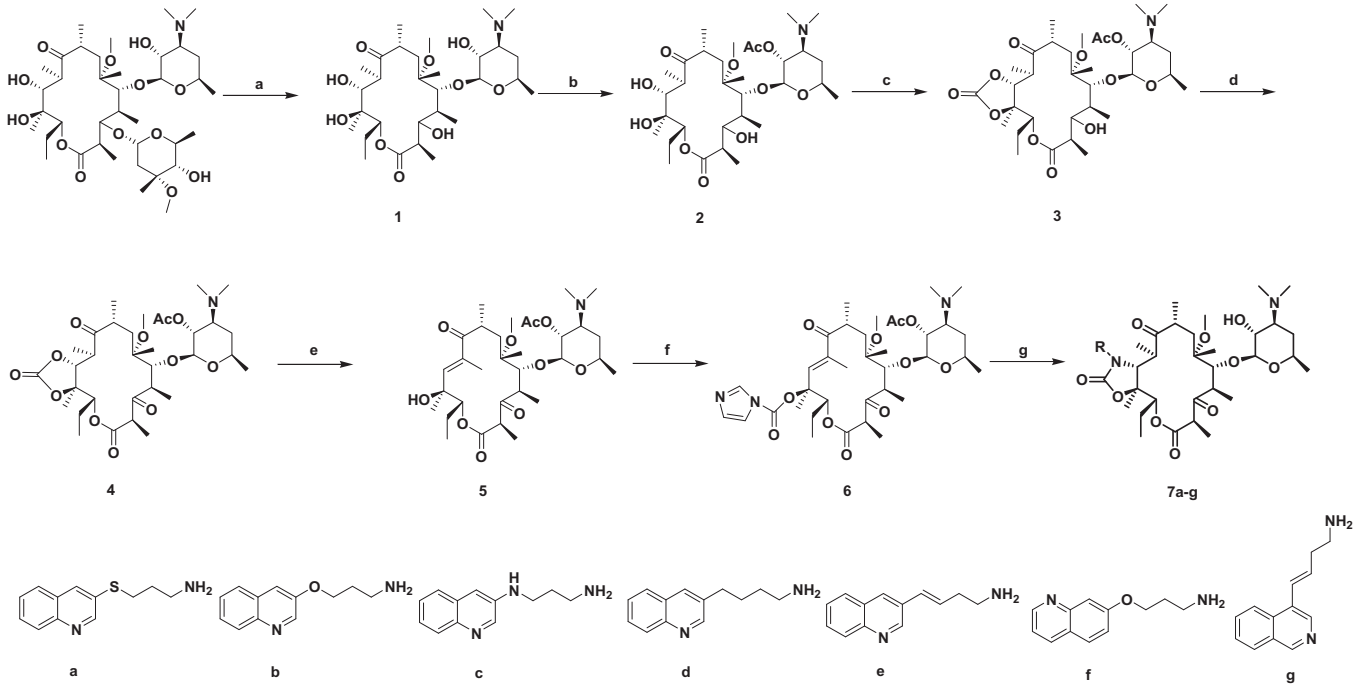
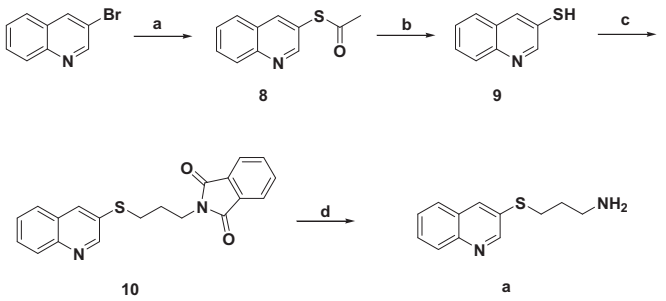


Fig. 2. Chemical structures of I, II, and III.

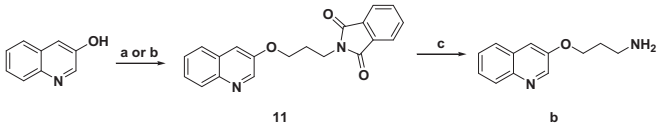


Scheme 1. Reagents and conditions: (a) HCl, H_2O, room temperature 96%; (b) acetic anhydride, Et_3N, CH_2Cl_2, room temperature, 84%; (c) trichloromethyl chloroformate, pyridine, CH_2Cl_2, 0 °C to room temperature, 75%; (d) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 °C, 70%; (e) DBU, acetone, reflux, 75%; (f) CDI, NaH, DMF, −15 °C, 80%; (g) **a–g**, MeCN/H_2O, reflux, overnight.

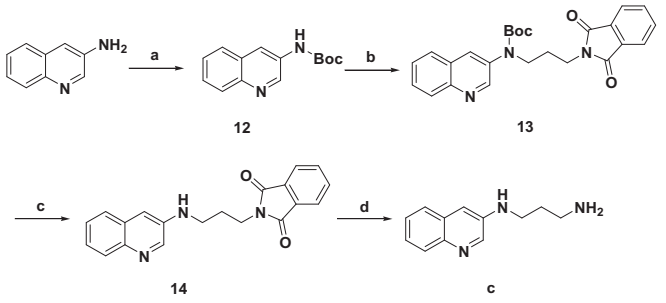
Schemes 2–5 outline the syntheses of amines **a–g**. 3-Bromoquinoline was chosen as the starting material for the synthesis of amine **a**. By the Buchwald-Hartwig reaction, 3-bromoquinoline was reacted with potassium thioacetate in 1,4-dioxane under microwave conditions, with DIEA as the base, $Pd_2(dba)_3$ as the catalyst, and xantphos as the ligand, to give compound **8**. The acetyl of compound **8** was hydrolyzed by KOH. Compound **9** was treated with one equivalent of *N*-(3-bromopropyl)phthalimide in dimethylformamide (DMF) at 90 °C to afford compound **10** in a yield of 68% for two steps. After removing the phthalimide group of compound **10** in a solution of 85% aqueous



Scheme 2. Reagents and conditions: (a) CH_3COSK, DIEA, $Pd_2(dba)_3$, xantphos, 1,4-dioxane, microwave, 54%; (b) KOH, EtOH, reflux; (c) *N*-(3-bromopropyl) phthalimide, K_2CO_3, DMF, 90 °C, 68% for two steps; (d) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux.



Scheme 3. Reagents and conditions: (a) *N*-(3-bromopropyl)phthalimide, K_2CO_3, DMF, 90 °C, 92%; (b) *N*-(3-hydroxypropyl)phthalimide, PPh_3, DEAD, 88%; (c) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux.



Scheme 4. Reagents and conditions: (a) $(Boc)_2O$, NaHMDS, THF, 0 °C to room temperature, 1 h, 90%; (b) *N*-(3-bromopropyl)phthalimide, NaH, DMF, 90 °C, 95%; (c) TFA, DCM, 0 °C, 8 h, 96%; (d) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 80 °C.

hydrazine in ethanol, amine **a** was obtained.

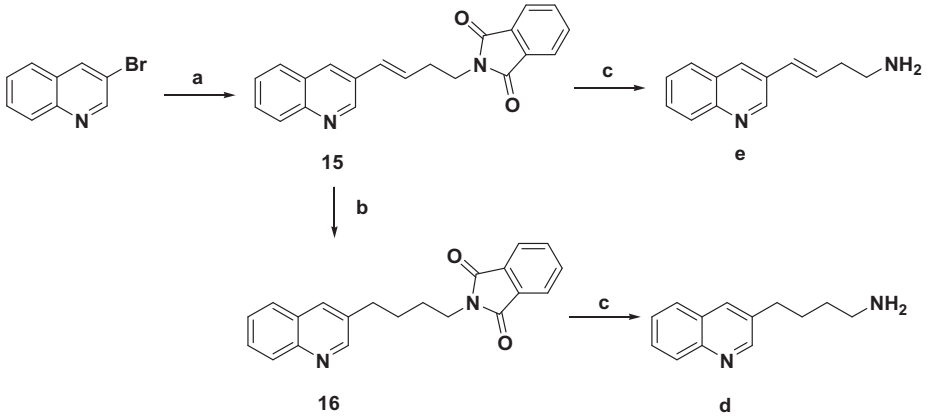
3-Hydroxyquinoline was chosen as the starting material for synthesis of amine **b**. Two methods were used to obtain compound **11**. One procedure was similar to the synthesis of compound **10**, where 3-hydroxyquinoline was treated with one equivalent of *N*-(3-bromopropyl) phthalimide in DMF at 90 °C. The other was the coupling of 3-hydroxyquinoline with *N*-(3-hydroxypropyl)phthalimide by the Mitsunobu reaction. After removing the phthalimide group of compound **11** in a solution of 85% aqueous hydrazine in ethanol, amine **b** was obtained. Amine **f** was obtained by a similar procedure as that used to synthesize amine **b**.

3-Aminoquinoline was chosen as the starting material for the synthesis of amine **c**, which was reacted with $(Boc)_2O$ in the presence of NaHMDS as the base in tetrahydrofuran (THF) to give compound **12**. Compound **13** was obtained by a procedure similar to that which was used to obtain compound **10**. After removing the Boc protective group and phthalimide group, amine **c** was obtained.

3-Bromoquinoline was also chosen as the starting material for the synthesis of amines **e** and **d**. By the Heck reaction, 3-bromoquinoline was reacted with *N*-(but-3-enyl)phthalimide in acetonitrile under argon gas, with TEA as the base, $Pd(OAc)_2$ as the catalyst and PPh_3 as the ligand, to give compound **15**. Compound **15** was reduced by Pd/C under H_2 gas in EtOH to give compound **16**. Removing the phthalimide group from compounds **15** and **16** gave corresponding amines **d** and **e**. Amide **g** was obtained by a similar procedure as that used to synthesize amine **e**, with 3-bromoisoquinoline as the starting material. The conditions of the Heck reaction were changed to 120 °C in DMF, Na_2CO_3 as the base, $Pd(dba)_2$ as the catalyst, and PPh_3 as the ligand.

With the targets **7a–g** in hand, five compounds **7a–e** with different linker atoms were chosen to evaluate their antibacterial activities against several macrolide-sensitive and macrolide-resistant strains. The results are showed in Table 1. When compared with clarithromycin and telithromycin, **7b**, **7d**, and **7e** showed excellent activities against both macrolide-sensitive and macrolide-resistant strains. Among them, **7e** displayed the best antibacterial activities, especially against methicillin-sensitive *S. pneunoniae* and *S. pyogenes*. The results indicated that a carbon-carbon double bond as the linker was more favorable for the activities of ketolides than a single bond against both sensitive and resistant pathogens. Next, target **7e** was chosen as a lead, and new ketolides were designed and synthesized to screen the influence of substituted quinoline on their antibiotic activity (Fig. 3) (See Table 2).

Scheme 6 outlines a general approach for the syntheses of amines **h–n**, which were coupled with building block **6** to give the corresponding **7h–n**. Some 6-substituted or 7-substituted quinolines were chosen as starting materials, and these were bromized by bromine in CCl4, with pyridine as the base, to give corresponding 3-bromoquinoline derivatives **17–23**. By the Heck reaction, compounds **17–23** were reacted with *N*-(but-3-enyl)phthalimide in DMF under argon gas, NaOAc as the base, $Pd(OAc)_2$ as the catalyst, and PPh_3 as the ligand, to give compounds **24–30** respectively. Removing the phthalimide group of compounds **24–30** gave corresponding amines **h–n**, which would couple with building block **6** in acetonitrile/water to give targets **7h–7n**, respectively.



Scheme 5. Reagents and conditions: (a) *N*-(but-3-enyl)phthalimide, $Pd(OAc)_2$, PPh_3, CH_3CN, TEA, reflux, 12 h, 86%; (b) H_2, Pd/C, EtOH, room temperature, 18 h, 94%; (c) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 80 °C.

Table 1
In vitro antibacterial activities of the target **7a-7e.**

	S. aureus		*S. epidermidis*		*S. pneunonia*		*S. pyogenes*		*H. influenzae*	
	11B122	11B117	11X315	11C176	11G364	11 J011	11L264	11 N369	11P042	11Q373
7a	0.125	> 64	0.125	0.125	0.008	0.125	0.016	0.5	16	32
7b	0.125	> 64	0.062	0.25	≤0.004	0.062	0.008	1	1	8
7c	0.5	> 64	0.5	0.5	0.016	0.5	0.031	64	8	8
7d	0.125	64	0.062	0.062	≤0.004	0.062	0.008	0.5	0.5	4
7e	0.125	64	0.062	0.062	≤0.004	0.031	≤0.004	0.25	1	4
CLR	0.031	> 64	0.125	> 64	0.031	64	0.016	> 64	8	8
TEL	0.062	> 64	0.062	0.031	0.016	0.031	0.008	0.125	1	4

CLR: Clarithromycin; TEL: telithromycin.

There are some reports describing the synthesis of C2-fluoroketolides, which demonstrate favorable activities against some pathogens.[15–19] Herein, we report an efficient procedure to synthesize C2-fluoroketolides (Scheme 7). Building block **6** was chosen as the starting materials, which was treated with NISF in the presence of *t*-BuOK in DMF/THF to give compound **31**, following deprotection in methanol to smoothly give building block **32** as a key intermediate. Building block **32** was coupled with amine **b** or **e** in acetonitrile/water to give targets **33b** or **33e**. Moreover, compound **31** could also be directly coupled with side chains to give target molecules. The removal of the acetyl group of compound **31** helped to reduce the amount of side chains, and the targets separated and purified. The advantage of this new procedure for synthesis of C2-F ketolides was efficient in that that multiple targets could be synthesized via only one step from building block **32**. All the target compounds were confirmed by HRMS, ^{1}H NMR, and ^{13}C NMR spectra.

The antibacterial activities of the target compounds **7a–n** were tested against several macrolide-sensitive and macrolide-resistant strains. Clarithromycin and telithromycin were chosen as the reference compounds. The *in vitro* antibacterial activity were reported as minimum inhibitory concentrations (MICs), which was determined by the broth microdilution method as recommended by the Clinical and Laboratory Standards Institute (CLSI).[20]

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

As shown in Table 1, 5 compounds **7a–7e** and two reference compounds, clarithromycin and telithromycin, were tested and their MIC values were analyzed and compared. Among them, the linker atom of **7a–7e** was S, O, N, C, and C=C respectively. Compared to clarithromycin, the synthesized targets displayed approximately equivalent antibacterial activity against the sensitive pathogens and obviously more activity against the resistant ones. Compared to telithromycin, only compound **7c** showed slightly weaker activity against methicillin-sensitive *S. aureus* and *S. epidermidis.* The activities of others were similar to that of telithromycin against *S. aureus* and *S. epidermidis*. The activities of **7a** and **7c** were similar to that of telithromycin against *S. pneunoniae.* The activities of **7b, 7d**, and **7e** were slightly stronger than that of telithromycin against erythromycin-sensitive *S. pneunoniae.* The activities of **7a–7d** were similar to that of telithromycin against *S. pyogenes.* The activity of **7e** was slightly stronger than that of telithromycin against erythromycin-sensitive *S. pyogenes.* The activities of **7a** and **7c** were slightly weaker than that of telithromycin against *H. influenzae.* The activities of **7b**, **7d**, and **7e** were similar to that of telithromycin against *H. influenzae.*

ATCC29213 is a strain of methicillin-sensitive *Staphylococcus aureus*

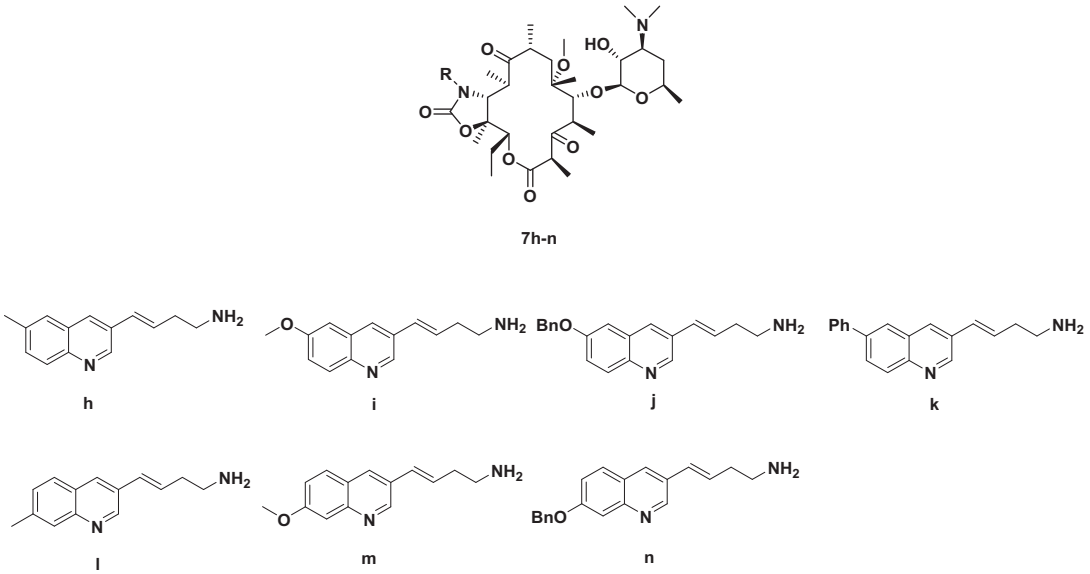
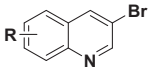
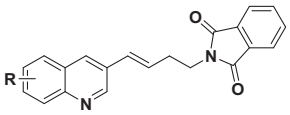
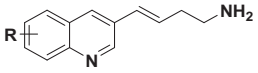
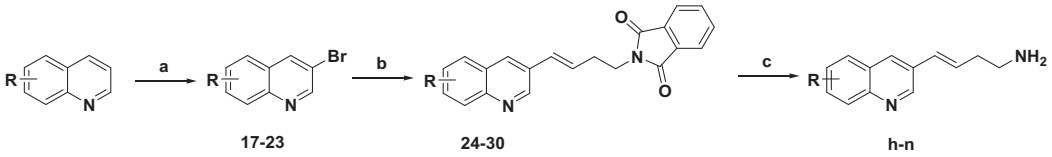


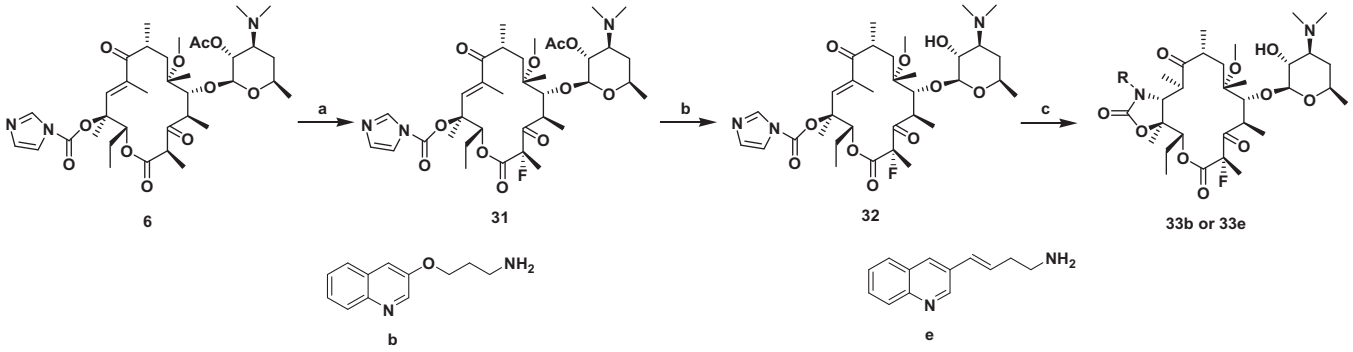
Fig. 3. The structure of compounds **7h–n** and **h–n**.

Table 2
The structure of compounds **17–30** and **h–n**.

R	6-Me	6-OMe	6-OBn	6-Ph	7-Me	7-OMe	7-OBn
	17	18	19	20	21	22	23
	24	25	26	27	28	29	30
	h	i	j	k	l	m	n



Scheme 6. Reagents and conditions: (a) Br_2, pyridine, CCl_4, reflux, 2 h; (b) *N*-(but-3-enyl)phthalimide, $Pd(OAc)_2$, PPh_3, NaOAc, DMF, 120 °C, overnight.



Scheme 7. Reagents and conditions: (a) NISF, *t*-BuOK, DMF/THF, −20 °C, 2 h, 90%; (b) MeOH, reflux, 12 h, 95%; (c) **b** or **e**, MeCN/H_2O, reflux.

Table 3
In vitro antibacterial activities of the target **7f–7n**, **33b** and **33e**.

m	*S. aureus*		*S. epidermidis*		*S. pyogenes*		*M. catarrhalis*		*E. coli*	*KPN*	*PAE*
	ATCC 29,213 MSSA	*ATCC 33,591* MRSA	*ATCC 12,228* MSSE	*13–3* MRSE	*12–8* MSSP	*12–1* MRSP	*12–1* CSMS	*12–2* CRMS	*ATCC 25,922* ESBLs(-)	*ATCC 700,603* ESBLs(+)	*ATCC 27,853* –
7f	0.015	256	0.03	> 256	0.015	> 256	0.015	64	16	128	32
7g	0.015	64	0.03	64	0.015	64	0.015	32	16	64	32
7h	0.015	32	0.06	64	0.015	32	0.015	16	64	> 256	64
7i	0.015	64	0.015	128	0.015	32	0.015	16	16	128	32
7j	1	8	1	8	0.125	8	1	4	> 256	> 256	> 256
7k	1	4	0.5	8	0.125	8	0.125	2	> 256	> 256	> 256
7l	0.06	64	0.06	128	0.015	64	0.015	32	64	> 256	64
7m	0.06	64	0.015	64	0.015	32	0.015	8	64	> 256	64
7n	1	8	1	16	0.25	8	0.5	8	> 256	> 256	> 256
33b	0.015	64	0.015	128	0.015	64	0.015	64	8	32	16
33e	0.015	32	0.015	32	0.015	16	0.015	16	8	32	16
CLR	0.12	> 256	0.06	> 256	0.03	128	0.008	> 256	16	128	128
TEL	0.015	> 256	0.015	> 256	0.03	> 256	0.125	> 256	8	64	32

KPN: Klebsiella pneumoniae; PAE: Pseudomonas aeruginosa; CLR: Clarithromycin; TEL: telithromycin.

(MSSA), and ATCC 33591 is a strain of methicillin-resistant *Staphylococcus aureus* (MRSA). ATCC12228 is methicillin-sensitive *Staphylococcus epidermidis* (MSSE), and 13–3 is a strain of methicillin-resistant *S. epidermidis* (MRSE). Additional, 12–8 is a strain of methicillin-sensitive *Streptococcus pyogenes* (MSSP), and 12–1 is a strain of methicillin-resistant *S. pyogenes* (MRSP). Some Gram-negative bacteria such as clarithromycin-sensitive *Moraxella catarrhalis* 12–1 (CSMC), clarithromycin-resistant *M. catarrhalis* 12–2 (CRMC), *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 700603, and *Pseudomonas aeruginosa* ATCC 27,853 were also assessed. All the resistant strains chosen for this test are constitutively resistant strains supplied by the Ministry of Health National Antimicrobial Resistance Investigation Net (MOHNARIN, China).

As shown in Table 3, 11 compounds **7f–7n**, **33b**, **33e** and two

references compounds, clarithromycin and telithromycin, were tested and their MIC values were analyzed and compared. Among them, the compound **7f** carried a 7-quinoline ring and compound **7g** carried an isoquinoline ring. The compounds **7h–7k** had a 6-substituted quinoline ring and **7l–7n** had a 7-substituted quinoline ring. Compared to telithromycin, compound **7f** showed similar activities against both sensitive and resistant pathogens. The activities of **7g** were similar to that of telithromycin against sensitive pathogens and slightly stronger than that against resistant pathogens. Compared to telithromycin, compounds **7h**, **7i**, **7l**, and **7m** displayed similar activities against sensitive pathogens and were slightly stronger than those against resistant ones. The activities of **7j**, **7k**, and **7n** were weaker than that of telithromycin against sensitive pathogens, while they were stronger than that of telithromycin against resistant one and exhibited no activities against Gram-negative bacteria. Compounds **33b** and **33e** displayed a significant improvement of activities against both sensitive and resistant pathogens.

Compared with the activities of compounds **7a–7d**, whose linker atoms were S, O, N and C, respectively, compound **7d** displayed the strongest antibiotic activity, which indicate that the carbon atom is favorable. When comparing the activities of compound **7d** with telithromycin, a target in which the quinoline ring was replaced with the imidazole-pyridine of telithromycin, compound **7d** displayed similar activities as those of telithromycin, while exhibiting 4-fold stronger activity than that of telithromycin against methicillin-sensitive *S. epidermidis*. The activity of **7e** was slightly stronger than that of **7d**, which indicates that the carbon-carbon double bond was favored over the carbon-carbon single bond. By the all, N as linker atom was unfavorable the activities against methicillin-sensitive *S. aureus* (0.5) and methicillin-resistant *S. aureus* (> 64). O, C, and C═C as linker atoms were favorable against methicillin–sensitive *S. epidermidis* (0.062), but only C, and C═C were favorable against methicillin-resistant *S. epidermidis* (0.062). The similar trend was found against methicillin-resistant erythromycin-sensitive *S. pneunoniae* (≤0.004), but C═C was more favorable against erythromycin-resistant *S. pneunoniae* (≤0.004). The carbon-carbon double bond was more favorable against both sensitive and resistant *S. pyogenes* and *H. influenzae*.

The antibacterial activities of **7f**, **7g** were similar to that of telithromycin, which indicated that 7-quinoline and the isoquinoline ring were both favorable. Compounds **7h**, **7i**, **7l**, and **7m** showed similar antibacterial activities, which indicates that a similar substituent at the 6-position or 7-position of the quinoline ring did not affect the activities. The same trend was also found when comparing the activities of compounds **7j**, **7i** with compound **7n**. The activities of compounds **7h**, **7i**, **7l**, and **7m**, which carried small volume substituents (methyl or methoxyl), were stronger against sensitive pathogens than compounds **7j**, **7i**, and **7n**, which carried large ones (phenyl or benzyloxyl), while being weaker against resistant pathogens. The results indicated that small volume substituents were favorable the activities against MSSA, MSSE, MSSP, and CSMS at the 6-position or 7-position of the quinoline ring, and the phenyl substituent was more favorable the activities than telithromycin against MRSA (4: > 256), MRSE (8: > 256), MRSP (8: > 256), and CRMS (2: > 256). Two C2-F ketolides, compounds **33b** and **33e**, not only displayed excellent activities against macrolide-sensitive and macrolide-resistant pathogens, but also showed better or similar activities against Gram-negative bacteria, compared with clarithromycin and telithromycin.

In summary, a series of novel ketolides was synthesized that carried different quinoylallyl side chains. Some of them showed a similar antibacterial spectrum and comparable activity to telithromycin. Among them, two C2-F ketolides, compounds **33b** and **33e**, displayed excellent activities against both Gram-positive bacteria and some Gram-negative bacteria, and these were the best candidates for further investigation. The current study presents data that can contribute to the development of new macrolide antibiotics to effectively combat the growing problems of resistant strains.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2018.06.039.

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