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Synthesis and antibacterial activity of new 9-*O*-arylpropenyloxime ketolides

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ABSTRACT

A novel series of 9-*O*-arylpropenyloxime ketolide was synthesized and evaluated for their antibacterial activity. This series of ketolide exhibited potent activity against clinically isolated gram-positive strains including *Staphylococcus pneumoniae* and *Straptococcus Pyogenes*.

Multidrug-resistance bacteria have become an increasing problem for the management of serious infections. On average, worldwide penicillin resistance in *Staphylococcus pneumoniae* is about 20%, ranging from under 10% in Africa to almost 40% in Asia; nearly one quarter of all US isolated are resistant to penicillin.[1,2] The resistance of *Staphylococcus pyogenes* has been increasing in recent year. High rates of resistance to erythromycin and azithromycin have also reported as high as 78% in Taiwan 2001 and with high rates in Spain and Italy.[3]

Although many of the older antibiotics remain effective, new drug development crucially need resolve to increase in drug resistance among these important pathogens. Macrolide antibiotics have been used safely and effectively for treating community-acquired respiratory tract infections since 1950's. Recently a new class of erythromycin A derivatives, known as ketolides, has developed the enhanced antibacterial activity against antimicrobial resistant pathogens.[4] The first ketolide telithromycin is to reach the market and cethromycin has been clinical trials (Fig. 1).[5] These new generation of ketolides have been structural characteristics which contained a long chained aromatic ring besides having 3-keto group instead of 3-cladinose sugar ring. This tethered aromatic ring has known as important factor to ribosomal binding sites and relates to inhibition of resistance mechanism.[6]

Herein we describe the synthesis of new 9-*O*-arylpropenyloxime ketolides which introduced in long chain aromatic ring on 9-oxime position, represented by the structures **3** and the evaluation of their antibacterial activity (Fig. 2).

9-*O*-Arylpropenyloxime ketolide derivatives (**3a**–**l**) were synthesized by Heck coupling reaction of 9-(*E*)-allyloxime ketolide **8**[7] with several aryl halides. (Scheme 1) Palladium acetate and 2-methoxyphenylbromide were added to the solution of 9-allyloxime ketolide **8** in acetonitrile in the presence of tri(*o*-tolyl)phosphine catalyst to give 3-methoxyphenyl substituted 9-propenyloxime derivative **3a**.[8] Compounds **3b**–**3l** were similarly synthesized from 3-methoxyphenylbromide, 3,4-dimethoxyphenylbromide, 3-bromopyridine, 3-bromoquinoline, 3-bromopyrimidine, 4-methoxyphenylbromide, bromothiophene, bromoisoquinoline, 3-bromoindol, 1-bromoindanone, 2(3-bromophenyl)-1,3-dioxolane and 1,3-benzodioxole-5-bromide in moderate yield. All new compounds were purified by flash column chromatography and were characterized by NMR spectra, such as ^{1}H, ^{13}C, homo-COSY, HMQC, HMBC and HSQC NMR spectrum.

Compound **8** was synthesized by the five steps outlined Scheme 2. Hydroxylamine was added to the clarithromycin[9] in ethanol solution in presence of triethylamine to give 9-hydroxyoxime derivative **4**,[10] which was converted into 9-allyloxime **5** by reacting with allyl bromide and sodium hydride. Then the cladinose was hydrolyzed with 2 N hydrochloric acid followed by acetylation of the 2′-hydroxy group with acetic anhydride gave 3-hydroxy intermediates **6**.[11] Oxidation of the 3-hydroxy group was efficiently performed with Corey–Kim reagent[12] followed by deprotecting of the 2'-acetyl group with methanol provided the corresponding ketolide **8** in a 70% yield. The only 3-OH group except for the 11-OH group is oxidized under Corey–Kim oxidation condition, which is well known method for the 14-membered macrolide chemistry.[13]

The 9-arylpropenyloxime derivatives **3a**–**3l** were tested for in vitro antimicrobial activity against gram-positive strains such as Staphylococcus aureus (MRSA, MSSA), *Streptococcus pneumonia*

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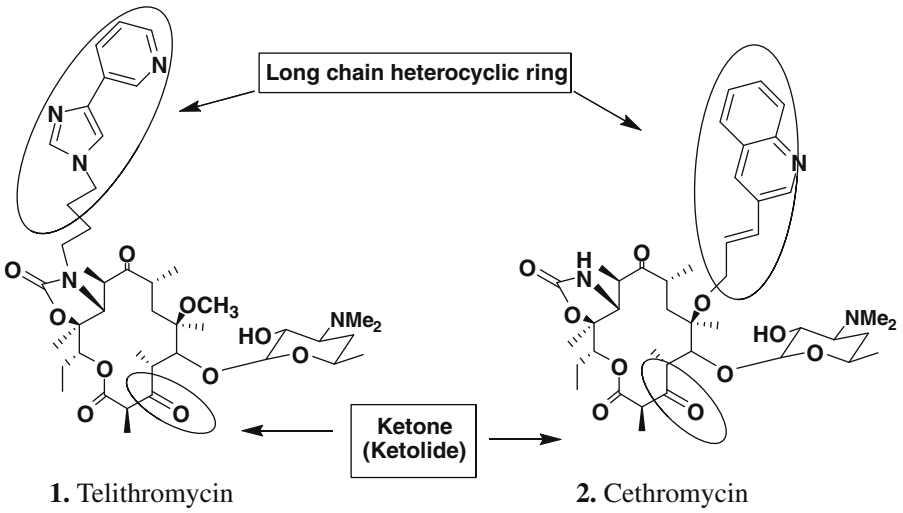


Figure 1. The structural character of recently developed macrolides.

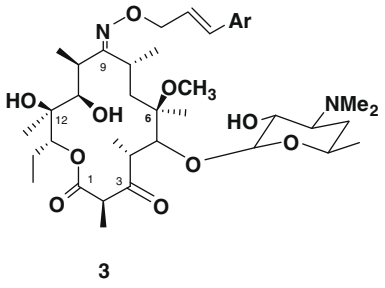
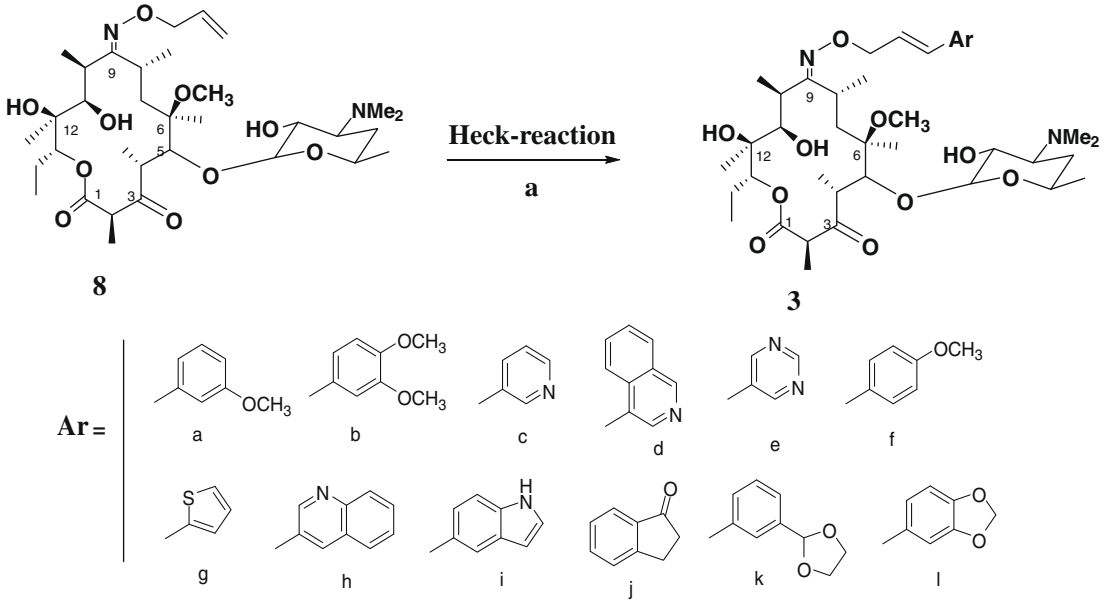


Figure 2. New 9-arylpropenyloxime ketolides.

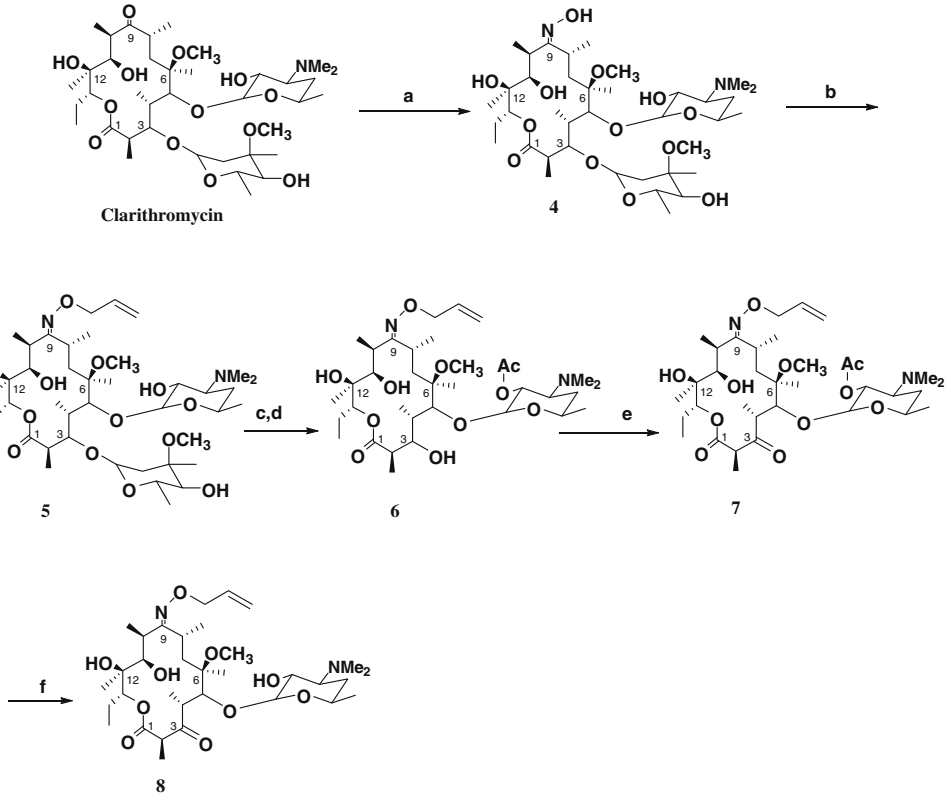
(penicillin resistance and intermediate, PRSP), and *Streptococcus pyogenes* clinically acquired in Korea.[14] The ATCC29213 for the methicillin susceptible *Streptococcus aureus* (MSSA), ATCC49619 for *S.* pneumoniae and ATCC8668 for *S.* pyogenes were tested as a corresponding standard strains. The minimum inhibitory concentration (MIC) values of produced by the Muller–Hinton agar dilution method[15] for the compounds **3a**–**3l** are reported Table 1.

From the analysis of the MIC values of antibacterial inhibitory activities, most of the ketolide derivatives were active against clinically isolated gram-positive strains. The ketolides were inactive against MRSA strains and showed moderate activity against MSSA, as was common with ketolide antibiotics.

All compounds showed potent activity against the *S. pneumoniae* and *S. pyogenes*. And also clinical isolated strains *S. pneumoniae* including penicillin intermediate and penicillin susceptible *S. pneumoniae* strains, and three strains of clinically gained *S. pyogenes* explored to highly effect on synthesized ketolides. These clinically isolated penicillin-resistant *S. pneumoniae* (PRSPs) showed almost no inhibition by erythromycin (MIC_{50} >128 μM) as reference of macrolides antibiotics.[16] However, most of the synthesized ketolides displayed good activity against clinically isolated resistant strains which have 0.06 μM of MIC values. Particularly, the nitrogen contained heteroaromatic derivatives such as pyridine

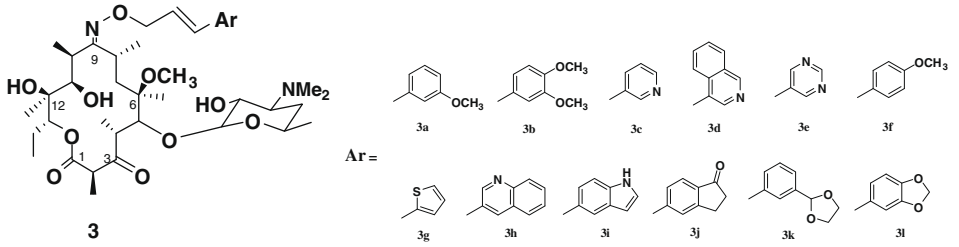


Scheme 1. Reagent and conditions: (a) $Pd(OAc)_2$, $P(o\text{-}Tolyl)_3$, TEA, CH_3CN/DMF (3/1), ArX (compound, yield); 3-methoxyphenylbromide (**3a**, 22%), 3,4-dimethoxyphenylbromide (**3b**, 15%), 3-bromopyridine (**3c**, 30%), 3-bromoquinoline (**3d**, 16%), bromopyrimidine (**3e**, 12%), 4-methoxyphenylbromide (**3f**, 72%), 2-bromothiophene (**3g**, 38%), bromoisoquinoline (**3h**, 36%), 3-bromoindol (**3i**, 26%), 1-bromoindanone (**3j**, 41%), 2(3-bromophenyl)-1,3-dioxolane (**3k**, 48%), 1,3-dioxole-5-bromide (**3l**, 56%).



Scheme 2. Reagent and conditions: (a) Hydroxylamine, triethylamine, EtOH, 49%; (b) NaH, allylbromide, Ether/DMF (50/50), N_2 gas, reflux (8 h), 95%; (c) 12 N HCl, H_2O, 87%; (d) Ac_2O, K_2CO_3, acetone, 40 °C, 89%; (e) NCS, dimethylsulfide, triethylamine, CH_2Cl_2, −10 °C, 70%; (f) MeOH, 97%.

Table 1
In vitro antibacterial activity of 9-*O*-propenylaryloxime ketolides against gram-positive organisms (MIC, μg/mL)[a]



Organism	MIC[a] (μg/mL)											
	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**	**3k**	**3l**
S. *aureus* ATCC29213	2	1	0.5	0.25	0.5	2	0.5	1	1	1	0.5	1
MRSA1[b]	128	128	128	128	128	128	128	128	128	128	128	128
MRSA2[b]	128	128	128	128	128	126	128	128	128	128	128	128
MRSA3[b]	2	1	0.5	0.25	0.5	2	0.25	0.5	1	1	1	1
MSSA1[c]	2	0.5	0.25	0.25	0.5	2	0.5	1	1	1	1	1
MSSA2[c]	2	1	0.25	0.25	0.5	1	0.25	0.5	1	1	1	0.5
MSSA3[c]	2	1	0.25	0.25	0.5	1	0.25	0.5	1	1	0.5	0.5
S. *pneumoiae* ATCC49619	1	0.25	0.125	0.06	0.25	0.5	0.06	0.25	0.25	0.25	0.25	0.25
Penicillin I1[d]	64	32	64	64	128	64	32	32	32	64	64	64
Penicillin I2[d]	1	0.5	0.25	0.06	0.5	0.5	0.125	0.5	0.25	0.25	0.25	0.25
penicillin I3[d]	64	0.5	0.06	4	1	0.5	0.125	1	0.25	8	0.25	0.25
Penicillin S1[e]	0.25	0.06	0.06	0.06	0.125	0.25	0.06	0.25	0.06	0.06	0.06	0.06
penicillin S2[e]	0.25	0.06	0.06	0.06	0.125	0.25	0.06	0.25	0.06	0.06	0.06	0.06
S. pyogenes ATCC8668	1	0.25	0.25	0.06	0.25	0.5	0.06	0.25	0.25	0.25	0.25	0.25
S. pyogenes 1[f]	0.25	0.06	0.06	0.06	0.06	0.25	0.06	0.06	0.06	0.06	0.06	0.06
S. pyogenes 2[f]	1	0.25	0.06	0.06	0.25	0.5	0.06	0.25	0.25	0.25	0.25	0.25
S. pyogenes 3[f]	1	0.25	0.06	0.06	0.25	0.5	0.06	0.25	0.25	0.25	0.25	0.25

[a] Minimum inhibitory concentration by agar dilution method.
[b] Clinical strains of methicillin resistances. *S. aureus*.
[c] Clinically islated methicillin susceptible *S. aureus*.
[d] Clinically isolated penicillin intermediate resistanct *S. pneumonie*.
[e] Clinically isolated penicillin susceptible *S. pneumonias*.
[f] Clinically isolated *S. pyogenes*.

(**3c**), quinoline (**3d**) and sulfur contained thienyl (**3g**) derivatives were highly potent compounds within a series. But isoquinoline derivative (**3h**) and pyrimidine substituent (**3e**) showed less potency than the quinoline compound (**3d**) which having in different placed nitrogen of ring. It seems to be important factor of the position of nitrogen in the heteroaryl ring.

The compounds having methoxy group in phenyl ring such as **3a** (Ar = 3-OMePh), **3b** (Ar = 3,4-$(OMe)_2$Ph) and **3f** (Ar = 4-OMePh) and compounds having cyclic-ether type group, **3k** (Ar = 3-CH{O(-$CH_2)_2$O}Ph) and **3l** (Ar = 3-O(CH_2)-4-O–Ph) were showed lower activities against clinical strains of PRSPs. The potency of **3j** containing fused cyclopentanone also was low. Compound **3g** (Ar = thienyl) and **3i** (Ar = indol) exhibited good potency.

In summary, a new series of 9-*O*-arylpropenyloxime ketolide was designed, synthesized and evaluated for antibacterial activity against clinically isolated gram-positive strains in Korea. Compounds **3d** (Ar = quinoyl) or **3g** (Ar = thienyl) which having nitrogen or sulfur atom substituted heteroaryls were most potent against *S. pneumoniae and S. pyogenes* in clinical strains. These findings present a good opportunity for the development of new macrolide antibiotics to effectively combat the growing problems of resistance strains in Korea.

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7. Representative spectroscopic data of **8**: ^{1}H NMR (300 MHz, $CDCl_3$) ppm ^{1}H NMR (300 MHz, $CDCl_3$) ppm 0.85 (t, *J* = 7.32 Hz, 3H, 15-*CH*$_2$), 0.98 (d, *J* = 6.90 Hz, 3H), 1.15 (d, *J* = 1.97 Hz, 3H), 1.22 (s, 3H, 12-*Me*), 1.25 (d, *J* = 6.06 Hz, 3H), 1.30 (d, *J* = 2.89 Hz, 3H), 1.32 (d, *J* = 2.0 Hz, 3H), 1.38 (s, 3H, 6-*Me*), 1.46–1.57 (m, 2H), 1.65 (m, 1H), 1.69 (m, 1H), 1.97 (m, 1H), 2.26 (s, 6H, *NMe*$_2$), 2.46 (m, 1H), 2.56 (m, 1H), 2.74 (s, 3H, 6-*OMe*), 3.04 (m, 1H), 3.15–3.22 (m, 2H), 3.32 (m, 1H), 3.45 (m, 1H), 3.57 (m, 1H), 3.68 (m, 1H), 3.85 (m, 1H), 3.89 (m, 1H), 4.31 (dd, *J* = 6.36 Hz, 7.24 Hz, 2H), 4.46–4.49 (m, 3H), 5.18 (m, 1H), 5.22 (dd, *J* = 17.2 Hz, 16.8 Hz, 2H), 5.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 11.0, 14.7, 14.8, 15.4, 16.6, 18.8, 19.93, 21.6, 21.9, 26.7, 31.0, 33.2, 38.0, 40.7 (*NMe*$_2$), 46.3, 50.2, 51.3, 66.2, 69.8, 70.5, 70.7, 74.0, 75.0, 77.1, 78.1, 78.4, 103.6, 118.0, 134.6, 169.7 (C-9), 169.9 (C-1), 205.8 (C-3).
8. Representative spectroscopic data of **3**; compound **3a**: ^{1}H NMR (300 MHz, $CDCl_3$) ppm 0.85 (t, *J* = 7.31 Hz, 3H), 0.99 (d, *J* = 6.89 Hz, 3H), 1.15–1.01 (m, 9H), 1.19 (s, 3H), 1.72–1.45 (m, 4H), 1.97 (m, 1H), 2.25 (m, 6H), 2.48 (m, 2H), 2.55 (m, 1H), 2.76 (m, 3H), 3.26 (m, 5H), 3.54 (m, 2H), 3.78 (m, 1H), 3.81 (s, 3H), 3.82 (m, 4H), 4.29 (m, 2H), 4.53 (m, 2H), 5.11 (m, 1H), 6.33 (m, 1H), 6.55 (d, *J* = 19.05 Hz, 1H), 6.81 (d, *J* = 7.57 Hz, 2H), 6.91 (s, 1H), 6.98 (d, *J* = 7.66 Hz, 1H), 7.23 (t, *J* = 7.91 Hz, 1H). (75 MHz, $CDCl_3$) ppm 11.1, 14.8, 17.1, 18.9, 20.0, 21.6, 21.9, 28.7, 33.3, 38.4, 40.6, 40.8, 47.1, 47.9, 50.3, 51.3, 55.6, 66.3, 69.9, 70.8, 74.1, 74.7, 78.2, 78.5, 79.8, 80.0, 83.8, 88.0, 103.9, 112.2, 113.9, 119.5, 126.1, 129.9, 130.7, 133.3, 138.5, 169.7, 170.2, 205.8. compound **3b**: ^{1}H NMR (300 MHz, $CDCl_3$) ppm 0.85 (t, *J* = 7.25 Hz, 3H), 0.99 (d, *J* = 6.85 Hz, 3H), 1.05 (m, 1H), 1.15 (d, *J* = 10.68 Hz, 3H), 1.22 (s, 3H), 1.25 (s, 3H), 1.30 (d, *J* = 7.65 Hz, 3H), 1.33 (d, *J* = 6.7 Hz, 3H), 1.38 (s, 3H), 1.68–1.46 (m, 4H), 1.97 (m, 2H), 2.26 (m, 6H), 2.48 (m, 1H), 2.60 (m, 1H), 2.74 (s, 3H), 3.19 (m, 4H), 3.57 (m, 1H), 3.65 (m, 1H), 3.88 (s, 3H), 3.90 (s, 3H), 4.31 (m, 2H), 4.33 (s, 1H), 4.61 (m, 2H), 5.11 (m, 1H), 6.19 (m, 1H), 6.55 (d, *J* = 15.81 Hz, 1H), 6.82 (d, *J* = 8.40 Hz, 1H), 6.92 (d, *J* = 7.53 Hz, 1H), 6.93 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$);ppm 11.1, 14.7, 15.0, 15.5, 16.6, 18.9, 20.1, 21.6, 21.9, 26.8, 28.7, 33.3, 38.4, 40.6, 47.1, 50.3, 51.3, 56.2, 56.3, 66.3, 69.8, 70.7, 70.7, 74.1, 74.9, 77.6, 78.2, 78.5, 103.9, 109.4, 111.5, 120.1, 123.8, 130.2, 133.4, 149.4, 169.7, 170.0, 205.9.
9. Clarithromycin was supported by Chong Kun Dang Corporation, CKD research institute on purpose of research.
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