The Journal of Antibiotics (2016), 1–13

www.nature.com/ja

ORIGINAL ARTICLE

Synthesis and structure–activity relationships of novel lincomycin derivatives part 3: discovery of the 4-(pyrimidin-5-yl)phenyl group in synthesis of 7(*S*)-thiolincomycin analogs

Yoshinari Wakiyama, Ko Kumura, Eijiro Umemura, Satomi Masaki, Kazutaka Ueda, Yasuo Sato, Takashi Watanabe, Yoko Hirai and Keiichi Ajito

Novel lincomycin derivatives possessing an aryl phenyl group or a heteroaryl phenyl group at the C-7 position via sulfur atom were synthesized by Pd-catalyzed cross-coupling reactions of 7(*S*)-7-deoxy-7-thiolincomycin (5) with various aryl halides. This reaction is the most useful method to synthesize a variety of 7(*S*)-7-deoxy-7-thiolincomycin derivatives. On the basis of analysis of structure–activity relationships of these novel lincomycin derivatives, we found that (a) the location of basicity in the C-7 side chain was an important factor to enhance antibacterial activities, and (b) compounds 22, 36, 42, 43 and 44 had potent antibacterial activities against a variety of *Streptococcus pneumoniae* with *erm* gene, which cause severe respiratory infections, even compared with our C-7-modified lincomycin analogs (1–4) reported previously. Furthermore, 7(*S*)-configuration was found to be necessary for enhancing antibacterial activities from comparison of configurations at the 7-position of 36 (*S*-configuration) and 41 (*R*-configuration).
The Journal of Antibiotics advance online publication, 5 October 2016; doi:10.1038/ja.2016.114

INTRODUCTION

Macrolide antibiotics, which are protein-synthesis inhibitors, have effective antibacterial activity against bacterial strains, for example, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophillus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae* and so on, and have been used in clinical site over many years. Recently, resistant bacteria, especially *S. pneumoniae* with *erm* gene, have markedly increased,[1–3] which cause serious problems in bacterial respiratory infections. Although clarithromycin[4] and azithromycin[5] are currently available in clinical site, they are partially influenced by efflux pumps produced by *S. pneumoniae mef* gene and are not effective enough against resistant bacteria such as *S. pneumoniae* and *S. pyogenes* with *erm* gene (Figure 1, Table 1). Telithromycin (TEL)[6] is effective enough against *S. pneumoniae* with *erm* gene, but has potential to cause a serious liver damage[7,8] and loss of consciousness.[9,10] So, TEL has scarcely been used in Japan. Furthermore, the production cost of TEL is assumed to be relatively high owing to its complicated structure. Novel azalides[11] were generated starting from 16-membered macrolides, and several optimized 16-membered azalides[12] were effective against resistant *S. pneumoniae* and *S. pyogenes* with *erm* gene. These analogs are, however, still under research process and have not been developed yet. Currently available oral antibiotics are not effective enough against resistant bacteria with *erm* and *mef* genes, causing respiratory infections, and have some problems in safety or taste in clinical site.

Lincomycin (LCM)[13–16] was isolated as a secondary metabolite from the fermentation broth of *Streptomyces lincolnensis*. Clindamycin (CLDM)[17] was synthesized by chemical modification of LCM and possessed a chlorine atom at the C-7 position with 7(*S*)-configuration. CLDM exhibited improved antibacterial activities compared with LCM, but it was also not effective against resistant pathogens with *erm* gene as in the case of LCM (Figure 1, Table 1).

LCM and CLDM inhibit protein synthesis of bacteria in a similar manner to macrolide antibiotics. X-ray crystallographic analysis[18–20] indicated that CLDM had several major interactions by hydrogen bonding in 23S rRNA, and its binding site was closely located to that of macrolide antibiotics. Furthermore, they are effective against pathogens with *mef* gene in clinical isolate (Table 1). As an overview, CLDM exhibited the following positive characters: (1) availability of p.o. and i.v. administrations (switch therapy is possible), (2) good distribution to tissue and cells, (3) suppression[21] of toxin production by Streptococcal strains and (4) expected reasonable production cost of CLDM derivatives. Thus, LCM derivatives might be more clinically valuable than macrolide antibiotics, if they are effective against pathogens with *erm* gene.

Chemical modifications at the C-7 position of LCM have been investigated by several research groups.[16,17,22–34] One of their reports

Pharmaceutical Research Center, Meiji Seika Pharma Co., Ltd., Yokohama, Japan
Correspondence: Dr K Ajito, Pharmaceutical Research Center, Meiji Seika Pharma Co., LTD., 760 Morooka-cho, Kohoku-ku, Yokohama 222-8567, Japan.
E-mail: keiichi.ajito@meiji.com
Received 28 June 2016; revised 31 July 2016; accepted 5 August 2016

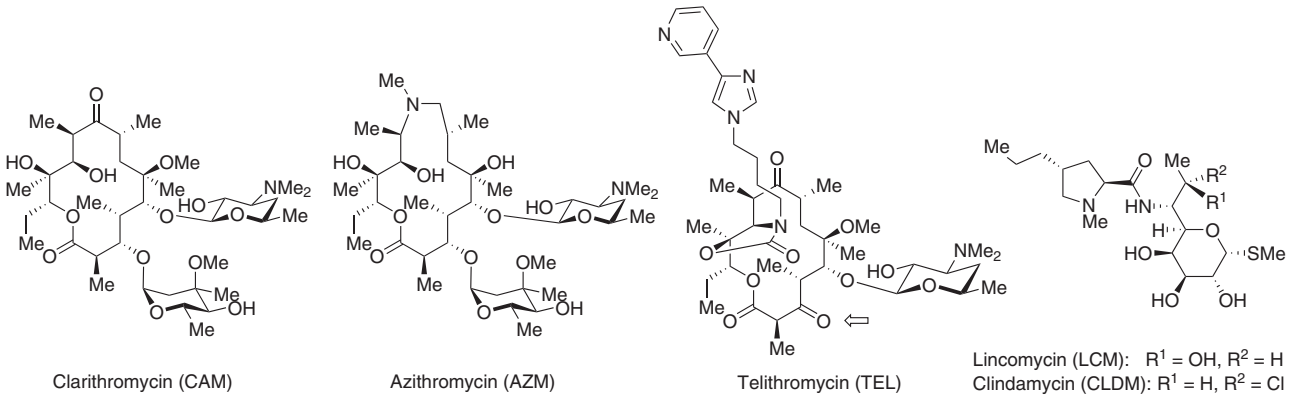


Figure 1 Chemical structures of clarithromycin, azithromycin, telithromycin, lincomycin and clindamycin.

Table 1 Antibacterial activities (MIC, μg ml^{-1}) of the representative macrolides, LCM, CLDM and previously reported LCM derivatives (1–4)

Test organism[a]	*Characteristics*[b]	*CAM*	*AZM*	*LCM*	*CLDM*	***1***	***2***	***3***	***4***
Streptococcus pneumoniae DP1 typeI	susceptible	0.03	0.06	1	0.06	0.06	0.06	0.06	0.03
S. pneumoniae-2	susceptible	0.03	0.03	1	0.12	0.06	0.06	0.06	0.03
S. pneumoniae-3	susceptible	0.015	0.03	0.25	0.06	0.03	0.03	0.06	0.06
S. pneumoniae-4	*ermAM* methylase (c)	>128	>128	>128	>128	8	8	8	2
S. pneumoniae-5	*ermAM* methylase (c)	>128	>128	>128	>128	32	8	2	2
S. pneumoniae-6	*ermAM* methylase (c) + *mefE*	>128	>128	>128	>128	64	64	8	4
S. pneumoniae-7	*ermAM* methylase (i)	>128	>128	128	128	16	8	2	1
S. pneumoniae-8	*ermAM* methylase (i)	>128	>128	128	128	8	8	1	N.T.
S. pneumoniae-9	*mefE* efflux	0.5	0.5	1	0.12	0.03	0.06	0.03	0.03
Streptococcus pyogenes cook	susceptible	0.015	0.06	0.12	0.06	0.03	0.06	0.06	0.03
S. pyogenes-2	*ermAM* methylase (c)	>128	>128	>128	128	4	2	4	2
S. pyogenes-3	*mefE* efflux	8	8	0.25	0.12	0.06	0.12	0.06	0.25
Haemophilus influenzae	susceptible	2	0.25	8	16	8	16	4	8
H. influenzae-2	susceptible	4	1	16	8	4	8	4	16
H. influenzae-3	susceptible	8	2	16	16	32	32	16	64
H. influenzae-4	Δacr	0.5	0.5	4	1	0.25	0.5	0.25	0.25

Abbreviations: AZM, azithromycin; CAM, clarithromycin; CLDM, clindamycin; LCM, lincomucin; MIC, minimum inhibitory concentration; N.T., not tested.
Gray shading indicates target strains.
[a]All strains except standard organisms were clinically isolated.
[b]'c' indicates constitutive and 'i' indicates inducible.

mentioned that 7(*S*)-7-*O*-methyllincomycin had stronger activities than 7(*R*)-7-*O*-methyllincomycin (7(*S*)-7-OMe>7(*R*)-7-OMe)[27,28] and it possessed 3.5 times stronger activities against *Sarcina lutea* than LCM. Derivatives possessing a larger alkoxy group or a substituted alkoxy group exhibited weaker antibacterial activities compared with LCM. On the other hand, 7(*S*)-7-alkylthio-7-deoxylincomycin and 7(*S*)-7-deoxy-7-(substituted-alkylthio)lincomycin were stronger than LCM against Gram-positive or Gram-negative organisms *in vitro*.[29,31] 7(*R*)-7-Deoxy-7-(imidazol-2-yl-thio) lincomycin[34] had similar antibacterial activities as LCM. According to the accumulated SAR information so far, a sulfur atom may be preferable to an oxygen atom to improve antibacterial activities in chemical modifications at the C-7 position of LCM. Furthermore, antibacterial activities are influenced by both configuration and structure of a substituent at the C-7 position.

X-ray crystallographic analyses[18,20] between bacterial ribosomal RNA and bacterial peptide-synthesis inhibitors, including CLDM and macrolide antibiotics, have already been reported. According to their reports, CLDM had enough three-dimensional empty space for an additional moiety around the C-7 position. So, we hypothesized that antibacterial activities may be improved by filling the above space with an appropriate substituent. We have reported synthesis and biological evaluation of several 7(*S*)-7-arylthio-7-deoxylincomycin derivatives so far.[35–41] As far as we know, we reported LCM analogs possessing antibacterial activities against resistant pathogens with *erm* gene for the first time.[35] We recently reported 7(*S*)-thiolincomycin analogs as the first-generation derivatives in our research. Compounds **1** and **2** (Figure 2) exhibited improved antibacterial activities against resistant *S. pneumoniae* with *erm* and *mef* genes compared with CAM, AZM, LCM and CLDM[39] as shown in Table 1. Furthermore, we also reported novel derivatives **3** and **4**,[40] which had stronger activities than compounds **1** and **2**. Comparing with compounds **1–4**, we newly hypothesized that a benzene ring and a hetero ring with basicity are important to enhance antibacterial activities against resistant bacteria with *erm* and *mef* genes. In this article, we report synthesis and biological evaluation of novel LCM analogs possessing a benzene ring and a hetero ring with basicity via sulfur atom with the 7(*S*)-configuration.

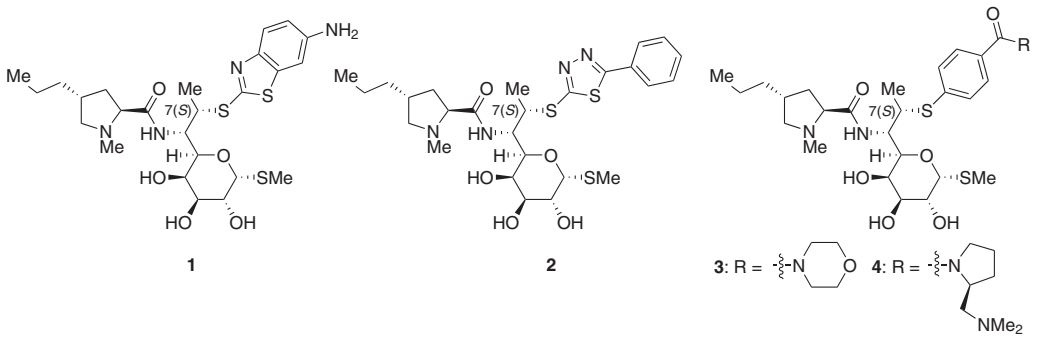
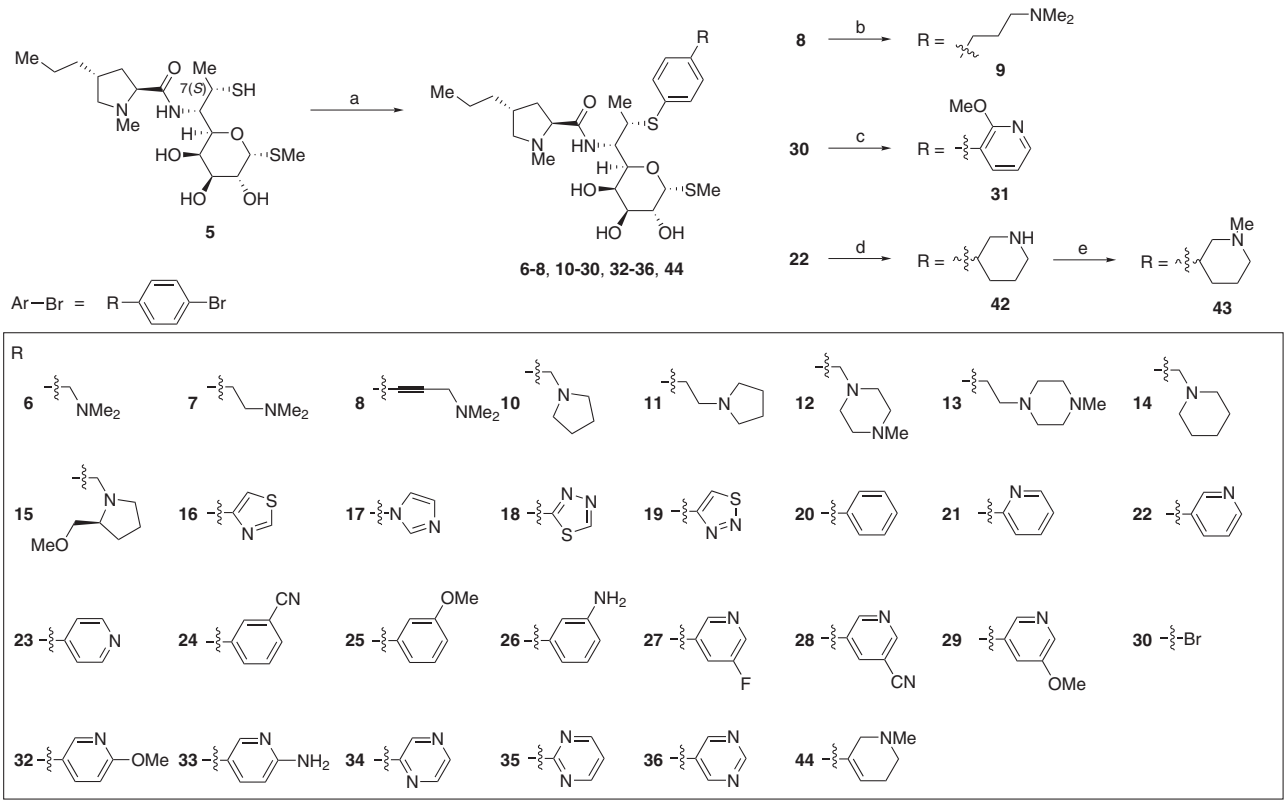


Figure 2 Previously reported LCM analogs modified at the C-7 position.



Scheme 1 Synthesis of 7(*S*)-7-arylphenylthio-7-deoxylincomycin, 7(*S*)-7-deoxy-7-heteroarylphenylthiolincomycin or 7(*S*)-7-aminoalkylphenylthio-7-deoxylincomycin derivatives. Conditions were as follows: (a) Ar-Br, Xantphos, $Pd_2(DBA)_3$, iPr_2NEt, dioxane, reflux, 2–21 h, (b) Pd/C, H_2, MeOH, r.t., overnight, (c) (2-methoxypyridin-3-yl)boronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DMF, H_2O, 80 °C, 8 h, (d) Pt black, H_2, MeOH, 1 *N* HCl, r.t., 11 days, (e) HCHO, AcOH, $NaBH(OAc)_3$, MeOH, r.t., 30 min.

RESULTS AND DISCUSSION

Synthesis of 7(*S*)-7-deoxy-7-(substituted-phenylthio)lincomycin derivatives

Synthesis of 7(*S*)-7-deoxy-7-(substituted-phenylthio)lincomycin derivatives is shown in Scheme 1. We have already reported synthetic route of compound **5**.[35–37,40] We applied a different synthetic route for compound **5** from the previously reported route by Magerlein *et al.*[25] We first prepared a key intermediate **5** derived from LCM in six steps in order to construct the same configuration at the C-7 position as CLDM in the final target molecules. A palladium-catalyzed cross-coupling reaction using **5** with various aryl halides is a widely applicable method to synthesize novel LCM derivatives in our research compared with Mitsunobu reaction or an S_N2 reaction in application of a methanesulfonyl intermadiate.[35–37,40,42] In this reaction, aryl halides such as aryl bromide, aryl iodide and aryl triflate can be used.[42] Compounds **6–8**, **10–30**, **32–36** and **44** were synthesized by the cross-coupling reaction to investigate the antibacterial activities of aliphatic and aromatic amine compounds having a benzene ring and a basic moiety via sulfur atom at the C-7 position of LCM. Compound **9** was synthesized by reduction of a triple bond in compound **8** to evaluate its antibacterial activity compared with that of compound **6** or **7** focusing on the distance between a phenyl group and a dimethylamino group. Compound **31** was also prepared in application of Suzuki-Miyaura cross-coupling reaction from **30**. This type of

reaction, the palladium-catalyzed cross-coupling reaction of arylboronic acid with a LCM intermediate (**30**) possessing an aryl bromide moiety via sulfur at the C-7 position, was reported for the first time. The pyridine ring of compound **22** was reduced to give the corresponding piperidin-3-yl derivative (**42**). Then, compound **42** was converted to the desired *N*-methyl derivative (**43**) by reductive aminoalkylation. Compounds **42** and **43** were isolated as a mixture of each diastereoisomer.

Synthesis of 7(*R*)-7-deoxy-7-(4-(pyrimidin-5-yl)phenylthio) lincomycin

Synthesis of 7(*R*)-7-deoxy-7-(4-(pyrimidin-5-yl)phenylthio)lincomycin (**41**) is shown in Scheme 2. We prepared compound **41** possessing a 4-(pyrimidin-5-yl)phenyl group with 7(*R*)-configuration via sulfur atom at the C-7 position of LCM in order to evaluate its activity compared with that of compound **36** with the 7(*S*)-configuration. Preparation of **41** began with protection of all hydroxyl groups of CLDM. The protected compound **37** was reacted with potassium thioacetate by an S_N2 reaction to give the corresponding thioacetate (**38**). Compound **39** was prepared by removing all TMS groups of compound **38** under the acidic condition and followed by the removal of the acetyl group to give a key intermediate **40**. The desired pyrimidinylphenylthio derivative (**41**) with 7(*R*)-configuration was synthesized in application of 5-(4-bromophenyl)pyrimidine.

SAR analysis of LCM derivatives possessing an aliphatic amine as a substituent on the phenyl group at the C-7 position

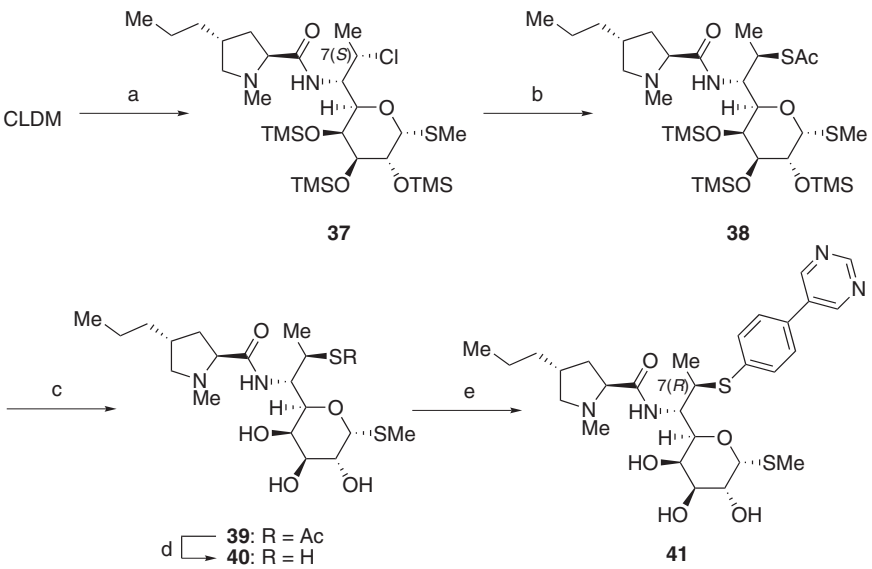
Antibacterial activities of LCM derivatives possessing an aliphatic amine as a substituent on the phenyl group at the C-7 position via sulfur atom are shown in Table 2. As described above, we newly hypothesized that a benzene ring and a hetero ring with basicity were important to enhance antibacterial activities against resistant bacteria with *erm* gene. So, we first evaluated the distance between the phenyl group and the dimethylamino group in the C-7 substituent. As a result, compounds **6** and **7**, which possessed one or two carbon atom (s) between the phenyl group and the dimethylamino group, exhibited relatively potent antibacterial activities against resistant *S. pneumoniae* with *erm* gene and *H. influenzae* compared with **9**. Next, we fixed the number of carbon atom(s) between the phenyl group and the basic functionality as one or two, and we replaced the dimethylamino group with a hetero ring such as pyrrolidine, mono-*N*-methylpiperazine and piperidine. Consequently, compounds **10**, **11** and **14** had similar antibacterial activities as compounds **6** and **7**. On the other hand, we reported[40] that a 2-(methoxymethyl)pyrrolidine group was an important moiety to enhance antibacterial activities against resistant bacteria with *erm* gene. Then, we introduced the 2-methoxymethyl group on the pyrrolidine ring of **10** to afford **15**. Consequently, the desired product **15** exhibited four times potent activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene compared with **10**. These results suggest that a phenyl group and a basic moiety (especially, a hetero ring with a substituent) are important to enhance antibacterial activities against resistant bacteria with *erm* gene, and the number of carbon atoms between the phenyl group and the basic functionality might be optimized with one or two.

SAR analysis of LCM derivatives possessing a heteroaryl group as a substituent on the phenyl group at the C-7 position

Novel aromatic derivatives possessing a phenyl or a heteroaryl group as a substituent on the phenyl group at the C-7 position via sulfur atom were synthesized and their antibacterial activities are shown in Table 3. Consequently, the heterocyclic substituent on the phenyl group at the C-7 position also improved antibacterial activities against resistant pathogens. Especially, compounds **19** and **22** had potent activities against resistant *Streptococcus* strains with *erm* gene and *H. influenzae*. Moreover, antibacterial activities of **22**, when compared with those of **21** or **23** suggested that the location of the nitrogen atom was an important factor to enhance antibacterial activities.

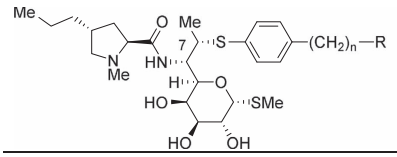
SAR analysis of LCM derivatives possessing a substituted phenyl or pyridinyl group as a substituent on the phenyl group at the C-7 position

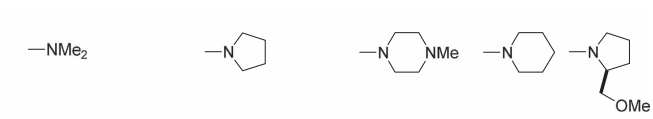
Antibacterial activities of alternative biaryl derivatives possessing a substituted phenyl or pyridinyl group as a substituent on the phenyl group at the C-7 position are shown in Table 4. As a



Scheme 2 Synthesis of 7(*R*)-7-deoxy-7-thiolincomycin **40** and compound **41**. Conditions were as follows: (a) TMSCl, HMDS, Py, r.t., 1 h, (b) KSAc, DMF, 100 °C, 18 h, (c) 1 *N* HCl, MeOH, r.t., 10 min, (d), NaOMe, MeOH, r.t., 20 min, (e) Xantphos, $Pd_2(DBA)_3$, iPr_2NEt, dioxane, reflux, 6 h.

Table 2 Antibacterial activities (MIC, μg ml^{-1}) of dimethylamino derivatives and cyclicaminoalkyl derivatives





		R								
		n	1	2	3	1	2	1	2	1	1
Test organism[a]	Characteristics[b]		**6**	**7**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Streptococcus pneumoniae DP1 TypeI	susceptible		0.015	≦0.008	0.015	0.015	0.015	0.03	0.06	0.015	0.03
S. pneumoniae -2	susceptible		0.015	0.015	0.015	0.015	0.015	0.03	0.06	0.015	0.03
S. pneumoniae -3	susceptible		0.03	0.015	0.015	0.03	0.03	0.03	0.06	0.03	0.06
S. pneumoniae -4	*ermAM* methylase(c)		8	4	64	4	8	64	>128	4	1
S. pneumoniae -5	*ermAM* methylase(c)		8	4	64	4	8	32	128	2	1
S. pneumoniae -6	*ermAM* methylase(c) + *mefE*		16	8	64	8	32	64	>128	8	2
S. pneumoniae -7	*ermAM* methylase(i)		1	1	4	0.5	2	4	0.5	0.25	0.12
S. pneumoniae -9	*mefE* efflux		≦0.008	≦0.008	≦0.008	≦0.008	0.015	0.015	0.06	≦0.008	0.015
Streptococcus pyogenes Cook	susceptible		0.03	0.015	0.03	0.03	0.06	0.06	0.12	0.03	0.06
S. pyogenes -2	*ermAM* methylase(c)		2	N.T.	16	2	4	8	32	4	0.5
S. pyogenes -3	*mefE* efflux		0.03	0.015	0.015	0.03	0.03	0.06	0.12	0.03	0.06
Haemophilus influenzae	susceptible		8	2	32	2	8	16	64	4	4
H. influenzae -2	susceptible		4	2	8	4	8	16	64	4	8
H. influenzae -3	susceptible		16	8	32	16	32	64	>128	16	16
H. influenzae -4	⊿acr		0.25	0.25	0.5	0.25	0.5	0.5	2	0.25	0.25

Abbreviations: MIC, minimum inhibitory concentration; N.T., not tested.
Gray shading indicates target strains.
[a]All strains except standard organisms were clinically isolated.
[b]'c' indicates constitutive and 'i' indicates inducible.

result, the 5-methoxypyridin-3-yl derivative (**29**) exhibited significantly stronger activities against resistant bacteria than the 3-methoxyphenyl derivative (**25**) or the 6-methoxypyridin-3-yl derivative (**32**). The pyridine analog (**29**) was shown to be the most potent among substituted pyridine analogs. However, it was less potent when compared with non-substituted pyridine analog (**22**).

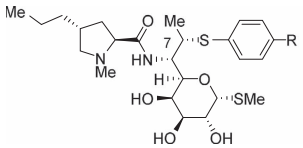
SAR analysis of optimized LCM derivatives possessing a six-membered hetero ring as a substituent on the phenyl group at the C-7 position

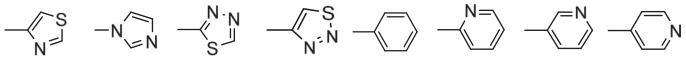
Antibacterial activities of optimized LCM derivatives possessing a six-membered hetero ring as a substituent on the phenyl group at the C-7 position are shown in Table 5. A pyrimidine analog (**36**) exhibited slightly improved antibacterial activities compared with the pyridine-3-yl analog (**22**) against *S. pneumoniae* and *H. influenzae*. Moreover, non-aromatic derivatives **42–44** also exhibited potent antibacterial activities against *S. pneumoniae* with *erm* gene and markedly improved activities against both *S. pyogenes* with *erm* gene and *H. influenza*e. We have already reported the importance of 7(*S*)-configuration to enhance antibacterial activities.[39] Then, we also investigated the importance of 7(*S*) stereochemistry in pyrimidinylphenyl analogs. As a result, we could reconfirm that 7 (*S*)-configuration was important to improve antibacterial activities based on the comparison results of potency between compound **36** (7(*S*)-configuration) and compound **41** (7(*R*)-configuration). According to the previously reported docking simulation analysis[40] of 7(*S*)-7-deoxy-7-(4-morpholinocarbonylphenylthio)lincomycin, it was supposed that steric hindrance occurs between the 8-methyl group and a carbohydrate moiety in compound **41**, and its three-dimensional structure is not appropriate for antibacterial activity.

CONCLUSION

We were interested in LCM analogs possessing a phenyl ring and a hetero ring with basicity via sulfur atom focusing on the 7(*S*)-configuration at the C-7 position. We synthesized a variety of LCM analogs in application of the Pd-catalyzed cross-coupling reaction[35–37,40] of 7(*S*)-7-deoxy-7-thiolincomycin (**5**) with an aryl bromide or an aryl iodide. This methodology was very useful to synthesize various 7(*S*)-7-thio-modified LCM analogs. Antibacterial activities of LCM analogs with a linear moiety, which possessed one or two carbon atom(s) between the phenyl group and the dimethylamino group, were relatively effective against resistant bacteria. Furthermore, we found that the location of the nitrogen atom was important to improve antibacterial activities based on the results of compounds **21–23**. Consequently, we found that compounds **22**, **36** and **42–44** had potent antibacterial activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene and *H. influenzae*. On the other hand, we confirmed that the 7(*S*)-configuration was important to enhance antibacterial activities in the comparison results of potency between compound **36** (7(*S*)-configuration) and compound **41** (7(*R*)-configuration). Antibacterial activities against *S. pneumoniae* with *erm* gene of our novel derivatives reported in this article were catching up with those of TEL, and the activities against *S. pyogenes* with *erm* gene and *Streptococcus* strains with *mef* gene of our selected derivative were stronger than those of TEL as shown in Table 5. We selected the 4-(pyrimidin-5-yl)phenyl group in compound **36** as the C-7 substituent for further medicinal chemistry toward generation of candidates, because it exhibits physicochemical stability without additional stereochemistry. In order to investigate other possibilities of novel semi-synthetic LCM antibiotics, alternative modifications of LCM analogs possessing a 7-thiothiadiazolyl group are in progress. On the basis of the information stated in this article, we will continually explore novel chemical modifications focusing on clinically promising LCM derivatives which exhibit potent antibacterial activities against resistant *S. pneumoniae* and *S. pyogenes* with *erm* and *mef* genes.

Table 3 Antibacterial activities (MIC, μg ml^{-1}) of a variety of heteroaromatic derivatives and compound 20



R = 

Test organism[a]	Characteristics[b]	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**
Streptococcus pneumoniae DP1 TypeI	susceptible	0.03	0.015	0.015	≦0.008	0.25	0.03	≦0.008	0.03
S. pneumoniae -2	susceptible	0.03	0.015	0.015	≦0.008	0.25	0.06	≦0.008	0.03
S. pneumoniae -3	susceptible	0.03	0.015	0.015	0.015	0.25	0.03	0.015	0.03
S. pneumoniae -4	*ermAM* methylase(c)	4	4	2	1	32	8	0.5	8
S. pneumoniae -5	*ermAM* methylase(c)	8	4	8	N.T.	>64	16	1	16
S. pneumoniae -6	*ermAM* methylase(c) + *mefE*	16	16	32	4	>64	>64	2	>64
S. pneumoniae -7	*ermAM* methylase(i)	4	1	1	0.5	16	4	0.25	4
S. pneumoniae -8	*ermAM* methylase(i)	1	2	2	0.12	16	4	0.25	4
S. pneumoniae -9	*mefE* efflux	0.015	≦0.008	≦0.008	≦0.008	0.25	0.03	≦0.008	0.03
Streptococcus pyogenes Cook	susceptible	0.015	0.015	0.015	≦0.008	0.25	0.03	0.015	0.03
S. pyogenes -2	*ermAM* methylase(c)	4	1	4	0.5	16	8	0.5	8
S. pyogenes -3	*mefE* efflux	0.03	0.015	0.03	≦0.008	0.25	0.03	0.015	0.06
Haemophilus influenzae	susceptible	16	8	16	4	>64	32	4	16
H. influenzae -2	susceptible	8	4	8	2	32	16	2	16
H. influenzae -3	susceptible	>64	16	32	8	>128	>64	16	>64
H. influenzae -4	⊿acr	0.25	0.12	0.25	0.03	4	0.25	0.06	0.25

Abbreviations: MIC, minimum inhibitory concentration; N.T., not tested.
Gray shading indicates target strains.
[a]All strains except standard organisms were clinically isolated.
[b]'c' indicates constitutive and 'i' indicates inducible.

EXPERIMENTAL PROCEDURE

General methods

^{1}H NMR spectra were measured with a BRUKER Ascend 400 NMR spectrometer (BRUKER, Coventry, UK) for 400 MHz, JEOL JNM-GSX 400 NMR spectrometer (JEOL,Tokyo, Japan) for 400 MHz or a Varian Gemini 300 NMR spectrometer (Varian, Palo Alto, CA, USA) for 300 MHz in $CDCl_3$ or CD_3OD. TMS (0 p.p.m.) in $CDCl_3$ or CD_3OD was used as an internal reference standard. Mass spectra (MS) were obtained on a JEOL JMS-700 mass spectrometer (JEOL) or Agilent Technologies 6530-Q-TOF LC/MS mass spectrometer (Agilent Technologies, Santa Clara, CA, USA). The optical rotations were recorded with Jasco P-2300 digital polarimeter (Jasco, Tokyo, Japan). Column chromatography was performed with silica gel (Wakogel C200, Wako Pure Chemical Industries, Osaka, Japan). Preparative thin-layer chromatography was performed with silica gel (Merck, Darmstadt, Germany: TLC plates Silica gel 60 F254). All organic extracts were dried over anhydrous $MgSO_4$, and the solvent was removed with a rotary evaporator under reduced pressure.

7(*S*)-7-Deoxy-7-(4-((dimethylamino)methyl)phenylthio)lincomycin (6)

To a solution of 1-(4-bromophenyl)-*N*, *N*-dimethylmethanamine (23.2 mg, 0.108 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) (10.4 mg, 0.018 mmol) and tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) (8.3 mg, 9.6 μmol) in 1,4-dioxane (1 ml) were added to compound **5** (38.2 mg, 0.090 mmol) and *N*,*N*-diisopropylethylamine (31.4 μl, 0.180 mmol) and refluxed for 3 h. The mixture was filtrated by either Chromatodisc (0.45 μm) (KURABO INDUSTRIES, Osaka, Japan) or celite. The filtered solid were washed with MeOH three times and then the assembled solution was concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq. NH_4OH = 10/1/0.1) to obtain the title compound as an off-white solid (39.4 mg, 78%). $[\alpha]_D^{24}$ +98.0° (*c* 1.94, MeOH); ESI-MS m/z 556 $(M+H)^+$ as $C_{27}H_{45}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{27}H_{45}N_3O_5S_2$: 556.2879, found: 556.2883; ^{1}H NMR (400 MHz, CD_3OD) δ 0.89–0.98 (m, 3 H), 1.29 (d, *J* = 6.9 Hz, 3 H), 1.31–1.41 (m, 4 H), 1.95–2.05 (m, 1 H), 1.97 (s, 3 H), 2.06–2.13 (m, 1 H), 2.13–2.22 (m, 1 H), 2.26 (s, 6 H), 2.41 (s, 3 H), 3.00 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.25 (dd, *J* = 8.1, 5.6 Hz, 1 H), 3.49 (s, 2 H), 3.58 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.72–3.78 (m, 1 H), 3.87 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.34 (br dd, *J* = 9.7, 0.5 Hz, 1 H), 4.42 (dd, *J* = 9.7, 2.6 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.26–7.32 (m, 2 H), 7.37–7.43 (m, 2 H).

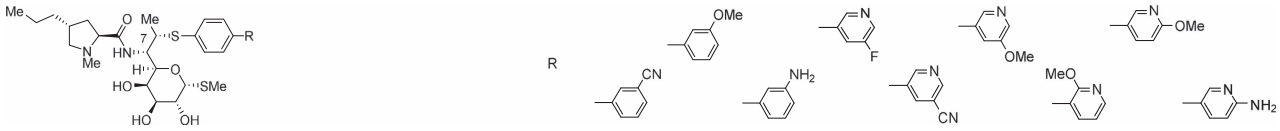
7(*S*)-7-Deoxy-7-(4-(2-(dimethylamino)ethyl)phenylthio)lincomycin (7)

Compound **5** (106 mg, 0.251 mmol), 2-(4-bromophenyl)-*N*, *N*-dimethylethan-1-amine (124.9 mg, 0.547 mmol), Xantphos (15.8 mg, 0.027 mmol), $Pd_2(dba)_3$ (12.9 mg, 0.014 mmol) and *N*,*N*-diisopropylethylamine (64.0 μl, 0.368 mmol) in 1,4-dioxane (3 ml) were treated for 14 h according to the similar procedure as described for the preparation of **6** to afford **7** (85.7 mg, 60%) as a colorless solid. $[\alpha]_D^{24}$ +102° (*c* 0.64, MeOH); ESI-MS (*m/z*) 570 $(M+H)^+$ as $C_{28}H_{47}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{28}H_{47}N_3O_5S_2$: 570.3035, found: 570.3034; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.98 (m, 3 H), 1.26 (d, *J* = 6.8 Hz, 3 H), 1.30–1.42 (m, 4 H), 1.79–1.91 (m, 1 H), 1.95–2.04 (m, 1 H), 2.01 (s, 3 H), 2.05–2.12 (m, 1 H), 2.12–2.23 (m, 1 H), 2.31 (s, 6 H), 2.39 (s, 3 H), 2.52–2.60 (m, 2 H), 2.74–2.82 (m, 2 H), 2.98 (dd, *J* = 10.7, 4.6 Hz, 1 H), 3.24 (dd, *J* = 8.0, 5.6 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.74 (m, 1 H), 3.81 (dq, *J* = 6.8, 2.6 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.5 Hz, 1 H), 4.33 (br dd, *J* = 9.8, 0.5 Hz, 1 H), 4.39 (dd, *J* = 9.8, 2.6 Hz, 1 H), 5.26 (d, *J* = 5.5 Hz, 1 H), 7.17–7.24 (m, 2 H), 7.34–7.41 (m, 2 H).

7(*S*)-7-Deoxy-7-(4-(3-(dimethylamino)prop-1-yn-1-yl)phenylthio) lincomycin (8)

Compound **5** (66.2 mg, 0.157 mmol), 3-(4-bromophenyl)-*N*, *N*-dimethyl-prop-2-yn-1-amine (42.3 mg, 0.178 mmol), Xantphos (9.8 mg, 0.017 mmol), $Pd_2(dba)_3$ (6.5 mg, 7.1 μmol) and *N*,*N*-diisopropylethylamine (38.9 μl, 0.224 mmol) in 1,4-dioxane (0.75 ml) were treated for 14 h according to the similar procedure as described for the preparation of **6** to afford **8** (59.4 mg, 65%) as a colorless solid. FAB-MS (*m/z*) 580 $(M+H)^+$ as $C_{29}H_{45}N_3O_5S_2$; FAB-HRMS $(M+H)^+$ calcd. for $C_{29}H_{45}N_3O_5S_2$: 580.2879, found: 580.2878; ^{1}H NMR (400 MHz, CD_3OD) δ 0.85–1.00 (m, 3 H), 1.26–1.42 (m, 4 H), 1.34

Table 4 Antibacterial activities (MIC, μg ml^{-1}) of substituted phenyl derivatives and substituted pyridinyl derivatives



Test organism[a]	Characteristics[b]	24	25	26	27	28	29	31	32	33
Streptococcus pneumoniae DP1 TypeI	susceptible	0.03	0.12	0.06	0.015	0.015	0.015	0.06	0.12	0.03
S. pneumoniae -2	susceptible	0.03	0.12	0.06	0.03	0.03	0.015	0.06	0.12	0.03
S. pneumoniae -3	susceptible	0.03	0.12	0.06	0.015	0.015	0.015	0.06	0.12	0.03
S. pneumoniae -4	*ermAM* methylase(c)	4	32	2	4	2	1	16	>64	>64
S. pneumoniae -5	*ermAM* methylase(c)	4	32	4	4	2	1	8	>64	32
S. pneumoniae -6	*ermAM* methylase(c) + *mefE*	16	32	16	8	4	8	32	>64	>64
S. pneumoniae -7	*ermAM* methylase(i)	2	8	2	0.5	0.25	0.5	1	32	N.T.
S. pneumoniae -8	*ermAM* methylase(i)	1	8	1	N.T.	N.T.	0.5	N.T.	N.T.	N.T.
S. pneumoniae -9	*mefE* efflux	0.015	0.03	0.03	≦0.008	≦0.008	0.015	0.03	0.03	0.015
Streptococcus pyogenes Cook	susceptible	0.015	0.12	0.06	0.03	0.03	0.015	0.06	0.03	0.03
S. pyogenes -2	*ermAM* methylase(c)	2	16	1	1	1	1	4	32	2
S. pyogenes -3	*mefE* efflux	0.06	0.25	0.06	0.03	0.03	0.015	0.06	0.12	0.03
Haemophilus influenzae	susceptible	32	>64	16	16	32	16	32	128	32
H. influenzae -2	susceptible	16	32	8	16	16	8	16	32	16
H. influenzae -3	susceptible	>64	>128	32	32	32	32	>64	>128	>64
H. influenzae -4	⊿acr	0.5	2	0.25	0.25	0.25	0.12	0.5	2	0.25

Abbreviations: MIC, minimum inhibitory concentration; N.T., not tested.
Gray shading indicates target strains.
[a]All strains except standard organisms were clinically isolated.
[b]'c' indicates constitutive and 'i' indicates inducible.

(d, J=6.9 Hz, 3 H), 1.78–1.90 (m, 1 H), 1.92–2.03 (m, 1 H), 1.94 (s, 3 H), 2.03–2.11 (m, 1 H), 2.11–2.22 (m, 1 H), 2.37 (s, 6 H), 2.38 (s, 3 H), 2.97 (dd, J=10.6, 4.7 Hz, 1 H), 3.24 (dd, J=8.2, 5.7 Hz, 1 H), 3.48 (s, 2 H), 3.58 (dd, J=10.2, 3.2 Hz, 1 H), 3.75 (br dd, J=3.2, 0.6 Hz, 1 H), 3.89 (dq, J=6.9, 2.8 Hz, 1 H), 4.10 (dd, J=10.2, 5.6 Hz, 1 H), 4.36 (br dd, J=9.8, 0.6 Hz, 1 H), 4.45 (dd, J=9.8, 2.8 Hz, 1 H), 5.26 (d, J=5.6 Hz, 1 H), 7.35–7.42 (m, 4 H).

7(*S*)-7-Deoxy-7-(4-(3-(dimethylamino)propyl)phenylthio) lincomycin (9)

To a solution of compound **8** (21.4 mg, 0.037 mmol) in MeOH (2 ml) was added Pd/C (10.4 mg) and then vigorously stirred in hydrogen atmosphere at room temperature for 14 h. The mixture was filtrated with celite. The filtered solid was washed with MeOH three times and then the assembled solution was concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/CH_3OH/28% aq. NH_4OH=10/1/0.1) to obtain the title compound (**9**) (13.7 mg, 64%) as a colorless solid. $[\alpha]_D^{23}$ +87.1° (c 0.22, MeOH); ESI-MS (m/z) 584 $(M+H)^+$ as $C_{29}H_{49}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{29}H_{49}N_3O_5S_2$: 584.3192, found: 584.3192; ^{1}H NMR (400 MHz, CD_3OD) δ 0.90–0.97 (m, 3 H), 1.26 (d, J=7.0 Hz, 3 H), 1.31–1.41 (m, 4 H), 1.76–1.91 (m, 3 H), 1.95–2.04 (m, 1 H), 2.01 (s, 3 H), 2.05–2.12 (m, 1 H), 2.12–2.23 (m, 1 H), 2.28 (s, 6 H), 2.39 (s, 3 H), 2.37–2.44 (m, 2 H), 2.62 (t, J=7.7 Hz, 2 H), 2.98 (dd, J=10.6, 4.6 Hz, 1 H), 3.24 (dd, J=8.1, 5.5 Hz, 1 H), 3.57 (dd, J=10.3, 3.3 Hz, 1 H), 3.73 (m, 1 H), 3.80 (dq, J=7.0, 2.4 Hz, 1 H), 4.10 (dd, J=10.3, 5.6 Hz, 1 H), 4.33 (br dd, J=9.8, 0.6 Hz, 1 H), 4.38 (dd, J=9.8, 2.4 Hz, 1 H), 5.26 (d, J=5.6 Hz, 1 H), 7.15–7.21 (m, 2 H), 7.34–7.39 (m, 2 H).

7(*S*)-7-Deoxy-7-(4-(pyrrolidin-1-ylmethyl)phenylthio)lincomycin (10)

Compound **5** (97.5 mg, 0.231 mmol), 1-(4-bromobenzyl)pyrrolidine (90.1 mg, 0.375 mmol), Xantphos (14.6 mg, 0.025 mmol), $Pd_2(dba)_3$ (11.1 mg, 0.012 mmol) and *N*,*N*-diisopropylethylamine (119.9 μl, 0.689 mmol) in 1,4-dioxane (2 ml) were treated for 3 h according to the similar procedure as described for the preparation of **6** to afford **10** (115.5 mg, 86%) as an off-white solid. $[\alpha]_D^{23}$ +102° (c 3.96, MeOH); ESI-MS (m/z) 582 $(M+H)^+$ as $C_{29}H_{47}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{29}H_{47}N_3O_5S_2$: 582.3035, found: 582.3027; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.97 (m, 3 H), 1.28 (d, J=6.9 Hz, 3 H), 1.30–1.41 (m, 4 H), 1.75–1.83 (m, 4 H), 1.83–1.91 (m, 1 H), 1.98 (s, 3 H), 1.94–2.04 (m, 1 H), 2.05–2.11 (m, 1 H), 2.12–2.23 (m, 1 H), 2.40 (s, 3 H), 2.48–2.58 (m, 4 H), 2.99 (dd, J=10.6, 4.6 Hz, 1 H), 3.24 (dd, J=8.1, 5.6 Hz, 1 H), 3.59 (dd, J=10.2, 3.2 Hz, 1 H), 3.61 (s, 2 H), 3.72–3.76 (m, 1 H), 3.86 (dq, J=6.9, 2.6 Hz, 1 H), 4.11 (dd, J=10.2, 5.6 Hz, 1 H), 4.30–4.36 (m, 1 H), 4.42 (dd, J=9.7, 2.6 Hz, 1 H), 5.28 (d, J=5.6 Hz, 1 H), 7.28–7.34 (m, 2 H), 7.36–7.42 (m, 2 H).

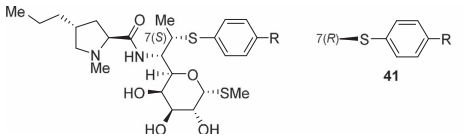
7(*S*)-7-Deoxy-7-(4-(2-(pyrrolidin-1-yl)ethyl)phenylthio)lincomycin (11)

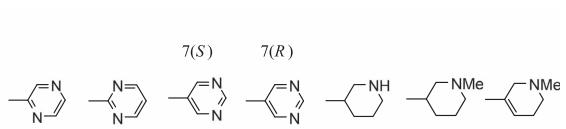
Compound **5** (83.0 mg, 0.196 mmol), 1-(4-bromophenethyl)pyrrolidine (50.0 mg, 0.197 mmol), Xantphos (11.0 mg, 0.019 mmol), $Pd_2(dba)_3$ (9.0 mg, 0.010 mmol) and *N*,*N*-diisopropylethylamine (172.5 μl, 0.990 mmol) in 1,4-dioxane (3 ml) were treated for 3 h according to the similar procedure as described for the preparation of **6** to afford **11** (82.0 mg, 70%) as a colorless solid. $[\alpha]_D^{25}$ +68.0° (c 0.25, MeOH); ESI-MS (m/z) 596 $(M+H)^+$ as $C_{30}H_{49}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{30}H_{49}N_3O_5S_2$: 596.3192, found: 596.3171; ^{1}H NMR (400 MHz, CD_3OD) δ 0.89–0.97 (m, 3 H), 1.27 (d, J=6.9 Hz, 3 H), 1.31–1.42 (m, 4 H), 1.82–1.92 (m, 5 H), 1.95–2.04 (m, 1 H), 2.01 (s, 3 H), 2.05–2.12 (m, 1 H), 2.12–2.25 (m, 1 H), 2.39 (s, 3 H), 2.66–2.75 (m, 4 H), 2.75–2.89 (m, 4 H), 2.98 (dd, J=10.6, 4.6 Hz, 1 H), 3.24 (dd, J=8.0, 5.6 Hz, 1 H), 3.58 (dd, J=10.2, 3.3 Hz, 1 H), 3.71–3.76 (m, 1 H), 3.81 (dq, J=6.9, 2.5 Hz, 1 H), 4.10 (dd, J=10.2, 5.6 Hz, 1 H), 4.33 (br dd, J=9.8, 0.5 Hz, 1 H), 4.39 (dd, J=9.8, 2.5 Hz, 1 H), 5.26 (d, J=5.6 Hz, 1 H), 7.18–7.24 (m, 2 H), 7.34–7.41 (m, 2 H).

7(*S*)-7-Deoxy-7-(4-((4-methylpiperazin-1-yl)methyl)phenylthio) lincomycin (12)

Compound **5** (100.2 mg, 0.237 mmol), 1-(4-bromobenzyl)-4-methylpiperazine (144.3 mg, 0.536 mmol), Xantphos (14.6 mg, 0.025 mmol), $Pd_2(dba)_3$ (11.0 mg, 0.012 mmol) and *N*,*N*-diisopropylethylamine (119.9 μl, 0.689 mmol) in 1,4-dioxane (2 ml) were treated for 4 h according to the similar procedure as described for the preparation of **6** to afford **12** (132.7 mg, 92%) as a colorless solid. $[\alpha]_D^{25}$ +93.2° (c 2.52, MeOH); ESI-MS (m/z) 611 $(M+H)^+$ as $C_{30}H_{50}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{30}H_{50}N_4O_5S_2$: 611.3301, found: 611.3285; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.97 (m, 3 H), 1.28 (d, J=6.8 Hz, 3 H), 1.28–1.41 (m, 4 H), 1.80–1.91 (m, 1 H), 1.95–2.04 (m, 1 H), 1.98 (s, 3 H), 2.04–2.12 (m, 1 H), 2.12–2.23 (m, 1 H), 2.27 (s, 3 H), 2.30–2.92 (m, 8 H), 2.40 (s, 3H), 2.99 (dd, J=10.7, 4.6 Hz, 1 H), 3.25 (dd, J=8.1, 5.7 Hz, 1 H), 3.51 (s, 2 H), 3.58 (dd, J=10.2, 3.3 Hz, 1 H), 3.71–3.77 (m, 1 H), 3.85 (dq, J=6.8, 2.6 Hz, 1 H), 4.10 (dd, J=10.2, 5.6 Hz, 1 H),

Table 5 Antibacterial activities (MIC, μg ml^{-1}) of optimized derivatives with a heterocycle and TEL





Test organism[a]	Characteristics[b]	**34**	**35**	**36**	**41**	**42**	**43**	**44**	TEL
Streptococcus pneumoniae DP1 TypeI	susceptible	0.015	0.015	≦0.008	0.06	0.015	0.015	≦0.008	≦0.008
S. pneumoniae -2	susceptible	0.015	0.015	≦0.008	0.06	0.015	0.015	0.015	≦0.008
S. pneumoniae -3	susceptible	0.015	0.015	≦0.008	0.06	0.03	0.03	0.015	≦0.008
S. pneumoniae -4	*ermAM* methylase(c)	1	4	0.5	>128	0.5	0.5	0.5	0.5
S. pneumoniae -5	*ermAM* methylase(c)	1	8	1	>128	1	0.5	0.5	2
S. pneumoniae -6	*ermAM* methylase(c) + *mefE*	4	>64	2	>128	2	1	1	1
S. pneumoniae -7	*ermAM* methylase(i)	0.5	1	0.25	>64	0.25	0.25	0.5	0.03
S. pneumoniae -8	*ermAM* methylase(i)	0.25	2	0.25	>64	0.25	0.25	0.25	0.03
S. pneumoniae -9	*mefE* efflux	≦0.008	≦0.008	≦0.008	0.06	≦0.008	≦0.008	0.015	0.06
Streptococcus pyogenes Cook	susceptible	≦0.008	0.015	≦0.008	0.03	0.015	0.015	0.015	≦0.008
S. pyogenes -2	*ermAM* methylase(c)	0.5	4	0.5	32	0.12	0.25	0.12	16
S. pyogenes -3	*mefE* efflux	0.015	0.03	0.015	0.03	0.03	0.03	0.015	0.25
Haemophilus influenzae	susceptible	8	16	4	>128	2	2	1	0.5
H. influenzae -2	susceptible	4	8	2	128	4	2	2	2
H. influenzae -3	susceptible	16	>64	8	>128	8	8	8	1
H. influenzae -4	⊿acr	0.12	0.25	0.06	2	0.12	0.06	0.12	0.25

Abbreviations: MIC, minimum inhibitory concentration; TEL, telithromycin.
Gray shading indicates target strains.
[a]All strains except standard organisms were clinically isolated.
[b]'c' indicates constitutive and 'i' indicates inducible.

4.29–4.35 (m, 1 H), 4.41 (dd, J=9.8, 2.6 Hz, 1 H), 5.27 (d, J=5.6 Hz, 1 H), 7.26–7.33 (m, 2 H), 7.36–7.43 (m, 2 H).

7(*S*)-7-Deoxy-7-(4-(2-(4-methylpiperazin-1-yl)ethyl)phenylthio) lincomycin (13)

Compound **5** (90.0 mg, 0.213 mmol), 1-(4-bromophenethyl)-4-methylpiperazine (60.0 mg, 0.212 mmol), Xantphos (12.0 mg, 0.021 mmol), $Pd_2(dba)_3$ (9.7 mg, 0.011 mmol) and *N*,*N*-diisopropylethylamine (184.6 μl, 1.060 mmol) in 1,4-dioxane (3 ml) were treated for 2 h according to the similar procedure as described for the preparation of **6** to afford **13** (89.0 mg, 67%) as an off-white solid. $[\alpha]_D^{23}$ +90.7° (*c* 2.05, MeOH); ESI-MS (*m/z*) 625 $(M+H)^+$ as $C_{31}H_{52}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{31}H_{52}N_4O_5S_2$: 625.3457, found: 625.3461; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.98 (m, 3 H), 1.26 (d, J=6.9 Hz, 3 H), 1.30–1.40 (m, 4 H), 1.79–1.92 (m, 1 H), 1.94–2.04 (m, 1 H), 2.00 (s, 3 H), 2.05–2.12 (m, 1 H), 2.12–2.23 (m, 1 H), 2.31 (s, 3 H), 2.39 (s, 3 H), 2.41–2.88 (m, 8 H), 2.58–2.64 (m, 2 H), 2.75–2.84 (m, 2 H), 2.99 (dd, J=10.6, 4.6 Hz, 1 H), 3.24 (dd, J=8.0, 5.6 Hz, 1 H), 3.58 (dd, J=10.2, 3.3 Hz, 1 H), 3.71–3.76 (m, 1 H), 3.80 (dq, J=6.9, 2.4 Hz, 1 H), 4.10 (dd, J=10.2, 5.6 Hz, 1 H), 4.31–4.35 (m, 1 H), 4.38 (dd, J=9.8, 2.4 Hz, 1 H), 5.26 (d, J=5.6 Hz, 1 H), 7.17–7.23 (m, 2 H), 7.34–7.40 (m, 2 H).

7(*S*)-7-Deoxy-7-(4-(piperidin-1-ylmethyl)phenylthio)lincomycin (14)

Compound **5** (98.1 mg, 0.232 mmol), 1-(4-bromobenzyl)piperidine (95.3 mg, 0.375 mmol), Xantphos (14.7 mg, 0.025 mmol), $Pd_2(dba)_3$ (10.8 mg, 0.012 mmol) and *N*,*N*-diisopropylethylamine (119.9 μl, 0.689 mmol) in 1,4-dioxane (2 ml) were treated for 3.5 h according to the similar procedure as described for the preparation of **6** to afford **14** (123.4 mg, 89%) as an off-white solid. $[\alpha]_D^{23}$ +97.7° (*c* 4.26, MeOH); ESI-MS (*m/z*) 596 $(M+H)^+$ as $C_{30}H_{49}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{30}H_{49}N_3O_5S_2$: 596.3192, found: 596.3184; ^{1}H NMR (400 MHz, CD_3OD) δ 0.86–0.97 (m, 3 H), 1.29 (d, J=6.9 Hz, 3 H), 1.31–1.40 (m, 4 H), 1.40–1.50 (m, 2 H), 1.52–1.64 (m, 4 H), 1.79–1.91 (m, 1 H), 1.93–2.04 (m, 1 H), 1.98 (s, 3 H), 2.04–2.12 (m, 1 H), 2.12–2.23 (m, 1 H), 2.30–2.48 (m, 4 H), 2.39 (s, 3 H), 2.99 (dd, J=10.6, 4.6 Hz, 1 H), 3.24 (dd, J=8.1, 5.7 Hz, 1 H), 3.46 (s, 2 H), 3.59 (dd, J=10.2, 3.2 Hz, 1 H), 3.72–3.77 (m, 1 H), 3.86 (dq, J=6.9, 2.6 Hz, 1 H), 4.11 (dd, J=10.2, 5.6 Hz, 1 H), 4.30–4.36 (m, 1 H), 4.41 (dd, J=9.7, 2.6 Hz, 1 H), 5.28 (d, J=5.6 Hz, 1 H), 7.25–7.32 (m, 2 H), 7.35–7.41 (m, 2 H).

7(*S*)-7-Deoxy-7-(4-((2(*S*)-(methoxymethyl)pyrrolidin-1-yl)methyl) phenylthio)lincomycin (15)

Compound **5** (70.0 mg, 0.166 mmol), (*S*)-1-(4-bromobenzyl)-2-(methoxymethyl)pyrrolidine (96.5 mg, 0.340 mmol), Xantphos (9.7 mg, 0.017 mmol), $Pd_2(dba)_3$ (7.6 mg, 8.3 μmol) and *N*,*N*-diisopropylethylamine (87.6 μl, 0.503 mmol) in 1,4-dioxane (2 ml) were treated under microwave irradiation for 30 min according to the similar procedure as described for the preparation of **6** to afford **15** (61.0 mg, 59%) as a colorless solid. $[\alpha]_D^{23}$ +72.0° (*c* 1.52, MeOH); ESI-MS (*m/z*) 626 $(M+H)^+$ as $C_{31}H_{51}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{31}H_{51}N_3O_6S_2$: 626.3298, found: 626.3297; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.98 (m, 3 H), 1.28 (d, J=6.9 Hz, 3 H), 1.31–1.40 (m, 4 H), 1.54–1.63 (m, 1 H), 1.64–1.75 (m, 2 H), 1.80–2.05 (m, 3 H), 2.00 (s, 3 H), 2.05–2.12 (m, 1 H), 2.12–2.22 (m, 1 H), 2.22–2.31 (m, 1 H), 2.40 (s, 3 H), 2.69–2.79 (m, 1 H), 2.84–2.91 (m, 1 H), 2.99 (dd, J=10.6, 4.6 Hz, 1 H), 3.24 (dd, J=8.1, 5.6 Hz, 1 H), 3.32–3.36 (m, 1 H), 3.33 (s, 3 H), 3.37–3.46 (m, 2 H), 3.58 (dd, J=10.2, 3.2 Hz, 1 H), 3.72–3.76 (m, 1 H), 3.85 (dq, J=6.9, 2.5 Hz, 1 H), 4.04–4.14 (m, 2 H), 4.31–4.37 (m, 1 H), 4.40 (dd, J=9.8, 2.5 Hz, 1 H), 5.27 (d, J=5.6 Hz, 1 H), 7.28–7.34 (m, 2 H), 7.36–7.41 (m, 2 H).

7(*S*)-7-Deoxy-7-(4-(thiazol-4-yl)phenylthio)lincomycin (16)

Compound **5** (100.0 mg, 0.237 mmol), 4-(4-bromophenyl)thiazole (100.0 mg, 0.416 mmol), Xantphos (10.0 mg, 0.017 mmol), $Pd_2(dba)_3$ (10.0 mg, 0.011 mmol) and *N*,*N*-diisopropylethylamine (82.6 μl, 0.474 mmol) in 1,4-dioxane (2 ml) were treated for 6 h according to the similar procedure as described for the preparation of **6** to afford **16** (93.6 mg, 68%) as a colorless solid. $[\alpha]_D^{19}$ +98.1° (*c* 0.62, MeOH); ESI-MS (*m/z*) 582 $(M+H)^+$ as $C_{27}H_{39}N_3O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{27}H_{39}N_3O_5S_3$: 582.2130, found: 582.2131; ^{1}H NMR (400 MHz, CD_3OD) δ 0.89–0.96 (m, 3 H), 1.27–1.36 (m, 4 H), 1.36 (d, J=6.9 Hz, 3 H), 1.81–1.91 (m, 1 H), 1.95–2.04 (m, 1 H), 2.00 (s, 3 H), 2.05–2.13 (m, 1 H), 2.13–2.24 (m, 1 H), 2.40 (s, 3 H), 3.02 (dd, J=10.5, 4.8 Hz, 1 H), 3.23 (dd, J=8.2, 5.6 Hz, 1 H), 3.60 (dd, J=10.2, 3.3 Hz, 1 H), 3.74–3.79 (m, 1 H), 3.90 (dq, J=6.9, 2.6 Hz,

1 H), 4.11 (dd, $J=10.2$, 5.6 Hz, 1 H), 4.37–4.42 (m, 1 H), 4.45 (dd, $J=9.7$, 2.6 Hz, 1 H), 5.27 (d, $J=5.6$ Hz, 1 H), 7.48–7.54 (m, 2 H), 7.88–7.95 (m, 3 H), 9.05 (d, $J=2.0$ Hz, 1 H).

7(*S*)-7-Deoxy-7-(4-(1*H*-imidazol-1-yl)phenylthio)lincomycin (17)

Compound **5** (100.0 mg, 0.237mmol), 1-(4-bromophenyl)-1*H*-imidazole (70.0 mg, 0.314 mmol), Xantphos (10.0 mg, 0.017 mmol), $Pd_2(dba)_3$ (10 mg, 0.011 mmol) and *N*,*N*-diisopropylethylamine (82.6 µl, 0.474 mmol) in 1,4-dioxane (5 ml) were treated for 4 h according to the similar procedure as described for the preparation of **6** to afford **17** (56.5 mg, 42%) as a colorless solid. $[\alpha]_D^{25}$ +97.8° (*c* 1.40, MeOH); ESI-MS (*m/z*) 565 $(M+H)^+$ as $C_{27}H_{40}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{27}H_{40}N_4O_5S_2$: 565.2518, found: 565.2522; ^{1}H NMR (400 MHz, CD_3OD) δ 0.89–0.96 (m, 3 H), 1.26–1.41 (m, 4 H), 1.34 (d, $J=6.9$ Hz, 3 H), 1.81–1.92 (m, 1 H), 1.96–2.06 (m, 1 H), 2.01 (s, 3 H), 2.06–2.14 (m, 1 H), 2.14–2.25 (m, 1 H), 2.43 (s, 3 H), 3.04 (dd, $J=10.6$, 4.8 Hz, 1 H), 3.25 (dd, $J=8.3$, 5.7 Hz, 1 H), 3.59 (dd, $J=10.2$, 3.2 Hz, 1 H), 3.78 (br dd, $J=3.2$, 0.5 Hz, 1 H), 3.91 (dq, $J=6.9$, 2.8 Hz, 1 H), 4.11 (dd, $J=10.2$, 5.5 Hz, 1 H), 4.37 (br dd, $J=9.7$, 0.5 Hz, 1 H), 4.48 (dd, $J=9.7$, 2.8 Hz, 1 H), 5.27 (d, $J=5.5$ Hz, 1 H), 7.14–7.17 (m, 1 H), 7.53–7.60 (m, 5 H), 8.13–8.17 (m, 1 H).

7(*S*)-7-Deoxy-7-(4-(1,3,4-thiadiazol-2-yl)phenylthio)lincomycin (18)

Compound **5** (100.0 mg, 0.237 mmol), 2-(4-bromophenyl)-1,3,4-thiadiazole (100.0 mg, 0.415 mmol), Xantphos (20.0 mg, 0.035 mmol), $Pd_2(dba)_3$ (20.0 mg, 0.022 mmol) and *N*,*N*-diisopropylethylamine (82.6 µl, 0.474 mmol) in 1,4-dioxane (2 ml) were treated for 6 h according to the similar procedure as described for the preparation of **6** to afford **18** (88.3 mg, 64%) as a colorless solid. $[\alpha]_D^{20}$ +71.9° (*c* 0.40, MeOH); ESI-MS (*m/z*) 583 $(M+H)^+$ as $C_{26}H_{38}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{26}H_{38}N_4O_5S_3$: 583.2083, found: 583.2089; ^{1}H NMR (400 MHz, CD_3OD) δ 0.90–0.96 (m, 3 H), 1.28–1.41 (m, 4 H), 1.41 (d, $J=6.9$ Hz, 3 H), 1.82–1.94 (m, 1 H), 1.91 (s, 3 H), 1.98–2.08 (m, 1 H), 2.09–2.25 (m, 2 H), 2.45 (s, 3 H), 3.09 (dd, $J=10.3$, 4.7 Hz, 1 H), 3.29 (dd, $J=7.9$, 5.4 Hz, 1 H), 3.59 (dd, $J=10.2$, 3.2 Hz, 1 H), 3.79 (br dd, $J=3.2$, 0.5 Hz, 1 H), 4.03 (dq, $J=6.8$, 2.8 Hz, 1 H), 4.10 (dd, $J=10.2$, 5.6 Hz, 1 H), 4.39 (br dd, $J=9.7$, 0.5 Hz, 1 H), 4.54 (dd, $J=9.7$, 2.8 Hz, 1 H), 5.26 (d, $J=5.6$ Hz, 1 H), 7.52–7.57 (m, 2 H), 7.93–7.99 (m, 2 H), 9.43 (s, 1 H).

7(*S*)-7-Deoxy-7-(4-(1,2,3-thiadiazol-4-yl)phenylthio)lincomycin (19)

Compound **5** (100.0 mg, 0.237 mmol), 4-(4-bromophenyl)-1,2,3-thiadiazole (100.0 mg, 0.415 mmol), Xantphos (10.0 mg, 0.017 mmol), $Pd_2(dba)_3$ (10.0 mg, 0.011 mmol) and *N*,*N*-diisopropylethylamine (82.6 µl, 0.474 mmol) in 1,4-dioxane (3 ml) were treated for 6 h according to the similar procedure as described for the preparation of **6** to afford **19** (71.7 mg, 52%) as a colorless solid. $[\alpha]_D^{20}$ +71.8° (*c* 0.35, MeOH); ESI-MS (*m/z*) 583 $(M+H)^+$ as $C_{26}H_{38}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{26}H_{38}N_4O_5S_3$: 583.2083, found: 583.2085; ^{1}H NMR (400 MHz, CD_3OD) δ 0.89–0.96 (m, 3 H), 1.26–1.38 (m, 4 H), 1.39 (d, $J=6.9$ Hz, 3 H), 1.82–1.93 (m, 1 H), 1.96–2.06 (m, 1 H), 1.98 (s, 3 H), 2.07–2.24 (m, 2 H), 2.44 (s, 3 H), 3.06 (dd, $J=10.6$, 4.8 Hz, 1 H), 3.26 (dd, $J=8.3$, 5.6 Hz, 1 H), 3.60 (dd, $J=10.2$, 3.2 Hz, 1 H), 3.78 (br dd, $J=3.2$, 0.6 Hz, 1 H), 3.96 (dq, $J=6.9$, 2.7 Hz, 1 H), 4.11 (dd, $J=10.2$, 5.6 Hz, 1 H), 4.41 (br dd, $J=9.8$, 0.6 Hz, 1 H), 4.49 (dd, $J=9.8$, 2.7 Hz, 1 H), 5.27 (d, $J=5.6$ Hz, 1 H), 7.55–7.60 (m, 2 H), 8.05–8.09 (m, 2 H), 9.25 (s, 1 H).

7(*S*)-7-([1,1′-Biphenyl]-4-ylthio)-7-deoxylincomycin (20)

Compound **5** (72.3 mg, 1.71 mmol), 4-bromo-1,1′-biphenyl (84.7 mg, 0.363 mmol), Xantphos (10.8 mg, 0.019 mmol), $Pd_2(dba)_3$ (8.1 mg, 8.8 µmol) and *N*,*N*-diisopropylethylamine (60.0 µl, 0.344 mmol) in 1,4-dioxane (1 ml) were treated for 4 h according to the similar procedure as described for the preparation of **6** to afford **20** (90.0 mg, 92%) as a colorless solid. $[\alpha]_D^{26}$ +101° (*c* 1.16, MeOH); ESI-MS (*m/z*) 575 $(M+H)^+$ as $C_{30}H_{42}N_2O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{30}H_{42}N_2O_5S_2$: 575.2613, found: 575.2608; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.95 (m, 3 H), 1.25–1.40 (m, 4 H), 1.34 (d, $J=6.9$ Hz, 3 H), 1.79–1.90 (m, 1 H), 1.95–2.03 (m, 1 H), 2.02 (s, 3 H), 2.03–2.09 (m, 1 H), 2.10–2.21 (m, 1 H), 2.39 (s, 3 H), 2.99 (dd, $J=10.6$, 4.6 Hz, 1 H), 3.21 (dd, $J=8.3$, 5.8 Hz, 1 H), 3.60 (dd, $J=10.2$, 3.3 Hz, 1 H), 3.73–3.80 (m, 1 H), 3.88 (dq, $J=6.9$, 2.5 Hz, 1 H), 4.12 (dd, $J=10.2$, 5.5 Hz, 1 H), 4.36–4.41 (m, 1 H), 4.42 (dd, $J=9.7$, 2.5 Hz, 1 H), 5.28 (d, $J=5.5$ Hz, 1 H), 7.31–7.36 (m, 1 H), 7.39–7.46 (m, 2 H), 7.48–7.54 (m, 2 H), 7.56–7.64 (m, 4 H).

7(*S*)-7-Deoxy-7-(4-(pyridin-2-yl)phenylthio)lincomycin (21)

Compound **5** (70.6 mg, 0.167 mmol), 2-(4-bromophenyl)pyridine (77.8 mg, 0.332 mmol), Xantphos (11.4 mg, 0.020 mmol), $Pd_2(dba)_3$ (7.9 mg, 8.6 µmol) and *N*,*N*-diisopropylethylamine (58.0 µl, 0.333 mmol) in 1,4-dioxane (1 ml) were treated for 3 h according to the similar procedure as described for the preparation of **6** to afford **21** (87.9 mg, 91%) as a colorless solid. $[\alpha]_D^{25}$ +86.7° (*c* 2.58, MeOH); ESI-MS (*m/z*) 576 $(M+H)^+$ as $C_{29}H_{41}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{29}H_{41}N_3O_5S_2$: 576.2566, found: 576.2558; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.95 (m, 3 H), 1.28–1.37 (m, 4 H), 1.37 (d, $J=6.9$ Hz, 3 H), 1.95–2.04 (m, 1 H), 1.95–2.05 (m, 1 H), 1.97 (s, 3 H), 2.05–2.11 (m, 1 H), 2.11–2.22 (m, 1 H), 2.41 (s, 3 H), 3.02 (dd, $J=10.6$, 4.8 Hz, 1 H), 3.23 (dd, $J=8.3$, 5.6 Hz, 1 H), 3.61 (dd, $J=10.2$, 3.2 Hz, 1 H), 3.76–3.82 (m, 1 H), 3.95 (dq, $J=6.9$, 2.6 Hz, 1 H), 4.13 (dd, $J=10.2$, 5.5 Hz, 1 H), 4.37–4.43 (m, 1 H), 4.49 (dd, $J=9.7$, 2.6 Hz, 1 H), 5.29 (d, $J=5.5$ Hz, 1 H), 7.34 (ddd, $J=6.9$, 5.0, 1.7 Hz, 1 H), 7.49–7.56 (m, 2 H), 7.81–7.91 (m, 2 H), 7.91–7.96 (m, 2 H), 8.61 (ddd, $J=4.9$, 1.6, 1.0 Hz, 1 H).

7(*S*)-7-Deoxy-7-(4-(pyridin-3-yl)phenylthio)lincomycin (22)

Compound **5** (109.3 mg, 0.259 mmol), 3-(4-bromophenyl)pyridine (89.7 mg, 0.383 mmol), Xantphos (15.2 mg, 0.026 mmol), $Pd_2(dba)_3$ (12.5 mg, 0.014 mmol) and *N*,*N*-diisopropylethylamine (88.9 µl, 0.511 mmol) in 1,4-dioxane (1.8 ml) were treated for 5.5 h according to the similar procedure as described for the preparation of **6** to afford **22** (131.0 mg, 88%) as a colorless solid. $[\alpha]_D^{24}$ +83.9° (*c* 0.37, MeOH); ESI-MS (*m/z*) 576 $(M+H)^+$ as $C_{29}H_{41}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{29}H_{41}N_3O_5S_2$: 576.2566, found: 576.2573; ^{1}H NMR (400 MHz, CD_3OD) δ 0.89–0.96 (m, 3 H), 1.26–1.41 (m, 4 H), 1.36 (d, $J=6.9$ Hz, 3 H), 1.80–1.91 (m, 1 H), 1.96–2.05 (m, 1 H), 1.98 (s, 3 H), 2.05–2.12 (m, 1 H), 2.12–2.23 (m, 1 H), 2.41 (s, 3 H), 3.00 (dd, $J=10.6$, 4.6 Hz, 1 H), 3.24 (dd, $J=8.1$, 5.7 Hz, 1 H), 3.59 (dd, $J=10.2$, 3.3 Hz, 1 H), 3.76–3.80 (m, 1 H), 3.94 (dq, $J=6.9$, 2.7 Hz, 1 H), 4.11 (dd, $J=10.2$, 5.6 Hz, 1 H), 4.38 (br dd, $J=9.7$, 0.4 Hz, 1 H), 4.47 (dd, $J=9.7$, 2.7 Hz, 1 H), 5.27 (d, $J=5.6$ Hz, 1 H), 7.51 (ddd, $J=8.0$, 4.9, 0.7 Hz, 1 H), 7.54–7.58 (m, 2 H), 7.62–7.68 (m,2 H), 8.09 (ddd, $J=8.0$, 2.3, 1.6 Hz, 1 H), 8.52 (dd, $J=4.9$, 1.6 Hz, 1 H), 8.77–8.82 (m, 1 H).

7(*S*)-7-Deoxy-7-(4-(pyridin-4-yl)phenylthio)lincomycin (23)

Compound **5** (61.9 mg, 0.146 mmol), 4-(4-bromophenyl)pyridine (67.5 mg, 0.288 mmol), Xantphos (8.8 mg, 0.015 mmol), $Pd_2(dba)_3$ (6.9 mg, 7.5 µmol) and *N*,*N*-diisopropylethylamine (50.0 µl, 0.287 mmol) in 1,4-dioxane (1 ml) were treated for 6.5 h according to the similar procedure as described for the preparation of **6** to afford **23** (72.6 mg, 86%) as an off-white solid. $[\alpha]_D^{25}$ +87.3° (*c* 2.15, MeOH); ESI-MS (*m/z*) 576 $(M+H)^+$ as $C_{29}H_{41}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{29}H_{41}N_3O_5S_2$: 576.2566, found: 576.2562; ^{1}H NMR (400 MHz, CD_3OD) δ 0.87–0.97 (m, 3 H), 1.26–1.40 (m, 4 H), 1.38 (d, $J=6.9$ Hz, 3 H), 1.80–1.92 (m, 1 H), 1.95 (s, 3 H), 1.97–2.07 (m, 1 H), 2.07–2.14 (m, 1 H), 2.14–2.24 (m, 1 H), 2.43 (s, 3 H), 3.04 (dd, $J=10.6$, 4.8 Hz, 1 H), 3.25 (dd, $J=8.2$, 5.6 Hz, 1 H), 3.61 (dd, $J=10.2$, 3.2 Hz, 1 H), 3.77–3.82 (m, 1 H), 3.97 (dq, $J=6.9$, 2.7 Hz, 1 H), 4.13 (dd, $J=10.2$, 5.6 Hz, 1 H), 4.35–4.43 (m, 1 H), 4.51 (dd, $J=9.8$, 2.7 Hz, 1 H), 5.28 (d, $J=5.6$ Hz, 1 H), 7.51–7.58 (m, 2 H), 7.68–7.78 (m, 4 H), 8.54–8.60 (m, 2 H).

7(*S*)-7-(3′-Cyano-[1,1′-biphenyl]-4-ylthio)-7-deoxylincomycin (24)

Compound **5** (85.2 mg, 0.202 mmol), 4'-bromo-[1,1'-biphenyl]-3-carbonitrile (104.0 mg, 0.403 mmol), Xantphos (12.7 mg, 0.022 mmol), $Pd_2(dba)_3$ (10.4 mg, 0.011 mmol) and *N*,*N*-diisopropylethylamine (69.9 µl, 0.402 mmol) in 1,4-dioxane (1 ml) were treated for 4 h according to the similar procedure as described for the preparation of **6** to afford **24** (49.4 mg, 41%) as a colorless solid. $[\alpha]_D^{24}$ +91.6° (*c* 1.97, MeOH); ESI-MS (*m/z*) 600 $(M+H)^+$ as

$C_{31}H_{41}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{31}H_{41}N_3O_5S_2$: 600.2566, found: 600.2559; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.97 (m, 3 H), 1.27–1.39 (m, 4 H), 1.35 (d, *J*=6.9 Hz, 3 H), 1.80–1.91 (m, 1 H), 1.95–2.05 (m, 1 H), 1.98 (s, 3 H), 2.06–2.21 (m, 1 H), 2.13–2.24 (m, 1 H), 2.42 (s, 3 H), 3.02 (dd, *J*=10.6, 4.6 Hz, 1 H), 3.24 (dd, *J*=8.1, 5.7 Hz, 1 H), 3.61 (dd, *J*=10.2, 3.3 Hz, 1 H), 3.76–3.81 (m, 1 H), 3.93 (dq, *J*=6.9, 2.7 Hz, 1 H), 4.12 (dd, *J*=10.2, 5.6 Hz, 1 H), 4.36–4.42 (m, 1 H), 4.48 (dd, *J*=9.7, 2.7 Hz, 1 H), 5.28 (d, *J*=5.6 Hz, 1 H), 7.50–7.55 (m, 2 H), 7.60–7.66 (m, 3 H), 7.67–7.71 (m, 1 H), 7.90–7.96 (m, 1 H), 7.96–8.00 (m, 1 H).

7(*S*)-7-Deoxy-7-(3′-methoxy-[1,1′-biphenyl]-4-ylthio)lincomycin (25)

Compound **5** (56.1 mg, 1.33 mmol), 4'-bromo-3-methoxy-1,1'-biphenyl (45.6 mg, 0.173 mmol), Xantphos (8.1 mg, 0.014 mmol), $Pd_2(dba)_3$ (6.3 mg, 6.9 μmol) and *N*,*N*-diisopropylethylamine (46.0 μl, 0.264 mmol) in 1,4-dioxane (1 ml) were treated for 6 h according to the similar procedure as described for the preparation of **6** to afford **25** (69.0 mg, 86%) as a colorless solid. $[\alpha]_D^{24}$ +100° (*c* 2.76, MeOH); ESI-MS (*m/z*) 605 $(M+H)^+$ as $C_{31}H_{44}N_2O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{31}H_{44}N_2O_6S_2$: 605.2719, found: 605.2712; ^{1}H NMR (400 MHz, CD_3OD) δ 0.87–0.95 (m, 3 H), 1.24–1.37 (m, 4 H), 1.33 (d, *J*=6.9 Hz, 3 H), 1.79–1.89 (m, 1 H), 2.01 (s, 3 H), 1.95–2.09 (m, 2 H), 2.09–2.20 (m, 1 H), 2.38 (s, 3 H), 3.00 (dd, *J*=10.6, 4.8 Hz, 1 H), 3.20 (dd, *J*=8.3, 5.7 Hz, 1 H), 3.61 (dd, *J*=10.2, 3.3 Hz, 1 H), 3.74–3.79 (m, 1 H), 3.83 (s, 3 H), 3.88 (dq, *J*=6.9, 2.6 Hz, 1 H), 4.13 (dd, *J*=10.2, 5.5 Hz, 1 H), 4.36–4.42 (m, 1 H), 4.44 (dd, *J*=9.8, 2.6 Hz, 1 H), 5.29 (d, *J*=5.5 Hz, 1 H), 6.91 (ddd, *J*=8.2, 2.5, 0.9 Hz, 1 H), 7.11–7.14 (m, 1 H), 7.14–7.19 (m, 1 H), 7.30–7.37 (m, 1 H), 7.46–7.51 (m, 2 H), 7.54–7.59 (m, 2 H).

7(*S*)-7-(3′-Amino-[1,1′-biphenyl]-4-ylthio)-7-deoxylincomycin (26)

Compound **5** (66.9 mg, 0.158 mmol), 4′-bromo-[1,1'-biphenyl]-3-amine (75.9 mg, 0.306 mmol), Xantphos (10.0 mg, 0.017 mmol), $Pd_2(dba)_3$ (7.3 mg, 8.0 μmol) and *N*,*N*-diisopropylethylamine (53.5 μl, 0.307 mmol) in 1,4-dioxane (1 ml) were treated for 6 h according to the similar procedure as described for the preparation of **6** to afford **26** (47.6 mg, 51%) as a colorless solid. $[\alpha]_D^{28}$ +142° (*c* 0.51, MeOH); ESI-MS (*m/z*) 590 $(M+H)^+$ as $C_{30}H_{43}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{30}H_{43}N_3O_5S_2$: 590.2722, found: 590.2713; ^{1}H NMR (400 MHz, CD_3OD) δ 0.89–0.95 (m, 3 H), 1.25–1.40 (m, 4 H), 1.33 (d, *J*=6.9 Hz, 3 H), 1.80–1.91 (m, 1 H), 1.95–2.05 (m, 1 H), 2.01 (s, 3 H), 2.05–2.21 (m, 2 H), 2.40 (s, 3 H), 3.02 (dd, *J*=10.5, 4.6 Hz, 1 H), 3.23 (dd, *J*=8.1, 5.6 Hz, 1 H), 3.60 (dd, *J*=10.2, 3.3 Hz, 1 H), 3.74–3.79 (m, 1 H), 3.86 (dq, *J*=6.9, 2.3 Hz, 1 H), 4.11 (dd, *J*=10.2, 5.6 Hz, 1 H), 4.36–4.41 (m, 1 H), 4.43 (dd, *J*=9.7, 2.3 Hz, 1 H), 5.27 (d, *J*=5.6 Hz, 1 H), 6.71 (ddd, *J*=7.9, 2.2, 0.9 Hz, 1 H), 6.92 (ddd, *J*=7.7, 1.7, 1.0 Hz, 1 H), 6.96–7.00 (m, 1 H), 7.13–7.19 (m, 1 H), 7.45–7.50 (m, 2 H), 7.52–7.57 (m, 2 H).

7(*S*)-7-Deoxy-7-(4-(5-fluoropyridin-3-yl)phenylthio)lincomycin (27)

Compound **5** (66.0 mg, 0.156 mmol), 3-(4-bromophenyl)-5-fluoropyridine (50.0 mg, 0.198 mmol), Xantphos (10.0 mg, 0.017 mmol), $Pd_2(dba)_3$ (10.0 mg, 0.011 mmol) and *N*,*N*-diisopropylethylamine (13.5 μl, 0.077 mmol) in 1,4-dioxane (1.5 ml) were treated for 3 h according to the similar procedure as described for the preparation of **6** to afford **27** (72.0 mg, 73%) as a colorless solid. $[\alpha]_D^{25}$ +88.5° (*c* 1.78, MeOH); ESI-MS (*m/z*) 594 $(M+H)^+$ as $C_{29}H_{40}FN_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{29}H_{40}FN_3O_5S_2$: 594.2472, found: 594.2473; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.96 (m, 3 H), 1.26–1.40 (m, 4 H), 1.36 (d, *J*=7.0 Hz, 3 H), 1.79–1.92 (m, 1 H), 1.93–2.06 (m, 1 H), 1.97 (s, 3 H), 2.07–2.14 (m, 1 H), 2.14–2.24 (m, 1 H), 2.43 (s, 3 H), 3.04 (dd, *J*=10.5, 4.6 Hz, 1 H), 3.22–3.29 (m, 1 H), 3.60 (dd, *J*=10.1, 2.8 Hz, 1 H), 3.76–3.82 (m, 1 H), 3.93–4.01 (m, 1 H), 4.12 (dd, *J*=10.1, 5.5 Hz, 1 H), 4.36–4.41 (m, 1 H), 4.47–4.53 (m, 1 H), 5.28 (d, *J*=5.5 Hz, 1 H), 7.51–7.58 (m, 2 H), 7.64–7.71 (m, 2 H), 7.87–7.94 (m, 1 H), 8.41–8.47 (m, 1 H), 8.69 (s, 1 H).

7(*S*)-7-(4-(5-Cyanopyridin-3-yl)phenylthio)-7-deoxylincomycin (28)

Compound **5** (66.0 mg, 0.156 mmol), 5-(4-bromophenyl)nicotinonitrile (50.0 mg, 0.193 mmol), Xantphos (20.0 mg, 0.035 mmol), $Pd_2(dba)_3$ (10.0 mg, 0.011 mmol) and *N*,*N*-diisopropylethylamine (60.0 μl, 0.344 mmol) in 1,4-dioxane (1.5 ml) were treated for 6 h according to the similar procedure as described for the preparation of **6** to afford **28** (55.0 mg, 59%) as a colorless solid. $[\alpha]_D^{25}$ +87.4° (*c* 0.81, MeOH); ESI-MS (*m/z*) 601 $(M+H)^+$ as $C_{30}H_{40}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{30}H_{40}N_4O_5S_2$: 601.2518, found: 601.2512; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.97 (m, 3 H), 1.29–1.41 (m, 4 H), 1.37 (d, *J*=6.8 Hz, 3 H), 1.83–1.92 (m, 1 H), 1.95 (s, 3 H), 1.98–2.08 (m, 1 H), 2.08–2.25 (m, 2 H), 2.44 (s, 3 H), 3.05 (dd, *J*=10.6, 4.8 Hz, 1 H), 3.27 (dd, *J*=8.1, 5.6 Hz, 1 H), 3.59 (dd, *J*=10.1, 3.2 Hz, 1 H), 3.79 (br dd, *J*=3.2, 0.6 Hz, 1 H), 3.98 (dq, *J*=6.8, 2.7 Hz, 1 H), 4.11 (dd, *J*=10.1, 5.6 Hz, 1 H), 4.39 (br dd, *J*=9.7, 0.6 Hz, 1 H), 4.50 (dd, *J*=9.7, 2.7 Hz, 1 H), 5.27 (d, *J*=5.6 Hz, 1 H), 7.53–7.60 (m, 2 H), 7.68–7.73 (m, 2 H), 8.45–8.49 (m, 1 H), 8.87 (d, *J*=1.8 Hz, 1 H), 9.08 (d, *J*=2.2 Hz, 1 H).

7(*S*)-7-Deoxy-7-(4-(5-methoxypyridin-3-yl)phenylthio)lincomycin (29)

Compound **5** (70.2 mg, 0.166 mmol), 3-(4-bromophenyl)-5-methoxypyridine (70.1 mg, 0.265 mmol), Xantphos (10.2 mg, 0.018 mmol), $Pd_2(dba)_3$ (8.1 mg, 8.8 μmol) and *N*,*N*-diisopropylethylamine (57.5 μl, 0.330 mmol) in 1,4-dioxane (1 ml) were treated for 6 h according to the similar procedure as described for the preparation of **6** to afford **29** (78.0 mg, 78%) as a colorless solid. $[\alpha]_D^{26}$ +86.8° (*c* 2.82, MeOH); ESI-MS (*m/z*) 606 $(M+H)^+$ as $C_{30}H_{43}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{30}H_{43}N_3O_6S_2$: 606.2672, found: 606.2660; ^{1}H NMR (400 MHz, CD_3OD) δ 0.83–0.99 (m, 3 H), 1.27–1.39 (m, 4 H), 1.35 (d, *J*=7.0 Hz, 3 H), 1.80–1.91 (m, 1 H), 1.95–2.05 (m, 1 H), 1.99 (s, 3 H), 2.06–2.13 (m, 1 H), 2.13–2.24 (m, 1 H), 2.42 (s, 3 H), 3.03 (dd, *J*=10.6, 4.7 Hz, 1 H), 3.24 (dd, *J*=8.2, 5.6 Hz, 1 H), 3.61 (dd, *J*=10.1, 3.3 Hz, 1 H), 3.77–3.82 (m, 1 H), 3.90–3.98 (m, 1 H), 3.94 (s, 3 H), 4.13 (dd, *J*=10.1, 5.5 Hz, 1 H), 4.36–4.42 (m, 1 H), 4.49 (dd, *J*=9.8, 2.7 Hz, 1 H), 5.29 (d, *J*=5.5 Hz, 1 H), 7.50–7.56 (m, 2 H), 7.59 (br dd, *J*=2.7, 1.7 Hz, 1 H), 7.61–7.67 (m, 2 H), 8.21 (d, *J*=2.7 Hz, 1 H), 8.39 (d, *J*=1.7 Hz, 1 H).

7(*S*)-7-(4-Bromophenylthio)-7-deoxylincomycin (30)

Compound **5** (100.0 mg, 0.237 mmol), 1-bromo-4-iodobenzene (133.8 mg, 0.473 mmol), Xantphos (27.4 mg, 0.047 mmol), $Pd_2(dba)_3$ (21.7 mg, 0.024 mmol) and *N*,*N*-diisopropylethylamine (82.6 μl, 0.474 mmol) in 1,4-dioxane (1 ml) were treated for 3 h according to the similar procedure as described for the preparation of **6** to afford **30** (100.2 mg, 73%) as a colorless solid. ^{1}H NMR (400 MHz, CD_3OD) δ 0.87–0.98 (m, 3 H), 1.27–1.40 (m, 4 H), 1.31 (d, *J*=6.9 Hz, 3 H), 1.76–1.90 (m, 1 H), 1.93–2.03 (m, 1 H), 1.98 (s, 3 H), 2.06 (dd, *J*=10.1, 8.6 Hz, 1 H), 2.10–2.22 (m, 1 H), 2.37 (s, 3 H), 2.98 (dd, *J*=10.6, 4.6 Hz, 1 H), 3.22 (dd, *J*=8.1, 5.7 Hz, 1 H), 3.60 (dd, *J*=10.2, 3.2 Hz, 1 H), 3.72–3.79 (m, 1 H), 3.85 (dq, *J*=6.9, 2.7 Hz, 1 H), 4.12 (dd, *J*=10.2, 5.6 Hz, 1 H), 4.31–4.37 (m, 1 H), 4.42 (dd, *J*=9.7, 2.7 Hz, 1 H), 5.28 (d, *J*=5.6 Hz, 1 H), 7.31–7.37 (m, 2 H), 7.44–7.50 (m, 2 H).

7(*S*)-7-Deoxy-7-(4-(2-methoxypyridin-3-yl)phenylthio)lincomycin (31)

To a solution of compound **30** (100.2 mg, 0.173 mmol) in DMF (1 ml) and water (0.25 ml) were added $Pd(PPh_3)_4$ (12.5 mg, 0.011 mmol), 2-methoxypyridine-3-boronic acid (62.6 mg, 0.409 mmol) and Na_2CO_3 (37.6 mg, 0.355 mmol) and then stirred at 80 °C for 10 h. The solution were diluted with ethyl acetate and water, and then filtrated with celite. The filtered solid was washed with ethyl acetate three times. The obtained solution was extracted with ethyl acetate and then the organic layer was dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq NH_4OH=10/1/0.1) to obtain the title compound as an off-white solid (74.1 mg, 71%). $[\alpha]_D^{24}$ +97.8° (*c* 3.63, MeOH); ESI-MS (*m/z*) 606 $(M+H)^+$ as $C_{30}H_{43}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{30}H_{43}N_3O_6S_2$: 606.2672, found: 606.2670; ^{1}H NMR (400 MHz, CD_3OD) δ 0.87–0.96 (m, 3 H), 1.27–1.39 (m, 4 H), 1.35 (d, *J*=6.9 Hz, 3 H), 1.79–1.90 (m, 1 H), 1.96–2.04 (m, 1 H), 1.99 (s, 3 H), 2.06 (dd, *J*=10.2, 8.5 Hz, 1 H), 2.11–2.24 (m, 1 H), 2.39 (s, 3 H), 2.99 (dd, *J*=10.6, 4.6 Hz, 1 H), 3.23 (dd, *J*=8.3, 5.7 Hz, 1 H), 3.60 (dd,

J=10.1, 3.2 Hz, 1 H), 3.74–3.79 (m, 1 H), 3.89 (dq, *J*=6.9, 2.5 Hz, 1 H), 3.93 (s, 3 H), 4.12 (dd, *J*=10.1, 5.6 Hz, 1 H), 4.35–4.40 (m, 1 H), 4.42 (dd, *J*=9.7, 2.5 Hz, 1 H), 5.27 (d, *J*=5.6 Hz, 1 H), 7.03 (dd, *J*=7.3, 5.0 Hz, 1 H), 7.44–7.55 (m, 4 H), 7.69 (dd, *J*=7.3, 1.8 Hz, 1 H), 8.11 (dd, *J*=5.0, 1.8 Hz, 1 H).

7(*S*)-7-Deoxy-7-(4-(6-methoxypyridin-3-yl)phenylthio)lincomycin (32)
Compound **5** (41.1 mg, 0.0973 mmol), 5-(4-bromophenyl)-2-methoxypyridine (38.6 mg, 0.146 mmol), Xantphos (11.3 mg, 0.0195 mmol), $Pd_2(dba)_3$ (8.9 mg, 0.0097 mmol) and *N*,*N*-diisopropylethylamine (33.9 µl, 0.195 mmol) in 1,4-dioxane (0.82 ml) treated for 6 h according to the similar procedure as described for the preparation of **6** to afford **32** (53.4 mg, 91%) as a colorless solid. $[\alpha]_D^{29}$ +96.1° (*c* 2.60, MeOH); ESI-MS (*m/z*) 606 $(M+H)^+$ as $C_{30}H_{43}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{30}H_{43}N_3O_6S_2$: 606.2672, found: 606.2664; ^{1}H NMR (400 MHz, CD_3OD) δ 0.87–0.96 (m, 3 H), 1.27–1.37 (m, 4 H), 1.33 (d, *J*=6.8 Hz, 3 H), 1.79–1.91 (m, 1 H), 1.96–2.04 (m, 1 H), 2.01 (s, 3 H), 2.04–2.10 (m, 1 H), 2.11–2.22 (m, 1 H), 2.40 (s, 3 H), 3.01 (dd, *J*=10.6, 4.7 Hz, 1 H), 3.22 (dd, *J*=8.1, 5.7 Hz, 1 H), 3.61 (dd, *J*=10.2, 3.3 Hz, 1 H), 3.75–3.80 (m, 1 H), 3.89 (dq, *J*=6.8, 2.6 Hz, 1 H), 3.93 (s, 3 H), 4.13 (dd, *J*=10.2, 5.6 Hz, 1 H), 4.36–4.40 (m, 1 H), 4.45 (dd, *J*=9.8, 2.6 Hz, 1 H), 5.29 (d, *J*=5.**6** Hz, 1 H), 6.86 (dd, *J*=8.6, 0.6 Hz, 1 H), 7.46–7.58 (m, 4 H), 7.92 (dd, *J*=8.6, 2.6 Hz, 1 H), 8.37 (br dd, *J*=2.6, 0.6 Hz, 1 H).

7(*S*)-7-(4-(6-Aminopyridin-3-yl)phenylthio)-7-deoxylincomycin (33)
Compound **5** (100.0 mg, 0.237 mmol), 5-(4-bromophenyl)pyridin-2-amine (100.0 mg, 0.401 mmol), Xantphos (10.0 mg, 0.017 mmol), $Pd_2(dba)_3$ (10.0 mg, 0.011 mmol) and *N*,*N*-diisopropylethylamine (10.0 µl, 0.057 mmol) in 1,4-dioxane (5 ml) were treated for 6 h according to the similar procedure as described for the preparation of **6** to afford **33** (18.0 mg, 13%) as a colorless solid. $[\alpha]_D^{25}$ +101° (*c* 0.33, MeOH); ESI-MS (*m/z*) 591 $(M+H)^+$ as $C_{29}H_{42}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{29}H_{42}N_4O_5S_2$: 591.2675, found: 591.2678; ^{1}H NMR (400 MHz, CD_3OD) δ 0.89–0.96 (m, 3 H), 1.25–1.40 (m, 4 H), 1.33 (d, *J*=6.9 Hz, 3 H), 1.80–1.91 (m, 1 H), 1.95–2.05 (m, 1 H), 2.03 (s, 3 H), 2.05–2.12 (m, 1 H), 2.12–2.21 (m, 1 H), 2.40 (s, 3 H), 3.01 (dd, *J*=10.6, 4.6 Hz, 1 H), 3.23 (dd, *J*=8.1, 5.4 Hz, 1 H), 3.59 (dd, *J*=10.2, 3.3 Hz, 1 H), 3.73–3.78 (m, 1 H), 3.85 (dq, *J*=6.9, 2.4 Hz, 1 H), 4.11 (dd, *J*=10.2, 5.6 Hz, 1 H), 4.36–4.40 (m, 1 H), 4.43 (dd, *J*=9.8, 2.4 Hz, 1 H), 5.27 (d, *J*=5.6 Hz, 1 H), 6.66 (dd, *J*=8.7, 0.7 Hz, 1 H), 7.46–7.55 (m, 4 H), 7.75 (dd, *J*=8.7, 2.4 Hz, 1 H), 8.17 (br dd, *J*=2.4, 0.7 Hz, 1 H).

7(*S*)-7-Deoxy-7-(4-(pyrazin-2-yl)phenylthio)lincomycin (34)
Compound **5** (100.0 mg, 0.237 mmol), 2-(4-bromophenyl)pyrazine (70.0 mg, 0.298 mmol), Xantphos (10.0 mg, 0.017 mmol), $Pd_2(dba)_3$ (10.0 mg, 0.011 mmol) and *N*,*N*-diisopropylethylamine (82.6 µl, 0.474 mmol) in 1,4-dioxane (2 ml) were treated for 4 h according to the similar procedure as described for the preparation of **6** to afford **34** (65.0 mg, 48%) as a colorless solid. $[\alpha]_D^{19}$ +85.2° (*c* 1.01, MeOH); ESI-MS (*m/z*) 577 $(M+H)^+$ as $C_{28}H_{40}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{28}H_{40}N_4O_5S_2$: 577.2518, found: 577.2515; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.96 (m, 3 H), 1.27–1.38 (m, 4 H), 1.39 (d, *J*=6.9 Hz, 3 H), 1.82–1.92 (m, 1 H), 1.95 (s, 3 H), 1.97–2.07 (m, 1 H), 2.07–2.14 (m, 1 H), 2.14–2.24 (m, 1 H), 2.43 (s, 3 H), 3.05 (dd, *J*=10.6, 4.8 Hz, 1 H), 3.26 (dd, *J*=8.1, 5.6 Hz, 1 H), 3.60 (dd, *J*=10.2, 3.3 Hz, 1 H), 3.76–3.81 (m, 1 H), 3.99 (dq, *J*=6.9, 2.7 Hz, 1 H), 4.12 (dd, *J*=10.2, 5.6 Hz, 1 H), 4.40 (br dd, *J*=9.8, 0.6 Hz, 1 H), 4.51 (dd, *J*=9.8, 2.7 Hz, 1 H), 5.27 (d, *J*=5.6 Hz, 1 H), 7.53–7.58 (m, 2 H), 8.04–8.08 (m, 2 H), 8.52 (d, *J*=2.5 Hz, 1 H), 8.66 (dd, *J*=2.5, 1.5 Hz, 1 H), 9.10 (d, *J*=1.5 Hz, 1 H).

7(*S*)-7-Deoxy-7-(4-(pyrimidin-2-yl)phenylthio)lincomycin (35)
Compound **5** (105.7 mg, 0.250 mmol), 2-(4-bromophenyl)pyrimidine (116.3 mg, 0.495 mmol), Xantphos (15.0 mg, 0.026 mmol), $Pd_2(dba)_3$ (11.6 mg, 0.013 mmol) and *N*,*N*-diisopropylethylamine (86.0 µl, 0.494 mmol) in 1,4-dioxane (1.5 ml) were treated for 6 h according to the similar procedure as described for the preparation of **6** to afford **35** (134.0 mg, 93%) as a colorless solid. $[\alpha]_D^{26}$ +83.6° (*c* 4.97, MeOH); ESI-MS (*m/z*) 577 $(M+H)^+$ as $C_{28}H_{40}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{28}H_{40}N_4O_5S_2$: 577.2518, found: 577.2512; ^{1}H NMR (400 MHz, CD_3OD) δ 0.86–0.95 (m, 3 H), 1.22–1.37 (m, 4 H), 1.39 (d, *J*=6.8 Hz, 3 H), 1.79–1.90 (m, 1 H), 1.93–2.07 (m, 2 H), 1.94 (s, 3 H), 2.07–2.23 (m, 1 H), 2.39 (s, 3 H), 3.00 (dd, *J*=10.6, 4.7 Hz, 1 H), 3.20 (dd, *J*=8.3, 5.9 Hz, 1 H), 3.63 (dd, *J*=10.2, 3.4 Hz, 1 H), 3.75–3.82 (m, 1 H), 3.99 (dq, *J*=6.8, 2.6 Hz, 1 H), 4.14 (dd, *J*=10.2, 5.5 Hz, 1 H), 4.38–4.43 (m, 1 H), 4.51 (dd, *J*=9.8, 2.6 Hz, 1 H), 5.30 (d, *J*=5.5 Hz, 1 H), 7.33 (t, *J*=4.9 Hz, 1 H), 7.47–7.54 (m, 2 H), 8.31–8.39 (m, 2 H), 8.82 (d, *J*=4.9 Hz, 2 H).

7(*S*)-7-Deoxy-7-(4-(pyrimidin-5-yl)phenylthio)lincomycin (36)
Compound **5** (69.5 mg, 0.164 mmol), 5-(4-bromophenyl)pyrimidine (74.6 mg, 0.317 mmol), Xantphos (10.1 mg, 0.017 mmol), $Pd_2(dba)_3$ (7.8 mg, 8.5 µmol) and *N*,*N*-diisopropylethylamine (55.0 µl, 0.316 mmol) in 1,4-dioxane (1 ml) were treated for 6 h according to the similar procedure as described for the preparation of **6** to afford **36** (74.7 mg, 79%) as an off-white solid. $[\alpha]_D^{28}$ +142° (*c* 0.51, MeOH); ESI-MS (*m/z*) 577 $(M+H)^+$ as $C_{28}H_{40}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{28}H_{40}N_4O_5S_2$: 577.2518, found: 577.2508; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.96 (m, 3 H), 1.27–1.42 (m, 4 H), 1.37 (d, *J*=6.9 Hz, 3 H), 1.81–1.91 (m, 1 H), 1.96 (s, 3 H), 1.97–2.06 (m, 1 H), 2.06–2.13 (m, 1 H), 2.12–2.24 (m, 1 H), 2.43 (s, 3 H), 3.02 (dd, *J*=10.6, 4.8 Hz, 1 H), 3.25 (dd, *J*=8.3, 5.7 Hz, 1 H), 3.60 (dd, *J*=10.1, 3.2 Hz, 1 H), 3.77–3.82 (m, 1 H), 3.98 (dq, *J*=6.9, 2.8 Hz, 1 H), 4.12 (dd, *J*=10.1, 5.6 Hz, 1 H), 4.35–4.42 (m, 1 H), 4.50 (dd, *J*=9.7, 2.8 Hz, 1 H), 5.28 (d, *J*=5.6 Hz, 1 H), 7.54–7.60 (m, 2 H), 7.68–7.73 (m, 2 H), 9.07 (s, 2 H), 9.13 (s, 1 H).

7(*S*)-7-Chloro-7-deoxy-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (37)
To a solution of CLDM (1.0 g, 2.353 mmol) in pyridine (5 ml) were added trimethylchlorosilane (1.19 ml, 9.389 mmol), hexamethyldisilazane (1.97 ml, 9.42 mmol) and stirred at room temperature for 2 h, then the solution was added to the saturated aqueous $NaHCO_3$. The desired compound was extracted with hexane and then the organic phase was dried over Na_2SO_4, filtrated and concentrated under reduced pressure to obtain the title compound (1.47 g, 97%) as a colorless solid. ESI-MS (*m/z*) 641 $(M+H)^+$ as $C_{27}H_{57}ClN_2O_5SSi_3$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 9 H), 0.14 (s, 9 H), 0.18 (s, 9 H), 0.84–0.94 (m, 3 H), 1.22–1.35 (m, 4 H), 1.44 (d, *J*=6.8 Hz, 3 H), 1.78–1.91 (m, 1 H), 1.92–2.10 (m, 3 H), 2.16 (s, 3 H), 2.41 (s, 3 H), 3.00 (dd, *J*=10.8, 3.7 Hz, 1 H), 3.18 (dd, *J*=7.3, 5.4 Hz, 1 H), 3.62 (dd, *J*=9.5, 2.4 Hz, 1 H), 3.74 (d, *J*=2.4 Hz, 1 H), 4.02 (d, *J*=9.9 Hz, 1 H), 4.16 (dd, *J*=9.5, 5.6 Hz, 1 H), 4.46–4.54 (m, 1 H), 4.56–4.64 (m, 1 H), 5.26 (d, *J*=5.6 Hz, 1 H), 7.67 (d, *J*=10.5 Hz, 1 H).

7(*R*)-7-Acetylthio-7-deoxylincomycin (39)
To a solution of compound **37** (1.47 g, 2.29 mmol) in DMF (10 ml) was added potassium thioacetatate (1.31 g, 11.4 mmol) and stirred at 100 °C for 18 h to give 7(*R*)-7-acetylthio-7-deoxy-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (**38**). Compound **38** was dissolved with 1 *N* HCl and MeOH, and it was stirred at room temperature for 10 min. After the reaction mixture was washed with diethyl ether, ethyl acetate and the saturated aqueous $NaHCO_3$ were added to the aqueous layer. The desired compound was extracted with ethyl acetate and then the organic layer was dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3/CH_3OH$=50/1 → 10/1) to obtain the title compound (187.2 mg, 18%) as a colorless solid. ESI-MS (*m/z*) 465 $(M+H)^+$ as $C_{20}H_{36}N_2O_6S_2$; ^{1}H NMR (400 MHz, CD_3OD) δ 0.85–0.99 (m, 3 H), 1.26–1.42 (m, 4 H), 1.32 (d, *J*=7.1 Hz, 3 H), 1.75–1.88 (m, 1 H), 1.92–2.25 (m, 3 H), 2.16 (s, 3 H), 2.29 (s, 3 H), 2.38 (s, 3 H), 2.94 (dd, *J*=10.5, 5.1 Hz, 1 H), 3.21 (dd, *J*=8.6, 6.1 Hz, 1 H), 3.51 (dd, *J*=10.3, 3.3 Hz, 1 H), 3.72–3.77 (m, 1 H), 4.04 (dq, *J*=7.1, 3.7 Hz, 1 H), 4.08–4.13 (m, 1 H), 4.14–4.19 (m, 1 H), 4.44 (dd, *J*=9.4, 3.7 Hz, 1 H), 5.27 (d, *J*=5.6 Hz, 1 H).

7(*R*)-7-Deoxy-7-mercaptolincomycin (40)
To a solution of compound **39** (187.2 mg, 0.403 mmol) in MeOH (2 ml) was added 4.1 M sodium methoxide in MeOH solution (0.295 ml, 1.209 mmol) and stirred at room temperature for 20 min. The mixture was diluted with saturated aqueous NH_4Cl and concentrated under reduced pressure. The resulting residue was diluted with ethyl acetate and 10% aqueous $NaHCO_3$. Then, the desired compound was extracted with ethyl acetate, dried over

Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3/CH_3OH = 50/1 \rightarrow 10/1$) to obtain the title compound (35.6 mg, 20%) as a colorless solid. ESI-MS (*m/z*) 423 $(M+H)^+$ as $C_{18}H_{34}N_2O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{18}H_{34}N_2O_5S_2$: 423.1987, found: 423.1982; ^1H NMR (400 MHz, CD_3OD) δ 0.88–0.97 (m, 3 H), 1.25–1.40 (m, 4 H), 1.33 (d, *J* = 7.0 Hz, 3 H), 1.77–1.88 (m, 1 H), 1.95–2.09 (m, 2 H), 2.11 (s, 3 H), 2.16–2.27 (m, 1 H), 2.41 (s, 3 H), 2.97 (dd, *J* = 10.5, 4.8 Hz, 1 H), 3.21 (dd, *J* = 8.4, 6.1 Hz, 1 H), 3.33–3.41 (m, 1 H), 3.55 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.80–3.85 (m, 1 H), 4.09 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.20–4.30 (m, 2 H), 5.24 (d, *J* = 5.6 Hz, 1 H).

7(*R*)-7-Deoxy-7-(4-(pyrimidin-5-yl)phenylthio)lincomycin (41)

Compound **40** (35.6 mg, 0.084 mmol), 5-(4-bromophenyl)pyrimidine (23.8 mg, 0.101 mmol), Xantphos (9.7 mg, 0.017 mmol), $Pd_2(dba)_3$ (7.7 mg, 8.4 μmol) and *N*,*N*-diisopropylethylamine (29.4 μl, 0.169 mmol) in 1,4-dioxane (1 ml) were treated for 6.5 h according to the similar procedure as described for the preparation of **6** to afford **41** (21.8 mg, 45%) as a colorless solid. $[\alpha]_D^{24}$ +142° (*c* 1.05, MeOH); ESI-MS (*m/z*) 577 $(M+H)^+$ as $C_{28}H_{40}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{28}H_{40}N_4O_5S_2$: 577.2518, found: 577.2510; ^1H NMR (400 MHz, CD_3OD) δ 0.88–0.96 (m, 3 H), 1.27–1.37 (m, 4 H), 1.38 (d, *J* = 7.1 Hz, 3 H), 1.79–1.90 (m, 1 H), 1.95–2.05 (m, 1 H), 2.08 (dd, *J* = 10.1, 8.7 Hz, 1 H), 2.14 (s, 3 H), 2.16–2.27 (m, 1 H), 2.46 (s, 3 H), 3.01 (dd, *J* = 10.5, 5.0 Hz, 1 H), 3.24 (dd, *J* = 8.4, 6.1 Hz, 1 H), 3.53 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.74–3.78 (m, 1 H), 3.84 (dq, *J* = 7.1, 3.8 Hz, 1 H), 4.08 (dd, *J* = 10.2, 5.7 Hz, 1 H), 4.22 (d, *J* = 9.4 Hz, 1 H), 4.45 (dd, *J* = 9.4, 3.8 Hz, 1 H), 5.26 (d, *J* = 5.7 Hz, 1 H), 7.54–7.61 (m, 2 H), 7.65–7.72 (m, 2 H), 9.06 (s, 2 H), 9.12 (s, 1 H).

7(*S*)-7-Deoxy-7-(4-(piperidin-3-yl)phenylthio)lincomycin (42)

To a solution of compound **22** (12.4 mg, 0.022 mmol) in MeOH (1 ml) were added 1 *N* HCl (0.1 ml) and Pt black (12.8 mg) and stirred at room temperature for 22 h under the hydrogen gas atmosphere. Then, Pt black (12.4 mg) was added to the solution and stirred at room temperature for 3 days under the hydrogen gas atmosphere. The mixture was filtrated with celite and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq. $NH_4OH = 4/1/0.1$) to obtain the title compound (4.2 mg, 34%) as a colorless solid. $[\alpha]_D^{29}$ +97.9° (*c* 0.74, MeOH); ESI-MS (*m/z*) 582 $(M+H)^+$ as $C_{29}H_{47}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{29}H_{47}N_3O_5S_2$: 582.3035, found: 582.3028; ^1H NMR (400 MHz, CD_3OD) δ 0.88–0.99 (m, 3 H), 1.27 (d, *J* = 6.9 Hz, 3 H), 1.30–1.41 (m, 4 H), 1.61–1.70 (m, 2 H), 1.77–1.90 (m, 2 H), 1.92–2.04 (m, 2 H), 1.98 (s, 3 H), 2.05–2.12 (m, 1 H), 2.12–2.23 (m, 1 H), 2.38 (s, 3 H), 2.59–2.78 (m, 3 H), 2.98 (dd, *J* = 10.6, 4.7 Hz, 1 H), 3.40–3.12 (m, 2 H), 3.24 (dd, *J* = 8.2, 5.6 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.74 (br dd, *J* = 3.3, 0.5 Hz, 1 H), 3.81 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.29–4.35 (m, 1 H), 4.38 (dd, *J* = 9.8, 2.6 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.18–7.24 (m, 2 H), 7.35–7.41 (m, 2 H).

7(*S*)-7-Deoxy-7-(4-(1-methylpiperidin-3-yl)phenylthio)lincomycin (43)

To a solution of compound **42** (17.9 mg, 0.031 mmol) in MeOH (1 ml) were added acetic acid (0.0175 ml, 0.306 mmol), 37% aqueous formaldehyde (0.0230 ml, 0.309 mmol) and sodium acetoxy borohydride (68.2 mg, 0.306 mmol) and stirred at room temperature for 40 min. The mixture was concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH = 10/1/0.1$) to obtain the title compound (13.9 mg, 76%) as a colorless solid. $[\alpha]_D^{18}$ +91.0° (*c* 0.64, MeOH); ESI-MS (*m/z*) 596 $(M+H)^+$ as $C_{30}H_{49}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{30}H_{49}N_3O_5S_2$: 596.3192, found: 596.3177; ^1H NMR (400 MHz, CD_3OD) δ 0.89–0.97 (m, 3 H), 1.27 (d, *J* = 6.9 Hz, 3 H), 1.31–1.39 (m, 4 H), 1.44–1.56 (m, 1 H), 1.69–1.82 (m, 1 H), 1.82–1.94 (m, 3 H), 1.95–2.05 (m, 1 H), 1.98 (s, 3 H), 2.06–2.13 (m, 1 H), 2.13–2.25 (m, 3 H), 2.39 (s, 6 H), 2.83 (tt, *J* = 11.9, 3.4 Hz, 1 H), 2.95–3.06 (m, 3 H), 3.25 (dd, *J* = 8.1, 5.7 Hz, 1 H), 3.57 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.71–3.76 (m, 1 H), 3.82 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.30–4.35 (m, 1 H), 4.39 (dd, *J* = 9.8, 2.6 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H), 7.20–7.25 (m, 2 H), 7.35–7.42 (m, 2 H).

7(*S*)-7-Deoxy-7-(4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl) phenylthio)lincomycin (44)

Compound **5** (162.6 mg, 0.385 mmol), 5-(4-bromophenyl)-1-methyl-1,2,3,6-tetrahydropyridine (114.9 mg, 0.456 mmol), Xantphos (22.8 mg, 0.039 mmol), $Pd_2(dba)_3$ (17.7 mg, 0.019 mmol) and *N*,*N*-diisopropylethylamine (130.1 μl, 0.747 mmol) in 1,4-dioxane (2.5 ml) were treated for 6 h according to the similar procedure as described for the preparation of **6** to afford **44** (175.9 mg, 77%) as a colorless solid. $[\alpha]_D^{17}$ +89.1° (*c* 1.63, MeOH); ESI-MS (*m/z*) 594 $(M+H)^+$ as $C_{30}H_{47}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd. for $C_{30}H_{47}N_3O_5S_2$: 594.3035, found: 594.3039; ^1H NMR (400 MHz, CD_3OD) δ 0.89–0.97 (m, 3 H), 1.30 (d, *J* = 6.9 Hz, 3 H), 1.30–1.41 (m, 4 H), 1.80–1.91 (m, 1 H), 1.94–2.03 (m, 1 H), 1.98 (s, 3 H), 2.04–2.10 (m, 1 H), 2.11–2.22 (m, 1 H), 2.37 (s, 3 H), 2.41 (dt, *J* = 6.1, 3.0 Hz, 2 H), 2.48 (s, 3 H), 2.62–2.69 (m, 2 H), 2.98 (dd, *J* = 10.7, 4.7 Hz, 1 H), 3.22 (dd, *J* = 8.1, 5.7 Hz, 1 H), 3.33–3.38 (m, 2 H), 3.58 (dd, *J* = 10.2, 2.6 Hz, 1 H), 3.72–3.76 (m, 1 H), 3.84 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.32–4.37 (m, 1 H), 4.41 (dd, *J* = 9.7, 2.6 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 6.20–6.25 (m, 1 H), 7.33–7.37 (m, 2 H), 7.38–7.42 (m, 2 H).

In vitro antibacterial activity

Minimum inhibitory concentration (μg ml^{-1}) was determined by the agar dilution method, which was described in Clinical and Laboratory Standards Institute (M7-A5 in 2000). Test strains of *S. pneumoniae* and *S. pyogenes* were subjected to seed culture using brain heart infusion agar (Becton Dickinson and Company, Tokyo, Japan) and 5% defibrinated horse blood. Test strains of *H. influenzae* were subjected to seed culture using sensitivity disk agar-N 'Nissui' (Nissui, Tokyo, Japan), 5% defibrinated horse blood, 5 μg ml^{-1} Hemin and 15 μg ml^{-1} nicotinamide adenine dinucleotide. A 5 μl portion of cell suspension of the test strains having about 10^6 CFU per ml was inoculated into sensitivity disk agar-N supplemented with 5% defibrinated horse blood, 5 μg ml^{-1} Hemin and 15 μg ml^{-1} NAD, and incubated at 37 °C for 18–22 h. Then, the minimum inhibitory concentration was measured.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank Mr A. Tamura, Dr E. Shitara and Dr T. Yoshida for encouragement and valuable discussion. We are grateful to Professor Emeritus Dr M. Konno for supervision through our in-house drug-discovery program in lincomycin field. We also thank Ms M. Ishii for direction in intellectual properties, Ms T. Miyara, Ms R. Hiruta Ms S. Miki and Ms K. Kaneda for analytical and synthetic chemistry, Mr Y. Takayama and Ms K. Yamada for biological studies, and Ms M. Takagi for English manuscript.

1 Reinert, R. R., van der Linden, M. & Al-Lahham, A. Molecular characterization of the first telithromycin-resistant *Streptococcus pneumoniae* isolate in Germany. *Antimicrob. Agents Chemother.* **49**, 3520–3522 (2005).
2 Kim, S. H. *et al.* Changing trends in antimicrobial resistance and serotypes of *Streptococcus pneumoniae* isolates in Asian countries: an Asian Network for Surveillance of Resistant Pathogens (ANSORP) study. *Antimicrob. Agents Chemother.* **56**, 1418–1426 (2012).
3 Ajito, K., Miura, T., Furuuchi, T. & Tamura, A. Sixteen-membered macrolides: chemical modifications and future applications. *Heterocycles* **89**, 281–352 (2014).
4 Morimoto, S., Takahashi, Y., Watanabe, Y. & Omura, S. Chemical modification of erythromycins. I. Synthesis and antibacterial activity of 6-*O*-methylerythromycins A. *J. Antibiot.* **37**, 187–189 (1984).
5 Slobodan, D. *et al.* Erythromycin series. Part 13. Synthesis and structure elucidation of 10-dihydro-10-deoxo-11-methyl-11-azaerythromycin A. *J.Chem. Res. Synop.* 152–153 (1998).
6 Denis, A. *et al.* Synthesis and antibacterial activity of HMR 3647 a new ketolide highly potent against erythromycin-resistant and susceptible pathogens. *Bioorg. Med. Chem. Lett.* **9**, 3075–3080 (1999).
7 Clay, K. D. *et al.* Severe hepatotoxicity of telithromycin: three case reports and literature review. *Ann. Intern. Med.* **144**, 415–420 (2006).
8 Ross, D. B. The FDA and the case of ketek. *N. Engl. J. Med.* **356**, 1601–1604 (2007).

9 Gleason, P. P., Walters, C., Heaton, A. H. & Schafer, J. A. Telithromycin: the perils of hasty adoption and persistence of off-label prescribing. *J. Manag. Care Pharm.* **13**, 20–25 (2007).
10 Department of Health and Human Services. Telithromycin (marketed as ketek). Available at: http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm107824.htm. Accessed 20 September 2014.
11 Miura, T. *et al.* Novel azalides derived from sixteen-membered macrolides. I. Isolation of the mobile dialdehyde and its one-pot macrocyclization with an amine. *J. Antibiot.* **60**, 407–435 (2007).
12 Miura, T. *et al.* Novel azalides derived from 16-membered macrolides. III. Azalides modified at the C-15 and 4" positions: Improved antibacterial activities. *Bioorg. Med. Chem.* **18**, 2735–2747 (2010).
13 Mason, D. J., Dietz, A. & Deboer, C. Lincomycin, a new antibiotic I. Discovery and biological properties. *Antimicrob. Agents Chemother.* **1962**, 554–559 (1962).
14 Magerlein, B. J. & Lincomycin, X. The chemical synthesis of lincomycin. *Tetrahedron Lett.* **1**, 33–36 (1970).
15 Howarth, G. B., Szarek, W. A. & Jones, J. K. N. The synthesis of lincomycin. *J. Chem. Soc. (c)* **16**, 2218–2224 (1970).
16 Perlman, D. *Structure-Activity Relationships Among the Semisynthetic Antibiotics*, Academic Press, New York/San Francisco/London A Subsidiary of Harcourt Brace Jovanovich, Publishers 600–651 (1977).
17 Retsema, J. *et al.* Spectrum and mode of action of azithromycin (CP-62,993), a new 15-membered-ring macrolide with improved potency against gram-negative organisms. *Antimicrob. Agents Chemother.* **1987**, 1939–1947 (1987).
18 Schlünzen, F. *et al.* Structural basis for the interaction of antibiotics with the peptidyl transferase centre in eubacteria. *Nature* **413**, 814–821 (2001).
19 Poehlsgaard, J. & Douthwaite, S. The macrolide binding site on the bacterial ribosome. *Curr. Drug Targets Infect. Disord.* **2**, 67–78 (2002).
20 Tu, D., Blaha, G., Moore, P. B. & Steitz, T. A. Structures of MLS_BK antibiotics bound to mutated large ribosomal subunits provide a structural explanation for resistance. *Cell* **121**, 257–270 (2005).
21 Shan, P. J., Vakil, N. & Kabakov, A. Role of intravenous immune globulin in streptococcal toxic shock syndrome and *Clostridium difficile* infection. *Am. J. Health. Syst. Pharm.* **72**, 1013–1019 (2015).
22 Hoeksema, H. Octoses from antibiotics. The Upjohn Company, Kalamazoo, Mich. Abstr. Pap. Division of Carbohydrate Chemistry, 149th Meet. *Am. Chem. Soc. Detroit, Mich.* p. 9C (1965).
23 Magerlein, B. J., Birkenmeyer, R. D. & Kagan, F. Chemical modification of lincomycin. *Antimicrob. Agents Chemother.* **1966**, 727–736 (1966).
24 Sinkula, A. A., Morozowich, W., Lewis, C. & Mackellar, F. A. Synthesis and bioactivity of lincomycin-7-monoesters. *J. Pharm. Sci.* **58**, 1389–1392 (1969).
25 Magerlein, B. J. & Kagan, F. Lincomycin. IX. 7-Thiol and thioamido analogs of lincomycin. *J. Med. Chem.* **12**, 974–977 (1969).
26 Lewis, J. G. *et al.* Novel Antimicrobial 7-methyl Lincosamides: Prolamide Analogs. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Poster F-1388. (Washington, DC, USA, 2004).
27 Bannister, B. Modifications of lincomycin involving the carbohydrate portion. Part III. The 7-*O*-methyl and 6-de-(1-hydroxyethyl) analogs. *J. Chem. Soc. Perkin Trans. I* **16**, 1676–1682 (1973).
28 Bannister, B. Modifications of lincomycin involving the carbohydrate portion. Part IV. (7*S*)-7-alkoxy-7-deoxy-analogues. *J. Chem. Soc. Perkin Trans. I* **1974**, 360–369 (1974).
29 Bannister, B. & Mydlow, P. K. The *S*-alkylation of sulphides by an activated carbohydrate epimine under acidic catalysis: the formation of α-acetamido-sulphides. Part 5. The introduction of functionality into the sulphide substituent. *J. Chem. Res. (S)* **1989**, 90–91 (1989).
30 Bannister, B. The *S*-alkylation of sulphides by an activated carbohydrate epimine under acidic catalysis: the formation of α-acetamido-sulphides. Part 4. Reaction with dithioacetals and monothioacetals. *J. Chem. Soc. Perkin. Trans. I* **1980**, 540–552 (1980).
31 Bannister, B. (7*S*)-7-deoxy-7-substituted-alkylthio-lincomycin. *S*-Alkylation of sulphides by an activated epimine under acidic catalysis: formation of α-acetamido-sulphides. *Tetrahedron* **40**, 1633–1660 (1984).
32 Bannister, B. (The Upjohn company). Derivatives of lincomycin and its analogs and process. US Patent US3915954 A (1973).
33 Bannister, B. (The Upjohn company). Derivatives of lincomycin and its analogs and process. Canadian Patent CA-971956 A1 (1972).
34 Sztaricskai, F. *et al.* Semisynthetic modification of antibiotic lincomycin. *J. Antibiot.* **49**, 941–943 (1996).
35 Umemura, E. *et al.* Lincomycin derivative and antibacterial agent containing the same as active ingredient. Japanese patent: WO/2007/066805 A1, 14 June (2007).
36 Wakiyama, Y. *et al.* Lincomycin derivatives and antibacterial agents containing the same as the active ingredient. Japanese patent: WO/2008/146917 A1, 4 December (2008).
37 Umemura, E. *et al.* Lincosamide derivative, and antibacterial agent comprising the same as active WO/2008/146919 A1, 4 December (2008).
38 Umemura, E. *et al.* Synthesis of novel lincomycin derivatives and their *in vitro* antibacterial activities. *J. Antibiot.* **66**, 195–198 (2013).
39 Wakiyama, Y. *et al.* Synthesis and structure-activity relationships of novel lincomycin derivatives. Part 1. Newly generated antibacterial activities against Gram-positive bacteria with *erm* gene by C-7 modification. *J. Antibiot.* **69**, 368–380 (2016).
40 Wakiyama, Y. *et al.* Synthesis and structure-activity relationships of novel lincomycin derivatives. Part 2. Synthesis of 7(S)-7-deoxy-7-(4-morpholinocarbonylphenylthio)lincomycin and its 3-dimensional analysis with rRNA. *J. Antibiot.* **69**, 428–439 (2016).
41 Kumura, K. *et al.* Synthesis and antibacterial activity of novel lincomycin derivatives. I. Enhancement of antibacterial activities by introduction of substituted azetidines. *J. Antibiot.* **69**, 440–445 (2016).
42 Itoh, T. & Mase, T. A general palladium-catalyzed coupling of aryl bromides/triflates and thiols. *Org. Lett.* **6**, 4587–4590 (2004).