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ORIGINAL ARTICLE

Synthesis and structure–activity relationships of novel lincomycin derivatives. Part 2. Synthesis of 7(*S*)-7-deoxy-7-(4-morpholino carbonylphenylthio)lincomycin and its 3-dimensional analysis with rRNA

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Lincomycin derivatives, which possess a hetero ring at the C-7 position via sulfur atom, were synthesized by three types of reactions: (1) Mitsunobu reaction of 2,3,4-tris-*O*-(trimethylsiliyl)lincomycin (1) with the corresponding thiol, (2) S_N2 reaction of 7-*O*-methanesulfonyl-2,3,4-tris-*O*-(trimethylsiliyl)lincomycin (2) with the corresponding thiol and (3) Pd-catalyzed cross-coupling reaction of 7-deoxy-7-epi-7-mercaptolincomycin (35) with the corresponding aryl halides. As a result, compound 28 had potent antibacterial activities against major pathogens, which caused respiratory infections, even compared with clindamycin. On the other hand, compound 38 showed most potent activities against a variety of *Streptococcus pneumoniae* with *erm* gene.
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INTRODUCTION

Macrolide antibiotics possess a broad spectrum of antibacterial activities against *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophillus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae* and so on. Macrolide antibiotics have been used in clinical sites over many years. Recently, resistant bacteria, especially *S. pneumoniae* with *erm* gene, have markedly increased,[1–3] which are causing serious problems in the field of bacterial respiratory infections.

Macrolide antibiotics inhibit chain elongation of bacterial protein by binding to 23S ribosomal RNA,[4–7] and consequently inhibit bacterial protein synthesis. However, clarithromycin[8] and azithromycin[9] are not effective enough against resistant bacteria such as *S. pneumoniae* with *erm* gene (Figure 1, Table 1). On the other hand, telithromycin (TEL)[10] and some of our novel macrolide derivatives[11] synthesized from 16-membered macrolide are effective against resistant *S. pneumoniae* with *erm* gene.

TEL, however, has possibility to cause serious liver damage,[12] and it is scarcely used in Japan. No oral antibiotic, which is effective against resistant bacteria of *S. pneumoniae* and does not have any problems in safety or taste, has been launched so far.

Lincomycin (LCM)[13–16] and clindamycin (CLDM)[17] inhibit bacterial protein synthesis similar to macrolide antibiotics. X-ray crystallographic analysis indicates that there are several major interactions by a hydrogen bonding between the peptidyl transferase cavity (A2058Ec, A2059Ec and G2520Ec) and hydroxyl groups at the sugar portion of CLDM.[4,6] This observation suggests that it is difficult to improve antibacterial activity by chemical modification at the sugar moiety. In fact, 2-deoxylincomycin[18] was reported to have weaker antibacterial activities even when compared with LCM.

LCM was isolated as a secondary metabolite from the fermentation broth of *Streptomyces lincolnensis*. CLDM was synthesized by the chemical modification of LCM (Figure 1), and antimicrobial activities and pharmacokinetics of CLDM were improved in comparison with those of LCM. Furthermore, chemical modifications at the C-7 position of LCM were investigated by Hoeksema *et al.*,[19] Magerlein *et al.*,[20,21] Sinkula *et al.*,[22] Birkenmeyer *et al.*,[17] Lewis *et al.*,[23] Bannister *et al.*,[18,24–30] Sztaricskai and Ōmura *et al.*[31] and so on. As a result, some of the LCM derivatives possessing a substituent at the C-7 position via sulfur atom with 7(*S*)-configuration had potent antibacterial activities when compared with LCM. But no LCM derivatives were effective against resistant bacteria of *S. pneumoniae* or *S. pyogenes* with *erm* gene that caused problems in clinical sites.

On the other hand, we had already reported LCM derivatives possessing a hetero ring at the 7 position via sulfur atom[32–34] with 7(*S*)-configuration. Among them, 7(*S*)-7-(6-amino-benzothiazol-2-yl-thio)-7-deoxylincomycin, 7(*S*)-7-deoxy-7-(4-methoxycarbonyl-phenylthio)lincomycin, 7(*S*)-7-(5-amino-1,3,4-thiadiazol-2-yl-thio)-

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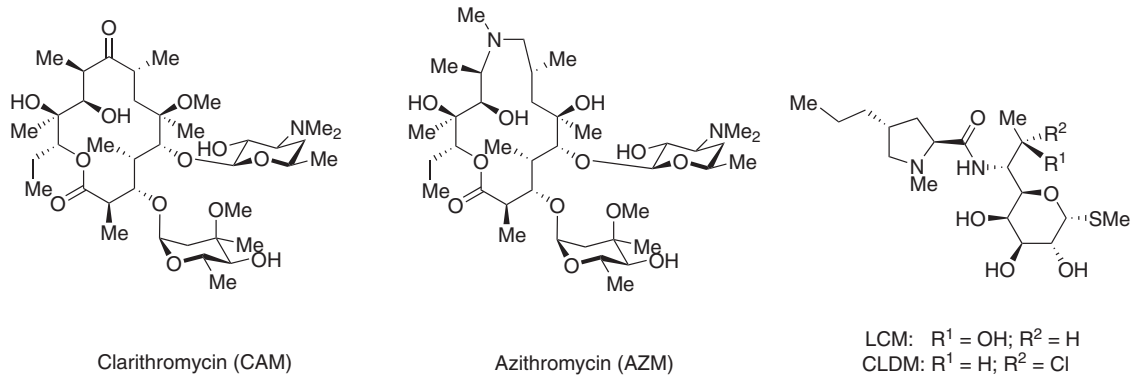


Figure 1 Chemical structures of the representative macrolides, lincomycin (LCM) and clindamycin (CLDM).

Table 1 Antibacterial activities of the representative macrolides, lincomycin (LCM) and clindamycin (CLDM)

Test organism[a]	*Characteristics*[b]	*CAM*	*AZM*	*LCM*	*CLDM*
Streptococcus pneumoniae DP1 type I	Susceptible	0.03	0.06	1	0.06
S. pneumoniae-2	Susceptible	0.03	0.03	1	0.12
S. pneumoniae-3	Susceptible	0.015	0.03	0.25	0.06
S. pneumoniae-4	*ermAM* methylase (c)	>128	>128	>128	>128
S. pneumoniae-5	*ermAM* methylase (c)	>128	>128	>128	>128
S. pneumoniae-6	*ermAM* methylase (c) + *mefE*	>128	>128	>128	>128
S. pneumoniae-7	*ermAM* methylase (i)	>128	>128	128	128
S. pneumoniae-8	*ermAM* methylase (i)	>128	>128	128	128
S. pneumoniae-9	*mefE* efflux	0.5	0.5	1	0.12
Streptococcus pyogenes Cook	Susceptible	0.015	0.06	0.12	0.06
S. pyogenes-2	*ermAM* methylase (c)	>128	>128	>128	128
S. pyogenes-3	*mefE* efflux	8	8	0.25	0.12
Haemophilus influenzae-1	Susceptible	2	0.25	8	16
H. influenzae-2	Susceptible	4	1	16	8
H. influenzae-3	Susceptible	8	2	16	16
H. influenzae-4	⊿acr	0.5	0.5	4	1

Abbreviations: AZM, azithromycin; CAM, clarithromycin.
MIC ($\mu g\,ml^{-1}$).
[a]All strains except standard organisms were clinically isolated.
[b](c): constitutive; (i): inducible.

7-deoxylincomycin and 7(*S*)-7-deoxy-7-(5-phenyl-1,3,4-thiadiazol-2-yl-thio)lincomycin had potent activities against resistant bacteria of *S. pneumoniae* and *S. pyogenes* with *erm* gene when compared with LCM or CLDM.

In this article, we report synthesis of novel LCM derivatives and their potent antibacterial activities against resistant bacteria of *S. pneumoniae* and *S. pyogenes* with *erm* gene. We also discuss SARs of these molecules focusing on substituted phenylthio groups at the 7-position of LCM with 7(*S*)-configuration.

RESULTS AND DISCUSSION

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

Synthesis of 7(*S*)-7-deoxy-7-(substituted-arylthio)lincomycin derivatives is shown in Scheme 1. Because we had utilized compounds **1** and **2** as key intermediates in our drug discovery program, we also applied these intermediates to synthesize a variety of derivatives in this article, which had the same 7(*S*)-configuration as CLDM. Compound **2** is a very useful intermediate to synthesize LCM derivatives, and it was first synthesized by us with one step from compound **1**. An S_N2 reaction of **2** under basic condition with the corresponding thiol gave desired molecules **3** and **4**. Other desired molecules **5–8** were directly synthesized from **1**.

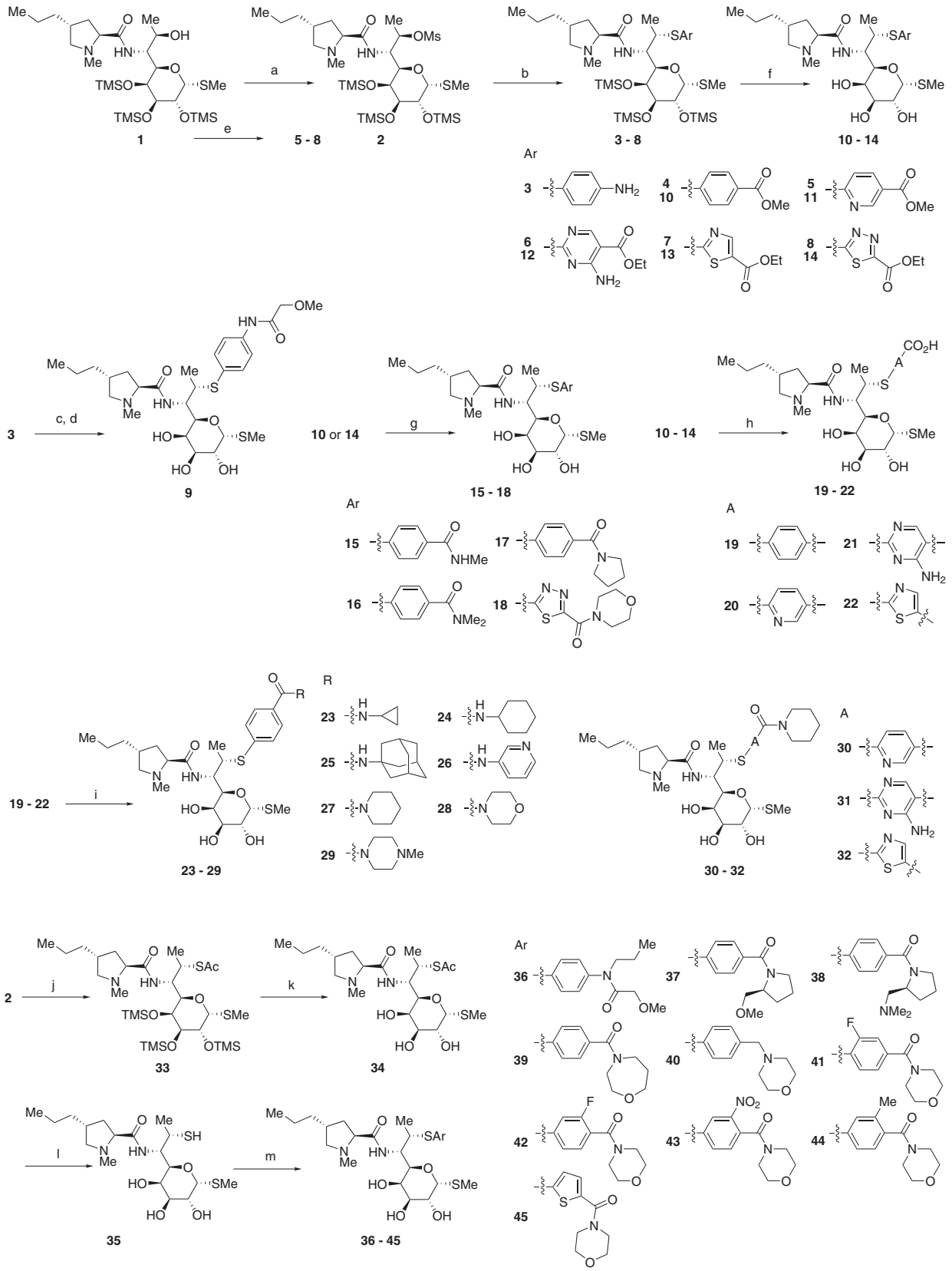
Compound **3** was treated with methoxymethylcarbonyl chloride and Et_3N, followed by deprotection of TMS (trimethylsilyl) groups under the 1 N HCl condition provided **9** in 99% yield with two steps. On the other hand, TMS groups of ester compounds (**4–8**) were deprotected under the 1 N HCl condition to give the corresponding analogs (**10–14**) in good-to-excellent yields. Amido analogs **15–17** and **18** were prepared from the corresponding ester compounds (**10** and **14**) by aminolysis, respectively. Carboxylic acid derivatives **19–22** were prepared by hydrolysis of the ester precursors (**10–13**) under the 1 N NaOH condition and then followed by condensation with a variety of amines to give the corresponding amido analogs (**23–32**).

On the other hand, compound **33** was prepared from the methanesulfonate (**2**) with KSAc under the heat (80 °C) condition. Both TMS groups and an acetyl group were successively removed under the 1 N HCl condition and then the sodium methoxide condition to give a key intermediate, compound **35**. Pd-catalyzed cross-coupling reactions[35] of **35** with an aryl bromide or an aryl iodide, which are more powerful than Mitsunobu reactions of **1** or S_N2 reactions of **2** in our research, were used to synthesize further novel derivatives. Consequently, we synthesized a variety of LCM analogs **36–45**.

SAR analysis of LCM derivatives possessing a substituted phenyl moiety at the C-7 position via sulfur atom with 7(*S*)-configuration

Antibacterial activities of LCM derivatives possessing a substituted phenyl moiety at the C-7 position via sulfur atom are shown in Table 2. In our medicinal chemistry research, we have already had SAR information suggestion that a carbonyl group or an ester function was important to enhance antibacterial activities in the case of 7-thio-phenyl derivatives such as compound **46** (Figure 2). Thus, we first replaced the thiadiazolyl group in our selected compound **47** with a phenyl group. As a result, **9** generally showed stronger antibacterial activities than **47**.

Compound **36**, which possessed a propyl group at the methoxymethylcarbonylamino group of **9**, had the strongest activities against resistant *Streptococcus* species with *erm* gene, but exhibited comparable activities to **47** against *H. influenzae*. Next, we were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interested in changing the direction of an amide bond, and we constructed a CONH-type bond instead of a NHCO-type to provide **15**. This compound had similar activities as **9**. To accumulate the SAR information around the C-7 position, we substituted the methyl group in **15**, respectively, with a larger group such as a cyclopropyl, cyclohexyl, adamantyl and pyridin-3-yl group, and compounds **23**–**26** were prepared. Modification of the R moiety on 7(*S*)-7-sulfur-Ph-CONHR derivatives could not improve the antibacterial activities of **15**.

SAR analysis of LCM derivatives possessing a 4-(*N, N*-disubstituted-carbamoyl)phenyl group at the C-7 position via sulfur atom with 7(*S*)-configuration

Conversions of the methylamino group of **15** to other dialkylamino groups were accomplished and antibacterial activities of the resulting compounds are shown in Table 3. Compound **16** also showed almost the same antibacterial spectrum as that of **15**. A variety of substituted amino functional groups (pyrrolidinyl, piperidinyl, morpholinyl, 1,4-oxazepanyl, 1-methylpiperazinyl group) were constructed to improve antibacterial activities. Consequently, the morpholinyl derivative (**28**) had strong activities against major pathogens which caused respiratory infections, that is, *S. pneumoniae*, *S. pyogenes* and *H. influenzae*. Compounds **37** and **38** possessing a substituent in the pyrrolidine ring were prepared. Although compounds **37** and **38** exhibited potent activities against *S. pneumoniae and S. pyogenes* with *erm* gene and/or *mef* gene, they showed weaker activities against *H. influenzae* than **28**. On the other hand, the tertiary amino analog (**40**) generally showed comparable antibacterial activities to **28**.

SAR analysis of LCM derivatives possessing a morpholinyl-carbonylphenyl group at the C-7 position via sulfur atom with 7(*S*)-configuration

Next, we consequently introduced several kinds of substituents on the phenyl group of **28**, and the antibacterial activities of compounds **41** to **44** are shown in Table 4. Introducing a substituent on the phenyl group of **28** did not improve its antibacterial activities, even though it was an electron-withdrawing group or an electron-donating group.

SAR analysis of LCM derivatives possessing a morpholin-1-yl-carbonylaryl moiety at the C-7 position via sulfur atom with 7(*S*)-configuration

Antibacterial activities of LCM derivatives possessing a morpholin-1-yl-carbonylaryl moiety are shown in Table 5. Conversion of the benzene ring to other hetero rings did not enhance antibacterial activities of **28**.

Docking simulation of the key compound 28

Finally, we investigated three-dimensional analysis[4,6–7] of **28** and the peptidyl transferase, and the result is shown in Figure 3. (Docking simulation was calculated by data on bacteria, *Haloarcula marismortui* (Hm).) The analysis indicated that an oxygen atom of a carbonyl group in the C-7 side chain of **28** has a hydrogen bonding with U2620Hm (Docking simulation was calculated by data on bacteria, *Haloarcula marismortui* (Hm).) (U2585Ec) (The numbers in parenthesis are expressed as the case of *Escherichia coli* (Ec).) on 23S rRNA (ribosomal RNA). Furthermore, an ethylene part of the morpholine ring in **28** was analyzed and determined to have a hydrophobic interaction of CH-π stacking with uracil (cytosine) ring of U2621Hm (C2586Ec) on 23S rRNA.

CONCLUSION

At the beginning of our LCM analogs research program, we were interested in LCM derivatives possessing a hetero ring at the C-7 position via sulfur atom with 7(*S*)-configuration. We synthesized them by two reactions; (1) Mitsunobu reaction of 2,3,4-tris-*O*-(trimethylsilyl)lincomycin (**1**) with the corresponding thiol and (2) S_N2 reaction of 7-*O*-methanesulfonyl-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (**2**) with the corresponding thiol. These synthetic procedures, however, had limitation in preparation of various LCM-7-thio-aryl analogs in order to investigate their SAR. So, we have developed a novel synthetic route for a variety of 7-thio-modified LCM derivatives by the application of Pd-catalyzed cross-coupling reaction[35] of 7-deoxy-7-epi-7-mercaptolincomycin (**35**) with an aryl bromide or an aryl iodide. This methodology was very useful to synthesize a various 7-thio-modified LCM analogs.

We first synthesized and biologically evaluated 7(*S*)-7-deoxy-7-thiophenyl analogs possessing either the NHCO-type or the CONH-type bond at the C-7 substituent. As a result, compound **28** possessing the morpholine ring had potent antibacterial activities against major pathogens that caused respiratory infections, even when compared with CLDM. A substitution introduced on the benzene ring of **28**, however, did not enhance antibacterial activities. Furthermore, conversion of the phenyl group of **28** to other hetero rings also decreased antibacterial activities. Finally, compounds **37** and **38** showed the strongest antibacterial activities against *S. pneumoniae and S. pyogenes* with *erm* gene, but, antibacterial activities against *H. influenzae* of these analogs were not improved compared with those of CLDM.

To investigate the possibilities of novel semi-synthetic LCM antibiotics, alternative modifications of LCM analogs possessing the 7-thiophenyl group or 7-thiothiadiazolyl group are now in progress. On the basis of information in this article, we will continuously explore novel chemical modifications focusing on clinically promising

Scheme 1 Synthesis of 7(*S*)-7-arylthio-7-deoxylincomycin derivatives. Conditions and Results: (a) methanesulfonyl chloride, Et_3N, $CHCl_3$, r.t., 3 h, quant; (b) (**3**): (1) 4-aminobenzenethiol, K_2CO_3, DMF, 100 °C, 4.5 h, (2) 1 N HCl, MeOH, r.t., 45 min, 67%, (3) trimethylchlorosilane, hexamethyldisilazane, pyridine, r.t., 20 h, 97% (**3**). Because a part of TMS groups was removed during S_N2 reaction with aminobenzenethiol, total deprotection and total re-protection by TMS groups were performed. (**4**): methyl 4-mercaptobenzoate, K_2CO_3, DMF, 80 °C, 1 h, not isolated (**4**); (c) 2-methoxyacetyl chloride, Et_3N, THF, 3 h; (d) 1 N HCl, MeOH, r.t., 40 min, two steps 99%; (e) triphenylphosphine, diethylazodicarboxylate or diisopropylazodicarboxylate, the corresponding HS-Ar, THF or toluene, 0 °C to r.t., 7–16 h, not isolated (**5**–**8**); (f) 1 N HCl, MeOH, r.t., 1 h, three steps 71% from **2** to **10**, two steps 76% from **1** to **11**, two steps 74% from **1** to **12**, two steps 66% from **1** to **13**, two steps 45% from **1** to **14**; (g) the corresponding amine, MeOH or EtOH, reflux, 18% (**15**), 16% (**16**), 33% (**17**), 64% (**18**); (h) 1 N or 5 N NaOH, MeOH or EtOH, r.t., quant (**19**), 81% (**20**), not isolated (**21**), not isolated (**22**); (i) the corresponding amine, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl or *N,N*′-dicyclohexylcarbodiimide, 1-hydroxybenzotriazole, DMF, r.t. to 60 °C, 1–48 h, Et_3N (**21** and **22** only), 45% (**23**), 25% (**24**), 55% (**25**), 29% (**26**), 63% (**27**), 63% (**28**), 69% (**29**), 70% (**30**), two steps 6% from **12** to **31**, two steps 7% from **13** to **32**; (j) KSAc, DMF, 60 °C, 4 h, two steps 88% from **2** to **33**; (k) 2 N HCl, MeOH, r.t., 10 min, 97%; (l) sodium methoxide, MeOH, r.t., 20 min, 94%; (m) Ar–Br or Ar–I, Xantphos, $Pd_2(dba)_3$, *N,N*-diisopropylethylamine, 1,4-dioxane, reflux, 2–21 h, 76% (**36**), 79% (**37**), 82% (**38**), 73% (**39**), 75% (**40**), 82% (**41**), 81% (**42**), 80% (**43**), 78% (**44**), 76% (**45**). quant, quantitative; r.t., room temperature; TMS, trimethylsilyl.

LCM derivatives that exhibit potent antibacterial activities against resistant *S. pneumoniae*, *S. pyogenes* with *erm* gene and *H. influenzae*.

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 for 400 MHz or a Varian Gemini 300 NMR spectrometer for 300 MHz in $CDCl_3$ or CD_3OD. TMS (0 p.p.m.) in $CDCl_3$ or CD_3OD was used as internal reference standard. Mass spectra (MS) were obtained on a JEOL JMS-700 mass spectrometer 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) or Diaion HP-20 (Mitsubishi Chemical, Tokyo, Japan). Preparative thin-layer chromatography (preparative TLC) was performed with silica gel (Merck: 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-O-Methanesulfonyl-2,3,4-tris-O-(trimethylsilyl)lincomycin (2). To a solution of 2,3,4-tris-*O*-(trimethylsilyl)lincomycin (**1**) (4.0 g, 6.42 mmol) in $CHCl_3$ (20 ml) were added Et_3N (2.24 ml, 16.1 mmol), methanesulfonyl chloride (0.99 ml, 12.8 mmol) and stirred at room temperature for 3 h. The mixture was added to $CHCl_3$ (60 ml), washed with saturated aqueous (aq) $NaHCO_3$ (50 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The title compound was obtained as a colorless solid (4.50 g, quantitative). ESI-MS (*m/z*) 701 $(M+H)^+$ as $C_{28}H_{60}N_2O_8S_2Si_3$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 9 H), 0.14 (s, 9 H), 0.17 (s, 9 H), 0.89 (br t, $J=6.9$ Hz, 3 H), 1.21–1.36 (m, 4 H), 1.40 (d, $J=6.6$ Hz, 3 H), 1.79–1.89 (m, 1 H), 1.92–2.09 (m, 3 H), 2.11 (s, 3 H), 2.40 (s, 3 H), 2.99 (dd, $J=10.7$, 3.7 Hz, 1 H), 3.09 (s, 3 H), 3.14–3.21 (m, 1 H), 3.52 (dd, $J=9.5$, 2.4 Hz, 1 H), 3.75 (br d, $J=2.4$ Hz, 1 H), 3.90 (d, $J=9.7$ Hz, 1 H), 4.15 (dd, $J=9.5$, 5.6 Hz, 1 H), 4.70–4.78 (m, 1 H), 5.09–5.15 (m, 1 H), 5.16 (d, $J=5.6$ Hz, 1 H), 7.61 (d, $J=10.7$ Hz, 1 H).

7(S)-7-(4-Aminophenylthio)-7-deoxy-2,3,4-tris-O-(trimethylsilyl)lincomycin (3). To a solution of compound **2** (5.62 g, 8.02 mmol) in DMF (50 ml) were added K_2CO_3 (3.33 g, 24.1 mmol), 4-aminobenzenethiol (2.01 g, 16.1 mmol) and stirred at 100 °C for 4.5 h. The mixture was diluted with 1 N HCl (100 ml)-MeOH (50 ml), reacted at room temperature for 45 min and then concentrated under reduced pressure. The resulting residue was dissolved by water, washed with Et_2O. The mixture was added to the saturated aq $NaHCO_3$, then extracted with EtOAc, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/28% aq $NH_4OH=20/1/0.1$) to obtain the 7(*S*)-7-(4-aminophenylthio)-7-deoxylincomycin as a colorless solid (2.77 g, 67%). $[\alpha]_D^{28}$ +142.0° (*c* 0.51, MeOH); ESI-MS (*m/z*) 514 $(M+H)^+$ as $C_{24}H_{39}N_3O_5S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{24}H_{39}N_3O_5S_2$: 514.2409, found: 514.2411; ^{1}H NMR (400 MHz, CD_3OD) δ 0.89–0.98 (m, 3 H), 1.20 (d, $J=7.1$ Hz, 3 H), 1.30–1.41 (m, 4 H), 1.80–1.90 (m, 1 H), 1.92–2.00 (m, 1 H), 2.04–2.21 (m, 2 H), 2.17 (s, 3 H), 2.34 (s, 3 H), 2.98 (dd, $J=10.6$, 4.6 Hz, 1 H), 3.24 (dd, $J=8.2$, 5.6 Hz, 1 H), 3.53 (dq, $J=7.1$, 2.8 Hz, 1 H), 3.60 (dd, $J=10.3$, 3.3 Hz, 1 H), 3.68–3.72 (m, 1 H), 4.10 (dd, $J=10.3$, 5.6 Hz, 1 H), 4.25 (dd, $J=9.9$, 2.8 Hz, 1 H), 4.38 (br d, $J=9.9$ Hz, 1 H), 5.27 (d, $J=5.6$ Hz, 1 H), 6.62–6.68 (m, 2 H), 7.20–7.26 (m, 2 H).

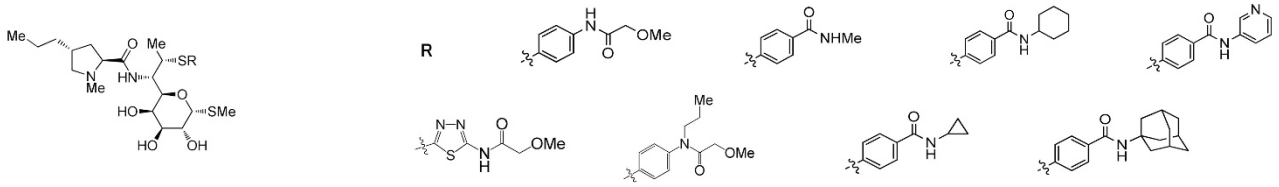
To a solution of 7(*S*)-7-(4-aminophenylthio)-7-deoxylincomycin (2.0 g, 3.9 mmol) in pyridine (20 ml) were added trimethylchlorosilane (2.0 ml, 15.7 mmol), hexamethyldisilazane (2.1 ml, 16.0 mmol) and stirred at room temperature for 20 h, then it was concentrated under reduced pressure. The residue was diluted with water, then extracted with EtOAc, washed with water and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to obtain the title compound as a colorless solid (2.77 mg, 97%). $[\alpha]_D^{28}$ +106.6° (*c* 1.15, $CHCl_3$); ESI-MS (*m/z*) 730 $(M+H)^+$ as $C_{33}H_{63}N_3O_5S_2Si_3$; TOF-ESI-HR-MS (M+H)+ calcd for $C_{33}H_{63}N_3O_5S_2Si_3$: 730.3595, found: 730.3583; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 9 H), 0.14 (s, 9 H), 0.19 (m, 9 H), 0.84–0.95 (m, 3 H), 1.12 (d, $J=6.8$ Hz, 3 H), 1.20–1.39 (m, 4 H), 1.78–1.89 (m, 1 H), 1.91–2.11 (m, 3 H), 2.21 (s, 3 H), 2.44 (s, 3 H), 2.98 (dd, $J=10.8$, 4.0 Hz, 1 H), 3.15–3.25 (m, 1 H), 3.59–3.79 (m, 5 H), 4.12–4.22 (m, 2 H), 4.55–4.65 (m, 1 H), 5.28 (d, $J=5.6$ Hz, 1 H), 6.55–6.63 (m, 2 H), 7.12–7.22 (m, 2 H), 7.63 (d, $J=10.6$ Hz, 1 H).

7(S)-7-Deoxy-7-(4-methoxyacetamidophenylthio)lincomycin (9). To a solution of compound **3** (100 mg, 0.14 mmol) in THF (1 ml) were added Et_3N (0.058 ml, 0.42 mmol), 2-methoxyacetyl chloride (0.019 ml, 0.21 mmol) and stirred at room temperature for 3 h. The mixture was diluted with 1 N HCl (2.6 ml)-MeOH (1.3 ml), reacted at room temperature for 40 min, and then concentrated under reduced pressure. The resulting residue was dissolved by water, washed with Et_2O. The mixture was added to $NaHCO_3$ (70 mg), then extracted with EtOAc, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH=9/2/0.2$) to obtain the title compound as a colorless solid (80 mg, 99%). $[\alpha]_D^{28}$ +109.3° (*c* 2.16, MeOH); ESI-MS (*m/z*) 586 $(M+H)^+$ as $C_{27}H_{43}N_3O_7S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{27}H_{43}N_3O_7S_2$: 586.2621, found: 586.2621; ^{1}H NMR (400 MHz, CD_3OD) δ 0.87–0.97 (m, 3 H), 1.27 (d, $J=7.0$ Hz, 3 H), 1.29–1.40 (m, 4 H), 1.79–1.89 (m, 1 H), 1.92–2.02 (m, 1 H), 2.02–2.09 (m, 1 H), 2.06 (s, 3 H), 2.10–2.21 (m, 1 H), 2.36 (s, 3 H), 2.97 (dd, $J=10.6$, 4.5 Hz, 1 H), 3.22 (dd, $J=7.9$, 6.0 Hz, 1 H), 3.48 (s, 3 H), 3.59 (dd, $J=10.3$, 3.5 Hz, 1 H), 3.70–3.82 (m, 2 H), 4.03 (s, 2 H), 4.11 (dd, $J=10.3$, 5.5 Hz, 1 H), 4.30–4.43 (m, 2 H), 5.28 (d, $J=5.5$ Hz, 1 H), 7.39–7.46 (m, 2 H), 7.58–7.66 (m, 2 H).

7(S)-7-Deoxy-7-(4-methoxycarbonylphenylthio)lincomycin (10). To a solution of compound **2** (5.63 g, 8.0 mmol) in DMF (20 ml) were added K_2CO_3 (3.33 g, 24.1 mmol), methyl 4-mercaptobenzoate (2.70 g, 16.1 mmol), stirred at 80 °C for 1 h and concentrated under reduced pressure. The resulting residue (compound **4**) in MeOH (20 ml) was added to 1 N HCl (80 ml), stirred at room temperature for 1 h and concentrated under reduced pressure. The resulting residue was dissolved by water, washed with Et_2O. The mixture was added to the saturated aq $NaHCO_3$, then extracted with EtOAc, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/28% aq $NH_4OH=20/1/0.1$) to obtain the title compound as a colorless solid (3.19 g, 71%). $[\alpha]_D^{24}$ +84.6° (*c* 0.97, MeOH); ESI-MS (*m/z*) 557 $(M+H)^+$ as $C_{26}H_{40}N_2O_7S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{26}H_{40}N_2O_7S_2$: 557.2355, found: 557.2359; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.96 (m, 3 H), 1.29–1.37 (m, 4 H), 1.40 (d, $J=6.8$ Hz, 3 H), 1.79–1.91 (m, 1 H), 1.84 (s, 3 H), 1.96–2.05 (m, 1 H), 2.05–2.12 (m, 1 H), 2.12–2.25 (m, 1 H), 2.40 (s, 3 H), 3.00 (dd, $J=10.6$, 4.8 Hz, 1 H), 3.24 (dd, $J=8.2$, 5.7 Hz, 1 H), 3.58 (dd, $J=10.2$, 3.2 Hz, 1 H), 3.78 (br dd, $J=3.2$, 0.7 Hz,1 H), 3.89 (s, 3 H), 4.03 (dq, $J=6.8$, 2.8 Hz,1 H), 4.10 (dd, $J=10.2$, 5.6 Hz, 1 H), 4.37 (br dd, $J=9.7$, 0.7 Hz, 1 H), 4.52 (dd, $J=9.7$, 2.8 Hz, 1 H), 5.24 (d, $J=5.6$ Hz, 1 H), 7.42–7.49 (m, 2 H), 7.90–7.97 (m, 2 H).

7(S)-7-Deoxy-7-(5-methoxycarbonylpyridin-2-ylthio)lincomycin (11). To a solution of compound **1** (200 mg, 0.32 mmol) in THF (3 ml) at 0 °C were added triphenylphosphine (84.2 mg, 0.32 mmol), diisopropylazodicarboxylate (0.065 ml, 0.32 mmol), methyl 6-mercaptonicotinate (36.2 mg, 0.21 mmol), stirred at room temperature for 7 h and concentrated under reduced pressure. The resulting residue (compound **5**) in MeOH (3 ml) was added to 1 N HCl (3 ml), stirred at room temperature for 40 min and concentrated under reduced pressure. The resulting residue was dissolved by water, washed with Et_2O. The mixture was added to $NaHCO_3$ (150 mg), then extracted with EtOAc, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH=9/2/0.2$) to obtain the title compound as a colorless solid (91 mg, 76%). $[\alpha]_D^{28}$ +71.2° (*c* 0.25, MeOH); ESI-MS (*m/z*) 558 $(M+H)^+$ as $C_{25}H_{39}N_3O_7S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{25}H_{39}N_3O_7S_2$: 558.2308, found: 558.2301; ^{1}H NMR (400 MHz, CD_3OD) δ 0.86–0.99 (m, 3 H), 1.29–1.40 (m, 4 H), 1.48 (d, $J=6.8$ Hz, 3 H), 1.79 (s, 3 H), 1.80–1.90 (m, 1 H), 1.97–2.11 (m, 2 H), 2.12–2.26 (m, 1 H), 2.36 (s, 3 H), 2.99 (dd, $J=10.5$, 5.0 Hz, 1 H), 3.25 (dd, $J=8.4$, 6.0 Hz, 1 H), 3.55 (dd, $J=10.3$, 3.2 Hz, 1 H), 3.77 (br dd, $J=3.2$, 0.6 Hz, 1 H), 3.91 (s, 3 H), 4.09 (dd, $J=10.3$, 5.6 Hz, 1 H), 4.33 (br dd, $J=9.7$, 0.6 Hz, 1 H), 4.45 (dq, $J=6.8$, 3.2 Hz,1 H),

Table 2 Antibacterial activities of 7(*S*)-7-deoxy-7-(4-substituted-phenylthio)-LCM derivatives



Test organism[a]	*Characteristics*[b]	**47**	**9**	**36**	**15**	**23**	**24**	**25**	**26**
Streptococcus pneumoniae DP1 Type I	susceptible	0.06	0.015	0.06	0.06	0.06	0.12	0.25	0.03
S. pneumoniae -2	susceptible	0.03	0.015	0.06	0.06	0.12	0.12	0.25	0.03
S. pneumoniae -3	susceptible	0.12	0.03	0.06	0.06	0.06	0.12	0.25	0.03
S. pneumoniae -4	*ermB* methylase (c)	64	4	2	4	16	16	32	32
S. pneumoniae -5	*ermB* methylase (c)	64	8	2	8	16	16	32	16
S. pneumoniae -6	*ermB* methylase (c) + *mefE*	64	32	4	32	32	64	64	64
S. pneumoniae -7	*ermB* methylase (i)	8	4	0.5	4	4	8	32	8
S. pneumoniae -8	*ermAM* methylase (i)	8	2	0.5	4	8	8	16	8
S. pneumoniae -9	*mefE* efflux	0.06	0.015	0.03	0.03	0.06	0.12	0.25	0.03
Streptococcus pyogenes Cook	susceptible	0.06	0.03	0.06	0.06	0.06	0.12	0.25	0.015
S. pyogenes -2	*ermB* methylase (c)	8	4	1	8	8	8	32	8
S. pyogenes -3	*mefE* efflux	0.06	0.03	0.06	0.12	0.06	0.12	0.25	0.03
Haemophilus influenzae -1	susceptible	32	8	8	8	16	32	32	32
H. influenzae -2	susceptible	16	4	16	8	16	16	32	16
H. influenzae -3	susceptible	32	16	64	16	32	64	>128	64
H. influenzae -4	⊿acr	0.5	0.12	0.25	0.25	0.5	0.5	2	0.25

MIC (μg ml^{-1}).
[a]All strains except standard organisms were clinically isolated.
[b](c): constitutive; (i): inducible.
Grey shading strains are target strains.

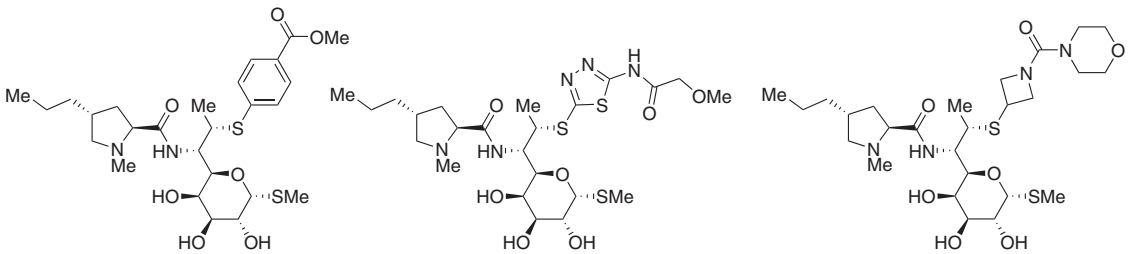


Figure 2 Basic molecule **46** and alternative series of our novel LCM derivatives **47** and **48**. LCM, lincomycin.

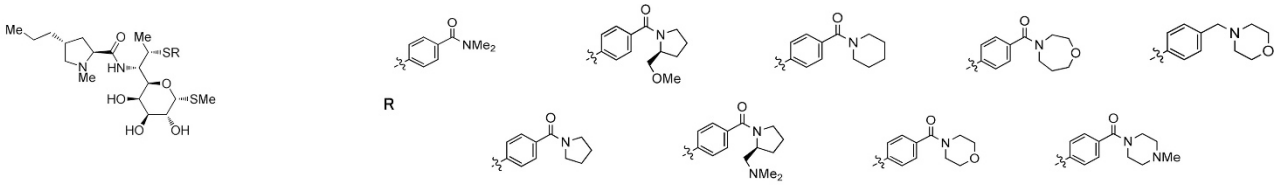
4.52 (dd, J=9.7, 3.2 Hz, 1 H), 5.22 (d, J=5.6 Hz, 1 H), 7.39 (dd, J=8.4, 0.8 Hz, 1 H), 8.10 (dd, J=8.4, 2.2 Hz, 1 H), 8.96 (dd, J=2.2, 0.8 Hz, 1 H).

7(S)-7-(4-Amino-5-ethoxycarbonylpyrimidin-2-ylthio)-7-deoxylincomycin (12). Compound **1** (1.87 g, 3.0 mmol), triphenylphosphine (1.18 g, 6.86 mmol), diethylazodicarboxylate (0.71 ml, 390 mmol), ethyl 4-amino-2-mercaptopyrimidine-5-carboxylate (894 mg, 4.49 mmol) and toluene (24 ml) were treated according to the similar procedure as described for the preparation of **11** to afford **12** (1.3 g, 74%) as a colorless solid. $[\alpha]_D^{29}$ +43.3° (*c* 6.21, MeOH); ESI-MS (*m/z*) 588 $(M+H)^+$ as $C_{25}H_{41}N_5O_7S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{25}H_{41}N_5O_7S_2$: 588.2526, found: 588.2519; ^{1}H NMR (400 MHz, CD_3OD) δ 0.87–0.96 (m, 3 H), 1.26–1.38 (m, 4 H), 1.36 (t, J=7.1 Hz, 3 H), 1.49 (d, J=6.8 Hz, 3 H), 1.77–1.87 (m, 1 H), 1.87 (s, 3 H), 1.95–2.10 (m, 2 H), 2.10–2.26 (m, 1 H), 2.36 (s, 3 H), 2.98 (dd, J=10.5, 5.1 Hz, 1 H), 3.22 (dd, J=8.5, 6.1 Hz, 1 H), 3.57 (dd, J=10.2, 3.4 Hz, 1 H), 3.77–3.82 (m, 1 H), 4.11 (dd, J=10.2, 5.6 Hz, 1 H), 4.29–4.40 (m, 4 H), 4.51 (dd, J=9.7, 3.2 Hz, 1 H), 5.24 (d, J=5.6 Hz, 1 H), 8.58 (s, 1 H).

7(S)-7-Deoxy-7-(5-ethoxycarbonylthiazol-2-ylthio)lincomycin (13). Compound **1** (930 mg, 1.49 mmol), triphenylphosphine (600 mg, 2.29 mmol), diethylazodicarboxylate (0.4 ml, 2.20 mmol), ethyl 2-mercaptothiazole-5-carboxylate (350 mg, 1.85 mmol) and toluene (15 ml) were treated according to the similar procedure as described for the preparation of **11** to afford **13** (569.2 mg, 66%) as a colorless solid. $[\alpha]_D^{28}$ +85.7° (*c* 0.32, MeOH); ESI-MS (*m/z*) 578 $(M+H)^+$ as $C_{24}H_{39}N_3O_7S_3$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{24}H_{39}N_3O_7S_3$: 578.2028, found: 578.2023; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.96 (m, 3 H), 1.29–1.39 (m, 4 H), 1.35 (t, J=7.1 Hz, 3 H), 1.52 (d, J=6.8 Hz, 3 H), 1.78–1.89 (m, 1 H), 1.94 (s, 3 H), 1.96–2.10 (m, 2 H), 2.13–2.27 (m, 1 H), 2.36 (s, 3 H), 2.98 (dd, J=10.4, 5.1 Hz, 1 H), 3.24 (dd, J=8.5, 6.1 Hz, 1 H), 3.55 (dd, J=10.3, 3.3 Hz, 1 H), 3.77–3.81 (m, 1 H), 4.10 (dd, J=10.3, 5.6 Hz, 1 H), 4.29–4.40 (m, 4 H), 4.58 (dd, J=9.8, 3.2 Hz, 1 H), 5.24 (d, J=5.6 Hz, 1 H), 8.21 (s, 1 H).

7(S)-7-Deoxy-7-(5-ethoxycarbonyl-1,3,4-thiadiazol-2-ylthio)lincomycin (14). Compound **1** (950 mg, 1.52 mmol), triphenylphosphine (550 mg, 2.10 mmol), diethylazodicarboxylate (0.5 ml, 2.74 mmol), ethyl 5-mercapto-1,3,4-thiadiazole-2-carboxylate (141 mg, 0.75 mmol) and toluene (20 ml) were treated according to the similar procedure as described for the preparation of **11** to afford **14** (345.3 mg, 45%) as a colorless solid. $[\alpha]_D^{29}$ +90.7° (*c* 0.63, EtOH); ESI-MS (*m/z*) 579 $(M+H)^+$ as $C_{23}H_{38}N_4O_7S_3$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{23}H_{38}N_4O_7S_3$: 579.1981, found: 579.1976; ^{1}H NMR (400 MHz, CD_3OD) δ 0.87–0.97 (m, 3 H), 1.28–1.38 (m, 4 H), 1.41 (t, J=7.1 Hz, 3 H), 1.57 (d, J=7.0 Hz, 3 H), 1.78–1.90 (m, 1 H), 1.94 (s, 3 H), 1.97–2.12 (m, 2 H), 2.13–2.28 (m, 1 H), 2.38 (s, 3 H), 3.01 (dd, J=10.4, 5.1 Hz, 1 H), 3.26 (dd, J=8.6, 6.1 Hz, 1 H), 3.55 (dd, J=10.2, 3.2 Hz, 1 H), 3.81 (br dd, J=3.2, 0.8 Hz, 1 H), 4.10 (dd, J=10.2, 5.6 Hz, 1 H), 4.41 (br dd, J=9.8, 0.8 Hz, 1 H), 4.47 (q, J=7.1 Hz, 2 H), 4.53 (dq, J=7.0, 3.2 Hz, 1 H), 4.62 (dd, J=9.8, 3.2 Hz, 1 H), 5.25 (d, J=5.6 Hz, 1 H).

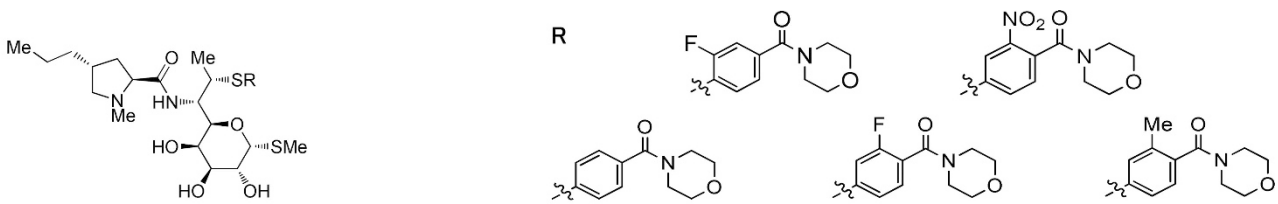
Table 3 Antibacterial activities of 7(*S*)-7-deoxy-7-(4-*(N,N*-disubstituted-carbamoyl)phenylthio)-LCM derivatives



Test organism[a]	*Characteristics*[b]	16	17	37	38	27	28	39	29	40
Streptococcus pneumoniae DP1 TypeI	susceptible	0.03	0.12	0.03	0.03	0.06	0.06	0.03	0.12	0.03
S. pneumoniae -2	susceptible	0.03	0.06	0.06	0.03	0.06	0.06	0.06	0.12	0.03
S. pneumoniae -3	susceptible	0.03	0.12	0.06	0.06	0.06	0.06	0.06	0.12	0.03
S. pneumoniae -4	*ermB* methylase (c)	8	4	2	2	2	8	8	16	8
S. pneumoniae -5	*ermB* methylase (c)	8	4	2	2	4	2	4	16	8
S. pneumoniae -6	*ermB* methylase (c) + *mefE*	32	16	8	4	8	8	16	32	32
S. pneumoniae -7	*ermB* methylase (i)	4	2	1	1	2	2	2	8	2
S. pneumoniae -8	*ermAM* methylase (i)	4	2	1	ND	ND	1	2	8	2
S. pneumoniae -9	*mefE* efflux	0.03	0.06	0.015	0.03	0.06	0.03	0.015	0.12	0.015
Streptococcus pyogenes Cook	susceptible	0.03	0.12	0.06	0.03	0.06	0.06	0.03	0.12	0.03
S. pyogenes -2	*ermB* methylase (c)	4	4	2	2	2	4	2	8	4
S. pyogenes -3	*mefE* efflux	0.03	0.12	0.06	0.25	0.06	0.06	0.03	0.12	0.03
Haemophilus influenzae -1	susceptible	8	8	8	8	8	4	8	8	8
H. influenzae -2	susceptible	8	8	8	16	8	4	8	8	8
H. influenzae -3	susceptible	32	32	32	64	16	16	32	64	32
H. influenzae -4	⊿acr	0.25	0.5	0.12	0.25	0.25	0.25	0.12	1	0.25

Abbreviations: LCM, lincomycin; ND, not determined.
MIC (μg ml^{-1}).
[a]All strains except standard organisms were clinically isolated.
[b](c): constitutive; (i): inducible.
Grey shading strains are target strains.

Table 4 Antibacterial activities by substituent effects on the phenyl group of 28

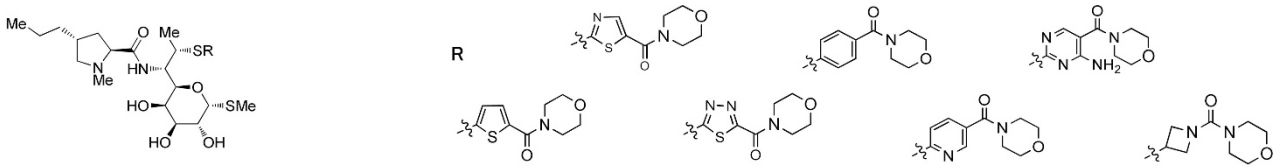


Test organism[a]	*Characteristics*[b]	28	41	42	43	44
Streptococcus pneumoniae DP1 TypeI	*susceptible*	0.06	0.06	0.06	0.06	0.06
S. pneumoniae -2	*susceptible*	0.06	0.06	0.12	0.12	0.06
S. pneumoniae -3	*susceptible*	0.06	0.06	0.12	0.12	0.06
S. pneumoniae -4	*ermB methylase (c)*	8	8	16	32	8
S. pneumoniae -5	*ermB methylase (c)*	2	16	16	32	8
S. pneumoniae -6	*ermB methylase (c) + mefE*	8	128	128	>128	64
S. pneumoniae -7	*ermB methylase (i)*	2	8	8	8	4
S. pneumoniae -8	*ermAM methylase (i)*	1	8	8	8	4
S. pneumoniae -9	*mefE efflux*	0.03	0.03	0.03	0.06	0.03
Streptococcus pyogenes Cook	susceptible	0.06	0.06	0.06	0.06	0.06
S. pyogenes -2	*ermB* methylase (c)	4	8	8	8	4
S. pyogenes -3	*mefE* efflux	0.06	0.06	0.12	0.12	0.06
Haemophilus influenzae -1	*susceptible*	4	16	16	16	16
H. influenzae -2	*susceptible*	4	16	16	32	16
H. influenzae -3	*susceptible*	16	64	64	64	32
H. influenzae -4	⊿acr	0.25	0.25	0.5	0.5	0.25

MIC (μg ml^{-1}).
[a]All strains except standard organisms were clinically isolated.
[b](c): constitutive; (i): inducible.
Grey shading strains are target strains.

7(S)-7-Deoxy-7-(4-methylcarbamoylphenylthio)lincomycin (15). To a solution of compound **10** (100 mg, 0.18 mmol) in 30% methylamine methanol solution (1.2 ml) was refluxed 20 h and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq NH_4OH = 9/2/0.2) to obtain the title compound as a colorless solid (18.0 mg, 18%). $[\alpha]_D^{33}$ +80.5° (*c* 0.65, MeOH); ESI-MS (*m/z*) 556 $(M+H)^+$ as $C_{26}H_{41}N_3O_6S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{26}H_{41}N_3O_6S_2$: 556.2515, found: 556.2515; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.97 (m, 3 H), 1.30–1.41 (m, 4 H), 1.37 (d, *J* = 6.8 Hz, 3 H), 1.80–1.95 (m, 1 H), 1.87 (s, 3 H), 1.97–2.06 (m, 1 H), 2.08–2.25 (m, 2 H), 2.43 (s, 3 H), 2.90 (s, 3 H), 3.06 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.27 (dd, *J* = 7.9, 5.4 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.75–3.80 (m, 1 H), 3.98 (dq, *J* = 6.8, 2.8 Hz, 1 H),

Table 5 Antibacterial activities of 7(*S*)-7-deoxy-7-((morpholin-1-yl-carbonyl)arylthio)-LCM derivatives



Test organism[a]	*Characteristics*[b]	**45**	**32**	**18**	**28**	**30**	**31**	**48**
Streptococcus pneumoniae DP1 TypeI	susceptible	0.03	0.03	0.03	0.06	0.06	0.5	0.12
S. pneumoniae -2	susceptible	0.06	0.03	0.06	0.06	0.12	1	0.12
S. pneumoniae -3	susceptible	0.06	0.03	0.03	0.06	0.06	0.5	0.12
S. pneumoniae -4	*ermB* methylase (c)	>128	16	32	8	32	16	16
S. pneumoniae -5	*ermB* methylase (c)	>128	16	64	2	8	16	16
S. pneumoniae -6	*ermB* methylase (c) + *mefE*	>128	32	128	8	32	64	32
S. pneumoniae -7	*ermB* methylase (i)	16	4	16	2	ND	8	8
S. pneumoniae -8	*ermAM* methylase (i)	16	4	16	1	ND	16	ND
S. pneumoniae -9	*mefE* efflux	0.06	0.03	0.03	0.03	ND	0.5	0.12
Streptococcus pyogenes Cook	susceptible	0.03	0.03	0.03	0.06	0.12	0.5	0.12
S. pyogenes -2	*ermB* methylase (c)	8	8	16	4	4	8	4
S. pyogenes -3	*mefE* efflux	0.06	ND	0.06	0.06	0.12	0.5	0.12
Haemophilus influenzae -1	susceptible	16	8	16	4	16	16	4
H. influenzae -2	susceptible	8	8	16	4	16	32	8
H. influenzae -3	susceptible	32	32	64	16	32	64	16
H. influenzae -4	⊿acr	0.25	0.25	0.5	0.25	0.5	1	1

Abbreviations: LCM, lincomycin; ND, not determined.
MIC (μg ml^{-1}).
[a]All strains except standard organisms were clinically isolated.
[b](c): constitutive; (i): inducible.
Grey shading strains are target strains.

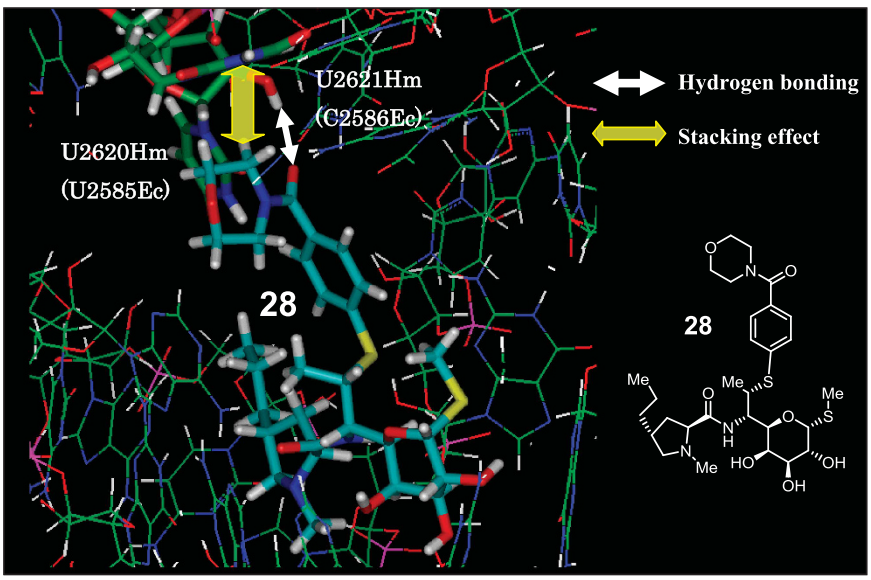


Figure 3 Three-dimensional analysis of **28** and the peptidyl transferase.

4.10 (dd, J=10.2, 5.5 Hz, 1 H), 4.37 (br dd, J=9.7, 0.6 Hz, 1 H), 4.51 (dd, J=9.7, 2.8 Hz, 1 H), 5.25 (d, J=5.5 Hz, 1 H), 7.42–7.48 (m, 2 H), 7.72–7.78 (m, 2 H).

7(S)-7-Deoxy-7-(4-dimethylcarbamoylphenylthio)lincomycin (16). Compound **10** (300 mg, 0.54 mmol) and 2 M dimethylamine methanol solution (20 ml) were treated according to the similar procedure as described for the preparation of **15** to afford **16** (48.6 mg, 16%) as a colorless solid. $[\alpha]_D^{31}$ +90.9° (*c* 1.12, MeOH); ESI-MS (*m/z*) 570 $(M+H)^+$ as $C_{27}H_{43}N_3O_6S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{27}H_{43}N_3O_6S_2$: 570.2672, found: 570.2681; ^{1}H NMR (400 MHz, CD_3OD) δ 0.89–0.96 (m, 3 H), 1.29–1.42 (m, 4 H), 1.36 (d, J=6.9 Hz, 3 H), 1.82–1.90 (m, 1 H), 1.92 (s, 3 H), 1.97–2.07 (m, 1 H), 2.08–2.26 (m, 2 H), 2.44 (s, 3 H), 3.00 (s, 3 H), 3.05 (dd, J=10.6, 4.8 Hz, 1 H), 3.08 (s, 3 H), 3.28 (dd, J=8.1, 5.5 Hz, 1 H), 3.58 (dd, J=10.2, 3.2 Hz, 1 H), 3.75–3.80 (m, 1 H), 3.97 (dq, J=6.9, 2.7 Hz, 1 H), 4.10 (dd, J=10.2, 5.5 Hz, 1 H), 4.35 (br dd, J=9.7, 0.5 Hz, 1 H), 4.49 (dd,

J=9.7, 2.7 Hz, 1 H), 5.26 (d, J=5.5 Hz, 1 H), 7.36–7.42 (m, 2 H), 7.44–7.50 (m, 2 H).

7(S)-7-Deoxy-7-(4-pyrrolidinocarbonylphenylthio)lincomycin (17). A solution of compound **10** (100 mg, 0.18 mmol) and pyrrolidine (0.95 ml) were treated according to the similar procedure as described for the preparation of **15** to afford **17** (35.0 mg, 33%) as a colorless solid. $[\alpha]_D^{30}$ +64.2° (*c* 0.24, MeOH); ESI-MS (*m/z*) 596 $(M+H)^+$ as $C_{29}H_{45}N_3O_6S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{29}H_{45}N_3O_6S_2$: 596.2828, found: 596.2825; ^{1}H NMR (400 MHz, CD_3OD) δ 0.90–0.97 (m, 3 H), 1.30–1.43 (m, 4 H), 1.36 (d, J=6.8 Hz, 3 H), 1.85–2.02 (m, 5 H), 1.91 (s, 3 H), 2.03–2.12 (m, 1 H), 2.17–2.32 (m, 2 H), 2.54 (s, 3 H), 3.22–3.30 (m, 1 H), 3.35–3.42 (m, 1 H), 3.47 (t, J=6.6 Hz, 2 H), 3.55–3.61 (m, 3 H), 3.79 (br dd, J=3.1, 0.5 Hz, 1 H), 3.96 (dq, J=6.8, 2.6 Hz, 1 H), 4.10 (dd, J=10.2, 5.6 Hz, 1 H), 4.38 (br dd, J=9.7, 0.5 Hz, 1 H), 4.53 (dd, J=9.7, 2.6 Hz, 1 H), 5.25 (d, J=5.6 Hz, 1 H), 7.43–7.51 (m, 4 H).

7(S)-7-Deoxy-7-(5-morpholinocarbonyl-1,3,4-thidiazol-2-ylthio)lincomycin (18). To a solution of compound **14** (50 mg, 0.09 mmol) in EtOH (1 ml) was added morpholine (0.1 ml) and refluxed for 3 h and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq NH_4OH=9/2/0.2) to obtain the title compound as a colorless solid (34.5 mg, 64%). $[\alpha]_D^{31}$ +73.4° (*c* 0.92, MeOH); ESI-MS (*m/z*) 620 $(M+H)^+$ as $C_{25}H_{41}N_5O_7S_3$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{25}H_{41}N_5O_7S_3$: 620.2246, found: 620.2239; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.97 (m, 3 H), 1.27–1.40 (m, 4 H), 1.57 (d, J=6.8 Hz, 3 H), 1.79–1.90 (m, 1 H), 1.96 (s, 3 H), 1.97–2.11 (m, 2 H), 2.14–2.27 (m, 1 H), 2.38 (s, 3 H), 3.00 (dd, J=10.5, 5.1 Hz, 1 H), 3.25 (dd, J=8.5, 6.1 Hz, 1 H), 3.55 (dd, J=10.3, 3.2 Hz, 1 H), 3.72–3.83 (m, 7 H), 4.10 (dd, J=10.3, 5.6 Hz, 1 H), 4.24 (br t, J=4.7 Hz, 2 H), 4.39 (dd, J=9.8, 0.7 Hz, 1 H), 4.47 (dq, J=6.8, 3.2 Hz, 1 H), 4.61 (dd, J=9.8, 3.2 Hz, 1 H), 5.25 (d, J=5.6 Hz, 1 H).

7(S)-7-(4-Carboxylphenylthio)-7-deoxylincomycin (19). To a solution of compound **10** (1.84 g, 3.3 mmol) in MeOH (20 ml) was added 1 M aq NaOH (5 ml) and stirred at room temperature for 19 h. The mixture was diluted with 1 N HCl (5 ml) and concentrated under reduced pressure. The resulting residue was purified by Diaion HP-20 (Mitsubishi Chemical) column chromatography to obtain the title compound as a colorless solid (1.78 g, quant). $[\alpha]_D^{28}$ +161.2° (*c* 0.34, DMF); ESI-MS (*m/z*) 543 $(M+H)^+$ as $C_{25}H_{38}N_2O_7S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{25}H_{38}N_2O_7S_2$: 543.2199, found: 543.2194; ^{1}H NMR (400 MHz, CD_3OD) δ 0.89–0.97 (m, 3 H), 1.29–1.45 (m, 4 H), 1.38 (d, J=6.8 Hz, 3 H), 1.87 (s, 3 H), 1.92–2.03 (m, 1 H), 2.03–2.13 (m, 1 H), 2.17–2.29 (m, 1 H), 2.30–2.38 (m, 1 H), 2.57 (s, 3 H), 3.36 (dd, J=10.3, 5.2 Hz, 1 H), 3.41 (dd, J=9.0, 6.1 Hz, 1 H), 3.58 (dd, J=10.2, 3.3 Hz, 1 H), 3.80 (br dd, J=3.3, 0.8 Hz, 1 H), 3.98 (dq, J=6.8, 2.7 Hz, 1 H), 4.09 (dd, J=10.2, 5.6 Hz, 1 H), 4.40 (br dd, J=9.8, 0.8 Hz, 1 H), 4.55 (dd, J=9.8, 2.7 Hz, 1 H), 5.25 (d, J=5.6 Hz, 1 H), 7.38–7.44 (m, 2 H), 7.88–7.95 (m, 2 H).

For the qualified analytical purpose, the above colorless solid was further purified by reverse-phase column chromatography (Biotage SNAP Ultra C18, 25 µm, room temperature, 12.0 ml min^{-1}, H_2O/MeOH=100/0–0/100) to obtain the highly purified title compound as a colorless solid.

7(S)-7-(5-Carboxylpyridin-2-ylthio)-7-deoxylincomycin (20). Compound **11** (621.8 mg, 1.12 mmol), 1 M aq NaOH (6.2 ml) and MeOH (6.2 ml) were treated according to the similar procedure as described for the preparation of **19** to afford **20** (488.1 mg, 81%) as a colorless solid. $[\alpha]_D^{29}$ +90.4° (*c* 0.30, DMF); ESI-MS (*m/z*) 544 $(M+H)^+$ as $C_{24}H_{37}N_3O_7S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{24}H_{37}N_3O_7S_2$: 544.2151, found: 544.2151; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.98 (t, J=7.1 Hz, 3 H), 1.25–1.50 (m, 4 H), 1.46 (d, J=7.0 Hz, 3 H), 1.83 (s, 3 H), 1.96–2.16 (m, 2 H), 2.20–2.33 (m, 1 H), 2.38–2.47 (m, 1 H), 2.62 (s, 3 H), 3.45–3.55 (m, 2 H), 3.56 (dd, J=10.2, 3.2 Hz, 1 H), 3.80–3.83 (m, 1 H), 4.10 (dd, J=10.2, 5.6 Hz, 1 H), 4.32–4.42 (m, 2 H), 4.53 (dd, J=9.7, 3.2 Hz, 1 H), 5.24 (d, J=5.6 Hz, 1 H), 7.30–7.35 (m, 1 H), 8.09 (dd, J=8.4, 2.1 Hz, 1 H), 8.92–8.97 (m, 1 H).

7(S)-7-(4-Cyclopropylcarbamoylphenylthio)-7-deoxylincomycin (23). To a solution of compound **19** (100 mg, 0.18 mmol) in DMF (1 ml) were added 1-hydroxybenzotriazole (37.3 mg, 0.28 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl (53.0 mg, 0.28 mmol) and cyclopropylamine (0.019 ml, 0.28 mmol) and stirred at room temperature for 4 h. The mixture was diluted with saturated aq $NaHCO_3$ (10 ml), then extracted with EtOAc, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq NH_4OH=9/2/0.2) to obtain the title compound as a colorless solid (48.0 mg, 45%). $[\alpha]_D^{29}$ +84.0° (*c* 1.77, MeOH); ESI-MS (*m/z*) 582 $(M+H)^+$ as $C_{28}H_{43}N_3O_6S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{28}H_{43}N_3O_6S_2$: 582.2672, found: 582.2669; ^{1}H NMR (400 MHz, CD_3OD) δ 0.59–0.66 (m, 2 H), 0.75–0.84 (m, 2 H), 0.89–0.98 (m, 3 H), 1.29–1.42 (m, 4 H), 1.37 (d, J=6.8 Hz, 3 H), 1.80–1.92 (m, 1 H), 1.87 (s, 3 H), 1.96–2.05 (m, 1 H), 2.06–2.25 (m, 2 H), 2.41 (s, 3 H), 2.83 (tt, J=7.4, 3.8 Hz, 1 H), 3.03 (dd, J=10.5, 4.8 Hz, 1 H), 3.26 (dd, J=8.1, 5.6 Hz, 1 H), 3.58 (dd, J=10.2, 3.2 Hz, 1 H), 3.77 (br dd, J=3.2, 0.6 Hz, 1 H), 3.98 (dq, J=6.8, 2.8 Hz, 1 H), 4.10 (dd, J=10.2, 5.6 Hz, 1 H), 4.37 (br dd, J=9.7, 0.6 Hz, 1 H), 4.50 (dd, J=9.7, 2.8 Hz, 1 H), 5.25 (d, J=5.6 Hz, 1 H), 7.40–7.47 (m, 2 H), 7.70–7.78 (m, 2 H).

7(S)-7-(4-Cyclohexylcarbamoylphenylthio)-7-deoxylincomycin (24). Compound **19** (100 mg, 0.18 mmol) and cyclohexylamine (0.031 ml, 0.28 mmol) were treated according to the similar procedure as described for the preparation of **23** to afford **24** (29.0 mg, 25%) as a colorless solid. $[\alpha]_D^{30}$ +105.0° (*c* 1.91, $CHCl_3$); ESI-MS (*m/z*) 624 $(M+H)^+$ as $C_{31}H_{49}N_3O_6S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{31}H_{49}N_3O_6S_2$: 624.3141, found: 624.3149; ^{1}H NMR (400 MHz, CD_3OD) δ 0.89–0.97 (m, 3 H), 1.16–1.47 (m, 9 H), 1.37 (d, J=6.9 Hz, 3 H), 1.64–1.73 (m, 1 H), 1.77–1.97 (m, 5 H), 1.89 (s, 3 H), 1.97–2.06 (m, 1 H), 2.07–2.26 (m, 2 H), 2.41 (s, 3 H), 3.02 (dd, J=10.6, 4.8 Hz, 1 H), 3.26 (dd, J=8.2, 5.6 Hz, 1 H), 3.58 (dd, J=10.2, 3.3 Hz, 1 H), 3.77 (br dd, J=3.3, 0.6 Hz, 1 H), 3.79–3.90 (m, 1 H), 3.98 (dq, J=6.9, 2.7 Hz, 1 H), 4.10 (dd, J=10.2, 5.6 Hz, 1 H), 4.37 (br dd, J=9.7, 0.6 Hz, 1 H), 4.50 (dd, J=9.7, 2.7 Hz, 1 H), 5.25 (d, J=5.6 Hz, 1 H), 7.41–7.47 (m, 2 H), 7.72–7.78 (m, 2 H).

7(S)-7-(4-(Adamant-1-yl)carbamoylphenylthio)-7-deoxylincomycin (25). Compound **19** (100 mg, 0.18 mmol) and 1-adamantylamine (0.04 mg, 0.28 mmol) were treated according to the similar procedure as described for the preparation of **23** to afford **25** (68.6 mg, 55%) as a colorless solid. $[\alpha]_D^{31}$ +74.5° (*c* 1.95, MeOH); ESI-MS (*m/z*) 676 $(M+H)^+$ as $C_{35}H_{53}N_3O_6S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{35}H_{53}N_3O_6S_2$: 676.3454, found: 676.3453; ^{1}H NMR (400 MHz, CD_3OD) δ 0.87–0.98 (m, 3 H), 1.29–1.42 (m, 4 H), 1.35 (d, J=6.8 Hz, 3 H), 1.68–1.80 (m, 6 H), 1.81–1.95 (m, 1 H), 1.90 (s, 3 H), 1.96–2.05 (m, 1 H), 2.06–2.24 (m, 11 H), 2.42 (s, 3 H), 3.04 (dd, J=10.5, 4.9 Hz, 1 H), 3.27 (dd, J=8.1, 5.6 Hz, 1 H), 3.59 (dd, J=10.2, 3.3 Hz, 1 H), 3.76–3.79 (m, 1 H), 3.97 (dq, J=6.8, 2.7 Hz, 1 H), 4.10 (dd, J=10.2, 5.6 Hz, 1 H), 4.36 (br dd, J=9.8, 0.5 Hz, 1 H), 4.50 (dd, J=9.8, 2.7 Hz, 1 H), 5.26 (d, J=5.6 Hz, 1 H), 7.39–7.45 (m, 2 H), 7.66–7.72 (m, 2 H).

7(S)-7-Deoxy-7-(4-(pyridin-3-yl)carbamoylphenylthio)lincomycin (26). Compound **19** (40.5 mg, 0.075 mmol) and 3-aminopyridine (10.5 mg, 0.11 mmol) were treated according to the similar procedure as described for the preparation of **23** to afford **26** (13.5 mg, 29%) as a colorless solid. $[\alpha]_D^{30}$ +31.1° (*c* 0.10, MeOH); ESI-MS (*m/z*) 619 $(M+H)^+$ as $C_{30}H_{42}N_4O_6S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{30}H_{42}N_4O_6S_2$: 619.2624, found: 619.2623; ^{1}H NMR (400 MHz, CD_3OD) δ 0.93 (br t, J=6.9 Hz, 3 H), 1.26–1.45 (m, 4 H), 1.41 (d, J=6.8 Hz, 3 H), 1.85–1.98 (m, 1 H), 1.88 (s, 3 H), 2.01–2.11 (m, 1 H), 2.15–2.28 (m, 2 H), 2.50 (s, 3 H), 3.14–3.24 (m, 1 H), 3.30–3.38 (m, 1 H), 3.59 (dd, J=10.2, 3.2 Hz, 1 H), 3.80 (br d, J=3.2 Hz,1 H), 4.04 (dq, J=6.8, 2.7 Hz, 1 H), 4.11 (dd, J=10.2, 5.6 Hz, 1 H), 4.41 (br d, J=9.8 Hz, 1 H), 4.57 (dd, J=9.8, 2.7 Hz, 1 H), 5.27 (d, J=5.6 Hz, 1 H), 7.45 (br ddd, J=8.3, 4.8, 0.7 Hz, 1 H), 7.48–7.55 (m, 2 H), 7.88–7.96 (m, 2 H), 8.25 (ddd, J=8.3, 2.4, 1.4 Hz, 1 H), 8.31 (br dd, J=4.8, 1.4 Hz, 1 H), 8.86–8.91 (m, 1 H).

7(S)-7-Deoxy-7-(4-piperidinocarbonylphenylthio)lincomycin (27). Compound **19** (100 mg, 0.18 mmol) and piperidine (0.027 ml, 0.28 mmol) were treated according to the similar procedure as described for the preparation of **23** to afford **27** (71 mg, 63%) as a colorless solid. $[\alpha]_D^{32}$ +65.4° (*c* 0.18, MeOH); ESI-MS (*m/z*) 610 $(M+H)^+$ as $C_{30}H_{47}N_3O_6S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd

for $C_{30}H_{47}N_3O_6S_2$: 610.2985, found: 610.2981; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.97 (m, 3 H), 1.30–1.42 (m, 4 H), 1.36 (d, J=6.8 Hz, 3 H), 1.48–1.77 (m, 7 H), 1.85–1.97 (m, 1 H), 1.92 (s, 3 H), 1.99–2.10 (m, 1 H), 2.14–2.27 (m, 2 H), 2.47 (s, 3 H), 3.08–3.17 (m, 1 H), 3.32–3.45 (m, 2 H), 3.57 (dd, J=10.1, 3.2 Hz, 1 H), 3.61–3.74 (m, 2 H), 3.77 (br d, J=3.2 Hz, 1 H), 3.95 (dq, J=6.8, 2.5 Hz, 1 H), 4.10 (dd, J=10.1, 5.6 Hz, 1 H), 4.36 (br d, J=9.8 Hz, 1 H), 4.50 (br dd, J=9.8, 2.5 Hz, 1 H), 5.25 (d, J=5.6 Hz, 1 H), 7.32–7.37 (m, 2 H), 7.44–7.49 (m, 2 H).

7(S)-7-Deoxy-7-(4-morpholinocarbonylphenylthio)lincomycin (28). Compound **19** (200 mg, 0.37 mmol) and morpholine (0.048 ml, 0.55 mmol) were treated according to the similar procedure as described for the preparation of **23** to afford **28** (142 mg, 63%) as a colorless solid. $[\alpha]_D^{31}$ +78.7° (*c* 2.08, MeOH); ESI-MS (*m/z*) 612 $(M+H)^+$ as $C_{29}H_{45}N_3O_7S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{29}H_{45}N_3O_7S_2$: 612.2777, found: 612.2772; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.97 (m, 3 H), 1.28–1.42 (m, 4 H), 1.35 (d, J=6.8 Hz, 3 H), 1.81–1.91 (m, 1 H), 1.91 (s, 3 H), 1.97–2.06 (m, 1 H), 2.07–2.14 (m, 1 H), 2.14–2.25 (m, 1 H), 2.43 (s, 3 H), 3.03 (dd, J=10.6, 4.8 Hz, 1 H), 3.27 (dd, J=8.3, 5.7 Hz, 1 H), 3.33–3.57 (m, 2 H), 3.57 (dd, J=10.2, 3.3 Hz, 1 H), 3.57–3.85 (m, 6 H), 3.77 (br dd, J=3.3, 0.6 Hz, 1 H), 3.97 (dq, J=6.8, 2.7 Hz, 1 H), 4.10 (dd, J=10.2, 5.6 Hz, 1 H), 4.35 (br dd, J=9.7, 0.6 Hz, 1 H), 4.49 (dd, J=9.7, 2.7 Hz, 1 H), 5.26 (d, J=5.6 Hz, 1 H), 7.36–7.42 (m, 2 H), 7.45–7.52 (m, 2 H).

7(S)-7-Deoxy-7-(4-(4-methylpiperazin-1-yl)carbonylphenylthio)lincomycin (29). Compound **19** (67.8 mg, 0.12 mmol) and 1-methylpiperazine (0.021 ml, 0.19 mmol) were treated according to the similar procedure as described for the preparation of **23** to afford **29** (54.0 mg, 69%) as a colorless solid. $[\alpha]_D^{31}$ +77.0° (*c* 1.31, MeOH); ESI-MS (*m/z*) 625 $(M+H)^+$ as $C_{30}H_{48}N_4O_6S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{30}H_{48}N_4O_6S_2$: 625.3094, found: 625.3091; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.98 (m, 3 H), 1.27–1.42 (m, 4 H), 1.36 (d, J=6.8 Hz, 3 H), 1.81–1.95 (m, 1 H), 1.91 (s, 3 H), 1.97–2.07 (m, 1 H), 2.08–2.25 (m, 2 H), 2.33 (s, 3 H), 2.36–2.58 (m, 4 H), 2.43 (s, 3 H), 3.05 (dd, J=10.6, 4.8 Hz, 1 H), 3.28 (dd, J=8.1, 5.5 Hz, 1 H), 3.38–3.61 (m, 2 H), 3.57 (dd, J=10.1, 3.2 Hz, 1 H), 3.61–3.88 (m, 3 H), 3.97 (dq, J=6.8, 2.7 Hz, 1 H), 4.10 (dd, J=10.1, 5.5 Hz, 1 H), 4.35 (br dd, J=9.7, 0.5 Hz, 1 H), 4.49 (dd, J=9.7, 2.7 Hz, 1 H), 5.25 (d, J=5.5 Hz, 1 H), 7.35–7.40 (m, 2 H), 7.45–7.51 (m, 2 H).

7(S)-7-Deoxy-7-(5-molpholinocarbonylpyridin-2-ylthio)lincomycin (30). Compound **20** (96.9 mg, 0.18 mmol) and morpholine (0.024 ml, 0.28 mmol) were treated according to the similar procedure as described for the preparation of **23** to afford **30** (76.7 mg, 70%) as a colorless solid. $[\alpha]_D^{29}$ +55.4° (*c* 2.46, MeOH); ESI-MS (*m/z*) 613 $(M+H)^+$ as $C_{28}H_{44}N_4O_7S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{28}H_{44}N_4O_7S_2$: 613.2730, found: 613.2735; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.97 (m, 3 H), 1.27–1.41 (m, 4 H), 1.47 (d, J=6.9 Hz, 3 H), 1.79 (s, 3 H), 1.82–1.92 (m, 1 H), 2.02 (ddd, J=13.0, 7.9, 5.1 Hz, 1 H), 2.07–2.14 (m, 1 H), 2.14–2.27 (m, 1 H), 2.39 (s, 3 H), 3.03 (dd, J=10.5, 5.1 Hz, 1 H), 3.26 (dd, J=8.4, 5.9 Hz, 1 H), 3.40–3.83 (m, 8 H), 3.55 (dd, J=10.2, 3.2 Hz, 1 H), 3.75–3.80 (m, 1 H), 4.10 (dd, J=10.2, 5.6 Hz, 1 H), 4.34 (br dd, J=9.8, 0.4 Hz, 1 H), 4.43 (dq, J=6.9, 3.1 Hz, 1 H), 4.52 (dd, J=9.8, 3.1 Hz, 1 H), 5.23 (d, J=5.6 Hz, 1 H), 7.38 (dd, J=8.3, 0.9 Hz, 1 H), 7.67 (dd, J=8.3, 2.3 Hz, 1 H), 8.49 (dd, J=2.3, 0.9 Hz, 1 H).

7(S)-7-(4-Amino-5-molpholinocarbonylpyrimidin-2-ylthio)-7-deoxylincomycin (31). To a solution of compound **12** (117.2 mg, 0.2 mmol) in MeOH (1 ml) was added 1 M aq NaOH (0.3 ml) and stirred at room temperature for 10 h. The mixture was diluted with 1 N HCl (0.3 ml) and concentrated under reduced pressure. The resulting residue (crude compound **21**), morpholine (0.008 ml, 0.092 mmol), *N,N*'-dicyclohexylcarbodiimide (30.7 mg, 0.15 mmol), 1-hydroxybenzotriazole (20.3 mg, 0.15 mmol) and Et_3N (0.012 ml, 0.09 mmol) were treated according to the similar procedure as described for the preparation of **23** to afford **31** (7.7 mg, 6%) as a colorless solid. $[\alpha]_D^{31}$ +22.4° (*c* 0.11, MeOH); ESI-MS (*m/z*) 629 $(M+H)^+$ as $C_{27}H_{44}N_6O_7S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{27}H_{44}N_6O_7S_2$: 629.2791, found: 629.2792; ^{1}H NMR (400 MHz, CD_3OD) δ 0.84–0.97 (m, 3 H), 1.24–1.39 (m, 4 H), 1.47 (d, J=6.8 Hz, 3 H), 1.78–1.91 (m, 1 H), 1.86 (s, 3 H), 1.94–2.10 (m, 2 H), 2.12–2.26 (m, 1 H), 2.37 (s, 3 H), 2.98 (dd, J=10.5, 5.1 Hz, 1 H), 3.22 (dd, J=8.4, 6.2 Hz, 1 H), 3.50–3.74 (m, 9 H), 3.75–3.80 (m, 1 H), 4.09 (dd, J=10.2, 5.6 Hz, 1 H), 4.29–4.38 (m, 2 H), 4.49 (dd, J=9.8, 3.2 Hz, 1 H), 5.22 (d, J=5.6 Hz, 1 H), 7.96 (s, 1 H).

7(S)-7-Deoxy-7-(5-molpholinocarbonylthiazol-2-ylthio)lincomycin (32). To a solution of compound **13** (430 mg, 0.74 mmol) in EtOH (8 ml) was added 5 M aq NaOH (0.3 ml) and stirred at room temperature for 1 h. The mixture was diluted with 5 N HCl (0.3 ml) and concentrated under reduced pressure. The resulting residue (crude compound **22**), morpholine (0.32 ml, 3.70 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl (212.8 mg, 1.11 mmol), 1-hydroxybenzotriazole (150 mg, 1.11 mmol) and Et_3N (1.03 ml, 7.40 mmol) were treated according to the similar procedure (60 °C, 2 days) as described for the preparation of **23** to afford **32** (29.9 mg, 7%) as a colorless solid. $[\alpha]_D^{27}$ +84.5° (*c* 3.39, MeOH); ESI-MS (*m/z*) 619 $(M+H)^+$ as $C_{26}H_{42}N_4O_7S_3$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{26}H_{42}N_4O_7S_3$: 619.2294, found: 619.2288; ^{1}H NMR (400 MHz, CD_3OD) δ 0.86–0.97 (m, 3 H), 1.26–1.41 (m, 4 H), 1.51 (d, J=7.0 Hz, 3 H), 1.77–1.89 (m, 1 H), 1.96 (s, 3 H), 1.96–2.11 (m, 2 H), 2.11–2.27 (m, 1 H), 2.37 (s, 3 H), 2.99 (dd, J=10.4, 5.1 Hz, 1 H), 3.24 (dd, J=8.4, 6.1 Hz, 1 H), 3.56 (dd, J=10.2, 3.2 Hz, 1 H), 3.66–3.77 (m, 8 H), 3.77–3.82 (m, 1 H), 4.10 (dd, J=10.2, 5.6 Hz, 1 H), 4.30 (dq, J=7.0, 3.2 Hz, 1 H), 4.36 (br dd, J=9.8, 0.5 Hz, 1 H), 4.57 (dd, J=9.8, 3.2 Hz, 1 H), 5.26 (d, J=5.6 Hz, 1 H), 7.93 (s, 1 H).

7(S)-7-Acetylthio-7-deoxy-2,3,4-tris-O-(trimethylsilyl)lincomycin (33). To a solution of compound **2** (200 mg, 0.29 mmol) in DMF (0.65 ml) was added potassium ethanethioate (163 mg, 1.4 mmol) at 60 °C for 4 h. The mixture was diluted with EtOAc and washed with 10% aq $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc=3/1) to obtain the title compound as a colorless solid (170 mg, 88%). ESI-MS (*m/z*) 681 $(M+H)^+$ as $C_{29}H_{60}N_2O_6S_2Si_3$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09–0.20 (m, 27 H), 0.84–0.93 (m, 3 H), 1.20–1.47 (m, 7 H), 1.76–1.87 (m, 1 H), 1.90–2.09 (m, 6 H), 2.31 (s, 3 H), 2.40 (s, 3 H), 2.93–3.02 (m, 1H), 3.12–3.20 (m, 1H), 3.56 (dd, J=9.5, 2.4 Hz, 1 H), 3.72 (d, J=2.4 Hz, 1 H), 3.94 (d, J=10.0 Hz, 1 H), 4.07 (dt, J=7.1, 2.2 Hz, 1 H), 4.15 (dd, J=9.5, 5.6 Hz, 1 H), 4.55 (ddd, J=10.7, 10.0, 2.2 Hz, 1 H), 5.18 (d, J=5.6 Hz, 1 H), 7.34 (d, J=10.7 Hz, 1 H).

7(S)-7-Acetylthio-7-deoxylincomycin (34). To a solution of compound **33** (10.6 g, 16 mmol) in MeOH (50 ml) was added 2 N HCl (39 ml) and stirred at room temperature for 10 min. The mixture was diluted with 10% aq $NaHCO_3$ (30 ml) and concentrated under reduced pressure. The resulting residue was diluted with EtOAc and washed with 10% aq NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (EtOAc/methanol=19/1) to obtain the title compound as a colorless solid (7.05 g, 97%). ESI-MS (*m/z*) 465 $(M+H)^+$ as $C_{20}H_{36}N_2O_6S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{20}H_{36}N_2O_6S_2$: 465.2093, found: 465.2092; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–0.95 (m, 3 H), 1.22–1.42 (m, 7 H), 1.82–2.13 (m, 7 H), 2.35–2.44 (m, 7 H), 2.72 (d, J=10.0 Hz, 1 H), 3.05 (dd, J=10.5, 4.6 Hz, 1 H), 3.19–3.28 (m, 1 H), 3.46–3.56 (m, 1 H), 3.61 (br s, 1H), 3.94 (d, J=10.2 Hz, 1 H), 4.11 (dd, J=10.5, 4.6 Hz, 1 H), 4.17 (dq, J=7.1, 2.4 Hz, 1 H), 4.25 (ddd, J=10.2, 9.5, 2.4 Hz, 1 H), 5.07 (d, J=2.9 Hz, 1 H), 5.31 (d, J=5.6 Hz, 1 H), 7.79 (d, J=9.5 Hz, 1 H).

7(S)-7-Deoxy-7-mercaptolincomycin (35). To a solution of compound **34** (7.05 g, 15.2 mmol) in MeOH (50 ml) was added sodium methoxide (2.46 g, 45.5 mmol) and stirred at room temperature for 20 min. The mixture was diluted with saturated aq NH_4Cl and concentrated under reduced pressure. The resulting residue was diluted with EtOAc and washed with 10% aq $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/28% aq NH_4OH=95/5/0.1) to obtain the title compound as a colorless solid (6.06 g, 94%). $[\alpha]_D^{26}$ +152.6° (*c* 0.98, MeOH); ESI-MS (*m/z*) 423 $(M+H)^+$ as $C_{18}H_{34}N_2O_5S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{18}H_{34}N_2O_5S_2$: 423.1987, found: 423.1987; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.96 (m, 3 H), 1.28 (d, J=7.1 Hz, 3 H), 1.28–1.41 (m, 4 H), 1.81–1.93 (m, 1 H), 1.96–2.05 (m, 1 H), 2.06–2.23 (m, 2 H), 2.17 (s, 3 H), 2.43 (s, 3 H), 3.02 (dd, J=10.8, 4.6 Hz, 1 H), 3.25 (dd, J=8.3, 5.6 Hz, 1 H), 3.54 (dd, J=10.2, 3.3 Hz, 1 H), 3.58 (dq, J=7.1, 2.0 Hz, 1 H), 3.70 (br dd, J=3.3,

0.6 Hz, 1 H), 4.04 (br dd, J = 10.0, 0.6 Hz, 1 H), 4.09 (dd, J = 10.2, 5.7 Hz, 1 H), 4.26 (dd, J = 10.0, 2.0 Hz, 1 H), 5.25 (d, J = 5.7 Hz, 1 H).

7(S)-7-Deoxy-7-(4-(methoxy-N-propylacetamido)phenylthio)lincomycin (36). To a solution of compound **35** (70 mg, 0.17 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) (9.7 mg, 0.017 mmol) and tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) (7.6 mg, 0.0084 mmol) in 1,4-dioxane (1 ml) were added *N*-(4-bromophenyl)-2-methoxy-*N*-propylacetamide (94.7 mg, 0.33 mmol) and *N,N*-diisopropylethylamine (0.06 ml, 0.33 mmol) and refluxed for 6 h. The mixture was diluted with saturated aq $NaHCO_3$ (15 ml), then extracted with EtOAc, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq NH_4OH = 9/2/0.2) to obtain the title compound as a colorless solid (79.0 mg, 76%). $[\alpha]_D^{30}$ +83.2° (*c* 2.21, MeOH); ESI-MS (*m/z*) 628 $(M+H)^+$ as $C_{30}H_{49}N_3O_7S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{30}H_{49}N_3O_7S_2$: 628.3090, found: 628.3086; ^{1}H NMR (400 MHz, CD_3OD) δ 0.90 (t, J = 7.5 Hz, 3 H), 0.88–0.97 (m, 3 H), 1.32–1.42 (m, 4 H), 1.36 (d, J = 6.9 Hz, 3 H), 1.52 (sxt, J = 7.4 Hz, 2 H), 1.82–1.97 (m, 1 H), 1.93 (s, 3 H), 2.03 (ddd, J = 12.7, 7.6, 5.0 Hz, 1 H), 2.08–2.26 (m, 2 H), 2.45 (s, 3 H), 3.06 (dd, J = 10.5, 4.8 Hz, 1 H), 3.23–3.30 (m, 4 H), 3.58 (dd, J = 10.2, 3.2 Hz, 1 H), 3.61–3.68 (m, 2 H), 3.72–3.80 (m, 3 H), 3.94 (dq, J = 6.9, 2.6 Hz, 1 H), 4.11 (dd, J = 10.2, 5.6 Hz, 1 H), 4.35 (br d, J = 9.7, 0.5 Hz, 1 H), 4.49 (dd, J = 9.7, 2.6 Hz, 1 H), 5.27 (d, J = 5.6 Hz, 1 H), 7.20–7.27 (m, 2 H), 7.46–7.52 (m, 2 H).

7(S)-7-Deoxy-7-(4-((S)-2-methoxymethylpyrrolidinocarbonyl)phenylthio)lincomycin (37). Compound **35** (70 mg, 0.17 mmol) and (*S*)-(4-bromophenyl)(2-(methoxymethyl)pyrrolidin-1-yl)methanone (98.7 mg, 0.33 mmol) were treated according to the similar procedure as described for the preparation of **36** to afford **37** (84.0 mg, 79%) as a colorless solid. $[\alpha]_D^{31}$ +46.2° (*c* 1.85, MeOH); ESI-MS (*m/z*) 640 $(M+H)^+$ as $C_{31}H_{49}N_3O_7S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{31}H_{49}N_3O_7S_2$: 640.3090, found: 640.3092; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.97 (m, 3 H), 1.29–1.40 (m, 4 H), 1.36 (d, J = 6.8 Hz, 3 H), 1.69–1.81 (m, 1 H), 1.81–1.90 (m, 1 H), 1.91 (s, 3 H), 1.90–2.27 (m, 7 H), 2.42 (s, 3 H), 3.02 (dd, J = 10.6, 4.8 Hz, 1 H), 3.04–3.14 (m, 1 H), 3.27 (dd, J = 8.1, 5.7 Hz, 1 H), 3.39 (s, 3 H), 3.46–3.67 (m, 4 H), 3.78 (br dd, J = 3.2, 0.6 Hz, 1 H), 3.97 (dq, J = 6.8, 2.6 Hz, 1 H), 4.10 (dd, J = 10.2, 5.6 Hz, 1 H), 4.36 (br d, J = 9.7 Hz, 1 H), 4.49 (dd, J = 9.7, 2.6 Hz, 1 H), 5.26 (d, J = 5.6 Hz, 1 H), 7.41–7.50 (m, 4 H).

7(S)-7-Deoxy-7-(4-((S)-2-dimethylaminomethylpyrrolidinocarbonyl)phenylthio) lincomycin (38). Compound **35** (70 mg, 0.17 mmol) and (*S*)-(4-bromophenyl)(2-((dimethylamino)methyl)pyrrolidin-1-yl)methanone (103.7 mg, 0.33 mmol) were treated according to the similar procedure as described for the preparation of **36** to afford **38** (90.0 mg, 82%) as a colorless solid. $[\alpha]_D^{31}$ +33.2° (*c* 2.39, MeOH); ESI-MS (*m/z*) 653 $(M+H)^+$ as $C_{32}H_{52}N_4O_6S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{32}H_{52}N_4O_6S_2$: 653.3407, found: 653.3399; ^{1}H NMR (400 MHz, CD_3OD) δ 0.86-0.97 (m, 3 H), 1.25-1.42 (m, 7 H), 1.75–2.25 (m, 13 H), 2.38 (s, 6 H), 2.41 (s 3 H), 2.76 (br dd, J = 11.7, 3.2 Hz, 1 H), 3.00 (dd, J = 10.6, 4.8 Hz, 1 H), 3.26 (dd, J = 8.2, 5.9 Hz, 1 H), 3.35–3.46 (m, 1 H), 3.48–3.68 (m, 2 H), 3.75–3.80 (m, 1 H), 3.92–4.20 (m, 1 H), 4.10 (dd, J = 10.1, 5.6 Hz, 1 H), 4.35 (d, J = 9.7 Hz, 1 H), 4.49 (dd, J = 9.7, 2.6 Hz, 1 H), 5.26 (d, J = 5.6 Hz, 1 H), 7.40–7.53 (m, 4 H).

7(S)-7-Deoxy-7-(4-(1,4-oxazepane-4-carbonyl)phenylthio)lincomycin (39). Compound **35** (70 mg, 0.17 mmol) and (4-bromophenyl)(1,4-oxazepan-4-yl) methanone (49.0 mg, 0.17 mmol) were treated according to the similar procedure as described for the preparation of **36** to afford **39** (79.0 mg, 73%) as a colorless solid. $[\alpha]_D^{31}$ +74.3° (*c* 3.26, MeOH); ESI-MS (*m/z*) 626 $(M+H)^+$ as $C_{30}H_{47}N_3O_7S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{30}H_{47}N_3O_7S_2$: 626.2934, found: 626.2934; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.97 (m, 3 H), 1.28–1.41 (m, 4 H), 1.35 (d, J = 6.8 Hz, 3 H), 1.75–1.91 (m, 2 H), 1.92 (s, 3 H), 1.94–2.06 (m, 2 H), 2.07–2.26 (m, 2 H), 2.43 (s, 3 H), 3.04 (dd, J = 10.6, 4.8 Hz, 1 H), 3.28 (dd, J = 5.6, 2.4 Hz, 1 H), 3.49–3.57 (m, 2 H), 3.58 (dd, J = 10.1, 2.3 Hz, 1 H), 3.67 (br t, J = 4.9 Hz, 1 H), 3.73–3.88 (m, 6 H), 3.96 (dq, J = 6.8, 2.5 Hz, 1 H), 4.10 (dd, J = 10.1, 5.6 Hz, 1 H), 4.35 (br d, J = 9.7 Hz, 1 H), 4.49 (dd, J = 9.7, 2.5 Hz, 1 H), 5.26 (d, J = 5.6 Hz, 1 H), 7.34–7.42 (m, 2 H), 7.43–7.52 (m, 2 H).

7(S)-7-Deoxy-7-(4-morpholinomethylphenylthio)lincomycin (40). Compound **35** (70 mg, 0.17 mmol) and 4-(4-bromobenzyl)morpholine (84.8 mg, 0.33 mmol) were treated according to the similar procedure as described for the preparation of **36** to afford **40** (74.0 mg, 75%) as a colorless solid. $[\alpha]_D^{28}$ +98.2° (*c* 2.63, MeOH); ESI-MS (*m/z*) 598 $(M+H)^+$ as $C_{29}H_{47}N_3O_6S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{29}H_{47}N_3O_6S_2$: 598.2985, found: 598.2983; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88–0.97 (m, 3 H), 1.28 (d, J = 6.9 Hz, 3 H), 1.29–1.41 (m, 4 H), 1.80–1.91 (m, 1 H), 1.95–2.04 (m, 1 H), 1.98 (s, 3 H), 2.05–2.12 (m, 1 H), 2.12–2.23 (m, 1 H), 2.35–2.50 (m, 4 H), 2.40 (s, 3 H), 2.99 (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), 3.57 (dd, J = 10.3, 3.2 Hz, 1 H), 3.63–3.71 (m, 4 H), 3.74 (br dd, J = 3.2, 0.5 Hz, 1 H), 3.85 (dq, J = 6.9, 2.6 Hz, 1 H), 4.10 (dd, J = 10.3, 5.5 Hz, 1 H), 4.32 (br dd, J = 9.8, 0.5 Hz, 1 H), 4.41 (dd, J = 9.8, 2.6 Hz, 1 H), 5.26 (d, J = 5.5 Hz, 1 H), 7.28–7.34 (m, 2 H), 7.36–7.43 (m, 2 H).

7(S)-7-Deoxy-7-(2-fluoro-4-morpholinocarbonylphenylthio)lincomycin (41). Compound **35** (190.7 mg, 0.45 mmol) and (4-bromo-3-fluorophenyl)(morpholino)methanone (260 mg, 0.90 mmol) were treated according to the similar procedure as described for the preparation of **36** to afford **41** (232 mg, 82%) as a colorless solid. $[\alpha]_D^{31}$ +82.4° (*c* 8.43, MeOH); ESI-MS (*m/z*) 630 $(M+H)^+$ as $C_{29}H_{44}FN_3O_7S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{29}H_{44}FN_3O_7S_2$: 630.2683, found: 630.2673; ^{1}H NMR (400 MHz, CD_3OD) δ 0.87–0.97 (m, 3 H), 1.30 (d, J = 6.9 Hz, 3 H), 1.28–1.92 (m, 4 H), 1.79–1.92 (m, 1 H), 1.98 (s, 3 H), 1.98–2.05 (m, 1 H), 2.06–2.13 (m, 1 H), 2.13–2.26 (m, 1 H), 2.42 (s, 3 H), 3.01 (dd, J = 10.6, 4.7 Hz, 1 H), 3.27 (dd, J = 8.3, 5.7 Hz, 1 H), 3.35–3.82 (m, 10 H), 4.01 (dq, J = 6.9, 2.7 Hz, 1 H), 4.10 (dd, J = 10.2, 5.5 Hz, 1 H), 4.32 (br dd, J = 9.7, 0.4 Hz, 1 H), 4.49 (dd, J = 9.7, 2.7 Hz, 1 H), 5.26 (d, J = 5.5 Hz, 1 H), 7.22–7.28 (m, 2 H), 7.55–7.62 (m, 1 H).

7(S)-7-Deoxy-7-(3-fluoro-4-morpholinocarbonylphenylthio)lincomycin (42). Compound **35** (187 mg, 0.44 mmol) and (4-bromo-2-fluorophenyl)(morpholino)methanone (255 mg, 0.89 mmol) were treated according to the similar procedure as described for the preparation of **36** to afford **42** (227 mg, 81%) as a colorless solid. $[\alpha]_D^{31}$ +73.4° (*c* 5.35, MeOH); ESI-MS (*m/z*) 630 $(M+H)^+$ as $C_{29}H_{44}FN_3O_7S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{29}H_{44}FN_3O_7S_2$: 630.2683, found: 630.2685; ^{1}H NMR (400 MHz, CD_3OD) δ 0.87–0.96 (m, 3 H), 1.27–1.38 (m, 4 H), 1.39 (d, J = 6.8 Hz, 3 H), 1.79–1.89 (m, 1 H), 1.92 (s, 3 H), 1.96–2.12 (m, 2 H), 2.12–2.26 (m, 1 H), 2.40 (s, 3 H), 2.99 (dd, J = 10.6, 4.8 Hz, 1 H), 3.25 (dd, J = 8.4, 5.9 Hz, 1 H), 3.31–3.40 (m, 2 H), 3.57 (dd, J = 10.1, 3.2 Hz, 1 H), 3.59–3.66 (m, 2 H), 3.70–3.81 (m, 5 H), 3.99 (dq, J = 6.8, 2.8 Hz, 1 H), 4.11 (dd, J = 10.1, 5.6 Hz, 1 H), 4.33 (br dd, J = 9.6, 0.4 Hz, 1 H), 4.52 (dd, J = 9.6, 2.8 Hz, 1 H), 5.27 (d, J = 5.6 Hz, 1 H), 7.24 (dd, J = 10.2, 1.5 Hz, 1 H), 7.27–7.32 (m, 1 H), 7.33–7.39 (m, 1 H).

7(S)-7-Deoxy-7-(4-morpholinocarbonyl-3-nitrophenylthio)lincomycin (43). Compound **35** (70 mg, 0.17 mmol) and (4-bromo-2-nitrophenyl)(morpholino)methanone (104 mg, 0.33 mmol) were treated according to the similar procedure as described for the preparation of **36** to afford **43** (87.0 mg, 80%) as a colorless solid. $[\alpha]_D^{31}$ +60.4° (*c* 2.62, MeOH); ESI-MS (*m/z*) 657 $(M+H)^+$ as $C_{29}H_{44}N_4O_9S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{29}H_{44}N_4O_9S_2$: 657.2628, found: 657.2632; ^{1}H NMR (400 MHz, CD_3OD) δ 0.87–0.97 (m, 3 H), 1.28–1.39 (m, 4 H), 1.41 (d, J = 6.9 Hz, 3 H), 1.79–1.90 (m, 1 H), 1.93 (s, 3 H), 1.97–2.12 (m, 2 H), 2.13–2.26 (m, 1 H), 2.41 (s, 3 H), 3.00 (dd, J = 10.6, 4.8 Hz, 1 H), 3.20–3.34 (m, 3 H), 3.57 (dd, J = 10.2, 3.2 Hz, 1 H), 3.62 (t, J = 4.8 Hz, 2 H), 3.67–3.88 (m, 5 H), 4.04 (dq, J = 6.9, 2.9 Hz, 1 H), 4.10 (dd, J = 10.2, 5.6 Hz, 1 H), 4.35 (br dd, J = 9.5, 0.7 Hz, 1 H), 4.55 (dd, J = 9.5, 2.9 Hz, 1 H), 5.26 (d, J = 5.6 Hz, 1 H), 7.45 (d, J = 8.0 Hz, 1 H), 7.81 (dd, J = 8.0, 1.8 Hz, 1 H), 8.16 (d, J = 1.8 Hz, 1 H).

7(S)-7-Deoxy-7-(3-methyl-4-morpholinocarbonylphenylthio)lincomycin (44). Compound **35** (70 mg, 0.17 mmol) and (4-bromo-2-methylphenyl)(morpholino)methanone (94.1 mg, 0.33 mmol) were treated according to the similar procedure as described for the preparation of **36** to afford **44** (81 mg, 78%) as a colorless solid. $[\alpha]_D^{29}$ +81.7° (*c* 2.65, MeOH); ESI-MS (*m/z*) 626 $(M+H)^+$ as $C_{30}H_{47}N_3O_7S_2$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{30}H_{47}N_3O_7S_2$: 626.2934, found: 626.2925; ^{1}H NMR (400 MHz, CD_3OD) δ 0.89–0.97 (m, 3 H), 1.26–1.42 (m, 4 H), 1.33 (d, J = 6.8 Hz, 3 H), 1.80–1.91 (m, 1 H), 1.95 (s, 3 H), 2.01 (ddd, J = 12.8, 7.9, 4.7 Hz, 1 H), 2.06–2.13

(m, 1 H), 2.13–2.24 (m, 1 H), 2.28 (s, 3 H), 2.42 (s, 3 H), 3.00 (dd, $J=10.6$, 4.6 Hz, 1 H), 3.21–3.29 (m, 3 H), 3.53–3.64 (m, 3 H), 3.68–3.82 (m, 5 H), 3.93 (dq, $J=6.8$, 2.7 Hz, 1 H), 4.10 (dd, $J=10.2$, 5.6 Hz, 1 H), 4.32 (br dd, $J=9.7$, 0.5 Hz, 1 H), 4.46 (dd, $J=9.7$, 2.7 Hz, 1 H), 5.26 (d, $J=5.6$ Hz, 1 H), 7.16 (d, $J=7.8$ Hz, 1 H), 7.27–7.34 (m, 2 H).

7(S)-7-Deoxy-7-(5-morpholinocarbonylthiophen-2-ylthio)lincomycin (45). Compound **35** (90.4 mg, 0.21 mmol) and (5-bromothiophen-2-yl)(morpholino)methanone (69 mg, 0.21 mmol) were treated according to the similar procedure as described for the preparation of **36** to afford **45** (100 mg, 76%) as a colorless solid. $[\alpha]_D^{29}$ +102.9° (*c* 2.49, MeOH); ESI-MS (*m/z*) 618 $(M+H)^+$ as $C_{27}H_{43}N_3O_7S_3$; TOF-ESI-HR-MS $(M+H)^+$ calcd for $C_{27}H_{43}N_3O_7S_3$: 618.2341, found: 618.2347; ^{1}H NMR (400 MHz, CD_3OD) δ 0.87–0.96 (m, 3 H), 1.25–1.40 (m, 4 H), 1.33 (d, $J=7.0$ Hz, 3 H), 1.78–1.89 (m, 1 H), 1.99 (ddd, $J=12.8$, 7.9, 4.7 Hz, 1 H), 2.02–2.09 (m, 1 H), 2.11–2.23 (m, 1 H), 2.17 (s, 3 H), 2.37 (s, 3 H), 2.98 (dd, $J=10.6$, 4.8 Hz, 1 H), 3.22 (dd, $J=8.4$, 5.9 Hz, 1 H), 3.58 (dd, $J=10.3$, 3.2 Hz, 1 H), 3.66–3.79 (m, 10 H), 4.11 (dd, $J=10.3$, 5.6 Hz, 1 H), 4.34 (br dd, $J=9.6$, 0.6 Hz, 1 H), 4.42 (dd, $J=9.6$, 3.0 Hz, 1 H), 5.29 (d, $J=5.6$ Hz, 1 H), 7.18 (d, $J=3.8$ Hz, 1 H), 7.32 (d, $J=3.8$ Hz, 1 H).

In vitro antibacterial activity

MIC ($\mu g\,ml^{-1}$) 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 (BHIA; 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' (SDA; Nissui, Tokyo, Japan), 5% defibrinated horse blood, 5 $\mu g\,ml^{-1}$ Hemin and 15 $\mu g\,ml^{-1}$ NAD. A 5 µl portion of cell suspension of the test strains having about 10^6 CFU per ml was inoculated into SDA supplemented with 5% defibrinated horse blood, 5 $\mu g\,ml^{-1}$ Hemin and 15 $\mu g\,ml^{-1}$ NAD, and incubated at 37 °C for 18–22 h. Then, MIC was measured.

Docking simulation of the key compound 28

Docking simulation was performed with Insight II (Accelrys, San Diego, CA, USA) using CHARMm force fields. The crystal structure of azithromycin bound to the 50S ribosomal subunit from *Haloarcula marismortui* (PDB entry 1M1K)[7] was used for the docking template. In preparation for docking simulation, the azithromycin and the RNA residues other than around the ligand binding site were removed from the template. In docking simulation, **28** was manually placed in the ligand binding site refer to crystal structure of CLDM bound to the 50S ribosomal subunit from *Haloarcula marismortui* (PDB entry 1YJN),[6] and minimized in the template.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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