ORIGINAL ARTICLE

Synthesis and antibacterial activity of novel lincomycin derivatives. III. Optimization of a phenyl thiadiazole moiety

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Lincomycin derivatives that have a 5-(2-nitrophenyl)-1,3,4-thiadiazol-2-yl thio moiety at the 7-position were synthesized. 5-Substituted 2-nitrophenyl derivatives showed potent antibacterial activities against *Streptococcus pneumoniae* and *Streptococcus pyogenes* with *erm* gene. Antibacterial activities of the 4,5-di-substituted 2-nitrophenyl derivatives were generally comparable to those of telithromycin (TEL) against *S. pneumoniae* with *erm* gene and clearly superior to those of TEL against *S. pyogenes* with *erm* gene. Compounds 6 and 10c that have a methoxy group at the 5-position of the benzene ring exhibited activities comparable to TEL against *Haemophilus influenzae*. These results suggest that lincomycin derivatives modified at the 7-position would be promising compounds as a clinical candidate. We would like to dedicate this article to the special issue for late Professor Dr. Hamao Umezawa in *The Journal of Antibiotics*.
The Journal of Antibiotics advance online publication, 5 July 2017; doi:10.1038/ja.2017.59

INTRODUCTION

Macrolide antibiotics have been widely used for respiratory infections over many years. Especially, clarithromycin[1] and azithromycin[2] (Figure 1) are clinically important macrolides derived from a natural product, erythromycin (EM). Clarithromycin is distinct from EM in improved pharmacokinetics because of its stability in acidic condition. Azithromycin has a long plasma half-life and good tissue distribution, and shows stronger antibacterial activity than EM against Gram-negative bacteria such as *Haemophilus influenzae*. However, an emergence of macrolide-resistant bacteria, such as *Streptococcus pneumonia*, has been causing serious clinical problems.[3,4] Ketolides, such as TEL,[5] cethromycin,[6] solithromycin[7] and nafithromycin[8] (Figure 1), newly developed/derived from natural EM, show antibacterial activities against resistant pathogens. Much effort has been made to launch ketolides, which were effective against macrolide-resistant bacteria, but only TEL has been marketed so far. Its safety problems,[9] however, make it difficult to be used in the clinical site. Another promising class is 16-membered azalides[10] that are effective against resistant *S. pneumoniae* and *S. pyogenes* with *erm* gene. These compounds, however, are still under research process and have not entered clinical phase. Thus, currently there is no clinically available drug that is effective against resistant *S. pneumoniae* with *erm* and *mef* genes and free of safety or taste problem.

Lincomycin (LCM)[11] was produced by *Streptomyces lincolnensis* and has been used as antibacterial agent mainly against Gram-positive bacteria. Chemical modification of LCM led to clindamycin (CLDM)[12] that has an enhanced antibacterial activity against

S. pneumoniae and an improved pharmacokinetic profile (Figure 2). Lincosamide antibiotics inhibit protein synthesis acting on 50S ribosome in a similar way to macrolide antibiotics. This similar mode of action led to cross-resistance against clinically problematic *S. pneumoniae* and *S. pyogenes* with *erm* gene.[13] Thus, CLDM shows almost no antibacterial activity against these resistant pathogens as shown in Table 1. CLDM, however, is attractive because of its safety and effectiveness against resistant pathogens with efflux pump. On the other hand, macrolide antibiotics, including ketolides, are influenced by efflux pumps of resistant *S. pneumoniae* and *S. pyogenes* with *mef* gene. In addition, CLDM has no gastrointestinal side effect based on the mode of action of a motilin receptor known in EM.[14] As a rare case, furthermore, CLDM has been reported to be effective for invasive group A streptococcal infections caused by *S. pyogenes*.[15] A simple chemical structure of CLDM compared with that of macrolide is a positive characteristic, too. On the basis of these reasons, we initiated chemical modifications of lincosamide in order to generate a novel antibacterial agent that is effective against resistant *S. pneumoniae* and *S. pyogenes* with *erm* and *mef* genes.

The crystal structures of bacterial 23S ribosomal RNA complexed with CLDM showed that the sugar moiety of CLDM had several hydrogen bonding and played a pivotal role in its binding mode.[16] On the other hand, a hydrophobic space was observed around the C-7 position of CLDM in X-ray crystallographic analysis. It is known that modifications at the C-7 position of LCM tend to give comparable antibacterial activity to that of LCM.[17,18] We reported chemical modifications of LCM and clarified
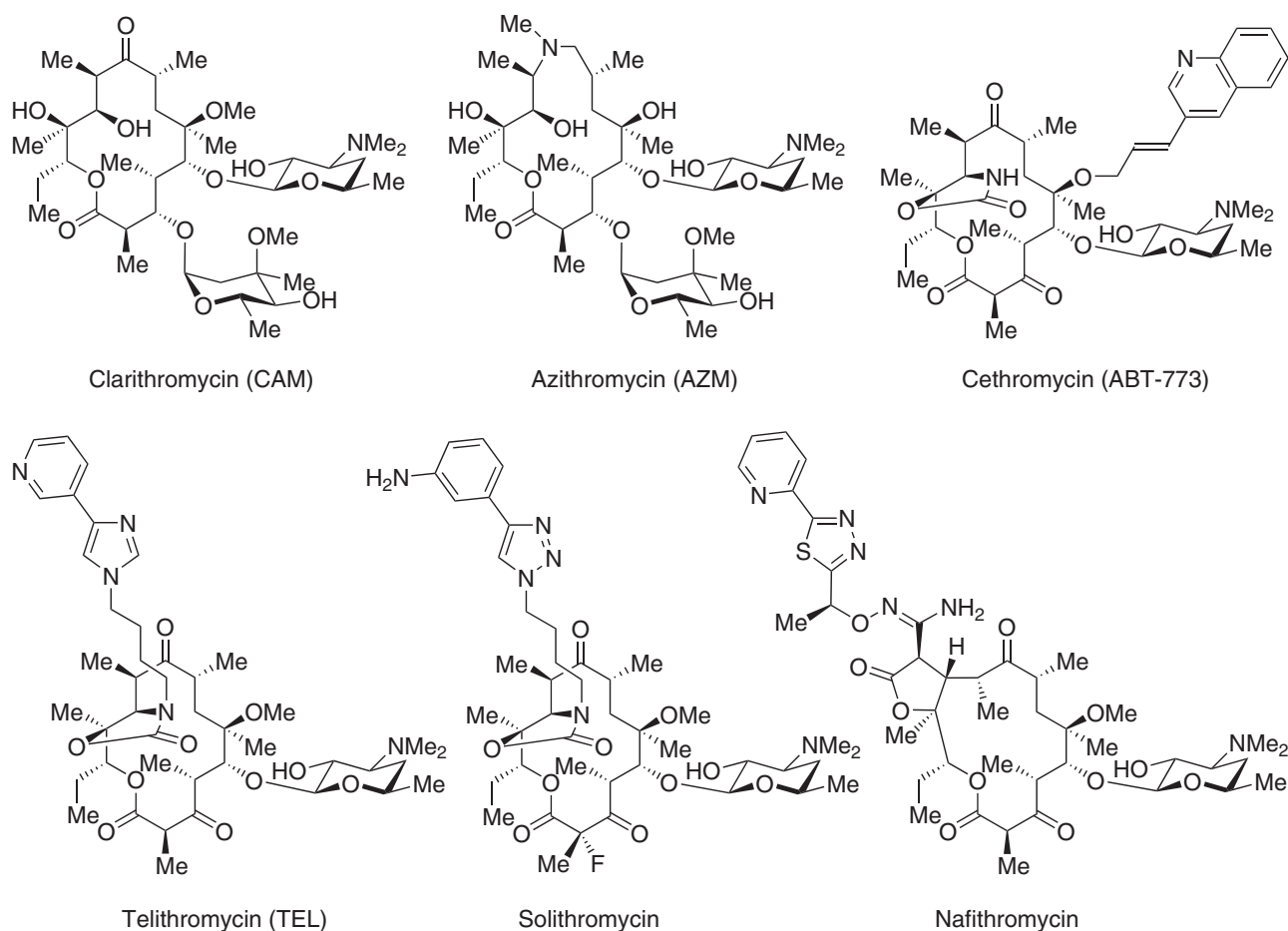
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Figure 1 Clinically important macrolides, clarithromycin and azithromycin, and representative novel ketolides.
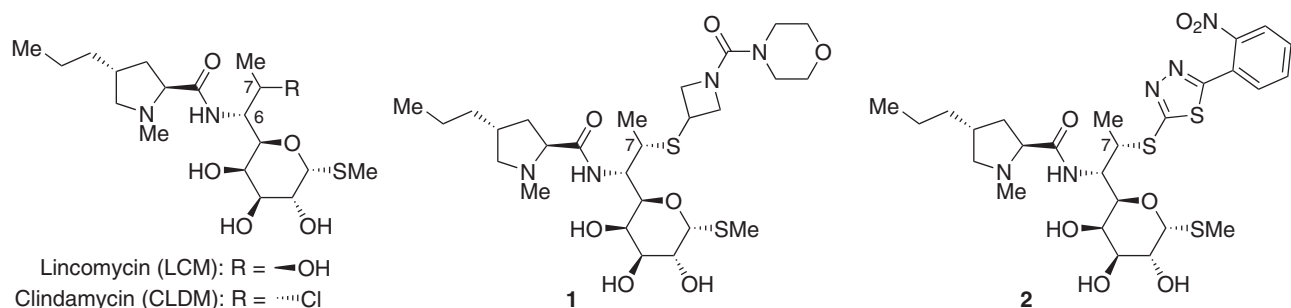

Figure 2 Structures of LCM, CLDM, compounds **1** and **2**.

that (7S)-7-arylthio-7-deoxylincomycin derivatives[19–22] and (7S)-7-(azetidin-3-yl-thio)-7-deoxylincomycin derivatives[23] exhibited moderate to strong antibacterial activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene. Compound **1** that has a substituted azetidin-3-yl-thio moiety at the 7-position exhibited moderate antibacterial activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene. Compound **2** that tethered a phenyl thiadiazol-2-yl thio moiety to the 7-position showed antibacterial activities against those resistant pathogens. The *ortho* nitro group of **2** played a key role for the enhancement of antibacterial activity of *S. pneumoniae* with *erm* gene.[22] In this article, we report further optimization of the phenyl moiety of **2** in order to achieve potent antibacterial activity against *S. pneumoniae* and *S. pyogenes* with *erm* gene.

Chemistry

Introductions of a substituent at the 4- and 5-positions of the 2-nitrophenyl group using a nucleophilic aromatic substitution (SNAr) reaction of fluoro-benzene and a nucleophile were planned. Mono-fluoro compounds **4a** and **4b**, and difluoro compound **4c** were prepared by our method reported previously, which was the Mitsunobu reaction of 2, 3, 4-tris-O-(trimethylsilyl) lincomycin (**3**)[24] and the corresponding thiols followed by acidic treatment (Scheme 1). A major reason of relatively low yield of these Mitsunobu reactions was explained by generation of an N-connected byproduct in the thiadiazole moiety instead of the desired S-connected derivative. Compound **6** was synthesized by an SNAr reaction of (7S)-7-deoxy-7-mercaptolincomyicn (**5**)[21] and

Table 1 Antibacterial activities of LCM, CLDM and our reported LCM derivatives (MIC; μg ml^{-1})^a

| No.	Test organism^b	Characteristics	LCM	CLDM	*1*	*2*
1	*Streptococcus pneumoniae* DP1 TypeI	Susceptible	1	0.13	0.13	0.06
2	*S. pneumoniae* #2	Susceptible	1	0.13	0.13	0.06
3	*S. pneumoniae* #3	Susceptible	0.25	0.13	0.13	0.13
4	*S. pneumoniae* #4	*ermB* methylase (c)	>128	>128	16	4
5	*S. pneumoniae* #5	*ermB* methylase (c)	>128	>128	8	8
6	*S. pneumoniae* #6	*ermB* methylase (c) + *mefE*	>128	>128	16	64
7	*S. pneumoniae* #7	*ermB* methylase (i)	128	>128	8	4
8	*S. pneumoniae* #8	*ermB* methylase (i)	128	>128	ND	4
9	*S. pneumoniae* #9	*mefE* efflux	1	0.13	0.13	0.06
10	*S. pneumoniae* #10	*mefE* efflux	1	0.13	0.13	0.06
11	*Streptococcus pyogenes* Cook	Susceptible	0.13	0.13	0.13	0.06
12	*S. pyogenes* #2	*ermB* methylase (c)	>128	>128	4	4
13	*S. pyogenes* #3	*mefE* efflux	0.25	0.13	0.13	0.13
14	*Haemophilus influenzae* #1	Susceptible	8	8	4	16
15	*H. influenzae* #2	Susceptible	16	8	8	8
16	*H. influenzae* #3	Susceptible	16	32	16	64

Abbreviations: c, constitutive; i, inducible; CLDM, clindamycin; LCM, lincomycin.
^{a}Gray shading strains are target strains.
^{b}All strains except standard organisms were clinically isolated.
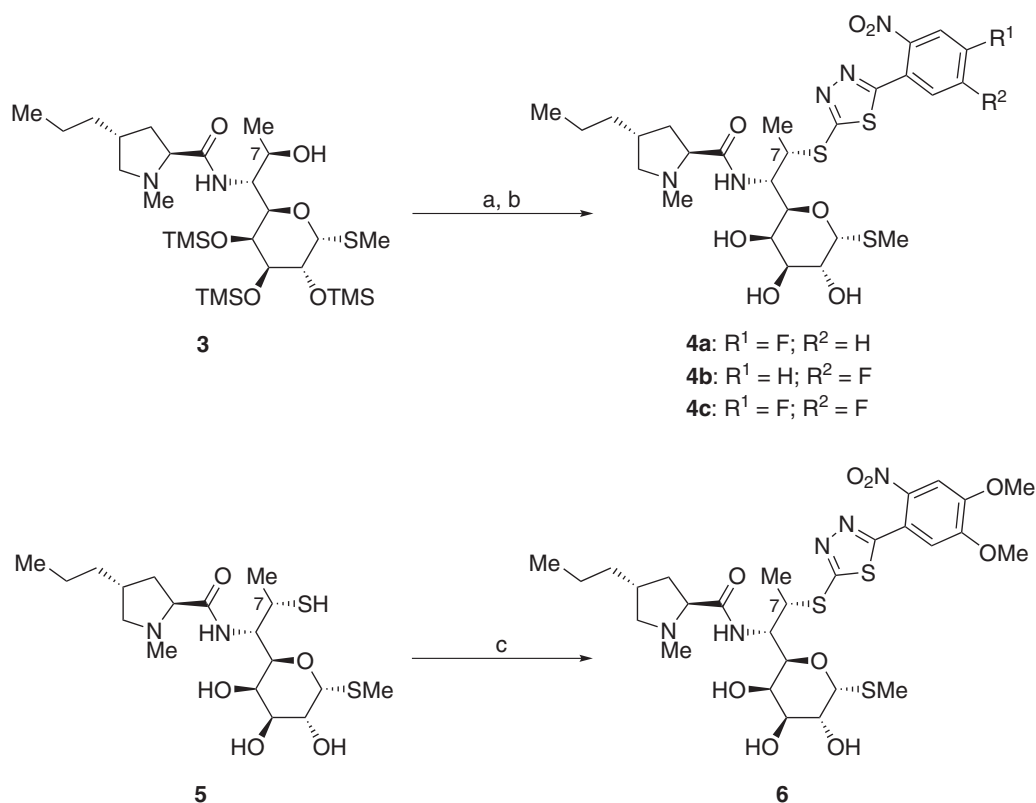
Scheme 1 Synthesis of (7S)-7-(5-phenyl-1,3,4-thiadiazol-2-yl-thio)-7-deoxylincomycin derivatives. Reagents: (a) ArSH, DEAD, PPh$_3$, toluene, 0 °C, 30 min, then rt, 3 h; (b) 1 N HCl, MeOH, rt, 30 min, two steps 34% from **3** to **4a**, two steps 19% from **3** to **4b**, two steps 33% from **3** to **4c**; (c) 2-(4,5-dimethoxy-2-nitrophenyl)-5-(methylsulfonyl)-1,3,4-thiadiazole, NaHMDS, DMF, rt, 20 min, 67%.

2-(4,5-dimethoxy-2-nitrophenyl)-5-(methylsulfonyl)-1,3,4-thiadiazole. The derivatization of **4a**, **4b** and **4c** is shown in Scheme 2. Compound **7a** that has a 4-dimethylamino group was obtained from 4-fluoro compound **4a**. Synthesis of 2-nitro-4-methoxy derivative using sodium methoxide and **4a** was unsuccessful probably because of poor reactivity of 4-fluoro atom in **4a**. Treatment of 5-fluoro compound **4b** with amines, such as dimethylamine and methylamine, gave **7b** and **8b** in good yields. Compounds **7c**, **8c** and **9c** were obtained from 4,5-difluoro compound **4c** in the similar way to **4b**. Methoxy derivatives **10b** and **10c** were prepared by reaction of sodium methoxide with **4b** and **4c**, respectively.
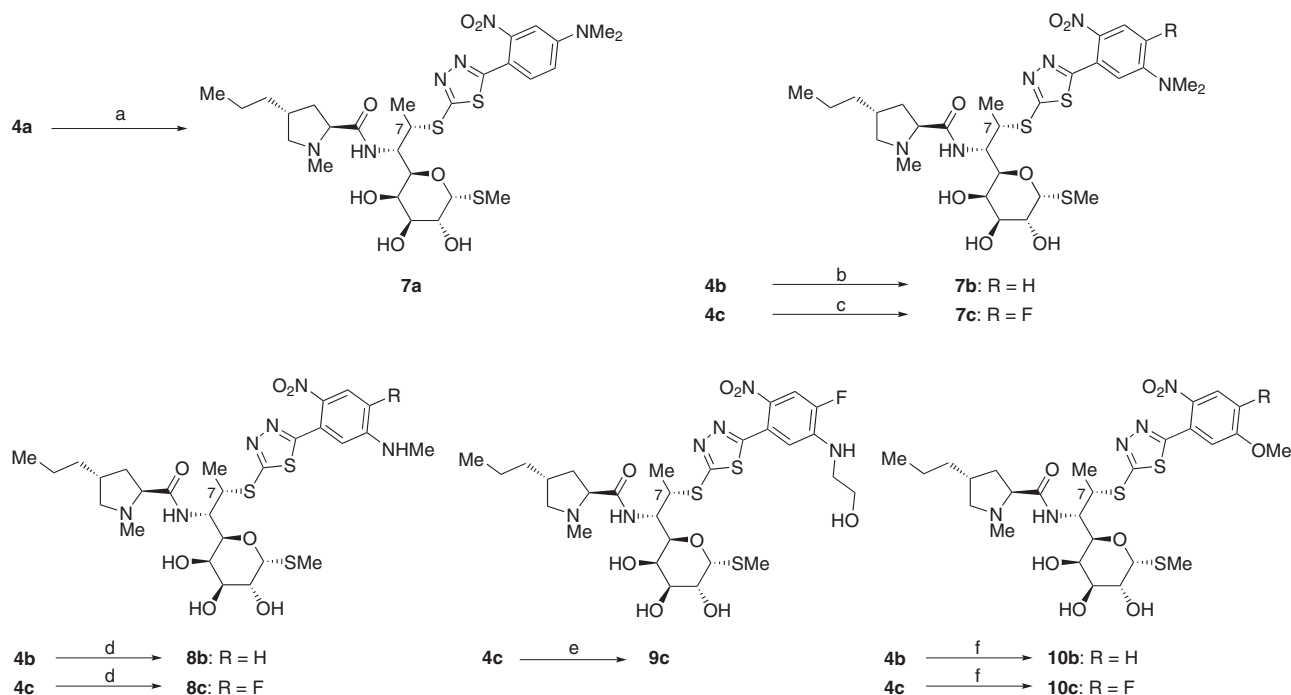
Scheme 2 Synthesis of (7*S*)-7-(5-phenyl-1,3,4-thiadiazol-2-yl-thio)-7-deoxylincomycin derivatives. Reagents: (a) 2*M* dimethylamine in methanol, 80 °C, 16 h, 81%; (b) 2*M* dimethylamine in methanol, rt, 1 h, 87%; (c) 2*M* dimethylamine in methanol, 50 °C, 3.5 h, 87%; (d) 40% methylamine in methanol, rt, 1 h, 75% from **4b** to **8b**, 98% from **4c** to **8c**; (e) 2-aminoethanol, 50 °C, 2 h, 86%; (f) 28% sodium methoxide methanol solution, rt, 64% from **4b** to **10b**, 70% from **4c** to **10c**.

RESULTS AND DISCUSSION

Antibacterial activities of 2,4- or 2,5-di-substituted derivatives are shown in Table 2. 4-Fluoro derivative **4a** showed somehow enhanced antibacterial activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene compared with **2**, and its potency especially against *S. pneumoniae* with *erm* and *mef* gene (strain #6) was clearly enhanced. In contrast, dimethylamino derivative **7a** exhibited enhanced antibacterial activities against susceptible strains of *S. pneumoniae* and *S. pyogenes*, but the effect of the dimethylamino group on antibacterial activity against resistant strains of *S. pneumoniae* (#4–8) was unclear. In the case of 5-fluoro derivative **4b**, the antibacterial activity decreased against almost all of the test organisms. It should be noted that the antibacterial activities of 5-dimethylamino derivative **7b**, 5-methylamino derivative **8b** and 5-methoxy derivative **10b** were significantly improved against all of the Gram-positive pathogens compared with **2**, and showed comparable antibacterial activities against constitutive-resistant *S. pneumoniae* with *erm* gene (#4 and 5) to those of TEL. The antibacterial activities of **7b**, **8b** and **10b** against *S. pyogenes* with *erm* gene were further improved and 32 times stronger than that of TEL. The antibacterial activity of **10b** against *H. influenzae* was also improved compared with **2** but it is still weaker than that of TEL. On the basis of the results obtained above, we performed further optimization focusing on the 4- and 5-substituents on the benzene ring.

Antibacterial activities of 2,4,5-tri-substituted derivatives are shown in Table 3. As expected, compound **7c** that has the 5-dimethylamino group and the 4-fluoro group showed stronger antibacterial activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene as well as *S. pneumoniae* with *erm* and *mef* gene (#6) than 5-dimethylamino derivative **7b** did. Similar antibacterial profiles were confirmed not only in methylamine derivative **8c**, but also **10c** that has a methoxy group at the 5-position of the phenyl group. Furthermore,

4,5-dimethoxy derivative **6** showed an antibacterial profile similar to **10c**. It indicates that electronic property of the substituent at the 4-position is not important for antibacterial activity. Antibacterial activities of the 2,4,5-tri-substituted derivatives (**7c**, **8c**, **10c** and **6**) against *S. pneumoniae* with *erm* gene were generally comparable to those of TEL and they were significantly superior to TEL against *S. pyogenes* with *erm* gene. As for antibacterial activity against *H. influenzae*, **10c** and **6** exhibited generally stronger activities than **7c**, **8c** and **9c** and their activities have been getting closer to those of TEL.

CONCLUSIONS

A series of LCM derivatives that have the 5-(2-nitrophenyl)-1,3,4-thiadiazol-2-yl thio moiety at the 7-position in *S*-configuration were synthesized. Introductions of a substituent at the 4- and 5-positions of the 2-nitrophenyl group were accomplished by the S_NAr reaction of fluoro-benzene **4a**, **4b** or **4c** and a nucleophile. The other method was the S_NAr reaction of (7*S*)-7-deoxy-7-mercaptolincomyicn (**5**)[21] and 5-(methylsulfonyl)-1,3,4-thiadiazole derivative (Scheme 1, condition (c)). From the results of antibacterial activities of 2-nitro-5-substituted phenyl derivatives, the modification led to significant improvement in antibacterial activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene. Moreover, an additional substituent at the 4-position, such as a fluoro atom or a methoxy group, further improved the antibacterial activities of 2-nitro-5-substituted phenyl derivatives against *S. pneumoniae* and *S. pyogenes* with *erm* gene. Antibacterial activities of the 2-nitro-4,5-di-substituted phenyl derivatives (**7c**, **8c**, **10c** and **6**) against *S. pneumoniae* with *erm* gene were generally comparable to those of TEL, and they were significantly superior to TEL against *S. pyogenes* with *erm* gene. Compounds **10c** and **6** that have a methoxy group at the 5-position of the benzene ring exhibited activities comparable to TEL against *H. influenzae*.

Table 2 Antibacterial activities of novel LCM derivatives and telithromycin (MIC; µg ml^{-1})^a

No.	Test organism^b	Characteristics	2	4a	7a	4b	7b	8b	10b	TEL
1	*Streptococcus pneumoniae* DP1 TypeI	Susceptible	0.06	0.06	0.015	0.5	0.015	0.015	0.015	≤0.008
2	*S. pneumoniae* #2	Susceptible	0.06	0.06	0.015	0.5	0.015	0.015	0.015	≤0.008
3	*S. pneumoniae* #3	Susceptible	0.13	0.06	0.015	0.25	0.015	0.015	0.015	≤0.008
4	*S. pneumoniae* #4	*ermB* methylase (c)	4	2	16	16	1	0.5	1	0.5
5	*S. pneumoniae* #5	*ermB* methylase (c)	8	8	4	16	0.5	0.5	1	1
6	*S. pneumoniae* #6	*ermB* methylase (c) + *mefE*	64	8	32	32	4	2	4	1
7	*S. pneumoniae* #7	*ermB* methylase (i)	4	2	2	16	0.5	0.5	0.25	0.06
8	*S. pneumoniae* #8	*ermB* methylase (i)	4	2	2	16	0.25	0.25	0.25	0.06
9	*S. pneumoniae* #9	*mefE* efflux	0.06	0.03	0.015	0.25	≤0.008	≤0.008	≤0.008	0.06
10	*S. pneumoniae* #10	*mefE* efflux	0.06	0.06	0.015	0.25	0.015	≤0.008	≤0.008	0.06
11	*Streptococcus pyogenes* Cook	Susceptible	0.06	0.03	0.015	0.5	0.03	0.015	0.015	0.015
12	*S. pyogenes* #2	*ermB* methylase (c)	4	2	2	16	0.5	0.5	0.5	16
13	*S. pyogenes* #3	*mefE* efflux	0.13	0.06	0.03	0.5	0.03	0.015	0.015	0.5
14	*Haemophilus influenzae* #1	Susceptible	16	8	16	32	8	8	4	0.5
15	*H. influenzae* #2	Susceptible	8	8	16	16	4	4	4	2
16	*H. influenzae* #3	Susceptible	64	64	64	64	16	16	8	1

Abbreviations: c, constitutive; i, inducible; TEL, telithromycin.
^{a}All antibacterial evaluations were performed as hydrochloride. Gray shading strains are target strains.
^{b}All strains except standard organisms were clinically isolated.

Table 3 Antibacterial activities of novel LCM derivatives and telithromycin (MIC; µg ml^{-1})ᵃ

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No.	Test organism[b]	Characteristics	7c	8c	9c	10c	6	TEL
1	*Streptococcus pneumoniae* DP1 TypeI	Susceptible	0.015	≤0.008	0.015	0.015	0.015	≤0.008
2	*S. pneumoniae* #2	Susceptible	0.015	≤0.008	0.015	0.015	0.015	≤0.008
3	*S. pneumoniae* #3	Susceptible	0.03	≤0.008	0.015	0.03	0.015	≤0.008
4	*S. pneumoniae* #4	*ermB* methylase (c)	0.5	0.25	1	ND	0.5	0.5
5	*S. pneumoniae* #5	*ermB* methylase (c)	0.5	0.25	1	0.5	0.25	1
6	*S. pneumoniae* #6	*ermB* methylase (c) + *mefE*	1	1	2	1	1	1
7	*S. pneumoniae* #7	*ermB* methylase (i)	0.13	0.13	0.25	0.25	0.25	0.06
8	*S. pneumoniae* #8	*ermB* methylase (i)	0.13	0.13	0.25	0.25	0.25	0.06
9	*S. pneumoniae* #9	*mefE* efflux	0.015	≤0.008	≤0.008	≤0.008	≤0.008	0.06
10	*S. pneumoniae* #10	*mefE* efflux	0.015	≤0.008	≤0.008	≤0.008	0.015	0.06
11	*Streptococcus pyogenes* Cook	susceptible	0.03	0.015	0.03	0.015	0.03	0.015
12	*S. pyogenes* #2	*ermB* methylase (c)	0.25	0.25	0.5	0.5	0.25	16
13	*S. pyogenes* #3	*mefE* efflux	0.03	0.015	0.03	0.03	0.015	0.5
14	*Haemophilus influenzae* #1	Susceptible	4	4	4	2	2	0.5
15	*H. influenzae* #2	Susceptible	2	2	2	1	2	2
16	*H. influenzae* #3	Susceptible	2	4	4	2	2	1

Abbreviations: c, constitutive; i, inducible; TEL, telithromycin.
ᵃAll antibacterial evaluations were performed as hydrochloride. Gray shading strains are target strains.
ᵇAll strains except standard organisms were clinically isolated.

It is noteworthy that a single modification at the 7-position realized comparable activity to that of TEL against target-resistant pathogens. LCM analogs have a promising framework to overcome the resistant *S. pneumoniae* and *S. pyogenes* with *erm* gene.

EXPERIMENTAL PROCEDURE

General

^{1}H NMR spectra were measured with Varian Gemini-300 (Varian Inc., Palo Alto, CA, USA) for 300 MHz, JEOL JNM-GSX 400 (JEOL Ltd, Tokyo, Japan) for 400 MHz or BRUKER Ascend 400 NMR spectrometer (BRUKER Corporation, Coventry, UK) for 400 MHz in CDCl$_3$ or CD$_3$OD with 0.03% TMS as an internal standard. ^{13}C NMR spectra were measured with BRUKER Ascend 400 NMR spectrometer (BRUKER Corporation) for 100 MHz. Mass spectra were obtained on a JEOL JMS-FABmate spectrometer or 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). The melting points were measured with Yanaco MP-S (Yanaco, Tokyo, Japan). The infrared spectra were measured with Jasco FT/IR-410 (Jasco). Column chromatography was performed with silica gel 60N (Kanto Chemical, Tokyo, Japan, spherical, neutral).

(7S)-7-Deoxy-7-[5-(4-fluoro-2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio]lincomycin (4a)

To a solution of **3** (240 mg, 0.39 mmol) in toluene (5 ml) at 0 °C were added triphenylphosphine (150 mg, 0.57 mmol) and diethylazodicarboxylate (0.10 ml, 0.55 mmol) and stirred at 0 °C for 30 min and 5-(4-fluoro-2-nitrophenyl)-1,3,4-thiadiazole-2-thiol (120 mg, 0.47 mmol) was added and stirred at room temperature for 3 h. The mixture was concentrated under reduced pressure. To the resulting mixture were added methanol (5 ml), 1N hydrochloric acid (0.7 ml) and stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure and the resulting residue was dissolved by water and washed with ethyl acetate. To the mixture was added NaHCO$_3$, and the mixture was extracted with ethyl acetate. The organic phase was concentrated under reduced pressure and the resulting residue was purified by preparative TLC (CHCl$_3$/CH$_3$OH/28% aq NH$_4$OH = 20/1/0.1) to afford **4a** (132 mg, 34%) as colorless solid.

$[\alpha]_D^{22}$ +67° (*c* 0.73, CH$_3$OH); ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.09 (br d, *J* = 9.1 Hz, 1H), 7.69–7.85 (m, 2H), 7.37–7.54 (m, 1H), 5.35 (d, *J* = 5.3 Hz, 1H), 5.21–5.33 (m, 1H), 4.31–4.54 (m, 2H), 4.24 (br d, *J* = 10.2 Hz, 1H), 4.16 (dd, *J* = 9.9, 5.3 Hz, 1H), 3.68–3.83 (m, 1H), 3.58 (dd, *J* = 10.2, 3.3 Hz, 1H), 3.35 (br s, 1H), 3.06–3.22 (m, 1H), 2.41 (s, 3H), 2.18 (s, 3H), 1.83–2.15 (m, 4H), 1.57 (d, *J* = 6.6 Hz, 3H), 1.26–1.42 (m, 4H), 0.81–1.01 (m, 3H); HRMS (ESI) *m/z* calcd for C$_{26}$H$_{37}$FN$_5$O$_7$S$_3$ 646.1834, found 646.1841 (M+H)$^+$.

(7S)-7-Deoxy-7-[5-(5-fluoro-2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio]lincomycin (4b)

Reaction of **3** (690 mg, 1.01 mmol) with 5-(5-fluoro-2-nitrophenyl)-1,3,4-thiadiazole-2-thiol (200 mg, 1.55 mmol) gave **4b** as a colorless solid in 19% yield by a similar procedure to **4a**. $[\alpha]_D^{22}$ +66° (*c* 0.18, CH$_3$OH); ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.09 (d, *J* = 9.2 Hz, 1H), 8.12 (dd, *J* = 9.0, 4.9 Hz, 1H), 7.46 (dd, *J* = 8.1, 2.7 Hz, 1H), 7.36–7.43 (m, 1H), 5.36 (d, *J* = 5.6 Hz, 1H), 5.33 (br s, 1H), 4.33–4.48 (m, 2H), 4.23 (d, *J* = 10.0 Hz, 1H), 4.15 (dd, *J* = 10.0, 5.5 Hz, 1H), 3.71 (br s, 1H), 3.52–3.63 (m, 1H), 3.29–3.37 (m, 1H), 3.10 (dd, *J* = 10.5, 4.6 Hz, 1H), 2.40 (s, 3H), 2.19 (s, 3H), 2.05–2.16 (m, 2H), 1.85–2.02 (m, 2H), 1.58 (d, *J* = 7.0 Hz, 4H), 0.85–0.95 (m, 3H); HRMS (ESI) *m/z* calcd for C$_{26}$H$_{37}$FN$_5$O$_7$S$_3$ 646.1834, found 646.1840 (M+H)$^+$.

(7S)-7-Deoxy-7-[5-(4,5-difluoro-2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio]lincomycin (4c)

Reaction of **3** (240 mg, 0.39 mmol) with 5-(4,5-difluoro-2-nitrophenyl)-1,3,4-thiadiazole-2-thiol gave (140 mg, 0.51 mmol) as a colorless solid in 33% yield by a similar procedure to **4a**. ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.03 (d, *J* = 8.2 Hz, 1H), 7.95–8.04 (m, 1H), 7.59–7.68 (m, 1H), 5.35 (d, *J* = 5.6 Hz, 1H), 5.29 (br s, 1H), 4.29–4.51 (m, 2H), 4.09–4.27 (m, 2H), 3.67–3.78 (m, 1H), 3.57 (dd, *J* = 10.2, 2.7 Hz, 1H), 3.28–3.38 (m, 1H), 3.10 (dd, *J* = 10.2, 4.6 Hz, 1H), 2.40 (s, 3H), 2.17 (s, 3H), 2.03–2.15 (m, 2H), 1.86–2.02 (m, 2H), 1.57 (d, *J* = 7.1 Hz, 3H), 1.27–1.36 (m, 4H), 0.85–0.96 (m, 3H); HRMS (ESI) *m/z* calcd for C$_{26}$H$_{36}$F$_2$N$_5$O$_7$S$_3$ 664.1739, found 664.1735 (M+H)$^+$.

(7S)-7-Deoxy-7-[5-(4,5-dimethoxy-2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio]lincomycin (6)

To a solution of **5**[21] (74 mg, 0.18 mmol) in *N,N*-dimethylformamide (0.5 ml) were added 1 M sodium hexamethyldisilazane tetrahydrofuran solution (0.33 ml) and 2-(4,5-dimethoxy-2-nitrophenyl)-5-(methylsulfonyl)-1,3,4-thiadiazole (63 mg, 0.18 mmol) and the mixture was stirred at room temperature for 20 min. The mixture was diluted with ethyl acetate and washed with water. The organic phase was dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (CHCl$_3$/CH$_3$OH/28% aq NH$_4$OH = 10/1/0.1) to afford **6** (75 mg, 67%) as a colorless solid; MP 222–227 °C (dec.); $[\alpha]_D^{23}$ +65° (*c* 0.20, CH$_3$OH); IR (KBr) 3364.21, 2922.59, 2866.67, 2866.67, 2787.60, 2360.44, 1654.62, 1614.13, 1547.59, 1508.06 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.94 (br d, *J* = 9.0 Hz, 1H), 7.66 (s, 1H), 7.14 (s, 1H), 5.36 (d, *J* = 5.6 Hz, 1H), 5.27 (br s, 1H), 4.36–4.46 (m, 2H), 4.25 (d, *J* = 10.0 Hz, 1H), 4.15 (dd, *J* = 10.2, 5.6 Hz, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.58 (dd, *J* = 10.0, 3.7 Hz, 1H), 3.33 (dd, *J* = 7.7, 5.2 Hz, 1H), 3.09 (dd, *J* = 10.7, 4.4 Hz, 1H), 2.39 (s, 3H), 2.17 (s, 3H), 2.04–2.16 (m, 2H), 1.85–2.01 (m, 2H), 1.57 (d, *J* = 6.8 Hz, 3H), 1.26–1.40 (m, 4H), 0.85–0.94 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 178.94, 164.79, 164.40, 152.80, 150.67, 141.11, 118.40, 113.44, 108.11, 89.01, 71.70, 71.10, 69.37, 68.47, 68.19, 62.60, 56.73, 56.70, 53.15, 44.81, 41.81, 38.13, 38.04, 35.72, 21.59, 18.81, 14.75, 14.29; HRMS (ESI) *m/z* calcd for C$_{28}$H$_{42}$N$_5$O$_9$S$_3$ 688.2139, found 688.2150 (M+H)$^+$.

(7S)-7-Deoxy-7-[5-(4-dimethylamino-2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio]lincomycin (7a)

A solution of **4a** (70 mg, 0.11 mmol) in 2M dimethylamine methanol solution (1.0 ml) was stirred at 80 °C for 16 h in a sealed tube. The mixture was concentrated under reduced pressure and the resulting residue was purified by preparative TLC (CHCl$_3$/CH$_3$OH/28% aq NH$_4$OH = 20/2/0.2) to afford **7a** (59 mg, 81%) as a colorless solid. $[\alpha]_D^{22}$ +69° (*c* 1.0, CH$_3$OH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.20 (d, *J* = 9.0 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.09 (d, *J* = 2.7 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.7 Hz, 1H), 5.39 (br s, 1H), 5.35 (d, *J* = 5.5 Hz, 1H), 4.37–4.45 (m, 1H), 4.23–4.31 (m, 2H), 4.14 (dd, *J* = 10.1, 5.5 Hz, 1H), 3.71 (d, *J* = 3.4 Hz, 1H), 3.57 (dd, *J* = 10.0, 3.4 Hz, 1H), 3.37 (dd, *J* = 8.2, 5.6 Hz, 1H), 3.11 (s, 6H), 3.06–3.11 (m, 1H), 2.38 (s, 3H), 2.19 (s, 3H), 2.04–2.18 (m, 2H), 1.85–2.00 (m, 2H), 1.54 (d, *J* = 7.1 Hz, 3H), 1.29–1.37 (m, 4H), 0.85–0.95 (m, 3H); HRMS (ESI) *m/z* calcd for C$_{28}$H$_{43}$N$_6$O$_7$S$_3$ 671.2350, found 671.2346 (M+H)$^+$.

(7S)-7-Deoxy-7-[5-(5-dimethylamino-2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio]lincomycin (7b)

A solution of **4b** (27 mg, 0.042 mmol) in 2M dimethylamine methanol solution (1.0 ml) was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure and the resulting residue was purified by preparative TLC (CHCl$_3$/CH$_3$OH/28% aq NH$_4$OH = 20/2/0.2) to afford **7b** (24 mg, 87%) as a colorless solid. $[\alpha]_D^{22}$ +73° (*c* 0.70, CH$_3$OH); ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.94 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 9.1 Hz, 1H), 6.69–6.79 (m, 2H), 5.36 (d, *J* = 5.4 Hz, 1H), 5.19–5.34 (m, 1H), 4.34–4.48 (m, 2H), 4.27 (br d, *J* = 10.2 Hz, 1H), 4.15 (dd, *J* = 9.9, 5.4 Hz, 1H), 3.72 (br d, *J* = 3.4 Hz, 1H), 3.59 (dd, *J* = 10.2, 3.4 Hz, 1H), 3.30–3.39 (m, 1H), 3.16 (s, 6H), 3.05–3.13 (m, 1H), 2.40 (s, 3H), 2.18 (s, 3H), 1.86–2.15 (m, 4H), 1.57 (d, *J* = 6.9 Hz, 3H), 1.21–1.42 (m, 4H), 0.85–0.95 (m, 3H); HRMS (ESI) *m/z* calcd for C$_{28}$H$_{43}$N$_6$O$_7$S$_3$ 671.2350, found 671.2346 (M+H)$^+$.

(7S)-7-Deoxy-7-[5-(5-dimethylamino-4-fluoro-2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio]lincomycin (7c)

A solution of **4c** (10 mg, 0.015 mmol) in 2M dimethylamine methanol solution (1.0 ml) was stirred at 50 °C for 3.5 h in a sealed tube. The mixture was concentrated under reduced pressure and the resulting residue was purified by

preparative TLC (CHCl$_3$/CH$_3$OH/28% aq NH$_4$OH = 20/2/0.2) to afford **7c** (9.0 mg, 87%) as a colorless solid. [α]$_D^{23}$ +91° (*c* 0.35, CH$_3$OH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.94 (br d, *J* = 9.0 Hz, 1H), 7.94 (d, *J* = 14.1 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 5.36 (d, *J* = 5.6 Hz, 1H), 5.28 (br d, 1H), 4.36–4.47 (m, 2H), 4.26 (d, *J* = 10.0 Hz, 1H), 4.18–4.23 (m, 1H), 4.15 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.68–3.75 (m, 1H), 3.58 (dd, *J* = 10.1, 3.5 Hz, 1H), 3.33 (dd, *J* = 7.9, 5.5 Hz, 1H), 3.16–3.19 (m, 1H), 3.15 (s, 3H), 3.15 (s, 3H), 3.07–3.13 (m, 1H), 2.40 (s, 3H), 2.03–2.16 (m, 3H), 1.85–2.02 (m, 3H), 1.57 (d, *J* = 7.1 Hz, 3H), 1.26–1.35 (m, 4H), 0.85–0.94 (m, 3H); HRMS (ESI) *m/z* calcd for C$_{28}$H$_{42}$FN$_6$O$_7$S$_3$ 689.2256, found 689.2258 (M+H)$^+$.

(7S)-7-Deoxy-7-[5-(5-methylamino-2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio]lincomycin (8b)

Reaction of **4b** (30 mg, 0.046 mmol) with 40% methylamine methanol solution (1.0 ml) gave **8b** (23 mg, 75%) as a colorless solid by a similar procedure to **7b**. [α]$_D^{22}$ +73° (*c* 0.69, CH$_3$OH); ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.89 (br d, *J* = 8.5 Hz, 1H), 8.10–8.18 (m, 1H), 6.63–6.72 (m, 2H), 5.36 (d, *J* = 5.2 Hz, 1H), 5.17–5.34 (m, 1H), 4.92–5.04 (m, 1H), 4.34–4.48 (m, 2H), 4.27 (d, *J* = 9.9 Hz, 1H), 4.15 (dd, *J* = 10.1, 5.2 Hz, 1H), 3.71–3.78 (m, 1H), 3.60 (dd, *J* = 9.9, 3.3 Hz, 1H), 3.29–3.38 (m, 1H), 3.11 (dd, *J* = 10.2, 4.7 Hz, 1H), 2.95 (d, *J* = 4.9 Hz, 3H), 2.40 (s, 3H), 2.16 (s, 3H), 1.81–2.14 (m, 4H), 1.56 (d, *J* = 6.6 Hz, 3H), 1.24–1.38 (m, 4H), 0.85–0.96 (m, 3H); HRMS (FAB) *m/z* calcd for C$_{27}$H$_{41}$N$_6$O$_7$S$_3$ 657.2193, found 657.2192 (M+H)$^+$.

(7S)-7-Deoxy-7-[5-(4-fluoro-5-methylamino-2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio]lincomycin (8c)

Reaction of **4c** (7.0 mg, 0.011 mmol) with 40% methylamine methanol solution (1.0 ml) gave **8c** (7.0 mg, 98%) as a colorless solid by a similar procedure to **7b**. MP 220–225 °C (dec.); [α]$_D^{22}$ +64° (*c* 0.47, CH$_3$OH); IR (KBr) 3397.96, 2922.59, 2782.78, 2369.12, 1654.62, 1577.49 and 1527.35 cm^{-1}; ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.98 (d, *J* = 11.9 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 5.28 (d, *J* = 5.6 Hz, 1H), 4.61 (dd, *J* = 9.8, 3.0 Hz, 1H), 4.41–4.49 (m, 2H), 4.11 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.82 (d, *J* = 3.1 Hz, 1H), 3.55–3.63 (m, 2H), 3.00–3.05 (m, 1H), 2.92 (s, 3H), 2.40 (s, 3H), 2.04–2.10 (m, 1H), 2.03 (s, 3H), 1.82–1.89 (m, 1H), 1.58 (d, *J* = 7.1 Hz, 3H), 1.28–1.36 (m, 4H), 0.88–0.94 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 178.93, 165.07, 164.77, 151.06, 148.59, 142.50, 142.38, 135.50, 135.42, 123.96, 123.93, 112.79, 112.72, 112.67, 112.56, 88.99, 71.67, 71.11, 69.38, 68.47, 68.20, 62.61, 53.19, 44.76, 41.82, 38.11, 38.04, 35.72, 29.74, 21.59, 18.86, 14.72, 14.29; HRMS (ESI) *m/z* calcd for C$_{27}$H$_{40}$FN$_6$O$_7$S$_3$ 675.2099, found 675.2103 (M+H)$^+$.

(7S)-7-Deoxy-7-{5-[4-fluoro-5-(2-hydroxyethylamino)-2-nitrophenyl]-1,3,4-thiadiazol-2-ylthio}lincomycin (9c)

A solution of **4c** (12 mg, 0.018 mmol) in 2-ethanolamine (0.5 ml) was stirred at 50 °C for 2 h. The mixture was diluted with ethyl acetate and washed with water. The organic phase was dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (CHCl$_3$/CH$_3$OH/28% aq NH$_4$OH = 20/2/0.2) to afford **9c** (11 mg, 86%) as a colorless solid. [α]$_D^{23}$ +63° (*c* 0.42, CH$_3$OH); ^{1}H NMR (400 MHz, CD$_3$OD) δ 8.00 (d, *J* = 11.9 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 5.28 (d, *J* = 5.6 Hz, 1H), 4.62 (dd, *J* = 9.9, 3.0 Hz, 1H), 4.41–4.49 (m, 2H), 4.12 (dd, *J* = 10.3, 5.6 Hz, 1H), 3.80–3.84 (m, 1H), 3.73 (t, *J* = 5.6 Hz, 2H), 3.58 (dd, *J* = 10.3, 3.2 Hz, 1H), 3.42 (t, *J* = 5.6 Hz, 2H), 3.25–3.29 (m, 1H), 3.03 (dd, *J* = 10.5, 5.1 Hz, 1H), 2.40 (s, 3H), 2.16–2.27 (m, 1H), 2.04–2.10 (m, 1H), 2.04 (s, 3H), 1.99–2.03 (m, 1H), 1.81–1.91 (m, 1H), 1.58 (d, *J* = 7.1 Hz, 3H), 1.29–1.38 (m, 4H), 0.89–0.95 (m, 3H); HRMS (ESI) *m/z* calcd for C$_{28}$H$_{42}$FN$_6$O$_8$S$_3$ 705.2205, found 705.2209 (M+H)$^+$.

(7S)-7-Deoxy-7-[5-(5-methoxy-2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio]lincomycin (10b)

A solution of **4b** (17 mg, 0.026 mmol) in methanol (0.50 ml) was added 28% methanol solution of sodium methoxide (0.10 ml) stirred at room temperature for 1 h. The mixture was diluted with ethyl acetate and washed with water. The organic phase was dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (CHCl$_3$/CH$_3$OH/28% aq NH$_4$OH = 20/2/0.2) to afford **10b** (11 mg, 64%) as a colorless solid. [α]$_D^{23}$ +56° (*c* 0.36, CH$_3$OH); ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.91–9.14 (m, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.05–7.20 (m, 2H), 5.36 (d, *J* = 5.4 Hz, 1H), 5.09–5.34 (m, 1H), 4.56–4.73 (m, 1H), 4.34–4.50 (m, 1H), 4.08–4.29 (m, 1H), 3.94 (s, 3H), 3.58–3.83 (m, 2H), 2.69–3.00 (m, 2H), 2.46–2.64 (m, 1H), 1.99–2.40 (m, 7H), 1.87–1.95 (m, 1H), 1.51–1.65 (m, 3H), 1.17–1.48 (m, 3H), 0.82–0.99 (m, 1H); HRMS (ESI) *m/z* calcd for C$_{27}$H$_{40}$N$_5$O$_8$S$_3$ 658.2034, found 658.2040 (M+H)$^+$.

(7S)-7-Deoxy-7-[5-(4-fluoro-5-methoxy-2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio]lincomycin (10c)

Reaction of **4c** (14 mg, 0.021 mmol) gave **10c** (10 mg, 70%) as a colorless solid by a similar procedure to **10b**. [α]$_D^{23}$ +84° (*c* 0.30, CH$_3$OH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.94 (br d, *J* = 8.8 Hz, 1H), 7.96 (d, *J* = 10.2 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 5.36 (d, *J* = 5.6 Hz, 1H), 5.23–5.31 (m, 1H), 4.38–4.48 (m, 2H), 4.24 (d, *J* = 10.0 Hz, 1H), 4.14–4.17 (m, 1H), 4.03 (s, 3H), 3.71 (d, *J* = 3.2 Hz, 1H), 3.58 (dd, *J* = 10.0, 3.4 Hz, 1H), 3.30–3.34 (m, 1H), 3.09 (dd, *J* = 10.5, 4.4 Hz, 1H), 2.40 (s, 3H), 2.17 (s, 3H), 2.06–2.15 (m, 2H), 1.85–2.01 (m, 3H), 1.58 (d, *J* = 6.8 Hz, 3H), 1.28–1.37 (m, 4H), 0.87–0.93 (m, 3H); HRMS (ESI) *m/z* calcd for C$_{27}$H$_{39}$N$_5$O$_8$S$_3$ 676.1939, found 676.1947 (M+H)$^+$.

In vitro antibacterial activity

Minimum inhibitory concentration (MIC) was determined by the agar dilution method. Test strains were subjected to seed culture using sensitivity test broth (STB, Nissui Pharmaceutical, Tokyo, Japan) cultured on blood agar plate for *S. pneumoniae*, *S. pyogenes* and *H. influenzae*. A 5 μl portion of cell suspension of the test strains having about 10^6 CFU per ml was inoculated into sensitivity disk agar (SDA, Nissui Pharmaceutical) supplemented with 5% horse blood and incubated at 37 °C for 20 h. Then, MIC was defined as the lowest drug concentration that prevented visible growth.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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