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A new type of ketolides bearing an *N*-aryl-alkyl acetamide moiety at the C-9 iminoether synthesis and structure–activity relationships

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Abstract—A new type of ketolides, bearing an *N*-aryl-alkyl acetamide moiety at the C-9 iminoether and a cyclic carbonate at the C-11,12 position was prepared and the antibacterial activities of the compounds were evaluated. Some of the derivatives showed potent antibacterial activity against both *Haemophilus influenzae* and *Streptococcus pneumoniae*, which are clinically important respiratory tract pathogens. Among the derivatives prepared, compound **5s** with a quinolin-4-yl moiety was found to have potent and well-balanced activity against *S. pneumoniae* and *H. influenzae* including erythromycin-resistant strains.

1. Introduction

The macrolide antibiotic erythromycin A (EM) has been widely used for the treatment of gram-positive bacterial infections. However due to its acid instability and low bioavailability, new semi-synthetic analogues of EM have been pursued. Clarithromycin (CAM)[1] is one of the semi-synthetic analogues of EM, which has good acid stability in the stomach and bioavailability. Azithromycin (AZM)[2] is another analogue that has an improved T1/2 and enhanced activity against gram-negative pathogens. Though these compounds have improved properties, they are still inactive against erythromycin-resistant strains, which have increased significantly in recent years.[3]

Recently, 3-keto derivatives of EM, called ketolides,[4] have been developed (Fig. 1). They are active against erythromycin-resistant strains, while maintaining their activity against erythromycin-susceptible ones. RU-004[5] (Hoechst-Marion Roussel) is a pioneer compound, which was evaluated clinically, and Telithromycin[6] (Aventis Pharma) is the first ketolide, which was launched on the market in 2001 in the EU.

Both them are 3-keto derivatives of CAM with an aryl-alkyl moiety at the C-11,12 cyclic carbamate group. Another derivative of ketolides, ABT-773[7] (cethromycin, Abbott Laboratories), has an aryl-alkyl moiety at its C-6 position.

Though all the above three C-9 keto compounds are effective for erythromycin-resistant strains and have potent activity against *H. influenzae* and *S. pneumoniae*, no ketolide derivatives exhibiting potent activity have thus far been reported with an aryl-alkyl moiety at the C-9 position.[8] The location of the aryl group on the ketolide skeleton is considered to be a very important factor for the activity against such pathogens.

In this paper, we describe the synthesis and the structure–activity relationships of ketolides with an aryl-alkyl moiety on the C-9 iminoether group and a cyclic carbonate at the C-11,12 position.

2. Synthesis

9-Iminoether derivatives were prepared using allyl ether **1**[9] as a starting material. Since compounds with a C-11,12 carbonate showed potent antibacterial activities in the series of C-9 oxime derivatives,[9] we prepared 9-iminoether derivatives with a C-11,12 carbonate moiety. We used carboxylic acid **3**, readily accessible from **1** by

Keywords: Ketolide; *N*-aryl-alkyl acetamide; 9-Iminoether; Erythromycin resistant; Macrolide; C-11,12 carbonate.
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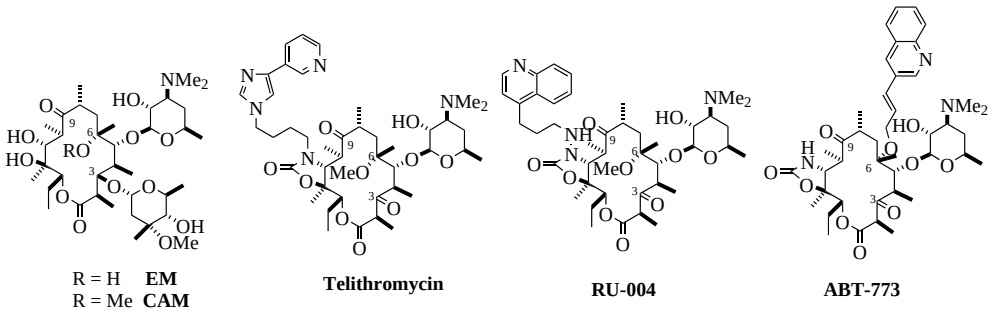
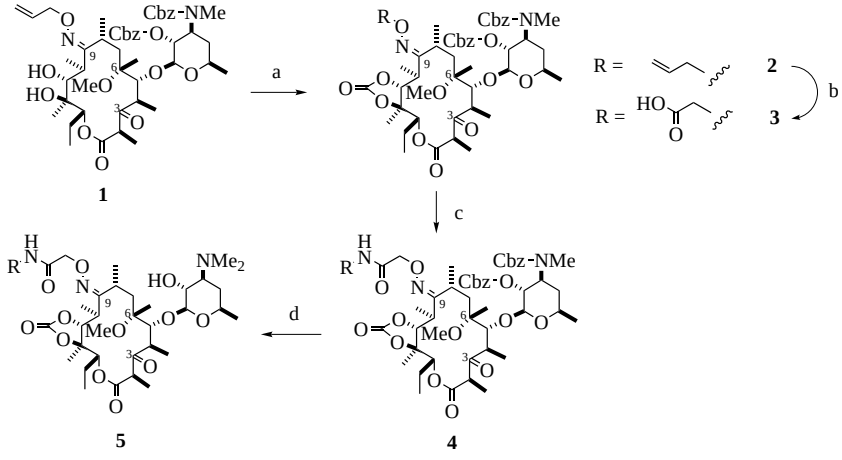


Figure 1. Structure of macrolide antibiotics.

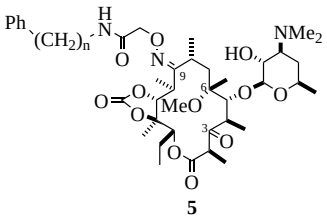
carbonate formation, followed by oxidation of allyl ether, as a key intermediate for the introduction of a variety of substituents at the C-9 iminoether by amide linkage. Amidation of **3** with various primary amines using oxalyl chloride and a catalytic amount of dimethylformamide gave **4**, which was subjected to deprotection and subsequent N-methylation (20% $Pd(OH)_2/H_2$, HCHO aq), afforded amide derivatives **5**, as shown in Scheme 1. We prepared the derivatives **5a**–**5f** with various lengths of methylene linker (Table 1) and **5g**–**5s** with a variety of aryl groups (Tables 3 and 4).

Another amide derivative having an *N*-methyl carbamoyl derivative **8** was prepared, as shown in Scheme 2. Amide **6** prepared from **3** and *N*-methylpropargylamine coupled with iodobenzene (Sonogashira coupling) gave **7**, which was subjected to deprotection, and subsequent N-methylation afforded *N*-methyl carbamoyl derivative **8**. Derivatives other than amides were prepared, as shown in Schemes 3 and 4. Compound **11** with a methylene spacers instead of amide **5d**, was prepared by coupling **1** with triflate **9** (Suzuki coupling) to give **10** (a mixture of *E*/*Z* isomers), which was converted to **11** by

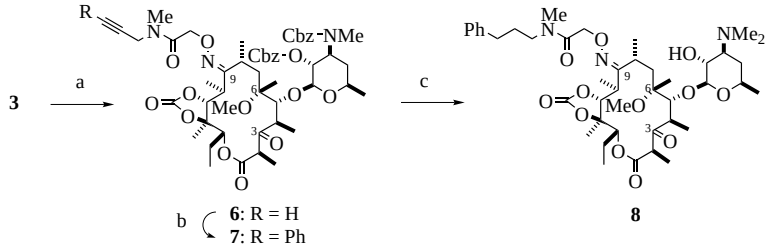


Scheme 1. Reagents and conditions: (a) $(CCl_3O)_2CO$, pyridine, THF; (b) (1) O_3, SMe_2, (2) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, Me2C=CHMe; (c) $(ClCO)_2$, cat. DMF, RNH_2; (d) (1) H_2, 20% $Pd(OH)_2/C$, (2) H_2, 20% $Pd(OH)_2/C$, HCHO aq acetate buffer (pH 4.4).

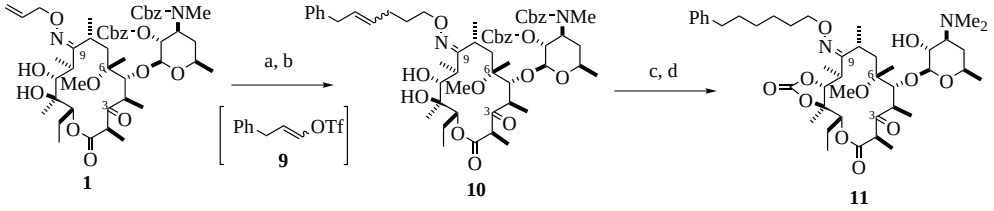
Table 1. In vitro antibacterial activities of compounds **5a**–**5f**



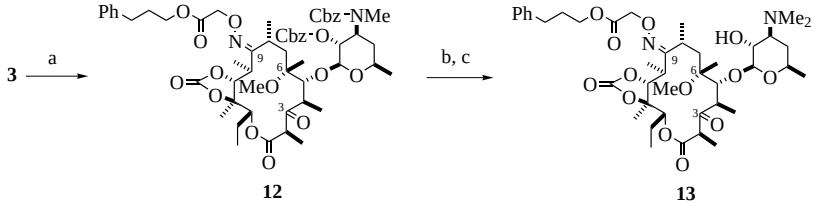
Strain	MIC (μg/mL)						
	5a (n = 0)	**5b** (n = 1)	**5c** (n = 2)	**5d** (n = 3)	**5e** (n = 4)	**5f** (n = 5)	CAM
S.aureus Smith	0.2	0.2	0.39	0.2	0.39	0.78	0.2
S. aureus SR17347(EM-R)	0.78	0.39	0.78	0.2	0.39	0.78	>100
S. pneumoniae Type I	0.025	0.025	0.05	0.025	0.025	0.1	0.025
S. pneumoniae SR16651(EM-R)	>100	>100	100	0.78	25	6.25	>100
H. influenzae SR88562	50	25	50	6.25	50	25	3.13



Scheme 2. Reagents and conditions: (a) $(ClCO)_2$, cat. DMF, *N*-methylpropargylamine; (b) PhI, NEt3, CuI, cat. $Cl_2Pd(PPh_3)_2$, CH_3CN; (c) (1) H_2, 20% $Pd(OH)_2/C$, (2) H_2, 20% $Pd(OH)_2/C$, HCHO aq acetate buffer (pH 4.4).

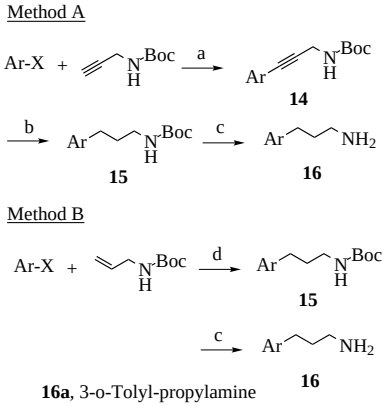


Scheme 3. Reagents and conditions: (a) 9-BBN, THF; (b) cat. $Cl_2Pd(PPh_3)_2$, 1 N NaOH, 9; (c) $(CCl_3O)_2CO$, pyridine, THF; (d) H_2, 20% $Pd(OH)_2/C$; (e) H_2, 20% $Pd(OH)_2/C$, HCHO aq acetate buffer (pH 4.4).



Scheme 4. Reagents and conditions: (a) (1) $(ClCO)_2$, cat. DMF, toluene; (2) 3-phenyl-1-propanol, pyridine, cat. DMAP, toluene; (b) H_2, 20% $Pd(OH)_2/C$; (c) H_2, 20% $Pd(OH)_2/C$, HCHO aq acetate buffer (pH 4.4).

carbonate formation, and subsequent deprotection and N-methylation. An ester derivative **13** was prepared via esterification of **3** with 3-phenyl propanol.



16a, 3-o-Tolyl-propylamine
16b, 3-mTolyl-propylamine
16c, 3-p-Tolyl-propylamine
16d, 3-(4-Fluoro-phenyl)-propylamine
16e, 3-(4-Nitro-phenyl)-propylamine
16f, 3-Biphenyl-4-yl-propylamine
16g, 3-Naphthalen-2-yl-propylamine
16h, 3-Naphthalen-1-yl-propylamine
16i, 3-Quinolin-3-yl-propylamine
16j, 3-Quinolin-4-yl-propylamine

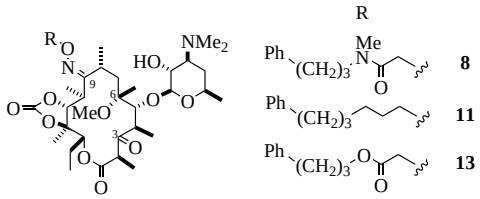
Scheme 5. Reagents and conditions: (a) NEt_3, CuI, cat. $Cl_2Pd(PPh_3)_2$; (b) H_2, 20% $Pd(OH)_2/C$; (c) CF_3CO_2H; (d) 9-BBN, cat. $Cl_2Pd(PPh_3)_2$, 1 N NaOH.

3-Arylpropylamines used for the synthesis of **5** were prepared, as shown in Scheme 5. Other amines, not listed in Scheme 5, were commercially available or prepared from the corresponding 3-arylpropanols.

3. Results and discussion

All the ketolides prepared were evaluated in vitro by the standard agar dilution method with various strains. Their antibacterial activities against erythromycin-susceptible and -resistant *S. aureus* and *S. pneumoniae*, including one strain of *H. influenzae*, are shown in Table 1. All ketolides showed potent antibacterial activities against both erythromycin-susceptible and -resistant *S. aureus* and erythromycin-susceptible *S. pneumoniae*. Their activities against erythromycin-susceptible strains were almost comparable to CAM. Although all ketolides shown in Table 1 displayed potent activities against erythromycin-resistant *S. aureus*, they showed weak activities against erythromycin-resistant *S. pneumoniae* and *H. influenzae*, except for compound **5d**. As for the activity of *H. influenzae*, **5d** showed superior activity to other ketolides, but its activity was slightly inferior to that of CAM. It was considered that the spacer length between the amide and the phenyl ring was an important factor in the activity against erythromycin-resistant *S. pneumoniae*

Table 2. In vitro antibacterial activities of **5d** and its analogues **8**, **11**, and **13**



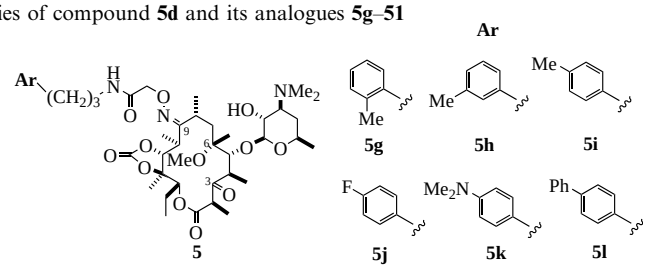
Strain	MIC (μg/mL)				
	5d	**8**	**11**	**13**	CAM
S. aureus Smith	0.2	0.39	3.13	0.78	0.2
S. aureus SR17347(EM-R)	0.2	0.39	3.13	0.78	>100
S. pneumoniae Type I	0.025	0.05	0.78	0.2	0.025
S. pneumoniae SR16651(EM-R)	0.78	6.25	6.25	6.25	>100
H. influenzae SR88562	6.25	12.5	>100	25	3.13

and *H. influenzae*, and the spacer of three methylenes was found to be the most favorable.

We next examined the effect of the amide group and its N–H bond. Table 2 presents the antibacterial activity of **5d** and its analogues **8**, **11**, and **13** with the same spacer length as **5d**. Clearly, the analogues **8**, **11**, and **13** are less active than **5d** against the strains tested, especially against erythromycin-resistant strains. Compound **13** bearing an ester group showed a much lower antibacterial activity and compound **11** almost lost its activity. *N*-Methylcarbamoyl analogue **8** was less active than **5d** against erythromycin-resistant *S. pneumoniae*, while retaining an almost comparable activity to **5d** against other strains. These results strongly suggest that amide is the best linkage for the C-9 iminoether moiety and the NH group of the amide also plays an important role in the activity against erythromycin-resistant *S. pneumoniae*.

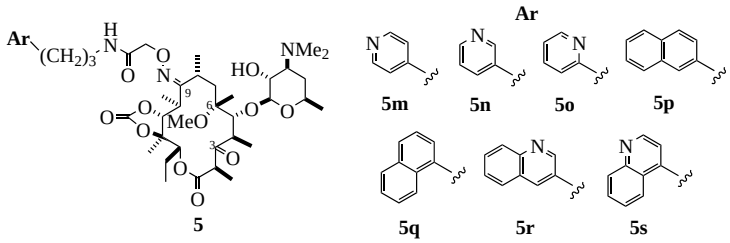
Next, the effects of the substituent on the phenyl ring were examined. Table 3 presents the activities of **5d** derivatives with a substituent on the phenyl ring. The introduction of a methyl substituent (**5g**–**5i**) resulted in a remarkable decrease of their activity against erythromycin-resistant *S. pneumoniae*. Among them, **5i** with a para-substituent showed a rather strong activity, but the activity against erythromycin-resistant *S. pneumoniae* was much lower than that of **5d**. Other analogues with a para-substituted phenyl group (**5j**–**5l**) also showed weak activity. The results given in Table 3 clearly showed that substituents on a phenyl ring were not effective for antibacterial activities, and we next focused our investigation on aryl rings other than phenyl. Therefore, derivatives **5m**–**5s** bearing various aryl ring groups were prepared and the antibacterial activities of the representative compounds are given in Table 4. Compounds **5m**, **5n**, and **5o** bearing a pyridine ring showed increased activity against *H. influenzae* compared to **5d**, but their activity against erythromycin-resistant *S. pneumoniae* was much more inferior to that of **5d**, though it maintained the activity against other strains. Compounds **5p** and **5q** bearing a naphthalene ring exhibited interesting activities against erythromycin-resistant *S. pneumoniae* and *H. influenzae*, respectively. As for the activity against erythromycin-resistant *S. pneumoniae*, compound **5p** with a β-naphthyl substituent showed activity twice as potent as **5d**, whereas **5q** with an α-naphthyl one showed a much lower activity. On the other hand, against *H. influenzae*, compound **5q** was twice as active as **5d**, while **5p** showed activity comparable to that of **5d**. These findings that the β-naphthyl moiety contributes to the activity against erythromycin-resistant *S. pneumoniae* and the α-naphthyl one to the activity against *H. influenzae* led us to the design of com-

Table 3. In vitro antibacterial activities of compound **5d** and its analogues **5g**–**5l**



Strain	MIC (μg/mL)							
	5d	**5g**	**5h**	**5i**	**5j**	**5k**	**5l**	CAM
S. aureus Smith	0.2	0.2	0.39	0.39	0.2	0.39	1.56	0.2
S. aureus SR17347(EM-R)	0.2	0.2	0.39	0.39	0.39	0.39	1.56	>100
S. pneumoniae Type I	0.025	0.025	0.025	0.025	0.025	0.05	0.2	0.025
S. pneumoniae SR16651(EM-R)	0.78	25	12.5	6.25	6.25	50	6.25	>100
H. influenzae SR88562	6.25	6.25	6.25	6.25	6.25	12.5	>100	3.13

Table 4. In vitro antibacterial activities of compound **5d** and its analogues **5m–5s**



Strain	MIC (μg/mL)								
	5d	**5m**	**5n**	**5o**	**5p**	**5q**	**5r**	**5s**	CAM
S. aureus Smith	0.2	0.2	0.2	0.2	0.39	0.39	0.2	0.2	0.2
S. aureus SR17347(EM-R)	0.2	0.2	0.2	0.39	0.39	0.39	0.2	0.2	>100
S. pneumoniae Type I	0.025	0.025	0.025	0.025	0.05	0.025	0.0125	0.0125	0.025
S. pneumoniae SR16651(EM-R)	0.78	100	50	100	0.39	12.5	0.1	0.78	>100
H. influenzae SR88562	6.25	3.13	1.56	3.13	6.25	3.13	3.13	0.78	3.13

Table 5. In vivo efficacy in the mouse lung infection models

Compound	*S. pneumoniae*			Rat
	MIC (μg/mL)	ED_{50} (mg/kg)	Mouse serum free (%)	Lung AUC (0–6 h) (μg h/g)[a]
5d	0.025	21.8	2.9	26
5s	0.0125	35.9	5.9	19
CAM	0.025	11.6	52.8	221

[a] Dose 20 mg/kg (PO).

pounds **5r** and **5s** with a quinolynyl moiety. As shown in Table 4, as expected, both compounds had potent activities including erythromycin-resistant *S. pneumoniae* and *H. influenzae*. Between the two, compound **5s** with a quinolin-4-yl moiety was considered to be the better one in terms of its balanced activity against erythromycin-resistant *S. pneumoniae* and *H. influenzae*, while **5r** with the quinolin-3-yl moiety showed remarkable activity against erythromycin-resistant *S. pneumoniae*.

The in vivo efficacy (ED_{50}) of **5s** and **5d**, as well as that of CAM, in the mouse lung infection model was evaluated, as presented in Table 5. It was disappointing to find that these ketolides bearing an *N*-aryl-propyl actetamide group were less efficacious in vivo than CAM in the lung infection model although they had in vitro activity as potent as CAM. The weak in vivo efficacy was presumably attributed to their low free fraction in mouse serum and their poor pharmacokinetic properties. The lung AUCs of **5d** and **5s** in mice would be much lower than that of CAM as in the case with the AUC in rats shown in Table 5.

4. Molecular modeling

We conducted an extensive study on ketolides bearing an *N*-aryl-alkyl acetamide group at the C-9 iminoether, and found the analogue **5s** to be a ketolide with potent and balanced antibacterial activities. A macrolide has two faces on its molecular surface, a hydrophobic face and a hydrophilic one, which can be easily differentiated on its molecular model. The hydrophilic face has most of the oxygen-containing groups. Conformational analysis of RU-004[10] and ABT-773[7] indicated that their aryl groups were located on their hydrophilic face with almost the same spatial positioning. We conducted the conformational analysis of **5s** with RU-004 and ABT-773 by locating the aryl groups in a similar spatial area with the computer software MOE.[11] Although many conformations arose from superposing compound **5s** on the other, we finally obtained a conformation of the three compounds with their aryl groups located in almost the same spatial area. As shown in Figure 2, all aryl groups of **5s** (green), RU-004 (red), and ABT-773 (blue) can occupy almost the same spatial area on the hydrophilic face. The conformation depicted in this

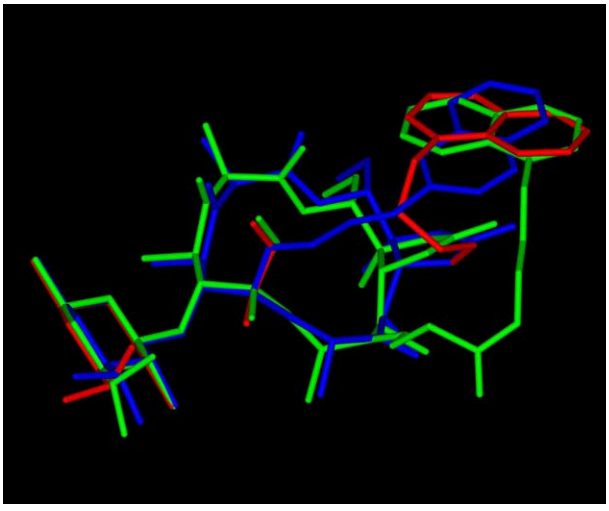


Figure 2. Conformation model of **5s** (green), **RU-004** (red), and **ABT-773** (blue).

model[12] is similar to that of ABT-773 in a complex with ribosome,[13] leading to the suggestion that this type of ketolide bearing an *N*-aryl-propyl acetamide group at the C-9 iminoether could be promising as a compound against pathogens resistant to erythromycin.

5. Conclusion

A series of ketolides bearing an *N*-aryl-propyl acetamide group at the C-9 iminoether was found to have potent activities against key respiratory pathogens, including erythromycin-resistant ones. Extensive study on the modification of the C-9 iminoether moiety revealed that the amide and its NH group were essential for potent activity, and led to the discovery of novel compounds, such as, **5s**, with potent activity against the key respiratory pathogens. Although this type of ketolides showed excellent activities in vitro, they exhibited poor in vivo efficacy in experimental animal infection models, presumably due to their poor pharmacokinetic profiles. These results directed us to the pursuit of other derivatives with an improved pharmacokinetic profile along with potent activities, which will be reported elsewhere in the future.

6. Experimental

Infrared (IR) spectra were taken on a JASCO FT/IR-700 spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Gemini-300. Chemical shifts are reported in ppm using tetramethylsilane (TMS) as an internal standard. HR-MS (FAB)/MS (FAB) were recorded on a JEOL LMS-SX/SX 102A and HR-MS (SI)/MS (SI) were recorded on a Hitachi M-90. Analytical thin layer chromatography (TLC) was carried out on Merck precoated TLC plates silica gel 60 F_{254} and visualized with UV light or 10% H_2SO_4 containing 5% ammonium molybdate and 0.2% ceric sulfate. Flash chromatography was performed with Merck silica gel 60 (230–400 mesh).

6.1. Measurement of in vitro antibacterial activity

MICs were determined by a serial twofold dilution method in Sensivity Disk Agar-N (Nissui Pharmaceutical, Tokyo, Japan). The overnight cultures of antibacterial strains in Mueller–Hinton broth (Becton Dickinson) were diluted to about 10^6 CFU/ml. Bacterial suspensions of 1 μL were spotted onto agar plates containing various concentrations of an antibiotic and incubated for 20 h at 37 °C before the MICs were scored.

6.2. Preparation of compound 3

A solution of compound **2**[9] (5.0 g, 5.42 mmol) in CH_2Cl_2 (50 mL)–MeOH (10 mL) was cooled to −78 °C, and O_3 gas was bubbled through the solution with stirring until the solution turned blue. Next, N_2 gas was bubbled through the solution with stirring until the blue color discharged. After that, Me_2S (2 mL, 27.2 mmol) was added to the reaction mixture at −78 °C with stirring for 30 min at −78 °C. The reaction mixture was poured into H_2O and extracted with $CHCl_3$ (50 mL). The aqueous layer was extracted with $CHCl_3$ (50 mL) and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was diluted with tert-BuOH (30 mL) and H_2O (10 mL), and to this solution were added 2-methy-2-butene (2.7 mL, 25.4 mmol), $NaH_2PO_4{\cdot}2H_2O$ (850 mg, 5.45 mmol), and 80% $NaClO_2$ (2.2 g, 11.2 mmol) at room temperature. After stirring for 3.5 h at room temperature, to the reaction mixture was added 1 N HCl (50 mL) under cooling with an ice-water bath. The mixture was poured into H_2O and extracted with $CHCl_3$ (50 mL). The aqueous layer was extracted with $CHCl_3$ (50 mL) and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silicagel (*n*-hexane/AcOEt = 1/1–1/4 and $CHCl_3$/MeOH = 4/1) to give 4.95 g of compound **3** as a colorless foam (two conformers 97%).

MS (FAB) 963^+(M+Na$^+$); HRMS (FAB) calcd for $C_{48}H_{64}N_2O_{17}Na$ (M+Na$^+$) 963.4103, found 963.4106; Anal. calcd for $C_{48}H_{64}N_2O_{17}(H_2O)_2$: C, 59.01; H, 7.01; N, 2.87, found: C, 58.95; H, 6.76; N, 2.93; IR (KBr) 3430, 3065, 3032, 2975, 2938, 2881, 1809, 1752, 1703, 1618, 1497, 1455, 1406, 1382, 1329, 1290, 1253, 1167, 1113, 1082, 1067 (cm^{-1}); ^{1}H NMR ($CDCl_3$) δ 2.66 (3H, s), 2.80, 2.84 (3H, two s); ^{13}C NMR ($CDCl_3$) δ 10.3, 13.0, 13.8, 13.9, 14.1, 15.3, 15.5, 18.5, 19.7, 20.6, 21.0, 22.3, 26.5, 28.9, 29.6, 33.0, 35.7, 36.2, 37.8, 46.9, 47.0, 49.5, 50.9, 54.8, 60.4, 67.2, 67.3, 68.7, 69.4, 69.6, 70.9, 74.6, 76.2, 76.4, 78.1, 82.7, 84.8, 100.6, 125.2, 127.5, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.4, 129.0, 135.4, 135.5, 136.6, 154.3, 154.4, 156.1, 156.5, 167.1, 167.2, 169.0, 203.8, 204.1 (two rotational isomers were observed by ^{1}H NMR and ^{13}C NMR spectra).

6.3. Preparation of compound 5d

6.3.1. Amidation. To a solution of **3** (300 mg, 0.318 mmol) in toluene (6 mL) were added DMF (2 μL, 0.03 mmol) and oxalyl chloride (59 μL, 0.636 mmol) at room temperature, and the reaction mixture was stirred for 90 min at room temperature. To this solution, phenylpropylamine (181 μL, 1.27 mmol) was added, and the reaction mixture was stirred for another 15 min. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with AcOEt (20 mL). The aqueous layer was extracted with AcOEt (20 mL) and combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silicagel (*n*-hexane/AcOEt = 4/1–1/1) to give 298 mg of compound **4** bearing *N*-phenypropylacetamide group as a colorless foam (89%).

MS (FAB) 1080^+(M+Na$^+$); HRMS (FAB) calcd for $C_{57}H_{75}N_3O_{16}Na$ (M+Na$^+$) 1080.5045, found 1080.5056; IR (KBr) 3434, 33371, 3063, 3029, 2974, 2938, 2879, 1811, 1752, 1702, 1604, 1586, 1532, 1497, 1455, 1381, 1330, 1289, 1253, 1167, 1113, 1067, 1003

(cm^{-1}); ^1H NMR ($CDCl_3$) δ 2.65 (3H, s), 2.80, 2.84 (3H, two s); ^{13}C NMR ($CDCl_3$) δ 10.2, 12.9, 13.8, 15.3, 15.5, 18.8, 19.8, 20.5, 22.3, 26.2, 29.0, 30.8, 33.1, 35.7, 36.1, 37.6, 38.7, 46.9, 47.0, 49.6, 50.9, 54.8, 67.1, 67.2, 68.7, 69.3, 69.5, 72.9, 74.6, 76.1, 78.2, 82.2, 84.4, 100.6, 125.7, 127.5, 127.6, 127.8, 127.9, 128.2, 128.3, 128.4, 135.4, 135.5, 136.6, 141.4, 153.7, 154.3, 154.4, 156.0, 156.4, 167.2, 169.0, 170.1, 203.6, 203.8 (two rotational isomers were observed by ^1H NMR and ^{13}C NMR spectra).

6.3.2. Deprotection and N-methylation. This colorless foam **4** (298 mg) with *N*-phenypropylacetamide was diluted with EtOH (24 mL) and 0.2 M acetate buffer (6 mL, pH 4.4). To this solution was added 20% $Pd(OH)_2/C$ (89 mg, 0.168 mmol) with stirring at room temperature under a H_2 atmosphere for 1 h. After confirming the disappearance of **4** by TLC, 37% aqueous HCHO (2.1 mL) was added to the reaction mixture and stirred at room temperature under H_2 atmosphere for an additional 2 h. The mixture was filtered and concentrated. After being diluted with water, the mixture was basified with 5% aqueous $NaHCO_3$ and then extracted with AcOEt. The resultant residue was purified by column chromatography on silicagel ($CHCl_3$/MeOH = 80/1–40/1) to give 182 mg of compound **5d** as a colorless foam (87%).

MS (FAB) $804^+(M+H^+)$; HRMS (FAB) calcd for $C_{42}H_{66}N_3O_{12}$ ($M+H^+$) 804.4647, found 804.4650; IR (KBr) 3433, 3061, 2973, 2936, 2878, 2785, 1809, 1751, 1716, 1671, 1536, 1495, 1455, 1380, 1321, 1284, 1259, 1232, 1166, 1110, 1078, 1048 (cm^{-1}); ^1H NMR ($CDCl_3$) δ 0.89 (3H, t, J = 7.2 Hz), 1.01 (3H, d, J = 6.9 Hz), 1.24 (3H, d, J = 6.3 Hz), 1.26 (3H, d, J = 6.9 Hz), 1.27 (3H, d, J = 7.5 Hz), 1.37 (3H, d, J = 6.9 Hz), 1.38 (3H, s), 1.56 (3H, s), 1.20–1.94 (8H, m), 2.31 (6H, s), 2.55 (2H, m), 2.66 (2H, t, J = 8.1 Hz), 2.69 (3H, s), 3.02 (1H, quintet, J = 7.5 Hz), 3.16–3.28 (2H, m), 3.32–3.46 (1H, m), 3.48–3.74 (2H, m), 3.83 (1H, q, J = 6.9 Hz), 4.22 (1H, d, J = 7.5 Hz), 4.31 (1H, d, J = 7.2 Hz), 4.45 (2H, s), 4.82 (1H, s), 5.00 (1H, dd, J = 2.4 and 9.9 Hz), 6.90 (1H, brt, J = 5.4 Hz), 7.12–7.30 (5H, m); ^{13}C NMR ($CDCl_3$) δ 10.3, 12.9, 14.3, 15.4, 15.6, 18.8, 19.9, 21.1, 22.3, 26.3, 28.5, 30.9, 33.1, 38.0, 38.8, 40.1, 47.6, 49.8, 51.0, 65.9, 69.3, 70.2, 73.0, 76.1, 78.4, 78.6, 82.3, 84.5, 103.6, 125.7, 128.3, 128.4, 141.5, 153.8, 167.5, 169.2, 170.3, 203.9.

6.4. Preparation of compounds 5a, 5b, 5c, 5e, and 5f

Compounds **5a**, **5b**, **5c**, **5e**, and **5f** were prepared in the same procedure as that described for the synthesis of **5d** with aniline, benzylamine, phenethylamine, 4-phenyl-butylamine, and 5-phenyl-pentylamine,[15] respectively.

6.4.1. Compound 5a. MS (FAB) $762^+(M+H^+)$; HRMS (FAB) calcd for $C_{39}H_{60}N_3O_{12}$ ($M+H^+$) 762.4177, found 762.4174; IR (KBr) 3413, 3361, 2972, 2936, 2879, 2786, 1810, 1751, 1714, 1685, 1636, 1600, 1536, 1499, 1456, 1444, 1379, 1361, 1320, 1284, 1256, 1235, 1167, 1141, 1109, 1078, 1047, 1006 (cm^{-1}); ^1H NMR ($CDCl_3$) δ 0.91 (3H, t, J = 7.5 Hz), 1.06 (3H, d, J = 6.6 Hz), 1.25 (3H, d, J = 7.2 Hz), 1.27 (3H, d, J = 8.4 Hz), 1.31 (3H, d, J = 6.6 Hz), 1.36 (3H, d, J = 6.6 Hz), 1.41 (3H, s), 1.58 (3H, s), 1.54–1.94 (5H, m), 2.29 (6H, s), 2.40–2.65 (3H, m), 2.63 (3H, s), 3.02 (1H, quintet, J = 7.8 Hz), 3.20 (1H, dd, J = 7.5 and 9.9 Hz), 3.40–3.80 (3H, m), 3.84 (1H, q, J = 6.9 Hz), 4.21 (1H, d, J = 8.1 Hz), 4.30 (1H, d, J = 7.2 Hz), 4.59 (2H, s), 4.87 (1H, s), 5.03 (1H, dd, J = 2.1 and 10.2 Hz), 7.06–7.59 (5H, m), 8.53 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 10.3, 13.0, 14.3, 15.5, 15.6, 18.8, 19.9, 21.1, 22.3, 26.5, 28.3, 33.2, 38.1, 40.1, 47.6, 49.7, 51.0, 65.8, 69.4, 70.2, 73.5, 76.1, 78.4, 78.6, 82.3, 84.6, 103.7, 120.1, 124.3, 128.9, 137.3, 153.9, 168.4, 168.6, 169.1, 203.8.

6.4.2. Compound 5b. MS (FAB) $776^+(M+H^+)$; HRMS (FAB) calcd for $C_{40}H_{62}N_3O_{12}$ ($M+H^+$) 776.4333, found 776.4338; IR (KBr) 3435, 2974, 2938, 2879, 1810, 1751, 1715, 1675, 1530, 1455, 1379, 1323, 1283, 1258, 1231, 1166, 1110, 1078, 1048 (cm^{-1}); ^1H NMR ($CDCl_3$) δ 0.92 (3H, t, J = 8.4 Hz), 0.93 (3H, d, J = 7.2 Hz), 1.16 (3H, d, J = 6.9 Hz), 1.25 (3H, d, J = 6.3 Hz), 1.26 (3H, d, J = 7.5 Hz), 1.33 (3H, s), 1.36 (3H, d, J = 6.6 Hz), 1.53 (3H, s), 1.40–1.98 (6H, m), 2.27 (6H, s), 2.40–2.53 (2H, m), 2.52 (3H, s), 2.91 (1H, br s), 2.99 (1H, quintet, J = 7.8 Hz), 3.17 (1H, dd, J = 7.2 and 9.9 Hz), 3.49–3.70 (2H, m), 3.81 (1H, q, J = 6.6 Hz), 4.18 (1H, d, J = 7.8 Hz), 4.29 (1H, d, J = 7.5 Hz), 4.42 (1H, dd, J = 5.1 and 14.7 Hz), 4.53 (1H, dd, J = 5.1 and 14.7 Hz), 4.52 (2H, s), 4.72 (1H, s), 4.93 (1H, dd, J = 2.7 and 9.9 Hz), 7.04 (1H, t, J = 5.1 Hz), 7.20–7.38 (5H, m); ^{13}C NMR ($CDCl_3$) δ 10.4, 13.0, 14.2, 15.3, 15.5, 18.7, 19.8, 21.1, 22.4, 26.3, 28.2, 33.1, 38.0, 40.1, 43.2, 47.5, 49.6, 51.0, 65.8, 69.4, 70.2, 72.9, 76.3, 78.2, 78.5, 82.4, 84.4, 103.6, 127.4, 128.1, 128.6, 137.9, 153.8, 167.7, 168.9, 170.1, 204.0.

6.4.3. Compound 5c. MS (FAB) $790^+(M+H^+)$; HRMS (FAB) calcd for $C_{41}H_{64}N_3O_{12}$ ($M+H^+$) 790.4490, found 790.4492; IR (KBr) 3432, 3062, 2973, 2937, 2879, 2784, 1810, 1751, 1716, 1675, 1604, 1531, 1496, 1455, 1380, 1363, 1322, 1305, 1284, 1257, 1234, 1166, 1141, 1110, 1078, 1047, 1004 (cm^{-1}); ^1H NMR ($CDCl_3$) δ 0.90 (3H, t, J = 6.9 Hz), 0.95 (3H, d, J = 7.2 Hz), 1.21 (3H, d, J = 6.9 Hz), 1.26 (3H, d, J = 6.0 Hz), 1.28 (3H, d, J = 7.5 Hz), 1.35 (3H, s), 1.37 (3H, d, J = 7.2 Hz), 1.56 (3H, s), 1.44–1.99 (5H, m), 2.29 (6H, s), 2.40–2.60 (2H, m), 2.65 (3H, s), 2.87 (2H, m), 3.02 (1H, quintet, J = 7.2 Hz), 3.20 (1H, t, J = 8.1 Hz), 3.32 (1H, br s), 3.40–3.70 (5H, m), 3.83 (1H, q, J = 6.9 Hz), 4.21 (1H, d, J = 8.4 Hz), 4.31 (1H, d, J = 6.9 Hz), 4.46 (2H, s), 4.82 (1H, s), 5.03 (1H, dd, J = 2.4 and 10.2 Hz), 6.89 (1H, t, J = 5.4 Hz), 7.18–7.36 (5H, m); ^{13}C NMR ($CDCl_3$) δ 10.3, 12.9, 14.2, 15.3, 15.6, 18.8, 19.8, 21.1, 22.3, 26.3, 28.3, 33.1, 35.6, 38.0, 40.1, 40.2, 47.6, 49.6, 51.0, 65.8, 69.4, 70.2, 72.9, 76.1, 78.3, 78.6, 82.3, 84.6, 103.7, 126.2, 128.4, 128.7, 138.9, 153.9, 167.4, 169.2, 170.1, 203.9.

6.4.4. Compound 5e. MS (FAB) $818^+(M+H^+)$; HRMS (FAB) calcd for $C_{43}H_{68}N_3O_{12}$ ($M+H^+$) 818.4803, found 818.4801; IR (KBr) 3435, 2973, 2937, 2879, 2786, 1809, 1752, 1716, 1654, 1456, 1379, 1324, 1283, 1260, 1229,

1166, 1110, 1079, 1049 (cm^{-1}); ^1H NMR ($CDCl_3$) δ 0.90 (3H, t, J = 7.8 Hz), 1.01 (3H, d, J = 7.2 Hz), 1.25 (6H, d, J = 5.7 Hz), 1.28 (3H, d, J = 7.8 Hz), 1.38 (3H, d, J = 6.6 Hz), 1.39 (3H, s), 1.56 (3H, s), 1.42–1.96 (8H, m), 2.27 (6H, s), 2.40–2.60 (2H, m), 2.63 (2H, t, J = 7.8 Hz), 2.68 (3H, s), 2.90–3.42 (6H, m), 3.50–3.74 (2H, m), 3.84 (1H, q, J = 6.9 Hz), 4.22 (1H, d, J = 8.1 Hz), 4.30 (1H, d, J = 7.2 Hz), 4.45 (2H, s), 4.82 (1H, s), 5.04 (1H, dd, J = 2.4 and 10.5 Hz), 6.86 (1H, brt, J = 5.7 Hz), 7.14–7.29 (5H, m); ^{13}C NMR ($CDCl_3$) δ 10.1, 12.7, 14.1, 15.1, 15.5, 18.6, 19.7, 21.0, 22.1, 26.1, 28.0, 28.5, 28.9, 32.9, 35.2, 37.8, 38.7, 40.0, 47.4, 49.6, 50.8, 65.6, 69.3, 70.0, 72.7, 75.9, 78.2, 78.5, 82.1, 84.4, 103.5, 125.4, 128.0, 128.2, 142.1, 153.6, 167.3, 169.0, 170.0, 203.7.

6.4.5. Compound 5f. MS (FAB) $832^+(M+H^+)$; HRMS (FAB) calcd for $C_{44}H_{70}N_3O_{12}$ ($M+H^+$) 832.4959, found 832.4968; IR (KBr) 3435, 2972, 2936, 2877, 2857, 2785, 1811, 1751, 1717, 1671, 1534, 1496, 1455, 1380, 1362, 1323, 1304, 1283, 1258, 1234, 1219, 1167, 1142, 1109, 1078, 1048, 1004 (cm^{-1}); ^1H NMR ($CDCl_3$) δ 0.85 (3H, t, J = 7.2 Hz), 1.00 (3H, d, J = 7.2 Hz), 1.24 (3H, d, J = 6.3 Hz), 1.26 (3H, d, J = 6.9 Hz), 1.28 (3H, d, J = 7.2 Hz), 1.37 (3H, d, J = 7.2 Hz), 1.39 (3H, s), 1.56 (3H, s), 1.22–1.96 (12H, m), 2.26 (6H, s), 2.40–2.65 (5H, m), 2.69 (3H, s), 3.02 (1H, quintet, J = 7.8 Hz), 3.10–3.40 (3H, m), 3.48–3.75 (2H, m), 3.84 (1H, q, J = 6.9 Hz), 4.22 (1H, d, J = 8.1 Hz), 4.30 (1H, d, J = 7.2 Hz), 4.45 (2H, s), 4.82 (1H, s), 5.02 (1H, dd, J = 2.7 and 10.2 Hz), 6.87 (1H, brt, J = 5.7 Hz), 7.12–7.28 (5H, m); ^{13}C NMR ($CDCl_3$) δ 10.2, 12.9, 14.3, 15.3, 15.6, 18.9, 19.9, 21.1, 22.3, 26.3, 26.6, 28.1, 29.3, 31.1, 33.1, 35.7, 38.0, 39.1, 40.2, 47.6, 49.8, 51.0, 65.8, 69.5, 70.3, 73.0, 76.1, 78.4, 78.7, 82.3, 84.5, 103.8, 125.5, 128.1, 128.4, 142.6, 153.8, 167.4, 169.2, 170.2, 203.9.

6.5. Preparation of compounds 5g–5l

Compounds **5g**–**5l** were prepared in the same procedure as that described for the synthesis of **5d** with 3-o-tolyl-propylamine (**16a**), 3-m-tolyl-propylamine (**16b**), 3-p-tolyl-propylamine (**16c**), 3-(4-fluoro-phenyl)-propyl-amine (**16d**), 3-(4-nitro-phenyl)-propylamine (**16e**), and 3-biphenyl-4-yl-propylamine (**16f**), respectively.

6.5.1. Compound 5g. MS (FAB) $818^+(M+H^+)$; HRMS (FAB) calcd for $C_{43}H_{68}N_3O_{12}$ ($M+H^+$) 818.4803, found 818.4803; IR ($CHCl_3$) 3426, 3350, 2970, 2934, 2870, 2830, 2780, 1805, 1751, 1715, 1663, 1536, 1490, 1455, 1381, 1361, 1345, 1322, 1305, 1282, 1256, 1230, 1220, 1165, 1139, 1107, 1074, 1046, 1004 (cm^{-1}); ^1H NMR ($CDCl_3$) δ 0.89 (3H, t, J = 7.2 Hz), 1.01 (3H, d, J = 6.6 Hz), 1.24 (3H, d, J = 5.4 Hz), 1.26 (3H, d, J = 6.0 Hz), 1.28 (3H, d, J = 6.9 Hz), 1.37 (3H, d, J = 6.9 Hz), 1.39 (3H, s), 1.56 (3H, s), 1.25–1.94 (8H, m), 2.28 (6H, s), 2.29 (3H, s), 2.47 (1H, m), 2.56 (1H, q, J = 6.9 Hz), 2.63 (2H, t, J = 8.1 Hz), 2.69 (3H, s), 3.02 (1H, quintet, J = 7.5 Hz), 3.19 (1H, dd, J = 7.5 and 10.2 Hz), 3.27 (1H, m), 3.41 (1H, m), 3.45–3.75 (2H, m), 3.83 (1H, q, J = 6.9 Hz), 4.22 (1H, d, J = 8.1 Hz), 4.30 (1H, d, J = 6.9 Hz), 4.47 (2H, s), 4.82 (1H, s), 5.00 (1H, dd, J = 2.4 and 9.9 Hz), 6.92 (1H, brt, J = 5.7 Hz), 7.02–7.18 (4H, m); ^{13}C NMR ($CDCl_3$) δ 10.2, 12.9, 14.2, 15.3, 15.6, 18.8, 19.2, 19.9, 21.1, 22.2, 26.3, 28.1, 29.7, 30.4, 33.1, 38.0, 39.0, 40.2, 47.6, 49.7, 51.0, 65.8, 69.5, 70.2, 73.0, 76.0, 78.3, 78.6, 82.3, 84.5, 103.7, 125.8, 128.6, 130.0, 135.8, 139.6, 153.8, 167.4, 169.1, 170.2, 203.9.

6.5.2. Compound 5h. MS (FAB) $818^+(M+H^+)$; HRMS (FAB) calcd for $C_{43}H_{68}N_3O_{12}$ ($M+H^+$) 818.4803, found 818.4802; IR ($CHCl_3$) 3426, 3350, 2998, 2970, 2934, 2870, 2782, 1805, 1751, 1715, 1663, 1607, 1536, 1454, 1381, 1361, 1345, 1322, 1305, 1282, 1255, 1229, 1219, 1165, 1139, 1107, 1075, 1046, 1004 (cm^{-1}); ^1H NMR ($CDCl_3$) δ 0.89 (3H, t, J = 7.2 Hz), 1.01 (3H, d, J = 6.9 Hz), 1.24 (3H, d, J = 6.0 Hz), 1.26 (3H, d, J = 6.6 Hz), 1.28 (3H, d, J = 6.9 Hz), 1.37 (3H, d, J = 6.9 Hz), 1.39 (3H, s), 1.56 (3H, s), 1.15–1.93 (8H, m), 2.28 (6H, s), 2.31 (3H, s), 2.48 (1H, m), 2.56 (1H, q, J = 6.9 Hz), 2.62 (2H, t, J = 7.8 Hz), 2.68 (3H, s), 3.02 (1H, quintet, J = 7.8 Hz), 3.19 (1H, dd, J = 7.2 and 10.5 Hz), 3.22 (1H, m), 3.37 (1H, m), 3.48–3.73 (2H, m), 3.83 (1H, q, J = 6.9 Hz), 4.21 (1H, d, J = 8.1 Hz), 4.30 (1H, d, J = 7.2 Hz), 4.45 (2H, s), 4.82 (1H, s), 5.00 (1H, dd, J = 2.4 and 9.9 Hz), 6.88 (1H, brt, J = 5.7 Hz), 6.95–7.02 (3H, m), 7.15 (1H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 10.2, 12.9, 14.2, 15.3, 15.6, 18.8, 19.9, 21.1, 21.3, 22.3, 26.3, 28.1, 30.9, 33.1, 33.2, 38.0, 38.8, 40.2, 47.6, 49.7, 51.0, 65.8, 69.5, 70.2, 73.0, 76.0, 78.4, 78.7, 82.3, 84.5, 103.7, 125.3, 126.5, 128.1, 129.1, 137.7, 141.4, 153.8, 167.4, 169.1, 170.2, 203.9.

6.5.3. Compound 5i. MS (FAB) $818^+(M+H^+)$; HRMS (FAB) calcd for $C_{43}H_{68}N_3O_{12}$ ($M+H^+$) 818.4803, found 818.4799; IR ($CHCl_3$) 3426, 3354, 2970, 2934, 2870, 2780, 1805, 1751, 1715, 1663, 1537, 1515, 1454, 1380, 1361, 1345, 1323, 1305, 1282, 1256, 1230, 1220, 1165, 1139, 1107, 1075, 1046, 1004 (cm^{-1}); ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, J = 7.2 Hz), 1.01 (3H, d, J = 6.6 Hz), 1.24 (3H, d, J = 5.4 Hz), 1.26 (3H, d, J = 6.0 Hz), 1.28 (3H, d, J = 6.9 Hz), 1.37 (3H, d, J = 6.3 Hz), 1.38 (3H, s), 1.55 (3H, s), 1.16–2.05 (8H, m), 2.27 (6H, s), 2.29 (3H, s), 2.46 (1H, m), 2.56 (1H, q, J = 6.9 Hz), 2.61 (2H, t, J = 7.8 Hz), 2.68 (3H, s), 3.02 (1H, quintet, J = 7.5 Hz), 3.18 (1H, dd, J = 7.5 and 9.9 Hz), 3.23 (1H, m), 3.36 (1H, m), 3.45–3.72 (2H, m), 3.83 (1H, q, J = 7.2 Hz), 4.21 (1H, d, J = 7.8 Hz), 4.30 (1H, d, J = 7.2 Hz), 4.45 (2H, s), 4.81 (1H, s), 5.00 (1H, dd, J = 2.7 and 10.2 Hz), 6.86 (1H, brt, J = 6.0 Hz), 7.06–7.15 (4H, m); ^{13}C NMR ($CDCl_3$) δ 10.2, 12.9, 14.2, 15.3, 15.6, 18.8, 19.9, 20.9, 21.1, 22.2, 26.3, 28.1, 30.9, 32.7, 33.1, 38.0, 38.7, 40.2, 47.6, 49.7, 51.0, 65.8, 69.5, 70.2, 72.9, 76.0, 78.4, 78.7, 82.3, 84.5, 103.7, 128.2, 128.9, 135.0, 138.4, 153.8, 167.5, 169.1, 170.2, 203.9.

6.5.4. Compound 5j. MS (FAB) $822^+(M+H^+)$; HRMS (FAB) calcd for $C_{42}H_{65}F_1N_3O_{12}$ ($M+H^+$) 822.4552, found 822.4551; IR (KBr) 3435, 2973, 2938, 2878, 2785, 1811, 1751, 1717, 1673, 1601, 1533, 1509, 1456, 1380, 1362, 1323, 1304, 1283, 1257, 1220, 1166, 1142, 1109, 1078, 1048, 1004 (cm^{-1}); ^1H NMR ($CDCl_3$) δ 0.89 (3H, t, J = 7.2 Hz), 1.02 (3H, d, J = 6.9 Hz), 1.24 (3H, d, J = 5.7 Hz), 1.26 (3H, d, J = 6.6 Hz), 1.28 (3H,

d, J = 6.9 Hz), 1.37 (3H, d, J = 6.9 Hz), 1.39 (3H, s), 1.56 (3H, s), 1.54–1.93 (8H, m), 2.27 (6H, s), 2.40–2.60 (2H, m), 2.63 (2H, t, J = 8.1 Hz), 2.68 (3H, s), 3.02 (1H, quintet, J = 7.5 Hz), 3.16–3.75 (5H, m), 3.84 (1H, q, J = 7.2 Hz), 4.22 (1H, d, J = 8.1 Hz), 4.30 (1H, d, J = 7.2 Hz), 4.44 (2H, s), 4.82 (1H, s), 4.98 (1H, dd, J = 2.4 and 9.9 Hz), 6.90–6.98 (2H, m), 6.99 (1H, t, J = 5.1 Hz), 7.13–7.19 (2H, m); ^{13}C NMR ($CDCl_3$) δ 10.2, 12.9, 14.3, 15.3, 15.5, 18.9, 19.9, 21.1, 22.3, 26.3, 28.2, 31.0, 32.4, 33.2, 38.0, 38.7, 40.2, 47.6, 49.8, 51.1, 65.9, 69.6, 70.3, 73.0, 76.1, 78.5, 78.6, 82.3, 84.6, 103.8, 114.7, 115.2, 129.6, 129.8, 137.2, 137.3, 153.7, 158.8, 163.6, 167.6, 169.2, 170.3, 203.8.

6.5.5. Compound 5k. MS (SI) 847^+(M+H$^+$); HRMS (SI) calcd for $C_{44}H_{71}N_4O_{12}$ (M+H$^+$) 847.4986, found 846.4993; IR (KBr) 3451, 2974, 2938, 2880, 2786, 1810, 1751, 1689, 1632, 1591, 1457, 1380, 1324, 1284, 1257, 1231, 1166, 1110, 1078, 1048 (cm^{-1}); ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, t, J = 7.2 Hz), 1.01 (3H, d, J = 6.9 Hz), 1.24 (3H, d, J = 6.9 Hz), 1.25 (3H, d, J = 6.3 Hz), 1.28 (3H, d, J = 6.9 Hz), 1.37 (3H, d, J = 6.9 Hz), 1.38 (3H, s), 1.55 (3H, s), 1.54–1.94 (8H, m), 2.28 (6H, s), 2.30–2.50 (2H, m), 2.56 (2H, m), 2.69 (3H, s), 2.89 (6H, s), 3.02 (1H, quintet, J = 7.8 Hz), 3.15–3.74 (5H, m), 3.83 (1H, q, J = 6.9 Hz), 4.21 (1H, d, J = 8.1 Hz), 4.30 (1H, d, J = 7.2 Hz), 4.46 (2H, s), 4.82 (1H, s), 5.02 (1H, dd, J = 2.4 and 9.9 Hz), 6.60–6.71 (2H, m), 6.76 (1H, m), 7.03–7.09 (2H, m); ^{13}C NMR ($CDCl_3$) δ 10.2, 12.9, 14.2, 15.3, 15.5, 18.7, 19.7, 21.0, 22.2, 26.2, 28.1, 29.5, 31.0, 31.9, 33.1, 37.9, 38.7, 40.0, 40.8, 47.5, 49.6, 50.9, 65.7, 69.3, 70.1, 72.9, 76.0, 78.3, 78.6, 82.2, 84.4, 103.6, 113.0, 128.8, 129.6, 148.9, 153.7, 167.3, 169.0, 170.0, 203.8.

6.5.6. Compound 5l. MS (FAB) 880^+(M+H$^+$); HRMS (FAB) calcd for $C_{48}H_{70}N_3O_{12}$ (M+H$^+$) 880.4960, found 880.4963; IR ($CHCl_3$) 3436, 3354, 3024, 3006, 2976, 2936, 2874, 1805, 1751, 1715, 1665, 1536, 1485, 1454, 1410, 1381, 1362, 1346, 1319, 1305, 1282, 1256, 1229, 1220, 1166, 1139, 1107, 1078, 1045, 1004 (cm^{-1}); ^{1}H NMR ($CDCl_3$) δ 0.86 (3H, t, J = 7.5 Hz), 1.01 (3H, d, J = 6.9 Hz), 1.23 (3H, d, J = 6.0 Hz), 1.25 (3H, d, J = 6.6 Hz), 1.28 (3H, d, J = 6.9 Hz), 1.38 (3H, d, J = 7.2 Hz), 1.39 (3H, s), 1.56 (3H, s), 1.54–1.94 (8H, m), 2.26 (6H, s), 2.26–2.48 (1H, m), 2.56 (1H, q, J = 6.9 Hz), 2.70 (3H, s), 2.70 (2H, t, J = 7.5 Hz), 3.02 (1H, quintet, J = 7.5 Hz), 3.14–3.74 (6H, m), 3.84 (1H, q, J = 7.2 Hz), 4.22 (1H, d, J = 8.1 Hz), 4.30 (1H, d, J = 7.2 Hz), 4.46 (2H, s), 4.83 (1H, s), 5.00 (1H, dd, J = 2.4 and 9.9 Hz), 6.96 (1H, t, J = 5.4 Hz), 7.26–7.59 (9H, m); ^{13}C NMR ($CDCl_3$) δ 10.2, 12.9, 14.2, 15.3, 15.6, 18.8, 19.9, 21.1, 22.2, 26.3, 28.1, 30.8, 32.7, 33.1, 38.0, 38.8, 40.2, 47.6, 49.8, 51.0, 65.8, 69.5, 70.2, 73.0, 76.0, 78.4, 78.6, 82.3, 84.5, 103.7, 126.8, 126.9, 127.0, 128.6, 128.7, 138.6, 140.7, 141.1, 153.8, 167.5, 169.2, 170.3, 203.8.

6.6. Preparation of compounds 5m–5s

Compounds **5m**–**5s** were prepared by the same procedure as that described for the synthesis of **5d** with 3-pyridin-4-yl-propylamine,[16] 3-pyridin-3-yl-propylamine,[16] 3-pyridin-2-yl-propylamine,[16] 3-naphthalen-2-yl-propylamine (**16g**), 3-naphthalen-1-yl-propylamine (**16h**), 3-quinolin-3-yl-propylamine (**16i**), and 3-quinolin-4yl-propylamine (**16j**), respectively.

6.6.1. Compound 5m. MS (FAB) 805^+(M+H$^+$); HRMS (FAB) calcd for $C_{41}H_{65}N_4O_{12}$ (M+H$^+$) 805.4599, found 805.4604; IR (KBr) 3432, 2971, 2934, 2877, 2784, 1809, 1751, 1716, 1674, 1603, 1534, 1456, 1416, 1378, 1322, 1305, 1284, 1259, 1222, 1166, 1110, 1078, 1048 (cm^{-1}); ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, t, J = 6.6 Hz), 1.01 (3H, d, J = 6.9 Hz), 1.25 (3H, d, J = 6.6 Hz), 1.27 (3H, d, J = 9.0 Hz), 1.28 (3H, d, J = 9.3 Hz), 1.38 (3H, d, J = 5.4 Hz), 1.39 (3H, s), 1.57 (3H, s), 1.54–1.94 (8H, m), 2.30 (6H, s), 2.44–2.70 (4H, m), 2.69 (3H, s), 2.95–3.05 (1H, m), 3.14–3.23 (2H, m), 3.40–3.98 (5H, m), 4.23 (1H, d, J = 7.5 Hz), 4.30 (1H, d, J = 7.2 Hz), 4.43 (2H, s), 4.83 (1H, s), 4.98 (1H, brd J = 10.8 Hz), 7.18 (3H, br s), 8.48 (2H, br s); ^{13}C NMR ($CDCl_3$) δ 10.2, 12.8, 14.3, 15.3, 15.6, 18.8, 19.9, 21.1, 22.2, 26.3, 28.3, 29.6, 32.4, 33.1, 37.9, 38.7, 40.1, 47.6, 49.8, 51.0, 65.8, 69.4, 70.2, 72.9, 75.9, 78.4, 78.6, 82.3, 84.6, 103.7, 123.9, 149.5, 153.8, 167.6, 169.3, 170.5, 203.8.

6.6.2. Compound 5n. MS (SI) 805^+(M+H$^+$); HRMS (SI) calcd for $C_{41}H_{65}N_4O_{12}$ (M+H$^+$) 805.4595, found 805.4606; IR (KBr) 3433, 2972, 2937, 2878, 2784, 1810, 1751, 1716, 1673, 1575, 1534, 1456, 1423, 1380, 1363, 1322, 1305, 1284, 1258, 1234, 1220, 1167, 1142, 1109, 1079, 1048, 1005 (cm^{-1}); ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, t, J = 7.2 Hz), 1.01 (3H, d, J = 6.9 Hz), 1.24 (3H, d, J = 6.3 Hz), 1.26 (3H, d, J = 6.0 Hz), 1.28 (3H, d, J = 6.6 Hz), 1.38 (3H, d, J = 6.9 Hz), 1.39 (3H, s), 1.56 (3H, s), 1.54–1.94 (8H, m), 2.29 (6H, s), 2.44–2.67 (4H, m), 2.69 (3H, s), 3.01 (1H, quintet, J = 7.5 Hz), 3.15–3.75 (5H, m), 3.85 (1H, q, J = 6.9 Hz), 3.93 (1H, br s), 4.22 (1H, d, J = 7.8 Hz), 4.30 (1H, d, J = 7.2 Hz), 4.45 (2H, s), 4.83 (1H, s), 4.99 (1H, dd, J = 2.7 and 10.5 Hz), 7.11 (1H, brt, J = 5.7 Hz), 7.21 (1H, m), 7.57 (1H, brd, J = 8.1 Hz), 8.44 (2H, m); ^{13}C NMR ($CDCl_3$) δ 10.2, 12.9, 14.3, 15.3, 15.6, 18.8, 19.9, 21.1, 22.2, 26.3, 28.3, 30.2, 30.6, 33.1, 37.9, 38.6, 40.1, 47.6, 49.8, 51.0, 65.8, 69.4, 70.2, 72.9, 75.9, 78.4, 78.6, 82.3, 84.6, 103.7, 123.3, 135.9, 136.9, 147.2, 149.7, 153.8, 167.6, 169.3, 170.4, 203.8.

6.6.3. Compound 5o. MS (FAB) 805^+(M+H$^+$); HRMS (FAB) calcd for $C_{41}H_{65}N_4O_{12}$ (M+H$^+$) 805.4599, found 805.4594; IR (KBr) 3434, 2972, 2937, 2878, 2784, 1810, 1751, 1716, 1674, 1591, 1568, 1533, 1456, 1380, 1363, 1322, 1305, 1284, 1257, 1233, 1219, 1167, 1109, 1078, 1048, 1004 (cm^{-1}); ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, t, J = 7.5 Hz), 1.03 (3H, d, J = 6.9 Hz), 1.25 (3H, d, J = 6.9 Hz), 1.27 (3H, d, J = 7.2 Hz), 1.27 (3H, d, J = 5.8 Hz), 1.37 (3H, d, J = 6.9 Hz), 1.37 (3H, s), 1.56 (3H, s), 1.54–1.96 (6H, m), 1.99 (2H, t, J = 7.8 Hz), 2.47 (6H, br s), 2.55 (2H, m), 2.69 (3H, s), 2.84 (2H, t, J = 7.2 Hz), 3.03 (1H, quintet, J = 7.8 Hz), 3.21–3.74 (5H, m), 3.83 (1H, q, J = 6.9 Hz), 4.21 (1H, d, J = 7.5 Hz), 4.34 (1H, d, J = 7.2 Hz), 4.46 (2H, s), 4.82 (1H, s), 5.03 (1H, dd, J = 2.4 and 9.9 Hz), 6.90 (1H, m), 7.06–7.11 (1H, m), 7.19 (1H, d, J = 7.8 Hz), 7.58 (1H, dt, J = 2.1 and 7.8 Hz), 8.49 (1H, m); ^{13}C NMR

($CDCl_3$) δ 10.3, 13.0, 14.3, 15.3, 15.6, 18.9, 19.9, 21.1, 22.3, 26.4, 28.3, 29.2, 33.2, 35.3, 38.1, 38.5, 40.2, 47.6, 49.8, 51.1, 65.9, 69.5, 70.3, 73.0, 76.1, 78.4, 78.7, 82.4, 84.6, 103.7, 121.0, 122.8, 136.3, 149.1, 153.8, 161.2, 167.4, 169.2, 170.2, 203.9.

6.6.4. Compound 5p. MS (FAB) $854^+(M+H^+)$; HRMS (FAB) calcd for $C_{46}H_{68}N_3O_{12}$ ($M+H^+$) 854.4803, found 854.4810; IR ($CHCl_3$) 3428, 3350, 2970, 2934, 2870, 2780, 1805, 1751, 1714, 1661, 1537, 1507, 1454, 1381, 1361, 1345, 1322, 1304, 1282, 1256, 1232, 1222, 1165, 1138, 1107, 1078, 1047, 1004 (cm^{-1}); ^1H NMR ($CDCl_3$) δ 0.81 (3H, t, J = 7.5 Hz), 1.01 (3H, d, J = 6.9 Hz), 1.22 (3H, d, J = 6.0 Hz), 1.26 (3H, d, J = 6.9 Hz), 1.27 (3H, d, J = 7.5 Hz), 1.37 (3H, d, J = 7.2 Hz), 1.38 (3H, s), 1.55 (3H, s), 1.16–1.92 (6H, m), 1.99 (2H, quintet, J = 7.8 Hz), 2.27 (6H, s), 2.29 (3H, s), 2.46 (1H, m), 2.56 (1H, q, J = 6.9 Hz), 2.70 (3H, s), 2.83 (2H, t, J = 7.8 Hz), 3.01 (1H, quintet, J = 7.8 Hz), 3.18 (1H, dd, J = 7.8 and 9.9 Hz), 3.28 (1H, m), 3.43 (1H, m), 3.45–3.74 (2H, m), 3.83 (1H, q, J = 6.9 Hz), 4.22 (1H, d, J = 7.5 Hz), 4.29 (1H, d, J = 7.8 Hz), 4.46 (2H, s), 4.82 (1H, s), 4.98 (1H, dd, J = 2.4 and 9.9 Hz), 6.95 (1H, brt, J = 5.7 Hz), 7.31–7.45 (3H, m), 7.65 (1H, br s), 7.73–7.79 (3H, m); ^{13}C NMR ($CDCl_3$) δ 10.1, 12.9, 14.2, 15.3, 15.6, 18.8, 19.9, 21.1, 22.2, 26.3, 28.1, 30.7, 33.1, 33.3, 38.0, 38.9, 40.2, 47.6, 49.8, 51.0, 65.8, 69.5, 70.2, 73.0, 76.0, 78.4, 78.7, 82.3, 84.5, 103.7, 124.9, 125.7, 126.3, 127.2, 127.4, 127.8, 131.9, 133.6, 139.0, 153.8, 162.8, 167.5, 169.2, 170.2, 203.8.

6.6.5. Compound 5q. MS (FAB) $854^+(M+H^+)$; HRMS (FAB) calcd for $C_{46}H_{68}N_3O_{12}$ ($M+H^+$) 854.4803, found 854.4799; IR (KBr) 3435, 2972, 2937, 2877, 1811, 1751, 1716, 1675, 1532, 1456, 1380, 1362, 1323, 1304, 1283, 1258, 1233, 1219, 1167, 1142, 1109, 1078, 1048, 1004 (cm^{-1}); ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, J = 7.2 Hz), 1.00 (3H, d, J = 7.2 Hz), 1.22 (3H, d, J = 6.0 Hz), 1.25 (3H, d, J = 7.5 Hz), 1.27 (3H, d, J = 7.8 Hz), 1.37 (3H, d, J = 7.2 Hz), 1.38 (3H, s), 1.55 (3H, s), 1.24–2.08 (8H, m), 2.27 (6H, s), 2.46 (1H, m), 2.56 (1H, q, J = 6.6 Hz), 2.69 (3H, s), 2.68–2.86 (1H, br s), 3.01 (1H, quintet, J = 8.1 Hz), 3.12 (2H, t, J = 7.5 Hz), 3.19 (1H, m), 3.28–3.73 (4H, m), 3.83 (1H, q, J = 6.9 Hz), 4.21 (1H, d, J = 8.4 Hz), 4.29 (1H, d, J = 7.5 Hz), 4.47 (2H, s), 4.83 (1H, s), 5.01 (1H, dd, J = 2.7 and 9.9 Hz), 6.93 (1H, brt, J = 5.4 Hz), 7.33–7.54 (4H, m), 7.69 (1H, dd, J = 0.6 and 7.8 Hz), 7.83 (1H, dd, J = 1.5 and 8.1 Hz), 8.03 (1H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 10.3, 12.9, 14.3, 15.4, 15.6, 18.9, 19.9, 21.1, 22.3, 26.4, 28.2, 30.2, 33.2, 38.0, 39.1, 40.2, 47.6, 49.8, 51.1, 65.9, 69.5, 70.3, 73.0, 76.1, 78.4, 78.7, 82.3, 84.6, 103.7, 123.7, 125.4, 125.5, 125.8, 125.9, 126.6, 128.7, 131.8, 133.8, 137.5, 153.8, 167.5, 169.2, 170.3, 203.9.

6.6.6. Compound 5r. MS (FAB) $855^+(M+H^+)$; HRMS (FAB) calcd for $C_{45}H_{67}N_4O_{12}$ ($M+H^+$) 855.4755, found 855.4747; IR (KBr) 3433, 2972, 2937, 2878, 2784, 1810, 1751, 1717, 1673, 1637, 1569, 1534, 1496, 1456, 1380, 1363, 1323, 1305, 1283, 1258, 1234, 1219, 1167, 1141, 1109, 1079, 1048, 1004 (cm^{-1}); ^1H NMR ($CDCl_3$) δ 0.81 (3H, t, J = 7.2 Hz), 1.01 (3H, d, J = 6.9 Hz), 1.23 (3H, d, J = 6.0 Hz), 1.27 (3H, d, J = 6.6 Hz), 1.28 (3H, d, J = 7.2 Hz), 1.36 (3H, d, J = 6.6 Hz), 1.39 (3H, s), 1.55 (3H, s), 1.24–2.06 (8H, m), 2.27 (6H, s), 2.58 (1H, m), 2.56 (1H, q, J = 6.6 Hz), 2.70 (3H, s), 2.86 (2H, t, J = 8.1 Hz), 3.01 (1H, quintet, J = 7.8 Hz), 3.18 (1H, dd, J = 7.2 and 10.2 Hz), 3.22–3.74 (4H, m), 3.83 (1H, q, J = 7.2 Hz), 4.22 (1H, d, J = 8.1 Hz), 4.29 (1H, d, J = 7.5 Hz), 4.46 (2H, s), 4.83 (1H, s), 4.98 (1H, dd, J = 2.4 and 7.8 Hz), 7.16 (1H, br s,), 7.50 (1H, m), 7.64 (1H, m), 7.80 (1H, dd, J = 0.9 and 8.1 Hz), 8.02 (1H, d, J = 1.2 Hz), 8.05 (1H, d, J = 8.4 Hz), 8.79 (1H, d, J = 2.1 Hz); ^{13}C NMR ($CDCl_3$) δ 10.1, 12.9, 14.3, 15.3, 15.6, 18.8, 19.9, 21.1, 22.2, 26.3, 28.2, 30.4, 30.5, 33.1, 38.0, 38.8, 40.2, 47.6, 49.8, 51.0, 65.9, 69.5, 70.2, 73.0, 75.9, 78.4, 78.6, 82.3, 84.6, 103.7, 125.2, 126.4, 127.5, 128.2, 128.4, 129.0, 134.2, 146.8, 152.0, 153.8, 167.6, 169.3, 170.5, 203.8.

6.6.7. Compound 5s. MS (SI) $855^+(M+H^+)$; HRMS (SI) calcd for $C_{45}H_{67}N_4O_{12}$ ($M+H^+$) 855.4751, found 855.4749; IR (KBr) 3434, 2971, 2935, 2877, 2854, 2784, 1811, 1751, 1717, 1673, 1591, 1533, 1509, 1456, 1380, 1362, 1322, 1305, 1284, 1257, 1234, 1219, 1167, 1141, 1109, 1078, 1048, 1004 (cm^{-1}); ^1H NMR ($CDCl_3$) δ 0.87 (3H, t, J = 7.2 Hz), 1.00 (3H, d, J = 6.9 Hz), 1.23 (3H, d, J = 6.0 Hz), 1.24 (3H, d, J = 7.5 Hz), 1.28 (3H, d, J = 7.2 Hz), 1.37 (3H, d, J = 7.2 Hz), 1.39 (3H, s), 1.56 (3H, s), 1.54–2.12 (8H, m), 2.27 (6H, s), 2.46 (1H, m), 2.56 (1H, q, J = 7.2 Hz), 2.69 (3H, s), 3.01 (1H, quintet, J = 7.5 Hz), 3.13 (2H, dd, J = 4.2 and 8.4 Hz), 3.18 (1H, dd, J = 7.5 and 9.9 Hz), 3.33 (1H, m), 3.54 (3H, m), 3.68 (1H, m), 3.83 (1H, q, J = 6.9 Hz), 4.22 (1H, d, J = 8.1 Hz), 4.29 (1H, d, J = 7.5 Hz), 4.44 and 4.49 (2H, Abq, J = 14.1 Hz), 4.85 (1H, s), 4.99 (1H, dd, J = 2.7 and 10.5 Hz), 7.23 (1H, brt, J = 6.3 Hz), 7.31 (1H, d, J = 4.5 Hz), 7.57 (1H, m), 7.69 (1H, m), 8.05 (1H, dd, J = 0.9 and 8.4 Hz), 8.09 (1H, d, J = 8.1 Hz), 8.81 (1H, d, J = 4.5 Hz); ^{13}C NMR ($CDCl_3$) δ 10.2, 12.9, 14.3, 15.3, 15.6, 18.8, 19.9, 21.1, 22.2, 26.3, 28.2, 29.3, 29.7, 33.1, 38.0, 39.0, 40.2, 47.6, 49.8, 51.0, 65.8, 69.5, 70.3, 73.0, 75.9, 78.4, 78.6, 82.3, 84.6, 103.7, 120.6, 123.5, 126.3, 127.5, 128.9, 130.0, 147.5, 148.2, 150.2, 153.8, 167.6, 169.3, 170.5, 203.8.

6.7. Preparation of compound 8

6.7.1. Amidation. Compound **6** was prepared from **3** with *N*-methylpropargylamine in 82% yield as a colorless foam by the same procedure as that described for the synthesis of **5d**.

MS (FAB) $992^+(M+H^+)$; HRMS (FAB) calcd for $C_{52}H_{70}N_3O_{16}$ ($M+H^+$), 992.4756 found 992.4747; IR (KBr) 3428, 3290, 3064, 3032, 2975, 2938, 2880, 1809, 1752, 1702, 1587, 1496, 1455, 1405, 1382, 1350, 1330, 1289, 1255, 1167, 1114, 1068 (cm^{-1}); ^1H NMR ($CDCl_3$) δ 2.66 (3H, s), 2.81, 2.85 (3H, two s), 3.00, 3.12 (3H, two s); ^{13}C NMR ($CDCl_3$) δ 10.3, 13.0, 13.8, 15.4, 15.5, 15.6, 15.7, 18.7, 19.7, 20.6, 22.4, 26.2, 26.3, 28.8, 28.9, 33.1, 33.4, 33.7, 35.7, 36.2, 37.8, 39.2, 47.0, 47.1, 49.5, 49.6, 51.0, 54.7, 54.8, 67.1, 67.2, 68.7, 69.3, 69.5, 71.1, 72.0, 72.8, 74.7, 76.3, 78.2, 78.3, 78.4, 82.6, 84.6, 100.7, 127.5, 127.7, 127.8, 127.9, 128.2, 128.3, 128.4, 135.5, 135.6, 136.7, 154.3, 154.4, 154.5, 156.1, 156.5, 158.8,

165.8, 165.9, 168.6, 168.8, 169.0, 203.7, 203.9 (two rotational isomers were observed by ^{1}H NMR and ^{13}C NMR spectra).

6.7.2. Coupling reaction. To a solution of **6** (256 mg, 0.262 mmol) in CH_3CN (5 mL) were successively added NEt_3 (36 μL, 0.26 mmol), CuI (5 mg, 0.026 mmol), *p*-iodobenzene (59 μL, 0.524 mmol), and $Cl_2Pd(PPh_3)_2$ (9.2 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 1 h. The mixture was filtered and diluted with water, and then the mixture was extracted with AcOEt. The resultant residue was purified by column chromatography on silicagel (*n*-hexane/AcOEt = 8/1–1/1) to give 192 mg of compound **7** as a colorless foam (87%).

MS (FAB) $1068^+(M+H^+)$; HRMS (FAB) calcd for $C_{58}H_{74}N_3O_{16}$ ($M+H^+$), 1068.5069, found 1068.5073; IR (KBr) 3429, 3064, 3032, 2974, 2938, 2880, 1810, 1752, 1702, 1658, 1489, 1455, 1404, 1382, 1350, 1330, 1288, 1254, 1167, 1114, 1068 (cm^{-1}); ^{1}H NMR ($CDCl_3$) δ 2.67 (3H, s), 2.81, 2.85 (3H, two s), 3.07, 3.17 (3H, two s); ^{13}C NMR ($CDCl_3$) δ 10.3, 13.0, 13.8, 15.4, 15.5, 15.6, 18.8, 19.7, 20.6, 22.4, 26.3, 26.4, 28.8, 28.9, 33.0, 33.1, 33.5, 33.7, 35.7, 36.2, 37.8, 39.9, 47.1, 47.2, 49.5, 49.6, 51.0, 54.8, 67.1, 67.2, 68.7, 69.3, 69.5, 71.2, 74.8, 76.3, 76.4, 78.3, 78.4, 82.6, 83.7, 83.9, 84.4, 84.6, 100.7, 122.4, 122.7, 127.6, 127.7, 127.9, 128.2, 128.3, 128.4, 131.7, 131.8, 135.5, 135.6, 136.7, 154.3, 154.4, 154.5, 156.1, 158.8, 165.7, 165.9, 168.5, 168.8, 169.0, 203.7, 203.9 (two rotational isomers were observed by ^{1}H NMR and ^{13}C NMR spectra).

6.7.3. Hydrogenation, deprotection, and N-methylation. Subsequently, **7** (192 mg, 0.182 mmol) was diluted with EtOH (16 mL) and 0.2 M acetate buffer (4 mL, pH 4.4). To this solution was added 20% $Pd(OH)_2$/C (58 mg, 0.109 mmol) and stirred at room temperature under H_2 atmosphere for 2 h. After confirming the disappearance of **7** by TLC, 37% aqueous HCHO (2 mL) was added to the reaction mixture and stirred at room temperature under H_2 atmosphere for an additional 1 h. The mixture was filtered and concentrated. After being diluted with water, the mixture was basified with 5% aqueous $NaHCO_3$ and then extracted with AcOEt. The resultant residue was purified by column chromatography on silicagel ($CHCl_3$/MeOH = 80/1–40/1) to give 118 mg of compound **8** as a colorless foam (79%).

MS (FAB) $818^+(M+H^+)$; HRMS (FAB) calcd for $C_{43}H_{68}N_3O_{12}$ ($M+H^+$) 818.4803, found 818.4805; IR (KBr) 3447, 3060, 2972, 2937, 2878, 2785, 1809, 1752, 1717, 1653, 1560, 1541, 1495, 1455, 1380, 1361, 1323, 1304, 1283, 1258, 1233, 1219, 1167, 1142, 1109, 1079, 1048, 1005 (cm^{-1}); ^{1}H NMR ($CDCl_3$) δ 2.27 (6H, s), 2.68, 2.70 (3H, two s), 2.92, 3.00 (3H, two s); ^{13}C NMR ($CDCl_3$) δ 10.3, 13.1, 14.3, 15.4, 15.5, 15.8, 18.8, 18.9, 21.2, 22.4, 26.5, 28.2, 28.6, 29.6, 29.8, 32.7, 33.1, 33.2, 34.6, 38.3, 40.2, 47.5, 47.8, 48.7, 49.7, 51.0, 65.9, 69.5, 70.3, 70.9, 71.4, 76.3, 78.5, 79.4, 82.7, 84.7, 84.8, 103.8, 125.8, 126.1, 128.3, 128.4, 128.5, 140.9, 141.7, 154.4, 165.7, 165.8, 168.7, 168.8, 169.1, 204.0 (two rotational isomers were observed by ^{1}H NMR and ^{13}C NMR spectra).

6.8. Preparation of compound 11

Compound **1**[9] (2.96 g, 3.3 mmol) was dissolved in THF (30 mL) under N_2 atmosphere. To this solution was added 0.5 M 9-BBN (19.8 mL, THF solution) and stirred at room temperature for 1 h. After cooling the mixture with an ice-water bath, trifluoro methanesulfonic acid 3-phenyl-propenyl ester **9**[14] (0.8 g, 3 mmol) in THF (2 mL), $Cl_2Pd(PPh_3)_2$ (118 mg, 0.168 mmol), and 1 N NaOH (9.9 mL) were added to the mixture successively. After being stirred at room temperature for an additional 1 h, the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with AcOEt (150 mL). The aqueous layer was extracted with AcOEt (70 mL) and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silicagel (*n*-hexane/AcOEt = 4/1–1/1) to give 2.26 g of compound **10** as a colorless foam (mixture of *E*/*Z* isomers. 77%).

MS (FAB) $1015^+(M+H^+)$; HRMS (FAB) calcd for $C_{57}H_{79}N_2O_{14}$ ($M+H^+$) 1015.5531, found 1015.5547; IR (KBr) 3507, 3383, 3065, 3031, 3013, 2976, 2938, 2876, 1744, 1695, 1495, 1454, 1407, 1381, 1351, 1333, 1293, 1263, 1223, 1212, 1205, 1168, 1115, 1069 (cm^{-1}); ^{1}H NMR ($CDCl_3$) δ 2.70 (3H, s), 2.81, 2.85 (3H, two s).

Compound **10** (880 mg, 0.87 mmol) was dissolved in THF (13 mL) under N_2 atmosphere. To this solution were added pyridine (0.7 mL, 8.65 mmol) and $(CCl_3O)_2$-CO (570 mg, 1.92 mmol) with stirring overnight at room temperature. The reaction mixture was carefully quenched with saturated aqueous $NaHCO_3$ under cooling with an ice-water bath and stirred for 0.5 h at room temperature. After separating the organic layer, the aqueous layer was extracted with AcOEt (30 mL), and the combined organic layer was washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silicagel (*n*-hexane/AcOEt = 4/1–1/2) to give 680 mg of compound bearing C-11,12 carbonate group as a colorless foam (89%). Subsequently, deprotection and N-methylation were performed by the same procedure as that described for the synthesis of **5d**, and compound **11** (344 mg, colorless foam) was obtained in 76% yield.

MS (FAB) $789^+(M+H^+)$; HRMS (FAB) calcd for $C_{43}H_{69}N_2O_{11}$ ($M+H^+$) 789.4901, found 789.4908; IR (KBr) 3458, 3061, 2973, 2936, 2876, 2785, 1810, 1751, 1716, 1627, 1603, 1496, 1455, 1381, 1361, 1324, 1305, 1284, 1257, 1219, 1167, 1142, 1110, 1076, 1048, 1005 (cm^{-1}); ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, t, J = 7.2 Hz), 0.963 (3H, d, J = 6.9 Hz), 1.19–1.32 (12H, m), 1.37 (6H, d, J = 6.9 Hz), 140 (3H, s), 1.54 (3H, s), 1.50–1.95 (7H, m), 2.26 (6H, s), 2.38–2.55 (2H, m), 2.60 (2H, t, J = 7.5 Hz), 2.68 (3H, s), 3.04 (1H, m), 3.18 (1H, dd, J = 7.2 and 10.2 Hz), 3.42–3.70 (3H, m), 3.82 (1H, q, J = 6.6 Hz), 3.93–4.07 (2H, m), 4.18 (1H, d,

J = 8.4 Hz), 4.29 (1H, d, J = 7.5 Hz), 4.77 (1H, s), 5.04 (1H, dd, J = 2.4 and 9.9 Hz), 7.15–7.29 (5H, m).

^{13}C NMR ($CDCl_3$) δ 10.4, 13.2, 14.3, 15.5, 15.9, 18.9, 19.7, 21.2, 22.5, 26.0, 26.1, 28.2, 29.1, 31.5, 33.0, 35.9, 38.3, 40.2, 47.9, 49.6, 51.1, 65.9, 69.5, 70.4, 73.6, 76.4, 78.4, 79.5, 83.0, 84.7, 103.9, 125.6, 128.2, 128.4, 142.8, 154.5, 163.5, 169.1, 204.0.

6.9. Preparation of compound 13

To a solution of **3** (100 mg, 0.106 mmol) in toluene (6 mL) were added DMF (1 μL, 0.01 mmol) and oxalyl chloride (12 μL, 0.13 mmol) at room temperature, and the reaction mixture was stirred for 30 min at room temperature. To this solution, 3-phenyl-1-propanol (29 μL, 0.21 mmol), pyridine (17 μL, 0.21 mmol), and *N*,*N*-dimethylamino pyridine (1 mg) were added and the reaction mixture was stirred overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with AcOEt (20 mL). The aqueous layer was extracted with AcOEt (20 mL) and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silicagel (*n*-hexane/AcOEt = 4/1–1/1) to give 88 mg of compound **8** bearing an ester group as a colorless foam (78%).

MS (FAB) 1059$^+$(M+H$^+$); HRMS (FAB) calcd for $C_{57}H_{75}N_2O_{17}$ (M+H$^+$) 1059.5066, found 1059.5050; IR (KBr) : 3433, 3063, 3029, 2973, 2938, 2879, 1811, 1752, 1703, 1633, 1605, 1497, 1455, 1382, 1351, 1329, 1289, 1254, 1213, 1167, 1112, 1084, 1067, 1047 (cm^{-1}); ^{1}H NMR ($CDCl_3$) δ 2.69 (3H, s), 2.81, 2.85 (3H, two s); ^{13}C NMR ($CDCl_3$) δ 10.4, 13.1, 13.8, 15.3, 15.6, 15.7, 18.7, 19.6, 20.6, 22.4, 26.5, 28.8, 30.0, 32.0, 33.1, 35.7, 36.1, 37.8, 47.0, 47.1, 49.5, 50.9, 54.7, 63.8, 67.0, 67.1, 68.6, 69.2, 69.4, 70.3, 74.6, 76.3, 78.1, 78.3, 82.4, 84.4, 100.5, 125.7, 127.3, 127.5, 127.6, 127.7, 128.0, 128.1, 128.2, 135.2, 135.3, 136.4, 140.8, 154.0, 154.1, 154.2, 155.8, 156.2, 165.5, 168.6, 169.7, 203.3, 203.5 (two rotational isomers were observed by ^{1}H NMR and ^{13}C NMR spectra).

Compound **13** (12 mg) was prepared in 32% yield from **12** (51 mg) as a colorless foam by the same procedure as that described for the synthesis of **5d**.

MS (SI) 805$^+$(M+H$^+$); HRMS (SI) calcd for $C_{42}H_{65}N_2O_{13}$ (M+H$^+$) 805.4483, found 805.4486; IR (KBr) 3447, 2924, 2877, 2851, 2785, 1810, 1752, 1653, 1636, 1628, 1604, 1569, 1560, 1542, 1508, 1497, 1456, 1381, 1362, 1323, 1304, 1284, 1258, 1167, 1142, 1108, 1084, 1047, 1004 (cm^{-1}); ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, t, J = 7.2 Hz), 1.03 (3H, d, J = 6.9 Hz), 1.23 (3H, d, J = 6.0 Hz), 1.25 (3H, d, J = 6.9 Hz), 1.27 (3H, d, J = 7.8 Hz), 1.37 (3H, d, J = 6.9 Hz), 1.42 (3H, s), 1.54 (3H, s), 1.54–2.02 (8H, m), 2.27 (6H, s), 2.40–2.60 (3H, m), 2.69 (2H, t, J = 7.8 Hz), 2.72 (3H, s), 3.05 (1H, quintet, J = 7.8 Hz), 3.19 (1H, dd, J = 7.2 and 9.9 Hz), 3.48–3.74 (2H, m), 3.83 (1H, q, J = 6.9 Hz), 4.16 (2H, t, J = 6.6 Hz), 4.20 (1H, d, J = 7.5 Hz), 4.30 (1H, d, J = 7.2 Hz), 4.54 and 4.67 (2H, Abq, J = 16.5 Hz), 4.77 (1H, s), 5.02 (1H, dd, J = 2.7 and 9.6 Hz), 7.12–7.30 (5H, m); ^{13}C NMR ($CDCl_3$) δ 10.4, 13.2, 14.3, 15.3, 15.8, 18.8, 19.7, 21.1, 22.5, 26.7, 28.2, 29.7, 30.1, 32.1, 38.3, 40.2, 47.8, 49.7, 51.1, 64.0, 65.9, 69.5, 70.3, 70.5, 76.4, 78.5, 79.5, 82.5, 84.8, 103.8, 126.0, 128.4, 128.5, 141.1, 154.3, 166.0, 169.1, 170.1, 204.1.

6.10. Preparation of compound 16i (Method A)

To a solution of *N*-Boc-propargylamine (4.66 g, 30 mmol) in CH_3CN (50 mL) were successively added NEt_3(6.96 mL, 30 mmol), CuI (76 mg, 0.4 mmol), 3-bromo-quinoline (1.34 mL, 10 mmol), and $Cl_2Pd(PPh_3)_2$ (140 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 1 h and for 5 h at 60 °C. The mixture was cooled to room temperature and filtered, then diluted with 5% aqueous $NaHCO_3$, and finally extracted with AcOEt. The resultant residue was purified by column chromatography on silicagel (*n*-hexane/AcOEt = 4/1–1/1) to give 2.8 g of compound **14i** (99%).

^{1}H-NMR ($CDCl_3$) δ 1.49 (9H, s), 4.23 (2H, d, J = 5.4 Hz), 4.83 (1H, br s), 7.57 (1H, m), 7.73 (1H, m), 7.78 (1H, d, J = 8.4 Hz), 8.08 (1H, d, J = 8.7 Hz), 8.21 (1H, d, J = 1.8 Hz), 8.89 (1H, d, J = 1.8 Hz).

Compound **14i** (2.8 g, 9.9 mmol) was dissolved in EtOH (60 mL). To this solution was added 20% $Pd(OH)_2$/C (754 mg, 1.4 mmol) with stirring at room temperature under H_2 atmosphere for 2 h. The mixture was filtered and concentrated, and 2.7 g of compound **15i** was obtained (95%).

^{1}H NMR ($CDCl_3$) δ 1.45 (9H, s), 1.94 (2H, m), 2.88 (2H, t, J = 7.2 Hz), 3.23 (2H, m), 4.62 (1H, br s), 7.59 (1H, m), 7.73 (1H, m), 7.82 (1H, d, J = 8.4 Hz), 8.08 (1H, m), 8.21 (1H, dd, J = 1.2 and 9.6 Hz), 8.81 (1H, d, J = 2.1 Hz).

Compound **15i** (2.8 g, 9.4 mmol) was dissolved in CH_2Cl_2 (30 mL) and stirred on an ice-water bath. To this solution was added CF_3CO_2H (6 mL), and the reaction mixture was stirred at room temperature for 1 h and concentrated in vacuo. The resultant residue was quenched with diluted aqueous NaOH and extracted with AcOEt. The aqueous layer was extracted with AcOEt, and the combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Finally, 2.7 g of compound **16i** was obtained (95%).

^{1}H NMR ($CDCl_3$) δ 2.02 (2H, m), 2.81 (2H, t, J = 10.8 Hz), 2.93 (2H, m), 5.04 (2H, br s), 7.48 (1H, m), 7.62 (1H, m), 7.69 (1H, d, J = 8.4 Hz), 7.88 (1H, d, J = 2.4 Hz), 8.00 (1H, d, J = 8.1 Hz), 8.73 (1H, d, J = 1.5 Hz).

6.11. Preparation of compound 16e (Method B)

N-Boc-allylamine (500 mg, 3.2 mmol) was dissolved in THF (5 mL) under N_2 atmosphere. To this solution was added 0.5 M 9-BBN (9.5 mL, THF solution), with

stirring at room temperature for 2 h. Next, 1-iodo-4-nitro-benzene (633 mg, 2.5 mmol), $Cl_2Pd(PPh_3)_2$ (111 mg, 0.16 mmol), and 1 N NaOH (4.7 mL) were successively added to the mixture. After stirring at room temperature for an additional 1.5 h, the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with AcOEt (150 mL). The aqueous layer was extracted with AcOEt (70 mL), and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified on silicagel column (*n*-hexane/AcOEt = 10/1–2/1) to give 651 mg of compound **15e** (91%).

^{1}H NMR ($CDCl_3$) δ 1.45 (9H, s), 1.85 (2H, m), 2.75 (2H, t, J = 8.1 Hz), 3.17 (2H, m), 4.58 (1H, br s), 7.34 (2H, d, J = 8.4 Hz), 8.15 (2H, d, J = 8.4 Hz).

Compound **15e** (600 mg, 2.1 mmol) was dissolved in CH_2Cl_2 (6 mL) and stirred on an ice-water bath. To this solution was added CF_3CO_2H (6 mL), and the reaction mixture was stirred at room temperature for 1 h and concentrated in vacuo. The resultant residue was quenched with diluted aqueous NaOH and extracted with AcOEt. The aqueous layer was extracted with AcOEt, and the combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified on silicagel column to give 331 mg of compound **16e** (86%).

^{1}H NMR ($CDCl_3$) δ 1.83 (2H, m), 2.04 (2H, br s), 2.78 (2H, t, J = 6.3 Hz), 2.78 (2H, t, J = 7.8 Hz), 7.35 (2H, d, J = 8.4 Hz), 8.14 (2H, d, J = 8.4 Hz).

6.12. Preparation of compounds 16a–16d, and 16h

Compounds **16a**–**16d**, and **16h** were prepared in the same procedure (Method B) as that described for the synthesis of **16e** with 1-iodo-2-methyl-benzene, 1-iodo-3-methyl-benzene, 1-iodo-4-methyl-benzene, 1-fluoro-4-iodo-benzene, and 1-iodo-naphthalene, respectively.

6.12.1. 6a(CF_3CO_2H salt). ^{1}H NMR ($CDCl_3$) δ 1.91 (2H, m), 2.24 (3H, s), 2.62 (2H, t, J = 7.8 Hz), 2.94 (2H, m), 7.05–7.12 (4H, m), 7.67 (3H, br s).

6.12.2. 16b(CF_3CO_2H salt). ^{1}H NMR ($CDCl_3$) δ 1.82 (2H, m), 2.32 (3H, s), 2.62 (2H, t, J = 7.8 Hz), 2.74 (2H, t, J = 7.2 Hz), 6.98–7.22 (7H, m).

6.12.3. 16c(CF_3CO_2H salt). ^{1}H NMR ($CDCl_3$) δ 1.94 (2H, m), 2.60 (2H, t, J = 7.5 Hz), 2.92 (2H, m), 7.01 (2H, d, J = 7.8 Hz), 7.08 (2H, d, J = 7.8 Hz), 7.52 (3H, br s).

6.12.4. 16d. ^{1}H NMR ($CDCl_3$) δ 1.87 (2H, m), 2.61 (2H, t, J = 7.8 Hz), 2.84 (2H, t, J = 7.5 Hz), 4.10–4.90 (2H, br s), 6.92–7.11 (4H, m).

6.12.5. 16h. ^{1}H NMR ($CDCl_3$) δ 1.94 (2H, m), 2.83 (2H, t, J = 7.2 Hz), 3.06 (2H, t, J = 7.8 Hz), 3.75 (2H, br s), 7.27 (1H, d, J = 6.9 Hz), 7.35 (1H, t, J = 8.1 Hz), 7.42–7.51 (2H, m), 7.69 (1H, d, J = 8.1 Hz), 7.81–7.84 (1H, m), 7.95–7.99 (1H, m).

6.13. Preparation of compounds 16f, 16g, and 16j

Compounds **16f**, **16g**, and **16j** were prepared in the same procedure (Method A) as that described for the synthesis of **16i** with 4-bromo-biphenyl, 2-bromo-naphthalene, and 4-iodo-quinoline,[17] respectively.

6.13.1. 16f. ^{1}H NMR ($CDCl_3$) δ 1.71 (2H, br s), 1.82 (2H, m), 2.70 (2H, t, J = 7.8 Hz), 2.77 (2H, t, J = 6.9 Hz), 7.24–7.60 (9H, m).

6.13.2. 16g. ^{1}H NMR ($CDCl_3$) δ 1.38 (2H, br s), 1.86 (2H, m), 2.77 (2H, t, J = 7.2 Hz), 2.82 (2H, t, J = 7.5 Hz), 7.34 (1H, dd, J = 1.8 and 8.4 Hz), 7.38–7.48 (2H, m), 7.62 (1H, d, J = 0.6 Hz), 7.76–7.81 (3H, m).

6.13.3. 16j. ^{1}H NMR ($CDCl_3$) δ 1.82 (2H, m), 2.84 (2H, t, J = 7.2 Hz), 3.13 (2H, t, J = 7.5 Hz), 7.24 (1H, d, J = 4.5 Hz), 7.55 (1H, m), 7.70 (1H, m), 8.06 (1H, d, J = 7.2 Hz), 8.12 (1H, d, J = 7.5 Hz), 8.81 (1H, d, J = 4.2 Hz).

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16. 3-Pyridin-4-yl-propylamine, 3-Pyridin-2-yl-propylamine were prepared from 3-(4-pyridyl)-1-propanol, 3-(3-pyridyl)-1-propanol, and 3-(2-pyridyl)-1-propanol, respectively Gibson, J. S.; Pilichowska, S. *Angew. Chem. Int. Ed.* **1968**, *7*, 919–9303-Pyridin-4-yl-propylamine; ^{1}H NMR ($CDCl_3$) δ 1.29 (2H, br s), 1.78 (2H, m), 2.67 (2H, t, J = 7.8 Hz), 2.75 (2H, t, J = 7.2 Hz), 7.12 (2H, d, J = 5.7 Hz), 8.49 (2H, d, J = 5.7 Hz).; 3-Pyridin-3-yl-propylamine; ^{1}H NMR ($CDCl_3$) δ 1.35 (2H, br s), 1.78 (2H, m), 2.67 (2H, t, J = 8.2 Hz), 2.75 (2H, t, J = 6.8 Hz), 7.18–7.24 (1H, m), 7.47–7.54 (1H, m), 8.42–8.46 (2H, m).; 3-Pyridin-2-yl-propylamine; ^{1}H NMR ($CDCl_3$) δ 2.02 (2H, m), 2.94 (2H, t, J = 10.8 Hz), 2.95 (2H, t, J = 9.9 Hz), 5.02 (2H, br s), 7.10–7.21 (2H, m), 7.58–7.64 (1H, m), 8.43–8.52 (1H, m).
17. Tsumambac, G. E.; Villalobos, C. N. *Synlett* **2003**, *12*, 1801–1804.