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A new type of ketolide bearing an *N*-aryl-alkyl acetamide moiety at the C-9 iminoether: Synthesis and structure–activity relationships (2)

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Abstract—A new type of ketolide bearing an *N*-aryl-alkyl acetamide moiety at the C-9 iminoether and its analogues were prepared, and their antibacterial activities and pharmacokinetic properties were evaluated. We found that the introduction of an (*R*)-alkyl group between the amide and iminoether groups could improve the pharmacokinetic properties while maintaining the activity against erythromycin-resistant *Streptococcus pneumoniae*. Among the ketolides prepared with the (*R*)-alkyl group, compound **5p** with an *N*-(3-quinoxalin-6-yl-propyl)-propionamide moiety was found to have in vivo efficacy comparable to CAM with potent in vitro antibacterial activities against the key respiratory pathogens including *Haemophilus influenzae* and erythromycin-resistant *S. pneumoniae*.

1. Introduction

The macrolide antibiotics have been used for respiratory tract infections, especially for those caused by Gram-positive pathogens. Among them, clarithromycin[1] (CAM) has favorable pharmacokinetic properties and has been used against the key respiratory tract pathogens.

However, second-generation derivatives of erythromycin A (EM) typified by CAM do not have activity against erythromycin (EM)-resistant strains, which have increased significantly in recent years. Third-generation derivatives of EM, the ketolides such as telithromycin[2] and cethromycin,[3] have potent activity against key respiratory pathogens including *Haemophilus influenzae* and EM-resistant *Streptococcus pneumoniae* (Fig. 1).

These two ketolides have structural similarity in terms of the aryl-alkyl group and the C-11,12 carbamate moiety. We have already reported a new type of 9-iminoether ketolide[4] with C-11,12-carbonate and an *N*-aryl-alkyl acetamide group at the C-9 iminoether moiety such as **1**[4] and **2**[4] (Fig. 2), which showed potent antibacterial activities in vitro. However, it was disappointing that they exhibited only poor in vivo efficacy compared to CAM in the lung infection model. That is likely to be due to their pharmacokinetic profile, especially their

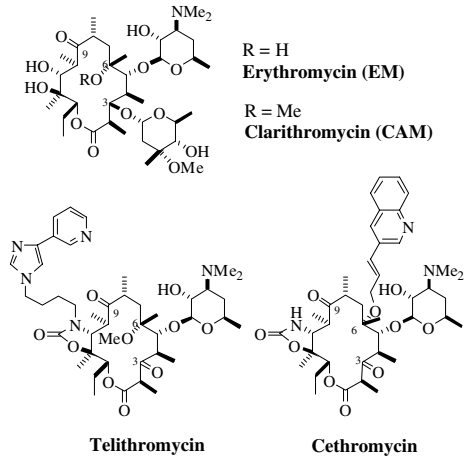

Figure 1. Structure of macrolide antibiotics.

Keywords: Ketolide; Antibacterial activity; C-9 iminoether; *N*-Aryl-alkyl acetamide; Pharmacokinetic property; Erythromycin-resistant; Macrolide; Antibiotic.
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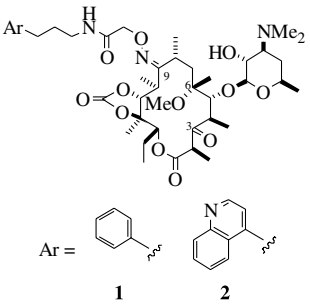


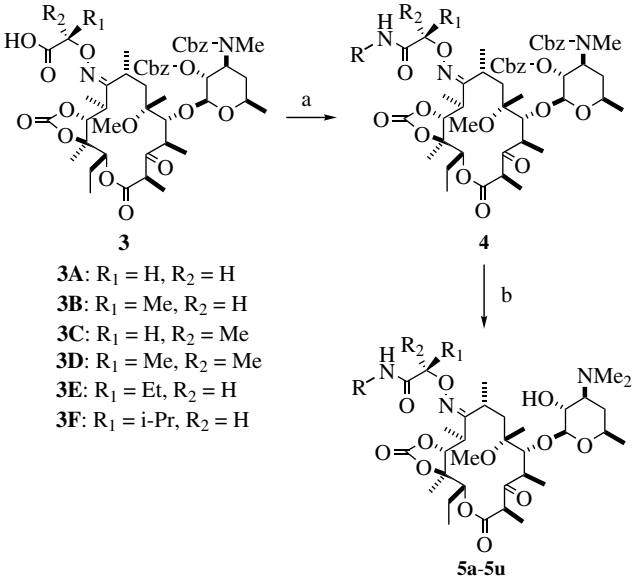
Figure 2. Structure of 9-iminoether ketolide.

low total amount of distribution in lung tissue and low free rate in plasma.

We report herein the modification of 9-iminoether ketolide and optimization of the aryl group to improve the pharmacokinetic profile while maintaining their potent antibacterial activities.

2. Synthesis

9-Iminoether derivatives bearing an *N*-aryl-alkylamide group were prepared by using carboxylic acid **3**. Amidation of **3** with various primary amines by using oxalyl chloride and a catalytic amount of dimethylformamide gave **4**, which was subjected to deprotection and subsequent N-methylation, to afford amide derivatives **5a**–**u** as shown in Scheme 1. In the step for deprotection and subsequent N-methylation, we used method A ((1) 20% $Pd(OH)_2$; (2) 20% $Pd(OH)_2$, H_2, HCHO aq) for compound **5a**–**i**, and method B[5] ((1) TMS-I, $AlCl_3$/anisole; (2) HCO_2H, HCHO aq) for compound **5j**–**u**,



Scheme 1. Reagents and conditions. Method A: (a) $(ClCO)_2$, cat. DMF, RNH_2; (b) 1—H_2, 20% $Pd(OH)_2$/C; 2—H_2, 20% $Pd(OH)_2$/C, HCHO aq, acetate buffer (pH 4.4). Method B: (a) $(ClCO)_2$, cat. DMF, RNH_2; (b) 1—TMSI, $AlCl_3$/anisole; 2—HCOOH, HCHO aq.

since compounds with heteroaryls cannot be prepared by catalytic hydrogenation.

Compound **3A** was prepared by the procedure described in our previous paper.[4] Compounds **3B**–**F** were prepared from 9-oxime-C-11,12-diol **6**[6] as shown in Scheme 2. Treatment of **6** with allyl α-bromocarboxylate **7** and NaH gave compound **8**, which was transformed into **9** bearing C-11,12 carbonate using triphosgene and pyridine in THF. The conversion from allyl ester **9** to carboxylic acid **3** was accomplished using catalytic $Pd(PPh_3)_4$ and PPh_3 and pyrrolidine.

3-Aryl-propylamines used for the synthesis of **5** were prepared as shown in Schemes 3–5. Other amines not listed in the above schemes were commercially available or prepared by known methods. Allyl α-bromocarboxylates **7** used for the synthesis of carboxylic acid **3** were prepared from the corresponding α-bromocarboxylic acids, which are commercially available.

3. Results and discussion

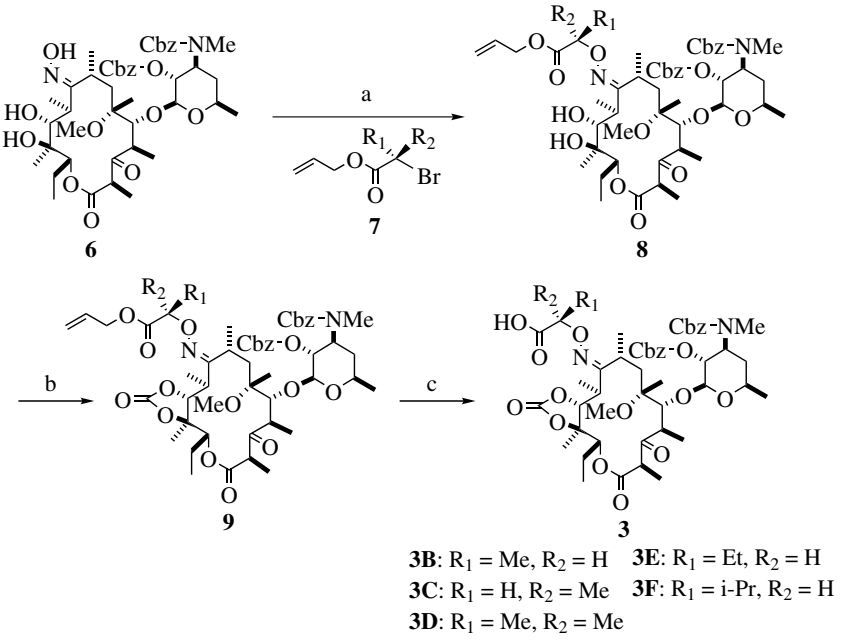
All the ketolides were evaluated in vitro by standard agar dilution method with various strains. Their antibacterial activity against both EM-susceptible and -resistant *Staphylococcus aureus* and *S. pneumoniae* along with one strain of *Haemophilus influenzae* are shown in Tables 1–5.

In our previous paper,[4] we presented the ketolides shown in Figure 2 and demonstrated that their propyl linker between their amide and aryl groups was essential for the potent antibacterial activities.

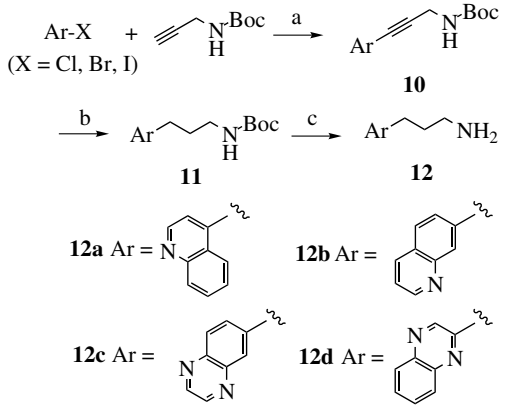
These ketolides had potent antibacterial activities against key respiratory pathogens, including EM-resistant strains. On the other hand, they had poor pharmacokinetic properties (low total amount of antibiotics distributed in lung tissue and low free rate in plasma), which seemed to lead to weak in vivo efficacy.

For the improvement of these properties with maintaining potent antibacterial activity, we utilized **1**[4] as a model compound. First, we examined the effect of the hetero atoms in the linker between the aryl and amide groups, and also the effect of the substituent group between the amide and iminoether.

Table 1 presents the antibacterial activities of **5a**–**d** bearing a hetero atom in their linker and **5e**–**g** bearing a substituent between the amide and iminoether groups. All analogues bearing the hetero atom linker lost the activity against EM-resistant *S. pneumoniae* though compounds **5b** and **d** showed activity twice as potent as **1** against *H. influenzae*. On the other hand, among the derivatives with substituent group between the amide and iminoether groups, compound **5e** bearing the (*R*)-methyl group showed activity as potent as **1** against EM-resistant *S. pneumoniae*. These results prompted us to prepare compound **5h** and **i** bearing (*R*)-ethyl and (*R*)-isopropyl groups.



Scheme 2. Reagents and conditions: (a) NaH/DMF, **6**; (b) $(CCl_3O)_2CO$, pyridine/THF; (c) $Pd(PPh_3)_4$, PPh_3, pyrrolidine/CH_3CN.

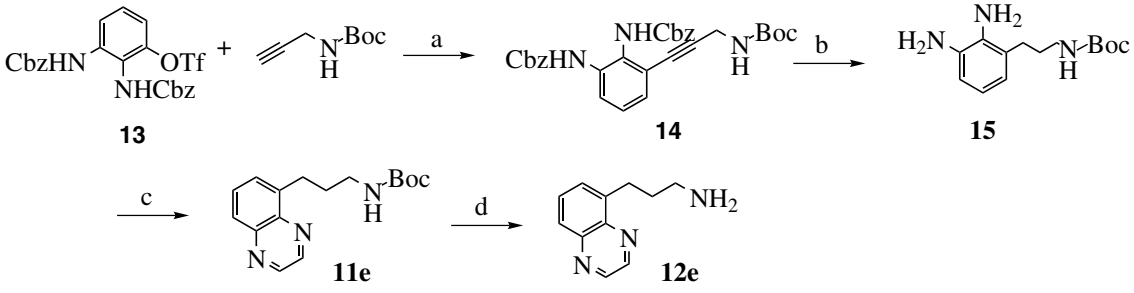


Scheme 3. Reagents and conditions: (a) NEt_3, CuI, cat. $Cl_2Pd(PPh_3)_2$; (b) H_2, 5% Pd/C; (c) TMS-I.

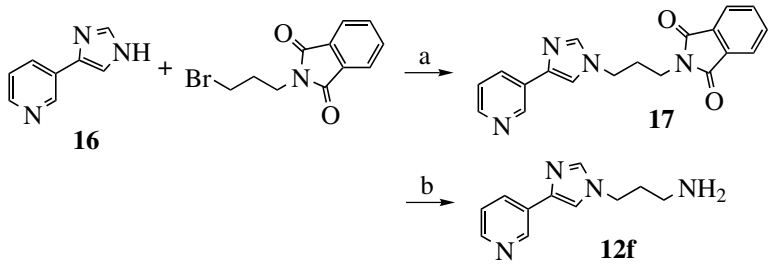
Table 2 summarizes the activities of analogues bearing an (*R*)-alkyl group between the amide and imionoether groups. All compounds in Table 2 with the (*R*)-alkyl group showed potent antibacterial activities against Gram-positive EM-susceptible strains, while maintaining potent antibacterial activity against EM-resistant *S. pneumoniae*. However, compound **5i** showed somewhat decreased activity against *H. influenzae* and EM-resistant *S. aureus*.

Since compounds **5e** and **h** had potent activities comparable to that of **1**, their lung AUCs were also evaluated (Table 3). It is noteworthy that these values increase with increasing molecular weight of the substituent, and their lung AUCs are superior to that of CAM.

Further improvement of the pharmacokinetic profiles was achieved by investigating aryl groups other than the phenyl ring. The derivatives of **5e**,**h**, and **1** prepared are shown in Figure 3 (**5j**–**u**). The antibacterial activities, lung AUCs, and serum free rate of the derivatives listed in Figure 3 are summarized in Table 4. All compounds showed activities nearly equal to that of telithromycin against the strains listed in Table 4 including the EM-resistant ones. From the viewpoint of lung AUC improvement, the (*R*)-methyl group was found to be better than the (*R*)-ethyl group for all aryl groups in Table 4.

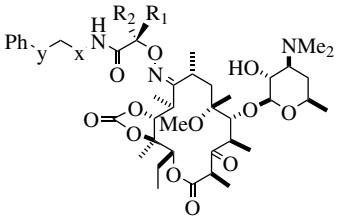


Scheme 4. Reagents and conditions: (a) NEt_3, CuI, cat. $Cl_2Pd(PPh_3)_2$; (b) H_2, 10% $Pd(OH)_2/C$, CH_3CO_2H; (c) $(CHO)_2$, EtOH, reflux; (d) TMS-I.



Scheme 5. Reagents and conditions: (a) NaH/DMF; (b) NH_2NH_2/EtOH, reflux.

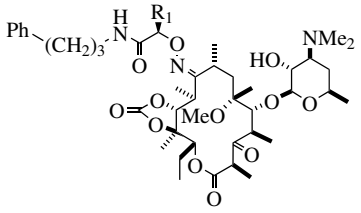
Table 1. In vitro antibacterial activities of compounds **5a**–**g** and **1**



	5a	5b	5c	5d	5e	5f	5g	1
R_1	H	H	H	H	Me	H	Me	H
R_2	H	H	H	H	H	Me	Me	H
x	O	CH_2	NMe	CH_2	CH_2	CH_2	CH_2	CH_2
y	CH_2	O	CH_2	NMe	CH_2	CH_2	CH_2	CH_2

Strain	MIC [μg/mL]								
	5a	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**1**	CAM
S. aureus Smith	0.2	0.2	0.39	0.2	0.2	0.39	0.78	0.2	0.2
S. aureus SR17347 (EM-R)	0.39	0.2	0.39	0.39	0.39	0.39	0.78	0.2	>100
S. pneumoniae Type I	0.025	0.025	0.05	0.05	0.05	0.1	0.05	0.025	0.025
S. pneumoniae SR16651 (EM-R)	100	25	100	12.5	0.78	100	12.5	0.78	>100
H. influenzae SR88562	12.5	3.13	12.5	3.13	6.25	6.25	12.5	6.25	3.13

Table 2. In vitro antibacterial activities of compounds **5e**,**h**,**i**, and **1**



	5e	5h	5i	1
R_1	Me	Et	i-Pr	H

Strain	MIC [μg/mL]				
	5e	**5h**	**5i**	**1**	CAM
S. aureus Smith	0.2	0.39	0.39	0.2	0.2
S. aureus SR17347 (EM-R)	0.39	0.39	0.78	0.2	>100
S. pneumoniae Type I	0.05	0.05	0.025	0.025	0.025
S. pneumoniae SR16651 (EM-R)	0.78	0.78	0.78	0.78	>100
H. influenzae SR88562	6.25	6.25	12.5	6.25	3.13

Table 3. The lung AUCs* of **5e**,**h**, and **1** in rats

	5e	5h	1	CAM
Lung AUC (0–6 h) [μg h/g]	181	347	26	221
Lung AUC (0–24 h) [μg h/g]	641	1360	—	359

*Dose 20 mg/kg (po).

Significant improvement of lung AUCs was observed for compound **5m** bearing the 7-quinolyl group and **5p** with the 6-quinoxalyl group, while in the case of compounds **2** and **5j** bearing the 4-quinolyl group, the improvement was not notable. Compound **5u** bearing the imidazole-pyridine group, which is the same moiety of telithromycin, also showed potent antibacterial activities but its pharmacokinetic profile was inferior to those of the other derivatives. Among the derivatives listed in Table 4, compound **5p** bearing the 6-quinoxalyl group was found to be the best analogue in terms of its potent antibacterial activities, superior lung AUCs, and serum free rate. The in vivo efficacy of **5p**, examined using the model of mouse infected by EM-susceptible *S. pneumoniae*, was found to show equal activity to that of CAM (Table 5).

4. Conclusion

A new type of ketolide bearing an *N*-arylpropylacetamide group at the C-9-iminoether moiety and its derivatives were prepared, and their antibacterial activities, lung AUCs, and serum free rates were evaluated. For improvement of lung AUCs while maintaining potent activities against EM-resistant strains, extensive structural modification was performed, which finally led to the discovery of derivatives with an (*R*)-alkyl substituent between the amide and iminoether groups at the C-9 position. Among them, compound **5p** bearing the

Table 4. In vitro antibacterial activities, lung AUCs in rats (dose 20 mg/kg (po)), and mouse serum free rates of compounds **5j**–**u**, telithromycin, and CAM

Strain	MIC [μg/mL]							
	2	**5j**	**5k**	**51**	**5m**	**5n**	Telithromycin	
S. aureus Smith	0.2	0.2	0.2	0.2	0.2	0.2	0.2	
S. aureus SR17347(EM-R)	0.2	0.2	0.2	0.2	0.2	0.2	0.39	
S. pneumoniae Type I	0.2	0.025	0.025	0.025	0.025	0.0125	0.0125	
S. pneumoniae SR16651 (EM-R)	0.78	0.2	0.2	0.1	0.05	0.1	0.2	
H. influenzae SR88562	0.78	3.13	3.13	1.56	3.13	3.13	1.56	
Lung AUC (0–6 h) [μg h/g]	19.1	48.3	—	72.7	267	131	12.0	
Lung AUC (0–24 h) [μg h/g]	59.4	144	—	—	671	532	30.8	
Mouse serum free (%)	5.9	2.6	6.8	3.6	4.0	—	9.4	
	5o	**5p**	**5q**	**5r**	**5s**	**5t**	**5u**	CAM
S. aureus Smith	0.1	0.2	0.2	0.2	0.39	0.2	0.39	0.2
S. aureus SR17347 (EM-R)	0.1	0.2	0.39	0.2	0.39	0.2	0.39	>100
S. pneumoniae Type I	0.0125	0.025	0.025	0.025	0.025	0.025	0.0125	0.025
S. pneumoniae SR16651 (EM-R)	0.1	0.1	0.1	0.39	0.1	0.05	0.1	>100
H. influenzae SR88562	3.13	3.13	6.25	6.25	3.13	3.13	3.13	3.13
Lung AUC (0–6 h) [μg h/g]	20.0	154	111	76.4	9.71	92	7.3	221
Lung AUC (0–24 h) [μg h/g]	49.3	389	315	154	21	248	20.2	359
Mouse serum free (%)	11.0	8.2	4.5	4.3	6.8	6.5	—	52.8

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

Compound	*S. pneumoniae*	
	MIC [μg/mL]	ED_{50} [mg/kg]
5p	0.025	10.8
CAM	0.025	10.8

N-(3-quinoxalin-6-yl-propyl)-propionamide group was identified as the best compound with balanced potent activities and superior pharmacokinetic profiles. This compound showed excellent activities against the key respiratory pathogens including EM-resistant strains in vitro, and also exhibited potent in vivo efficacy equal to that of CAM in experimental animal infection models.

5. Experimental

Infrared (IR) spectra were determined on a JASCO FT/IR-700 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini-300 (300 MHz) and Gemini-300 (75 MHz) spectrometers, respectively. Chemical shifts are reported in parts per million from TMS (in $CDCl_3$) as the internal standard. HR-FAB/MS 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 with silica gel 60 F_{254} and visualized with UV light or 10% H_2SO_4 containing 5% ammonium molybdate and 0.2%

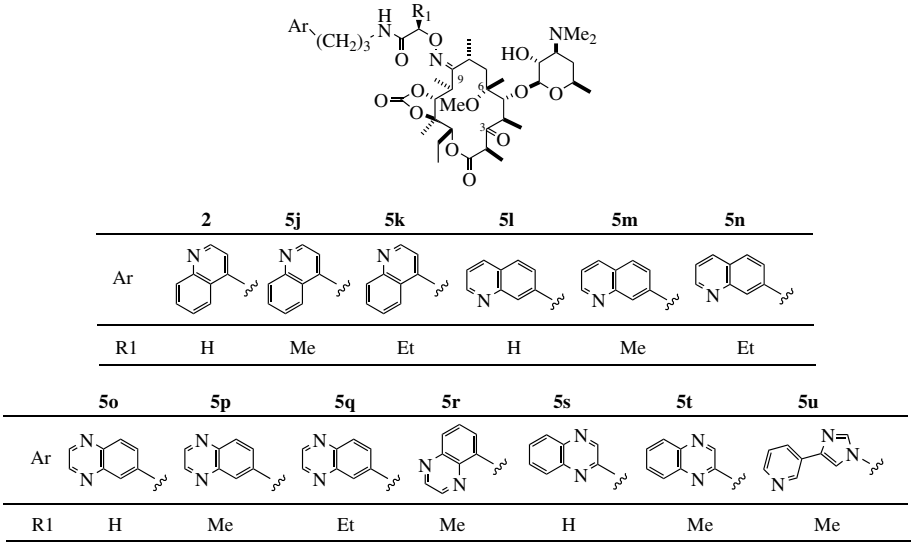


Figure 3. Structures of compounds **5j**–**u** and **2**.

ceric sulfate. Flash chromatography was performed with Merck silica gel 60 (230–400 mesh).

5.1. Measurement of in vitro antibacterial activity

MICs were determined by a serial twofold dilution method in Sensitivity Disk Agar-N (Nissui Pharmaceutical, Tokyo, Japan). 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.

5.2. Preparation of compound 3D

To a solution of **6**[6] (500 mg, 0.583 mmol) in DMF (10 mL) was added NaH 58 mg (60% in mineral oil 1.46 mmol) under cooling on an ice-water bath, and the mixture was stirred for 30 min. To this solution, 2-bromo-2-methyl-propionic acid allyl ester **7d** (302 mg, 1.46 mmol) in DMF (1 mL) was added and the reaction mixture was stirred another 30 min under cooling on an ice-water bath. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with AcOEt (40 mL). The aqueous layer was extracted with AcOEt (40 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 silica gel (*n*-hexane:AcOEt, 8:1–2:1) to give 521 mg of **8d** as a colorless foam (91%).

5.2.1. Compound 8d. MS (FAB): 983^+($M+H^+$). HR-MS (FAB) calcd for $C_{52}H_{75}N_2O_{16}$: 983.5117. Found: 983.5118.

IR (KBr): 3438, 3066, 3033, 2980, 2938, 2877, 1747, 1706, 1648, 1634, 1497, 1455, 1406, 1381, 1351, 1333, 1285, 1254, 1172, 1115, 1085, 1068, 1033, 983, 961, 935, 893, 824, 783, 754, 698, 617, 595, 576, 525, 471 (cm^{-1}).

^1H NMR ($CDCl_3$) δ (ppm): 2.72 (3H, s), 2.81 and 2.85 (3H, two s).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.6, 13.8, 13.9, 14.8, 16.2, 18.4, 19.3, 20.6, 21.5, 23.8, 24.3, 26.2, 28.9, 33.1, 35.7, 36.2, 37.2, 45.6, 45.7, 49.7, 50.7, 54.8, 65.4, 67.0, 67.1, 68.4, 68.5, 69.3, 69.5, 69.8, 73.5, 74.5, 76.3, 77.4, 77.9, 78.0, 80.8, 100.0, 118.2, 127.3, 127.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.3, 131.7, 135.0, 135.1, 136.4, 154.1, 154.2, 155.8, 156.2, 169.0, 169.5, 173.2, 205.1, 205.5.

To a solution of **8d** (520 mg, 0.528 mmol) in THF (15 mL) were added $(CCl_3CO)_2O$ (313 mg, 1.06 mmol) and pyridine (427 μL, 5.28 mmol) under cooling on an ice-water bath, and the mixture was stirred overnight at room temperature. The reaction mixture was quenched carefully with saturated aqueous $NaHCO_3$ under cooling on 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 (20 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 silica gel (*n*-hexane:AcOEt, 3:1–2:1) to give 530 mg of **9d** as a colorless foam (99%).

5.2.2. Compound 9d. MS (FAB): 1031^+ ($M+Na^+$). HR-MS (FAB) calcd for $C_{53}H_{72}N_2O_{17}Na$: 1031.4729. Found: 1031.4758.

IR (KBr): 3423, 3065, 2978, 2939, 2880, 1812, 1752, 1704, 1647, 1587, 1497, 1455, 1381, 1362, 1329, 1288, 1253, 1166, 1114, 1085, 1067, 1048, 1003, 988, 930, 826, 782, 769, 755, 697, 623, 596, 518, 457 (cm^{-1}).

^1H NMR ($CDCl_3$) δ (ppm): 2.67 (3H, s), 2.81 and 2.85 (3H, two s).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.4, 13.0, 13.8, 15.2, 15.7, 15.9, 18.8, 19.5, 20.6, 22.4, 23.7, 24.4, 26.0, 28.8, 33.1, 35.6, 36.1, 37.6, 47.1, 47.2, 49.4, 51.0, 54.6, 65.2, 67.0, 67.1, 68.6, 69.1, 69.4, 74.5, 76.2, 76.3, 78.1, 81.0, 82.4, 84.2, 100.5, 117.6, 127.3, 127.4, 127.6, 127.7, 128.0, 128.1, 132.0, 135.2, 135.3, 136.4, 153.9, 154.1, 154.2, 155.7, 156.1, 163.3, 168.6, 173.3, 203.3, 203.5.

Compound **9d** (520 mg, 0.515 mmol) was dissolved with CH_3CN (7 mL) and AcOEt (7 mL) under N_2 atmosphere. After cooling this solution on an ice-water bath, $Pd(PPh_3)_4$ (60 mg, 0.05 mmol), PPh_3 (27 mg, 0.1 mmol), pyrrolidine (65 μL, 0.77 mmol), and H_2O (700 μL) were added successively to the mixture. After stirring at room temperature for an additional hour, the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with AcOEt (30 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 silica gel (*n*-hexane:AcOEt, 1:1–1:4) to give 480 mg of compound **3D** as a colorless foam (96%).

5.2.3. Compound 3D. MS (FAB): 969^+ ($M+H^+$). HR-MS (FAB) calcd for $C_{50}H_{69}N_2O_{17}$: 969.4596. Found: 969.4612.

IR (KBr): 3422, 3065, 3033, 2979, 2939, 2880, 1814, 1752, 1705, 1587, 1497, 1455, 1382, 1360, 1330, 1291, 1254, 1168, 1114, 1084, 1067, 1048, 1003, 988, 970, 932, 919, 826, 782, 755, 697, 628, 594, 542, 519, 457 (cm^{-1}).

^1H NMR ($CDCl_3$) δ (ppm): 2.65 (3H, s), 2.80 and 2.84 (3H, two s).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.3, 12.9, 13.8, 15.2, 15.3, 18.5, 19.5, 20.6, 22.3, 23.8, 24.6, 26.3, 28.9, 33.3, 35.7, 36.1, 37.6, 46.7, 46.8, 49.6, 50.9, 54.7, 67.0, 67.1, 68.6, 69.2, 69.4, 74.5, 76.2, 78.0, 81.3, 82.0, 84.2, 100.3, 127.3, 127.4, 127.6, 127.7, 127.8, 128.0, 128.1, 128.2, 128.3, 130.0, 131.7, 131.9, 134.7, 134.8, 135.1, 135.3, 136.3, 153.3, 154.1, 154.2, 155.8, 156.2, 167.6, 168.7, 175.0, 203.4, 203.7.

5.3. Preparation of compounds 3A–C,E, and F

Preparation of **3A** was reported in our previous paper. Compounds **3B**, **3C**, **3E**, and **3F** were prepared in the same procedure described for the synthesis of **3D** with (*S*)-2-bromo-propionic acid allyl ester **7b**, (*R*)-2-bromo-propionic acid allyl ester **7c**, (*S*)-2-bromo-butyric acid allyl ester **7e**, and (*S*)-2-bromo-3-methyl-butyric acid allyl ester **7f**, respectively.

5.3.1. Compound 3B. MS (FAB): 955^+ ($M+H^+$). HR-MS (FAB) calcd for $C_{49}H_{67}N_2O_{17}$: 955.4440. Found: 955.4450.

IR (KBr): 3423, 3065, 3033, 2978, 2939, 2881, 1813, 1752, 1704, 1497, 1455, 1382, 1330, 1291, 1254, 1167, 1114, 1084, 1066, 1048, 991, 951, 897, 826, 782, 770, 754, 739, 698, 624, 519, 457 (cm^{-1}).

^1H NMR ($CDCl_3$) δ (ppm): 2.66 (3H, s), 2.81 and 2.84 (3H, two s).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.3, 12.9, 13.8, 15.1, 15.2, 15.4, 15.7, 18.5, 19.6, 20.6, 22.3, 26.4, 28.9, 33.2, 35.7, 36.2, 37.7, 46.6, 46.7, 49.6, 50.9, 54.7, 67.1, 67.2, 68.6, 69.2, 69.4, 74.6, 76.2, 76.6, 78.0, 82.1, 84.3, 100.3, 127.4, 127.5, 127.6, 127.7, 128.0, 128.1, 128.2, 135.2, 135.3, 136.4, 153.4, 154.1, 154.3, 155.9, 156.2, 167.9, 168.7, 172.8, 203.4, 203.7.

5.3.2. Compound 3C. MS (FAB): 955^+ ($M+H^+$). HR-MS (FAB) calcd for $C_{49}H_{67}N_2O_{17}$: 955.4440. Found: 955.4442.

IR (KBr): 3429, 3065, 3033, 2977, 2939, 2881, 1812, 1752, 1704, 1587, 1497, 1455, 1382, 1331, 1289, 1254, 1166, 1113, 1083, 1068, 1048, 1003, 953, 899, 826, 782, 769, 755, 739, 698, 624, 595, 575, 518, 458 (cm^{-1}).

^1H NMR ($CDCl_3$) δ (ppm): 2.65 (3H, s), 2.81 and 2.84 (3H, two s).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.3, 13.0, 13.8, 15.3, 16.9, 18.5, 19.5, 20.6, 22.3, 26.5, 28.8, 33.1, 35.7, 36.2, 37.7, 46.9, 49.4, 50.9, 54.7, 67.1, 67.2, 68.6, 69.2, 69.4, 74.6, 76.2, 78.1, 78.4, 82.4, 84.4, 84.7, 100.4, 127.4, 127.5, 127.6, 127.7, 128.0, 128.1, 128.2, 135.0, 135.1, 135.3, 135.8, 136.4, 153.8, 154.1, 154.2, 155.8, 156.2, 166.8, 168.7, 176.1, 203.4, 203.6.

5.3.3. Compound 3E. MS (FAB): 969^+ ($M+H^+$). HR-MS (FAB) calcd for $C_{50}H_{69}N_2O_{17}$: 969.4596. Found: 969.4603.

IR (KBr): 3422, 3065, 3033, 2975, 2938, 2880, 1813, 1752, 1704, 1497, 1456, 1383, 1330, 1291, 1254, 1167, 1114, 1083, 1066, 989, 953, 934, 909, 826, 782, 769, 754, 739, 698, 625, 595, 576, 518, 457 (cm^{-1}).

^1H NMR ($CDCl_3$) δ (ppm): 2.67 (3H, s), 2.80 and 2.84 (3H, two s).

^{13}C NMR ($CDCl_3$) δ (ppm): 9.6, 10.3, 13.0, 13.8, 15.1, 15.2, 15.4, 18.6, 19.5, 20.6, 22.4, 23.5, 26.4, 28.9, 33.3, 35.7, 36.2, 37.7, 46.6, 46.7, 49.6, 50.9, 54.7, 67.1, 67.2, 68.7, 69.2, 69.4, 74.6, 76.2, 78.0, 81.4, 82.1, 84.3, 100.3, 127.4, 127.5, 127.6, 127.7, 128.0, 128.1, 128.2, 135.2, 135.3, 136.4, 153.4, 154.1, 154.3, 155.9, 156.2, 167.9, 168.7, 172.3, 203.5, 203.7.

5.3.4. Compound 3F. MS (FAB): 983^+ ($M+H^+$). HR-MS (FAB) calcd for $C_{51}H_{71}N_2O_{17}$: 983.4753. Found: 983.4745.

IR (KBr): 3429, 3065, 3033, 2973, 2938, 2879, 1812, 1752, 1705, 1497, 1456, 1383, 1330, 1291, 1254, 1167, 1114, 1067, 990, 933, 913, 782, 769, 754, 739, 698 (cm^{-1}).

^1H NMR ($CDCl_3$) δ (ppm): 2.68 (3H, s), 2.81 and 2.85 (3H, two s).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.3, 13.0, 13.8, 14.8, 15.0, 15.5, 17.2, 18.6, 19.1, 19.5, 20.6, 22.4, 26.5, 29.4, 33.3, 35.7, 37.6, 46.5, 49.6, 50.9, 54.7, 67.1, 68.7, 69.2, 69.4, 74.6, 76.2, 78.0, 82.0, 84.2, 85.0, 100.2, 127.4, 127.5, 127.7, 128.0, 128.2, 135.3, 136.4, 153.3, 154.1, 154.3, 155.8, 156.2, 168.3, 168.7, 171.3, 203.5.

5.4. Preparation of compound 5e

5.4.1. Amidation. To a solution of **3B** (100 mg, 0.10 mmol) in toluene (6 mL) were added DMF (2 μL, 0.03 mmol) and oxalyl chloride (11 μL, 0.12 mmol) at room temperature, and the reaction mixture was stirred for 30 min at room temperature. To this solution, phenylpropylamine (30 μL, 0.21 mmol) was added, and the reaction mixture was stirred 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 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 silica gel (*n*-hexane:AcOEt, 4:1–1:1) to give 105 mg of compound **4** bearing (*R*)-*N*-(3-phenyl-propyl)-propionamide group as a colorless foam (94%).

MS (FAB) 1072^+ ($M+H^+$); HRMS (FAB) calcd for $C_{58}H_{78}N_3O_{16}$ ($M+H^+$): 1072.5382. Found: 1072.5384.

IR (KBr): 3565, 2971, 2879, 2833, 1804, 1749, 1700, 1524, 1497, 1455, 1377, 1329, 1287, 1249, 1164, 1111, 1046 (cm^{-1}).

^1H NMR ($CDCl_3$) δ 2.62 (3H, s), 2.80, 2.84 (3H, two s).

^{13}C NMR ($CDCl_3$) δ 10.2, 12.9, 13.9, 15.3, 15.5, 15.6, 15.9, 18.8, 19.8, 20.6, 22.3, 26.1, 28.9, 30.8, 33.2, 35.7, 36.2, 37.5, 39.0, 46.9, 47.0, 49.6, 51.0, 54.7, 67.1, 67.2, 68.7, 69.2, 69.4, 74.6, 76.0, 77.5, 78.2, 78.4, 82.2, 84.3, 100.4, 125.5, 127.4, 127.5, 127.7, 127.8, 128.0, 128.1, 128.2, 135.3, 135.4, 136.4, 141.5, 153.3, 154.1, 154.3, 155.8, 156.2, 165.7, 168.8, 171.7, 203.3, 203.5.

5.4.2. Deprotection and N-methylation (method A). This colorless foam **4** (100 mg, 0.093 mmol) with (*R*)-*N*-(3-phenyl-propyl)-propionamide was diluted with EtOH (10 mL) and 0.2 M acetate buffer (3 mL, pH 4.4). To this solution was added 20% $Pd(OH)_2/C$ (30 mg, 0.056 mmol) with stirring at room temperature under H_2 atmosphere for 1 h. After confirming the disappearance of **4** by TLC, 37% aqueous HCHO (1 mL) was added to the reaction mixture and stirring was continued 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 silica gel ($CHCl_3$/MeOH, 80/1–40/1) to give 61 mg of compound **5e** as a colorless foam (80%).

5.4.3. Compound 5e. MS (FAB): 818^+ ($M+H^+$). HR-MS (FAB) calcd for $C_{43}H_{68}N_3O_{12}$: 818.4803. Found: 818.4809.

IR (KBr): 3438, 3061, 2974, 2938, 2878, 2785, 1812, 1752, 1717, 1673, 1529, 1497, 1455, 1379, 1322, 1283, 1257, 1233, 1167, 1142, 1109, 1082, 1047, 1005, 992, 952, 932, 899, 835, 801, 773, 750, 700, 630, 573, 555, 533, 455 (cm^{-1}).

^1H NMR ($CDCl_3$) δ (ppm): 0.89 (3H, t, J = 7.2 Hz), 1.00 (3H, d, J = 6.9 Hz), 1.23 (3H, d, J = 6.0 Hz), 1.26 (3H, d, J = 6.6 Hz), 1.27 (3H, d, J = 7.5 Hz), 1.38 (3H, d, J = 6.9 Hz), 1.38 (3H, s), 1.43 (3H, d, J = 6.9 Hz), 1.56 (3H, s), 1.20–1.94 (7H, m), 2.27 (6H, s), 2.40–2.51 (1H, m), 2.55 (1H, q, J = 7.2 Hz), 2.65 (3H, s), 2.65 (2H, t, J = 7.8 Hz), 3.02 (1H, quintet, J = 7.8 Hz), 3.04–3.16 (2H, m), 3.17 (1H, dd, J = 7.5 and 10.2 Hz), 3.41 (1H, sextet, J = 6.6 Hz), 3.48–3.75 (2H, m), 3.82 (1H, q, J = 6.6 Hz), 4.21 (1H, d, J = 8.4 Hz), 4.30 (1H, d, J = 7.2 Hz), 4.49 (1H, q, J = 6.9 Hz), 4.82 (1H, s), 4.98 (1H, dd, J = 3.0 and 10.2 Hz), 7.01 (1H, t, J = 5.7 Hz), 7.10–7.30 (5H, m).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.2, 12.9, 14.3, 15.3, 15.7, 15.9, 18.9, 19.9, 21.2, 22.2, 26.2, 28.2, 30.8, 33.0, 33.2, 37.9, 39.0, 40.2, 47.7, 49.7, 51.1, 65.8, 69.5, 70.3, 76.0, 78.4, 78.5, 78.6, 82.4, 84.5, 103.7, 125.6, 128.2, 128.3, 141.7, 153.8, 166.1, 169.1, 172.0, 203.9.

5.5. Preparation of compound 5p

5.5.1. Amidation. To a solution of **3B** (153 mg, 0.16 mmol) in toluene (6 mL) was added DMF (2 μL, 0.03 mmol) and oxalyl chloride (17 μL, 0.19 mmol) at room temperature, and the reaction mixture was stirred for 90 min at room temperature. To this solution was added **12c** (120 mg, 0.64 mmol) dissolved in THF (0.3 mL), and the reaction mixture was stirred 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 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 silica gel to give 170 mg of compound **4** bearing (*R*)-*N*-(3-quinoxalin-6-yl-propyl)-propionamide group as a colorless foam (94%).

MS (FAB): 1124^+ ($M+H^+$). HR-MS (FAB) calcd for $C_{60}H_{78}N_5O_{16}$: 1124.5444. Found: 11124.5453.

IR (KBr): 3359, 2931, 2853, 1087, 1749, 1699, 1532, 1498, 1455, 1380, 1329, 1289, 1251, 1166, 1112, 1066, 1047 (cm^{-1}).

^1H NMR ($CDCl_3$) δ (ppm): 2.63 (3H, s), 2.80 and 2.84 (3H, two s).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.2, 12.9, 13.9, 15.3, 15.7, 18.8, 19.8, 20.6, 22.2, 26.1, 29.6, 30.5, 33.0, 33.3, 35.7, 36.1, 37.5, 38.9, 47.0, 47.1, 49.6, 50.9, 54.6, 67.1, 67.2, 68.6, 69.2, 69.4, 74.6, 75.8, 77.4, 78.1, 78.2, 82.2, 84.3, 100.4, 127.3, 127.5, 127.6, 127.7, 128.0, 128.2, 128.9, 131.4, 135.2, 135.3, 136.4, 141.5, 142.9, 143.8, 144.3, 144.5, 153.4, 154.1, 154.2, 155.8, 156.2, 165.6, 168.8, 171.8, 203.3, 203.4.

5.5.2. Deprotection and N-methylation (method B). This colorless foam **4** (120 mg, 0.11 mmol) with (*N*-3-quinoxalin-6-yl-propyl)-propionamide was dissolved with CH_2Cl_2 (1.2 mL), and iodotrimethylsilane (TMS-I, 61 μL, 0.44 mmol) was added to the solution at room temperature under N_2 atmosphere. After being stirred for 1 h at room temperature, the reaction mixture was cooled to 0 °C. To this were added $AlCl_3$ (57 mg, 0.44 mmol) and anisole (2 mL) dissolved in CH_2Cl_2 (2.4 mL) with stirring for 40 min at 0 °C. The reaction mixture was diluted with H_2O (1 mL) and *n*-hexane (8 mL) at 0 °C, and the precipitate was collected, washed three times with *n*-hexane, and dissolved with MeOH–$CHCl_3$ (2–10 mL). This solution was poured into saturated aqueous $NaHCO_3$ and extracted twice with $CHCl_3$–MeOH (10:1), and the combined organic layer was washed with diluted aqueous $Na_2S_2O_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resultant residue was dissolved with MeOH (3 mL), then 98% HCO_2H (8 μL) and 35% aqueous HCHO (55 μL) were added with stirring at 75 °C for 3 h. After cooling to room temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt (2× 20 mL). The combined extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 40/1–5/1) to give 77 mg of compound **5p** as a colorless foam (80%).

5.5.3. Compound 5p. MS (FAB): 870^+ ($M+H^+$). HR-MS (FAB) calcd for $C_{45}H_{68}N_5O_{12}$: 870.4864. Found: 870.4873.

IR (KBr): 3435, 2974, 2937, 2878, 2784, 1811, 1751, 1716, 1673, 1530, 1499, 1455, 1367, 1322, 1284, 1257, 1234, 1218, 1167, 1141, 1109, 1082, 1047, 1005, 992, 954, 931, 897, 866, 832, 773, 755, 693, 666, 631, 573, 458, 408 (cm^{-1}).

^1H NMR ($CDCl_3$) δ (ppm): 0.85 (3H, t, J = 7.2 Hz), 1.00 (3H, d, J = 6.9 Hz), 1.21 (3H, d, J = 6.0 Hz), 1.25 (3H,

d, J = 7.5 Hz), 1.27 (3H, d, J = 7.2 Hz), 1.36 (3H, d, J = 6.9 Hz), 1.39 (3H, s), 1.44 (3H, d, J = 6.9 Hz), 1.56 (3H, s), 1.20–1.94 (6H, m), 2.03 (2H, m), 2.26 (6H, s), 2.45 (1H, m), 2.55 (1H, q, J = 7.2 Hz), 2.67 (3H, s), 2.92 (2H, dd, J = 6.9 and 8.7 Hz), 3.01 (1H, quintet, J = 7.5 Hz), 3.10–3.22 (2H, m), 3.46–3.58 (2H, m), 3.64–3.75 (1H, m), 3.82 (1H, q, J = 6.9 Hz), 4.21 (1H, d, J = 8.4 Hz), 4.29 (1H, d, J = 7.2 Hz), 4.49 (1H, q, J = 6.9 Hz), 4.84 (1H, s), 4.99 (1H, dd, J = 2.7 and 10.5 Hz), 7.20 (1H, br t, J = 5.7 Hz), 7.70 (1H, dd, J = 1.8 and 8.7 Hz), 7.91 (1H, d, J = 1.8 Hz), 8.01 (1H, d, J = 8.7 Hz), 8.77 (1H, d, J = 8.7 Hz), 8.78 (1H, d, J = 8.7 Hz).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.2, 12.9, 14.3, 15.3, 15.6, 15.8, 18.9, 19.9, 21.1, 22.3, 26.2, 28.3, 30.5, 33.1, 33.4, 37.9, 39.0, 40.2, 47.6, 49.8, 51.1, 65.9, 69.5, 70.3, 76.0, 78.4, 78.5, 82.4, 84.6, 103.7, 127.8, 129.1, 131.6, 141.8, 143.2, 144.1, 144.6, 144.8, 153.8, 166.4, 169.3, 172.2, 203.9.

5.6. Preparation of compounds 5a–d

Compounds **5a**–**d** were prepared from **3A** by the procedure described for the synthesis of **5e** with *O*-phenethylhydroxylamine,[7] 2-phenoxyethylamine,[8] *N*-methyl-*N*-phenethyl-hydrazine,[9] and *N*-methyl-*N*-phenyl-ethylenediamine,[10] respectively.

5.6.1. Compound 5a. MS (FAB): 806^+ ($M+H^+$). HRMS (FAB) calcd for $C_{41}H_{64}N_3O_{13}$: 806.4439. Found: 806.4441.

IR (KBr): 3438, 2973, 2937, 2878, 2785, 1811, 1751, 1717, 1679, 1637, 1599, 1588, 1528, 1497, 1457, 1380, 1363, 1324, 1303, 1285, 1244, 1169, 1141, 1109, 1078, 1048, 1004, 993, 953, 931, 891, 773, 755, 693, 555, 512 (cm^{-1}).

^{1}H NMR ($CDCl_3$) δ (ppm): 0.88 (3H, t, J = 7.2 Hz), 1.00 (3H, d, J = 7.2 Hz), 1.18 (3H, d, J = 6.6 Hz), 1.24 (3H, d, J = 6.3 Hz), 1.27 (3H, d, J = 7.8 Hz), 1.37 (3H, d, J = 6.9 Hz), 1.38 (3H, s), 1.53 (3H, s), 1.20–1.92 (6H, m), 2.27 (6H, s), 2.38–2.52 (1H, m), 2.53 (1H, q, J = 6.6 Hz), 2.70 (3H, s), 3.02 (1H, quintet, J = 8.1 Hz), 3.18 (1H, dd, J = 7.5 and 10.2 Hz), 3.50–3.75 (4H, m), 3.83 (1H, q, J = 6.9 Hz), 4.07 (2H, t, J = 5.4 Hz), 4.21 (1H, d, J = 7.8 Hz), 4.30 (1H, d, J = 7.2 Hz), 4.46 and 4.54 (2H, ABq, J = 15.3 Hz), 4.81 (1H, s), 5.01 (1H, dd, J = 3.0 and 10.2 Hz), 6.86–6.96 (3H, m), 7.03 (1H, br t, J = 6.0 Hz), 7.22–7.29 (2H, m).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.2, 13.0, 14.2, 15.2, 15.5, 18.8, 19.8, 21.1, 22.2, 26.4, 28.1, 33.2, 38.0, 38.4, 40.1, 47.5, 49.6, 51.0, 65.7, 66.3, 69.4, 70.1, 72.7, 76.0, 78.2, 78.5, 82.1, 84.4, 103.4, 114.2, 120.6, 129.2, 153.6, 158.2, 167.3, 168.8, 170.1, 203.6.

5.6.2. Compound 5b. MS (FAB): 806^+ ($M+H^+$). HR-MS (FAB) calcd for $C_{41}H_{64}N_3O_{13}$ 806.4439. Found: 806.4438.

IR (KBr): 3431, 2973, 2938, 2879, 2785, 1811, 1752, 1700, 1654, 1637, 1497, 1455, 1380, 1323, 1305, 1283, 1257, 1233, 1167, 1142, 1109, 1080, 1048, 1004, 992, 953, 932, 892, 834, 773, 751, 700, 631, 558, 529, 458 (cm^{-1}).

^{1}H NMR ($CDCl_3$) δ (ppm): 0.91 (3H, t, J = 7.5 Hz), 1.00 (3H, d, J = 6.9 Hz), 1.25 (3H, d, J = 6.0 Hz), 1.26 (3H, d, J = 6.3 Hz), 1.28 (3H, d, J = 7.8 Hz), 1.36 (3H, s), 1.38 (3H, d, J = 7.2 Hz), 1.56 (3H, s), 1.20–1.92 (5H, m), 2.32 (6H, s), 2.30–2.37 (1H, m), 2.55 (1H, q, J = 6.3 Hz), 2.69 (3H, s), 3.01 (1H, m), 3.02 (3H, t, J = 7.2 Hz), 3.22 (1H, m), 3.50–3.74 (3H, m), 3.84 (1H, q, J = 6.9 Hz), 4.17–4.27 (3H, m), 4.32 (1H, d, J = 7.2 Hz), 4.44 and 4.52 (2H, ABq, J = 15.0 Hz), 4.89 (1H, s), 5.00 (1H, dd, J = 2.7 and 10.2 Hz), 7.16–7.32 (5H, m), 9.51 (1H, br s).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.2, 12.9, 14.3, 15.4, 15.5, 18.7, 19.9, 21.1, 22.2, 26.3, 28.2, 33.1, 34.4, 38.0, 40.2, 47.5, 49.8, 51.0, 65.8, 69.5, 70.2, 72.3, 76.0, 78.3, 78.4, 82.3, 84.6, 103.6, 126.1, 128.3, 128.9, 137.9, 153.6, 167.5, 167.9, 169.1, 204.0.

5.6.3. Compound 5c. MS (FAB): 819^+ ($M+H^+$). HRMS (FAB) calcd for $C_{42}H_{67}N_4O_{12}$: 819.4755. Found: 819.4755.

IR (KBr): 3429, 2974, 2938, 2880, 2786, 1808, 1752, 1716, 1674, 1600, 1570, 1528, 1508, 1456, 1376, 1361, 1323, 1304, 1283, 1257, 1235, 1212, 1166, 1142, 1108, 1079, 1049, 1004, 992, 953, 932, 893, 860, 835, 801, 773, 749, 693, 634, 581, 551, 517, 456 (cm^{-1}).

^{1}H NMR ($CDCl_3$) δ (ppm): 0.90 (3H, t, J = 7.5 Hz), 0.95 (3H, d, J = 7.2 Hz), 1.23 (3H, d, J = 6.6 Hz), 1.25 (3H, d, J = 5.9 Hz), 1.28 (3H, d, J = 8.1 Hz), 1.36 (3H, s), 1.37 (3 H, d, J = 6.0 Hz), 1.56 (3H, s), 1.20–1.98 (5H, m), 2.27 (6H, s), 2.40–2.52 (1H, m), 2.55 (1H, q, J = 6.6 Hz), 2.67 (3H, s), 2.95 (3H, s), 2.90–3.06 (2H, m), 3.19 (1H, m), 3.26–3.70 (7H, m), 3.84 (1H, q, J = 6.9 Hz), 4.21 (1H, d, J = 8.1 Hz), 4.30 (1H, d, J = 6.6 Hz), 4.42 (2H, s), 4.84 (1H, s), 5.04 (1H, dd, J = 3.0 and 10.5 Hz), 6.64–6.72 (1H, m), 6.76–6.83 (2H, m), 7.08–7.25 (3H, m).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.3, 12.9, 14.3, 15.3, 15.5, 18.8, 19.9, 21.2, 22.3, 26.3, 28.3, 33.2, 36.2, 38.0, 38.1, 40.2, 47.6, 49.7, 51.0, 51.6, 65.9, 69.5, 70.3, 72.9, 76.1, 78.4, 78.6, 82.4, 84.7, 103.7, 112.4, 116.4, 129.1, 149.3, 153.8, 167.4, 169.2, 170.6, 203.9.

5.6.4. Compound 5d. MS (FAB): 819^+ ($M+H^+$). HR-MS (FAB) calcd for $C_{42}H_{67}N_4O_{12}$: 819.4755. Found: 819.4762.

IR (KBr): 3432, 3062, 2972, 2937, 2878, 2786, 1811, 1751, 1686, 1654, 1647, 1637, 1629, 1559, 1541, 1523, 1508, 1497, 1456, 1380, 1362, 1323, 1304, 1283, 1257, 1233, 1219, 1167, 1142, 1109, 1079, 1048, 1004, 993, 953, 932, 892, 859, 834, 800, 773, 751, 700, 669, 629, 555, 515, 454 (cm^{-1}).

^{1}H NMR ($CDCl_3$) δ (ppm): 0.90 (3H, t, J = 7.5 Hz), 1.01 (3H, d, J = 6.9 Hz), 1.25 (3H, d, J = 6.6 Hz), 1.27 (3H, d, J = 7.8 Hz), 1.28 (3H, d, J = 7.8 Hz), 1.37 (3H, d, J = 6.9 Hz), 1.40 (3H, s), 1.56 (3H, s), 1.20–1.98 (6H, m), 2.27 (6H, s), 2.40–2.63 (2H, m), 2.66 (3H, s), 2.72 (3H, s), 2.68–2.74 (2H, m), 2.80–3.25 (5H, m), 3.45–3.75 (2H, m), 3.84 (1H, q, J = 6.6 Hz), 4.23 (1H, d, J = 8.1 Hz), 4.30 (1H, d, J = 7.2 Hz), 4.33 and 4.44 (2H, ABq, J = 15.3 Hz), 4.82 (1H, s), 5.04 (1H, dd, J = 2.7 and 10.2 Hz), 7.17–7.32 (5H, m), 7.54 (1H, br s).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.2, 13.0, 14.3, 15.4, 15.6, 18.9, 19.9, 21.1, 22.3, 26.4, 28.2, 29.7, 33.1, 34.0, 38.1, 40.2, 46.4, 47.6, 50.0, 51.0, 60.9, 65.9, 69.5, 70.3, 72.6, 76.1, 78.4, 78.9, 82.4, 84.5, 103.8, 125.9, 128.3, 128.7, 139.8, 153.9, 168.3, 168.6, 169.2, 203.9.

5.7. Preparation of compounds 5f–i

Compounds **5f–i** were prepared by the procedure described for the synthesis of **5e** with 3-phenylpropylamine from **3C–F**, respectively.

5.7.1. Compound 5f. MS (FAB): 818^+ ($M+H^+$). HR-MS (FAB) calcd for $C_{43}H_{68}N_3O_{12}$: 818.4803. Found: 818.4803.

IR (KBr): 3438, 3061, 2974, 2937, 2878, 2785, 1811, 1751, 1717, 1671, 1525, 1497, 1455, 1379, 1321, 1283, 1257, 1233, 1167, 1142, 1109, 1082, 1048, 1005, 992, 953, 932, 899, 835, 802, 773, 749, 700, 621, 573, 510, 420 (cm^{-1}).

^{1}H NMR ($CDCl_3$) δ (ppm): 0.89 (3H, t, J = 7.2 Hz), 1.01 (3H, d, J = 7.2 Hz), 1.23 (3H, d, J = 6.6 Hz), 1.24 (3H, d, J = 6.0 Hz), 1.28 (3H, d, J = 7.5 Hz), 1.37 (3H, d, J = 6.9 Hz), 1.40 (3H, s), 1.46 (3H, d, J = 7.2 Hz), 1.55 (3H, s), 1.20–1.94 (7H, m), 2.27 (6H, s), 2.40–2.51 (1H, m), 2.55 (1H, q, J = 6.6 Hz), 2.65 (2H, t, J = 7.8 Hz), 2.68 (3H, s), 3.03 (1H, quintet, J = 7.8 Hz), 3.18 (1H, dd, J = 7.5 and 9.9 Hz), 3.25–3.40 (3H, m), 3.50–3.74 (2H, m), 3.84 (1H, q, J = 6.6 Hz), 4.22 (1H, d, J = 7.8 Hz), 4.30 (1H, d, J = 7.2 Hz), 4.58 (1H, q, J = 6.9 Hz), 4.80 (1H, s), 5.02 (1H, dd, J = 2.7 and 10.2 Hz), 6.74 (1H, t, J = 5.7 Hz), 7.18–7.32 (5H, m).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.3, 13.0, 14.2, 15.5, 15.7, 17.5, 18.8, 19.7, 21.2, 22.3, 26.3, 28.2, 31.1, 33.1, 38.1, 38.7, 40.2, 47.7, 49.7, 51.0, 65.8, 69.5, 70.3, 76.2, 78.3, 78.8, 79.2, 82.5, 84.5, 103.7, 125.8, 128.2, 128.3, 128.4, 141.5, 153.9, 166.5, 169.1, 172.8, 203.9.

5.7.2. Compound 5g. MS (FAB): 832^+ ($M+H^+$). HR-MS (FAB) calcd for $C_{44}H_{70}N_3O_{12}$: 832.4960. Found: 832.4946.

IR (KBr): 3443, 3062, 2975, 2938, 2878, 2785, 1812, 1751, 1717, 1669, 1525, 1498, 1455, 1378, 1362, 1323, 1305, 1284, 1258, 1218, 1166, 1109, 1083, 1047, 1005, 992, 954, 930, 835, 801, 771, 750, 699, 580, 558, 457 (cm^{-1}).

^{1}H NMR ($CDCl_3$) δ (ppm): 0.90 (3H, t, J = 7.2 Hz), 0.99 (3H, d, J = 6.9 Hz), 1.24 (3H, d, J = 5.4 Hz), 1.26 (3H, d, J = 6.6 Hz), 1.28 (3H, d, J = 7.8 Hz), 1.38 (3H, d, J = 6.9 Hz), 1.40 (3H, s), 1.45 (3H, s), 1.49 (3H, s), 1.56 (3H, s), 1.20–1.94 (7H, m), 2.27 (6H, s), 2.40–2.51 (1H, m), 2.57 (1H, q, J = 6.9 Hz), 2.64 (2H, t, J = 8.4 Hz), 2.68 (3H, s), 3.03 (1H, quintet, J = 7.5 Hz), 3.12–3.32 (3H, m), 3.35 (1H, septet, J = 7.2 Hz), 3.48–3.77 (2H, m), 3.83 (1H, q, J = 6.6 Hz), 4.22 (1H, d, J = 7.8 Hz), 4.31 (1H, d, J = 7.2 Hz), 4.84 (1H, s), 5.01 (1H, dd, J = 2.4 and 9.9 Hz), 7.10–7.30 (6H, m).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.3, 12.9, 14.3, 15.3, 15.6, 18.8, 19.7, 21.2, 22.3, 24.3, 25.2, 26.2, 28.2, 31.0, 33.2, 37.9, 38.9, 40.2, 47.6, 49.8, 51.1, 65.9, 69.5, 70.3, 76.1, 78.4, 78.5, 82.5, 82.7, 84.5, 103.7, 125.6, 128.2, 128.4, 141.8, 153.8, 166.0, 169.2, 174.8, 204.0.

5.7.3. Compound 5h. MS (FAB): 832^+ ($M+H^+$). HR-MS (FAB) calcd for $C_{44}H_{70}N_3O_{12}$: 832.4960. Found: 832.4955.

IR (KBr): 3437, 3085, 3061, 2972, 2937, 2878, 2785, 1811, 1751, 1717, 1673, 1527, 1497, 1455, 1380, 1362, 1324, 1304, 1283, 1257, 1233, 1167, 1141, 1109, 1081, 1048, 1005, 990, 954, 932, 912, 863, 835, 801, 771, 750, 700, 669, 631, 575, 555, 533, 455, 430 (cm^{-1}).

^{1}H NMR ($CDCl_3$) δ (ppm): 0.89 (3H, t, J = 7.2 Hz), 0.95 (3H, t, J = 7.5 Hz), 1.00 (3H, d, J = 7.2 Hz), 1.23 (3H, d, J = 6.0 Hz), 1.26 (3H, d, J = 6.6 Hz), 1.28 (3H, d, J = 7.2 Hz), 1.38 (3H, d, J = 6.9 Hz), 1.39 (3H, s), 1.55 (3H, s), 1.20–2.05 (10H, m), 2.26 (6H, s), 2.44 (1H, m), 2.56 (1H, q, J = 6.9 Hz), 2.65 (2H, t, J = 7.8 Hz), 2.68 (3H, s), 3.03 (1H, quintet, J = 7.5 Hz), 3.11–3.22 (2H, m), 3.39 (1H, sextet, J = 6.9 Hz), 3.48–3.76 (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), 4.3 (1H, t, J = 5.1 Hz), 4.82 (1H, s), 4.98 (1H, dd, J = 3.0 and 10.2 Hz), 6.83 (1H, t, J = 5.7 Hz), 7.11–7.29 (5H, m).

^{13}C NMR ($CDCl_3$) δ (ppm): 9.6, 10.2, 12.9, 14.3, 15.3, 15.6, 19.0, 19.9, 21.2, 22.3, 23.6, 26.4, 28.2, 30.9, 33.2, 37.9, 38.9, 40.2, 47.6, 49.8, 51.1, 65.9, 69.5, 70.3, 76.1, 78.5, 82.3, 83.5, 84.5, 103.7, 125.6, 128.2, 128.4, 141.7, 153.8, 166.6, 169.2, 171.6, 204.0.

5.7.4. Compound 5i. MS (FAB): 846^+ ($M+H^+$). HR-MS (FAB) calcd for $C_{45}H_{72}N_3O_{12}$: 846.5116. Found: 846.5109.

IR (KBr): 3436, 3061, 2965, 2930, 2874, 2854, 2785, 1810, 1750, 1717, 1671, 1527, 1496, 1455, 1381, 1323, 1304, 1284, 1257, 1233, 1219, 1167, 1141, 1109, 1079, 1047, 1007, 992, 954, 931, 913, 862, 835, 800, 777, 750, 699, 668, 577, 529, 456, 419 (cm^{-1}).

^{1}H NMR ($CDCl_3$) δ (ppm): 0.89 (3H, t, J = 7.2 Hz), 0.94 (3H, t, J = 6.9 Hz), 1.01 (6H, d, J = 7.2 Hz), 1.24 (3H, d, J = 7.5 Hz), 1.25 (3H, d, J = 6.0 Hz), 1.28 (3H, d, J = 7.5 Hz), 1.38 (3H, d, J = 6.6 Hz), 1.41 (3H, s), 1.56 (3H, s), 1.20–1.94 (9H, m), 2.30 (6H, s), 2.40–2.60

(3H, m), 2.64 (2H, t, J = 8.4 Hz), 2.71 (3H, s), 2.87 (1H, br s), 3.04 (1H, quintet, J = 7.2 Hz), 3.16–3.41 (3H, m), 3.50–3.80 (2H, m), 3.83 (1H, q, J = 6.9 Hz), 4.19 (1H, d, J = 3.9 Hz), 4.24 (1H, d, J = 7.8 Hz), 4.32 (1H, d, J = 7.2 Hz), 4.82 (1H, s), 4.99 (1H, dd, J = 3.0 and 10.5 Hz), 6.64 (1H, t, J = 5.7 Hz), 7.12–7.30 (5H, m).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.3, 13.0, 14.3, 15.2, 15.4, 17.0, 19.0, 19.5, 19.9, 21.2, 22.4, 26.5, 28.4, 29.5, 29.7, 31.2, 33.2, 37.9, 38.9, 40.2, 47.5, 49.8, 51.2, 66.0, 69.5, 70.3, 76.3, 78.3, 78.6, 82.2, 84.6, 87.2, 103.6, 125.7, 128.3, 128.4, 141.7, 153.9, 166.9, 169.2, 171.6, 204.1.

5.8. Preparation of compounds 5l,o, and s

Compounds **5l**,**o**, and **s** were prepared from **3A** by the procedure described for the synthesis of **5p** with **12b**,**c**, and **d**, respectively.

5.8.1. Compound 5l. MS (FAB): 855$^+$ ($M+H^+$). HR-MS (FAB) calcd for $C_{45}H_{67}N_4O_{12}$: 855.4755. Found: 855.4766.

IR (KBr): 3434, 2973, 2937, 2878, 2784, 1810, 1751, 1716, 1672, 1625, 1596, 1534, 1503, 1455, 1380, 1363, 1320, 1284, 1257, 1233, 1219, 1167, 1142, 1109, 1079, 1047, 1004, 992, 953, 931, 892, 835, 801, 772, 754, 695, 664, 615, 555, 530, 479, 456 (cm^{-1}).

^{1}H NMR ($CDCl_3$) δ (ppm): 0.86 (3H, t, J = 7.5 Hz), 1.01 (3H, d, J = 6.6 Hz), 1.23 (3H, d, J = 5.0 Hz), 1.25 (3H, d, J = 7.2 Hz), 1.28 (3H, d, J = 7.2 Hz), 1.36 (3H, d, J = 7.2 Hz), 1.39 (3H, s), 1.55 (3H, s), 1.54–1.92 (7H, m), 2.01 (2H, quintet, J = 7.8 Hz), 2.27 (6H, s), 2.46 (1H, m), 2.59 (1H, q, J = 6.9 Hz), 2.69 (3H, s), 2.89 (2H, t, J = 8.4 Hz), 3.02 (1H, quintet, J = 7.8 Hz), 3.18 (1H, dd, J = 7.8 and 10.2 Hz), 3.30 (1H, m), 3.44 (1H, m), 3.50–3.74 (2H, m), 3.83 (1H, q, J = 6.9 Hz), 4.22 (1H, d, J = 7.8 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 10.2 Hz), 6.96 (1H, t, J = 5.4 Hz), 7.33 (1H, dd, J = 3.9 and 8.1 Hz), 7.45 (1H, dd, J = 1.5 and 8.4 Hz), 7.74 (1H, d, J = 8.7 Hz), 7.89 (1H, s), 8.10 (1H, dd, J = 1.2 and 8.1 Hz), 8.86 (1H, m).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.2, 12.9, 14.3, 15.3, 15.5, 18.9, 19.9, 21.1, 22.3, 26.3, 28.2, 30.7, 33.2, 33.4, 33.4, 38.0, 38.8, 40.2, 47.6, 49.8, 51.0, 65.8, 69.5, 70.3, 73.0, 76.1, 78.4, 78.7, 82.3, 84.6, 103.7, 120.3, 126.7, 127.6, 127.8, 128.0, 135.6, 143.4, 148.5, 150.2, 153.8, 167.6, 169.2, 170.3, 203.9.

5.8.2. Compound 5o. MS (FAB): 856$^+$ ($M+H^+$). HR-MS (FAB) calcd for $C_{44}H_{66}N_5O_{12}$: 856.4708. Found: 856.4716.

IR (KBr): 3434, 2972, 2937, 2878, 2784, 1810, 1751, 1716, 1673, 1619, 1533, 1498, 1455, 1365, 1323, 1304, 1284, 1257, 1233, 1218, 1167, 1141, 1109, 1078, 1048, 1004, 992, 955, 931, 893, 831, 773, 755, 664, 628, 556, 513, 457, 407 (cm^{-1}).

^{1}H NMR ($CDCl_3$) δ (ppm): 0.86 (3H, t, J = 7.5 Hz), 1.01 (3H, d, J = 6.9 Hz), 1.23 (3H, d, J = 6.3 Hz), 1.27 (3H, d, J = 6.9 Hz), 1.28 (3H, d, J = 7.5 Hz), 1.37 (3H, d, J = 6.6 Hz), 1.39 (3H, s), 1.56 (3H, s), 124–1.92 (7H, m), 2.04 (2H, quintet, J = 7.8 Hz), 2.27 (6H, s), 2.46 (1H, m), 2.57 (1H, q, J = 7.2 Hz), 2.70 (3H, s), 2.92 (2H, t, J = 7.5 Hz), 3.02 (1H, quintet, J = 7.5 Hz), 3.18 (1H, dd, J = 7.2 and 10.2 Hz), 3.29 (1H, m), 3.42–3.60 (2H, m), 3.61–3.76 (1H, m), 3.83 (1H, q, J = 6.9 Hz), 4.22 (1H, d, J = 8.1 Hz), 4.30 (1H, d, J = 7.2 Hz), 4.46 (2H, s), 4.84 (1H, s), 5.01 (1H, dd, J = 3.0 and 10.5 Hz), 7.12 (1H, t, J = 5.4 Hz), 7.69 (1H, dd, J = 1.5 and 8.7 Hz), 7.91 (1H, d, J = 1.5 Hz), 8.02 (1H, d, J = 8.7 Hz), 8.78 (1H, d, J = 8.4 Hz), 8.79 (1H, d, J = 8.4 Hz).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.2, 12.9, 14.3, 15.3, 15.6, 18.9, 19.9, 21.1, 22.2, 26.3, 28.2, 30.5, 33.2, 33.3, 38.0, 38.8, 40.2, 47.6, 49.8, 51.1, 65.9, 69.6, 70.3, 73.0, 76.0, 78.5, 78.6, 82.3, 84.6, 103.8, 127.8, 129.2, 131.6, 141.8, 143.2, 144.1, 144.4, 144.8, 153.8, 167.7, 169.3, 170.5, 203.9.

5.8.3. Compound 5s. MS (FAB): 856$^+$ ($M+H^+$). HR-MS (FAB) calcd for $C_{44}H_{66}N_5$ O_{12} 856.4708. Found: 856.4714.

IR (KBr): 3433, 3063, 2972, 2937, 2878, 2784, 1810, 1751, 1716, 1673, 1533, 1491, 1455, 1380, 1363, 1322, 1304, 1284, 1258, 1233, 1219, 1167, 1141, 1109, 1078, 1048, 1005, 992, 953, 931, 893, 859, 835, 801, 762, 695, 666, 628, 611, 557, 532, 456, 409 (cm^{-1}).

^{1}H NMR ($CDCl_3$) δ (ppm): 0.85 (3H, t, J = 7.2 Hz), 1.01 (3H, d, J = 6.6 Hz), 1.23 (3H, d, J = 6.0 Hz), 1.26 (3H, d, J = 6.6 Hz), 1.28 (3H, d, J = 7.5 Hz), 1.35 (3H, d, J = 6.6 Hz), 1.39 (3H, s), 1.55 (3H, s), 1.24–1.92 (7H, m), 2.15 (2H, quintet, J = 7.2 Hz), 2.26 (6H, s), 2.44 (1H, m), 2.56 (1H, q, J = 6.9 Hz), 2.71 (3H, s), 2.96–3.08 (1H, m), 3.01 (1H, quintet, J = 7.8 Hz), , 3.08 (2H, t, J = 7.8 Hz), 3.17 (1H, dd, J = 7.5 and 10.5 Hz), 3.36 (1H, m), 3.46–3.59 (2H, m), 3.62–3.75 (1H, m), 3.82 (1 H, q, J = 6.9 Hz), 4.22 (1H, d, J = 7.8 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 10.2 Hz), 7.12 (1H, t, J = 6.0 Hz), 7.65–7.76 (2H, m), 8.02–8.07 (2H, m), 8.78 (1H, s).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.2, 12.9, 14.3, 15.4, 15.5, 18.9, 19.9, 21.1, 22.3, 26.3, 28.2, 28.6, 33.2, 33.5, 38.0, 38.7, 40.2, 47.6, 49.8, 51.0, 65.9, 69.5, 70.3, 73.0, 76.0, 78.4, 78.7, 82.3, 84.6, 103.8, 128.8, 129.0, 129.1, 129.7, 141.3, 142.1, 145.8, 153.8, 156.6, 167.6, 169.2, 170.4, 203.8.

5.9. Preparation of compounds 5j,m,r,t, and u

Compounds **5j**,**m**,**r**,**t**, and **u** were prepared from **3B** by the procedure described for the synthesis of **5p** with **12a**,**b**,**e**,**d**, and **f**, respectively.

5.9.1. Compound 5j. MS (FAB): 869$^+$ ($M+H^+$). HR-MS (FAB) calcd for $C_{46}H_{69}N_4O_{12}$: 869.4912. Found: 869.4914.

IR (KBr): 3435, 2974, 2938, 2878, 2784, 1810, 1751, 1717, 1673, 1591, 1569, 1528, 1509, 1456, 1379, 1322,

1284, 1257, 1235, 1167, 1142, 1109, 1082, 1047, 1005, 992, 952, 931, 902, 835, 813, 801, 757, 694, 665, 631, 573, 532, 454, 431 (cm^{-1}).

^1H NMR ($CDCl_3$) δ (ppm): 0.87 (3H, t, J = 7.2 Hz), 1.00 (3H, d, J = 6.9 Hz), 1.22 (3H, d, J = 6.0 Hz), 1.27 (6H, d, J = 6.9 Hz), 1.37 (3H, d, J = 6.9 Hz), 1.39 (3H, s), 1.45 (2H, d, J = 6.9 Hz), 1.56 (3H, s), 1.20–1.95 (6H, m), 2.06 (2H, quintet, J = 7.2 Hz), 2.27 (6H, s), 2.47 (2H, m), 2.55 (1H, q, J = 6.9 Hz), 2.66 (3H, s), 3.01 (1H, quintet, J = 7.8 Hz), 3.12 (2H, dd, J = 6.6 and 8.4 Hz), 3.10–3.27 (3H, m), 3.48–3.76 (4H, m), 3.83 (1H, q, J = 6.6 Hz), 4.21 (1H, d, J = 8.1 Hz), 4.29 (1H, d, J = 7.5 Hz), 4.50 (1H, q, J = 6.9 Hz), 4.85 (1H, s), 4.97 (1H, dd, J = 2.7 and 10.2 Hz), 7.26–7.34 (2H, m), 7.56 (1H, m), 7.68 (1H, m), 8.08 (2H, m), 8.80 (1H, br s).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.2, 12.8, 14.3, 15.2, 15.7, 15.8, 18.8, 19.9, 21.1, 22.2, 26.2, 28.3, 29.2, 33.0, 37.9, 39.1, 40.2, 47.7, 49.7, 51.0, 65.8, 69.5, 70.3, 75.9, 78.3, 78.5, 82.4, 84.7, 103.7, 120.6, 123.6, 126.3, 127.6, 128.9, 130.0, 147.8, 148.2, 150.2, 153.8, 166.3, 169.3, 172.3, 203.8.

5.9.2. Compound 5m. MS (FAB): 869^+ ($M+H^+$). HR-MS (FAB) calcd for $C_{46}H_{69}N_4O_{12}$: 869.4912. Found: 869.4921.

IR (KBr): 3436, 2974, 2937, 2878, 2784, 1810, 1751, 1716, 1672, 1625, 1596, 1529, 1503, 1455, 1379, 1320, 1284, 1257, 1234, 1167, 1142, 1109, 1082, 1047, 1005, 992, 952, 931, 897, 835, 801, 772, 754, 694, 663, 615, 573, 555, 530, 479, 456 (cm^{-1}).

^1H NMR ($CDCl_3$) δ (ppm): 0.85 (3H, t, J = 7.2 Hz), 1.00 (3H, d, J = 7.2 Hz), 1.21 (3H, d, J = 6.3 Hz), 1.27 (6H, d, J = 6.9 Hz), 1.37 (3H, d, J = 7.2 Hz), 1.39 (3H, s), 1.44 (2H, d, J = 6.9 Hz), 1.56 (3H, s), 1.20–1.92 (7H, m), 2.03 (2H, quintet, J = 7.8 Hz), 2.26 (6H, s), 2.44 (1H, m), 2.55 (1H, q, J = 6.6 Hz), 2.67 (3H, s), 2.88 (2H, t, J = 8.1 Hz), 3.02 (1H, quintet, J = 7.8 Hz), 3.12–3.22 (2H, m), 3.43–3.76 (3H, m), 3.82 (1H, q, J = 7.2 Hz), 4.21 (1H, d, J = 7.8 Hz), 4.29 (1H, d, J = 7.5 Hz), 4.51 (1H, q, J = 6.6 Hz), 4.84 (1H, s), 4.99 (1H, dd, J = 2.7 and 10.2 Hz), 7.07 (1H, t, J = 6.0 Hz), 7.32 (1H, dd, J = 4.2 and 8.4 Hz), 7.46 (1H, dd, J = 1.5 and 8.4 Hz), 7.73 (1H, d, J = 8.4), 7.90 (1H, s), 8.10 (1H, dd, J = 1.2 and 8.1 Hz), 8.86 (1H, dd, J =1.5 and 4.2 Hz).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.2, 12.9, 14.3, 15.3, 15.6, 16.0, 18.9, 19.9, 21.1, 22.3, 26.3, 28.2, 30.6, 33.1, 33.5, 37.9, 39.0, 40.2, 47.6, 49.8, 51.1, 65.8, 69.5, 70.3, 76.0, 78.5, 78.6, 82.5, 84.6, 103.7, 120.3, 126.7, 127.6, 127.9, 128.0, 135.7, 143.6, 148.5, 150.2, 153.9, 166.3, 169.2, 172.1, 203.9.

5.9.3. Compound 5r. MS (FAB): 870^+ ($M+H^+$). HR-MS (FAB) calcd for $C_{45}H_{68}N_5O_{12}$: 870.4864. Found: 870.4867.

IR (KBr): 3436, 2973, 2937, 2878, 2784, 1811, 1751, 1716, 1674, 1577, 1528, 1490, 1456, 1379, 1361, 1322, 1283, 1257, 1233, 1167, 1142, 1109, 1082, 1047, 1005, 993, 952, 931, 900, 865, 835, 801, 771, 682, 632, 573, 533, 453, 431 (cm^{-1}).

^1H NMR ($CDCl_3$) δ (ppm): 0.87 (3H, t, J = 7.2 Hz), 0.99 (3H, d, J = 6.6 Hz), 1.20 (3H, d, J = 6.0 Hz), 1.26 (3H, d, J = 6.3 Hz), 1.27 (3H, d, J = 7.5 Hz), 1.36 (3H, d, J = 7.2 Hz), 1.39 (3H, s), 1.45 (3H, d, J = 6.9 Hz), 1.55 (3H, s), 1.20–1.94 (6H, m), 2.03 (2H, quintet, J = 7.5 Hz), 2.26 (6H, s), 2.44 (1H, m), 2.54 (1H, q, J = 7.2 Hz), 2.66 (3H, s), 3.01 (1H, quintet, J = 7.5 Hz), 3.13–3.25 (2H, m), 3.30 (2H, t, J = 7.5 Hz), 3.43–3.58 (3H, m), 3.63–3.74 (1H, m), 3.81 (1H, q, J = 6.3 Hz), 4.20 (1H, d, J = 8.1 Hz), 4.28 (1H, d, J = 7.2 Hz), 4.52 (1H, q, J = 6.9 Hz), 4.82 (1H, s), 4.94 (1H, dd, J = 2.7 and 10.2 Hz), 7.07 (1H, br t, J = 5.7 Hz), 7.67 (1H, dd, J = 2.7 and 7.2 Hz), 7.70 (1H, dd, J = 6.9 and 7.2 Hz), 7.94 (1H, dd, J = 2.7 and 6.9 Hz), 8.83 (1H, d, J = 5.7 Hz), 8.84 (1H, d, J = 5.7 Hz).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.2, 12.9, 14.2, 15.3, 15.7, 16.1, 18.9, 19.9, 21.1, 22.2, 26.3, 28.0, 28.2, 30.3, 33.0, 37.9, 39.0, 40.2, 47.7, 49.7, 51.0, 65.8, 69.5, 70.3, 75.9, 78.4, 78.5, 78.6, 82.4, 84.5, 103.8, 127.4, 129.3, 129.8, 141.2, 141.7, 143.1, 143.7, 144.5, 153.8, 166.3, 169.1, 172.0, 203.9.

5.9.4. Compound 5t. MS (FAB): 870^+ ($M+H^+$). HR-MS (FAB) calcd for $C_{45}H_{68}N_5O_{12}$: 870.4864. Found: 870.4874.

IR (KBr): 3435, 3062, 2974, 2937, 2878, 2784, 1811, 1751, 1716, 1672, 1530, 1492, 1455, 1410, 1364, 1322, 1284, 1257, 1234, 1167, 1141, 1109, 1082, 1047, 1005, 992, 952, 931, 899, 835, 801, 762, 694, 665, 631, 610, 573, 556, 532, 457, 409 (cm^{-1}).

^1H NMR ($CDCl_3$) δ (ppm): 0.84 (3H, t, J = 7.2 Hz), 1.00 (3H, d, J = 6.9 Hz), 1.22 (3H, d, J = 6.3 Hz), 1.27 (6H, d, J = 6.6 Hz), 1.35 (3H, d, J = 6.9 Hz), 1.39 (3H, s), 1.44 (3H, d, J = 6.9 Hz), 1.55 (3H, s), 1.20–1.92 (6H, m), 2.15 (2H, quintet, J = 8.1 Hz), 2.25 (6H, s), 2.47 (1H, m), 2.55 (1H, q, J =7.2 Hz), 2.67 (3H, s), 3.01 (1H, quintet, J = 7.8 Hz), 3.08 (2H, dd, J = 6.6 and 9.0 Hz), 3.18 (1H, dd, J = 7.5 and 10.2 Hz), 3.15–3.28 (1H, m), 3.49–3.76 (4H, m), 3.82 (1H, q, J = 6.6 Hz), 4.22 (1H, d, J = 8.1 Hz), 4.29 (1H, d, J = 7.2 Hz), 4.51 (1H, q, J = 6.6 Hz), 4.83 (1H, s), 4.99 (1H, dd, J = 2.7 and 10.5 Hz), 7.22 (1H, br t, J = 5.7 Hz), 7.65–7.76 (2H, m), 8.03–8.07 (2H, m), 8.78 (1H, s).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.1, 12.8, 14.3, 15.3, 15.6, 15.8, 18.8, 19.9, 21.1, 22.2, 26.2, 28.3, 28.6, 33.0, 33.7, 37.9, 38.9, 40.2, 47.6, 49.8, 51.0, 65.8, 69.4, 70.3, 75.9, 78.4, 78.5, 78.6, 82.4, 84.6, 103.7, 128.7, 129.0, 129.1, 129.7, 141.2, 142.2, 145.9, 153.8, 156.8, 166.3, 169.2, 172.2, 203.8.

5.9.5. Compound 5u. MS (FAB): 885^+ ($M+H^+$). HR-MS (FAB) calcd for $C_{45}H_{69}N_6O_{12}$: 885.4973. Found: 885.4971.

IR (KBr): 3430, 2975, 2937, 2879, 2784, 1806, 1749, 1716, 1673, 1600, 1575, 1533, 1500, 1457, 1407, 1375,

1322, 1284, 1234, 1166, 1141, 1110, 1081, 1047, 1006, 993, 950, 835, 811, 775, 755, 711, 694, 628, 572, 555, 530, 460, 435 (cm^{-1}).

^1H NMR ($CDCl_3$) δ (ppm): 0.86 (3H, t, J = 7.2 Hz), 0.99 (3H, d, J = 6.9 Hz), 1.23 (3H, d, J = 6.0 Hz), 1.26 (3H, d, J = 7.2 Hz), 1.27 (3H, d, J = 7.2 Hz), 1.37 (3H, d, J = 6.9 Hz), 1.39 (3H, s), 1.43 (3H, d, J = 6.6 Hz), 1.56 (3H, s), 1.20–1.94 (7H, m), 2.13 (2H, m), 2.27 (6H, s), 2.46 (1H, m), 2.55 (1H, q, J = 6.9 Hz), 2.65 (3H, s), 2.95–3.25 (3H, m), 3.50–3.75 (4H, m), 3.83 (1H, q, J = 6.9 Hz), 4.22 (1H, d, J = 8.1 Hz), 4.29 (1H, d, J = 7.2 Hz), 4.44 (1H, q, J = 6.9 Hz), 4.83 (1H, s), 4.95 (1H, dd, J = 2.7 and 10.2 Hz), 7.28 (1H, br t, J = 6.3 Hz), 7.40 (1H, m), 7.47 (1H, s), 7.61 (1H, s), 8.08 (1H, m), 8.44 (1H, m), 9.00 (1H, s).

^{13}C NMR ($CDCl_3$) δ (ppm): 10.1, 12.7, 14.3, 15.2, 15.4, 15.7, 18.8, 19.9, 21.1, 22.1, 26.2, 28.3, 30.8, 32.9, 36.6, 37.8, 40.2, 45.2, 47.7, 49.7, 51.0, 65.8, 69.5, 70.3, 75.8, 78.1, 78.4, 78.6, 82.4, 84.8, 103.7, 123.4, 130.4, 132.0, 138.0, 139.0, 146.5, 147.5, 153.9, 166.5, 169.5, 172.6, 203.7.

5.10. Preparation of compound 5k,n and q

Compounds **5k**,**n** and **q** were prepared from **3E** by the procedure described for the synthesis of **5p** with **12a**,**b** and **c**, respectively.

5.10.1. Compound 5k. MS (SI): 883^+ ($M+H^+$). HR-MS (SI): calcd for $C_{47}H_{71}N_4O_{12}$: 883.5065. Found: 883.5069.

IR (KBr): 3435, 2971, 2937, 2877, 2784, 1810, 1751, 1716, 1673, 1592, 1569, 1526, 1509, 1456, 1380, 1362, 1323, 1305, 1284, 1257, 1233, 1167, 1141, 1109, 1082, 1047, 1005, 990, 954, 932, 912, 835, 813, 800, 764, 694, 631, 574, 515, 454, 431 (cm^{-1}).

^1H NMR ($CDCl_3$) δ (ppm): 0.87 (3H, t, J = 7.5 Hz), 0.98 (3H, t, J = 7.2 Hz), 1.00 (3H, d, J = 7.2 Hz), 1.22 (3H, d, J = 6.3 Hz), 1.27 (3H, d, J = 6.6 Hz), 1.28 (3H, d, J = 7.8 Hz), 1.37 (3H, d, J = 6.9 Hz), 1.40 (3H, s), 1.56 (3 H, s), 1.20–2.10 (10 H, m), 2.27 (6H, s), 2.46 (1H, m), 2.56 (1H, q, J = 6.9 Hz), 2.69 (3H, s), 3.02 (1H, quintet, J = 7.5 Hz), 3.12 (2H, dd, J = 6.0 and 8.7 Hz), 3.14–3.32 (2H, m), 3.52 (2H, m), 3.74 (1H, m), 3.83 (1H, q, J = 6.9 Hz), 4.22 (1H, d, J = 8.1 Hz), 4.30 (1H, d, J = 6.3 Hz), 4.32 (1H, t, J = 6.6 Hz), 4.85 (1H, s), 4.97 (1H, dd, J = 2.4 and 10.2 Hz), 7.09 (1H, t, J = 5.7 Hz), 7.32 (1H, d, J = 4.5 Hz), 7.56 (1H, m), 7.68 (1H, m), 8.05 (1H, d, J = 8.7 Hz), 8.09 (1H, d, J = 8.4 Hz), 8.81 (1H, br s).

^{13}C NMR ($CDCl_3$) δ (ppm): 9.8, 10.3, 12.8, 14.3, 15.2, 15.6, 18.9, 19.9, 21.1, 22.2, 23.5, 26.3, 28.2, 29.3, 29.4, 33.1, 37.8, 39.0, 40.2, 47.6, 49.8, 51.1, 65.9, 69.5, 70.3, 76.0, 78.5, 78.6, 82.3, 83.4, 84.6, 103.7, 120.6, 123.6, 126.3, 127.6, 128.9, 130.1, 147.8, 148.2, 150.3, 153.9, 166.8, 169.3, 171.9, 203.9.

5.10.2. Compound 5n. MS (SI): 883^+ ($M+H^+$). HR-MS (SI): calcd for $C_{47}H_{73}N_4O_{12}$: 883.5065. Found: 883.5068.

IR (KBr): 3437, 2971, 2937, 2877, 2784, 1810, 1751, 1716, 1673, 1625, 1596, 1526, 1504, 1455, 1380, 1363, 1321, 1284, 1257, 1232, 1167, 1142, 1109, 1081, 1047, 1005, 990, 953, 932, 912, 835, 801, 772, 693, 660, 633, 615, 574, 555, 531, 478, 457 (cm^{-1}).

^1H NMR($CDCl_3$) δ (ppm): 0.85 (3H, t, J = 7.5 Hz), 0.96 (3H, t, J = 7.5 Hz), 1.01 (3H, d, J = 6.9 Hz), 1.21 (3H, d, J = 6.3 Hz), 1.27 (3H, d, J = 6.3 Hz), 1.27 (3H, d, J = 7.5 Hz), 1.36 (3H, d, J = 6.9 Hz), 1.40 (3H, s), 1.56 (3H, s), 1.20–2.06 (11H, m), 2.27 (6H, s), 2.45 (1H, m), 2.56 (1H, q, J = 6.9 Hz), 2.69 (3H, s), 2.88 (2H, t, J = 7.2 Hz), 3.03 (1H, quintet, J = 7.8 Hz), 3.13–3.28 (2H, m), 3.40–3.58 (3H, m), 3.72 (1H, m), 3.82 (1H, q, J = 6.9 Hz), 4.22 (1H, d, J = 7.8 Hz), 4.30 (1H, d, J = 6.9 Hz), 4.33 (1H, dd, J = 4.8 and 7.8 Hz), 4.84 (1H, s), 5.00 (1H, dd, J = 3.0 and 10.5 Hz), 6.89 (1H, t, J = 5.7 Hz), 7.32 (1H, dd, J = 4.2 and 8.4 Hz), 7.45 (1H, dd, J = 1.5 and 8.4 Hz), 7.73 (1H, d, J = 8.4), 7.89 (1H, s), 8.10 (1H, dd, J = 1.2 and 8.1 Hz), 8.86 (1H, dd, J = 1.5 and 4.2 Hz).

^{13}C NMR ($CDCl_3$) δ (ppm): 9.7, 10.2, 12.9, 14.3, 15.3, 15.6, 19.0, 19.9, 21.1, 22.3, 23.7, 26.4, 28.3, 30.8, 33.2, 33.5, 37.9, 38.9, 40.2, 47.6, 49.8, 51.1, 65.9, 69.5, 70.3, 76.1, 78.5, 78.6, 82.3, 83.5, 84.6, 103.8, 120.3, 126.7, 127.6, 127.9, 128.1, 135.7, 143.6, 148.6, 150.2, 153.9, 166.7, 169.3, 171.7, 204.0.

5.10.3. Compound 5q. MS (SI): 884^+ ($M+H^+$). HR-MS (SI): calcd for $C_{46}H_{70}N_5O_{12}$: 884.5017. Found: 884.5020.

IR (KBr): 3435, 2971, 2937, 2878, 2784, 1810, 1751, 1717, 1671, 1637, 1527, 1499, 1456, 1379, 1324, 1304, 1284, 1257, 1233, 1218, 1167, 1140, 1109, 1080, 1048, 1005, 990, 956, 931, 912, 866, 831, 772, 755, 693, 557, 459, 407 (cm^{-1}).

^1H NMR ($CDCl_3$) δ (ppm): 0.86 (3H, t, J = 7.2 Hz), 0.97 (3H, t, J = 7.5 Hz), 1.01 (3H, d, J = 7.2 Hz), 1.22 (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 = 6.9 Hz), 1.40 (3H, s), 1.56 (3H, s), 1.20–2.06 (11H, m), 2.26 (6H, s), 2.45 (1H, m), 2.56 (1H, q, J = 6.9 Hz), 2.69 (3H, s), 2.91 (2H, t, J = 7.5 Hz), 3.02 (1H, quintet, J = 7.5 Hz), 3.17 (1H, dd, J = 7.2 and 9.9 Hz), 3.15–3.26 (1H, m), 3.43–3.58 (3H, m), 3.72 (1H, m), 3.83 (1H, q, J = 6.9 Hz), 4.22 (1H, d, J = 7.8 Hz), 4.30 (1H, d, J = 7.5 Hz), 4.30 (1H, dd, J = 4.5 and 7.5 Hz), 4.84 (1H, s), 5.00 (1H, dd, J = 2.7 and 10.2 Hz), 7.02 (1H, t, J = 6.0 Hz), 7.69 (1H, dd, J = 1.8 and 8.7 Hz), 7.91 (1H, d, J = 1.8 Hz), 8.01 (1H, d, J = 8.7 Hz), 8.78 (1H, d, J = 8.7 Hz), 8.79 (1H, d, J = 8.7 Hz).

^{13}C NMR ($CDCl_3$) δ (ppm): 9.8, 10.2, 12.9, 14.3, 15.3, 15.6, 15.7, 18.9, 19.9, 21.2, 22.2, 23.6, 26.4, 28.2, 30.6, 33.1, 33.4, 37.8, 38.8, 40.2, 47.6, 49.8, 51.1, 65.9, 69.5, 70.3, 76.0, 78.5, 82.3, 83.4, 84.6, 84.7, 103.8, 127.8, 129.1, 131.7, 141.8, 143.2, 144.1, 144.5, 144.8, 153.8, 153.9, 166.8, 169.3, 171.9, 204.0.

5.11. Preparation of compound 12d

To a solution of *N*-Boc-propargylamine (4.96 g, 32 mmol) in CH_3CN (50 mL) were successively added NEt_3 (4.44 mL, 32 mmol), CuI (122 mg, 0.64 mmol), 2-chloro-quinoxaline (2.64 g, 16 mmol), and $Cl_2Pd(PPh_3)_2$ (224 mg, 0.32 mmol). The reaction mixture was stirred at room temperature for 2 h. The mixture was filtered and poured into 5% aqueous $NaHCO_3$, and extracted with AcOEt. The resultant residue was purified by column chromatography on silica gel (*n*-hexane:AcOEt, 4:1–1:1) to give 4.51 g of compound **10d** (99%).

^{1}H NMR ($CDCl_3$) δ (ppm): 1.48 (9H, s), 4.29 (2H, d, J = 5.7 Hz), 4.89 (1H, br s), 7.75–7.82 (2H, m), 8.04–8.11 (2H, m), 8.87 (1H, s).

Compound **10d** (4.51 g, 16 mmol) was dissolved in EtOH (80 mL) and AcOEt (80 mL). To this solution was added 5% Pd/C (640 mg) with stirring at room temperature under H_2 atmosphere for 1 h. The mixture was filtered and concentrated, and the resultant residue was purified by column chromatography on silica gel (*n*-hexane:AcOEt, 2:1–1:8) to give 2.20 g of compound **11d** (48%).

^{1}H NMR ($CDCl_3$) δ (ppm): 1.44 (9H, s), 2.08 (2H, m), 3.08 (2H, t, J = 7.5 Hz), 3.28 (2H, m), 4.85 (1H, br s), 7.71–7.76 (2H, m), 8.02–8.10 (2H, m), 8.75 (1H, s).

Compound **11d** (2.14 g, 7.45 mmol) was dissolved with CH_2Cl_2 (37 mL) and stirred at −30 °C. To this solution was added TMSI (1.48 mL, 10.4 mmol), and the reaction mixture was stirred on an ice-water bath for 1 h. The reaction mixture was poured into diluted aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$/MeOH (5/1). The aqueous layer was extracted with $CHCl_3$/MeOH (5/1), and the combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Finally, 970 mg of compound **12d** was obtained (69%).

^{1}H NMR ($CDCl_3$) δ (ppm): 2.02 (2H, m), 2.84 (2H, t, J = 6.9 Hz), 3.09 (2H, t, J = 7.8 Hz), 7.71–7.78 (2H, m), 8.02–8.10 (2H, m), 8.76 (1H, s).

5.12. Preparation of compounds 12a–c

Compounds **12a**–**c** were prepared by the procedure described for the synthesis of **12d** from 4-iodo-quinoline,[4] 7-bromo-quinoline,[11] and 6-bromo-quinoxaline, respectively.

5.12.1. Compound 12a. ^{1}H NMR ($CDCl_3$) δ (ppm): 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).

5.12.2. Compound 12b. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.89 (2H, m), 2.79 (2H, t, J = 7.2 Hz), 2.89 (2H, t, J = 8.1 Hz), 7.34 (1H, dd, J = 4.2 and 8.1 Hz), 7.41 (1H, dd, J = 1.8 and 8.7 Hz), 7.74 (1H, d, J = 8.7 Hz), 7.90 (1H, s), 8.12 (1H, m), 8.88 (1H, dd, J = 1.8 and 4.2 Hz).

5.12.3. Compound 12c. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.92 (2H, m), 2.55 (2H, br s), 2.79 (2H, t, J = 7.2 Hz), 2.92 (2H, t, J = 7.5 Hz), 7.67 (1H, dd, J = 2.8 and 8.4 Hz), 7.90 (1H, d, J = 1.2 Hz), 8.05 (1H, d, J = 8.4 Hz), 8.81 (1H, d, J = 6.3 Hz), 8.82 (1H, d, J = 6.3 Hz).

5.13. Preparation of compound 12e

To a solution of *N*-Boc-propargylamine (3.72 g, 23.7 mmol) in CH_3CN (51 mL) were successively added NEt_3 (3.34 mL, 23.7 mmol), CuI (61 mg, 0.32 mmol), compound **13**[12] (4.53 g, 7.9 mmol), and $Cl_2Pd(PPh_3)_2$ (112 mg, 0.16 mmol). The reaction mixture was stirred at room temperature for 1 h and then for 4 h at 70 °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 silica gel (*n*-hexane:AcOEt, 4:1–1:1) to give 1.08 g of compound **14** (26%).

^{1}H NMR ($CDCl_3$) δ (ppm): 1.45 (9H, s), 4.09 (2H, d, J = 5.1 Hz), 4.74 (1H, br s), 5.18 (2 H, s), 5.22 (2H, s), 6.84 (1H, br s), 7.18–7.40 (12H, m), 7.78 (1H, br s), 7.85 (1H, br s).

Compound **14** (1.05 g, 1.98 mmol) was dissolved in EtOH (10.5 mL) and AcOEt (10.5 mL). To this solution were added CH_3CO_2H (2.6 mL) and 10% Pd/C (210 mg) with stirring at room temperature under H_2 atmosphere for 2 h. The mixture was filtered and concentrated. The resultant residue was diluted with aqueous $NaHCO_3$ 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 to give 530 mg of compound **15** (91%).

^{1}H NMR ($CDCl_3$) δ (ppm): 1.45 (9H, s), 1.80 (2H, m), 2.55 (2H, t, J = 8.1 Hz), 3.17 (2H, dt, J = 6.3 and 6.6 Hz), 3.30 (4H, br s), 4.63 (1H, br s), 6.59–6.68 (3H, m).

Compound **15** (400 mg, 1.5 mmol) was dissolved in EtOH (6 mL). To this solution was added $(CHO)_2$-$2NaHSO_3$-H_2O (glyoxal sodium bisulfite) (0.47 g, 1.77 mmol) in hot water with stirring and the reaction mixture was refluxed for 0.5 h and cooled to room temperature. The mixture was poured into 5% aqueous $NaHCO_3$ and extracted with AcOEt. The resultant residue was purified by column chromatography on silica gel (*n*-hexane:AcOEt, 4:1–1:8) to give 187 mg of compound **11e** (43%).

^{1}H NMR ($CDCl_3$) δ (ppm): 1.45 (9H, s), 1.96 (2H, m), 3.17 (2H, dt, J = 6.3 and 6.9 Hz), 3.30 (2H, t, J = 7.5 Hz), 5.00 (1H, br s), 7.63 (1H, dd, J = 1.5 and 7.2 Hz), 7.70 (1H, dd, J = 7.2 and 8.4 Hz), 7.98 (1H, dd, J = 1.5 and 8.4 Hz), 8.84 (1H, d, J = 3.0 Hz), 8.85 (1H, d, J = 3.0 Hz).

Compound **12e** was prepared from **11e** by the procedure described for the synthesis of **12d** from **11d**.

5.13.1. Compound 12e. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.92 (2H, m), 2.77 (2H, t, J = 6.6 Hz), 3.32 (2H, t, J = 7.5 Hz), 7.63 (1H, dd, J = 1.5 and 7.8 Hz), 7.71 (1H, dd, J = 7.8 and 8.1 Hz), 7.97 (1H, dd, J = 1.5 and 8.1 Hz), 8.84 (2H, br s).

5.14. Preparation of compound 12f

To a solution of NaH 208 mg (60% in mineral oil 5.2 mmol) in DMF (1 mL) was added dropwise compound **16**[13] (620 mg, 4.0 mmol) in DMF (3 mL) at room temperature, and the mixture was stirred for 30 min. To this solution, 3-bromo-propylphthalimide 1.31 g (4.8 mmol) in DMF (3 mL) was added dropwise and the reaction mixture was stirred for 4.5 h at 70 °C. The reaction mixture was cooled to room temperature, poured into H_2O, and extracted with AcOEt. The aqueous layer was extracted with AcOEt, 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 silica gel ($CHCl_3$:MeOH, 80:1–5:1) to give 840 mg of compound **17** (63%).

5.14.1. Compound 17. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.27 (2H, m), 3.80 (2H, t, J = 6.6 Hz), 4.07 (2H, t, J = 6.9 Hz), 7.28 (1H, m), 7.36 (1H, d, J = 1.2 Hz), 7.62 (1H, d, J = 1.2 Hz), 7.69–7.84 (4H, m), 8.03 (1H, dt, J = 1.8 and 8.1 Hz), 8.46 (1H, dd, J = 1.5 and 4.8 Hz), 8.92 (1H, d, J = 1.8 Hz).

Compound **17** (810 mg, 2.4 mmol) was dissolved in EtOH (15 mL). To this solution was added H_2NNH_2–H_2O (0.24 mL, 4.8 mmol) with stirring at room temperature, and the solution was refluxed for 8 h. The reaction mixture was cooled to room temperature, and filtered and concentrated. The resultant residue was diluted with 2 N NaOH (20 mL) and extracted with $CHCl_3$. The aqueous layer was extracted with $CHCl_3$, and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give 485 mg of compound **12f** (82%).

5.14.2. Compound 12f. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.96 (2H, m), 2.77 (2H, t, J = 6.9 Hz), 4.11 (2H, t, J = 7.2 Hz), 7.29 (2H, m), 7.56 (1H, s), 8.09 (1H, dt, J = 1.5 and 8.1 Hz), 8.47 (1H, dd, J = 1.2 and 4.8 Hz), 8.96 (1H, d, J = 2.1 Hz).

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