A54145, A NEW LIPOPEPTIDE ANTIBIOTIC COMPLEX: ISOLATION AND CHARACTERIZATION†

D. S. FUKUDA, R. H. DU BUS, P. J. BAKER, D. M. BERRY and J. S. MYNDERSE*

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285, U.S.A.

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A54145 is a complex of acidic lipopeptide antibiotics which are produced by *Streptomyces fradiae* and are active against Gram-positive bacteria. The A54145 complex was isolated by adsorption on Diaion HP-20 nonfunctionalized macroreticular resin and/or ion exchange on Amberlite IRA-68 anion exchange resin. Antibacterial factors A, A_1, B, B_1, C, D, E, and F were obtained in purified form by repeated preparative reverse phase HPLC on C_8 and/or C_{18} bonded-phase supports. The molecular formulae of the factors are $C_{72}H_{109}N_{17}O_{27}$ (factors A and A_1), $C_{73}H_{111}N_{17}O_{27}$ (factors B, B_1, C, and D), $C_{74}H_{113}N_{17}O_{27}$ (factor E), and $C_{71}H_{107}N_{17}O_{27}$ (factor F). The identities of the acyl side chains were established as 8-methylnonanoyl (factors F, A, and B_1), *n*-decanoyl (factors A_1 and B), and 8-methyldecanoyl (factors C, D, and E).

The first communication in this series[1] described the taxonomy and fermentation of *Streptomyces fradiae* NRRL 18158, a spontaneous mutant which was isolated from a soil sample obtained from Mexico. The fermentations of NRRL 18159 and NRRL 18160, nitrosoguanidine-induced mutants of NRRL 18158, were also described. NRRL 18158, NRRL 18159, and NRRL 18160 are referred to as culture A54145. This paper describes the isolation and characterization of eight acidic lipopeptide factors (A, A_1, B, B_1, C, D, E, and F) produced by culture A54145.

Materials and Methods

General Methods

UV spectra were run on a Cary model 118 spectrophotometer. IR spectra were recorded on a Nicolet MX-1 FT-IR spectrometer. Optical rotations were determined on a Perkin-Elmer model 241 polarimeter. FAB mass spectra were run on a Varian-MAT 731 or a VG Analytical ZAB 3 mass spectrometer. Amino acid analyses were performed on a Beckman model 6300 amino acid analyzer. Authentic fatty acid standards were purchased from The Foxboro Company. *p*-Nitrobenzyl-8 was purchased from Pierce Chemical Company.

HPLC Assay of A54145 Factors

Individual A54145 factors were identified and quantitated by analytical HPLC on a DuPont Zorbax 150-C_8 column (4.6 × 250 mm). The mobile phase consisted of CH_3CN - 0.2% aq triethylamine phosphate, pH 3 (35 : 65). With a mobile phase flow rate of 2.0 ml/minute, the following Rt's were observed for the A54145 factors: A, 12.1 minutes; A_1, 13.1 minutes; B, 14.9 minutes; B_1, 13.7 minutes; C, 17.0 minutes; D, 19.6 minutes; E, 22.4 minutes; and F, 9.4 minutes.

Isolation and Purification of A54145 Factors A and F

Whole broth (4,600 liters) produced by fermentation of NRRL 18159 was adjusted to pH 6.5 with

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hydrochloric acid and then filtered through a filter press with 4% Celite 545. Diaion HP-20 macroreticular resin (200 liters) was added to the filtered broth and the pH was maintained at 6.0 while the broth was stirred. After 2 hours the resin was collected by filtration and the filtrate was discarded. The resin was washed with water (800 liters, 35 minutes with agitation), then with CH_3CN-H_2O (15:85, 400 liters, 3 minutes with agitation) and the washes discarded. Antibacterial activity was eluted from the resin with CH_3CN-H_2O (1:1, 2×600 liters, 35 minutes each with agitation). The combined eluates (1,200 liters) were applied to a column containing Amberlite IRA-68 (AcO^-) anion exchange resin (100 liters, equilibrated in CH_3CN-H_2O) which was then washed with CH_3CN-H_2O (500 liters) and CH_3CN-0.2 N HOAc (1:1, 300 liters). The column was then eluted with additional CH_3CN-0.2 N HOAc (1:1, 750 liters), which was concentrated and lyophilized to give crude A54145 antibiotic complex (3.65 kg). A portion (60 g) of this crude complex was dissolved in pyridine-HOAc-H_2O, (1:1:98, 350 ml) and subjected to preparative reverse phase HPLC (RPHPLC) on an 8 cm × 1 m column (Jobin Yvon Chromatospac Prep 100) containing octadecylsilanized Quantum LP-1 silica gel (LP-1/C_{18}). The column was developed with pyridine-HOAc-H_2O (1:1:98, 4 liters), pyridine-HOAc-H_2O-CH_3CN-MeOH (1:1:63:25:10, 47 liters), and CH_3CN-H_2O (1:1, 10 liters) at a flow rate of 100 ml/minute, collecting 0.5 liter fractions. Fractions 29~31 yielded A54145F-enriched material (2.54 g), fractions 35~39 yielded A54145A-enriched material (5.1 g), and fractions 51~81 yielded A54145C-enriched material (1.04 g).

A54145A-enriched material (1.0 g) was purified by RPHPLC on columns (2~2.2 × 30 cm) packed with DuPont Zorbax ODS (12 μm) eluting with pyridine-HOAc-H_2O-CH_3CN-MeOH (1:1:70:18:10) at a flow rate of 9 ml/minute to give A54145A (212 mg). A54145F-enriched material (800 mg) was purified on a column (2.2 × 50 cm) packed with LP-1/C_{18} resin (20 μm), eluting in a mobile phase consisting of pyridine-HOAc-H_2O-CH_3CN (1:1:65:33) at a flow rate of 8 ml/minute to give A54145F (366.2 mg).

Isolation and Purification of A54145 Factors B, C, D, and E

Whole broth (217 liters) produced by fermentation of NRRL 18159 was filtered through a filter press with 3% Hyflo Super-Cel filter aid. The pH of the filtered broth (185 liters) was adjusted to 6.4, using 5 N HCl. Diaion HP-20 macroreticular resin (20 liters) was added to the filtered broth; after stirring at room temperature, the resin was collected by filtration and the filtrate was discarded. The resin was washed with water (60 liters, with agitation), then with CH_3CN-H_2O (15:85, 40 liters, with agitation) and the washes discarded. Antibacterial activity was eluted from the resin with CH_3CN-H_2O (1:1, 2×30 liters, with agitation). The combined eluates (60 liters) were applied to a column containing Amberlite IRA-68 (AcO^-) anion exchange resin (6.3×81 cm). The effluent, CH_3CN-H_2O wash (1:1, 10 liters), and CH_3CN-0.1 N HOAc wash (1:1, 10 liters) were discarded. The column was then eluted with additional CH_3CN-1.0 N HOAc (1:1, 14 liters), which was concentrated and lyophilized to give crude A54145 antibiotic complex (101.1 g).

Crude A54145 complex (60 g, dissolved in 400 ml of pyridine-HOAc-H_2O, 1:1:98) was subjected to preparative RPHPLC on an 8 cm × 1 m column (Jobin Yvon Chromatospac Prep 100) containing octadecylsilanized Quantum LP-1 silica gel (LP-1/C_{18}). The column was developed with pyridine-HOAc-H_2O (1:1:98, 4 liters), pyridine-HOAc-H_2O-CH_3CN-MeOH (1:1:68:20:10, 10.5 liters), pyridine-HOAc-H_2O-CH_3CN-MeOH (1:1:63:25:10, 22 liters), and pyridine-HOAc-H_2O-CH_3CN-MeOH (1:1:61:27:10, 44 liters) at a flow rate of 100 ml/minute, collecting 0.5 liter fractions. Fractions 114~161 were combined on the basis of analytical HPLC results and concentrated and lyophilized to give A54145 complex (8.5 g) enriched in factors B, C, D, and E. This complex was rechromatographed under the same conditions except that column development was accomplished with pyridine-HOAc-H_2O (1:1:98, 4 liters), pyridine-HOAc-H_2O-CH_3CN-MeOH (1:1:63:25:10, 16.5 liters), pyridine-HOAc-H_2O-CH_3CN-MeOH (1:1:58:30:10, 9.5 liters), pyridine-HOAc-H_2O-CH_3CN-MeOH (1:1:53:35:10, 11.5 liters), and CH_3CN-MeOH (1:1, 8 liters). Fractions 76~78 yielded A54145B-enriched material (1.75 g), fractions 79~83 yielded A54145C-enriched material (1.02 g), and fractions 84~99 yielded A54145D-enriched material (0.8 g).

A54145B-enriched material (500 mg) was purified by RPHPLC on columns (2~2.2 × 30 cm) packed with DuPont Zorbax ODS (12 μm) eluting with pyridine-HOAc-H_2O-CH_3CN-MeOH (1:1:56:32:10) to give A54145B (330 mg). A54145D-enriched material (750 mg) was purified by two successive RPHPLC

runs on a column (2.2 × 30 cm) packed with DuPont Zorbax ODS (12 μm) eluting with pyridine - HOAc - H_2O - CH_3CN - MeOH (1 : 1 : 61 : 32 : 5) to give A54145D (70 mg). A54145C-enriched materials (11.76 g) combined from both Chromatospac preparative HPLC runs described above were subjected to RPHPLC on a column (4.6 × 60 cm) packed with LP-1/C_{18} resin (20 μm) eluting with pyridine - HOAc - H_2O - CH_3CN - MeOH (1 : 1 : 53 : 35 : 10) to give further-enriched A54145C (817.8 mg) and A54145E (1.17 g) preparations. Purified A54145C (27.6 mg) was afforded by repeated (2×) HPLC of the further enriched preparation (817.8 mg) on a column (2.2 × 50 cm) packed with LP-1/C_{18} resin (20 μm), using a mobile phase consisting of pyridine - HOAc - H_2O - CH_3CN (1 : 1 : 67 : 31). Purified A54145E (16.1 mg) was obtained by successive HPLC of the further-enriched A54145E preparation on LP-1/C_{18} (2.2 × 50 cm; pyridine - HOAc - H_2O - CH_3CN, 1 : 1 : 66 : 32) and DuPont Zorbax ODS (5 μm, 2～9.4 mm × 25 cm; pyridine - HOAc - H_2O - CH_3CN, 1 : 1 : 67 : 31).

Isolation and Purification of A54145 Factor A_1

Whole broth (103 liters) produced by fermentation of NRRL 18158 was filtered and subjected to batchwise absorption/desorption with Diaion HP-20 as in the example immediately above. The combined eluates were applied to a column (4.0 × 78.0 cm) containing BioRad BioRex 5 (Cl^-) anion exchange resin and eluted with a gradient of 0.1 N - 1.0 N NaCl. Fractions containing antibacterial activity were combined and desalted over a column (4 × 40 cm) of Diaion HP-20. Active fractions were concentrated and lyophilized to give crude A54145 antibiotic complex (12.08 g). Crude A54145 (2 g) was subjected to preparative RPHPLC on a Waters PrepPak 500 C_{18} column; elution was accomplished with a linear gradient from H_2O to CH_3CN - H_2O (1 : 1) buffered with 1% $NH_4H_2PO_4$. A54145A_1 containing fractions were combined and desalted over a Diaion HP-20 column, then repeatedly rechromatographed on columns (2～2.2 × 30 cm) packed with DuPont Zorbax ODS (12 μm) eluting with pyridine - HOAc - H_2O - CH_3CN (1 : 1 : 66 : 32), CH_3CN - MeOH - 0.042 N NH_4OAc (25 : 12.5 : 62.5), CH_3CN - MeOH - 0.037 N NH_4OAc (25 : 5 : 70), and CH_3CN - MeOH - 0.036 N NH_4OAc (20 : 7 : 73), to give purified A54145 A_1 (12.21 mg).

Isolation and Purification of A54145 Factor B_1

Whole broth (100 liters) produced by fermentation of NRRL 18160 was filtered and subjected to batchwise absorption/desorption with Diaion HP-20 as in the examples above. The CH_3CN - H_2O (15 : 85) eluate was concentrated and lyophilized to give crude antibiotic (248.2 g). A portion of crude antibiotic (60 g) was subjected to preparative HPLC on an LP-1/C_{18} column (2.2 × 60 cm). A54145B_1 enriched material eluted with pyridine - HOAc - H_2O - CH_3CN (1 : 1 : 63 : 35) was further purified over columns (2～2.2 × 30 cm) containing Amicon Matrex silica LC (C_{18}, 10 μm) to give purified A54145B_1 (207 mg).

Determination of *N*-Acyl Substituents of A54145 Factors

The *N*-acyl substituents of the A54145 lipopeptide factors were determined by hydrolysis of the acyl group followed by derivatization of the resultant fatty acids to the *p*-nitrobenzyl (PNB) esters. The HPLC Rt's were compared to those of PNB esters of authentic fatty acids using a DuPont Zorbax ODS column (4.6 × 250 mm) and a mobile phase consisting of CH_3CN - H_2O (80 : 20). At a flow rate of 2.0 ml/minute, the following representative Rt's were observed for PNB esters of authentic fatty acids: *n*-Nonanoyl-PNB ester (*n*C_9-PNB), 5.9 minutes; 8-methylnonanoyl-PNB ester (*i*C_{10}-PNB), 7.4 minutes; *n*-decanoyl-PNB ester (*n*C_{10}-PNB), 8.0 minutes; 8-methyldecanoyl-PNB ester (*a*C_{11}-PNB), 9.9 minutes; *n*-undecanoyl-PNB ester (*n*C_{11}-PNB), 11.2 minutes; 10-methylundecanoyl-PNB ester (*i*C_{12}-PNB), 14.3 minutes; and *n*-dodecanoyl-PNB ester (*n*C_{12}-PNB), 15.8 minutes.

In a typical example, A54145A (0.71 mg) was weighed into a 5-ml vacuum hydrolysis tube and 6 N HCl (1.0 ml) added. The tube was evacuated and then placed in a 107 °C heating block for 16 hours. After cooling, CH_2Cl_2 (0.5 ml) was added and the tube was shaken. CH_2Cl_2 phase (0.5 ml) was removed and placed into a 1 ml reaction vial. CH_2Cl_2 (100 μl) and *O*-(PNB)-*N*,*N*'-(diisopropyl)isourea (0.1 M solution in CH_2Cl_2 (Pierce *p*-nitrobenzyl-8), 100 μl) were added and the solution stirred at 80°C for 2 hours. The cooled reaction solution was blown dry under a stream of N_2, redissolved in CH_3CN, and analyzed by HPLC as above.

Results and Discussion

The A54145 antibiotic complex was isolated from broth filtrate by batch-mode adsorption onto Diaion HP-20 macroreticular resin, followed by ion exchange on anion exchange resins directly from the mixed organic/aqueous Diaion HP-20 eluent. Fig. 1 shows an example of this procedure. Later isolations successfully omitted the anion exchange step (see isolation and purification of A54145 factor B_1, Materials and Methods section). Individual A54145 factors were separated and purified by repeated HPLC on various reverse phase columns. A total of eight factors were isolated in sufficient quantity for structure elucidation. Fig. 2 shows a representative isolation scheme, the purification of factors A, C, and F.

The A54145 antibiotics are soluble in water, methanol, *N*,*N*-dimethylfomamide, and dimethyl sulfoxide; but are insoluble or only slightly soluble in acetone, ethyl acetate, chloroform, diethyl ether, benzene, and hydrocarbon solvents. The factors give a positive reaction with ninhydrin, char with sulfuric acid, and stain with iodine.

Preliminary ^{1}H NMR studies[2] suggested that the A54145 antibiotics are acylated cyclic peptides which bear structural similarities to the cyclic lipopeptide A21978C[3]. Amino acid analysis (see Table 1, physico-chemical properties of A54145 factors) indicated the presence of two aspartate (aspartic acid and/or asparagine), one threonine, one

Fig. 1. Isolation of A54145 antibiotic complex.

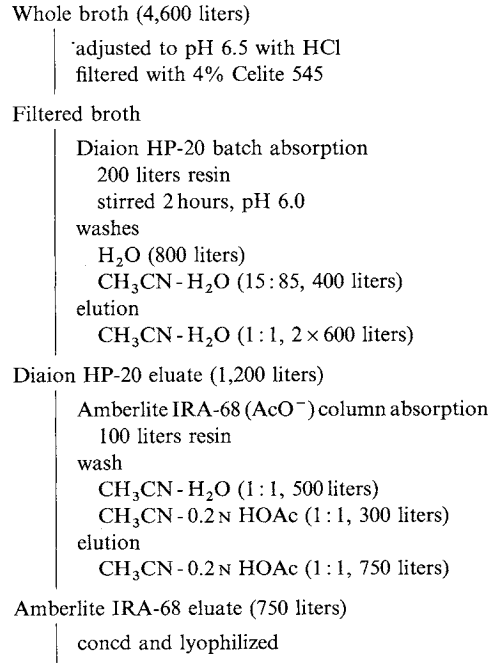


Fig. 2. Purification of A54145 factors A, C, and F.

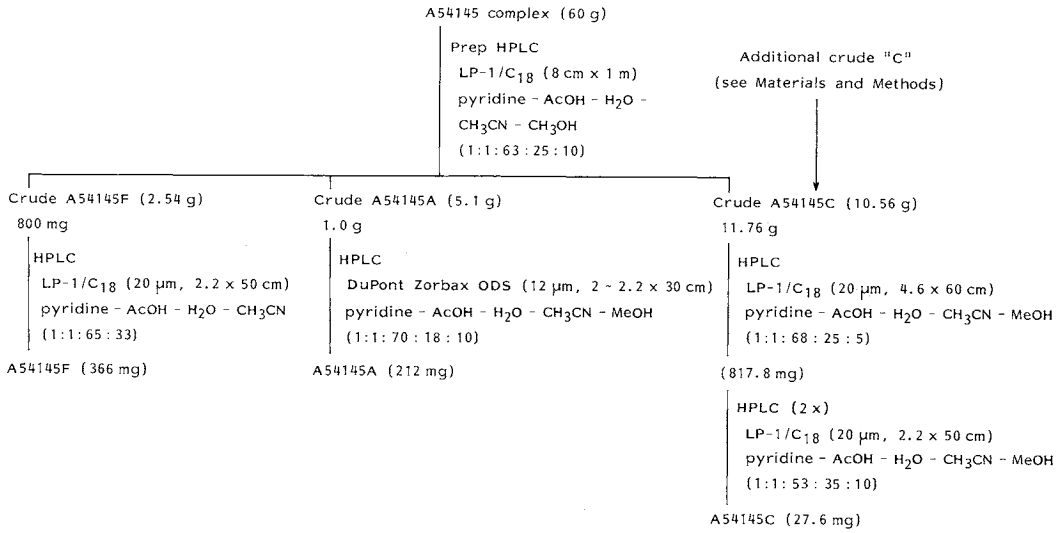


Table 1. Physico-chemical properties of A54145 factors.

	A54145A	A54145A$_1$	A54145B	A54145B$_1$
Appearance	White amorphous powder	White amorphous powder	White amorphous powder	White amorphous powder
Molecular formula	$C_{72}H_{109}N_{17}O_{27}$ (MW 1,643)	$C_{72}H_{109}N_{17}O_{27}$ (MW 1,643)	$C_{73}H_{111}N_{17}O_{27}$ (MW 1,657)	$C_{73}H_{111}N_{17}O_{27}$ (MW 1,657)
Mass spectrometry				
HR-MS Calcd:	1,644.7757 (M+H)	1,644.7757 (M+H)	1,658.7914 (M+H)	1,658.7914 (M+H)
Found:	1,644.7778 (FAB-MS)	1,644.7691 (FAB-MS)	1,658.7954 (FAB-MS)	1,658.7911 (FAB-MS)
UV λ_{max}^{EtOH} nm (ε)	219 (35,000), 280 (5,250), 288 (4,600)	220 (41,623), 281 (5,750), 289 (4,950)	220 (41,854), 281 (5,613), 289 (5,084)	221 (39,100), 282 (5,500), 290 (4,740)
IR (KBr) cm^{-1}			3335~3313, 2930, 1660, 1531, 1407, 1255	3307, 2958, 2931, 1658, 1531, 1408, 1254, 1235
$[\alpha]_{589}^{25}$	No rotation (CH_3OH)	−10.4°(*c* 0.69, CH_3OH)	−8.55°(*c* 0.47, H_2O)	
$[\alpha]_{365}^{25}$	−14.0° (*c* 1.0, CH_3OH)		−36.32° (*c* 0.47, H_2O)	
Amino acid analysis	Asp 973 (2), Thr 441 (1), Glu 1056 (2), Gly 528 (1), Ala 549 (1), Ile 469 (1), Lys 501 (1), Trp 465 (1)	Asp 1209 (2), Thr 554 (1), Glu 1209 (2), Gly 636 (1), Ala 617 (1), Ile 576 (1), Lys 604 (1), Trp 514 (1)	Asp 1039 (2), Thr 466 (1), Glu 564 (1), Gly 528 (1), Ala 525 (1), Ile 491 (1), Lys 514 (1), Trp 491 (1), 3-MG 512 (1)	Asp 935 (2), Thr 422 (1), Glu 556 (1), Gly 480 (1), Ala 434 (1), Ile 438 (1), Lys 467 (1), Trp 440 (1), 3-MG 426 (1)

	A54145C	A54145D	A54145E	A54145F
Appearance	White amorphous powder	White amorphous powder	White amorphous powder	White amorphous powder
Molecular formula	$C_{73}H_{111}N_{17}O_{27}$ (MW 1,657)	$C_{73}H_{111}N_{17}O_{27}$ (MW 1,657)	$C_{74}H_{113}N_{17}o_{27}$ (MW 1,671)	$C_{71}H_{107}N_{17}O_{27}$ (MW 1,629)
Mass spectrometry				
HR-MS Calcd:	1,658.7914 (M+H)	1,658.7914 (M+H)	1,672.8069 (M+H)	1,630.7601 (M+H)
Found:	1,658.7905 (FAB-MS)	1,658.7913 (FAB-MS)	1,672.8065 (FAB-MS)	1,630.7634 (FAB-MS)
UV λ_{max}^{EtOH} nm (ε)	219 (29,500), 281 (4,200), 288 (3,600)	219 (37,500), 280 (5,200), 289 (4,500)	221 (29,714), 278 (4,577), 289 (4,044)	219 (36,750), 280 (5,100), 288 (4,450)
IR (KBr) cm^{-1}	3357~3290, 2928, 1662, 1539, 1406	3336~3302, 2931, 1660, 1534, 1407, 1255	3392~3311, 2928, 1658, 1539, 1406	3337~3314, 2932, 1659, 1532, 1407, 1255,
$[\alpha]_{589}^{25}$				−3.0° (*c* 1.0, H_2O)
$[\alpha]_{365}^{25}$				−6.0° (*c* 1.0, H_2O)
Amino acid analysis	Asp 934 (2), Thr 414 (1), Glu 594 (1),Gly 501 (1), Ala 459 (1), Val 359 (1), Lys 451 (1), Trp 308 (1), 3-MG 487 (1)	Asp 1011 (2), Thr 427 (1), Glu 967 (2), Gly 515 (1), Ala 487 (1), Ile 434 (1), Lys 543 (1), Trp 577 (1)	Asp 826 (2), Thr 367 (1), Glu 494 (1), Gly 437 (1), Ala 422 (1), Ile 378 (1), Lys 410 (1), Trp 387 (1), 3-MG 437 (1)	Asp 959 (2), Thr 428 (1), Glu 965 (2), Gly 494 (1), Ala 487 (1), Val 363 (1), Lys 492 (1), Trp 452 (1)

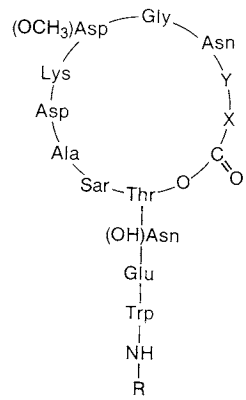
Table 2. HPLC determination of A54145 factor acyl substituents as PNB esters (see Materials and Methods section for experimental details).

Factor	Rt of PNB ester (minutes)					
	Acyl PNB derivative	nC_9PNB	iC_{10}PNB	Standards nC_{10}PNB	aC_{11}PNB	nC_{11}PNB
A	7.9	6.3	**7.9**	8.6	—	—
A_1	7.8	6.0	7.2	**7.8**	9.3	10.5
B	7.8	6.0	7.2	**7.8**	9.3	10.5
$B+B_1$	7.2, 7.8	6.0	**7.2**	7.8	9.3	10.5
C	10.0	6.0	7.4	8.0	**9.9**	11.2
D	10.0	6.1	7.6	8.3	**10.1**	11.4
E	9.6	5.8	7.3	7.9	**9.7**	10.9
F	7.9	6.3	**7.9**	8.6	—	—

glutamate, one glycine, one alanine, one lysine, one tryptophan, and three unidentified amino acid residues in each of the eight A54145 antibiotic factors. Each factor also contains either an isoleucine (factors A, A_1, B, B_1, D, and E) or a valine residue (factors C and F) and either a second glutamate (factors A, A_1, D, and F) or a 3-methylglutamate residue (factors B, B_1, C, and E).

The acyl substituents of isolated A54145 factors were determined by hydrolysis of of the acyl group followed by the derivatization of the resultant fatty acids to the PNB esters. The HPLC retention times of the PNB esters were compared to those of PNB esters of authentic fatty acids. The 8-methylnonanoyl (iC_{10}) substituent is present in A54145 factors A, B_1, and F; *n*-decanoyl (nC_{10}) in factors A_1 and B; and 8-methyldecanoyl (aC_{11}) in factors C, D, and E (Table 2).

Fig. 3. Structure of A54145 complex antibiotics.



Factor	X	Y	R
A	Ile	Glu	8-Methylnonanoyl (iC_{10})
A_1	Ile	Glu	*n*-Decanoyl (nC_{10})
B	Ile	3-MethylGlu	*n*-Decanoyl (nC_{10})
B_1	Ile	3-MethylGlu	8-Methylnonanoyl (iC_{10})
C	Val	3-MethylGlu	8-Methyldecanoyl (aC_{11})
D	Ile	Glu	8-Methyldecanoyl (aC_{11})
E	Ile	3-MethylGlu	8-Methyldecanoyl (aC_{11})
F	Val	Glu	8-Methylnonanoyl (iC_{10})

The structure elucidation of A54145 lipopeptide antibiotics[2] (Fig. 3) and the preparation of A54145 antibiotic analogs by chemical reacylation of microbially deacylated *N*-Lys-protected-A54145 complex[4,5] are described in separate reports. Each A54145 factor exhibits *in vitro* activity (MIC 0.26~16 μg/ml) against strains of *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae*[6]. The antibacterial activity of A54145 factors and semisynthetic derivatives, resistance development studies, calcium dependency, and *in vivo* evaluation are reported in full in a separate publication[7].

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References

1) BOECK, L. D.; H. R. PAPISKA, R. W. WETZEL, J. S. MYNDERSE, D. S. FUKUDA, F. P. MERTZ & D. M. BERRY: A54145, a new lipopeptide antibiotic complex: Discovery, taxonomy, fementation and HPLC. J. Antibiotics 43: 587~593, 1990
2) HUNT, A. H.; R. E. CHANCE, M. G. JOHNSON, J. L. OCCOLOWITZ, J. S. MYNDERSE, D. S. FUKUDA & H. A. KIRST: A54145, a complex of new cyclic lipopeptides containing unusual amino acids. Structural studies. Program and Abstracts of the 28th Intersci. Conf. on Antimicrob. Agents Chemother., No. 969, p. 281, Los Angeles, Oct. 23~26, 1988
3) DEBONO, M.; M. BARNHART, C. B. CARRELL, J. A. HOFFMANN, J. L. OCCOLOWITZ, B. J. ABBOTT, D. S. FUKUDA, R. L. HAMILL, K. BIEMANN & W. C. HERLIHY: A21978C, a complex of new acidic peptide antibiotics: Isolation, chemistry, and mass spectral structure elucidation. J. Antibiotics 40: 761~777, 1987
4) FUKUDA, D. S.; P. J. BAKER, M. DEBONO, R. M. MOLLOY & J. S. MYNDERSE: A54145, a new lipopeptide antibiotic complex—Deacylation and reacylation. Program and Abstracts of the 28th Intersci. Conf. on Antimicrob. Agents Chemother., No. 970, p. 281, Los Angeles, Oct. 23~26, 1988
5) FUKUDA, D. S.; M. DEBONO, R. M. MOLLOY & J. S. MYNDERSE: A54145, a new lipopeptide antibiotic complex: Microbial and chemical modification. J. Antibiotics 43: 601~606, 1990
6) COUNTER, F. T.; D. S. FUKUDA, J. OTT, P. W. ENSMINGER, J. S. MYNDERSE, D. A. PRESTON & C. Y. E. WU: A54145, a new lipopeptide antibiotic complex—Microbiological evaluation. Program and Abstracts of the 28th Intersci. Conf. on Antimicrob. Agents Chemother., No. 971, p. 282, Los Angeles, Oct. 23~26, 1988
7) COUNTER, F. T.; N. E. ALLEN, D. S. FUKUDA, J. N. HOBBS, J. OTT, P. W. ENSMINGER, J. S. MYNDERSE, D. A. PRESTON & C. Y. E. WU: A54145, a new lipopeptide antibiotic complex: Microbiological evaluation. J. Antibiotics 43: 616~622, 1990