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Note

Synthesis and immunoadjuvant activity of *N*-[2-*O*-(2-acetamido-2,3,di-deoxy-6-thio-D-glucopyranose-3-yl)-D-lactoyl]-L-alanyl-D-isoglutamine derivatives*

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In our continuing efforts to elucidate the relationships between the biological activities of *N*-acetylmuramoyl-L-alanyl-D-isoglutamine** (MDP) and the structure of the carbohydrate moiety, and to obtain glycopeptide adjuvants that exhibit strong activity and lower toxicity, it was demonstrated that replacement[2,3] of the hydroxyl group at C-1 of the sugar moiety by a thiol or an acylthio group caused potent antitumor and anti-infection activities, based on the immune reaction, that are not found for MDP itself, as well as strong, immunoadjuvant activities. In view of these facts, we now describe the synthesis of (*N*-acetyl-6-thiomuramoyl)-L-alanyl-D-isoglutamine derivatives, and their immunoadjuvant activity.

O-Deisopropylidenation of 2-acetamido-1-*O*-benzoyl-2-deoxy-4,6-*O*-isopropylidene-3-*O*-[D-1-(methoxycarbonyl)ethyl]-α-D-glucopyranose[2] (**1**) under mildly acidic conditions gave crystalline **2** in quantitative yield. Selective bromination of the primary hydroxyl group on C-6 in **2** with carbon tetrabromide and triphenylphosphine in pyridine afforded the 6-bromo derivative **3** in good yield, and **3** was acetylated with acetic anhydride in pyridine to give the 4-*O*-acetyl derivative **4**; significant signals in the n.m.r. spectrum of **4** were a one-proton triplet at δ 5.16 ($J_{3,4} = J_{4,5} = 9.0$ Hz, H-4), and a one-proton doublet at δ 6.76 ($J_{1,2}$ 3.0 Hz, H-1). Other n.m.r. data, given in the Experimental section, are consistent with structure **4**. *O*-Debenzoylation of **4** with sodium methoxide in methanol for 2 h at −20° gave **5**, and (tetrahydropyran-2-yl)ation of **5** afforded 2-acetamido-4-*O*-acetyl-6-bromo-2,6-dideoxy-3-*O*-[D-1-(methoxycarbonyl)ethyl]-1-*O*-(tetrahydropyran-2-yl)-α-D-glucopyranose (**6**) in good yield. The structure of compound **6** was based on n.m.r. spectroscopy; the spectrum showed the *O*-acetyl group at δ 2.13, the H-4

*Studies on Immunoadjuvant Active Compounds, Part 27. For Part 26, see ref. 1.
**N-[2-O-(2-Acetamido-2,3-dideoxy-D-glucopyranose-3-yl)-D-lactoyl]-L-alanyl-D-isoglutamine.

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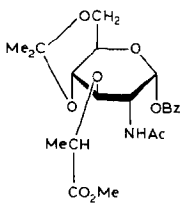
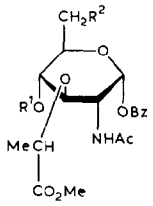


1

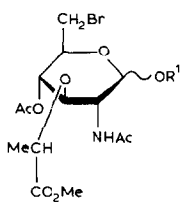
Bz = PhCO



2 R^1 = H, R^2 = OH

3 R^1 = H, R^2 = Br

4 R^1 = Ac, R^2 = Br



5 R^1 = H

6 R^1 = Thp

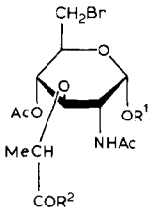
Thp = tetrahydropyran-2-yl

atom as a triplet at δ 4.98 ($J_{3,4} = J_{4,5} = 8.5$ Hz), and the H-1 atom as a doublet at δ 5.51 ($J_{1,2}$ 3.6 Hz), indicating the structure shown for the 4-*O*-acyl α-D-pyranose form **6**.

Saponification of the methyl ester group in **6** with 0.1M aqueous potassium hydroxide in 1,4-dioxane at room temperature gave the free acid, which was used for the next reaction without purification. Coupling of the acid with the methyl ester of L-alanyl-D-isoglutamine was conducted with dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide (HOSu) as the activating agents, to afford *N*-{2-*O*-[2-acetamido-4-*O*-acetyl-6-bromo-2,3,6-trideoxy-1-*O*-(tetrahydropyran-2-yl)-α-D-glucopyranose-3-yl]-D-lactoyl}-L-alanyl-D-isoglutamine methyl ester (**7**) in almost quantitative yield. Treatment of **7** with potassium thioacetate in dry acetone gave the 6-acetylthio derivative **8** in 90% yield; significant signals in the n.m.r. spectrum of **8** were two three-proton singlets at δ 2.16 (*O*-acyl) and 2.33 (*S*-acetyl), and a one-proton triplet at δ 4.91 ($J_{3,4} = J_{4,5} = 9.0$ Hz, H-4). Other n.m.r. data are given in the Experimental section, and are consistent with structure **8**. Hydrolysis of the tetrahydropyranyl group in **8** under mildly acidic conditions gave compound **11**.

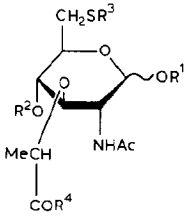
In order to synthesize lipophilic analogs of the 6-thiomuramoyl derivative **11** bearing the lipid moiety at C-6 of the sugar skeleton, condensation, with octadecanoyl chloride in pyridine–dichloromethane, of the product formed by selective hydrolysis of the *O*-acetyl and *S*-acetyl groups in **8** gave **9**, which was converted, by hydrolytic removal of the tetrahydropyranyl group under mild, acidic conditions, into *N*-[2-*O*-(2-acetamido-2,3-dideoxy-6-*S*-octadecanoyl-6-thio-D-glucopyranose-3-yl)-D-lactoyl]-L-alanyl-D-isoglutamine methyl ester (**12**) in good yield. On the other hand, treatment, with octadecyl bromide, of the sodium salt formed from **8** by addition of sodium methoxide in methanol afforded the 6-*S*-octadecyl derivative **10**, which was converted into *N*-[2-*O*-(2-acetamido-2,3-dideoxy-6-*S*-octadecyl-6-thio-D-glucopyranose-3-yl)-D-lactoyl]-L-alanyl-D-isoglutamine methyl ester (**13**) by heating with aqueous 70% acetic acid for 4 h at 50°.

The immunoadjuvant activities of compounds **11–13** on the induction of the delayed type of hypersensitivity to *N*-acetyl-L-tyrosine-3-azobenzene-4′-arsonic acid in guinea-pigs were examined[4]. Surprisingly, all of these compounds had completely lost the activity, although the 6-*O*-acyl- and 6-*N*-acyl-MDP analogs exhibited strong, immunoadjuvant activities[5–7].



7 R^1 = Thp, R^2 = a

a = L-Ala-D-isoGln—OMe



8 R^1 = Thp, R^2 = R^3 = Ac
9 R^1 = Thp, R^2 = H, R^3 = b
10 R^1 = Thp, R^2 = H, R^3 = c
11 R^1 = H, R^2 = R^3 = Ac
12 R^1 = R^2 = H, R^3 = b
13 R^1 = R^2 = H, R^3 = c
8 – 13 R^4 = a

b = octadecanoyl

c = octadecyl

EXPERIMENTAL

General methods. — Melting points were determined with a Yanagimoto micro melting-point apparatus and are uncorrected. Evaporations were conducted *in vacuo*. Preparative chromatography was performed on silica gel (Waco Co; 200 mesh) with the solvent systems specified. Specific rotations were determined with a Union PM-201 polarimeter, and i.r. spectra were recorded with a Jasco A-100 spectrophotometer. N.m.r. spectra were recorded at 90 MHz with a Hitachi R-22 spectrometer, and the data were confirmed by use of decoupling techniques.

2-Acetamido-1-O-benzoyl-2-deoxy-3-O-[D-*1-(methoxycarbonyl)ethyl*]-*α*-D-*glucopyranose* (**2**). — A solution of 2-acetamido-1-*O*-benzoyl-2-deoxy-4,6-*O*-isopropylidene-3-*O*-[D-1-(methoxycarbonyl)ethyl]-*α*-D-glucopyranose[2] (**1**; 6.7 g) in aqueous 70% acetic acid (30 mL) was heated for 3 h at 40°, and evaporated; the residue crystallized from ethyl acetate–ether, to give **2** (5.92 g, 97%) as needles; m.p. 182°, $[\alpha]_D^{25}$ +155° (*c* 0.5, chloroform); ν_{max}^{Nujol} 3450 and 3260 (OH, NH), 1720 and 1260 (ester), 1640 and 1540 (amide), and 700 cm^{-1} (phenyl).

Anal. Calc. for $C_{19}H_{25}NO_9$: C, 55.47; H, 6.13; N, 3.40. Found: C, 55.36; H, 6.20; N, 3.42.

2-Acetamido-1-O-benzoyl-6-bromo-2,6-dideoxy-3-O-[D-*1-(methoxycarbonyl)ethyl*]-*α*-D-*glucopyranose* (**3**). — To a solution of **2** (5.0 g) in dry pyridine (40 mL) were added, with stirring, triphenylphosphine (4.78 g) and carbon tetrabromide (4.84 g) at 0°, and the mixture was stirred for 5 h at room temperature, the course of the reaction being monitored by t.l.c. Methanol (10 mL) was now added to the mixture, which was evaporated. The residue was chromatographed on a column of silica gel (300 g) with chloroform, and then with 200:1 chloroform–methanol. The latter eluate afforded **3** (4.1 g, 71%) as needles, after recrystalliza-

tion from ether; m.p. 167°, $[\alpha]_D^{25}$ +121° (*c* 0.5, chloroform); ν_{max}^{Nujol} 3330 and 3280 (OH, NH), 1730, 1710, 1260, and 1250 (ester), 1645 and 1530 (amide), and 700 cm^{-1} (phenyl).

Anal. Calc. for $C_{19}H_{24}BrNO_8$: C, 48.11; H, 5.10; N, 2.95. Found: C, 47.98; H, 5.06; N, 2.98.

*2-Acetamido-4-*O*-acetyl-1-*O*-benzoyl-6-bromo-2,6-dideoxy-3-*O*-[*D*-1-(methoxycarbonyl)ethyl]-α-*D*-glucopyranose* (**4**). — Compound **3** (1.12 g) was acetylated with acetic anhydride (6 mL) and pyridine (10 mL) for 3 h at room temperature. The product crystallized from ether, to give **4** (1.15 g, 94%) as needles; m.p. 176°, $[\alpha]_D^{25}$ +90° (*c* 0.2, chloroform); ν_{max}^{Nujol} 3300 (NH), 1750, 1730, 1260, and 1230 (ester), 1670 and 1540 (amide), and 700 cm^{-1} (phenyl); n.m.r. data (in chloroform-*d*): δ 1.42 (d, 3 H, $J_{Me,CH}$ 7.2 Hz, MeCH), 1.98 (s, 3 H, AcN), 2.18 (s, 3 H, AcO), 3.20 –3.53 (m, 2 H, H-6,6'), 3.82 (s, 3 H, MeO), 4.34 (q, 1 H, $J_{CH,Me}$ 7.2 Hz, CHMe), 5.16 (t, 1 H, $J_{3,4} = J_{4,5}$ = 9.0 Hz, H-4), 6.76 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), and 7.33–8.04 (m, 6 H, NH, Ph).

Anal. Calc. for $C_{21}H_{26}BrNO_9$: C, 48.85; H, 5.08; N, 2.71. Found: C, 48.83; H, 5.11; N, 2.68.

*2-Acetamido-4-*O*-acetyl-6-bromo-2,6-dideoxy-3-*O*-[*D*-1-(methoxycarbonyl)-ethyl]-*D*-glucopyranose* (**5**). — To a solution of **4** (674 mg) in methanol (50 mL) was added sodium metal (10 mg), and the mixture was kept for 2 h at −20°, and then treated with Amberlite IR-120 (H^+) resin. The solution was evaporated to give a crystalline mass. Recrystallization from ether afforded **5** (431 mg, 80%) as needles; m.p. 188°, $[\alpha]_D^{25}$ +91° (*c* 0.22, chloroform; equil.); ν_{max}^{Nujol} 3280 and 3100 (NH, OH), 1740 and 1230 (ester), and 1650 and 1560 cm^{-1} (amide).

Anal. Calc. for $C_{14}H_{22}BrNO_8$: C, 40.79; H, 5.38; N, 3.40. Found: C, 40.85; H, 5.48; N, 3.42

*2-Acetamido-4-*O*-acetyl-6-bromo-2,6-dideoxy-3-*O*-[*D*-1-(methoxycarbonyl)-ethyl]-1-*O*-(tetrahydropyran-2-yl)-α-*D*-glucopyranose* (**6**). — To a solution of **5** (200 mg) in dry 1,4-dioxane (10 mL) were added 3,4-dihydropyran (190 mg) and *p*-toluenesulfonic acid monohydrate (10 mg), and the mixture was stirred for 2 h at room temperature, and then treated with Amberlite IRA-140 (OH^-) resin, to remove the acid. The solution was evaporated, and the residue was chromatographed on a column of silica gel (50 g) with chloroform, and then with 200:1 chloroform–methanol. The latter eluate afforded compound **6** (230 mg, 95%) as a syrup; $[\alpha]_D^{25}$ +88° (*c* 0.3, chloroform); ν_{max}^{film} 3340 (NH), 1750 and 1240 (ester), and 1670 and 1550 cm^{-1} (amide); n.m.r. data (in chloroform-*d*): δ 1.38 (d, 3 H, $J_{Me,CH}$ 7.0 Hz, MeCH), 1.42–1.85 (m, 6 H, 3 CH_2), 2.00–2.17 (m, 2 H, CH_2), 2.04 (s, 3 H, AcN), 2.13 (s, 3 H, AcO), 3.78 (s, 3 H, MeO), 4.25 (q, 1 H, $J_{CH,Me}$ 7.0 Hz, CHMe), 4.98 (t, 1 H, $J_{3,4} = J_{4,5}$ = 8.5 Hz, H-4), 5.51 (d 1 H, $J_{1,2}$ 3.6 Hz, H-1), and 7.50 (d, 1 H, $J_{NH,2}$ 5.0 Hz, NH).

Anal. Calc. for $C_{19}H_{30}BrNO_9$: C, 45.97; H, 6.09; N, 2.82. Found: C, 45.81; H, 6.15; N, 2.82.

N-{*2-*O*-[2-Acetamido-4-*O*-acetyl-6-bromo-2,3,6-trideoxy-1-*O*-(tetrahydropyran-2-yl)-α-*D*-glucopyranose-3-yl]-*D*-lactoyl}-*L*-alanyl-*D*-isoglutamine methyl*

ester (**7**). — To a solution of **6** (290 mg) in 1,4-dioxane (4 mL) was added 0.1M aqueous potassium hydroxide (6.05 mL), and the solution was stirred for 10 min at room temperature, treated with Amberlite IRC-50 (H^+) resin, and the solution evaporated, to afford the free acid. To a cooled solution of the acid in dry 1,4-dioxane (2 mL) were added *N*-hydroxysuccinimide (89 mg) and dicyclohexylcarbodiimide (207 mg), and the mixture was stirred for 30 min at room temperature. L-Alanyl-D-isoglutamine methyl ester trifluoroacetate (309 mg) and triethylamine (0.4 mL) were added to the mixture, and it was stirred for 3 h at room temperature. After evaporation of the solvent, the residue was chromatographed on a column of silica gel (50 g) with (*a*) chloroform, (*b*) 150:1, (*c*) 80:1, and (*d*) 20:1 chloroform–methanol. Eluant (*d*) afforded **7** (365 mg, 96%) as crystals; m.p. 109°, $[\alpha]_D^{25}$ +16.5° (*c* 0.5, chloroform); ν_{max}^{KBr} 3400–3270 (NH), 1750 and 1240 (ester), and 1660 and 1540 cm^{-1} (amide); n.m.r. data (in chloroform-*d*): δ 1.29, 1.44 (2 d, 6 H, $J_{Me,CH}$ 6.5 and 7.0 Hz, 2 MeCH), 1.46–1.82 (m, 6 H, 3 CH_2), 1.94 (s, 3 H, AcN), 2.02 (s, 3 H, AcO), 3.67 (s, 3 H, MeO), 4.91 (t, 1 H, $J_{3,4} = J_{4,5} = 8.5$ Hz, H-4), 5.11 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1), and 5.90, 6.38, 7.05, and 7.36 (5 H, 3 NH, NH_2).

Anal. Calc. for $C_{27}H_{43}BrN_4O_{12}$: C, 49.62; H, 6.63; N, 8.57. Found: C, 49.98; H, 6.81; N, 8.55.

N-{2-O-[*2-Acetamido-4-O-acetyl-6-S-acetyl-2,3-dideoxy-1-O-(tetrahydropyran-2-yl)-6-thio-α*-D-*glucopyranose-3-yl*]-D-*lactoyl*}-L-*alanyl*-D-*isoglutamine methyl ester* (**8**). — To a solution of **7** (100 mg) in dry acetone (3 mL) was added potassium thioacetate (100 mg), and the mixture was stirred overnight at room temperature, and evaporated to a syrup which was chromatographed on a column of silica gel (50 g) with (*a*) chloroform, (*b*) 150:1, (*c*) 80:1, and (*d*) 20:1 chloroform–methanol. Eluant (*d*) afforded **8** (95 mg, 90%) as a syrup; $[\alpha]_D^{25}$ +40° (*c* 0.8, chloroform); ν_{max}^{film} 3300 (NH), 1745 and 1240 (ester), 1700 (*S*-acetyl), and 1660 and 1540 cm^{-1} (amide); n.m.r. data (in chloroform-*d*): δ 1.28, 1.42 (2 d, 6 H, $J_{Me,CH}$ 6.2 and 6.5 Hz, 2 MeCH), 1.35–1.70 (m, 6 H, 3 CH_2), 1.93 (s, 3 H, AcN), 2.16 (s, 3 H, AcO), 2.33 (s, 3 H, AcS), 4.91 (t, 1 H, $J_{3,4} = J_{4,5} = 9.0$ Hz, H-4), 5.04 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), and 6.40, 6.78, 7.15, and 7.60 (5 H, 3 NH, NH_2).

Anal. Calc. for $C_{29}H_{46}N_4O_{13}S$: C, 50.42; H, 6.71; N, 8.11. Found: C, 50.28; H, 6.93; N, 8.05.

N-{2-O-[*2-Acetamido-2,3-dideoxy-6-S-octadecanoyl-1-O-(tetrahydropyran-2-yl)-6-thio-α*-D-*glucopyranose-3-yl*]-D-*lactoyl*}-L-*alanyl*-D-*isoglutamine methyl ester* (**9**). — To an ice-cooled solution of **8** (118 mg) in methanol (3 mL) was added sodium metal (6 mg), and the mixture was stirred for 30 min at 0°, treated with Amberlite IR-120 (H^+) resin (1.0 g) to remove the base, and then evaporated. To a solution of the residue in pyridine (1 mL) and dichloromethane (2 mL) was added dropwise, with stirring, a solution of octadecanoyl chloride (64 mg) in dry dichloromethane (1 mL), and the mixture was stirred for 1.5 h at 0°; methanol (1 mL) was added to the mixture, which was then extracted with chloroform. The extract was washed with water, dried (sodium sulfate), and evaporated. The residue was chromatographed on a silica gel plate (Kieselgel 60 F-254; E. Merck, Darmstadt,

West Germany) with 5:1 chloroform–methanol, to afford **9** (80 mg, 54%) as a syrup; $[\alpha]_D^{25}$ +31° (*c* 0.6, chloroform); ν_{max}^{film} 3350–3270 (OH, NH), 2930 and 2850 (Me, methylene), 1735 and 1250 (ester), 1700 (*S*-acyl), and 1660 and 1550 cm^{-1} (amide); n.m.r. data (in chloroform-*d*): δ 0.89 (near t, 3 H, J_{Mc,CH_2} 5.2 Hz, $MeCH_2$), 1.98 (s, 3 H, AcN), 3.76 (s, 3 H, MeO), and 5.08 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1).

Anal. Calc. for $C_{45}H_{77}N_4O_{13}S$: C, 59.21; H, 8.67; N, 6.42. Found: C, 59.09; H, 8.73; N, 6.30.

N-{*2-O-[2-Acetamido-2,3-dideoxy-6-S-octadecyl-1-O-(tetrahydropyran-2-yl)-6-thio-α-*D-*glucopyranose-3-yl]-*D-*lactoyl*}-L-*alanyl*-D-*isoglutamine methyl ester* (**10**). — To an ice-cooled solution of **8** (100 mg) in dry methanol (1 mL) was added sodium metal (5.4 mg), and the mixture was stirred for 30 min at 0°. A solution of octadecyl bromide (77 mg) in dichloromethane (1 mL) was added, with stirring, to the mixture, and it was stirred for 2 h at room temperature, and then evaporated. The product was purified by chromatography on a plate of silica gel, according to the procedure described for **9**, to afford **10** (90 mg, 72%) as a syrup; $[\alpha]_D^{25}$ +43.5° (*c* 0.5, chloroform); ν_{max}^{film} 3400–3260 (OH, NH), 2940 and 2850 (Me, methylene), 1730 and 1250 (ester), and 1660 and 1550 cm^{-1} (phenyl); n.m.r. data (in chloroform-*d*): δ 0.89 (near t, 3 H, $J_{Mc,CH}$ 6.0 Hz, $MeCH_2$), 1.98 (s, 3 H, AcN), 3.70 (s, 3 H, MeO), and 5.07 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1).

Anal. Calc. for $C_{43}H_{77}N_4O_{11}S$: C, 60.18; H, 9.04; N, 6.53. Found: C, 60.01; H, 9.23; N, 6.49.

N-[*2-O-(2-Acetamido-4-O-acetyl-6-S-acetyl-2,3-dideoxy-6-thio-*D-*glucopyranose-3-yl)-*D-*lactoyl*]-L-*alanyl*-D-*isoglutamine methyl ester* (**11**). — A solution of **8** (64 mg) in 70% aqueous acetic acid (2 mL) was heated for 4 h at 50°; it was then evaporated to a syrup which crystallized from ether, to give **11** (41 mg, 73%); m.p. 164–166°, $[\alpha]_D^{25}$ +31.8° (*c* 0.7, chloroform; equil.); ν_{max}^{KBr} 3450–3300 (OH, NH), 1740 and 1240 (ester), and 1660 and 1555 cm^{-1} (amide).

Anal. Calc for $C_{24}H_{38}N_4O_{12}S$: C, 47.51; H, 6.31; N, 9.24. Found: C, 47.35; H, 6.29; N, 9.14.

N-[*2-O-(2-Acetamido-2,3-dideoxy-6-S-octadecanoyl-6-thio-*D-*glucopyranose-3-yl)-*D-*lactoyl*]-L-*alanyl*-D-*isoglutamine methyl ester* (**12**). — Hydrolysis of the tetrahydropyranyl group in **9** (59 mg) with 70% aqueous acetic acid (2 mL), as already described, gave **12** (40 mg, 75%) as crystals; m.p. 131–133°, $[\alpha]_D^{25}$ +29° (*c* 0.3, chloroform; equil.); ν_{max}^{KBr} 3400–3300 (OH, NH), 2940 and 2850 (Me, methylene), 1740 and 1250 (ester), and 1660 and 1540 cm^{-1} (amide).

Anal. Calc. for $C_{38}H_{67}N_4O_{11}S$: C, 57.92; H, 8.57; N, 7.11. Found: C, 57.65; H, 8.73; N, 6.92.

N-[*2-O-(2-Acetamido-2,3-dideoxy-6-S-octadecyl-6-thio-*D-*glucopyranose-3-yl)-*D-*lactoyl*]-L-*alanyl*-D-*isoglutamine methyl ester* (**13**). — Hydrolysis of the tetrahydropyranyl group in **10** (22 mg), as described for **11**, afforded **13** (14 mg, 71%) as an amorphous mass: $[\alpha]_D^{25}$ +14° (*c* 0.5, chloroform; equil.); ν_{max}^{KBr} 3350–3280 (OH, NH), 2930 and 2840 (Me, methylene), 1730 and 1250 (ester), and 1660 and 1540 cm^{-1} (amide).

Anal. Calc. for $C_{38}H_{69}N_4O_{10}S$: C, 58.96; H, 8.99; N, 7.24. Found: C, 58.73; H, 9.20; N, 7.13.

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