

Synthesis and Antifungal Activity of Rhodopeptin Analogs (1): Modification of the East and South Amino Acid Moieties

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Spectroscopic and analytical data

Valyl-((*R*)-3-nonyl- β -alanyl)-glycine ethyl ester (**5**)

a pale yellow oil.

¹H-NMR (400MHz, CDCl₃) δ : 0.87 (3H, t, J=7.3 Hz), 1.06 (3H, d, J=7.3 Hz), 1.08 (3H, d, J=7.3 Hz), 1.18-1.34 (17H, m), 1.45-1.62 (2H, m), 2.11-2.29 (1H, m), 2.32-2.53 (2H, m), 3.78-3.92 (2H, m), 3.96-4.20 (3H, m), 4.22-4.38 (1H, m), 7.72-8.06 (4H, m).

*N*²-*tert*-Butoxycarbonyl-*N*⁵-benzyloxycarbonylornithyl-valyl-((*R*)-3-nonyl- β -alanyl)-glycine ethyl ester (**6**)

a white solid.

¹H-NMR (400MHz, CDCl₃) δ : 0.87 (3H, t, J=7.3 Hz), 0.98 (6H, br), 1.20-1.35 (14H, m), 1.29 (3H, t, J=7.3 Hz), 1.44 (9H, s), 1.48-1.95 (6H, m), 2.00-2.12 (1H, m), 2.20-2.32 (1H, m), 2.40-2.53 (1H, m), 3.07-3.25 (1H, m), 3.33-3.48 (1H, m), 3.70 (1H, dd, J=17.6, 4.4 Hz), 3.90-4.00 (1H, m), 4.21 (2H, q, J=7.3 Hz), 4.15-4.39 (3H, m), 5.00-5.18 (2H, m), 5.06 (1H, br), 5.10 (1H, br), 6.91 (1H, br), 7.15 (1H, br), 7.23-7.40 (6H, m).

Cyclo[glycyl-ornithyl-valyl-(*R*)-3-nonyl- β -alanyl] hydrochloride (**7**)

a white powder.

IR (KBr): 3284, 2964, 2932, 2860, 2500, 2028, 1650, 1546, 1468, 1444 cm⁻¹.

¹H-NMR (400MHz, CD₃OD) δ : 0.86-0.97 (9H, m), 1.21-1.42 (14H, m), 1.50-1.62 (2H, m), 1.65-1.92 (4H, m), 2.26 (2H, dd, J=13.9, 8.7 Hz), 2.57 (1H, dd, J=13.9, 4.5 Hz), 2.92-3.02 (3H, m), 3.97 (1H, d, J=8.2 Hz), 4.14-4.22 (2H, m), 4.30-4.40 (1H, m).

EI/MS: *m/z* 467 (M⁺).

Anal Calcd for C₂₄H₄₅N₅O₄·HCl·H₂O: C, 55.21; H, 9.27; N, 13.41. Found: C, 54.99; H, 8.92; N, 12.98.

N-*tert*-Butoxycarbonyl- γ -methylleucyl-((*R*)-3-undecyl- β -alanine) methyl ester (**11**)

a pale yellow oil.

¹H-NMR (400MHz, CD₃OD) δ : 0.88 (3H, t, J=6.8 Hz), 0.96 (9H, s), 1.15-1.62 (22H, m), 1.44 (9H, s), 2.40-2.60 (2H, m), 3.67 (3H, s), 4.00-4.30 (2H, m), 4.98-5.12 (1H, m), 6.67-6.80 (1H, m).

N-*tert*-Butoxycarbonyl-glycyl-(*N*⁶-benzyloxycarbonyllysyl)- γ -methylleucyl-(*R*)-3-undecyl- β -alanine methyl ester (**12**)

a white solid.

¹H-NMR (400MHz, CD₃OD) δ : 0.88 (3H, t, J=6.9 Hz), 0.85-0.98 (9H, m), 1.17-2.00 (28H, m), 1.44 (9H, s), 2.38-2.53 (2H, m), 3.10-3.38 (2H, m), 3.61 (3H, s), 3.68-3.90 (2H, m), 4.10-4.50 (3H, m), 5.13-5.43 (4H, m), 6.68-6.98 (2H, m), 7.10-7.44 (6H, m).

Cyclo[glycyl-lysyl-(γ -methylleucyl)-(*R*)-3-undecyl- β -alanyl] hydrochloride (**13**)

a white powder.

IR (KBr): 3296, 3052, 2932, 2860, 1864, 1658, 1540, 1470 cm⁻¹.

¹H-NMR (400MHz, CD₃OD) δ : 0.89 (3H, t, J=6.8 Hz), 0.93 (9H, s), 1.22-1.60 (23H, m), 1.63-1.82 (4H, m), 2.11 (1H, dd, J=13.5, 9.3 Hz), 2.27 (1H, dd, J=15.0, 10.2 Hz), 2.58 (1H, dd, J=15.0, 4.7 Hz), 2.87-2.97 (2H, m), 3.33-3.37 (1H, m), 4.01-4.09 (1H, m), 4.10-4.17 (2H, m), 4.32-4.48 (1H, m), 7.01 (1H, d, J=6.1 Hz), 7.73 (1H, d, J=9.2 Hz), 8.42-8.49 (1H, m), 8.60 (1H, d, J=6.1 Hz).

EI/MS: m/z 537 (M^+).

H-R EI/MS: m/z Calcd for $C_{29}H_{55}N_5O_4$: 537.4254. Found: 537.4250.

Anal Calcd for $C_{29}H_{55}N_5O_4 \cdot HCl \cdot H_2O$: C, 58.81; H, 9.87; N, 11.82. Found: C, 58.35; H, 9.40; N, 11.57.

Cyclo[glycyl-arginyl-valyl-(*R*)-3-nonyl- β -alanyl] hydrochloride (**14**)

a white powder.

IR (KBr): 3308, 2932, 2860, 1920, 1652, 1546, 1470 cm^{-1} .

1H -NMR (400MHz, CD_3OD) δ : 0.82-1.02 (9H, m), 1.20-1.42 (14H, m), 1.47-2.08 (6H, m), 2.16-2.32 (2H, m), 2.49-2.60 (1H, m), 3.10-3.35 (3H, m), 3.93-4.03 (1H, m), 4.10-4.26 (2H, m), 4.18-4.41 (1H, m), 7.22-7.37 (2H, m), 8.40-8.51 (1H, m).

FAB/MS: m/z 510 (MH^+).

Anal Calcd for $C_{25}H_{47}N_7O_4 \cdot HCl \cdot 5/2H_2O$: C, 50.79; H, 9.04; N, 16.59. Found: C, 50.60; H, 8.80; N, 16.72.

Cyclo[glycyl-histidyl-valyl-(*R*)-3-nonyl- β -alanyl] hydrochloride (**15**)

a white powder.

IR (KBr): 3812, 3304, 2932, 2860, 1668, 1544, 1432 cm^{-1} .

1H -NMR (400MHz, CD_3OD) δ : 0.82-1.05 (9H, m), 1.08-1.72 (16H, m), 1.92-2.15 (1H, m), 2.20-2.63 (2H, m), 3.05-3.40 (3H, m), 3.68-4.50 (4H, m), 7.10-7.55 (2H, m), 8.72-8.92 (1H, m).

EI/MS: m/z 490 (M^+).

FAB/MS: m/z 491 (MH^+).

H-R EI/MS: m/z Calcd for $C_{25}H_{42}N_6O_4$: 490.3268. Found: 490.3265.

Cyclo[glycyl- α -glutamyl-valyl-(*R*)-3-nonyl- β -alanyl] (**16**)

a pale yellow powder.

IR (KBr): 3304, 3072, 2964, 2932, 2860, 1658, 1546, 1468 cm^{-1} .

1H -NMR (400MHz, CD_3OD) δ : 0.50-1.70 (27H, m), 1.70-2.60 (5H, m), 3.40-4.50 (5H, m).

EI/MS: m/z 482 (M^+).

Anal Calcd for $C_{24}H_{42}N_4O_6 \cdot 3/4H_2O$: C, 58.10; H, 8.84; N, 11.29. Found: C, 58.22; H, 8.46; N, 11.07.

Cyclo[glycyl- N^6 -methyllysyl-valyl-(*R*)-3-nonyl- β -alanyl] (**17**)

a white powder.

IR (KBr): 3292, 2964, 2932, 2860, 2784, 2432, 1648, 1546, 1470, 1444 cm^{-1} .

1H -NMR (400MHz, CD_3OD) δ : 0.83-1.10 (9H, m), 1.20-2.15 (23H, m), 2.30-2.60 (2H, m), 2.71 (3H, s), 2.92-3.08 (2H, m), 3.62-3.77 (2H, m), 3.95-4.07 (1H, m), 4.07-4.30 (2H, m), 7.19-7.25 (1H, m), 7.72-7.84 (3H, m), 8.50-8.60 (1H, m).

EI/MS: m/z 495 (M^+).

H-R EI/MS: m/z Calcd for $C_{26}H_{49}N_5O_4$: 495.3785. Found: 495.3790.

Cyclo[glycyl- N^6 -isopropyllysyl-valyl-(*R*)-3-nonyl- β -alanyl] hydrochloride (**18**)

a pale yellow powder.

IR (KBr): 3292, 3060, 2964, 2932, 2860, 2452, 1652, 1548, 1470 cm^{-1} .

1H -NMR (400MHz, $DMSO-d_6$) δ : 0.78-0.92 (9H, m), 1.08-1.80 (29H, m), 1.95-2.30 (2H, m), 2.80-2.90 (2H, m), 3.05-3.20 (2H, m), 3.88-4.00 (2H, m), 4.00-4.13 (2H, m), 6.72 (1H, d, $J = 9.5$ Hz), 7.00 (1H, br), 7.12 (1H, br), 7.25 (1H, br), 7.35 (1H, d, $J = 9.2$ Hz).

EI/MS: m/z 523 (M^+).

FAB/MS: m/z 524 (MH^+).

H-R EI/MS: m/z Calcd for $C_{28}H_{53}N_5O_4$: 523.4098. Found: 523.4119.

Cyclo[glycyl- N^6, N^6 -dimethyllysyl-valyl-(*R*)-3-nonyl- β -alanyl] hydrochloride (**19**)

a white powder.

IR (KBr): 3296, 3080, 2964, 2932, 2860, 2696, 2520, 2472, 1650, 1548, 1470, 1444, 1410 cm^{-1} .

¹H-NMR (400MHz, CD₃OD) δ: 0.84-1.05 (9H, m), 1.21-1.68 (20H, m), 1.70-1.95 (3H, m), 2.20-2.32 (1H, m), 2.52-2.60 (1H, m), 2.89 (6H, s), 3.07-3.19 (3H, m), 3.97-4.05 (1H, m), 4.13-4.25 (2H, m), 4.30-4.40 (1H, m), 7.18-7.45 (2H, m), 7.79-7.87 (1H, m), 8.38-8.47 (1H, m).

EI/MS: *m/z* 509 (M⁺).

H-R EI/MS: *m/z* Calcd for C₂₇H₅₁N₅O₄: 509.3941. Found: 509.3931.

Cyclo[glycyl-*N*⁶-benzyl-*N*⁶-methyllysyl-valyl-(*R*)-3-nonyl-β-alanyl] hydrochloride (**20**)
a white powder.

IR (KBr): 3804, 3672, 3296, 3072, 2964, 2932, 2860, 2648, 1650, 1548, 1470 cm⁻¹.

¹H-NMR (400MHz, CD₃OD) δ: 0.86-1.03 (9H, m), 1.15-1.55 (18H, m), 1.64-1.85 (3H, m), 2.06 (3H, s), 2.10-2.21 (2H, m), 2.46 (1H, dd, *J* = 14.2, 5.0 Hz), 2.70 (2H, s), 2.95-3.20 (3H, m), 3.90 (1H, d, *J* = 7.7 Hz), 4.01-4.41 (4H, m), 7.15-7.23 (1H, m), 7.38-7.45 (5H, m), 7.50-7.55 (1H, m), 7.58-7.64 (1H, m), 8.32-8.37 (1H, m).

EI/MS: *m/z* 585 (M⁺).

HR-EI/MS: *m/z* Calcd for C₃₃H₅₅N₅O₄: 585.4254. Found: 585.4249.

Cyclo[glycyl-*N*⁶-acetyllysyl-valyl-(*R*)-3-nonyl-β-alanyl] (**21**)

a white powder.

IR (KBr): 3300, 3084, 2960, 2932, 2860, 2464, 2416, 1644, 1546, 1462 cm⁻¹.

¹H-NMR (400MHz, CD₃OD) δ: 0.70-0.92 (9H, m), 1.10-1.59 (22H, m), 1.59-1.72 (1H, m), 1.79 (1H, s), 2.19-2.25 (2H, m), 2.90-3.10 (3H, m), 3.90-4.20 (4H, m), 4.02-4.11 (1H, m), 7.18-7.31 (1H, m), 7.36-7.50 (1H, m), 7.72-7.90 (2H, m).

EI/MS: *m/z* 523 (M⁺).

Anal. Calcd for C₂₇H₄₉N₅O₅·5/4H₂O: C, 59.37; H, 9.50; N, 12.82. Found: C, 59.49; H, 9.30; N, 12.48.

Cyclo[glycyl-lysyl-lysyl-(*R*)-3-nonyl-β-alanyl] dihydrochloride (**22**)

a white powder.

IR (KBr): 3300, 3076, 2932, 2864, 1680, 1648, 1552, 1472, 1436 cm⁻¹.

¹H-NMR (400MHz, DMSO-*d*₆) δ: 0.86 (3H, t, *J*=7.0 Hz), 1.23(m), 1.30-1.70 (m), 1.77 (1H, m), 2.20 (1H, dd, *J*=13.9, 6.6 Hz), 2.37 (1H, dd, *J*=13.9, 5.0 Hz), 2.76 (4H, br), 3.40 (1H, dd, *J*=13.6, 6.1 Hz), 3.82 (1H, dd, *J*=13.3, 5.8 Hz), 3.96 (1H, m), 4.04 (2H, m), 6.83 (1H, d, *J*=9.3 Hz), 7.30 (1H, d, *J*=7.7 Hz), 7.69 (3H, br), 8.28 (1H, t, *J*=6.1 Hz), 8.47 (1H, d, *J*=7.1 Hz).

EI/MS: *m/z* 510 (M⁺).

HR-EI/MS: *m/z* Calcd for C₂₆H₅₀N₆O₄: 510.3894. Found: 510.3897.

Cyclo[glycyl-lysyl-glutamyl-(*R*)-3-nonyl-β-alanyl] hydrochloride (**23**)

a white powder.

IR (KBr): 3812, 3296, 3064, 2932, 2860, 1650, 1544, 1446 cm⁻¹.

¹H-NMR (400MHz, DMSO-*d*₆) δ: 0.85 (3H, t, *J*=7.0 Hz), 1.23 (16H, m), 1.30-1.70 (5H, m), 2.00 (1H, m), 2.17 (2H, m), 2.37 (2H, m), 2.76 (2H, m), 3.52 (1H, dd, *J*=13.5, 7.3 Hz), 3.78 (1H, dd, *J*=13.5, 5.4 Hz), 3.95 (1H, m), 4.07 (1H, m), 4.14 (1H, m), 6.66 (1H, d, *J*=9.3 Hz), 7.42 (1H, d, *J*=8.2 Hz), 7.66 (3H, br), 8.26 (1H, t, *J*=6.7 Hz), 8.53 (1H, d, *J*=6.5 Hz).

FAB/MS: *m/z* 512 (MH⁺).

Anal Calcd for C₂₅H₄₅N₅O₆·HCl·29/10H₂O: C, 50.01; H, 8.70; N, 11.67. Found: C, 50.01; H, 8.59; N, 11.26.

Cyclo[glycyl-lysyl-valyl-(*R*)-3-undecyl-β-alanyl] hydrochloride (**24**)

a white powder.

IR (KBr): 3308, 3060, 2964, 2928, 2856, 1654, 1538, 1468 cm⁻¹.

¹H-NMR (400MHz, CDCl₃-CD₃OD (1:1, v/v)) δ: 0.92 (9H, m), 1.28 (16H, br), 1.55 (2H, m), 1.72 (2H, m), 1.82 (2H, m), 2.28 (2H, m), 2.57 (2H, m), 2.92 (2H, t, *J*=6.7 Hz), 3.70 (2H, m), 4.00 (1H, m), 4.18 (2H, m), 4.34 (1H, m).

EI/MS: *m/z* 509 (M⁺).

H-R EI/MS: *m/z* Calcd for C₂₇H₅₁N₅O₄: 509.3941. Found: 509.3943.

Anal Calcd for C₂₇H₅₁N₅O₄·HCl·2H₂O: C, 55.70; H, 9.70; N, 12.03. Found: C, 55.94; H, 9.30; N, 11.60.

Cyclo[glycyl-lysyl-isoleucyl-(*R*)-3-undecyl-β-alanyl] hydrochloride (**25**)

a white powder.

IR (KBr): 3282, 3070, 2960, 2921, 2852, 1648, 1546, 1467, 1440 cm⁻¹.

¹H-NMR (400MHz, CD₃OD) δ: 0.86-0.96 (9H, m), 1.20-1.62 (26H, m), 1.62-2.02 (4H, m), 2.25 (1H, dd, J=14.2, 8.4 Hz), 2.55 (1H, dd, J=14.2, 5.4 Hz), 2.88-2.97 (2H, m), 4.02-4.08 (1H, m), 4.13-4.22 (2H, m), 4.29-4.41 (1H, m), 7.23 (1H, d, J=8.6 Hz), 7.38 (1H, J=9.3 Hz), 7.60 (1H, J=7.8 Hz), 8.40-8.47 (1H, m).

FAB/MS: *m/z* 524 (MH⁺).

H-R FAB/MS: *m/z* Calcd for C₂₈H₅₃N₅O₄: 524.4176. Found: 524.4149.

Cyclo[glycyl-lysyl-leucyl-(*R*)-3-undecyl-β-alanyl] hydrochloride (**26**)

a white powder.

IR (KBr): 3434, 3299, 3288, 3070, 2956, 2921, 2852, 1650, 1544, 1467, 1434 cm⁻¹.

¹H-NMR (400MHz, CD₃OD) δ: 0.80-1.00 (9H, m), 1.18-1.90 (30H, m), 2.26 (1H, dd, J=14.2, 9.0 Hz), 2.50-2.62 (1H, m), 2.88-3.00 (2H, m), 3.98-4.20 (2H, m), 4.20-4.45 (2H, m), 7.15 (1H, d, J=7.3 Hz), 7.55 (1H, d, J=9.5 Hz), 7.60-7.68 (1H, m), 8.42-8.59 (1H, m).

FAB/MS: *m/z* 524 (MH⁺).

H-R FAB/MS: *m/z* Calcd for C₂₈H₅₃N₅O₄: 524.4176. Found: 524.4158.

Cyclo[glycyl-lysyl-(β-cyclohexylalanyl)-(*R*)-3-undecyl-β-alanyl] hydrochloride (**27**)

a white powder.

IR (KBr): 3292, 3060, 2932, 2856, 1658, 1546, 1450, 1410 cm⁻¹.

¹H-NMR (400MHz, CD₃OD) δ: 0.89 (3H, t, J=6.7 Hz), 0.85-1.07 (2H, m), 1.11-1.90 (37H, m), 2.27 (1H, dd, J=14.6, 9.2 Hz), 2.58 (1H, dd, J=14.6, 5.0 Hz), 2.93 (2H, t, J=7.6 Hz), 3.30-3.40 (2H, m), 4.02-4.27 (2H, m), 4.30-4.47 (1H, m), 7.14 (1H, d, J=6.8 Hz), 7.45-7.55 (2H, m), 7.81-7.89 (1H, m), 8.38-8.47 (1H, m), 8.58 (1H, d, J=6.1 Hz).

EI/MS: *m/z* 563 (M⁺).

HR-EI/MS: *m/z* Calcd for C₃₁H₅₇N₅O₄: 563.4411. Found: 563.4405.

Cyclo[glycyl-lysyl-*tert*-leucyl-(*R*)-3-undecyl-β-alanyl] hydrochloride (**28**)

a pale yellow powder.

IR (KBr): 3296, 3056, 2932, 2860, 1992, 1780, 1658, 1538, 1468 cm⁻¹.

¹H-NMR (400MHz, CD₃OD) δ: 0.89 (3H, t, J=6.6 Hz), 1.00 (9H, s), 1.20-1.62 (24H, m), 1.62-1.90 (3H, m), 2.15-2.27 (1H, m), 2.43-2.55 (1H, m), 2.92 (2H, t, J=7.3 Hz), 3.97-4.05 (1H, m), 4.15-4.29 (2H, m), 4.32-4.47 (1H, m), 7.15 (1H, d, J=7.3 Hz), 7.66 (1H, d, J=8.8 Hz), 8.06 (1H, d, J=7.3 Hz), 8.11-8.15 (1H, m).

EI/MS: *m/z* 523 (M⁺).

HR-EI/MS: *m/z* Calcd for C₂₈H₅₃N₅O₄: 523.4098. Found: 523.4079.