Synthesis and Antifungal Activity of Rhodopeptin Analogs (2): Modification of the West Amino Acid Moiety

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Spectroscopic and analytical data

N-(4-Methoxyphenyl)-2,2-difluoro-3-hydroxytetradecanamide (**3**)
a white powder.
mp 110.0-111.0°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, J = 7.2 Hz), 1.27 (br s), 1.50-1.70 (m), 2.51 (1H, d, J = 5.8 Hz), 3.81 (3H, s), 4.17 (1H, m), 6.90 (2H,d, J = 8.5 Hz), 7.47 (2H, d, J = 8.5 Hz), 7.97 (1H, br s).
EI/MS: *m/z* 357 (M^+).
Anal. Calcd for $C_{19}H_{29}F_2NO_3$: C, 63.85; H, 8.18; N, 3.92; F, 10.63. Found: C, 63.99; H,8.13; N, 3.94; F, 10.47.

3,3-Difluoro-1-(4-methoxyphenyl)-4-nonylazetidine-2-one (**4**)
a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, J = 7.2 Hz), 1.26-1.50 (m), 1.73 (2H, m), 2.02 (2H, m), 3.81 (3H, s), 4.34 (1H, m), 6.92 (2H, d, J = 8.8 Hz), 7.34 (2H, d, J = 8.8 Hz).

Methyl 2,2-Difluoro-3-(4-methoxyphenylamino)dodecanoate (**5**)
a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, J = 7.2 Hz), 1.22-1.28 (m), 1.43 (2H, m), 1.80 (1H, m), 3.71 (3H, s), 3.74 (3H, s), 3.90 (1H, m), 6.60 (2H, d, J = 8.8 Hz), 6.75 (2H, d, J = 8.8 Hz).

Methyl 3-Amino-2,2-difluorododecanoate (**6**)
a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, J = 7.2 Hz), 1.26-1.30 (m), 1.56 (2H, m), 3.19 (1H, m), 3.89 (3H, s).

N^5-Benzyloxycarbonyl-N^2-*tert*-butoxycabonyl-ornithyl-γ-methyl-leucyl-(2,2-difluoro-3-nonyl-β-alanyl)-glycine *tert*-Butyl Ester (**8a,b**)
8a: a colorless amorphous powder.
^{1}H-NMR (CD_3OD-$CDCl_3$) δ: 0.88 (3H, t, J=7.0Hz), 0.97 (9H, s), 1.26 (12H, br s), 1.45 (9H, s), 1.49 (9H, s), 1.3-1.85 (m), 3.16 (2H, m), 3.86 (1H, d, J= 16.6Hz), 4.07 (2H, m), 4.34 (1H, m), 4.48 (1H, m), 5.08 (2H, s), 7.34 (5H, m).
8b: a colorless amorphous powder.
^{1}H-NMR (CD_3OD-$CDCl_3$) δ: 0.88 (3H, t, J=7.0Hz), 0.95 (9H, s), 1.26 (12H, br s), 1.45 (9H, s), 1.48 (9H, s), 1.3-1.8 (m), 3.16 (2H, m), 3.90 (2H, m), 4.05 (1H, m), 4.42 (1H, m), 4.53 (1H, m), 5.08 (2H, s), 7.34 (5H, m).

Cyclo{glycyl-ornithyl-(g-methyl-leucyl)-(2,2-difluoro-3-nonyl-b-alanyl)} (**9a,b**)
9a: a white powder.
^{1}H-NMR (DMSO-d_6) δ: 0.86 (12H, m), 1.22 (12H, m), 1.4-1.7 (6H, m), 2.09 (1H, dd, J=13.6, 6.0Hz), 2.80 (2H, m), 3.82 (3H, m), 4.26 (1H, dd, J=13.9, 6.0Hz), 4.45 (1H, m), 7.27 (1H, d, J = 7.6Hz), 7.48 (1H, d, J = 9.7 Hz), 7.76 (3H, br), 8.94 (2H, m).

Anal. Calcd for $C_{26}H_{47}F_2N_5O_4 \cdot HCl \cdot 1.5H_2O$: C, 52.47; H, 8.64; N, 11.77. Found: C, 52.89; H, 8.20; N, 11.54.
IR (KBr): 3308, 2928, 2860, 1690, 1664, 1534, 1470 cm^{-1}.

9b: a white powder.
^{1}H-NMR (CD_3OD-$CDCl_3$) δ: 0.89 (3H, t, J=7.0Hz), 0.97 (9H, s), 1.28 (12H, m), 1.58-2.0 (6H, m), 2.99 (2H, m), 3.82 (1H, d, J=16.4Hz), 3.98 (1H, d, J=16.4Hz), 4.42 (1H, m), 4.53 (2H, m),
IR (KBr): 3288, 3048, 2960, 2932, 2860, 1700, 1536, 1470 cm^{-1}.
HR-MS: Calcd for $C_{26}H_{47}F_2N_5O_4$: 531.3596. found: 531.3577.

(*3R, 4R*)-1-(4-Methoxyphenyl)-3-methyl-4-undecylazetidine-2-one (**13**)
a colorless oil.
^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.3 Hz), 1.26 (16H, br s), 1.37 (3H, d, J = 7.3 Hz), 1.54 (4H, m), 2.06 (1H, m), 2.90 (1H, qd, J = 7.3, 2.0Hz), 3.59 (1H, m), 3.79 (3H, s), 6.87 (2H, d J = 9.3 Hz), 7.30 (2H, d, J = 9.3 Hz).

(*3R, 4R*)-1-(*tert*-Butoxycarbonyl)-3-methyl-4-undecylazetidine-2-one
a colorless cryst.
^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.2 Hz), 1.26 (18H, br s), 1.32 (3H, d, J = 7.3 Hz), 1.52 (9H, s), 2.10 (1H, m), 2.79 (1H, qd, J = 7.3, 3.4 Hz), 3.51 (1H, td, J = 9.3, 3.4 Hz).

N^6-Benzyloxycarbonyl-N^2-*tert*-butoxycarbonyl-lysyl-γ-methyl-leucyl-[(*2R,3R*)-2-methyl-3-undecyl-β-alanyl]-glycine Ethyl Ester (**15**)
a white amorphous powder.
^{1}H-NMR (CD_3OD-$CDCl_3$) δ: 0.88 (3H, t, J = 7.2 Hz), 0.97 (9H, s), 1.11 (3H, d , J = 7.3 Hz), 1.26 (16H, m), 1.44 (9H, s), 1.4 - 1.85 (4H, m), 2.56 (1H, m), 3.14 (2H, m), 3.88 (2H, m), 4.04 (2H, m), 4.20 (2H, q, J = 7.3 Hz), 4.33 (1H, m), 5.09 (2H, s), 7.35 (5H, m).

Cyclo{glycyl-lysyl-(γ-methyl-leucyl)-[(*2R, 3R*)-2-methyl-3-undecyl-β-alanyl]} (**16**)
a white powder.
^{1}H-NMR (DMSO-d_6) δ: 0.85 (12H, m), 1.02 (3H, d , J = 7.1 Hz), 1.23 (16H, m), 1.3 -1.65 (4H, m), 2.05 (1H, dd, J = 13.9, 5.5 Hz), 2.39 (1H, m), 2.74 (2H, m), 3.57 (1H, dd, J = 13.0, 7.0 Hz), 3.83 (3H, m), 4.12 (1H, dd, J = 13.1, 6.3 Hz), 6.83 (1H, d, J = 9.8 Hz), 7.39 (1H, d, J = 7.4 Hz), 7.86 (3H, brs), 8.16 (1H, t, J = 6.1 Hz), 8.82 (1H, d, J = 6.5Hz).
IR (KBr): 3308, 3052, 2928, 2856, 1652, 1534, 1466 cm^{-1}.
HR-MS: Calcd for $C_{30}H_{57}N_5O_4$: 551.4411. Found: 551.4410.

Methyl (*2R, 3S*)-2,3-Dihydroxytridecanoate (**18**)
a white powder.
^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.2 Hz), 1.26 (14H, br s), 1.4 - 1.65 (4H, m), 1.88 (1H, d, J = 8.8 Hz), 3.03 (1H, d, J = 5.4 Hz), 3.84 (3H, s), 3.89 (1H, m), 4.11 (1H, dd, J = 5.4, 2.0 Hz).

(*2R, 3S*)-2,3-Epoxytridecanoic Acid (**20**)
a white powder.
^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.2 Hz), 1.26 (14H, br s), 1.47 (2H, m), 1.65 (2H, m), 3.19 (1H, m), 3.27 (1H, d, J = 2.0 Hz).

(*2R, 3R*)-3-Azido-2-hydroxytridecanoic Acid (**21**)
a colorless oil.
^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.2 Hz), 1.26 (16H, brs), 1.60 - 1.85 (2H, m), 3.62 (1H, m), 4.42 (1H, d, J = 2.5 Hz).

Methyl (*2S, 3S*)-2,3-Epoxytridecanoate (**22**)
a colorless oil.
^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.2 Hz), 1.26 (14H, br s), 1.40 - 1.75 (4H, m), 3.17 (1H, m), 3.53 (1H, d, J = 4.4 Hz), 3.80 (3H, s).

(*2S, 3R*)-3-Azido-2-hydroxytridecanoic Acid (**23**)
a colorless oil.
^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.2 Hz), 1.26 (16H, m), 1.4 - 1.95 (2H, m), 3.60 (1H, m), 4.28 (1H, d, J = 2.0 Hz).

N-[(*2S, 3R*)-3-Azido-2-hydroxytridecanoyl]glycine Ethyl Ester (**24a,b**)
24a: a waxy solid.
^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.2 Hz), 1.27 (14H, m), 1.4 -1.8 (4H, m), 3.28 (1H, d, J = 6.8 Hz), 3.84 (1H, m), 4.04 (1H, m), 4.12-4.27 (3H, m), 7.18 (1H, t, J = 4.9 Hz).
24b: a colorless oil.
^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.2 Hz), 1.26 (14H, br s), 1.30 (3H, t, J = 7.3 Hz), 1.56 (4H, m), 2.96 (1H, m), 3.70 (1H, m), 4.06 (2H, t, J = 5.4 Hz), 4.23 (2H, q, J = 7.3 Hz), 4.30 (1H, m), 7.08 (1H, m).

N-tert-Butoxycarbonyl-γ-methyl-leucyl-[(*2S,3R*)-3-decyl-2-hydroxy-β-alanyl]-glycine Ethyl Ester (**25a,b**)
25a: a white amorphous powder.
^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.2 Hz), 0.96 (9H, s), 1.24 (16H, brs), 1.29 (3H, t, J=7.3Hz), 1.41 (9H, s), 1.79 (1H, dd, J= 14.7, 4.9 Hz), 3.81 (1H, dd, J = 17.6, 3.9 Hz), 3.93 (1H, m), 4.03 (1H, m), 4.15 (1H, dd, J = 6.8, 4.4 Hz), 4.21 (2H, q, J = 7.3 Hz), 4.34 (1H, dd, J = 17.6, 7.3 Hz), 4.44 (1H, d, J = 7.3 Hz), 4.88 (1H, d, J = 7.3 Hz), 6.94 (1H, d, J = 8.8 Hz), 7.64 (1H, m).
25b: a white amorphous powder.
^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.2 Hz), 0.97 (9H, s), 1.24 (16H, br s), 1.30 (3H, t, J=7.3Hz), 1.43 (9H, s), 1.6 - 1.9 (4H, m), 3.72 (1H, dd, J = 17.6, 4.9 Hz), 4.05 (1H, m), 4.21 (2H, q, J = 7.3 Hz), 4.28 (1H, m), 4.36 (1H, dd, J = 17.6, 7.8 Hz), 4.69 (1H, m), 5.04 (1H, d, J = 7.8 Hz), 7.03 (1H, d, J = 8.3 Hz), 7.66 (1H, m).

N^6-Benzyloxycarbonyl-N^2-*tert*-butoxycarbonyl-lysyl-γ-methyl-leucyl-[(*2S,3R*)-3-decyl-2-hydroxy-β-alanyl]-glycine Ethyl Ester (**26a**,**b**)
26a: a white amorphous powder.
^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.2 Hz), 0.93 (9H, s), 1.24 (16H, br s), 1.29 (3H, t, J = 7.3 Hz), 1.43 (9H, s), 1.4 - 1.95 (4H, m), 3.18 (2H, m), 4.0 - 4.4 (6H, m), 4.63 (1H, m), 5.09 (2H, s), 5.26 (2H, m), 6.70 (1H, m), 6.96 (1H, m), 7.35 (5H, m), 7.49 (1H, m).
26b: a white amorphous powder.
^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.2 Hz), 0.95 (9H, s), 1.24 (16H, brs), 1.28 (3H, t, J = 7.3 Hz), 1.42 (9H, s), 1.4 - 1.9 (4H, m), 3.19 (2H, m), 3.78 (1H, m), 4.01 (1H, m), 4.14 (1H, m), 4.20 (2H, q, J = 7.3 Hz), 4.33 (2H, m), 4.46 (1H, m), 5.10 (2H, s), 5.21 (1H, m), 5.35 (1H, m), 6.45 (1H, m), 7.12 (1H, m), 7.35 (5H, m), 7.60 (1H, m).

Cyclo{glycyl-lysyl-(γ-methyl-leucyl)-[(2S, 3R)-3-decyl-2-hydroxy-β-alanyl]} (**27a,b**)
27a: a white powder.
^{1}H-NMR (DMSO-d_6) δ: 0.84 (12H, m), 1.22 (16H, brs), 1.3 -1.65 (4H, m), 1.96 (1H, dd, J = 13.4, 8.0 Hz), 2.74 (2H, m), 3.43 (1H, m), 3.88 (2H, m), 4.02 (1H, dd, J = 13.0, 8.0 Hz), 4.20 (2H, m), 6.91 (1H, m), 7.34 (1H, d, J = 9.1 Hz), 7.69 (1H, m), 7.81 (3H, br), 8.60 (1H, d, J = 7.1 Hz).
IR (KBr): 3296, 3056, 2932, 2860, 1658, 1534, 1468 cm^{-1}.
HR-EI/MS: m/z Calcd for $C_{28}H_{53}N_5O_5$: 539.4047. Found: 539.4050.
27b: a white powder.

^{1}H-NMR (DMSO-d_6) δ: 0.86 (12H, m), 1.23 (16H, br s), 1.3 -1.6 (4H, m), 2.15 (1H, dd, J = 14.3, 3.5 Hz), 2.74 (2H, m), 3.51 (1H, m), 3.85 (1H, dd, J = 13.5, 6.8 Hz), 3.91 (1H, d, J = 3.8 Hz), 4.01 (2H, m), 4.26 (1H, td, J = 8.7, 3.7 Hz), 6.53 (1H, d, J = 9.6 Hz), 7.70 (3H, br), 7.85 (1H, d, J = 8.8 Hz), 8.10 (1H, m), 8.53 (1H, d, J = 6.1 Hz).
IR (KBr): 3308, 3068, 2960, 2932, 2860, 1652, 1540, 1470 cm^{-1}.
HR-EI/MS: m/z Calcd for $C_{28}H_{53}N_5O_5$: 539.4047. Found: 539.4041.

Protocol of the acute toxicity (MTD) assay: Strain of Slc:ddY mice, female, 5 weeks of age, 19 - 25 g of body weight, were injected intravenously with the compounds dissolved in H_2O.
Number of mice used; 3.
Survival observation was made daily after 14 days of injection.