

Synthesis and Biological Activity of Novel Statine Derivatives Containing Ferrocenyl Moiety

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Boc-Leu-NH-CH₂Fc **14**

Yellow sticky oil, yield 73.5%, $[\alpha]_D^{20} = -1.8^\circ$ (c 0.11, MeOH); IR (KBr): 3313, 3093, 2967, 2872, 1655, 1520, 1293 and 1168 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 0.93-0.98 {m, 6H, (CH₃)₂CH}, 1.05-1.09 (m, 1H, CHMe₂), 1.44 {s, 9H, (CH₃)₃}, 1.65-1.76 (m, 2H, CH₂CHMe₂), 3.72 (d, $J=0.8$ Hz, 1H, CHCO), 4.11-4.16 (m, 11H, C₅H₄, C₅H₅, CH₂N), 4.87 (br, 1H, NH), 6.38 (br, 1H, NH). Anal. Calcd for C₂₅H₂₉FeN₃O₃: C 59.18, H 5.76, N 8.28; found C 59.20, H 5.83, N 8.24.

Boc-Phe-NH-CH₂Fc **17**

Yellow sticky oil, yield 71.4%, $[\alpha]_D^{20} = +3.1^\circ$ (c 0.16, MeOH); IR (KBr): 3415, 3004, 2926, 1711, 1516, 1419, 1362, 1222, 1031, 903 and 531 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 1.39 {s, 9H, (CH₃)₃}, 3.05 (d, $J=8$ Hz, 2H, CH₂Ph), 4.03-4.19 (m, 11H, C₅H₄, C₅H₅, CH₂N), 4.32 (br, 1H, CHCO), 5.10 (s, 1H, NH), 6.10 (s, 1H, NH), 7.18-7.30 (m, 5H, ArH). Anal. Calcd for C₂₅H₃₀FeN₃O₃: C 64.94, H 6.54, N 6.06; found C 65.17, H 6.83, N 6.21.

Boc-Val-NH-CH₂Fc **18**

Yellow sticky oil, yield 77.2%, $[\alpha]_D^{20} = -0.6^\circ$ (c 0.51, MeOH); IR (KBr): 3311, 3092, 2967, 2874, 1656, 1520, 1244 and 1169 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 0.96 (q, $J=0.8$ Hz, 6H, (CH₃)₂CH), 1.17-1.25 (m, 1H, CHMe₂), 1.44 {s, 9H, (CH₃)₃}, 3.87 (t, $J=0.4$ Hz, 1H, CHCO), 4.13-4.17 (m, 11H, C₅H₄, C₅H₅, CH₂N), 5.00 (br, 1H, NH), 6.15 (br, 1H, NH). Anal. Calcd for C₂₁H₃₀FeN₃O₃: C 60.88, H 7.30, N 6.76; found C 60.75, H 7.18, N 6.55.

Boc-Nph-NH-CH₂Fc **19**

Yellow sticky oil, yield 65.5%, $[\alpha]_D^{20} = +0.97^\circ$ (c 0.23, MeOH); IR (KBr): 3305, 3086, 2931, 2868, 1656, 1602, 1521, 1452, 1345, 1248, 1165, 1021, 854 and 486 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 1.39 {s, 9H, (CH₃)₃}, 3.11

(q, $J=0.8$ Hz, 2H, CH₂Ph), 3.21-3.26 (m, 1H, CHCO), 4.05-4.19 (m, 11H, C₅H₄, C₅H₅, CH₂N), 5.08 (d, $J=5.6$ Hz, 1H, NH), 6.07 (d, $J=6.6$ Hz, 1H, NH), 7.33 (q, $J=8.8$ Hz, 2H, ArH), 8.15 (q, $J=6.4$ Hz, 2H, ArH). Anal. Calcd for C₂₅H₂₉FeN₃O₃: C 59.18, H 5.76, N 8.28; found C 59.20, H 5.83, N 8.24.

Boc-Val-Phe-NH-CH₂Fc **20**

Yellow sticky oil, yield 71.4%, $[\alpha]_D^{20} = -9.4^\circ$ (c 0.16, MeOH); IR (KBr): 3422, 2932, 1663, 1497, 1439, 1390, 1253, 1101 and 700 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 0.79-0.91 {m, 6H, (CH₃)₂CH}, 1.38 {s, 9H, (CH₃)₃}, 1.43-1.45 (m, 1H, CHMe₂), 2.99 (m, 2H, CH₂Ph), 3.04 (t, $J=1.6$ Hz, 1H, CHCO), 3.87 (t, $J=6$ Hz, 1H, CHCO), 4.04-4.17 (m, 11H, C₅H₄, C₅H₅, CH₂N), 4.62 (d, $J=6.4$ Hz, 1H, NH), 4.81 (br, 1H, NH); 6.17 (br, 1H, NH); 7.28-7.16 (m, 5H, ArH). Anal. Calcd for C₃₀H₃₉FeN₃O₄: C 64.17, H 7.00, N 7.48; found C 64.31, H 7.14, N 7.36.

Boc-Statine-Leu-NH-CH₂Fc **1**

Yellow solid, yield 49.2%, m.p. 71-72 °C, $[\alpha]_D^{20} = -41^\circ$ (c 0.10, MeOH); IR (KBr): 3325, 3092, 2957, 2930, 2870, 1689, 1645, 1535, 1465, 1366, 1248, 1169, 1045, 881 and 644 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 0.75-0.98 {m, 12H, (CH₃)₂CH, (CH₃)₂CHCH₂}, 1.23-1.49 (m, 6H, CH₂CHMe₂, CH₂CHMe₂), 1.53 {s, 9H, (CH₃)₃}, 2.23-2.40 (m, 2H, CH₂CO), 3.64-3.74 (m, 1H, NCH-Bu-i), 3.87-3.95 (m, 2H, NCHCO, CH-O), 3.97-4.09 (m, 11H, C₅H₄, C₅H₅, CH₂N), 4.30 (q, 1H, $J=8$ Hz, NH), 4.65 (d, $J=8$ Hz, 1H, NH), 6.32 (d, $J=8$ Hz, 1H, NH). MALDI-TOF MS: $m/z = 586$ [M+1]⁺. Anal. Calcd for C₃₀H₄₇FeN₃O₅: C 61.53, H 8.09, N 7.18; found C 61.64, H

Boc-Statine-Phe-NH-CH₂Fc **2**

Yellow solid, yield 53.6%, m.p. 79-81 °C, $[\alpha]_D^{20} = -44^\circ$ (c 0.21, MeOH); IR (KBr): 3310, 3088, 3031, 2956, 2929, 2869, 1688, 1643, 1532, 1452, 1365, 1248, 1168, 1044, 817 and 744 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 0.75-0.86

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{m, 6H, (CH₃)₂CHCH₂}, 1.33-1.43 (m, 3H, CH₂CHMe₂), 1.56 {s, 9H, (CH₃)₃}, 2.17-2.36 (m, 2H, CH₂CO), 2.90-3.07 (m, 2H, CH₂Ph), 3.45-3.57 (m, 1H, NCH-Bu-i), 3.84-3.93 (m, 2H, NCHCO, CH-O), 3.95-4.04 (m, 11H, C₅H₄, C₅H₅, CH₂N), 4.62 (d, *J*=9.6 Hz, 1H, NH), 5.98 (br, 1H, NH), 6.46 (d, *J*=8 Hz, 1H, NH), 7.10-7.20 (m, 5H, ArH). MALDI-TOF MS: *m/z* =619 (M⁺). Anal. Calcd for C₃₃H₄₅FeN₃O₅: C 63.97, H 7.32, N 6.78; found C 63.74, H 7.45, N 6.62.

Boc-(3R, 4S)-Statine-Phe-NH-CH₂Fc 3

Yellow solid, yield 53.6%, m.p. 85-87 °C, [α]_D²⁰ = -30.7° (*c* 0.17, MeOH); IR (KBr): 3333, 3088, 2953, 2930, 2853, 1681, 1633, 1532, 1449, 1368, 1248, 1169, 698 and 670 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 0.85-0.93 (m, 6H, (CH₃)₂CHCH₂), 1.31-1.33 (m, 3H, CH₂CHMe₂), 1.57 {s, 9H, (CH₃)₃}, 2.25-2.43 (m, 2H, CH₂CO), 3.00-3.14 (m, 2H, CH₂Ph), 3.52-3.59 (m, 1H, NCH-Bu-i), 3.73-3.91 (m, 2H, NCHCO, CH-O), 4.03-4.10 (m, 11H, C₅H₄, C₅H₅, CH₂N), 5.99 (br, 1H, NH), 6.38 (d, *J*=7.6 Hz, 1H, NH), 6.47 (d, *J*=8.0 Hz, 1H, NH), 7.17-7.24 (m, 5H, ArH). MALDI-TOF MS: *m/z* =619 (M⁺). Anal. Calcd for C₃₃H₄₅FeN₃O₅: C 63.97, H 7.32, N 6.78; found C 63.81, H 7.19, N 6.90.

Boc-Statine-Val-NH-CH₂Fc 4

Yellow solid, yield 50.7%, m.p. 86-88 °C [lit. ^[15] 86-88 °C], [α]_D²⁰ = -41.4° (*c* 0.23, MeOH); IR (KBr): 3326, 3095, 2929, 2851, 1688, 1631, 1533, 1444, 1367, 1246, 1167, 1046, 821, 641 and 482 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 0.82-0.95 {m, 12H, (CH₃)₂CH, (CH₃)₂CHCH₂}, 1.20-1.48 (m, 4H, CHMe₂, CH₂CHMe₂), 1.59 {s, 9H, (CH₃)₃}, 2.32-2.43 (m, 2H, CH₂CO), 3.48 (q, 1H, *J*=0.4 Hz, NCH-Bu-i), 3.83-3.95 (m, 2H, NCHCO, CH-O), 4.12-4.21 (m, 11H, C₅H₄, C₅H₅, CH₂N), 4.73 (d, *J*=12 Hz, 1H, NH), 6.24 (br, 1H, NH), 6.51 (d, *J*=8 Hz, 1H, NH). MALDI-TOF MS: *m/z* =571 (M⁺). Anal. Calcd for C₂₉H₄₅FeN₃O₅: C 60.94, H 7.94, N 7.35; found C 60.85, H 7.88, N 7.29.

Boc-(3R, 4S)-Statine-Val-NH-CH₂Fc 5

Yellow solid, yield 54.3%, m.p. 89-91 °C, [α]_D²⁰ = -27° (*c* 0.21, MeOH); IR (KBr): 3326, 3091, 2954, 2932, 2871, 1685, 1626, 1538, 1440, 1367, 1277, 1175, 1041, 744 and 483 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 0.80-0.95 {m, 12H, (CH₃)₂CH, (CH₃)₂CHCH₂}, 1.44 {s, 9H, (CH₃)₃}, 1.50-1.68 {m, 4H, CHMe₂, CH₂CHMe₂}, 2.33-2.40 (m, 2H, CH₂CO), 3.46-3.56 (m, 1H, NCH-Bu-i), 3.71-3.95 (m, 2H, NCHCO, CH-O), 4.02-4.18 (m, 11H, C₅H₄, C₅H₅, CH₂N), 4.73 (d, *J*=9.6 Hz, 1H, NH), 6.22 (br, 1H, NH), 6.51 (d, *J*=8.4 Hz, 1H, NH). MALDI-TOF MS: *m/z* =572 [M+H]⁺. Anal. Calcd for C₂₉H₄₅FeN₃O₅: C 60.94, H 7.94, N 7.35; found C 60.73, H 8.01, N 7.17.

Boc-Statine-Nph-NH-CH₂Fc 6

Yellow solid, yield 40.5%, m.p. 96-98 °C, [α]_D²⁰ = -39° (*c* 0.15, MeOH); IR (KBr): 3319, 3077, 2956, 1689, 1647, 1522, 1445, 1345, 1167, 1046, 845 and 486 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 0.92 {q, *J*=1.2 Hz, 6H, (CH₃)₂CH}, 1.07-1.11 (m, 1H, CHMe₂), 1.44 {s, 9H, (CH₃)₃}, 1.56-1.71 (m, 2H, CH₂CHMe₂), 2.31-2.40 (m, 2H, CH₂CO), 3.14-3.22 (m, 2H, CH₂-Ar), 3.43-3.51 (m, 1H, NCH-Bu-i), 3.71-3.95 (m, 2H, NCHCO, CH-O), 4.07-4.16 (m, 11H, C₅H₄, C₅H₅, CH₂N), 4.71 (d, *J*=4.4 Hz, 1H, NH), 6.42 (d, *J*=4.4 Hz, 1H, NH), 6.69 (d, *J*=8.0 Hz, 1H, NH), 7.33 (q, *J*=5.2 Hz, 2H, ArH), 8.08 (q, *J*=8.4 Hz, 2H, ArH). MALDI-TOF MS: *m/z* =664 (M⁺). Anal. Calcd for C₃₃H₄₄FeN₄O₇: C 59.64, H 6.67, N 8.43; found C 59.67, H 6.71, N 8.53.

Boc-Statine-Val-Phe-NH-CH₂Fc 7

Yellow solid, yield 30.2%, m.p. 166-168 °C, [α]_D²⁰ = -53° (*c* 0.10, MeOH); IR (KBr): 3422, 2932, 1663, 1497, 1439, 1390, 1253, 1101 and 700 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 0.86-0.99 {m, 12H, (CH₃)₂CH, (CH₃)₂CHCH₂}, 1.28-1.38 (m, 2H, CHMe₂, CHMe₂), 1.44 {s, 9H, (CH₃)₃}, 1.50-1.69 {m, 2H, CH₂-Pr-i}, 2.49-2.62 (m, 2H, CH₂CO), 3.05-3.17 (m, 2H, CH₂Ph, NCH-Bu-i), 3.50 (t, *J*=3.6 Hz, 1H, NCHCO), 3.89 (br, 1H, CH-O), 4.00-4.17 (m, 12H, NCHCO, C₅H₄, C₅H₅, CH₂N), 4.86 (d, *J*=7.6 Hz, 1H, NH), 5.04 (d, *J*=8.4 Hz, 1H, NH), 5.51 (br, 1H, NH), 6.38 (br, 1H, NH), 7.30-7.10 (m, 5H, ArH). MALDI-TOF MS: *m/z* =718 (M⁺). Anal. Calcd for C₃₈H₅₄FeN₄O₆: C 63.50, H 7.57, N 7.80; found C 63.62, H 7.66, N 7.65.

Boc-Val-Statine-Val-NH-CH₂Fc 8

Yellow solid, yield 32.4%, m.p. 142-144 °C, [α]_D²⁰ = -49° (*c* 0.10, MeOH); IR (KBr): 3326, 3086, 2929, 2850, 1687, 1627, 1573, 1534, 1367, 1245, 1167, 1087 and 642 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 0.81-0.96 {m, 18H, (CH₃)₂CH, (CH₃)₂CH, (CH₃)₂CHCH₂}, 1.04-1.43 (m, 3H, CHMe₂, CHMe₂, CHMe₂), 1.57 {s, 9H, (CH₃)₃}, 1.61-1.70 (CH₂-Pr-i), 2.33-2.38 (2H, CH₂CO), 3.45-3.56 (m, 2H, NCH-Bu-i, NCHCO), 3.71-3.99 (m, 2H, NCHCO, CH-O), 4.02-4.17 (m, 11H, C₅H₄, C₅H₅, CH₂N), 4.76 (d, *J*=9.2 Hz, 1H, NH), 6.21 (br, 1H, NH), 6.51 (d, *J*=8.8 Hz, 1H, NH), 6.65 (br, 1H, NH). MALDI-TOF MS: *m/z* =670 (M⁺). Anal. Calcd for C₃₄H₅₄FeN₄O₆: C 60.89, H 8.12, N 8.35; found C 61.01, H 8.20, N 8.29.

Boc-Statine-NH-CH₂Fc 9

Yellow solid, yield 57.7%, m.p. 109-111 °C, [α]_D²⁰ = -21° (*c* 0.17, MeOH); IR (KBr): 3327, 3095, 2929, 2850, 1688, 1627, 1534, 1366, 1246, 1168, 816, 643 and 482 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 0.88 {q, *J*=0.4 Hz, 6H, (CH₃)₂CH}, 1.26-1.39 (m, 3H, CH₂CHMe₂), 1.58 {s,

9H, (CH₃)₃}, 2.28-2.39 (m, 2H, CH₂CO), 3.39-3.56 (m, 1H, NCH-Bu-i), 3.95-3.98 (m, 1H, CH-O), 4.01-4.20 (m, 11H, C₅H₄, C₅H₅, CH₂N), 4.72 (d, *J*=9.6 Hz, 1H, NH), 6.09 (br, 1H). MALDI-TOF MS: *m/z* =472 (M⁺). Anal. Calcd for C₂₄H₃₆FeN₂O₄: C 61.02, H 7.68, N 5.93; found C 61.44, H 7.65, N 6.01.

Boc-AHPPA-Statine-Val-NH-CH₂Fc 10

Yellow solid, yield 20.3%, m.p. 125-127 °C [lit. ^[15] 125-127 °C], [α]_D²⁰ = -62.6° (*c* 0.10, MeOH); IR (KBr): 3323, 3088, 2960, 2928, 1648, 1534, 1451, 1366, 1247, 1167, 1047, 817, 699 and 483 cm⁻¹. ¹H NMR (CDCl₃): δ 0.82-0.98 {m, 12H, (CH₃)₂CH, (CH₃)₂CH₂CH}, 1.33-1.38 (m, 2H, CHMe₂, CHCH₂Me₂), 1.42 {s, 9H, (CH₃)₃}, 1.54-1.69 (m, 2H, CHCH₂Me₂), 2.24-2.53 (m, 4H, CH₂CO, CH₂CO), 2.91 (t, 2H, *J*=2.8 Hz, CH₂Ph), 3.49-3.52 (m, 1H, NCHCO), 3.74-3.78 (m, 2H, CH-O, CH-O), 4.01-4.09 (m, 2H, NCHBn, NCHBu-i), 4.12-4.26 (m, 11H, C₅H₄, C₅H₅, CH₂N), 4.97 (d, 1H, *J*=8.8 Hz, NH), 6.24 (br, 1H, NH), 6.38 (br, 1H, NH), 6.76 (d, 1H, *J*=8.8 Hz, NH), 7.18-7.27

(m, 5H, ArH). MALDI-TOF MS: *m/z* =762 (M⁺). Anal. Calcd for C₄₀H₅₈FeN₄O₇ · H₂O: C 61.53, H 7.75, N 7.18; found C 61.55, H 7.78, N 7.21.

FcCO-Val-Statine-Phe-OMe 11

Yellow solid, yield 27.6%, m.p. 105-107 °C, [α]_D²⁰ = -50° (*c* 0.13, MeOH); IR (KBr): 3447, 3097, 2925, 1774, 1678, 1488, 1367, 1260, 1055, 881, 746, 523 and 493 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 0.91-0.99 {m, 12H, (CH₃)₂CH₂, (CH₃)₂CH₂}, 1.39-1.42 (m, 2H, CHMe₂, CHMe₂), 1.59-1.75 (m, 2H, CH₂-Pr-i), 2.37-2.38 (d, *J*=6.4 Hz, 2H, CH₂CO), 3.01 (q, *J*=6.4 Hz, 2H, CH₂Ph), 3.10 (q, *J*=5.6 Hz, 2H, NCH-Bu-i), 3.73 (s, 3H, CH₃O), 4.02-4.12 (br, 1H, NCHCO), 4.21 (s, 5H, Fc), 4.27 (d, *J*=2 Hz, 2H, FcCO), 4.71 (d, *J*=1.2 Hz, 2H, FcCO), 4.79 (q, *J*=6.4 Hz, 1H, NH), 5.98 (d, *J*=7.6 Hz, 1H, NH), 6.41 (d, *J*=9.2 Hz, 1H), 7.07-7.24 (m, 5H, ArH). MALDI-TOF MS: *m/z* =647 (M⁺). Anal. Calcd for C₃₄H₄₅FeN₃O₆: C 63.06, H 7.00, N 6.49; found C 63.23, H 7.11, N 6.38.