CHEMMEDCHEM
Chemistry & Drug Discovery

Supporting Information

Supplemental information to:

The potential of P1 site alterations in peptidomimetic protease inhibitors, as suggested by virtual screening, explored via the use of C-C-coupling linker reagents[**]

Steffen Weik,[a] Torsten Luksch,[b] Andreas Evers,[b] Jark Böttcher,[b] Christoph A. Sotriffer,[b] Andrej Hasilik,[c] Hans-Gerhard Löffler,[c] Gerhard Klebe,[b] and Jörg Rademann*[a]

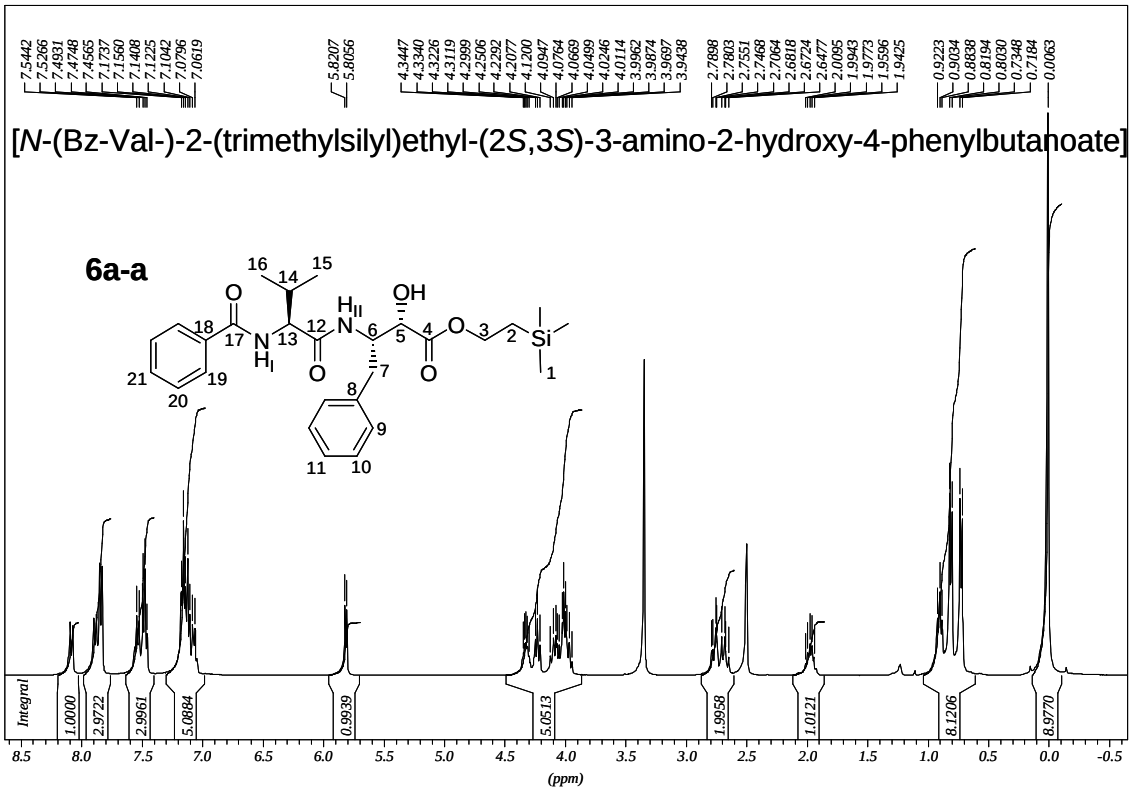
[*],[a] Prof. Dr. J. Rademann, Dr. S. Weik, Leibniz Institute for Molecular Pharmacology (FMP), Robert-Rössle-Str. 10, 13125 Berlin and Free University Berlin, Takustr. 3, 14195 Berlin, Germany. Fax: (+49)30 94793280, E-mail: rademann@fmp-berlin.de

[b] Prof. Dr. G. Klebe, T. Luksch, Dr. A. Evers, J. Böttcher, Dr. C. A. Sotriffer, Institute for Pharmaceutical Chemistry, University Marburg, Marbacher Weg 6, 35032 Marburg.

[c] Prof. Dr. A. Hasilik, Dr. H.-G. Löffler, Institute for Physiological Chemistry, University Marburg, Karl-von-Frisch-Str. 1, 35043 Marburg, Germany.

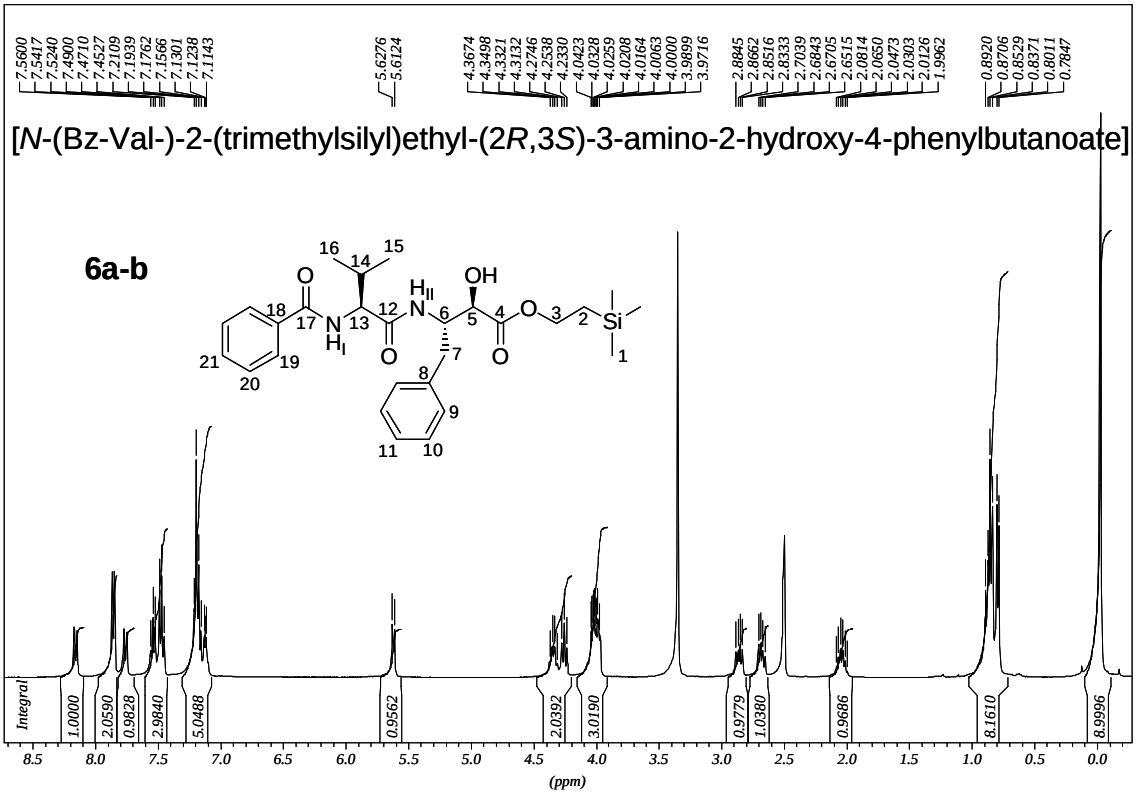
[**] Essential parts of this work were presented at the 28th European Peptide Symposium in Prague, Czech Republic, 5.-10. September 2004, and at Eurocombi 3 in Winchester, England, 18.-22. July 2005, where it was assigned a poster award.

6aa [*N*-(Bz-Val-)-2-(trimethylsilyl)ethyl-(2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoate]: ^{1}H NMR (400.16 MHz, DMSO-d_6): δ 8.09 (d, ^{3}J = 9.09 Hz, 1H, NH_{I}), 7.89 (d, ^{3}J = 8.84, 1H, NH_{II}), 7.84 (d, ^{3}J = 7.58 Hz, 2H, arom. C*H*), 7.46 – 7.56 (m, 3H, arom. C*H*), 7.05 – 7.17 (m, 5H, arom. C*H*), 5.81 (d, ^{3}J = 6.06 Hz, 1H, α-CHO*H*), 4.28 – 4.37 (m, 1H, β-C*H*), 4.23 (dd, ^{3}J = 8.59 Hz, 8.59 Hz, 1H, α-C*H* Val), 3.96 – 4.04 (m, 1H, α-C*H*OH), 3.92 – 4.13 (m, 2H, OCH_2), 2.64 – 2.80 (m, 2H, γ-CH_2), 1.92 – 2.02 (m, 1H, β-C*H* Val), 0.87 – 0.98 (m, 2H, SiCH_2), 0.81 (d, ^{3}J = 6.57 Hz, 3H, CH_3 Val), 0.72 (d, ^{3}J = 6.57 Hz, 3H, CH_3 Val), 0.01 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (100.62 MHz, DMSO-d_6): δ 172.22 (C_4), 170.41 (C_{12}), 166.20 (C_{17}), 138.45 (C_8), 134.41 (C_{18}), 131.26 (C_{21}), 129.20 (C_9), 128.23 (C_{10}), 127.92 (C_{19}), 127.48 (C_{20}), 125.93 (C_{11}), 72.43 (C_5), 62.34 (C_3), 59.11 (C_{13}), 52.67 (C_6), 35.01 (C_7), 30.20 (C_{14}), 19.29, 18.69 (C_{15}, C_{16}), 16.86 (C_2), -1.52 (C_1); ESI/MS: calcd [M(TMSE-ester) = $C_{27}H_{38}N_2O_5Si$], 498.25 Da; found (MNa^+), *m/z* 521.3 Da.

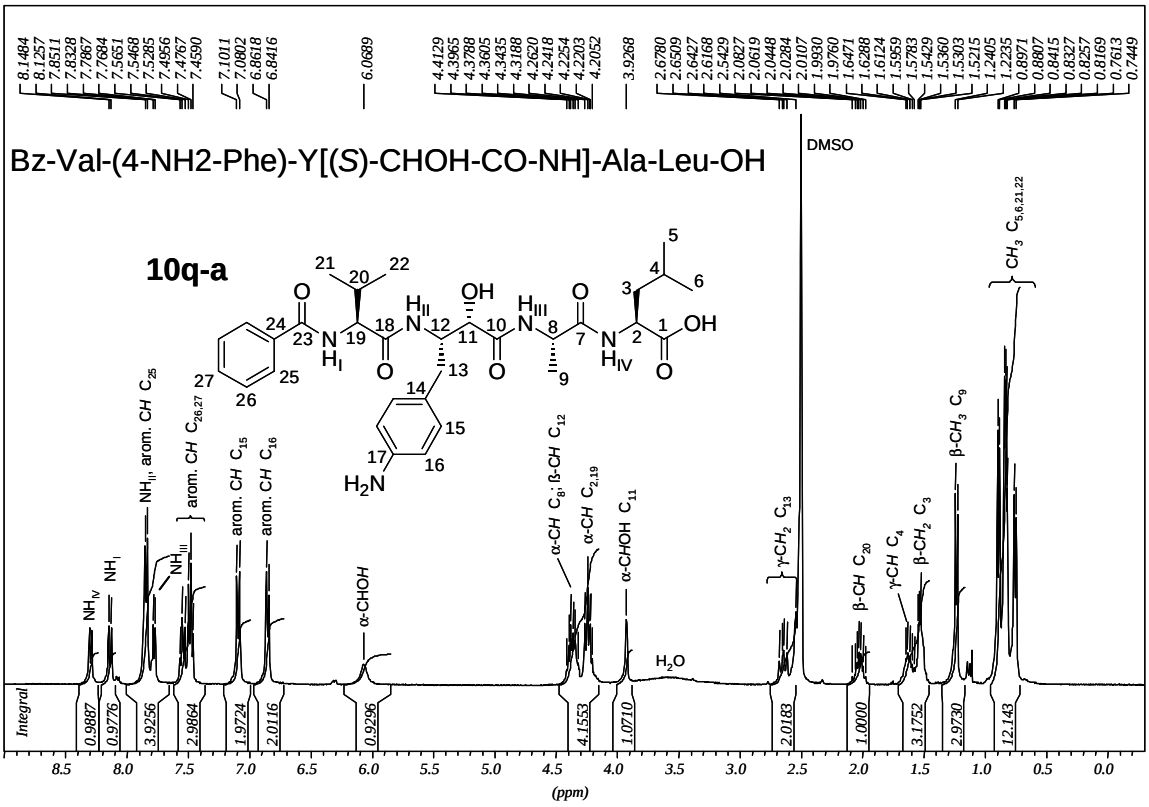


6a-b [*N*-(Bz-Val-)-2-(trimethylsilyl)ethyl-(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoate]:

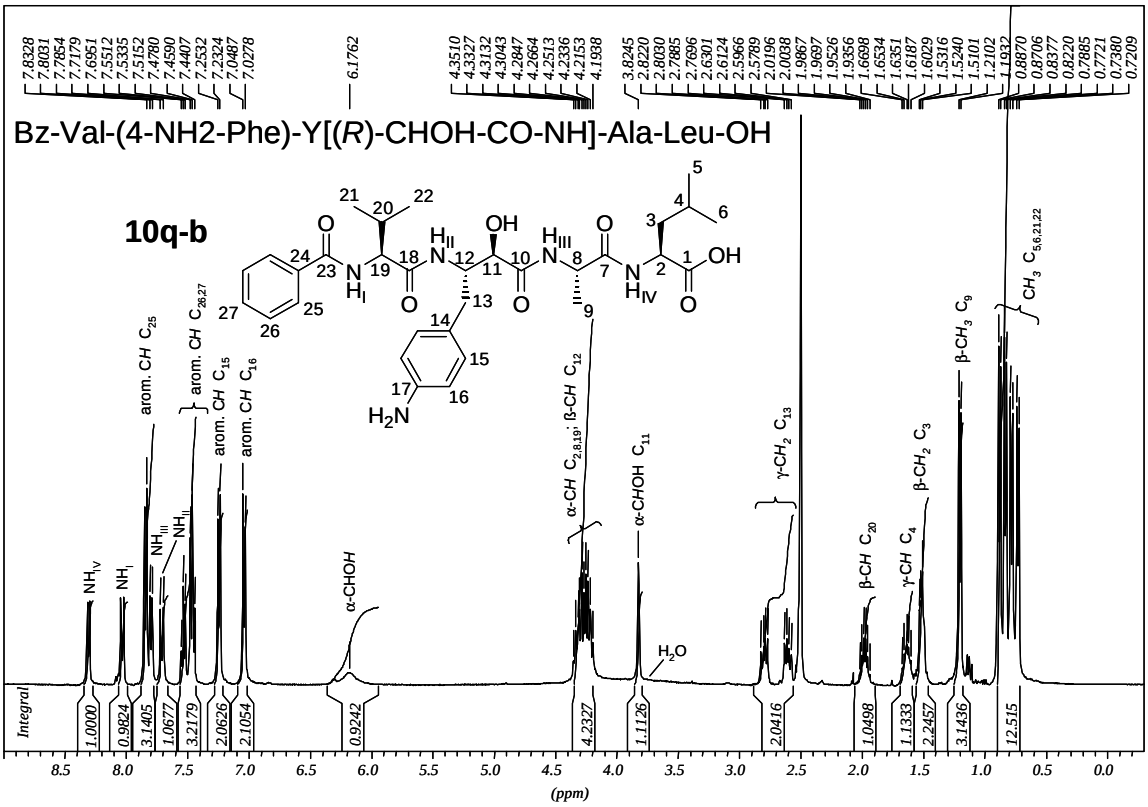
^{1}H NMR (400.16 MHz, DMSO-d_6): δ 8.16 (d, ^{3}J = 8.59 Hz, 1H, NH_{I}), 7.86 (d, ^{3}J = 7.33 Hz, 2H, arom. C*H*), 7.76 (d, ^{3}J = 9.35 Hz, 1H, NH_{II}), 7.44 – 7.57 (m, 3H, arom. C*H*), 7.09 – 7.23 (m, 5H, arom. C*H*), 5.62 (d, ^{3}J = 6.06 Hz, 1H, α-CHO*H*), 4.30 – 4.38 (m, 1H, β-C*H*), 4.25 (dd, ^{3}J = 8.34 Hz, 8.34 Hz, 1H, α-C*H* Val), 3.97 – 4.04 (m, 1H, α-C*H*OH), 3.99 – 4.09 (m, 2H, OCH_2), 2.64 – 2.89 (m, 2H, γ-CH_2), 1.99 – 2.09 (m, 1H, β-C*H* Val), 0.85 – 0.95 (m, 2H, SiCH_2), 0.84 (d, ^{3}J = 6.56 Hz, 3H, CH_3 Val), 0.79 (d, ^{3}J = 6.56 Hz, 3H, CH_3 Val), -0.03 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (100.62 MHz, DMSO-d_6): δ 172.29 (C_4), 170.43 (C_{12}), 166.33 (C_{17}), 138.38 (C_8), 134.42 (C_{18}), 131.24 (C_{21}), 129.11 (C_9), 128.20 (C_{10}, C_{19}), 127.50 (C_{20}), 126.15 (C_{11}), 70.36 (C_5), 62.32 (C_3), 59.03 (C_{13}), 53.08 (C_6), 37.08 (C_7), 29.87 (C_{14}), 19.34, 18.54 (C_{15}, C_{16}), 16.77 (C_2), -1.55 (C_1); ESI/MS: calcd [M(TMSE-ester) = $C_{27}H_{38}N_2O_5Si$], 498.25 Da; found (MNa^{+}), *m/z* 521.3 Da.



10qa {*N*-[*N*-(Bz-Val-)-(2*S*,3*S*)-3-amino-4-(4-aminophenyl)-2-hydroxybutanoyl]-Ala-Leu-OH}: ^{1}H NMR (400.16 MHz, DMSO-d_6): δ 8.30 (d, ^{3}J = 7.83 Hz, 1H, NH_{IV}), 8.14 (d, ^{3}J = 9.09 Hz, 1H, NH_{I}), 7.81 – 7.91 (m, 3H, arom. CH C_{25}, NH_{II}), 7.78 (d, ^{3}J = 7.33 Hz, 1H, NH_{III}), 7.45 – 7.58 (m, 3H, arom. CH $C_{26,27}$), 7.09 (d, ^{3}J = 8.34 Hz, 2H, arom. CH C_{15}), 6.85 (d, ^{3}J = 8.09 Hz, 2H, arom. CH C_{16}), 6.07 (bs, 1H, α-CHOH), 4.30 – 4.43 (m, 2H, α-CH Ala C_8, β-CH C_{12}), 4.15 – 4.29 (m, 2H, α-CH Leu C_2, α-CH Val C_{19}), 3.93 (bs, 1H, α-CHOH C_{11}), 2.27 – 2.49 (m, 2H, γ-CH_2 C_{13}), 1.97 – 2.08 (m, 1H, β-CH Val C_{20}), 1.58 – 1.69 (m, 1H, γ-CH Leu C_4), 1.47 – 1.57 (m, 2H, β-CH_2 Leu C_3), 1.23 (d, ^{3}J = 6.82 Hz, 3H, CH_3 Ala C_9), 0.89 (d, ^{3}J = 6.57 Hz, 3H, CH_3 Leu C_5/C_6), 0.80 – 0.86 (m, 6H, CH_3 Leu C_5/C_6, CH_3 Val C_{21}/C_{22}), 0.75 (d, ^{3}J = 6.57 Hz, 3H, CH_3 Val C_{21}/C_{22}); ^{13}C NMR (100.62 MHz, DMSO-d_6): δ 173.84 (C_1), 171.89 (C_7), 170.85 (C_{10}), 170.46 (C_{20}), 166.41 (C_{25}), 134.50, 131.27, 130.01, 128.27, 127.50, 119.27 ($C_{14,15,16,17,24,25,26,27}$), 73.25 ($C_{11}$), 59.09 ($C_{19}$), 52.98 ($C_{12}$), 50.18 ($C_2$), 47.38 ($C_8$), 39.34 ($C_3$), 33.51 ($C_{13}$), 30.27 ($C_{20}$), 24.27 ($C_4$), 22.88, 21.26 ($C_5$, C_6), 19.42, 18.64 (C_{21}, C_{22}), 19.05 (C_9); ESI/MS: calcd [M(norstatine) = $C_{31}H_{43}N_5O_7$], 597.32 Da; found (MH^+), *m/z* 598.4.



10qb {*N*-[*N*-(Bz-Val-)-(2*R*,3*S*)-3-amino-4-(4-aminophenyl)-2-hydroxybutanoyl]-Ala-Leu-OH]}: ^{1}H NMR (400.16 MHz, DMSO-d_6): δ 8.31 (d, ^{3}J = 7.83 Hz, 1H, NH_{IV}), 8.03 (d, ^{3}J = 8.59 Hz, 1H, NH_{I}), 7.84 (d, ^{3}J = 7.33 Hz, 2H, arom. CH C_{25}), 7.80 (d, ^{3}J = 7.08 Hz, 1H, NH_{III}), 7.71 (d, ^{3}J = 9.09 Hz, 1H, NH_{II}), 7.43 – 7.56 (m, 3H, arom. CH $C_{26,27}$), 7.24 (d, ^{3}J = 8.34 Hz, 2H, arom. CH C_{15}), 7.04 (d, ^{3}J = 8.34 Hz, 2H, arom. CH C_{16}), 6.18 (bs, 1H, α-CHOH), 4.17 – 4.36 (m, 4H, α-CH Ala C_8, β-CH C_{12}, α-CH Leu C_2, α-CH Val C_{19}), 3.82 (bs, 1H, α-CHOH C_{11}), 2.57 – 2.83 (m, 2H, γ-CH_2 C_{13}), 1.93 – 2.03 (m, 1H, β-CH Val C_{20}), 1.58 – 1.68 (m, 1H, γ-CH Leu C_4), 1.46 – 1.55 (m, 2H, β-CH_2 Leu C_3), 1.20 (d, ^{3}J = 6.82 Hz, 3H, CH_3 Ala C_9), 0.88 (d, ^{3}J = 6.57 Hz, 3H, CH_3 Leu C_5/C_6), 0.83 (d, ^{3}J = 6.32 Hz, 3H, CH_3 Leu C_5/C_6), 0.78 (d, ^{3}J = 6.57 Hz, 3H, CH_3 Val C_{21}/C_{22}), 0.73 (d, ^{3}J = 6.82 Hz, 3H, CH_3 Val C_{21}/C_{22}); ^{13}C NMR (100.62 MHz, DMSO-d_6): δ 173.86 (C_1), 171.90 (C_7), 170.89 (C_{10}), 170.37 (C_{20}), 166.43 (C_{25}), 134.45, 131.22, 130.37, 128.24, 127.48, 121.00 ($C_{14,15,16,17,24,25,26,27}$), 70.91 ($C_{11}$), 58.66 ($C_{19}$), 52.76 ($C_{12}$), 50.20 ($C_2$), 47.48 ($C_8$), 39.74 ($C_3$), 36.73 ($C_{13}$), 30.19 ($C_{20}$), 24.22 ($C_4$), 22.91, 21.22 ($C_{5,6}$), 19.39 ($C_9$), 19.13, 18.34 ($C_{21,22}$); ESI/MS: calcd [M(norstatine) = $C_{31}H_{43}N_5O_7$], 597.32 Da; found (MH^+), *m/z* 598.4.


Bz-Val-(4-NH2-Phe)-Y[(R)-CHOH-CO-NH]-Ala-Leu-OH
10q-b
NH_IV
NH_I
NH_III
NH_II
arom. CH C_25
arom. CH C_26,27
arom. CH C_15
arom. CH C_16
α-CHOH
α-CH C_2,8,19; β-CH C_12
α-CHOH C_11
H_2O
γ-CH_2 C_13
β-CH C_20
γ-CH C_4
β-CH_2 C_3
β-CH_3 C_9
CH_3 C_5,6,21,22
Integral
1.0000
0.9824
3.1405
1.0677
3.2179
2.0626
2.1054
0.9242
4.2327
1.1126
2.0416
1.0498
1.1333
2.2457
3.1436
12.515
(ppm)