## Supporting Information

# 1,4-Disubstituted-[1,2,3]triazolyl-Containing Analogues of MT-II: Design, Synthesis, Conformational Analysis, and Biological Activity

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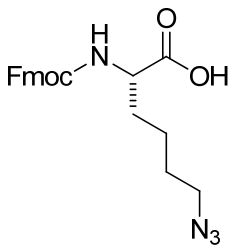
### Synthesis of $N^{\alpha}$-Fmoc-ω-azido-α-amino acids and $N^{\alpha}$-Fmoc-ω-alkynyl-α-amino acids

$N^{\alpha}$-Fmoc-ω-azido-α-amino- and $N^{\alpha}$-Fmoc-ω-ynoic-α-amino acids with different length of the side chain, were synthesized according to the procedure described in the literature.[1,2] Briefly, the $N^{\alpha}$-Fmoc-ω-azido-α-amino acids (1-4) were synthesized by diazo-transfer reaction starting from the correspondent $N^{\alpha}$-protected ω-amino-α-amino acids. The $N^{\alpha}$-Fmoc-ω-alkynyl-α-amino acids (5-7) were synthesized by alkylation of a Ni(II) complex of the Schiff base formed between glycine and (S)-2-(N-benzylprolyl)aminobenzophenone, as a chiral inducer, with alk-ω-ynyl bromides. 2S-[[(9H-Fluoren-9-ylmethoxy)carbonyl]amino]-4-pentynoic acid and Fmoc-S-Pra-OH (8) were purchased from Iris Biotech GmbH.

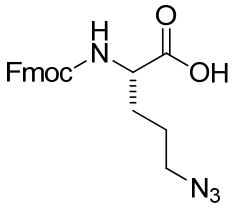
### 6–Azido–2S-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]hexanoic acid (6-Azido-Fmoc-L-norleucine) (1)




Yield 70%. RP-UPLC: $R_t$ 4.28 min (50-100% B in 5 min). IR (KBr): 2100 $cm^{-1}$ ($N_3$). ESI-MS: *m/z* calcd for $C_{21}H_{22}N_4NaO_4$ $[M + Na]^+$: 417.15; found 417.2. $[\alpha]_D =$ –2.5 (*c* 1.0, MeOH). $^1H$ NMR ($CDCl_3$, 400 MHz,): δ 7.74 (d, 2H, $J_{3,4} = J_{5,6} = 7.4$ Hz, fluorenyl 4-H and 5-H), 7.54 (d, 2H, $J_{1,2} = J_{7,8} = 7.4$ Hz, fluorenyl 1-H and 8-H), 7.37 (*pseudo* t, 2H, fluorenyl 3-H and 6-H), 7.28 (*pseudo* t, 2H, fluorenyl 2-H and 7-H), 6.19 (s broad, COOH), 5.46 (m, 1H, NH), 4.49–4.33 (m, 3H, $CH_2$–O and α-H), 4.18 (t, 1H, $J = 6.4$ Hz, fluorenyl 9-H), 3.24–3.21 (m, 2H, ε-$H_2$), 1.70–1.42 (m, 6H,3 × $CH_2$). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 176.97 (COOH), 156.35 (CONH), 143.75, 143.60, and 141.28 (fluorenyl C-4a, C-4b, C-8a, and C-9a), 127.74, 127.06, and 125.01 (fluorenyl C-2 and C-7), 120.00 (fluorenyl C-1 and C-8), 67.14 ($CH_2$–O), 53.90 (C-α), 51.02 (C-ε), 47.07 (fluorenyl C-9), 31.68 ($CH_2$), 28.31 ($CH_2$),

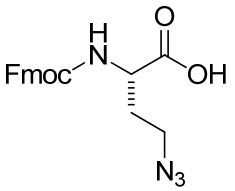
22.55 ($CH_2$). Anal. Calcd for $C_{21}H_{22}N_4O_4$: C, 63.95; H, 5.62; N, 14.20. Found: C, 64.01; H, 5.58; N, 14.23.

**5-Azido-2S-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino] pentanoic acid (5-azido-Fmoc-L-Norvaline) (2)**



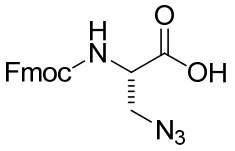

Yield 83%. RP-UPLC: $R_t$ 3.81 min (50-100% B in 5 min). IR (KBr): 2100 ($N_3$) $cm^{-1}$. ESI-MS:*m/z* calcd for $C_{20}H_{20}N_4NaO_4$ $[M + Na]^+$ 403.14; found 403.3. $[\alpha]_D = -2.3$ (*c* 1.0, MeOH). $^1H$ NMR ($CDCl_3$, 400 MHz,): δ 7.76 (d, 2H, $J_{3,4} = J_{5,6}$ = 7.6 Hz, fluorenyl 4-H and 5-H), 7.61 (*pseudo* d, 2H, $J_{1,2} = J_{7,8}$ = 7.6 Hz, fluorenyl 1-H and 8-H), 7.40 (*pseudo* t, 2H, fluorenyl 3-H and 6-H), 7.31 (*pseudo* t, 2H, fluorenyl 2-H and 7-H), 6.16 (s broad, COOH), 5.34 (m, 1H, NH), 4.45–4.40 (m, 3H, $CH_2$–O and α-H), 4.22 (t, 1H, *J* = 6.6 Hz, fluorenyl 9-H), 3.37–3.30 (m, 2H, δ-$H_2$), 2.01–1.46 (m, 4H, 2 × $CH_2$). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 175.72 (COOH), 156.72 (CONH), 143.75, 143.57, and 141.33 (fluorenyl C-4a, C-4b, C-8a, and C-9a), 127.76, 127.08, and 125.00 (fluorenyl C-2 and C-7), 120.02 (fluorenyl C-1 and C-8), 67.12 ($CH_2$–O), 53.16 (C-α), 50.76 (C-δ), 47.15 (fluorenyl C-9), 29.62 ($CH_2$), 24.81 ($CH_2$). Anal. Calcd for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.09; H, 5.25; N, 14.80.

**4-Azido-2S-[[(9H-fluoren-9-ylmethoxy) carbonyl]amino] butanoic acid (Fmoc-Abu(γ-$N_3$)-OH) (3)**



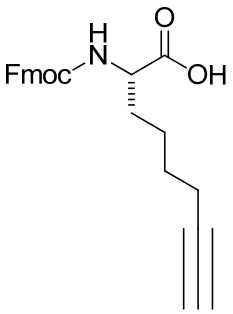

Yield 89%. RP-UPLC: $R_t$ 3.34 min (50-100% B in 5 min). IR: 2100 $cm^{-1}$ ($N_3$). ESI-MS: *m/z* calcd for $C_{19}H_{18}N_4NaO_4$ $[M + Na]^+$ 389.12; found 389.4. $[\alpha]_D = -11.5$ (*c* 1.0, MeOH). $^1H$ NMR ($CDCl_3$, 400 MHz,): δ 7.75 (*pseudo* d, 2H, *J* = 7.6 Hz, fluorenyl 4-H and 5-H), 7.54 (*pseudo* d, 2H, *J* = 7.4 Hz, fluorenyl 1-H and 8-H), 7.39 (*pseudo* t, 2H, fluorenyl 3-H and 6-H), 7.31 (*pseudo* t, 2H, fluorenyl 2-H and 7-H), 6.14 (s broad, COOH), 5.63 (m, 1H, NH), 4.53–4.41 (m, 3H, $CH_2$–O and α-H), 4.21 (t, 1H, *J* = 6.8 Hz, fluorenyl 9-H), 3.42–3.39 (m, 2H, γ-$H_2$), 2.19–1.96 (m, 6H, 3 × $CH_2$). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 172.71 (COOH), 156.26 (CONH), 143.53 and 141.29 (fluorenyl C-4a, C-4b, C-8a, and C-9a), 127.76, 127.08, 125.04, 124.99 (fluorenyl C-2, C-7), 120.00 (fluorenyl C-1, C-8), 67.17 ($CH_2$-O), 51.70 (C-α), 47.68 (C-γ), 47.09 (fluorenyl C-9), 31.21 ($CH_2$). Anal. Calcd for $C_{19}H_{18}N_4O_4$: C, 62.29; H, 4.95; N, 15.29. Found: C, 62.36; H, 4.99; N, 15.24.

**3-Azido-2S-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino] propanoic acid (3-Azido-Fmoc-L-Alanine) (4)**



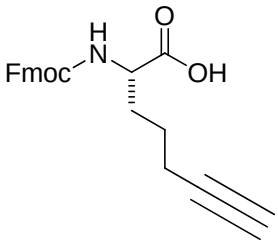

Yield 75 %. RP-UPLC: $R_t$ 4.02 min (50-100% B in 5 min). IR: 2100 $cm^{-1}$ ($N_3$). ESI-MS: *m/z* calcd for $C_{18}H_{16}N_4NaO_{44}$ $[M + Na]^+$ 375.12; found 375.4. $^1H$ NMR ($CDCl_3$, 400 MHz,): d 7.70 (*pseudo* d, 2H, J = 7.4 Hz, fluorenyl 4-H and 5-H), 7.48 (*pseudo* d, 2H, J = 7.6 Hz, fluorenyl 1-H and 8-H), 7.40 (*pseudo* t, 2H, fluorenyl 3-H and 6-H), 7.28 (*pseudo* t, 2H, fluorenyl 2-H and 7-H), 6.3 (s broad, COOH), 5.78 (m, 1H, NH), 4.57–4.45 (m, 3H, $CH_2$–O and α-H), 4.32 (t, 1H, J = 6.8 Hz, fluorenyl 9-H), 3.52–3.35 (m, 2H, γ-H2). Anal. Calcd for $C_{18}H_{16}N_4O_4$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.46; H, 4.98; N, 15.68.

**2S-[[(9H-Fluoren-9-ylmethoxy)carbonyl]amino]-7-octynoic acid (5)**



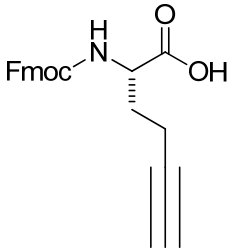

Yield 38%. TLC: Rf 0.5 (DCM/MeOH 10:1). RP-UPLC: $R_t$ 4.12 min (50–100% B in 5 min). ESI-MS: *m/z* calcd for $C_{23}H_{23}NNaO_4$ $[M + Na]^+$ 400.15; found 400.3. $[\alpha]_{D\,=}$ –3.1 (*c* 1.0, MeOH). $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.75 (*pseudo* d, 2H, *J* = 7.6 Hz, fluorenyl 4-H and 5-H), 7.59 (*pseudo* d, 2H, *J* = 7.6 Hz, fluorenyl 1-H and 8-H), 7.37 (*pseudo* t, 2H, fluorenyl 3-H and 6-H), 7.28 (*pseudo* t, 2H, fluorenyl 3-H and 6-H), 5.79 (broad s, COOH), 5.48 (m, 1H, NH), 4.44–4.38 (m, 3H, $CH_2$–O and α-H), 4.21 (t, 1H, *J* = 6.8 Hz, fluorenyl 9-H), 2.08–1.99 (m, 3H), 1.94 (t, 1H, *J* = 2.4 Hz, HC≡C), 1.80–1.75 (m, 1H), 1.58–1.42 (m, 4H, 2 × $CH_2$). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 176.63 (COOH), 156.17 (CONH), 143.83, 143.67 and 141.29 (fluorenyl C-4a, C-4b, C-8a, and C-9a), 127.71, 127.06, 125.04 (fluorenyl C-2 to C-7), 119.98 (fluorenyl C-1 and C-8), 83.97 (HC≡C), 68.69 ($CH_2$-O), 67.06 (HC≡C), 53.83 (C-α), 47.15 (fluorenyl C-9), 31.73 and 27.81 (C-β and δ), 24.31 (C-γ), 18.15 (C-ε).

**2*S*-[[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino]-6-heptynoic acid (6)**




Yield 28%. TLC: Rf 0.47 (DCM/MeOH 9:1). RP-UPLC: $R_t$ 3.54 min (50–100% B in 5 min). ESI-MS: *m/z* calcd for $C_{22}H_{21}NNaO_4$ $[M + Na]^+$ 386.14; found 386.2. $[\alpha]_{D\,=}$ –3.0 (*c* 1.0, MeOH). $^1$H NMR($CDCl_3$, 400 MHz): δ 7.73 (d, 2H, *J* = 7.2 Hz, fluorenyl 4-H and 5-H), 7.57 (d, 2H, *J* = 7.4 Hz, fluorenyl 1-H and 8-H), 7.39 (*pseudo* t, 2H, fluorenyl 3-H and 6-H), 7.30 (*pseudo* t, 2H, fluorenyl 2-H and 7-H), 6.60 (broad s, COOH), 5.51 (m, 1H, NH), 4.43–4.35 (m, 3H, $CH_2$–O and α-H), 4.18 (t, 1H, *J* = 6.6 Hz, fluorenyl 9-H), 2.08–1.99 (m, 3H), 1.94 (t, 1H, *J* = 2.4 Hz, HC≡C), 1.80–1.75 (m, 1H), 1.58–1.42 (m, 2H, $CH_2$). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 177.06 (COOH), 156.26 (CONH), 143.81, 143.62 and 141.27 (fluorenyl C-4a, C-4b, C-8a, and C-9a), 127.70, 127.06 and 125.05 (fluorenyl C-2 to C-7), 119.96 (fluorenyl C-1 and C-8), 83.49 (HC≡C), 69.11 ($CH_2$-O), 67.06 (HC≡C), 53.77 (C-α), 47.11 (fluorenyl C-9), 31.33 (C-β), 24.28 (C-γ), 18.01 (C-δ).

**2S-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]-5-hexynoic acid (7)**




Yield 32%. RP-UPLC: Rt 3.37 min (50–100% B in 5 min). ESI-MS: m/z calcd for $C_{21}H_{19}NNaO_4$ $[M + Na]^+$ 372.14; found 372. $^1$H NMR ($CDCl_3$, 400 MHz): d 7.73 (d, 2H, J = 7.2 Hz, fluorenyl 4-H and 5-H), 7.56 (d, 2H, J = 7.3 Hz, fluorenyl 1-H and 8-H), 7.37 (pseudo t, 2H, fluorenyl 3-H and 6-H), 7.30 (pseudo t, 2H, fluorenyl 2-H and 7-H), 6.71 (s broad, COOH), 5.8 (m, 1H, NH), 4.48–4.30 (m, 3H, $CH_2$–O and α-H), 4.21 (t, 1H, J = 6.7 Hz, fluorenyl 9-H), 2.45–2.31 (m, 3H), 2.22–2.10 (m, 1H), 2.00 (t, 1H, J = 2.1 Hz, HC≡C).

**Table 1s.** Backbone dihedral angles: Mean values of ψ and φ angles relative to the most representative MT-II conformers.

| Backbone Dihedrals | | | |
|---|---|---|---|
| **MT-II analog IA** | **Residue** | **Phi** | **Psi** |
| | **Nle[4]** | - | - |
| | **Pra[5]** | -42.03 | -25.08 |
| | **His[6]** | -112.09 | 58.51 |
| | **D-Phe[7]** | -168.5 | -36.63 |
| | **Arg[8]** | -109.84 | 5.61 |
| | **Trp[9]** | -138.45 | -66.72 |
| | **Nle(ε-$N_3$)[10]** | - | - |
| **MT-II analog IV** | | | |
| | **Nle[4]** | - | - |
| | **Oct(7yl)[5]** | -77.94 | 73.72 |
| | **His[6]** | -175.17 | -53.06 |
| | **D-Phe[7]** | -57.43 | -17.87 |
| | **Arg[8]** | -114.27 | -11.7 |
| | **Trp[9]** | 45.88 | 30.26 |
| | **Ala(β-$N_3$)[10]** | - | - |
| **MT-II analog V** | | | |
| | **Nle[4]** | - | - |
| | **Nle(ε-$N_3$)[5]** | -160.14 | -38.82 |
| | **His[6]** | -85.92 | -32.61 |
| | **D-Phe[7]** | -44.39 | -30.89 |
| | **Arg[8]** | -130.48 | -13.26 |
| | **Trp[9]** | 68.88 | 8.26 |
| | **Pra[10]** | - | - |

**Table 2s.** Proton chemical shifts of [1,2,3]triazolyl-containing cyclopeptides IA in DMSO-d6 at 300 K**.**

| Residue | NH | $C^{\alpha}H$ | $C^{\beta}H$ | $C^{\gamma}H$ | $C^{\delta}H$ | Others | Δα |
|---|---|---|---|---|---|---|---|
| **Nle**[4] | 7.789 | 4.299 | **Qβ** 1.831 | **Qγ** 1.745 | **Qδ** 1.621 | **Qε** 1.237 | |
| **Pra**[5] | 8.168 | 4.120 | **Hβ2** 2.921<br>**Hβ3** 2.453 | | | | |
| **His**[6] | 8.332 | 4.244 | **Qβ** 2.436 | | **Hδ2** 5.890 | **Hε1** 9.456 | -0.386 |
| **D-Phe**[7] | 7.665 | 4.876 | **Qβ** 3.647 | | **Qδ** 7.296 | **Qε** 6.891 | 0.216 |
| **Arg**[8] | 8.185 | 3.962 | **Hβ2** 1.889<br>**Hβ3** 1.708 | **Qγ** 1.570 | **Qδ** 3.197 | **Hε** 7.660 | -0.418 |
| **Trp**[9] | 9.175 | 4.855 | **Hβ2** 2.893<br>**Hβ3** 2.765 | | **Hδ1** 6.952 | **Hε1** 10.791<br>**Hε3** 7.174<br>**HH2** 7.071<br>**HZ2** 7.529<br>**HZ3** 7.333 | 0.155 |
| **Nle(ε-$N_3$)**[10] | 8.848 | 3.752 | **Qβ** 1.958 | **Qγ** 1.252 | **Qδ** 1.347 | **Qε** 1.822<br>**HZ** 7.083 | |

**Table 3s.** Proton chemical shifts of [1,2,3]triazolyl-containing cyclopeptides IB in DMSO-d6 at 300 K.

| Residue | NH | $C^{\alpha}H$ | $C^{\beta}H$ | $C^{\gamma}H$ | $C^{\delta}H$ | Others |
|---|---|---|---|---|---|---|
| **Nle**[4] | 8.108 | 4.222 | **Qβ** 1.617 | **Qγ** 1.478 | **Qδ** 1.228 | **Qε** 0.853 |
| **Pra**[5] | 7.917 | 4.651 | **Hβ2** 3.174<br>**Hβ3** 3.037 | | | |
| **His**[6] | 8.313 | 4.298 | **Qβ** 2.724 | | **Hδ2** 6.862 | **Hε1** 7.258 |
| **D-Phe**[7] | 8.600 | 4.281 | **Hβ2** 3.177<br>**Hβ3** 2.849 | | | |
| **Arg**[8] | 8.716 | 4.205 | **Hβ2** 1.658<br>**Hβ3** 1.538 | **Qγ** 1370 | **Qδ** 3.014 | **Hε** 7.544<br>**QH2** 7.674 |
| **Trp**[9] | 8.083 | 4.505 | **Hβ2** 3.203<br>**Hβ3** 3.022 | | **Hδ1** 7.233 | **Hε1** 10.028<br>**Hε3** 7.778<br>**HH2** 7.372 |
| **Nle(ε-$N_3$)**[10] | 7.787 | 4.229 | **Qβ** 1.771 | **Qγ** 1.240 | **Qδ** 1.625 | **Qε** 3.039 |

**Table 4s**. Proton chemical shifts of [1,2,3]triazolyl-containing cyclopeptides IV in DMSO-d6 at 300 K.

| Residue | NH | $C^{\alpha}H$ | $C^{\beta}H$ | $C^{\gamma}H$ | $C^{\delta}H$ | Others |
|---|---|---|---|---|---|---|
| **Nle**[4] | 8.080 | 4.212 | **Qβ** 1.518 | **Qγ** 1.745 | **Qδ** 1.252 | **Qε** 0.873 |
| **Oct(7yl)**[5] | 7.980 | 4.212 | **Qβ** 1.931 | **Hγ2** 1.623<br>**Hγ3** 1.716 | **Qδ** 1.284 | **Qε** 1.484 |
| **His**[6] | 8.438 | 4.528 | **Hβ2** 2.959<br>**Hβ3** 2.792 | | **Hδ2** 7.173 | **Hε1** 10.826 |
| **D-Phe**[7] | 8.376 | 4.615 | **Hβ2** 3.038<br>**Hβ3** 2.763 | **Qγ** 1.379 | **Qδ** 7.218 | |
| **Arg**[8] | 7.933 | 4.278 | **Hβ2** 1.667<br>**Hβ3** 1.519 | **Qγ** 1.379 | **Qδ** 3.055 | **Hε** 7.603 |
| **Trp**[9] | 8.192 | 4.565 | **Hβ2** 3.139<br>**Hβ3** 3.021 | | **Hδ1** 7.282 | **Hε1** 10.890<br>**Hε3** 7.637<br>**HH2** 7.186<br>**HZ2** 7.359<br>**HZ3** 7.359 |
| **Ala(β-$N_3$)**[10] | 8.368 | 4.670 | 2.814 | | | |

**Table 5s**. Proton chemical shifts of [1,2,3]triazolyl-containing cyclopeptides V in DMSO-d6 at 300 K.

| Residue | NH | $C^{\alpha}H$ | $C^{\beta}H$ | $C^{\gamma}H$ | $C^{\delta}H$ | Others |
|---|---|---|---|---|---|---|
| **Nle**[4] | 8.052 | 4.244 | **Qβ** 1.639 | **Qγ** 1.527 | **Qδ** 1.275 | **Qε** 0.880 |
| **Nle(ε-$N_3$)**[5] | 7.973 | 4.295 | **Hβ2** 1.803<br>**Hβ3** 1.752 | **Qγ** 1.229 | **Qδ**1.614 | **HZ** 7.871<br>**Qε** 3.037 |
| **His**[6] | 8.188 | 4.576 | **Hβ2** 3.218<br>**Hβ3** 3.038 | | **Hδ2** 6.726 | **Hε1** 7.320 |
| **D-Phe**[7] | 8.102 | 4.557 | **Hβ2** 3.057<br>**Hβ3** 2.891 | | | |
| **Arg**[8] | 8.192 | 4.226 | **Hβ2** 1.654<br>**Hβ3** 1.552 | **Qγ** 1.408 | **Qδ** 3.041 | **Hε** 7.423<br>**QH2** 7.242 |
| **Trp**[9] | 8.341 | 4.450 | **Hβ2** 3.204<br>**Hβ3** 3.021 | | **Hδ1** 7.386 | **Hε1** 10.852<br>**Hε3** 7.672<br>**HH2** 7.115<br>**HZ3** 7.041 |
| **Pra**[10] | 8.379 | 4.348 | **Hβ2** 3.111<br>**Hβ3** 2.766 | | | |

References:

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