3rd International Electronic Conference on Medicinal Chemistry
1-30 November 2017
chaired by Dr. Jean Jacques Vanden Eynde
sponsored by pharmaceuticals

Fragments of peptoid 1: Synthesis of *N*-substituted glycine monomers

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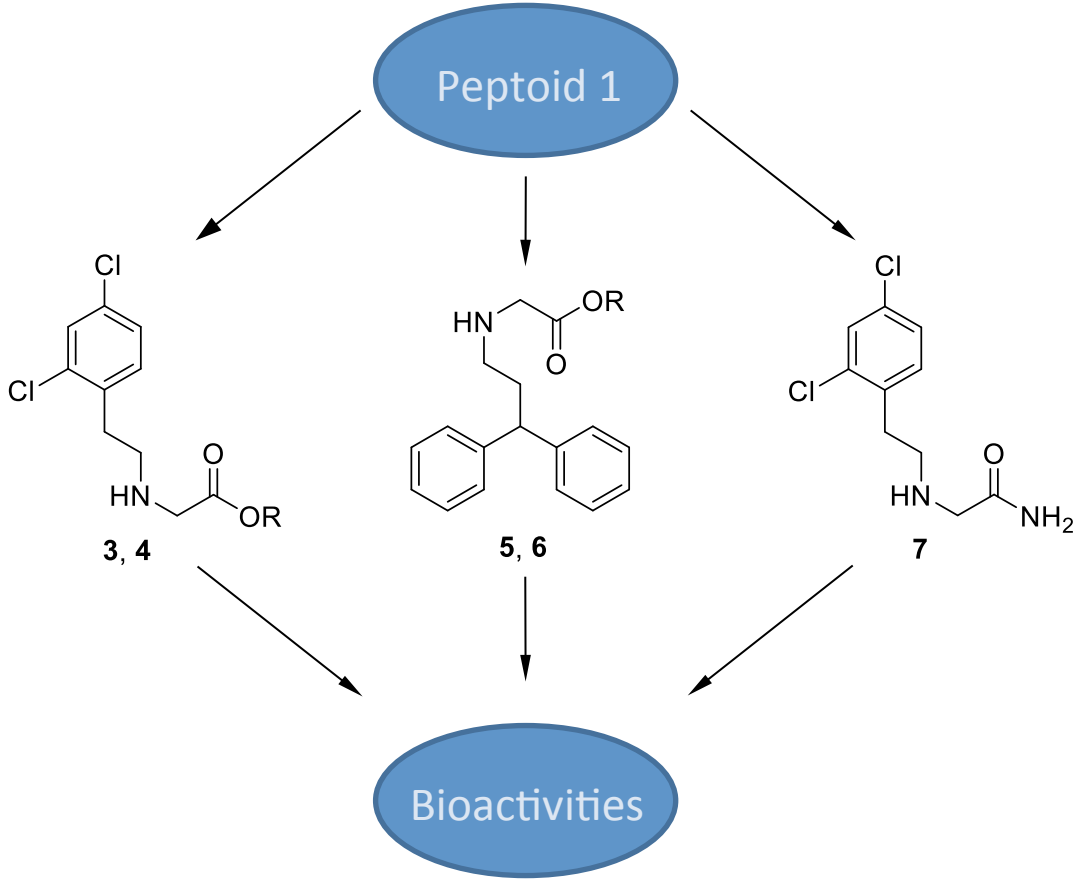


Abstract:

Peptoids are *N*-substituted glycine oligomers comprising multiple biomedical applications. In particular, they are used in nanotechnological approaches. In this context, their application is typically focused on larger oligomers, which form two-dimensional structures, but are difficult to be synthesized. However, a short peptoid of three *N*-substituted glycine building blocks, referred to as peptoid 1, is known to inhibit the proapoptotic protein APAF1. Herein, we report on the preparation of various peptoidic building blocks of peptoid 1. The synthesis was conducted by alkylation of two different amine components, 2-(2,4-dichlorophenyl)ethylamine and 3,3-diphenylpropylamine with *tert*-butyl bromoacetate, benzyl bromoacetate, and 2-bromoacetamide, respectively. The resulting glycine derivatives have been characterized by NMR and LC/MS data. The new peptoid units will be provided to biochemical studies, e.g. to the evaluation of protease-inhibiting properties, in order to perform a fragment-based approach.

Keywords: peptoids; building blocks; *N*-alkylations

Introduction

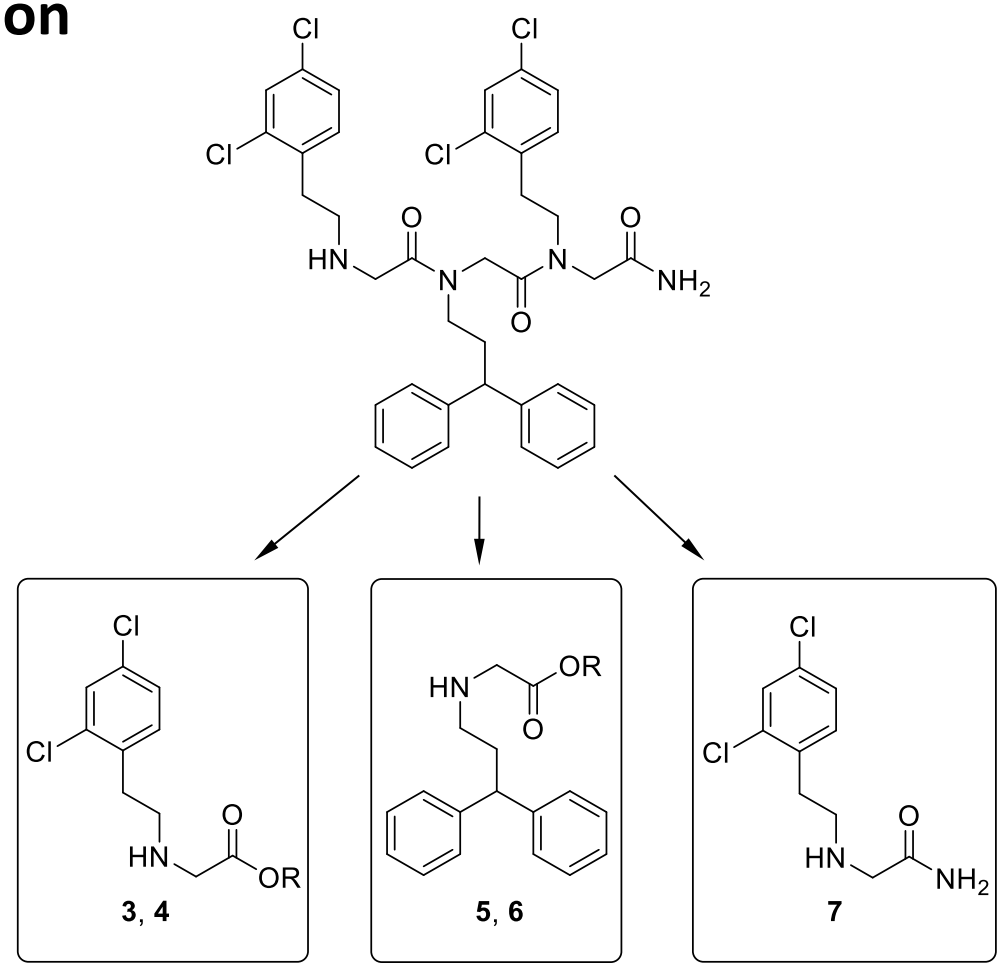
The assembly of several *N*-substituted glycine substructures formes the so-called peptoids. Their composition is similar to that of peptides, with the difference that the side chain is shifted from the α-carbon to the amino group nitrogen.[1] These compounds are used, e.g. in nanotechnology, to form ultrathin two-dimensional nanosheets, which can be further functionalized or engineered.[2]

The comparable short peptoid 1 consists of three different glycine units and is responsible for inhibition of the apoptotic protease activating factor 1 (APAF1). This proapoptotic protein is involved in the mitochondrial pathway of apoptosis and leads to apoptosome formation and activation of procaspase-9 to caspase-9.[3]

Our study is aimed at synthesizing peptoid 1 fragments to examine if such small building blocks might have biological activities.

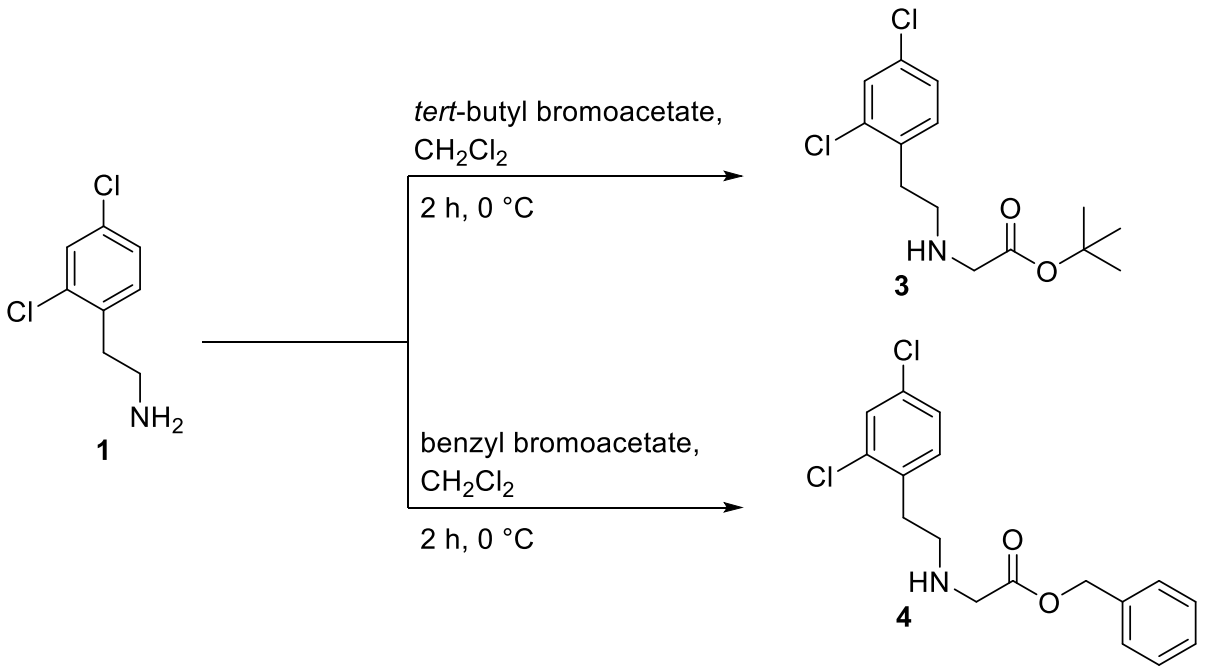
1) Zuckermann, R. N.; Kodadek, T. *Curr. Opin. Mol. Ther.* **2009**, *11*, 299-307.
2) Nam, K. T. et al. *Nat. Mater.* **2010**, *9*, 454-460.
3) Mondragón, L. et al. *J. Med. Chem.* **2008**, *51*, 521-529.

Introduction



Peptoid 1 and derived fragments.

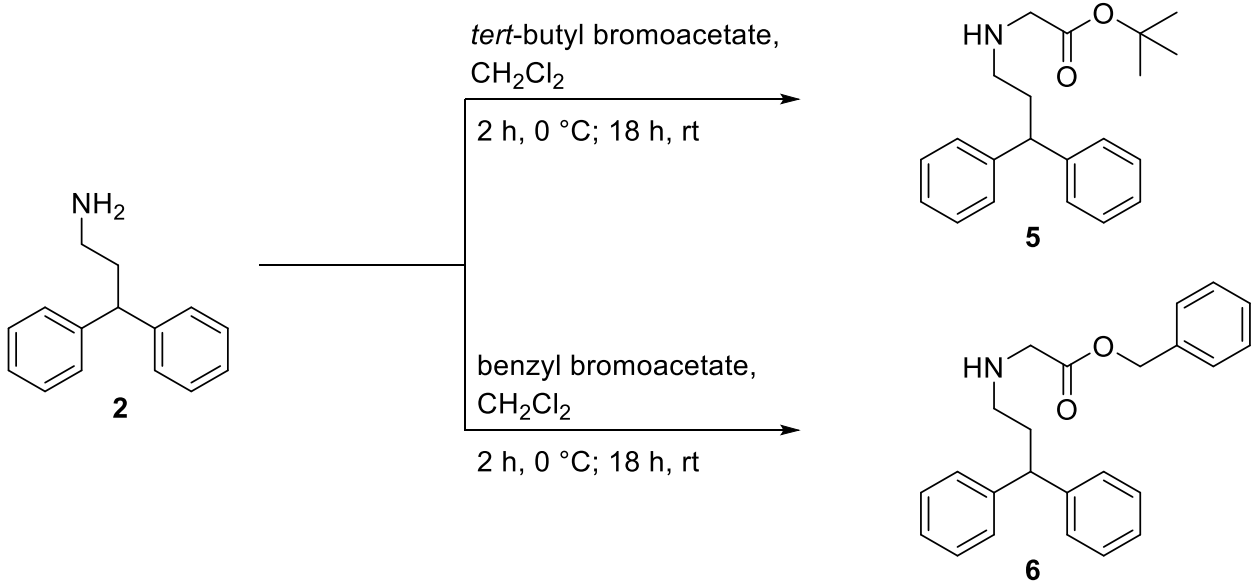
Synthesis



Compounds **3**[4] and **4** were obtained in 74% and 67% yield after column chromatography (petroleum ether / ethyl acetate 1:1) in a purity of 100% and 95% based on LC/MS analysis, respectively.

4) Messeguer, J. et al. *Tetrahedron* **2010**, *66*, 2444-2454.

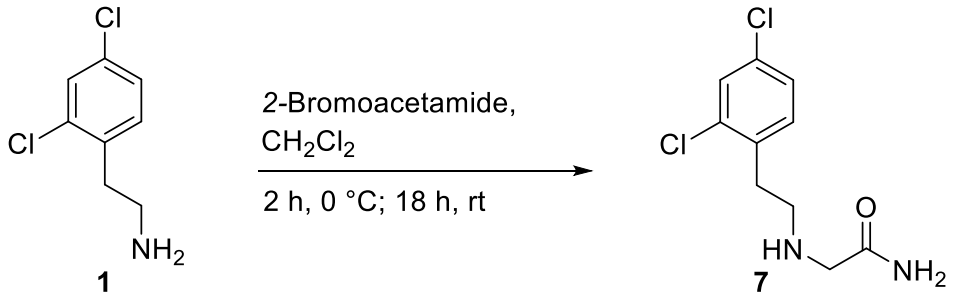
Synthesis



Compounds **5**[5] and **6** were obtained in 73% and 78% yield after column chromatography (petroleum ether / ethyl acetate 2:1 or 1:1) in a purity of 99% and 80% based on LC/MS analysis, respectively.

5) Temal, T. et al. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2451-2454.

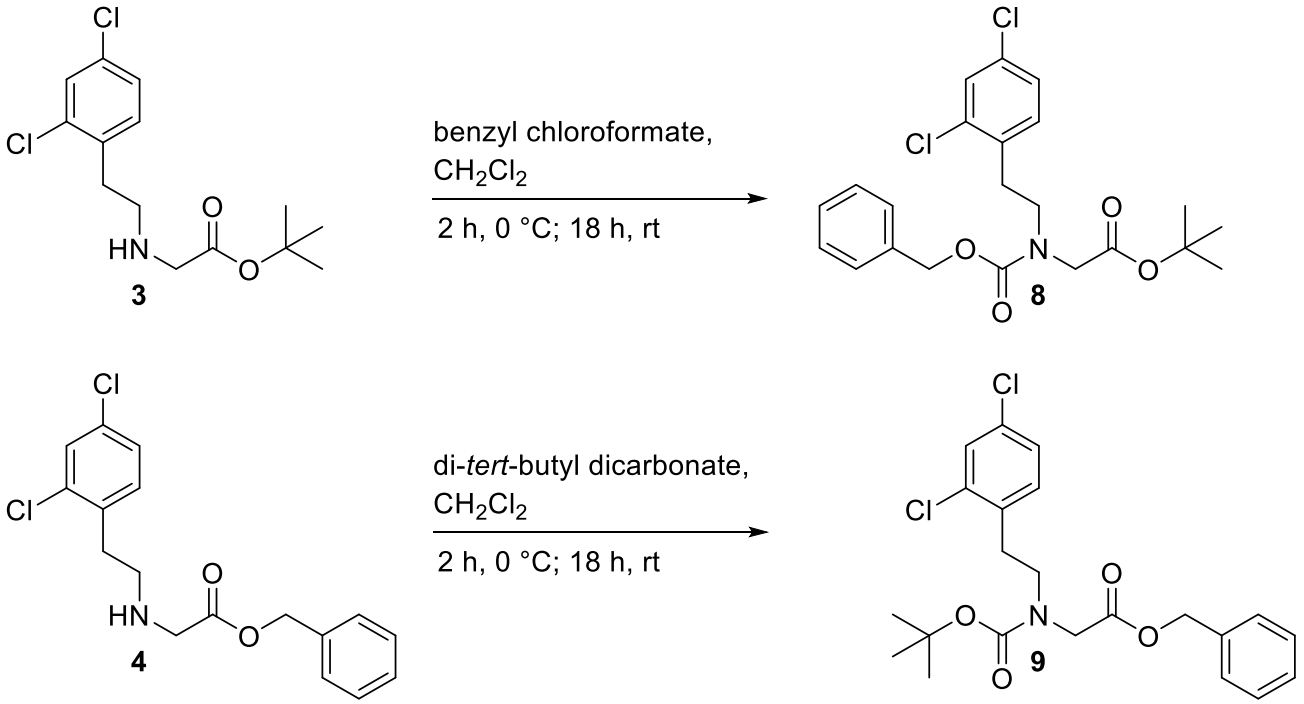
Synthesis



Compound **7**[6] was obtained in 48% yield after column chromatography (CH_2Cl_2/ MeOH 9:1) in a purity of 99% based on LC/MS analysis.

6) Moure, A. et al. *Chem. Eur. J.* **2011**, *17*, 7927-7939.

Synthesis



Compounds **8** and **9** were obtained in 86% and 84% yield after column chromatography (petroleum ether / ethyl acetate 14:1 or 4:1) as isomeric mixtures (ratio approximately 1+1 and 2+1) in a purity of 100% and 98% based on LC/MS analysis, respectively.

NMR Spectra
(δ; DMSO-d_6; ^{1}H NMR, 500 MHz; ^{13}C NMR, 125 MHz)

3: 1.39 (s, 9H, $(CH_3)_3$), 1.95 (s, 1H, NH), 2.69 – 2.74 (m, 2H, $NHCH_2C\underline{H}_2$), 2.76 – 2.81 (m, 2H, $NHC\underline{H}_2CH_2$), 3.20 (s, 2H, CH_2CO), 7.32 – 7.34 (dd, ^3J = 8.2 Hz, ^4J = 2.2 Hz, 1H, 5-H), 7.37 –7.39 (d, ^3J = 8.3 Hz, 1H, 6-H), 7.52 (d, ^4J = 2.2 Hz, 1H, 3-H); 27.90 ($(CH_3)_3$), 32.94 ($NHCH_2\underline{C}H_2$), 48.21 ($NH\underline{C}H_2CH_2$), 51.06 ($\underline{C}H_2CO$), 80.18 ($\underline{C}(CH_3)_3$), 127.34 (C-5), 128.62 (C-3 or C-6), 131.53 (C-4), 132.52 (C-3 or C-6), 134.03 (C-2), 137.02 (C-1), 171.58 (CO).

5: 1.35 (s, 9H, $(CH_3)_3$), 2.08 – 2.15 (m, 2H, $NHCH_2C\underline{H}_2$), 2.38 (t, ^3J = 7.1 Hz, 2H, $NHC\underline{H}_2CH_2$), 3.11 (s, 2H, $C\underline{H}_2CO$), 4.01 (t, ^3J = 7.8 Hz, 1H, $CHPh_2$), 7.09 – 7.17 (m, 2H, 4-H), 7.22 – 7.30 (m, 8H, 2-H, 3-H, 5-H, 6-H); a signal for NH was not visible; 27.85 ($(CH_3)_3$), 35.29 ($NHCH_2\underline{C}H_2$), 47.18 ($NH\underline{C}H_2CH_2$), 48.26 ($\underline{C}H_2CO$), 51.38 ($CHPh_2$), 80.05 ($\underline{C}(CH_3)_3$), 126.05 (C-4), 127.68 (C-2, C-6), 128.45 (C-3, C-5), 145.26 (C-1), 171.66 (CO).

NMR Spectra
(δ; DMSO-d_6; ^{1}H NMR, 500 MHz; ^{13}C NMR, 125 MHz)

6: 2.09 – 2.16 (m, 2H, $NHCH_2C\underline{H}_2$), 2.42 (t, ^3J = 7.1 Hz, 2H, $NHC\underline{H}_2CH_2$), 3.30 (s, 2H, $C\underline{H}_2CO$), 4.01 (t, ^3J = 7.8 Hz, 1H, $CHPh_2$), 5.07 (s, 2H, OCH_2), 7.09 – 7.18 (m, 2H, 4-H), 7.18 – 7.39 (m, 13H, 2-H, 3-H, 5-H, 6-H, 2´-H – 6´-H); a signal for NH was not visible; 35.23 ($NHCH_2\underline{C}H_2$), 47.27 ($NH\underline{C}H_2CH_2$), 48.30 ($\underline{C}H_2CO$), 50.46 ($CHPh_2$), 65.51 (OCH_2), 126.09 (C-4), 127.70 (C-2, C-6), 128.08 (C-2´, C-6´), 128.14 (C-4´), 128.48 (C-3, C-5), 128.54 (C-3´, C-5´), 136.25 (C-1´), 145.25 (C-1), 172.21 (CO).

7: 2.17 (s, 1H, NH), 2.69 (t, ^3J = 7.2 Hz, 2H, $NHCH_2C\underline{H}_2$), 2.80 (t, ^3J = 7.2 Hz, 2H, $NHC\underline{H}_2CH_2$), 3.04 (s, 2H, $C\underline{H}_2CO$), 6.96, 7.15 (each s, each 1H, NH_2), 7.33 (dd, ^3J = 8.3 Hz, ^4J = 2.2 Hz, 1H, 5-H), 7.38 (d, ^3J = 8.2 Hz, 1H, 6-H), 7.53 (d, ^4J = 2.2 Hz, 1H, 3-H); 33.03 ($NHCH_2\underline{C}H_2$), 48.84 ($NH\underline{C}H_2CH_2$), 51.95 ($\underline{C}H_2CO$), 127.37 (C-5), 128.65 (C-3 or C-6), 131.54 (C-4), 132.53 (C-3 or C-6), 134.04 (C-2), 137.02 (C-1), 173.56 (CO).

NMR Spectra
(δ; DMSO-d_6; ^{1}H NMR, 500 MHz; ^{13}C NMR, 125 MHz)

8 (isomeric mixture, ratio approximately 1+1 (A+B)): 1.36, 1.41 (each s, 18H (A+B), $(CH_3)_3$), 2.92 and 2.93 (each t, ^3J = 7.6 Hz, ^3J = 7.7 Hz, 4H (A+B), $NCH_2C\underline{H}_2$), 3.48 and 3.50 (each t, ^3J = 6.8 Hz, ^3J = 6.7 Hz, 4H (A+B), $NC\underline{H}_2CH_2$), 3.92, 3.94 (each s, 4H (A+B), CH_2CO), 4.99, 5.03 (each s, 4H (A+B), OCH_2), 7.26 – 7.42 (m, 14H (A+B), 2´-H – 6´-H, 5-H, 6-H), 7.49 (d, ^4J = 1.8 Hz, 1H (A or B), 3-H), 7.57 (d, ^4J = 2.2 Hz, 1H (A or B), 3-H); 27.74, 27.85 ($(CH_3)_3$), 30.95, 31.53 ($NCH_2\underline{C}H_2$), 47.51, 48.09 ($N\underline{C}H_2CH_2$), 49.61, 49.78 ($\underline{C}H_2CO$), 66.42, 66.68 (OCH_2), 81.03, 81.11 ($\underline{C}(CH_3)_3$), 127.36, 127.43, 127.49, 127.74, 127.86, 128.00, 128.37, 128.43, 128.73, 131.90, 131.94, 132.58, 132.70, 134.24 (C-2 – C-6, C-2´ – C-6´), 135.65, 135.74 (C-1´), 136.64, 136.81 (C-1), 155.31, 155.57 ($N\underline{C}OOCH_2Ph$), 168.74, 168.89 ($CH_2\underline{C}O$); two signals for (C-2 – C-6, C-2´ – C-6´) (A+B) are not visible.

NMR Spectra
(δ; DMSO-d_6; ^{1}H NMR, 500 MHz; ^{13}C NMR, 125 MHz)

9 (isomeric mixture of A (major) and B (minor)): 1.22 and 1.23 (each s, 18H (A and B), $(CH_3)_3$), 2.87 (t, ^3J = 7.0 Hz, 4H (A+B), $NCH_2C\underline{H}_2$), 3.43 and 3.45 (each t, ^3J = 7.0 Hz and ^3J = 6.6 Hz, 4H (B and A), $NC\underline{H}_2CH_2$), 3.97, 4.05 (each s, 4H (B and A), $C\underline{H}_2CO$), 5.14 and 5.15 (each s, 4H (A and B), OCH_2), 7.28 – 7.40 (m, 14H (A+B), 5-H, 6-H, 2´-H – 6´-H), 7.53 and 7.55 (each d, ^4J = 2.2 Hz and 1.8 Hz, 2H (B and A), 3-H); 27.79, 27.82 ($(CH_3)_3$), 31.14, 31.52 ($NCH_2\underline{C}H_2$), 47.30, 47.44 ($N\underline{C}H_2CH_2$), 48.48, 49.42 ($\underline{C}H_2CO$), 65.98, 66.05 (OCH_2), 79.27, 79.32 ($\underline{C}(CH_3)_3$), 127.35, 127.40, 127.97, 128.18, 128.21, 128.27, 128.53, 128.65, 131.82, 131.92, 132.59, 133.04, 134.26 (C-2 – C-6, C-2´ – C-6´), 134.36, 135.87 (C-1´), 135.97, 136.01 (C-1), 154.36, 154.72 ($N\underline{C}OOC(CH_3)_3$), 169.86, 170.01 ($CH_2\underline{C}O$); three signals for (C-2 – C-6, C-2´ – C-6´) (A+B) are not visible.

Outlook

The new synthesized compounds **3**-**9** were derived from peptoid 1 and synthesized by *N*-alkylation of two different amine components, which are present in the peptoid 1 structure. In further experiments they will be examined in various assay to determine their bioactive potential, e.g. enzyme inhibitory effects. The corresponding biological data might then be utilized in a fragment-based approach to re-generate larger peptidomimetic compounds.

Acknowledgments

We thank Dr. Janina Schmitz and Christian Steinebach for support.