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First Synthesis of N-Linked-Glycopeptoid as New Glycopeptidomimetics

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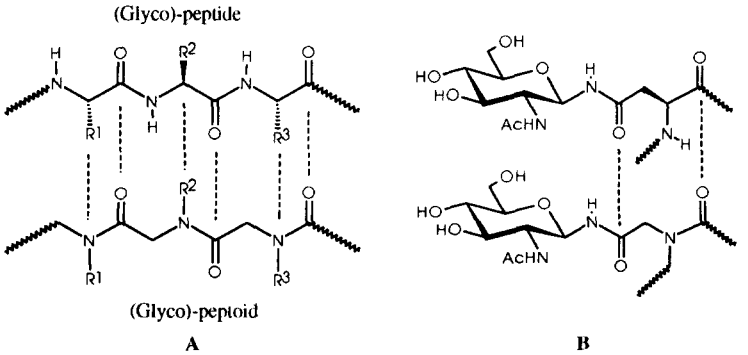
Abstract: The first N-linked glycopeptoid containing N-acetylglucosaminide (D-GlcNAc) was synthesized using the oligo(N-substituted glycines) (NSGs) approach. The strategy presented herein offers the advantage of a convergent synthesis.

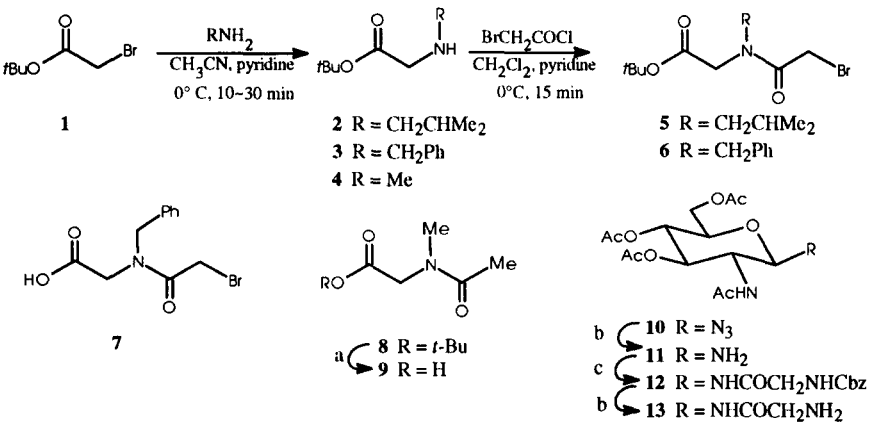
The potential therapeutic values of numerous synthetic peptides have been hampered by poor oral bioavailability and metabolic instability.[1] Few successful alternative approaches to solve these drawbacks have included the synthesis of peptidomimetics[2,3] and glycopeptides.[4,5] Another novel solution to these problems has involved the design of non-peptide peptidomimetics utilizing carbohydrates as scaffolding.[6] An additional variant has recently suggested the use of peptoids which are composed of N-substituted glycines (NSGs) having no chiral centers and a wide plethora of potential side chain structures.[7,8] Moreover, the peptoid approach is also amenable to solid-phase synthesis.[9] Since the problems of oral bioavailabilty may still prevail with peptoids, we suggest herein a new combinatorial strategy which links the advantages of both the peptoid and the glycopeptides approaches (Scheme 1). As a first model, an asparagine linked N-acetylglucosaminide pentapeptoid has been prepared. In this model, the sequence H_2N-Leu-Asn(D-GlcNAc)-Phe-Lys-Ala-OH has been replaced by t-BuO_2CCH_2-Nleu-Nasn(D-GlcNAc)-Nphe-Nlys-Nala-N-Ac.



Scheme 1. **A)** Comparison of a (glyco)-peptide sequence and a (glyco)-peptoid based on oligo(N-substituted glycines) (NSGs). **B)** Typical asparagine-linked N-acetylglucosaminide linkage and its N-linked peptoid mimic.

The strategy depicted herein is commensurate with that of the submonomer approach described by Zuckermann *et al*[9] and presents some analogy with the synthesis of peptide nucleic (PNA) monomers.[10] The N-substituted glycine building blocks were prepared from t-butyl bromoacetate **1** to which was added the primary amines. The first leucine, phenylalanine and alanine analogs **2-4** were synthesized by additions (CH_3CN, pyridine, 0°C, 10~30 min) of their corresponding isobutylamine (75%), benzylamine (78%) and methylamine (55%) respectively (Scheme 2). The use of pyridine as base, the short reaction times and the use of only one equivalent of primary amines allowed to minimize higher N-alkylation (<10%). The secondary amines **2** and **3** were then treated with bromoacetyl chloride in a mixture of CH_2Cl_2 and pyridine (0°C, 15 min) to afford the C-terminal and internal N-bromoacetyl derivatives **5** (91%) and **6** (93 %), respectively. Sarcosine *tert*-butyl ester **4** was kept as the N-terminal residue and was therefore transformed into N-acetylsarcosine *tert*-butyl ester **8** by treatment with acetyl chloride in pyridine (95%). For a convergent approach, **8** was transformed into acid **9** by treatment with 33% trifluoroacetic acid (TFA) in CH_2Cl_2 (r.t., 3 h., 95%). It is worth mentioning that, as expected,[11] these secondary amides exist as rotational isomers. Thus, the ^{1}H-NMR spectrum of **5**, **6** and **8** (and **9**) showed rotational isomer ratios of 1:1.4, 1:1.2 and 1: 2.5 respectively.

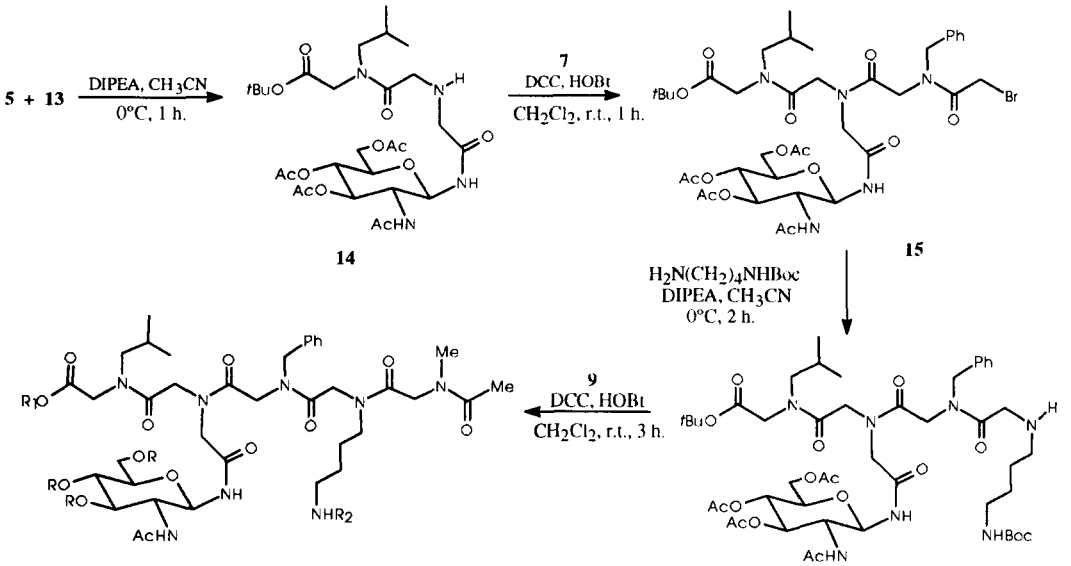
The key asparagine linked N-acetylglucosaminide mimic was synthesized from the glycosyl azide **10** prepared under stereospecific phase transfer catalyzed conditions (PTC).[12] The anomeric azide group of **10** was reduced by catalytic hydrogenation (10% Pd-C, MeOH) to provide glycosyl amine **11** in quantitative yield. Treatment of **11** with N-Cbz-glycine in the presence of DCC-HOBt in dry dichloromethane gave crystalline **12** in 80% yield (mp 183-185°C, $[\alpha]_D$ +21.2°, c 1.0, $CHCl_3$). Deprotection of the benzyloxy-carbonyl group in **12** under neutral condition by hydrogenation over 10% Pd-C at normal pressure and temperature gave **13** in essentially quantitative yield.[13]



Scheme 2. *a*: TFA, CH_2Cl_2, (1:2, v/v), r.t., 3 h.; *b*: H_2, 10% Pd-C, MeOH, r. t., 30 min.; *c*: $CbzNHCH_2CO_2H$, DCC, HOBt, r. t., 3 h.

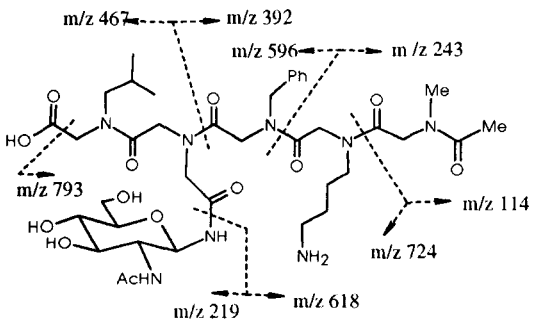
The first dipeptoid unit **14** was obtained by coupling N-bromoacetyl derivative **5** with amine **13** in the presence of diisopropylethylamine (DIPEA) in CH_3CN (0°C, 1 h.) to give **14** in 70% yield (Scheme 3). The ^{1}H-, ^{13}C-NMR and mass spectra of **14** are in good agreement with the assigned structure.

The glycopeptoid unit **14** was further elongated by treatment with acid **7**. Acid **7** was obtained by hydrolysis of the t-butyl ester of **6** with TFA in CH_2Cl_2 as described above for **8** (96%). Coupling of acid **7** to amine **14** was accomplished with DCC-HOBt (CH_2Cl_2, r.t., 1 h.) as above and afforded glycotripeptoid **15** in 85% yield after silica gel column chromatography. Compound **15** showed a complex ^{1}H-NMR spectrum due to the presence of mixture of rotational isomers. Condensation of **15** with mono N-(tert-butoxycarbonyl) butanediamine ($H_2N(CH_2)_4NHCbz$) with DIPEA in CH_3CN (0°C, 2 h.) furnished **16** in 75% yield.



Scheme 3

Finally, the N-terminal unit **9** was condensed with amine **16** by employing DCC-HOBt in dry dichloromethane to afford fully protected glycopentapeptoid **17** in 81% yield after silica gel column chromatography (mp 104-105°C, $[\alpha]_D$ -9.8°, c 1.1, $CHCl_3$). Compound **17** was then sequentially deprotected under Zemplén conditions (NaOMe, MeOH, r.t., 30 min, pH 9.0) to provide **18** quantitatively. Treatment of **18** in TFA (o.n., r.t.) gave pure 19 (100%). The structure of **19** was fully confirmed by its typical peptide fragmentation as shown by its mass spectrum (FAB-MS, pos., Scheme 4).



Scheme 4. FAB-MS (pos) fragmentation pattern of glycopentapeptoid **19**, m/z 837 $[M+1]^+$, (38.9%).

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13. All new compounds showed satisfactory spectral and elemental/mass analysis. Selected spectroscopic an analytical data are as follow. Compound **5** (rotamers): ^{1}H-NMR ($CDCl_3$), δ (ppm): 0.77-0.87 (2d, 6H, J=6.6 Hz, $CH(CH_3)_2$); 1.35, 1.37 (2s, 9H, $C(CH_3)_3$); 1.73 (m, 1H, $CH(CH_3)_2$); 3.68-4.02 (m, 6H, 3x CH_2); MS (CI, m/z): 308 (M^+, 71.8%). **6**: ^{1}H-NMR ($CDCl_3$), δ (ppm): 1.37, 1.40 (2s, 9H, $C(CH_3)_3$), 3.83 -3.89 (4s, 4H, 2xCH_2); 4.06, 4.64 (2s, 2H, CH_2), 7.19-7.34 (m, 5H, C_6H_5); MS (CI, m/z) 342 (M^+, 12.9). **8**: ^{1}H-NMR ($CDCl_3$), δ (ppm): 1.3, 1.32 (2s, 9H, C(CH3)$_3$), 1.88, 1.96 (2s, 3H, $COCH_3$), 2.8, 2.92 (2s, 3H, NCH_3), 3.74, 3.86 (2s, 2H, CH_2); MS (CI, m/z): 190 ($[M+1]^+$, 29%). **12**: ^{1}H-NMR ($CDCl_3$), δ (ppm): 1.92, 2.01, 2.02, 2.04 (4s, 3H each, N-, O-Ac), 3.77-3.84 (m, 2H), 4.05 (dd, 1H, J=2.0, 11.0 Hz), 4.13 (m, 1H), 4.25 (dd, 1H, J=4.4, 12.5 Hz), 5.08 (m, 2H), 5.11 (s, 2H), 5.43 (t, 1H, J=13.0 Hz), 6.24 (d, 1H, J=8.0 Hz), 7.3 (m, 5H), 7.54 (d, 1H, J=8.2 Hz); ^{13}C-NMR ($CDCl_3$), δ (ppm): 213.8, 172.2, 171.7, 170.6, 170.25, 169.2, 156.4, 136.1, 128.5, 128.24, 80.2, 73.5, 72.7, 67.8, 67.3, 61.7, 53.4, 53.2, 44.4, 23.0, 20.7, 20.6, 20.57; MS (CI, m/z): 538 ($[M+1]^+$, 4.4%). Anal. calcd. for $C_{24}H_{31}N_3O_{11}$: C, 53.63, H, 5.82, N, 7.82; Found: C, 53.70, H, 5.87, N 7.88. **14**: ^{1}H-NMR ($CDCl_3$), δ (ppm): 0.75 (2d, 6H, J=6.8 Hz), 1.31, 1.32(2s, 9H), 1.75 (m, 1H), 1.78 (s, 3H, NAc), 1.89(s, 3H, OAc), 1.90 (s, 3H, OAc), 1.94 (s, 3H, OAc), 2.53 (bs, 1H, NH), 2.9 (d, 1H, J=7.5 Hz), 3.06-3.38 (m, 5H), 3.7-4.2 (m , 6H), 4.9- 5.12 (m, 3H), 6.25 (d, 1H, J=8.9 Hz), 8.1(t, 1H, J=8.5 Hz); MS (CI, m/z): 631([M+1],100%). **17**: MS (FAB, m/z): 1119 (M^+, 2.1%); HRMS (FAB): Found $[M]^+$ 1119.5828, Calcd. for $C_{53}H_{82}N_8O_{18}$: 1119.5825. Anal. calcd. for $C_{53}H_{82}N_8O_{18}$: C, 56.86, H, 7.38, N 10.01; Found: C, 56.44, H, 7.43, N, 9.52.

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