Dear Author,

Any queries or remarks that have arisen during the processing of your manuscript are listed below and highlighted by flags in the proof. Please check your proof carefully and mark all corrections at the appropriate place in the proof (e.g., by using on-screen annotation in the PDF file) or compile them in a separate list.

For correction or revision of any artwork, please consult [http://www.elsevier.com/artworkinstructions](http://www.elsevier.com/artworkinstructions).

**Articles in Special Issues:** Please ensure that the words ‘this issue’ are added (in the list and text) to any references to other articles in this Special Issue.

<table>
<thead>
<tr>
<th>Location in article</th>
<th>Query / remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Queries</td>
<td>Please insert your reply or correction at the corresponding line in the proof</td>
</tr>
</tbody>
</table>

**Uncited references:** References that occur in the reference list but not in the text – please position each reference in the text or delete it from the list.

**Missing references:** References listed below were noted in the text but are missing from the reference list – please make the list complete or remove the references from the text.

---

**Electronic file usage**

Sometimes we are unable to process the electronic file of your article and/or artwork. If this is the case, we have proceeded by:

- [ ] Scanning (parts of) your article
- [ ] Rekeying (parts of) your article
- [ ] Scanning the artwork

Thank you for your assistance.
Synthesis of new glycosyl biuret and urea derivatives as potential glycoenzyme inhibitors
Nóra Felföldi, Marietta Tóth, Evangelia D. Chrysina, Maria-Despoina Charavgi, Kyra-Melinda Alexacou, László Somsák

The deprotected biuret derivatives showed moderate inhibitory effect against rabbit muscle glycogen phosphorylase b and human salivary α-amylase.
Synthesis of new glycosyl biuret and urea derivatives as potential glycoenzyme inhibitors

Nóra Felföldi a, Marietta Tóth a, Evangelia D. Chryssina b, Maria-Despoina Charavgi b, Kyra-Melinda Alexacou b, László Somsák a,*

a Department of Organic Chemistry, University of Debrecen, POB 20, H-4010 Debrecen, Hungary
b Institute of Organic and Pharmaceutical Chemistry, The National Hellenic Research Foundation, 48, Vas. Constantinou Ave. 116 35 Athens, Greece

Article history:
Received 14 July 2009
Received in revised form 11 October 2009
Accepted 20 October 2009
Available online xxxx

Keywords:
Glycosyl urea
Glycosyl biuret
Inhibitor
α-Amylase
Glycogen phosphorylase

1. Introduction

Carbohydrate processing enzymes (glycoenzymes) catalyze the assembly and degradation of vital oligo- and polysaccharides. Discovery of inhibitors of glycoenzymes and revealing their structure–activity relationship (SAR) is a principal trend in the development of carbohydrate-based drugs. During our previous research several inhibitors of glycosidase 2–5 and glycogen phosphorylase 6,7 (GP) enzymes were synthesized and characterized. The first nanomolar glucose-based inhibitor of rabbit muscle GPb (RMGPb) was identified among N-acyl-β-D-glucopyranosyl ureas A (for selected examples see Table 1, entries 1–3) have been investigated so far. Derivatives A exhibited weaker binding to RMGPb in comparison to B. To study the effect of a longer linker of similar composition, synthesis of biuret derivatives C was envisaged. As the series of compounds B investigated so far contained mainly apolar residues R (e.g., methyl, cyclohexyl, (substituted)phenyl and naphthyl), an effort to exploit polar interactions in the β-pocket by substituting sugar rings for R in both B and C was also planned.

© 2009 Elsevier Ltd. All rights reserved.

PhNCO in refluxing toluene in the presence of 1 equiv of H2O, the reaction mixture. When 6 and 1 equiv of PhNH2 were reacted in boiling toluene. Finally, no reaction occurred between 6,7. This unexpected result could be explained by the presence of water and 1 equiv of PhNH2 were reacted in boiling toluene. Finally, heating of 7 in neat PhNCO gave biuret 9. All attempts to avoid the formation of these products by carefully drying the solvents and reactants as well as the use of molecular sieves in the reaction mixtures failed. Structural elucidation of the new biurets 8 and 9 was straightforward by MS and NMR measurements as follows from the selected characteristic data shown in Scheme 1.

Coupling of a glycosylurea and a glycosylisocyanate could give 1,5-bis-glycosyl biuret derivatives. However, the use of commercial OCNCO as a bielectrophilic reagent14,15, and glycosylamines as nucleophiles offered a simpler and shorter synthetic pathway towards such target compounds. Thus, reaction of glycupronosylamine 211 with 0.5 equiv of OCNCO gave cleanly the expected 1,5-bis-glycosyl biuret 12. (Scheme 2). Asymmetric derivatives could also be obtained in two-step, one-pot reactions from 2 by the addition of 1 equiv of OCNCO followed by a second glycosylamine 1016 or 1117,18 to give 14 or 16, respectively. Deacetylation was performed by the Zemplén protocol to result in high yields of biurets 13, 15 and 17.

To obtain N-acyl-β-D-glucopyranosyl ureas with a sugar part in the acyl group the reaction of isocyanate 319 with O-peracetylated anhydro-aldonamide 1819 was investigated first (Scheme 3). When 3 and 18 were reacted in refluxing EtOAc in equimolar amounts the conversion of 18 was 25%, and the expected acylurea 20 could be isolated in 32% yield. Raising the temperature to the boiling point of toluene gave a 56% conversion of 18 and 50% isolated yield for 20. A satisfactory result was achieved by applying 3 in a twofold excess for a full conversion of 18, and the yield of 20 increased to 89%. From a reaction of 3 and O-perbenzoylated anhydro-aldonamide 1920 (molar ratio 2:1) in boiling toluene 22 was obtained in a 98% yield. In each of the above reactions bis-glycu-

copolyranosyl urea 21 was also isolated in various amounts which could be due to the presence of traces of water in the mixtures.21 Attempted deprotection of acyl ureas 20 and 23 was successful under neither basic nor acidic transesterification conditions because cleavage of the N-acyl moiety was faster than removal of the O-acyl-protection groups. Bis-glycupronosyl urea 21 was deprotected under Zemplén conditions to give 2222 in satisfactory yield.

The deprotected compounds were tested for their potency to inhibit rabbit muscle glycogen phosphorylase b activity according to the protocol described earlier,23,24 and the results are summarized in Table 1. Compounds with two sugar moieties attached to the terminal nitrogens of either urea 22 (entry 4) or biurets 13, 15 and 17 (entries 9–11) showed very low inhibition of the enzyme activity. Comparison with the inhibition shown by the phenylbiuret derivative 5 (entry 8) this may reveal that the highly polar sugar residues opposite to the β-D-glucopyranosyl part of the compounds are unfavourable for the binding. Among biurets the β-D-xylopyranosyl derivative 17 proved the most efficient, and this may be in accord with the less polar character of this residue with compounds 13 and 15, respectively. A comparison of the phenyl substituted derivatives (entries 1, 5 and 8) allows to conclude that the acyl urea linker is superior to the urea and the biuret type ones.

Compounds 13 and 22 were also tested against human salivary α-amylase according to the method reported earlier,23 and exhibited inhibition in the low millimolar range (IC50 10.7 and 8.3 mM, respectively).

In conclusion, synthesis of 1-(β-D-glucopyranosyl) biurets with an aromatic and several β-D-glucopyranosyl residues in the 5-position allowed to extend structure–activity relationships of glucose analogue inhibitors of glycogen phosphorylase. Introduction of the highly polar sugar moieties resulted in weak binding. The length of the linker composed of NHCO elements between the β-D-glucopyranosyl and the aromatic parts of the inhibitors proved to be optimal in the acyl urea series.

---

Table 1 Inhibition of rabbit muscle glycogen phosphorylase b (RMGPb) by selected glucose derivatives and the new compounds

<table>
<thead>
<tr>
<th>Entry</th>
<th>Inhibition (µM)</th>
<th>R</th>
<th>Entry</th>
<th>Inhibition (Kₗ) (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₁ 18³</td>
<td>5</td>
<td>4</td>
<td>4.6²</td>
</tr>
<tr>
<td>2</td>
<td>IC₅₀ 350⁷</td>
<td>6</td>
<td>5</td>
<td>15.2⁷</td>
</tr>
<tr>
<td>3</td>
<td>K₅ 5.2⁷</td>
<td>7</td>
<td>0</td>
<td>0.35⁷</td>
</tr>
<tr>
<td>4</td>
<td>IC₅₀ 1209 ± 8</td>
<td>K₅ 725 ± 5</td>
<td>17</td>
<td>987 ± 127</td>
</tr>
</tbody>
</table>

³Kₗ values were calculated for comparison purposes by the Cheng–Prusoff equation:²³ Kₗ = IC₅₀/(1 + [S]/K_m).

---

2. Results and discussion

The synthesis of the protected 1-β-D-glucopyranosyl-5-phenyl biuret 4 was achieved by a reaction of phenylurea with β-D-glucopyranosylisocyanate 3⁴ generated in situ from glycosylamine 2¹¹ obtained by catalytic reduction of glucosylazide 1¹² (Scheme 1). Compound 4 was isolated by crystallization from MeOH, and deprotection was effected by acid-catalyzed transesterification to give 5.

We have also attempted to produce 4 in a somewhat shorter way from β-D-glucosyl urea 6¹³ and PhNCO. In refluxing EtOAc no reaction occurred between 6 and 1.5 equiv of PhNCO. Using the same ratio of the reagents in boiling toluene allowed isolation of 1-β-D-glucosyl-3-phenyl urea 7¹⁹ in 41% yield. Performing the reaction in neat, boiling PhNCO gave compound 7 as well as biuret derivatives 8 and 9 in 4%, 24% and 31% isolated yields, respectively. This unexpected result could be explained by the presence of water in the reaction mixture. When 6 was reacted with 1 equiv of PhNCO in refluxing toluene in the presence of 1 equiv of H₂O, the formation of 7 could be observed. Urea 7 was also formed when 6 and 1 equiv of PhNH₂ were reacted in boiling toluene. Finally,
**Scheme 1.** Reagents and conditions: (a) H2, Raney-Ni, EtOAc, rt; (b) (Cl)3CO, CO, NaHCO3, CH2Cl2, H2O, rt; (c) PhNHNCO2H, toluene, reflux; (d) AcCl, CHCl3–MeOH, rt; (e) PPh3, EtOAc, NH3, CO2, rt; and (f) neat PhNCO, reflux.

**Scheme 2.** Reagents and conditions: (a) OCNCl, Et3N, dry THF, N2 atm, rt; (b) OCNCl, dry THF, N2 atm, –26 °C; (c) 10 or 11, Et3N, dry THF, N2 atm, 0–25 °C; and (d) cat. NaOMe, abs MeOH, rt.

**3. Experimental**

**3.1. General methods**

Melting points were measured in open capillary tubes or on a Koffler hot-stage and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter at rt. NMR spectra were recorded with Bruker 360 (360/90 MHz for 1H/13C) or Bruker 400 (400/100 MHz for 1H/13C) or Avance DRX 500 (500/125 MHz for 1H/13C) spectrometers. Chemical shifts are referenced to internal TMS (1H), or to the residual solvent signals (13C). 1H NMR assignments were established on the basis of gradient enhanced DQF-COSY spectra. Proton chemical shifts and scalar coupling constants were extracted from the resolution enhanced 1D proton spectra. COSY spectra were recorded with 512 × 2 k data points, spectral widths 4000 Hz, number of transients 4 and recycle delay of 1.8 s. Microanalyses were performed on a Carlo–Erba analyser Type 1106. ESIMS were recorded with a Bruker microTOF-Q instrument. TLC was performed on DC-Alurolle Kieselgel 60 F254 (Merck), and the plates were visualized under UV light and by gentle heating.

For column chromatography Kieselgel 60 (Merck, particle size 0.063–0.200 mm) was used. Flasks were flame-dried before performing the reactions. Organic solutions were dried over anhydrous MgSO4, and concentrated under diminished pressure at 40–50 °C (water bath).

**3.2. 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-5-phenyl biuret (4)**

2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosylisocyanate (3) prepared in situ by Ichikawa’s method10 from glucosylamine2 0.6 g (1.73 mmol) was dissolved in toluene (12 mL) and then treated with phenyl urea (0.47 g, 3.46 mmol). The mixture was refluxed and monitored by TLC (2:1 EtOAc–hexane). When the reaction was complete, the solvent was evaporated, and the residue was crystallized from MeOH to give 0.37 g (42%) of 4. Mp: 207–209 °C; [α]D25 –15 (c 1.68, acetone); 1H NMR (CDCl3, 360 MHz) δ (ppm) 9.42 (s, 1H, NH), 7.44–7.12 (m, 6H, Ar, NH), 5.33 (t, 1H, J3,4 = 10.0 Hz, H-3), 5.233 (t, 1H, H-1), 5.10 (t, 1H, J1,2 = 9.5 Hz, H-2), 4.93 (t, 1H, J2,3 = 9.2 Hz, H-2), 4.33 (dd, 1H, J1,2 = 12.6 Hz, H-6), 4.12 (dd, 1H, J5,6 = 2.1 Hz, H-6′), 3.87 (ddd, 1H, J5,6 = 5.0 Hz, H-5′), 2.44 (s, 1H, NH), 2.10, 2.08, 2.05 (s, 12H, 4 × OCOCH3). 13C NMR (CDCl3, 90 MHz) δ (ppm) 170.7, 170.4, 170.0, 169.5 (CO), 155.0, 152.3 (NHCONH), 136.8, 129.4, 129.1, 124.4, 120.5 (Ar), 78.9 (C-1), 73.3, 72.9, 70.0, 68.0 (C-2–C-5), 61.7 (C-6), 20.7, 20.6, 20.56, 20.5 (CH3). ESIMS: [M+Na]+ calcd 532.46,
3.3. 1-(β-D-Glucopyranosyl)-5-phenyl biuret (5)

Biuret 4 (250 mg, 0.49 mmol) was dissolved in a mixture of MeOH and CHCl₃ (1:1). A catalytic amount of AcCl was added and the mixture was stirred at rt. The reaction was monitored by TLC (2:1 EtOAc–hexane). When the reaction was complete, it was neutralized with solid NaHCO₃, and then filtered and the solvent was evaporated. The residue was separated from the solution by column chromatography (9:1 CHCl₃–MeOH to give 162 mg (97%) of 5 as a white powder.

Yield: 36 mg (24%), colourless syrup.

3.4. Reaction of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl urea (6) with phenylisocyanate

Urea 6 (100 mg, 0.26 mmol) was refluxed in neat phenylisocyanate (1 mL). The reaction was monitored by TLC (2:1 EtOAc–hexane). When the reaction was complete, the excess amount of phenylisocyanate was removed by distillation with hexane. The formed precipitate was filtered, dissolved in CHCl₃ and washed with satd aq NaHCO₃. The organic layer was separated, dried and the solvent was evaporated. The residue was separated from the solution by column chromatography (50:1 CHCl₃–acetone) to give, in the order of elution, compounds 8 and 9 (70% (4%)).

3.4.1. 3-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-1,5-diphenyl biuret (8)

Yield: 36 mg (24%), colourless syrup, R₉ = 0.89 (25:1 CHCl₃–acetone) [λ]D +0.2 (c 1.71, DMSO), ¹H NMR (CDCl₃, 360 MHz) δ (ppm) 10.73 (s, 1H, N(CONHCH₂H₂)), 8.75 (s, 1H, N(CONHCH₂H₂)), 7.51–7.09 (m, 10H, Ar), 6.32 (d, 1H, J₃,4 = 10.0 Hz, H-1), 5.66 (t, 1H, J₁,₂ = 9.5 Hz, H-3), 5.39 (t, 1H, J₃,4 = 9.5 Hz, H-4), 5.16 (t, 1H, J₃,4 = 10.0 Hz, H-2), 4.52 (dd, 1H, J₃,4 = 12.6 Hz, H-6), 4.18 (dd, 1H, J₃,4 = 2.1 Hz, H-6), 4.05 (dd, 1H, J₃,4 = 3.7 Hz, H-5), 2.13, 2.06, 2.04, 2.00 (s, 12H, 4×OCOCH₃), ¹³C NMR (CDCl₃ + DMSO-d₆, 90 MHz) δ (ppm) 168.6, 167.9, 167.2, 167.7 (C0), 151.8, 151.1 (NCON), 138.3–149.0 (Ar), 160.9 (C-1), 73.1, 71.4, 66.3, 66.1 (C-2–C-5), 60.1 (C-6), 19.2, 19.1, 19.0, 18.9 (CH₂). ESIMS: [M+Na]+ calcd for C₂₈H₃₁N₃O₁₁ (585.57): 608.56, found: 608.19.

Scheme 3.
3.6. General procedure I for the synthesis of 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-5-(per-O-acetyl-β-D-glycosyranosyl)biurets 14 and 16

Glucosylamine \(^{21}\) (100 mg, 0.29 mmol) was dissolved in dry THF (2 mL), and some freshly heated molecular sieves were added. The mixture was cooled to \(-20^\circ\text{C}\), OCNCl (23 \(\mu\L\), 0.29 mmol) was added, and stirred at \(-26^\circ\text{C}\) under nitrogen atmosphere for a day. Then a solution of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamine \(^{16}\) (10 mg, 0.29 mmol) or 2,3,5-tri-O-acetyl-β-D-xylopyranosylamine \(^{17,18}\) (11 mg, 0.29 mmol) in dry THF (2 mL) and Et\(_3\)N (40 \(\mu\L\), 0.29 mmol) were added, and the mixture was allowed to warm up to rt. When the reaction was complete (TLC, 10:1 EtOAc–hexane) the insoluble materials were filtered off with suction, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (7:1 EtOAc–hexane) the insoluble materials were filtered off with suction, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (7:1 EtOAc–hexane).

3.6.1. 1-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-5-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)biuret (14)

Prepared according to General procedure I (Section 3.6) from glucosylamine 2 (100 mg, 0.29 mmol) and galactosylamine 10 (100 mg, 0.29 mmol). Yield: 183 mg (83%) colourless syrup.

3.6.2. 1-(2,3,4,6-Tetra-O-acetyl-β-D-xylopyranosyl)-5-(2,3,5-tri-O-acetyl-β-D-xylopyranosyl)biuret (16)

Prepared according to General procedure I (Section 3.6) from glucosylamine 2 (100 mg, 0.29 mmol) and xylosylamine 11 (80 mg, 0.29 mmol). Yield: 171 mg (86%) 

3.7. General procedure II for the removal of O-acetyl protecting groups

An O-peracetylated compound (100 mg) was dissolved in dry MeOH (1 mL), and a solution of NaOMe (1 M in MeOH) was added to the solution in a catalytic amount. The reaction mixture was kept at rt. When the reaction was complete (TLC, 7:3 CH\(_2\)Cl\(_2\)–MeOH) the solution was neutralized with a cation exchange resin Amberlyst 15 (H\(^+\) form). Filtration and removal of the solvent resulted in the corresponding deacetylated sugar derivatives.

3.7.1. 1,5-Bis-(β-D-glucopyranosyl)biuret (13)

Prepared according to General procedure II (Section 3.7) from biuret 12 (100 mg, 0.13 mmol). Yield: 54 mg (96%) colourless syrup.

3.7.2. 1-(β-D-Galactopyranosyl)-5-(β-D-glucopyranosyl)biuret (15)

Prepared according to General procedure II (Section 3.7) from biuret 14 (100 mg, 0.13 mmol). Yield: 53 mg (98%) colourless syrup.

3.7.3. 1-(β-D-Glucopyranosyl)-5-(β-D-xylopyranosyl)biuret (17)

Prepared according to General procedure II (Section 3.7) from biuret 16 (100 mg, 0.14 mmol). Yield: 55 mg (96%) colourless syrup.

3.8. 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)urea (20)

Prepared according to General procedure I (Section 3.6) from glucosylamine 2 (100 mg, 0.29 mmol) and xylosylamine 11 (80 mg, 0.29 mmol). Yield: 171 mg (86%) 

3.9. Preparation of glycopyranosyl)biurets 14 and 16

Glucosylamine \(^{21}\) (100 mg, 0.29 mmol) was dissolved in dry THF (2 mL), and some freshly heated molecular sieves were added. The mixture was cooled to \(-20^\circ\text{C}\), OCNCl (23 \(\mu\L\), 0.29 mmol) was added, and stirred at \(-26^\circ\text{C}\) under nitrogen atmosphere for a day. Then a solution of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamine \(^{16}\) (10 mg, 0.29 mmol) or 2,3,5-tri-O-acetyl-β-D-xylopyranosylamine \(^{17,18}\) (11 mg, 0.29 mmol) in dry THF (2 mL) and Et\(_3\)N (40 \(\mu\L\), 0.29 mmol) were added, and the mixture was allowed to warm up to rt. When the reaction was complete (TLC, 10:1 EtOAc–hexane) the insoluble materials were filtered off with suction, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (7:1 EtOAc–hexane) the insoluble materials were filtered off with suction, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (7:1 EtOAc–hexane)
3.9. 3,13-Bis-(β-ᴅ-glucopyranosyl)urea (22)

Prepared according to General procedure II (Section 3.7) from urea 21 (190 mg, 0.26 mmol). Yield 80 mg (79%) amorphous solid. Lit.27 Mp: 207 °C (dec.). \( R_t = 0.45 \) (1:3 CHCl₃-methanol); \( J^a_{2} \) = 23 (c 0.59, DMSO). \( J^b_{2} \) = 32.8 (c 2, water); \( 1^H \) NMR (D₂O): 4.86 (d, 1H, \( J = 9.2, 9.7 \) Hz in each, H-2, H-3, H-4), 3.51–3.48 (m, 1H, H-5).

\( ^{13}C \) NMR (D₂O); \( \delta \) (ppm) 159.6 (CO), 81.5 (C-1), 77.9, 77.2, 72.6, 70.0 (C-2 to C-6), 61.3 (C-6).

3.10. 1-(2,3,4,6-Tetra-β-ᴅ-glucopyranosyl)-3-(2,3,4,6-tetra-β-ᴅ-glucopyranosylanhydroxy)benzylamine (23)

C-(2,3,4,6-Tetra-O-benzoyl-β-ᴅ-glucopyranosyl)formamide20 (19, 54 mg, 0.086 mmol) was dissolved in dry toluene (1 mL), and some molecular sieves were added followed by crystalline isocyanate 310 (64 mg, 0.172 mmol), and the reaction mixture was heated to reflux temperature. When the reaction was complete (TLC, 5:1 EtOAc–hexane) the molecular sieves were filtered off (748.64): C, 48.13; H, 5.39; N, 3.74. Found: C, 48.20; H, 5.43; N, 3.79.

\( ^{13}C \) NMR (D₂O): \( \delta \) (ppm) 20.7, 20.6, 20.5 (CH₃), 152.7, 151.7, 151.6 (C-6-Gal), 73.1, 72.8, 69.8, 69.6, 68.6, 68.1 (2 × C-2 to C-5), 62.8, 61.6 (2 × C-6), 20.5, 20.4 (CH₃), Anal. Calcd for C₁₀H₁₄N₂O₂ (996.92): C, 60.24; H, 4.85; N, 2.81. Found: C, 60.19; H, 4.90; N, 2.89.

**Acknowledgements**

This work was supported by the Hungarian Scientific Research Fund (OTKA 45927). This work was supported by the EU Marie Curie Early Stage Training (EST) Contract No. MEST-CT-020575 a Marie Curie Host Fellowships for the Transfer of Knowledge (ToK) Contract No. MTKD-CT-2006-042776. The authors thank **Professor K. E. Kövér** and Mr. M. Herczeg for advice on and help with 2D NMR spectra, and Dr. Gy. Gyémánt for performing the α-amylase assay.

**References**