Synthesis of glucose derivatives modified at the 4-OH as potential chain-terminators of cellulose biosynthesis; herbicidal activity of simple monosaccharide derivatives†

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A series of D-glucose derivatives that have been modified at C-4 were synthesised from D-galactose as potential chain terminators of cellulose biosynthesis. Two compounds displayed herbicidal activity in pre-emergence tests and in addition a cell expansion assay at higher concentrations revealed symptomology of a third compound that was indicative of inhibition of cellulose biosynthesis.

Introduction

Increasing global food output becomes a key objective as the population of the world itself continues to rise.[1] However, achieving this goal by increasing the proportion of the planet's surface used for agricultural purposes, for example by the clearing of native forests, would not only be catastrophic from an immediate ecological perspective, but may have serious long term consequences for the sustainability of the biosphere.[2] In future, continued increases in agricultural productivity from the currently farmed areas of the planet will therefore be necessary in order to feed an increased population. One of several undertakings that will facilitate this objective is the development of new herbicides to substantially increase agricultural output from currently farmed areas. However not all herbicides are environmentally benign, and their increased and indiscriminate use could in certain cases have serious environmental and health effects. Future herbicides should therefore be as safe as possible.

Inhibition of cellulose biosynthesis[3] represents a potentially safe herbicidal mode of action, which should in principle be non-toxic to animals, fish, and other wildlife. Several chemically diverse classes of herbicidal cellulose biosynthesis inhibitors[4,5] are known, which include compounds such as dichlobenil and isoxaben. The specific molecular targets have not yet been fully characterised for these herbicides, but it is unlikely that they act by competitive inhibition[6] of cellulose synthase enzymes. Cellulose synthases, encoded for by a family of genes called *CesA*,[7] contain motifs characteristic of family 2[8] glycosyl transferase enzymes, and use UDP-glucose as the donor substrate to catalyse the addition of glucose units to growing β(1–4) glucan chains. The design and synthesis of competitive inhibitors of glycosyl transferases that are potent enough and posses the correct pharmacokinetic properties to display significant biological activity *in vivo* is fraught with difficulty, since such inhibitors are required to mimic a reaction transition state that effectively involves three distinct species—the glycosyl acceptor, the nucleoside di-phosphate, and the glycosyl donor. The fact that none of the known inhibitors of cellulose biosynthesis have yet been identified as competitive inhibitors of cellulose synthases is therefore unsurprising.

An alternative strategy to inhibition of cellulose biosynthesis may prove useful, which would be complementary to the different modes of action of other cellulose biosynthesis inhibitors. Such an approach would be to affect chain termination of cellulose biosynthesis using glucose derivatives that have been modified at the hydroxyl group at the 4-position,[9] which is where subsequent glucose units would be added to the growing oligosaccharide chain. Chain-termination processes have found widespread use as a means of DNA sequencing,[10] and as the basis of several anti-viral therapies currently in clinical use.[11] Moreover chain termination has previously been implicated in the biological effects of some modified monosaccharide derivatives on mammalian glycoconjugate[12] and glycosoaminoglycan biosynthesis.[13] More recently attempts to develop both new anti-fungal[14] and anti-mycobacterial agents[15] by the use of a chain termination approach have been reported, with varying degrees of success.

Cellulose is comprised of 36 parallel β(1–4) glucan chains, consisting of between 8000 and 15 000 repeating monosaccharide units. Although the precise details of cellulose biosynthesis are still quite poorly understood[16] it is known that the β(1–4) glucan chains, which are the constituents of cellulose fibrils, are assembled stepwise by large complexes of cellulose synthases by transfer of glucose residues to growing oligomeric chains. Potential chain terminators of this process are therefore D-glucose residues in which the 4-OH has been modified; if such materials are processed by a cellulose synthase then their transfer to the terminus of a growing β(1–4) glucan chain will result in a chain termination step since the required 4-OH at which subsequent units would be added will now be lacking. Alternatively glucose derivatives modified at the 4-position could act as competitive inhibitors of cellulose synthase enzymes, or additionally interfere with cellulose formation in another manner.

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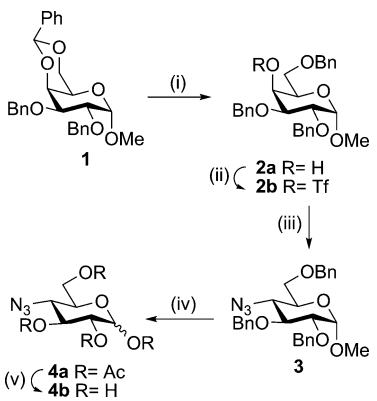
In order to investigate the potential for simple monosaccharide derivatives to display herbicidal activity a variety of glucose derivatives modified at the 4-hydroxyl were synthesised. These materials were screened for potential herbicidal activity in pre- and post-emergence assays, and in certain cases plant cell morphology was also investigated to elucidate if any compounds produced particular cellular effects that were indicative of inhibition of cellulose biosynthesis.

Results and discussion

Synthesis

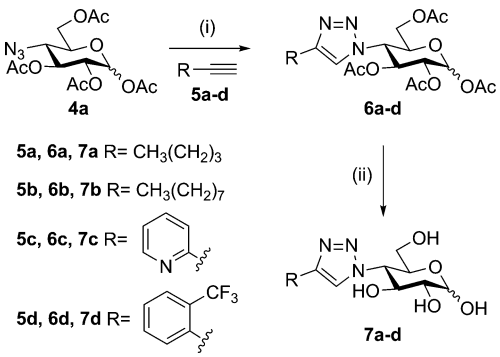
Replacement of the 4-hydroxyl group of glucose was envisaged by substitution with azide, which had the attraction that this functional group could be further elaborated into a variety of other derivatives by click chemistry,[17] or amide synthesis. In order to probe chemical space in the search for compounds that may either be processed by cellulose synthases or competitively inhibit them, two alkyl derivatives with different chain lengths and two aromatic derivatives were targeted. The decision to install hydrophobic residues at C-4, whilst perhaps appearing counter-intuitive, would have the advantage of reducing compound polarity and thus of improving the ability of de-protected compounds to penetrate intracellularly.

Introduction of nitrogen at C-4 would necessitate an inversion of configuration and so a *galacto* configured starting material was required. Selective access to the 4-OH of a *galacto* monosaccharide derivative was achieved by regioselective reductive ring-opening of the 4,6-benzylidene acetal of the methyl pyranoside **1**,[18] which was achieved by treatment with sodium cyanoborohydride and HCl in ether.[11] Reaction of the secondary alcohol **2a**[19] with triflic anhydride and pyridine in dichloromethane gave the triflate **2b**, which was immediately reacted with sodium azide in DMF to give the *gluco* configured azide **3**[20] (Scheme 1). Exhaustive acetolysis of the methyl pyranoside **3** with a mixture of sulfuric acid, acetic anhydride, and acetic acid then yielded the tetra-acetate **4a**,[21] as a mixture of anomers. Tetraacetate **4a** acted as a divergent intermediate for the synthesis of a variety of protected and deprotected triazoles and amides in which structural variation was introduced at the 4-position. Additionally removal of the acetate protecting groups yielded 4-azido glucose **4b**,[9] which was also screened for herbicidal activity.



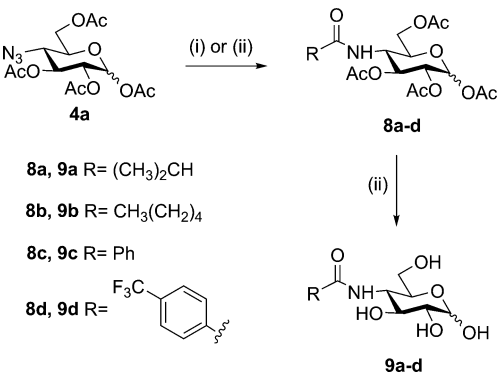
Scheme 1 *Reagents and conditions:* (i) $NaBH_3CN$, HCl, THF, 0 °C to rt, 83%; (ii) Tf_2O, pyridine; (iii) NaN_3, DMF, rt; 84% over two steps; (iv) H_2SO_4, Ac_2O, AcOH, rt, 88%; (v) NaOMe, MeOH, rt, quant.

Conversion of the peracetylated azide **4a** into a selection of triazoles was undertaken by the use of the modified Huisgen 1,3-dipolar cycloaddition in which azide **4a** was reacted with a selection of alkynes **5a–d** in the presence of a Cu(I) salt.[22,23] Cu(I) was generated *in situ* by the addition of sodium ascorbate to a solution of $CuSO_4$ and the mixture of azide and alkyne was heated to 40 °C in a 1 : 1 mixture of water and *tert*-butanol.[24] Reactions proceeded smoothly and the desired triazoles **6a–d** were produced in good to excellent yield (83–91%, Scheme 2). Finally, in order to assess any herbicidal activity of a series of fully deprotected derivatives, the acetates were removed by treatment of the triazoles **6a–d** with a solution of sodium methoxide in methanol, yielding the corresponding polyols **7a–d** in quantitative yield.



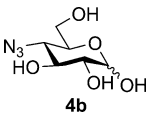
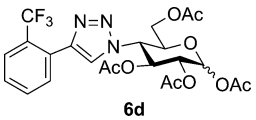
Scheme 2 *Reagents and conditions:* (i) **5a–d**, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, ^{t}BuOH, H_2O, 40 °C; **6a**, 91%, **6b**, 86%, **6c**, 83%, **6d**, 84%; (ii) NaOMe, MeOH, quant.

In order to avoid potential complications of acetyl migration and the formation of acetamide side-products, conversion of the azide **4a** into a series of amides was undertaken *via* a direct Staudinger ligation using the appropriate acid chloride[25] (Scheme 3). An initial reaction of azide **4a** with isobutyryl chloride and triphenylphosphine produced the corresponding amide **8a** in low yield, and additionally this was difficult to separate from the triphenylphosphine oxide by-product. However the use of tri-*n*-butylphosphine as an alternative was found to be beneficial; reaction of **4a** with isobutyryl chloride and *n*-Bu_3P in dichloromethane at reflux resulted in production of the corresponding amide **8a**



Scheme 3 *Reagents and conditions:* (i) **4a**, RCOCl, *n*-Bu_3P, CH_2Cl_2, reflux; **8a**, 37%, **8d**, 61%; (ii) **4a**, RCO_2Cl, Ph_3P, CH_2Cl_2, reflux; **8b**, 33%, **8c**, 59%; (iii) NaOMe, MeOH, quant.

Table 1 Pre- and post-emergence test results on four different weed species

Compound[a]	Rate (g/ha)	Post-emergence test					Pre-emergence test				
		AMARE	DIGSA	ALOMY	CHEAL	Pt type[b]	AMARE	DIGSA	ALOMY	CHEAL	Pt type[b]
 **4b**	1000	0	0	0	0	—	70	90	20	70	ST
 **6d**	1000	0	0	0	0	—	40	30	70	50	ST

[a] Test compounds were sprayed on plants at 2500 L/ha after one-day cultivation (pre-emergence) and after 8 days cultivation (post-emergence). Controls of unsprayed plants, and plants sprayed with a known herbicide were also cultivated in order to provide a comparison with which to gauge results. After an incubation period of 13 days results were evaluated as percentage herbicide effect (100% = total damage to plant; 0% = no damage to plant). [b] The symptoms recorded (Pt type) were Stunt (ST).

in an improved, but still moderate yield (37%). Similar reaction using *n*-Bu_3P and 4-trifluoromethylbenzoyl chloride produced the corresponding amide **8d** in a more acceptable 61% yield. Although the use of tri-*n*-butylphosphine was beneficial in these two cases, particularly with respect to product purification, it was not found to be an absolute requirement for the success of the reaction. For example treatment of both hexanoyl chloride and benzoyl chloride with **4a** and triphenyl phosphine in refluxing dichloromethane gave the corresponding amides **8b** and **8c** in moderate yields (33% and 59% respectively). Variation of other parameters was also investigated. In the case of the synthesis of **8d** neither changing the reaction solvent to toluene, nor the corresponding increase in reaction temperature achieved at reflux did little to alter either the rate of reaction or yield of product. For the synthesis of benzamide **8c** a Staudinger reaction of **4a** with benzoic acid[26] was also investigated to provide direct comparison of the reactivity of an acid and an acid chloride in the Staudinger process. Interestingly reaction of azide **4a** with triphenylphosphine and benzoic acid in refluxing dichloromethane did not result in any appreciable reaction. Finally with the selection of desired amides **8a–d** in hand, removal of the acetate protecting groups was achieved by treatment with a solution of sodium methoxide in methanol, yielding the corresponding tetraols **9a–d** in quantitative yields (Scheme 3).

Herbicidal screening

Potential herbicidal activity of the putative chain termination compounds **4a**,**b**, **6a–d**, **7a–d**, **8a–d**, **9a–d** was assessed using two types of assay. Firstly, a series of pre-emergence and post-emergence tests were performed on two broadleaf weeds: *Amaranthus retroflexus* (AMARE) and *Chenopodium album* (CHEAL) and two grass weeds: *Alopecurus myosuroides* (ALOMY) and *Digitaria sanguinalis* (DIGSA). Plants for the pre-emergence test were grown in sand, and plants for the post emergence test were grown in sandy loam soil. Damage to the plant was qualified as stunting of emerging plant growth, chlorosis of leaves, or complete inhibition of growth and recorded as percentage herbicide effect. Pre-emergence activity was recorded in two compounds at application rates of 1000 grams per hectare (g/ha). Deprotected 4-azido glucose **4b** showed stunting and almost complete inhibition of growth of DIGSA (rating: 90%), and also significant effects on both AMARE (rating: 70%) and CHEAL (rating: 70%) (Table 1). The protected trifluorophenyl triazole **6d** also showed weaker activity, though interestingly was most active against ALOMY (rating: 70%) (Table 1). However neither of these compounds displayed any activity in the post emergence tests.[27] None of the other compounds tested displayed significant herbicidal activity in either the pre- or the post-emergence studies.

Secondly a cell expansion assay on bright yellow 2 (BY2) tobacco cells was undertaken with a selection of the putative chain termination compounds, which were chosen as the acetylated and deprotected pairs and **8b/9b**, **8c/9c**, and **6c/7c**. Several control experiments were also carried out on BY2 cells including monitoring the effects of DMSO alone, and the actions of a known thiazolidinone herbicide **10**[28] and Oryzalin **11**,[29] a standard cellulose biosynthesis inhibitor and a standard microtubule inhibitor respectively. Treatment of the BY2 cells with Oryzalin caused round swelling typical of microtubule inhibition which occurs as the internal scaffolding of cells is disrupted. In contrast treatment with the thiazolidinone caused large and non-uniform swelling and a high degree of clumping, which presumably occurs to compensate for the lack of cellulose that provides the cells' scaffolding, and is typical of cellulose biosynthesis inhibition. Whilst the majority of the tested compounds did not display any effect at concentrations up to 500 ppm, the pyridinyl acetylated triazole **6c** showed toxicity at 500 ppm, and cellulose biosynthesis type symptomatology at 167 ppm (Fig. 1); cells showed large non-uniform clumping as was observed in the assay with thiazolidinone **10**, suggesting that **6c** acted *via* inhibition of cellulose biosynthesis, rather than by microtubule inhibition or another mode of action.

Finally the cell expansion assay on BY2 tobacco cells was repeated with the two compounds which had proved active in the pre-emergence test, namely azide **4b** and trifluoromethylphenyl triazole **6d**. Both of these compounds did display cell toxicity, though only at the highest concentration investigated (500 ppm). However neither displayed symptomology diagnostic for either inhibition of cellulose biosynthesis or for de-polymerisation of

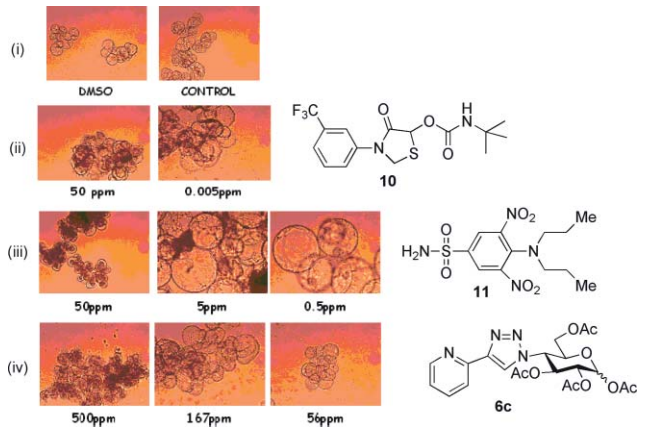


Fig. 1 Cell expansion studies of effect of compounds on tobacco BY2 cells; (i) DMSO alone, and control; (ii) thiazolidinone **10**; (iii) Oryzalin **11**; (iv) acetylated pyridinyl triazole **6c**.

microtubules, indicating a different mode of action against BY2 cells in these cases.

In conclusion a series of D-glucose derivatives that have been modified at C-4 have been synthesised as potential inhibitors of cellulose biosynthesis. Either click chemistry or Staudinger reaction allowed the rapid, if un-optimised, synthesis of a small series of compounds for herbicidal screening. The herbicidal activity of both 4-azido glucose **4b** and the trifluoromethylphenyl triazole **6d** in pre-emergence tests demonstrated for the first time that simple monosaccharide derivatives can indeed display herbicidal activity, though cell expansion assays indicated that their mode of action, at least on BY2 cells, was probably not by inhibition of cellulose biosynthesis. However at higher concentrations a similar cell expansion assay indicated that another member of the set, pyridyl triazole **6c**, not only displayed toxicity to plant cells but did indeed give symptomology consistent with inhibition of cellulose biosynthesis. Despite the herbicidal activity of 4-azido glucose **4b**, a caveat to these findings is that triazoles **6c** and **6d** do contain extended functionality which may on its own be responsible for their observed herbicidal activity; in these cases the possibility that the carbohydrate portion of these molecules acts largely as a bystander cannot as yet be ruled out.[30] Further investigations into the mode of action of these compounds and the synthesis and screening of further monosaccharide derivatives as potential inhibitors of cellulose biosynthesis or other plant-specific pathways are currently underway, and their results will be reported in due course.

Experimental

General

Melting points were recorded on a Kofler hot block and are uncorrected. Proton and carbon nuclear magnetic resonance (δ_H, δ_C) spectra were recorded on Bruker DPX 250 (250 MHz), Bruker DPX 400 (400 MHz), Bruker DQX 400 (400 MHz), Bruker AVC 500 (500 MHz) or Bruker AMX 500 (500 MHz) spectrometers. All chemical shifts are quoted on the δ-scale in ppm using residual solvent as an internal standard. Low-resolution and high-resolution mass spectra were recorded on a Waters 31 LCT Premier XE spectrometer with electrospray ionisation (ESI+ or ESI–) and on a Bruker micrOTOF (ESI) spectrometer, respectively. m/z values are reported in Daltons and are followed by their percentage abundance in parentheses. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g/100 mL. Microanalyses were performed by the Inorganic Chemistry Laboratory Elemental Analysis service, Oxford University, UK. Thin layer chromatography (t.l.c.) was carried out on Merck Kieselgel $60F_{254}$ pre-coated glass-backed plates. Visualisation of the plates was achieved using a u.v. lamp (λ_{max} = 254 or 365 nm), and/or ammonium molybdate (5% in 2 M sulfuric acid), or sulfuric acid (5% in ethanol). Flash column chromatography was carried out using Sorbsil C60 40/60 silica. Dichloromethane was distilled from calcium hydride, or dried on an alumina column. Anhydrous THF, DMF, pyridine, methanol and toluene were purchased from Fluka over molecular sieves. 'Petrol' refers to the fraction of light petrol ether boiling in the range of 40–60 °C. Compounds **2a**,[19] **3**,[20] **4a**[21] and **4b**[9] were prepared using the routes shown in Scheme 1, and exhibited spectroscopic data in agreement with those reported previously.

4-Butyl-1-(1′,2′,3′,6′-tetra-*O*-acetyl-4′-deoxy-D-glucopyranosyl)-1,2,3-triazole (6a). Azide **4a** (139 mg, 0.37 mmol) and 1-hexyne **5a** (43 μL, 2.3 mmol) were suspended in a 1 : 1 mixture of *t*-BuOH and distilled water (1.6 mL). Sodium L-ascorbate (30 mg, 0.15 mmol), and $CuSO_4 \cdot 5H_2O$ (19 mg, 0.08 mmol) were then added. The resulting mixture was stirred at 40 °C for 30 min after which t.l.c. (petrol–ethyl acetate, 3 : 2) indicated formation of a single product (R_f 0.3) and complete consumption of starting material (R_f 0.6). The resulting mixture was diluted with ethyl acetate (10 mL), washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol–ethyl acetate, 1 : 1) to afford the *n*-butyl triazole **6a** (155 mg, 91%), as a clear oil; ν_{max} (KBr) 3071 (m, C=CH), 1749 (br, C=O), 1552 (s, C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) (α : β, 6 : 1), 0.93 (0.5H, t, *J* 7.17 Hz, CH_3-β), 0.93 (3H, t, *J* 7.25 Hz, CH_3-α), 1.24–1.28 (0.3H, m, CH_2-β), 1.32–1.39 (2H, m, CH_2-α), 1.60–1.68 (2.3H, m, CH_2-α, CH_2-β), 1.86 (0.5H, s, $COCH_3$-β), 1.88 (3H, s, $COCH_3$-α), 2.03 (3H, s, $COCH_3$-α), 2.05 (0.5H, s, $COCH_3$-β), 2.06 (0.5H, s, $COCH_3$-β), 2.07 (3H, s, $COCH_3$-α), 2.15 (0.5H, s, $COCH_3$-β), 2.26 (3H, s, $COCH_3$-α), 2.70–2.73 (2.3H, m, CH_2-α, CH_2-β), 3.78 (1H, dd, $J_{5,6}$ 3.5 Hz, $J_{6,6'}$ 12.6 Hz, H-6′α), 3.81–3.84 (0.2H, m, H-6′β), 4.12–4.14 (0.2H, m, H-6″β), 4.17 (1H, dd, $J_{5,6'}$ 2.0 Hz, $J_{6,6'}$ 12.3 Hz, H-6″α), 4.44 (0.2H, d at, *J* 3.8 Hz, *J* 10.2 Hz, H-5′β), 4.68–4.73 (2.2H, m, H-4′α, H-4′β, H-5′α), 5.17–5.20 (1.2H, m, H-2′α, H-2′β), 5.65–5.70 (0.2H, m, H-3′β), 5.87 (1H, at, *J* 9.9 Hz, H-3′α), 5.90 (0.2H, d, $J_{1,2}$ 8.2 Hz, H-1′β), 6.42 (1H, d, $J_{1,2}$ 3.8 Hz, H-1′α), 7.26 (0.2H, s, C=CH-β), 7.29 (1H, s, C=CH-α); δ_C (100.6 MHz, $CDCl_3$) α (major) anomer only: 13.8 (CH_3) 20.5, 20.6, 20.7, 20.8 ($COCH_3$), 21.2, 23.4, 31.7, (CH_2), 59.6 (C-4′), 60.2 (C-6′) 70.0 (C-3′), 70.1, 70.4 (C-2′, C-5′), 95.5 (C-1′), 120.7 (C=*C*H), 148.8 (*C*=CH), 168.9, 168.9, 169.8, 170.2 (*C*OCH$_3$); m/z (ES^+) 911 (2M + H^+, 100), 478 (M + Na^+, 5), 456 (M + H^+, 50%); HRMS (ES^+) Calcd. for $C_{20}H_{29}N_3O_9$ (MH^+) 456.1977. Found 456.1972.

4-Octyl-1-(1′,2′,3′,6′-tetra-*O*-acetyl-4′-deoxy-D-glucopyranosyl)-1,2,3-triazole (6b). Azide **4a** (225 mg, 0.60 mmol) and 1-decyne **5b** (110 μL, 0.60 mmol), were suspended in a mixture of 1 : 1 *t*-BuOH and distilled water (2.4 mL). Sodium L-ascorbate (48 mg,

0.24 mmol), and $CuSO_4 \cdot 5H_2O$ (30 mg, 0.12 mmol) were then added. The resulting mixture was stirred at 40 °C for 1 h after which t.l.c. (petrol–ethyl acetate, 3 : 2) indicated formation of a single product (R_f 0.4) and complete consumption of starting material (R_f 0.6). The resulting mixture was diluted with ethyl acetate (10 mL), washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography (petrol–ethyl acetate, 1 : 1) to afford the octyl triazole **6b** (266 mg, 86%), as a colourless waxy solid; ν_{max} (thin film) 3065 (m, C=C-H), 1744 (br, C=O), 1552 (m, C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) (α : β, 6 : 1), 0.86–0.89 (3.5H, m, CH_3-α, CH_3-β), 1.19–1.32 (11.7H, m, 5 × CH_2-α, 5 × CH_2-β), 1.62–1.66 (2.3H, m, CH_2-α, CH_2-β), 1.86 (0.5H, s, $COCH_3$-β), 1.87 (3H, s, $COCH_3$-α), 2.03 (3H, s, $COCH_3$-α), 2.04 (0.5H, s, $COCH_3$-β), 2.05 (0.5H, s, $COCH_3$-β), 2.07 (3H, s, $COCH_3$-α), 2.14 (0.5H, s, $COCH_3$-β), 2.25 (3H, s, $COCH_3$-α), 2.67–2.71 (2.3H, m, CH_2-α, CH_2-β), 3.77 (1H, dd, $J_{5,6}$ 3.1 Hz, $J_{6,6'}$ 12.4 Hz, H-6′α), 3.81 (0.2H, dd, $J_{5,6'}$ 4.1 Hz, $J_{6,6'}$ 12.4 Hz, H-6′β), 4.14 (0.2H, dd, $J_{5,6'}$ 2.7 Hz, $J_{6,6'}$ 12.3 Hz, H-6″β), 4.17 (1H, dd, $J_{5,6'}$ 1.9 Hz, $J_{6,6'}$ 12.6 Hz, H-6″α), 4.44–4.48 (0.2H, m, H-5′β), 4.66–4.68 (0.2H, m, H-4′β), 4.70–4.72 (2H, m, H-4′α, H-5′α), 5.17–5.23 (1.2H, m, H-2′α, H-2′β), 5.67 (0.2H, at, *J* 9.7 Hz, H-3′β), 5.84–5.91 (1.2H, m, H-3′α, H-1′β), 6.42 (1H, d, $J_{1,2}$ 3.8 Hz, H-1′α), 7.26 (0.2H, s, C=C*H*-β), 7.29 (1H, s, C=C*H*-α); δ_C (100.6 MHz, $CDCl_3$) α (major) anomer: 14.1 (2 × CH_3), 20.2, 20.4, 20.6, 21.0 ($CO\mathit{C}H_3$), 22.6, 25.5, 29.1, 29.2, 29.3, 29.3, 31.8 (CH_2), 59.6 (C-4′), 61.6 (C-6′), 69.1 (C-3′), 69.6 (C-2′), 69.8 (C-5′), 89.1 (C-1′), 120.6 (C=*C*H), 148.7 (*C*=CH), 168.8, 168.8, 169.8, 170.2 ($\mathit{C}OCH_3$); *m/z* (ES^+) 534 (M+ Na^+, 90), 512 (M + H^+, 60%); HRMS (ES^+) Calcd. for $C_{24}H_{37}N_3O_9$ (MNa^+) 534.2422. Found 534.2421. Found C, 56.54; H, 7.35; N, 8.21. $C_{24}H_{37}N_3O_9$ requires C, 56.35; H, 7.29; N, 8.21%.

4-Pyridin-2-yl-1-(1′,2′,3′,6′-tetra-*O*-acetyl-4′-deoxy-D-glucopyranosyl)-1,2,3-triazole (6c). Azide **4a** (180 mg, 0.48 mmol) and 2-ethynyl pyridine **5c** (59 μL, 0.48 mmol) were suspended in a 1 : 1 mixture of *t*-BuOH and distilled water (2 mL). Sodium L-ascorbate (38 mg, 0.19 mmol), and $CuSO_4 \cdot 5H_2O$ (24 mg, 0.1 mmol) were then added. The resulting mixture was stirred at 40 °C for 1 h after which t.l.c. (petrol–ethyl acetate, 1 : 1) indicated formation of a single product (R_f 0.2) and complete consumption of starting material (R_f 0.7). The resulting mixture was diluted with ethyl acetate (10 mL), washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography (petrol–ethyl acetate, 1 : 1) to afford the pyridyl triazole **6c** (191 mg, 83%), as a colourless foam. Recrystallisation from hot absolute ethanol gave pure α-anomer as colourless crystals; mp 188–189 °C; $[\alpha]_D^{25}$ +43.7 (*c*, 0.75 in $CHCl_3$); ν_{max} (KBr) 3071 (m, C=C-H), 1749 (br, C=O), 1552 (s, C=N) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.89 (3H, s, $COCH_3$), 2.03 (3H, s, $COCH_3$), 2.06 (3H, s, $COCH_3$), 2.27 (3H, s, $COCH_3$), 3.79 (1H, dd, $J_{5,6}$ 3.4 Hz, $J_{6,6'}$ 12.7 Hz, H-6′), 4.23 (1H, dd, $J_{5,6'}$ 2.4 Hz, $J_{6,6'}$ 12.7 Hz, H-6″), 4.77–4.87 (2H, m, H-4′, H-5′), 5.23 (1H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 10.0 Hz, H-2′), 5.96 (1H, at, *J* 10.0 Hz, H-3′), 6.44 (1H, d, *J* 3.6 Hz, H-1′), 7.24–7.28 (1H, m, ArH), 7.79 (1H, m, ArH), 8.17–8.18 (1H, m, ArH), 8.21 (1H, s, C=CH), 8.57–8.59 (1H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 20.2, 20.4, 20.6, 20.9 (CH_3), 59.9 (C-4′), 61.5 (C-6′), 69.5 (C-3′), 69.6 (C-2′), 69.8 (C-5′), 89.1 (C-1′), 120.4, 122.1, 123.3, 137.0 (ArCH), 148.6, 149.4, 149.5 (ArCH, 2 × ArC), 168.8, 169.0, 169.8, 170.1 ($\mathit{C}OCH_3$); *m/z* (ES^+) 953 (2M + H^+, 90), 477 (M + H^+, 100%); HRMS (ES^+) Calcd. for $C_{21}H_{24}N_4O_9$ (MNa^+) 499.1435. Found 499.1434.

4-Trifluoromethylphen-2-yl-1-(1′,2′,3′,6′-tetra-*O*-acetyl-4′-deoxy-D-glucopyranosyl)-1,2,3-triazole (6d). Azide **4a** (180 mg, 0.48 mmol) and 2-ethynyl-α,α,α-trifluorotoluene **5d** (67 μL, 0.48 mmol) were suspended in a 1 : 1 mixture of *t*-BuOH and distilled water (2 mL). Sodium L-ascorbate (38 mg, 0.19 mmol), and $CuSO_4 \cdot 5H_2O$ (24 mg, 0.1 mmol) were then added. The resulting mixture was stirred at 40 °C for 4 h after which t.l.c. (petrol–ethyl acetate, 3 : 2) indicated formation of a single product (R_f 0.3) and complete consumption of starting material (R_f 0.6). The resulting mixture was diluted with ethyl acetate (10 mL), washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography (petrol–ethyl acetate, 3 : 2) to give the trifluoromethylphenyl triazole **6d** (217 mg, 84%) as a colourless foam; ν_{max} (thin film) 1753 (br, C=O), 1643 (m, C=C), 1316 (s, C-F) cm^{-1}; δ_H (400 MHz, $CDCl_3$) (α : β, 6 : 1), 1.9 (0.5H, s, $COCH_3$-β), 1.91 (3H, s, $COCH_3$-α), 2.05 (3H, s, $COCH_3$-α), 2.06 (0.5H, s, $COCH_3$-β), 2.07 (0.5H, s, $COCH_3$-β), 2.08 (3H, s, $COCH_3$-α), 2.16 (0.5H, s, $COCH_3$-β), 2.28 (3H, s, $COCH_3$-α), 3.82 (1H, dd, $J_{5,6}$ 3.4 Hz, $J_{6,6'}$ 12.8 Hz, H-6′α), 3.85–3.89 (0.2H, m, H-6′β), 4.25–4.29 (1.2H, m, H-6″α, H-6″β), 4.63 (0.2H, d at, *J* 2.5 Hz, *J* 10.6 Hz, H-5′β), 4.75–4.83 (1.2H, m, H-4′α, H-4′β), 4.91 (1H, d at, *J* 2.7 Hz, $J_{4,5}$ 10.6 Hz, H-5′α), 5.23 (1H, dd, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 10.0 Hz, H-2′α), 5.25–5.26 (0.2H, m, H-2′β), 5.79 (0.2H, at, *J* 10.2 Hz, H-3′β), 5.95–6.02 (1.2H, m, H-3′α, H-1′β), 6.45 (1H, d, *J* 3.8 Hz, H-1′α), 7.50–7.54 (1.2H, m, ArH), 7.64–7.68 (1.2H, m, ArH), 7.75–7.78 (2.3H, m, C=C*H*, ArH), 7.97–7.99 (1.2H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) α (major) anomer only: 20.0, 20.4, 20.5, 20.9 ($CO\mathit{C}H_3$), 59.7 (C-4′), 61.6 (C-6′), 69.2 (C-5′), 69.6 (C-2′ and C-3′), 89.1 (C-1′), 124.1 (d, J_{C-F} 273.7 Hz, CF_3), 126.2 (q, J_{C-F} 5.9 Hz, ArCH), 123.5 (q, J_{C-F} 5.9 Hz, ArCH), 127.3 (q, J_{C-F} 30.5 Hz, ArC), 128.7, 128.8 (ArC, C=*C*H), 131.8, 132.2 (ArCH), 144.2 (*C*=CH), 168.7, 168.8, 169.8, 170.0 ($\mathit{C}OCH_3$); *m/z* (ES^+) 566 (M + Na^+, 80), 544 (M + H^+, 100%); HRMS (ES^+) Calcd. for $C_{23}H_{24}N_3O_9F_3$ (MNa^+) 566.1357. Found 566.1349; Found: C, 50.82; H, 4.58; N, 7.74. $C_{23}H_{24}N_3O_9F_3$ requires C, 50.83; H, 4.58; N, 7.73%.

4-Butyl-1-(4′-deoxy-D-glucopyranose)-1,2,3-triazole (7a). Acetylated triazole **6a** (115 mg, 0.25 mmol) was dissolved in methanol (5 mL). Freshly prepared NaOMe (0.025 mL of a 1 M solution) was then added portion-wise. The reaction was monitored by t.l.c. (DCM–methanol, 4 : 1) which upon completion indicated the formation of a single product (R_f 0.3). Amberlight IR-120 (H^+) was then added until the solution reached pH 7; the solution was filtered and concentrated *in vacuo* to give the de-protected triazole **7a** (73 mg, 100%) as a white solid, mp 109–110 °C; ν_{max} (thin film) 3453 (br, OH), 2385 (w, C-H), 1642 (m, C=C) cm^{-1}; δ_H (400 MHz, methanol-d4) (α : β, 1.5 : 1) 0.98 (5.1H, t, *J* 7.6 Hz, CH_3-α, CH_3-β), 1.35–1.45 (3.4H, m, CH_2-α, CH_2-β), 1.65–1.71 (3.4H, m, CH_2-α, CH_2-β), 2.71–2.75 (3.4H, m, CH_2-α, CH_2-β), 3.14–3.20 (3.4H, m, H-6′α, H-6′β), 3.30 (0.7H, ad, *J* 9.1 Hz, H-2′β), 3.46–3.48 (1.7H, m, H-6″α, H-6″β), 3.55 (1H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 9.5 Hz, H-2′α), 4.02–4.05 (0.7H, m, H-5′β), 4.09 (0.7H, at, *J* 9.5 Hz, H-3′β), 4.37 (1H, at, *J* 9.5 Hz, H-3′α), 4.42–4.47 (1.7H, m, H-4′α, H-4β), 4.50–4.52 (1H, m, H-5′α), 4.72 (0.7H, d,

$J_{1,2}$ 7.9 Hz, H-1′β), 5.28 (1H, d, J_{1-2} 3.6 Hz, H-1′α), 7.75 (0.7H, s, C=CH-β), 7.78 (1H, s, C=CH-α); δ_C (100.6 MHz, methanol-d4) 14.4 (2 × CH_3), 23.3, 26.0, 26.1, 32.7 (CH_2), 61.7, 63.2, 63.7, 63.8, 71.3, 72.1, 74.5, 75.4, 76.1, 77.0 (C-2′, C-3′, C-4′, C-5′, C-6′), 94.3, 98.5 (C-1′), 124.2, 124.4 (C=*C*H), 148.7, 148.8 (*C*=CH); *m/z* (ES^+) 575 (2M + H^+, 50), 288 (M + H^+, 100%); HRMS (ES^+) Calcd. for $C_{12}H_{21}N_3O_5$ (MNa^+) 310.1373. Found 310.1363.

4-Octyl-1-(4′-deoxy-D-glucopyranose)-1,2,3-triazole (7b). Octyl triazole **6b** (90 mg, 0.18 mmol) was dissolved in methanol (5 mL). Freshly prepared NaOMe (0.02 mL of a 1 M solution) was then added portion-wise. The reaction was monitored by t.l.c. (DCM–methanol, 4 : 1) which upon completion indicated the formation of a single product (R_f 0.5). Amberlight IR-120 (H^+) was added until the solution reached pH 7; the solution was filtered and concentrated *in vacuo* to give de-protected triazole **7b** (62 mg, 100%) as a white solid, mp 95–96 °C; ν_{max} (thin film) 3233 (br, OH), 1749 (m, C=C) cm^{-1}; δ_H (400 MHz, DMSO-d6) (α : β, 1 : 1), 0.83 (5.4H, t, *J* 6.7 Hz, CH_3-α, CH_3-β), 1.22–1.26 (18H, m, 5 × CH_2-α, 5 × CH_2-β), 1.55–1.57 (3.8H, m, CH_2-α, CH_2-β), 2.58 (3.8H, m, CH_2-α, CH_2-β), 2.98 (1.8H, m, H-6′α, H-6′β), 3.07–4.14 (2.8H, m, H-2β, H-6″α, H-6″β), 3.32 (0.8H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 9.5 Hz, H-2′α), 3.81–3.87 (1.8H, m, H-5′α, H-5′β), 3.84 (1H, at, *J* 9.5 Hz, H-3′β), 4.09 (0.8H, at, *J* 9.5 Hz, H-3′α), 4.21–4.25 (1.8H, m, H-4′α, H-4′β), 4.53 (1H, d, $J_{1,2}$ 7.9 Hz, H-1′β), 5.07 (0.8H, d, *J* 3.6 Hz, H-1′α), 7.75 (1H, s, C=CH), 7.78 (0.8H, s, C=CH); δ_C (100.6 MHz, DMSO-d6) 13.9, 14.0 (CH_3), 20.7, 22.0, 28.4, 28.5, 28.6, 28.7, 28.8 (CH_2), 60.0, 60.1, 62.0, 62.2, 69.7, 69.9, 72.6, 73.5, 74.3, 75.1 (C-2′, C-3′, C-4′, C-5′, C-6′), 92.3, 96.7 (C-1′), 122.2, 122.6 (C=C*H*), 146.3, 146.5 (*C*=CH); *m/z* (ES^+) 687 (2M + H^+, 80), 398 (M + Na^+, 25), 344 (M + H^+, 100%); HRMS (ES^+) Calcd. for $C_{16}H_{29}N_3O_5$ (MNa^+) 366.1999 Found 366.1998.

4-Pyridin-2-yl-1-(4′-deoxy-D-glucopyranose)-1,2,3-triazole (7c). Acetylated triazole **6c** (40 mg, 0.08 mmol) was dissolved in methanol (5 mL). Freshly prepared NaOMe (0.01 mL of a 1 M solution) was added portion-wise. The reaction was monitored by t.l.c. (DCM–methanol, 4 : 1) which upon completion indicated the formation of a single product (R_f 0.6). Amberlight IR-120 (H^+) was added until the solution reached pH 7; the solution was filtered and concentrated *in vacuo* to afford de-protected triazole **7c** (22 mg, 100%) as a colourless foam; ν_{max} (thin film) 3356 (br, OH), 1667 (m, C=C), 1560 (s, C=N) cm^{-1}; δ_H (400 MHz, methanol-d4) (α : β, 1 : 1), 3.23–3.29 (3H, m, H-2′β, H-6′α, H-6′β), 3.34–3.38 (3H, m, H-2′α, H-6″α, H-6″β), 3.72–3.81 (1H, m, H-5′β), 4.10–4.18 (2H, m, H-5′α, H-3′α), 4.43 (1H, at, *J* 9.1 Hz, H-3′β), 4.52–4.63 (2H, m, H-4′α, H-4′β), 4.76 (1H, d, $J_{1,2}$ 7.9 Hz, H-1′β), 5.30 (1H, d, $J_{1,2}$ 3.5 Hz, H-1′α), 7.19–7.22 (2H, m, ArH), 7.35–7.38 (2H, m, ArH), 7.89–7.93 (2H, m, ArH), 8.47, 8.49 (C=CH), 8.56–8.61 (2H, m, ArH); δ_C (100.6 MHz, methanol-d4) 61.7, 61.8 (C-6′), 64.1, 64.2, 64.2, 72.1, 74.4, 75.5, 75.9, 76.9 (C-2′, C-3′, C-4′, C-5′), 94.3, 98.5 (C-1′), 121.6, 124.0, 125.3, 125.3, 125.4, 138.9 (ArCH, ArC, C=*C*H), 148.1, 148.2 (*C*=CH); *m/z* (ES^+) 639 (2M + Na^+, 100), 331 (M + Na^+, 100), 309 (M + H^+, 40%); HRMS (ES^+) Calcd. for $C_{13}H_{16}N_4O_5$ (MNa^+) 331.1013. Found 331.1015.

4-Trifluoromethylphen-2-yl-1-(4′-deoxy-D-glucopyranose)-1,2,3-triazole (7d). Trifluoromethylphenyl triazole **6d** (96 mg, 0.17 mmol) was dissolved in methanol (5 mL). Freshly prepared NaOMe (0.02 mL of a 1 M solution) was then added portion-wise. The reaction was monitored by t.l.c. (DCM–methanol, 4 : 1) which upon completion indicated the formation of a single product (R_f 0.5). Amberlight IR-120 (H^+) was added until the solution reached pH 7; the solution was filtered and concentrated *in vacuo* to afford de-protected triazole **7d** (66 mg, 100%) as a yellow solid; mp 69–70 °C; ν_{max} (thin film) 3233 (br, OH), 1652 (m, C=C), 1320 (s, C-F) cm^{-1}; δ_H (400 MHz, methanol-d4) (α : β, 1 : 1), 3.21–3.25 (2H, m, H-6′α, H-6′β), 3.26–3.35 (1H, m, H-2′β), 3.52–3.54 (2H, m, H-6″α, H-6″β), 3.56 (1H, dd, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 9.1 Hz, H-2′α), 3.71–3.74 (1H, m, H-5′β), 4.18 (1H, at, *J* 9.5 Hz, H-3′β), 4.45 (1H, at, *J* 9.1 Hz, H-3′β), 4.56–4.6 (3H, m, H-4′α, H-4′β, H-3′α), 4.76 (1H, d, $J_{1,2}$ 7.9 Hz, H-1′β), 5.3 (1H, d, *J* 3.6 Hz, H-1′α), 7.64 (2H, m, ArH), 7.73–7.79 (4H, m, ArH), 7.86 (2H, m, ArH), 8.14, 8.17 (C=CH); δ_C (100.6 MHz, methanol-d4), 61.7, 61.8 (C-6′), 64.0, 64.2, 71.4, 72.0, 74.6, 75.3, 76.1, 77.0 (C-2′, C-3′, C-4′, C-5′), 94.5, 98.6 (C-1′), 125.6 (d, J_{C-F} 271.3 Hz, CF_3), 126.6, 127.4, 129.3, 129.6, 130.2, 130.3, 130.7, 133.3, 133.5 (C=*C*H, ArCH, ArC), 145.1, 145.2 (*C*=CH); *m/z* (ES^+) 773 (2M + Na^+, 100), 751 (2M + H^+, 40), 398 (M + Na^+, 75), 376 (M + H^+, 85%); HRMS (ES^+) Calcd. for $C_{15}H_{16}N_3O_5F_3$ (MNa^+) 398.0934. Found 398.0933.

1,2,3,6-Tetra-*O*-acetyl-4-isobutylamido-4-deoxy-D-glucopyranoside (8a). Azide **4a** (100 mg, 0.27 mmol) was dissolved in dry DCM (20 mL) under an atmosphere of argon. PBu_3 (50 mg, 0.27 mmol) and isobutyryl chloride (0.03 mL, 0.27 mmol) were added, and the reaction mixture was allowed to stir at reflux. After 48 h, t.l.c. (petrol–ethyl acetate, 5 : 4) indicated the formation of a single product (R_f 0.25) and complete consumption of the starting material (R_f 0.6). The solution was concentrated *in vacuo* and purified by flash column chromatography (petrol–ethyl acetate, 6 : 4) to give isobutyl amide **8a** (52 mg, 37%) as a white solid; ν_{max} (thin film) 3519 (br, NH), 1748 (br, C=O), 1654 (br, NC=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) (α : β, 17 : 1), 1.11 (6.4H, m, $CH(CH_3)_2$-α, $CH(CH_3)_2$-β), 2.02 (3H, s, $OCCH_3$-α), 2.03 (0.2H, s, $COCH_3$-β), 2.04 (0.2H, s, $COCH_3$-β), 2.05 (3H, s, $COCH_3$-α), 2.09 (0.2H, s, $COCH_3$-β), 2.10 (3H, s, $COCH_3$-α), 2.12 (0.2H, s, $COCH_3$-β), 2.17 (3H, s, $COCH_3$-α), 3.73–3.76 (0.1H, m, H-5β), 4.00 (1H, dt, *J* 10.8 Hz, *J* 3.4 Hz, H-5α), 4.09–4.13 (0.2H, m, H-6β, H-6′β), 4.17 (2H, m, H-6α, H-6′α), 4.21–4.29 (1.1H, m, H-4α, H-4β), 4.98–5.03 (0.1H, m, H-2β), 5.11 (1H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 10.2 Hz, H-2α), 5.14–5.16 (0.1H, m, H-3β), 5.35 (1H, at, *J* 10.4 Hz, H-3α), 5.53 (1.1H, m, NH-α, NH-β), 5.68 (0.1H, d, $J_{1,2}$ 8.2 Hz, H-1β), 6.37 (1H, d, *J* 3.6 Hz, H-1α); δ_C (100.6 MHz, $CDCl_3$) α (major) anomer only: 19.3, 19.3 ($(CH_3)_2CH$), 20.5, 20.7, 20.8, 20.9 ($COCH_3$), 35.7 ($(CH_3)_2CH$), 49.7 (C-4), 62.6 (C-6), 69.3 (C-2), 69.3 (C-3), 71.8 (C-5), 89.3 (C-1), 168.7, 169.6, 170.9, 171.5, 177.0 (*C*OCH_3, CONH); *m/z* (ES^+) 857.2 (2M + Na^+, 100), 852.3 (2M + NH_4^+, 95), 440 (M + Na^+, 30), 418 (M + H^+, 25%); HRMS (ES^+) Calcd. for $C_{18}H_{27}NO_{10}$ (MNa^+) 440.1527. Found 440.1524.

1,2,3,6-Tetra-*O*-acetyl-4-deoxy-4-hexamido-D-glucopyranoside (8b). Azide **4a** (240 mg, 0.64 mmol) was dissolved in dry DCM (20 mL) under an atmosphere of argon. PPh_3 (170 mg, 0.64 mmol) and hexanoyl chloride (0.09 mL, 0.64 mmol) were then added, and the reaction mixture was allowed to stir at reflux. After 38 h, t.l.c. (petrol–ethyl acetate, 5 : 4) indicated formation of single product (R_f 0.25) and complete consumption of starting material (R_f 0.6). The solution was concentrated *in vacuo* and purified by

flash column chromatography (petrol–ethyl acetate, 6 : 4) to give hexamide **8b** (94 mg, 33%) as a colourless oil; ν_{max} (thin film) 3742 (br, NH), 1641 (br, NC=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) (α : β, 10 : 1), 0.88–0.90 (3.3H, m, CH_3), 1.22–1.35 (4.4H, m, 2 × CH_2), 2.08–2.13 (2.2H, m, CH_2), 1.54–1.60 (2.2H, m, CH_2), 2.02 (3H, s, $COCH_3$-α), 2.04 (0.3H, s, $COCH_3$-β), 2.05 (0.3H, s, $COCH_3$-β), 2.06 (3H, s, $COCH_3$-α), 2.09 (0.3H, s, $COCH_3$-β), 2.10 (3H, s, $COCH_3$-α), 2.14 (0.3H, s, $COCH_3$-β), 2.17 (3H, s, $COCH_3$-α), 3.73–3.76 (0.1H, m, H-5β), 3.99 (0.1H, d at, *J* 4.1 Hz, $J_{4,5}$ 10.7 Hz, H-5α), 4.08–4.20 (2.2H, m, H-6α, H-6α, H-6β, H-6β), 4.21–4.29 (1.1H, m, H-4α, H-4β), 5.03–5.07 (0.1H, m, H-2β), 5.11 (1H, dd, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 10.1 Hz, H-2α), 5.13–5.15 (0.1H, m, H-3β), 5.33 (1H, at, *J* 10.4 Hz, H-3α), 5.50–5.52 (1.1H, m, NH-α, NH-β), 5.68 (0.1H, d, $J_{1,2}$ 7.9 Hz, H-1β), 6.36 (1H, d, *J* 3.5 Hz, H-1α); δ_C (100.6 MHz, CD_3OH) α (major) anomer only: 13.9 (CH_3), 20.5, 20.7, 20.8, 20.9 ($CO\mathit{C}H_3$), 22.3, 25.2, 31.3, 36.6 (CH_2), 49.9 (C-4), 62.6 (C-6), 69.3 (C-2), 69.4 (C-3), 71.7 (C-5), 89.3 (C-1) 168.7, 169.6, 170.9, 171.5, 173.2 ($\mathit{C}OCH_3$, CONH); *m/z* (ES^+) 913.3 (2M + Na^+, 80), 908 (2M+ NH_4^+, 100), 855 (2M + H^+, 50%), 468 (M + Na^+, 30), 463 (M + NH_4^+, 40), 446 (M + H^+, 50%) HRMS (ES^+) Calcd. for $C_{20}H_{31}NO_{10}$ (MNa^+) 468.1840. Found 468.1825.

1,2,3,6-Tetra-*O*-acetyl-4-benzamido-4-deoxy-D-glucopyranoside (8c). Azide **4a** (35 mg, 0.09 mmol) was dissolved in dry DCM (2 mL) under an atmosphere of argon. PPh_3 (25 mg, 0.09 mmol) and benzoyl chloride (22 μL, 0.18 mmol) were then added, and the reaction mixture was allowed to stir at reflux. After 5 days, t.l.c. (petrol–ethyl acetate, 1 : 1) indicated the formation of a single product (R_f 0.25) and complete consumption of the starting material (R_f 0.6). The solution was diluted with DCM (5 mL), washed with sodium bicarbonate (5 mL of a saturated aqueous solution), brine, dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography (petrol–ethyl acetate, 1 : 1) to give benzamide **8c** (25 mg, 59%) as a white solid; ν_{max} (thin film) 3630 (br, NH), 1644 (br, NC=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) (α : β, 9 : 1), 2.0 (0.4H, s, $COCH_3$-β), 2.01 (3H, s, $COCH_3$-α), 2.04 (3H, s, $COCH_3$-α), 2.06 (0.4H, s, $COCH_3$-β), 2.07 (0.4H, s, $COCH_3$-β), 2.09 (3H, s, $COCH_3$-α), 2.13 (0.4H, s, $COCH_3$-β), 2.18 (3H, s, $COCH_3$-α), 4.11 (1H, d at, *J* 3.1 Hz, $J_{4,5}$ 10.1 Hz, H-5α), 4.20–4.27 (0.4H, m, H-5β), 4.25 (2.3H, m, H-6α, H-6′α, H-6β, H-6′β), 4.46–4.48 (1.1H, m, H-4α, H-4β), 5.05–5.11 (0.1H, m, H-2β), 5.08 (1H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 10.3 Hz, H-2α), 5.33 (0.1H, at, *J* 10.3 Hz, H-3β), 5.48 (1H, at, *J* 10.3 Hz, H-3α), 5.74 (0.1H, d, $J_{1,2}$ 8.1 Hz, H-1β), 6.29 (1H, d, *J* 9.2 Hz, NH-α), 6.34 (0.1H, d, *J* 9.4 Hz, NH-β), 6.41 (1H, d, *J* 3.6 Hz, H-1α), 7.41–7.46 (2.3H, m, ArH), 7.49–7.54 (1.1H, m, ArH-α, ArH-β), 7.70–7.72 (2.3H, m, 2 × ArH-α, 2 × ArH-β); δ_C (100.6 MHz, $CDCl_3$) α (major) anomer only: 20.5, 20.7, 20.8, 20.9 ($CO\mathit{C}H_3$), 50.8 (C-4), 62.9 (C-6), 69.3 (C-3), 69.4 (C-2), 71.8 (C-5), 89.3 (C-1), 126.9, 128.8, 130.8, 132.1, 133.3 (ArCH), 167.3, 168.8, 169.6, 170.1, 171.9 ($\mathit{C}OCH_3$, CONH); *m/z* (ES^+) 925 (2M + Na^+, 30), 474 (M + Na^+, 60%); HRMS (ES^+) Calcd. for $C_{21}H_{25}NO_{10}$ (MNa^+) 474.1371. Found 474.1368.

1,2,3,6-Tetra-*O*-acetyl-4-(4-trifluoromethyl)-benzamido-4-deoxy-D-glucopyranoside (8d). Azide **4a** (45 mg, 0.12 mmol) was dissolved in dry DCM (5 mL) under an atmosphere of argon. PBu_3 (36 μL, 0.14 mmol) and 4-trifluoromethyl benzoyl chloride (22 μL, 0.14 mmol) were then added, and the reaction mixture was allowed to stir at reflux. After 48 h, t.l.c. (petrol–ethyl acetate, 3 : 2) indicated the formation of a single product (R_f 0.3) and complete consumption of the starting material (R_f 0.5). The solution was then concentrated *in vacuo* and purified by flash column chromatography (petrol–ethyl acetate, 3 : 2) to give trifluoromethylbenzamide **8d** (38 mg, 61%) as a colourless foam; ν_{max} (thin film) 3520 (br, NH), 1652 (br, NC=O), 1360 (s, C-F) cm^{-1}; δ_H (400 MHz, $CDCl_3$) (α : β, 5 : 1), 2.01 (0.6H, s, $COCH_3$-β), 2.02 (3H, s, $COCH_3$-α), 2.04 (3H, s, $COCH_3$-α), 2.07 (0.6H, s, $COCH_3$-β), 2.08 (0.6H, s, $COCH_3$-β), 2.10 (3H, s, $COCH_3$-α), 2.13 (0.6H, s, $COCH_3$-β), 2.18 (3H, s, $COCH_3$-α), 3.87–3.91 (0.2H, m, H-5β), 4.10–4.14 (1H, ddd, J_{5-4} 10.7 Hz, J_{5-6} 7.6 Hz, $J_{5-6'}$ 2.8 Hz, H-5α), 4.24–4.26 (2.4H, m, H-6α, H-6′α, H-6β, H-6β), 4.39–4.49 (1.2H, m, H-4α, H-4β), 5.20 (1H, dd, J_{2-3} 10.4 Hz, J_{2-1} 3.8 Hz, H-2α), 5.23–5.26 (0.2H, m, H-3β), 5.30 (0.2H, at, *J* 10.4 Hz, H-2β), 5.48 (1H, at, *J* 10.4 Hz, H-3α), 5.74 (0.2H, d, $J_{1,2}$ 8.3 Hz, H-1β), 6.41 (1H, d, $J_{1,2}$ 3.5 Hz, H-1α), 6.44 (1H, d, *J* 9.1 Hz, NH-α), 6.63 (0.2H, d, *J* 9.1 Hz, NH-β), 7.70–7.72 (2.4H, m, 2 × ArH-α, 2 × ArH-β), 7.83–7.85 (2.4H, m, 2 × ArH-α, 2 × ArH-β); δ_C (100.6 MHz, $CDCl_3$) α (major) anomer only: 20.5, 20.7, 20.8, 20.9 ($CO\mathit{C}H_3$), 50.9 (C-4), 62.9 (C-6), 69.2 (C-2), 69.5 (C-3), 71.7 (C-5), 89.3 (C-1) 125.8, 127.5 (ArCH), 133.5, 136.5 (ArC), 166.1, 168.7, 169.6, 171.0, 172.0 ($\mathit{C}OCH_3$, CONH); *m/z* (ES^+) (M + NH_4^+, 100%); HRMS (ES^+) Calcd. for $C_{22}H_{24}F_3NO_{10}$ (MNa^+) 542.1245. Found 542.1244.

4-Isobutylamido-4-deoxy-D-glucopyranose (9a). Acetylated amide **8a** (70 mg, 0.17 mmol) was dissolved in methanol (5 mL). Freshly prepared NaOMe (0.01 mL of a 1 M solution) was then added portion-wise. The reaction was monitored by t.l.c. (DCM–methanol, 4 : 1) which upon completion indicated the formation of a single product (R_f 0.7). Amberlight IR-120 (H^+) was then added until the solution was at pH 7; the solution was filtered and concentrated *in vacuo* to afford de-protected amide **9a** (47 mg, 100%) as a white solid; mp 169–170 °C; ν_{max} (thin film) 3320 (br, OH), 1745 (br, C=O), 1658 (br, NC=O), cm^{-1}; δ_H (400 MHz, methanol-d4) (α : β, 1 : 1), 1.16 (12H, m, $(C\mathit{H}_3)_2$CH-β, $(C\mathit{H}_3)_2$CH-α), 2.52 (2H, m, $(CH_3)_2C\mathit{H}$-α, $(CH_3)_2C\mathit{H}$-β), 3.16–3.24 (1H, m, H-2β), 3.44 (1H, dd, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 9.1 Hz, H-2α), 3.48–3.52 (2H, m, H-4α, H-4β), 3.54–3.60 (5H, m, H-5β, H-6α, H-6′α, H-6β, H-6′β,), 3.66–3.72 (2H, m, H-3α, H-3β), 3.79–3.83 (3H, m, H-5α, NH-α, NH-β), 4.48 (1H, d, $J_{1,2}$ 7.6 Hz, H-1β) 5.18 (1H, d, *J* 3.5 Hz, H-1α); δ_C (100.6 MHz, methanol-d4) 19.7, 19.9 (CH_3), 36.4, 37.2 ($(CH_3)_2\mathit{C}H$), 53.0, 53.1, 63.0, 63.1, 71.9, 72.4, 74.6, 75.2, 77.1, 77.4 (C-2, C-3, C-4, C-5, C-6), 94.1, 98.3 (C-1), 181.2, 181.3 (CONH); *m/z* (ES^+) 521 (2M + Na^+, 50), 272 (M + Na^+, 35), 250.1 (M + H^+, 10%); HRMS (ES^+) Calcd. for $C_{10}H_{19}NO_6$ (MNa^+) 272.1105. Found 272.1101.

4-Deoxy-4-hexamido-D-glucopyranose (9b). Protected amide **8b** (69 mg, 0.15 mmol) was dissolved in methanol (5 mL). Freshly prepared NaOMe (0.016 mL of a 1 M solution) was then added portion-wise. The reaction was monitored by t.l.c. (DCM–methanol, 4 : 1) which upon completion indicated the formation of a single product (R_f 0.7). Amberlight IR-120 (H^+) was then added until the solution was at pH 7; the solution was filtered and concentrated *in vacuo* to afford de-protected amide **9b** (43 mg, 100%) as a white solid, mp 136–138 °C; ν_{max} (thin film) 3443 (br, OH), 1643 (s, NC=O) cm^{-1}; δ_H (400 MHz, methanol-d4) (α : β, 1 : 1), 0.93–0.96 (3.3H, m, CH_3-α, CH_3-β), 1.34–1.40 (4.4H, m, 2 × CH_2-α, 2 × CH_2-β), 1.62–1.68 (2.2H, m, CH_2-α, CH_2-β), 2.24–2.28

(2.2H, m, CH_2-α, CH_2-β), 3.15–3.21 (0.1H, m, H-2β), 3.43 (1H, dd, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 9.14 Hz, H-2α), 3.46–3.54 (1.1H, m, H-4α, H-4β), 3.56–3.62 (2.2H, m, H-6α, H-6′α, H-6β, H-6′β), 3.68–3.74 (1.1H, m, H-3α, H-3β), 3.77–3.82 (2.2H, m, H-5α, H-5β, NH-α, NH-β), 4.48 (0.1H, d, $J_{1,2}$ 7.6 Hz, H-1β), 5.17 (1H, d, J 3.5 Hz, H-1α); δ_C (100.6 MHz, methanol-d4) 14.3 (2 × CH_3), 23.5, 26.8, 26.8, 26.9, 32.6, 37.2 (CH_2), 53.3, 53.4, 63.1, 63.2, 72.0, 72.3, 74.6, 75.1, 77.0, 77.3 (C-2, C-3, C-4, C-5, C-6), 94.0, 98.2 (C-1), 177.4, 177.5 (CONH); m/z (ES^+) 577.3 (2M + Na^+, 100), 300.1 (M + Na^+, 70), 278.2 (M + H^+, 20%); HRMS (ES^+) Calcd. for $C_{12}H_{23}O_6N$ (MNa^+) 300.1418. Found 300.1421.

4-Benzamido-4-deoxy-D-glucopyranose (9c). Acetylated benzamide **8c** (100 mg, 0.22 mmol) was dissolved in methanol (5 mL). Freshly prepared NaOMe (0.023 mL of a 1 M solution) was then added portion-wise. The reaction was monitored by t.l.c. (DCM–methanol, 4 : 1) which upon completion indicated the formation of a single product (R_f 0.7). Amberlight IR-120 (H^+) was then added until the solution was at pH 7; solution was filtered and concentrated *in vacuo* to afford de-protected benzamide **9c** (63 mg, 100%) as a colourless solid; mp 140–141 °C; ν_{max} (thin film) 3645 (br, NH), 1632 (br, C=O) cm^{-1}; δ_H (400 MHz, methanol-d4) (α : β, 1 : 1), 3.25–3.28 (1H, m, H-2β), 3.50–3.54 (2H, m, H-2α, H-4β), 3.58–3.71 (6H, m, H-4α, H-5β, H-6α, H-6′α, H-6β, H-6′β), 3.89–4.02 (5H, m, H-3α, H-3β, H-5α, NH-α, NH-β), 4.55 (1H, d, $J_{1,2}$ 7.6 Hz, H-1β), 5.22 (1H, d, $J_{1,2}$ 3.8 Hz, H-1α), 7.87 (5H, m, 5 × ArH), 7.47–7.51 (5H, m, 5 × ArH); δ_C (100.6 MHz, methanol-d4) 54.0, 54.1, 63.2, 63.3, 72.1, 72.3, 74.6, 75.1, 77.2, 77.3 (C-2, C-3, C-4, C-5, C-6), 94.1, 98.3 (C-1), 128.5, 128.6, 129.5, 132.8, 132.9, 135.6 135.6 (ArC, ArCH), 171.3 171.4 (CONH). m/z (ES^+) (2M + Na^+, 90), (M + H^+, 75%); HRMS (ES^+) Calcd. for $C_{13}H_{17}NO_6$ (MNa^+) 306.0948. Found 306.0946.

(4-Trifluoromethyl)-benzamido-4-deoxy-D-glucopyranose (9d). Protected trifluoromethylbenzamide **8d** (69 mg, 0.15 mmol) was dissolved in methanol (5 mL). Freshly prepared NaOMe (0.016 mL of a 1 M solution) was then added portion-wise. The reaction was monitored by t.l.c. (DCM–methanol, 4 : 1) which upon completion indicated the formation of a single product (R_f 0.7). Amberlight IR-120 (H^+) was then added until the solution was at pH 7; the solution was filtered and concentrated *in vacuo* to afford de-protected trifluorobenzamide **9d** (43 mg, 100%) as a pale yellow solid, mp 72–73 °C; ν_{max} (thin film) 3345 (br, OH), 1662 (br, NC=O), 1357 (s, C-F) cm^{-1}; δ_H (400 MHz, methanol-d4) (α : β, 1 : 1), 3.26–3.31 (1H, m, H-2β), 3.4–3.80 (6H, m, H-2α, H-4β, H-6α, H-6′α, H-6β, H-6′β), 3.88–4.15 (7H, m, H-3α, H-3β, H-4α H-5α, H-5β, NH-α, NH-β), 4.67 (1H, d, $J_{1,2}$ 7.9 Hz, H-1β), 5.23 (1H, d, J 3.5 Hz, H-1α), 7.80–7.96 (4H, m, ArH), 8.07–8.20 (4H, m, ArH); δ_C (100.6 MHz, methanol-d4) 54.3, 54.4 (C-5), 63.3, 63.4 (C-6), 72.1, 72.3, 74.7, 75.3, 77.2, 77.3 (C-2, C-3, C-4), 94.2, 98.4 (C-1), 126.5, 126.6, 126.7, 129.4, 129.5, 129.9, 129.7, 130.0 (ArCH, ArC), 169.6, 172.9 (CONH); m/z (ES^+) 725.2 (2M + Na^+, 10), 352 (M + H^+, 50%); HRMS (ES^+) Calcd. for $C_{14}H_{16}O_6NF_3$ (MNa^+) 374.0822. Found 374.0823.

Pre- and post-emergence assays

Seeds of the four test species *Amaranthus retroflexus* (AMARE, red root pigweed), *Chenopodium album* (CHEAL, lambs quarters), *Alopecurus myosuroides* (ALOMY, blackgrass) and *Digitaria sanguinalis* (DIGSA, large crab grass) were sown in pots containing sandy loam soil (post-emergence) and sand (pre-emergence). After cultivation for either one day (pre-emergence), or for 8 days (post-emergence) under controlled conditions in a glasshouse, the plants were sprayed at a rate of 2500 L/ha with an aqueous spray solution derived from the formulation of the tested compound (1000 g/ha) in an acetone–water (50 : 50) solution containing 0.5% Tween 20. The test plants were then grown in a glasshouse under controlled conditions (at 24/16 °C, day/night; 14 hours per day light; 65% humidity), and watered twice daily. The results were evaluated as percentage herbicide effect (100% = total damage to plant; 0% = no damage to plant) 13 days after herbicide application for both pre- and post-emergence tests.

Cell expansion assays

Solutions of compounds for testing were dissolved in 100% DMSO. Solutions of the control inhibitors thiazolidinone **10** and Orazylin **11** and were made up at concentrations of 50 ppm, 5 ppm and 0.5 ppm, by ten-fold serial dilution. Solutions of compounds **6c**, **7c**, **8b**, **9b**, **8c** and **9c**, were made up at 500 ppm, 167 ppm, and 56 ppm by three-fold serial dilution. Compounds **4b** and **6d** were made up at concentrations of 500 ppm, 250 ppm, 125 ppm, and 62.5 ppm by two-fold serial dilution. Freshly split BY2 tobacco cells (1 ml) were then treated with 10 µl aliquots of either the test compound or control inhibitor solutions, and the cells were then incubated. Cell morphology was examined after 7 days with a ×20 microscopic lens.

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