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Design and synthesis of aryl/hetarylmethyl phosphonate-UMP derivatives as potential glucosyltransferase inhibitors

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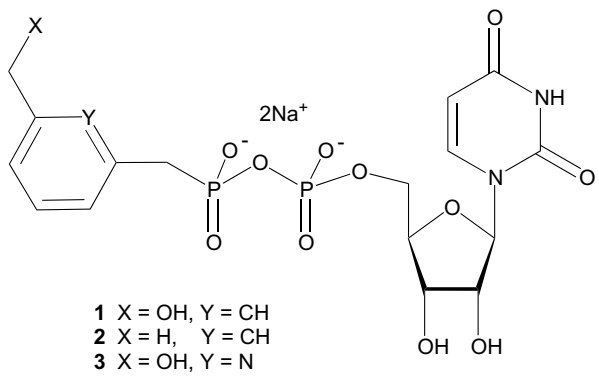
Abstract—A novel class of glucosyltransferase inhibitors has been designed and synthesised. The designed inhibitors **1**–**4** provide conformational mimicry of the transition-state in glucosyltransfer reactions. The key synthetic steps involve a Michaelis–Arbuzov reaction followed by coupling with uridine-5′-morpholidophosphate as activated UMP derivative.

In recent times, much progress has been made towards a broader understanding of the functions of complex oligosaccharide structures. It is a well documented fact that carbohydrates, in addition to their well-known role as a source of energy, are crucial in various biological processes such as cell–cell recognition, tumor cell metastasis, and leukocyte adhesion during inflammation.[1,2] However, the molecular basis of many processes are often still uncertain despite tremendous progress made in this field. The glycosyltransferases of the Leloir pathway are key catalysts for the synthesis of oligosaccharides and glycoconjugates in vivo.[3–12] These enzymes transfer activated monosaccharide units in the form of their nucleotide mono- or diphosphate derivatives to a specific free hydroxy group of the acceptor molecule. Inhibition or modulation of this transfer reaction provides an excellent opportunity for intervention of the oligosaccharide biosynthesis and to obtain a more complete understanding of the structure–activity relationship of oligosaccharides on a molecular basis.[13]

Earlier, we had reported[14] the synthesis of a transition-state based analog of galactosyltransferase which exhibited high inhibitor properties towards galactosyltransferases. Encouraged by this, we have recently reported[15] transition-state based analogs of sialyltransferases which showed very high affinity towards the enzyme in the nanomolar range. However, the sugar mimicking aryl analogs of CMP-Neu5Ac turned out to be potent inhibitors exhibiting very high binding affinity to α(2–6)-sialyltransferase.[16] Based upon these observations, we report herein the synthesis of sugar mimicking aryl/hetarylmethyl phosphonate UMP derivatives **1**–**4** as potential glucosyl- (or eventually galactosyl-) transferase inhibitors.



1 X = OH, Y = CH
2 X = H, Y = CH
3 X = OH, Y = N
4 X = H, Y = N

The required benzyl bromide derivatives **9** and **10**[17] were prepared from their corresponding methyl precursors **5** and **6**, respectively, by treating them with *N*-bromo succinimide (NBS) in the presence of catalytic amounts of dibenzoyl peroxide (DBP) in refluxing carbon tetrachloride (Scheme 1). The bromides **9** and **10** on Michaelis–Arbuzov reaction with tris-trimethylsilyl phosphite in toluene at 95°C for 4 h furnished the respective bis-trimethylsilylphosphonates **13** and **14** in quantitative yield (^{1}H NMR). The bis-trimethylsilylphosphonates are highly labile to moisture and had to be stored under argon; they were used in the next step without further purification. The deprotection of the TMS groups and subsequent preparation of sodium

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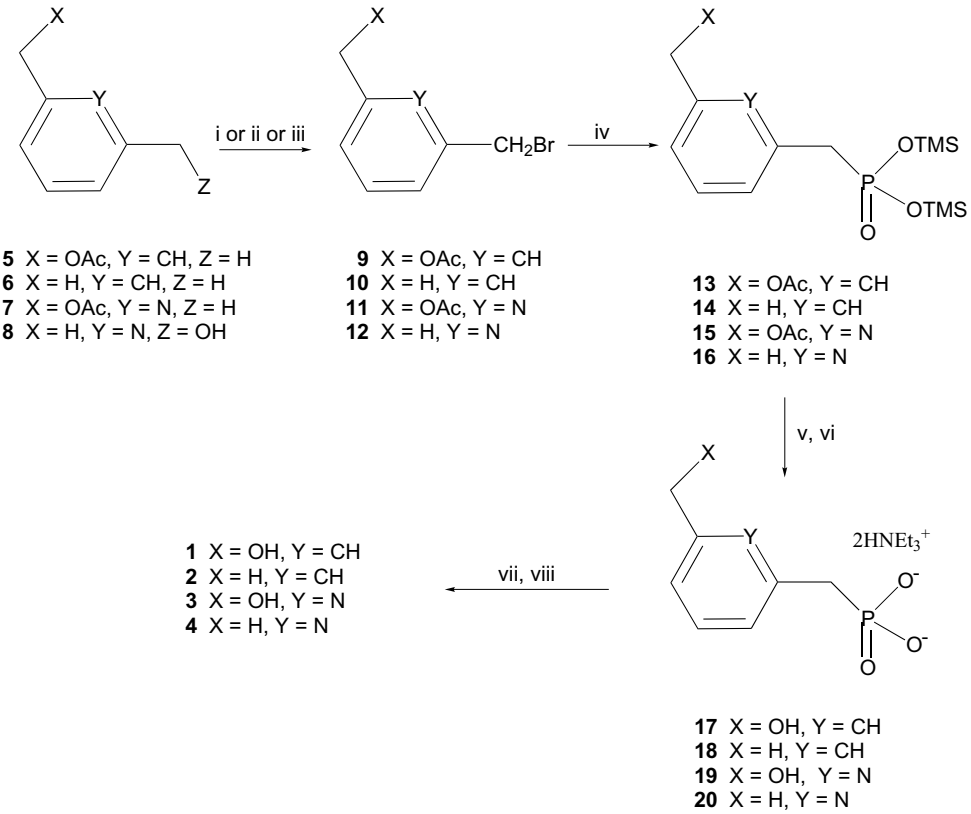

Scheme 1. *Reagents and conditions*: (i) NBS, cat. DBP, CCl_4, reflux, 4 h, 40–45% (for **5** and **6**); (ii) NBS, cat. AIBN, CCl_4, reflux, Hg-lamp, 8 h, 45% (for **7**); (iii) CBr_4, PPh_3, NEt_3, CH_2Cl_2, 0°C, 1 h, 42% (for **8**); (iv) $P(OTMS)_3$, toluene, 95°C, 3.5–4 h, quant.; (v) 0.2 M NaOMe/MeOH, 0°C, 30 min, Amberlite IR-120 (H^+ form); (vi) Amberlite IR-120 ($HNEt_3^+$ form), 80–90% (two steps); (vii) UMP-morpholidate, 1*H*-tetrazole, py, 3 days, rt, RP-18; (viii) Amberlite IR-120 (Na^+ form), 42–52%.

salts were carried out by treating the phosphonates **13** and **14** with sodium methanolate in methanol at 0°C for 30 min, which after usual work up furnished disodium salts; they were transformed into their corresponding bis-triethylammonium salts **17** and **18** by ion exchange (Amberlite IR-120, $HNEt_3^+$ form). The structural assignments of **17**, **18** and all intermediates are based on NMR (^1H, ^{13}C and ^{31}P) and MS (EI, FAB or MALDI) data.

Finally, reaction of bis-triethylammonium salts **17** and **18** with uridine-5′-morpholidophosphate as activated

Table 1. NMR data of **1**–**4**

H #	**1**	**2**	**3**	**4**
H-5	5.77 (d, $J_{5,6}=8.0$ Hz)	5.78 (d, $J_{5,6}=8.1$ Hz)	5.74 (d, $J_{5,6}=7.8$ Hz)	5.80 (d, $J_{5,6}=8.1$ Hz)
H-6	7.75 (d, $J_{6,5}=8.0$ Hz)	7.78 (d, $J_{6,5}=8.1$ Hz)	7.72 (d, $J_{6,5}=7.8$ Hz)	7.79 (m)
H-1′	5.86 (d, $J_{1',2'}=4.9$ Hz)	5.85 (d, $J_{1',2'}=4.9$ Hz)	5.87 (d, $J_{1',2'}=5.0$ Hz)	5.82 (d, $J_{1',2'}=4.2$ Hz)
H-2′	4.20 (dd, $J_{2',3'}=J_{2',1'}=4.9$ Hz)	4.21 (dd, $J_{2',3'}=J_{2',1'}=4.9$ Hz)	4.20 (dd, $J_{2',3'}=J_{2',1'}=5.0$ Hz)	4.21 (m)
H-3′	4.12 (m)	4.11 (m)	4.13 (dd, $J_{3',2'}=J_{3',4'}=4.9$ Hz)	4.21 (m)
H-4′	4.12 (m)	4.11 (m)	4.11 (m)	4.13 (m)
H-5′	3.96 (m, H-5a′), 4.02 (m, H-5b′)	3.95 (m, H-5a′), 4.04 (m, H-5b′)	3.98 (m, H-5a′), 4.03 (m, H-5b′)	4.06 (m, H-5a′), 4.13 (m, H-5b′)
H-1″	3.10 (d, $J=21.4$ Hz, 2H)	3.05 (d, $J=21.4$ Hz, 2H)	3.28 (d, $J=21.8$ Hz, 2H)	3.00 (d, $J=19.6$ Hz, 2H)
Ar-*H*	7.14–7.25 (m, 4H)	6.99–7.14 (m, 4H)	7.24 (d, $J_{5'',6''}=7.6$ Hz, H-5″), 7.30 (d, $J_{7'',6''}=7.6$ Hz, H-7″), 7.67 (dd, $J_{6'',5''}=J_{6'',7''}=7.6$ Hz, H-6″)	7.20 (d, $J_{5'',6''}=7.7$ Hz, H-5″), 7.33 (d, $J_{7'',6''}=7.8$ Hz, H-7″), 7.79 (m, H-6″)
Ar-CH_3	–	2.22 (s, 3H)	–	2.46 (s, 3H)
Ar-CH_2OH	4.53 (s, 2H)	–	4.59 (s, 2H)	–
^{31}P	−9.95 (d, $J=27.6$ Hz, $P(O)O_3$), 15.04 (d, $J=27.6$ Hz, $CP(O)O_2$)	−10.30 (d, $J=27.7$ Hz, $P(O)O_3$), 15.10 (d, $J=27.7$ Hz, $CP(O)O_2$)	−10.00 (d, $J=27.6$ Hz, $P(O)O_3$), 12.20 (d, $J=27.6$ Hz, $CP(O)O_2$)	−9.63 (bd, $P(O)O_3$), 17.14 (bd, $CP(O)O_2$)

UMP derivative in the presence of 1*H*-tetrazole[18] in pyridine for 3 days at rt afforded **1** and **2** (Table 1) as white powders, respectively (after isolation and purification by HPLC,[19] ion exchange, Amberlite IR-120 (Na^+ form) and lyophilisation). The structural assignments of **1** and **2** are based on NMR (^1H, ^{13}C and ^{31}P) and MS (FAB or MALDI) data.

In a similar fashion, synthesis of **3** and **4** were also carried out (Scheme 1). Treatment of **7** with NBS in the presence of catalytic amounts of α,α′-azo-isobutyronitrile (AIBN) in CCl_4 and irradiation of the reaction mixture for 8 h with a Hg-lamp furnished **11**, whereas bromide **12**[20,21] was prepared by treatment of **8** with $CBr_4/Ph_3P/Et_3N$ in CH_2Cl_2 at 0°C. Subsequent reactions of bromides **11** and **12** with tris-trimethylsilyl phosphite furnished the corresponding phosphonates **15** and **16** which were transformed into their bis-triethylammonium salts **19** and **20** in the usual way. Their reaction with uridine-5′-morpholidiphosphate in the presence of 1*H*-tetrazole in pyridine for 3 days at rt furnished **3** and **4** (Table 1) as white powders, respectively (after isolation and purification by HPLC,[19] ion exchange, Amberlite IR-120 (Na^+ form) and lyophilisation). The structures of **3** and **4** were assigned on the basis of NMR (^1H, ^{13}C and ^{31}P) and MS (FAB or MALDI) data.

In conclusion, we report on the design and synthesis of inhibitors **1**–**4** as mimetics of UDP-Glc (or UDP-Gal). These novel classes of compounds are presumed to feature potent inhibition of glucosyltransferases (or galactosyltransferases) because they are structurally related to the transition states. Biological evaluations are currently under investigation and we expect that this will give us insight into various mechanisms of several metabolic processes. The biological activity data of inhibitors **1**–**4** will be reported in due course.

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19. HPLC conditions: Shimadzu LC8A preparative pump and a Rainin Dynamax UV 1 detector at 254 nm; column used: Eurospher RP-18, 7 μm, 250×16 mm (Knauer, Germany); mobile phase: 0.05 M triethylammonium bicarbonate buffer+2–8% acetonitrile.
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