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Note

Facile one-pot synthesis of sugar–quinoline derivatives

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ABSTRACT

Seven different sugar–quinoline derivatives were synthesised in a 'one-pot' reaction from their corresponding *C*-β-glycoside derivatives. The compounds were characterised by NMR spectroscopy and elemental analysis.

The chemistry of nitrogen heterocycles, viz. lactam,[1,2] pyrrole,[3,4] indole[5,6] and quinoline[7,8] derivatives, has been extensively developed for more than 100 years due to the diversity of biological activities and pharmaceutical applications found among these compounds. 2-Arylated quinolines are present in nature and occur in the structures of 5-lipoxygenase inhibitors,[9] leucotriene antagonists,[10] LTD4 receptor antagonists[11] and other biologically active molecules. In particular, quinoline derivatives have been found to act as antimalarial,[12–14] antibacterial,[15] antiasthmatic, antihypertensive and anti-inflammatory[16] drugs. Quinolines are also important components in industrial antioxidants and dyes. In addition to medicinal and industrial applications, polyquinolines are found to undergo hierarchical self-assembly into nano- and *meso*-structures with enhanced electronic and photonic properties.[17,18] In its original form for the synthesis of quinoline derivatives, the Friedländer synthesis consisted of a reaction between an aromatic *o*-aminoaldehyde and an aldehyde or ketone bearing an α-CH_2 functionality. Thus, new synthetic routes to quinolines could have major impact on the potential applications of these useful compounds.

4,6-*O*-Butylidene-D-glucopyranose was synthesised from D-glucose by adopting a procedure reported in the literature.[19,20] *C*-β-Glycosidic ketones **2a**–**g** were synthesised by the Knoevenagel condensation of 2,4-pentanedione with sugar derivatives, such as 4,6-*O*-butylidene-D-glucopyranose, D-glucose, D-xylose and D-galactose.[21–23] Although the synthesis of *C*-β-glycosidic ketones of peracetylated derivatives is described in the literature,[21–23] in the present report, we have extended the methodology to partially protected sugar derivatives. Among many alternative routes to quinoline and substituted quinolines, their synthesis using the Friedländer method seems to have created significant interest as documented by reports in the literature.[24] In continuation of our ongoing research in the area of saccharide chemistry,[25] we have reported a facile one-pot synthesis of sugar–quinoline derivatives. In our case, we have used the protected, partially protected and unprotected *C*-β-glycosidic ketones for the synthesis of quinoline derivatives. Reaction of substituted 2-aminobenzaldehyde (**1**) with a series of *C*-β-glycosidic ketones in the presence of pyrrolidine (25%) as an organic catalyst in 1:3 CH_2Cl_2–MeOH resulted in a 62–85% yield of the sugar–quinoline derivatives (Scheme 1). With other bases, such as triethylamine, NaOH, KOH, piperidine and pyridine, the yields obtained were less than 40%. The structures of the resulting *C*-β-glycosides **2a**–**g** were determined by ^1H and ^{13}C NMR spectroscopy and elemental analysis. The appearance of a peak at 2.13 ppm in the ^1H NMR spectrum and at 207 ppm in the ^{13}C NMR spectrum corresponds to $-CH_3$ and $-C{=}O$ groups, respectively. The formation of sugar-based quinoline derivatives **3a**–**g** was determined from the ^1H and ^{13}C NMR studies. The ^1H NMR spectrum of **3e** notably exhibited a large coupling constant for the H-1′ signal ($J_{H1',H2'}$ 9.5 Hz), indicating a *trans*-diaxial orientation of H-1′, and H-2′ as expected for a β-D-configured glucopyranose moiety.[21] Structures of the sugar moieties, amounts of reactants, reaction conditions and product yields are given in Table 1.

Thus, we have designed and synthesised quinoline–sugar derivatives having a methylene group that favours flexibility of the molecule as is observed with sugar–β-lactam derivatives.[26] Some of the quinoline-based derivatives exhibit different biological activities.[12–16] The quinoline derivatives reported in this paper may also

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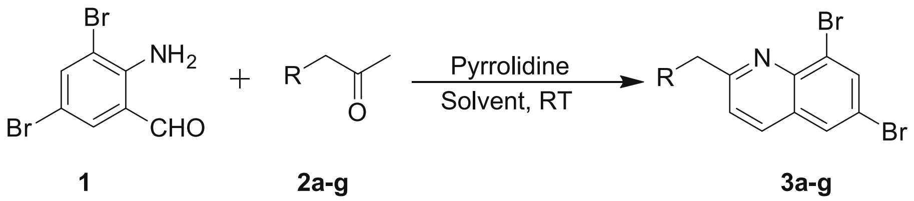
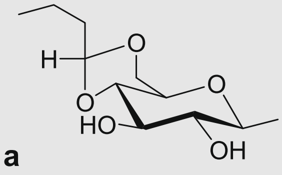
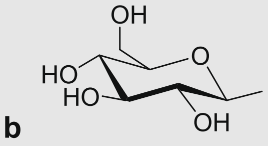
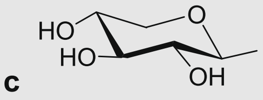
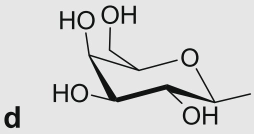
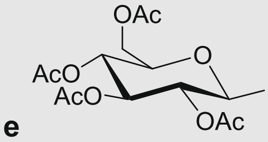
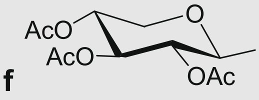
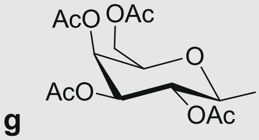


Scheme 1. Synthesis of sugar-based quinoline derivatives.

Table 1
Friedländar condensation of *C*-β-glycosidic ketones with 2-amino-3,5-dibromobenzaldehyde

Entry	*R* (2/3)	**2a**–**g** (mg)	Time (h)	Yield of **3a**–**g** in mg (%)
1		274	10	403 (78)
2		220	12	332 (72)
3		190	13	315 (73)
4		220	12	315 (68)
5		388	18	455 (72)
6		316	18	372 (67)
7		388	18	390 (62)

be presumed to have activities against different microbes, and these studies are in progress. Moreover, a few of these sugar-based quinoline derivatives exhibited gelation properties. A detailed investigation of these gelator molecules is in progress.

1. Experimental

1.1. General methods

D-Glucose, D-xylose, D-galactose and 2-amino-3,5-dibromobenzaldehyde were obtained from Sigma–Aldrich Chemicals Pvt. Ltd, USA and were of high purity. Butyraldehyde and the organic catalyst (pyrrolidine) were obtained from SRL, India. Other reagents such as hydrochloric acid, sodium hydrogen carbonate and solvents (AR Grade) were obtained from Sd-fine, India, in high purity and were used without any further purification. Acetic anhydride was purchased from Fischer Chemicals Pvt. Ltd, India. Column chromatography was performed on silica gel (100–200 mesh). NMR spectra were recorded on a Bruker DRX 300 MHz instrument in either $CDCl_3$ or DMSO-d_6 (with a few drops of $CDCl_3$). Chemical shifts are referenced to internal TMS. Elemental analyses were performed using a Perkin–Elmer 2400 series

CHNS/O analyser. While assigning the spectral data, several abbreviations were used, and these include 'Ar' for aromatic, 'Ace' for acetal, 'Sac' and H-1′–H-6′ for saccharide, and Ha and Hb for the methylene protons that connect between the sugar and heterocyclic moieties.

1.2. 1-(4,6-*O*-Butylidene-β-D-glucopyranosyl)propan-2-one (2a)

Compounds **2b**–**g** were synthesised by adopting the procedure reported in the literature,[21–23] and the purity of these samples was found to be satisfactory. The synthetic procedure for **2a** is as follows: To a solution of 4,6-*O*-butylidene-d-glucopyranose (2.34 g, 10.0 mmol) in 1:9 H_2O–THF were added $NaHCO_3$ (3.36 g, 4 equiv) and 2,4-pentanedione (2.05 mL, 2 equiv). The reaction mixture was stirred at reflux temperature for 36 h, and then cooled to room temperature. The resultant mixture was filtered, and the residue was washed well with CH_2Cl_2. The pale-yellow residue thus obtained was purified by column chromatography (4:6 hexane–EtOAc) to get the expected product: Yield: 2.33 g (85%); mp 102–104 °C; ^1H NMR ($CDCl_3$): δ 4.44–4.47 (t, *J* = 5.1 Hz, 1H, Ace-H), 4.03–4.08 (dd, *J* = 9.9 Hz, *J* = 4.2 Hz, 1H, H-4′), 3.72–3.79 (ddd, *J* = 3.3 Hz, *J* = 8.4 Hz, *J* = 17.4 Hz, 1H, H-1′), 3.61 (t, *J* = 8.7 Hz, 1H, H-3′), 3.11–3.38 (m, 4H, H-2′, H-5′, H-6′a, H-6′b), 2.96–2.99 (m, 2H, Sac-OH), 2.79–2.86 (dd, *J* = 3.9 Hz, *J* = 16.5 Hz, 1H, Hb), 2.54–2.62 (dd, *J* = 8.0 Hz, *J* = 16.3 Hz, 1H, Ha), 2.13 (s, 3H, $-CH_3$), 1.52–1.59 (m, 2H, $-CH_2$), 1.31–1.39 (m, 2H, $-CH_2$), 0.83–0.88 (t, *J* = 7.5 Hz, 3H, $-CH_3$); ^{13}C NMR ($CDCl_3$): δ 207.3 (–OC–CH_3),102.5 (Ace-C), 80.5 (C-5′), 76.1 (C-3′), 75.1 (C-1′), 74.2 (C-2′), 70.6 (C-4′), 68.3 (C-6′), 46.1 ($-CH_2$–CO), 36.2 (–CO–CH_3), 30.9 ($-CH_2$), 17.4 ($-CH_2$), 13.9 (CH_3). Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 56.63; H, 8.26.

1.3. General procedure for the synthesis of sugar–quinoline derivatives

To a solution of *C*-β-glycosidic ketone (**2**, 1.0 mmol) in 1:3 CH_2Cl_2–MeOH were added pyrrolidine (25%) and 2-amino-3,5-dibromobenzaldehyde (**1**, 0.335 g, 1.2 mmol). After stirring at room temperature for a given period of time, the solvent was evaporated under reduced pressure. The crude product was slurried with silica gel and purified by flash column chromatography. For details (amount of reagents, reaction times and yields of products) see Table 1.

1.3.1. Physicochemical and spectral data for 2-(4,6-*O*-butylidene-β-D-glucopyranosylmethyl)-6,8-dibromoquinoline (3a)

White solid; mp 160–162 °C; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 8.14 (d, *J* = 1.8 Hz, 1H, Ar-H), 8.03 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.95 (d, *J* = 1.8 Hz, 1H, Ar-H), 7.41 (d, *J* = 8.4 Hz, 1H, Ar-H), 5.06 (d, *J* = 3.6 Hz, 1H, Sac-OH), 4.50 (t, *J* = 5.0 Hz, 1H, Ace-H), 4.11–4.16 (dd, *J* = 4.2 Hz, *J* = 11.5 Hz, 1H, H-4′), 3.77–3.88 (ddt, *J* = 4.8 Hz, *J* = 9.3 Hz, 2H, H-1′, H-3′), 3.49–3.31 (m, 6H, H-5′, H-6′a, H-6′b, H-2, Hb, Sac-OH), 3.19 (t, *J* = 8.9 Hz, 1H, Ha), 1.65–1.62 (m, 2H, $-CH_2$), 1.38–1.45 (m, 2H, $-CH_2$), 0.90 (t, *J* = 7.4 Hz, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$): δ 160.1 (Ar-C), 143.0 (Ar-C), 136.4 (Ar-C), 136.1 (Ar-C), 129.5 (Ar-C), 128.7 (Ar-C), 125.2 (Ar-C), 124.5 (Ar-C), 119.6 (Ar-C), 102.5 (Ace-C), 80.7 (C-5′), 78.7 (C-3′), 74.4 (C-1′), 74.4 (C-2′), 71.2 (C-4′), 68.4 (C-6′), 41.6 (CH_2-Ar), 36.2 ($-CH_2$), 17.4 ($-CH_2$), 13.9 ($-CH_3$). Anal. Calcd for $C_{20}H_{23}Br_2NO_5$: C, 46.44; H, 4.48; Br, 30.90; N, 2.71. Found: C, 46.13; H, 4.55; N, 2.83.

1.3.2. Physicochemical and spectral data for 2-(β-D-glucopyranosylmethyl)-6,8-dibromoquinoline (3b)

White solid; mp 164–165 °C; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 8.07 (s, 1H, Ar-H), 8.02 (d, *J* = 7.8 Hz, 1H, Ar-H), 8.00 (s, 1H, Ar-H), 7.58 (d, *J* = 8.4 Hz, 1H, Ar-H), 4.99 (s, 1H, Sac-OH), 4.74 (s, 2H, Sac-OH), 3.74–3.81 (m, 2H, Sac-H), 3.56–3.69 (m, 3H, Sac-H) 3.49 (m, 2H, Sac-H) 3.10–3.23 (m, 3H, Sac-H, Ha, Hb). ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 161.5 (Ar-C), 142.7 (Ar-C), 135.1 (Ar-C), 134.7 (Ar-C), 129.2 (Ar-C), 128.3 (Ar-C), 124.8 (Ar-C), 124.0 (Ar-C), 118.0 (Ar-C), 79.5 (C-5′), 78.2 (C-3′), 78.0 (C-1′), 73.6 (C-2′), 70.4 (C-4′), 61.6 (C-6′), 41.0 (CH_2-Ar). Anal. Calcd for $C_{16}H_{17}Br_2NO_5$: C, 41.50; H, 3.70; Br, 34.51; N, 3.02. Found: C, 41.02; H, 3.93; N, 3.28.

1.3.3. Physicochemical and spectral data for 2-(β-D-xylopyranosylmethyl)-6,8-dibromoquinoline (3c)

White solid; mp 198–200 °C; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 8.10 (s, 1H, Ar-H), 8.04 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.97 (s, 1H, Ar-H), 7.48 (d, *J* = 8.1 Hz, 1H, Ar-H), 4.81 (s, 1H, Sac-OH), 4.50 (s, 2H, Sac-OH), 3.84–3.89 (dd, *J* = 4.5 Hz, *J* = 10.8 Hz, 1H, Sac-H), 3.76 (t, *J* = 7.1 Hz, 1H, Sac-H), 3.43–3.58 (m, 3H, Sac-H), 3.29–2.98 (m, 3H, Sac-H, Ha, Hb). ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 166.2 (Ar-C), 148.0 (Ar-C), 140.4 (Ar-C), 140.1 (Ar-C), 134.3 (Ar-C), 133.5 (Ar-C), 130.2 (Ar-C), 129.1 (Ar-C), 123.5 (Ar-C), 84.2 (C-3′), 83.5 (C-1′), 78.5 (C-5′), 75.0 (C-2′), 74.7 (C-4′), 46.2 (CH_2-Ar). Anal. Calcd for $C_{15}H_{15}Br_2NO_4$: C, 41.60; H, 3.49; Br, 36.90; N, 3.23. Found: C, 42.01; H, 3.10; N, 3.06.

1.3.4. Physicochemical and spectral data for 2-(β-D-galactopyranosylmethyl)-6,8-dibromoquinoline (3d)

White solid; mp 137–139 °C; ^1H NMR ($CDCl_3$+DMSO-d_6): δ 8.02 (d, *J* = 1.8 Hz, 1H, Ar-H), 7.85 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 7.47 (d, *J* = 8.4 Hz, 1H, Ar-H), 4.77 (s, 1H, Sac-OH), 4.08 (s, 1H, Sac-OH), 3.92 (s, 2H, Sac-OH), 3.64 (t, *J* = 5.4 Hz, 4H, Sac-H), 3.50–3.56 (m, 3H, Sac-H, H-1′, Hb), 3.16–3.24 (dd, *J* = 7.5 Hz, *J* = 14.7 Hz, 1H, Ha). ^{13}C NMR ($CDCl_3$+DMSO-d_6): δ 161.7 (Ar-C), 142.4 (Ar-C), 135.0 (Ar-C), 134.7 (Ar-C), 129.1 (Ar-C), 128.3 (Ar-C), 124.9 (Ar-C), 124.1 (Ar-C), 118.0 (Ar-C), 78.8 (C-5′), 77.9 (C-3′), 74.6 (C-1′), 71.2 (C-2′), 68.7 (C-4′), 60.8 (C-6′), 41.0 (CH_2-Ar). Anal. Calcd for $C_{16}H_{17}Br_2NO_5$: C, 41.50; H, 3.70; Br, 34.51; N, 3.02. Found: C, 41.08; H, 3.51; N, 3.24.

1.3.5. Physicochemical and spectral data for 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylmethyl)-6,8-dibromoquinoline (3e)

White solid; mp 102–104 °C; ^1H NMR ($CDCl_3$): δ 8.13, (d, *J* = 2.1 Hz, 1H, Ar-H), 7.96 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.92 (d, *J* = 2.1 Hz, 1H, Ar-H), 7.38 (d, *J* = 8.4 Hz, 1H, Ar-H), 5.28 (t, *J* = 10.7 Hz, 1H, H-4′), 5.0–5.12 (m, 2H, H-2′, H-3′), 4.33–4.37 (m, 1H, Sac-H-6′b), 4.16–4.22 (dd, *J* = 5.4 Hz, *J* = 9.5 Hz, 1H, H-1′), 3.98–4.03 (dd, *J* = 2.1 Hz, *J* = 12.0 Hz, 1H, H-6′a), 3.68–3.73 (ddd, *J* = 2.5 Hz, *J* = 5.1 Hz, *J* = 9.9 Hz, 1H, H-5′), 3.20–3.25 (m, 2H, Ha, Hb), 1.95–2.07 (m, 12H, 4X-$OCOCH_3$). ^{13}C NMR ($CDCl_3$): δ 170.5 (–C=O), 170.4 (–C=O), 169.8 (–C=O), 169.5 (–C=O), 159.3 (Ar-C), 143.5 (Ar-C), 135.7 (Ar-C), 135.3 (Ar-C), 129.4 (Ar-C), 128.7 (Ar-C), 125.8 (Ar-C), 124.2 (Ar-C), 119.2 (Ar-C), 76.6 (C-5′), 75.8 (C-1′), 74.4 (C-3′), 71.8 (C-2′), 68.8 (C-4′), 62.2 (C-6′), 40.5 (CH_2-Ar), 20.7 and 20.6 (4X-$OCOCH_3$). Anal. Calcd for $C_{24}H_{25}Br_2NO_9$: C, 45.66; H, 3.99; Br, 25.32; N, 2.22. Found: C, 45.32; H, 3.63; N, 2.45.

1.3.6. Physicochemical and spectral data for 2-(2,3,4,-tri-*O*-acetyl-*β*-D-xylopyranosylmethyl)-6,8-dibromoquinoline (3f)

Colourless syrup; ^1H NMR ($CDCl_3$): δ 8.12 (d, *J* = 1.8 Hz, 1H, Ar-H), 7.98 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.93 (s, 1H, Ar-H), 7.38 (d, *J* = 8.4 Hz, 1H, Ar-H), 5.21 (t, *J* = 9.4 Hz, 1H, H-5′b), 4.94–5.00 (m, 1H, H-1′), 4.83 (t, *J* = 9.51 Hz, 1H, H-5′a), 4.02–4.08 (dd, *J* = 5.7 Hz, *J* = 11.1 Hz, 1H, H-3′), 3.88–3.94 (ddd, *J* = 1.8 Hz, *J* = 4.8 Hz, *J* = 18.6 Hz, 1H, H′4), 3.30 (t, *J* = 11.0 Hz, 1H, H-2′), 2.65- 2.74 (dd, *J* = 9.0 Hz, *J* =16.4 Hz, 1H, Hb), 2.44–2.50 (dd, *J* = 2.4 Hz, *J* = 16.5 Hz, 1H, Ha) 2.03–2.18 (m, 9H, 3X-$OCOCH_3$). ^{13}C NMR ($CDCl_3$): δ 170.2 (–C=O), 169.9 (–C=O), 169.8 (–C=O), 159.4 (Ar-C), 143.6 (Ar-C), 135.7 (Ar-C), 135.5 (Ar-C), 129.4 (Ar-C), 128.8 (Ar-C), 125.8 (Ar-C), 124.1 (Ar-C), 119.1 (Ar-C), 74.4 (C-5′), 73.6

(C-1′), 71.8 (C-3′), 69.2 (C-2′), 66.7 (C-4′), 45.4 (*C*H$_2$-Ar), 31.0 and 20.6 (3X-OCO*C*H$_3$). Anal. Calcd for $C_{21}H_{21}Br_2NO_7$: C, 45.10; H, 3.79; Br, 28.58; N, 2.50. Found: C, 45.63; H, 4.12; N, 2.82.

1.3.7. Physicochemical and spectral data for 2-(2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosylmethyl)-6,8-dibromoquinoline (3g)

Colourless syrup; ^{1}H NMR (CDCl$_3$): δ 8.12 (s, 1H, Ar-H), 7.97 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.93 (d, *J* = 1.5 Hz, 1H, Ar-H), 7.41 (d, *J* = 8.4 Hz, 1H, Ar-H), 5.43 (t, *J* = 4.4 Hz, 1H, H-4′), 5.02–5.15 (m, 2H, H-2′, H-3′), 3.90–4.090 (m, 4H, H-6′a, H-6′b, H-1, H-5′), 2.75–2.84 (dd, *J* = 9.0 Hz, *J* = 16.4 Hz, 1H, Hb), 2.17 (dd, *J* = 3.0 Hz, *J* = 16.5 Hz, 1H, Ha), 1.98–2.04 (m, 12H, 4X-OCOCH$_3$). ^{13}C NMR (CDCl$_3$): δ 170.4 (–C=O), 170.3 (–C=O), 170.1 (–C=O), 170.0 (–C=O), 159.6 (Ar-C), 143.5 (Ar-C), 135.6 (Ar-C), 135.3 (Ar-C), 129.4 (Ar-C), 128.7 (Ar-C), 125.7 (Ar-C), 124.2 (Ar-C), 119.1 (Ar-C), 74.3 (C-5′), 74.2 (C-1′), 71.8 (C-3′), 69.0 (C-2′), 67.6 (C-4′), 61.4 (C-6′), 45.5 (*C*H$_2$-Ar), 20.7 (OCO*C*H$_3$), 20.6 and 20.5 (3X-OCO*C*H$_3$). Anal. Calcd for $C_{24}H_{25}Br_2NO_9$: C, 45.66; H, 3.99; Br, 25.32; N, 2.22. Found: C, 46.02; H, 4.23; N, 2.63.

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