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Note

Synthesis of β-*C*-glycopyranosyl-1,4-naphthoquinone derivatives and their cytotoxic activity

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Abstract—β-*C*-Glucosyl and β-*C*-galactosyl-1,4-dimethoxynaphthalenes have been synthesized using a $F_3CCO_2Ag/SnCl_4$ promoted Friedel–Crafts electrophilic substitution reaction. Both glycosyl acetates and methyl glycosides can be used as glycosyl donors. Further oxidation afforded the corresponding β-*C*-glycosyl-1,4-naphthoquinones. The in vitro cytotoxic activity of these compounds was evaluated against the A375 cell line.

Keywords: *C*-Glycosyl compounds; 1,4-Naphthoquinone; Aryl C-glycosylations; Cytotoxicity

Considerable effort has been devoted to the synthesis of *C*-glycosyl compounds owing to their natural occurrence, their biological interest, and synthetic utility.[1] Among naturally occurring *C*-glycosyl compounds, aryl *C*-glycosyl derivatives are present in a variety of biologically important natural products as papulacandins, pluramycins, vineomycin, gilvocarcin V, and urdamycin A, which are recognized for their various biological activities including antibiotic, antitumoral, and antiplatelet aggregation activities.[2] Wide structural variety can be found among *C*-glycosyl-arenes, including spiroketals in papulacandins or quinones in pluramycins and angucyclines.[2] Naturally occurring naphthoquinones such as lapachol and β-lapachone possess anti-tumoral, anti-inflammatory, bactericidal, fungicidal, and virucidal activities.[3] Furthermore, we have found that β-*C*-glucopyranosyl-benzoquinone showed inhibitory activity against protein tyrosine phosphatase 1B (PTP1B)[4] and glycogen phosphorylase *b* (GPb).[5] Synthesis of *C*-glycosyl-quinone derivatives is therefore a valuable choice to find new biologically active compounds.[6] Aryl *C*-glycosyl compounds can be prepared by Friedel–Crafts alkylation, arylation with organometallic aromatic derivatives, palladium-mediated cross-coupling, O–C glycosyl rearrangement, free radical reaction or umpolung strategy.[1a–e,7] $SnCl_4/F_3CCO_2Ag$ has been reported to be a powerful combination for promoting aryl-β-C-glycosylation between readily available sugar acetates and aromatic substrates with good stereoselectivity.[8] As a part of a continuing program on *C*-glycosyl compounds synthesis,[4,5,9] we describe herein the $SnCl_4/F_3CCO_2Ag$ promoted synthesis of *C*-glycosyl-naphthoquinones with potential biological activities.

Treatment of 1,4-dimethoxynaphthalene with β-D-glucopyranose penta-acetate (**1**) in the presence of $F_3CCO_2Ag/SnCl_4$ at 35–40 °C, in anhydrous alcohol free dichloromethane, afforded the β-*C*-glucopyranosyl derivative **2** (60%) (Scheme 1). Mild oxidation of **2** with ceric ammonium nitrate (CAN) in aqueous acetonitrile led to the desired β-*C*-glucopyranosyl-1,4-naphthoquinone (**3**), which was isolated as moderately stable yellow needles (83%). Removal of the acetyl protecting groups under Zemplén conditions failed probably because of the addition of the methoxy anion to the naphthoquinone, affording a complex mixture. To get the water

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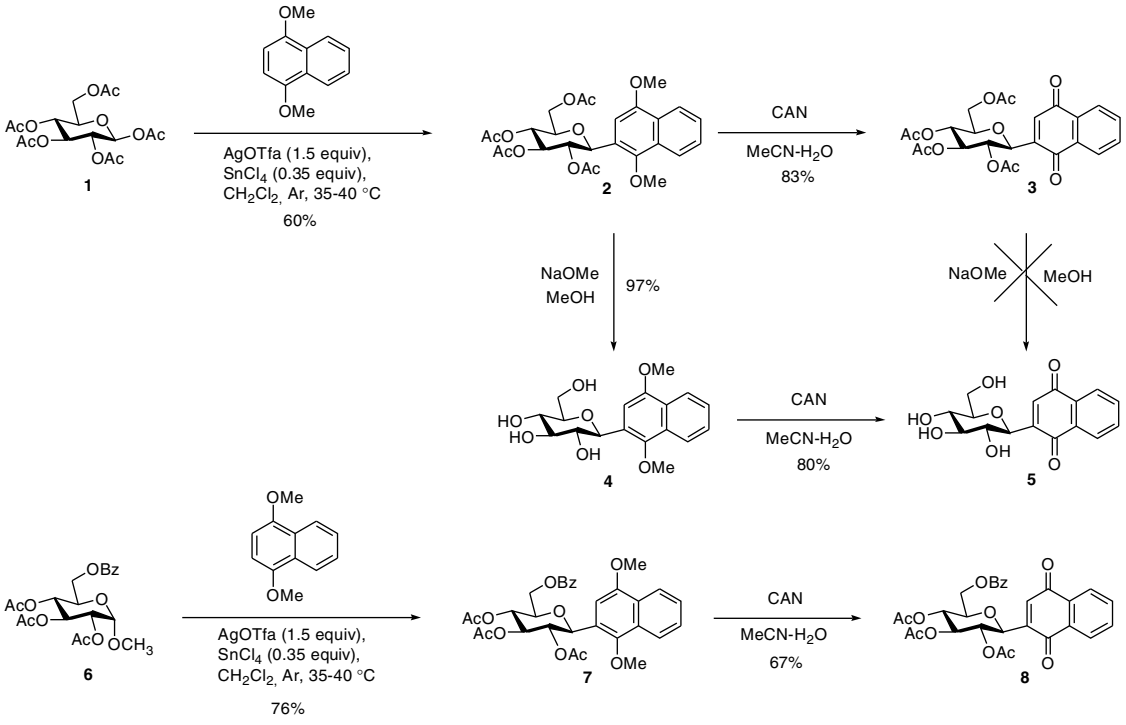
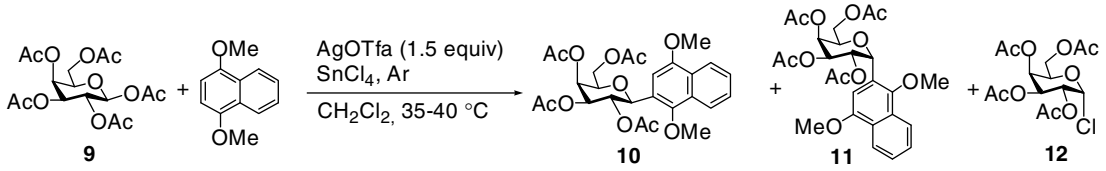


Scheme 1. Synthesis of the β-*C*-glucopyranosyl-naphthoquinone derivatives.

soluble derivative, **2** was first deacetylated with MeONa to afford the *C*-glucosyl-naphthalene **4** (97%), which was then oxidized with CAN to give the deprotected *C*-glucopyranosyl-1,4-naphthoquinone (**5**) in 80% yield. Furthermore, we found that methyl glycosides can also be used as glycosyl donors in $F_3CCO_2Ag/SnCl_4$ catalyzed aryl-C-glycosylation; reaction of 1,4-dimethoxynaphthalene with methyl 2,3,4-tri-*O*-acetyl-6-*O*-benzoyl-α-D-glucopyranoside (**6**)[10] afforded the corresponding β-*C*-glucopyranosyl derivative **7** in 76% yield (Scheme 1). Oxidation of **7** with CAN led to the β-*C*-glucopyranosyl-naphthoquinone **8** in 67% yield.

However, the stereoselectivity of the C-glycosylation was quite sensitive to the amount and addition rate of $SnCl_4$ in the case of the *galacto* derivative. As shown in Table 1, the reaction of 1,4-dimethoxynaphthalene with β-D-galactopyranose penta-acetate (**9**) catalyzed by dropwise addition of 0.35 equiv of $SnCl_4$ during 1 h afforded the β-*C*-galactoside **10** as the only isolated stereoisomer (entry 1). If we accelerated the addition rate (20–30 min, entry 2), a mixture of α- and β-anomer as well as the α-chloride **12** was obtained. Formation of the α-chloride has already been observed previously.[5] With 1 equiv of $SnCl_4$, a mixture of α- and β-anomer

Table 1. Effect of $SnCl_4$ on the C-glycosylation of galactose penta-acetate



Entry	$SnCl_4$ (equiv)	Addition time (min)	Product ratio[a]			
			Yield[b] (%)	**10**	**11**	**12**
1	0.35	60	65	100	—	—
2	0.35	20–30	58	50	30	20
3	1	60	55	80	20	—
4	1	20–30	45	35	35	30
5	2	20	33	nd[c]	nd[c]	nd[c]

[a] Estimated from ^{1}H NMR spectra.
[b] Isolated yield after purification by chromatography.
[c] Not determined.

was formed whatever be the addition rate of $SnCl_4$ (entries 3 and 4). Further increase in the amount of $SnCl_4$ (2 equiv, entry 5) with the addition realized within 20 min gave a worse yield. Consequently, the optimized reaction condition should be a very slow addition of 0.35 equiv $SnCl_4$ to the reaction mixture before heating at 35–40 °C. Under these conditions, methyl 2,3,4-tri-*O*-acetyl-6-*O*-benzoyl-α-D-galactopyranoside (**16**)[11] was successfully converted into the β-*C*-galactopyranosyl derivative **17** in 65% yield (Scheme 2). The corresponding β-*C*-galactosyl-1,4-naphthoquinones **13** and **18** could be obtained after oxidation with CAN. Deacetylation followed by oxidation of **10** furnished the fully deprotected galactosyl-naphthoquinone **15**.

The cytotoxic activity of the synthesized *C*-glycosyl-naphthoquinones was evaluated by MTT tetrazolium dye assay against A375 cell line (human melanoma cell).[12] Results are summarized in Table 2 with their 50% inhibitory concentration (IC_{50} values). 1,4-Naphthoquinone was used as reference compound for comparison.[13] The fully deprotected *C*-glycosyl-naphthoquinones **5** and **15** were inactive against the A375 cell line, while both the 6-*O*-acetyl (compounds **3** and **13**) and the 6-*O*-benzoyl-naphthoquinone derivatives (compounds **8** and **18**) exhibited an enhanced cytotoxic activity compared to 1,4-naphthoquinone. The IC_{50} values of all protected glycosyl naphthoquinones are around 50 μM. No significant difference was noticed between *gluco* and *galacto* derivatives (**3** vs **13**), nor in the nature of the protecting group at O–6 (acetyl for **3** and **13**, benzoyl for **8** and **18**).

In summary, we have reported the synthesis of β-*C*-glucosyl and β-*C*-galactosyl-1,4-dimethoxynaphthalenes using $F_3CCO_2Ag/SnCl_4$ promoted Friedel–Crafts electrophilic substitution reactions. Both glycosyl acetate and methyl glycoside can be employed as glycosyl donors. Mild oxidation converted *C*-glycosyl-1,4-dimethoxynaphthalenes into the corresponding *C*-glycosyl-naphthoquinone derivatives. The cytotoxicity of these new naphthoquinone derivatives was evaluated against the A375 cell line. Acetyl and/or benzoyl protected *C*-glycosyl-naphthoquinones showed promising antiproliferative activity against human melanoma cell.

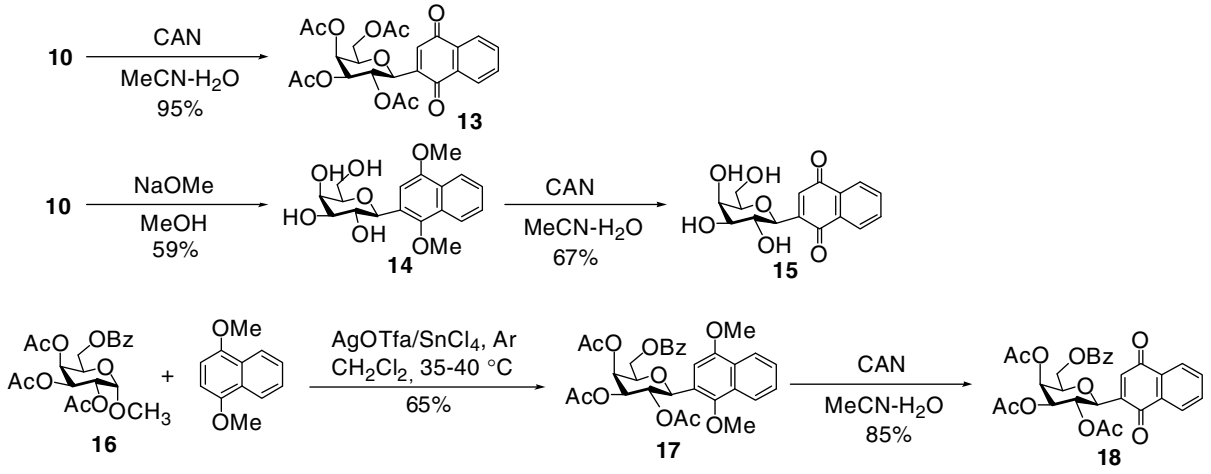
Table 2. Cytotoxic activity against A375 cell line of β-*C*-glycosyl-1,4-naphthoquinones

Compound	IC_{50} (μM)
1,4-Naphthoquinone	120.8
3	46
5	—
8	36
13	62
15	—
18	36

1. Experimental

1.1. General methods

Melting points were determined with a Büchi capillary apparatus and are not corrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter at room temperature. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-500 spectrometer in $CDCl_3$, with Me_4Si as the internal reference, or in D_2O. Mass spectra (ESI) and high resolution mass spectra (HRMS) were recorded on a MA1212 instrument using standard conditions. IR was obtained using a Perkin–Elmer 2000 FTIR instrument. Reactions were monitored by TLC on Silica Gel 60 F_{254} (E. Merck) plates exposed to H_2SO_4 (10% in 1:1 EtOH–water) spray followed by charring (≈50 °C). Column chromatography was performed with Silica Gel Geduran Si 60 (E. Merck). Solvents were distilled before use. Water was distilled twice. Microanalyses were performed at the analytical



Scheme 2. Synthesis of the β-*C*-galactopyranosyl-naphthoquinones.

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1.2. General procedure I for the C-glycosylation reaction of glycosyl donors with aromatic acceptors

To a soln of the glycosyl donor (1 equiv) and the aromatic acceptor (2 equiv) in dry alcohol-free CH_2Cl_2 (7–10 mL/mmol), F_3CCO_2Ag (1.5 equiv) was added in one portion. The mixture was stirred at rt in the dark, then 0.35 equiv of $SnCl_4$ (1 M soln in CH_2Cl_2) was added dropwise for 1 h under Ar. After stirring for 5–8 h at 35–40 °C, saturated $NaHCO_3$ was added and the mixture was stirred again for 20 min. The soln was filtered off and the filtrate was extracted with CH_2Cl_2. The combined CH_2Cl_2 soln was washed with brine and dried over anhyd $MgSO_4$, then concentrated under diminished pressure. The residue was purified by column chromatography.

1.3. General procedure II for the Zemplén-deacetylation

To a soln of the acetyl protected derivative in dry MeOH, 1–2 drops of a ~1 M methanolic NaOMe soln were added, and the reaction mixture was kept at rt until completion of the reaction (TLC 10:1 CH_2Cl_2–MeOH). Resin (H^+ form) was then added to remove sodium ion, the resin was filtered off, and the solvent removed under diminished pressure. If the residue was chromatographically not uniform, it was purified by column chromatography or by crystallization.

1.4. General procedure III for mild oxidation of 1,4-dimethoxynaphthalene derivatives

A soln of CAN (3 equiv) in water (1–2 mL/mmol) was added to a soln of the 1,4-dimethoxynaphthalene derivative in MeCN (1–2 mL/mmol). After stirring at rt in the dark for 1 h, the mixture was extracted with CH_2Cl_2 (3×15 mL). The combined CH_2Cl_2 soln was washed with brine and dried over anhyd $MgSO_4$, then concentrated under diminished pressure. The crude product was purified by column chromatography.

1.5. 2-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,4-dimethoxynaphthalene (2)

Prepared from **1** (342 mg, 0.88 mmol) and 1,4-dimethoxynaphthalene (330 mg, 1.75 mmol) according to the General procedure I. The residue was purified by column chromatography (5:1 petroleum ether–EtOAc). Yield: 274 mg (60%); brown oil, R_f 0.45 (1:2 EtOAc–petroleum ether); $[\alpha]_D^{23}$ −17.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23, 8.05 (2d, 2H, *J* 8.3, 8.2 Hz, H-5, H-8, Ar*H*), 7.53 (m, 2H, H-6, H-7, Ar*H*), 6.76 (s, 1H, H-3, Ar*H*), 5.56 (t, 1H, $J_{3',2'} = J_{3',4'}$ 9.8 Hz, H-3′), 5.44 (t, 1H, $J_{4',3'} = J_{4',5'}$ 9.3 Hz, H-4′), 5.30 (t, 1H, $J_{2',1'} = J_{2',3'}$ 9.7 Hz, H-2′), 5.13 (d, 1H, $J_{1',2'}$ 10.2 Hz, H-1′), 4.27 (dd, 1H, $J_{6'a,5'}$ 5.2 Hz, $J_{6'a,6'b}$ 12.4 Hz, H-6′a), 4.15 (dd, 1H, $J_{6'b,5}$ 2.0, $J_{6'b,6'a}$ 12.3 Hz, H-6′b), 4.01 (s, 3H, OCH_3), 3.97 (m, 1H, H-5′), 3.94 (s, 3H, OCH_3), 2.08, 2.05, 2.05, 2.03 (4s, 12H, $4 \times$ COCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$): 171.4, 171.0, 170.3, 169.8 ($4 \times$ *C*OCH$_3$), 153.0, 149.5 (C-1, C-4, Ar*C*), 128.8, 127.8, 127.5, 126.9, 124.1, 123.3, 122.9 (C-2, C-5 to C-10, Ar*C*), 102.1 (C-3, Ar*C*), 77.1, 75.5, 74.9, 71.6, 69.6 (C-1′ to C-5′), 64.0 (C-6′), 63.3 (O*C*H$_3$), 56.4 (O*C*H$_3$), 21.4, 21.1 (CO*C*H$_3$). IR (KBr) *v* 1755 (*CO*CH$_3$) cm^{-1}. ESIMS: *m*/*z* 541.1 $[M+Na]^+$, 557.1 $[M+K]^+$. HRESIMS: calcd for $C_{26}H_{30}O_{11}Na$: 541.1686; found: *m*/*z* 541.1684.

1.6. 2-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,4-naphthoquinone (3)

Prepared from **2** (280 mg, 0.54 mmol) according to the General procedure III. The residue was purified by column chromatography: 3:2 petroleum ether–EtOAc, then recrystallized from 1:1 CH_2Cl_2–petroleum ether. Yield: 220 mg (83%), yellow needles; mp 159–162 °C; R_f 0.55 (2:3 EtOAc–petroleum ether); $[\alpha]_D^{23}$ −10.9 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (m, 2H, H-5, H-8, Ar*H*), 7.56 (m, 2H, H-6, H-7, Ar*H*), 7.12 (s, 1H, H-3, Ar*H*), 5.41 (t, 1H, $J_{3',2'} = J_{3',4'}$ 9.4 Hz, H-3′), 5.18 (t, 1H, $J_{4',3'} = J_{4',5'}$ 9.7 Hz, H-4′), 5.05 (t, 1H, $J_{1',2'}$ 9.6 Hz, H-2′), 4.87 (d, 1H, $J_{1',2'}$ 9.8 Hz, H-1′), 4.27 (dd, 1H, $J_{6'a,5'}$ 4.9 Hz, $J_{6'a,6'b}$ 12.5 Hz, H-6′a), 4.16 (dd, 1H, $J_{6'b,5'}$ 2.0, $J_{6'b,6'a}$ 12.6 Hz, H-6′b), 3.86 (m, 1H, H-5′), 2.10, 2.05, 2.02, 1.87 (4s, 12H, $4 \times$ COCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$): 185.2, 184.1 ($2 \times$ C=O, naphthoquinone), 171.4, 170.8, 170.3, 170.2 ($4 \times$ *C*OCH$_3$), 146.7 (C-3, Ar*C*), 136.7, 134.9, 134.7, 132.5, 127.2, 127.1 (C-2, C-4 to C-10, Ar*C*), 77.0, 74.5, 73.3, 72.9, 69.1 (C-1′ to C-5′), 62.8 (C-6′), 21.4, 21.3, 21.1 (CO*C*H$_3$). IR (KBr) *v* 1746 (*CO*CH$_3$), 1668 (*CO*, naphthoquinone) cm^{-1}; ESIMS: *m*/*z* 511.1 $[M+Na]^+$. HRESIMS calcd for $C_{24}H_{24}O_{11}Na$: 511.1216; found: *m*/*z* 511.1218. Anal. Calcd for $C_{24}H_{24}O_{11}$: C, 59.02; H, 4.95. Found: C, 58.92; H, 4.88.

1.7. 2-(β-D-Glucopyranosyl)-1,4-dimethoxynaphthalene (4)

Prepared from **2** (91 mg, 0.18 mmol) according to the General procedure II. The residue was purified by column chromatography (2:1 EtOAc–EtOH), and recrystallized from Et_2O. Yield: 60 mg (97%), white crystals, mp 80–83 °C; R_f 0.40 (8:1 EtOAc–MeOH); $[\alpha]_D^{23}$ +2.3 (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, D_2O): δ 8.20, 8.07 (2d, 2H, *J* 8.3, 8.3 Hz, H-5, H-8, Ar*H*), 7.60 (m, 2H, H-6, H-7, Ar*H*), 6.96 (s, 1H, H-3, Ar*H*), 4.87 (d, 1H, $J_{1',2'}$ 9.7 Hz, H-1′), 3.98, 3.90 (2s, 6H, $2 \times$ OCH_3),

3.85–3.56 (m, overlapping, 6H, H-2′ to H-5′, H-6′a, H-6′b); ^{13}C NMR (125.8 MHz, D_2O): 155.0, 150.9 (C-1, C-4, Ar*C*), 130.6, 130.2, 129.6, 129.1, 128.4, 125.0, 124.7 (C-2, C-5 to C-10, Ar*C*), 105.4 (C-3, Ar*C*), 83.1, 80.3, 78.3, 75.7, 72.6 (C-1′ to C-5′), 66.1 (C-6′), 63.7 (O*C*H$_3$), 58.8 (O*C*H$_3$). IR (KBr) ν 3404 (OH) cm^{-1}; ESIMS: m/z 373.1 $[M+Na]^+$, 723.2 $[2M+Na]^+$; HRESIMS: calcd for $C_{18}H_{22}O_7Na$, 373.1263; found m/z 373.1259. Anal. Calcd for $C_{18}H_{22}O_7$: C, 61.71; H, 6.33. Found: C, 61.50; H, 6.33.

1.8. 2-(β-D-Glucopyranosyl)-1,4-naphthoquinone (5)

Prepared from **4** (35 mg, 0.01 mmol) according to the General procedure III. The residue was purified by column chromatography (1:8 MeOH–$CHCl_3$); yield: 26 mg (80%), orange oil; R_f 0.42 (6:1 $CHCl_3$–MeOH); ^{1}H NMR (500 MHz, D_2O): δ 8.03, 7.98 (2m, 2H, H-5, H-8, Ar*H*), 7.81 (m, 2H, H-6, H-7, Ar*H*), 7.13 (s, 1H, H-3, Ar*H*), 4.64 (d, 1H, $J_{1',2'}$ 9.8 Hz, H-1′), 3.88 (dd, 1H, $J_{6'b,5'}$ 1.3 Hz, $J_{6'b,6'a}$ 12.6 Hz, H-6′b), 3.75 (dd, 1H, $J_{6'a,5'}$ 5.1 Hz, $J_{6'a,6'b}$ 12.4 Hz, H-6′a), 3.61 (t, 1H, $J_{3',2'} = J_{3',4'}$ 8.7 Hz, H-3′), 3.57–3.50 (m, overlapping, 3H, H-2′, H-4′, H-5′); ^{13}C NMR: (125.8 MHz, D_2O): 189.6, 187.5 (2 × C=O, naphthoquinone), 150.5 (C-3, Ar*C*), 139.0 (C-2, Ar*C*), 137.5, 137.3 (C-7, C-8, Ar*C*), 134.2, 133.8 (C-9, C-10, Ar*C*), 129.4, 128.8 (C-5, C-6, Ar*C*), 83.0, 80.0, 77.2, 76.4, 72.4 (C-1′ to C-5′), 63.6 (C-6′). IR (KBr) ν 3412 (OH), 1663 (*CO*, naphthoquinone) cm^{-1}; ESIMS: m/z 343.1 $[M+Na]^+$, 359.1 $[M+K]^+$; HRESIMS: calcd for $C_{16}H_{16}O_7Na$: 343.0794; found: m/z 343.0793. Anal. Calcd for $C_{16}H_{16}O_7$: C, 60.00; H, 5.04. Found: C, 60.17; H, 4.98.

1.9. 2-(2,3,4-Tri-*O*-acetyl-6-*O*-benzoyl-β-D-glucopyranosyl)-1,4-dimethoxynaphthalene (7)

Prepared from **6** (797 mg, 1.88 mmol) according to the General procedure I. The residue was purified by column chromatography (5:1 petroleum ether–EtOAc). Yield: 824 mg (76%) brown oil, R_f 0.49 (1:3 EtOAc–petroleum ether); $[\alpha]_D^{27}$ +57.4 (*c* 1.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14–7.95 (m, 4H, H-5 to H-8, Ar*H*), 7.52–7.34 (m, 5H, *Ph*), 6.67 (s, 1H, H-3, Ar*H*), 5.49–5.34 (m, 3H, H-2′ to H-4′), 5.10 (d, 1H, $J_{1',2'}$ 9.9 Hz, H-1′), 4.49 (dd, 1H, $J_{6'b,5'}$ 2.4 Hz, $J_{6'b,6'a}$ 12.2 Hz, H-6′b), 4.32 (dd, 1H, $J_{6'a,5'}$ 4.9 Hz, $J_{6'a,6'b}$ 12.2 Hz, H-6′a), 4.06 (m, 1H, H-5), 3.87, 3.84 (2s, 6H, 2 × OC*H*$_3$), 2.01, 1.95, 1.66 (3s, 9H, 3 × COC*H*$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): 170.8, 171.7, 170.2 (3 × *C*OCH$_3$), 166.8 (*C*OPh), 153.0, 149.5 (C-1, C-4, Ar*C*), 133.9, 130.4, 130.4, 129.1, 128.8, 127.8, 127.4, 126.8, 124.2, 123.2, 122.9 (C-2, C-5 to C-10, Ar*C*, C-1″ to C-6″, CO*Ph*), 102.2 (C-3, Ar*C*), 77.1, 75.5, 74.9, 71.7, 69.9 (C-1′ to C-5′), 64.0 (C-6′), 63.8 (O*C*H$_3$), 56.3 (O*C*H$_3$), 21.3, 21.1 (CO*C*H$_3$); IR (KBr) ν 1755 (*CO*CH$_3$), 1724 (*CO*Ph) cm^{-1}; ESIMS: m/z 603.3 $[M+Na]^+$, 619.3 $[M+K]^+$; HRESIMS: calcd for $C_{31}H_{32}O_{11}Na$: 603.1842; found: m/z 603.1852.

1.10. 2-(2,3,4-Tri-*O*-acetyl-6-*O*-benzoyl-β-D-glucopyranosyl)-1,4-naphthoquinone (8)

Prepared from **7** (700 mg, 1.21 mmol) according to the General procedure III. The residue was purified by column chromatography (3:2 petroleum ether–EtOAc). Yield: 448 mg (67%) brown oil; R_f 0.66 (1:2 EtOAc–petroleum ether); $[\alpha]_D^{27}$ −7.1 (*c* 3.1, $CHCl_3$); ^{1}H NMR (500 MHz $CDCl_3$): δ 8.00 (m, 4H, H-5, H-8, Ar*H*, Ph*H*), 7.68 (m, 2H, Ar*H*), 7.51 (t, 1H, *J* 7.6 Hz, *Ph*), 7.39 (t, 2H, *J* 7.8 Hz, *Ph*), 7.03 (s, 1H, H-3, Ar*H*), 5.58 (t, 1H, $J_{3',4'} = J_{3',2'}$ 9.4 Hz, H-3′), 5.22 (t, 1H, $J_{4',5'} = J_{4',3'}$ 9.7 Hz, H-4′), 4.89 (t, 1H, $J_{2',3'} = J_{2',1'}$ 9.7 Hz, H-2′), 4.84 (d, 1H, $J_{1',2'}$ 9.7 Hz, H-1′), 4.46 (dd, 1H, $J_{6'b,5}$ 2.2 Hz, $J_{6'b,6'a}$ 12.8 Hz, H-6′b), 4.34 (dd, 1H, $J_{6'a,5'}$ 4.8 Hz, $J_{6'a,6'b}$ 12.4 Hz, H-6′a), 3.94 (m, 1H, H-5), 1.99, 1.95, 1.80 (3s, 9H, 3 × COC*H*$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): 185.4, 184.1 (2 × C=O, naphthoquinone), 170.8, 170.3, 170.2 (3 × *CO*CH$_3$), 166.9 (*CO*Ph), 146.7, 136.6, 134.8, 134.6, 133.9, 132.5, 130.5, 130.2, 129.1, 128.8, 127.1, 127.0 (C-2, C-5 to C-10, Ar*C*, *Ph*), 104.9 (C-3, Ar*C*), 77.0, 74.5, 73.3, 72.9, 69.6 (C-1′ to C-5′), 63.3 (C-6′), 21.2, 21.1 (CO*C*H$_3$); IR (KBr) ν 1755 (*CO*CH$_3$), 1724 (*CO*Ph), 1666 (*CO*, naphthoquinone) cm^{-1}; ESIMS: m/z 573.3 $[M+Na]^+$, 589.2 $[M+K]^+$; HRESIMS: calcd for $C_{29}H_{26}O_{11}Na$: 573.1373; found: m/z 573.1375. Anal. Calcd for $C_{29}H_{26}O_{11}$: C, 63.27; H, 4.76. Found: C, 63.54; H, 4.91.

1.11. 2-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-1,4-dimethoxynaphthalene (10)

Prepared from **9** (1.05 g, 2.69 mmol) according to the General procedure I. The residue was purified by column chromatography (5:1 petroleum ether–EtOAc). Yield: 907 mg (65%) brown oil, R_f 0.45 (1:2 EtOAc–petroleum ether); $[\alpha]_D^{23}$ +6.9 (*c* 3.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24, 8.06 (2d, 2H, *J* 8.2, 8.1 Hz, H-5, H-8, Ar*H*), 7.63 (m, 2H, H-6, H-7, Ar*H*), 6.81 (s, 1H, H-3, Ar*H*), 5.73 (t, 1H, $J_{2',3'} = J_{2',1'}$ 10.0 Hz, H-2′), 5.58 (d, 1H, *J* 3.1 Hz, H-4′), 5.29 (dd, 1H, $J_{3',4'}$ 3.2 Hz, $J_{3',2'}$ 9.9 Hz, H-3′), 5.10 (d, 1H, $J_{1',2'}$ 10.1 Hz, H-1′), 4.21–4.13 (m, overlapping, 3H, H-5′, H-6′a, H-6′b), 4.02, 3.95 (2s, 6H, 2 × OC*H*$_3$), 2.26, 2.02, 2.01, 1.73 (4s, 12H, 4 × COC*H*$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): 171.1, 171.0, 170.9, 169.8 (4 × *C*OCH$_3$), 152.9, 149.5 (C-1, C-4, Ar*C*), 128.8, 127.8 127.4, 126.8, 124.4, 123.2, 122.9 (C-2, C-5 to C-10, Ar*C*), 102.5 (C-3, Ar*C*), 75.7, 75.6, 73.4, 68.9, 68.7 (C-1′ to C-5′), 64.0 (C-6′), 62.6 (O*C*H$_3$), 56.4 (O*C*H$_3$), 21.5, 21.3, 21.2 (CO*C*H$_3$). IR (KBr) ν 1749 (*CO*CH$_3$) cm^{-1}. ESIMS:

m/*z* 541.1 $[M+Na]^+$, 557.1 $[M+K]^+$, 1059.2 $[2M+Na]^+$, 1075.2 $[2M+K]^+$; HRESIMS: calcd for $C_{26}H_{30}O_{11}Na$: 541.1686; found: *m*/*z* 541.1685.

1.12. 2-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-1,4-naphthoquinone (13)

Prepared from **10** (907 mg, 1.75 mmol) according to the General procedure III. The residue was purified by column chromatography (3:2 petroleum ether–EtOAc), then recrystallized from 1:1 CH_2Cl_2–petroleum ether. Yield: 810 mg (95%), yellow crystals; mp 109–112 °C; R_f 0.55 (2:3 EtOAc–petroleum ether); $[\alpha]_D^{23}$ +4.9 (*c* 0.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.09 (m, 2H, H-5, H-8, Ar*H*), 7.77 (m, 2H, H-6, H-7, Ar*H*), 7.21 (s, 1H, H-3, Ar*H*), 5.53 (d, 1H, *J* 2.7 Hz, H-4′), 5.25 (dd, 1H, $J_{3',2'}$ 10.1 Hz, $J_{3',4'}$ 3.2 Hz, H-3′), 5.19 (t, 1H, $J_{2',1'} = J_{2',3'}$ 9.8 Hz, H-2′), 4.86 (d, 1H, $J_{1',2'}$ 9.2 Hz, H-1′), 4.19–4.06 (m, overlapping, 3H, H-6′a, H-6′b, H-5′), 2.21, 2.05, 2.00, 1.88 (4s, 12H, 4 × COC*H*$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): 185.4, 184.3 (2 × C=O, naphthoquinone), 171.1, 170.9, 170.6 (*C*OCH$_3$), 147.2 (C-3, Ar*C*), 136.9, 134.8, 134.7, 132.5, 127.1, 127.0 (C-2, C-4 to C-10, Ar*C*), 75.5, 73.0, 72.5, 70.9, 68.2 (C-1′ to C-5′), 62.4 (C-6′), 21.4, 21.3, 21.2 (CO*C*H$_3$). IR (KBr) *v* 1750 (*CO*CH$_3$), 1670 (*CO*, naphthoquinone) cm^{-1}; ESIMS: *m*/*z* 511.1 $[M+Na]^+$. HRESIMS: calcd for $C_{24}H_{24}O_{11}Na$, 511.1216; found: *m*/*z* 511.1172. Anal. Calcd for $C_{24}H_{24}O_{11}$: C, 59.02; H, 4.95. Found: C, 58.89; H, 4.99.

1.13. 2-(β-D-Galactopyranosyl)-1,4-dimethoxynaphthalene (14)

Prepared from **10** (246 mg, 0.47 mmol) according to the General procedure II. The residue was purified by column chromatography (2:1 EtOAc–EtOH), and recrystallized from Et_2O. Yield: 98 mg (59%) white crystals, mp 70–72 °C; R_f 0.40 (8:1 EtOAc–MeOH); $[\alpha]_D^{23}$ +5.2 (*c* 1.1, MeOH); ^1H NMR (500 MHz, D_2O): δ 8.21, 8.08 (2d, 2H, *J* 8.4 Hz, 8.2 Hz, H-5, H-8, Ar*H*), 7.60 (m, 2H, H-6, H-7, Ar*H*), 7.09 (s, 1H, H-3, Ar*H*), 4.83 (d, 1H, $J_{1',2'}$ 9.8 Hz, H-1′), 4.08 (d, 1H, *J* 3.3 Hz, H-4′), 4.02(dd, 1H, $J_{2',1'}$ 9.7 Hz, $J_{2',3'}$ 7.4 Hz, H-2′), 4.00, 3.91 (2s, 6H, 2 × OC*H*$_3$), 3.89 (m, 1H, H-5′), 3.83 (dd, 1H, $J_{3',2'}$ 7.5 Hz, $J_{3',4'}$ 3.4 Hz, H-3′), 3.72 (m, overlapping, 2H, H-6′a, H-6′b); ^{13}C NMR (125.8 MHz, D_2O): 154.9, 150.7 (C-1, C-4, Ar*C*), 130.5, 123.0, 129.1, 129.0, 128.7, 124.8, 124.7 (C-2, C-5 to C-10, Ar*C*), 105.5 (C-3, Ar*C*), 82.0, 78.7, 77.1, 73.1, 72.0 (C-1′ to C-5′), 66.0 (C-6′), 63.8 (O*C*H$_3$), 58.7 (O*C*H$_3$). IR (KBr) *v* 3412 (OH) cm^{-1}; ESIMS: *m*/*z* 373.0 $[M+Na]^+$, 723.1 $[2M+Na]^+$; HRESIMS: calcd for $C_{18}H_{22}O_7Na$: 373.1263; found: *m*/*z* 373.1265. Anal. Calcd for $C_{18}H_{22}O_7$: C, 61.71; H, 6.33. Found: C, 61.44; H, 6.26.

1.14. 2-(β-D-Galactopyranosyl)-1,4-naphthoquinone (15)

Prepared from **14** (40 mg, 0.01 mmol) according to the General procedure III. The residue was purified by column chromatography (8:1 CH_3OH–$CHCl_3$). Yield: 25 mg (67%), brown oil, R_f 0.42 (6:1 $CHCl_3$–MeOH); ^1H NMR (500 MHz, D_2O): δ 7.98 (m, 2H, H-5, H-8, Ar*H*), 7.81 (m, 2H, H-6, H-7, Ar*H*), 7.18 (s, 1H, H-3, Ar*H*), 4.60 (d, 1H, $J_{1',2'}$ 9.8 Hz, H-1′), 4.04 (d, 1H, *J* 2.7 Hz, H-4′), 3.83–3.71 (m, overlapping, 5H, H-2′, H-3′, H-5′, H-6′a, H-6′b); ^{13}C NMR (125.8 MHz, D_2O): 189.7, 187.6 (2 × C=O, naphthoquinone), 150.8 (C-3, Ar*C*), 139.0 (C-2, Ar*C*), 137.5, 137.3 (C-7, C-8, Ar*C*), 134.2, 133.8 (C-9, C-10, Ar*C*), 129.5, 128.8 (C-5, C-6, Ar*C*), 82.3, 76.8, 76.7, 74.6, 72.0 (C-1′ to C-5′), 64.0 (C-6′). IR (KBr) *v* 3429 (OH), 1663 (*CO*, naphthoquinone) cm^{-1}; ESIMS: *m*/*z* 343.1 $[M+Na]^+$, 359.1 $[M+K]^+$, 663.2 $[2M+Na]^+$; HRESIMS: calcd for $C_{16}H_{16}O_7Na$: 343.0794; found: *m*/*z* 343.0793. Anal. Calcd for $C_{16}H_{16}O_7$: C, 60.00; H, 5.04. Found: C, 59.83; H, 5.00.

1.15. 2-(2,3,4-Tri-*O*-acetyl-6-*O*-benzoyl-β-D-galactopyranosyl)-1,4-dimethoxynaphthalene (17)

Prepared from **16** (661 mg, 1.56 mmol) according to the General procedure I. The residue was purified by column chromatography (5:1 petroleum ether–EtOAc); Yield: 583 mg (65%) brown oil, R_f 0.31 (1:3 EtOAc–petroleum ether); ^1H NMR ($CDCl_3$, 500 MHz): δ 8.24, 8.05 (2d, 2H, *J* 8.2 Hz, 8.1 Hz, H-5, H-8, Ar*H*), 7.97 (d, 2H, *J* 7.5 Hz, *Ph*), 7.56–7.48 (m, 3H, H-6, H-7, Ar*H*, *Ph*), 7.41 (t, 2H, *J* 7.8 Hz, *Ph*), 6.85 (s, 1H, H-3, Ar*H*), 5.78 (t, $J_{2',1'} = J_{2',3'}$ 10.0 Hz, H-2′), 5.71 (d, 1H, $J_{4',3'}$ 3.2 Hz, H-4′), 5.35 (dd, 1H, $J_{3',4'}$ 3.4 Hz, $J_{3',2'}$ 10.0 Hz, H-3′), 5.15 (d, 1H, $J_{1',2'}$ 10.1 Hz, H-1′), 4.49 (dd, 1H, $J_{6'a,5'}$ 4.2 Hz, $J_{6'a,6'b}$ 10.8 Hz, H-6′a), 4.38 (t, 1H, *J* 4.2 Hz, H-5′), 4.34 (dd, 1H, $J_{6'b,5'}$ 3.9 Hz, $J_{6'b,6'a}$ 10.3 Hz, H-6′b), 4.03, 3.92 (2s, 6H, 2 × OC*H*$_3$), 2.28, 2.02, 1.73 (3s, 9H, 3 × COC*H*$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): 171.9, 171.8, 169.9 (3 × *C*OCH$_3$), 166.7 (*C*OPh), 152.89, 149.6 (C-4, C-1, Ar*C*), 133.9, 130.4, 130.3, 130.1, 129.2, 129.1, 128.8, 127.8, 127.4, 126.8, 124.3, 123.2, 122.9 (C-2, C-5 to C-10, Ar*C*, C-1″ to C-6″, *Ph*), 102.5 (C-3, Ar*C*), 75.8, 75.6, 73.3, 68.9, 68.8 (C-1′ to C-5′), 62.9 (C-6′), 62.8 (O*C*H$_3$), 56.4 (O*C*H$_3$), 21.5, 21.3, 21.2 (3 × CO*C*H$_3$); IR (KBr) *v* 1749 (*CO*CH$_3$), 1731 (*CO*Ph) cm^{-1}; ESIMS: *m*/*z* 603.2 $[M+Na]^+$, 619.2 $[M+K]^+$, 1183.4 $[2M+Na]^+$; HRESIMS: calcd for $C_{31}H_{32}O_{11}$, 603.1842; found: *m*/*z* 603.1862.

1.16. 2-(2,3,4-Tri-*O*-acetyl-6-*O*-benzoyl-β-D-galactopyranosyl)-1,4-naphthoquinone (18)

Prepared from **17** (539 mg, 0.93 mmol) according to the General procedure III. The residue was purified by column chromatography (3:2 petroleum ether–EtOAc).

Yield: 436 mg (85%) brown oil, R_f 0.46 (1:2 EtOAc–petroleum ether); $[\alpha]_D^{28}$ +0.2 (*c* 1.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.10 (m, 2H, H-5, H-8, Ar*H*), 8.03 (d, 2H, *J* 7.1 Hz, *Ph*), 7.77 (m, 2H, H-6′, H-7′, Ar*H*), 7.58 (t, 1H, *J* 7.5 Hz, *Ph*), 7.46 (t, 2H, *J* 7.9 Hz, H-3″, H-5″, *Ph*), 7.11 (d, 1H, *J* 1.6 Hz, H-3, Ar*H*), 5.63 (m, 1H, H-5′), 5.51 (d, 1H, $J_{4',3'}$ 3.9 Hz, H-4′), 5.32 (dd, 1H, $J_{3',2'}$ 9.6 Hz, $J_{3',4'}$ 3.8 Hz, H-3′), 5.26 (t, 1H, $J_{2',1'} = J_{2',3'}$ 9.6 Hz, H-2′), 4.66 (dd, 1H, $J_{6'b,5'}$ 3.9 Hz, $J_{6'b,6'a}$ 12.1 Hz, H-6′b), 4.53 (dd, 1H, $J_{6'a,5'}$ 6.8 Hz, $J_{6'a,6'b}$ 12.0 Hz, H-6′a), 4.25 (d, 1H, $J_{1',2'}$ 9.1 Hz, H-1′), 2.17 2.14, 1.87 (3s, 9H, 3 × COC*H*$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): 185.4, 184.2 (2 × C═O, Ar*C*), 171.1, 170.8, 170.6 (3 × *C*OCH$_3$), 166.6 (*C*OPh), 147.2, 136.8, 134.8, 134.0, 132.5, 130.4, 130.3, 129.1, 128.8, 127.0, 126.9 (C-2, C-5 to C-10, Ar*C*, *Ph*), 97.9 (C-3, Ar*C*), 75.5, 73.0, 72.4, 70.9, 68.3 (C-1′ to C-5′), 62.7 (C-6′), 21.3, 21.2 (CO*C*H$_3$); IR (KBr) *v* 1751 (*CO*CH$_3$), 1727 (*CO*Ph), 1662 (*CO*, naphthoquinone); ESIMS: *m*/*z* 573.2 $[M+Na]^+$, 589.2 $[M+K]^+$; HRESIMS: calcd for $C_{29}H_{26}O_{11}Na$: 573.1373; found: *m*/*z* 573.1353. Anal. Calcd for $C_{29}H_{26}O_{11}$: C, 63.27; H, 4.76. Found: C, 63.30; H, 4.66.

1.17. In vitro antitumor assays

The human A375 melanoma cells were purchased from the Cell Bank of Type Culture Collection of the Chinese Academy of Sciences (Shanghai, China).

1.17.1. Antiproliferative assays (MTT). The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) colorimetric assay was performed as described by Mosman.[12a] A375 Cells were placed within 96-well culture plates (10^4 cells/well), respectively, and allowed to attach for 24 h before treatment. The cells were treated with the compounds prepared ranging from 10 to 160 μM or without the tested compound (vehicle control, 0.1% Me_2SO). The cytotoxicity of the compounds was evaluated after 24 h of culture using the MTT assay. Absorbance in control and drug-treated wells was measured in an Automated Microplate Reader (Multiskan Mk3, Thermo Electron Corporation) at 550 nm. The cytotoxicity of the compounds was expressed as IC_{50} (concentration of 50% cytotoxicity, which was extrapolated from linear regression analysis of experimental data).

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