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New chalcone-3-*O*-glycoside derivatives: Synthesis and characterization

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Abstract

Seven novel carbohydrate conjugates of new chalcone-3-*O*-glycosides were synthesized and characterized. Starting from the substituted 3′-hydroxyarylmethylacetophenone derivatives (chalcones) with α-acetobromoglucose in anhydrous acetone were synthesized 2,3,4,6-tetra-*O*-acetyl-3′-*O*-β-D-glucopyranosyloxychalcones. Deblocking the latter with CH_3ONa in dry methanol results in substituted chalcone-3-*O*-glycosides (3′-*O*-β-D-glucopyranosyloxychalcones). The structures of the newly synthesized chalcone-3-*O*-glycosides were characterized based on ^{1}H nuclear magnetic resonance, ^{13}C nuclear magnetic resonance, mass spectroscopy, and Fourier-transform infrared spectroscopy.

Keywords

chalcone, chalcone-3-*O*-glycosides, characterization, nuclear magnetic resonance, synthesis

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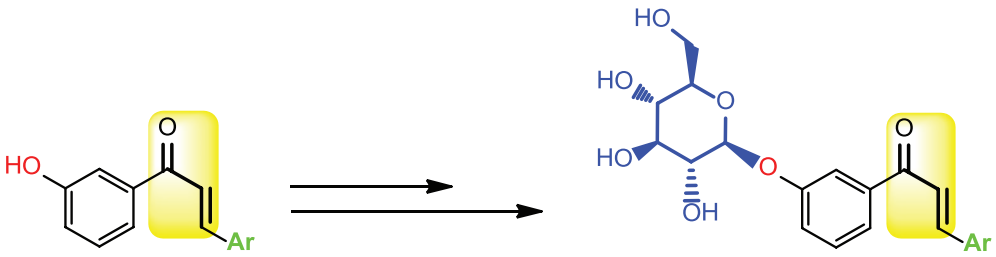

Compound Aril= 2-thienyl
4-nitrophenyl
4-(dimethylamino)phenyl
4-methoxyphenyl
4-fluorophenyl
4-chlorophenyl
4-bromophenyl

Chalcone-3-*O*-glycoside derivatives

Introduction

Chalcones, compounds bearing the 1,3-diaryl-2-propen-1-one system, play a vital role in chemical compounds associated with diverse pharmacological activities.[1] Due to their flexible structures, chalcones can bind effectively to many kinds of enzymes or receptors and exhibit a broad spectrum of biological activities such as anticancer,[2] anti-HIV,[3] anti-inflammatory,[4,5] anti-invasive,[6,7] and antibacterial properties.[8]

Glycosylation of small biologically active molecules, either of natural or synthetic origin, has an effect on their solubility, and bioactivity. Notably, β-glucosylation improves the drug's targeting to cells as well as their "solubility" in cell membranes.[9,10] *O*-glycosides are a family of carbohydrates widely found in plants with carbon–oxygen bond formation employing activated sugar.[11,12] Phenolic hydroxyl groups occur in the free state or in combined form as *O*-glycosides in plants where they play many interesting biological activities,

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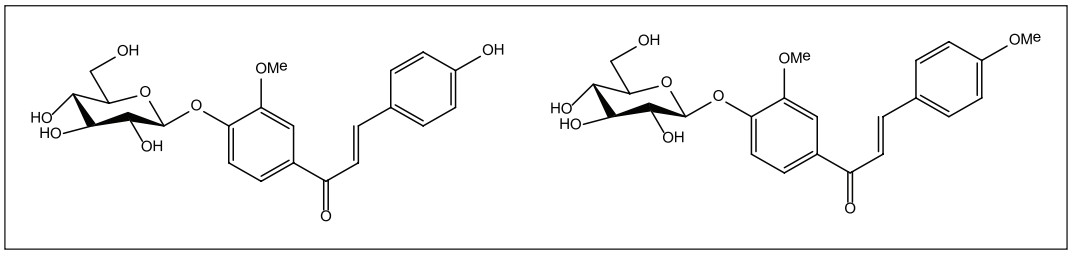
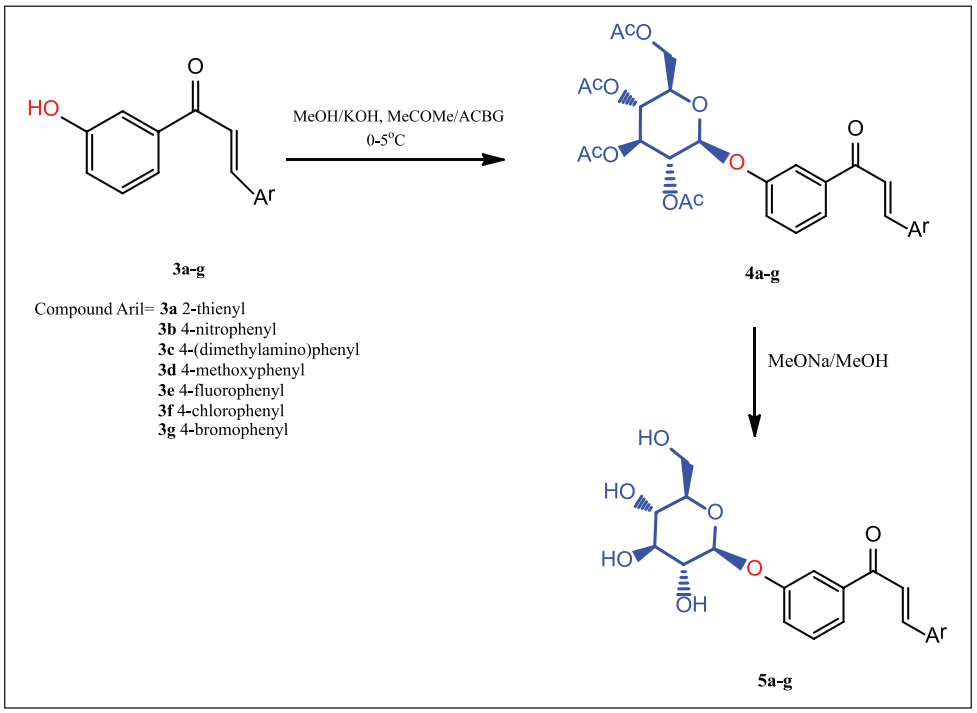


Scheme 1. Structures of isolated chalcone glycosides from *Brassica rapa* L. "hidabeni."
4′-*O*-β-D-Glucopyranosyl-4-hydroxy-3′methoxychalcone (**1**).
4′-*O*-β-D-Glucopyranosyl-3′,4-dimethoxychalcone (**2**).



Scheme 2. General route for the synthesis of chalcone-3-*O*-glycosides (**5a–g**).

such as antitumor activity and inhibitors of the metabolic process.[13]

Much attention has been paid to chalcones as potential biological agents after the discovery of the natural chalcone-*O*-glycosides which demonstrated a broad spectrum of antibiotic, antifungal, and anti-HIV activity.[14] The isolation of some chalcone glycosides (see Scheme 1) from the aerial parts of *Brassica rapa* L. "hidabeni" has been reported.[15] However, to the best of the author's knowledge, few reports have been dedicated to the synthesis and inhibitory activity of chalcone derivatives containing an *O*-glycoside skeleton.

In this study, preliminary results in the organic synthesis of some new chalcone-3-*O*-glycosides will be reported. Scheme 2 shows the synthetic analysis of the target molecules. Target molecules in this study are chalcones with various sugar substitutions at 3-position.

Results and discussion

First, substituted chalcones starting from 3-hydroxyacetophenone and different aldehydes were synthesized at room temperature according to the Claisen–Schmidt condensation method, which is a single-step process and a practical method for the synthesis of substituted chalcone derivatives (Scheme 2).[16]

In the second step, *O*-glucosylation reactions were performed by condensing α-acetobromoglucose (ACBG) and 3-hyroxychalcones (**3a–g**) at 0–5 °C using 5% aqueous potassium hydroxide (KOH) solution in dry acetone under an inert atmosphere.[13] Deacetylation by methanolic MeONa solution gave, after purification, chalcone-3-*O*-glycosides (**5a–g**) in good yield in favor of the β-anomer from 2,3,4,6-tetra-*O*-acetyl-3′-*O*-β-glucopyranosyloxybenzlideneacetophenones **4a–g** see (Scheme 2).[17]

The synthesis of chalcone-3-*O*-glycosides was achieved in this second step. The structures of all the compounds were confirmed by nuclear magnetic resonance (NMR), liquid chromatography–mass spectrometry (LC/MS–MS), and Fourier-transform infrared spectroscopy (FTIR; attenuated total reflection (ATR)), spectroscopy. The results were consistent with the predicted structures for all the new chalcone-3-*O*-glycosides, as described in section "Experiment".

The β-configuration of the glycosidic bond was confirmed from ^{1}H NMR and ^{13}C NMR. In the ^{1}H NMR spectrum of **5a–g**, the anomeric proton appeared as a doublet at ~δ 5.03 (d, ~7.6 Hz) that confirmed the β-orientation of the sugar unit.[18] Characteristic pyranosyl ring protons were located at δ 3.40–3.96.

In the proton-decoupled ^{13}C NMR, the anomeric carbon was located at δ ~101.00, which is consistent with the formation of the β-glucoside **5a–g**. The mass spectrum of 3-((2*E*)-3-(2-thienyl)prop-2-enol-yl)phenyl hexopyranoside (**5a**) also confirmed the proposed structure of the chalcone-3-*O*-glycoside. The molecular ion peak was observed at *m*/*z* 393.0825 as $(M+H)^+$, (100; see Electronic Supplementary Information (ESI)).

The structure of 3-((2*E*)-3-(2-thienyl)prop-2-enol-yl) phenyl hexopyranoside (**5a**) was confirmed by the appearance of the –C=O band at 1651 cm^{-1} in the FTIR spectrum. The characteristic bands at 3343 and 1651 cm^{-1} indicated the existence of –OH and –C=O groups, respectively.

In the ^{1}H NMR spectra of the synthesized chalcone-3-*O*-glycoside derivatives (**5a–g**), the α,β-protons resonated as doublet doublets (dd) between δ 7.74 and 7.59, which is characteristic for α,β-unsaturated carbonyl compounds. The olefinic H-atoms of chalcone-3-*O*-glycoside (**5a–g**) were shown to be *trans* based on their *J* values of 15.4–15.7 Hz for Hα and Hβ.[19]

In the ^{13}C NMR spectra of the compound **5e**, the characteristic carbon–fluorine signals appear at 131.32/131.29 (C_2''), 115.74/115.52 (C_3''), 165.44/162.95 (C_4''), 131.32/131.29 (C_5''), and 115.74/115.52 (C_6'') (see ESI).[20]

The mass spectra of compounds **5a–g** showed molecular ion peaks at the appropriate *m*/*z* values confirming their molecular mass. In the ^{1}H and ^{13}C NMR spectra of compounds **5a–g**, in particular, anomeric protons and anomeric carbons showed peaks at, respectively, δ_H 5.03 (1H, d) and δ_C 101.00 ppm; which are an indication of the β-configuration of the chalcone-3-*O*-glycosides (**5a–g**).

Conclusion

The synthesis of seven new chalcone-3-*O*-glycosides, which can be used to make more glycosylated chalcone, is reported in this study. The structures of the synthesized chalcone and chalcone-3-*O*-glycoside have been confirmed by NMR, LC/MS–MS, and FTIR (ATR) spectroscopy. Chalcones are important α,β-unsaturated ketones and constitute a class of naturally occurring substances, which are very attractive bioactive starting materials for the synthesis of substituted chalcone-*O*-glycosides.

Experiment

^{1}H and ^{13}C NMR spectra were recorded on a 400 (100)-MHz Bruker Avance spectrometer in methanol-d_4; δ is given in ppm relative to Me_4Si (tetramethylsilane (TMS)) as an internal standard. The following abbreviations are used: s = singlet, d = doublet, dd = doublet doublet, t = triplet, m = multiplet, bs = broad singlet, bd = broad doublet. The high-resolution accurate masses were determined using Micromass Quattro LC–MS/MS. The IR spectra were recorded on a Perkin Elmer 1600 Fourier transform infrared (FTIR-ATR) spectrophotometer. Compounds **3a–g** were synthesized by the method described by Narender et al.[21] NMR, MS, IR data, and melting point of the known compounds were consistent with those reported previously.[22–28]

*Synthesis of chalcones (**3a–g**): general procedure*

Compounds **3a–g** were synthesized according to the previously reported procedure.[22–28]

*Synthesis of 2,3,4,6-tetra-O-acetyl-3′-O-β-glucopyranosyloxybenzlideneacetophenones (**4a–g**): general procedure*

The 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0.411 g, 1 mmol) was dissolved in dry acetone (20 mL) and cooled to 0–3 °C. To this, a solution of the potassium salt of 3′-hydroxybenzylideneacetophenones (1 mmol) in 5% methanolic KOH (10 mL) was added dropwise under a nitrogen atmosphere. The resulting mixture was stirred at 0–3 °C for 8 h and the reaction was allowed to proceed for an additional 10 h at room temperature. After stirring for 19 h, the resultant solution was partitioned with EtOAc, distilled water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified using silica gel 230–400 mesh eluting with 20% MeOH in $CHCl_3$ to obtain compounds **4a–g** as orange syrups.

*The general method for 3′-O-β-glucopyranosyloxybenzlideneacetophenones **5a–g***

A freshly prepared solution of MeONa–MeOH (3 mL, 0.05 M) was added to a solution of 2,3,4,6-tetra-*O*-acetyl-3′-*O*-β-glucopyranosyloxybenzlideneacetophenones **4a–g** (0.1 g) in 20 mL dry methanol and kept at room temperature under a nitrogen atmosphere. The progress of the reaction was followed by silica gel thin-layer chromatography (TLC; $CHCl_3$–MeOH, 3:1). The reaction was stopped after 24 h. The mixture was extracted with EtOAc (3 × 10 mL), the combined organic phases were successively washed with H_2O (2 × 10 mL), dried over Na_2SO_4 and concentrated. The syrupy residue was purified on silica gel using $CHCl_3$–MeOH (9/1 to 7/3, then 6/4, v/v).

3-[(2E)-3-(2-thienyl)prop-2-enol-yl]phenyl hexopyranoside (**5a**): Orange oil; yield 98 mg (25%); ^{1}H NMR (CD_3OD): δ 7.45 (d, *J* = 15.6 Hz, 1H), 7.94 (d, *J* = 15.6 Hz, 1H), 7.75 (bs, 1H), 7.40 (bd, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.16 (dd, *J* = 8.2, 4.6 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 5.06 (d, *J* = 7.6 Hz, 1H), 3.60–3.40 (m, 4H), 3.72 (dd, *J* = 12.4, 4.1 Hz, 1H), 3.94 (dd, *J* = 12.4, 2.1 Hz, 1H); ^{13}C NMR (CD_3OD): δ 189.84, 122.13, 137.45, 139.21, 116.97, 158.03, 122.98, 129.60, 122.13, 140.01, 132.36, 128.24, 129.53, 101.00, 73.49, 76.84, 69.95, 76.52, 61.04; MS

(ESI) *m/z* for $C_{19}H_{20}O_7S$ $[M+1]^+$: 393 (90), 282 (50); IR (ATR) (*v*, cm^{-1}): 3343, 2962, 1651, 1574, 1251, 1071, 711.

3-[(2E)-3-(4-nitrophenyl)prop-2-enol-yl]phenyl hexopyranoside (**5b**): Orange oil; yield 87 mg (20%); ^1H NMR (CD_3OD): δ 7.83 (d, *J*=15.6 Hz, 1H), 7.93 (d, *J*=15.6 Hz, 1H), 7.80 (bs, 1H), 7.40 (dd, *J*=7.6, 3.2 Hz, 1H), 7.52 (t, *J*=7.6 Hz, 1H), 7.84 (m, 1H), 8.00 (d, *J*=7.8 Hz, 2H), 8.32 (d, *J*=7.8 Hz, 2H), 5.06 (d, *J*=7.6 Hz, 1H), 3.60–3.40 (m, 4H), 3.72 (dd, *J*=12.4, 4.1 Hz, 1H), 3.94 (dd, *J*=12.4, 2.1 Hz, 1H); ^{13}C NMR (CD_3OD): δ 189.57, 123.68, 141.56, 138.83, 115.84, 158.08, 121.73, 129.65, 122.43, 141.12, 129.27, 125.42, 148.59,125.42, 129.27, 100.97, 74.34, 76.95, 70.22, 76.55, 61.17; MS (ESI) *m/z* for $C_{21}H_{21}NO_9$ $[M+Na]^+$: 454 (25), 282 (100); IR (ATR) (*v*, cm^{-1}): 3364, 2926, 1669, 1515, 1337, 1246, 1046, 754.

3-[(2E)-3-(4-dimethylaminophenyl)prop-2-enol-yl]phenyl hexopyranoside (**5c**): Orange oil; yield 94 mg (22%); ^1H NMR (CD_3OD): δ 7.72 (d, *J*=15.4 Hz, 1H), 7.78 (d, *J*=15.4 Hz, 1H), 7.42 (s, 1H), 7.34 (dd, *J*=9.4, 2.1 Hz, 1H), 7.48 (m, 1H), 7.50 (d, *J*=7.8 Hz, 1H), 7.64 (d, *J*=7.8 Hz, 2H), 6.78 (d, *J*=7.8 Hz, 2H), 3.06 (s, 6H), 5.02 (d, *J*=7.7 Hz, 1H), 3.60–3.40 (m, 4H), 3.74 (dd, *J*=12.2, 3.7 Hz, 1H), 3.94 (dd, *J*=12.2, 2.1 Hz, 1H); ^{13}C NMR (CD_3OD): δ 190.70, 122.27, 146.83, 140.11, 116.00, 157.97, 122.27, 129.41, 122.06, 122.27, 130.58, 111.60, 152.65, 111.60, 130.28, 58.09, 101.03, 73.51, 76.88, 70.17, 76.53, 61.09; MS (ESI) *m/z* for $C_{23}H_{27}NO_7$ $[M+1]^+$: 430 (95), 282 (15); IR (ATR) (*v*, cm^{-1}): 3376, 2923, 1644, 1571, 1243, 1076, 785.

3-[(2E)-3-(4-methoxyphenyl)prop-2-enol-yl]phenyl hexopyranoside (**5d**): Yellow oil; yield 124 mg (30%); ^1H NMR (CD_3OD): δ 7.60 (d, *J*=15.7 Hz, 1H), 7.72 (d, *J*=15.7 Hz, 1H), 7.74 (m, 1H), 7.38 (m, 1H), 7.49 (t, *J*=7.7 Hz, 1H), 7.74 (m, 1H), 7.73 (d, *J*=7.6 Hz, 2H), 7.00 (d, *J*=7.6 Hz, 2H), 3.75 (s, 3H), 5.01 (d, *J*=7.8 Hz, 1H), 3.60–3.40 (m, 4H), 3.74 (dd, *J*=12.2, 4.1 Hz, 1H), 3.94 (dd, *J*=12.3, 2.2 Hz, 1H); ^{13}C NMR (CD_3OD): δ 190.56, 123.33, 146.83, 140.14, 139.57, 116.52, 158.00, 122.21, 129.41, 122.60, 127.79, 131.42, 114.13, 162.16, 131.42, 114.13, 54.53, 101.00, 73.50, 76.88, 69.94, 76.52, 61.10; MS (ESI) *m/z* for $C_{22}H_{24}O_8$ $[M+1]^+$: 417 (100); IR (ATR) (*v*, cm^{-1}): 3290, 2924, 1656, 1585, 1250, 1022, 793.

3-[(2E)-3-(4-fluorophenyl)prop-2-enol-yl]phenyl hexopyranoside (**5e**): Yellow oil; yield 113 mg (28%); ^1H NMR (CD_3OD): δ 7.70 (d, *J*=15.6 Hz, 1H), 7.82 (d, *J*=15.6 Hz, 1H), 7.39 (m, 1H), 7.20 (d, *J*=7.7 Hz, 1H), 7.48 (t, *J*=7.7 Hz, 1H), 7.18 (d, *J*=7.8 Hz, 1H), 7.86–7.75 (m, 4H), 5.03 (d, *J*=7.6 Hz, 1H), 3.60–3.40 (m, 4H), 3.72 (dd, *J*=12.1, 4.0 Hz, 1H), 3.96 (bd, *J*=12.2 Hz, 1H); ^{13}C NMR (CD_3OD): δ 190.22, 122.69, 143.66, 139.23, 116.47, 158.01, 122.33, 129.58, 122.69, 131.47, 131.32/131.29, 115.74/115.52, 165.44/162.95, 131.32/131.29, 115.74/115.52, 103.98, 74.73, 76.78, 70.70, 76.52, 61.13; MS (ESI) *m/z* for $C_{21}H_{21}FO_7$ $[M+1]^+$: 405 (100); IR (ATR) (*v*, cm^{-1}): 3310, 2926, 1672, 1580, 1225, 1045, 790.

3-[(2E)-3-(4-chlorophenyl)prop-2-enol-yl]phenyl hexopyranoside (**5f**): Yellow oil; yield 85 mg (20%); ^1H NMR (CD_3OD): δ 7.40 (d, *J*=15.6 Hz, 1H), 7.52 (d, *J*=15.6 Hz, 1H), 7.80 (m, 1H), 7.30 (m, 1H), 7.44 (m, 1H), 7.78 (m, 1H), 7.78 (d, *J*=7.8 Hz, 2H), 7.46 (d, *J*=7.8 Hz, 2H), 5.01 (d, *J*=7.7 Hz, 1H), 3.60–3.40 (m, 4H), 3.74 (dd, *J*=12.3, 4.1 Hz, 1H), 3.94 (bd, *J*=12.3 Hz, 1H); ^{13}C NMR (CD_3OD): δ 190.09, 122.33, 143.33, 139.16, 116.16, 158.05, 122.20, 129.88, 122.33, 133.61, 129.59, 129.38, 136.12, 129.38, 129.88, 100.99, 73.50, 76.91, 69.98, 76.54, 61.13; MS (ESI) *m/z* for $C_{21}H_{21}ClO_7$ $[M+1]^+$: 421 (90); IR (ATR) (*v*, cm^{-1}): 3348, 2919, 1658, 1579, 1245, 1010, 822, 782.

3-[(2E)-3-(4-bromophenyl)prop-2-enol-yl]phenyl hexopyranoside (**5g**): Yellow oil; yield 116 mg (25%); ^1H NMR (CD_3OD): δ 7.45 (d, *J*=15.4 Hz, 1H), 7.48 (d, *J*=15.4 Hz, 1H), 7.74 (bs, 1H), 7.33 (m, 1H), 7.40 (m, 1H), 7.78 (m, 1H), 7.60 (d, *J*=7.6 Hz, 2H), 7.69 (d, *J*=7.6 Hz, 2H), 5.03 (d, *J*=7.8 Hz, 1H), 3.60–3.40 (m, 4H), 3.72 (dd, *J*=12.1, 3.9 Hz, 1H), 3.95 (dd, *J*=12.1, 1.3 Hz, 1H); ^{13}C NMR (CD_3OD): δ 190.09, 124.40, 143.42, 139.13, 116.48, 158.02, 122.24, 129.60, 122.73, 133.96, 129.60, 131.58, 124.42, 129.60, 131.58, 100.97, 74.19, 76.89, 69.97, 76.53, 61.13; MS (ESI) *m/z* for $C_{21}H_{21}BrO_7$ $[M]^+$: 465 (95); IR (ATR) (*v*, cm^{-1}): 3362, 2921, 1662, 1579, 1249, 1069, 776.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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