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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimicrobial activity of 7-alkoxyhesperetin derivatives

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Abstract Some new 7-alkoxyhesperetin derivatives, 7-methoxy-(**c**), 7-butoxy-(**d**), 7-octyloxy-(**e**), 7-decyloxy-(**f**), and 7-dodecyloxyhesperetin(**g**), were synthesized and confirmed by UV, IR, ^{1}H NMR, and MS spectra data. The series of the synthesized compounds has been screened for their antibacterial activity in vitro and evaluated their structure–activity relationships. Substitution of the H with alkyl groups at C-7-OH led to significant change of their antibacterial activity. The antibacterial activity of 7-alkoxyhesperetin derivatives increased with the elongating of the length of aliphatic chain, and the maximum activity was reached at twelve carbon atoms. Compound **f** showed the highest antibacterial activity among all the compounds.

Keywords Synthesis · 7-alkoxyhesperetin derivatives · Hesperetin · Antibacterial activity

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Introduction

Natural products including thousands of compounds are important for plant biology and human nutrition, and they have been applied for therapeutic purposes in traditional medicine. Hesperidin is one of the most abundant flavonoids and is present in a large number of fruits and vegetables (Garg *et al.*, 2001). Many studies reported that hesperidin and its derivatives possessed a broad range of pharmacological properties, including antimicrobial (Bae *et al.*, 2000), antioxidant (Gorinstein *et al.*, 2007; Etcheverry *et al.*, 2008), anti-inflammatory (Galati *et al.*, 1994; Yeh *et al.*, 2007), antihypertensive (Galati *et al.*, 1996), antihypercholesterolaemic (Son *et al.*, 1991; Jeong *et al.*, 2003), antimetastatic (Hsiao *et al.*, 2007; Yeh *et al.*, 2009), and antitumor (Shen *et al.*, 2004) activities.

Hesperetin, aglycone of hesperidin, was found to show a significant cholesterol-lowering ability (Lee *et al.*, 1999). Hesperetin ester and ether derivatives possessing a long alkyl chain were synthesized and examined for their hypocholesterolemic activities in high cholesterol-fed mice. Hesperetin 7-O-lauryl ether and 7-O-oleyl ether exhibited strong cholesterol-lowering effects (Jeong *et al.*, 2003).

Hesperetin dihydrochalcone (DHC), which is the poorly soluble aglycone portion of neohesperidin DHC, is sweet. DuBois reported that water-soluble derivatives of hesperetin DHC could be prepared by attaching carboxyalkyl chains to the hydroxyl group at position 4. These compounds, although intensely sweet, were found to suffer from the poor taste-timing characteristics and have limited solubility in the pH range of beverage systems. Thus, 15 sulfonated hesperetin DHC derivatives were prepared, which led to high water solubility throughout the useful pH range and, as the result of the increase in hydrophilic

character, might have provided the DHC sweeteners with improved taste-timing characteristics (DuBois *et al.*, 1977).

Although, lots of new hesperidin derivatives and their bioactivities were studied, no previous studies are available on the synthesis and antibacterial activity in vitro of a series of 7-alkoxyhesperetin derivatives. The aim of this study is to synthesize these compounds and evaluate their structure and antibacterial activity relationships.

Results and discussion

Chemistry

The spectra data and other characterization of compounds **b**–**g** are shown in the experimental section. The IR spectra of the compounds show absorption bands at $v = 3418$ cm^{-1} for OH, $v = 2850$–2924 cm^{-1} for CH_3 and CH_2, $v = 1635$ cm^{-1} for C=O, and 1440–1574 cm^{-1} for Ar-stretching mode. ^1H NMR spectra of the compounds show a common $\delta = 2.7$ (dd, $J = 2.8$, 17.1 Hz, 1H, 3-H cis), 3.8 (s, 3H, 4′-OCH_3), 3.0 (dd, $J = 12.67$, 17.09 Hz, 1H, 3-H trans), 5.3 (dd, $J = 2.75$, 12.52 Hz, 1H, 2-H), 5.9–6.9 (m, 5H, Ar–H), and 12.0 (s, 1H, 5-OH) ppm. The distinct ^1H NMR spectra of 7-alkoxylhesperetin derivatives show $\delta = 0.8$ (CH_3), 1.2–1.7 (CH_2) and 3.9 (OCH_2) ppm. All these spectra data confirm the structure of the compounds.

Antibacterial activity of 7-alkoxyhesperetin derivatives

Agar well diffusion assay and 2-fold serial dilution test are two different methods to evaluate the antibacterial activity of 7-alkoxyhesperetin derivatives. Agar well diffusion assay is the first method to compare the antibacterial activities of the different kinds of synthesized compounds under the same condition of the designed compound dosage and bacterial concentration. At the same time, this method is also used to decide the initial dosage of the compounds (400 μg/mL) against the microorganisms and the concentration of the bacteria (10^5 CFU/mL), but this method cannot easily measure the MICs of these compounds. The 2-fold serial dilution test is the another method used to evaluate the antibacterial effect. In the second method, the initially dilute concentration of these compounds and the designed bacterial concentration are based on the screening result of the first method, and then the MICs of the active compounds can easily be obtained.

Diameter of inhibitory zone (DIZ) and minimum inhibitory concentration (MIC) of 7-alkoxyhesperetin derivatives against microbial are presented in Tables 1 and 2. Antibacterial activities of compounds **c**–**g** were increased 4- to 64-fold over that of compounds **a**–**b** which possessed relatively weaker inhibitory effects. Compounds **c**–**g** displayed broad antibacterial spectra and exerted stronger antibacterial effects. The antibacterial effect of 7-alkoxyhesperetin derivatives increased with the increase of the length of aliphatic chain, and the maximum activity was reached at twelve carbon atoms. Four selected bacterial strains *Bacillus subtilis*, *Staphylococcus aureus*, *Proteus vulgaris*, and *Escherichia coli* were more sensitive to the synthesized compounds. 7-Alkoxyhesperetin derivatives displayed a good range of inhibition (1.5–3.9 mm) against different bacteria strains at the dose level of 400 μg/mL; compound **f** showed the maximum activity (MIC = 6.25 μg/mL) against *Staphylococcus aureus* among all the compounds, perhaps due to the attribution of the presence of long alkoxy group. Besides, compounds possessing hydroxyl and methoxy groups in the benzene ring were found to be moderately to highly active against all the bacterial strains. Rest of the compounds were found to be either inactive or presenting a MIC value more than 400 μg/mL.

Table 1 Average diameters of inhibitory zone (mm) of 7-alkoxyhesperetin derivatives on microbials at the dose level of 400 μg/mL

Sr. no	Compound	Gram-positive bacteria		Gram-negative bacteria	
		B. subtilis	*S. aureus*	*P. vulgaris*	*E. coli*
1	Negative control	–	–	–	–
2	Streptomycin sulfate	2.2	2.8	4.6	5.3
3	**a**	–	–	0.8	–
4	**b**	0.8	–	1.6	–
5	**c**	0.7	1.8	2.2	0.7
6	**d**	1.8	2.6	2.0	1.6
7	**e**	2.0	3.1	2.6	2.5
8	**f**	2.0	3.9	3.3	2.2
9	**g**	1.5	3.6	2.8	1.8

All experiments were run in triplicate; – not detected

Table 2 Minimum inhibitory concentration (MIC, μg/mL) of 7-alkoxyhesperetin derivatives on microbials

Sr. no	Compound	Gram-positive bacteria		Gram-negative bacteria	
		B. subtilis	*S. aureus*	*P. vulgaris*	*E. coli*
1	Negative control	–	–	–	–
2	Streptomycin sulfate	50	25	3.13	1.56
3	**a**	–	–	200	–
4	**b**	200	–	100	–
5	**c**	200	100	50	200
6	**d**	100	25	50	100
7	**e**	50	12.5	25	25
8	**f**	50	6.25	12.5	50
9	**g**	100	6.25	25	100

All experiments were run in triplicate; – not detected

Conclusion

In this study, 7-alkoxyhesperetin derivatives were synthesized successfully. Substitution of the H with alkyl groups at C-7-OH exhibit promising antibacterial activity. As we know, with the elongating of the hydrocarbon chains of 7-alkoxyhesperetin, the antibacterial effect increased correspondingly. A major reason is probably attributed to the increase of the hydrophobic property, because the synthesized compounds were mainly dependent on the hydrophobic interaction with membrane proteins of bacteria to inhibit bacteria growth (Ye *et al.*, 2005).

Bacteria biofilms are biomolecular lipid layers: the hydrocarbon chains in lipid bilayers provide a virtually impenetrable barrier to ionic and polar substances since their hydrophobic property. The fat-soluble substances simply diffuse through the lipid bilayer below their concentration gradients (Trudy and James, 2000). The stronger hydrophobic property of the substances makes it easier for them to diffuse through membranes (Liu *et al.*, 2001).

Moreover, according to the study on the structure–activity relationships of synthesized compounds, it is concluded that this method is useful as a template for future development through modification or derivatisation to design more potent biologically active compounds, and this preliminarily biological study is encouraging to further explore their broad spectra pharmacological activities.

Experimental

Chemistry

Hesperetin (99% purity) was provided by Chemistry Institute of Pharmaceutical Resource of Southwest University; other reagents were of analytical grade purchased from Chongqing Chemical Reagent Co. Ltd (P.R. China).

Melting points, TLC, UV, IR, MS, and ^{1}H NMR, were used to confirm the structures of new compounds. Melting points (M. P.) were taken on the Netzsch Differential Scanning Calorimetry (DSC 200PC) and are uncorrected. Thin-layer chromatography (TLC) was run on the silica gel-GF_{254}-coated glass plates with mixtures of petroleum (60–90 °C) and ethyl acetate as developer and visualized at 254 nm with ultraviolet light. Ultraviolet (UV) spectra were obtained in methanol with a Hitachi Model U-1800 spectrophotometer. Infrared (IR) spectra were recorded on a Perkin–Elmer Model 137 instrument using KBr pellets. Mass spectrometry (MS) spectra were collected on Agilent 5973N instrument using ESI mode. Proton nuclear magnetic resonance (^{1}H NMR) spectra were determined using Bruker Model Avance DMX 300 spectrometer (300 M) with TMS as an internal standard and $CDCl_3$/DMSO as solvent.

Microorganisms and media

Four pathogenic microorganisms used for the antibacterial assay were kindly provided by Chongqing Medical University. They are Gram-positive (G^+) bacteria, viz., *Bacillus subtilis* (ATCC 9372), *Staphylococcus aureus* (ATCC 25923), Gram-negative (G^-) bacteria, viz., *Proteus vulgaris* (ATCC 14153), and *Escherichia coli* (ATCC 25922). The bacteria were grown in beef-extract peptone medium.

Agar well diffusion assay

Antibacterial activities of synthesized compounds were tested by agar diffusion method (Wang *et al.*, 2009; Yang *et al.*, 2007). Overnight culture of the respective test bacteria was adjusted to 10^5 CFU (colony-forming units) per mL, 1 mL; of such a culture was added to 15 mL respective medium, evenly mixed and poured into Petri dishes

(9 cm in diameter). The compounds were, respectively, dissolved in H_2O containing 1% DMF to reach final concentrations ranging from 0.78 to 400 μg/mL as the test solutions and sterilized by filtration through 0.45-μm sterilizing Millipore express filter. The discs (6 mm in diameter) were then applied; 10 μL of the test solutions and control were added to each disc, respectively. Petri dishes were incubated at 37 °C for 24 h (bacteria). The average diameters of inhibition zone (DIZ) surrounding the discs were measured visually, which did not include the diameter of the paper disc. DIZ was expressed in millimeters. The H_2O/1% DMF was used as negative control. Streptomycin sulfate was used as antibacterial positive control. All the experiments were run in triplicate.

Minimum inhibitory concentration (MIC)

Minimum inhibitory concentration (MIC) was determined as the lowest concentration of compound which completely inhibited the bacterial growth after incubation time. MIC was evaluated using the 2-fold serial dilution test (Ma, 2001). The compounds were dissolved in H_2O containing 1% DMF and diluted to different concentrations ranging from 0.78 to 400 μg/mL. The mixtures of serious dilutions of compounds and the microbes (10^5 CFU/mL) in different media were incubated at 37 °C for 24 h (bacteria). Microbial growth was tested by measuring the absorbance at 655 nm with a spectrophotometer. The H_2O/1% DMF was used as a control. Streptomycin sulfate was used as positive control. All the experiments were run in triplicate.

Procedure for preparing hesperetin from hesperidin

The hesperetin was synthesized by literature procedure (Thomas Seitz and Wingard, 1978). A 500-mL, three-necked flask, equipped with magnetic stir bar and condenser, was charged with 3.5 g (5.73 mmol) of purified hesperidin, 280 mL of dry CH_3OH, and 10 mL of 96% H_2SO_4. The solution was refluxed for 7.5 h and poured into 1.2 L of ethyl acetate. The mixture was washed with 15% aqueous NaCl (1 × 280 mL), H_2O (3 × 420 mL, final was colorless), saturated aqueous NaCl, and dried (Na_2SO_4). Evaporation afforded pale-yellow powder. The crude product was dissolved in acetone (70 mL) and added dropwise (60 min) to a vigorously stirred (overhead) mixture of 700 mL solution (H_2O:acetic acid = 150:1,v/v) maintained at 95–100 °C. The slurry was cooled to 45 °C and the hesperetin filtered and dried in vacuo.

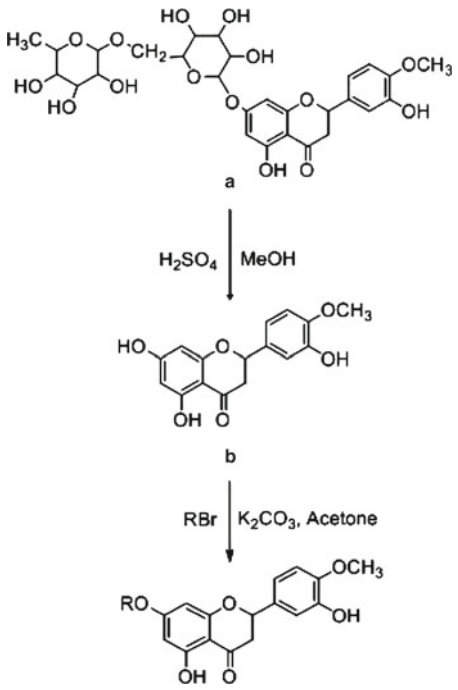
R_f: 0.29 (Petroleum ether:acetic ether = 2:1, V/V); Yield: 65.4%; Mp 224–226 °C; UV (MeOH, λ_{max}): 288, 325 nm; IR (KBr, ν_{max} cm^{-1}): 3499, 3433 (OH), 1635 (C=O), 1586, 1514, 1473, and 1442 (Ar); ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.67 (dd, J = 2.84, 17.08 Hz, 1H, 3-H cis), 3.01 (dd, J = 12.67, 17.09 Hz, 1H, 3-H trans), 3.8 (s, 3H, 4′-OCH_3), 5.29 (dd, J = 2.75, 12.52 Hz, 1H, 2-H), and 5.88–6.95 (m, 5H, Ar–H); MS (*m/z*, %): 300.78 (M^+−1,12), 285.74 (100), 241.73 (62), 198.76 (47), 173.76 (21), and 124.81 (36).

Synthesis of 7-alkoxyhesperetin derivatives

The 7-alkoxyhesperetin derivatives were synthesized according to the previous literature (Shan *et al.*, 2008). A 250-mL, three-necked flask, equipped with magnetic stir bar and condenser, was charged with 1.0 g (3.31 mmol) of purified hesperetin, 2.4 g (17.4 mmol) of dry K_2CO_3, and 70 mL of dry acetone, 1.2 mL of RBr (Fig. 1), The solution was refluxed for 7.5 h at 56 °C, Then to the mixture solution was added 0.2 g (0.662 mmol) of hesperetin, and 1.2 g (8.7 mmol) of dry K_2CO_3, and allowed to continue to react at 56 °C for 3 h. The slurry was cooled at 45 °C and dried in vacuo. The crude product was purified by a silica-gel column (petroleum ether:ethyl acetate = 10:1, V/V) to obtain the target compound as colorless crystalline solid.

7-Methoxyhesperetin

R_f: 0.55 (petroleum ether:acetic ether = 1:1,V/V); yield: 28.9%; Mp 167–169 °C; UV (MeOH, λ_{max}): 288 nm; IR



R=: c CH_3 (1") d $CH_3(CH_2)_2CH_2$ (4", 3"-2", 1") e $CH_3(CH_2)_6CH_2$ (8", 7"-2", 1")

f $CH_3(CH_2)_{10}CH_2$ (12", 11"-2", 1") g $CH_3(CH_2)_{14}CH_2$ (16", 15"-2", 1")

Fig. 1 Protocol for the synthesis of 7-alkoxyhesperetin derivatives

(KBr, ν_{max} cm^{-1}): 3399 (OH), 2946 (CH_3), 1645 (C=O), and 1593, 1515, 1568, and 1455 (Ar); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.75 (dd, $J = 2.85$, 17.16 Hz, 1H, 3-H cis), 3.03 (dd, $J = 12.96$, 17.13 Hz,1H, 3-H trans), 3.81 (s, 3H, 4′-OCH_3), 3.92 (s, 3H,7-OCH_3), 5.3 (dd, $J = 2.58$, 12.75 Hz, 1H, 2-H), 5.7 (s, 1H, 3′-OH), 6.05 (d, 2H, 6, 8-H), 6.88–7.04 (m, 3H, 2′,5′, 6′-H), and 12.02 (s, 1H, 5-OH); MS (*m/z*, %): 316.68 (M^++1, 16), 298.82(13), 192.69 (54), 176.71 (100), and 166.71 (75).

7-Butoxyhesperetin

R_f: 0.57 (petroleum ether:acetic ether = 1:1, V/V); yield: 15%; Mp 111–113 °C, UV (MeOH, λ_{max}): 286.5 nm; IR (KBr, ν_{max} cm^{-1}): 3543, 3436 (OH), 2961, 2944, 2874 (CH_3, CH_2), 1631 (C=O), 1594, 1521, and 1444 (Ar). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.94 (t, 3H, 4″-CH_3), 1.42–1.77 (m, 4H, 2″, 3″-CH_2), 2.74 (dd, $J = 2.67$, 17.04 Hz, 1H, 3-H cis), 3.02 (dd, $J = 12.96$, 17.1Hz, 1H, 3-H trans), 3.91 (d, 3H, 4′-OCH_3), 3.97 (d, 2H, 1″-OCH_2), 5.29 (dd, $J = 2.35$, 12.75 Hz, 1H, 2-H), 6.03 (s, 1H, 3′-OH), 6.05 (d, 2H, 6, 8-H), 6.87–6.73 (m, 3H, 2′, 5′, 6′-H), 12 (s, 1H, 5-OH); MS (*m/z*, %): 358.92 (M^++1, 7), 302.81 (10), 234.74 (32), 208.72 (53), 176.71 (100), and 152.73 (62).

7-Octoxyhesperetin

R_f: 0.67 (petroleum ether:acetic ether = 2:1,V/V); yield: 12%; Mp 98–102 °C; UV (MeOH, λ_{max}): 290 nm; IR (KBr, ν_{max} cm^{-1}): 3421 (OH), 2923 (CH_3), 1637 (C=O), 1516 (Ar), 1161, 1092 (–C–O–C); ^{1}H NMR (300 MHz, DMSO, δ ppm): 0.83 (t, 3H, 8″-CH_3), 1.26–1.69 (m, 12H, 2″-7″-CH_2), 2.7 (dd, $J = 2.25$, 17.31 Hz, 1H, 3-H cis), 3.2 (dd, $J = 12.64$, 17.31 Hz, 1H, 3-H trans), 3.99 (d, 3H, 4′-OCH_3), 4.03 (d, 2H, 1″-OCH_2), 5.45 (dd, $J = 2.68$, 12.7 Hz, 1H, 2-H), 6.08 (d, 2H, 6, 8-H), 6.87–6.95 (m, 3H, 2′, 5′, 6′-H), 9.1 (s, 1H, 3′-OH), 12.09 (s, 1H, 5-OH); MS (*m/z*, %): 415.07 (M^++1).

7-Dodecyloxyhesperetin

R_f: 0.7 (petroleum ether:acetic ether = 2:1,V/V); yield: 8.9%; Mp 109–112 °C; UV (MeOH, λ_{max}): 212, 289, and 329 nm; IR (KBr, ν_{max} cm^{-1}): 3418 (OH), 2924, 2850 (CH_3, CH_2),1635 (C=O), and 1574, 1515, and 1440 (Ar); ^{1}H NMR (300 MHz, DMSO, δ ppm): 0.83 (t, 3H, 12″-CH_3), 1.24–1.67 (m, 20H, 2″-11″-CH_2), 2.7 (dd, $J = 2.6$, 17.31 Hz, 1H, 3-H cis), 3.19 (dd, $J = 10.14$, 17.61 Hz, 1H, 3-H trans), 3.77 (s, 3H, 4′-OCH_3), 3.98 (t, 2H, 1″-OCH_2), 5.44 (dd, $J = 2.45$, 12.75 Hz, 1H, 2-H), 6.06 (d, 2H, 6, 8-H), 6.86–6.95 (m, 3H, 2′, 5′, 6′-H), 9.13 (s, 1H, 3′-OH), 12.1 (s, 1H, 5-OH); MS (*m/z*, %): 471 (M^++1, 9), 453.07 (17), 347.01 (46), 320.98 (95), 302.83 (38), 176.72 (100), and 152.72 (60).

7-Hexadecyloxyhesperetin

R_f: 0.75 (petroleum ether:acetic ether = 2:1,V/V); yield: 5.3%; Mp 110–113 °C; UV (MeOH, λ_{max}): 286.5 nm; IR (KBr, ν_{max} cm^{-1}): 3423 (OH), 2919, 2851 (CH_3, CH_2), 1637 (C=O), and 1517 (Ar); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.86 (t, 3H, 16″-CH_3), 1.26–1.78 (m, 28H, 2″-15″-CH_2), 2.8 (dd, $J = 2.3$, 17.1 Hz, 1H, 3-H cis), 3.02 (dd, $J = 12.7$, 17.13 Hz, 1H, 3-H trans), 3.92 (s, 3H, 4′-OCH_3), 3.95 (d, 2H, 1″-OCH_2), 5.29 (dd, $J = 2.57$, 12.78 Hz, 1H, 2-H), 5.71 (s, 1H, 3′-OH), 6.03 (d, 2H, 6, 8-H), 6.87–7.76 (m, 3H, 2′, 5′, 6′-H), 12 (s, 1H, 5-OH); MS (*m/z*, %): 527.18 (M^++1, 75), and 372.98 (100).

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