Chem. Res. Chin. Univ., 2018, 34(4), 564—570 doi: 10.1007/s40242-018-8013-5

Synthesis and Activity Evaluation of Novel Prenylated Flavonoids as Antiproliferative Agents

Kingsadingthongkham VONGDETH[1,2], RAN Liqiong[1], YAN Lili [1]and WANG Qiuan[1*]

1. College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, P. R. China;

2. Department of Chemistry, Faculty of Natural Sciences, National University of Laos, Vientiane P. O. BOX7322 Lao P. D. R.

Abstract Twenty prenylated flavonoids **1—20** were synthesized by glycoside hydrolysis, dehydrogenation, selective *O*-methylation, *O*-prenylation and Claisen rearrangement reaction, from abundant and inexpensive natural flavonoids naringin, hespiredin, quercetin and myricetin. Among them, **1—7**, **10—15** and **17—20** are novel compounds, the natural product 3,3′,4′,7-tetramethoxy-8-prenyl-5-hydroxy flavonoid(**16**) was synthesized in a high yield. Their antiprolirative activities were evaluated *in vitro* on a panel of three human cancer cell lines(HeLa, HCC1954 and SK-OV-3). The results show that most of the target compounds displayed moderate to potent antiprolirative activities against the three cancer cells with half maximal inhibitory concentration(IC_{50}) values from 0.49 μmol/L to 95.07 μmol/L. Among them, 3′,4′,7-trimethoxyl-5-hydroxyl-8-prenyl flavonoid(**12**) exhibited the strongest antiprolirative activity against the three cancer cells mentioned above with IC_{50} values of 0.91—7.08 μmol/L. 3′,7-Dimethoxy-5-*O*-prenyl flavone(**6**) and 3′,4′,7-trimethoxy-5-*O*-prenyl flavone(**10**) showed selective antiproliferative activity against HCC1954 cells with IC_{50} value of 0.49 and 5.32 μmol/L, respectively.

Keywords Prenylated flavonoid; Claisen rearrangement; Antiproliferative activity; Cancer cell

1 Introduction

Flavonoids are a large family of polyphenolic compounds with various health and medicinal benefits[1—4]. Prenylated flavonoids belong to a large sub-class of flavonoids that are characteristic of one or several prenyl groups side-chain on the flavonoid skelection. It was reported that prenyl groups could increase the lipophilicity and confer to the molecule a strong affinity to biological membranes, and result in the significant enhancement of bioactivities[5].

Over the past few decades, an impressive number of antiproliferative and cytotoxic potency against various cancer cell lines have been demonstrated for prenylated flavonoids[6,7]. In general, the prenylation at C8 position of flavonoids results in higher antitumour activity[8]. For example, icaritin, a natural prenylated flavonoid isolated from *Epimedium* genus, was recognized as a novel anticancer agent that strongly inhibited the growth of breast cancer MDA-MB-453 and MCF-7 cells at the concentration of 2—3 μmol/L[9]. Sophoflavescenol, a C8 prenylated flavonoid isolated from *S. flavescans*, showed inhibitory activity against HL-60, LLC and A549 tumor cells[10]. Xanthohumol, the principal prenylated chalcone present in the female inflorescences of the hop plant *Humulus lupulus* L., has been found to have a potential "broad-spectrum" anticancer and cancer-prevention effect(applicable to both breast and prostate cancers)[11].

As part of our ongoing project to develop new anticancer agents through optimization of dietary natural polyphenolic compounds[12—14], we have designed a scaffold, in which the prenyl group is partially incorporated in the flavonoid moiety, and synthesized twenty prenylated flavonoids(Scheme 1). Furthermore, the antiproliferative activities *in vitro* of the synthesized target compounds against three human cancer cell lines, HeLa(cervical carcinoma), HCC1954(breast cancer) and SK-OV-3(ovarian cancer), were evaluated using cell counting Kit-8(CCK-8) assay.

2 Experimental

2.1 General Experimental Procedures

Melting points were measured on an XRC-I apparatus. Microwave heating was performed with an XH-MC-1 microwave reactor(Beijing Xianghua Science & Technology Development Co., China). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 instrument, using tetramethylsilane as an internal standard. Mass spectra(MS) or high-resolution mass spectra(HRMS) were determined with a VG Autospec-3000 or a Mat 95 XP spectrometer by the electron ionization(EI) method. Column chromatography was carried out on silica gel(200—300 mesh, Qingdao Ocean Chemical Products of China). Commercially available A. R. grade or chemical pure reagents, and anhydrous solvent removed water and redistilled were employed.

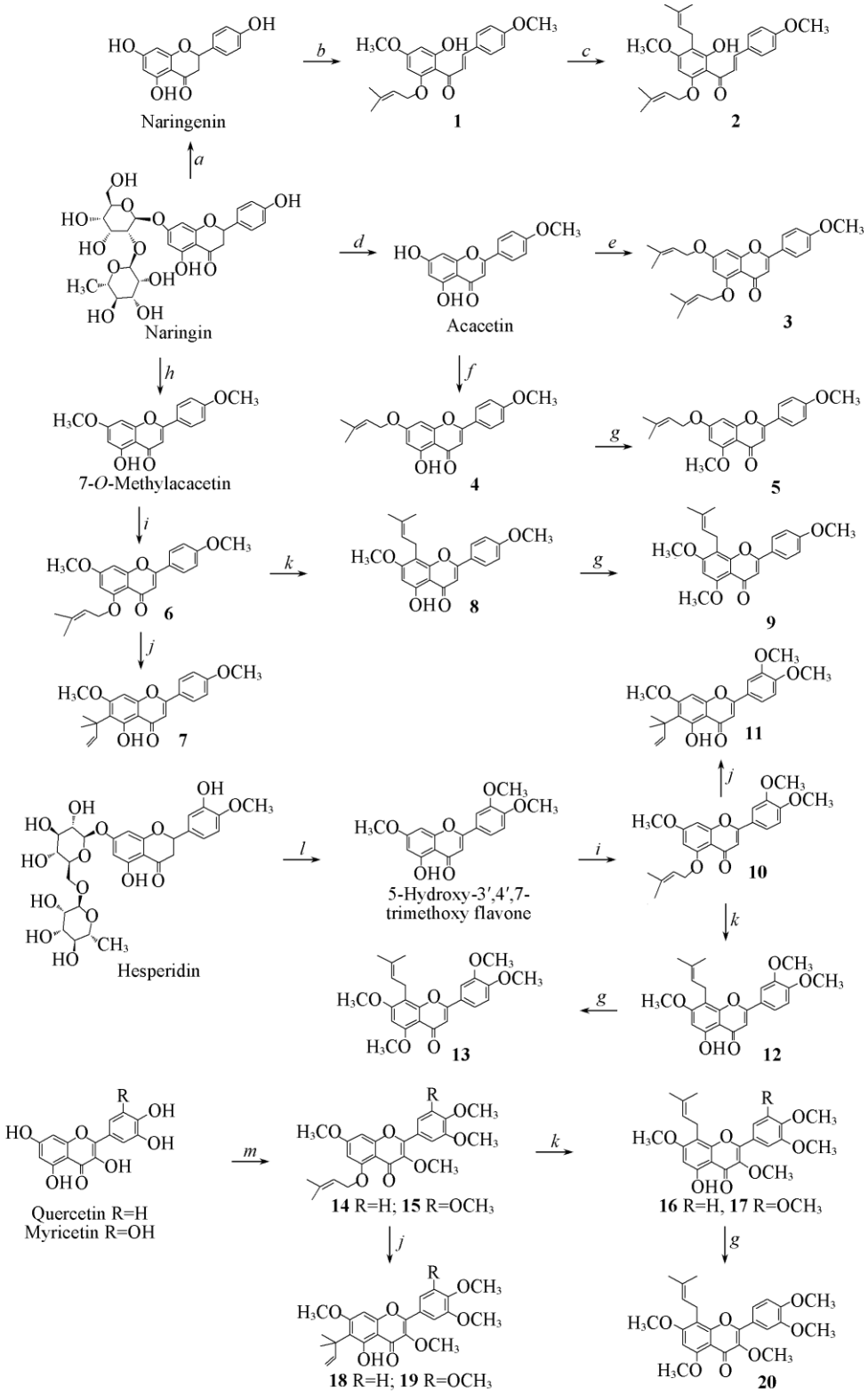
Naringenin, acacentin, 7-*O*-methyl acacetin and

*Corresponding authors. Email: wangqa@hnu.edu.cn

Received January 12, 2018; accepted March 23, 2018.

Supported by the National Natural Science Foundation of China(Nos.J1210040, 21173074).

5-hydroxy-3′,4′,7-trimethoxyflavone were prepared from naringin or hesperidin according to refs.[15,16]. ^{1}H and ^{13}C NMR, EI-MS, HRMS spectra and dose-response curves of synthesized compounds are shown in the Electronic Supplementary Material of this paper.



Scheme 1 Synthetic routes of prenylated flavonoids 1—20

Reagents and conditions: *a*. concentrated H_2SO_4, EtOH; *b*. (1) $(CH_3)_2SO_4$, K_2CO_3, acetone, r. t.; (2) prenyl bromide, K_2CO_3, acetone, 50 °C; *c*. (1) *N,N*-diethyl aniline, microwave reactor(700 W), 170 °C; (2) prenyl bromide, K_2CO_3, acetone, 50 °C; *d*. (1) I_2, pyridine, 95 °C; (2) $(CH_3)_2SO_4$, K_2CO_3, acetone, 45 °C; (3) concentrated H_2SO_4, EtOH; *e*. 2 mol prenyl bromide, K_2CO_3, acetone, 50 °C; *f*. prenyl bromide, K_2CO_3, acetone, 50 °C; *g*. $(CH_3)_2SO_4$, K_2CO_3, acetone, 45 °C; *h*. (1) I_2, pyridine, 95 °C; (2) $(CH_3)_2SO_4$, K_2CO_3, acetone, 50 °C; concentrated H_2SO_4, EtOH; *i*. prenyl bromide, K_2CO_3, acetone, 50 °C; *j*. *N,N*-diethyl aniline, 190 °C; *k*. *N,N*-diethyl aniline, microwave reactor(700 W), 170 °C; *l*. (1) I_2, pyridine, 95 °C; (2) concentrated H_2SO_4, EtOH; (3) $(CH_3)_2SO_4$, K_2CO_3, acetone, 50 °C; *m*. (1) $(CH_3)_2SO_4$, K_2CO_3, acetone, r. t.; (2) prenyl bromide, K_2CO_3, acetone, 50 °C.

2.2 Syntheses

*2.2.1 Synthesis of 4,4′-Dimethoxy-6′-O-prenyl-2′-hydroxy Chalcone(**1**)*

To a mixture of naringenin(5.0 g, 18.4 mmol) and anhydrous K_2CO_3(2.54 g, 18.4 mmol) in anhydrous acetone (50 mL) was added $(CH_3)_2SO_4$(1.7 mL, 18.4 mmol) dropwise with stirring. The reaction was allowed to proceed at room temperature for 1 h, and then the 3,3-dimethylallylbromide (0.25 mL, 2.2 mmol) in acetone(5 mL) was added dropwise, and stirred under reflux for 2 h. The reaction mixture was filtered and evaporated. The residue was subjected to chromatography on silica gel with petroleum ether/ethyl acetate(5:1, volume ratio) as eluent to give a light yellow solid of 3.8 g(10.30 mmol), yield 56%. m. p. 112—114 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 1.69, 1.79(6H, each s, CH_3), 3.76(3H, s, 4-OCH_3), 3.77(3H, s, 4′-OCH_3), 4.47(2H, d, J=6.8 Hz, CH_2), 5.56(1H, t, J=7.0 Hz, CH═), 5.89(1H, d, J=2.4 Hz, 3′-H), 6.02(1H, d, J=2.0 Hz, 5′-H), 6.82(2H, d, J=8.8 Hz, 3-H, 5-H), 7.45(2H, d, J=8.4 Hz, 2-H, 6-H), 7.67(1H, d, J=15.2 Hz, α-H), 7.92(1H, d, J=15.6 Hz, β-H), 14.5(1H, s, OH). ^{13}C NMR(100 MHz, $CDCl_3$), δ: 17.3(CH_3), 24.8(CH_3), 54.7(4-OCH_3), 54.5(4′-OCH_3), 64.5(OCH_2), 90.9(5′-C), 92.7(3′-C), 98.9(1′-C), 113.3(3-C, 5-C), 117.9(═CH), 124.6(1-C), 127.5(α-C), 129.0(2-C, 6-C), 138.8((CH_3)$_2$**C**═), 141.2(β-C), 160.2(4-C), 160.9(6′-C), 165.0(2′-C), 167.7(4′-C), 191.8(C═O). MS(EI), *m/z*: 368.2$[M]^+$.

*2.2.2 Synthesis of 4,4′-Dimethoxy-6′-O-prenyl-3′-prenyl-2′-hydroxy Chalcone(**2**)*

Compound **1**(200 mg, 0.54 mmol) was dissolved in *N,N*-diethylaniline(50 mL) and placed in the microwave reactor (700 W). After being stirred under nitrogen protection at 170 °C for 3 h, the mixture was cooled to 50 °C, then anhydrous K_2CO_3(0.29 g, 2.13 mmol) in acetone(15 mL) was added to it followed by stirring for 1 h. After that, 3,3- dimethylallylbromide(0.068 mL, 0.59 mmol) in acetone(5 mL) was added dropwise. The reaction process was monitored by TLC, the reaction was stopped after the raw materials disappeared. The organic phase was separated, the solvent was removed, and the residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate(15:1, volume ratio) as eluent to afford an orange solid of 106 mg(0.24 mmol), yield 45%. m. p. 121—122 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 1.60, 1.69, 1.71, 1.77(12H, each s, CH_3), 3.22(2H, d, J=8.0 Hz, 1‴-CH_2), 3.77(3H, s, 4-OCH_3), 3.82(3H, s, 4′-OCH_3), 4.51(2H, d, J=8.0 Hz, 1″-CH_2), 5.14(1H, t, J=7.0 Hz, 2‴-CH═), 5.55(1H, t, J=6.8 Hz, 2″- CH═), 5.93(1H, s, 5′-H), 6.82(2H, d, J=8.0 Hz, 3-H, 5-H), 7.45(2H, d, J=8.0 Hz, 2-H, 6-H), 7.65(1H, d, J=16.0 Hz, α-H), 7.88(1H, d, J=16.0 Hz, β-H), 14.27(1H, s, OH). ^{13}C NMR(100 MHz, $CDCl_3$), δ: 16.8(CH_3), 17.3(CH_3), 20.4(CH_3), 24.2(1‴-CH_2), 24.8(CH_3), 54.3(4-OCH_3), 54.5 (4′-OCH_3), 64.6(1″-CH_2), 86.4(5′-C), 105.5(3′-C), 108.9(1′-C), 113.2(3-C, 5-C), 117.9(2‴-CH═), 121.8(2″-CH═), 125.0 (1-C), 127.6(α-C), 129.0(2-C, 6-C), 130.3[3‴-(CH_3)$_2$**C**═], 138.5[3″-(CH_3)$_2$**C**═], 140.9(β-C), 159.7(4-C), 160.1(6′-C), 162.1(2′-C), 163.3(4′-C), 192.1(C═O). MS(EI), *m/z*: 436.2$[M]^+$.

*2.2.3 Synthesis of 4′-Methoxy-5,7-O,O-diprenyl Flavone(**3**)*

The mixture of acacetin(80 mg, 0.28 mmol) and hydrous K_2CO_3(200 mg, 1.45 mmol) in anhydrous acetone(12 mL) was stirred at 50 °C for 1 h, then 3,3-dimethylallylbromide(0.1 mL, 1.72 mmol) was added dropwise to the mixture. The reaction was allowed to proceed for 8 h. Then, the organic phase was separated, the solvent was removed, and the residue was recrystallized from petroleum ether and dichloromethane to afford a light yellow solid of 82 mg(0.20 mmol), yield 70%. m. p. 126—128 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.73(d, J=8.2 Hz, 2H, 2′-H, 6′-H), 6.96(d, J=8.4 Hz, 2H, 3′-H, 5′-H), 6.46(s, 1H, 8-H), 6.30(s, 1H, 3-H), 5.51(t, J=6.2 Hz, 1H, ═CH), 5.44(t, J=6.3 Hz, 1H, ═CH), 4.58(d, J=5.4 Hz, 2H, CH_2), 4.51(d, J=6.4 Hz, 2H, CH_2), 3.79(d, J=1.3 Hz, 3H, 4′-OCH_3), 1.75(s, 3H, CH_3), 1.71(s, 6H, 2CH_3), 1.66(s, 3H, CH_3). ^{13}C NMR(100 MHz, $CDCl_3$), δ: 176.41, 161.94, 160.93, 159.43, 159.03, 158.72, 138.28, 136.22, 126.53, 122.95, 118.58, 117.61, 113.28, 108.48, 106.65, 96.90, 92.50, 65.53, 64.25, 54.43, 24.83, 24.76, 17.37, 17.25. MS(EI), *m/z*: 420.1$[M]^+$.

*2.2.4 Synthesis of 4′-Methoxy-7-O-prenyl-5-hydroxy Flavone(**4**)*

The mixture of acacetin(80 mg, 0.28 mmol) and anhydrous K_2CO_3(200 mg, 1.45 mmol) in anhydrous acetone(12 mL) was stirred at 30 °C for 1 h. Then, 3,3-dimethylallylbromide (0.05 mL, 0.86 mmol) was added dropwise. The mixture was stirred for 2 h untill the reaction was completed(monitored by TLC). Filtration and evaporation of the solvent afforded the crude solid, which was purified by silica gel chromatography with petroleum ether/ethyl acetate(8:1, volume ratio) to afford a light yellow solid of 60 mg(0.17 mmol), yield 61%. m. p. 120—122 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 12.70(s, 1H, OH), 7.73(d, J=8.7 Hz, 2H, 2′-H, 6′-H), 6.91(d, J=8.7 Hz, 2H, 3′-H, 5′-H), 6.46(s, 1H, 8-H), 6.38(d, J=1.3 Hz, 1H, 3-H), 6.27(s, 1H, 6-H), 5.41(t, J=6.2 Hz, 1H, ═CH), 4.49(d, J=6.7 Hz, 2H, CH_2), 3.80(s, 3H, 4′-OCH_3), 1.74(s, 3H, CH_3), 1.69(s, 3H, CH_3). ^{13}C NMR(100 MHz, $CDCl_3$), δ: 181.35, 163.72, 162.89, 161.54, 161.06, 156.60, 138.13, 126.96, 122.53, 117.64, 113.44, 104.42, 103.24, 97.59, 92.18, 64.41, 54.48, 24.79, 17.25. MS(EI), *m/z*: 352.1$[M]^+$.

*2.2.5 Synthesis of 4′,5-Dimethoxy-7-O-prenyl Flavone(**5**)*

To the solution of compound **4**(60 mg, 0.17 mmol) and anhydrous K_2CO_3(200 mg, 1.45 mmol) in dry acetone(18 mL) was added solid sodium hydroxide(20 mg) and the mixture was stirred at 45 °C for 1 h. Then, 3,3-dimethylallylbromide(0.08 mL, 0.85 mmol) was added dropwise. The mixture was stirred for 45 min untill the reaction was completed(monitored by TLC), then cooled down to room temperature. Filtration and evaporation of the solvent afforded the crude solid, which was purified by silica gel chromatography with petroleum ether/ethyl acetate(1:1) to afford a light yellow solid of 47 mg(0.13 mmol), yield 76%. m. p. 96—98 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.73(d, J=8.3 Hz, 2H, 2′-H, 6′-H), 6.91(d, J=8.3 Hz, 2H, 3′-H, 5′-H), 6.51(s, 1H, 8-H), 6.48(s, 1H, 3-H), 6.31(s, 1H,

6-H), 5.44(t, *J*=6.3 Hz, 1H, ═CH), 4.53(d, *J*=6.8 Hz, 2H, CH_2), 3.86, 3.80(2s, 6H, 4′-OCH_3, 5-OCH_3), 1.76(s, 3H, CH_3), 1.72(s, 3H, CH_3). ^{13}C NMR(100 MHz, $CDCl_3$), *δ*: 176.65, 162.16, 161.01, 159.80, 159.65, 158.76, 138.50, 129.89, 127.81, 126.57, 122.83, 117.48, 113.32, 108.07, 106.60, 95.57, 92.42, 64.30, 55.38, 54.44, 28.67, 24.84. MS(EI), *m/z*: 366.1$[M]^+$.

*2.2.6 Synthesis of 4′,7-Dimethoxy-5-O-prenyl Flavone(**6**)*

The mixture of 7-*O*-methylacacetin(223 mg, 0.75 mmol) and anhydrous K_2CO_3(400 mg, 2.9 mmol) in dry acetone (12 mL) was stirred at 50 °C for 1 h. Then, 3,3-dimethylallylbromide(0.1 mL, 1.72 mmol) was added dropwise. The reaction mixture was stirred for 8 h untill the reaction was completed (monitored by TLC), then cooled down to room temperature. Filtration and evaporation of the solvent afforded the residue, which was recrystallized from petroleum ether and dichloromethane to afford a yellow solid of 184 mg(0.50 mmol), yield 67%. m. p. 95—97 °C. ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 7.75(d, *J*=8.7 Hz, 2H, 2′-H, 6′-H), 6.92(d, *J*=8.7 Hz, 2H, 3′-H, 5′-H), 6.49(s, 1H, 8-H), 6.47(s, 1H, 3-H), 6.29(d, *J*=1.6 Hz, 1H, 6-H), 5.51(t, *J*=5.9 Hz, 1H, ═CH), 4.61(d, *J*=6.3 Hz, 2H, CH_2), 3.82, 3.81(2s, 6H, 4′-OCH_3, 7-OCH_3), 1.72(s, 3H, CH_3), 1.69(s, 3H, CH_3). ^{13}C NMR(100 MHz, $CDCl_3$), *δ*: 176.62, 162.56, 161.03, 159.55, 159.01, 158.73, 136.41, 126.52, 122.83, 118.56, 113.29, 106.73, 96.36, 91.82, 65.76, 54.61, 54.45, 52.42, 24.73, 17.30. MS(EI), *m/z*: 366.1$[M]^+$.

*2.2.7 Synthesis of 4′,7-Dimethoxy-6-(1″,1″-dimethyl allyl)-5-hydroxy Flavone(**7**)*

Compound **6**(200 mg, 0.55 mmol) was dissolved in *N,N*-diethylaniline(15 mL), and stirred at 190 °C under nitrogen protection for 12 h, the reaction mixture was cooled to room temperature, then poured into dilute hydrochloric acid(10%) and stirred for 5 min. The reaction mixture was extracted with dichloromethane(10 mL×3), the organic layers were combined and dried with anhydrous Na_2SO_4, the solvent was evaporated to yield a crude material that was subjected to chromatography on silica gel using petroleum ether/ethyl acetate(volume ratio, 15:1) as eluent to afford a light yellow solid of 135 mg(0.37 mmol), yield 67%. m. p. 135—137 °C. ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 7.76(d, *J*=8.8 Hz, 2H, 2′-H, 6′-H), 6.94(d, *J*=8.8 Hz, 2H, 3′-H, 5′-H), 6.50(s, 1H, 8-H), 6.39(s, 1H, 3-H), 6.22(dd, *J*=17.4, 10.6 Hz, 1H, ═CH), 4.87, 4.83(2H, dd, J_1=17.4 Hz, 1.3 Hz, J_2=10.6, 1.3 Hz, ═CH_2), 3.83, 3.76(2s, 6H, 4′-OCH_3, 7-OCH_3), 3.76(s, 3H, CH_3), 1.53(s, 6H, 2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$), *δ*: 181.79, 163.70, 162.25, 161.48, 159.65, 155.22, 149.58, 126.92, 122.56, 116.69, 113.46, 105.75, 104.62, 103.45, 89.53, 54.51, 54.40, 52.41, 40.20, 27.93. MS(EI), *m/z*: 366.1$[M]^+$. HRMS(EI), *m/z* calcd. for $C_{22}H_{22}O_5[M]^+$: 366.1467; found: 366.1462.

*2.2.8 Synthesis of 7,4′-Dimethoxy-8-prenyl-5-hydroxy Flavone(**8**)*

Compound **6**(200 mg, 0.55 mmol) was dissolved in *N,N*-diethylaniline(15 mL) and placed in the microwave reactor (700 W). The mixture was stirred under nitrogen protection at 170 °C for 3 h, then cooled to room temperature, poured into dilute hydrochloric acid(10%) and stirred for 5 min. The reaction mixture was extracted with dichloromethane(10 mL×3), the organic layers were combined and dried with anhydrous Na_2SO_4, the solvent was evaporated to yield a crude material that was chromatographed on silica gel using petroleum ether/ethyl acetate(volume ratio 10:1) as eluent to afford a light yellow solid of 131 mg(0.36 mmol), yield 65%. m. p. 96—98 °C. ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 12.81(s, 1H, OH), 7.78 (d, *J*=8.6 Hz, 2H, 2′-H, 6′-H), 6.95(d, *J*=8.5 Hz, 2H, 3′-H, 5′-H), 6.50(s, 1H, 3-H), 6.33(s, 1H, 6-H), 5.15(t, *J*=6.5 Hz, 1H, ═CH), 3.83, 3.82(2s, 6H, 4′-OCH_3, 7-OCH_3), 3.46(d, *J*= 6.7 Hz, 2H, CH_2), 1.74(s, 3H, CH_3), 1.62(s, 3H, CH_3). ^{13}C NMR(100 MHz, $CDCl_3$), *δ*: 181.97, 161.52, 159.55, 153.36, 145.04, 144.81, 130.96, 127.04, 122.89, 121.30, 113.50, 102.87, 96.67, 94.15, 55.01, 54.51, 28.68, 24.74, 20.79, 16.93. MS(EI), *m/z*: 366.1$[M]^+$. The spectral data of this compound are in agreement with those reported in the literature[17].

*2.2.9 Synthesis of 4′,5,7-Trimethoxy-8-prenyl Flavone(**9**)*

According to a similar procedure as described for the synthesis of compound **5**, compound **9** was obtained as a white solid of 100 mg(0.26 mmol), yeild 72%. m. p. 151—153 °C. ^{1}H NMR (400 MHz, $CDCl_3$), *δ*: 7.76(d, *J*=8.1 Hz, 2H, 2′-H, 6′-H), 6.92(d, *J*=8.2 Hz, 2H, 3′-H, 5′-H), 6.51(s, 1H, 3-H), 6.35(s, 1H,6-H), 5.16(t, *J*=6.2 Hz, 1H, ═CH), 3.92, 3.88, 3.81(3s, 9H, 4′-OCH_3, 5-OCH_3, 7-OCH_3), 3.49(d, *J*=6.6 Hz, 2H, CH_2), 1.75(s, 3H, CH_3), 1.62(s, 3H, CH_3). ^{13}C NMR(100 MHz, $CDCl_3$), *δ*: 177.31, 161.07, 159.84, 159.66, 158.16, 155.25, 131.06, 126.65, 123.23, 121.30, 113.35, 108.99, 107.84, 106.16, 90.58, 55.45, 54.84, 54.41, 24.74, 20.97, 16.80. MS(EI), *m/z*: 380.1$[M]^+$. HRMS(EI), *m/z* calcd. for $C_{23}H_{24}O_5$: 380.1624$[M]^+$; found: 380.1618. The spectral data of this compound are in agreement with those reported in the literature[17].

*2.2.10 Synthesis of 3′,4′,7-Trimethoxy-5-O-prenyl Flavone(**10**)*

According to a similar procedure as described for the synthesis of compound **6**, compound **10** was obtained as a white solid of 103 mg(0.26 mmol), yield 84%. m. p. 136—138 °C. ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 7.44(d, *J*=8.4 Hz, 1H, 6′-H), 7.25(s, 1H, 2′-H), 6.89(d, *J*=8.5 Hz, 1H, 5′-H), 6.51(s, 1H, 8-H), 6.48(s, 1H, 3-H), 6.30(s, 1H, 6-H), 5.51(t, *J*=4.7 Hz, 1H, ═CH), 4.63(d, *J*=6.1 Hz, 2H, CH_2), 3.91, 3.89, 3.84(3s, 9H, 3′-OCH_3, 4′-OCH_3, 7-OCH_3), 1.72(s, 3H, CH_3), 1.69(s, 3H, CH_3). ^{13}C NMR(100 MHz, $CDCl_3$), *δ*: 176.44, 162.59, 159.54, 159.05, 158.81, 150.78, 148.19, 136.32, 123.28, 118.44, 110.15, 108.52, 107.74, 106.82, 98.79, 96.46, 91.76, 65.58, 55.12, 55.02, 54.69, 24.75, 17.30. MS(EI), *m/z*: 396.1$[M]^+$.

*2.2.11 Synthesis of 3′,4′,7-Trimethoxy-6-(1″,1″-dimethyl allyl)-5-hydroxy Flavone(**11**)*

According to a similar procedure as described for the synthesis of compound **7**, compound **11** was obtained as a light yellow solid of 99 mg(0.25 mmol), yield 65%. m. p. 147—149 °C. ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 13.53(s, 1H, OH), 7.45(d, *J*=8.4 Hz, 1H, 6′-H), 7.27(s, 1H, 2′-H), 6.91(d, *J*= 7.0 Hz, 1H, 5′-H), 6.51(s, 1H, 8-H), 6.40(s, 1H, 3-H), 6.23(dd, *J*=16.7, 11.3 Hz, 1H, ═CH), 4.86, 4.82(2H, dd, J_1=17.2 Hz, 1.3 Hz, J_2=10.5, 1.3 Hz, ═CH_2), 3.91, 3.90, 3.78(3s, 9H,

3′-OCH_3, 4′-OCH_3, 7-OCH_3), 1.53(s, 6H, CH_3). ^{13}C NMR(100 MHz, $CDCl_3$), δ: 181.70, 163.70, 162.38, 160.62, 159.78, 154.93, 151.22, 149.23, 148.35, 122.89, 118.89, 109.69, 107.28, 105.54, 104.64, 104.00, 89.31, 54.82, 53.93, 39.86, 27.85. MS(EI), *m/z*: 396.1$[M]^+$. HRMS(EI), *m/z* calcd. for $C_{23}H_{24}O_6$: 396.1573$[M]^+$; found: 396.1567.

*2.2.12 Synthesis of 3',4',7-Trimethoxy-8-prenyl-5-hydroxy Flavone(**12**)*

According to a similar procedure as described for the synthesis of compound **8**, compound **12** was obtained as a light yellow solid of 138 mg(0.35 mmol), yield 67%. m. p. 148—150 °C. ^1H NMR(400 MHz, $CDCl_3$), δ: 12.78(s, 1H, OH), 7.47(d, *J*=8.5 Hz, 1H, 6′-H), 7.32(s, 1H, 2′-H), 6.91(d, *J*=8.5 Hz, 1H, 5′-H), 6.51(s, 1H, 3-H), 6.34(s, 1H, 6-H), 5.19(t, *J*=6.4 Hz, 1H, ═CH), 3.90, 3.89, 3.83(3s, 9H, 3′-OCH_3, 4′-OCH_3, 7-OCH_3), 3.46(d, *J*=6.7 Hz, 2H, CH_2), 1.73(s, 3H, CH_3), 1.61(s, 3H, CH_3). ^{13}C NMR(100 MHz, $CDCl_3$), δ: 181.70, 162.79, 161.75, 159.56, 153.38, 150.78, 148.34, 131.16, 123.31, 120.92, 119.17, 109.89, 107.51, 106.59, 103.79, 102.88, 94.30, 55.02, 24.75, 20.80, 17.04. MS(EI), *m/z*: 396.1$[M]^+$.

*2.2.13 Synthesis of 3',4',5,7-Tetramethoxy-8-prenyl Flavone(**13**)*

According to a similar procedure as described for the synthesis of compound **9**, compound **13** was obtained as a light yellow solid of 72 mg(0.18 mmol), yield 70%. m. p. 164—166 °C. ^1H NMR(400 MHz, $CDCl_3$), δ: 7.44(d, *J*=8.4 Hz, 1H, 6′-H), 7.31(s, 1H, 2′-H), 6.89(d, *J*=8.5 Hz, 1H, 5′-H), 6.56(s, 1H, 3-H), 6.35(s, 1H, 6-H), 5.19(t, *J*=6.5 Hz, 1H, ═CH), 3.91, 3.87(2s, 12H, 3′-OCH_3, 4′-OCH_3, 5-OCH_3, 7-OCH_3), 3.49(d, *J*=6.6 Hz, 2H, CH_2), 1.73(s, 3H, CH_3), 1.61(s, 3H, CH_3). ^{13}C NMR(100 MHz, $CDCl_3$), δ: 176.86, 160.00, 159.58, 158.03, 155.58, 150.30, 147.93, 131.48, 123.54, 120.96, 118.70, 110.60, 109.08, 107.74, 105.77, 90.38, 55.39, 55.05, 54.94, 54.88, 24.56, 21.29, 16.63. MS(EI), *m/z*: 410.1$[M]^+$. HRMS(EI), *m/z* calcd. for $C_{24}H_{26}O_6$: 410.1729$[M]^+$; found: 410.1724.

*2.2.14 Synthesis of 3,3',4',7-Tetramethoxy-5-O-prenyl Flavonoid(**14**)*

According to a similar procedure as described for the synthesis of compound **6**, compound **14** was obtained as a white solid of 166 mg(0.39 mmol), yield 70%. m. p. 105—107 °C. ^1H NMR(400 MHz, $CDCl_3$), δ: 7.64(d, *J*=6.1 Hz, 2H, 2′-H, 6′-H), 6.91(d, *J*=8.9 Hz, 1H, 5′-H), 6.42(s, 1H, 8-H), 6.27(s, 1H, 6-H), 5.54(t, *J*=9.0 Hz, 1H, CH═), 4.62(d, *J*=6.1 Hz, 2H, CH_2), 3.90, 3.82, 3.80(3s, 12H, 3-OCH_3, 3′-OCH_3, 4′-OCH_3, 7-OCH_3), 1.72(s, 3H, CH_3), 1.69(s, 3H, CH_3). ^{13}C NMR(100 MHz, $CDCl_3$), δ: 162.58, 158.84, 157.81, 151.41, 149.44, 147.25, 139.75, 136.44, 122.37, 120.41, 118.23, 110.07, 109.72, 105.33, 95.98, 91.33, 65.54, 58.32, 55.12, 54.96, 54.62, 24.95, 17.51. MS(EI), *m/z*: 426.1$[M]^+$.

*2.2.15 Synthesis of 3,3',4',5',7-Pentamethoxy-5-O-prenyl Flavonoid(**15**)*

According to a similar procedure as described for the synthesis of compound **6**, compound **15** was obtained as a yellow solid of 91 mg(0.20 mmol), yield 77%. m. p. 113—115 °C. ^1H NMR(400 MHz, $CDCl_3$), δ: 7.28(s, 2H, 2′-H, 6′-H), 6.40(s, 1H, 8-H), 6.25(s, 1H, 6-H), 5.51(t, 1H, *J*=8.8 Hz, 1H, ═CH), 4.60(d, *J*=5.7 Hz, 2H, CH_2), 3.86, 3.81, 3.78(3s, 15H, 3-OCH_3, 3′-OCH_3, 4′-OCH_3, 5′-OCH_3, 7-OCH_3), 1.71(s, 3H, CH_3), 1.68(s, 3H, CH_3). ^{13}C NMR(100 MHz, $CDCl_3$), δ: 173.80, 163.79, 160.21, 158.73, 153.01, 152.16, 141.50, 139.94, 137.48, 126.04, 119.44, 109.74, 105.74, 97.12, 92.43, 66.54, 60.94, 60.07, 56.31, 55.74, 25.78, 18.41. MS(EI), *m/z*: 456.1$[M]^+$.

*2.2.16 Synthesis of 3,3',4',7-Tetramethoxy-8-prenyl-5-hydroxy Flavonoid(**16**)*

According to a similar procedure as described for the synthesis of compound **8**, compound **16** was obtained as a light yellow solid of 69 mg(0.16 mmol), yield 70%. m. p. 154—156 °C. ^1H NMR(400 MHz, $CDCl_3$), δ: 12.63(s, 1H, OH), 7.72(d, *J*=8.6 Hz, 1H, 6′-H), 7.68(s, 1H, 2′-H), 6.92(d, *J*=8.5 Hz, 1H, 5′-H), 6.33(s, 1H, 6-H), 5.16(t, 1H, *J*=8.9 Hz, ═CH), 3.91, 3.87, 3.83, 3.80(4s, 12H, 3-OCH_3, 3′-OCH_3, 4′-OCH_3, 7-OCH_3), 3.43(d, *J*=6.4 Hz, 2H, CH_2), 1.70(s, 3H, CH_3), 1.60(s, 3H, CH_3). ^{13}C NMR(100 MHz, $CDCl_3$), δ: 178.16, 161.52, 159.25, 154.69, 152.51, 150.48, 147.67, 137.57, 130.95, 122.37, 121.20, 120.91, 110.21, 109.79, 106.58, 104.40, 93.81, 58.74, 54.80, 24.72, 20.10, 16.60. MS(EI), *m/z*: 426.1$[M]^+$. The spectral data of this compound are in agreement with those reported in the literature[18].

*2.2.17 Synthesis of 3,3',4',5',7-Pentamethoxy-8-prenyl-5-hydroxy Flavonoid(**17**)*

According to a similar procedure as described for the synthesis of compound **8**, compound **17** was obtained as a light yellow solid of 82 mg(0.18 mmol), yield 82%. m. p. 116—118 °C. ^1H NMR(400 MHz, $CDCl_3$), δ: 12.57(s, 1H, OH), 7.39(s, 2H, 2′-H, 6′-H), 7.19(s, 1H, 6-H), 5.18((t, 1H, *J*=8.7 Hz, 1H, ═CH), 3.88, 3.85, 3.83(3s, 15H, 3-OCH_3, 3′-OCH_3, 4′-OCH_3, 5′-OCH_3, 7-OCH_3), 3.43(d, *J*=6.1 Hz, 2H, CH_2), 1.69(s, 3H, CH_3), 1.59(s, 3H, CH_3). ^{13}C NMR(100 MHz, $CDCl_3$), δ: 178.19, 161.61, 159.32, 154.34, 152.30, 152.17, 139.30, 138.09, 131.44, 127.76, 124.98, 121.04, 106.54, 104.86, 104.35, 93.84, 59.85, 58.97, 54.80, 28.25, 24.93, 20.31, 17.01. MS(EI), *m/z*: 456.1$[M]^+$. HRMS(EI), *m/z* calcd. for $C_{25}H_{28}O_8$: 456.1784; found: 456.1779.

*2.2.18 Synthesis of 3,3',4',7-Tetramethoxy-6-(1'',1''-dimethyl allyl)-5-hydroxy Flavonoid(**18**)*

According to a similar procedure as described for the synthesis of compound **7**, compound **18** was obtained as a light yellow solid of 71 mg(0.17 mmol), yield 74%. m. p. 130—132 °C. ^1H NMR(400 MHz, $CDCl_3$), δ: 13.38(s, 1H, OH), 7.66(d, *J*=8.7 Hz, 1H, 6′-H), 7.62(s, 1H, 2′-H), 6.91(d, *J*=8.5 Hz, 1H, 5′-H), 6.35(s, 1H, 8-H), 6.21(dd, *J*=17.4, 10.6 Hz, 1H, ═CH), 4.85, 4.83(2H, dd, J_1=17.3 Hz, 1.3 Hz, J_2=10.4, 1.3 Hz, ═CH_2), 3.90, 3.76(2s, 12H, 3-OCH_3, 3′-OCH_3, 4′-OCH_3, 7-OCH_3), 1.52(s, 6H, 2CH_3). ^{13}C NMR(100 MHz, $CDCl_3$), δ: 178.08, 163.77, 159.33, 154.23, 154.02, 150.26, 149.55, 147.73, 137.91, 121.89, 121.02, 116.50, 110.19, 109.81, 105.80, 105.00, 89.26, 58.96, 54.80, 54.17, 40.12, 28.24. MS(EI), *m/z*: 426.1$[M]^+$.

*2.2.19 Synthesis of 3,3',4',5',7-Pentamethoxy-6-(1'',1''-dimethyl allyl)-5-hydroxy Flavonoid(**19**)*

According to a similar procedure as described for the synthesis of compound **7**, compound **19** was obtained as a yellow

solid of 68 mg(0.15 mmol), yield 68%. m. p. 118—120 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 13.33(s, 1H, OH), 7.29(s, 2H, 2′-H, 6′-H), 6.35(s, 1H, 8-H), 6.21(dd, J=17.4, 10.6 Hz, 1H, ═CH), 4.87, 4.84(2H, dd, J_1=17.3 Hz, 1.3 Hz, J_2=10.5, 1.3 Hz, ═CH_2), 3.87, 3.77(2s, 15H, 3-OCH_3, 3′-OCH_3, 4′-OCH_3, 5′-OCH_3, 7-OCH_3), 1.52(s, 6H, $2CH_3$). ^{13}C NMR(100 MHz, $CDCl_3$), δ: 179.09, 164.94, 160.43, 155.28, 154.90, 153.15, 150.54, 140.51, 139.43, 125.53, 117.68, 106.89, 106.14, 105.99, 90.39, 61.04, 60.35, 56.38, 55.50, 41.25, 29.02. MS(EI), *m/z*: 456.1$[M]^+$.

*2.2.20 Synthesis of 3′,4′,3,5,7-Pentamethoxy-8-prenyl Flavonoid(**20**)*

According to a similar procedure as described for the synthesis of compound **9**, compound **20** was obtained as a white solid of 62 mg(0.14 mmol), yield 88%. m. p. 142—144 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.70(d, J=8.4 Hz, 2H, 6′-H, 2′-H), 6.90(d, J=8.3 Hz, 1H, 5′-H), 6.31(s, 1H, 6-H), 5.16(t, 1H, J=8.8 Hz, ═CH), 3.92, 3.88, 3.86, 3.85, 3.81(5s, 15H, 3-OCH_3, 3′-OCH_3, 4′-OCH_3, 5-OCH_3, 7-OCH_3), 3.44(d, J=5.9 Hz, 2H, CH_2), 1.67(s, 3H, CH_3), 1.59(s, 3H, CH_3). ^{13}C NMR(100 MHz, $CDCl_3$), δ: 173.49, 159.78, 158.29, 154.35, 151.29, 149.66, 147.61, 139.71, 131.22, 122.78, 121.21, 120.74, 110.02, 109.79, 108.56, 108.02, 90.32, 58.82, 55.34, 54.91, 54.88, 54.82, 24.71, 20.87, 16.93. MS(EI), *m/z*: 440.1$[M]^+$. HRMS(EI), *m/z*: calcd. for $C_{25}H_{28}O_7$: 440.1835$[M]^+$; found 440.1830.

2.3 Antiproliferative Activity *In vitro* Screening

Antiproliferative activities against HeLa, HCC1954 and SK-OV-3 cells were evaluated by CCK-8(Dojingdo, Kumamoto, Japan) assay according to the manufacturer's instructions[19]. This assay is based on the cleavage of the tetrazolium salt WST-8 by mitochondrial dehydrogenase in viable cells. Briefly, cells(1×10^3 cell/well) were incubated with 45 μL of culture medium in 384-well plates. After being adhered to the well, the cells were treated with 5 μL of tested compounds at different concentrations, and then cultured for 72 h before the addition of 5 μL of CCK-8 to the culture medium in each well. After incubation for 2 h at 37 °C, absorbance at 450 nm of the mixture in each well was measured with a fluorimeter(Novostar, BMG LABTECH, Germany). Each experiment was repeated 3 times, and the data represent the mean values. The half maximal inhibitory concentration(IC_{50}) values were calculated using the Graphpad prism 5 software.

3 Results and Discussion

The syntheses of the prenylated flavonoids **1—20** were performed according to the reaction pathways as illustreated in Scheme 1. The abundant and inexpensive natural flavonoids naringin, hesperidin, quercetin and myricetin were used as the starting materials. Firstly, naringenin, acacetin, 7-*O*-methylacacetin and 5-hydroxy-3′,4′,7-trimethoxyflavone were prepared from naringin or hespiredin by hydrolysis of glycosidic bond, dehydrogenation in I_2/pyridine, regioselective methylation, respectively. *O*-Prenylated chalcone **1** was prepared by regioselective *O*-methylation, *O*-prenylation and base-catalysed ring-opening reaction of naringenin with anhydrous potassium carbonate in dry acetone, followed by Claisen rearrangement under microwave heating(700 W) at 170 °C in *N,N*-diethylanilline and further *O*-prenylation afforded diprenylated chalcone **2**. *O*-Prenylattion of acacetin, 7-*O*-methylacacetin and 5-hydroxy-3′,4′,7-trimethoxyflavone provided the *O*-prenylated flavonoids **3**, **4**, **6** and **10**, respectively. Taking advantage of hydrogen bonding between the carbonyl and an *ortho*-phenolic-OH group, regioselective *O*-methylation of all hydroxyl groups except 5-OH and *O*-prenylation of 5-OH of quercetin or myricetin provided the *O*-prenylated flavonoids **14** and **15**.

Once prenyl ethers were available, our attention was focused on the formation of *C*-prenylated flavonoids from the *O*-prenylated flavonoids. The Claisen rearrangement as a key step in our synthetic strategy was investigated. *O*-Phenylated Claisen precursors **6**, **10**, **14** and **15** were subjected to Claisen rearrangement under conventional heating at 190 °C in *N,N*-diethylaniline, the *ortho*-rearranged products (the 3,3-dimethyallyl chain at 6-position) **7**, **11**, **18** and **19** were found to be the preferred ones in 55%—67% yields. However, in the case of microwave(700 W) heating at 170 °C, the *para*- rearranged products **8**, **12**, **16** and **17** were gained in 50%—62% yields through double sigmatropic rearrangement in the same system. The two types of products showed different ^{1}H NMR signals for —$C(CH_3)_2CH$═CH_2 at δ 4.83 and 4.87(2H, 2dd) and loss of H-6(C6 position), for —CH_2CH═$C(CH_3)_2$ at δ 3.42(2H, d) and loss of H8(C8 position) to allow an unambiguous identification of two isomers. The 5-*O*-methylation of compounds **4**, **8**, **12** and **16** with dimethyl sulfate and potassium carbonate in refluxing acetone gave the prenylated flavonoids **5**, **9**, **13** and **20**. Among them, compounds **1—7**, **10—15** and **17—20** are novel compounds, the natural product 3,3′,4′,7-tetramethoxy-8-prenyl-5-hydroxy flavonoid(**16**) was synthesized in high yield.

All synthetic prenylated flavonoids were screened *in vitro* for antiproliferative activity against three human cancer cell lines(HeLa, HCC1954 and SK-OV-3) by the CCK-8 method using *cis*-Platin, Paclitaxel and Staurosporine as positive controls. Their activities were expressed by IC_{50} values and the data presented in Table 1 are the mean values of at least three separate experiments. The results show that most of the synthesized target compounds exhibit moderate to potent antiproliferative activities with IC_{50} values of 0.49—95.07 μmol/L toward the three tested cancer cell lines.

Compounds **9**, **12**, **13**, **16**, **18**, **19** and **20** were equal or more potent against HeLa cells with IC_{50} values of 0.91—12.81 μmol/L than the positive control *cis*-Platin(IC_{50}=13.30 μmol/L), compounds **3**, **5**, **6**, **9**, **10—14** and **17—20** were more potent against HCC1954 cells with IC_{50} values of 0.49—19.33 μmol/L than the positive control *cis*-Platin(IC_{50}=29.32 μmol/L), and compounds **11—13** and **16—20** were more potent against SK-OV-3 cells with IC_{50} values of 6.75—16.96 μmol/L than the positive control *cis*-Platin(IC_{50}=18.66 μmol/L).

It is interesting to note that compound **12** displayed the strongest antiproliferative activity against these three cancer cells mentioned above with IC_{50} values from 0.91 μmol/L to 7.08 μmol/L, compounds **6** and **10** showed selective

antiproliferative activity against HCC1954 cells with IC_{50} value of 0.49 and 5.32 μmol/L respectively. Molecular recognition in target binding site in these cancer cells may be the reason for different behavior of these compounds.

Table 1 Half-maximal inhibitory concentrations(IC_{50}, μmol/L) of prenyled flavonoids 1—20 on the human cancer cell lines

Compound	HeLa	HCC1954	SK-OV-3
1	>100	>100	>100
2	63.35	>100	>100
3	>100	17.29	>100
4	>100	34.77	>100
5	38.71	18.94	39.31
6	>100	0.49	>100
7	47.28	82.74	95.07
8	46.23	86.55	21.46
9	12.81	19.33	>100
10	>100	5.32	>100
11	28.94	13.33	16.96
12	0.91	1.89	7.08
13	9.52	10.65	14.03
14	17.87	6.38	55.65
15	60.43	41.45	>100
16	7.32	>100	15.24
17	30.76	13.07	16.75
18	10.93	4.46	8.71
19	10.28	7.77	6.75
20	4.35	4.45	7.77
cis-Platin*	13.30	29.32	18.66
Paclitaxel*	0.007	0.045	0.029
Staurosporine*	0.034	0.168	0.053

* *cis*-Platin, Paclitaxel and Staurosporine were employed as positive controls.

4 Conclusions

Twenty prenylated flavonoids(among them, seventeen are novel compounds) were synthesized from natural flavonoids naringin, hesperidin, quercetin and myricetin. The natural product 3,3′,4′,7-tetramethoxy-8-prenyl-5-hydroxy flavonoid (**16**) was synthesized in high yield. The key step of the synthetic route was a regioselective Claisen rearrangement under microwave(700 W) heating or conventional heating to form the *C*-prenylated flavonoids from the *O*-prenylated flavonoids. The results of biological activity study showed that most of synthesized target prenylated flavonoids exhibited moderate to potent antiproliferative activities toward the three cancer cell lines. 3′,4′,7-Trimethoxyl-5-hydroxyl-8-prenyl flavonoids(**12**) and 3′,4′,3,5,7-pentamethoxy-8-prenyl flavonoid(**20**) exhibited the greatest potency with IC_{50} value below 10 μmol/L. 3′,7-Dimethoxy-5-*O*-prenyl flavone(**6**) and 3′,4′,7-trimethoxy-5-*O*-prenyl flavone(**10**) displayed selective antiproliferative activity against HCC1954 cells with IC_{50} value of 0.49 and 5.32 μmol/L, respectively. They are potential and selective anticancer agent and worthy of further investigation.

Electronic Supplementary Material

Supplementary material is available in the online version of this article at http://dx.doi.org/10.1007/s40242-018-8013-5.

References

[1] Raffa D., Maggio B., Raimondi M. V., Plescia F., Daidone G., *Eur. J. Med. Chem*., **2017**, *142*, 213

[2] Verma A. K., Pratap R., *Tetrahydron*, **2012**, *68*(41), 8523

[3] Vogel S., Ohmayer S., Brunner G., Heilmann J., *Bioorg. Med. Chem*., **2008**, *16*(8), 4286

[4] Lei Q., Zhang S., Liu M., Li J., Zhang X., Long Y., *Mol. Divers*., **2017**, *21*(4), 957

[5] Dong X., Liu Y., Yan J., Jiang C., Chen J., Liu T., Hu Y., *Bioorg. Med. Chem*., **2008**, *16*(17), 8151

[6] Neves M. P., Cidade H., Pinto M., Silva A. M. S., Gales L., Damas A. M., Lima R.T., Vasconcelos M. H., Nascimento M. S. J., *Eur. J. Med. Chem*., **2011**, *46*(6), 2562

[7] Wen Z., Zhang Y., Wang X., Zeng X., Hu Z., Liu Y., Xie Y., Liang G., Zhu J., Luo H., Xu B., *Eur. J. Med. Chem.*, **2017**, *133*, 227

[8] Basabe P., de Roman M., Marcos I. S., Diez D., Blanco A., Bodero O., Mollinedo F., *Eur. J. Med. Chem*., **2010**, *45*(9), 4258

[9] Wang C., Wu P., Shi J. F., Jiang Z. H., Wei X. Y., *Eur. J. Med. Chem*., **2015**, *100*, 139

[10] Jung A. H., Jin E. S., Choi J. R., Manh T. H., Kim S. Y., Min S. B., Son K. Y., Ahn R. B., Kim W. B., Sohn S. S., Choi S. J., *Arch. Pharm. Res*., **2011**, *34*(12), 2087

[11] Zhang B., Duan D., Ge C., Yao J., Liu Y., Li X., Fang J., *J. Med. Chem*., **2015**, *58*(4), 1795

[12] Chen M., Shi L., Tang J., Wang Q. A., *Chem. Res. Chinese Universities*, **2016**, *32*(5), 754

[13] Nguyen V. S., Li W., Li Y., Wang Q. A., *Med. Chem. Res*., **2017**, *26*, 1585

[14] Nguyen V. S., Shi L., Wang S. C., Wang Q. A., *Anti-cancer Agents Med. Chem.*, **2017**, *17*(1), 137

[15] Liu J. D., Chen L., Cai S. L., Wang Q. A., *Carbohyd. Res*., **2012**, *357*, 41

[16] Wu Z., Cai S. L., Fan W. J., Wang Q. A., *Chin. J. Org. Chem*., **2012**, *32*(7), 1296

[17] Ou L., Han S., Ding W., Che Z., Ye Z., Yang H., Zhang G., Lou Y., Chen J., Yu Y., *Mol. Divers*., **2011**, *15*(3), 665

[18] Pinhey J. T., Southwell I. A., *Aust. J. Chem*., **1973**, *26*(2), 409

[19] Song Y. P., Xin Z. Y., Wan Y. M., Li J. B., Ye B. P., Xue X. W., *Eur. J. Med. Chem*., **2015**, *90*, 695