Synthesis of Bioactive Natural Polymethoxyflavones and Their Vinyl Ether Derivatives

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Abstract Bioactive natural polymethoxyflavones **1—6** and their vinyl ether derivatives **7—15** were synthesized by bromination, aromatic nucleophilic substitution, methylation, benzyl protection, Friedel-Crafts acetylation, aldol condensation, cyclization, DDQ dehydrogenation, regioselective demethylation, debenzylation and *O*-prenylation or *O*-farnesylation with resorcinol and appropriate substituted benzaldehydes as starting materials. Among them, compounds **7—15** are new compounds. Natural products **2—4** were firstly total synthesized. The syntheses of compounds **1**, **5** and **6** were efficiently improved by the new synthetic routes. The structures of all synthetic compounds were confirmed by NMR, IR spectra and MS.

Keywords Flavonoid; Polymethoxyflavone; Prenylation; Farnesylation

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1 Introduction

Polymethoxyflavonoids(PMFs) are a class of natural products, which widely exist in Citrus plants possessing distinguished anticarcinogenic, antiinflammatory and antiviral activities[1—3]. Many *in vitro* and *in vivo* studies indicate the protective effects of PMF against the occurrence of cancer. For example, Nobiletin(3',4',5,6,7,8-hexamethoxyflavone) and Tangeretin(4',5',6,7,8-pentamethoxyflavone) isolated from *Citrus aurantium* showed inhibitory effects on human neuroblastoma SH-SY5Y cells[4]. 4-Demethyl tangeretin(4'-hydroxy-5,6,7,8-tetramethoxy flavone, **3**), exists particularly in tangerines, was shown to inhibit cancer proliferation[5]. Gardenin A(5-hydroxy-6,7,8,3',4',5'-hexamethoxyflavone, **4**) isolated from sweet orange(*Citrus sinenis*) peel, showed strong inhibitory activities against the proliferation and induced the apoptosis of HL-60 cell line[6]. Xanthomicrol(5,4'-dihydroxy-6,7,8-trimethoxyflavone, **6**) is the main cytotoxic component of *Dracocephalum kotschyii* and a potential anticancer agent[7].

In despite of many recent reports on PMFs and their biological activities[8,9], the synthesis of these compounds has been much less studied, the full potential of this class of compounds to be used as drugs has yet to be realized in terms of both more new molecule and diverse biological activity. Recently we have reported the total synthesis of Nobiletin and Tangeretin[10], as a continuation of our investigation of bioactive flavonoids and development of new antitumor activity compounds, we reported our studies on the synthesis of a series of bioactive natural polymethoxyflavones **1—6** and their vinyl ether derivatives **7—15**. Among them, compounds **7—15** are new compounds, natural products **2—4** were first total synthesized, the syntheses of products **1**, **5** and **6** were efficiently improved by 14% KOH(aq.) instead of 50% KOH(aq.) as condensater in aldol condensation step of the new synthetic routes.

2 Results and Discussion

The natural polymethoxylflavones **1—6** and their vinyl ether derivatives **7—15** were synthesized according to the route shown in Scheme 1. 2'-Hydroxy-3',4',5',6'-tetramethoxy acetophenone was prepared from resorcinol *via* reactions of bromination, methylation, aromatic nucleophilic substitution and Fridel-Crafts acetylation[10].

First, the hydroxyl groups of 3-methoxy-4-hydroxyl benzaldehyde and 4-hydroxyl benzaldehyde were protected with benzyl group. Aldol condensation of 2'-hydroxy-3',4',5',6'-tetramethoxyacetophenone with appropriately substituted benzaldehydes **16—18** in EtOH and KOH yielded corresponding chalcones **19—21**, which underwent cyclization in the presence of EtONa under heating conditions to yield corresponding flavanones **22—24**. The aldol condensation was very sensitive to the modification of reaction parameters, a significant excess of KOH(20—25 times) was required to force the reaction to completion. We used 14% KOH(aq.) instead of 50% KOH(aq.) as condensater in aldol condensation step, the concentration of alkali was reduced distinctly, the yields were not lowered compared with those reported in literature[11,12]. Consequently flavanones **22—24** were oxidized with 2,3-dichloxo-5,6-dicyanobenzoquinone(DDQ) to afford compounds **1**, **25** and **26** in good yields, and subsequent hydrogenolysis of benzyl ethers **25** and **26** in the presence of Pd/C catalyst gave corresponding ploymethoxyflavones **2** and **3** bearing a hydroxyl group on the B ring. Then promoted by a Lewis acid aluminum chloride and with anhydrous acetonitrile as the solvent, the reactions of compounds **1**, **25** and **26** underwent regioselective demethylation of the C_5-methoxy group to give 5-hydroxypolymethoxy

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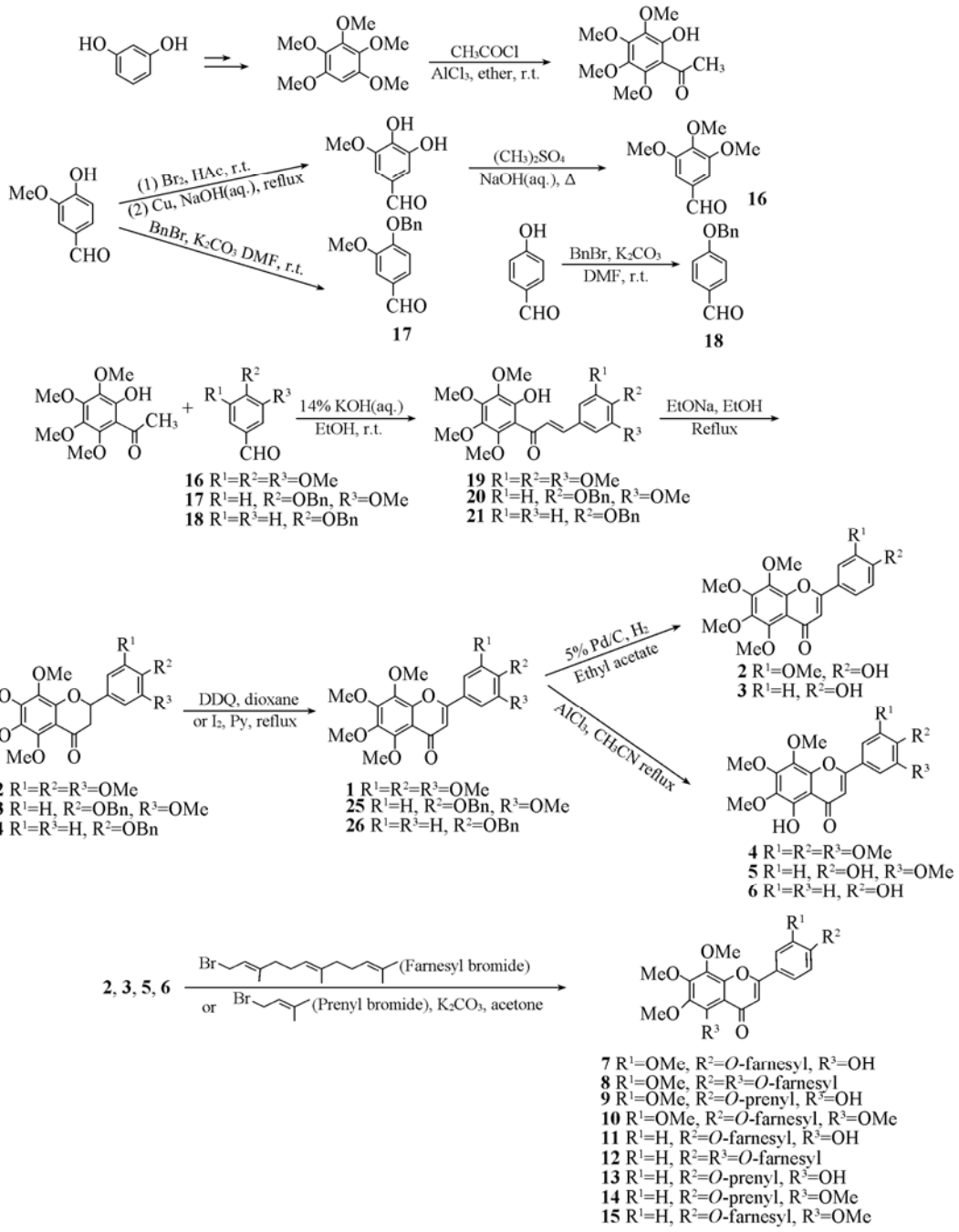

Scheme 1 Synthetic routes of natural polymethoxy flavones 1—6 and their vinyl ether derivatives 7—15

flavones **4—6** in good yields due to the neighboring-group participation of the C_4-carbonyl oxygen.

Prenyl or farnesyl moieties can potentially substitute for conventional lipids as lipophilic carriers of bioactive molecules. The introduction of a prenyl or farnesyl moiety in bioactive molecules is an important post-translational modification centre to many cellular processes[13,14]. Next, we turned our attention to the modification of hydroxyed polymethoxyflavone by the prenyl or farnesyl group, and hydroxyed polymethoxyflavones **2**, **3**, **5** and **6** were reacted respectively with commercially available prenyl bromide or *trans, trans*-farnesyl bromide in the prescence of anhydrous potassium carbonate and anhydrous acetone at ambient temperature to give nine *O*-preyl or *O*-farnesyl substituted polymethoxyflavone derivatives **7—15**.

3 Experimental

Melting points were measured on an XRC-I apparatus and were uncorrected. IR spectra were recorded on a bruker Tensor-27 spectrometer, ^{1}H NMR spectra were recorded on a bruker AM-400 instrument with tetramethylsilane as an internal standard, coupling constants(*J*) in Hz, mass spectra were determined with a ZAB-HS spectrometer by means of the ESI or FAB method. All the solvents were dried by standard procedures. 2'-Hydroxy-3',4',5',6'-tetramethoxyacetophenone was prepared from resorcinol by the reported procedure[10]. 3,4,5-Trimethoxybenzaldehyde, 3-methoxy-4-benzyloxybenzaldehyde and 4-benzyloxybenz aldehyde were prepared according

to previous methods[15,16].

3.1 Synthesis of 2'-Hydroxy-3',4',5',6',3,4,5-heptamethoxylchalcone(19)

A solution of 3,4,5-trimethoxybenzaldehyde(**16**, 574 mg, 2.93 mmol) and 2-hydroxy-3,4,5,6-tetramethoxyacetophenone (625 mg, 2.44 mmol) in 80% ethanol(26 mL) containing KOH(3.37 g, 60 mmol) was stirred at room temperature overnight. The mixture was acidified with 20% HCl to pH 5—6, then extracted with ethyl acetate. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*, the residue was applied to silica gel chromatography with petroleum ether-ethyl acetate(volume ratio 4:1) as eluent to give 629 mg of compound **19** as orange solid, yield 60%, m. p. 60—62 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 3.87(s, 3H, OCH_3), 3.90(each s, 6H, OCH_3), 3.91(s, 3H, OCH_3), 3.93(each s, 6H, OCH_3), 4.11(s, 3H, C6′-OCH_3), 6.87(s, 2H, C2-H, C6-H), 7.78(d, J=15.6 Hz, 1H, H-β), 7.83(d, J=15.6 Hz, 1H, H-α), 13.23(s, 1H, C2′-OH). ESI-MS, m/z: 435[M+H]$^+$.

3.2 Synthesis of 2'-Hydroxy-3',4',5',6',3-pentamethoxy-4-benzyloxylchalcone(20)

Compound **20** was prepared from 3-methoxy-4-benzyloxyl benzaldehyde(**17**) and 2-hydroxy-3,4,5,6-tetramethoxyacetophenone as described for the preparation of compound **19** from compound **16** and 2-hydroxy-3,4,5,6-tetramethoxyacetophenone. Orange solid, yield 43%. m. p. 92—94 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.86(s, 3H, OCH_3), 3.88(each s, 6H, OCH_3), 3.89(s, 3H, OCH_3), 4.10(s, 3H, C6′-OCH_3), 5.20(s, 2H, $ArCH_2$), 6.90(d, J=8.0 Hz, 1H, C5-H), 7.17—7.20(m, 2H, C2-H, C6-H), 7.31—7.45(m, 5H, Ar—H), 7.77(d, J=15.6 Hz, 1H, H-β), 7.78(d, J=16.4 Hz, 1H, H-α), 13.30(s, 1H, C2′-OH). ESI-MS, m/z: 481[M+H]$^+$.

3.3 Synthesis of 2'-Hydroxy-3',4',5',6'-tetramethoxy-4-benzyloxyl chalcone(21)

Compound **21** was prepared from 4-benzyloxylbenzaldehyde(**18**) and 2-hydroxy-3,4,5,6-tetramethoxy acetophenone as described for the preparation of compound **19** from compound **16** and 2-hydroxy-3,4,5,6-tetramethoxy acetophenone. Orange solid, yield 45%. m. p. 93—95 °C(lit.[15]: 95—98 °C). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.86(s, 3H, OCH_3), 3.88(s, 3H, OCH_3), 3.89(s, 3H, OCH_3), 4.10(s, 3H, C6′-OCH_3), 5.20(s, 2H, $ArCH_2$), 7.00(d, J=9.2 Hz, 2H, C3-H, C5-H), 7.39—7.43(m, 5H, Ar—H), 7.60(d, J=8.4 Hz, 2H, C2-H, C6-H), 7.82(d, J=15.6 Hz, 1H, H-β), 7.83(d, J=15.6 Hz, 1H, H-α), 13.29(s, 1H, C2′-OH). ESI-MS, m/z: 451[M+H]$^+$.

3.4 Synthesis of 5,6,7,8,3',4',5'-Heptamethoxylflavanone(22)

A solution of compound **19(**648 mg, 1.5 mmol) in ethanol(30 mL) containing EtONa(856 mg, 0.5 mmol) was heated to reflux for 3 h. Upon concentration, the resultant material was mixed with water(10 mL), and extracted twice with ethyl acetate(50 mL×2). The combined organic layer was concentrated and purified by silica gel chromatography with petroleum ether-ethyl acetate(volume ratio 5:1) as eluent to give 438 mg of compound **22** as light yellow solid, yield 67.7%, m. p. 123—125 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 2.86(dd, J=16.4, 2.8 Hz, 1H, C3-H *cis*), 3.05(dd, J=16.4, 12.8 Hz, 1H, C3-H *trans*), 3.86(s, 3H, OCH_3), 3.87(each s, 6H, OCH_3), 3.88(each s, 6H, OCH_3), 3.90(s, 3H, OCH_3), 4.10(s, 3H, C5-OCH_3), 5.39(dd, J=12.8, 2.8 Hz, 1H, C2-H), 6.70(s, 2H, C2′-H, C6′-H). ESI-MS, m/z: 435[M+H]$^+$.

3.5 Synthesis of 5,6,7,8,3'-Pentamethoxy-4'-benzyloxyflavanone(23)

Compound **23** was prepared from compound **20** as described for the preparation of compound **22** from compound **19**. Light yellow solid, yield 54%. m. p. 102—104 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 2.85(dd, J=2.8, 16.4 Hz, 1H, C3-H *cis*), 3.00(dd, J=12.8, 16.4 Hz, 1H, C3-H *trans*), 3.84(s, 3H, OCH_3), 3.85(s, 3H, OCH_3), 3.90(s, 3H, OCH_3), 3.92(s, 3H, OCH_3), 4.06(s, 3H, C5-OCH_3), 5.18(s, 2H, $ArCH_2$), 5.37(dd, J=12.8, 2.8 Hz, 1H, C2-H), 6.90(d, J=8.4 Hz, 1H, C5′-H), 6.93(dd, J=8.4, 1.6 Hz, 1H, C6′-H), 7.03(d, J=2.0 Hz, 1H, C2′-H), 7.31—7.45(m, 5H, Ar—H). ESI-MS, m/z: 481[M+H]$^+$.

3.6 Synthesis of 5,6,7,8-Tetramethoxy-4-benzyloxylflavanone(24)

Compound **24** was prepared from compound **21** as described for the preparation of compound **22** from compound **19**. Light yellow solid, yield 61%. m. p. 112—114 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 2.84(1H, dd, J=16.4, 2.8 Hz, C3-H *cis*), 3.03(1H, dd, J=16.8 , 12.8 Hz, C3-H *trans*), 3.83(s, 3H, OCH_3), 3.85(s, 3H, OCH_3), 3.90(s, 3H, OCH_3), 4.06(s, 3H, C5-OCH_3), 5.09(s, 2H, Bn-CH_2), 5.38(1H, dd, J=12.8, 2.8 Hz, C2-H), 7.01(d, 2H, J=8.4 Hz, C3′-H, C5′-H), 7.38—7.43(m, 7H, C2′-H, C6′-H, Bn-Ar—H). ESI-MS, m/z: 451[M+H]$^+$.

3.7 Synthesis of 5,6,7,8,3',4',5'-Heptamethoxylflavone(1)

A solution of compound **22**(82 mg, 0.19 mmol) and DDQ(64 mg, 0.28 mmol) in dry dioxane(10 mL) was refluxed for 8 h. The reaction mixture was cooled, concentrated and purified by silica gel chromatography with petroleum ether-ethyl acetate(volume ratio 3:2) as eluent to give 47 mg of compound **1** as light yellow needles, yield 58%. m. p. 100—101 °C(lit.[17]: 101.5—102.5 °C). ^{1}H NMR(400 MHz, $CDCl_3$), δ: 3.94(s, 3H, OCH_3), 3.96(each s, 12H, OCH_3), 4.03(s, 3H, OCH_3), 4.12(s, 3H, C5-OCH_3), 6.67(s, 1H, C3-H), 6.70(s, 2H, C2′-H, C6′-H). IR(KBr), $\tilde{\nu}$/cm^{-1}: 3428, 2956, 2837, 1645, 1590. HRMS(FBA), m/z: 433.4279[M+H]$^+$(calcd. for $C_{22}H_{25}O_9$: 433.4285).

3.8 Synthesis of 5,6,7,8,3′-Pentamethoxy-4′-benzyloxylflavone(25)

Compound **25** was prepared from compound **23** as described for the preparation of compound **1** from compound **22.** Light yellow solid, yield 79%. m. p. 152—153 °C. ^{1}H NMR

(400 MHz, $CDCl_3$), δ: 3.95(each s, 6H, OCH_3), 3.99(s, 3H, OCH_3), 4.02(s, 3H, OCH_3), 4.10(s, 3H, C5-OCH_3), 5.25(s, 2H, $ArCH_2$), 6.63(s, 1H, C2-H), 6.99(d, J=8.4 Hz, 1H, C5′-H), 7.33—7.51(m, 7H, Ar—H, C2′-H, C6′-H). ESI-MS, m/z: 479 $[M+H]^+$.

3.9 Synthesis of 5,6,7,8-Tetramethoxy-4′-benzyloxylflavone(26)

Compound **26** was prepared from compound **24** as described for the preparation of compound **1** from compound **22**. Light yellow solid, yield 75%. m. p. 112—114 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.95(each s, 6H, OCH_3), 4.02(s, 3H, OCH_3), 4.10(s, 3H, C5-OCH_3), 5.16(s, 2H, $ArCH_2$), 7.09(d, J=9.2 Hz, 2H, C3′-H, C5′-H), 7.34—7.46(m, 5H, Ar—H), 7.87(d, J=9.2 Hz, 2H, C2′-H, C6′-H). ESI-MS, m/z: 449 $[M+H]^+$.

3.10 Synthesis of 4′-Hydroxy-5,6,7,8,3′-pentamethoxylflavone(2)

Compound **25**(60 mg, 0.12 mmol) was dissolved in methanol-ethyl acetate(volume ratio 2:1, 9 mL) and to this solution 5% palladium on carbon(5 mg) was added. Hydrogen gas was introduced at 275.8 kPa for 30 min while shaking. The reaction mixture was concentrated and purified by silica gel chromatography with petroleum ether-ethyl acetate(volume ratio 2:1) as eluent to give 41 mg of compound **2** as a yellow solid, yield 84%. m. p. 142—143 °C(lit.[18]: 140—142 °C). ^{1}H NMR(400 MHz, $CDCl_3$), δ: 3.95(s, 3H, OCH_3), 3.96(s, 3H, OCH_3), 3.98(s, 3H, OCH_3), 4.03(s, 3H, OCH_3), 4.11(s, 3H, C5-OCH_3), 6.63(s, 1H, C3-H), 7.06(d, J=8.4 Hz, 1H, C5′-H), 7.40(d, J=2.0 Hz, 1H, C2′-H), 7.53(dd, J=8.4, 2.0 Hz, 1H, C6′-H). IR(KBr), $\tilde{\nu}$/cm^{-1}: 3310, 2936, 1630. HRMS(FAB), m/z: 389.3766$[M+H]^+$(calcd. for $C_{20}H_{21}O_8$: 389.3759).

3.11 Synthesis of 4′-Hydroxy-5,6,7,8-tetramethoxylflavone(3)

Compound **3** was prepared from compound **26** as described for the preparation of compound **1** from compound **22**. Light yellow solid, yield 86%. m. p. 196—197 °C(lit.[19]: 197—199 °C). ^{1}H NMR(400 MHz, $CDCl_3$), δ: 3.95(s, 3H, OCH_3), 3.96(s, 3H, OCH_3), 4.03(s, 3H, OCH_3), 4.12(s, 3H, C5-OCH_3), 6.76(s, 1H, C3-H), 7.01(d, J=8.4 Hz, 2H, C3′-H, C5′-H), 7.84(d, J=8.4 Hz, 2H, C2′-H, C6′-H). HRMS(FAB), m/z: 359.3490$[M+H]^+$(calcd. for $C_{19}H_{19}O_7$: 359.3500).

3.12 Synthesis of 5-Hydroxy-6,7,8,3′,4′,5′-hexamethoxylflavone(4)

Compound **1** was dissolved in anhydrous CH_3CN(10 mL). After stirring for 10 min, anhydrous $AlCl_3$ was added to it, the solution was stirred for 20—40 min. The reaction mixture was concentrated and purified by silica gel chromatography with petroleum ether-ethyl acetate(volume ratio 5:2) as eluent to give 53 mg of compound **4** as a yellow solid, yield 97.5%. m. p. 163—165 °C(lit.[20]: 161—162 °C). ^{1}H NMR(400 MHz, $CDCl_3$), δ: 3.95(s, 3H, OCH_3), 3.97(each s, 9H, OCH_3), 3.98(s, 3H, OCH_3), 4.12(s, 3H, OCH_3), 6.64(s, 1H, C3-H), 7.18(s, 2H, C2′-H, C6′-H), 12.46(s, 1H, C_5-OH). HRMS(FAB), m/z: 419.4026$[M+H]^+$(calcd. for $C_{21}H_{23}O_9$：419.4019).

3.13 Synthesis of 5,4′-Dihydroxy-6,7,8,3′-tetramethoxylflavone(5)

Compound **5** was prepared from compound **25** as described for the preparation of compound **4** from compound **1**. Yellow solid, yield 94%. m. p. 155—158 °C(lit.[21]: 192 °C). ^{1}H NMR(400 MHz, $CDCl_3$), δ: 3.96(s, 3H, OCH_3), 3.98(s, 3H, OCH_3), 4.01(s, 3H, OCH_3), 4.12(s, 3H, OCH_3), 6.08(s, 1H, C4′-OH), 6.60(s, 1H, C3-H), 7.05(d, J=8.0 Hz, 1H, C5′-H), 7.41(d, J=1.6 Hz, 1H, C2′-H), 7.05(dd, J=8.0, 1.6 Hz, 1H, C6′-H), 12.55(s, 1H, C5-OH). HRMS(FAB), m/z: 375.3483 $[M+H]^+$(calcd. for $C_{19}H_{19}O_8$: 375.3494).

3.14 Synthesis of 5,4′-Dihydroxy-6,7,8-trimethoxylflavone(6)

Compound **6** was prepared from compound **26** as described for the preparation of compound **4** from compound **1.** Yellow solid, yield 90%. m. p. 225—227 °C(lit.[7]: 227—230 °C). ^{1}H NMR(400 MHz, DMSO-d_6), δ: 3.82(s, 3H, OCH_3), 3.92(s, 3H, OCH_3), 4.02(s, 3H, OCH_3), 6.90(s, 1H, C3-H), 6.96(d, J=9.2 Hz, 2H, C3′-H, C5′-H), 7.95(d, J=8.8 Hz, 2H, C2′-H, C6′-H), 10.44(s, 1H, C4′-OH), 12.79(s, 1H, C5-OH). HRMS(FAB), m/z: 345.3238$[M+H]^+$(calcd. for $C_{18}H_{17}O_7$: 345.3234).

3.15 Synthesis of 5-Hydroxy-6,7,8,3′-tetramethoxy-4′-*O*-farnesylflavone(7) and 6,7,8,3'-tetramethoxy-5,4'-*O*, *O*-difarnesylflavone(8)

To a mixture of compound **5**(58 mg, 0.15 mmol) and anhydrous K_2CO_3(83 mg, 0.6 mmol) in dry acetone(5 mL) was added dropwise a solution of *trans,trans*-farnesyl bromide (0.05 mol, 0.21 mmol) in acetone(2 mL) upon stirring for 3 h, and then the reaction mixture was filtered and evaporated. The residue was sujected to chromatography on silica gel with petroleum ether-ethyl acetate(volume ratio 10:1) as eluent to give 7.5 mg of compound **7** as a yellow oil(yield 87%) and 12 mg of compound **8** as a yellow oil(yield 10%).

Compound **7**: ^{1}H NMR(400 MHz, $CDCl_3$), δ: 1.59(s, 6H, C11″-CH_3, C7″-CH_3), 1.67(s, 3H, C11″-CH_3), 1.77(s, 3H, C3″-CH_3), 1.98—2.11(m, 8H, C4″-CH_2, C5″-CH_2, C8″-CH_2, C9″-CH_2), 3.96(s, 3H, OCH_3), 3.97(s, 3H, OCH_3), 3.98(s, 3H, OCH_3), 4.12(s, 3H, OCH_3), 4.72(d, J=6.4 Hz, 2H, C1″-CH_2), 5.06—5.11(m, 2H, C6"-H, C10"-H), 5.52(t, J=6.4 Hz, 1H, C2"-H), 6.61(s, 1H, C3-H), 6.98(d, J=8.4 Hz, 1H, C5′-H), 7.42(d, J=2.4 Hz, 1H, C2′-H), 7.55(dd, J=8.4, 2.0 Hz, 1H, C6′-H), 12.56(s, 1H, C5-OH). IR(KBr), $\tilde{\nu}$/cm^{-1}: 3361, 2929, 2847, 2362, 2329, 1740, 1654, 1593, 1513, 1460, 1430, 1372, 1272, 1224, 1144, 1111, 1075, 1036, 918, 840, 749. HRMS (FAB), m/z: 579.6995$[M+H]^+$(calcd. for $C_{34}H_{43}O_8$: 579.7004).

Compound **8**: ^{1}H NMR(400 MHz, $CDCl_3$), δ: 1.60—1.77 (each s, 24H, $C_{farnesyl}$-CH_3), 1.96—2.13(m, 16H, C4″-CH_2, C5″-CH_2, C8″-CH_2, C9″-CH_2), 3.96(each s, 6H, OCH_3), 4.01(s,

3H, OCH_3), 4.10(s, 3H, OCH_3), 4.61—4.72(each d, *J*=6.4, 7.6 Hz, 4H, C1″-CH_2), 5.06—5.14(m, 4H, C6"-H, C10"-H), 5.51—5.74(each t, *J*=6.2, 7.0 Hz, 2H, C2"-H), 6.61(s, 1H, C3-H), 6.98(d, *J*=8.8 Hz, 1H, C5′-H), 7.42(d, *J*=2.0 Hz, 1H, C2′-H), 7.53(dd, *J*=8.4, 2.0 Hz, 1H, C6′-H). HRMS(FAB), *m*/*z*: 784.0527$[M+H]^+$(calcd. for $C_{49}H_{67}O_8$: 784.0515).

3.16 Synthesis of 5-Hydroxy-6,7,8,3′-tetramethoxy-4′-*O*-prenylflavone(9)

Compound **9** was prepared from compound **5** and prenyl bromide as described for the preparation of compound **7** from compound **5** and *trans,trans*-farnesy bromide. Light yellow solid, yield 88%, m. p.＞220 °C. ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 1.78—1.80(each s, 6H, C3"-CH_3), 3.96(s, 3H, OCH_3), 3.97(s, 3H, OCH_3), 3.99(s, 3H, OCH_3), 4.12(s, 3H, OCH_3), 4.68(d, *J*=7.2 Hz, 2H, C1″-CH_2), 5.52(t, *J*=6.2 Hz, 1H, C2"-H), 6.62(s, 1H, C3-H), 6.99(d, *J*=8.4 Hz, 1H, C5′-H), 7.42(d, *J*=2.4 Hz, 1H, C2′-H), 7.56(dd, *J*=8.4, 2.4 Hz, 1H, C6′-H), 12.57(s, 1H, C_5-OH). HRMS(FAB), *m*/*z*: 443.4659$[M+H]^+$(calcd. for $C_{24}H_{27}O_8$: 443.4664).

3.17 Synthesis of 5,6,7,8,3′-Pentamethoxy-4′-*O*-farnesylflavone(10)

Compound **10** was prepared from compound **2** as described for the preparation of compound **7** from compound **5**. Yellow oil, yield 70%. ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 1.60(s, 6H, C11″-CH_3, C7″-CH_3), 1.67(s, 3H, C11″-CH_3), 1.77(s, 3H, C3″-CH_3), 1.98—2.10(m, 8H, C4″-CH_2, C5″-CH_2, C8″-CH_2, C9″-CH_2), 3.96(each s, 9H, OCH_3), 4.01(s, 3H, OCH_3), 4.11(s, 3H, OCH_3), 4.71(d, *J*=6.8 Hz, 2H, C1″-CH_2), 5.06—5.12(m, 2H, C6"-H, C10"-H), 5.53(t, *J*=6.4 Hz, 1H, C2"-H), 6.62(s, 1H, C3-H), 6.98(d, *J*=8.4 Hz, 1H, C5′-H), 7.42(d, *J*=2.0 Hz, 1H, C2′-H), 7.55(dd, *J*=8.4, 2.0 Hz, 1H, C6′-H). HRMS(FBA), *m*/*z*: 593.7259$[M+H]^+$(calcd. for $C_{35}H_{45}O_8$: 593.7270).

3.18 Synthesis of 5-Hydroxy-6,7,8-trimethoxy-4′-*O*-farnesylflavone(11) and 6,7,8-trimethoxy-5,4′-*O*, *O*-difarnesylflavone(12)

Compounds **11** and **12** were prepared from compound **6** as described for the preparation of compound **7** from compound **5**. Yellow oils, yield of compound **11**: 76%, yield of compound **12**: 21%.

Compound **11**: ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 1.60(s, 6H, C11″-CH_3, C7″-CH_3), 1.67(s, 3H, C11″-CH_3), 1.77(s, 3H, C3″-CH_3), 1.98—2.13(m, 8H, C4″-CH_2, C5″-CH_2, C8″-CH_2, C9″-CH_2), 3.85(s, 3H, OCH_3), 3.94(s, 3H, OCH_3), 4.10(s, 3H, OCH_3), 4.63(d, 2H, *J*=6.8 Hz, C1″-CH_2), 5.08—5.12(m, 2H, C6"-H, C10"-H), 5.50(t, *J*=6.4 Hz, 1H, C2"-H), 6.60(s, 1H, C3-H), 7.03(d, *J*=8.8 Hz, 2H, C3′-H, C5′-H), 7.88(d, *J*=8.8 Hz, 2H, C2′-H, C6′-H), 12.61(s, 1H, C5-OH). HRMS(FBA), *m*/*z*: 549.6752$[M+H]^+$(calcd. for $C_{33}H_{41}O_7$: 549.6744).

Compound **12**: ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 1.60—1.77(each s, 24H, $C_{farnesyl}$-CH_3), 2.05—2.13(m, 16H, C4″-CH_2, C5″-CH_2, C8″-CH_2, C9″-CH_2), 3.96(s, 3H, OCH_3), 4.02(s, 3H, OCH_3), 4.10(s, 3H, OCH_3), 4.60—4.63(each d, *J*=3.6, 2.8 Hz, 4H, C1″-CH_2), 5.07—5.13(m, 4H, C6"-H, C10"-H), 5.49—5.74(each t, 2H, *J*=6.6, 5.6 Hz, C2"-H), 6.60(s, 1H, C3-H), 7.02(d, *J*=9.2 Hz, 2H, C3′-H, C5′-H), 7.88(d, *J*=8.8 Hz, 2H, C2′-H, C6′-H). HRMS(FBA), *m*/*z*: 754.0268$[M+H]^+$(calcd. for $C_{48}H_{65}O_7$: 754.0255).

3.19 Synthesis of 5-Hydroxy-6,7,8-trimethoxy-4′-*O*-prenylflavone(13)

Compound **13** was prepared from compound **6** and prenyl bromide as described for the preparation of compound **7** from compound **5**. Yellow solid, yield 45%. m. p. 112—114 °C. ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 1.78—1.82(each s, 6H, C3"-CH_3), 3.94(s, 3H, OCH_3), 3.97(s, 3H, OCH_3), 4.10(s, 3H, OCH_3), 4.61(d, *J*=6.8 Hz, 2H, C1″-CH_2), 5.51(t, *J*=7.0 Hz, 1H, C2"-H), 6.60(s, 1H, C3-H), 7.04(d, *J*=9.2 Hz, 2H, C3′-H, C5′-H), 7.88(d, *J*=9.2 Hz, 2H, C2′-H, C6′-H), 12.60(s, 1H, C5-OH). IR(KBr), $\tilde{\nu}$/cm^{-1}: 3316, 2936, 2855, 2360, 2333, 1735, 1653, 1605, 1508, 1431, 1373, 1262, 1224, 1182, 1115, 1072, 1033, 832. HRMS(FAB), *m*/*z*: 413.4413$[M+H]^+$(calcd. for $C_{23}H_{25}O_7$: 413.4404).

3.20 Synthesis of 5,6,7,8-Tetramethoxy-4′-*O*-prenylflavone(14)

Compound **14** was prepared from compound **3** and prenyl bromide as described for the preparation of compound **7** from compound **5**. White solid, yield 52%. m. p. 104—106 °C. ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 1.78—1.82(each s, 6H, C3"-CH_3), 3.95(each s, 6H, OCH_3), 4.03(s, 3H, OCH_3), 4.11(s, 3H, OCH_3), 4.60(d, *J*=6.8 Hz, 2H, C1″-CH_2), 5.51(t, *J*=6.8 Hz, 1H, C2"-H), 6.61(s, 1H, C3-H), 7.03(d, *J*=8.8 Hz, 2H, C3′-H, C5′-H), 7.87(d, *J*=9.2 Hz, 2H, C2′-H, C6′-H). HRMS(FAB), *m*/*z*: 427.4676$[M+H]^+$(calcd. for $C_{24}H_{27}O_7$: 427.4670).

3.21 Synthesis of 5,6,7,8-Tetramethoxy-4′-*O*-farnesylflavone(15)

Compound **15** was prepared from compound **3** as described for the preparation of compound **7** from compound **5**. Yellow oil, yield 51%. ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 1.60(s, 6H, C11″-CH_3, C7″-CH_3), 1.67(s, 3H, C11″-CH_3), 1.77(s, 3H, C3″-CH_3), 1.96—2.17(m, 8H, C4″-CH_2, C5″-CH_2, C8″-CH_2, C9″-CH_2), 3.95(each s, 6H, OCH_3), 4.01(s, 3H, OCH_3), 4.11(s, 3H, OCH_3), 4.62(d, *J*=6.8 Hz, 2H, C1″-CH_2), 5.07—5.13(m, 2H, C6"-H, C10"-H), 5.50(t, *J*=5.6 Hz, 1H, C2"-H), 6.64(s, 1H, C3-H), 7.03(d, *J*=8.8 Hz, 2H, C3′-H, C5′-H), 7.87(d, *J*=8.8 Hz, 2H, C2′-H, C6′-H). HRMS(FAB), *m*/*z*: 563.7015$[M+H]^+$(calcd. for $C_{34}H_{43}O_7$: 563.7010).

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