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Design, synthesis, and structure–activity relationships of bavachinin analogues as peroxisome proliferator-activated receptor γ agonists

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Abstract: Bavachinin analogues with systematic modifications at the A-, B-, and C-rings were designed, synthesized, and subjected to in vitro bioevaluation as peroxisome proliferator-activated receptor γ (PPAR-γ) agonists. In total, 30 molecules, including flavanone and flavone analogues, were evaluated by reporter gene assays for the PPAR-γ agonist activity. Preliminary structure–activity relationships of PPAR-γ agonist activity of bavachinin analogues were initially summarized and analogues **2b**, **3**, **4a**, **4b**, **11c**, **11d**, and **12b** were found with higher PPAR-γ agonist activities compared to bavachinin.

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by a disruption in glucose homeostasis, manifesting as hyperglycemia, abnormalities in lipid and protein metabolism, and the development of both acute- and long-term complications.[1] Diabetes increases the risk of ocular, renal, neurologic, cardiovascular, peripheral vascular, and metabolic conditions; these conditions increase the risk of premature mortality and lead to an excess increase in the body weight and physical inactivity.[2–4] In 2011, the WHO announced that 347 million people worldwide have diabetes, an estimated 3.4 million people died from complications of hyperglycemia in 2004, and this mortality will double from 2005 to 2030.[5]

Peroxisome proliferator-activated receptors (PPARs) belong to a family of ligand-activated nuclear receptors that consist of three subtypes: PPAR-α, PPAR-β/δ, and PPAR-γ.[6] PPAR-γ is a key regulator of gene expression of metabolism, inflammation, and other pathways in various types of cells, especially adipocytes.[7] The crucial role of PPAR-γ in lipid metabolism, adipogenesis, glucose homeostasis, and insulin sensitization is well documented.[8] PPAR-γ agonists, such as thiazolidinediones, including the widely used drug rosiglitazone, have been used in clinical practice to treat diabetes for several years and have been shown to lower blood glucose levels and improve insulin sensitivity.[9–10]

Recently, natural compounds, including flavones, flavanones, and isoflavones, exhibited excellent PPAR-γ agonist activity.[11] Bavachinin (Figure 1) is a naturally occurring flavanone isolated from the seeds of *Psoralea Corylifolia*.[12] It exhibits various biological activities, such as inhibition of the production of nitric oxide and antiangiogenic, antitumor, antiallergic, and antibacterial activities.[13–16] Our previous study showed that bavachinin exhibits unique synergistic effects with synthetic PPAR-γ and PPAR-α agonists on carbohydrate and lipid metabolism in *db/db* and diet-induced obese mice.[17] Meanwhile naturally occurring bavachinin is a mixture of two enantiomers with *S* and *R* configurations, and the value of enantiomeric excess is approximately 24.3%. A study of the two enantiomers suggested that (*S*)-bavachinin and (*R*)-bavachinin have similar PPAR-γ agonist activity.[18]

In the present study, structural modifications of bavachinin were performed focus on its PPAR-γ agonist activity. A novel series of racemic bavachinin analogues with systematic modifications at the A-, B-, and C-rings were designed and synthesized. Several analogues were selected to perform the further study.

Results and Discussion

Bavachinin **1**, exhibiting a conspicuous PPAR-γ agonist activity, was used as a lead compound for designing analogues (Figure 2). Our previous docking study showed that in the A-ring, an isopentenyl group at the C-6 position and a methoxyl group at the C-7 position may have a remarkable effect on the PPAR-γ agonist activity of bavachinin **1**. In the present study, those two groups at the C-6 and C-7 positions were removed, and the isopentenyl side chain was substituted with an isopentyl or geranyl chain. Previous structure–activity relationship studies have shown that a hydroxyl group at the C-4′ position in the B-ring is necessary for PPAR-γ agonist activity. Therefore, this group was modified through esterification, etherification, and halogen substitution. A hydroxyl group and halogen atom were introduced at the C-3′ position in the B-ring to investigate the PPAR-γ agonist activity. To determine whether the B-ring has a role in PPAR-γ agonist activity, the B-ring was removed and substituted with a heterocyclic ring. In the C-ring, flavone-related molecules with various substituents were designed through oxidation reaction. Flavones are distinguished from flavanones solely by the presence of the 2,3-double bond in the chromone ring.

The analogues **2a–2g** were synthesized through the esterification or Williamson ether reaction of bavachinin **1** with appropriate acyl halides or alkyl/aromatic halides in acetone in the presence of K_2CO_3 (Scheme 1).[19–22] Oxidizing bavachinin **1** with iodine in dimethyl sulfoxide (DMSO) yielded flavones **3**.[23] The analogues **4a–4c** were synthesized using the procedure used for preparing **2a–2g** by employing appropriate acyl halides or alkyl/aromatic halides.

Bavachinin analogues, **11a–11f**, were generated through the synthesis route outlined in Scheme 2. The 2'-hydroxy acetophenones **5a–5b** were treated with prenyl bromide or geranyl bromide in acetone in the presence of K_2CO_3 to yield **6a–6c**, which provided the intermediates **7a, 7b,** and **7d** in N,N-diethyl aniline through Claisen rearrangement.[24]

The intermediates **7a–7e** were treated with appropriate aromatic aldehydes, **8b, 8d,** and **8f**, in ethyl alcohol in the presence of potassium trimethylsilanolate and then neutralized with saturated NH_4Cl and extracted with ethyl acetate, yielding chalcones **9a–9f**.[25]

Regioselective cyclization of **9a–9f** through reflux with potassium fluoride in methyl alcohol yielded corresponding methoxymethylated flavanones **10a–10f**. The methoxymethylated flavanones were demethoxymethylated by hydrogen chloride in methyl alcohol to obtain the desired flavanones **11a–11f.**[26] Oxidizing the corresponding flavanones **11b** and **11d** with iodine in DMSO generated **12a** and **12b**.

Bavachinin analogues, **14a–14f**, were prepared through the synthesis route outlined in Scheme 3. The intermediate **7b** was treated with appropriate heteroaromatic aldehydes in ethyl alcohol in the presence of sodium hydroxide to obtain chalcones **13a–13f.**[27] The chalcones **13a–13f** were cyclized using KF as a base in methyl alcohol to yield flavanones **14a–14f**. Oxidizing the flavanones**14a–14c** with iodine in DMSO generated **15a–15c**.

The intermediate **7b** was subjected to condensation with N,N-dimethylformamide dimethylacetal to obtain the intermediate **16** and cyclization using glacial acetic acid to yield the corresponding chromone **17**.[28]

To identify new PPAR-γ modulators, reporter gene assays were conducted to analyze the effects of analogues on the PPAR-γ ligand binding domain (LBD).[29] Commercially available PPAR-γ agonists, rosiglitazone, was used as positive controls for PPAR-γ activity. In total, 30 synthesized analogues of the bavachinin were analyzed. The results are summarized in Table 1.

In Table 1, we discovered that introducing an aromatic ester group at the 4'-hydroxyl position of the B-ring (**2b–2d**) resulted in increased PPAR-γ agonist activity; whereas introducing an aliphatic ester group (**2a**) resulted in reduced PPAR-γ agonist activity. However, introducing an ether group at the same position (**2e–2g**) markedly reduced the PPAR-γ agonist activity compared with that of bavachinin. Changing the single bond at C-2 and C-3 position of the C-ring to double bond (**3**) and introducing an ester group at the 4'-hydroxyl position of the B-ring of **3** (**4a–4b**) significantly increased the PPAR-γ agonist activity compared with that of bavachinin However, introducing with steric hindrance at the 4'-hydroxyl position of the B-ring of **3** (**4c**) results in decreased PPAR-γ activity. The effects of various substitutions on the A-ring and B-ring of bavachinin were evaluated. A total of 19 analogues, **11a–11f**, **12a–12b**, **14a–14f**, **15a–15c**, and **16–17** were synthesized with different substituents on either the A-ring or the B-ring. Removing the methoxyl group at the C-7 position (**11a**) or the isopentenyl group at the C-6 position (**11f**) of the A-ring and substituting the isopentenyl chain at the C-7 position of the A-ring with a geranyl chain (**11e**) resulted in reduced PPAR-γ agonist activity. However, substituting the isopentenyl chain at the C-7 position of the A-ring with an isopentyl chain (**11d**) increased the PPAR-γ agonist activity. The presence of an electron-donating substituent at the C-3' position (3'-OH, **11b**) or an electron-withdrawing substituent at the C-3' position (3'-F, **11c**) of the B-ring increased the PPAR-γ agonist activity. In the flavone series (**12a–12b**), oxidizing the C-ring of flavanone **11b** (**12a**) reduced the PPAR-γ agonist activity and oxidizing the C-ring of flavanone **11d** (**12b**) increased the PPAR-γ agonist activity. Substituting the hydroxyl group at the C-4' position of the B-ring with a fluorine atom (**14a–14b, 15a–15b**) markedly reduced the PPAR-γ agonist activity. Changing the phenyl ring of the B-ring to a heterocyclic ring, creating thiazole, pyridine, or imidazole analogues (**14c, 14e, 14f, 15c**), markedly reduced the PPAR-γ agonist activity. Complete removal of the B-ring (**17**) markedly reduced PPAR-γ agonist activity. This demonstrates the importance of the B-ring in enhancing the PPAR-γ agonist activity. Analogues **2b**, **3**, **4a**, **4b**, **11c**, **11d**, and **12b** (EC_{50} = 2.53, 1.13, 0.78, 0.43, 3.30, 13.61, and 3.55 μM, respectively) exhibited a substantially higher PPAR-γ agonist activity compared to bavachinin **1** (EC_{50} = 18.74 μM).

Conclusions

The key structure–activity relationships trends of bavachinin **1** PPAR-γ agonist activity from the present study are listed as follows: (i) In the A-ring, an isopentenyl group at the C-6 position and methoxyl group at the C-7 position are indispensable for the PPAR-γ agonist activity, the results also suggest that an aliphatic chain in the C-6 position is crucial for the PPAR-γ agonist activity, and the

aliphatic chain should not be too long; (ii) In the B-ring, changing hydroxyl group at C-4' position to aromatic ester group increases the PPAR-γ agonist activity, meanwhile changing hydroxyl group to aliphatic ester group or ether group reduce PPAR-γ agonist activity. The phenyl ring structure is essential for the PPAR-γ agonist activity, and replacing this phenyl ring with imidazole, thiazole, or pyridine rings markedly reduce the PPAR-γ agonist activity; (iii) In the C-ring, changing the single bond at C-2 and C-3 position to double bond markedly increases the PPAR-γ agonist activity. Analogues **2b**, **3**, **4a**, **4b**, **11c**, **11d**, and **12b** were found with higher PPAR-γ agonist activity compared to bavachinin **1**. In future studies, it might be useful to generate pan-PPAR agonists in order to combine antidiabetic and antiobesity effects. Further in vitro pan-PPAR evaluation of these compounds is underway.

Experimental Section

All starting materials were obtained from commercial suppliers and used without further purification. The ^{1}H and ^{13}C spectra were taken on Bruker Avance III 500 or 400, NMR spectrometer operating at 500 MHz or 400 MHz for ^{1}H NMR, 150 MHz, 125 MHz or 100 MHz for ^{13}C NMR, using TMS as the internal standard and $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts were reported ind values (ppm) relative to that of the internal TMS. The abbreviations s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, and b = broad were used throughout. ^{13}C NMR spectra were recorded with complete proton decoupling. The ESI-MS or EI-MS was recorded on Finnigan LCQ/DECA or Thermo-DFS, respectively. The HRMS were obtained from Mcromass Q-TOF Ultima (ESI) or Thermo Fisher Scientific DFS (EI) spectrometer. Silica gel F254 was used in analytical thin-layer chromatography (TLC) and silica gel was used in column chromatography, respectively, and the visualization was accomplished with UV light (254 nm).

General procedure for the preparation of **2a–2g**

To a solution of bavachinin **1** and anhydrous potassium carbonate in acetone was added acyl halides or alkyl/aromatic halides. The reaction processing for obtaining **2a–2d** was different from that of **2e–2g**. For **2a–2d**, the reaction mixture was stirred at room temperature for 2 h. For **2e–2g**, the reaction mixture was stirred at reflux for 2 h. The reaction mixture was quenched with deionized water and extracted with ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried over sodium sulfate, filtrated, and evaporated under vacuum. The crude material was purified by silica gel column chromatography with petroleum ether/ethyl acetate to afford **2a–2g**.

4'-propanoyloxy-7-methoxy-6-isopentenyl-flavanone (2a)

1 (50 mg, 0.15 mmol), propionyl chloride (17.04 mg, 0.18 mmol) and anhydrous potassium carbonate (800 mg, 5.79 mmol) were used to give a colorless solid **2a** (46.2 mg, 79%). **2a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 6.48 (s, 1H), 5.47 (dd, *J* = 13.3, 3.0 Hz, 1H), 5.29 (t, *J* = 7.3 Hz, 1H), 3.88 (s, 3H), 3.27 (d, *J* = 7.3 Hz, 2H), 3.02 (dd, *J* = 16.7, 13.4 Hz, 1H), 2.83 (dd, *J* = 16.9, 2.9 Hz, 1H), 2.63 (q, *J* = 7.4 Hz, 2H), 1.76 (s, 3H), 1.72 (s, 3H), 1.30 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.5, 172.8, 164.1, 162.1, 150.9, 136.4, 133.1, 127.3, 127.1, 125.0, 122.0, 121.7, 114.0, 98.8, 79.5, 55.8, 44.4, 27.8, 27.8, 25.9, 17.8, 9.1. ESI-MS m/z (%): 395.1 $[M+H]^+$; 393.2 $[M-H]^-$. HR ESI-MS calcd for $C_{24}H_{26}O_5Na$ 417.1678 $[M+Na]^+$, found 417.1684.

4'-benzoyloxy-7-methoxy-6-isopentenyl-flavanone (2b)

1 (50 mg, 0.15 mmol), benzoyl chloride (25.33 mg, 0.18 mmol) and anhydrous potassium carbonate (800 mg, 5.79 mmol) were used to give a pale yellow solid **2b** (39.4 mg, 60%). **2b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.7 Hz, 2H), 7.71 (s, 1H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.61–7.51 (m, 4H), 7.32 (d, *J* = 8.3 Hz, 2H), 6.50 (s, 1H), 5.51 (dd, *J* = 13.3, 2.9 Hz, 1H), 5.30 (t, *J* = 7.5 Hz, 1H), 3.89 (s, 3H), 3.28 (d, *J* = 7.3 Hz, 2H), 3.05 (dd, *J* = 16.8, 13.3 Hz, 1H), 2.86 (dd, *J* = 16.8, 3.0 Hz, 1H), 1.77 (s, 3H), 1.73 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.5, 165.1, 164.2, 162.1, 151.1, 136.6, 133.7, 133.1, 130.2, 129.3, 128.6, 127.4, 127.1, 125.1, 122.2, 121.7, 114.0, 98.8, 79.5, 55.8, 44.4, 27.8, 25.9, 17.8. ESI-MS m/z (%): 465.1 $[M+Na]^+$; 441.2 $[M-H]^-$. HR ESI-MS calcd for $C_{28}H_{26}O_5Na$ 465.1678 $[M+Na]^+$, found 465.1672.

4'-(4-toluoyloxy)-7-methoxy-6-isopentenyl-flavanone (2c)

1 (50 mg, 0.15 mmol), p-toluoyl chloride (28.38 mg, 0.18 mmol) and anhydrous potassium carbonate (800 mg, 5.79 mmol) were used to give a white solid **2c** (32.1 mg, 48%). **2c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.9 Hz, 2H), 7.71 (s, 1H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.49 (s, 1H), 5.51 (dd, *J* = 13.4, 2.8 Hz, 1H), 5.30 (t, *J* = 7.3 Hz, 1H), 3.89 (s, 3H), 3.28 (d, *J* = 7.3 Hz, 2H), 3.05 (dd, *J* = 16.9, 13.3 Hz, 1H), 2.86 (dd, *J* = 16.8, 3.0 Hz, 1H), 2.49 (s, 3H), 1.77 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.5, 165.1, 164.1, 162.1, 151.2, 144.6, 136.5, 133.0, 130.3, 129.3, 127.4, 127.1, 126.6, 125.0, 122.2, 121.7, 114.0, 98.8, 79.5, 55.8, 44.4, 27.8, 25.9, 21.8, 17.8. ESI-MS m/z (%): 479.2 $[M+Na]^+$. HR ESI-MS calcd for $C_{29}H_{28}O_5Na$ 479.1829 $[M+Na]^+$, found 479.1832.

4'-(4-anisoyloxy)-7-methoxy-6-isopentenyl-flavanone (2d)

1 (50 mg, 0.15 mmol), p-anisoyl chloride (30.28 mg, 0.18 mmol) and anhydrous potassium carbonate (800 mg, 5.79 mmol) were used to give a white solid **2d** (39.4 mg, 56%). **2d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.6 Hz, 2H), 7.71 (s, 1H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.49 (s, 1H), 5.50 (dd, *J* = 13.1, 2.9 Hz, 1H), 5.30 (t, *J* = 7.5 Hz, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.27 (d, *J* = 7.3 Hz, 2H), 3.05 (dd, *J* = 16.9, 13.3 Hz, 1H), 2.86 (dd, *J* = 16.9, 3.0 Hz, 1H), 1.77 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.6, 164.8, 164.1, 164.0, 162.1, 151.2, 136.4, 133.1, 132.4, 127.4, 127.1, 125.0, 122.2, 121.7,

121.6, 114.0, 113.9, 98.8, 79.5, 55.8, 55.6, 44.4, 27.8, 25.9, 17.8. ESI-MS m/z (%): 473.1 $[M+H]^+$. HR ESI-MS calcd for $C_{29}H_{28}O_6Na$ 495.1778 $[M+Na]^+$, found 495.1778.

4'-benzyloxy-7-methoxy-6-isopentenyl-flavanone (2e)

1 (50 mg, 0.15 mmol), benzyl bromide (25.88 mg, 0.15 mmol) and anhydrous potassium carbonate (800 mg, 5.79 mmol) were used to give a white solid **2e** (20 mg, 32%). **2e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.52–7.31 (m, 7H), 7.05 (d, *J* = 8.6 Hz, 2H), 6.47 (s, 1H), 5.41 (dd, *J* = 13.4, 2.9 Hz, 1H), 5.30 (t, *J* = 7.5 Hz, 1H), 5.12 (s, 2H), 3.87 (s, 3H), 3.27 (d, *J* = 7.3 Hz, 2H), 3.06 (dd, *J* = 16.8, 13.4 Hz, 1H), 2.80 (dd, *J* = 16.8, 2.9 Hz, 1H), 1.77 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.9, 164.0, 162.2, 159.0, 136.7, 132.9, 131.2, 128.6, 128.0, 127.7, 127.4, 127.0, 124.8, 121.7, 115.1, 113.9, 98.7, 79.7, 70.0, 55.7, 44.1, 27.8, 25.8, 17.7. ESI-MS m/z (%): 451.1 $[M+Na]^+$. HR ESI-MS calcd for $C_{28}H_{29}O_4$ 429.2060 $[M+H]^+$, found 429.2064.

4'-isopentenyloxy-7-methoxy-6-isopentenyl-flavanone (2f)

1 (55 mg, 0.16 mmol), prenyl bromide (28.38 mg, 0.18 mmol) and anhydrous potassium carbonate (880 mg, 6.37 mmol) were used to give a white solid **2f** (41.3 mg, 63%). **2f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.47 (s, 1H), 5.52 (t, *J* = 6.8 Hz, 1H), 5.41 (dd, *J* = 13.4, 2.8 Hz, 1H), 5.30 (t, *J* = 7.0 Hz, 1H), 4.56 (d, *J* = 6.7 Hz, 2H), 3.86 (s, 3H), 3.26 (d, *J* = 7.3 Hz, 2H), 3.06 (dd, *J* = 16.8, 13.4 Hz, 1H), 2.79 (dd, *J* = 16.8, 2.9 Hz, 1H), 1.83 (s, 3H), 1.78 (s, 3H), 1.76 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.0, 164.1, 162.3, 159.2, 138.5, 133.0, 130.8, 127.7, 127.1, 124.8, 121.8, 119.5, 114.9, 114.0, 98.8, 79.9, 64.8, 55.8, 44.1, 27.8, 25.9, 25.9, 18.2, 17.8. ESI-MS m/z (%): 429.2 $[M+Na]^+$. HR ESI-MS calcd for $C_{26}H_{30}O_4Na$ 429.2042 $[M+Na]^+$, found 429.2049.

4'-methoxy-7-methoxy-6-isopentenyl-flavanone (2g)

1 (40 mg, 0.12 mmol), methyl iodide (34.2 mg, 0.24 mmol) and anhydrous potassium carbonate (600 mg, 4.34 mmol) were used to give a colorless oil **2g** (32.6 mg, 78%). **2g**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.47 (s, 1H), 5.42 (dd, *J* = 13.4, 2.9 Hz, 1H), 5.30 (t, *J* = 7.2 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.26 (d, *J* = 7.3 Hz, 2H), 3.06 (dd, *J* = 16.8, 13.4 Hz, 1H), 2.80 (dd, *J* = 16.8, 2.9 Hz, 1H), 1.76 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.0, 164.1, 162.3, 159.9, 133.0, 131.0, 127.7, 127.1, 124.8, 121.7, 114.2, 114.0, 98.8, 79.8, 55.8, 55.4, 44.2, 27.8, 25.9, 17.8. ESI-MS (ESI) m/z (%): 375.2 $[M+Na]^+$. HR ESI-MS calcd for $C_{22}H_{25}O_4$ 353.1747 $[M+H]^+$, found 353.1747.

4'-hydroxyl-7-methoxy-6-isopentenyl-flavone (3)

To a solution of bavachinin 1 (250 mg, 0.74 mmol) in DMSO (10 mL) was added iodine (94 mg, 0.74 mmol). The reaction mixture was stirred at 90 ˚C for 3 h. After cooling, the reaction mixture was quenched with a saturated solution of sodium thiosulfate (10 mL) and extracted with ethyl acetate (2 × 10 mL). The organic layers were combined, washed with deionized water (2 × 10 mL) and saturated sodium chloride solution (10 mL), dried over sodium sulfate, filtrated, and evaporated under vacuum. The crude material was purified by silica gel column chromatography with petroleum ether/ethyl acetate to afford a pale yellow powder **3** (122 mg, 49%). **3**: ^{1}H NMR (400 MHz, DMSO) δ 10.28 (s, 1H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.70 (s, 1H), 7.29 (s, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.78 (s, 1H), 5.30 (t, *J* = 7.5 Hz, 1H), 3.96 (s, 3H), 3.32 (d, *J* = 7.4 Hz, 2H), 1.74 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 176.2, 162.4, 161.5, 160.7, 156.0, 132.7, 128.0, 128.0, 123.9, 121.7, 121.4, 116.4, 115.8, 104.6, 99.3, 56.3, 27.6, 25.5, 17.6. ESI-MS m/z (%): 337.3 $[M+H]^+$; 335.1 $[M-H]^-$. HR ESI-MS calcd for $C_{21}H_{21}O_4$ 337.1440 $[M+H]^+$, found 337.1441.

General procedure for the preparation of **4a–4c**

To a solution of **3** and anhydrous potassium carbonate in acetone was added acyl halides or alkyl/aromatic halides. The reaction processing for obtaining **4a–4b** was different from that of **4c**. For **4a–4b**, the reaction mixture was stirred at room temperature for 2 h. For **4c**, the reaction mixture was stirred at reflux for 2 h. The reaction mixture was quenched with deionized water and extracted with ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution (10 mL), dried over sodium sulfate, filtrated, and evaporated under vacuum. The crude material was purified by silica gel column chromatography with petroleum ether/ethyl acetate to afford **4a–4c**.

4'-acetyloxy-7-methoxy-6-isopentenyl-flavone (4a)

3 (50 mg, 0.15 mmol), acetyl chloride (14.4 mg, 0.18 mmol) and anhydrous potassium carbonate (800 mg, 5.79 mmol) were used to give a white solid **4a** (47.9 mg, 85%). **4a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.96 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.94 (s, 1H), 6.76 (s, 1H), 5.35 (t, *J* = 7.4 Hz, 1H), 3.99 (s, 3H), 3.40 (d, *J* = 7.4 Hz, 2H), 2.37 (s, 3H), 1.78 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 169.0, 162.2, 161.8, 156.7, 152.9, 133.5, 129.6, 129.4, 127.4, 125.3, 122.3, 121.3, 117.2, 107.6, 98.2, 56.0, 28.2, 25.9, 21.2, 17.8. ESI-MS m/z (%): 379.1 $[M+H]^+$. HR ESI-MS calcd for $C_{23}H_{23}O_5$ 379.1540 $[M+H]^+$, found 379.1540.

4'-(4-nitrobenzoyloxy)-7-methoxy-6-isopentenyl-flavone (4b)

3 (50 mg, 0.15 mmol), 4-nitrobenzoyl chloride (28 mg, 0.15 mmol) and anhydrous potassium carbonate (800 mg, 5.79 mmol) were used to give a pale yellow solid **4b** (37.5 mg, 52%). **4b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45–8.40 (m, 4H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.99 (s, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 6.96 (s, 1H), 6.80 (s, 1H), 5.36 (t, *J* = 7.6 Hz, 1H), 4.00 (s, 3H), 3.40 (d, *J* = 7.2 Hz, 2H), 1.79 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 162.9, 162.3, 161.6, 156.7, 152.7, 151.1, 134.5, 133.6, 131.4, 130.3, 129.6, 127.7, 125.3, 123.8, 122.2, 121.2, 117.2, 107.8, 98.2, 56.0, 28.3, 25.9, 17.8. ESI-MS m/z (%): 486.1 $[M+H]^+$; 484.0 $[M-H]^-$. HR ESI-MS calcd for $C_{28}H_{24}O_7N$ 486.1547 $[M+H]^+$, found 486.1552.

4'-(3,4-difluorobenzyloxy)-7-methoxy-6-isopentenyl-flavone (4c)

3 (50 mg, 0.15 mmol), 3,4-difluorobenzyl bromide (32 mg, 0.15 mmol) and anhydrous potassium carbonate (800 mg, 5.79 mmol) were used to give a white solid **4c** (36.5 mg, 53%). **4c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.89 (d, *J* = 8.7 Hz, 2H), 7.36–7.17 (m, 3H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.92 (s, 1H), 6.71 (s, 1H), 5.35 (t, *J* = 7.6 Hz, 1H), 5.11 (s, 2H), 3.98 (s, 3H), 3.39 (d, *J* = 7.4 Hz, 2H), 1.78 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 162.4, 162.1, 160.7, 156.6, 150.50 (dd, *J* = 249.0, 12.8 Hz, 1C), 150.15 (dd, *J* = 248.9, 12.5 Hz, 1C), 133.4, 133.37–133.20 (m, 1C), 129.2, 127.9, 125.3, 125.0, 123.35 (dd, *J* = 6.4, 3.6 Hz, 1C), 121.3, 117.54 (d, *J* = 17.4 Hz, 1C), 117.2, 116.50 (d, *J* = 17.9 Hz, 1C), 115.2, 106.4, 98.2, 68.9, 55.9, 28.2, 25.9, 17.8. ESI-MS m/z (%): 463.2 $[M+H]^+$. HR ESIMS calcd for $C_{28}H_{25}O_4F_2$ 463.1715 $[M+H]^+$, found 463.1713.

General procedure for the preparation of **7a**, **7b**, **7d**

To a solution of **5a–5b** and anhydrous potassium carbonate in acetone was added alkyl halides. Then the reaction mixture was stirred at reflux for 5 h. The reaction mixture was quenched with deionized water and extracted with ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried over sodium sulfate, filtrated, and evaporated under vacuum to afford crude **6a–c**. The crude product was used for the next reaction step directly without further purification.

6a–6c was dissolved in diethylaniline and the solution was stirred at reflux under an inert atmosphere for 4 h. After cooling, the reaction mixture was quenched with 2N aqueous HCl and extracted with ethyl acetate. The organic layers were combined, washed with deionized water and saturated sodium chloride solution, dried over sodium sulfate, filtrated, and evaporated under vacuum. The residue was purified by silica gel column chromatography with petroleum ether/ethyl acetate to afford **7a**, **7b**, **7d**.

2'-hydroxyl-5'-isopentenylacetophenone (7a)

2'-Hydroxyacetophenone **5a** (3.0 g, 0.02 mol), prenyl bromide (3.62 g, 0.02 mol) and anhydrous potassium carbonate (9.12 g, 0.07 mol) were used to give a colorless oil **6a**. **6a** and diethylaniline (20 mL) were used to give a yellow oil **7a** (1.76 g, 39%). **7a**: ^{1}H NMR δ (400 MHz, $CDCl_3$) 12.14 (s, 1H), 7.51 (s, 1H), 7.31 (dd, *J* = 8.5, 1.6 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 5.31 (t, *J* = 7.5 Hz, 1H), 3.31 (d, *J* = 7.3 Hz, 2H), 2.64 (s, 3H), 1.78 (s, 3H), 1.75 (s, 3H). ESI-MS m/z (relative intensity): 203.2 $[M-H]^-$.

2'-hydroxyl-4'-methoxyl-5'-isopentenylacetophenone (7b)

2'-Hydroxy-4'-methoxylacetophenone **5b** (3.00 g, 0.02 mol), prenyl bromide (3.23 g, 0.02 mol) and anhydrous potassium carbonate (10.00 g, 0.07 mol) were used to give a yellow oil **6b**. **6b** and diethylaniline (20 mL) were used to give a yellow oil **7b** (2.37 g, 56%). **7b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.74 (s, 1H), 7.42 (s, 1H), 6.41 (s, 1H), 5.27 (t, *J* = 7.3 Hz, 1H), 3.88 (s, 3H), 3.24 (d, *J* = 7.3 Hz, 2H), 2.56 (s, 3H), 1.78 (s, 3H), 1.73 (s, 3H) . LRMS (EI) *m/z* (%): 234 $[M^+]$.

2'-hydroxyl -4'-methoxy-5'-isopentylacetophenone (7c)

To a solution of **7b** (530 mg, 2.13 mmol) in ethanol (10 mL) was added 10% Pd-C (230 mg, 0.21 mmol). The flask was placed under a hydrogen atmosphere. The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was filtered and extracted with deionized water (10 mL) and ethyl acetate (2 × 10 mL). The organic layers were combined, washed with saturated sodium chloride solution (10 mL), dried over sodium sulfate, filtrated, and evaporated under vacuum. The residue was purified by silica gel column chromatography with petroleum ether/ethyl acetate to afford a yellow oil **7c** (508.8 mg, 95%). **7c**: ^{1}H NMR (400 MHz $CDCl_3$) δ 12.72 (s, 1H), 7.42 (s, 1H), 6.39 (s, 1H), 3.86 (s, 3H), 2.57 (s, 3H), 2.56–2.50 (m, 2H), 1.64–1.55 (m, 1H), 1.49–1.38 (m, 2H) 0.97 (s, 3H), 0.95 (s, 3H). ESI-MS m/z (%): 237.2 $[M+H]^+$.

2'-hydroxyl-4'-methoxyl-5'-geranylacetophenone (7d)

2'-Hydroxy-4'-methoxylacetophenone **5b** (2.0 g, 0.01 mol), geranyl bromide (2.6 g, 0.01 mol) and anhydrous potassium carbonate (8.3 g, 0.06 mol) were used to give a colorless oil **6c**. **6c** and diethylaniline (20 mL) were used to give a corlorless oil **7d** (1.27 g, 35%). **7d**: ^{1}H NMR δ (400 MHz, $CDCl_3$) 12.73 (s, 1H), 7.43 (s, 1H), 6.41 (s, 1H), 5.32 – 5.27 (m, 1H), 5.16 – 5.12 (m, 1H), 3.88 (s, 3H), 3.25 (d, *J* = 7.2 Hz, 2H), 2.56 (s, 3H), 2.21 – 2.11 (m, 2H), 2.10 – 2.01 (m, 2H), 1.81 – 1.71 (m, 3H), 1.70 – 1.68 (m, 3H), 1.63 – 1.62(m, 3H). ESI-MS m/z (relative intensity): 301.2 $[M-H]^-$.

General procedure for the preparation of **8b**, **8d**, **8f**

To a solution of hydroxylbenzaldehydes **8a**, **8c**, **8e** and anhydrous potassium carbonate in acetone was added chloromethyl methyl ether slowly. After that, the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with deionized water and extracted with ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried over sodium sulfate, filtrated, and evaporated under vacuum. The residue was purified by silica gel column chromatography with petroleum ether/ethyl acetate to afford **8b**, **8d**, **8f**.

4-methoxymethoxylbenzaldehyde (8b)

8a (1.50 g, 0.012 mol), chloromethyl methyl ether (1.25 g, 0.015 mol) and anhydrous potassium carbonate (6.80 g, 0.049 mol) were used to give a colorless oil **8b** (1.63 g, 79.95%). **8b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.86 (d, *J* = 8.7 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 2H), 5.27 (s, 2H), 3.51 (s, 3H). LRMS (EI) *m/z* (%): 166 $[M]^+$.

3,4-dimethoxymethoxylbenzaldehyde (8d)

8c (500 mg, 3.62 mmol), chloromethyl methyl ether (714 mg, 8.87 mmol) and anhydrous potassium carbonate (2.00 g, 0.014 mol) were used to give a colorless oil **8d** (646 mg, 79%). **8d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.70 (d, *J* = 1.9 Hz, 1H), 7.53 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 5.35 (s, 2H), 5.31 (s, 2H), 3.54 (s, 3H), 3.54 (s, 3H).

3-fluoro-4-methoxymethoxylbenzaldehyde (8f)

8e (500 mg, 3.50 mmol), chloromethyl methyl ether (345 mg, 4.20 mmol) and anhydrous potassium carbonate (1.93 g, 0.014 mol) were used to give a colorless oil **8f** (285 mg, 43%). **8f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.65–7.63 (m, 2H), 7.37–7.33 (m, 1H), 5.34 (s, 2H), 3.55 (s, 3H). LRMS (ESI) *m/z* (%): 185.6 $[M+H]^+$.

General procedure for the preparation of chalcones **9a**–**9f**

To a solution of **7a–7e** and **8b, 8d, 8f** in ethanol was added potassium trimethylsilanolate. Then the reaction mixture was stirred at reflux under an inert atmosphere for 4 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic layers were combined, washed with deionized water and saturated sodium chloride solution, dried over sodium sulfate, filtrated, and evaporated under vacuum. The crude material was purified by silica gel column chromatography with petroleum ether/ethyl acetate to afford **9a–9f**.

1-(2'-hydroxy-5'-isopentenyl)-3-(4-methoxymethoxyphenyl)-2E-propen-1-one (9a)

7a (1.76 g, 0.01 mol), **8b** (1.44 g, 0.01 mol) and potassium trimethylsilanolate (4.14 g, 0.03 mol) were used to give a bright yellow oil **9a** (1.12 g, 37%). **9a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.78 (s, 1H), 7.91 (d, *J* = 15.4 Hz, 1H), 7.69 (d, *J* = 1.8 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 15.5 Hz, 1H), 7.34 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 1H), 5.34 (t, *J* = 7.4 Hz, 1H), 5.26 (s, 2H), 3.52 (s, 3H), 3.36 (d, *J* = 7.3 Hz, 2H), 1.80 (s, 3H), 1.77 (s, 3H). ESI-MS m/z (%): 353.2 $[M+H]^+$.

1-(2'-hydroxy-4'-methoxy-5'-isopentenyl)-3-(3,4-dimethoxymethoxyphenyl)-2E-propen-1-one (9b)

7b (652 mg, 2.78 mmol), **8d** (630 mg, 2.78 mmol) and potassium trimethylsilanolate (1.32 g, 0.009 mol) were used to give a bright yellow needles **9b** (460.3 mg, 37%). **9b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.50 (s, 1H), 7.83 (d, *J* = 15.4 Hz, 1H), 7.61 (s, 1H), 7.51 (s, 1H), 7.45 (d, *J* = 15.4 Hz, 1H), 7.30–7.21 (m, 2H), 6.46 (s, 1H), 5.32 (s, 4H), 5.30 (s, 1H), 3.90 (s, 3H), 3.58 (s, 3H), 3.55 (s, 3H), 3.28 (d, *J* = 8.4 Hz, 1H), 1.81 (s, 3H), 1.76 (s, 3H). ESI-MS m/z (%): 442.9 $[M+H]^+$.

1-(2'-hydroxy-4'-methoxy-5'-isopentenyl)-3-(3-fluorine-4-methoxymethoxyphenyl)-2E-propen-1-one (9c)

7b (363 mg, 1.55 mmol), **8f** (285 mg, 1.55 mmol) and potassium trimethylsilanolate (668 mg, 4.65 mmol) were used to give a bright yellow needles **9c** (218.9 mg, 35%). **9c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.41 (s, 1H), 7.79 (d, *J* = 15.4 Hz, 1H), 7.59 (s, 1H), 7.46 (d, *J* = 15.3 Hz, 1H), 7.45–7.42 (m, 1H), 7.37–7.35 (m, 1H), 7.26–7.24 (m, 1H), 6.47 (s, 1H), 5.32–5.28 (m, 3H), 3.90 (s, 3H), 3.56 (s, 3H), 3.28 (d, *J* = 7.2 Hz, 2H), 1.80 (s, 3H), 1.76 (s, 3H). ESIMS m/z (%): 401.1 $[M+H]^+$.

1-(2'-hydroxy-4'-methoxy-5'-isopentyl)-3-(4-methoxymethoxyphenyl)-2E-propen-1-one (9d)

7c (500 mg, 2.12 mmol), **8b** (352 mg, 2.12 mmol) and potassium trimethylsilanolate (1.00 g, 0.007 mol) were used to give a bright yellow solid **9d** (261 mg, 32%). **9d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.51 (s, 1H), 7.88 (d, *J* = 15.6 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.61 (s, 1H), 7.50 (d, *J* = 15.4 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.46 (s, 1H), 5.26 (s, 2H), 3.89 (s, 3H), 3.52 (s, 3H), 2.63–2.55 (m, 2H), 1.67–1.61 (m, 1H), 1.53–1.42 (m, 2H), 1.00 (s, 3H), 0.98 (s, 3H). ESI-MS m/z (%): 385.3 $[M+H]^+$.

1-(2'-hydroxy-4'-methoxy-5'-geranyl)-3-(4-methoxymethoxyphenyl)-2E-propen-1-one (9e)

7d (1.2 g, 0.004 mol), **8b** (0.7 g, 0.004 mol) and potassium trimethylsilanolate (1.9 g, 0.013 mol) were used to give a yellow oil **9e** (0.7 g, 39%). **9e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.54 (s, 1H), 7.87 (d, *J* = 15.4 Hz, 1H), 7.63 (s, 1H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 15.4 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 2H), 6.47 (s, 1H), 5.34 (t, *J* = 7.3 Hz, 1H), 5.25 (s, 2H), 5.18 (t, *J* = 7.0 Hz, 1H), 3.90 (s, 3H), 3.52 (s, 3H), 3.29 (d, *J* = 7.3 Hz, 2H), 2.23–2.14 (m, 2H), 2.14–2.01 (m, 2H), 1.80–1.60 (m, 9H). ESI-MS m/z (%): 451.1 $[M+H]^+$; 449.2 $[M-H]^-$.

1-(2'-hydroxy-4'-methoxy)-3-(4-methoxymethoxyphenyl)-2E-propen-1-one (9f)

5b (1.0 g, 0.006 mol), **8b** (1.0 g, 0.006 mol) and potassium trimethylsilanolate (2.87 g, 0.02 mol) were used to give a yellow solid **9f** (1.1 g, 58%). **9f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.56 (s, 1H), 7.89 (d, *J* = 15.7 Hz, 1H), 7.86 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 15.4 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.52–6.50 (m, 2H), 5.25 (s, 2H), 3.89 (s, 3H), 3.52 (s, 3H). ESI-MS m/z (%): 315.3 $[M+H]^+$.

General procedure for the preparation of methoxymethylated flavanones **10a**–**10f**

To a solution of **9a–9f** in methanol was added potassium fluoride. Then the reaction mixture was stirred at reflux for 8 h. The reaction mixture was quenched with deionized water and extracted with ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried over sodium sulfate, filtrated, and evaporated under vacuum. The residue was purified by silica gel column chromatography with petroleum ether/ethyl acetate to afford **10a–10f**.

4'-methoxymethoxy-6-isopentenyl-flavanone (10a)

9a (345 mg, 0.98 mmol) and potassium fluoride (180 mg, 3.10 mmol) were used to give a pale yellow solid **10a** (218 mg, 63%). **10a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 1.7 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.35 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 1H), 5.42 (dd, *J* = 13.4, 2.8 Hz, 1H), 5.31 (t, *J* = 7.5 Hz, 1H), 5.22 (s, 2H), 3.51 (s, 3H), 3.34 (d, *J* = 7.1 Hz, 2H), 3.10 (dd, *J* = 16.9, 13.4 Hz, 1H), 2.86 (dd, *J* = 16.8, 2.7 Hz, 1H), 1.77 (s, 3H), 1.74 (s, 3H). ESI-MS m/z (%): 353.1 $[M+H]^+$.

3',4'-dimethoxymethoxy-7-methoxy-6-isopentenyl-flavanone (10b)

9b (460.3 mg, 1.04 mmol) and potassium fluoride (230 mg, 3.96 mmol) were used to give a white solid **10b** (269.3 mg, 59%). **10b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.31 (d, *J* = 2.0 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.09 (dd, *J* = 8.6, 1.6 Hz, 1H), 6.48 (s, 1H), 5.40 (dd, *J* = 13.6, 2.7 Hz, 1H), 5.31 (s, 1H), 5.29 (d, *J* = 4.8 Hz, 4H), 3.87 (s, 3H), 3.55 (s, 3H), 3.55 (s, 3H), 3.26 (d, *J* = 7.5 Hz, 2H), 3.05 (dd, *J* = 16.8, 13.4 Hz, 1H), 2.80 (dd, *J* = 16.9, 2.9 Hz, 1H), 1.76 (s, 3H), 1.72 (s, 3H). ESI-MS m/z (%): 443.0 $[M+H]^+$.

3'-fluorine-4'-methoxymethoxy-7-methoxy-6-isopentenyl-flavanone (10c)

9c (218.9 mg, 0.55 mmol) and potassium fluoride (110 mg, 1.89 mmol) were used to give a pale yellow oil **10c** (165.8 mg, 76%). **10c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.33– 7.21 (m, 2H), 7.16 (d, *J* = 9.0 Hz, 1H), 6.47 (s, 1H), 5.41 (dd, *J* = 13.1, 2.9 Hz, 1H), 5.30 (t, *J* = 7.2 Hz, 1H), 5.26 (s, 2H), 3.88 (s, 3H), 3.55 (s, 3H), 3.26 (d, *J* = 7.4 Hz, 2H), 2.99 (dd, *J* = 16.8, 13.2 Hz, 1H), 2.81 (dd, *J* = 16.8, 3.0 Hz, 1H), 1.76 (s, 3H), 1.71 (s, 3H). ESI-MS m/z (%): 401.3 $[M+H]^+$.

4'-methoxymethoxy-7-methoxy-6-isopentyl-flavanone (10d)

9e (260 mg, 0.68 mmol) and potassium fluoride (180 mg, 3.10 mmol) were used to give a pale yellow oil **10d** (160 mg, 62%). **10d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.46 (s, 1H), 5.43 (dd, *J* = 13.5, 2.8 Hz, 1H), 5.23 (s, 2H), 3.86 (s, 3H), 3.51 (s, 3H), 3.06 (dd, *J* = 16.9, 13.5 Hz, 1H), 2.80 (dd, *J* = 16.9, 2.9 Hz, 1H), 2.61–2.52 (m, 2H), 1.61–1.54 (m, 1H), 1.49–1.43 (m, 2H), 0.96 (s, 3H), 0.95 (s, 3H). ESI-MS m/z (%): 385.2 $[M+H]^+$.

4'-methoxymethoxy-7-methoxy-6-geranyl-flavanone (10e)

9e (700 mg, 1.55 mmol) and potassium fluoride (350 mg, 6.02 mmol) were used to give a pale yellow oil **10e** (172 mg, 24.56%). **10e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.47 (s, 1H), 5.42 (dd, *J* = 13.4, 2.8 Hz, 1H), 5.30 (t, *J* = 7.0 Hz, 1H), 5.22 (s, 2H), 5.13 (t, *J* = 7.2 Hz, 1H), 3.86 (s, 3H), 3.51 (s, 3H), 3.28 (d, *J* = 7.1 Hz, 2H), 3.06 (dd, *J* = 16.8, 13.4 Hz, 1H), 2.80 (dd, *J* = 16.8, 2.9 Hz, 1H), 2.16–2.09 (m, 2H), 2.09–1.97 (m, 2H), 1.76–1.62 (m, 9H). ESI-MS m/z (%): 451.0 $[M+H]^+$.

4'-methoxymethoxy-7-methoxy-flavanone (10f)

9f (1.1 g, 0.004 mol) and potassium fluoride (0.6 g, 0.01 mol) were used to give a yellow solid **10f** (0.6 g, 55%). **10f**: ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.89 (d, *J* = 9.0 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.64 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.51 (d, *J* = 2.3 Hz, 1H), 5.45 (dd, *J* = 12.9, 2.6 Hz, 1H), 5.23 (s, 2H), 3.86 (s, 3H), 3.51 (s, 3H), 3.08 (dd, *J* = 16.8, 13.3 Hz, 1H), 2.82 (dd, *J* = 16.9, 2.9 Hz, 1H). ESI-MS m/z (%): 313.1 $[M-H]^-$.

General procedure for the preparation of demethoxymethylated flavanones **11a**–**11f**

To a solution of **10a–10f** in methanol was added 3N aqueous HCl. Then the reaction mixture was stirred at reflux for 10 min. After cooling, the reaction mixture was quenched with deionized water and extracted with ethyl acetate. The organic layers were combined washed with saturated sodium chloride solution, dried over sodium sulfate, filtrated and evaporated under vacuum. The crude material was purified by silica gel column chromatography with petroleum ether/ethyl acetate to afford **11a**–**11f**.

4'-hydroxyl-6-isopentenyl-flavanone (11a)

10a (218 mg, 0.62 mmol) and 3N aqueous HCl (3.1 mL) were used to give a pale yellow solid **11a** (130 mg, 68%). **11a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 2.1 Hz, 1H), 7.37–7.34 (m, 3H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 2H), 6.12 (s, 1H), 5.41 (dd, *J* = 13.3, 2.7 Hz, 1H), 5.31 (t, *J* = 7.2 Hz, 1H), 3.33 (d, *J* = 7.3 Hz, 2H), 3.11 (dd, *J* = 16.9, 13.3 Hz, 1H), 2.87 (dd, *J* = 16.9, 2.8 Hz, 1H), 1.77 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 159.7, 155.8, 136.5, 134.7, 132.7, 130.3, 127.5, 125.5, 122.1 120.0, 117.7, 115.3, 78.9, 44.0, 32.9, 25.3, 17.4. ESI-MS m/z (%): 309.2 $[M+H]^+$. HR ESI-MS calcd for $C_{20}H_{19}O_3$ 307.1340 $[M-H]^-$, found 307.1342.

3',4'-dihydroxyl-7-methoxy-6-isopentenyl-flavanone (11b)

10b (200 mg, 0.45 mmol) and 3N aqueous HCl (2.26 mL) were used to give a pale yellow solid **11b** (96.5 mg, 60%). **11b**: ^{1}H NMR (400 MHz, DMSO) δ 9.07 (s, 1H), 9.02 (s, 1H), 7.47 (s, 1H), 6.90 (s, 1H), 6.78–6.73 (m, 2H), 6.60 (s, 1H), 5.40 (dd, *J* = 12.7, 3.0 Hz, 1H), 5.23 (t, *J* = 7.5 Hz, 1H), 3.84 (s, 3H), 3.18 (d, *J* = 7.4 Hz, 2H), 3.06 (dd, *J* = 16.8, 12.7 Hz, 1H), 2.63 (dd, *J* = 16.8, 3.0 Hz, 1H), 1.71 (s, 3H), 1.65 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 190.4, 163.4, 161.9, 145.6, 145.2, 132.2, 129.8, 126.0, 123.4, 121.9, 117.9, 115.3, 114.3, 113.5, 99.3, 79.2, 56.1, 43.2, 27.3, 25.6, 17.6. ESI-MS m/z (%): 355.1 $[M+H]^+$. HR ESI-MS calcd for $C_{21}H_{23}O_5$ 355.1545 $[M+H]^+$, found 355.1535.

3'-fluorine-4'-hydroxyl-7-methoxy-6-isopentenyl-flavanone (11c)

10c (160 mg, 0.40 mmol) and 3N aqueous HCl (2.0 mL) were used to give a white solid **11c** (89.2 mg, 63%). **11c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.25 (s, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 7.07 (t, *J* = 8.5 Hz, 1H), 6.47 (s, 1H), 5.43–5.35 (m, 2H), 5.29 (t, *J* = 7.4 Hz, 1H), 3.88 (s, 3H), 3.26 (d, *J* = 7.4 Hz, 2H), 3.00 (dd, *J* = 16.9, 13.1 Hz, 1H), 2.80 (dd, *J* = 16.9, 3.0 Hz, 1H), 1.76 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.0, 163.7, 161.5, 150.44 (d, *J* = 238.2 Hz, 1C), 143.32 (d, *J* = 14.4 Hz, 1C), 132.6, 131.41 (d, *J* = 5.7 Hz, 1C), 126.6, 124.6, 122.33 (d, *J* = 3.2 Hz, 1C), 121.1, 117.0, 113.36 (d, *J* = 12.5 Hz, 1C), 113.2, 98.3, 78.6, 55.3, 43.7, 27.3, 25.4, 17.3. ESI-MS m/z (%): 357.4 $[M+H]^+$. HR ESI-MS calcd for $C_{21}H_{22}O_4F$ 357.1497 $[M+H]^+$, found 357.1495.

4'-hydroxyl-7-methoxy-6-isopentyl-flavanone (11d)

10d (160 mg, 0.42 mmol) and 3N aqueous HCl (2.1 mL) were used to give a pale yellow solid **11d** (112.7 mg, 80%). **11d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.37 (d, *J* = 8.3 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.46 (s, 1H), 5.62 (s, 1H), 5.41 (dd, *J* = 13.5, 2.8 Hz, 1H), 3.86 (s, 3H), 3.07 (dd, *J* = 16.7, 13.5 Hz, 1H), 2.80 (dd, *J* = 16.7, 2.7 Hz, 1H), 2.58– 2.54 (m, 2H), 1.65–1.55 (m, 1H), 1.51–1.40 (m, 2H), 0.96 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.4, 164.4, 162.2, 156.2, 131.0, 128.0, 127.2, 126.3, 115.7, 113.8, 98.8, 79.8, 55.7, 44.1, 38.8, 28.0, 27.2, 22.6. ESI-MS m/z (%): 341.2 $[M+H]^+$. HR ESIMS calcd for $C_{21}H_{25}O_4$, 341.1753, $[M+H]^+$, found 341.1763.

4'-hydroxyl-7-methoxy-6-geranyl-flavanone (11e)

10e (90 mg, 0.20 mmol) and 3N aqueous HCl (1 mL) were used to give a pale yellow oil **11e** (25 mg, 31%). **11e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.3 Hz, 2H), 6.47 (s, 1H), 5.61 (s, 1H), 5.41 (dd, *J* = 13.3, 2.9 Hz, 1H), 5.30 (t, *J* = 7.0 Hz, 1H), 5.17–5.09 (m, 1H), 3.86 (s, 3H), 3.27 (d, *J* = 7.3 Hz, 2H), 3.06 (dd, *J* = 17.0, 13.3 Hz, 1H), 2.80 (dd, *J* = 16.8, 2.9 Hz, 1H), 2.16–2.08 (m, 2H), 2.08–2.02 (m, 2H), 1.76–1.62 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 163.8, 161.9, 155.7 136.1, 131.0, 130.5, 127.5, 126.7, 124.5, 123.8, 121.2, 115.2, 113.4, 98.3, 79.3, 55.3, 43.7, 39.3, 27.3, 26.2, 25.3, 17.3, 15.7. ESI-MS m/z (%): 407.0 $[M+H]^+$; 405.1 $[M-H]^-$. HR ESI-MS calcd for $C_{26}H_{30}O_4Na$ 429.2042 $[M+Na]^+$, found 429.2030.

4'-hydroxyl-7-methoxy-flavanone (11f)

10f (150 mg, 0.48 mmol) and 3N aqueous HCl (2.4 mL) were used to give a yellow solid **11f** (43 mg, 33%). **11f**: ^{1}H NMR (400 MHz, DMSO) δ 9.60 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 6.66 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.60 (d, *J* = 2.3 Hz, 1H), 5.50 (dd, *J* = 13.1, 2.8 Hz, 1H), 3.81 (s, 3H), 3.18 (dd, *J* = 16.8, 13.1 Hz, 1H), 2.66 (dd, *J* = 16.8, 2.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 190.4, 165.6, 163.3, 157.7, 129.1, 128.3, 128.0, 115.1, 114.4, 109.9, 101.0, 79.2, 55.8, 43.1. ESI-MS m/z (%): 271.2 $[M+H]^+$; 269.1 $[M-H]^-$. HR ESI-MS calcd for $C_{16}H_{14}O_4Na$ 293.0790 $[M+Na]^+$, found 293.0783.

General procedure for the preparation of demethoxymethylated flavones **12a–12b**

To a solution of **11b**, **11d** in DMSO was added iodine. The reaction mixture was stirred at 90 °C for 3 h. After cooling, the reaction mixture was quenched with a saturated solution of sodium thiosulfate and extracted with ethyl acetate. The organic layers were combined, washed deionized water and saturated sodium chloride solution, dried over sodium sulfate, filtrated, and evaporated under vacuum. The crude material was purified by silica gel column chromatography with petroleum ether/ethyl acetate to afford **12a–12b**.

3',4'-dihydroxyl-7-methoxy-6-isopentenyl-flavone (12a)

11b (70 mg, 0.20 mmol) and iodine (25 mg, 0.20 mmol) were used to give a yellow powder **12a** (50 mg, 72%). **12a**: ^{1}H NMR (400 MHz, DMSO) δ 7.70 (s, 1H), 7.43–7.41 (m, 2H), 7.24 (s, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 6.66 (s, 1H), 5.30 (t, *J* = 7.6 Hz, 1H), 3.96 (s, 3H), 3.33– 3.31(m, 2H), 1.73 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 176.2, 162.6, 161.5, 156.0, 149.1, 145.7, 132.7, 128.0, 124.0, 122.1, 121.5, 118.5, 116.4, 115.9, 113.3, 104.6, 99.2, 56.3, 27.6, 25.6, 17.6. ESI-MS m/z (%): 353.2 $[M+H]^+$. HR ESI-MS calcd for $C_{21}H_{21}O_5$ 353.1389 $[M+H]^+$, found 353.1384.

4'-hydroxyl-7-methoxy-6-isopentyl-flavone (12b)

11d (66 mg, 0.19 mmol) and iodine (25 mg, 0.19 mmol) were used to give a pale yellow solid **12b** (36.5 mg, 56%). **12b**: ^{1}H NMR (400 MHz, DMSO) δ 10.29 (s, 1H), 7.95 (d, *J* = 8.6 Hz, 2H), 7.74 (s, 1H), 7.28 (s, 1H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.77 (s, 1H), 3.95 (s, 3H), 2.67–2.60 (m, 2H), 1.61–1.51 (m, 1H), 1.48–1.42 (m, 2H), 0.94 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 176.7, 162.9, 162.2, 161.1, 156.4, 129.8, 128.5, 124.7, 122.3, 116.9, 116.3, 105.1, 99.8, 56.8, 38.8, 27.8, 27.5, 22.9. ESI-MS m/z (%): 339.3 $[M+H]^+$. HR ESI-MS calcd for $C_{21}H_{23}O_4$ 339.1596 $[M+H]^+$, found 339.1588.

General procedure for the preparation of chalcones **13a–13f**

To a stirred solution of **7b** and aromatic/heteroaromatic aldehydes in ethanol was added sodium hydroxide. Then the reaction mixture was stirred at room temperature for 72 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic layers were combined, washed with deionized water saturated sodium chloride solution, dried over sodium sulfate, filtrated, and evaporated under vacuum. The residue was purified by silica gel column chromatography with petroleum ether/ethyl acetate to afford **13a–13f**.

1-(2'-hydroxy-4'-methoxy-5'-isopentenyl)-3-(4-fluorinephenyl)-2E-propen-1-one (13a)

7b (500 mg, 2.13 mmol), 4-fluorobenzaldehyde (265 mg, 2.13 mmol) and sodium hydroxide (256 mg, 6.40 mmol) were used to give a yellow needles **13a** (200 mg, 28%). **13a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.40 (s, 1H), 7.86 (d, *J* = 15.4 Hz, 1H), 7.67 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.60 (s, 1H), 7.51 (d, *J* = 15.4 Hz, 1H), 7.16 (t, *J* = 8.4 Hz, 2H), 6.47 (s, 1H), 5.30 (t, *J* = 7.3 Hz, 1H), 3.91 (s, 3H), 3.28 (d, *J* = 7.4 Hz, 2H), 1.80 (s, 3H), 1.76 (s, 3H). ESI-MS m/z (%): 341.2 $[M+H]^+$.

1-(2'-hydroxy-4'-methoxy-5'-isopentenyl)-3-(3,4-difluorinephenyl)-2E-propen-1-one (13b)

7b (300 mg, 1.28 mmol), 3,4-difluorobenzaldehyde (182 mg, 1.28 mmol) and sodium hydroxide (154 mg, 3.85 mmol) were used to give a yellow needles **13b** (118 mg, 26%). **13b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.31 (s, 1H), 7.78 (d, *J* = 15.2 Hz, 1H), 7.58 (s, 1H), 7.49 (d, *J* = 15.3 Hz, 1H), 7.54–7.44 (m, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.27–7.19 (m, 1H), 6.47 (s, 1H), 5.29 (t, *J* = 7.3 Hz, 1H), 3.91 (s, 3H), 3.29 (d, *J* = 7.2 Hz, 2H), 1.80 (s, 3H), 1.76 (s, 3H). ESI-MS m/z (%): 359.3 $[M+H]^+$.

1-(2'-hydroxy-4'-methoxy-5'-isopentenyl)-3-(4-methylthiazole-5-yl)-2E-propen-1-one (13c)

7b (350 mg, 1.49 mmol), 4-Methylthiazole-5-carboxaldehyde (190 mg, 1.49 mmol) and sodium hydroxide (180 mg, 4.50 mmol) were used to give a yellow solid **13c** (163.7 mg, 32%). **13c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.32 (s, 1H), 8.77 (s, 1H), 8.04 (d, *J* = 15.0 Hz, 1H), 7.53 (s, 1H), 7.27 (d, *J* = 15.4 Hz, 1H), 6.46 (s, 1H), 5.30 (t, *J* = 7.9 Hz, 1H), 3.91 (s, 3H), 3.28 (d, *J* = 7.3 Hz, 2H), 2.66 (s, 3H), 1.82 (s, 3H), 1.75 (s, 3H). ESI-MS m/z (%): 342.2 $[M-H]^-$.

1-(2'-hydroxy-4'-methoxy-5'-isopentenyl)-3-phenyl-2E-propen-1-one (13d)

7b (1.53 g, 0.007 mol), benzaldehyde (0.69 g, 0.007 mol) and sodium hydroxide (0.84 g, 0.021 mol) were used to give a yellow needles **13d** (1.24 g, 59%). **13d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.43 (s, 1H), 7.90 (d, *J* = 15.5 Hz, 1H), 7.70–7.60 (m, 2H), 7.62 (s, 1H), 7.59 (d, *J* = 15.5 Hz, 1H), 7.50–7.43 (m, 3H), 6.47 (s, 1H), 5.31 (t, *J* = 7.2 Hz, 1H), 3.91 (s, 3H), 3.29 (d, *J* = 7.2 Hz, 2H), 1.80 (s, 3H), 1.76 (s, 3H). ESI-MS m/z (%): 323.1 $[M+H]^+$; 321.2 $[M-H]^-$.

1-(2'-hydroxy-4'-methoxy-5'-isopentenyl)-3-(pyridine-4-yl)-2E-propen-1-one (13e)

7b (200 mg, 0.85 mmol), 4-pyridinecarboxaldehyde (91 mg, 0.85 mmol) and sodium hydroxide (102 mg, 2.56 mmol) were used to give a yellow needles **13e** (96.7 mg, 35%). **13e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.21 (s, 1H), 8.73 (d, *J* = 5.2 Hz, 2H), 7.78 (d, *J* = 15.6 Hz, 1H), 7.71 (d, *J* = 15.6 Hz, 1H), 7.58 (s, 1H), 7.50 (d, *J* = 5.3 Hz, 2H), 6.48 (s, 1H), 5.29 (t, *J* = 7.4 Hz, 1H)., 3.92 (s, 3H), 3.29 (d, *J* = 7.3 Hz, 2H), 1.80 (s, 3H), 1.76 (s, 3H). ESI-MS m/z (%): 324.2 $[M+H]^+$.

1-(2'-hydroxy-4'-methoxy-5'-isopentenyl)-3-(1-N,N-dimethylsulfuryl-imidazole-4-yl)-2E-propen-1-one (13f)

7b (104 mg, 0.44 mmol), 1-N,N-dimethylsulfuryl-imidazole-4-aldehyde (90 mg, 0.44 mmol) and sodium hydroxide (54 mg, 1.35 mmol) were used to give a yellow needles **13f** (58.3 mg, 31%). **13f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.44 (s, 1H), 7.98 (s, 1H), 7.88 (d, *J* = 15.1 Hz, 1H), 7.72 (d, *J* = 15.0 Hz, 1H), 7.69 (s, 1H), 7.48 (s, 1H), 6.46 (s, 1H), 5.27–5.22 (m, 1H), 3.90 (s, 3H), 3.27 (d, *J* = 7.1 Hz, 2H), 2.94 (s, 6H), 1.76 (s, 3H), 1.75 (s, 3H). EI-MS m/z (%): 419 $[M^+]$.

General procedure for the preparation of flavanones **14a**–**14f**

To a solution of **13a–13f** and potassium fluoride in methanol. The reaction mixture was stirred at reflux for 8 h. Then, the reaction mixture was quenched with deionized water and extracted with ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried over sodium sulfate, filtrated, and evaporated under vacuum. The crude material was purified by silica gel column chromatography with petroleum ether/ethyl acetate to afford **14a–14f**.

4'-fluorine-7-methoxy-6-isopentenyl-flavanone (14a)

13a (170 mg, 0.50 mmol) and potassium fluoride (85 mg, 1.46 mmol) were used to give a white solid **14a** (121 mg, 71%). **14a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.48 (dd, *J* = 8.4, 5.3 Hz, 2H), 7.14 (t, *J* = 8.5 Hz, 2H), 6.48 (s, 1H), 5.45 (dd, *J* = 13.6, 3.1 Hz, 1H), 5.29 (t, *J* = 7.4 Hz, 1H), 3.88 (s, 3H), 3.27 (d, *J* = 7.4 Hz, 2H), 3.02 (dd, *J* = 16.8, 13.4 Hz, 1H), 2.81 (dd, *J* = 16.8, 2.9 Hz, 1H), 1.76 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.5, 164.2, 162.0, 162.79 (d, *J* = 247.6 Hz, 1C), 134.8, 133.1, 128.04 (d, *J* = 8.3 Hz, 2C), 127.1, 125.1, 121.7, 115.77 (d, *J* = 21.7 Hz, 2C), 113.9, 98.8, 79.4, 55.8, 44.4, 27.8, 25.9, 17.8. ESI-MS m/z (%) 341.2 $[M+H]^+$. HR ESI-MS calcd for $C_{21}H_{22}O_3F$ 341.1547 $[M+H]^+$, found 341.1553.

3',4'-difluorine-7-methoxy-6-isopentenyl-flavanone (14b)

13b (100 mg, 0.50 mmol) and potassium fluoride (50 mg, 1.46 mmol) were used to give a pale yellow solid **14b** (46.3 mg, 46%). **14b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.39–7.30 (m, 1H), 7.24–7.14 (m, 2H), 6.45 (s, 1H), 5.41 (dd, *J* = 13.0, 3.1 Hz, 1H), 5.31–5.22 (m, 1H), 3.86 (s, 3H), 3.24 (d, *J* = 7.3 Hz, 2H), 2.94 (dd, *J* = 16.8, 13.0 Hz, 1H), 2.80 (dd, *J* = 16.8, 3.2 Hz, 1H), 1.74 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.4, 163.7, 161.2, 150.00 (dd, *J* = 249.6, 13.1 Hz, 1C), 150.00 (dd, *J* = 249.6, 13.1 Hz, 1C), 135.68–135.43 (m, 1C), 132.7, 126.6, 124.8, 121.67 (dd, *J* = 6.3, 3.7 Hz, 1C), 121.1, 117.16 (d, *J* = 17.5 Hz, 1C), 114.91 (d, *J* = 18.1 Hz, 1C), 113.4, 98.2, 78.2, 55.3, 43.8, 27.3, 25.4, 17.3. ESI-MS m/z (%): 357.2 $[M-H]^-$. HR ESI-MS calcd for $C_{21}H_{21}O_3F_2$ 359.1453 $[M+H]^+$, found 359.1446.

2,3-Dihydro-7-methoxy-2-(4-methylthiazole-5-yl)-6-isopentenyl-4H-1-benzopyran-4-one (14c)

13c (60 mg, 0.17 mmol) and potassium fluoride (30 mg, 0.52 mmol) were used to give a pale yellow solid **14c** (28.5 mg, 48%). **14c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.71 (s, 1H), 6.45 (s, 1H), 5.76 (dd, *J* = 13.2, 3.1 Hz, 1H), 5.28 (t, *J* = 7.5 Hz, 1H), 3.88 (s, 3H), 3.27 (d, *J* = 7.4 Hz, 2H), 3.04 (dd, *J* = 16.8, 13.0 Hz, 1H), 2.88 (dd, *J* = 16.7, 3.1 Hz, 1H), 2.52 (s, 3H), 1.76 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.4, 164.2, 161.7, 151.8, 151.0, 133.2, 129.5, 127.1, 125.5, 121.5, 113.8, 98.7, 73.4, 55.9, 44.9, 27.8, 25.9, 17.8, 15.5. ESI-MS m/z (%): 344.2 $[M+H]^+$. HR ESI-MS calcd for $C_{19}H_{22}O_3NS$ 344.1320 $[M+H]^+$, found 344.1315.

7-methoxy-6-isopentenyl-flavanone (14d)

13d (1.14 g, 0.004 mol) and potassium fluoride (0.6 g, 0.010 mol) were used to give a white solid **14d** (0.68 g, 60%). **14d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.53–7.38 (m, 5H), 6.49 (s, 1H), 5.47 (dd, *J* = 13.4, 2.9 Hz, 1H), 5.30 (t, *J* = 7.4 Hz, 1H), 3.88 (s,

3H), 3.27 (d, *J* = 7.3 Hz, 2H), 3.05 (dd, *J* = 16.8, 13.4 Hz, 1H), 2.83 (dd, *J* = 16.9, 2.9 Hz, 1H), 1.77 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 164.1, 162.2, 138.9, 133.0, 128.8, 128.7, 127.1, 126.2, 124.9, 121.7, 114.0, 98.8, 80.1, 55.8, 44.4, 27.8, 25.9, 17.8. ESI-MS m/z (%): 323.2 $[M+H]^+$; 321.2 $[M-H]^-$. HR ESI-MS calcd for $C_{21}H_{22}O_3Na$ 345.1467 $[M+Na]^+$, found 345.1459.

2,3-Dihydro-7-methoxy-2-(4-pyridine-4-yl)-6-isopentenyl -4H-1-benzopyran-4-one (14e)

13e (96.7 mg, 0.30 mmol) and potassium fluoride (50 mg, 0.86 mmol) were used to give a white solid **14e** (51.6 mg, 53%). **14e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 6.1 Hz, 2H), 7.67 (s, 1H), 7.40 (d, *J* = 6.9 Hz, 2H), 6.49 (s, 1H), 5.47 (dd, *J* = 12.0, 4.2 Hz, 1H), 5.31– 5.21 (m, 1H), 3.88 (s, 3H), 3.24 (d, *J* = 7.2 Hz, 2H), 2.98–2.80 (m, 2H), 1.74 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.0, 163.8, 161.1, 149.8, 147.3, 132.7, 126.6, 125.0, 121.0, 120.0, 113.5, 98.2, 77.6, 55.4, 43.4, 27.3, 25.3, 17.3. ESI-MS m/z (%): 324.3 $[M+H]^+$. HR ESI-MS calcd for $C_{20}H_{22}O_3N$ 324.1594 $[M+H]^+$, found 324.1586.

2,3-Dihydro-7-methoxy-2-(1-N,N-dimethylsulfuryl-imidazole-4-yl)-6-isopentenyl-4H-1-benzopyran-4-one (14f)

13f (58 mg, 0.14 mmol) and potassium fluoride (29 mg, 0.50 mmol) were used to give a white solid **14f** (30 mg, 52%). **14f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.68 (s, 1H), 7.34 (s, 1H), 6.48 (s, 1H), 5.53 (dd, *J* = 12.1, 3.4 Hz, 1H), 5.28 (t, *J* = 7.2 Hz, 1H), 3.87 (s, 3H), 3.25 (d, *J* = 7.9 Hz, 2H), 3.16 (dd, *J* = 16.8, 12.1 Hz, 1H), 2.97 (dd, *J* = 16.9, 3.5 Hz, 1H), 2.91 (s, 6H), 1.76 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.1, 164.1, 161.5, 141.6, 137.0, 133.1, 127.0, 125.1, 121.6, 115.4, 114.1, 98.8, 74.0, 55.8, 41.6, 38.2, 27.8, 25.9, 17.8. EI-MS m/z (%): 419 $[M^+]$. HR EI-MS calcd for $C_{20}H_{25}SN_3O_5$ 419.1515 $[M^+]$, found 419.1509.

General procedure for the preparation of flavones **15a–15c**

To a solution of **13a–13c** in DMSO was added iodine. The reaction mixture was stirred at 90 °C for 3 h. After cooling, the reaction mixture was quenched with a saturated solution of sodium thiosulfate and extracted with ethyl acetate. The organic layers were combined, washed with deionized water and saturated sodium chloride solution, dried over sodium sulfate, filtrated, and evaporated under vacuum. The crude material was purified by silica gel column chromatography with petroleum ether/ethyl acetate to afford **15a–15c**.

4'-fluorine-7-methoxy-6-isopentenyl-flavone (15a)

13a (205 mg, 0.60 mmol) and iodine (77 mg, 0.60 mmol) were used to give a white solid **15a** (80 mg, 39%). **15a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.93 (dd, *J* = 8.7, 5.3 Hz, 2H), 7.23 (t, *J* = 8.5 Hz, 2H), 6.93 (s, 1H), 6.73 (s, 1H), 5.35 (t, *J* = 7.5 Hz, 1H), 3.99 (s, 3H), 3.39 (d, *J* = 7.6 Hz, 2H), 1.78 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 164.56 (d, *J* = 252.7 Hz, 1C), 162.3, 161.7, 156.6, 133.6, 129.5, 128.29 (d, *J* = 8.9 Hz, 2C), 128.2, 125.3, 121.2, 117.1, 116.22 (d, *J* = 21.9 Hz, 2C), 107.4, 98.2, 56.0, 28.2, 25.9, 17.8. ESI-MS m/z (%): 339.3 $[M+H]^+$. HR ESI-MS calcd for $C_{21}H_{19}O_3FNa$ 361.1216 $[M+Na]^+$, found 361.1207.

3',4'-difluorine-7-methoxy-6-isopentenyl-flavone (15b)

13b (106 mg, 0.30 mmol) and iodine (38 mg, 0.30 mmol) were used to give a white solid **15b** (49.1 mg, 47%). **15b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.82–7.72 (m, 1H), 7.67 (dd, *J* = 8.4, 3.6 Hz, 1H), 7.33 (q, *J* = 8.6 Hz, 1H), 6.93 (s, 1H), 6.71 (s, 1H), 5.34 (t, *J* = 7.9 Hz, 1H), 3.99 (s, 3H), 3.39 (d, *J* = 7.4 Hz, 3H), 1.78 (s, 3H), 1.73 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 162.4, 160.3, 156.6, 152.15 (dd, *J* = 254.8, 12.6 Hz, 1C), 150.65 (dd, *J* = 249.9, 13.0 Hz, 1C), 133.7, 129.7, 129.13 (dd, *J* = 5.9, 3.9 Hz, 1C), 125.3, 122.65 (dd, *J* = 6.8, 3.5 Hz, 1C), 121.1, 118.12 (d, *J* = 18.0 Hz, 1C), 117.1, 115.46 (d, *J* = 19.4 Hz, 1C), 107.9, 98.2, 56.0, 28.2 25.9, 17.8. ESI-MS m/z (%): 357.3 $[M+H]^+$. HR ESI-MS calcd for $C_{21}H_{18}O_3F_2Na$ 379.1122 $[M+Na]^+$, found 379.1132.

7-methoxy-2-(4-methylthiazole-5-yl)-6- isopentenyl-4H-1-benzopyran-4-one (15c)

13c (100 mg, 0.29 mmol) and iodine (37 mg, 0.29 mmol) were used to give a pale yellow powder **15c** (61.1 mg, 61%). **15c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.96 (s, 1H), 6.85 (s, 1H), 6.58 (s, 1H), 5.34 (t, *J* = 7.5 Hz, 1H), 3.98 (s, 3H), 3.39 (d, *J* = 7.4 Hz, 2H), 2.80 (s, 3H), 1.78 (s, 3H), 1.73 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 162.4, 157.2, 156.5, 154.2, 153.5, 133.7, 129.7, 125.3, 124.5, 121.1, 116.9, 110.3, 98.0, 56.0, 28.2, 25.9, 18.1, 17.8. ESI-MS m/z (%): 342.3 $[M+H]^+$. HR ESI-MS calcd for $C_{19}H_{20}O_3NS$ 342.1164 $[M+H]^+$, found 342.1155.

1-(2'-hydroxy-4'-methoxy-5'-isopentenyl)-3-(dimethylamino)-2E-propen-1-one (16)

7b (2.11 g, 0.009 mol) was diluted with DMF/DMA (10 mL, 0.037 mol), and the reaction mixture was stirred at reflux under an inert atmosphere for 5 h. After cooling, the reaction mixture was quenched with deionized water (30 mL) and extracted with ethyl acetate (2 × 30 mL). The organic layers were combined, washed with saturated sodium chloride solution (30 mL), dried over sodium sulfate, filtrated, and evaporated under vacuum to afford a yellow needle **16** (2.50 g, 96%). **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 12.2 Hz, 1H), 7.41 (s, 1H), 6.41 (s, 1H), 5.69 (d, *J* = 12.2 Hz, 1H), 5.29 (t, *J* = 7.2 Hz, 1H), 3.85 (s, 3H), 3.25 (d, *J* = 7.2 Hz, 2H), 2.99 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 164.0, 162.3, 153.8, 132.3, 128.6, 122.9, 120.3, 113.0, 99.4, 89.9, 55.5, 45.2, 37.3, 28.1, 25.8, 17.8. ESI-MS m/z (%): 290.3 $[M+H]^+$. HR ESI-MS calcd for $C_{17}H_{23}NO_3Na$ 312.1576 $[M+Na]^+$, found 312.1567.

7-methoxy-6-isopentenyl-4H-1-benzopyran-4-one (17)

16 (2.50 g, 0.009 mol) was diluted with anhydrous acetic acid (10 mL, 0.175 mol), and the reaction mixture was stirred at reflux under an inert atmosphere for 1 h. The reaction mixture was quenched with deionized water (20 mL) and extracted with ethyl acetate (2 × 20 mL). The organic layers were combined, washed with saturated sodium chloride solution (20 mL), dried over sodium sulfate, filtrated, and evaporated under vacuum. The residue was purified by silica gel column chromatography with petroleum ether/ethyl

acetate to afford a yellow solid **17** (1.55 g, 73.36%). **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.79 (d, *J* = 6.0 Hz, 1H), 6.81 (s, 1H), 6.30 (d, *J* = 6.0 Hz, 1H), 5.33 (t, *J* = 7.6 Hz, 1H), 3.95 (s, 3H), 3.37 (d, *J* = 7.4 Hz, 2H), 1.77 (s, 3H), 1.73 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 162.1, 157.0, 154.6, 133.5, 129.4, 125.3, 121.2, 118.2, 112.9, 98.2, 55.9, 28.2, 25.9, 17.8. ESI-MS m/z (%): 245.2 $[M+H]^+$. HR ESI-MS calcd for $C_{15}H_{17}O_3$ 245.1172 $[M+H]^+$, found 245.1169.

Reporter gene assay

The reporter gene assays were performed using the Dual-Luciferase Reporter Assay System (Promega, USA) as previously described.[30] 293T cells were seeded in 48-well plates at 5×10^4 per well. After cultured in 37 ℃ in DMEM (Gibco) containing 10% FBS for 20 h, cells were co-transfected with the expression plasmids pCMX-Gal-mPPAR γ LBD, the Gal4 reporter vector MH100×4-TK-Luc and pREP7 reporter using FuGENE-HD (Roche, Switzerland). The transfection system containing 2 μg of Gal-mPPAR γ LBD and the Gal4 reporter vector MH100×4-TK-Luc, 0.3 μg of pREP7 reporter plasmids and 10 μL FuGENE-HD per mL DMEM. After transfection for 24 h, the PPAR γ agonist rosiglitazone (0.01μM, 0.03μM, 0.1μM, 0.3μM, 1μM, 3μM, 10μM) and compounds (0.1μM, 0.3μM, 1μM, 3μM, 10μM, 30μM, 100μM) were added to the fresh medium, respectively. Then the luciferase reporter assays were measured using the Dual-Luciferase Reporter Assay System (Promega, Madison, WI, USA). Renilla luciferase activity was used to normalize the transfection efficiencies. All transfection experiments were repeated at least three times independently in triplicate or quadruplicate.

Acknowledgements

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Keywords: Bavachinin • PPAR-γ • Structure–activity relationships • Reporter–gene assay • Structural modification • Diabetes mellitus

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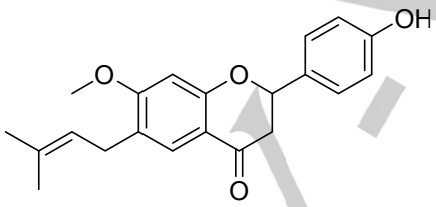

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Figure 1. Structure of the bavachinin **1**.

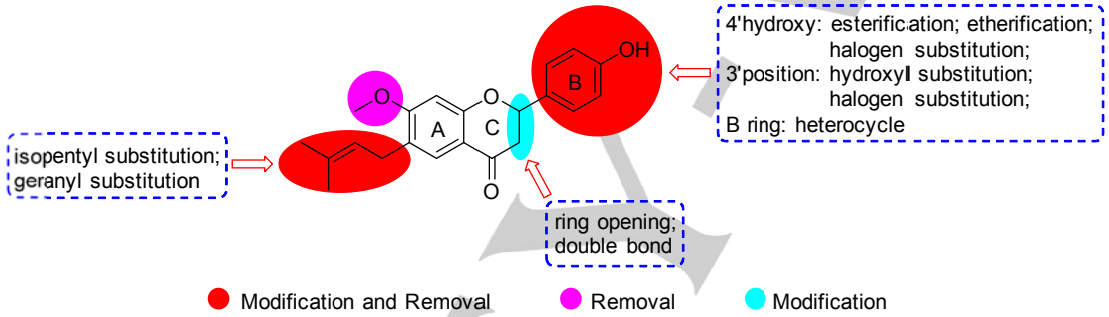
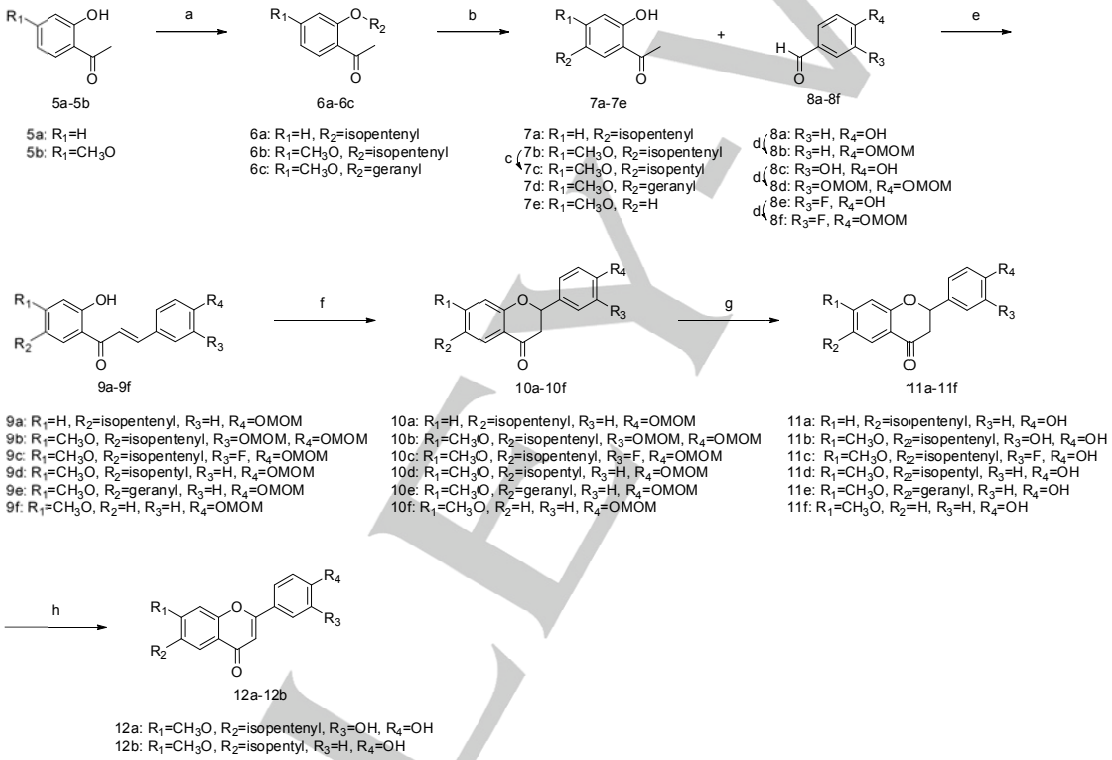
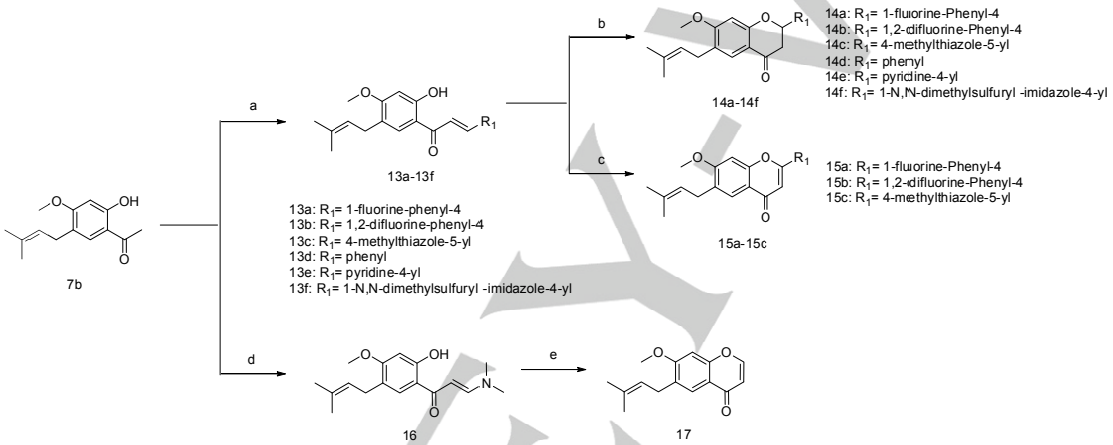


Figure 2. Design rationale of the target PPAR-γ agonists.

Scheme 1. Reagents and conditions: (a) RCOX, K_2CO_3, Acetone, rt, 2 h (**2a**–**2d**) or RX, K_2CO_3, Acetone, reflux, 2 h (**2e**–**2g**); (b) I_2, DMSO, 90 ℃, 3 h; (c) Acyl halides, K_2CO_3, Acetone, rt, 2 h (**4a**–**4b**) or RX, K_2CO_3, Acetone, reflux, 2 h (**4c**).



Scheme 2. Reagents and conditions: (a) RX, K_2CO_3, Acetone, reflux, 5 h; (b) $PhNEt_2$, reflux, 4 h; (c) H_2, Pd-C, C_2H_5OH, rt, 5 h; (d) MOMCl, K_2CO_3, Acetone, rt, 2 h; (e) $(CH_3)_3SiOK$, C_2H_5OH, reflux, 4 h; (f) KF, CH_3OH, reflux, 8 h; (g) HCl, CH_3OH, reflux, 10 min; (h) I_2, DMSO, 90 ℃, 3 h.



Scheme 3. Reagents and conditions: (a) aromatic/heteroaromatic aldehyde , NaOH, C_2H_5OH, rt, 72 h; (b) KF, CH_3OH, reflux, 8 h; (c) I_2, DMSO, 90 ℃, 3 h; (d) DMF-DMA, reflux, 5 h; (e) CH_3COOH, reflux, 1 h.

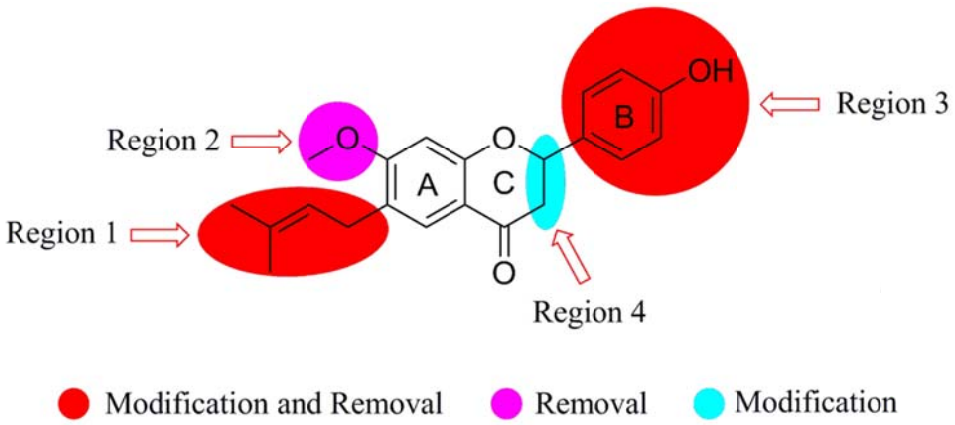
Table 1. Effective concentrations (EC_{50}) of test analogues for vitro PPAR-γ activity

Analogue	PPAR-γ-LBD EC_{50} (μM)	Relative Max Activity (%)[b]	Analogue	PPAR-γ-LBD EC_{50} (μM)	Relative Max Activity (%)
rosiglitazone	0.08	300%	**11d**	13.61	65%
bavachinin **1**	18.74	100%	**11e**	114.33	79%
2a	37.06	121%	**11f**	n.a.	
2b	2.53	92%	**12a**	42.53	57%
2c	18.25	49%	**12b**	3.55	71%
2d	11.03	54%	**14a**	n.a.	
2e	n.a.[a]		**14b**	n.a.	
2f	n.a.		**14c**	26.29	39%
2g	n.a.		**14d**	10.74	103%
3	1.13	79%	**14e**	n.a.	
4a	0.78	74%	**14f**	n.a.	
4b	0.43	84%	**15a**	29.38	78%
4c	n.a.		**15b**	n.a.	
11a	47.07	79%	**15c**	n.a.	
11b	11.25	48%	**16**	n.a.	
11c	3.30	78%	**17**	26.42	30%

[a] n.a.: no activity.

[b]Relative Max Activity was normalized by Bavachinin.

Entry for the Table of Contents



	EC_{50} (μM)
bavachinin	18.74
2b	2.53
3	1.13
4a	0.78
4b	0.43
11c	3.30
11d	13.61
12b	3.55