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ORIGINAL RESEARCH

Bavachinin analogues as agonists of pan-peroxisome proliferator-activated receptors

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Abstract

Peroxisome proliferator-activated receptors (PPARs) agonists contribute to the regulation of glucose, lipid, and cholesterol metabolism and have emerged as key targets to treat metabolic syndrome. In our previous study, the natural compound bavachinin was found to have pan-PPAR agonist activity. In this study, five isoflavones, three isoflavanones, and five scaffold-hopping analogues of bavachinin were designed, synthesised, and evaluated through reporter gene assays for pan-PPAR agonist activity. The analogue 2-(4-hydroxyphenyl)-6-isopentenyl-7-methoxy-2,3-dihydroquinolin-4(1H)-one (**21**) was identified as a pan-PPAR agonist, exhibiting substantially higher PPAR α/β agonist activity and equal PPAR-γ agonist activity than does bavachinin.

Keywords Bavachinin · Metabolic syndrome · PPARs · Reporter gene assaysThese authors contributed equally: Jingyu Yi, Guoxin Du.

Introduction

Metabolic syndrome (MS) is a multiplex risk factor for cardiovascular disease and type 2 diabetes as well as abdominal obesity, dyslipidaemia, insulin resistance, and elevated blood pressure (Grundy 2016). In the United States, approximately 25% of the adult population has MS, and the prevalence increases with age, with certain ethnic groups being particularly affected (Malan-Müller et al. 2016). The current therapy for MS requires multiple medications, including antihypertensives, insulin sensitisers, and cholesterol-lowering agents, which increase the side effects, drug−drug interactions, and economic costs (Beltrán-Sánchez et al. 2013).

Peroxisome proliferator-activated receptors (PPARs) belong to a family of ligand-activated nuclear receptors and consist of three subtypes: PPAR-α, PPAR-β/δ, and PPAR-γ. PPAR-α is mainly found in hepatocytes, smooth muscle cells, and vascular endothelial cells and improves lipid metabolism. Fibrate-derived PPAR-α agonists (clofibrate and bezafibrate) are used in the treatment of dyslipidaemia (Fu et al. 2003). PPAR-γ contributes to lipid and glucose metabolism in various cells, including adipocytes. PPAR-γ agonists (rosiglitazone and pioglitazone) are used in clinical practice to treat diabetes (Weidner et al. 2012). PPAR-β/δ is distributed throughout the body and is involved in lipid metabolism, fatty acid oxidation, and energy dissipation (Cairns 2004). PPARs contribute to the regulation of glucose, lipid, and cholesterol metabolism and have therefore emerged as key targets for treating MSs such as diabetes, dyslipidaemia and atherosclerosis. There is a strong medical need for the development of efficient pan-PPAR agonists, because they have the ability to activate all three PPAR isoforms. Some research programmes have aimed to

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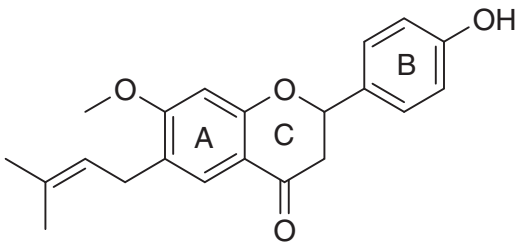


Fig. 1 Chemical structure of bavachinin

develop agonists that combine the therapeutic effects of both PPAR-γ, PPAR-α, and PPAR-β selective agonists (Pourcet et al. 2006).

Bavachinin (BVC, Fig. 1) is a naturally occurring flavanone isolated from the seeds of *Psoralea corylifolia* (Ma et al. 2016). It exhibits various biological characteristics, including antiangiogenic, antitumour, antiallergic, and antibacterial activity (Du et al. 2015). Our previous study showed that natural bavachinin exhibits potential PPAR agonist activity, which when combined with the PPAR-γ agonist rosiglitazone and PPAR-α agonist fibrates, can also be used to lower glucose and triacylglycerol levels in *db/db* mice (Feng et al. 2016). However, further in vitro metabolic studies showed that its metabolism is faster than previously thought and that its biological availability is lower than expected (Xie et al. 2016).

In our previous work, we studied the structure-activity relationship of bavachinin and screened potential PPAR-γ agonists. A series of bavachinin analogues with systematic modifications at the A, B, and C rings was designed, synthesised, and subjected to in vitro bioevaluation as PPAR-γ agonists (Du et al. 2017). This paper introduces our efforts to further the study of the structure-activity relationship of bavachinin.

Results and discussion

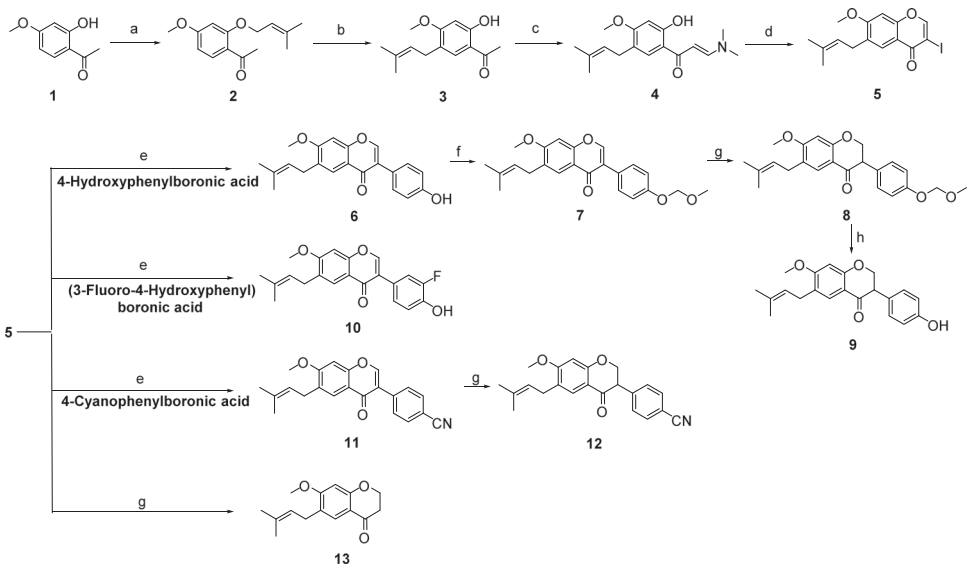
Chemistry

Bavachinin was used as a lead compound for designing analogues. Because some isoflavones were identified as potent pan-PPAR agonists (Matin et al. 2013) and several isoflavones isolated from the seeds of *Psoralea corylifolia* along with bavachinin also exhibited PPAR γ agonist activity (Ma et al. 2016), some isoflavones and isoflavanones that maintained an unchanged A-ring structure were designed in Scheme 1 to determine whether the B-ring linked site played a role in pan-PPAR agonist activity. Some scaffold-hopping analogues of the C-ring were designed in Schemes 2–4 under the assumption that the introduction of nitrogen elements could improve pan-PPAR agonist activity.

Bavachinin analogues **6**–**13** were generated through the synthetic route outlined in Scheme 1. Commercially available paeonol **1** was treated with prenyl bromide in acetone in the presence of potassium carbonate to yield **2**. The Claisen rearrangement was carried out in N,N-dimethylformamide to obtain the intermediate **3** (Liu et al. 2010). Intermediate **4** was obtained through the condensation reaction between **3** with N,N-dimethylformamide dimethylacetal. Subsequently, 3-iodochromone **5** was obtained through a cascade reaction involving one-pot, two-step ring closure and iodination through the addition of I_2 in methanol (Mutai et al. 2015). Some derivatives of prenyl isoflavones (**6**, **10**, **11**) were synthesised from **5** and various phenylboronic acids (PBA) through a Suzuki coupling reaction, which employed poly(ethylene glycol) 6000 (PEG 6000) as the ligand, along with palladium diacetate and sodium carbonate in methanol (Biegasiewicz et al. 2014). Isoflavanone **11** was reduced to produce **12** in anhydrous tethrahydrofun (THF) using lithium triisobutylhydroborate as a reducing agent (Wang and Xu 2017). However, this reduction reaction was not feasible on the substrate 3-iodochromone **5**, without the B-ring, and resulted in the unexpected formation of compound **13**. In addition, a MOM-mask was necessary for the synthesis of isoflavanone **9** for the phenol group.

C1 position N-substituted analogues **22** and **23** were prepared through the synthesis route outlined in Scheme 2. The *p*-methoxybenzyl (PMB) group was introduced to the phenolic hydroxy of 4-hydroxy-benzaldehyde **14** to form **15**. Subsequently, **17** was prepared from 4-bromo-3-methoxyaniline **16** through an improved Friedel–Crafts reaction (Gim et al. 2014). Compound **15** was treated with **17** in ethyl alcohol in the presence of NaOH, yielding the intermediate **18**. Regioselective cyclisation of **18** through reflux with antimony trichloride in acetonitrile yielded the corresponding flavanone, intermediate **19**. Compound **20** was synthesised from **19** and 3,3-dimethylallylboronic acid pinacol ester through a Suzuki coupling reaction using Pd $(dppf)_2Cl_2$ as a catalyst. Subsequently, *p*-toluenesulfonic acid was used successfully for deprotection of the PMB group to obtain **21**. Oxidising the corresponding **20** and **21** with iodine in dimethyl sulfoxide generated **23** and **22**, respectively.

The C3 position N-substituted analogue **32** was synthesised through the method outlined in Scheme 3. **25** was prepared through the esterification of 4-methoxysalicylic acid **24**. The intermediate **26** was synthesised from **25** through a bromination substitution reaction (Gisch et al. 2007). The *ρ*-sulfonyl benzene sulfonyl (Ts) group was introduced to the phenolic hydroxy of the intermediate **26** to form **27** in the presence of triethanolamine (TEA). Then, **28** was prepared using **27** through a Suzuki coupling reaction with 3,3-dimethylallylboronic acid pinacol ester (Farmer



Scheme 1 Reagents and conditions: **a** Prenyl bromide, K_2CO_3, acetone, reflux, 5 h; **b** $PhNEt_2$, reflux, 4 h; **c** DMF-DMA, reflux, 15 h; **d** I_2, MeOH, r.t., 24 h; **e** Na_2CO_3, $Pd(OAc)_2$, PEG 6000, 50 °C, 2 h; **f** CH_3OCH_2Cl, K_2CO_3, acetone, rt, 2 h; **g** Lithium triisobutylhydroborate, THF, −78 °C, 2 h; **h** 3N-HCl, MeOH, reflux, 25 min

et al. 2012). After the alkaline hydrolysis of **28** in sodium hydroxide (NaOH) solution, salicylic acid analogue **29** was formed. Compound **30** was synthesised through the condensation of **29** in the presence of HATU ((1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (Jin et al. 2017). Cyclisation of **15** and **30** using piperidine yielded **31**. Tetra-*n*-butylammonium fluoride was used successfully for the deprotection of the TBS group to obtain the end product, **32**.

C1, 3 position N-substituted analogue **40** was synthesised through the route outlined in Scheme 4. Intermediate **37** was prepared using 2-amino-4-methoxybenzoic acid **33** as a raw material through esterification, bromination, Suzuki coupling reaction, and alkaline hydrolysis under the reaction conditions used in Scheme 3. Through the cyclisation of **37** in the presence of triphosgene, **38** was obtained (Wehle et al. 2016), and **39** was prepared from **38** through aminolysis (Wang et al. 2015). End-product **40** was synthesised through the condensation of **39** in the presence of ρ-toluenesulfonic acid.

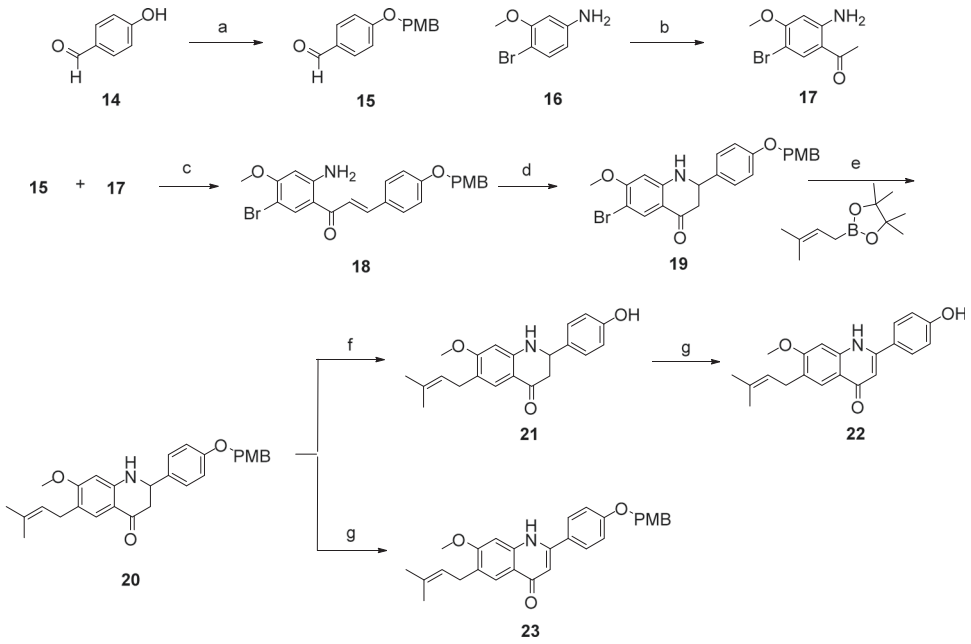
PPAR agonist activity

To identify new pan-PPAR modulators, reporter gene assays were conducted to analyse the effects of analogues on the PPAR α/β/γ ligand binding domain (LBD) (Del Bas et al. 2012). Commercially available PPAR-α, PPAR-β, and PPAR-γ agonists, namely fenofibric acid, GW7647, and pioglitazone, were used as positive controls for PPAR α/β/γ activity. In total, 13 synthesised analogues of bavachinin were analysed. The results are summarised in Table 1. Analogues **7**, **10**, and **21** (25 μM) exhibited potential PPAR-α agonist activity. Analogues **7**, **21**, and **40** (25 μM) exhibited potential PPAR-β agonist activity. Analogues **21**, **40** (25 μM) exhibited potential PPAR-γ agonist activity.

Furthermore, we retested the selected analogues at doses of 0.1, 0.3, 1, 3, 10, 30, and 100 μM using the same assay to obtain the effective concentration (EC_{50}) of the selected analogues for in vitro PPAR α, PPAR-β, and PPAR-γ activity separately. The results are summarised in Table 1. In the PPAR-α agonist activity test, analogues **7** and **10** (EC_{50}=28.57 and 38.67 μM, respectively) decreased the PPAR-α agonist activity, whereas analogue **21** (EC_{50} = 22.28 μM) exhibited a substantially higher activity compared with that of bavachinin (EC_{50} = 12.46 μM). Introducing an N atom at C1 position resulted in greater PPAR-α agonist activity than found with bavachinin. Analogues **7** and **40** (EC_{50} = 0.71 and 0.84 μM, respectively) exhibited less PPAR-β agonist activity relative to bavachinin. Analogue **21** (EC_{50} = 3.54 μM) significantly increased the PPAR-β agonist activity compared with bavachinin (EC_{50} = 10.80 μM). Introducing a N atom at the C1 position likely produces greater PPAR-β agonist activity than that doing so at the C3 position. Analogue **40** (EC_{50} = 0.40 μM) markedly decreased PPAR-γ agonist activity, whereas analogue **21** (EC_{50} = 65.33 μM) showed approximately equal PPAR-γ agonist activity when compared with bavachinin (EC_{50} = 14.46 μM).

Conclusions

With bavachinin as a lead compound, some isoflavones and isoflavanones maintained an unchanged A-ring structure (**6**, **7**, **8**, **9**, **10**, **11**, **12**), and some scaffold-hopping analogues of the C-ring (**21**, **22**, **23**, **32**, **40**) were designed and synthesised. Changing the analogues into isoflavones or isoflavanones reduced pan-PPAR agonist activity when compared with bavachinin. The position at which the N element is introduced is crucial. The C3 and C1, 3 position



Scheme 2 Reagents and conditions: **a** PMBCl, DMF, K_2CO_3, rt, 16 h; **b** BCl_3, $AlCl_3$, CH_3CN, 70 °C, 16 h; **c** NaOH, EtOH, 60 °C,12 h; **d** $SbCl_3$, CH_3CN, reflux, 6 h; **e** Pd(dppf)$_2Cl_2$, Cs_2CO_3, DMF, 70 °C,12 h; **f** Ts-OH, THF/MeOH, 50 °C, 15 h; **g** I_2, DMSO, 75 °C, 1 h

(of C-ring) N-substituted analogues **32** and **40** reduced pan-PPAR agonist activity, whereas C1 position N-substituted analogue **21** enhanced it. The results suggest that the introduction of nitrogen element in C1 position basically not affected pan-PPAR agonist activity of BVC. Analogue **21** is a potent pan-PPAR agonist that exhibits substantially higher PPAR α/β agonist activity and equal PPAR-γ agonist activity when compared with bavachinin.

Materials and methods

All starting materials were obtained from commercial suppliers and used without further purification. The ^1H and ^{13}C spectra were taken on Bruker Avance III 500 or 400 or 300 MHz for ^1H NMR, and 125, or 100 or 75 MHz for ^{13}C NMR, with tetramethylsilane (TMS) as the internal standardand. ^{13}C NMR spectra were recorded with complete proton decoupling. The ESI-MS was recorded on Finnigan LCQ/DECA. The HRMS were obtained from Mcromass Q-TOF Ultima (ESI). Silica gel F254 was used in analytical thin-layer chromatography (TLC), and silica gel was used in column chromatography; visualizations were accomplished with UV light (254 nm).

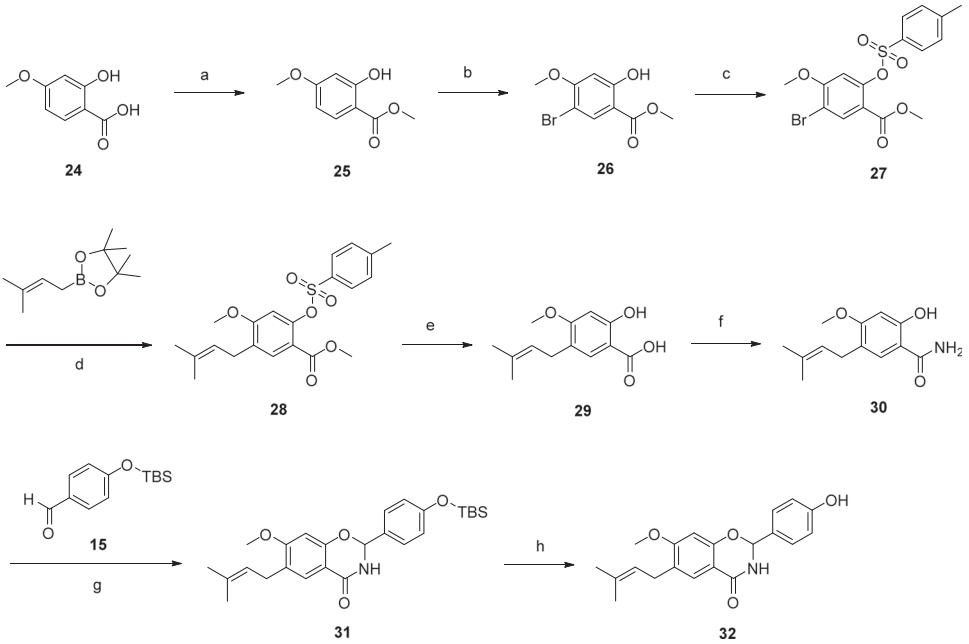
PPAR transactivation assay

Reporter gene assays were performed using the Dual-Luciferase Reporter Assay System (Promega, Madison, WI, USA). In brief, 293 T cells were seeded in 48-well plates at 4000 cells per well. After being cultured at 37 °C in Dulbecco's Modified Eagle's Medium (DMEM) (Gibco) containing 10% FBS for 24 h, cells were cotransfected with the expression plasmids pCMX-Gal-mPPAR-α (or PPAR-β, PPAR-γ) LBD, Gal4 reporter vector MH100 × 4-TK-Luc and pREP7 reporter by using FuGENE-HD (Roche, Switzerland). The transfection system contained 2 mg of Gal-mPPAR-γ LBD, Gal4 reporter vector MH100 × 4-TK Luc, 0.3 mg of pREP7 (Renilla luciferase) reporter plasmids, and 8 μL FuGENE-HD per mL of DMEM. Renilla luciferase activity was used to normalise the transfection efficiencies. For the primary screen, the compounds (25 μM) and the PPAR-α, PPAR-β, and PPAR-γ agonists, fenofibric acid, GW7647, and pioglitazone (20 μM), were added to the medium and incubated for another 24 h, after which the cells were lysed and harvested. The cell lysate was mixed with luciferin solution and luminescence was measured with the FB 12 Luminometer (Berthold Detection Systems GmbH, Pforzheim, Germany). To further winnow our primary screen, we retested the positive compounds at doses of 0.1, 0.3, 1, 3, 10, 30, and 100 μM using the same assay. All experiments were performed in triplicate.

Experimental section for synthesis

Preparation of 2′-hydroxyl-4′-methoxyl-5′-isopentenylacetophenone (3)

To a solution of paeonol **1** (4.15 g, 25.0 mmol) and anhydrous potassium carbonate (12.10 g, 87.5 mmol) in acetone (60 mL), prenyl bromide (3.70 g, 25.0 mmol) was added. Subsequently, 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



Scheme 3 Reagents and conditions: **a** H_2SO_4, CH_3OH, reflux, 48 h; **b** Br_2, DCM, rt, 3 h; **c** p-TsCl, TEA, DCM, rt 3 h; **d** $Pd(dppf)_2Cl_2$, Cs_2CO_3, DMF, 70 °C, 15 h; **e** NaOH, THF/CH_3OH/H_2O, 50 °C, 16 h; **f** NH_3/THF, HATU, DIPEA, DCM, rt, 16 h; **g** piperidine, toluene, 100 °C, 16 h; **h** TBAF, DCM, 0 °C, 15 min

were combined, washed with saturated sodium chloride solution, dried over sodium sulfate, filtrated, and evaporated under vacuum to produce crude **2**. The crude product **2** was used for the next reaction step directly without further purification.

Product **2** was dissolved in diethylaniline (40 mL), 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 through silica gel column chromatography with petroleum ether/ethyl acetate to afford a yellow oil, designated as **3** (1.97 g, 33.7%). **3**: ^{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, 3 H).

Preparation of 1-(2′-hydroxy-4′-methoxy-5′-isopentenyl)-3-(dimethylamino)-2E-propen-1-one (4)

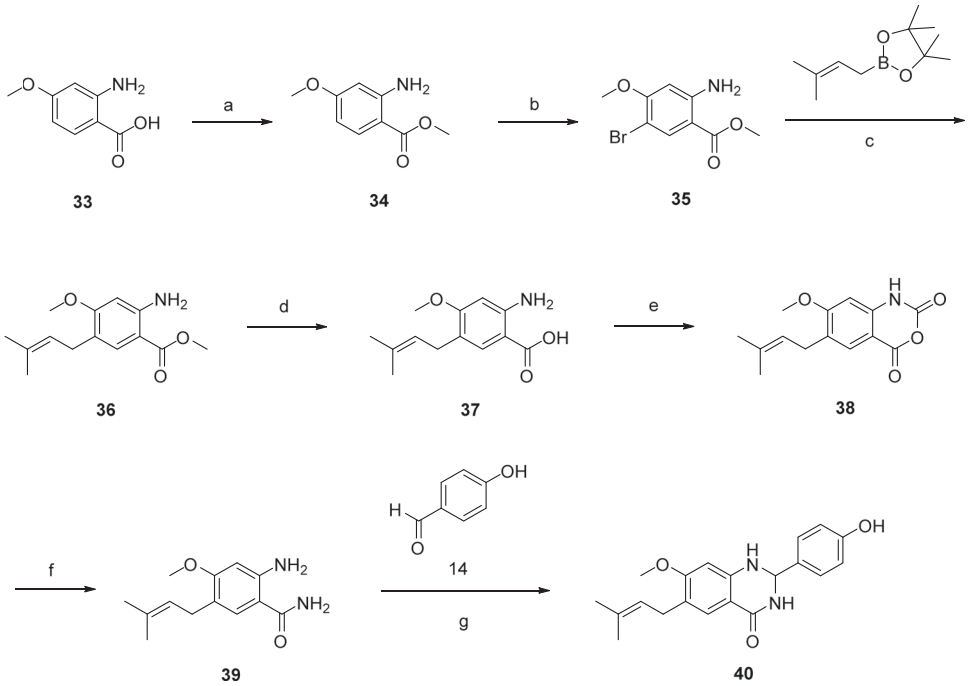
3 (2.34 g, 10.0 mmol) was diluted with DMF/DMA (5.31 mL, 40.0 mmol), and the reaction mixture was stirred at reflux under an inert atmosphere for 15 h. After cooling, the reaction mixture was quenched with deionized water and extracted with ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried over sodium sulfate, filtrated, and evaporated under vacuum to afford a yellow needle **4** (2.80 g, 96.9%). **4**: ^{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, 1 H), 3.85 (s, 3 H), 3.25 (d, J = 7.2 Hz, 2 H), 3.15 (s, 3 H), 2.94 (s, 3 H), 1.73 (s, 3 H).

Preparation of 3-iodo-7-methoxy-6-isopentenyl-4H-chromen-4-one (5)

4 (2.76 g, 10.0 mmol) and iodine were diluted with anhydrous methanol (40 mL), and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with saturated sodium thiosulfate 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 a yellow solid **5** (1.4 g, 37.8%). **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.95 (s, 1H), 6.78 (s, 1H), 5.29 (m, 1H), 3.93 (s, 3H), 3.35 (d, J = 7.1 Hz, 2H), 1.75 (s, 3H), 1.70 (s, 3H).

General method for Suzuki coupling

A round bottom flask was charged with methanol (54 mL) and Na_2CO_3 (1.8 g, 16.7 mmol) and allowed to stir. PEG 6000 (49.8 g) was ground to fine consistency and added to the flask with $Pd(OAc)_2$ (163.0 mg, 0.73 mol). The reaction mixture was then warmed to 50 °C in an oil bath. Once the mixture turned black, **5** and phenylboronic acids were added and left to stir for 2 h. After the reaction, the resulting mixture was emptied into a Büchner funnel, and the filtrate was quenched with deionized water and extracted with ethyl acetate. The organic layers were combined, washed with



Scheme 4 Reagents and conditions: **a** CH_3OH, H_2SO_4, reflux, 24 h; **b** Br_2, DCM, rt, 20 h; **c** $Pd(dppf)_2Cl_2$, Cs_2CO_3, DMF, 70 °C, 24 h; **d** NaOH, CH_3OH, THF, H_2O, 60 °C, 12 h; **e** Triphosgene, THF, rt, 2 h; **f** $(NH_4)_2CO_3$, 1,4-dioxane, 60 °C, 7 h; **g** TsOH, DMF, rt, 2 h

saturated sodium chloride solution, dried over sodium sulfate, filtrated, and evaporated under vacuum. The residue was purified by silica gel column chromatography to afford the target product **6**, **10**, **11**.

Preparation of 3-(4-hydroxyphenyl)-6-isopentenyl-7-methoxy-4H-chromen-4-one (6)

5 (370.0 mg, 1.0 mmol) and 4-hydroxyphenylboronic acid (206.9 mg, 1.5 mmol) were added to the mixture of Pd $(OAc)_2$ solution (10.8 mL). **6** (200.0 mg, 60.0%) was purified by silica gel column chromatography with dichloromethane/methanol. **6**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.55 (s, 1 H), 8.36 (s, 1H), 7.81 (s, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.14 (s, 1H), 6.82 (d, J = 8.4 Hz, 2H), 5.30 (t, J = 6.6 Hz, 1H), 3.94 (s, 3H), 3.32 (d, 2H), 1.73 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (125MHz, DMSO-d_6) δ 175.0, 162.0, 157.6, 156.5, 153.3, 133.2, 130.4×2, 128.7, 125.1, 124.1, 122.9, 121.9, 117.4, 115.4×2, 99.3, 56.8, 28.1, 26.0, 18.0; HR-ESI-MS *m/z*: Anal. Calcd. for $C_{21}H_{21}O_4$ 337.1441; found 337.1434 $[M + H]^+$.

Preparation of 7-methoxy-3-(4-(methoxymethoxy)phenyl)-6-(isopentenyl)-4H-chromen-4-one (7)

To a solution of hydroxylbenzaldehydes **6** (43.6 mg, 0.13 mmol) and anhydrous potassium carbonate (72.0 mg, 0.52 mmol) in acetone (3 mL) was added chloromethyl methyl ether (25.2 mg, 0.32 mmol) 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 white powder **7** (40.0 mg, 81.0%). **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.90 (s, 1H), 7.50 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 6.80 (s, 1H), 5.35 – 5.30 (m, 1H), 5.21 (s, 2H), 3.93 (s, 3H), 3.49 (s, 3H), 3.37 (d, J = 7.3 Hz, 2H), 1.75 (s, 3H), 1.71 (s, 3H).

Preparation of 7-methoxy-3-(4-(methoxymethoxy)phenyl)-6-(isopentenyl)chroman-4-one (8)

7 (36.0 mg, 0.1 mmol) was diluted with anhydrous THF (1 mL), and the reaction mixture was cooled to –78 °C under an inert atmosphere for 3 h, and a solution of a solution of 1.0 M L-selectride in THF (0.24 mL) was added slowly via syringe. The reaction mixture was stirred at –78 °C for 2 h and quenched slowly by the addition of MeOH, then 1.0 M HCl. After cooling, the reaction mixture was 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 a white powder **8** (13 mg, 34.0%). **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.20 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.39 (s, 1H), 5.26 (t, J = 7.4 Hz, 1H), 5.15 (s, 2H), 4.60 (dd, J = 6.6, 3.1Hz, 2H), 3.87 (s, 3H), 3.83 (d, J = 7.3 Hz, 1H), 3.46 (s, 3H), 3.23 (d, J = 7.2 Hz, 2H), 1.72 (s, 3H), 1.68 (s, 3H).

Table 1 In vitro cell-based PPAR transactivation activity

Compounds	PPARα		PPAR β		PPAR γ	
	% max[a] (Mean ± SD)	EC_{50} (μM) (Mean ± SD)	% max (Mean ± SD)	EC_{50}(μM) (Mean ± SD)	% max (Mean ± SD)	EC_{50}(μM) (Mean ± SD)
Fenofibric acid	151.29 ± 6.02	10.82 ± 0.73	–	–	–	–
GW0742	–	–	322.99 ± 10.56	0.11 ± 0.03	–	–
Pioglitazone	–	–	–	–	315.77 ± 11.60	0.07 ± 0.02
Bavachinin	100.00 ± 12.64	12.46 ± 0.76	100.00 ± 6.62	10.80 ± 0.61	100.00 ± 15.99	14.46 ± 4.25
5	33.45 ± 1.71	ND[b]	15.32 ± 1.28	ND	4.64 ± 0.38	ND
6	22.74 ± 1.48	ND	44.40 ± 5.10	ND	15.69 ± 2.22	ND
7	62.31 ± 6.82	28.57 ± 3.01	61.77 ± 7.90	0.71 ± 0.26	14.63 ± 1.26	ND
8	38.32 ± 3.85	ND	21.25 ± 9.39	ND	8.79 ± 1.89	ND
9	49.51 ± 3.68	ND	25.93 ± 2.95	ND	8.13 ± 1.22	ND
10	62.46 ± 5.61	38.67 ± 2.70	47.03 ± 13.20	ND	21.40 ± 6.83	ND
11	42.63 ± 6.46	ND	12.50 ± 1.08	ND	2.21 ± 0.25	ND
12	31.52 ± 1.68	ND	11.57 ± 1.03	ND	8.76 ± 0.15	ND
21	114.73 ± 9.09	22.28 ± 2.35	97.51 ± 15.57	3.54 ± 1.49	98.83 ± 20.89	65.33 ± 28.64
22	53.20 ± 12.16	ND	28.82 ± 11.92	ND	31.16 ± 1.42	ND
23	15.18 ± 0.54	ND	25.98 ± 15.70	ND	4.63 ± 1.55	ND
32	34.54 ± 2.13	ND	19.66 ± 3.31	ND	14.41 ± 1.91	ND
40	45.00 ± 4.85	ND	84.85 ± 12.48	0.84 ± 0.22	50.22 ± 11.30	0.40 ± 0.01

The concentration of positive control fenofibric acid, GW0742 and pioglitazone were 20 μM, and the test analogues of bavachinin were used at 25 μM

[a]Relative maximal activity normalized by that of bavachinin

[b]Not determined

Preparation of 7-methoxy-3-(4-hydroxyphenyl)-6-(isopentenyl)chroman-4-one (9)

To a solution of **8** (10.0 mg, 0.026 mmol) in methanol (1 mL) was added 3N aqueous HCl (0.5 mL). Then the reaction mixture was stirred at reflux for 25 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 **9** (7.0 mg, 79.7%). **9**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.58 (s, 1H), 7.07 (d, $J = 8.5$ Hz, 2H), 6.73 (d, $J = 8.5$ Hz, 2H), 6.51 (s, 1H), 5.25 (tt, $J = 7.3$, 1.4 Hz, 1H), 4.60–4.52 (m, 2H), 3.88 (s, 3H), 3.83 (dd, $J = 8.0$, 5.4 Hz, 1H), 3.21 (d, $J = 7.3$ Hz, 2H), 1.73 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 192.4, 163.9, 162.4, 156.1, 132.0, 128.8 × 2, 126.3, 126.1, 124.0, 121.1, 114.6×2, 113.2, 97.8, 71.4, 54.5, 50.5, 26.7, 24.0, 15.9. HR-ESI-MS *m/z*: Anal. Calcd. for $C_{21}H_{21}O_4$ 337.1445; found 337.1445 $[M + H]^+$.

Preparation of 3-(3-fluoro-4-hydroxyphenyl)-6-isopentenyl-7-methoxy-4H-chromen-4-one (10)

5 (185.0 mg, 0.5 mmol) and (3-fluoro-4-hydroxyphenyl) boronic acid (116.9 mg, 0.75 mmol) were added to the mixture of $Pd(OAc)_2$ solution (10.8 mL). **10** (29.0 mg, 16%) was purified by silica gel column chromatography with dichloromethane/methanol. **10**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.18 (d, $J = 1.7$ Hz, 1H), 7.89 (s, 1H), 7.32 (dd, $J = 12.4$, 2.0 Hz, 1H), 7.17–7.11 (m, 1H), 7.02 (s, 1H), 6.96 (t, $J = 8.7$ Hz, 1H), 5.37–5.26 (m, 1H), 3.96 (s, 3H), 3.36 (d, $J = 7.3$ Hz, 2H), 1.76 (s, 3H), 1.71 (s, 3H); HR-ESI-MS *m/z*: Anal. Calcd. for $C_{21}H_{20}FO_4$ 335.1340; found 335.1345 $[M + H]^+$.

Preparation of 3-(4-Cyanophenyl)-6-isopentenyl-7-methoxy-4H-chromen-4-one (11)

5 (185.0 mg, 0.5 mmol) and 4-cyanophenylboronic acid (109.5 mg, 0.8 mmol) were added to the mixture of Pd $(OAc)_2$ solution (10.8 mL). **11** (60.0 mg, 34.0%) was purified by silica gel column chromatography with petroleum ether/ethyl acetate**. 11**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.99 (s, 1H), 7.72 (s, 4H), 6.83 (s, 1H), 5.32 (t, J = 7.3 Hz, 1H), 3.96 (s, 3H), 3.38 (d, J = 7.3 Hz, 2H), 1.76 (s, 3H), 1.72 (s, 3H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 162.4, 156.6, 152.9, 137.1, 133.7, 132.1 × 2, 130.0, 129.5×2, 125.9, 123.7, 121.0, 118.8, 117.6, 111.6, 98.0, 56.0, 28.2, 25.8, 17.8; HR-ESI-MS *m/z*: Anal. Calcd. for $C_{22}H_{20}NO_3$ 346.1438; found 346.1443 $[M + H]^+$.

Preparation of 4-(7-methoxy-6-(isopentenyl)-4-oxochroman-3-yl)benzonitrile (12)

The procedure was the same as described in *1.2.8*. **11** (20.7 mg, 0.06 mmol) was diluted with anhydrous THF (2 mL), and a solution of a solution of 1.0 M L-selectride in THF (0.15 mL) was added slowly, affording a white powder **12** (15 mg, 72.0%). **12**: ^{1}H NMR (500 MHz, $CDCl_3$) δ7.67 (s, 1H), 7.62 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 6.40 (s, 1H), 5.27–5.22 (m, 1H), 4.72–4.54 (m, 2H), 3.98–3.91 (m, 1H), 3.88 (s, 3H), 3.23 (d, J = 7.2 Hz), 1.73 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.3, 164.4, 162.1, 141.1, 133.2, 132.4 × 2, 129.3 × 2, 127.7, 125.5, 121.4, 118.6, 113.6, 111.6, 98.5, 71.1, 55.8, 51.7, 27.7, 25.8, 17.7. HR-ESI-MS *m/z*: Anal. Calcd. for $C_{22}H_{20}NO_3$ 346.1449; found 346.1446 $[M-H]^-$.

Preparation of 7-methoxy-6-isopentenyl-chroman-4-one (13)

The procedure was the same as described in *1.2.8*. **5** (185 mg, 0.5 mmol) was diluted with anhydrous THF (3 mL), and a solution of a solution of 1.0 M L-selectride in THF (1.2 mL) was added slowly, affording a pale-yellow solid **13** (40 mg, 32.5%). **13**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 1H), 6.36 (s, 1H), 5.26 (t, J = 7.2 Hz, 1H), 4.49 (t, J = 6.4 Hz, 2H), 3.85 (s, 3H), 3.22 (d, J = 7.3 Hz, 2H), 2.73 (t, J = 6.4Hz, 2H), 1.73 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.6, 163.9, 162.4, 132.9, 127.2, 124.7, 121.7, 114.4, 98.5, 67.4, 55.7, 37.4, 27.7, 25.8, 17.7; HR-ESI-MS *m/z*: Anal. Calcd. for $C_{15}H_{19}O_3$ 247.1329; found 247.1330 $[M + H]^+$.

Preparation of 4-((4-methoxybenzyl)oxy) benzaldehyde (15)

To a mixture of 4-hydroxy-benzaldehyd **14** (3.7 g, 30.0 mmol) and K_2CO_3 (12.4 g, 90.0 mmol) in DMF (40 mL) was added 4-methoxybenzylchloride (3.5 g, 30.0 mmol) portionwise. The mixture was stirred at room temperature 16 h. It was diluted with 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 white solid **15** (6.2 g, 85.3%).

Preparation of 1-(2-amino-5-bromo-4-methoxyphenyl)-ethanone (17)

To a solution of 4-bromo-3-methoxyaniline pe="Bold">16 (6 g, 30.0 mmol) in dichloromethane (30 mL) was added boron trichloride (1 N, 33.0 mL, 33.0 mmol) dropwise over 30 min at 0 °C under N_2. Acetonitrile (3.2 mL, 60.0 mmol) and aluminium chloride (4.4 g, 33.0 mmol) was added and the mixture was stirred at 0 °C under N_2 for 30 min and the stirred at 70 °C for 16 h. The resulting mixture was cooled to 0 °C and 2 N HCl was added to the solution and the mixture was stirred at 70 °C for 1 h. It was cooled to RT and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. It was then concentrated and the residue was purified by silica gel column chromatography eluting with cyclohexane/EA (50:1) to give brown solid **17** (3.7 g, 50.7%). **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1 H), 6.48 (s, 2 H), 6.10 (s, 1 H), 3.89 (s, 3 H), 2.53 (s, 3 H).

Preparation of compound 18

To a solution of compound **15** (1.7 g, 6.5 mmol) in EtOH (20 mL) were added compound **17** (1.2 g, 5.0 mmol) and NaOH (0.8 g, 20.0 mmol). The mixture was was stirred at 60 °C for 12 h. It was cooled to RT and filtered. The filter cake was washed with EtOH (3 mL) and dried to give yellow solid compound **18** (2.2 g, 93.2%). **18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1 H), 7.70 (d, J = 15.3 Hz, 1 H), 7.59 (d, J = 8.4 Hz, 2H), 7.44–7.33 (m, 3H), 6.96 (dd, J = 21.1, 8.3 Hz, 4H), 6.59 (s, 2H), 6.13 (s, 1H), 5.04 (s, 2H), 3.89 (s, 3H), 3.82 (s, 3H).

Preparation of 6-bromo-7-methoxy-2-(4-((4-methoxybenzyl)oxy)phenyl)-2,3-dihydroquinolin-4(1H)-one (19)

To a solution of compound **18** (933.0 mg, 2.00 mmol) in CH_3CN (15 mL) was added $SbCl_3$ (136.8 mg, 0.60 mmol). The mixture was stirred at reflux for 6 h. The filter cake was washed with CH_3CN and dried to give yellow solid compound **19** (495.0 mg, 53.3%). **19**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.35 (dd, J = 8.5, 5.7 Hz, 4H), 6.95 (dd, J = 22.2, 8.7 Hz, 4H), 6.13 (s, 1H), 5.00 (s, 2H), 4.67 (dd, J = 13.6, 3.9 Hz, 1H), 4.54 (s, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 2.81 (dd, J = 16.3, 13.5 Hz, 1H), 2.69 (dd, J = 16.4, 3.8 Hz, 1H).

Preparation of 7-methoxy-2-(4-((4-methoxybenzyl)oxy) phenyl)-6-(isopentenyl)-2,3-dihydroquinolin-4(1H)-one (20)

To a solution of compound **19** (468.0 mg, 1.0 mmol) in DMF (15 mL) were added 4,4,5,5-tetramethyl-2-(3-methylbut-2-enyl)-1,3,2-dioxaborolane (0.59 mL, 2.5 mmol), $Pd(dppf)_2Cl_2$ (245 mg, 0.3 mmol) and Cs_2CO_3 (977.5 mg, 3.0 mmol). The mixture was stirred at 70 °C for 12 h with the protection of N_2. It was cooled to RT and diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine. It was dried over Na_2SO_4 and filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography eluting with cyclohexane/EA (20:1) to give pale-yellow powder **20** (198.0 mg, 43.0%). **20**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.35 (dd, $J = 8.6$, 4.2 Hz, 4H), 6.94 (dd, $J = 24.0$, 8.6 Hz, 4H), 6.07 (s, 1H), 5.26 (t, $J = 7.3$ Hz, 1H), 4.99 (s, 2H), 4.64 (dd, $J = 13.8$, 3.5 Hz, 1H), 4.41 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.19 (d, $J = 7.3$ Hz, 2H), 2.78 (dd, $J = 16.1$, 13.9 Hz, 1H), 2.65 (dd, $J = 16.2$, 2.7 Hz, 1H), 1.72 (s, 3H), 1.69 (s, 3H).

Preparation of 2-(4-hydroxyphenyl)-6-isopentenyl-7-methoxy-2,3-dihydroquinolin-4(1H)-one (21)

To a solution of compound **20** (110.0 mg, 0.25 mmol) in THF (2 mL) and MeOH (2 mL) was added 4-methylbenzenesulfonic acid monohydrate (215.0 mg, 1.25 mmol). The mixture was stirred at 50 °C for 15 h. The mixture was cooled to room temperature and diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine. It was dried over Na_2SO_4 and filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography eluting with CH_2Cl_2/MeOH (100:1) to give pale-yellow powder **21** (18.0 mg, 0.05 mmol) and CH_2Cl_2/MeOH (50:1). **21**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.47 (s, 1H), 7.31 (d, $J = 8.5$ Hz, 2H), 6.81 (d, $J = 8.5$ Hz, 2H), 6.31 (s, 1H), 5.29–5.22 (m, 1H), 4.60 (dd, $J = 13.4$, 4.1 Hz, 1H), 3.84 (s, 3H), 3.17 (d, $J = 7.3$ Hz, 2H), 2.76 (dd, $J = 16.2$, 13.4 Hz, 1H), 2.58 (dd, $J = 16.2$, 4.1Hz, 1H), 1.75 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 193.6, 164.3, 156.9, 154.3, 132.3, 131.8, 127.5 × 2, 126.7, 122.2, 120.8, 114.9 × 2, 111.2, 95.8, 57.5, 54.6, 45.5, 27.2, 24.5, 16.3; HR-ESI-MS *m/z*: Anal. Calcd. for $C_{21}H_{24}NO_3$ 338.1751; found 338.1761 $[M + H]^+$.

Preparation of 2-(4-hydroxyphenyl)-7-methoxy-6-(isopentenyl)quinolin-4(1H)-one (22)

To a solution of compound **21** (20.0 mg, 0.06 mmol) in DMSO (2 mL) was added iodine (7.6 mg, 0.03 mmol). The reaction mixture was stirred at 75 °C for 1 h. After cooling, the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$ and extracted with ethyl acetate. The organic layers were combined, washed with brine. It was dried over Na_2SO_4 and filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography eluting with CH_2Cl_2/MeOH (uv254, 20:1) to give pale-yellow powder **22** (7.0 mg, 34.8%). **22**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.96 (s, 1H), 7.64 (d, $J = 8.7$ Hz, 2H), 7.12 (s, 1H), 6.96 (d, $J = 8.7$ Hz, 2H), 6.45 (s, 1), 5.35 (t, $J = 7.3$ Hz, 1H), 3.97 (s, 3H), 3.36–3.29 (m, 2H), 1.77 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 178.3, 161.4, 159.9, 151.2, 140.9, 132.7, 128.8, 128.4, 124.7, 124.2, 121.4, 118.0, 115.6, 105.5, 97.0, 54.8, 27.9, 24.6, 16.4; HR-ESI-MS *m/z*: Anal. Calcd. for $C_{21}H_{22}NO_3$ 336.1594; found 336.1589 $[M + H]^+$.

Preparation of 7-methoxy-2-(4-((4-methoxybenzyl)oxy) phenyl)-6-(isopentenyl)quinolin-4(1H)-one (23)

To a solution of compound **20** (45.7 mg, 0.10 mmol) in DMSO (5 mL) was added iodine (12.6 mg, 0.05 mmol). The reaction mixture was stirred at 75 °C for 1 h. After cooling, the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$ and extracted with ethyl acetate. The organic layers were combined, washed with brine. It was dried over Na_2SO_4 and filtered. The residue was evaporated under vacuum without purify, affording a pale-yellow powder **23** (21.0 mg, 46.2%). **23**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.80 (m, $J = 8.8$ Hz, 3H), 7.41 (d, $J = 8.5$ Hz, 2H), 7.27 (s, 1H), 7.20 (d, $J = 8.8$ Hz, 2H), 6.96 (d, $J = 8.5$ Hz, 2H), 6.43 (s, 1H), 5.30 (t, $J = 7.1$ Hz, 1H), 5.13 (s, 2H), 3.92 (s, 3H), 3.76 (s, 3H), 3.34 (d, $J = 7.3$ Hz, 2H), 1.73 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.5, 160.3, 159.1, 149.7, 132.4, 129.6, 128.8, 128.7, 128.5, 127.7, 125.8, 124.0, 121.7, 117.4, 115.3, 113.9, 105.20, 98.39, 69.2, 55.8, 55.1, 27.9, 25.6, 17.6; ESI-MS (*m/z*): 456.2 $[M + H]^+$.

Preparation of methyl-2-hydroxy-4-methoxybenzoate (25)

To a solution of 4-methoxysalicylic acid **24** (4.0 g, 23.8 mmol) in MeOH (40 mL) was added H_2SO_4 (6 mL). The mixture was stirred at reflux for 48 h. It was then concentrated and the residue was diluted with water (50 mL), the pH of the mixture was adjusted to 5~6 with K_2CO_3 and the aqueous solution of was extracted with DCM (40 mL × 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and filtered. The residue was purified by silica gel column chromatography eluting with PE/EA to give pale-yellow oil **25** (4.3 g, 99.2%). **25**: ESI-MS (*m/z*): 183.1 $[M + H]^+$.

Preparation of methyl 5-bromo-2-hydroxy-4-methoxybenzoate (26)

To a solution of compound **25** (4.0 g, 22.0 mmol) in DCM (40 mL) was added Br_2 (3.9 g, 24.2 mmol) dropwise over 10 min at 0 °C. The mixture was stirred at 0 °C or 30 min and then stirred at room temperature for 3 h. It was concentrated and the residue was purified by silica gel column chromatography eluting with PE/EA to give white solid **26** (5.0 g, 81.14%). **26**: ESI-MS (*m/z*): 260.9 $[M + H]^+$.

Preparation of methyl 5-bromo-4-methoxy-2-(tosyloxy) benzoate (27)

To a solution of compound **26** (5.0 g, 19.2 mmol) in DCM (50 mL) were added 4-methylbenzene-1-sulfonyl chloride (5.1 g, 26.9 mmol) and TEA (7.8 g, 76.9 mmol). The mixture was stirred at room temperature for 3 h. It was concentrated and the residue was purified by silica gel column chromatography eluting with PE/EA to give pale-yellow solid **27** (7.5 g, 94.3 %). **27**: ESI-MS (*m/z*): 415.0 $[M + H]^+$.

Preparation of methyl 4-methoxy-5-(isopentenyl)-2-(tosyloxy) benzoate (28)

To a solution of compound **27** (2.7 g, 6.52 mmol) in DMF (20 mL) were added 4,4,5,5-tetramethyl-2-(3-methylbut-2-enyl)-1,3,2-dioxaborolane (1.7 g, 8.47 mmol), $Pd(dppf)_2Cl_2$ (0.5 g, 0.65 mmol) and Cs_2CO_3 (4.2 g, 13.04 mmol). The mixture was stirred at 70 °C for 15 h with the protection of N_2. It was cooled to room temperature and diluted with water (50 mL) and extracted with EA (50 mL × 3). The combined organic layers were washed with brine (80 mL × 3). It was dried over Na_2SO_4 and filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography eluting with PE/EA to give pale-yellow oil **28** (1.0 g, 38.02%). **28**: ESI-MS (*m/z*): 405.1 $[M + H]^+$.

Preparation of 2-hydroxy-4-methoxy-5-(isopentenyl) benzoic acid (29)

To a solution of compound **28** (1.0 g, 2.5 mmol) in THF (24 mL), MeOH (8 mL) and H_2O (8 mL) was added NaOH (0.5 g, 12.4 mmol). The mixture was stirred at 50 °C for 16 h. It was cooled to room temperature and concentrated. The residue was dissolved in H_2O (15 mL). The pH of the mixture was adjusted to 5~6 with 1 N HCl solution. It was then extracted with EA (25 mL × 3). The combined organic layers were washed with brine (80 mL). It was dried over Na_2SO_4 and filtered. The filtrate was concentrated to give white solid **29** (0.54 g, 92.44%). **29**: ESI-MS (*m/z*): 237.0 $[M + H]^+$.

Preparation of 2-hydroxy-4-methoxy-5-(isopentenyl) benzamide (30)

To a solution of compound **29** (0.54 g, 2.28 mmol) in DCM (6 mL) were added HATU (1.30 g, 3.43 mmol), DIPEA (0.88 g, 6.86 mmol) and NH_3/THF (1 N, 22.8 mL, 22.8 mmol). The mixture was stirred at room temperature for 16 h. It was diluted with water (20 mL) and extracted with EA (40 mL × 3). The combined organic layers were washed with brine (80 mL). It was dried over Na_2SO_4 and filtered. The filtrate was concentrated and the residue was purified by prep-TLC to give yellow solid **30** (0.25 g, 46.49%). **30**: ESI-MS (*m/z*): 236.1 $[M + H]^+$.

Preparation of compound 31

A mixture of compound **30** (0.54 g, 1.06 mmol), compound **15** (0.40 g, 1.69 mmol) and piperidine (0.02 g, 0.21 mmol) in toluene (5 mL) was stirred at 100 °C for 16 h. The mixture was cooled to RT and concentrated. The residue was purified by prep-TLC to give pale-yellow solid **31** (0.07 g, 14.52%). **31**: ESI-MS (*m/z*): 454.2 $[M + H]^+$.

Preparation of compound 32

To a solution of compound **31** (70 mg, 0.15 mmol) in DCM (5 mL) was added TBAF (81 mg, 0.31 mmol) at 0 °C for 15 min. It was then diluted with water (20 mL) and extracted with DCM (15 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep-TLC to give compound yellow solid **32** (20 mg, 38.19%). **32**: ^1H NMR (400 MHz, CD_3OD-$CDCl_3$) 7.62 (s, 1 H), 7.47 – 7.38 (d, $J = 8.6$ Hz, 2 H), 6.88 (d, $J = 8.6$ Hz, 2 H), 6.44 (s, 1 H), 6.08 (s, 1 H), 5.30 – 5.21 (m, 1 H), 3.82 (s, 3 H), 3.24 (d, $J = 7.3$ Hz, 2 H), 1.72 (s, 3 H), 1.68 (s, 3 H); ^{13}C NMR (100 MHz, CD_3OD-$CDCl_3$) δ 165.3, 162.9, 158.7, 158.1, 132.9, 128.6×2, 127.8, 126.9, 125.3, 121.7, 115.5 × 2, 109.4, 98.3, 85.7, 55.6, 27.7, 25.5, 17.5. ESI-MS (*m/z*): 340.3 $[M + H]^+$; HR-ESI-MS *m/z*: Anal. Calcd. for $C_{20}H_{22}NO_4$ 340.1543; found 340.1536 $[M + H]^+$.

Preparation of 2-amino-4-methoxybenzoate (34)

To a solution of 2-amino-4-methoxybenzoic acid **33** (5.0 g, 0.03 mol) in methanol (50 mL) was added strong sulphuric acid (9 mL). The solution was stirred at reflux for 24 h. It was cooled to room temperature and the pH of the mixture was adjusted to 5~6 with saturated sodium carbonate solution. The solution was extracted with EA (100 mL*2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated, affording white powder **34** (4.11 g, 75.92%). **34**: ^1H NMR

(400 MHz, $CDCl_3$) 7.81 (d, $J = 8.9$ Hz, 1 H), 6.25 (dd, $J =$ 9.0, 2.5 Hz, 1H), 6.13 (d, $J = 2.4$ Hz, 1H), 5.80 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H).

Preparation of 2-amino-5-bromo-4-methoxybenzoate (35)

To a solution of compound **34** (4.0 g, 0.02 mol) in DCM (200 mL) was added bromine (1.36 mL, 0.02 mol). The mixture was stirred at room temperature for 20 h. It was diluted with saturated sodium hydrogen sulfite (50 mL) and the aqueous solution was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The residue was purified by silica gel column chromatography eluting with PE/EA to give white powder **35** (4.71 g, 82.06%). **35**: ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.04 (s, 1H), 6.14 (s, 1H), 5.87 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H).

Preparation of 2-amino-4-methoxy-5-(isopentenyl)benzoate (36)

To a solution of compound **35** (500 mg, 1.92 mmol) in DMF (10 mL) were added 4,4,5,5-tetramethyl-2-(3-methylbut-2-enyl)-1,3,2-dioxaborolane (452 mg, 2.31 mmol), $Pd(dppf)_2Cl_2$ (140 mg, 0.19 mmol) and Cs_2CO_3 (1253 mg, 3.85 mmol). The mixture was stirred at 70 °C for 24 h with the protection of N_2. It was cooled to RT and diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine. It was dried over Na_2SO_4 and filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography eluting with cyclohexane/EA (uv254, 20:1) to give pale-yellow powder **36** (198.0 mg, 43.0%). **36**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.35 (dd, $J =$ 8.6, 4.2 Hz, 4H), 6.94 (dd, $J = 24.0$, 8.6Hz, 4H), 6.07 (s, 1H), 5.26 (t, $J = 7.3$ Hz, 1H), 4.99 (s, 2H), 4.64 (dd, $J =$ 13.8, 3.5 Hz, 1H), 4.41 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.19 (d, $J = 7.3$ Hz, 2H), 2.78 (dd, $J = 16.1$, 13.9 Hz, 1H), 2.65 (dd, $J = 16.2$, 2.7 Hz, 1H), 1.72 (s, 3H), 1.69 (s, 3H).

Preparation of 2-amino-4-methoxy-5-(isopentenyl)benzoic acid (37)

To a solution of compound **36** (380 mg, 1.52 mmol) in mixed solution of THF (15 mL), methanol (5 mL) and deionized water (5 mL) were added NaOH (305 mg, 7.62 mmol). The solution was stirred at 60 °C for 12 h. After removing the THF and methanol by reduced pressure distillation, the pH of the mixture was adjusted to 4 with 1 N hydrochloric acid solution and the aqueous solution was extracted with EA (20 mL*2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated, affording yellow solid **37** (300 mg, 83.66%). **37**: ^{1}H NMR (400 MHz, DMSO-d_6) 7.38 (s, 1H), 6.26 (s, 1H), 5.22–5.14 (m, 1H), 3.74 (s, 3H), 3.06 (d, $J =$ 7.4 Hz, 2H), 1.68 (s, 3H), 1.63 (s, 3H). ESI-MS (*m/z*): 234.1 $[M\text{-}H]^-$.

Preparation of compound 38

To a solution of compound **37** (300 mg, 1.28 mmol) in THF (15 mL) were added triphosgene (378 mg, 1.28 mmol). The solution was stirred at room temperature for 2 h. The reaction solution was diluted with water (15 mL) and extracted with ethyl acetate (15 mL × 2). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated, affording yellow solid **38** (320 mg, 96.05%). **38**: ^{1}H NMR (400 MHz, DMSO-d_6) 11.66 (s, 1H), 7.57 (s, 1H), 6.60 (s, 1H), 5.23 (t, $J = 7.4$ Hz, 1H), 3.88 (s, 3H), 3.22 (d, $J = 7.4$ Hz, 2 H), 1.71 (s, 3H), 1.65 (s, 3H). ESI-MS (*m/z*): 260.1 $[M\text{-}H]^-$.

Preparation of 2-amino-4-methoxy-5-(isopentenyl) benzamide (39)

To a solution of compound **38** (320 mg, 1.22 mmol) in 1,4-dioxane (15 mL) were added ammonium carbonate (1176 mg, 12.24 mmoL). The solution was stirred at 60 °C for 7 h. The reaction solution was diluted with water (15 mL) and extracted with ethyl acetate (15 mL × 2). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated, affording pale-yellow solid **39** (240 mg, 83.64%). **39**: ^{1}H NMR (400 MHz, DMSO-d_6) 7.55 (s, 1H), 7.30 (s, 1H), 6.74 (s, 1H), 6.60 (s, 2H), 6.22 (s, 1H), 5.21 (t, $J = 7.3$ Hz, 1H), 3.71 (s, 3H), 3.06 (d, $J = 7.2$ Hz, 2H), 1.66 (s, 3H), 1.65 (s, 3H). ESI-MS (*m/z*): 235.0 $[M + H]^+$.

Preparation of 2-(4-hydroxyphenyl)-7-methoxy-6-(isopentenyl)-2,3-dihydroquinazolin-4(1H)-one (40)

To a solution of compound **39** (100 mg, 0.43 mmol) and p-hydroxybenzaldehyde (104 mg, 0.85 mmol) in DMF (20 mL) were stirred and added p-toluenesulfonic acid (16 mg, 0.085 mmol). The solution was stirred at room temperature for 2 h. The reaction solution was diluted with water (20 mL) and extracted with ethyl acetate (20 mL×2). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography eluting with PE/EA to give white solid **40** (100 mg, 69.24%). **40**: ^{1}H NMR (400 MHz, DMSO-d_6) 9.48 (s, 1H), 7.83 (s, 1H), 7.31 (s, 1H), 7.27 (d, $J = 8.3$ Hz, 2H), 6.80 (s, 1H), 6.74 (d, J = 8.2 Hz, 2H), 6.27 (s, 1H), 5.58 (s, 1H), 5.20 (t, J = 7.5 Hz, 1H), 3.71 (s, 3H), 3.09 (d, $J = 7.4$ Hz, 2H), 1.68 (s, 3H), 1.63 (s, 3H). ^{13}C NMR δ

(150 MHz, DMSO-d_6) 164.4, 161.6, 158.0, 148.7, 132.4, 131.7, 128.6, 128.2, 123.3, 119.2, 115.4, 107.9, 96.3, 67.2, 55.7, 27.7, 26.1, 18.0. ESI-MS (*m/z*): 337.3 $[M-H]^-$. HR-ESI-MS *m/z*: Anal. Calcd. for $C_{20}H_{21}N_2O_3$ 337.1552; found 337.1544 $[M+H]^+$.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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