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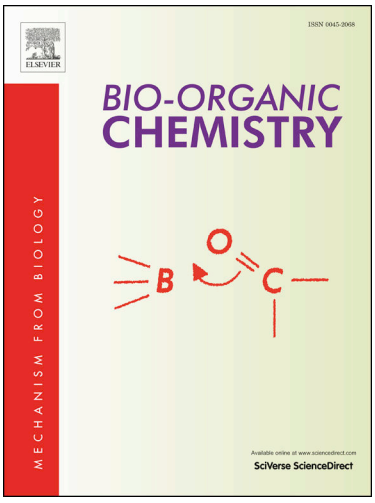

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Total synthesis and anti-inflammatory evaluation of violacin A and its analogues

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ABSTRACT

A concise total synthesis of an exceedingly potent anti-inflammatory agent violacin A as well as the preparation of thirty analogues of this lead from commercially available orcinol are described. Highlights of our synthetic efforts involve Friedel-Crafts acylation, the regioselective etherification and esterification of phenolic hydroxyl groups, and Baker-Venkatamaran rearrangement to form basic skeleton of violacin A. The deprotection reaction with Pd-catalytic was involved to avoid the elimination of the hemiacetal hydroxyl at C2. In addition, all synthetic compounds were screened for anti-inflammatory activity against nitric oxide (NO) production using lipopolysaccharide (LPS)-induced Raw264.7 cells. A range of violacin A derivatives **11b**, **11d**, **11f**, **12e**, **12g**, **13g**, **17d-g** exhibited stronger anti-inflammatory effect than that of violacin A. Notably, halogeno-benzyloxy substituent at C-7 were favourable for anti-inflammatory activities of violacin A derivatives. Additionally, Western blot results indicated halogeno-benzyloxy derivatives inhibited pro-inflammatory cytokines releases correlated with the suppression of NF-κB signaling pathway.

Keywords: Violacin A; Total synthesis; NF-κB; Anti-inflammatory activity.

1. Introduction

Currently, nonsteroidal anti-inflammatory drugs (NSAIDs) and anti-cytokine biologics are available for inflammation treatment, but their side effects or excessive costs frequently limit their use [1,2]. In the pursuit of safer, more economics and more effective compounds of less side effects, the natural-occurring products have been a vital source of therapeutics targeting inflammation.

Chromanones and chromones were widely distributed in nature and exhibited broad spectrum of biological activities such as anti-inflammatory, antioxidant, and antitumor activities [3-5], and had being considered as privileged scaffolds in drug discovery. Chromanones usually possessed a chroman-4-one skeleton and were distinct from chromones with a C2-C3 single bond. Along with their potent bioactivities and unique structures, the total synthesis of these scaffolds have attracted interest from the synthetic community. However, the total synthesis strategy for the chromanone with a hemiacetal hydroxyl at C2 was rarely reported [6-9], notably the hydroxyl was easily eliminated to form a conjugated double bond with the carbonyl group at C4 under acidic conditions. Faced with the intriguing question and the natural scarcity, we embarked on a program directed toward the total synthesis of violacin A (Fig. 1), which was first identified from a fermentation broth of *Streptomyces violaceoruber* obtained from healthy adult *Equus burchelli* (zebra) and presented remarkable anti-inflammatory effect in our previous study [10]. In this study, we described an efficient synthesis of violacin A involving the construction of basic skeleton of target molecule by NaH-promoted Baker-Venkatamaran rearrangement, followed by Pd-catalyzed deprotection. Simultaneously, as scaffolds for development of novel anti-inflammatory drugs, we became interested in preparing derivatives with etherification at C7-OH, alkyl and hydroxyl substituents at C2 or acetalization at C2′. So we designed and synthesized twenty-five new and five known derivatives of violacin A based on its total synthetic route in the search for more suitable candidates for clinical study. Subsequently, the inhibitory effects of target

compounds and intermediates on nitric oxide (NO) release were evaluated using lipopolysaccharide (LPS)-induced Raw264.7 macrophage and anti-inflammatory mechanism was also investigated by using derivative **17d** as a representative.

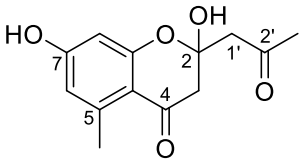
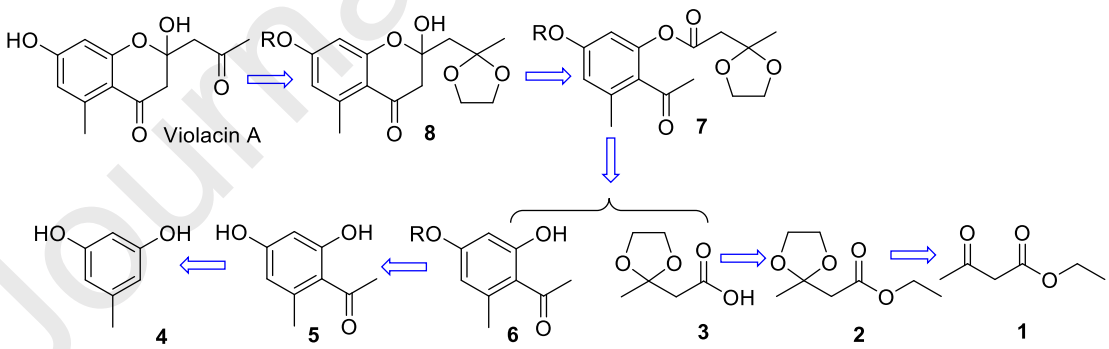


Fig. 1. The structure of violacin A.

2. Results and discussion

2.1. Chemistry

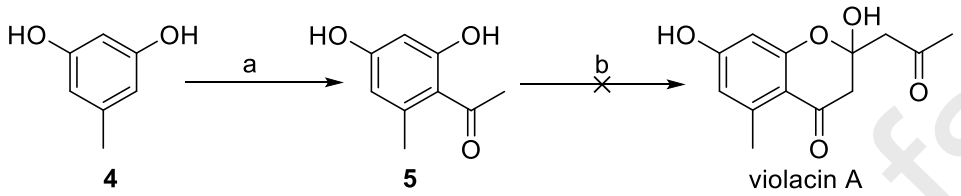
Retrosynthetic analysis for the synthesis of violacin A is shown in Scheme 1. The ketone **8** serves as a pretarget molecule, which results from Baker-Venkatamaran rearrangement of **7**. Intermediate **7** in turn could be assembled from ortho-hydroxy acetophenone derivative **6** and acid **3**. Aromatic building block **6** is derived from commercially available orcinol **4** through Friedel-Crafts acylation reaction and followed by regioselective *O*-etherification. Acid building block **3** could be obtained from the hydrolysis of fructone, which could be prepared from regioselectivity ketalization of carbonyls of **1**.



Scheme 1. Retrosynthetic analysis of **1**.

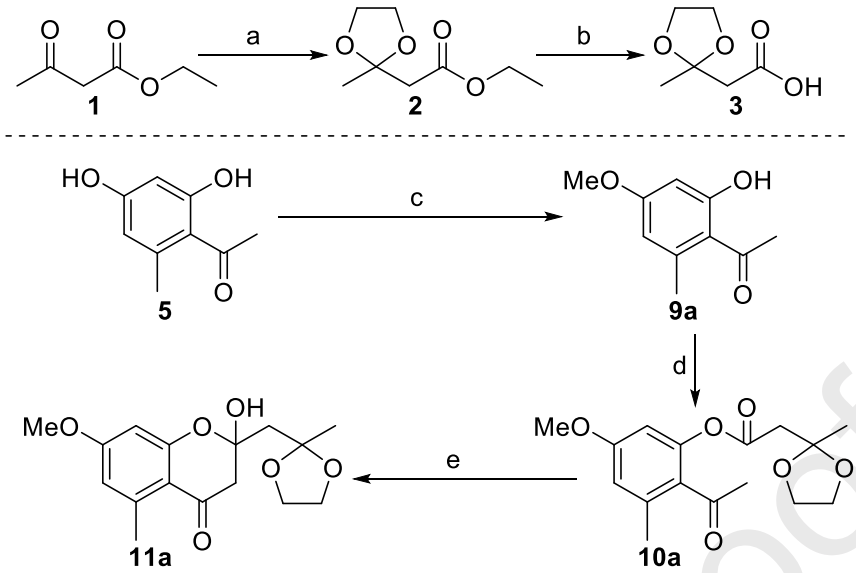
The synthesis was initiated with the synthesis of 2,4-dihydroxy-6-methyl-acetophenone **5** from commercially available orcinol (**4**) following a literature protocol [11]. And the yield was increased to 82%, when the 3A molecular sieve was added to the reaction system, which was possibly attributed to water absorption and the ease of

diffusion of the reactants and products [12]. Subsequently, **5** undergoes a condensation reaction with **1** in one-pot, in order to efficiently and quickly achieve the target molecule violacin A, but it was unsuccessful, probably due to the self-condensation of ethyl acetate **1** under the action of sodium hydride (Scheme 2).



Scheme 2. Synthetic trials towards violacin A. Reagents and conditions: (a) AcOH, BF_3-Et_2O, 3A Molecular sieve, 90 °C, 18 h; (b) Ethyl acetoacetate, NaH, THF, reflux, 3.5 h.

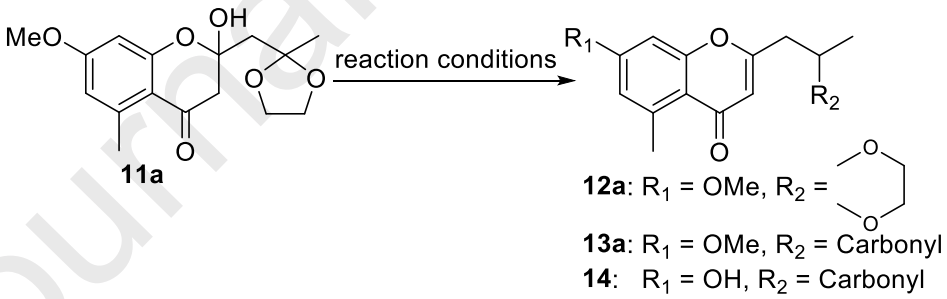
Therefore, we had to revise the synthesis strategy. The dihydric phenol **5** and **1** were also chosen as the starting materials for the new synthesis approach. Etherification of **5** with iodomethane in refluxing acetone in the presence of potassium carbonate achieved the selective methylation of the less encumbered phenolic group to provide the methyl ether **9a** [13,14]. At the same time, the carbonyl group of β-keto ester **1** was protected using standard methodology providing ketal **2**. Further ester hydrolysis under basic conditions gave compound **3** [15,16]. Then, **10a** was obtained by connecting building blocks **9a** and **3** by esterification reaction under Steglich conditions. Treatment of a dry THF solution of ester **10a** with KO*t*Bu or NaH as a base smoothly afforded the key hemiacetal **11a** (Baker-Venkatamaran rearrangement), and in terms of yield, the use of NaH as the base (92%) was significantly better than KO*t*Bu (60%) (Scheme 3).



Scheme 3. Synthesis of intermediate **11a**. Reagents and conditions: (a) *p*-TSA, ethylene glycol, benzene, refluxe, 20 h; (b) 2 N $KOH_{(aq.)}$, ethanol, rt, 4 h; (c) MeI, K_2CO_3, acetone, reflux, 5 h; (d) Comp. **3**, DCC, DMAP, DCM, rt, 20 h; (e) NaH, THF, reflux, 3.5 h.

Unfortunately, this approach to obtain violacin A from hemiacetal **11a** was thwarted in the progress of removals of the *O*-methyl and ketal groups (Table 1) by several attempts with relatively mild reaction conditions [17-19]. Invariably, deprotection was accompanied by elimination of hemiacetal hydroxyl at C2 position.

Table 1. Attempts at deprotection of **11a**.

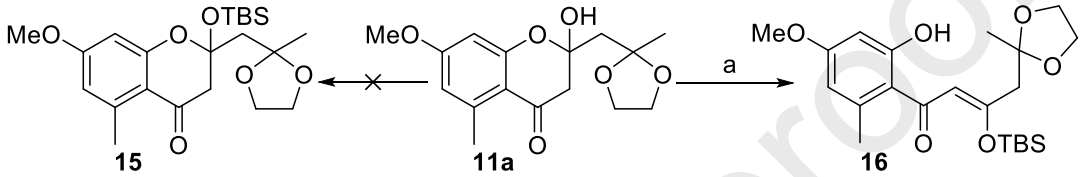


entry	reagents	solvent	T (°C)	time (h)	Yield (%)[a]		
					12a	**13a**	**14** [20]
1	$AlCl_3$	CH_2Cl_2	0	6	0	0	0
2	$AlCl_3$	CH_2Cl_2	r.t.	15	30	0	0
3	$AlCl_3$	CH_3CN	r.t.	15	35	0	0
4	BBr_3	CH_2Cl_2	-60	8	40	32	0

5	BBr_3	CH_2Cl_2	0	8	28	45	0
6	BBr_3	CH_2Cl_2	r.t.	18	0	0	85
7	Me_3SiI	CH_2Cl_2	-20	0.5	30	50	0
8	Me_3SiI	CH_2Cl_2	0	0.5	10	82	0

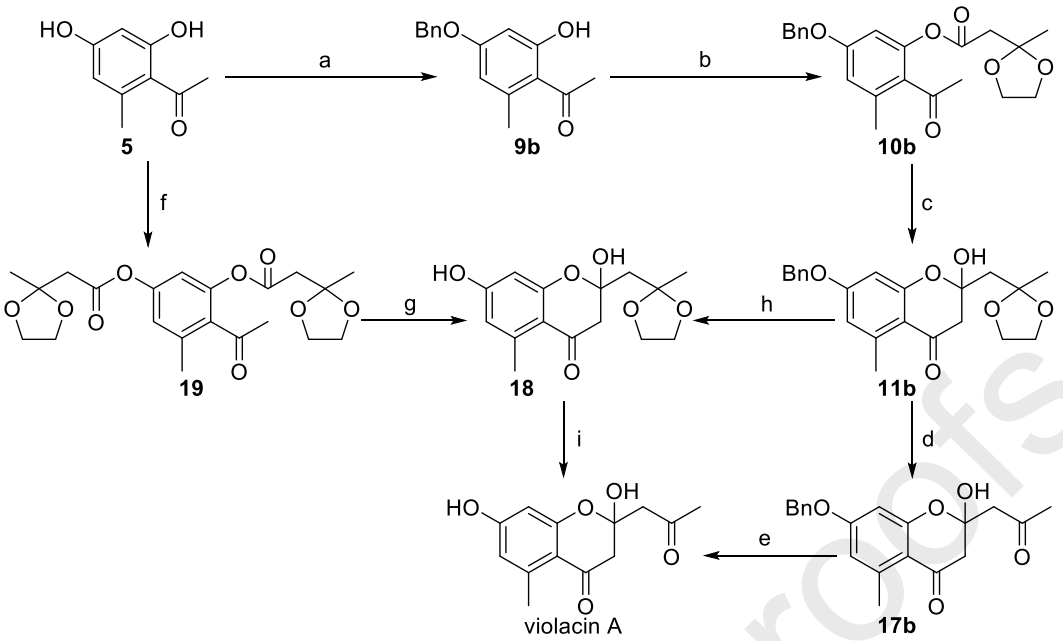
[a]Isolated yields.

Therefore, we tried to protect the hydroxyl at C2 with TBS. Regrettably, the failure of this approach was announced at the time of obtaining **16** (Scheme 4).



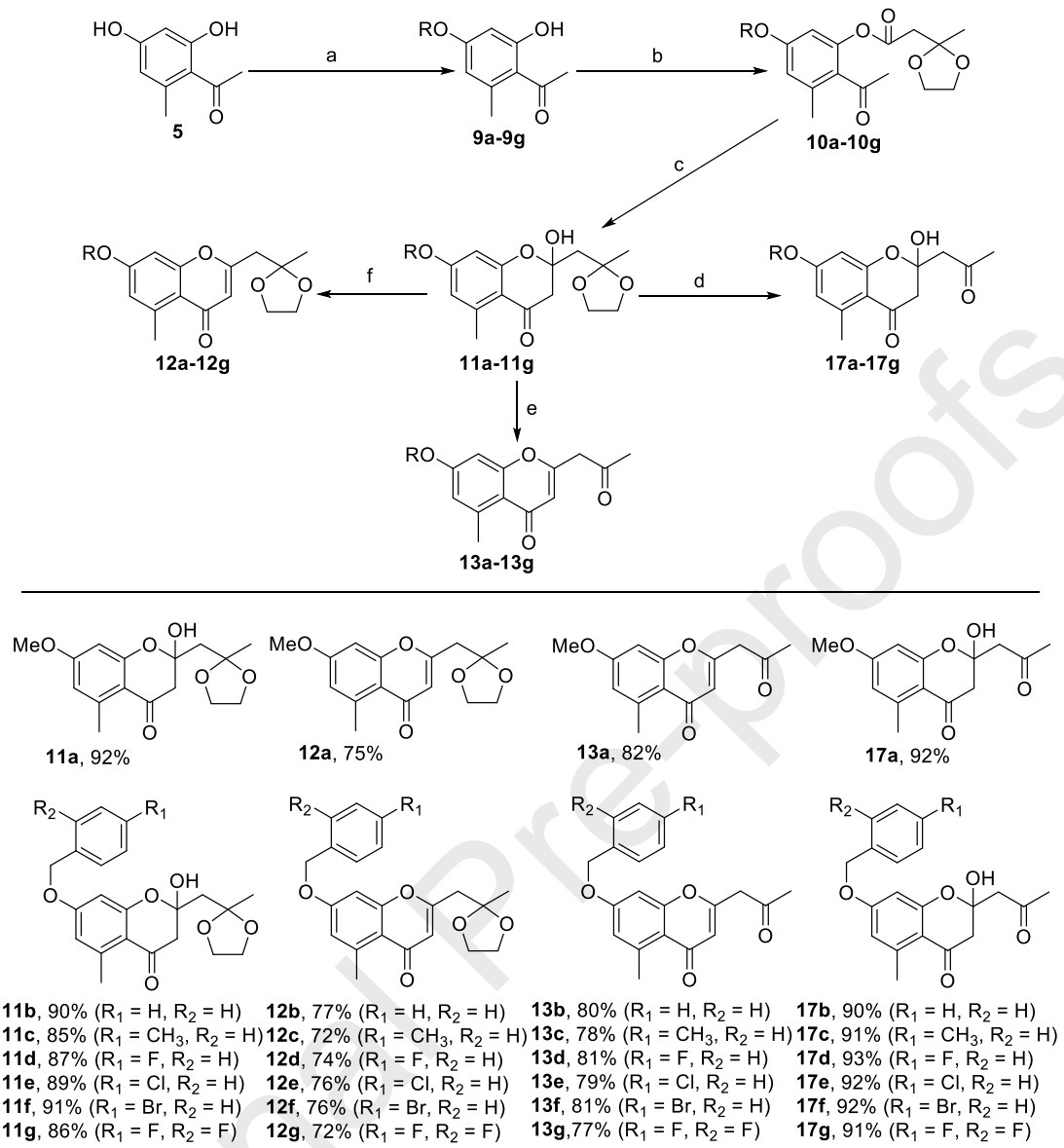
Scheme 4. Synthesis of compound **16.** Reagents and conditions: (a) TBDMSCl, im, DCM, rt, 10 h.

To avoid this obstacle, recourse was taken to the *O*-benzylated **9b**, which was obtained with a less selectively than the corresponding *O*-methylation from treating the dihydric phenol **5** with benzyl chloride, potassium carbonate and sodium iodide in refluxing acetonitrile. Then, the **9b** further transformed into the key intermediate **11b** by the same protocol as that used to synthesize **9a** from **11a**. Afterwards, in order to keep away from the elimination of the hemiacetal hydroxyl at C2 of **11b**, a soft Lewis acid $PdCl_2(CH_3CN)_2$ was used to remove the ketal protecting group [21]. Thus, on treatment with a catalytic amount of the palladium catalyst at 0 ^oC, in acetone and darkness, **11b** easily underwent ketal hydrolysis to give **17b**. Finally, hydrogenolysis [22] of **17b** proceeded prospectively to obtain a nearly quantitative yield of violacin A. Remarkably, violacin A was also produced from **18**, which was obtained by hydrogenation of **11b** or NaH-promoted cyclization of **19** from esterification of dihydric phenol **5** with acid **3**. At this point, the quantity of catalyst $PdCl_2(CH_3CN)_2$ was increased to 0.3 eq. over the previous 0.2 eq. (Scheme 5).



Scheme 5. Total synthesis of violacin A. Reagents and conditions: (a) BnCl, K_2CO_3, NaI, CH_3CN, reflux, 1.5 h; (b) Comp. **3**, DCC, DMAP, DCM, rt, 20 h; (c) NaH, THF, reflux, 3.5 h; (d) $PdCl_2(CH_3CN)_2$, acetone, 0 °C; (e) H_2, Pd-C, MeOH, rt, overnight; (f) Comp. **3**, DCC, DMAP, DCM, rt, 20 h; (g) NaH, THF, reflux, 3.5 h; (h) H_2, Pd-C, MeOH, rt, overnight; (i) $PdCl_2(CH_3CN)_2$, acetone, 0 °C.

With the total synthetic approach of violacin A, various 7-methyl or substituted benzyl derivatives **11a-11g** and **17a-17g** were prepared in similar yields. To construct other structural analogues, we performed the Me_3SiI-mediated hydrolysis of all compounds **11a-11g**. Hemiacetal hydroxyl and ketal moieties were readily removed by using Me_3SiI [18] in dichloromethane at 0°C to furnish the corresponding products **13a-13g**. At the same time, **12a-12g** were also obtained from **11a-11g** by treating with methanolic K_2CO_3 in good yields (Scheme 6).



Scheme 6. Synthesis of violacin A derivatives. Reagents and conditions: (a) K_2CO_3, NaI, Alkyl chloride/bromide/iodide, reflux; (b) Comp. **3**, DCC, DMAP, DCM, rt, 20 h; (c) NaH, THF, reflux, 3.5 h; (d) $PdCl_2(CH_3CN)_2$, acetone, 0 ^oC; (e) Me_3SiI, DCM, 0 ^oC, 20 min; (f) K_2CO_3, MeOH, rt, 24 h.

2.2. Effects of compounds on the production of NO in LPS-induced Raw 264.7 cells

Inflammation has been known as an early response of host against pathogenic challenge. In this process, activated inflammatory cells can secrete increased amounts of NO [23]. Macrophages play a key role in the progress of inflammation, and measuring the production of NO in LPS-stimulated Raw 264.7 cells are widely used for evaluating the anti-inflammatory effects of molecules. Since cytotoxicity of the tested compound would inhibit the cell viability to produce false positive results in the process

of anti-inflammatory evaluation, the MTT assay was firstly carried out. The results showed the double bond at C-2 could increase the cytotoxicity of target compounds (**12b-d**, **12f** and **13b-f**), while C-7 methoxyl or 2,4-difluorobenzyloxyl possibly decreased the cytotoxicity (**12a**, **12g**, **13a**, and **13g**) (Fig. 2A). Then, the anti-inflammatory activities of violacin A and synthetic derivatives (**11a-f**, **12a**, **12e**, **12g**, **13g**, **14**, **17a-b**, **17d-g**) without cytotoxcities were evaluated by Griess method using LPS-stimulated Raw264.7 cells. A commercial regent, minocycline, was selected as a positive control. As shown in figure 2B, compounds **11b**, **11d-f**, **12e**, **12g**, **13g**, **17b,** and **17d-g** were found to display potent inhibitory activities against NO production, stronger than those of minocycline and violacin A. The further investigation also demonstrated that the anti-inflammatory effect of tested compounds were dose-dependent (Fig. 2C). In particular, the results indicated that benzyloxyl, especially halogeno-benzyloxyl, could dramatically improve the anti-inflammatory effect of synthetized molecule.

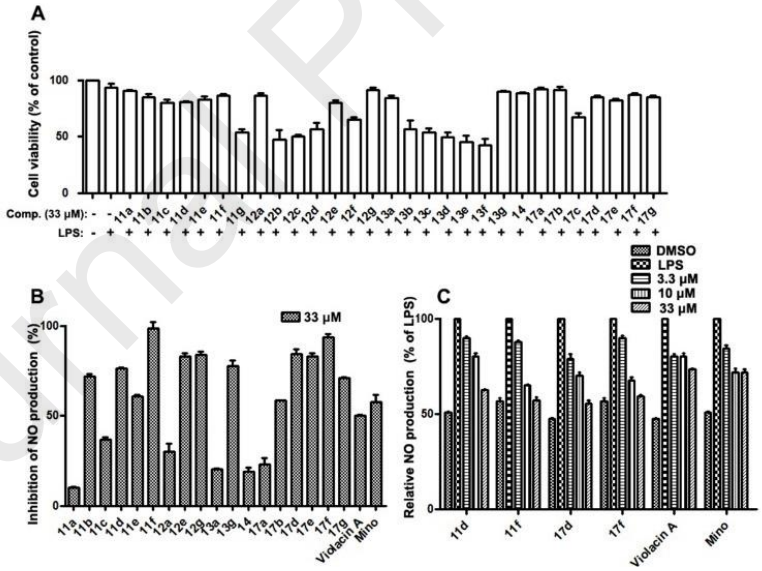


Fig. 2. The cell viability and effect of synthetic compounds on the production of nitric oxide (NO) in lipopolysaccharide (LPS)-induced RAW264.7 cells. The cytotoxicity of synthetic compounds (33 μM) was measured by MTT assay (**A**). The production of NO was determined by Griess method. The cells were treated, respectively, with the 33 μM of synthetic compounds for 2 h, and then stimulated with LPS (1 μg/mL) for 24 h, then the culture medium was collected to detect NO release. The inhibition of NO production calculated through OD values (**B**). Cells were respectively pretreated with the different concentrations of **11d**, **11f**, **17d**, **17f**, violacin A, and Mino (0, 3.3, 10, and 33 μM) for 2 h and then stimulated with or without LPS (1 μg/mL) for

24 h (**C**). The data represent the means ± SD values of three independent experiments.

*2.3. Compound **17d** suppressed release of IL-6, IL-1β and TNF-α in LPS-induced Raw264.7 cells*

The release of pro-inflammatory cytokines, including factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) plays an important role in inducing inflammation [25]. The effect of the halogeno-benzyloxyl violacin compound **17d** on the secretion of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 in LPS-stimulated Raw264.7 cells were further investigated through Elisa assay. The release levels of TNF-α, IL-1β, and IL-6 in model cells were dramatically inhibited in a dose-dependent manner after treatment with **17d**. The results indicated that halogeno-benzyloxyl derivative **17d** could reduce the release of pro-inflammatory cytokines to present anti-inflammatory potential.

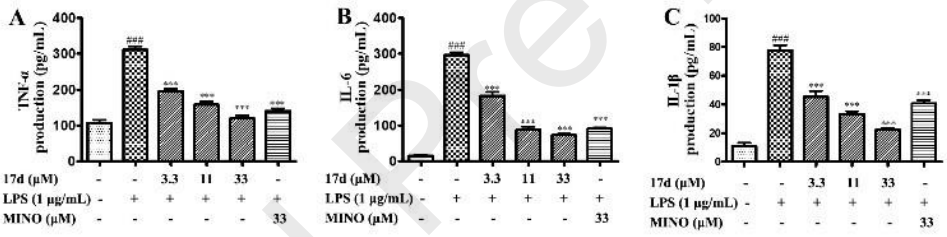


Fig. 3. Effect of **17d** on LPS-induced release of IL-6, IL-1β, and TNF-α in RAW 264.7 cells. The cells were treated with different concentrations of **17d** (0~33 μM) for 2 h, and then stimulated with or without LPS (1 μg/mL) for 12 h. The culture medium was collected to detect the production of TNF-α (**A**), IL-6 (**B**) and IL-1β (**C**) were measured using Elisa kits. Minocycline (MINO) was used as the positive control. The results show mean ± SD values of triplicate tests (### $p < 0.001$ vs. control group; *** $p < 0.001$, vs. LPS group).

*2.4. Compounds **17d** inhibits the activation of NF-κB signaling pathway in LPS-induced Raw264.7 cells*

A number of studies have shown that nuclear factor-κB (NF-κB) signaling pathway plays a key role in inflammatory responses. Upon activation, phosphorylation, ubiquitination and degradation of NF-κB p65 inhibitor IKB-α results in p65 release and translocation to nucleus [26]. The phosphorylation of p65 also involved in the process of signaling transduction pathway activation [27]. In the current study, the effect of **17d** on the NF-κB activation was further investigated. The results revealed that **17d** could

markedly inhibit the phosphorylation of IκB-α and p65, and increase the accumulation of IκB-α in the LPS-stimulated cells. The detection of the protein levels of p65 in the cytosol and nucleus of cells indicated that **17d** attenuated the translocation of p65 from the cytosol to the nucleus. These events demonstrated that **17d** effectively inhibited the NF-κB activation to suppress the inflammatory effect in LPS-stimulated cells.

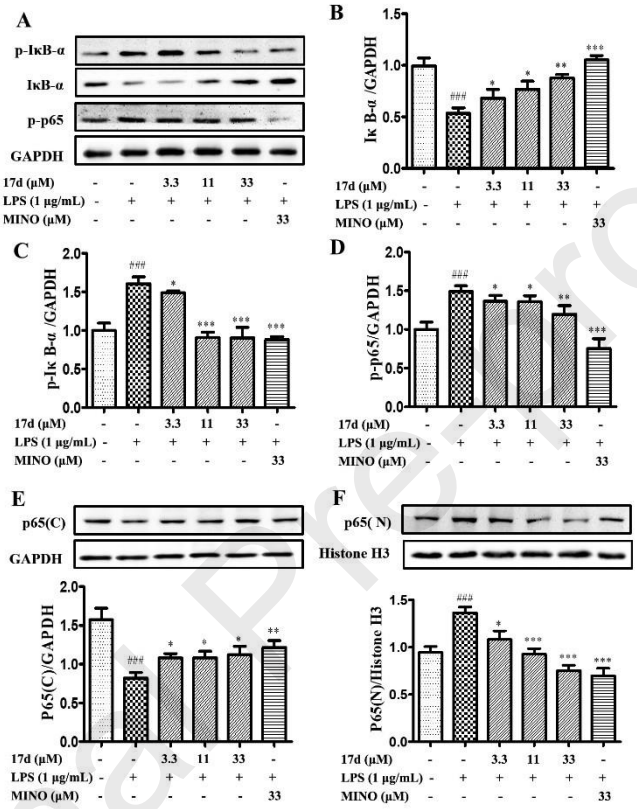


Fig. 4. Effect of **17d** on LPS-induced activation of NF-κB pathway in RAW264.7 cells. Cells were pretreated with various concentrations of concentrations (0~33 uM) of **17d** or MINO (uM) for 2 h and then stimulated with or without LPS (1 μg/mL) for 30 min. The protein levels of phospho-p65, phospho-IκB-α, and IκB-α were analyzed using Western blot (**A**-**D**). Cytosolic (**E**) and nuclear (**F**) protein were prepared and the expression of p65 were determined by Western blot. Data are expressed as the mean ± SD values of three independent experiments. ###, $p < 0.001$ was compared to control. *, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$ compared to LPS.

3. Conclusions

In conclusion, we described the concise total synthesis of violacin A and its analogues *via* the Friedel-Crafts acylation, regioselective etherification of phenolic hydroxyl, Baker-Venkatamaran rearrangement, and deprotection reaction with Pd-catalytic etc. from commercially available orcinol. In addition, violacin A and synthetic

derivatives without cytotoxicities were tested for anti-inflammatory activity using lipopolysaccharide (LPS)-induced Raw264.7 cells. Generally, a range of violacin A derivatives potently inhibited NO production, compared to minocycline as a positive control. Notably, derivatives **11b**, **11d**, **11f**, **12e**, **12g**, **13g**, and **17d-g** were found to exhibit anti-inflammatory activity stronger than that of violacin A. The NO inhibition effect indicated that substitutions at the C7 position of the chromanone moiety, particularly with the halogeno-benzyloxy substituent, were more favourable for NO release inhibition. The halogeno-benzyloxy derivative **17d** showed a stronger inhibition on the production of production of NO, IL-1β, IL-6, and TNF-α *via* inhibition of the signaling pathways of NF-κB in Raw 264.7 cells. Therefore, these compounds based on natural product violacin A may be valuable leads for the development of new anti-inflammatory drugs.

4. Experimental section

4.1. Chemistry

Reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere. THF were freshly distilled from sodium/benzophenone ketyl and transferred *via* syringe. Dichloromethane was freshly distilled from P_2O_5. Commercially available reagents were used as received. IR spectra were recorded with a Bruker Tensor 27 FT-IR spectrometer (film). 1D NMR spectra were collected on a Bruker AV-600 spectrometer. The solvent used for NMR spectroscopy was deuteriated chloroform or dimethyl sulfoxide, using tetramethylsilane as the internal reference. Chemical shifts are given in parts per million, and *J* values are given in Hertz. HRESIMS were measured with an Agilent G6230 TOF mass spectrometer. All chromatographic manipulations used silica gel (100-200 mesh, 200-300 mesh, Qingdao Marine Chemical Ltd., Qingdao, China) as the adsorbent. Reactions were monitored using thin layer chromatography (TLC) on aluminum. TLC plates were visualized by UV radiation at a wavelength of 254 nm or stained by exposure to an ethanolic solution of concentrated sulfuric acid and anisaldehyde, followed by charring where appropriate.

The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

4.2. Synthetic methods of all compounds

*4.2.1. Synthesis of compound **5***

To a solution of orcinol **4** (5.0 g, 40.3 mmol) and 3A molecular sieve in acetic acid (23.1 mL, 403 mmol) was added BF_3-Et_2O (7.62 mL, 60.4 mmol) by dropwise at room temperature. After stirring for 18 h at 90 ^oC, the reaction mixture was quenched by addition of saturated ammonium chloride solution. The acetic acid was removed by distillation under reduced pressure, the residue was dissolved in EtOAc and washed with saturated sodium carbonate solution, water and brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the crude product on silica gel column chromatography (EtOAc/petroleum ether = 1:6) afforded **5** (5.0 g, 75%) as a colorless solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.40 (s, 1H), 6.19 (d, *J* = 2.6 Hz, 1H), 6.17 (d, *J* = 2.6 Hz, 1H), 5.62 (s, 1H), 2.56 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.2, 166.8, 160.9, 142.9, 115.6, 111.9, 101.8, 33.1, 25.2.

*4.2.2. General procedure for the synthesis of compounds **9b-9g***

Benzyl bromide or benzyl chloride with different substituents was added to a stirred suspension of anhydrous potassium carbonate (3.0 eq.) and sodium iodide (0.2 eq.) in acetonitrile, containing **5**, and the mixture was refluxed for 1.5 h. After filtration and evaporation, dichloromethane was added, and the organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated under vacuum. The residue was purified by silica gel column chromatography EtOAc/Petroleum ether (1/12) as eluents.

*4.2.2.1. 1-(4-(benzyloxy)-2-hydroxy-6-methylphenyl)ethan-1-one (**9b**)*. Reagent: benzyl chloride. Followed the above procedure gave **9b** as a colorless oil. Yield 54%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.54 (s, 1H), 7.40 (m, 4H), 7.34 (m, 1H), 6.38 (d, *J* = 2.7 Hz, 1H), 6.37 (d, *J* = 2.7 Hz, 1H), 5.06 (s, 2H), 2.62 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (150

MHz, $CDCl_3$) δ 204.0, 167.1, 163.5, 141.9, 136.0, 128.7 (2×C), 128.3, 127.5 (2×C), 115.3, 112.4, 100.0, 70.0, 33.1, 25.2.

*4.2.2.2. 1-(2-hydroxy-6-methyl-4-((4-methylbenzyl)oxy)phenyl)ethan-1-one (**9c**).* Reagent: *p*-methylbenzyl chloride. Followed the above procedure gave **9c** as a white solid. Yield 42%; IR ν_{max} (thin film)/cm^{-1} 1609, 1370, 1259, 1176, 878. ^1H NMR (600 MHz, $CDCl_3$) δ 13.55 (s, 1H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 6.37 (d, *J* = 2.6 Hz, 1H), 6.35 (d, *J* = 2.6 Hz, 1H), 5.01 (s, 2H), 2.62 (s, 3H), 2.55 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.0, 167.1, 163.5, 141.9, 138.1, 132.9, 129.4 (2×C), 127.7 (2×C), 115.2, 112.5, 100.0, 69.9, 33.0, 25.2, 21.2. HRMS (ESI) *m/z* calcd for $C_{17}H_{19}O_3$ $[M + H]^+$ 271.1334, found 271.1335.

*4.2.2.3. 1-(4-((4-fluorobenzyl)oxy)-2-hydroxy-6-methylphenyl)ethan-1-one (**9d**).* Reagent: *p*-fluorobenzyl chloride. Followed the above procedure gave **9d** as a white solid. Yield 45%; IR ν_{max} (thin film)/cm^{-1} 2361, 2336, 1598, 1313. ^1H NMR (600 MHz, $CDCl_3$) δ 13.54 (s, 1H), 7.38 (dd, *J* = 8.4, 5.3 Hz, 2H), 7.08 (t, *J* = 8.6 Hz, 2H), 6.36 (d, *J* = 2.7 Hz, 1H), 6.35 (d, *J* = 2.7 Hz, 1H), 5.02 (s, 2H), 2.63 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.1, 167.1, 163.2, 162.7 (d, *J* = 246.8 Hz), 142.0, 131.8 (d, *J* = 3.2 Hz), 129.5 (d, *J* = 8.5 Hz, 2×C), 115.7, 115.49 (d, *J* = 26.8 Hz, 2×C), 112.4, 100.0, 69.3, 33.1, 25.2. HRMS (ESI) *m/z* calcd for $C_{16}H_{16}O_3F$ $[M + H]^+$ 275.1083, found 275.1091.

*4.2.2.4. 1-(4-((4-chlorobenzyl)oxy)-2-hydroxy-6-methylphenyl)ethan-1-one (**9e**).* Reagent: *p*-chlorobenzyl chloride. Followed the above procedure gave **9e** as a white solid. Yield 51%; IR ν_{max} (thin film)/cm^{-1} 1611, 1370, 1258, 1176, 846. ^1H NMR (600 MHz, $CDCl_3$) δ 13.53 (s, 1H), 7.33 (m, 4H), 6.35 (s, 2H), 5.03 (s, 2H), 2.63 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.1, 167.1, 163.1, 142.0, 134.5, 134.1, 128.9 (2×C), 128.8 (2×C), 115.5, 112.4, 100.0, 69.1, 33.1, 25.2. HRMS (ESI) *m/z* calcd for $C_{16}H_{16}O_3Cl$ $[M + H]^+$ 291.0788, found 291.0798.

*4.2.2.5. 1-(4-((4-bromobenzyl)oxy)-2-hydroxy-6-methylphenyl)ethan-1-one (**9f**).* Reagent: *p*-bromobenzyl bromide. Followed the above procedure gave **9f** as a white

solid. Yield 53%; IR ν_{max} (thin film)/cm^{-1} 1611, 1371, 1259, 1175, 875. ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.52 (s, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 6.35 (s, 2H), 5.01 (s, 2H), 2.63 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.1, 167.0, 163.1, 142.0, 135.0, 131.8 (2×C), 129.1 (2×C), 122.2, 115.5, 112.3, 100.0, 69.2, 33.1, 25.2. HRMS (ESI) *m/z* calcd for $C_{16}H_{16}O_3Br$ $[M + H]^+$ 335.0283, found 335.0281.

*4.2.2.6. 1-(4-((2,4-difluorobenzyl)oxy)-2-hydroxy-6-methylphenyl)ethan-1-one **(9g)**.* Reagent: 2,4-difluorobenzyl bromide. Followed the above procedure gave **9g** as a white solid. Yield 47%; IR ν_{max} (thin film)/cm^{-1} 1615, 1505, 1266, 1171, 968, 836. ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.52 (s, 1H), 7.43 (dt, *J* = 8.4, 6.3 Hz, 1H), 6.91 (brt, *J* = 8.4 Hz, 1H), 6.86 (brt, *J* = 8.7 Hz, 1H), 6.39 (d, *J* = 2.6 Hz, 1H), 6.35 (d, *J* = 2.6 Hz, 1H), 5.07 (s, 2H), 2.63 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.1, 167.0, 163.0, 163.0 (dd, *J* = 250.0, 12.1 Hz), 160.7 (dd, *J* = 250.0, 12.1 Hz), 142.1, 130.9 (dd, *J* = 9.9, 5.5 Hz), 119.2 (dd, *J* = 14.5, 3.4 Hz), 115.5, 112.2, 111.6 (dd, *J* = 21.4, 3.9 Hz), 104.06 (t, *J* = 25.3 Hz), 99.9, 63.2, 33.1, 25.2. HRMS (ESI) *m/z* calcd for $C_{16}H_{15}O_3F_2$ $[M + H]^+$ 293.0989, found 293.0998.

*4.2.3. General procedure for the synthesis of compounds **10a-10g***

The acetophenone **9a-9g**, the acid **3** (1.0 eq.) and *p*-dimethylaminopyridine (0.2 eq.) were dissolved in dichloromethane. Afterwards, N,N'-dicyclohexyl-carbimide (2.0 eq.) were added portionwise. The reaction mixture was stirred for 20 h at room temperature, filtered and the organic phase was washed with saturated sodium carbonate solution and brine. After drying the solution over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography EtOAc/Petroleum ether (1/5) as eluents.

*4.2.3.1. 2-acetyl-5-methoxy-3-methylphenyl 2-(2-methyl-1,3-dioxolan-2-yl)acetate **(10a)**.* Followed the above procedure gave **10a** as a colorless oil. Yield 85%; IR ν_{max} (thin film)/cm^{-1} 2929, 1764, 1694, 1615, 1317, 1147, 1084, 1044. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.55 (d, *J* = 2.4 Hz, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 3.95 (m, 4H), 3.72 (s, 3H), 2.82 (s, 2H), 2.38 (s, 3H), 2.23 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ

202.6, 167.5, 160.4, 148.4, 137.5, 127.4, 114.2, 107.6, 105.7, 65.0 (2×C), 55.5, 44.2, 32.1, 24.8, 20.0. HRMS (ESI) *m/z* calcd for $C_{16}H_{21}O_6$ $[M + H]^+$ 309.1338, found 309.1337.

*4.2.3.2.2-acetyl-5-(benzyloxy)-3-methylphenyl 2-(2-methyl-1,3-dioxolan-2-yl)acetate (**10b**).* Followed the above procedure gave **10b** as a colorless oil. Yield 87%; IR ν_{max} (thin film)/cm^{-1} 1764, 1694, 1611, 1317, 1146, 1083, 1044. ^1H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 4H), 7.34 (m, 1H), 6.71 (d, *J* = 2.3 Hz, 1H), 6.60 (d, *J* = 2.3 Hz, 1H), 5.04 (s, 2H), 4.01 (s, 4H), 2.88 (s, 2H), 2.46 (s, 3H), 2.29 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.6, 167.5, 159.5, 148.3, 137.6, 136.2, 128.7 (2×C), 128.2, 127.6 (3×C), 114.9, 107.6, 106.6, 70.2, 64.9 (2×C), 44.2, 32.1, 24.8, 20.0. HRMS (ESI) *m/z* calcd for $C_{22}H_{25}O_6$ $[M + H]^+$ 385.1651, found 385.1670.

*4.2.3.3.2-acetyl-3-methyl-5-((4-methylbenzyl)oxy)-phenyl 2-(2-methyl-1,3-dioxolan-2-yl) - acetate (**10c**).* Followed the above procedure gave **10c** as a colorless oil. Yield 82%; IR ν_{max} (thin film)/cm^{-1} 2927, 1764, 1694, 1611, 1352, 1145, 1082, 1044. ^1H NMR (600 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.7 Hz, 2H), 7.19 (d, *J* = 7.7 Hz, 2H), 6.69 (d, *J* = 2.3 Hz, 1H), 6.59 (d, *J* = 2.3 Hz, 1H), 4.99 (s, 2H), 4.01 (s, 4H), 2.88 (s, 2H), 2.45 (s, 3H), 2.36 (s, 3H), 2.29 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.6, 167.5, 159.6, 148.4, 138.1, 137.5, 133.2, 129.4 (2×C) , 127.7 (2×C), 127.6, 115.0, 107.6, 106.6, 70.2, 65.0 (2×C), 44.2, 32.1, 24.8, 21.2, 20.0. HRMS (ESI) *m/z* calcd for $C_{23}H_{27}O_6$ $[M + H]^+$ 399.1808, found 399.1830.

*4.2.3.4.2-acetyl-5-((4-fluorobenzyl)oxy)-3-methylphenyl 2-(2-methyl-1,3-dioxolan-2-yl) - acetate (**10d**).* Followed the above procedure gave **10d** as a colorless oil. Yield 85%; IR ν_{max} (thin film)/cm^{-1} 2928, 1764, 1694, 1612, 1512, 1421, 1223, 1146, 1083, 834. ^1H NMR (600 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.08 (m, 2H), 6.69 (d, *J* = 2.4 Hz, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 4.99 (s, 2H), 4.01 (s, 4H), 2.88 (s, 2H), 2.46 (s, 3H), 2.29 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.6, 167.5, 162.7 (d, *J* = 246.8 Hz), 159.3, 148.3, 137.6, 132.0 (d, *J* = 3.1 Hz), 129.5 (d, *J* = 8.6 Hz, 2×C), 127.8, 115.61 (d,

J = 22.0 Hz, 2×C), 114.9, 107.6, 106.6, 69.6, 65.0 (2×C), 44.2, 32.1, 24.8, 20.0. HRMS (ESI) *m/z* calcd for $C_{22}H_{24}O_6F$ $[M + H]^+$ 403.1557, found 403.1587.

*4.2.3.5.2-acetyl-5-((4-chlorobenzyl)oxy)-3-methylphenyl 2-(2-methyl-1,3-dioxolan-2-yl)-acetate (**10e**).* Followed the above procedure gave **10e** as a colorless oil. Yield 86%; IR ν_{max} (thin film)/cm^{-1} 2931, 1763, 1694, 1611, 1379, 1146, 1085, 1045. ^1H NMR (600 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.34 (m, 2H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 5.00 (s, 2H), 4.01 (s, 4H), 2.88 (s, 2H), 2.46 (s, 3H), 2.29 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.6, 167.5, 159.3, 148.3, 137.6, 134.7, 134.0, 128.9 (2×C), 128.8 (2×C), 127.9, 114.9, 107.6, 106.6, 69.4, 65.0 (2×C), 44.2, 32.1, 24.8, 20.0. HRMS (ESI**)** *m/z* calcd for $C_{22}H_{24}O_6Cl$ $[M + H]^+$ 419.1261, found 419.1280.

*4.2.3.6. 2-acetyl-5-((4-bromobenzyl)oxy)-3-methylphenyl 2-(2-methyl-1,3-dioxolan-2-yl) -acetate (**10f**).* Followed the above procedure gave **10f** as a colorless oil. Yield 89%; IR ν_{max} (thin film)/cm^{-1} 2932, 1762, 1694, 1611, 1316, 1146, 1075, 1045. ^1H NMR (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.58 (d, *J* = 2.4 Hz, 1H), 4.99 (s, 2H), 4.01 (s, 4H), 2.88 (s, 2H), 2.45 (s, 3H), 2.29 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.6, 167.5, 159.2, 148.3, 137.6, 135.3, 131.8 (2×C), 129.1 (2×C), 127.9, 122.1, 114.9, 107.6, 106.6, 69.4, 65.0 (2×C), 44.2, 32.1, 24.8, 20.0. HRMS (ESI) *m/z* calcd for $C_{22}H_{24}O_6Br$ $[M + H]^+$ 463.0756, found 463.0762.

*4.2.3.7. 2-acetyl-5-((2,4-difluorobenzyl)oxy)-3-methylphenyl 2-(2-methyl-1,3-dioxolan-2-yl)-acetate (**10g**).* Followed the above procedure gave **10g** as a colorless oil. Yield 83%; IR ν_{max} (thin film)/cm^{-1} 2929, 1764, 1695, 1611, 1144, 1095, 1045, 850. ^1H NMR (600 MHz, $CDCl_3$) δ 7.44 (td, *J* = 8.4, 6.4 Hz, 1H), 6.91 (m, 1H), 6.85 (ddd, *J* = 9.9, 8.8, 2.5 Hz, 1H), 6.70 (d, *J* = 2.3 Hz, 1H), 6.61 (d, *J* = 2.3 Hz, 1H), 5.05 (s, 2H), 4.02 (s, 4H), 2.89 (s, 2H), 2.46 (s, 3H), 2.30 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.6, 167.6, 163.0 (dd, *J* = 250.0, 11.9 Hz), 160.7 (dd, *J* = 250.0, 11.9 Hz), 159.1, 148.3, 137.6, 130.9 (dd, *J* = 9.9, 5.5 Hz), 128.0, 119.4 (dd, *J* = 14.7, 3.8 Hz), 114.8, 111.6 (dd, *J* = 21.4, 3.8 Hz), 107.6, 106.6, 104.0 (t, *J* = 25.4 Hz), 64.9 (2×C),

63.4, 44.2, 32.1, 24.8, 20.0. HRMS (ESI) *m/z* calcd for $C_{22}H_{23}O_6F_2$ $[M + H]^+$ 421.1463, found 421.1465.

*4.2.4. General procedure for the synthesis of compounds **11a-11g***

The ester **10a-10g** was dissolved in THF under N_2 atmosphere. At 0 °C, the suspension of sodium hydride (20 eq.) was injected through a syringe gradually. The mixture was slowly heated to reflux and stirred for 3.5 h. Then, reaction mixture was cooled to 0 °C and added EtOAc and neutralized with hydrochloric acid until neutral. Then extracted with EtOAc. The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography EtOAc/Petroleum ether (1/4) as eluents.

*4.2.4.1. 2-hydroxy-7-methoxy-5-methyl-2-((2-methyl-1,3-dioxolan-2-yl)methyl)chroman-4-one (**11a**).* Followed the above procedure gave **11a** as a white solid. Yield 92%; IR ν_{max} (thin film)/cm^{-1} 3402, 2929, 1606, 1451, 1153, 1042. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.30 (d, *J* = 2.6 Hz, 1H), 6.21 (d, *J* = 2.6 Hz, 1H), 5.92 (brs, 1H), 3.98 (m, 4H), 3.75 (s, 3H), 2.75 (s, 2H), 2.55 (s, 3H), 2.34 (d, *J* = 14.8 Hz, 1H), 2.03 (d, *J* = 14.8 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.0, 164.3, 161.3, 143.7, 113.4, 112.1, 109.7, 100.9, 99.9, 64.8, 64.3, 55.4, 50.2, 45.2, 26.1, 23.1. HRMS (ESI) *m/z* calcd for $C_{16}H_{21}O_6$ $[M + H]^+$ 309.1338, found 309.1339.

*4.2.4.2. 7-(benzyloxy)-2-hydroxy-5-methyl-2-((2-methyl-1,3-dioxolan-2-yl)methyl)-chroman-4-one (**11b**).* Followed the above procedure gave **11b** as a light yellow solid. Yield 90%; IR ν_{max} (thin film)/cm^{-1} 3416, 1675, 1605, 1451, 1155, 1038. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (m, 4H), 7.34 (m, 1H), 6.46 (d, *J* = 2.5 Hz, 1H), 6.36 (d, *J* = 2.5 Hz, 1H), 6.00 (brs, 1H), 5.06 (m, 2H), 4.03 (m, 4H), 2.82 (s, 2H), 2.62 (s, 3H), 2.40 (d, *J* = 14.7 Hz, 1H), 2.09 (d, *J* = 14.7 Hz, 1H), 1.58 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.0, 163.4, 161.3, 143.8, 136.1, 128.7 (2×C), 128.2, 127.5 (2×C), 113.5, 112.7, 109.7, 100.9, 100.9, 70.0, 64.8, 64.3, 50.2, 45.1, 26.1, 23.1. HRMS (ESI) *m/z* calcd for $C_{22}H_{25}O_6$ $[M + H]^+$ 385.1651, found 385.1649.

*4.2.4.3. 2-hydroxy-5-methyl-2-((2-methyl-1,3-dioxolan-2-yl)methyl)-7-((4-methylbenzyl)-oxy)chroman-4-one (**11c**).* Followed the above procedure gave **11c** as a light yellow solid. Yield 85%; IR ν_{max} (thin film)/cm^{-1} 2925, 1676, 1606, 1570, 1451, 1276, 1154, 1803. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 6.44 (dd, *J* = 2.5, 0.9 Hz, 1H), 6.36 (d, *J* = 2.5 Hz, 1H), 5.99 (s, 1H), 5.02 (d, *J* = 3.3 Hz, 2H), 4.04 (m, 4H), 2.82 (s, 2H), 2.61 (s, 3H), 2.40 (d, *J* = 14.7 Hz, 1H), 2.36 (s, 3H), 2.09 (d, *J* = 14.7 Hz, 1H), 1.58 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.0, 163.5, 161.3, 143.7, 138.1, 133.1, 129.4 (2×C), 127.7 (2×C), 113.5, 112.7, 109.7, 100.9, 100.9, 70.0, 64.8, 64.3, 50.2, 45.1, 26.1, 23.1, 21.2. HRMS (ESI) *m/z* calcd for $C_{23}H_{27}O_6$ $[M + H]^+$

399.1808, found 399.1817.

*4.2.4.4. 7-((4-fluorobenzyl)oxy)-2-hydroxy-5-methyl-2-((2-methyl-1,3-dioxolan-2-yl)-methyl)chroman-4-one (**11d**).* Followed the above procedure gave **11d** as a light yellow solid. Yield 87%; IR ν_{max} (thin film)/cm^{-1} 3326, 2928, 1606, 1570, 1225, 1153, 833. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.08 (m, 2H), 6.44 (d, *J* = 2.5 Hz, 1H), 6.35 (d, *J* = 2.5 Hz, 1H), 6.01 (m, 1H), 5.03 (m, 2H), 4.04 (m, 4H), 2.82 (s, 2H), 2.62 (s, 3H), 2.40 (d, *J* = 14.7 Hz, 1H), 2.10 (d, *J* = 14.7 Hz, 1H), 1.59 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.0, 163.2, 162.6 (d, *J* = 246.8 Hz), 161.3, 143.9, 131.9 (d, *J* = 3.2 Hz), 129.4 (d, *J* = 8.0 Hz, 2×C), 115.6 (d, *J* = 22.0 Hz, 2×C), 113.7, 112.6, 109.7, 101.0, 100.9, 69.4, 64.8, 64.3, 50.3, 45.1, 26.1, 23.1. HRMS (ESI) *m/z* calcd for $C_{22}H_{24}O_6F$ $[M + H]^+$ 403.1557, found 403.1563.

*4.2.4.5. 7-((4-chlorobenzyl)oxy)-2-hydroxy-5-methyl-2-((2-methyl-1,3-dioxolan-2-yl)-methyl)chroman-4-one (**11e**).* Followed the above procedure gave **11e** as a light yellow solid. Yield 89%; IR ν_{max} (thin film)/cm^{-1} 3329, 2927, 1676, 1606, 1451, 1155, 1087, 1041, 845. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 6.44 (d, *J* = 2.7 Hz, 1H), 6.33 (d, *J* = 2.7 Hz, 1H), 6.00 (s, 1H), 5.04 (m, 2H), 4.04 (m, 4H), 2.82 (s, 2H), 2.62 (s, 3H), 2.40 (d, *J* = 14.7 Hz, 1H), 2.10 (d, *J* = 14.7 Hz, 1H), 1.58 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.0, 163.1, 161.3, 143.9, 134.6, 134.1,

128.9 (2×C), 128.8 (2×C), 113.7, 112.6, 109.7, 101.0, 100.9, 69.2, 64.8, 64.3, 50.3, 45.1, 26.1, 23.1. HRMS (ESI) *m/z* calcd for $C_{22}H_{24}O_6Cl$ $[M + H]^+$ 419.1261, found 419.1260.

*4.2.4.6. 7-((4-bromobenzyl)oxy)-2-hydroxy-5-methyl-2-((2-methyl-1,3-dioxolan-2-yl)-methyl)chroman-4-one (**11f**).* Followed the above procedure gave **11f** as a light yellow solid. Yield 91%; IR ν_{max} (thin film)/cm^{-1} 3400, 2928, 1605, 1570, 1451, 1312, 1155, 1040, 887. ^1H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.43 (d, *J* = 2.5 Hz, 1H), 6.33 (d, *J* = 2.5 Hz, 1H), 6.00 (s, 1H), 5.03 (m, 2H), 4.04 (m, 4H), 2.82 (s, 2H), 2.62 (s, 3H), 2.40 (d, *J* = 14.7 Hz, 1H), 2.10 (d, *J* = 14.7 Hz, 1H), 1.58 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.0, 163.0, 161.2, 143.9, 135.2, 131.8 (2×C), 129.1 (2×C), 122.2, 113.7, 112.6, 109.7, 101.0, 100.9, 69.2, 64.8, 64.3, 50.2, 45.1, 26.0, 23.1. HRMS (ESI) *m/z* calcd for $C_{22}H_{24}O_6Br$ $[M + H]^+$ 463.0756, found 463.0758.

*4.2.4.7. 7-((2,4-difluorobenzyl)oxy)-2-hydroxy-5-methyl-2-((2-methyl-1,3-dioxolan-2-yl)-methyl)chroman-4-one (**11g**).* Followed the above procedure gave **11g** as a light yellow solid. Yield 86%; IR ν_{max} (thin film)/cm^{-1} 3411, 2928, 1676, 1606, 1572, 1275, 1153, 1040, 849. ^1H NMR (600 MHz, $CDCl_3$) δ 7.44 (td, *J* = 8.4, 6.3 Hz, 1H), 6.91 (m, 1H), 6.86 (ddd, *J* = 10.0, 8.8, 2.5 Hz, 1H), 6.44 (d, *J* = 2.5 Hz, 1H), 6.37 (d, *J* = 2.5 Hz, 1H), 6.01 (s, 1H), 5.08 (s, 2H), 4.06 (m, 4H), 2.82 (s, 2H), 2.62 (s, 3H), 2.41 (d, *J* = 14.8 Hz, 1H), 2.10 (d, *J* = 14.8 Hz, 1H), 1.60 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.0, 163.0 (dd, *J* = 250.0, 11.9 Hz), 162.9, 161.3, 160.6 (dd, *J* = 250.0, 11.9 Hz), 143.9, 130.9 (dd, *J* = 9.7, 5.2 Hz), 119.3 (dd, *J* = 14.5, 4.0 Hz), 113.8, 112.5, 111.6 (dd, *J* = 21.4, 3.8 Hz), 109.7, 104.00 (t, *J* = 25.4 Hz), 101.0, 100.7, 64.8, 64.3, 63.2, 50.2, 45.2, 26.1, 23.1. HRMS (ESI) *m/z* calcd for $C_{22}H_{23}O_6F_2$ $[M + H]^+$ 421.1463, found 421.1468.

*4.2.5. General procedure for the synthesis of compounds **12a-12g***

A solution of **11a-11g** in methanol was treated with anhydrous potassium carbonate (3.0 eq.) at room temperature and the mixture was stirred 24 h. Filtered and evaporated the filtrate at reduced pressure, and the residue is taken up in DCM, washed with 10%

aqueous hydrochloric acid and brine and dried over anhydrous Na_2SO_4. The solvent removed at reduced pressure and the residue was purified by silica gel column chromatography EtOAc/Petroleum ether (1/3) as eluents.

*4.2.5.1. 7-methoxy-5-methyl-2-((2-methyl-1,3-dioxolan-2-yl)methyl)-4H-chromen-4-one (**12a**).* Followed the above procedure gave **12a** as a light yellow solid. Yield 75%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.63 (d, *J* = 2.5 Hz, 1H), 6.60 (d, *J* = 2.5 Hz, 1H), 6.07 (s, 1H), 3.94-3.84 (m, 4H), 3.79 (s, 3H), 2.79 (s, 2H), 2.74 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.5, 162.4, 162.3, 159.8, 142.6, 116.3, 116.2, 114.0, 108.5, 98.4, 65.0 (2×C), 55.6, 43.4, 24.8, 23.0.

*4.2.5.2. 7-(benzyloxy)-5-methyl-2-((2-methyl-1,3-dioxolan-2-yl)methyl)-4H-chromen-4-one (**12b**).* Followed the above procedure gave **12b** as a light yellow solid. Yield 77%; IR ν_{max} (thin film)/cm^{-1} 2975, 2833, 2721, 1651, 1606, 1394, 1154. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (m, 4H), 7.36 (m, 1H), 6.78 (d, *J* = 2.5 Hz, 1H), 6.77 (d, *J* = 2.5 Hz, 1H), 6.17 (s, 1H), 5.12 (s, 2H), 4.04-3.79 (m, 4H), 2.87 (s, 2H), 2.81 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.5, 162.5, 161.5, 159.7, 142.7, 135.9, 128.7 (2×C), 128.3, 127.5 (2×C), 116.8, 116.4, 113.8, 108.4, 99.4, 70.2, 65.0 (2×C), 43.4, 24.8, 23.0. HRMS (ESI) *m/z* calcd for $C_{22}H_{23}O_5$ $[M + H]^+$ 367.1545, found 367.1547.

*4.2.5.3. 5-methyl-2-((2-methyl-1,3-dioxolan-2-yl)methyl)-7-((4-methylbenzyl)oxy)-4H-chromen-4-one (**12c**).* Followed the above procedure gave **12c** as a light yellow solid. Yield 72%; IR ν_{max} (thin film)/cm^{-1} 2930, 1651, 1607, 1383, 1276, 1160, 1044. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 6.79 (d, *J* = 2.5 Hz, 1H), 6.77 (d, *J* = 2.5 Hz, 1H), 6.25 (s, 1H), 5.07 (s, 2H), 3.95 (m, 4H), 2.88 (s, 2H), 2.80 (s, 3H), 2.37 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.5, 162.8, 161.7, 159.8, 142.7, 138.3, 132.8, 129.4 (2×C), 127.7 (2×C), 117.0, 116.1, 113.6, 108.4, 99.4, 70.2, 65.0 (2×C), 43.5, 24.8, 23.1, 21.2. HRMS (ESI) *m/z* calcd for $C_{23}H_{25}O_5$ $[M + H]^+$ 381.1702, found 381.1719.

*4.2.5.4. 7-((4-fluorobenzyl)oxy)-5-methyl-2-((2-methyl-1,3-dioxolan-2-yl)methyl)-4H-chromen-4-one (**12d**).* Followed the above procedure gave **12d** as a light yellow solid.

Yield 74%; IR ν_{max} (thin film)/cm^{-1} 2928, 1651, 1607, 1351, 1276, 1224, 1154, 1045, 831. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (m, 2H), 7.10 (m, 2H), 6.77 (d, *J* = 2.5 Hz, 1H), 6.75 (d, *J* = 2.5 Hz, 1H), 6.19 (s, 1H), 5.07 (s, 2H), 3.96 (m, 4H), 2.87 (s, 2H), 2.81 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.5, 162.7 (d, *J* = 246.8 Hz), 162.5, 161.3, 159.7, 142.8, 131.6 (d, *J* = 3.3 Hz), 129.4 (d, *J* = 8.8 Hz, 2×C), 116.7, 116.4, 115.7 (d, *J* = 21.1 Hz, 2×C), 113.8, 108.4, 99.4, 69.6, 65.0 (2×C), 43.4, 24.8, 23.0. HRMS (ESI) *m/z* calcd for $C_{22}H_{22}O_5F$ $[M + H]^+$ 385.1451, found 385.1476.

*4.2.5.5. 7-((4-chlorobenzyl)oxy)-5-methyl-2-((2-methyl-1,3-dioxolan-2-yl)methyl)-4H-chromen-4-one (**12e**).* Followed the above procedure gave **12e** as a light yellow solid. Yield 76%; IR ν_{max} (thin film)/cm^{-1} 2929, 1651, 1607, 1383, 1277, 1159, 1091, 1045, 851. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (m, 4H), 6.77 (s, 2H), 6.28 (s, 1H), 5.09 (s, 2H), 3.96 (m, 4H), 2.89 (s, 2H), 2.81 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.5, 163.0, 161.4, 159.8, 142.9, 134.3, 134.2, 128.9 (2×C), 128.8 (2×C), 116.9, 116.2, 113.5, 108.4, 99.4, 69.5, 65.0 (2×C), 43.5, 24.8, 23.1. HRMS (ESI) *m/z* calcd for $C_{22}H_{22}O_5Cl$ $[M + H]^+$ 401.1156, found 401.1163.

*4.2.5.6. 7-((4-bromobenzyl)oxy)-5-methyl-2-((2-methyl-1,3-dioxolan-2-yl)methyl)-4H-chromen-4-one (**12f**).* Followed the above procedure gave **12f** as a light yellow solid. Yield 76%; IR ν_{max} (thin film)/cm^{-1} 2927, 1651, 1608, 1384, 1159, 1096, 1044. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 6.75 (s, 2H), 6.17 (s, 1H), 5.07 (s, 2H), 3.97 (m, 2H), 3.92 (m, 2H), 2.87 (s, 2H), 2.81 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.4, 162.5, 161.2, 159.7, 142.8, 134.9, 131.9 (2×C), 129.1 (2×C), 122.3, 116.7, 116.5, 113.9, 108.4, 99.5, 69.4, 65.0 (2×C), 43.4, 24.8, 23.0. HRMS (ESI) *m/z* calcd for $C_{22}H_{22}O_5Br$ $[M + H]^+$ 445.0651, found 445.0668.

*4.2.5.7. 7-((2,4-difluorobenzyl)oxy)-5-methyl-2-((2-methyl-1,3-dioxolan-2-yl)methyl)-4H-chromen-4-one (**12g**).* Followed the above procedure gave **12g** as a light yellow solid. Yield 72%; IR ν_{max} (thin film)/cm^{-1} 2927, 1651, 1607, 1385, 1278, 1160, 1102, 851. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (td, *J* = 8.4, 6.2 Hz, 1H), 6.93 (m, 1H), 6.88 (m, 1H), 6.80 (d, *J* = 2.5 Hz, 1H), 6.75 (d, *J* = 2.5 Hz, 1H), 6.19 (s, 1H), 5.12 (s, 2H), 3.96 (m,

4H), 2.88 (s, 2H), 2.81 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ179.5, 163.1 (dd, *J* = 250.0, 11.9 Hz), 162.6, 161.1, 160.6 (dd, *J* = 250.0, 11.9 Hz), 159.7, 142.9, 130.9 (dd, *J* = 9.7, 5.2 Hz), 119.3 (dd, *J* = 14.5, 4.0 Hz), 116.6 (2×C), 113.9, 111.6 (dd, *J* = 21.4, 3.8 Hz), 108.4, 104.1 (t, *J* = 25.4 Hz), 99.4, 65.0 (2×C), 63.5, 43.4, 24.8, 23.0. HRMS (ESI) *m/z* calcd for $C_{22}H_{21}O_5F_2$ $[M + H]^+$ 403.1357, found 403.1359.

*4.2.6. General procedure for the synthesis of compounds **13a-13g***

To a solution of **11a-11g** in DCM is added neat trimethylsilyl iodide (1.5 eq.) through a pipette at 0 °C and the mixture was stirred for 20 min. The excess trimethylsilyl iodide is destroyed by adding methanol (5.0 eq.). The volatile components are removed at reduced pressure and the residue is taken up in DCM, washed with aqueous sodium bisulfite, aqueous sodium bicarbonate and brine and dried over anhydrous Na_2SO_4. The solvent removed at reduced pressure and the residue was purified by silica gel column chromatography EtOAc/Petroleum ether (1/3) as eluents.

*4.2.6.1. 7-methoxy-5-methyl-2-(2-oxopropyl)-4H-chromen-4-one (**13a**).* Followed the above procedure gave **13a** as a light yellow solid. Yield 82%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.62 (d, *J* = 2.5 Hz, 1H), 6.59 (d, *J* = 2.5 Hz, 1H), 6.03 (s, 1H), 3.79 (s, 3H), 3.55 (s, 2H), 2.73 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.5, 179.3, 162.6, 159.7, 159.3, 142.8, 116.4, 116.2, 113.8, 98.5, 55.6, 48.6, 29.8, 23.0.

*4.2.6.2. 7-(benzyloxy)-5-methyl-2-(2-oxopropyl)-4H-chromen-4-one (**13b**).* Followed the above procedure gave **13b** as a light yellow solid. Yield 80%; IR ν_{max} (thin film)/cm^{-1} 2926, 1652, 1607, 1453, 1384, 1159. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (m, 4H), 7.36 (m, 1H), 6.79 (d, *J* = 2.4 Hz, 1H), 6.75 (d, *J* = 2.4 Hz, 1H), 6.20 (s, 1H), 5.12 (s, 2H), 3.64 (s, 2H), 2.81 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.3, 179.3, 161.8, 159.7, 159.7, 142.9, 135.7, 128.8 (2×C), 128.4, 127.5 (2×C), 117.2, 116.1, 113.6, 99.4, 70.3, 48.6, 29.8, 23.1. HRMS (ESI) *m/z* calcd for $C_{20}H_{19}O_4$ $[M + H]^+$ 323.1283, found 323.1292.

*4.2.6.3. 5-methyl-7-((4-methylbenzyl)oxy)-2-(2-oxopropyl)-4H-chromen-4-one (**13c**).* Followed the above procedure gave **13c** as a light yellow solid. Yield 78%; IR ν_{max} (thin

film)/cm^{-1} 2925, 1653, 1608, 1383, 1158. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (d, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 6.80 (d, *J* = 2.4 Hz, 1H), 6.75 (d, *J* = 2.4 Hz, 1H), 6.31 (s, 1H), 5.08 (s, 2H), 3.66 (s, 2H), 2.80 (s, 3H), 2.37 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.2, 179.3, 162.1, 160.2, 159.9, 142.9, 138.3, 132.6, 129.5 (2×C), 127.7 (2×C), 117.4, 115.7, 113.2, 99.4, 70.3, 48.6, 29.8, 23.1, 21.2. HRMS (ESI) *m/z* calcd for $C_{21}H_{21}O_4$ $[M + H]^+$ 337.1440, found 337.1452.

*4.2.6.4. 7-((4-fluorobenzyl)oxy)-5-methyl-2-(2-oxopropyl)-4H-chromen-4-one (**13d**).* Followed the above procedure gave **13d** as a light yellow solid. Yield 81%; IR ν_{max} (thin film)/cm^{-1} 2924, 1652, 1607, 1512, 1384, 1225, 1156, 831. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (m, 2H), 7.10 (m, 2H), 6.77 (d, *J* = 2.4 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 6.13 (s, 1H), 5.07 (s, 2H), 3.63 (s, 2H), 2.81 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ201.4, 179.3, 162.7 (d, *J* = 246.8 Hz), 161.5, 159.6, 159.5, 142.9, 131.6 (d, *J* = 3.3 Hz), 129.4 (d, *J* = 8.6 Hz, 2×C), 117.0, 116.3, 115.7 (d, *J* = 21.1 Hz, 2×C), 113.8, 99.4, 69.6, 48.6, 29.8, 23.0. HRMS (ESI) *m/z* calcd for $C_{20}H_{18}O_4F$ $[M + H]^+$ 341.1189, found 341.1198.

*4.2.6.5. 7-((4-chlorobenzyl)oxy)-5-methyl-2-(2-oxopropyl)-4H-chromen-4-one (**13e**).* Followed the above procedure gave **13e** as a light yellow solid. Yield 79%; IR ν_{max} (thin film)/cm^{-1} 2925, 1652, 1607, 1384, 1278, 1159. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (m, 4H), 6.78 (d, *J* = 2.4 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 6.25 (s, 1H), 5.09 (s, 2H), 3.65 (s, 2H), 2.81 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.2, 179.3, 161.6, 159.9, 159.8, 143.0, 134.3, 134.2, 129.0 (2×C), 128.8 (2×C), 117.2, 116.1, 113.5, 99.5, 69.5, 48.6, 29.8, 23.1. HRMS (ESI) *m/z* calcd for $C_{20}H_{18}O_4Cl$ $[M + H]^+$ 357.0894, found 357.0909.

*4.2.6.6. 7-((4-bromobenzyl)oxy)-5-methyl-2-(2-oxopropyl)-4H-chromen-4-one (**13f**).* Followed the above procedure gave **13f** as a light yellow solid. Yield 81%; IR ν_{max} (thin film)/cm^{-1} 2925, 1653, 1607, 1383, 1282, 1159. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 2.5 Hz, 1H), 6.71 (d, *J* = 2.5 Hz, 1H), 6.23 (brs, 1H), 5.07 (s, 2H), 3.65 (s, 2H), 2.81 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (150

MHz, $CDCl_3$) δ 201.2, 179.3, 161.6, 159.9, 159.7, 143.0, 134.8, 131.9 (2×C), 129.1 (2×C), 122.4, 117.1, 116.2, 113.5, 99.5, 69.5, 48.6, 29.8, 23.1. HRMS (ESI) *m/z* calcd for $C_{20}H_{18}O_4Br$ $[M + H]^+$ 401.0388, found 401.0390.

*4.2.6.7. 7-((2,4-difluorobenzyl)oxy)-5-methyl-2-(2-oxopropyl)-4H-chromen-4-one (**13g**).* Followed the above procedure gave **13g** as a light yellow solid. Yield 77%; IR ν_{max} (thin film)/cm^{-1} 2927, 1651, 1607, 1278, 1160, 1102, 851. ^1H NMR (600 MHz, $CDCl_3$) δ 7.46 (td, *J* = 8.4, 6.3 Hz, 1H), 6.93 (m, 1H), 6.88 (ddd, *J* = 10.0, 8.7, 2.6 Hz, 1H), 6.77 (d, *J* = 2.2 Hz, 1H), 6.76 (d, *J* = 2.2 Hz, 1H), 6.18 (s, 1H), 5.12 (s, 2H), 3.65 (d, *J* = 2.9 Hz, 2H), 2.81 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.3, 179.2, 163.0 (dd, *J* = 250.1, 12.0 Hz), 161.6, 161.3, 160.6 (dd, *J* = 250.1, 12.0 Hz), 159.7, 143.0, 130.8 (dd, *J* = 9.7, 5.4 Hz), 119.3 (dd, *J* = 14.6, 3.7 Hz), 116.9, 116.4, 113.7, 111.6 (dd, *J* = 21.4, 3.8 Hz), 104.0 (t, *J* = 25.4 Hz), 99.3, 63.5, 48.6, 29.8, 23.0. HRMS (ESI) *m/z* calcd for $C_{20}H_{17}O_4F_2$ $[M + H]^+$ 359.1095, found 359.1110.

*4.2.7. Synthesis of compound **16***

A solution of **11a** (50 mg, 0.162 mmol) in DCM (3.0 mL) was treated with imidazole (13 mg, 0.194 mmol) and tert-butyldimethylsilyl chloride (37 mg, 0.243 mmol) at room temperature and the mixture was stirred overnight. The reation mixture was diluted with DCM, washed with sat. aq. ammonium chloride solution and brine, and dried over anhydrous Na_2SO_4. Filtration, conentration, and silica gel column chromatography (EtOAc/petroleum ether = 1:8) gave the **16** (24.0 mg, 35%); IR ν_{max} (thin film)/cm^{-1} 2955, 2933, 1601, 1467, 1333, 1257, 1197, 1158, 1046, 838, 783. ^1H NMR (600 MHz, $CDCl_3$) δ 15.51 (s, 1H), 6.20 (d, *J* = 2.4 Hz, 1H), 6.05 (d, *J* = 2.4 Hz, 1H), 5.65 (s, 1H), 3.84 – 3.75 (m, 4H), 3.60 (s, 3H), 2.49 (s, 2H), 2.12 (s, 3H), 1.29 (s, 3H), 0.76 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.0, 188.1, 160.8, 154.1, 138.8, 122.6, 108.7, 108.4, 105.7, 103.3, 64.8 (2×C), 55.2, 48.0, 25.6 (3×C), 24.5, 20.3, 18.1, -4.4 (2×C). HRMS (ESI) *m/z* calcd for $C_{22}H_{35}O_6Si$ $[M + H]^+$ 423.2203, found 423.2199.

*4.2.8. General procedure for the synthesis of compounds **17a-17g***

A solution of **11a-11g** in acetone was cooled to 0 °C and the reaction flask was covered with aluminium foil to protect the catalyst from light. $PdCl_2(CH_3CN)_2$ (cat.) was then added. The reaction is maintained at 0 °C and monitored by NMR for completion, the dark orange reaction mixture was diluted with EtOAc and was washed with ice cold brine. The organic phase was dried over anhydrous Na_2SO_4, the solvent removed at reduced pressure and the residue was purified by silica gel column chromatography EtOAc/Petroleum ether (1/4) as eluent.

*4.2.8.1. 2-hydroxy-7-methoxy-5-methyl-2-(2-oxopropyl)chroman-4-one (**17a**).* Followed the above procedure gave **17a** as a light yellow solid. Yield 92%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.38 (d, *J* = 2.4 Hz, 1H), 6.26 (d, *J* = 2.5 Hz, 1H), 6.03 (s, 1H), 3.80 (s, 3H), 3.26 (d, *J* = 16.7 Hz, 1H), 2.78 (s, 2H), 2.72 (d, *J* = 16.7 Hz, 1H), 2.61 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.2, 190.0, 164.4, 161.0, 143.8, 113.3, 112.6, 100.7, 99.9, 55.4, 49.3, 48.8, 32.3, 23.1.

*4.2.8.2. 7-(benzyloxy)-2-hydroxy-5-methyl-2-(2-oxopropyl)chroman-4-one (**17b**).* Followed the above procedure gave **17b** as a light yellow solid. Yield 90%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 4H), 7.27 (m, 1H), 6.40 (d, *J* = 2.6 Hz, 1H), 6.28 (d, *J* = 2.6 Hz, 1H), 5.97 (s, 1H), 5.04 – 4.92 (m, 2H), 3.19 (d, *J* = 16.8 Hz, 1H), 2.71 (d, *J* = 1.5 Hz, 2H), 2.64 (d, *J* = 16.7 Hz, 1H), 2.54 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.2, 190.0, 163.5, 161.0, 143.8, 136.1, 128.7 (2×C), 128.3, 127.5 (2×C), 113.5, 113.3, 100.8, 100.7, 70.0, 49.3, 48.8, 32.3, 23.1.

*4.2.8.3.2-hydroxy-5-methyl-7-((4-methylbenzyl)oxy)-2-(2-oxopropyl)chroman-4-one(**17c**).* Followed the above procedure gave **17c** as a light yellow solid. Yield 91%; IR ν_{max} (thin film)/cm^{-1} 3394, 2924, 1675, 1606, 1451, 1277, 1155. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 6.46 (d, *J* = 2.5 Hz, 1H), 6.34 (d, *J* = 2.5 Hz, 1H), 6.03 (s, 1H), 5.00 (m, 2H), 3.25 (d, *J* = 16.7 Hz, 1H), 2.78 (s, 2H), 2.71 (d, *J* = 16.7 Hz, 1H), 2.61 (s, 3H), 2.36 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.2, 190.0, 163.6, 160.9, 143.8, 138.1, 133.0, 129.4 (2×C), 127.6

(2×C), 113.4, 113.3, 100.7, 100.7, 70.0, 49.3, 48.8, 32.2, 23.1, 21.2. HRMS (ESI) *m/z* calcd for $C_{21}H_{23}O_5$ $[M + H]^+$ 355.1545, found 355.1563.

*4.2.8.4.7-((4-fluorobenzyl)oxy)-2-hydroxy-5-methyl-2-(2-oxopropyl)chroman-4-one (**17d**).* Followed the above procedure gave **17d** as a light yellow solid. Yield 93%; IR ν_{max} (thin film)/cm^{-1} 3395, 1675, 1605, 1512, 1225, 1154, 832. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (m, 2H), 7.08 (m, 2H), 6.45 (d, *J* = 2.5 Hz, 1H), 6.33 (d, *J* = 2.5 Hz, 1H), 6.06 (brs, 1H), 5.00 (m, 2H), 3.26 (d, *J* = 16.7 Hz, 1H), 2.79 (s, 2H), 2.72 (d, *J* = 16.7 Hz, 1H), 2.61 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.2, 190.0, 163.3, 162.7 (d, *J* = 246.8 Hz), 161.0, 143.9, 131.8 (d, *J* = 3.2 Hz), 129.4 (d, *J* = 8.1 Hz, 2×C), 115.6 (d, *J* = 21.7 Hz, 2×C), 113.6, 113.2, 100.8, 100.8, 69.4, 49.3, 48.8, 32.2, 23.1. HRMS (ESI) *m/z* calcd for $C_{20}H_{20}O_5F$ $[M + H]^+$ 359.1295, found 395.1312.

*4.2.8.5.7-((4-chlorobenzyl)oxy)-2-hydroxy-5-methyl-2-(2-oxopropyl)chroman-4-one (**17e**).* Followed the above procedure gave **17e** as a light yellow solid. Yield 92%; IR ν_{max} (thin film)/cm^{-1} 3396, 1675, 1605, 1276, 1156. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 6.45 (d, *J* = 2.5 Hz, 1H), 6.31 (d, *J* = 2.5 Hz, 1H), 6.05 (s, 1H), 5.01 (m, 2H), 3.25 (d, *J* = 16.8 Hz, 1H), 2.78 (s, 2H), 2.72 (d, *J* = 16.8 Hz, 1H), 2.61 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.2, 190.0, 163.2, 160.9, 143.9, 134.6, 134.1, 128.9 (2×C), 128.8 (2×C), 113.6, 113.2, 100.8 (2×C), 69.2, 49.3, 48.8, 32.2, 23.1. HRMS (ESI) *m/z* calcd for $C_{20}H_{20}O_5Cl$ $[M + H]^+$ 375.0999, found 375.1012.

*4.2.8.6.7-((4-bromobenzyl)oxy)-2-hydroxy-5-methyl-2-(2-oxopropyl)chroman-4-one(**17f**).* Followed the above procedure gave **17f** as a light yellow solid. Yield 92%; IR ν_{max} (thin film)/cm^{-1} 3398, 1675, 1605, 1276, 1155, 1052. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 6.45 (d, *J* = 2.5 Hz, 1H), 6.31 (d, *J* = 2.5 Hz, 1H), 6.05 (s, 1H), 5.00 (m, 2H), 3.25 (d, *J* = 16.8 Hz, 1H), 2.78 (s, 2H), 2.72 (d, *J* = 16.8 Hz, 1H), 2.61 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.2, 190.0 163.1, 160.9, 143.9, 135.1, 131.8 (2×C), 129.0 (2×C), 122.2, 113.6, 113.2, 100.8

(2×C), 69.2, 49.3, 48.8, 32.2, 23.1. HRMS (ESI) *m/z* calcd for $C_{20}H_{20}O_5Br$ $[M + H]^+$ 419.0494, found 419.0495.

*4.2.8.7.7-((2,4-difluorobenzyl)oxy)-2-hydroxy-5-methyl-2-(2-oxopropyl)chroman-4-one (**17g**)*. Followed the above procedure gave **17g** as a light yellow solid. Yield 91%; IR ν_{max} (thin film)/cm^{-1} 3396, 1677, 1606, 1275, 1155. ^1H NMR (600 MHz, $CDCl_3$) δ 7.44 (td, *J* = 8.4, 6.3 Hz, 1H), 6.91 (tdd, *J* = 8.2, 2.5, 1.1 Hz, 1H), 6.86 (ddd, *J* = 10.0, 8.8, 2.5 Hz, 1H), 6.46 (d, *J* = 2.5 Hz, 1H), 6.35 (d, *J* = 2.5 Hz, 1H), 6.05 (s, 1H), 5.06 (s, 2H), 3.26 (d, *J* = 16.8 Hz, 1H), 2.79 (s, 2H), 2.72 (d, *J* = 16.8 Hz, 1H), 2.62 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.2, 190.0, 163.0 (dd, *J* = 250.1, 12.0 Hz), 163.0, 160.9, 160.6 (dd, *J* = 250.1, 12.0 Hz), 144.0, 130.8 (dd, *J* = 9.7, 5.4 Hz), 119.3 (dd, *J* = 14.6, 3.7 Hz), 113.7, 113.02, 111.6 (dd, *J* = 21.4, 3.8 Hz), 104.0 (t, *J* = 25.4 Hz), 100.8, 100.7, 63.3, 49.3, 48.8, 32.3, 23.1. HRMS (ESI) *m/z* calcd for $C_{20}H_{19}O_5F_2$ $[M + H]^+$ 377.1201, found 377.1212.

*4.2.9. Synthesis of compound **18***

To a stirred solution of **11b** (200 mg, 0.52mmol) in MeOH (20 mL) was added in one portion 5% Pd on C (200 mg). The reaction vessel was successively evacuated and purged with H_2 (1 atm) several times and stirred vigorously for overnight. The mixture was then filtered through Celite, and the filter pad was washed with copious amounts of MeOH and the filtrate was concentrated in vacuo to afford phenol (176 mg, quant.) as a light yellow solid; B: Followed the procedure of **11a-11g**, **19** as the material, yield 65%; ^1H NMR (600 MHz,$CDCl_3$) δ 7.44 (brs, 1H), 6.35 (d, *J* = 2.4 Hz, 1H), 6.31 (d, *J* = 2.4 Hz, 1H), 6.06 (s, 1H), 4.06 (m, 4H), 2.84 (m, 2H), 2.60 (s, 3H), 2.41 (d, *J* = 14.8 Hz, 1H), 2.11 (d, *J* = 14.8 Hz, 1H), 1.60 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.0, 162.0, 161.6, 144.4, 113.3, 113.0, 109.7, 102.2, 100.8, 64.8, 64.3, 50.0, 45.2, 26.0, 23.1. HRMS (ESI) *m/z* calcd for $C_{15}H_{18}O_6Na$ $[M + Na]^+$ 317.1001, found 317.0996.

*4.2.10. Synthesis of compound **19***

Followed the procedure of **10a-10g**, **5** as the material, the acid **3** (2.2 eq.) and *p*-dimethylaminopyridine (0.2 eq.), N,N'-dicyclohexylcarbimide (4.0 eq.), gave 19 as a

colorless oil, yield 38%; IR ν_{max} (thin film)/cm^{-1} 2933, 1765, 1702, 1247, 1171, 1085, 1045. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.87 (d, *J* = 2.1 Hz, 1H), 6.85 (d, *J* = 2.1 Hz, 1H), 4.04 (m, 4H), 4.01 (brs, 4H), 2.89 (s, 2H), 2.87 (s, 2H), 2.47 (s, 3H), 2.29 (s, 3H), 1.58 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.7, 167.4, 167.1, 150.7, 147.2, 136.8, 132.4, 121.3, 113.8, 107.6, 107.5, 65.0 (2×C), 64.9 (2×C), 44.2, 44.1, 32.0, 24.8, 24.7, 19.4. HRMS(ESI) *m/z* calcd for $C_{21}H_{26}O_9Na$ $[M + Na]^+$ 445.1475, found 445.1465.

4.2.11. Synthesis of compound violacin A

Followed the procedure of **18**, **17b** as the material, yield quant.; B: Followed the procedure of **17a-17g**, **18** as the material, yield 85%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.33 (s, 1H), 7.07 (d, *J* = 2.3 Hz, 1H), 6.26 (d, *J* = 2.3 Hz, 1H), 6.14 (d, *J* = 2.3 Hz, 1H), 3.08 – 2.94 (m, 3H), 2.61 (d, *J* = 16.0 Hz, 1H), 2.45 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 205.6, 191.0, 163.2, 161.4, 142.9, 113.1, 112.4, 102.0, 100.3, 52.8, 47.9, 32.3, 23.0.

4.3. Biology assay

4.3.1. Cell culture and cell viability assay

The Raw264.7 cells were in DMEM supplemented with 10% FBS, 2 mM glutamine, 100 U/mL of penicillin, and 100 μg/mL of streptomycin at 37 °C in a 5% CO_2 atmosphere. The cell viability was measured by MTT assay. RAW264.7 cells were plated at 2 × 10^5 cells per well in 96-well-plates and incubated overnight. After that, the cells were pretreated with or without test compound for 2 h and then induced with LPS (1 μg/mL). After 24 h incubation at 37 °C, 20 μL of MTT (5 mg/mL) was added and incubated for 4 h at 37 ◦C; then the cell medium was discarded and 150 μL of DMSO was added. The OD values of the culture plate at 570 nm was measured using a microplate reader (Synergy HT, BioTek, Winooski, VT, USA). The results were represented as the mean SD from three independent experiments. The cell viability (%) = A_{570} (test compound)/A_{570} (control) × 100%.

4.3.2. Determination of nitric oxide (NO) production

Nitric oxide (NO) production was measured using the Griess methods. The cells were plated at 0.8×10^6 cells/well in 6-well-plates and cultured for 24 h. The cells were pretreated with various compounds (0, 3.3, 10, 33 μM) for 2 h and then stimulated with 1 μg/mL LPS for 24 h. The NO concentration was examined according to a previously described protocol.[21] 50 μL of cell supernatant was collected into a new 96-well plate, and then 50 μL of 1% (w/v) sulfanilamide in 5% (v/v) phosphoric acid solution was added and incubated in the dark at room temperature for 5 min. After that, 50 μL of 0.1% (w/v) N-(1-naphthyl) ethylenediamine solution was added to the mixture, and the OD values of the 96-well plate were measured at 540 nm using a microplate reader. The results were represented as the mean SD from three independent experiments. The inhibition of NO production (%) = [A_{540} (LPS) - A_{540} (test compound)] / [A_{540} (LPS) - A_{540} (DMSO)] × 100%.; Relative NO production (%) = A_{540} (test compound)/A_{540} (LPS) × 100%.

4.3.3. Measurement of cytokine (IL-1β, IL-6 and TNF-α)

The cells were seeded in 6-well-plates at a density of the 0.8×10^6 cells per well. After the cells were cultured overnight, they were pretreated with various compounds (0, 3.3, 11, and 33 μM) and 33 μM Minocycline (Mino, positive control) for 2 h, respectively. Then, they were stimulated with LPS (1 μg/mL) for 12 h and the production of IL-1β, IL-6 and TNF-α in the culture supernatant was detected using Elisa kits (R&D systems, Abingdon, UK) as literature method [24].

4.3.4. Western blot analyses

The Raw264.7 cells were pretreated with 17d (0-33 μM) or Mino (33 μM) for 2 h, and then induced with LPS (1 μg/mL) for 30 min. After that, the cells were harvested and lysed with ice-cold lysis buffer. Total protein, cytoplasmic and nuclear proteins were respectively extracted using the protein extraction kit (Beyotime, Shanghai, China), according to the manufacturer's instructions. The protein concentration was measured using a BCA protein assay kit (Beyotime, Beijing, China). Equal amounts of protein were separated by 10% SDS-PAGE. After that they were transferred to 0.45 μm

PVDF membranes (Millipore, Billerica, MA, USA). After being blocked with 5% skimmed milk for 1 h, the blots were incubated with specific primary antibodies, followed by incubation with HRP-secondary antibody. Blots were exposed using the enhanced chemiluminescence detection kit (Millipore, Billerica, MA, USA) and analyzed using Bio-Rad ChemiDoc™XRS + System (Bio-Rad, Hercules, CA, USA).

4.4. Statistical analyses

At least three independent experiments were carried out. All of the data were expressed as the mean ± S.D. and analyzed for statistical significance using the Student's *t*-test. The p values < 0.05 (*) were considered significant.

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Conflicts of interest

The authors have declared no conflict of interest.

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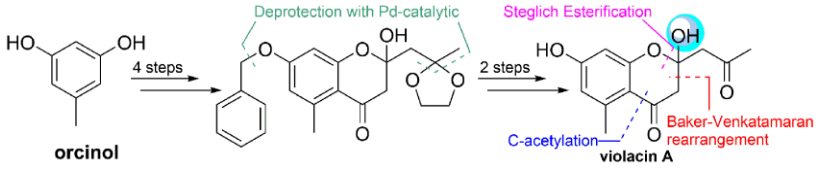

Highlights

1. A chromanone violacin A with exceedingly potent anti-inflammatory activity was firstly synthesized *via* Friedel-Crafts acylation, selective protection of phenolic hydroxyl groups, esterification, Baker-Venkatamaran rearrangement and deprotections with Pd-catalytic from orcinol.
2. Thirty derivatives (**11a-g**, **12a-g, 13a-g**, **14**, **17a-g** and **18**) were designed and obtained by similar synthetic procedure with violacin A. Twenty-five of them were new compounds (**11a-g**, **12b-g, 13b-g**, **17c-g**, and **18**), which were characterized by the detailed spectra analysis.
3. All synthetic compounds were tested for anti-inflammatory activity using LPS-induced Raw264.7 cells. Generally, a range of violacin A derivatives potently inhibited NO production. Notably, derivatives **11b**, **11d-f**, **12e**, **12g**, **13g**, **17d-g** were found to exhibit anti-inflammatory activity stronger than that of violacin A.
4. A representative analogous **17d** inhibited pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 releases correlated with the suppression of NF-κB signaling pathway.