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# Biomimetic synthesis and anti-inflammatory evaluation of violacin A analogues

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ABSTRACT

Violacin A, a chromanone derivative, isolated from a fermentation broth of *Streptomyces violaceoruber*, has excellent anti-inflammatory potential. Herein, a biogenetically modeled approach to synthesize violacin A and twenty-five analogues was described, which involved the preparation of aromatic polyketide precursor through Claisen condensation and its spontaneous cyclization. The inhibitory effect on nitric oxide (NO) production of all synthetic molecules was evaluated by lipopolysaccharide (LPS)-induced Raw264.7 cells. The results revealed that introduction of aliphatic amine moieties on C-7 obviously improved the anti-inflammation effect of violacin A, and also the aromatic ether instead of ketone group at side chain was favorable to increase the activity. Among them, analogue 7a and 16d were screened as the most effective anti-inflammatory candidates. Molecular mechanism research revealed that 7a and 16d acquired anti-inflammatory ability due to the inhibition of NF-κB signaling pathway.

## 1. Introduction

Violacin A was first isolated from a fermentation broth of *Streptomyces violaceoruber*, and presented excellent anti-inflammatory effect through down-regulating nuclear factor-κB (NF-κB) signaling pathway [1]. NF-κB pathway plays a critical role in the progress of inflammation and had been used as a potential target for anti-inflammatory therapy [2,3]. The anti-inflammatory potential and novel molecular structure of violacin A have caused our intense concern.

Although violacin A has been successful synthesized through eight-step reaction with 25% total yield in our previous research [4], the synthetic process and its overall yield could not meet the need for further research. In addition, our previous preliminary structure–activity relationship (SAR) studies have revealed that the benzyloxyl group introduction at the C-7 could obviously change the anti-inflammatory activity of violacin A, and the absence of ketone group at the side chain might not influence its activity [4]. However, the relative role of 7-*O*-substituent and the alkyl side chain on the scaffold in the anti-inflammatory effect of violacin A still needs to be clarified.

In order to construct new synthetic strategy, the plausible biosynthetic pathway for violacin A was designed (Scheme 1) according to the similar natural products in the literature. Violacin A was assumed to be biogenetically originated from polyketide precursor, which derived from the Aldol condensation of the acetyl-CoA and malonyl-CoA [5]. After that, β-ketoacid product was constructed by Aldol condensation, aromatization and hydrolyzation [5]. And then, it underwent spontaneous decarboxylation to form aromatic polyketide precursor [6], which would produce violacin A through forming cyclic hemiacetal [7]. In the current study, on basis of biosynthetic pathway analysis of violacin A, a new synthesis strategy was introduced, which greatly shortened the reaction period and increased the overall yield to 42%. In order to further investigate the SAR, a series of analogues (**7a-7p** and **16a-16i**) were designed and synthesized using the similar approach. The inhibitory effect of all synthesized analogues on nitric oxide (NO) production was evaluated using lipopolysaccharide (LPS)-induced Raw264.7 cells. As the most potential chemical molecule, the anti-inflammatory mechanism of **7a** and **16d** was related to inhibition of NF-κB signaling pathway.

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## 2. Results and discussion

### 2.1. Chemistry

According to the biosynthetic pathway analysis, the retrosynthetic analysis of violacin A was described in Scheme 2. Violacin A was obtained through intramolecular cyclization of aromatic polyketide **4**. Meanwhile, polyketide **4** served as a pretarget molecule, which could be constructed by Claisen condensation of methyl 2,4-dihydroxy-6-methylbenzoate (**2**) and acetylacetone (**3**). And then the intermediate **2** could be prepared from starting material methyl acetoacetate (**1**).

Guided by the foregoing retrosynthetic strategy, the synthesis was initiated with the synthesis of intermediate **2** from commercially available methylacetoacetate (**1**) following a literature protocol [8]. According to the literature [9,10], aromatic triketone was prepared by the Claisen condensation of methyl benzoate and dilithioacetylacetone, and the *ortho*-hydroxyl aromatic triketone could spontaneously form the cyclic hemiketal. Herein, intermediate **2** was reacted with bromomethyl methyl ether (MOMBr) to form MOM ether **2a** [11], and then **4a** was obtained through Claisen condensation of **2a** and acetylacetone (**3**) in the presence of lithium diisopropylamide (LDA) in anhydrous tetrahydrofuran (THF). We expected deprotection of MOM ether **4a** to give *ortho*-hydroxyl aromatic polyketide and further producing violacin A. Unfortunately, violacin A was not obtained, but the dehydration product of violacin A (**4b**) was detected in the reaction system. We speculated that the dehydration of violacin A happened in the acidic condition after deprotection of **4a** using 1 *N* HCl. Considering the hemiacetal hydroxyl of violacin A was easily eliminated to form a conjugated double bond with the carbonyl group at C-4 under acidic conditions, benzyl group was introduced to protect free phenolic hydroxyl. Intermediate **2** treated with benzyl chloride and anhydrous potassium carbonate ($K_2CO_3$) in refluxing acetonitrile to get benzyl ether **2b** [12]. And then **4c** was obtained through Claisen condensation of **2b** and acetylacetone (**3**) in the presence of LDA in anhydrous THF. In particular, the $^1$H NMR and $^{13}$C NMR spectrum of **4c** revealed it's a mixture of tautomers containing one bisenol, two monoenol and one unenolized triketone tautomer (Figure S11, S12) according to literature [10]. Finally, violacin A was successfully obtained while the benzyl was removed by catalytic hydrogenation of **4c** in ethanol at room temperature (Scheme 3).

In order to further investigate the effect of 7-*O*-substituent in the molecule on anti-inflammatory activity, we designed analogues **7a-7p**, structurally characterized by different aliphatic amine, alkyl alcohol and phenol moieties linked to the C-7 position of molecule by 2-oxy-acetyl group. To accomplish this, acylation of relevant amines **5a-5j**, phenols **5 k–5 m** or alcohols **5n–5o** with bromoacetyl bromide in the presence of triethylamine in anhydrous dichloromethane (DCM) at 0 °C provided the intermediate **6a-6o** [13,14]. Subsequently, 2-bromoacetamide and 2-bromoacetate further etherification with violacin A in the presence of anhydrous $K_2CO_3$ in acetone at 45 °C to give analogues **7a-7p** (Scheme 4).

To explore the role of alkyl side chain at C-2 in the anti-inflammatory effect, analogues **16a-16i** were prepared using the similar synthetic approach for violacin A (Scheme 5). The Frise rearrangement of orcinol (**8**) was catalyzed by boron trifluoride etherate in acetic acid to form 2,4-dihydroxy-6-methyl phenylacetone (**9**) [15], which treated with benzyl chloride and anhydrous $K_2CO_3$ in refluxing acetonitrile to provide the benzyl ether **10**. At the same time, acetals **12a-12f** were constructed by the etherification of phenols **11a-11f** and 2-(2-bromoethyl)-1,3-dioxolane in the presence of anhydrous $K_2CO_3$ in N,*N*-Dimethylformamide (DMF) at 65 °C [16]. Acetals **12a-12f** were easily hydrolyzed in acetic acid aqueous solution at 45 °C to produce aldehydes **13a-13f** [17]. Simultaneously, β-hydroxyketones **14a-14i** were prepared by Aldol reaction of **10** and relevant aldehyde (**13a-13f**, butyraldehyde, pentanal or hexanal) with LDA in anhydrous THF at −78 °C. Afterwards, **14a-14i** underwent oxidation by Dess-Martin periodinane in anhydrous DCM at 0 °C to give 1, 3-diketone **15a-15i** [18]. Just like that of **4c**, **15a-15i** were the mixture of keto-enol tautomers according to their $^1$H and $^{13}$C NMR spectra (Figure S111-S128). Finally, the catalytic hydrogenation of **15a-15i** in ethanol at room temperature afforded analogues **16a-16i**.

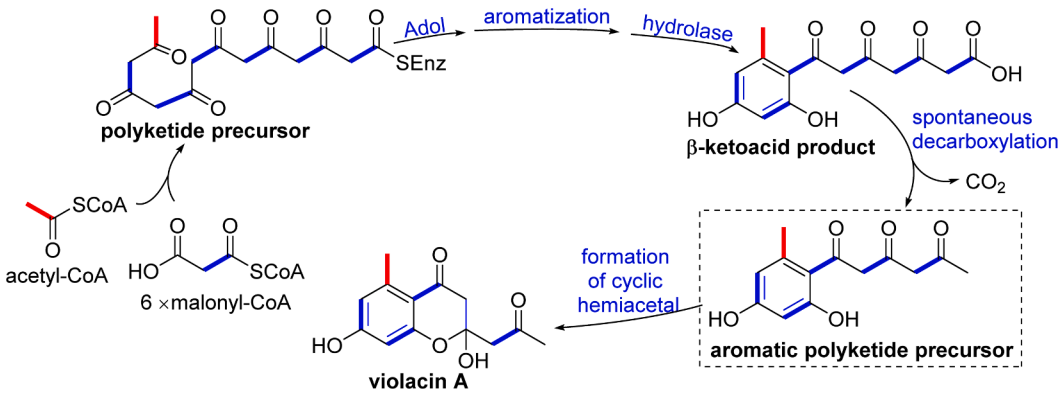
### 2.2. Biological evaluation

#### 2.2.1. NO production inhibition in LPS-induced RAW 264.7 cells

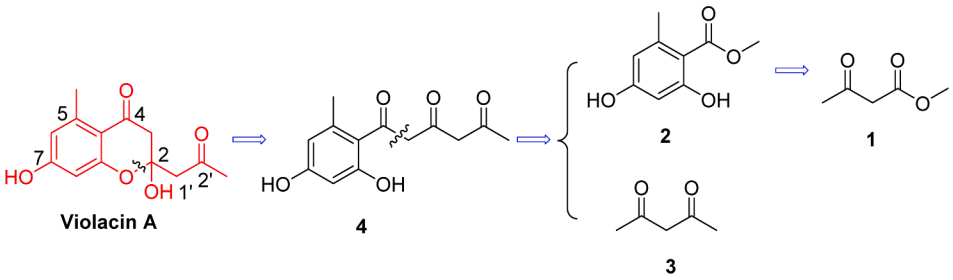
In order to avoid the false positive results in anti-inflammatory evaluation, cytotoxicity of the synthesized molecules against RAW 264.7 cells was measured by MTT assay. As shown in Fig. 1A, all of synthesized analogues had not obviously cytotoxicity against RAW264.7 cells, except for compounds **7m** and **16e**.

As a significant pro-inflammatory mediator, the production of NO in LPS-stimulated Raw264.7 cells was used to evaluate the anti-inflammatory activity of compound [19,20]. Here, the inhibitory effect of all synthetic analogues without cytotoxicity on production of NO were measured by Griess method, and dexamethasone (DXM) was selected as a positive control. The results indicated that **7b**, **7e**, **7n**, **16b**, **16c**, and **16f-16i** presented comparable inhibitory activity against NO production to that of violacin A. In particular, **7a**, **7d**, **16a**, and **16d** had stronger inhibitory activities against NO production than violacin A (Fig. 1B). The further investigation also demonstrated that the anti-inflammatory effect of **7a** and **16d** were dose-dependent (Fig. 1C, D).

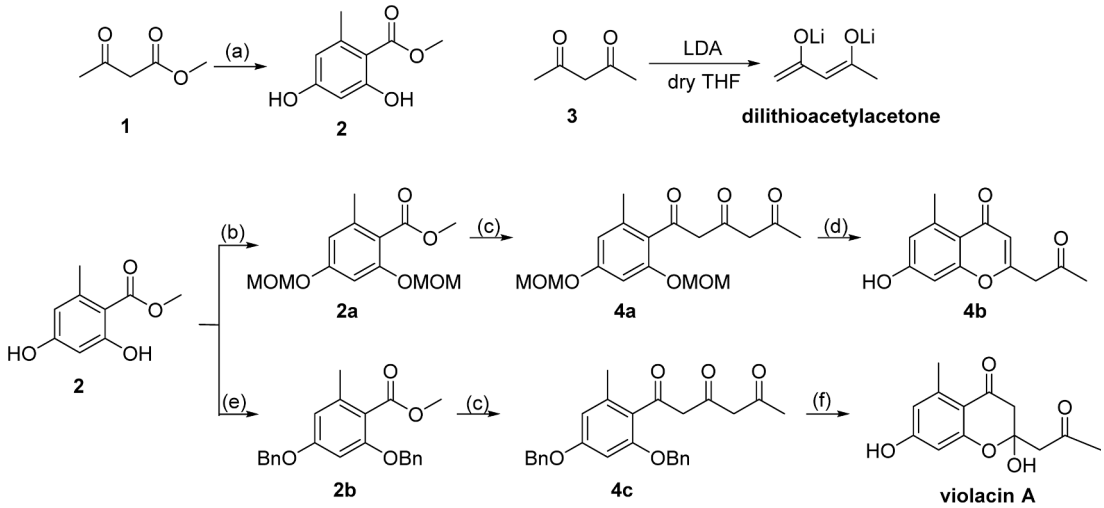
Among the 7-*O*-substituted analogues, anti-inflammatory activities of molecules with linear aliphatic amine moieties were obviously superior to that of analogues with cycloaliphatic amine moieties (**7a-7e** *vs.* **7f-7j**). However, the introduction of extra phenol or alcohol units obviously decreased the anti-inflammatory effect (**7k**, **7l**, **7o** and **7p**), except for **7n**. Analogues **16g-16i** showed the similar activities as that of violacin A. The results indicated that the carbonyl group at the side-chain was not necessary for anti-inflammatory activity. Meanwhile, all of the analogues (**16a-16d** and **16f**) with aromatic ether moieties




**Scheme 1.** Proposed biosynthetic pathway of violacin A.




**Scheme 2.** Retrosynthetic analysis of violacin A.




**Scheme 3.** Total synthesis of violacin A. Reagents and conditions: (a) NaH (1.3 eq.), LDA (0.95 eq.), anhydrous THF, -78 °C to 0 °C to r.t., 17 h, reflux, 26 h; (b) MOMBr (2.2 eq.), NaH (3.0 eq.), anhydrous THF, 0 °C, 1 h; (c) acetylacetone (**3**, 2.0 eq.), LAD (4.0 eq.), anhydrous THF, 0 °C to r.t., 12 h; (d) 1*N* HCl/MeOH (v/v 1:2), r.t., 5 h; (e) BnCl (2.1 eq.), $K_2CO_3$ (3.0 eq.), MeCN, reflux, 2.5 h; (f) $H_2$, 5 % Pd/C (w/w 5:1), EtOH, r.t., 2.5 h.

instead of ketone group at side chain presented the comparative or superior activity compared with that of violacin A. Notably, aromatic ether moiety with an electron-withdrawing substituent dramatically improved the anti-inflammatory activity of the molecules (**16d** *vs.* **16b**, **16c**).

### *2.2.2. **7a** and **16d** suppresses LPS-induced NF-κB signaling pathway activation*

The NF-κB signaling pathway plays a critical role in the occurrence and process of inflammation [2]. The phosphorylation of IκB-α could alleviate its inhibitory effects on the activities of NF-κB, which resulted in the translocation of NF-κB p65 subunit to the nucleus, leaded to the transcriptional synthesis of pro-inflammatory genes, such as NO by upregulating the expression of inducible nitric synthase (iNOS). The phosphorylation of p65 subunit was closely associated with the transcriptional activity of NF-κB [21–23]. To further confirm anti-inflammatory potential of synthesized analogues, the effects of **7a** and **16d** on the regulation of NF-κB signaling pathway and expression of iNOS were further investigated. As shown in Fig. 2 (A-D and G-J), phosphorylations of IκB-α and p65 were significantly inhibited in LPS-stimulated Raw 264.7 cells after **7a** or **16d** treatment. In the meantime, the amount of intracellular iNOS significantly decreased in the **7a** or **16d**-treated cells (Fig. 2 E, F, K and L). The results indicated that **7a** and **16d** effectively inhibited LPS-stimulated NF-κB activation and reduced the expression level of iNOS.

## 3. Conclusions

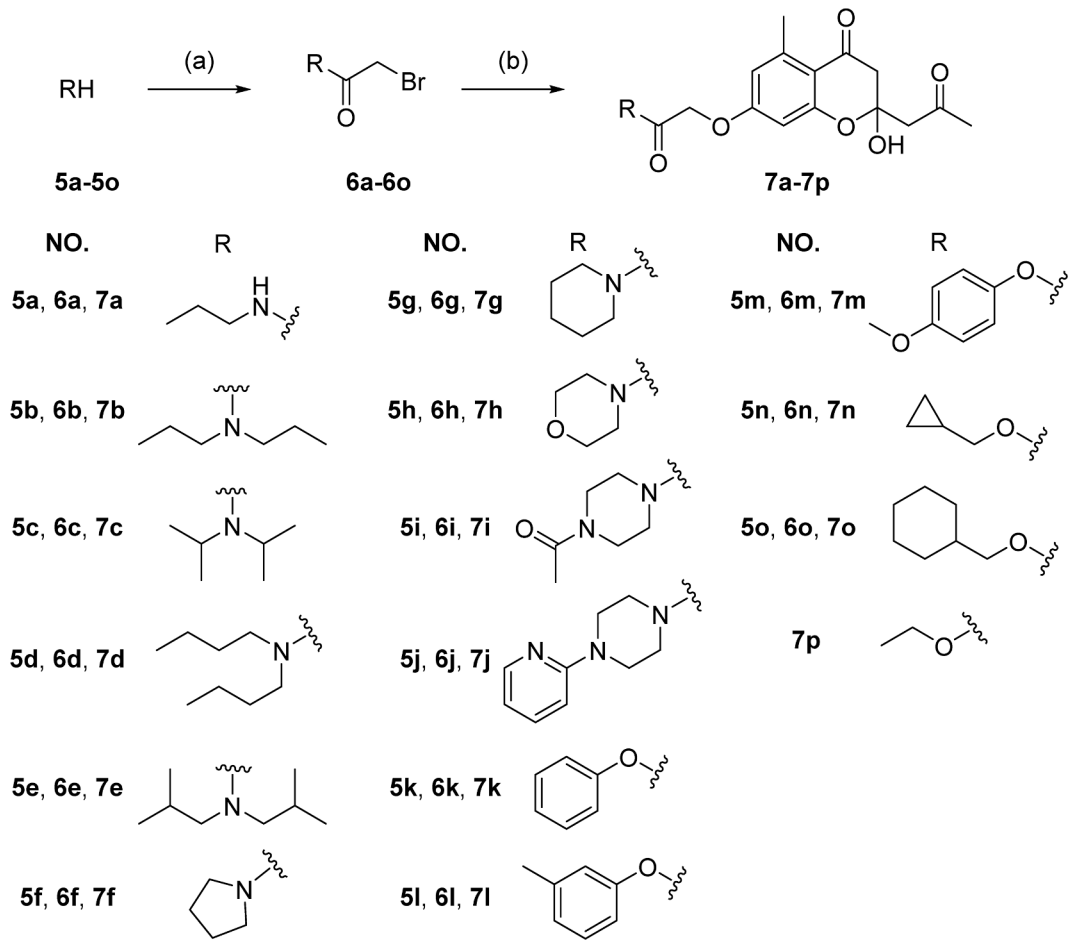
In summary, we described a biomimetic synthetic strategy of violacin A, which greatly shortened the reaction period and increased the overall yield to 42%. Meanwhile, twenty-five analogues of violacin A were designed and synthesized by the similar strategy. Among analogues, **7a**, **7d**, **16a** and **16d** revealed stronger inhibitory activities against NO production than that of violacin A. The SAR analysis demonstrated that the carbonyl group at the side-chain was not critical for the activity. The introduction of aliphatic amine moieties at C-7 position or aromatic ether moiety with an electron-withdrawing substituent at the side chain could significantly enhance the anti-inflammatory activity. Furthermore, the anti-inflammatory effect of synthesized analogues **7a** and **16d** was closely related with the inhibition of NF-κB signaling pathway in RAW 264.7 cells. NF-κB signaling pathway had been widely recognized as a promising therapeutically-relevant biological target in the therapy of inflammatory diseases. **7a** and **16d** could be further explored as novel anti-inflammatory candidates by *in vivo* investigation.

## 4. Material and methods

### *4.1. Chemisty*

All reagents were purchased from commercial suppliers. Reactions requiring anhydrous conditions were carried out under an inert atmosphere of dry nitrogen. Fresh THF was obtained by distillation over sodium wire using benzophenone as indicator. DCM was freshly distilled from calcium hydride.

All reactions were monitored by using thin layer chromatography (TLC) which was performed on Merck Silica Gel 60 $F_{254}$ plates, TLC were visualized by UV radiation (254 nm) or stained by exposure to an ethanolic solution of concentrated sulfuric acid and anisaldehyde. Silica gel (300–400 mesh, Qingdao Marine Chemical Ltd., Qingdao, China)




**Scheme 4.** Synthesis of violacin A analogues **7a-7p**. Reagants and conditions: (a) Bromoacetyl bromide (1.2 eq.), $Et_3N$ (1.5 eq.), anhydrous $CH_2Cl_2$, 0 °C, 0.5 h; (b) Violacin A (0.67 eq.), $K_2CO_3$ (1.33 eq.), Acetone, 45 °C, 4 h.

was used for the flash chromatography separations. $^1$H NMR (600 MHz) and $^{13}$C NMR (150 MHz) spectra were measured on a Bruker AV-600 spectrometer using tetramethylsilane as internal standard in deuteriated chloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO-$d_6$). The coupling constants (*J*) were expressed in Hertz (Hz), signal multiplicity was designed as s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, hept = heptet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets, brq = broad quintet. HRESIMS were measured with an Agilent G6230 TOF mass spectrometer.

#### 4.1.1. General procedure *A*: Synthesis of benzyl ether

The mixed solution of corresponding resorcinol (1.0 equiv.), benzyl chloride (2.1 equiv.) and anhydrous $K_2CO_3$ (3.0 equiv.) in acetonitrile was stirred for 2.5 h at 85 °C. Upon completion of the reaction, the mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was diluted with water and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $Na_2SO_4$, after filtration, concentrated *in vacuo*. The residual oil was pulped with *n*-hexane, filtered with a Buchner funnel and the filter cake was washed with *n*-hexane to provide the desired product.

#### 4.1.2. General procedure *B*: Catalytic hydrogenation to remove benzyl

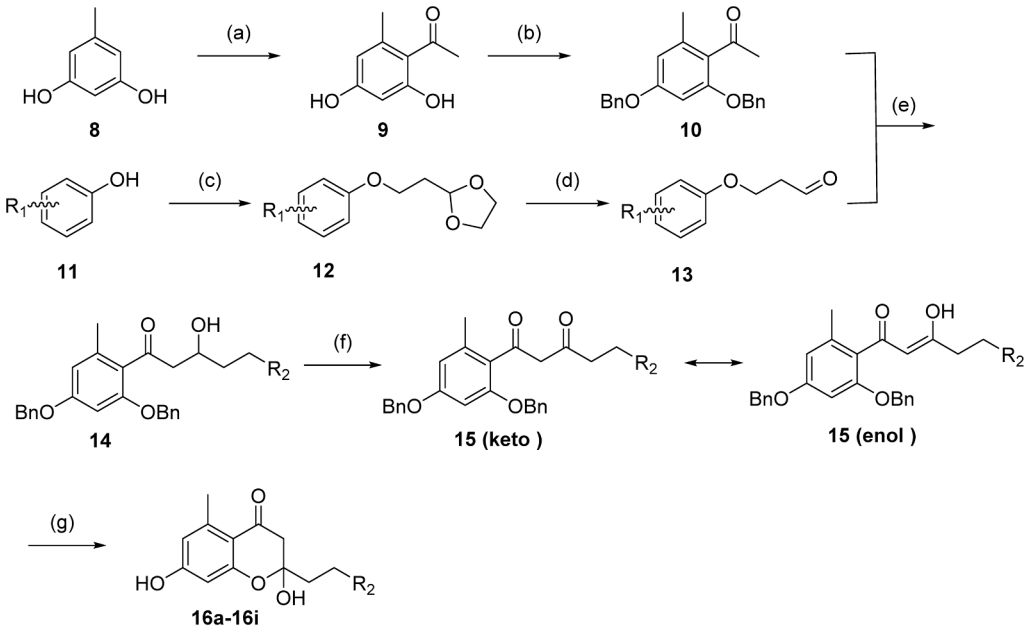
A mixture of benzyl ether and 5% Pd/C (20 wt%) in ethanol was stirred under 1 atmosphere of $H_2$ gas at room temperature for 2.5 h. And then the reaction mixture was filtered with a Buchner funnel and the residue was washed with ethanol. The filtrate was concentrated under reduced pressure and the resulting residue was diluted with water and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $Na_2SO_4$. After filtration, the solvent was removed in a rotary evaporator to give residual yellow oil. Purification of the crude product by flash chromatography column afforded the desired product.

#### 4.1.3. General procedure *C*: Synthesis of aromatic polyketide

According to the literature [10], the solution of LDA (4.0 equiv.) was added dropwise to the solution of acetylacetone (2.0 equiv.) in anhydrous THF at −10 °C under an atmosphere of $N_2$. After stirring for 30 min, the solution of methyl benzoate (1.0 equiv.) in anhydrous THF was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and allowed to warm to room temperature with stirring for 12 h. Upon completion of the reaction, the solution was quenched with a saturated aqueous solution of $NH_4Cl$ at 0 °C and the organic layer was separated. Aqueous layer was diluted with brine and extracted three times with ethyl acetate. The combined organic layers were dried over $Na_2SO_4$, after filtration, eliminated under reduced pressure. The residue was purified by silica gel column chromatography.

#### 4.1.4. Methyl 2,4-dihydroxy-6-methylbenzoate (*2*)

According to the literature [8], to a suspension of NaH (9.64 g, 60%, 223.6 mmol) in anhydrous THF (100 mL) was added dropwise a solution of methyl acetoacetate (20.00 g, 172.0 mmol) in anhydrous THF (50 mL) at 0 °C under an atmosphere of $N_2$. After stirring for 1 h, the reaction mixture was cooled to −78 °C and LDA (2.0 M solution in THF, 81.7 mL, 163.4 mmol) was added dropwise and stirred for 30 min. After that, the




| NO. | $R_1$ |
|---|---|
| **11a**, **12a**, **13a**: | H |
| **11b**, **12b**, **13b**: | 3-methly |
| **11c**, **12c**, **13c**: | 4-methoxy |
| **11d**, **12d**, **13d**: | 3-trifluoromethyl |
| **11e**, **12e**, **13e**: | 4-trifluoromethyl |
| **11f**, **12f**, **13f**: | 3-fluoro |

| NO. | $R_2$ |
|---|---|
| **14a**, **15a**, **16a**: | phenoxy |
| **14b**, **15b**, **16b**: | 3-methylphenoxy |
| **14c**, **15c**, **16c**: | 4-methoxyphenoxy |
| **14d**, **15d**, **16d**: | 3-trifluoromethylphenoxy |
| **14e**, **15e**, **16e**: | 4-trifluoromethylphenoxy |
| **14f**, **15f**, **16f**: | 3-fluorophenoxy |
| **14g**, **15g**, **16g**: | methyl |
| **14h**, **15h**, **16h**: | ethyl |
| **14i**, **15i**, **16i**: | propyl |

**Scheme 5.** Synthesis of violacin A analogues **16a-16i**. Reagants and conditions: (a) $BF_3$-$Et_2O$ (1.5 eq.), AcOH (10.0 eq.), 3 Å molecular sieve, 90 °C, 24 h; (b) BnCl (2.1 eq.), $K_2CO_3$ (3.0 eq.), MeCN, reflux, 2.5 h; (c) 2-(2-bromoethyl)-1,3-dioxolane (1.1 eq.), $K_2CO_3$ (2.0 eq.), DMF, 65 °C, overnight; (d) AcOH/$H_2O$ (v/v 4:1), 45 °C, 5 h; (e) LAD (2.0 eq.), anhydrous THF, -78 °C, overninght; (f) Dess-Martin reagent (1.3 eq.), anhydrous $CH_2Cl_2$, 0 °C, 2 h; (g) $H_2$, 5 % Pd/C (w/w 5:1), EtOH, r.t., 2.5 h.

mixture was stirred 17 h at room temperature and then was allowed to warm up 85 °C for additional 26 h. Upon completion of the reaction, the solution was acidified with 2 *N* HCl till pH 2–3 at 0 °C and the organic layer was separated. Aqueous layer was diluted with brine (50 mL) and extracted with ethyl acetate (3 × 100 mL), combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography column (Petroleum ether/EtOAc, 8:1) to afford compound **2** as a light-yellow solid (11.78 g, 75.1%). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 11.79 (s, 1H), 6.28 (d, $J$ = 2.5 Hz, 1H), 6.23 (d, $J$ = 2.5 Hz, 1H), 5.55 (brs, 1H), 3.93 (s, 3H), 2.49 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 172.15, 165.25, 160.27, 144.02, 111.35, 105.62, 101.24, 51.93, 24.30.

### 4.1.5. *Methyl 2,4-bis(methoxymethoxy)-6-methylbenzoate (**2a**)*

To a solution of compound **2** (910 mg, 5.0 mmol) in anhydrous THF (10 mL) was added slowly NaH (600 mg, 60%, 15.0 mmol) at −10 °C. After stirring for 15 min, the solution of bromomethyl methyl ether (1.37 g, 11.0 mmol) in anhydrous THF (15 mL) was added dropwise, and then the mixture was stirred for 1 h. Upon completion of the reaction, the mixture was quenched with a saturated aqueous solution of $NH_4Cl$ (5 mL) and the organic layer was separated. Aqueous layer was diluted with brine (10 mL) and extracted with ethyl acetate (3 × 15 mL), combined organic layers were dried over $Na_2SO_4$, after filtration, eliminated under reduced pressure. The crude product was purified by flash chromatography column (petroleum ether/EtOAc, 40:1) to afford the tittle compound as a yellow oil (1.24 g, 91.8%). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 6.67 (d, $J$ = 1.9 Hz, 1H), 6.55 (d, $J$ = 1.9 Hz, 1H), 5.15 (s, 2H), 5.15 (s, 2H), 3.89 (s, 3H), 3.47 (s, 3H), 3.46 (s, 3H), 2.28 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 168.50, 158.72, 155.39, 138.03, 118.48, 110.67, 101.25, 94.78, 94.23, 56.20, 56.11, 52.07, 19.81.

### 4.1.6. *1-[2,4-bis(methoxymethoxy)-6-methylphenyl]-1,3,5-hexanetrione (**4a**)*

The tittle compound was synthesized as described in the general procedure **C** using LDA (2.0 M solution in THF, 4 mL, 8.0 mmol), acetylacetone (400 mg, 4.0 mmol) and **2a** (540 mg, 2.0 mmol) in anhydrous THF (4 mL). The crude product was purified by flash chromatography column (petroleum ether/EtOAc, 10:1) to afford the tittle compound as a yellow oil (174 mg, 51.5%). The mixture of keto-enol tautomers containing approximately 31.3% 1′,5′-bisenol tautomer (I), 31.3% 1′-monoenol tautomer (II), 31.3% 5′-monoenol tautomer (III) and 6.1% unenolized triketone tautomer (IV). The ratio of tautomer was calculated by characteristic proton signals in $^1$H NMR according to the literature [10]. $^1$H NMR (600 MHz, Chloroform-*d*), tautomer I: $\delta$ 5.78 (s, 1H), 5.64 (s, 1H), 2.30 (s, 3H), 2.01 (s, 3H); II: $\delta$ 5.33 (s, 1H), 2.32 (s, 3H), 2.27 (s, 3H); III: $\delta$5.23 (s, 1H), 3.82 (s, 2H), 2.30 (s, 3H), 2.06 (s, 3H); IV: $\delta$ 4.30 (s, 2H), 3.77 (s, 2H), 2.28 (s, 3H), 2.27 (s, 3H).

### 4.1.7. *7-hydroxy-5-methyl-2-(2-oxopropyl)-4H-1-benzopyran-4-one (**4b**)*

To a solution of compound **4a** (200 mg, 0.6 mmol) in methanol (4 mL) was added 1 *N* HCl (2 mL) at room temperature. After stirring 2 h, the solution was concentrated under reduced pressure, and then the resulting residue was diluted with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with

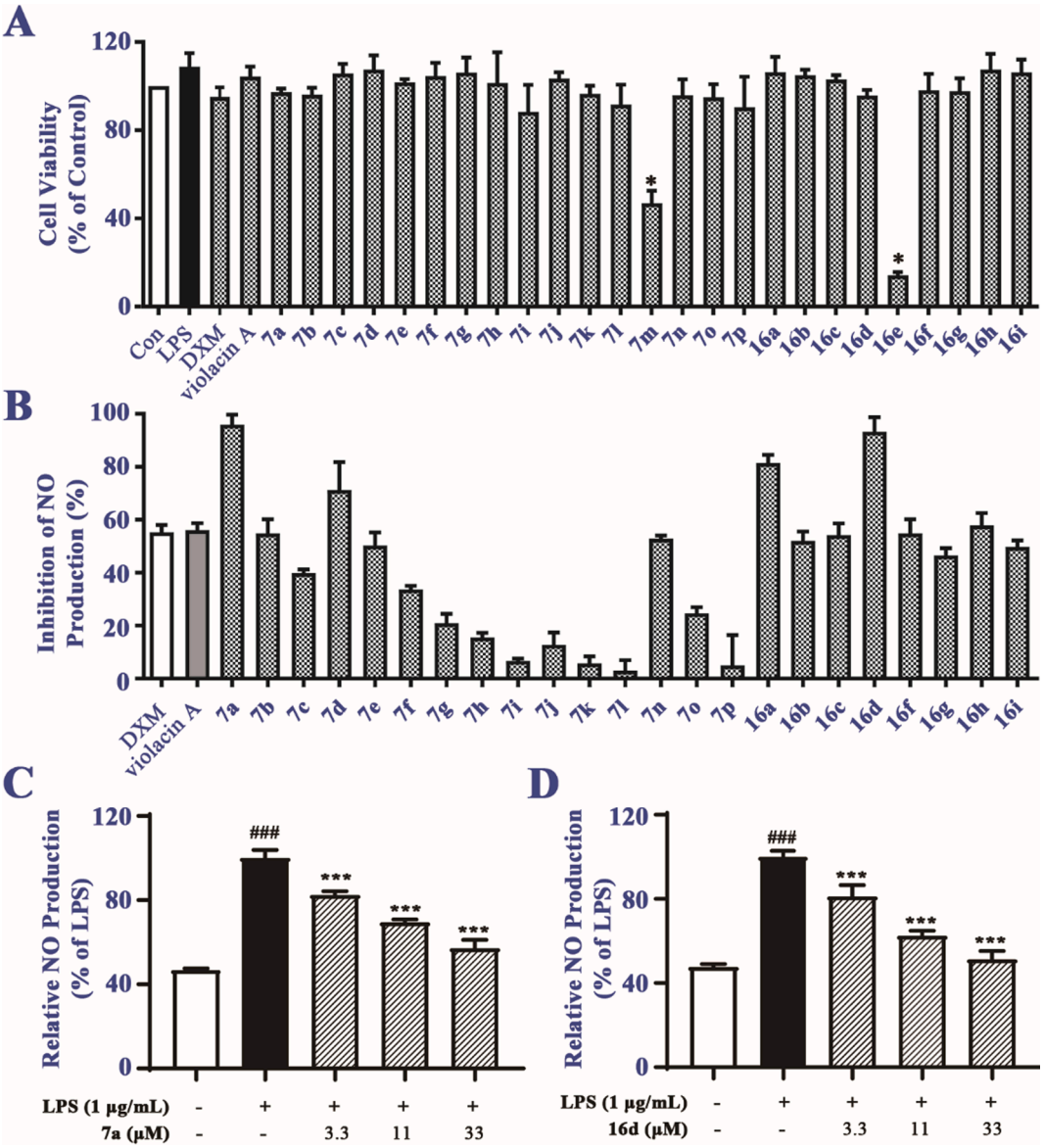



**Fig. 1.** The cell viability and anti-inflammatory activity in LPS-induced RAW264.7 cells. (**A**) The cell viability was evaluated by MTT assay. (**B**) The production of NO was determined by Griess method. RAW264.7 cells were pretreated with synthetic molecule (33 μM) for 2 h and were stimulated by LPS (1 μg / mL) for 24 h, and then the cell supernatant was collected to detect NO release. (C, D) RAW264.7 cells were pretreated with different concentrations (0, 3.3, 11, and 33 μM) of **7a** and **16d** for 2 h and then stimulated with or without LPS (1 μg/mL) for 24 h. The data show means ± SD values of three independent experiments (* $p < 0.05$ *vs.* control group; ### $p < 0.001$ *vs.* control group; *** $p < 0.001$ *vs.* LPS group).

brine, dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography column (petroleum ether/EtOAc, 8:1) to afford the tittle compound as a yellow oil (98 mg, 71.4%). $^1$H NMR (600 MHz, DMSO-*d*) $\delta$ 10.60 (s, 1H), 6.63 (d, $J = 2.3$ Hz, 1H), 6.60 (d, $J = 2.3$ Hz, 1H), 6.05 (s, 1H), 3.86 (s, 2H), 2.66 (s, 3H), 2.22 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-*d*) $\delta$ 207.99, 183.34, 166.23, 165.76, 164.41, 146.79, 121.89, 119.55, 118.07, 105.77, 52.59, 35.06, 27.64.

#### 4.1.8. *Methyl 2,4-bis(benzyloxy)-6-methylbenzoate (**2b**)*

Followed general procedure **A**, compound **2** (3.00 g, 16.5 mmol), benzyl chloride (4.38 g, 34.6 mmol) and anhydrous $K_2CO_3$ (6.83 g, 49.4 mmol) in acetonitrile (100 mL) gave the tittle compound as a white solid (5.41 g, 95.0%). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.41 – 7.28 (m, 10*H*), 6.43 (d, $J = 2.1$ Hz, 1H), 6.43 (d, $J = 2.1$ Hz, 1H), 5.06 (s, 2H), 5.02 (s, 2H), 3.87 (s, 3H), 2.30 (s, 3H). $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 168.65, 160.36, 157.20, 138.38, 136.69, 136.48, 128.62 (2 × C), 128.47 (2 × C), 128.10, 127.75, 127.49 (2 × C), 126.83 (2 × C), 117.08, 108.11, 98.45, 70.37, 70.04, 52.02, 19.95.

#### 4.1.9. *1-[2,4-bis(benzyloxy)-6-methylphenyl]-1,3,5-hexanetrione (**4c**)*

The tittle compound was synthesized as described in the general procedure **C** using LDA (2.0 M solution in THF, 27.6 mL, 55.2 mmol), acetylacetone (2.76 g, 27.6 mmol) and **2b** (5.00 g, 13.8 mmol) in anhydrous THF (56 mL). The crude product was purified by flash chromatography column (petroleum ether/EtOAc, 8:1) to afford the tittle compound as a yellow oil (3.23 g, 54.4%). The mixture of keto-enol tautomers containing approximately 31.3% 1′,5′-bisenol tautomer (I), 31.3% 1′-monoenol tautomer (II), 31.3% 5′-monoenol tautomer (III) and 6.1% unenolized triketone tautomer (IV). The ratio of tautomer was caculated by characteristic proton signals in $^1$H NMR according to the literature [10]. $^1$H NMR (600 MHz, Chloroform-*d*), tautomer I: $\delta$ 5.84 (s, 1H), 5.40 (s, 1H), 2.33 (s, 3H), 1.96 (s, 3H); II: $\delta$ 5.39 (s, 1H), 3.38 (s, 2H), 2.34 (s, 3H), 2.18 (s, 3H); III: $\delta$5.21 (s, 1H), 3.78 (s, 2H), 2.28 (s,

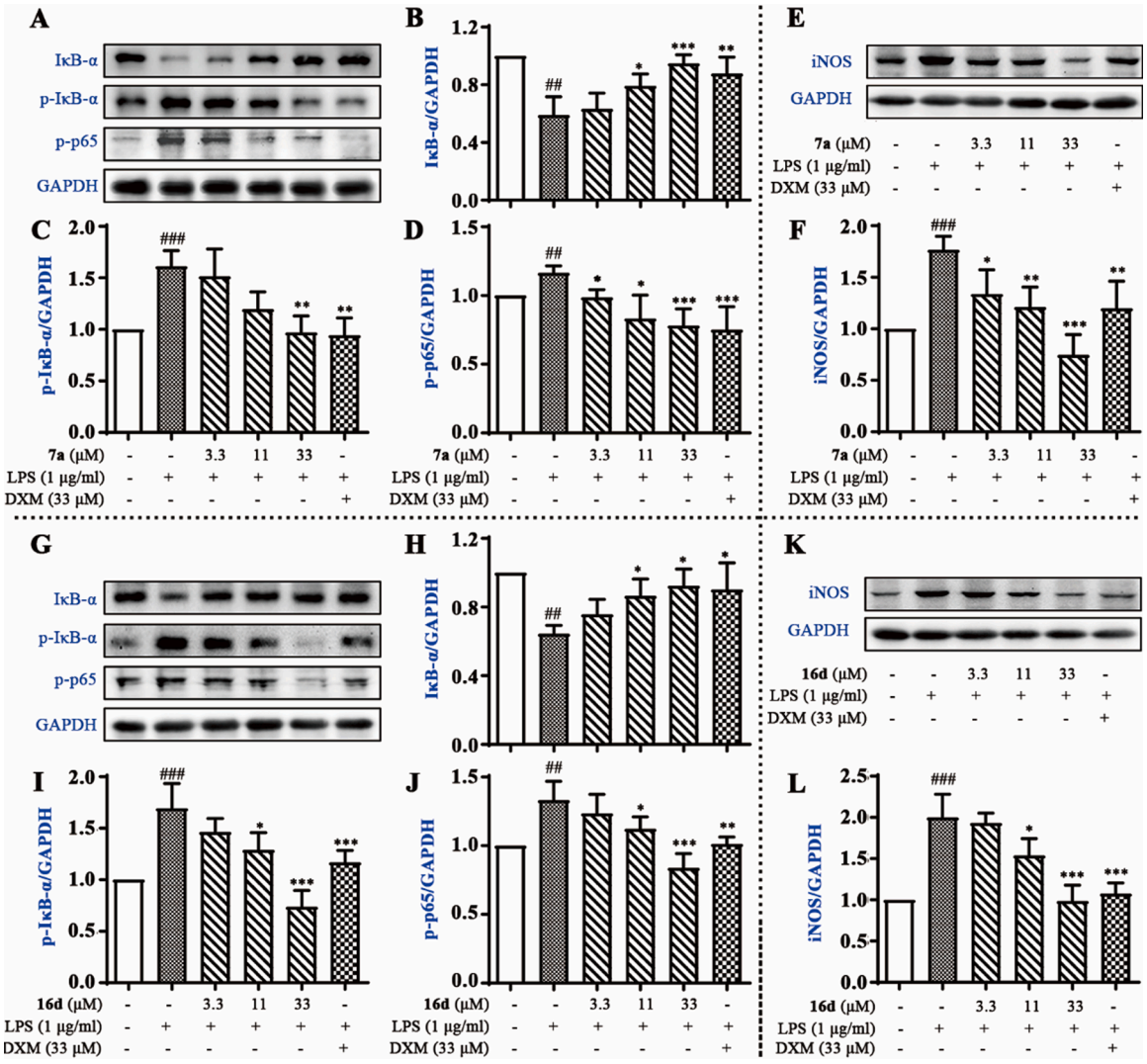



**Fig. 2.** **7a** and **16d** inhibited NF-κB activation and iNOS expression in LPS-induced RAW 264.7 cells. RAW 264.7 cells were pretreated with the different concentrations (0, 3.3, 11 and 33 μM) of **7a** (A-F) and **16d** (G-L) for 2 h, then stimulated with or without LPS (1 μg/mL) for 30 min or 24 h (for iNOS protein). IκB-α, p-IκB-α, p-p65 and iNOS were analyzed by Western blot. The data show means ± SD values of three independent experiments. (## $p < 0.01$, ###$p < 0.001$ *vs.* control group; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs.* LPS group).

3H), 2.01 (s, 3H); IV: $\delta$ 4.00 (s, 2H), 3.49 (s, 2H), 2.28 (s, 3H), 2.14 (s, 3H).

#### 4.1.10. *Violacin a*

The tittle compound was synthesized as described in the general procedure **B** using compound **4a** (2.00 g) and 5% Pd/C (400 mg, 20 wt %) in ethanol (20 mL). Purification by flash column chromatography ($CH_2Cl_2$/MeOH, 8:1) afforded target compound as a yellow powder (1.09 g, 95.2% yield). $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 10.35 (s, 1H), 7.08 (d, $J$ = 2.1 Hz, 1H), 6.25 (d, $J$ = 2.3 Hz, 1H), 6.14 (d, $J$ = 2.3 Hz, 1H), 3.04 (dd, $J$ = 16.0, 2.1 Hz, 1H), 3.03 (d, $J$ = 15.0 Hz, 1H), 2.98 (d, $J$ = 15.0 Hz, 1H), 2.61 (d, $J$ = 16.0 Hz, 1H), 2.45 (s, 3H), 2.19 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 205.58, 191.03, 163.13, 161.33, 142.87, 113.03, 112.34, 101.99, 100.28, 52.75, 47.91, 32.33, 23.03. HRMS (ESI) *m/z* calcd for $C_{13}H_{14}O_5$ $[M + H]^+$ 250.0841, found 251.0927.

#### 4.1.11. *Synthesis of compounds* ***6a-6o***

General procedure: The substituted amine, phenol or alcohol (**5a-5o**, 5.0 mmol) was dissolved in anhydrous DCM (10 mL) and triethylamine (756 mg, 7.5 mmol) was added at 0 °C. After that the solution of bromoacetyl bromide (1.21 g, 6.0 mmol) in anhydrous DCM (5 mL) was gradually added. The reaction mixture was stirred for 1.5 h and then the saturated aqueous solution of $NaHCO_3$ (15 mL) was added, extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography column to provide compound **6a-6o**.

*4.1.11.1. 2-bromo-N-propylacetamide (**6a**).* The tittle compound was synthesized as described in the general procedure using propylamine (295 mg, 5.0 mmol). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 50:1) to afford the desired product as a light yellow oil (587 mg, 65.3% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 6.52 (brs, 1H), 3.88 (s, 2H), 3.25 (q, $J$ = 7.0 Hz, 2H), 1.57 (sext, $J$ = 7.0 Hz, 2H), 0.94 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 165.23, 41.89, 29.42, 22.57, 11.28.

*4.1.11.2. 2-bromo-N,N-dipropylacetamide (**6b**).* The tittle compound was synthesized as described in the general procedure using dipropylamine (505 mg, 5.0 mmol). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 80:1) to afford the desired product as a light yellow oil (794 mg, 71.6% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 3.84 (s, 2H), 3.29 (t, $J$ = 7.8 Hz, 2H), 3.26 (t, $J$ = 7.8 Hz,

2H), 1.64 (sext, $J = 7.5$ Hz, 2H), 1.57 (sext, $J = 7.5$ Hz, 2H), 0.94 (t, $J = 7.5$ Hz, 3H), 0.89 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 166.43, 50.41, 47.69, 26.50, 22.33, 20.47, 11.24 (2 × C).

*4.1.11.3. 2-bromo-N,N-bis(1-methylethyl)acetamide* ***(6c)***. The tittle compound was synthesized as described in the general procedure using diisopropylamine (505 mg, 5.0 mmol). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 80:1) to afford the desired product as a light yellow oil (746 mg, 67.3% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 3.95 (hept, $J = 6.8$ Hz, 1H), 3.81 (s, 2H), 3.47 – 3.38 (m, 1H), 1.38 (d, $J = 6.8$ Hz, 6H), 1.25 (d, $J = 6.8$ Hz, 6H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 165.31, 50.44, 46.25, 28.75, 20.67 (2 × C), 20.09 (2 × C).

*4.1.11.4. 2 2-bromo-N,N-dibutylacetamide* ***(6d)***. The tittle compound was synthesized as described in the general procedure using dibutylamine (645 mg, 5.0 mmol). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 30:1) to afford the desired product as a light yellow oil (768 mg, 61.5% yield).$^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 3.83 (s, 2H), 3.31 (t, $J = 7.7$ Hz, 2H), 3.28 (t, $J = 7.7$ Hz, 2H), 1.59 (quint, $J = 7.7$ Hz, 2H), 1.52 (quint, $J = 7.7$ Hz, 2H), 1.38 – 1.28 (m, 4H), 0.96 (t, $J = 7.4$ Hz, 3H), 0.92 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 166.27, 48.55, 45.92, 31.27, 29.36, 26.53, 20.10 (2 × C), 13.89, 13.80.

*4.1.11.5. 2-bromo-N,N-bis(2-methylpropyl)acetamide* ***(6e)***. The tittle compound was synthesized as described in the general procedure using diisobutylamine (645 mg, 5.0 mmol). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 50:1) to afford the desired product as a light yellow oil (789 mg, 63.1% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 3.86 (s, 2H), 3.19 (d, $J = 7.6$ Hz, 2H), 3.14 (d, $J = 7.6$ Hz, 2H), 2.08 – 2.00 (m, 1H), 1.97 – 1.89 (m, 1H), 0.93 (d, $J = 6.7$ Hz, 6H), 0.89 (d, $J = 6.7$ Hz, 6H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 167.20, 56.22, 52.99, 27.89, 26.75, 26.35, 20.08 (2 × C), 20.05 (2 × C).

*4.1.11.6. 2-bromo-1-(1-pyrrolidinyl)ethanone* ***(6f)***. The tittle compound was synthesized as described in the general procedure using pyrrolidine (355 mg, 5.0 mmol). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 40:1) to afford the desired product as a light yellow oil (704 mg, 73.4% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 3.80 (s, 2H), 3.52 (t, $J = 6.8$ Hz, 2H), 3.49 (t, $J = 7.0$ Hz, 2H), 2.00 (quint, $J = 6.8$ Hz, 2H), 1.89 (quint, $J = 6.9$ Hz, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 165.07, 47.08, 46.45, 27.39, 26.17, 24.33.

*4.1.11.7. 2-bromo-1-(1-piperidinyl)ethanone* ***(6 g)***. The tittle compound was synthesized as described in the general procedure using piperidine (425 mg, 5.0 mmol). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 40:1) to afford the desired product as a light yellow oil (773 mg, 75.1% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 3.86 (s, 2H), 3.55 (t, $J = 5.6$ Hz, 2H), 3.44 (t, $J = 5.1$ Hz, 2H), 1.67 – 1.63 (m, 4H), 1.56 (quint, $J = 5.4$ Hz, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 165.01, 47.92, 43.24, 26.18 (2 × C), 25.36, 24.26.

*4.1.11.8. 2-bromo-1-(4-morpholinyl)ethanone* ***(6 h)***. The tittle compound was synthesized as described in the general procedure using morpholine (435 mg, 5.0 mmol). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 30:1) to afford the desired product as a light yellow oil (720 mg, 69.3% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 3.85 (s, 2H), 3.74 (t, $J = 4.8$ Hz, 2H), 3.69 (t, $J = 4.8$ Hz, 2H), 3.63 (t, $J = 4.8$ Hz, 2H), 3.52 (t, $J = 4.8$ Hz, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 165.41, 66.60, 66.35, 47.15, 42.41, 25.40.

*4.1.11.9. 1-(4-acetyl-1-piperazinyl)-2-bromoethanone* ***(6i)***. The tittle compound was synthesized as described in the general procedure using 1-(1-piperazinyl)ethanone (640 mg, 5.0 mmol). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 20:1) to afford the desired product as a light yellow oil (710 mg, 57.1% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 3.87 (s, 2H), 3.72 – 3.59 (m, 4H), 3.58 – 3.46 (m, 4H), 2.12 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 169.25, 165.59, 46.40, 45.69, 42.05, 41.10, 25.48, 21.37; $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 169.04, 165.32, 46.65, 45.93, 41.85, 40.86, 25.56, 21.39.

*4.1.11.10. 2-bromo-1-[4-(2-pyridinyl)-1-piperazinyl]ethanone* ***(6j)***. The tittle compound was synthesized as described in the general procedure using 1-(2-pyridinyl)-piperazine (957 mg, 5.0 mmol). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 30:1) to afford the desired product as a light yellow oil (649 mg, 45.7% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 8.20 (dd, $J = 5.1$, 1.9 Hz, 1H), 7.52 (ddd, $J = 8.8$, 7.2, 2.0 Hz, 1H), 6.70 – 6.66 (m, 2H), 3.90 (s, 2H), 3.75 (t, $J = 5.4$ Hz, 2H), 3.69 (t, $J = 5.0$ Hz, 2H), 3.64 (t, $J = 5.0$ Hz, 2H), 3.54 (t, $J = 5.4$ Hz, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 165.40, 158.71, 147.74, 137.92, 114.08, 107.43, 46.38, 45.06 (2 × C), 41.75, 25.72.

*4.1.11.11. Phenyl 2-bromoacetate* ***(6 k)***. The tittle compound was synthesized as described in the general procedure using phenol (470 mg, 5.0 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 30:1) to afford the desired product as a light yellow oil (870 mg, 81.0% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.40 (t, $J = 7.9$ Hz, 2H), 7.26 (t, $J = 7.3$ Hz, 1H), 7.12 (d, $J = 7.9$ Hz, 2H), 4.05 (s, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 165.80, 150.38, 129.56 (2 × C), 126.36, 121.06 (2 × C), 25.56.

*4.1.11.12. 3-methylphenyl 2-bromoacetate* ***(6 l)***. The tittle compound was synthesized as described in the general procedure using 3-methylphenol (540 mg, 5.0 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 30:1) to afford the desired product as a light yellow oil (836 mg, 73.1% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.28 (t, $J = 7.8$ Hz, 1H), 7.07 (d, $J = 7.8$ Hz, 1H), 6.94 (d, $J = 2.3$ Hz, 1H), 6.92 (dd, $J = 7.8$, 2.3 Hz, 1H), 4.04 (s, 2H), 2.37 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 165.91, 150.33, 139.85, 129.27, 127.16, 121.62, 117.99, 25.58, 21.31.

*4.1.11.13. 4-methoxyphenyl 2-bromoacetate* ***(6 m)***. The tittle compound was synthesized as described in the general procedure using 4-methoxyphenol (620 mg, 5.0 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 20:1) to afford the desired product as a light yellow oil (988 mg, 80.7% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.04 (d, $J = 9.0$ Hz, 2H), 6.90 (d, $J = 9.0$ Hz, 2H), 4.03 (s, 2H), 3.80 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 166.18, 157.57, 143.88, 121.85 (2 × C), 114.51 (2 × C), 55.59, 25.55.

*4.1.11.14. Cyclopropylmethyl 2-bromoacetate* ***(6n)***. The tittle compound was synthesized as described in the general procedure using cyclopropanemethanol (360 mg, 5.0 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 50:1) to afford the desired product as a light yellow oil (635 mg, 71.4% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 4.01 (d, $J = 7.4$ Hz, 2H), 3.86 (s, 2H), 1.19 – 1.12 (m, 1H), 0.61 – 0.58 (m, 2H), 0.35 – 0.29 (m, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 167.37, 71.15, 26.10, 9.62, 3.34 (2 × C).

*4.1.11.15. Cyclohexylmethyl 2-bromoacetate* ***(6o)***. The tittle compound was synthesized as described in the general procedure using cyclohexylmethanol (571 mg, 5.0 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 50:1) to afford the desired product as a light yellow oil (838 mg, 76.0% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 3.98 (d, $J = 6.6$ Hz, 2H), 3.83 (s, 2H), 1.76 – 1.71 (m, 4H), 1.70 – 1.66 (m, 2H), 1.29 – 1.21 (m, 2H), 1.20 – 1.15 (m,

1H), 1.02 – 0.94 (m, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 167.34, 71.33, 36.97, 29.48 (2 × C), 26.27, 25.96, 25.59 (2 × C).

#### 4.1.12. Synthesis of compounds **7a-7p**

General procedure: The mixed solution of violacin A (100 mg, 0.4 mmol), corresponding **6** or ethyl bromoacetate (0.6 mmol), anhydrous $K_2CO_3$ (110 mg, 0.8 mmol) in acetone (15 mL) was stirred for 5 h at 45 °C. Upon completion of the reaction, the mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was diluted with water (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography column to provide compound **7a-7p**.

##### 4.1.12.1. 2-[[3,4-dihydro-2-hydroxy-5-methyl-2-(2-oxopropyl)-4-oxo-2H-1-benzo- pyran-7-yl]oxy]-N-propyl-acetamide (7a).

The tittle compound was synthesized as described in the general procedure using compound **6a** (108 mg, 0.6 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 2:1) to afford the desired product as a white solid (60 mg, 43.0% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 6.50 (t, $J$ = 6.0 Hz, 1H), 6.40 (d, $J$ = 2.5 Hz, 1H), 6.26 (d, $J$ = 2.5 Hz, 1H), 6.15 (brs, 1H), 4.45 (s, 2H), 3.29 (brq, $J$ = 7.5 Hz, 2H), 3.23 (d, $J$ = 16.7 Hz, 1H), 2.80 (brd, $J$ = 15.9 Hz, 1H), 2.76 (d, $J$ = 15.9 Hz, 1H), 2.73 (d, $J$ = 16.7 Hz, 1H), 2.60 (s, 3H), 2.33 (s, 3H), 1.55 (sext, $J$ = 7.3 Hz, 2H), 0.92 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 209.05, 190.09, 167.26, 161.45, 160.93, 144.24, 114.31, 112.60, 100.93, 100.89, 67.06, 49.35, 48.68, 40.81, 32.27, 23.08, 22.77, 11.31. HRMS (ESI) *m/z* calcd for $C_{18}H_{23}NO_6$ $[M + H]^+$ 350.1598, found 350.1610.

##### 4.1.12.2. 2-[[3,4-dihydro-2-hydroxy-5-methyl-2-(2-oxopropyl)-4-oxo-2H-1-benzo- pyran-7-yl]oxy]-N,N-dipropyl-acetamide (7b).

The tittle compound was synthesized as described in the general procedure using compound **6b** (133 mg, 0.6 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 5:1) to afford the desired product as a white solid (65 mg, 41.6% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 6.41 (d, $J$ = 2.5 Hz, 1H), 6.27 (d, $J$ = 2.5 Hz, 1H), 6.10 (brs, 1H), 4.70 (d, $J$ = 13.6 Hz, 1H), 4.67 (d, $J$ = 13.6 Hz, 1H), 3.31 (t, $J$ = 7.7 Hz, 2H), 3.24 (d, $J$ = 16.7 Hz, 1H), 3.23 (t, $J$ = 7.7 Hz, 2H), 2.80 (d, $J$ = 15.9 Hz, 1H), 2.77 (d, $J$ = 15.9 Hz, 1H), 2.73 (d, $J$ = 16.7 Hz, 1H), 2.60 (s, 3H), 2.32 (s, 3H), 1.67 – 1.60 (m, 2H), 1.60 – 1.54 (m, 2H), 0.95 (t, $J$ = 7.4 Hz, 3H), 0.88 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 209.07, 190.15, 166.51, 162.69, 160.86, 143.86, 113.77, 112.78, 100.74, 100.71, 66.80, 49.42, 48.89, 48.66, 47.58, 32.23, 23.11, 22.14, 20.64, 11.34, 11.26. HRMS (ESI) *m/z* calcd for $C_{21}H_{29}NO_6$ $[M + H]^+$ 392.2068, found 392.2071.

##### 4.1.12.3. 2-[[3,4-dihydro-2-hydroxy-5-methyl-2-(2-oxopropyl)-4-oxo-2H-1-benzo- pyran-7-yl]oxy]-N,N-bis(1-methylethyl)-acetamide (7c).

The tittle compound was synthesized as described in the general procedure using compound **6c** (133 mg, 0.6 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 3:1) to afford the desired product as a white solid (73 mg, 46.7% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 6.43 (d, $J$ = 2.5 Hz, 1H), 6.30 (d, $J$ = 2.5 Hz, 1H), 6.08 (brs, 1H), 4.62 (d, $J$ = 13.2 Hz, 1H), 4.59 (d, $J$ = 13.2 Hz, 1H), 3.96 (hept, $J$ = 6.1 Hz, 1H), 3.45 (hept, $J$ = 6.8 Hz, 1H), 3.25 (d, $J$ = 16.7 Hz, 1H), 2.80 (d, $J$ = 15.9 Hz, 1H), 2.77 (d, $J$ = 15.9 Hz, 1H), 2.72 (d, $J$ = 16.7 Hz, 1H), 2.60 (s, 3H), 2.32 (s, 3H), 1.41 (d, $J$ = 6.8 Hz, 6H), 1.23 (d, $J$ = 6.1 Hz, 6H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 209.16, 190.07, 165.71, 162.68, 160.86, 143.90, 113.74, 112.81, 100.74, 100.71, 68.44, 49.26, 48.71 (2 × C), 48.70, 46.26, 32.23, 23.10, 20.90, 20.89, 20.30 (2 × C). HRMS (ESI) *m/z* calcd for $C_{21}H_{29}NO_6$ $[M + H]^+$ 392.2068, found 392.2088.

##### 4.1.12.4. 2-[[3,4-dihydro-2-hydroxy-5-methyl-2-(2-oxopropyl)-4-oxo-2H-1-benzo- pyran-7-yl]oxy]-N,N-dibutyl-acetamide (7d).

The tittle compound was synthesized as described in the general procedure using compound **6d** (150 mg, 0.6 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 5:1) to afford the desired product as a white solid (79 mg, 47.1% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 6.41 (d, $J$ = 2.5 Hz, 1H), 6.27 (d, $J$ = 2.5 Hz, 1H), 6.09 (brs, 1H), 4.69 (d, $J$ = 13.7 Hz, 1H), 4.66 (d, $J$ = 13.7 Hz, 1H), 3.34 (t, $J$ = 7.7 Hz, 2H), 3.26 (t, $J$ = 7.7 Hz, 2H), 3.24 (d, $J$ = 16.7 Hz, 1H), 2.79 (dd $J$ = 16.0, 1.8 Hz, 1H), 2.77 (d, $J$ = 16.0 Hz, 1H), 2.73 (d, $J$ = 16.7 Hz, 1H), 2.60 (s, 3H), 2.32 (s, 3H), 1.58 (quint, $J$ = 7.7 Hz, 2H), 1.52 (quint, $J$ = 7.7 Hz, 2H), 1.38 – 1.32 (m, 2H), 1.32 – 1.27 (m, 2H), 0.96 (t, $J$ = 7.4 Hz, 3H), 0.92 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 209.10, 190.09, 166.37, 162.69, 160.84, 143.86, 113.76, 112.79, 100.72, 100.70, 66.82, 49.33, 48.68, 47.07, 45.74, 32.22, 31.04, 29.50, 23.10, 20.16, 20.12, 13.85, 13.82. HRMS (ESI) *m/z* calcd for $C_{23}H_{33}NO_6$ $[M + H]^+$ 420.2381, found 420.2401.

##### 4.1.12.5. 2-[[3,4-dihydro-2-hydroxy-5-methyl-2-(2-oxopropyl)-4-oxo-2H-1-benzo- pyran-7-yl]oxy]-N,N-bis(2-methylpropyl)acetamide (7e).

The tittle compound was synthesized as described in the general procedure using compound **6e** (150 mg, 0.6 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 3:1) to afford the desired product as a white solid (71 mg, 42.4% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 6.41 (d, $J$ = 2.6 Hz, 1H), 6.26 (d, $J$ = 2.6 Hz, 1H), 6.06 (brs, 1H), 4.73 (d, $J$ = 13.9 Hz, 1H), 4.70 (d, $J$ = 13.9 Hz, 1H), 3.26 – 3.21 (m, 3H), 3.12 (d, $J$ = 7.6 Hz, 2H), 2.79 (d, $J$ = 15.9 Hz, 1H), 2.76 (d, $J$ = 15.9 Hz, 1H), 2.71 (d, $J$ = 16.7 Hz, 1H), 2.60 (s, 3H), 2.32 (s, 3H), 2.03 – 1.96 (m, 2H), 0.95 (d, $J$ = 6.6 Hz, 6H), 0.86 (d, $J$ = 6.7 Hz, 6H), 0.85 (d, $J$ = 6.7 Hz, 6H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 209.11, 190.09, 167.19, 162.65, 160.80, 143.86, 113.76, 112.74, 100.84, 100.70, 66.68, 54.32, 52.57, 49.30, 48.69, 32.25, 27.29, 26.13, 23.09, 20.07 (2 × C), 20.05 (2 × C). HRMS (ESI) *m/z* calcd for $C_{23}H_{33}NO_6$ $[M + H]^+$ 420.2381, found 420.2404.

##### 4.1.12.6. 2,3-dihydro-2-hydroxy-5-methyl-2-(2-oxopropyl)-7-[2-oxo-2-(1-pyrrolidin- yl)ethoxy]-4H-1-benzopyran-4-one (7f).

The tittle compound was synthesized as described in the general procedure using compound **6f** (115 mg, 0.6 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 1:1) to afford the desired product as a white solid (3 mg, 43.6% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 6.44 (d, $J$ = 2.5 Hz, 1H), 6.28 (d, $J$ = 2.5 Hz, 1H), 6.12 (brs, 1H), 4.63 (d, $J$ = 13.9 Hz, 1H), 4.60 (d, $J$ = 13.9 Hz, 1H), 3.52 (t, $J$ = 6.9 Hz, 2H), 3.49 (t, $J$ = 7.2 Hz, 2H), 3.24 (d, $J$ = 16.7 Hz, 1H), 2.80 (brd, $J$ = 15.9 Hz, 1H), 2.77 (d, $J$ = 15.9 Hz, 1H), 2.74 (d, $J$ = 16.7 Hz, 1H), 2.60 (s, 3H), 2.32 (s, 3H), 1.99 (quint, $J$ = 7.2 Hz, 2H), 1.87 (quint, $J$ = 6.9 Hz, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 209.12, 190.14, 165.58, 162.58, 160.88, 143.91, 113.83, 112.83, 100.73, 100.67, 67.43, 49.43, 48.66, 46.28, 45.97, 32.26, 26.24, 23.80, 23.11. HRMS (ESI) *m/z* calcd for $C_{19}H_{23}NO_6$ $[M + H]^+$ 362.1598, found 362.1619.

##### 4.1.12.7. 2,3-dihydro-2-hydroxy-5-methyl-2-(2-oxopropyl)-7-[2-oxo-2-(1-piperidinyl)-ethoxy]-4H-1-benzopyran-4-one (7 g).

The tittle compound was synthesized as described in the general procedure using compound **6 g** (123 mg, 0.6 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 1:1) to afford the desired product as a white solid (65 mg, 43.3% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 6.43 (d, $J$ = 2.5 Hz, 1H), 6.29 (d, $J$ = 2.5 Hz, 1H), 6.12 (d, $J$ = 2.0 Hz, 1H), 4.68 (d, $J$ = 13.4 Hz, 1H), 4.65 (d, $J$ = 13.4 Hz, 1H), 3.61 – 3.52 (m, 2H), 3.46 – 3.40 (m, 2H), 3.24 (d, $J$ = 16.7 Hz, 1H), 2.81 (dd, $J$ = 15.9, 2.2 Hz, 1H), 2.77 (d, $J$ = 15.9 Hz, 1H), 2.74 (d, $J$ = 16.7 Hz, 1H), 2.60 (s, 3H), 2.32 (s, 3H), 1.68 – 1.64 (m, 2H), 1.62 – 1.58 (m, 2H), 1.58 – 1.54 (m, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 209.07, 190.15, 165.16, 162.55, 160.87, 143.87, 113.80, 112.77,

100.70, 100.68, 67.08, 49.44, 48.62, 46.34, 43.25, 32.22, 26.45, 25.48, 24.37, 23.09. HRMS (ESI) *m/z* calcd for $C_{20}H_{25}NO_6$ $[M + Na]^+$ 398.1574, found 398.1586.

*4.1.12.8. 2,3-dihydro-2-hydroxy-5-methyl-2-(2-oxopropyl)-7-[2-oxo-2-(4-morpholin- yl)ethoxy]-4H-1-benzopyran-4-one (**7 h**).* The tittle compound was synthesized as described in the general procedure using compound **6 h** (125 mg, 0.6 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 2:1) to afford the desired product as a white solid (63 mg, 41.8% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 6.42 (d, $J = 2.5$ Hz, 1H), 6.30 (d, $J = 2.5$ Hz, 1H), 6.11 (brs, 1H), 4.70 (d, $J = 13.4$ Hz, 1H), 4.67 (d, $J = 13.4$ Hz, 1H), 3.69 (t, $J = 4.8$ Hz, 4H), 3.63 (d, $J = 4.8$ Hz, 2H), 3.54 (t, $J = 4.8$ Hz, 2H), 3.25 (d, $J = 16.8$ Hz, 1H), 2.80 (d, $J = 15.9$ Hz, 1H), 2.77 (d, $J = 15.9$ Hz, 1H), 2.74 (d, $J = 16.8$ Hz, 1H), 2.61 (s, 3H), 2.33 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 209.13, 190.06, 165.65, 162.16, 160.87, 144.07, 114.03, 112.63, 100.78, 100.70, 67.07, 66.76, 66.64, 49.33, 48.66, 45.81, 42.42, 32.22, 23.10. HRMS (ESI) *m/z* calcd for $C_{19}H_{23}NO_7$ $[M + H]^+$ 378.1547, found 378.1550.

*4.1.12.9. 2,3-dihydro-2-hydroxy-5-methyl-2-(2-oxopropyl)-7-[2-oxo-2-(4-acetyl-1- piperazinyl)ethoxy]-4H-1-benzopyran-4-one (**7i**).* The tittle compound was synthesized as described in the general procedure using compound **6i** (149 mg, 0.6 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 3:1) to afford the desired product as a white solid (72 mg, 43.1% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 6.42 (d, $J = 2.5$ Hz, 1H), 6.30 (d, $J = 2.5$ Hz, 1H), 6.14 (brs, 1H), 4.73 (d, $J = 13.7$ Hz, 1H), 4.70 (d, $J = 13.7$ Hz, 1H), 3.67 – 3.60 (m, 4H), 3.59 – 3.47 (m, 4H), 3.24 (d, $J = 16.7$ Hz, 1H), 2.81 (d, $J = 16.0$ Hz, 1H), 2.77 (d, $J = 16.0$ Hz, 1H), 2.74 (d, $J = 16.7$ Hz, 1H), 2.61 (s, 3H), 2.33 (s, 3H), 2.12 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 209.05, 190.04, 169.34, 165.93, 162.04, 160.87, 144.14, 114.10, 112.54, 100.79, 100.73, 67.10, 49.37, 48.65, 45.85, 45.08, 42.10, 41.44, 32.23, 23.10, 21.35; $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 209.12, 190.04, 169.09, 165.75, 161.94, 160.90, 144.14, 114.15, 112.49, 100.82, 100.68, 67.48, 49.37, 48.65, 46.31, 45.41, 41.96, 41.03, 32.23, 23.10, 21.40. HRMS (ESI) *m/z* calcd for $C_{21}H_{26}N_2O_7$ $[M + H]^+$ 419.1813, found 419.1825.

*4.1.12.10. 2,3-dihydro-2-hydroxy-5-methyl-2-(2-oxopropyl)-7-[2-oxo-2-[4-(2-pyri- dinyl)-1-piperazinyl]ethoxy]-4H-1-benzopyran-4-one (**7j**).* The tittle compound was synthesized as described in the general procedure using compound **6j** (170 mg, 0.6 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 2:1) to afford the desired product as a white solid (62 mg, 34.2% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 8.20 (dd, $J = 5.0$, 1.8 Hz, 1H), 7.52 (ddd, $J = 8.6$, 7.0, 1.8 Hz, 1H), 6.69 (dd, $J = 7.0$, 5.0 Hz, 1H), 6.67 (d, $J = 8.6$ Hz, 1H), 6.45 (d, $J = 2.5$ Hz, 1H), 6.32 (d, $J = 2.5$ Hz, 1H), 6.11 (brs, 1H), 4.75 (d, $J = 13.4$ Hz, 1H), 4.72 (d, $J = 13.4$ Hz, 1H), 3.80 – 3.72 (m, 2H), 3.68 – 3.62 (m, 4H), 3.57 – 3.50 (m, 2H), 3.25 (d, $J = 16.8$ Hz, 1H), 2.79 (d, $J = 15.9$ Hz, 1H), 2.76 (d, $J = 15.9$ Hz, 1H), 2.72 (d, $J = 16.8$ Hz, 1H), 2.61 (s, 3H), 2.33 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 209.17, 190.01, 165.71, 162.24, 160.89, 158.87, 147.95, 144.11, 137.81, 114.12, 114.05, 112.70, 107.36, 100.80, 100.73, 67.28, 49.28, 48.72, 45.32, 45.19, 45.09, 41.83, 32.26, 23.14. HRMS (ESI) *m/z* calcd for $C_{24}H_{27}N_3O_6$ $[M + Na]^+$ 476.1792, found 476.1794.

*4.1.12.11. Phenyl 2-[[3,4-dihydro-2-hydroxy-5-methyl-2-(2-oxopropyl)-4-oxo-2H- 1-benzopyran-7-yl]oxy]acetate (**7 k**).* The tittle compound was synthesized as described in the general procedure using compound **6 k** (129 mg, 0.6 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 3:1) to afford the desired product as a white solid (75 mg, 57.5% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.40 (t, $J = 7.8$ Hz, 2H), 7.26 (brt, $J = 8.4$ Hz, 1H), 7.12 (brd, $J = 7.8$ Hz, 2H), 6.48 (d, $J = 2.5$ Hz, 1H), 6.32 (d, $J = 2.5$ Hz, 1H), 6.08 (brs, 1H), 4.87 (s, 2H), 3.26 (d, $J = 16.8$ Hz, 1H), 2.79 (s, 2H), 2.72 (d, $J = 16.8$ Hz, 1H), 2.63 (s, 3H), 2.32 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 209.13, 190.01, 166.64, 162.05, 160.85, 149.95, 144.16, 129.59 (2 × C), 126.34, 121.18 (2 × C), 114.20, 112.76, 100.85, 100.74, 64.98, 49.20, 48.75, 32.21, 23.10. HRMS (ESI) *m/z* calcd for $C_{21}H_{20}O_7$ $[M + H]^+$ 385.1282, found 385.1282.

*4.1.12.12. 3-methylphenyl 2-[[3,4-dihydro-2-hydroxy-5-methyl-2-(2-oxopropyl)-4- oxo-2H-1-benzopyran-7-yl]oxy]acetate (**7 l**).* The tittle compound was synthesized as described in the general procedure using compound **6 l** (137 mg, 0.6 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 5:1) to afford the desired product as a white solid (77 mg, 56.3% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.27 (t, $J = 7.9$ Hz, 1H), 7.07 (d, $J = 7.6$ Hz, 1H), 6.93 (brs, 1H), 6.91 (brd, $J = 8.0$ Hz, 1H), 6.48 (d, $J = 2.4$ Hz, 1H), 6.32 (d, $J = 2.4$ Hz, 1H), 6.09 (brs, 1H), 4.85 (s, 2H), 3.25 (d, $J = 16.8$ Hz, 1H), 2.79 (s, 2H), 2.72 (d, $J = 16.8$ Hz, 1H), 2.63 (s, 3H), 2.36 (s, 3H), 2.32 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 209.12, 190.02, 166.72, 162.07, 160.85, 149.89, 144.12, 139.86, 129.28, 127.12, 121.73, 118.10, 114.17, 112.75, 100.84, 100.75, 65.00, 49.20, 48.74, 32.20, 23.10, 21.31. HRMS (ESI) *m/z* calcd for $C_{22}H_{22}O_7$ $[M + H]^+$ 399.1438, found 399.1439.

*4.1.12.13. 4-methoxphenyl 2-[[3,4-dihydro-2-hydroxy-5-methyl-2-(2-oxopropyl)-4- oxo-2H-1-benzopyran-7-yl]oxy]acetate (**7 m**).* The tittle compound was synthesized as described in the general procedure using compound **6 m** (147 mg, 0.6 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 1:1) to afford the desired product as a white solid (73 mg, 51.3% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.03 (d, $J = 9.0$ Hz, 2H), 6.90 (d, $J = 9.0$ Hz, 2H), 6.47 (d, $J = 2.5$ Hz, 1H), 6.31 (d, $J = 2.5$ Hz, 1H), 6.08 (brs, 1H), 4.85 (s, 2H), 3.80 (s, 3H), 3.25 (d, $J = 16.8$ Hz, 1H), 2.79 (s, 2H), 2.72 (d, $J = 16.8$ Hz, 1H), 2.63 (s, 3H), 2.32 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 209.12, 190.04, 166.99, 162.07, 160.85, 157.55, 144.11, 143.40, 121.96 (2 × C), 114.54 (2 × C), 114.16, 112.74, 100.84, 100.73, 64.97, 55.60, 49.22, 48.72, 32.19, 23.09. HRMS (ESI) *m/z* calcd for $C_{22}H_{22}O_8$ $[M + Na]^+$ 437.1207, found 437.1228.

*4.1.12.14. Cyclopropylmethyl 2-[[3,4-dihydro-2-hydroxy-5-methyl-2-(2-oxopropyl)- 4-oxo-2H-1-benzopyran-7-yl]oxy]acetate (**7n**).* The tittle compound was synthesized as described in the general procedure using compound **6n** (116 mg, 0.6 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 3:1) to afford the desired product as a white solid (61 mg, 50.2% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 6.43 (d, $J = 2.5$ Hz, 1H), 6.24 (d, $J = 2.5$ Hz, 1H), 6.05 (brs, 1H), 4.64 (s, 2H), 4.05 (d, $J = 7.4$ Hz, 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), 1.19 – 1.12 (m, 1H), 0.61 – 0.57 (m, 2H), 0.32 – 0.28 (m, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 209.11, 190.00, 168.23, 162.28, 160.81, 143.98, 113.97, 112.77, 100.77, 100.67, 70.36, 65.02, 49.23, 48.73, 32.22, 23.08, 9.75, 3.39, 3.38. HRMS (ESI) *m/z* calcd for $C_{19}H_{22}O_7$ $[M + Na]^+$ 385.1258, found 385.1267.

*4.1.12.15. Cyclohexylmethyl 2-[[3,4-dihydro-2-hydroxy-5-methyl-2-(2-oxopropyl)- 4-oxo-2H-1-benzopyran-7-yl]oxy]acetate (**7o**).* The tittle compound was synthesized as described in the general procedure using compound **6o** (141 mg, 0.6 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 3:1) to afford the desired product as a white solid (73 mg, 52.7% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 6.41 (d, $J = 2.5$ Hz, 1H), 6.23 (d, $J = 2.5$ Hz, 1H), 6.04 (brs, 1H), 4.63 (s, 2H), 4.02 (d, $J = 6.4$ Hz, 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), 1.74 – 1.68 (m, 4H), 1.67 – 1.64 (m, 2H), 1.27 – 1.19 (m, 2H), 1.18 – 1.10 (m, 1H), 0.98 – 0.90 (m, 2H);. $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 209.09, 189.98, 168.23, 162.29, 160.81, 143.99, 113.97, 112.68,

100.77, 100.70, 70.52, 64.95, 49.23, 48.73, 37.01, 32.22, 29.47 (2 × C), 26.22, 25.57 (2 × C), 23.07. HRMS (ESI) *m/z* calcd for $C_{22}H_{28}O_7$ [M + Na]$^+$ 427.1727, found 427.1756.

*4.1.12.16. Ethyl 2-[[3,4-dihydro-2-hydroxy-5-methyl-2-(2-oxopropyl)-4-oxo-2H-1- benzopyran-7-yl]oxy]acetate (**7p**).* The tittle compound was synthesized as described in the general procedure using ethyl bromoacetate (100 mg, 0.6 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 5:1) to afford the desired product as a white solid (76 mg, 68.3% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 6.41 (d, $J$ = 2.5 Hz, 1H), 6.22 (d, $J$ = 2.5 Hz, 1H), 6.05 (s, 1H), 4.61 (s, 2H), 4.28 (q, $J$ = 7.1 Hz, 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), 1.30 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 209.11, 190.03, 168.09, 162.26, 160.82, 143.99, 113.98, 112.75, 100.78, 100.62, 64.99, 61.59, 49.25, 48.71, 32.21, 23.07, 14.14. HRMS (ESI) *m/z* calcd for $C_{17}H_{20}O_7$ [M + H]$^+$ 337.1282, found 337.1256.

*4.1.13. 2,4-dihydroxy-6-methylacetophenone (**9**)*

To a mixed solution of orcinol (10.0 g, 80.6 mmol) and 3 Å molecular sieve in acetic acid (46 mL, 805.5 mmol), boron trifluoride etherate (15.2 mL, 120.9 mmol) was added dropwise at room temperature for 1 h. The mixture was stirred at 90 °C for 24 h and then cooled to room temperature. The reaction solution was quenched by addition of a saturated aqueous solution of $NH_4Cl$ (25 mL) and was filtered to remove residual 3 Å molecular sieve. The solvent was removed under vacuum, and then the residue was diluted with saturated aqueous solution of $NaHCO_3$ (30 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with water and brine, dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was pulped with $Et_2O$ (5 mL), filtered with a Buchner funnel and the solid was washed with ether (3 mL) to provide compound **9** as a yellow solid (10.43 g, yield 77.9%). $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 10.60 (brs, 1H), 9.77 (brs, 1H), 6.17 (d, $J$ = 2.1 Hz, 1H), 6.11 (d, $J$ = 2.1 Hz, 1H), 2.43 (s, 3H), 2.17 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 203.60, 160.36, 159.53, 139.56, 119.49, 110.11, 100.75, 32.89, 21.48.

*4.1.14. 1-[2,4-bis(benzyloxy)-6-methylphenyl]ethanone (**10**)*

Followed general procedure **A**, compound **9** (5.0 g, 30.1 mmol), benzyl chloride (8.0 g, 63.2 mmol) and anhydrous $K_2CO_3$ (12.5 g, 90.3 mmol) in acetonitrile (100 mL) gave the tittle compound as a white solid (9.81 g, yield 94.1%). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.42 – 7.31 (m, 10*H*), 6.45 (d, $J$ = 2.2 Hz, 1H), 6.43 (d, $J$ = 2.2 Hz, 1H), 5.03 (s, 2H), 5.03 (s, 2H), 2.47 (s, 3H), 2.26 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 204.56, 160.15, 157.42, 138.00, 136.48, 136.28, 128.64 (2 × C), 128.60 (2 × C), 128.13, 128.05, 127.51 (2 × C), 127.28 (2 × C), 124.65, 108.53, 97.97, 70.43, 70.05, 32.55, 20.03.

*4.1.15. Synthesis of compounds **12a-12f***

General procedure: The solution of the substituted phenols (**11a-11f**, 10.0 mmol) and anhydrous $K_2CO_3$ (2.76 g, 20.0 mmol) in DMF (40 mL) was stirred 30 min at room temperature, and then 2-(2-bromoethyl)-1,3-dioxolane (1.99 g, 11.0 mmol) was added slowly and the mixture was allowed to warm up 65 °C overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. After that, the resulting residue was diluted with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography column to provide compound **12a-12f**.

*4.1.15.1. 2-(2-phenoxyethyl)-1,3-dioxolane (**12a**).* The tittle compound was synthesized as described in the general procedure using phenol (940 mg, 10.0 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 25:1) to afford the desired product as a colorless oil (1.43 g, 73.7% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.27 (t, $J$ = 7.8 Hz, 2H), 6.94 (t, $J$ = 7.8 Hz, 1H), 6.91 (d, $J$ = 7.8 Hz, 2H), 5.10 (t, $J$ = 4.8 Hz, 1H), 4.12 (t, $J$ = 6.5 Hz, 2H), 4.03 – 3.95 (m, 2H), 3.91 – 3.85 (m, 2H), 2.16 (dt, $J$ = 6.5, 4.8 Hz, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 158.75, 129.41 (2 × C), 120.68, 114.47 (2 × C), 102.05, 64.91 (2 × C), 63.44, 33.81.

*4.1.15.2. 2-[2-(3-methylphenoxy)ethyl]-1,3-dioxolane (**12b**).* The tittle compound was synthesized as described in the general procedure using 3-methylphenol (1.08 g, 10.0 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 25:1) to afford the desired product as a colorless oil (1.46 g, 70.2% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.15 (t, $J$ = 7.8 Hz, 1H), 6.76 (d, $J$ = 7.5 Hz, 1H), 6.73 (d, $J$ = 2.3 Hz, 1H), 6.71 (dd, $J$ = 8.1, 2.3 Hz, 1H), 5.09 (t, $J$ = 4.9 Hz, 1H), 4.11 (t, $J$ = 6.5 Hz, 2H), 4.03 – 3.96 (m, 2H), 3.91 – 3.84 (m, 2H), 2.32 (s, 3H), 2.15 (dt, $J$ = 6.5, 4.9 Hz, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 158.78, 139.43, 129.14, 121.51, 115.34, 111.32, 102.07, 64.91 (2 × C), 63.40, 33.84, 21.52.

*4.1.15.3. 2-[2-(4-methoxyphenoxy)ethyl]-1,3-dioxolane (**12c**).* The tittle compound was synthesized as described in the general procedure using 4-methoxyphenol (1.24 g, 10.0 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 15:1) to afford the desired product as a colorless oil (1.47 g, 65.6% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 6.85 (d, $J$ = 9.2 Hz, 2H), 6.82 (d, $J$ = 9.2 Hz, 2H), 5.09 (t, $J$ = 4.9 Hz, 1H), 4.07 (t, $J$ = 6.5 Hz, 2H), 4.02 – 3.96 (m, 2H), 3.91 – 3.85 (m, 2H), 3.76 (s, 3H), 2.14 (dt, $J$ = 6.5, 4.9 Hz, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 153.78, 152.93, 115.46 (2 × C), 114.57 (2 × C), 102.10, 64.91 (2 × C), 64.24, 55.71, 33.90.

*4.1.15.4. 2-[2-[3-(trifluoromethyl)phenoxy]ethyl]-1,3-dioxolane (**12d**).* The tittle compound was synthesized as described in the general procedure using 3-(trifluoromethyl)phenol (1.62 g, 10.0 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 25:1) to afford the desired product as a colorless oil (1.89 g, 72.1% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.38 (t, $J$ = 8.0 Hz, 1H), 7.20 (d, $J$ = 7.7 Hz, 1H), 7.14 (brs, 1H), 7.07 (dd, $J$ = 8.3, 2.2 Hz, 1H), 5.10 (t, $J$ = 4.8 Hz, 1H), 4.16 (t, $J$ = 6.5 Hz, 2H), 4.04 – 3.97 (m, 2H), 3.93 – 3.86 (m, 2H), 2.18 (dt, $J$ = 6.5, 4.8 Hz, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 158.90, 131.77 (q, $J_{C\text{-}F}$ = 32.3 Hz), 129.92, 123.96 (q, $J_{C\text{-}F}$ = 272.4 Hz), 117.97, 117.39 (q, $J_{C\text{-}F}$ = 3.9 Hz), 111.27 (q, $J$ = 3.9 Hz), 101.96, 64.97 (2 × C), 63.89, 33.64.

*4.1.15.5. 2-[2-[4-(trifluoromethyl)phenoxy]ethyl]-1,3-dioxolane (**12e**).* The tittle compound was synthesized as described in the general procedure using 4-(trifluoromethyl)phenol (1.62 g, 10.0 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 25:1) to afford the desired product as a colorless oil (2.01 g, 76.7% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.53 (d, $J$ = 8.5 Hz, 2H), 6.96 (d, $J$ = 8.5 Hz, 2H), 5.09 (t, $J$ = 4.8 Hz, 1H), 4.16 (t, $J$ = 6.5 Hz, 2H), 4.04 – 3.97 (m, 2H), 3.93 – 3.86 (m, 2H), 2.18 (td, $J$ = 6.5, 4.8 Hz, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 161.24, 126.86 (q, $J_{C\text{-}F}$ = 3.7 Hz, 2 × C), 124.44 (q, $J_{C\text{-}F}$ = 271.0 Hz), 122.84 (q, $J_{C\text{-}F}$ = 32.7 Hz), 114.43 (2 × C), 101.83, 64.98 (2 × C), 63.82, 33.59.

*4.1.15.6. 2-[2-(3-fluorophenoxy)ethyl]-1,3-dioxolane (**12f**).* The tittle compound was synthesized as described in the general procedure using 3-fluorophenol (1.12 g, 10.0 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 25:1) to afford the desired product as a colorless oil (1.44 g, 67.9% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.21 (brq, $J$ = 7.6 Hz, 1H), 6.69 (dd, $J$ = 8.3, 2.3 Hz, 1H), 6.66 – 6.60 (m, 2H), 5.09 (t, $J$ = 4.8 Hz, 1H), 4.10 (t, $J$ = 6.5 Hz, 2H), 4.03 – 3.97 (m, 2H), 3.92 – 3.86 (m, 2H), 2.16 (dt, $J$ = 6.5, 4.8 Hz, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 163.60 (d, $J_{C\text{-}F}$ = 244.9 Hz), 160.26 (d, $J_{C\text{-}F}$ = 10.9 Hz), 130.14 (d, $J_{C\text{-}F}$ = 10.0 Hz), 110.27 (d, $_{C\text{-}}$

$_{F}J$ = 2.8 Hz), 107.49 (d, $J_{C\text{-}F}$ = 21.5 Hz), 102.19 (d, $J_{C\text{-}F}$ = 24.9 Hz), 101.90, 64.95 (2 × C), 63.85, 33.64.

*4.1.16. General procedure for the synthesis of compounds **13a-13f***

The solution of required compound **12a-12f** (2.25 mmol), acetic acid (20 mL) and water (5 mL) was stirred at 45 °C for 5 h, and the solvent was then removed under reduced pressure. The residue was diluted with a saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated *in vacuo*. The resulting residues (**13a-13f**) were used without further purification [17].

*4.1.17. Synthesis of compounds **14a-14i***

General procedure: A solution of **10** (520 mg, 1.5 mmol) in anhydrous THF (2 mL) was added gradually to the solution of LDA (2.0 M solution in THF, 1.5 mL, 3.0 mmol) in anhydrous THF (3 mL) at −78 °C under an atmosphere of $N_2$. After 30 min, the solution of corresponding aldehyde (**13a-13f**, butyraldehyde, pentanal or hexanal, 2.25 mmol) in anhydrous THF (2 mL) was added dropwise and the mixture was stirred overnight. Upon completion of the reaction, the mixture was quenched by addition of a saturated aqueous solution of $NH_4Cl$ (5 mL) at 0 °C and the organic layer was separated. Aqueous layer was diluted with brine (5 mL) and extracted with ethyl acetate (3 × 10 mL), combined organic layers were dried over $Na_2SO_4$, filtered, eliminated under reduced pressure. The crude product was purified by flash chromatography column to afford compound **14a-14i**.

*4.1.17.1. 1-[2,4-bis(benzyloxy)-6-methylphenyl]-3-hydroxy-5-phenoxy-1-pentanone (**14a**).* The tittle compound was synthesized as described in the general procedure using compound **13a** (338 mg, 2.25 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 15:1) to afford the desired product as a yellow oil (316 mg, 42.4% yield). $^1$H NMR (600 MHz, Chloroform-*d*) *δ* 7.42 – 7.26 (m, 12H), 6.93 (t, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 2H), 6.45 (brs, 1H), 6.44 (brs, 1H), 5.04 (s, 2H), 5.01 (s, 2H), 4.35 – 4.29 (m, 1H), 4.03 (t, *J* = 6.2 Hz, 2H), 3.41 (brs, 1H), 3.13 (dd, *J* = 17.4, 2.8 Hz, 1H), 2.87 (dd, *J* = 17.3, 8.9 Hz, 1H), 2.26 (s, 3H), 1.90 – 1.78 (m, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) *δ* 207.67, 160.51, 158.75, 157.54, 138.41, 136.38, 135.96, 129.39 (2 × C), 128.68 (2 × C), 128.67 (2 × C), 128.28, 128.18, 127.51 (4 × C), 123.82, 120.64, 114.45 (2 × C), 108.72, 98.02, 70.64, 70.10, 65.92, 64.64, 51.16, 35.85, 20.06.

*4.1.17.2. 1-[2,4-bis(benzyloxy)-6-methylphenyl]-3-hydroxy-5-(3-methylphenoxy)-1- pentanone (**14b**).* The tittle compound was synthesized as described in the general procedure using compound **13b** (370 mg, 2.25 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 15:1) to afford the desired product as a yellow oil (309 mg, 40.3% yield). $^1$H NMR (600 MHz, Chloroform-*d*) *δ* 7.41 – 7.30 (m, 10*H*), 7.14 (t, *J* = 7.8 Hz, 1H), 6.75 (brd, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 2.1, 1H), 6.66 (d, *J* = 8.2, 2.1 Hz, 1H), 6.45 (d, *J* = 2.2 Hz, 1H), 6.44 (d, *J* = 2.2 Hz, 1H), 5.04 (s, 2H), 5.01 (s, 2H), 4.34 – 4.29 (m, 1H), 4.02 (t, *J* = 6.3 Hz, 2H), 3.42 (brs, 1H), 3.12 (dd, *J* = 17.3, 2.9 Hz, 1H), 2.87 (dd, *J* = 17.3, 8.9 Hz, 1H), 2.31 (s, 3H), 2.26 (s, 3H), 1.88 – 1.79 (m, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) *δ* 207.71, 160.53, 158.80, 157.57, 139.45, 138.45, 136.42, 136.01, 129.17, 128.72 (2 × C), 128.71 (2 × C), 128.31, 128.22, 127.55 (2 × C), 127.53 (2 × C), 123.87, 121.52, 115.35, 111.36, 108.75, 98.06, 70.66, 70.14, 66.03, 64.67, 51.21, 35.91, 21.56, 20.10.

*4.1.17.3. 1-[2,4-bis(benzyloxy)-6-methylphenyl]-3-hydroxy-5-(4-methoxyphenoxy)-1- pentanone (**14c**).* The tittle compound was synthesized as described in the general procedure using compound **13c** (406 mg, 2.25 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 8:1) to afford the desired product as a yellow oil (345 mg, 43.7% yield). $^1$H NMR (600 MHz, Chloroform-*d*) *δ* 7.42 – 7.28 (m, 10*H*), 6.81 (d, *J* = 9.2 Hz, 2H), 6.79 (d, *J* = 9.2 Hz, 2H), 6.45 (d, *J* = 2.0 Hz, 1H), 6.43 (d, *J* = 2.0 Hz, 1H), 5.04 (s, 2H), 5.01 (s, 2H), 4.35 – 4.28 (m, 1H), 3.98 (t, *J* = 6.2 Hz, 2H), 3.76 (s, 3H), 3.41 (brs, 1H), 3.12 (dd, *J* = 17.3, 2.7 Hz, 1H), 2.87 (dd, *J* = 17.3, 8.9 Hz, 1H), 2.26 (s, 3H), 1.88 – 1.76 (m, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) *δ* 207.64, 160.48, 157.52, 153.73, 152.92, 138.39, 136.38, 135.97, 128.67 (2 × C), 128.66 (2 × C), 128.26, 128.18, 127.51 (2 × C), 127.49 (2 × C), 123.84, 115.38 (2 × C), 114.56 (2 × C), 108.71, 98.02, 70.62, 70.09, 66.00, 65.46, 55.71, 51.19, 35.93, 20.04.

*4.1.17.4. 1-[2,4-bis(benzyloxy)-6-methylphenyl]-3-hydroxy-5-[3-(trifluoromethyl)- phenoxy]-1-pentanone (**14d**).* The tittle compound was synthesized as described in the general procedure using compound **13d** (491 mg, 2.25 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 15:1) to afford the desired product as a yellow oil (386 mg, 45.6% yield). $^1$H NMR (600 MHz, Chloroform-*d*) *δ* 7.41 – 7.33 (m, 10*H*), 7.30 – 7.28 (m, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 2.1 Hz, 1H), 7.01 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.46 (d, *J* = 2.2 Hz, 1H), 6.44 (d, *J* = 2.2 Hz, 1H), 5.04 (s, 2H), 5.01 (s, 2H), 4.33 – 4.27 (m, 1H), 4.07 – 4.01 (m, 2H), 3.45 (brs, 1H), 3.13 (dd, *J* = 17.4, 2.7 Hz, 1H), 2.85 (dd, *J* = 17.4, 9.0 Hz, 1H), 2.26 (s, 3H), 1.89 – 1.78 (m, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) *δ* 207.73, 160.60, 158.94, 157.63, 138.50, 136.35, 135.90, 131.71 (q, $J_{C\text{-}F}$ = 32.2 Hz), 129.89, 128.68 (4 × C), 128.32, 128.20, 127.56 (2 × C), 127.51 (2 × C), 123.97 (q, $J_{C\text{-}F}$ = 272.4 Hz), 123.68, 117.86, 117.27 (q, $J_{C\text{-}F}$ = 3.9 Hz), 111.30 (q, $J_{C\text{-}F}$ = 3.9 Hz), 108.77, 98.02, 70.67, 70.11, 65.56, 64.87, 51.01, 35.71, 20.09.

*4.1.17.5. 1-[2,4-bis(benzyloxy)-6-methylphenyl]-3-hydroxy-5-[4-(trifluoromethyl)- phenoxy]-1-pentanone (**14e**).* The tittle compound was synthesized as described in the general procedure using compound **13e** (491 mg, 2.25 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 15:1) to afford the desired product as a yellow oil (396 mg, 46.7% yield). $^1$H NMR (600 MHz, Chloroform-*d*) *δ* 7.51 (d, *J* = 8.5 Hz, 2H), 7.43 – 7.28 (m, 10*H*), 6.90 (d, *J* = 8.5 Hz, 2H), 6.46 (d, *J* = 2.1 Hz, 1H), 6.44 (d, *J* = 2.1 Hz, 1H), 5.04 (s, 2H), 5.01 (s, 2H), 4.32 – 4.26 (m, 1H), 4.09 – 4.03 (m, 2H), 3.44 (brs, 1H), 3.13 (dd, *J* = 17.4, 2.6 Hz, 1H), 2.85 (dd, *J* = 17.4, 9.0 Hz, 1H), 2.26 (s, 3H), 1.90 – 1.76 (m, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) *δ* 207.70, 161.27, 160.60, 157.62, 138.51, 136.34, 135.92, 128.68 (4 × C), 128.30, 128.21, 127.53 (2 × C), 127.51 (2 × C), 126.81 (q, $J_{C\text{-}F}$ = 3.7 Hz, 2 × C), 124.45 (q, $J_{C\text{-}F}$ = 271.0 Hz), 123.66, 122.70 (q, $J_{C\text{-}F}$ = 32.6 Hz), 114.40 (2 × C), 108.77, 98.03, 70.66, 70.11, 65.51, 64.82, 51.01, 35.64, 20.09.

*4.1.17.6. 1-[2,4-bis(benzyloxy)-6-methylphenyl]-3-hydroxy-5-(3-fluorophenoxy)-1- pentanone (**14f**).* The tittle compound was synthesized as described in the general procedure using compound **13f** (379 mg, 2.25 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 15:1) to afford the desired product as a yellow oil (342 mg, 44.3% yield). $^1$H NMR (600 MHz, Chloroform-*d*) *δ* 7.42 – 7.28 (m, 10*H*), 7.18 (q, *J* = 7.8 Hz, 1H), 6.65 – 6.61 (m, 2H), 6.56 (brd, *J* = 10.0 Hz, 1H), 6.46 (d, *J* = 2.1 Hz, 1H), 6.44 (d, *J* = 2.1 Hz, 1H), 5.04 (s, 2H), 5.00 (s, 2H), 4.32 – 4.26 (m, 1H), 4.02 – 3.96 (m, 2H), 3.42 (brs, 1H), 3.11 (dd, *J* = 17.3, 2.7 Hz, 1H), 2.85 (dd, *J* = 17.3, 8.9 Hz, 1H), 2.26 (s, 3H), 1.87 – 1.75 (m, 2H); $^{13}$C NMR (150 MHz, Chloroform-*d*) *δ* 207.67, 163.57 (d, $J_{C\text{-}F}$ = 244.8 Hz), 160.56, 160.18 (d, $J_{C\text{-}F}$ = 10.7 Hz), 157.59, 138.46, 136.36, 135.91, 130.10 (d, $J_{C\text{-}F}$ = 10.0 Hz), 128.68 (2 × C), 128.66 (2 × C), 128.31, 128.18, 127.54 (2 × C), 127.50 (2 × C), 123.71, 110.25 (d, $J_{C\text{-}F}$ = 2.8 Hz), 108.75, 107.38 (d, $J_{C\text{-}F}$ = 21.2 Hz), 102.14 (d, $J_{C\text{-}F}$ = 24.8 Hz), 98.01, 70.65, 70.09, 65.63, 64.89, 51.05, 35.69, 20.07.

*4.1.17.7. 1-[2,4-bis(benzyloxy)-6-methylphenyl]-3-hydroxy-1-hexanone (**14 g**).* The tittle compound was synthesized as described in the general

procedure using butyraldehyde (162 mg, 2.25 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 10:1) to afford the desired product as a yellow oil (256 mg, 38.1% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.42 – 7.32 (m, 10*H*), 6.45 (d, $J$ = 2.1 Hz, 1H), 6.43 (d, $J$ = 2.1 Hz, 1H), 5.04 (s, 2H), 5.01 (s, 2H), 4.06 – 4.02 (m, 1H), 3.23 (brs, 1H), 3.07 (dd, $J$ = 17.4, 2.4 Hz, 1H), 2.71 (dd, $J$ = 17.4, 9.3 Hz, 1H), 2.25 (s, 3H), 1.45 – 1.39 (m, 1H), 1.37 – 130 (m, 1H), 1.29 – 1.21 (m, 2H), 0.85 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (150 MHz, Chloroform-d) $\delta$ 208.26, 160.45, 157.49, 138.32, 136.42, 135.99, 128.66 (2 × C), 128.65 (2 × C), 128.25, 128.17, 127.56 (2 × C), 127.51 (2 × C), 123.99, 108.69, 98.01, 70.64, 70.10, 68.01, 51.14, 38.70, 20.01, 18.56, 14.02.

*4.1.17.8. 1-[2,4-bis(benzyloxy)-6-methylphenyl]-3-hydroxy-1-heptanone (**14 h**).* The tittle compound was synthesized as described in the general procedure using pentanal (194 mg, 2.25 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 10:1) to afford the desired product as a yellow oil (252 mg, 37.6% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.41 – 7.33 (m, 10*H*), 6.45 (d, $J$ = 2.2 Hz, 1H), 6.43 (d, $J$ = 2.2 Hz, 1H), 5.04 (s, 2H), 5.01 (s, 2H), 4.05 – 4.01 (m, 1H), 3.24 (brs, 1H), 3.07 (dd, $J$ = 17.4, 2.4 Hz, 1H), 2.71 (dd, $J$ = 17.4, 9.3 Hz, 1H), 2.25 (s, 3H), 1.46 – 1.41 (m, 1H), 1.32 – 1.23 (m, 4H), 1.22 – 1.17 (m, 1H), 0.86 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 208.29, 160.45, 157.49, 138.33, 136.42, 136.01, 128.67 (2 × C), 128.66 (2 × C), 128.26, 128.18, 127.54 (2 × C), 127.51 (2 × C), 124.01, 108.70, 98.02, 70.64, 70.11, 68.29, 51.14, 36.29, 27.53, 22.65, 20.02, 14.05.

*4.1.17.9. 1-[2,4-bis(benzyloxy)-6-methylphenyl]-3-hydroxy-1-octanone (**14i**).* The tittle compound was synthesized as described in the general procedure using hexanal (226 mg, 2.25 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 10:1) to afford the desired product as a yellow oil (273 mg, 40.7% yield). $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.41 – 7.33 (m, 10*H*), 6.45 (d, $J$ = 2.2 Hz, 1H), 6.43 (d, $J$ = 2.2 Hz, 1H), 5.04 (s, 2H), 5.01 (s, 2H), 4.05 – 4.01 (m, 1H), 3.24 (d, $J$ = 2.8 Hz, 1H), 3.07 (dd, $J$ = 17.3, 2.4 Hz, 1H), 2.71 (dd, $J$ = 17.4, 9.3 Hz, 1H), 2.25 (s, 3H), 1.45 – 1.40 (m, 1H), 1.34 – 1.31 (m, 1H), 1.30 – 1.20 (m, 6H), 0.87 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 208.28, 160.44, 157.48, 138.31, 136.42, 136.00, 128.66 (2 × C), 128.65 (2 × C), 128.25, 128.17, 127.52 (2 × C), 127.50 (2 × C), 124.01, 108.69, 98.02, 70.63, 70.10, 68.30, 51.14, 36.58, 31.80, 25.04, 22.59, 20.01, 14.06.

### *4.1.18. Synthesis of compounds **15a-15i***

General procedure: The **14a-14i** (0.5 mmol) was dissolved in DCM (10 mL) and Dess-Martin reagent (275 mg, 0.65 mmol) was added at 0 °C. The mixture was stirred for 2 h and then saturated aqueous solution of $Na_2S_2O_3$ (3 mL) and saturated aqueous solution of $NaHCO_3$ (5 mL) were added. After that the organic layer was separated, aqueous layer was extracted with DCM (3 × 10 mL), combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude products were purified by flash column chromatography to give compound **15a-15i**.

*4.1.18.1. Mixture of tautomers, 1-[2,4-bis(benzyloxy)-6-methylphenyl]-3-hydroxy-5- phenoxy-2-penten-1-one and 1-[2,4-bis(benzyloxy)-6-methylphenyl]-5-phenoxy-1,3- pentanedione (**15a**).* The tittle compound was synthesized as described in the general procedure using **14a** (249 mg, 0.5 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 25:1) to afford the desired product as a yellow oil (201 mg, 80.1% yield). According to the characteristic proton signals in $^1$H NMR, the product was a mixture of enol-keto tautomers containing approximately 76.9% enol-tautomer and 23.1% keto-tautomer. Enol-tautomer: $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 15.63 (brs, 1H), 7.42 – 7.28 (m, 10*H*), 7.28 – 7.26 (m, 2H), 6.95 (t, $J$ = 7.5 Hz, 1H), 6.87 (d, $J$ = 8.2 Hz, 2H), 6.45 (d, $J$ = 2.4 Hz, 2H), 5.87 (s, 1H), 5.03 (s, 4H), 4.23 (t, $J$ = 6.5 Hz, 2H), 2.80 (t, $J$ = 6.5 Hz, 2H), 2.33 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 190.61, 186.75, 160.44, 158.47, 157.34, 139.40, 136.59, 136.47, 129.44 (2 × C), 128.64 (2 × C), 128.50 (2 × C), 128.13, 127.83, 127.50 (2 × C), 126.91 (2 × C), 120.93, 119.93, 114.57 (2 × C), 108.65, 104.27, 98.44, 70.48, 70.04, 63.66, 38.41, 20.42. Keto-tautomer: $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.42 – 7.28 (m, 10*H*), 7.25 – 7.23 (m, 2H), 6.95 (t, $J$ = 7.5 Hz, 1H), 6.82 (d, $J$ = 8.2 Hz, 2H), 6.45 (d, $J$ = 2.4 Hz, 2H), 5.04 (s, 2H), 5.02 (s, 2H), 4.08 (t, $J$ = 6.5 Hz, 2H), 3.98 (s, 2H), 2.80 (t, $J$ = 6.5 Hz, 2H), 2.31 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 202.38, 198.80, 160.96, 158.47, 158.16, 139.98, 136.26, 135.74, 129.38 (2 × C), 128.77 (2 × C), 128.68 (2 × C), 128.44, 128.22, 127.82 (2 × C), 127.52 (2 × C), 122.88, 120.81, 114.44 (2 × C), 109.06, 97.89, 70.77, 70.10, 62.36, 59.08, 42.52, 20.52.

*4.1.18.2. Mixture of tautomers, 1-[2,4-bis(benzyloxy)-6-methylphenyl]-3-hydroxy-5-(3- methylphenoxy)-2-penten-1-one and 1-[2,4-bis(benzyloxy)-6-methylphenyl]-5-(3- methylphenoxy)-1,3- pentanedione (**15b**).* The tittle compound was synthesized as described in the general procedure using **14b** (255 mg, 0.5 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 25:1) to afford the desired product as a yellow oil (211 mg, 82.4% yield). According to the characteristic proton signals in $^1$H NMR, the product was a mixture of enol-keto tautomers containing approximately 78.4% enol-tautomer and 21.6% keto-tautomer. Enol-tautomer: $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 15.63 (brs, 1H), 7.42 – 7.27 (m, 10*H*), 7.15 (t, $J$ = 7.8 Hz, 1H), 6.77 (brd, $J$ = 8.0 Hz, 1H), 6.70 (d, $J$ = 2.2 Hz, 1H), 6.68 (dd, $J$ = 8.0, 2.2 Hz, 1H), 6.46 (brs, 1H), 6.45 (brs, 1H), 5.87 (s, 1H), 5.03 (s, 4H), 4.22 (t, $J$ = 6.6 Hz, 2H), 2.80 (t, $J$ = 6.6 Hz, 2H), 2.33 (s, 3H), 2.31 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 190.67, 186.77, 160.44, 158.50, 157.34, 139.49, 139.40, 136.60, 136.48, 129.17, 128.65 (2 × C), 128.51 (2 × C), 128.14, 127.83, 127.51 (2 × C), 126.90 (2 × C), 121.76, 119.96, 115.42, 111.43, 108.65, 104.26, 98.45, 70.48, 70.05, 63.61, 38.44, 21.51, 20.41. Keto-tautomer: $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.42 – 7.27 (m, 10*H*), 7.13 (t, 7.8 Hz, 1H), 6.75 (brd, $J$ = 8.4 Hz, 1H), 6.64 (brs, 1H), 6.62 (brd, 8.0 Hz, 1H), 6.46 (brs, 1H), 6.45 (brs, 1H), 5.04 (s, 2H), 5.02 (s, 2H), 4.07 (t, $J$ = 6.4 Hz, 2H), 3.98 (s, 2H), 2.80 (t, $J$ = 6.5 Hz, 2H), 2.30 (s, 6H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 202.47, 198.83, 160.96, 158.50, 158.16, 140.00, 139.42, 136.27, 135.76, 129.12, 128.77 (2 × C), 128.68 (2 × C), 128.43, 128.22, 127.79 (2 × C), 127.53 (2 × C), 122.90, 121.64, 115.29, 111.33, 109.07, 97.90, 70.76, 70.11, 62.34, 59.08, 42.58, 29.70, 20.53.

*4.1.18.3. Mixture of tautomers, 1-[2,4-bis(benzyloxy)-6-methylphenyl]-3-hydroxy-5-(4- methoxyphenoxy)-2-penten-1-one and 1-[2,4-bis(benzyloxy)-6-methylphenyl]-5-(4- methoxyphenoxy)-1,3- pentanedione (**15c**).* The tittle compound was synthesized as described in the general procedure using **14c** (264 mg, 0.5 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 15:1) to afford the desired product as a yellow oil (214 mg, 81.2% yield). According to the characteristic proton signals in $^1$H NMR, the product was a mixture of enol-keto tautomers containing approximately 76.9% enol-tautomer and 23.1% keto-tautomer. Enol-tautomer: $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 15.64 (brs, 1H), 7.42 – 7.25 (m, 10*H*), 6.81 (brs, 4H), 6.45 (d, $J$ = 2.3 Hz, 1H), 6.44 (d, $J$ = 2.3 Hz, 1H), 5.86 (s, 1H), 5.03 (s, 4H), 4.18 (t, $J$ = 6.5 Hz, 2H), 3.76 (s, 3H), 2.77 (t, $J$ = 6.5 Hz, 2H), 2.33 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 190.71, 186.78, 160.43, 157.33, 153.97, 152.63, 139.39, 136.60, 136.48, 128.64 (2 × C), 128.50 (2 × C), 128.13, 127.82, 127.51 (2 × C), 126.90 (2 × C), 119.96, 115.67 (2 × C), 114.58 (2 × C), 108.65, 104.28, 98.45, 70.47, 70.04, 64.53, 55.70, 38.51, 20.41. Keto-tautomer: $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.42 – 7.25 (m, 10*H*), 6.80 (d, $J$ = 9.0 Hz, 2H), 6.75 (d, $J$ = 9.0 Hz, 2H), 6.44 (brs, 2H), 5.03 (s, 2H), 5.01 (s, 2H), 4.03 (t, $J$ = 6.4 Hz, 2H), 3.97 (s, 2H), 3.75 (s, 3H), 2.77 (t, $J$ = 6.4 Hz, 2H), 2.30 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 202.50, 198.83, 160.95, 158.15, 153.87, 152.65,

139.98, 136.27, 135.76, 128.77 (2 × C), 128.68 (2 × C), 128.42, 128.22, 127.79 (2 × C), 127.52 (2 × C), 122.90, 115.47 (2 × C), 114.54 (2 × C), 109.07, 97.90, 70.75, 70.10, 63.18, 59.08, 55.70, 42.65, 20.52.

*4.1.18.4. Mixture of tautomers, 1-[2,4-bis(benzyloxy)-6-methylphenyl]-3-hydroxy −5-[3-(trifluoromethyl)-phenoxy]-2-penten-1-one and 1-[2,4-bis (benzyloxy)-6-methyl -phenyl]-5-[3-(trifluoro- methyl)phenoxy]-1,3-pentanedione (**15d**).* The tittle compound was synthesized as described in the general procedure using **14d** (282 mg, 0.5 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 25:1) to afford the desired product as a yellow oil (222 mg, 78.8% yield). According to the characteristic proton signals in $^{1}$H NMR, the product was a mixture of enol-keto tautomers containing approximately 76.9% enol-tautomer and 23.1% keto-tautomer. Enol-tautomer: $^{1}$H NMR (600 MHz, Chloroform-*d*) $\delta$ 15.60 (brs, 1H), 7.42 – 7.29 (m, 10*H*), 7.27 (t, $J$ = 7.4 Hz, 1H), 7.21 (d, $J$ = 8.2 Hz, 1H), 7.10 (brs, 1H), 7.02 (brd, $J$ = 8.2 Hz, 1H), 6.46 (brs, 2H), 5.87 (s, 1H), 5.04 (s, 2H), 5.03 (s, 2H), 4.25 (t, $J$ = 6.5 Hz, 2H), 2.81 (t, $J$ = 6.5 Hz, 2H), 2.34 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 190.30, 186.58, 160.52, 158.64, 157.40, 139.50, 136.55, 136.45, 131.79 (q, $J_{C\text{-}F}$ = 32.3 Hz), 129.96, 128.65 (2 × C), 128.49 (2 × C), 128.15, 127.86, 127.51 (2 × C), 126.93 (2 × C), 123.90 (q, $J_{C\text{-}F}$ = 272.4 Hz), 119.74, 117.98, 117.62 (q, $J_{C\text{-}F}$ = 3.9 Hz), 111.39 (q, $J_{C\text{-}F}$ = 3.7 Hz), 108.70, 104.32, 98.44, 70.50, 70.05, 63.98, 38.25, 20.44. Keto-tautomer: $^{1}$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.42 – 7.29 (m, 10*H*), 7.27 (t, $J$ = 7.4 Hz, 1H), 7.18 (d, $J$ = 8.2 Hz, 1H), 7.04 (brs, 1H), 6.97 (brd, $J$ = 8.3 Hz, 1H), 6.46 (brs, 2H), 5.04 (s, 2H), 5.02 (s, 2H), 4.07 (t, $J$ = 6.5 Hz, 2H), 3.97 (s, 2H), 2.81 (t, $J$ = 6.5 Hz, 2H), 2.31 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 201.95, 198.72, 161.03, 158.64, 158.21, 140.00, 136.24, 135.69, 131.72 (q, $J_{C\text{-}F}$ = 32.2 Hz), 129.90, 128.78 (2 × C), 128.69 (2 × C), 128.49, 128.24, 127.92 (2 × C), 127.52 (2 × C), 123.92 (q, $J_{C\text{-}F}$ = 272.4 Hz), 122.82, 117.85, 117.48 (q, $J_{C\text{-}F}$ = 3.7 Hz), 111.31 (q, $J_{C\text{-}F}$ = 3.8 Hz), 109.10, 97.89, 70.82, 70.12, 62.66, 59.08, 42.17, 20.52.

*4.1.18.5. Mixture of tautomers, 1-[2,4-bis(benzyloxy)-6-methylphenyl]-3-hydroxy-5- [4-(trifluoromethyl)-phenoxy]-2-penten-1-one and 1-[2,4-bis (benzyloxy)-6-methyl -phenyl]-5-[4-(trifluoro- methyl)phenoxy]-1,3-pentanedione (**15e**).* The tittle compound was synthesized as described in the general procedure using **14e** (282 mg, 0.5 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 25:1) to afford the desired product as a yellow oil (226 mg, 80.2% yield). According to the characteristic proton signals in $^{1}$H NMR, the product was a mixture of enol-keto tautomers containing approximately 76.9% enol-tautomer and 23.1% keto-tautomer. Enol-tautomer: $^{1}$H NMR (600 MHz, Chloroform-*d*) $\delta$ 15.60 (brs, 1H), 7.51 (d, $J$ = 8.5 Hz, 2H), 7.42 – 7.26 (m, 10*H*), 6.91 (d, $J$ = 8.5 Hz, 2H), 6.46 (d, $J$ = 2.6 Hz, 2H), 5.87 (s, 1H), 5.04 (s, 2H), 5.03 (s, 2H), 4.26 (t, $J$ = 6.5 Hz, 2H), 2.82 (t, $J$ = 6.5 Hz, 2H), 2.33 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 190.32, 186.56, 160.95, 160.54, 157.40, 139.50, 136.58, 136.45, 128.66 (2 × C), 128.51 (2 × C), 128.16, 127.86, 127.53 (2 × C), 126.90 (2 × C), 126.85 (q, $J_{C\text{-}F}$ = 3.9 Hz, 2 × C), 124.39 (q, $J_{C\text{-}F}$ = 270.9 Hz), 123.05 (q, $J_{C\text{-}F}$ = 32.7 Hz), 119.72, 114.49 (2 × C), 108.71, 104.32, 98.45, 70.49, 70.06, 63.91, 38.21, 20.45. Keto-tautomer: $^{1}$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.50 (d, $J$ = 8.5 Hz, 2H), 7.42 – 7.26 (m, 10*H*), 6.86 (d, $J$ = 8.5 Hz, 2H), 6.46 (d, $J$ = 2.6 Hz, 2H), 5.04 (s, 2H), 5.02 (s, 2H), 4.09 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 2H), 2.81 (t, $J$ = 6.3 Hz, 2H), 2.30 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 201.94, 198.72, 161.05, 160.95, 158.22, 140.01, 136.23, 135.71, 128.78 (2 × C), 128.70 (2 × C), 128.51, 128.25, 127.90 (2 × C), 127.52 (2 × C), 126.85 (q, $J_{C\text{-}F}$ = 3.9 Hz, 2 × C), 124.39 (q, $J_{C\text{-}F}$ = 270.9 Hz), 123.05 (q, $J_{C\text{-}F}$ = 32.7 Hz), 122.80, 114.39 (2 × C), 109.11, 97.91, 70.81, 70.13, 62.61, 59.07, 42.13, 20.53.

*4.1.18.6. Mixture of tautomers, 1-[2,4-bis(benzyloxy)-6-methylphenyl]-3-hydroxy-5-(3- fluorophenoxy)-2-penten-1-one and 1-[2,4-bis(benzyloxy)-6-methylphenyl]-5-(3- fluorophenoxy)-1,3- pentanedione (**15f**).* The tittle compound was synthesized as described in the general procedure using **14f** (257 mg, 0.5 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 25:1) to afford the desired product as a yellow oil (197 mg, 76.7% yield). According to the characteristic proton signals in $^{1}$H NMR, the product was a mixture of enol-keto tautomers containing approximately 78.7% enol-tautomer and 21.3% keto-tautomer. Enol-tautomer: $^{1}$H NMR (600 MHz, Chloroform-*d*) $\delta$ 15.60 (brs, 1H), 7.41 – 7.27 (m, 10*H*), 7.20 (brq, $J$ = 8.2 Hz, 1H), 6.68 – 6.62 (m, 2H), 6.58 (dt, $J$ = 10.9, 2.4 Hz, 1H), 6.46 (d, $J$ = 2.5 Hz, 1H), 6.45 (d, $J$ = 2.5 Hz, 1H), 5.86 (s, 1H), 5.04 (s, 2H), 5.03 (s, 2H), 4.20 (t, $J$ = 6.5 Hz, 2H), 2.79 (t, $J$ = 6.5 Hz, 2H), 2.34 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 190.40, 186.69, 163.59 (d, $J_{C\text{-}F}$ = 245.2 Hz), 160.52, 159.88 (d, $J_{C\text{-}F}$ = 10.8 Hz), 157.41, 139.49, 136.59, 136.49, 130.22 (d, $J_{C\text{-}F}$ = 9.9 Hz), 128.68 (2 × C), 128.54 (2 × C), 128.18, 127.90, 127.54 (2 × C), 126.97 (2 × C), 119.84, 110.30 (d, $J_{C\text{-}F}$ = 2.8 Hz), 108.71, 107.78 (d, $J_{C\text{-}F}$ = 21.3 Hz), 104.31, 102.37 (d, $J_{C\text{-}F}$ = 24.8 Hz), 98.47, 70.53, 70.08, 64.00, 38.26, 20.46. Keto-tautomer: $^{1}$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.41 – 7.27 (m, 10*H*), 7.20 (brq, $J$ = 8.2 Hz, 1H), 6.68 – 6.62 (m, 2H), 6.52 (dt, $J$ = 10.9, 2.4 Hz, 1H), 6.46 (d, $J$ = 2.5 Hz, 1H), 6.45 (d, $J$ = 2.5 Hz, 1H), 5.04 (s, 2H), 5.02 (s, 2H), 4.04 (t, $J$ = 6.4 Hz, 2H), 3.96 (s, 2H), 2.79 (t, $J$ = 6.4 Hz, 2H), 2.30 (s, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 202.10, 198.77, 163.56 (d, $J_{C\text{-}F}$ = 245.1 Hz), 161.04, 159.89 (d, $J_{C\text{-}F}$ = 10.9 Hz), 158.22, 140.04, 136.28, 135.73, 130.16 (d, $J_{C\text{-}F}$ = 10.0 Hz), 128.81 (2 × C), 128.72 (2 × C), 128.52, 128.27, 127.92 (2 × C), 127.56 (2 × C), 122.85, 110.18 (d, $J_{C\text{-}F}$ = 2.7 Hz), 109.12, 107.65 (d, $J_{C\text{-}F}$ = 21.0 Hz), 102.26 (d, $J_{C\text{-}F}$ = 24.8 Hz), 97.92, 70.83, 70.15, 62.70, 59.09, 42.26, 20.55.

*4.1.18.7. Mixture of tautomers, 1-[2,4-bis(benzyloxy)-6-methylphenyl]-3-hydroxy-2- hexen-1-one and 1-[2,4-bis(benzyloxy)-6-methylphenyl]-1,3-hexanedione (**15 g**).* The tittle compound was synthesized as described in the general procedure using **14 g** (209 mg, 0.5 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 20:1) to afford the desired product as a yellow oil (177 mg, 85.2% yield). According to the characteristic proton signals in $^{1}$H NMR, the product was a mixture of enol-keto tautomers containing approximately 80.0% enol-tautomer and 20.0% keto-tautomer. Enol-tautomer: $^{1}$H NMR (600 MHz, Chloroform-*d*) $\delta$ 15.72 (brs, 1H), 7.42 – 7.27 (m, 10*H*), 6.45 (brs, 2H), 5.76 (s, 1H), 5.04 (s, 2H), 5.03 (s, 2H), 2.33 (s, 3H), 2.28 (t, $J$ = 7.5 Hz, 2H), 1.62 (sext, $J$ = 7.5 Hz, 1H), 0.93 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 193.60, 187.44, 160.29, 157.20, 139.17, 136.64, 136.55, 128.64 (2 × C), 128.45 (2 × C), 128.12, 127.78, 127.51 (2 × C), 126.95 (2 × C), 120.56, 108.57, 103.54, 98.42, 70.46, 70.05, 40.36, 20.32, 19.23, 13.76. Keto-tautomer: $^{1}$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.42 – 7.27 (m, 10*H*), 6.44 (brs, 2H), 5.04 (s, 2H), 5.02 (s, 2H), 3.90 (s, 2H), 2.31 (t, $J$ = 7.4 Hz, 2H), 2.30 (s, 3H), 1.46 (sext, $J$ = 7.4 Hz, 2H), 0.80 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 204.86, 199.26, 160.84, 158.04, 139.85, 136.33, 135.87, 128.73 (2 × C), 128.68 (2 × C), 128.39, 128.20, 127.78 (2 × C), 127.52 (2 × C), 123.13, 109.03, 97.89, 70.74, 70.10, 58.74, 45.17, 20.44, 16.72, 13.55.

*4.1.18.8. Mixture of tautomers, 1-[2,4-bis(benzyloxy)-6-methylphenyl]-3-hydroxy-2- hepten-1-one and 1-[2,4-bis(benzyloxy)-6-methylphenyl]-1,3-heptanedione (**15 h**).* The tittle compound was synthesized as described in the general procedure using **14 h** (216 mg, 0.5 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 20:1) to afford the desired product as a yellow oil (173 mg, 76.7% yield). According to the characteristic proton signals in $^{1}$H NMR, the product was a mixture of enol-keto tautomers containing approximately 80.0% enol-tautomer and 20.0% keto-tautomer. Enol-tautomer: $^{1}$H NMR (600 MHz, Chloroform-*d*) $\delta$ 15.72 (s, 1H), 7.42 – 7.27 (m, 10*H*), 6.45 (brs, 2H), 5.76 (s, 1H), 5.04 (s, 2H), 5.03 (s, 2H), 2.32 (s, 3H), 2.30 (t, $J$ = 7.4 Hz, 2H), 1.57 (quint, $J$ = 7.4 Hz, 2H), 1.34 (sext, $J$ = 7.4 Hz, 2H), 0.90 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$

193.94, 187.30, 160.28, 157.20, 139.16, 136.65, 136.55, 128.63 (2 × C), 128.44 (2 × C), 128.11, 127.77, 127.50 (2 × C), 126.93 (2 × C), 120.54, 108.58, 103.46, 98.43, 70.46, 70.04, 38.22, 27.89, 22.37, 20.31, 13.83. Keto-tautomer: $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.42 – 7.27 (m, 10*H*), 6.44 (brs, 2H), 5.04 (s, 2H), 5.02 (s, 2H), 3.90 (s, 2H), 2.31 (t, $J$ = 7.4 Hz, 2H), 2.30 (s, 3H), 1.42 (quint, $J$ = 7.4 Hz, 2H), 1.34 (sext, $J$ = 7.4 Hz, 2H), 0.83 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 204.98, 199.27, 160.84, 158.05, 139.86, 136.33, 135.88, 128.73 (2 × C), 128.67 (2 × C), 128.37, 128.20, 127.74 (2 × C), 127.52 (2 × C), 123.13, 109.04, 97.89, 70.73, 70.10, 58.75, 43.03, 25.37, 22.12, 20.44, 13.83.

*4.1.18.9. Mixture of tautomers, 1-[2,4-bis(benzyloxy)-6-methylphenyl]-3-hydroxy-2- octen-1-one and 1-[2,4-bis(benzyloxy)-6-methylphenyl]-1,3-octanedione **(15i)**.* The tittle compound was synthesized as described in the general procedure using **14i** (224 mg, 0.5 mmol). The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 20:1) to afford the desired product as a yellow oil (179 mg, 80.7% yield). According to the characteristic proton signals in $^1$H NMR, the product was a mixture of enol-keto tautomers containing approximately 80.0% enol-tautomer and 20.0% keto-tautomer. Enol-tautomer: $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 15.72 (brs, 1H), 7.42 – 7.27 (m, 10*H*), 6.45 (brs, 2H), 5.76 (s, 1H), 5.03 (s, 2H), 5.03 (s, 2H), 2.33 (s, 3H), 2.30 (t, $J$ = 7.4 Hz, 2H), 1.60 (qiunt, $J$ = 7.4 Hz, 2H), 1.34 – 1.26 (m, 4H), 0.88 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 194.04, 187.22, 160.28, 157.19, 139.15, 136.67, 136.55, 128.64 (2 × C), 128.45 (2 × C), 128.11, 127.77, 127.50 (2 × C), 126.90 (2 × C), 120.54, 108.58, 103.45, 98.46, 70.46, 70.05, 38.51, 31.44, 25.49, 22.40, 20.31, 13.94. Keto-tautomer: $^1$H NMR (600 MHz, Chloroform-*d*) $\delta$ 7.42 – 7.27 (m, 10*H*), 6.44 (brs, 2H), 5.03 (s, 2H), 5.02 (s, 2H), 3.90 (s, 2H), 2.32 (t, $J$ = 7.5 Hz, 2H), 2.30 (s, 3H), 1.44 (qiunt, $J$ = 7.5 Hz, 2H), 1.23 (qiunt, $J$ = 7.5 Hz, 2H), 1.17 – 1.11 (m, 2H), 0.85 (t, $J$ = 7.3 Hz, 3H);$^{13}$C NMR (150 MHz, Chloroform-*d*) $\delta$ 204.99, 199.27, 160.84, 158.05, 139.86, 136.33, 135.88, 128.73 (2 × C), 128.67 (2 × C), 128.37, 128.20, 127.74 (2 × C), 127.52 (2 × C), 123.13, 109.04, 97.89, 70.73, 70.10, 58.76, 43.29, 31.17, 22.98, 22.42, 20.45, 13.92.

*4.1.19. Synthesis of compounds **16a**-**16i***

*4.1.19.1. 2,3-dihydro-2,7-dihydroxy-5-methyl-2-(2-phenoxyethyl)-4H-1-benzopyran-4-one **(16a)**.* The tittle compound was synthesized as described in the general procedure **B** using compound **15a** (100 mg) and 5% Pd/C (20 mg, 20 wt%) in ethanol (5 mL). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 25:1) to afford the desired product as a yellow oil (52 mg, 80.8% yield). $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 10.32 (s, 1H), 7.31 – 7.27 (m, 2H), 6.96 – 6.92 (m, 4H), 6.26 (d, $J$ = 2.3 Hz, 1H), 6.18 (d, $J$ = 2.3 Hz, 1H), 4.15 (brd, $J$ = 7.0 Hz, 2H), 3.01 (dd, $J$ = 15.9, 1.9 Hz, 1H), 2.62 (d, $J$ = 15.9 Hz, 1H), 2.46 (s, 3H), 2.36 (dt, $J$ = 14.0, 7.0 Hz, 1H), 2.26 (dt, $J$ = 14.0, 6.8 Hz, 1H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 191.37, 163.09, 161.68, 158.73, 142.81, 129.98 (2 × C), 121.06, 114.87 (2 × C), 112.91, 112.43, 102.07, 101.38, 63.73, 48.39, 39.96, 23.03. HRMS (ESI) *m/z* calcd for $C_{18}H_{18}O_5$ $[M + H]^+$ 315.1227, found 315.1214.

*4.1.19.2. 2,3-dihydro-2,7-dihydroxy-5-methyl-2-[2-(3-methylphenoxy) ethyl]-4H-1- benzopyran-4-one **(16b)**.* The tittle compound was synthesized as described in the general procedure **B** using compound **15b** (100 mg) and 5% Pd/C (20 mg, 20 wt%) in ethanol (5 mL). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 25:1) to afford the desired product as a yellow oil (59 mg, 89.7% yield). $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 10.34 (brs, 1H), 7.16 (t, $J$ = 7.8 Hz, 1H), 6.94 (brs, 1H), 6.78 (brs, 1H), 6.77 – 6.73 (m, 2H), 6.26 (d, $J$ = 2.3 Hz, 1H), 6.18 (d, $J$ = 2.3 Hz, 1H), 4.12 (brt, $J$ = 7.0 Hz, 2H), 3.00 (d, $J$ = 16.0 Hz, 1H), 2.62 (d, $J$ = 16.0 Hz, 1H), 2.46 (s, 3H), 2.34 (dt, $J$ = 13.9, 6.9 Hz, 1H), 2.28 (s, 3H), 2.24 (dt, $J$ = 13.9, 6.8 Hz, 1H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 191.39, 163.10, 161.68, 158.75, 142.80, 139.47, 129.70, 121.79, 115.44, 112.90, 112.41, 111.91, 102.06, 101.40, 63.65, 48.37, 39.95, 23.05, 21.57. HRMS (ESI) *m/z* calcd for $C_{19}H_{20}O_5$ $[M + H]^+$ 329.1384, found 329.1376.

*4.1.19.3. 2,3-dihydro-2,7-dihydroxy-5-methyl-2-[2-(4-methoxyphenoxy) ethyl]-4H-1-benzopyran-4-one **(16c)**.* The tittle compound was synthesized as described in the general procedure **B** using compound **15c** (100 mg) and 5% Pd/C (20 mg, 20 wt%) in ethanol (5 mL). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 25:1) to afford the desired product as a yellow oil (59 mg, 90.3% yield). $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 10.33 (s, 1H), 6.92 (d, $J$ = 2.1 Hz, 1H), 6.89 (d, $J$ = 9.1 Hz, 2H), 6.86 (d, $J$ = 9.1 Hz, 2H), 6.26 (d, $J$ = 2.4 Hz, 1H), 6.17 (d, $J$ = 2.3 Hz, 1H), 4.08 (brt, $J$ = 6.9 Hz, 2H), 3.69 (s, 3H), 3.00 (dd, $J$ = 16.0, 2.2 Hz, 1H), 2.61 (d, $J$ = 16.0 Hz, 1H), 2.46 (s, 3H), 2.33 (dt, $J$ = 13.9, 6.9 Hz, 1H), 2.23 (dt, $J$ = 13.9, 6.6 Hz, 1H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 191.39, 163.08, 161.68, 153.82, 152.75, 142.80, 115.75 (2 × C), 115.06 (2 × C), 112.89, 112.42, 102.06, 101.41, 64.27, 55.78, 48.38, 40.02, 23.05. HRMS (ESI) *m/z* calcd for $C_{19}H_{20}O_6$ $[M + H]^+$ 345.1333, found 345.1316.

*4.1.19.4. 2,3-dihydro-2,7-dihydroxy-5-methyl-2-[2-[3-(trifluoromethyl) phenoxy]- ethyl]-4H-1-benzopyran-4-one **(16d)**.* The tittle compound was synthesized as described in the general procedure **B** using compound **15d** (100 mg) and 5% Pd/C (20 mg, 20 wt%) in ethanol (5 mL). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 25:1) to afford the desired product as a yellow oil (58 mg, 85.3% yield). $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 10.33 (s, 1H), 7.53 (t, $J$ = 8.3 Hz, 1H), 7.31 – 7.27 (m, 3H), 6.97 (d, $J$ = 2.0 Hz, 1H), 6.26 (d, $J$ = 2.3 Hz, 1H), 6.18 (d, $J$ = 2.3 Hz, 1H), 4.24 (brt, $J$ = 6.9 Hz, 2H), 3.04 (dd, $J$ = 15.9, 2.0 Hz, 1H), 2.64 (d, $J$ = 15.9 Hz, 1H), 2.47 (s, 3H), 2.39 (dt, $J$ = 14.0, 6.9 Hz, 1H), 2.29 (dt, $J$ = 14.0, 6.8 Hz, 1H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 191.35, 163.09, 161.65, 159.08, 142.80, 131.18, 130.79 (q, $J_{C\text{-}F}$ = 31.5 Hz), 124.49 (q, $J_{C\text{-}F}$ = 272.4 Hz), 119.32, 117.62 (q, $J_{C\text{-}F}$ = 3.9 Hz), 112.91, 112.41, 111.33 (q, $J_{C\text{-}F}$ = 3.9 Hz), 102.07, 101.27, 64.49, 48.25, 39.97, 23.05. HRMS (ESI) *m/z* calcd for $C_{19}H_{17}F_3O_5$ $[M + H]^+$ 383.1101, found 383.1100.

*4.1.19.5. 2,3-dihydro-2,7-dihydroxy-5-methyl-2-[2-[4-(trifluoromethyl) phenoxy]- ethyl]-4H-1-benzopyran-4-one **(16e)**.* The tittle compound was synthesized as described in the general procedure **B** using compound **15e** (100 mg) and 5% Pd/C (20 mg, 20 wt%) in ethanol (5 mL). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 25:1) to afford the desired product as a yellow oil (55 mg, 80.3% yield). $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 10.33 (s, 1H), 7.66 (d, $J$ = 8.6 Hz, 2H), 7.16 (d, $J$ = 8.6 Hz, 2H), 6.98 (d, $J$ = 2.2 Hz, 1H), 6.26 (d, $J$ = 2.3 Hz, 1H), 6.18 (d, $J$ = 2.3 Hz, 1H), 4.25 (brt, $J$ = 6.9 Hz, 2H), 3.02 (dd, $J$ = 16.0, 2.2 Hz, 1H), 2.63 (d, $J$ = 15.9 Hz, 1H), 2.46 (s, 3H), 2.39 (dt, $J$ = 14.0, 7.0 Hz, 1H), 2.30 (dt, $J$ = 13.7, 6.6 Hz, 1H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 191.29, 163.10, 161.63, 161.62, 142.82, 127.43 (q, $J_{C\text{-}F}$ = 3.9 Hz, 2 × C), 125.04 (q, $J_{C\text{-}F}$ = 272.4 Hz), 121.60 (q, $J_{C\text{-}F}$ = 32.0 Hz), 115.42 (2 × C), 112.93, 112.41, 102.01, 101.26, 64.41, 48.33, 39.72, 23.04. HRMS (ESI) *m/z* calcd for $C_{19}H_{17}F_3O_5$ $[M + H]^+$ 383.1101, found 383.1118.

*4.1.19.6. 2,3-dihydro-2,7-dihydroxy-5-methyl-2-[2-(3-fluorophenoxy) ethyl]-4H-1- benzopyran-4-one **(16f)**.* The tittle compound was synthesized as described in the general procedure **B** using compound **15f** (100 mg) and 5% Pd/C (20 mg, 20 wt%) in ethanol (5 mL). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 25:1) to afford the desired product as a yellow oil (56 mg, 86.4% yield). $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 10.35 (brs, 1H), 7.31 (q, $J$ = 7.8 Hz, 1H), 6.96 (brs, 1H), 6.86 (brd, $J$ = 11.3 Hz, 1H), 6.81 (brd, $J$ = 8.4 Hz, 1H), 6.77 (brt, $J$ = 8.4 Hz, 1H), 6.26 (d, $J$ = 2.2 Hz, 1H), 6.18 (d, $J$ = 2.2 Hz, 1H), 4.17 (brt, $J$ = 6.9 Hz, 2H), 3.01 (d, $J$ = 16.0 Hz, 1H), 2.62 (d, $J$ = 16.0

Hz, 1H), 2.46 (s, 3H), 2.36 (dt, $J = 13.8$, 7.0 Hz, 1H), 2.27 (dt, $J = 13.8$, 6.7 Hz, 1H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 191.35, 163.48 (d, $J_{C\text{-}F} =$ 242.8 Hz), 163.10, 161.65, 160.27 (d, $J_{C\text{-}F} = 11.0$ Hz), 142.81, 131.16 (d, $J_{C\text{-}F} = 10.1$ Hz), 112.92, 112.41, 111.34 (d, $J_{C\text{-}F} = 2.7$ Hz), 107.67 (d, $J_{C\text{-}F} = 21.2$ Hz), 102.39 (d, $J_{C\text{-}F} = 24.9$ Hz), 102.07, 101.28, 64.38, 48.28, 39.96, 23.05. HRMS (ESI) *m/z* calcd for $C_{18}H_{17}FO_5$ $[M + Na]^+$ 355.0952, found 355.0953.

*4.1.19.7. 2,3-dihydro-2,7-dihydroxy-5-methyl-2-propyl-4H-1-benzopyran-4-one (**16 g**).* The tittle compound was synthesized as described in the general procedure **B** using compound **15 g** (100 mg) and 5% Pd/C (20 mg, 20 wt%) in ethanol (5 mL). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 15:1) to afford the desired product as a yellow oil (49 mg, 85.7% yield). $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 10.27 (brs, 1H), 6.61 (s, 1H), 6.23 (d, $J = 2.4$ Hz, 1H), 6.13 (d, $J = 2.4$ Hz, 1H), 2.84 (d, $J = 15.8$ Hz, 1H), 2.47 (d, $J = 15.8$ Hz, 1H), 2.45 (s, 3H), 1.83 – 1.71 (m, 2H), 1.45 – 1.38 (m, 2H), 0.91 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 191.72, 163.04, 162.02, 142.69, 112.69, 112.45, 102.49, 101.98, 47.70, 42.86, 23.03, 17.12, 14.57. HRMS (ESI) *m/z* calcd for $C_{13}H_{16}O_4$ $[M + H]^+$ 237.1121, found 237.1118.

*4.1.19.8. 2-butyl-2,3-dihydro-2,7-dihydroxy-5-methyl-4H-1-benzopyran-4-one (**16 h**).* The tittle compound was synthesized as described in the general procedure **B** using compound **15 h** (100 mg) and 5% Pd/C (20 mg, 20 wt%) in ethanol (5 mL). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 15:1) to afford the desired product as a yellow oil (52 mg, 89.4% yield). $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 10.26 (s, 1H), 6.60 (d, $J = 2.2$ Hz, 1H), 6.23 (d, $J = 2.3$ Hz, 1H), 6.13 (d, $J = 2.3$ Hz, 1H), 2.83 (d, $J = 15.7$ Hz, 1H), 2.47 (d, $J = 15.7$ Hz, 1H), 2.45 (s, 3H), 1.84 – 1.73 (m, 2H), 1.41 – 1.35 (m, 2H), 1.34 – 1.28 (m, 2H), 0.89 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 191.71, 163.02, 162.02, 142.69, 112.68, 112.46, 102.57, 101.98, 47.71, 39.98, 25.87, 23.03, 22.76, 14.40. HRMS (ESI) *m/z* calcd for $C_{14}H_{18}O_4$ $[M + H]^+$ 251.1278, found 251.1269.

*4.1.19.9. 2,3-dihydro-2,7-dihydroxy-5-methyl-2-pentyl-4H-1-benzopyran-4-one (**16i**).* The tittle compound was synthesized as described in the general procedure **B** using compound **15i** (100 mg) and 5% Pd/C (20 mg, 20 wt%) in ethanol (5 mL). The crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 25:1) to afford the desired product as a yellow oil (49 mg, 81.9% yield). $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 10.26 (s, 1H), 6.60 (d, $J = 2.1$ Hz, 1H), 6.23 (d, $J = 2.3$ Hz, 1H), 6.12 (d, $J = 2.3$ Hz, 1H), 2.84 (dd, $J = 15.8$, 2.1 Hz, 1H), 2.47 (d, $J = 15.9$ Hz, 1H), 2.45 (s, 3H), 1.83 – 1.72 (m, 2H), 1.43 – 1.36 (m, 2H), 1.33 – 1.25 (m, 4H), 0.88 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 191.71, 163.01, 162.02, 142.69, 112.68, 112.46, 102.57, 101.97, 47.70, 40.61, 31.82, 23.36, 23.03, 22.52, 14.38. HRMS (ESI) *m/z* calcd for $C_{15}H_{20}O_4$ $[M + H]^+$ 265.1434, found 265.1434.

### 4.2. Biological activities

#### 4.2.1. Cell culture and cell cytotoxicity

The Raw264.7 cells were cultured in DMEM (Corning, Wujiang, Jiangsu Province, China) supplemented with 10% fetal bovine serum (Lonsera, Uruguay), 2 mM glutamine (Biological Industries, Israel), 100 U/mL of penicillin (TBD, Tianjin, China) and 100 μg/mL of streptomycin (TBD, Tianjin, China) at 37 °C with 5% $CO_2$ atmosphere. The cells were seeded in a 96-well plate at $8 \times 10^3$ cells / well for 24 h, and then were pretreated with or without synthetic molecules for 24 h. After that, the cell viability was measured by MTT assay as previously described [24,25].

#### 4.2.2. Determination of NO

RAW264.7 cells were cultured in a 24-well plate with $1.4 \times 10^5$cells / well for 24 h. Cells were pretreated with synthetic molecules (33 μM) for 2 h and were induced with LPS (1 μg / mL). After 24 h, the cell supernatant was collected for further research. The NO production was measured by Griess reagent assay as previously described [24,25] and the inhibition of NO production calculation was calculated by formula:

$$\text{inhibition rate } (\%) = \frac{A_{540}(\text{LPS}) - A_{540}(\text{test compound})}{A_{540}(\text{LPS}) - A_{540}(\text{DMSO})} \times 100\%$$

#### 4.2.3. Western blotting

RAW264.7 cells were cultured in a 6-well plate with $0.8 \times 10^6$ cells / well for 24 h. Cells were pretreated with compound **7a, 16d** or positive control (DXM) for 2 h and then induced with LPS (1 μg / mL). After 30 min or 24 h (for iNOS protein), the cells were harvested and lysed with RIPA buffer and then the total protein was extracted by Protein Extraction Kits (Beyotime, Shanghai, China). The concentration of total protein was determined by BCA protein assay kit (Beyotime, Shanghai, China). Equal quantities of protein (40–60 μg) were separated by 10% SDS-PAGE and then were transferred to 0.45 μm PVDF membranes (Millipore, Billerica, MA, America). The membranes were blocked with 5% milk for 1 h and incubated with the specific primary antibody p65 (1:1000, ABclonal, Boston, MA, America), p-p65 (1:1000, ABclonal, Boston, MA, America), IκB-α(1:2000, Cell Signaling Technology, Boston, MA, America), p-IκB-α (1:2000, Cell Signaling Technology, Boston, MA, America) and iNOS (1:2000, Cell Signaling Technology, Boston, MA, America) overnight at 4 °C. After washing three times with TBST, the membranes were incubated with HRP-secondary antibody for 1 h at room temperature. At last, the resulting bolts were treated with enhanced chemiluminescence reagents (Millipore, Billerica, MA, America) and detected by Bio-Rad ChemiDoc™XRS + System (Bio-Rad, Hercules, CA, USA).

#### 4.2.4. Statistical analyses

All experiments were repeated at least three times, experimental data were expressed as mean ± SD and analyzed statistically by Student's *t* test. The differences were assumed to be statistically significant at $p < 0.05$.

## Declaration of Competing Interest

The authors declared no conflict of interest.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2021.104898.

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