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CONCISE ARTICLE

# Inspired by magnolol: design of NSAIDs-based compounds with excellent anti-inflammatory effect

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Wenfeng Liu,[a, 1] Yuan Yue,[a, 1] Yonglian Li,[b] Xi Zheng,[a, c] Kun Zhang*[a] and Zhiyun Du*[a]

Magnolol is a major active constituent of *Magnolia officinalis*, which is a natural traditional Chinese medicine. Inspired by magnolol, showed a wide diversity of bioactivities, a series of magnolol derivatives containing nonsteroidal anti-inflammatory drugs (NSAIDs) were designed, synthesized and screened for their anti-inflammatory activities by using a TPA-induced mouse ear edema model. These results indicated that in comparison with magnolol and ketoprofen, topical application of A10 (magnolol derivative containing ketoprofen) prior to TPA treatment markedly suppressed the expressions of IL-1β, IL-6 and TNF-α, respectively. The further mechanical investigations demonstrated that A10 inhibited IKK and IκBα phosphorylation, thereby suppressing the activation of p65. Accordingly, A10 may be a potent anti-inflammatory agent capable of preventing inflammation-associated edema.

## 1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs), which possess a free carboxylic acid group (Fig. 1), have been widely used as over the counter drugs[1] to treat inflammatory and immune associated diseases, such as rheumatoid arthritis[2], pain[3], and cancer[4, 5]. However, long term oral administration of NSAIDs is frequently associated with serious adverse effects[6, 7], including gastric mucosal[8] and renal damage[9, 10]. In contrast to oral administration, topical application of NSAIDs provided numerous potential benefits, containing avoidance of first pass metabolism and gastrointestinal (GI) tract[11]. Herein, inspired by *Magnolia officinalis*, a natural traditional Chinese medicine which contains magnolol, kinds of novel anti-inflammatory agents were developed for transdermal application by linking magnolol with NSAIDs to improve their activities and avoid their adverse effects.

Magnolol is the main active constituent originally isolated from the bark of *Magnolia officinalis*[12], which has multiple pharmacological activities, such as anti-inflammatory[13], anti-oxidative[14], anti-anxiety[15] and anti-proliferative activities[16]. It was reported that magnolol had been considered as no safety concern food additive and dietary supplement[17]. Furthermore, magnolol was found to regulate the expression of pro-inflammatory cytokines including IL-1β, IL-6 and TNF-α[18, 19]. It was confirmed that pro-inflammatory cytokines were implicated in increasing transcriptional activity of nuclear factor-κB (NF-κB)[20]. NF-κB, well known as a key transcriptional factor consisting of p50 and p65, usually forms a multiprotein complex with inhibitor of NF-κB (IκB) in the inactive state[21]. On activation by 12-*O*-tetradecanoylphorbol-13-acetate (TPA), the inflammatory signal activates a set of the IκB kinase (IKK) complex, which is the major upstream kinase for IκBα phosphorylation. It was indicated that magnolol markedly inhibited phosphorylation of IκBα, thereby suppressing the expression of pro-inflammatory cytokines[22]. Recent findings identified magnolol as a promising anti-inflammatory agent that may be repositioned as a therapeutical agent to treat inflammatory and immune associated diseases[23].

Given all above, we proposed linking magnolol with NSAIDs, with the aim of obtaining unique anti-inflammatory agents. Therefore, firstly, a series of magnolol derivatives containing NSAIDs were designed, synthesized and screened for their anti-inflammatory activities by using a TPA-induced mouse ear edema model. Secondly, immunohistochemical analysis revealed that A10 suppressed TPA-induced IL-1β, IL-6 and TNF-α expression by inhibiting IKK/NF-κB signaling pathway. Accordingly, A10 may be a novel anti-inflammatory agent for the treatment of inflammation associated skin diseases.

[a] *Laboratory of Natural Medicinal Chemistry & Green Chemistry, Faculty of Light Industry and Chemical Engineering, Guangdong University of Technology, Guangzhou, 510006, China. E-mail: kzhang@gdut.edu.cn; zhiyundu@foxmail.com*
[b] *Guangdong Industry Technical College, Guangzhou, 510300, China.*
[c] *Susan Lehman Cullman Laboratory for Cancer Research, Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA.*

† Footnotes relating to the title and/or authors should appear here.
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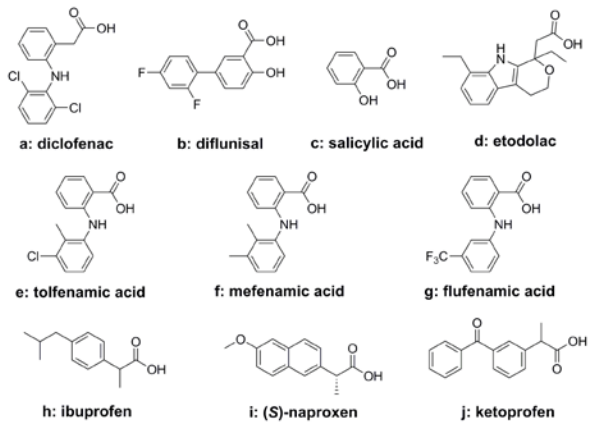



**Fig 1**. Chemical structures of NSAIDs possessing a free carboxylic acid group

## 2. Experimental Procedures

### 2.1. Material

Magnolol (assay of 99.5%) was obtained from Sinopharm Chemical Reagent Co. (Shanghai, China). NSAIDs were purchased from Sigma Chemical Co. (St. Louis, MO). TPA was supplied from Henan Cancer Hospital (Henan, China). DMSO, dichloromethane and other chemicals used were in the purest form available commercially. IL-1β, IL-6 and TNF-α were purchased from Bioss Biotechnology Co. (Beijing, China). Anti-rabbit and anti-mouse horseradish peroxidase (HRP)-conjugated secondary antibodies, anti-IKK, anti-Ser32 IkBα, anti-Ser536 p65, anti-phospho-Ser32 IkBα, and anti-phospho-Ser536 p65 antibodies were obtained from Beyotime Biotechnology Co. (Beijing, China).

### 2.2. Animals

Female BALB/c mice at 5-6 week old (3 per group for each assay, approval documents: SCXK/20130002) were supplied from Center of Animal Test of SUN Yat-sen University (Guangzhou, China). All animals were group housed (25±1 $^{o}$C at 50% relative humidity) and fed standard mouse chow diet and tap water ad libitum. All experiments were performed in compliance with the relevant laws and institutional guidelines, and the Center of Animal Test of SUN Yat-sen University has approved the experiments.

For mouse ear edema model, both ears of female BALB/c mice were topically treated with 15 μL vehicle (DMSO : methylene chloride = 20 : 80), acetone, curcumin, sulindac or combining of curcumin and sulindac (1 : 1, mol/mol) in 15 μL vehicle or sulindac-based compound in 15 μL vehicle, 6 min prior to TPA treatment (0.008 nM in acetone). The mice were then euthanized after 6 hours. Two ear punches (6 mm in diameter) from both ears were then taken and weighed. The inhibitory effects (IE) were expressed as the ratio of relative increase of the weight of the treated punch to that of a control punch; IE (%)=((TPA alone)−(test compound plus TPA)) / ((TPA)−(acetone))×100.

### 2.3. Preparation of magnolol derivatives containing NSAIDs

Magnolol (1.2 mmol) and NSAID (1.0 mmol or 2.0 mmol) were dissolved in $CH_2Cl_2$ (30 mL), and then EDCI (1.0 mmol or 2.0 mmol) and DMAP (0.1 mmol) were added into the solution. The reaction mixture was stirred for 1 hour at room temperature. Then the reaction was quenched with saturated aqueous $NaHCO_3$, extracted with ethyl acetate (3 x 30 mL), dried over $Na_2SO_4$, concentrated under reduced pressure and purified by silica gel chromatography (eluent:ethyl acetate/petroleum = 1/4 or 1/8) to give the target compounds for the further studies.

### 2.4. Characterization of magnolol derivatives containing NSAIDs

The melting points were determined on X-4 melting apparatus (Beijing, China) and were uncorrected. NMR spectra using a Bruker Ascend Ⅲ 400 spectrometer 400.13 MHz NMR spectrometer and 100.61 MHz NMR spectrometer were recorded. $^{1}$H NMR spectra in $CDCl_3$ were referenced at $\delta$ = 7.26 ppm. $^{13}$C NMR spectra in $CDCl_3$ were referenced at $\delta$ = 77.23 ppm. High resolution mass spectrometric analyses were performed on a FT Mass Spectrometer. Elemental analysis was obtained with Series II 2400 elemental analyzer (Perkin Elmer, USA). §

### 2.5. Histological appearance of mouse ears

BALB/c mice were all sacrificed after 6 hours. Both ears were removed in toto, fixed in 10% formalin, decalcified in EDTA buffer, subjected in a series progression of dehydration, and then embedded in paraffin. Samples were serially sectioned at 4 μm and processed routinely for H&E staining. The histological changes were obtained under microscope.

### 2.6. Determination of IL-1β, IL-6 and TNF-α

After sacrifice, both ears of BALB/c mice were removed and the deparaffinized skin sections (4 μm) were incubated with 1.2% $H_2O_2$ in PBS to quench the endogenous peroxidase activity. The primary antibody of proliferating cell nuclear antigen was diluted 100 times then applied to each section overnight at 4 $^{o}$C. After washing with PBS, the sections were incubated with a biotin-conjugated horseradish peroxidase antibody (1:200) for 1 h at room temperature. Finally, the peroxidase was detected using the 3, 3 diaminobenzidine tetrahydrochloride reaction, which produced the brown label in the epidermal tissue. The numbers of positive staining cells were counted in five different fields at both ends as well as in the middle for each section.

### 2.7. Assay of NF-κB p65, phospho-p65, IκBa, phospho-IκBa, IKK

NF-κB transcriptional activities were measured by immunohistochemistry analysis. Mouse ears were removed in toto, fixed in 10% formalin, decalcified in EDTA buffer, subjected in a series progression of dehydration, and then embedded in paraffin. Samples were serially sectioned at 4 μm and processed routinely for staining. The histological changes were examined under microscope.

### 2.8. Scoring the expression of biomarkers

For each female BALB/c mouse, ≥5 ducts per histologic type of TPA-induced ductal lesion were scored independently by two experienced investigators not aware of the identity of the specimens (×200). For IL-1β, IL-6, TNF-α, COX-2, PI3K p85, p-PI3K

p85, Akt, IKK, IκBα, p65, p-Akt, p-IκBα and p-p65, we used integrated optical density (IOD) as the semi-quantitative scoring system[24].

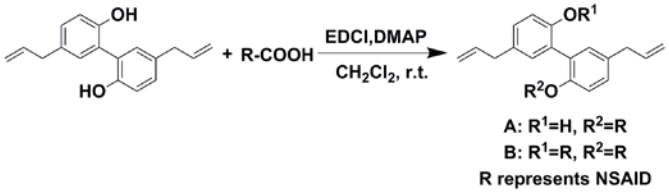
### 2.9. Statistical analysis

The results are presented as the mean ± SE. Data are presented as mean ± S.D. Comparison of more than two groups was made with a one-way analysis of variance ANOVA followed by Dunnett *t* test. *P* values less than 0.05 ($p < 0.05$) were considered indicative of significance.

## 3. Results and discussion

### 3.1. Chemistry

The synthetic routes for preparing compounds A1-A10 and B1-B10 were depicted in Scheme 1. Magnolol is reacted with NSAIDs in dichloromethane at room temperature to afford magnolol derivatives containing mono-NSAID or magnolol derivatives containing di-NSAIDs. Therefore, in order to obtain these mono-NSAID based compounds, one equivalent of NSAIDs is reacted in the esterification to ensure NSAID attached to the single terminal of magnolol. Similarly, two equivalents of NSAIDs are reacted in the esterification to ensure NSAIDs attached to both terminal of magnolol.




**Scheme 1.** General synthesis of Series A and Series B

**Table 1.** Chemical structures of magnolol derivatives containing NSAIDs

| Compd | $R^1$ | $R^2$ | Compd | $R^1$ | $R^2$ |
|---|---|---|---|---|---|
| **A1** | H | a | **B1** | a | a |
| **A2** | H | b | **B2** | b | b |
| **A3** | H | c | **B3** | c | c |
| **A4** | H | d | **B4** | d | d |
| **A5** | H | e | **B5** | e | e |
| **A6** | H | f | **B6** | f | f |
| **A7** | H | g | **B7** | g | g |
| **A8** | H | h | **B8** | h | h |
| **A9** | H | i | **B9** | i | i |
| **A10** | H | j | **B10** | j | j |

### 3.2. Dose-response effect of magnolol against TPA-induced mouse ear edema

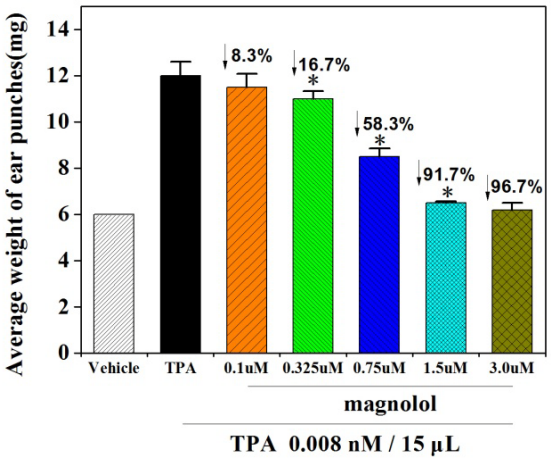



**Fig 2.** Dose-response relationship of magnolol on TPA-induced mouse ear edema. Data are expressed as mean ± S.D. (n = 3), *P < 0.05 (Dunnett *t* test), compared with TPA-treated mice.

To determine whether or not magnolol has any influence on decrease in the average weight of ear punches, we tested their anti-inflammatory activities in a dose-dependent manner by using a TPA-induced mouse ear edema model. Upon stimulation with TPA alone, the average weight of ear punches was significantly increased. (Fig. 2) When magnolol at different concentrations (0.1 μM, 0.325 μM, 0.75 μM, 1.5 μM and 3.0 μM) were applied topically onto mouse ears before TPA treatment, the average weight of ear punches were dose-dependently decreased. Inhibitory effect of magnolol at 0.75 μM on TPA-induced ear edema was statistically significant with a decrease in the average weight of ear punches by 58.3% (Fig. 2). These derivatives which linking magnolol with NSAIDs at 0.75 μM concentration showed that the majority of them decreased in the average weight of ear punches and their inhibitory abilities were comparable to or sometimes more pronounced than that of magnolol at the same concentration. When higher concentrations (1.5 μM and 3.0 μM) were used, magnolol caused more than 90% decrease in the average weight of ear punches. It was difficult to determine whether inhibitory abilities of these derivatives were comparable to or more pronounced than that of magnolol at the same concentration. Herein, we selected the concentration of 0.75 μM for our subsequent experiments to investigate the increase in the effectiveness of the derivatives.

### 3.3. Effects of magnolol derivatives containing NSAIDs on TPA-induced mouse ear edema

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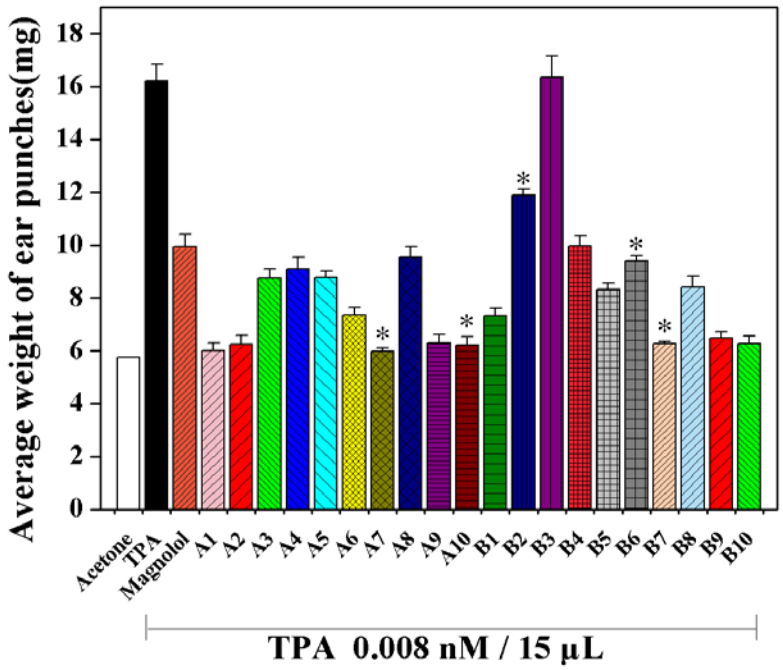



**Fig 3.** Effects of magnolol and 20 synthesized compounds on TPA-induced mouse ear edema. Data are expressed as mean ± S.D. (n = 3), *P < 0.05 (Dunnett *t* test), compared with TPA-treated mice.

According to previous dose-response experiments for magnolol, the concentration of these magnolol derivatives used in the initial screening was selected to be 0.75 μM. As shown in Fig. 4, topical application of TPA onto mouse ears resulted in the average weight of ear punches (6 mm diameter) increasing from 5.8 mg to 16.2 mg. The inhibitory effects of 17 compounds were found to more potent than that of magnolol. Furthermore, the effect of the tested compounds (up to 90% decrease) on TPA-induced mouse ear edema had descending order as follow: (A1 > A2 > A7 > A10 > B7 > B10 > A9 > B9).

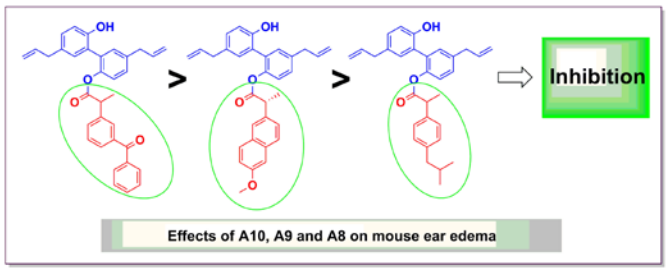



**Fig 4.** The most potent compounds containing propionic acid NSAID against TPA-induced mouse ear edema

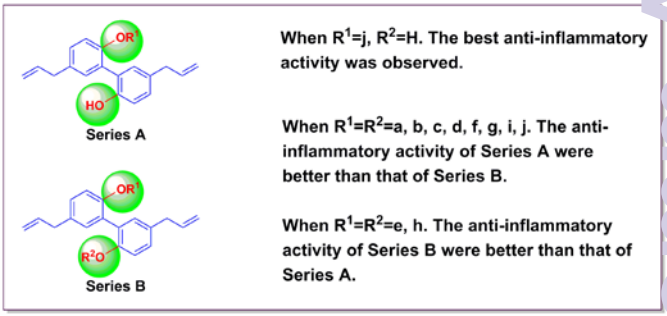


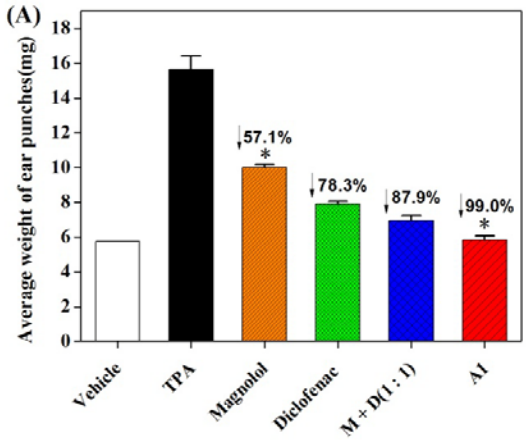

**Fig 5.** Anti-inflammatory structure activity relationship of the target compounds.

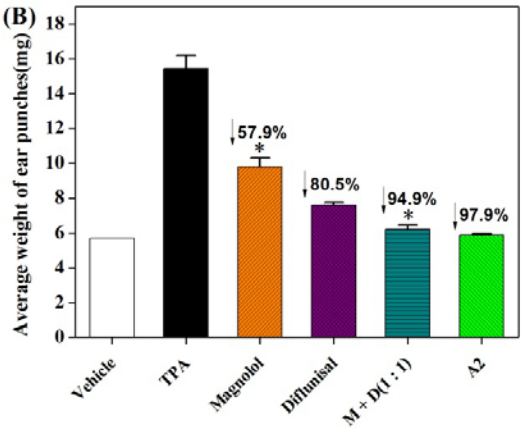
As illustrated in Fig 4 and 5, the most potent magnolol derivative containing propionic acid NSAID against mouse ear edema is A10. Moreover, Except A5 and A7, other magnolol derivatives containing mono-NSIAD showed higher potency to decrease the weights of ear punches than that of corresponding magnolol derivatives containing bis-NSAIDs. The possible reasons for this were that B1, B2, B3, B4, B6, B7, B9 and B10, magnolol derivatives containing bis-NSAIDs, have no free phenolic for binding at active site, weaker bioactivities and decreased solubility. However, further investigations are needed to confirm the reasons.

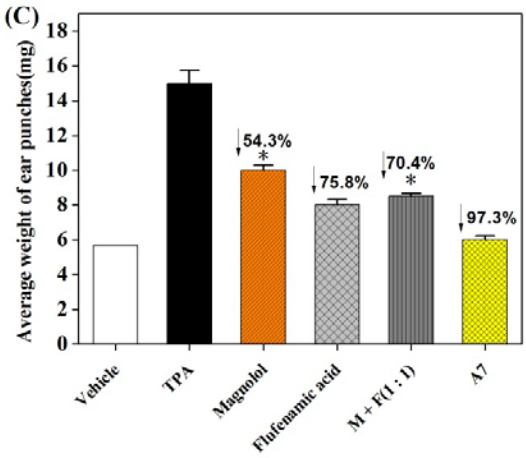
To investigate whether or not the anti-inflammatory activities of A1, A2, A7, A9, A10, B7, B9 and B10 (up to 90% decrease in initial screening) are better than magnolol, corresponding NSAID and

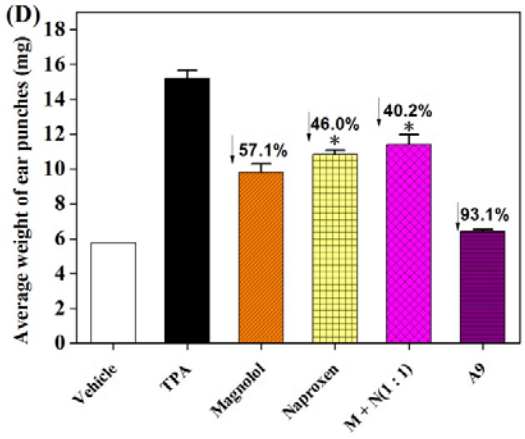
combination of magnolol and NSAID (1:1 or 1:2, mol/mol), we determine the average weight of ear punches by using the same topical inflammation model. As illustrated in Fig 6A-H, the average weight of ear punches increased upon treatment with TPA for 6 h, which was markedly decreased by A1, A2, A7, A9, A10, B7, B9 and B10 pretreatment. Furthermore, only A10 showed highest potency to decrease the average weightsd of ear punches than that of magnolol, the corresponding NSAID (ketoprofen) and co-treatment magnolol with ketoprofen (1:1) against TPA-induced mouse ear edema. (Fig 6E)

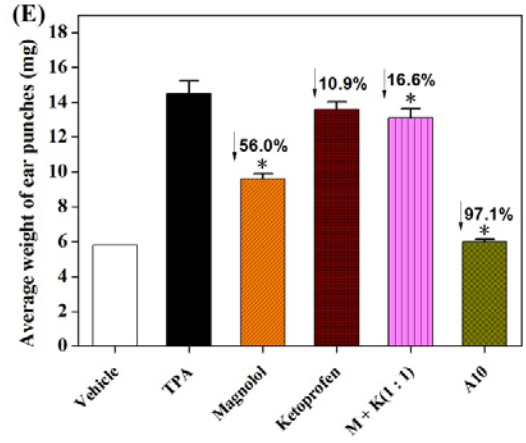
As shown in Fig. 6E, inhibitory effect of ketoprofen applied topically onto TPA-induced mouse ears was ineffective. It was previously shown that topical application of ketoprofen onto mouse ear was not effective on decreasing the average weight of ear punches[25]. The possible reason for the inactivity may be that ketoprofen did not regulate the expression of prostaglandin endoperoxide H synthase-2 (PGHS-2) in mouse ear edema in low dose[26]. The small effect of ketoprofen on reducing ear edema observed in our study may be related to a low dose used. Increasing the dose of ketoprofen may enhance its inhibitory effect on mouse ear edema.

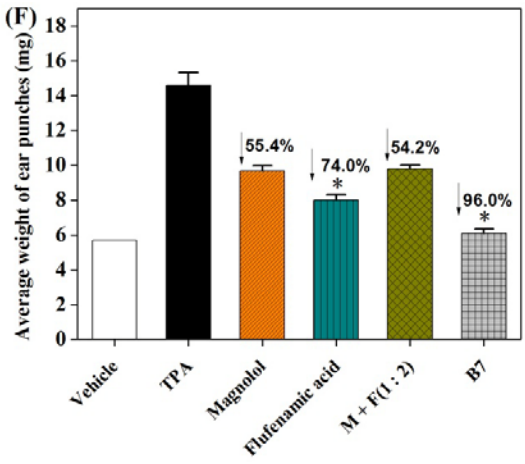


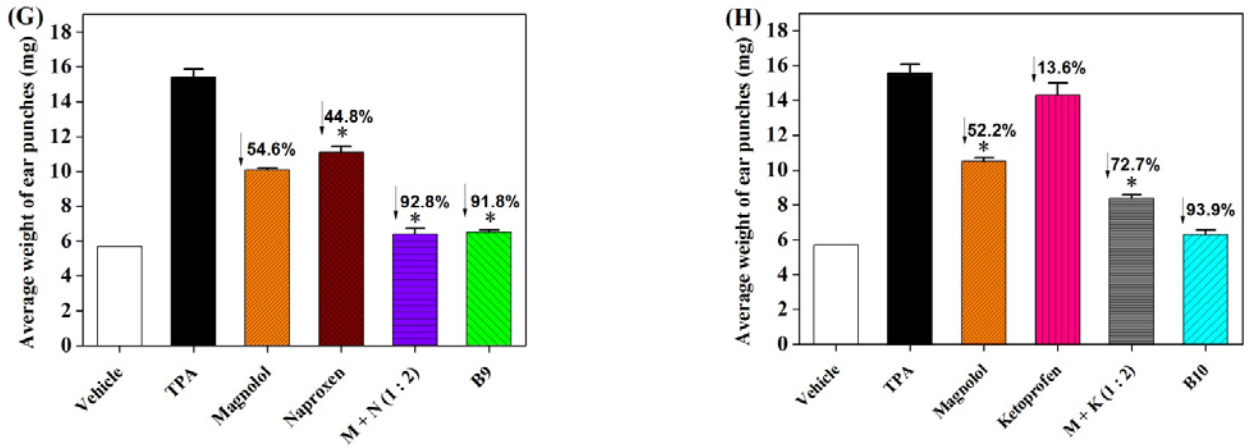



**Fig 6.** Effect of magnolol, NSAID, combination of magnolol and NSAID (1 : 1 or 1 : 2), and A1, A2, A7, A9, A10, B7, B9 and B10 on TPA-induced mouse ear edema. Data are expressed as mean ± S.D. (n = 3), *P < 0.05 (Dunnett *t* test), compared with TPA-treated mice.

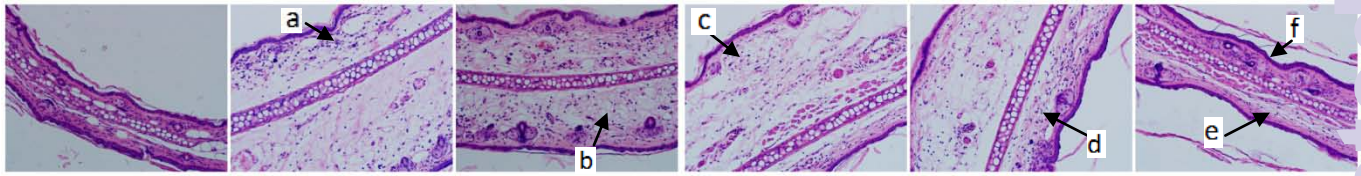
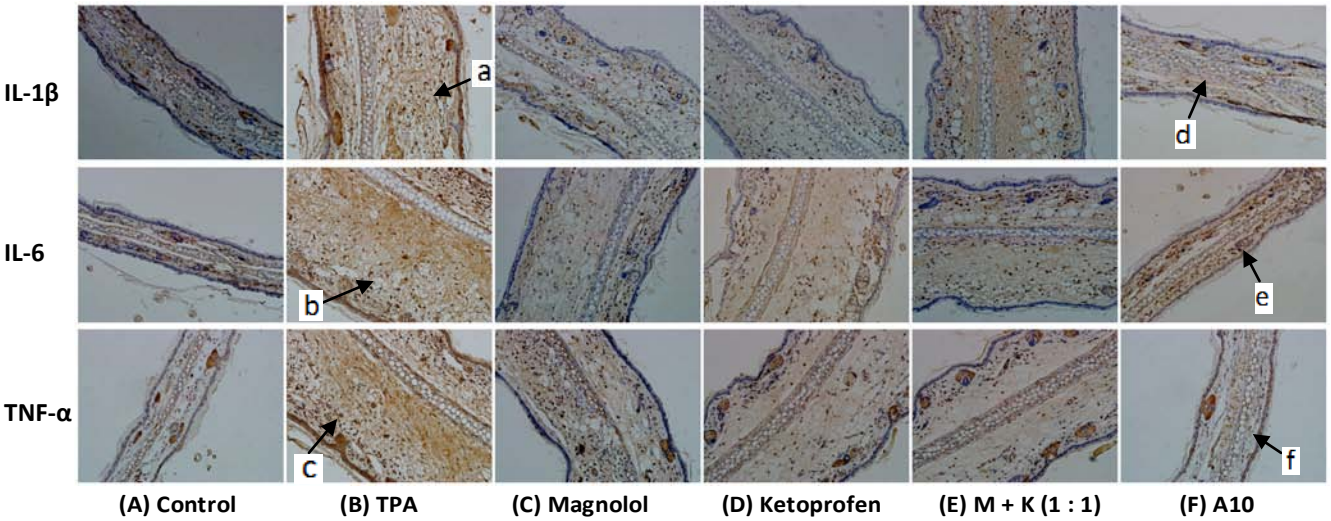



**Fig. 7** H&E staining for histological changes of TPA-induced mouse ears treated with acetone control, TPA, magnolol, ketoprofen, combination of magnolol and ketoprofen (1:1) and A10. Magnification 200×.

### 3.4. Effect of A10 on histological appearance of mouse ears

Histological appearance of mouse ears was determined after pretreatment with acetone (control group), and compounds (magnolol, ketoprofen, combination of magnolol and ketoprofen, and A10) prior to TPA treatment stained with H&E stain. The histological assessment is shown in Fig. 7A-F. Control group treated with acetone alone show the normal appearance in the epidermal layer without any significant lesion (Fig. 7A). Topical application of TPA onto mouse ears alone, inflammation induced by TPA shows the different appearances, such as epidermal hyperkeratosis, thickening of the stratum corneum (Fig. 7B) and an increase in infiltration of inflammatory cells (Fig. 7B-a). Moreover, topical application of magnolol, ketoprofen, combination of magnolol and ketoprofen or A10 prior to TPA application would decrease in the level of inflammatory cells infiltration, respectively (Fig. 7C-b, 7D-c, 7E-d and 7F-e). As shown in Fig. 7F-f, A10 significantly showed morphological alterations compared to TPA treatment.



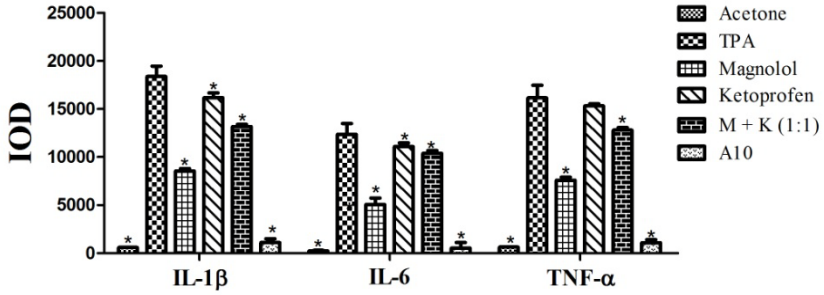



**Fig. 8** Immunohistochemical staining on IL-1β, IL-6 and TNF-α for mouse ears treated with acetone, TPA , magnolol, ketoprofen, combination of magnolol and ketoprofen (1:1) and A10. Data are expressed as mean ± S.D. (n = 3) *P ＜ 0.05 (Dunnett *t* test), compared with TPA-treated mice. Magnification 200×.

### 3.5. Effects of A10 on TPA-induced IL-1β, IL-6 and TNF-α

Among tested synthesized compounds, A10 was selected for further assessment of suppression of TPA-induced IL-1β, IL-6 and TNF-α expression. The levels of IL-1β, IL-6 and TNF-α were determined by immunohistochemical analysis. When TPA was applied topically onto ears of female BALB/c mice, the levels of IL-1β, IL-6 and TNF-α were markedly increased respectively (Fig. 8B-a, 8B-b and 8B-c). However, topical application of A10, 6 min prior to TPA treatment resulted in a significant reduction in the levels of IL-1β, IL-6 and TNF-α in mouse ear edema (Fig. 8F-d, 8F-e and 8F-f).

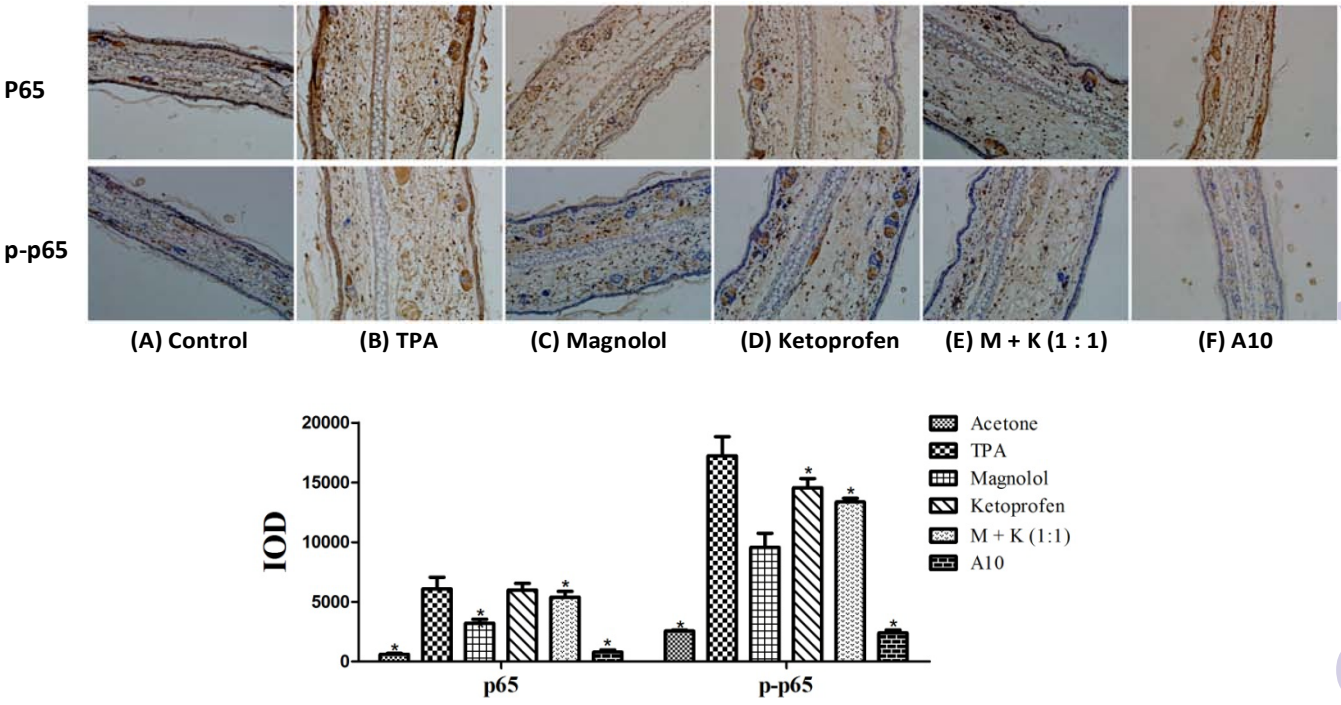



**Fig. 9** Immunohistochemical staining on p65 and phospho-p65 for mouse ears treated with acetone control, TPA, magnolol, ketoprofen, combination of magnolol and ketoprofen (1:1) and A10. Data are expressed as mean ± S.D. (n = 3) *P ＜ 0.05 (Dunnett *t* test), compared with TPA-treated mice. Magnification 200×.

### 3.6. A10 suppressed NF-κB nuclear translocation and activation in TPA-induced mouse ear edema

The inhibitory effects of A10 on NF-κB activation were determined by immunohistochemical analysis using a nonphosphorylated p65 antibody and an antiphospho-Ser536 p65 antibody. As described in Fig. 9, p65, the functional active subunit of NF-κB, translocated to nucleus after TPA treatment. Pretreatment with A10 onto mouse ears could markedly suppressed p65 translocation from cytoplasma to nucleus and strongly decreased the nuclear levels of phosphorylated p65, which is well connected with the transcriptional activity of NF-κB. It was found that compared with the control group, NF-κB transcriptional activity induced by TPA treatment was markedly increased, but significantly reduced by A10

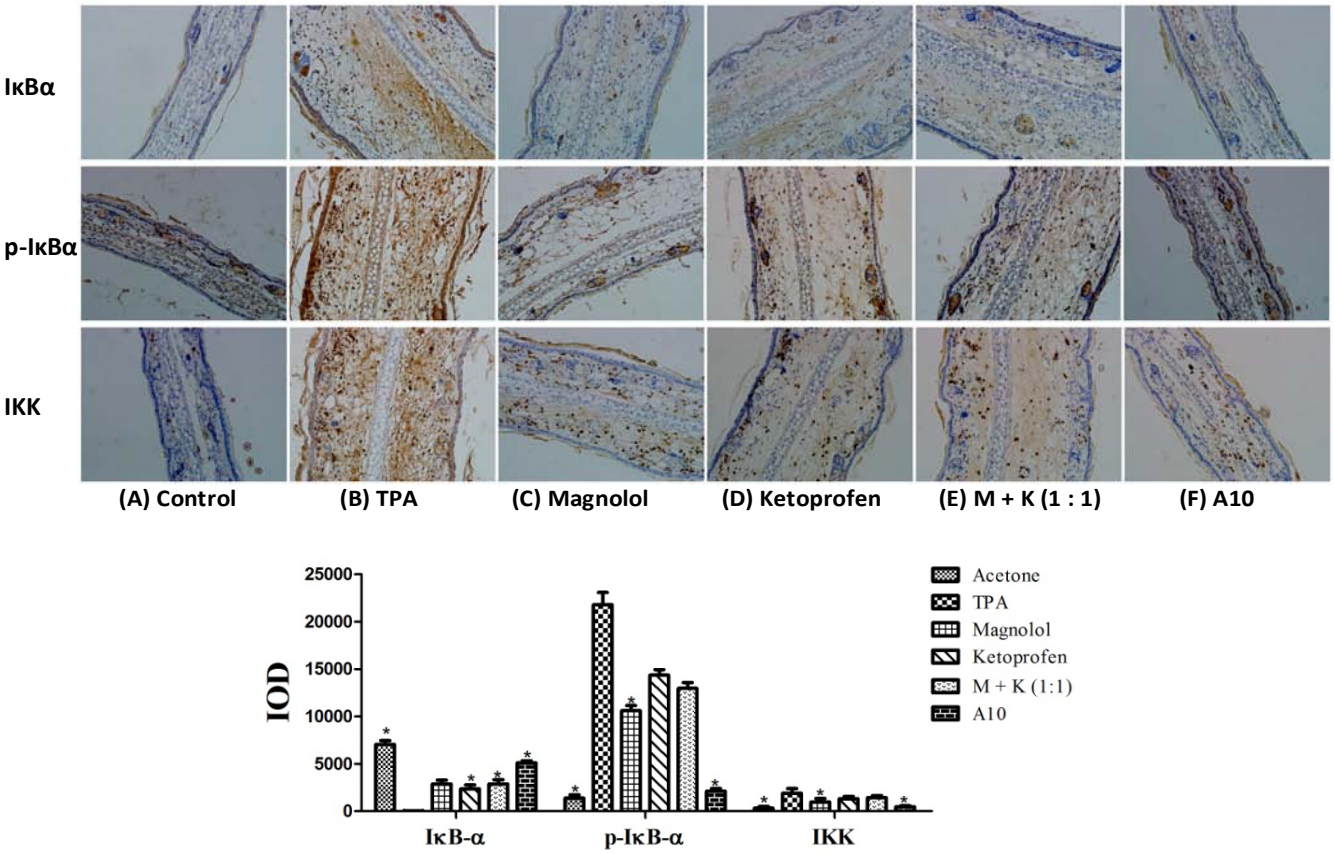



**Fig. 10** Immunohistochemical staining on IκBα, p-IκBα and IKK for mouse ears treated with acetone control, TPA, magnolol, ketoprofen, combination of magnolol and ketoprofen (1:1) and A10. Data are expressed as mean ± S.D. (n = 3) *$P < 0.05$ (Dunnett *t* test), compared with TPA-treated mice. Magnification 200×.

### 3.7. A10 suppressed the TPA-induced NF-κB activation by targeting IKK

To investigate whether or not A10 functions as an inhibitor of IKK/NF-κB signaling, phosphorylation of IκBα, the functional active subunit of NF-κB in TPA-induced mouse ear edema, was determined by immunohistochemical analysis using an antiphospho-Ser36 IκBα antibody and a nonphosphorylated IκB antibody (Fig. 10). Compared to that in the acetone-treated controls, topical application of TPA alone would cause significant increase in the phosphorylation of IκBα. However, pretreatment of A10 strongly blocked the phosphorylation of IκBα in mouse ears treated with TPA. These results suggested that A10 inhibited TPA-induced NF-κB activation by preventing IκBα phosphorylation, thus acting at or upstream of IκBα.

Because IKK represents the major upstream kinase for IκBα phosphorylation, it is important to investigate whether or not A10 inhibits IKK. As shown in Fig. 8, IKK activity was markedly increased in the IKK immunocomplex from mouse ears treated with TPA. A10 significantly inhibited TPA-induced IKK activity, thereby suggesting that A10 inhibited TPA-induced NF-κB activation at the level (or upstream) of IKK.

It has been demonstrated that ketoprofen, well known as a non-selective cyclooxygenase (COX) inhibitor, played a vital role in affecting the synthesis of prostaglandins, which were implicated in the inflammation-associated diseases[27]. However, animal experimental data in our present study confirmed that the anti-inflammatory mechanism of A10, linking ketoprofen with magnolol, is different from that of ketoprofen. The results indicated that A10 inhibited NF-κB-dependent inflammatory response by directly targeting IKK.

## Conclusions

In summary, long-term oral administration of NSAIDs was frequently associated with serious side effects, such as gastric mucosal[8] and renal damage[9, 10]. Novel anti-inflammatory agents are urgently needed for transdermal application. Inspired by *Magnolia officinalis*, a natural traditional Chinese medicine, which contains magnolol, a series of magnolol-containing NSAIDs were designed, synthesized and used for transdermal application to treat inflammation associated diseases. Furthermore, traditional Chinese medicines which are of natural origin possess various bioactive and pharmacological activities. It is worthwhile to investigate whether or not linking them with NSAIDs could have any influence on improving their bioactivities and avoiding the adverse effects of NSAIDs.

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[1]These two authors contributed equally to this work.

## Notes and references

§ Examination of sulindac-based compound by $^{1}$H NMR, $^{13}$C NMR, HRMS and Elemental analysis showed as following:

**1. 5,5'-diallyl-2'-hydroxy-[1,1'-biphenyl]-2-yl-2-(2-((2,6-dichlorophenyl)amino)phenyl) acetate (A1).** White oil, 92% yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.1 Hz, 2H), 7.23 (m, 1H), 7.19 (d, *J* = 1.9 Hz, 1H), 7.10(m, 2H), 7.04 (d, *J* = 7.5 Hz, 2H), 6.96 (t, *J* = 8.1 Hz, 1H), 6.89 (dd, *J* = 9.0, 5.2 Hz, 3H), 6.72 (m, 1H), 6.48 (d, *J* = 7.5 Hz, 2H), 5.91 (dddt, *J* = 33.6, 16.8, 10.1, 6.8 Hz, 2H), 5.13 (d, *J* = 1.5 Hz, 2H), 5.08 (m, 1H), 5.48 (m, 4H), 3.78 (s, 2H), 3.40 (m, 2H), 3.21 (d, *J* = 6.7 Hz, 2H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 171.06, 151.10, 146.81, 142.67, 138.90, 137.80, 136.73, 131.89, 130.90, 130.41, 130.16, 129.79-129.41, 128.81, 128.12, 124.15, 123.56, 122.80, 122.19, 118.36, 116.57, 116.31, 115.58, 39.45, 37.86-37.06. HRMS m/z 543.1366; calcd for $C_{32}H_{27}Cl_2NO_3$, 543.1368. Anal. Calcd for $C_{32}H_{27}Cl_2NO_3$: C, 70.59; H, 5.00; O, 8.82. Found C, 70.66; H, 5.01; O, 8.83.

**2. 5,5'-diallyl-2'-hydroxy-[1,1'-biphenyl]-2-yl-2',4'-difluoro-3-hydroxy-[1,1'-biphenyl]-4-carboxylate (A2).** White oil, 95% yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.90 (d, *J* = 1.3 Hz, 1H), 7.61 (m, 1H), 7.30(m, 4H), 7.01 (d, *J* = 8.7 Hz, 1H), 6.98 (dd, *J* = 4.3, 2.2 Hz, 2H), 6.92 (m, 2H), 6.81 (d, *J* = 8.8 Hz, 1H), 5.99 (d, *J* = 6.8 Hz, 1H), 5.76 (d, *J* = 6.7 Hz, 1H), 5.14 (m, 2H), 5.04 (s, 1H), 4.88 (m, 2H), 3.47 (d, *J* = 6.7 Hz, 2H), 3.21 (d, *J* = 6.6 Hz, 2H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 168.51, 161.41, 151.10, 146.24, 139.24, 137.47, 136.85, 136.62, 132.01, 131.87, 131.06, 130.62, 130.42, 130.01, 129.87, 129.64, 126.32, 123.28, 122.82, 117.88, 116.67, 115.96, 115.52, 111.77, 111.56, 104.69, 104.44, 104.18, 39.60, 39.15. HRMS m/z 498.1643; calcd for $C_{31}H_{24}F_2O_4$, 498.1643. Anal. Calcd for $C_{31}H_{24}F_2O_4$: C, 74.69; H, 4.85; O, 12.84. Found C, 74.68; H, 4.89; O, 12.81.

**3. 5,5'-diallyl-2'-hydroxy-[1,1'-biphenyl]-2-yl-2-((3-chloro-2-methylphenyl)amino)benzoate (A3).** Light yellow powder, 92% yield, mp 91.0-92.3°C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.71 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.37 (s, 1H), 7.23 (d, *J* = 2.0 Hz, 1H), 7.19 (m, 2H), 6.91(m, 2H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.76 (s, 1H), 6.74 (d, *J* = 8.8 Hz, 1H), 5.92 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H), 5.73 (m, 1H), 5.05 (ddd, *J* = 18.5, 15.1, 6.8 Hz, 2H), 4.96 (s, 1H), 4.85(m, 2H), 3.38 (d, *J* = 6.7 Hz, 2H), 3.16 (d, *J* = 6.6 Hz, 2H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 167.35, 151.27, 148.99, 146.98, 140.09, 138.76, 137.66, 136.79, 135.61, 134.93, 132.00, 131.86, 131.74, 130.70, 130.31, 129.69, 126.85, 125.89, 123.75, 123.26, 123.10, 117.09, 116.56, 116.12, 115.51, 113.76, 110.32, 39.45, 14.97. HRMS m/z 387.1551; calcd for $C_{25}H_{22}O_4$, 387.1552. Anal. Calcd for $C_{25}H_{22}O_4$: C, 77.70; H, 5.74; O, 16.56. Found C, 77.71; H, 5.75; O, 16.52.

**4. 5,5'-diallyl-2'-hydroxy-[1,1'-biphenyl]-2-yl-2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetate (A4).** White powder, 90% yield, mp 95.8–96.9°C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 2.0 Hz, 1H), 7.22 (d, *J* = 2.3 Hz, 1H), 7.05 (dd, *J* = 9.9, 5.0 Hz, 2H), 7.00 (dd, *J* = 8.0, 4.8 Hz, 2H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 5.93 (ddd, *J* = 35.0, 16.9, 10.1 Hz, 2H), 5.13 (m, 3H), 5.02 (m, 2H), 4.00 (m, 1H), 3.88 (m, 1H), 3.44 (d, *J* = 6.8 Hz, 2H), 3.27 (d, *J* = 6.7 Hz, 2H), 3.04 (d, *J* = 16.6 Hz, 1H), 2.82 (ddd, *J* = 15.9, 12.3, 10.7 Hz, 4H), 2.70 (m, 1H), 1.69 (m, 4H), 1.30 (t, *J* = 7.6 Hz, 3H), 0.61 (t, *J* = 7.3 Hz, 3H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 171.86, 151.23, 146.67, 139.15, 137.57, 136.64, 135.38, 134.52, 132.18, 132.02, 130.55, 130.27, 129.92, 129.76, 126.74, 126.07, 123.71, 122.65, 120.43, 119.65, 108.59, 74.56, 60.69, 42.84, 42.01, 39.61, 39.30, 30.32, 27.06, 25.01, 24.06, 22.40, 13.84, 7.49. HRMS m/z 535.2725; calcd for $C_{35}H_{37}NO_4$, 535.2723. Anal. Calcd for $C_{35}H_{37}NO_4$: C, 78.48; H, 6.96; O, 11.95. Found C, 78.49; H, 6.95; O, 11.98.

**5 5,5'-diallyl-2'-hydroxy-[1,1'-biphenyl]-2-yl-2-hydroxybenzoate (A5).** Yellow powder, 93%, mp 101.3-101.7°C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.92 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.31 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.23 (d, *J* = 1.4 Hz, 1H), 7.18 (dd, *J* = 13.1, 4.9 Hz, 2H), 7.08 (t, *J* = 7.9 Hz, 1H), 6.98 (m, 2H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.66 (m, 1H), 5.99 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H), 5.81 (ddt, *J* = 16.9, 10.3, 6.6 Hz, 1H), 5.13 (m, 3H), 4.95 (dd, *J* = 12.4, 6.0 Hz, 2H), 3.45 (d, *J* = 6.8 Hz, 2H), 3.24 (d, *J* = 6.6 Hz, 2H), 2.22 (s, 3H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 169.17-168.85, 161.91, 151.13, 146.35, 139.18, 137.55, 136.49, 131.91, 130.75-129.35, 123.29, 122.98, 119.39, 117.59, 116.62, 116.02, 115.55, 111.64, 39.59, 39.19. HRMS m/z 509.1761; calcd for $C_{32}H_{28}ClNO_3$, 509.1758. Anal. Calcd for $C_{32}H_{28}ClNO_3$: C, 75.36; H, 5.53; O, 9.41. Found C, 75.35; H, 5.56; O, 9.44.

**6. 5,5'-diallyl-2'-hydroxy-[1,1'-biphenyl]-2-yl-2-((2,3-dimethylphenyl)amino)benzoate (A6).** Light yellow powder, 92% yield, mp 94.1-95.5°C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.90 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.29 (d, *J* = 1.7 Hz, 1H), 7.21 (d, *J* = 3.1 Hz, 2H), 7.07 (m, 2H), 6.99 (m, 3H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 6.60 (s, 1H), 5.99 (d, *J* = 6.9 Hz, 1H), 5.82 (d, *J* = 6.6 Hz, 1H), 5.20 (s, 1H), 5.12(m, 2H), 4.95 (m, 2H), 3.45 (d, *J* = 6.8 Hz, 2H), 3.24 (d, *J* = 6.6 Hz, 2H), 2.29 (s, 3H), 2.07 (s, 3H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 167.43, 151.31, 150.03, 147.08, 138.64, 138.31, 137.70, 136.83, 134.88, 132.54, 132.07-131.59, 130.71, 130.38, 129.6, 127.00, 125.92, 123.85, 123.30, 116.52, 116.17, 115.50, 109.4, 39.46, 20.64, 13.97. HRMS calcd for $C_{33}H_{31}NO_3$ $[M + H]^+$ 489.6150, found 489.6149. HRMS m/z 489.2301; calcd for $C_{33}H_{31}NO_3$, 489.2304. Anal. Calcd for $C_{33}H_{31}NO_3$: C, 80.95; H, 6.38; O, 9.80. Found C, 80.94; H, 6.38; O, 9.81.

**7. 5,5'-diallyl-2'-hydroxy-[1,1'-biphenyl]-2-yl-2-((3-(trifluoromethyl)phenyl)amino)benzoate (A7).** Pale green powder, 91% yield, mp 99.3-100.1°C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.93 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.41 (d, *J* = 5.1 Hz, 2H), 7.37(m, 1H), 7.31(m, 4H), 7.23 (t, *J* = 5.8 Hz, 2H), 6.98 (m, 2H), 6.78 (m, 2H), 5.99 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H), 5.82 (ddt, *J* = 16.9, 10.3, 6.6 Hz, 1H), 5.14 (m, 2H), 4.96 (dd, *J* = 12.5, 5.9 Hz, 2H), 3.45 (d, *J* = 6.7 Hz, 2H), 3.24 (d, *J* = 6.6 Hz, 2H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 167.22, 151.18

147.14, 146.82, 141.25, 138.91, 137.63, 136.75, 134.96, 132.17, 131.96, 131.91, 131.87, 131.64, 130.68, 130.19, 129.93, 129.79, 129.66, 124.71, 123.56, 123.22, 119.80, 118.39, 118.11, 116.57, 116.04, 115.52, 114.16, 111.79, 39.62, 39.24. HRMS m/z 530.1899; calcd for $C_{32}H_{26}F_3NO_3$, 530.1898. Anal. Calcd for $C_{32}H_{26}F_3NO_3$: C, 72.58; H, 4.95; O, 9.06. Found C, 72.57; H, 4.99; O, 9.02.

**8. 5,5'-diallyl-2'-hydroxy-[1,1'-biphenyl]-2-yl-2-(4-isobutylphenyl)propanoate (A8).** White oil, 91% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.19 (m, 2H), 7.03(m, 5H), 6.86 (dd, *J* = 17.7, 5.1 Hz, 2H), 5.94 (ddd, *J* = 12.5, 10.1, 5.9 Hz, 2H), 5.07 (m, 4H), 3.69 (d, *J* = 7.2 Hz, 1H), 3.40 (d, *J* = 6.7 Hz, 2H), 3.29 (d, *J* = 6.7 Hz, 2H), 2.43 (d, *J* = 7.2 Hz, 2H), 1.84 (dt, *J* = 13.5, 6.8 Hz, 1H), 1.30 (d, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 6H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 173.70, 151.31, 146.97, 140.56, 138.62, 137.74, 136.77, 136.69, 131.89, 131.83, 130.59, 130.16, 129.57, 129.36, 127.11, 123.95, 122.65, 116.42, 115.59, 45.04, 39.44, 30.20, 22.45, 18.42. HRMS m/z 454.2511; calcd for $C_{31}H_{34}O_3$, 454.2508. Anal. Calcd for $C_{31}H_{34}O_3$: C, 81.90; H, 7.54; O, 10.56. Found C, 81.91; H, 7.55; O, 10.55.

**9. (S)-5,5'-diallyl-2'-hydroxy-[1,1'-biphenyl]-2-yl-2-(6-methoxynaphthalen-2-yl)propanoate (A9).** White oil, 97% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 13.6, 8.8 Hz, 2H), 7.49 (s, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.11(m, 3H), 7.06 (d, *J* = 2.0 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.83 (m, 2H), 6.66 (d, *J* = 8.2 Hz, 1H), 5.85 (m, 2H), 5.01 (m, 4H), 3.83 (m, 4H), 3.33 (d, *J* = 6.7 Hz, 2H), 3.13 (d, *J* = 6.6 Hz, 2H), 1.40 (d, *J* = 7.2 Hz, 3H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 173.65, 157.76, 151.37, 147.01, 138.59, 137.82, 136.88, 134.67, 133.85, 131.84, 130.54, 129.50, 129.03, 127.28, 126.13, 123.92, 122.66, 118.93, 116.40, 115.58, 105.69, 55.35, 45.28, 39.42, 29.81, 20.84, 18.41. HRMS m/z 478.2147; calcd for $C_{32}H_{30}O_4$, 478.2144. Anal. Calcd for $C_{32}H_{30}O_4$: C, 80.31; H, 6.32; O, 13.37. Found C, 80.31; H, 6.302; O, 13.33.

**10. 5,5'-diallyl-2'-hydroxy-[1,1'-biphenyl]-2-yl-2-(3-benzoylphenyl)propanoate (A10).** White oil, 88% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 2H), 7.69 (s, 1H), 7.61 (m, 2H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.33 (d, *J* = 7.4 Hz, 2H), 7.22 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.15 (d, *J* = 1.9 Hz, 1H), 7.00 (m, 2H), 6.86 (d, *J* = 1.6 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 5.93 (dddt, *J* = 23.5, 16.9, 10.2, 6.7 Hz, 2H), 5.39 (s, 1H), 5.05 (m, 4H), 3.80 (d, *J* = 7.2 Hz, 1H), 3.41 (d, *J* = 6.7 Hz, 2H), 3.26 (d, *J* = 6.6 Hz, 2H), 1.36 (d, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 196.90, 172.82, 151.48, 146.86, 139.92, 138.61, 137.75, 137.36, 136.83, 132.72, 131.87, 131.63, 130.68, 130.50, 130.24, 129.55, 129.39, 129.13, 128.56, 128.40, 123.97, 122.43, 116.45, 116.09, 115.58, 45.31, 39.44, 18.30. HRMS m/z 502.2145; calcd for $C_{34}H_{30}O_4$, 502.2144. Anal. Calcd for $C_{34}H_{30}O_4$: C, 81.25; H, 6.02; O, 12.73. Found C, 81.22; H, 6.00; O, 12.74.

**11. 5,5'-diallyl-[1,1'-biphenyl]-2,2'-diyl-bis(2-(2-((2,6-dichlorophenyl)amino)phenyl)acetate) (B1).** White oil, 77% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.9, 1.5 Hz, 4H), 7.51 (td, *J* = 8.0, 1.6 Hz, 6H), 7.23(m, 4H), 7.19 (m, 2H), 7.15 (m, 2H), 7.07 (d, *J* = 8.1 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 5.98 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 2H), 5.84 (m, 1H), 5.08 (s, 2H), 5.01 (d, *J* = 1.4 Hz, 4H), 3.42 (d, *J* = 6.7 Hz, 1H), 3.34 (d, *J* = 6.7 Hz, 4H), 2.24 (s, 4H), 1.98 (s, 1H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 170.93, 146.20, 142.69, 137.96, 136.88, 131.10, 130.08, 129.91, 129.61, 128.89, 127.94, 124.00, 122.15, 118.25, 116.24, 39.46, 37.98, 29.73. HRMS m/z 822.1401; calcd for $C_{46}H_{36}Cl_4N_2O_4$, 822.1400. Anal. Calcd for $C_{46}H_{36}Cl_4N_2O_{43}$: C, 67.17; H, 4.41; O, 7.78. Found C, 67.16; H, 4.40; O, 7.75.

**12. 5,5'-diallyl-[1,1'-biphenyl]-2,2'-diyl-bis(2',4'-difluoro-3-hydroxy-[1,1'-biphenyl]-4-carboxylate) (B2).** White oil, 72% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 2H), 7.92 (s, 2H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.20 (m, 7H), 7.01 (d, *J* = 8.7 Hz, 2H), 6.84 (dt, *J* = 19.4, 8.5 Hz, 4H), 5.81 (dd, *J* = 17.2, 9.7 Hz, 2H), 4.98 (m, 5H), 3.34 (d, *J* = 6.6 Hz, 4H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 168.29, 161.45, 145.69, 138.47, 136.64, 131.34, 130.87, 130.34, 130.03, 129.44, 126.25, 123.81, 122.13, 117.91, 116.40, 111.71, 111.48, 104.61, 104.36, 104.10, 39.41. HRMS m/z 730.1981; calcd for $C_{44}H_{30}F_4O_6$, 730.1979. Anal. Calcd for $C_{44}H_{30}F_4O_6$: C, 72.32; H, 4.14; O, 13.14. Found C, 72.35; H, 4.10; O, 13.13.

**13. 5,5'-diallyl-[1,1'-biphenyl]-2,2'-diyl-bis(2-hydroxybenzoate) (B3).** White oil, 51% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 10.31 (d, *J* = 6.2 Hz, 2H), 7.92 (d, *J* = 1.0 Hz, 1H), 7.77 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.58 (m, 1H), 7.45 (m, 1H), 7.18 (m, 2H), 6.97 (dd, *J* = 16.1, 8.5 Hz, 2H), 6.84 (ddd, *J* = 8.0, 7.4, 1.4 Hz, 3H), 5.82 (m, 2H), 4.98 (m, 4H), 3.34(m, 4H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 168.60, 162.00, 145.71, 138.26, 136.45, 131.33, 130.26, 130.00, 129.35, 122.40, 119.37, 117.63, 116.35, 111.71, 39.44, 29.70. HRMS m/z 506.1731; calcd for $C_{32}H_{26}O_6$, 506.1729. Anal. Calcd for $C_{32}H_{26}O_6$: C, 75.88; H, 5.17; O, 18.95. Found C, 75.87; H, 5.18; O, 18.91.

**14. 5,5'-diallyl-[1,1'-biphenyl]-2,2'-diyl-bis(2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetate) (B4).** White oil, 78% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 2H), 7.37 (d, *J* = 7.7 Hz, 2H), 7.22 (m, 4H), 7.07 (t, *J* = 7.5 Hz, 2H), 7.00 (dd, *J* = 7.5, 3.1 Hz, 4H), 5.93 (d, *J* = 8.2 Hz, 2H), 5.09 (t, *J* = 11.9 Hz, 4H), 3.964 (m, 4H), 3.38 (s, 4H), 3.07 (d, *J* = 16.9 Hz, 3H), 2.80 (m, 10H), 1.87 (s, 3H), 1.30 (m, 7H), 0.65 (s, 6H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 171.41, 146.06, 138.45, 136.64, 135.56, 134.49, 131.28, 130.31, 129.34, 126.60, 126.12, 122.26, 120.36, 119.63, 108.58, 74.45, 60.64, 42.80, 39.52, 30.30, 24.00, 22.40, 13.72, 7.42. HRMS m/z 804.4136; calcd for $C_{52}H_{56}N_2O_6$, 804.4138. Anal. Calcd for $C_{52}H_{56}N_2O_6$: C, 77.58; H, 7.01; O, 11.92. Found C, 77.59; H, 7.00; O, 11.96.

**15. 5,5'-diallyl-[1,1'-biphenyl]-2,2'-diyl-bis(2-((3-chloro-2-methylphenyl)amino)benzoate) (B5).** Light yellow powder, 79% yield, mp 88.1-89.0°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 2H), 7.94 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.17 (m, 8H), 7.08 (s, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.66 (t, *J* = 7.6 Hz, 2H), 5.83 (d, *J* = 6.8 Hz, 2H), 4.99 (dd, *J* = 20.8, 5.5 Hz, 4H), 3.34 (d, *J* = 6.6 Hz, 4H), 2.21 (s, 6H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 167.01, 148.93, 146.37, 140.18, 137.65, 136.85, 135.57, 134.71, 132.02, 131.63, 131.38, 130.51, 129.12, 126.81, 125.76, 122.94, 122.69, 117.02, 116.15, 113.76, 110.64, 39.53, 29.73, 14.95. HRMS m/z 752.2212; calcd for $C_{46}H_{38}Cl_2N_2O_4$, 752.2209. Anal. Calcd for $C_{46}H_{38}Cl_2N_2O_4$: C, 73.30; H, 5.08; O, 8.49. Found C, 73.33; H, 5.07; O, 8.51.

**16. 5,5'-diallyl-[1,1'-biphenyl]-2,2'-diyl-bis(2-((2,3-dimethylphenyl)amino)benzoate) (B6).** Light yellow powder, 71% yield, mp 105.1-105.4°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 2H), 7.94 (d, *J* = 8.0 Hz, 2H), 7.16 (dt, *J* = 8.2, 7.3 Hz, 6H), 7.07 (d, *J* = 7.7

Hz, 2H), 7.01 (d, *J* = 7.8 Hz, 2H), 6.94 (d, *J* = 7.3 Hz, 2H), 6.69 (d, *J* = 8.6 Hz, 2H), 6.56 (t, *J* = 7.6 Hz, 2H), 5.81 (ddd, *J* = 16.6, 8.5, 5.1 Hz, 2H), 4.94 (t, *J* = 13.4 Hz, 4H), 3.30 (d, *J* = 6.6 Hz, 4H), 2.25 (d, *J* = 11.7 Hz, 8H), 2.06 (d, *J* = 5.2 Hz, 6H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 167.16, 149.96, 146.52, 138.53, 138.20, 137.53, 136.95, 134.65, 132.42, 132.02, 131.40, 130.75-130.51, 129.09, 126.86, 125.91, 123.10, 122.80, 117.65-115.02, 113.58, 109.92, 39.58, 29.76, 20.64, 13.99. HRMS m/z 712.3328; calcd for $C_{48}H_{44}N_2O_4$, 712.3301. Anal. Calcd for $C_{48}H_{44}N_2O_4$: C, 80.87; H, 6.22; O, 8.98. Found C, 80.87; H, 6.23; O, 8.99.

**17. 5,5'-diallyl-[1,1'-biphenyl]-2,2'-diyl-bis(2-((3-(trifluoromethyl)phenyl)amino)benzoate) (B7).** Light yellow powder, 65% yield, mp 100.7-102.0°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 2H), 7.95 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.39 (d, *J* = 5.9 Hz, 2H), 7.34 (dd, *J* = 11.9, 4.7 Hz, 4H), 7.29 (d, *J* = 12.2 Hz, 3H), 7.22 (d, *J* = 11.7 Hz, 1H), 7.16 (s, 4H), 6.75 (t, *J* = 7.6 Hz, 2H), 5.82 (dd, *J* = 16.9, 10.1 Hz, 2H), 5.06-4.91 (m, 4H), 3.33 (d, *J* = 6.7 Hz, 4H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 166.90, 147.12, 146.33, 141.40, 137.88, 136.83, 134.82, 132.25, 131.98, 131.66, 131.42, 130.43, 129.90, 129.23, 128.04, 125.33, 124.53, 122.66, 119.68, 118.40, 118.04, 116.21, 114.20, 112.13, 39.54. HRMS m/z 792.2424; calcd for $C_{46}H_{34}F_6N_2O_4$, 792.2423. Anal. Calcd for $C_{46}H_{34}F_6N_2O_4$: C, 69.69; H, 4.32; O, 8.07. Found C, 69.72; H, 4.34; O, 8.08.

**18. 5,5'-diallyl-[1,1'-biphenyl]-2,2'-diyl-bis(2-(4-isobutylphenyl)propanoate) (B8).** White oil, 70% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.10 (m, 2H), 7.03 (dt, *J* = 11.2, 8.2 Hz, 10H), 6.91 (d, *J* = 8.2 Hz, 2H), 5.93 (dd, *J* = 16.9, 10.0 Hz, 2H), 5.14 – 5.01 (m, 4H), 3.65 (q, *J* = 7.1 Hz, 2H), 3.35 (d, *J* = 6.5 Hz, 4H), 2.43 (d, *J* = 7.2 Hz, 4H), 1.83 (td, *J* = 13.5, 6.7 Hz, 2H), 1.29 (d, *J* = 6.9 Hz, 7H), 0.90 (d, *J* = 6.6 Hz, 12H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 173.05, 146.46, 140.34, 137.39, 137.05, 131.13, 130.29, 129.22, 128.75, 127.23, 122.01, 116.13, 45.09, 44.93, 44.85, 39.51, 30.21, 22.45. HRMS m/z 642.3708; calcd for $C_{44}H_{50}O_4$, 642.3709. Anal. Calcd for $C_{44}H_{50}O_4$: C, 82.21; H, 7.84; O, 9.95. Found C, 82.20; H, 7.87; O, 9.96.

**19. (S)-5,5'-diallyl-2'-(((S)-2-(6-methoxynaphthalen-2-yl)propanoyl)oxy)-[1,1'-biphenyl]-2-yl-2-(7-methoxynaphthalen-2-yl)propanoate (B9).** White oil, 77% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 6H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.07 (m, 4H), 6.89 (m, 4H), 6.71 (d, *J* = 8.2 Hz, 2H), 5.81 (m, 2H), 4.99 (m, 4H), 3.86 (s, 6H), 3.77 (d, *J* = 7.1 Hz, 2H), 3.16 (d, *J* = 6.6 Hz, 4H), 1.38 (d, *J* = 7.0 Hz, 6H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 172.88, 157.72, 146.37, 137.20, 135.02, 133.79, 131.03, 130.21, 129.50, 129.02, 128.71, 127.06, 126.26, 121.94, 118.80, 116.11, 105.61, 55.34, 45.27, 39.41, 18.33. HRMS m/z 690.2978; calcd for $C_{46}H_{42}O_6$, 690.2981. Anal. Calcd for $C_{46}H_{42}O_6$: C, 79.98; H, 6.13; O, 13.90. Found C, 79.94; H, 6.15; O, 13.91.

**20. 5,5'-diallyl-[1,1'-biphenyl]-2,2'-diyl-bis(2-(3-benzoylphenyl)propanoate) (B10).** White oil, 73% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.79 (m, 4H), 7.65 (s, 3H), 7.58 (t, *J* = 7.4 Hz, 2H), 7.46 (t, *J* = 7.1 Hz, 4H), 7.32 (d, *J* = 7.2 Hz, 4H), 7.10 (d, *J* = 7.7 Hz, 2H), 7.01 (s, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 5.89 (m, 2H), 5.05 (m, 4H), 3.66 (s, 2H), 3.32 (d, *J* = 6.3 Hz, 4H), 1.33 (d, *J* = 6.2 Hz, 6H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 196.28, 172.32, 146.27, 140.07, 137.69, 137.50, 136.87, 132.49, 131.64, 131.12, 130.18, 130.07, 129.31, 128.96, 128.51, 128.32, 121.91, 116.24, 45.06, 39.45, 18.29. HRMS m/z 738.2982; calcd for $C_{50}H_{42}O_6$, 738.2981. Anal. Calcd for $C_{50}H_{42}O_6$: C, 81.28; H, 5.73; O, 12.99. Found C, 81.29; H, 5.75; O, 12.97.

Over all, the data suggested the chemical integrities of magnolol derivatives containing NSAIDs were identical to the target compounds.

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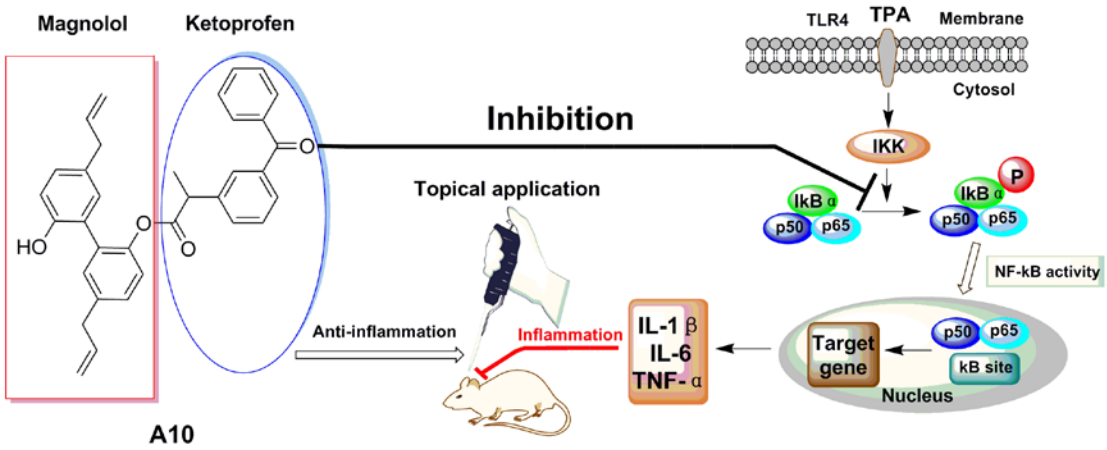


*Graphical abstract:* A10 was selected to elucidate the anti-inflammatory mechanism at the transcriptional level, suggesting its potential to serve as a novel anti-inflammatory agent.