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Synthesis of either C2- or C4'-alkylated derivatives of honokiol and their biological evaluation for anti-inflammatory activity

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Abstract

Honokiol, a biphenolic neolignan isolated from *Magnolia officinalis*, was reported to have a promising anti-inflammatory activity for the treatment of various diseases. There are many efforts on the synthesis and structure-activity relationship of honokiol derivatives. However, regioselective *O*-alkylation of honokiol remains a challenge and serves as a tool to provide not only some derivatives but also chemical probes for target identification and mode of action. In this study, we examined the reaction condition for regioselective *O*-alkylation, in which C2 and C4'-alkylated analogs of honokiol were synthesized and evaluated for inhibitory activity on nitric oxide production and cyclooxygenase-2 expression. Furthermore, we successfully synthesized a potential photoaffinity probe consisting of biotin and benzophenone based on a C4'-alkylated derivative.

Keywords

Magnolia officinalis, honokiol, anti-inflammatory activity, *O*-alkylation, photoaffinity probe

1. Introduction

Macrophages and lymphocytes play an important role in the innate and adaptive immunity of hosts. These functions are mediated by various factors, such as cytokines, that have various defensive roles against pathogens.¹ However, overproduction of inflammatory molecules can give the host severe immunopathological symptoms, such as acute and chronic inflammatory diseases.² Production of inflammatory molecules is triggered by mitogenic stimulation with various bacterial products, such as lipopolysaccharide (LPS). Nitric oxide (NO) has been implicated in physiological and pathological processes, such as nonspecific host defense, chronic inflammation, and vasodilation. Inducible nitric oxide synthase (iNOS) is involved in the pathological processes related to NO overproduction and is expressed in response to proinflammatory cytokines, such as interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α), in various cell types, including macrophages, endothelial cells, and smooth muscle cells.³

Thus, effective modulation of the overproduction state has been considered as a therapeutic target in various types of inflammation.⁴ Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely prescribed drugs because they exhibit anti-inflammatory effects by inhibiting cyclooxygenase (COX) in arachidonic acid metabolism.⁵ There are two human enzymes that catalyze the same biochemical reactions, namely COX-1 and COX-2, but their amino acid sequence, tissue distribution, and physiology differ greatly. Long-term use of NSAIDs for treating pain and inflammation is often accompanied by side effects, such as gastrointestinal (GI) toxicity, hemorrhage, and inhibition of renal function.⁶ Development of COX-2 selective inhibitors is a reasonable strategy for designing NSAIDs to eliminate side effects because the common side effects of these NSAIDs are due to COX-1 inhibition. Some COX-2 selective inhibitors, such as celecoxib, have an excellent effect with minimal adverse effects on humans. Concerns regarding cardiovascular events in thrombosis have been raised despite the initial success following introduction of selective COX-2 inhibitors. There has been continued progress in the development of new anti-inflammatory drugs with reduced risk of GI and cardiovascular diseases.⁷

Biphenolic natural neolignans isolated from the bark of *Magnolia officinalis*, such as honokiol, 4'-*O*-methylhonokiol, magnolol, and obovatol, have been used as traditional medicines for treating gastrointestinal disorders, anxiety, and allergy. Recent studies

revealed that honokiol and its analogs have various biological activities, such as antiangiogenesis,^{8,9} anticancer,¹⁰ anti-inflammatory,¹¹ antibacterial,¹² osteoclast genesis-suppressing,¹³ hepatoprotective,¹⁴ and neuroprotective activities.¹⁵ Honokiol and its derivatives were reported to target multiple signaling pathways, including the NF- κ B,¹⁶ p53,¹⁷ EGFR,¹⁸ GPR55,¹⁹ and PI3K/mTOR pathways.²⁰ Previously, we have synthesized a series of derivatives of honokiol and 4'-*O*-methylhonokiol for improved inhibitory activities against COX-2 and PGF₁ production.¹¹ Some analogs were found to prevent NO production in LPS-activated macrophages.²⁰

Recently, the anti-neuroinflammatory effects of honokiol on heterocyclic bioisosteres in LPS-activated BV-2 cells have been reported.²¹ However, the target of honokiol is still unknown, and to date, only one X-ray co-crystal structure of honokiol derivative has been suggested (PDB ID: 4OC7) to be selective for the RXR/coactivator interaction.²² These promising activities have prompted us to synthesize honokiol analogs to develop anti-inflammatory agents and photoaffinity probes to elucidate its binding targets and mechanisms of action.

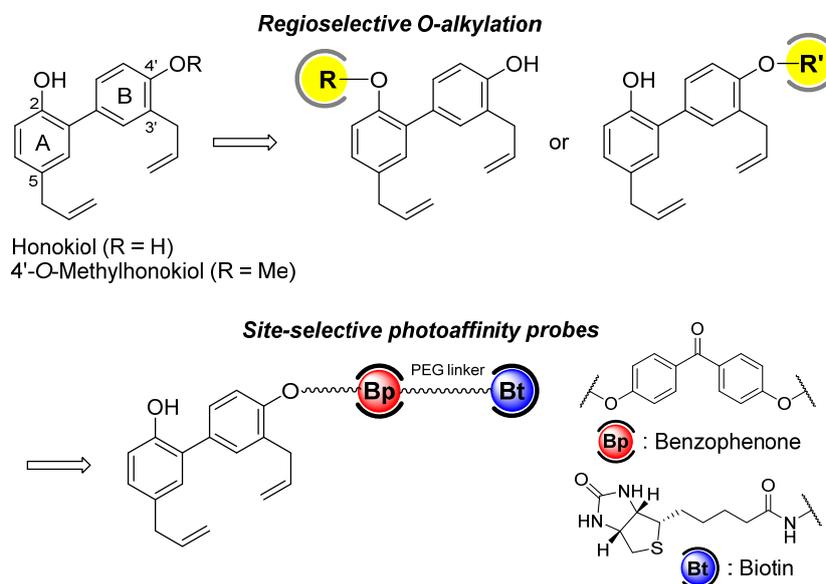


Figure 1. Structure of natural neolignans and photoaffinity probe.

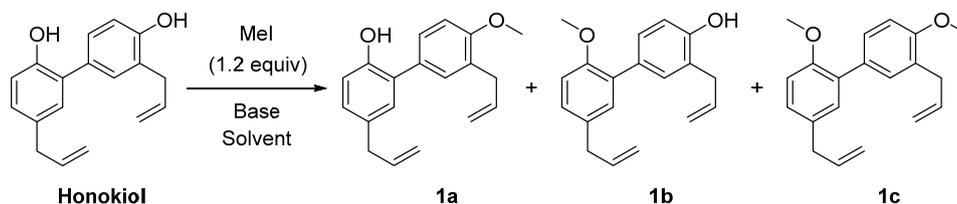
2. Results and Discussion

Honokiol and 4'-*O*-methylhonokiol consist of a 5,3'-diallyl-biphenyl skeleton bearing hydroxy group in the C2 of the A ring, or hydroxyl and methoxy groups in the C4' of the B

ring, respectively. The previous study¹¹ showed that 4'-*O*-methylhonokiol exerts higher anti-inflammatory activity than those of honokiol and various honokiol analogs, as examined using COX-1 and COX-2 enzyme assay and LTB₄ formation assay. Thus, we contemplated efficient synthesis of mono-alkylated analogs on either the 2- or 4'-position for elongating the regioselective chain and designing site-selective photoaffinity probes, which would be useful to elucidate directly binding proteins.

Our first synthesis commenced with a study on regioselective *O*-methylation of honokiol to determine which phenol group is more reactive under various alkylation conditions.

Table 1. Regioselective *O*-methylation of honokiol^a



entry	base	Solvent	isolated yield (%)		
			1a	1b	1c
1	LiOH	DMSO /H ₂ O	33	27	32
2	NaOH	DMSO /H ₂ O	20	46	30
3	KOH	DMSO /H ₂ O	21	50	10
4	K ₂ CO ₃	DMSO /H ₂ O	30	50	15
5	Cs ₂ CO ₃	DMSO /H ₂ O	35	21	15
6	Cs ₂ CO ₃	Acetone	30	15	15
7	<i>t</i> -BuOK	THF	20	18	15
8	KHMDS	DMSO	7	15	7
9	NaH	THF	-	-	38
10	Et ₃ N	THF		N/R	
11	<i>i</i> Pr ₂ NEt	THF		N/R	

^aReaction conditions: a) for entry 1–6, 60 °C, overnight; b) for entry 7–9, 0 °C, 1 h; c) for entry 10–11, reflux, overnight.

Studies on regioselective *O*-methylation of honokiol were performed under different base and solvent conditions, as shown in Table 1. Briefly, 1 equivalent of commercially available honokiol, 1.2 equivalent of iodomethane, and 3 equivalents of base were used to

yield 4'-*O*-methylhonokiol (**1a**), 2'-*O*-methylhonokiol (**1b**), and 2,4'-dimethylhonokiol (**1c**). The methylation using LiOH and NaOH in aqueous dimethyl sulfoxide (DMSO) yielded three alkylated compounds (**1a–c**), whereas that using KOH and K₂CO₃ afforded **1b** as a major product. Interestingly, C4'-alkylation occurred twice as much as C2-alkylation when Cs₂CO₃ was used as a base. The result was likely to be different depending on the metal cation. The yield and selectivity with strong bases, such as *t*-BuOK, KHMDS, and NaH, were not favorable, and the alkylation reaction did not work with amine bases, such as triethylamine and *N,N*-diisopropylethylamine. Because the chemical environment of the phenol group on the A ring and B ring was similar, regioselective alkylation was not completely achieved. However, with the automatic flash column chromatography system, both 4'-*O*- and 2'-*O*-alkylated products were easily separated with more than 95% purity and fully analyzed by NMR, mass spectrometry before their biological evaluation.^{8,23,24} Interestingly, the comparison of ¹³C-NMR spectra of honokiol, 4'-*O*-methylhonokiol (**1a**), 2'-*O*-methylhonokiol (**1b**), and 2,4'-dimethylhonokiol (**1c**) enable us to confirm the aspect of their NMR spectra when other groups were alkylated at the C2 and C4'-position of honokiol, respectively, as shown in Figure 2.

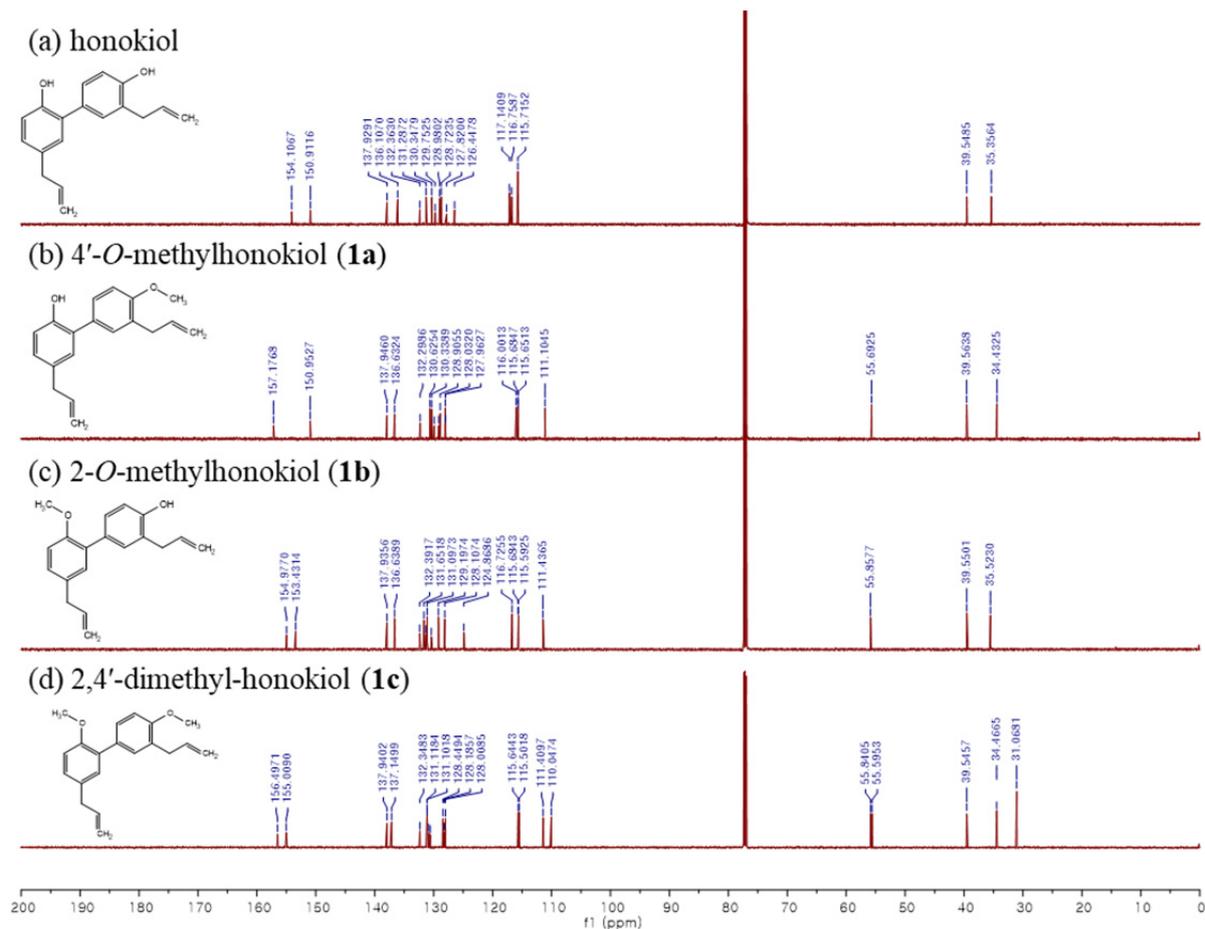


Figure 2. ^{13}C -NMR comparison of natural honokiol and its methylated analogs (**1a–1c**).

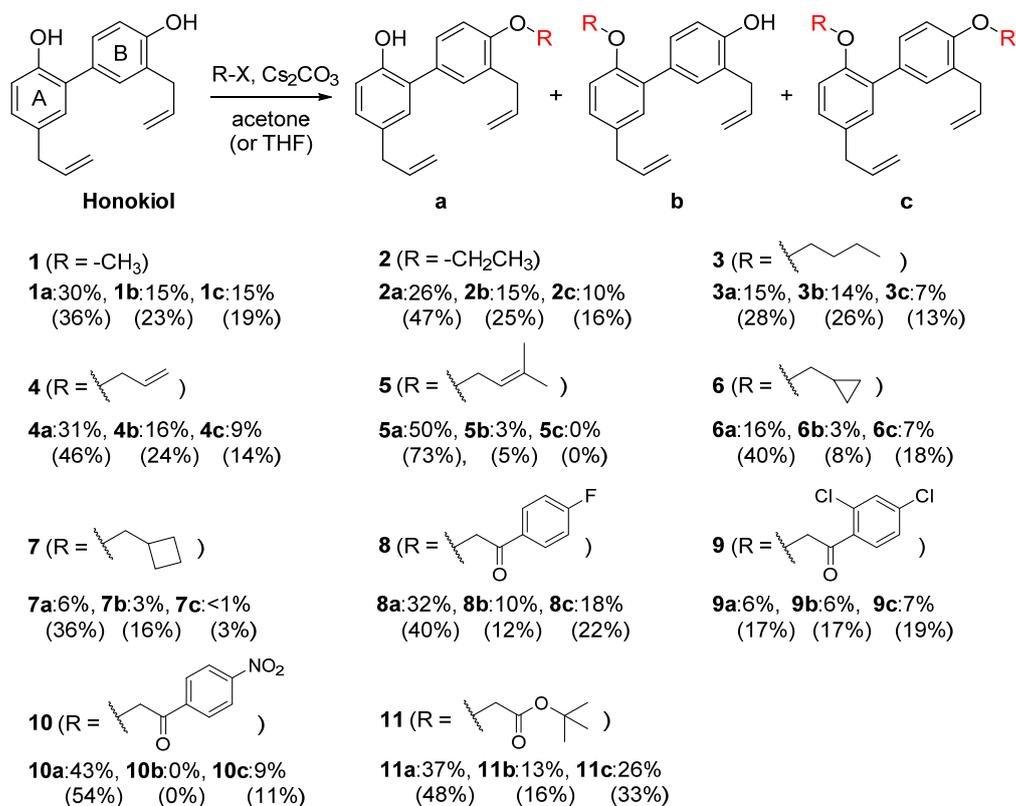


Chart 1. Synthesis of *O*-alkylation analogs of honokiol. Reagents and conditions: a) for **1–7**, iodomethane, iodoethane, 1-bromobutane, allyl bromide, 3,3-dimethylallyl bromide, cyclopropylmethyl bromide, cyclobutylmethyl bromide, Cs₂CO₃, acetone, reflux, 24 h; b) for **8–11**, 2-bromo-4'-fluoroacetophenone, 2-bromo-2',4'-dichloroacetophenone, 2-bromo-4'-nitroacetophenone, *tert*-butyl bromoacetate, Cs₂CO₃, THF, 1 h. Yields based on recovered starting material in parentheses.

We turned to the alkylation using various alkylating agents and Cs₂CO₃ in acetone, as shown in Chart 1. Similar to that of methylation, the reactivity of aliphatic alkylation was sluggish and the yield was not satisfactory. However, a slightly C4'-selectively alkylated compound was found as a major product. Ethyl, *n*-butyl, cyclopropylmethyl, and cyclobutylmethyl were not well incorporated on the phenol groups of honokiol. Allyl and prenyl were introduced on the C4'-position slightly selectively, similar to methyl. The *O*-alkylation with phenacyl bromides, such as 2-bromo-4'-fluoroacetophenone, 2-bromo-2',4'-dichloroacetophenone, and 2-bromo-4'-nitroacetophenone, as alkylating agents afforded C4'-alkylated analogs (**8a–10a**) of honokiol in moderate yield. The reaction

of *tert*-butyl bromoacetate afforded a C4'-alkylated analog (**11a**) in moderate yield.

In a previous study, we found that modifications of 4'-*O*-methylhonokiol through introduction of methyl, isopropyl, and prenyl groups at phenol slightly decrease the inhibitory activity of COX-2 enzyme¹¹. Compared with other synthesized analogs, **11a** showed the most promising anti-inflammatory activity; thus, it was exploited as an intermediate to obtain C4'-labeled photoaffinity probe of honokiol.²⁵ By the treatment with trifluoroacetic acid in dichloromethane, the *tert*-butyl ester group of **11a** was removed to afford carboxylic acid **12**, as shown in Chart 2. Acid **12** was coupled with the bifunctional molecule **13**, which consists of benzophenone²⁶ and biotin, under PyAOP/HOAt-mediated reaction condition to finally afford the desired photoaffinity probe **14** in good yield.

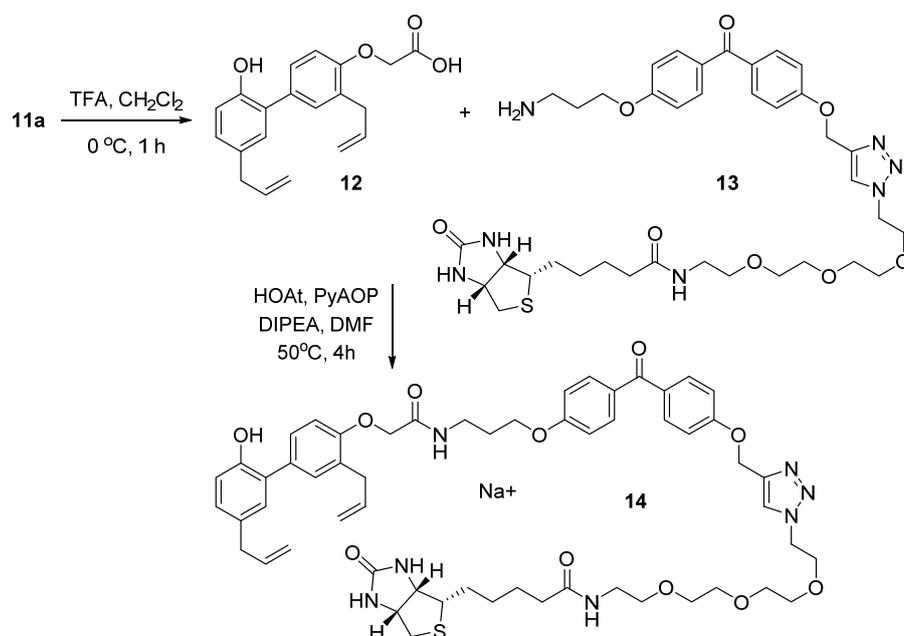


Chart 2. Synthesis of C4'-labeled photoaffinity probe of honokiol.

The cell viability of RAW264.7 cells following treatment with honokiol and its analogs was examined by the MTT assay. The cells were treated in the presence or absence of honokiol analogs at different concentrations (0–20 μM). As shown in Table 2, it did not show cell cytotoxicity at 5 μM concentration of all new synthetic compounds similar to honokiol, suggesting that the derivatives are little toxic. The inhibitory activities of honokiol analogs on nitric oxide (NO) production and COX-2 expression were evaluated in RAW264.7 cells treated with 10 ng/mL or 100 ng/mL LPS in the presence or absence of compounds at different concentrations (0–10 μM). The inhibitory effects of the synthesized

honokiol analogs on NO production are shown in Figure 3 and Table 2. The carbon elongation in the 2- or 4'-hydroxy position with methoxy, ethoxy, allyl, prenyl, cyclobutylmethyl, and cyclopropylmethyl groups does not improve the inhibitory activity on NO production regardless of the C2 or C4' position, although ethyl, prenyl and cyclobutyl derivatives exhibited the similar activity with honokiol (**2a**, **2b**, **5a**, **5b**, **7a**, and **7b**; $5.1 < IC_{50} < 8.3 \mu M$). Meanwhile, the introduction of two phenacyl groups on the hydroxyl of the C4' position increased the NO inhibitory activity (**8a** and **9a**; $IC_{50} = 4.8$ and $4.5 \mu M$). Next, we examined the expression level of COX-2 enzyme by western blotting. All compounds showed direct inhibition of COX-2 enzyme, with a range of 65–93% inhibition in the presence of LPS 100 nM. Contrary to the results of NO production, the analog **3a**, whose *n*-butoxy group was replaced with hydroxyl group, significantly suppressed the expression of COX-2. Some analogs, such as **2a**, **2b**, **6a**, **6b**, and **7a**, moderately inhibited the expression of COX-2. Fortunately, *tert*-butoxyacyl derivative (**11a**) and a photoaffinity probe (**15**) of honokiol maintained a moderate inhibition of NO production and COX-2 expression compared to those of honokiol without drastic loss of activity. Based on the prediction of log P value (SLogP), most alkylated compounds were regarded to have slightly more lipophilic properties than honokiol.

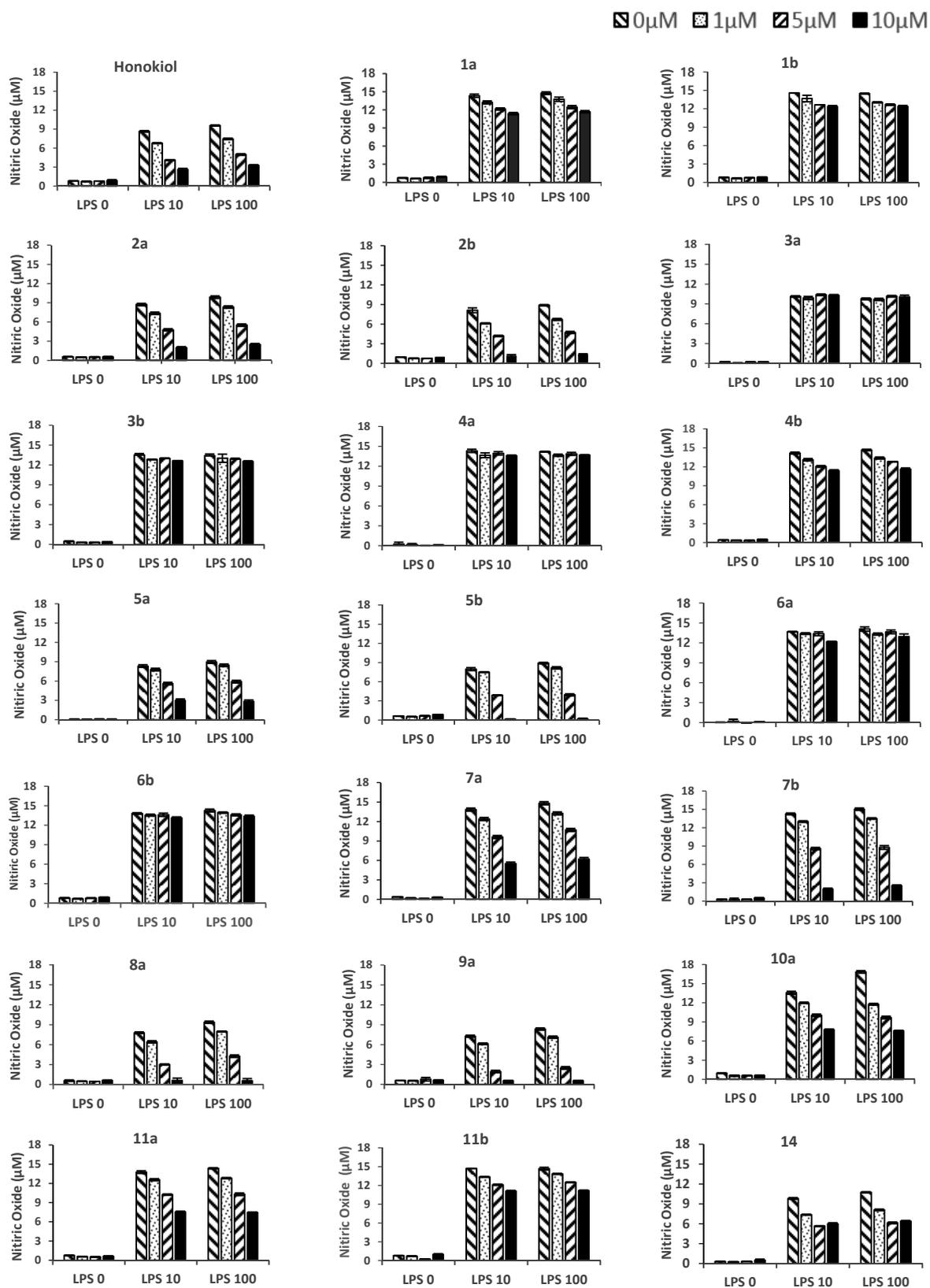


Figure 3. Inhibitory activity of honokiol analogs on nitric oxide production in LPS-activated RAW264.7 cells.

Table 2. Anti-inflammatory effect of compounds on nitric oxide production and COX-2 expression, logP value and, cell viability.

compound	IC ₅₀ (μM) of NO production ^a		COX-2 expression (%) ^b	SLogP ^c	cell viability (%) ^c
	LPS 10 ng/mL	LPS 100 ng/mL			
Honokiol	6.2	6.7	75 ± 0.85	3.9	104.7 ± 5.8
1a	24.9	24.2	94 ± 9.7	4.2	99.9 ± 1.7
1b	23.7	25.9	86 ± 4.7	4.2	104.3 ± 2.2
2a	6.1	6.3	84 ± 8.1	4.6	107.6 ± 1.8
2b	5.3	5.4	89 ± 4.7	4.6	99.3 ± 4.3
3a	>100	>100	70 ± 7.1	5.4	97.4 ± 4.6
3b	>100	>100	93 ± 11	5.4	103.3 ± 0.9
4a	18.5	25.7	89 ± 7.0	4.6	97.1 ± 5.8
4b	18.8	19.6	100 ± 1.3	4.6	106.2 ± 1.2
5a	7.8	7.4	93 ± 8.0	5.5	104.0 ± 3.8
5b	5.1	5.0	ND ^e	5.5	89.2 ± 3.6
6a	39.9	41.0	83 ± 3.8	5.0	96.7 ± 2.5
6b	>100	>100	88 ± 6.9	5.0	104.5 ± 1.8
7a	8.3	8.7	86 ± 8.2	5.4	100.5 ± 7.9
7b	5.9	6.0	ND	5.4	101.9 ± 4.4
8a	4.8	5.0	91 ± 13	5.9	91.8 ± 3.8
9a	4.5	4.6	87 ± 4.0	6.8	87.4 ± 1.6
10a	16.9	18.4	93 ± 12	5.3	109.9 ± 3.9
11a	13.3	13.3	91 ± 10	4.9	91.1 ± 4.6
11b	25.7	24.2	99 ± 4.5	4.9	102.0 ± 2.3
12	103.8	86.4	ND	3.7	104.2 ± 0.8
14	11.2	10.7	86 ± 4.0	6.5	95.6 ± 3.1

^aEach compound was defined as the concentration (μM) that caused 50% inhibition of NO production in LPS-activated RAW 264.7 cells. ^bThe expression ratio was calculated as a band density ratio of COX-2 to β-actin in the treatment with 5 μM of each compound. Representative data from three independent experiments. ^cSlogP was derived by applying the rules of Wildman and Crippen and represents a good estimate of the actual logP of the molecule. ^dThe effect of treatment with 5 μM of each compound was determined by MTT assay, and the results are expressed in percentage (%)

3. Conclusion

The regioselective *O*-alkylation of honokiol was aimed to synthesize either C2- or

C4'-alkylated derivatives for developing anti-inflammatory agents. To investigate regioselectivity, we conducted *O*-methylation under various reaction conditions, such as iodomethane and dimethyl sulfate as an alkylating agent, as well as potassium carbonate, cesium carbonate, Et₃N, and NaH as a base. The yield of *O*-methylation was moderate, and all compounds, including recovered honokiol, could be separated successfully. By treatment with Cs₂CO₃ and DMSO/H₂O, 4'-*O*-methylhonokiol, which is also a natural product, was obtained as a major product. Several analogs, namely C4'-alkyl-, C2-alkyl-, and C2,C4'-dialkyl-honokiol were synthesized through *O*-alkylation using Cs₂CO₃ as a base.

We confirmed that almost all compounds showed low cytotoxicity in macrophages, and several analogs showed improved inhibitory activities than that of honokiol against NO production and/or COX-2 expression. Moreover, a photoaffinity probe in which biotin and benzophenone were linked to the C4' position was synthesized, and it showed a moderate inhibitory activity without drastic loss of activity. This study provided a basis for further development of these compounds as novel therapeutics for inflammatory diseases and cancer. Our next step is to identify the putative binding targets essential for signaling pathways in inflammation by using the honokiol-based photoaffinity probe.

4. Experimental

4.1 Chemistry

All starting materials and reagents were obtained from commercial suppliers and used without further purification. Air- and moisture-sensitive reactions were performed under nitrogen atmosphere. Flash column chromatography was performed using silica gel 60 (230–400 mesh; Merck, Darmstadt, Germany) with the indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel plates (Merck). ¹H-(600 MHz) and ¹³C-NMR (150 MHz) spectra were recorded on an AVANCE III System 600 MHz spectrometer (Bruker, Billerica, MA, USA) as solutions in CDCl₃ or DMSO-d₆. High-resolution mass spectra (HRMS) were obtained using JMS-700(JEOL) with electron ionization or Thermo Scientific, Q Exactive™ HF-X Hybrid Quadrupole-Orbitrap™ Mass Spectrometer (Germering, Germany) using ESI (electrospray ionization). Low-resolution

mass spectra (LRMS) were obtained using a Waters Auto Purification instrument. Spectral data are available in Supplementary Materials.

4.1.1 Synthesis of honokiol analogs

3',5'-diallyl-4'-methoxy-[1,1'-biphenyl]-2-ol (1a) and 3,5'-diallyl-2'-methoxy-[1,1'-biphenyl]-4-ol (1b). To an acetone solution (10 mL) of honokiol (1.13 g, 4.24 mmol) was added Cs₂CO₃ (1.38 g, 4.24 mmol), by 1 M iodomethane in THF (0.5 mL, 5.08 mmol). After stirring at reflux overnight, the reaction mixture was diluted in ethyl acetate, washed with water and brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate : n-hexane = 1 : 19 to 1 : 2) to afford **1a** (330 mg, 30%, BORSM 36%), **1b** (210 mg, 15%, BORSM 23%), **1c** (182 mg, 15%, BORSM 19%), and recovered honokiol (280 mg). For **1a**, ¹H NMR (600 MHz, CDCl₃) δ 7.28 (d, *J* = 8.3 Hz, 1H), 7.23 (s, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 7.03 (s, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.05–5.93 (m, 2H), 5.11–5.06 (m, 4H), 5.04 (bs, 1H), 3.88 (s, 3H), 3.43 (d, *J* = 6.6 Hz, 2H), 3.35 (d, *J* = 6.6 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 157.2, 151, 138, 136.6, 132.3, 130.6, 130.3, 129.9, 129.1, 128.9, 128.0, 128, 116.0, 115.7, 115.7, 111.1, 55.7, 39.6, 34.4; HRMS (EI) *m/z*: [M] calcd for C₁₉H₂₀O₂ 280.1463; found 280.1466. For **1b**, ¹H NMR (600 MHz, CDCl₃) δ 7.31 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.28 (d, *J* = 2.2 Hz, 1H), 7.11–.09 (m, 2H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.10–5.95 (m, 2H), 5.24–5.20 (m, 2H), 5.11–5.04 (m, 2H), 5.03 (bs, 1H) 3.79 (s, 3H), 3.46 (d, *J* = 6.4 Hz, 2H), 3.37 (d, *J* = 6.7 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 154.8, 153.3, 137.8, 136.5, 132.3, 131.5, 131.2, 131, 130.3, 129.1, 128, 124.7, 116.6, 115.6, 115.5, 111.3, 55.7, 39.4, 35.4; HRMS (EI) *m/z*: [M] calcd for C₁₉H₂₀O₂ 280.1463; found 280.1461. For **1c**, ¹H NMR (600 MHz, CDCl₃) δ 7.41–7.39 (m, 1H), 7.34 (s, 1H), 7.15 (s, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 6.92 (dd, *J* = 8.3, 0.9 Hz, 2H), 6.09–5.98 (m, 2H), 5.14–5.10 (m, 2H), 5.09–5.06 (m, 2H), 3.88 (d, *J* = 1.0 Hz, 3H), 3.81 (d, *J* = 1.2 Hz, 3H), 3.46 (d, *J* = 6.5 Hz, 2H), 3.40 (d, *J* = 6.4 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 156.5, 155.0, 137.9, 137.2, 132.3, 131.1, 131.1, 130.8, 130.6, 128.5, 128.2, 128.0, 115.6, 115.5, 111.4, 110.0, 55.8, 55.6, 39.6, 34.5; LRMS (ESI) *m/z*: calcd for C₂₀H₂₂O₂ [M+Na]⁺ 317.15; found 317.25.

3',5'-diallyl-4'-ethoxy-[1,1'-biphenyl]-2-ol (2a) and 3,5'-diallyl-2'-ethoxy-[1,1'-biphenyl]-4-ol (2b). To an acetone solution (10 mL) of honokiol (30 mg, 0.11 mmol) was

added Cs₂CO₃ (100 mg, 0.3 mmol), followed by iodoethane (21 μL, 0.11 mmol) diluted in 5 mL of acetone. After stirring at reflux overnight, the reaction mixture was diluted in ethyl acetate, washed with water and brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate : n-hexane = 1 : 19 to 1 : 2) to afford **2a** (16 mg, 26%, BORSM 47%), **2b** (8 mg, 15%, BORSM 25%), **2c** (5 mg, 10%, BORSM 16%), and recovered honokiol (22 mg). For **2a**, ¹H NMR (600 MHz, CDCl₃) δ 7.26–7.25 (m, 1H), 7.23 (d, *J* = 1.9 Hz, 1H), 7.06 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.03 (d, *J* = 1.7 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.05–5.95 (m, 2H), 5.14 (d, *J* = 1.1 Hz, 1H), 5.13–5.08 (m, 2H), 5.06 (d, *J* = 10.0 Hz, 1H), 4.09 (q, *J* = 7.0 Hz, 2H), 3.44 (d, *J* = 6.7 Hz, 2H), 3.35 (d, *J* = 6.7 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 156.6, 151, 138, 136.7, 132.3, 130.6, 130.3, 130.1, 128.9, 128.9, 128.0, 128, 116, 115.7, 115.6, 112.0, 63.9, 39.6, 34.6, 15.0; HRMS (EI) *m/z*: [M] calcd for C₂₀H₂₂O₂ 294.1620; found 294.1626. For **2b**, ¹H NMR (600 MHz, CDCl₃) δ 7.34–7.33 (m, 2H), 7.13 (d, *J* = 2.2 Hz, 1H) 7.07–7.06 (m, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.09–6.03 (m, 1H), 6.02–5.95 (m, 1H), 5.23–5.16 (m, 2H), 5.11–5.04 (m, 2H), 4.95 (s, 1H), 4.01–3.98 (q, *J* = 7.0 Hz, 2H), 3.45 (d, *J* = 6.4 Hz, 2H), 3.37 (d, *J* = 6.7 Hz, 2H), 1.34 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 154.4, 153.2, 138, 136.7, 132.5, 131.8, 131.5, 131, 130.6, 129.1, 128.1, 124.7, 116.7, 115.7, 115.5, 113.1, 64.3, 39.6, 35.4, 15.0; HRMS (EI) *m/z*: [M] calcd for C₂₀H₂₂O₂ 294.1620; found 293.1638. For **2c**, ¹H NMR (600 MHz, CDCl₃) δ 7.40–7.36 (m, 2H), 7.14 (d, *J* = 2.3 Hz, 1H), 7.06 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.88 (t, *J* = 8.2 Hz, 2H), 6.07–5.96 (m, 2H), 5.13–5.08 (m, 2H), 5.07–5.03 (m, 2H), 4.08 (q, *J* = 7.0 Hz, 2H), 4.00 (q, *J* = 7.0 Hz, 2H), 3.44 (d, *J* = 6.7 Hz, 2H), 3.37 (d, *J* = 6.7 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H), 1.34 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 155.8, 154.4, 138.0, 137.3, 132.4, 131.2, 131.0, 130.8, 130.7, 128.3, 128.1, 127.9, 115.6, 115.5, 113.0, 111, 64.3, 63.8, 39.6, 34.6, 15.1, 15.0; LRMS (ESI) *m/z*: calcd for C₂₂H₂₆O₂ [M+H]⁺ 322.20; found 323.29.

3',5'-diallyl-4'-butoxy-[1,1'-biphenyl]-2-ol (3a) and 3,5'-diallyl-2'-butoxy-[1,1'-biphenyl]-4-ol (3b). To an acetone solution (2 mL) of honokiol (50 mg, 0.18 mmol) was added Cs₂CO₃ (183 mg, 0.5 mmol), followed by 1-bromobutane (20 μL, 0.18 mmol). After stirring at reflux overnight, the reaction mixture was diluted in ethyl acetate, washed with water and brine, dried over MgSO₄, and concentrated under reduced pressure. The residue

was purified by flash column chromatography on silica gel (ethyl acetate : n-hexane = 1 : 19 to 1 : 2) to afford pure **3a** (8 mg, 15%, BORSM 28%), **3b** (9 mg, 14%, BORSM 26%), **3c** (5 mg, 7%, BORSM 13%), and recovered honokiol (23 mg). For **3a**, ^1H NMR (600 MHz, CDCl_3) δ 7.26–7.23 (m, 1H), 7.22 (d, $J = 2.2$ Hz, 1H), 7.05 (dd, $J = 8.2, 2.2$ Hz, 1H), 7.02 (d, $J = 2.1$ Hz, 1H), 6.94 (d, $J = 8.3$ Hz, 1H), 6.90 (d, $J = 8.2$ Hz, 1H), 6.04–5.94 (m, 2H), 5.14 (bs, 1H), 5.12–5.03 (m, 4H), 4.02 (t, $J = 6.3$ Hz, 2H), 3.43 (d, $J = 6.8$ Hz, 2H), 3.35 (d, $J = 6.7$ Hz, 2H), 1.84–1.79 (m, 2H), 1.57–1.50 (m, 2H), 1.00 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 156.9, 151.1, 138.1, 136.9, 132.4, 130.7, 130.5, 130.2, 129.0, 129.0, 128.2, 128.1, 116.1, 115.8, 115.8, 112.0, 68.1, 39.7, 34.8, 31.7, 19.7, 14.2; HRMS (EI) m/z : [M] calcd for $\text{C}_{22}\text{H}_{26}\text{O}_2$ 322.1933; found 322.1932. For **3b**, ^1H NMR (600 MHz, CDCl_3) δ 7.34 (d, $J = 2.1$ Hz, 1H), 7.31 (dd, $J = 8.2, 2.2$ Hz, 1H), 7.12 (d, $J = 2.3$ Hz, 1H), 7.06 (dd, $J = 8.3, 2.3$ Hz, 1H), 6.88 (d, $J = 8.3$ Hz, 1H), 6.84 (d, $J = 8.2$ Hz, 1H), 6.10–6.02 (m, 1H), 6.02–5.88 (m, 1H), 5.22–5.15 (m, 2H), 5.12–5.02 (m, 2H), 3.92 (t, $J = 6.4$ Hz, 2H), 3.45 (d, $J = 6.4$ Hz, 2H), 3.36 (d, $J = 6.7$ Hz, 2H), 1.72–1.64 (m, 2H), 1.47–1.38 (m, 2H), 0.91 (t, $J = 7.4$ Hz, 3H); HRMS (EI) m/z : [M] calcd for $\text{C}_{22}\text{H}_{26}\text{O}_2$ 322.1933; found 321.1926. For **3c**, ^1H NMR (600 MHz, CDCl_3) δ 7.37 (d, $J = 2.2$ Hz, 1H), 7.33 (dd, $J = 8.4, 2.3$ Hz, 1H), 7.12 (d, $J = 2.3$ Hz, 1H), 7.05 (dd, $J = 8.3, 2.3$ Hz, 1H), 6.87 (t, $J = 8.7$ Hz, 2H), 6.00 (m, 2H), 5.11–5.00 (m, 4H), 4.00 (t, $J = 6.4$ Hz, 2H), 3.92 (t, $J = 6.4$ Hz, 2H), 3.42 (d, $J = 6.7$ Hz, 2H), 3.36 (d, $J = 6.7$ Hz, 2H), 1.83–1.77 (m, 2H), 1.72–1.66 (m, 2H), 1.53 (dd, $J = 15.1, 7.5$ Hz, 2H), 1.43 (m, 2H), 0.99 (t, $J = 7.4$ Hz, 3H), 0.91 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 159.4, 154.4, 137.9, 137.2, 132.1, 131.1, 130.9, 130.6, 128.1, 127.9, 127.7, 115.4, 115.2, 112.5, 110.6, 68.2, 67.7, 39.5, 34.6, 31.5, 31.4, 29.7, 19.4, 19.4, 13.9, 13.8; LRMS (ESI) m/z : calcd for $\text{C}_{26}\text{H}_{34}\text{O}_2$ [M+Na] $^+$ 401.25; found 401.36.

3,5'-diallyl-4'-(allyloxy)-[1,1'-biphenyl]-2-ol (4a) and 3,5'-diallyl-2'-(allyloxy)-[1,1'-biphenyl]-4-ol (4b). To an acetone solution (2 mL) of honokiol (60 mg, 0.22 mmol) was added Cs_2CO_3 (220 mg, 0.67 mmol), followed by allyl bromide (20 μL , 0.22 mmol). After stirring at reflux overnight, the reaction mixture was diluted in ethyl acetate, washed with water and brine, dried over MgSO_4 , and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate : n-hexane = 1 : 19 to 1 : 2) to afford **4a** (21 mg, 31%, BORSM 46%), **4b** (11 mg, 16%, BORSM 24%), **4c** (7.5 mg, 9%, BORSM 14%), and recovered honokiol (20 mg). For **4a**, ^1H NMR (600 MHz,

CDCl₃) δ 7.29–7.22 (m, 2H), 7.08–7.00 (m, 3H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.13–5.99 (m, 1H), 6.03–5.93 (m, 1H), 5.46 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.31 (dd, *J* = 10.6, 1.5 Hz, 1H), 5.13–5.04 (m, 5H), 4.60 (d, *J* = 5.0 Hz, 1H), 3.47 (d, *J* = 6.7 Hz, 3H), 3.35 (d, *J* = 6.7 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 156.1, 150.9, 137.9, 136.6, 133.4, 132.3, 130.7, 130.3, 130.2, 129.3, 128.9, 127.9, 127.9, 117.3, 116.0, 115.6, 115.6, 112.3, 69.0, 39.5, 34.6; HRMS (EI) *m/z*: [M] calcd for C₂₁H₂₂O₂ 306.1620; found 306.1614. For **4b**, ¹H NMR (600 MHz, CDCl₃) δ 7.37 (dd, *J* = 6.9, 2.0 Hz, 2H), 7.13 (d, *J* = 2.2 Hz, 1H), 7.07 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.85 (d, *J* = 8.9 Hz, 1H), 6.09–5.95 (m, 3H), 5.33 (dd, *J* = 17.3, 1.7 Hz, 1H), 5.24–5.15 (m, 3H), 5.12–5.04 (m, 2H), 4.96 (bs, 1H), 4.50 (d, *J* = 4.8 Hz, 2H), 3.46 (d, *J* = 6.4 Hz, 2H), 3.37 (d, *J* = 6.7 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 153.9, 153.3, 137.9, 136.6, 133.6, 132.7, 131.8, 131.3, 131.0, 130.8, 129.2, 128.0, 124.7, 116.8, 116.7, 115.7, 115.5, 113.3, 69.4, 39.5, 35.4; HRMS (EI) *m/z*: [M] calcd for C₂₁H₂₂O₂ 306.1620; found 306.1614. For **4c**, ¹H NMR (600 MHz, CDCl₃) δ 7.44–7.35 (m, 2H), 7.16 (d, *J* = 2.3 Hz, 1H), 7.09 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.91 (dd, *J* = 8.3, 6.2 Hz, 2H), 6.14–5.97 (m, 4H), 5.49–5.46 (m, 1H), 5.38–5.37 (m, 1H), 5.32–5.29 (m, 1H), 5.23–5.21 (m, 1H), 5.14–5.10 (m, 2H), 5.08–5.05 (m, 2H), 4.61–4.60 (m, 2H), 4.53–4.52 (m, 2H), 3.48 (d, *J* = 6.6 Hz, 2H), 3.39 (d, *J* = 6.7 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 155.5, 154.0, 137.9, 137.2, 133.8, 133.6, 132.7, 131.3, 131.1, 131.0, 130.9, 128.4, 128, 117.0, 116.9, 115.7, 115.6, 113.3, 111.3, 69.5, 69, 39.6, 34.7; LRMS (ESI) *m/z*: calcd for C₂₄H₂₆O₂ [M+Na]⁺ 401.24; found 401.36.

3',5-diallyl-4'-((3-methylbut-2-en-1-yl)oxy)-[1,1'-biphenyl]-2-ol (5a) and 3,5'-diallyl-2'-((3-methylbut-2-en-1-yl)oxy)-[1,1'-biphenyl]-4-ol (5b). To an acetone solution (2 mL) of honokiol (40 mg, 0.15 mmol) was added Cs₂CO₃ (146 mg, 0.45 mmol), followed by 3,3-dimethylallyl bromide (22 mg, 0.15 mmol). After stirring at reflux overnight, the reaction mixture was diluted in ethyl acetate, washed with water and brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate : n-hexane = 1 : 19 to 1 : 2) to afford **5a** (25 mg, 50%, BORSM 73%), **5b** (1.6 mg, 3%, BORSM 5%), and recovered honokiol (13 mg). For **5a**, ¹H NMR (600 MHz, CDCl₃) δ 7.26–7.21 (m, 2H), 7.05–7.00 (m, 2H), 6.94 (d, 1H, *J* = 8.3 Hz), 6.90 (d, 1H, *J* = 8.2 Hz), 6.04–5.93 (m, 2H), 5.52–5.48 (m, 1H), 5.19 (s, 1H), 5.11–5.03 (m, 4H), 4.57 (d, 2H, *J* = 6.5 Hz), 3.43 (d, 2H, *J* = 6.8 Hz), 3.34 (d, 2H, *J* =

6.7 Hz), 1.80 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 156.3, 150.8, 137.8, 137.5, 136.5, 132.1, 130.4, 130.1, 128.7, 127.8, 127.7, 119.9, 115.8, 115.5, 115.4, 112.2, 65.2, 39.4, 34.4, 25.7, 18.3; HRMS (EI) m/z : [M] calcd for $\text{C}_{23}\text{H}_{26}\text{O}_2$ 334.1933; found 334.1935. For **5b**, ^1H NMR (600 MHz, CDCl_3) δ 7.25–7.20 (m, 2H), 6.92–6.91 (m, 1H), 6.90–6.88 (m, 1H), 6.09–5.91 (m, 3H), 5.37–5.33 (m, 1H), 5.25 (s, 1H), 5.23–5.17 (m, 2H), 5.11–5.06 (m, 2H), 5.05–5.02 (m, 1H), 3.46 (d, 2H, $J = 6.4$ Hz), 3.37 (d, 2H, $J = 7.2$ Hz), 3.32 (d, 2H, $J = 6.8$ Hz), 1.75 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 153.9, 149.0, 138.0, 136.2, 133.6, 131.8, 131.4, 130.2, 129.2, 128.9, 128.1, 127.9, 127.7, 126.1, 122.4, 117.0, 116.5, 115.5, 39.6, 35.4, 29.6, 25.9, 18.0; HRMS (EI) m/z : [M] calcd for $\text{C}_{23}\text{H}_{26}\text{O}_2$ 334.1933; found 334.1927.

3',5-diallyl-4'-(cyclopropylmethoxy)-[1,1'-biphenyl]-2-ol (6a) and 4-(2-(cyclopropylmethoxy)-5-(prop-2-en-1-yl)phenyl)-2-(prop-2-en-1-yl)phenol (6b).

To an acetone solution (2 mL) of honokiol (50 mg, 0.18 mmol) was added Cs_2CO_3 (0.15 mg, 0.45 mmol), followed by cyclopropylmethyl bromide (25 mg, 0.18 mmol). After stirring at reflux overnight, the reaction mixture was diluted in ethyl acetate, washed with water and brine, dried over MgSO_4 , and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate : n-hexane = 1 : 19 to 1 : 2) to afford **6a** (10 mg, 16%, BORSM 40%), **6b** (2 mg, 3%, BORSM 8%), **6c** (5 mg, 7%, BORSM 18%), and recovered honokiol (30 mg). For **6a**, ^1H NMR (600 MHz, CDCl_3) δ 7.25 (d, $J = 2.4$ Hz, 2H), 7.04 (dd, $J = 8.2, 2.2$ Hz, 1H), 7.02 (d, $J = 2.1$ Hz, 1H), 6.92–6.89 (m, 2H), 6.06–5.93 (m, 2H), 5.13–5.04 (m, 5H), 3.88 (d, 2H, $J = 6.7$ Hz), 3.46 (d, 2H, $J = 6.8$ Hz), 3.34 (d, 2H, $J = 6.8$ Hz), 1.32–1.27 (m, 1H), 0.64–0.63 (m, 2H), 0.38–0.37 (m, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 156.4, 150.8, 137.8, 136.6, 132.1, 130.4, 130.1, 128.8, 128.7, 127.8, 127.8, 115.8, 115.5, 115.4, 112.1, 72.7, 39.4, 34.5, 10.3, 3.0; HRMS (EI) m/z : [M] calcd for $\text{C}_{22}\text{H}_{24}\text{O}_2$ 320.1776; found 320.1774. For **6b**, ^1H NMR (600 MHz, CDCl_3) δ 7.46–7.32 (m, 2H), 7.13 (d, $J = 2.3$ Hz, 1H), 7.05 (dd, $J = 8.3, 2.3$ Hz, 1H), 6.86 (dd, $J = 17.2, 8.3$ Hz, 2H), 6.1–6.03 (m, 1H), 6.01–5.94 (m, 1H), 5.23–5.22 (m, 1H), 5.17–5.15 (m, 1H), 5.10–5.05 (m, 1H), 5.04 (m, 1H), 4.96 (bs, 1H), 3.77 (d, $J = 6.7$ Hz, 2H), 3.46 (d, $J = 6.4$ Hz, 2H), 3.36 (d, $J = 6.7$ Hz, 2H), 1.20–1.16 (m, 1H), 0.55–0.52 (m, 2H), 0.28–0.25 (m, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 154.4, 153.2, 137.9, 136.6, 132.6, 131.9, 131.4, 130.9, 130.8, 129.1, 128.0, 124.6, 116.6, 115.6, 115.5, 113.8, 73.5, 39.6, 35.4,

10.4, 3.2; HRMS (EI) m/z : [M] calcd for $C_{22}H_{24}O_2$ 320.1776; found 320.1775. For **6c**, 1H NMR (600 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.39–7.35 (m, 1H), 7.14 (s, 1H), 7.06 (dd, $J = 8.2, 1.7$ Hz, 1H), 6.90–6.85 (m, 2H), 6.11–6.03 (m, 1H), 6.03–5.95 (m, 1H), 5.16–5.08 (m, 2H), 5.08–5.02 (m, 2H), 3.88 (d, $J = 6.6$ Hz, 2H), 3.77 (d, $J = 6.7$ Hz, 2H), 3.48 (d, $J = 5.8$ Hz, 2H), 3.37 (d, $J = 6.5$ Hz, 2H), 1.33–1.28 (m, 1H), 1.23–1.16 (m, 1H), 0.63 (d, $J = 7.0$ Hz, 2H), 0.55 (d, $J = 8.0$ Hz, 2H), 0.38 (d, $J = 4.8$ Hz, 2H), 0.28 (d, $J = 4.8$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.9, 154.5, 138, 137.4, 132.6, 131.3, 131.1, 131.0, 130.9, 128.3, 128.3, 127.9, 115.6, 115.5, 113.7, 111.3, 73.5, 72.7, 39.6, 34.8, 10.6, 10.5, 3.2, 3.2; LRMS (ESI) m/z : calcd for $C_{26}H_{30}O_2$ $[M+Na]^+$ 397.21; found 397.38.

3',5'-diallyl-4'-(cyclobutylmethoxy)-[1,1'-biphenyl]-2-ol (7a) and 3,5'-diallyl-2'-(cyclobutylmethoxy)-[1,1'-biphenyl]-4-ol (7b). To an acetone solution (4 mL) of honokiol (140 mg, 0.52 mmol) was added Cs_2CO_3 (0.51 g, 1.6 mmol), followed by cyclobutylmethyl bromide (72 μ l, 0.63 mmol). After stirring at reflux overnight, the reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate : n-hexane = 1/19 : 1/1) to afford **7a** (10 mg, 6%, BORSM 36%), **7b** (4.5 mg, 3%, BORSM 16%), **7c** (1 mg, 0.5%, BORSM 3%), and recovered honokiol (112 mg). For **7a**, 1H NMR (600 MHz, $CDCl_3$) δ 7.27–7.23 (m, 2H), 7.05 (dd, $J = 8.2, 2.2$ Hz, 1H), 7.03 (d, $J = 2.1$ Hz, 1H), 6.93 (d, $J = 8.3$ Hz, 1H), 6.90 (d, $J = 8.2$ Hz, 1H), 6.04–5.94 (m, 2H), 5.12–5.04 (m, 5H), 3.97 (d, $J = 6.3$ Hz, 2H), 3.44 (d, $J = 6.8$ Hz, 2H), 3.34 (d, $J = 6.7$ Hz, 2H), 2.86–2.79 (m, 2H), 2.17–2.13 (m, 2H), 2.01–1.92 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.1, 150.9, 137.9, 136.6, 133.4, 132.3, 130.7, 130.3, 130.2, 129.3, 128.9, 127.9, 127.9, 117.3, 116.0, 115.6, 115.6, 112.3, 69.0, 39.5, 34.6; HRMS (EI) m/z : [M] calcd for $C_{23}H_{26}O_2$ 334.1933; found 334.1935. For **7b**, 1H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, $J = 2.1$ Hz, 1H), 7.32 (dd, $J = 8.2, 2.2$ Hz, 1H), 7.13 (d, $J = 2.2$ Hz, 1H), 7.06 (dd, $J = 8.3, 2.3$ Hz, 1H), 6.88 (d, $J = 8.3$ Hz, 1H), 6.84 (d, $J = 8.2$ Hz, 1H), 6.09–6.01 (m, 1H), 6.00–5.95 (m, 1H), 5.22–5.18 (m, 1H), 5.18–5.16 (m, 1H), 5.10–5.07 (m, 1H), 5.06–5.04 (m, 1H), 4.94 (bs, 1H), 3.88 (d, $J = 6.3$ Hz, 2H), 3.45 (d, $J = 6.3$ Hz, 2H), 3.36 (d, $J = 6.7$ Hz, 2H), 2.74–2.66 (m, 1H), 2.06–2.00 (m, 2H), 1.94–1.78 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.6, 153.3, 138.0, 136.7, 132.4, 132, 131.5, 130.9, 130.6, 129.2, 128.0, 124.5, 116.7, 115.6, 115.5, 113, 72.7, 39.6, 35.6, 34.9, 25, 18.6.;

HRMS (EI) m/z : [M] calcd for $C_{23}H_{26}O_2$ 334.1933; found 334.1940.

2-((3,5'-diallyl-2'-hydroxy-[1,1'-biphenyl]-4-yl)oxy)-1-(4-fluorophenyl)ethan-1-one (8a) and 2-((3',5-diallyl-4'-hydroxy-[1,1'-biphenyl]-2-yl)oxy)-1-(4-fluorophenyl)ethan-1-one (8b). To a Tetrahydrofuran solution (4 mL) of honokiol (140 mg, 0.52 mmol) was added Cs_2CO_3 (0.51 g, 1.6 mmol), followed by 4-fluorophenacyl bromide (0.14 g, 0.62 mmol). After stirring 1 h at ambient temperature, the reaction mixture was diluted in ethyl acetate, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate : n-hexane = 1 : 19 to 1 : 2) to afford **8a** (67 mg, 32%, BORSM 40%), **8b** (21 mg, 10%, BORSM 12%), **8c** (50 mg, 18%, BORSM 22%), and recovered honokiol (27 mg). For **8a**, 1H NMR (600 MHz, $CDCl_3$) δ 8.09–8.06 (m, 2H), 7.27 (d, $J = 2.2$ Hz, 1H), 7.24 (dd, $J = 8.3, 2.3$ Hz, 1H), 7.21–7.16 (m, 2H), 7.05 (dd, $J = 8.2, 2.1$ Hz, 1H), 7.00 (d, $J = 2.1$ Hz, 1H), 6.89 (d, $J = 8.2$ Hz, 1H), 6.85 (d, $J = 8.3$ Hz, 1H), 6.04–5.93 (m, 2H), 5.27 (s, 2H), 5.10–5.04 (m, 5H), 3.50 (d, $J = 6.6$ Hz, 2H), 3.34 (d, $J = 6.7$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.4, 155.5, 150.9, 137.9, 136.5, 132.4, 131.3, 131.2, 131.2, 130.3, 129.1, 128.1, 127.7, 116.3, 116.3, 116.2, 115.8, 115.7, 112.2, 71.3, 39.5, 34.5.; HRMS (EI) m/z : [M] calcd for $C_{26}H_{23}FO_3$ 402.1631; found 402.1635. For **8b**, 1H NMR (600 MHz, $CDCl_3$) δ 7.95–7.92 (m, 2H), 7.33–7.30 (m, 2H), 7.09–7.01 (m, 4H), 6.83 (dd, $J = 8.3, 5.4$ Hz, 2H), 6.04–5.97 (m, 2H), 5.10–5.06 (m, 5H), 3.41 (d, $J = 6.4$ Hz, 2H), 3.36 (d, $J = 6.8$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.8, 166.9, 165.2, 153.4, 153.3, 137.5, 136.4, 131.7, 131.3, 131.2, 131.1, 129.1, 128.0, 116.6, 115.9, 115.8, 115.8, 115.5, 113.4, 71.9, 39.4, 35.3. For **8c**, 1H NMR (600 MHz, $CDCl_3$) δ 8.11–8.05 (m, 2H), 7.95–7.90 (m, 2H), 7.36–7.34 (m, 2H), 7.20–7.15 (m, 2H), 7.12 (d, $J = 2.2$ Hz, 1H), 7.10–7.03 (m, 3H), 6.83 (d, $J = 8.4$ Hz, 1H), 6.78 (d, $J = 9.0$ Hz, 1H), 6.01–5.92 (m, 2H), 5.22 (s, 2H), 5.09 (s, 2H), 5.07–5.00 (m, 4H), 3.44 (d, $J = 6.6$ Hz, 2H), 3.35 (d, $J = 6.7$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.8, 193.7, 155.0, 153.4, 137.6, 136.9, 133.9, 131.7, 131.4, 131.3, 131.2, 131.0, 128.7, 128.3, 116.2, 116.0, 115.9, 115.9, 115.8, 113.4, 111.2, 72.0, 71.5, 39.5, 34.5; LRMS (ESI) m/z : calcd for $C_{34}H_{28}F_2O_2$ [M+Na] $^+$ 561.18; found 561.32.

2-((3,5'-diallyl-2'-hydroxy-[1,1'-biphenyl]-4-yl)oxy)-1-(2,4-dichlorophenyl)ethan-1-one (9a) and 2-((3',5-diallyl-4'-hydroxy-[1,1'-biphenyl]-2-yl)oxy)-1-(2,4-dichlorophenyl)ethan-1-one (9b). To an acetone solution (4 mL) of honokiol (140

mg, 0.52 mmol) was added Cs₂CO₃ (0.51 g, 1.6 mmol), followed by 4-nitrophenacyl bromide (77 μ l, 0.62 mmol). After stirring for 1 h at ambient temperature, the reaction mixture was diluted in ethyl acetate, washed with water and brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate : n-hexane = 1 : 19 to 1 : 2) to afford **9a** (14 mg, 6%, BORSM 17%), **9b** (14 mg, 6%, BORSM 17%), **9c** (23 mg, 7%, BORSM 19%), and recovered honokiol (64 mg). For **9a**, ¹H NMR (600 MHz, CDCl₃) δ 7.56 (d, *J* = 8.3 Hz, 1H), 7.48 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.24 (s, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 7.00 (s, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 5.96–5.85 (m, 3H), 5.18 (s, 2H), 5.09–4.99 (m, 4H), 3.35 (t, *J* = 7.3 Hz, 4H); ¹³C NMR (150 MHz, CDCl₃) δ 197.5, 155.2, 150.9, 138.6, 137.9, 136.3, 134.9, 132.9, 132.4, 131.2, 130.5, 130.4, 130.3, 130.2, 129.1, 128.1, 127.7, 127.6, 116.1, 115.8, 115.7, 112.0, 73.1, 39.5, 34.4; HRMS (EI) *m/z*: [M] calcd for C₂₆H₂₂Cl₂O₃ 452.0946; found 452.0947. For **9c**, ¹H NMR (600 MHz, CDCl₃) δ 7.54 (d, *J* = 8.3 Hz, 1H), 7.48 (d, *J* = 1.9 Hz, 1H), 7.38–7.33 (m, 2H), 7.29 (d, *J* = 1.9 Hz, 1H), 7.22–7.16 (m, 3H), 7.08–7.04 (m, 2H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 1H), 5.99–5.92 (m, 1H), 5.89–5.82 (m, 1H), 5.13 (s, 2H), 5.10–5.04 (m, 2H), 4.99 (s, 2H), 4.97–4.91 (m, 2H), 3.35 (d, *J* = 6.7 Hz, 2H), 3.27 (d, *J* = 6.6 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 198.25, 197.92, 154.56, 153.13, 138.38, 138.02, 137.60, 136.73, 135.10, 135.04, 133.83, 132.85, 132.74, 131.57, 131.46, 131.38, 131.12, 130.98, 130.90, 130.43, 130.16, 128.46, 128.22, 127.57, 127.32, 115.94, 115.60, 112.95, 110.57, 73.68, 73.00, 39.49, 34.48; LRMS (ESI) *m/z*: calcd for C₃₄H₂₆Cl₄O₄ [M+Na]⁺ 661.04; found 661.25.

2-((3,5'-diallyl-2'-hydroxy-[1,1'-biphenyl]-4-yl)oxy)-1-(4-nitrophenyl)ethan-1-one (10a). To a tetrahydrofuran solution (2 mL) of honokiol (50 mg, 0.18 mmol) was added Cs₂CO₃ (183 mg, 0.56 mmol), followed by 2-bromo-4'-nitroacetophenone (46 mg, 0.18). After stirring 1 h at room temperature, the reaction mixture was diluted in ethyl acetate, washed with water and brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate : n-hexane = 1 : 19 to 1 : 2) to afford **10a** (35 mg, 43%, BORSM 54%), **10c** (10 mg, 9%, BORSM 11%), and recovered honokiol (10 mg). ¹H NMR (600 MHz, CDCl₃) δ 8.37–8.34 (m, 2H), 8.21–8.18 (m, 2H), 7.28 (dd, 2H, *J* = 5.1, 2.1 Hz), 7.05 (dd, 1H, *J* = 8.2, 2.2 Hz), 7.01 (d, 1H, *J* = 2.1 Hz), 6.88 (dd, 2H, *J* = 14.2, 8.2 Hz), 6.00–5.94 (m, 2H), 5.30 (s, 2H),

5.10–5.02 (m, 5H), 3.47 (d, 2H, $J = 6.6$ Hz), 3.34 (d, 2H, $J = 6.7$ Hz); ^{13}C NMR (150 MHz, CDCl_3) δ 194.0, 155.1, 150.8, 150.8, 139.1, 137.8, 136.3, 132.4, 131.4, 130.9, 130.3, 130.2, 129.7, 129.1, 128.1, 127.5, 124.1, 116.3, 115.8, 115.7, 112.0, 71.6, 39.5, 34.4; HRMS (EI) m/z : [M] calcd for $\text{C}_{26}\text{H}_{23}\text{NO}_5$ 429.1576; found 429.1574. For **10c**, ^1H NMR (600 MHz, CDCl_3) δ 8.24 (dd, $J = 8.9, 1.7$ Hz, 2H), 7.98 (dd, $J = 9.0, 1.0$ Hz, 2H), 7.80 (dd, $J = 9.0, 1.1$ Hz, 2H), 7.42 (dd, $J = 9.0, 2.1$ Hz, 1H), 7.20 (d, $J = 2.0$ Hz, 1H), 7.16–7.11 (m, 1H), 7.08–7.00 (m, 1H), 6.86–6.76 (m, 1H), 5.99–5.88 (m, 1H), 5.09–4.98 (m, 2H), 4.82 (d, $J = 15.0$ Hz, 1H), 4.57 (d, $J = 10.8$ Hz, 1H), 4.23–4.18 (m, 1H), 3.90 (dd, $J = 9.2, 6.9$ Hz, 1H), 3.34 (dd, $J = 19.1, 7.0$ Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 209.8, 155.2, 153.5, 151.1, 147.5, 147.1, 137.6, 136.9, 133.6, 131.9, 131.7, 131.2, 130.9, 128.8, 128.6, 126.6, 126.5, 123.7, 123.3, 116, 113.2, 111.0, 75.0, 74.6, 49.3, 39.5; LRMS (ESI) m/z : calcd for $\text{C}_{34}\text{H}_{28}\text{O}_2$ [M+H] $^+$ 593.19; found 593.35.

tert-butyl 2-((3,5'-diallyl-2'-hydroxy-[1,1'-biphenyl]-4-yl)oxy)acetate (11a) and tert-butyl 2-((3',5-diallyl-4'-hydroxy-[1,1'-biphenyl]-2-yl)oxy)acetate (11b). To a tetrahydrofuran solution (2 mL) of honokiol (200 mg, 0.75 mmol) was added Cs_2CO_3 (245 mg, 0.75 mmol), followed by *tert*-butyl bromoacetate (220 mg, 1.13). After stirring 1 h at ambient temperature, the reaction mixture was diluted in ethyl acetate, washed with water and brine, dried over MgSO_4 , and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate : n-hexane = 1 : 19 to 1 : 2) to afford **11a** (107 mg, 37%, BORSM 48%), **11b** (36 mg, 13%, BORSM 16%), **11c** (97 mg, 26%, BORSM 33%), and recovered honokiol (43 mg). For **11a**, ^1H NMR (600 MHz, CDCl_3) δ 7.24 (d, 2H, $J = 2.3$ Hz), 7.06–7.04 (m, 1H), 7.02 (d, 1H, $J = 2.2$ Hz), 6.90 (d, 1H, $J = 8.2$ Hz), 6.80 (d, 1H, $J = 8.0$ Hz), 6.01 (dd, 2H, $J = 44.3, 6.9$ Hz), 5.14–5.04 (m, 5H), 4.58 (s, 2H), 3.51 (d, 2H, $J = 6.7$ Hz), 3.35 (d, 2H, $J = 6.7$ Hz), 1.51 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 167.9, 155.4, 150.8, 137.7, 136.3, 132.1, 130.8, 130.2, 130.1, 129.9, 128.8, 127.7, 127.6, 116.0, 115.5, 115.5, 111.8, 82.4, 65.9, 39.4, 34.3, 28.1; HRMS (EI) m/z : [M] calcd for $\text{C}_{24}\text{H}_{28}\text{O}_4$ 380.1988; found 380.1987. For **11b**, ^1H NMR (600 MHz, CDCl_3) δ 7.40 (dd, $J = 8.2, 2.2$ Hz, 1H), 7.36 (d, $J = 2.1$ Hz, 1H), 7.14 (d, $J = 2.2$ Hz, 1H), 7.06 (dd, $J = 8.3, 2.2$ Hz, 1H), 6.84 (d, $J = 8.3$ Hz, 1H), 6.79 (d, $J = 8.4$ Hz, 1H), 6.10–6.03 (m, 1H), 6.00–5.93 (m, 1H), 5.23–5.20 (m, 1H), 5.18–5.16 (m, 1H), 5.10–5.04 (m, 3H), 5.01 (bs, 1H), 4.46 (s, 2H), 3.46 (d, $J = 6.4$ Hz, 2H), 3.37 (d, $J = 6.7$ Hz, 2H), 1.48 (s, 9H);

^{13}C NMR (150 MHz, CDCl_3) δ 168.5, 153.5, 153.3, 137.7, 136.7, 133.4, 131.6, 131.3, 130.8, 130.8, 129.2, 127.8, 125.0, 116.4, 115.7, 115.5, 112.8, 82.3, 66.5, 39.5, 35.3, 28.1; HRMS (EI) m/z : [M] calcd for $\text{C}_{24}\text{H}_{28}\text{O}_4$ 380.1988; found 380.1986. For **11c**, ^1H NMR (600 MHz, CDCl_3) δ 7.44 (dd, $J = 8.4, 2.3$ Hz, 1H), 7.40 (d, $J = 2.2$ Hz, 1H), 7.13 (d, $J = 2.3$ Hz, 1H), 7.05 (dd, $J = 8.3, 2.3$ Hz, 1H), 6.77 (dd, $J = 10.7, 8.4$ Hz, 2H), 6.11–6.04 (m, 1H), 6.00–5.94 (m, 1H), 5.14–5.03 (m, 4H), 4.55 (s, 2H), 4.44 (s, 2H), 3.51 (d, $J = 6.7$ Hz, 2H), 3.36 (d, $J = 6.7$ Hz, 2H), 1.51 (s, 9H), 1.46 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.3, 168.3, 155.0, 153.4, 137.8, 137.1, 133.4, 131.5, 131.4, 131.4, 130.8, 128.8, 128.5, 128, 115.8, 115.6, 112.9, 111.1, 82.3, 82.2, 66.5, 66.4, 39.5, 34.6, 28.2, 28.2; LRMS (ESI) m/z : calcd for $\text{C}_{30}\text{H}_{38}\text{O}_6$ [M+Na] $^+$ 517.25; found 517.37.

2-((3,5'-diallyl-2'-hydroxy-[1,1'-biphenyl]-4-yl)oxy)acetic acid (12). To a CH_2Cl_2 solution (3.0 mL) of *tert*-butyl acetate (**11a**) (50 mg, 0.13 mmol) was added trifluoroacetic acid (1 mL). After stirring for 2 h at ambient temperature, the reaction mixture was concentrated under reduced pressure to afford crude the carboxylic acid (**12**) (45 mg, 95%). ^1H NMR (600 MHz, DMSO-d_6) δ 9.25 (s, 1H), 7.30 (d, $J = 8.5$ Hz, 1H), 6.99 (s, 1H), 6.91 (d, $J = 8.1$ Hz, 1H), 6.86 (d, $J = 8.4$ Hz, 1H), 6.82 (d, $J = 8.2$ Hz, 1H), 6.05–5.97 (m, 1H), 5.97–5.90 (m, 1H), 5.12–4.98 (m, 6H), 4.69 (s, 2H), 3.39 (d, $J = 6.6$ Hz, 2H), 3.33 (s, 1H), 3.28 (d, $J = 6.6$ Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 170.4, 154.3, 152.4, 138.3, 137, 131.2, 130.4, 130.2, 130.1, 127.8, 127.8, 127.4, 127.3, 115.9, 115.6, 115.3, 111.1, 65.0, 38.8, 34.0; HRMS (EI) m/z : [M] calcd for $\text{C}_{20}\text{H}_{20}\text{O}_4$ 324.1362; found 324.1362.

***N*-(2-(2-(2-(2-(4-((4-(4-(3-(2-((3,5'-diallyl-2'-hydroxy-[1,1'-biphenyl]-4-yl)oxy)acetamido)propoxy)benzoyl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethyl)-5-((3*aS*,4*S*,6*aR*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide (14).** To a CH_2Cl_2 solution (3.0 mL) of *tert*-butyl acetate (**12b**) (23 mg, 0.05 mmol) was added trifluoroacetic acid (0.3 mL). After stirring for 2 h at ambient temperature, the reaction mixture was concentrated under reduced pressure to afford crude the carboxylic acid (**13**) (20 mg, 98%). To a DMF solution (3 mL) of carboxylic acid (**13**) (50 mg, 0.15 mmol) were added HOAt (63 mg, 0.46 mmol), PyAOP (161 mg, 0.308 mmol), and DIPEA (0.22 mL, 1.26 mmol). After stirring for 24 h, the reaction mixture was diluted in ethyl acetate, dried over MgSO_4 , and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel ($\text{MeOH} : \text{CH}_2\text{Cl}_2 = 1 : 10$) to afford

biotin probe (**14**) (25 mg, 20%, BORSM 31%) and recovered starting material **13** (18 mg). ¹H NMR (600 MHz, CDCl₃) δ 9.16 (s, 1H), 7.84 (s, 1H), 7.72–7.67 (m, 4H), 7.41 (dd, 1H, *J* = 8.4, 2.1 Hz), 7.37 (d, 1H, *J* = 1.7 Hz), 7.01 (dd, 2H, *J* = 10.5, 2.9 Hz), 6.98 (s, 1H), 6.91–6.85 (m, 4H), 6.80–6.77 (m, 1H), 6.72 (d, 1H, *J* = 4.6 Hz), 6.28 (s, 1H), 5.95–5.86 (m, 2H), 5.57 (s, 1H), 5.23 (s, 2H), 5.03–4.94 (m, 4H), 4.52 (t, 2H, *J* = 4.8 Hz), 4.49 (s, 1H), 4.42–4.38 (m, 1H), 4.23–4.19 (m, 1H), 4.00 (t, 2H, *J* = 5.6 Hz), 3.84 (t, 2H, *J* = 4.8 Hz), 3.56–3.54 (m, 2H), 3.52 (d, 8H, *J* = 1.2 Hz), 3.47 (t, 2H, *J* = 4.9 Hz), 3.37 (d, 2H, *J* = 5.9 Hz), 3.35–3.33 (m, 2H), 3.26 (d, 2H, *J* = 6.6 Hz), 3.07–2.97 (m, 2H), 2.82–2.78 (m, 1H), 2.66 (d, 1H, *J* = 12.7 Hz), 2.13 (dd, 2H, *J* = 9.7, 4.9 Hz), 2.05–2.00 (m, 2H), 1.69–1.53 (m, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 194.3, 173.3, 168.8, 163.8, 162.0, 161.4, 153.9, 152.9, 143.2, 138.1, 137.5, 132.9, 132.2, 132.2, 131.8, 131.1, 130.6, 130.5, 130.2, 128.7, 128.2, 127.6, 127.3, 124.3, 116.2, 115.3, 115.2, 114.3, 114.0, 111.3, 70.5, 70.3, 70.3, 70.0, 69.8, 69.4, 67.5, 65.6, 62.0, 61.7, 60.2, 55.5, 50.3, 40.5, 39.4, 39.1, 36.2, 35.8, 35.1, 28.9, 28.2, 28.1, 25.5; HRMS (ESI/QTOF) *m/z*: [M+Na] calcd for C₅₇H₆₉N₇NaO₁₁S 1082.4668; found 1082.4673.

4.2 Biological assays

4.2.1 Cell viability assay

The cell viability was measured using soluble 3-(4, 5-dimethyl- thiazol-2-yl)-2, 5-diphenyl-tetrazolium bromide (MTT; Sigma, Cat. No. M5655) that converts into insoluble purple formazan by metabolic enzymes in live cells. 5×10⁴ RAW264.7 cells were seeded in 96 well plates and treated with various concentration of honokiol derivatives. Following 24 h incubation, the MTT solution were added to each well and additionally incubated at 37 °C for 2 h. Then, the supernatant was removed and the formazan was dissolved with Dimethyl sulfoxide (DMSO, Sigma, D-2650). The quantitative absorbance was measured at 540nm with ELISA reader (Molecular Devices, SpectraMax M2).

4.2.2 Nitric oxide production assay

To observe the production of nitric oxide (NO), 4×10⁵ RAW264.7 cells were seeded and activated by LPS (InVivogen, Cat. No. tlrl-eklps) in 24 well plates. Consistent with LPS activation, the cells also treated with honokiol derivatives and incubated for 24 h at 37°C. After 24 h incubation, the supernatant was transferred to 96-well plate and Griess

reagent A (1% Sulfanilamide, Sigma, Cat. No. S9251; 2% Phosphoric acid, Sigma, Cat. No. 345245) and Gries reagent B (*N*-(1-Naphthyl) ethylenediamine dihydrochloride (NED), TCI, Cat. No. N0063) were sequentially incubated for 20 min each at room temperature. The NO concentration was determined by absorbance at 540 nm using ELISA reader (Molecular Devices, SpectraMax M2).

4.2.3 Western blotting

2.5×10^6 RAW 264.7 cells were stimulated with LPS (10 ng/ml or 100 ng/ml) (InvivoGen, Cat. No. 13106MM) with or without honokiol derivatives (5 μ M) respectively and lysed with a cold lysis buffer containing 50 mM Tris-HCl (Amresco, Cat No.0826), 2 mM EDTA (Biosesang, Cat No.E2002), 1% NP-40 (Millipore, Cat. No.492016), protease inhibitors (Roche, Cat No. 11836170001), and PhoSTOP (Roche, Cat. No. 04906837001). Lysates were clearly collected and electrophoresed by SDS-PAGE and transferred to PVDF blotting membrane (GE Healthcare, Cat. No. 10600023). The membrane was incubated with rabbit anti-COX-2 antibody (Cell Signaling Technology, Cat. No. 4842), mouse anti-iNOS antibody (BD Biosciences, Cat. No 610329), mouse anti- β -actin antibody (Santa Cruz Biotechnology, Cat. No sc-47778) respectively, followed by detection using the corresponding horseradish peroxidase (HRP)-conjugated goat anti-mouse IgG (Jackson ImmunoResearch Laboratories, Cat. No. 115-036-003), goat anti-rabbit IgG (Bio-Rad, Cat. No. 170-6515) respectively, and enhanced chemiluminescence (ECL) (Bio-Rad, Cat. No. 170-0561). The membranes were scanned with a Fusion Solo chemiluminescence imaging system (Vilber).

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Conflict of Interest (COI)

The authors declare no conflict of interest.

Supplementary Materials

The online version of this article contains supplementary materials.

References

- 1) Janeway Jr, C. A., Travers, P., Walport, M., & Shlomchik, M. J., Principles of innate and adaptive immunity, 2001.
- 2) Chen, L., Deng, H., Cui, H., Fang, J., Zuo, Z., Deng, J. and Zhao, L., *Oncotarget*, **9**, 7204-7218 (2018).
- 3) Joo, T., Sowndhararajan, K., Hong, S., Lee, J., Park, S. Y., Kim, S., and Jhoo, J. W., *Saudi. J. Biol. Sci.*, **21**, 427-435 (2014).
- 4) Venkatesha, S. H., Dudics, S., Acharya, B., and Moudgil, K. D., *Int. J. Mol. Sci.*, **16**, 887-906 (2015).
- 5) Meek, I.L., Van de Laar, M. A. and Vonkeman, H. E., *Pharmaceuticals*, **3**, 2146-2162 (2010).
- 6) Drini, M., *Aust. Prescr.*, **40**, 91-93 (2017).
- 7) Varga, Z., Sabzwari, S. R. A. and Vargova, V., *Cureus*, **9**, e1144 (2017).
- 8) Ma, L., Chen, J., Wang, X., Liang, X., Luo, Y., Zhu, W and Peng, A., *J. Med. Chem.*, **54**, 6469-6481 (2011).
- 9) Sulaiman, R.S., Basavarajappa, H.D. and Corson, T. W., *Exp. Eye Res.*, **129**, 161-171 (2014).
- 10) Bai, X., Cerimele, F., Ushio-Fukai, M., Waqas, M., Campbell, P. M., Govindarajan, B., and Murad, E., *J. Biol. Chem.*, **278**, 35501-35507 (2003).
- 11) Lee, B., Kwak, J. H., Huang, S. W., Jang, J. Y., Lim, S., Kwak, Y. S., and Lee, H., *Bioorg. Med. Chem.*, **20**, 2860-2868 (2012).
- 12) Kim, H. I., Kim, J. A., Choi, E. J., Harris, J. B., Jeong, S. Y., Son, S. J., and Shin, O. S., *Biosci. Biotechnol. Biochem.*, **79**, 475-483 (2015).
- 13) Ahn, K. S., Sethi, G., Shishodia, S., Sung, B., Arbiser, J. L., and Aggarwal, B. B., *Mol. Cancer Res.*, **4**, 621-633 (2006).
- 14) Jeong, Y.H., Hur, H.J., Jeon, E.J., Park, S.J., Hwang, J.T., Lee, A.S., Lee, K.W., and Sung, M.J., *Molecules*, **23**, E194 (2018).
- 15) Yang, L., Wang, Z., Lei, H., Chen, R., Wang, X., Peng, Y., and Dai, J., *Tetrahedron*, **70**, 8244-8251 (2014).
- 16) Chilampalli, S., Zhang, X., Fahmy, H., Kaushik, R.S., Zeman, D., Hildreth,

- M.B., and Dwivedi, C., *Anticancer Res*, **30**, 777-783 (2010).
- 17) Leeman-Neill, R. J., Cai, Q., Joyce, S. C., Thomas, S. M., Bhola, N. E., Neill, D. B., and Grandis, J. R., *Clinical Cancer Res.*, **16**, 2571-2579 (2010).
- 18) Rempel, V., Fuchs, A., Hinz, S., Karcz, T., Lehr, M., Koetter, U., and Müller, C. E., *ACS Med. Chem. Lett.*, **4**, 41-45 (2013).
- 19) Yeh, P. S., Wang, W., Chang, Y. A., Lin, C. J., Wang, J. J., and Chen, R. M., *Cancer Lett.*, **370**, 66-77 (2016).
- 20) Kim, S., Ka, S.-O, Lee, Y., Park, B.-H., Fei, X.; Jung, J.-K., Seo, S.-Y., Bae, E. J. *PLoS One*, **10**, e0117120 (2015).
- 21) Yuan, Y., Subedi, L., Lim, D., Jung, J. K., Kim, S. Y., and Seo, S. Y., *Bioorg. Med. Chem. Lett.*, **29**, 329-333 (2019).
- 22) Scheepstra, M., Nieto, L., Hirsch, A.K., Fuchs, S., Leysen, S., Lam, C.V., *Angew. Chem. Int. Ed.*, **53**, 6443-6448 (2014).
- 23) For the ¹H- and ¹³C-NMR data of **1a** and **1b**, Fukuyama, Y., Otoshi, Y., Miyoshi, K., Nakamura, K., Kodama, M., Nagasawa, M., Hasegawa, T., Okazaki, H., and Sugawara, M., *Tetrahedron*, **48**, 377-392 (1992).
- 24) For the ¹H- and ¹³C-NMR data of **1c**, see Schühly, W., Hüfner, A.; Pferschy-Wenzig, E. M., Prettnner, E., Adams, M., Bodensieck, A., Kunert, O., Oluwemimo, A., Haslinger, E., Bauer, R., *Bioorg. Med. Chem.*, **17**, 4459-4465 (2009).
- 25) Smith, E, Collins, I., *Future Med. Chem.*, **7**, 159-183 (2015).
- 26) Lee, B., Sun, W., Lee, H., Basavarajappa, H., Sulaiman, R. S., Sishtla, K., and Seo, S.-Y., *Bioorg. Med. Chem. Lett.*, **26**, 4277-4281 (2016).