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RESEARCH ARTICLE

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Allylphenols as a new class of human 15-lipoxygenase-1 inhibitors

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Abstract

In this study, a series of mono- and diallylphenol derivative were designed, synthesized, and evaluated as potential human 15-lipoxygenase-1 (15-hLOX-1) inhibitors. Radical scavenging potency of the synthetic allylphenol derivatives was assessed and the results were in accordance with lipoxygenase (LOX) inhibition potency. It was found that the electronic natures of allyl moiety and *para* substituents play the main role in radical scavenging activity and subsequently LOX inhibition potency of the synthetic inhibitors. Among the synthetic compounds, 2,6-diallyl-4-(hexyloxy)phenol (**42**) and 2,6-diallyl-4-aminophenol (**47**) showed the best results for LOX inhibition (IC_{50} = 0.88 and 0.80 μM, respectively).

KEYWORDS

15-hLOX-1, allylphenol, Claisen rearrangement, DPPH, MBTH

1 | INTRODUCTION

Catalyzed peroxidation of unsaturated lipid in animals and plants is intimately linked to the activity of 15-lipoxygenase (LOX) enzymes. The activity of LOX enzymes causes a variety of diseases such as inflammation, sensitivities, skin disorder, and some cancers in mammals.

There are two enzymatic pathways for stereospecific peroxidation of polyunsaturated fatty acids such as linoleic acid (LA) and arachidonic acid (AA): cyclooxygenase and LOX pathway (Butovich & Lukyanova, 2008). The LOX enzymes are a family of iron-containing proteins in animals and plants that play a key role in catalyzing AA conversion to hydroperoxyeicosatetraenoic acids, hydroxyeicosatetraenoic acids, and particularly leukotrienes, potent mediators of hypersensitivity and inflammatory reactions (Pontiki & Hadjipavlou-Litina, 2008). Mammalian LOXs are commonly classified into six major groups according to insertion of molecular oxygen into AA: 5-LOX (arachidonate 5-LOX), 12-LOX (arachidonate 12-LOX; platelet LOX), 12/15-LOX or 15-LOX-1 (arachidonate 15-LOX-I; reticulocyte 15-LOX) and 15-LOX-2 (arachidonate 15-LOX-II), 12R-LOX (arachidonate 12R-LOX) and eLOX-3 (Epidermis-type LOX) (Butovich & Lukyanova, 2008).

The immediate products of fatty acid oxidation by LOX have been shown to be associated with acute and chronic diseases such as stroke, myocardial infarction, asthma, cancer, inflammation and many other diseases and pathological states. Due to the importance of LOX as therapeutic target, there is currently much interest for the discovery and synthesis of novel and potent LOX inhibitors (Alavi, Sadeghian, Seyedi, Salimi, & Eshghi, 2018; Mousavian et al., 2020; Sadeghian, Seyedi, Saberi, Arghiania, & Riazi, 2008).

Three main categories have been classified for inhibition of the LOX activity. They are: (a) redox inhibitors, which inhibit the formation of radical or trap it in redox cycle of hydroperoxidation, (b) iron-ligand inhibitors, which are excellent ligands to forming complex whit the iron core of the enzyme active site, (c) nonredox competitive inhibitors, which compete with AA for occupying the active site (Pontiki & Hadjipavlou-Litina, 2008).

At the recent decade, several quantitative structure activity relationship studies concerning LOX inhibitors base on pyridazinone

analogues (Kim, Martin, Brooks, Dyer, & Carter, 1994), catechol derivatives (Naito et al., 1991), hydroxamic acids (Summers et al., 1990), saturated monohydric alcohols (Mitsuda, Yasumoto, & Yamamoto, 1967), ω-phenylalkylhydroxamic acids, ω-naphthylalkylhydroxamic acids, eicosatetraenoic acids, and 1H-benzimidazole-4-ols (Gupta & Gupta, 1990) have been done (Pontiki & Hadjipavlou-Litina, 2002; Pontiki & Hadjipavlou-Litina, 2003; Pontiki & Hadjipavlou-Litina, 2008). All of the mentioned researches showed that various parameters, such as hydrophobicity, molecular size and electronic properties, affected inhibitory potency of LOX inhibitors.

Eugenol (4-allyl-2-methoxyphenol) is a natural allyl phenol mainly extracted from clove, basil, cinnamon, and nutmeg. The mentioned compound is known as bactericidal (Devi, Nisham, Sakthivel, & Pandian, 2010), monoamine oxidase inhibitor (Kabuto, Tada, & Kohno, 2007), antioxidant, and anti-inflammatory agent (Baskaran, Periyasamy, & Venkatraman, 2010; Jirovetz et al., 2006; Ogata, Hoshi, Urano, & Endo, 2000). It is widely used as a flavoring agent in food and cosmetic products. LOX inhibitory activity of eugenol esters on soybean 15-LOX (SLO) was firstly reported by our research team in 2008. In the mentioned work, it was found that acylation of phenol hydroxyl mainly did not decrease the LOX inhibitory activity of eugenol and in some cases inhibitory potency significantly was increased. Finally, it was concluded that similarity between allyl benzenes moiety of the synthetic esters and 1,4-dien portion of LA was the key factor of the inhibitory activity (Sadeghian et al., 2008).

SLO inhibitory activity of some allyl aryl ethers such as methyl eugenol was also reported (Sadeghian, Seyedi, Attaran, Jabbari, & Jafari, 2011). A few of them showed more activity compared to eugenol.

Herein, LOX inhibitory activity of some synthetic hydroxyallybenzenes (allylphenols) was studied. Considering antioxidant and radical scavenging property of phenols, substitution of allyl on benzenes ring could possibly increase the LOX inhibitory activity of these compounds. Based on the aforementioned theory a series of 4-hydroxyallylbenzens and 4-hydroxydiallylbenzens were synthesized (by considering the electronic property of the substituents) and then their LOX inhibitory activity were studied against human 15-LOX-1 (15-hLOX-1).

2 | RESULTS AND DISCUSSION

First, LOX inhibitory activity of eugenol (*para* substitution of OH toward allyl moiety) was measured in comparison with its isomer, 2-hydroxy-4-methoxyallylbenzene (**22**), with *ortho* substitution of OH toward allyl portion. In both of them, there is mesomeric effect (electron donation) between OH and allyl group. It was interesting that LOX inhibitory potency of eugenol was eightfold less than its isomer while radical scavenging activity of it was twofold lower. So it was decided to develop new derivatives of **22** by considering the electron-donating-withdrawing nature of the substituents and finally observing the mentioned structural changes on their inhibitory potency.

The desired allyl and diallyl phenols were synthesized by Claisen rearrangement on the related allyoxyphenols. After preparation and full characterization of the monoallyl compounds, The LOX inhibitory potency was studied against 15-hLOX-1 using the modified oxidative coupling of 3-methyl-2-benzothiazolinone (MBTH) with 3-(dimethylamino) benzoic acid (DMAB), which was reported by Alavi et al. (Alavi et al., 2018). After investigating the enzyme inhibition results of the monoallyl compounds, the best inhibitors were selected for converting to diallyl analogs.

15-hLOX-1 was prepared from isolated human eosinophil based on the procedure reported by Jabbari et al. (Jabbari, Mousavian, Seyedi, Bakavoli, & Sadeghian, 2017).

Among para-substituted phenols, which ones have no commercially accessible starting materials, were synthesized according to previous literatures (Figure 1) (Vyas & Shah, 1951).

The allylation procedure for synthesis of mono and diallylphenols was carried out according to the procedure reported by Claisen (Claisen, 1912). For this purpose, compounds **10–18** as starting materials were prepared by coupling the hydroquinone with the related alkyl bromide and subsequently allylbromide. Finally, the products were heated at 180°C (Claisen rearrangement) to forming of monoallyl compounds (**19–27**) (Figure 1) (Sanford, Lis, & McPherson, 2009). Finally, the obtained products were evaluated for both15-hLOX-1 inhibition and radical scavenging.

Evaluation of LOX inhibitory activities of monoallyl phenols was firstly carried out. Among the mentioned monoallyl compounds, 2-allyl-4-methoxyphenol (compound **22**) was the most potent LOX inhibitor by IC_{50} value of 3.7 μM. Replacing the 4-methoxy group by the other electron-donating and electron-withdrawing groups such as hydrogen (**19**), chloro (**20**), methyl (**21**), aldehyde (**26**), and NO_2 (**27**) lead to decrease in LOX inhibition activities (Table 1).

The Lineweaver–Burk plot showed that 2-allyl-4-methoxyphenol (compound **22**) inhibited LOX activity by noncompetitive mechanism (Figure 2).

Due to good LOX inhibition result of **22**, compounds **23** (O-pentyl), **24** (O-hexyl), and **25** (O-heptyl) were synthesized to considering the effect of the chain length of 4-alkoxy moiety on LOX inhibitory potency.

Evaluation of enzymatic inhibitory results showed that increasing of the alkoxy chain length from methyl to hexyl leads to more than two folds increase of inhibition activity: IC_{50} (**22**) = 3.7 μM versus IC_{50} (**24**) = 1.4 μM.

Radical scavenging activities of the monoallylphenol compounds were comparatively tested using DPPH bleaching method. It is worth noting that the results of radical scavenging activity of monoallylphenols were nearly consistent with LOX inhibition potency (Table 1).

Conformity between IC_{50} variations and DPPH bleaching indicates that the electronic property is the major factor for the LOX inhibition potency of the aforementioned allylphenol compounds (Table 1).

It seems that the electronic nature of both **X** (substituted group at the *para* position of phenol ring) and the allyl moiety has an effective role on LOX inhibition and radical scavenging potency.

In order to clarify the effective role of the allyl moiety on LOX inhibition activity, some derivatives without allyl group were synthesized and both LOX inhibition and DPPH bleaching activities of them were evaluated (Table 1, entry **2–5**). The results showed that elimination of the allyl side chain lead to missing of LOX inhibition.

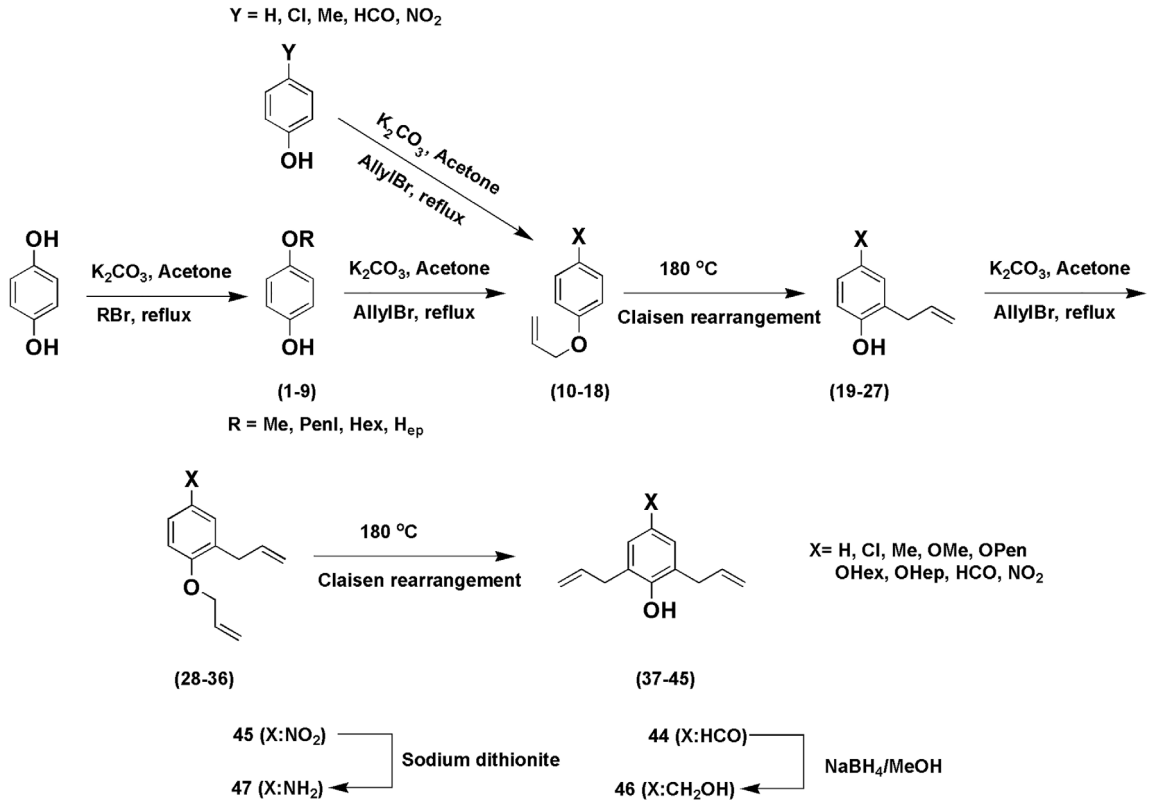
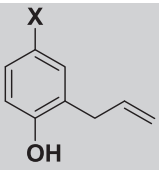
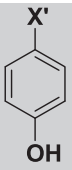


FIGURE 1 General procedure for the synthesis of mono and diallyl phenols

TABLE 1 Lipoxygenase inhibition and DPPH bleaching potencies of the synthetic monoallyl compounds in comparison with 4-methyl-2-(4 methylpiperazinyl)pyrimido[4, 5-b]benzothiazine (4-MMPB)

Compd.	X	IC_{50} (μM) LOX inhibition	IC_{50} (μM) (DPPH bleaching)	Compd.	X'	IC_{50} (μM) LOX inhibition	IC_{50} (μM) (DPPH bleaching)
19	H	>1,000	301.3 ± 15.5	2	Me	>1,000	169 ± 10.4
20	Cl	>1,000	>1,000	3	Cl	>1,000	>1,000
21	Me	>1,000	>1,000	4	OMe	>1,000	29.7 ± 2.9
22	OMe	3.7 ± 0.2	42.9 ± 6.3	5	OPen	>1,000	10.5 ± 1.1
23	OPen	1.8 ± 0.1	33.2 ± 3.1	4-MMPB	-	18 ± 0.1	-
24	OHex	1.4 ± 0.2	31.5 ± 2.5	NDGA	-	-	5.1 ± 1.2
25	OHep	1.9 ± 0.2	17.4 ± 1.9	Eugenol	-	32.4 ± 2.3	95.5 ± 4.1
26	CO	55.9 ± 3.8	356.2 ± 15.7				
27	NO_2	27.9 ± 0.4	401.2 ± 18.4				

Note: Data are shown as ±*SD*.

The previous results indicated that the electronic nature of the substituents at position 4 of the phenol ring significantly affects LOX inhibition potency. After confirming the effective role of the allyl moiety, to reach more potent allyl phenols inhibitors, diallyl derivatives were designed and synthesized.

Structure modification from mono allyl to diallyl led to significant increase in LOX inhibition potency compared to the corresponding compounds of **19–21** (more than500 folds decrease in IC_{50}). It was interesting that no significant changes observed for diallyl derivatives of **22–27**:**40–45** (less than two folds decrease in IC_{50}). The results are shown in Table 2.

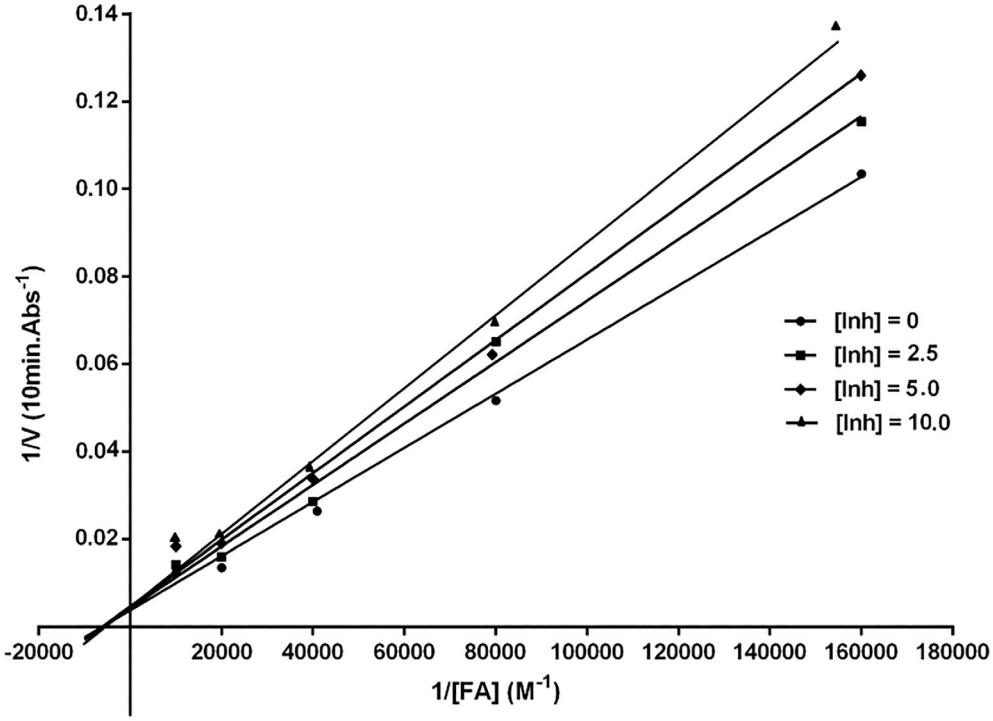
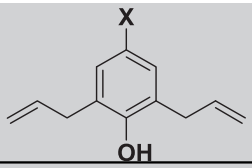


FIGURE 2 Lineweaver–Burk plots of 15-hLOX-1 inhibition by compound 22

TABLE 2 Lipoxygenase inhibition and DPPH bleaching potencies of the synthetic diallyl compounds in comparison with 4-methyl-2-(4 methylpiperazinyl)pyrimido[4, 5-b]benzothiazine (4-MMPB)



Compd.	X	IC_{50} (μM) LOX inhibition	IC_{50} (μM) (DPPH bleaching)	Compd.	X	IC_{50} (μM) LOX inhibition	IC_{50} (μM) (DPPH bleaching)
37	H	2.17 ± 0.12	108.1 ± 6.1	46	CH_2OH	3.00 ± 0.22	74.5 ± 6.8
38	Cl	1.46 ± 0.10	37.0 ± 2.6	47	NH_2	0.80 ± 0.04	27.6 ± 2.4
39	Me	1.35 ± 0.15	37.1 ± 3.1	4-MMPB	-	18 ± 0.1	-
40	OMe	1.30 ± 0.10	16.4 ± 1.3				
41	OPen	1.21 ± 0.02	16.1 ± 1.1				
42	OHex	0.88 ± 0.02	14.1 ± 1.0				
43	OHep	1.20 ± 0.11	15.0 ± 0.9				
44	CO	49.26 ± 3.80	356.2 ± 15.7				
45	NO_2	10.98 ± 0.04	385.2 ± 18.4				

Note: Data are shown as ±*SD*.

Among the diallyl derivatives, compound **42** (X: OHex) showed the best inhibitory activity by IC_{50} value of 0.88 μM, after that compounds **43**, **41**, and **40** were in the next rank. It is interesting that the same variation was seen for radical scavenging activity.

Compounds **40–43** were synthesized according to the former synthetic procedure of 2-allyl-4-substituted phenol derivatives (**19–27**) via furthermore allylation and Claisen rearrangement. In comparison with **40** (IC_{50} = 1.30 μM), increase of the alkoxy chain length showed no significant variations in LOX inhibition.

3,5-diallyl-4-hydroxybenzaldehyde (**44**) and 2,6-diallyl-4-nitrophenol (**45**) in comparison with the other diallyl phenols showed lower LOX inhibition and radical scavenging activities. So, it was decided to change the electron-withdrawing groups (aldehyde and nitro) to electro-donating substituents via synthesis of the related alcohol (**46**) and amine (**47**). So 2,6-diallyl-4-(hydroxymethyl)phenol (**46**) and 2,6-diallyl-4-aminophenol (**47**) were synthesized via reduction procedures(Figure 1) (Redemann & Redemann, 1949).As shown in Table 2 2,6-diallyl-4-aminophenol (**47**) showed more potent LOX inhibition (IC_{50} = 0.80 μM) than **46** (IC_{50} = 3.0 μM).

3 | CONCLUSIONS

In summary, we have synthesized and introduced a new series of mono and diallyl phenols as LOX inhibitors. Radical scavenging potency of the synthetic diallyl phenols was assessed and the result showed the important role of the allyl moieties and *para* substitutions in LOX inhibition potency. DPPH bleaching assessments indicate that the electronic property of the substituents is the major factor in LOX inhibition variations. Among the synthetic compounds, 2,6-diallyl-4-alkoxyphenols and 2,6-diallyl-4-aminophenol showed the best result for LOX inhibition. As the synthesized allyl phenols inhibit the LOX activity by noncompetitive redox mechanism and also by considering the main role of their electronic properties in enzyme inhibition, doing docking analyses is not advantage.

4 | EXPERIMENTAL

4.1 | Instruments

1H NMR (300 MHz) spectra were obtained by using a Bruker Avance DRX-300 Fourier transformer spectrometer. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. The melting points were recorded on an electrothermal type 9,100 melting point apparatus. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was obtained on a Thermo Finnigan Flash EA microanalyzer. All measurements of DPPH bleaching and LOX activities were carried out using Spekol 1,500 spectrophotometer and BioTek ELX800 plate reader. The 2-Hydroxy-3-methoxybenzaldehyde, 2-Hydroxy-4-methoxybenzaldehyde and 2-Hydroxy-6-methoxybenzaldehyde were obtained from Alfa Aesar and other chemicals were purchased from Sigma, Aldrich, and Merck Co.

4.2 | Enzyme preparation

Enzyme preparation was done according to the pervious method which had been reported by Jabbari et al. (Jabbari et al., 2017).

4.3 | LOX inhibitory assessment

LA and two assay solutions (A and B) were prepared in advance. Solution A was 50 mM DMAB in an l00 mM phosphate buffer (pH 7.0).

Solution B was a mixture of l0 mM MBTH (3 ml), hemoglobin (5 mg/ml, 3 ml) in 50 mM phosphate buffer at pH 5.0 (25 ml). An LA solution was prepared by mixing 5.6 mg of LA (Sigma Aldrich, L1376) with 0.5 ml methanol and then diluted with KOH 100 mM to a final volume of 5 ml (4 mM).

In the standard assay, the sample in DMSO (12.5 μL), 15-LOX-1 (90–115 units/ml; 30 μL), and phosphate buffer, and pH 7.0 (50 mM; 435 μL) were mixed in 48-well plates, and preincubation was carried out for 10 min at 30°C. A control test was performed with the same volume of ethanol. After the preincubation, LA solution (25 μL) was added to start the peroxidation reaction at 30°C, and, 10 min later, solution A (135 μL) and then solution B (65 μL) were added to start the color formation. Furthermore, 3 min later, 100 μL of a 2% SDS solution was added to terminate the reaction. The absorbance at 598 nm was compared with the control test. These experiments were performed in triplicate. The data analysis was performed using graphpad prism 5.01.

4.4 | Determination of DPPH bleaching

DPPH solution of 25 μM in absolute ethanol was prepared. This solution was added to an equal volume of the solution of the test compounds (dissolved in ethanol) to obtain a desired concentration. Ethanol was used as control solution. After 30 min at room temperature, the absorbance was recorded at 517 nm and compared to NDGA (nordihydroguaiaretic acid).

4.5 | General procedure for preparation of *p*-alkyloxyphenol (5–7)

A mixture of hydroquinone (10.0 g, 90.82 mmol) and desired alkyl bromide (40 mmol), anhydrous potassium carbonate (40 mmol), and dried acetone (40 ml) was heated under reflux for 6 hr and then cooled. The mixture was diluted with 100 ml water and 1 M NaOH (50 ml) was added and extracted with EtOAc for removing the 1,4-dialkoxybenzene. Acidified the solution by 1 M HCl and extracted by EtOAc.

Then the organic phase was washed with water (3*100) and dried over sodium sulfate. After evaporating the organic layer, the alkyl substituted products obtained as white powder (Vyas & Shah, 1951).

4.6 | General procedure for preparation of 10–18

A mixture of p-substituted phenol (0.1 mol), ally1 bromide (0.15 mol), and anhydrous potassium carbonate (0.1 mol) in 50 ml of dry acetone was heated under reflux condition for 8 hr. After cooling, the mixture was diluted with 200 ml water and the organic phase was separated. Then the organic phase was washed with 1 M NaOH (2*50 ml) and dried over potassium carbonate. The mixture was filtered yielding to colorless to pale yellow oil (Hong, Lee, Tsai, & Liao, 1998; Kürti & Czakó, 2005).

4.7 | General procedure for preparation of 19–27*via* the Claisen rearrangement

The corresponding allyloxyl compounds **10–18** were heated to 180°C for 2 hr to undergo Claisen reaction as the known procedure (Wang,

Hsu, Lin, & Huang, 2002) to give **19–27**. The reaction mixture was cooled, dissolved in hexane (50 ml), and extracted with sodium hydroxide solution (3*25 ml). The combined aqueous solutions were acidified with concentrated hydrochloric acid and extracted with methyl *tert*-butyl ether (50 ml). The combined organic layers were dried over sodium sulfate and filtered. After evaporating the ether, the product was obtained as oil (White, Donald, Schmitt, Girard, & Fife, 1958).

4.8 | General procedure for the preparation of 28–36

In a similar manner as described for **10–18**, To a solution of **19–27** (50 mmol) in acetone (30 ml), dry powdered potassium carbonate (9.1 g, 66 mmol) and allyl bromide (5.4 ml, 62 mmol) were added, and the mixture was stirred under reflux for 8 hr. After cooling, the mixture was diluted with 200 ml water and the organic phase was separated. The organic phase was washed with 1 M NaOH (2*50 ml) and dried over potassium carbonate. After filtering, the product obtained as oil and it was employed for the next step without further purification (Yashiro, Hanaya, Shoji, & Sugai, 2015).

4.9 | General procedure for preparation of 37–45*via* the Claisen rearrangement of 28–36

In a similar manner as described for **19–27**, the 2-allyl-*p*-substituted phenol **28–36** was heated to 180°C for 2 hr. The red-brownish reaction mixture was cooled, dissolved in hexane (50 ml), and extracted with sodium hydroxide solution (3*25 ml). The combined aqueous solutions were acidified with hydrochloric acid (36%) and extracted with methyl *tert*-butyl ether (50 ml). The combined organic layers were dried over sodium sulfate and filtered. After evaporating the organic layer, the crude product was purified by chromatography on silica gel (ethyl acetate: hexane 1:8) to obtain the pure product.

4.10 | General procedure for preparation of 2,6-diallyl-4-(hydroxymethyl)phenol (46)

2,6-diallyl-4-(hydroxymethyl)phenol was prepared by reduction of **44** with sodium borohydride as previously reported (Yang et al., 2016). A solution of **44** (40 mmol) in cooled methanol (50 ml) was treated with sodium borohydride (2.3 g, 60 mmol) at 0°C during 2 hr. The solvent was removed under reduced pressure and the residue was poured into water (50 ml), and extracted with EtOAc. The organic layer was dried by anhydrous sodium sulfate, filtered, and the solvent removed under reduced pressure to afford the crude product.

The crude product was purified by chromatography (ethyl acetate: hexane 1:8) affording the pure product as yellowish oil **46.**

4.11 | General procedure for preparation of 2,6-diallyl-4-aminophenol (47)

A mixture of **45** (5.5 mmol) and 2.1 g (12 mmol) of sodium dithionite ($Na_2S_2O_4$) in 15 ml of deionized water and 4 ml of ammonium hydroxide was heated to 50°C for 1 hr. After cooling, the precipitated solid was filtered, washed with water, and crystallized from normal hexane to afford compound **47** as pure yellowish crystals (Redemann & Redemann, 1949).

4.12 | 2-allyl-4-(pentyloxy)phenol (23)

Yellow powder (mp: 53–55°C),^{1}H NMR (301 MHz, Chloroform-*d*) δ 6.75 (d, 1H), 6.74 (s, 1H), 6.60 (s, 1H), 6.05–5.84 (m, 1H), 5.09 (m, 1H), 5.06–5.01 (m, 1H), 4.68 (s, 1H), 3.85–3.80 (t, *J* = 6.8 Hz, 2H), 3.29 (d, *J* = 6.3 Hz, 2H), 1.67 (m, 2H), 1.41–1.24 (m, 4H), 0.85 (t, *J* = 7.0 Hz, 3H);^{13}C NMR (76 MHz, Chloroform-*d*) δ 153.18, 147.87, 136.26, 126.46, 116.69, 116.42, 115.40, 113.28, 68.67, 35.32, 29.12, 28.25, 22.53, 14.08. MS (EI, 70 eV): m/z = 220 [M^+]; Anal. calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.40; H, 9.10.

4.13 | 2-allyl-4-(hexyloxy)phenol (24)

Yellow powder (mp: 70–72°C), ^{1}H NMR (301 MHz, Chloroform-*d*) δ 6.76 (d, 1H), 6.74 (s, 1H), 6.66 (s, 1H), 5.88 (m, 1H), 5.09 (m, 1H), 5.07–5.03 (m, 1H), 4.63 (s, 1H), 3.82 (t, *J* = 6.3 Hz, 2H), 3.29 (d, *J* = 6.3 Hz, 2H), 1.73–1.62 (m, 2H), 1.38 (m, 2H), 1.25 (m, 4H), 0.83 (t, *J* = 6.2 Hz 3H);^{13}C NMR (76 MHz, Chloroform-*d*) δ 153.19, 147.86, 136.25, 126.42, 117.51, 115.68, 115.39, 113.29, 68.67, 35.34, 31.65, 29.39, 25.78, 22.65, 14.09. MS (EI, 70 eV): m/z = 234 [M^+]; Anal. calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.85; H, 9.45.

4.14 | 2-allyl-4-(heptyloxy)phenol (25)

White powder (mp: 83–85°C), ^{1}H NMR (301 MHz, Chloroform-*d*) δ 6.65 (d, *J* = 8.2 Hz, 1H), 6.61 (s, 1H), 6.57 (d, J = 6.2 Hz, 1H), 6.01–5.84 (m, 1H), 5.13–5.02 (m, 2H), 4.66 (s, 1H), 3.81 (t, *J* = 6.6 Hz, 2H), 3.29 (d, *J* = 6.3 Hz, 2H), 1.67 (p, *J* = 6.5 Hz, 2H), 1.34 (m, 2H), 1.23 (m, 6H), 0.81 (m, *J* = 6.8, 3H); ^{13}C NMR (76 MHz, Chloroform-*d*) δ 153.30, 147.85, 136.24, 126.42, 116.71, 116.45, 115.41, 113.31, 68.62, 35.35, 31.83, 29.44, 29.13, 26.06, 22.66, 14.15. MS (EI, 70 eV): m/z = 248 [M^+]; Anal. calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.40; H, 9.75.

4.15 | 2-allyl-4-nitrophenol (27)

Slightly yellow powder (mp: 79–80°C), 1H NMR (301 MHz, Chloroform-*d*) δ 7.99 (s, 1H), 7.98 (d, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 9.1 Hz, 1H), 6.29 (s, 1H), 5.93 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.19–5.06 (m, 2H), 3.39 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (76 MHz, Chloroform-*d*) δ 160.06, 141.35,

134.65, 126.86, 126.40, 124.33, 117.89, 115.81, 34.47. MS (EI, 70 eV): m/z = 179 [M^+]; Anal. calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N. 7.82. Found: C, 60.12; H, 5.00; N. 7.78.

4.16 | 2,6-diallylphenol (37)

Colorless oil, ^{1}H NMR (301 MHz, Chloroform-*d*) δ 7.10 (d, *J* = 7.5 Hz, 2H), 6.93 (t, *J* = 6.5 Hz, 1H), 6.18–6.04 (m, 2H), 5.27–5.24 (m, 2H), 5.26 (s, 1H), 5.21 (t, *J* = 1.5 Hz, 2H), 3.50 (d, *J* = 6.4 Hz, 4H); ^{13}C NMR (76 MHz, Chloroform-*d*) δ 152.70, 136.67, 128.78, 125.72, 120.72, 116.44, 35.35. MS (EI, 70 eV): m/z = 174 [M^+]; Anal. calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.72; H, 8.09.

4.17 | 2,6-diallyl-4-chlorophenol (38)

Yellowish oil,^{1}H NMR (301 MHz, Chloroform-*d*) δ 6.90 (s, 2H), 5.99–5.79 (m, 2H), 5.11–5.09 (m, 2H), 5.07–5.04 (m, 2H), 5.03 (s, 1H), 3.27 (d, *J* = 6.4 Hz, 4H); ^{13}C NMR (76 MHz, Chloroform-*d*) δ 151.22, 135.73, 128.28, 127.42, 117.08, 116.26, 35.05. MS (EI, 70 eV): m/z = 208 [M^+]; Anal. calcd for $C_{12}H_{13}ClO$: C, 69.07; H, 6.28. Found: C, 69.10; H, 6.27.

4.18 | 2,6-diallyl-4-methylphenol (39)

Yellow oil, ^{1}H NMR (301 MHz, Chloroform-*d*) δ 6.73 (s, 2H), 5.92 (ddt, *J* = 16.7, 10.2, 6.4 Hz, 2H), 5.11–5.05 (dq, *J* = 8.2, 1.6 Hz, 1H), 5.03 (m, 2H), 4.92 (s, 1H), 3.28 (d, *J* = 6.4 Hz, 4H), 2.16 (s, 3H); ^{13}C NMR (76 MHz, Chloroform-*d*) δ 150.38, 136.81, 129.83, 129.27, 125.52, 116.31, 35.38, 20.57. MS (EI, 70 eV): m/z = 189 [M^+]; Anal. calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 83.05; H, 8.74.

4.19 | 2,6-diallyl-4-methoxyphenol (40)

Yellow oil, 1H NMR (301 MHz, Chloroform-*d*) δ 6.51 (s, 2H), 6.03–5.85 (m, 2H), 5.10 (m, 2H), 5.07–5.03 (m, 2H), 4.70 (s, 1H), 3.68 (s, 3H), 3.31 (d, *J* = 6.4 Hz, 4H); ^{13}C NMR (76 MHz, Chloroform-*d*) δ 153.39, 146.43, 136.41, 126.84, 116.47, 113.81, 55.65, 35.52. MS (EI, 70 eV): m/z = 204 [M^+]; Anal. calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 77.01; H, 7.96.

4.20 | 2,6-diallyl-4-(hexyloxy)phenol (42)

Yellow oil, ^{1}H NMR (301 MHz, Chloroform-*d*) δ 6.50 (s, 2H), 5.91 (m, 2H), 5.08 (dq, *J* = 4.5, 1.5 Hz, 1H), 5.04 (t, *J* = 1.5 Hz, 2H), 4.70 (s, 1H), 3.80 (t, *J* = 6.6 Hz, 2H), 3.29 (d, *J* = 6.4 Hz, 4H), 1.74–1.60 (m, 2H), 1.43–1.30 (m, 2H), 1.24 (m, 4H), 0.82 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (76 MHz, Chloroform-*d*) δ 153.29, 147.86, 136.25, 126.41, 116.68, 113.28, 68.59, 35.33, 31.65, 29.40, 25.77, 22.65, 14.09. MS (EI, 70 eV): m/z = 274 [M^+]; Anal. calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.54; H, 9.45.

4.21 | 2,6-diallyl-4-(heptyloxy)phenol (43)

Yellow oil, ^{1}H NMR (301 MHz, Chloroform-*d*) δ 6.50 (s, 2H), 6.07–5.84 (m, 2H), 5.15–5.02 (m, 4H), 4.67 (s, 1H), 3.80 (t, *J* = 6.6 Hz, 2H), 3.30 (d, *J* = 6.4 Hz, 4H), 1.70–1.62 (m, 2H), 1.43–1.17 (m, 8H), 0.82 (t,, *J* = 6.6 Hz, 3H); ^{13}C NMR (76 MHz, Chloroform-*d*) δ 152.96, 146.29, 136.47, 126.76, 116.41, 114.52, 68.45, 35.52, 31.83, 29.47, 29.13, 26.07, 22.65, 14.14. MS (EI, 70 eV): m/z = 288 [M^+]; Anal. calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.69; H, 9.12.

4.22 | 3,5-diallyl-4-hydroxybenzaldehyde (44)

Yellow powder (mp: 53–55°C),^{1}H NMR (301 MHz, Chloroform-*d*) δ 9.76 (s, 1H), 7.51 (s, 2H), 6.03–5.91 (m, 2H), 5.90 (s, 1H), 5.15 (m, 2H), 5.11 (dq, *J* = 7.9, 1.4 Hz, 1H), 3.40 (d, *J* = 6.4 Hz, 4H); ^{13}C NMR (76 MHz, Chloroform-*d*) δ 191.29, 158.40, 135.50, 130.97, 129.70, 126.33, 117.42, 34.98. MS (EI, 70 eV): m/z = 202 [M^+]; Anal. calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.16; H, 7.08.

4.23 | 2,6-diallyl-4-nitrophenol (45)

Yellow oil, ^{1}H NMR (301 MHz, Chloroform-*d*) δ 7.68 (s, 2H), 7.09 (s, 1H), 5.93 (m, 2H), 5.89–5.69 (m, 4H), 3.49 (d, *J* = 6.4 Hz, 4H).^{13}C NMR (76 MHz, Chloroform-*d*) δ 161.06, 151.35, 136.65, 126.86, 117.98, 115.91, 33.47. MS (EI, 70 eV): m/z = 219 [M^+]; Anal. calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.80; H, 6.00; N, 6.40.

4.24 | 2,6-diallyl-4-(hydroxymethyl)phenol (46)

Yellowishoil,^{1}H NMR (301 MHz, Chloroform-*d*) δ 6.93 (s, 2H), 6.74 (s, 1H), 5.93 (m, 2H), 5.15–4.95 (m, 4H), 4.48 (s, 2H), 3.33 (d, *J* = 6.1 Hz, 4H), 2.00 (s, 1H)^{13}C NMR (76 MHz, Chloroform-*d*) δ 150.88, 136.74, 129.06, 125.58, 116.29, 111.52, 68.85, 35.37. MS (EI, 70 eV): m/z = 204 [M^+]; Anal. calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 77.01; H, 8.08.

4.25 | 2,6-diallyl-4-aminophenol (47)

Yellow crystals (mp: 77–78°C),^{1}H NMR (301 MHz, Chloroform-*d*) δ 6.43 (s, 2H), 6.02 (ddt, *J* = 16.0, 10.9, 6.4 Hz, 2H), 5.18 (dq, *J* = 6.5, 1.7 Hz, 2H), 5.14 (m, 2H), 3.36 (b, 7H); ^{13}C NMR (76 MHz, Chloroform-*d*) δ 145.34, 139.65, 136.68, 126.98, 116.21, 115.75, 35.34. MS (EI, 70 eV): m/z = 189 [M^+]; Anal. calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.16; H, 7.99; N, 7.40.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon request.

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