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Structure–activity relationships of chalcone analogs as potential inhibitors of ADP- and collagen-induced platelet aggregation

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ABSTRACT

In an effort to develop potent antiplatelet agents, 12 *O*-prenylated (**2–13**) and 10 *O*-allylated (**14–23**) chalcones were synthesized and screened for in vitro inhibitory effects on aggregation of washed rabbit platelets induced by ADP (20 μM) and collagen (10 μg/mL). In addition, the platelet aggregation activity of previously synthesized Mannich bases of heterocyclic chalcones (MBHC) (**24–62**) was evaluated. The preliminary structure–activity relationships suggested that the antiplatelet activity was governed to a great extent by the presence of a pyridyl ring-B and a hydroxy group at position C-3′ in ring-A of the MBHC templates.

1. Introduction

Platelet aggregation plays a central role in thrombosis (clot formation). Platelet-mediated thrombus formation in the coronary artery is a primary factor in the development of thrombotic disorders, such as unstable angina, myocardial infarction, stroke[1,2] and peripheral vascular diseases.[3] Normally, the blood is not aggregated in the blood vessels, but when bleeding occurs, blood aggregation is generated as a physiological defense reaction. Platelet aggregation is also caused by physiological substances, such as thrombin and prostaglandin endoperoxide, and can lead to an arterial thrombosis.[4] Platelet aggregation is induced by the action of endogenous agonists, such as arachidonic acid (AA), adenosine diphosphate (ADP), platelet-activating factor (PAF), thrombin and collagen.[5] The inhibition of platelet function represents a promising approach for the treatment of thrombotic diseases. Many antiplatelet drugs have been used clinically, but have certain disadvantages such as notable side effects and inefficient therapy.[6,7] Therefore, pursuit of new antiplatelet drugs that are more effective and safer with fewer side effects is very important.

Chalcones, which are classified as polyphenolic compounds, are basically flavonoids and are ubiquitously present in plants, especially in fruits and vegetables.[8] The literature cited in relation to chalcones in recent years indicates that there is a growing interest in evaluating the pharmaceutically important biological activities of chalcones and their derivatives, presuming their role in the prevention of various degenerative diseases and other human ailments. Many pharmacological activities have been reported for these compounds: anticancer, anti-inflammatory, immunomodulatory, antibacterial, antioxidant and immunosuppressive, as well as antiprotozoan activity, including trypanocidal, leishmanicidal, and antimalarial.[9–17] Lin et al.[18] also reported that 2′,5′-dihydroxychalcones exhibited good selective inhibitory effects on AA-induced platelet aggregation. Therefore, in the present study, we synthesized a series of 4′-*O*-prenylated (**2–13**) and 4′-*O*-allylated chalcones (**14–23**) with various B-ring substituents, and screened the compounds for inhibitory effects on aggregation of washed rabbit platelets induced by ADP and collagen at concentrations of 20 μM and 10 μg/mL, respectively. Moreover, we also evaluated 39 previously synthesized[19] Mannich bases of heterocyclic chalcones (MBHC) (**24–62**) in these assays. Preliminary structure–activity relationship (SAR) correlations are also discussed.

2. Results and discussion

We evaluated **2–23** for inhibitory effects on ADP- and collagen-induced washed rabbit platelet aggregation (Table 1). Compound **20** showed potent inhibitory effects (70.4%) on ADP-induced aggregation, while **15**, **17**, **19** and **20** with 2,3-dimethoxy, 2,5-dimethoxy, 2,4-dimethoxy, and 3,4,5-trimethoxy benzene ring-B moieties, respectively, showed potent inhibition (44.7%, 57.2%,

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Table 1
Inhibitory percentages of **2–62** (50 μg/mL) on platelet aggregation induced by ADP (20 μM) and collagen (10 μg/mL).

Compound	ADP (n = 3)	Collagen (n = 3)	Compound	ADP (n = 3)	Collagen (n = 3)
2	21.4	12.6	33	32.3	0.0
3	23.0	13.4	34	100.0	96.1
4	15.7	4.0	35	97.2	29.2
5	42.7	39.2	36	36.7	7.1
6	16.4	6.3	37	26.4	11.1
7	21.3	19.7	38	17.2	19.7
8	22.8	14.9	39	23.4	0.0
9	20.7	8.7	40	99.3	63.5
10	20.0	17.3	41	100.0	56.4
11	25.7	17.3	42	100.0	79.4
12	24.3	10.3	43	34.2	20.3
13	27.1	7.9	44	18.4	4.7
14	26.4	14.9	45	23.4	25.0
15	30.8	44.7	46	21.4	12.5
16	21.4	7.9	47	12.8	0.0
17	33.6	57.2	48	100.0	78.6
18	24.9	5.5	49	24.9	50.0
19	35.2	53.4	50	100.0	98.4
20	70.4	43.2	51	100.0	95.3
21	21.6	0.0	52	100.0	100.0
22	30.8	13.4	53	100.0	60.8
23	25.6	6.3	54	100.0	83.5
24	100.0	12.5	55	79.1	65.5
25	100.0	93.7	56	100.0	89.8
26	29.0	3.2	57	100.0	100.0
27	14.2	11.1	58	100.0	78.0
28	100.0	46.9	59	99.3	57.6
29	22.5	0.0	60	100.0	95.2
30	16.5	0.0	61	100.0	93.7
31	100.0	43.0	62	100.0	98.4
32	39.3	2.3	Clopidogrel (9.6 μg/mL)	85.2	3.5

The antiplatelet aggregation (%) was calculated by the following equation: Antiplatelet aggregation (%) = [1 − (platelet aggregation potency of sample/platelet aggregation potency of vehicle)] × 100%.

53.4% and 43.2%, respectively) on collagen-induced platelet aggregation, as compared with the reference compound clopidogrel (3.5% inhibition at 30 μM).

Thirty-nine previously synthesized MBHC analogs (**24–62**) (Scheme 3) were also evaluated on the platelet aggregation induced by ADP and collagen at concentrations of 20 μM and 10 μg/mL, respectively (Table 1).

Compound **24** was a potent inhibitor (100%) of ADP-induced platelet aggregation, but only a weak inhibitor (12.5%) of collagen-induced aggregation. However, when the C-4′ hydroxyl in **24** was replaced with a methoxy group as in **25**, the potency increased to 93.7% inhibition in the collagen-induced assay, and remained at 100% in the ADP-induced assay.

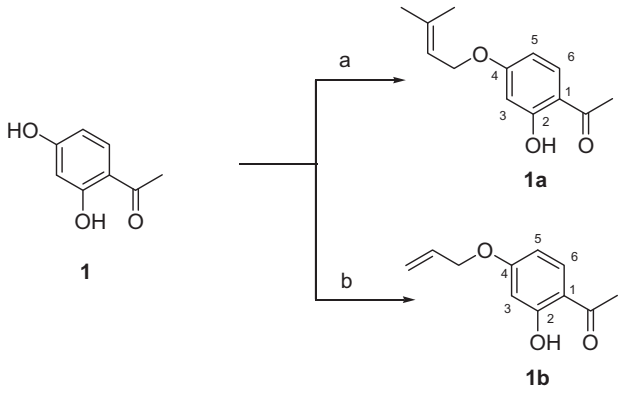
Compounds **28** and **31** with 3-pyridyl and 4-pyridyl ring-B moieties, respectively, showed potent inhibition (100%) of ADP-induced platelet aggregation and moderate inhibition (46.9% and 43%, respectively) of collagen-induced aggregation. When the pyridine ring-B was replaced with 2-furan (**29**), 5-methylfuran (**30**), phenyl (**32**) or 3-methyl-2-thiophene (**33**), the resulting compounds showed drastically decreased inhibitory effects on ADP induced platelet aggregation and no inhibition on collagen induced platelet aggregation. Compound **34**, which differs structurally from **28** only by having a methoxy rather than ethoxy group at position C-4′, potently inhibited both ADP- and collagen-induced platelet aggregations by 100% and 96.1%, respectively. Replacement of the 3-pyridyl moiety in **34** with a phenyl moiety in **35** resulted in essentially equipotent inhibition (97.2%) of ADP-induced platelet aggregation and weak inhibition of collagen-induced platelet aggregation. With the addition of a 4-methoxy group on the phenyl ring of **35**, the inhibitory effects decreased in both assays (see **36**, Table 1). In addition, analogs **37** and **38**, which have 2-thiophene and 2-furan ring-B moieties, respectively, exhibited no inhibition of either ADP- or collagen-induced platelet aggregation. These results clearly indicated that a heteroaromatic pyridine ring-B moiety was required for maximal inhibition of platelet aggregation with these compounds.

In compounds **40–42**, ring-A is substituted at C-3′ with a morpholine Mannich base and at C-4′ with a hydroxy group, while the B-ring is 2-pyridine, 3-pyridine and 4-pyridine, respectively. These three compounds exhibited significant inhibitory effects on ADP-induced platelet aggregation (99.3%, 100% and 100%) and moderate effects (63.5%, 56.4% and 79.4%) on collagen-induced platelet aggregation. Following the similar trend with compounds **28** versus **29**–**33** and **34** versus **35**–**38**, when the pyridine moieties of **40–42** were replaced with phenyl (**43**), furan (**44**), thiophene (**45**), 3-methyl-2-thiophene (**46**) or 5-methyl-2-furan (**47**), decreased inhibitory effects were observed on both ADP- and collagen-induced platelet aggregations.

Analogs **50**, **51** and **52** have hydroxy and morpholine Mannich base groups at positions C-3′ and C-4′, respectively, in ring-A, and thus, are positional isomers of **40**, **41** and **42**. Compounds **50**–**52** exhibited potent inhibitory effects on both ADP- (100%) and collagen- (95.3–100%) induced platelet aggregation. The latter inhibitory effects were greater than those of **40**–**42**. Compounds **48** and **57** are also positional isomers in ring-A, with the hydroxy group at C-4′ in the former and C-3′ in the latter compound. Compound **48** exhibited 100% inhibition of ADP- and 78.6% inhibition of collagen-induced platelet aggregation, while **57** exhibited 100% inhibition of both ADP- and collagen-induced aggregation. Based on these results, a hydroxy group at position C-3′ resulted in greater inhibition of platelet aggregation induced by collagen in this compound series (**50–52** and **57**). Compounds **53–56**, which have hydroxy and morpholine Mannich base groups at positions C-3′ and C-2′, respectively, were more potent inhibitors of both

ADP- and collagen-induced platelet aggregation than the positional isomers **44–46** and **43**, respectively, which have the hydroxy and morpholine Mannich base groups at positions C-4′ and C-3′.

Compounds **58–62**, which have 2-(*N*-morpholinylmethyl or *N*-piperidylmethyl)-3-hydroxy-4-methoxyphenyl B-ring groups, showed potent inhibition (100%) of ADP-induced platelet aggregation and moderate to potent inhibition (57.6–98.4%) of collagen-induced platelet aggregation.



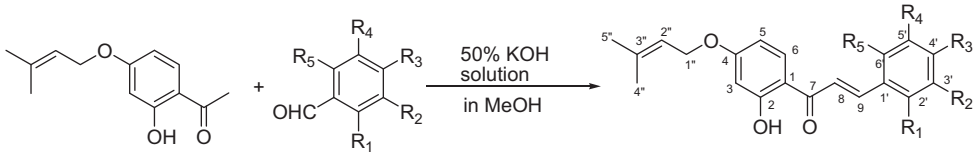
Scheme 1. Reagents and conditions: (a) K_2CO_3, Me_2CO, prenyl bromide, reflux at 80 °C, 8 h (b) K_2CO_3, Me_2CO, allyl bromide, reflux at 80 °C, 8 h

3. Conclusion

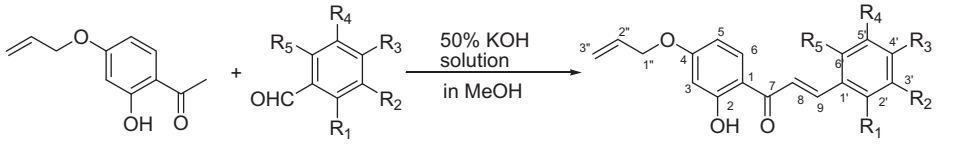
In conclusion, MBHC showed good inhibitory effects on both ADP- and collagen-induced platelet aggregations. Among the 61 compounds tested, 19 showed full inhibitory activity at 50 μg/mL in the ADP-induced model, while 9 compounds (**25**, **34**, **50**–**52**, **57**, **60**–**62**) showed >90% to full inhibitory activity in both models. The preliminary SAR suggested that, among compounds **2–62,** the antiplatelet activity was governed to a greater extent by a pyridyl group substituent as ring-B and hydroxy group at position C-3′ in ring-A of the MBHC templates. The SAR of the active compounds merits further investigation to find the optimal lead structure with maximum inhibitory activity. Because some MBHC were full inhibitors of platelet aggregation, additional potential evaluation should be carried out with lower concentrations of compounds, and the anti-platelet action mechanisms of potential leads also need further analysis.

4. Experimental section

Melting points were measured using a Buchi melting point apparatus B-540 and are uncorrected. IR spectra were determined on a Shimadzu FT-IR Prestige 21 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer, using tetramethylsilane (TMS) as internal standard; all chemical shifts were reported in parts per million (ppm, δ). EIMS and HRE-IMS spectra were obtained on a VG-70-250S mass spectrometer.



2. $R_1 = R_2 = R_3 = OMe$, $R_4 = R_5 = H$
3. $R_1 = R_4 = R_5 = H$, $R_2 = OH$, $R_3 = OMe$
4. $R_2 = R_5 = H$, $R_1 = R_3 = R_4 = OMe$
5. $R_2 = R_4 = R_5 = H$, $R_1 = R_3 = OMe$
6. $R_1 = R_2 = R_3 = R_4 = R_5 = H$
7. $R_3 = R_4 = R_5 = H$, $R_1 = R_2 = OMe$
8. $R_2 = R_3 = R_5 = H$, $R_1 = R_4 = OMe$
9. $R_1 = R_3 = R_5 = H$, $R_2 = R_4 = OMe$
10. $R_1 = R_4 = R_5 = H$, $R_2 = R_3 = OCH_2O$
11. $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = OMe$
12. $R_1 = R_4 = R_5 = H$, $R_2 = R_3 = OMe$
13. $R_1 = R_5 = H$, $R_2 = R_3 = R_4 = OMe$



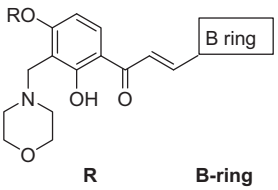
14. $R_1 = R_2 = R_3 = OMe$, $R_4 = R_5 = H$
15. $R_1 = R_2 = OMe$, $R_3 = R_4 = R_5 = H$
16. $R_1 = R_4 = R_5 = H$, $R_2 = R_3 = OCH_2O$
17. $R_2 = R_3 = R_5 = H$, $R_1 = R_4 = OMe$
18. $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = OMe$
19. $R_2 = R_4 = R_5 = H$, $R_1 = R_3 = OMe$
20. $R_1 = R_5 = H$, $R_2 = R_3 = R_4 = OMe$
21. $R_2 = R_5 = H$, $R_1 = R_3 = R_4 = OMe$
22. $R_1 = R_3 = R_5 = H$, $R_2 = R_4 = OMe$
23. $R_1 = R_2 = R_3 = R_4 = R_5 = H$

Scheme 2.

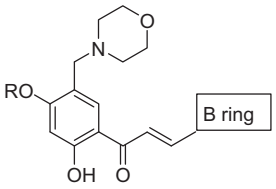
Elemental analyses were determined by Elementer Vario EL III and gave combustion values for C, H, N and S. Column chromatography was performed on silica gel (70–230 mesh, 230–400 mesh). TLC was conducted on precoated Kieselgel 60 F254 plates (Merck), and the spots were detected by examination under a UV lamp.

4.1. 1-(2-Hydroxy-4-(3-methylbut-2-enyloxy)phenyl)ethanone (1a)

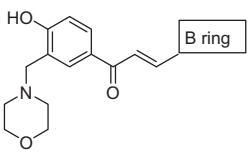
To a solution of 2,4-dihydroxyacetophenone (**1**, 15.2 g, 100 mmol) in dry acetone (100 mL) at room temperature was



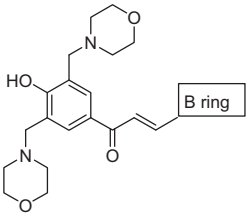
R	B-ring
24. H	2-pyridyl
25. Me	2-pyridyl
26. isopropyl	2-thiophene
27. prenyl	3-methyl-2-thiophene



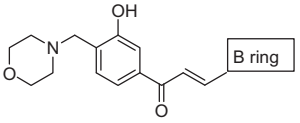
R	B-ring
28. ethyl	3-pyridyl
29. ethyl	2-furan
30. ethyl	5-methyl-2-furan
31. ethyl	2-pyridyl
32. ethyl	phenyl
33. ethyl	3-methyl-2-thiophene
34. methyl	3-pyridyl
35. methyl	phenyl
36. methyl	4-$CH_3OC_6H_4$
37. methyl	2-thiophene
38. methyl	2-furan
39. isopropyl	2-thiophene



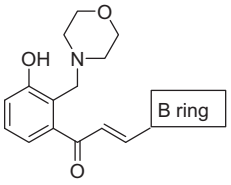
B-ring
40. 2-pyridyl
41. 3-pyridyl
42. 4-pyridyl
43. phenyl
44. 2-furan
45. 2-thiophene
46. 3-methyl-2-thiophene
47. 5-methyl-2-furan



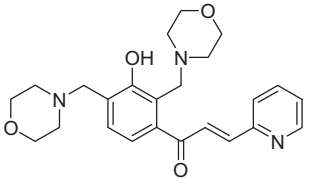
B-ring
48. 2-pyridyl
49. 3-methyl-2-thiophene



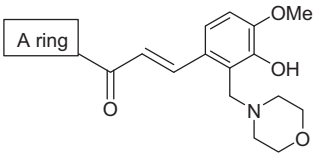
B-ring
50. 2-pyridyl
51. 3-pyridyl
52. 4-pyridyl



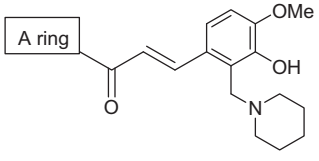
B-ring
53. 2-furan
54. 2-thiophene
55. 3-methyl-2-thiophene
56. phenyl



57.



A-ring
58. 3-Me-C_6H_4
59. 4-Me-C_6H_4



A-ring
60. 2-thiophene
61. 2-furan
62. 3-pyridyl

Scheme 3.

added freshly ignited K_2CO_3 (6.0 g), followed by prenyl bromide (11.8 mL, 100 mmol). The reaction mixture was refluxed for 8 h at 80 °C. The reaction progress was monitored by TLC. Upon reaction completion, the mixture was filtered, and the solvent evaporated under reduced pressure. The resulting crude product was purified by column chromatography over a silica gel column, eluting with 9:1 (hexane:EtOAc) to give 2-hydroxy-4-*O*-prenylacetophenone (**1a**) as a colorless solid (19.5 g) in 89% yield (Scheme 1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.74 (1H, s, 2-OH), 7.60 (1H d, J = 8.0 Hz, H-6), 6.44 (1H, dd, J = 8.0, 2.0 Hz, H-5), 6.40 (1H, d, J = 2.0, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.3, 165.2, 164.9, 138.7, 132.0, 118.5, 113.5, 107.8, 101.2, 64.9, 25.8, 25.5, 17.9.

4.2. 1-(4-(Allyloxy)-2-hydroxyphenyl)ethanone (1b)

To a solution of 2,4-dihydroxyacetophenone (**1**, 15.2 g, 100 mmol) in dry acetone (100 mL) was added freshly ignited K_2CO_3 (6.0 g), followed by allyl bromide (8.6 mL, 100 mmol). The reaction mixture was treated as described for the above procedure to yield 2-hydroxy-4-*O*-allylacetophenone (**1b**) as yellow oil (14.8 g) in 77% yield (Scheme 1).^{1}H NMR (300 MHz, $CDCl_3$): δ 12.68 (1H, s, 2-OH), 7.56 (1H, d, J = 9.0 Hz, H-6), 6.39 (1H, d, J = 3.0 Hz, H-3), 6.35 (1H, dd, J = 9.0, 3.0 Hz, H-5), 5.96 (1H, m, H-2′), 5.35 (2H, m, H-3′), 4.50 (1H, d, J = 6.3 Hz, H-1′), 2.50 (3H, s, Me).

5. General procedure for the synthesis of chalcones (2–23)

A solution of 50% KOH (50 mL) was added drop wise to a well-stirred mixture of 2-hydroxy-4-*O*-prenylacetophenone **1a** (5 mmol) and different substituted aldehydes (5 mmol) in MeOH at room temperature. After 24–36 h, the solvent was removed under reduced pressure and acidified with 5% HCl (30–60 mL). The aqueous layer was extracted with EtOAc, washed with brine, dried (Na_2SO_4), and then concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with hexane:EtOAc mixtures to afford oxyprenylated chalcones **2**–**13** in high yield (Scheme 2). A similar procedure applied for the synthesis of oxyallylated chalcones (**14–23**) from **1a,b** (10 mmol) and different substituted aldehydes (10 mmol) (Scheme 2)

5.1. (*E*)-1-[2-Hydroxy-4-(3-methylbut-2-enyloxy)phenyl]-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one (2)

The compound was isolated as a yellow solid (1.5 g) in 75% yield, mp 83–84 °C. IR (neat) 2938, 2840, 1632 (C═O), 1565 (C═C), 1495, 1465, 1435, 1415, 1359, 1303, 1282, 1256, 1211, 1133, 1096, 1045, 1009, 946, 859 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 13.47 (1H, s, 2-OH), 8.01 (1H, d, J = 15.6 Hz, H-9), 7.77 (1H, d, J = 9.0 Hz, H-6), 7.58 (1H, d, J = 15.6, H-8), 7.33 (1H, d, J = 9.0 Hz, H-6′), 6.67 (1H, dd, J = 9.0, 3.0 Hz, H-5), 6.44 (1H, d, J = 9.0 Hz, H-5′), 5.43 (1H, t, J = 6.3 Hz, H-2″), 4.52 (2H, d, J = 6.3 Hz, H-1″), 3.93, 3.88 (9H, m, 3× OMe), 1.77 (3H, s, H-4″), 1.72 (3H, s, H-5″).13C NMR (75 MHz, $CDCl_3$): δ 192.2, 166.5, 165.3, 155.9, 153.9, 142.4, 139.7, 139.1, 131.1, 124.2, 121.9, 119.4, 118.7, 114.1, 108.1, 107.6, 101.6, 65.1, 61.4, 60.9, 56.1, 25.8, 18.2. EIMS *m/z* (% rel intensity): 398 (24) [M]$^+$, 367 (22), 330 (8), 300 (31), 299 (100), 181 (9), 137 (8), 69 (20); HREIMS *m/z* Calcd for $C_{23}H_{26}O_6$, 398.1729. Found 398.1729. Elemental Analysis: Calcd C, 69.33; H, 6.58. Found C, 69.12; H, 6.51.

5.2. (*E*)-1-[2-Hydroxy-4-(3-methylbut-2-enyloxy)phenyl]-3-(3-hydroxy-4-methoxyphenyl) prop-2-en-1-one (3)

The compound was isolated as a yellow solid (1.08 g) in 61% yield, mp 138–139 °C. IR (neat) 2932, 1633 (C═O), 1569 (C═C), 1510, 1458, 1440, 1266, 1210, 1130, 1028, 977, 854, 796 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.60 (1H, s, 2-OH), 7.80 (1H, d, J = 15.3 Hz, H-9), 7.79 (1H, d, J = 9.0 Hz, H-6), 7.43 (1H, d, J = 15.3 Hz, H-8), 7.26 (1H, d, J = 9.0 Hz, H-6′), 7.14 (1H, d, J = 2.5 Hz, H-2′), 6.87 (1H, d, J = 9.0 Hz, H-5′), 6.48 (2H, m, J = 9.0 Hz, H-3,5), 5.48 (1H, t, J = 6.0 Hz, H-2″), 4.57 (2H, d, J = 6.0 Hz, H-1″), 3.95 (3H, s, 4′-OMe), 1.81 (3H, s, 4″-Me), 1.76 (3H, s, 5″-Me).13C NMR (75 MHz, $CDCl_3$): δ 191.7, 166.5, 165.4, 148.9, 145.9, 144.2, 139.1, 131.1, 128.4, 122.9 118.7, 118.4, 114.0, 113.0, 110.5, 108.1, 101.7, 65.1, 56.0, 25.8, 18.2. EIMS *m/z* (% rel intensity): 354 (43) [M]$^+$, 286 (100), 285 (53), 269 (14), 163 (17), 150 (27), 137 (71), 69 (43); HREIMS *m/z* Calcd for $C_{21}H_{22}O_5$, 354.1467. Found 354.1465. Elemental Analysis: Calcd C, 71.17; H, 6.26. Found 71.46; H, 6.58.

5.3. (*E*)-1-[2-Hydroxy-4-(3-methylbut-2-enyloxy) phenyl]-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one (4)

The compound was isolated as a yellow solid (1.01 g) in 50% yield, mp 102–103 °C. IR (neat) 2935, 2836, 1628 (C═O), 1554 (C═C), 1510, 1466, 1376, 1287, 1256, 1208, 1125, 1028, 850, 744, 630 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.69 (1H, s, 2-OH), 8.17 (1H, d, J = 15.3 Hz, H-9), 7.83 (1H, d, J = 9.0 Hz, H-6), 7.54 (1H, d, J = 15.3 Hz, H-8), 7.13 (1H, s, H-6′), 6.54 (3H, m, H-5,3,3′), 6.50 (1H, t, J = 6.0 Hz, H-2″), 4.57 (2H, d, J = 6.0 Hz, H-2′), 3.98 (3H, s, OMe), 3.93 (6H, s, 2xOMe), 1.81 (3H, s, H-4″), 1.76 (3H, s, H-5″). 13C NMR (75 MHz, $CDCl_3$): δ 192.1, 166.4, 165.1, 154.8, 152.6, 143.2, 139.6, 139.0, 130.9, 118.6, 118.0, 115.3, 114.1, 111.6, 107.9, 101.5, 96.7, 65.0, 56.5, 56.2, 56.0, 25.7, 18.1. EIMS *m/z* (% rel intensity): 398 (52) [M]$^+$, 367 (10), 330 (15), 299 (100), 181 (22), 137 (7), 69 (16); HREIMS *m/z* Calcd for $C_{23}H_{26}O_6$, 398.1729. Found, 398.1730. Elemental Analysis: Calcd C, 69.33; H, 6.58. Found C, 69.34; H, 6.55.

5.4. (*E*)-3-(2,4-Dimethoxyphenyl)-1-[2-hydroxy-4-(3-methylbut-2-enyloxy)phenyl]prop-2-en-1-one (5)

The compound was isolated as a yellow solid (1.42 g) in 77% yield, mp 72–73 °C. IR (neat) 2937, 2838, 1629(C═O), 1608(C═C), 1555, 1505, 1438, 1418, 1361, 1315, 1295, 1215, 1160, 1026, 1001, 942, 835 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 13.71 (1H, s, 2-OH), 8.11 (1H, d, J = 15.0 Hz, H-9), 7.79 (1H, d, J = 9.0 Hz, H-6), 7.61 (1H, d, J = 9.0 Hz, H-6′), 7.59 (1H, d, J = 15.0 Hz, H-8), 6.52 (4H, m, H-3, 5, 3′, 5′), 5.47 (1H, t, J = 6.0 Hz, H-2″), 4.54 (2H, d, J = 6.0 Hz, H-1″), 3.89 (3H, s, OMe), 3.83 (3H, s, OMe), 1.79 (3H, s, H-4″), 1.74 (3H, s, H-5″).13C NMR (75 MHz, $CDCl_3$): δ 192.3, 166.4, 165.1, 163.2, 160.5, 140.0, 138.9, 131.1, 131.1, 118.8, 118.1, 116.9, 114.2, 107.8, 105.5, 101.6, 98.3, 65.1, 55.5, 55.4, 25.8, 18.2. EIMS *m/z* (% rel intensity): 368 (56) [M]$^+$, 300 (51), 269 (100), 191 (8), 164 (29), 151 (63), 137 (16), 69 (35); HREIMS *m/z* Calcd for $C_{22}H_{24}O_5$, 368.1624. Found, 368.1621. Elemental Analysis: Calcd C, 71.71; H, 6.57. Found C, 71.77; H, 6.61.

5.5. (*E*)-1-[2-Hydroxy-4-(3-methylbut-2-enyloxy)phenyl]-3-phenylprop-2-en-1-one (6)

The compound was isolated as a yellow solid (1.08 g) in 70% yield, mp 113–114 °C. IR (neat) 2926, 1631 (C═C), 1609 (C═O), 1578, 1500, 1415, 1358, 1275, 1217, 1138, 990, 875, 828, 763, 729 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 13.45 (1H, s, 2-OH), 7.89 (1H, d, J = 15.3 Hz, H-9), 7.82 (1H, d, J = 9.0 Hz, H-6), 7.63 (2H, m, H-2′, 6′), 7.60 (1H, d, J = 15.3 Hz, H-8), 7.43 (3H, m, H-3′, 4′, 5′), 6.49 (2H, m, H-3, 5), 5.47 (1H, t, J = 6.0 Hz, H-2″), 4.56 (2H, d, J = 6.0 Hz, H-1″), 1.81 (3H, s, H-4″), 1.76 (3H, s, H-5″).13C NMR (75 MHz, $CDCl_3$): δ 191.2, 166.1, 165.0, 143.7, 138.6, 134.2, 130.7,

130.1, 128.4, 128.4, 128.0, 128.0, 119.8, 118.1, 113.4, 107.7, 101.2, 64.6, 25.3, 17.7. EIMS *m/z* (% rel intensity): 308 (19) $[M]^+$, 240 (100), 239 (72), 223 (8), 163 (58), 137 (13) 103 (8), 69 (39); HREIMS *m/z* Calcd for $C_{20}H_{20}O_3$, 308.1412. Found, 308.1411. Elemental Analysis: Calcd C, 77.90; H, 6.54. Found C, 77.84; H, 6.50.

5.6. (*E*)-3-(2,3-Dimethoxyphenyl)-1-[2-hydroxy-4-(3-methylbut-2-enyloxy)phenyl]prop-2-en-1-one (7)

The compound was isolated as a pale yellow solid (1.2 g) in 65% yield, 108–109 °C. IR (neat) 2932, 2836, 1640 (C=O), 1613 (C=C), 1577, 1478, 1454, 1360, 1273, 1229, 1141, 1073, 1001, 974, 827, 742 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 13.47 (1H, s, 2-OH), 8.16 (1H, d, *J* = 15.6 Hz, H-9), 7.82 (1H, d, *J* = 9.0 Hz, H-6), 7.67 (1H, d, *J* = 15.6 Hz, H-8), 7.29 (1H, d, *J* = 9 Hz, H-6′), 7.10 (1H, t, *J* = 9, 2.4 Hz, H-5), 6.98 (1H, d, *J* = 8.1 Hz, H-4′), 6.49 (2H, m, H-3, 5′), 5.49 (1H, t, *J* = 6.6 Hz, H-2″), 4.57 (2H, d, *J* = 6.6 Hz, H-1″), 3.90 (6H, s, 2xOMe), 1.81 (3H, s, H-4″), 1.76 (H, s, H-5″).13C NMR (75 MHz, $CDCl_3$): δ 192.1, 166.6, 165.5, 153.2, 149.0, 139.2, 139.1, 131.2, 129.0, 124.2, 121.9, 119.7, 118.6, 118.4, 114.2, 114.1, 108.2, 101.7, 65.1, 61.3, 55.9, 25.8, 18.2. EIMS *m/z* (% rel intensity): 368 (16) $[M]^+$, 300 (17), 270 (17), 269 (100), 163 (3), 137 (6), 69 (17); HREIMS *m/z* Calcd for $C_{22}H_{24}O_5$, 368.1624. Found, 368.1623. Elemental Analysis: Calcd C, 71.72; H, 6.57. Found C, 71.63; H, 6.50.

5.7. (*E*)-3-(2,5-Dimethoxyphenyl)-1-[2-hydroxy-4-(3-methylbut-2-enyloxy)phenyl]prop-2-en-1-one (8)

The compound was isolated as a yellow solid (1.35 g) in 73% yield, mp 125–126 °C. IR (neat) 2937, 1632(C=O), 1572 (C=C), 1498, 1464, 1424, 1360, 1284, 1253, 1224, 1135, 1047, 1002, 857, 807 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 13.52 (1H, s, 2-OH), 8.14 (1H, d, *J* = 15.6 Hz, H-9), 7.81 (1H, d, *J* = 8.7 Hz, H-6), 7.64 (1H, d, *J* = 15.6 Hz, H-8), 7.15 (1H, d, *J* = 2.7 Hz, H-6′), 6.94 (1H, dd, *J* = 9.0, 3.0 Hz, H-5), 6.85 (1H, d, *J* = 9.0 Hz, H-3′), 6.48 (2H, m, H-3, 4′), 5.48 (1H, t, *J* = 6.6 Hz, H-2″), 4.56 (2H, d, *J* = 6.6 Hz, H-1″), 3.88 (3H, s, OMe), 3.82 (3H, s, OMe), 1.80 (3H, s, H-4″), 1.75 (3H, s, H-5″).13C NMR (75 MHz, $CDCl_3$): δ 192.2, 166.5, 165.3, 153.4, 153.4, 139.7, 139.1, 131.2, 124.3, 121.2, 118.6, 117.2, 114.1, 114.0, 112.4, 108.1, 101.6, 65.1, 56.0, 55.8, 25.7, 18.2. EIMS *m/z* (% rel intensity): 368 (24) $[M]^+$, 300 (20), 269 (100), 164 (5), 137 (7), 69 (17); HREIMS *m/z* Calcd for $C_{22}H_{24}O_5$, 368.1624. Found, 368.1621. Elemental Analysis: Calcd C, 71.72; H, 6.57. Found C, 71.72; H, 6.55.

5.8. (*E*)-3-(3,5-Dimethoxyphenyl)-1-[2-hydroxy-4-(3-methylbut-2-enyloxy)phenyl]prop-2-en-1-one (9)

The compound was isolated as a yellow solid (1.15 g) in 62% yield, mp 142–143 °C. IR (neat) 2938, 1642 (C=O), 1600 (C=C), 1570, 1502, 1466, 1450, 1427, 1371, 1275, 1257, 1216, 1194, 1156, 1057, 967, 866, 835 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.41 (1H, s, 2-OH), 7.81 (1H, d, *J* = 7.2 Hz, H-6), 7.79 (1H, d, *J* = 15.6 Hz, H-9), 7.54 (1H, d, *J* = 15.6 Hz, H-8), 6.78 (2H, s, H-2′, 6′), 6.50 (3H, m, H-3, 5, 4′), 5.48 (1H, t, *J* = 6.6 Hz, H-2″), 4.57 (2H, d, *J* = 6.6 Hz, H-1″), 3.84 (3H, s, OMe), 3.82 (3H, s, OMe), 1.81 (3H, s, 4″-Me), 1.76 (3H, s, H-5″).13C NMR (75 MHz, $CDCl_3$): δ 191.6, 166.6, 165.6, 161.0, 161.0, 144.3, 13.2, 136.7, 131.2, 120.8, 118.6, 113.9, 108.3, 106.4, 106.4, 102.7, 101.7, 65.2, 55.4, 55.4, 25.8, 18.2. EIMS *m/z* (% rel intensity): 368 (32) $[M]^+$, 299 (31), 300 (100), 269 (27), 191 (8), 163 (27), 137 (10), 69 (46); HREIMS *m/z* Calcd for $C_{22}H_{24}O_5$, 368.1624. Found, 368.1624. Elemental Analysis: Calcd C, 71.72; H, 6.57. Found C, 71.78; H, 6.56.

5.9. (*E*)-3-(Benzo[d][1,3]dioxol-5-yl)-1-[2-hydroxy-4-(3-methylbut-2-enyloxy)phenyl]prop-2-en-1-one (10)

The compound was isolated as a bright yellow solid (1.23 g) in 69% yield, mp 125–126 °C. IR (neat) 2911, 1634 (C=O), 1571 (C=C C=C), 1503, 1489, 1447, 1375, 1248, 1215, 1038, 971, 933, 794 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.45 (1H, s, 2-OH), 7.79 (2H, m, H-6, 6′), 7.40 (1H, d, *J* = 15.3 Hz, H-9), 7.15 (1H, d, *J* = 15.3 Hz, H-8), 7.10 (1H, d, *J* = 2.5 Hz, H-2′), 6.84 (1H, d, *J* = 7.5 Hz, H-5′), 6.48 (2H, m, *J* = 8.1 Hz, H-3, 5), 6.02 (2H, s, -OCH_2O-), 5.48 (1H, t, *J* = 6.6 Hz, H-2″), 4.56 (2H, d, *J* = 6.6 Hz, H-1″), 1.81 (3H, s, H-4″), 1.75 (3H, s, H-5″).13C NMR (75 MHz, $CDCl_3$): δ 191.6, 166.5, 165.4, 149.9, 148.4, 144.1, 139.1, 131.0, 129.2, 125.3, 118.6, 118.2, 113.9, 108.6, 108.1, 106.6, 101.6, 101.6, 65.1, 25.7, 18.2. EIMS *m/z* (% rel intensity): 352 (41) $[M]^+$, 385 (18) 284 (100), 283 (45), 267 (9), 163 (13), 148 (42), 135 (60), 69 (46); HREIMS *m/z* Calcd for $C_{21}H_{20}O_5$, 352.1311. Found, 352.1311. Elemental Analysis: Calcd C, 71.58; H, 5.72. Found C, 71.49; H, 5.74.

5.10. (*E*)-1-[2-Hydroxy-4-(3-methylbut-2-enyloxy)phenyl]-3-(4-methoxyphenyl)prop-2-en-1-one (11)

The compound was isolated as a yellow solid (1.35 g) in 79% yield, mp 97–98 °C. IR (neat) 2957, 294, 1624 (C=O), 1558 (C=C), 1505, 1415, 1362, 1277, 1215, 1169, 1130, 1007, 968, 627 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 13.55 (1H, s, 2-OH), 7.86 (1H, d, *J* = 15.3 Hz, H-9), 7.81 (1H, d, *J* = 9.0 Hz, H-6), 7.62 (2H, d, *J* = 9.0 Hz, H-2′, 6′), 7.46 (1H, d, *J* = 15.3 Hz, H-8), 6.94 (2H, d, *J* = 9.0 Hz, H-3′, 5′), 6.51 (1H, d, *J* = 2.1 Hz, H-3), 6.49 (1H, dd, *J* = 9.0, 2.1 Hz, H-5), 5.49 (1H, t, *J* = 6.0 Hz, H-2″), 4.57 (2H, d, *J* = 6.0 Hz, H-1″), 3.87 (3H, s, H-4′), 1.81 (3H, s, H-4″), 1.76 (3H, s, H-5″).13C NMR (75 MHz, $CDCl_3$): δ 191.8, 166.5, 165.3, 161.7, 144.1, 139.1, 131.0, 130.3, 130.3, 127.5, 118.6, 117.8, 114.4, 114.4, 114.0, 108.1, 101.6, 65.1, 55.4, 25.7, 18.2. EIMS *m/z* (% rel intensity): 338 (41) $[M]^+$, 270 (100), 269 (56), 253 (9), 121 (51), 69 (43); HREIMS *m/z* Calcd for $C_{21}H_{22}O_4$, 338.1518. Found, 338.1516. Elemental Analysis: Calcd C, 74.54; H, 6.55. Found C, 74.48; H, 6.58.

5.11. (*E*)-3-(3,4-Dimethoxyphenyl)-1-[2-hydroxy-4-(3-methylbut-2-enyloxy)phenyl]prop-2-en-1-one (12)

The compound was isolated as a yellow solid (1.2 g) in 65% yield, mp 108–109 °C. IR (neat) 2938, 2840, 1630 (C=O), 1566 (C=C), 1495, 1465, 1414, 1359, 1282, 1256, 1235, 1211, 1132, 1096, 1045, 1008, 796 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 13.58 (1H, s, 2-OH), 7.86 (1H, d, *J* = 15.0 Hz, H-9) 7.85 (1H, d, *J* = 9.0 Hz, H-6), 7.46 (1H, d, *J* = 15.0 Hz, H-8), 7.29 (1H, dd, *J* = 9, 3.0 Hz, H-6′), 7.19 (1H, br s, H-2′), 6.93 (1H, d, *J* = 9.0 Hz, H-5′), 6.55 (1H, d, *J* = 3.0, H-3), 6.52 (1H, dd, *J* = 9.0, 3.0 Hz, H-5), 5.51 (1H, t, *J* = 6.0 Hz, H-2″), 4.59 (2H, d, *J* = 6.0 Hz, H-1″), 3.96–3.99 (6H, s, 2× OMe), 1.84 (3H, s, H-4″), 1.79 (3H, s, H-5″).13C NMR (75 MHz, $CDCl_3$): δ 191.6, 166.5, 165.3, 151.5, 149.2, 144.4, 139.1, 131.0, 127.7, 123.2, 118.6, 118.0, 113.9, 111.1, 110.1, 108.1, 101.6, 65.1, 55.9, 55.9, 25.7, 18.2. EIMS *m/z* (% rel intensity): 368 (64) $[M]^+$, 300 (100), 299 (42), 285 (12), 164 (44), 151 (81), 69 (48); HREIMS *m/z* Calcd for $C_{22}H_{24}O_5$, 368.1624. Found, 368.1621. Elemental Analysis: Calcd C, 71.72; H, 6.57. Found C, 71.51; H, 6.61.

5.12. (*E*)-1-[2-Hydroxy-4-(3-methylbut-2-enyloxy)phenyl]-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (13)

The compound was isolated as a yellow solid (1.2 g) in 60% yield, mp 143–144 °C. IR (neat) 2942, 1641 (C=O), 1571 (C=C), 1503, 1465, 1451, 1420, 1371, 1333, 1268, 1249, 1214, 1123, 970, 836, 800 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.47 (1H, s,

2-OH), 7.83 (1H, d, *J* = 9.0 Hz, H-6), 7.77 (1H, d, *J* = 15.0 Hz, H-9), 7.43 (1H, d, *J* = 15.0 Hz, H-8), 6.84 (2H, s, H-2′, 6′), 6.49 (1H, d, *J* = 2.4 Hz, H-3), 6.47 (1H, dd, *J* = 9.0 Hz, 2.4 Hz, H-5), 5.45 (1H, t, *J* = 6.0 Hz, H-2″), 4.54 (2H, d, *J* = 6.0 Hz, H-1″), 3.91 (9H, s, 3xOMe), 1.79 (3H, s, H-4″), 1.74 (3H, s, H-5″).13C NMR (75 MHz, $CDCl_3$): δ 191.5, 166.6, 165.5, 153.4, 144.4, 140.5, 139.1, 131.1, 130.2, 119.4, 118.6, 113.9, 108.2, 105.7, 105.3, 101.6, 65.2, 60.9, 56.2, 56.2, 25.8, 18.2. EIMS *m/z* (% rel intensity): 398 (76) $[M]^+$, 330 (100), 329 (20), 299 (14), 287 (9), 194 (30), 181 (72), 163 (14), 137 (8), 69 (44); HREIMS *m/z* Calcd for $C_{23}H_{26}O_6$, 398.1729. Found, 398.1731. Elemental Analysis: Calcd C, 69.33; H, 6.58. Found C, 69.20; H, 6.57.

5.13. (*E*)-1-(4-[Allyloxy)-2-hydroxyphenyl]-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one (14)

The compound was isolated as a yellow solid (2.5 g) in 67% yield, mp 122–123 °C. IR (neat) 2945, 2828, 1629 (C=O), 1575 (C=C), 1505, 1465, 1435, 1413, 1363, 1283, 1257, 1217, 1194, 1132, 1094, 1041, 1003, 986, 969, 938, 906, 862, 835, 799 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 13.57 (1H, s, 2-OH), 8.06 (1H, d, *J* = 15.6 Hz, H-9), 7.82 (1H, d, *J* = 9.0 Hz, H-6), 7.63 (1H, d, *J* = 15.6 Hz, H-8), 7.37 (1H, d, *J* = 9.0 Hz, H-6′), 6.72 (1H, d, *J* = 9.0 Hz, H-5′), 6.51 (1H, d, *J* = 3.0 Hz, H-3), 6.48 (1H, dd, *J* = 9.0, 3.0 Hz, H-5), 5.44 (1H, m, H-2″), 5.37 (2H, m, H-3″), 4.58 (2H, d, *J* = 6.0 Hz, H-1″), 3.97 (3H, s, OMe), 3.92 (3H, s, OMe), 3.90 (3H, s, OMe).^{13}C NMR (75 MHz, $CDCl_3$): δ 192.2, 166.4, 164.8, 155.9, 153.9, 142.4, 139.8, 132.2, 131.1, 124.2, 121.8, 119.4, 118.3, 114.3, 107.9, 107.5, 101.8, 68.9, 61.3, 60.9, 56.0. EIMS *m/z* (% rel intensity): 370 (15) $[M]^+$, 339 (100), 298 (8), 270 (2); HREIMS *m/z* Calcd for $C_{21}H_{22}O_6$, 370.1416. Found, 370.1419. Elemental Analysis: Calcd C, 68.10; H, 5.99. Found C, 68.13; H, 6.03.

5.14. (*E*)-1-[4-(Allyloxy)-2-hydroxyphenyl]-3-(2,3-dimethoxyphenyl)prop-2-en-1-one (15)

The compound was isolated as a pale yellow solid (2.7 g) in 79% yield, mp 129–130 °C. IR (neat) 2941, 2835, 1632, 1572, 1497, 1464, 1425, 1361, 1254, 1224, 1133, 1046, 1015, 856, 806 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.51 (1H, s, 2-OH), 8.15 (1H, d, *J* = 15.6 Hz, H-9), 7.82 (1H, d, *J* = 9.0 Hz, H-6), 7.66 (1H, d, *J* = 15.6 Hz, H-8), 7.15 (1H, dd, *J* = 9.0, 3.0 Hz, H-6′), 6.88 (1H, d, *J* = 9. Hz, H-5′), 6.50 (2H, m, H-3, 4′), 6.05 (1H, m, H-2″), 5.38 (2H, m, H-3″), 4.59 (2H, d, *J* = 5.1 Hz, H-1″), 3.88 (3H, s, OMe), 3.82 (3H, s, OMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.3, 166.5, 164.9, 153.4, 153.4, 139.8, 132.2 131.3, 124.3, 121.2, 118.3, 117.3, 114.3, 114.0, 112.4, 107.9, 101.8, 68.9, 56.1, 55.8. EIMS *m/z* (% rel intensity): 340 (52) $[M]^+$, 310 (26), 309 (100), 268 (13), 240 (5), 203 (8), 164 (10), 69 (1); HREIMS *m/z* Calcd for $C_{20}H_{20}O_5$, 340.1311. Found, 340.1308. Elemental Analysis: Calcd C, 70.57; H, 5.92. Found C, 70.37; H, 5.92.

5.15. (*E*)-1-[4-(Allyloxy)-2-hydroxyphenyl]-3-(benzo[d][1,3]dioxol-5-yl)prop-2-en-1-one (16)

The compound was isolated as a yellow solid (2.4 g) in 74% yield, mp 152–153 °C. IR (neat) 2909, 1627 (C=O), 1564 (C=C), 1490, 1446, 1377, 1290, 1252, 1218, 1123, 1103, 1039, 931, 799 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 13.47 (1H, s, 2-OH), 7.80 (1H, d, *J* = 15.0 Hz, H-9), 7.79 (1H, d, *J* = 9.0 Hz, H-6), 7.39 (1H, d, *J* = 15.0 Hz, H-8), 7.16 (1H, d, *J* = 0.9 Hz, H-2′), 7.13 (1H, br d, *J* = 8.1 Hz, H-6′), 6.85 (1H, d, *J* = 8.1 Hz, H-5′), 6.52 (1H, d, *J* = 2.4 Hz, H-3), 6.47 (1H, d, *J* = 9.0 Hz, H-5), 6.03 (1H, m, H-2″), 6.02 (2H, s, –OCH_2O–), 5.38 (2H, m, H-3″), 4.58 (2H, d, *J* = 5.1 Hz, H-1″).13C NMR (75 MHz, $CDCl_3$): δ 191.6, 166.5, 165.0, 150.0, 148.4, 144.2, 132.2, 131.1, 129.2, 125.3, 118.3, 118.2, 114.2, 108,.6, 108.0, 106.6, 101.9, 101.6, 68.9; EIMS, *m/z* (% rel intensity): 324 (100), $[M]^+$, 323 (32), 283 (21), 255 (10), 203 (15), 148 (69), 135 (44); HREIMS *m/z* Calcd for $C_{19}H_{16}O_5$, 324.0998. Found, 324.0997. Elemental Analysis: Calcd C, 70.36; H, 4.97. Found C, 70.38; H, 5.01.

5.16. (*E*)-1-[4-(Allyloxy)-2-hydroxyphenyl]-3-(2,5-dimethoxyphenyl)prop-2-en-1-one (17)

The compound was isolated as a yellow solid (2.2 g) in 64% yield, mp 101–102 °C. IR (neat) 2941, 2835, 1632 (C=O), 1496 (C=C), 1464, 1425, 1361, 1287, 1255, 1179, 1133, 1047, 1016, 984, 856 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 13.51 (1H, s, 2-OH), 8.15 (1H, d, *J* = 15.3 Hz, H-9), 7.82 (1H, d, *J* = 9.0 Hz, H-6), 7.66 (1H, d, *J* = 15.3 Hz, H-8), 7.16 (1H, d, *J* = 2.4 Hz, H-6′), 6.95 (1H, dd, *J* = 9.0, 2.4 Hz, H-5), 6.88 (1H, d, *J* = 9.0 Hz, H-3′), 6.52 (1H, dd, *J* = 9.0, 2.1 Hz, H-4′), 6.47 (1H, d, *J* = 2.1 Hz, H-3), 6.05 (1H, m, H-2″), 5.38 (2H, m, H-3″), 4.59 (2H, d, *J* = 6.0 Hz, H-1″), 3.89 (3H, s, OMe), 3.83 (3H, s, OMe).^{13}C NMR (75 MHz, $CDCl_3$): δ 192.3, 166.5, 164.9, 153.4, 153.4, 139.8, 132.2, 131.3, 124.3, 121.2, 118.3, 117.3, 114.3, 114.0, 112.4, 107.9, 101.8, 68.9, 56.1, 55.8. EIMS *m/z* (% rel intensity): 340 (40) $[M]^+$, 310 (21), 309 (100), 268 (11), 203 (6), 164 (8); HREIMS *m/z* Calcd for $C_{20}H_{20}O_5$, 340.1311. Found, 340.1308. Elemental Analysis: Calcd C, 70.57; H, 5.92. Found C, 70.42; H, 5.84.

5.17. (*E*)-1-[4-(Allyloxy)-2-hydroxyphenyl]-3-(4-methoxyphenyl)prop-2-en-1-one (18)

The compound was isolated as a yellow solid (2.6 g) in 83% yield, mp 126–127 °C. IR (neat) 2914, 2841, 1626 (C=O), 1562 (C=C), 1505, 1416, 1370, 1279, 1219, 1139, 1006, 975, 885, 810 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 13.82 (1H, s, 2-OH), 7.86 (1H, d, *J* = 15.3 Hz, H-9), 7.83 (1H, d, *J* = 9.0 Hz, H-6), 7.61 (2H, d, *J* = 9.0 Hz, H-2′, 6′), 7.45 (1H, d, *J* = 15.3 Hz, H-8), 6.94 (2H, d, *J* = 9.0 Hz, H-3′, 5′), 6.52 (1H, d, *J* = 3.0 Hz, H-3), 6.50 (1H, dd, *J* = 9.0, 3.0 Hz, H-5), 6.05 (1H, m, H-2″), 5.41 (2H, m, H-3″), 4.59 (2H, d, *J* = 6.0 Hz, H-1″), 3.86 (3H, s, OMe).^{13}C NMR (75 MHz, $CDCl_3$): δ 191.8, 166.5, 164.9, 161.8, 144.2, 132.2, 131.1, 130.3, 130.3, 127.5, 118.3, 117.8, 114.4, 114.4, 114.2, 108.0, 101.9, 68.9, 55.4. EIMS *m/z* (% rel intensity): 310 (100) $[M]^+$, 309 (54), 269 (39), 241 (22), 203 (20), 161 (21), 134 (100), 121 (56). HREIMS *m/z* Calcd for $C_{19}H_{18}O_4$, 310.1205. Found, 310.1204. Elemental Analysis: Calcd C, 73.53; H, 5.85. Found C, 73.46; H, 5.88.

5.18. (*E*)-1-[4-(Allyloxy)-2-hydroxyphenyl]-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (19)

The compound was isolated as a yellow solid (2.0 g) in 58% yield, mp 129–130 °C. IR (neat) 2945, 1627 (C=O), 1550 (C=C), 1501, 1413, 1360, 1295, 1253, 1216, 1138, 991, 833 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 13.70 (1H, s, 2OH), 8.11 (1H, d, *J* = 15.3 Hz, H-9), 7.80 (1H, d, *J* = 9.0 Hz, H-6), 7.58 (1H, d, *J* = 15.3 Hz, H-8), 7.53 (1H, dd, *J* = 9.0, 2.4 Hz, H-6), 6.49 (4H, m, H-3, 5, 3′, 5′), 6.02 (1H, m, H-2″), 5.36 (2H, m, H-3″), 4.56 (2H, d, *J* = 6.0 Hz, H-1″), 3.90 (3H, s, OMe), 3.84 (3H,s, OMe).^{13}C NMR (75 MHz, $CDCl_3$): δ 192.4, 166.3, 164.6, 163.1, 160.4, 140.1, 132.2, 131.1, 131.1, 118.2, 118.1, 116.9, 114.3, 107.6, 105.4, 101.7, 98.3, 68.8, 55.4, 55.4. EIMS *m/z* (% rel intensity): 341 (19), 340 (90) $[M]^+$, 339 (17), 309 (100), 299 (19), 164 (50), 151 (66), 149 (24), 121 (10), 69 (3); HREIMS *m/z* Calcd for $C_{20}H_{20}O_5$, 340.1311. Found, 340.1312. Elemental Analysis: Calcd C, 70.57; H, 5.92. Found C, 70.33; H, 5.86.

5.19. (*E*)-1-[4-(Allyloxy)-2-hydroxyphenyl]-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (20)

The compound was isolated as a light yellow solid (2.3 g) in 62% yield, mp 171–172 °C. IR (neat) 2984, 2838, 1640, 1575, 1502, 1451, 1419, 1371, 1332, 1270, 1218, 1193, 1125, 1007, 971, 861, 837 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 13.68 (1H, s, 2-OH), 7.83 (1H, d, *J* = 9.0 Hz, H-6), 7.79 (1H, d, *J* = 15.0 Hz, H-9), 7.44 (1H, d, *J* = 15.0 Hz, H-8), 6.86 (2H, s, H-2′, 6′), 6.51 (1H, dd, *J* = 9.0, 3.0 Hz, H-5), 6.47 (1H, d, *J* = 3.0 Hz, H-3), 6.03 (1H, m, H-2″), 5.39 (2H, m, H-3″), 4.58 (2H, d, *J* = 6.0 Hz, H-1″), 3.90–3.93 (9H, s, 3xOMe).^{13}C NMR (75 MHz, $CDCl_3$): δ 191.5, 166.5, 165.0, 153.4, 153.4, 144.5, 140.5, 132.1, 131.1, 130.2, 119.3, 118.3, 114.1, 108.0, 105.7, 105.7, 101.8, 68.9, 60.9, 56.2, 56.2. EIMS *m/z* (% rel intensity): 370 (100) $[M]^+$, 369 (18), 329 (16), 301 (9), 194 (38), 181 (82), 179 (18). HREIMS *m/z* Calcd for $C_{21}H_{22}O_6$, 370.1416. Found, 370.1419. Elemental Analysis: Calcd C, 68.10; H, 5.99. Found C, 68.16; H, 6.00.

5.20. (*E*)-1-(4-[Allyloxy)-2-hydroxyphenyl]-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one (21)

The compound was isolated as a bright yellow solid (2.5 g) in 67% yield, mp 116–117 °C. IR (neat) 2936, 2836, 1628 (C═O), 1556 (C═C), 1510, 1466, 1410, 1375, 1342, 1208, 1126, 1028, 985, 850, 745, 649 cm^{-1}.^{1}H NMR (300 MHz,$CDCl_3$): δ 13.68 (1H, s, 2-OH), 8.18 (1H, d, *J* = 15.6 Hz, H-9), 7.83 (1H, d, *J* = 9.0 Hz, H-6), 7.54 (1H, d, *J* = 15.6 Hz, H-8), 7.12 (1H, s, H-6′), 6.50 (3H, m, H-3, 5, 3′), 6.08 (1H, m, H-2″), 5.41 (2H, m, H-3″), 4.59 (2H, d, *J* = 6.0 Hz, H-1″), 3.92–3.96 (9H, s, 3 × OMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.3, 166.4, 164.7, 154.8, 152.7, 143.3, 139.8, 132.2, 131.1, 118.3, 118.1, 115.4, 114.4, 111.7, 107.8, 101.8, 96.8, 68.9, 56.6, 56.3, 56.0. EIMS *m/z* (% rel intensity): 370 (75) $[M]^+$, 340 (29), 339 (100), 301 (10), 298 (20), 214 (27), 194 (22), 181 (34). HREIMS *m/z* Calcd for $C_{21}H_{22}O_6$, 370.1416. Found 370.1416. Elemental Analysis: Calcd C, 68.10; H, 5.99. Found 68.21; H, 5.85.

5.21. (*E*)-1-(4-[Allyloxy)-2-hydroxyphenyl]-3-(3,5-dimethoxyphenyl)prop-2-en-1-one (22)

The compound was isolated as a yellow solid (2.69 g) in 79% yield, mp 142–143 °C. IR (neat) 2937, 2841, 1639 (C═O), 1600 (C═C), 1573, 1502, 1460, 1428, 1369, 1276, 1256, 1193, 1156, 1060, 971, 927, 861, 836 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.39 (1H, s, 2-OH), 7.82 (1H, d, *J* = 9.0 Hz, H-6), 7.78 (1H, d, *J* = 15.0 Hz, H-9), 7.51 (1H, d, *J* = 15.0 Hz, H-8), 6.78 (2H, s, H-2′, 6′), 6.49 (3H, m, H-3,5,4′), 6.04 (1H, m, H-2″), 5.38 (2H, m, H-3″), 4.59 (2H, d, *J* = 3.6 Hz, H-1″), 3.84 (6H, s, 2× OMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.7, 166.6, 165.2, 161.0, 144.4, 136.6, 132.1, 131.3, 120.8, 118.4, 114.1, 108.1, 106.4, 102.8, 101.9, 69.0, 55.4. EIMS *m/z* (% rel intensity): 340 (100) $[M]^+$, 339 (31), 299 (62), 271 (27), 257 (16), 243 (18), 203 (78), 191 (26), 164 (46), 148 (35), 91 (28), 77 (32). HREIMS *m/z* Calcd for $C_{20}H_{20}O_5$, 340.1311. Found, 340.1310. Elemental Analysis: Calcd C, 70.57; H, 5.72. Found C, 70.43; H, 5.87.

5.22. (*E*)-1-[4-(Allyloxy)-2-hydroxyphenyl]-3-phenylprop-2-en-1-one (23)

The compound was isolated as a pale yellow solid (1.8 g) in 64% yield, mp 83–84 °C. IR (neat) 3024, 2895, 1647 (C═O), 1577 (C═C), 1504, 1450, 1369, 1298, 1276, 1217, 1194, 1175, 1106, 976, 920, 869, 03, 764, 732, 697 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 13.42 (1H, s, 2-OH), 7.88 (1H, d, *J* = 15.6 Hz, H-9), 7.83 (1H, d, *J* = 9.0 Hz, H-6), 7.64 (2H, m, H-2′, 6′), 7.57 (1H, d, *J* = 15.6 Hz, H-8), 7.42 (3H, m, H-3′, 4, 5′), 6.53 (1H, d, *J* = 1.5 Hz, H-3), 6.51 (1H, br d, *J* = 9.0 Hz, H-5), 6.03 (1H, m, H-2″), 5.38 (2H, m, H-3″), 4.58 (2H, d, *J* = 4.5 Hz, H-1″).13C NMR (75 MHz, $CDCl_3$): δ 191.7, 166.5, 165.1, 144.3, 134.7, 132.2, 131.2, 130.6, 128.9, 128.4, 120.2, 118.3, 114.1, 108.0, 101.8, 68.9. EIMS *m/z* (% rel intensity): 280 (97), $[M]^+$, 279 (53), 239 (29), 203 (88), 192 (28), 177 (71), 165 (98), 137 (48), 131 (43), 103 (89), 77 (100). HREIMS *m/z* Calcd for $C_{18}H_{16}O_3$, 280.1099. Found 280.1101. Elemental Analysis: Calcd C, 77.12; H, 5.75. Found 76.39; H, 5.77.

6. Preparation of the platelet suspension

Washed platelet suspension was prepared as previously described with some modifications.[20–22] In brief, blood was collected from the marginal ear vein of New Zealand white rabbits into tubes containing one-sixth volume of acid-citrate dextrose as anticoagulant. The blood was centrifuged at 1000*g* for 8 min at room temperature. The upper portion was kept as platelet-rich plasma (PRP) after mixing with EDTA to a final concentration of 5 mM and re-centrifuged at 2000*g* for 12 min. The platelet pellet was suspended in modified Ca^{2+}-free Tyrode′s buffer (137 mM NaCl, 2.8 mM KCl, 2 mM $MgCl_2$, 0.33 mM NaH_2PO_4, 5 mM glucose, 10 mM HEPES) with 0.35% bovine serum albumin, heparin (50 unit/mL), and apyrase (1 unit/mL) and then was incubated at 37 °C for 20 min. After centrifugation at 2000*g* for 6 min, the washed platelet pellet was resuspended in Tyrode's buffer containing 1 mM Ca^{2+}. For the aggregation test, the platelet numbers were counted by hemacytometer calculator and adjusted to 2.5×10^8 platelets/mL.

6.1. Measurement of Platelet Aggregation

Platelet aggregation was measured turbid metrically with a light-transmission Platelet Aggregation Chromogenic Kinetic System PACK4 (Helena Laboratories, Beaumont TX) with some modifications[20-22]. The platelet suspension was stirred at 900 rpm and incubated with an appropriate amount of vehicle (dimethyl sulfoxide, DMSO), 50 μg/mL of test compounds in DMSO, and positive control (30 μM of clopidogrel) at 37 °C for 2 min. Aggregation was induced with ADP (20 μM) or collagen (10 μg/mL). The transmission of washed platelet suspension was assigned 0% aggregation while transmission through Tyrode′s buffer was assigned 100% aggregation. The extent of platelet aggregation was measured as the maximal increase in light transmission within 4 min after the addition of an inducer. To eliminate or minimize any possible effects of the solvent, the final concentration of DMSO in the platelet suspension was fixed at 0.5%.

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References and notes

1. Davis, M. J.; Thomas, A. C. *Br. Heart J.* **1985**, *53*, 363–373.
2. Trip, M. D.; Cats, V. M.; Capelle, F. J. L.; Vreeken, J. N. *Engl. J. Med.* **1990**, *322*, 1549–1554.
3. Genton, E.; Clagett, G. P.; Salzman, E. W. *Chest* **1986**, *89*, 75S–81S.
4. Fuster, V.; Badimon, L.; Badimon, J. J.; Chesebro, J. H. N. *Engl. J. Med.* **1992**, *326*, 242–250.
5. Arita, H.; Hansaki, K. *Prog. Lipid Res.* **1989**, *28*, 273–301.

6. Schror, K. *Drugs* **1995**, *50*, 7–28.
7. Bennett, J. S. *Annu. Rev. Med.* **2001**, *52*, 161–184.
8. Calliste, C. A.; Le Bail, J. C.; Trouilas, P.; Pouget, C.; Habrioux, G.; Chulia, A. J.; Duroux, J. L. *Anticancer Res.* **2001**, *21*, 3949–3956.
9. Jahng, Y.; Zhao, L.; Moon, Y.; Basnet, A.; Kim, E.; Chang, H. W.; Ju, H. K.; Jeong, T. C.; Lee, E. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2559–2562.
10. Modzelewska, A.; Pettit, C.; Achanta, G.; Davidson, N. E.; Huang, P.; Khan, S. R. *Bioorg. Med. Chem.* **2006**, *14*, 3491–3495.
11. Suksamrarn, A.; Poomsing, P.; Aroonrerk, N.; Punjanon, T.; Suksamrarn, S.; Kongkum, S. *Arch. Pharm. Res.* **2003**, *26*, 816–820.
12. Nam, N. H.; Kim, Y.; You, Y. J.; Hong, D. H.; Kim, H. M.; Ahn, B. Z. *European J. Med. Chem.* **2003**, *38*, 179–187.
13. Lee, Y. S.; Lim, S. S.; Shin, K. H.; Kim, Y. S.; Ohuchi, K.; Jung, S. H. *Biol. Pharm. Bull.* **2006**, *29*, 1028–1031.
14. Dominguez, J. N.; Leon, C.; Rodrigues, J.; Dominguez, N. G. D.; Gut, J.; Rosenthal, P. J. *J. Med. Chem.* **2005**, *48*, 3654–3658.
15. Narender, T.; Khaliq, T.; Shweta, N.; Gupta, S. *Bioorg. Med. Chem.* **2005**, *13*, 6543–6550.
16. Opletalova, V. *Ceska Slov. Farm.* **2000**, *49*, 278–284.
17. Gacche, R. N.; Dhole, N. A.; Kamble, S. G.; Bandagar, B. P. *J. Enzyme. Inhib. Med. Chem.* **2007**, *1*, 1–4.
18. Lin, C. N.; Hsieh, K. H.; Ko, H. H.; Hsu, M. F.; Lin, H. C.; Chang, Y. L.; Chung, M. I.; Kang, J. J.; Wang, J. P.; Teng, C. M. *Drug Dev. Res.* **2001**, *53*, 9–14.
19. Vijaya Bhaskar Reddy, M.; Su, C. R.; Chiou, W. F.; Liu, Y. N.; Chen, R. Y. H.; Bastow, K. F.; Lee, K. H.; Wu, T. S. *Bioorg. Med. Chem.* **2008**, *16*, 7358–7370.
20. Tsai, W. J.; Hsieh, H. T.; Chen, C. C.; Kuo, Y. C.; Chen, C. F. *Eur. J. Pharmacol.* **1998**, *346*, 103–110.
21. Hung, C. C.; Tsai, W. J.; Yang, L. M.; Kuo, Y. H. *Bioorg. Med. Chem.* **2005**, *13*, 1791–1797.
22. Hsu, H. C.; Yang, W. C.; Tsai, W. J.; Chen, C. C.; Huang, H. Y.; Tsai, Y. C. *Biochem. Biophys. Res. Commun.* **2006**, *345*, 1033–1038.