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Efficient synthesis of functionalized 6-arylsalicylates via microwave-promoted Suzuki cross-coupling reaction

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ABSTRACT

Functionalized 6-arylsalicylate substructures occur in a variety of pharmacologically relevant natural products and bioactive compounds. They are also broadly used as important intermediates in organic synthesis. Traditional synthetic methods have suffered from some drawbacks, such as relatively harsh reaction conditions, narrow range of substrates, and poor yields. Utilizing microwave irradiation, the synthesis of functionalized 6-arylsalicylates via a Suzuki cross-coupling has been developed with a wide range of substrates. Almost all the reactions proceeded smoothly and afforded moderate to excellent yields of products, which indicated that electronic effects and steric modifications have little effect on this reaction.

1. Introduction

Functionalized 6-arylsalicylate substructures occur in a variety of pharmacologically relevant natural products and bioactive compounds.[1–4] For example (Fig. 1), amaroswerin, has been described as a novel hepatoprotective glycoside ester.[1] Cyandiones A and B are novel phenolic acetophenones isolated from the rhizome of *Cynanchum taiwanianum*.[2a,2b] Cyandione A has been shown to be an antioxidant,[2] while Cyandione B has exhibited significant in vitro cytotoxic activity and also displayed anti-inflammatory activity.[2] Graphislactones and their derivatives represent high antitumor-active.[3] Dimethoxypyrimidinylsalicylic acid also showed potent herbicidal activity as a result of the inhibition of acetohydroxy acid synthase.[4] In addition, numerous important pharmaceutical lead structures contain functionalized 6-arylsalicylates, and they have also been broadly used as important intermediates in organic synthesis.[5]

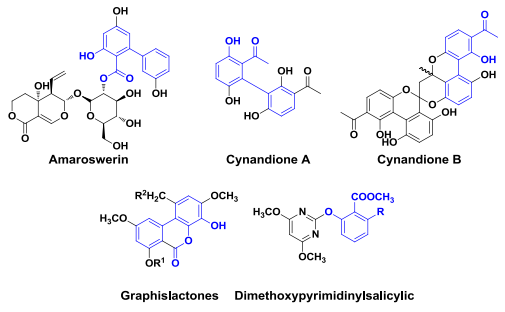

Fig. 1. Pharmacologically active functionalized 6-arylsalicylates and their derivatives.

Two traditional methods have been developed for the synthesis of functionalized 6-arylsalicylates. The first pathway relied on transition-metal-catalyzed cyclization reactions.

Although this method has been broadly applied, the synthesis of sterically encumbered 6-arylsalicylates is still very difficult or with low yield.[6] The second method involved formal [3+3] cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-trimethylsilyloxy-2-en-1-ones, which was developed by Chan et al.[1a,7] This method also suffered from some drawbacks, such as relatively harsh reaction conditions, narrow range of substrates, and poor yields. Thus, the development of an efficient method to prepare functionalized 6-arylsalicylates is of great interest.

Microwave irradiation has emerged as a powerful technique for promoting a variety of chemical reactions.[8] Reactions performed under microwave irradiation conditions benefit from significant enhancements in rate and higher product yields. In recent years, we have developed some new methods for efficient synthesis of heterocyclic compounds under microwave irradiation.[9] Not long ago,

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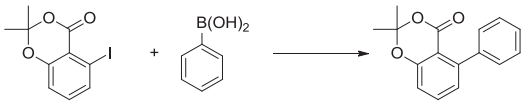
we developed a convenient method for the synthesis of bulky 4-substituted isatins by using microwave-assisted Suzuki cross-coupling reactions.[9e] Herein, as a continuation of our research on the synthesis of structurally diverse heterocyclic compounds, we report the synthesis of functionalized 6-arylsalicylates via a Suzuki cross-coupling under microwave irradiation.

2. Result and discussion

The aryl iodide (**1**) was prepared by using a previously reported synthetic strategy.[10] To optimize the conditions for the palladium-catalyzed Suzuki cross-coupling reaction, we selected the reaction between aryl iodide (**1**) and phenylboronic acids (**2a**) as a model. As shown in Table 1, microwave irradiation can also dramatically accelerate these reactions and increase the reaction yields. In addition, during optimization, the concentration, the stoichiometric ratio of the catalyst, and the temperature proved to be important parameters for this reaction. The yield was notably increased to 96% when the reaction was carried out at 110 °C, with 1 mol % of $Pd(PPh_3)_4$, 2 equiv of $NaHCO_3$, protected by N_2, under microwave irradiation. We also noted that the reaction could not take place without Pd catalysis (entry **3**). If the reaction was carried out at 100 °C, with 1% of $Pd(PPh_3)_4$, the transformation was incomplete (Table 1, entry **10**). And then, as compared to the microwave irradiation, conventional heating methods have longer reaction time and lower reaction yields (Table 1, entry **11**).

Table 1
Optimization of the reaction conditions[a]



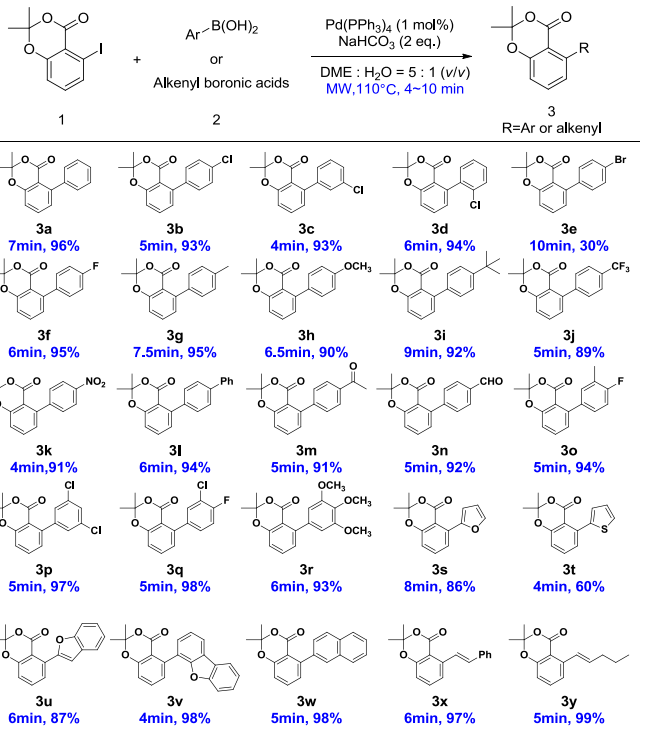
1 2a 3a

Entry	Temp (°C)	1:2a	$Pd(PPh_3)_4$	Base	Time (min)	Yield[b] (%)
1	MW:130[c]	1:1	5 mol %	$NaHCO_3$	0.5	70%
2	MW:130	1:1	5 mol %	$NaHCO_3$	5	49%
3	MW:130	1:1	0 mol %	$NaHCO_3$	5	0%
4	MW:120	1:1	5 mol %	$NaHCO_3$	5	59%
5	MW:120	1:1	2 mol %	$NaHCO_3$	7	90%
6	MW:120	1:1	1 mol %	$NaHCO_3$	7	92%
7	MW:120	1:1	0.5 mol %	$NaHCO_3$	10	87%
8	MW:120	1:1	0.2 mol %	$NaHCO_3$	13	53%
9	MW:110	1:1	1 mol %	$NaHCO_3$	7	96%
10	MW:100	1:1	1 mol %	$NaHCO_3$	25	40%
11	120[d]	1:1	1 mol %	$NaHCO_3$	480	82%[e]

[a] Unless otherwise noted, all the reactions were carried out at 0.5 mmol scale in the solution of DME (3 ml) and H_2O (0.6 ml) with 1 mol % of $Pd(PPh_3)_4$, 2 equiv of base, protected by N_2.
[b] Isolated yields.
[c] Microwave irradiation.
[d] Conventional heating method.
[e] 1 mmol scale in the solution of DME (6 ml) and H_2O (1.2 ml).

With the optimized conditions defined, we investigated the scope of substrates by employing a variety of arylboronic acids substituted with electron-donating and electron-withdrawing groups. As shown in Table 2, significant structural variations in the arylboronic acid components were well tolerated and afforded the corresponding functionalized 6-arylsalicylates (**3**) in moderate to good yields. Both electron-rich and electron-poor arylboronic acids could be successfully utilized in this transformation. Most groups, such as methyl, methoxy, *tert*-butyl, nitro, and trifluoromethyl, showed no significant effects on the transformation and afforded good yields of products (Table 2, **3g**–**k**). Even potentially problematic bromo-substituted arylboronic acid, could get product **3e** with acceptable yields. It should be noted that incorporation of halogen-substituents at the *ortho*, *meta* or *para* positions in arylboronic acids did not retard the reaction, demonstrating that steric modification can be accomplished without compromising the efficiency of the process (Table 2, **3b**–**d**). More importantly, the reaction proved to be tolerant of valuable but unstable substituents, such as formyl and acetyl groups (Table 2, compounds **3m** and **3n**).

Table 2
The reaction with aryl iodide (**1**) and various arylboronic acids or alkenyl boronic acids[a]



[a] Unless otherwise noted, all the reactions were carried out at 0.5 mmol scale in the solution of DME (3 mL) and H_2O (0.6 mL) with 1 mol% of $Pd(PPh_3)_4$, 2 equiv of $NaHCO_3$, protected by N_2.

Very promisingly, polysubstituted phenylboronic acids, furan-2-ylboronic acid, thiophen-2-ylboronic acid, dibenzofuran-4-ylboronic acid, naphthalen-1-ylboronic acid, and benzofuran-2-ylboronic acid also reacted with aryl iodide (**1**) very well and gave moderate to excellent yields of products (Table 2, **3o**–**w**).

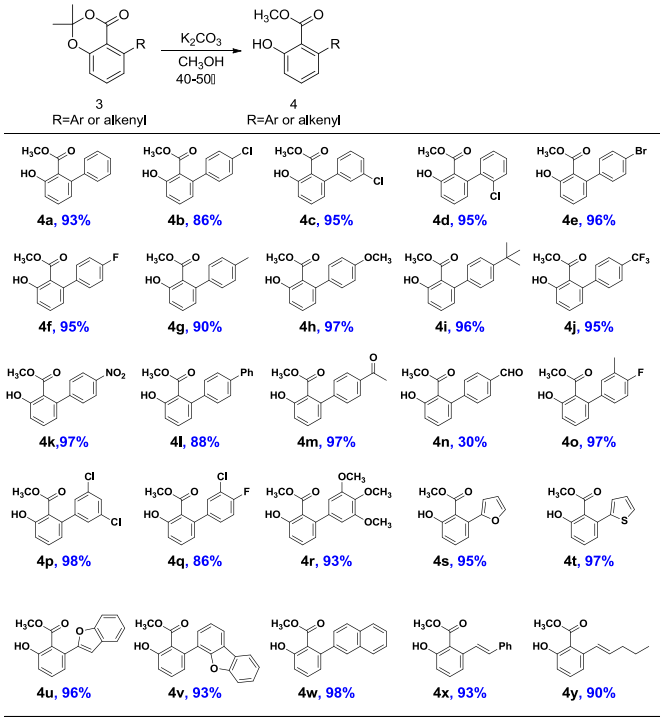
We also extended the substrates to alkenyl boronic acids. Not surprisingly, the process showed good functional group compatibility for the alkenyl reagents (Table 2, **3x**, **3y**).

Finally, we removed the protecting groups of functionalized 6-arylsalicylates (**3**) successfully to obtain the target compounds 6-arylsalicylates (**4**). For almost all the substrates with different substituents at **3**, deprotection proceeded smoothly and afforded moderate to excellent yields of products (Table 3).

3. Conclusion

In summary, we have developed a convenient method for the synthesis of functionalized 6-arylsalicylates (**4**) from aryl iodide (**1**) by using microwave-assisted Suzuki cross-coupling reactions. The reactions are applicable to a wide range of substrates and produce a variety of densely functionalized 6-arylsalicylates (**4**) in good to excellent yields within a very short time.

Table 3
The synthesis of functionalized 6-arylsalicylates(**4**) from functionalized 6-arylsalicylates (**3**)[a]



[a] Unless otherwise noted, all the reactions were carried out at 1 mmol scale in the solution of CH_3OH (10 mL) with 1.1 equiv of K_2CO_3 at 40-50℃.

4. Experimental section

4.1. General information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. All the solvents were treated according to general methods. Flash column chromatography (FC) was performed using 200–300 mesh silica gel.

^{1}H NMR spectra were recorded on 400/600 (400/600 MHz) spectrophotometers. Chemical shifts (δ) are reported in parts per million from the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm, DMSO: 2.50 ppm). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, m=multiplet, q=quaternary), coupling constants (Hertz) and integration. ^{13}C NMR spectra were recorded on 400/600 (100/150 MHz) spectrophotometers ($CDCl_3$: 77.0 ppm, DMSO: 39.5 ppm) with complete proton decoupling. Mass spectra were measured on a Trace MS spectrometer. Elemental analysis was determined on an elementary analysis instrument. Microwave irradiation reactions were carried out on a Smith synthesizer™ instrument.

4.2. General procedure for the synthesis of compounds 3a–y

Aryl iodide **1** (152 mg, 0.5 mmol) and **2a** (61 mg, 0.5 mmol) were dissolved in DME (3 mL) and H_2O (0.6 mL) in a microwave vial under a nitrogen atmosphere. $Pd(PPh_3)_4$ (0.005 mmol, 5.78 mg) and sodium bicarbonate (84 mg, 1 mmol) were added, and the reaction mixture was irradiated in a microwave apparatus at 110 °C for 4–10 min. After the reaction mixture was cooled to ambient temperature, the product was concentrated, and the crude mixture was purified by silica gel column chromatography using petroleum ether/acetone (20/1 to 10/1) as eluent to give the title compound **3a** (122 mg) in 96% yield.

*4.2.1. 2,2-Dimethyl-5-phenyl-4H-benzo[d][1,3]dioxin-4-one (**3a**).* White solid, 122 mg, 96% yield; mp: 164–165 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (t, J=7.8 Hz, 1H), 7.40 (dt, J=7.2, 6.0 Hz, 3H), 7.35–7.30 (m, 2H), 7.01 (d, J=7.8 Hz, 1H), 6.97 (d, J=8.4 Hz, 1H), 1.79 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.31, 156.96, 145.82, 140.00, 134.89, 128.42, 127.79, 127.47, 125.63, 116.25, 111.80, 105.11, 25.46. IR (KBr) 3053, 3001, 2938, 1729, 1597, 1574, 1470, 1380, 1320, 1274, 1258, 1207, 1107, 1045, 945, 894, 814, 763, 698 cm^{-1}. EIMS: m/z=254.11 (M^+). Anal. Calcd for ($C_{16}H_{14}O_3$): C, 75.57; H, 5.55. Found: C, 75.64; H, 5.77.

*4.2.2. 5-(4-Chlorophenyl)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (**3b**).* Yellow solid, 134 mg, 93% yield; mp: 175–176 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (t, J=7.8 Hz, 1H), 7.37 (d, J=8.4 Hz, 2H), 7.26 (t, J=4.2 Hz, 4H), 6.98 (dd, J=12.6, 7.8 Hz, 2H), 1.79 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.38, 157.07, 144.49, 138.47, 135.13, 133.58, 129.84, 128.04, 125.54, 116.73, 111.64, 105.30, 25.49. IR (KBr) 3094, 3008, 2990, 1726, 1598, 1581, 1468, 1393, 1381, 1326, 1298, 1278, 1203, 1088, 1053, 945, 836, 810, 697 cm^{-1}. EIMS: m/z=288.11 (M^+). Anal. Calcd for ($C_{16}H_{13}ClO_3$): C, 66.56; H, 4.54. Found: C, 66.38; H, 4.79.

*4.2.3. 5-(3-Chlorophenyl)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (**3c**).* White solid, 134 mg, 93% yield; mp: 157–158 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, J=7.8 Hz, 1H), 7.37–7.32 (m, 2H), 7.31 (s, 1H), 7.20 (d, J=7.2 Hz, 1H), 6.99 (dd, J=14.4, 7.8 Hz, 2H), 1.80 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.18, 156.98, 144.12, 141.77, 135.09, 133.54, 128.99, 128.38, 127.53, 126.85, 125.49, 116.89, 111.63, 105.32, 25.47. IR (KBr) 3086, 3057, 3020, 2994, 2942, 1731, 1597, 1582, 1563, 1467, 1378, 1319, 1275, 1236, 1204, 1117, 1045, 947, 797, 780, 692 cm^{-1}. EIMS: m/z=288.13 (M^+). Anal. Calcd for ($C_{16}H_{13}ClO_3$): C, 66.56; H, 4.54. Found: C, 66.60; H, 4.57.

*4.2.4. 5-(2-Chlorophenyl)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (**3d**).* White solid, 135 mg, 94% yield; mp: 180–181 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (t, J=7.8 Hz, 1H), 7.44–7.41 (m, 1H), 7.38–7.31 (m, 2H), 7.28 (dd, J=7.2, 2.4 Hz, 1H), 7.03 (d, J=8.4 Hz, 1H), 6.93 (d, J=7.8 Hz, 1H), 1.78 (s, 3H), 1.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.20, 156.34, 142.08, 139.11, 135.12, 132.23, 129.70, 128.98, 128.87, 126.75, 125.31, 117.12, 113.10, 105.46, 26.81, 24.28. IR (KBr) 3057, 3016, 2990, 2938, 1732, 1586, 1461, 1384, 1329, 1280, 1200, 1072, 1052, 942, 808, 762, 710 cm^{-1}. EIMS: m/z=288.14 (M^+). Anal. Calcd for ($C_{16}H_{13}ClO_3$): C, 66.56; H, 4.54. Found: C, 66.60; H, 4.43.

*4.2.5. 5-(4-Bromophenyl)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (**3e**).* White solid, 50 mg, 30% yield; mp: 191–192 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (dd, J=7.8, 5.4 Hz, 3H), 7.20 (d, J=8.4 Hz, 2H), 6.98 (dd, J=16.2, 7.8 Hz, 2H), 1.79 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.34, 157.09, 144.51, 138.97, 135.13, 130.99, 130.16, 125.49, 121.87, 116.76, 111.62, 105.32, 25.52. IR (KBr) 3090, 3008, 2998, 1725, 1599, 1582, 1392, 1381, 1326, 1298, 1278, 1238, 1203, 1053, 944, 809 cm^{-1}. EIMS: m/z=333.17 (M^+). Anal. Calcd for ($C_{16}H_{13}BrO_3$): C, 57.68; H, 3.93. Found: C, 57.70; H, 3.80.

*4.2.6. 5-(4-Fluorophenyl)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (**3f**).* White solid, 129 mg, 95% yield; mp: 178–179 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (t, J=8.0 Hz, 1H), 7.32–7.27 (m, 2H), 7.09 (t, J=7.6 Hz, 2H), 6.98 (d, J=8.0 Hz, 2H), 1.79 (d, J=2.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.58, 161.13, 159.42, 157.07, 144.75, 135.99, 135.04, 130.21, 130.12, 125.67, 116.53, 114.94, 114.72, 111.77, 105.25, 25.50. IR (KBr) 3064, 3032, 2991, 2942, 1728, 1601, 1582, 1512, 1474, 1385, 1329, 1280, 1215, 1199, 1049, 942, 898, 840, 807, 785,

696 cm^{-1}. EIMS: m/z=272.13 (M^+). Anal. Calcd for ($C_{16}H_{13}FO_3$): C, 70.58; H, 4.81. Found: C, 70.60; H, 4.92.

*4.2.7. 2,2-Dimethyl-5-(p-tolyl)-4H-benzo[d][1,3]dioxin-4-one (**3g**).* White solid, 127 mg, 95% yield; mp: 168–169 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J=8.0 Hz, 1H), 7.28–7.22 (m, 4H), 7.00 (d, J=8.0 Hz, 1H), 6.95 (d, J=8.4 Hz, 1H), 2.40 (s, 3H), 1.80 (d, J=2.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.45, 157.02, 145.92, 137.27, 137.10, 134.87, 128.64, 128.37, 125.66, 116.02, 111.84, 105.09, 25.49, 21.20. IR (KBr) 3050, 3022, 2994, 2935, 2918, 2866, 1730, 1599, 1584, 1470, 1381, 1324, 1273, 1255, 1200, 1237, 1106, 1044, 942, 801, 781, 695 cm^{-1}. EIMS: m/z=268.13 (M^+). Anal. Calcd for ($C_{17}H_{16}O_3$): C, 76.10; H, 6.01. Found: C, 75.95; H, 5.91.

*4.2.8. 5-(4-Methoxyphenyl)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (**3h**).* White solid, 128 mg, 90% yield; mp: 165–166 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.50 (t, J=7.8 Hz, 1H), 7.28 (d, J=8.4 Hz, 2H), 7.00 (d, J=7.8 Hz, 1H), 6.94 (dd, J=8.4, 6.0 Hz, 3H), 3.85 (s, 3H), 1.79 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.61, 159.16, 157.09, 145.61, 134.90, 132.29, 129.75, 125.66, 115.85, 113.37, 111.73, 105.08, 55.10, 25.49. IR (KBr) 3079, 3034, 2994, 2938, 2831, 1729, 1603, 1469, 1445, 1322, 1275, 1246, 1200, 1176, 1106, 1043, 942, 841, 804, 778, 694 cm^{-1}. EIMS: m/z=284.12 (M^+). Anal. Calcd for ($C_{17}H_{16}O_4$): C, 71.82; H, 5.67. Found: C, 71.95; H, 5.42.

*4.2.9. 5-(4-(tert-Butyl)phenyl)-2,2-dimethyl-4H-benzo[d][1,3] dioxin-4-one (**3i**).* White solid, 143 mg, 92% yield; mp: 117–118 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, J=8.0 Hz, 1H), 7.42 (d, J=8.4 Hz, 2H), 7.27 (dd, J=9.2, 2.8 Hz, 2H), 7.01 (dd, J=7.6, 1.0 Hz, 1H), 6.95 (d, J=8.4 Hz, 1H), 1.79 (s, 6H), 1.6 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.49, 157.02, 150.26, 145.90, 137.02, 134.85, 128.18, 125.77, 124.81, 115.99, 111.82, 105.05, 34.45, 31.26, 25.50. IR (KBr) 3005, 2968, 2905, 2864, 1745, 1598, 1583, 1473, 1392, 1381, 1324, 1270, 1201, 1097, 1041, 940, 846, 805, 766, 692, 567 cm^{-1}. EIMS: m/z=310.20 (M^+). Anal. Calcd for ($C_{20}H_{22}O_3$): C, 77.39; H, 7.14. Found: C, 77.24; H, 7.11.

*4.2.10. 2,2-Dimethyl-5-(4-(trifluoromethyl)phenyl)-4H-benzo[d][1,3] dioxin-4-one (**3j**).* White solid, 144 mg, 89% yield; mp: 177–178 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.66 (d, J=7.8 Hz, 2H), 7.56 (t, J=7.8 Hz, 1H), 7.43 (d, J=7.8 Hz, 2H), 7.03 (d, J=8.4 Hz, 1H), 6.98 (d, J=7.8 Hz, 1H), 1.80 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.34, 157.15, 144.28, 143.82, 135.25, 129.67, 129.35, 128.90, 125.55, 124.85, 122.84, 117.22, 111.72, 105.50, 25.54. IR (KBr) 3093, 3006, 2944, 2898, 1726, 1708, 1600, 1579, 1475, 1392, 1328, 1276, 1178, 1108, 1052, 944, 854, 811, 699 cm^{-1}. EIMS: m/z=322.14 (M^+). Anal. Calcd for ($C_{17}H_{13}F_3O_3$): C, 63.36; H, 4.07. Found: C, 63.45; H, 4.24.

*4.2.11. 2,2-Dimethyl-5-(4-nitrophenyl)-4H-benzo[d][1,3]dioxin-4-one (**3k**).* Yellow solid, 136 mg, 91% yield; mp: 181–182 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 8.27 (d, J=8.4 Hz, 2H), 7.59 (t, J=7.8 Hz, 1H), 7.48 (d, J=8.4 Hz, 2H), 7.07 (d, J=8.4 Hz, 1H), 6.99 (d, J=7.8 Hz, 1H), 1.81 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.30, 157.15, 147.09, 146.92, 143.17, 135.45, 129.47, 125.21, 123.07, 117.76, 111.46, 105.66, 25.48. IR (KBr) 3142, 3101, 3001, 2938, 1730, 1596, 1571, 1468, 1383, 1324, 1280, 1239, 1205, 1109, 1049, 1008, 855, 805, 749, 786, 697 cm^{-1}. EIMS: m/z=299.17 (M^+). Anal. Calcd for ($C_{16}H_{13}NO_5$): C, 64.21; H, 4.38; N, 4.68. Found: C, 64.12; H, 4.30; N, 4.79.

*4.2.12. 5-([1,1′-Biphenyl]-4-yl)-2,2-dimethyl-4H-benzo[d][1,3] dioxin-4-one (**3l**).* White solid, 155 mg, 94% yield; mp: 198–199 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.65 (dd, J=11.4, 4.8 Hz, 4H), 7.55 (t, J=7.8 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.42 (d, J=8.4 Hz, 2H), 7.36 (t, J=7.2 Hz, 1H), 7.08–7.05 (m, 1H), 7.00–6.97 (m, 1H), 1.82 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.57, 157.17, 145.58, 140.72, 140.39, 139.05, 135.03, 129.05, 128.68, 127.25, 127.11, 126.69, 125.78, 116.39, 111.88, 105.27, 25.59. IR (KBr) 3074, 3050, 3026, 2993, 2937, 1733, 1596, 1580, 1470, 1383, 1324, 1300, 1277, 1202, 1102, 1049, 940, 764, 694 cm^{-1}. EIMS: m/z=330.17 (M^+). Anal. Calcd for ($C_{22}H_{18}O_3$): C, 79.98; H, 5.49. Found: C, 80.17; H, 5.37.

*4.2.13. 5-(4-Acetylphenyl)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (**3m**).* White solid, 136 mg, 91% yield; mp: 157–158 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 8.01 (d, J=8.4 Hz, 2H), 7.56 (t, J=7.8 Hz, 1H), 7.43 (d, J=8.4 Hz, 2H), 7.01 (dd, J=18.0, 7.8 Hz, 2H), 2.65 (s, 3H), 1.81 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.60, 159.26, 157.07, 144.98, 144.52, 135.93, 135.16, 128.75, 127.93, 125.35, 117.06, 111.65, 105.40, 26.57, 25.50. IR (KBr) 3079, 3047, 2999, 2945, 1734, 1676, 1598, 1585, 1395, 1326, 1273, 1240, 1204, 1045, 942, 808, 776, 696 cm^{-1}. EIMS: m/z=296.26 (M^+). Anal. Calcd for ($C_{18}H_{16}O_4$): C, 72.96; H, 5.44. Found: C, 72.80; H, 5.49.

*4.2.14. 4-(2,2-Dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)-benzaldehyde (**3n**).* Yellow solid, 130 mg, 92% yield; mp: 183–184 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.93 (d, J=7.8 Hz, 2H), 7.57 (t, J=7.8 Hz, 1H), 7.49 (d, J=7.8 Hz, 2H), 7.04 (d, J=8.4 Hz, 1H), 7.00 (d, J=7.8 Hz, 1H), 1.81 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.89, 159.26, 157.11, 146.41, 144.30, 135.28, 135.24, 129.28, 129.23, 125.32, 117.28, 111.64, 105.49, 25.52. IR (KBr) 3080, 3001, 2991, 2857, 1730, 1694, 1602, 1585, 1475, 1384, 1325, 1292, 1276, 1209, 1045, 839, 806, 785, 697 cm^{-1}. EIMS: m/z=282.26 (M^+). Anal. Calcd for ($C_{17}H_{14}O_4$): C, 72.33; H, 5.00. Found: C, 72.30; H, 5.15.

*4.2.15. 5-(4-Fluoro-3-methylphenyl)-2,2-dimethyl-4H-benzo[d][1,3]-dioxin-4-one (**3o**).* White solid, 134 mg, 94% yield; mp: 159–160 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.51 (t, J=7.8 Hz, 1H), 7.14 (d, J=7.2 Hz, 1H), 7.10 (s, 1H), 7.03 (t, J=9.0 Hz, 1H), 7.00–6.94 (m, 2H), 2.31 (s, 3H), 1.80 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.22, 159.78, 159.46, 157.09, 145.09, 135.76, 134.97, 131.54, 131.49, 127.62, 127.54, 125.72, 124.38, 124.20, 116.37, 114.62, 114.40, 111.85, 105.24, 25.56, 14.60. IR (KBr) 3087, 2991, 2942, 2923, 2864, 1736, 1722, 1598, 1580, 1503, 1472, 1328, 1276, 1241, 1224, 1199, 1180, 1102, 1049, 923, 809, 760, 698 cm^{-1}. EIMS: m/z=286.21 (M^+). Anal. Calcd for ($C_{17}H_{15}FO_3$): C, 71.32; H, 5.28. Found: C, 71.22; H, 5.34.

*4.2.16. 5-(3,5-Dichlorophenyl)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (**3p**).* Yellow solid, 157 mg, 97% yield; mp: 139–140 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.55 (t, J=7.8 Hz, 1H), 7.37 (d, J=1.8 Hz, 1H), 7.19 (d, J=1.8 Hz, 2H), 7.03 (d, J=8.4 Hz, 1H), 6.95 (d, J=7.8 Hz, 1H), 1.80 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.02, 157.04, 142.93, 142.70, 135.26, 134.18, 127.51, 127.02, 125.34, 117.48, 111.54, 105.52, 25.52. IR (KBr) 3085, 3058, 2991, 2934, 1734, 1583, 1562, 1383, 1325, 1280, 1239, 1198, 1130, 1051, 859, 795, 772, 696 cm^{-1}. EIMS: m/z=322.17 (M^+). Anal. Calcd for ($C_{16}H_{12}Cl_2O_3$): C, 59.46; H, 3.74. Found: C, 59.49; H, 3.67.

*4.2.17. 5-(3-Chloro-4-fluorophenyl)-2,2-dimethyl-4H-benzo[d][1,3]-dioxin-4-one (**3q**).* Yellow solid, 150 mg, 98% yield; mp: 154–155 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.54 (t, J=7.8 Hz, 1H), 7.38–7.33 (m, 1H), 7.20–7.13 (m, 2H), 7.01 (d, J=8.4 Hz, 1H), 6.96 (d, J=7.8 Hz, 1H), 1.79 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.32, 158.90, 157.15, 156.42, 143.37, 137.09, 135.23, 130.55, 128.58, 128.51, 125.60, 120.32, 117.14, 116.12, 115.91, 111.70, 105.47, 25.57. IR (KBr) 3077, 3060, 2988, 1726, 1599, 1577, 1503, 1471, 1324, 1279, 1261, 1239, 1200, 1103, 1051, 811, 697 cm^{-1}. EIMS: m/z=306.04 (M^+). Anal. Calcd for ($C_{16}H_{12}ClFO_3$): C, 62.65; H, 3.94. Found: C, 62.46; H, 3.98.

*4.2.18. 2,2-Dimethyl-5-(3,4,5-trimethoxyphenyl)-4H-benzo[d][1,3]-dioxin-4-one (**3r**).* Yellow solid, 160 mg, 93% yield; mp: 156–157 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.52 (t, J=7.8 Hz, 1H), 7.03 (d, J=7.8 Hz, 1H), 6.98 (d, J=8.4 Hz, 1H), 6.52 (s, 2H), 3.91 (s, 3H), 3.87 (s, 6H), 1.80 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.18, 157.00, 152.58, 145.77, 137.52, 135.67, 134.88, 125.69, 116.39, 111.70, 105.95, 105.14, 60.78,

55.97, 25.53. IR (KBr) 3082, 3023, 2993, 2966, 2942, 1740, 1580, 1474, 1448, 1411, 1314, 1277, 1253, 1115, 1046, 1006, 828, 814 cm^{-1}. EIMS: m/z=344.17 (M^+). Anal. Calcd for ($C_{19}H_{20}O_6$): C, 66.27; H, 5.85. Found: C, 66.35; H, 5.80.

*4.2.19. 5-(Furan-2-yl)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (**3s**).* White solid, 105 mg, 86% yield; mp: 103–104 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.55–7.50 (m, 2H), 7.32 (d, J=7.8 Hz, 1H), 6.94 (d, J=8.4 Hz, 1H), 6.82 (d, J=3.0 Hz, 1H), 6.52 (dd, J=3.0, 1.8 Hz, 1H), 1.78 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.02, 157.05, 151.22, 142.89, 135.08, 133.35, 123.73, 116.63, 111.45, 111.00, 110.37, 105.17, 25.35. IR (KBr) 3090, 3001, 2985, 1726, 1600, 1584, 1381, 1326, 1207, 1177, 1109, 1054, 944, 846, 812, 699 cm^{-1}. EIMS: m/z=244.24 (M^+). Anal. Calcd for ($C_{14}H_{12}O_4$): C, 68.85; H, 4.95. Found: C, 69.02; H, 5.05.

*4.2.20. 2,2-Dimethyl-5-(thiophen-2-yl)-4H-benzo[d][1,3]dioxin-4-one (**3t**).* Yellow solid, 79 mg, 60% yield; mp: 130–131 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.49 (t, J=7.8 Hz, 1H), 7.40 (d, J=4.8 Hz, 1H), 7.14 (d, J=7.2 Hz, 2H), 7.10–7.06 (m, 1H), 6.97 (d, J=8.4 Hz, 1H), 1.78 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.03, 157.15, 140.65, 137.88, 134.88, 127.22, 126.98, 126.49, 126.26, 116.89, 112.19, 105.17, 25.45. IR (KBr) 3101, 3066, 3001, 2940, 1728, 1581, 1472, 1382, 1316, 1274, 1232, 1205, 1089, 1046, 939, 844, 808, 784, 706, 698 cm^{-1}. EIMS: m/z=260.09 (M^+). Anal. Calcd for ($C_{14}H_{12}O_3S$): C, 64.60; H, 4.65; S, 12.32. Found: C, 64.57; H, 4.71; S, 12.41.

*4.2.21. 5-(Benzofuran-2-yl)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (**3u**).* Yellow solid, 128 mg, 87% yield; mp: 146–147 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, J=7.8 Hz, 1H), 7.58 (t, J=7.8 Hz, 1H), 7.51 (d, J=8.4 Hz, 1H), 7.45 (d, J=7.8 Hz, 1H), 7.34–7.28 (m, 1H), 7.24 (t, J=7.8 Hz, 1H), 7.13 (s, 1H), 7.03 (d, J=7.8 Hz, 1H), 1.82 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.82, 157.14, 155.03, 153.52, 135.18, 133.15, 128.69, 124.81, 124.65, 122.73, 121.31, 117.76, 111.76, 111.16, 106.50, 105.41, 25.41. IR (KBr) 3082, 3060, 3034, 3015, 2991, 2937, 1735, 1572, 1471, 1282, 1201, 1045, 802, 780, 755, 694 cm^{-1}. EIMS: m/z=294.14 (M^+). Anal. Calcd for ($C_{18}H_{14}O_4$): C, 73.46; H, 4.79. Found: C, 73.33; H, 4.76.

*4.2.22. 5-(Dibenzo[b,d]furan-4-yl)-2,2-dimethyl-4H-benzo[d][1,3]-dioxin-4-one (**3v**).* White solid, 169 mg, 98% yield; mp: 210–211 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 8.00–7.93 (m, 2H), 7.65–7.60 (m, 1H), 7.49 (dd, J=7.2 1.3 Hz, 1H), 7.44 (t, J=7.8 Hz, 1H), 7.39 (dt, J=9.0, 4.2 Hz, 2H), 7.34–7.30 (m, 1H), 7.19 (dd, J=7.8, 1.2 Hz, 1H), 7.07 (dd, J=8.4, 1.2 Hz, 1H), 1.91 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.55, 156.74, 155.87, 153.41, 139.15, 135.19, 126.89, 126.32, 125.71, 124.82, 124.25, 123.83, 122.97, 122.67, 120.74, 120.45, 116.90, 113.53, 111.35, 105.44. IR (KBr) 3081, 3002, 2944, 1734, 1590, 1469, 1450, 1410, 1323, 1277, 1194, 1043, 912, 843, 810, 795, 756, 695 cm^{-1}. EIMS: m/z=344.15 (M^+). Anal. Calcd for ($C_{22}H_{16}O_4$): C, 76.73; H, 4.68. Found: C, 76.65; H, 4.63.

*4.2.23. 2,2-Dimethyl-5-(naphthalen-2-yl)-4H-benzo[d][1,3]dioxin-4-one (**3w**).* Yellow solid, 150 mg, 98% yield; mp: 175–176 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.86 (dt, J=15.6, 6.0 Hz, 3H), 7.82 (s, 1H), 7.56 (t, J=7.8 Hz, 1H), 7.49 (dd, J=6.0, 3.0 Hz, 2H), 7.43 (dd, J=8.4, 1.5 Hz, 1H), 7.11 (d, J=7.8 Hz, 1H), 7.01 (d, J=8.4 Hz, 1H), 1.83 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.46, 157.07, 145.76, 137.77, 135.05, 133.13, 132.63, 128.08, 127.61, 127.33, 127.02, 126.79, 125.98, 116.41, 111.85, 105.23, 25.52. IR (KBr) 3077, 3052, 2993, 1735, 1721, 1597, 1578, 1483, 1460, 1391, 1318, 1273, 1244, 1199, 1095, 1044, 936, 824, 805, 752, 699 cm^{-1}. EIMS: m/z=304.14 (M^+). Anal. Calcd for ($C_{20}H_{16}O_3$): C, 78.93; H, 5.30. Found: C, 78.82; H, 5.44.

*4.2.24. (E)-2,2-Dimethyl-5-styryl-4H-benzo[d][1,3]dioxin-4-one (**3x**).* White solid, 136 mg, 97% yield; mp: 104–105 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 8.27 (d, J=16.2 Hz, 1H), 7.59 (d, J=7.8 Hz, 2H), 7.50 (t, J=7.8 Hz, 1H), 7.43 (d, J=7.8 Hz, 1H), 7.38 (t, J=7.8 Hz, 2H), 7.30 (d, J=7.2 Hz, 1H), 7.09 (d, J=16.2 Hz, 1H), 6.89 (d, J=8.4 Hz, 1H), 1.74 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.37, 156.82, 141.76, 136.95, 135.11, 132.64, 128.56, 128.06, 127.04, 126.63, 120.90, 116.08, 110.83, 105.13, 25.54. IR (KBr) 3082, 3058, 3039, 3023, 2993, 1722, 1595, 1577, 1472, 1451, 1392, 1321, 1288, 1272, 1249, 1078, 1048, 961, 925, 802, 752, 694 cm^{-1}. EIMS: m/z=280.11 (M^+). Anal. Calcd for ($C_{18}H_{16}O_3$): C, 77.12; H, 5.75. Found: C, 77.03; H, 5.66.

*4.2.25. (E)-2,2-Dimethyl-5-(pent-1-en-1-yl)-4H-benzo[d][1,3]dioxin-4-one (**3y**).* Yellow oil, 122 mg, 99% yield. ^1H NMR (600 MHz, $CDCl_3$) δ 7.50–7.37 (m, 2H), 7.24 (d, J=7.8 Hz, 1H), 6.82 (d, J=8.4 Hz, 1H), 6.30–6.18 (m, 1H), 2.26 (q, J=7.2 Hz, 2H), 1.71 (s, 6H), 1.53 (dd, J=15.0, 7.2 Hz, 2H), 0.97 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.34, 156.67, 142.56, 135.42, 134.96, 128.07, 121.18, 115.39, 110.46, 105.00, 35.17, 25.57, 22.30, 13.71. IR (neat) 3083, 2962, 2875, 1736, 1686, 1672, 1595, 1476, 1391, 1321, 1216, 1165, 1118, 1079, 1050, 982, 963, 922, 849 cm^{-1}. EIMS: m/z=246.08 (M^+). Anal. Calcd for ($C_{15}H_{18}O_3$): C, 73.15; H, 7.37. Found: C, 73.22; H, 7.42.

4.3. General procedure for the synthesis of compounds 4a–y

To a stirred solution of **3a** (254 mg, 1 mmol) in MeOH (10 ml) was added K_2CO_3 (152 mg, 1.1 mmol) at room temperature. The resulting mixture was stirred at 40–50 °C for 4–10 h and then allowed to cool to room temperature. The solvent was evaporated in vacuo. The mixture was quenched with saturated aqueous NH_4Cl and 1 N aqueous HCl, and extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by flash column chromatography (hexane/acetone=5/1) gave **4a** (212 mg, 0.93 mmol) in 93% yield.

*4.3.1. Methyl 3-hydroxy-[1,1′-biphenyl]-2-carboxylate (**4a**).* Colorless oil, 212 mg, 93% yield. ^1H NMR (600 MHz, $CDCl_3$) δ 10.64 (s, 1H), 7.42 (t, J=8.4 Hz, 1H), 7.36 (t, J=7.2 Hz, 2H), 7.33 (d, J=7.2 Hz, 1H), 7.23 (d, J=7.2 Hz, 2H), 7.01 (d, J=8.4 Hz, 1H), 6.81 (d, J=7.2 Hz, 1H), 3.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.29, 161.25, 144.78, 142.59, 133.61, 128.03, 127.56, 126.79, 122.53, 116.57, 112.06, 51.65. IR (KBr) 3060, 3023, 2952, 2848, 1667, 1602, 1572, 1439, 1344, 1270, 1220, 1172, 898, 816 cm^{-1}. EIMS: m/z=228.38 (M^+). Anal. Calcd for ($C_{14}H_{12}O_3$): C, 73.67; H, 5.30. Found: C, 73.55; H, 5.40.

*4.3.2. Methyl 4′-chloro-3-hydroxy-[1,1′-biphenyl]-2-carboxylate (**4b**).* Yellow oil, 225 mg, 86% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 10.73 (s, 1H), 7.40 (t, J=8.0 Hz, 1H), 7.36–7.30 (m, 2H), 7.18–7.12 (m, 2H), 7.04–6.99 (m, 1H), 6.75 (dd, J=7.6, 0.8 Hz, 1H), 3.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.05, 161.54, 143.45, 141.14, 133.79, 132.81, 129.40, 127.74, 122.47, 117.06, 111.75, 51.79. IR (neat) 3170, 3082, 3007, 2950, 2851, 1664, 1603, 1578, 1494, 1448, 1436, 1337, 1278, 1212, 1173, 1125, 1082, 1100, 1069, 898, 840, 811, 709, 688 cm^{-1}. EIMS: m/z=262.13 (M^+). Anal. Calcd for ($C_{14}H_{11}ClO_3$): C, 64.01; H, 4.22. Found: C, 64.21; H, 4.21.

*4.3.3. Methyl 3′-chloro-3-hydroxy-[1,1′-biphenyl]-2-carboxylate (**4c**).* Yellow oil, 249 mg, 95% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 10.75 (s, 1H), 7.41 (t, J=8.0 Hz, 1H), 7.28 (dt, J=10.0, 2.0 Hz, 2H), 7.24 (s, 1H), 7.09 (dt, J=6.8, 2.0 Hz, 1H), 7.02 (d, J=8.4 Hz, 1H), 6.76 (d, J=7.6 Hz, 1H), 3.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.97, 161.56, 144.38, 143.17, 133.82, 133.38, 128.76, 128.11, 126.88, 126.39, 122.39, 117.24, 111.69, 51.81. IR (neat) 3062, 3004, 2953, 2854, 1736, 1671, 1596, 1576, 1563, 1448, 1409, 1342, 1276, 1255, 1220, 1173, 1125, 1106, 1079, 1066, 965, 921, 882, 837, 817 cm^{-1}. EIMS: m/z=262.10 (M^+). Anal. Calcd for ($C_{14}H_{11}ClO_3$): C, 64.01; H, 4.22. Found: C, 64.06; H, 4.12.

*4.3.4. Methyl 2′-chloro-3-hydroxy-[1,1′-biphenyl]-2-carboxylate (**4d**).* Yellow oil, 249 mg, 95% yield. ^1H NMR (600 MHz, $CDCl_3$) δ 11.11 (s, 1H), 7.46 (t, J=7.8 Hz, 1H), 7.39 (d, J=8.4 Hz, 1H), 7.31–7.24 (m, 2H), 7.21 (dd, J=6.6, 1.8 Hz, 1H), 7.06 (d, J=8.4 Hz, 1H), 6.71 (d,

J=7.2 Hz, 1H), 3.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.82, 161.68, 141.48, 141.44, 134.07, 132.42, 129.67, 128.50, 128.15, 126.24, 122.36, 117.49, 112.04, 51.97. IR (neat) 3060, 3004, 2952, 2848, 1668, 1604, 1576, 1443, 1343, 1282, 1219, 1173, 1105, 1049, 902, 817, 758, 710, 695 cm^{-1}. EIMS: *m*/*z*=262.12 (M^+). Anal. Calcd for ($C_{14}H_{11}ClO_3$): C, 64.01; H, 4.22. Found: C, 63.90; H, 4.34.

*4.3.5. Methyl 4′-bromo-3-hydroxy-[1,1′-biphenyl]-2-carboxylate (**4e**).* Yellow oil, 295 mg, 96% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.73 (s, 1H), 7.49 (d, *J*=8.4 Hz, 2H), 7.41 (t, *J*=7.8 Hz, 1H), 7.10 (d, *J*=8.4 Hz, 2H), 7.02 (d, *J*=7.8 Hz, 1H), 6.75 (d, *J*=7.2 Hz, 1H), 3.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.97, 161.52, 143.39, 141.58, 133.76, 130.64, 129.71, 122.36, 120.91, 117.05, 111.64, 51.77. IR (neat) 3154, 3079, 3050, 2996, 2950, 2846, 1663, 1601, 1576, 1495, 1446, 1391, 1337, 1276, 1213, 1174, 1124, 1095, 1066, 1007, 963, 897, 838, 810, 790, 709, 671 cm^{-1}. EIMS: *m*/*z*=307.11 (M^+). Anal. Calcd for ($C_{14}H_{11}BrO_3$): C, 54.75; H, 3.61. Found: C, 54.83; H, 3.53.

*4.3.6. Methyl 4′-fluoro-3-hydroxy-[1,1′-biphenyl]-2-carboxylate (**4f**).* Yellow oil, 234 mg, 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 7.44–7.33 (m, 1H), 7.23–7.10 (m, 2H), 7.08–7.02 (m, 2H), 7.02–6.98 (m, 1H), 6.79–6.73 (m, 1H), 3.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.14, 163.15, 161.46, 160.72, 143.66, 138.63, 133.68, 129.63, 129.55, 122.57, 116.84, 114.57, 114.35, 111.97, 51.73. IR (neat) 3066, 3044, 3007, 2954, 1736, 1669, 1606, 1574, 1512, 1447, 1343, 1310, 1282, 1221, 1173, 1160, 1123, 1094, 901, 842, 813 cm^{-1}. EIMS: *m*/*z*=246.12 (M^+). Anal. Calcd for ($C_{14}H_{11}FO_3$): C, 68.29; H, 4.50. Found: C, 68.02; H, 4.57.

*4.3.7. Methyl 3-hydroxy-4′-methyl-[1,1′-biphenyl]-2-carboxylate (**4g**).* Yellow oil, 218 mg, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (s, 1H), 7.38 (dd, *J*=12.0, 4.4 Hz, 1H), 7.14 (dd, *J*=18.8, 8.0 Hz, 4H), 7.02–6.92 (m, 1H), 6.84–6.72 (m, 1H), 3.50 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.40, 161.14, 144.79, 139.63, 136.44, 133.56, 128.30, 127.96, 122.63, 116.33, 112.14, 51.66, 21.14. IR (neat) 3047, 3024, 2993, 2952, 2922, 1667, 1602, 1576, 1446, 1343, 1281, 1264, 1172, 1123, 900, 809 cm^{-1}. EIMS: *m*/*z*=242.18 (M^+). Anal. Calcd for ($C_{15}H_{14}O_3$): C, 74.36; H, 5.82. Found: C, 74.23; H, 5.79.

*4.3.8. Methyl 3-hydroxy-4′-methoxy-[1,1′-biphenyl]-2-carboxylate (**4h**).* Yellow oil, 252 mg, 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.56 (s, 1H), 7.38 (t, *J*=8.0 Hz, 1H), 7.19–7.13 (m, 2H), 6.97 (d, *J*=8.4 Hz, 1H), 6.90 (t, *J*=5.6 Hz, 2H), 6.79 (d, *J*=7.6 Hz, 1H), 3.84 (s, 3H), 3.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.43, 161.14, 158.62, 144.39, 134.98, 133.53, 129.18, 122.63, 116.20, 113.02, 112.16, 55.20, 51.74. IR (neat) 3375, 3042, 3008, 2957, 2931, 2835, 1687, 1598, 1567, 1513, 1447, 1431, 1291, 1240, 1197, 1175, 1162, 1109, 1088, 1028, 1067, 897, 842, 807, 710, 639 cm^{-1}. EIMS: *m*/*z*=258.18 (M^+). Anal. Calcd for ($C_{15}H_{14}O_4$): C, 69.76; H, 5.46. Found: C, 69.59; H, 5.38.

*4.3.9. Methyl 4′-(tert-butyl)-3-hydroxy-[1,1′-biphenyl]-2-carboxylate (**4i**).* Yellow oil, 273 mg, 96% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.55 (s, 1H), 7.39 (dd, *J*=15.6, 7.8 Hz, 3H), 7.16 (d, *J*=8.4 Hz, 2H), 6.99 (d, *J*=8.4 Hz, 1H), 6.83 (d, *J*=7.8 Hz, 1H), 3.48 (s, 3H), 1.36 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.40, 161.12, 149.74, 144.78, 139.54, 133.53, 127.75, 124.41, 122.51, 116.30, 112.22, 51.59, 34.46, 31.33. IR (neat) 3409, 3074, 3034, 2962, 2867, 1681, 1603, 1575, 1442, 1329, 1267, 1202, 1163, 1120, 1091, 1063, 902, 840, 808, 713, 593 cm^{-1}. EIMS: *m*/*z*=284.20 (M^+). Anal. Calcd for ($C_{18}H_{20}O_3$): C, 76.03; H, 7.09. Found: C, 76.09; H, 6.99.

*4.3.10. Methyl 3-hydroxy-4′-(trifluoromethyl)-[1,1′-biphenyl]-2-carboxylate (**4j**).* Yellow oil, 281 mg, 95% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.81 (s, 1H), 7.63 (d, *J*=7.8 Hz, 2H), 7.44 (t, *J*=7.8 Hz, 1H), 7.35 (d, *J*=7.8 Hz, 2H), 7.06 (d, *J*=8.4 Hz, 1H), 6.76 (d, *J*=7.2 Hz, 1H), 3.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.83, 161.73, 146.43, 143.24, 136.06, 133.88, 132.33, 129.12, 128.41, 124.44, 122.32, 118.97, 117.47, 114.41, 111.58, 109.71, 51.72, 51.59. IR (neat) 3071, 3052, 3012, 2961, 1671, 1617, 1603, 1574, 1449, 1325, 1275, 1216, 1167, 1112, 1064, 1017, 851, 814, 712, 664, 607 cm^{-1}. EIMS: *m*/*z*=296.13 (M^+). Anal. Calcd for ($C_{15}H_{11}F_3O_3$): C, 60.82; H, 3.74. Found: C, 60.72; H, 3.72.

*4.3.11. Methyl 3-hydroxy-4′-nitro-[1,1′-biphenyl]-2-carboxylate (**4k**).* Yellow solid, 267 mg, 97% yield; mp: 130–131 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.88 (s, 1H), 8.25 (d, *J*=8.4 Hz, 2H), 7.47 (t, *J*=7.8 Hz, 1H), 7.40 (d, *J*=8.4 Hz, 2H), 7.09 (d, *J*=8.4 Hz, 1H), 6.76 (d, *J*=7.2 Hz, 1H), 3.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.43, 161.81, 149.53, 146.66, 142.20, 133.99, 128.93, 122.77, 122.06, 117.95, 111.17, 51.84. IR (KBr) 3101, 2964, 2923, 2846, 1664, 1596, 1573, 1518, 1441, 1346, 1276, 1212, 1173, 1124, 1107, 1064, 852, 818, 755, 713, 697 cm^{-1}. EIMS: *m*/*z*=273.13 (M^+). Anal. Calcd for ($C_{14}H_{11}NO_5$): C, 61.54; H, 4.06; N, 5.13. Found: C, 61.58; H, 3.97; N, 5.21.

*4.3.12. Methyl 3-hydroxy-[1,1′:4′,1″-terphenyl]-2-carboxylate (**4l**).* Yellow solid, 267 mg, 88% yield; mp: 96–97 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.65 (s, 1H), 7.66 (d, *J*=7.8 Hz, 2H), 7.62 (d, *J*=8.4 Hz, 2H), 7.47 (t, *J*=7.8 Hz, 2H), 7.43 (t, *J*=7.8 Hz, 1H), 7.37 (t, *J*=7.2 Hz, 1H), 7.31 (d, *J*=8.4 Hz, 2H), 7.02 (d, *J*=8.4 Hz, 1H), 6.86 (d, *J*=7.8 Hz, 1H), 3.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.26, 161.31, 144.32, 141.56, 140.52, 139.47, 133.65, 128.75, 128.53, 127.28, 126.87, 126.17, 122.52, 116.65, 111.97, 51.66. IR (KBr) 3401, 3063, 3026, 2948, 1663, 1599, 1570, 1441, 1348, 1274, 1222, 1176, 1119, 1066, 848, 815, 767, 711, 698 cm^{-1}. EIMS: *m*/*z*=304.23 (M^+). Anal. Calcd for ($C_{20}H_{16}O_3$): C, 78.93; H, 5.30. Found: C, 78.82; H, 5.21.

*4.3.13. Methyl 4′-acetyl-3-hydroxy-[1,1′-biphenyl]-2-carboxylate (**4m**).* Yellow solid, 262 mg, 97% yield; mp: 98–99 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.77 (s, 1H), 7.97 (d, *J*=8.4 Hz, 2H), 7.44 (t, *J*=7.8 Hz, 1H), 7.33 (d, *J*=8.4 Hz, 2H), 7.05 (d, *J*=7.8 Hz, 1H), 6.78 (d, *J*=7.2 Hz, 1H), 3.49 (s, 3H), 2.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.71, 170.74, 161.45, 147.58, 143.41, 135.39, 133.75, 128.26, 127.62, 122.15, 117.28, 111.53, 51.70, 26.53. IR (KBr) 3342, 3189, 3015, 2953, 1680, 1600, 1573, 1446, 1355, 1267, 1215, 1170, 1123, 957, 842, 812, 709, 686 cm^{-1}. EIMS: *m*/*z*=270.19 (M^+). Anal. Calcd for ($C_{16}H_{14}O_4$): C, 71.10; H, 5.22. Found: C, 71.12; H, 5.14.

*4.3.14. Methyl 4′-formyl-3-hydroxy-[1,1′-biphenyl]-2-carboxylate (**4n**).* Yellow solid, 77 mg, 30% yield; mp: 101–102 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.80 (s, 1H), 10.07 (s, 1H), 7.90 (d, *J*=8.4 Hz, 2H), 7.45 (t, *J*=7.8 Hz, 1H), 7.40 (d, *J*=7.8 Hz, 2H), 7.07 (d, *J*=8.4 Hz, 1H), 6.78 (d, *J*=6.6 Hz, 1H), 3.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.93, 170.71, 161.64, 149.09, 143.27, 134.82, 133.89, 129.03, 128.77, 122.14, 117.56, 111.44, 51.76. IR (KBr) 3439, 2961, 2832, 2733, 1698, 1672, 1599, 1573, 1446, 1307, 1275, 1213, 1170, 1122, 1095, 838, 809, 709 cm^{-1}. EIMS: *m*/*z*=256.16 (M^+). Anal. Calcd for ($C_{15}H_{12}O_4$): C, 70.31; H, 4.72. Found: C, 70.22; H, 4.84.4.

*4.3.15. Methyl 4′-fluoro-3-hydroxy-3′-methyl-[1,1′-biphenyl]-2-carboxylate (**4o**).* Yellow oil, 254 mg, 97% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.62 (s, 1H), 7.40 (t, *J*=7.8 Hz, 1H), 7.05 (d, *J*=7.2 Hz, 1H), 7.03–6.96 (m, 3H), 6.77 (dd, *J*=7.8, 1.2 Hz, 1H), 3.53 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.21, 161.68, 161.27, 159.26, 143.85, 138.24, 133.58, 130.94, 127.01, 126.93, 123.96, 123.79, 122.54, 116.62, 114.17, 113.95, 112.02, 51.68, 14.43. IR (neat) 3046, 3001, 2954, 2923, 1737, 1667, 1604, 1574, 1504, 1446, 1344, 1287, 1233, 1180, 1121, 1094, 1065, 942, 852, 813 cm^{-1}. EIMS: *m*/*z*=260.17 (M^+). Anal. Calcd for ($C_{15}H_{13}FO_3$): C, 69.22; H, 5.03. Found: C, 69.03; H, 5.13.

*4.3.16. Methyl 3′,5′-dichloro-3-hydroxy-[1,1′-biphenyl]-2-carboxylate (**4p**).* Yellow solid, 291 mg, 98% yield; mp: 65–66 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.85 (s, 1H), 7.43 (t, *J*=7.8 Hz, 1H), 7.34 (s, 1H), 7.13 (s, 2H), 7.05 (d, *J*=8.4 Hz, 1H), 6.74 (d, *J*=7.2 Hz, 1H), 3.58 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.58, 161.78, 145.44, 141.66, 133.93, 131.97, 126.80, 126.63, 122.16, 117.82, 111.36, 51.94. IR (KBr) 3077, 2991, 2948, 2899, 2843, 1662, 1595, 1579, 1557, 1441, 1407, 1337, 1273, 1219, 1176, 1117, 1098, 1060, 848, 816, 795, 709, 685 cm^{-1}. EIMS: m/z=297.16 (M^+). Anal. Calcd for ($C_{14}H_{10}Cl_2O_3$): C, 56.59; H, 3.39. Found: C, 56.62; H, 3.26.

*4.3.17. Methyl 3′-chloro-4′-fluoro-3-hydroxy-[1,1′-biphenyl]-2-carboxylate (**4q**).* Yellow solid, 241 mg, 86% yield; mp: 64–65 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.80 (s, 1H), 7.42 (t, J=7.8 Hz, 1H), 7.30–7.27 (m, 1H), 7.13 (t, J=8.4 Hz, 1H), 7.11–7.06 (m, 1H), 7.04 (d, J=8.4 Hz, 1H), 6.75 (d, J=7.2 Hz, 1H), 3.56 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.80, 161.66, 158.33, 155.87, 142.19, 139.65, 133.82, 130.03, 127.94, 127.86, 122.44, 119.87, 117.40, 115.70, 115.49, 112.36, 111.61, 51.86. IR (KBr) 3082, 3060, 3045, 2957, 1665, 1605, 1578, 1505, 1448, 1350, 1283, 1262, 1234, 1218, 1177, 1124, 1100, 1060, 816, 733 cm^{-1}. EIMS: m/z=280.13 (M^+). Anal. Calcd for ($C_{14}H_{10}ClFO_3$): C, 59.91; H, 3.59. Found: C, 59.79; H, 3.68.

*4.3.18. Methyl 3-hydroxy-3′,4′,5′-trimethoxy-[1,1′-biphenyl]-2-carboxylate (**4r**).* Yellow solid, 295 mg, 93% yield; mp: 103–104 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.52 (s, 1H), 7.41 (t, J=7.8 Hz, 1H), 7.01 (d, J=8.4 Hz, 1H), 6.84 (d, J=7.2 Hz, 1H), 6.45 (s, 2H), 3.90 (s, 3H), 3.85 (s, 6H), 3.56 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.97, 160.67, 152.34, 144.23, 138.04, 136.74, 133.25, 122.01, 116.35, 112.21, 105.22, 60.65, 55.87, 51.66. IR (KBr) 3427, 3045, 2968, 2946, 2842, 2831, 1660, 1587, 1507, 1468, 1442, 1417, 1351, 1259, 1244, 1209, 1121, 1005, 844, 817, 748, 720, 669 cm^{-1}. EIMS: m/z=318.24 (M^+). Anal. Calcd for ($C_{17}H_{18}O_6$): C, 64.14; H, 5.70. Found: C, 64.21; H, 5.73.

*4.3.19. Methyl 2-(furan-2-yl)-6-hydroxybenzoate (**4s**).* Yellow solid, 207 mg, 95% yield; mp: 117–118 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.24 (s, 1H), 7.47 (s, 1H), 7.41 (t, J=7.8 Hz, 1H), 7.00 (dd, J=13.2, 7.8 Hz, 2H), 6.47 (d, J=3.0 Hz, 1H), 6.43 (d, J=3.0 Hz, 1H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.68, 160.46, 153.62, 142.24, 133.56, 132.47, 121.57, 117.53, 111.97, 111.12, 107.27, 52.38. IR (KBr) 3334, 3146, 3071, 3028, 3004, 2950, 2843, 1704, 1605, 1588, 1572, 1502, 1451, 1439, 1336, 1305, 1277, 1248, 1170, 1124, 1107, 1067, 1032, 943, 886, 868, 792, 751, 738, 764, 642 cm^{-1}. EIMS: m/z=218.10 (M^+). Anal. Calcd for ($C_{12}H_{10}O_4$): C, 66.05; H, 4.62. Found: C, 66.14; H, 4.64.

*4.3.20. Methyl 2-hydroxy-6-(thiophen-2-yl)benzoate (**4t**).* Yellow oil, 227 mg, 97% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.48 (s, 1H), 7.39 (s, 1H), 7.32 (d, J=5.4 Hz, 1H), 7.02 (dd, J=8.4, 4.2 Hz, 2H), 6.93 (dd, J=14.4, 5.4 Hz, 2H), 3.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.92, 160.98, 143.33, 136.51, 133.40, 126.55, 125.79, 125.19, 123.54, 117.41, 113.01, 51.99. IR (neat) 3371, 3105, 3012, 2957, 2923, 2849, 1699, 1579, 1464, 1435, 1326, 1291, 1225, 1163, 1121, 1089, 1067, 1032, 794, 767, 712 cm^{-1}. EIMS: m/z=234.08 (M^+). Anal. Calcd for ($C_{12}H_{10}O_3S$): C, 61.52; H, 4.30; S, 13.69. Found: C, 61.45; H, 4.43; S, 13.66.

*4.3.21. Methyl 2-(benzofuran-2-yl)-6-hydroxybenzoate (**4u**).* Yellow solid, 257 mg, 96% yield; mp: 69–70 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.62 (d, J=7.8 Hz, 1H), 7.50–7.44 (m, 2H), 7.30 (t, J=7.2 Hz, 1H), 7.28–7.23 (m, 1H), 7.10 (dd, J=12.0, 7.8 Hz, 2H), 6.81 (s, 1H), 3.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.56, 160.90, 156.20, 155.02, 133.81, 132.23, 128.73, 124.25, 122.79, 122.45, 121.01, 118.63, 112.18, 110.82, 103.86, 52.45. IR (KBr) 3434, 3068, 3028, 3001, 2950, 1679, 1571, 1451, 1431, 1338, 1279, 1221, 1202, 1160, 1118, 1106, 814, 799, 745, 705 cm^{-1}. EIMS: m/z=268.13 (M^+). Anal. Calcd for ($C_{16}H_{12}O_4$): C, 71.64; H, 4.51. Found: C, 71.56; H, 4.42.

*4.3.22. Methyl 2-(dibenzo[b,d]furan-4-yl)-6-hydroxybenzoate (**4v**).* Yellow solid, 296 mg, 93% yield; mp: 105–106 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.88 (s, 1H), 7.97 (d, J=7.8 Hz, 1H), 7.96–7.90 (m, 1H), 7.51 (dd, J=12.0, 6.6 Hz, 2H), 7.43 (t, J=7.8 Hz, 1H), 7.39 (d, J=3.0 Hz, 2H), 7.35 (t, J=7.2 Hz, 1H), 7.11 (d, J=8.4 Hz, 1H), 6.98 (d, J=7.2 Hz, 1H), 3.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.15, 161.52, 155.98, 153.27, 138.43, 134.16, 127.12, 127.02, 126.73, 124.06, 123.46, 123.09, 122.76, 122.68, 120.61, 119.63, 117.54, 112.71, 111.64, 51.73. IR (KBr) 3439, 3221, 3063, 3039, 2996, 2950, 2848, 1669, 1600, 1570, 1448, 1407, 1342, 1307, 1262, 1221, 1188, 1117, 1103, 1063, 929, 816, 762, 744, 706 cm^{-1}. EIMS: m/z=318.23 (M^+). Anal. Calcd for ($C_{20}H_{14}O_4$): C, 75.46; H, 4.43. Found: C, 75.62; H, 4.30.

*4.3.23. Methyl 2-hydroxy-6-(naphthalen-2-yl)benzoate (**4w**).* Yellow oil, 272 mg, 98% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.74 (s, 1H), 7.90–7.84 (m, 2H), 7.81 (d, J=8.4 Hz, 1H), 7.73 (s, 1H), 7.53–7.49 (m, 2H), 7.47–7.43 (m, 1H), 7.34 (dd, J=8.4, 1.8 Hz, 1H), 7.05 (dd, J=8.4, 1.2 Hz, 1H), 6.90 (dd, J=7.2, 0.6 Hz, 1H), 3.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.21, 161.38, 144.57, 140.16, 133.67, 133.00, 132.15, 128.54, 127.86, 127.50, 127.14, 126.62, 126.04, 125.76, 122.88, 116.69, 111.97, 51.57. IR (neat) 3047, 3020, 2953, 1666, 1598, 1571, 1446, 1338, 1277, 1238, 1213, 1191, 1171, 1119, 1084, 1065, 909, 863, 813, 748, 713 cm^{-1}. EIMS: m/z=278.16 (M^+). Anal. Calcd for ($C_{18}H_{14}O_3$): C, 77.68; H, 5.07. Found: C, 77.58; H, 5.17.

*4.3.24. (E)-Methyl 2-hydroxy-6-styrylbenzoate (**4x**).* Yellow oil, 238 mg, 93% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.20 (s, 1H), 7.70 (d, J=16.2 Hz, 1H), 7.50 (d, J=7.8 Hz, 2H), 7.39 (dt, J=15.6, 7.8 Hz, 3H), 7.30 (d, J=7.2 Hz, 1H), 7.09 (d, J=7.8 Hz, 1H), 6.95 (d, J=8.4 Hz, 1H), 6.83 (d, J=16.2 Hz, 1H), 3.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.51, 162.26, 141.00, 137.35, 134.34, 130.81, 129.50, 128.65, 127.71, 126.53, 119.55, 116.91, 110.74, 52.43. IR (neat) 3436, 3085, 3055, 3023, 3007, 2948, 1664, 1594, 1569, 1448, 1434, 1332, 1315, 1258, 1214, 1199, 1170, 1113, 1064, 997, 966, 804, 757, 727, 702 cm^{-1}. EIMS: m/z=254.16 (M^+). Anal. Calcd for ($C_{16}H_{14}O_3$): C, 75.57; H, 5.55. Found: C, 75.55; H, 5.45.

*4.3.25. (E)-Methyl2-hydroxy-6-(pent-1-en-1-yl)benzoate (**4y**).* Yellow oil, 198 mg, 90% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.11 (s, 1H), 7.33 (t, J=7.8 Hz, 1H), 6.94–6.86 (m, 3H), 6.05–5.79 (m, 1H), 3.95 (s, 3H), 2.20 (d, J=7.2 Hz, 2H), 1.51 (dd, J=14.4, 7.2 Hz, 2H), 0.97 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.57, 161.94, 141.72, 134.02, 132.70, 130.80, 119.69, 116.00, 110.40, 51.93, 34.90, 22.14, 13.47. IR (neat) 3054, 2999, 2957, 2923, 2872, 1733, 1664, 1602, 1572, 1448, 1344, 1275, 1256, 1216, 1168, 1118, 1068, 966, 948, 823, 808 cm^{-1}. EIMS: m/z=220.20 (M^+). Anal. Calcd for ($C_{13}H_{16}O_3$): C, 70.89; H, 7.32. Found: C, 70.91; H, 7.29.

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