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BF_3·Etherate-Mediated Friedel–Crafts Arylation of 2-Hydroxy-1,4-benzoxazines: Synthesis of 2-Aryl-1,4-benzoxazine Derivatives

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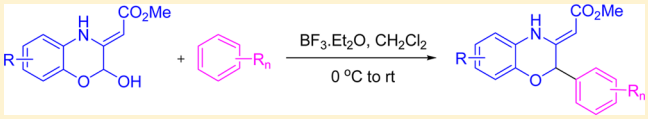
Supporting Information

ABSTRACT: BF_3·etherate-mediated carbon–carbon bond formation by the Friedel–Crafts arylation of 2-hydroxybenzoxazine derivatives with various electron-rich arenes is reported. The current protocol provides an easy access for the synthesis of a series of densely substituted 2-aryl-1,4-benzoxazine derivatives under mild conditions.



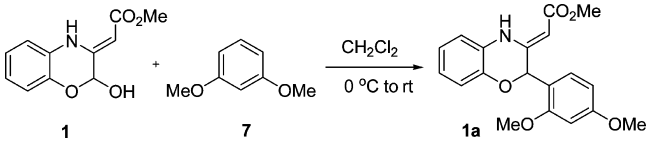
Carbon–carbon (C–C) bond-forming reactions have become very essential tools in modern organic synthesis because of their applications in the synthesis of various complex natural products.[1] Since heterocyclic compounds are ubiquitous in nature, the synthesis of novel derivatives of heterocyclic compounds by C–C bond-forming reactions has gained much importance recently.[2,3] A number of methodologies[4] for C–C bond construction have been developed. In particular, the formation of a C–C bond by direct reaction of a C–OH bond with a C–H bond would be an environmentally friendly process as it would generate water as the byproduct. Over the past decade, significant progress has been made in the development of direct dehydrative coupling methodologies.[5] In the field of heterocyclic chemistry, 1,4-benzoxazine derivatives have engrossed a significant place as a result of their occurrence in various natural products and biologically active molecules. 1,4-Benzoxazine derivatives were found to exhibit a wide range of biological activities such as antipsychotic agents,[6] vasodilator agents,[7] antibacterial agents,[8] and antagonists[9] and have also been used in the treatment of heart disease,[10] diabetes,[11] and neurodegenerative and cardiovascular disorders.[12]

Recently, 2-aryl-1,4-benzoxazine derivatives were found to be active against *Toxoplasma gondii* tachyzoite proliferation.[13] In continuation of our interest in the development of novel methodologies for the synthesis of heterocyclic compounds,[14] herein we report a simple and efficient synthesis of 2-aryl-1,4-benzoxazine derivatives by the BF_3·etherate-mediated Friedel–Crafts arylation of 2-hydroxy-1,4-benzoxazine derivatives with various electron-rich arenes under mild conditions.

In a preliminary experiment, a solution of 2-hydroxy-1,4-benzoxazine **1** and 1,3-dimethoxybenzene (**7**) in CH_2Cl_2 was cooled to 0 °C, and trifluoroacetic acid (TFA) was added; the reaction contents were then allowed to stir at room temperature. The reaction proceeded smoothly and was found to be complete in 4 h as shown by TLC. After purification by column chromatography, the corresponding aryl benzoxazine derivative **1a** was isolated in 52% yield. Encouraged with the result obtained, we carried out the reaction of **1** and **7** under the influence of various Brønsted and Lewis acids to optimize the reaction conditions.

When the reaction performed with the Brønsted acids *p*-TSA·H_2O and TfOH, the product **1a** was obtained in 48 and 54% yield, respectively; however, no product formation was observed in the presence of montmorillonite or Amberlyst (Table 1, entries 1–5). Furthermore, we screened the reaction with Lewis acids such as $ZrCl_4$, $ZnCl_2$, $FeCl_3$, $SnCl_4$, and BF_3·etherate (entries 6–11). It was found that among the tested Lewis acids, BF_3·etherate afforded the desired product **1a** in the best yield (entry 10).

Table 1. Optimization of the Reaction Conditions[a]



Entry	Reagent	Time (h)	Yield[b] (%)
1	TFA	12	52
2	*p*-TSA·H_2O	4	48
3	TfOH	1	54
4[c]	montmorillonite	12	–
5[c]	Amberlyst	12	–
6	$ZrCl_4$	3	61
7	$ZnCl_2$	3	58
8	$FeCl_3$	1	66
9	$SnCl_4$	1	71
10	**BF_3·etherate**	**1**	**79**
11	BF_3·etherate[d]	4	62
12	–	24	–

[a]Reactions were performed with **1** (0.5 mmol), **7** (0.6 mmol), and the reagent (0.5 mmol) in 5 mL of CH_2Cl_2. [b]Yields of pure and isolated products. [c]The reaction was performed at rt. [d]0.25 mmol of reagent was used.

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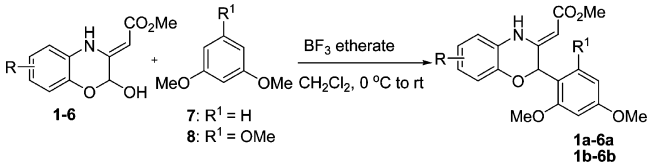
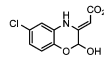
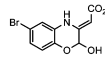
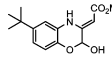
With the optimized conditions in hand, we then evaluated the scope of the reaction of diversely substituted 2-hydroxy-1,4-benzoxazine derivatives with various nucleophiles. When the reactions of 2-hydroxy-1,4-benzoxazine derivatives **1**−**6** were carried out with 1,3-dimethoxybenzene (**7**) in the presence of BF_3·etherate, the reactions proceeded smoothly to furnish the corresponding products **1a**−**6a** in 1 h in good yields. It was observed that the benzoxazine derivatives possessing a moderately electron-withdrawing substituent such as −Cl or −Br on the aromatic ring gave the products **4a** and **5a** in marginally higher yields in comparison with those bearing an electron-releasing substituent such as −Me or −*tert*-butyl (Table 2, entries 7 and 9 vs 3, 5, and 11). The same trend was

Table 2. Scope of the Substrates[a]



Entry	Substrate	R^1	Time (min)	Product	Yield[b] (%)
1		H	60	**1a**	79
2		OMe	45	**1b**	77
3		H	60	**2a**	71
4		OMe	45	**2b**	67
5		H	60	**3a**	69
6		OMe	45	**3b**	70
7		H	60	**4a**	76
8		OMe	45	**4b**	72
9		H	60	**5a**	74
10		OMe	45	**5b**	76
11		H	60	**6a**	65
12		OMe	45	**6b**	62

[a]Reactions were performed with **1** (0.5 mmol) and **7** or **8** (0.6 mmol) in 5 mL of CH_2Cl_2. [b]Yields of pure and isolated products.

observed when the reactions of **1**−**6** were carried out with 1,3,5-trimethoxybenzene (**8**). For instance, benzoxazine derivatives **4** and **5** having the −Cl or −Br substituent on the aromatic ring delivered the products in 72% and 76% yield, respectively (entries 8 and 10). However, the benzoxazine derivatives bearing the −Me or −*tert*-butyl substituent provided the respective products in 67%, 70%, and 62% yield (entries 4, 6, and 12). The reactions of **1**−**6** with **8** were complete in 45 min, whereas in case of **7**, the reactions reached completion in 1 h, which may be due to the fact that the former arene is more nucleophilic.

To explore further the applicability of the current protocol to phenolic nucleophiles, we then selected *p*-cresol (**9**) for our study. The hydroxybenzoxazine derivatives **1**−**6** reacted with *p*-cresol in the presence of BF_3·etherate under the standard conditions to give the corresponding products within 2 h in good yields (Figure 1). Similarly, upon treatment with 2,6-dimethoxyphenol (**10**) in the presence of BF_3·etherate, benzoxazine derivatives **1**−**5** provided the respective Friedel−Crafts adducts **1d**−**5d** in good yields (Figure 2). Unfortunately, under similar conditions benzoxazine derivative **6** failed to give any product upon treatment with 2,6-dimethoxyphenol.

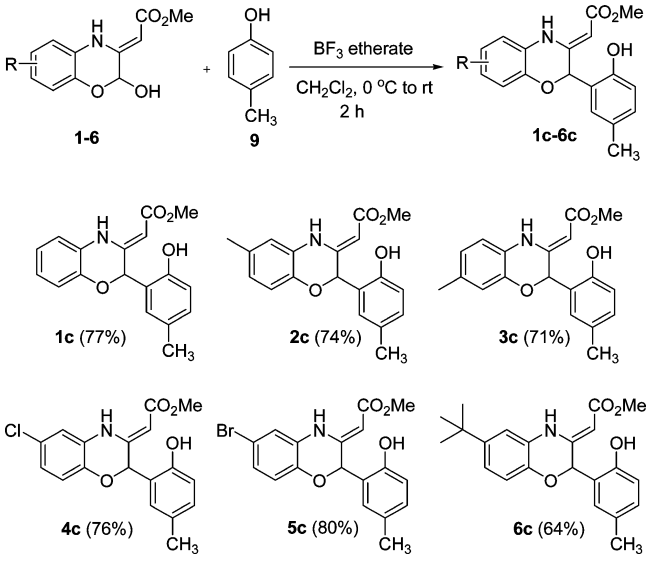


Figure 1. Friedel−Crafts arylation of 2-hydroxy-1,4-benzoxazine derivatives with *p*-cresol.

The reactions of benzoxazine derivatives **1**−**6** with 2,6-di-*tert*-butylphenol (**11**) bearing *tert*-butyl groups also reacted smoothly, affording the Friedel−Crafts adducts in good yields. The results are summarized in Figure 3. The yields of the products **2e**, **4e**, **5e**, and **6e** from the reaction of phenol **11** and benzoxazine derivatives **2**, **4**, **5**, and **6** were relatively less in comparison with those obtained from phenol **9**. One of the reasons may be the diminished reactivity of the intermediate (oxonium ion) due to the presence of substitutions such as methyl, chloro, and bromo at position 6 of the benzoxazine moiety. The structure elucidation of all the pure and isolated products was done on the basis of the collective information obtained from the IR, ^{1}H, ^{13}C NMR, and HRMS spectral data. The presence of a broad singlet in the range of 10.37−10.60 ppm in the ^{1}H NMR spectra of these compounds indicates the NH proton. The vinylic proton on the carbon α to the ester functionality resonates in the range of 5.38−6.24 ppm. The proton on carbon-2 bearing the aryl moiety resonates in the range of 4.35−4.51 ppm. The structure of compound **4b** was further confirmed by single-crystal X-ray analysis (Figure 4).[15]

In summary, we have developed a simple and efficient method for the direct Friedel−Crafts reaction of 2-hydroxy-1,4-benzoxazine derivatives. By means of the current protocol, various substituted 2-arylbenzoxazine derivatives of potential biological significance can be synthesized under mild conditions. Further investigation of the reactivity of these 2-hydroxy-1,4-benzoxazine derivatives is in progress in our laboratory.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, chemicals were purchased at the highest purity grade available and were used without further purification. IR spectra of the compounds are expressed as wavenumbers (cm^{-1}). NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard. Chemical shifts of ^{1}H NMR spectra are given in parts per million with respect to TMS, and coupling constants (J) are reported in hertz. The signals from solvent $CDCl_3$ at 7.26 and 77.0 ppm were set as the reference peaks in ^{1}H NMR and ^{13}C NMR spectra, respectively. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublets, dt

dx.doi.org/10.1021/jo402254n | J. Org. Chem. 2013, 78, 12819−12824

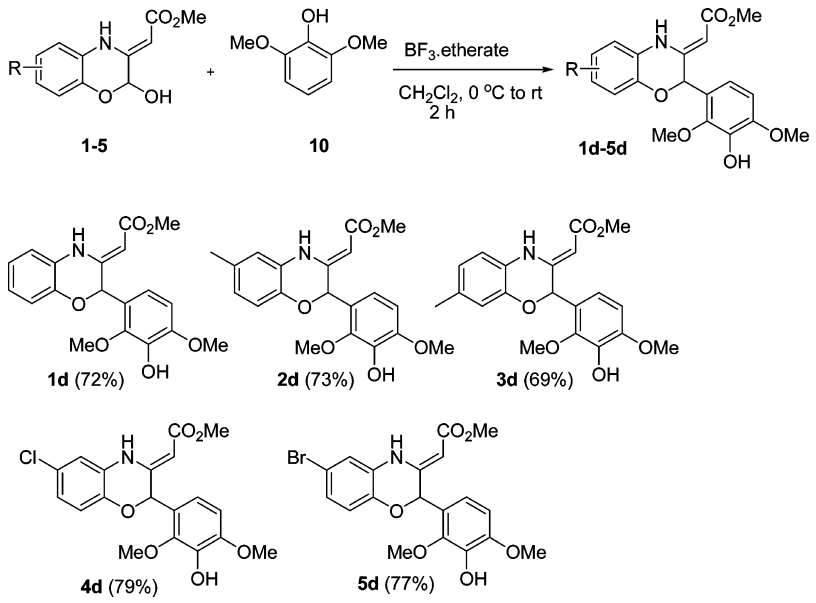


Figure 2. Friedel–Crafts arylation of 2-hydroxy-1,4-benzoxazine derivatives with 2,6-dimethoxyphenol.

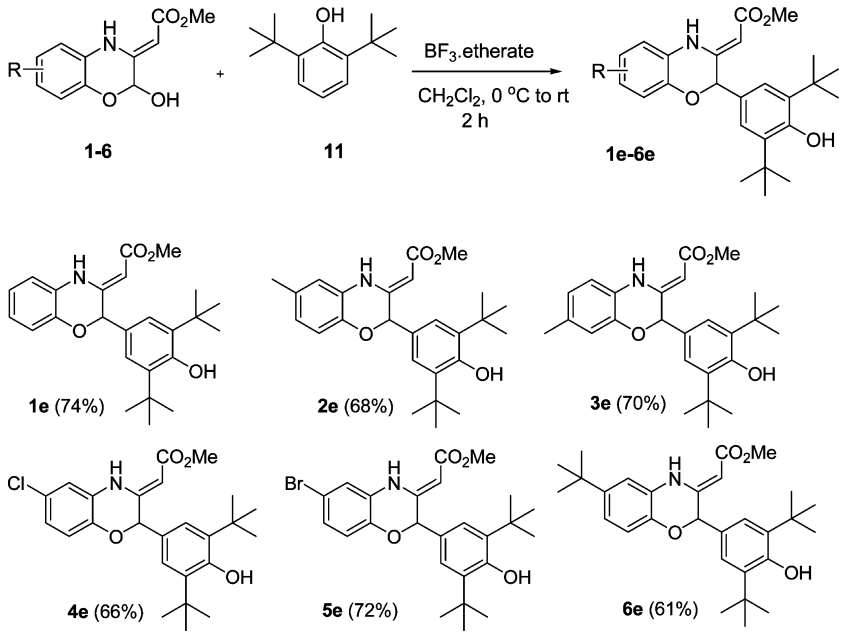


Figure 3. Friedel–Crafts arylation of 2-hydroxy-1,4-benzoxazine derivatives with 2,6-di-*tert*-butylphenol.

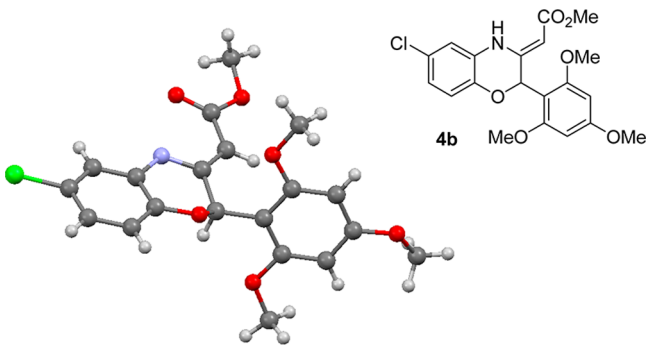


Figure 4. Single-crystal X-ray structure of compound **4b**.

= doublet of triplets, t = triplet, q = quartet, m = multiplet, br = broad. HRMS was performed on a microOTOF-Q II mass spectrometer.

General Procedure for Friedel–Crafts Arylation of 2-Hydroxy-1,4-benzoxazine Derivatives. To a mixture of 2-hydroxybenzoxazine derivative (0.5 mmol) and electron-rich arene (0.6 mmol) was added 5 mL of CH_2Cl_2, and the mixture was cooled to 0 °C. BF_3·etherate (0.5 mmol) was added slowly dropwise, and the mixture was allowed to stir at rt for 45–60 min (2 h in the case of phenol derivatives). After completion of the reaction as shown by TLC, the reaction was quenched with 5 mL of sat. $NaHCO_3$ solution. The organic layer was separated, washed with water twice, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (100–200 mesh) using 10–20% ethyl acetate/hexanes as the eluting system.

*(Z)-Methyl 2-(2-(2,4-Dimethoxyphenyl)-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**1a**).* Yield: 134 mg (79%) as a white solid, mp 108–110 °C. IR (KBr) ν_{max}: 3312, 1660, 1613, 1507, 1218, 1115, 1039 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.48 (br s, 1H), 7.26 (d, J = 9.5 Hz, 1H), 6.96–6.84 (m, 4H), 6.51–6.49 (m, 2H), 5.94 (s, 1H),

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4.39 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 161.5, 158.3, 152.7, 144.8, 129.5, 127.3, 122.5, 122.5, 117.1, 116.9, 115.3, 104.8, 98.4, 84.2, 71.1, 55.6, 55.3, 50.6. HRMS (ES^+) m/z: calcd for $[C_{19}H_{19}NO_5 + Na]^+$, 364.1155; found, 364.1149.

(Z)-Methyl 2-(2-(2,4-Dimethoxyphenyl)-6-methyl-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**2a**). Yield: 128 mg (71%) as a white solid, mp 138−140 °C. IR (KBr) ν_{max}: 3270, 1665, 1617, 1507, 1282, 1155, 1039 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.43 (br s, 1H), 7.26 (d, J = 9.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.72 (s, 1H), 6.67 (dd, J = 1.5, 8.0 Hz, 1H), 6.50−6.48 (m, 2H), 5.91 (s, 1H), 4.38 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.66 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 161.4, 158.2, 152.8, 142.6, 132.0, 129.5, 126.9, 122.9, 116.9, 116.7, 115.8, 104.8, 98.4, 84.0, 71.1, 55.6, 55.2, 50.5, 20.7. HRMS (ES^+) m/z: calcd for $[C_{20}H_{21}NO_5 + Na]^+$, 378.1312; found, 378.1325.

(Z)-Methyl 2-(2-(2,4-Dimethoxyphenyl)-7-methyl-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**3a**). Yield: 122 mg (69%) as a white solid, mp 128−130 °C. IR (KBr) ν_{max}: 3374, 1665, 1607, 1515, 1398, 1273, 1153, 1035 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.45 (br s, 1H), 7.26 (d, J = 9.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.74−6.71 (m, 2H), 6.49−6.47 (m, 2H), 5.93 (s, 1H), 4.37 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.66 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 161.4, 158.2, 152.6, 144.5, 132.4, 129.5, 124.7, 122.9, 117.6, 116.9, 115.0, 104.7, 98.4, 83.5, 71.0, 55.5, 55.2, 50.4, 20.8. HRMS (ES^+) m/z: calcd for $[C_{20}H_{21}NO_5 + Na]^+$, 378.1312; found, 378.1322.

(Z)-Methyl 2-(6-Chloro-2-(2,4-dimethoxyphenyl)-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**4a**). Yield: 143 mg (76%) as a white solid, mp 158−160 °C. IR (KBr) ν_{max}: 3360, 1656, 1605, 1504, 1398, 1264, 1114, 1073 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.46 (br s, 1H), 7.21 (d, J = 9.0 Hz, 1H), 6.88 (t, J = 1.0 Hz, 1H), 6.79 (d, J = 1.0 Hz, 2H), 6.49−6.48 (m, 2H), 5.90 (s, 1H), 4.42 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 161.6, 158.3, 151.8, 143.3, 129.5, 128.3, 127.1, 122.0, 118.1, 116.5, 115.1, 104.8, 98.5, 85.5, 71.2, 55.6, 55.3, 50.7. HRMS (ES^+) m/z: calcd for $[C_{19}H_{18}ClNO_5 + Na]^+$, 398.0766; found, 398.0765.

(Z)-Methyl 2-(6-Bromo-2-(2,4-dimethoxyphenyl)-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**5a**). Yield: 154 mg (74%) as a white solid, mp 168−170 °C. IR (KBr) ν_{max}: 3358, 1657, 1608, 1510, 1385, 1259, 1120, 1062 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.46 (br s, 1H), 7.22 (d, J = 9.5 Hz, 1H), 7.02 (d, J = 2.0 Hz, 1H), 6.94 (dd, J = 2.5, 9.0 Hz, 1H), 6.74 (d, J = 8.5 Hz, 1H), 6.49−6.48 (m, 2H), 5.90 (s, 1H), 4.42 (d, J = 1.0 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 161.6, 158.3, 151.7, 143.9, 129.5, 128.7, 125.0, 118.5, 117.9, 116.5, 114.3, 104.9, 98.5, 85.5, 71.2, 55.7, 55.4, 50.7. HRMS (ES^+) m/z: calcd for $[C_{19}H_{18}BrNO_5 + Na]^+$, 442.0261; found, 442.0260.

(Z)-Methyl 2-(6-tert-Butyl-2-(2,4-dimethoxyphenyl)-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**6a**). Yield: 128 mg (65%) as a brown solid, mp 146−148 °C. IR (KBr) ν_{max}: 3297, 1671, 1612, 1507, 1261, 1117, 1004 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.51 (br s, 1H), 7.28 (d, J = 8.5 Hz, 1H), 6.93 (d, J = 2.5 Hz, 1H), 6.90 (dd, J = 2.0, 8.5 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 6.52 (dd, J = 2.5, 8.5 Hz, 1H), 6.49 (d, J = 2.0 Hz, 1H), 5.93 (s, 1H), 4.35 (s, 1H), 3.81 (s, 3H), 3.81 (s, 3H), 3.67 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 161.4, 158.3, 153.1, 145.7, 142.6, 129.6, 126.6, 119.3, 116.9, 116.3, 112.6, 104.9, 98.4, 83.8, 71.1, 55.6, 55.3, 50.5, 34.3, 31.4. HRMS (ES^+) m/z: calcd for $[C_{23}H_{27}NO_5 + Na]^+$, 420.1781; found, 420.1780.

(Z)-Methyl 2-(2-(2,4,6-Trimethoxyphenyl)-2H-benzo[b][1,4]-oxazin-3(4H)-ylidene)acetate (**1b**). Yield: 142 mg (77%) as a brown solid, mp 110−111 °C. IR (KBr) ν_{max}: 3346, 1661, 1605, 1503, 1218, 1155, 1066 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.57 (br s, 1H), 6.90−6.82 (m, 4H), 6.24 (s, 1H), 6.15 (s, 2H), 4.40 (s, 1H), 3.80 (s, 3H), 3.71 (s, 6H), 3.65 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 162.2, 159.8, 154.7, 145.1, 126.6, 122.0, 121.7, 116.3, 114.8, 105.3, 90.9, 80.8, 68.8, 55.6, 55.0, 50.2. HRMS (ES^+) m/z: calcd for $[C_{20}H_{21}NO_6 + Na]^+$, 394.1261; found, 394.1255.

(Z)-Methyl 2-(6-Methyl-2-(2,4,6-trimethoxyphenyl)-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**2b**). Yield: 129 mg (67%) as a brown solid, mp 128−130 °C. IR (KBr) ν_{max}: 3284, 1665, 1600, 1504, 1280, 1116, 1003 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.49 (br s, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.68 (s, 1H), 6.65 (d, J = 8.0 Hz, 1H), 6.18 (s, 1H), 6.15 (s, 2H), 4.36 (s, 1H), 3.82 (s, 3H), 3.73 (s, 6H), 3.65 (s, 3H), 2.78 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 162.2, 159.9, 155.1, 143.1, 131.3, 126.5, 122.5, 116.2, 115.5, 105.4, 91.1, 80.8, 69.0, 55.8, 55.2, 50.3, 20.7. HRMS (ES^+) m/z: calcd for $[C_{21}H_{23}NO_6 + Na]^+$, 408.1418; found, 408.1418.

(Z)-Methyl 2-(7-Methyl-2-(2,4,6-trimethoxyphenyl)-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**3b**). Yield: 135 mg (70%) as a white solid, mp 118−120 °C. IR (KBr) ν_{max}: 3240, 1662, 1614, 1517, 1462, 1270, 979 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.51 (br s, 1H), 6.75 (d, J = 7.5 Hz, 1H), 6.71 (s, 1H), 6.69 (s, 1H), 6.20 (s, 1H), 6.15 (s, 2H), 4.35 (s, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.64 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 162.2, 159.8, 154.9, 145.0, 131.9, 124.2, 122.2, 117.0, 114.6, 105.4, 91.0, 80.2, 68.9, 55.7, 55.1, 50.2, 20.7. HRMS (ES^+) m/z: calcd for $[C_{21}H_{23}NO_6 + Na]^+$, 408.1418; found, 408.1417.

*(Z)-Methyl 2-(6-Chloro-2-(2,4,6-trimethoxyphenyl)-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate(**4b**).* Yield: 147 mg (72%) as pale-yellow crystals (from CH_2Cl_2/EtOAc/hexanes 1/0.2/0.8 in 3 days), mp 136−138 °C. IR (KBr) ν_{max}: 3381, 1657, 1619, 1499, 1272, 1117, 1041 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.53 (br s, 1H), 6.84 (t, J = 1.5 Hz, 1H), 6.77 (d, J = 1.0 Hz, 2H), 6.19 (s, 1H), 6.14 (s, 2H), 4.41 (d, J = 1.0 Hz, 1H), 3.81 (s, 3H), 3.71 (s, 6H), 3.64 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 162.4, 159.8, 154.0, 143.8, 127.7, 126.3, 121.5, 117.3, 114.7, 105.3, 91.1, 82.2, 68.9, 55.8, 55.2, 50.4. HRMS (ES^+) m/z: calcd for $[C_{20}H_{20}ClNO_6 + Na]^+$, 428.0871; found, 428.0876.

(Z)-Methyl 2-(6-Bromo-2-(2,4,6-trimethoxyphenyl)-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**5b**). Yield: 171 mg (76%) as a brown solid, mp 158−160 °C. IR (KBr) ν_{max}: 3244, 1656, 1615, 1521, 1466, 1269, 1034 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.52 (br s, 1H), 6.98 (d, J = 2.0 Hz, 1H), 6.92 (dd, J = 2.0, 8.5 Hz, 1H), 6.72 (d, J = 8.5 Hz, 1H), 6.19 (s, 1H), 6.14 (s, 2H), 4.40 (d, J = 1.0 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 6H), 3.64 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 162.4, 159.9, 154.0, 144.3, 128.1, 124.5, 117.8, 117.5, 113.4, 105.4, 91.1, 82.2, 68.9, 55.8, 55.3, 50.5. HRMS (ES^+) m/z: calcd for $[C_{20}H_{20}BrNO_6 + Na]^+$, 472.0366; found, 472.0364.

(Z)-Methyl 2-(6-tert-Butyl-2-(2,4,6-trimethoxyphenyl)-2H-benzo-[b][1,4]oxazin-3(4H)-ylidene)acetate (**6b**). Yield: 131 mg (62%) as a brown solid, mp 138−140 °C. IR (KBr) ν_{max}: 3384, 1662, 1608, 1507, 1258, 1114, 1043 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.6 (br s, 1H), 6.92 (s, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.5 Hz, 1H), 6.22 (s, 1H), 6.16 (s, 2H), 4.38 (s, 1H), 3.80 (s, 3H), 3.71 (s, 6H), 3.65 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 162.2, 159.8, 155.1, 144.9, 142.9, 126.1, 118.8, 115.7, 112.1, 105.3, 92.5, 91.0, 80.5, 68.9, 55.6, 55.0, 50.1, 34.0, 31.2. HRMS (ES^+) m/z: calcd for $[C_{24}H_{29}NO_6 + Na]^+$, 450.1887; found, 450.1880.

(Z)-Methyl 2-(2-(2-Hydroxy-5-methylphenyl)-2H-benzo[b][1,4]-oxazin-3(4H)-ylidene)acetate (**1c**). Yield: 119 mg (77%) as a brown solid, mp 140−142 °C. IR (KBr) ν_{max}: 3442, 1658, 1619, 1502, 1285, 1230, 1169 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.41 (br s, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.98−6.94 (m, 3H), 6.89 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 8.0 Hz, 1H), 6.35 (br s, 1H), 5.73 (s, 1H), 4.47 (s, 1H), 3.68 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 152.6, 150.7, 143.8, 131.3, 129.8, 129.4, 127.4, 123.5, 122.5, 120.3, 117.1, 116.8, 115.6, 85.1, 75.7, 50.8. HRMS (ES^+) m/z: calcd for $[C_{18}H_{17}NO_4 + Na]^+$, 334.1050; found, 334.1045.

(Z)-Methyl 2-(2-(2-Hydroxy-5-methylphenyl)-6-methyl-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**2c**). Yield: 120 mg (74%) as a brown solid, mp 120−122 °C. IR (KBr) ν_{max}: 3432, 2958, 1668, 1618, 1511, 1448, 1261, 1228, 1166 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.35 (br s, 1H), 7.06 (dd, J = 1.5, 8.0 Hz, 1H), 6.93 (s, 1H), 6.83 (d, J = 8.0 Hz, 2H), 6.69 (s, 1H), 6.67 (d, J = 8.0 Hz, 1H), 6.34 (br s, 1H), 5.67 (s, 1H), 4.46 (s, 1H), 3.68 (s, 3H), 2.27 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 152.8, 150.6, 141.5, 133.3, 131.3, 129.7, 129.4, 127.1, 123.1, 120.2, 117.0,

116.8, 116.2, 85.1, 76.3, 50.7, 20.8, 20.5. HRMS (ES^+) m/z: calcd for $[C_{19}H_{19}NO_4 + Na]^+$, 348.1206; found, 348.1210.

*(Z)-Methyl 2-(2-(2-Hydroxy-5-methylphenyl)-7-methyl-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**3c**).* Yield: 115 mg (71%) as a brown solid, mp 114−115 °C. IR (KBr) ν_{max}: 3441, 2962, 1659, 1609, 1508, 1441, 1256, 1231, 1169 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.37 (br s, 1H), 7.06 (d, J = 8.5 Hz, 1H), 6.94 (s, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.77−6.76 (m, 3H), 6.46 (br s, 1H), 5.70 (s, 1H), 4.44 (s, 1H), 3.68 (s, 3H), 2.25 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 152.8, 150.6, 143.6, 132.6, 131.3, 129.7, 129.3, 125.0, 124.0, 120.4, 117.6, 116.9, 115.4, 84.6, 75.9, 50.7, 20.8, 20.5. HRMS (ES^+) m/z: calcd for $[C_{19}H_{19}NO_4 + Na]^+$, 348.1206; found, 348.1215.

*(Z)-Methyl 2-(6-Chloro-2-(2-hydroxy-5-methylphenyl)-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**4c**).* Yield: 132 mg (76%) as a pale-yellow solid, mp 150−152 °C. IR (KBr) ν_{max}: 3368, 2916, 1645, 1602, 1495, 1437, 1272, 1226, 1169 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.41 (br s, 1H), 7.07 (dd, J = 2.0, 8.5 Hz, 1H), 6.94 (d, J = 1.5 Hz, 1H), 6.88 (d, J = 2.0 Hz, 1H), 6.86−6.84 (m, 1H), 6.82−6.80 (m, 2H), 6.03 (br s, 1H), 5.71 (s, 1H), 4.51 (s, 1H), 3.69 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 152.4, 149.9, 142.4, 131.5, 130.0, 129.3, 128.4, 128.2, 122.2, 120.1, 118.1, 116.8, 115.5, 86.4, 75.5, 50.9, 20.5. HRMS (ES^+) m/z: calcd for $[C_{18}H_{16}ClNO_4 + Na]^+$, 368.0660; found, 368.0644.

*(Z)-Methyl 2-(6-Bromo-2-(2-hydroxy-5-methylphenyl)-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**5c**).* Yield: 156 mg (80%) as a brown solid, mp 134−136 °C. IR (KBr) ν_{max}: 3385, 2922, 1663, 1607, 1598, 1497, 1297, 1268, 1223, 1164 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.41 (br s, 1H), 7.07 (dd, J = 1.5, 8.5 Hz, 1H), 7.03 (d, J = 2.0 Hz, 1H), 6.96 (dd, J = 2.5, 8.5 Hz, 1H), 6.94 (d, J = 1.5 Hz, 1H), 6.81 (d, J = 6.0 Hz, 1H), 6.80 (d, J = 5.5 Hz, 1H), 5.98 (br s, 1H), 5.72 (s, 1H), 4.51 (d, J = 0.5 Hz, 1H), 3.69 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 152.5, 149.8, 142.9, 131.5, 130.1, 129.3, 128.9, 125.1, 120.2, 118.6, 118.4, 116.9, 115.5, 86.5, 75.6, 50.9, 20.5. HRMS (ES^+) m/z: calcd for $[C_{18}H_{16}BrNO_4 + Na]^+$, 412.0155; found, 412.0158.

*(Z)-Methyl 2-(6-tert-Butyl-2-(2-hydroxy-5-methylphenyl)-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**6c**).* Yield: 118 mg (64%) as a brown solid, mp 178−180 °C. IR (KBr) ν_{max}: 3430, 2954, 1663, 1621, 1504, 1436, 1264, 1226, 1166 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.44 (br s, 1H), 7.07 (dd, J = 2.0, 8.0 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 6.93−6.88 (m, 3H), 6.83 (d, J = 8.0 Hz, 1H), 5.69 (s, 1H), 4.43 (s, 1H), 3.68 (s, 3H), 2.26 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 152.9, 151.0, 146.9, 141.6, 131.3, 129.7, 129.6, 126.9, 126.8, 120.3, 119.5, 117.0, 116.4, 112.9, 76.3, 50.7, 34.4, 31.4, 20.5. HRMS (ES^+) m/z: calcd for $[C_{22}H_{25}NO_4 + Na]^+$, 390.1676; found, 390.1679.

*(Z)-Methyl 2-(2-(3-Hydroxy-2,4-dimethoxyphenyl)-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**1d**).* Yield: 128 mg (72%) as a brown solid, mp 108−110 °C. IR (KBr) ν_{max}: 3480, 2940, 1666, 1620, 1500, 1448, 1266, 1225, 1163 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.49 (br s, 1H), 6.95−6.92 (m, 1H), 6.91−6.88 (m, 1H), 6.87−6.85 (m, 2H), 6.84 (d, J = 8.5 Hz, 1H), 6.64 (d, J = 8.5 Hz, 1H), 5.88 (s, 1H), 5.63 (br s, 1H), 4.40 (d, J = 0.5 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 152.5, 148.4, 145.5, 144.5, 138.4, 127.3, 122.6, 122.5, 122.3, 118.9, 117.1, 115.3, 106.4, 84.5, 71.8, 61.3, 56.2, 50.7. HRMS (ES^+) m/z: calcd for $[C_{19}H_{19}NO_6 + Na]^+$, 380.1105; found, 380.1100.

*(Z)-Methyl 2-(2-(3-Hydroxy-2,4-dimethoxyphenyl)-6-methyl-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**2d**).* Yield: 135 mg (73%) as a white solid, mp 123−125 °C. IR (KBr) ν_{max}: 3468, 2938, 1652, 1626, 1504, 1452, 1274, 1237, 1156 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.45 (br s, 1H), 6.82 (d, J = 8.5 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.73 (dd, J = 1.0, 8.0 Hz, 1H), 6.69 (s, 1H), 6.63 (d, J = 9.0 Hz, 1H), 5.86 (s, 1H), 5.60 (br s, 1H), 4.38 (s, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.66 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 152.5, 148.3, 145.6, 144.3, 138.4, 132.6, 124.8, 123.1, 122.5, 118.9, 117.7, 115.1, 106.4, 83.9, 71.8, 61.3, 56.2, 50.6, 20.9. HRMS (ES^+) m/z: calcd for $[C_{20}H_{21}NO_6 + Na]^+$, 394.1261; found, 394.1254.

*(Z)-Methyl 2-(2-(3-Hydroxy-2,4-dimethoxyphenyl)-7-methyl-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**3d**).* Yield: 128 mg (69%) as a brown solid, mp 138−140 °C. IR (KBr) ν_{max}: 3404, 2946, 1669, 1612, 1517, 1470, 1277, 1222, 1163 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.45 (br s, 1H), 6.82 (d, J = 8.5 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.74−6.72 (m, 1H), 6.69 (s, 1H), 6.63 (d, J = 8.5 Hz, 1H), 5.86 (s, 1H), 5.60 (br s, 1H), 4.38 (s, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.66 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 152.5, 148.3, 145.6, 144.3, 138.4, 132.6, 124.8, 123.1, 122.5, 118.9, 117.7, 115.1, 106.4, 83.9, 71.8, 61.3, 56.2, 50.6, 20.9. HRMS (ES^+) m/z: calcd for $[C_{20}H_{21}NO_6 + Na]^+$, 394.1261; found, 394.1264.

*(Z)-Methyl 2-(6-Chloro-2-(3-hydroxy-2,4-dimethoxyphenyl)-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**4d**).* Yield: 156 mg (79%) as a brown solid, mp 160−162 °C. IR (KBr) ν_{max}: 3465, 2931, 1665, 1622, 1503, 1456, 1265, 1228, 1172 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.49 (br s, 1H), 6.89 (d, J = 2.0 Hz, 1H), 6.81−6.76 (m, 3H), 6.63 (d, J = 8.5 Hz, 1H), 5.86 (s, 1H), 5.65 (br s, 1H), 4.45 (d, J = 0.5 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 151.6, 148.5, 145.5, 143.0, 138.4, 128.2, 127.3, 122.1, 122.0, 118.8, 118.1, 115.2, 106.3, 85.7, 71.9, 61.2, 56.2, 50.8. HRMS (ES^+) m/z: calcd for $[C_{19}H_{18}ClNO_6 + Na]^+$, 414.0715; found, 414.0712.

*(Z)-Methyl 2-(6-Bromo-2-(3-hydroxy-2,4-dimethoxyphenyl)-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**5d**).* Yield: 168 mg (77%) as a brown solid, mp 168−170 °C. IR (KBr) ν_{max}: 3472, 2936, 1658, 1626, 1498, 1447, 1256, 1220, 1162 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.48 (br s, 1H), 7.03 (d, J = 2.0 Hz, 1H), 6.94 (dd, J = 2.0, 8.5 Hz, 1H), 6.79 (d, J = 8.5 Hz, 1H), 6.73 (d, J = 9.0 Hz, 1H), 6.63 (d, J = 8.5 Hz, 1H), 5.85 (s, 1H), 5.61 (br s, 1H), 4.45 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 151.5, 148.5, 145.4, 143.5, 138.4, 128.6, 125.1, 122.1, 118.8, 118.6, 118.0, 114.5, 106.3, 85.8, 71.9, 61.2, 56.2, 50.8. HRMS (ES^+) m/z: calcd for $[C_{19}H_{18}BrNO_6 + Na]^+$, 458.0210; found, 458.0209.

*(Z)-Methyl 2-(2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**1e**).* Yield: 151 mg (74%) as a yellow solid, mp 180−182 °C. IR (KBr) ν_{max}: 3626, 2953, 1662, 1600, 1501, 1435, 1268, 1222, 1160 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.45 (br s, 1H), 7.18 (s, 2H), 6.93 (dt, J = 1.5, 7.5 Hz, 2H), 6.89−6.87 (m, 2H), 5.42 (s, 1H), 5.31 (s, 1H), 4.42 (s, 1H), 3.69 (s, 3H), 1.42 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 154.5, 152.8, 144.7, 136.0, 127.4, 126.5, 125.0, 122.6, 122.5, 117.2, 115.3, 85.1, 78.2, 50.7, 34.3, 30.2. HRMS (ES^+) m/z: calcd for $[C_{25}H_{31}NO_4 + Na]^+$, 432.2145; found, 432.2144.

*(Z)-Methyl 2-(2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-6-methyl-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**2e**).* Yield: 144 mg (68%) as a yellow solid, mp 182−184 °C. IR (KBr) ν_{max}: 3643, 2944, 1654, 1621, 1528, 1425, 1264, 1224, 1159 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.39 (br s, 1H), 7.18 (s, 2H), 6.83 (d, J = 8.5 Hz, 1H), 6.70 (s, 1H), 6.68 (d, J = 8.0 Hz, 1H), 5.38 (s, 1H), 5.30 (s, 1H), 4.40 (s, 1H), 3.69 (s, 3H), 2.28 (s, 3H), 1.42 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 154.4, 153.0, 142.6, 136.0, 132.2, 127.1, 126.6, 125.0, 123.0, 116.8, 115.9, 85.0, 78.3, 50.6, 34.4, 30.2, 20.8. HRMS (ES^+) m/z: calcd for $[C_{26}H_{33}NO_4 + Na]^+$, 446.2302; found, 446.2297.

*(Z)-Methyl 2-(2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-7-methyl-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**3e**).* Yield: 148 mg (70%) as a yellow solid, mp 171−173 °C. IR (KBr) ν_{max}: 3630, 2958, 1665, 1617, 1516, 1436, 1273, 1226, 1158 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.44 (br s, 1H), 7.21 (s, 2H), 6.79−6.74 (m, 3H), 5.42 (s, 1H), 5.33 (s, 1H), 4.42 (s, 1H), 3.70 (s, 3H), 2.27 (s, 3H), 1.44 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 154.4, 152.8, 144.5, 135.9, 132.4, 126.6, 125.0, 124.9, 123.0, 117.7, 115.0, 84.4, 76.7, 50.6, 34.3, 30.2, 20.9. HRMS (ES^+) m/z: calcd for $[C_{26}H_{33}NO_4 + Na]^+$, 446.2302; found, 446.2317.

*(Z)-Methyl 2-(6-Chloro-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**4e**).* Yield: 146 mg (66%) as a yellow solid, mp 188−189 °C. IR (KBr) ν_{max}: 3631, 2953, 1672, 1623, 1499, 1435, 1262, 1220, 1160 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.44 (br s, 1H), 7.17 (s, 2H), 6.88−6.86 (m, 1H), 6.85 (s, 1H), 6.82 (dd, J = 1.5, 8.5 Hz, 1H), 5.40 (s, 1H), 5.33 (s, 1H),

4.47 (s, 1H), 3.70 (s, 3H), 1.42 (s, 18 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 154.6, 151.9, 143.3, 136.1, 128.4, 127.3, 126.1, 125.0, 122.1, 118.2, 115.2, 86.4, 76.7, 50.8, 34.4, 30.2. HRMS (ES^+) m/z: calcd for $[C_{25}H_{30}ClNO_4 + Na]^+$, 466.1756; found, 466.1742.

*(Z)-Methyl 2-(6-Bromo-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**5e**).* Yield: 176 mg (72%) as a yellow solid, mp 180−182 °C. IR (KBr) ν_{max}: 3629, 2953, 1672, 1622, 1598, 1497, 1433, 1265, 1219, 1156 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.42 (br s, 1H), 7.15 (s, 2H), 7.01 (d, J = 2.0 Hz, 1H), 6.96 (dd, J = 2.0, 8.5 Hz, 1H), 6.80 (d, J = 8.5 Hz, 1H), 5.39 (s, 1H), 5.31 (s, 1H), 4.46 (s, 1H), 3.69 (s, 3H), 1.41 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 154.6, 151.8, 143.8, 136.1, 128.8, 126.1, 125.0, 124.9, 118.6, 118.0, 114.5, 86.5, 78.2, 50.8, 34.4, 30.2. HRMS (ES^+) m/z: calcd for $[C_{25}H_{30}BrNO_4 + Na]^+$, 510.1250; found, 510.1252.

*(Z)-Methyl 2-(6-tert-Butyl-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (**6e**).* Yield: 141 mg (61%) as a brown solid, mp 140−142 °C. IR (KBr) ν_{max}: 3610, 2952, 1659, 1624, 1434, 1261, 1227, 1158 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.51 (br s, 1H), 7.19 (s, 2H), 6.94 (s, 1H), 6.92 (dd, J = 2.0, 8.5 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 5.42 (s, 1H), 5.33 (s, 1H), 4.42 (s, 1H), 3.71 (s, 3H), 1.43 (s, 18H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 154.5, 153.2, 145.8, 142.4, 135.9, 126.7, 126.7, 125.0, 119.4, 116.5, 112.6, 84.6, 78.3, 50.6, 34.3, 34.3, 31.4, 30.1. HRMS (ES^+) m/z: calcd for $[C_{29}H_{39}NO_4 + Na]^+$, 488.2771; found, 488.2768.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all new products, ORTEP diagram for **4b**, and X-ray data for **4b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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