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The Synthesis of 5-Hydroxybenzofurans via Tandem *In Situ* Oxidative Coupling and Cyclization

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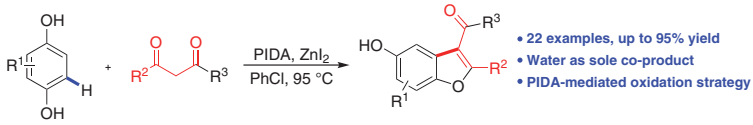

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Abstract A series of 5-hydroxybenzofurans have been prepared by PIDA-mediated oxidation and coupling cyclization of β-dicarbonyl compounds and hydroquinones. The reaction functionalizes C(sp^2)–H of hydroquinones directly with yields of target molecules up to 96%.

Key words 5-hydroxybenzofurans, oxidation, dearomatization, aromatic C(sp^2)–H functionalization, one-pot reaction

Benzofurans have attracted much attention because they possess a broad range of biological activities and they are found extensively in natural products.[1] Consequently, a wide range of synthetic methodologies have been developed for the construction of this privileged structure.[2] Many synthetic approaches to benzofurans involving intramolecular cyclization have been reported.[3] In recent years, transition-metal-catalyzed C–H activation and functionalization has attracted much attention.[4] Furthermore, cross-dehydrogenative coupling (CDC) has become an efficient strategy for the formation of C–C bonds through an oxidative coupling reaction catalyzed by copper or iron in the presence of oxidants,[5,6] and CDC reaction-based methods for the synthesis of benzofurans have been developed recently.[7] Moreover, there are many reports of the preparation of dihydrobenzofurans based on [3+2] cycloaddition of quinones with electron-rich olefins,[8] and enantioselective processes employing benzoquinones or *N*-tosyl-*p*-benzoquinone imines have been developed.[9]

5-Hydroxybenzofuran derivatives display a range of biological activities (Figure 1). Among these are antitumor activity and potent selectivity to human umbilical vein endothelial cells.[10] In addition, 5-hydroxybenzofuran derivatives are efficient anti-estrogen breast cancer agents, demonstrating strong hydrogen-bond interactions and good inhibitory activity.[11] In addition, these derivatives can act as inhibitors of mTOR signaling, controlling cell growth, metabolism and autophagy,[12] and they show antifungal,[13] antiproliferative[14] and anti-inflammatory activity.[15]

In traditional approaches, 5-hydroxybenzofurans are formed by Michael addition.[16] In 2006, Gu *et al.* discovered a method for preparing 5,6-dihydroxylated benzofuran derivatives by oxidation–Michael addition, although this protocol suffers from disadvantages such as limited substrate scope and low yields.[17] Liu *et al.* reported a $CuBr_2/BF_3{\cdot}OEt_2$ catalyzed reaction for the preparation of 5-hydroxybenzofurans via Michael addition and cyclization of benzoquinones and ketene dithioacetals[18] (Scheme 1b). However, there remains a need to develop simple and efficient methods for the synthesis of 5-hydroxybenzofurans due to the drawbacks of many existing methods.

Herein, we report a practical and powerful aromatic C(sp^2)-H functionalization-based method for the preparation of 5-hydroxybenzofurans via oxidative coupling of simple phenols and β-dicarbonyl compounds (Scheme 1c).

In an initial study, we chose phenol **1a** and ethyl acetoacetate **2a** as model substrates in the presence of various oxidants and catalysts (Table 1) to induce the initial adduct

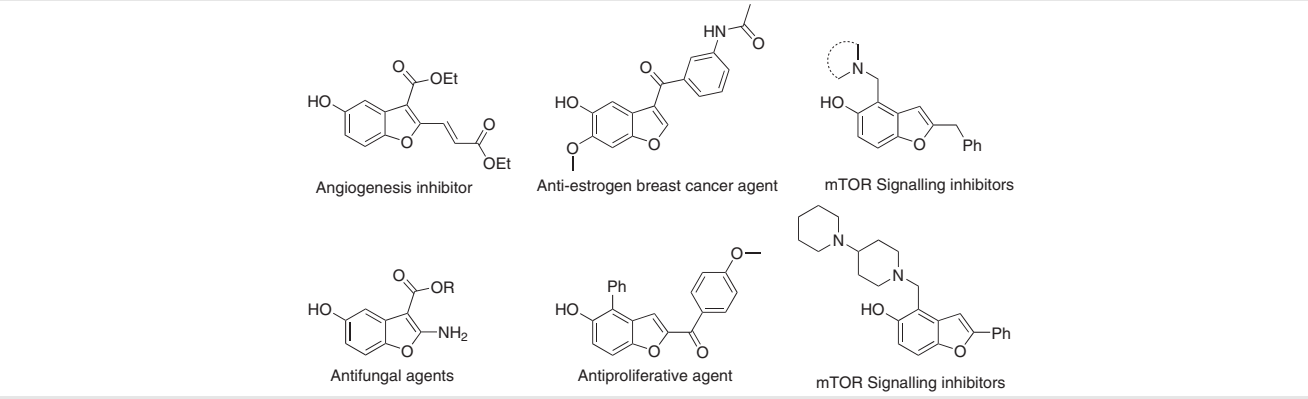
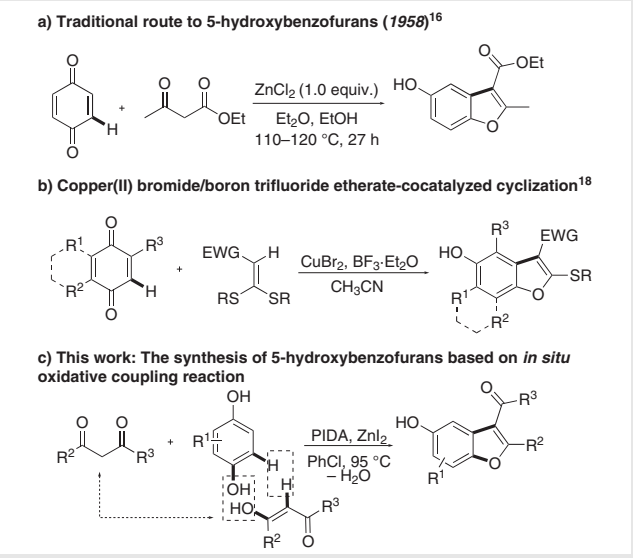


Figure 1 Pharmaceutical compounds containing the 5-hydroxybenzofuran subunit



Scheme 1 Syntheses of 5-hydroxybenzofurans

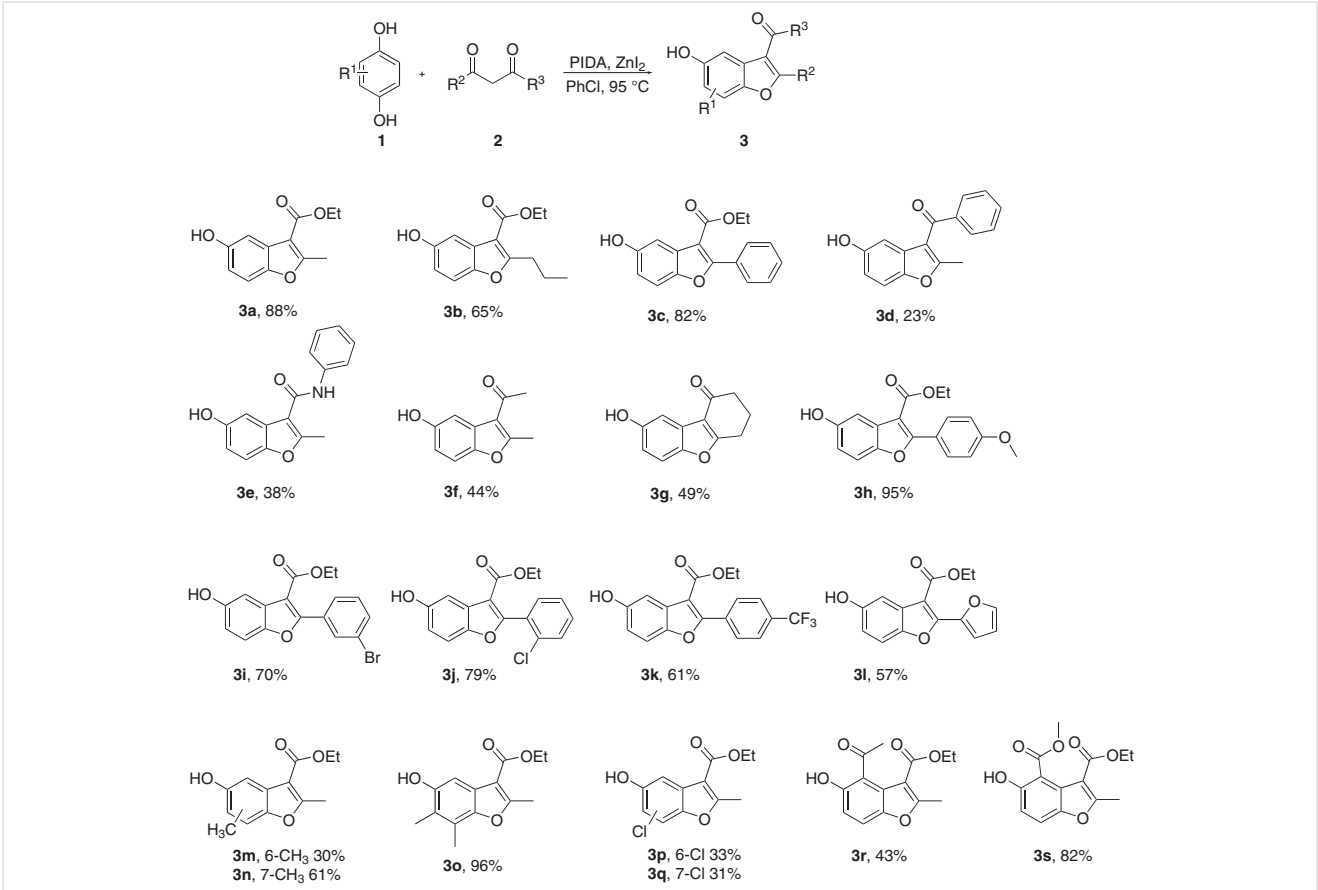
to undergo *in situ* oxidative dearomatization and coupling-cyclization. Initially, we explored the impact of the oxidant (entries 1–7). Gratifyingly, the yield of **3a** was 61% when the oxidant selected was phenyliodine(III) diacetate (PIDA). We then screened catalysts for promoting the coupling-cyclization step and the results showed that the use of ZnI_2 as Lewis acid catalyst led to best yields (entries 1–7 and 14–24). The effect of solvent on reaction was further examined, and the reaction in chlorobenzene and toluene showed good yields (entries 14, 15, 21–24). When the reaction was carried out at 75–110 °C, the yield of product tended to be slightly higher with increased temperature (entries 14, 21–24), with the optimal reaction temperature being 95 °C. Ultimately, the yield of **3a** was improved to 88% with adjustments of the substrate ratio (entry 24).

Table 1 Optimization of the 5-Hydroxybenzofuran Formation[a]

1a **2a** **3a**

Entry	Catalyst	Oxidant	solvent	Temp. (°C)	Yield (%)[d]
1	ZnI_2	DDQ	DCE	85	40
2	ZnI_2	PIFA	DCE	85	21
3	ZnI_2	PIDA	DCE	85	61
4	ZnI_2	CAN	DCE	85	53
5[b]	ZnI_2	I_2/H_2O_2	DCE	85	35
6	ZnI_2	IBX	DCE	85	36
7	ZnI_2	air	DCE	85	ND
8	$ZnCl_2$	PIDA	DCE	85	27
9	$FeCl_3$	PIDA	DCE	85	54
10	$BF_3{\cdot}OEt_2$	PIDA	DCE	85	20
11	$AlCl_3$	PIDA	DCE	85	trace
12	LiCl	PIDA	DCE	85	ND
13	$TiCl_4$	PIDA	DCE	85	ND
14	ZnI_2	PIDA	PhCl	85	75
15	ZnI_2	PIDA	$PhCH_3$	85	69
16	ZnI_2	PIDA	$CHCl_3$	85	64
17	ZnI_2	PIDA	DMF	85	ND
18	ZnI_2	PIDA	THF	85	trace
19	ZnI_2	PIDA	CH_3CN	85	35
20	ZnI_2	PIDA	EtOH	85	trace
21	ZnI_2	PIDA	PhCl	75	58
22	ZnI_2	PIDA	PhCl	95	81
23	ZnI_2	PIDA	PhCl	110	83
24[c]	ZnI_2	PIDA	PhCl	95	88

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (1.00 mmol), catalyst (0.25 mmol), oxidant (0.55 mmol) in solvent (5 mL) was stirred for 6 hours at the given temperature.
[b] I_2 (2.50 mmol), H_2O_2 (0.55 mmol).
[c] **2a** (3.0 equiv).
[d] Isolated yield.



Scheme 2 *Reagents and conditions*: **1** (0.50 mmol), **2** (1.00 mmol), ZnI_2 (0.25 mmol), PIDA (0.55 mmol), PhCl (5 mL), reflux, 95 °C, 6 h.

Using the optimized reaction conditions, we examined the substrate scope and generality of the oxidative coupling reaction for the synthesis of 5-hydroxybenzofurans (Scheme 2). Firstly, we investigated a broad range of β-dicarbonyl compounds, and obtained diverse products **3** in moderate yields (Scheme 2). Generally, the yield of product became lower as the size of the acyl group increased. We speculate that this is the result of the combined effect of the size of the acyl group and ease of enolization of the β-ketoesters, with substrates **2d–g** also being less liable to enolization.

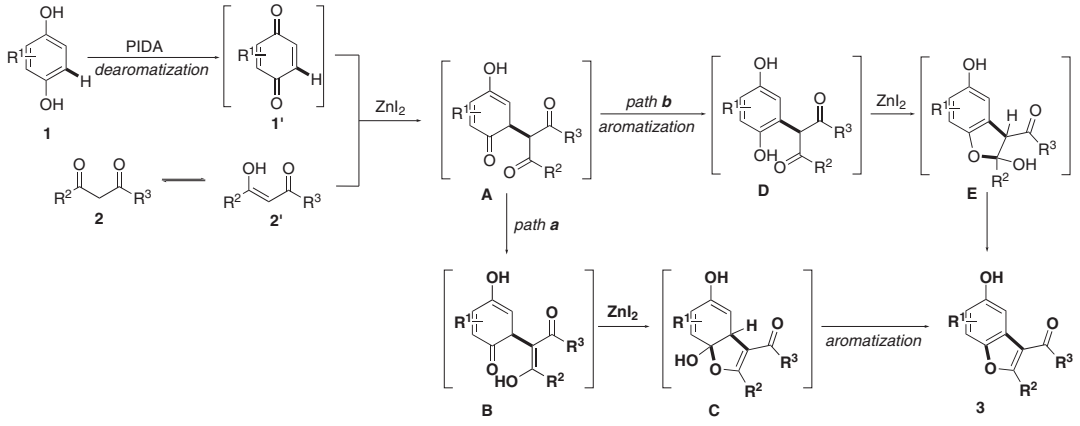
Additionally, we studied the impact of electron-withdrawing and electron-donating groups of substituted aryl-β-ketoesters, with yields being poor when electron-withdrawing groups were present on the aromatic ring (**3i–k**).

Finally, we evaluated a broad range of hydroquinone substrates and found that the yield of product was as high as 96% with a substrate containing an electron-donating group (**3o**). When mono-substituted hydroquinones were used as substrates, isomeric products **3m**,**n**, **3p**,**q** were obtained. It should be noted that the benzofuran product was obtained in only 38% yield when *p*-benzoquinone was selected as substrate without *in situ* oxidation.

Based on our experimental work, two plausible reaction pathways for the PIDA mediated tandem *in situ* oxidative coupling cyclization can be proposed (Scheme 3). Initially, intermediate **1′** reacts with tautomer **2′** of the β-dicarbonyl precursor, producing coupling intermediate **A** by 1,4-Michael addition. However, from **A**, there are two possible routes towards the target product.

Path a proceeds by intramolecular cyclization of keto-enol tautomer **B**, followed by aromatization of intermediate **C**. Path b involves aromatization after coupling, generating intermediate **D**, followed by cyclization and formation of the product. However, path a is favored because if the mechanism follows path b, the yield of product would be higher with hydroquinone substrates possessing electron-withdrawing groups, contrary to the results observed.

In conclusion, this work presents a practical and scalable approach for preparation of 5-hydroxybenzofurans by PIDA-mediated tandem oxidative-cyclization based on *in situ* oxidation of hydroquinones. The methodology is superior to traditional approaches.



Scheme 3 Proposed reaction mechanism

Synthesis of 3; General Procedure

A mixture of **1** (0.50 mmol), **2** (1.00 mmol), ZnI_2 (0.25 mmol), and PIDA (0.55 mmol) in chlorobenzene (5 mL) was stirred at 95 °C for 6 hours. After the reaction was complete, the mixture was quenched with water. The organic phase was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel to obtain **3a–s**.

Ethyl 5-Hydroxy-2-methylbenzofuran-3-carboxylate (3a)

Yield: 88%; white solid; mp 136–137 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.37 (s, 1 H), 7.37 (d, *J* = 8.8 Hz, 1 H), 7.28 (d, *J* = 2.6 Hz, 1 H), 6.76 (dd, *J* = 8.8, 2.6 Hz, 1 H), 4.33 (d, *J* = 7.1 Hz, 2 H), 2.69 (s, 3 H), 1.37 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 163.7, 163.5, 154.1, 147.0, 126.4, 112.8, 111.1, 108.1, 106.0, 59.9, 14.1 (2C).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{12}O_4$: 220.0736; found: 220.0733.

Ethyl 5-Hydroxy-2-propylbenzofuran-3-carboxylate (3b)

Yield: 65%; white solid; mp 105–106 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.35 (s, 1 H), 7.36 (d, *J* = 8.8 Hz, 1 H), 7.30 (d, *J* = 2.5 Hz, 1 H), 6.76 (dd, *J* = 8.8, 2.6 Hz, 1 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 3.05 (t, *J* = 7.4 Hz, 2 H), 1.63–1.76 (m, 2 H), 1.34 (t, *J* = 7.1 Hz, 3 H), 0.90 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.9, 163.4, 154.2, 147.1, 126.4, 112.9, 111.2, 107.9, 106.1, 59.9, 29.4, 20.8, 14.1, 13.5.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{16}O_4$: 248.1049; found: 248.1051.

Ethyl 5-Hydroxy-2-phenylbenzofuran-3-carboxylate (3c)

Yield: 82%; white solid; mp 154–155 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.52 (s, 1 H), 7.93 (dd, *J* = 6.7, 3.0 Hz, 2 H), 7.53–7.44 (m, 4 H), 7.43 (d, *J* = 2.5 Hz, 1 H), 6.89 (dd, *J* = 8.8, 2.6 Hz, 1 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 163.0, 160.2, 154.4, 147.4, 130.2, 129.1 (2C), 128.4, 128.0 (2C), 127.4, 114.3, 111.6, 108.3, 106.6, 60.3, 13.9.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{14}O_4$: 282.0892; found: 282.0889.

(5-Hydroxy-2-methylbenzofuran-3-yl)(phenyl)methanone (3d)

Yield: 23%; yellow solid; mp 196–197 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.30 (s, 1 H), 7.76–7.73 (m, 2 H), 7.71–7.64 (m, 1 H), 7.60–7.53 (m, 2 H), 7.41 (d, *J* = 8.8 Hz, 1 H), 6.80 (d, *J* = 2.4 Hz, 1 H), 6.75 (dd, *J* = 8.8, 2.5 Hz, 1 H), 2.39 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 191.7, 162.8, 154.4, 147.5, 139.4, 133.0, 129.0 (2C), 128.9 (2C), 127.6, 116.6, 113.4, 111.6, 105.9, 15.0.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{12}O_3$: 252.0786; found: 252.0788.

5-Hydroxy-2-methyl-*N*-phenylbenzofuran-3-carboxamide (3e)

Yield: 38%; brown solid; mp 210–211 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.08 (s, 1 H), 9.36 (s, 1 H), 7.78 (d, *J* = 7.5 Hz, 2 H), 7.45–7.35 (m, 3 H), 7.19–7.04 (m, 2 H), 6.79 (dd, *J* = 8.8, 2.5 Hz, 1 H), 2.65 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 161.9, 158.0, 153.7, 146.9, 139.0, 128.6 (2C), 126.9, 123.5, 119.9 (2C), 118.1, 113.5, 112.7, 111.1, 13.7.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{13}NO_3$: 267.0895; found: 267.0899.

1-(5-Hydroxy-2-methylbenzofuran-3-yl)ethanone (3f)

Yield: 44%; yellow solid; mp 238 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.33 (s, 1 H), 7.40–7.33 (m, 2 H), 6.74 (dd, *J* = 8.7, 2.6 Hz, 1 H), 2.73 (s, 3 H), 2.55 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 193.7, 163.2, 154.3, 146.8, 126.6, 117.1, 112.8, 111.0, 106.4, 30.7, 15.3.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{10}O_3$: 190.0630; found: 190.0627.

8-Hydroxy-3,4-dihydrodibenzo[*b*,*d*]furan-1(2*H*)-one (3g)

Yield: 49%; pale-yellow solid; mp 154–156 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.42 (s, 1 H), 7.43 (d, *J* = 8.8 Hz, 1 H), 7.27 (d, *J* = 2.6 Hz, 1 H), 6.76 (dd, *J* = 8.8, 2.6 Hz, 1 H), 3.01 (t, *J* = 6.2 Hz, 2 H), 2.49 (d, *J* = 6.9 Hz, 2 H), 2.16 (p, *J* = 6.4 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 194.3, 171.9, 154.6, 147.8, 124.0, 115.6, 113.0, 111.6, 105.6, 37.3, 23.2, 21.9.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{10}O_3$: 202.0630; found: 202.0628.

Ethyl 5-Hydroxy-2-(4-methoxyphenyl)benzofuran-3-carboxylate (3h)

Yield: 95%: white solid; mp 172–173 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.47 (s, 1 H), 7.96 (d, J = 9.0 Hz, 2 H), 7.48 (d, J = 8.8 Hz, 1 H), 7.41 (d, J = 2.5 Hz, 1 H), 7.08 (d, J = 9.0 Hz, 2 H), 6.86 (dd, J = 8.8, 2.5 Hz, 1 H), 4.34 (q, J = 7.1 Hz, 2 H), 3.86 (s, 3 H), 1.35 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 163.3, 160.8, 160.5, 154.3, 147.1, 130.8 (2C), 127.5, 121.4, 113.8, 113.5 (2C), 111.4, 107.0, 106.6, 60.2, 55.3, 13.9.

HRMS (EI): m/z [M]$^+$ calcd for $C_{18}H_{16}O_5$: 312.0998; found: 312.1001.

Ethyl 2-(3-Bromophenyl)-5-hydroxybenzofuran-3-carboxylate (3i)

Yield: 70%; pale-yellow solid; mp 169 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.51 (s, 1 H), 8.12 (t, J = 1.8 Hz, 1 H), 7.88 (d, J = 8.0 Hz, 1 H), 7.67 (dd, J = 8.0, 1.1 Hz, 1 H), 7.48–7.39 (m, 2 H), 7.38 (d, J = 2.5 Hz, 1 H), 6.86 (dd, J = 8.9, 2.6 Hz, 1 H), 4.28 (q, J = 7.1 Hz, 2 H), 1.30 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 162.8, 158.1, 154.5, 147.5, 132.8, 131.6, 131.2, 130.1, 127.9, 127.2, 121.2, 114.8, 111.7, 109.1, 106.6, 60.4, 13.9.

HRMS (EI): m/z [M]$^+$ calcd for $C_{17}H_{13}BrO_4$: 359.9997; found: 359.9994.

Ethyl 2-(2-Chlorophenyl)-5-hydroxybenzofuran-3-carboxylate (3j)

Yield: 79%; white solid; mp 161–162 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.59 (s, 1 H), 7.70 (dd, J = 7.6, 1.7 Hz, 1 H), 7.66 (dd, J = 8.1, 1.3 Hz, 1 H), 7.62–7.56 (m, 1 H), 7.54 (d, J = 9.0 Hz, 1 H), 7.55–7.46 (m, 1 H), 7.45 (d, J = 2.6 Hz, 1 H), 6.93 (dd, J = 8.9, 2.6 Hz, 1 H), 4.20 (q, J = 7.1 Hz, 2 H), 1.14 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 162.4, 158.1, 154.6, 147.9, 133.0, 132.2, 131.8, 129.3, 129.3, 126.9, 126.2, 114.6, 111.9, 111.0, 106.1, 60.1, 13.7.

HRMS (EI): m/z [M]$^+$ calcd for $C_{17}H_{13}ClO_4$: 316.0502; found: 316.0504.

Ethyl 5-Hydroxy-2-(4-(trifluoromethyl)phenyl)benzofuran-3-carboxylate (3k)

Yield: 61%; pale-yellow solid; mp 157–159 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.56 (s, 1 H), 8.12 (d, J = 8.1 Hz, 2 H), 7.83 (d, J = 8.1 Hz, 2 H), 7.48 (d, J = 8.9 Hz, 1 H), 7.40 (d, J = 2.5 Hz, 1 H), 6.90 (dd, J = 8.8, 2.6 Hz, 1 H), 4.30 (q, J = 7.1 Hz, 2 H), 1.30 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 162.8, 158.0, 154.6, 147.7, 132.9, 129.9 (q, J = 31.3 Hz), 129.8 (2C), 127.0, 124.9 (q, J = 3.9 Hz, 2C), 123.9 (q, J = 273.7 Hz), 114.9, 111.8, 109.7, 106.6, 60.5, 13.8.

HRMS (EI): m/z [M]$^+$ calcd for $C_{18}H_{13}F_3O_4$: 350.0766; found: 350.0765.

Ethyl 2-(Furan-2-yl)-5-hydroxybenzofuran-3-carboxylate (3l)

Yield: 57%; pale-yellow solid; mp 155–156 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.51 (s, 1 H), 7.98 (dd, J = 1.8, 0.7 Hz, 1 H), 7.72 (dd, J = 3.6, 0.8 Hz, 1 H), 7.47 (d, J = 8.9 Hz, 1 H), 7.37 (d, J = 2.5 Hz, 1 H), 6.85 (dd, J = 8.9, 2.6 Hz, 1 H), 6.76 (dd, J = 3.6, 1.7 Hz, 1 H), 4.36 (q, J = 7.1 Hz, 2 H), 1.39 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 162.6, 154.6, 150.8, 147.0, 145.5, 143.3, 126.6, 116.1, 114.45, 112.5, 111.6, 106.7, 106.6, 60.4, 14.1.

HRMS (EI) m/z [M]$^+$ calcd for $C_{15}H_{12}O_5$: 272.0685; found: 272.0689.

Ethyl 5-Hydroxy-2,6-dimethylbenzofuran-3-carboxylate (3m)

Yield: 30%; white solid; 173 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.34 (s, 1 H), 7.31 (s, 1 H), 7.27 (s, 1 H), 4.32 (q, J = 7.1 Hz, 2 H), 2.67 (s, 3 H), 2.21 (s, 3 H), 1.37 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 163.6, 162.5, 152.4, 146.9, 123.9, 122.0, 111.8, 108.0, 105.2, 59.8, 16.5, 14.2, 14.1.

HRMS (EI): m/z [M]$^+$ calcd for $C_{13}H_{14}O_4$: 234.0892; found: 234.0890.

Ethyl 5-Hydroxy-2,7-dimethylbenzofuran-3-carboxylate (3n)

Yield: 61%; white solid; mp 175–178 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.23 (s, 1 H), 7.10 (d, J = 2.4 Hz, 1 H), 6.59 (d, J = 2.5 Hz, 1 H), 4.31 (q, J = 7.1 Hz, 2 H), 2.68 (s, 3 H), 2.37 (s, 3 H), 1.37 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 163.6, 163.2, 154.0, 146.1, 125.8, 120.8, 113.8, 108.3, 103.6, 59.8, 14.5, 14.2, 14.1.

HRMS (EI): m/z [M]$^+$ calcd for $C_{13}H_{14}O_4$: 234.0892; found: 234.0891.

Ethyl 5-Hydroxy-2,6,7-trimethylbenzofuran-3-carboxylate (3o)

Yield: 96%; white solid; mp 142–143 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.21 (s, 1 H), 7.17 (s, 1 H), 4.29 (q, J = 7.1 Hz, 2 H), 2.64 (s, 3 H), 2.28 (s, 3 H), 2.12 (s, 3 H), 1.36 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 163.7, 162.1, 152.2, 146.5, 122.5, 120.1, 119.2, 108.2, 102.8, 59.7, 14.1, 14.1, 11.7, 11.6.

HRMS (EI): m/z [M]$^+$ calcd for $C_{14}H_{16}O_4$: 248.1049; found: 234.0890.

Ethyl 6-Chloro-5-hydroxy-2-methylbenzofuran-3-carboxylate (3p)

Yield: 33%; white solid; mp 184–186 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.12 (s, 1 H), 7.63 (s, 1 H), 7.46 (s, 1 H), 4.30 (q, J = 7.1 Hz, 2 H), 2.66 (s, 3 H), 1.36 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 164.2, 163.1, 150.0, 146.3, 125.2, 117.3, 111.9, 107.9, 106.7, 60.1, 14.1, 14.1.

HRMS (EI): m/z [M]$^+$ calcd for $C_{12}H_{11}ClO_4$: 254.0346; found: 254.0342.

Ethyl 7-Chloro-5-hydroxy-2-methylbenzofuran-3-carboxylate (3q)

Yield: 31%; white solid; mp 209–210 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.76 (s, 1 H), 7.20 (d, J = 2.3 Hz, 1 H), 6.83 (d, J = 2.3 Hz, 1 H), 4.31 (q, J = 7.1 Hz, 2 H), 2.70 (s, 3 H), 1.35 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 164.6, 162.9, 154.8, 142.6, 127.8, 114.7, 112.8, 108.8, 105.3, 60.2, 14.2, 14.1.

HRMS (EI): m/z [M]$^+$ calcd for $C_{12}H_{11}ClO_4$: 254.0346; found: 254.0345.

Ethyl 4-Acetyl-5-hydroxy-2-methylbenzofuran-3-carboxylate (3r)

Yield: 43%; yellow solid; mp 145 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.87 (s, 1 H), 7.46 (d, J = 8.9 Hz, 1 H), 6.89 (d, J = 8.9 Hz, 1 H), 4.22 (q, J = 7.1 Hz, 2 H), 2.61 (s, 3 H), 2.53 (s, 3 H), 1.27 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 201.5, 162.9, 162.7, 150.6, 146.9, 122.1, 120.8, 113.3, 112.4, 109.2, 60.0, 31.9, 14.1, 13.9.

HRMS (EI): m/z [M]$^+$ calcd for $C_{14}H_{14}O_5$: 262.0841; found: 262.0840.

3-Ethyl 4-Methyl 5-hydroxy-2-methylbenzofuran-3,4-dicarboxylate (3s)

Yield: 82%; white solid; mp 144–146 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.81 (s, 1 H), 7.52 (d, *J* = 8.9 Hz, 1 H), 6.92 (d, *J* = 8.9 Hz, 1 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 3.78 (s, 3 H), 2.62 (s, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.4, 162.9, 162.8, 151.9, 146.7, 123.1, 113.4, 113.4, 111.9, 109.3, 60.3, 51.4, 14.1, 13.9.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{14}O_6$: 278.0790; found: 278.0789.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1843-6641.

References and Notes

(1) (a) Hayta, S. A.; Arisoy, M.; Arpaci, O. T.; Aki, I. Y. E.; Zkan, S.; Kaynak, F. *Eur. J. Med. Chem.* **2008**, *43*, 2568. (b) Khanam, H.; Shamsuzzaman, *Eur. J. Med. Chem.* **2015**, *97*, 483. (c) Nevagi, R. J.; Dighe, S. N. *Eur. J. Med. Chem.* **2015**, *97*, 561.

(2) For recent reviews, see: (a) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (e) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

(3) (a) Takasugi, M.; Nagao, S.; Masamune, T.; Shirats, A.; Takahashi, K. *Tetrahedron Lett.* **1978**, 797. (b) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75. (c) Takasugi, M.; Nagao, S.; Ueno, S.; Masamune, T.; Shirata, A.; Takahashi, K. *Chem. Lett.* **1978**, *7*, 1239.

(4) Selected recent reviews, see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (c) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624.

(5) (a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (b) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (d) Xie, X. G.; Chen, B.; Lu, J. P.; Han, J. J.; She, X. G.; Pan, X. F. *Tetrahedron Lett.* **2004**, *45*, 6235. (e) Yang, Z.; Liu, H. B.; Lee, C. M.; Chang, H. M.; Wong, H. N. C. *J. Org. Chem.* **1992**, *57*, 7248. (f) Katritzky, A. R.; Ji, Y.; Fang, Y.; Prakash, I. *J. Org. Chem.* **2001**, *66*, 5613.

(6) (a) Dupont, R.; Cotelie, P. *Tetrahedron* **2001**, *57*, 5585. (b) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 297.

(7) (a) Umesh, A. K.; Regev, P.; Hagit, G.; Rivka, O.; Raz, Z.; Doron, P. *Chem. Eur. J.* **2013**, *19*, 13575. (b) Eden, G.; Yulia, V.; Almog, R.; Sachin, N.; Kavitha, S. *Angew. Chem. Int. Ed.* **2015**, *54*, 4198.

(8) (a) Bertolini, F.; Pineschi, M. *Org. Prep. Proced. Int.* **2009**, *41*, 385. (b) Sheppard, T. D. *J. Chem. Res.* **2011**, *35*, 377. (c) Engler, T. A.; Chai, W.; Lynch, K. O. *Tetrahedron Lett.* **1995**, *36*, 7003. (d) Engler, T. A.; Chai, W. K.; LaTessa, O. *J. Org. Chem.* **1996**, *61*, 9297. (e) Lomberget, T.; Baragona, F.; Fenet, B.; Barret, R. *Org. Lett.* **2006**, *8*, 3919. (f) Fan, R.; Li, W.; Ye, Y.; Wang, L. *Adv. Synth. Catal.* **2008**, *350*, 1531. (g) Baragona, F.; Lomberget, T.; Duchamp, C.; Henriques, N.; Lo Piccolo, E.; Diana, P.; Montalbano, A.; Barret, R. *Tetrahedron* **2011**, *67*, 873.

(9) Enantioselective [3+2] cycloaddition: (a) Jensen, K. L.; Franke, P. T.; Nielsen, L. T.; Daasbjerg, K.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2010**, *49*, 129. (b) Sun, X.-X.; Zhang, H.-H.; Li, G.-H.; Meng, L.; Shi, F. *Chem. Commun.* **2016**, *52*, 2968. (c) Gelis, C.; Bekkaye, M.; Lebée, C.; Blanchard, F.; Masson, G. *Org. Lett.* **2016**, *18*, 3422.

(10) Chen, Y.; Chen, S.; Lu, X.; Cheng, H.; Oua, Y.; Cheng, H.; Zhou, G.-C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1851.

(11) Li, X.-Y.; He, B.-F.; Luo, H.-J.; Huang, N.-Y.; Deng, W.-Q. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4617.

(12) Salome, C.; Ribeiro, N.; Chavagnan, T.; Thuaud, F.; Serova, M.; de Gramont, A.; Faivre, S.; Raymond, E.; Desaubry, L. *Eur. J. Med. Chem.* **2014**, *81*, 181.

(13) Ryu, C.-K.; Song, A. L.; Lee, J. Y.; Hong, J. A.; Yoon, J. H.; Kim, A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6777.

(14) Romagnoli, R.; Baraldi, P. G.; Sarkar, T.; Cara, C. L.; Lopez, O. C.; Carrion, M. D.; Preti, D.; Tolomeo, M.; Balzarini, J.; Hamel, E. *Med. Chem.* **2008**, *4*, 558.

(15) Yadav, P.; Sinph, P.; Tewari, A. K. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2251.

(16) Giza, C. A.; Hinman, R. L. *J. Org. Chem.* **1964**, *29*, 1453.

(17) Pei, L. X.; Li, Y. M.; Bu, X. Z.; Gu, L. Q.; Chan, A. S. C. *Tetrahedron Lett.* **2006**, *47*, 2615.

(18) Liu, Y.-J.; Wang, M.; Yuan, H.-J.; Liu, Q. *Adv. Synth. Catal.* **2010**, *352*, 884.