JOC The Journal of Organic Chemistry

NOTE

pubs.acs.org/joc

K_2CO_3-Promoted Domino Reactions: Construction of Functionalized 2,3-Dihydrobenzofurans and Clofibrate Analogues

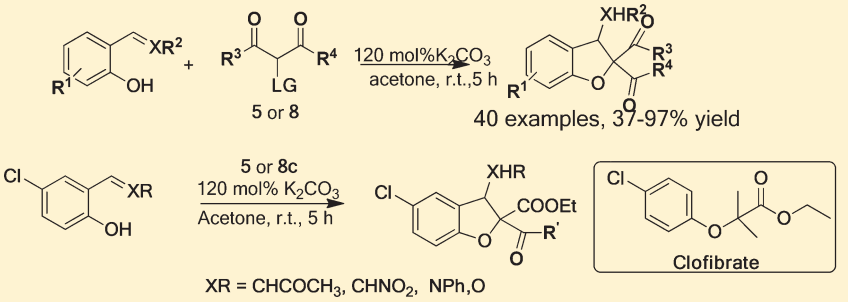
Qu-Bo Li,[†] Fei-Ting Zhou,[†] Zheng-Geng Liu,[†] Xue-Feng Li,[‡] Wei-Dong Zhu,[†] and Jian-Wu Xie*[,†]

[†]Key Laboratory of the Ministry of Education for Advanced Catalysis Materials, Department of Chemistry and Life Science, Zhejiang Normal University, 321004 Jinhua, People's Republic of China

[‡]College of Chemistry and Environment Protection Engineering, Southwest University for Nationalities, Chengdu, People's Republic of China

Supporting Information

ABSTRACT:



The K_2CO_3-catalyzed domino reactions (Michael alkylation, Mannich alkylation, and aldol alkylation) of salicylic aldehyde derivatives (2-hydroxyaryl-α,β-unsaturated ketones, 2-hydroxyarylnitroalkenes, 2-hydroxyarylimines, and salicylic aldehydes) and 2-halo-1,3-dicarbonyl compounds (diethyl α-bromomalonate, diethyl α-chloromalonate, ethyl 2-chloroacetoacetate, and 3-chloropentane-2,4-dione) were carried out under mild conditions to provide a series of functionalized 2,3-dihydrobenzofurans in moderate to excellent yields. The novel transformations simultaneously gave a series of clofibrate analogues, which possess various substitution patterns.

Furan heterocycles occupy a central position in modern heterocyclic chemistry, principally because this heterocyclic ring is an important recognition element in many natural products and biologically active compounds.[1] Among this class of compounds, 2,3-dihydrobenzofurans are recognized to be very important due to their biological activities[2] and their applications in a wide range of chemical transformations and other important targets. Natural products and pharmaceuticals possessing the dihydrobenzofuran skeleton exhibit a wide range of biological activities (Figure 1).[3] For example, (+)-Conocarpan, which was first isolated from the wood of *Conocarpus erectus*,[4] exhibits a diverse array of biological activities, including insecticidal,[5] antifungal,[6] and antitrypanosomal properties.[7] Megapodiol is an antileukemic agent,[8] and Furaquinocines are antibiotics.[9] More and more, 2,3-dihydrobenzofurans have been developed for the treatment of traumatic and ischemic central nervous system (CNS) injury[3a,10] and have been reported to be useful in the treatment of arteriosclerosis, hepatopathy, and cerebrovascular disease.[3b] Consequently, new and efficient methods for the preparation of this important heterocyclic ring system are of contemporary interest because of the many reported applications in the fields of medicinal and agrochemistry. Classical routes for the formation of dihydrobenzofurans include biomimetic couplings of quinones and phenylpropenyl moieties,[11] radical,[12] transition-metal-mediated cyclizations,[13] benzyne,[14] electrocyclic,[15] anionic,[16] organocatalytic, and dehydrative techniques.[17] As part of our medicinal chemistry research program, we required a robust facile synthesis of 2,3-dihydrobenzofuran derivatives wherein we could vary the different substitutions. Herein we report an efficient, mild, and convenient method for the preparation of these derivatives by domino reactions (Michael alkylation, Mannich alkylation, and aldol alkylation).

Recently, we have established that 2-hydroxyaryl-α,β-unsaturated ketones could behave as acceptors and donors in domino reactions (eq 1) under easily mild conditions.[18] Encouraged by the successful results mentioned above, we conceived that 2,3-dihydrobenzofuran derivatives **A** could be synthesized as well from the reaction of **C** with nucleophile **5** (Scheme 1). The proposed synthetic route is described in Scheme 1. We envisioned that the target compound **A** could be traced back to **B**, which might be generated from the domino reaction of diethyl

Received: April 28, 2011
Published: July 27, 2011

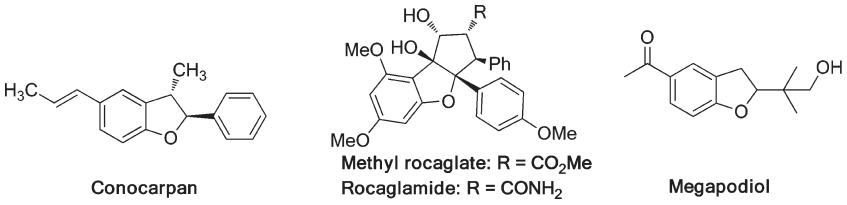
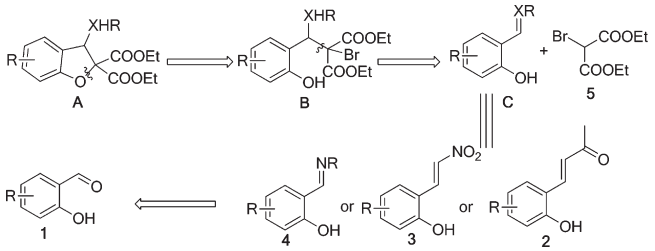
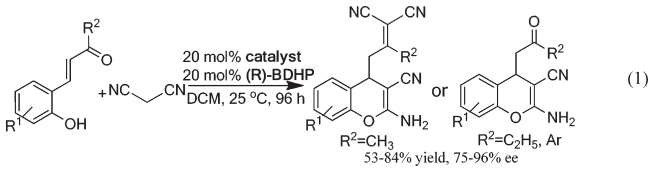


Figure 1. Natural products and pharmaceuticals that contain dihydrobenzofuran rings.

Scheme 1. General Strategy for the Synthesis of Dihydrobenzofuran Derivatives



α-bromomalonate (DBM) **5** with **C** (**2**−**4**). The compounds **2**−**4** were readily obtained from salicylic aldehydes **1**.

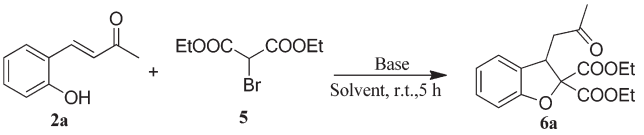


(1)

In an initial study, we studied the domino reaction of **5** with 2-hydroxyphenyl-α,β-unsaturated ketone **2a**, which can easily be prepared in good yields according to the reported procedure.[19] A series of organic solvents and bases were screened for the domino reaction. A few representative results are shown in Table 1. To our delight, the domino reaction proceeded smoothly to provide desired product **6a** when the reaction was carried out in the presence of bases (120 mol %) in THF at room temperature for 5 h (Table 1, entries 1−4). A good yield was obtained when the domino reaction was catalyzed by K_2CO_3 (78% yield, entry 2). However, when the stronger base KOH was used as the catalyst, the reaction became complicated and low yield was isolated (entry 1). Similarly, when the reaction was catalyzed with the weaker base KOAc, the reaction rate was very slow and a low yield was obtained after 5 h (entry 3). However, the organic base DABCO (1,4-diazabicyclo[2.2.2]octane) was used as the catalyst, and the yield of the desired product was higher than those using KOH and KOAc as the catalysts but still lower than that using K_2CO_3 as the catalyst (entry 4). Subsequently, we investigated the effects of solvent on the reactivity when K_2CO_3 was used as the catalyst. A rather low yield was obtained when toluene was used as the solvent (entry 5). Among the solvents examined, the use of acetone gave the best result (entry 6). However, the yield was dramatically decreased when ethanol was used (entry 7). We were pleased to find that the domino reaction proceeded smoothly to provide desired product 2,3-dihydrobenzofuran **6a** using water as solvent, but the yield was low due to the low solubility of **2a** in water (entry 8).

With the optimal reaction conditions [K_2CO_3 (120 mol %), acetone, room temperature] in hand, the scope of the domino

Table 1. Reaction of 2-Hydroxyaryl-α,β-unsaturated Ketone 2a and Diethyl α-Bromomalonate 5 under Different Conditions[a]



entry	base	solvent	yield[b] (%)
1	KOH	THF	46
2	K_2CO_3	THF	78
3	KOAc	THF	31
4	DABCO	THF	60
5	K_2CO_3	toluene	54
6	K_2CO_3	acetone	86
7	K_2CO_3	ethanol	66
8	K_2CO_3	H_2O	47

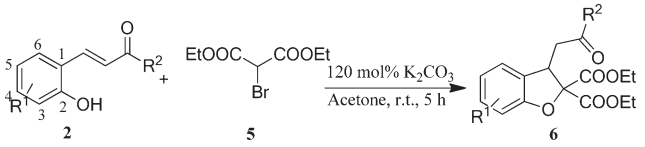
[a] Otherwise noted, reactions performed with 0.20 mmol of **2a**, 0.40 mmol of **5**, 120 mol % of base in 1 mL of solvent at room temperature. [b] Isolated yield.

reaction of **5** with 2-hydroxyaryl-α,β-unsaturated ketones **2** was explored. The results are summarized in Table 2. To assess the impact of the structural and functional motifs on the reaction, we tested a range of 2-hydroxyaryl-α,β-unsaturated ketones **2**. For all cases, diethyl α-bromomalonate **5** reacted with 2-hydroxyaryl-α,β-unsaturated ketones **2**, leading to the corresponding polysubstituted 2,3-dihydrobenzofuran derivatives **6** in moderate to excellent yields. For instance, reaction of 2-hydroxyaryl-α,β-unsaturated ketone **2b** and **5** gave rise to the desired product **6b** in 90% yield (Table 2, entry 2). When 2-hydroxyaryl-α,β-unsaturated ketone **2d** was employed in the above reaction, the desired product **6d** was isolated in 83% yield (Table 2, entry 4). A lower yield was obtained when 2-hydroxyaryl-α,β-unsaturated ketone **2c** was used as a replacement (70% yield, Table 2, entry 3). The reaction with aromatic enones **2g**−**2i** also gave desired products **6g**−**6i** in good yields (Table 2, entries 5−9).

Clofibrate is a lipid lowering agent used for controlling the high cholesterol and triacylglyceride level in the blood.[20,21] In order to study the activity of clofibrate and related analogues, there is an eager desire for a new synthetic method that allows the easy preparation of clofibrate analogues with high efficiency and, more importantly, good feasibility to assemble various substitution patterns.[22] Gratifyingly, this novel transformation could be applied in the synthesis of clofibrate analogues containing 2,3-dihydrobenzofurans (Table 2). Under the same conditions, clofibrate analogues were obtained with good to excellent yields (74−95% yield). Aromatic enones with electron-donating substituents on the ortho, meta, or para positions afford clofibrate analogues with slightly inferior yields (Table 2,

dx.doi.org/10.1021/jo2008675 |J. Org. Chem. 2011, 76, 7222–7228

Table 2. Reaction Scopes of 2-Hydroxyaryl-α,β-unsaturated Ketones in the Domino Reaction[a]



entry	R^1	R^2 (2)	6	yield[b] (%)
1	H	CH_3 (**2a**)	**6a**	86
2	5-Br	CH_3 (**2b**)	**6b**	90
3	5-NO_2	CH_3 (**2c**)	**6c**	70
4	4-CH_3O	CH_3 (**2d**)	**6d**	83
5	H	*p*-BrC_6H_4 (**2e**)	**6e**	78
6	H	*m*-BrC_6H_4 (**2e**)	**6f**	71
7	H	*p*-MeC_6H_4 (**2f**)	**6g**	80
8	5-Br	*p*-MeC_6H_4 (**2g**)	**6h**	77
9	5-Br	*p*-ClC_6H_4 (**2h**)	**6i**	72
10	5-Cl	CH_3 (**2i**)	**6j**	95
11	5-Cl	Ph (**2j**)	**6k**	80
12	5-Cl	*p*-$MeOC_6H_4$ (**2k**)	**6l**	75
13	5-Cl	*m*-$MeOC_6H_4$ (**2l**)	**6m**	70
14	5-Cl	*o*-$MeOC_6H_4$ (**2m**)	**6n**	74
15	5-Cl	*p*-MeC_6H_4 (**2n**)	**6o**	81
16	5-Cl	*p*-BrC_6H_4 (**2o**)	**6p**	79

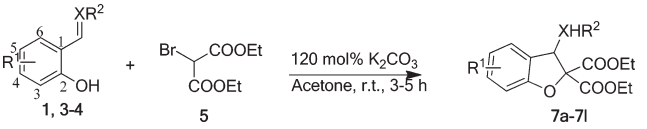
[a] Otherwise noted, reactions performed with 0.20 mmol of **2**, 0.40 mmol of **5**, 120 mol % of K_2CO_3 in 1 mL of acetone at room temperature. [b] Isolated yield.

entries 12−14). The structure of clofibrate analogues was first characterized by spectroscopic analysis, then the structure was established unambiguously by X-ray analysis.[23]

Having succeeded in synthesizing 2,3-dihydrobenzofuran derivatives **6** possessing three carbonyl groups from 2-hydroxyaryl-α,β-unsaturated ketones **2** and **5** under base-mediated conditions, we turned our attention to the possible synthesis of 2,3-dihydrobenzofuran derivatives which possess other useful groups, such as nitro, amino, and hydroxyl groups. A series of potential substrates (**1**, **3**, and **4**) were investigated. The results are summarized in Table 3. Only moderate yields were isolated when 2-hydroxyarylnitroalkenes (**3a**−**3d**) were treated with **5** (Table 3, entries 1−4). This could be explained by the relatively slower nitroalkene polymerization under the base conditions. The electronic effect was very marginal when 2-hydroxyarylimines **4** were treated with **5**, and 2,3-dihydrobenzofuran derivatives **7e**−**7h** possessing a phenylamino group were obtained in good yields (Table 3, entries 5−8). During our ongoing studies of the domino reaction, salicylic aldehydes **1a**−**1e** exhibited high reactivity.[24] The domino reaction of salicylic aldehydes to **5** proceeded with clean products **7i**−**7l** in good to excellent yields (Table 3, entries 9−12). It is worthy of note that clofibrate analogues with different useful functionalities were also obtained in good to excellent yields (Table 3, entries 3, 6, and 10).

To extend the scope of the domino reaction further, other 2-halo-1,3-dicarbonyl compounds **8a**−**8c**, which also contain another leaving group, were utilized as nucleophiles in the domino reaction under the same conditions as aforementioned (Table 4). The domino process took place with diethyl α-chloromalonate, which possesses a different leaving group (Cl), to provide the

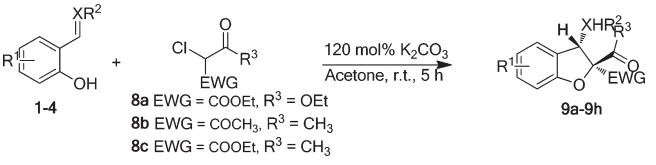
Table 3. Synthesis of Differently Substituted 2, 3-Dihydrobenzofurans[a]



entry	R^1	XR^2	7	yield[b] (%)
1[c]	H	$CHNO_2$ (**3a**)	**7a**	55
2[c]	5-F	$CHNO_2$ (**3b**)	**7b**	47
3[c]	5-Cl	$CHNO_2$ (**3c**)	**7c**	68
4[c]	5-Br	$CHNO_2$ (**3d**)	**7d**	50
5[c]	H	NC_6H_5 (**4a**)	**7e**	82
6[c]	5-Cl	NC_6H_5 (**4b**)	**7f**	87
7[c]	5-Br	NC_6H_5 (**4c**)	**7g**	82
8[c]	4-MeO	NC_6H_5 (**4d**)	**7h**	87
9[d]	H	O (**1a**)	**7i**	92
10[d]	5-Cl	O (**1b**)	**7j**	97
11[d]	5-Br	O (**1c**)	**7k**	94
12[d]	4-MeO	O (**1d**)	**7l**	83

[a] Otherwise noted, reactions performed with 0.20 mmol of **1** or **3** or **4**, 0.40 mmol of **5**, and 120 mol % of K_2CO_3 in 1 mL of acetone at room temperature. [b] Isolated yield. [c] For 3 h. [d] For 5 h.

Table 4. Domino Reaction of 2-Hydroxyaryl-α,β-unsaturated Ketones 2, 2-Hydroxyarylimines 4, 2-Hydroxyarylnitroalkenes 3, and Salicylic Aldehydes 1 to 1,3-Dicarbonyl Compounds (8a and 8b)[a]



entry	substrates (1−4)	substrate (8)	product	yield[b] (%) (dr)[d]
1	**1a**	**8a**	**7i**	81
2	**2a**	**8a**	**6a**	75
3	**3a**	**8a**	**7a**	57
4	**4a**	**8a**	**7e**	77
5[c]	**2j**	**8b**	**9a**	37
6	**3a**	**8b**	**9b**	48
7	**4**	**8b**	**9c**	69
8	**1b**	**8b**	**9d**	63
9[c]	**2j**	**8c**	**9e**	41 (>99:1)
10	**3a**	**8c**	**9f**	54 (79:21)
11	**4a**	**8c**	**9g**	61 (>99:1)
12	**1b**	**8c**	**9h**	57 (57:43)

[a] Otherwise noted, reactions performed with 0.20 mmol of **1** or **2** or **3** or **4**, 0.40 mmol of **5**, 120 mol % of K_2CO_3 in 1 mL of acetone at room temperature. [b] Isolated yield. [c] At 40 °C. [d] Determined by ^1H NMR.

desired products, and it appeared that the yields were somewhat low (Table 4, entries 1−4). Moreover, the domino reactions of other 2-halo-1,3-dicarbonyl compounds **8b**,**8c** with 2-hydroxyarylimine,

dx.doi.org/10.1021/jo2008675 |J. Org. Chem. 2011, 76, 7222–7228

2-hydroxyarylnitroalkene, and salicylic aldehyde proceeded to provide desired products **9a**−**9f**. Moderate yields were obtained when **1b** and **4a**, respectively, were treated with 2-chloro-1,3-dicarbonyl compounds **8b** and **8c** (entries 7,8 and 11,12). 2-Hydroxyarylnitroalkene **2j** furnished 2,3-dihydrobenzofuran derivatives in low yields (37 and 41%, in Table 4, entries 6 and 10). The reactions were very slow for bulkier aromatic enone **2j** under the same conditions. Fortunately, desired products **9a** and **9e** were obtained when the reaction temperature was increased (Table 4, entries 5 and 9). Moreover, 2,3-dihydrobenzofuran derivatives **9f** and **9h** were isolated as a mixture of diastereomers, while **9e** and **9g** were obtained with high diastereoselectivities (Table 4, entries 9−12). The relative stereochemistry of products **9e**−**9h** was established by single-crystal X-ray diffraction study of compound **9g**.[23]

In conclusion, we have developed an efficient, mild, and convenient domino reaction to synthesize differently substituted 2,3-dihydrobenzofurans in moderate to excellent yields from readily available starting materials. In this transformation, a broad substrate scope has been demonstrated. This methodology provides facile access to various multifunctional clofibrate analogues that, to date, have not been reported in the literature. The 2,3-dihydrobenzofuran products may serve as a platform for further manipulation leading to structurally unique benzofurans and other pharmaceutically intriguing compounds. Our future efforts will focus on an asymmetric version of this reaction and biological activities of clofibrate analogues.

EXPERIMENTAL SECTION

General Procedure for the Domino Reaction of 2-Hydroxyaryl-α,β-unsaturated Ketones 2 with Diethyl α-Bromomalonate (DBM) 5. First, 64.8 mg (0.4 mmol) of 2-hydroxyphenyl-α,β-unsaturated ketone (**2a**), 189 mg (0.8 mmol) of diethyl α-bromomalonate (**5**), and 65.8 mg (0.48 mmol) of K_2CO_3 were stirred in acetone (1.5 mL) at room temperature for 5 h. The solvent was removed and flash chromatography on silica gel (15% ethyl acetate/petroleum ether) gave **6a** as pale yellow oil (110 mg, 86% yield).

Diethyl 3-(2-Oxopropyl)benzofuran-2,2(3*H*)-dicarboxylate (6a): pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15−7.09 (m, 2H), 6.93−6.88 (m, 2H), 4.76−4.73 (m, 1H), 4.31−4.24 (m, 4H), 2.91−2.72 (m, 2H), 2.17 (s, 3H), 1.31−1.26 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 166.6, 157.2, 128.9, 128.0, 124.6, 122.1, 110.1, 110.0, 109.9, 62.7, 62.4, 45.3, 42.8, 30.3, 14.0, 13.9; IR (KBr) cm^{-1} 3446, 2979, 1757, 1734, 1670, 1602, 1573; ESI-HRMS calcd for $C_{17}H_{20}O_6$ + Na 343.1169, found 343.1152.

Diethyl 5-Bromo-3-(2-oxopropyl)benzofuran-2,2(3*H*)-dicarboxylate (6b): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.22 (m, 2H), 6.81 (d, J = 8.5 Hz, 1H), 4.74−4.71 (m, 1H), 4.33−4.26 (m, 4H), 2.95−2.73 (m, 2H), 2.20 (s, 3H), 1.32−1.20 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 167.1, 166.4, 156.7, 132.0, 130.9, 128.0, 114.2, 111.8, 91.7, 63.1, 62.8, 45.1, 42.9, 30.4, 14.2, 14.1; IR (KBr) cm^{-1} 3398, 2881, 1741, 1726, 1668, 1551, 1568; ESI-HRMS calcd for $C_{17}H_{19}BrO_6$ + Na 421.0270, found 421.0265;

Diethyl 5-Nitro-3-(2-oxopropyl)benzofuran-2,2(3*H*)-dicarboxylate (6c): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16−8.00 (m, 2H), 7.01 (d, J = 8.9 Hz, 1H), 4.80−4.76 (m, 1H), 4.40−4.27 (m, 4H), 3.06−2.89 (m, 2H), 2.25 (s, 3H), 1.35−1.23 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 166.5, 166.0, 162.8, 143.4, 130.2, 126.5, 121.5, 110.3, 92.7, 63.5, 63.2, 44.8, 42.6, 30.3, 14.3, 14.2; IR (KBr) cm^{-1} 3448, 2978, 1756, 1737, 1668, 1606, 1576; ESI-HRMS calcd for $C_{17}H_{19}NO_8$ + Na 388.1012, found 388.1005.

Diethyl 6-Methoxy-3-(2-oxopropyl)benzofuran-2,2(3*H*)-dicarboxylate (6d): gray solid; mp 52−54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 8.3 Hz, 1H), 6.51−6.42 (m, 2H), 4.68−4.65 (m, 1H), 4.34−4.23 (m, 4H), 3.74 (s, 3H), 2.88−2.68 (m, 2H), 2.17 (s, 3H), 1.33−1.28 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 167.2, 166.5, 160.8, 158.4, 124.8, 119.9, 107.7, 96.5, 91.8, 62.6, 62.4, 55.4, 45.4, 42.3, 30.3, 14.0, 13.8; IR (KBr) cm^{-1} 3447, 2974, 1767, 1735, 1671, 1602, 1574; ESI-HRMS calcd for $C_{18}H_{22}O_7$ + Na 373.1270, found 373.1266.

Diethyl 3-(2-(4-Bromophenyl)-2-oxoethyl)benzofuran-2,2(3*H*)-dicarboxylate (6e): white solid; mp 95−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.16−7.08 (m, 2H), 6.94−6.83 (m, 2H), 4.98−4.94 (m, 1H), 4.31−4.24 (m, 4H), 3.46−3.20 (m, 2H), 1.30−1.21 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 167.6, 157.6, 135.5, 132.3, 132.3, 132.3, 129.9, 129.8, 129.3, 128.9, 128.3, 125.0, 122.5, 110.4, 110.3, 91.6, 63.0, 43.4, 40.87, 14.3, 14.2; IR (KBr) cm^{-1} 3444, 2977, 1755, 1732, 1668, 1600, 1571; ESI-HRMS calcd for $C_{22}H_{21}BrO_6$ + Na 483.0419, found 483.0414.

Diethyl 3-(2-(3-Bromophenyl)-2-oxoethyl)benzofuran-2,2(3*H*)-dicarboxylate (6f): white solid; mp 101−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.74 (m, 2H), 7.61−7.59 (m, 2H), 7.18−7.12 (m, 2H), 6.98−6.89 (m, 2H), 5.02−5.98 (m, 1H), 4.35−4.18 (m, 4H), 3.44−3.29 (m, 2H), 1.34−1.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 167.3, 166.7, 157.3, 135.1, 132.0, 129.6, 129.0, 128.6, 128.0, 124.7, 122.2, 110.1, 91.3, 62.8, 62.5, 43.1, 40.5, 14.0, 14.0; IR (KBr) cm^{-1} 3461, 2980, 1759, 1742, 1670, 1590, 1568; ESI-HRMS calcd for $C_{22}H_{21}BrO_6$ + Na 483.0419, found 483.0416.

Diethyl 3-(2-Oxo-2-(*p*-tolyl)ethyl)benzofuran-2,2(3*H*)-dicarboxylate (6g): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.2 Hz, 2H), 7.32−7.10 (m, 4H), 6.99−6.85 (m, 2H), 5.05−5.01 (m, 1H), 4.34−4.28 (m, 4H), 3.48−3.27 (m, 2H), 2.41 (s, 3H), 1.34−1.23 (m, 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 167.6, 167.0, 157.6, 144.6, 134.3, 129.7, 129.2, 128.6, 128.4, 125.1, 122.4, 110.3, 110.2, 91.7, 63.0, 62.7, 43.4, 40.8, 21.9, 14.3, 14.2; IR (KBr) cm^{-1} 3440, 2973, 1752, 1729, 1665, 1599, 1562; ESI-HRMS calcd for $C_{23}H_{24}O_6$ + Na 419.1478, found 419.1474.

Diethyl 5-Bromo-3-(2-oxo-2-(*p*-tolyl)ethyl)benzofuran-2,2(3*H*)-dicarboxylate (6h): white solid; mp 79−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.1 Hz, 2H), 7.27 (t, J = 6.5 Hz, 4H), 6.83 (d, J = 9.1 Hz, 1H), 4.99−4.95 (m, 1H), 4.35−4.20 (m, 4H), 3.48−3.43 (m, 1H), 3.30−3.24 (m, 1H), 2.40 (s, 3H), 1.32−1.24 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 167.2, 166.7, 156.9, 144.8, 134.1, 132.1, 131.2, 129.7, 128.5, 128.3, 114.4, 111.9, 92.1, 63.2, 62.9, 43.3, 40.5, 22.0, 14.3; IR (KBr) cm^{-1} 3451, 2985, 1762, 1739, 1661, 1616, 1569; ESI-HRMS calcd for $C_{23}H_{23}BrO_6$ + Na 497.0585, found 497.0581.

Diethyl 5-Bromo-3-(2-(4-chlorophenyl)-2-oxoethyl)benzofuran-2,2(3*H*)-dicarboxylate (6i): white solid; mp 95−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 7.29−7.25 (m, 2H), 6.84 (d, J = 8.5 Hz, 1H), 4.94 (d, J = 3.6 Hz, 1H), 4.34−4.28 (m, 4H), 3.47−3.22 (m, 2H), 1.33−1.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 166.9, 166.3, 156.5, 140.1, 134.5, 131.9, 130.5, 129.5, 129.1, 127.9, 114.1, 111.7, 91.7, 62.9, 62.7, 43.0, 40.3, 14.0, 13.9; IR (KBr) cm^{-1} 3439, 2957, 1768, 1740, 1663, 1581, 1550; ESI-HRMS calcd for $C_{22}H_{20}BrClO_6$ + Na 517.0007, found 517.0024.

Diethyl 5-Chloro-3-(2-oxopropyl)benzofuran-2,2(3*H*)-dicarboxylate (6j): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08−6.98 (m, 2H), 6.78 (d, J = 8.5 Hz, 1H), 4.67−4.63 (m, 1H), 4.29−4.16 (m, 4H), 2.89−2.83 (m, 1H), 2.73−2.66 (m, 1H), 2.13 (s, 3H), 1.26−1.22 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 167.2, 166.5, 156.3, 130.4, 129.1, 127.1, 125.2, 111.3, 91.9, 63.1, 62.9, 45.2, 43.0, 30.5, 14.3, 14.2; IR (KBr) cm^{-1} 3445, 2968, 1748, 1728, 1666, 1608, 1556; ESI-HRMS calcd for $C_{17}H_{19}ClO_6$ + Na 377.0754, found 377.0750.

Diethyl 5-Chloro-3-(2-oxo-2-phenylethyl)benzofuran-2,2(3*H*)-dicarboxylate (6k): yellow solid; mp 91−93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.6 Hz, 2H), 7.59−7.53 (m, 1H), 7.47 (t, J = 7.0 Hz, 2H), 7.18−7.06 (m, 2H), 6.87 (d, J = 9.0 Hz, 1H),

4.98−4.94 (m 1H), 4.35−4.19 (m, 4H), 3.50−3.45 (m, 1H), 3.33−3.26 (m, 1H), 1.33−1.24 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 167.4, 166.8, 156.5, 136.7, 134.0, 130.7, 129.3, 129.2, 128.5, 127.4, 125.6, 111.5, 92.3, 63.3, 63.1, 43.5, 40.8, 14.5, 14.4; IR (KBr) cm^{-1} 3441, 2975, 1767, 1721, 1664, 1618, 1563; ESI-HRMS calcd for $C_{22}H_{21}ClO_6$ + Na 439.0935, found 439.0931.

Diethyl 5-Chloro-3-(2-(4-methoxyphenyl)-2-oxoethyl) benzofuran-2,2(3*H*)-dicarboxylate (6l): yellow solid; mp 89−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.9 Hz, 2H), 7.13−7.11 (m, *J*2H), 7.00−6.81 (m, 3H), 4.98−4.95 (m, 1H), 4.36−4.29 (m, 4H), 3.87 (s, 3H), 3.42−3.26 (m, 2H), 1.32−1.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 167.3, 166.7, 164.1, 156.4, 130.7, 130.7, 129.7, 129.1, 127.2, 125.5, 114.2, 111.3, 92.2, 63.2, 62.9, 55.8, 43.5, 40.2, 14.3, 14.3; IR (KBr) cm^{-1} 3450, 2972, 1751, 1727, 1663, 1603, 1563; ESI-HRMS calcd for $C_{23}H_{23}ClO_7$ + Na 469.1026, found 469.1024.

Diethyl 5-Chloro-3-(2-(3-methoxyphenyl)-2-oxoethyl) benzofuran-2,2(3*H*)-dicarboxylate (6m): yellow solid; mp 87−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 2H), 7.37 (s, 1H), 7.12 (d, J = 5.9 Hz, 3H), 6.88 (d, J = 9.1 Hz, 1H), 4.98−4.95 (m, 1H), 4.36−4.20 (m, 4H), 3.85 (s, 3H), 3.47−3.30 (m, 2H), 1.33−1.21 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 167.3, 166.7, 160.2, 156.4, 137.9, 130.5, 130.1, 129.2, 127.2, 125.4, 120.9, 120.4, 112.6, 111.3, 92.2, 63.2, 63.0, 55.7, 43.4, 40.7, 14.3, 14.3; IR (KBr) cm^{-1} 3439, 2973, 1756, 1738, 1666, 1605, 1560; ESI-HRMS calcd for $C_{23}H_{23}ClO_7$ + Na 469.1026, found 469.1022.

Diethyl 5-Chloro-3-(2-(2-methoxyphenyl)-2-oxoethyl) benzofuran-2,2(3*H*)-dicarboxylate (6n): yellow solid; mp 85−87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.7 Hz, 1H), 7.54−7.43 (m, 1H), 7.18−7.07 (m, 2H), 7.06−7.01 (m, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 4.90−4.88 (m, 1H), 4.47−4.18 (m, 4H), 3.85 (d, J = 2.2 Hz, 3H), 3.49--3.29 (m, 2H), 1.32−1.26 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 167.4, 166.9, 159.2, 156.5, 134.6, 131.1, 131.0, 129.0, 127.5, 127.2, 125.7, 121.2, 112.0, 111.3, 92.5, 63.2, 62.8, 55.8, 55.8, 55.8, 46.1, 43.7, 14.4, 14.3; IR (KBr) cm^{-1} 3440, 2982, 1755, 1736, 1667, 1612, 1579; ESI-HRMS calcd for $C_{23}H_{23}ClO_7$ + Na 469.1026, found 469.1024.

Diethyl 5-Chloro-3-(2-oxo-2-(*p*-tolyl)ethyl)benzofuran-2, 2(3*H*)-dicarboxylate (6o): white solid; mp 119−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 2H), 7.26 (t, J = 9.4 Hz, 2H), 7.17−7.12 (m, 2H), 6.95 (d, J = 8.0 Hz, 1H), 6.87 (t, J = 7.5 Hz, 1H), 5.03−5.00 (m, 1H), 4.34−4.13 (m, 4H), 3.46−3.41 (m, 1H), 3.30−3.24 (m, 1H), 2.39 (s, 3H), 1.32−1.22 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 167.6, 167.0, 157.6, 144.6, 134.3, 129.7, 129.2, 128.6, 128.4, 125.1, 122.4, 110.3, 110.2, 91.7, 63.0, 62.7, 43.4, 40.8, 21.9, 14.3, 14.2; IR (KBr) cm^{-1} 3443, 2977, 1760, 1734, 1670, 1607, 1571; ESI-HRMS calcd for $C_{23}H_{23}ClO_6$ + Na 453.1085, found 453.1075.

Diethyl 3-(2-(4-Bromophenyl)-2-oxoethyl)-5-chlorobenzofuran-2,2(3*H*)-dicarboxylate (6p): white solid; mp 106−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.9 Hz, 2H), 7.61 (d, J = 7.9 Hz, 2H), 7.19−7.04 (m, 2H), 6.88 (d, J = 8.4 Hz, 1H), 4.95−4.91 (m, 1H), 4.38− 4.18 (m, 4H), 3.43−3.22 (m, 2H), 1.33−1.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 167.4, 166.8, 156.5, 135.4, 132.5, 130.5, 130.0, 129.4, 129.3, 127.4, 125.5, 111.5, 92.2, 63.3, 63.1, 43.4, 40.7, 14.4, 14.4; IR (KBr) cm^{-1} 3451, 2984, 1762, 1733, 1675, 1604, 1577; ESI-HRMS calcd for $C_{22}H_{20}BrClO_6$ + Na 517.0022, found 517.0018.

Diethyl 3-(Nitromethyl)benzofuran-2,2(3*H*)-dicarboxylate (7a): yellow solid; mp 52−54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.14 (m, 1H), 7.13 (d, J = 7.5 Hz, 1H), 7.03−6.94 (m, 2H), 5.05 (t, J = 6.8 Hz, 1H), 4.85−4.64 (m, 2H), 4.38−4.27 (m, 4H), 1.34−1.30 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 165.7, 157.3, 130.3, 124.2, 123.4, 122.7, 110.7, 89.8, 74.9, 63.3, 63.2, 45.4, 13.9, 13.8; IR (KBr) cm^{-1} 2985, 1765, 1718, 1561, 1483; ESI-HRMS calcd for $C_{15}H_{17}NO_7$ + Na 346.0910, found 346.0897.

Diethyl 5-Fluoro-3-(nitromethyl)benzofuran-2,2(3*H*)-dicarboxylate (7b): yellow solid; mp 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (t, J = 5.8 Hz, 2H), 6.87 (d, J = 7.7 Hz, 1H), 5.01 (s, 1H), 4.85−4.80 (m, 1H), 4.66−4.63 (m, 1H), 4.36−4.28 (m, 4H), 1.34−1.26 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 165.4, 116.9, 116.7, 111.7, 111.5, 111.3, 111.3, 90.3, 74.5, 63.4, 63.3, 45.4, 13.9; IR (KBr) cm^{-1} 2987, 1763, 1744, 1560, 1485; ESI-HRMS calcd for $C_{15}H_{16}FNO_7$ + Na 364.0806, found 364.0796.

Diethyl 5-Chloro-3-(nitromethyl)benzofuran-2,2(3*H*)-dicarboxylate (7c): yellow solid; mp 101−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.21 (m, 1H), 7.12 (d, J = 1.2 Hz, 1H), 6.93 (d, J = 8.6 Hz, 1H), 5.00 (s, 1H), 4.80 (d, J = 6.5 Hz, 1H), 4.66 (d, J = 7.0 Hz, 1H), 4.36−4.28 (m, 4H), 1.32 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 156.1, 130.3, 127.6, 125.4, 124.4, 124.4, 111.8, 90.2, 74.5, 63.4, 63.4, 45.3, 13.8; IR (KBr) cm^{-1} 2989, 1770, 1746, 1555, 1478; ESI-HRMS calcd for $C_{15}H_{17}NO_7$ + Na 346.0898, found 346.0891.

Diethyl 5-Bromo-3-(nitromethyl)benzofuran-2,2(3*H*)-dicarboxylate (7d): yellow solid; mp 214−216 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.6 Hz, 1H), 7.26 (s, 1H), 6.88 (d, J = 8.6 Hz, 1H), 5.01 (s, 1H), 4.80 (d, J = 6.4 Hz, 1H), 4.66 (d, J = 7.0 Hz, 1H), 4.36−4.28 (m, 4H), 1.32 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 165.3, 156.6, 133.2, 127.3, 125.9, 114.6, 112.3, 90.1, 74.5, 63.4, 63.3, 45.2, 13.9, 13.8; IR (KBr) cm^{-1} 2966, 1757, 1746, 1549, 1478; ESI-HRMS calcd for $C_{15}H_{16}BrNO_7$ + Na 424.0001, found 424.0005.

Diethyl 3-(Phenylamino)benzofuran-2,2(3*H*)-dicarboxylate (7e): gray solid; mp 137−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.23 (m, 2H), 7.20 (t, J = 7.8 Hz, 2H), 7.07−6.91 (m, 2H), 6.83 (d, J = 7.9 Hz, 2H), 6.76 (t, J = 7.3 Hz, 1H), 6.17 (d, J = 9.0 Hz, 1H), 4.40−4.29 (m, 1H), 4.28−4.09 (m, 1H), 4.07−3.92 (m, 1H), 3.91 (d, J = 9.0 Hz, 1H), 3.76−3.74(m, 1H), 1.33 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 165.5, 157.8, 146.2, 130.6, 129.2, 125.6, 125.4, 122.5, 118.5, 113.4, 110.8, 92.6, 62.7, 62.3, 61.6, 13.9, 13.5; IR (KBr) cm^{-1} 3398, 2987, 1752, 1736, 1621, 1476; ESI-HRMS calcd for $C_{20}H_{21}NO_5$ + Na 378.1310, found 378.1312.

Diethyl 5-Chloro-3-(phenylamino)benzofuran-2,2(3*H*)-dicarboxylate (7f): white solid; mp 143−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.18 (m, 4H), 6.93 (d, J = 8.5 Hz, 1H), 6.84−6.78 (m, 3H), 6.15 (d, J = 9.5 Hz, 1H), 4.40−4.29 (m, 2H), 4.05−3.97 (m, 2H), 3.76−3.73 (m, 1H), 1.33 (t, J = 7.1 Hz, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 165.6, 156.8, 146.3, 130.9, 129.6, 127.8, 127.6, 125.9, 119.2, 113.9, 112.3, 93.6, 63.3, 62.8, 61.7, 14.3, 13.9; IR (KBr) cm^{-1} 3394, 2983, 1750, 1734, 1602, 1473; ESI-HRMS calcd for $C_{20}H_{20}ClNO_5$ + Na 412.0932, found 412.0922.

Diethyl 5-Bromo-3-(phenylamino)benzofuran-2,2(3*H*)-dicarboxylate (7g): white solid; mp 151−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.2 Hz, 1H), 7.38−7.36 (m, 1H), 7.22−7.18 (m, 2H), 6.90−6.76 (m, 4H), 6.15 (d, J = 7.7 Hz, 1H), 4.45−3.94 (m, 4H), 3.76−3.70 (m, 1H), 1.35−0.9 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 165.5, 157.3, 146.3, 133.8, 129.7, 129.7, 129.6, 128.8, 128.3, 119.3, 114.6, 113.9, 112.8, 93.5, 63.3, 62.8, 61.7, 14.3, 13.9; IR (KBr) cm^{-1} 3401, 2991, 1761, 1742, 1618, 1477; ESI-HRMS calcd for $C_{20}H_{20}BrNO_5$ + Na 456.0412, found 456.0409.

Diethyl 6-Methoxy-3-(phenylamino)benzofuran-2,2(3*H*)-dicarboxylate (7h): pale yellow solid; mp 126−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.18 (m, 4H), 6.81 (d, J = 8.5 Hz, 1H), 6.57−6.53 (m, 3H), 6.09 (d, J = 9.5 Hz, 1H), 4.43−4.24 (m, 2H), 4.10−4.02 (m, 2H), 3.90−3.70 (m, 3H), 1.33 (t, J = 7.1 Hz, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 165.9, 162.5, 159.6, 146.6, 129.6, 126.0, 118.8, 117.8, 113.8, 109.5, 96.8, 63.1, 62.7, 61.7, 56.0, 14.4, 13.9; IR (KBr) cm^{-1} 3396, 2987, 1755, 1735, 1608, 1476; ESI-HRMS calcd for $C_{21}H_{23}NO_6$ + Na 408.1411, found 408.1418.

Diethyl 3-Hydroxybenzofuran-2,2(3*H*)-dicarboxylate (7i): gray green solid; mp 79−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.2 Hz, 1H), 7.31−7.27 (m, 1H), 7.02−6.98 (m, 2H), 5.90 (d, J = 7.7 Hz, 1H), 4.35−4.18 (m, 4H), 3.24 (d, J = 7.8 Hz, 1H), 1.32−1.24 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 165.7, 158.7, 131.4, 131.4, 126.2, 126.1, 122.8, 111.2, 93.2, 76.6, 63.1, 63.0, 14.4, 14.2; IR

(KBr) cm^{-1} 3446, 2979, 1762, 1738, 1466; ESI-HRMS calcd for $C_{14}H_{16}O_6$ + Na 303.0866, found 303.0839.

Diethyl 5-Chloro-3-hydroxybenzofuran-2,2(3*H*)-dicarboxylate (7j): white solid; mp 89−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 7.2 Hz, 1H), 7.20−7.17 (m, 1H), 6.88−6.86 (m, 2H), 5.85 (d, J = 7.7 Hz, 1H), 4.28−4.15 (m, 4H), 3.80 (d, J = 7.8 Hz, 1H), 1.26−1.22 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 165.4, 157.2, 131.2, 128.0, 127.4, 126.1, 112.2, 93.7, 76.1, 63.2, 63.1, 14.2, 14.1; IR (KBr) cm^{-1} 3442, 2977, 1755, 1735, 1470; ESI-HRMS calcd for $C_{14}H_{15}ClO_6$ + Na 337.0476, found 337.0449.

Diethyl 5-Bromo-3-hydroxybenzofuran-2,2(3*H*)-dicarboxylate (7k): gray green solid; mp 101−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 7.2 Hz, 1H), 7.47−7.37 (m, 1H), 6.89−6.87 (m, 2H), 5.88 (d, J = 7.7 Hz, 1H), 4.35−4.20 (m, 4H), 3.28 (d, J = 7.8 Hz, 1H), 1.32−1.26 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 165.5, 157.9, 134.3, 129.2, 128.5, 114.7, 113.0, 93.6, 76.3, 63.4, 63.3, 14.4, 14.3; IR (KBr) cm^{-1} 3440, 2974, 1753, 1731, 1471; ESI-HRMS calcd for $C_{14}H_{15}BrO_6$ + Na 380.9943, found 380.9938.

Diethyl 3-Hydroxy-6-methoxybenzofuran-2,2(3*H*)-dicarboxylate (7l): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 9.0 Hz, 1H), 6.55−6.53 (m, 2H), 5.82 (d, J = 7.8 Hz, 1H), 4.34−4.19 (m, 4H), 3.76 (s, 3H), 1.32−1.26 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 165.7, 162.8, 160.3, 126.4, 118.3, 109.4, 109.4, 96.8, 94.2, 76.2, 63.1, 63.0, 55.9, 14.4, 14.2; IR (KBr) cm^{-1} 3451, 2982, 1760, 1742, 1474; ESI-HRMS calcd for $C_{15}H_{18}O_7$ + Na 333.0943, found 333.0937.

1,1′-(5-Chloro-3-(2-oxo-2-phenylethyl)-2,3-dihydrobenzofuran-2,2-diyl)diethanone (9a): gray solid; mp 124.1−126.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 7.3 Hz, 2H), 7.57 (s, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.16−6.90 (m, 1H), 7.09 (s, 1H), 6.91 (d, J = 8.5 Hz, 1H), 4.68−4.66 (m, 1H), 3.49−3.44 (m, 1H), 3.32−3.28 (m, 1H), 2.41 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.3, 201.2, 196.8, 155.8, 136.2, 133.6, 130.5, 128.9, 128.7, 128.7, 127.1, 125.3, 110.8, 101.3, 42.4, 39.3, 29.7, 28.2, 26.1; IR (KBr) cm^{-1} 3447, 2982, 1771, 1768, 1667, 1609, 1547; ESI-HRMS calcd for $C_{20}H_{17}ClO_4$ + Na 379.0708, found 379.0698.

1,1′-(3-(Nitromethyl)-2,3-dihydrobenzofuran-2,2-diyl)diethanone (9b): yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.23 (m, 1H), 7.10 (d, J = 7.5 Hz, 1H), 7.02−6.93 (m, 2H), 4.77 (d, J = 5.3 Hz, 2H), 4.63 (s, 1H), 2.48 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9, 157.1, 130.2, 124.5, 123.3, 122.7, 110.5, 99.8, 87.5, 74.1, 44.7, 28.2, 25.9; IR (KBr) cm^{-1} 2991, 1779, 1774, 1568, 1508; ESI-HRMS calcd for $C_{13}H_{13}NO_5$ + Na 286.0686, found 286.0698.

1,1′-(3-(Phenylamino)-2,3-dihydrobenzofuran-2,2-diyl)diethanone (9c): white solid; mp 141.1−143.3 °C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.28−7.21 (m, 3H), 7.07−7.02 (m, 2H), 6.83 (t, J = 7.9 Hz, 3H), 5.94 (d, J = 8.0 Hz, 1H), 3.62 (s, 1H), 2.28 (t, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7, 201.8, 157.3, 146.8, 130.6, 129.9, 125.8, 122.8, 119.30, 113.8, 110.7, 61.6, 27.6, 26.5; IR (KBr) cm^{-1} 3403, 2985, 1763, 1759, 1618, 1480; ESI-HRMS calcd for $C_{18}H_{17}NO_3$ + Na 318.1101, found 318.1100.

1,1′-(3-Hydroxy-2,3-dihydrobenzofuran-2,2-diyl)diethanone (9d): white solid; mp 103.1−105.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 2.2 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 6.94 (d, J = 8.6 Hz, 1H), 5.78 (d, J = 6.2 Hz, 1H), 4.00 (d, J = 6.4 Hz, 1H), 2.32 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7, 201.7, 156.5, 131.1, 128.5, 127.5, 126.3, 111.5, 103.8, 75.4, 27.8, 26.8; IR (KBr) cm^{-1} 3445, 2982, 1757, 1742, 1465; ESI-HRMS calcd for $C_{12}H_{11}ClO_4$ + Na 277.0238, found 277.0244.

Ethyl 2-Acetyl-5-chloro-3-(2-oxo-2-phenylethyl)-2,3-dihydrobenzofuran-2-carboxylate (9e): colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93−7.91 (m, 2H), 7.56 (d, J = 7.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 7.13−7.10 (m, 2H), 6.86 (d, J = 8.1 Hz, 1H), 4.88−4.86 (m, 1H), 4.28−4.21 (m, 2H), 3.43−3.28 (m, 1H), 3.28−3.26 (m, 1H), 2.34 (d, J = 2.2 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 196.6, 166.8, 155.8, 136.9, 133.1, 130.5, 128.1, 128.8, 128.6, 127.8, 125.5, 110.3, 96.7, 62.7, 41.9, 40.5, 25.6, 14.7; IR (KBr) cm^{-1} 3446, 2978, 1764, 1712, 1664, 1618, 1563; ESI-HRMS calcd for $C_{21}H_{19}ClO_5$ + Na 409.0813, found 409.0817.

Ethyl 2-Acetyl-3-(nitromethyl)-2,3-dihydrobenzofuran-2-carboxylate (9f): yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, J = 8.5 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 6.99−6.96 (m, 2H), 4.96 (s, 1H), 4.73 (d, J = 6.6 Hz, 1H), 4.62 (d, J = 6.9 Hz, 1H), 4.33−4.27 (m, 2H), 2.48 (s, 1H), 2.33 (s, 2H), 1.33−1.27 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 165.7, 156.7, 130.3, 130.7, 124.71, 124.7, 123.6, 122.7, 122.6, 110.9, 110.5, 94.2, 75.1, 73.6, 63.4, 63.3, 45.2, 43.6, 27.9, 25.4, 13.9, 13.8; IR (KBr) cm^{-1} 2981, 1772, 1716, 1549, 1490; ESI-HRMS calcd for $C_{14}H_{15}NO_6$ + Na 316.0792, found 316.0797.

Ethyl 2-Acetyl-3-(phenylamino)-2,3-dihydrobenzofuran-2-carboxylate (9g): gray solid; mp 122.1−124.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 7.4 Hz, 2H), 7.18 (d, J = 7.8 Hz, 2H), 7.01−6.98 (m, 2H), 6.83 (d, J = 8.0 Hz, 2H), 6.75 (s, 1H), 6.12 (s, 1H), 4.06−4.02 (m, 1H), 3.87 (s, 1H), 3.79−3.74 (m, 1H), 2.36 (s, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 165.7, 157.9, 146.7, 130.6, 129.5, 129.3, 129.1, 125.2, 125.0, 122.2, 118.7, 113.1, 110.4, 96.9, 62.7, 59.6, 26.3, 13.3; IR (KBr) cm^{-1} 3447, 2969, 1751, 1727, 1537; ESI-HRMS calcd for $C_{19}H_{19}NO_4$ + Na 348.1206, found 348.1212.

Ethyl 2-Acetyl-5-chloro-3-hydroxy-2,3-dihydrobenzofuran-2-carboxylate (9h): white solid; mp 72.1−75.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.33 (m, 1H), 7.27−7.24 (m, 1H), 6.95−6.90 (m, 1H), 5.86 (s, 1H), 4.31−4.20 (m, 2H), 3.76 (s, 1H), 2.32 (s, 2H), 2.30 (s, 1H), 1.31−1.24 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.0, 199.6, 166.7, 165.2, 157.9, 156.3, 130.5, 130.1, 128.5, 127.9, 127.4, 127.20, 126.7, 111.9, 111.8, 98.2, 97.5, 76.2, 74.5, 62.4, 27.7, 25.8, 13.9, 13.8; IR (KBr) cm^{-1} 3451, 2976, 1748, 1741, 1455; ESI-HRMS calcd for $C_{13}H_{13}ClO_5$ + Na 307.0344, found 307.0343.

Crystal Data for 6k: $C_{22}H_{21}ClO_6$ (416.84120), triclinic, $P\bar{1}$, a = 9.0198(4) Å, b = 11.6551(6) Å, c = 11.6797(5) Å, U = 1060.22(9) Å^3, Z = 2, specimen 0.586 × 0.378 × 0.259 mm^3, T = 296(2) K, SIEMENS P4 diffractometer, absorption coefficient 2.090 mm^{-1}, reflections collected 17 106, independent 5709 [R(int) = 0.0394], refinement by full-matrix least-squares on F^2, data/restraints/parameters 5709/0/262, goodness-of-fit on F^2 = 1.056, final R indices [$I > 2\sigma(I)$] $R1$ = 0.0735, $wR2$ = 0.2184, R indices (all data) $R1$ = 0.1263, $wR2$ = 0.2603, largest diff. peak and hole 0.664 and −0.550 Å^{-3}.

Crystal Data for 6p: $C_{22}H_{20}BrClO_6$ (495.74), monoclinic, space group $P2(1)/c$, a = 15.7744(6) Å, b = 10.0072(4) Å, c = 14.5277(5) Å, U = 2131.50(14) Å^3, Z = 4, specimen 0.499 × 0.453 × 0.364 mm^3, T = 296(2) K, SIEMENS P4 diffractometer, absorption coefficient 2.090 mm^{-1}, reflections collected 17 622, independent 4844 [R(int) = 0.0497], refinement by full-matrix least-squares on F^2, data/restraints/parameters 4844/0/271, goodness-of-fit on F^2 = 1.036, final R indices [$I > 2\sigma(I)$] $R1$ = 0.0483, $wR2$ = 0.1232, R indices (all data) $R1$ = 0.0902, $wR2$ = 0.1413, largest diff. peak and hole 0.697 and −0.598 Å^{-3}.

Crystal Data for 9g: $C_{19}H_{19}NO_4$ (325.35), triclinic, space group $P\bar{1}$, a = 7.9833(5) Å, b = 11.2090(7) Å, c = 11.4737(12) Å, U = 848.75(12) Å^3, Z = 2, specimen 0.257 × 0.0157 × 0118 mm^3, T = 296(2) K, SIEMENS P4 diffractometer, absorption coefficient 0.090 mm^{-1}, reflections collected 17 622, independent 13 331 [R(int) = 0.0277], refinement by full-matrix least-squares on F^2, data/restraints/parameters 3846/0/271, goodness-of-fit on F^2 = 1.036, final R indices [$I > 2\sigma(I)$] $R1$ = 0.0533, $wR2$ = 01429, R indices (all data) $R1$ = 0.0979, $wR2$ = 0.1429, largest diff. peak and hole 0.260 and −0.210 Å^{-3}.

■ ASSOCIATED CONTENT

Supporting Information. Copies of NMR spectra and X-ray structural data for **6k**, **6p**, **9g** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*E-mail: xiejw@zjnu.cn.

ACKNOWLEDGMENT

We are grateful for the financial support from the National Natural Science Foundation of China (20902083), the Natural Science Foundation of Zhejiang Province, China (Y4090082, R4080084), and the Program for Changjiang Scholars and Innovative Research Team in Chinese Universities (IRT0980).

REFERENCES

(1) (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. (b) Durani, N.; Jain, R.; Saeed, A.; Dikshit, D. K.; Durani, S.; Kapil, R. S. *J. Med. Chem.* **1989**, *32*, 1700. (c) McCallion, G. D. *Curr. Org. Chem.* **1999**, *3*, 67. (d) Mortensen, D. S.; Rodriguez, A. L.; Carlson, K. E.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2001**, *33*, 3838.

(2) (a) Shi, G. Q.; Dropinski, J. F.; Zhang, Y.; Santini, C.; Sahoo, S. P.; Berger, J. P.; MacNaul, K. L.; Zhou, G.; Agrawal, A.; Alvaro, R.; Cai, T.-q.; Hernandez, M.; Wright, S. D.; Moller, D. E.; Heck, J. V.; Meinke, P. T. *J. Med. Chem.* **2005**, *48*, 5589. (b) Nichols, D. E.; Hoffman, A. J.; Oberlender, R. A.; Riggs, R. M. *J. Med. Chem.* **1986**, *29*, 302. (c) Kataoka, K.; Shiota, T.; Takeyasu, T.; Minoshima, T.; Watanabe, K.; Tanaka, H.; Mochizuki, T.; Taneda, K.; Ota, M.; Tanabe, H.; Yamaguchi, H. *J. Med. Chem.* **1996**, *39*, 1262.

(3) (a) Ohkawa, S.; Fukatsu, K.; Miki, S.; Hashimoto, T.; Sakamoto, J.; Doi, T.; Nagai, Y.; Aono, T. *J. Med. Chem.* **1997**, *40*, 559.(b) Aono, T.; Ohkawa, S.; Doi, T. EP Patent 483772, 1992.

(4) Hayashi, T.; Thomson, R. H. *Phytochemistry* **1975**, *14*, 1085.

(5) Chauret, D. C.; Bernard, C. B.; Arnason, J. T.; Durst, T. *J. Nat. Prod.* **1996**, *59*, 152.

(6) De Campos, M. P.; Filho, V. C.; Da Silva, R. Z.; Yunes, R. A.; Zacchino, S.; Juarez, S.; Bella Cruz, R. C.; Bella Cruz, A. *Biol. Pharm. Bull.* **2005**, *28*, 1527.

(7) Luize, P. S.; Ueda-Nakamura, T.; Filho, B. P. D.; Cortez, D. A. G.; Nakamura, C. V. *Biol. Pharm. Bull.* **2006**, *29*, 2126.

(8) Jarvis, B. B.; Pena, N. B.; Comezoglu, S. N.; Rao, M. M. *Phytochemistry* **1986**, *25*, 533.

(9) Saito, T.; Suzuki, T.; Morimoto, M.; Akiyama, C.; Ochiai, T.; Takeuchi, K.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1998**, *120*, 11633.

(10) Sartorelli, S.; Benevides, P. J. C.; Ellensohn, R. M.; Rocha, M. V. A. F.; Moreno, P. R. H.; Kato, M. J. *Plant Sci.* **2001**, *161*, 1083.

(11) (a) Mangas-Sánchez, J.; Busto, E.; Gotor-Fernández, V.; Gotor, V. *Org. Lett.* **2010**, *12*, 3498. (b) Benbow, J. W.; Katoch-Rouse, R. *J. Org. Chem.* **2001**, *66*, 4965. (c) Engler, T. A.; Wei, D.; Letavic, M. A.; Combrink, K. D.; Reddy, J. P. *J. Org. Chem.* **1994**, *59*, 6588. (d) Engler, T. A.; Combrink, K. D.; Ray, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 7931. (e) Bolzacchini, E.; Brunow, G.; Meinardi, S.; Orlandi, M.; Rindone, B.; Rummakko, P.; Setala, H. *Tetrahedron Lett.* **1998**, *39*, 3291. (f) Kerns, M. L.; Conroy, S. M.; Swenton, J. S. *Tetrahedron Lett.* **1994**, *35*, 7529. (g) Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* **1992**, *57*, 2135. (h) Wang, S.; Gates, B. D.; Swenton, J. S. *J. Org. Chem.* **1991**, *56*, 1979. (i) Shizuri, Y.; Nakamura, K.; Yamamura, S. *J. Chem. Soc., Chem. Commun.* **1985**, 530.

(12) (a) Kuethe, J. T.; Wong, A.; Journet, M.; Davies, I. W. *J. Org. Chem.* **2005**, *70*, 3727. (b) Jiménez, M. C.; Miranda, M. A.; Tormas, R. *J. Org. Chem.* **1998**, *63*, 1323. (c) Meijs, G. F.; Beckwith, A. L. J. *J. Am. Chem. Soc.* **1986**, *108*, 5890.

(13) (a) Wang, X.; Lu, Y.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 12203. (b) Szlosek-Pinaud, M.; Diaz, P.; Martinez, J.; Lamaty, F. *Tetrahedron* **2007**, *63*, 3340. (c) Larock, R. C.; Yang, H.; Pace, P.; Narayanan, K.; Russell, C. E.; Cacchi, S.; Fabrizi, G. *Tetrahedron* **1998**, *54*, 7473.7343.

(14) Birkett, M. A.; Knight, D. W.; Mitchell, M. B. *Tetrahedron Lett.* **1993**, *34*, 6939.

(15) Ponpipom, M. M.; Yue, B. Z.; Bugianesi, R. L.; Brooker, D. R.; Chang, M. N.; Shen, T. Y. *Tetrahedron Lett.* **1986**, *27*, 309.

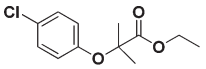
(16) Solladié, G.; Boeffel, D.; Maignan, J. *Tetrahedron* **1995**, *51*, 9559.

(17) (a) Bertolini, F.; Crotti, P.; Di Bussolo, V.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **2007**, *72*, 7761. (b) Stafford, J. A.; Valvano, N. L. *J. Org. Chem.* **1994**, *59*, 4346. (c) Procopiou, P. A.; Brodie, A. C.; Deal, M. J.; Hayman, D. F. *Tetrahedron Lett.* **1993**, *34*, 7483.

(18) Xie, J.-W.; Huang, X.; Fan, L.-P.; Xu, D.-C.; Li, X.-S.; Su, H.; Wen, Y.-H. *Adv. Synth. Catal.* **2009**, *351*, 3077.

(19) Cui, P.; Liu, X.-H.; Zhi, L.-P.; Wang, X.-H.; Song, B.-A.; Zuo, R.-B. *Yingyong Huaxue* **2008**, *25*, 820.

(20)



Structure of Clofibrate

(21) (a) Steiner, G. *Diabetes Vasc. Dis. Res.* **2007**, *4*, 368. (b) Abourbih, S.; Filion, K. B.; Joseph, L.; Schiffrin, E. L.; Rinfret, S.; Poirier, P.; Pilote, L.; Genest, J.; Eisenberg, M. *J. Am. J. Med.* **2009**, *122*, 962.e1. (c) Jun, M.; Foote, C.; Lv J. Neal, B.; Patel, A.; Nicholls, S. J.; Grobbee, D. E.; Cass, A.; Chalmers, J.; Perkovic, V. *Lancet* **2010**, *375*, 1875.

(22) Witiak, D. T.; Loh, W.; Feller, D. R.; Baldwin, J. R.; Newman, H. A. I.; Sober, C. L.; Cavestri, R. C. *J. Med. Chem.* **1979**, *22*, 699.

(23) X-ray crystal data of compounds **6k**, **6p**, and **9g** can be found in the Supporting Information.

(24) Leonardi, A.; Nava, G.; Nardi, D. *Farmaco* **1983**, *38*, 290.