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Lewis Acid-Catalyzed Synthesis of Benzofurans and 4,5,6,7-Tetrahydrobenzofurans from Acrolein Dimer and 1,3-Dicarbonyl Compounds

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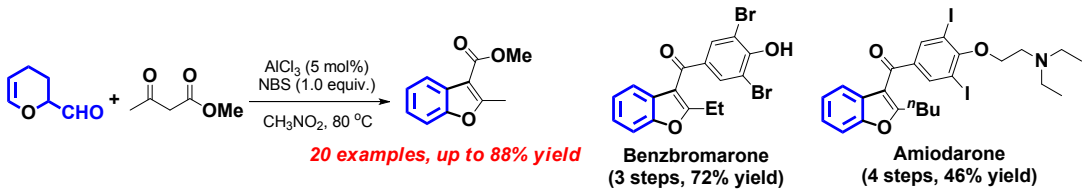


ABSTRACT: 2,3-Disubstituted benzofurans were synthesized from acrolein dimer and 1,3-dicarbonyl compounds by using *N*-bromosuccinimide as an oxidizing agent. The method was used to synthesize two commercial drug molecules, benzbromarone and amiodarone. The proposed mechanism of the reaction involves an NBS-assisted auto-tandem catalysis with Lewis acid catalyst. To proof the proposed mechanism, an intermediate was isolated successfully, which can be converted to 4,5,6,7-tetrahydrobenzofurans.

Introduction

Benzofuran is an important naturally occurring *O*-benzoheterocycle. Many benzofuran derivatives were used in the pharmaceutical and pesticide industries because of their promising biological activities.[1] Therefore, developing a synthetic protocol of benzofuran has been a priority in synthetic chemistry. In general, the present synthetic methods can be divided into two approaches. In the first approach, benzofuran skeletons are constructed from pre-functionalized

phenyl-containing building blocks, such as phenol,[2] salicylaldehyde,[3] and 2-methoxybenzoic acid.[4] In the second approach, benzofuran skeletons are constructed through a 4+2 benzannulation of furan derivatives and suitable reagents, such as 2,5-dimethoxyltetrahydrofuran,[5] 2-alkoxy-3,4-dihydrofuran,[6] and α-bromochalcones or α-bromocinnamates.[7] All synthetic methodologies were established based on the use of aromatic precursors. However, the synthesis of benzofurans with these approaches suffers from some drawbacks, such as pre-functionalization of starting materials, inefficient reaction with electron deficient substrates, or the use of harsh conditions. The construction of benzofuran skeletons from nonaromatic precursors could be an alternative route to access these privileged heterocycles.[8] However, this strategy is rarely used because of the lack of a suitable substrate to construct the two fused aromatic rings simultaneously. A tandem Michael addition and intramolecular cyclization reaction of benzoquinone and ketones or their activated congeners is probably the most simple one, to the best our knowledge, of synthesizing benzofurans from nonaromatic substrates.[9] Unfortunately, the applicability of this reaction is limited, and it works only for the synthesis of 5-hydroxybenzofurans, which have been infrequently used in organic synthesis.

Recently, we have found that *N*-bromosuccinimide (NBS) can act as an oxidizing reagent to cooperate with a Lewis acid catalyst, and the established combined Lewis acid/NBS system can construct five- and six-membered aromatic rings.[10] In this article, we report a facile way to construct a six-and-five two-aromatic-ring fused heterocycle, namely benzofuran, by using easily available chemicals, acrolein dimer and 1,3-dicarbonyl compounds, as precursors. This reaction involves the use of Lewis acid as a catalyst and NBS as an oxidizing agent. This approach not

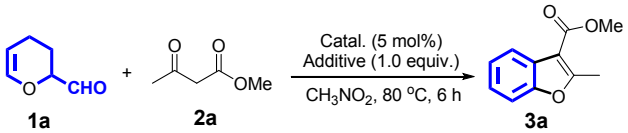
only provides an easy way to synthesize 2,3-disubstituted benzofurans but also enables synthesis of benzofuran-based drug molecules.

Results and Discussion

Initially, acrolein dimer **1a** was treated with methyl acetoacetate **2a** at 80 °C. We expect a benzofuran derivative **3a** can be formed. No reaction was observed in the absence of catalyst (**Table 1**, entry 1). When $AlCl_3$ was employed as a catalyst, the selectivity to **3a** was rather poor in nitromethane (**Table 1**, entry 2). Surprisingly, **3a** could be obtained in 88% yield when 1.0 equivalent of NBS was added into the reaction system (entry 3). NBS cannot catalyze this reaction (entry 4). Several Lewis and Brønsted acids were then examined as catalysts in the presence of NBS. $FeCl_3{\cdot}6H_2O$ and $CuBr_2$ afforded only 23% and 18% yields, respectively (entries 5 and 6). When $Sc(OTf)_3$ was used as a catalyst, although **3a** could be isolated in 80% yield, some inseparable by-products were formed simultaneously (entry 7). *p*-Toluenesulfonic acid (*p*-TsOH) was not applicable in this reaction because only 8% of yield was obtained (entry 8). Some other halogenation reagents were also examined. With bromine and *N*-chlorosuccinimide (NCS), only a trace amount of **3a** was formed (entries 9 and 10). When 1,3-dibromo-5,5-dimethylhydantoin (DDH) was used, **3a** can be isolated in 73% yield (entry 11). Some commonly used oxidant, MnO_2, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and $AgCO_3$, were proven unable to initiate this transformation (entries 12–14). Further investigation revealed that decrease of the amount of NBS or $AlCl_3$ led to dramatic yield drop (entries 15–17). Reaction temperature also played an important role in ensuring the completion of the reaction. Only 38% yield was obtained at 50 °C (entry 18). The effect of solvent was then investigated. Among all the solvents tested, nitromethane clearly stood out, with acetonitrile and 1,2-dichloroethane in the second place

(entries 19 and 20). Toluene and ethanol were proven inappropriate (entries 21 and 22). Therefore, the optimal conditions were identified as follows: 5 mol% $AlCl_3$ catalyst, 1.0 equivalent of NBS, nitromethane solvent, 80 °C, and 6 h. The reaction can be scaled up to 10 mmol without significant loss in the reaction yield (entry 23).

Table 1: Condition optimization for the model reaction.[a]



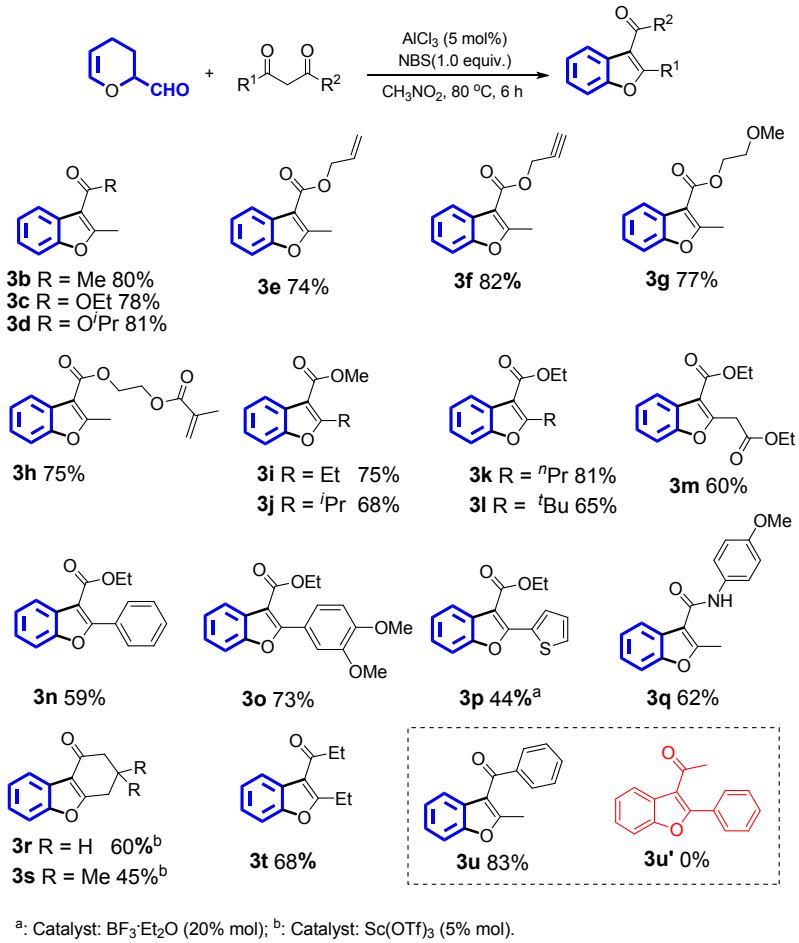
1a 2a 3a

Entry	Catalyst	Additive	Yield (%)
1	—	—	NR
2	$AlCl_3$	—	Trace
3	$AlCl_3$	NBS	88
4	—	NBS	NR
5	$FeCl_3·6H_2O$	NBS	23
6	$CuBr_2$	NBS	18
7	$Sc(OTf)_3$	NBS	80
8	*p*-TsOH	NBS	8
9	$AlCl_3$	Br_2	Trace
10[b]	$AlCl_3$	NCS	Trace
11[c]	$AlCl_3$	DDH	73
12	$AlCl_3$	MnO_2	Trace
13	$AlCl_3$	DDQ	Trace
14	$AlCl_3$	$AgCO_3$	Trace
15	$AlCl_3$	NBS (0.3 equiv.)	26
16	$AlCl_3$	NBS (0.6 equiv.)	45
17[d]	$AlCl_3$	NBS	49
18[e]	$AlCl_3$	NBS	38
19[f]	$AlCl_3$	NBS	71
20[g]	$AlCl_3$	NBS	60
21[h]	$AlCl_3$	NBS	NR
22[i]	$AlCl_3$	NBS	Trace
23[j]	$AlCl_3$	NBS	80

[a]: **1a**: 0.6 mmol, **2a**: 0.5 mmol, nitromethane: 1 mL, catalyst: 0.025 mmol, 80 °C, 6 h. [b]: NCS is *N*-chlorosuccinimide. [c]: DDH is 1,3-dibromo-5,5-dimethylhydantoin. [d]: $AlCl_3$: 2 mol%. [e]: 50 °C. [f]: solvent: acetonitrile. [g]: solvent: 1,2-dichloroethane. [h]: solvent: toluene. [i]: solvent: EtOH. [j]: reaction scale: 10 mmol.

We probed substrate toleration with respect to 1,3-dicarbonyl component, and the results are shown in **Figure 1**. Acetylacetone reacted smoothly with **1a** to form **3b** in 80% yield. 1,3-Dicarbonyl compounds bearing ester and ether groups participated in this reaction readily, affording the desired benzofurans in good to excellent yield (**3b**–**3g**). The double and triple bonds in 1,3-dicarbonyl compounds can be delivered uneventfully into the product skeletons without modification (**3e** and **3f**). Our attempt to use an acrylate-functionalized 1,3-dicarbonyl compound was also successful, and the desired product **3h** was obtained in 75% yield. The acetyl of **2a** can be replaced by some bulky acyl groups, such as *n*-propanoyl, *n*-butanoyl, isobutanoyl, and pivaloyl, without affecting significantly the synthesis efficiency (**3i**–**3l**). Diethyl 1,3-acetonedicarboxylate also participated smoothly in this reaction, and the expected products **3m** were obtained in 60% yield. However, the yields obtained with 1,3-dicarbonyl compounds having an aroyl group, such as benzoyl and thiophen-2-oyl, were slightly inferior to those obtained with **2a** (**3n** and **3p**). This finding may result from the electron-withdrawing properties of these groups. In addition, replacing benzoyl with an electron-donating group-substituted congener, 3,4-dimethoxybenzoyl, increased the yield from 59% to 73% (**3n** and **3o**). *β*-Ketoamide can also be used in this reaction, with which a benzofuran derivative having an amide moiety **3q** could be obtained in 62% yield. A similar compound was reported to exhibit promising biological activities.[11] The reactions of **1a** with cyclic diketones, such as 1,3-cyclohexadione and dimedone, encountered a reactivity problem. Fortunately, this problem can be solved by changing the catalyst from $AlCl_3$ to $Sc(OTf)_3$ (**3r** and **3s**). When benzoylacetone was used in this reaction, two products should be formed theoretically. However, this reaction was exclusively regioselective, and only **3u** was isolated.

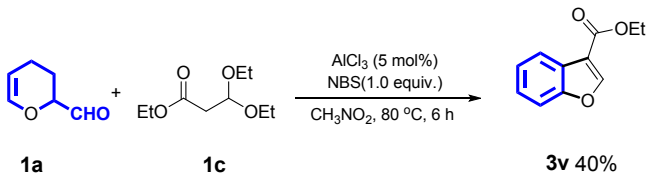
Figure 1. Substrate scope of benzofuran synthesis.



a: Catalyst: $BF_3{\cdot}Et_2O$ (20% mol); b: Catalyst: $Sc(OTf)_3$ (5% mol).

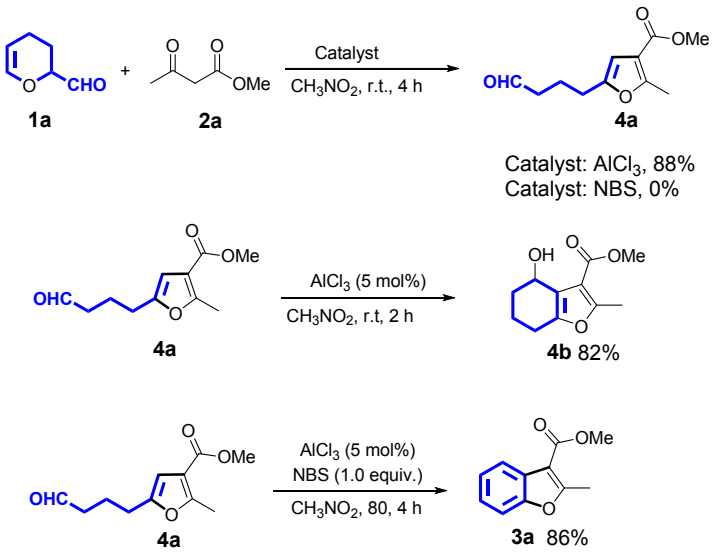
Ethyl 3,3-diethoxypropanoate also able to react smoothly with **1a** in the presence of $AlCl_3$ catalyst, affording ethyl benzofuran-3-carboxylate **3v** in 40% yield (**Scheme 1**). It should be noted that the **3v**-type benzofurans are core substances for the synthesis of drug molecules with antifungal anti-mycobacterial and antifungal activity.[12] Previous methods were generally established by multi-step synthesis, which involved either the use of noble metal-based catalysts, Pd and Rh complexes,[13] or a precursor that is not commercially available.[13(c)] Reaction in **Scheme 1** offered thus a straightforward way to access these valuable benzofuran derivatives starting from easily available starting materials.

Scheme 1. Synthesis of **3v**.



Control experiments were carried out to gain insights into this reaction. Compound **1a** was treated with **2a** in the presence of catalytic amount of $AlCl_3$ and in the absence of NBS (**Scheme 2**). A furanyl-containing butyraldehyde **4a** was formed rapidly at room temperature. NBS was inactive for the synthesis of **4a**. In the absence of NBS, **4a** can be converted into **4b** in 82% yield at room temperature with the aid of $AlCl_3$ catalyst. In the presence of 1.0 equivalent of NBS, **4a** can be converted directly to **3a** (**Scheme 2**).

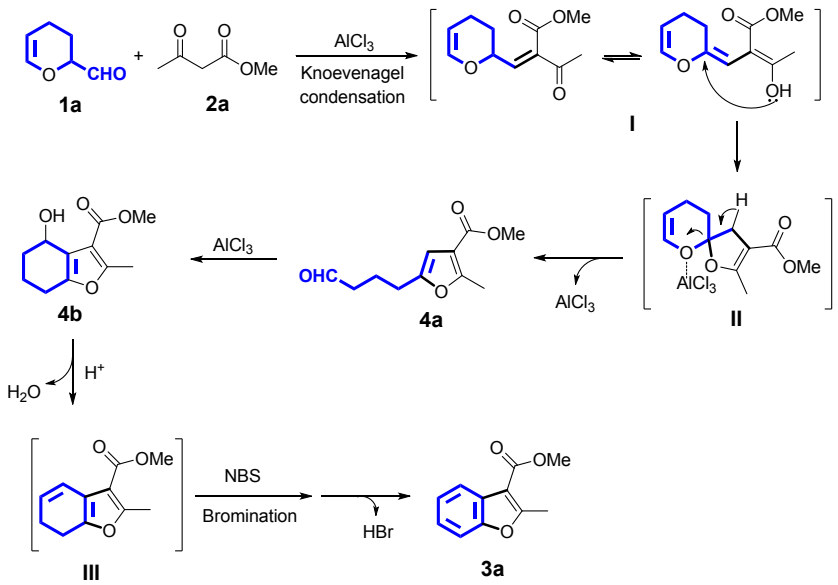
Scheme 2. Control experiments.



Basing on all these results, we speculate that **4a** is a key intermediate of this reaction. A possible mechanism was proposed in **Figure 2**. Initially, Knoevenagel condensation of **1a** and **2a** occurred, thereby leading to the formation of an intermediate **I**, which is equilibrium to its corresponding enol isomer. Intermediate **II** was generated through an intramolecular *oxa*-Michael addition of the enol form of intermediate **I**. Subsequently, it can be converted to **4a** through a

ring-opening rearrangement reaction with the aid of a Lewis acid catalyst. The simultaneous existence of an electrophilic aldehyde-carbonyl and a nucleophilic furanyl group in the molecular skeleton of **4a** enabled an intramolecular nucleophilic addition of the furanyl to the aldehyde group. Therefore, **4b** can be formed. Then, **4b** underwent a dehydration to give intermediate **III**. Finally, **3a** was formed through dehydrobromination of intermediate **III**. On the basis of this mechanism, the model reaction can also be considered as a new example of auto-tandem catalysis,[14] in which the product was formed through a domino acid-acid-catalyzed reaction. Interestingly, the use of NBS as an additive played a key role in rendering the reaction as well as the auto-tandem catalysis to be possible.

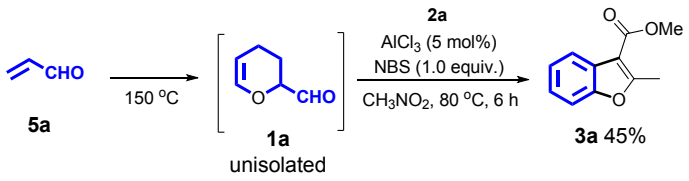
Figure 2. Proposed mechanism



We also attempted to synthesize benzofuran directly using acrolein and 1,3-dicarbonyl as starting materials. However, a complex inseparable mixture was obtained. We suspected that acrolein may be extremely reactive under these conditions, and as a result, the reaction with 1,3-dicarbonyl proceeded non-selectively. As an alternative, a one-pot two-step strategy was developed. As shown in **Scheme 3**, acrolein was initially heated at 150 °C in a sealed tube in the

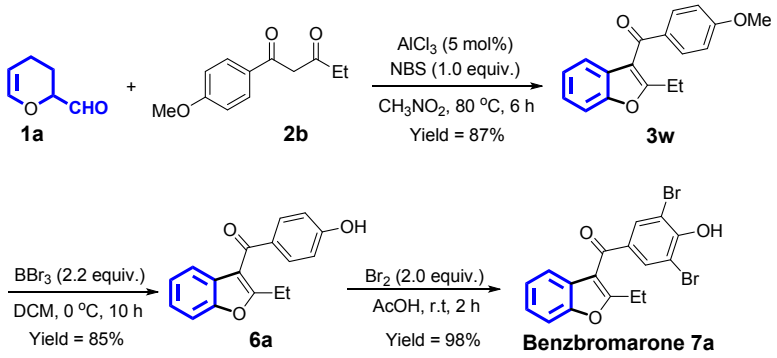
presence of hydroquinone for 4 h. Then, the mixture was subjected to vacuum conditions (20 mmHg) for removing the unreacted acrolein. The residual organic phase was mixed subsequently with **2a**, $AlCl_3$ and solvent. The mixture was then treated at 80 °C for 6 h. With this method, **3a** can be obtained in 45% yield. Although the yield was not very high, because it omitted the isolation step of **1a**, this protocol provided a convenient way to synthesize benzofuran derivative.

Scheme 3. Synthesis of **3a** from acrolein.



Benzbromarone is a urate-lowering drug that acts directly on the renal tubule, increasing uric acid renal excretion by inhibiting urate reabsorption through one or more transporter proteins.[15] Although many methods have been developed for its synthesis, a convenient and efficient pathway is still in demand. Existing synthetic methods often suffer from some drawbacks, such as tedious procedure, harsh reaction conditions, and low reaction yield, this compound was synthesized with a 53.1% yield starting from phenol and formaldehyde through a seven–step synthesis.[16] With the present methodology, the key benzbromarone intermediate **3w** can be prepared in one step in 87% yield from two commercially available compounds (**1a** and **2b**). Benzbromarone was obtained *via* a known procedure, including demethylation and bromination reactions. With this three-step approach, benzbromarone can be synthesized in 72.4% total yield from the starting materials **1a** and **2b** (**Scheme 4**).

Scheme 4. Synthesis of benzbromarone.

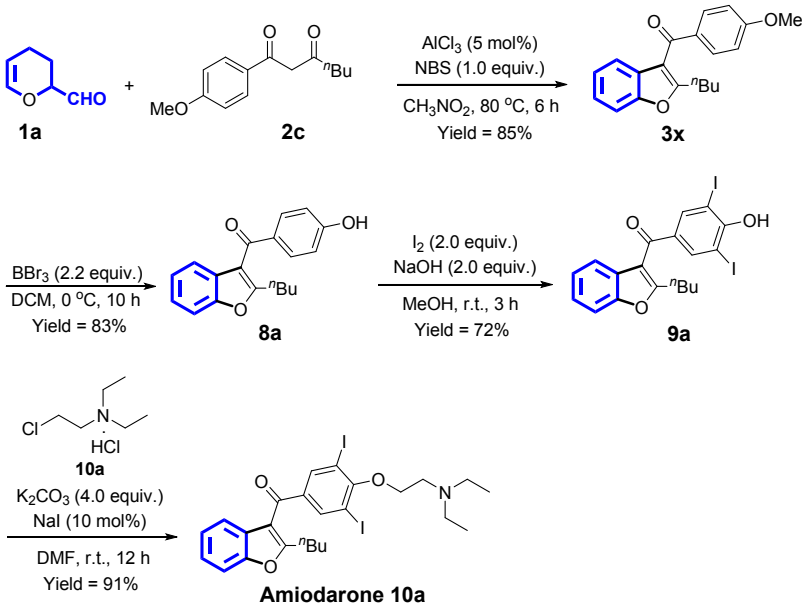


The synthetic protocol of benzofurans also allowed us to establish a four-step method to synthesize amiodarone, which is able to block myocardial potassium channels and inhibit adrenergic receptors.[17] In the first step, the benzofuran derivative **3x** was prepared from **1a** and 1,3-dicarbonyl compound **2c** in 85% yield (**Scheme 5**). Similar to the protocol of accessing benzbromarone, **3x** can be converted to **9a** through a demethylation and iodate process. Finally, the desired product **10a** was obtained through an *O*-alkylation reaction. The total yield of this method reached 46.2% from the starting materials **1a** and **2c**. Compared with the reported method, this protocol features easy operation reaction procedure and avoids the usage of harsh reaction conditions.[18] The reactions in **Scheme 4** and **Scheme 5** demonstrated that the methodology developed here is indeed useful.[19]

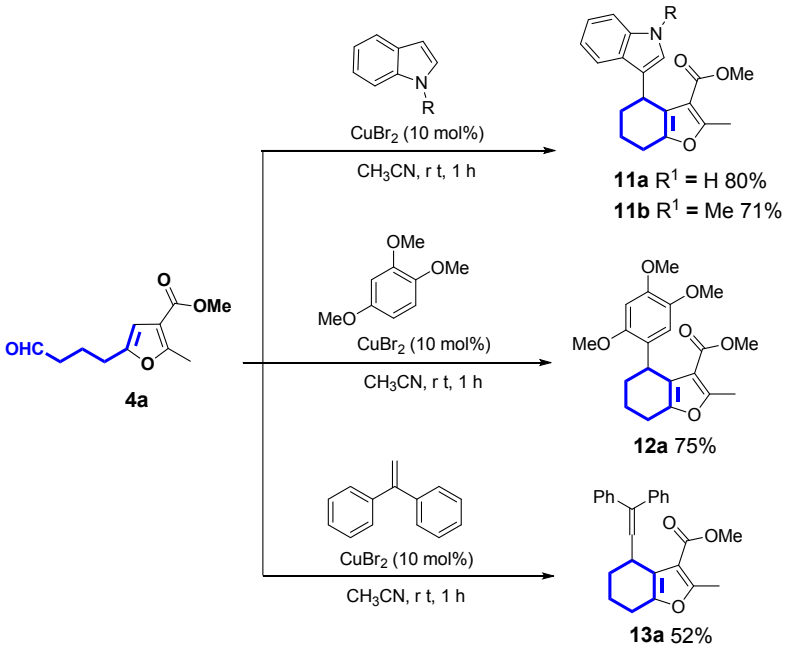
Compound **4a** possesses both nucleophilic and electrophilic sites. Therefore, it can be used as a bifunctional reagent to construct a 4,5,6,7-tetrahydrobenzofuran scaffold. As shown in **Scheme 6**, two indol-3-yl-substituted 4,5,6,7-tetrahydrobenzofuran derivatives, **11a** and **11b**, were obtained in good yield by treating **4a** with *N*-H indole and *N*-methylindole in the presence of 10 mol% of $CuBr_2$ (**Scheme 6**). Other commonly available nucleophiles, such as 1,2,4-trimethoxybenzene and 1,1-diphenylethylene, can also react with **4a,** producing the tetrahydrobenzofuran derivatives, **12a**

and **13a**, in 75% and 52% yields, respectively. These reactions further extended the product diversity of this synthetic methodology.

Scheme 5. Synthesis of amidarone.



Scheme 6. Synthesis of 4,5,6,7-tetrahydrobenzofurans from **4a**.



Conclusion

In summary, a facile method to synthesize benzofurans was developed starting from acrolein dimer and 1,3-dicarbonyl compounds by using NBS as an oxidizing agent. With this method, two drug molecules, benzbromarone and amiodarone, were synthesized. The reaction was established by two reaction sequences, which were all driven by a single acid catalyst. 4,5,6,7-Tetrahydrobenzofurans can also be synthesized from a furanyl-containing butyraldehyde that was confirmed to be an intermediate of forming the benzofuran product.

Experimental Sections

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. The reactions were monitored by TLC with Haiyang GF-254 silica gel plates (Qingdao Haiyang chemical industry Co. Ltd, Qingdao, China) using UV light or $KMnO_4$ as visualizing agents as needed. Flash column chromatography was performed using 200-300 mesh silica gel at increased pressure. ^1H NMR spectra and ^{13}C NMR spectra were respectively recorded on Brüker AV-400 spectrometers. Chemical shifts (δ) were expressed in ppm with TMS as the internal standard, and coupling constants (*J*) were reported in Hz. High-resolution mass spectra (HRMS) were obtained on Brüker Compass Data Analysis 4.0.

Typical procedure for the synthesis of benzofuran derivative. The reactions were conducted in a 10 mL of V-type flask equipped with triangle magnetic stirring. In a typical reaction, **1a** (0.6 mmol) was mixed with **2a** (0.5 mmol), NBS (0.5 mmol) and $AlCl_3$ (5 mol%) in nitromethane (1.0 mL). The mixture was then stirred at 80 ^oC for 6 h. After reaction, the product was obtained by isolation with silica column chromatography (eluting solution: petroleum ether / ethyl acetate = 20/1 (v/v)). Tests for substrate scope were all performed with an analogous procedure. In the large

scale synthesis of **3a**, the product was isolated by silica column chromatography (eluting solution: petroleum ether / ethyl acetate = 20/1 (v/v)).

Confirmation of the regioselectivity of the synthetic reaction of 3u.[20] Sodium borohydride (0.6 mmol) was added to a methanol solution of the reaction product coming from benzoylacetone and acrolein dimer (0.3 mmol, 1 mL methanol). And the mixture was stirred at room temperature for 0.5 h. Then it was poured into an aqueous solution of HCl (1 wt%, 5 mL). Then, the mixture was extracted with dichloromethane (20 mL × 3). The product was obtained by isolation with silica column chromatography (eluting solution: petroleum ether / ethyl acetate = 2/1 (v/v)) in 90 % (64.2 mg) yield.

Procedure for the synthesis of 4a. The reactions were conducted in a 10 mL of V-type flask equipped with triangle magnetic stirring. Compound **1a** (0.6 mmol) was mixed with **2a** (0.5 mmol) and $AlCl_3$ (5 mol%) in nitromethane (1.0 mL). The mixture was then stirred at room temperature for 4 h. After reaction, the product **4a** was obtained by isolation with silica column chromatography (eluting solution: petroleum ether / ethyl acetate = 5/1 (v/v)) in 88% yield (92.4 mg).

Procedure for the synthesis of 3a from acrolein.[21] Acrolein (0.5 mol) and hydroquinone (2.5 mmol) was placed in a teflon vessel, the teflon vessel was sealed and placed in a stainless steel autoclave. The autoclave was heated at 150 °C for 4 h. After the autoclave was cooled to room temperature, the rest of acrolein and other volatile components were removed under reduced pressure to gain the crude product **1a** (yellow oil). Then, **1a** (0.6 mmol) was mixed with **2a** (0.5 mmol), NBS (0.5 mmol) and $AlCl_3$ (5 mol %) in nitromethane (1mL) in a 10 mL of V-type flask equipped with triangle magnetic stirring. The mixture was then stirred at 80 °C for 6 h. After

reaction, the product **3a** was obtained by isolation with silica column chromatography (eluting solution: petroleum ether / ethyl acetate = 30/1 (v/v)) in 45% (42.8 mg) yield.

Procedure for the synthesis of 2b and 2c.[22] Methyl propionate (25 mmol) was mixed with 1-(4-methoxyphenyl)ethanone (3.0 g, 20 mmol) and sodium hydride (30.0 mmol, 60% suspension in mineral oil) in THF (100 mL). Then the mixture was heated to reflux for overnight. After that, it was quenched with water (100 mL) and acidified with 1 N HCl. The solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (100 mL × 3). The combined organic phase was washed with brine (25 mL) and dried over anhydrous Na_2SO_4. After removing volatile components, the organic residue was subjected to an isolation with silica column chromatography (eluting solution: petroleum ether / ethyl acetate = 10/1 (v/v)). **2b** was obtained in 82 % yield. Synthesis of **2c** was performed with an analogous procedure.

Procedure for the synthesis of benzbromarone 7a. Compound **1a** (6.0 mmol) was mixed with **2b** (5.0 mmol), NBS (5.0 mmol), $AlCl_3$ (5 mol%) and nitromethane (30 mL) in a 100 mL of round bottomed flask equipped with magnetic stirring. The mixture was then stirred at 80 ^oC for 6 h. After completion of the reaction, brine (50 mL) was added. And then, the aqueous phase was extracted by ethyl acetate (40 mL × 3). The acquired organic phase was dried by anhydrous Na_2SO_4. After removing volatile components, the organic residue was subjected to an isolation with silica column chromatography (eluting solution: petroleum ether / ethyl acetate = 20/1 (v/v)). Compound **3w** was obtained in 87 % (1.22 g) yield. Then, **3w** (1.22 g) was dissolved in dichloromethane (20 mL), and cooled to -10 °C. A dichlromethane solution of boron tribromide (4.8 mmol, in 10 mL CH_2Cl_2) was added carefully to the stirred solution of **3w**. The reaction mixture was allowed to stir at room temperature for 5 h. Then, a dichloromethane solution of

boron tribromide (4.8 mmol, in 10 mL CH_2Cl_2) was added again and the solution was stirred for another 5 h. The reaction mixture was quenched then by ice-water (50 mL) and stirred for 15 min. The organic phase was separated and extracted with saturated sodium bicarbonate solution (30 mL × 3). The alkaline extract was washed with dichloromethane (30 mL × 3). The acquired organic phase was dried by anhydrous Na_2SO_4. After removing volatile components, the organic residue was subjected to an isolation with silica column chromatography (eluting solution: petroleum ether / ethyl acetate = 5/1 (v/v)). Compound **6a** was obtained in 85 % yield (981.5 mg).[23] **6a** (981.5 mg) was dissolved in an aqueous solution acetic acid (20 mL, 75_{wt}%). An aqueous acetic acid solution of bromine (2.0 equiv, in 20 mL 75_{wt}% solvent) was added into the previous solution slowly at room temperature. Then the mixture was stirred for 2 h at room temperature. Water (50 mL) was added to the reaction mixture. And the aqueous phase was extracted by ethyl acetate (30 mL × 3). The combined organic phase was washed by saturated aqueous solution of $NaHCO_3$ and brine. Then it was dried over anhydrous Na_2SO_4. After removing the volatile components under reduced pressure, the product **7a** was purified by silica column chromatography (eluting solution: petroleum ether / ethyl acetate = 3/1 (v/v)) in 98% (1.52 g) yield.[16(a)]

Procedure for the synthesis of amiodarone 10a.[18(a)] Compound **1a** (6.0 mmol) was mixed with **2c** (5.0 mmol), NBS (5.0 mmol), $AlCl_3$ (5 mol %) and nitromethane (30.0 mL) in a 100mL of round bottomed flask equipped with magnetic stirring. The mixture was stirred at 80 ^oC for 6 h. After completion of the reaction, brine (50 mL) was added. And then, the aqueous phase was extracted by ethyl acetate (40 mL × 3). The acquired organic phase was dried over anhydrous Na_2SO_4. After removing the volatile components, the organic residue was subjected to an isolation with silica column chromatography (eluting solution: petroleum ether / ethyl acetate = 20/1 (v/v)).

Compound **3x** was obtained in 85 % yield (1.3 g). **3x** (1.3 g) was dissolved in dichloromethane (30 mL), and cooled to -10 °C. A dicloromethane solution of boron tribromide (1.1 equiv in 15 mL CH_2CH_2) was added carefully to the stirred solution. The mixture was allowed to stir at room temperature for overnight. Then, a dichloromethane solution of boron tribromide (1.1 equiv in 15 mL CH_2CH_2) was added again and the solution was stirred for another 5 h. The reaction was then quenched by ice-water (50 mL) and stirred for 15 min. The organic phase was separated and extracted with a saturated aqueous solution of sodium bicarbonate (30 mL × 3). Then, the alkaline extract was washed with dichloromethane (50 mL × 3). The acquired organic phase was dried over anhydrous Na_2SO_4. After removing the volatile components, the organic residue was subjected to an isolation with silica column chromatography (eluting solution: petroleum ether / ethyl acetate = 5/1 (v/v)). Compound **8a** was obtained in 83 % yield (1.04 g). Compound **8a** (1.04 g) and sodium hydroxide (2.0 equiv) was added in MeOH (20 mL). Iodine (2.0 equiv) was added then at 0 ^oC. After 3 h of stirring at room temperature, the reaction was quenched with an aqueous solution of HCl (1N, 40 mL), and then extracted with ethyl acetate. The combined organic extracts were washed with a saturated aqueous solution of $Na_2S_2O_3$. The acquired organic phase was dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was subjected then to an isolation with silica column chromatography (eluting solution: petroleum ether / ethyl acetate = 3/1 (v/v)). Compound **9a** was obtained in 72 % yield (1.38 g). To a DMF solution of **9a** (1.38 g, 20 mL solvent), K_2CO_3 (4.0 equiv), 2-diethylaminoethylchloride hydrochloride (1.0 equiv), and NaI (0.1 equiv) were added. The mixture was stirred at room temperature for overnight. The reaction was quenched with water and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, and finally concentrated under reduced pressure.

The product **10a** was obtained by isolation with silica column chromatography (eluting solution: petroleum ether / ethyl acetate = 2/1 (v/v)) in 91% yield (1.48 g).

Characterization data of compounds

Methyl 2-methylbenzofuran-3-carboxylate (**3a**):[24] brown oil, 88% yield (83.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 ^{o}C) δ = 7.98–7.90 (m, 1H), 7.45–7.37 (m, 1H), 7.26 (ddd, J = 7.2, 4.8, 2.0 Hz, 2H), 3.93 (s, 3H), 2.75 ppm (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ^{o}C) δ = 165.0, 163.8, 153.7, 126.2, 124.4, 123.8, 121.8, 110.8, 109.0, 51.5, 14.5 ppm

1-(2-Methylbenzofuran-3-yl)ethanone **(3b)**:[24] yellow oil, 80% yield (69.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 ^{o}C) δ = 8.01–7.88 (m, 1H), 7.45 (dd, J = 6.5, 2.5 Hz, 1H), 7.37–7.28 (m, 2H), 2.78 (s,3H), 2.64 ppm (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ^{o}C) δ = 194.4, 163.0, 153.7, 126.2, 124.5, 124.1, 121.5, 117.7, 111.2, 31.3, 15.53 ppm

Ethyl 2-methylbenzofuran-3-carboxylate (**3c**):[24] light brown oil, 78% yield (79.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 ^{o}C) δ = 7.92–7.83 (m, 1H), 7.38–7.31 (m, 1H), 7.24–7.17 (m, 2H), 4.33 (q, J = 7.1Hz, 2H), 2.69 (s, 3H), 1.37 ppm (t, J = 7.1Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, 25 ^{o}C) δ = 163.5, 163.4, 153.0, 125.6, 124.6, 124.0, 121.2, 111.0, 108.3, 60.1, 14.2, 14.1 ppm.

Isopropyl 2-methylbenzofuran-3-carboxylate (**3d**):[25] light yellow oil, 81% yield (88.3 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 ^{o}C) δ = 8.01–7.91 (m, 1H), 7.47–7.37 (m, 1H), 7.32–7.22 (m, 2H), 5.29 (dt, J = 12.5, 6.2 Hz, 1H), 2.77 (s, 3H), 1.42 ppm (d, J = 6.3 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ^{o}C) δ = 164.2, 163.6, 153.7, 126.5, 124.3, 123.8, 121.9, 110.8, 109.5, 67.9, 22.3, 14.5 ppm.

Allyl 2-methylbenzofuran-3-carboxylate **(3e)**: yellow oil, 74% yield (79.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 ^{o}C) δ = 8.01–7.89 (m, 1H), 7.48–7.39 (m, 1H), 7.32–7.25 (m, 2H), 6.09 (m, 1H), 5.44 (d, J = 17.2 Hz, 1H), 5.32 (d, J = 10.4 Hz, 1H), 4.87 (d, J = 5.6 Hz, 2H), 2.78 ppm (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ^{o}C) δ = 164.3, 164.0, 153.8, 132.5, 126.3, 124.5, 124.0, 121.9, 118.4, 110.9, 109.0, 65.1, 14.6 ppm. IR (KBr) v: 3080, 2929, 2853, 1713, 1595, 1452, 1396, 1230, 1175, 1079, 996, 748 cm^{-1}, HRMS (TOF, ESI): m/z calcd for $C_{13}H_{12}NaO_3$, [M + Na]$^{+}$ 239.0684, found 239.0688.

Prop-2-yn-1-yl 2-methylbenzofuran-3-carboxylate (**3f**): yellow solid, mp: 45–47 ^{o}C, 82% yield (87.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 ^{o}C) δ = 7.98 (dd, J = 6.2, 2.7 Hz, 1H), 7.43 (dd, J = 6.3, 2.4 Hz, 1H), 7.33–7.26 (m, 2H), 4.96 (d, J = 2.4 Hz, 2H), 2.79 (s, 3H), 2.54 ppm (t, J = 2.4 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ^{o}C) δ = 164.6, 163.7, 153.7, 126.0, 124.6, 124.1, 121.9, 110.9, 108.5, 77.8, 75.1, 51.9, 14.7 ppm, IR (KBr) v: 3308, 2957, 2925, 1720, 1455, 1398, 1231, 1178, 1105, 1080, 801, 751 cm^{-1}, HRMS (TOF, ESI): m/z calcd for $C_{13}H_{10}NaO_3$, [M + Na]$^{+}$ 237.0528, found 237.0545.

2-Methoxyethyl 2-methylbenzofuran-3-carboxylate (**3g**): yellow oil, 77% yield (90.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 ^{o}C) δ = 8.03–7.93 (m, 1H), 7.49–7.37 (m, 1H), 7.33–7.22 (m, 2H), 4.54–4.45 (m, 2H), 3.80–3.71 (m, 2H), 3.45 (s, 3H), 2.78 ppm (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ^{o}C) δ = 164.5, 164.0, 153.8, 126.3, 124.4, 124.0, 122.0, 110.9, 109.0, 70.8, 63.2, 59.1, 14.6 ppm. IR (KBr) v: 2927, 2890, 1714, 1598, 1477, 1452, 1343, 1286, 1236, 1178, 1085, 1006, 805, 783, 753 cm^{-1}, HRMS (TOF, ESI): m/z calcd for $C_{13}H_{14}NaO_4$, [M + Na]$^{+}$ 257.0790, found 257.0794.

2-(Methacryloyloxy)ethyl2-methylbenzofuran-3-carboxylate (**3h**): brown oil, 75% yield (108 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 ^{o}C) δ = 7.94 (dd, J = 6.1, 3.0 Hz, 1H), 7.46–7.40 (m, 1H), 7.30–7.25 (m, 2H), 6.18 (s, 1H), 5.60 (s, 1H), 4.61 (dd, J = 6.0, 2.9 Hz, 2H), 4.54 (dd, J = 5.8, 3.1Hz, 2H), 2.77 (s, 3H), 1.97 ppm (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ^{o}C) δ = 167.3, 164.2, 153.8, 136.1, 126.3, 126.2, 124.5, 124.0, 121.8, 110.9, 108.8, 62.6, 62.0, 18.4, 14.6 ppm, IR (KBr) v: 2958, 2927, 1719, 1453, 1235, 1171, 1088, 1009, 752 cm^{-1}, HRMS (TOF, ESI): m/z calcd for $C_{16}H_{16}KO_5$, $[M + K]^+$ 327.0635, found 327.0650.

Methyl 2-ethylbenzofuran-3-carboxylate (**3i**):[25] yellow oil, 75% yield (76.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 ^{o}C) δ = 8.01–7.92 (m, 1H), 7.49–7.41 (m, 1H), 7.31–7.26 (m, 2H), 3.95 (s, 3H), 3.21 (q, J = 7.6Hz, 2H), 1.36 ppm (t, J = 7.6Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ^{o}C) δ = 168.6, 165.0, 153.8, 126.3, 124.4, 123.9, 122.0, 111.0, 108.0, 51.5, 21.9, 12.2 ppm.

Methyl 2-isopropylbenzofuran-3-carboxylate (**3j**):[24] light yellow oil, 68% yield (74.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 ^{o}C) δ = 8.00–7.92 (m, 1H), 7.50–7.39 (m, 1H), 7.28 (dd, J = 10.2, 7.0 Hz, 2H), 4.04 (dd, J = 13.9, 6.9 Hz, 1H), 3.95 (s, 3H), 1.37 ppm (d, J = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ^{o}C) δ = 171.7, 165.0, 153.7, 126.3, 124.4, 123.8, 122.1, 111.1, 107.0, 51.5, 27.7, 20.7 ppm.

Ethyl 2-propylbenzofuran-3-carboxylate (**3k**):[24] yellow oil, 81% yield (93.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 ^{o}C) δ = 8.02–7.93 (m, 1H), 7.47–7.40 (m, 1H), 7.29 (dd, J = 8.9, 5.2 Hz, 2H), 4.41 (q, J = 7.1 Hz, 2H), 3.17 (t, J = 7.5 Hz, 2H), 1.88–1.76 (m, 2H), 1.45 (t, J = 7.1 Hz, 3H), 1.01 ppm (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ^{o}C) δ = 167.5, 164.6, 153.8, 126.4, 124.4, 123.8, 122.0, 111.0, 108.9, 60.4, 30.2, 21.5, 14.5, 14.0 ppm.

Ethyl 2-(*tert*-butyl)benzofuran-3-carboxylate (**3l**): yellow oil, 65% yield (79.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 ^{o}C) δ = 7.98–7.91 (m, 1H), 7.44 (dd, J = 6.0, 3.1 Hz, 1H),7. 28 (dt, J = 7.9, 4.3 Hz, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.54 (d, J = 5.1 Hz, 9H), 1.46 ppm (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ^{o}C) δ = 172.1, 164.5, 152.3, 127.6, 124.3, 123.7, 122.1, 111.0, 108.1, 60.6, 35.3, 28.4, 14.5 ppm. IR (KBr) v: 2977, 2934, 2872, 1720, 1554, 1451, 1342, 1237, 1139, 1065, 750 cm^{-1}. HRMS (TOF, ESI) calcd for: $C_{15}H_{18}NaO_3$, $[M + Na]^+$ 269.1154, found 269.1129.

Ethyl 2-(2-ethoxy-2-oxoethyl)benzofuran-3-carboxylate (**3m**): yellow oil, 60% yield (82.8 mg); ^{1}H NMR (400 MHz, DMSO-d_6, 25 ^{o}C) δ = 7.98–7.90 (m, 1H), 7.70–7.63 (m, 1H), 7.40 (dt, J = 5.3, 3.4 Hz, 2H), 4.33 (dd, J = 14.8, 7.7 Hz, 4H), 4.13 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.19 ppm (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, 25 ^{o}C) δ = 167.9, 163.0, 158.7, 153.3, 125.4, 125.1, 124.3, 121.5, 111.4, 110.2, 61.0, 60.4, 34.1, 14.0, 13.9 ppm. IR (KBr) v: 2958, 2926, 2855, 1744, 1715, 1453, 1377, 1238, 1185, 1072, 750 cm^{-1}. HRMS (TOF, ESI) calcd for: $C_{15}H_{16}NaO_5$, $[M + Na]^+$ 299.0895, found 299.0886.

Ethyl 2-phenylbenzofuran-3-carboxylate (**3n**):[24] yellow oil, 59% yield (78.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 ^{o}C) δ = 8.11–8.06 (m, 1H), 8.03 (dd, J = 6.6, 3.0 Hz, 2H), 7.54 (dd, J = 5.2, 3.9 Hz, 1H), 7.51–7.46 (m, 3H), 7.39–7.32 (m, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.41 ppm (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ^{o}C) δ = 164.2, 160.9, 154.0, 130.4, 129.8, 129.7, 128.2, 127.3, 125.3, 124.1, 122.9, 111.3, 109.2, 60.8, 14.4 ppm.

Ethyl 2-(3,4-dimethoxyphenyl)benzofuran-3-carboxylate (**3o**): light yellow solid, mp: 110–112 ^{o}C, 73% yield (118.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 ^{o}C) δ = 8.05 (dd, J = 6.3, 2.9 Hz, 1H), 7.80–7.69 (m, 2H), 7.52 (dd, J = 6.2, 2.9 Hz, 1H), 7.38–7.29 (m, 2H), 6.97 (d, J = 8.3 Hz,

1H), 4.43 (q, J = 7.1 Hz, 2H), 3.98 (s, 3H), 3.95 (s, 3H), 1.44 ppm (t, J = 7.1Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ = 164.4, 160.8, 153.6, 151.0, 148.6, 127.5, 125.1, 124.0, 123.2, 122.8, 122.3, 112.7, 111.1, 110.7, 108.2, 60.7, 56.2, 56.1, 14.5 ppm. IR (KBr) v: 2959, 2936, 2907, 2837, 1710, 1604, 1561, 1509, 1451, 1255, 1219, 1091, 1027, 861, 751 cm^{-1}. HRMS (TOF, ESI) calcd for: $C_{19}H_{18}NaO_5$, $[M + Na]^+$ 349.1047, found 349.1065.

Ethyl 2-(thiophen-2-yl)benzofuran-3-carboxylate (**3p**): yellow oil, 44% yield (59.8 mg); ^1H NMR (400 MHz, DMSO-d_6, 25 °C) δ = 8.25 (dd, J = 3.7, 0.9 Hz, 1H), 7.98–7.94 (m, 1H), 7.92 (dd, J = 5.0, 0.9 Hz, 1H), 7.65 (d, J = 7.3 Hz, 1H), 7.44–7.34 (m, 2H), 7.28 (dd, J = 4.9, 3.9 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.39 ppm (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ = 163.2, 154.9, 152.7, 131.7, 131.6, 130.2, 128.2, 126.3, 126.0, 124.6, 122.4, 111.2, 106.6, 60.9, 14.3 ppm, IR (KBr) v: 2930, 2853, 1709, 1568, 1451, 1237, 1086, 1058, 748, 709 cm^{-1}. HRMS (TOF, ESI) calcd for: $C_{15}H_{12}KO_3S$, $[M + K]^+$ 311.0144, found 311.0150.

N-(4-Methoxyphenyl)-2-methylbenzofuran-3-carboxamide (**3q**): white solid, mp: 126–128 °C, 62% yield (87.1 mg); ^1H NMR (400 MHz, $CDCl_3$, TMS, 25 °C) δ = 7.73–7.67 (m, 1H), 7.51 (dt, J = 9.0, 8.3 Hz, 4H), 7.36–7.29 (m, 2H), 6.92 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H), 2.76 ppm (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ = 162.3, 160.8, 156.9, 153.8, 130.9, 125.5, 124.5, 123.9, 122.3, 119.1, 114.5, 112.3, 111.7, 55.7, 14.1 ppm. IR (KBr) v: 3297, 2921, 2837, 1643, 1606, 1515, 1454, 1234, 1177, 1025, 826,745 cm^{-1}, HRMS (TOF, ESI): m/z calcd for $C_{17}H_{15}NNaO_3$, $[M + Na]^+$ 304.0950, found 304.0943.

3,4-Dihydrodibenzo[*b,d*]furan-1(*2H*)-one (**3r**):[24] yellow oil, 60% yield (55.8 mg); ^1H NMR (400 MHz, $CDCl_3$, TMS, 25 °C) δ = 8.11–8.00 (m, 1H), 7.52–7.42 (m, 1H), 7.36–7.28 (m, 2H), 3.04 (t, J = 6.3 Hz, 2H), 2.64–2.56 (m, 2H), 2.28 ppm (dt, J = 12.7, 6.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (100

MHz, $CDCl_3$, 25 °C) δ = 194.9, 170.9, 154.7, 125.1, 124.6, 123.9, 122.0, 116.7, 111.2, 38.0, 24.0, 22.6 ppm.

3,3-Dimethyl-3,4-dihydrodibenzo[*b,d*]furan-1(2*H*)-one (**3s**):[24] yellow oil, 45% yield (48.2 mg), ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 °C) δ = 8.05 (dd, *J* = 5.6, 3.2 Hz, 1H), 7.48 (dd, *J* = 5.9, 3.0 Hz, 1H), 7.35 – 7.30 (m, 2H), 2.91 (s, 2H), 2.49 (s, 2H), 1.21 ppm (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ = 194.3, 170.1, 155.1, 125.0, 124.6, 123.8, 121.9, 115.5, 111.3, 52.4, 37.9, 35.4, 28.8 ppm.

1-(2-Ethylbenzofuran-3-yl)propan-1-one (**3t**):[24] yellow oil, 68% yield (68.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 °C) δ = 7.91 (dd, *J* = 6.0, 2.9 Hz, 1H), 7.47 (dd, *J* = 6.0, 3.0 Hz, 1H), 7.35–7.28 (m, 2H), 3.20 (q, *J* = 7.5 Hz, 2H), 3.00 (q, *J* = 7.2 Hz, 2H), 1.37 (t, *J* = 7.5 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ = 197.6, 167.7, 153.8, 126.0, 124.4, 124.0, 121.6, 116.3, 111.3, 36.5, 22.6, 12.1, 7.9 ppm.

(2-Methylbenzofuran-3-yl)(phenyl)methanone (**3u**):[24] yellow oil, 83% yield (97.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 °C) δ = 7.82 (d, *J* = 7.4 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.52–7.45 (m, 3H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.30–7.26 (m, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 2.55 ppm (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ = 192.3, 162.1, 153.8, 139.5, 132.8, 129.3, 128.7, 127.1, 124.5, 123.7, 121.5, 117.1, 111.0, 14.8 ppm.

(2-Methylbenzofuran-3-yl)(phenyl)methanol: [26] yellow oil, 90 % yield (64.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$ TMS, 25 °C) δ = 7.41 (d, *J* = 7.5 Hz, 2H), 7.31 (dt, *J* = 12.7, 8.2 Hz, 4H), 7.22 (dd, *J* = 14.4, 7.2 Hz, 1H), 7.17–7.12 (m, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 5.96 (s, 1H), 2.51 (d, *J* = 18.3 Hz, 1H), 2.38 ppm (s, 3H).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, TMS, 25 °C) δ = 154.1, 152.2, 142.6, 128.5, 127.5, 127.4, 126.0, 123.5, 122.5, 120.3, 117.0, 110.7, 68.9, 12.6 ppm.

Ethyl benzofuran-3-carboxylate (**3v**):[13(a)] yellow oil, 40% yield (38.0 mg); ^{1}H NMR: (400 MHz, DMSO-d$_6$, 25 ^{o}C) δ = 8.75 (s, 1H), 7.98 (dd, J = 6.2, 2.4 Hz, 1H), 7.71 (dd, J = 6.6, 1.9 Hz, 1H), 7.47 – 7.37 (m, 2H), 4.35 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$, 25 ^{o}C) δ = 163.1, 155.4, 152.8, 126.0, 124.8, 124.6, 121.9, 114.2, 112.4, 60.8, 14.7.

Methyl 2-methyl-5-(4-oxobutyl)furan-3-carboxylate (**4a**): light brown oil, 88% yield (92.4 mg); ^{1}H NMR (400 MHz, CDCl$_3$, TMS, 25 ^{o}C) δ = 9.77 (s, 1H), 6.26 (s, 1H), 3.80 (s, 3H), 2.62 (t, J = 7.3 Hz, 2H), 2.55–2.47 (m,5H), 1.96 (m, J = 7.3Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$, 25 ^{o}C) δ = 201.8, 164.7, 158.2, 152.9, 113.7, 106.3, 51.3, 43.0, 27.0, 20.4, 13.8 ppm. IR (KBr) v: 2953, 2723, 1719, 1585, 1442, 1370, 1228, 1087, 1031, 779 cm^{-1}, HRMS (TOF, ESI) calcd for: $C_{11}H_{14}NaO_4$, $[M + Na]^+$ 233.0790, found 233.0792.

Methyl 4-hydroxy-2-methyl-4,5,6,7-tetrahydrobenzofuran-3-carboxylate (**4b**): yellow oil, 82% yield (86.1 mg); ^{1}H NMR: (400 MHz, DMSO-d$_6$, 25 ^{o}C) δ = 4.77 (d, J = 3.5 Hz, 1H), 4.55 (d, J = 4.3 Hz, 1H), 3.75 (s, 3H), 2.51 (d, J = 1.7 Hz, 2H), 2.48 (s, 3H), 1.96 – 1.86 (m, 1H), 1.76 – 1.68 (m, 2H), 1.65 – 1.58 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$, 25 ^{o}C) δ = 164.8, 157.6, 151.1, 120.5, 112.4, 60.9, 51.7, 31.9, 22.7, 17.9, 14.0 ppm. IR (KBr) v: 3458, 2949, 2931, 2857, 1718, 1690, 1455, 1272, 1091 cm^{-1}, HRMS (TOF, ESI) calcd for: $C_{11}H_{14}NaO_4$, $[M + Na]^+$ 233.0790, found 233.0786.

1-(4-Methoxyphenyl)pentane-1,3-dione (a mixture of enol and ketone form) (**2b**):[27] pink oil, 82% yield (3.37g); ^{1}H NMR (400 MHz, CDCl$_3$, TMS, 25 ^{o}C) δ = 16.30 (s, 0.8H), 7.93 (d, J = 8.8 Hz, 0.4 H), 7.87 (d, J = 8.8 Hz, 1.6 H), 6.94 (d, J = 8.8 Hz, 2H), 6.12 (s, 0.8 H), 4.04 (s, 0.4 H), 3.86 (s, 3H), 2.61 (q, J = 7.2 Hz, 0.4 H), 2.44 (q, J = 7.5 Hz, 1.6 H), 1.21 (t, J = 7.5 Hz, 2.4 H), 1.07

ppm (t, J = 7.2 Hz, 0.6 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$ TMS, 25 °C) δ = 196.0, 184.1, 164.2, 163.2, 131.3, 129.2, 127.8, 114.1, 114.0, 94.6, 55.7, 55.6, 53.8, 36.7, 32.0, 10.1, 7.7 ppm.

(2-Ethylbenzofuran-3-yl)(4-methoxyphenyl)methanone (**3w**):[15(b)] light yellow oil, 87% yield (1.22 g); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 °C) δ = 7.85 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.2 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.28 (dd, J = 10.9, 3.7 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 2.91 (q, J = 7.5Hz, 2H), 1.34 (t, J = 7.5 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ = 190.6, 165.5, 163.6, 153.8, 132.0, 131.8, 127.3, 124.3, 123.5, 121.4, 116.3, 113.8, 111.1, 55.6, 21.9, 12.5 ppm.

(2-Ethylbenzofuran-3-yl)(4-hydroxyphenyl)methanone (**6a**):[28] light yellow solid, mp: 122–124 °C, 85% yield (981.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 °C) δ = 7.79 (d, J = 8.6 Hz, 2H), 7.48 (d, J = 8.2 Hz, 1H), 7.41 (d, J = 7.7 Hz, 1H), 7.30 – 7.25 (m, 1H), 7.19 (t, J = 7.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 2H), 2.91 (q, J = 7.5 Hz, 2H), 1.33 ppm (t, J = 7.5 Hz, 3H), $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ = 191.8, 166.0, 161.1, 153.8, 132.3, 131.4, 127.2 124.5, 123.6, 121.4, 116.3, 115.6, 111.1, 22.0, 12.5 ppm.

(3,5-Dibromo-4-hydroxyphenyl)(2-ethylbenzofuran-3-yl)methanone (**7a**):[16(a)] white solid, mp: 150–152 °C, 98% yield (1.52 g); ^{1}H NMR (400 MHz, $CDCl_3$,TMS, 25 °C) δ = 7.99 (s, 2H), 7.50 (d, J = 8.2 Hz, 1H), 7.42 (d, J = 7.7 Hz, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.26–7.22 (m, 1H), 2.91 (q, J = 7.5 Hz, 2H), 1.36 ppm (t, J = 7.5 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, TMS, 25 °C) δ = 188.0, 166.6, 153.9, 153.3, 133.9, 133.6, 126.7, 124.8, 124.0, 121.1, 115.5, 111.3, 110.2, 22.1, 12.4 ppm.

1-(4-Methoxyphenyl)heptane-1,3-dione (a mixture of enol and ketone form) (**2c**):[28] pink oil, 80 % yield (3.74g); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ = 16.58 (s, 0.8 H), 7.92 (t, J = 8.7 Hz, 2H),

7.02 (d, J = 8.9 Hz, 2H), 6.40 (s, 0.8 H), 4.17 (s, 0.4 H), 3.82 (d, J = 3.6 Hz, 3H), 2.55 (t, J = 7.3 Hz, 0.4 H), 2.41–2.34 (m, 1.6 H), 1.56 (dt, J = 15.1, 7.5 Hz, 1.6 H), 1.44 (dd, J = 15.0, 7.4 Hz, 0.4 H), 1.35–1.20 (m, 2H), 0.89–0.80 ppm (m, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6, 25 °C) δ = 205.4, 194.8, 193.3, 183.6, 163.4, 162.9, 130.8, 129.4, 129.1, 126.8, 114.0, 113.8, 95.1, 55.4, 55.3, 52.7, 42.4, 37.6, 27.5, 25.0, 21.8, 21.6, 13.7, 13.6 ppm.

2-Butylbenzofuran-3-yl)(4-methoxyphenyl)methanone (**3x**):[16(b)] light yellow oil, 85% yield (1.3 g); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 °C) δ = 7.84 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.2 Hz, 1H), 7.36 (d, J = 7.3 Hz, 1H), 7.26 (dd, J = 9.4, 5.9 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 2.91 (t, J = 7.6 Hz, 2H), 1.80–1.71 (m, 2H), 1.36 (dd, J = 15.0, 7.4 Hz, 2H), 0.89 ppm (t, J = 7.4 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ = 190.7, 164.8, 163.6, 153.8, 132.1, 131.8, 127.4, 124.3, 123.4, 121.4, 116.9, 113.8, 111.1, 55.6, 30.3, 28.0, 22.5, 13.8 ppm

(2-Butylbenzofuran-3-yl)(4-hydroxyphenyl)methanone (**8a**):[18(a)] light yellow solid, mp: 120–122 °C, 83% yield (1.04 g); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 °C) δ = 10.46 (s, 1H), 7.68 (d, J = 8.6 Hz, 2H), 7.62 (d, J = 8.1 Hz, 1H), 7.33 (dd, J = 15.7, 7.9 Hz, 2H), 7.24 (t, J = 7.4 Hz, 1H), 6.89 (d, J = 8.6 Hz, 2H), 2.80 (t, J = 7.5 Hz, 2H), 1.65 (dt, J = 15.0, 7.5 Hz, 2H), 1.23 (dd, J = 14.7, 7.3 Hz, 2H), 0.80 (t, J = 7.4 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ = 189.3, 163.1, 162.2, 153.0, 131.6, 129.7, 126.8, 124.5, 123.6, 120.7, 116.4, 115.3, 111.1, 29.5, 27.1, 21.6, 13.4 ppm.

(2-Butylbenzofuran-3-yl)(4-hydroxy-3,5-diiodophenyl)methanone (**9a**):[29] brown solid, mp: 145–147 °C, 72% yield (1.38 g); ^{1}H NMR (400 MHz, CDCl3, TMS, 25 °C) δ = 8.10 (s, 2H), 7.62 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.33 (dd, J = 11.3, 4.1 Hz, 1H), 7.26 (t, J = 7.4 Hz,

1H), 2.82–2.70 (m, 2H), 1.74–1.63 (m, 2H), 1.26 (dt, *J* = 14.7, 7.4 Hz, 2H), 0.83 (t, *J* = 7.3 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100MHz, $CDCl_3$, 25 °C) δ = 187.5, 165.7, 157.2, 153.7, 140.7, 135.2, 126.6, 124.6, 123.8, 121.0, 115.9, 111.2, 82.1, 30.1, 28.2, 22.6, 13.8 ppm.

(2-Butylbenzofuran-3-yl)(4-(2-(diethylamino)ethoxy)-3,5-diiodophenyl)methanone (**10a**):[18(a)] light brown solid, mp: 100–102 °C, 91% yield (1.48 g); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 °C) δ = 8.21 (s, 2H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.27 – 7.22 (m, 1H), 4.15 (t, *J* = 6.7 Hz, 2H), 3.10 (t, *J* = 6.7 Hz, 2H), 2.87–2.82 (m, 2H), 2.73 (q, *J* = 7.1 Hz, 4H), 1.82–1.73 (m, 2H), 1.36 (dd, *J* = 15.0, 7.4 Hz, 2H), 1.12 (t, *J* = 7.1 Hz, 6H), 0.92 (t, *J* = 7.3 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ = 187.9, 166.3, 161.6, 153.8, 140.8, 138.4, 126.5, 124.8, 124.0, 121.2, 116.0, 111.2, 91.0, 71.5, 52.2, 47.8, 30.2, 28.3, 22.7, 13.8, 12.1 ppm

Methyl 4-(1*H*-indol-3-yl)-2-methyl-4,5,6,7-tetrahydrobenzofuran-3-carboxylate (**11a**): light yellow oil, 80% yield (74.1 mg); ^{1}H NMR: (400 MHz, DMSO-d_6, 25 °C) δ = 10.65 (s, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 7.2 Hz, 1H), 6.98 (t, *J* = 7.1 Hz, 1H), 6.58 (d, *J* = 1.8 Hz, 1H), 4.51 (s, 1H), 3.37 (s, 3H), 2.67 – 2.54 (m, 2H), 2.50 (s, 3H), 1.89 – 1.86 (m, 2H), 1.70 – 1.67 (m, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6, 25 °C) δ = 163.9, 157.1, 149.7, 136.5, 126.2, 122.7, 120.7, 119.3, 118.9, 118.2, 118.1, 112.1, 111.4, 50.6, 29.7, 29.0, 22.3, 18.0, 13.8 ppm. IR (KBr) v: 3411, 2934, 2853, 1664, 1554, 1423, 1357, 742 cm^{-1}, HRMS (TOF, ESI) calcd for: $C_{19}H_{19}NO_3$, $[M + H]^+$ 310.1443, found 310.1444.

Methyl 2-methyl-4-(1-methyl-1*H*-indol-3-yl)-4,5,6,7-tetrahydrobenzofuran-3-carboxylate (**11b**): yellow oil, 71% yield (68.8 mg); ^{1}H NMR: (400 MHz, DMSO-d_6, 25 °C) δ = 7.57 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.60 (s, 1H), 4.52

(s, 1H), 3.66 (s, 3H), 3.39 (s, 3H), 2.66 – 2.54 (m, 2H), 2.51 (s, 3H), 1.88 – 1.83 (m, 2H), 1.69 – 1.66 (m, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6, 25 °C) δ = 163.8, 157.1, 149.7, 136.8, 127.2, 126.5, 120.9, 119.2, 118.4, 118.2, 118.1, 112.1, 109.5, 50.6, 32.1, 29.7, 28.8, 22.2, 17.8, 13.8 ppm. IR (KBr) v: 2927, 2853, 1715, 1467, 1444, 1259, 1090, 741 cm^{-1}, HRMS (TOF, ESI) calcd for: $C_{20}H_{21}NO_3$, $[M + H]^+$ 324.1600, found 324.1595.

Methyl 2-methyl-4-(2,4,5-trimethoxyphenyl)-4,5,6,7-tetrahydrobenzofuran-3-carboxylate (**12a**): light yellow oil, 75% yield (81.0 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 °C) δ = 6.55 (s, 1H), 6.32 (s, 1H), 4.55 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.66 (s, 3H), 3.46 (s, 3H), 2.61 (dd, J = 23.5, 12.1 Hz, 2H), 2.55 (s, 3H), 1.96 – 1.85 (m, 1H), 1.75 – 1.72 (m, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ = 164.7, 158.2, 151.0, 150.9, 147.6, 142.4, 126.3, 118.8, 113.9, 112.5, 97.8, 57.1, 56.6, 56.2, 50.5, 31.5, 30.4, 23.0, 18.9, 14.0. IR (KBr) v: 2937, 2849, 1711, 1508, 1439, 1315, 1206, 1090, 1035, 816 cm^{-1}, HRMS (TOF, ESI) calcd for: $C_{20}H_{24}NaO_6$, $[M + Na]^+$ 383.1471, found 383.1464.

Methyl 4-(2,2-diphenylvinyl)-2-methyl-4,5,6,7-tetrahydrobenzofuran-3-carboxylate (**13a**): yellow oil, 52% yield (58.0 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 °C) δ = 7.43 – 7.37 (m, 2H), 7.33 (d, J = 7.2 Hz, 3H), 7.25 – 7.14 (m, 5H), 6.02 (d, J = 9.5 Hz, 1H), 3.82 – 3.75 (m, 1H), 3.56 (s, 3H), 2.60 (d, J = 14.9 Hz, 2H), 2.52 (s, 3H), 1.99 – 1.89 (m, 1H), 1.82 – 1.76 (m, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ = 165.1, 158.0, 149.2, 143.3, 140.4, 140.1, 134.0, 130.0, 128.1, 128.0, 127.5, 127.0, 126.8, 120.1, 112.7, 51.1, 32.6, 31.2, 22.9, 19.8, 13.9. IR (KBr) v: 2927, 2855, 1717, 1662, 1444, 1216, 1088, 765, 701 cm^{-1}, HRMS (TOF, ESI) calcd for: $C_{25}H_{24}O_3$, $[M + H]^+$ 373.1804, found 373.1802.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. copies of ^{1}H NMR and ^{13}C NMR.

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Notes

The authors declare no competing financial interest.

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