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Interrupting Base-Mediated Benzofuran Ring Transformation with Michael Acceptors

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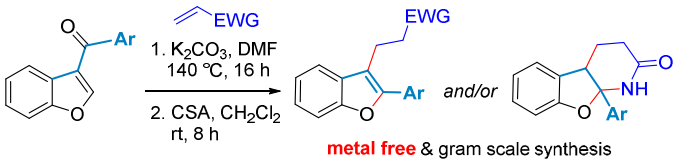


ABSTRACT: Simple two-stage approach for the synthesis of 3-(2-arylbenzofuran-3-yl)propanoates and propanamides has been developed employing simple acrylates and acrylamides and readily available 3-aroylbenzofurans. The key step of this process involves a base-mediated ring opening of the 3-aroylbenzofurans and subsequent Michael addition of the resulting 1,3-dicarbonyl intermediate with acrylate/acrylamide followed by the deformylation in one-pot. The resulting products undergo an acid-mediated dehydrative cyclization to arrive at these targets.

The alkali-mediated ring transformation of the benzofuran skeleton *via* the opening of the O(1)–C(2) bond constitutes an interesting area for mechanistic studies [Figure 1].[1] This has been pioneered by Royer and his co-workers in the latter half of the last century.[2,3] Specifically, the benzofurans bearing an electron withdrawing group such as carbonyl at the C(3) undergo a facile opening of O(1)–C(2) and subsequent dealkanoylation [losing C(2)] followed by dehydrative ring closure with the carbonyl on C(3) resulting in a new benzofuran derivative wherein the substituent attached to carbonyl becomes the C(2) substituent [Figure 1a]. This has been projected as a simple tool for the synthesis of 2-arylbenzofurans. However, its applicability in synthetic design has not been explored. After a long-interval, in 2015, Chi and co-workers have tapped into the potential of such a benzofuran ring transformation [Barbier has earlier reported a similar rearrangement of the natural product marginalin (Figure 1b)][4] to prepare C(2)-substituted

benzofuran-3-carboxylates which otherwise are prepared in general by cross-coupling chemistry [Figure 1c].[5] In a seminal contribution, Xie and co-workers have identified such an opening and ring transformation during the amidation of 2-arylbenzofuran-3-carboxylate intermediate used in the synthesis of the HCV polymerase inhibitor GSK852A [Figure 1d].[6] Given the facile opening of the 3-aroylbenzofurans [*via* a Michael addition of hydroxide anion at the C(2) of benzofuran followed by benzofuran ring opening leading to a phenoxide ion (see Scheme SI-1 for a detailed mechanism][3b] and deformylation with strong alkali bases, we speculated that when mild bases such as a carbonate were employed, there existed the possibility of trapping the intermediate enolate of 1,3-dicarbonyl with a Michael acceptor prior to the deformylation.[7] The cyclization of the resulting Michael addition product after the deformylation should result in the synthesis of a 2,3-disubstituted benzofuran derivative.

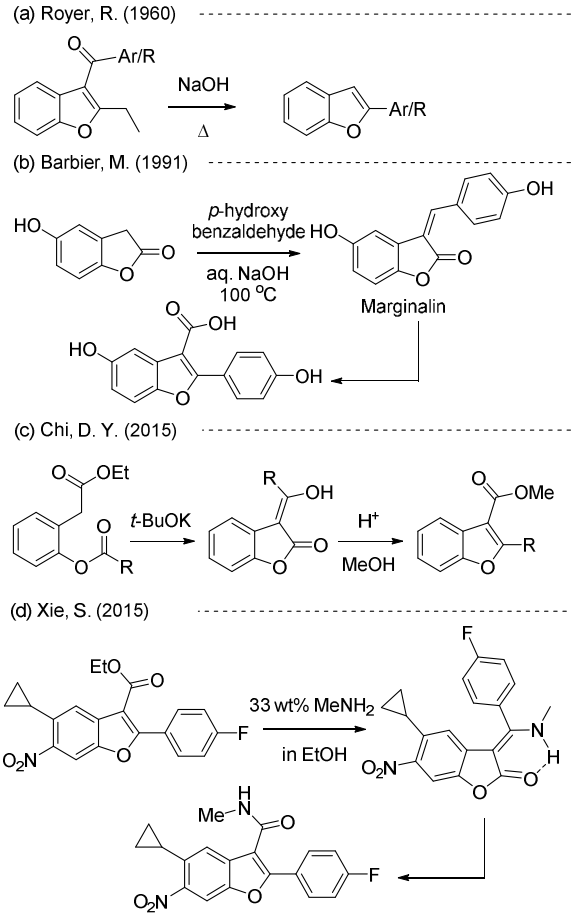
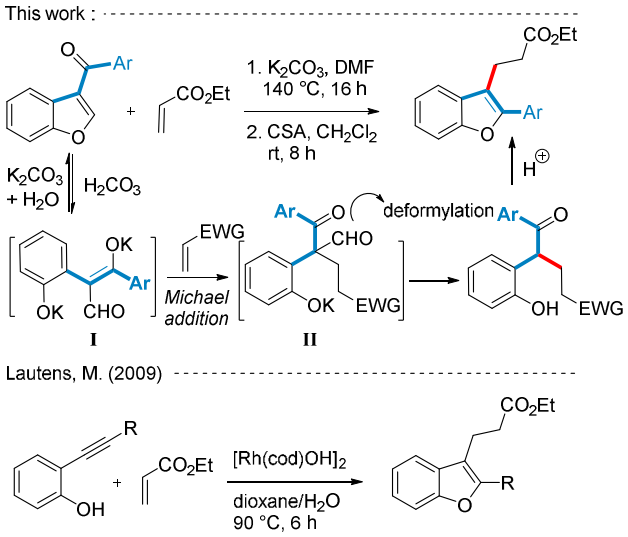


Figure 1. Representative benzofuran ring transformations

For example, as shown in Scheme 1, when an acrylate is employed as a Michael acceptor during the ring transformation of 3-benzoyl benzofuran, the expected product is the 3-(2-phenylbenzofuran-3-yl)propanoate that had been earlier synthesized by a Rh-catalyzed cyclization of o-alkynylphenols followed by intermolecular conjugate addition.[8]

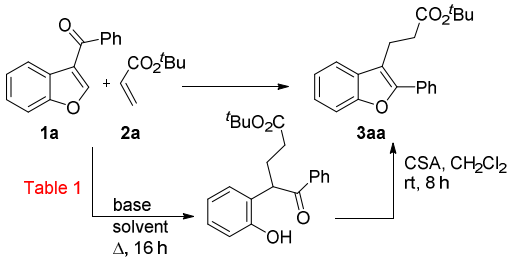
Scheme 1. Proposal on interrupting base-mediated benzofuran transformation with Michael acceptors to synthesize 2,3-disubstituted benzofurans



With this proposal, our initial experimentation began by screening various solvents employing benzofuran **1a**[9] and acrylate **2a** as substrates and K_2CO_3 (5 equiv) as a base. The reactions were initiated at rt and heated up to 140 °C. For the cases where there was a new product, the reactions were subjected for a simple aqueous work up and the resulting crude was immediately treated with 1 equiv of camphorsulphonic acid (CSA) in dichloromethane to obtain the newly formed benzofuran directly. The reaction of benzofuran **1a** with acrylate **2a** in the presence of K_2CO_3 in 1,2-dichloroethane did not result in the formation of the product either at room temperature or at 110 ºC (Table 1, entries 1, 2). Further, the reaction in aqueous medium at 110 ºC also failed to generate the desired product (Table 1, entry 3). The reactions in toluene and 1,4-dioxane are not fruitful for the projected transformation (Table 1, entries 4, 5). In polar solvents like DMSO, NMP and DMF, the formation of a new product was noticed which upon treatment with CSA gave the intended product in 65%, 57% and 69% yields respectively (Table 1, entries 6–8). Considering the better yields obtained in DMF solvent, further

optimization/control experiments proceeded with the same solvent. Variable temperature experiments employing DMF as solvent and K_2CO_3 as base revealed that the reaction was incomplete at lower temperatures with 44% and 28% starting material recovered at 100 °C and 120 °C respectively (Table 1, entries 9, 10). Further, on reducing K_2CO_3 from 5 to 2 equiv, the formation of product **3aa** after CSA cyclization was observed in 73% yield (Table 1, entry 11).

Table 1. Optimization of reaction conditions[a]



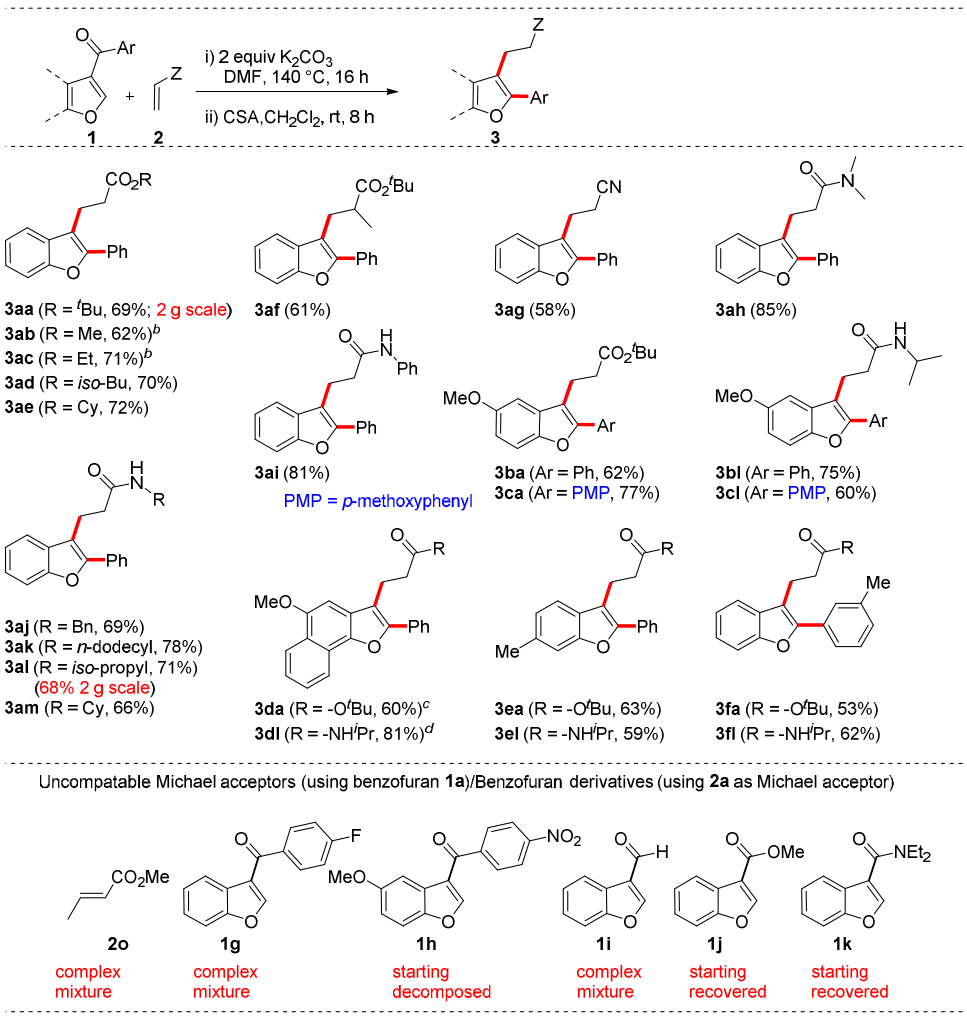
entry	base	solvent	temp.	yield[b]
1.	K_2CO_3	1,2-DCE	rt	--
2.	K_2CO_3	1,2-DCE	110 °C	--
3.	K_2CO_3	H_2O	110 °C	--
4.	K_2CO_3	toluene	140 °C	--
5.	K_2CO_3	1,4-dioxane	140 °C	--
6.	K_2CO_3	DMSO	140 °C	65%
7.	K_2CO_3	NMP	140 °C	57%
8.	K_2CO_3	DMF	140 °C	69%
9.	K_2CO_3	DMF	100 °C	46%[c]
10.	K_2CO_3	DMF	120 °C	67%[d]
11.	**K_2CO_3**	**DMF**	140 °C	**73%**[e]
12.	—	DMF	140 °C	--
13.	Cs_2CO_3	DMF	140 °C	63%
14.	K^{t}OBu	DMF	140 °C	52%
15.	CsOAc	DMF	140 °C	61%[f]
16.	NaOAc	DMF	140 °C	--
17.	$NaHCO_3$	DMF	140 °C	--

[a]Reaction conditions: i) **1a** (0.22 mmol), **2a** (0.44 mmol), base (1.1 mmol), DMF (3 mL), Δ, 16 h. ii) CSA (0.22 mmol), CH_2Cl_2 (10 mL). [b]Isolated yields after CSA reaction. [c]Reaction at 100 °C and Yield based on 44% recovered S.M. [d]Reaction at 120 °C and yield based on 28% recovered **1a**. [e]Reaction with (0.44 mmol) of K_2CO_3. [f]Yield based on 46% recovered **1a**.

Next examined was the compatibility of other bases for the current transformation. As shown in Table 1, there was no reaction when NaOAc and $NaHCO_3$ were used as the bases. With both Cs_2CO_3 and K^{t}OBu, the reaction proceeds smoothly and provides the final product **3aa** in 63% and 52% yields respectively (Table 1, entries 13, 14). On the other hand, with CsOAc, the reaction was sluggish and recovered 46% of the starting material (Table 1, entry 15) along with the isolation of **3aa** in 61% yield. Further, the compatibility of the Lewis acids for the cyclization step was examined by employing other Lewis acids such as PTSA, $ZnCl_2$, HCl and $Cu(OTf)_2$. The reaction proceeded in all cases resulting in the product **3aa** in 52%, 68%, 70% and 71% yields respectively. This suggests that CSA was better and for further experiments we proceeded by employing the same.

After optimizing the conditions, the scope of different acrylates, acrylonitrile and acrylamides has been explored using benzofuran **1a**. All these reactions have been carried out by employing 2 equiv. K_2CO_3 in DMF at 140 ºC for 16 h (Scheme 2). The crude products that resulted after the aqueous workups were directly subjected for the cyclization with CSA to get the desired disubstituted benzofuran. Coming to the different acrylates employed, with methyl-, ethyl acrylates, nearly 33% of the ester hydrolysed product was observed along with the desired products **3ab**, **3ac**. In other cases, the reactions proceeded smoothly and provided the corresponding disubstituted benzofurans in good yields.

Scheme 2. Scope of Michael acceptors and benzofurans[a]



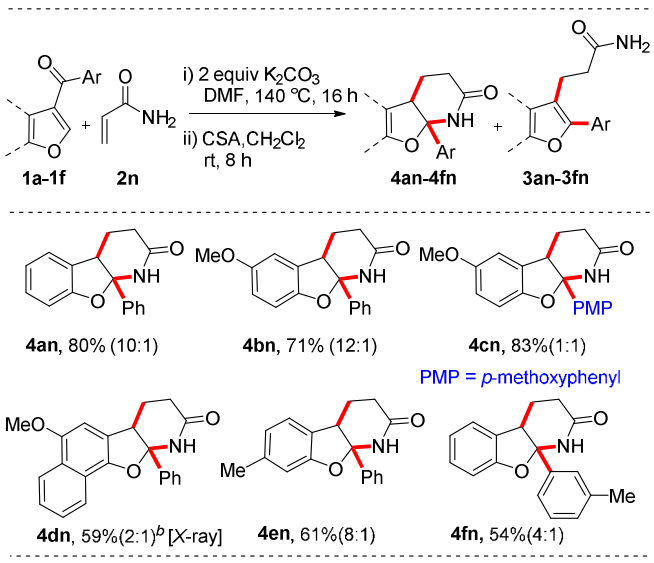
[a]Reaction conditions: i) **1** (1 equiv), **2** (2 equiv), DMF (3 mL). ii) CSA (1 equiv for acrylate and 3 equiv for acrylamide), CH_2Cl_2 (10 mL). Isolated yields after CSA reaction. [b]For **3ab**, **3ac** – the corresponding acid resulting from the ester hydrolysis were obtained in 30% and 32% respectively and the combined yields were given. [c]Yield based on 28% recovered starting material. [d]Yield based on 24% recovered starting material.

Interestingly, when methyl crotonate **2o** was employed as a Michael acceptor, a complex reaction mixture was obtained[10] On the other hand; acrylonitrile was found to be compatible for the current transformation and provided the corresponding product in 58% yield. Coming to the acrylamides, initially *N*,*N*'-dimethylacrylamide has been employed as the Michael acceptor along with **1a**, which provided the desired benzofuran **3ah** in 85% yield. Similarly, the reaction of benzofuran **1a** with other acrylamides **2i**–**2m** proceeded smoothly resulting in the disubstituted benzofurans **3ai**–**3am** in very good yields. The generality of this methodology has been further examined by employing benzofuran substrates **1b**–**1f**[8] having different substituents either on benzofuran or on the aroyl phenyl ring and employing the acrylate **2a** and acrylamide **2l**. With

benzofurans **1b**, **1c**, **1e** and **1f**, the reactions proceeded well and resulted in the isolation of the corresponding disubstituted benzofurans in good yields. However, in case of benzofuran **1d**, the reactions with both **2a** and **2l** were sluggish and the starting material was recovered along with the required product. Prolonged heating during the first step was found to be of no use in this case. In case of the benzofurans **1g** and **1h** where the pendant aryl ring has an electron withdrawing group positioned para to the carbonyl, their reactions with acrylate **1a** were found to be unsuccessful resulting in either complex mixture or the decomposition of the starting aroylbenzofuran This is anticipated considering the earlier Royer's report on similar 3-aroylbenzofurans which undergo oxidative dearylation under the base-mediated ring transformation conditions leading to the corresponding benzofuran-3-carboxylic acid.

Next, we examined the compatibility of the simple acrylamide under these conditions employing benzofuran **1b** as a substrate (Scheme 3). Interestingly, after following the usual two-step sequence, the product isolated in 71% yield was found to be a 12:1 inseparable mixture of cyclized product **4bn** and disubstitued benzofuran **3bn**.[11] Similarly, when we explored this reaction with the other benzofurans **1a**, **1c**–**1e**, the products obtained were found to be the separable mixtures of cyclized and uncyclized derivatives in varying proportions. However benzofuran **1f** gave inseparable mixtures of cyclised and uncyclized products. In case of benzofuran **1d**, the reaction was incomplete, with the recovery of the starting material. As observed with the acrylates, the reaction of benzofuran **1g** with acrylamide **2n also** led to a complex mixture.

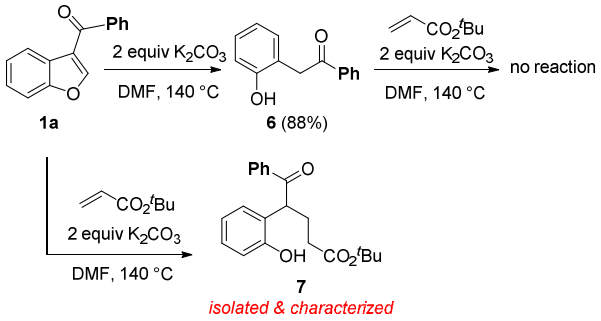
Scheme 3. Reactions with simple acrylamide and substrate scope[a]



[a]Reaction conditions: i) **1** (1 equiv), **2** (2 equiv), DMF (3 mL). ii) CSA (3 equiv), CH_2Cl_2 (10 mL). Isolated yields after CSA reaction. [b]Yield based on 48% recovered S.M. The ratio in the parenthesis is that of **4**:**3**.

After having established the proposed hypothesis, next we carried out some control experiments to track the reaction pathway. As a first step, we conducted experiments to examine what happens to benzofuran **1a** in the absence of a Michael acceptor. As shown in Scheme 4, heating **1a** in DMF along with 2 equiv of K_2CO_3 at 140 °C for 16 h led to the isolation of the known deformylated product **6**[12] in 88% yield. This proved the point that K_2CO_3 is sufficiently basic enough to open the benzofuran, that the deformylation proceeds as expected under the current conditions and that the subsequent dehydrative cyclization requires an acid. To learn about the occurrence of the Michael addition prior or after deformylation, we subjected the resulting ketone **6** under current conditions in the presence of acrylate **2a**. As expected, even after heating for 16 h, the starting ketone **6** was found to be intact. No traces of the expected product **3aa** were seen after subjecting the crude product isolated from this reaction to CSA-mediated cyclization. These results suggested that Michael addition with acrylates preceedes over the deformylation event.

Scheme 4. Control experiments



In conclusion, we have hypothesized the possibility of trapping the base-mediated ring opened [O(1)–C(2)] products of 3-aroylbenzofurans with Michael acceptors prior to the decarbonylation as a simple means of preparing the 3-(2-arylbenzofuran-3-yl)propanoates and propanamides and executed it successfully. Acrylates, methacrylates, acrylonitrile and acrylamides have been found to be suitable Michael acceptors although crotonates are not. Given the use of simple commercial reagents (including those used in the preparation of starting 3-aroylbenzofurans) to arrive at these end-products and reasonable yields without any metal-catalysts, the current approach for their synthesis underscores its suitability in preparing these key intermediates on large scales.

EXPERIMENTAL SECTION

General information:

Air- and/or moisture-sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in oven-dried glassware. Commercial reagents were used without purification. DMF was used directly from the commercial bottle and CH_2Cl_2 distilled over CaH_2 was used. Column chromatography was carried out by using silica gel (60−120, 100−200, 230−400 mesh). ^1H and ^{13}C NMR chemical shifts are reported in ppm relative to chloroform-D (δ = 7.25) or TMS and coupling constants (J) are reported in hertz (Hz). The following abbreviations have been used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. The multiplicity of carbons has been assigned with the help of DEPT spectra. IR spectra were recorded as films. High Resolution Mass Spectra (HRMS) were recorded on a Q Exactive Hybrid Quadrupole Orbitrap Mass Spectrometer, where the mass analyser used for analysis is orbitrap.

General experimental procedure : 3-Aroylbenzo[*b*]furan (0.1 mmol) was placed in a screw cap pressure tube and dissolved in DMF (3mL), which was then evacuated and back filled with argon. To this, were added acrylate or acrylamide (0.2 mmol) and K_2CO_3 (0.2 mmol) and the contents were stirred at 140 ^oC (bath temperature) for 16 h. The reaction mixture was cooled to room temperature, diluted with water and compound extracted using ethylacetate. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude reaction mixture, without column chromatography, was dissolved in CH_2Cl_2 (10 mL). To this camphorsulphonic acid (0.1 mmol for acrylate/0.3 mmol for acrylamide) was added and stirred for 8 h at room temperature. After completion of reaction, as indicated by TLC, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with water, dried over Na_2SO_4 and concentrated. The resulting crude product was purified by column chromatography (petroleum ether/ethyl acetate).

***tert*-Butyl 3-(2-phenylbenzofuran-3-yl)propanoate** (**3aa**): Isolated by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Yield 73%, (53 mg); Brown liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.63–2.67 (m, 2H), 3.23–3.26 (m, 2H), 7.24–7.27 (m, 1H (chloroform peak merged)), 7.30 (td, J = 1.4, 8.0 Hz, 1H), 7.38 (tt, J = 1.2, 7.4 Hz, 1H), 7.47–7.50 (m, 3H), 7.60 (dd, J = 1.1, 7.4 Hz, 1H), 7.80 (dd, J = 1.3, 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.0 (t), 28.0 (q, 3C), 35.3 (t), 80.6 (s), 111.1(d), 114.5 (s), 119.6 (d), 122.5 (d), 124.4 (d), 126.9 (d, 2C), 128.3 (d), 128.7 (d, 2C), 130.0 (s), 131.0 (s), 151.0 (s), 153.9 (s), 172.1 (s) ppm; IR ($CHCl_3$) 692, 744, 1147, 1365, 1453, 1727, 2925 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{22}O_3Na$: 345.1461 $[M+Na]^+$; found: 345.1461.

Methyl 3-(2-phenylbenzofuran-3-yl)propanoate (**3ab**): Isolated by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Yield 62%, (20 mg, (32%) ester, 18 mg, (30%) acid); Pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72–2.76 (m, 2H), 3.26–3.30 (m, 2H), 3.66 (s, 3H), 7.25 (td, J = 1.1, 7.3 Hz, 1H), 7.30 (td, J = 1.3, 7.5 Hz, 1H), 7.36–7.40 (m, 1H), 7.48 (t, J = 7.7 Hz, 3H), 7.57 (dd, J = 1.1, 7.2 Hz, 1H), 7.77–7.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8 (t), 33.8 (t), 51.8 (q), 111.1 (d), 114.2 (s), 119.3 (d), 122.5 (d), 124.5 (d), 126.9 (d, 2C), 128.4 (d), 128.8 (d, 2C), 129.8 (s), 130.9 (s), 151.1 (s), 153.9 (s), 173.2 (s) ppm; IR ($CHCl_3$) 741, 1213, 1364, 1447, 1733, 3021 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{16}O_3Na$: 303.0992 $[M+Na]^+$; found: 303.0985.

Ethyl 3-(2-phenylbenzofuran-3-yl)propanoate (**3ac**): Isolated by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Yield 71%, (26 mg, (39%) ester, 19 mg, (32%) acid); Pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, J = 7.1 Hz, 3H), 2.67 (t, J = 8.2 Hz, 2H), 3.23 (t, J = 8.2 Hz, 2H), 4.07 (q, J = 7.1 Hz, 2H), 7.18–7.22 (m, 1H), 7.23–7.27 (m, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.6 Hz, 3H), 7.53 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 19.8 (t), 34.1 (t), 60.6 (t), 111.1 (d), 114.3 (s), 119.4 (d), 122.5 (d), 124.5 (d), 126.9 (d, 2C), 128.3 (d), 128.8 (d, 2C), 129.9 (s), 130.9 (s), 151.1 (s), 153.9 (s), 172.8 (s) ppm; IR ($CHCl_3$) 757, 1155, 1367, 1457, 1725, 2925 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{19}O_3$: 295.1329 $[M+H]^+$; found: 295.1325.

Isobutyl 3-(2-phenylbenzofuran-3-yl)propanoate (**3ad**): Isolated by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Yield 70%, (51 mg); Pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.81 (d, J = 6.7 Hz, 6H), 1.81 (sep, J = 6.7 Hz, 1H), 2.68 (t, J = 8.1 Hz, 2H), 3.22 (t, J = 8.2 Hz, 2H), 3.78 (d, J = 6.7 Hz, 2H), 7.17–7.20 (m, 1H), 7.22–7.25 (m, 1H), 7.31 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.8 Hz, 3H), 7.51 (d, J = 7.5 Hz, 1H), 7.72 (d, J = 7.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.0 (q, 2C), 19.9 (t), 27.6 (d), 34.1 (t), 70.8 (t), 111.1 (d), 114.3 (s), 119.4 (d), 122.5 (d), 124.5 (d), 126.9 (d, 2C), 128.3 (d), 128.8 (d, 2C), 129.9 (s), 130.9 (s), 151.1 (s), 153.9 (s), 172.9 (s) ppm; IR ($CHCl_3$) 690, 743, 1217, 1368, 1454, 1731, 2963 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{22}O_3Na$: 345.1461 $[M+Na]^+$; found: 345.1457.

Cyclohexyl 3-(2-phenylbenzofuran-3-yl)propanoate (**3ae**): Isolated by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Yield 72%, (56 mg); White solid; Mp 65–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18–1.33 (m, 5H), 1.43–1.47 (m, 1H), 1.59–1.64 (m, 2H), 1.70–1.73 (m, 2H), 2.65 (t, J = 8.2 Hz, 2H), 3.20 (t, J = 8.2 Hz, 2H), 4.68 (m, 1H), 7.16–7.20 (m, 1H), 7.21–7.25 (m, 1H), 7.31 (t, J = 7.4 Hz, 1H), 7.39–7.43 (m, 3H), 7.52 (d, J = 7.4 Hz, 1H), 7.72 (d, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.0 (t), 23.7 (t, 2C), 25.3 (t), 31.5 (t, 2C), 34.5 (t), 72.9 (d), 111.1 (d), 114.4 (s), 119.5 (d), 122.5 (d), 124.5 (d), 126.9 (d, 2C), 128.3 (d), 128.8 (d, 2C), 129.9 (s), 131.0 (s), 151.1 (s), 153.9 (s), 172.3 (s) ppm; IR ($CHCl_3$) 693, 737, 1009, 1056, 1170, 1359, 1448, 1726, 2927 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{24}O_3Na$: 371.1618 $[M+Na]^+$; found: 371.1611.

***tert*-Butyl 2-methyl-3-(2-phenylbenzofuran-3-yl)propanoate** (**3af**): Isolated by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Yield 61%, (46 mg); Pale

yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (d, J = 6.8 Hz, 3H), 1.27 (s, 9H), 2.76–2.83 (m, 1H), 2.91 (dd, J = 8.9, 14.4 Hz, 1H), 3.26 (dd, J = 6.3, 14.4 Hz, 1H), 7.16–7.18 (m, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.30 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.9 Hz, 3H), 7.53 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.9 (q), 27.9 (q, 3C), 28.3 (t), 40.5 (d), 80.3 (s), 111.0 (d), 113.8 (s), 120.0 (d), 122.4 (d), 124.4 (d), 126.9 (d, 2C), 128.2 (d), 128.7 (d, 2C), 130.4 (s), 131.1 (s), 151.5 (s), 153.8 (s), 175.4 (s) ppm; IR ($CHCl_3$) 691, 751, 1155, 1366, 1455, 1726, 2928, 2970 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{24}O_3Na$: 359.1618 $[M+Na]^+$; found: 359.1614.

3-(2-Phenylbenzofuran-3-yl)propanenitrile (**3ag**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.3); Yield 58%, (32 mg); Brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$): 2.74 (t, J = 7.4 Hz, 2H), 3.32 (t, J = 7.5 Hz, 2H), 7.29 (td, J = 1.1, 7.4 Hz, 1H), 7.34 (td, J = 1.4, 7.3 Hz, 1H), 7.42 (tt, J = 1.4, 7.4 Hz, 1H), 7.48–7.57 (m, 4H), 7.74 (dd, J = 1.4, 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 17.4 (t), 20.8 (t), 111.4 (d), 112.1 (s), 118.9 (d), 119.0 (s), 122.9 (d), 124.9 (d), 127.1 (d, 2C), 128.9 (d), 129.0 (d, 2C), 129.1 (s), 130.3 (s), 152.2 (s), 154.0 (s) ppm; IR ($CHCl_3$) 691, 748, 1448, 1639, 2245, 2923, 3420 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{13}ONNa$: 270.0889 $[M+Na]^+$; found: 270.0888.

***N,N*-Dimethyl-3-(2-phenylbenzofuran-3-yl)propanamide** (**3ah**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.2); Yield 85%, (56 mg); Yellow solid; Mp 64–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59 (t, J = 8.2 Hz, 2H), 2.75 (s, 3H), 2.82 (s, 3H), 3.20 (t, J = 8.1 Hz, 2H), 7.11–7.20 (m, 2H), 7.24–7.26 (m, 1H), 7.34–7.39 (m, 3H), 7.46 (d, J = 7.5 Hz, 1H), 7.69 (d, J = 7.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.9 (t), 32.9 (t), 35.4 (q), 37.1 (q), 111.1 (d), 115.0 (s), 119.4 (d), 122.5 (d), 124.5 (d), 126.7 (d, 2C), 128.2 (d), 128.8 (d, 2C), 130.1 (s), 131.0 (s), 150.9 (s), 153.9 (s), 172.1 (s) ppm; IR ($CHCl_3$) 756, 1145, 1260, 1456, 1641, 2926 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{20}O_2N$: 294.1489 $[M+H]^+$; found: 294.1487.

***N*-Phenyl-3-(2-phenylbenzofuran-3-yl)propanamide** (**3ai**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.4); Yield 81%, (62 mg); Pale white solid; Mp 153–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.76 (t, J = 7.9 Hz, 2H), 3.40 (t, J = 7.8 Hz, 2H), 7.05–7.09 (m, 2H), 7.22–7.32 (m, 4H), 7.36–7.38 (m, 3H), 7.46–7.51 (m, 3H), 7.61 (d, J = 7.6 Hz, 1H), 7.81 (d, J = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.0 (t), 37.0 (t), 111.1

(d), 114.4 (s), 119.5 (d), 120.0 (d, 2C), 122.6 (d), 124.4 (d), 124.6 (d), 126.8 (d, 2C), 128.4 (d), 128.8 (d, 2C), 128.9 (d, 2C), 129.8 (s), 130.8 (s), 137.5 (s), 151.1 (s), 153.9 (s), 170.2 (s) ppm; IR ($CHCl_3$) 697, 757, 1250, 1446, 1542, 1667, 2925, 3295 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{20}O_2N$: 342.1489 $[M+H]^+$; found: 342.1477.

***N*-Benzyl-3-(2-phenylbenzofuran-3-yl)propanamide** (**3aj**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.4); Yield 69%, (55 mg); White solid; Mp 149–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.56 (t, J = 7.5 Hz, 2H), 3.29 (t, J = 7.6 Hz, 2H), 4.28 (d, J = 5.6 Hz, 2H), 5.52 (br. s., 1H), 7.00–7.01 (m, 2H), 7.16–7.20 (m, 4H), 7.24 (dt, J = 1.2, 8.1 Hz, 1H), 7.30 (t, J = 7.4 Hz, 1H), 7.41 (dd, J = 7.6, 14.2 Hz, 3H), 7.54 (d, J = 7.36 Hz, 1H), 7.73 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3 (t), 36.3 (t), 43.7 (t), 111.1 (d), 114.5 (s), 119.6 (d), 122.6 (d), 124.5 (d), 126.8 (d, 2C), 127.5 (d), 127.7 (d, 2C), 128.4 (d), 128.6 (d, 2C), 128.8 (d, 2C), 130.0 (s), 130.9 (s), 137.9 (s), 151.1 (s), 153.9 (s), 171.7 (s) ppm; IR ($CHCl_3$) 669, 764, 1215, 1517, 1668, 3022 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{21}O_2NNa$: 378.1465 $[M+Na]^+$; found: 378.1458.

***N*-Dodecyl-3-(2-phenylbenzofuran-3-yl)propanamide** (**3ak**) : Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.3); Yield 78%, (76 mg); Grey solid; Mp 105–106 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.93 (t, J = 6.7 Hz, 3H), 1.29–1.35 (m, 20H), 2.61 (t, J = 7.6 Hz, 2H), 3.17 (q, J = 6.6 Hz, 2H), 3.36 (t, J = 7.6 Hz, 2H), 5.38 (t, J = 6.2 Hz, 1H), 7.24–7.35 (m, 2H), 7.37–7.46 (m, 1H), 7.49–7.57 (m, 3H), 7.62–7.66 (m, 1H), 7.84–7.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (q), 20.4 (t), 22.7 (t), 26.8 (t), 29.2 (t), 29.3 (t, 2C), 29.5 (t), 29.6 (t, 3C), 31.9 (t), 36.3 (t), 39.6 (t), 111.1 (d), 114.6 (s), 119.6 (d), 122.5 (d), 124.5 (d), 126.8 (d, 2C), 128.3 (d), 128.8 (d, 2C), 130.0 (s), 130.9 (s), 151.0 (s), 153.8 (s), 171.8 (s) ppm; IR ($CHCl_3$) 756, 1458, 1551, 1639, 2853, 2919, 3304 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{40}O_2N$: 434.3054 $[M+H]^+$; found: 434.3052.

***N*-Isopropyl-3-(2-phenylbenzofuran-3-yl)propanamide** (**3al**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.4); Yield 71%, (49 mg); White solid; Mp 132–134 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.97 (d, J = 6.6 Hz, 6H), 2.54 (t, J = 7.6 Hz, 2H), 3.30 (t, J = 7.6 Hz, 2H), 3.95–4.02 (m, 1H), 5.10 (d, J = 6.5 Hz, 1H), 7.24 (td, J = 1.0, 7.4 Hz, 1H), 7.29 (td, J = 1.3, 7.8 Hz, 1H), 7.37 (tt, J = 1.2, 7.4 Hz, 1H), 7.46–7.51 (m, 3H), 7.60 (d, J = 7.6 Hz, 1H), 7.80–7.82 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 20.3 (q, 2C), 22.6 (t), 36.4

(d), 41.4 (t), 111.1 (d), 114.7 (s), 119.6 (d), 122.5 (d), 124.5 (d), 126.8 (d, 2C), 128.3 (d), 128.8 (d, 2C), 130.0 (s), 130.9 (s), 151.0 (s), 153.8 (s), 170.9 (s) ppm; IR ($CHCl_3$) 623, 769, 1452, 1636, 2923, 3294, 3387 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{22}O_2N$: 308.1645 $[M+H]^+$; found: 308.1640.

***N*-Cyclohexyl-3-(2-phenylbenzofuran-3-yl)propanamide** (**3am**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.4); Yield 66%, (52 mg); White solid; Mp 183–185°C; ^1H NMR (400 MHz, $CDCl_3$): δ 0.84–0.91 (m, 2H), 0.98–1.04 (m, 1H), 1.16–1.29 (m, 3H), 1.46–1.50 (m, 2H), 1.67–1.70 (m, 2H), 2.51 (t, J = 7.6 Hz, 2H), 3.27 (t, J = 7.6 Hz, 2H), 3.63–3.65 (m, 1H), 5.09 (d, J = 7.2 Hz, 1H), 7.21–7.26 (m, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.40–7.45 (m, 3H), 7.56 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4 (t), 24.7 (t, 2C), 25.4 (t), 32.9 (t, 2C), 36.5 (t), 48.2 (d), 111.1 (d), 114.7 (s), 119.6 (d), 122.5 (d), 124.5 (d), 126.8 (d, 2C), 128.3 (d), 128.8 (d, 2C), 130.0 (s), 131.0 (s), 151.0 (s), 153.9 (s), 170.9 (s) ppm; IR ($CHCl_3$) 758, 1218, 1548, 1641, 2931, 3288 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{26}O_2N$: 348.1958 $[M+H]^+$; found: 348.1955.

***tert*-Butyl 3-(5-methoxy-2-phenylbenzofuran-3-yl)propanoate** (**3ba**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); Yield 62%, (43 mg); Pale yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.63 (t, J = 8.2 Hz, 2H), 3.20 (t, J = 8.2 Hz, 2H), 3.88 (s, 3H), 6.89 (dd, J = 2.2, 8.8 Hz, 1H), 7.03 (d, J = 2.2 Hz, 1H), 7.35–7.38 (m, 2H), 7.47 (t, J = 7.5 Hz, 2H), 7.76 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.0 (t), 28.0 (q), 28.1 (q, 2C), 35.2 (t), 56.0 (q), 80.6 (s), 102.2 (d), 111.5 (d), 113.0 (d), 114.6 (s), 126.8 (d, 2C), 128.2 (d), 128.7 (d, 2C), 130.5 (s), 131.1 (s), 148.9 (s), 151.9 (s), 155.8 (s), 172.2 (s) ppm; IR ($CHCl_3$) 759, 1153, 1215, 1469, 1723, 2929 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{25}O_4$: 353.1747 $[M+H]^+$; found: 353.1745.

***N*-Isopropyl-3-(5-methoxy-2-phenylbenzofuran-3-yl)propanamide** (**3bl**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.4); Yield 75%, (50 mg); White solid; Mp 193–194 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (d, J = 6.6 Hz, 6H), 2.52 (t, J = 7.6 Hz, 2H), 3.26 (t, J = 7.7 Hz, 2H), 3.87 (s, 3H), 3.94–4.05 (m, 1H), 5.12 (d, J = 6.5 Hz, 1H), 6.89 (dd, J = 2.5, 8.8 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 7.34–7.37 (m, 2H), 7.47 (t, J = 7.6 Hz, 2H), 7.78 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3 (t), 22.6 (q, 2C), 36.4 (t), 41.4 (d), 56.1 (q), 102.1 (d), 111.5 (d), 113.2 (d), 114.9 (s), 126.7 (d, 2C), 128.3 (d), 128.8 (d, 2C), 130.5

(s), 131.0 (s), 148.8 (s), 151.8 (s), 155.9 (s), 171.0 (s) ppm; IR ($CHCl_3$) 767, 1216, 1467, 1554, 1636, 2966, 3293 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{24}O_3N$: 338.1751 $[M+H]^+$; found: 338.1745.

***tert*-Butyl 3-(5-methoxy-2-(4-methoxyphenyl)benzofuran-3-yl)propanoate** (**3ca**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.4); Yield 77%, (46 mg); Brown liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.60 (t, J = 8.0 Hz, 2H), 3.16 (t, J = 8.0 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 6.86 (dd, J = 2.4, 8.8 Hz, 1H), 7.00 (dd, J = 3.0, 5.9 Hz, 3H), 7.34 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.0 (t), 28.0 (q, 3C), 35.2 (t), 55.3 (q), 56.0 (q), 80.6 (s), 102.1 (d), 111.3 (d), 112.4 (d), 113.2 (s), 114.2 (d, 2C), 123.8 (s), 128.3 (d, 2C), 130.7 (s), 148.7 (s), 152.1 (s), 155.8 (s), 159.6 (s), 172.3 (s) ppm; IR ($CHCl_3$) 672, 763, 1030, 1165, 1216, 1252, 1468, 1608, 1720, 2972, 3018 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{27}O_5$: 383.1853 $[M+H]^+$; found: 383.1847.

***N*-Isopropyl-3-(5-methoxy-2-(4-methoxyphenyl)benzofuran-3-yl)propanamide** (**3cl**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.4); Yield 60%, (39 mg); Light brown solid; Mp 136–137 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 0.98 (d, J = 6.5 Hz, 6H), 2.50 (t, J = 7.5 Hz, 2H), 3.22 (t, J = 7.5 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 3.94–4.03 (m, 1H), 5.12 (d, J = 6.6 Hz, 1H), 6.86 (dd, J = 0.6, 8.7 Hz, 1H), 6.99 (d, J = 8.4 Hz, 3H), 7.34 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.3 (t), 22.6 (q, 2C), 36.3 (t), 41.4 (d), 55.3 (q), 56.0 (q), 102.0 (d), 111.3 (d), 112.5 (d), 113.3 (s), 114.3 (d, 2C), 123.7 (s), 128.2 (d, 2C), 130.7 (s), 148.6 (s), 152.0 (s), 155.8 (s), 159.6 (s), 171.1 (s) ppm; IR ($CHCl_3$) 761, 1030, 1215, 1466, 1644, 2925, 3022, 3408 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{26}O_4N$: 368.1856 $[M+H]^+$; found: 368.1854.

***tert*-Butyl 3-(5-methoxy-2-phenylnaphtho[1,2-*b*]furan-3-yl)propanoate** (**3da**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); Yield 60%, (29 mg), 14 mg S.M recovered; Light brown solid; Mp 124–126 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.67 (t, J = 7.7 Hz, 2H), 3.29 (t, J = 7.7 Hz, 2H), 4.07 (s, 3H), 6.94 (s, 1H), 7.37 (t, J = 6.7 Hz, 1H), 7.46–7.51 (m, 3H), 7.60 (t, J = 7.1 Hz, 1H), 7.85 (d, J = 7.3 Hz, 2H), 8.30 (t, J = 9.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.1 (t), 28.1 (q, 3C), 35.5 (t), 56.0 (q), 80.6 (s), 95.3 (d), 116.1 (s), 119.8 (d), 121.6 (s), 123.1 (d), 124.2 (s), 124.5 (d), 124.7 (s), 126.5 (d, 2C), 126.9 (d), 127.8 (d), 128.8 (d, 2C), 131.4 (s), 144.4 (s), 150.5 (s), 152.1 (s), 172.3 (s) ppm; IR ($CHCl_3$)

667, 758, 1143, 1216, 1367, 1732, 2926, 2965 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{27}O_4$: 403.1904 $[M+H]^+$; found: 403.1900.

***N*-Isopropyl-3-(5-methoxy-2-phenylnaphtho[1,2-*b*]furan-3-yl)propanamide** (**3dl**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.5); Yield 81%, (40 mg), 12 mg S.M recovered; Brown solid; Mp 190–192 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (d, J = 6.6 Hz, 6H), 2.56 (t, J = 7.5 Hz, 2H), 3.35 (t, J = 7.5 Hz, 2H), 3.96–4.03 (m, 1H), 4.06 (s, 3H), 5.13 (d, J = 7.0 Hz, 1H), 6.96 (s, 1H), 7.36 (t, J = 7.3 Hz, 1H), 7.46–7.52 (m, 3H), 7.60 (t, J = 7.6 Hz, 1H), 7.86 (d, J = 7.8 Hz, 2H), 8.29 (t, J = 9.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.5 (t), 22.6 (q, 2C), 36.7 (t), 41.4 (d), 56.0 (q), 95.4 (d), 116.4 (s), 119.9 (d), 121.6 (s), 123.2 (d), 124.3 (s), 124.6 (d), 124.8 (s), 126.4 (d, 2C), 126.9 (d), 127.9 (d), 128.9 (d, 2C), 131.4 (s), 144.3 (s), 150.4 (s), 152.2 (s), 171.1 (s) ppm; IR ($CHCl_3$) 623, 763, 1224, 1377, 1456, 1639, 2928, 2967, 3293 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{26}O_3N$: 388.1907 $[M+H]^+$; found: 388.1905.

***tert*-Butyl 3-(6-methyl-2-phenylbenzofuran-3-yl)propanoate** (**3ea**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); Yield 63%, (45 mg); Pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.49 (s, 3H), 2.62–2.66 (m, 2H), 3.20–3.24 (m, 2H), 7.08 (d, J = 7.7 Hz, 1H), 7.30 (s, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.46–7.49 (m, 3H), 7.78 (d, J = 7.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.0 (t), 21.7 (q), 28.0 (q, 3C), 35.3 (t), 80.6 (s), 111.3 (d), 114.4 (s), 119.1 (d), 123.8 (d), 126.7 (d, 2C), 127.5 (s), 128.0 (d), 128.7 (d, 2C), 131.2 (s), 134.7 (s), 150.4 (s), 154.3 (s), 172.2 (s) ppm; IR ($CHCl_3$) 748, 1148, 1216, 1366, 1727, 2971 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{24}O_3Na$: 359.1618 $[M+Na]^+$; found: 359.1614.

***N*-Isopropyl-3-(6-methyl-2-phenylbenzofuran-3-yl)propanamide** (**3el**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.5); Yield 59%, (40 mg); White solid; Mp 164–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (d, J = 6.5 Hz, 6H), 2.47 (s, 3H), 2.52 (t, J = 7.8 Hz, 2H), 3.27 (t, J = 7.8 Hz, 2H), 3.94–4.02 (m, 1H), 5.18 (br. d, J = 6.8 Hz, 1H), 7.06 (d, J = 7.9 Hz, 1H), 7.28 (s, 1H), 7.33–7.36 (m, 1H), 7.44–7.49 (m, 3H), 7.77–7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4 (t), 21.7 (q), 22.6 (q, 2C), 36.4 (t), 41.4 (d), 111.3 (d), 114.6 (s), 119.1 (d), 123.9 (d), 126.6 (d, 2C), 127.5 (s), 128.1 (d), 128.8 (d, 2C), 131.1 (s), 134.8 (s), 150.4 (s), 154.3 (s), 171.1 (s) ppm; IR ($CHCl_3$) 762, 1217, 1545, 1639, 2925, 3293 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{24}O_2N$: 322.1802 $[M+H]^+$; found: 322.1802.

***tert*-Butyl 3-(2-(*m*-tolyl)benzofuran-3-yl)propanoate** (**3fa**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); Yield 53%, (38 mg); Pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.44 (s, 3H), 2.63–2.67 (m, 2H), 3.22–3.26 (m, 2H), 7.20 (d, J = 7.5 Hz, 1H), 7.25 (ddd, J = 1.1, 6.6, 7.5 Hz, 1H), 7.30 (td, J = 1.5, 7.7 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.58–7.62 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.0 (t), 21.6 (q), 28.0 (q, 3C), 35.3 (t), 80.6 (s), 111.0 (d), 114.4 (s), 119.5 (d), 122.4 (d), 124.1 (d), 124.3 (d), 127.6 (d), 128.6 (d), 129.1 (d), 130.0 (s), 130.9 (s), 138.4 (s), 151.2 (s), 153.9 (s), 172.2 (s) ppm; IR ($CHCl_3$) 744, 1148, 1217, 1365, 1453, 1726, 2928, 2972 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{24}O_3Na$: 359.1618 $[M+Na]^+$; found: 359.1614.

***N*-Isopropyl-3-(2-(*m*-tolyl)benzofuran-3-yl)propanamide** (**3fl**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.5); Yield 62%, (42 mg); White solid; Mp 125–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (d, J = 6.6 Hz, 6H), 2.43 (s, 3H), 2.53 (t, J = 7.7 Hz, 2H), 3.29 (t, J = 7.7 Hz, 2H), 3.94–4.03 (m, 1H), 5.17 (d, J = 6.9 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 7.23 (td, J = 7.4, 0.9 Hz, 1H), 7.28 (td, J = 7.4, 1.6 Hz, 1H), 7.36 (t, J = 7.7 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.58–7.63 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3 (t), 21.6 (q), 22.6 (q, 2C), 36.4 (t), 41.3 (d), 111.0 (d), 114.6 (s), 119.6 (d), 122.5 (d), 123.9 (d), 124.4 (d), 127.4 (d), 128.7 (d), 129.1 (d), 130.0 (s), 130.8 (s), 138.5 (s), 151.1 (s), 153.8 (s), 171.0 (s) ppm; IR ($CHCl_3$) 744, 1217, 1368, 1454, 1645, 2926, 3299 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{24}O_2N$: 322.1802 $[M+H]^+$; found: 322.1801.

9a-Phenyl-3,4,4a,9a-tetrahydrobenzofuro[2,3-*b*]pyridin-2(1*H*)-one (**4an**): Isolated by column chromatography (petroleum ether/ethyl acetate = 6:4, R_f = 0.4); Yield 80%, (48 mg); Brown gummy liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.18–2.33 (m, 4H), 3.68 (br. s., 1H), 6.35 (br. s., 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 7.04 (d, J = 7.2 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 7.29–7.35 (m, 3H), 7.49 (d, J = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.5 (t), 27.3 (t), 47.7 (d), 98.7 (s), 110.2 (d), 121.8 (d), 123.8 (d), 125.1 (d, 2C), 126.6 (s), 128.8 (d, 2C), 129.0 (d), 129.3 (d), 142.2 (s), 158.0 (s), 173.1 (s) ppm; IR ($CHCl_3$) 761, 1229, 1470, 1670, 2928, 3387 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{16}O_2N$: 266.1176 $[M+H]^+$; found: 266.1172.

Inseparable mixture of 6-methoxy-9a-phenyl-3,4,4a,9a-tetrahydrobenzofuro[2,3-*b*]pyridin-2(1*H*)-one (**4bn**) **and 3-(5-methoxy-2-phenylbenzofuran-3-yl)propanamide** (**3bn**): Isolated by column chromatography (petroleum ether/ethyl acetate = 6:4, R_f = 0.4); Yield 71%, (42 mg) ;

Brown solid; Mp 103–107 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.19–2.27 (m, 2H), 2.29–2.42 (m, 2H), 2.68–2.71 (m, 0.16H), 3.18–3.21 (m, 0.16H), 3.71 (t, J = 4.5 Hz, 1H), 3.77 (s, 3H), 3.84 (s, 0.23H), 6.45 (br. s., 1H), 6.67 (d, J = 2.1 Hz, 1H), 6.76 (dd, J = 2.3, 8.7 Hz, 1H), 6.83 (d, J = 8.6 Hz, 1H), 6.88 (dd, J = 2.4, 8.8 Hz, 0.08H), 6.99 (d, J = 2.2 Hz, 0.09H), 7.35–7.41 (m, 3H), 7.45 (d, J = 7.7 Hz, 0.14H), 7.55 (d, J = 7.4 Hz, 2H), 7.73 (d, J = 7.8 Hz, 0.17H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.7 (t), 22.2 (t), 27.3 (t), 33.7 (t), 48.1 (d), 56.0 (q), 98.9 (s), 101.8 (d), 110.0 (d), 110.3 (d), 111.5 (d), 113.2 (d), 113.9 (d), 114.5 (s), 125.1 (d, 2C), 126.7 (d, 2C) 127.6 (s), 128.2 (d), 128.7 (d, 2C), 128.8 (d, 2C), 128.9 (d), 142.2 (s), 148.8 (s), 151.9 (s), 152.0 (s), 155.1 (s), 155.8 (s), 173.0 (s) ppm; IR ($CHCl_3$) 764, 1213, 1484, 1673, 2931, 3219 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{17}O_3NNa$: 318.1101 $[M+Na]^+$; found: 318.1095.

6-Methoxy-9a-(4-methoxyphenyl)-3,4,4a,9a-tetrahydrobenzofuro[2,3-*b*]pyridin-2(1*H*)-one (**4cn**): Isolated by column chromatography (petroleum ether/ethyl acetate = 6:4, R_f = 0.3); Yield 40%, (23 mg); White solid; Mp 163–166 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.19–2.22 (m, 2H), 2.29–2.37 (m, 2H), 3.68 (t, J = 4.2 Hz, 1H), 3.77 (s, 3H), 3.81 (s, 3H), 6.13 (s, 1H), 6.67 (d, J = 2.0 Hz, 1H), 6.75 (dd, J = 2.4, 8.7 Hz, 1H), 6.82 (d, J = 8.7 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 22.1 (t), 27.3 (t), 48.2 (d), 55.4 (q), 56.0 (q), 99.0 (s), 110.1 (d), 110.4 (d), 113.9 (d), 114.0 (d, 2C), 126.5 (d, 2C), 127.7 (s), 134.3 (s), 152.0 (s), 155.1 (s), 160.0 (s), 172.8 (s) ppm; IR ($CHCl_3$) 623, 1029, 1252, 1480, 1600, 1670, 2923, 3329 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{20}O_4N$: 326.1387 $[M+H]^+$; found: 326.1386.

3-(5-methoxy-2-(4-methoxyphenyl)benzofuran-3-yl)propanamide (**3cn**): Isolated by column chromatography (petroleum ether/ethyl acetate = 1:1, R_f = 0.3); Yield 43%, (25 mg); Pale white solid; Mp 164–165 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.61 (t, J = 8.1 Hz, 2H), 3.24 (t, J = 7.9 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 5.27–5.32 (m, 2H), 6.86 (dd, J = 2.6, 8.8 Hz, 1H), 6.99–7.00 (m, 3H), 7.35 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 19.9 (t), 35.1 (t), 55.3 (q), 56.0 (q), 101.9 (d), 111.4 (d), 112.5 (d), 113.0 (s), 114.3 (d, 2C), 123.6 (s), 128.2 (d, 2C), 130.6 (s), 148.7 (s), 152.1 (s), 155.8 (s), 159.6 (s), 174.4 (s) ppm; IR ($CHCl_3$) 763, 1215, 1468, 1649, 2927, 3407 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{19}O_4NNa$: 348.1206 $[M+Na]^+$; found: 348.1203.

5-Methoxy-10a-phenyl-7,8,10,10a-tetrahydronaphtho[2',1':4,5]furo[2,3-*b*]pyridin-9(6b*H*)-one (**4dn**): Isolated by column chromatography (petroleum ether/ethyl acetate = 6:4, R_f = 0.3);

Yield 39%, (23 mg); Brown solid; Decomposed at 235 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.28–2.34 (m, 3H), 2.38–2.42 (m, 1H), 3.91 (br. S, 1H), 3.96 (s, 3H), 6.36 (s, 1H), 6.57 (s, 1H), 7.36–7.42 (m, 3H), 7.48–7.56 (m, 2H), 7.60 (d, J = 7.6 Hz, 2H), 7.97 (d, J = 8.2 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 23.1 (t), 27.6 (t), 49.4 (d), 56.0 (q), 98.8 (s), 99.3 (d), 118.0 (s), 120.8 (s), 121.3 (d), 122.7 (d), 125.1 (d, 2C), 125.7 (d), 126.1 (s), 126.6 (d), 128.9 (d, 2C), 128.9 (d), 142.7 (s), 147.2 (s), 151.4 (s), 173.6 (s) ppm; IR ($CHCl_3$) 670, 764, 1215, 1652, 3021, 3412 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{19}O_3NNa$: 368.1257 $[M+Na]^+$; found: 368.1255.

3-(5-methoxy-2-phenylnaphtho[1,2-*b*]furan-3-yl)propanamide (**3dn**): Isolated by column chromatography (petroleum ether/ethyl acetate = 1:1, R_f = 0.3); Yield 20%, (11 mg); Brown solid; Decomposed at 173 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.66 (t, J = 7.7 Hz, 2H), 3.37 (t, J = 7.7 Hz, 2H), 4.06 (s, 3H), 5.34 (br. s., 2H), 6.95 (s, 1H), 7.37 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.8 Hz, 3H), 7.60 (t, J = 7.4 Hz, 1H), 7.85 (d, J = 7.8 Hz, 2H), 8.28 (d, J = 8.2 Hz, 1H), 8.30 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.1 (t), 35.5 (t), 56.0 (q), 95.2 (d), 116.0 (s), 119.8 (d), 121.6 (s), 123.1 (d), 124.3 (s), 124.7 (d), 126.4 (d, 2C), 127.0 (d), 127.9 (d), 128.9 (d, 2C), 128.9 (s), 131.4 (s), 144.4 (s), 150.5 (s), 152.2 (s), 174.3 (s) ppm; IR ($CHCl_3$) 623, 770, 1646, 2926, 3421 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{20}O_3N$: 346.1438 $[M+H]^+$; found: 346.1433.

7-Methyl-9a-phenyl-3,4,4a,9a-tetrahydrobenzofuro[2,3-*b*]pyridin-2(1*H*)-one (**4en**): Isolated by column chromatography (petroleum ether/ethyl acetate = 6:4, R_f = 0.3); Yield 61%, (36 mg); Brown gummy liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.19–2.24 (m, 2H), 2.25–2.33 (m, 2H), 2.35 (s, 3H), 3.70 (br. s, 1H), 6.31 (br. s., 1H), 6.75 (s, 1H), 6.79 (d, J = 7.6 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 7.35–7.41 (m, 3H), 7.55 (d, J = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.6 (q), 22.6 (t), 27.3 (t), 47.5 (d), 98.9 (s), 110.9 (d), 122.5 (d), 123.4 (d), 123.5 (s), 125.1 (d, 2C), 128.8 (d, 2C), 128.9 (d), 139.6 (s), 142.3 (s), 158.3 (s), 173.1 (s) ppm; IR ($CHCl_3$) 700, 759, 945, 1262, 1453, 1673, 2924, 3216 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{18}O_2N$: 280.1332 $[M+H]^+$; found: 280.1330.

Inseparable mixture of 9a-(*m*-Tolyl)-3,4,4a,9a-tetrahydrobenzofuro[2,3-*b*]pyridin-2(1*H*)-one (**4fn**) **& 3-(2-(*m*-Tolyl)benzofuran-3-yl)propanamide** (**3fn**)**:** Isolated by column chromatography (petroleum ether/ethyl acetate = 6:4, R_f = 0.3); Yield 54%, (32 mg); Brown gummy liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18–2.27 (m, 4H), 2.30 (s, 3H), 2.35 (s, 0.75H), 2.67 (t, J = 8.2 Hz, 0.45H), 3.18 (t, J = 7.9 Hz, 0.45H), 3.68 (br. s., 1H), 6.52 (br. s., 1H), 6.87 (d,

J = 7.9 Hz, 1H), 6.92 (t, *J* = 7.3 Hz, 1H), 7.05 (d, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 7.4 Hz, 1.35H), 7.16–7.24 (m, 3.11H), 7.29 (d, *J* = 8.4 Hz, 2.44H), 7.42 (d, *J* = 8.0 Hz, 0.31H), 7.48–7.53 (m, 0.83H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7 (t), 21.5 (q), 21.6 (q), 22.3 (t), 27.3 (t), 33.8 (t), 47.7 (d), 98.8 (s), 110.3 (d), 111.1 (d), 114.1 (s), 119.4 (d), 121.8 (d), 122.2 (d), 122.5 (d), 123.8 (d), 124.0 (d), 124.4 (d), 125.8 (d), 126.6 (s), 127.6 (d), 128.7 (d), 128.8 (d), 129.2 (d), 129.3 (d), 129.7 (d), 129.9 (s), 130.8 (s), 138.5 (s), 138.7 (s), 142.1 (s), 151.4 (s), 153.9 (s), 158.1 (s), 173.4 (s), 176.6 (s) ppm; IR ($CHCl_3$) 749, 1460, 1480, 1641, 3442 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{18}O_2N$: 280.1332 $[M+H]^+$; found: 280.1330.

3-(2-Phenylbenzofuran-3-yl)propanoic acid (**9**): Isolated by column chromatography (petroleum ether/ethyl acetate = 8:2, R_f = 0.3); Light brown solid; Mp 104–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 2.83 (t, *J* = 8.3 Hz, 2H), 3.33 (t, *J* = 8.0 Hz, 2H), 7.29–7.31 (m, 1H), 7.33–7.36 (m, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.51–7.55 (m, 3H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 19.6 (t), 33.7 (t), 111.2 (d), 113.9 (s), 119.3 (d), 122.6 (d), 124.6 (d), 126.9 (d, 2C), 128.4 (d), 128.8 (d, 2C), 129.8 (s), 130.9 (s), 151.3 (s), 153.9 (s), 178.3 (s) ppm; IR ($CHCl_3$) 756, 1153, 1250, 1452, 1678, 2926, 3408 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{14}O_3Na$: 289.0835 $[M+Na]^+$; found: 289.0833.

***tert*-Butyl 4-(2-hydroxyphenyl)-5-oxo-5-phenylpentanoate** (**7**): Isolated by column chromatography (petroleum ether/ethyl acetate = 8:2, R_f = 0.3); Yield 82%, (63 mg); Pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.12–2.29 (m, 3H), 2.36–2.44 (m, 1H), 4.94 (t, *J* = 7.0 Hz, 1H), 6.78 (dt, *J* = 0.9, 7.4 Hz, 1H), 6.93–6.98 (m, 2H), 7.09–7.13 (m, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.99–8.01 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.0 (t), 28.0 (q, 3C), 32.7 (t), 47.1 (d), 81.3 (s), 117.9 (d), 120.9 (d), 124.8 (s), 128.6 (d, 2C), 128.8 (d, 2C), 128.9 (d), 129.2 (d), 133.5 (d), 136.0 (s), 154.4 (s), 174.1 (s), 201.6 (s) ppm; IR ($CHCl_3$) 623, 692, 1153, 1248, 1593, 1676, 2926, 3413 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{24}O_4Na$: 363.1567 $[M+Na]^+$; found: 363.1562.

4-(2-Hydroxyphenyl)-*N*-isopropyl-5-oxo-5-phenylpentanamide (**8**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.3); Yield 85%, (62 mg); Light brown solid; Mp 164–165 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14 (d, *J* = 6.6 Hz, 3H), 1.16 (d, *J* = 6.6 Hz, 3H), 2.07–2.11 (m, 1H), 2.14–2.21 (m, 2H), 2.27–2.34 (m, 1H), 4.05–4.14 (m, 1H), 5.10 (dd, *J* = 5.7, 8.5 Hz, 1H), 5.62 (d, *J* = 7.6 Hz, 1H), 6.73 (t, *J* = 7.4 Hz, 1H), 6.86 (dd, *J* =

1.5, 7.7 Hz, 1H), 7.00 (d, J = 8.1 Hz, 1H), 7.07–7.11 (m, 1H), 7.34 (t, J = 7.7 Hz, 2H), 7.44 (t, J = 7.4 Hz, 1H), 7.95 (d, J = 7.9 Hz, 2H), 9.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5 (q, 2C), 28.5 (t), 33.1 (t), 41.9 (d), 45.3 (d), 118.5 (d), 120.7 (d), 125.6 (s), 127.8 (d), 128.5 (d, 2C), 128.8 (d, 3C), 133.1 (d), 135.8 (s), 154.7 (s), 173.5 (s), 200.3 (s) ppm; IR ($CHCl_3$) 766, 1452, 1592, 1629, 2923, 3374 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{23}O_3NNa$: 348.1570 $[M+Na]^+$; found: 348.1564.

2-(2-Hydroxyphenyl)-1-phenylethan-1-one (**6**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); Yield 88%, (42 mg); Light yellow solid; Mp 107–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.28 (s, 2H), 6.87 (td, J = 1.2, 7.4 Hz, 1H), 6.95 (dd, J = 1.2, 8.6 Hz, 1H), 7.15–7.18 (m, 2H), 7.50 (t, J = 7.5 Hz, 2H), 7.61 (tt, J = 1.2, 7.3 Hz, 1H), 7.69 (s, 1H), 8.08–8.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.1 (t), 117.7 (d), 120.8 (d), 121.0 (s), 128.8 (d, 2C), 129.1 (d, 3C), 131.0 (d), 134.1 (d), 135.8 (s), 155.6 (s), 201.2 (s) ppm; IR ($CHCl_3$) 738, 1007, 1208, 1446, 1674, 2918, 3408, 3672 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{12}O_2Na$: 235.0730 $[M+Na]^+$; found: 235.0728.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

- ^{1}H/^{13}C NMR and HRMS spectra for all new compounds (PDF).
- X-ray crystallographic file for compound **4dn**

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Notes

The authors declare no competing financial interests.

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