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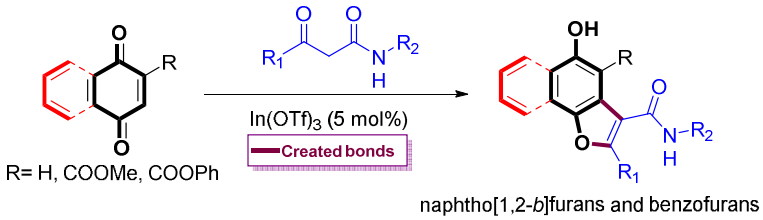
Graphic Abstract

Regioselective Synthesis of Novel and Diverse Naphtho[1,2-*b*]furan-3-carboxamides and Benzofuran-3-carboxamides by Cascade Formal [3 + 2] Cycloaddition

Likai Xia and Yong Rok Lee*

The regioselective synthesis of diverse naphtho[1,2-*b*]furan-3-amides and benzofuran-3-amides was accomplished by the $In(OTf)_3$-catalyzed cascade formal [3+2] cycloaddition of 1,4-naphthoquinones or benzoquinones with β-ketoamides.



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ARTICLE

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Likai Xia and Yong Rok Lee*

A novel and efficient $In(OTf)_3$-catalyzed cascade formal [3 + 2] cycloaddition of 1,4-naphthoquinones or benzoquinones with β-ketoamides was developed to provide naphtho[1,2-*b*]furan-3-carboxamides and benzofuran-3-carboxamides. This methodology has broad substrate scope that can afford novel and diverse naphtho[1,2-*b*]furan-3-carboxamides and benzofuran-3-carboxamides with high regioselectivity in good to excellent yields. Furthermore, this methodology is expected to be applicable to the synthesis of biologically-active complex molecules bearing naphtho[1,2-*b*]furan-3-carboxamides and benzofuran-3-carboxbenzamides.

Naphtho[1,2-*b*]furans and benzofurans are very important structural units found in diverse natural and synthetic products.[1] They possess a broad spectrum of biological activities and have been used as precursors for the synthesis of bioactive materials.[1,2] Among these, synthetic naphtho[1,2-*b*]furan-3-carboxamides and benzofuran-3-carboxamides have been shown to have a range of significant pharmacological properties (Figure 1). For example, compound **1** is an efficient material for altering the lifespan of eukaryotic organisms.[3] Compound **2** is a strong 5-HT_{1B} receptor antagonist for the treatment of depression, which shows a 10-fold selectivity over other 5-HT receptor subtypes and dopaminergic receptors.[4] Compound **3** is a potential drug for the treatment of hyperproliferative diseases in mammals, particularly humans.[5] Compound **4** exhibits a significant antiviral activity (IC_{50} = 0.686 μM) in a human liver-derived cell line (Huh-7-Clone A), which may be used to treat or prevent hepatitis C virus (HCV).[6]

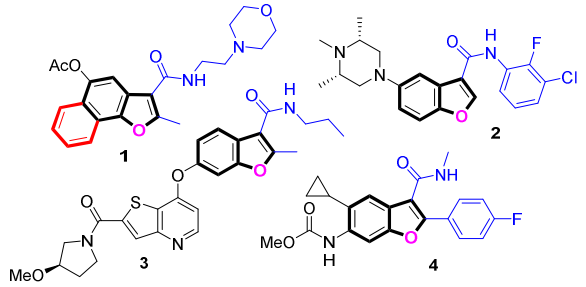
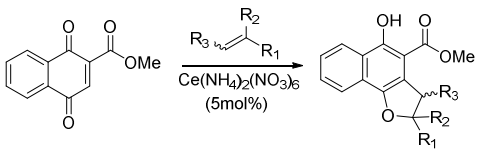


Fig. 1 Selected examples of biologically active naphtho[1,2-*b*]furan-3-carboxamides and benzofuran-3-carcoxamides

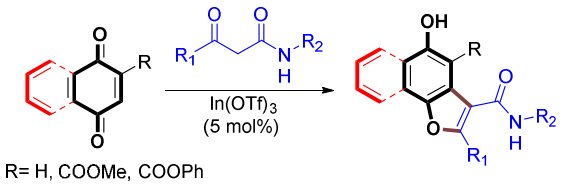
Because of their importance, considerable effort has been made to develop general synthetic methods for the assembly of substituted naphtho[1,2-*b*]furans and benzofurans.[7] Accordingly, a number of synthetic approaches to naphtho[1,2-*b*]furans and benzofurans from 1,4-naphthoquinones or benzoquinones have been reported.[8-14] The general methods for the synthesis of naphtho[1,2-*b*]furans include the annulation of silyloxydienes[8] or *N*-(*t*-butoxycarbonyl)-2-*t*-butyldimethylsilyloxypyrroles to 1,4-napththoquinones,[9] the Lewis acid-catalyzed addition of 2-*t*-butyldimethyloxythiophene to 1,4-naphthoquinones,[10] Sakurai allylation of 1,4-naphthoquinone with allyltrimethylsilane,[11] and the ytterbium triflate-catalyzed conjugate addition of β-ketoesters to 1,4-naphthoquinones.[12] In addition, the asymmetric synthesis of 2,3-dihydronaphtho[1,2-*b*]furan-2-ols by organocatalyzed reaction of quinones with aldehydes has been developed.[13] Examples of the synthesis of benzofuran derivatives starting from 1,4-benzoquinones have also been developed.[14] Nevertheless, there is still a demand for general and practical methods that can efficiently provide novel and diverse naphtho[1,2-*b*]furans and benzofurans bearing various substituents. To the best of our knowledge, the efficient and facile one-step synthesis of biologically interesting naphtho[1,2-*b*]furan-3-carboxamides and benzofuran-3-carboxamides from readily available starting materials has not been reported to date.

Recently, we have developed a methodology for the synthesis of dihydronaphtho[1,2-*b*]furans by the ceric ammonium nitrate-catalyzed reactions of 1,4-naphthoquinones with olefins (Scheme 1).[15] This reaction provided a rapid synthetic route for various dihydronaphtho[1,2-*b*]furans. However, using this methodology, it is difficult to directly synthesize naphtho[1,2-*b*]furan derivatives starting from 1,4-naphthoquinones.



Scheme 1. The reported method for dihydronaphtho[1,2- *b*]furans

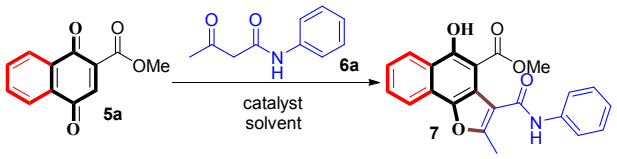
As part of an ongoing study to provide novel naphtho[1,2-*b*]furans and benzofurans, the Lewis acid-catalyzed cycloaddition of 1,4-naphthoquinones or benzoquinones to β-ketoamides was carried out. $In(OTf)_3$-catalyzed [3+2] cycloaddition of 1,4-naphthoquinones or benzoquinones to β-ketoamides has not been described previously. Herein, we report on $In(OTf)_3$-catalyzed cascade reactions between 1,4-naphthoquinones or benzoquinones and β-ketoamides for the synthesis of novel and diverse naphtho[1,2-*b*]furan-3-carboxamides and benzofuran-3-carboxamides in good to excellent yield with high regioselectivity (Scheme 2).



Scheme 2. $In(OTf)_3$-catalyzed cascade reaction for naphtho[1,2-*b*]furan-3-carboxamides and benzofuran-3-carboxamides

To afford naphtho[1,2-*b*]furan-3-carboxamides, a reaction of readily available methyl 1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate (**5a**) with 3-oxo-*N*-phenylbutanamide **6a** was first investigated using several catalysts and solvents (Table 1). A trace amount of product **7** was produced using 10 mol% AgOTf in acetonitrile at room temperature for 12 h (entry 1). In contrast, no products were formed in the presence of 10 mol % of $CaCl_2$, LiBr, $MgBr_2$, $PrCl_3$, $ZnCl_2$, or ZnI_2 in acetonitrile at room temperature for 12 h (entries 2-7). With the inorganic base, $CsCO_3$ (20 mol%), for 12 h, only intractable mixtures were obtained (entry 8). With $BF_3{\cdot}OEt_2$ (30 mol%) at room temperature for 8 h, the desired product **7** was isolated but only in 25% yield. Importantly, compound **7** was produced in 45-75% yield with 5 mol% $FeCl_3$, $Y(OTf)_3$, $Cu(OTf)_2$, $PdCl_2$ or $RuCl_3$ (entries 10-14). The catalytic activity was examined further using several indium catalysts (entries 15-21). No products were obtained in the presence of 20 mol% of indium(III) oxide, indium tin oxide (Aldrich, nanopowder, <50 nm particle size) or indium(III) acetate (entries 15-17). Interestingly, indium(III) triflate exhibited superior catalytic activity to the other Lewis acids examined (entries 18-21). The best yield (95%) was obtained in acetonitrile at room temperature for 1 h (entry 21). The yields were decreased when other solvents, such as toluene, dichloromethane, THF, and nitromethane, were used (entries 22-25). Compound **7** was separated easily by column chromatography and identified by spectroscopic analyses. Two strong carbonyl IR peaks at 1672 and 1649 cm^{-1} were assigned to an ester group on the aromatic ring and an amide group on the furan ring, respectively. The ^1H NMR spectrum exhibited a phenolic OH peak at δ = 11.60 (s, 1H) ppm, an amide NH peak at 9.44 (s, 1H) ppm, and two methyl peaks at 3.29 (s, 3H) and 2.20 (s, 3H) ppm, respectively.

Table 1. Reaction of **5a** with **6a** under several catalysts and solvents[a]



entry	catalysts	[loading]	solvent	time (h)	yield (%)[b]
1	AgOTf	10 mol%	MeCN	12	trace
2	$CaCl_2$	10 mol%	MeCN	12	0
3	LiBr	10 mol%	MeCN	12	0
4	$MgBr_2$	10 mol%	MeCN	12	0
5	$PrCl_3$	10 mol%	MeCN	12	0
6	$ZnCl_2$	10 mol%	MeCN	12	0
7	ZnI_2	10 mol%	MeCN	12	0
8	$CsCO_3$	20 mol%	MeCN	12	0
9	$BF_3{\cdot}Et_2O$	30 mol%	MeCN	8	25
10	$FeCl_3$	5 mol%	MeCN	10	45
11	$Y(OTf)_3$	5 mol%	MeCN	10	55
12	$Cu(OTf)_2$	5 mol%	MeCN	10	60
13	$PdCl_2$	5 mol%	MeCN	5	70
14	$RuCl_3$	5 mol%	MeCN	5	75
15	In_2O_3	20 mol%	MeCN	12	0
16	Nano In_2O_3/SnO_2	20 mol%	MeCN	12	0
17	$In(OAc)_3$	20 mol%	MeCN	12	0
18	$InCl_3$	5 mol%	MeCN	8	40
19	$InCl_3{\cdot}4H_2O$	5 mol%	MeCN	8	45
20	$InBr_3$	5 mol%	MeCN	1	85
21	$In(OTf)_3$	5 mol%	MeCN	1	95
22	$In(OTf)_3$	5 mol%	toluene	6	86
23	$In(OTf)_3$	5 mol%	CH_2Cl_2	5	92
24	$In(OTf)_3$	5 mol%	THF	8	30
25	$In(OTf)_3$	5 mol%	$MeNO_2$	10	20

[a]Reaction conditions: **5a** (0.5 mmol), **6a** (0.5 mmol), solvent (5.0 mL), room temperature. Consumption of **5a** was monitored by TLC.
[b]Isolated yields.

To explore the scope and limitations of this methodology, the reactions of various 1,4-naphthoquinones with several β-ketoamides were examined further under optimized reaction conditions. The results are summarized in Table 2. The reactions between methyl 1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate (**5a**) and *N*-aryl-3-oxobutanamides **6b-6g** with electron-donating or -withdrawing groups on the aromatic ring in the presence of 5 mol% $In(OTf)_3$ in acetonitrile at room temperature for 1-2 h afforded products **8-13** in 85-98% yield (entries 1-6). Similarly, a reaction of **5a** with *N*-benzyl-3-oxobutanamide (**6h**) or 3-oxo-*N*,3-diphenylpropanamide (**6i**) produced compounds **14** and **15** in 81% and 78% yield, respectively (entries 7 and 8). Using phenyl 1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate (**5b**), the desired products **16-23** were also formed in 75-94% yield (entries 9-16). These results showed that electron-donating or -withdrawing groups on the benzene ring of *N*-aryl-3-oxobutanamides **6a-6g** did not significantly influence the reaction process or yield. In particular, molecules with an electron-withdrawing group on the 1,4-naphthoquinones gave the expected products in high yields (entries 1-16). These reactions provided rapid routes to the synthesis of a variety of novel and diverse naphtho[1,2-*b*]furan-3-carboxamides with excellent regioselectivity. On the other hand, reactions bearing electron-donating groups, such as OH or OMe, on the 1,4-naphthoquinone ring did not provide the desired products (entries 17-18). This is probably due to increase of electron density by electron-donating groups such as OH or OCH_3 at C-3 on 1,4-naphthoquinones, which may prohibit the reactions. With 1,4-naphthoquinone **5e** without any electron-donating or withdrawing substituents, the desired product **26** was obtained in 45% yield.

Further reactions between 1,4-quinones **5f-5g** and β-ketoamides **6a-6i** were investigated to assess the utility of this methodology. The results are collected in Table 3. The reactions of methyl 3,6-dioxocyclohexa-1,4-diene-1-carboxylate (**5f**) with various β-ketoamides **6a-6i** in the presence of 5 mol% of $In(OTf)_3$ in acetonitrile at room temperature for 1-3 h provided the desired benzofuran-3-amides **27-35** in 78–98% yield. Additional reactions between benzoquinone (**5g**) and β-ketoamides **6a-6d**, **6g**, and **6i** afforded products **36-41** in 81-98% yield. Notably, no other regioisomers were detected in these reactions.[16]

Table 2. In(OTf)$_3$-catalyzed reactions of 1,4-naphthoquinones with various β-ketoamides[a]

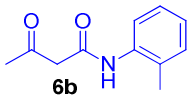
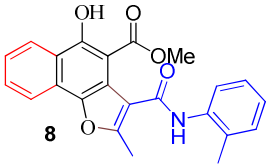
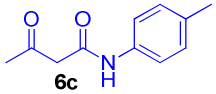
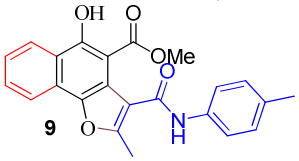
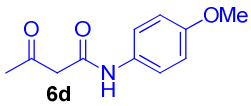
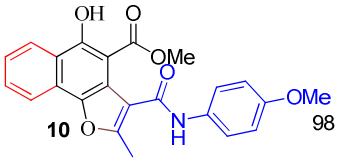
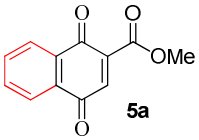
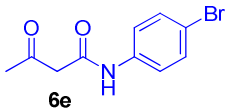
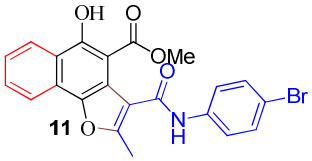
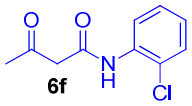
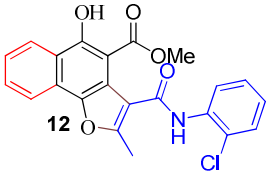
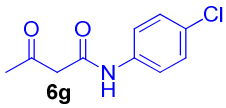
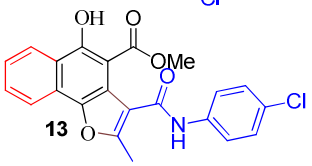
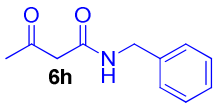
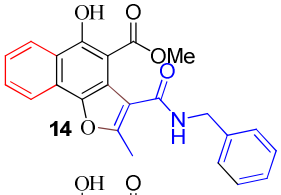
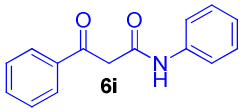
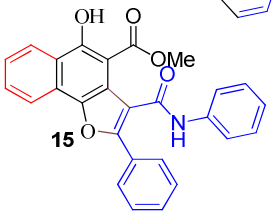
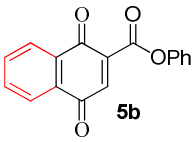
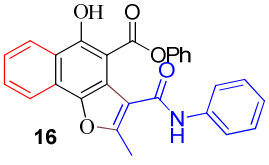
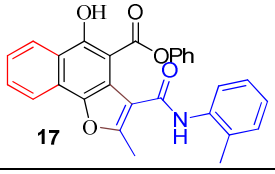
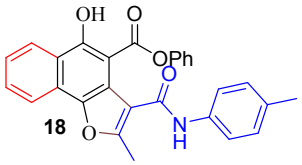
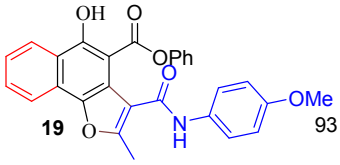
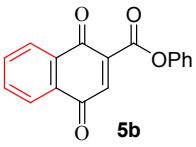
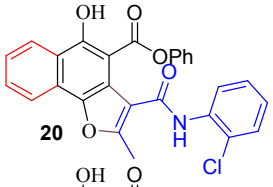
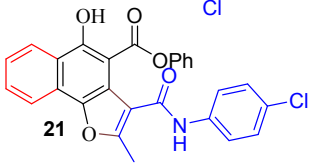
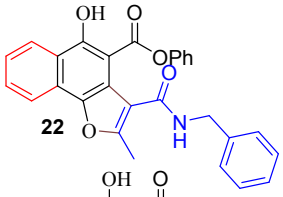
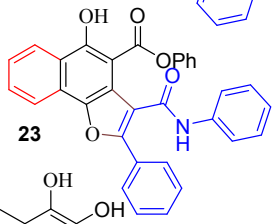
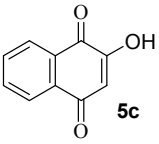
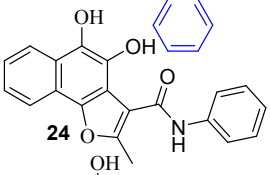
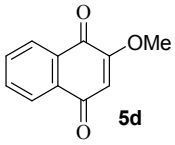
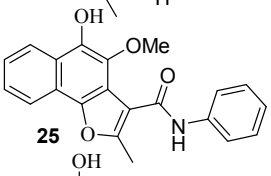
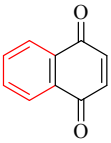
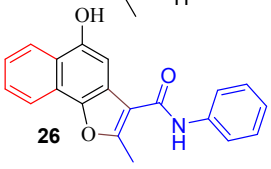
entry	1,4-Naphthoquinones	β-ketoamides	condition	products	yield (%)[b]
1		 **6b**	rt, 2h	 **8**	85
2		 **6c**	rt, 1h	 **9**	94
3		 **6d**	rt, 1h	 **10**	98
4	 **5a**	 **6e**	rt, 1h	 **11**	92
5		 **6f**	rt, 1.5h	 **12**	86
6		 **6g**	rt, 1h	 **13**	91
7		 **6h**	rt, 3h	 **14**	81
8		 **6i**	rt, 3h	 **15**	78
9	 **5b**	**6a**	rt, 1h	 **16**	94
10		**6b**	rt, 2h	 **17**	83

Table 2. *(Contd.)*

entry	1,4-Naphthoquinones	β-ketoamides	condition	products	yield (%)[b]
11		**6c**	rt, 1h	 **18**	92
12		**6d**	rt, 1h	 **19**	93
13	 **5b**	**6f**	rt, 2h	 **20**	78
14		**6g**	rt, 1h	 **21**	88
15		**6h**	rt, 3h	 **22**	78
16		**6i**	rt, 3h	 **23**	75
17	 **5c**	**6a**	rt, 12h	 **24**	0
18	 **5d**	**6a**	rt, 12h	 **25**	0
19	 **5e**	**6a**	rt, 3h	 **26**	45

[a] Reaction conditions: 1,4-naphthoquinones (0.5 mmol), β-ketoamides (0.5 mmol), catalyst $In(OTf)_3$ (5 mol%), acetonitrile (5.0 mL), room temperature.
[b] Isolated yields.

Table 3. In(OTf)$_3$-catalyzed reactions of quinones with various β-ketoamides[a]

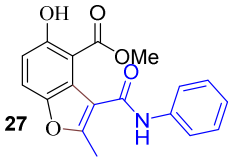
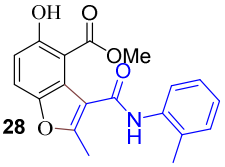
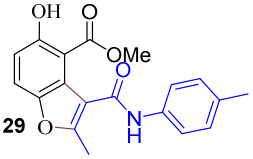
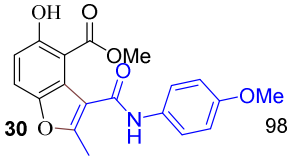
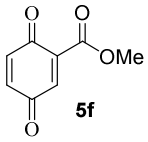
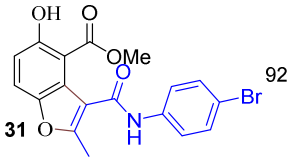
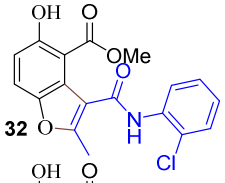
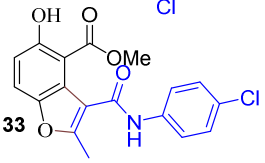
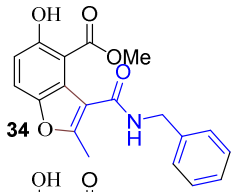
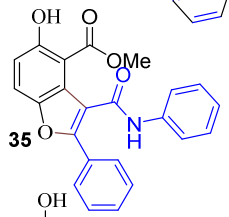
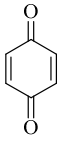
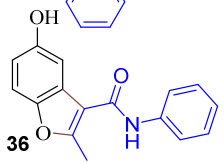
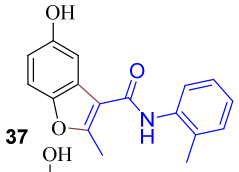
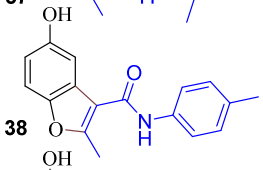
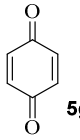
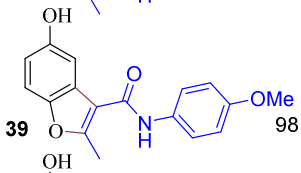
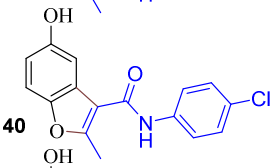
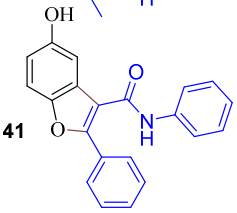
entry	1,4-quinones	β-ketoamides	condition	products	yield (%)[b]
1		**6a**	rt, 2h	 **27**	85
2		**6b**	rt, 2h	 **28**	85
3		**6c**	rt, 1h	 **29**	94
4		**6d**	rt, 1h	 **30**	98
5	 **5f**	**6e**	rt, 1h	 **31**	92
6		**6f**	rt, 1h	 **32**	86
7		**6g**	rt, 1h	 **33**	91
8		**6h**	rt, 3h	 **34**	81
9		**6i**	rt, 3h	 **35**	78
10	 **5g**	**6a**	rt, 1h	 **36**	94

Table 3. *(Contd.)*

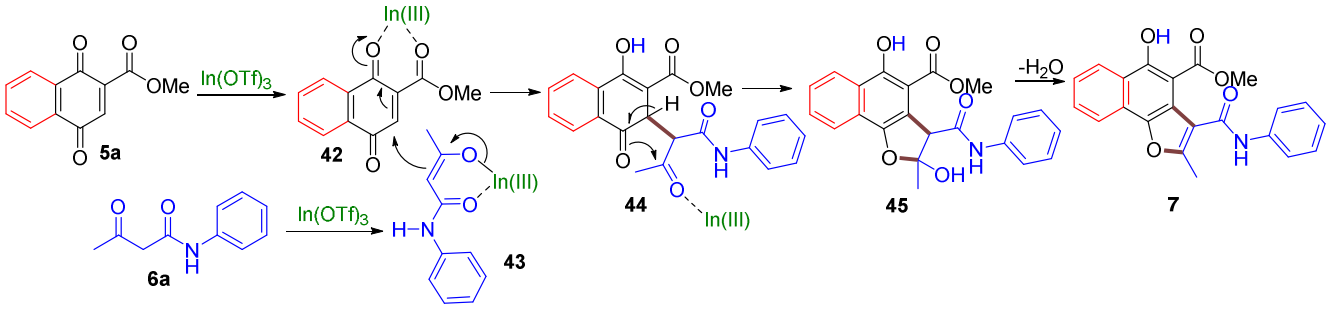
entry	1,4-quinones	β-ketoamides	condition	products	yield (%)[b]
11		**6b**	rt, 2h	 **37**	83
12		**6c**	rt, 1h	 **38**	94
13	 **5g**	**6d**	rt, 1h	 **39**	98
14		**6g**	rt, 1h	 **40**	91
15		**6i**	rt, 3h	 **41**	81

[a] Reaction conditions: 1,4-quinones (0.5 mmol), β-ketoamides (0.5 mmol), catalyst $In(OTf)_3$ (5 mol%), acetonitrile (5.0 mL), room temperature.
[b] Isolated yields.

The formation of **7** can be explained by the mechanism proposed in Scheme 3. The methyl 1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate (**5a**) first gives complex **42** in the presence of $In(OTf)_3$ catalyst to enhance the reactivity of addition.[17] On the other hand, $In(OTf)_3$ catalyzes the enolization of the β-ketoamide **6a** to produce a more reactive nucleophile **43**, which attacks complex **42** to give another intermediate **44**. The aromatization of **44** followed by intramolecular cyclization gives hemiacetal **45**, which undergoes dehydration to give the final product **7**.[17] The mechanism for the formation of benzofuran-3-carboxamides could also be deduced from similar catalytic processes.

Conclusions

In summary, a novel and efficient synthetic route to biologically interesting naphtho[1,2-*b*]furan-3-carboxamides and benzofuran-3-carboxamides starting from readily available 1,4-naphthoquinones and benzoquinones has been developed. The key strategy is the $In(OTf)_3$-catalyzed regioselective formal [3+2] cycloaddition of 1,4-naphthoquinones or benzoquinones with β-ketoamides. The two compound libraries are expected to be used in the treatment of depression or the treatment of viral infections, such as HCV infections, and diseases associated with such infections.



Scheme 3. The mechanism for formation of **7**

Acknowledgements

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Experimental section

General Experimental Details

All chemicals were purchased from Sigma-Aldrich, Fluka, or Tokyo Chemical Industry (TCI). All reagents were analytical grade or above and used as received, unless otherwise noted. All experiments were conducted in a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) containing a fluorescent indicator were used for analytical TLC, and flash column chromatography was performed using silica gel 9385 (Merck). The ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded on a Bruker Model DPX-300 (at 300 and 75 MHz, respectively) or Varian VNS-600 spectrometers (at 600 and 150 MHz, respectively). The Fourier transform infrared (FT-IR) spectra were recorded on a Jasco FTIR 5300 spectrophotometer. The high-resolution mass spectra **(**HRMS) were recorded on a JEOL JMS-700 mass spectrometer (positive ion EI mode) at the Korea Basic Science Institute.

General Procedure for the Synthesis of naphtho[1,2-*b*]furans 7-23, 26, and benzofurans 27-41. Indium(III) trifluoromethanesulfonate (Synonym: $In(OTf)_3$, indium(III) triflate, 5 mol%) was added to a stirred solution of 1,4-naphthoquinones or benzoquinones (0.5 mmol) and the corresponding β-ketoamides (0.5 mmol) in MeCN (5.0 mL) at room temperature. The reaction progress was monitored by TLC. After all the starting material had been consumed, water (10 mL) was added and the solution was extracted with ethyl acetate (10 mL x 3). Evaporation of the solvent and purification by column chromatography on silica gel using hexane-ethyl acetate (10:1) gave the products.

Methyl 5-hydroxy-2-methyl-3-(phenylcarbamoyl)naphtho[1,2-*b*]furan-4-carboxylate (7). Yellow solid; yield 178 mg, 95%; mp 237-238 ºC; IR (KBr): 3398, 2926, 1672, 1649, 1533, 1441, 1378, 1343, 1311, 1255, 1170, 1110, 987, 765, 703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6, ratio 4:1) δ 11.60 (s, 1H), 9.44 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 7.8 Hz, 2H), 7.29 (dd, J = 7.8, 7.2 Hz, 1H), 7.13-7.08 (m, 1H), 6.97-6.92 (m, 2H), 6.71 (dd, J = 7.5, 6.9 Hz, 1H), 3.29 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6, ratio 4:1) δ 170.29, 163.68, 157.78, 153.84, 142.22, 138.76, 129.57, 128.29, 124.61, 124.08, 123.41, 123.15, 121.61, 119.00, 118.78, 117.24, 117.02, 98.72, 51.40, 12.64. HRMS: m/z [M$^+$] calcd. for $C_{22}H_{17}NO_5$ 375.1107; found: 375.1104.

Methyl 5-hydroxy-2-methyl-3-(*o*-tolylcarbamoyl)naphtho[1,2-*b*]furan-4-carboxylate (8). Yellow solid; yield 165 mg, 85%; mp 237-237 ºC; IR (KBr): 3392, 2922, 2854, 1646, 1513, 1442, 1344, 1236, 1161, 1109, 1052, 987, 735 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.24 (s, 1H), 9.67 (s, 1H), 8.19 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.63 (t, J = 7.2 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.44 (dd, J = 7.5, 7.2 Hz, 1H), 7.08 (dd, J = 7.2, 6.9 Hz, 2H), 6.95 (dd, J = 7.5, 6.9 Hz, 1H), 3.54 (s, 3H), 2.50 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.46, 162.69, 155.29, 154.48, 142.35, 136.30, 131.46, 130.60, 130.41, 126.07, 125.68, 125.26, 124.65, 124.43, 123.11, 122.02, 119.50, 118.53, 117.18, 101.27, 51.98, 18.25, 13.43. HRMS: m/z [M$^+$] calcd. for $C_{23}H_{19}NO_5$ 389.1263; found: 389.1261.

Methyl 5-hydroxy-2-methyl-3-(*p*-tolylcarbamoyl)naphtho[1,2-*b*]furan-4-carboxylate (9). Yellow solid; yield 183 mg, 94%; mp 236-237 ºC; IR (KBr): 3339, 2922, 2854, 1671, 1647, 1600, 1528, 1443, 1344, 1254, 1166, 1108, 816, 765 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.56 (brs, 1H), 10.35 (s, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.1 Hz, 1H), 7.81 (dd, J = 8.1, 7.2 Hz, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.62 (dd, J = 8.1, 7.2 Hz, 1H), 7.17 (d, J = 8.1 Hz, 2H), 3.61 (s, 3H), 2.58 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.65, 162.76, 155.94, 154.45, 142.26, 136.98, 132.43, 130.56, 129.27, 125.72, 124.42, 123.22, 121.90, 119.53, 119.17, 118.20, 117.47, 100.68, 52.05, 20.53, 13.14. HRMS: m/z [M$^+$] calcd. for $C_{23}H_{19}NO_5$ 389.1263; found: 389.1265.

Methyl 5-hydroxy-3-((4-methoxyphenyl)carbamoyl)-2-methylnaphtho[1,2-*b*]furan-4-carboxylate (10). Yellow solid; yield 199 mg, 98%; mp 225-226 ºC; IR (KBr): 3407, 2922, 2852, 1736, 1665, 1513, 1447, 1345, 1279, 1243, 1165, 1111, 761 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.55 (s, 1H), 10.29 (s, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.81 (dd, J = 7.8, 7.2 Hz, 1H), 7.71 (d, J = 9.0 Hz, 2H), 7.62 (dd, J = 7.8, 7.2 Hz, 1H), 6.94 (d, J = 9.0 Hz, 2H), 3.75 (s, 3H), 3.62 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.63, 162.46, 155.85, 155.37, 154.42, 142.26, 132.66, 130.54, 125.71, 124.42, 123.20, 121.90, 120.62, 119.52, 118.23, 117.46, 113.99, 100.76, 55.21, 52.06, 13.14. HRMS: m/z [M$^+$] calcd. for $C_{23}H_{19}NO_6$ 405.1212; found: 405.1215.

Methyl 5-hydroxy-3-((4-methoxyphenyl)carbamoyl)-2-methylnaphtho[1,2-*b*]furan-4-carboxylate (11). Yellow solid; yield 208 mg, 92%; mp 231-232 ºC; IR (KBr): 3424, 3316, 2921, 2853, 1653, 1587, 1510, 1447, 1387, 1346, 1229, 1163, 815, 767 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (brs, 1H), 10.58 (s, 1H), 8.34 (d, J = 8.4 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 7.81-7.78 (m, 3H), 7.63-7.54 (m, 3H), 3.61 (s, 3H), 3.03 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.64, 163.20, 156.17, 154.69, 142.30, 138.81, 131.75, 130.59, 125.75, 124.44, 123.24, 121.94, 121.14, 119.52, 118.01, 117.20, 115.18, 100.48, 52.08, 13.14. HRMS: m/z [M$^+$] calcd. for $C_{22}H_{16}BrNO_5$ 453.0212; found: 453.0214.

Methyl 3-((2-chlorophenyl)carbamoyl)-5-hydroxy-2-methylnaphtho[1,2-*b*]furan-4-carboxylate (12). Yellow solid; yield 176 mg, 86%; mp 180-181 ºC; IR (KBr): 3398, 3062, 2953, 1662, 1586, 1515, 1442, 1345, 1247, 1167, 1109, 1056, 991, 759 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.49 (s, 1H), 10.06 (s, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 7.95-7.92 (m, 1H), 7.80 (t, J = 7.5 Hz, 1H), 7.61 (dd, J = 7.8, 7.5 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.42 (dd, J = 7.5, 6.9 Hz, 1H), 7.25 (dd, J = 7.5, 7.2 Hz, 1H), 3.75 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.51, 161.93, 155.61, 155.01, 142.37, 134.85, 130.46, 129.75, 127.55, 127.02, 126.66, 126.49, 125.69, 124.42, 123.14, 122.00, 119.49, 118.39, 116.73, 100.96, 51.87, 13.40. HRMS: m/z [M$^+$] calcd. for $C_{22}H_{16}ClNO_5$ 409.0717; found: 409.0716.

Methyl 3-((4-chlorophenyl)carbamoyl)-5-hydroxy-2-methylnaphtho[1,2-*b*]furan-4-carboxylate (13). Yellow solid; yield 186 mg, 91%; mp 242-243 ºC; IR (KBr): 3411, 3318, 2921, 2852, 1652, 1590, 1510, 1446, 1229, 1162, 1106, 818, 764, 686 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.59 (s, 1H), 10.57 (s, 1H), 8.35 (d, J = 8.1 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 7.85-7.78 (m, 3H), 7.62 (dd, J = 7.8, 7.5 Hz, 1H), 7.43 (d, J = 8.7 Hz, 2H), 3.60 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.61, 163.14, 156.11, 154.70, 142.30, 138.39, 130.60, 128.84, 127.13, 125.77, 124.44, 123.23, 121.95, 120.74, 119.53, 118.03,

117.18, 100.54, 52.07, 13.13. HRMS: m/z [M^+] calcd. for $C_{22}H_{16}ClNO_5$ 409.0717; found: 409.0717.

Methyl 3-(benzylcarbamoyl)-5-hydroxy-2-methylnaphtho[1,2-*b*]furan-4-carboxylate (14). Yellow solid; yield 158 mg, 81%; mp 185-186 ºC; IR (KBr): 3304, 3064, 2924, 2855, 1644, 1534, 1447, 1345, 1250, 1168, 1116, 749, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/DMSO-d_6, ratio 1:1) δ 11.79 (s, 1H), 8.18 (d, J = 8.4 Hz, 1H), 8.08 (brs, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.53 (dd, J = 7.8, 7.2 Hz, 1H), 7.38-7.16 (m, 6H), 4.48, (d, J = 6.0 Hz, 2H), 3.60 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6, ratio 1:1) δ 170.37, 165.10, 157.53, 153.59, 142.31, 138.48, 129.49, 128.02, 127.45, 126.73, 124.54, 124.04, 123.39, 121.57, 119.03, 117.31, 116.41, 98.85, 50.86, 42.93, 12.66. HRMS: m/z [M^+] calcd. for $C_{23}H_{19}NO_5$ 389.1263; found: 389.1262.

Methyl 5-hydroxy-2-phenyl-3-(phenylcarbamoyl)naphtho[1,2-*b*]furan-4-carboxylate (15). Yellow solid; yield 170 mg, 78%; mp 241-242 ºC; IR (KBr): 3411, 2925, 1658, 1599, 1538, 1444, 1349, 1251, 1156, 1110, 762, 688 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.02 (brs, 1H), 10.63 (s, 1H), 8.41 (d, J = 8.4 Hz, 2H), 7.99 (d, J = 7.2 Hz, 2H), 7.89 (t, J = 7.5 Hz, 1H), 7.77 (d, J = 7.8 Hz, 2H), 7.70 (dd, J = 8.1, 7.2 Hz, 1H), 7.52 (dd, J = 7.8, 7.2 Hz, 2H), 7.46 (d, J = 7.2 Hz, 1H), 7.38 (t, J = 7.8 Hz, 2H), 7.12 (dd, J = 7.5, 7.2 Hz, 1H), 3.61 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.90, 163.36, 157.23, 152.09, 142.82, 139.42, 130.96, 129.42, 129.32, 129.12, 129.02, 126.51, 126.13, 124.58, 123.74, 123.40, 122.62, 120.13, 119.19, 118.69, 116.92, 100.16, 52.20. HRMS: m/z [M^+] calcd. for $C_{27}H_{19}NO_5$ 437.1263; found: 437.1266.

Phenyl 5-hydroxy-2-methyl-3-(phenylcarbamoyl)naphtho[1,2-*b*]furan-4-carboxylate (16) Yellow solid; yield 205 mg, 94%; mp 295-296 ºC; IR (KBr): 3410, 3270, 3057, 2986, 1710, 1663, 1587, 1532, 1497, 1438, 1353, 1263, 1195, 1142, 1092, 896, 743, 697 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.30 (s, 1H), 10.50 (s, 1H), 8.38 (d, J = 8.1 Hz, 1H), 8.18 (d, J = 8.1 Hz, 1H), 7.82 (dd, J = 7.8, 7.5 Hz, 1H), 7.63 (dd, J = 7.8, 7.5 Hz, 1H), 7.55 (d, J = 7.8 Hz, 2H), 7.25-7.14 (m, 7H), 6.70 (t, J = 7.2 Hz, 1H), 2.62 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.84, 162.80, 156.19, 154.91, 149.64, 142.57, 139.13, 130.70, 129.11, 128.45, 126.09, 125.84, 124.54, 123.36, 122.17, 122.0, 119.60, 119.45, 118.21, 117.44, 115.34, 101.05, 13.36. HRMS: m/z [M^+] calcd. for $C_{27}H_{19}NO_5$ 437.1263; found: 437.1261.

Phenyl 5-hydroxy-2-methyl-3-(*o*-tolylcarbamoyl)naphtho[1,2-*b*]furan-4-carboxylate (17). Yellow solid; yield 187 mg, 83%; mp 195-196 ºC; IR (KBr): 3374, 3056, 2986, 2926, 1710, 1672, 1599, 1431, 1357, 1265, 1191, 1146, 1100, 895, 833, 739, 600 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.14 (s, 1H), 9.77 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 8.23 (d, J = 8.1 Hz, 1H), 7.83 (t, J = 7.5 Hz, 1H), 7.65 (dd, J = 7.8, 7.2 Hz, 1H), 7.34-7.25 (m, 5H), 7.21-7.13 (m, 2H), 7.04 (dd, J = 7.2, 6.6 Hz, 1H), 6.96 (dd, J = 7.5, 6.9 Hz, 1H), 2.73 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.40, 162.54, 155.25, 154.42, 149.80, 142.48, 135.81, 131.35, 130.12, 129.89, 128.84, 125.81, 125.40, 125.22, 124.94, 124.83, 124.25, 123.05, 122.10, 121.92, 119.27, 118.47, 116.94, 101.54, 17.67, 13.28. HRMS: m/z [M^+] calcd. for $C_{28}H_{21}NO_5$ 451.1420; found: 451.1417.

Phenyl 5-hydroxy-2-methyl-3-(*p*-tolylcarbamoyl)naphtho[1,2-*b*]furan-4-carboxylate (18). Yellow solid; yield 208 mg, 92%; mp 243-244 ºC; IR (KBr): 3371, 3285, 2925, 1651, 1598, 1515, 1261, 1187, 1145, 1096, 742, 700 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.24 (brs, 1H), 10.22 (s, 1H), 8.41 (d, J = 8.1 Hz, 1H), 8.21 (d, J = 8.1 Hz, 1H), 7.83 (dd, J = 7.8, 7.2 Hz, 1H), 7.63 (dd, J = 7.8, 7.5 Hz, 1H), 7.41 (d, J = 7.8 Hz, 2H), 7.26-7.16 (m, 5H), 7.00 (d, J = 8.1 Hz, 2H), 2.63 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.53, 162.19, 155.84, 154.46, 149.47, 142.34, 136.33, 131.95, 130.24, 128.70, 128.42, 125.62, 125.40, 124.21, 123.13, 121.94, 121.64 (4 Ar-C), 119.37, 119.24, 115.06, 100.97, 20.13, 12.92. HRMS: m/z [M^+] calcd. for $C_{28}H_{21}NO_5$ 451.1420; found: 451.1422.

Phenyl 5-hydroxy-3-((4-methoxyphenyl)carbamoyl)-2-methylnaphtho[1,2-*b*]furan-4-carboxylate (19). Yellow solid; yield 217 mg, 93%; mp 276-277 ºC; IR (KBr): 3334, 3058, 2953, 2856, 1668, 1643, 1512, 1413, 1354, 1264, 1103, 1031, 895, 744 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.26 (brs, 1H), 10.06 (s, 1H), 8.42 (d, J = 7.5 Hz, 1H), 8.21 (d, J = 7.2 Hz, 1H), 7.82 (dd, J = 7.5, 7.2 Hz, 1H), 7.63 (dd, J = 8.1, 6.9 Hz, 1H), 7.40 (d, J = 5.7 Hz, 2H), 7.25 (d, J = 5.7 Hz, 2H), 7.18-7.15 (m, 3H), 6.77-6.75 (m, 2H), 3.72 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.58, 162.14, 155.99, 155.29, 154.36, 149.50, 142.37, 132.02, 130.24, 128.66, 125.59, 125.38, 124.19, 123.20, 121.94, 121.59, 120.94, 119.22, 118.07, 117.33, 113.43, 100.93, 55.06, 12.81. HRMS: m/z [M^+] calcd. for $C_{28}H_{21}NO_6$ 467.1369; found: 467.1366.

Phenyl 3-((2-chlorophenyl)carbamoyl)-5-hydroxy-2-methylnaphtho[1,2-*b*]furan-4-carboxylate (20). Yellow solid; yield 184 mg, 78%; mp 255-256 ºC; IR (KBr): 3401, 3315, 3207, 3057, 2923, 1667, 1583, 1517, 1481, 1436, 1349, 1263, 1194, 1097, 741, 703 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.28 (s, 1H), 9.89 (s, 1H), 8.43 (d, J = 8.1 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H), 7.83 (dd, J = 7.5, 7.2 Hz, 1H), 7.64 (dd, J = 7.5, 7.2 Hz, 1H), 7.43-7.28 (m, 7H), 7.15-7.04 (m, 2H), 2.75 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.45, 162.63, 155.76, 154.85, 149.62, 142.43, 134.35, 130.21, 128.99, 128.87, 126.80, 126.50, 126.01, 125.81, 125.42, 124.22, 123.11, 122.00, 121.78, 119.24, 118.22, 116.55, 115.06, 101.07, 13.20. HRMS: m/z [M^+] calcd. for $C_{27}H_{18}ClNO_5$ 471.0874; found: 471.0873.

Phenyl 3-((4-chlorophenyl)carbamoyl)-5-hydroxy-2-methylnaphtho[1,2-*b*]furan-4-carboxylate (21). Yellow solid; yield 207 mg, 88%; mp > 300 ºC; IR (KBr): 3417, 3317, 3059, 2959, 2926, 2862, 1713, 1661, 1490, 1458, 1266, 1184, 1130, 1083, 816, 760 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.33 (s, 1H), 10.62 (s, 1H), 8.39 (d, J = 8.1 Hz, 1H), 8.20 (d, J = 8.1 Hz, 1H), 7.84 (dd, J = 8.1, 7.2 Hz, 1H), 7.67-7.61 (m, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.22-7.16 (m, 4H), 7.12-7.09 (m, 2H), 2.60 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.74, 162.89, 156.37, 154.97, 149.50, 142.55, 138.05, 130.83, 129.12, 128.27, 126.09, 125.94, 124.56, 123.39, 122.18, 121.86, 120.83, 119.63, 118.09, 117.25, 115.30, 100.86, 13.31. HRMS: m/z [M^+] calcd. for $C_{27}H_{18}ClNO_5$ 471.0874; found: 471.0872.

Phenyl 3-(benzylcarbamoyl)-5-hydroxy-2-methylnaphtho[1,2-*b*]furan-4-carboxylate (22). Yellow solid; yield 176 mg, 78%; mp 225-226 ºC; IR (KBr): 3324, 3061, 2924, 2855, 1659, 1533, 1449, 1344, 1265, 1232, 1193, 1028, 738, 700 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.16 (s, 1H), 8.91 (t, J = 5.4 Hz, 1H), 8.37 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 8.1 Hz, 1H), 7.81 (dd, J = 7.8, 7.2 Hz, 1H), 7.62 (dd, J = 7.8, 7.5 Hz, 1H), 7.54-7.49 (m, 2H), 7.38-7.33 (m, 3H), 7.29-7.24 (m, 3H), 7.21-7.17 (m, 2H), 4.12 (d, J = 5.4 Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.72, 164.08, 155.64, 154.43, 149.94, 142.55, 139.02, 130.59, 129.50, 128.35, 127.57, 127.33, 126.95, 126.36, 125.78, 124.52, 123.27, 122.12, 119.59, 118.46, 116.86, 101.47, 42.55, 13.34. HRMS: m/z [M^+] calcd. for $C_{28}H_{21}NO_5$ 451.1420; found: 451.1419.

Phenyl 5-hydroxy-2-phenyl-3-(phenylcarbamoyl)naphtho[1,2-*b*]furan-4-carboxylate (23). Yellow solid; yield 187 mg, 75%; mp > 300

ºC; IR (KBr): 3426, 3389, 2925, 1644, 1534, 1489, 1442, 1261, 1142, 1028, 760, 687 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.75 (brs, 1H), 10.54 (s, 1H), 8.46 (d, J = 8.4 Hz, 1H), 8.41 (d, J = 8.1 Hz, 1H), 7.98 (d, J = 6.9 Hz, 2H), 7.90 (t, J = 7.5 Hz, 1H), 7.69 (dd, J = 7.8, 7.2 Hz, 1H), 7.51-7.44 (m, 5H), 7.21-7.08 (m, 6H), 6.97 (dd, J = 7.2, 6.6 Hz, 1H), 6.82-6.80 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.01, 162.80, 157.45, 152.15, 149.18, 142.87, 138.88, 130.73, 129.07, 128.67 (Ar-4C), 128.02, 126.17, 126.05, 125.72, 124.40, 123.40, 123.03, 122.58, 121.73, 119.84, 119.17, 118.59, 116.93, 115.11, 100.25. HRMS: m/z [M^+] calcd. for $C_{32}H_{21}NO_5$ 499.1420; found: 499.1422.

5-Hydroxy-2-methyl-*N*-phenylnaphtho[1,2-*b*]furan-3-carboxamide (26). Yellow solid; yield 71 mg, 45%; mp 247-248 ºC; IR (KBr): 3378, 1642, 1597, 1536, 1443, 1358, 1333, 1267, 1140, 1049, 886, 832, 751, 691 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.52 (s, 1H), 8.29 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 5.7 Hz, 1H), 7.65 (dd, J = 7.5, 7.2 Hz, 1H), 7.51 (d, J = 7.5, 7.2 Hz, 1H), 7.02-6.93 (m, 3H), 6.80 (d, J = 6.9 Hz, 2H), 2.63 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.50, 153.19, 147.22, 142.88, 137.55, 127.77, 126.38, 123.81, 123.74, 123.52, 123.38, 123.08, 120.63, 119.53, 119.04, 116.24, 109.15, 13.09. HRMS: m/z [M^+] calcd. for $C_{20}H_{15}NO_3$ 317.1052; found: 317.1051.

Methyl 5-hydroxy-2-methyl-3-(phenylcarbamoyl)benzofuran-4-carboxylate (27). White solid; yield 138 mg, 85%; mp 178-179 ºC; IR (KBr): 3242, 3191, 3129, 3066, 2955, 2855, 1662, 1599, 1538, 1496, 1440, 1221, 892, 812, 753, 697, 616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.78 (s, 1H), 8.91 (s, 1H), 7.64 (d, J = 7.8 Hz, 2H), 7.30 (dd, J = 8.1, 7.5 Hz, 2H), 7.19 (d, J = 9.0 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 6.65 (d, J = 9.0 Hz, 1H), 3.44 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.71, 164.13, 158.81, 156.79, 147.11, 138.31, 128.94, 124.28, 123.73, 119.23, 117.61, 115.70, 113.61, 102.91, 51.64, 12.85. HRMS: m/z [M^+] calcd. for $C_{18}H_{15}NO_5$ 325.0950; found: 325.0952.

Methyl 5-hydroxy-2-methyl-3-(*o*-tolylcarbamoyl)benzofuran-4-carboxylate (28) White solid; yield 144 mg, 85%; mp 184-185 ºC; IR (KBr): 3236, 3056, 2957, 1662, 1589, 1523, 1441, 1367, 1335, 1259, 1222, 1168, 1128, 1057, 902, 816, 743, 616 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.33 (s, 1H), 10.10 (s, 1H), 7.90-7.86 (m, 2H), 7.54-7.52 (m, 2H), 7.40 (dd, J = 7.2, 6.6 Hz, 1H), 7.20 (d, J = 9.0 Hz, 1H), 3.83 (s, 3H), 2.89 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.11, 162.26, 156.74, 153.75, 147.01, 136.35, 132.00, 130.65, 126.17, 125.55, 125.32, 125.14, 115.16, 113.54, 109.04, 51.63, 18.34, 13.71. HRMS: m/z [M^+] calcd. for $C_{19}H_{17}NO_5$ 339.1107; found: 339.1106.

Methyl 5-hydroxy-2-methyl-3-(*p*-tolylcarbamoyl)benzofuran-4-carboxylate (29). White solid; yield 159 mg, 94%; mp 209-210 ºC; IR (KBr): 3232, 3113, 3055, 2955, 2858, 1662, 1602, 1533, 1437, 1219, 893, 814, 737, 161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.76 (s, 1H), 8.77 (s, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 9.0 Hz, 1H), 7.08 (d, J = 8.1 Hz, 2H), 6.22 (d, J = 9.0 Hz, 1H), 3.43 (s, 3H), 2.31, (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.76, 163.88, 158.80, 156.75, 147.13, 135.83, 133.82, 129.41, 123.81, 119.19, 117.58, 115.78, 113.54, 102.96, 51.66, 20.79, 12.86. HRMS: m/z [M^+] calcd. for $C_{19}H_{17}NO_5$ 339.1107; found: 339.1104.

Methyl 5-hydroxy-3-((4-methoxyphenyl)carbamoyl)-2-methylbenzofuran-4-carboxylate (30). White solid; yield 174 mg, 98%; mp 192-193 ºC; IR (KBr): 3245, 3127, 3079, 2956, 2849, 1649, 1599, 1512, 1438, 1335, 1219, 1025, 903, 814, 711, 615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.88 (s, 1H), 7.89 (brs, 1H), 7.57 (d, J = 9.0 Hz, 2H), 7.37 (d, J = 9.0 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 6,78 (d, J = 9.0 Hz, 1H), 3.79 (s, 3H), 3.58 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.03, 163.70, 159.26, 157.23, 156.35, 147.50, 131.41, 124.11, 120.72, 118.06, 116.05, 114.24, 114.03, 103.34, 55.45, 51.95, 13.12. HRMS: m/z [M^+] calcd. for $C_{19}H_{17}NO_6$ 355.1056; found: 355.1056.

Methyl 3-((4-bromophenyl)carbamoyl)-5-hydroxy-2-methylbenzofuran-4-carboxylate (31). White solid; yield 185 mg, 92%; mp 216-217 ºC; IR (KBr): 3235, 3176, 3053, 2956, 1665, 1595, 1530, 1491, 1437, 1396, 1220, 1171, 1068, 1009, 896, 817, 736, 622, 510 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.72 (s, 1H), 10.35 (brs, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.82 (d, J = 9.0 Hz, 1H), 7.73 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 9.0 Hz, 1H), 3.71 (s, 3H), 2.70 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.10, 162.55, 157.05, 154.53, 146.93, 138.72, 131.77, 124.97, 121.28, 115.82, 115.41, 115.29, 113.71, 108.02, 51.66, 13.38. HRMS: m/z [M^+] calcd. for $C_{18}H_{14}BrNO_5$ 403.0055; found: 403.0056.

Methyl 3-((2-chlorophenyl)carbamoyl)-5-hydroxy-2-methylbenzofuran-4-carboxylate (32). White solid; yield 154 mg, 86%; mp 194-195 ºC; IR (KBr): 3400, 3309, 2958, 1670, 1589, 1516, 1437, 1366, 1334, 1267, 1221, 1166, 1082, 890, 812, 752, 616, 584, 533 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.09 (s, 1H), 10.07 (s, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 8.7 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.25 (dd, J = 7.8, 7.5 Hz, 1H), 6.94 (d, J = 9.0 Hz, 1H), 3.69 (s, 3H), 2.64 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.10, 162.52, 157.32, 153.94, 147.01, 134.87, 129.79, 127.62, 127.56, 126.93 (Ar-2C), 125.22, 115.31, 114.77, 113.61, 108.80, 51.58, 13.73. HRMS: m/z [M^+] calcd. for $C_{18}H_{14}ClNO_5$ 359.0561; found: 359.0559.

Methyl 3-((4-chlorophenyl)carbamoyl)-5-hydroxy-2-methylbenzofuran-4-carboxylate (33). White solid; yield 163 mg, 91%; mp 226-227 ºC; IR (KBr): 3234, 3180, 3108, 2956, 2854, 1663, 1597, 1532, 1495, 1437, 1220, 1090, 1009, 896, 817, 737, 614 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.63 (s, 1H), 8.79 (s, 1H), 7.46 (d, J = 8.7 Hz, 2H), 7.16 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 1H), 6.56 (d, J = 9.0 Hz, 1H), 3.32 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.57, 164.18, 158.85, 156.90, 147.12, 136.80, 129.32, 129.00, 123.54, 120.42, 117.73, 115.43, 113.82, 102.82, 51.68, 12.92. HRMS: m/z [M^+] calcd. for $C_{18}H_{14}ClNO_5$ 359.0561; found: 359.0562.

Methyl 3-(benzylcarbamoyl)-5-hydroxy-2-methylbenzofuran-4-carboxylate (34). White solid; yield 137 mg, 81%; mp 147-148 ºC; IR (KBr): 3234, 3064, 2952, 2855, 1664, 1538, 1437, 1337, 1224, 1062, 1009, 964, 813, 736, 703, 613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.63 (s, 1H), 7.22-7.11 (m, 7H), 6.58 (d, J = 9.0 Hz, 1H), 4.33 (d, J = 6.0 Hz, 2H), 3.44 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.82, 165.32, 158.71, 156.57, 147.20, 138.03, 128.50, 127.67, 127.36, 124.06, 117.57, 115.21, 113.45, 103.21, 50.99, 43.50, 12.72. HRMS: m/z [M^+] calcd. for $C_{19}H_{17}NO_5$ 339.1107; found: 339.1108.

Methyl 5-hydroxy-2-phenyl-3-(phenylcarbamoyl)benzofuran-4-carboxylate (35). White solid; yield 151 mg, 78%; mp 193-194 ºC; IR (KBr): 3246, 3192, 3130, 3061, 2956, 2855, 1663, 1603, 1538, 1495, 1440, 1345, 1226, 1119, 1021, 977, 881, 814, 753, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.90 (s, 1H), 8.87 (s, 1H), 7.45-7.41 (m, 4H), 7.17-7.06 (m, 6H), 6.98 (dd, J = 7.5, 7.0 Hz, 1H), 6.57 (d, J = 9.0 Hz, 1H), 3.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.72, 164.34, 159.41, 154.48, 147.10, 138.26, 129.28, 128.85, 128.48, 126.18, 124.29, 119.47, 118.06, 114.93, 114.47, 103.13, 51.56. HRMS: m/z [M^+] calcd. For $C_{23}H_{17}NO_5$ 387.1107; found: 387.1107.

5-Hydroxy-2-methyl-*N*-phenylbenzofuran-3-carboxamide (36). White solid; yield 126 mg, 94%; mp 210-211 ºC; IR (KBr): 3408, 1649, 1601,

1535, 1445, 1169, 1025, 994, 756, 693 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.07 (s, 1H), 9.36 (s, 1H), 7.76 (d, J = 7.5 Hz, 2H), 7.40-7.34 (m, 3H), 7.13-7.09 (m, 2H), 6.77 (dd, J = 8.7, 2.4 Hz, 1H), 2.62 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.13, 158.17, 153.81, 147.10, 139.16, 128.75, 126.99, 123.65, 120.10, 113.57, 112.80, 111.24, 105.27, 13.83. HRMS: m/z [M^+] calcd. for $C_{16}H_{13}NO_3$ 267.0895; found: 267.0898.

5-Hydroxy-2-methyl-*N*-(*o*-tolyl)benzofuran-3-carboxamide (37). White solid; yield 117 mg, 83%; mp 202-203 ºC; IR (KBr): 1641, 1592, 1529, 1453, 1371, 1178, 1118, 802, 754, 688 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.50 (s, 1H), 9.32 (s, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.38 (d, J = 8.7 Hz, 1H), 7.30-7.18 (m, 4H), 6.77 (d, J = 8.4 Hz, 1H), 2.66 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.04, 158.21, 153.76, 147.06, 136.48, 132.94, 130.38, 127.09, 126.07, 125.68 (Ar-2C), 113.17, 112.70, 111.14, 105.33, 18.31, 13.90. HRMS: m/z [M^+] calcd. for $C_{17}H_{15}NO_3$ 281.1052; found: 281.1053.

5-Hydroxy-2-methyl-*N*-(*p*-tolyl)benzofuran-3-carboxamide (38). White solid; yield 132 mg, 94%; mp 191-192-123 ºC; IR (KBr): 3246, 3054, 2986, 1646, 1596, 1520, 1459, 1369, 1265, 1194, 1077, 960, 895, 809, 743 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.01 (s, 1H), 9.40 (s, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.7 Hz, 1H), 7.19-7.16 (m, 3H), 6.81 (dd, J = 8.7, 2.4 Hz, 1H), 2.64 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.12, 158.17, 153.93, 147.25, 136.76, 132.77, 129.25, 127.17, 120.36, 113.76, 112.91, 111.33, 105.43, 20.66, 13.92. HRMS: m/z [M^+] calcd. for $C_{17}H_{15}NO_3$ 281.1052; found: 281.1055.

5-Hydroxy-*N*-(4-methoxyphenyl)-2-methylbenzofuran-3-carboxamide (39). White solid; yield 146 mg, 98%; mp 192-123 ºC; IR (KBr): 3396, 2965, 1642, 1513, 1459, 1367, 1290, 1240, 1193, 1077, 1029, 827, 767 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.90 (s, 1H), 9.31 (brs, 1H), 7.67 (d, J = 8.7 Hz, 2H), 7.37 (d, J = 8.7 Hz, 1H), 7.12 (d, J = 2.4 Hz, 1H), 6.95 (d, J = 9.0 Hz, 2H), 6.78 (dd, J = 8.7, 2.1 Hz, 1H), 3.75 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.81, 157.94, 155.64, 153.79, 147.15, 132.25, 127.07, 121.81, 113.89, 113.62, 112.77, 111.21, 105.34, 55.25, 13.82. HRMS: m/z [M^+] calcd. for $C_{17}H_{15}NO_4$ 297.1001; found: 297.1003.

***N*-(4-chlorophenyl)-5-hydroxy-2-methylbenzofuran-3-carboxamide (40).** White solid; yield 137 mg, 91%; mp 234-235 ºC; IR (KBr): 3410, 1643, 1513, 1467, 1366, 1238, 1025, 991, 824, 761 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 10.21 (s, 1H), 9.40 (s, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.43-7.37 (m, 3H), 7.16 (d, J = 1.8 Hz, 1H), 6.81 (dd, J = 8.7, 2.1 Hz, 1H), 2.64 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.42, 158.71, 153.99, 147.29, 138.24, 128.78, 127.52, 126.99, 121.81, 113.50, 113.03, 111.41, 105.48, 13.97. HRMS: m/z [M^+] calcd. for $C_{16}H_{12}ClNO_3$ 301.0506; found: 301.0508.

5-Hydroxy-*N*,2-diphenylbenzofuran-3-carboxamide (41). White solid; yield 133 mg, 91%; mp 197-198 ºC; IR (KBr): 3409, 3303, 2856, 1641, 1595, 1534, 1444, 1371, 1189, 1097, 802, 752, 689 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.60 (s, 1H), 9.48 (s, 1H), 7.91 (d, J = 7.2 Hz, 2H), 7.76 (d, J = 7.8 Hz, 2H), 7.56-7.45 (m, 4H), 7.42-7.36 (m, 2H), 7.14 (t, J = 7.2 Hz, 1H), 7.05 (s, 1H), 6.90 (dd, J = 8.4, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.20, 154.13, 153.26, 147.17, 139.00, 129.59, 129.34, 128.96, 128.89, 128.30, 126.67, 123.97, 119.90, 114.49, 114.12, 111.84, 104.64. HRMS: m/z [M^+] calcd. for $C_{21}H_{15}NO_3$ 329.1052; found: 329.1050.

Notes and references

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