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Design and synthesis of novel *n*-butyphthalide derivatives as promising botanical fungicides

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Abstract: In order to obtain novel botanical fungicides, three series of novel 6-substituted *n*-butyphthalide derivatives have been designed and synthesized *via* nucleophilic addition, reduction, nitrification, amination, sulfonation, Sandmeyer and Suzuki reaction. The mycelium growth rate method was used to evaluate the inhibition activity against eight phytopathogenic fungi *in vitro*. Preliminary bioassay tests showed that compounds **6f**, **6n**, **6p**, **6r** and **7a** exhibited better activity for some fungi at 50 μg/mL than the positive drug hymexazol and lead compound *n*-butyphthalide (NBP). The preliminary structure–activity relationships indicated that the antifungal activity is significantly affected by the substituents on the benzene ring.

Keywords: antifungal activity; *n*-butyphthalide derivatives; phytopathogenic fungi; structure–activity relationship.

1 Introduction

Plant disease is a natural disaster caused by plant pathogenic fungi, which not only tremendously influence the yield and quality of grain, vegetables and fruits, but also some pathogenic fungi can produce carcinogenic, neurotoxic or teratogenic secondary metabolites (such as aflatoxin and zearalenone) in the process of growth and metabolism in the host body. Therefore, the development of novel compounds that effectively inhibit these agricultural diseases is still highly desirable [1]. Phthalides are a relatively small group of natural compounds found in several plant and fungal genera, which usually possess a broad scope of pharmacological and biological activities [2, 3], such as the three compounds (Z)-butylidenephthalide (**1**), *n*-butylphthalide (**2**) and (Z)-ligustilide (**3**) (Figure 1). Identified in the essential oil of *Lingusticum chuanxiong*, these were shown to exhibit antifungal [4], antiplatelet [5], neuroprotection [6], anticancer [7], anti-inflammatory [8] and insecticidal effects [9, 10]. However, to the best of our knowledge, phthalide compounds were rarely reported on their structural modifications based on agricultural bioactivities. Thus, in continuation of our aim to search for novel bioactive molecules with anti-phytopathogenic effects [11–16], we selected *n*-butylphthalide as the lead compound. Three series of 6-substitued phthalide derivatives were designed, synthesized and evaluated for their antifungal activities against eight phytopathogenic fungi *in vitro*.

2 Results and discussion

As shown in Scheme 1, the lead compound *n*-butylphthalide (**2**) was synthesized according to our previous method. (Z)-butylidenephthalide (**1**) was prepared by the nucleophilic addition of phthalic anhydride with *n*-BuLi, followed by dehydration in toluene with *p*-toluenesulfonic acid (p-TsOH) as catalyst. Then compound **2** was obtained by the treatment of compound **1** with Pd/C in 94.5% yield [17]. Afterward, compound **2** was nitrated using potassium nitrate in H_2SO_4 to obtain the corresponding nitro compound **3**, which was reduced with iron powder and NH_4Cl in THF/H_2O to give amino compound **4** [18]. Compound **4** was subjected to standard Sandmeyer reactions to give the 6-bromobutylphthalide (**5**). Finally, the target compounds **6a–s** were prepared by suzuki reaction of compound **5**, and compounds **7a–f** and **8a–c** were synthesized by sulfonylation and acylation reaction of compound **4** (Scheme 2). All the target compounds are new compounds and their

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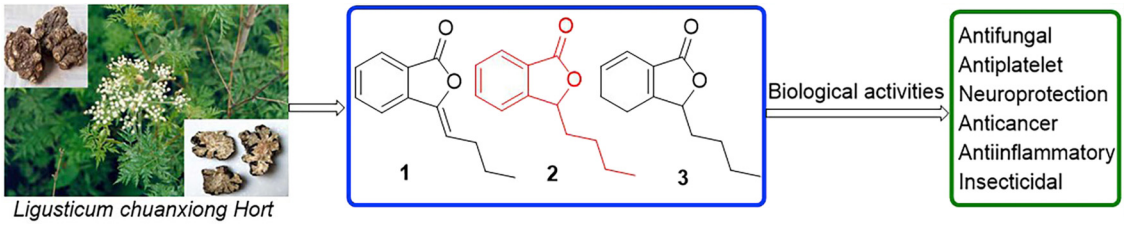
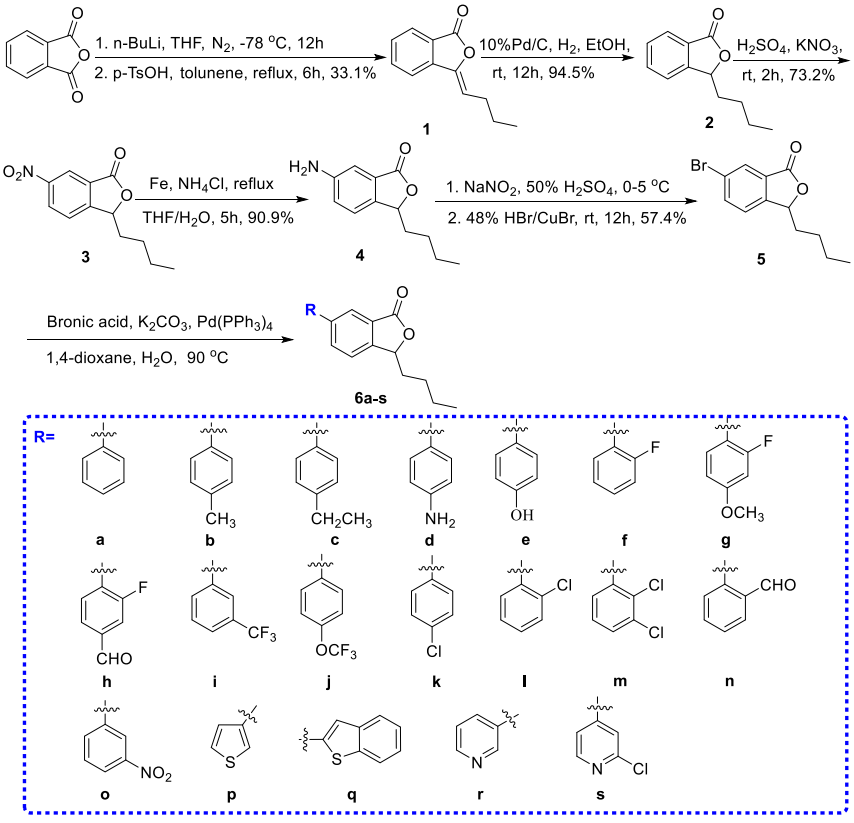


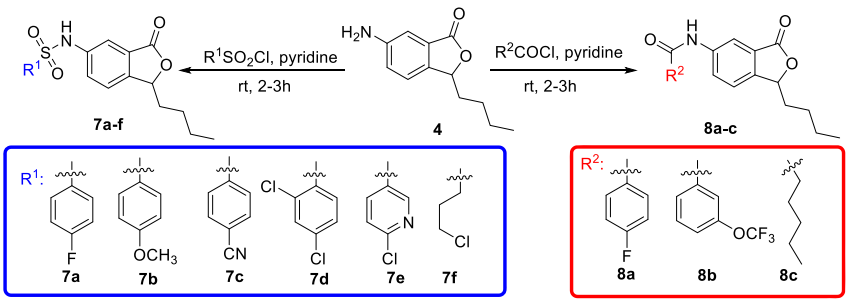
Figure 1: The structure of some phthalides and their biological activities.

structures were characterized by spectrometric methods including ^{1}H NMR, ^{13}C NMR and high-resolution mass spectra (HRMS).

Using the commercially available agricultural fungicide hymexazol as the positive control, the antifungal activity *in vitro* of compounds **6a–s**, **7a–f** and **8a–c** were assayed according to the mycelium growth rate method. Eight plant pathogenic fungi *Fusarium sulphureum* (FS), *Thanatephorus cucumeris* (TC), *Fusarium oxysporum* (FO), *Fusarium graminearum* (FG), *Botrytis cinerea* (BC), *Valsa*



Scheme 1: Synthetic route for the target compounds **6a–s**.



Scheme 2: Synthetic route for the target compounds **7a–f** and **8a–c**.

mali (VM), *Sclerotiua sclerotiorum* (SS) and *Alternaria solani* (AS) were used as tested fungi.

As is shown in Table 1, most of the derivatives displayed certain inhibitory effects on the growth of the tested phytopathogenic fungi. Compounds **6h**, **6n**, **6p** and **6r** showed the good antifungal activity against FS with the inhibition values of 56.0–72.0%, which were better than the positive compound hymexazol (55.9%), but inferior to the lead compound *n*-butylphthalide (76.5%). Unfortunately, all the target compounds possessed rather weak activity against TC strains except **6r** (62.4%). For FO strains, compound **6f** (55.9%) showed the similar fungicidal activity with NBP (59.4%), and compounds **6a** (46.8%), **6r** (47.8%), **6s** (46.8%), **7a** (45.1%) and **7e** (49.2%) had a slightly lower value than that of **6f**. For FG strains, seven compounds (**6a**, **6b**, **6f**, **6k**, **6n**, **6p** and **6r**) exhibited relatively higher activity (44.4–65.8%) than hymexazol (42.4%), especially the activity of compound **6n** (65.8%) was close to that of NBP (69.2%). Furthermore, compounds **6a**, **6f**, **6n**, **6o**, **6p**, **6r** and **7a** also showed better antifungal activity (50.7–79.0%) against AS than that of hymexazol (48.3%) and NBP (50.2%). Toward BC strains, it was worth mentioning that except compounds **8a–c**, all derivatives generally exhibited more pronounced antifungal activity (>21.2%) than the lead compound NBP (13.2%), especially the activity of compound **6e** (82.3%) was significantly superior to that of hymexazol (69.2%). For SS strains, only the activity of compound **6r** (70.7%) was comparable to NBP (68.0%) and hymexazol (68.4%). Moreover, all the target compounds except **8a–c** exhibited better antifungal activity against VM than the positive compound hymexazol (10.1%), but failed to exceed that of NBP (63.2%) except for **6r** (74.3%). In general, compounds **6a**, **6f**, **6n**, **6r**, **6s** and **7a** displayed good and broad-spectrum antifungal activities against several phytopathogenic fungi.

Table 1: Antifungal activities of compounds **6a–s**, **7a–f**, and **8a–c** at 50 μg mL^{-1}.

Compounds		Average inhibition rate ± SD (%) (n = 3)							
No.	**R**	**FS**	**TC**	**FO**	**FG**	**BC**	**VM**	**SS**	**AS**
6a	Ph	47.3 ± 1.4	38.6 ± 0.8	46.8 ± 1.6	44.4 ± 1.4	53.8 ± 3.5	51.9 ± 0.9	40.4 ± 1.7	53.6 ± 1.4
6b	4-CH_3Ph	37.3 ± 1.4	28.6 ± 0.4	26.2 ± 2.7	48.6 ± 1.6	38.6 ± 2.3	48.7 ± 0.9	31.9 ± 1.4	44.2 ± 1.1
6c	4-EtPh	32.5 ± 0.5	38.0 ± 0.4	23.0 ± 1.4	31.9 ± 1.4	32.6 ± 2.6	21.7 ± 0.4	36.2 ± 1.4	26.1 ± 1.4
6d	4-NH_2Ph	34.0 ± 2.4	18.3 ± 1.7	22.5 ± 1.4	13.6 ± 1.6	30.3 ± 2.6	24.9 ± 1.9	17.4 ± 0.2	31.9 ± 2.1
6e	4-OHPh	42.7 ± 3.6	17.6 ± 0.7	39.2 ± 1.4	37.2 ± 1.4	82.3 ± 1.3	43.1 ± 1.6	61.6 ± 0.6	37.0 ± 2.4
6f	2-FPh	52.3 ± 1.8	43.5 ± 0.9	55.9 ± 0.6	46.1 ± 1.1	62.1 ± 1.3	49.2 ± 2.7	39.3 ± 0.8	50.7 ± 2.7
6g	2-F, 4-OCH_3Ph	19.0 ± 2.4	27.2 ± 0.8	18.0 ± 1.6	30.6 ± 1.2	24.6 ± 0.7	28.0 ± 0.9	27.1 ± 3.2	36.2 ± 3.4
6h	2-F, 4-CHOPh	61.3 ± 1.4	38.0 ± 2.4	25.2 ± 1.6	31.9 ± 1.4	42.4 ± 1.3	58.2 ± 1.6	32.9 ± 0.8	23.9 ± 0.6
6i	3- CF_3Ph	38.7 ± 0.5	29.6 ± 1.4	16.2 ± 2.7	22.6 ± 1.6	27.3 ± 2.3	28.0 ± 2.4	31.4 ± 0.8	29.0 ± 2.7
6j	4-OCF_3Ph	21.4 ± 2.5	20.0 ± 1.1	19.4 ± 2.8	26.6 ± 1.3	32.2 ± 2.4	17.7 ± 1.2	18.4 ± 0.8	30.4 ± 2.1
6k	4-ClPh	39.7 ± 0.7	35.2 ± 2.4	37.0 ± 2.7	47.5 ± 2.4	31.8 ± 2.3	40.1 ± 1.7	37.2 ± 1.7	46.2 ± 2.5
6l	2-ClPh	49.3 ± 3.6	17.4 ± 1.6	33.3 ± 1.6	20.2 ± 0.7	46.2 ± 3.5	29.1 ± 1.8	15.0 ± 1.7	49.3 ± 1.5
6m	2,3-diClPh	34.7 ± 1.6	12.7 ± 1.1	17.1 ± 3.1	37.0 ± 1.4	34.5 ± 1.7	23.8 ± 1.6	14.0 ± 3.1	42.8 ± 1.7
6n	2-CHOPh	60.0 ± 2.4	43.9 ± 0.4	42.9 ± 1.6	65.8 ± 0.8	57.7 ± 2.3	58.2 ± 0.9	39.4 ± 0.8	55.6 ± 1.7
6o	3-NO_2Ph	18.3 ± 0.6	22.5 ± 1.3	14.0 ± 2.8	44.0 ± 1.6	23.5 ± 4.7	41.0 ± 1.7	26.1 ± 1.4	52.3 ± 0.5
6p	3-thienyl	56.0 ± 1.2	27.7 ± 0.8	39.6 ± 4.1	52.3 ± 0.8	45.5 ± 0.3	47.1 ± 0.7	31.9 ± 2.5	59.4 ± 2.1
6q	2-benzothienyl	22.7 ± 2.7	24.4 ± 0.6	8.1 ± 2.7	13.2 ± 1.6	21.2 ± 1.3	16.4 ± 1.8	14.0 ± 2.2	27.5 ± 2.7
6r	3-pyridyl	72.0 ± 2.4	62.4 ± 1.6	47.8 ± 2.7	47.3 ± 0.8	60.1 ± 1.3	74.3 ± 0.5	70.7 ± 3.3	79.0 ± 2.1
6s	4-(2-Cl-pyridyl)-	40.5 ± 0.4	42.7 ± 0.8	46.8 ± 4.1	36.1 ± 1.4	43.9 ± 2.6	62.4 ± 1.2	38.6 ± 0.8	46.4 ± 1.0
7a	4-FPhSO_2NH	50.9 ± 0.1	46.8 ± 1.1	45.1 ± 2.8	30.9 ± 3.5	44.4 ± 2.1	54.2 ± 0.1	54.4 ± 3.0	54.6 ± 3.2
7b	4-OCH_3PhSO_2NH	45.7 ± 0.7	31.7 ± 1.2	29.4 ± 0.2	37.0 ± 3.1	33.3 ± 1.2	37.3 ± 1.2	28.3 ± 0.1	27.3 ± 0.8
7c	4-CNPhSO_2NH	32.2 ± 2.4	13.9 ± 2.7	28.5 ± 1.4	12.4 ± 4.4	32.0 ± 0.4	22.0 ± 2.4	32.6 ± 0.5	22.7 ± 3.2
7d	2,4-diClPhSO_2NH	42.4 ± 1.2	24.1 ± 1.8	27.5 ± 0.1	24.7 ± 2.6	36.2 ± 1.5	25.4 ± 1.2	37.0 ± 1.5	18.2 ± 0.4
7e	5-(2-Cl-pyridyl)SO_2NH	44.1 ± 1.2	31.7 ± 0.9	49.2 ± 2.8	12.4 ± 4.3	42.1 ± 0.7	44.1 ± 1.2	50.0 ± 0.7	31.8 ± 0.3
7f	Cl$(CH_2)_3SO_2$NH	39.0 ± 2.4	21.5 ± 1.8	29.4 ± 0.4	40.7 ± 1.7	29.0 ± 1.6	39.0 ± 0.6	32.6 ± 1.3	18.2 ± 0.6
8a	4-FPhCONH	13.6 ± 0.6	4.2 ± 1.1	2.0 ± 1.4	16.1 ± 2.4	7.2 ± 0.2	8.5 ± 1.2	7.1 ± 1.3	13.6 ± 0.3
8b	4-OCF_3PhCONH	6.1 ± 0.8	3.4 ± 1.2	2.0 ± 2.8	1.4 ± 1.2	3.1 ± 2.1	2.1 ± 1.0	10.9 ± 1.5	9.1 ± 3.2
8c	$CH_3(CH_2)_4$CONH	8.5 ± 1.2	5.1 ± 1.8	3.9 ± 1.4	2.5 ± 1.6	1.9 ± 2.4	1.0 ± 0.8	10.9 ± 1.2	13.6 ± 2.1
n-butylphthalide (NBP)		76.5 ± 0.7	74.2 ± 0.6	59.4 ± 1.2	69.2 ± 0.2	13.2 ± 0.1	63.2 ± 0.2	68.0 ± 0.9	50.2 ± 0.3
Hymexazol		55.9 ± 2.4	75.9 ± 0.9	39.2 ± 2.8	42.4 ± 2.8	71.4 ± 1.8	10.1 ± 0.4	68.4 ± 1.3	48.3 ± 2.5

Although it is difficult to extract clear structure–activity relationships (SARs) from the presented biological data, the conclusion still can be summarized is that the spectrum of antifungal activity is significantly impacted by the presence of substituents. Firstly, compared with the lead compound NBP, introduction of benzene ring can enhance the activity against BC and AS (**6a** *vs* NBP), and introduction of pyridine ring can increase the activity against BC, VM, SS and AS but decrease the activity against other fungi (**6r** *vs* NBP). Meanwhile, bringing chlorine atom to the compound **6r** afforded the moderate potent compound **6s**. Secondly, introduction of 4-OH on the benzene ring of compound **6a** only significantly enhances the activity against BC strains (**6e** *vs* NBP). Thirdly, for the halogenated compounds, introduction of 2-F afforded the slightly more potent compound than that of 2-Cl (**6f** *vs* **6l**), and monohalogenated compounds display better antifungal activity than polyhalogenated compounds against all phytopathogenic fungi at the concentration of 50 μg/mL (**6f** *vs* **6i** and **6j**, **6m** *vs* **6k** and **6l**). Furthermore, it is noticeable that bearing a thiophene group at *R* position exhibited more pronounced antifungal effects than that of benzothiophene group (**6p** *vs* **6q**). Finally, compounds with sulfonylamine substitutions (**7a–f**) were found to have varying degree of antifungal activity. Amongst them, compound **7a** with para-fluorine substitution was found to be more active than that of others. But unfortunately, compounds having the amide substitutions (**8a–c**) showed worse activity than aryl (**6a–s**) and sulfonamide substitutions (**7a–f**).

Meanwhile, the effects of compounds on the growth of VM and FS at the concentration of 50 μg/mL were shown in Figure 2. It can be seen clearly that the mycelium diameter was significantly smaller than that of the positive control hymexazol after treated of VM stains with tested compounds **6r**, **6h**, **6s**, **6n** and **6b**. Similarly, the mycelium growth also reflected that the compound **6r** had better inhibitory effects on FS strains than that of **6n**, **6p**, **6h**, **6f** and hymexazol.

3 Conclusion

In summary, 28 novel *n*-butyphthalide derivatives were synthesized and evaluated for their antifungal activities against eight phytopathogenic fungi *in vitro* at the concentration of 50 μg/mL. Among all the derivatives, compounds **6a**, **6f**, **6n**, **6r**, **6s** and **7a** generally exhibited the promising and broad-spectrum antifungal activities, especially compound **6r** displayed the more pronounced antifungal activity than the lead compound NBP and hymexazol against VM, SS and AS strains. It clearly demonstrated that introduction of appropriate substituents on the 6-position of NBP would lead to more potent derivatives. It also implied that **6r** might be considered as new promising lead candidates for further design and synthesis of agricultural fungicides.

4 Experimental section

4.1 General information

All reagents and solvents were of reagent grade or purified according to standard methods before use. Thin-layer chromatography (TLC) and preparative thin-layer chromatography (PTLC) were used with silica gel 60 GF254 (Qingdao Haiyang Chemical Co., Ltd., China). Melting points (m. p.) were determined on a digital m.p. apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance NEO 400 and 100 MHz

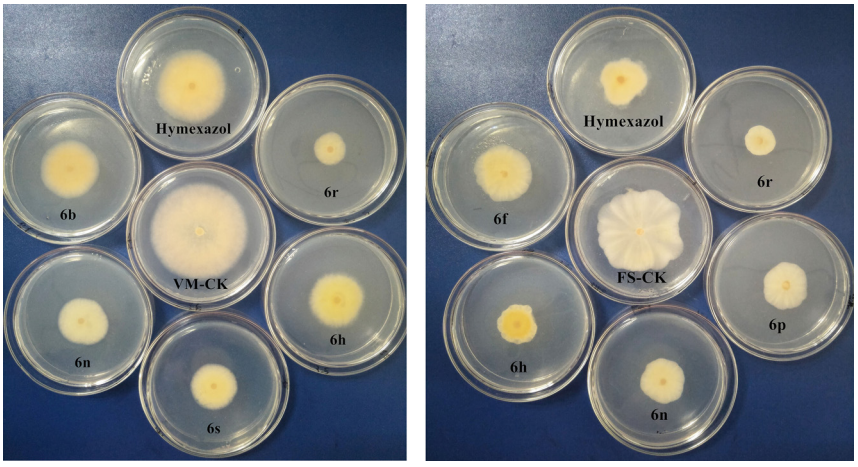


Figure 2: Effects of compounds on the growth of *Valsa mali* (VM) and *Fusarium sulphureum* (FS) (CK: blank control group).

instruments, respectively, using TMS as the internal standard and $CDCl_3$ or DMSO-d_6 as the solvent. HRMS were carried out with an APEX II Bruker 4.7T AS instrument.

4.1.1 Synthesis of (Z)-3-butylidene-3H-isobenzofuran-1-one (1)[17]

To a mixture of phthalic anhydride (40.0 g, 270 mmol) in anhydrous THF (50 mL), *n*-butyllithium (100 mL, 1.0 eq, 2.7 M *n*-hexane solution) was added dropwise and reacted at −78 °C under N_2. When the reaction was complete according to TLC analysis, the reaction was quenched with water. Subsequently, the reaction mixture was adjusted to pH 1–2 with 10% HCl and extracted with EtOAc (3 × 150 mL). The combined organic phase was washed with brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated to give 40.0 g of a brown oily liquid. Then anhydrous toluene (150 mL) and *p*-toluenesulfonic acid (4.6 g, 27.0 mmol) were added and the reaction mixture was refluxed for 6 h. When the reaction was complete (TLC control), the organic solvent was removed. The crude material was purified by silica gel column chromatography to give compound **1** (16.8 g, 33.1%) as an oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, 1H, *J* = 8.0 Hz), 7.67–7.63 (m, 2H), 7.52 (t, 1H, *J* = 8.0 Hz), 5.67 (t, 1H, *J* = 8.0 Hz), 2.48–2.42 (m, 2H), 1.58–1.52 (m, 2H), 1.00 (t, 3H, *J* = 7.6 Hz, CH_3); HRMS (ESI) calcd for $C_{12}H_{13}O_2$ $[M+H]^+$ *m/z*: 189.0914, found 189.0916.

4.1.2 Synthesis of 3-*n*-butyl-3H-isobenzofuran-1-one (NBP, 2)

10% Palladium on carbon (800 mg) was added to a solution of compound **1** (16.0 g, 84.8 mmol) in ethanol (150 mL) under an atmosphere of hydrogen. The reaction mixture was stirred at room temperature over night and the palladium removed by filtration through Celite. The filter cake was washed with ethanol (3 × 70 mL) and the filtrates were concentrated. The residue was purified by silica gel column chromatography to give compound **2** (17.0 g, 94.5%) in yield as a colorless oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, 1H, *J* = 7.6 Hz), 7.67 (m, 1H), 7.54 (t, 1H, *J* = 7.6 Hz), 7.45 (d, 1H, *J* = 7.6 Hz), 5.49 (dd, 1H, *J* = 8.0, 4.8 Hz), 2.08–2.00 (m, 1H), 1.80–1.74 (m, 1H), 1.50–1.34 (m, 4H), 0.92 (t, 3H, *J* = 6.8 Hz, CH_3); HRMS (ESI) calcd for $C_{12}H_{14}O_2Na$ $[M+H]^+$ *m/z*: 213.0886, found 213.0884.

4.1.3 Synthesis of 6-nitro-3-*n*-butylphthalide (3)[18]

To a stirred solution of the corresponding intermediates **2** (16.0 g, 75.5 mmol) in H_2SO_4 (30 mL) was added KNO_3 (9.7 g, 95.9 mmol) at 0–5 °C. After the addition, the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into ice and extracted with ethyl acetate (80 mL × 3). The combined organic layers were washed with brine (50 mL × 2), dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified with column chromatography to give compound **3** (13.0 g, 73.2%) as light yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, 1H, *J* = 2.0 Hz), 8.57 (dd, 1H, *J* = 8.4, 2.0 Hz), 7.68 (d, 1H, *J* = 8.4 Hz), 5.62–5.59 (m, 1H), 2.16–2.08 (m, 1H), 1.87–1.78 (m, 1H), 1.45–1.36 (m, 4H), 0.94 (t, 3H, *J* = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 155.3, 149.0, 128.8, 127.9, 123.2, 121.3, 81.5, 34.1, 26.8, 22.3, 13.7.

4.1.4 Synthesis of 3-butyl-6-amino-1(3H)-isobenzofuranone (4)

To a stirred solution of the intermediate **3** (12.0 g, 51.0 mmol) in THF/H_2O (60 mL/15 mL) was added iron powder (28.4 g, 0.51 mol) and NH_4Cl (2.05 g, 38.3 mmol). Then, the mixture was heated to reflux for 5 h under an argon atmosphere. After complete reaction, the mixture was filtered and the filtrate was concentrated. The resulting residue was purified by column chromatography to afford the compound **4** (9.5 g, 90.9%) as a white solid. m.p. 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, 1H, *J* = 8.0 Hz), 7.10 (d, 1H, *J* = 2.0 Hz), 6.97 (dd, 1H, *J* = 8.4, 2.4 Hz), 5.38–5.35 (m, 1H),3.95 (s, 2H, NH_2), 1.99–1.92 (m, 1H), 1.74–1.66 (m, 1H), 1.47–1.32 (m, 4H), 0.91 (t, 3H, *J* = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 147.5, 140.1, 127.4, 122.3, 121.4, 109.7, 81.4, 34.7, 26.8, 22.4, 13.8. HRMS (ESI) calcd. for $C_{12}H_{16}NO_2$ $[M+H]^+$ *m/z*: 206.1181, found 206.1184.

4.1.5 Synthesis of 3-butyl-6-bromo-1(3H)-isobenzofuranone (5)

A mixture of 6-amino-3-*n*-butylphthalide **4** (6.0 g, 29.25 mmol) in 48% HBr (5 mL) and H_2O (5 mL) in a three-neck flask was cooled in an ice bath. A solution of $NaNO_2$ (2.13 g, 30.9 mmol) in H_2O (30 mL) was added slowly and stirred at 0 °C for 40 min. Then, this mixture of CuBr (4.4 g, 30.7 mmol) and 48% HBr (37.5 mL) was slowly added into the diazonium solution. When the addition was complete, the solution was stirred at 80 °C for 2 h and room temperature for 12 h. The reaction mixture was extracted with AcOEt (60 mL × 3), and the organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. Removal of solvent followed by column chromatographic purification afforded **5** as a white solid (4.5 g, 57.4%). m.p. 68–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, 1H, *J* = 1.6 Hz), 7.79 (dd, 1H, *J* = 8.0, 1.6 Hz), 7.33 (d, 1H, *J* = 8.0 Hz), 5.45–5.42

(m, 1H), 2.07–1.98 (m, 1H), 1.80–1.71 (m, 1H), 1.48–1.33 (m, 4H), 0.92 (t, 3H, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 148.7, 136.9, 128.7, 128.3, 123.3, 122.9, 81.3, 34.2, 26.7, 22.3, 13.8; HRMS (ESI) calcd for $C_{12}H_{14}BrO_2$ $[M+H]^+$ *m/z*: 269.0177, found 269.0176.

4.2 The general procedures for synthesis of compounds 6a–s

In a 25 mL round-bottom flask containing dioxane/H_2O (*V*:*V* = 5:1) (3 mL), K_2CO_3 (207 mg, 1.5 mmol), 3-butyl-6-bromo-1(3H)-isobenzofuranone (135 mg, 0.5 mmol), substituted boronic acid (0.65 mmol) and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) were added and reacted at 90 °C under N_2. When the reaction was complete (TLC control), the organic solvent was removed. The crude material was then purified by silica gel column chromatography to give desired products **6a–s**, which were characterized by m. p., ^{1}H NMR, ^{13}C NMR and HR-MS.

4.2.1 3-Butyl-6-phenylisobenzofuran-1(3H)-one (6a)

Yield: 95%, colorless oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 1.6 Hz, 1H), 7.90 (dd, J = 8.0, 1.6 Hz, 1H), 7.62–7.59 (m, 2H), 7.51–7.46 (m, 3H), 7.42–7.38 (m, 1H), 5.52–5.50 (m, 1H), 2.10–2.03 (m, 1H), 1.85–1.76 (m, 1H), 1.54–1.36 (m, 4H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 148.8, 142.6, 139.4, 133.0, 129.0, 128.1, 127.2, 126.9, 123.9, 122.1, 81.4, 34.5, 26.9, 22.4, 13.8; HRMS (ESI) calcd for $C_{18}H_{19}O_2$ $[M + H]^+$ *m/z*: 267.1385, found 267.1386.

4.2.2 3-Butyl-6-p-tolylisobenzofuran-1(3H)-one (6b)

Yield: 56%, colorless oily liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 8.0 Hz, 1H), 8.00 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 5.68–5.65 (m, 1H), 2.36 (s, 3H), 2.12–2.05 (m, 1H), 1.77–1.68 (m, 1H), 1.41–1.27 (m, 4H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.2, 149.3, 141.8, 138.0, 136.3, 133.2, 130.1, 127.3, 126.6, 123.6, 122.6, 81.5, 33.9, 26.9, 22.3, 21.1, 14.2; HRMS (ESI) calcd for $C_{19}H_{21}O_2$ $[M+H]^+$ *m/z*: 281.1542, found 281.1543.

4.2.3 3-Butyl-6-(4-ethylphenyl)isobenzofuran-1(3H)-one (6c)

Yield: 63%, colorless oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.89 (dd, J = 8.0, 1.6 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 7.6 Hz, 2H), 5.52–5.49 (m, 1H), 2.74 (q, J = 7.6 Hz, 2H), 2.10–2.02 (m, 1H), 1.85–1.75 (m, 1H), 1.52–1.36 (m, 4H), 1.30 (t, J = 7.6 Hz, 3H), 0.94 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 148.6, 144.4, 142.6, 136.8, 132.9, 128.6, 127.1, 126.9, 123.7, 122.0, 81.4, 34.5, 28.5, 26.9, 22.4, 15.5, 13.8; HRMS (ESI) calcd for $C_{20}H_{23}O_2$ $[M+H]^+$ *m/z*: 295.1698, found 295.1696.

4.2.4 6-(4-Aminophenyl)-3-butylisobenzofuran-1(3H)-one (6d)

Yield: 81%, light yellow solid, m. p. 145–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.83 (dd, J = 8.0, 1.6 Hz, 1H), 7.44–7.41 (m, 3H), 6.78 (d, J = 8.4 Hz, 2H), 5.50–5.47 (m, 1H), 3.71 (br, 2H, NH_2), 2.08–2.01 (m, 1H), 1.82–1.74 (m, 1H), 1.53–1.35 (m, 4H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 147.8, 146.6, 142.5, 132.2, 129.5, 128.1, 126.8, 122.8, 121.9, 115.4, 81.4, 34.5, 26.9, 22.4, 13.8; HRMS (ESI) calcd for $C_{18}H_{20}NO_2$ $[M+H]^+$ *m/z*: 282.1494, found 282.1496.

4.2.5 3-Butyl-6-(4-hydroxyphenyl)isobenzofuran-1(3H)-one (6e)

Yield: 69%, white acicular solid, m. p. 194–195 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.85 (dd, J = 8.0, 1.6 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 5.53–5.50 (m, 1H), 2.09–2.02 (m, 1H), 1.84–1.75 (m, 1H), 1.54–1.36 (m, 4H), 0.94 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 155.9, 148.3, 142.2, 132.6, 128.5, 126.8, 123.3, 122.0, 116.1, 116.0, 81.5, 34.5, 26.9, 22.4, 13.8; HRMS (ESI) calcd for $C_{18}H_{19}O_3$ $[M+H]^+$ *m/z*: 283.1334, found 283.1336.

4.2.6 3-Butyl-6-(2-fluorophenyl)isobenzofuran-1(3H)-one (6f)

Yield: 55%, white solid, m. p. 59–61 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, J = 8.0 Hz, 1H), 7.94 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 7.50–7.46 (m, 1H), 7.39–7.33 (m, 2H), 5.72–5.69 (m, 1H), 2.15–2.07 (m, 1H), 1.79–1.70 (m, 1H), 1.43–1.30 (m, 4H) , 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.0, 160.7, 158.3, 150.0, 136.5, 135.4, 131.4, 130.8, 127.3, 126.3, 125.6, 123.4, 116.7, 81.6, 33.9, 27.0, 22.3, 14.2; HRMS (ESI) calcd for $C_{18}H_{18}FO_2$ $[M+H]^+$ *m/z*: 285.1291, found 285.1294.

4.2.7 3-Butyl-6-(2-fluoro-4-methoxyphenyl) isobenzofuran-1(3H)-one (6g)

Yield: 77%, colorless oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.83–7.80 (m, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 8.8 Hz, 1H), 6.82 (dd, J = 8.4, 2.4 Hz, 1H), 6.76

(dd, J = 8.4, 2.4 Hz, 1H), 5.52–5.49 (m, 1H), 3.85 (s, 3H, OCH_3), 2.11–2.02 (m, 1H), 1.84–1.75 (m, 1H), 1.52–1.36 (m, 4H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 161.5, 159.0, 148.7, 137.0, 134.6, 130.9, 126.6, 125.5, 121.7, 119.7, 110.6, 102.3, 81.4, 55.6, 34.5, 26.9, 13.8; HRMS (ESI) calcd for $C_{19}H_{20}FO_3$ $[M+H]^+$ *m/z*: 315.1396, found 315.1397.

4.2.8 4-(1-Butyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-3-fluorobenzaldehyde (6h)

Yield: 77%, colorless oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H, CHO), 8.13 (s, 1H), 8.02–7.98 (m, 1H), 7.94 (dd, J = 8.0, 2.0 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 7.2 Hz, 1H), 5.58–5.55 (m, 1H), 2.15–2.05 (m, 1H), 1.88–1.79 (m, 1H), 1.55–1.38 (m, 4H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.6, 170.0, 166.2, 163.6, 150.4, 147.6, 139.9, 132.9, 129.5, 127.4, 124.2, 123.4, 122.6, 115.2, 81.4, 34.3, 26.8, 22.4, 13.8; HRMS (ESI) calcd for $C_{19}H_{18}FO_3$ $[M+H]^+$ *m/z*: 313.1240, found 313.1343.

4.2.9 3-Butyl-6-(3-(trifluoromethyl)phenyl) isobenzofuran-1(3H)-one (6i)

Yield: 86%, white solid, m. p. 86–87 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18–8.16 (m, 2H), 8.10–8.09 (d, 2H), 7.82–7.72 (m, 3H), 5.72–5.69 (m, 1H), 2.15–2.08 (m, 1H), 1.76–1.70 (m, 1H), 1.38–1.32 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.0, 150.3, 140.2, 133.8, 131.7, 130.6, 130.5, 130.2, 126.8, 125.9, 125.1, 124.1, 123.8, 123.6, 81.5, 33.9, 26.9, 22.3, 14.2; HRMS (ESI) calcd for $C_{19}H_{18}F_3O_2$ $[M+H]^+$ *m/z*: 335.1259, found 335.1262.

4.2.10 3-Butyl-6-(4-(trifluoromethoxy)phenyl) isobenzofuran-1(3H)-one (6j)

Yield: 86%, white solid, m. p. 68–69 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.87 (dd, J = 8.0, 1.6 Hz, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 5.54–5.51 (m, 1H), 2.11–2.04 (m, 1H), 1.85–1.76 (m, 1H), 1.52–1.38 (m, 4H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 149.2, 141.2, 138.2, 132.9, 128.6, 127.1, 123.9, 122.3, 121.7, 121.5, 119.2, 81.4, 34.4, 26.9, 22.4, 13.8; HRMS (ESI) calcd for $C_{19}H_{18}F_3O_3$ $[M+H]^+$ *m/z*: 351.1208, found 351.1209.

4.2.11 3-Butyl-6-(4-chlorophenyl)isobenzofuran-1(3H)-one (6k)

Yield: 87%, white solid, m. p. 63–64 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.86 (dd, J = 8.0, 1.6 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 5.53–5.50 (m, 1H), 2.10–2.03 (m, 1H), 1.84–1.76 (m, 1H), 1.50–1.36 (m, 4H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 147.3, 139.6, 136.1, 132.6, 131.0, 127.4, 126.6, 125.3, 122.0, 120.4, 79.6, 32.6, 25.0, 20.6, 12.0; HRMS (ESI) calcd for $C_{18}H_{18}ClO_2$ $[M+H]^+$ *m/z*: 301.0995, found 301.0997.

4.2.12 3-Butyl-6-(2-chlorophenyl)isobenzofuran-1(3H)-one (6l)

Yield: 38%, light yellow solid, m. p. 96–97 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86–7.78 (m, 3H), 7.62–7.60 (m, 1H), 7.51–7.45 (m, 3H), 5.72–5.69 (m, 1H), 2.16–2.08 (m, 1H), 1.79–1.70 (m, 1H), 1.45–1.32 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.0, 150.0, 140.1, 138.8, 135.9, 132.1, 131.7, 130.4, 130.3, 128.2, 125.9, 125.7, 123.1, 81.6, 33.9, 27.1, 22.3, 14.2; HRMS (ESI) calcd for $C_{18}H_{18}ClO_2$ $[M+H]^+$ *m/z*: 301.0995, found 301.0998.

4.2.13 3-Butyl-6-(2,3-dichlorophenyl)isobenzofuran-1(3H)-one (6m)

Yield: 90%, white solid, m.p. 57-58 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86-7.83 (m, 2H), 7.81 (s, 1H), 7.73 (dd, J = 7.2, 2.4 Hz, 1H), 7.50-7.45 (m, 2H), 5.73-5.70 (m, 1H), 2.16- 2.08 (m, 1H), 1.79-1.70 (m, 1H), 1.46-1.31 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 150.4, 141.3, 139.9, 135.8, 132.8, 130.7, 130.2, 128.9, 126.0, 125.7, 123.1, 81.7, 33.9, 27.1, 22.3, 14.2; HRMS (ESI) calcd for $C_{18}H_{17}Cl_2O_2$ $[M+H]^+$ m/z: 335.0606, found 335.0607.

4.2.14 3-(1-Butyl-3-oxo-1,3-dihydroisobenzofuran-5-yl) benzaldehyde (6n)

Yield: 82%, white solid, m.p. 76–75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H, CHO), 8.06 (dd, J = 7.6, 1.2 Hz, 1H), 7.93 (s, 1H), 7.71–7.65 (m, 2H), 7.59–7.53 (m, 2H), 7.45–7.43 (m, 1H), 5.58–5.55 (m, 1H), 2.13–2.06 (m, 1H), 1.87–1.79 (m, 1H), 1.56–1.38 (m, 4H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 170.0, 149.7, 143.7, 139.3, 135.8, 133.9, 133.6, 130.9, 128.6, 128.5, 126.8, 126.5, 121.7, 81.4, 34.48, 26.9, 22.4, 13.8; HRMS (ESI) calcd for $C_{19}H_{19}O_3$ $[M+H]^+$ *m/z*: 395.1334, found 395.1337.

4.2.15 3-Butyl-6-(3-nitrophenyl)isobenzofuran-1(3H)-one (6o)

Yield: 71%, white solid, m. p. 96–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.28–8.26 (m, 1H), 8.13 (s, 1H), 7.96–7.93 (m, 2H), 7.70 (t, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H),

5.58–5.55 (m, 1H), 2.13–2.06 (m, 1H), 1.87–1.78 (m, 1H), 1.55–1.37 (m, 4H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 150.0, 148.8, 141.1, 140.1, 133.1, 132.9, 130.1, 127.4, 124.1, 122.9, 122.7, 122.1, 81.5, 34.4, 26.8, 22.4, 13.8; HRMS (ESI) calcd for $C_{18}H_{18}NO_4$ $[M+H]^+$ *m/z*: 312.1236, found 312.1239.

4.2.16 3-Butyl-6-(thiophen-3-yl)isobenzofuran-1(3H)-one (6p)

Yield: 98%, colorless oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 0.8 Hz, 1H), 7.90 (d, J = 8.0, 1.6 Hz, 1H), 7.54–7.53 (m, 1H), 7.46–7.41 (m, 3H), 5.51–5.48 (m, 1H), 2.09–2.02 (m, 1H), 1.83–1.74 (m, 1H), 1.51–1.33 (m, 4H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 148.6, 140.5, 137.15, 132.2, 126.9, 126.1, 123.0, 122.1, 121.5, 81.4, 34.4, 26.8, 22.4, 13.8; HRMS (ESI) calcd for $C_{16}H_{17}O_2S$ $[M+H]^+$ *m/z*: 273.0949, found 273.0951.

4.2.17 6-(Benzo[b]thiophen-2-yl)-3-butylisobenzofuran-1(3H)-one (6q)

Yield: 71%, white solid, m. p. 114–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 1.2 Hz, 1H), 8.00 (dd, J = 8.0, 1.6 Hz, 1H), 7.85 (d, J = 8.8 Hz,1H), 7.81 (dd, J = 7.2, 1.6 Hz, 1H), 7.62 (s, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.39–7.33 (m, 2H), 5.52–5.49 (m, 1H), 2.09–2.02 (m, 1H), 1.84–1.75 (m, 1H), 1.53–1.36 (m, 4H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 149.5, 142.1, 140.4, 139.6, 135.7, 132.1, 127.2, 124.9, 124.8, 123.9, 123.1, 122.3, 120.8, 81.5, 34.4, 26.8, 22.4, 13.8; HRMS (ESI) calcd for $C_{20}H_{19}O_2S$ $[M+H]^+$ *m/z*: 323.1106, found 323.1107.

4.2.18 3-Butyl-6-(pyridin-3-yl)isobenzofuran-1(3H)-one (6r)

Yield: 35%, colorless oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 1.6 Hz, 1H), 8.67 (dd, J = 4.8, 1.6 Hz, 1H), 8.09 (d, J = 1.2 Hz,1H), 7.93–7.88 (m, 2H), 7.57 (d, J = 8.0 Hz, 1H), 7.45–7.41 (m, 1H), 5.56–7.53 (m, 1H), 2.13–2.05 (m, 1H), 1.87–1.77 (m, 1H), 1.51–1.37 (m, 4H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 149.7, 149.2, 148.2, 139.2, 135.1, 134.6, 132.9, 127.3, 124.1, 123.8, 122.5, 81.4, 34.4, 26.8, 22.4, 13.8; HRMS (ESI) calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$ *m/z*: 268.1338, found 268.1340.

4.2.19 3-Butyl-6-(2-chloropyridin-4-yl)isobenzofuran-1(3H)-one (6s)

Yield: 60%, colorless oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 5.2 Hz, 1H), 8.13 (d, J = 1.6 Hz, 1H), 7.92 (dd, J = 8.0, 2.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.58 (s, 1H), 7.47 (dd, J = 5.2, 1.6 Hz, 1H), 5.57–5.54 (m, 1H), 2.14–2.04 (m, 1H), 1.88–1.77 (m, 1H), 1.54–1.36 (m, 4H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 152.5, 151.0, 150.3, 149.8, 138.3, 132.7, 127.5, 124.2, 122.8, 122.2, 120.5, 81.4, 34.3, 26.8, 22.4, 13.8; HRMS (ESI) calcd for $C_{17}H_{17}ClNO_2$ $[M+H]^+$ *m/z*: 302.0948, found 302.0950.

4.3 The general procedures for synthesis of compounds 7a–f and 8a–d

A solution of compound **4** (0.4 mmol) and the corresponding R^1SO_2Cl or R^2COCl (0.18 mmol) in pyridine (1.5 mL) was stirred at room temperature. When the reaction was complete, as checked by TLC analysis, the solution of the mixture was diluted with AcOEt (30 mL). Subsequently, the solution was washed with water (15 mL), 0.1 N aqueous HCl (25 mL) and brine (25 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography to give the target products **7a–f** and **8a–d**, which were characterized by m. p., ^{1}H NMR, ^{13}CNMR and HRMS.

4.3.1 *N*-(1-butyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-fluorobenzenesulfonamide (7a)

Yield 75.7%, white solid, m. p. 112–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.82 (m, 2H), 7.54–7.52 (m, 2H), 7.421 (s, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.15 (t, J = 8.4 Hz, 2H), 5.43–5.40 (m, 1H), 2.05–1.95 (m, 1H), 1.75–1.67 (m, 1H), 1.47–1.31 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 166.7, 164.1, 146.8, 137.6, 134.6, 130.0, 127.5, 122.9, 117.5, 116.7, 116.5, 81.5, 34.3, 26.8, 22.3, 13.8; HRMS (ESI) calcd for $C_{18}H_{19}FNO_4S$ $[M+H]^+$ *m/z*: 364.1019, found 364.1020.

4.3.2 *N*-(1-Butyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methoxybenzenesulfonamide (7b)

Yield 80.0%, white solid, m. p. 153–154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.8 Hz, 2H), 7.53–7.51 (m, 2H), 7.34–7.31 (m, 2H), 6.92 (d, J = 9.2 Hz, 2H), 5.41–5.38 (m, 1H), 3.83 (s, 3H), 2.01–1.94 (m, 1H), 1.74–1.66 (m, 1H), 1.46–1.31 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 163.4, 146.4, 138.1, 130.0, 129.4, 127.3, 122.8, 117.1, 114.4, 81.4, 55.6, 34.3, 26.8, 22.3, 13.8; HRMS (ESI) calcd for $C_{19}H_{22}NO_5S$ $[M+H]^+$ *m/z*: 376.1219, found 376.1221.

4.3.3 *N*-(1-butyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-cyanobenzenesulfonamide (7c)

Yield 84.7%, white solid, m. p. 160–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.54–7.52 (m, 2H), 7.39–7.33 (m, 2H), 5.45–5.42 (m, 1H), 2.03–1.97 (m, 1H), 1.76–1.67 (m, 1H), 1.46–1.34 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 147.3, 142.9, 137.0, 133.1, 127.8, 123.1, 117.9, 117.2, 116.9, 81.5, 34.3, 26.9, 22.3, 13.8; HRMS (ESI) calcd for $C_{19}H_{19}N_2O_4S$ $[M+H]^+$ *m/z*: 371.1066, found 371.1069.

4.3.4 *N*-(1-butyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-2,4-dichlorobenzenesulfonamide (7d)

Yield 59.9%, yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.65 (s, 1H), 7.59 (d, *J* = 2.0 Hz, 1H), 7.54–7.51 (m, 2H), 7.35–7.32 (m, 2H), 5.40–5.37 (m, 1H), 2.01–1.92 (m, 1H), 1.72–1.64 (m, 1H), 1.46–1.30 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 147.0 140.4, 136.9, 134.4, 132.9, 132.4, 131.7, 127.7, 127.5, 127.2, 123.0, 117.3, 81.4, 34.3, 26.9, 22.3, 13.8; HRMS (ESI) calcd for $C_{18}H_{18}Cl_2NO_4S$ $[M+H]^+$ *m/z*: 415.0334, found 415.0336.

4.3.5 *N*-(1-butyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-6-chloropyridine-3-sulfonamide (7e)

Yield 84.1%, white solid, m. p. 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.4 Hz, 1H), 8.06 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.89 (s, 1H), 7.62–7.60 (m, 2H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 5.46–5.43 (m, 1H), 2.05–1.96 (m, 1H), 1.78–1.69 (m, 1 H), 1.47–1.33 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 156.1, 148.4, 147.4, 137.4, 137.1, 134.5, 127.8, 127.5, 124.9, 123.2, 118.0, 81.8, 34.3, 26.9, 22.3, 13.8; HRMS (ESI) calcd for $C_{17}H_{18}ClN_2O_4S$ $[M+H]^+$ *m/z*: 381.0676, found 381.0678.

4.3.6 *N*-(1-butyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-3-chloropropane-1-sulfonamide (7f)

Yield 84.7%, white solid, m. p. 100–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 1.6 Hz, 1H), 7.64 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.48 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 5.49–5.46 (m, 1H), 3.68 (t, *J* = 6.0 Hz, 2H), 3.36 (t, *J* = 7.2 Hz, 2H), 2.36–2.30 (m, 2H), 2.06–1.99 (m, 1H), 1.81–1.72 (m, 1H), 1.50–1.34 (m, 4H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 146.5, 138.1, 127.6, 126.7, 123.2, 116.6, 81.7, 49.5, 42.5, 34.3, 26.8, 26.6, 22.4, 13.8; HRMS (ESI) calcd for $C_{15}H_{21}ClNO_4S$ $[M+H]^+$ *m/z*: 346.0880, found 346.0881.

4.3.7 *N*-(1-butyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-fluorobenzamide (8a)

Yield 76.4 %, white solid, m. p. 210–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H, NH), 8.31 (d, *J* = 1.6 Hz, 1H), 8.08–8.05 (m, 3H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.42 (t, *J* = 8.8 Hz, 2H), 5.63–5.61 (m, 1H), 2.08–2.01 (m, 1H), 1.74–1.68 (m, 1H), 1.40–1.23 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.3, 165.2, 145.6, 140.4, 131.0, 130.9, 126.91, 126.3, 123.3, 116.0, 115.87, 115.82, 81.5, 34.0, 26.8, 22.3, 14.2; HRMS (ESI) calcd for $C_{19}H_{19}FNO_3$ $[M+H]^+$ *m/z*: 328.1349, found 328.1350.

4.3.8 *N*-(1-butyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-3-(trifluoromethoxy)benzamide (8b)

Yield 74.6%, white solid, m. p. 200–202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H, NH), 8.43 (d, *J* = 8.0 Hz, 1H), 8.13 (s, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 7.91 (s, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.47–7.42 (m, 2H), 5.51–5.49 (m, 1H), 2.07–2.01 (m, 1H), 1.81–1.73 (m, 1H), 1.50–1.34 (m, 4H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 164.4, 149.5, 145.8, 139.2, 136.2, 130.3, 126.8, 126.7, 125.5, 124.5, 122.5, 120.4, 116.7, 81.9, 34.4, 26.8, 22.4, 13.8; HRMS (ESI) calcd for $C_{20}H_{19}F_3NO_4$ $[M+H]^+$ *m/z*: 394.1266, found 394.1267.

4.3.9 *N*-(1-butyl-3-oxo-1,3-dihydroisobenzofuran-5-yl) hexanamide (8d)

Yield 65.9%, white solid, m. p. 132–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.0 Hz, 1H), 8.07 (s, 1H, NH), 7.88 (d, *J* = 1.6 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 5.47–5.44 (m, 1H), 2.45 (t, *J* = 7.6 Hz, 2H), 2.05–1.98 (m, 1H), 1.78–1.71 (m, 3H), 1.47–1.31 (m, 8H), 0.92–0.88 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 170.7, 145.2, 139.5, 126.6, 126.2, 122.3, 115.8, 81.7, 37.6, 34.4, 31.4, 26.8, 25.2, 22.4, 13.9, 13.8; HRMS (ESI) calcd for $C_{18}H_{26}NO_3$ $[M+H]^+$ *m/z*: 304.1913, found 304.1917.

4.4 Biological assay

The synthesized compounds were screened *in vitro* for their antifungal activities against eight phytopathogenic fungi

by poisoned food technique. Eight phytopathogenic fungi such as FS, *T. cucumeris* (TC), *F. oxysporum* (FO), *F. graminearum* (FG), *B. cinerea* (BC), *B. cinerea Per.et Fries* (BP), *V. mali* (VM), *S. sclerotiorum* (SS) and *A. solani* (AS) were used for the assays. Potato dextrose agar (PDA) medium was prepared in the flasks and sterilized. The synthesized compounds were dissolved in acetone before mixing with PDA, and the concentration of test compounds in the medium was fixed at 50 μg/mL. The medium was then poured into sterilized Petri dishes. All types of fungi were incubated in PDA at 27 ± 0.5 °C for 5 days to get new mycelium for the antifungal assays, and a mycelia disk of approximately 4 mm diameter cut from culture medium was picked up with a sterilized inoculation needle and inoculated in the center of the PDA Petri dishes. The inoculated Petri dishes were incubated at 27 ± 0.5 °C for 4 days. Acetone without any compounds mixed with PDA served as a control, while hymexazol, a commercial agricultural fungicide, was used as positive control. For each treatment, three replicates were conducted. The radial growths of the fungal colonies were measured and the data were statistically analyzed. The inhibitory effects of the test compounds on these fungi *in vitro* were calculated by the formula: Inhibition rate (%) = $(C-T) \times 100/(C-4\ \text{mm})$, where C represents the diameter of fungi growth on untreated PDA, and T represents the diameter of fungi on treated PDA. Statistical analysis was processed by the SPSS 21.0 (SPSS Inc., Chicago, USA) software.

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