Synthesis and Biological Activity of *O*-Methyl Methyl 1-(Substituted Phenoxyacetoxy)-1-(thien-2-yl)methylphosphinates

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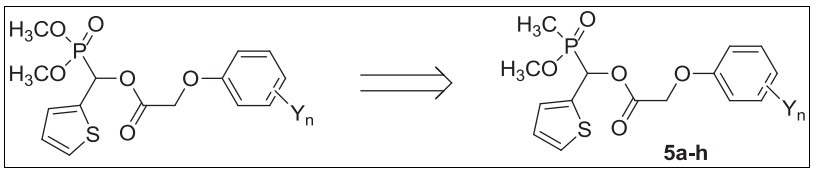

A series of novel *O*-methyl methyl 1-(substituted phenoxyacetoxy)-1-(thien-2-yl)methylphosphinates **5a–h** were synthesized. Their structures were confirmed by IR, ^{1}H NMR, mass spectroscopy, and elemental analyses. The results of preliminary bioassays show that some of the title compounds exhibit moderate to good herbicidal and fungicidal activities. For example, the title compounds **5c**, **5d**, and **5g** possess 90–100% inhibition against the tested plants at the concentration of 10 mg/L and 100 mg/L, whereas the title compounds **5a**, **5b**, **5c**, and **5h** possess 70–94% inhibition against *Phyricularia grisea* and *Sclerotinia sclerotiorum* at the concentration of 50 mg/L.

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INTRODUCTION

α-Substituted alkylphosphonate derivatives have received considerable attention in medicine and pesticide chemistry due to their biological activities over the past two decades [1–4]. Especially, in our previous work, a series of 1-(substituted phenoxyacetoxy)alkylphosphonates, as potent pyruvate dehydrogenase complex inhibitors, were synthesized and showed notable bioactivities [5–7]. Substituted pyridine and thiophene derivatives, as an important class of agrochemicals, have played a major role in crop protection. And as typical heterocyclic groups, pyridinyl and thienyl are often introduced in the design of bioactive compounds [8–10]. Therefore, a series of *O, O*-dimethyl 1-(substituted phenoxyacetoxy)-1-(pyrid-2-yl or thien-2-yl)methylphosphonates were synthesized, and some of them exhibited excellent herbicidal and fungicidal activities [11].

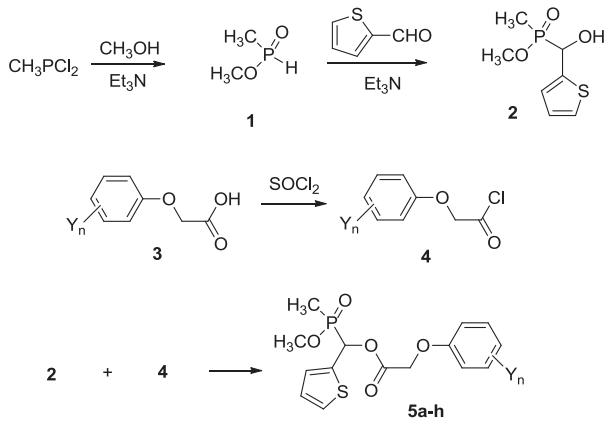
On the other hand, bioisosterism is an important concept of bioactive compound design[12,13]. The phosphinate group is often used for bioisosteric replacement of phosphonate group in bioactive molecules to obtain more bioactivity or safety, which encouraged us to replace the phosphonate group with phosphinate group and further study the structure–activity relationship. Herein, we reported the synthesis of new *O*-methyl methyl 1-(substituted phenoxyacetoxy)-1-(thien-2-yl) methylphosphinates **5** (Scheme 1) and their evaluation for herbicidal and fungicidal activities.

RESULTS AND DISCUSSION

The reaction of *O*,*O*-dialkyl phosphonates with aldehydes is a convenient method used to synthesize 1-hydroxyphosphonates, which have been reported in many literatures [14–16]. However, there are few reports on the reaction of *O*-methyl methylphosphinate **1** with thiophene-2-carbaldehyde. On the basis of the synthetic method of 1-hydroxyphosphonates, 1-hydroxyphosphinate **2** was synthesized by the reaction of intermediate **1** with thiophene-2-carbaldehyde using triethylamine as a catalyst. Triethylamine is an important catalyst, which is essential to the addition reaction mentioned earlier. Without the use of the triethylamine as a catalyst, the reaction was greatly slowed, and the yields were very low. The title compounds **5a–h** were prepared by condensation of intermediates **2** with substituted phenoxyacetyl chlorides **4** in the presence of triethylamine as a base in chloroform (Scheme 1).

The structures of **5a–h** were characterized by ^{1}H NMR, IR, MS, and elemental analysis. Compound **5h** was further analyzed by ^{31}P NMR. The ^{1}H NMR spectrum shows that the proton signals corresponding to methyl, methoxy, and methylidyne attached to phosphorus appear as two doublets, respectively. For example, the CH_3 signals of compound **5a** appear at δ 1.49 (d, $J = 14.8$ Hz), 1.56 (d, $J = 14.8$ Hz), the CH_3O signals at δ 3.69 (d, $J = 12.4$ Hz), 3.75 (d, $J = 12.4$ Hz), and CH signal at δ 6.50 (d, $J = 10.8$ Hz), 6.58 (d, $J = 10.8$ Hz), respectively. The magnetic nucleus phosphorus makes these proton signals

Scheme 1. Synthetic route of compounds **5a–h**.



split into a doublet, and the low rate of environment exchange caused by the slow rotation of the P–C bond is the probable reason for two doublets signals. And the signal strength of these two doublets is different, which indicates that the ratio of two conformations is different. The signal corresponding to the methylene group (CH_2) flanked by the phenoxy group, and carbonyl group appears as a quartet, the outside peaks smaller in size, which belongs to the AB system with the difference in chemical shift between the two mutually coupled protons A and B.

The corresponding IR spectrum revealed normal absorption bands at 1740–1770 cm^{-1} (C═O) and 3060–3090 cm^{-1} (Ar–H). The mass spectra of the title compound **5** revealed the existence of the molecular ion peaks, which were in good accordance with the given structures of products.

Biological activities

Herbicidal activity. The preliminary herbicidal activity of **5a–h** was evaluated against *Brassica napus* (rape) and *Echinochloa crus-galli* (barnyard grass) at the concentration of 100 mg/L and 10 mg/L using the known procedure [17]. As shown in Table 1, **5c**, **5d**, and **5g** displayed notable herbicidal activity against the tested plants, with more than 90% inhibitory rate to the growth of the stem and the root at the concentration of 10 mg/L. The title compounds showed higher inhibitory activities against the growth of the root than that of the stem. For example, compounds **5c–5d** showed 96% inhibitory rate against the root of *E. crusgalli* at the concentration of 10 mg/L but only 36–46% inhibitory rate against the stem of *E. crusgalli* at the same concentration. Comparing herbicidal activities among the title compounds in Table 1, it was found that the X and Y groups have great impact on the herbicidal activity. The title compounds with 4-Cl, 3-CH_3-4-Cl, and 2,4-Cl_2 as Y_n (**5c**, **5d**, and **5g**) show higher inhibitory rate (>90%) against the root of the tested plants at the concentration of 10 mg/L.

Fungicidal activity. The fungicidal activities of **5a–h** were evaluated by the classic plate method at the concentration of 50 mg/L, which was described in the experimental part. The six fungi *Fusarium oxysporum* (Fusarium wilt), *Phyricularia grisea* (Rice blast), *Botrytis cinereapers* (Gray mold), *Gibberella zeae* (Telomorph), *Sclerotinia sclerotiorum* (Sclerotiniose), and *Cercospora beticola* (Brown spot), belong to the group of field fungi and were isolated from corresponding crops. As listed in Table 2, most compounds display moderate to good fungicidal activity against the six aforementioned fungi. For example, compounds **5c** and **5h** possessed more than 88% inhibitory activity against rice blast and sclerotiniose. It was found that Y_n groups on the phenoxy ring had great impact on the fungicidal activity. As for rice blast and sclerotiniose, 4-Cl and 2,6-Cl_2 groups on the phenoxy ring was the most promotive, followed by 3-CF_3 and 2-F.

In conclusion, a series of novel *O*-methyl methyl 1-(substituted phenoxyacetoxy)-1-(thien-2-yl)methylphosphinates **5a–h** were designed and synthesized. The results of preliminary bioassays showed that compounds 5**c**, **5d**, and **5g** displayed notable herbicidal activity against the tested

Table 1

Structure and herbicidal activity of compound **5**.

		Ech				Bra			
		Stem		Root		Stem		Root	
No.	Y_n	10 mg/L	100 mg/L	10 mg/L	100 mg/L	10 mg/L	100 mg/L	10 mg/L	100 mg/L
5a	3-CF_3	39	64	47	93	49	97	60	99
5b	2-F	57	61	71	80	−8	31	4	72
5c	4-Cl	46	64	96	98	92	97	99	100
5d	3-CH_3,4-Cl	36	54	96	98	95	97	100	100
5e	2-Cl,5-CH_3	57	61	58	82	8	56	40	94
5f	2,3-Cl_2	68	82	60	96	3	54	26	93
5g	2,4-Cl_2	39	89	98	98	97	100	100	100
5h	2,6-Cl_2	68	68	76	87	21	92	47	97

Ech: *Echinochloa crus-galli*; Bra, *Brassica napus*.

Table 2

Fungicidal activity of compound **5**.

No.	Y_n	Fus	Phy	Bot	Gib	Scl	Cer
5a	3-CF_3	61	71	84	41	71	46
5b	2-F	43	43	72	41	82	46
5c	4-Cl	39	57	91	56	94	54
5d	3-CH_3,4-Cl	26	29	41	29	71	39
5e	2-Cl,5-CH_3	35	36	38	29	59	32
5f	2,3-Cl_2	30	50	59	41	65	29
5g	2,4-Cl_2	35	29	19	24	41	21
5h	2,6-Cl_2	57	50	88	47	88	46

Fus: *Fusarium oxysporum*; Phy: *Phyricularia grisea*; Bot: *Botrytis cinereapers*; Gib: *Gibberella zeae*; Scl: *Sclerotinia sclerotiorum*; Cer: *Cercospora beticola*;

plants, with more than 90% inhibitory rate to the growth of the stem and the root at the concentration of 10 mg/L. In addition, compounds **5c** and **5h** possessed more than 88% inhibitory activity against rice blast and sclerotiniose. These results indicated that the title compound **5** could be modified and used as lead compounds for further study.

EXPERIMENTAL

Chemicals and reagents were obtained from commercial sources, and all of the solvents were dried and purified by standard techniques prior to use. Column chromatography was carried out with Merck silica gel (200–300 meshes). Refractive index (n_D^{20}) was measured on an Abbe refractometer and was uncorrected. IR spectra were recorded as KBr pellets on a Perkin-Elmer Fourier transform infrared spectrophotometer (USA). ^{1}H NMR and ^{31}P NMR were recorded on Varian XL-400 spectrometer (Salt Lake City, USA) at 400 MHz using tetramethylsilane as internal standard (solvent $CDCl_3$). Chemical shifts (δ) are given in ppm, coupling constants (*J*) are in Hz, and multiplicities are implicated by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). MS spectra were analyzed on a Finnigan TRACE spectrometer (Ramsey, USA) and API2000LC/MS (Framingham, USA). Elemental analyses were performed by a Vario EL III elemental analyzer (Hanau, Germany).

Procedure for the synthesis of intermediate 2. A solution of dichloro(methyl)phosphine (5.85 g, 50 mmol) in dry benzene (40 mL) was added dropwise with stirring to a cooled solution of methanol (3.84 g, 120 mmol) and triethylamine (5.05 g, 50.0 mmol) under nitrogen at 0–5°C. After allowing the reaction mixture to stand for 1 h and then filtered, the filtrate was condensed to give *O*-methyl methylphosphinate **1**, which was used directly without further purification.

A solution of *O*-methyl methylphosphinate **1** (1.88 g, 20.0 mmol) prepared earlier in dry benzene (20 mL) was added with stirring to a solution of thiophene-2-carbaldehyde (2.69 g, 24.0 mmol) and catalyst triethylamine (1.01 g, 10.0 mmol) under nitrogen at 0–5°C. After the reaction mixture was stirred for 6–8 h at 50–60°C, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel and elution with petroleum ether/acetone (3:1, v/v) to give *O*-methyl methyl 1-hydroxy-1-(thien-2-yl)methylphosphinate **2**.

General procedure for the synthesis of intermediates 4. A mixture containing substituted phenoxyacetyl acid **3** (4.0 mmol) and thionyl chloride (4 mL) was added into a 15-mL flask and refluxed for 5–6 h. Excess thionyl chloride was evaporated off under reduced pressure, and a light yellow oil **4** was obtained with a yield of 85–90%, which was used directly without further purification.

General procedure for the synthesis of title compounds 5a–h. A solution of substituted phenoxyacetyl chlorides **4** (3.3 mmol) in dichloromethane (15 mL) was added to a stirred mixture of *O*-methyl methyl 1-hydroxy-1-(thien-2-yl) methylphosphinate **2** (3 mmol) and triethylamine (3.3 mmol) in chloroform (20 mL) at 20–25°C. The resultant mixture was stirred for 3–5 h at room temperature and then for 1–2 h at 40°C. The dichloromethane layer was washed with 0.1 M hydrochloric acid, saturated sodium hydrogen carbonate solution and brine, dried, and concentrated. The residue was purified by column chromatography on silica gel and elution with petroleum ether/ acetone (4:1, v/v) to give the corresponding pure title compounds **5a–h**. Their structures were confirmed by ^{1}H NMR, IR, MS, and elemental analysis. And the physicochemical properties and spectroscopic data for compounds **5a–h** are as follows.

Data for O-methyl methyl 1-(thioen-2-yl)-1-(3-trifluoromethyl-phenoxyacetoxy)methylphosphinate (5a). Yellowish oil, yield, 62%; n_D^{20}, 1.5421; IR (KBr, cm^{-1}): ν 3079, 2953, 2851, 1743, 1593, 1456, 1428, 1224, 1173, 1043, 897, 719. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49, 1.56 (d, 3H, CH_3, J = 14.8 Hz), 3.69, 3.75 (d, 3H, OCH_3, J = 12.4 Hz), 4.80, 4.87 (q, AB system, 2H, OCH_2CO, J_{AB} = 15.4 Hz), 6.50, 6.58 (d, 1H, OCHP, J = 10.8 Hz), 6.92–7.37 (m, 7H, ArH); MS *m/z* (%): 408 (M^+, 5.63), 315 (1.05), 205 (6.65), 189 (8.28), 175 (36.30), 161 (1.47), 145 (76.68), 111 (49.37), 93 (100), 63 (56.77). *Anal*. Calcd for $C_{16}H_{16}F_3O_5PS$: C, 47.06; H, 3.95. Found: C, 46.65; H, 4.40.

Data for O-methyl methyl 1-(2-fluorophenoxyacetoxy)-1-(thioen-2-yl)methylphosphinate (5b). Yellowish oil, yield, 66%; n_D^{20}, 1.5240; IR (KBr, cm^{-1}): ν 3074, 2924, 2852, 1741, 1592, 1506, 1428, 1226, 1174, 1040, 898, 753. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48, 1.55 (d, 3H, CH_3, J = 14.4 Hz), 3.69, 3.75 (d, 3H, OCH_3, J = 12.4 Hz), 4.79, 4.86 (q, AB system, 2H, OCH_2CO, J_{AB} = 15.0 Hz), 6.52, 6.60 (d, 1H, OCHP, J = 10.8 Hz), 6.90–7.36 (m, 7H, ArH); MS *m/z* (%): 358 (M^+, 2.26), 205 (5.32), 170 (48.16), 125 (67.78), 111 (38.07), 93 (100), 63 (80.45). *Anal*. Calcd for $C_{15}H_{16}FO_5PS$: C, 50.28; H, 4.50. Found: C, 50.67; H, 4.56.

Data for O-methyl methyl 1-(4-chlorophenoxyacetoxy)-1-(thioen-2-yl)methylphosphinate (5c). Yellowish oil, yield, 70%; n_D^{20}, 1.4868; IR (KBr, cm^{-1}): ν 3092, 2924, 2852, 1739, 1596, 1492, 1429, 1236, 1174, 1042, 899, 709. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47, 1.54 (d, 3H, CH_3, J = 14.4 Hz), 3.68, 3.74 (d, 3H, OCH_3, J = 12.4 Hz), 4.80, 4.87 (q, AB system, 2H, OCH_2CO, J_{AB} = 15.6 Hz), 6.45, 6.53 (d, 1H, OCHP, J = 9.8 Hz), 6.85–7.39 (m, 7H, ArH); MS *m/z* (%): 374 (M^+, 15.62), 205 (24.10), 189(59.65), 141 (43.40), 111 (100), 93 (86.24), 63 (60.88). *Anal*. Calcd for $C_{15}H_{16}ClO_5PS$: C, 48.07; H, 4.30. Found: C, 47.95; H, 4.00.

Data for O-methyl methyl 1-(4-chloro-3-methylphenoxyacetoxy)-1-(thioen-2-yl)methylphosphinate (5d). Yellowish oil, yield, 72%; n_D^{20}, 1.5423; IR (KBr, cm^{-1}): ν 3059, 2955, 2851, 1771, 1590, 1493, 1436, 1224, 1170, 1041, 900, 748. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47, 1.54 (d, 3H, CH_3, J = 14.0 Hz), 2.28 (s, 3H, cPhCH_3), 3.69, 3.75 (d, 3H, OCH_3, J = 12.4 Hz), 4.78, 4.85 (q, AB system, 2H, OCH_2CO, J_{AB} = 15.4 Hz), 6.52, 6.60 (d, 1H, OCHP, J = 10.4 Hz), 6.90–7.36 (m, 6H, ArH); MS *m/z* (%): 388 (M^+, 3.06), 205 (1.88), 189(8.65), 155 (18.06), 141 (20.17), 125

(40.78), 111 (32.17), 93 (100), 63 (88.47). *Anal*. Calcd for $C_{16}H_{18}ClO_5PS$: C, 49.43; H, 4.67. Found: C, 49.56; H, 4.21.

Data for O-methyl methyl 1-(2-chloro-5-methylphenoxyacetoxy)-1-(thioen-2-yl)methylphosphinate (5e). Yellowish oil, yield, 75%; n_D^{20}, 1.5382; IR (KBr, cm^{-1}): ν 3077, 2957, 2853, 1770, 1580, 1456, 1435, 1271, 1180, 1051, 891, 772. ^1H NMR (400 MHz, $CDCl_3$) δ 1.49, 1.53 (d, 3H, CH_3, $J = 13.8$ Hz), 2.27 (s, 3H, $PhCH_3$), 3.70, 3.77 (d, 3H, OCH_3, $J = 12.4$ Hz), 4.78, 4.85 (q, AB system, 2H, OCH_2CO, $J_{AB} = 15.4$ Hz), 6.56, 6.62 (d, 1H, OCHP, $J = 10.4$ Hz), 6.68–7.27 (m, 6H, ArH); MS *m/z* (%): 388 (M^+, 1.77), 205 (3.04), 189(6.17), 155 (20.88), 141 (5.73), 125 (35.97), 111 (49.39), 93 (100), 63 (59.87). *Anal*. Calcd for $C_{16}H_{18}ClO_5PS$: C, 49.43; H, 4.67. Found: C, 49.55; H, 4.66.

Data for O-methyl methyl 1-(2,3-dichlorophenoxyacetoxy)-1-(thioen-2-yl)methylphosphinate (5f). Yellowish oil, yield, 61%; n_D^{20}, 1.5241; IR (KBr, cm^{-1}): ν 3081, 2955, 2852, 1770, 1579, 1458, 1436, 1232, 1178, 1042, 893, 771. ^1H NMR (400 MHz, $CDCl_3$) δ 1.45, 1.50 (d, 3H, CH_3, $J = 14.4$ Hz), 3.67, 3.73 (d, 3H, OCH_3, $J = 12.4$ Hz), 4.81, 4.88 (q, AB system, 2H, OCH_2CO, $J_{AB} = 15.4$ Hz), 6.44, 6.52 (d, 1H, OCHP, $J = 8.8$ Hz), 6.75–7.39 (m, 6H, ArH); MS *m/z* (%): 408 (M^+, 4.68), 315 (2.11), 205 (2.46), 203 (1.17), 189(2.17), 175 (17.02), 161 (3.44), 145 (18.83), 111 (66.65), 93 (100), 63 (43.64). *Anal*. Calcd for $C_{15}H_{15}Cl_2O_5PS$: C, 44.03; H, 3.69. Found: C, 43.72; H, 3.72.

Data for O-methyl methyl 1-(2,4-dichlorophenoxyacetoxy)-1-(thioen-2-yl)methylphosphinate (5g). Yellowish oil, yield, 64%; n_D^{20}, 1.5121; IR (KBr, cm^{-1}): ν 3075, 2923, 2852, 1749, 1584, 1478, 1437, 1246, 1182, 1042, 898, 756. ^1H NMR (400 MHz, $CDCl_3$) δ 1.47, 1.62 (d, 3H, CH_3, $J = 15.6$ Hz), 3.68, 3.74 (d, 3H, OCH_3, $J = 12.4$ Hz), 4.80, 4.87 (q, AB system, 2H, OCH_2CO, $J_{AB} = 15.0$ Hz), 6.49, 6.54 (d, 1H, OCHP, $J = 10.4$ Hz), 6.72–7.40 (m, 6H, ArH); MS *m/z* (%): 408 (M^+, 11.68), 315 (4.96), 309 (6.61), 205 (7.96), 203 (2.51), 189 (9.07), 175 (31.71), 161 (6.46), 145 (32.14), 111 (79.22), 93 (100), 63 (41.93). *Anal*. Calcd for $C_{15}H_{15}Cl_2O_5PS$: C, 44.03; H, 3.69. Found: C, 44.40; H, 3.72.

Data for O-methyl methyl 1-(2,6-dichlorophenoxyacetoxy)-1-(thioen-2-yl)methylphosphinate (5h). Yellowish oil, yield, 63%; n_D^{20}, 1.5186; IR (KBr, cm^{-1}): ν 3076, 2954, 2851, 1775, 1568, 1456, 1439, 1227, 1175, 1042, 895, 786. ^1H NMR (400 MHz, $CDCl_3$) δ 1.51, 1.57 (d, 3H, CH_3, $J = 14.0$ Hz), 3.70, 3.77 (d, 3H, OCH_3, $J = 10.8$ Hz), 4.75, 4.82 (q, AB system, 2H, OCH_2CO, $J_{AB} = 14.8$ Hz), 6.51, 6.60 (d, 1H, OCHP, $J = 7.6$ Hz), 7.03–7.40 (m, 6H, ArH); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 46.1, 46.6; MS *m/z* (%): 408 (M^+, 5.89), 315 (4.97), 205 (6.50), 203 (1.28), 189(5.12), 175 (22.93%), 161 (1.09), 145 (26.87), 111 (74.13), 93 (100), 63 (41.72). *Anal*. Calcd for $C_{15}H_{15}Cl_2O_5PS$: C, 44.03; H, 3.69. Found: C, 43.55; H, 3.74.

Biological activity testing. The preliminary herbicidal activity of title compounds **5a–h** was measured according to the modified method described previously [17]. A set amount of each sample was dissolved in *N*, *N*-dimethylformamide (DMF) to which a drop of an emulsifier, Tween 80, was added. The solution was then diluted with water until it reached the concentrations required. The amounts of DMF and the emulsifier were set as low as possible but still sufficient to make a uniform emulsion even at high concentrations. A solution (5 mL) was placed on a filter paper (diameter = 5.5 cm) in Petri dishes (diameter = 9.0 cm), and 10 rape seeds were placed on the filter paper after soaking in water for 6 h. The Petri dishes were kept at 28°C for 3 days with 10 h of lighting and 14 h in the dark. The experiments were conducted in three replicates. The lengths of roots and shoots were measured after 72 h of treatment, and the growth inhibitory rate related to untreated control was determined.

The fungicidal activity measurement method was adapted from Ref [11]. The phosphonates were dissolved in DMF (0.5–1.0 mL) to the concentration of 1000 mg/L. The solutions (1 mL) were mixed rapidly with thawed potato glucose agar culture medium (9 mL) under 50°C. The mixtures were poured into Petri dishes. After the dishes were cooled, the solidified plates were incubated with 4-mm mycelium disk, inverted and incubated at 28°C for 48 h. Distilled water was used as the blank control. Three replicates of each test were carried out. The mycelial elongationradius (millimeter) of fungi settlements was measured after 48 h of culture. The growth inhibitory rates were calculated with the following equation: $I = [(C - T)/C] \times 100\%$. Here, I is the growth inhibitory rate (%), T is the treatment group fungi settlement radius (millimeter), and C is the radius of the blank control.

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