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Synthesis and bioactivity evaluation of novel benzamide derivatives containing a diphenyl ether moiety

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A series of novel benzamide derivatives with a diphenyl ether moiety were synthesized and evaluated for antifungal and insecticidal activities on the basis of the principle of splicing-up bioactive substructures. Most of the novel benzamide derivatives exhibited moderate to good antifungal activities against five plant pathogen fungi, and compound **17** has shown good antifungal activity against *S. ampelimum* with EC₅₀ values of 0.95 mg/L and is hoped to be a potential lead compound. © Pesticide Science Society of Japan

Keywords: synthesis, benzamide derivatives, antifungal activity, insecticidal activity, diphenyl ether.

Introduction

Agricultural plant diseases and insect pests are two causes of major economic damage to agriculture in the world.^{1,2)} The fungicide market has been generally dominated since the 1970s by several chemical classes of carboxamides, methoxyacrylates, pyrimidinamines, triazoles and so on.^{3–5)} Carboxamide fungicides, such as the commercial fungicides benodanil, mepronil and flutolanil (Fig. 1), have played an important role in the field of agrochemicals,^{6,7)} can inhibit the growth of pathogenic fungi and can cause their eventual death by interfering with the respiration of the pathogen.^{8,9)}

In our previous research, many substituted diphenyl ether derivatives were synthesized and found to have good antimicrobial activities,^{10,11)} and many natural diphenyl ether derivatives also elicited pharmacologically powerful activities,^{12–14)} such as an-

tifungal, antibiotic, antimitotic and immunosuppressive activities.^{15–17)}

Hence, whether the amide derivatives containing a diphenyl ether moiety will have good bioactivities is of interest. To extend our research on developing novel amide derivatives as a fungicide, we have integrated a benzamide scaffold with a diphenyl ether moiety to search for novel agrochemicals with a higher potential of antifungal activities on the basis of the principle of splicing-up bioactive substructures (Fig. 2).

Here we report the synthesis of novel benzamides containing a diphenyl ether moiety and evaluation of antifungal and insecticidal activities.

Materials and Methods

1. General

All the reagents used were commercial and were used without further purification unless otherwise indicated. Analytical thin-layer chromatography and preparative thin-layer chromatography were performed with silica gel plates using silica gel 60 GF254 (Qingdao Haiyang Chemical Co., Ltd., Qingdao, Shandong Province, China). ¹H NMR spectra were obtained in deuteriochloroform solution on a Bruker 400 MHz spectrometer using tetramethylsilane (TMS) as an internal standard and MS data were obtained on a MALDI-TOF/TOF Mass Spectrometer (Bruker).

2. Synthesis

2.1. Synthesis of 2-aryloxyanilines (**4a–4f**)

2.1.1. Synthesis of 1-nitro-2-aryloxybenzenes (**3a–3f**)

KOH (66 mmol) was added to compounds **1a–1f** (66 mmol) at 90°C, and the mixture was stirred for 15 min. Then compound **2** (60 mmol) was added slowly. The mixture was stirred for another 2 hr at 150°C. Finally, the reaction mixture was extracted with ethyl acetate, and the solvent was removed in vacuum to give compounds **3a–3f** in yields of 86–98%.

2.1.2. Synthesis of 2-aryloxyanilines (**4a–4f**)

To a slurry mixture of iron powder (150 mmol) and compounds **3a–3f** (50 mmol) in absolute ethanol (40 mL), a solution of concentrated hydrochloric acid (5 mL) in ethanol (10 mL) was added dropwise for a period of 10 min at 80°C. The resulting mixture was stirred for another 2 hr at 80°C. Finally, the reaction mixture was alkalized by NaOH solution and filtered. The solvent in the collected filtrate was removed in vacuum to give crude products. The crude products were purified by column chromatography on silica gel to give compounds **4a–4f** in yields of 38–51%.^{18,19)}

2.2. General procedure for the preparation of carboxylic acid chloride (**6**)

Thionyl chloride (15 mL) was added to a corresponding acid (10 mmol), and the mixture was refluxed for 1 hr. Excess thionyl

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Fig. 1. Commercial fungicides benodanil, mepronil and flutolanil.

Fig. 2. Design strategy of the target compounds.

chloride was removed in vacuum. The crude product **6** was used in subsequent reactions without further purification.²⁰⁾

2.3. General procedure for the synthesis of benzamide derivatives (**7–19**)

A mixture of NaOH aq. solution (2 mol/L, 20 mL), 1,4-dioxane (2 mL) and compounds **4a–4f** (5 mmol) was dissolved and cooled to 0°C in an ice bath. While stirring the mixture, compound **6** (10 mmol) was added slowly. Afterward, the resulting reaction mixture was stirred for another 2 hr at room temperature. The mixture was then extracted with ethyl acetate, and the solvent was removed in vacuum. The crude products were purified by column chromatography on silica gel to give compounds **7–19** in yields of 45.8–84.6%.^{21,22)} All the compounds are listed in Table 1 and the spectral data of ¹H NMR are as follows.

N-(2-Phenoxyphenyl)-2-methylbenzamide (**7**). Brown solid. Yield: 70.5%. ¹H NMR (400 MHz, CDCl₃): δ 2.48 (3H, s), 6.92 (1H, d, *J*=8.4 Hz), 7.05–7.07 (3H, m), 7.13 (1H, t), 7.19–7.24 (2H, m), 7.29 (2H, d, *J*=8.0 Hz), 7.50 (1H, d, *J*=8.4 Hz), 7.76 (2H, d, *J*=1.6 Hz), 8.45 (1H, s), 8.65 (1H, d, *J*=8.4 Hz); MS *m/z* 304.2 (M+1).

N-[2-(2-Chlorophenoxy)phenyl]-2-methylbenzamide (**8**). Brown solid. Yield: 65.6%. ¹H NMR (400 MHz, CDCl₃): δ 2.48 (3H, s), 6.80 (1H, d, *J*=8.4 Hz), 6.99 (1H, d, *J*=8.4 Hz), 7.03–7.07 (1H, t), 7.19–7.24 (2H, m), 7.29 (2H, d, *J*=8.8 Hz), 7.50 (2H, d, *J*=2.0 Hz), 7.76 (2H, d, *J*=8.4 Hz), 8.49 (1H, s), 8.65 (1H, d, *J*=8.4 Hz); MS *m/z* 338.2 (M+1).

N-[2-(4-Chlorophenoxy)phenyl]-2-methylbenzamide (**9**). Yellow solid. Yield: 57.4%. ¹H NMR (400 MHz, CDCl₃):

δ 2.48 (3H, s), 6.80 (1H, d, *J*=8.4 Hz), 6.96 (1H, d, *J*=8.4 Hz), 7.05–7.07 (1H, t), 7.21–7.24 (2H, m), 7.29 (2H, d, *J*=8.0 Hz), 7.50 (2H, d, *J*=2.4 Hz), 7.76 (2H, d, *J*=8.4 Hz), 8.49 (1H, s), 8.65 (1H, d, *J*=8.8 Hz); MS *m/z* 338.2 (M+1).

N-[2-(2,4-Dichlorophenoxy)phenyl]-2-methylbenzamide (**10**). Brown solid. Yield: 66.4%. ¹H NMR (400 MHz, CDCl₃): δ 2.48 (3H, s), 6.80 (1H, d, *J*=8.4 Hz), 6.99 (1H, d, *J*=8.0 Hz), 7.03–7.07 (1H, t), 7.19–7.24 (2H, m), 7.29 (2H, d, *J*=8.4 Hz), 7.50 (1H, d, *J*=2.4 Hz), 7.76 (2H, d, *J*=8.4 Hz), 8.49 (1H, s), 8.65 (1H, d, *J*=8.4 Hz); MS *m/z* 394.2 (M+Na).

N-[2-(2-Methylphenoxy)phenyl]-2-methylbenzamide (**11**). Yellow solid. Yield: 78.1%. ¹H NMR (400 MHz, CDCl₃): δ 2.26 (3H, s), 2.48 (3H, s), 6.92 (1H, d, *J*=8.4 Hz), 7.02–7.05 (1H, m), 7.19–7.24 (3H, m), 7.30 (1H, m), 7.39 (2H, d, *J*=8.4 Hz), 7.60 (1H, d, *J*=8.8 Hz), 7.72 (2H, d, *J*=8.0 Hz), 8.49 (1H, s), 8.65 (1H, d, *J*=8.8 Hz); MS *m/z* 318.2 (M+1).

N-[2-(4-Methoxyphenoxy)phenyl]-2-methylbenzamide (**12**). Yellow solid. Yield: 84.6%. ¹H NMR (400 MHz, CDCl₃): δ 2.34 (3H, s), 2.48 (3H, s), 6.92 (1H, d, *J*=8.4 Hz), 7.06 (1H, m), 7.21–7.24 (3H, m), 7.30 (1H, m), 7.39 (2H, d, *J*=8.4 Hz), 7.60 (1H, d, *J*=8.0 Hz), 7.73–7.77 (2H, d, *J*=8.4 Hz), 8.49 (1H, s), 8.65 (1H, d, *J*=8.4 Hz); MS *m/z* 318.3 (M+1).

N-[2-(2,4-Dichlorophenoxy)phenyl]-2-nitrobenzamide (**13**). Gray solid. Yield: 45.8%. ¹H NMR (400 MHz, CDCl₃): δ 6.80 (1H, d, *J*=8.4 Hz), 6.99 (1H, d, *J*=8.0 Hz), 7.03–7.07 (1H, t), 7.31–7.34 (2H, m), 7.41 (2H, d, *J*=8.0 Hz), 7.58 (1H, d, *J*=2.0 Hz), 7.86 (2H, d, *J*=8.4 Hz), 8.45 (1H, s), 8.65 (1H, d, *J*=8.8 Hz); MS *m/z* 425.0 (M+Na).

N-(2-Phenoxyphenyl)-2-chlorobenzamide (**14**). Yellow solid. Yield: 62.7%. ¹H NMR (400 MHz, CDCl₃): δ 6.85 (1H, d, *J*=8.4 Hz), 6.99 (1H, d, *J*=8.4 Hz), 7.05–7.09 (3H, m), 7.15–7.18 (2H, m), 7.27 (2H, d, *J*=8.4 Hz), 7.48 (1H, d, *J*=2.0 Hz), 7.71 (2H, d, *J*=8.0 Hz), 8.50 (1H, s), 8.63 (1H, d, *J*=8.8 Hz); MS *m/z* 324.2 (M+1).

N-[2-(2-Chlorophenoxy)phenyl]-2-chlorobenzamide (**15**). Pale yellow solid. Yield: 75.8%. ¹H NMR (400 MHz, CDCl₃): δ 6.85 (1H, d, *J*=8.4 Hz), 6.99 (1H, d, *J*=8.4 Hz), 7.05–7.09 (1H, m), 7.10–7.13 (1H, t), 7.15–7.18 (2H, m), 7.26 (2H, d, *J*=8.4 Hz), 7.48 (1H, d, *J*=2.0 Hz), 7.71 (2H, d, *J*=8.4 Hz), 8.50 (1H, s), 8.63 (1H, d, *J*=8.8 Hz); MS *m/z* 358.0 (M+1).

N-[2-(4-Chlorophenoxy)phenyl]-2-chlorobenzamide (**16**). Pale yellow solid. Yield: 73.2%. ¹H NMR (400 MHz, CDCl₃): δ 6.90 (1H, d, *J*=8.4 Hz), 7.00 (1H, d, *J*=8.4 Hz), 7.04–7.06 (1H, m), 7.13 (1H, t), 7.18–7.21 (2H, m), 7.29 (2H, d, *J*=8.4 Hz), 7.50 (1H, d, *J*=2.4 Hz), 7.71 (2H, d, *J*=8.0 Hz), 8.48 (1H, s), 8.65 (1H, d, *J*=8.8 Hz); MS *m/z* 358.0 (M+1).

Fig. 3. Synthesis of 2-aminoaryloxybenzenes **4a–4f**. Fig. 4. Synthesis of target compounds **7–19**.Table 1. Synthesized novel benzamide derivatives **7–20**

Compound	R ₁	R ₂	Compound	R ₁	R ₂
7	CH ₃	H	14	Cl	H
8	CH ₃	2-Cl	15	Cl	2-Cl
9	CH ₃	4-Cl	16	Cl	4-Cl
10	CH ₃	2,4-Cl ₂	17	Cl	2,4-Cl ₂
11	CH ₃	2-CH ₃	18	Cl	2-CH ₃
12	CH ₃	4-CH ₃	19	Cl	4-CH ₃
13	NO ₂	2,4-Cl ₂	20	4-CH ₃	2,4-Cl ₂

N-[2-(2,4-Dichlorophenoxy)phenyl]-2-chlorobenzamide (**17**). Yellow solid. Yield: 65.6%. ¹H NMR (400 MHz, CDCl₃): δ 6.85 (1H, d, *J*=8.4 Hz), 6.99 (1H, d, *J*=8.4 Hz), 7.05 (1H, t), 7.15–7.18 (2H, m), 7.26 (2H, d, *J*=8.4 Hz), 7.48 (1H, d, *J*=2.4 Hz), 7.71 (2H, d, *J*=8.4 Hz), 8.50 (1H, s), 8.63 (1H, d, *J*=8.8 Hz); MS *m/z* 391.2 (M+1).

N-[2-(2-Methylphenoxy)phenyl]-2-chlorobenzamide (**18**). Yellow solid. Yield: 59.2%. ¹H NMR (400 MHz, CDCl₃): δ 2.26 (3H, s), 6.85 (1H, d, *J*=8.4 Hz), 6.97 (1H, d, *J*=8.4 Hz), 7.05–7.09 (2H, m), 7.15–7.18 (2H, m), 7.25–7.28 (2H, d, 8.8 Hz), 7.48 (1H, d, *J*=2.4 Hz), 7.71 (2H, d, *J*=8.8 Hz), 8.50 (1H, s), 8.63 (1H, d, *J*=8.4 Hz); MS *m/z* 338.0 (M+1).

N-[2-(4-Methylphenoxy)phenyl]-2-chlorobenzamide (**19**). Yellow solid. Yield: 68.5%. ¹H NMR (400 MHz, CDCl₃): δ 2.36 (3H, s), 6.92 (1H, d, *J*=8.4 Hz), 7.06 (1H, m), 7.21–7.24 (3H, m), 7.28 (1H, m), 7.30–7.34 (2H, d, *J*=8.4 Hz), 7.50 (1H, d, *J*=2.4 Hz), 7.73–7.77 (2H, d, *J*=8.4 Hz), 8.49 (1H, s), 8.65 (1H, d, *J*=8.8 Hz); MS *m/z* 338.0 (M+1).

N-[2-(2,4-Dichlorophenoxy)phenyl]-4-methylbenzamide (**20**). Yellow solid. yield: 57.3%. ¹H NMR (400 MHz, CDCl₃): δ 2.42 (3H, s), 6.80 (1H, d, *J*=8.4 Hz), 6.99 (1H, d, *J*=8.8 Hz), 7.03–7.07 (2H, t), 7.19–7.24 (1H, m), 7.29 (2H, d, *J*=8.0 Hz), 7.50 (1H, d, *J*=2.4 Hz), 7.76 (2H, d, *J*=8.4 Hz), 8.49 (1H, s), 8.63 (1H, d, *J*=8.4 Hz); MS *m/z* 372.2 (M+1).

3. Biological assay

3.1. Assay of antifungal activity

For preliminary evaluation of compounds **7–20** the antifungal tests of *Rhizoctonia solani*, *Gibberella zeae*, *Valsa mali*, *Botrytis cinerea* and *Sphaceloma ampelimum* were carried out using the plate growth rate method.²³⁾ The fungi were obtained from the Institute of Pesticide and Crop Protection, Sichuan University.

The tested compounds were dissolved in acetone and added to a sterile agarized Czapek-Dox medium at 45°C. In primary

screenings compounds were used at a concentration of 20 mg/L. The control sample contained only one equivalent of acetone. The media were poured onto 8 cm Petri dishes (10 mL for each dish) and after 2 days were inoculated with 4 mm Potato Dextrose Agar (medium) discs of overgrown mycelium. The Petri dishes were incubated at 26°C in the dark. Two or 7 days after inoculation the diameters of the cultures were measured. The percentage of inhibition of fungal growth was determined by comparison between the development of fungi colonized on media containing compounds and on the control. Carbendazim and boscalid, the commercial fungicides, were used as a positive control. Three replicates of each test were carried out and results were examined statistically.

3.2. Assay of insecticidal activity

Insecticidal activity of compounds **7–20** against oriental migratory locusts was tested by the dipping method.²⁴⁾ The results were compared with the activity of a commercial insecticide avermectin.

Fifty milligrams of the sample was weighed and dissolved in 1 mL of acetone. Then a 49 mL mixture of 1 % Tween 80 and water was added into the solution and the mixture (50 mL, 1000 mg/L) was obtained. In the meantime, a mixture of acetone : 1 % Tween 80 solution = 1 : 49 was used as a blank control solution. Fresh rice leaf (10 cm in length) made by punch was immersed into the prepared test solution for 5 sec, then it was placed into the bag and 30 healthy locusts were caught into the bag. Finally, the bag was placed in a constant-temperature room (28°C) and observed. The number of dead and live locusts was counted every 24 hr, and after 3 days, a corrected mortality rate was calculated.

Results and Discussion

1. Chemistry

The synthesis of intermediate and target compounds was performed as illustrated in Fig. 3, Fig. 4 and Table 1. To synthesize target compounds **7–19**, the intermediates **4a–4f** were prepared

in two steps. First, compound **2** was reacted with compounds **1a–1f** under KOH by substitution reaction to produce compounds **3a–3f**. Then compounds **3a–3f** were reduced by the combined action of Fe and HCl to obtain compounds **4a–4f**.

Meanwhile compound **5** was reacted with SOCl₂ to obtain compound **6**. Finally, compound **6** was reacted with compounds **4a–4f** by amidation to gain target compounds **7–19**.

2. Biological activity

2.1. In vitro antifungal activity

The results of the antifungal activity of compounds **7–20**, boscalid and carbendazim at 20 mg/L against *R. solani*, *G. zeae*, *V. mali*, *B. cirerea* and *S. ampelimum* are listed in Table 2, in which the antifungal activities are expressed as inhibition of growth. We compared the growth rate of fungi on a medium containing a vehicle with the growth rate of fungi on a pure medium. The result indicated that the vehicle for compounds showed no visible antifungal activity.

The results in Table 2 show that target compounds **7–19** were active against nearly five fungi at 20 mg/L except for compound **13**. Most of compounds **7–19** showed very strong antifungal activities against *R. solani* and *S. ampelimum*. Specifically compound **17** displayed stronger antifungal activities against *S. ampelimum* than other compounds and the inhibition of growth of compound **17** reached 100%.

By comparing the molecular structures of compound **13** with those of other compounds, we could see that the R₁ group of compound **13** was a nitro group (a strongly electron-withdrawing group), however, the R₁ group of other compounds was a methyl group (an electron-donating group) or a chlorine atom (a weakly electron-withdrawing group).

Meanwhile we discovered that when the R₁ group was a methyl group, compound **8**, **9** or **10** containing an R₂ group that was a chlorine atom shown better antifungal activities than compound **11** or **12** containing an R₂ group that was a methyl group. For example, the inhibition of **8** against *S. ampelimum* was 84.64%, but the inhibition of **11** was only 66.35%. In addition, when the R₁ group of compound **15**, **16** or **17** was a chlorine atom, compound **17** with two chlorine atoms in diphenyl ether moiety showed better antifungal activities than compounds **15** and **16** with one chlorine atom.

In addition, we synthesized compound **20** having a methyl group at the 4-position (Fig. 5). By comparing the antifungal activities of compounds **10** and **20**, we could clearly see that compound **10** displayed better antifungal activities than compound **20**. This result is also in accord with data reported before that ortho methyl group at the amide group enhanced the compound's antifungal activities.²⁵⁾

To analyze the antifungal activities of our compounds, compounds **9**, **16** and **17** with stronger antifungal activities against *S. ampelimum* were selected for further research and their EC₅₀ values are listed in Table 3.

Fig. 5. Structure of target compound **20**.

Table 2. Antifungal activities of benzamide derivatives **7–20** at 20 mg/L

Compound	Inhibition of growth (%)				
	<i>R. solani</i>	<i>G. zeae</i>	<i>V. mali</i>	<i>B. cirerea</i>	<i>S. ampelimum</i>
7	60.97	53.12	35.80	68.33	49.20
8	74.82	46.97	68.20	54.20	84.64
9	91.00	65.65	60.93	48.70	86.56
10	89.20	52.70	74.21	66.67	86.95
11	65.88	59.80	53.33	65.00	66.35
12	76.71	40.33	44.20	58.33	61.85
13	7.50	3.71	12.01	5.51	3.39
14	71.61	17.90	18.94	4.72	75.00
15	69.97	33.21	30.08	13.33	80.00
16	72.19	49.10	41.40	21.01	93.33
17	77.38	27.42	34.12	12.58	100
18	53.33	22.00	11.93	5.51	63.33
19	65.51	25.00	24.28	7.50	69.20
20	15.75	1.61	8.85	—	12.93
Carbendazim	94.00	91.10	100	49.50	38.00
Boscalid	88.20	11.21	13.25	74.69	100

Table 3. EC₅₀ values of compounds **9**, **16** and **17**

Compound	<i>S. ampelimum</i>
	EC ₅₀ (mg/L)
9	3.19
16	1.70
17	0.95
Carbendazim	33.54
Boscalid	0.740

Table 4. Insecticidal activities of compounds **7–20**

Compound	Corrected mortality rate (%)		Compound	Corrected mortality rate (%)	
	500 mg/L	1000 mg/L		500 mg/L	1000 mg/L
7	8	36	15	8	36
8	15	40	16	10	38
9	6	38	17	—	18
10	2	20	18	—	20
11	8	36	19	12	40
12	10	42	20	6	36
13	—	25	Avermectin (100mg/L)		100
14	—	25			

As shown in Table 3, the three compounds tested had higher antifungal activities against *S. ampelimum*. Additionally, each EC₅₀ value of the three compounds was much less than that of carbendazim and was close to that of boscalid. Compound **17** had the best antifungal activity against *S. ampelimum* and its EC₅₀ value reached 0.95 mg/L. It is possible that compound **17** will become a potential lead compound for further structural optimization.

2.2. In vivo insecticidal activity

Because amide derivatives are also a kind of important insecticide,²⁶⁾ in order to expand use of target compounds we tried to test their insecticidal activity and chose an easily obtained oriental migratory locust as a test object.

The insecticidal activity of compounds **7–20** (500 mg/L and 1000 mg/L) and avermectin (100 mg/L) against the oriental migratory locust was studied. The corrected mortality rates for the compounds are listed in Table 4.

As shown in Table 4, compounds **7–20** had some insecticidal activities against the oriental migratory locust at 500 mg/L and 1000 mg/L. However, their corrected mortality rates were lower than that of avermectin. It is observed that their insecticidal activities against locusts were poor, and their molecular structures need to be further optimized.

Conclusion

In summary, 14 novel benzamide derivatives **7–20** have been synthesized and evaluated for their antifungal activity against

five plant pathogenic fungi (*R. solani*, *G. zeae*, *V. mali*, *B. cirerea* and *S. ampelimum*) and insecticidal activity against the oriental migratory locust. The results showed that some of the synthesized compounds exhibited strongly antifungal activities at 20 mg/L. Most of benzamide derivatives showed excellent activities against *R. solani* and *S. ampelimum*. Compound **17** showed the strongest activity against *S. ampelimum* (EC₅₀=0.95 mg/L), close to the activity of boscalid. Furthermore, these preliminary results are promising and beneficial for further studies in developing new and more effective fungicides in the agrochemical field. Further structural modification and biological evaluation of our compounds are ongoing in our laboratory.

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