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Synthesis of Novel 6-Aryloxy-4-chloro-2-phenylpyrimidines as Fungicides and Herbicide Safeners

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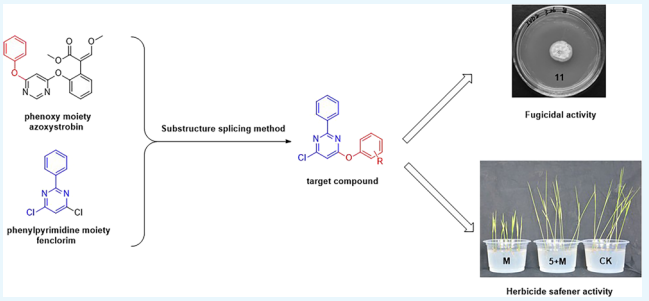
ABSTRACT: Fenclorim is a commercial herbicide safener with fungicidal activity used for chloroacetanilide herbicides, which might be suitable as a lead compound for screening novel fungicides. However, little has been reported so far on the structure−activity relationship of fungicidal activities of fenclorim or its analogues. Here, a series of 4-chloro-6-substituted phenoxy-2-phenylpyrimidine derivatives was synthesized by a substructure splicing route using fenclorim as a lead compound. The structures of synthesized derivatives were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. Their fungicidal and herbicide safening activities were then evaluated. The results revealed that compound **11** had the best fungicidal activity against *Sclerotinia sclerotiorum* and *Thanatephorus cucumeris*, which was better than that of the control pyrimethanil. Moreover, compounds **3**, **5**, and **25** exhibited excellent safening activities against fresh weight, plant height, and root length, respectively. Such activities were significantly improved when compared to fenclorim. In summary, these findings look promising for the preparation of new fungicides and herbicide safeners based on the structure of fenclorim.



1. INTRODUCTION

Pyrimidine derivatives are well known for their pharmacological activities, including antiviral,[1] anticancer,[2−4] anti-inflammatory,[5] acaricidal,[6] insecticidal,[7] herbicidal,[8] herbicide safener,[9] and even fungicidal activities.[10−12] Commonly used commercial pyrimidine fungicides include diflumetorim (Figure 1a), pyrimethanil (Figure 1b), and azoxystrobin (Figure 1c). These molecules can be employed for efficient control over plant pathogenic fungi, such as ascomycetes, basidiomycetes, and deuteromycetes, often found in vegetables, fruits, and grain crops.[10,13−17] However, the widespread application of some commercial pyrimidine fungicide agents led to the development of resistance.[18−20] For example, the destructive plant pathogen *Phytophthora capsici* has developed great resistance to azoxystrobin in southern China.[21] Hence, the design and development of novel pyrimidine derivatives with promising fungicidal activities are required.

Azoxystrobin, which is a famous synthetic methoxyacrylate fungicide, was first discovered by Imperial Chemical Industries (ICI).[22] Azoxystrobin binds to the Q_0 site of the cytochrome *bc*1 enzyme complex to block electron transfer and freeze adenosine triphosphate production, causing the mitochondrial respiration of pathogenic fungi to be hindered.[23] Azoxystrobin is primarily composed of two substituted phenoxy moieties, a pyrimidinyl moiety and a methyl (*E*)-*β*-methoxyacrylate moiety. The reported structure−activity relationship (SAR) of fungicidal activities of azoxystrobin indicates that a methoxyacrylate moiety (Figure 1c, in pink) and a phenoxy moiety at the sixth position on the pyrimidine ring in azoxystrobin (Figure 1c, in red) are active substructures.[24,25] The methoxyacrylate moiety in azoxystrobin is often used as an active group in designing novel fungicides, while the phenoxy moiety is not.[26−30]

Herbicides are observed to cause phytotoxicity toward crops when used for controlling weeds under field conditions.[31] Herbicide safeners are compounds that selectively protect crops from herbicide damage without reducing the herbicidal efficiency on target weed species.[32,33] In 1970, the Gulf Oil Company developed the first commercialized herbicide safener, 1,8-naphthalic anhydride, to protect maize from thiocarbamate herbicide injury.[34] After that, about 20 commercial herbicide safeners, for example, dichlormid, benoxacar, cloquintocet-mexyl, and flurazole, have been launched in the market to protect crops.[18] The main safener mechanism could be ascribed to the enhancement of the detoxifying enzymes [*e.g.*, glutathione *S*-transferase (GST), cytochrome P450 oxidases, UDP-glucuronosyltransferases, and peroxidase].[35−37]

Among all commercial herbicide safeners, fenclorim (4,6-dichloro-2-phenyl-pyrimidine) is a pyrimidine-type herbicide

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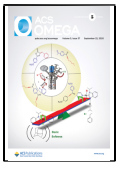

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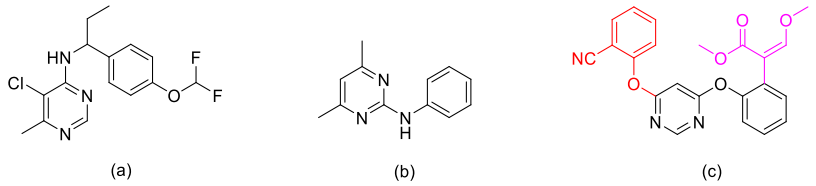
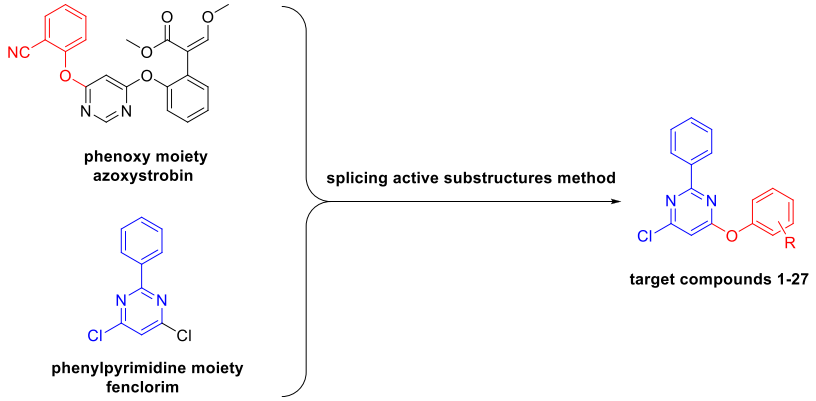
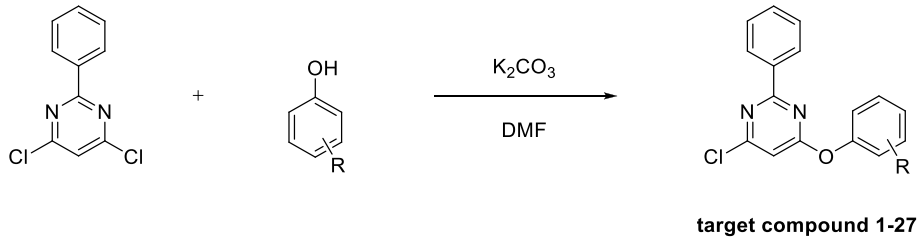


Figure 1. Chemical structures of (a) diflumetorim, (b) pyrimethanil, and (c) azoxystrobin.

Scheme 1. Design Strategy of Target Compounds 1−27



Scheme 2. Synthesis Route of Target Compounds 1−27



1: R = -H
2: R = 2-CH_3
3: R = 3-CH_3
4: R = 4-CH_3
5: R = 2-OCH_3
6: R = 3-OCH_3
7: R = 4-OCH_3
8: R = 2-$COOCH_3$
9: R = 3-$COOCH_3$
10: R = 4-$COOCH_3$
11: R = 2-Cl
12: R = 4-Cl
13: R = 2-Br
14: R = 3-Br
15: R = 4-Br
16: R = 2-F
17: R = 3-F
18: R = 4-F
19: R = 2-CN
20: R = 3-CN
21: R = 4-CN
22: R = 2-CF_3
23: R = 3-CF_3
24: R = 4-CF_3
25: R = 3,5-CH_3
26: R = 3,5-OCH_3
27: R = 3,5-CN

safener used for chloroacetanilide herbicides.[38,39] When fenclorim is soaked with rice seeds in pre-sowing applications or combination with chloroacetanilide herbicides on rice seedlings, it improves the tolerance of rice seedlings to chloroacetanilide herbicides. Fenclorim detoxifies herbicides by improving the GST expression, catalyzing the conjugation of chloroacetanilide herbicides with glutathione in rice.[40,41] We previously evaluated the fungicide activity of fenclorim and proved it could be used as a fungicide-lead compound as this compound showed certain fungicide activity toward fungi such as *Sclerotinia sclerotiorum*, *Fusarium oxysporum*, *Fusarium graminearum*, and *Thanatephorus cucumeris*.[42,43] However, to the best of our knowledge, only a few reports have so far described the SAR of fungicidal activities of fenclorim or its analogues, indicating that more studies are needed.[44] Besides, it should be noted that these research studies revealed that strategic structural modifications of the chemical skeleton of fenclorim at the position of chlorine atom on the pyrimidine ring can yield novel molecules with new interesting properties.[45]

The splicing active substructures method (a combination of the active groups in two different high active compounds to construct a new structure with potential biological activities) is commonly used for the preparation of novel pesticides.[46−51] Hence, to screen for fungicides with high activities, a series of 4-chloro-6-phenoxy-2-phenylpyrimidine analogues was synthesized in this study by combining the phenoxy group in azoxystrobin and phenylpyrimidine moieties in fenclorim *via* this method (Scheme 1). The structures of the synthesized compounds were identified by ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectroscopy (HRMS). The fungicidal activities of synthesized analogues were then evaluated, and pyrimethanil, a pyrimidine-type fungicide, was used as a positive control. Since these compounds showed similar structures as fenclorim, the herbicide safening activities were also tested. The data looked promising and would provide guidance for the discovery of novel fungicides and herbicide safeners based on fenclorim structure.

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2. RESULTS AND DISCUSSION

2.1. Synthesis and Characterization of Target Compounds 1−27. Target compounds **1**−**27** were prepared by the synthetic route outlined in Scheme 2. Compounds **1**−**27** were synthesized in *N*,*N*-dimethylformamide (DMF) by one-pot reactions of fenclorim with substituted phenols in 32−75% yields in the presence of K_2CO_3 as a base.[52]

The chemical structures of target compounds were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopies. Here, compound **11** was selected as the model compound. The ^{1}H NMR spectrum of compound **11** clearly showed the hydrogen proton of pyrimidine ring as a singlet at 6.84 ppm along with protons of the phenyl ring and phenoxy group as triplets at 8.21 and 8.18 ppm and multiplicities at 7.52−7.55, 7.35−7.48, and 7.29−7.32 ppm. The ^{13}C NMR spectrum of compound **11** showed the resonance of the pyrimidine ring at 104.8, 162.2, 164.8, and 169.5 ppm, while those of the phenyl ring and phenoxy group were recorded at 123.8−148.3 ppm. Moreover, HRMS data of compound **11** agreed well with the calculated data based on chemical formula.

2.2. Crystal Structure of Compound 11. The chemical structure of the representative compound **11** was further identified by X-ray single crystallography. Selected and refined crystal data of compound **11** are listed in Table S1. The crystal structure and crystal packing diagrams of compound **11** are presented in Figures 2 and S1, and selected molecular structure parameters are provided in Table S2.

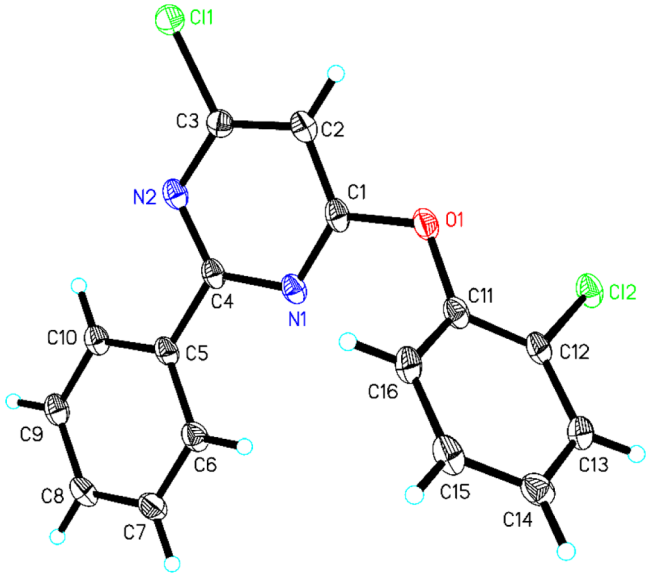

Figure 2. Crystal structure of compound **11**.

As shown in Figure 2, the skeleton of 6-aryloxy-4-chloro-2-phenylpyrimidines was constructed by two benzene rings and a chlorine-substituted pyrimidine ring. Substituted benzene ring connected to pyrimidine through an oxygen atom (Figure 2). Furthermore, the bonds N(2)−C(3) (1.328(6) Å), N(1)−C(4) (1.351(6) Å), N(2)−C(4) (1.339(7) Å), and N(1)−C(1) (1.321(6) Å) in the pyrimidine ring were similar to bonds N−C (1.307−1.366 Å) in pyrimidine reported previously.[53−55] The bonds in two phenyl rings, such as C(5)−C(10) (1.397(7) Å), C(6)−C(7) (1.383(7) Å), C(5)−C(6) (1.393(7) Å), C(11)−C(12) (1.383(7) Å), C(12)−C(13) (1.387(7) Å), and C(13)−C(14) (1.380(7) Å) were also similar to the reported C−C bonds in phenyl (1.359−1.399 Å).[56−58] The chloro-substituted benzene ring was connected to the phenylpyrimidine ring through an oxygen atom with a C(1)−O(1)−C(11) bond angle of 119.3(4)°.

2.3. Evaluation of Fungicidal Activities. *S. sclerotiorum*, *T. cucumeris*, *F. graminearum*, and *F. oxysporum* are pervasive plant pathogenic fungal species, which cause great damage to the production of crop plants.[59−62] Hence, we investigated the fungicidal activities of target compounds **1**−**27** toward these fungi in primary screen (50 mg/L) and pyrimethanil, a pyrimidine-type fungicide for controlling fungus such as *S. sclerotiorum*,[42,63] was used as a positive control, and the results are listed in Table 1. It was found that the fungicidal activities of target compounds against *S. sclerotiorum* (89−97%) and *T. cucumeris* (50−89%) were better than those against *F. graminearu* (7−42%) and *F. oxysporum* (7−60%). All target compounds **1**−**27** showed excellent activities against *S. sclerotiorum*, comparable to the positive controls fenclorim and pyrimethanil. The target compounds displayed lower fungicidal activities against *T. cucumeris* when compared to that of pyrimethanil in the primary screen test but exhibited higher fungicidal activities compared to that of fenclorim. In particular, compound **1** with no substitution in the phenoxy group showed the best fungicidal activity against *T. cucumeris* (89%). Compounds **1**−**7**, **11**−**13**, **15**−**17**, **18**−**19**, and **22** exhibited similar patterns of fungicidal activities against *F. oxysporum* when compared to their fungicidal activities against *F. graminearu*. Among all compounds, **1** and **16** had the highest activities against *F. graminearu* (42%) and *F. oxysporum* (60%), respectively. Fenclorim exhibited poor activity against *F. oxysporum* (26%), and pyrimethanil did not show good activity against *F. graminearu* (27%) and *F. oxysporum* (23%).

Based on the analysis of the experimental results, the SAR for fungicidal activities of target compounds were determined as follows: (1) the target compounds with substituents on phenoxy moiety exhibited similar excellent activities against *S. sclerotiorum*, indicating that insertion of phenoxy moiety into the structure of fenclorim might be beneficial for the enhancement of fungicidal activities against *S. sclerotiorum*; (2) substituents on phenoxy moiety were generally more active against *T. cucumeris* at ortho-position than at para- and meta-positions. With the exception of chlorine atoms, methyl and methoxycarbonyl-substituted compounds, activity against *T. cucumeris* was lower with substituents at meta-position (**6**, **14**, **17**, **20**, and **23**); (3) comparing compounds **2**−**7** and **16**−**24**, electron-donating substituents (methyl and methoxy groups) on phenoxy moiety were more active at ortho-position than para- and meta-positions against *F. graminearu* and *F. oxysporum*. On the other hand, when the substituent groups were fluorine atoms and cyano and trifluoromethyl groups, the activity against *F. graminearu* showed the following pattern: ortho-position > meta-position > para-position. (4) Comparing compounds **25**−**27**, there was no significant difference in the fungicidal activities against all four pathogenic bacteria between monosubstituted and disubstituted compounds.

To further investigate the fungicidal activities of the as-prepared compounds, median effective concentrations (EC_{50} values) of the control and the compounds with high activities (inhibitory rate > 80%) against *S. slerotiorum* and *T. cucumeris*, which were chosen as representative plant pathogens, were compared, and the data are listed in Tables 2 and 3. As shown in Table 2, the tested compounds (**1**−**27** and pyrimethanil)

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ACS Omega 2020, 5, 23996−24004

Table 1. Fungicidal Activities of Target Compounds 1−27 against Four Pathogenic Bacteria (50 mg/L)[a]

		inhibitory rate (%)			
compd	R	*S. sclerotiorum*	*T. cucumeris*	*F. oxysporum*	*F. gaminearu*
1	−H	95 ± 0	89 ± 2	42 ± 2	48 ± 1
2	2-CH_3	93 ± 1	84 ± 1	26 ± 2	46 ± 1
3	3-CH_3	89 ± 2	83 ± 1	11 ± 2	35 ± 3
4	4-CH_3	95 ± 1	78 ± 0	11 ± 2	44 ± 1
5	2-OCH_3	92 ± 1	80 ± 2	26 ± 1	40 ± 0
6	3-OCH_3	96 ± 1	74 ± 0	15 ± 2	27 ± 1
7	4-OCH_3	95 ± 0	75 ± 8	25 ± 2	32 ± 1
8	2-$COOCH_3$	89 ± 1	70 ± 1	9 ± 2	19 ± 1
9	3-$COOCH_3$	94 ± 1	66 ± 4	10 ± 1	15 ± 2
10	4-$COOCH_3$	93 ± 0	54 ± 2	20 ± 4	11 ± 3
11	2-Cl	96 ± 0	85 ± 2	27 ± 2	44 ± 3
12	4-Cl	92 ± 1	71 ± 2	19 ± 3	25 ± 0
13	2-Br	93 ± 0	81 ± 1	25 ± 1	35 ± 1
14	3-Br	95 ± 0	74 ± 2	16 ± 1	23 ± 2
15	4-Br	94 ± 0	77 ± 2	7 ± 2	27 ± 1
16	2-F	95 ± 1	86 ± 2	22 ± 2	60 ± 1
17	3-F	97 ± 1	84 ± 1	21 ± 1	45 ± 1
18	4-F	95 ± 1	86 ± 1	18 ± 1	37 ± 2
19	2-CN	96 ± 1	71 ± 3	15 ± 3	25 ± 2
20	3-CN	93 ± 1	50 ± 1	16 ± 1	12 ± 3
21	4-CN	95 ± 1	52 ± 3	17 ± 3	7 ± 1
22	2-CF_3	95 ± 1	76 ± 1	20 ± 1	38 ± 0
23	3-CF_3	95 ± 1	65 ± 2	14 ± 2	19 ± 3
24	4-CF_3	95 ± 1	69 ± 3	11 ± 3	14 ± 1
25	3,5-CH_3	94 ± 0	67 ± 2	14 ± 3	17 ± 3
26	3,5-OCH_3	95 ± 1	61 ± 3	13 ± 4	19 ± 1
27	3,5-CN	95 ± 1	61 ± 3	20 ± 1	11 ± 1
fenclorim		88 ± 1	40 ± 0	26 ± 1	75 ± 2
pyrimethanil		91 ± 3	98 ± 0	27 ± 0	23 ± 0

[a]*S. sclerotiorum* means *Sclerotinia sclerotiorum*; *T. cucumeris* means *Thanatephorus cucumeris*; *F. graminearum* means *Fusarium graminearum*. *F. oxysporum* means *Fusarium oxysporum*. The experiments were repeated three times to ensure better reproducibility.

displayed moderate to excellent fungicidal activity with EC_{50} values varying from 0.93 to 33.17 mg/L. Compound **2**, **4**, **6**, **11**, **17**, and **19** had better fungicidal activity against *S. sclerotiorum* than that of both fenclorin and commercial fungicide pyrimethanil, and compound **11** exhibited the best fungicidal activity. In general, ortho substitution is better than meta and para: except for ester and fluorine miniseries where meta is better than para and ortho.

All target compounds with high activity against *S. sclerotiorum* demonstrated nearly complete inhibition of *S. sclerotiorum* based on the results of the preliminary screening. Moreover, considering the EC_{50} test results, some of these compounds showed stronger fungicidal activity than pyrimethanil. These indicated that they might be potential candidates for controlling *S. sclerotiorum* and useful lead compounds to design new fungicides. Hence, more compounds of this series will be synthesized, and their EC_{50} values against *S. sclerotiorum* will be tested to be used for building a quantitative SAR model in the future together with those reported in this article.

Also, compounds **1**−**3**, **11**, **13**, **16**−**18**, and pyrimethanil exhibited moderate to good fungicidal activities against *T. cucumeris* with EC_{50} values ranging from 3.33 to 25.25 mg/L (Table 3). Compounds **11** and **18** showed better fungicidal activities than pyrimethanil, and moreover, the fungicidal activities of compound **11** against *S. slerotiorum* and *T. cucumeris* were the best of the series, thus being the most interesting compound of the series. The results of fungicidal activities above also revealed that a combination of substituted phenoxy groups with phenylpyrimidine moiety in fenclorim may form novel pyrimidine-type fungicides with improved activities against the tested plant pathogens than commercial fungicide pyrimethanil.

2.4. Evaluation of Herbicide Safening Activities. The effects of target compounds **1**−**27** (1 mg/L) on the growth of rice plant height, root length, and fresh weight were evaluated, and the data are depicted in Table 4. Note that the results were represented as the relative value of plant height, root length, and fresh weight. Compared to nontreated controls, the relative changes in growth indices of compounds **1**−**27** varied from 92 to 99% for plant height, 91−100% for root length, and 92−100% for fresh weight. For security testing of rice plants, these data indicated that compounds **1**−**27** had very low inhibitory effects on the growth of rice seedlings.

The herbicide safening activities of target compounds **1**−**27** were also evaluated due to their similar structures as that of fenclorim. Table 5 compares the relative values of plant height, root length, and fresh weight. The biological activities indicated that the growth of height (51%), root length (48%), and fresh weight (65%) of the rice plant was significantly inhibited by metolachlor (**M**, 0.25 μM). By combining target compounds **1**−**27** with **M**, the rice plant injury from **M** was alleviated. The relative values of plant height under combined treatment with compounds **1**−**27** and **M** varied from 60 to 92%, where the highest value (92% for

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Table 2. Median Effective Concentrations (EC_{50} Values) of Compound 1−27 and Pyrimethanil with High Activities against *S. sclerotiorum*[a]

compd	regression equation	EC_{50} (mg/L)	R^2
1	$y = 4.7129 + 1.3468x$	1.63	0.9658
2	$y = 4.4548 + 1.1389x$	2.93	0.9459
3	$y = 3.2423 + 1.7133x$	10.61	0.9887
4	$y = 4.6088 + 1.6642x$	1.72	0.9684
5	$y = 3.4569 + 1.9498x$	6.19	0.9837
6	$y = 3.7257 + 3.6264x$	2.25	0.8736
7	$y = 3.4406 + 2.3434x$	4.63	0.9921
8	$y = 2.6144 + 2.3831x$	10.02	0.9671
9	$y = 3.3492 + 2.0168x$	6.58	0.9926
10	$y = 3.0060 + 2.2181x$	7.92	0.9954
11	$y = 5.0418 + 1.3366x$	0.93	0.9841
12	$y = 3.3324 + 1.9899x$	6.89	0.9935
13	$y = 3.0490 + 2.1184x$	8.34	0.9851
14	$y = 0.1807 + 4.4782x$	11.92	0.9316
15	$y = 1.4425 + 5.3152x$	16.30	0.9556
16	$y = 1.4142 + 4.8817x$	20.60	0.9666
17	$y = 3.9169 + 3.5435x$	2.02	0.8825
18	$y = 0.3326 + 4.1711x$	13.15	0.9096
19	$y = 3.7449 + 4.7318x$	1.84	0.9544
20	$y = 3.1576 + 2.3194x$	6.23	0.9820
21	$y = -1.3728 + 5.4696x$	14.63	0.9370
22	$y = 0.2663 + 4.3309x$	12.39	0.9189
23	$y = 0.2400 + 4.0280x$	15.20	0.9194
24	$y = 1.8941 + 4.5332x$	33.17	0.8941
25	$y = -1.4069 + 5.1238x$	17.80	0.9576
26	$y = -2.0993 + 5.1383x$	24.08	0.8887
27	$y = -0.1213 + 5.3025x$	9.24	0.9613
Fenclorim	$y = 3.3612 + 1.1608x$	25.81	0.0945
Pyrimethanil	$y = 4.5148 + 1.2897x$	2.38	0.9721

[a]The experiments were carried out three times to ensure better reproducibility. To obtain E[C_{50} values, data of fungicidal activities were statistically analyzed by the SPSS 22.0 software package.

Table 3. Median Effective Concentrations (EC_{50} Values) of Compound 1−3, 11, 13, 16−18, and Pyrimethanil with High Activities against *T. cucumeris*[a]

compd	regression equation	EC_{50} (mg/L)	R^2
1	$y = -1.3229 + 5.5673x$	13.67	0.9233
2	$y = 2.5735 + 2.4618x$	9.68	0.9269
3	$y = 1.3842 + 5.5297x$	14.27	0.9370
5	$y = 0.3677 + 3.9391x$	15.00	0.9019
11	$y = 4.3517 + 1.2403x$	3.33	0.9631
13	$y = 2.0194 + 5.0056x$	25.25	0.8824
16	$y = 3.8307 + 1.5370x$	5.76	0.9830
17	$y = 2.8427 + 2.0571x$	11.19	0.9864
18	$y = 4.3211 + 1.2048x$	3.66	0.9862
pyrimethanil	$y = 4.0854 + 1.3827x$	4.59	0.9534

[a]The experiments were carried out three times to ensure better reproducibility. To obtain EC_{50} values, data of fungicidal activities were statistically analyzed by SPSS 22.0 software package.

non-treated control) was recorded with combined treatment of compounds **5** (R = 2-OCH_3) and **M**, followed by **M** and then compound **8** (84%). The relative values of root length under the combined treatment of compounds **1**−**27** and **M** ranged from 62 to 97%. Compounds **1**−**3**, **6**, **10**−**11**, **13**, **15**, and **25**−**27** exhibited better or similar activities when compared to the control fenclorim (85%). Compound **25** with no substitution

Table 4. Effect of Target Compounds 1−27 on the Growth in Rice Plant Heights, Root Lengths, and Fresh Weight at a Concentration of 1 mg/L[a]

		safening effect (% of non-treated control)		
compd	*R*	plant height	root length	fresh weight
1	−H	97 ± 1	99 ± 2	97 ± 1
2	2-CH_3	98 ± 1	98 ± 1	99 ± 1
3	3-CH_3	98 ± 1	94 ± 2	98 ± 1
4	4-CH_3	93 ± 1	96 ± 2	95 ± 2
5	2-OCH_3	99 ± 1	99 ± 2	99 ± 0
6	3-OCH_3	96 ± 2	98 ± 1	92 ± 2
7	4-OCH_3	97 ± 1	99 ± 0	98 ± 1
8	2-CO_2CH_3	97 ± 2	99 ± 1	97 ± 2
9	3-CO_2CH_3	96 ± 1	100 ± 1	99 ± 1
10	4-CO_2CH_3	98 ± 1	98 ± 0	97 ± 1
11	2-Cl	99 ± 0	98 ± 1	94 ± 2
12	4-Cl	99 ± 0	98 ± 1	98 ± 1
13	2-Br	99 ± 0	94 ± 3	98 ± 1
14	3-Br	96 ± 1	93 ± 2	96 ± 1
15	4-Br	92 ± 2	96 ± 1	94 ± 1
16	2-F	98 ± 1	98 ± 2	98 ± 1
17	3-F	97 ± 1	96 ± 2	100 ± 0
18	4-F	94 ± 3	92 ± 2	99 ± 1
19	2-CN	96 ± 2	95 ± 2	99 ± 1
20	3-CN	99 ± 0	100 ± 0	95 ± 1
21	4-CN	99 ± 1	99 ± 3	94 ± 0
22	2-CF_3	99 ± 0	99 ± 0	94 ± 2
23	3-CF_3	94 ± 3	91 ± 2	93 ± 2
24	4-CF_3	93 ± 2	97 ± 1	95 ± 1
25	3-CH_3, 5-CH_3	99 ± 0	95 ± 1	98 ± 2
26	3-OCH_3, 5-OCH_3	98 ± 1	98 ± 2	98 ± 1
27	3-CN, 5-CN	98 ± 2	94 ± 2	97 ± 1

[a]All experiments were performed in triplicate.

displayed the best activity on root length (97%). The relative values of fresh weight for combined treatment of compounds **1**−**27** were in the range of 81−97%, where compound **3** (97%) displayed the highest safener activity that was significantly larger than that of fenclorim (89%).

On the basis of the experimental results, the SAR for safening activities of these compounds were as follows: (1) combining phenoxy group in azoxystrobin and phenylpyrimidine moieties in fenclorim decreased the safening effect on plant height of rice seedlings, with the exception of **5** with 2-OCH_3 moiety; (2) comparing **2**, **6**, **10**−**11**, **13**, **15**, and **25**, it was indicated that introducing the methyl moiety, methoxyl moiety, methoxycarbonyl moiety, chlorine atom, and 3,5-dimethyl moiety might enhance the safening effect on root length of rice seedlings. However, an explicit relationship was not found between the positions of the substituents and the safening effect on root length; (3) bromine atoms on the phenoxy moiety were equal or more active than fluorine atoms for the safening effect on root length. (4) The hydrogen atoms on the phenoxy ring were superior to all electron-donating groups and electron-withdrawing groups, with the exception of the 3,5-dimethyl moiety. (5) No significant differences were observed in the herbicide safening activities between the monosubstituted and disubstituted compounds.

3. CONCLUSIONS

A series of 6-aryloxy-4-chloro-2-phenylpyrimidines was successfully synthesized by a one-pot and splicing active

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Table 5. Herbicide Safening Effect of 7-Day-Old Rice Seedlings Treated with Metolachlor on Plant Height, Root Length, and Fresh Weight[a]

	safening effect (% of non-treated control)		
compd	plant height	root length	fresh weight
M	51 ± 1	48 ± 2	65 ± 1
1 + **M**	78 ± 1	97 ± 0	93 ± 1
2 + **M**	67 ± 1	87 ± 1	87 ± 2
3 + **M**	68 ± 1	82 ± 2	97 ± 0
4 + **M**	68 ± 0	76 ± 2	82 ± 1
5 + **M**	92 ± 1	69 ± 3	88 ± 3
6 + **M**	72 ± 0	94 ± 2	86 ± 2
7 + **M**	79 ± 2	74 ± 1	81 ± 1
8 + **M**	84 ± 2	77 ± 2	93 ± 2
9 + **M**	74 ± 2	77 ± 1	87 ± 2
10 + **M**	73 ± 2	92 ± 2	83 ± 2
11 + **M**	72 ± 1	89 ± 1	91 ± 2
12 + **M**	72 ± 1	65 ± 1	93 ± 2
13 + **M**	74 ± 2	88±±2	90 ± 1
14 + **M**	73 ± 1	62 ± 2	90 ± 2
15 + **M**	72 ± 1	91 ± 2	92 ± 1
16 + **M**	71 ± 1	66 ± 1	81 ± 0
17 + **M**	69 ± 2	56 ± 2	84 ± 2
18 + **M**	69 ± 2	62 ± 1	85 ± 2
19 + **M**	75 ± 1	67 ± 1	93 ± 2
20 + **M**	62 ± 1	76 ± 2	86 ± 4
21 + **M**	60 ± 0	64 ± 3	93 ± 2
22 + **M**	64 ± 1	72 ± 1	92 ± 2
23 + **M**	63 ± 1	70 ± 2	86 ± 1
24 + **M**	63 ± 3	71 ± 0	86 ± 2
25 + **M**	76 ± 1	97 ± 1	93 ± 1
26 + **M**	67 ± 2	84 ± 1	84 ± 1
27 + **M**	71 ± 0	83 ± 2	89 ± 2
F + **M**	85 ± 1	85 ± 2	88 ± 1

[a]All experiments were performed in triplicates. **M**: 0.25 μM metolachlor. **1**−**27** + **M**: combined treatment of 1 mg/L compounds **1**−**27** and 0.25 μM metolachlor. **F** + **M**: combined treatment of 1 mg/L fenclorim and 0.25 μM metolachlor.

substructures method. The structures of the synthesized compounds were confirmed by NMR, HRMS, and X-ray crystal structure analyses. Their fungicidal and herbicide safening activities were evaluated. The data revealed that compound **11** possessed the best fungicidal activity against *S. sclerotiorum* and *T. cucumeris*, indicating potent activity when compared to the control fenclorin and pyrimethanil. On the other hand, compound **5** exhibited excellent safener activity on plant height, which was significantly higher than that of control fenclorim. Compound **25** displayed the best herbicide safener activity on root length. Compound **3** exhibited the highest safener activity on fresh weight, which was significantly larger than that of fenclorim. Hence, incorporation of the phenoxy group in azoxystrobin and phenylpyrimidine moieties in fenclorim could lead to the formation of novel compounds with high safener herbicide and fungicidal activities.

4. EXPERIMENTAL SECTION

4.1. Materials and Characterization. Fenclorim (purity 98%), substituted phenols (purity 97−99%), and anhydrous potassium carbonate (purity 99%) were provided by Jilin Chinese Academy of Sciences-Yanshen Technology Co., Ltd. (Jilin, China). DMF, petroleum ether (PE), and dichloromethane (DCM) were obtained from Sinopharm Chemical Reagent Co., Ltd. (Beijing, China) and used as received without further purification. The melting points were measured by a Hanon MP100 automatic melting point apparatus on open capillary tubes (Jinan Hanon Instruments Co., Ltd., Jinan, China). ^{1}H NMR and ^{13}C NMR spectra of target compounds were obtained on a Varian Mercury-Plus 300 spectrometer (Varian, Inc., Salt Lake, USA) operating at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR), respectively, or a Bruker AVANCE-500 spectrometer (Bruker Optics, Ettlingen, BW, Germany) operating at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR). High-resolution mass spectral data were recorded on an FTICR-MS Varian 7.0 T FTICR-MS instrument (Varian IonSpec, Lake Forest, USA). X-ray single-crystal structure data were collected on a Rigaku SuperNova, Dual, Cu at zero, AtlasS2 diffractometer (Agilent, CA, USA).

4.2. Synthesis of Compounds 1−27. A modified procedure was used for the synthesis of target compounds **1**−**27** (Scheme 2).[52] First, fenclorim (4.4 mmol, 1.00 g) and anhydrous K_2CO_3 (8.8 mmol, 1.22 g) were dissolved in DMF (30 mL). Substituted phenols (4.4 mmol) were added in a dropwise manner into the mixed solution and then stirred at 60 °C for 4 h followed by cooling down, pouring into water, and filtering to yield crude products as residue. The products were further purified by column chromatography with DCM/PE (1/10) to obtain pure target compounds **1**−**27**.

Physical and chemical properties, ^{1}H NMR, ^{13}C NMR, and HRMS data, ^{1}H NMR and ^{13}C NMR spectra of **1**−**27** (Figures S2−S55) can be found in the Supporting Information.

4.3. Crystal Structure Analysis. Compound **11** was first recrystallized from ethanol to obtain a suitable colorless single crystal. X-ray single-crystal structure data of compound **11** was then collected on a Rigaku SuperNova, Dual, Cu at zero, AtlasS2 diffractometer (Agilent, CA, USA) equipped with Mo Kα radiation (λ = 1.54184 Å) at 100.00(10) K. The data processing was accomplished with SHELXL program. Using Olex2,[64] the crystal structure of compound **11** was directly solved by ShelXT structure solution program and refined with ShelXL refinement package by means of least squares method.[65,66] Selected crystallographic data of compound **11** are listed in Table S1, and some molecular structure parameters are described in Table S2. The crystallographic structural data of compound **11** were deposited at the Cambridge Crystallographic Data Centre (CCDC) under CCDC number of 1966186. These data can be accessed free of charge at https://www.ccdc.cam.ac.uk/structures or by application to CCDC, 12 Union Road, Cambridge CB2 1EZ, United Kingdom (Tel: +44-1223-336408; Fax: +44-1223-336033; E-mail: deposit@ccdc.cam.ac.uk).

4.4. Evaluation of Fungicidal Activity. The fungicidal activities of compounds **1**−**27** were tested *in vitro* against four fungus species by mycelium growth rate method reported in the literature.[67] The employed fungus species were *S. sclerotiorum*, *T. cucumeris*, *F. graminearum*, and *F. oxysporum*. The solutions were prepared by dissolving 10 mg of compounds **1**−**27** in 1 mL of dimethyl sulfoxide (DMSO) to yield a concentration of 10 mg/mL. The solutions were then mixed with 199 mL potato dextrose agar. Next, media containing compounds **1**−**27** at concentrations of 50 mg/L for initial screening were poured into sterile Petri dishes (d = 9 cm) followed by cooling down. Mycelia disks of 0.5 cm diameter were then inoculated on the center of the Petri dishes

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at 25 °C for 2 days. DMSO without any other compounds was employed as the non-treated control. The treated hypha diameter was measured using a cross bracketing method, and commercial fungicide pyrimethanil and fenclorim were used as positive controls. The inhibition rate of compounds **1**−**27** against fungi was calculated according to eq 1

$$\text{inhibition rate } (\%) = (C_0 - C)/(C - 0.5\text{ cm}) \times 100\% \quad (1)$$

when C_0 is the colony diameter of control and C is the colony diameter of the treated sample. All experiments in this work were repeated three times, and the bioassay results were the average of three replicates. The test concentrations used for calculating EC_{50} values were 25, 12.5, 6.25, 3.13, and 1.56 mg/L, respectively. All statistical analyses were performed by the SPSS 22.0 software package (IBM, NY, USA). The EC_{50} values were calculated using log-probit analysis.

4.5. Evaluation of Herbicide Safening Activity. The germination method reported in the literature was used for rice seed experiments (*Oryza sativa* L. ssp. Indica).[68] To this end, healthy rice seeds with uniform size and full-grain were sterilized for 15 min by 5% sodium hypochlorite solution and then thoroughly washed by distilled water. They were then soaked in distilled water for 24 h at 28 °C and were germinated for 36 h in the dark in a climatic cabinet at 28 °C. The herbicide safening activities were evaluated under laboratory conditions according to the literature methods. Uniformly germinated paddy rice seedlings were selected before emergence and transplanted in 0.3% agar media containing 0.25 μM metolachlor (**M**), 1 mg/L of compounds **1**−**27**, combined fenclorim (**F**) with 1 mg/L, and 0.25 μM **M**, and combined compounds **1**−**27** with 1 mg/L and 0.25 μM **M** for the primary screening test. Agar medium without compounds was used as the non-treated control. Fifty seeds were put on plates for each test and then incubated for 14 h under growth light intensity of 110−130 μE m^{-2} s^{-1} at 30 °C followed by 10 h dark photoperiod at 25 °C. The indices of plant height, root length, and fresh weight-related to herbicide safening activities were measured after 7 days. The herbicide safening effects of plant height, root length, or fresh weight relative value used for SAR analysis were calculated by eqs 2−4

$$R_1 = X_n/X_0 \times 100\% \quad (2)$$

$$R_2 = Y_n/Y_0 \times 100\% \quad (3)$$

$$R_3 = Z_n/Z_0 \times 100\% \quad (4)$$

where R_1 is the relative value of plant height, X_n is the plant height foreach treatment, and X_0 is the average plant height of the non-treated control. R_2 represents the average relative value of root length, Y_n is the root length of each treatment, and Y_0 is the average root length of the non-treated control. R_3 is the fresh weight of the non-treated control. Z_n is the fresh weight of each treatment, and Z_0 is the average fresh weight of the non-treated control. Note that all experiments were performed three times to ensure better reproducibility, and the bioassay results (the average of three replicates) were obtained according to a similar method in the reference we reported before.[69] All statistical analyses were performed using the SPSS 22.0 software package (IBM, NY, USA).

4.6. Data Analysis. Data in the experiments were examined *via* a one-way analysis of variance, and the value of $P < 0.05$ was considered to be significant.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c03300.

Crystal packing diagrams of **11**; selected crystallographic data of **11**; selected molecular structure parameters of **11**; physical and chemical properties, ^{1}H NMR, ^{13}C NMR, and HRMS data of **1**−**27**; and ^{1}H NMR and ^{13}C NMR spectra of **1**−**27** (PDF)

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Notes

The authors declare no competing financial interest.

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