


Article

Synthesis, Crystal Structure, Herbicide Safening, and Antifungal Activity of *N*-(4,6-Dichloropyrimidine-2-yl)Benzamide

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Abstract: The compound *N*-(4,6-dichloropyrimidine-2-yl)benzamide (C₁₁H₇Cl₂N₃O) was synthesized and the corresponding structure was confirmed by ¹H NMR, ¹³C NMR, HRMS, IR, and single-crystal X-ray diffraction. The compound crystallized in a monoclinic system with space group *P* 2₁/*c*, where *a* = 14.9156(6), *b* = 16.6291(8), *c* = 14.4740(6) Å, β = 95.160(2)°, *V* = 3575.5(3) Å³, *Z* = 12, *D*_c = 1.494 g·cm⁻³, *F*(000) = 1632, μ(MoKα) = 3.182 mm⁻¹, final *R* = 0.0870, and *wR* = 0.2331 with *I* > 2σ(*I*). The crystal structure was found to be stabilized by intermolecular hydrogen bonding interactions N–H···O and C–H···Cl. Furthermore, the results from biological assays indicated that the compound showed a similar protective effect on metolachlor injury in rice seedlings compared to fenclorim at a concentration of 4.0 mg·L⁻¹. Moreover, the compound exhibited an improved antifungal activity compared to pyrimethanil against *S. sclerotiorum* and *F. oxysporum*. Potentially, these results lay the foundation for the development of novel herbicide safeners and fungicides.

Keywords: synthesis; crystal structure; benzamide; herbicide safeners; antifungal activity

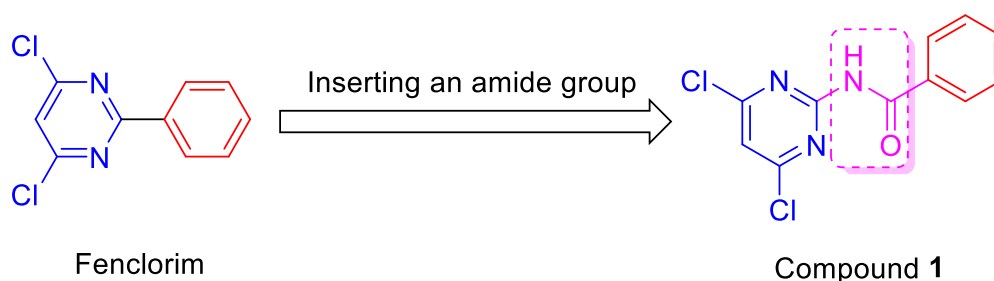
1. Introduction

Herbicides are frequently used for the control of weeds both in an effort to ensure the adequate production of food crops and to meet increased production requirements. However, when used under field conditions, herbicides often exhibit a negative effect on crop growth and yield, including corn, cereal, and rice [1–7]. In order to protect crops from potential injuries caused by herbicides, the use of herbicide safeners is the most straightforward and cost-effective method [8,9]. A herbicide safener, which is generally used in combination with herbicides or can be added to seeds by pre-sowing seed treatments, can effectively reduce herbicide-induced toxicity to crop plants and enhance the selectivity of herbicides in crops [9,10]. In 1970, the first commercialized herbicide safener (1,8-naphthalic anhydride, NA) was reported by Hoffman et al. and was designed to protect corn from thiocarbamate herbicide injury [11–13]. Since then, a number of synthetic herbicide safeners, e.g., dichlormid, oxime ether, fenchlorazole-ethyl, flurazole, and dymron, have been commercialized for crop protection [14–18].

Fenclorim represents a pyrimidine-type herbicide safener that is mainly used to enhance the tolerance of rice to chloroacetanilide herbicides via improving the expression of glutathione

S-transferases (GSTs), which catalyze the conjugation of chloroacetanilide herbicides with glutathione in rice to detoxify herbicides [19,20]. Fenclorim is used in combination with chloroacetanilide herbicides on rice seedlings or by soaking the seeds in pre-sowing applications while maintaining the susceptibility of chloroacetanilide herbicides to target weeds [21,22]. However, only a few structure–activity relationship (SAR) reports on fenclorim or its derivatives can be found in the literature that offer guidance to further identify novel herbicide safeners.

Amide compounds associated with unique pharmacological activities are usually used as drugs or pesticides and exhibit antimicrobial [23], antiviral [24], anticancer [25], insecticide [26,27], fungicide [28], herbicide [29] and even herbicide safener activities [30]. For this reason and to further screen candidates with improved herbicide safener activities, the amide compound (*N*-(4,6-dichloropyrimidine-2-yl)benzamide) (**1**) was synthesized via insertion of an amide group between the chlorinated substituted pyrimidine ring and the phenyl ring of fenclorim (cf. Scheme 1). The corresponding compound structure was confirmed by ^1H NMR, ^{13}C NMR, HRMS, IR, and single-crystal X-ray diffraction. Furthermore, the herbicide safener activity to protect rice from chloroacetanilide herbicide metolachlor injury was tested. Since some herbicide safeners may also serve as fungicides [4,31], we have also evaluated the antifungal activity of Compound **1**.



Scheme 1. Design strategy of Compound **1**.

2. Materials and Methods

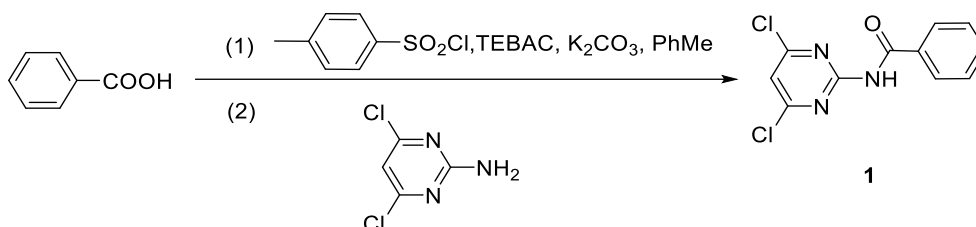
2.1. General Techniques

Benzoic acid, 4-methylbenzenesulfonyl chloride, benzyltriethylammonium chloride (TEBAC) and 4,6-dichloropyrimidine-2-amine were purchased from Shanghai Macklin Biochemical Co., Ltd. (Shanghai, China). Potassium carbonate (K_2CO_3) was purchased from Sinopharm Group Co., Ltd. (Shanghai, China). All other reagents obtained from commercial sources were dried and further purified. The melting point was measured on a Hanon MP100 automatic melting point apparatus (Jinan Hanon Instruments Co., Ltd., Jinan, Shandong, China) using an open capillary tube. ^1H and ^{13}C NMR spectra for Compound **1** were obtained on a Bruker Avance-500 spectrometer operating at 500 MHz (^1H) and 125 MHz (^{13}C), respectively. Chemical shifts are reported in ppm (δ). High-resolution mass spectral analysis was carried out on an FTICR-MS Varian 7.0 T FTICR-MS instrument (Varian IonSpec, Lake Forest, CA, USA), and infrared spectra (IR) were obtained via ATR-method (attenuated total reflection) on a TENSOR II-Bruker FT-IR spectrometer (Bruker Optics, Ettlingen, BW, Germany). Single-crystal X-ray structure was measured on a Bruker SMART APEX II X-ray single crystal diffractometer (Bruker AXS, Karlsruhe, BW, Germany).

2.2. Synthetic Procedure

A modified procedure based on methods reported in the literature [32,33] was used. The synthetic route of Compound **1** is outlined in Scheme 2. A mixture of benzoic acid (1.00 g, 8.19 mmol), 4-methylbenzenesulfonyl chloride (1.56 g, 8.19 mmol), TEBAC (0.19 g, 8.19 mmol), and K_2CO_3 (4.53 g, 32.76 mmol) in dry toluene (60 mL) was stirred under reflux for 1 h. Afterwards, 4,6-dichloropyrimidine-2-amine (1.34 g, 8.19 mmol) was added and stirring was continued for 40 min

under reflux. The resulting precipitate was filtered off, and the solvent was removed. The solid residue was subjected to column chromatography (petroleum ether/ethyl acetate, 6:1) to obtain 0.95 g (43.24%) of a white solid. m.p. 155–156 °C; ^1H NMR (500 MHz, CDCl_3) δ [ppm]: 7.15 (s, 1H, PyH), 7.50–7.53 (m, 2H, ArH), 7.60–7.63 (m, 1H, ArH), 7.92–7.94 (m, 2H, ArH), 8.72 (s, 1H, NH). ^{13}C NMR (125 MHz, CDCl_3) δ [ppm]: 116.33, 127.55, 128.98, 133.00, 133.28, 157.08, 162.57, 164.07. IR (ATR) ν : 3228(NH), 1693 (C=O) cm^{-1} ; MS (ESI+) m/z : 268.0035 ($[\text{M} + \text{H}]^+$); found: 268.0039.



Scheme 2. Synthetic route for Compound 1.

2.3. Structure Determination

Single crystals of Compound 1 were obtained by recrystallization from a solution of methanol at room temperature. The crystal dimensions were $0.170 \times 0.100 \times 0.040 \text{ mm}^3$. The reflection data of Compound 1 was collected by using X-radiation ($\lambda = 1.34139 \text{ \AA}$) at 296(2) K via a Bruker SMART APEX II X-ray single crystal diffractometer (Bruker AXS, Karlsruhe, BW, Germany). A total of 37,976 reflections were collected by employing an ψ - ω scan mode, 6797 of which were independent with $R_{\text{int}} = 0.0675$ and 4973 were observed with $I > 2\sigma(I)$. The structure of Compound 1 was solved via a direct method using SHELXS-97 (University of Gottingen, Gottingen, NI, Germany). The solutions were refined by full-matrix least squares techniques on F^2 by SHELXL-2013 program [34]. The final cycle of refinement gave $R = 0.0870$ and $wR = 0.2337$ with $w = 1/[\sigma^2(F_o^2) + (0.1114 P)^2 + 6.0571 P]$, where $P = (F_o^2 + 2F_c^2)/3$ included 449 parameters. Selected crystallographic data of the Compound 1 is provided in Table 1.

Table 1. Selected crystallographic data of Compound 1.

Compound	1
CCDC No.	1810908
Empirical formula	$\text{C}_{11}\text{H}_7\text{Cl}_2\text{N}_3\text{O}$
Formula weight	268.10
Crystal system	Monoclinic
Space group	P 21/c
Unit cell dimensions	$a = 14.9156(6) \text{ \AA}$, $\alpha = 90^\circ$ $b = 16.6291(8) \text{ \AA}$, $\beta = 95.160(2)^\circ$ $c = 14.4740(6) \text{ \AA}$, $\gamma = 90^\circ$
Volume/ \AA^3	3575.5(3)
Z	12
$D_c/\text{g}\cdot\text{cm}^{-3}$	1.494
μ/mm^{-1}	3.182
$F(000)$	1632
Crystal size/ mm^3	$0.170 \times 0.100 \times 0.040$
$\theta_{\text{min}}/\theta_{\text{max}}/^\circ$	3.471/54.979
Limiting indices	$-18 \leq h \leq 15$, $-20 \leq k \leq 20$, $-17 \leq l \leq 17$
Reflections collected	37,976
Independent reflections	6797 [$R(\text{int}) = 0.0675$]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6797/0/449
Goodness-of-fit on F^2	1.049
$R_1/wR_2[I > 2\sigma(I)]$	0.0870/0.2337
$R_1/wR_2(\text{all data})$	0.1110/0.2540
Largest diff. peak and hole/ $\text{e}\cdot\text{\AA}^{-1}$	0566/−0.346

2.4. Herbicide Safener Activity

Herbicide safener activities of Compound 1 and fenclorim were evaluated using a method reported previously [35].

2.5. Antifungal Activity

The antifungal activities of Compound 1, fenclorim and pyrimethanil were tested in vitro. The following four fungal strains were used according to published procedures: *Sclerotinia sclerotiorum*, *Fusarium oxysporum*, *Fusarium graminearum*, and *Thanatephorus cucumeris* [36,37].

3. Results and Discussion

3.1. Crystal Structure

Compound 1 crystallized in the monoclinic system. The $P 2_1/c$ space group and the molecular structure of Compound 1 are depicted in Figure 1. Selected molecular structure parameters (bond lengths, bond angles, and torsion angles) for Compound 1 can be found summarized in Table 1. The packing arrangement of Compound 1 is shown in Figure 2. The crystal data for Compound 1 was deposited at the Cambridge Crystallographic Data Centre (12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) as supplementary publication No. CCDC-1810908. Crystallographic data for this crystal is available free of charge at the following website: http://www.ccdc.cam.ac.uk/data_request/cif or from the Cambridge Crystallographic Data Centre.

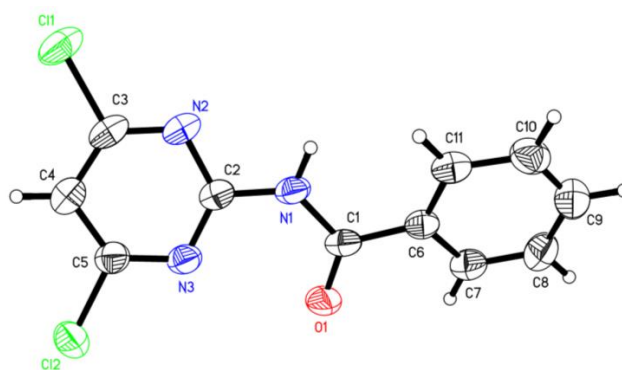


Figure 1. Crystal structure of Compound 1.

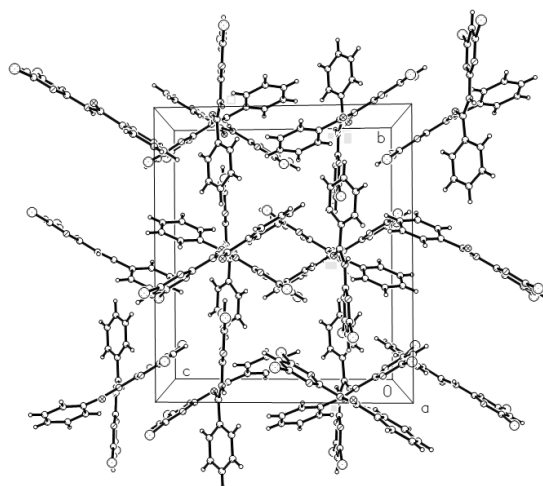


Figure 2. Packing arrangement of Compound 1 in the unit cell.

As shown in Table 2, the bond lengths and bond angles of the aromatic rings (phenyl and pyrimidine) in this crystal structure are in accordance with the general normal ranges [38–41]. The phenyl ring and pyrimidine ring were both connected by an amide group, and the C(1)=O(1) bond length in this amide group was 1.223(6) Å. The latter is similar to the general C=O double-bond length reported in the literature [42–44]. The bond angles of C(1)–N(1)–C(2) and N(1)–C(1)–C(6) were 128.7(4)° and 117.4(4)°, respectively. The secondary amide group adopted a trans-conformation, and the torsion angle of C(2)–N(1)–C(1)–C(6) was –177.2(4)°. The N and O atoms in the amide group were nearly coplanar, with a torsion angle of 3.6(8)° for C(2)–N(1)–C(1)–O(1). The mean plane of the pyrimidine ring, defined as C(2)–N(2)–C(3)–C(4)–C(5)–N(3), and the phenyl ring, defined as C(6)–N(7)–C(8)–C(9)–C(10)–C(11), formed angles of 32.0°, indicating the pyrimidine and phenyl rings were not coplanar.

Table 2. Selected molecular structure parameters.

Bond	Distance (Å)	Bond	Distance (Å)
Cl(1)–C(3)	1.735(5)	Cl(2)–C(5)	1.732(6)
N(1)–C(1)	1.370(6)	N(1)–C(2)	1.376(7)
N(1)–H(1)	0.8600	N(2)–C(3)	1.307(7)
O(1)–C(1)	1.223(6)	C(3)–C(4)	1.387(8)
C(4)–C(5)	1.373(7)	C(4)–H(4)	0.9300
C(7)–C(8)	1.359(8)	N(2)–C(2)	1.350(6)
C(9)–C(10)	1.360(9)	C(9)–H(9)	0.9300
C(10)–C(11)	1.383(8)	N(3)–C(5)	1.316(7)
Angle	(°)	Angle	(°)
C(1)–N(1)–C(2)	128.7(4)	O(1)–C(1)–N(1)	120.6(5)
C(8)–C(7)–C(6)	120.2(5)	C(3)–N(2)–C(2)	115.0(4)
O(1)–C(1)–C(6)	122.0(4)	N(1)–C(1)–C(6)	117.4(4)
C(7)–C(8)–C(9)	119.8(6)	C(11)–C(6)–C(1)	123.5(5)
C(10)–C(9)–C(8)	121.7(6)	C(8)–C(7)–C(6)	120.2(5)
Torsion	(°)	Torsion	(°)
C(2)–N(1)–C(1)–O(1)	3.6(8)	C(2)–N(1)–C(1)–C(6)	–177.2(4)
C(3)–N(2)–C(2)–N(1)	–178.9(4)	C(11)–C(6)–C(7)–C(8)	–0.7(8)
C(2)–N(2)–C(3)–C(4)	–0.4(7)	C(3)–C(4)–C(5)–Cl(2)	–179.4(4)
O(1)–C(1)–C(6)–C(7)	19.3(7)	C(7)–C(6)–C(11)–C(10)	–0.7(7)

The crystal packing characteristics of Compound 1 in the unit cell are described in Figure 2. Three adjacent molecules (cf. Figure 3) in the crystal packing are found to be linked by intermolecular hydrogen bonding interactions (N–H⋯O and C–H⋯Cl). The N⋯O distances between donor (D) and acceptor (A) were 2.981(5) Å for N(7)–H(7A)⋯O(2), 2.968(5) Å for N(4)–H(4A)⋯O(1), and 2.851(5) Å for N(1)–H(1)⋯O(3), respectively. The C⋯Cl distances between donor (D) and acceptor (A) were 3.874(6) Å for C(26)–H(26)⋯Cl(1) and 3.893(6) Å for C(15)–H(15)⋯Cl(2), respectively. Details of hydrogen bonding in this crystal structure are listed in Table 3.

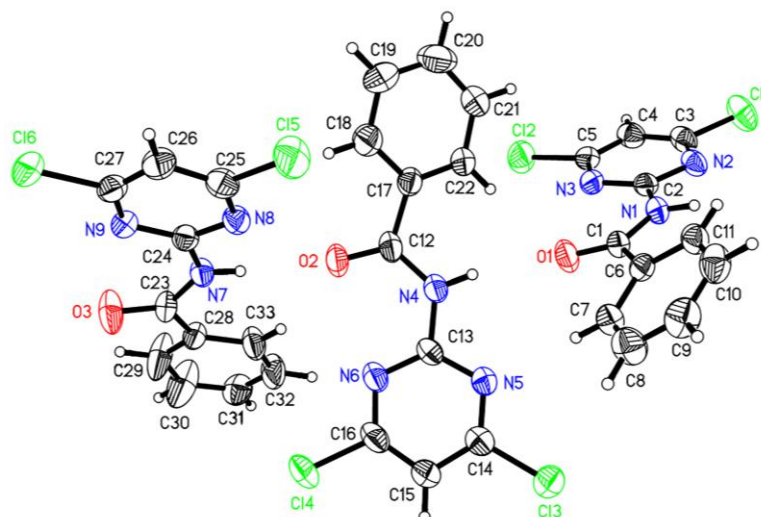


Figure 3. Structure of hydrogen bond trimer.

Table 3. Hydrogen bonding interactions in Compound 1.

D–H···A	d(D–H)/(Å)	d(H···A)/(Å)	d(D···A)/(Å)	<(DHA)/(°)
N(7)–H(7A)···O(2)	0.86	2.15	2.981(5)	163.4
N(4)–H(4A)···O(1)	0.86	2.12	2.968(5)	170.0
C(26)–H(26)···Cl(1) #1	0.93	2.96	3.874(6)	166.8
C(15)–H(15)···Cl(2) #2	0.93	2.98	3.893(6)	167.4
N(1)–H(1)···O(3) #3	0.86	2.05	2.851(5)	155.3

Symmetry transformations used to generate equivalent atoms: #1: $x + 1, y, z$; #2: $-x + 1, -y + 1, -z$; #3: $-x + 1, -y + 1, -z + 1$.

3.2. Spectroscopic Properties

The structure of Compound 1 was confirmed via melting point, ^1H NMR, ^{13}C NMR, IR, and HRMS analysis. Signals corresponding to the C–H proton in the pyrimidine ring and N–H proton in the amide group were observed at δ 7.15 and δ 8.72, respectively. The signals corresponding to the protons on the benzene ring were observed at δ 7.50–7.94. In the IR spectra of Compound 1, a strong absorption band was found at 1693 and 3228 cm^{-1} . The latter was attributed to the presence of the C=O and N–H stretching vibration of amide. The HRMS data of Compound 1 was in good agreement with the theoretical data that was calculated on the basis of the molecular formula.

3.3. Biological Activity

3.3.1. Evaluation of Herbicide Safener Activity

The herbicide safening effect of Compound 1 (C) as well as the positive control fenclorim (F) were measured by shoot height, root length, fresh biomass, and emergence rate correspond to safening [45] on 7-day-old rice seedlings as shown in Table 4. The growth rate of the rice seedlings was significantly suppressed by metolachlor (M) at a concentration of $0.25\ \mu\text{M}$, with 51.17%, 48.46%, 65.42%, and 57.67% of the non-treated control in shoot height, root length, fresh biomass, and emergence rate, respectively. Furthermore, the rice seedling injury from metolachlor was found to be alleviated by Compound 1 and fenclorim. The recovery rates of the injured rice seedlings after application of Compound 1 were 82.26%, 91.03%, and 78.52% of the non-treated control values in shoot height, root length, and fresh biomass, respectively. The latter was similar to the recovery rates upon using fenclorim. Similar to the above results, the emergence rate (87.47%) during the combined treatment of $4\text{ mg}\cdot\text{L}^{-1}$ of Compound 1 and $0.25\ \mu\text{M}$ of metolachlor (C + M) was similar to that (94.00%) in

the combined treatment of 4 mg·L⁻¹ fenclorim and 0.25 µM metolachlor (F + M). The data obtained indicated that, compared to fenclorim, Compound 1 exhibited a similar protective effect on metolachlor injured rice seedlings at a concentration of 4.0 mg·L⁻¹.

Table 4. Herbicide safening effect of 7-day-old rice seedlings treated with metolachlor. The combined formulations were 4 mg·L⁻¹ Compound 1/0.25 µM metolachlor (C + M) and 4 mg·L⁻¹ fenclorim/0.25 µM metolachlor (F + M). The measured parameters were plant height, root length, fresh weight, and emergence rate.¹

Compd.	Safening Effect (% of Non-Treated Control)			
	Plant Height	Root Length	Fresh Weight	Emergence Rate
M	51.17 ± 0.75	48.46 ± 0.38	65.42 ± 0.86	57.67 ± 1.15
C + M	82.26 ± 0.21	91.03 ± 0.72	78.52 ± 0.68	87.47 ± 0.92
F + M	86.18 ± 0.23	95.10 ± 0.70	82.22 ± 0.74	94.00 ± 1.00

¹ All experiments were performed in triplicate. The values present the means of three replicates ± SE of each mean. M: 0.25 µM metolachlor; C + M: combined treatment of 4 mg·L⁻¹ Compound 1 and 0.25 µM metolachlor; F + M: combined treatment of 4 mg·L⁻¹ fenclorim and 0.25 µM metolachlor. The emergence rate represents the percentage of the shoot height at more than 25 mm per plate.

3.3.2. Evaluation of Antifungal Activity

The IC₅₀ value of Compound 1, fenclorim as well as the positive control pyrimethanil against *Sclerotinia sclerotiorum*, *Fusarium oxysporum*, *Fusarium graminearum*, and *Thanatephorus cucumeris* are illustrated in Table 5. Compound 1 exhibited the highest overall activity with an IC₅₀ of 1.23 mg·L⁻¹ against *Sclerotinia sclerotiorum* and 9.97 mg·L⁻¹ against *Fusarium oxysporum*. The latter activity values were superior to the commercial agent pyrimethanil (8.39 mg·L⁻¹ against *Sclerotinia sclerotiorum* and 23.44 mg·L⁻¹ against *Fusarium oxysporum*). Moreover, fenclorim exhibited fungicidal activities, with an IC₅₀ of 18.11 mg·L⁻¹ against *Sclerotinia sclerotiorum*, 27.33 mg·L⁻¹ against *Fusarium oxysporum*, 39.53 mg·L⁻¹ against *Fusarium graminearum*, and 28.46 mg·L⁻¹ against *Thanatephorus cucumeris*. These results indicated that fenclorim could be further used as a lead compound to develop novel fungicides.

Table 5. IC₅₀ values of Compound 1, fenclorim and pyrimethanil against *Sclerotinia sclerotiorum*, *Fusarium oxysporum*, *Fusarium graminearum*, and *Thanatephorus cucumeris* ¹.

Compound	IC ₅₀ (±SD) mg·L ⁻¹			
	<i>S. sclerotiorum</i>	<i>F. oxysporum</i>	<i>F. graminearu</i>	<i>T. cucumeris</i>
1	1.23 ± 1.24	9.97 ± 0.15	33.50 ± 0.43	21.72 ± 0.25
fenclorim	18.11 ± 1.08	27.33 ± 0.03	39.53 ± 0.31	28.46 ± 0.30
pyrimethanil	8.39 ± 0.45	23.44 ± 0.57	30.68 ± 0.04	7.59 ± 0.15

¹ *S. sclerotiorum*: *Sclerotinia sclerotiorum*; *F. oxysporum*: *Fusarium oxysporum*; *F. graminearum*: *Fusarium graminearum*; *T. cucumeris*: *Thanatephorus cucumeris*. The experiment was carried out in three triplicates. The data of the fungicidal activities were statistically analyzed using the SPSS 22.0 software package to obtain IC₅₀ values. The latter represent the mean ± standard deviation (SD) of triplicate experiments.

4. Conclusions

In summary, the compound *N*-(4,6-dichloropyrimidine-2-yl)benzamide was synthesized and characterized by ¹H NMR, ¹³C NMR, HRMS, IR, and X-ray diffraction. The synthesis followed a strategy of inserting an amide group between a chlorinated substituent and a phenyl ring of fenclorim. The biological assay results indicated Compound 1 showed a similar protective effect on metolachlor injury in rice seedlings compared to fenclorim at a concentration of 4.0 mg·L⁻¹ and featured an even better antifungal activity compared to pyrimethanil against *S. sclerotiorum* and *F. oxysporum*. Potentially, the results obtained will lay the foundation for the design and development of novel herbicide safeners and fungicides.

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Author Contributions: Wen-Na Zheng synthesized the crystalline material, wrote the manuscript, carried out experimental work, and analyzed the crystal data; Zhe-Yuan Zhu, Ya-Nan Deng, Zhong-Chi Wu, and Yong Zhou helped in the bioassay experiments; Xiao-Mao Zhou provided the bioassay materials; Lian-Yang Bai supervised the entire study; Xi-Le Deng helped with the design of the experiments and revised the manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

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