molecules

MDPI

Article

Synthesis of Novel Pyrazole Derivatives Containing Phenylpyridine Moieties with Herbicidal Activity

Zengfei Cai [1], Wenliang Zhang [1], Zhongjie Yan [2] and Xiaohua Du [1,*]

[1] Catalytic Hydrogenation Research Center, Zhejiang Key Laboratory of Green Pesticides and Cleaner Production Technology, Zhejiang Green Pesticide Collaborative Innovation Center, Zhejiang University of Technology, Hangzhou 310014, China
[2] Agrowin (Ningbo) Bioscience Co., Ltd., Ningbo 315100, China
* Correspondence: duxiaohua@zjut.edu.cn

Abstract: To discover new compounds with favorable herbicidal activity, a range of phenylpyridine moiety-containing pyrazole derivatives were designed, synthesized, and identified via NMR and HRMS. Their herbicidal activities against six species of weeds were evaluated in a greenhouse via both pre- and post-emergence treatments at 150 g a.i./hm^2. The bioassay revealed that a few compounds exhibited moderate herbicidal activities against *Digitaria sanguinalis*, *Abutilon theophrasti*, and *Setaria viridis* in post-emergence treatment. For instance, compounds **6a** and **6c** demonstrated 50% inhibition activity against *Setaria viridis*, which was slightly superior to pyroxasulfone. Thus, compounds **6a** and **6c** may serve as the new possible leading compounds for the discovery of post-emergence herbicides.

Keywords: synthesis; pyrazole; phenylpyridine; herbicidal activity

Citation: Cai, Z.; Zhang, W.; Yan, Z.; Du, X. Synthesis of Novel Pyrazole Derivatives Containing Phenylpyridine Moieties with Herbicidal Activity. *Molecules* **2022**, *27*, 6274. https://doi.org/10.3390/molecules27196274

Academic Editor: Jianwu Xie

Received: 22 August 2022
Accepted: 20 September 2022
Published: 23 September 2022

1. Introduction

Pyrazole-containing compounds, a class of five-membered heterocyclic compounds with simple synthetic routes, have been widely used in the study of biologically active molecules such as in medicine [1,2], pesticides [3,4], and veterinary drugs [5,6]. In the field of agriculture, a variety of small molecules containing pyrazole groups have been developed as pesticide products (Figure 1), such as fungicides [7,8], insecticides [9–12], and herbicides [13–15]. Zhang et al. demonstrated that a series of novel substituted pyrazole aminopropyl isothiocyanates exhibited certain herbicidal activity against *Echinochloa crusgalli*, *Cyperus iria*, *Dactylis glomerata*, and *Trifolium repens* [16]. A class of 1-acyl-3-phenylpyrazol benzophenones was prepared by Ye et al. using dimethylformamide dimethyl acetal and 1, 3-diphenylpropane-1, 3-dione as the starting materials, which showed good herbicidal activity [17]. Liu et al. reported that a class of novel pyrazole aromatic ketone derivatives exhibited excellent herbicidal activity against various broadleaf weeds treated post-emergence [18]. The promising pesticide pyroxasulfone [19] discovered by Kumiai Chemical is a pre-emergence herbicide that could provide excellent control of grass and broadleaf weeds in corn and soybean fields.

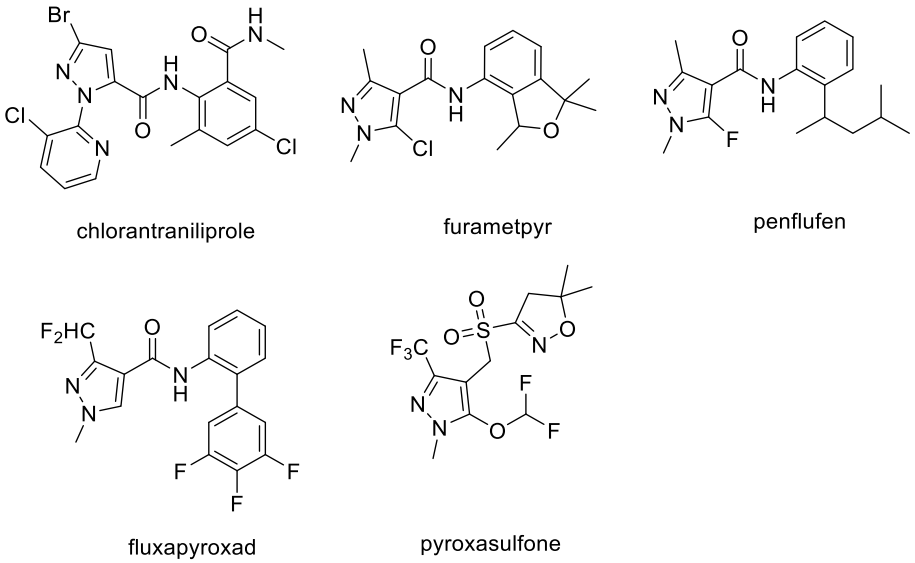


Figure 1. Structures of the reported pyrazole-containing compounds [9,19].

Substituted phenylpyridines discovered by Schaefer et al. exhibited good inhibition activity against weeds [20,21]. Substituted 3-(pyridin-2-yl)benzenesulfonamide derivatives disclosed by Liu et al. showed excellent inhibitory activity against a variety of weeds [22–24]. Du et al. also reported that a range of kresoxim-methyl derivatives containing phenylpyridine moieties exhibited higher inhibitory activities against broadleaf weeds than mesotrione [25,26].

Herein, 10 novel pyrazole derivatives containing phenylpyridine moieties were obtained via the principle of active substructure splicing, and the structures of these target compounds were confirmed by NMR and HRMS. In addition, the inhibitory activities of the resultant compounds against broadleaf and grass weeds were determined.

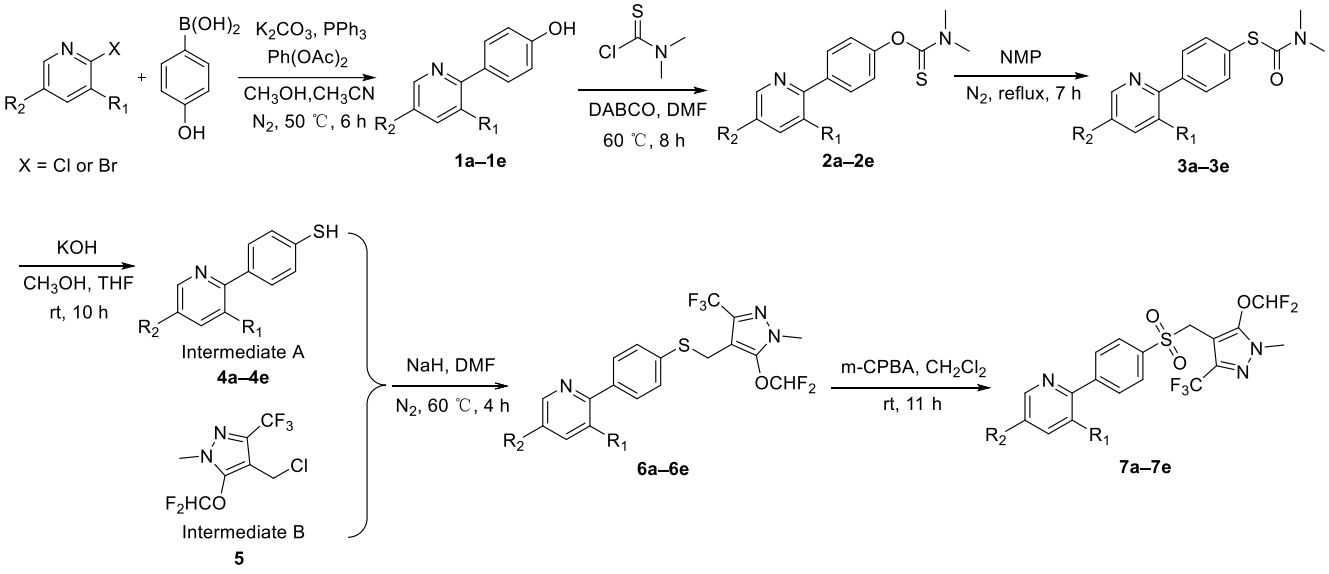
2. Results and Discussion

2.1. Chemistry

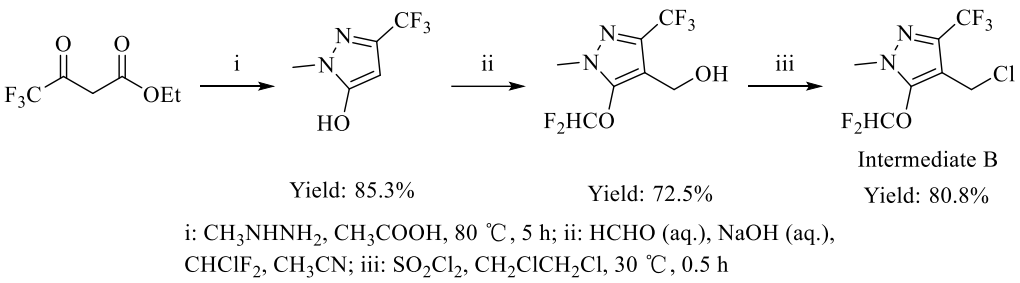
As can be seen from Schemes 1 and 2, all target compounds were obtained by multi-step reactions using substituted pyridines and ethyl 4,4,4-trifluoroacetoacetate as starting materials. Intermediates A (**4a**–**4e**) were prepared from substituted pyridine and p-hydroxyphenylboronic acid via multi-step reactions, such as the Suzuki cross-coupling reaction, nucleophilic substitution reaction, Newman–Kwart rearrangement reaction, and hydrolysis reaction [27,28]. Intermediate B was obtained via a simple three-step reaction as per the previously disclosed method, using ethyl 4,4,4-trifluoroacetoacetate as the starting material [29]. The target compounds **6a**–**6e** were prepared via a nucleophilic substitution reaction from intermediates A and B; compounds **6a**–**6e** were oxidized to yield compounds **7a**–**7e** using 3-chloroperbenzoic acid as the oxidant, according to previously disclosed methods [30]. After synthesis, all target compounds were characterized via HRMS and NMR. The NMR and HRMS spectra of all the target compounds are shown in the Supplementary Materials.

2.2. Greenhouse Herbicidal Activity Assays

According to the herbicidal activity test results, none of the target compounds exhibited herbicidal activities for pre-emergence. As can be seen from Table 1, a few target compounds exhibited moderate herbicidal activities. Of these, at 150 g a.i./hm^2, compounds **6a** and **6c** exhibited 50–60% inhibitory activities when used for the post-emergence treatment of the weeds *Digitaria sanguinalis* (*DS*), *Abutilon theophrasti* (*AT*), and *Eclipta prostrate* (*EP*). Furthermore, the inhibitory activities of compounds **6a** and **6c** against *EP* were superior to pyroxasulfone.



Scheme 1. Synthetic route to title compounds.



Scheme 2. Synthetic route to intermediate B.

Table 1. The structures and herbicidal activities of pyrazole derivatives at a 150 g a.i./hm^2 post-emergence treatment dose in a greenhouse assay setting.

Compound	Chemical Structure		Weed [a]					
	R_1	R_2	*EC*	*DS*	*SV*	*AT*	*AR*	*EP*
6a	Cl	CF_3	0 [b]	50	0	50	0	50
6b	Br	Cl	0	0	0	30	0	30
6c	Cl	F	0	60	0	60	0	50
6d	F	Cl	0	30	0	30	0	0
6e	Cl	CH_3	0	0	0	20	0	0
7a	Cl	CF_3	0	0	0	0	0	0
7b	Br	Cl	0	0	0	0	0	0
7c	Cl	F	0	0	0	20	0	0
7d	F	Cl	0	0	0	20	0	0
7e	Cl	CH_3	0	0	0	0	0	0
pyroxasulfone	/		60	75	60	50	50	0

[a] *EC, Echinochloa crusgalli; DS, Digitaria sanguinalis; SV, Setaria viridis; AT, Abutilon theophrasti; AR, Amaranthus retroflexus; EP, Eclipta prostrate.* [b] All the data were determined three times.

From previous studies on the herbicidal activity of pyrazole derivatives, it can be seen that some reported pyrazole derivatives showed good herbicidal activity. According to the study of Zhou et al. [31], the herbicidal activity of some substituted phenylpyrazole derivatives against *Abutilon theophrasti*, at 150 g a.i./hm^2, was above 90%. Although

compounds **6a** and **6c** of this work exhibited moderate herbicidal activities, they could also be further optimized as lead compounds to obtain compounds with higher activity.

From Table 1, we can see that the herbicidal activities of compound **6** were obviously better than those of compound **7**, indicating that the structure containing 4-(pyridin-2-yl)phenylene sulfide was beneficial to the improvement of the activity. According to the SAR of compound **6** in the field of herbicidal activity, when the 3-position of pyridine was a chlorine atom and the 5-position was a fluorine atom or a trifluoromethyl group, compound **6** exhibited the best herbicidal activity for post-emergence.

3. Materials and Methods

3.1. Instrumentation

All reagents and other materials were purchased from commercial sources and used without additional purification unless otherwise noted. A B-545 melting point instrument (Buchi, Hangzhou, China) was used to determine the melting point without calibration. A Bruker AV-400 spectrometer (Billerica, MA, USA) was used to generate NMR spectra with DMSO-d_6 serving as the solvents. An Agilent 6545 Q-TOF LCMS spectrometer (Santa Clara, CA, USA) was used for mass spectrometry.

3.2. Synthesis

The synthesis approach for pyrazole derivatives containing substituted 4-(pyridin-2-yl)benzene moieties in this work is outlined in Scheme 1.

3.2.1. Synthesis of Intermediates A (**4a**–**4e**)

4-(3-Chloro-5-trifluoromethylpyridin-2-yl) thiophenol intermediate (**4a**) is taken as an example.

2,3-Dichloro-5-trifluoromethylpyridine (1.08 g, 5 mmol), potassium carbonate (1.38 g, 10 mmol), triphenylphosphorus (0.13 g, 10 mol%), p-hydroxybenzeneboronic acid (0.76 g, 5.5 mmol), palladium(II) acetate (5 mol%, 0.06 g), CH_3OH (5 mL), and CH_3CN (10 mL) were mixed and stirred at 50 °C for 6 h under N_2. Thereafter, the mixture was extracted using ethyl acetate (30 mL×3), rinsed using brine, and concentrated. The remaining residue was then recrystallized using ethanol and water as solvents at 70 °C to obtain 1.22 g of compound **1a**.

Compound **1a** (13.65 g, 50 mmol), 1,4-diazabicyclo[2.2.2]octane (11.22 g, 100 mmol), dimethylcarbamothioic chloride (11.22 g, 100 mmol), and *N*,*N*-dimethylformamide (250 mL) were mixed and stirred at 60 °C for 8 h. Thereafter, the mixture was extracted using ethyl acetate (100 mL × 3), rinsed using brine, and concentrated to give a yellow solid **2a**, which was used in the next reaction without further purification.

The yellow solid **2a** synthesized in the previous step and *N*-methyl pyrrolidone (100 mL) were stirred under reflux for 7 h under N_2. Thereafter, the mixture was extracted using ethyl acetate (100 mL × 3), rinsed using brine, and concentrated to give a yellow solid **3a**, which was used in the next reaction without further purification.

The yellow solid **3a** (3.61 g, 10 mmol), 85% potassium hydroxide (0.69 g, 10.5 mmol), tetrahydrofuran (20 mL), and methanol (10 mL) were mixed and stirred at 20 °C for 10 h. Thereafter, the mixture was made more acidic using hydrochloric acid, extracted thrice using ethyl acetate (30 mL×3), rinsed using brine, and concentrated. Residues were then purified via silica gel column chromatography using ethyl acetate (EA) and petroleum ether (PE) (V_{EA}:V_{PE}=1:10) to obtain 3.15 g of yellow solid of intermediate **4a**.

3.2.2. Synthesis of Intermediate B

4-(Chloromethyl)-5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1H-pyrazole was prepared using the method disclosed previously, which is indicated in Scheme 2.

3.2.3. General Approach to the Synthesis of Compounds **6a**–**6e** and **7a**–**7e**

The target compounds **6a** and **7a** are taken as examples.

Compound **4a** (0.44 g, 1.5 mmol), 60% NaH (0.12 g, 3 mmol), and *N*,*N*-dimethylformamide (10 mL) were mixed and stirred at 20 °C for 30 min under N_2. Next, 4-(chloromethyl)-5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1H-pyrazole **5** (0.48 g, 1.8 mmol) was added followed by stirring for 4 h at 60 °C. Thereafter, the mixture was extracted thrice using ethyl acetate (30 mL × 3), rinsed using brine, and concentrated. Residues were then purified via silica gel column chromatography using ethyl acetate (EA) and petroleum ether (PE) (V_{EA}:V_{PE} = 1:10) to obtain 0.56 g of white solid of target compound **6a**.

Compound **6a** (0.20 g, 0.19 mmol) and 85% m-chloroperoxybenzoic acid (0.19 g, 0.93 mmol) in dichloromethane (5 mL) were mixed and stirred at 20 °C for 11 h. Thereafter, the mixture was evaporated to remove the solvent. Residues were then purified via silica gel column chromatography using ethyl acetate (EA) and petroleum ether (PE) (V_{EA}:V_{PE}=1:5) to obtain 0.07 g of white solid of target compound **7a**.

3-chloro-2-(4-(((5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)methyl)thio) phenyl)-5-(trifluoromethyl)pyridine (**6a**): White solid; Yield 72.1%; M.p. 68.3–70.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.04 (d, J = 0.9 Hz, 1H), 8.58 (d, J = 1.3 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.31 (t, J = 71.5 Hz, 1H), 4.17 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 159.10, 144.95 (q, J = 3.5 Hz), 143.70 (t, J = 3.1 Hz), 138.24, 137.50 (q, J = 37.2 Hz), 136.34 (q, J = 3.5 Hz), 135.01, 130.46, 129.99, 128.33, 125.41 (q, J = 33.1 Hz), 123.32 (q, J = 273.9 Hz), 121.52 (q, J = 270.5 Hz), 116.78 (t, J = 268.4 Hz), 104.65, 36.24, 24.40. HRMS (ESI): calculated for $C_{19}H_{13}ClF_8N_3OS$ $[M+H]^+$ 518.0335 and found to be 518.0333.

3-bromo-5-chloro-2-(4-(((5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl) methyl)thio)phenyl)pyridine (**6b**): Yellow oil; Yield 75.7%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.73 (d, J = 2.1 Hz, 1H), 8.47 (d, J = 2.1 Hz, 1H), 7.63 − 7.60 (m, 2H), 7.48 − 7.44 (m, 2H), 7.30 (t, J = 71.6 Hz, 1H), 4.15 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 155.01, 146.95, 143.24 (t, J = 3.6 Hz), 140.58, 137.04 (q, J = 37.1 Hz), 136.75, 136.22, 129.94, 129.90, 128.03, 121.07 (q, J = 270.6 Hz), 119.05, 116.32 (t, J = 268.6 Hz), 104.31, 35.78, 24.13. HRMS (ESI): calculated for $C_{18}H_{13}BrClF_5N_3OS$ $[M+H]^+$ 527.9566 and found to be 527.9562.

3-chloro-2-(4-(((5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)methyl)thio) phenyl)-5-fluoropyridine (**6c**): Yellow solid; Yield 67.1%; M.p. 74.3–76.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.70 (d, J = 2.6 Hz, 1H), 8.22 (dd, J = 8.5, 2.5 Hz, 1H), 7.65 − 7.61 (m, 2H), 7.48 − 7.43 (m, 2H), 7.30 (t, J = 71.5 Hz, 1H), 4.15 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.96 (d, J = 261.1 Hz), 151.96 (d, J = 4.0 Hz), 143.69 (t, J = 3.7 Hz), 137.48 (q, J = 37.1 Hz), 136.96 (d, J = 5.4 Hz), 136.71, 135.58, 130.35, 129.59 (d, J = 4.6 Hz), 128.67, 126.11 (d, J = 21.5 Hz), 121.53 (q, J = 270.5 Hz), 116.79 (t, J = 268.5 Hz), 104.80, 36.23, 24.63. HRMS (ESI): calculated for $C_{18}H_{13}ClF_6N_3OS$ $[M+H]^+$ 468.0367 and found to be 468.0368.

5-chloro-2-(4-(((5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)methyl)thio) phenyl)-3-fluoropyridine (**6d**): Yellow solid; Yield 81.2%; M.p. 79.9–82.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.63 (s, 1H), 8.20 (d, J = 10.9 Hz, 1H), 7.88 (d, J = 7.7 Hz, 2H), 7.50 (d, J = 7.7 Hz, 2H), 7.31 (t, J = 71.4 Hz, 1H), 4.16 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 156.26 (d, J = 265.6 Hz), 144.42 (d, J = 4.6 Hz), 143.22, 142.85 (d, J = 10.3 Hz), 137.68, 137.03 (q, J = 37.3 Hz), 131.84 (d, J = 5.9 Hz), 129.96 (d, J = 3.8 Hz), 128.93 (d, J = 6.2 Hz), 128.42, 125.09 (d, J = 23.9 Hz), 121.07 (q, J = 270.3 Hz), 116.33 (t, J = 268.5 Hz), 104.28, 35.79, 23.98. HRMS (ESI): calculated for $C_{18}H_{13}ClF_6N_3OS$ $[M+H]^+$ 468.0367 and found to be 468.0366.

3-chloro-2-(4-(((5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)methyl) thio)phenyl)-5-methylpyridine (**6e**): Yellow solid; Yield 79.0%; M.p. 106.4–108.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.47 (s, 1H), 7.89 (s, 1H), 7.64 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 7.30 (t, J = 71.5 Hz, 1H), 4.14 (s, 2H), 3.79 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 151.78, 148.43, 143.24 (t, J = 3.8 Hz), 138.44, 137.03 (q, J = 37.1 Hz), 136.08, 135.94, 134.06, 129.88, 128.48, 128.26, 121.08 (q, J = 270.6 Hz), 116.35 (t, J = 268.4 Hz), 104.41, 35.78, 24.27, 17.03. HRMS (ESI): calculated for $C_{19}H_{16}ClF_5N_3OS$ $[M+H]^+$ 464.0617 and found to be 464.0617.

3-chloro-2-(4-(((5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)methyl) sulfonyl)phenyl)-5-(trifluoromethyl)pyridine (**7a**): White solid; Yield 34.4%; M.p. 95.5–98.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.11 (d, J = 1.1 Hz, 1H), 8.67 (d, J = 1.3 Hz, 1H), 8.01 − 7.93 (m, 4H), 7.26 (t, J = 71.8 Hz, 1H), 4.58 (s, 2H), 3.80 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.94, 144.85 (t, J = 4.1 Hz), 144.70 (q, J = 3.9 Hz), 142.25, 138.68, 138.14 (q, J = 37.2 Hz), 136.06 (q, J = 3.5 Hz), 130.43, 130.03, 128.16, 125.86 (q, J = 33.3 Hz), 122.76 (q, J = 274.2 Hz), 120.60 (q, J = 270.9 Hz), 116.63 (t, J = 267.7 Hz), 96.20, 49.50, 36.03. HRMS (ESI): calculated for $C_{19}H_{13}ClF_8N_3O_3S$ $[M+H]^+$ 572.0052 and found to be 572.0050.

3-bromo-5-chloro-2-(4-(((5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl) methyl)sulfonyl)phenyl)pyridine (**7b**): White solid; Yield 49.0%; M.p. 136.9–139.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.80 (s, 1H), 8.56 (s, 1H), 7.90 (s, 4H), 7.25 (t, J = 71.8 Hz, 1H), 4.57 (s, 2H), 3.80 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 154.19, 147.21, 144.81 (t, J = 3.7 Hz), 143.78, 140.74, 138.18, 138.15 (q, J = 37.0 Hz), 130.92, 130.36, 128.02, 120.62 (q, J = 270.4 Hz), 119.28, 116.61 (t, J = 269.9 Hz), 96.22, 49.48, 36.05. HRMS (ESI): calculated for $C_{18}H_{13}BrClF_5N_3O_3S$ $[M+H]^+$ 581.9284 and found to be 581.9286.

3-chloro-2-(4-(((5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)methyl) sulfonyl)phenyl)-5-fluoropyridine (**7c**): White solid; Yield 95.0%; M.p. 106.8–109.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.76 (d, J = 2.5 Hz, 1H), 8.29 (dd, J = 8.5, 2.5 Hz, 1H), 7.91 (s, 4H), 7.24 (t, J = 71.8 Hz, 1H), 4.56 (s, 2H), 3.79 (s, 3H).^{13}C NMR (101 MHz, DMSO-d_6) δ: 158.46 (d, J = 262.0 Hz), 151.07 (d, J = 4.1 Hz), 145.29 (t, J = 3.6 Hz), 143.05, 138.60 (q, J = 37.0 Hz), 138.52, 137.18 (d, J = 23.1 Hz), 130.82, 130.05 (d, J = 5.0 Hz), 128.52, 126.28 (d, J = 21.6 Hz), 121.06 (q, J = 270.1 Hz), 117.08 (t, J = 267.6 Hz), 96.69, 49.97, 36.47.HRMS (ESI): calculated for $C_{18}H_{12}ClF_6N_3O_3SNa$ $[M+Na]^+$ 522.0084 and found to be 522.0084.

5-chloro-2-(4-(((5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)methyl) sulfonyl)phenyl)-3-fluoropyridine (**7d**): Yellow oil; Yield 85.0%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.72 (d, J = 1.1 Hz, 1H), 8.30 (dd, J = 11.0, 1.9 Hz, 1H), 8.16 (d, J = 7.4 Hz, 2H), 7.96 (d, J = 8.5 Hz, 2H), 7.26 (t, J = 71.8 Hz, 1H), 4.56 (s, 2H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.16 (d, J = 266.8 Hz), 145.30 (t, J = 4.6 Hz), 142.20 (d, J = 10.5 Hz), 139.78 (d, J = 5.8 Hz), 139.04, 138.60 (q, J = 37.2 Hz), 131.92 (d, J = 4.2 Hz), 129.86 (d, J = 6.2 Hz), 129.02, 125.96 (d, J = 23.9 Hz), 121.06 (q, J = 270.5 Hz), 117.07 (t, J = 267.3 Hz), 96.62, 49.97, 36.48. HRMS (ESI): calculated for $C_{18}H_{12}ClF_6N_3O_3SNa$ $[M+Na]^+$ 522.0084 and found to be 522.0085.

3-chloro-2-(4-(((5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)methyl) sulfonyl)phenyl)-5-methylpyridine (**7e**): White solid; Yield 80.7%; M.p. 116.9–119.8 °C.^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.53 (s, 1H), 7.97 (s, 1H), 7.95 − 7.85 (m, 4H), 7.26 (t, J = 71.8 Hz, 1H), 4.56 (s, 2H), 3.80 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 151.36, 149.13, 145.29 (t, J = 3.2 Hz), 143.80, 139.03, 138.61 (q, J = 37.5 Hz), 138.24, 135.60, 130.75, 129.27, 128.42, 121.08 (q, J = 269.3 Hz), 117.10 (t, J = 267.5 Hz), 96.68, 49.97, 36.47, 17.57. HRMS (ESI): calculated for $C_{19}H_{15}ClF_5N_3O_3SNa$ $[M+Na]^+$ 518.0335 and found to be 518.0337.

3.3. Herbicidal Activity Test

Levels of herbicidal activity for compounds **6a**–**6e** and **7a**–**7e** against the monocotyledonous weeds *Digitaria sanguinalis (DS)*, *Echinochloa crusgalli (EC)*, and *Setaria viridis (SV)*, and the dicotyledonous weeds *Abutilon theophrasti (AT)*, *Amaranthus retroflexus (AR)*, and *Eclipta prostrate (EP)* were determined using previously disclosed methods [32], with the results being listed in Table 1.

4. Conclusions

In conclusion, 10 novel pyrazole derivatives containing phenylpyridine moieties were prepared using pyroxasulfone as the lead compound. Among these, compounds **6a** and **6c** possessed moderate activity (50%) against *EP* for post-emergence at 150 g a.i./hm^2, which was slightly superior to pyroxasulfone. This study suggested that it may be the introduction of the phenylpyridine structure that allowed the target compounds to exhibit herbicidal

activity at post-emergence only. Thus, compounds **6a** and **6c** may be lead compounds for further structural optimization.

Supplementary Materials: The following supporting information is available online at: https://www.mdpi.com/article/10.3390/molecules27196274/s1. Figure S1–30: ^{1}H NMR, ^{13}C NMR, and HRMS spectra of target compounds **6a**–**6e** and **7a**–**7e**.

Author Contributions: Z.C. and W.Z., carried out experimental work; Z.C. prepared the manuscript; X.D. designed the material and supervised the project; and Z.Y. and X.D. revised the paper. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: We are grateful to Yong-Hua Li (Zhejiang Research Institute of Chemical Industry) for assistance with the bioactivity assay.

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

Samples Availability: Samples of the compounds are not available from authors.

References

1. Masumoto, E.; Kashige, N.; Nagabuchi, H.; Okabe-Nakahara, F.; Maruoka, H. Synthesis and evaluation for biological activities of 2-thio-acylated thiazoles containing pyrazole moiety. *Heterocycles* **2019**, *98*, 1736–1746. [CrossRef]
2. Karrouchi, K.; Radi, S.; Ramli, Y.; Taoufik, J.; Mabkhot, Y.N.; Al-aizari, F.A.; Ansar, M. Synthesis and pharmacological activities of pyrazole derivatives: A review. *Molecules* **2018**, *23*, 134. [CrossRef] [PubMed]
3. Liu, Y.X.; Liu, S.H.; Li, Y.H.; Song, H.B.; Wang, Q.M. Synthesis and biological evaluation of arylhydrazinocyanoacrylates and *N*-aryl pyrazolecarboxylates. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2953–2956. [CrossRef] [PubMed]
4. He, B.; Wang, D.-W.; Yang, W.-C.; Chen, Q.; Yang, G.-F. Advances in research on 4-hydroxyphenylpyruvate dioxygenase (HPPD) structure and pyrazole-containing herbicides. *Chin. J. Org. Chem.* **2017**, *37*, 2895–2904. [CrossRef]
5. Bizikova, P.; Linder, K.E.; Olivry, T. Fipronil-amitraz–S-methoprene-triggered pemphigus foliaceus in 21 dogs: Clinical, histological and immunological characteristics. *Vet. Dermatol.* **2014**, *25*, 103–113. [CrossRef]
6. Aloisi, A.; Franchet, A.; Ferrandon, D.; Bianco, A.; Menard-Moyon, C. Fluorescent-Fipronil: Design and synthesis of a stable conjugate. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 2631. [CrossRef] [PubMed]
7. Du, S.-J.; Li, Z.-H.; Tian, Z.-M.; Xu, L. Synthesis, antifungal activity and QSAR of novel pyrazole amides as succinate dehydrogenase inhibitors. *Heterocycles* **2018**, *96*, 74–85. [CrossRef]
8. Lei, P.; Zhang, X.-B.; Xu, Y.; Xu, G.-F.; Liu, X.-L.; Yang, X.-L.; Zhang, X.-H.; Ling, Y. Synthesis and fungicidal activity of pyrazole derivatives containing 1,2,3,4-tetrahydroquinoline. *Chem. Cent. J.* **2016**, *10*, 40–45. [CrossRef]
9. Zhong, L.-K.; Jiang, T.; Zhang, F.; Fu, Q.; Liu, X.-H.; Xu, T.-M.; Ding, C.-R.; Chen, J.; Yuan, J.; Tan, C.-X. Synthesis and insecticidal activity of 3-arylisoxazoline-pyrazole-5-carboxamide derivatives. *Chin. J. Org. Chem.* **2019**, *39*, 2655–2662. [CrossRef]
10. Song, H.-J.; Liu, Y.-X.; Xiong, L.-X.; Li, Y.-Q.; Yang, N.; Wang, Q.-M. Design, synthesis, and insecticidal evaluation of new pyrazole derivatives containing imine, oxime ether, oxime ester, and dihydroisoxazoline groups based on the inhibitor binding pocket of respiratory complex I. *J. Agric. Food. Chem.* **2013**, *61*, 8730–8736. [CrossRef]
11. Qu, S.-H.; Zhu, L.-F.; Wang, Q.; Wang, X.-L. Design, synthesis and insecticidal activity of 3-arylisoxazoline-*N*-alkylpyrazole-5-carboxamide derivatives against *Tetranychus urticae* Koch. *Heterocycles* **2022**, *104*, 511–523. [CrossRef]
12. Ren, Z.-L.; Zhang, J.; Li, H.-D.; Chu, M.-J.; Zhang, L.-S.; Yao, X.-K.; Xia, Y.; Lv, X.-H.; Cao, H.-Q. Design, synthesis and biological evaluation of α-aminophosphonate derivatives containing a pyrazole moiety. *Chem. Pharm. Bull.* **2016**, *64*, 1755–1762. [CrossRef] [PubMed]
13. He, B.; Dong, J.; Lin, H.-Y.; Wang, M.-Y.; Li, X.-K.; Zheng, B.-F.; Chen, Q.; Hao, G.-F.; Yang, W.-C.; Yang, G.-F. Pyrazole-isoindoline-1,3-dione hybrid: A promising scaffold for 4-hydroxyphenylpyruvate dioxygenase inhibitors. *J. Agric. Food Chem.* **2019**, *67*, 10844–10852. [CrossRef]
14. Mu, J.-X.; Zhai, Z.-W.; Tan, C.-X.; Weng, J.-Q.; Wu, H.-K.; Duke, S.O.; Zhang, Y.-G.; Liu, X.-H. Synthesis and herbicidal activity of 1,2,4-triazole derivatives containing a pyrazole moiety. *J. Heterocycl. Chem.* **2019**, *56*, 968–971. [CrossRef]
15. Fu, Q.; Kang, S.-J.; Zhong, L.-K.; Chen, J.; Tan, C.-X.; Weng, J.-Q.; Xu, T.-M.; Liu, X.-H. Synthesis and herbicidal activity of new pyrazole ketone derivatives. *Phosphorus Sulfur Silicon Relat. Elem.* **2021**, *196*, 200–205. [CrossRef]
16. Wu, H.; Feng, J.-T.; Lin, K.-C.; Zhang, X. Synthesis and Herbicidal activity of substituted pyrazole isothiocyanates. *Molecules* **2012**, *17*, 12187–12196. [CrossRef]
17. Fu, Y.; Wang, M.-X.; Zhang, D.; Hou, Y.-W.; Gao, S.; Zhao, L.-X.; Ye, F. Design, synthesis, and herbicidal activity of pyrazole benzophenone derivatives. *RSC Adv.* **2017**, *7*, 6858–46865. [CrossRef]
18. Fu, Q.; Cai, P.-P.; Cheng, L.; Zhong, L.-K.; Tan, C.-X.; Shen, Z.-H.; Han, L.; Xu, T.-M.; Liu, X.-H. Synthesis and herbicidal activity of novel pyrazole aromatic ketone analogs as HPPD inhibitor. *Pest Manag. Sci.* **2020**, *76*, 868–879. [CrossRef]

19. Goodrich, L.V.; Butts-Wilmsmeyer, C.J.; Bollero, G.A.; Riechers, D.E. Sequential pyroxasulfone applications with fluxofenim reduce sorghum injury and increase weed control. *Agron. J.* **2018**, *110*, 1915–1924. [CrossRef]
20. Schaefer, P.; Hampreche, G.; Puhl, M.; Westphalen, K.O.; Zagaret, C. Synthesis and herbicidal activity of phenylpyridines—A new lead. *Chim. Int. J. Chem.* **2003**, *57*, 715–719. [CrossRef]
21. Schaefer, P.; Hampreche, G.; Heistracher, E.; Koenig, H.; Klintz, R.; Muenster, P.; Rang, H.; Westphalen, K.O.; Gerber, M.; Walter, H. Preparation of Substituted 2-Phenylpyriden Herbicides. DE Patent DE4323916A1, 19 January 1995.
22. Xie, Y.; Chi, H.W.; Guan, A.Y.; Liu, C.L.; Ma, H.J.; Cui, D.L. Design, synthesis, and herbicidal activity of novel substituted 3-(pyridin-2-yl)benzenesulfonamide derivatives. *J. Agric. Food Chem.* **2014**, *62*, 12491–12496. [CrossRef] [PubMed]
23. Xie, Y.; Peng, W.; Ding, F.; Liu, S.J.; Ma, H.J.; Liu, C.L. Quantitative structure-activity relationship (QSAR) directed the discovery of 3-(pyridin-2-yl)benzenesulfonamide derivatives as novel herbicidal agents. *Pest Manag. Sci.* **2017**, *74*, 189–199. [CrossRef]
24. Xie, Y.; Chi, H.W.; Guan, A.Y.; Liu, C.L.; Ma, H.J.; Cui, D.L. Synthesis and evaluation of substituted 3-(pyridin-2-yl)-benzenesulfonamide derivatives as potent herbicidal agents. *Bioorg. Med. Chem.* **2016**, *24*, 428–434. [CrossRef]
25. Cao, Y.Y.; Mao, D.J.; Wang, W.W.; Du, X.H. Kresoxim-methyl derivatives: Synthesis and herbicidal activities of (pyridinylphenoxymethylene)phenyl methoxyiminoacetates. *J. Agric. Food Chem.* **2017**, *65*, 6114–6121. [CrossRef] [PubMed]
26. Cao, Y.Y.; Wang, W.W.; Du, X.H. Synthesis, crystal structure and herbicidal activity of methyl (*E*)-*α*-(methoxyimino)-2-((4-(3-chloro-5-(trifluoromethyl)-pyridine-2-yl)phenoxy)methyl)benzeneacetate. *Chin. J. Struct. Chem.* **2019**, *38*, 1123–1128. [CrossRef]
27. Cao, Y.-Y.; Cai, Z.-F.; Zhang, W.-L.; Du, X.-H. Synthesis and herbicidal activity of novel *β*-methoxyacrylate derivatives containing a substituted phenylpyridine moiety. *Chem. Res. Chin. Univ.* **2019**, *35*, 1008–1011. [CrossRef]
28. Harvey, J.N.; Jover, J.; Lloyd-Jones, G.C.; Moseley, J.D.; Murray, P.; Renny, J.S. The Newman-Kwart rearrangement of O-aryl thiocarbamates: Substantial reduction in reaction temperatures through palladium catalysis. *Angew. Chem. Int. Ed.* **2009**, *48*, 7612–7615. [CrossRef]
29. Shen, Y.-H.; Zhu, Y.-C.; Xiong, G.-Y. Method for Synthesizing Pyroxasulfone and Its Application for Pesticide. WO Patent WO2022000603A1, 6 January 2022.
30. Pujol Dilme, M.D.; Harrak Serifi, Y.; Pouplana Sole, R.; Rosell Pellise, G.; Basset Olive, J. Preparation of Phenyl Methyl Sulfones as Antiinflammatory and Antitumor Agents. WO Patent WO 2012004443, 12 January 2012.
31. Zhou, Y.; Xue, N.; Wang, G.; Qu, J. Synthesis, structure and herbicidal activity of substituted phenyl pyrazole derivatives. *J. Chem. Res.* **2010**, *12*, 684–688. [CrossRef]
32. Cai, Z.-F.; Zhang, W.-L.; Cao, Y.-Y.; Du, X.-H. Synthesis and herbicidal activities of 2-phenylpyridine compounds containing alkenyl moieties. *J. Heterocycl. Chem.* **2022**, *59*, 1247–1252. [CrossRef]