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ARTICLE

Design, Synthesis, and Fungicidal Activity of Novel Analogues of Pyrrolnitrin

Ming-Zhong Wang, Han Xu, Qi Feng, Li-Zhong Wang, Su-Hua Wang, and Zheng-Ming Li*

State Key Laboratory of Elemento-organic Chemistry, Research Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

A series of novel analogues of pyrrolnitrin containing a thiophene moiety were designed and synthesized by a facile method, and their structures were characterized by ^{1}H nuclear magnetic resonance (NMR) and high-resolution mass spectrometry. The isomers **IV-h** and **V-h** were isolated, and their structures were identified by 2D NMR, including heteronuclear multiple-quantum coherence (HMQC), heteronuclear multiple-bond correlation (HMBC), and nuclear Overhauser effect spectrometry (NOESY) spectra. Their fungicidal activities against five fungi were evaluated, and the results indicated that some of the title compounds showed excellent fungicidal activities *in vitro* against *Alternaria solani*, *Gibberella zeae*, *Physalospora piricola*, *Fusarium omysporum*, and *Cercospora arachidicola* at the dosage of 50 μg mL^{-1}. Some compounds shown moderate activity at low dosage. Compound **V-h** could be considered as a leading structure for further design of agricultural fungicides.

KEYWORDS: Pyrrolnitrin; thiophene; fungicidal activities; leading structure; synthesized

INTRODUCTION

Pyrrolnitrin (**A**, **Figure 1**) is an antibiotic first isolated from the bacterial cells of *Pseudomonas* by Arima et al. (*1*), and the structure was established by the same author (*1*). The antibiotic was totally synthesized by Nakano et al. in 1965 (*1*). It was also isolated from a non-obligate predator bacterial strain 679-2, which has growth-inhibitory properties against bacteria, fungi, and other predator bacteria and yet with an ability to thrive in the absence of prey microorganisms (*2*). Pyrrolnitrin is one of the most important natural products inhibiting *Mycobacterium tuberculosis* in early days (*3*), and this structure has been studied in crop protection. Fenpiclonil (**B**, **Figure 1**) and fludioxonil (**C**, **Figure 1**) were discovered as a novel class of agrochemical fungicides on the basis of the synthetic optimization of the natural structure (*4*). Both compounds have broad-spectrum activity across many classes of fungi and are safe to mammals and the environment (*4*).

In the design of new fungicides, when the pyrrole group in pyrrolnitrin was replaced by furanone, pyrazole, and isoxazolinol, respectively, all of the analogues reported were found to be devoid of biological activity (*5*). The thiophene and pyrrole rings are considered to be bioisosteric analogues, and there are many fungicides that have the thiophene group, such as bethoxazin (*6*), penthiopyrad (*7*), ethaboxam (*8*), etc. Therefore, in this paper, the pyrrole ring was replaced by the thiophene ring. To study the structure−activity relationship (SAR) of those analogues, the thiophene and aromatic rings of some analogues were nitrified to know whether that might improve or decrease the fungicide activity (*9*). In addition, adding some halogen atoms to the aromatic ring might enhance the lipophilic ability and fungicidal activity of those compounds (*4*). A total of 24 analogues (**D**, **Figure 1**) were synthesized with a facile synthetic method. The target compounds were evaluated for fungicide activity *in vitro* against five fungi, and some compounds showed moderate activity at low dosage.

*To whom correspondence should be addressed. Telephone: +86-22-23503732. E-mail: nkzml@vip.163.com.

MATERIALS AND METHODS

Instruments. ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, heteronuclear multiple-quantum coherence (HMQC), heteronuclear multiple-bond correlation (HMBC), and nuclear Overhauser effect spectrometry (NOESY) spectra were obtained at 300 MHz using a Bruker AV300 spectrometer or at 400 MHz using a Varian Mercury Plus400 spectrometer in $CDCl_3$ solution, with tetramethylsilane as the internal standard. Chemical-shift values (δ) were given in parts per million (ppm). High-resolution mass spectrometry (HRMS) data were obtained on a VG ZAB-HS instrument. The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. Yields were not optimized. The reagents were all analytically or chemically pure. All solvents and liquid reagents were dried by standard methods in advance and distilled before use. 1-Bromo-2-nitro-benzene (**II-a**) and all halogen−benzene were bought from the Alfa Aesar Company (Tianjin, China). Fenpiclonil (**B**) was bought from the laboratory of Dr. Ehrenstorfer-Schäfers (Augsburg, Germany).

General Synthetic Procedures for II-b−II-h. A mixture of 65% nitric acid (1.5 mL) and 1-bromo-4-fluorobenzene (**I-b**, 3.4 mL, 30 mmol) in 98% sulfuric acid (12.0 mL) was kept 15 min at 0 °C, then poured onto crushed ice (20 g), and extracted with dichloromethane (2 × 20 mL), and the solvent was removed. The residue was purified by flash chromatography on silica gel eluting with petroleum ether (60−90 °C) to provide

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II-b as a light yellow crystal (*10*). Compounds **II-c**, **II-d**, **II-e**, **II-f**, **II-g**, and **II-h** were prepared through the same process. In compounds **II-e** and **II-f** preparation procedures, the mixture was kept 40 min at 0 °C and then poured onto crushed ice. In compounds **II-g** preparation procedures, the mixture was kept 60 min at 60 °C and then poured onto crushed ice. Compound **II-h** was obtained from **II-c**, and the mixture was kept 30 min at 60 °C and then poured onto crushed ice. All of the substituents at the aromatic rings were listed in **Scheme 1**.

Data for ***II-b***. Yield, 61.1%. mp, 37−39 °C (acetone/petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.19−7.25 (m, 1H, Ar−H), 7.62 (dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HF}$ = 3.0 Hz, 1H, Ar−H), 7.74 (dd, $^3J_{HF}$ = 9.0 Hz, $^4J_{HH}$ = 5.1 Hz, 1H, Ar−H).

Data for ***II-c***. Yield, 59.2%. mp, 39−41 °C (acetone/petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.15−7.19 (m, 1H, Ar−H), 7.39 (dd, $^3J_{HF}$ = 8.1 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, Ar−H), 7.89 (dd, $^4J_{HF}$ = 5.4 Hz, $^3J_{HH}$ = 9.0 Hz, 1H, Ar−H).

Data for ***II-d***. Yield, 48.7%. mp, 65−67 °C (acetone/petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, Ar−H), 7.68 (d, $^3J_{HH}$ = 8.7 Hz, 1H, Ar−H), 7.85 (s, 1H, Ar−H).

Data for ***II-e***. Yield, 90.0%. mp, 63−65 °C (acetone/petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.61 (d, $^4J_{HH}$ = 2.4 Hz, 1H, Ar−H), 7.66 (d, $^4J_{HH}$ = 2.4 Hz, 1H, Ar−H).

Data for ***II-f***. Yield, 49.5%. mp, 24−26 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (d, $^3J_{HF}$ = 8.0 Hz, 1H, Ar−H), 7.83 (d, $^4J_{HF}$ = 6.8 Hz, 1H, Ar−H).

Data for ***II-g***. Yield, 67.8%. mp, 100−102 °C (acetone/petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.73 (s, 1H, Ar−H).

Data for ***II-h***. Yield, 55.0%. mp, 95−97 °C (acetone/petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.78 (d, $^3J_{HF}$ = 9.6 Hz, 1H, Ar−H), 8.72 (d, $^4J_{HF}$ = 6.9 Hz, 1H, Ar−H).

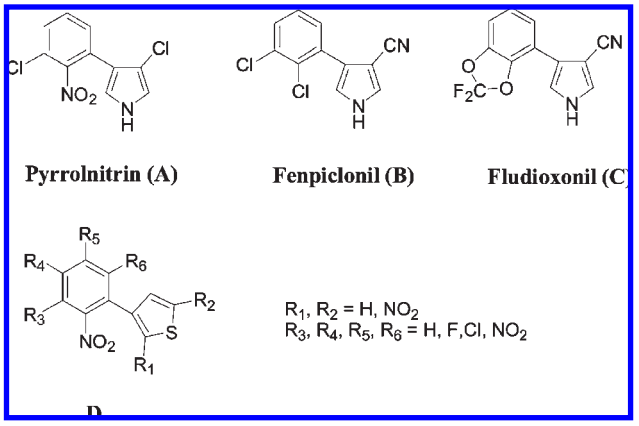


Figure 1. Chemical structures of compounds **A**−**D**.

Synthesis of 3-Bromo-thiophene. 3-Bromo-thiophene was synthesized through an improved procedure referenced in the literature (*11*, *12*): A solution of thiophene (93.0 g, 1.1 mol) in 130 mL of chloroform was cooled to 0 °C. Bromine (150 mL, 2.9 mol) was added dropwise over 4.5 h and then refluxed for 3.5 h, after which 200 mL of 2 M sodium hydroxide was added and stirred for 0.5 h, then extracted with chloroform (150 mL), washed with water, and dried, and then the solvent was removed to afford a light reddish oil, which was used in the subsequent step without further purification. In a 2 L flask equipped with a distillation apparatus, zinc powder (220 g, 3.3 mol) was added to 500 mL of water; glacial acetic acid was then added (210 mL, 3.64 mol). The crude product obtained above was added. The mixture was stirred and refluxed for 8 h. The subsequent steps of distillation are the same as in the literature. Distillation afforded 3-bromo-thiophene as a colorless liquid. Yield, 80.8%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.90 (dd, $^4J_{HH}$ = 2.1 Hz, $^3J_{HH}$ = 4.2 Hz, 1H), 7.08 (d, $^3J_{HH}$ = 4.2 Hz, 1H), 7.10 (s, 1H).

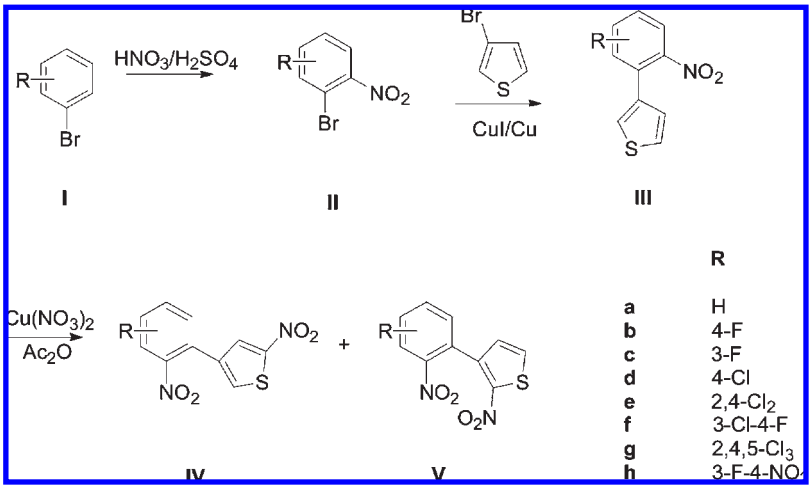
General Synthetic Procedures for Target Compounds III-a−III-h. Compound **III-a** was synthesized by a facile method according to the literature (*13*). Cuprous iodide (7.6 g, 39.8 mmol) and 3-bromo-thiophene (8.2 g, 50.0 mmol) were mixed together and heated to 160 °C for 1 h. Then, the bath temperature was raised and maintained at 200 °C. With stirring, compound **II-a** (8.0 g, 39.8 mmol) was dissolved in 3-bromo-thiophene (16.4 g, 100.0 mmol) before it was added dropwise into the above mixture. The process of adding would need 50 min. During the above adding process, copper powder (24.0 g, 375.0 mmol) was added in five portions. After **II-a** was added up, the mixture reacted for 15 h while keeping the bath temperature between 200 and 210 °C. Upon cooling, the products were extracted with dichloromethane (2 × 50 mL) and the extraction was filtered through celite and evaporated to give a brown oil, which was purified by flash chromatography on silica gel eluting with petroleum ether (60−90 °C) to provide an orange oil **III-a** (3.27 g; yield, 40.1%). Compounds **III-b**, **III-c**, **III-d**, **III-e**, **III-f**, **III-g**, and **III-h** were prepared according to the same process. All of the substituents at the aromatic rings were listed in **Scheme 1**.

Data for ***III-a***. Yield, 40.1%; oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.96 (dd, $^4J_{HH}$ = 1.2 Hz, $^3J_{HH}$ = 5.1 Hz, 1H, thiophene), 7.21 (d, $^4J_{HH}$ = 1.2 Hz, 1H, thiophene), 7.25 (dd, $^4J_{HH}$ = 3 Hz, $^3J_{HH}$ = 5.1 Hz, 1H, thiophene), 7.32 (t, $^3J_{HH}$ = 7.5 Hz, 1H, Ar−H), 7.36 (t, $^3J_{HH}$ = 7.8 Hz, 1H, Ar−H), 7.44 (dd, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 7.5 Hz, 1H, Ar−H), 7.66 (d, $^3J_{HH}$ = 7.8 Hz, 1H, Ar−H). HRMS, *m*/*z* 205.0156. Calcd for $C_{10}H_7NO_2S$, 205.0197. All of the data are the same as the known compound (*13*).

Data for ***III-b***. Yield, 39.8%; oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.06 (d, $^3J_{HH}$ = 4.8 Hz, 1H, thiophene), 7.31 (d, $^4J_{HH}$ = 2.4 Hz, 1H, thiophene), 7.33 (dt, $^4J_{HH}$ = 2.4 Hz, $^3J_{HF}$ = 8.0 Hz, 1H, Ar−H), 7.40 (dd, $^4J_{HH}$ = 3.2 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, thiophene), 7.49 (dd, $^4J_{HF}$ = 5.6 Hz, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 7.55 (dd, $^4J_{HH}$ = 2.4 Hz, $^3J_{HF}$ = 8.0 Hz, 1H, Ar−H). HRMS, *m*/*z* 223.0103. Calcd for $C_{10}H_6FNO_2S$, 223.0109.

Data for ***III-c***. Yield, 42.2%; oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.07 (dd, $^3J_{HH}$ = 5.2 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, thiophene), 7.12−7.16

Scheme 1. Synthetic Routes to the Title Compounds **III**, **IV**, and **V**



(m, 1H, Ar−H), 7.19 (dd, $^4J_{HH}$ = 2.4 Hz, $^3J_{HF}$ = 8.8 Hz, 1H, Ar−H), 7.36−7.37 (m, 1H, thiophene), 7.41 (dd, $^4J_{HH}$ = 2.8 Hz, $^3J_{HH}$ = 5.2 Hz, 1H, thiophene), 7.88 (dd, $^4J_{HF}$ = 5.2 Hz, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H). HRMS, *m*/*z* 223.0103. Calcd for $C_{10}H_6FNO_2S$, 223.0113.

Data for ***III-d***. Yield, 34.8%; oil. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.07 (dd, $^4J_{HH}$ = 1.2 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, thiophene), 7.33−7.34 (m, 1H, thiophene), 7.40 (dd, $^4J_{HH}$ = 2.8 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, thiophene), 7.45 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.57 (dd, $^4J_{HH}$ = 2.0 Hz, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.81 (d, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H). HRMS, *m*/*z* 238.9807. Calcd for $C_{10}H_6ClNO_2S$, 238.9806.

Data for ***III-e***. Yield, 45.3%. mp, 70−72 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.07 (dd, $^4J_{HH}$ = 1.2 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, thiophene), 7.28 (dd, $^4J_{HH}$ = 1.2 Hz, $^4J_{HH}$ = 2.8 Hz, 1H, thiophene), 7.45 (dd, $^4J_{HH}$ = 2.8 Hz, $^3J_{HH}$ = 5.1 Hz, 1H, thiophene), 7.69 (d, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 7.71 (d, $^4J_{HH}$ = 2.4 Hz, 1H, Ar−H). HRMS, *m*/*z* 272.9418. Calcd for $C_{10}H_5Cl_2NO_2S$, 272.9414.

Data for ***III-f***. Yield, 35.0%; oil. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.06 (dd, $^4J_{HH}$ = 1.2 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, thiophene), 7.34 (dd, $^4J_{HH}$ = 1.2 Hz, $^4J_{HH}$ = 2.8 Hz, 1H, thiophene), 7.41 (dd, $^4J_{HH}$ = 2.8 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, thiophene), 7.57 (d, $^4J_{HF}$ = 7.2 Hz, 1H, Ar−H), 7.71 (d, $^3J_{HF}$ = 8.0 Hz, 1H, Ar−H). HRMS, *m*/*z* 256.9713. Calcd for $C_{10}H_5ClFNO_2S$, 256.9747.

Data for ***III-g***. Yield, 45.8%; mp, 66−68 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.10 (d, $^3J_{HH}$ = 4.8 Hz, 1H, thiophene), 7.37 (s, 1H, thiophene), 7.43 (dd, $^4J_{HH}$ = 2.8 Hz, $^3J_{HH}$ = 5.1 Hz, 1H, thiophene), 7.74 (s, 1H, Ar−H). HRMS, *m*/*z* 306.9028. Calcd for $C_{10}H_4Cl_3NO_2S$, 306.9027.

Data for ***III-h***. Yield, 35.8%; viscosity. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 6.98 (d, $^3J_{HH}$ = 5.2 Hz, 1H, thiophene), 7.34 (t, $^3J_{HH}$ = 5.2 Hz, 1H, thiophene), 7.37 (s, 1H, thiophene), 7.38 (s, 1H, Ar−H), 8.47 (d, $^3J_{HF}$ = 6.8 Hz, 1H, Ar−H). HRMS, *m*/*z* 267.9955. Calcd for $C_{10}H_5FN_2O_4S$, 267.9954.

General Synthetic Procedures for Target Compounds IV-a−V-h. Nitration of compound **III-a** (2.0 g, 9.8 mmol) in 10 mL of acetic anhydride was added dropwise to a solution of $Cu(NO_3)_2 \cdot 3H_2O$ (2.4 g, 9.9 mmol) in 10 mL of acetic anhydride. The solution was held at 10−12 °C for 2 h. Then, the copper salts were removed by filtration, and the residue was poured into ice water. Continuous extraction with dichloromethane (2 × 20 mL) gave a thick oil, which was evaporated and purified by flash chromatography on silica gel eluting with petroleum ether (60−90 °C) to provide a brown mixture, which consisted of 60% **IV-a** ($^4J_{HH}$ = 2.0 Hz, thiophene) and 40% **V-a** ($^3J_{HH}$ = 5.2 Hz, thiophene), as determined by ^{1}H NMR (*14*, *15*). Compounds **IV-a** and **V-a** were isolated with preparative thin-layer chromatography [elution solvent: ethyl acetate/petroleum ether (60−90 °C), 1:9 (v/v)]. Compounds **IV-b**−**V-h** were prepared according to the same process, except compounds **IV-g**, **V-g**, **IV-h**, and **V-h**, which were isolated with preparative thin-layer chromatography [elution solvent: chloroform/petroleum ether (60−90 °C), 1:3 (v/v)]. All of the substituents at the aromatic rings were listed in **Scheme 1**.

Data for ***IV-a***. Yield, 44.6%. mp, 118−120 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.48 (d, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 7.49 (d, $^4J_{HH}$ = 2.0 Hz, 1H, thiophene), 7.59 (t, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 7.69 (t, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 7.93 (d, $^4J_{HH}$ = 1.6 Hz, 1H, thiophene), 7.98 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H). HRMS, *m*/*z* 250.0047. Calcd for $C_{10}H_6NO_2S$, 250.0048. All of the data are the same as the known compound (*15*).

Data for ***IV-b***. Yield, 49.3%. mp, 97−99 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 6.99 (d, $^4J_{HH}$ = 4.0 Hz, 1H, thiophene), 7.43 (dt, $^3J_{HF}$ = 7.6 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, Ar−H), 7.56 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HF}$ = 5.6 Hz,1H, Ar−H), 7.71 (dd, $^3J_{HF}$ = 7.6, $^4J_{HH}$ = 2.4 Hz, 1H, Ar−H), 7.89 (d, $^4J_{HH}$ = 4.0 Hz, 1H, thiophene). HRMS, *m*/*z* 267.9936. Calcd for $C_{10}H_5FNO_2S$, 267.9954.

Data for ***IV-c***. Yield, 49.0%. mp, 99−101 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.02 (d, $^4J_{HH}$ = 4.0 Hz, 1H, thiophene), 7.25 (dt, $^3J_{HF}$ = 7.6 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, Ar−H), 7.33 (ddt, $^3J_{HF}$ = 9.6 Hz, $^3J_{HH}$ = 9.2 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, Ar−H), 7.89 (d, $^4J_{HH}$ = 4.0 Hz, 1H, thiophene), 8.06 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HF}$ = 4.8, 1H, Ar−H). HRMS, *m*/*z* 267.9955. Calcd for $C_{10}H_5FNO_2S$, 267.9954.

Data for ***IV-d***. Yield, 42.2%. mp, 136−138 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.35 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 7.41 (d, $^4J_{HH}$ = 2.0 Hz, 1H, thiophene), 7.58 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 7.83 (d, $^4J_{HH}$ = 2.0 Hz, 1H, thiophene), 7.90 (d, $^4J_{HH}$ = 2.0, 1H, Ar−H). HRMS, *m*/*z* 283.9651. Calcd for $C_{10}H_5ClNO_2S$, 283.9658.

Data for ***IV-e***. Yield, 41.7%. mp, 96−98 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.45 (d, $^4J_{HH}$ = 1.6 Hz, 1H, thiophene), 7.50 (s, 1H, Ar−H), 7.82 (d, $^4J_{HH}$ = 2.0 Hz, 1H, thiophene), 8.20 (s, 1H, Ar−H). HRMS, *m*/*z* 317.9266. Calcd for $C_{10}H_4Cl_2NO_2S$, 317.9268.

Data for ***IV-f***. Yield, 46.1%. mp, 107−109 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.01 (d, $^4J_{HH}$ = 4.0 Hz, 1H, thiophene), 7.63 (d, $^4J_{HF}$ = 7.2 Hz, 1H, Ar−H), 8.20 (d, $^3J_{HF}$ = 7.6 Hz, 1H, Ar−H), 7.89 (d, $^4J_{HH}$ = 4.0 Hz, 1H, thiophene). HRMS, *m*/*z* 301.9569. Calcd for $C_{10}H_4ClFNO_2S$, 301.9564.

Data for ***IV-g***. Yield, 42.1%. mp, 105−107 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.54 (d, $^4J_{HH}$ = 1.6 Hz, 1H, thiophene), 7.79 (s, 1H, Ar−H), 7.91 (d, $^4J_{HH}$ = 2.0 Hz, 1H, thiophene). HRMS, *m*/*z* 351.8868. Calcd for $C_{10}H_3Cl_3NO_2S$, 351.8879.

Data for ***IV-h***. Yield, 34.2%. mp, 113−115 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.48 (d, $^3J_{HF}$ = 10.0 Hz, H-6′), 7.64 (d, $^4J_{HH}$ = 1.6 Hz, H-2), 7.93 (d, $^4J_{HH}$ = 1.6 Hz, H-4), 8.79 (d, $^4J_{HF}$ = 6.8 Hz, H-3′). ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: 120.9, 121.2 (dd, C-6′), 122.8 (d, C-3′), 126.5 (d, C-2), 129.8 (d, C-4), 132.6 (s, C-3), 135.4 (s, C-1′), 142.6 (s, C-5′), 152.2 (s, C-5), 154.2 (s, C-2′), 156.9 (s, C-4′). HRMS, *m*/*z* 312.9802. Calcd for $C_{10}H_4FN_3O_6S$, 312.9804.

Data for ***V-a***. Yield, 29.4%. mp, 108−110 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.01 (d, $^3J_{HH}$ = 5.2 Hz, 1H, thiophene), 7.38 (dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, Ar−H), 7.59 (d, $^3J_{HH}$ = 5.2 Hz, 1H, thiophene), 7.64 (dt, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.6 Hz, 1H, Ar−H), 7.72 (dt, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, Ar−H), 8.25 (dt, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, Ar−H). HRMS, *m*/*z* 249.0057 $[M-1]^+$. Calcd for $C_{10}H_6NO_2S$, 250.0048. All of the data are the same as the known compound (*15*).

Data for ***V-b***. Yield, 24.0%. mp, 132−134 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 6.92 (d, $^3J_{HH}$ = 5.2 Hz, 1H, thiophene), 7.30 (dt, $^3J_{HH}$ = 8.4 Hz, $^4J_{HF}$ = 5.6 Hz, 1H, Ar−H), 7.37 (dt, $^3J_{HH}$ = 8.4 Hz, $^3J_{HF}$ = 7.2 Hz, 1H, Ar−H), 7.53 (d, $^3J_{HH}$ = 5.2 Hz, 1H, thiophene), 7.88 (d, $^3J_{HF}$ = 8.0 Hz, 1H, Ar−H). HRMS, *m*/*z* 267.9947. Calcd for $C_{10}H_5FNO_2S$, 267.9954.

Data for ***V-c***. Yield, 20.9%. mp, 150−152 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 6.92 (d, $^3J_{HH}$ = 5.6 Hz, 1H, thiophene), 7.01 (dd, $^3J_{HF}$ = 8.4 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, Ar−H), 7.37 (ddt, $^3J_{HF}$ = 9.2 Hz, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, Ar−H), 7.54 (d, $^3J_{HH}$ = 5.2 Hz, 1H, thiophene), 8.24 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HF}$ = 4.8, 1H, Ar−H). HRMS, *m*/*z* 267.9966. Calcd for $C_{10}H_5FNO_2S$, 267.9954.

Data for ***V-d***. Yield, 26.0%. mp, 108−110 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 6.91 (d, $^3J_{HH}$ = 5.2 Hz, 1H, thiophene), 7.25 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.54 (d, $^3J_{HH}$ = 5.6 Hz, 1H, thiophene), 7.62 (dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 8.16 (d, $^4J_{HH}$ = 2.0, 1H, Ar−H). HRMS, *m*/*z* 283.9639. Calcd for $C_{10}H_5ClNO_2S$, 283.9658. All of the data are the same as the known compound (*6*).

Data for ***V-e***. Yield, 24.5%. mp, 118−120 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.01 (d, $^3J_{HH}$ = 5.2 Hz, 1H, thiophene), 7.47 (s, 1H, Ar−H), 7.63 (d, $^3J_{HH}$ = 5.2 Hz, 1H, thiophene), 8.52 (s, 1H, Ar−H). HRMS, *m*/*z* 317.9265. Calcd for $C_{10}H_4Cl_2NO_2S$, 317.9268.

Data for ***V-f***. Yield, 20.2%. mp, 125−127 °C (acetone/petroleum ether).^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 6.99 (d, $^3J_{HH}$ = 5.6 Hz, 1H, thiophene), 7.47 (d, $^4J_{HF}$ = 7.2 Hz, 1H, Ar−H), 7.63 (d, $^3J_{HH}$ = 5.6 Hz, 1H, thiophene), 8.08 (d, $^3J_{HF}$ = 8.0 Hz, 1H, Ar−H). HRMS, *m*/*z* 301.9569. Calcd for $C_{10}H_4ClFNO_2S$, 301.9564.

Data for ***V-g***. Yield, 20.4%; oil. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.03 (d, $^3J_{HH}$ = 4.0 Hz, 1H, thiophene), 7.81 (s, 1H, Ar−H), 7.89 (d, $^3J_{HH}$ = 4.0 Hz, 1H, thiophene). HRMS, *m*/*z* 351.8876. Calcd for $C_{10}H_3Cl_3NO_2S$, 351.8879.

Data for ***V-h***. Yield, 22.1%; viscosity. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.06 (d, $^3J_{HH}$ = 4.0 Hz, H-4), 7.49 (d, $^3J_{HF}$ = 10.0 Hz, 1H, H-6′), 7.85 (d, $^3J_{HH}$ = 4.0 Hz, H-5), 8.68 (d, $^4J_{HF}$ = 6.8 Hz, 1H, H-3′). ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: 121.6, 121.8 (dd, C-6′), 122.8 (d, C-3′), 127.2 (d, C-4), 127.4 (d, C-5), 133.0 (s, C-3), 135.8 (s, C-1′), 139.1 (s, C-2), 143.1 (s, C-5′),

Table 1. Fungicidal Activity of the Compounds **III-a**−**V-h**[a]

compound	concentration (μg mL^{-1})	*A. solani* inhibition (%)	*G. zeae* inhibition (%)	*P. piricola* inhibition (%)	*F. omysporum* inhibition (%)	*C. arachidicola* inhibition (%)
III-a	50	75	65	88	68	18
	20	30	43	68	31	0
	10	0	13	20	12	0
III-b	50	55	39	80	75	0
	20	35	30	20	50	0
	10	10	8	0	0	0
III-c	50	75	65	72	87	25
	20	25	43	36	50	12
	10	5	21	0	18	0
III-d	50	55	39	80	75	25
	20	20	21	38	43	6
	10	0	13	14	25	0
III-e	50	60	39	82	87	25
	20	55	26	72	81	18
	10	20	8	42	56	0
III-f	50	60	47	80	87	25
	20	35	30	74	43	18
	10	0	0	64	18	0
III-g	50	49	47	90	36	50
III-h	50	68	100	100	100	100
IV-a	50	22	25	20	0	20
	20	16	7	9	0	16
	10	6	1	0	0	8
IV-b	50	41	12	46	25	44
	20	25	0	10	17	27
	10	6	0	4	7	11
IV-c	50	35	16	27	28	33
	20	16	0	8	10	22
	10	0	0	0	0	0
IV-d	50	19	4	2	17	2
	20	0	0	0	0	0
	10	0	0	0	0	0
IV-e	50	41	24	25	39	27
	20	32	16	17	32	16
	10	25	8	10	21	5
IV-f	50	25	0	14	10	16
	20	16	0	2	7	11
	10	0	0	0	0	0
IV-g	50	34	0	24	4	35
	20	26	0	10	0	20
	10	17	0	0	0	5
IV-h	50	58	54	100	60	100
V-a	50	25	23	30	22	25
	20	16	14	25	13	16
	10	9	6	0	0	8
V-b	50	48	0	14	17	16
	20	25	0	4	7	0
	10	9	0	0	0	0
V-c	50	29	0	10	21	11
	20	16	0	0	0	0
	10	0	0	0	0	0
V-d	50	9	0	25	17	0
	20	0	0	10	0	0
	10	0	0	0	0	0
V-e	50	38	0	27	28	27
	20	32	0	17	14	11
	10	16	0	2	10	0
V-f	50	61	20	42	39	18
	20	54	4	36	28	5
	10	48	0	12	14	0
V-g	50	34	0	40	22	40
	20	26	0	13	0	25
	10	0	0	0	0	5
V-h	50	100	100	100	100	85
fenpiclonil	50	100	100	100	18	100

[a] The data are the average of three duplicate results.

Table 2. EC_{50} Values of the Compounds **III-g**, **III-h**, **IV-h**, **V-h**, and Fenpiclonil

III-g	$y = a + bx$	EC_{50}	R	III-h	$y = a + bx$	EC_{50}	R
A. solani		>50		*A. solani*	$y = 2.392 + 1.860x$	25.20	0.99
G. zeae		>50		*G. zeae*	$y = 0.559 + 3.084x$	27.53	0.99
P. piricola	$y = 3.399 + 1.023x$	36.67	0.96	*P. piricola*	$y = 4.044 + 1.481x$	4.41	0.99
F. omysporum		>50		*F. omysporum*	$y = 1.855 + 2.628x$	4.42	0.99
C. arachidicola		>50		*C. arachidicola*	$y = 3.127 + 2.190x$	7.16	0.99
IV-h				**V-h**			
A. solani	$y = 2.868 + 1.398x$	33.49	0.99	*A. solani*	$y = 3.461 + 1.045x$	29.62	0.94
G. zeae	$y = 1.458 + 2.795x$	18.50	0.97	*G. zeae*	$y = 3.104 + 2.059x$	8.33	0.95
P. piricola	$y = 4.048 + 1.481x$	4.39	0.99	*P. piricola*	$y = 3.854 + 2.070x$	3.57	0.99
F. omysporum	$y = 3.584 + 0.893x$	38.44	0.94	*F. omysporum*	$y = 3.932 + 1.434x$	5.55	0.99
C. arachidicola	$y = 3.443 + 1.602x$	9.36	0.96	*C. arachidicola*	$y = 3.798 + 1.487x$	6.42	0.99
fenpiclonil							
A. solani	$y = 5.340 + 1.322x$	0.55	0.96				
G. zeae	$y = 4.584 + 1.780x$	1.71	0.97				
P. piricola	$y = 5.226 + 2.352x$	0.80	0.99				
F. omysporum		>50					
C. arachidicola	$y = 5.477 + 1.153x$	0.38	0.95				

153.9 (s, C-2′), 156.6 (s, C-4′). HRMS, *m*/*z* 312.9817. Calcd for $C_{10}H_4FN_3O_6S$, 312.9804.

Bioassays. The fungicidal activity of the compounds **III-a**−**III-h** and **IV-a**−**V-h** were tested *in vitro* against *Alternaria solani*, *Gibberella zeae*, *Physalospora piricola*, *Fusarium omysporum*, and *Cercospora arachidicola*, and their relative inhibitory ratio (%) has been determined using the mycelium growth rate method (*16*). Fenpiclonil was used as a control. After the mycelia grew completely, the diameters of the mycelia were measured, and the inhibition rate is calculated according to the formula:

$$I = (D1 - D2)/D1 \times 100\%$$

In the formula, I is the inhibition rate, $D1$ is the average diameter of mycelia in the blank test, and $D2$ is the average diameter of mycelia in the presence of those compounds. The inhibition ratios of those compounds at the dose of 50, 20, and 10 μg mL^{-1} have been determined, and the experimental results are summarized in **Table 1**. The EC_{50} values of the high fungicidal activity compounds **III-g**, **III-h**, **IV-h**, and **V-h** and fenpiclonil have been calculated by the Scatchard method. The results are summarized in **Table 2**.

RESULTS AND DISCUSSION

Synthesis and Structure Elucidation. In the previous paper, compound **III-a** was synthesized using 1-bromo-2-nitrobenzene and 3-iodothiophene by the Ullmann coupling reaction but the yield was not reported (*13*). Under the same conditions, **III-a** was synthesized using 1-bromo-2-nitrobenzene and 3-bromo-thiophene, which reacted for 20 h with 20.0% yield and obtained the byproduct 2,2′-dinitrobiphenyl (yield, 80.0%). One molecular equivalent of cuprous iodide was added, mixed with 3-bromothiophene, and then heated to 160 °C for 1 h before 1-bromo-2-nitrobenzene was added. Compound **III-a** (yield, 40.1%) and 2,2′-dinitrobiphenyl (yield, 59.9%) were obtained after 15 h. The other target compounds were all synthesized in this novel way. Regrettably, 2-bromo-1-nitro-4-(trifluoromethyl)benzene, 1-bromo-3-nitrobenzene, and 2-bromo-1-nitro-3-(trifluoromethyl) benzene were not successful in obtaining the corresponding target compounds. Additionally, in the process of the synthesis of 3-bromo-thiophene, the production of bromization of thiophene in the first step was used in the subsequent step without further purification and had a satisfactory yield (80.8%).

Because the compounds **IV-a**−**V-h** were not easily separated, they were finally isolated with the preparative layer chromatography. The structures of two important compounds (**IV-h** and **V-h**) were elucidated by 1D and 2D NMR.

The molecular formula of **IV-h** was revealed as $C_{10}H_4FN_3O_6S$ by HRMS data $[M]^+$ (calcd., 312.9804; found, 312.9802). The ^1H and ^{13}C NMR (Data for **IV-h**) spectra showed the signals of six quaternary, four CH, carbon atoms. Considering the reagents, the HMQC spectra showed that $\delta_H = 7.48$ (d, H-6′) and $\delta_H = 8.79$ (d, H-3′) belong to the Ar−H, which was confirmed by $^3J_{HF} = 10.0$ Hz and $^4J_{HF} = 6.8$ Hz; $\delta_H = 7.64$ (d, H-2) and $\delta_H = 7.93$ (d, H-4) belong to the thiophene ring, which was confirmed by the $^4J_{HH} = 1.6$ Hz. The chemical-shift value of C-6′ in the ^{13}C NMR spectra was split by Ar−F into two signals $\delta = 120.9$ and 121.2, which was confirmed by the HMQC spectra.

On the basis of the HMBC spectra, the correlations between H-6′ ($\delta_H = 7.48$) and C-1′, C-5′, C-2′, and C-4′ [$\delta_C = 135.4$ (s, C-1′), 142.6 (s, C-5′), 154.2 (s, C-2′), and 156.9 (s, C-4′)], the correlations between H-3′ ($\delta_H = 8.79$) and C-1′, C-5′, C-2′, and C-4′ [$\delta_C = 135.4$ (s, C-1′), 142.6 (s, C-5′), 154.2 (s, C-2′), and 156.9 (s, C-4′)], the correlations between H-2 ($\delta_H = 7.64$) and C-3 and C-4 [$\delta_C = 132.6$ (s, C-3) and 129.8 (d, C-4)], the correlations between H-4 ($\delta_H = 7.93$) and C-1′, C-2, C-3, and C-5 [$\delta_C = 135.4$ (s, C-1′), 126.5 (d, C-2), 132.6 (s, C-3), and 152.2 (s, C-5)] indicated that the structure of **IV-h** should be as follows in **Figure 2**.

In the NOESY spectra, the correlations between H-6′ ($\delta_H = 7.48$) and H-4 ($\delta_H = 7.93$) indicated that H-6′ and H-4 are on the same side.

The ^1H and ^{13}C NMR (Data for **V-h**) spectra of **V-h** are the same as those of **IV-h** on the whole. However, there are evident differences in the 2D NMR as follows: In the HMBC spectra, the correlations between H-6′ ($\delta_H = 7.49$) and C-1′, C-5′, C-2′, and C-4′ [$\delta_C = 135.8$ (s, C-1′), 143.1 (s, C-5′), 153.9 (s, C-2′), and 156.6 (s, C-4′)], the correlations between H-3′ ($\delta_H = 8.68$) and C-1′, C-5′, C-2′, and C-4′ [$\delta_C = 135.8$ (s, C-1′), 143.1 (s, C-5′), 153.9 (s, C-2′), and 156.6 (s, C-4′)], the correlations between H-4 ($\delta_H = 7.06$) and C-5, C-3, C-2, and C-1′ [$\delta_C = 127.4$ (d, C-5), 133.0 (s, C-3), 139.1 (s, C-2), and 135.8 (s, C-1′)], the correlations between H-5 ($\delta_H = 7.85$) and C-4 and C-2 [$\delta_C = 127.2$ (d, C-4) and 139.1 (s, C-2)] indicated that the structure of **V-h** should be as follows in **Figure 2**.

In the NOESY spectra, the correlations between H-4 ($\delta_H = 7.06$) and H-5 ($\delta_H = 7.85$) indicated that H-4 and H-5 are nearby.

Biological Assay and SAR. The data in **Table 1** show the fungicidal activities against *A. solani*, *G. zeae*, *P. piricola*, *F. omysporum*, and *C. arachidicola* of the title compounds

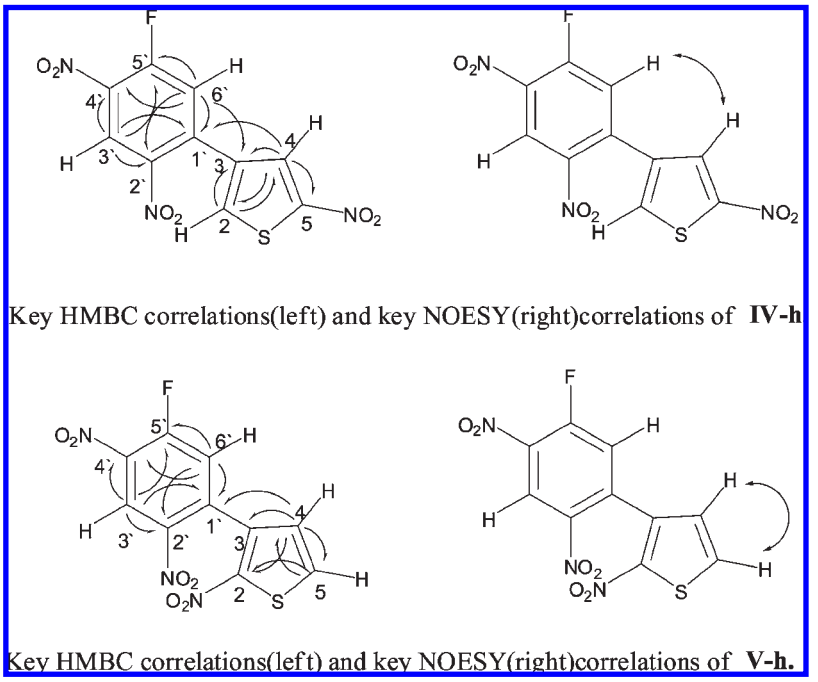


Figure 2. Key HMBC correlations and key NOESY correlations of **IV-h** and **V-h**.

III-a−**V-h**. The data in **Table 2** show the EC_{50} values of the high fungicidal activity compounds **III-g**, **III-h**, **IV-h**, and **V-h** and the commercial fungicide fenpiclonil.

Fungicidal Activity against A. solani. The screening data of **Table 1** indicated that, at the dosage of 50 μg mL^{-1}, some compounds of **III-a**−**V-h** exhibited excellent activity against *A. solani*. For instance, the inhibition activity of **III-a**−**III-h** were more than 50%, and the inhibition activity of **V-h** was equal to the commercialized fenpiclonil. At the dosage of 20 and 10 μg mL^{-1}, the fungicidal activities evidently decreased and the fungicidal activities of compounds **IV-a**−**V-h** are lower than those of **III-a**−**III-h**. It may be owing to the nitration of the thiophene ring that resulted in the activity to be decreased.

Fungicidal Activity against G. zeae. At the dosage of 50 μg mL^{-1}, compounds of **III-a**, **III-c**, and **IV-h** exhibited moderate activity and **IV-f**, **IV-g**, **V-b**−**V-e**, and **V-g** exhibited no activity. However, the fungicidal activity of **III-h** and **V-h** were equal to the fenpiclonil at this dosage. As the concentration of compounds **III-a**−**V-h** declining, its biological activity decreased.

Fungicidal Activity against P. piricola. At the dosage of 50 μg mL^{-1}, compounds of **III-a**−**III-h** exhibited excellent activity, while **IV-a**−**IV-g** and **V-a**−**V-g** exhibited low activity against *P. piricola*. Compound **III-g** showed 90% inhibition, which might be owing to the biological activity of adding halogen atoms to the aromatic ring. The fungicidal activities of **III-h**, **IV-h**, and **V-h** were the same as fenpiclonil at this dosage. Although at the low concentrations the fungicidal activities evidently declined, **III-h**, **IV-h**, and **V-h** still exhibited moderate activity, which can be shown from their EC_{50} values (**Table 2**). This might be owing to the biological activity of adding nitro to the aromatic ring.

Fungicidal Activity against F. omysporum. The biological activity rules of **III-a**−**V-h** against *F. omysporum* are generally the same as the test against *P. piricola*. The EC_{50} value of **V-h** against *F. omysporum* is 5.55 μg mL^{-1}, while that of fenpiclonil is more than 50 μg mL^{-1} (**Table 2**).

Fungicidal Activity against C. arachidicola. The screening data of **Table 1** indicated that most target compounds exhibited low activity against *C. arachidicola*, except for **III-h**, **IV-h**, and **V-h**. At the dosage of 50 μg mL^{-1}, **III-h**, **IV-h**, and fenpiclonil exhibited 100% inhibition against *C. arachidicola* and **V-h** showed 85% inhibition. Owning to adding nitro to the aromatic ring might be essential for high fungicidal activity.

The screening data of **Tables 1** and **2** indicated that, athough the fungicidal activities of most target compounds are lower than that of fenpiclonil, compound **V-h** has higher fungicidal activity than fenpiclonil against *F. omysporum*. Therefore, the **V-h** could be developed as a leading compound for further structural optimization.

In conclusion, a novel and facile procedure for preparation analogues of pyrrolnitrin from 3-bromo-thiophene with corresponding substituted nitrobenzene was described, and 24 3-(2-nitrophenyl) thiophene derivatives were synthesized. The results of the bioassay showed that some of these title compounds exhibited favorable fungicidal activities against *A. solani*, *G. zeae*, *P. piricola*, *F. omysporum*, and *C. arachidicola* at the dosage of 50 μg mL^{-1}; **III-h**, **IV-h**, and **V-h** still exhibited moderate activity against *P. piricola* at low dosage. Although the fungicidal activities of most target compounds are lower than that of fenpiclonil, the EC_{50} value of **V-h** against *F. omysporum* is 5.55 μg mL^{-1}, while that of fenpiclonil is more than 50 μg mL^{-1} (**Table 2**). Therefore, the **V-h** could be developed as a leading compound for further structural optimization. The possible SAR is as follows: The nitration of the thiophene ring may result from the activity to be decreased. The adding of halogen atoms and nitro to the aromatic ring might be essential for high fungicidal activity.

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