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Design, synthesis and fungicidal activities of phenazine-1-carboxamida conjugates of 1,3,4-thia(oxa)diazole

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Abstract: Phenazine-1-carboxylic acid (PCA), isolated from *Pseudomonas,* is a very important fungicidal agent. PCA and its derivatives revealed good biological activities in the field of medicine and agrichemicals. In this paper, two series of PCA derivatives containing 1,3,4-thiadiazole and 1,3,4-oxadiazole were designed and synthesized to explore novel fungicidal candidates. Their *in vitro* and *in vivo* fungicidal activities were evaluated. The title compounds **I$_8$** (X=S, R=2-OCH$_3$) and **I$_{22}$** (X=O, R=2-OCH$_3$) had EC$_{50}$ vaues of 33.25 μg/mL and 46.52 μg/mL against *Fusarium graminearum*, respectively, which were about 3-4 times better than of PCA (EC$_{50}$ = 128.54 μg/mL). *In vivo* results showed that compounds **I$_8$** and **I$_{22}$** gave better bioactivity (inhibitory rates of 58.69% and 55.37% at 500 μg/mL, respectively) against *F. graminearum* than that of PCA (25.14%). Preliminary structure-activity relationship study found that the introduction of electron-donating groups were favored to improving the activity of the derivatives, and the substitution at *ortho*-position of benzene ring would be favored to fungicidal activity. The substitution position of the same substituent on the benzene ring was in the order of *o* > *p* > *m* according to the bioactivity.These results can be used to guide the further structural modification of these compounds for novel fungicidal agent.

Keywords: phenazine-1-carboxylic acid; 1,3,4-thiadiazole; 1,3,4-oxadiazole; fungicidal activity

含 1,3,4-噻 (噁) 二唑吩嗪-1-甲酰胺类衍生物的合成与杀菌活性

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摘 要：对广泛存在于链霉菌和铜绿假单胞菌中的一种天然活性物质——申嗪霉素进行了结构修饰，合成了一系列高活性的含 1,3,4-噻 (噁) 二唑的申嗪霉素衍生物 **I$_1$**~**I$_{28}$**。杀菌活性测定结果表明：所有目标化合物对禾谷镰刀菌具有较好的杀菌活性，均明显优于母体申嗪霉素。离体杀菌活性测定结果显示，化合物 **I$_8$** (EC$_{50}$ = 33.25 μg/mL) 和化合物 **I$_{22}$** (EC$_{50}$ = 46.52 μg/mL) 对禾谷镰刀菌的杀菌活性是申嗪霉素 (EC$_{50}$ = 128.54 μg/mL) 的 3~4 倍。活体杀菌活性显示，在 500 μg/mL

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质量浓度下，化合物 $\mathbf{I_8}$ (58.69%) 和化合物 $\mathbf{I_{22}}$ (55.37%) 对禾谷镰刀菌的抑制率是申嗪霉素 (25.14%) 的两倍。构效关系分析结果表明，在苯环上引入吸电子基团对化合物的活性不利；而引入给电子基团则有利于提高其杀菌活性。同时，同一取代基在苯环上的取代位置依据活性的高低排列顺序为：邻位>对位>间位。这些结果可用于指导该类化合物的进一步结构改造。

关键词: 吩嗪-1-甲酸；1,3,4-噻二唑；1,3,4-噁二唑；杀菌活性

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0 Introduction

Phenazine-1-carboxylic acid (PCA), the bioactive product in *Pseudomonas fluorescens* isolated from plant roots, has been registered as a biocide "Shenqinmycin" in China to control rice sheath blight. PCA plays a key role in inhibiting fungal infection and contributing to ecological balance[1] . The first activity research of PCA was carried out as a well known microbial pesticide, and then it be applied in medicine field, including antiviral[2], antitumorigenic[3], antitubercular[4] and antibacteria[5]. Due to its broad-spectrum biological activity, low toxicity and ecological friendliness, PCA also has been widely used in the field of agriculture[6], for the control of fungal diseases caused by *Fusarium oxysporum*[7], *Rhizoctonia solani*[8], *Botrytis cinerea*[9] and *Fusarium graminearum*[10].

Nitrogen-containing heterocycles, display extremely extensive and excellent biological activities, have long been concerned in medicinal chemistry. Recently, our group has been committed to the bioactivity development of nitrogen-based heterocyclic derivatives, such as 1,3-thiazolidine-2-thione[11], tetrahydroquinoline[12], 3,5-dimethylpyrazole[13], thiazolidin-2-cyanamide[14] and 2,4-disubstituted oxazole[15]. Furthermore, 1,3,4-thiadiazole and 1,3,4-oxadiazole are known important class of five-membered heterocyclics, with worth expecting biological activities, such as insecticidal[16], fungicidal[17-18], herbicidal[19-20] and anticancer activities[21-22]. In our previous work, 1,3,4-thiadiazole derivatives have very good fungicidal activities[23]. The most promising candidate showed EC_{50} value of 5.7 μg/mL against *Phytophthora infestans*, about two-ninth and one-fifth of the positive controls of bupidoline and carbendazim, respectively. In addition, another study about 1,3,4-oxadiazole derivatives showed *in vivo* fungicidal activity against *B. cinerea* and *R. solanii* at 500 μg/mL obviously[24].

It is well known that amide bonds have been widely recognized as the common type of bond in drug molecules[25]. In this work, according to the reasonable structure optimization and amide bond link mode, two series of PCA derivatives containing 1,3,4-thia(oxa)diazol were designed and synthesized to obtain more promissing fungicidal agents (**Scheme 1**). All title compounds were final product and characterized by mass spectrometry, elemental analysis, and nuclear magnetic resonance spectroscopy, and their fungicidal activities were evaluated. The preliminary structure-activity relationships of these compounds will be elucidated. The synthetic routes of compounds $\mathbf{I_1}$-$\mathbf{I_{28}}$ were shown in **Scheme 2**.

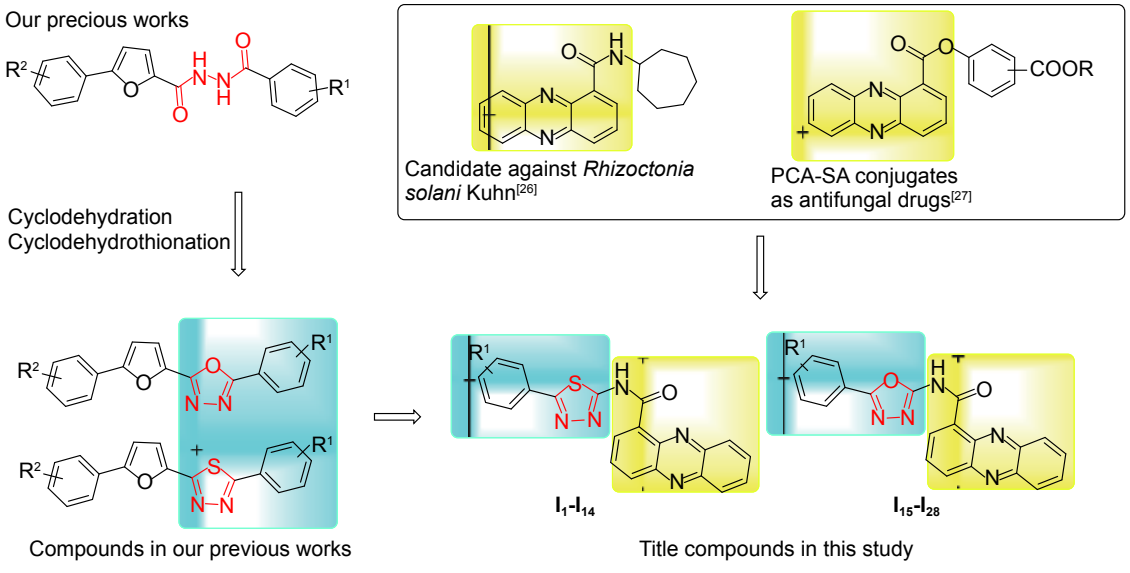
1 Materials and methods

1.1 Instrumental analysis

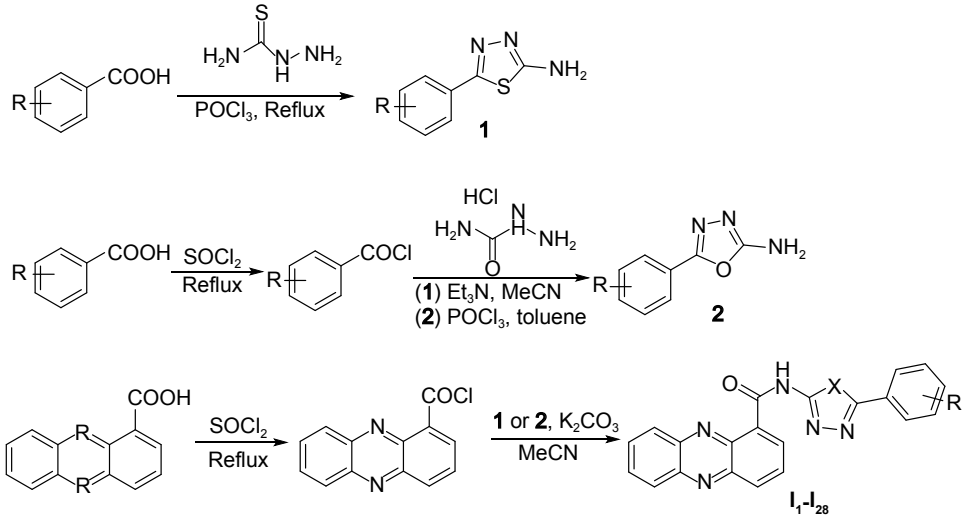
The melting points were determined with a Cole-Parmer melting point apparatus while the thermometer was uncorrected. ^{1}H NMR spectra were recorded on Bruker Avance DRX spectrometer at 600 MHz. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F254), and spots were visualized with ultraviolet (UV) light. Elemental analysis was carried out with a Flash EA 1112 elemental analyzer and was performed at the laboratories of the Institute of Chemistry, Chinese Academy of Sciences. All strains were provided by Institute of Plant Protection, Chinese Academy of Agricultural Sciences.

1.2 Synthetic procedures

1.2.1 General procedure for the synthesis of 2-amino-5-aryl-1,3,4-thiadiazole A mixture of thiosemicarbazide (10 mmol) and aryl substituted



Scheme 1 The proposed synthetic route for the title compounds



Scheme 2 The synthetic route of the novel phenazine-1-carboxylic acid derivatives

carboxylic acid (10 mmol), and phosphorus oxychloride (5 mL) was refluxed for 0.5 hours. Upon completion of the reaction, turned off the heat and cooled to room temperature. Ice water (100 mL) was added to system very slowly till complete decomposition of $POCl_3$ then the mixture was basified to pH 8 by 50% NaOH solution. The formed precipitate was filtered, washed with water, and dried to afford the corresponding 1,3,4-thiadiazol-2-amines.

1.2.2 General procedure for the synthesis of 2-amino-5-aryl-1,3,4-oxadiazole Substituted benzoyl chloride obtained by reacting corresponding substituted benzoic acid (10 mmol) with dichlorosulfoxide (10 mL) for 2 h was slowly added to semicarbazide hydrochloride (10 mmol), triethylamine (20 mmol) and acetonitrile (30 mL) at low temperature, and then the reaction was transferred to room temperature stirring for 6 h. Reaction liquid filtration. The solid was heated with phosphorus oxychloride and toluene for reflux for 3 h. When the reaction liquid was cooled to room temperature, 100 mL ice water was added to quench excess phosphorus oxychloride, and 50% NaOH solution was used to adjust the pH to 8.0. The formed precipitate was filtered, washed with water, and dried to afford the corresponding 1,3,4-oxadiazole-2-amines.

1.2.3 General synthetic procedure for the title compounds $\mathbf{I_1}$-$\mathbf{I_{28}}$ The title compounds were obtained by reaction of the key intermediates with phenazine-1-formyl chloride, **1** or **2**, potassium

carbonate and acetonitrile. The reaction was transferred to room temperature and stirred for 1 h. After the reaction, dichloromethane and water were added to extract, and the organic layer was concentrated to obtain the crude product. The product was purified by column chromatography (40 mm × 250 mm) on silica gel using dichloromethane and methanol *V*/*V* 95 : 5) as the eluent to yield the title compounds **I_1-I_{28}**.

1.3 Fungicidal activity

1.3.1 *In vitro* fungicidal activity *In vitro* fungicidal activities of the compounds **I_1-I_{28}** were tested against *M. oryzae, B. cinerea, P. capsici, R. solani* and *F. graminearum*, using a plate method (PDA medium)[28-29]. Their relative inhibition rate (%) was determined using the mycelium growth rate method[30-31]. The PCA was assessed under the same conditions as the positive control. After the mycelia grew completely, the diameters of the mycelia were measured and the inhibition rate was calculated according to the formula (1).

$$I/\% = [(D_1 - D_2)/D_1] \times 100 \quad (1)$$

In the formula: I is the inhibition rate, %; D_1 is the average diameter of mycelia in the blank test, and D_2 is the average diameter of mycelia in the presence of those compounds[32].

1.3.2 *In vivo* fungicidal activity Because the *in vitro* fungicidal activities of the compounds with electron-donating groups were generally better than the compounds with electron-withdrawing groups, we chose the compounds with electron-donating groups for the further experiments. Using the pot culture test[33], twelve compounds with electron-donating groups and two compounds without substituent were selected for *in vivo* fungicidal activitytests against five phytopathogenic fungi including *M. oryzae, B. cinerea, P. capsici, R. solani* and *F. graminearum*. Compounds were prepared into a solution with a concentration of 500 μg/mL. PCA was assessed under the same conditions as the positive control. The culture plates were cultivated at (24 ± 1) °C. The rice, cucumber, pepper and wheat seeds were soaked in water for 2 h at 50 °C and then kept moist for 24 h at 28 °C in an incubator. When the radicles were 0.5 cm, the seeds grow in plastic pots containing a 1 : 1(*V*/*V*) mixture of vermiculite and peat. Cucumber, pepper and wheat were at the stage of two seed leaves and rice was at the stage of three seed leaves. Tested compounds were confected to 2.5% EC (emulsifiable concentration) formulations, in which pesticide emulsifier 600 (2.125%) and pesticide emulsifier 500 (0.375%) were the additives, DMSO (0.1%) was the solvent, and xylene was the co-solvent. The formulation was diluted to 500 μg/mL by water. The pathogenic fungi were inoculated to the surface of seed leaves and then the solution of title compounds was sprayed using a hand sprayer. Three replicates for each treatment were conducted. After inoculation, the plants were maintained at (24 ± 1) °C and above 80% relative humidity. When the untreated plant (blank control) fully developed symptoms, the fungicidal activity was assessed. To determine the average disease index, the area of inoculated leaves covered by disease symptoms was evaluated and compared to that of untreated ones. The relative control efficacy of compounds compared to the blank assay was calculated by using the following formula (2).

$$E_r/\% = [(I_{CK} - I_{PT})/I_{CK}] \times 100 \quad (2)$$

In the formula, E_r is relative control efficacy, I_{CK} is the average disease index during the blank assay and I_{PT} is the average disease index after treatment during testing.

2 Results and discussion

2.1 Synthesis of the title compounds

Physical and chemical data of the title compounds **I_1-I_{28}** were listed in **Table 1**. ^{1}H NMR were listed in **Table 2**.

2.2 Fungicidal activity

2.2.1 *In vitro* fungicidal activity All the title compounds were primarily screened *in vitro* against five phytopathogenic fungi, *F. graminearum*, *P. capsici*, *R. solani, M. oryzae* and *B. cinerea,* with PCA as control. The results of the preliminary bioassay were shown in **Table 3**. The results showed that all title compunds with EC_{50} values between 33.25 and 99.45 μg/mL, which exhibited better

Table 1 Physical and chemical data of title compounds $\mathbf{I_1}$-$\mathbf{I_{28}}$

Compd.	X	R	Appearance	Yield/%	Elemental analysis (Calcd., %)		
					C	H	N
$\mathbf{I_1}$	S	H	Yellow solid	84	65.78(65.98)	3.42(3.82)	18.27(18.54)
$\mathbf{I_2}$	S	2-Cl	Yellow solid	82	60.36(60.12)	2.89(3.04)	16.76(16.53)
$\mathbf{I_3}$	S	3-Cl	Yellow solid	91	60.36(60.55)	2.89(2.64)	16.76(16.89)
$\mathbf{I_4}$	S	4-Cl	Yellow solid	90	60.36(60.60)	2.89(3.01)	16.76(16.49)
$\mathbf{I_5}$	S	2-F	Yellow solid	89	62.83(62.99)	3.01(3.22)	17.45(17.19)
$\mathbf{I_6}$	S	3-F	Yellow solid	90	62.83(62.61)	3.01(2.86)	17.45(17.68)
$\mathbf{I_7}$	S	4-F	Yellow solid	93	62.83(63.03)	3.01(3.25)	17.45(17.27)
$\mathbf{I_8}$	S	2-OCH_3	Yellow solid	94	63.91(64.12)	3.66(3.87)	16.94(16.72)
$\mathbf{I_9}$	S	3-OCH_3	Yellow solid	88	63.91(63.82)	3.66(3.49)	16.94(17.11)
$\mathbf{I_{10}}$	S	4-OCH_3	Yellow solid	93	63.91(64.19)	3.66(3.92)	16.94(16.71)
$\mathbf{I_{11}}$	S	2-CH_3	Yellow solid	91	66.48(66.25)	3.80(3.61)	17.62(17.83)
$\mathbf{I_{12}}$	S	3-CH_3	Yellow solid	89	66.48(66.66)	3.80(3.98)	17.62(17.48)
$\mathbf{I_{13}}$	S	4-CH_3	Yellow solid	91	66.48(66.30)	3.80(3.59)	17.62(17.91)
$\mathbf{I_{14}}$	S	4-CF_3	Yellow solid	90	58.53(58.75)	2.68(2.41)	15.51(15.68)
$\mathbf{I_{15}}$	O	H	Yellow solid	88	68.66(68.79)	3.57(3.38)	19.06(19.29)
$\mathbf{I_{16}}$	O	2-Cl	Yellow solid	89	62.77(62.98)	3.01(3.22)	17.43(17.16)
$\mathbf{I_{17}}$	O	3-Cl	Yellow solid	88	62.77(63.01)	3.01(2.86)	17.43(17.24)
$\mathbf{I_{18}}$	O	4-Cl	Yellow solid	94	62.77(62.54)	3.01(3.18)	17.43(17.59)
$\mathbf{I_{19}}$	O	2-F	Yellow solid	91	65.45(65.71)	3.14(3.37)	18.17(18.29)
$\mathbf{I_{20}}$	O	3-F	Yellow solid	80	65.45(65.22)	3.14(3.01)	18.17(18.33)
$\mathbf{I_{21}}$	O	4-F	Yellow solid	83	65.45(65.67)	3.14(2.86)	18.17(17.91)
$\mathbf{I_{22}}$	O	2-OCH_3	Yellow solid	85	66.49(66.24)	3.80(3.62)	17.62(17.87)
$\mathbf{I_{23}}$	O	3-OCH_3	Yellow solid	80	66.49(66.71)	3.80(4.06)	17.62(17.41)
$\mathbf{I_{24}}$	O	4-OCH_3	Yellow solid	88	66.49(66.67)	3.80(3.58)	17.62(17.70)
$\mathbf{I_{25}}$	O	2-CH_3	Yellow solid	81	69.28(69.01)	3.96(4.15)	18.36(18.24)
$\mathbf{I_{26}}$	O	3-CH_3	Yellow solid	86	69.28(69.52)	3.96(4.20)	18.36(18.12)
$\mathbf{I_{27}}$	O	4-CH_3	Yellow solid	88	69.28(69.45)	3.96(3.75)	18.36(18.54)
$\mathbf{I_{28}}$	O	4-CF_3	Yellow solid	80	60.69(60.91)	2.78(2.54)	16.09(16.37)

fungicidal activities against *F. graminearum* than PCA(EC_{50} = 128.54 μg/mL).

In particular, compounds $\mathbf{I_8}$, $\mathbf{I_{11}}$ and $\mathbf{I_{22}}$, which had more potential fungicidal activities against *F. graminearum*, had about 3-4 times the activity of PCA. Although the compounds had no significant inhibitory activities against *P. capsici*, $\mathbf{I_{22}}$ (EC_{50} 7.24 g/mL) still achieved the same level as PCA (EC_{50} 7.26 g/mL). In addition, compound $\mathbf{I_8}$ (EC_{50} = 8.64 μg/mL) showed similar fungicidal activity to PCA (EC_{50} = 7.56 μg/mL) against *R. solani*. Unfortunately, in the other two phytopathogenic fungi *M. oryzae* and *B. cinerea*, the title compounds failed to exceed the activity of PCA, but compound $\mathbf{I_{22}}$ still showed promising activity (EC_{50} = 16.56 μg/mL against *M. oryzae*, EC_{50} = 45.08 μg/mL against *B. cinerea*) to PCA (EC_{50} = 12.63 μg/mL, EC_{50} = 19.76 μg/mL). Thus, compound $\mathbf{I_{22}}$ may be a candidate for a broad spectrum of fungicidal agents, while compound $\mathbf{I_8}$ was a specific candidate against *F. graminearum* and *R. solani*.

2.2.2 *In vivo* fungicidal activity To further confirms the bioactivity of the title compounds, *in vivo* fungicidal activities against five fungi were assessed and the results were presented in **Table 4**. Tendency of the results was nearly in consistent with that of the *in vitro* bioactivity. For *F. graminearum*, the bioactivities of all compounds were between 40.46% and 58.69%, which were better than PCA. Especially, for compounds $\mathbf{I_8}$ (58.69%) and $\mathbf{I_{22}}$

Table 2 ^{1}H NMR of title compounds $\mathbf{I_1}$-$\mathbf{I_{28}}$

Compd.	^{1}H NMR (Chloroform-*d*, 400 MHz), δ	ESI-MS
$\mathbf{I_1}$	15.05 (s, 1H), 9.10 (dd, *J* = 7.2, 1.5 Hz, 1H), 8.54 (ddd, *J* = 7.7, 6.1, 1.5 Hz, 2H), 8.33 (dd, *J* = 8.6, 1.4 Hz, 1H), 8.10 – 8.00 (m, 4H), 8.00 – 7.94 (m, 1H), 7.50 (qd, *J* = 4.8, 1.6 Hz, 3H)	384.3
$\mathbf{I_2}$	15.13 (s, 1H), 9.18 – 9.12 (m, 1H), 8.63 – 8.56 (m, 2H), 8.40 – 8.33 (m, 2H), 8.13 – 8.09 (m, 1H), 8.09 – 8.05 (m, 1H), 8.02 (ddd, *J* = 8.2, 6.7, 1.5 Hz, 1H), 7.58 (dt, *J* = 7.9, 3.1 Hz, 1H), 7.49 – 7.43 (m, 2H)	418.2
$\mathbf{I_3}$	15.14 (s, 1H), 9.12 (dd, *J* = 7.2, 1.5 Hz, 1H), 8.61 – 8.53 (m, 2H), 8.38 – 8.32 (m, 1H), 8.12 – 8.03 (m, 3H), 8.00 (ddd, *J* = 8.3, 6.6, 1.6 Hz, 1H), 7.89 (dt, *J* = 6.4, 1.9 Hz, 1H), 7.49 – 7.42 (m, 2H)	418.3
$\mathbf{I_4}$	15.10 (s, 1H), 8.32 (dd, *J* = 8.8, 1.5 Hz, 1H), 8.21 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.03 – 7.97 (m, 1H), 7.81 – 7.73 (m, 3H), 7.65 (dd, *J* = 5.8, 3.4 Hz, 2H), 7.62 – 7.56 (m, 1H), 7.48 – 7.42 (m, 2H)	418.1
$\mathbf{I_5}$	15.10 (s, 1H), 9.13 (dd, *J* = 7.1, 1.4 Hz, 1H), 8.61 – 8.52 (m, 2H), 8.44 (td, *J* = 7.6, 1.7 Hz, 1H), 8.38 – 8.31 (m, 1H), 8.12 – 8.06 (m, 1H), 8.06 – 8.02 (m, 1H), 8.00 (ddd, *J* = 8.2, 6.6, 1.5 Hz, 1H), 7.49 (tdd, *J* = 8.2, 4.8, 2.2 Hz, 1H), 7.33 (td, *J* = 7.8, 1.1Hz, 1H), 7.30 – 7.27 (m, 1H)	402.1
$\mathbf{I_6}$	15.14 (s, 1H), 9.12 (dd, *J* = 7.1, 1.3 Hz, 1H), 8.70 – 8.45 (m, 2H), 8.41 – 8.29 (m, 1H), 8.14 – 7.91 (m, 3H), 7.88 – 7.70 (m, 2H), 7.48 (td, *J* = 7.9, 5.8 Hz, 1H), 7.22 – 7.15 (m, 1H)	402.3
$\mathbf{I_7}$	15.10 (s, 1H), 9.12 (d, *J* = 6.9 Hz, 1H), 8.62 – 8.48 (m, 2H), 8.35 (d, *J* = 8.3 Hz, 1H), 8.03 (tt, *J* = 13.6, 7.5 Hz, 5H), 7.21 (t, *J* = 8.5 Hz, 2H)	402.2
$\mathbf{I_8}$	15.01 (s, 1H), 9.15 (dd, *J* = 7.1, 1.5 Hz, 1H), 8.63 – 8.53 (m, 3H), 8.40 – 8.32 (m, 1H), 8.13 – 8.02 (m, 2H), 8.02 – 7.97 (m, 1H), 7.54 – 7.45 (m, 1H), 7.17 (td, *J* = 7.6, 1.1 Hz, 1H), 7.10 (dd, *J* = 8.4, 1.1 Hz, 1H), 4.12 (s, 3H)	414.4
$\mathbf{I_9}$	15.09 (s, 1H), 9.12 (dd, *J* = 7.1, 1.5 Hz, 1H), 8.61 – 8.51 (m, 2H), 8.38 – 8.31 (m, 1H), 8.12 – 7.95 (m, 3H), 7.64 (t, *J* = 2.0 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.04 (dd, *J* = 8.3, 2.6 Hz, 1H), 3.92 (s, 3H)	414.1
$\mathbf{I_{10}}$	15.01 (s, 1H), 9.11 (dd, *J* = 7.2, 1.5 Hz, 1H), 8.59 – 8.50 (m, 2H), 8.37 – 8.30 (m, 1H), 8.10 – 7.93 (m, 5H), 7.06 – 6.98 (m, 2H), 3.89 (s, 3H)	414.3
$\mathbf{I_{11}}$	15.11 (s, 1H), 9.16 – 9.10 (m, 1H), 8.62 – 8.53 (m, 2H), 8.40 – 8.30 (m, 1H), 8.12 – 7.98 (m, 3H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.46 – 7.32 (m, 3H), 2.70 (s, 3H)	398.4
$\mathbf{I_{12}}$	15.04 (s, 1H), 9.11 (dd, *J* = 7.2, 1.5 Hz, 1H), 8.56 (ddd, *J* = 8.9, 3.4, 1.4 Hz, 2H), 8.38 – 8.30 (m, 1H), 8.11 – 8.02 (m, 2H), 7.99 (ddd, *J* = 8.3, 6.6, 1.5 Hz, 1H), 7.90 – 7.79 (m, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 2.46 (s, 3H)	398.1
$\mathbf{I_{13}}$	15.02 (s, 1H), 9.10 (dd, *J* = 7.2, 1.5 Hz, 1H), 8.54 (ddd, *J* = 8.6, 4.7, 1.5 Hz, 2H), 8.36 – 8.29 (m, 1H), 8.08 – 8.05 (m, 1H), 8.05 – 8.01 (m, 1H), 7.98 (ddd, *J* = 8.2, 6.6, 1.6 Hz, 1H), 7.92 (d, *J* = 7.9 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 2.43 (s, 3H)	398.2
$\mathbf{I_{14}}$	15.19 (s, 1H), 9.12 (dd, *J* = 7.2, 1.5 Hz, 1H), 8.62 – 8.51 (m, 2H), 8.41 – 8.31 (m, 1H), 8.16 (d, *J* = 8.1 Hz, 2H), 8.13 – 7.96 (m, 3H), 7.78 (d, *J* = 8.1 Hz, 2H)	452.3
$\mathbf{I_{15}}$	8.46 (dd, *J* = 8.7, 1.4 Hz, 1H), 8.39 (s, 1H), 8.31 – 8.23 (m, 1H), 8.21 – 8.14 (m, 1H), 8.04 (dd, *J* = 6.9, 1.4 Hz, 1H), 7.95 (dd, *J* = 8.7, 6.8 Hz,1H), 7.85 (dddd, *J* = 21.6, 8.2, 6.6, 1.5 Hz, 2H), 7.64 – 7.56 (m, 2H), 7.49 – 7.40 (m, 1H), 7.40 – 7.26 (m, 2H)	368.3
$\mathbf{I_{16}}$	14.84 (s, 1H), 9.14 (dd, *J* = 7.1, 1.5 Hz, 1H), 8.57 (dd, *J* = 8.7, 1.5 Hz, 1H), 8.46 – 8.38 (m, 1H), 8.38 – 8.31 (m, 1H), 8.14 – 7.95 (m, 4H), 7.59 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.55 – 7.40 (m, 2H)	402.2
$\mathbf{I_{17}}$	8.47 (dd, *J* = 8.7, 1.4 Hz, 1H), 8.41 (s, 1H), 8.31 – 8.25 (m, 1H), 8.20 – 8.13 (m, 1H), 8.04 (dd, *J* = 6.8, 1.4 Hz, 1H), 7.95 (dd, *J* = 8.7, 6.9Hz, 1H), 7.86 (dddd, *J* = 20.8, 8.2, 6.6, 1.4 Hz, 2H), 7.57 (t, *J* = 1.7 Hz, 1H), 7.50 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.41 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H)	402.3
$\mathbf{I_{18}}$	14.80 (s, 1H), 9.13 (dt, *J* = 7.2, 1.2 Hz, 1H), 8.57 (dt, *J* = 8.6, 1.1 Hz, 1H), 8.44 (dd, *J* = 8.2, 1.5 Hz, 1H), 8.35 (dd, *J* = 8.7, 1.5 Hz, 1H), 8.14 – 7.95 (m, 5H), 7.56 – 7.48 (m, 2H)	402.2
$\mathbf{I_{19}}$	14.81 (s, 1H), 9.15 (dd, *J* = 7.2, 1.5 Hz, 1H), 8.57 (dd, *J* = 8.7, 1.5 Hz, 1H), 8.47 – 8.39 (m, 1H), 8.39 – 8.31 (m, 1H), 8.23 – 8.12 (m, 1H), 8.12 – 7.95 (m, 3H), 7.56 (dddd, *J* = 8.4, 7.4, 5.0, 1.8 Hz, 1H), 7.36 – 7.31 (m, 1H), 7.31 – 7.27 (m, 1H)	386.2
$\mathbf{I_{20}}$	14.82 (s, 1H), 9.14 (dd, *J* = 7.1, 1.4 Hz, 1H), 8.58 (dd, *J* = 8.7, 1.4 Hz, 1H), 8.47 – 8.42 (m, 1H), 8.38 – 8.34 (m, 1H), 8.12 – 7.94 (m, 4H), 7.87 (dt, *J* = 9.2, 2.3 Hz, 1H), 7.53 (td, *J* = 7.9, 5.6 Hz, 1H), 7.24 (d, *J* = 1.8 Hz, 2H)	386.3
$\mathbf{I_{21}}$	14.77 (s, 1H), 9.14 (dd, *J* = 7.2, 1.5 Hz, 1H), 8.58 (dd, *J* = 8.7, 1.5 Hz, 1H), 8.50 – 8.41 (m, 1H), 8.40 – 8.32 (m, 1H), 8.17 (ddd, *J* = 9.9, 5.2, 2.5 Hz, 2H), 8.12 – 7.96 (m, 3H), 7.23 (d, *J* = 8.6 Hz, 2H)	386.3
$\mathbf{I_{22}}$	8.44 (dd, *J* = 8.8, 1.3 Hz, 1H), 8.34 – 8.23 (m, 2H), 8.22 – 8.15 (m, 1H), 8.10 (dd, *J* = 6.8, 1.3 Hz, 1H), 7.98 – 7.78 (m, 3H), 7.54 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.41 – 7.32 (m, 1H), 6.89 (td, *J* = 7.8, 0.8 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 3.24 (s, 3H)	398.4
$\mathbf{I_{23}}$	14.74 (s, 1H), 9.15 (dd, *J* = 7.2, 1.5 Hz, 1H), 8.57 (dd, *J* = 8.7, 1.5 Hz, 1H), 8.49 – 8.41 (m, 1H), 8.40 – 8.32 (m, 1H), 8.14 – 7.95 (m, 3H), 7.81 – 7.66 (m, 2H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.12 – 7.06 (m, 1H), 3.93 (s, 3H)	398.3
$\mathbf{I_{24}}$	14.67 (s, 1H), 9.14 (dd, *J* = 7.2, 1.5 Hz, 1H), 8.56 (dd, *J* = 8.7, 1.5 Hz, 1H), 8.48 – 8.41 (m, 1H), 8.39 – 8.32 (m, 1H), 8.15 – 7.95 (m, 5H), 7.04 (d, *J* = 8.9 Hz, 2H), 3.91 (s, 3H)	398.2
$\mathbf{I_{25}}$	8.45 (dd, *J* = 8.7, 1.4 Hz, 1H), 8.38 (s, 1H), 8.30 – 8.23 (m, 1H), 8.21 – 8.13 (m, 1H), 8.04 (dd, *J* = 6.8, 1.4 Hz, 1H), 7.99 – 7.93 (m, 1H), 7.93 – 7.84 (m, 1H), 7.82 (ddd, *J* = 8.2, 6.6, 1.5 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.10 (s, 2H), 2.32 (s, 3H)	382.2
$\mathbf{I_{26}}$	8.46 (dd, *J* = 8.7, 1.4 Hz, 1H), 8.38 (s, 1H), 8.30 – 8.23 (m, 1H), 8.22 – 8.14 (m, 1H), 8.04 (dd, *J* = 6.8, 1.4 Hz, 1H), 7.95 (dd, J = 8.7, 6.8 Hz, 1H), 7.85 (dddd, *J* = 21.2, 8.2, 6.6, 1.5 Hz, 2H), 7.41 (dd, *J* = 4.3, 1.8 Hz, 2H), 7.21 (q, *J* = 8.2, 7.8 Hz, 2H), 2.26 (s, 3H)	382.3
$\mathbf{I_{27}}$	8.45 (dd, *J* = 8.8, 1.4 Hz, 1H), 8.38 (s, 1H), 8.30 – 8.23 (m, 1H), 8.21 – 8.13 (m, 1H), 8.04 (dd, *J* = 6.8, 1.4 Hz, 1H), 7.94 (dd, *J* = 8.7, 6.8 Hz, 1H), 7.84 (dddd, *J* = 21.8, 8.2, 6.6, 1.5 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 2.32 (s, 3H)	382.3
$\mathbf{I_{28}}$	14.88 (s, 1H), 9.13 (dd, *J* = 7.2, 1.5 Hz, 1H), 8.58 (dd, *J* = 8.7, 1.5 Hz, 1H), 8.52 – 8.40 (m, 1H), 8.39 – 8.32 (m, 1H), 8.32 – 8.26 (m, 2H), 8.13 – 7.96 (m, 3H), 7.85 – 7.77 (m, 2H)	436.2

Table 3 EC_{50} values (μg/mL) against *M. oryzae, B. cinerea, P. capsici, R. solani* and *F. graminearum*

Compd.	*F. graminearum*	*P. capsici*	*R. solani*	*M. oryzae*	*B.cinerea*
PCA	128.54 ± 4.68	7.26 ± 1.05	7.56 ± 0.99	12.63 ± 1.14	19.76 ± 1.31
I_1	71.25 ± 2.95	58.17 ± 3.12	52.45 ± 1.96	65.21 ± 2.89	78.15 ± 2.65
I_2	78.23 ± 3.03	67.15 ± 2.24	64.89 ± 2.03	72.15 ± 2.35	89.54 ± 3.01
I_3	99.45 ± 4.08	89.25 ± 3.17	84.36 ± 3.08	92.14 ± 3.12	102.47 ± 4.01
I_4	86.12 ± 4.11	68.58 ± 2.64	72.78 ± 2.61	78.56 ± 3.14	90.13 ± 3.12
I_5	74.12 ± 3.26	72.34 ± 2.98	69.78 ± 2.35	68.47 ± 2.58	90.65 ± 2.99
I_6	98.31 ± 3.46	89.17 ± 3.22	97.54 ± 3.97	89.22 ± 2.64	120.34 ± 3.25
I_7	80.24 ± 3.95	80.57 ± 2.99	75.81 ± 2.68	80.17 ± 2.99	98.54 ± 3.13
I_8	33.25 ± 2.06	31.25 ± 2.01	8.64 ± 1.11	25.23 ± 1.95	46.28 ± 2.01
I_9	62.48 ± 3.11	54.27 ± 2.61	34.62 ± 2.06	56.47 ± 2.08	71.56 ± 2.56
I_{10}	49.47 ± 2.35	39.46 ± 1.94	15.78 ± 1.64	42.13 ± 1.97	61.54 ± 2.11
I_{11}	45.95 ± 2.21	41.03 ± 1.96	24.38 ± 1.98	35.48 ± 1.34	52.47 ± 1.98
I_{12}	67.36 ± 3.12	55.36 ± 1.33	49.31 ± 2.08	65.78 ± 2.54	77.67 ± 2.31
I_{13}	50.49 ± 2.68	49.55 ± 1.65	40.27 ± 2.31	55.87 ± 2.31	70.15 ± 1.96
I_{14}	84.12 ± 3.02	125.34 ± 4.74	82.06 ± 3.21	80.49 ± 3.21	128.56 ± 4.56
I_{15}	66.39 ± 2.46	54.23 ± 2.03	52.38 ± 2.26	49.34 ± 2.31	65.72 ± 1.98
I_{16}	70.23 ± 2.34	57.35 ± 1.65	61.26 ± 3.06	50.23 ± 2.22	68.23 ± 2.35
I_{17}	85.34 ± 3.05	68.14 ± 2.37	75.34 ± 2.61	61.58 ± 2.61	80.66 ± 3.14
I_{18}	76.55 ± 2.61	60.89 ± 2.16	63.33 ± 2.39	52.36 ± 2.13	74.13 ± 3.02
I_{19}	75.06 ± 2.80	60.37 ± 2.31	55.14 ± 2.11	53.57 ± 1.98	70.56 ± 2.68
I_{20}	89.61 ± 3.22	71.24 ± 3.04	69.46 ± 2.49	63.89 ± 3.01	86.49 ± 3.28
I_{21}	80.07 ± 2.67	65.81 ± 2.68	60.18 ± 2.65	52.38 ± 2.41	78.05 ± 2.66
I_{22}	**46.52 ± 3.54**	**7.24 ± 1.01**	**26.16 ± 2.01**	**16.56 ± 1.34**	**45.08 ± 2.05**
I_{23}	53.53 ± 2.67	34.51 ± 2.68	40.23 ± 2.13	42.34 ± 1.96	59.23 ± 2.34
I_{24}	49.97 ± 2.39	22.37 ± 1.67	36.72 ± 1.94	31.43 ± 1.99	52.11 ± 2.16
I_{25}	56.48 ± 2.03	30.64 ± 2.53	48.83 ± 2.53	36.54 ± 1.25	44.54 ± 2.25
I_{26}	53.13 ± 2.15	24.35 ± 1.84	30.22 ± 1.83	34.13 ± 1.67	51.37 ± 1.99
I_{27}	62.08 ± 3.15	49.72 ± 2.38	46.57 ± 2.05	46.31 ± 2.05	60.52 ± 1.97

Table 4 Fungicidal activity of compounds against five plant fungi *in vivo* at 500 μg/mL (inhibition rate/%)

Compd.	*F. graminearum*	*P. capsici*	*R. solani*	*M. oryzae*	*B.cinerea*
PCA	25.14 ± 0.86	93.48 ± 1.67	90.25 ± 1.69	92.18 ± 1.63	80.57 ± 1.35
I_1	45.68 ± 1.03	48.21 ± 1.07	60.23 ± 1.36	52.14 ± 1.02	35.21 ± 0.98
I_8	**58.69 ± 1.14**	**66.89 ± 1.32**	**91.34 ± 1.58**	**69.38 ± 1.34**	**63.45 ± 1.37**
I_9	45.69 ± 1.03	50.23 ± 1.24	69.16 ± 1.35	52.33 ± 1.20	40.12 ± 1.25
I_{10}	50.39 ± 1.31	59.21 ± 1.38	77.59 ± 1.63	62.55 ± 1.36	45.68 ± 1.34
I_{11}	52.61 ± 1.22	60.33 ± 1.39	68.28 ± 1.29	68.16 ± 1.64	56.95 ± 1.54
I_{12}	44.33 ± 0.99	49.62 ± 1.09	60.14 ± 1.46	44.83 ± 1.04	36.49 ± 0.99
I_{13}	49.61 ± 1.21	55.97 ± 1.22	63.21 ± 1.43	45.82 ± 1.11	40.55 ± 1.06
I_{15}	40.46 ± 1.11	50.29 ± 1.62	45.86 ± 1.03	50.23 ± 1.22	32.56 ± 1.02
I_{22}	**55.37 ± 1.37**	**94.23 ± 1.98**	**76.38 ± 1.38**	**85.94 ± 1.86**	**48.37 ± 1.23**
I_{23}	43.66 ± 1.35	64.55 ± 1.32	55.67 ± 1.61	56.28 ± 1.32	42.28 ± 1.09
I_{24}	50.15 ± 2.01	70.54 ± 1.54	62.13 ± 1.30	60.71 ± 1.56	45.68 ± 1.37
I_{25}	42.68 ± 1.35	70.61 ± 1.60	66.71 ± 1.65	62.13 ± 1.34	42.88 ± 1.26
I_{26}	35.27 ± 0.97	52.68 ± 1.34	51.46 ± 1.05	51.04 ± 1.05	38.98 ± 0.99
I_{27}	40.57 ± 1.09	60.11 ± 1.75	60.57 ± 1.62	56.69 ± 1.18	41.21 ± 1.21

(55.37%), the control effect was about twice of that of PCA (25.14%) at 500 μg/mL. Moreover, the fungicidal activity of compound **I_8** (91.34%) against *R. solani* was similar to that of PCA (90.25%). The *in vivo* fungicidal activity of compound **I_{22}** (94.23%, 76.38%, 85.94%) against *P. capsici*, *R. solani* and *M. oryzae* were better than or similar to that of PCA (93.48%, 90.25%, 92.18%). These results further confirmed the broad spectrum and specific fungicidal activity of compounds **I_8** and **I_{22}**.

2.3 Structure-activity relationship

In addition, we discussed preliminary structure-activity studies on these PCA derivatives according to the bioactivity data against *F. graminearum*. In the substituted compounds, **-CH_3** and **-CH_3O** (**I_8**, **I_9**, **I_{10}**, **I_{11}**, **I_{12}**, **I_{13}**, **I_{22}**, **I_{23}**, **I_{24}**, **I_{25}**, **I_{26}**, **I_{27}**) substituent showed better activities than **Cl** and **F** substituent (**I_2**, **I_3**, **I_4**, **I_5**, **I_6**, **I_7**, **I_{16}**, **I_{17}**, **I_{18}**, **I_{19}**, **I_{20}**, **I_{21}**). In a word, introducing electron-withdrawing group into benzene ring was not conducive to the activity of the compounds, and obviously reduces their biological activity. While introducing electron-donating group was conducive to improving their bioactivity. At the same time, the substitution of the same substituent at different positions on the benzene ring also affects the activity of the compounds. The substitution position of the same substituent on the benzene ring was in the order of *o*>*p*>*m* according to the bioactivity. The preliminary structure-activity relationship study will provide the theoretical basis for the study of these compounds.

3 Conclusions

In summary, a series of novel structures of phenazine-1-carboxylic acid derivatives containing 1,3,4-thiadiazole and 1,3,4-oxadiazole were designed. The title compounds were characterized by mass spectrometry, elemental analysis, and nuclear magnetic resonance spectroscopy. All the title compounds exhibited significant *in vitro* fungicidal activities and *in vivo* fungicidal activities against phytopathogenic fungi. Especially compounds **I_8** (X=S, R=2-OCH_3) and **I_{22}** (X=O, R=2-OCH_3) had better fungicide activities than that of PCA for *F. graminearum*. Compound **I_{22}** exhibited broad spectra fungicidal activities, while compound **I_8** was a candidate against *F. graminearum* and *R. solani* specifically. The stucture-activity relationship results showed that the introduction of electron-withdrawing group into benzene ring was not favor to the activity of the compounds, while the introduction of electron-donating group was conducive to improving the activity of the compounds. At the same time, the substitution position on the benzene ring were in the order of *o*>*p*>*m* according to the bioactivity. These results can be used to guide the further structural modification of these compounds.

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