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Synthesis and bioactivities of diamide derivatives containing a phenazine-1-carboxamide scaffold

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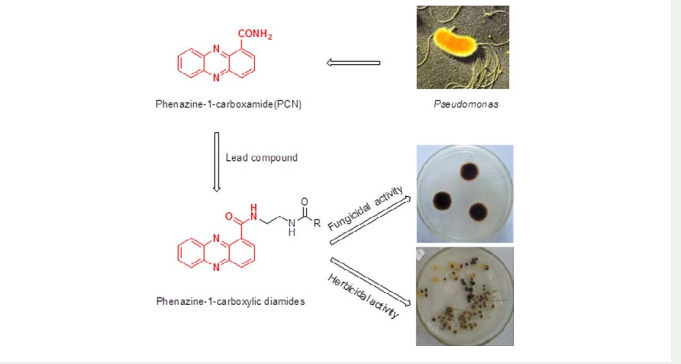
ABSTRACT

Taking natural product phenazine-1-carboxamide (PCN) as a lead compound, a series of novel phenazine-1-carboxylic acid diamide derivatives were designed and synthesised. Their structures were confirmed by ^{1}H-NMR and HRMS. The bioassays showed that some of the target compounds exhibited promising *in vitro* fungicidal activities, and exhibited excellent and selective herbicidal activities. Particularly, compounds **c**, **h**, **o** and **s** displayed root length inhibition activities against *barnyard grass* with the rate of more than 80%. Compound **c** exhibited the best activity among all the target compounds against *barnyard grass* stalk length with the IC_{50} value of 0.158 mmol/L, and compound **o** exhibited the best and wide spectrum inhibition against *barnyard grass* root length and *rape* in both root length and stalk length herbicidal activities with its IC_{50} values of 0.067, 0.048 and 0.059 mmol/L respectively. The analysis of preliminary Structure-Activity Relationships provides the theoretical basis for further design of phenazine-1-carboxylic acid.



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1. Introduction

Phenazine-1-carboxamide (PCN, Figure 1) is a very important natural analogue of Phenazine-1-carboxylic acid (PCA, Figure 1), often isolated from the metabolites of *Pseudomonas* and *Streptomycetes* (Gao et al. 2012; Puopolo et al. 2013; Hu et al. 2005; Laursen and Nielsen 2004), showed five to ten times in fungicidal activity against *Rhizoctonia solani* as much as PCA which registered as a biofungicide 'Shenqinbactin' against sheath blight on rice in China (Commare et al. 2002; Su et al. 2010; Zhou et al. 2010). In 2010, a series of structurally diverse phenazine-1-carboxylic acid amide and diamide derivatives were designed and synthesised by Ye Long et al., the biological evaluation against *R. solani* indicated that some compounds exhibited a significant level of activity with IC_{50} values 8 to 23-fold lower than that of PCA (Ye et al. 2010). Noteworthy, compound **A** and **B** (Figure 1) as the diamide analogues also exhibited excellent fungicidal activities against *R. solani*.

Diamides are significant organic compounds with various biological activities, such as antibacterial (Wang et al. 2017), anti-tumor (Ubaradka et al. 2015; Zabiulla et al. 2016), anti-fungal (Sharma et al. 2008; Nayyab et al. 2017; Pejchalová et al. 2017), insecticidal (Clark et al. 2008; Zhang et al. 2012), antiviral and anti-inflammatory activities (Rajakumar et al. 2012; Saudi et al. 2016), etc. For example, both penicillin (Figure 2(C)) which first isolated by British bacteriologist Fleming (Gaynes 2017), and the synthesised compound amoxicillin (Figure 2(D)), both have played important roles in protecting human health (Van et al. 2016). In recent years, diamides have been more and more important in agrochemicals, such as some commercialised pesticides, chlorantraniliprole (Figure 2(E)) and flubendiamide (Figure 2(F)), displaying high effective insecticidal activities at a lower concentration and safe for mammals, and applied widely as effective insecticides for the control of *lepidoptera* pests (Kavallieratos et al. 2013; Cui et al. 2017). Because of the low toxicity and high efficiency, the research of diamides has become a hot topic in new pesticide creation.

Combination of active substructure and natural lead compounds is a very important method for novel pesticide creation (Prabhakar et al. 2003). In this study, to find higher bioactive lead compounds, a series of PCA-diamide derivatives (**a–s**, Figure 3) were designed and synthesised by using natural product phenazine-1-carboxamide (PCN) as a lead compound. Considering the structural and chemical diversity and to discuss their possible

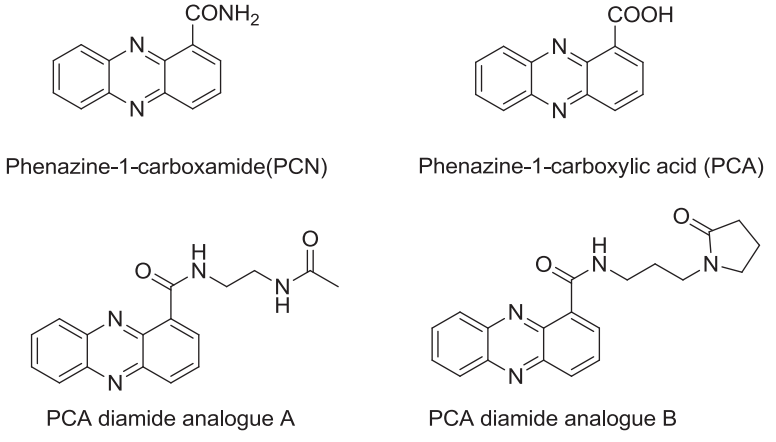

Figure 1. Structures of PCN, PCA and PCA diamide analogues.

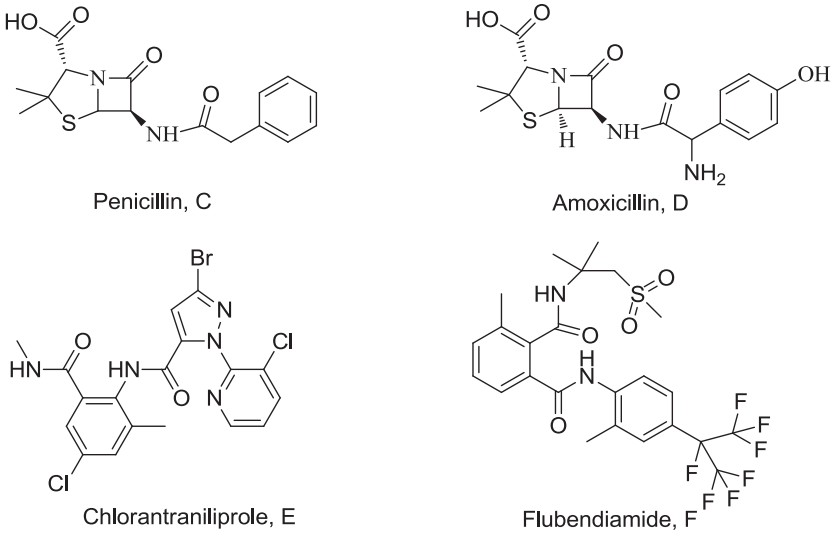

Figure 2. Structures of some diamides.

Structure-Activity Relationships (SARs). Different active substructures, such as alkanoyl groups and aroyl groups, were introduced into the target compounds **a-s**. All target compounds were evaluated for their fungicidal and herbicidal activities.

2. Results and discussion

2.1. Chemistry

The synthetic route of all target compounds **a-s** is described in Figure 3. Treatment of PCA with oxalyl chloride at reflux temperature in CH_2Cl_2 solution afforded intermediate **2** after the evaporation of CH_2Cl_2. And the methyl ester of PCA **3** was prepared by adding excessive methyl alcohol into intermediate **2**, ammonolysis reaction of PCA methyl ester with ethylenediamine in the solution of CH_3OH afforded intermediate **4**. Reacted corresponding acids **5** with $SOCl_2$ at reflux temperature afforded intermediate **6** after the evaporation of $SOCl_2$. The target compounds **a-s** were then synthesised by reacting compound **4** to corresponding intermediate **6** in CH_2Cl_2, and utilising triethylamine as a base at 0 °C. The structures of derivatives **a-s** were characterised by ^{1}H-NMR, and high resolution mass spectrum (HR-MS). (Analysis data of all the synthesised compounds are available in Supplementary Information).

2.2. Fungicidal activities

Firstly, the fungicidal activities of all target compounds **a-s** were screened by using the mycelium growth rate method against six phytopathogenic fungi (Chen 1991), *Rhizoctonia solani*, *Fusaium graminearum*, *Altemaria solani*, *Fusarium oxysporum*, *Sclerotinia sclerotiorum* and *Pyricularia oryzae*, at a concentration of 0.2 mmol/L. The phenazine-1carboxylic acid (PCA) was used as the positive control. Their fungicidal activities are showed in Table 1. Results indicated that all target compounds **a-s** showed some *in vitro* fungicidal activities against six phytopathogenic fungi, but most lower than PCA. Among the tested fungi,

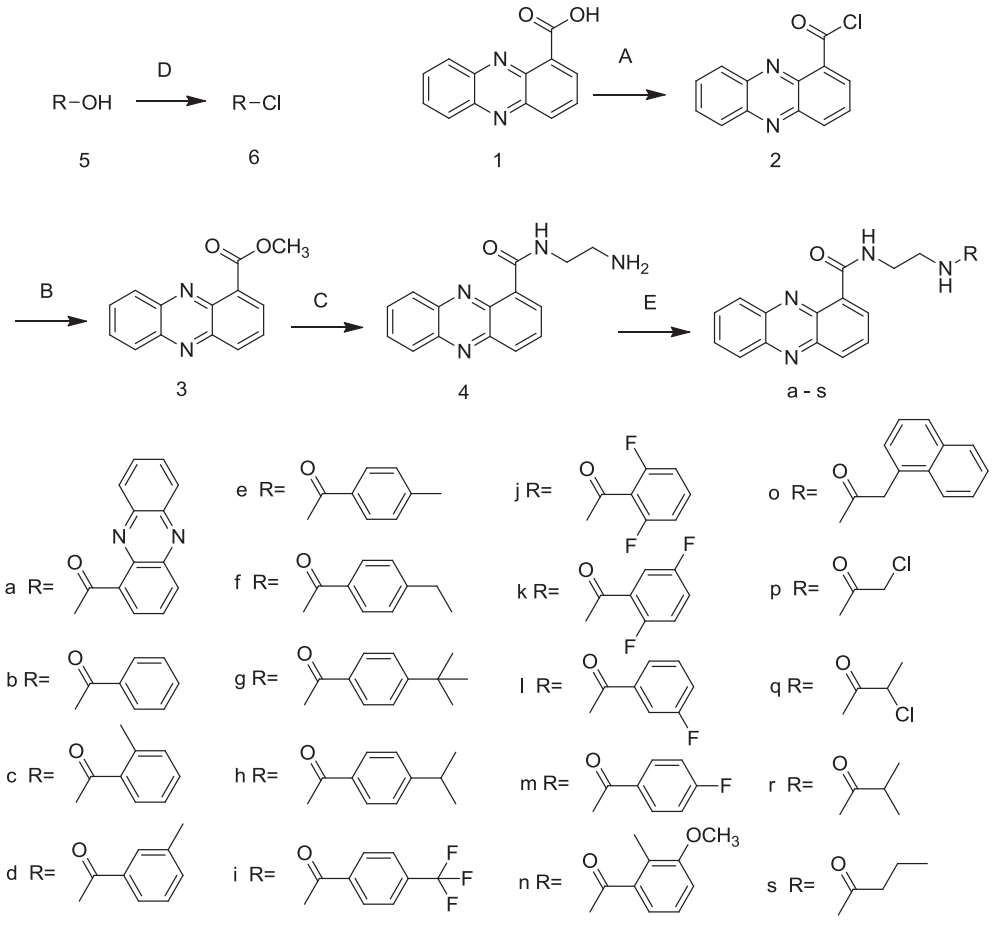

Figure 3. Synthetic route of the target compounds **a-s**. (**A**) Oxalyl chloride, CH_2Cl_2, DMF, reflux, 8 h; (**B**) methyl alcohol, room temperature, 1 h; (**C**) ethylenediamine, CH_3OH, room temperature, 0 °C to reflux, 2 h; (**D**) $SOCl_2$, reflux, 6 h; (**E**) intermediate **6**, 0 °C, 1 h.

compounds **a-s** have the best fungicidal activities against *R. solani* and *A. solani*, with some compounds showing the inhibitory rates of more than 50% (**f**, **g**, **k**, **q**). Particularly, compound **k** showed the most potent fungicidal activities against *R. solani* and compound **f** showed the best fungicidal activities against *P. oryzae* with the inhibitory rates of 72.7 and 82.0% respectively. On the whole, through the discussion of Structure-Activity Relationships, we can get a conclusion that the structures of R as aroyl groups are more active than as alkanoyl groups. And the substituents of the aroyl groups in the *para-position* displayed higher fungicidal activities than in other position.

2.3. Herbicidal activities

The herbicidal activities of all target compounds **a-s** were tested by using a plate method against *barnyard grass* (gramineae) and *rape* (dicotyledones) (Chen 1991), at a dosage of 0.5 mmol/L, and a commercial herbicide Fenoxaprop-P-ethyl was used as positive control

Table 1. Inhibitory rates of target compounds against six pathogenic fungi *in vitro*.

Compd.	Inhibitory ratio under 0.2 mmol/L (%)					
	R. solani	*F. graminearum*	*A. solani*	*F. oxysporum*	*S. sclerotiorum*	*P. oryzae*
a	48.6 ± 1.2	26.3 ± 0.9	35.4 ± 0.9	12.5 ± 0.3	14.2 ± 0.3	24.7 ± 0.0
b	46.9 ± 0.9	28.8 ± 0.6	36.7 ± 0.6	10.0 ± 0.6	28.2 ± 1.2	29.3 ± 0.0
c	14.9 ± 0.9	27.1 ± 0.6	33.0 ± 0.0	15.0 ± 1.5	18.3 ± 0.9	24.7 ± 0.6
d	39.4 ± 0.6	28.8 ± 0.6	32.0 ± 0.9	11.9 ± 1.5	30.8 ± 2.0	26.2 ± 0.3
e	34.8 ± 1.5	24.9 ± 0.3	36.0 ± 0.9	37.7 ± 0.3	23.5 ± 3.2	38.6 ± 0.0
f	55.4 ± 0.2	43.7 ± 0.6	56.1 ± 0.3	18.2 ± 0.3	46.5 ± 4.7	82.0 ± 1.2
g	59.3 ± 1.9	47.0 ± 2.1	54.0 ± 0.9	17.5 ± 0.0	47.5 ± 3.6	71.2 ± 0.6
h	36.5 ± 0.3	29.3 ± 0.3	39.8 ± 1.2	17.5 ± 0.0	16.8 ± 2.2	43.3 ± 0.6
i	44.6 ± 1.2	33.2 ± 1.3	39.8 ± 4.2	23.8 ± 3.3	36.0 ± 4.4	27.8 ± 1.5
j	13.9 ± 0.8	21.0 ± 0.3	31.7 ± 0.3	12.5 ± 0.3	12.6 ± 0.3	24.7 ± 0.6
k	72.7 ± 2.3	27.7 ± 1.3	65.1 ± 0.3	16.9 ± 0.3	36.0 ± 1.7	38.6 ± 0.0
l	37.1 ± 1.6	22.1 ± 2.1	41.0 ± 0.9	15.7 ± 0.6	15.2 ± 1.7	51.0 ± 4.8
m	49.9 ± 0.3	59.7 ± 0.3	47.2 ± 0.3	35.2 ± 1.2	47.5 ± 5.0	35.5 ± 3.2
n	52.8 ± 0.2	21.6 ± 1.5	31.7 ± 0.3	19.4 ± 0.0	51.7 ± 9.3	31.6 ± 0.6
o	50.7 ± 2.2	28.2 ± 0.3	40.4 ± 1.5	11.9 ± 0.0	19.4 ± 1.0	27.0 ± 0.0
p	13.9 ± 1.0	23.8 ± 0.6	33.6 ± 1.5	14.4 ± 0.3	11.6 ± 0.0	54.9 ± 0.0
q	59.0 ± 0.3	28.8 ± 0.6	63.8 ± 0.7	18.2 ± 0.3	35.5 ± 7.8	58.0 ± 1.3
r	35.5 ± 1.5	26.0 ± 2.4	36.0 ± 0.9	17.5 ± 0.0	26.7 ± 3.2	41.7 ± 0.3
s	33.5 ± 1.2	26.0 ± 0.3	38.5 ± 1.0	19.4 ± 0.0	31.9 ± 8.1	46.4 ± 0.3
PCA	89.5 ± 1.5	92.8 ± 1.5	82.1 ± 0.3	73.6 ± 0.6	87.5 ± 2.1	86.0 ± 0.0

Notes: Each treatment had three replicates (Mean ± SD). The phenazine-1carboxylic acid (PCA) was used as the positive control.

Table 2. Herbicidal activity of target compounds against *barnyard grass* and *rape*. (Inhibition rate/%).

Compd.	*Barnyard grass*		*Rape*	
	Root	Stalk	Root	Stalk
a	0.0 ± 0.0	41.4 ± 4.8	41.9 ± 7.8	47.5 ± 3.6
b	59.4 ± 10.4	45.3 ± 6.2	36.9 ± 12.3	48.3 ± 6.1
c	95.6 ± 1.7	73.8 ± 1.7	89.5 ± 4.1	68.3 ± 6.1
d	25.5 ± 4.7	33.8 ± 5.2	66.0 ± 9.6	60.1 ± 6.1
e	0.0 ± 0.0	20.1 ± 3.2	39.7 ± 6.7	38.7 ± 4.7
f	0.0 ± 0.0	8.2 ± 4.3	53.9 ± 8.8	53.7 ± 2.4
g	19.1 ± 9.1	42.2 ± 4.0	37.5 ± 10.4	56.4 ± 7.2
h	81.3 ± 4.8	47.7 ± 3.1	49.5 ± 8.2	51.2 ± 2.9
i	0.0 ± 0.0	2.7 ± 3.3	42.3 ± 7.9	59.9 ± 3.7
j	43.1 ± 10.8	60.4 ± 6.0	36.5 ± 9.8	54.4 ± 5.3
k	7.6 ± 11.3	21.0 ± 3.6	40.7 ± 8.4	45.8 ± 4.5
l	22.5 ± 8.0	33.8 ± 3.3	51.5 ± 8.5	51.3 ± 4.6
m	49.3 ± 7.6	50.5 ± 4.7	69.1 ± 8.9	59.8 ± 8.1
n	81.5 ± 3.9	69.2 ± 3.5	32.7 ± 11.9	45.4 ± 4.4
o	97.7 ± 1.1	56.6 ± 4.7	100.0 ± 0.0	100.0 ± 0.0
p	74.3 ± 5.4	60.0 ± 5.0	37.3 ± 13.0	36.1 ± 7.9
q	50.2 ± 4.6	22.6 ± 6.3	54.1 ± 9.1	49.4 ± 10.2
r	22.5 ± 7.0	22.8 ± 4.4	38.9 ± 4.9	44.1 ± 4.2
s	88.2 ± 4.3	41.0 ± 4.9	49.6 ± 7.1	45.5 ± 5.4
PCA	63.4 ± 6.5	26.2 ± 3.9	40.3 ± 11.5	50.5 ± 7.7
Fenoxaprop-P-ethyl	84.7 ± 1.6	70.9 ± 0.9	62.5 ± 6.2	36.3 ± 4.6

Notes: Each treatment had three replicates (Mean ± SD). The Fenoxaprop-P-ethyl was used as the positive control. All compounds were tested at the concentration of 0.5 mmol/L.

at the same concentration. Their herbicidal activities are listed in Table 2. The results indicated that, most target compounds showed herbicidal activities against *barnyard grass* and *rape*, and compounds **c**, **o** and **s** exhibited potent herbicidal activities against *barnyard grass* root

length, with the inhibition rates of 95.6, 97.7, 88.2%, respectively, which were higher than those of the positive control herbicide Fenoxaprop-P-ethyl (84.7%). Moreover, compound **c** also exhibited better herbicidal activities (73.8%) against *barnyard grass* stalk length than positive control herbicide Fenoxaprop-P-ethyl (70.9%). Especially, compound **o** exhibited 100% inhibition against the *rape* in both root length and stalk length, and showed excellent and wide spectrum herbicidal activities against both gramineae and dicotyledones plants. Three compounds (**e**, **f**, and **i**) had selective activities against dicotyledones and no toxic harm to gramineae.

Compounds **c**, **o**, and **s** were chosen as the typical compounds to determine IC_{50} values against *barnyard grass* and *rape*, which exhibited more than 85% inhibitory activity against *barnyard grass* and *rape* stalk length or root length. The IC_{50} values of the chosen compounds are presented in Table 3. The most effective compound against *barnyard grass* root length was **o** with an IC_{50} = 0.067 mmol, and compound **c** exhibited the best activity against *barnyard grass* stalk length with the IC_{50} value of 0.158 mmol/L, which is comparable to the positive control herbicide Fenoxaprop-P-ethyl with its IC_{50} values of 0.176 and 0.184 mmol/L against *barnyard grass* stalk length and root length respectively. Compound **o** exhibited the most potent activity against *rape* both in root length and stalk length with IC_{50} values of 0.048 mmol/L and 0.059 mmol/L respectively, 6 to 8 folds lower than the IC_{50} values of positive control herbicide Fenoxaprop-P-ethyl.

To analysis the preliminary structure-activity relationships, the herbicidal activities of compounds **a-m** with R = aroyl groups were compared to the compounds **o-s** with R = alkanoyl groups. It is shown that the structures of R as alkanoyl groups help to improve their herbicidal activities. Particularly, compounds **o** with R = 1-naphthalene acetyl exhibited best herbicidal activities against gramineae and dicotyledones among all of target compounds. We speculate that it may due to the 1-naphthylacetic acid, which is regarded as an important plant growth regulator. Further comparison of the compounds **a-m** with R = aroyl groups, showed that, the compounds of aromatic ring substituted at the same position with CH_3, $C(CH_3)_3$ (**d**, **g**) generally exhibited better herbicidal activities than the componds substituted with F, CF_3 (**l**, **i**). It implied that introducing electron-donating group substituents in aromatic ring was beneficial to herbicidal activities. Additionally, compound **e** showed worse herbicidal activities than **b** and **c**, which revealed the substituents of the aroyl groups in the *para-position* indicated lower herbicidal activities than other position. And the introduction of halogen atoms, such as fluorine atom or helium atom, had no obvious effect on herbicidal activities.

Table 3. IC_{50} values (mmol/L) of phenazine-1-carboxylic acid diamide derivatives.

	Barnyard grass		*Rape*	
Compd.	Root	Stalk	Root	Stalk
c	0.073 ± 0.006	0.158 ± 0.004	0.100 ± 0.007	0.226 ± 0.006
o	0.067 ± 0.003	0.399 ± 0.008	0.048 ± 0.003	0.059 ± 0.005
s	0.122 ± 0.005	>0.5	0.463 ± 0.011	>0.5
Fenoxaprop-P-ethyl	0.176 ± 0.005	0.184 ± 0.004	0.322 ± 0.006	>0.5

Notes: Each treatment had three replicates (Mean ± SD). The Fenoxaprop-P-ethyl was used as the positive control.

3. Conclusion

In summary, we have successfully synthesised a series of novel phenazine-1-carboxylic acid diamide derivatives **a-s**, and their structures were confirmed by ^{1}H-NMR and HRMS. The bioassays showed that some of compounds exhibited promising *in vitro* fungicidal activities against six phytopathogenic fungi. Surprisingly, most target compounds displayed herbicidal activities against *barnyard grass* and *rape*, and some of them showed potent herbicidal activities, such as compounds **c**, **o** and **s**. Especially, compound **o** exhibited the most potent activity among all the target compounds against *rape* both in root length and stalk length with its IC_{50} values of 0.048 and 0.059 mmol/L respectively. The analysis of preliminary Structure-Activity Relationships indicated that, the structures of R as alkanoyl groups and electron-donating group substituents of the aroyl groups were beneficial to herbicidal activities. The substituents of the aroyl groups in the *para-position* indicated lower herbicidal activities than other position. The synthesis, fungicidal activities and herbicidal activities study of phenazine-1-carboxylic acid diamide derivatives provides the theoretical basis for further design of phenazine-1-carboxylic acid.

Disclosure statement

No potential conflict of interest was reported by the authors.

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