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Design, synthesis, and insecticidal/acaricidal evaluation of novel pyrimidinamine derivatives containing phenyloxazole moiety

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Abstract

A series of novel pyrimidinamine derivatives containing phenyloxazole moiety were designed and synthesized, and their structures were characterized by ^{1}H NMR, MS, and elemental analyses. The bioassay results displayed that some compounds exhibited remarkable insecticidal activities against *Aphis fabae* and *Tetranychus cinnabarinus*. Especially, 5-chloro-6-ethyl-2-methyl-*N*-((2-(*p*-tolyl)oxazol-4-yl)methyl)pyrimidin-4-amine (**9o**) showed potent activity against *A. fabae*, superior to that of the commercial insecticide, imidacloprid. In addition, 5-chloro-6-ethyl-2-methyl-*N*-((2-(4-(trifluoromethyl)phenyl) oxazol-4-yl)methyl)pyrimidin-4-amine (**9r**) showed potent activities against *T. cinnabarinus*, inferior to that of the commercial insecticide spirotetramat. The structure–activity relationship study for the target compounds was also discussed.

Keywords Pyrimidinamines · Phenyloxazole moiety · Insecticidal/acaricidal activities · Structure–activity relationship study

Introduction

Nitrogen-containing heterocyclic structures play an indispensable role in agrochemicals (Liu et al. 2018a, b, 2019; Yan et al. 2018a, b) by helding broad-spectrum activity, high efficiency, and good environmental compatibility. Among these, pyrimidine heterocyclic structures have been being one research focus in the development of agrochemicals because of their high biological activity as herbicides (Wang et al. 2017), insecticides (Chai et al. 2010; Wierenga et al. 2000), and fungicides (Guan et al. 2017a, b), and being widely used in modern agriculture (Liu et al. 2017).

Pyrimidinamines are one of the most important pyrimidine insecticides, which belong to an important kind mitochondrial respiration inhibitors interrupting the mitochondrial electron transport by inhibition of NADH: ubiquinone oxidoreductase (complex I) (Miyoshi 1998). Among these pyrimidinamine derivatives (Fig. 1), pyrimidifen is the representative pyrimidinamine insecticide targeting mitochondrial complex I electron transport inhibitors (MET I); its structure is significantly different from MET I inhibitors that are commercially available (Guan et al. 2017a, b), which indicates that pyrimidifen may be a promising template for the discovery of new insecticide candidates.

In addition, oxazole rings have been widely introduced into drug molecular design, and its derivatives show a broad-spectrum of biological activities, such as insecticidal (Song et al. 2012; Wang et al. 2015), herbicidal (Zhao et al. 2009; Li et al. 2006), fungicidal (Yan et al. 2018a, b; Reddy et al. 2015), and pharmacological activity (Zhang et al. 2018; Abhale et al. 2017). Moreover, oxazole ring often has been used as a bioisostere of triazole, imidazole, benzimidazole, and other radical groups,

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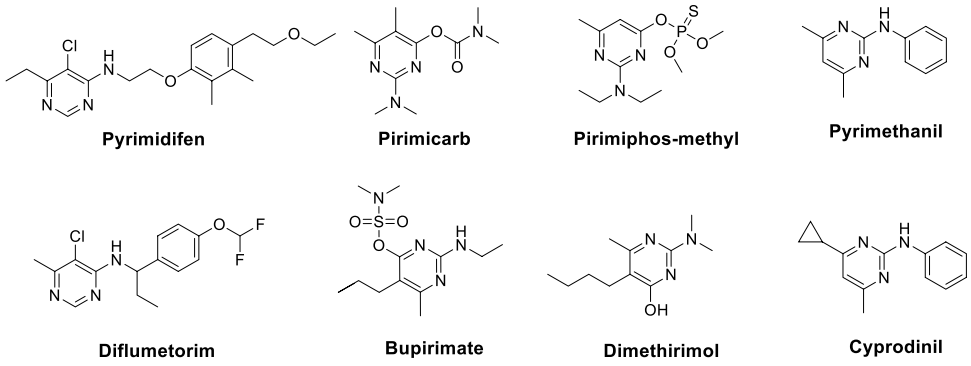


Fig. 1 Some commercial pyrimidinamine agrochemicals

since it can interact with various enzymes and receptors in vivo (Skepper et al. 2010). Oxazoles functionalized at the second and fourth positions with distinct oxidation state of appending carbon atom have found significant application in the synthesizing more complex structures (Mathew et al. 2013). Because of their utilities as building blocks for complex natural products, much attention has been focused on the preparation of 2,4-substituted oxazoles in the past 20 years. (Prager et al. 1997).

It is precisely because of the extensive application, pests have developed resistance to pyrimidine compounds. Consequently, it is urgent to use all our available knowledge to protect the longevity of pyrimidinamine insecticides by discovering new pyrimidinamines with novel structural fragment to diminish the resistance of crop pests. In the present study, we have introduced an oxazole ring in the pyrimidifen by molecular "plug in" method (Fig. 2) to achieve novel pyrimidinamines molecules with improved insecticidal activities. A detailed synthesis, biological evaluation, and structure–activity relationships (SAR) study of this series of compounds are as discussed below.

Experimental

Chemistry

All of the starting materials and reagents, unless otherwise noted, were commercially available and used without further purification. Melting points were determined on WPS-1B melting point apparatus made in shanghai physical optics instrument plant. ^{1}H NMR spectra was obtained with a Varian INOVA-300 spectrometer using tetramethylsilane (TMS) as the internal standard and deuteriochloroform ($CDCl_3$) or deuteriodimethylsulfoxide (DMSO-d_6) as the solvent. Liquid chromatography–mass spectrometry (LC–MS) was recorded with an Agilent 1260/6120 Series and gas chromatography–mass spectrometry (GC–MS) was recorded with an Agilent 7890-5975C Series. Elemental analyses were obtained with a Vario EL III from Elementar. Column chromatography was performed using 200–300 mesh silica gel.

The general synthetic methods for compounds **9a–r** are shown in Scheme 1. Representative procedures are given below, but yields are not optimized. All reactions were carried out under a protective atmosphere of dry nitrogen or utilizing a calcium chloride tube.

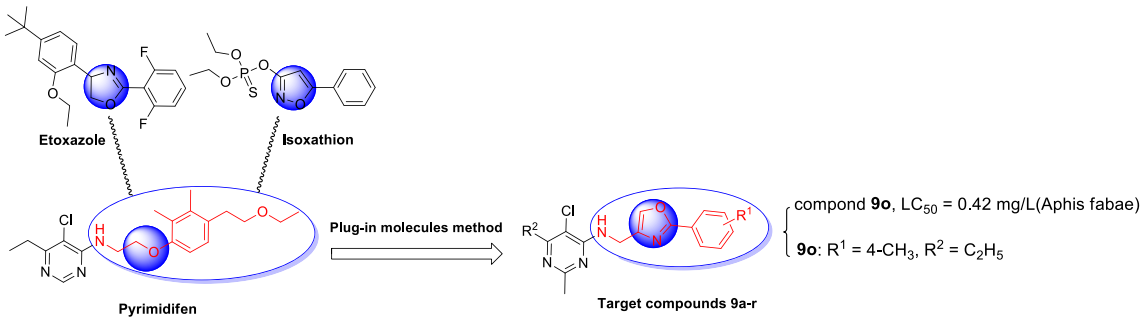
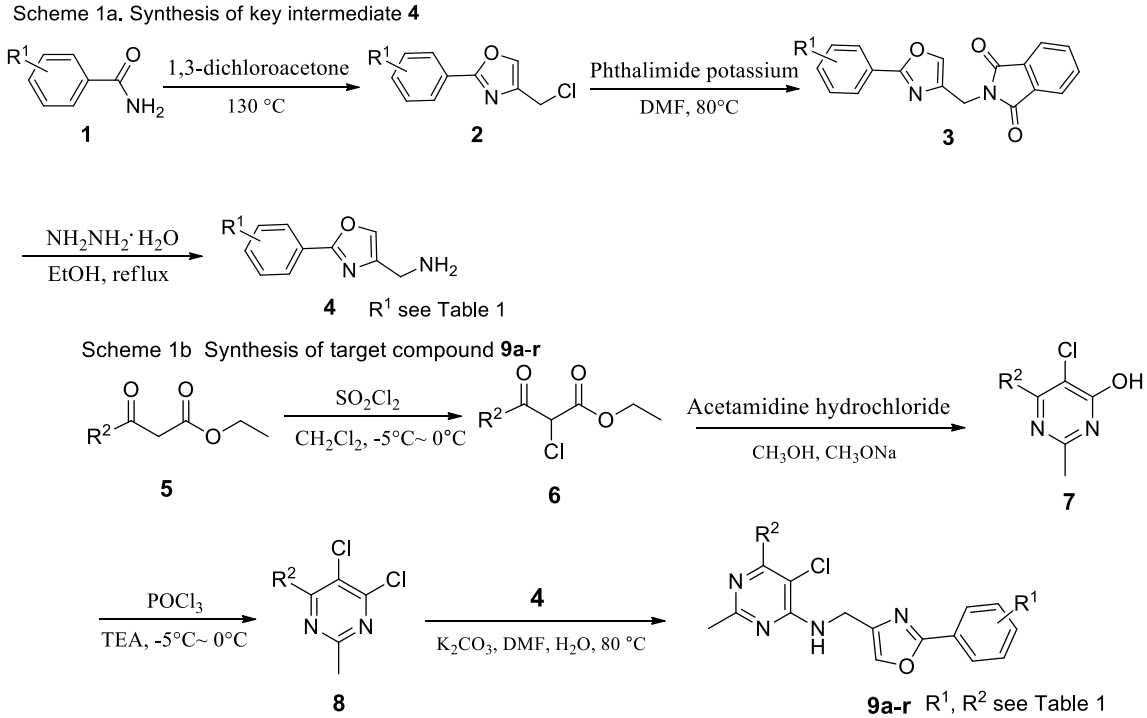


Fig. 2 Design strategy of the target compounds **9a–r**



Scheme 1 Synthesis of target compound **9a–r**

General procedure for the preparation of intermediate 2

A mixture of benzamides (**1**) (120 mmol) and 1,3-dichloroacetone (19.1 g, 150 mmol) was heated at 130 °C for 1–2 h. After the mixture was cooled to room temperature, 150 mL of ethyl acetate was added and the mixture was washed twice with saturated Na_2CO_3 solution. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to give intermediates **2,** in 85–98% yield, without further purification.

General procedure for the preparation of intermediate 4

Intermediate **2** (100 mmol) was dissolved in 100 mL N, *N*-dimethylformamide (DMF), then potassium phthalimide (22.2 g, 120 mmol) was added in portions. The mixture was heated at 80 °C for 3 h. After cooling to room temperature, the reaction solution was poured into ice water. The precipitate was collected by filtration and washed with water to furnish **3**.

Obtained compound **3** (100 mmol) and 80% hydrazine hydrate (150 mmol) in 200 mL of EtOH were refluxed for 3–5 h. The suspension was cooled and filtered. The filtrate was concentrated under reducing pressure and the residue was treated with cold water (100 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layer was washed twice with water (2 × 50 mL), dried over Na_2SO_4, and concentrated under reducing pressure to give intermediate **4** in 56–62% yield. Compound **4** was used directly for the synthesis of final target compound **9** without further purification.

General procedure for the preparation of intermediate 6

A 250 mL three-necked round-bottomed flask containing compound **5** and dichloromethane (100 mL) was stirred for 15 min at − 5–0 °C, and then, sulfuryl chloride (31.5 g, 230 mmol) was added slowly dropwise, and the reaction mixture was stirred overnight at room temperature. Water (100 mL) was added, and the mixture was extracted with dichloromethane (2 × 100 mL) and the organic layer was combined and dried over Na_2SO_4, filtered, and concentrated under reducing pressure to give the liquid intermediate **6** in 89–95% yield.

General procedure for the preparation of intermediate 7

Acetamidine hydrochloride (7.5 g, 85 mmol) and methanol (100 mL) were taken to a 500 mL three-necked round-bottom flask and stirred for 10 min. Sodium methoxide (30%, 15.3 g, 80 mmol) was added dropwise at − 5–0 °C and then stirred for 0.5 h. Intermediate 6 (85 mmol) was added dropwise and the reaction was continued for 0.5 h at the same temperature and heated under reflux for 3 h. The reaction mixture was cooled to room temperature and filtrated. The filtrate was concentrated under reducing pressure. The

residue was recrystallized from ethyl acetate (50 mL) to obtain pure solid **7** in 53–60% yield.

General procedure for the preparation of intermediate 8

Phosphorous oxychloride was slowly added to compound **7** in a 500 mL three-neck round bottom flask at 0 °C. After stirring for 5–10 min, triethylamine (9.1 g, 90 mmol) was added dropwise at the same temperature. The reaction mixture was allowed to warm to ambient temperature and stirred for overnight. The excess phosphorous oxychloride was distilled off under reducing pressure. The residue was dissolved in ethyl acetate (60 mL). The organic layers washed with saturated brine and dried over Na_2SO_4. After the solvent was removed, the crude product was separated by column chromatography [v (petroleum ether):v (ethyl acetate) = 20:1] to give the intermediates **8** in 45–52% yield.

General procedure for the preparation of target compounds 9a–r

A mixture of intermediates **8** (5 mmol), (2-phenyloxazol-4-yl)methanamines **4** (5 mmol), and anhydrous potassium carbonate (1.4 g, 10 mmol) were taken in a 1:1 DMF:Water (20 mL) and heated at 80 °C for 3–4 h. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured into saturated saline and extracted with ethyl acetate (3 × 50 mL). The combined organic layers was dried over Na_2SO_4 and removed under reducing pressure to give the crude product. The residue was recrystallized from the mixture of petroleum ether (50 mL) and ethyl acetate (10 mL) to give pure target compounds **9** in 79–86% yield.

Biological assay

The insecticidal/acarcidal activity test of the target compounds was conducted according to our previous studies (Liu et al. 2009a, b, 2015, 2018a, b; Cao et al. 2017). Stock solution of 1.0 g/L for each test compound was prepared in DMF and then diluted to the required concentration with water containing Tween 80 (0.4 mg/L).

Activity against *Aphis fabae*

These insects were reared in a room maintained at 25 °C, 65 (± 5)% relative humidity, and 14:10 h light/dark. The horse bean seedlings with *A. fabae* were dipped in the test solution for 5–10 s, then allowed to dry with a filter paper, transferred to a beaker (100 mL) containing water (10 mL), and kept at 25 °C. The mortality was determined based on the number and the size of live larvae in the treated bottles relative to that in the untreated controls after 24 h. A control experiment was performed under the same conditions. All experiments and the respective controls were conducted in three replicates, and results were averaged. The dose–response data were analyzed by probit analysis (Finney 1971), and the activities for *A. fabae* were further evaluated as LC_{50} values.

Activity against *Tetranychus cinnabarinus*

Fifty adults of *T. cinnabarinus* were transferred to three horse bean seedlings, and 24 h later, the horse bean seedlings with acarids were dipped in the test solutions for 5–10 s, then allowed to dry with filter paper, transferred to a beaker (100 mL) containing water (10 mL) and kept at 25 °C. Each assay contained three replications. Mortality was assessed 24 h after the treatment. Control groups were tested with water only. The dose–response data were analyzed by probit analysis.

Results and discussion

Synthesis

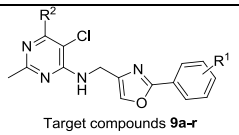
The synthesis pathway of target compounds is shown in Scheme 1. Their structures were confirmed by ^{1}H NMR, MS, and elemental analyses. The synthesis and characterization of intermediates **2** were according to our previously reported methods (Huang et al. 2017; Yan et al. 2018a, b). The chemical structure, physical properties, yield, and biological activities of target compounds **9a**–**r** are presented in Table 1. ^{1}H NMR, MS, and elemental analysis data are listed in Table 2. The observed molecular weight for each compound of **9a**–**r** was as expected in the MS analysis.

Insecticidal activity

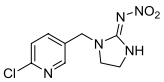
The mortality data of **9a**–**r** against against *A. fabae* and *T. cinnabarinus* are shown in Table 1. It indicated that all target compounds **9a**–**r** have excellent insecticidal activity against *A. fabae* at 500 mg/L, and parts of them still display potential insecticidal activity at lower test concentration. For example, the mortality of **9a**, **9b**, **9d**–**f**, **9h**, **9j**–**o,** and **9r** against *A. fabae* at 500 mg/L was 100%. More importantly, the compounds **9k**, **9o**, and **9p** show 100% insecticidal activity against *A. fabae* at 50 mg/L, which is equal to the mortality of the commercial insecticide, imidacloprid.

In addition, as shown in Table 1, it is obvious that most of target compounds exhibit high acaricidal activity against *T. cinnabarinus* at 500 mg/L, and some of them display good acaricidal activity at 50 mg/L. For instance, the mortality of **9a**, **9d**, **9h**–**k**, **9o,** and **9q** against *T. cinnabarinus* at 500 mg/L was 100%. Compounds **9j**, **9k**, **9l,**

Table 1 Chemical structure, physical properties, yield, and biological activities of compounds **9a–r**



Target compounds **9a-r**

Comp	Chemical structure		Formula	Yield(%)	Appearance	M.p. (°C)	*Tc* (%)/ mg/L		*Af* (%)/ mg/L	
	R^1	R^2					500	50	500	50
9a	H	CH_3	$C_{16}H_{15}ClN_4O$	75	Yellow solid	101.9-103.9	100	–	100	–
9b	2-Cl	CH_3	$C_{16}H_{14}Cl_2N_4O$	82	White solid	124.9-126.1	59.5	–	100	86.5
9c	2,4-di Cl	CH_3	$C_{16}H_{13}Cl_3N_4O$	80	Grey solid	145.2-146.9	90.7	21.7	98.9	64.9
9d	2-CH_3	CH_3	$C_{17}H_{17}ClN_4O$	85	White solid	120.2-121.2	100	71.4	100	83.2
9e	3-CH_3	CH_3	$C_{17}H_{17}ClN_4O$	86	White solid	103.1-103.9	83.8	11.7	100	79.5
9f	4-CH_3	CH_3	$C_{17}H_{17}ClN_4O$	79	White solid	145.2-146.6	82.5	56.8	100	93.6
9g	2,4-di CH_3	CH_3	$C_{18}H_{19}ClN_4O$	81	White solid	113.7-116.4	92.6	24.1	95.6	77.9
9h	4- C_2H_5	CH_3	$C_{18}H_{19}ClN_4O$	54	Yellow solid	101.4-103.9	100	21.2	100	69.7
9i	4-CF_3	CH_3	$C_{17}H_{14}ClF_3N_4O$	85	White solid	118.0-119.2	100	23.8	90.7	16.2
9j	H	C_2H_5	$C_{17}H_{17}ClN_4O$	84	Yellow solid	88.3-88.9	100	93.9	100	98.1
9k	2-Cl	C_2H_5	$C_{17}H_{16}Cl_2N_4O$	81	White solid	84.4-84.9	100	97.8	100	100
9l	2,4-di Cl	C_2H_5	$C_{17}H_{15}Cl_3N_4O$	81	White solid	86.8-88.9	93.7	93.6	100	92.8
9m	2-CH_3	C_2H_5	$C_{18}H_{19}ClN_4O$	86	White solid	92.7-94.1	90.2	49.1	100	82.1
9n	3-CH_3	C_2H_5	$C_{18}H_{19}ClN_4O$	87	Yellow solid	63.8-66.0	92.8	82.9	100	98.8
9o	4-CH_3	C_2H_5	$C_{18}H_{19}ClN_4O$	85	White solid	82.3-83.1	100	45.3*	100	100
9p	2,4-di CH_3	C_2H_5	$C_{19}H_{21}ClN_4O$	84	Yellow solid	80.8-83.8	81.3	–	98.2	100
9q	4- C_2H_5	C_2H_5	$C_{19}H_{21}ClN_4O$	84	Yellow solid	92.0-94.7	100	4.2	90.7	83.4
9r	4-CF_3	C_2H_5	$C_{18}H_{16}ClF_3N_4O$	83	Yellow solid	82.0-83.8	95.4	98.4	100	98.1
Spirotetramat							100	100		
Imidacloprid									100	100

Tc Tetranychus cinnabarinus, *Af Aphis fabae*

*20 mg/L

and **9r** have more over 93.0% acaricidal activity against *T. cinnabarinus* at 50 mg/L. Compounds **9n** and **9o** still have more than 80.0% acaricidal activity against *T. cinnabarinus* at 50 mg/L.

To further evaluate the activity level of target compounds, compounds with high insecticidal activities against *T. cinnabarinus* and *A. fabae* were singled out to calculate the regression equation, and the median lethal concentration (LC_{50}) value of these compounds, which is shown in Tables 3 and 4, respectively. To our amazement, compound **9o** has LC_{50} (mg/L) values of 0.42 against *A. fabae*, which is better than that of the commercial insecticide, imidacloprid (0.51, Table 3). Moreover, compound **9r** has LC_{50} values of 4.27 against *T. cinnabarinus*, inferior to that of the commercial insecticide spirotetramat (2.27, Table 4).

Structure–activity relationship study

The general structure of target compounds **9** was optimized through the R^1 and R^2 groups, and the choices of substituents can significantly affect insecticidal activity (Table 1).

When R^1 is kept constant, the insecticidal activities of the synthesized compounds are influenced by the nature of the R^2 group. When R^2 group is changed from methyl to ethyl, the insecticidal activities of the corresponding compound are dramatically increased. For example, activity order against *A. fabae:* **9j > 9a**; **9k > 9b**; **9l > 9c**; **9m > 9d**; **9n > 9e**; **9o > 9f**; **9p > 9g**; **9q > 9h**; **9r > 9i**; and activity order against *T. cinnabarinus:* **9j > 9a**; **9k > 9b**; **9l > 9c**; **9n > 9e**; **9o > 9f**; **9r > 9i**.

When R^2 is kept constant, the insecticidal activities of the synthesized compounds are influenced by the nature of the

Table 2 ^{1}H NMR, MS, and elemental analysis data of compounds **9a**–**r**

Comp	^{1}H NMR (δ); MS (m/e); elemental analysis
9a	^{1}H NMR ($CDCl_3$) δ: 2.45 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 4.67 (dd, J = 5.7, 0.9 Hz, 2H, CH_2), 5.90 (br, 1H, NH), 7.45–7.49 (m, 3H, Ph H), 7.67 (t, J = 0.9 Hz, 1H, oxzole H), 8.02–8.05 (m, 2H, Ph H); GC–MS M^+ = 314; Calcd: C, 61.05; H, 4.80; N, 17.80, found: C, 61.02; H, 4.83; N, 17.82
9b	^{1}H NMR ($CDCl_3$) δ: 2.43 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 4.70 (dd, J = 5.7, 0.9 Hz, 2H, CH_2), 5.87 (br, 1H, NH), 7.33–7.42 (m, 2H, Ph H), 7.48–7.52 (m, 1H, Ph H), 7.74 (t, J = 0.9 Hz, 1H, oxazole H), 7.95–7.98 (m, 1H, Ph H); GC–MS M^+ = 348; Calcd: C, 55.03; H, 4.04; N, 16.04, found: C, 55.02; H, 4.07; N, 16.08
9c	^{1}H NMR ($CDCl_3$) δ: 2.46 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 4.70 (dd, J = 5.7, 0.9 Hz, 2H, CH_2), 5.92 (br, 1H, NH), 7.35 (q, J = 5.7, 1H, Ph H), 7.53 (d, J = 2.1, 1H, Ph H), 7.74 (d, J = 0.9 Hz, 1H, oxazole H), 7.94 (d, J = 8.4 Hz, 1H, Ph H); HPLC–MS Pos $[M+1]^+$ = 385; Calcd: C, 50.09; H, 3.42; N, 14.60, found: C, 50.03; H, 3.46; N, 14.63
9d	^{1}H NMR ($CDCl_3$) δ: 2.44 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 4.68 (dd, J = 5.4, 0.9 Hz, 2H, CH_2), 5.91 (br, 1H, NH), 7.28–7.37 (m, 3H, Ph H), 7.68 (t, J = 0.9 Hz, 1H, oxazole H), 7.95–7.98 (m, 1H, Ph H); HPLC–MS Pos $[M+1]^+$ = 329; Calcd: C, 62.10; H, 5.21; N, 17.04, found: C, 62.08; H, 5.23; N, 17.10
9e	^{1}H NMR ($CDCl_3$) δ: 2.42 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 4.66 (dd, J = 5.7, 0.9 Hz, 2H, CH_2), 5.83 (br, 1H, NH), 7.27–7.37 (m, 2H, Ph H), 7.64 (d, J = 0.9 Hz, 1H, oxazole H), 7.80–7.86 (m, 2H, Ph H); GC–MS M^+ = 328; Calcd: C, 62.10; H, 5.21; N, 17.04, found: C, 62.04; H, 5.23; N, 17.11
9f	^{1}H NMR ($CDCl_3$) δ: 2.41 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 4.66 (dd, J = 5.4, 0.9 Hz, 2H, CH_2), 5.86 (br, 1H, NH), 7.25–7.28 (m, 2H, Ph H), 7.63 (t, J = 1.2 Hz, 1H, oxazole H), 7.90–7.93 (m, 2H, Ph H); HPLC–MS Pos $[M+1]^+$ = 329; Calcd: C, 62.10; H, 5.21; N, 17.04, found: C, 62.05; H, 5.23; N, 17.11
9g	^{1}H NMR ($CDCl_3$) δ: 2.36 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 4.67(dd, J = 5.4, 1.2 Hz, 2H, CH_2), 5.89 (br, 1H, NH), 7.08–7.10 (m, 2H, Ph H), 7.65 (t, J = 0.9 Hz, 1H, oxazole H), 7.85 (d, J = 8.4, 1H, Ph H); GC–MS M^+ = 342; Calcd: C, 63.06; H, 5.59; N, 16.34, found: C, 63.03; H, 5.63; N, 16.40
9h	^{1}H NMR ($CDCl_3$) δ: 1.24–1.34(m, 5H, CH_2CH_3, 2.43 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 4.65 (dd, J = 5.7, 0.4 Hz, 2H, CH_2), 5.85 (br, 1H, NH), 7.27 (d, J = 8.1 Hz, 2H, Ph H), 7.66 (t, J = 0.9 Hz, 1H, oxazole H), 7.92 (dd, J = 6.6, 1.6 Hz, 2H, Ph H); GC–MS M^+ = 342; Calcd: C, 63.06; H, 5.59; N, 16.34, found: C, 63.01; H, 5.66; N, 16.41
9i	^{1}H NMR ($CDCl_3$) δ: 2.44 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 4.68 (dd, J = 5.7, 0.9 Hz, 2H, CH_2), 5.84 (br, 1H, NH), 7.71 (dd, J = 8.4, 0.9 Hz, 2H, Ph H), 7.72 (d, J = 0.9 Hz, 1H, oxazole H), 8.13 (dd, J = 8.4, 0.6 Hz, 2H, Ph H); HPLC–MS Pos $[M+1]^+$ = 383; Calcd: C, 53.34; H, 3.69; N, 14.64, found: C, 53.31; H, 3.72; N, 14.71
9j	^{1}H NMR ($CDCl_3$) δ: 1.24 (t, J = 7.5 Hz, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.76 (q, J = 7.5 Hz, 2H, CH_2), 4.67 (dd, J = 5.7, 0.9 Hz, 2H, CH_2), 5.85 (br, 1H, NH), 7.44–7.48 (m, 3H, Ph H), 7.66 (s, 1H, oxazole H), 8.02–8.05 (m, 2H, Ph H); GC–MS M^+ = 328; Calcd: C, 62.10; H, 5.21; N, 17.04, found: C, 62.05; H, 5.28; N, 17.07
9k	^{1}H NMR ($CDCl_3$) δ: 1.24 (t, J = 7.5 Hz, 3H, CH_3), 2.53 (s, 3H, CH_3), 2.76 (q, 7.5 Hz, 2H, CH_2), 4.70 (dd, J = 5.4, 0.9 Hz, 2H, CH_2), 5.88 (br, 1H, NH), 7.35–7.42 (m, 2H, Ph H), 7.49–7.53 (m, 1H, Ph H), 7.75 (t, J = 0.9 Hz, 1H, oxazole H), 7.96–7.99 (m, 1H, Ph H); GC–MS M^+ = 362; Calcd: C, 56.21; H, 4.44; N, 15.42, found: C, 56.15; H, 4.50; N, 15.43
9l	^{1}H NMR ($CDCl_3$) δ: 1.26 (t, J = 7.5 Hz, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.76 (q, J = 7.5 Hz, 2H, CH_2), 4.69 (dd, J = 5.7, 0.9 Hz, 2H, CH_2), 5.87 (br, 1H, NH), 7.74 (t, J = 0.9 Hz, 1H, oxazole H), 7.33–7.95 (m, 3H, Ph H); HPLC–MS Pos $[M+1]^+$ = 399; Calcd: C, 51.34; H, 3.80; N, 14.09, found: C, 51.32; H, 3.82; N, 14.13
9m	^{1}H NMR ($CDCl_3$) δ: 1.22 (t, J = 7.5 Hz, 3H, CH_3), 2.53 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 2.77 (q, J = 7.5 Hz, 2H, CH_2), 4.88 (dd, J = 5.4, 1.2 Hz, 2H, CH_2), 5.92 (br, 1H, NH), 7.68 (t, J = 0.9 Hz, 1H, oxazole H), 7.28–7.98 (m, 4H, Ph H); HPLC–MS Pos $[M+1]^+$ = 343; Calcd: C, 63.06; H, 5.59; N, 16.34, found: C, 63.02; H, 5.63; N, 16.45
9n	^{1}H NMR ($CDCl_3$) δ: 1.25 (t, J = 7.5 Hz, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 2.75 (q, J = 7.5 Hz, 2H, CH_2), 4.66 (dd, J = 5.4, 0.6 Hz, 2H, CH_2), 5.86 (br, 1H, NH), 7.65 (t, J = 0.9 Hz, 1H, oxazole H), 7.28–7.87 (m, 4H, Ph H); GC–MS M^+ = 342; Calcd: C, 63.06; H, 5.59; N, 16.34, found: C, 63.05; H, 5.67; N, 16.45
9o	^{1}H NMR ($CDCl_3$) δ: 1.24 (t, J = 7.5 Hz, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.76 (q, J = 7.5 Hz, 2H, CH_2), 4.66 (dd, J = 5.4, 0.9 Hz, 2H, CH_2), 5.86 (br, 1H, NH), 7.27 (d, J = 4.5 Hz, 2H, Ph H), 7.63 (t, J = 0.9 Hz, 1H, oxazole H), 7.90–7.93 (m, 2H, Ph H); HPLC–MS Pos $[M+1]^+$ = 343; Calcd: C, 63.06; H, 5.59; N, 16.34, found: C, 63.04; H, 5.69; N, 16.37
9p	^{1}H NMR (DMSO-*d6*) δ: 1.15 (t, J = 7.5 Hz, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 2.65 (q, J = 7.5 Hz,2H, CH_2), 4.53 (dd, J = 5.1, 0.9 Hz, 2H, CH_2), 5.76 (br, 1H, NH), 7.12–7.17 (m, 1H, Ph H), 7.57 (t, J = 5.7 Hz, 1H, Ph H), 7.77 (d, J = 7.8 Hz, 1H, Ph H), 7.94 (s, 1H, oxazole H); GC–MS M^+ = 356; Calcd: C, 63.95; H, 5.93; N, 15.70, found: C, 63.87; H, 5.95; N, 15.81
9q	^{1}H NMR ($CDCl_3$) δ: 1.21–1.34 (m, 6H, CH_3), 2.52 (s, 3H, CH_3), 2.69–2.79 (m, 4H, CH_3), 4.65 (d, J = 5.4 Hz, 2H, CH_2), 5.85 (br, 1H, NH), 7.27 (d, J = 8.1 Hz, 2H, Ph H), 7.63 (s, 1H, oxazole H), 7.93 (m, 2H, Ph H); GC–MS M^+ = 356; Calcd: C, 63.95; H, 5.93; N, 15.70, found: C, 63.89; H, 5.97; N, 15.85
9r	^{1}H NMR ($CDCl_3$) δ: 1.24 (t, J = 7.5 Hz, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.72 (q, J = 7.5 Hz, 2H, CH_2), 4.68 (dd, J = 5.7, 0.9 Hz, 2H, CH_2), 5.84 (br, 1H, NH), 7.71 (s, 1H, oxazole H), 7.72–7.74 (m, 2H, Ph H), 8.13 (d, J = 8.1 Hz, 2H, Ph H); HPLC–MS Pos $[M+1]^+$ = 396; Calcd: C, 54.49; H, 4.06; N, 14.36, found: C, 54.42; H, 4.22; N, 14.41

Table 3 LC_{50} values of target compounds against *A. fabae*

Compound	Regression equation	Correlation	LC_{50} (mg/L)
9j	$y=4.9431+3.7159x$	0.9141	1.04
9k	$y=3.2005+2.6737x$	0.9946	4.71
9n	$y=4.9237+1.8064x$	0.9947	1.10
9o	$y=5.6005+1.5785x$	0.9491	0.42
9p	$y=5.1814+1.5046x$	0.9402	0.65
9r	$y=1.6427+3.79244x$	0.9260	7.68
Imidacloprid	$y=5.5894+2.0180x$	0.9661	0.51

Table 4 LC_{50} values of target compounds against *T. cinnabarinus*

Compound	Regression equation	Correlation	LC_{50} (mg/L)
9k	$y=3.1309+1.7484x$	0.9888	11.72
9r	$y=2.1127+4.5769x$	0.9618	4.27
Spirotetramat	$y=4.6328+1.0340x$	0.9594	2.27

R^1 group. Modification of the R^1 group from a hydrogen to 2-methyl, 3-methyl, 4-methyl, 4-trifluoromethyl, 2,4-dimethyl, 2,4-dichloro, 4-ethyl groups shows the different levels of insecticidal activities. When R^2 is methyl group, the activity order against *A. fabae* of the corresponding compound is **9f > 9b > 9d > 9e > 9g > 9h > 9c ≫ 9i**. Obviously, the activity against *A. fabae* of the corresponding compounds with R^2 = methyl decreased significantly after the electron-donating group were replaced by electron-withdrawing group. Meanwhile, when R^1 is 2-methyl or 4-methyl, its corresponding compound has better activity against *T. cinnabarinus* than compounds with other substituents.

When R^2 is ethyl, the activity order against *A. fabae* of the corresponding compound is **9o > 9p > 9j > 9n > 9k > 9r > 9 l > 9q > 9m**. It suggests that compounds with R^1 = 4-methyl exhibited excellent insecticidal activities against *A. fabae*, superior to that of the commercial insecticide imidacloprid. Whereas, when 4-methyl was replaced by 4-ethyl or 2-methyl, the insecticidal activity against *A. fabae* of corresponding compound declines sharply. Furthermore, when R^1 is the electron-withdrawing groups, 4-trifluoromethyl, in particular, the insecticidal activity against *T. cinnabarinus* of corresponding compound is better than that of compounds with other substituents.

In summary, the structure–activity relationships of all synthesized compounds can be summarized as follows:

Activity order against *A. fabae* of R^1 (R^2 = methyl): 4-CH_3 > 2-Cl > 2-CH_3 > 3-CH_3 > 2,4-di CH_3 > 4-C_2H_5 > 2,4-di Cl ≫ 4-CF_3.

Activity order against *T. cinnabarinus* of R^1 (R^2 = methyl): 2-CH_3 > 4-CH_3 > 2,4-di CH_3, 4-CF_3 > 4-C_2H_5, 2,4-di Cl > 3-CH_3.

Activity order against *A. fabae* of R^1 (R^2 = ethyl): 4-CH_3 > 2,4-di CH_3 > 3-CH_3, H > 2-Cl > 4-CF_3 > 2,4-di Cl > 4-C_2H_5 > 2-CH_3.

Activity order against *T. cinnabarinus* of R^1 (R^2 = ethyl): 4-CF_3 > 2-Cl, H, 2,4-di Cl > 3-CH_3 > 2-CH_3 > 4-CH_3 > 4-C_2H_5 > 2,4-di CH_3.

Activity order of R^2: ethyl > methyl.

Further studies on the biological activity and structure–activity relationships of this series of compounds are in progress.

Conclusions

To search for potent insecticidal agents, novel pyrimidinamine derivatives containing phenyloxazole moiety were designed and synthesized, and their structures were characterized by ^{1}H NMR, MS, and elemental analyses. The bioassay results displayed that most compounds exhibited remarkable insecticidal activities against *T. cinnabarinus* and *A. fabae*. Especially, 5-chloro-6-ethyl-2-methyl-*N*-((2-(*p*-tolyl)oxazol-4-yl)methyl)pyrimidin-4-amine (**9o**) showed potent activities against *A. fabae*, superior to that of the commercial insecticide imidacloprid (Table 3). In addition, 5-chloro-6-ethyl-2-methyl-*N*-((2-(4-(trifluoromethyl) phenyl)oxazol-4-yl)methyl)pyrimidin-4-amine (**9r**) showed potent activities against *T. cinnabarinus*, inferior to that of the commercial insecticide spirotetramat (Table 4). Apparent structure–activity relationships study indicated that variances among R^1 and R^2 group can greatly affect insecticidal activity (Table 1).

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