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Synthesis and insecticidal activities of novel 1*H*-pyrazole-5-carboxylic acid derivatives

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Abstract: Fourteen 1*H*-pyrazole-5-carboxylic acid derivatives containing oxazole and thiazole rings were synthesized and characterized by ¹H NMR, mass spectrometry and elemental analysis. Most target compounds were obtained in overall yields in the range of 30–50%. The insecticidal activities of these new compounds against *Aphis fabae* were evaluated. The bioassays' results indicate that some of these compounds exhibit good activities, especially compound **7h** which shows 85.7% mortality against *A. fabae* at a concentration of 12.5 mg/L. This activity is comparable to that of the commercial insecticide imidacloprid.

Keywords: insecticidal activity; oxazole; pyrazole; structure-activity relationship; thiazole.

Introduction

The pyrazole ring plays an important role in drug design [1]. In particular, 1*H*-pyrazole-5-carboxamide derivatives have been the focus of increasing interest over the past decades because of their low toxicity and high bioactivity [2–4]. For instance, the commercial product tebufenpyrad (Figure 1) displays excellent insecticidal activity [5] and pyrazole-5-carboxylic acid is often incorporated as a

core structure into pesticide molecules for the purpose of improving bioactivity [6–9]. Oxazole and thiazole rings have also gained importance in the agrochemical field. There are many oxazole and thiazole derivatives being developed commercially, such as famoxadone, metamidofop, ethaboxam and trifluzamide [10–13]. In our previous work, a series of 1*H*-pyrazole-5-carboxamide and thiazole derivatives had been designed and synthesized, but their bioactivities were unsatisfactory [14–17]. Insecticidal activities of new compounds synthesized as part of this work were tested at the concentration of 500 mg/L against the target pests *Aphis fabae*, *Mythimna separata* and spider mites. The results of the preliminary bioassay show that the compounds are active against *Aphis fabae* only. A subsequent bioassay against *A. fabae* at a lower concentration was carried out.

Results and discussion

In this work, in the search for novel compounds with insecticidal activity, several pyrazole carboxylic acid derivatives were designed guided by the lead compound tebufenpyrad. As shown in Figure 1, an oxazole or thiazole ring (moiety **A**) was introduced into the 1*H*-pyrazole-5-carboxamide. The group on pyrazole ring (moiety **B**) was altered and the amide group was replaced with an ester group (moiety **C**). All target compounds **7a–n** were synthesized as shown in Scheme 1 and characterized using ¹H nuclear magnetic resonance (NMR), mass spectroscopy (MS) and elemental analysis. Preparation of key intermediates was similar to our previous work [18].

The insecticidal activities against *A. fabae* of compounds **7** are shown in Table 1. The data indicate that most of the compounds show excellent activity at 500 mg/L and some of them display potent activity at lower concentration. For example, the mortality of **7f**, **7h** and **7i** against *A. fabae* at 200 mg/L remains 100%. Compound **7h** induces mortality greater than 80% against *A. fabae* at a concentration of 12.5 mg/L and this activity is comparable to that of the commercial insecticide imidacloprid (89.8% mortality against *A. fabae*).

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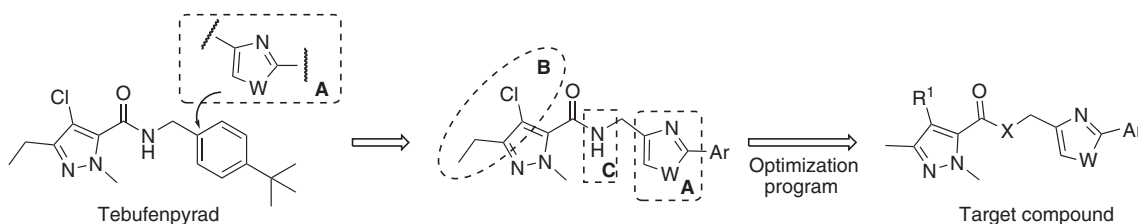
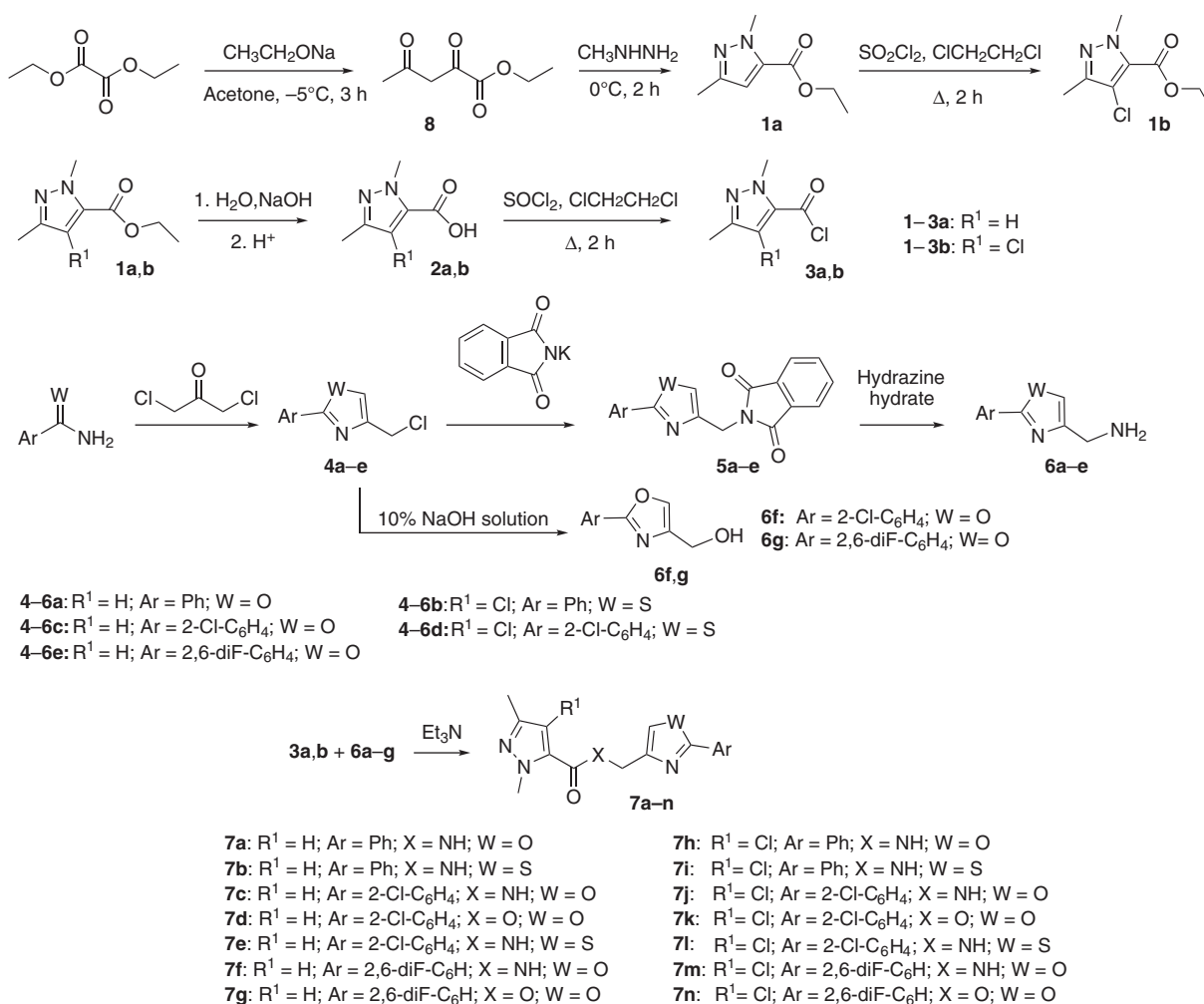


Figure 1 Design strategy of the target compounds.



Scheme 1 Synthesis of target compounds 7a-n.

The structure-activity relationship appears to be following a general trend. On the basis of the bioassay data, the substituents R^1 , Ar and W show a significant relationship with the activity. When R^1 , Ar and W are kept constant, the influence of X on the insecticidal activities shows a regular change. The insecticidal activities of the target compounds increase when the X is an NH rather than O moiety. More specifically, in the substituted pyrazoles, amide derivatives display better activities

than carboxylate ester counterparts. For example, compounds 7c and 7j are much more active than 7d and 7k, respectively.

Conclusions

In the search for potent insecticidal agents, a series of 1H-pyrazole-5-carboxylic acid derivatives (esters and

Table 1 Activities against *Aphis fabae* of compounds 7.

Compound	Mortality rate against <i>A. fabae</i> (%)			
	500 mg/L	200 mg/L	50 mg/L	12.5 mg/L
7a	93.8	90.2	52.5	35.2
7b	100.0	48.2	34.8	35.0
7c	79.6	85.2	49.1	15.8
7d	25.0	—	—	—
7e	94.8	84.1	41.8	38.3
7f	100.0	100.0	25.2	8.8
7g	100.0	67.3	50.3	15.8
7h	100.0	100.0	91.1	85.7
7i	100.0	100.0	56.9	32.9
7j	100.0	95.3	74.8	46.7
7k	56.7	—	—	—
7l	98.3	87.0	78.6	55.6
7m	30.0	—	—	—
7n	56.7	—	—	—
Imidacloprid	100.0	100.0	100.0	89.8

amides) were designed and synthesized. Most of the compounds display good insecticidal activity against *A. fabae*. The best compound **7h** displays 85.7% mortality rate at concentration of 12.5 mg/L.

Experimental

Melting points were measured on a WPS-1B melting-point apparatus (made in Shanghai Physical Optics Instrument Plant) and are uncorrected. ^1H NMR spectra were recorded in CDCl_3 on a Varian INOVA-300 instrument using trimethylsilyl (TMS) as the internal standard. High resolution mass spectra were acquired using an Agilent 5973-6890 gas chromatography-mass spectrometer (GC-MS) and an Agilent 1100 liquid chromatography-mass spectrometer (LC-MS). Column chromatography was performed using 200–300 mesh silica gel.

Synthesis of ethyl 2,4-dioxovalerate (**8**)

A solution of sodium ethoxide (30.0 g, 0.45 mol) in anhydrous ethanol (300 mL) was maintained at -5°C and slowly treated for 3 h with a solution of diethyl oxalate (46.7 g, 0.32 mol) in acetone (14.7 g, 0.3 mol). The mixture was then poured into ice water, and after acidification with 1 M hydrochloric acid to pH 4 the aqueous phase was extracted with ethyl acetate. The extract was washed twice with water, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give 46.5 g (94% yield, 96% purity) of a yellow liquid. Without further purification, compound **8** was used in the subsequent reaction.

Synthesis of ethyl 1,3-dimethyl-1H-pyrazole-5-carboxylate (**1a**)

In 300 mL of anhydrous ethanol was dissolved **8** (46.5 g) with stirring below -5°C . Then, aqueous methylhydrazine (0.38 mol) was added

slowly and the solution was stirred below 0°C for 2 h. The solvent was removed under reduced pressure and the aqueous phase was extracted with ethyl acetate. The organic layer was washed twice with water and dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to yield 39.3 g (92% yield, 90% purity) of a yellow oil (ref. [19] indicates this as a colorless solid, mp $40\text{--}42^\circ\text{C}$). Without further purification, compound **1a** was used in the next reaction. The NMR data of **1a** and the literature values [19] are virtually identical. ^1H NMR (CDCl_3): δ 1.37 (t, $J=7.15$ Hz, 3H, CH_3), 2.26 (d, $J=0.40$ Hz, 3H, CH_3), 4.11 (s, 3H, CH_3), 4.32 (q, $J=7.15$ Hz, 2H, CH_2), 6.61 (q, 1 H; $J=0.40$ Hz; CH); ^{13}C NMR (CDCl_3): δ 160.0, 146.9, 133.0, 110.4, 60.8, 39.1, 14.3, 13.3.

Synthesis of ethyl 1,3-dimethyl-4-chloro-1H-pyrazole-5-carboxylate (**1b**)

SO_2Cl_2 (8.04 g, 0.06 mol) was slowly added to a stirred solution of **1a** (10 g, 0.06 mol) in dichloroethane (50 mL) in an ice bath and the mixture was stirred under reflux for 2 h. The solvent was removed under reduced pressure and the residue was treated with an aqueous solution of NaCl. The mixture was extracted with ethyl acetate, washed twice with water, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to yield 10.0 g (95% yield, 88% purity) of a brown liquid.

Synthesis of compounds 2a,b

Compound **1a** (0.05 mol) was added to a solution of NaOH (6.0 g, 0.15 mol) in water (100 mL). After 4 h at 80°C , the mixture was poured into ice water and adjusted to an acidic pH. The resulting precipitate was filtered and dried to yield 4.6 g (60% yield, 92% purity) of a white solid. Compound **2b** was synthesized in a similar way.

1,3-Dimethyl-1H-pyrazole-5-carboxylic acid (2a) White solid; mp $172.6\text{--}172.9^\circ\text{C}$; ^1H NMR ($\text{DMSO}-d_6$): δ 2.26 (s, 3H, CH_3), 4.11 (s, 3H, CH_3), 6.61 (s, 1H, pyrazole-H), 6.66 (bs, 1H, NH), 12.75 (bs, 1H, COOH); LC-MS: m/z 140, $[\text{M}+1]^+$. Anal. Calcd for $\text{C}_6\text{H}_8\text{N}_2\text{O}_2$: C, 51.42; H, 5.75; N, 19.99; Found: C, 51.44; H, 5.71; N, 20.01.

4-Chloro-1,3-dimethyl-1H-pyrazole-5-carboxylic acid (2b) White solid, mp $216\text{--}217^\circ\text{C}$; ^1H NMR ($\text{DMSO}-d_6$): δ 2.24 (s, 3H, CH_3), 4.14 (s, 3H, CH_3), 12.75 (bs, 1H, COOH); LC-MS: m/z 174, $[\text{M}+1]^+$. Anal. Calcd for $\text{C}_6\text{H}_7\text{ClN}_2\text{O}_2$: C, 41.28; H, 4.04; N, 16.05; Found: C, 41.22; H, 4.10; N, 15.96.

Synthesis of 1,3-dimethyl-1H-pyrazolecarbonyl chloride (**3a**) and its analogue **3b**

A mixture of **2a** (0.01 mol) and thionyl chloride (2.95 g, 0.025 mol) in 1,2-dichloroethane (15 mL) was heated under reflux for 2 h and then concentrated under reduced pressure. Without further purification, the next reaction was carried out immediately. Compound **3b** was synthesized by using a similar procedure.

Synthesis of 4-(chloromethyl)-2-phenyloxazole (4a) and its analogues 4c and 4e

A mixture of benzamide (18.15 g, 150 mmol) and 1,3-dichloroacetone (19 g, 170 mmol) was ground thoroughly. Then the mixture was melted and the temperature was kept at 130°C for 2 h. After cooling to room temperature, 150 mL of ethyl acetate was added and the mixture was washed twice with saturated Na₂CO₃ solution. The organic solution was dried over Na₂SO₄, filtered and concentrated to furnish 25.3 g (94% purity) of **4a** as a yellow oil; yield 98%. Without further purification, the product **4a** was used in the next reaction. The analogues **4c** and **4e** were synthesized in a similar way.

Synthesis of 4-(chloromethyl)-2-phenylthiazole (4b) and its analogue 4d

A solution of thiobenzamide (20.5 g, 150 mmol) and 1, 3-dichloroacetone (19 g, 170 mmol) in ethanol (150 mL) was heated to reflux for 2 h. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was treated with ethyl acetate (150 mL) and water (100 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated to yield 29.1 g (90% yield, 88% purity) of **4b** as a yellow oil. Without further purification, the product was used in the next reaction. The analogue **4d** was synthesized in a similar way.

Synthesis of compounds 6a–e

To a solution of **4a** (0.045 mol) in *N,N*-dimethylformamide (DMF, 100 mL), potassium phthalimide (0.05 mol) was added portionwise. The mixture was stirred at 80°C for 5 h, poured into ice water and the resultant precipitate was collected by filtration and washed with water to furnish **5a** as brown solid. A mixture of **5a** thus obtained, ethanol (200 mL) and hydrazine hydrate (80%, 6.25 g, 0.1 mol) was heated under reflux for 5 h, and the resultant precipitate was separated by filtration and the filtrate was concentrated under reduced pressure. The residue was treated with cold water and the mixture was extracted with ethyl acetate. The extract was washed twice with water, dried over Na₂SO₄ and concentrated under reduced pressure to furnish 5.2 g (78% yield, 85% purity) of **6a** as a brown oil. Without further purification, the product was used in the subsequent reaction. The analogues **6b–e** were synthesized in a similar way.

(2-Phenyloxazol-4-yl)methanamine (6a) ¹H NMR (DMSO-*d*₆): δ 4.01 (s, 2H, CH₂), 7.56–7.59 (m, 3H, Ph H), 7.98–8.02 (m, 2H, Ph H), 8.29 (s, 1H, oxazole-H), 8.58 (bs, 2H, NH); LC-MS: *m/z* 175, [M+1]⁺. Anal. Calcd for C₁₀H₁₀N₂O: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.99; H, 5.84; N, 15.98.

(2-Phenylthiazol-4-yl)methanamine (6b) ¹H NMR (DMSO-*d*₆): δ 4.18 (s, 2H, CH₂), 7.49–7.56 (m, 3H, Ph H), 7.84 (s, 1H, thiazole-H), 7.97–7.99 (m, 2H, Ph H), 8.59 (bs, 2H, NH); LC-MS: *m/z* 191, [M+1]⁺. Anal. Calcd for C₁₀H₁₀N₂S: C, 63.13; H, 5.30; N, 14.72. Found: C, 63.10; H, 5.27; N, 14.81.

Synthesis of 4-(hydroxymethyl)-2-aryloxazoles 6f,g

A mixture of **4a** (0.01 mol), aqueous solution of NaOH (4 g, 10%) and THF (20 mL) was heated under reflux for 4 h, then cooled and concentrated under reduced pressure. The residue was treated with ethyl acetate (150 mL) and hydrochloric acid (10%, 100 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated to furnish 0.99 g (50% yield, 89% purity) of **6f** as a colorless oil. Without further purification, the product was used in the subsequent reaction. The analogue **6g** was synthesized in a similar way.

(2-(2-Chlorophenyl)oxazol-4-yl)methanol (6f) ¹H NMR (DMSO-*d*₆): δ 4.61 (s, 2H, CH₂), 7.36–7.49 (m, 3H), 7.77 (s, 1H), 7.97–7.91 (m, 1H), 8.29 (s, 1H); LC-MS: *m/z* 210, [M+1]⁺. Anal. Calcd for C₁₀H₈ClNO₂: C, 57.30; H, 3.85; N, 6.68. Found: C, 57.22; H, 4.88; N, 6.60.

Synthesis of compounds 7a–n

Compound **3a** (0.01 mol) was added dropwise to a solution of **6a** (0.01 mol) and triethylamine (0.02 mol) in THF (20 mL) at 0°C. The mixture was allowed to stand overnight, then poured into Na₂CO₃ solution and the aqueous phase was extracted with ethyl acetate. The extract was dried, filtered and concentrated. The residue was subjected to silica gel chromatography eluting with a gradient of petroleum ether-ethyl acetate (10:1/5:1) to yield **7a**. Compounds **7b–n** were synthesized in a similar manner.

1,3-Dimethyl-N-[(2-phenyloxazol-4-yl)methyl]-1H-pyrazole-5-carboxamide (7a) Yield 42.6% of a gray solid, mp 104–106°C; ¹H NMR (CDCl₃): δ 2.25 (s, 3H), 4.11 (s, 3H), 4.55 (dd, *J*=1.2 Hz, *J*=5.4 Hz, 2H), 6.34 (s, 1H), 6.66 (bs, 1H), 7.44–7.49 (m, 3H), 7.69 (t, *J*=0.9 Hz, 1H), 8.01–8.01 (m, 2H); GC-MS: *m/z* 296, M⁺, base peak at *m/z* 173. Anal. Calcd for C₁₆H₁₆N₄O₂: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.55; H, 5.42; N, 18.93.

1,3-Dimethyl-N-[(2-phenylthiazol-4-yl)methyl]-1H-pyrazole-5-carboxamide (7b) Yield 38% of a yellow solid; mp 105–106°C; ¹H NMR (CDCl₃): δ 2.26 (s, 3H), 4.11 (s, 3H), 4.70 (dd, *J*=5.7, 0.9 Hz, 2H), 6.35 (s, 1H), 6.76 (bs, 1H), 7.20 (s, 1H), 7.43–7.49 (m, 3H), 7.91–7.97 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ 168.8, 159.8, 153.2, 146.5, 135.4, 133.1, 129.9, 128.9, 126.3, 115.4, 105.8, 39.4, 38.7, 13.1; GC-MS: *m/z* 312, M⁺, base peak at *m/z* 189. Anal. Calcd for C₁₆H₁₆N₄OS: C, 61.52; H, 5.16; N, 17.93. Found: C, 61.41; H, 5.13; N, 18.03.

N-[(2-(2-Chlorophenyl)oxazol-4-yl)methyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (7c) Yield 42% of a brown oil; ¹H NMR (CDCl₃): δ 2.26 (s, 3H), 4.13 (s, 3H), 4.57 (d, *J*=5.4 Hz, 2H), 6.33 (s, 1H), 6.66 (bs, 1H), 7.34–7.54 (m, 3H), 7.77 (s, 1H), 7.94–7.97 (m, 1H); GC-MS: *m/z* 300, M⁺, base peak at *m/z* 207. Anal. Calcd for C₁₆H₁₅ClN₄O₂: C, 58.10; H, 4.57; N, 16.94. Found: C, 58.02; H, 4.66; N, 16.87.

(2-(2-Chlorophenyl)oxazol-4-yl)methyl-1,3-dimethyl-1H-pyrazole-5-carboxylate (7d) Yield 10% of a white solid; mp 86–87°C; ¹H NMR (CDCl₃): δ 2.25 (s, 3H), 4.12 (s, 3H), 5.32 (d, *J*=0.6 Hz, 2H), 6.62 (d, *J*=0.6 Hz, 1H), 7.33–7.52 (m, 3H), 7.77 (t, *J*=0.6 Hz, 1H), 7.96–7.99 (m, 1H); GC-MS: *m/z* 331, M⁺, base peak at *m/z* 208. Anal. Calcd for C₁₆H₁₄ClN₄O₃: C, 57.93; H, 4.25; N, 12.67. Found: C, 57.86; H, 4.32; N, 12.63.

***N*-[2-(2-Chlorophenyl)thiazol-4-yl)methyl]-1,3-dimethyl-1*H*-pyrazole-5-carboxamide (7e)** Yield 48% of a yellow solid; mp 109–110°C; ^1H NMR (CDCl_3): δ 2.27 (s, 3H), 4.17 (s, 3H), 4.74–4.76 (m, 2H), 6.33 (s, 1H), 6.76 (bs, 1H), 7.35–7.53 (m, 3H), 7.42 (s, 1H), 8.16–8.20 (m, 1H); GC-MS: m/z 346, M^+ , base peak at m/z 223. Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{ClN}_4\text{O}_2$: C, 55.41; H, 4.36; N, 16.15. Found: C, 55.37; H, 4.41; N, 16.18.

***N*-[2-(2,6-Difluorophenyl)oxazol-4-yl)methyl]-1,3-dimethyl-1*H*-pyrazole-5-carboxamide (7f)** Yield 39% of a yellow solid; mp 145–146°C; ^1H NMR (CDCl_3): δ 2.25 (s, 3H), 4.113 (s, 3H), 4.57 (dd, $J=5.4$, 0.9 Hz, 2H), 6.31 (s, 1H), 6.96 (bs, 1H), 7.02–7.08 (m, 2H), 7.42–7.48 (m, 1H), 7.82 (s, 1H); GC-MS: m/z 332, M^+ , base peak at m/z 209. Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{F}_2\text{N}_4\text{O}_2$: C, 57.83; H, 4.25; N, 16.86. Found: C, 57.78; H, 4.32; N, 16.82.

[2-(2,6-Difluorophenyl)oxazol-4-yl)methyl]-1,3-dimethyl-1*H*-pyrazole-5-carboxylate (7g) Yield 24% of a yellow solid; mp 97–98°C; ^1H NMR (CDCl_3): δ 2.36 (s, 3H), 4.123 (s, 3H), 5.34 (d, $J=0.9$ Hz, 2H), 6.66 (s, 1H), 7.02–7.08 (m, 2H), 7.42–7.47 (m, 1H), 7.90 (s, 1H); GC-MS: m/z 333, M^+ , base peak at m/z 166. Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{F}_2\text{N}_3\text{O}_3$: C, 57.66; H, 3.93; N, 12.61. Found: C, 57.70; H, 3.88; N, 12.60.

4-Chloro-1,3-dimethyl-*N*-[2-(phenyloxazol-4-yl)methyl]-1*H*-pyrazole-5-carboxamide (7h) Yield: 39% of a white solid; mp 123–124°C; ^1H NMR (CDCl_3): δ 2.24 (s, 3H), 4.13 (s, 3H), 4.61 (dd, $J=5.4$, 0.9 Hz, 2H), 7.34 (bs, 1H), 7.45–7.50 (m, 3H), 7.71 (s, 1H), 8.01–8.06 (m, 2H); GS-MS: m/z 330, M^+ , base peak at m/z 173. Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{ClN}_4\text{O}_2$: C, 58.10; H, 4.57; N, 16.94. Found: C, 58.14; H, 4.50; N, 16.99.

4-Chloro-1,3-dimethyl-*N*-[2-(phenylthiazol-4-yl)methyl]-1*H*-pyrazole-5-carboxamide (7i) Yield 30% of a white solid; mp 136–137°C; ^1H NMR (CDCl_3): δ 2.25 (s, 3H), 4.144 (s, 3H), 4.78 (dd, $J=5.1$, 0.6 Hz, 2H), 7.21 (s, 1H), 7.43–7.48 (m, 3H), 7.58 (bs, 1H), 7.92–7.97 (m, 2H); GC-MS: m/z 346, M^+ , base peak at m/z 189. Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{ClN}_4\text{OS}$: C, 55.41; H, 4.36; N, 16.15. Found: C, 55.47; H, 4.29; N, 16.20.

4-Chloro-*N*-[2-(2-chlorophenyl)oxazol-4-yl)methyl]-1,3-dimethyl-1*H*-pyrazole-5-carboxamide (7j) Yield 32% of a white solid; mp 92–94°C; ^1H NMR (CDCl_3): δ 2.24 (s, 3H), 4.14 (s, 3H), 4.64 (dd, $J=5.7$, 0.6 Hz, 2H), 7.34 (bs, 1H), 7.34–7.42 (m, 2H), 7.50–7.53 (m, 1H), 7.53 (s, 1H), 7.96–7.99 (m, 1H); LC-MS: m/z 365, $[\text{M}+1]^+$. Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{Cl}_2\text{N}_4\text{O}_2$: C, 52.62; H, 3.86; N, 15.34. Found: C, 52.71; H, 3.78; N, 15.26.

[2-(2-Chlorophenyl)oxazol-4-yl)methyl]-4-chloro-1,3-dimethyl-1*H*-pyrazole-5-carboxylate (7k) Yield 90% of a yellow oil; ^1H NMR (CDCl_3): δ 2.24 (s, 3H), 4.13 (s, 3H), 5.41 (s, 2H), 7.33–7.44 (m, 2H), 7.51 (s, 1H), 7.92 (s, 1H), 7.97–8.00 (m, 1H); LC-MS: m/z 366, $[\text{M}+1]^+$. Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{Cl}_2\text{N}_3\text{O}_3$: C, 52.48; H, 3.58; N, 11.47. Found: C, 52.55; H, 3.55; N, 11.44.

4-Chloro-*N*-[2-(2-chlorophenyl)thiazol-4-yl)methyl]-1,3-dimethyl-1*H*-pyrazole-5-carboxamide (7l) Yield 31% of a white solid; mp 136–137°C; ^1H NMR (CDCl_3): δ 2.25 (s, 3H), 4.14 (s, 3H), 4.84 (d, $J=5.4$ Hz, 2H), 7.38–7.42 (m, 3H), 7.51 (s, 1H), 7.64 (bs, 1H, NH), 8.31 (d, $J=9.2$ Hz, 1H); LC-MS: m/z 381, $[\text{M}+1]^+$. Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{Cl}_2\text{N}_3\text{O}_2\text{S}$: C, 50.40; H, 3.70; N, 14.69. Found: C, 50.43; H, 3.78; N, 14.64.

4-Chloro-*N*-[2-(2,6-difluorophenyl)oxazol-4-yl)methyl]-1,3-dimethyl-1*H*-pyrazole-5-carboxamide (7m) Yield 35% of a yellow solid; mp 125–127°C; ^1H NMR (CDCl_3): δ 2.13 (s, 3H), 2.17 (s, 3H), 4.02 (s, 3H), 4.62 (dd, $J=5.7$ Hz and 0.9 Hz, 2H), 6.49 (bs, 1H), 7.01–7.09 (m, 2H), 7.40–7.49 (m, 1H), 7.82 (t, $J=0.9$ Hz, 1H); GC-MS: m/z 346, M^+ , base peak at m/z 209. Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{ClF}_2\text{N}_4\text{O}_2$: C, 52.40; H, 3.57; N, 15.28. Found: C, 52.33; H, 3.55; N, 15.36.

[2-(2,6-Difluorophenyl)oxazol-4-yl)methyl]-4-chloro-1,3-dimethyl-1*H*-pyrazole-5-carboxylate (7n) Yield 32% of a gray solid; mp 149–150°C; ^1H NMR (CDCl_3): δ 2.24 (s, 3H), 4.10 (s, 3H), 5.42 (d, $J=0.9$ Hz, 2H), 7.02–7.09 (m, 2H), 7.42–7.47 (m, 1H), 7.96 (s, 1H); GC-MS: m/z 367, M^+ , base peak at m/z 166. Anal. Calcd for $\text{C}_{16}\text{H}_{12}\text{ClF}_2\text{N}_3\text{O}_3$: C, 52.26; H, 3.29; N, 11.43. Found: C, 52.20; H, 3.34; N, 11.40.

Biological assay

Stock solution of every test compound was prepared in DMF at a concentration of 1.0 g/L and then diluted to the required concentration (12.5–500 mg/L) with water containing Tween 80 (0.4 mg/L).

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. Each assay consisted of three analyses. After 24 h, mortalities were recorded and the results were averaged.

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