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DESIGN, SYNTHESIS AND INSECTICIDAL ACTIVITY OF 1-METHYL-3-(5-ARYL-4,5-DIHYDROISOXAZOL-3-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDES

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Abstract – Pyrazole and its derivatives are a kind of important heterocyclic compounds used in agrochemicals development. In this research, a series of novel 1-methyl-3-(5-aryl-4,5-dihydroisoxazol-3-yl)-1*H*-pyrazole-5-carboxamides were synthesized and confirmed by ^{1}H NMR, ^{13}C NMR and ESI-MS. The preliminary bioactivity indicated that most title compounds showed excellent potency against *Mythimna separate* (Walker) at 500 mg/L, compounds **ZJ4**, **ZJ12**, **ZJ16**, **ZJ17** showed moderate insecticidal activity against *Aphis craccivora* at 500 mg/L. Especially, compounds **ZJ4**, **ZJ12**, **ZJ17** exhibited around 60% insecticidal activities against *M. separate* at 100 mg/L. The results indicated that the potential of these pyrazole-5-carboxamides containing arylisoxazoline fragment to be utilized in pesticide discovery through further development.

INTRODUCTION

Summary of pesticide likeness analysis is widely used in agrochemicals development.[1] Pyrazole and its derivatives are a type of important heterocyclic compounds, which showing unique biological activities that researched in crop protection frequently.[2] In most instances, pyrazole containing substituted groups on different position would exhibit biological activity for diverse target. As like SDHI (succinate dehydrogenase inhibitor) fungicides, the pyrazole-4-carboxamide pharmacophore is still a research

hotspot that given some new products Pyrapropoyne, Inpyrfluxam, Isoflucypram etc.[3] On the other hand, pyrazole-5-carboxamides usually show positive insecticidal/acaricidal activity such as Cyenopyrafen, Tebufenpyrad and Chlorantraniliprole.[4] Thus, with the increase of resistant level of insects, searching for the novel, eco-friendly insecticides remains an urgent challenge for crop protection.

Recently, arylisoxazoline derivatives have received considerable attention due to their various bioactivities, including anticancer,[5] antibacterial,[6] antiviral,[7] antiinflammatory,[8] analgesics,[9] and antifungal drugs.[10] Besides, arylisoxazoline containing heterocycles showing their unique insecticidal activity in modern crop and animal protection especially, such as veterinary drug Afoxolaner,[11] and insecticide Fluxametamide,[12] the compounds are a relatively new class of agents inhibiting γ-aminobutyric acid (GABA)-gated and L-glutamate-gated chloride channels (GluCl).[13] In 2018, another new active ingredient named Isocycloseram from Syngenta also have the same arylisoxazoline pharmacophore.[14]

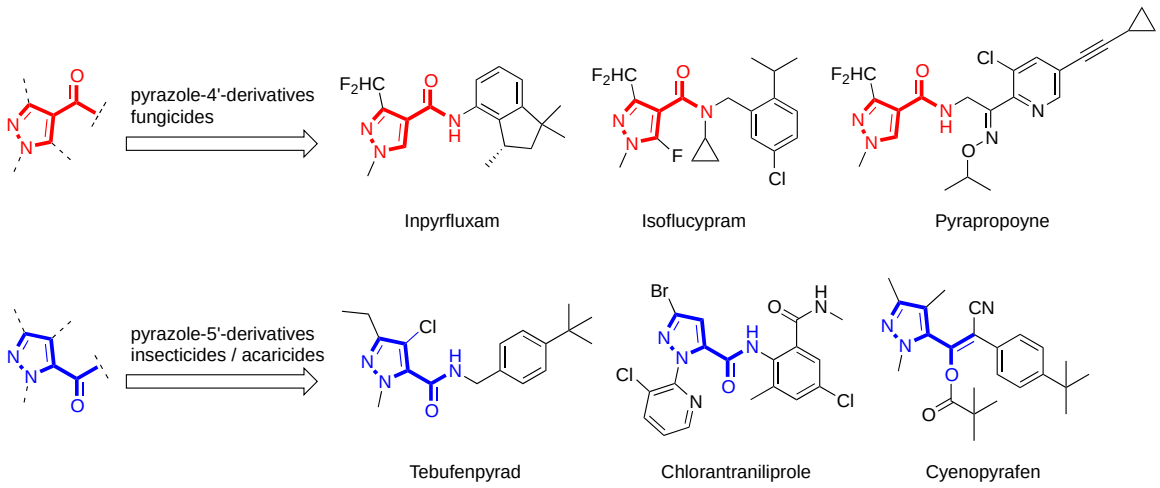


Figure 1. Substituted pyrazole derivatives as fungicicides and insecticides / acaricides

Hence, it has been widely assumed that the combination of arylisoxazoline into a pesticide likeness molecular fragment pyrazole-5-carboxamides is an effective approach for discovering new bioactive molecules. Therefore, a series of 3-arylisoxazoline-pyrazole-5-carboxamide derivatives were designed

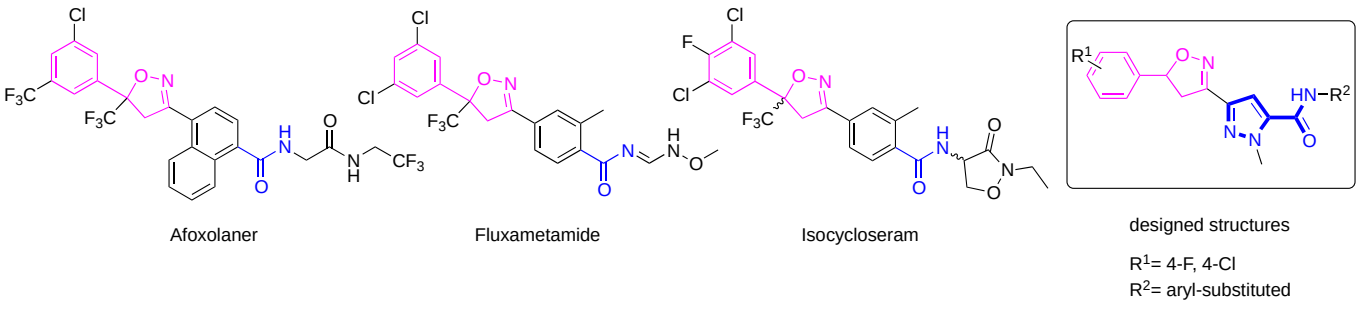
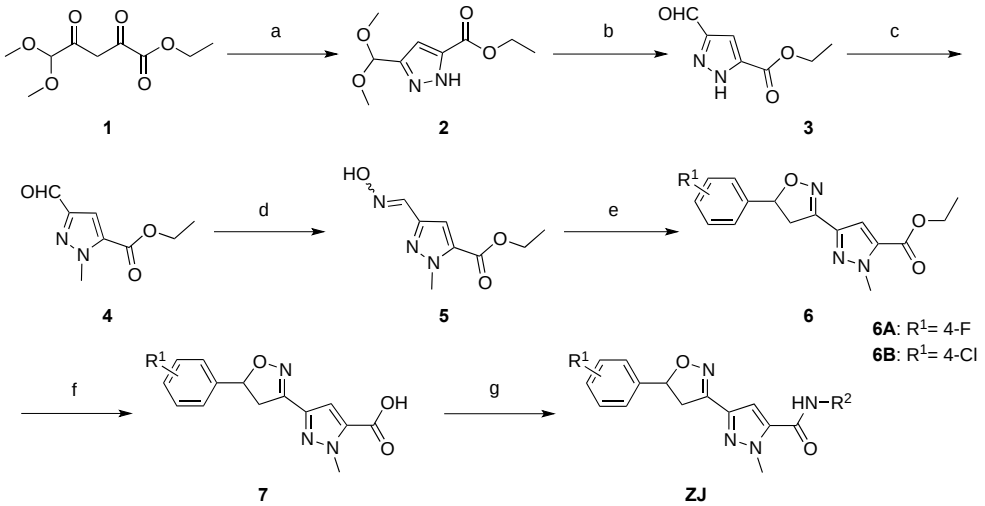


Figure 2. Design strategy of pyrazole-5-carboxamides containing arylisoxazoline moiety

and synthesized, and investigated their insecticidal activities against *Mythimna separate*, *Tetranychus cinnabarinus* and *Aphis craccivora*.

RESULTS AND DISCUSSION

Synthesis. The synthesis of the designed compounds **ZJ1**-**ZJ17** is summarized in Scheme 1. The synthesis of intermediate **2** is a classical Knorr pyrazole synthesis. In the preparation of **4**, a minor of regioisomer was produced that could be separated by column chromatography. The oxime **5** is prepared by aqueous hydroxylamine, due to its low completion by anhydrous hydroxylamine hydrochloride. The 1,3-dipolar cycloaddition between oxime **5** and substituted styrene gave intermediate **6** in a good yield, respectively. In the preparation of compound **7**, aqueous sodium hydroxide (10%) as the base could fulfill hydrolysis completely. The target compounds were prepared by amide synthesis method, trimethylamine (TEA) as the base would have similar yield compare to other common base.



ZJ1: R^1=4-F; R^2=3-CF_3-C_6H_4
ZJ2: R^1=4-F; R^2=2-Cl-C_6H_4
ZJ3: R^1=4-F; R^2=4-Me-C_6H_4
ZJ4: R^1=4-F; R^2=3-Cl-C_6H_4
ZJ5: R^1=4-F; R^2=2-MeO-C_6H_4
ZJ6: R^1=4-F; R^2=2-Me-C_6H_4
ZJ7: R^1=4-F; R^2=3-Me-C_6H_4
ZJ8: R^1=4-F; R^2=2-CO_2Me-C_6H_4
ZJ9: R^1=4-F; R^2=2,4-2Cl-C_6H_3
ZJ10: R^1=4-Cl; R^2=2-Cl-C_6H_4
ZJ11: R^1=4-Cl; R^2=4-Me-C_6H_4
ZJ12: R^1=4-Cl; R^2=2-MeO-C_6H_4
ZJ13: R^1=4-Cl; R^2=2-CO_2Me-C_6H_4
ZJ14: R^1=4-Cl; R^2=3-CF_3-C_6H_4
ZJ15: R^1=4-Cl; R^2=2,4-2Cl-C_6H_3
ZJ16: R^1=4-Cl; R^2=3-F-C_6H_4
ZJ17: R^1=4-Cl; R^2=2-Me-C_6H_4

Reagents and conditions: (a) hydrazine hydrate, AcOH, 0-5 ^oC, 96%; (b) AcOH (aq.), 60 ^oC, 87%; (c) K_2CO_3, dimethyl sulfate, acetone, rt, 74%; (d) hydroxylamine (aq.), THF, rt; (e) NCS, DMF, 60 ^oC; styrene, TEA, rt, 87% (**6A**), 84% (**6B**); (f) NaOH (aq.), THF, reflux, 93% (**7A**); (g) arylamine, TEA, THF.

Scheme 1. Synthesis of pyrazole-5-carboxamides containing arylisoxazoline scaffold

Insecticidal activity

The initial insecticidal activity of title compounds is listed in Table 1. The results showed that most of the designed compounds have moderate insecticidal activities against *M. separate* and *T. cinnabarinus*, but insecticidal potency for *A. craccivora*. For example, the preliminary bioassays indicated that **ZJ4-ZJ8**,

ZJ11-ZJ17, showed favorable activity, and had 80% - 100% mortality against *M. separate* at 500 mg/L. And, the results showed no obvious structure-activity relationship (SAR) with different substituted of R^1 on benzene. Among monosubstituted arylamine derivatives, *ortho*-substituted and *meta*-substituted were better than *para*-substituted arylamines, and the results showed no obvious difference between alkyl and halogen. In addition, compounds **ZJ4**, **ZJ12**, **ZJ16**, **ZJ17** showed moderate insecticidal activity against *T. cinnabarinus*. According to the rescreening bioassay results, compounds **ZJ4**, **ZJ12**, **ZJ17** showed insufficient activities against *M. separate* at 100 mg/L and 20 mg/L, and no activities against *T. cinnabarinus*.

Table 1. The insecticidal activity of title compounds against *M. separate*, *A. craccivora*, and *T. cinnabarinus* at 500 mg/L

Compound	R^1	R^2	Insecticidal activity, %		
			Mythimna separate	*Aphis craccivora*	*Tetranychus cinnabarinus*
ZJ1	4-F	3-CF_3-C_6H_4	63	0	0
ZJ2	4-F	2-Cl-C_6H_4	75	0	0
ZJ3	4-F	4-Me-C_6H_4	65	0	0
ZJ4	4-F	3-Cl-C_6H_4	100	80	0
ZJ5	4-F	2-MeO-C_6H_4	100	0	0
ZJ6	4-F	2-Me-C_6H_4	100	30	0
ZJ7	4-F	3-Me-C_6H_4	100	50	0
ZJ8	4-F	2-CO_2Me-C_6H_4	85	0	0
ZJ9	4-F	2,4-2Cl-C_6H_3	58	0	0
ZJ10	4-Cl	2-Cl-C_6H_4	75	30	0
ZJ11	4-Cl	4-Me-C_6H_4	85	0	0
ZJ12	4-Cl	2-MeO-C_6H_4	100	70	0
ZJ13	4-Cl	2-CO_2Me-C_6H_4	85	0	0
ZJ14	4-Cl	3-CF_3-C_6H_4	83	0	0
ZJ15	4-Cl	2,4-2Cl-C_6H_3	95	0	0
ZJ16	4-Cl	3-F-C_6H_4	100	70	0
ZJ17	4-Cl	2-Me-C_6H_4	100	80	0
Avermectin	-	-	100	100	100

Table 2. The insecticidal activity of title compounds against *A. craccivora* and *M. separate*

Compound	*M. separate* (%)		*A. craccivora* (%)
	100 mg/L	20 mg/L	100 mg/L
ZJ4	65	10	10
ZJ5	48	0	0
ZJ6	50	0	0
ZJ7	30	0	0
ZJ8	33	0	0
ZJ11	40	0	0
ZJ12	60	0	10
ZJ13	30	0	0
ZJ14	35	0	0
ZJ15	48	0	0
ZJ16	40	0	0
ZJ17	62	15	10
Avermectin	100	95	100

CONCLUSIONS

In summary, seventeen novel pyrazole-5-carboxamide derivatives containing arylisoxazoline fragment were designed, synthesized and characterized. The bioassay results showed that some of them exhibited good insecticidal activity against *M. separate* at 500 mg/L, and moderate activity at 100 mg/L. Therefore, to explore higher active compounds with insecticidal activity, further structural optimization and bioactivities are in progress.

EXPERIMENTAL

General remarks

^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker AV-600 spectrometer (Bruker Co., Switzerland) using TMS as an internal standard and $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shift values (δ) were given in parts per million (ppm). ESI-MS data were determined by LCQ-Advantage Thermo Finnigan instrument (ThermoFinnigan, MA). Melting points were determined by an X-4 apparatus and uncorrected. All solvents and reagents were commercially available for analytical reagent (AR) grade and dried prior to use. Analytical thin-layer chromatography was carried out on silica gel GF_{254}, and spots were visualized with ultraviolet light. All plant and insect materials were obtained from

the Zhejiang Base of National Southern Pesticide Research Centre, Zhejiang Research Institute of Chemical Industry (Hangzhou, China).

Synthetic procedure for 2

Aqueous hydrazine hydrate (80%, 6.88 g, 0.11 mol) was added to a solution of **1** (21.8 g, 0.1 mol) in glacial acetic acid (50 mL). The reaction mixture was stirred at 0-5 ºC for 5 h. The reaction completion was monitored by TLC. The crude **2** in AcOH was poured in ice-cold water. The solid thus separated out was filtered, washed, and dried to obtain **2**. Yield: 96%. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.38 (t, 3H, J = 7.2 Hz, CH_3), 3.37 (s, 6H, CH_3), 4.39 (q, 2H, J = 7.2 Hz, CH_2), 5.61 (s, 1H, CH), 6.88 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 14.2, 52.7, 61.2, 97.8, 107.0.

Synthetic procedure for 3

Intermediate **2** (3 g, 0.0149 mol) was added to an aqueous acetic acid (50%, 30 mL), the mixture was stirred at 60 ºC. When the reaction was complete according to TLC analysis, the mixture was concentrated under vacuum to afford the title compound **3** (1.6 g). Yield: 87%, viscous solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.42 (t, 3H, J = 7.2 Hz, CH_3), 4.44 (q, 2H, J = 7.2 Hz, CH_2), 7.35 (s, 1H, Ar-H), 10.03 (s, 1H, CH).

Synthetic procedure for 4

To potassium carbonate (26.5 g, 0.192 mol) and **3** (15 g, 0.096 mol) in acetone (450 mL), dimethyl sulfate (14.54 g, 0.115 mol) was added dropwise at room temperature. The reaction completion was monitored by TLC. The organic layer was filtered and concentrated. The crude product was purified by column chromatography to obtain the white solid **4** (12.1 g). Yield: 74%, white solid, mp 56-57 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.39 (t, 3H, J = 7.2 Hz, CH_3), 4.28 (s, 3H, N-CH_3), 4.39 (q, 2H, J = 7.2 Hz, CH_2), 7.34 (s, 1H, Ar-H), 9.96 (s, 1H, CH); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 14.2, 40.6, 61.6, 110.9, 134.6, 149.3, 159.3, 185.8.

Synthetic procedure for 5

To a solution of intermediate **4** (5.1 g, 0.03 mol) in THF (20 mL), aqueous hydroxylamine (15 mL, 21%, 0.045 mol) was added at room temperature. Then, the organic solvent was concentrated, the crude product was washed to obtain **5** without purification.

General procedure for synthesis of compounds 6A and 6B

Crude compound **5** (4.0 g, 0.022 mol) and NCS (3.26 g, 0.028 mol) were added to

N,*N*-dimethylformamide (DMF, 100 mL), the mixture was stirred at 60 °C. The reaction completion was monitored by TLC. Then, substituted styrene (0.021 mol) was added to the reaction mixture. TEA (2.8 g, 0.028 mol) was added dropwise to the mixture at room temperature. The resulting mixture was poured into H_2O (100 mL), and the aqueous layer was extracted with EtOAc (100 mL + 60 mL×2). The crude product was purified by column chromatography to obtain the white solid **6**. **6A**: yield: 87%, yellow solid, mp 68-69 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.39 (t, 3H, J = 7.2 Hz, CH_3), 3.37 (q, 1H, J = 7.8 Hz, CH_2), 3.81 (q, 1H, J = 11.4 Hz, CH_2), 4.18 (s, 3H, Ar-CH_3), 4.36 (q, 2H, J = 7.2 Hz, CH_2), 5.69 (q, 1H, J = 7.8 Hz, CH), 7.05 (t, 2H, J = 8.4 Hz, Ph-H), 7.28 (s, 1H, Ar-H), 7.35 (q, 2H, J = 5.4 Hz, Ph-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.2, 39.8, 43.0, 61.4, 81.7, 109.7, 115.5, 115.7, 127.7, 134.0, 136.5, 141.0, 151.5, 159.5, 161.7, 163.4. **6B**: yield: 84%, white solid, mp 70-71 °C, ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.37 (t, 3H, J = 7.2 Hz, CH_3), 3.36 (q, 1H, J = 8.4 Hz, CH_2), 3.81 (q, 1H, J = 11.4 Hz, CH_2), 4.18 (s, 3H, Ar-CH_3), 4.36 (q, 2H, J = 7.2 Hz, CH_2), 5.69 (q, 1H, J = 8.4 Hz, CH), 7.28 (s, 1H, Ar-H), 7.33 (q, 4H, J = 9.0 Hz, Ph-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.2, 39.8, 43.0, 61.4, 81.6, 109.7, 127.2, 128.9, 134.0, 139.3, 140.9, 151.5, 159.5.

Synthetic procedure for 7A

Intermediate **6A** (0.014 mol) was added to a solution of aqueous NaOH (50%, 30 mL) in THF (20 mL), the mixture was refluxed for 3 h. The resulting mixture was concentrated under reduced pressure. Then, the salt mixture was solved in water, neutralized with HCl to obtain crude product **7A**. Yield: 93%, viscous solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.31 (q, 1H, J = 8.4 Hz, CH_2), 3.83 (q, 1H, J = 10.4 Hz, CH_2), 4.11 (s, 3H, Ar-CH_3), 5.72 (q, 1H, J = 8.4 Hz, CH_2), 7.12 (s, 1H, Ar-H), 7.22 (t, 2H, J = 8.4 Hz, Ph-H), 7.43 (q, 2H, J = 5.4 Hz, Ph-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 47.5, 86.2, 114.2, 120.6, 120.7, 133.5, 140.0, 142.1, 145.4, 156.7, 165.5.

General procedure for the preparation of the title compounds

The experiment was performed according to the reported method.[15]

3-(5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-yl)-1-methyl-*N*-(3-(trifluoromethyl)phenyl)-1*H*-pyrazole-5-carboxamide (ZJ1):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.41 (q, 1H, J = 7.8 Hz, CH_2), 3.54 (q, 1H, J = 11.4 Hz, CH_2), 4.21 (s, 3H, Ar-CH_3), 5.69 (q, 1H, J = 8.4 Hz, CH), 7.02 (t, 2H, J = 8.4 Hz, Ph-H), 7.26–7.31 (m, 3H, Ar-H, Ph-H), 7.41–7.46 (m, 2H, Ph-H), 7.71 (d, 1H, J = 7.8 Hz, Ph-H), 7.95 (s, 1H, Ph-H), 8.20 (s, 1H, N-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 39.9, 42.9, 82.0, 105.5, 115.6, 115.8, 117.3, 121.6, 123.5, 127.6, 127.7, 129.6, 131.6, 136.1, 136.4, 137.6, 140.9, 151.9, 157.6. MS (ESI): 433 $[M + H]^+$.

3-(5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-yl)-1-methyl-*N*-(2-chlorophenyl)-1*H*-pyrazole-5-carboxamide (ZJ2):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.41 (q, 1H, J = 7.8 Hz, CH_2), 3.84 (q, 1H, J = 10.8 Hz, CH_2), 4.23 (s, 3H, Ar-CH_3), 5.72 (q, 1H, J = 7.8 Hz, CH), 7.06 (t, 2H, J = 9.0 Hz, Ph-H), 7.11–7.13 (m, 1H, Ph-H), 7.21 (s, 1H, Ar-H), 7.32–7.38 (m, 3H, Ph-H), 7.43 (d, 1H, J = 8.4, Ph-H), 8.29 (s, 1H, N-H), 8.41 (d, 1H, J = 8.4, Ph-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 39.9, 42.9, 81.9, 105.2, 115.6, 115.8, 121.9, 125.9, 127.7, 127.8, 127.9, 129.3, 133.9, 136.6, 141.1, 151.6, 157.1. MS (ESI): 399 $[M + H]^+$.

3-(5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-yl)-1-methyl-*N*-(*p*-tolyl)-1*H*-pyrazole-5-carboxamide (ZJ3):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.35 (s, 3H, Ph-CH_3), 3.40 (q, 1H, J = 7.8 Hz, CH_2), 3.83 (q, 1H, J = 10.8 Hz, CH_2), 4.21 (s, 3H, Ar-CH_3), 5.71 (q, 1H, J = 8.4 Hz, CH), 7.04–7.07 (m, 2H, Ph-H), 7.14 (s, 1H, Ar-H), 7.18 (d, 2H, J = 8.4 Hz, Ph-H), 7.34–7.36 (m, 2H, Ph-H), 7.45 (d, 2H, J = 8.4 Hz, Ph-H), 7.74 (s, 1H, N-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 21.0, 39.8, 42.9, 81.9, 104.9, 115.6, 115.8, 120.4, 127.7, 127.8, 129.7, 134.3, 135.0, 137.0, 140.9. MS (ESI): 379 $[M + H]^+$.

3-(5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-yl)-1-methyl-*N*-(3-chlorophenyl)-1*H*-pyrazole-5-carboxamide (ZJ4):

^{1}H NMR (600 MHz, DMSO) δ: 3.41 (q, 1H, J = 7.8 Hz, CH_2), 3.83 (q, 1H, J = 10.8 Hz, CH_2), 4.20 (s, 3H, Ar-CH_3), 5.69 (q, 1H, J = 8.4 Hz, CH), 7.03 (t, 2H, J = 9.0 Hz, Ph-H), 7.13–7.14 (m, 1H, Ph-H), 7.23–7.26 (m, 2H, Ar-H, Ph-H), 7.29–7.32 (m, 2H, Ph-H), 7.37–7.39 (m, 1H, Ph-H), 7.72 (t, 1H, J = 1.8 Hz, Ph-H), 8.11 (s, 1H, N-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 35.1, 38.2, 77.3, 100.8, 110.9, 111.0, 113.8, 115.9, 120.4, 123.0, 123.1, 125.3, 130.0, 131.3, 131.8, 133.4, 136.1, 152.8. MS (ESI): 399 $[M + H]^+$.

3-(5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-yl)-*N*-(2-methoxyphenyl)-1-methyl-1*H*-pyrazole-5-carboxamide (ZJ5):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.41 (q, 1H, J = 8.4 Hz, CH_2), 3.84 (q, 1H, J = 10.8 Hz, CH_2), 3.93 (s, 3H, CH_3), 4.23 (s, 3H, Ar-CH_3), 5.72 (q, 1H, J = 8.4 Hz, Ph-H), 6.93 (d, 1H, J = 8.4 Hz, Ph-H), 7.01 (t, 1H, J = 7.8 Hz, Ph-H), 7.06 (t, 2H, Ph-H), 7.09–7.13 (m, 1H, Ph-H), 7.16 (s, 1H, Ar-H), 7.35–7.38 (m, 2H, Ph-H), 8.41–8,43 (m, 2H, Ph-H, N-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 39.8, 42.9, 55.86, 81.7, 104.9, 110.1, 115.6, 115.8, 119.7, 121.1, 124.6, 126.9, 127.6, 127.7, 137.2, 140.9, 148.1, 151.8, 157.0. MS (ESI): 395 $[M + H]^+$.

3-(5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-yl)-1-methyl-*N*-(*o*-tolyl)-1*H*-pyrazole-5-carboxamide (ZJ6):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.29 (s, 3H, CH_3), 3.41 (q, 1H, J = 7.8 Hz, CH_2), 3.83 (q, 1H, J = 10.4 Hz, CH_2), 4.21 (s, 3H, Ar-CH_3), 5.66 (q, 1H, J = 8.4 Hz, CH), 7.03 (t, 2H, J = 8.4 Hz, Ph-H), 7.07 (dd, 1H, J = 1.2, 7.8 Hz, Ph-H), 7.19 (s, 1H, Ar-H), 7.23 (t, 1H, J = 9.0 Hz, Ph-H), 7.13–7.16 (m, 1H, Ph-H),

7.21–7.26 (m, 3H, Ph-H, Ar-H), 7.28–7.32 (m, 2H, Ph-H), 7.72–7.80 (m, 2H, Ph-H, N-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 17.8, 39.8, 42.9, 82.0, 105.1, 115.6, 115.7, 123.7, 126.2, 126.9, 127.7, 127.8, 130.8, 134.6, 136.2, 136.8, 140.9, 151.9, 157.5, 160.2. MS (ESI): 379 $[M + H]^+$.

3-(5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-yl)-1-methyl-*N*-(*m*-tolyl)-1*H*-pyrazole-5-carboxamide (ZJ7):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.35 (s, 3H, CH_3), 3.40 (q, 1H, J = 7.8 Hz, CH_2), 3.82 (q, 1H, J = 10.8 Hz, CH_2), 4.20 (s, 3H, Ar-CH_3), 5.69 (q, 1H, J = 7.8 Hz, CH), 6.99 (d, 1H, J = 7.8 Hz, Ph-H), 7.04 (t, 2H, J = 9.0 Hz, Ph-H), 7.19 (s, 1H, Ar-H), 7.23 (t, 1H, J = 7.8 Hz, Ph-H), 7.30–7.35 (m, 3H, Ph-H), 7.43 (s, 1H, Ph-H), 7.97 (s, 1H, N-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 21.5, 39.8, 42.9, 81.9, 105.2, 115.6, 115.8, 117.6, 121.1, 126.0, 127.7, 127.8, 129.0, 136.3, 136.9, 137.0, 139.2, 140.9, 151.9, 157.5. MS (ESI): 379 $[M + H]^+$.

Methyl 2-(3-(5-(4-fluorophenyl)-4,5-dihydroisoxazol-3-yl)-1-methyl-1*H*-pyrazole-5-carboxamido)-benzoate (ZJ8):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.42 (q, 1H, J = 7.8 Hz, CH_2), 3.85 (q, 1H, J = 10.8 Hz, CH_2), 3.97 (s, 3H, O-CH_3), 4.25 (s, 3H, Ar-CH_3), 5.72 (q, 1H, J = 7.8 Hz, CH), 7.07 (t, 2H, J = 9 Hz, Ph-H), 7.16 (t, 1H, J = 7.2 Hz, Ph-H), 7.36–7.40 (m, 3H, Ph-H, Ar-H), 7.58–7.63 (m, 1H, Ph-H), 8.09 (dd, 1H, J = 1.2, 8.4 Hz, Ph-H), 8.77 (d, 1H, J = 8.4 Hz, Ph-H), 12.08 (s, 1H, N-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 40.0, 43.1, 52.8, 81.8, 105.8, 115.3, 115.6, 115.7, 120.2, 123.2, 127.7, 131.1, 134.8, 136.6, 137.3, 141.1, 151.7, 157.7, 168.8. MS (ESI): 423 $[M + H]^+$.

***N*-(2,4-Dichlorophenyl)-3-(5-(4-fluorophenyl)-4,5-dihydroisoxazol-3-yl)-1-methyl-1*H*-pyrazole-5-carboxamide (ZJ9):**

^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.41 (q, 1H, J = 8.4 Hz, CH_2), 3.84 (q, 1H, J = 11.4 Hz, CH_2), 4.22 (s, 3H, Ar-CH_3), 5.72(q, 1H, J = 7.8 Hz, CH), 7.06 (t, 2H, J = 9.0 Hz, Ph-H), 7.20 (s, 1H, Ar-H), 7.31 (dd, 1H, J = 2.4, 9.0 Hz, Ph-H), 7.34–7.38 (m, 2H, Ph-H), 7.45 (d, 1H, J = 2.4 Hz, Ph-H), 8.23 (s, 1H, N-H), 8.38 (d, 1H, J = 9.0 Hz, Ph-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 39.9, 42.9, 82.0, 105.2, 115.6, 115.8, 122.2, 127.7, 128.1, 129.0, 132.6, 136.3, 141.2, 151.6, 157.0. MS (ESI): 433 $[M + H]^+$.

***N*-(2-Chlorophenyl)-3-(5-(4-chlorophenyl)-4,5-dihydroisoxazol-3-yl)-1-methyl-1*H*-pyrazole-5-carboxamide (ZJ10):**

^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.39 (q, 1H, J = 7.8 Hz, CH_2), 3.84 (q, 1H, J = 10.8 Hz, CH_2), 4.22 (s, 3H, Ar-CH_3), 5.71 (t, 1H, J = 10.2 Hz, CH), 7.11 (t, 1H, J = 7.8 Hz, Ph-H), 7.21 (s, 1H, Ar-H), 7.28–7.37 (m, 5H, Ph-H), 7.39–7.46 (m, 1H, Ph-H), 8.30 (s, 1H, Ph-H), 8.35–8.42 (m, 1H, N-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 39.9, 42.9, 81.8, 105.2, 121.8, 123.6, 125.5, 127.3, 127.8, 128.9, 129.3, 133.8, 134.0, 136.6, 139.1, 141.0, 151.6, 157.1. MS (ESI): 415 $[M + H]^+$.

3-(5-(4-Chlorophenyl)-4,5-dihydroisoxazol-3-yl)-1-methyl-*N*-(*p*-tolyl)-1*H*-pyrazole-5-carboxamide (ZJ11):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.33 (s, 3H, Ph-CH_3), 3.33 (q, 1H, J = 7.8 Hz, CH_2), 3.82 (q, 1H, J = 10.8 Hz, CH_2), 4.18 (s, 3H, Ar-CH_3), 5.66 (q, 1H, J = 7.8 Hz, CH), 7.13 (d, 2H, J = 8.4 Hz, Ph-H), 7.20 (s, 1H, Ar-H), 7.26 (d, 2H, J = 7.8 Hz, Ph-H), 7.31 (d, 2H, J = 8.4 Hz, Ph-H), 7.42 (d, 2H, J = 8.4 Hz, Ph-H), 7.97–8.10 (m, 1H, N-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 20.9, 39.8, 42.9, 81.8, 105.3, 120.7, 127.3, 128.9, 129.6, 134.4, 134.9, 137.1, 139.0, 140.7, 151.9, 157.5. MS (ESI): 395 $[M + H]^+$.

3-(5-(4-Chlorophenyl)-4,5-dihydroisoxazol-3-yl)-*N*-(2-methoxyphenyl)-1-methyl-1*H*-pyrazole-5-carboxamide (ZJ12):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.40 (q, 1H, J = 7.8 Hz, CH_2), 3.85 (q, 1H, J = 11.4 Hz, CH_2), 3.93 (s, 3H, O-CH_3), 4.22 (s, 3H, Ar-CH_3), 5.71 (q, 1H, J = 7.8 Hz, CH), 6.93 (d, 1H, J = 8.4 Hz, Ph-H), 7.00 (t, 1H, J = 7.8 Hz, Ph-H), 7.09–7.13 (m, 1H, Ph-H), 7.15 (s, 1H, Ar-H), 7.31 (q, 4H, J = 7.8 Hz, Ph-H), 8.37–8.44 (m, 2H, Ph-H, N-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 38.8, 42.9, 55.7, 81.6, 104.9, 110.0, 119.7, 121.1, 124.6, 126.9, 127.3, 128.9, 134.0, 137.2, 139.2, 140.8, 148.1, 151.8, 157.0. MS (ESI): 411 $[M + H]^+$.

Methyl 2-(3-(5-(4-chlorophenyl)-4,5-dihydroisoxazol-3-yl)-1-methyl-1*H*-pyrazole-5-carboxamido)-benzoate (ZJ13):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.40 (q, 1H, J = 7.8 Hz, CH_2), 3.85 (q, 1H, J = 11.4 Hz, CH_2), 3.97 (s, 3H, O-CH_3), 4.24 (s, 3H, Ar-CH_3), 5.71 (q, 1H, J = 8.4 Hz, CH), 7.13–7.17 (m, 1H, Ph-H), 7.32–7.37 (m, 5H, Ar-H, Ph-H), 7.57–7.62 (m, 1H, Ph-H), 8.08 (dd, 1H, J =1.8, 7.8 Hz, Ph-H), 8.76 (d, 1H, J = 8.4 Hz, Ph-H), 12.07 (s, 1H, N-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 40.0, 43.1, 52.8, 81.6, 105.8, 115.3, 120.2, 123.2, 127.3, 128.9, 131.1, 134.0, 134.8, 137.3, 139.4, 141.0, 141.1, 151.2, 157.7, 168.8. MS (ESI): 439 $[M + H]^+$.

3-(5-(4-Chlorophenyl)-4,5-dihydroisoxazol-3-yl)-1-methyl-*N*-(3-(trifluoromethyl)phenyl)-1*H*-pyrazole-5-carboxamide (ZJ14):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.40 (q, 1H, J = 7.8 Hz, CH_2), 3.84 (q, 1H, J = 10.8 Hz, CH_2), 4.20 (s, 3H, Ar-CH_3), 5.66 (q, 1H, J = 8.4 Hz, CH), 7.23 (d, 2H, J = 8.4 Hz, Ph-H), 7.29 (t, 2H, J = 8.4 Hz, Ph-H), 7.33 (s, 1H, Ar-H), 7.37–7.44 (m, 2H, Ph-H), 7.71 (d, 1H, J = 7.2 Hz, Ph-H), 7.94 (s, 1H, Ph-H), 8.50 (s, 1H, Ph-H, N-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 38.9, 43.0, 81.9, 105.8, 117.4, 121.5, 123.7, 127.3, 129.0, 129.5, 131.4, 134.3, 136.5, 137.7, 138.7, 140.6, 152.0, 157.7. MS (ESI): 449 $[M + H]^+$.

3-(5-(4-Chlorophenyl)-4,5-dihydroisoxazol-3-yl)-*N*-(2,4-dichlorophenyl)-1-methyl-1*H*-pyrazole-5-carboxamide (ZJ15):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.39 (q, 1H, J = 7.8 Hz, CH_2), 3.84 (q, 1H, J = 11.4 Hz, CH_2), 4.22 (s, 3H, Ar-CH_3), 5.71 (q, 1H, J = 7.8 Hz, CH), 7.21 (s, 1H, Ar-H), 7.27–7.37 (m, 5H, Ph-H), 7.44 (d, 1H, J = 2.4 Hz, Ph-H), 8.23 (s, 1H, Ph-H), 8.37 (d, 1H, J = 9.0 Hz, N-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 39.9, 42.9,

81.8, 105.3, 122.4, 124.0, 127.3, 128.0, 128.9, 129.0, 130.1, 132.6, 134.1, 136.3, 139.1, 141.1, 151.5, 157.0. MS (ESI): 449 $[M + H]^+$.

3-(5-(4-Chlorophenyl)-4,5-dihydroisoxazol-3-yl)-*N*-(3-fluorophenyl)-1-methyl-1*H*-pyrazole-5-carboxamide (ZJ16):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.39 (q, 1H, J = 9.6 Hz, CH_2), 3.84 (q, 1H, J = 11.4 Hz, CH_2), 4.20 (s, 3H, Ar-CH_3), 5.68 (q, 1H, J = 8.4 Hz, CH), 6.86 (td, 1H, J = 1.8, 7.8 Hz, Ph-H), 7.21 (d, 1H, J = 7.8 Hz, Ph-H), 7.23–7.29 (m, 4H, Ar-H, Ph-H), 7.32 (d, 2H, J = 7.8 Hz, Ph-H), 7.51–7.56 (m, 1H, Ph-H), 8.16 (s, 1H, N-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 39.9, 42.9, 81.9, 105.5, 107.9, 108.1, 111.7, 111.9, 115.8, 127.3, 129.0, 130.2, 134.2, 136.6, 138.9, 140.7, 151.9, 157.5. MS (ESI): 399 $[M + H]^+$.

3-(5-(4-Chlorophenyl)-4,5-dihydroisoxazol-3-yl)-1-methyl-*N*-(*o*-tolyl)-1*H*-pyrazole-5-carboxamide (ZJ17):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.26 (s, 3H, Ph-CH_3), 3.39 (q, 1H, J = 8.4 Hz, CH_2), 3.82 (q, 1H, J = 11.4 Hz, CH_2), 4.19 (s, 3H, Ar-CH_3), 5.55–5.66 (m, 1H, CH), 7.10–7.17 (m, 1H, Ph-H), 7.17–7.25 (m, 4H, Ar-H, Ph-H), 7.26–7.34 (m, 3H, Ph-H), 7.67–7.70 (m, 1H, Ph-H), 7.86–7.96 (m, 1H, N-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 17.8, 39.8, 42.9, 81.9, 105.3, 124.2, 126.3, 126.8, 127.3, 128.9, 130.7, 134.1, 134.6, 136.8, 138.9, 140.8, 152.0, 157.7. MS (ESI): 395 $[M + H]^+$.

Biological assay

Bioassays were performed on representative test organisms grown in the laboratory. The bioassay was repeated at each rate three times at 25±1 ºC according to statistical requirements. Assessments were made on a dead/alive basis and corrected by applying Abbott's formula.[16] All compounds were dissolved in *N*,*N*-dimethylformamide and diluted with distilled water containing Triton X-100 (0.1 mg/L) to obtain a series of concentrations of 500, 100 mg/L and others for bioassays. For comparative purposes, Avermectins as control was tested under the same conditions. Evaluation was based on a percentage scale of 0-100 (0 = no activity, 100 = total kill) with the standard deviations ±5%.

Insecticidal activity against *Mythimna separate*

The experiment was performed on fourth-instar larvae of the *M. separata* was tested by leaf-dip method according to our reported method.[17]

Insecticidal activity against *Tetranychus cinnabarinus* and *Aphis craccivora*

The insecticidal activity against *Tetranychus cinnabarinus* and *Aphis craccivora* was tested by foliar application according to the reported method.[18]

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