Synthesis, Nematocidal Activity and Docking Study of Novel Chiral 1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1*H*-pyrazole-4-carboxamide Derivatives

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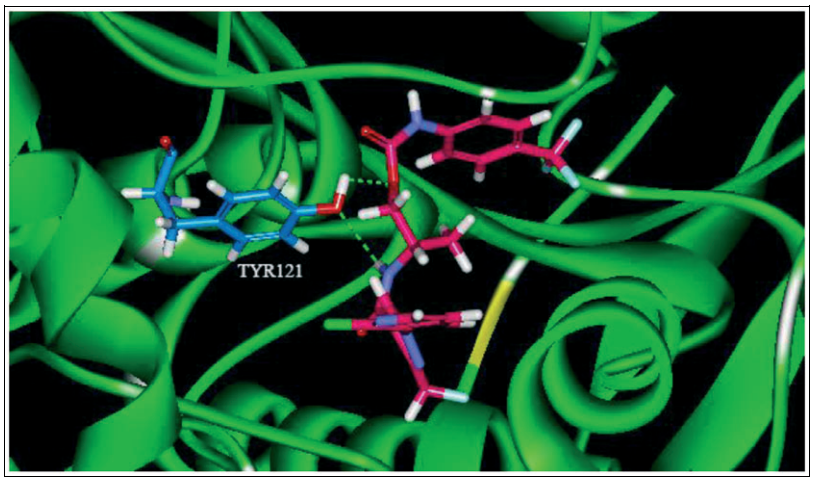

A novel series of pyrazole carboxamide derivatives had been designed, synthesized and some of them exhibited good nematocidal activity.

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INTRODUCTION

Highly efficient and broad-spectra fungicides played an important role in crop protecting [1–5]. In the past decades, many succinate dehydrogenase inhibitors [6–8] had been introduced into the market for protecting crops of fruit and vegetables, such as bixafen, fluxapyroxad, and benzovindiflupyr (Fig. 1). From the stucture–active relationship of these fungicides, the introduction of F, CHF_2, or CF_3 into pyrazole ring have been widely studied. Among them, difluoromethylpyrazole is a main key group for succinate dehydrogenase inhibitors fungicides. On the other hand, some novel diamides insecticides which target calcium channel of insect RyR have been commercialized by Dupont or Bayer company. For example, chlorantraniliprole is a representative of the anthranilic diamides containing pyrazole linked pyridine ring, attracted considerable attention because of its unique action mode.

In our previous work [9,10], to find high-active fungicides with efficacy, lower toxicity, broad spectrum, and environment friendly, some *N*-phenyl pyrazole carboxamide compounds were designed and synthesized, some of them possessed good fungicidal activity. In line with our continuous efforts to synthesize bioactive lead compounds for crop protection [11–16], here, we reported difluoromethylpyrazole derivatives containing flexible alkyl chain moieties (Scheme 1) and its *in vivo* biological activities against *Meloidogyne incognita*. We also discussed the relationship between structure and nematicidal activity preliminarily.

RESULTS AND DISCUSSION

Synthesis and spectra. The synthetic route is showed in Scheme 2. The intermediate 3-chloro-2-hydrazinylpyridine was synthesized by the method reported by our previous work [17]. There are many methods about the synthesis of pyrazole ring. The α,β-unsaturated ketone method towards trifluoromethylpyrazole intermediate have been investigated. In this step, the key intermediate pyrazole ring was synthesized using a,b-unsaturated ketone ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate as starting material according to the reference. Subsequently, the pyrazole acid was given by hydrolysis. Then, the amide intermediate was synthesized from acid chloride and amine. At last, (*S*)-1-(3-chloropyridin-2-yl)-

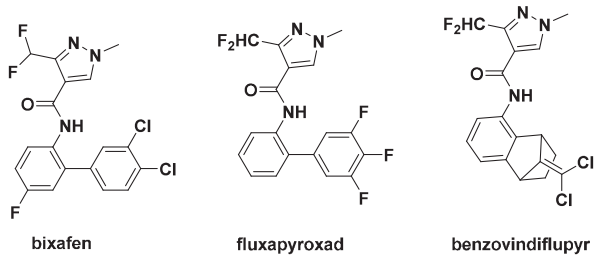


Figure 1. The representive succinate dehydrogenase inhibitors.

N-(1-hydroxypropan-2-yl)-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide reacted with different isocyanatobenzenes in CH_2Cl_2 was synthesized easily. This reaction was completed with higher yields.

All the compounds were identified and characterized by ^{1}H NMR, MS, and elemental analysis. The proton magnetic resonance spectra of pyrazole amide compounds have been recorded in $CDCl_3$. The CH proton signal of pyrazole ring can be found around 8 ppm, and the CH proton signals of pyridine structure of title compounds were obvious as double peaks or triple peaks around at ~6.4, ~7.1, and ~8.5 ppm, respectively. The mass spectra of pyrazole amide derivatives showed molecular ion peak. The measured elemental analyses were also consistent with the corresponding calculated values.

Nematocidal activity. The *in vivo* nematocidal activity of compounds **5a–5q** against *M. incognita* is listed in Table 1. Avermectin was used as controls. From Table 1, all the title compounds possessed good nematocidal activity against *M. incognita*. Among these compounds, compound **5b** (100%) and **5p** (100%) exhibited excellent control efficacy against *M. incognita* at a concentration of 40 mg/L. Also, most of title compound displayed good activity against *M. incognita* with >90% control efficacy, such as compound **5c**, **5f**, **5h**, **5j**, and **5q**. All the other compounds exhibited moderate activity (68–88%).

Docking study. High-resolution crystal structure of Acetyl cholinesterase (AchE) was downloaded from the protein data bank website (PDB ID: 1ODC), and all molecular docking calculations were performed on Discovery Studio software. From Figure 2, the O of the NHCOO serves as an H acceptor which has a strong H bond with the amino acid residue Tyr 121 of AchE. In contrast, the NH of the CONH serves as a H donor which has a strong H bond with the amino acid residue Tyr 121 of AchE.

EXPERIMENTAL

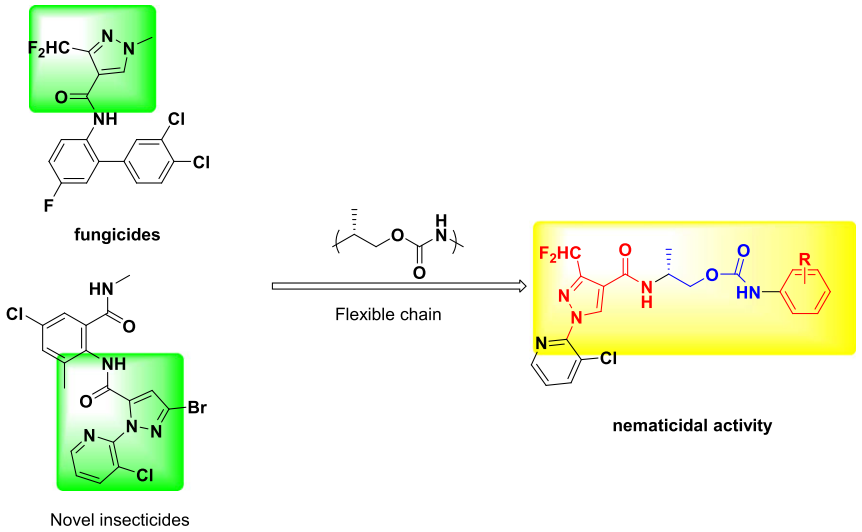
Chemistry. Melting points were determined by an X-4 apparatus and uncorrected. ^{1}H NMR spectra were measured on a Bruker AV-400 instrument using TMS as an internal standard and $CDCl_3$ as the solvent. All the reagents are of analytical grade or freshly prepared before use. The course of the reactions was monitored by TLC; analytical TLC was performed on silica gel GF_{254}.

General procedure

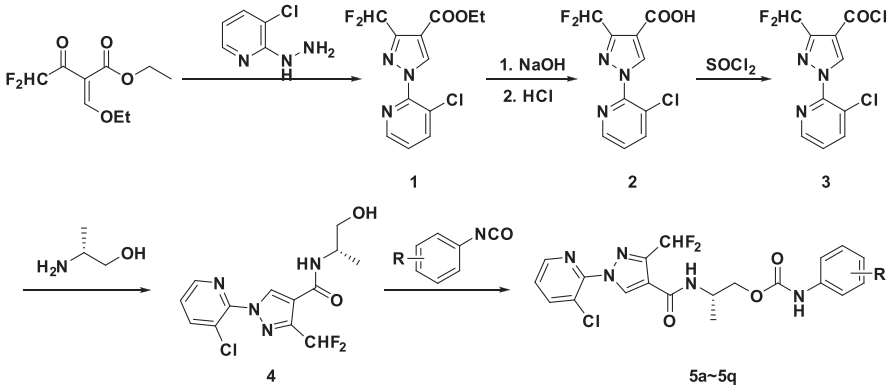
Ethyl-2-(ethoxymethylene)-4,4-difluoro-3-oxobutanoate (1). In a 500-mL four-necked flask, ethyl 4,4-difluoro-3-oxobutanoate (0.86 mol), triethyl orthoformate(1.41 mol), and acetic anhydride(2.58 mol) were added and heated at 120°C for 5 h. Then, the solvent was removed, and the product was then distilled under vacuum over a column to give a light yellow liquid, yield 89.61%.

1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carboxylic acid (2). To a solution of 3-chloro-2-hydrazinylpyridine (0.18 mol) in EtOH(120 mL) was

Scheme 1. The design strategy of title compounds. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



Scheme 2. The synthetic route of title compounds.



added ethyl -2-(ethoxymethylene)-4,4-difluoro-3-oxobutanoate (0.175 mol) in EtOH(60 mL) dropwisely. The mixture was stirred for 1 h and then further stirred at reflux temperature for 5 h. After the reaction is completed, the mixture was cooled and concentrated. The residue was recrystallized to give white solid. Then, ethyl 1-(3-chloropyridin-2-yl)-3-(difluoromethyl)-1*H*-pyrazole-4-carboxylate was hydrolysis to afford the acid with the yield 78.31%.

1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carbonyl chloride (3). To ethyl 1-(3-chloropyridin-2-yl)-3-(difluoromethyl)-1*H*-pyrazole-4-carboxylic acid **2** (0.12 mol) and $SOCl_2$ (80 mL) was refluxed for 4 h. After the reaction is completed, the excess of $SOCl_2$ was evaporated to give **3** as a white solid that was used without further purification.

Table 1

Control efficacy of compounds **5a–5q** against the tomato RKN disease caused by *M. incognita* in test tubes.

No.	R	Scoring	Inhibition rate (%)
5a	4-OCF_3	5.0	68.2
5b	4-CF_3	0	100
5c	4-CH_3	0.6	96.0
5d	2-Cl	1.8	88.4
5e	2-CH_3-3-Cl	1.8	88.4
5f	2,5-2CH_3	0.6	96.5
5g	2-CH_3	3.1	80.1
5h	2,6-2CH_3	1.3	92.0
5i	4-OEt	3.1	80.1
5j	4-Br	0.8	94.7
5k	4-OPh	3.1	80.1
5l	2-Cl-4-Br	3.8	76.1
5m	4-$CF(CF_3)_2$	2.8	82.3
5n	2-CH_3-3-CF_3	2.5	84.1
5o	3-CH_3	2.8	82.3
5p	3-F	0.0	100
5q	3-OCF_3	0.5	97.1
CK		15.7	0
Avermectin(5 ppm)		0	100

(S)-1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-N-(1-hydroxypropan-2-yl)-1H-pyrazole-4-carboxamide (4). To a solution of (S)-2-aminopropan-1-ol (93.04 mmol) and Et_3N (0.12 mol) in CH_2Cl_2 (130 mL), 1-(3-chloropyridin-2-yl)-3-(difluoromethyl)-1*H*-pyrazole-4-carbonyl chloride **4** (93.04 mmol) in CH_2Cl_2 (100 mL) was added dropwise under 0–5°C for 1 h. Then, the mixture was vigorously stirred at ambient temperature for 4 h and then evaporated under reduced pressure, and residue was purified by recrystallization using EtOAc to afford (*S*)-1-(2-chloropyridin-3-yl)-3-(difluoromethyl)-*N*-(1-hydroxypropan-2-yl) -1*H*-pyrazole-4-carboxamide with the yield 87.23%.

General procedure for the preparation of title compounds (5a–5q). A 100-mL round bottom was charged with (*S*)-1-(2-chloropyridin-3-yl)-3-(difluoromethyl)-*N*-(1-hydroxypropan-2-yl)-1*H*-pyrazole-4-carboxamide (1 mmol) with various substituted isocyanatobenzenes (1 mmol) in THF (10 mL). The mixture was stirred at room temperature for overnight. The target compounds were filtered, and crude solids were recrystallized from ethanol to give the title compounds **5**. All the compounds were synthesized according to this procedure (Scheme 2).

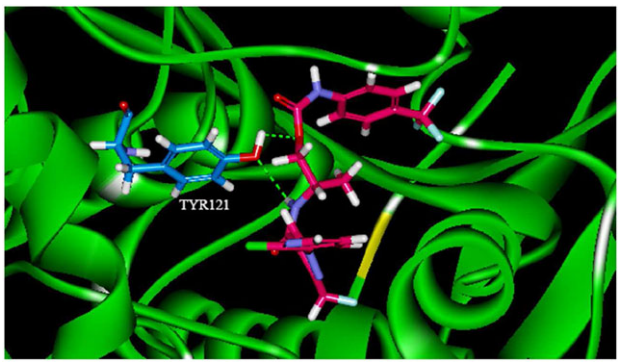


Figure 2. The docking mode of compound **5b** and acetyl cholinesterase. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(S)-2-(1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamido)propyl (4-(trifluoromethoxy)phenyl)carbamate (5a). White solid, yield 85%, m.p. 239–241°C. ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.52 (d, J = 4.7 Hz, 1H, Pyridine-H), 8.08–7.90 (m, 2H, Pyridine-H & Pyrazole-H), 7.61–7.29 (m, 4H, Pyridine-H & Ph-H & CHF_2), 7.16 (d, J = 8.5 Hz, 2H, Ph-H), 7.03 (s, 1H, NH), 6.67 (d, J = 7.3 Hz, 1H, NH), 4.48 (d, J = 7.0 Hz, 1H, NCH), 4.29 (dd, J_1 = 11.4 Hz, J_2 = 9.8 Hz, 2H, OCH_2), 1.32 (d, J = 6.7 Hz, 3H, CH_3). ESI-MS: 533 $[M+H]^+$; Elemental *Anal*. Calcd for $C_{21}H_{17}ClF_5N_5O_4$ (%):C, 47.25; H, 3.21; N, 13.12; found: C, 47.32; H, 3.25; N, 13.02.

(S)-2-(1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamido)propyl (4-(trifluoromethyl)phenyl)carbamate (5b). White solid, yield 85%, m.p. 122–124°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ8.52 (d, J = 4.7 Hz, 1H, Pyridine-H), 8.08–7.90 (m, 2H, Pyridine-H & Pyrazole-H), 7.61–7.29 (m, 4H, Pyridine-H & Ph-H & CHF_2), 7.16 (d, J = 8.5 Hz, 2H, Ph-H), 7.03 (s, 1H, NH), 6.67 (d, J = 7.3 Hz, 1H, NH), 4.48 (d, J = 7.0 Hz, 1H, NCH), 4.29 (dd, J_1 = 11.4 Hz, J_2 = 9.8 Hz, 2H, OCH_2), 1.32 (d, J = 6.7 Hz, 3H, CH_3). ESI-MS: 517 $[M+H]^+$; Elemental *Anal.* Calcd for $C_{21}H_{17}ClF_5N_5O_3$ (%):C, 48.71; H, 3.31; N, 13.52; found: C, 48.88; H, 3.44; N, 13.43.

(S)-2-(1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamido)propyl p-tolylcarbamate (5c). White solid, yield 90%, m.p. 147°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 4.6 Hz, 1H, Pyridine-H), 8.00 (s, 1H, Pyrazole-H), 7.95 (d, J = 8.0 Hz, 1H, Pyridine-H), 7.62–7.31 (m, 2H, Pyridine-H & CHF_2), 7.23 (d, J = 11.7 Hz, 2H, Ph-H), 7.10 (d, J = 8.0 Hz, 2H, Ph-H & NH), 6.88 (d, J = 7.0 Hz, 2H, Ph-H & NH), 4.50–4.38 (m, 1H, NCH), 4.27 (ddd, J_1 = 14.5 Hz, J_2 = 11.5 Hz, J_3 = 5.1 Hz, 2H, OCH_2), 2.30 (s, 3H, CH_3), 1.31 (d, J = 6.6 Hz, 3H, CH_3). ESI-MS: 463 $[M+H]^+$; Elemental *Anal*. Calcd for $C_{21}H_{20}ClF_2N_5O_3$ (%):C, 54.38; H, 4.35; N, 15.10; found: C, 54.45; H, 4.44; N, 15.04.

(S)-2-(1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamido)propyl (2-chlorophenyl)carbamate (5d). White solid, yield 88%, m.p. 117°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70–8.40 (m, 1H, Pyridine-H), 8.14 (s, 1H, Ph-H), 8.08–7.88 (m, 2H, Pyridine-H & Pyrazole-H), 7.46 (ddd, J_1 = 45.6 Hz, J_2 = 39.7 Hz, J_3 = 21.3 Hz, 3H, Pyridine-H, Ph-H & CHF_2), 7.33–7.27 (m, 2H, Ph-H), 7.03 (t, J = 7.8 Hz, 1H, NH), 6.69 (d, J = 6.7 Hz, 1H, NH), 4.48 (s, 1H, NCH), 4.34 (ddd, J_1 = 15.2 Hz, J_2 = 11.5 Hz, J_3 = 4.9 Hz, 2H, OCH_2), 1.36 (d, J = 6.7 Hz, 3H, CH_3). ESI-MS: 483 $[M+H]^+$; Elemental *Anal*. Calcd for $C_{20}H_{17}Cl_2F_2N_5O_3$ (%):C, 49.60; H, 3.54; N, 14.46; found: C, 49.70; H, 3.44; N, 14.67.

(S)-2-(1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamido)propyl (3-chloro-2-methylphenyl)carbamate (5e). White solid, yield 89%, m.p. 98°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, J = 4.6, 1.3 Hz, 1H, Pyridine-H), 8.08 (s, 1H, Ph-H), 8.01 (s, 1H, Pyrazole-H), 7.95 (dd, J_1 = 8.1 Hz, J_2 = 1.3 Hz, 1H, Pyridine-H), 7.64–7.29 (m, 2H, Pyridine-H & Ph-H), 7.00 (ddd, J_1 = 22.0 Hz, J_2 = 10.8 Hz, J_3 = 6.8 Hz, 2H, Ph-H & CHF_2), 6.87 (d, J = 7.0 Hz, 2H, NH), 4.51–4.41 (m, 1H, NCH), 4.41–4.22 (m, 2H, OCH_2), 3.88 (s, 3H, CH_3), 1.34 (d, J = 6.6 Hz, 3H, CH_3). ESI-MS: 497 $[M+H]^+$; Elemental *Anal*. Calcd for $C_{21}H_{19}Cl_2F_2N_5O_3$ (%):C, 50.62; H, 3.84; N, 14.05; found: C, 50.45; H, 3.64; N, 14.02.

(S)-2-(1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamido)propyl (2,5-dimethylphenyl)carbamate (5f). White solid, yield 87%, m.p. 143°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, J_1 = 4.7 Hz, J_2 = 1.5 Hz, 1H, Pyridine-H), 8.03–7.85 (m, 2H, Pyridine-H & Pyrazole-H), 7.64–7.30 (m, 3H, Pyridine-H, Ph-H & CHF_2), 7.05 (d, J = 7.6 Hz, 1H, Ph-H), 6.96–6.70 (m, 2H, NH & Ph-H), 6.50 (s, 1H, NH), 4.46 (s, 1H, NCH), 4.30 (ddd, J_1 = 14.7 Hz, J_2 = 11.6 Hz, J_3 = 5.2 Hz, 2H, OCH_2), 2.32 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 1.33 (d, J = 6.5 Hz, 3H, CH_3). ESI-MS: 477 $[M+H]^+$; Elemental *Anal*. Calcd for $C_{22}H_{22}ClF_2N_5O_3$ (%):C, 55.29; H, 4.64; N, 14.65; found: C, 55.31; H, 4.44; N, 14.68.

(S)-2-(1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamido)propyl o-tolylcarbamate (5g). White solid, yield 89%, m.p. 87°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59–8.44 (m, 1H, Pyridine-H), 7.96 (dd, J_1 = 13.4 Hz, J_2 = 6.7 Hz, 2H, Pyridine-H & Pyrazole-H), 7.63–7.33 (m, 3H, Pyridine-H, Ph-H & CHF_2), 7.24–7.12 (m, 2H, Ph-H), 7.07 (d, J = 7.0 Hz, 1H, Ph-H), 6.86 (s, 1H, NH), 6.61 (s, 1H, NH), 4.45 (s, 1H, NCH), 4.29 (ddd, J_1 = 14.8 Hz, J_2 = 11.5 Hz, J_3 = 5.2 Hz Hz, J_2 = 2H, OCH_2), 2.24 (s, 3H, CH_3), 1.31 (d, J = 6.5 Hz, 3H, CH_3). ESI-MS: 463 $[M+H]^+$; Elemental *Anal*. Calcd for $C_{21}H_{20}ClF_2N_5O_3$ (%):C, 54.38; H, 4.35; N, 15.10; found: C, 54.45; H, 4.44; N, 15.01.

(S)-2-(1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamido)propyl (2,6-dimethylphenyl)carbamate (5h). White solid, yield 88%, m.p. 76°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 4.0 Hz, 1H, Pyridine-H), 7.95 (d, J = 7.3 Hz, 2H, Pyridine-H & Pyrazole-H), 7.45 (dd, J_1 = 29.8 Hz, J_2 = 21.8 Hz, 2H, Pyridine-H & CHF_2), 7.08 (d, J = 8.0 Hz, 3H, Ph-H), 6.95 (s, 1H, NH), 6.28 (s, 1H, NH), 4.44 (d, J = 15.8 Hz, 1H, NCH), 4.41–4.17 (m, 2H, OCH_2), 2.21 (s, 6H, CH_3), 1.32 (d, J = 6.3 Hz, 3H, CH_3). ESI-MS: 477 $[M+H]^+$; Elemental *Anal*. Calcd for $C_{22}H_{22}ClF_2N_5O_3$ (%):C, 55.29; H, 4.64; N, 14.65; found: C, 55.31; H, 4.44; N, 14.68.

(S)-2-(1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamido)propyl (4-ethoxyphenyl)carbamate (5i). White solid, yield 88%, m.p. 78°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 4.7 Hz, 1H, Pyridine-H), 8.00 (s, 1H, Pyrazole-H), 7.95 (d, J = 8.0 Hz, 1H, Pyridine-H), 7.61–7.33 (m, 2H, Pyridine-H & CHF_2), 7.27 (s, 2H, Ph-H), 6.84 (d, J = 8.6 Hz, 3H, Ph-H & NH), 6.77 (s, 1H,

NH), 4.49–4.38 (m, 1H, NCH), 4.37–4.16 (m, 2H, OCH_2), 4.00 (q, J = 6.9 Hz, 2H, CH_2), 1.40 (t, J = 6.9 Hz, 3H, CH_3), 1.31 (d, J = 6.5 Hz, 3H, CH_3). ESI-MS: 493 [M + H]$^+$; Elemental *Anal*. Calcd for $C_{22}H_{22}ClF_2N_5O_4$ (%):C, 53.50; H, 4.49; N, 14.18; found: C, 53.65; H, 4.44; N, 14.02.

(S)-2-(1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamido)propyl (4-bromophenyl)carbamate (5j). White solid, yield 88%, m.p. 143°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 4.6 Hz, 1H, Pyridine-H), 8.01 (s, 1H, Pyrazole-H), 7.93 (d, J = 8.1 Hz, 1H, Pyridine-H), 7.56 (s, 1H, Pyridine-H), 7.52–7.17 (m, 6H, Ph-H, NH & CHF_2), 6.88 (d, J = 7.8 Hz, 1H, NH), 4.46 (dd, J_1 = 11.1 Hz, J_2 = 7.2 Hz, 1H, NCH), 4.23 (ddd, J_1 = 15.0 Hz, J_2 = 11.5 Hz, J_3 = 5.6 Hz, 2H, OCH_2), 1.27 (d, J = 6.7 Hz, 3H, CH_3). ESI-MS: 527 [M + H]$^+$; Elemental *Anal*. Calcd for $C_{20}H_{17}BrClF_2N_5O_3$ (%):C, 45.43; H, 3.24; N, 13.25; found: C, 45.35; H, 3.14; N, 13.34.

(S)-2-(1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamido)propyl (4-phenoxyphenyl)carbamate (5k). White solid, yield 85%, m.p. 138°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 4.7 Hz, 1H, Pyridine-H), 8.01 (s, 1H, Pyrazole-H), 7.96 (d, J = 8.0 Hz, 1H, Pyridine-H), 7.66–7.41 (m, 2H, Pyridine-H & CHF_2), 7.41–7.16 (m, 4H, Ph-H), 7.08 (t, J = 7.2 Hz, 1H, Ph-H), 6.98 (d, J = 8.3 Hz, 4H, Ph-H), 6.93 (s, 1H, NH), 6.80 (s, 1H, NH), 4.52–4.42 (m, 1H, NCH), 4.39–4.20 (m, 2H, OCH_2), 1.32 (d, J = 6.6 Hz, 3H, CH_3). ESI-MS: 541 [M + H]$^+$; Elemental *Anal*. Calcd for $C_{26}H_{22}ClF_2N_5O_4$ (%):C, 57.62; H, 4.09; N, 12.92;found: C, 57.67; H, 4.12; N, 13.05.

(S)-2-(1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamido)propyl (4-bromo-2-chlorophenyl)carbamate (5l). White solid, yield 89%, m.p. 140°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H, Pyridine-H), 8.02 (s, 1H, Pyrazole-H), 7.96 (d, J = 9.6 Hz, 1H, Pyridine-H), 7.57 (s, 1H, Pyridine-H), 7.53–7.45 (m, 2H, Ph-H & CHF_2), 7.44 (s, 1H, Ph-H), 7.41–7.34 (m, 1H, Ph-H), 7.31 (s, 1H, NH), 6.73 (d, J = 7.7 Hz, 1H, NH), 4.50 (dd, J_1 = 13.6 Hz, J_2 = 6.7 Hz, 1H, NCH), 4.31 (ddd, J_1 = 15.3 Hz, J_2 = 11.5 Hz, J_2 = 5.3 Hz, 2H, OCH_2), 1.33 (d, J = 6.8 Hz, 3H, CH_3). ESI-MS: 560 [M + H]$^+$; Elemental *Anal*. Calcd for $C_{20}H_{16}BrCl_2F_2N_5O_3$ (%):C, 42.65; H, 2.86; N, 12.44; found: C, 42.78; H, 2.98; N, 12.54.

(S)-2-(1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamido)propyl (4-(perfluoropropan-2-yl)phenyl)carbamate (5m). White solid, yield 86%, m.p. 176°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 4.6 Hz, 1H, Pyridine-H), 7.99 (dd, J_1 = 27.9 Hz, J_2 = 12.1 Hz, 2H, Pyridine-H & Pyrazole-H), 7.57–7.40 (m, 5H, Pyridine-H, Ph-H & CHF_2), 7.30 (d, J = 17.9 Hz, 1H, Ph-H), 7.17–6.99 (m, 1H, NH), 6.58 (s, 1H, NH), 4.56–4.46 (m, 1H, NCH), 4.40–4.22 (m, 2H, OCH_2), 1.33 (d, J = 6.6 Hz, 3H, CH_3). ESI-MS: 617 [M + H]$^+$; Elemental *Anal*. Calcd for $C_{23}H_{17}ClF_9N_5O_3$ (%):C, 44.71; H, 2.77; N, 11.34; found: C, 44.78; H, 2.98; N, 11.44.

(S)-2-(1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamido)propyl (2-methyl-3-(trifluoromethyl)phenyl)carbamate (5n). Yellow solid, yield 85%, m.p. 190°C. ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.51 (d, J = 4.5 Hz, 1H, Pyridine-H), 8.01 (s, 1H, Pyrazole-H), 7.95 (d, J = 8.0 Hz, 1H, Pyridine-H), 7.55 (s, 1H, Ph-H), 7.53 (d, J = 9.7 Hz, 3H, Pyridine-H, Ph-H & CHF_2), 7.50–7.46 (m, 1H, Ph-H), 7.30 (d, J = 12.0 Hz, 1H, NH), 6.66 (d, J = 7.8 Hz, 1H, NH), 4.50 (dd, J_1 = 10.9 Hz, J_2 = 6.8 Hz, 1H, NCH), 4.28 (ddd, J_1 = 15.2 Hz, J_2 = 11.5 Hz, J_3 = 5.6 Hz, 2H, OCH_2), 1.72 (s, 3H, CH_3), 1.31 (d, J = 6.7 Hz, 3H, CH_3). ESI-MS: 531 [M + H]$^+$; Elemental *Anal*. Calcd for $C_{22}H_{19}ClF_5N_5O_3$ (%):C, 49.68; H, 3.60; N, 13.17; found: C, 49.75; H, 3.46; N, 13.15.

(S)-2-(1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamido)propyl m-tolylcarbamate (5o). Oil, yield 87%, m.p. 82–84°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66–8.38 (m, 1H, Pyridine-H), 8.01 (s, 1H, Pyrazole-H), 7.99–7.83 (m, 1H, Pyridine-H), 7.47 (dd, J_1 = 53.0 Hz, J_2 = 46.6 Hz, 2H, Pyridine-H & CHF_2), 7.18 (d, J = 6.1 Hz, 3H, Ph-H), 6.91 (s, 2H, Ph-H & NH), 6.84 (d, J = 7.2 Hz, 1H, NH), 4.46 (s, 1H, NCH), 4.40–4.18 (m, 2H, OCH_2), 2.33 (s, 3H, CH_3), 1.31 (d, J = 6.7 Hz, 3H, CH_3). ESI-MS: 463 [M + H]$^+$; Elemental *Anal*. Calcd for $C_{21}H_{20}ClF_2N_5O_3$ (%):C, 54.38; H, 4.35; N, 15.10; found: C, 54.44; H, 4.42; N, 15.02.

(S)-2-(1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamido)propyl (3-fluorophenyl)carbamate (5p). White solid, yield 85%, m.p. 144–146°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 4.4 Hz, 1H, Pyridine-H), 8.15 (s, 1H, Ph-H), 8.01 (s, 1H, Pyrazole-H), 7.95 (d, J = 7.9 Hz, 1H, Pyridine-H), 7.66–7.32 (m, 3H, Pyridine-H, Ph-H & CHF_2), 7.30 (d, J = 7.1 Hz, 1H, Ph-H), 7.09 (t, J = 7.1 Hz, 2H, Ph-H & NH), 6.71 (d, J = 6.8 Hz, 1H, NH), 4.49 (s, 1H, NCH), 4.33 (ddd, J_1 = 14.9 Hz, J_2 = 11.4 Hz, J_2 = 5.0 Hz, 2H, OCH_2), 1.34 (d, J = 6.7 Hz, 3H, CH_3). ESI-MS: 467 [M + H]$^+$; Elemental *Anal.* Calcd for $C_{20}H_{17}ClF_3N_5O_3$ (%):C, 51.35; H, 3.66; N, 14.97; found: C, 51.38; H, 3.88; N, 15.02.

(S)-2-(1-(3-Chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamido)propyl (3-(trifluoromethoxy)phenyl)carbamate (5q). White solid, yield 85%, m.p. 239–241°C. ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.50 (d, J = 4.7 Hz, 1H, Pyridine-H), 8.06–7.87 (m, 2H, Pyridine-H & Pyrazole-H), 7.57–7.24 (m, 4H, Pyridine-H, Ph-H & CHF_2), 7.13 (d, J = 8.5 Hz, 2H, Ph-H), 7.05 (s, 1H, NH), 6.67 (d, J = 7.3 Hz, 1H, NH), 4.45 (d, J = 7.1 Hz, 1H, NCH), 4.29 (dd, J_1 = 11.4 Hz, J_2 = 9.8 Hz, 2H, OCH_2), 1.31 (d, J = 6.7 Hz, 3H, CH_3). ESI-MS: 533 [M + H]$^+$; Elemental *Anal*. Calcd for $C_{21}H_{17}ClF_5N_5O_4$ (%):C, 47.25; H, 3.21; N, 13.12; found: C, 47.33; H, 3.14; N, 13.02.

Nematicidal evaluation. Pure compounds (**5a–5q**) were dissolved in DMF and diluted with distilled water to obtain 40.0 mg/L concentrations for bioassays. The final concentration of DMF in each treatment never exceeded

1% v/v. The 1-week age tomato seedlings were planted in sterilized sand in test tubes (one seedling per test tube, tube size: 20 × 250 mm) and then treated the roots of each plant with 3 mL of test solution. Then, approximately 2000 living second-stage juveniles of *M. incognita* were inoculated into the rhizosphere sand of each plant. Avermectin at 5.0 mg/L served as positive control, and the negative control group was prepared in the same way but lacked the tested compound. All the test tubes were incubated at 20–25°C for 20 days, with 10 h in the daylight per day. The number of root knots of each plant was counted and recorded a Sscore. The inhibition rate on *M. incognita* was calculated by comparison with the negative control group:

$$\text{Inhibition rate}(\%) = (\text{score of negative control} - \text{score of treatment}) / \text{score of negative control} * 100\%$$

Scoring criteria: 0: 0–5 knots; 5: 6–10 knots; 10: 11–20 knots; 20: more than 20 knots.

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