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Synthesis and nematicidal activity of 4,5,5-trifluoro-*N*-(heteroaryl methyl) pent-4-enamide

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Abstract: Plant parasitic nematodes may cause severe damages to crops globally. In this study, fifteen novel 4,5,5-trifluoropent-4-enamide derivatives were designed and synthesized, and their nematicidal activities both *in vitro* and *in vivo* (in sand) were determined. Compounds with high activity in sand were further investigated for their *in vivo* activities in matrix. Results of the *in vitro* test showed that some of compounds exhibited better nematicidal activity. Among the synthesized molecules, compounds **B8** containing a furan ring exhibited excellent nematicidal activity against *Meloidogyne incognita* and *Bursaphelenchus xylophilus*, with $LC_{50/72\ h}$ values of 1.22 mg/L and 0.53 mg/L, respectively. Furthermore, most of the compounds showed 100% inhibition rate against *M. incognita* at 40 mg/L in sand in the *in vivo* test. Among which compound **B10** containing a benzothiazole ring showed the best nematicidal activity. It exhibited 66.0% inhibition rate at 2.5 mg/L. Results of the *in vivo* test in matrix showed that compound **B6** containing a thiophene ring was the most active compound. It showed 31.0% inhibition rate at 5 mg/L. Preliminary analysis on structure-activity relationship showed that the compounds containing non-substituted five-membered ring such as thiophene, furan and thiazole demonstrated better bioactivity than those compounds containing bulky six-membered ring or fused ring in the molecule.

Keywords: 4,5,5-trifluoropent-4-enamide; *Meloidogyne incognita*; *Bursaphelenchus xylophilus*; nematicidal activity

4,5,5-三氟-*N*-(杂芳基甲基) 戊-4-烯酰胺的合成及杀线虫活性

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摘 要：植物寄生线虫可能对全球农作物造成严重的危害。本研究设计合成了 15 个未见文献报道的 4,5,5-三氟戊-4-烯酰胺衍生物，并测定了它们的离体活性和在沙土中的活体杀线虫活性，且进一步研究了沙土活体活性较好的化合物在基质中的活体杀线虫活性。离体测试结果表明：部分目标化合物表现出较好的杀线虫活性，其中含呋喃环的化合物 **B8** 对南方根结线虫 *Meloidogyne incognita* 和松材线虫 *Bursaphelenchus xylophilus* 均表现出优异的杀线虫活性，$LC_{50/72\ h}$

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值分别为 1.22 mg/L 和 0.53 mg/L。此外，在沙土活体活性测试中，大部分化合物在 40 mg/L 时对南方根结线虫具有 100% 的抑制作用，其中含苯并噻唑环的化合物 **B10** 的活性最好，在 2.5 mg/L 时抑制率为 66.0%。在基质中的活体活性测试结果表明，含噻吩环的化合物 **B6** 活性最好，在 5 mg/L 时对南方根结线虫的抑制率为 31.0%。初步的构效关系分析显示，含无取代五元环如噻吩、呋喃和噻唑的化合物的活性优于含大体积的六元环或稠环的化合物。

关键词: 4,5,5-三氟戊-4-烯酰胺；南方根结线虫；松材线虫；杀线虫活性
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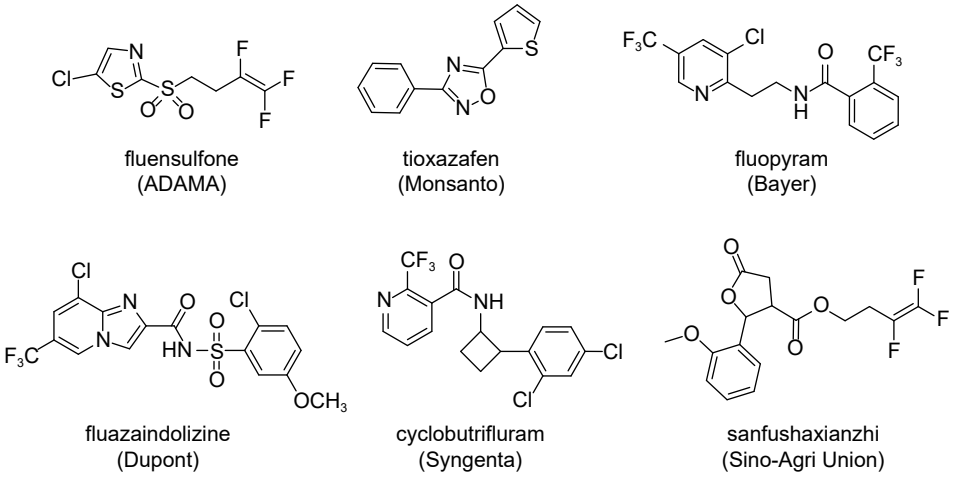
0 Introduction

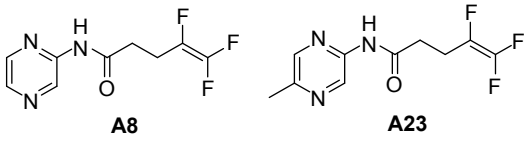
Nematode infestation is one of the major stresses affecting crop production worldwide. Plant parasitic nematodes could survive with a wide range of hosts and may damage more than 3 000 crops[1]. The crops causing major economic losses include citrus, sugar beet, soybean, tomato, strawberry, cotton, and sugar cane, etc.[2]. The global economic losses reach approximately 173 billion US dollars each year[3]. Among plant parasitic nematodes, root-knot nematodes and pine wood nematodes are more destructive than others. Root-knot nematodes feed on the roots of plants and cause the loss of nutrients in the plant roots, which may reduce the ability of plants to resist drought and adversity[4-5]. Pine wood nematodes could cause severe pine wood wilt, which has brought destructive harm to pine forests in North America, East Asia, and European countries[6]. Currently, nematode control is mainly achieved by synthetic fumigant and non-fumigant nematicides. Fumigant nematicides such as methyl bromide has been withdrawn from the market in many countries for causing the degradation of the ozone layer[7-9]. Non-fumigant organophosphates and carbamates nematicides, including fenamiphos[10], fosthiazate[11], carbofuran[12] and aldicarb, also quit the market gradually after the awakening of food safety and environmental protection awareness. More products with high efficacy, low toxicity, low-residual and good environmental compatibility are urgently needed.

Up to now, only six new nematicides products come out, including fluensulfone[13-15], tioxazafen[16-17], fluropyram[18-20], fluazaindolizine[21-22], cyclobutrifluram[23], and sanfushaxianzhi[24](**Scheme 1**). Although molecular design based on targets becomes a trend in the finding of pesticide lead compound, the target information of some new nematicides such as fluensulfone, tioxazafen, fluazaindolizine is unverified. Crystal structure of protein complex is unavailable, which cannot provide the template for homologous modeling, and makes it difficult to carry out molecular docking and virtual screen based on target. Thus, bioisosterism, fragment splicing, and scaffold hopping will still play an important role in the finding of nematicidal lead compound.

In our previous research, a series of amide derivatives containing the trifluorobutene moiety were designed and synthesized based on the structure of fluensulfone, and some compounds showed good nematicidal activitiy against *Meloidogyne incognita*[25] (**Scheme 2**).

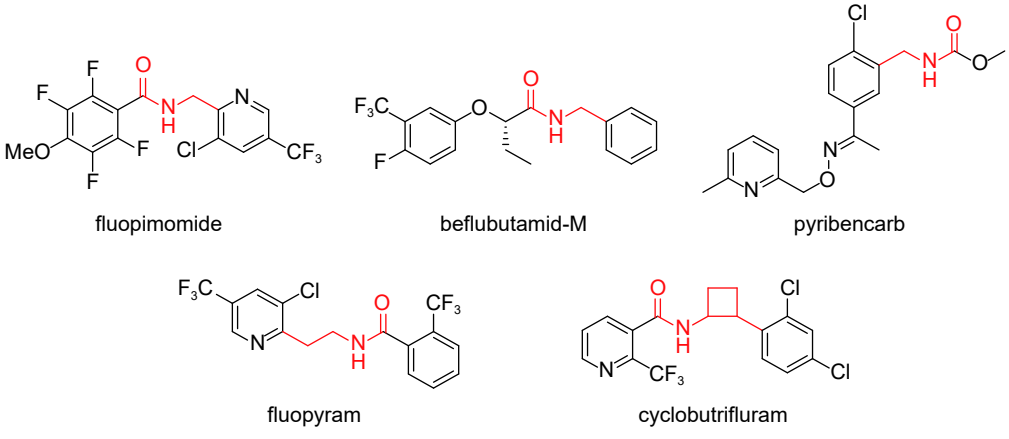


Scheme 1 Six new nematicides products



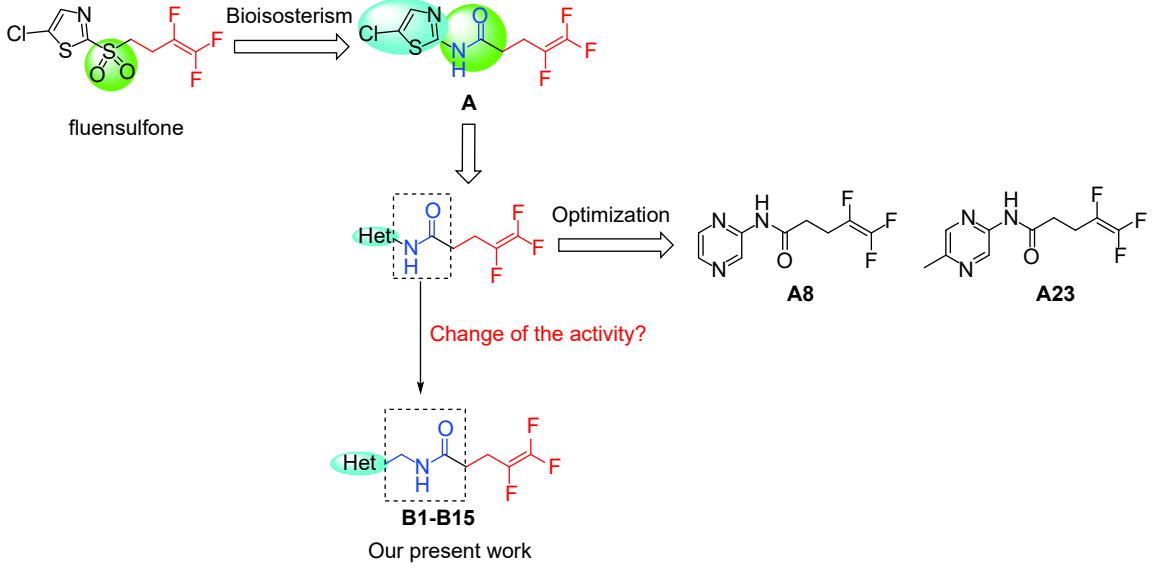
Scheme 2 Some high nematicidal activity compounds found in our previous report

In some pesticides, methylene was often introduced into amide bonds to adjust the flexibility of chain and change the binding mode with the target, such as fluopimomide, beflubutamid-M, and pyribencarb. In nematicides, it was found that ethylene and cyclobutyl were connected the amide bond of fluopyram and cyclobutrifluram, respectively (**Scheme 3**).



Scheme 3 Some pesticides containing methylene, ethylene, cyclobutyl to connect amide bond

In this study, methylene was introduced into amide bond of the molecules which were prepared in our previous work to explore the change of nematicidal activity, and thus compounds **B1-B15** (**Scheme 4**) were designed and synthesized. Their nematicidal activities against *M. incognita* and *Bursaphelenchus xylophilus* were evaluated. The synthetic routes of intermediate **a15** and compounds **B1-B15** were shown in **Scheme 5**.

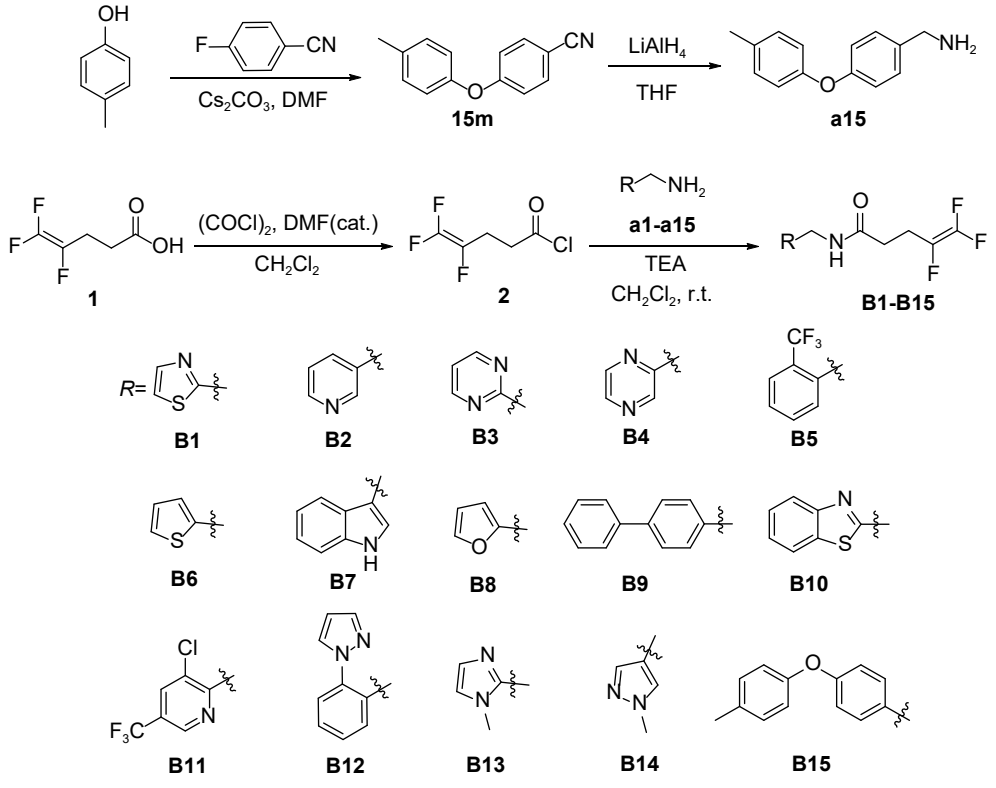


Scheme 4 Design of target compounds

1 Materials and methods

1.1 Chemicals and instruments

Melting point was determined by Büchi Melting Point B-540 instrument (Büchi Labortechnik AG, Flawil, Switzerland), uncorrected; NMR data were recorded by Brucker AM-400 nuclear magnetic resonance instrument (400 MHz), TMS was used as internal standard for ^{1}H and ^{13}C NMR, $CFCl_3$ was used as internal standard for ^{19}F NMR, $CDCl_3$ or DMSO-d_6 as solvent; chemical shifts were reported in δ, coupling constant (J) was presented in Hz. High resolution



Scheme 5 General synthetic route of intermediate a15 and target compounds B1-B15

mass spectrometry (HRMS) was performed on a waters micromass liquid chromatography-time of flight (LC-TOF) spectrometer under electrospray ionization conditions. The reagents and solvents used in the experiment were analytical or chemical purity, and without further purification. All reagents and solvents were commercially available.

1.2 General synthetic procedure for compounds

1.2.1 Synthesis of 4,5,5-trifluoropent-4-enoyl chloride (2) To a 100 mL single-necked bottle was added 4,5,5-trifluoropent-4-enoic acid **1** (2 mmol) and dichloromethane (15 mL), and then oxalyl chloride (2.5 mmol) dissolve in dichloromethane (10 mL) was added dropwise into the reaction solution at 0 ℃. After addition of oxalyl chloride, dimethyl formamide (0.05 mL) was added and the mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure to afford 4,5,5-trifluoropent-4-enoyl chloride (**2**) (Scheme 5).

1.2.2 Synthesis of (4-(*p*-tolyloxy) phenyl) methanamine (a15) To a 250 mL single-necked bottle was added 4-fluorobenzonitrile (20 mmol), *p*-cresol (22 mmol), dimethyl formamide (80 mL) and cesium carbonate (40 mmol). The mixture was heated to 100 ℃ for 4 h. Flask was allowed to cool to room temperature, and then the reaction mixture was removed under reduced pressure. Saturated aqueous sodium bicarbonate (30 mL) was added to the residue and the resulting mixture was extracted with dichloromethane (20 mL × 3). The organic layers were combined and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography to afford the 4-(*p*-tolyloxy) benzonitrile with the yield of 72%.

To a 100 mL single-necked bottle was added 4-(*p*-tolyloxy) benzonitrile (3 mmol) and dry tetrahydrofuran (15 mL). Then, $LiAlH_4$ (6 mmol) was added in batches (2 batches) under argon atmosphere at 0 ºC. After addition of $LiAlH_4$, the solution was stirred at room temperature for 4 h. Then, ice water (0.3 g), NaOH solution at 1 mol/L (0.3 mL) and water (0.9 g) were slowly added to the reaction solution at 0 ºC. The solution was stirred for 10 minutes, and then the reaction mixture was filtered through celite. The celite was washed three times with ethyl acetate and all organic solvents were collected. Saturated sodium chloride solution (30 mL) was added to the organic layer, and extracted with ethyl acetate (30 mL × 3). The organic layers were combined and dried over anhydrous sodium sulfate. The solvent was removed

under reduced pressure and the residue was purified by column chromatography to afford (4-(*p*-tolyloxy) phenyl) methanamine (**a15**), which was directly used in the next step (**Scheme 5**).

1.2.3 General synthetic procedure for target compounds (B1-B15) To a 100 mL single-necked bottle was added amine **a1-a15** (3 mmol), triethylamine (4.5 mmol) and dichloromethane (20 mL), and then 4,5,5-trifluoropent-4-enoyl chloride (**2**) (3 mmol) was dissolved in 10 mL dichloromethane and added dropwise into the reaction solution at room temperature. The solvent was removed under reduced pressure and saturated aqueous sodium bicarbonate (30 mL) was added to the residue, the mixture was extracted with dichloromethane (20 mL × 3). The organic layers were collected and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography to afford compounds **B1-B15**. All the compounds were synthesized according to this procedure (**Scheme 5**).

1.3 Compounds data

4,5,5-Trifluoro-*N*-(pyridin-3-ylmethyl)pent-4-enamide (**B1**): Yellow liquid, yield 51%. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.68 (d, J = 3.2 Hz, 1H), 7.29 (d, J = 3.2 Hz, 1H), 6.91 (s, 1H), 4.74 (d, J = 6.0 Hz, 2H), 2.78 − 2.56 (m, 2H), 2.48 (t, J = 7.4 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, full coupled), δ: −104.00 – −104.65 (m, 1F), −122.62 – −123.51 (m, 1F), −175.31 – −176.13 (m, 1F). ^{13}C NMR (101 MHz, $CDCl_3$), δ: 170.8, 167.0, 153.0 (ddd, $^1J_{CF}$ = 286.2, 274.0, $^2J_{CF}$ = 46.7 Hz), 142.1, 127.8 (ddd, $^1J_{CF}$ = 233.8, $^2J_{CF}$ = 53.2, 16.5 Hz), 119.9, 40.7, 31.7, 21.7 (dd, $^2J_{CF}$ = 21.8 Hz, $^3J_{CF}$ = 2.3 Hz). HRMS (ESI) calcd. for $C_9H_{10}F_3N_2OS$ (M + H) $^+$, 251.0467, found, 251.0468.

4,5,5-Trifluoro-*N*-(pyridin-3-ylmethyl)pent-4-enamide (**B2**): Yellow liquid, yield 72%. ^{1}H NMR (400 MHz, DMSO−d_6), δ: 8.53 (t, J = 5.0 Hz, 1H), 8.50 – 8.39 (m, 2H), 7.71 – 7.59 (m, 1H), 7.34 (dd, J = 7.6, 4.8 Hz, 1H), 4.30 (d, J = 6.0 Hz, 2H), 2.66 – 2.52 (m, 2H), 2.42 (t, J = 7.2 Hz, 2H). ^{19}F NMR (376 MHz, DMSO−d_6, full coupled), δ: −105.46 – −106.13 (m, 1F), −123.33 – −124.12 (m, 1F), −173.33 – −174.11 (m, 1F). ^{13}C NMR (101 MHz, DMSO−d_6), δ: 170.3, 152.5 (ddd, $^1J_{CF}$ = 283.2, 272.6 Hz, $^2J_{CF}$ = 47.8 Hz), 148.7, 148.0, 135.0, 134.9, 128.8 (ddd, $^1J_{CF}$ = 233.5 Hz, $^2J_{CF}$ = 52.9, 15.4 Hz), 123.4, 39.8, 30.6, 21.3 (dd, $^2J_{CF}$ = 21.5 Hz, $^3J_{CF}$ = 2.3 Hz). HRMS (ESI) calcd. for $C_{11}H_{12}F_3N_2O$ (M + H) $^+$, 245.0902, found, 245.0903.

4,5,5-Trifluoro-*N*-(pyrimidin-2-ylmethyl)pent-4-enamide (**B3**): Yellow liquid, yield 72%. ^{1}H NMR (400 MHz, DMSO−d_6), δ: 8.75 (d, J = 4.9 Hz, 2H), 8.53 (d, J = 4.6 Hz, 1H), 7.38 (t, J = 4.9 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 2.64 – 2.52 (m, 2H), 2.45 (t, J = 7.0 Hz, 2H). ^{19}F NMR (376 MHz, DMSO−d_6, full coupled), δ: −105.58 – −106.21 (m, 1F), −123.28 – −124.14 (m, 1F), −173.38 – −174.08 (m, 1F). ^{13}C NMR (101 MHz, DMSO−d_6), δ: 170.3, 166.9, 157.3, 152.6 (ddd, $^1J_{CF}$ = 282.9, 272.4 Hz, $^2J_{CF}$ = 47.8 Hz), 128.8 (ddd, $^1J_{CF}$ = 233.3 Hz, $^2J_{CF}$ = 52.9, 15.4 Hz), 119.7, 44.9, 30.6, 21.3 (dd, $^2J_{CF}$ = 21.6 Hz, $^3J_{CF}$ = 2.3 Hz). HRMS (ESI) calcd. for $C_{10}H_{10}F_3N_3NaO$ (M + Na) $^+$, 268.0673, found, 268.0676.

4,5,5-Trifluoro-*N*-(pyrazin-2-ylmethyl)pent-4-enamide (**B4**): Yellow liquid, yield 30%. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.59 (d, J = 6.8 Hz, 1H), 8.55 – 8.45 (m, 2H), 6.75 (s, 1H), 4.60 (d, J = 5.2 Hz, 2H), 2.73 – 2.58 (m, 2H), 2.51 (t, J = 7.4 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, full coupled), δ: −104.03 – −104.62 (m, 1F), −122.73 – −123.52 (m, 1F), −175.26 – −176.10 (m, 1F). ^{13}C NMR (101 MHz, CDCl3), δ: 170.9, 153.0 (ddd, $^1J_{CF}$ = 286.2, 273.9 Hz, $^2J_{CF}$ = 46.7 Hz), 152.34, 144.0, 143.7, 143.5, 127.8 (ddd, $^1J_{CF}$ = 233.8 Hz, $^2J_{CF}$ = 53.2, 16.3 Hz), 42.4, 31.8, 21.7 (dd, $^2J_{CF}$ = 21.9 Hz, $^3J_{CF}$ = 2.3 Hz). HRMS (ESI) calcd. for $C_{10}H_{10}F_3N_3NaO$ (M + Na) $^+$, 268.0673, found, 268.0676.

4,5,5-Trifluoro-*N*-(2-(trifluoromethyl)benzyl)pent-4-enamide (**B5**): Colorless liquid, yield 29%, ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.64 (d, J = 8.0 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.42 – 7.34 (m, 1H), 6.01 (s, 1H), 4.61 (d, J = 6.0 Hz, 2H), 2.72 – 2.57 (m, 2H), 2.43 (t, J = 7.4 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, full coupled) δ: −59.43 (s, 3F), −104.11 – −104.76 (m, 1F), −122.70 – −123.55 (m, 1F), −175.35 – −176.18 (m, 1F). ^{13}C NMR (101 MHz, $CDCl_3$), δ: 170.6, 153.0 (ddd, $^1J_{CF}$ = 284.4 and 272.3, $^2J_{CF}$ = 46.4 Hz), 136.4 (q, $^3J_{CF}$ = 2.8 Hz), 130.6, 132.3, 128.1 (q, $^2J_{CF}$ = 30.2 Hz), 127.8 (dd, $^1J_{CF}$ = 234.3, $^2J_{CF}$ = 53.0, 16.4 Hz), 127.7, 126.0 (q, $^3J_{CF}$ = 5.5 Hz), 124.4 (q, $^1J_{CF}$ = 272.0 Hz), 40.2, 31.9, 21.7 (dd, $^2J_{CF}$ = 21.7, $^3J_{CF}$ = 2.4 Hz). HRMS (ESI) calcd. for $C_{13}H_{12}F_6NO$ (M + H) $^+$, 312.0824, found, 312.0824.

4,5,5-Trifluoro-*N*-(thiophen-2-ylmethyl)pent-4-enamide (**B6**): Yellow liquid, yield 49%. ^{1}H NMR (400 MHz, DMSO−d_6), δ: 8.57 (J = 5.2 Hz, 1H), 7.38 (dd, J = 4.4, 2.0 Hz, 1H), 6.97 – 6.91 (m, 2H), 4.43 (d, J = 6.0 Hz, 2H), 2.65 – 2.52 (m, 2H), 2.38 (t, J = 7.2 Hz, 2H). ^{19}F NMR (565 MHz, $CDCl_3$, decoupled), δ: −104.2 (dd, J = 85.0, 32.2 Hz), −122.98 (dd, J = 114.2, 86.1 Hz), −175.70 (dd, J = 113.0, 32.2 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.5, 153.0 (ddd, $^1J_{CF}$ = 286.1, 273.8 Hz, $^2J_{CF}$ = 46.7 Hz), 140.7, 127.9 (ddd, $^1J_{CF}$ = 235.3 Hz, $^2J_{CF}$ = 52.5, 16.7 Hz), 126.9, 126.0, 125.2, 38.3, 31.8, 21.7 (dd, $^2J_{CF}$ = 21.8 Hz, $^3J_{CF}$ = 2.3 Hz). HRMS (ESI) calcd. for $C_{10}H_{10}F_3NNaOS$ (M + Na) $^+$, 272.0332, found, 272.0334.

N-((1*H*-indol-3-yl)methyl)-4,5,5-trifluoropent-4-enamide (**B7**): Reddish brown liquid, yield 30%. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.36 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.27 – 7.19 (m, 1H), 7.18 – 7.08 (m, 2H), 5.77 (s, 1H), 4.60 (d, J = 5.2 Hz, 2H), 2.80 – 2.55 (m, 2H), 2.37 (t, J =

7.6 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, full coupled), δ: −104.10 – −104.69 (m, 1F), −122.67 – −123.53 (m, 1F), −175.15 – −175.98 (m, 1F). ^{13}C NMR (101 MHz, $CDCl_3$), δ: 170.6, 153.0 (ddd, $^1J_{CF}$ = 286.1, 273.8 Hz, $^2J_{CF}$ = 46.8 Hz), 136.5, 128.0 (ddd, $^1J_{CF}$ = 234.1 Hz, $^2J_{CF}$ = 53.3, 16.3 Hz), 126.4, 123.4, 122.5, 119.9, 118.7, 112.2, 111.5, 35.3, 32.0, 21.8 (dd, $^2J_{CF}$ = 21.9 Hz, $^3J_{CF}$ = 2.3 Hz). HRMS (ESI) calcd. for $C_{14}H_{13}F_3N_2NaO$ (M + Na)$^+$, 305.087 7, found, 305.087 9.

4,5,5-Trifluoro-*N*-(furan-2-ylmethyl)pent-4-enamide (**B8**): White solid, yield 44%, m.p. 56.0−57.3 ºC. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.35 – 7.33 (m, 1H), 6.31 (dd, J = 3.2, 2.0 Hz, 1H), 6.25 – 6.18 (m, 1H), 5.99 (s, 1H), 4.43 (d, J = 5.6 Hz, 2H), 2.74 – 2.57 (m, 2H), 2.43 (t, J = 7.4 Hz, 2H). ^{19}F NMR (565 MHz, $CDCl_3$, decoupled) δ: −104.32 (dd, J = 85.0, 32.2 Hz), −123.07 (dd, J = 114.1, 86.0 Hz), −175.72 (dd, J = 114.3, 32.1 Hz). ^{13}C NMR (101 MHz, $CDCl_3$), δ: 170.5, 153.0 (ddd, $^1J_{CF}$ = 286.1, 273.9 Hz, $^2J_{CF}$ = 46.7 Hz), 151.0, 142.3, 127.9 (ddd, $^1J_{CF}$ = 233.9 Hz, $^2J_{CF}$ = 53.3, 16.3 Hz), 110.5, 107.5, 36.5, 31.8, 21.7 (dd, $^2J_{CF}$ = 21.9 Hz, $^3J_{CF}$ = 2.3 Hz). HRMS (ESI) calcd. for $C_{10}H_{10}F_3NNaO_2$ (M + Na)$^+$, 256.056 1, found, 256.056 3.

N-([1,1'-biphenyl]-4-ylmethyl)-4,5,5-trifluoropent-4-enamide (**B9**): White solid, yield 47%, m.p. 154.0−154.4 ºC. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.65 – 7.51 (m, 4H), 7.48 – 7.41 (m, 2H), 7.40 – 7.30 (m, 3H), 5.83 (s, 1H), 4.49 (d, J = 5.6 Hz, 2H), 2.79 – 2.61 (m, 2H), 2.47 (t, J = 7.4 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, full coupled), δ: −104.01 – −104.61 (m, 1F), −122.55 – −123.42 (m, 1F), −175.25 – −176.08 (m, 1F). ^{13}C NMR (101 MHz, DMSO−d_6), δ: 170.1, 152.6 (ddd, $^1J_{CF}$ = 283.3, 272.6 Hz, $^2J_{CF}$ = 47.9 Hz), 139.9, 138.7, 138.6, 128.9, 128.8 (ddd, $^1J_{CF}$ = 233.5 Hz, $^2J_{CF}$ = 52.9, 15.4 Hz), 127.8, 127.3, 126.6, 126.5, 41.8, 30.7, 21.3 (dd, $^2J_{CF}$ = 21.5 Hz, $^3J_{CF}$ = 2.2 Hz). HRMS (ESI) calcd. for $C_{18}H_{16}F_3NNaO$ (M + Na)$^+$, 342.108 1, found, 342.108 1.

N-(benzo[*d*]thiazol-2-ylmethyl)-4,5,5-trifluoropent-4-enamide (**B10**): Yellow solid, yield 85%, m.p. 73.0−74.2 ºC. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.96 (d, J = 8.0 Hz, 1H), 7.90 – 7.80 (m, 1H), 7.54 – 7.43 (m, 1H), 7.43 – 7.34 (m, 1H), 6.76 (s, 1H), 4.85 (d, J = 5.6 Hz, 2H), 2.81 – 2.62 (m, 2H), 2.53 (t, J = 7.4 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, full coupled), δ: −103.76 – −104.45 (m, 1F), −122.49 – −123.35 (m, 1F), −175.30 – −176.08 (m, 1F). ^{13}C NMR (101 MHz, $CDCl_3$), δ: 171.0, 168.3, 153.0 (ddd, $^1J_{CF}$ = 286.3, 274.0 Hz, $^2J_{CF}$ = 46.6 Hz), 152.3, 135.0, 127.8 (ddd, $^1J_{CF}$ = 233.7 Hz, $^2J_{CF}$ = 53.1, 16.3 Hz), 126.3, 125.4, 122.6, 121.8, 41.6, 31.7, 21.6 (dd, $^2J_{CF}$ = 21.9 Hz, $^3J_{CF}$ = 2.3 Hz). HRMS (ESI) calcd. for $C_{13}H_{12}F_3N_2OS$ (M + H)$^+$, 301.062 3, found, 301.062 3.

N-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)methyl)-4,5,5-trifluoropent-4-enamide (**B11**): Yellow liquid, yield 37%. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.72 (s, 1H), 7.95 (s, 1H), 7.05 (s, 1H), 4.73 (d, J = 4.4 Hz, 2H), 2.80 – 2.64 (m, 2H), 2.59 (t, J = 7.2 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, full coupled), δ: −62.26 (s, 3F), −103.98 – −104.66 (m, 1F), −122.60 – −123.47 (m, 1F), −175.30 – −176.12 (m, 1F). ^{13}C NMR (101 MHz, $CDCl_3$), δ: 170.3, 152.5 (dd, $^1J_{CF}$ = 281.4 and 271.0, $^2J_{CF}$ = 47.7 Hz), 143.7 (q, $^3J_{CF}$ = 2.8 Hz), 134.4 (q, $^3J_{CF}$ = 3.6 Hz), 130.0, 128.7 (dd, $^1J_{CF}$ = 232.0, $^2J_{CF}$ = 52.4, 15.4 Hz), 125.1 (q, $^2J_{CF}$ = 32.9 Hz), 123.9 (q, $^1J_{CF}$ = 271.2 Hz), 41.9, 30.5, 21.3 (dd, $^2J_{CF}$ = 21.5, $^3J_{CF}$ = 2.4 Hz). HRMS (ESI) calcd. for $C_{12}H_{10}ClF_6N_2O$ (M + H)$^+$, 347.038 7, found, 347.038 7.

N-(2-(1*H*-pyrazol-1-yl)benzyl)-4,5,5-trifluoropent-4-enamide (**B12**): Yellow solid, yield 88%, m.p. 53.2−55.2 ºC. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.74 (dd, J = 14.0, 2.0 Hz, 2H), 7.64 – 7.55 (m, 1H), 7.45 – 7.35 (m, 2H), 7.34 – 7.27 (m, 1H), 7.11 (s, 1H), 6.50 (t, J = 2.2 Hz, 1H), 4.30 (d, J = 6.0 Hz, 2H), 2.76 – 2.51 (m, 2H), 2.41 (t, J = 7.4 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, full coupled), δ: −104.37 – −104.99 (m, 1F), −122.93 – −123.76 (m, 1F), − 175.09 – −175.87 (m, 1F). ^{13}C NMR (101 MHz, DMSO−d_6), δ: 170.2, 152.5 (ddd, $^1J_{CF}$ = 283.3, 272.6 Hz, $^2J_{CF}$ = 47.9 Hz), 140.3, 138.6, 133.9, 131.4, 128.80 (ddd, $^1J_{CF}$ = 233.5 Hz, $^2J_{CF}$ = 52.9, 15.4 Hz), 128.2, 128.1, 127.6, 125.5, 106.6, 38.4, 30.6, 21.3 (dd, $^2J_{CF}$ = 21.5 Hz, $^3J_{CF}$ = 2.2 Hz). HRMS (ESI) calcd. for $C_{15}H_{14}F_3N_3NaO$ (M + Na)$^+$, 332.098 6, found, 332.098 8.

4,5,5-Trifluoro-*N*-((1-methyl-1*H*-imidazol-2-yl)methyl) pent-4-enamide (**B13**): Light yellow solid, yield 65%, m.p. 78.8−79.3 ºC. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.89 (s, 1H), 6.90 (d, J = 1.2 Hz, 1H), 6.83 (d, J = 1.2 Hz, 1H), 4.46 (d, J = 5.6 Hz, 2H), 3.69 (s, 3H), 2.75 – 2.57 (m, 2H), 2.48 (t, J = 7.4 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, full coupled), δ: −104.15 – −104.91 (m, 1F), −122.87 – −123.70 (m, 1F), −175.10 – −175.85 (m, 1F). ^{13}C NMR (101 MHz, DMSO−d_6), δ: 169.8, 152.5 (ddd, $^1J_{CF}$ = 283.2, 272.5 Hz, $^2J_{CF}$ = 47.8 Hz), 144.5, 128.8 (ddd, $^1J_{CF}$ = 233.5 Hz, $^2J_{CF}$ = 52.9, 15.4 Hz), 126.3, 121.8, 34.7, 32.2, 30.4, 21.2 (dd, $^2J_{CF}$ = 21.5 Hz, $^3J_{CF}$ = 2.2 Hz). HRMS (ESI) calcd. for $C_{10}H_{13}F_3N_3O$ (M + H)$^+$, 248.101 1, found, 248.101 0.

4,5,5-Trifluoro-*N*-((1-methyl-1*H*-pyrazol-4-yl)methyl) pent-4-enamide (**B14**): White solid, yield 40%, m.p. 62.9−63.6 ºC. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.36 (s, 1H), 7.31 (s, 1H), 5.96 (s, 1H), 4.25 (d, J = 5.6 Hz, 2H), 3.83 (s, 3H), 2.73 – 2.54 (m, 2H), 2.38 (t, J = 7.4 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, full coupled), δ: −104.20 – −104.82 (m, 1F), −122.75 – −123.63 (m, 1F), −175.28 – −176.08 (m, 1F). ^{13}C NMR (101 MHz, $CDCl_3$), δ: 170.4, 153.0 (ddd, $^1J_{CF}$ = 286.1, 273.8 Hz, $^2J_{CF}$ = 46.8 Hz), 138.5, 129.4, 127.9 (ddd, $^1J_{CF}$ = 233.8 Hz, $^2J_{CF}$ = 53.2, 16.3 Hz), 118.5, 38.8, 34.0, 31.9, 21.8 (dd, $^2J_{CF}$ = 21.8 Hz, $^3J_{CF}$ = 2.3 Hz). HRMS (ESI) calcd. for $C_{10}H_{13}F_3N_3O$ (M + H)$^+$, 248.101 1, found, 248.101 2.

4,5,5-Trifluoro-*N*-(4-(*p*-tolyloxy)benzyl)pent-4-enamide (**B15**): Light yellow solid, yield 48%, m.p. 102.0−103.7 ºC. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.21 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.00 – 6.87 (m, 4H), 5.74 (s, 1H), 4.41 (d, J = 5.6 Hz, 2H), 2.81 – 2.58 (m, 2H), 2.44 (t, J = 7.4 Hz, 2H), 2.34 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, full coupled), δ:

−104.02 – −104.71 (m, 1F), −122.59 – −123.50 (m, 1F), −175.28 – −176.06 (m, 1F). ^{13}C NMR (101 MHz, DMSO−d_6), δ: 175.2, 161.2, 159.6, 157.8 (ddd, $^1J_{CF}$ = 283.1, 272.6 Hz, $^2J_{CF}$ = 47.9 Hz), 139.4, 137.7, 135.6, 134.1, 134.0 (ddd, $^1J_{CF}$ = 234.3 Hz, $^2J_{CF}$ = 53.0, 15.7 Hz), 123.8, 123.3, 46.8, 35.9, 26.6 (dd, $^2J_{CF}$ = 21.5 Hz, $^3J_{CF}$ = 2.2 Hz), 25.4. HRMS (ESI) calcd. for $C_{19}H_{19}F_3NO_2$ $(M + H)^+$, 350.1369, found, 350.1367.

1.4 Nematicidal activity

The second-stage juveniles (J2) of *M. incognita* used in all tests were cultured by Huzhou Modern Agricultural Biotechnology Innovation Center, Chinese Academy of Sciences, China.

1.4.1 The *in vitro* nematicidal activity The compound was initially dissolved in acetone to obtain solution with the concentration of 10 000 mg/L, a certain amount of the above acetone solution was diluted to the determined concentration using distilled water containing surfactant. An equal volume of the suspensions of second-stage juveniles (J2) of *M. incognita* or *B. xylophilus* was added to a 96-well plate to form the final concentration to be measured (all compounds have good solubility and the solution is clear and transparent). Each well contained approximately 50 nematodes; each treatment was repeated twice. The 96-well plate was placed in an incubator and incubated at room temperature. The survival of nematodes was observed and recorded after 24 h, 48 h, and 72 h, respectively. Nematodes were considered dead if their bodies were straight or they did not move when strongly prodded their bodies with a needle. The LC_{50} values of tested compounds were calculated using the probit method. Fluensulfone was served as a positive control and the negative control was the solution above without the tested compound. The nematicidal corrected mortality was calculated according to formula (1)[25].

$$M = [(M_1 - M_2)/(1 - M_2)] \times 100\% \quad (1)$$

In this formula, M is corrected mortality (%), M_1 is mortality of treatment (%), M_2 is mortality of negative control (%).

1.4.2 The *in vivo* nematicidal activity The test was carried out by the tube method, which was divided into two types of sand and matrix. The compound was initially dissolved in acetone to obtain 10 000 mg/L solution, the solution was diluted to the tested concentration using distilled water containing surfactant (all compounds have good solubility and the solution is clear and transparent). The one-week-aged cucumber seedlings were replanted in sterilized sand (or matrix) in test tubes (one seedling per test tube, tube size: 20 mm × 250 mm), and the roots of each seedling were treated with 3 mL of test solution. Then approximately 2000 living J2 nematodes were inoculated into the rhizosphere sand of each host plant, fluensulfone was served as positive control, and the negative control group was prepared in the same way without compound to be tested. Distilled water without nematodes was served as blank control. Each treatment was repeated three times. All the test tubes were incubated at 25 ºC for 20 d, with 10 h in the daylight and 14 h in the dark per day. The number of root knots in each test tube were counted and recorded as a score. The inhibition on J2 of *M. incognita* was calculated according to the following formula (2).

$$I = [(S_1 - S_2)/S_1] \times 100\% \quad (2)$$

In this formula, I is inhibition rate (%), S_1 is score of negative control and S_2 is score of treatment.

Scoring criteria: 0: 0–5 knots; 5: 6–10 knots; 10: 11–20 knots; 20: more than 20 knots[25].

2 Result and discussion

2.1 *In vitro* nematicidal activity against *M. incognita*

According to the bioassay data of the *in vitro* test in **Table 1**, the mortality of compound **B1** against *M. incognita* was 87.0% after 72 h of treatment at the concentration of 40 mg/L. Then, the thiazole ring of compound **B1** was replaced by different heterocycles to synthesize compounds **B2-B15**. Among the synthesized compounds, the mortalities of **B6** and **B8** against *M. incognita* at the concentration of 40 mg/L were 89.0% and 93.0%, respectively. In order to further explore the nematicidal activities of these three compounds, their $LC_{50/72\ h}$ values were calculated. Among which compound **B8** containing a furan ring exhibited the best nematicidal activity with $LC_{50/72\ h}$ value of 1.22 mg/L (**Table 1**), but it was still inferior to that of compound **A23**[25].

2.2 *In vivo* nematicidal activity against *M. incognita* (sand)

First, the inhibitory activities of synthesized compounds against *M. incognita* in sand at the concentration of 40 mg/L were tested (**Table 2**). Results showed that compounds **B1-B4**, **B6-B8** and **B11** had 100% inhibition rate against *M. incognita* at

Table 1 *In vitro* nematicidal activity of the target compounds B1-B15, A8 and A23 against *M. incognita* (40 mg/L)

Compd.	Mortality/%			$LC_{50/72h}$ (95% Confidence interval)/(mg/L)
	24 h	48 h	72 h	
B1	2.90	34.2	**87.0**	10.2 (5.81–17.4)
B2	2.30	2.70	3.60	—
B3	1.40	2.40	3.20	—
B4	1.90	3.20	67.8	—
B5	1.90	2.40	3.30	—
B6	9.20	16.9	**89.0**	9.03 (3.52–12.6)
B7	1.40	2.40	2.80	—
B8	11.0	56.9	**93.0**	**1.22** (0.54–1.96)
B9	0.90	1.40	2.30	—
B10	1.40	2.80	20.3	—
B11	0.80	3.00	3.50	—
B12	0.50	1.40	2.40	—
B13	1.00	1.40	2.30	—
B14	2.40	2.80	10.6	—
B15	0.50	1.80	2.30	—
A8[25]	13.4	81.3	**85.0**	**2.02** (1.13–2.88)
A23[25]	38.9	90.8	**98.7**	**0.76** (0.66–0.89)
fluensulfone[a]	80.2	100.0	100.0	0.12 (0.02–0.44)
CK[b]	0.90	1.80	2.30	—

Note: [a]Fluensulfone at the concentration of 40 mg/L. [b]CK: negative control.

40 mg/L, while the inhibition rates of **B10** and **B14** were 97.3% and 92.5%, respectively. When the test concentration was reduced to 10 mg/L, compounds **B1**, **B2**, **B4**, **B6**, **B8** and **B10** could still maintain more than 50% root-knot inhibition rate. The inhibitory activities of these six compounds were further investigated by reducing the concentration, and it was found that compound **B10** containing a benzothiazole ring exhibited 66.0% inhibition rate at 2.5 mg/L.

2.3 *In vivo* nematicidal activity against *M. incognita* (matrix)

The *in vivo* test in matrix can simulate the real field environment of nematodes survival, which is important for the evaluation of the bioactivity and further modification of a nematicidal lead compound. Considering that compounds **B1, B2, B4, B6, B8** and **B10** showed good inhibitory activity at low concentration (10 mg/L) in sand, the activities of these six compounds against *M. incognita* in matrix were further tested. It was found that compounds **B1**, **B4**, **B6**, **B8** and **B10** showed more than 50% inhibition rate against *M. incognita* at 40 mg/L (**Table 3**). When the concentration was reduced to 20 mg/L,

Table 2 *In vivo* nematicidal activity of the target compounds B1-B15 against *M. incognita* in sand

Compd.	J2 of *M. incognita* inhibition/%				
	40 mg/L	20 mg/L	10 mg/L	5 mg/L	2.5 mg/L
B1	100.0	100.0	100.0	40.4	27.6
B2	100.0	78.1	75.4	63.9	5.80
B3	100.0	91.0	25.3	—	—
B4	100.0	100.0	76.7	0.00	0.00
B5	44.5	—	—	—	—
B6	100.0	100.0	100.0	75.7	44.2
B7	100.0	51.2	27.3	—	—
B8	100.0	98.1	68.3	29.8	1.00
B9	6.80	—	—	—	—
B10	**97.3**	**96.6**	**74.5**	**68.6**	**66.0**
B11	100.0	59.6	26.7	—	—
B12	25.3	—	—	—	—
B13	0.00	—	—	—	—
B14	92.5	80.8	8.20	—	—
B15	0.00	—	—	—	—
fluensulfone	100.0	100.0	100.0	100.0	100.0

compound **B6** containing a thiophene ring and compound **B8** bearing a furan ring still exhibited rather high bioactivities with more than 50% inhibition rate, while compound **B10** bearing a benzothiazole ring had only 21.6% inhibition rate, which exhibited excellent activity in sand. It was speculated that this compound might easily be decomposed by the composition in the matrix. After further reducing the concentration, it was found that compound **B6** containing a thiophene ring exhibited the best activity with 31.0% inhibition rate at 5 mg/L. But it was inferior to compound **A8**[25], which showed the inhibition rate of 56.2% at 5 mg/L. When the concentration was reduced to 2.5 mg/L, compound **B6** showed 21.1% inhibition rate against *M. incognita*, but the bioactivity of compound **A8** totally disappeared. Preliminary analysis on structure-activity relationship showed that the non-substituted five-membered ring such as thiophene, furan and thiazole was significant to *in vivo* activity in matrix of compounds we prepared. The work of chain extension or cyclobutyl replacement is in progress.

2.4 *In vitro* nematicidal activity against *B. xylophilus*

The *in vitro* nematicidal activities of these fifteen compounds against *B. xylophilus* were determined again, and the results were shown in **Table 4**. Compounds **B1**, **B6** and **B8** showed better activity

Table 3 *In vivo* nematicidal activity of highly active compounds against *M. incognita* in matrix

Compd.	J2 of *M. incognita* inhibition/%				
	40 mg/L	20 mg/L	10 mg/L	5 mg/L	2.5 mg/L
B1	53.4	31.9	7.30	—	—
B2	39.7	—	—	—	—
B4	69.0	44.0	8.20	—	—
B6	98.7	59.1	50.4	31.0	**21.1**
B8	76.7	56.5	43.1	23.7	14.6
B10	52.6	21.6	5.20	—	—
A8	100.0	100.0	87.5	**56.2**	—
A23	100.0	100.0	62.5	—	—
fluensulfone	100.0	100.0	100.0	100.0	75.4

against *B. xylophilus* and the inhibition rates were 87.9%, 94.3% and 100.0% after 72 h of treatment at the concentration of 40 mg/L, respectively, which is similar to that against *M. incognita* (**Table 1**). It was also found that fluensulfone exhibited no bioactivity against *B. xylophilus*. It indicated that the mechanism of these three compounds was different from that of fluensulfone. In order to further analyze and compare the activities of **B1**, **B6** and **B8** against *B. xylophilus*, $LC_{50/72\ h}$ values of these three compounds were tested, and shown in **Table 4**. Of these three compounds, compound **B8** containing a furan ring exhibited the best activity against *B. xylophilus*, with $LC_{50/72\ h}$ of 0.53 mg/L, followed by compound **B6** containing a thiophene ring (2.33 mg/L). Compound **B1** containing a thiazole ring showed the worst nematicidal activity, with $LC_{50/72\ h}$ of 14.7 mg/L. Since the bioactivity of compounds **A8** and **A23** against *B. xylophilus* had not been tested[25], the comparison could not be carried out continuously.

Table 4 *In vitro* nematicidal activity of the target compounds B1-B15 against *B. xylophilus* (40 mg/L)

Compd.	Mortality/%			$LC_{50/72\ h}$ (95% Confidence interval)/(mg/L)
	24 h	48 h	72 h	
B1	14.2	26.2	**87.9**	14.7 (8.61–32.4)
B2	0.00	1.60	4.10	—
B3	1.10	2.10	5.90	—
B4	1.50	2.60	5.60	—
B5	2.10	3.10	7.90	—
B6	63.6	72.4	**94.3**	2.33 (1.52–3.11)
B7	2.60	2.60	3.10	—
B8	81.9	85.1	**100.0**	**0.53** (0.11–1.10)
B9	1.10	1.60	2.70	—
B10	3.40	7.30	37.00	—
B11	1.10	2.60	6.80	—
B12	2.00	1.40	2.40	—
B13	0.00	1.60	2.60	—
B14	1.70	2.70	4.20	—
B15	0.60	2.70	4.20	—
fluensulfone[a]	0.00	0.90	0.90	—
Avermectin[b]	100.0	100.0	100.0	0.11 (0.04–0.18)
CK[c]	1.60	2.10	2.60	—

[a]Fluensulfone at the concentration of 40 mg/L. [b]Avermectin at the concentration of 5 mg/L. [c]CK: negative control.

3 Conclusion

In this paper, based on the structural characteristics of commercial nematicide fluensulfone, 15 novel 4,5,5-trifluoropent-4-enamide derivatives **B1-B15** were designed and synthesized by replacing the sulfone with methylene amide bond.

The biological activities of these compounds against *M. incognita* and *B. xylophilus* were tested. The results showed that compounds **B1**, **B6** and **B8** exhibited exciting *in vitro* activity against *M. incognita* and *B. xylophilus*, $LC_{50/72\ h}$ values of compound **B8** containing a furan ring were 1.22 mg/L and 0.53 mg/L, respectively. But the activity of compound **B8** against *M. incognita* was still inferior to compound **A23** ($LC_{50/72\ h}$, 0.76 mg/L) which was prepared in our previous work. In the *in vivo* test against *M. incognita*, most of the compounds were showed more than 90% inhibition rate at 40 mg/L in sand, among which compound **B10** containing a benzothiazole ring exhibited the best activity with 66.0% inhibition rate at 2.5 mg/L. However, in matrix, compound **B6** containing a thiophene ring was the most active compound, and showed 50.4% and 31.0% inhibition rate at 10 mg/L and 5 mg/L, respectively. When the concentration was reduced to 2.5 mg/L, compound **B6** still showed 21.1% inhibition rate against *M. incognita*, which was better than that of compound **A8**. Preliminary analysis on structure-activity relationship showed that the compounds containing non-substituted five-membered ring such as thiophene, furan and thiazole demonstrated better bioactivity than those compounds containing bulky six-membered ring or fused ring in the molecule. This result will be benefit for further structural modification of novel nematicidal lead compound.

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