Synthesis and Insecticidal Activity of Novel Thiazole Acrylonitrile Derivatives

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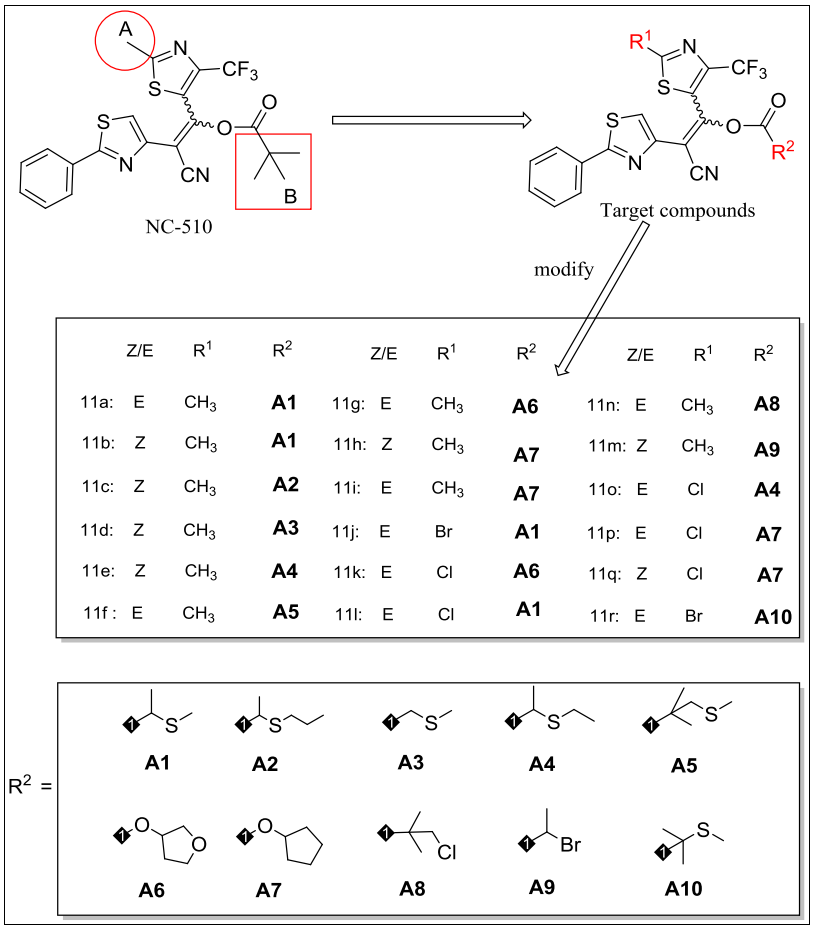


A series of novel thiazole acrylonitrile derivatives was designed and synthesized utilizing NC-510 as a precursor. Their structures were characterized by NMR spectrometry, MS, and elemental analysis. The results of bioassay indicated that some of these title compounds exhibited 100% mortality at 50 mg/L against *Aphis fabae*. In particular, the compound **11c** displayed the best activity: Its LC_{50} value achieved 1.45 mg/L, and its insecticidal potency is comparable with that of NC-510.

INTRODUCTION

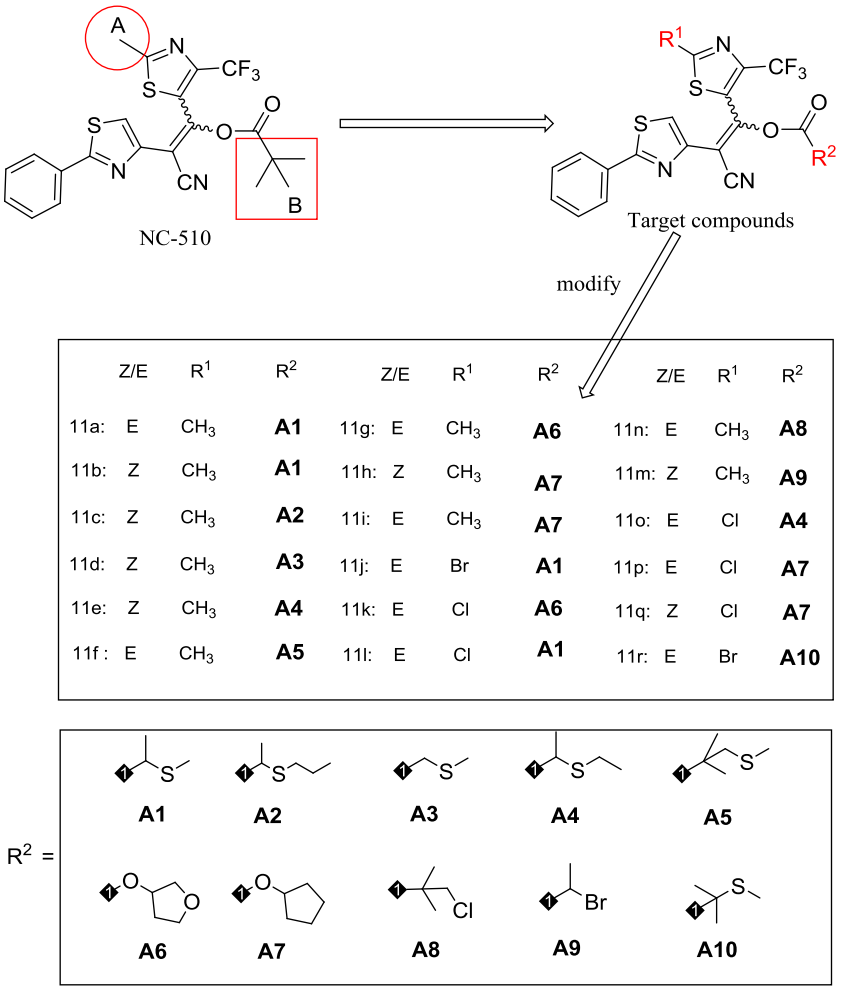
Thiazole derivative, an important class of heterocyclic compounds, has attracted wide attention due to its insecticidal [1], fungicidal [2], antiviral [3], herbicidal [4], and plant-growth-regulating activities [5]. Acrylonitrile compounds, which have been first synthesized by Allen and Birum in 1960s [6], also have excellent biological activities including insecticidal and herbicidal activities [7]. Since then, thousands of acrylonitrile analogues with biological activity were reported [8,9].

In recent years, the research of thiazole acrylonitrile compounds containing both thiazole and acrylonitrile moiety has gained increasing popularity because of their diverse characteristics [10], such as effective action mode, high efficiency, low toxicity, and low residue. Thus, a series of thiazole acrylonitrile compounds [11–15] has been developed. Among them, NC-510 (Fig. 1) [16] displayed excellent biological activity against *Aphis fabae* and other piercing-sucking mouthparts insects and showed no cross-resistance to currently available insecticides [17]. These results proved that thiazolyl acrylonitrile compounds are worth of further investigation.

Based on the aforementioned findings, we used NC-510 as a lead compound to design and to synthesize novel pesticides (Fig. 1). In this paper, 18 unreported thiazole acrylonitrile derivatives were designed and synthesized by adopting analogue synthesis and sub-structure theory. In our previous work [18], it is pointed out that a methyl group on the 2- position of the thiazole ring was required for the development of optimal insecticidal activity. Thus, the goal was to optimize the R^2 group. As shown in Figure 1, moiety B was optimized by replacing the tert-butyl with other 10 groups (**A1–A10**) that were isosteres each other. Meanwhile, moiety A was optimized as well. To search for novel analogues with unique biological activities, a synthetic screening program was carried out around compound **11a**–**11r**.

RESULTS AND DISCUSSION

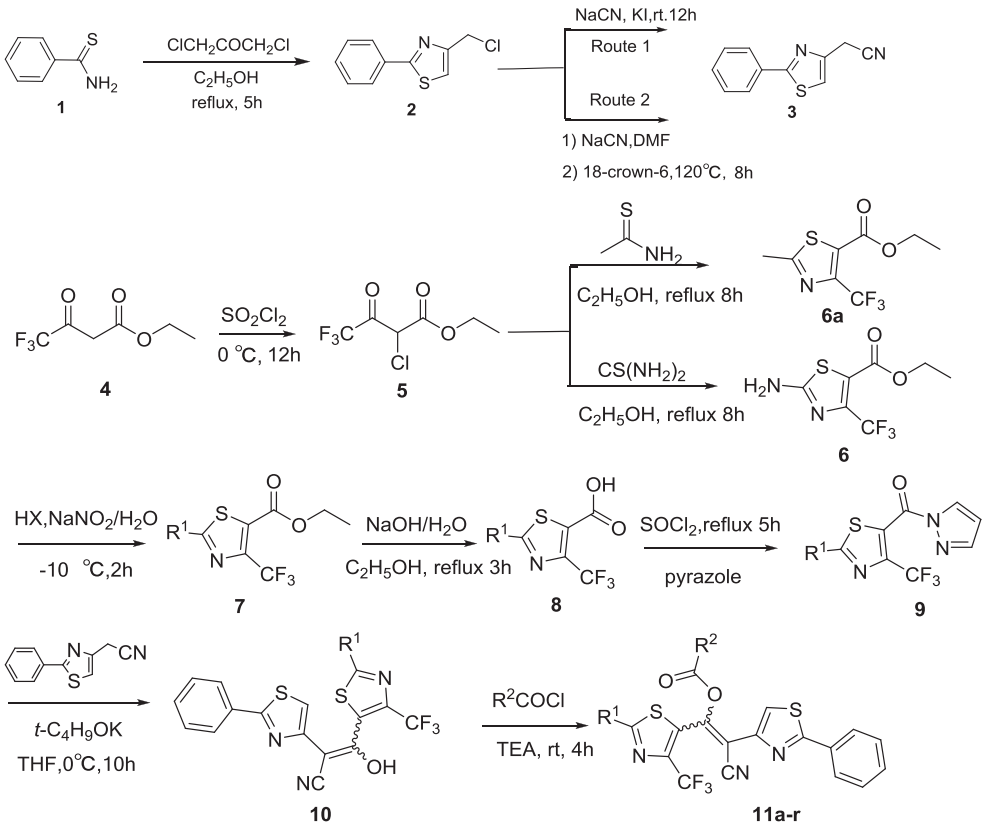
Synthesis. The synthetic route to the title compounds **11a–r** is shown in Scheme 1. A series of novel thiazole acrylonitrile analogues were synthesized by reacting compound **10** with desired acid chlorides in the room temperature in the presence of triethylamine. As shown in Scheme 1, two methods could be used to synthesize the key intermediate compound **3**, and route 1 was adopted because the utilization of KI improved the catalytic effect of NaCN, and route 1 therefore has milder reaction



	Z/E	R^1	R^2		Z/E	R^1	R^2		Z/E	R^1	R^2
11a:	E	CH_3	**A1**	11g:	E	CH_3	**A6**	11n:	E	CH_3	**A8**
11b:	Z	CH_3	**A1**	11h:	Z	CH_3	**A7**	11m:	Z	CH_3	**A9**
11c:	Z	CH_3	**A2**	11i:	E	CH_3	**A7**	11o:	E	Cl	**A4**
11d:	Z	CH_3	**A3**	11j:	E	Br	**A1**	11p:	E	Cl	**A7**
11e:	Z	CH_3	**A4**	11k:	E	Cl	**A6**	11q:	Z	Cl	**A7**
11f :	E	CH_3	**A5**	11l:	E	Cl	**A1**	11r:	E	Br	**A10**

Figure 1. Designs strategy of target molecules. [Color figure can be viewed at wileyonlinelibrary.com]

Scheme 1. General synthetic route for the target compounds **11a**–**r**.



condition, higher yield, and higher purity compared with route 2.

Because of the presence of the C=C bond, intermediate **10** and the target molecules **11a**–**r** have *Z*/*E* stereoisomerism. This stereoisomerism can be rapidly separated by column chromatography on silica gel. For unambiguous structure elucidation, ^{1}H NMR spectroscopy was used. Taking **11a** and **11b**, as examples, the resonance frequencies resulting from SCH_3 group of *E* form and *Z* form are 2.058 and 2.186 ppm, respectively, and the resonance frequencies resulting from CH_3 group of *E* form and *Z* form are 1.445 and 1.550 ppm respectively in the ^{1}H NMR spectrum because of the position with C≡N group. Taking **11h** and **11i** as examples, the resonance frequencies resulting from CH group of *E* form and *Z* form are 5.120 and 5.158 ppm, respectively, and the resonance frequencies resulting from CH_3 group of *E* form and *Z* form are 2.806 and 2.780 ppm respectively in the ^{1}H NMR spectrum because of the position with C ≡ N group.

Insecticidal activity. The screening date revealed that all title compounds **11a–r** had 100% mortality at 500 mg/L against *Aphids*. When the concentration was decreased to 50 mg/L, the compounds **11a-11e**, **11g**, **11j**, **11k**, and **11p** still exhibited 100% mortality against *Aphis fabae*, and seven compounds, **11f**, **11h**, **11i**, **11l**, **11n**, **11m, and 11r,** have insecticidal activity with 89.61%, 83.8%, 75.4%, 87.33%, 73.5%, 87.74%, and 83.08% mortality, respectively. In particular, with an LC_{50} value of 1.45 mg/L, **11c** showed an insecticidal activity slightly lower to the reference compound **NC-510** (LC_{50} = 0.61 mg/L).

Structure–activity relationship. The structure–activity relationship can be evaluated via parallel activity contrasting between the compounds of different substituents against *Aphis fabae* at the same concentration. The activities of the compounds **11a–r** depend on the $R^1$and R^2 moiety. The results showed that R^2 has an important effect on the activity: When R^1 = CH_3, and R^2 = **A7**, the compounds (**11h** and **11i**) had good activities; when R^2 are substituents containing sulfur atom, the compounds (**11a-11f**) showed moderate activities. In general, sequence of the substitution patterns of the R^2 in enhancement of the activity (R^1 is kept as methyl) is **A2** > **A4** > **A8** > **A7** > **A1** > **A3** > **A5** > **A6**. At the same time, *E*- and *Z*- isomers also have effect on the activity of compounds. By comparing the activities of compounds **11a** (*E* form) and **11b** (*Z* form) as well as **11h** (*Z* form) and **11i** (*E* form), the activity of the *Z* form is slightly better than that of the *E* form.

Table 1

Insecticidal activity against *Aphis fabae* for the target compounds.

Compound	Regression equation	Correlation	LC_{50} (mg/L)	Compound	Regression equation	Correlation	LC_{50} (mg/L)
11a	Y = 4.1882 + 1.6912×	0.9782	3.02	**11g**	Y = 3.4193 + 2.1839×	0.9872	5.29
11b	Y = 2.0768 + 6.5745×	0.8724	2.78	**11h**	Y = 3.9704 + 2.5928×	0.9585	2.49
11c	Y = 4.7634 + 1.4590×	0.9912	1.45	**11i**	Y = 3.9789 + 2.0924×	0.9423	3.08
11d	Y = 3.7867 + 1.7576×	0.9971	4.90	**11n**	Y = 4.3113 + 1.7923×	0.9294	2.42
11e	Y = 4.4397 + 1.4767×	0.9895	2.40	**NC-510**	Y = 5.4148 + 1.9063×	0.9977	0.61
11f	Y = 3.3186 + 2.3571×	0.9776	5.17				

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

CONCLUSION

In summary, a series of novel thiazole acrylonitrile compounds were synthesized, and their insecticidal activities were evaluated. The screening data revealed that compounds **11a–r** had good insecticidal activity, and in particular, **11b**, **11c**, **11e**, **11h**, and **11n** displayed excellent activities. Structure–activity relationships indicated that R^2 has an important effect on the activity, and the activity order for R^2 is **A2** > **A4** > **A8** > **A7** > **A1** > **A3** > **A5** > **A6** (Table 1).

EXPERIMENTAL

Materials and method. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. NMR spectra were obtained with a Varian INOVA-300 spectrometer using tetramethylsilane as internal standard and deuterochloroform ($CDCl_3$) as solvent. LC–MS were recorded with an Agilent 1100 series using the positive ion scan mode. Elemental analysis data were obtained on a PE2400 II elemental analyzer. Column chromatography was performed using a 200–300 mesh silica gel. Uncorrected melting points were taken on a WRS-1B digital melting point apparatus.

The general synthetic schemes for compounds are shown in Scheme 1. Reaction yields were not optimized. Every other compound was synthesized in a manner similar to that used for the representatives, and every new compound was identified and verified by ^{1}H NMR, LC–MS, and elemental analysis.

Synthesis of 4-chloromethyl-2-phenylthiazole (2). 1,3-Dichloropropan-2-one (25.4 g, 200 mmol) was added dropwise to a stirred mixture of anhydrous EtOH (100 mL), tetrahydrofuran (THF) (50 mL), and thiobenzamide (25.0 g, 182 mmol). After stirring at the room temperature for 0.5 h, the mixture was heated at reflux for 5–6 h. The reaction mixture was cooled to room temperature, poured into ice water, and then extracted with ethyl acetate. The combined organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude product **2** as a brown liquid, 36.2 g (95.2% yield, 93.7% purity), which was used in the following reaction without further purification.

Synthesis of 2-(2-phenylthiazole-4-yl)-acetonitrile (3). KI (0.83 g, 5 mmol) was added to a solution of compound **2** (20.9 g, 100 mmol) in DMF (150 mL). The mixture was stirred at room temperature for 20 min before sodium cyanide (5.88 g, 120 mmol) was added, and then the mixture was stirred at room temperature for 10–12 h until the staring materials was consumed (monitored by TLC). The reaction mixture was poured into ice water, and $FeCl_3$ was added before the mixture was extracted with ethyl acetate. The combined organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude product **3** as a black liquid, 16.7 g (83.5% yield, 92.3% purity), which was used in the following reaction without further purification.

Synthesis of ethyl 2-chloro-4,4,4-trifluoro-3-oxobutanoate (5). A solution of ethyl 4,4,4-trifluoro-3-oxobutanoate (92 g, 500 mmol) in dichloromethane (100 mL) was added dropwise to a solution of sulfonyl chloride (74.3 g, 550 mmol) in dichloromethane (30 mL) at a temperature ranging from −5 to 0°C. The mixture was stirred at room temperature for 10–12 h. The reaction mixture was poured into ice water and then extracted with dichloromethane. The combined organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude product compound **5** as a yellow liquid,108.2 g (99.3% yield, 99.1% purity), which was used in the following reaction without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.34 (t, J = 6.0 Hz, 3H, CH_3), 4.32 (q, J = 6.0 Hz, 2H, CH_2), 4.48 (s, 1H, CH).

Synthesis of 2-amino-4-(trifluoromethyl)thiazole-5-carboxylic acid ethyl ester (6). Thiourea (28.2 g, 370 mmol) was added to a solution of compound **5** (81.0 g, 370 mmol) in anhydrous EtOH (200 mL). The resulting mixture was heated at reflux for 8–10 h until the

staring materials was consumed (monitored by TLC). The reaction mixture was cooled to room temperature, poured into ice water, and a solid was formed. The solid was filtered and dried to afford the compound **6** as a white solid, 81.8 g (92.1% yield, 99.3% purity), mp 169.3–170.5°C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.33 (t, J = 6.0 Hz, 3H, CH_3), 4.30 (q, J = 6.0 Hz, 2H, CH_2), and 5.87 (s, 2H, NH).

Synthesis of 2-chloro-4-(trifluoromethyl)thiazole-5-carboxylic acid ethyl ester (7o). Compound **6** (48.0 g, 200 mmol) was slowly added to a solution of hydrochloric acid (4 M, 100 mL) at −10°C, and the mixture was stirred for 15 min before a solution of 40% aqueous sodium nitrite was added dropwise. The mixture was stirred at the same temperature for 2 h before stirred at room temperature for 2 h. The resulting mixture was poured into ice water, and a solid was formed. The solid was filtered and dried to afford the crude product as a brown solid, 45.6 g (88.0% yield, 93.6% purity), which was recrystallized from petroleum ether and ethyl acetate to afford the compound **7o** (R^1 = Cl) as a yellow solid, (97.8% purity), mp 58.2–58.6°C.

Synthesis of 2-chloro-4-(trifluoromethyl) thiazole-5-carboxylic acid (8o). Aqueous sodium hydroxide (0.2 M, 80 mL) was added to a solution of compound **7o** (25.9 g, 100 mmol) in anhydrous ethanol (40 mL). The resulting mixture heated at reflux for 3–5 h until the staring materials was consumed (monitored by TLC). The reaction mixture was poured into ice water and acidified with 40% hydrochloric acid to pH of about 2, extracted with ethyl acetate. The combined organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude product **8o** as a brown oil, 17.5 g (75.8% yield), which was used in the following reaction without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.37 (t, J = 6.0 Hz, 3H, CH_3), 4.38 (q, J = 6.0 Hz, 2H, CH_2).

Synthesis of (2-chloro-4(-trifluoromethyl) thiazole-5-yl)(1H-parazole-1-yl)-ketone (9o). Sulfoxide chloride (35.4 g, 300 mmol) was dropwise added to a solution of compound **8o** (23.1 g, 100 mmol) in 1,2-dichloroethane (120 mL), and the mixture was heated at reflux for 5–6 h. The mixture was cooled to room temperature, and the excess solvent and sulfoxide chloride was removed under reduced pressure to afford a brown liquid. Pyrazole (13.6 g, 200 mmol) was added to the brown liquid in dichloromethane (150 mL) and stirred for 2 h. Water was added and extracted with dichloromethane. The combined organic layer was dried over anhydrous sodium sulfate and concentrated to afford the crude compound **9o** as a brown oil, 45.2 g (80.5% yield). ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 7.80 (s, 1H, COOH).

Synthesis of 3-hydroxy-3-(2-chloro-4-(trifluoromethyl) thiazole-5-yl)-2-(2-phenylthiazole-4-yl)-acrylonitrile (10o). *t*-BuOK (5.6 g, 50 mmol) was slowly added to a solution of compound **9o** (14.0 g, 50 mmol) and compound **3** (10.0 g, 50 mmol) in THF (100 mL) at 0°C. The mixture was stirred at the room temperature for 10–12 h. The reaction mixture was poured into ice water and acidified with 40% hydrochloric acid to approximity pH 2, and the product was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the compound **10o** as a brown solid, 12.3 g (59.6% yield, 97.3% purity) mp 170.0–170.4°C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 7.45–7.50 (m, 3H, Ph H), 7.92–7.96 (m, 2H, Ph H), 8.28 (s, 1H, Thiazole H), 8.95 (s, 1H, OH).

Synthesis of 2-phenyl thiazole-3-substituted ester-3-(substituted thiazole-5-yl) acrylonitrile (11a–r). Compound **10o** (1.03 g, 2.5 mmol), THF (30 mL), and Et_3N (0.5 g, 5 mmol) were mixed in ice bath and stirred for 15 min. Then substituted acyl chloride (3 mmol) was dropwise added to the mixture and stirred at room temperature for 4 h. The reaction solution was poured into ice water and extracted with ethyl acetate. The organic layer was washed twice with water and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the crude product, and the residue was purified by silica-gel column chromatography (petroleum ether + ethyl acetate =30:1 *v*/v) to afford compound **11a–r** as a white, yellow, or brown solid.

^{1}H NMR data of compounds 11a–r. ***11a:(E)-2-cyano-1-(2-methyl-4-(trifluoromethyl)thiazol-5-yl)-2-(2-phenylthiazol-4-yl) vinyl 2-(methylthio)propanoate.*** Yield, 45.5%; yellow solid; mp 109.0–110.0°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.445 (d, J = 7.2 Hz, 3H, CH_3), 2.058 (s, 3H, CH_3), 2.803 (s, 3H, CH_3), 3.540 (q, J = 7.2 Hz, 1H, CH), 7.511–7.550 (m, 3H, Ph H), 7.882–7.959 (m, 2H, Ph H), 8.005 (s, 1H, Thiazole H). ^{13}C NMR, δ: 13.38, 15.88, 19.26, 41.22, 76.57, 118.16, 122.28, 126.55, 129.03, 129.38, 130.82, 131.09, 142.71, 146.21, 149.18, 158.56, 168.53, 169.25, 170.40. LC–MS (APCI, Pos) *m*/*z*: 496 $[M + H]^+$. Elemental *Anal*. (%) Calcd for $C_{21}H_{16}F_3N_3O_2S_3$: C 50.90, H 3.25, N 8.48; found C 50.80, H 3.12, N 8.17.

11b:(Z)-2-cyano-1-(2-methyl-4-(trifluoromethyl)thiazol-5-yl)-2-(2-phenylthiazol-4-yl)vinyl 2-(methylthio)propanoate. Yield, 32.5%; yellow solid; mp 108.6–110.1°C;^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.550 (d, J = 7.2 Hz, 3H, CH_3), 2.186 (s, 3H, CH_3), 2.783 (s, 3H, CH_3), 3.541 (q, J = 7.2 Hz, 1H, CH), 7.368–7.412 (m, 3H, Ph H), 7.531–7.576 (m, 2H, Ph H), 7.609 (s, 1H, Thiazole H). ^{13}C NMR, δ: 14.10, 16.17, 19.14, 41.68, 76.58, 118.26, 121.44, 126.37, 128.98, 129.41, 130.80, 131.57, 145.21, 146.16, 149.23, 158.59, 168.75, 169.83,170.27. LC–MS

(APCI, Pos) *m*/*z*: 496 $[M + H]^+$. Elemental *Anal*. (%) Calcd for $C_{21}H_{16}F_3N_3O_2S_3$: C 50.90, H 3.25, N 8.48; found C 50.81, H 3.34, N 8.18.

11c:(Z)-2-cyano-1-(2-methyl-4-(trifluoromethyl)thiazol-5-yl)-2-(2-phenylthiazol-4-yl)vinyl 2-(propylthio)propanoate. Yield, 37.8%; yellow solid; mp 100.0–101.0°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 0.931–1.021 (m, 3H, CH_3), 1.549 (d, *J* = 7.2 Hz, 3H, CH_3), 1.579–1.705 (m, 2H, CH_2), 2.559–2.660 (m, 2H, CH_2), 2.778 (s, 3H, CH_3), 3.560 (q, *J* = 7.5 Hz, 1H, CH), 7.366–7.428 (m, 3H, Ph H), 7.531–7.567 (m, 2H, Ph H), 7.599 (s, 1H, Thiazole H). ^{13}C NMR, δ: 13.29, 16.83, 19.11, 22.43, 33.58, 40.70, 76.58, 118.26, 121.39, 126.37, 128.97, 129.41, 130.80, 131.57, 145.23, 149.23, 158.59, 168.76, 169.10, 169.29, 170.24. LC–MS (APCI, Pos) *m*/*z*: 524 $[M + H]^+$. Elemental *Anal*. (%) Calcd for $C_{23}H_{20}F_3N_3O_2S_3$: C 52.76; H, 3.85; N, 8.03; found C 51.90, H 3.75, N 7.98.

11d:(Z)-2-cyano-1-(2-methyl-4-(trifluoromethyl)thiazol-5-yl)-2-(2-phenylthiazol-4-yl)vinyl 2-(methylthio)acetate. Yield, 41.3%; yellow solid; mp 108.0–109.0°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 2.185 (s, 3H, CH_3), 2.503 (s, 3H, CH_3), 3.414 (s, 2H, CH_2), 7.443–7.500 (m, 3H, Ph H), 7.591 (s, 1H, Thiazole H), 7.856–7.909 (m, 2H, Ph H). LC–MS (APCI, Pos) *m*/*z*: 482 $[M + H]^+$. Elemental *Anal*. (%) Calcd for $C_{20}H_{14}F_3N_3O_2S_3$: C 49.89, H 2.93, N 8.73; found C 49.78; H, 2.90 N, 8.65.

11e:(Z)-2-cyano-1-(2-methyl-4-(trifluoromethyl)thiazol-5-yl)-2-(2-phenylthiazol-4-yl)vinyl 2-(ethylthio)propanoate. Yield, 46.9%; yellow solid; mp 114.0–115.0°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.224 (q, *J* = 7.5 Hz, 3H, CH_3), 1.552 (d, *J* = 7.2 Hz, 3H, CH_3), 2.633–2.715 (m, 2H, CH_2), 2.777 (s, 3H, CH_3), 3.586 (q, *J* = 7.2 Hz, 1H, CH), 7.371–7.427 (m, 3H, Ph H), 7.532–7.568 (m, 2H, Ph H), 7.599 (s, 1H, Thiazole H). LC–MS (APCI, Pos) *m*/*z*: 510 $[M + H]^+$. Elemental *Anal*. (%) Calcd for $C_{22}H_{18}F_3N_3O_2S_3$: C 51.85, H 3.56, N 8.25; found C 51.74; H, 3.50; N, 8.14.

11f:(E)-2-cyano-1-(2-methyl-4-(trifluoromethyl)thiazol-5-yl)-2-(2-phenylthiazol-4-yl)vinyl 2,2-dimethyl-3-(methylthio) propanoate. Yield, 43.2%; brown solid; mp 104.0–105.0°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.308 (s, 6H, 2 CH_3), 2.117 (s, 2H, CH_2), 2.735 (s, 3H, CH_3), 2.809 (s, 3H, CH_3), 7.424–7.533 (m, 3H, Ph H), 7.820 (s, 1H, Thiazole H), 7.930–7.961 (m, 2H, Ph H). LC–MS (APCI, Pos) *m*/*z*: 524 $[M + H]^+$. Elemental *Anal*. (%) Calcd for $C_{23}H_{20}F_3N_3O_2S_3$: C 52.76, H 3.85,N 8.03; found C 51.90, H 3.75, N 7.98.

11g:(E)-2-cyano-1-(2-methyl-4-(trifluoromethyl)thiazol-5-yl)-2-(2-phenylthiazol-4-yl)vinyl (tetrahydrofuran-3-yl) carbonate. Yield, 32.7%; brown solid; mp 106.0–107.0°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 2.045–2.209 (m, 2H, CH_2), 2.797 (s, 3H, CH_3), 3.744–3.969 (m, 4H, 2 CH_2), 5.238–5.245 (m, 1H, CH), 7.450–7.567 (m, 3H, Ph H), 7.804 (s, 1H, Thiazole H), 7.939–7.971 (m, 2H, Ph H). LC–MS (APCI, Pos) *m*/*z*: 508 $[M + H]^+$. Elemental *Anal*. (%) Calcd for $C_{22}H_{16}F_3N_3O_4S_2$: C 52.07, H 3.18, N 8.28; found C 51.90, H 3.75, N 7.98.

11h:(Z)-2-cyano-1-(2-methyl-4-(trifluoromethyl)thiazol-5-yl)-2-(2-phenylthiazol-4-yl)vinyl cyclopentyl carbonate. Yield, 29.6%; yellow solid; mp 132.0–133.0°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.633–1.916 (m, 8H, 4 CH_2), 2.780 (s, 3H, CH_3), 5.158–5.212 (m, 1H, CH), 7.340–7.442 (m, 3H, Ph H), 7.539–7.581 (m, 2H, Ph H), 7.603 (s, 1H, Thiazole H). LC–MS (APCI, Pos) *m*/*z*: 506 $[M + H]^+$. Elemental *Anal*. (%) Calcd for $C_{23}H_{18}F_3N_3O_3S_2$: C 54.65, H 3.59, N 8.31; found C 53.90, H 3.52, N 8.28.

11i:(E)-2-cyano-1-(2-methyl-4-(trifluoromethyl)thiazol-5-yl)-2-(2-phenylthiazol-4-yl)vinyl cyclopentyl carbonate. Yield, 40.8%; yellow solid; mp 105.0–106.0°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.564–1.868 (m, 8H, 4 CH_2), 2.806 (s, 3H, CH_3), 5.120–5.148 (m, 1H, CH), 7.438–7.487 (m, 3H, Ph H), 7.788 (s, 1H, Thiazole H), 7.959–7.992 (m, 2H, Ph H). LC–MS (APCI, Pos) *m*/*z*: 506 $[M + H]^+$. Elemental *Anal*. (%) Calcd for $C_{23}H_{18}F_3N_3O_3S_2$: C 54.65, H 3.59, N 8.31; found C 52.98, H 3.48, N 8.28.

11j:(E)-1-(2-bromo-4-(trifluoromethyl)thiazol-5-yl)-2-cyano-2-(2-phenylthiazol-4-yl)vinyl 2-(methylthio)propanoate. Yield, 40.3%; yellow solid; mp 108.0–109.0°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.457 (d, *J* = 6.9 Hz, 3H, CH_3), 2.215 (s, 3H, CH_3), 3.347 (q, *J* = 7.2 Hz, 1H, CH), 7.466 (s, 1H, Thiazole H), 7.520–7.544 (m, 3H, Ph H), 7.886–7.913 (m, 2H, Ph H). LC–MS (APCI, Pos) *m*/*z*: 560 $[M + H]^+$. Elemental *Anal*. (%) Calcd for $C_{20}H_{13}BrF_3N_3O_2S_3$: C 42.86, H 2.34, N 7.50; found C 42.76, H 2.23, N 7.38.

11k:(E)-1-(2-chloro-4-(trifluoromethyl)thiazol-5-yl)-2-cyano-2-(2-phenylthiazol-4-yl)vinyl (tetrahydrofuran-3-yl) carbonate. Yield, 37.8%; yellow solid; mp 110.0–113.0°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 2.053–2.386 (m, 2H, CH_2), 3.793–3.988 (m, 4H, 2 CH_2), 5.268–5.298 (m, 1H, CH), 7.403–7.588 (m, 4H, Ph / Thiazole H), 7.928–7.967 (m, 2H, Ph H). LC–MS (APCI, Pos) *m*/*z*: 528 $[M + H]^+$. Elemental *Anal*. (%) Calcd for $C_{21}H_{13}ClF_3N_3O_4S_2$:; found C 47.78, H 2.48, N 7.96 C 47.70, H 2.43, N 7.88.

11l:(E)-1-(2-chloro-4-(trifluoromethyl)thiazol-5-yl)-2-cyano-2-(2-phenylthiazol-4-yl)vinyl 2-(methylthio)propanoate. Yield, 43.8%; yellow solid; mp 90.0–92.0°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.560 (d, *J* = 7.2 Hz, 3H, CH_3), 2.195 (s, 3H, CH_3), 3.518 (q, *J* = 6.9 Hz, 1H, CH), 7.404–7.465 (m, 3H, Ph H), 7.533–7.564 (m, 2H, Ph H), 7.704 (s, 1H, Thiazole H). LC–MS (APCI, Pos) *m*/*z*: 516 $[M + H]^+$. Elemental *Anal*. (%) Calcd for $C_{20}H_{13}ClF_3N_3O_2S_3$: C 46.56, H 2.54, N 8.14; found C 45.98, H 2.47, N 7.98.

11n:(E)-2-cyano-1-(2-methyl-4-(trifluoromethyl)thiazol-5-yl)-2-(2-phenylthiazol-4-yl)vinyl 3-chloro-2,2-dimethylpropanoate . Yield, 31.2%; yellow solid; mp 107.0–109.4°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm:1.326 (s, 6H, $2CH_3$), 2.797 (s, 3H, CH_3), 3.609 (s, 2H, CH_2), 7.425–7.497 (m, 3H, Ph H), 7.762 (s, 1H, Thiazole H), 7.900–7.941 (m, 2H, Ph H). LC–MS (APCI, Pos) *m*/*z*: 512 $[M + H]^+$. Elemental *Anal*. (%) Calcd for $C_{22}H_{17}ClF_3N_3O_2S_2$: C 51.61, H 3.35, N 8.21; found C 51.49, H 3.27, N 8.11.

11m:(Z)-2-cyano-1-(2-methyl-4-(trifluoromethyl)thiazol-5-yl)-2-(2-phenylthiazol-4-yl)vinyl 2-bromopropanoate. Yield, 44.6%; yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.844 (d, J = 7.2 Hz, 3H, CH_3), 2.814 (s, 3H, CH_3), 4.376 (q, J = 6.9 Hz, 1H, CH), 7.498–7.583 (m, 3H, Ph H), 7.628 (s, 1H, Thiazole H), 7.884–7.924 (m, 2H, Ph H). LC–MS (APCI, Pos) *m*/*z*: 528 $[M + H]^+$. Elemental *Anal*. (%) Calcd for $C_{20}H_{13}BrF_3N_3O_2S_2$:; found C 45.47, H 2.48, N 7.95 C 45.36, H 2.45, N 7.89.

11o:(E)-1-(2-chloro-4-(trifluoromethyl)thiazol-5-yl)-2-cyano-2-(2-phenylthiazol-4-yl)vinyl 2-(ethylthio)propanoate. Yield, 34.2%; brown oil; ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.233–1.349 (m, 3H, CH_3), 1.563 (d, J = 6.9 Hz, 3H, CH_3), 2.665–2.694 (q, 2H, CH_2), 3.608 (q, J = 7.2 Hz, 1H, CH), 7.522–7.563 (m, 3H, Ph H), 7.700 (s, 1H, Thiazole H), 7.889–7.921 (m, 2H, Ph H). LC–MS (APCI, Pos) *m*/*z*: 530 $[M + H]^+$. Elemental *Anal*. (%) Calcd for $C_{21}H_{15}ClF_3N_3O_2S_3$: C 47.59, H 2.85, N 7.93; found C 47.39, H 2.82, N 7.89.

11p:(E)-1-(2-chloro-4-(trifluoromethyl)thiazol-5-yl)-2-cyano-2-(2-phenylthiazol-4-yl)vinyl cyclopentyl carbonate. Yield, 37.8%; yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.254–1.285 (m, 2H, CH_2), 1.622–1.677 (m, 2H, CH_2), 1.779–1.896 (m, 4H, 2 CH_2), 5.146–5.166 (m, 1H, CH), 7.428–7.535 (m, 3H, Ph H), 7.826 (s, 1H, Thiazole H), 7.955–7.987 (m, 2H, Ph H). LC–MS (APCI, Pos) *m*/*z*: 526 $[M + H]^+$. Elemental *Anal*. (%) Calcd for $C_{22}H_{15}ClF_3N_3O_3S_2$: C 50.24, H 2.87, N 7.99; found C 50.01, H 2.77, N 7.89.

11q:(Z)-1-(2-chloro-4-(trifluoromethyl)thiazol-5-yl)-2-cyano-2-(2-phenylthiazol-4-yl)vinyl cyclopentyl carbonate. Yield, 27.5%; white solid; m. p. 147.0–148.9°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.253–1.286 (m, 2H, CH_2), 1.644–1.670 (m, 2H, CH_2), 1.881–1.944 (m, 4H, $2CH_2$), 5.203–5.216 (m, 1H, CH), 7.401–7.430 (m, 3H, Ph H), 7.533–7.566 (m, 2H, Ph H), 7.705 (s, 1H, Thiazole H). LC–MS (APCI, Pos) *m*/*z*: 526 $[M + H]^+$. Elemental *Anal*. (%) Calcd for $C_{22}H_{15}ClF_3N_3O_3S_2$: C 50.24, H 2.87, N 7.99; found C 50.09, H 2.76, N 7.89.

11r:(E)-1-(2-bromo-4-(trifluoromethyl)thiazol-5-yl)-2-cyano-2-(2-phenylthiazol-4-yl)vinyl 2-methyl-2-(methylthio)propanoate. Yield, 39.0%; white solid; m. p. 147.0–148.9°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.296 (s, 6H, $2CH_3$), 2.158 (s, 3H, CH_3), 7.461 (s, 1H, Thiazole H), 7.515–7.541 (m, 3H, Ph H), 7.881–7.907 (m, 2H, Ph H). LC–MS (APCI, Pos) *m*/*z*: 574 $[M + H]^+$. Elemental *Anal*. (%) Calcd for $C_{21}H_{15}BrF_3N_3O_2S_3$: C 43.91, H 2.63, N 7.32; found C 43.88, H 2.69, N 7.27.

Biological assay. Biological assay was carried out in the Laboratory of Biological Activities Test, Hunan Research Institute of Chemical Industry, Changsha, People's Republic of China. The biological evaluation of **11a–r** was undertaken according to the mortality rate.

Target insects. Stock colonies of *Aphis fabae* were reared in a conditioned room maintained at 25 (±5)°C, 65 (±5)% relative humidity and 12/12 h light: dark photoperiod.

Test methods. Test compounds were dissolved in DMF (0.2%) and then diluted to the required test concentrations with water containing Tween-80 (0.2%) [19].

The horse bean seedlings with *Aphis fabae* were dipped in the test solutions for 5–10 s, then allowed to dry with filter paper, transferred to a beaker (100 mL) containing water (10 mL), and kept at 25°C. Each assay contained three replications. After 24 h, mortality was recorded. The test was run three times, and results were averaged. The dose–response data were analyzed by probit analysis [20], and the activities were evaluated as LC_{50} values.

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