Design, Synthesis, and Acaricidal Activities of Novel Pyrazole Acrylonitrile Compounds

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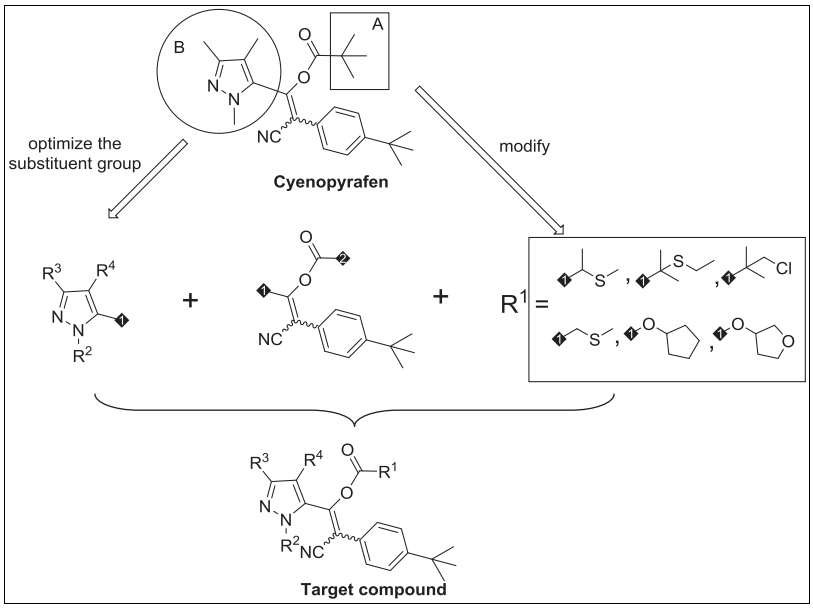


Using cyenopyrafen as the lead compound, a series of novel pyrazole acrylonitrile compounds were designed and synthesized via the reaction of butylphenylacetonitrile with the corresponding (substituted pyrazol-5-yl) methanone of pyrethroid alcohols in the presence of potassium tert-butoxide. These compounds showed prominent acaricidal activity against *Tetranchus urticae*. In particular, **IIf**, **IIh**, **IIo**, and **IIp** displayed excellent activities, which the median lethal concentrations were all lower 0.4 mg/L. In addition, the structure-activity relationship for the target compounds was discussed.

INTRODUCTION

Plant diseases pose threat to crop production and limit the development of agriculture worldwide. Pesticides applications in the recent agricultural system have effectively controlled many plant diseases; however, increasing resistances to current pesticides demands the development of new pesticides with excellent bioactivities [1,2]. Two novel classes of compounds, pyrazole compounds and acrylonitrile compounds, have become increasingly popular in the search of new pesticides. Pyrazole compounds are known for high biological activity, low toxicity, broad-spectrum, and structural changes. Numerous pyrazole derivatives have been developed as pesticides up to now. Among these compounds, fluazolate [3], fenpyroximate [4,5], fipronil [6], and pyraclostrobin [7], are all commercialization, which are widely used as herbicide, insecticide, and fungicide. Moreover, more and more novel pyrazole derivatives have been discovered to be excellent pesticide [8–10]. Acrylonitrile compounds have attracted attention because of the novel structure, high activity, low toxicity on mammals and fish, and no cross-resistance to existing insecticides. One of the best known acrylonitrile derivatives is cyenopyrafen (compound **I** in Fig. 1), which integrates the advantages of pyrazole compounds and acrylonitrile compounds and possesses high safety level on beneficial insects and high acaricidal activity [11]. Cyenopyrafen displays excellent bioactive to controlling spider mites (*Tetranychus*, *Oligonychus*, and *Panonychus*) during all life

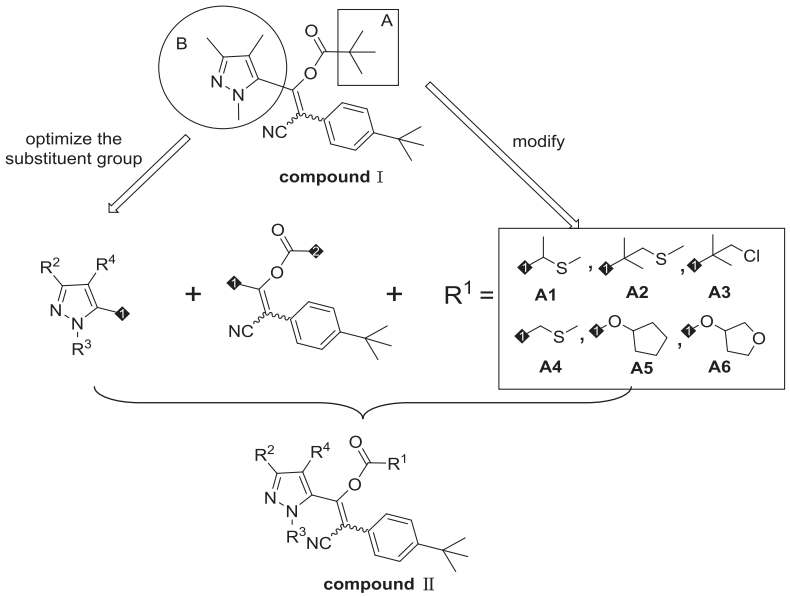


Figure 1. Molecular designs of compounds **I** to **II**.

stages, although some *Tetranchus urticae* strains might prossess cross-resistance [12].

Motivated by the aforementioned findings, we considered of using cyenopyrafen as a lead compound to design and synthesize several novel pesticides (Fig. 1), with the inhibition of microbial mitochondrial respiration as their primary mechanism of action [13,14]. Here are reported the design and syntheses of a series of 25 unreported cyenopyrafen derivatives (**II**) by using pro-drug theory, analogue synthesis, and sub-structure theory. As shown in Figure 1, moiety A was substituted to another six groups that were isosteres each other. Meanwhile, R^2, R^3, and R^4 of moiety B were optimized as well. To search for novel cyenopyrafen analogues with unique biological activities, a synthetic screening program was carried out around commercialized **I** and **II**. Besides, based on structural features of the commercialized cyenopyrafen, which exhibit remarkable acaricidal activities, the group of R^1, R^2, R^3, and R^4 of **II** was modified in order to study their structure–activity relationship.

RESULTS AND DISCUSSION

Synthesis. A series of novel pyrazole acrylonitrile derivatives **IIa–y** were designed and synthesized (Table 1). Their syntheses were summarized in Schemes 1 and 2; there were two routes to synthesize the key intermediate **5** (Scheme 2). Although route 1 was simpler than route 2, route 2 was used to synthesize intermediate **5** because we found that the yields of route 2 were higher than that of route 1. The structures of target **IIa–y** were determined by ^{1}H NMR.

Intermediate **5** undergo route 1 or route 2, yielding a mixture of the two isomeric products *E* and Z form, respectively. Intermediate **5** was not purified and next reaction was carried out, yielding target compounds of *E* and *Z* form. These are readily separable by column chromatography on silica gel. For unambiguous structure elucidation, we analyze ^{1}H NMR spectroscopy of **IIa–y**. According to the literature [11], the phenyl group of *E* isomer gives resonance frequencies above 7.40 ppm, whereas the corresponding signals of *Z* form were found below 7.35 ppm.

Acaricidal activities. In primary screening, all the compounds were active except **IIj** and **IIy** with over 95% mortality against *T. urticae* at 500 mg/L. All the compounds were screening at 12.5 mg/L further, and the result was shown in Table 1. Parts of the compounds with high acaricidal activities were singled out to calculate the regression equation, and the median lethal concentration (LC_{50}) value for these compounds was shown in Table 2. It was revealed that most of **II** exhibited high acaricidal activities against *T. urticae*. In particular, **IIf**, **IIh**, **IIo**, and **IIp** display excellent activities, which the LC_{50} was all lower 0.4 mg/L. Moreover, to our amazement, when **IIe** was mixed with the equal amount of **IIf**, the LC_{50} was decreased to 0.358 mg/L, and the acaricidal activity of this isomer-mixture was higher than that of each of them. To our delight, we achieved some compounds (**IIf**, **IIh**, **IIo**, **IIp**, and mixture of **IIe** and **IIf**) to defend *T. urticae* efficiently, which the acaricidal activities were similar to commercialized cyenopyrafen.

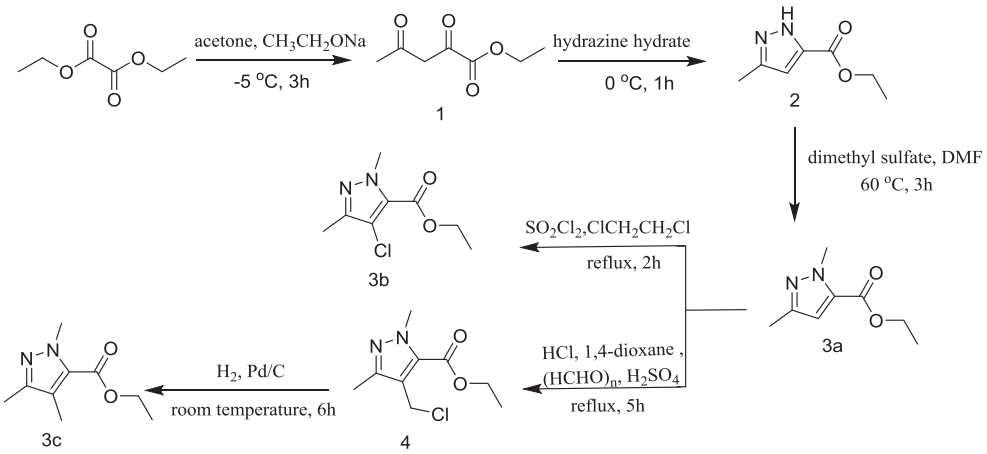
Structure–activity relationships. The activities of the compounds **IIa–y** depended on the R^1, R^3, and R^4 moiety. As we can see in Table 2, R^1 has an important effect on the activity: kept R^2, R^3, and R^4 as CH_3, when

Table 1

Acaricidal activities of the **I** and **IIa–y** against *Tetranchus urticae* at the test concentration of 12.5 mg/L.

No.	*Z*/*E* isomer	R^1	R^2	R^3	R^4	Test concentration (12.5 mg/L)
IIa	*Z*	A1	CH_3	CH_3	CH_3	100
IIb	*E*	A1	CH_3	CH_3	CH_3	100
IIc	*E*	A4	CH_3	CH_3	CH_3	100
IId	*E*	A2	CH_3	CH_3	CH_3	100
IIe	*Z*	A5	CH_3	CH_3	CH_3	100
IIf	*E*	A5	CH_3	CH_3	CH_3	100
IIg	*E*	A6	CH_3	CH_3	CH_3	86.22
IIh	*Z*	A3	CH_3	CH_3	CH_3	100
IIi	*E*	A1	CH_3	CH_3	H	72.23
IIj	*E*	A2	CH_3	CH_3	H	64.82
IIk	*Z*	A5	CH_3	CH_3	H	98.3
IIl	*E*	A5	CH_3	CH_3	H	98.41
IIm	*Z*	A6	CH_3	CH_3	H	99.14
IIn	*E*	A6	CH_3	CH_3	H	100
IIo	*E*	A3	CH_3	CH_3	Cl	96.05
IIp	*E*	A1	CH_3	CH_3	Cl	94.39
IIq	*Z*	A3	CH_3	CH_2CH_3	H	95.54
IIr	*E*	A1	CH_3	CH_2CH_3	H	99.59
IIs	*E*	A5	CH_3	CH_2CH_3	H	No test
IIt	*Z*	A6	CH_3	CH_2CH_3	H	100
IIu	*E*	A6	CH_3	CH_2CH_3	H	90.03
IIv	*E*	A6	CH_3	CH_2CH_3	Cl	93.33
IIw	*E*	A1	CH_3	CH_2CH_3	Cl	100
IIx	*E*	A2	CH_3	CH_2CH_3	Cl	100
IIy	*E*	A3	CH_2CH_3	CH_3	Cl	55.60
I(Z)	*Z*	tertiary butyl	CH_3	CH_3	CH_3	
I(E)	*E*	tertiary butyl	CH_3	CH_3	CH_3	

Scheme 1. Synthetic pathway to compound **3a–c**.



R^1 = 1-chloro-tert-butyl(A3), the compound (**IIh**) showed the highest activity; R^1 = cyclopentane-yl(A5), the compound (**IIf**) had good activity; R^1 = substituent-sulfane-yl, the compound (**IIa–d**) showed moderate activity. In general, for the synthesized compounds, the activity order for R^1 is 1-chloro-tert-butyl(A3) > cyclopentane-yl(A5). >substituent-sulfane-yl(A1, A2 or A4). Both R^3 and R^4 also affect the activity considerably: for the same R^1 (e.g., R^1 = ethyl(methyl)sulfane-3-yl), when $R^3 = CH_3$ and R^4 = Cl, the activity of the compound (**IIp**) was better than that of another substituent compound (**IIa**, **IIr**, and **IIw**).

It seems that the cis-trans isomers of compounds affect insecticidal activities unregularly. But we were surprised to find that the acaricidal activities of *E/Z* isomer mixture were higher than that of either *E* isomer or *Z* isomer existed individually, when this pair of *E/Z* isomer was mixed equally. For instance, when **IIe** was mixed with the equal amount of **IIf**, the LC_{50} was decreased to 0.358 mg/L that was lower both 0.414 mg/L of **IIe** and 0.364 mg/L of **IIf**.

Scheme 2. Synthetic pathway to compound **IIa–y**.

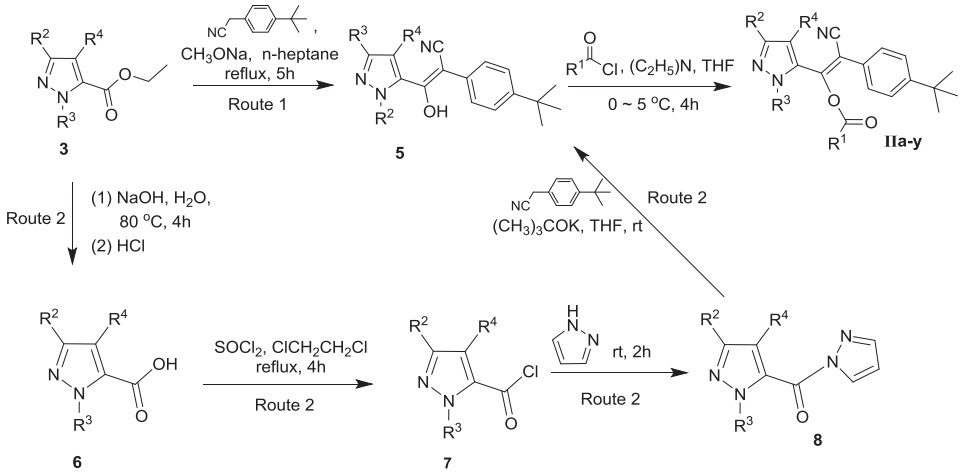


Table 2

Median lethal concentration (LC_{50}) of the target compounds against *Tetranchus urticae*.

Compound	Regression equation	Correlation	LC_{50} (mg/L)
IIa	$Y = 4.9113 + 2.5860x$	0.9697	1.08
IId	$Y = 4.6840 + 2.1718x$	0.9846	1.40
IIe	$Y = 5.8415 + 2.1995x$	0.9760	0.414
IIf	$Y = 5.8096 + 1.8420x$	0.9527	0.364
IIh	$Y = 6.1553 + 2.2927x$	0.9703	0.313
IIm	$Y = 5.0499 + 2.7971x$	0.9322	0.960
IIn	$Y = 5.0887 + 2.7174x$	0.9873	0.928
IIo	$Y = 6.0704 + 2.1887x$	0.9821	0.324
IIp	$Y = 6.8171 + 3.5426x$	0.9635	0.307
IIq	$Y = 5.1560 + 2.6318x$	0.9636	0.872
IIr	$Y = 4.5261 + 2.0691x$	0.9555	1.69
IIt	$Y = 5.4509 + 1.6726x$	0.9846	0.538
IIu	$Y = 4.2751 + 1.8975x$	0.9857	2.41
IIv	$Y = 4.9503 + 1.8083x$	0.9829	1.07
IIw	$Y = 4.6833 + 2.1541x$	0.9818	1.40
IIx	$Y = 4.5779 + 2.2126x$	0.9805	1.55
IIe/IIf (1:1)	$Y = 5.9581 + 2.1481x$	0.9875	0.358
I (Z)	$Y = 6.8386 + 2.7374x$	0.9710	0.213
I (E)	$Y = 6.8438 + 3.2561x$	0.9759	0.272

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 pyrazole acrylonitrile derivatives were synthesized, and their acaricidal activities were evaluated. The results of bioassays indicated that most of these title compounds exhibit higher acaricidal activities. In particulate, **IIe**, **IIf**, **IIh**, **IIo**, and **IIp** displayed excellent activities, which the median lethal concentration is 0.364 mg/L, 0.313 mg/L, 0.324 mg/L, and 0.307 mg/L. Structure–activity relationships indicated that R^1 has an important effect on the activity, and activity order for R^1 is 1-chloro-tert-butyl(A3) > cyclopentane-yl(A5). >substituent-sulfane-yl(A1, A2 or A4).

EXPERIMENTAL

Materials and methods. Melting points (m.p.) were measured on a WPS-1B melting-point apparatus (made in Shanghai Physical Optics Instrument Plant, Shanghai, China) and are uncorrected; ^{1}H NMR spectra were recorded in $CDCl_3$ with a Varian INOVA-300, using TMS as internal standard; infrared spectra were acquired on a PE System 2000 FT-IR spectrophotometer using KBr discs; high resolution mass spectra were acquired using a Agilent 5973-6890 gas chromatography-mass spectrometer (GC-MS) and a Agilent 1100 series liquid chromatography-mass spectrometer (LC-MS). Column chromatography was performed using 200–300 mesh silica gel. The solvents and reagents were used as received or were dried prior to use as needed.

Synthetic chemistry details

Synthesis of ethyl 2,4-dioxovalerate 1. In 300 mL of anhydrous ethanol was dissolved sodium ethylate (0.45 mol) with stirred below −10°C. Then the mixture solution of acetone (0.35 mol) and diethyl oxalate (0.37 mol) was added slowly, and keep the reaction temperature below −5°C for 3 h. The mixture was poured into ice water. After using HCl (1 mol/L) to keep pH around 4, the aqueous phase was extracted with ethyl acetate (EA). The organic layer was washed twice with water and dried over Na_2SO_4, filtered, and concentrated under reduced pressure, 48.70 g (88% yeild, 96% purity); yellow liquid was obtained.

Synthesis of ethyl 3-methyl-1H-pyrazole-5-carboxylate 2. In 300 mL of anhydrous ethanol was dissolved **1** (0.3 mol) with stirred below −5°C. Then hydrazine

hydrate (0.375 mol) was added slowly, and the solution was stirred below 0°C for 1 h. The solvent was removed under reduced pressure, and the aqueous phase was extracted with EA. The organic layer was washed twice with water and dried over Na_2SO_4, filtered, and concentrated under reduced pressure, 42.50 g (92% yeild, 90% purity); yellow solid was obtained, m.p. 80–82°C.

Synthesis of ethyl 1,3-dimethyl-1H-pyrazole-5-carboxylate 3a. In 120 mL of *N,N*-dimethylformamide (DMF) was dissolved **2** (10 g, 0.065 mol) and dimethyl sulfate (9.83 g,0.078 mol), and the solution was stirred at 60°C for 3 h. The progress of the reaction was monitored by thin layer chromatograph (TLC). After complete disappearance of the starting material, the solution was extracted with EA. The organic layer was washed twice with water and dried over Na_2SO_4, filtered, and concentrated under reduced pressure, 10.28 g (90% yeild, 85% purity); brown liquid was obtained.

Synthesis of ethyl 1,3-dimethyl-4-chlorine-1H-pyrazole-5-carboxylate 3b. SO_2Cl_2 (8.04 g, 0.06 mol) was slowly added to a stirred mixture of **3a** (10 g, 0.06 mol) and $ClCH_2CH_2Cl$ (50 mL) in ice bath. Then the solution was stirred under reflux for 2 h. The solvent was removed under reduced pressure, and the mixture was poured into NaCl solution. Then the aqueous phase was extracted with EA. The organic layer was washed twice with water and dried over Na_2SO_4, filtered, and concentrated under reduced pressure, 10.8 g (95% yeild, 94% purity); brown liquid was obtained.

Synthesis of ethyl 1,3-dimethyl-4-chloromethyl-1H-pyrazole-5-carboxylate 4. Paraformaldehyde (3.6 g, 0.12 mol), 1,4-dioxane (100 mL), and **3a** (10 g, 0.06 mol) were successively added to a stirred mixture of H_2SO_4 (0.6 g, 0.006 mol) and concentrated hydrochloric acid (12 g, 12 mol). After 5 h under reflux, the solvent was removed under reduced pressure, and the mixture was poured into ice water. Then the aqueous phase was extracted with EA. The organic layer was washed twice with water and dried over Na_2SO_4, filtered, and concentrated under reduced pressure, 9.07 g (70% yeild, 80% purity); yellow solid was obtained.

Synthesis of ethyl 1,3,4-trimethyl-1H-pyrazole-5-carboxylate 3c. The 5% Pd/C catalyst (0.54 g) and **4** (10.8 g, 0.05 mol) were, respectively, added to a stirred mixture of ethanol (50 mL) and water (mL), which were carried out in hydrogen atmosphere at room temperature for 6 h. After filtered the catalyst, the mixture solutions were poured into water, and then the aqueous phase was extracted with EA. The organic layer was washed with water and dried over Na_2SO_4, filtered, and concentrated under reduced pressure, 9.07 g (80% yeild, 90% purity); brown liquid was obtained.

Synthesis of 2-(4-(tert-butyl) phenyl)-3-hydroxy-3-(substituted pyrazol- 5-yl) acrylonitrile 5 (route 1). According to the literature [11], the butylphenylacetonitrile (3.80 g, 0.022 mol), ethylene glycol monomethylether (2 mL), *n*-heptane (50 mL), and **3** (, 0.022 mol) were mixed sufficiently for 0.5 h. After 1 h under reflux, 30% sodium methylate solutions (6.20 g, 0.03 mol) were added dropwise. Keep reflux for 5 h, and then the reaction solution was poured into ice water, and the mixture was extracted with EA to remove organic impurity. The aqueous phase was used HCl (1 mol/L) to keep weak acidity. Then the solutions were extracted with EA again. The organic layer was washed twice with water and dried over Na_2SO_4, filtered, and concentrated under reduced pressure; brown liquid was obtained (76–83% yeild).

Synthesis of substituted pyrazol carboxylic acid 6. Compound **3** (0.05 mol) was added to a stirred mixture of NaOH (6.0 g, 0.15 mol) and water (100 mL). After 4 h under 80°C, the mixture was poured into ice water and adjusts the pH to acidic. Then 10% HCl was slowly add to the solutions until precipitate large amount of solids. Filtered and the solids was dried, yield 70–79%.

Synthesis of substituted pyrazol acyl chloride 7. Compound **6** (0.04 mol) and thionyl chloride (9.5 g, 0.08 mol) were successively added to 100 mL 1,2-dichloroethane. After 4 h under reflux, the solvent was removed under reduced pressure; **7** was obtained, yield 78–89%.

Synthesis of (1H-pyrazol-1-yl) (substituted pyrazol-5-yl) methanone 8. Compound **7** (0.08 mol) and thionyl chloride (9.5 g, 0.08 mol) were successively added to 100 mL dichloromethane under room temperature for 2 h. Then the mixture was poured into water; the solutions were extracted with dichloromethane and dried over Na_2SO_4, filtered, and concentrated under reduced pressure; **8** was obtained, yield 91–95%.

Synthesis of 2-(4-(tert-butyl)phenyl)-3-hydroxy-3-(substituted pyrazol-5-yl)acrylonitrile 5 (route 2). Compound **8** (0.024 mol), 2-(4-(tert-butyl) phenyl) acetonitrile (4.20 g, 0.024 mol), and 30 mL tetrahydrofuran (THF) were mixed homogeneously in ice bath for 10 min. Then potassium tert-butoxide (0.026 mol) was slowly added to the mixture under 5°C, and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After complete disappearance of the starting material, the reaction solution was poured into ice water, and the mixture was extracted with EA to remove organic impurity. The aqueous phase was used HCl (1 mol/L) to keep weak acidity. Then the solutions were extracted with EA again. The organic layer was washed twice with water and dried over Na_2SO_4, filtered, and concentrated under reduced pressure; **5** was obtained, yield 76–80%.

Synthesis of 2-(4-(tert-butyl) phenyl)-3-hydroxy-3-(substituted pyrazol-5-yl) acrylonitrile IIa–y. Compound **5** (0.005 mol), THF (30 mL), and triethylamine (0.005 mol) were mixed homogeneously in ice bath for 10 min. Then substituted acyl chloride (0.01 mol) was added to the mixture dropwise

and, keep the reaction temperature below 5°C for 4 h. The reaction solution was poured into ice water, and the mixture was extracted with EA. The organic layer was washed twice with water and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, using petroleum ether and EA (30:1 v/v) as the eluent, to obtain **IIa–y** white, yellow, or brown oil.

IIa: yield, 27%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.269 (s, 9H, $3CH_3$), 1.546 (d, J = 6.9 Hz, 3H, CH_3), 1.904 (s, 3H, CH_3), 2.063 (s, 3H, CH_3), 2.163 (s, 3H, CH_3), 3.458 (s, 3H, CH_3), 3.528 (q, J = 7.2 Hz, H, CH), 7.045 (d, J = 9.0 Hz, 2H, Ph H), 7.291 (d, J = 8.4 Hz, 2H, Ph H). purity, 95% (high-performance liquid chromatography, HPLC); GC-MS $M^+ = 411$. *Anal.* calcd for $C_{23}H_{29}N_3O_2S$: C, 67.12; H, 7.10; N, 10.21. Found: C, 67.10; H, 7.20; N, 10.25.

IIb: yield, 25%. brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.340 (s, 9H, $3CH_3$), 1.394 (d, J = 7.2 Hz, 3H, CH_3), 1.849 (s, 3H, CH_3), 2.123 (s, 3H, CH_3), 2.219 (s, 3H, CH_3), 3.359 (q, J = 7.2 Hz, 1H, CH), 3.934 (s, 3H, CH_3), 7.446–7.476 (m, 2H, Ph H), 7.567 (d, J = 8.7 Hz, 2H, Ph H). purity, 97% (HPLC). GC-MS $M^+ = 411$. *Anal.* calcd for $C_{23}H_{29}N_3O_2S$: C, 67.12; H, 7.10; N, 10.21. Found: C,67.07; H, 7.33; N, 10.15.

IIc: yield, 25%. brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.340 (s, 9H, $3CH_3$), 1.975 (s, 3H, CH_3), 2.112 (s, 3H, CH_3), 2.201 (s, 3H, CH_3), 3.223 (s, 2H, CH_2), 3.907 (s, 3H, CH_3), 7.451 (d, J = 8.7 Hz, 2H, Ph H), 7.559 (d, J = 8.7 Hz, 2H, Ph H). purity, 93% (HPLC). GC-MS $M^+ = 397$. *Anal.* calcd for $C_{22}H_{27}N_3O_2S$: C, 66.47; H, 6.85; N, 10.57. Found: C, 66.50; H, 6.86; N, 10.50.

IId: yield, 25%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.220 (s, 6H, $2CH_3$), 1.388 (s, 9H, $3CH_3$), 1.974 (s, 3H, CH_3), 2.107 (s, 3H, CH_3), 2.201 (s, 3H, CH_3), 2.644 (s, 2H, CH_2), 3.971 (s, 3H, CH_3), 7.439–7.541 (m, 4H, Ph H). purity, 96% (HPLC). GC-MS $M^+ = 439$. *Anal.* calcd for $C_{25}H_{33}N_3O_2S$: C, 68.30; H, 7.57; N, 9.56. Found: C, 68.67; H, 7.47; N, 9.43.

IIe: yield, 24%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.275 (s, 9H, CH_3), 1.594–1.854 (m, 8H,$4CH_2$), 1.867 (s, 3H, CH_3), 2.180 (s, 3H, CH_3), 3.427 (s, 3H, CH_3), 5.106–5.124 (m, 1H, CH), 7.047–7.083 (m, 2H, Ph H), 7.285–7.322 (m, 2H, Ph H). purity, 97% (HPLC). LC-MS Pos $[M+1]^+ = 422$. *Anal.* calcd for $C_{25}H_{31}N_3O_3$: C, 71.23; H, 7.41; N, 9.97. Found: C, 71.19; H, 7.40; N, 9.99.

IIf: yield, 31%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.344 (s, 9H, CH_3), 1.598–1.646 (m, 8H, $4CH_2$), 2.107 (s, 3H, CH_3), 2.219 (s, 3H, CH_3), 3.884 (s, 3H, CH_3), 5.099–5.112 (m, 1H, CH), 7.456–7.485 (m, 2H, Ph H), 7.574–7.603 (m, 2H, Ph H). purity, 95% (HPLC). LC-MS Pos $[M+1]^+ = 422$. *Anal.* calcd for $C_{25}H_{31}N_3O_3$: C, 71.23; H, 7.41; N, 9.97. Found: C, 71.23; H, 7.41; N, 9.97.

IIg: yield, 25%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.345 (s, 9H, $3CH_3$), 1.850–1.929 (m, 2H, CH_2), 2.106 (s, 3H, CH_3), 2.221 (s, 3H, CH_3), 3.689–3.805 (m, 2H, CH_2), 3.821–3.878 (m, 2H, CH_2), 3.888 (s, 3H, CH_3), 5.133–5.139 (m, 1H, CH), 7.466 (d, J = 8.7 Hz, 2H, Ph H), 7.576–7.605 (m, 2H, Ph H). purity, 97% (HPLC). GC-MS $M^+ = 423$. *Anal.* calcd for $C_{24}H_{29}N_3O_4$: C, 68.06; H, 6.90; N, 9.92. Found: C, 68.36; H, 6.90; N, 9.92.

IIh: yield, 28%. white oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.228 (s, 6H, $2CH_3$), 1.336 (s, 9H, $3CH_3$), 2.102 (s, 3H, CH_3), 2.205 (s, 3H, CH_3), 3.514 (s, 2H, CH_2), 3.913 (s, 3H, CH_3), 7.263–7.497 (m, 4H, Ph H). purity, 96% (HPLC). GC-MS $M^+ = 427$. *Anal.* calcd for $C_{24}H_{30}ClN_3O_2$: C, 67.36; H, 7.07; N, 9.82. Found: C, 67.39; H, 7.27; N, 9.81.

IIi: yield, 21%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.334 (s, 9H, $3CH_3$), 1.370 (d, J = 6.9 Hz, 3H, CH_3), 1.874 (s, 3H, CH_3), 2.289 (s, 3H, CH_3), 3.341 (q, J = 7.2 Hz, 1H, CH), 3.996 (s, 3H, CH_3), 6.453 (d, J = 0.6 Hz, 1H, pyrazole H), 7.435 (d, J = 8.7 Hz, 2H, Ph H), 7.528–7.557 (m, 2H, Ph H). purity, 95% (HPLC). GC-MS $M^+ = 397$. *Anal.* calcd for $C_{22}H_{27}N_3O_2S$: C, 66.47; H, 6.85; N, 10.57. Found: C, 66.39; H, 6.79; N, 10.65.

IIj: yield, 25%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.209 (s, 6H, CH_3), 1.332 (s, 9H, CH_3), 2.007 (s, 3H, CH_3), 2.285 (s, 3H, CH_3), 2.647 (s, 2H, CH_2), 4.000 (s, 3H, CH_3), 6.353 (s, 1H, pyrazole H), 7.429–7.515 (m, 4H, Ph H). purity, 97% (HPLC). GC-MS $M^+ = 425$. *Anal.* calcd for $C_{24}H_{31}N_3O_2S$: C, 67.73; H, 7.34; N, 9.87. Found: C, 67.80; H, 7.30; N, 9.94.

IIk: yield, 32%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.281 (s, 9H, CH_3), 1.601–1.677 (m, 2H, CH_2), 1.701–1.898 (m, 6H, CH_2), 2.273 (s, 3H, CH_3), 3.267 (s, 3H, CH_3), 5.059–5.141 (m, 1H, CH), 6.282 (s, 1H, pyrazole H), 7.078 (d, J = 8.7 Hz, 2H, Ph H), 7.315 (d, J = 9.0 Hz, 2H, Ph H). purity, 95% (HPLC). LC-MS Pos $[M+1]^+ = 408$. *Anal.* calcd for $C_{24}H_{29}N_3O_3$: C, 70.74; H, 7.17; N, 10.31. Found: C, 70.82; H, 7.19; N, 10.30.

IIl: yield, 33%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.338 (s, 9H, CH_3), 1.546–1.809 (m, 8H, $4CH_2$), 2.301 (s, 3H, CH_3), 3.949 (s, 3H, CH_3), 4.992–5.030 (m, 1H, CH), 6.562 (d, J = 0.6 Hz, 1H, pyrazole H), 7.445 (d, J = 9.0 Hz, 2H, Ph H), 7.528–7.572 (m, 2H, Ph H). purity, 92% (HPLC). LC-MS Pos $[M+1]^+ = 408$. *Anal.* calcd for $C_{24}H_{29}N_3O_3$: C, 70.74; H, 7.17; N, 10.31. Found: C, 70.76; H, 7.11; N, 10.36.

IIm: yield, 26%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.284 (s, 9H, CH_3), 2.044–2.138 (m, 1H, CH_2), 2.154–2.250 (m, 1H, CH_2), 2.275 (s, 3H, CH_3), 3.267 (s, 3H, CH_3), 3.864–3.894 (m, 2H, CH_2), 3.912–3.960 (m, 2H, CH_2), 5.233–5.239 (m, 1H, CH), 6.291 (d, J = 0.6 Hz, 1H, pyrazole H), 7.081 (d, J = 8.7 Hz, 2H, Ph H), 7.332–7.351 (m, 2H, Ph H). purity, 93% (HPLC).

LC-MS Pos $[M+1]^+=410$. *Anal.* calcd for $C_{23}H_{27}N_3O_4$: C, 67.46; H, 6.65; N, 10.26. Found: C, 67.50; H, 6.72; N, 10.22.

IIn: yield, 26%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.341 (s, 9H, CH_3), 1.852–1.919 (m, 1H, 1/2CH_2), 2.080–2.160 (m, 1H, 1/2CH_2), 2.301 (s, 3H, CH_3), 3.671–3.818 (m, 2H, CH_2), 3.832–3.910 (m, 2H, CH_2), 3.954 (s, 3H, CH_3), 5.135–5.159 (m, 1H, CH), 6.548 (d, J = 0.3 Hz, 1H, pyrazole H), 7.458–7.570 (m, 4H, Ph H). purity, 96% (HPLC). LC-MS Pos $[M+1]^+=410$. *Anal.* calcd for $C_{23}H_{27}N_3O_4$: C, 67.46; H, 6.65; N, 10.26. Found: C, 67.54; H, 6.59; N, 10.18.

IIo: yield, 26%. yellow oil. ^{1}H NMR ($CDCl_3$ 300 MHz): 1.293 (s, 6H, 2CH_3), 1.341 (s, 9H, 3CH_3), 2.256 (s, 3H, CH_3), 3.574 (s, 2H, CH_2), 4.001 (s, 3H, CH_3), 7.457 (d, J = 8.7 Hz, 2H, Ph H), 7.542 (d, J = 9.0 Hz, 2H, Ph H). purity, 97% (HPLC). GC-MS $M^+=447$. *Anal.* calcd for $C_{23}H_{27}Cl_2N_3O_2$: C, 61.61; H, 6.07; N, 9.37. Found: C, 61.59; H, 6.12; N, 9.38.

IIp: yield, 25%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.343 (s, 9H, 3CH_3), 1.428 (d, J = 7.2 Hz, 3H, CH_3), 1.940 (s, 3H, CH_3), 2.262 (s, 3H, CH_3), 3.386 (q, J = 7.2 Hz, 1H, CH), 3.987 (s, 3H, CH_3), 7.459 (d, J = 9.0 Hz, 2H, Ph H), 7.623 (d, J = 9.0 Hz, 2H, Ph H). purity, 96% (HPLC). GC-MS $M^+=431$. *Anal.* calcd for $C_{22}H_{26}ClN_3O_2S$: C, 61.17; H, 6.07; N, 9.73. Found: C, 61.27; H, 6.12; N, 9.71.

IIq: yield, 23%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.218 (s, 6H, CH_3), 1.331 (s, 9H, CH_3), 1.525 (t, J = 7.2 Hz, 3H, CH_3), 2.302 (s, 3H, CH_3), 3.509 (s, 2H, CH_2), 4.243 (q, J = 7.5 Hz, 2H, CH_2), 6.335 (d, J = 0.6 Hz, 1H, pyrazole H), 7.455 (d, J = 1.8 Hz, 4H, Ph H). purity, 94% (HPLC). GC-MS $M^+=427$. *Anal.* calcd for $C_{24}H_{30}ClN_3O_2$: C, 67.36; H, 7.07; N, 9.82. Found: C, 67.38; H, 7.11; N, 9.77.

IIr: yield, 25%. brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.334 (s, 9H, CH_3), 1.366 (d, J = 6.9 Hz, 3H, CH_3), 1.497 (t, J = 7.5 Hz, 3H, CH_3), 1.856 (s, 3H, CH_3), 2.306 (s, 3H, CH_3), 3.308 (q, J = 7.2 Hz, 1H, CH), 4.227 (q, J = 7.2 Hz, 2H, CH_2), 6.447 (s, 1H, pyrazole H), 7.425–7.468 (m, 2H, Ph H), 7.523–7.566 (m, 2H, Ph H). purity, 96% (HPLC). GC-MS $M^+=411$. *Anal.* calcd for $C_{23}H_{29}N_3O_2S$: C, 67.12; H, 7.10; N, 10.21. Found: C, 67.08; H, 7.18; N, 10.1.

IIs: yield, 25%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.031 (t, J = 7.2 Hz, 3H, CH_3), 1.275 (s, 9H, CH_3), 1.598–1.662 (m, 2H, CH_2), 1.747–1.904 (m, 6H, CH_2), 2.279 (s, 3H, CH_3), 3.597 (q, J = 7.5 Hz, 2H, CH_2), 5.116–5.150 (m, 1H, CH), 6.222 (s, 1H, pyrazole H), 7.073–7.117 (m, 2H, Ph H), 7.298–7.342 (m, 2H, Ph H). purity, 95% (HPLC). GC-MS $M^+=421$. *Anal.* calcd for $C_{25}H_{31}N_3O_3$: C, 68.06; H, 6.90; N, 9.92. Found: C, 68.00; H, 6.93; N, 9.94.

IIt: yield, 27%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz):1.030 (t, J = 7.2 Hz, 3H,CH_3), 1.277 (s, 9H, CH_3), 2.153–2.204 (m, 2H, CH_2), 2.280 (s, 3H, CH_3), 3.609 (q, J = 7.2 Hz, 2H, CH_2), 3.868–3.895 (m, 2H, CH_2), 3.916–3.966 (m, 2H, CH_2), 5.233–5.241 (m, 1H, CH), 6.234 (s, 1H, pyrazole H), 7.084 (dd, J = 6.6, 2.1 Hz, 2H, Ph H), 7.311 (dd, J = 6.6, 1.8 Hz, 2H, Ph H). purity, 95% (HPLC). LC-MS Pos $[M+1]^+=424$. *Anal.* calcd for $C_{24}H_{29}N_3O_4$: C, 68.06; H, 6.90. Found: C, 68.11; H, 6.91; N, 9.85.

IIu: yield, 29%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.340 (s, 9H, CH_3), 1.463 (t, J = 7.2 Hz, 3H, CH_3), 1.855–2.145 (m, 2H, CH_2),2.313 (s, 3H, CH_3), 3.709–3.819 (m, 2H, CH_2), 3.832–3.869 (m, 2H, CH_2), 4.178 (q, J = 7.2 Hz, 2H, CH_2), 5.137 (d, J = 1.5 Hz, 1H, CH_2), 6.547 (s, 1H, pyrazole H), 7.454–7.568 (m, 4H, Ph H). purity, 95% (HPLC). LC-MS Pos $[M+1]^+=424$. *Anal.* calcd for $C_{24}H_{29}N_3O_4$: C, 68.06; H, 6.90; N, 9.92. Found: C, 68.07; H, 6.88; N, 9.86.

IIv: yield, 30%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.348 (s, 9H, CH_3), 1.462 (t, J = 6.9 Hz, 3H, CH_3) 2.093–2.205 (m, 2H, CH_2), 2.289 (s, 3H, CH_3), 3.754–3.945 (m, 4H, 2CH_2), 4.167 (q, J = 7.2 Hz, 2H, CH_2), 5.153–5.189 (m, 1H, CH), 7.480–7.515 (m, 2H, Ph H), 7.608 (dd, J = 6.6, 2.1 Hz, 2H, Ph H). purity, 98% (HPLC). LC-MS Pos $[M+1]^+=458$. *Anal.* calcd for $C_{24}H_{28}ClN_3O_4$: C, 62.95; H, 6.16; N, 9.18. Found: C, 63.01; H, 6.17; N, 9.15.

IIw: yield, 22%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.341 (s, 9H, CH_3), 1.418 (d, J = 6.9 Hz, 3H, CH_3), 1.494 (t, J = 7.2 Hz, 3H, CH_3), 1.918 (s, 3H, CH_3), 2.278 (s, 3H, CH3), 3.400 (q, J = 7.5 Hz, 1H, CH), 4.218 (q, J = 7.5 Hz, 2H, CH_2), 7.455 (dd, J = 6.9, 2.4 Hz, 2H, Ph H), 7.618 (dd, J = 6.6, 1.8 Hz, 2H, Ph H). purity, 97% (HPLC). GC-MS $M^+=445$. *Anal.* calcd for $C_{23}H_{28}ClN_3O_2S$: C, 61.94; H, 6.33; N, 9.42. Found: C, 61.98; H, 6.35; N, 9.34.

IIx: yield, 27%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.255 (s, 6H, CH_3), 1.340 (s, 9H, CH_3), 1.526 (t, J = 7.2 Hz, 3H,CH_3), 2.008 (s, 3H, CH_3), 2.271 (s, 3H, CH_3), 2.682 (s, 2H, CH_2), 4.228 (q, J = 7.2 Hz, 2H, CH_2), 7.451 (dd, J = 6.6, 1.8 Hz, 2H, Ph H), 7.562–7.591 (m, 2H, Ph H).purity, 94% (HPLC). GC-MS $M^+=473$. *Anal.* calcd for $C_{25}H_{32}ClN_3O_2S$: C, 63.34; H, 6.80; N, 8.86. Found: C, 63.30; H, 6.85; N, 8.88.

IIy: yield, 28%. yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.235–1.262 (m, 3H, CH_3), 1.287 (s, 6H, CH_3), 1.340 (s, 9H, CH_3), 2.635 (q, J = 7.8 Hz, 2H, CH_2), 3.560 (s, 2H, CH_2), 4.007 (s, 3H, CH_3), 7.453 (d, J = 8.7 Hz, 2H, Ph H), 7.537 (d, J = 8.7 Hz, 2H, Ph H). purity, 96% (HPLC). GC-MS $M^+=461$. *Anal.* calcd for $C_{24}H_{29}ClN_3O_2$: C, 62.34; H, 6.32; N, 9.09. Found: C, 62.29; H, 6.35; N, 9.11.

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 **IIa–y** was undertaken according to the mortality rate.

Insecticidal activities

Test insects. Stock colonies of *Mythimna separata, Aphis fabae*, and *T. urticae* were reared in a conditioned room maintained at 25 (±1) °C, 60 (±5)% relative humidity, and 14:10 h light : dark photoperiod.

Test compounds. Stock solutions of each test compound were prepared in acetone at a concentration of 1.0 g /L, and then diluted to the required test concentrations with water containing TritonX-100 (0.1 mL/L).

***Biological activity against Tetranchus urticae* [15].** Fifty larvae of *T. urticae* were transferred to three horse bean seedlings, and, 24 h later, the horse bean seedlings with acarids were dipped in the test solutions for 5–10 s, and 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. Mortality was assessed 24 h after the treatment. A number of live and dead insects were recorded. The test was run three times, and results were averaged. The dose–response data were analyzed by probit analysis [16], and the activities were evaluated as LC_{50} values (95% CL).

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REFERENCES AND NOTES

[1] Gisi, U.; Sierotzki, H. Eur J Plant Pathol 2008, 122, 157.
[2] Feng, J. T.; Wang, H.; Ren, S. X.; He, J.; Liu, Y.; Zhang, X. J Agric Food Chem 2012, 60, 3817.
[3] Paul, C. J.; Cameron, H. B.; Harold W. R. WO, 9602515. 1996.
[4] Swanson, M. B.; Ivancic, W. A.; Saxena, A. M.; Allton, J. D.; O'Brien, G. K.; Suzuki, T.; Nishizawa, H.; Nokata, M. J Agric Food Chem 1995, 43, 513.
[5] Motoba, K.; Nishizawa, H.; Suzuki, T.; Hamaguchi, H.; Uchida, M.; Funayama, S. Pestic Biochem Physiol 2000, 67, 73.
[6] Philipp, W. R.; Markus, B.; Hilmar, F. J Agric Food Chem 2011, 59, 4365.
[7] Fulcher, J. M.; Wayment, D. G.; White Jr., P. M.; Webber III, C. L. J Agric Food Chem 2014, 62, 2141.
[8] Wang, B. L.; Wu, J.; Liu, Q. X.; Li, Y. H.; Song, H. B.; Li, Z. M. Phosphorus Sulfur Silicon Relat Elem 2015, 190, 66.
[9] Wang, B. L.; Zhang, L. Y.; Zhan, Y. Z.; Zhang, Y.; Zhang, X.; Wang, L. Z.; Li, Z. M. J Fluorine Chem 2016, 184, 36.
[10] Wang, B. L.; Zhu, H. W.; Ma, Y.; Xiong, L. X.; Li, Q. Y.; Zhao, Y.; Zhang, J. F.; Chen, Y. W.; Zhou, S.; Li, Z. M. J Agric Food Chem 2013, 61, 5483.
[11] Yu, H. B.; Xu, M.; Cheng, Y.; Wu, H. F.; Luo, Y. M.; Li, B. ARKIVOC 2012, (vi), 26.
[12] Khalighi, M.; Tirry, L.; Van Leeuwen, T. Pest Manag Sci 2014, 70, 365.
[13] Nakahira, K. J Pestic Sci 2011, 36, 511.
[14] Hayashi, N.; Sasama, Y.; Takahashi, N.; Ikemi, N. Pest Manag Sci 2013, 69, 1080.
[15] Liu, A. P.; Wang, X. G.; Chen, C.; Pei, H. Pest Manag Sci 2009, 65, 229.
[16] Finney, J. (Ed) Probit Analysis, 3rd ed.; Cambridge University Press: Cambridge, UK, 1971.