# Design, synthesis, insecticidal activity and CoMFA study of novel pyrazole amides containing hydrazone substructure

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# Design, synthesis and insecticidal activities of novel pyrazole amides containing hydrazone substructures

**Jian Wu, Bao-An Song,* De-Yu Hu, Min Yue and Song Yang***

## Abstract

**BACKGROUND: Pyrazole and hydrazone derivatives possess good insecticidal activities; their substructural units are widely used in pesticide design. In an effort to discover new molecules with good insecticidal activities, a series of pyrazole amide derivatives containing hydrazone substructures were synthesised and bioassayed.**

**RESULTS: Bioassays demonstrated that some of the title compounds exhibited notable control of *Plutella xylostella* (Linnaeus), *Helicoverpa armigera* (Hübner), *Culex pipiens pallens, Laphygma exigua* (Hübner), *Spodoptera litura* (Fabricius), *Nilaparvata lugens* (Stål) and *Rhopalosiphum maidis* (Fitch) at 5, 10, 0.25, 200, 20, 100 and 500 mg $L^{-1}$ respectively. Comparative molecular field analysis (CoMFA) based on the bioactivities for *P. xylostella* was studied; the values of $q^2$ and $r^2$ for the CoMFA model were 0.701 and 0.964 respectively.**

**CONCLUSION: Some of the title compounds displayed good and broad-spectrum insecticidal activities against different insect species; the CoMFA model revealed that a bulky and negatively charged group at the 4-position of benzene could enhance insecticidal activity. These results could provide useful information for the design of novel insecticide containing substructural units of pyrazole amide and hydrazone.**


*Supporting information may be found in the online version of this article.*

**Keywords:** pyrazole amide derivatives; hydrazone; synthesis; CoMFA; insecticidal activity

## 1 INTRODUCTION

Crop damage from harmful pests has become more common in recent years, and the continued application of traditional pesticides can often lead to the development of more resistant pests, thus bringing about enormous losses in crop production.[1] In recent years, several insecticidal phthalic diamides (fluobendiamide, chlorantraniliprole and cyantraniliprole),[2–4] which act on the ryanodine receptor,[3,5–7] were discovered and commercialised; however, their insecticidal spectrum is limited. Recently, a chlorantraniliprole skeleton was found to be very significant in the discovery of novel insecticides,[8–12] and several modifications around its structure have been reported. A large number of compounds with these structures have demonstrated high insecticidal activities; some of these compounds are shown in Fig. 1.[8–12]

The hydrazone group is a highly efficient pharmacophore that is widely used in pesticide design. An example of such a pesticide is hydramethylnon,[13,14] the first insecticide containing a hydrazone moiety, which was commercialised in 1980. Many hydrazone derivatives with broad-spectrum activities have been reported as insecticidal agents,[15–19] including metaflumizone, which was discovered by BASF and commercialised in 2007.[20,21] More recently, Aggarwal *et al.*[22] described a series of substituted hydrazone derivatives possessing good activities against *Spodoptera litura* (Fabricius);[22] Liu and his coworkers[23] also reported several hydrazone derivatives exhibiting good insecticidal activities after modification of the fluobendiamide group.

New insecticidal molecules are developed in the present work on the basis of the following: incorporation of the substructural unit of hydrazone into the backbone of chlorantraniliprole and structural variation by the introduction of different kinds of moiety, resulting in pyrazole amides containing a hydrazone substructure with broad-spectrum activity (Fig. 2). Based on this hypothesis, a series of novel pyrazole derivatives containing hydrazone substructure are designed and synthesised (Fig. 3). Biological assays reveal that most of the synthesised compounds exhibit excellent insecticidal activities against different insect species. For example, compounds **15** to **17** display good activities not only against lepidoptera but also against diptera and homoptera [compound **17** showed superior activities compared with the commercial agent chlorantraniliprole on *Nilaparvata lugens* (Stål)]. Comparative molecular field analysis (CoMFA) based on *Plutella xylostella* (Linnaeus) is also discussed.

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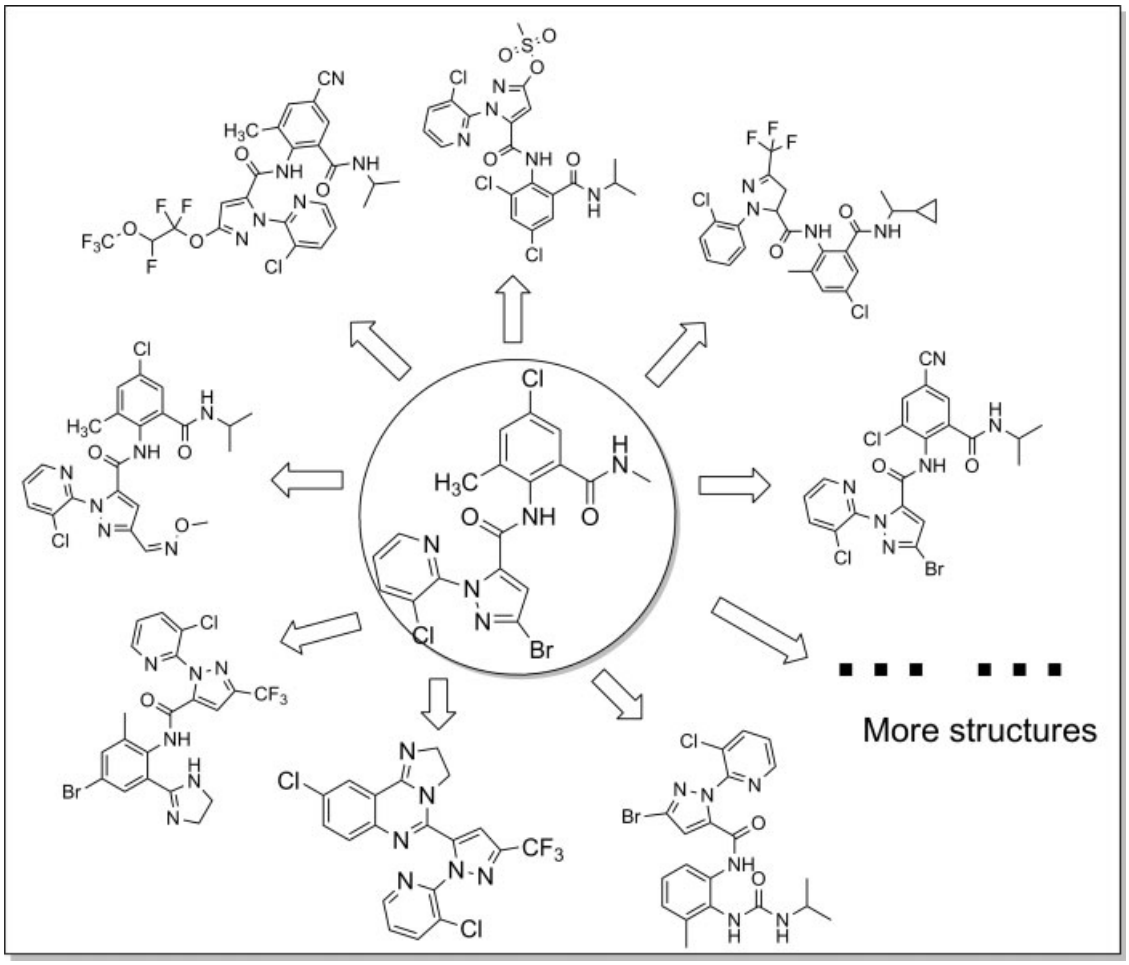


**Figure 1.** The compounds with high activity based on the structure of chlorantraniliprole.

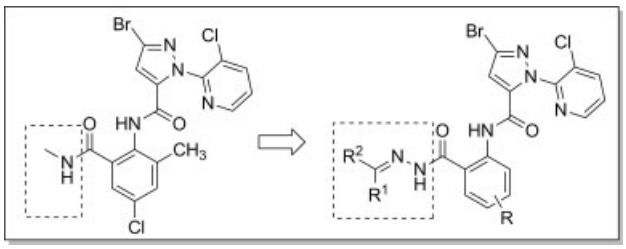

**Figure 2.** Structural features of the designed compound.

## 2 MATERIALS AND METHODS

### 2.1 General

Melting points were determined using a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and left uncorrected. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a JEOL ECX 500 NMR spectrometer operating at room temperature and 500 MHz using $CDCl_3$ or DMSO as solvents and TMS as an internal standard. Infrared spectra were recorded by KBr using a Bruker VECTOR 22 spectrometer. Elemental analysis was performed using an Elemental Vario-III CHN analyser. The course of the reactions was monitored by TLC; analytical TLC was performed on silica gel $GF_{254}$. All reagents were of analytical grade or chemically pure. All anhydrous solvents were dried and purified according to standard techniques just before use.

### 2.2 Chemical synthesis

#### *2.2.1 General procedure for intermediates (**4** to **10**)*

Intermediates **4** to **7** were prepared by following the known procedure.[11] 2-Amino-5-chloro-3-methylbenzoic acid (**8c**) was synthesised as described in Ref. 24, and intermediates **9** and **10** were prepared according to reported methods.[5,25] Detailed synthetic procedures for these intermediates can be found in the supporting information. The physical properties and $^{1}H$ NMR data of the intermediates are also listed in the supporting information.

#### *2.2.2 General procedure for the preparation of title compounds (**11** to **44**)*

Different ketones and aldehydes (or hemiacetals) (1 mmol) were added to a well-stirred solution of **10** (1 mmol) in ethanol (5 mL). The resulting mixture was stirred for 30 min at ambient temperature to afford a white solid, and then filtered and recrystallised from a mixture of ethanol and DMF (1 : 1 in volume). Compound **30** was synthesised by following the procedure for intermediate **10** but using 40% methyl hydrazine instead of 80% hydrazine hydrate. The representative data for **11** are shown below, and the data for **12** to **44** can be found in the supporting information.

Data for 3-bromo-*N*-{4-chloro-2-methyl-6-[2-(propan-2-ylidene)hydrazinecarbonyl] phenyl}-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (**11**): white solid; yield 85%; m.p.

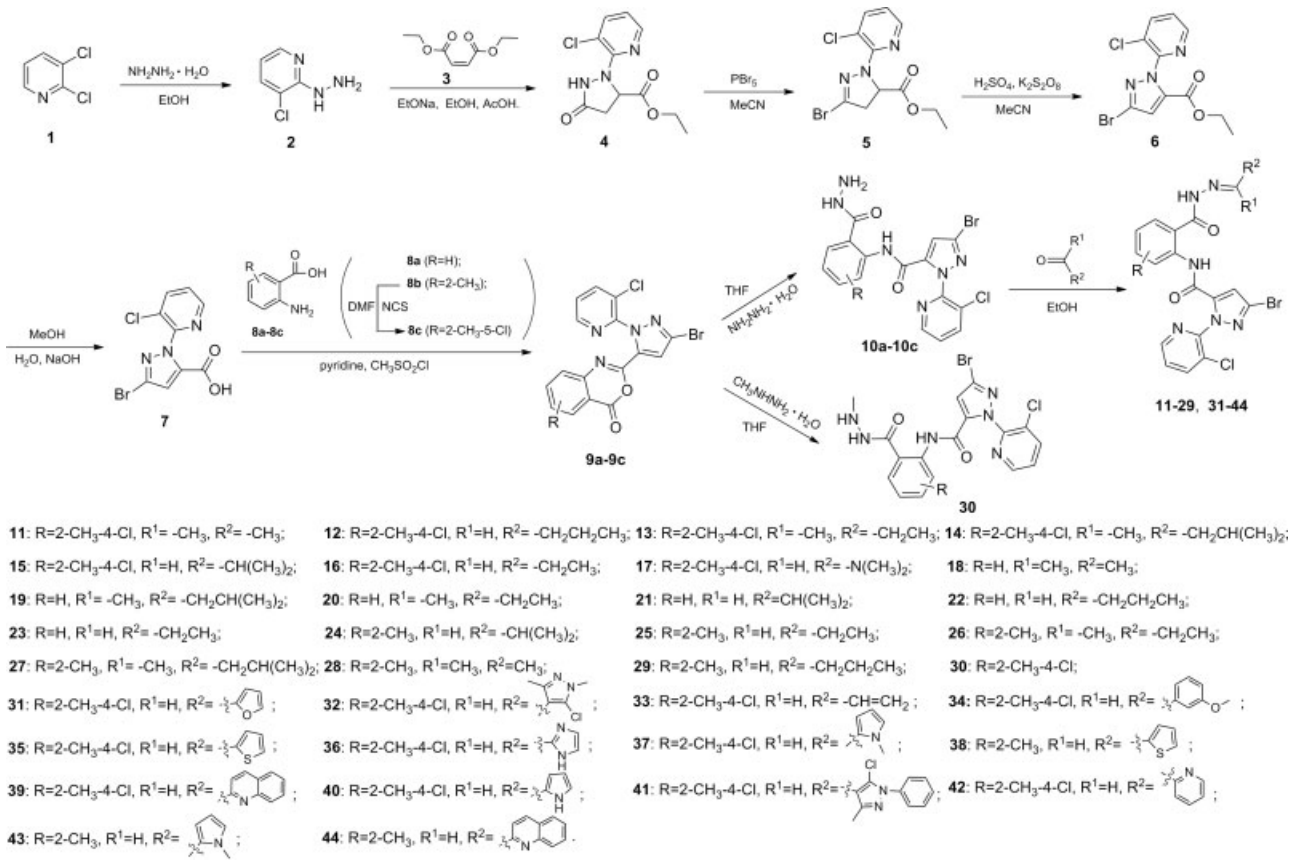


**Figure 3.** Synthetic route to compounds **11** to **44**.

229–231 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 12.27 (br s, 1H, –CONHAr), 10.26 (br s, 1H, –CONHN=), 8.44 (dd, 1H, $^4J_{HH}$ = 1.15 Hz, $^3J_{HH}$ = 4.60 Hz, 6-pyridine-H), 8.12 (dd, 1H, $^4J_{HH}$ = 1.15 Hz, $^3J_{HH}$ = 8.00 Hz, 4-pyridine-H), 7.56 (dd, 1H, $^3J_{HH}$ = 4.60 Hz, $^3J_{HH}$ = 8.00 Hz, 5-pyridine-H), 7.46 (s, 1H, 5-Ph-H), 7.34 (s, 1H, 3-Ph-H), 7.19 (s, 1H, pyrazole-H), 2.13 (s, 3H, Ph-$CH_3$), 1.92 (s, 3H, $CH_3$), 1.74 (s, 3H, $CH_3$); IR (KBr): $\nu$ 3325.2, 3282.8, 3261.6, 3012.8, 2991.5, 1664.5, 1653.0, 1627.9, 1577.7, 1558.4, 1541.1, 1458.1, 1340.5 cm$^{-1}$; anal. calc. for $C_{20}H_{17}BrCl_2N_6O_2$: C 45.83%, H 3.27%, N 16.03%; found: C 46.19%; H 3.46%; N 16.30%; MS (EI$^+$) calc. for $C_{20}H_{17}BrCl_2N_6O_2$ $(M+1)^+$, 524.20; found, 525.0.

## 2.3 Biological assay

All bioassays were performed on test organisms reared in the lab and repeated at 25 ± 1 °C according to statistical requirements. Mortalities were corrected using Abbott's formula.[26,27] Evaluations were based on a percentage scale (0 = no activity and 100 = complete eradication), at intervals of 5%.

### 2.3.1 *Insecticidal activity against* Plutella xylostella

The insecticidal activities for the synthesised compounds against *P. xylostella* were evaluated using previously reported procedures.[12,28,29] Fresh cabbage discs (diameter 2 cm) were dipped into the prepared solutions containing compounds **11** to **44** for 10 s, dried in air and placed in a petri dish (diameter 9 cm) lined with filter paper. Ten larvae of second-instar *P. xylostella* were carefully transferred to the petri dish. Avermectins, chlorantraniliprole and chlorpyrifos were used as controls; three replicates and at least five concentrations were performed for each experiment. Mortalities were determined after 72 h. The primary results and median lethal concentrations ($LC_{50}$) for these compounds are summarised in Tables 1 and 2 respectively.

### 2.3.2 *Insecticidal activity against* Helicoverpa armigera

The insecticidal activities of some of the synthesised compounds and avermectins against *Helicoverpa armigera* (Hübner) were evaluated by the diet-incorporated method.[30] A quantity of 3 mL of prepared solutions containing the compounds was added to the forage (27 g), subsequently diluted to different concentrations and then placed in a 24-pore plate. One larva was placed in each of the wells on the plate. Mortalities were determined after 72–96 h, and the results are given in Table 3.

### 2.3.3 *Insecticidal activity against* Culex pipiens pallens

The larvicidal activities of compounds **11** to **17**, **24** to **30** and **33** to **44** against *Culex pipiens pallens* were evaluated using the reported procedure.[31–33] The compounds were prepared at different concentrations by dissolving **1** to **17**, **24** to **30** and **33** to **44** in DMSO and then adding distilled water. Subsequently, ten larvae of fourth-instar *C. pipiens pallens* were placed into 10 mL of the test solution and raised for 24 h. Hexaflumuron was tested under the same conditions as the control. The results are summarised in Table 4.

### 2.3.4 *Insecticidal activity against* Laphygma exigua

Insecticidal activities against *Laphygma exigua* (Hübner) were tested using the method described in Ref. 34. Fresh leaf discs

  

**Table 1.** Insecticidal activity of compounds **11** to **44**, avermectins, chlorantraniliprole and chlorpyrifos against *Plutella xylostella*

| | Insecticidal activity (%) at different concentrations (mg $L^{-1}$) | | | | | | | Insecticidal activity (%) at different concentrations (mg $L^{-1}$) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Comp. | 100 | 50 | 25 | 20 | 10 | 5 | Comp. | 100 | 50 | 25 | 20 | 10 | 5 |
| **11** | 100 | 100 | 100 | 86 | 57 | 21 | **30** | 100 | 100 | 100 | 100 | 100 | 100 |
| **12** | 100 | 100 | 100 | 87 | 59 | 42 | **31** | 100 | 100 | 100 | 100 | 100 | 86 |
| **13** | 100 | 100 | 100 | 100 | 100 | 53 | **32** | 100 | 100 | 90 | 85 | 78 | 57 |
| **14** | 100 | 100 | 100 | 89 | 46 | 29 | **33** | 100 | 100 | 100 | 83 | 43 | / |
| **15** | 100 | 100 | 82 | 71 | 38 | 14 | **34** | 100 | 96 | 84 | 73 | 15 | 0 |
| **16** | 100 | 100 | 100 | 100 | 86 | 29 | **35** | 100 | 100 | 84 | 76 | 55 | 0 |
| **17** | 100 | 100 | 100 | 100 | 100 | 100 | **36** | 100 | 100 | 80 | 57 | 29 | 18 |
| **18** | 27 | / | / | / | / | / | **37** | 100 | 100 | 100 | 100 | 86 | 43 |
| **19** | 0 | / | / | / | / | / | **38** | 89 | 75 | 58 | 0 | / | / |
| **20** | 20 | / | / | / | / | / | **39** | 100 | 80 | 60 | 52 | 17 | 0 |
| **21** | 0 | / | / | / | / | / | **40** | 100 | 100 | 100 | 100 | 86 | 49 |
| **22** | 7 | / | / | / | / | / | **41** | 46 | 20 | 0 | / | / | / |
| **23** | 0 | / | / | / | / | / | **42** | 100 | 100 | 100 | 71 | 57 | 0 |
| **24** | 72 | 65 | 58 | 41 | 0 | / | **43** | 65 | 40 | 20 | 0 | / | / |
| **25** | 96 | 83 | 58 | 41 | 0 | / | **44** | 52 | 0 | / | / | / | / |
| **26** | 88 | 81 | 65 | 26 | 0 | / | Avermectins | 100 | 100 | 100 | 100 | 100 | 100 |
| **27** | 100 | 87 | 76 | 49 | 29 | 17 | Chlorantraniliprole | 100 | 100 | 100 | 100 | 100 | 100 |
| **28** | 64 | 45 | 0 | / | / | / | Chlorpyrifos | 100 | 90 | 83 | / | 67 | 40 |
| **29** | 100 | 100 | 100 | 100 | 100 | 53 | Blank control | 1 | 0 | 0 | 0 | 0 | 0 |

**Table 2.** Insecticidal activity of synthesised compounds and chlorpyrifos against *Plutella xylostella*

| Comp. | $y = a + bx$ | $r$ | $LC_{50}$ (mg $L^{-1}$) | 95% Confidence limits | $pLC_{50}$ |
|---|---|---|---|---|---|
| **11** | $y = 4.881 + 1.132x$ | 0.99 | 1.27 | 0.8268–1.9722 | 5.62 |
| **12** | $y = 4.383 + 1.349x$ | 0.99 | 2.86 | 1.400–3.0100 | 5.27 |
| **13** | $y = 4.829 + 1.542x$ | 0.98 | 1.29 | 0.8875–1.8745 | 5.62 |
| **14** | $y = 4.475 + 1.469x$ | 0.97 | 2.28 | 1.5738–3.2850 | 5.40 |
| **15** | $y = 3.293 + 3.043x$ | 0.99 | 3.64 | 3.0415–4.3526 | 5.17 |
| **16** | $y = 4.341 + 1.353x$ | 0.98 | 3.07 | 2.0100–4.7000 | 5.23 |
| **17** | $y = 5.279 + 1.883x$ | 0.95 | 0.71 | 0.5200–0.9700 | 5.88 |
| **25** | $y = 0.378 + 2.992x$ | 0.96 | 35.05 | 29.7317–40.3715 | 4.15 |
| **26** | $y = 0.899 + 2.448x$ | 0.99 | 47.34 | 36.7900–60.9100 | 4.03 |
| **27** | $y = 2.411 + 1.858x$ | 0.98 | 24.72 | 17.2507–35.3695 | 4.33 |
| **28** | $y = 0.946 + 3.045x$ | 0.99 | 21.49 | 18.1789–25.2296 | 4.36 |
| **29** | $y = 2.246 + 2.125x$ | 0.99 | 19.74 | 14.3489–27.1577 | 4.41 |
| **30** | $y = 5.243 + 1.953x$ | 0.99 | 0.75 | 0.5761–0.9765 | 5.82 |
| **31** | $y = 3.937 + 2.697x$ | 0.99 | 2.47 | 2.0553–2.9581 | 5.36 |
| **32** | $y = 3.423 + 1.778x$ | 0.99 | 7.71 | 5.5916–10.6362 | 4.91 |
| **35** | $y = 4.169 + 1.324x$ | 0.98 | 4.24 | 2.8314–6.3260 | 5.13 |
| **36** | $y = 2.290 + 2.361x$ | 0.95 | 14.04 | 12.0600–20.3500 | 4.60 |
| **37** | $y = 3.921 + 2.511x$ | 0.98 | 2.69 | 1.61539–4.4656 | 5.33 |
| **38** | $y = 0.185 + 2.704x$ | 0.99 | 60.29 | 44.2400–90.6000 | 3.96 |
| **39** | $y = 1.592 + 2.560x$ | 0.99 | 21.42 | 17.2300–26.6300 | 4.46 |
| **41** | $y = -0.485 + 3.175x$ | 0.98 | 53.39 | 44.4167–64.1385 | 4.11 |
| **42** | $y = 3.023 + 1.810x$ | 0.98 | 12.36 | 8.8090–17.0562 | 4.67 |
| **43** | $y = 1.252 + 2.823x$ | 0.99 | 21.25 | 17.4000–27.8400 | 4.41 |
| **44** | $y = 1.217 + 1.876x$ | 0.99 | 103.84 | 50.8700–212.1100 | 3.75 |
| Chlorpyrifos | $y = 3.730 + 1.44x$ | 0.98 | 7.61 | 5.2700–9.5400 | 4.66 |

**Table 3.** Insecticidal activity of synthesised compounds and avermectins against *Helicoverpa armigera*

| | Insecticidal activity (%) at different concentrations (mg $L^{-1}$) | | | | | Insecticidal activity (%) at diffferent concentrations (mg $L^{-1}$) | | | |
|---|---|---|---|---|---|---|---|---|---|
| Comp. | 100 | 50 | 25 | 10 | Comp. | 100 | 50 | 25 | 10 |
| **11** | 100 | 100 | 100 | 40 | **31** | 100 | 100 | 100 | 80 |
| **12** | 100 | 100 | 100 | 60 | **32** | 100 | 100 | 100 | 70 |
| **13** | 100 | 100 | 100 | 60 | **35** | 100 | 100 | 100 | 80 |
| **14** | 100 | 100 | 100 | 70 | **36** | 100 | 100 | 100 | 70 |
| **15** | 100 | 100 | 100 | 70 | **37** | 100 | 100 | 100 | 80 |
| **16** | 100 | 100 | 100 | 50 | **38** | 100 | 100 | 100 | 70 |
| **17** | 100 | 100 | 100 | 80 | **39** | 100 | 100 | 100 | 90 |
| **24** | 100 | 100 | 30 | / | **40** | 100 | 100 | 100 | 90 |
| **25** | 100 | 100 | 70 | / | **41** | 100 | 100 | 100 | 60 |
| **26** | 100 | 100 | 80 | / | **42** | 100 | 100 | 100 | 80 |
| **27** | 100 | 100 | 50 | / | **43** | 100 | 100 | 100 | 70 |
| **28** | 100 | 100 | 80 | / | **44** | 100 | 100 | 100 | 90 |
| **29** | 100 | 100 | 50 | / | Avermectins | 100 | 100 | 100 | 100 |
| **30** | 100 | 100 | 100 | 90 | Blank control | 1 | 0 | 0 | 0 |

**Table 4.** Insecticidal activity of synthesised compounds and hexaflumuron against *Culex pipiens pallens*

| | Insecticidal activity (%) at different concentrations (mg $L^{-1}$) | | | Insecticidal activity (%) at different concentrations (mg $L^{-1}$) | | | |
|---|---|---|---|---|---|---|---|
| Comp. | 2 | 1 | Comp. | 2 | 1 | 0.5 | 0.25 |
| **11** | 100 | 70 | **33** | 100 | 100 | 100 | 50 |
| **12** | 100 | 60 | **34** | 50 | / | / | / |
| **13** | 100 | 70 | **35** | 100 | 50 | / | / |
| **14** | 100 | 80 | **36** | 100 | 70 | / | / |
| **15** | 100 | 80 | **37** | 100 | 50 | / | / |
| **16** | 100 | 50 | **38** | 10 | / | / | / |
| **17** | 100 | 80 | **39** | 60 | / | / | / |
| **24** | 30 | / | **40** | 100 | 100 | 100 | 60 |
| **25** | 20 | / | **41** | / | 40 | / | / |
| **26** | 10 | / | **42** | 100 | 100 | 100 | 60 |
| **27** | 10 | / | **43** | 100 | 40 | / | / |
| **28** | 20 | / | **44** | 100 | 70 | / | / |
| **29** | 60 | / | Hexaflumuron | 100 | 100 | 100 | 100 |
| **30** | 100 | 50 | Blank control | 0 | 0 | 0 | 0 |

were dipped into the prepared solution for 3–5 s and then dried in air. The leaf discs were then placed in a petri dish (diameter 6 cm) lined with filter paper. Thirty larvae of third-instar *L. exigua* were transferred to the petri dish. Avermectins were used as the control; three replicates were performed for each experiment. Mortality was determined after 96 h and is listed in Table 5.

#### 2.3.5 *Insecticidal activity against* Spodoptera litura[35]

Fresh bean leaves were dipped in the solutions containing the compounds for 10 s and then air dried. The leaves were placed in a petri dish (diameter 6 cm) lined with filter paper, and ten larvae of second-instar *S. litura* were transferred to the petri dish. Chlorantraniliprole was also tested as a control; three replicates were conducted for each experiment. Mortality was determined after 96 h. The results are provided in Table 6.

#### 2.3.6 *Insecticidal activity against* Nilaparvata lugens *and* Rhopalosiphum maidis

Insecticidal activities against *N. lugens* and *Rhopalosiphum maidis* (Fitch) for compounds **11** to **13**, **15**, **17** and **30** were tested using the Potter spray method.[36] Forty third-instar larvae of *N. lugens* (or *R. maidis*) were treated at various concentrations with the test emulsions under a Potter spray tower at a pressure of 4.35 mg $cm^{-2}$, and then reared for 72–96 h. The same larvae, when similarly sprayed with chlorantraniliprole and emulsified water, served as controls. Three replicates were conducted for each experiment.

### 2.4 Molecular modelling and the alignment rule for CoMFA

Molecular modelling was performed using Sybyl 7.2 software (Tripos Inc., St Louis, MO). All the molecules were built with the SKETCH option in Sybyl in the default setting. Energy minimisations were carried out using the Gasteiger–Hückel

  

**Table 5.** Insecticidal activity of synthesised compounds and hexaflumuron against *Laphygma exigua*

| Comp. | Insecticidal activity (%) at different concentrations (mg $L^{-1}$) 600 | 200 | 100 | Comp. | Insecticidal activity (%) at different concentrations (mg $L^{-1}$) 600 | 200 | 100 |
|---|---|---|---|---|---|---|---|
| **11** | 95 | 86 | 48 | **32** | 0 | / | / |
| **12** | 82 | 57 | 39 | **33** | 83 | / | / |
| **13** | 46 | 0 | / | **34** | 64 | / | / |
| **14** | 68 | 43 | 0 | **35** | 86 | 62 | 36 |
| **15** | 83 | 71 | 27 | **36** | 90 | 65 | 31 |
| **16** | 71 | 35 | 0 | **38** | 87 | 54 | 40 |
| **17** | 64 | 29 | 0 | **39** | 93 | 86 | 69 |
| **24** | 69 | / | / | **40** | 79 | 58 | 47 |
| **25** | 78 | / | / | **41** | 47 | 21 | / |
| **26** | 81 | / | / | **42** | 69 | 43 | / |
| **27** | 91 | / | / | **43** | 0 | / | / |
| **28** | 72 | / | / | **44** | 55 | 29 | / |
| **29** | 96 | / | / | Avermectins | 100 | 100 | 100 |
| **30** | 100 | 100 | 76 | Blank control | 2 | 0 | 0 |
| **31** | 89 | 53 | / | | | | |

**Table 6.** Insecticidal activity of compounds **15** to **17** and chlorantraniliprole against *Spodoptera litura*

| Comp. | Insecticidal activity (%) at different concentrations (mg $L^{-1}$) 500 | 100 | 20 | 4 | Comp. | Insecticidal activity (%) at different concentrations (mg $L^{-1}$) 500 | 100 | 20 | 4 |
|---|---|---|---|---|---|---|---|---|---|
| **15** | 100 | 100 | 100 | 40 | Chlorantraniliprole | 100 | 100 | 100 | 100 |
| **17** | 100 | 100 | 100 | 80 | Blank control | 3 | 0 | 0 | 0 |
| **16** | 100 | 100 | 100 | 60 | | | | | |

charge, tripos force field and Powell conjugate gradient algorithm with a convergence criterion of 0.05 kcal $mol^{-1}$. Genetic algorithm (GA) conformational searches were conducted to determine a reasonably low-energy conformation for each compound. The $pLC_{50}$ for the studied compounds was calculated by taking the negative logarithm of the corresponding $LC_{50}$ (μM). The results are listed in Table 2.

The 3D structures were aligned on a common substructure, and the conformation of compound **30** (one of the most active compounds) was used as the template molecule (Fig. 4a). Five compounds (**26, 39, 41, 42** and **44**) were chosen randomly as a test set for the CoMFA models. The training set consisted of 19 compounds. The results of alignment are shown in Fig. 4b.

For the CoMFA calculations, molecules were placed in a rectangular grid and the interaction energies between a probe atom and all compounds were computed at the surrounding points using a volume-dependent lattice with a 2.0 Å grid spacing (default in SYBYL). Then, CoMFA was carried out in two steps using the partial least-squares (PLS) technique. Firstly, the number of components in the PLS models was obtained from the

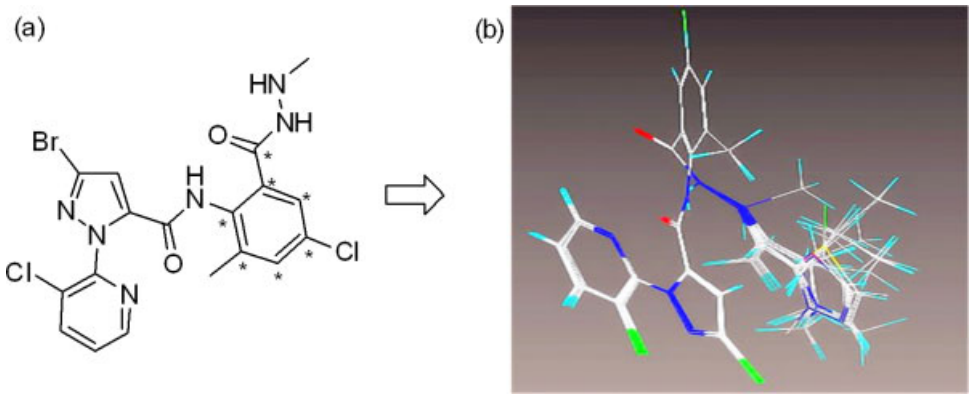


**Figure 4.** Superimposition of compounds for the CoMFA study: (a) molecular alignment template; (b) result of superimposition.

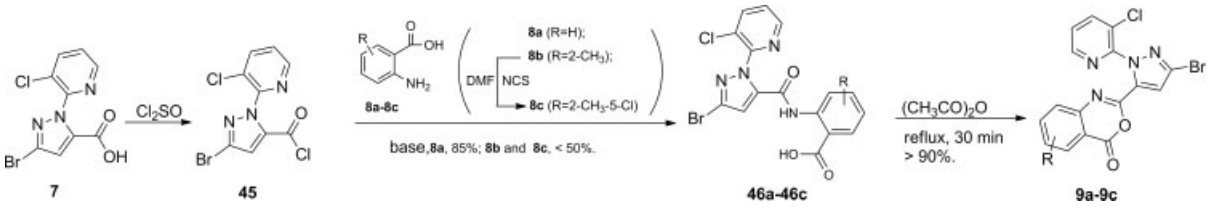


**Figure 5.** Synthetic route to intermediates **9a** to **9c**.

leave-one-out cross-validation procedure and optimised by using a $q^2$ value. The $r^2$ value was obtained from the second run, which was performed without cross-validation, using the optimal number of components previously determined. The CoMFA models were generated using steric and electrostatic probes with standard 30 kcal mol$^{-1}$ cut-offs.

## 3 RESULTS AND DISCUSSION

### 3.1 Synthesis

The synthetic route to title compounds **11** to **44** is outlined in Fig. 3. Firstly, the pyrazole-5-carboxylic acid (**7**) was obtained in five steps by following the known procedure.[5,11,37] Compounds **9a** to **9c** were prepared by cyclisation of 2-[3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carbox-amido]-substituted benzoic acid (**46a** to **46c**) in refluxing acetic anhydride[38] (Fig. 5) with >90% yield. However, the synthetic route in Fig. 5 had several shortcomings, which included long steps, poor stability of chloride (**45**), low yields and long reaction times, especially for **46**. A single-step alternative route[4,5,39] with a short reaction time carried out at room temperature was thus employed by treatment of **7** with **8a** and **8c** in the presence of pyridine and methanesulfonyl chloride in acetonitrile (Fig. 5).

Finally, **10a, 10b** and **10c** were conveniently obtained with >90% yield by treatment of **9a, 9b** and **9c** with 80% hydrazine hydrate. Subsequent treatment of **10** with different ketones and aldehydes (or hemiacetals) in ethanol at room temperature afforded the desired compounds (**11** to **29**, **21** to **44**) with excellent yields. Compound **30** was prepared by following the protocol for **10c** but using 40% methyl hydrazine instead of 80% hydrazine hydrate.

### 3.2 Biological assay

#### 3.2.1 *Insecticidal activity against* Plutella xylostella

As indicated in Tables 1 and 2, many of the synthesised compounds exhibited excellent insecticidal activities against *P. xylostella* at 5–100 mg L$^{-1}$. Compounds **17** and **30** showed 100% activity at 5 mg L$^{-1}$, much better than that of chlorpyrifos (40%) and almost the same as that of avermectins and chlorantraniliprole. The $LC_{50}$ values for compounds **11, 12, 13, 14, 15, 16, 17, 30, 31, 35** and **37** were 1.27, 2.86, 1.29, 2.28, 3.64, 3.0, 0.71, 0.75, 2.47, 4.24 and 2.69 mg L$^{-1}$ respectively (Table 2). Structure–activity relationships showed that changing the substituent on benzene could lead to a remarkable change in activity. For instance, the compounds with a methyl group at the 2-position and chorine at the 4-position (**11** to **17, 30** to **37, 39, 40** and **42**) of benzene displayed much higher activities than the compounds with a methyl group at the 2-position (**24** to **28, 38** and **44**). The compounds without any substituent on benzene (**18** to **23**) exhibited practically negligible activities. In addition, the substituents ($R^1$ and $R^2$) present in the functional group N=$R^1R^2$ were also a crucial factor that governed activity. Introduction of a heterocyclic group (**17, 30** to **37**) into N=$R^1R^2$ could increase the activity of the compound. However, the activity was found to decrease when a bulky $R^1$ or $R^2$ group was introduced.

#### 3.2.2 *Insecticidal activity against* Helicoverpa armigera

The bioassay results against *H. armigera* are presented in Table 3. Most of the compounds possessed excellent bioactivities. Compounds **11** to **16** displayed higher activities than compounds **24** to **29** at 25 mg L$^{-1}$ because of the chlorine at the 4-position of benzene. Moreover, the activities of the compounds were enhanced by increasing the chain length in the $R^1$ and $R^2$ groups. For example, the activities of compounds **13** (R = 2-$CH_3$–4-Cl, $R^1$ = $-CH_3$, $R^2$ = $-CH_2CH_3$) and **14** [R = 2-$CH_3$–4-Cl, $R^1$ = $-CH_3$, $R^2$ = $-CH_2CH(CH_3)_2$] were much better than that of **11** (R = 2-$CH_3$–4-Cl, $R^1$ = $R^2$ = $-CH_3$) at 10 mg L$^{-1}$. Moreover, the introduction of a heterocyclic group into N=$R^1R^2$ increased the insecticidal activities of the compounds (e.g. compounds **31, 39, 44**, etc.).

#### 3.2.3 *Insecticidal activity against* Culex pipiens pallens

As listed in Table 4, the tested compounds, except for **24** to **29, 34, 38, 39** and **41**, displayed 100% activities against *C. pipiens pallens* at concentrations of 2 mg L$^{-1}$. The compounds bearing an unsaturated hydrocarbon (**33**), pyrrole (**40**) and pyridine (**42**) displayed 100% activities at 0.5 mg L$^{-1}$. The chlorine at the 4-position of benzene enhanced the insecticidal activities of the compounds.

#### 3.2.4 *Insecticidal activity against* Laphygma exigua

As summarised in Table 5, the synthesised compounds showed moderate activities against *L. exigua*. Compound **30** controlled the larvae at 200 mg L$^{-1}$, and compounds **11, 27, 36** and **39** showed >90% activity against the larvae at 600 mg L$^{-1}$. Primary structure–activity relationships revealed that, when the benzene moiety was simultaneously substituted by methyl (at the 2-position) and chorine (at the 4-position), the activity on *L. exigua* increased. However, the introduction of longer alkyls into $R^1$ and $R^2$ groups decreased the activity of the compound. Furthermore, the type of heterocyclic group on the N=$R^1R^2$ moiety also affected the bioactivity of the compound. For instance, the compound with a quinoline ring (**39**) displayed good activity, while the compounds with pyrazole (**32**) and pyrrole (**33**) showed no insecticidal activities on *L. exigua*.

#### 3.2.5 *Insecticidal activity against* Spodoptera litura

The results from **Table 6** demonstrate that compounds **15, 16** and **17** exhibited good activities against *S. litura*, displaying 100% activity at 20 mg L$^{-1}$; compound **17** also exhibited 80% activity at 4 mg L$^{-1}$.

  

**Table 7.** PLS statistics of the CoMFA

| Cross-validation | | Non-cross-validation | | |
|---|---|---|---|---|
| $q^2$ | Component | $r^2$ | SEE | *F* |
| 0.701 | 6 | 0.964 | 0.137 | 73.41 |

**Table 8.** Results of experimental $pLC_{50}$ and predicted $pLC_{50}$

| Comp. | Act. | Pred. | Res. | Comp. | Act. | Pred. | Res. |
|---|---|---|---|---|---|---|---|
| **11** | 5.62 | 5.51 | 0.11 | **30** | 5.82 | 5.93 | −0.11 |
| **12** | 5.27 | 5.19 | 0.08 | **31** | 5.36 | 5.1 | 0.26 |
| **13** | 5.62 | 5.67 | −0.05 | **32** | 4.91 | 4.84 | 0.07 |
| **14** | 5.4 | 5.37 | 0.03 | **35** | 5.13 | 5.05 | 0.08 |
| **15** | 5.17 | 5.32 | −0.15 | **36** | 4.6 | 4.81 | −0.21 |
| **16** | 5.23 | 5.25 | −0.02 | **37** | 5.33 | 5.46 | −0.13 |
| **17** | 5.88 | 5.77 | 0.11 | **38** | 3.96 | 3.9 | 0.06 |
| **25** | 4.15 | 4.24 | −0.09 | **39** | 4.46 | 4.41 | 0.05 |
| **26** | 4.03 | 4.3 | −0.27 | **41** | 4.11 | 4.36 | −0.25 |
| **27** | 4.33 | 4.34 | −0.01 | **42** | 4.67 | 4.8 | −0.13 |
| **28** | 4.36 | 4.32 | 0.04 | **43** | 4.41 | 4.41 | 0 |
| **29** | 4.41 | 4.47 | −0.06 | **44** | 3.75 | 4.01 | −0.26 |

#### 3.2.6 *Insecticidal activity against* Nilaparvata lugens *and* Rhopalosiphum maidis

The bioassay results of compounds **11** to **13, 15, 17** and **20** on *N. lugens* and *R. maidis* indicated that these compounds had moderate insecticidal activities. For example, compounds **11** to **13, 15** and **17** displayed >70% activity against *N. lugens* and >94% activity against *R. maidis* at 200 mg $L^{-1}$; compound **17** had 80% activity against *N. lugens* and was superior to commercial chlorantraniliprole (20% activity) at 100 mg $L^{-1}$. Moreover, both **17** and **20** could completely eradicate *N. lugens* at 500 mg $L^{-1}$.

### 3.3 Comparative molecular field analysis (CoMFA) on *Plutella xylostella*

CoMFA is a powerful tool that may be used to study the 3D-QSAR models based on data from known active molecules. It examines differences in targeted properties related to changes in the shape of the steric and electrostatic fields surrounding the molecules.[40] For the CoMFA, PLS statistics tested on bioactivity against *P. xylostella* are presented in Table 7. The cross-validated $q^2$ value was 0.701 with six components, and the non-cross-validated conventional $r^2$ value was 0.964 with a standard error of estimation (SEE) of 0.137 and $F = 72.41$. The relative contributions between steric and electrostatic fields for the CoMFA model were 0.763 and 0.237 respectively, which revealed that the steric field made an important contribution to bioactivity. The activities of the training set compounds and test set compounds were predicted by the CoMFA model and are presented in Table 8. The correlations between the predicted $pLC_{50}$ and experimental $pLC_{50}$ are represented in Fig. 6. The proposed model predicted the activities successfully (Table 8 and Fig. 6).

The steric contribution contour map of CoMFA is shown in Fig. 7a. The yellow (20% contribution) and green (80% contribution) polyhedrals display regions around the molecule where bulky groups can decrease or enhance insecticidal activities

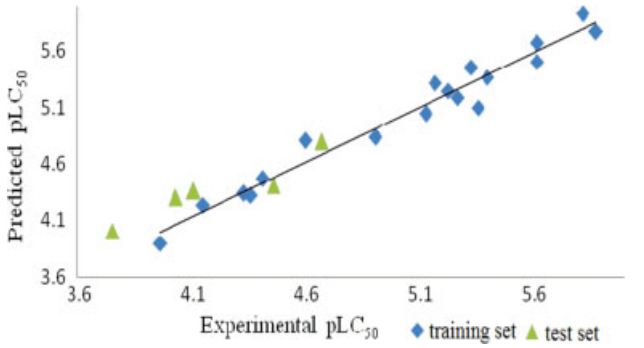


**Figure 6.** Scatter plot of the experimental activities versus predicted activities for the model of CoMFA.

respectively. Based on the steric contour, the presence of a 4-substituent on benzene is favourable, and a comparison between compounds **14** and **27** revealed that a change from a hydrogen to a chloro group at the 4-position can increase potency, which may be attributed to a desirable increase in the steric bulk of the group. A similar trend was observed from the activities of compounds **11** to **13, 15** and **16** (in which chlorine is present at the 4-position of benzene), showing more than a tenfold enhancement of activities compared with those of **25, 26, 28** and **29**, all of which had no substituent at the 4-position of benzene. Although the yellow region was mainly concentrated around the $N{=}R^1R^2$ group, a bulky group in this area had a negative effect on the insecticidal activities of the compounds. As a result, the activities of compound **41** (with a 5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl substitution pattern) and **44** (containing a quinoline ring) on *P. xylostella* were much lower than those of compounds **17** [with an $-N{=}CHN(CH_3)_2$ group] and **30** (with an $-NCH_3$ group).

The electrostatic contour plot is shown in Fig. 7b; blue (80% contribution) and red (20% contribution) polyhedrals indicate the regions of favourable activation with negative and positive charges respectively. A predominant feature of the electrostatic plot is the presence of a blue contour surrounding the benzene moiety, which indicates that the negatively charged group at the 4-position of benzene increased insecticidal activity against *P. xylostella*. Thus, compounds **11** to **17**, which possessed an electronegative substituent (chlorine) at the 4-position of the benzene ring, showed high activities, whereas compounds **25** to **29** (without an electronegative substituent at the 4-position of benzene) exhibited much lower activities. In addition, a small red contour, along with a large blue contour, was present near the $-N{=}R^1R^2$ region, where a suitable negatively charged group needs to be taken into consideration.

## 4 CONCLUSION

A series of novel pyrazole amide derivatives (**11** to **44**) containing hydrazone substructures were designed and synthesised. *In vivo* tests indicated that some of the compounds possessed excellent activities against *P. xylostella, H. armigera, C. pipiens pallens, L. exigua, S. litura, N. lugens* and *R. maidis*. In particular, the $LC_{50}$ values of compounds **11, 12, 13, 14, 15, 16, 17, 30, 31, 35** and **37** were 1.27, 2.86, 1.29, 2.28, 3.64, 3.0, 0.71, 0.75, 2.47, 4.24 and 2.69 mg $L^{-1}$ respectively. Compound **17** displayed 100% activity against *H. armigera* at 25 mg $L^{-1}$. These compounds, which contained unsaturated olefins (**33**), pyrrole (**40**) and pyridine (**42**), eradicated *C. pipiens pallens* completely (thus showing 100%

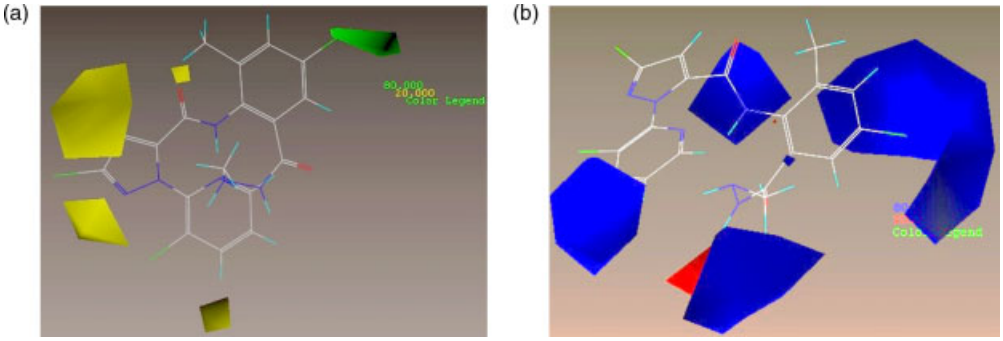


**Figure 7.** Steric map (a) and electrostatic map (b) from the CoMFA model.

activity) at 0.5 mg $L^{-1}$. Compound **30** showed 100% activity against *L. exigua* at 200 mg $L^{-1}$, and compounds **15, 16** and **17** displayed 100% activities against *S. litura* at 20 mg $L^{-1}$. The results of insecticidal activities also suggested that some of the title compounds had broad-spectrum insecticidal activities. For instance, compound **17** exhibited good activity against different insect species, such as *P. xylostella*, *H. armigera*, *C. pipiens pallens*, *N. lugens*, *R. maidis*, etc. A CoMFA study for compounds on *P. xylostella* was also discussed; the cross-validated $q^2$ value was 0.701 with six components, and the non-cross-validated conventional $r^2$ value was 0.964, with a standard error of estimation of 0.137 and $F = 72.41$. The results revealed that the presence of a bulky and negatively charged group at the 4-position of the benzene moiety enhanced insecticidal activity. The proposed model could predict the activity with reasonable accuracy and will be useful in the discovery of potent insecticides in the near future.

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## 5 SUPPORTING INFORMATION

Supporting information may be found in the online version of this article, where detailed procedures for the synthesis of **4** to **7**, **8c**, **9** and **10** and the analytical data for **9a** to **9c, 10a** to **10c** and **12** to **44** are listed.

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