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Design, synthesis and insecticidal activity of novel semicarbazones and thiosemicarbazones derived from chalcone

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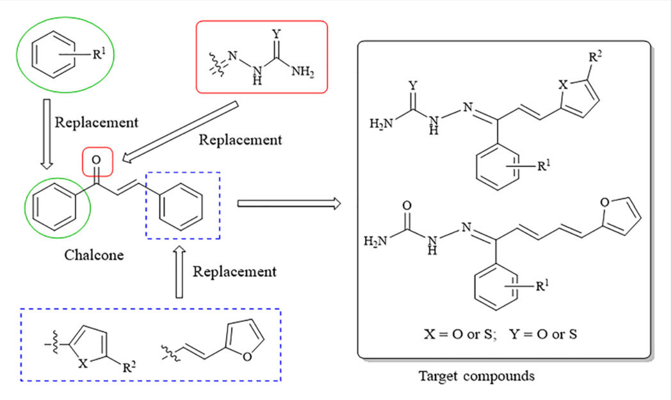
ABSTRACT

Thirty semicarbazone and thiosemicarbazone derivatives (**2a**–**w** and **4a**–**g**) from chalcones containing furan and thiophene ring were designed and synthesized. They were characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS. The crystal structure of compound **2r** was characterized by single crystal X-ray diffraction. It crystallizes in the monoclinic system with space group $P2_1/c$. The insecticidal activity of the synthesized compounds was screened against *Leucania separata* and *Pieris rapae* using beta-cypermethrin as the comparative standard. The results displayed that most of them had remarkable insecticidal activity. Among them, compounds **2e–g** showed better activity than beta-cypermethrin against *L. separata* and *P. rapae*. Compound **2p** also possessed a better activity than beta-cypermethrin against *P. rapae*. The insecticidal activities of these compounds have been reported for the first time.



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1. Introduction

Leucania separata is a crop pest with serious harm. It usually eats seedlings of plants, especially, maize, causing them to wither or disappear. Similarly, *Pieris rapae* is also a vegetable pest which can cause serious harm. It often devours leaves of plants including cabbage, which hinders their growth and even makes them die. In the past few decades, insecticides including dimethoate, omethoate and methomyl have been used to control these pests. However, their development of resistance to these insecticides has reduced the efficacy of insecticidal treatments (Yang et al. 1995; Peng et al. 1996). Therefore, the research and development of new pesticides against these pests are continually necessary (Cao et al. 2002; Xu et al. 2003; Zheng et al. 2003; Di et al. 2007; Liu et al. 2008).

Chalcones (1,3-diphenyl-2-propen-1-one) are an important class of natural products existing in various plants. They can also be obtained by chemical syntheses. They have been widely used as synthons in the synthetic field because they have the conjugated C = C and C = O double bonds, which can undertake various chemical reactions. Furthermore, chalcone derivatives have diverse and interesting biological properties including insecticidal activity (Figure S1) (Gao et al. 2001; Hou et al. 2002; Chen et al. 2007; Tao et al. 2007). Therefore, the discovery of novel chalcone derivatives with insecticidal activities attracts a great deal of attention around the world.

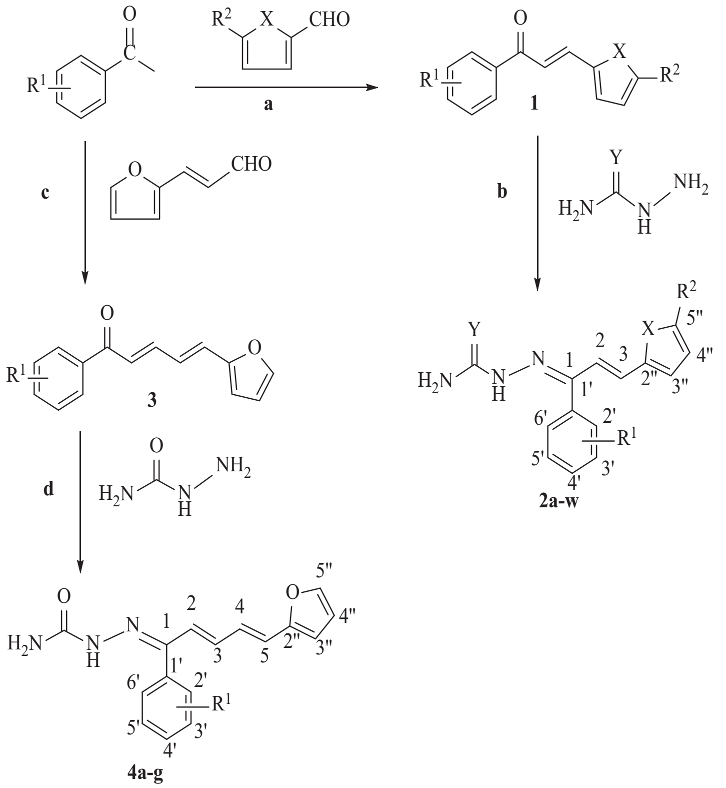
Semicarbazones and thiosemicarbazones are also important compounds. They contain the following scaffolds: NH_2–CO–NH–N = C< and NH_2–CS–NH–N = C<, respectively. Researches and development of their analogues play an important part in the pharmaceutical and insecticidal fields (Salgado and Hayashi 2007; Xue et al. 2007; Gan et al. 2014; Liu et al. 2014). Moreover, their derivatives usually exhibit good selectivity and low toxicity to non-target organisms (Alam et al. 2010; Aly et al. 2010). Therefore, compounds containing semicarbazones or thiosemicarbazones have huge potential in the agricultural field. It is necessary to discover their derivatives that have excellent insecticidal activity and novel structures.

In the current study, 30 semicarbazone and thiosemicarbazone derivatives were designed and synthesized by introducing semicarbazone or thiosemicarbazone moiety into chalcones (Figure S2). Meanwhile, their insecticidal activities against *L. separata* and *P. rapae* were evaluated in the laboratory to discover novel insecticides or lead compounds with simple structures and excellent performances. To the best of our knowledge, although the antifungal activities of them were reported in the two Chinese invention patents published by our research group (Tang, Yang, Gao, Liu, Gao, Xu et al. 2016; Tang, Yang, Gao, Liu, Gao, Zhang et al. 2016), their insecticidal activities have been discovered for the first time.

2. Results and discussion

2.1. Chemistry

The syntheses and chemical structures of the target compounds are shown in Scheme 1. The syntheses of the designed compounds were performed according to



2a: X = O, Y = O, R^1 = 4-F, R^2 = H **2b**: X = O, Y = O, R^1 = 4-Cl, R^2 = H **2c**: X = O, Y = O, R^1 = 4-Br, R^2 = H

2d: X = O, Y = O, R^1 = 3-Br, R^2 = H **2e**: X = O, Y = S, R^1 = 4-F, R^2 = H **2f**: X = O, Y = S, R^1 = 4-Cl, R^2 = H

2g: X = O, Y = S, R^1 = 4-Br, R^2 = H **2h**: X = O, Y = S, R^1 = 4-Ph, R^2 = H **2i**: X = S, Y = O, R^1 = 4-F, R^2 = H

2j: X = S, Y = O, R^1 = 4-Cl, R^2 = H **2k**: X = S, Y = O, R^1 = 4-Br, R^2 = H **2l**: X = S, Y = O, R^1 = 4-Ph, R^2 = H

2m: X = S, Y = O, R^1 = 3-Cl, R^2 = H **2n**: X = S, Y = O, R^1 = 3-Br, R^2 = H **2o**: X = S, Y = O, R^1 = 3,4-Cl_2, R^2 = H

2p: X = S, Y = S, R^1 = 4-F, R^2 = H **2q**: X = S, Y = S, R^1 = 4-Cl, R^2 = H **2r**: X = S, Y = S, R^1 = 4-Br, R^2 = H

2s: X = S, Y = S, R^1 = 4-Ph, R^2 = H **2t**: X = S, Y = S, R^1 = 3-Cl, R^2 = H **2u**: X = S, Y = S, R^1 = 4-F, R^2 = Br

2v: X = S, Y = S, R^1 = 4-Cl, R^2 = Br **2w**: X = S, Y = S, R^1 = 4-Br, R^2 = Br **4a**: R^1 = 4-F **4b**: R^1 = 4-Cl

4c: R^1 = 4-Br **4d**: R^1 = 4-Ph **4e**: R^1 = 3-Br **4f**: R^1 = 2,4-Cl_2 **4g**: R^1 = 3,4-Cl_2

Scheme 1. Synthetic method of target compounds **2a–w** and **4a–g**. Reagents and conditions: (a) EtOH/NaOH, 0–5°C; (b) EtOH/HOAc, 70°C, 20 h; (c) EtOH/NaOH, 0–5°C; (d) EtOH/HOAc, 70°C, 20 h

the methods reported previously and modified appropriately (Qian et al. 2010; Zhang et al. 2011). The structures of compounds **2a–w** and **4a–g** were confirmed by IR, ^{1}H NMR, ^{13}C NMR and HRMS. The results showed that their spectrum data were in agreement with the proposed structures.

Using compound **2r** as an example, the elucidations of its structure are described as follows:

IR(KBr) ν_{max} (cm^{-1}): 3403, 3267, 3157 (NH_2, NH); 1599, 1477, 848 (Phenyl); 1384 (C-N); 950 (H-C=C-H, *E*-configuration); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.03 (s, 1H, NH), 8.50 (s, 1H, NH_2), 8.17 (s, 1H, NH_2), 7.80 (d, $J = 7.8$ Hz, 2H, $C_{2'}$-H, $C_{6'}$-H), 7.55 (d, $J = 4.8$ Hz, 1H, $C_{3''}$-H), 7.28 (d, $J = 7.8$ Hz, 2H, $C_{3'}$-H, $C_{5'}$-H), 7.19 (s, 1H, $C_{5''}$-H), 7.05–7.03 (m, 1H, $C_{4''}$-H), 6.87 (d, $J = 16.2$ Hz, 1H, C_2-H), 6.58 (d, $J = 15.9$ Hz, 1H, C_3-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 178.40 (C=S), 149.21 (C-1), 141.45 (C-2″), 133.01 (C-3′, C-5′), 131.04 (C-2′, C-6′), 130.01 (C-1′), 129.88 (C-5″), 129.52 (C-3″), 128.72 (C-4″), 127.75 (C-3), 127.57 (C-4′), 123.79 (C-2).

2.2. Crystal structure analysis of compound 2r

The molecular structure of compound **2r** was determined by single crystal X-ray diffraction and is shown in Figure S3. Its crystal data and structure refinement are presented in Table S1. Its crystallographic information file is deposited at the Cambridge Crystallographic Data Center (CCDC No. 1405000). The selected structure parameters are displayed in Table S2.

As shown in Table S2 and Figure S3, the thiophene ring, C11–C14, N1–N3 and S2 are located in a plane. The dihedral angle between the plane and the phenyl ring is 67.1(6)°. The double bond between C11 and C12 forms an *E*-configuration, whereas the double bond between C13 and N1 presents a *Z*-configuration. The compound exhibits two intermolecular hydrogen bonds N3–H3A···Br1 and N3–H3B···S2. Their bond length is 2.849 Å and 2.707 Å, respectively. Their bond angle is 153.04° and 156.28°, respectively.

2.3. Insecticidal activity

Compared with the efficient insecticide beta-cypermethrin, all the synthesized compounds were submitted to laboratorial bioassay using *L. separata* and *P. rapae* as targets. The results are displayed in Tables S3 and S4. Compounds **2e–g** and **2p** displayed the best insecticidal activity. The insecticidal activity of **2e–g** against *L. separata* was even superior to beta-cypermethrin. The activity of **2e–g** and **2p** also surpassed beta-cypermethrin against *P. rapae*. **2p–r** and **4e** exhibited excellent activity against *L. separata* and their LC_{50} values were close to beta-cypermethrin. Likewise, the activity of **2q**, **2r** and **4b** was also close to beta-cypermethrin against *P. rapae*. **2d** and **2h** displayed good activity against *L. separata* and their LC_{50} values were 2.72 and 2.98 μg mL^{-1}, respectively. Similarly, **2n**, **2s**, **4d** and **4e** showed good insecticidal activity against *P. rapae*.

According to the results of **2a–c**, **2e–g**, **2i–m** and **2p–t**, it could be found that the activity of thiosemicarbazone derivatives was better than that of semicarbazone derivatives. If the activity of **2p–r** was compared with that of **2u–w**, respectively, it was obvious that when the hydrogen atom at position-5 of the thiophene ring was substituted by a bromine atom, the insecticidal activity of corresponding compound decreased. When the results of **2c**, **2k** and **4c** were compared with those of **2d**, **2n** and **4e**, respectively, it could be known that the compounds with a bromine atom at position-3 of the phenyl ring displayed a better activity than those with a bromine atom at position-4 of the phenyl ring, the cause of which needs to be further found out. However, in accordance with the results of **2j**, **2m**, **2q** and **2t**, it could be found that the compounds with a chlorine atom at position-4 of the phenyl ring exhibited a better activity than those with a chlorine atom at position-3 of the phenyl ring, which also needs to be further studied.

Although a definite structure-activity relationship could not be found through the above-mentioned findings, the interesting results obtained can be used for designing and synthesizing more analogues to further study their quantitative structure-activity relationship so that more bioactive compounds or lead compounds may be discovered.

3. Experimental

3.1. General

3.1.1. Biomaterials

Leucania separata was reared for generations in the laboratory. It was maintained at 22–24 °C, 60% relative humidity (RH) and 14:10 h light: dark photoperiod. Third-instar larvae of *L. separata* were used in the experiments. *P. rapae* was reared for generations in the laboratory. It was held at 24–26 °C, 75–95% RH and 12:12 h light: dark photoperiod. Third-instar larvae of *P. rapae* were used in the experiments.

3.1.2. Instrument and reagent

All chemicals and solvents were purchased from commercial sources unless specified otherwise. IR spectra were recorded on a Nicolet 380 spectrometer. NMR spectra (^{1}H NMR and ^{13}C NMR) were taken on a Bruker 300 MHz spectrometer using deuterated dimethyl sulfoxide (DMSO-d_6) as the solvent. HRMS data were taken on a LTQ Orbitrap Elite mass spectrometer. Melting points were determined using an X-4B micro-melting point apparatus and were not corrected.

3.2. Preparation of intermediates 1 and 3

As shown in Scheme 1, the derivative of acetophenone (0.01 mol) was dissolved in anhydrous ethanol (10 mL). 10% NaOH solution (5 mL) was added to the solution. The mixture of selected aldehyde (0.01 mol) and anhydrous ethanol (10 mL) was slowly added to the above solution in an ice box under stirring. The reaction was kept at 0–5 °C and monitored by thin layer chromatography (TLC) at 254 nm, whose developer was the mixture of petroleum ether (60–90 °C) and ethyl acetate in the ratio of 3:1(by volume). After the reaction was completed, distilled water was added to the reaction mixture. The pH value of the solution was adjusted to about 7 by 10% HCl. The solid that precipitated was filtered and washed with distilled water. The crude products were recrystallized from anhydrous ethanol to give intermediates **1** and **3**.

3.3. Synthetic procedure for target compounds

According to Scheme 1, semicarbazide or thiosemicarbazide (0.015 mol) was dissolved in 95% ethanol (20 mL). Glacial acetic acid (1.5 mL) was added to the solution. Intermediate **1** or **3** (0.015 mol) was completely dissolved in anhydrous ethanol (30 mL). Under stirring, the solution containing the intermediate was slowly added to the above mixture. The reaction continued about 20 h at 70 °C. Its process was monitored by TLC at 254 nm, whose developer was the mixture of petroleum ether (60–90 °C) and ethyl acetate in the ratio of 2:1(by volume). After the reaction was completed, the pH value of the solution was adjusted to about 7 by 10% NaOH. The solid that precipitated was filtered and washed with distilled water. For **2e–h** and **2p–w**, the resulting crude products were purified by silica gel column chromatography and eluted by the mixture of petroleum ether (60–90 °C) and ethyl acetate from 4:1 to 1:1 (by volume). For the others, crude products were recrystallized from anhydrous ethanol to give corresponding products. The purity of each synthesized compound was checked by TLC at 254 nm, whose developer was the mixture of petroleum ether (60–90 °C) and ethyl acetate in the ratio of 2:1 (by volume).

3.4. Determination of crystal structure of compound 2r

The pure sample of **2r** was dissolved in anhydrous ethanol and heated under reflux for 1 h. The solution obtained was placed at room temperature for four days. The yellow prismatic single crystal was obtained. A suitable crystal was selected and mounted on a Xcalibur, Eos diffractometer. The crystal was kept at 293.15 K during data collection. Using Olex2 (Dolomanov et al. 2009), the structure was solved with the Superflip (Palatinus and Chapuis 2007) structure solution program using Charge Flipping and refined with the ShelXL (Sheldrick 2008) refinement package using Least Squares minimisation.

3.5. Assay of insecticidal activity

The insecticidal activity of the target compounds against *L. separata* and *P. rapae* was determined according to the literatures (Tang et al. 2011; Tang and Hou 2011).

3.5.1. Assay of L. separata

The tested compounds and beta-cypermethrin (purity 95%) were dissolved in DMSO, respectively. The solution obtained was diluted into five different concentrations with 0.1% Tween-80 distilled water. Maize leaves were cut into strips (2 cm × 5 cm) and dipped in the solutions for 5 s. The leaves were allowed to air-dry and placed in Petri dishes (9 cm). Ten third-instar larvae of *L. separata* were put into one Petri dish. The Petri dishes were placed in the laboratory held at 22–24 °C, 60% RH and 14:10 h light: dark photoperiod. Control groups were treated with the corresponding solutions without the tested compound or beta-cypermethrin. The experiment for each concentration was replicated three times. Mortality was recorded 24 h after treatment. Percentage mortality was corrected according to the formula of Abbott and LC_{50}

values were calculated with the Statistics Package for the Social Sciences (SPSS) based on probit analysis.

3.5.2. Assay of P. rapae

The tested compounds and beta-cypermethrin (purity 95%) were dissolved in DMSO, respectively. The solution obtained was diluted into five different concentrations with 0.1% Tween-80 distilled water. Twenty third-instar larvae of *P. rapae* were selected from cabbage leaves. They were dipped in the solutions for 5 s within a small cage. They were placed on filter paper to absorb the surplus solutions. Then, they were transferred into Petri dishes (15 cm) with fresh cabbage leaves. The Petri dishes were placed in the laboratory held at 24–26 °C, 75–95% RH and 12:12 h light: dark photoperiod. Control groups were treated with the corresponding solutions without the tested compound or beta-cypermethrin. The experiment for each concentration was replicated three times. The following procedures were the same as the assay of *L. separata*.

4. Conclusion

Thirty semicarbazone and thiosemicarbazone derivatives from chalcones were designed and synthesized. The molecular structure of **2r** was determined by single crystal X-ray diffraction. Their insecticidal activity was evaluated against the above two pests. **2d–h**, **2n**, **2p–s**, **4e** and **4d** showed good insecticidal activity against one or two of the two pests. In particular, **2e–g** had the best insecticidal effects and their activity against the two pests even surpassed beta-cypermethrin. Similarly, the activity of **2p** against *P. rapae* was superior to beta-cypermethrin. Some interesting results have been obtained in respect to the relationship between structure and activity. Additionally, **2e–g** and **2p** can be further used as lead compounds to design and synthesize more analogues because they have simple structure and excellent insecticidal activity.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

Alam O, Mullick P, Verma SP, Gilani SJ, Khan SA, Siddiqui N, Ahsan W. 2010. Synthesis, anticonvulsant and toxicity screening of newer pyrimidine semicarbazone derivatives. Eur J Med Chem. 45(6):2467–2472.

Aly MM, Mohamed YA, El-Bayouki KAM, Basyouni WM, Abbas SY. 2010. Synthesis of some new 4(3*H*)-quinazolinone-2-carboxaldehyde thiosemicarbazones and their metal complexes and a study on their anticonvulsant, analgesic, cytotoxic and antimicrobial activities – Part-1. Eur J Med Chem. 45(8):3365–3373.

Cao S, Qian X, Song G, Huang Q. 2002. Syntheses and insecticidal activity of new 2-(5-(trifluoromethyl)pyridyloxymethyl)-1,3,4-oxadiazoles. J Fluor Chem. 117(1):63–66.

Chen L, Wang X, Lu T, Hou T. 2007. Lead optimization and insecticidal activity of analogues of daphneolone isolated from *Stellera chamaejasme* L. Pest Manag Sci. 63(9):928–934.

Di X, Liu Y, Liu Y, Yu X, Xiao H, Tian X, Gao R. 2007. Synthesis and insecticidal activities of pyridine ring derivatives of podophyllotoxin. Pestic Biochem Phys. 89(1):81–87.

Dolomanov OV, Bourhis LJ, Gildea RJ, Howard JAK, Puschmann H. 2009. Olex2: a complete structure solution, refinement and analysis program. J Appl Crystallogr. 42(2):339–341.

Gan C, Cui J, Su S, Lin Q, Jia L, Fan L, Huang Y. 2014. Synthesis and antiproliferative activity of some steroidal thiosemicarbazones, semicarbazones and hydrozones. Steroids. 87:99–107.

Gao P, Hou TP, Gao R, Cui Q, Liu SG. 2001. Activity of the botanical aphicides 1,5-diphenyl-1-pentanone and 1,5-diphenyl-2-penten-1-one on two species of *Aphididnae*. Pest Manag Sci. 57(3):307–310.

Hou T, Ciu Q, Chen S, Hou R, Liu S. 2002. New compounds against aphides from *Stellera chamaejasme* L. Chin J Org Chem. 22:67–70.

Liu YQ, Liu Y, Xiao H, Gao R, Tian X. 2008. Synthesis and insecticidal activities of novel derivatives of podophyllotoxin: Part XII. Pestic Biochem Phys. 91(2):116–121.

Liu Z, Wu S, Wang Y, Li R, Wang J, Wang L, Zhao Y, Gong P. 2014. Design, synthesis and biological evaluation of novel thieno[3,2-*d*] pyrimidine derivatives possessing diaryl semicarbazone scaffolds as potent antitumor agents. Eur J Med Chem. 87:782–793.

Palatinus L, Chapuis G. 2007. Superflip – a computer program for the solution of crystal structures by charge flipping in arbitrary dimensions. J Appl Crystallogr. 40(4):786–790.

Peng LN, Lin RS, Zeng J. 1996. Determination of the insecticidal resistance of *Pieris rapae*. J North West Agric Univ. 18:530–532.

Qian Y, Zhang HJ, Lv PC, Zhu HL. 2010. Synthesis, molecular modeling and biological evaluation of guanidine derivatives as novel antitubulin agents. Bioorg Med Chem. 18(23): 8218–8225.

Salgado VL, Hayashi JH. 2007. Metaflumizone is a novel sodium channel blocker insecticide. Vet Parasitol. 150(3):182–189.

Sheldrick GM. 2008. A short history of Shelx. Acta Crystallogr A: Found Crystallogr. 64(1): 112–122. A

Tang XR, Chen S, Wang L. 2011. Purification and identification of carvacrol from the root of *Stellera chamaejasme* and research on its insecticidal activity. Nat Prod Res. 25(3):320–325.

Tang XR, Hou TP. 2011. Isolation and identification of 2-isopropyl-5-methylphenol from *Stellera chamaejasme* and its insecticidal activity against *Aphis craccivora* and *Pieris rapae*. Nat Prod Res. 25(4):381–386.

Tang XR, Yang J, Gao S, Liu H, Gao Y, Xu ZH, Zeng Y, Zhang Y, Du Q, Wang L, Xihua University. 2016 Mar 30. Semicarbazone analogues and their preparation methods and applications. Chinese patent CN105439995A.

Tang XR, Yang J, Gao S, Liu H, Gao Y, Zhang Y, Xu ZH, Zeng Y, Li WY, Wang L, Xihua University. 2016 Apr 6. 1-(2-Furyl)-1,3-piperylene analogues and their preparation methods and applications. Chinese patent CN105461670A.

Tao L, Lin C, Hou T. 2007. Synthesis and structure–activity study of botanical aphicides 1,5-diphenyl-1-pentanone analogues. Pestic Biochem Phys. 89(1):60–64.

Xu X, Qian X, Li Z, Huang Q, Chen G. 2003. Synthesis and insecticidal activity of new substituted *N*-aryl-*N*′-benzoylthiourea compounds. J Fluor Chem. 121(1):51–54.

Xue CB, Zhang L, Luo WC, Xie XY, Jiang L, Xiao T. 2007. 3D-QSAR and molecular docking studies of benzaldehyde thiosemicarbazone, benzaldehyde, benzoic acid, and their derivatives as phenoloxidase inhibitors. Bioorg Med Chem. 15(5):2006–2015.

Yang CL, Gong GJ, Tan FJ, You ZP. 1995. Studies on resistance and mode of action of *Leucania separata*. Plant Prot. 21:2–5.

Zhang HJ, Qia Y, Zhu DD, Yang XG, Zhu HL. 2011. Synthesis, molecular modeling and biological evaluation of chalcone thiosemicarbazide derivatives as novel anticancer agents. Eur J Med Chem. 46(9):4702–4708.

Zheng X, Li Z, Wang Y, Chen W, Huang Q, Liu C, Song G. 2003. Syntheses and insecticidal activities of novel 2,5-disubstituted 1,3,4-oxadiazoles. J Fluor Chem. 123(2):163–169.