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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, biological activities, and 3D-QSAR studies of (R)-2-phenyl-4,5-dihydrothiazole-4-carboxamide derivatives containing a sulfonohydrazide moiety

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Abstract

To discover a novel lead structure for antiphytopathogenic fungus agent, a series of (R)-2-phenyl-4,5-dihydrothiazole-4-carboxamide derivatives containing a sulfonohydrazide moiety were designed and synthesized. They were determined by melting points, ^{1}H NMR, ^{13}C NMR, and elemental analysis (EA). The biological activity results revealed that these title compounds possessed antifungal and insecticidal activities. Some title compounds against Alternaria solani, Physalospora piricola, Cercospora arachidicola, Phytophthora capsici, Fusarium graminearum, and Sclerotinia sclerotiorum displayed moderate to good antifungal activities at 50 mg/L, especially, compounds **6b** and **6p** displayed good and broad-spectrum antifungal activities. The structure activity relationships were discussed. A 3D-QSAR model was established based on the antifungal activity against Phytophthora capsici, indicating that electrostatic and hydrophobic fields were the two most significant factors for antifungal activity. Hence, structure optimization based on the CoMSIA model was performed to find compound **6p** with excellent activity against Phytophthora capsici, and the EC_{50} values of compound **6p** were comparable to those of chlorothalonil. Furthermore, the insecticidal activity of compound **6p** against Culex pipiens larvae at 1 mg/L was considerable to that of chlorantraniliprole. Therefore, compound **6p** can be used as a novel lead structure for antiphytopathogenic fungus and insecticidal agent development.

Keywords (R)-2-phenyl-4,5-dihydrothiazole-4-carboxamide · Sulfonohydrazide · Antifungal activity · Insecticidal activity · Structure activity relationship

Introduction

The global population is expected to increase to over 9 billion by 2050, with the associated demand for increasing food production (Godfray et al. 2010; Ray et al. 2013). Plant diseases mainly caused by fungi, viruses, oomycetes, and bacteria have brought about severe losses to crops yield per year in the world, hence some efficient measures have been taken to resolve the issue of plant disease. It is well known that the application of agrochemicals plays a significant role in increasing the yield of crops. However, due to the widespread and frequent use of conventional agrochemicals with the same mechanism of action, the increasing resistance to agrochemicals has been a major problem in plant diseases control (Tabashnik et al. 2014; Forgash 1984). Therefore, to develop novel agrochemicals with novel mechanisms of action and eco-friendly characteristics has been an urgent task for scientists.

Supplementary information The online version of this article (https://doi.org/10.1007/s00044-020-02499-3) contains supplementary material, which is available to authorized users.

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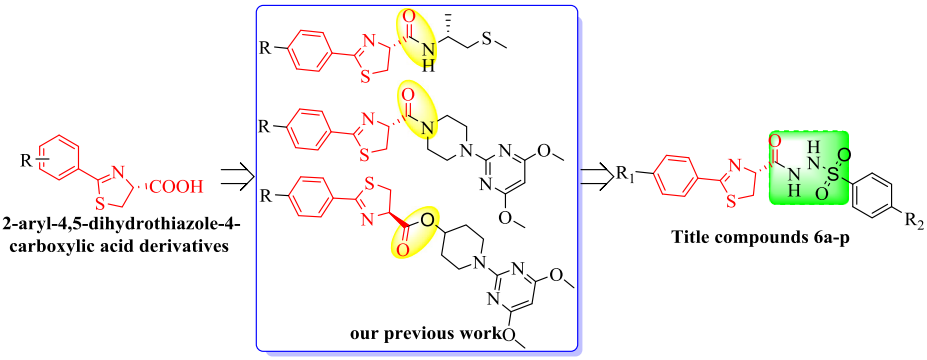
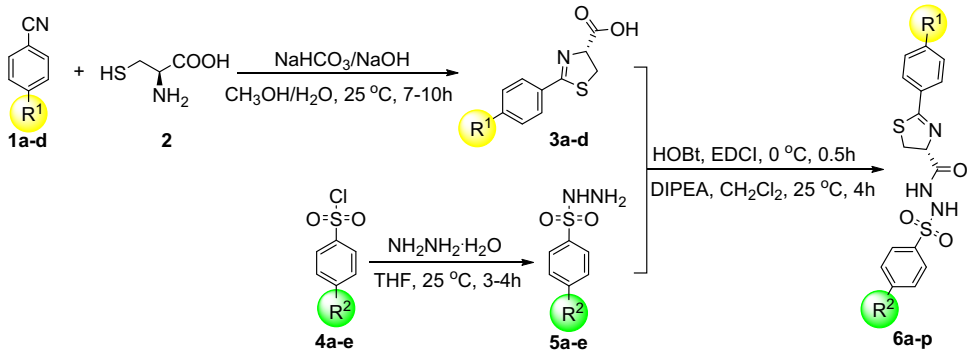


Fig. 1 Design of title compounds



Scheme 1 Synthetic route of title compounds

6a: R_1 = H, R_2 = H;
6b: R_1 = H, R_2 =Cl;
6c: R_1 = H, R_2 = CH_3;
6d: R_1 = H, R_2 = OCH_3;
6e: R_1 = H, R_2 = NO_2;
6f: R_1 = CH_3, R_2 = H;
6g: R_1 = CH_3, R_2 = Cl;
6h: R_1 = CH_3, R_2 = CH_3;
6i: R_1 = CH_3, R_2 = OCH_3;
6j: R_1 = CH_3; R_2= NO_2
6k: R_1 = NO_2, R_2 = H;
6l: R_1 = NO_2, R_2 = Cl;
6m: R_1 = NO_2, R_2 = CH_3;
6n: R_1 = NO_2, R_2 = OCH_3;
6o: R_1 = NO_2; R_2 = NO_2
6p: R_1 = Cl, R_2 = Cl

Natural products possess the characteristics of low toxicity, good biodegradability, and compatibility, so they have been widely used as commercial fungicides (Ma et al. 2013; Li et al. 2018), insecticides (Crouse et al. 2018; Tacoli et al. 2018), and herbicides (Duke et al. 2010). In the past years, many 2-aryl-4,5-dihydrothiazole-4-carboxylic acid derivatives with various biological and medicinal activities, including anti-HIV (Pattenden and Thom 1993), antibiotic (Zamri et al. 2003), and anticancer activity (Gududuru et al. 2005), have reported, whereas there is few report about the utilization in preventing plant disease. Recently, our research group have reported some (R)-2-aryl-4,5-dihydrothiazole-4-carboxylic acid derivatives with amide and ester moieties, which exhibited good and broad-spectrum antifungal activities (Fig. 1) (Liu et al. 2019, 2015). Sulfonyl hydrazine can act on many enzymes in organism to a variety of biological activities, such as antiviral (Selvakumar et al. 2017), antifungal (Dixit et al. 2010), antimicrobial (Siddiqa et al. 2014), antitumor (Kamal et al. 2007), and antioxidant activity (Ardjani and Mekelleche 2017).

Taking consideration of the above viewpoints, a series of (R)-2-phenyl-4,5-dihydrothiazole-4-carboxamide derivative containing a sulfonohydrazide moiety were designed and synthesized, and their antifungal and insecticidal activities were tested accordingly. The preliminary structure activity relationship (SAR) was investigated as well.

Materials and methods

^{1}H NMR and ^{13}C NMR were recorded on a Bruker AV400 spectrometer (400 MHz) using $CDCl_3$ or DMSO-d_6 as solvent. Chemical shift values (δ) were reported in ppm with tetramethylsilane as the internal standard. Melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and uncorrected. Elemental analyses were performed on a Vario EL elemental analyzer. (Elementar Co., Germany). Column chromatography purification was carried out using silica gel (200–300 mesh). Reagents were all analytically or chemically pure. All solvents were dried by standard methods in advance and distilled before use. Intermediates **3a–c** and **5a–e** were synthesized in Scheme 1 according to the literatures (Liu et al. 2015; Backes et al. 2015).

General synthetic procedure for title compounds 6a–p

1-Hydroxy-1H-benzotriazole (HOBt, 0.072 g, 0.53 mmol), N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDCI, 0.115 g, 0.6 mmol) and (R)-2-phenyl-4,5-dihydrothiazole-4-carboxylic acid **3** (0.5 mmol) were subsequently added to anhydrous dichloromethane (15 mL) at 0 °C. After stirred at room temperature for 0.5 h, benzenesulfonohydrazides **5** (0.5 mmol) and N,N-diisopropylethylamine (DIPEA) (0.142 g, 1.1 mmol) were subsequently added at 0 °C. The reaction was warmed to room temperature and stirred for 4 h, and then solvent was removed under reduced pressure to give the title compounds **6a–p**.

(*R*)-*N*′-(2-Phenyl-4,5-dihydrothiazole-4-carbonyl) benzenesulfonohydrazide (6a)

White solid, yield 56.1%, mp 185–186 °C (EtOAc). $[\alpha]_D^{20} = +16.2$ (*c* 1, MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.50 (1H, s, NH), 10.18 (1H, s, NH), 7.90–7.88 (4H, m, Ph-H), 7.57 (2H, dd, $J = 7.0$ Hz and $J = 7.2$ Hz, Ph-H), 7.53 (2H, d, $J = 7.5$ Hz, Ph-H), 7.50 (2H, d, $J = 7.7$ Hz, Ph-H), 5.38 (1H, t, $J = 9.1$ Hz, CH), 3.79 (1H, dd, $J = 10.9$ Hz, $J = 9.6$ Hz, 1/2CH_2), 3.63 (1H, dd, $J = 10.9$ Hz, $J = 8.5$ Hz, 1/2CH_2). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 169.59, 168.68, 132.50, 132.40, 131.92, 128.86, 128.57, 128.44, 127.50, 126.64, 78.19, 35.01. Elem. anal. calcd. for $C_{16}H_{15}N_3O_3S_2$ (%): C 53.17; H 4.18; N, 11.63. Found (%): C 53.19; H 4.22; N 11.67.

(*R*)-4-Chloro-*N*′-(2-phenyl-4,5-dihydrothiazole-4-carbonyl) benzenesulfonohydrazide (6b)

White solid, yield 66.2%, mp 193–194 °C (EtOAc). $[\alpha]_D^{20} = +14.1$ (*c* 1, MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.47 (1H, s, NH), 10.15 (1H, s, NH), 7.88 (2H, d, $J = 7.4$ Hz, Ph-H), 7.82 (2H, d, $J = 8.0$ Hz, Ph-H), 7.72 (2H, d, $J = 7.6$ Hz, Ph-H), 7.56 (1H, t, $J = 7.5$ Hz, Ph-H), 7.49 (2H, t, $J = 7.4$ Hz, Ph-H), 5.37 (1H, t, $J = 8.7$ Hz, CH), 3.80 (1H, dd, $J = 11.0$ Hz, $J = 9.6$ Hz, 1/2CH_2), 3.64 (1H, dd, $J = 10.9$ Hz, $J = 8.7$ Hz, 1/2CH_2). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 169.72, 168.01, 132.77, 132.20, 131.81, 130.63, 128.86, 127.85, 127.78, 125.84, 78.50, 35.62. Elem. anal. calcd. for $C_{16}H_{14}ClN_3O_3S_2$ (%): C 48.54; H 3.56; N 10.61. Found (%): C 48.58; H 3.59; N 10.66.

(*R*)-4-Methyl-*N*′-(2-phenyl-4,5-dihydrothiazole-4-carbonyl) benzenesulfonohydrazide (6c)

White solid, yield 57.2%, m. p. 182–183 °C (EtOAc). $[\alpha]_D^{20} = +14.7$ (*c* 1, MeOH) ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.48 (1H, s, NH), 10.15 (1H, s, NH), 7.88 (2H, d, $J = 7.5$ Hz, Ph-H), 7.77 (2H, d, $J = 8.1$ Hz, Ph-H), 7.57 (1H, t, $J = 7.5$ Hz, Ph-H), 7.49 (2H, t, $J = 7.4$ Hz, Ph-H), 7.31 (2H, d, $J = 8.0$ Hz, Ph-H), 5.34 (1H, t, $J = 9.0$ Hz, CH), 3.75 (1H, dd, $J = 10.8$ Hz, $J = 9.6$ Hz, 1/2CH_2), 3.59 (1H, dd, $J = 10.9$ Hz, $J = 8.7$ Hz, 1/2CH_2), 2.36 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 169.73, 168.50, 142.02, 132.52, 131.99, 129.83, 129.43, 128.62, 128.47, 127.54, 78.16, 34.96, 21.18. Elem. anal. calcd. for $C_{17}H_{17}N_3O_3S_2$ (%): C 54.38; H 4.56; N 11.19. Found (%): C 54.42; H 4.57; N 11.23.

(*R*)-4-Methoxy-*N*′-(2-phenyl-4,5-dihydrothiazole-4-carbonyl) benzenesulfonohydrazide (6d)

White solid, yield 51.5%, m. p. 192–193 °C (EtOAc). $[\alpha]_D^{20} = +14.2$ (*c* 1, MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.48 (1H, s, NH), 10.13 (1H, s, NH), 7.89 (2H, d, $J = 7.4$ Hz, Ph-H), 7.84 (2H, d, $J = 8.2$ Hz, Ph-H), 7.57 (1H, t, $J = 7.5$ Hz, Ph-H), 7.50 (2H, d, $J = 7.4$ Hz, Ph-H), 7.05 (2H, t, $J = 8.2$ Hz, Ph-H), 5.32 (1H, t, $J = 8.9$ Hz, CH), 3.83 (3H, s, OCH_3), 3.75 (1H, dd, $J = 10.9$ Hz, $J = 9.6$ Hz, 1/2CH_2), 3.59 (1H, dd, $J = 10.7$ Hz, $J = 8.8$ Hz, 1/2CH_2). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 169.80, 167.80, 162.06, 132.51, 131.94, 130.28, 128.58, 127.51, 125.07, 114.15, 78.08, 55.54, 35.03. Elem. anal. calcd. for $C_{17}H_{17}N_3O_4S_2$ (%): C 52.16; H 4.38; N 10.73. Found (%): C 52.19; H 4.38; N 10.77.

(*R*)-4-Nitro-*N*′-(2-phenyl-4,5-dihydrothiazole-4-carbonyl) benzenesulfonohydrazide (6e)

White solid, yield 54.2%, m. p. 184–185 °C (EtOAc). $[\alpha]_D^{20} = +14.6$ (*c* 1, MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.46 (1H, s, NH), 10.14 (1H, s, NH), 7.86 (2H, d, $J = 7.4$ Hz, Ph-H), 7.82 (2H, d, $J = 8.3$ Hz, Ph-H), 7.71 (2H, d, $J = 7.4$ Hz, Ph-H), 7.55 (1H, t, $J = 7.5$ Hz, Ph-H), 7.50 (2H, dd, $J = 7.6$ Hz and $J = 8.0$ Hz, Ph-H), 5.36 (1H, t, $J = 8.9$ Hz, CH), 3.79 (1H, dd, $J = 10.9$ Hz, $J = 9.5$ Hz, 1/2CH_2), 3.63 (1H, dd, $J = 10.8$ Hz, $J = 8.6$ Hz, 1/2CH_2). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 169.63, 167.92, 165.62, 132.12, 132.10, 131.72, 130.54, 128.76, 127.69, 125.75, 78.41, 35.53. Elem. anal. calcd. for $C_{16}H_{14}N_4O_5S_2$ (%): C 47.28; H 3.47; N 13.78. Found (%): C 47.31; H 3.49; N 13.82.

(*R*)-*N*′-[2-(*p*-Tolyl)-4,5-dihydrothiazole-4-carbonyl] benzenesulfonohydrazide (6f)

White solid, yield 54.3%, m. p. 187–188 °C (EtOAc). $[\alpha]_D^{20} = +16.5$ (*c* 1, MeOH) ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.40 (1H, s, NH), 10.03 (1H, s,

NH), 7.80 (2H, d, $J = 7.3$ Hz, Ph-H), 7.70 (2H, d, $J = 8.1$ Hz, Ph-H), 7.62 (1H, t, $J = 7.5$ Hz, Ph-H), 7.49 (2H, t, $J = 7.7$ Hz, Ph-H), 7.31 (2H, d, $J = 8.0$ Hz, Ph-H), 5.11 (1H, t, $J = 9.0$ Hz, CH), 3.56 (1H, dd, $J = 10.9$ Hz, $J = 9.6$ Hz, 1/2CH_2), 3.24 (1H, dd, $J = 11.0$ Hz, $J = 8.7$ Hz, 1/2CH_2), 2.37 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 169.26, 168.82, 142.42, 139.04, 133.55, 130.02, 129.82, 129.27, 128.68, 128.11, 77.92, 34.77, 21.50. Elem. anal. calcd. for $C_{17}H_{17}N_3O_3S_2$ (%): C 54.38; H 4.56; N 11.19; Found (%): C 54.39; H 4.63; N 11.23.

(*R*)-4-Chloro-*N*′-[2-(*p*-tolyl)-4,5-dihydrothiazole-4-carbonyl] benzenesulfonohydrazide (6g)

White solid, yield 53.8%, m. p. 179–180 °C (EtOAc). $[\alpha]_D^{20} = +17.8$ (*c* 1, MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 10.52 (1H, s, NH), 10.11 (1H, s, NH), 7.82 (2H, d, $J = 7.5$ Hz, Ph-H), 7.69 (2H, d, $J = 8.1$ Hz, Ph-H), 7.51 (2H, d, $J = 7.5$ Hz, Ph-H), 7.24 (2H, d, $J = 8.0$ Hz, Ph-H), 5.26 (1H, t, $J = 9.0$ Hz, CH), 3.67 (1H, dd, $J = 10.7$ Hz, $J = 9.4$ Hz, 1/2CH_2), 3.51 (1H, dd, $J = 10.7$ Hz, $J = 8.4$ Hz, 1/2CH_2), 2.29 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 169.25, 168.14, 141.56, 136.37, 130.72, 129.28, 128.96, 128.93, 128.27, 127.95, 77.59, 34.43, 20.65. Elem. anal. calcd. for $C_{17}H_{16}ClN_3O_3S_2$ (%): C 49.85; H 3.97; N 10.29; Found (%): C 49.89; H 3.98; N 10.33.

(*R*)-4-Methyl-*N*′-[2-(*p*-tolyl)-4,5-dihydrothiazole-4-carbonyl] benzenesulfonohydrazide (6h)

White solid, yield 63.1%, m. p. 210–211 °C (EtOAc). $[\alpha]_D^{20} = +17.4$ (*c* 1, MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.29 (1H, s, NH), 10.02 (1H, s, NH), 7.83 (2H, d, $J = 7.5$ Hz, Ph-H), 7.78 (2H, d, $J = 8.0$ Hz, Ph-H), 7.01–6.97 (4H, m, Ph-H), 5.26 (1H, t, $J = 9.0$ Hz, CH), 3.78 (6H, s, CH_3), 3.69 (1H, dd, $J = 11.0$ Hz, $J = 9.6$ Hz, 1/2CH_2), 3.54 (1H, dd, $J = 10.9$ Hz, $J = 8.6$ Hz, 1/2CH_2). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 167.74, 165.65, 128.18, 127.52, 127.32, 122.97, 122.78, 122.54, 112.05, 111.70, 75.98, 53.38, 32.94, 32.87. Elem. anal. calcd. for $C_{18}H_{19}N_3O_3S_2$ (%):C 55.51; H 4.92; N 10.79. Found (%): C 55.54; H 4.96; N 10.83.

(*R*)-4-Methoxy-*N*′-[2-(*p*-tolyl)-4,5-dihydrothiazole-4-carbonyl]benzenesulfonohydrazide (6i)

White solid, yield 54.3%, m. p. 180–181 °C (EtOAc). $[\alpha]_D^{20} = +17.1$ (*c* 1, MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.36 (1H, s, NH), 10.10 (1H, s, NH), 7.90 (2H, d, $J = 7.4$ Hz, Ph-H), 7.80 (2H, d, $J = 8.3$ Hz, Ph-H), 7.34 (2H, d, $J = 7.5$ Hz, Ph-H), 7.05 (2H, d, $J = 8.2$ Hz, Ph-H), 5.36 (1H, t, $J = 9.1$ Hz, CH), 3.84 (3H, s, OCH_3), 3.77 (1H, dd, $J = 10.8$ Hz, $J = 9.6$ Hz, 1/2CH_2), 3.62 (1H, dd, $J = 10.8$ Hz, $J = 8.5$ Hz, 1/2CH_2), 2.39 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 170.38, 169.07, 162.78, 142.64, 130.51, 130.10, 130.08, 129.12, 125.33, 114.49, 78.83, 56.17, 35.61, 21.83. Elem. anal. calcd. for $C_{19}H_{19}N_3O_4S$ (%): C 53.32; H 4.72; N 10.36. Found (%): C 53.35; H 4.76; N 10.39.

(*R*)-4-Nitro-*N*′-[2-(*p*-tolyl)-4,5-dihydrothiazole-4-carbonyl] benzenesulfonohydrazide (6j)

Yellow solid, yield 57.3%, m. p. 193–194 °C (EtOAc). $[\alpha]_D^{20} = +17.8$ (*c* 1, MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.60 (1H, s, NH), 10.19 (1H, s, NH), 7.90 (2H, d, $J = 7.5$ Hz, Ph-H), 7.78 (2H, d, $J = 8.1$ Hz, Ph-H), 7.59 (2H, d, $J = 7.5$ Hz, Ph-H), 7.32 (2H, d, $J = 8.0$ Hz, Ph-H), 5.35 (1H, t, $J = 9.0$ Hz, CH), 3.76 (1H, dd, $J = 10.9$ Hz, $J = 9.5$ Hz, 1/2CH_2), 3.60 (1H, dd, $J = 10.8$ Hz, $J = 8.6$ Hz, 1/2CH_2), 2.37 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 171.25, 170.14, 166.09, 143.56, 138.37, 131.28, 130.96, 130.93, 130.27, 129.95, 79.59, 36.43, 22.65. Elem. anal. calcd. for $C_{17}H_{16}N_4O_5S_2$ (%): C 48.56; H 3.84; N 13.33. Found (%): C 48.58; H 3.89; N 13.38.

(*R*)-*N*′-[2-(4-Nitrophenyl)-4,5-dihydrothiazole-4-carbonyl] benzenesulfonohydrazide (6k)

Yellow solid, yield 51.8%, m. p. 211–212 °C (EtOAc). $[\alpha]_D^{20} = +17.3$ (*c* 1, MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.49 (1H, s, NH), 10.18 (1H, s, NH), 7.92–7.88 (4H, m, Ph-H), 7.61–7.57 (3H, m, Ph-H), 7.50 (2H, t, $J = 7.9$ Hz, Ph-H), 5.39 (1H, t, $J = 8.8$ Hz, CH), 3.81 (1H, dd, $J = 11.1$ Hz, $J = 9.4$ Hz, 1/2CH_2), 3.65 (1H, dd, $J = 10.9$ Hz, $J = 8.6$ Hz, 1/2CH_2). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 169.51, 167.62, 165.47, 132.49, 131.97, 131.20, 130.21, 129.01, 128.60, 127.51, 78.21, 35.38. Elem. anal. calcd. for $C_{16}H_{14}N_4O_5S_2$ (%): C 47.28; H 3.47; N 13.78. Found (%): C 47.32; H 3.52; N 13.83.

(*R*)-4-Chloro-*N*′-[2-(4-nitrophenyl)-4,5-dihydrothiazole-4-carbonyl]benzenesulfonohydrazide (6l)

White solid, yield 59.3%, m. p. 198–199 °C (EtOAc). $[\alpha]_D^{20} = +14.9$ (*c* 1, MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.63 (1H, s, NH), 10.29 (1H, s, NH), 8.37 (2H, d, $J = 7.6$ Hz, Ph-H), 8.15 (2H, d, $J = 8.2$ Hz, Ph-H), 7.91 (2H, d, $J = 7.5$ Hz, Ph-H), 7.60 (2H, d, $J = 8.1$ Hz, Ph-H), 5.48 (1H, t, $J = 8.8$ Hz, CH), 3.89 (1H, dd, $J = 10.9$ Hz, $J = 9.6$ Hz, 1/2CH_2), 3.72 (1H, dd, $J = 10.8$ Hz, $J = 8.7$ Hz, 1/2CH_2). ^{13}C NMR spectrum

(101 MHz, DMSO-d_6), δ, ppm (J, Hz): 170.78, 168.99, 166.12, 150.83, 139.20, 138.39, 132.68, 131.25, 130.95, 130.28, 79.84, 37.15. Elem. anal. calcd. for $C_{16}H_{13}ClN_4O_5S_2$ (%): C 43.59; H 2.97; N 12.71. Found (%): C 43.63; H 2.99; N 12.75.

(*R*)-4-Methyl-*N*′-[2-(4-nitrophenyl)-4,5-dihydrothiazole-4-carbonyl]benzenesulfonohydrazide (6m)

White solid, yield 48.9%, m. p. 201–202 °C (EtOAc). $[\alpha]_D^{20} = +16.5$ (c 1, MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 10.63 (1H, s, NH), 10.22 (1H, s, NH), 7.93 (2H, d, $J = 7.7$ Hz, Ph-H), 7.80 (2H, d, $J = 8.1$ Hz, Ph-H), 7.62 (2H, d, $J = 7.6$ Hz, Ph-H), 7.35 (2H, d, $J = 8.0$ Hz, Ph-H), 5.37 (1H, t, $J = 8.8$ Hz, CH), 3.78 (1H, dd, $J = 11.0$ Hz, $J = 9.5$ Hz, 1/2CH_2), 3.62 (1H, dd, $J = 10.9$ Hz, $J = 8.6$ Hz, 1/2CH_2), 2.39 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (J, Hz): 168.75, 167.64, 163.59, 141.06, 130.22, 128.78, 128.46, 128.43, 127.77, 127.45, 77.09, 33.93, 20.15. Elem. anal. calcd. for $C_{17}H_{16}N_4O_5S_2$ (%): C 48.56; H 3.84; N 13.33. Found (%): C 48.59; H 3.86; N 13.37.

(*R*)-4-Methoxy-*N*′-[2-(4-nitrophenyl)-4,5-dihydrothiazole-4-carbonyl]benzenesulfonohydrazide (6n)

White solid, yield 52.5%, m. p. 197–198 °C (EtOAc). $[\alpha]_D^{20} = +14.7$ (c 1, MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 10.56 (1H, s, NH), 10.13 (1H, s, NH), 7.88 (2H, d, $J = 7.3$ Hz, Ph-H), 7.81 (2H, d, $J = 8.1$ Hz, Ph-H), 7.57 (2H, d, $J = 7.3$ Hz, Ph-H), 7.03 (2H, d, $J = 8.2$ Hz, Ph-H), 5.30 (1H, t, $J = 9.0$ Hz, CH), 3.80 (s, 3H, OCH_3), 3.72 (1H, dd, $J = 10.9$ Hz, $J = 9.5$ Hz, 1/2CH_2), 3.56 (1H, dd, $J = 10.8$ Hz, $J = 8.6$ Hz, 1/2CH_2). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (J, Hz): 169.13, 167.19, 161.45, 136.16, 130.63, 129.64, 128.80, 128.11, 124.43, 113.52, 77.42, 54.92, 34.38. Elem. anal. calcd. for $C_{17}H_{16}N_4O_6S_2$ (%): C 46.78; H 3.69; N 12.84. Found (%): C 46.85; H 3.73; N 12.87.

(*R*)-4-Nitro-*N*′-[2-(4-nitrophenyl)-4,5-dihydrothiazole-4-carbonyl]benzenesulfonohydrazide (6o)

White solid, yield 55.8%, m. p. 189–190 °C (EtOAc). $[\alpha]_D^{20} = +15.1$ (c 1, MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 10.66 (1H, s, NH), 10.27 (1H, s, NH), 7.98 (2H, d, $J = 7.7$ Hz, Ph-H), 7.91 (2H, d, $J = 8.3$ Hz, Ph-H), 7.82 (2H, d, $J = 7.6$ Hz, Ph-H), 7.68 (2H, d, $J = 8.3$ Hz, Ph-H), 5.46 (1H, t, $J = 8.7$ Hz, CH), 3.89 (1H, dd, $J = 10.9$ Hz, $J = 9.6$ Hz, 1/2CH_2), 3.73 (1H, dd, $J = 10.7$ Hz, $J = 8.8$ Hz, 1/2CH_2). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (J, Hz): 171.30, 169.66, 166.32, 138.69, 133.80, 133.60, 133.10, 132.22, 131.30, 130.62, 80.07, 37.20. Elem. anal. calcd. for $C_{16}H_{13}N_5O_7S_2$ (%): C 42.57; H 2.90; N 15.51. Found (%): C 42.59; H 2.95; N 15.54.

(*R*)-4-Chloro-*N*′-(2-phenyl-4,5-dihydrothiazole-4-carbonyl) benzenesulfonohydrazide (6p)

White solid, yield 68.3%, mp 184–185 °C (EtOAc). $[\alpha]_D^{20} = +14.6$ (c 1, MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 10.54 (1H, s, NH), 10.15 (1H, s, NH), 7.87 (2H, d, $J = 7.4$ Hz, Ph-H), 7.80 (2H, d, $J = 8.0$ Hz, Ph-H), 7.70 (2H, d, $J = 7.5$ Hz, Ph-H), 7.56 (2H, t, $J = 7.5$ Hz, Ph-H), 5.35 (1H, t, $J = 8.7$ Hz, CH), 3.78 (1H, dd, $J = 10.8$ Hz, $J = 9.5$ Hz, 1/2CH_2), 3.62 (1H, dd, $J = 10.9$ Hz, $J = 8.8$ Hz, 1/2CH_2). ^{13}C NMR spectrum, δ, ppm (J, Hz): 167.78, 166.15, 135.18, 130.29, 129.89, 129.60, 128.71, 127.79, 127.11, 123.94, 76.56, 33.69. Elem. anal. calcd. for $C_{16}H_{13}Cl_2N_3O_3S_2$ (%): C 44.66; H 3.05; N 9.77. Found (%): C 44.59; H 3.09; N 9.76.

Biological activity screening

Fungicidal activity

Title compounds **6a–p** against six phytopathogenic fungi (*Alternaria solani*, *Physalospora piricola*, *Cercospora arachidicola*, *Phytophthora capsici*, *Fusarium graminearum*, and *Sclerotinia sclerotiorum*) at the concentration of 50 mg/L were determined by the mycelium growth rate test according to the literatures (Liu et al. 2016), and calculated using the formula: Relative inhibition rate (%) = $(D_1 - D_2)/D_1 \times 100\%$, D_1 and D_2 are the average diameter of circle mycelia during the blank assay and test assay, respectively. Chlorothalonil and carbendazim were used as the control. The fungicidal activities of title compounds **6a–p** at 50 mg/L were shown in Table 1. The EC_{50} values of title compounds **6a–o** against *Phytophthora capsici* were displayed in Table 2. The EC_{50} values of title compound **6p** and chlorothalonil against six phytopathogenic fungi were shown in Table 3.

Insecticidal activity against *Culex pipiens*

The insecticidal activity of title compounds **6a–p** with chlorantraniliprole as positive control against *Culex pipiens* were evaluated in the greenhouse according to the reported method (Liu et al. 2016) in Table 4.

3D-QSAR calculation methods

The CoMSIA studies were carried out using a SYBYL 6.9 software from Tripos Inc (St. Louis, MO, USA). All molecules were built with the SKETCH option in SYBYL under default settings. CoMSIA contour maps were generated with partial least-squares coefficients (Liu et al. 2018). The partial least-squares was carried out to establish a linear relationship. Cross-validation was performed by using the "leave-one-out" method to obtain the optimal number of

Table 1 Antifungal activity of the title compounds **6a–p**, chlorothalonil, and carbendazim

Compd.	Antifungal activity, inhibition rate (%, 50 mg/L)					
	Alternaria solani	*Physalospora piricola*	*Cercospora arachidicola*	*Phytophthora capsici*	*Fusarium graminearum*	*Sclerotinia sclerotiorum*
6a	21.7	71.8	43.4	59.5	53.2	43.2
6b	**55.9**	**86.2**	**59.7**	**75.2**	**65.5**	**50.0**
6c	32.7	66.3	50.3	48.8	56.3	32.5
6d	34.8	67.9	49.5	55.3	43.7	35.6
6e	24.6	60.4	47.7	53.7	54.2	42.4
6f	22.7	66.3	57.6	60.3	46.7	36.2
6g	**55.2**	**84.8**	**64.2**	**65.7**	**56.9**	**43.5**
6h	31.7	63.1	48.9	48.5	37.4	31.7
6i	43.4	62.5	53.1	45.2	45.3	41.9
6j	22.6	60.1	47.3	56.2	44.7	24.3
6k	6.9	50.4	27.8	36.7	34.2	54.4
6l	18.6	55.2	47.8	38.9	33.5	**65.3**
6m	12.5	51.7	32.7	33.5	22.1	54.8
6n	8.9	48.9	36.5	21.7	21.0	50.2
6o	9.5	49.4	43.1	31.8	16.8	54.2
6p	**54.7**	**85.9**	**60.4**	**84.3**	**59.8**	**57.9**
Chlorothalonil	64.5	78.5	60.3	83.6	40.5	42.0
Carbendazim	38.3	45.6	12.1	31.4	94.1	93.7

The bold values were used to discuss the antifungal activity

Table 2 Antifungal activities as EC_{50} (mg/L) against *Phytophthora capsici* of title compounds **6a–o**

Compd.	EC_{50}	pEC_{50}[a]	pEC_{50}[b]	Compd.	EC_{50}	pEC_{50}[a]	pEC_{50}[b]
6a	19.3	1.71	1.74	**6i**	28.7	1.54	1.55
6b	8.4	2.08	2.09	**6g**	26.3	1.58	1.59
6c	26.1	1.58	1.55	**6k**	35.9	1.44	1.42
6d	23.5	1.63	1.65	**6l**	35.6	1.45	1.45
6e	22.8	1.64	1.65	**6m**	37.3	1.43	1.45
6f	19.2	1.72	1.75	**6n**	43.4	1.36	1.39
6g	17.8	1.70	1.72	**6o**	37.8	1.42	1.43
6h	25.5	1.59	1.57				

[a]Experimental antifungal activity (pEC_{50})

[b]Calculated antifungal activity (pEC_{50})

component and cross-validated coefficient q^2. The cross-validated coefficient q^2 and non-cross-validated correlation coefficient r^2 could estimate the predictive capability and modeling, respectively.

Results and discussion

Chemistry

The synthetic routes of the title compounds are shown in Scheme 1. (R)-2-Phenyl-4,5-dihydrothiazole-5-carboxylic acids **3** were prepared by treating benzonitrile derivatives **1** with L-cysteine **2** reference to our previous work (Liu et al. 2015) with some improvement. Intermediates **5** were prepared by treated benzenesulfonylchloride derivatives **4** with hydrazine hydrate in good yields (Backes et al. 2015). Then title compounds **6a–p** were prepared in moderate yields by coupling reaction of (R)-2-Phenyl-4,5-dihydrothiazole-5-carboxylic acids **3** and benzenesulfonohydrazides **5** in the presence of *N*,*N*-diisopropylethylamine (DIPEA) with 1-hydroxy-1*H*-benzotriazole (HOBT) and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDCI) as coupling reagent.

The chemical structures of title compounds **6a–p** were determined by ^{1}H NMR, ^{13}C NMR, and elemental analysis (EA). As shown in Fig. 2, the ^{1}H NMR spectra of **6f** (Fig. 2a), the two active proton signals of sulfonohydrazide moiety (–SO_2NHNHCO–) were observed at 10.40 ppm (s) and 10.03 ppm (s). The signal of CH of the 4,5-dihydrothiazole ring was assigned 5.11 ppm (t). The signals at 3.56 ppm (dd) and 3.24 ppm (dd) were assigned to the CH_2 of the 4,5-dihydrothiazole ring due to the adjacent chiral carbon. The ^{13}C NMR spectra of **6f** shown in Fig. 2b, the signal of sulfonohydrazide moiety (–SO_2NHNHCO–) appeared at 169.26 ppm, and the signals of C=N of the 4,5-dihydrothiazole ring appeared at 168.82 ppm. The signals of CH and CH_2 of the 4,5-dihydrothiazole ring appeared at 77.92 ppm and 34.77 ppm, respectively.

Table 3 Antifungal activities as EC_{50} (mg/L) of compound **6p** and chlorothalonil

Compd.	Fungus	EC_{50}	Compd.	Fungus	EC_{50}
6p	*Alternaria solani*	21.7	Chlorothalonil	*Alternaria solani*	17.8
	Physalospora piricola	6.5		*Physalospora piricola*	6.9
	Cercospora arachidicola	17.2		*Cercospora arachidicola*	15.5
	Phytophthora capsici	5.3		*Phytophthora capsici*	5.2
	Fusarium graminearum	17.7		*Fusarium graminearum*	18.1
	Sclerotinia sclerotiorum	14.6		*Sclerotinia sclerotiorum*	15.5

Table 4 Insecticidal activities against *Culex pipiens* larvae of the title compounds **6a–p** and chlorantraniliprole

Compd.	Insecticidal activity (%)		Compd.	Insecticidal activity (%)	
	2 mg/L	1 mg/L		2 mg/L	1 mg/L
6a	80	16.7	**6g**	43.3	10
6b	100	70	**6k**	16.7	3.3
6c	76.7	36.7	**6l**	36.7	6.7
6d	53.3	16.7	**6m**	20	3.3
6e	60	10	**6n**	33.3	3.3
6f	70	20	**6o**	6.7	0
6g	90	66.7	**6p**	100	80
6h	66.7	10	Chlorantraniliprole	100	100
6i	66.7	16.7			

Antifungal activity and 3D-QSAR

As shown in Table 1, most title compounds against six phytopathogenic fungi exhibited moderate to remarkable (in vitro) activities at the concentration of 50 mg/L, and even better than the control chlorothalonil or carbendazim. Moreover, compounds **6b** and **6g** exhibited good and broad-spectrum antifungal activities. Among compounds **6a–o**, when the substituent R_2 was the same, compounds **6a–e** ($R_1 = H$) and **6f–j** ($R_1 = CH_3$) against *Alternaria solani*, *Physalospora piricola*, *Cercospora arachidicola*, *Phytophthora capsici*, and *Fusarium graminearum* displayed better inhibitory activities than those of compounds **6k–o** ($R_1 = NO_2$). However, for *Sclerotinia sclerotiorum*, the substituent R_1 on the benzene ring of title compounds with the same R_2 exerted different influences on antifungal activity following the sequence $NO_2 > H$ and CH_3. Furthermore, **6l** ($R_1 = NO_2$, $R_2 = Cl$) against *Sclerotinia sclerotiorum* exhibited 65.3% antifungal activity, more effective than the control chlorothalonil. When the substituent R_1 was the same, the antifungal activities of title compounds with the $R_2 = Cl$ were better than others. For example, compound **6b** ($R_2 = Cl$) against *Alternaria solani*, *Physalospora piricola*, *Cercospora arachidicola*, *Phytophthora capsici*, *Fusarium graminearum*, and *Sclerotinia sclerotiorum* exhibited 55.9, 86.2, 59.7, 75.2, 65.5, and 50% antifungal activities, respectively, better than other compounds **6a** and **6c–e**. These results indicated that the different types of substituents R_1 and R_2 had obvious influences on the antifungal activities.

In order to give more information of SAR, based on pEC_{50} of title compounds against *Phytophthora capsici* as shown in Table 2, a brief 3D-QASR analysis was carried out using Sybyl 6.9 software. A across validated coefficient of $q^2 = 0.764$, and a correlation coefficient of $r^2 = 0.989$ were obtained as the best CoMSIA model. Due to the lowest EC_{50} value, compound **6b** was used as the template molecule. The order of the relative contribution to the built CoMSIA model was electrostatic (42.4%) > hydrophobic (37.6%) > H-bond acceptor (10.3%) > steric (9.7%) > H-bond donor (0%), revealing that the electrostatic and hydrophobic fields were the chief factors to the antifungal activities. As shown in the electrostatic CoMSIA contour map (Fig. 3a), the red contours around the R_2 group revealed that compounds at this position with proper negative charge groups could improve the antifungal activities, agreement with the order of activity in R_2 group Cl > H, CH_3, OCH_3, and NO_2. As for the hydrophobic CoMSIA contour map (Fig. 3b), the white contours around the R_1 and R_2 groups suggested that compounds with proper hydrophilic groups contributed to the antifungal activity, which was consistent in the antifungal activity. These results of the built CoMSIA model will help to the further structural optimization.

Based on the SAR and 3D-QSAR model, for purpose of improving the antifungal activity, we rationally designed and synthesized compound **6p** ($R_1 = Cl$, $R_2 = Cl$). The antifungal activity of **6p**, as displayed in Tables 1 and 3, was increased to some extent compared with other title compounds, which was consistent with the prediction of the CoMSIA model, revealing that the CoMSIA model displayed good predictability. The EC_{50} value of **6p** was 5.3 mg/L, equal to that of chlorothalonil (5.2 mg/L).

The EC_{50} values of compound **6p** against six phytopathogenic fungi were further tested and the result was shown in Table 3. The EC_{50} values of compound **6p** were comparable to chlorothalonil, which was in agreement with the antifungal acitivities shown in Table 1.

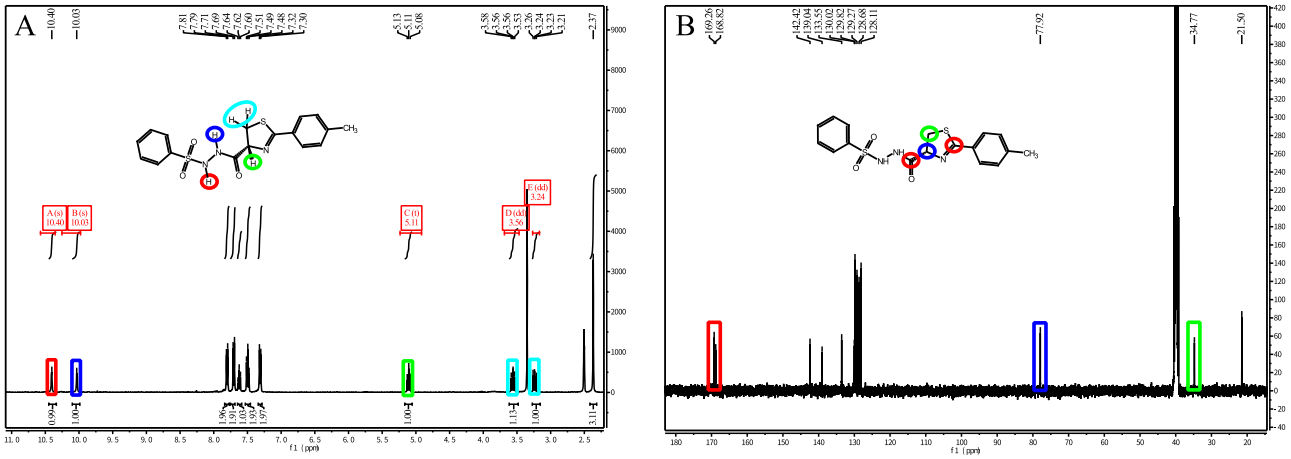


Fig. 2 ^{1}H NMR (**a**) and ^{13}C NMR (**b**) of title compound **6f**

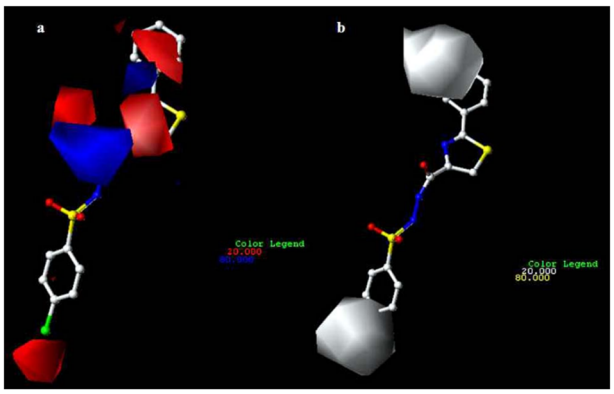


Fig. 3 The contour map of the electrostatic field (**a**) and hydrophobic field (**b**)

Insecticidal activity against *Culex pipiens* larvae

The insecticidal activities of title compounds **6a–p** against *Culex pipiens* larvae were tested and shown in Table 4. Most of them displayed moderate to good insecticidal activities at 2 mg/L. On the whole, the insecticidal activities of title compounds **6b**, **6g**, and **6p** with $R_2 = Cl$ were better than other compounds at 1 mg/L, in particular, compound **6p** exhibited 80% insecticidal activity, comparable to chlorantraniliprole, indicating that the substituent $R_1 = R_2 = Cl$ played a significant role in the insecticidal activities.

Conclusion

In conclusion, a series of (*R*)-2-phenyl-4,5-dihydrothiazole-4-carboxamide derivatives containing a sulfonohydrazide moiety were designed and synthesized. Their structures were confirmed by ^{1}H NMR, ^{13}C NMR and EA. All the title compounds were evaluated for fungicidal and insecticidal activities, and most of them against six antiphytopathogenic fungi exhibited moderate to excellent antifungal activities at 50 mg/L. The preliminary SAR was studied. The proper electron withdrawing groups in R_2 and proper hydrophilic groups in R_1 could improve the antifungal activity. The established CoMSIA model revealed that electrostatic and hydrophobic fields were the two most significant factors for antifungal activity. Therefore, based on the CoMSIA model, structure optimization was performed to find compound **6p** ($R_1 = R_2 = Cl$) with excellent antifungal activity against *Phytophthora capsici*, and the EC_{50} values of compound **6p** against six antiphytopathogenic fungi were comparable to those of chlorothalonil. Moreover, the insecticidal activity of compound **6p** against *Culex pipiens* larvae at 1 mg/L was 80%, close to that of chlorantraniliprole. So compound **6p** can be used as a novel lead structure for fungicide and insecticide development.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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