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Synthesis, insecticidal and fungicidal activities of methyl 2-(methoxyimino)-2-(2-((1-(*N*′-nitrocarbamimidoyl)-2-hydrocarbylidene-hydrazinyl)methyl)phenyl)acetates†

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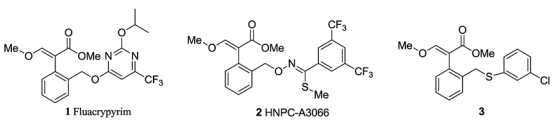
N′-Nitro-2-hydrocarbylidenehydrazinecarboximidamides and methoxyacrylates are two types of important agrochemicals. By combining their key fragments into one framework, a series of the title compounds was designed and synthesized. Some of these compounds have shown excellent insecticidal activities for aphides, for example, the LC_{50} values of compounds **6-06**, **6-11** and **6-19** against *M. persicae* and *H. amygdale* were found to be 1.9/14.4, 13.4/1.5 and 0.3/38.4 mg L^{-1} respectively. They were also effective against the mycelium growth of *B. cinerea in vitro*. Compound **6-04** could control (~100%) cucumber anthrax and rice blast at 100 mg L^{-1} *in vivo*, and inhibit the spore germination (~100%) of vegetable gray mold at 6.25 mg L^{-1}. These compounds could be considered as potential insecticidal or fungicidal candidates for crop protection. The results of structure–activity relationship (SAR) studies are discussed.

1 Introduction

Methoxyacrylate fungicides, some of the most potent and successful agrochemicals in recent decades,[1] originate from the natural product strobilurin A and have low toxicity, high efficiency and a broad spectrum of activity. Recently, many examples have proven that modification of the side chain of strobilurin fungicides is the most effective way to obtain new analogues with a higher activity.[2a–i] Based on biological activity similarities[3,4] and the principle of combination of active substructures,[5,6] a great many efforts have focused on the linkage of toxophore methoxyacrylate and other bioactive blocks to produce novel bioactive molecules, such as insecticides, herbicides and fungicides.[7] For example, fluacrypyrim (**1**),[8] which was developed by Nippon Soda Co., was the first acaricide bearing a methoxyacrylate moiety and also works on respiratory chain cyt bc_1. HPNC-A3066 (**2**) (ref. 9) exhibited a good efficacy of control against two-spotted spider mites, the European red mite (*Panonychus ulmi*) and citrus red mite (*Panonychus citri*). Whereas compound **3** was developed as a herbicide.[10]



Guadipyr (**4**) is a novel insecticide developed in our laboratory that has a high efficiency for controlling aphis, rice planthoppers and leaf hoppers, and a low toxicity to honeybees and earthworms.[11,12] The crucial moiety, *N*′-nitrohydrazinecarboximidamide, along with its structural analogs semicarbazones and thiosemicarbazones, is a core structure of many other bioactive molecules.[13–19] For this study, we considered combining (2-(2-methoxyimino)methoxycarbonyl methyl)benzyl, a very common toxophore in fungicides, such as in trifloxystrobin (**5**), with *N*′-nitrohydrazinecarboximidamides, so that a new class of bioactive compounds (**6**) could be created and investigated for agricultural application (Fig. 1).

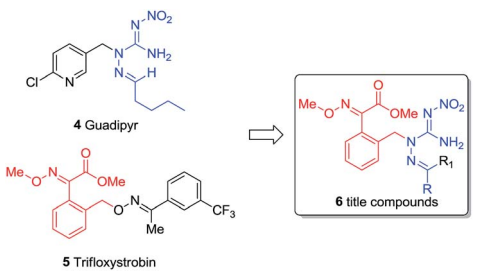


Fig. 1 Design of the title compounds.

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† Electronic supplementary information (ESI) available: The synthetic procedures and NMR spectra of the intermediates, and the NMR and HRMS spectra of the title compounds are freely available. See DOI: 10.1039/c5ra27359e

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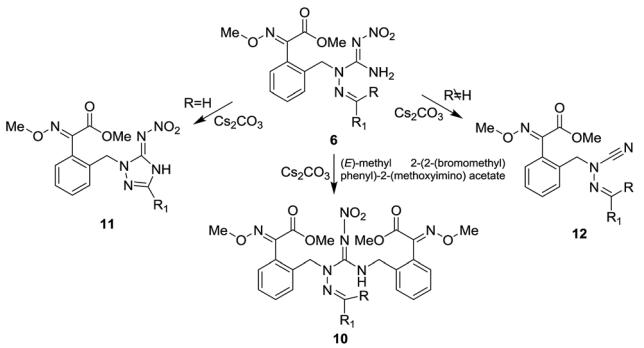
2 Results and discussion

Synthesis

A similar strategy as for guadipyr preparation[11] was used to produce **6**, in which 2-nitroguanidine **7** was hydrazinolated to give **8**, and the later was condensed with aldehydes or ketones to produce the key intermediate **9**. A direct nucleophilic substitution reaction between (*E*)-methyl 2-(2-(bromomethyl)phenyl)-2-(methoxyimino) acetate and **9** in the presence of a base gave the title compound **6** with low to moderate yields (Scheme 1). The hybrid compounds (**6**) exhibited both excellent insecticidal and fungicidal activities. In this paper we present the synthesis and bioactivities of the title compounds in detail. Their structure–activity relationships and some problems with the synthesis are also discussed.

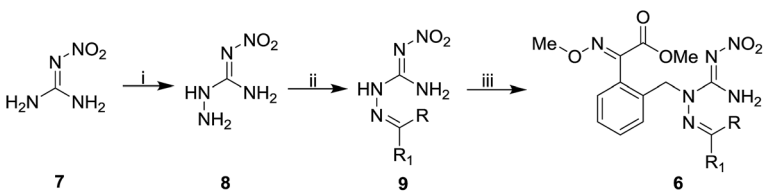
The synthetic yields of the target compounds were only between 14% and 47%, the reason being that compound **6** was also reactive under the condensation conditions used in the last step (Scheme 1), resulting in several byproducts. Firstly, compound **6** could be further alkylated to give the double substituted compound **10**. Secondly, when the carbonyl compound ($RR_1C{=}O$) was an aldehyde, compound **6** could be transformed into compound **11** *via* a complicated ring-closure/dehydrogenation process. When the carbonyl compound ($RR_1C{=}O$) was a ketone, although **11** could no longer be formed because of the absence of the hydrogen, another interesting denitroamine reaction took place and byproduct **12** was obtained (Scheme 2). Although these side reactions were unfavorable for the title compound preparation, the byproducts **11** and **12** were also attractive. Related research is being carried out in our laboratory.



Scheme 2 Side reactions during the condensation.

Structure–activity relationship (SAR) studies

Insecticidal activity. The insecticidal activities of the title compounds were evaluated using *Myzus perslcae* (Sulzer) and *Hyalopterus amygdale* Blananchard as the target pests and the results are summarized in Table 1. In general, all of the compounds displayed considerable to excellent insecticidal activity against the two kinds of aphids. Notably, compounds **6-06** and **6-19** exhibited exceptional insecticidal activities with a LC_{50} of 1.9 and 0.3 μg mL^{-1} against *M. perslcae*, respectively. For the aliphatic series (compounds **6-01** to **6-06**), when R_1 or R_2 was a bulky alkyl bearing side chain, the activity decreased sharply (compounds **6-02** and **6-03**). For the aromatic series, an *ortho*-substituent, no matter if it was electron-withdrawing or electron-donating, was the most important factor in enhancing the activity. For example, compounds **6-11** and **6-19** exhibited excellent activity in both assays. But this observation was not true for compound **6-23**, an *ortho*-hydroxyl substituted analog which had a much weaker activity, especially with *M. perslcae* (Sulzer). The reason might be that it could form unnecessary hydrogen bonds at the active site. When the hydroxyl group was moved to the *meta* position (compound **6-22**), the activity was enhanced remarkably. The presence of a *para*-substituent was another key factor affecting the activities. A weak electron-donating or -withdrawing substituent at this position, such as a chlorine atom (**6-10**, **6-12**) or alkyl group (**6-15**, **6-16**) was beneficial. But a strong substituent, such as a cyano (**6-09**), nitro (**6-13**), or alkyloxy (**6-17**, **6-20**) group significantly reduced the activity. These observations were used to clearly sketch out the outlines of a structure–activity relationship model for this series of compounds and to identify the direction for optimization.



i. 85% hydrazine hydrate, 55°C, 70%; ii. RR_1CO, HOAc, MeOH, 3-5h; iii. (*E*)-methyl 2-(2-(bromomethyl)phenyl)-2-(methoxyimino) acetate, K_2CO_3, Cs_2CO_3, KI, CH_3CN, 80°C

6-01 R=H, R_1=n-Pr	6-09 R=H, R_1=4-CNC_6H_4	6-17 R=H, R_1=4-$CH_3OC_6H_4$
6-02 R=H, R_1=n-PrMeCH	6-10 R=H, R_1=4-ClC_6H_4	6-18 R=H, R_1=3-$CH_3OC_6H_4$
6-03 R=H, R_1=Et_2CH	6-11 R=H, R_1=2-ClC_6H_4	6-19 R=H, R_1=2-$CH_3OC_6H_4$
6-04 R=H, R_1=C_6H_{13}	6-12 R=H, R_1=2,4-$Cl_2C_6H_3$	6-20 R=H, R_1=3,4-$(OCH_2O)C_6H_3$
6-05 R=Me, R_1=Me	6-13 R=H, R_1=4-$NO_2C_6H_4$	6-21 R=H, R_1=3-$PhOC_6H_4$
6-06 R=Et, R_1=Et	6-14 R=H, R_1=3-$NO_2C_6H_4$	6-22 R=H, R_1=3-OHC_6H_4
6-07 R=H, R_1=furan-2-yl	6-15 R=H, R_1=4-t-BuC_6H_4	6-23 R=H, R_1=2-OHC_6H_4
6-08 R=H, R_1=C_6H_5	6-16 R=H, R_1=4-$CH_3C_6H_4$	

Scheme 1 Preparation of the title compounds.

Table 1 Insecticidal activity (LC_{50}(95% confidence limit, μg mL^{-1})) of **6** against *M. perslcae* (Sulzer) and *H. amygdale* (Blanchard)

Compd.	MP[a]	HA[b]	Compd.	MP[a]	HA[b]
Imidacloprid	0.2(0.1–0.4)	1.3(0.7–2.3)	**6-12**	14.9(0.7–31.8)	87.4(68.1–119.1)
6-01	153.1(79.5–259.0)	5.2(1.5–9.7)	**6-13**	31.8(25.2–40.0)	136.8(113.5–172.0)
6-02	111.1(54.5–214.6)	30.4(20.3–41.1)	**6-14**	4.9(0.1–14.3)	34.3(18.2–53.9)
6-03	159.5(75.2–338.3)	97.7(58.0–289.0)	**6-15**	15.3(6.8–23.9)	24.4(11.2–43.1)
6-04	11.2(4.0–18.5)	81.7(33.5–124.3)	**6-16**	110.8(53.3–230.0)	7.3(2.4–12.8)
6-05	25.0(2.9–53.6)	110.4(50.9–301.4)	**6-17**	56.7(35.8–89.6)	>200
6-06	1.9(0.1–9.0)	14.4(5.1–24.2)	**6-18**	64.7(48.6–86.0)	48.7(27.4–105.4)
6-07	39.5(27.6–54.5)	12.0(8.0–16.0)	**6-19**	0.3(0.1–0.7)	38.4(27.1–52.6)
6-08	32.2(18.8–55.2)	13.7(1.7–27.0)	**6-20**	>200	45.6(12.5–108.3)
6-09	63.3(41.5–107.5)	122.3(67.4–351.2)	**6-21**	198.7(125.6–341.0)	118.3(72.3–305.4)
6-10	145.8(76.8–276.6)	3.0(0.1–8.6)	**6-22**	8.9(3.0–15.4)	46.9(30.1–67.5)
6-11	13.4(4.7–37.7)	1.5(0.003–6.0)	**6-23**	185.6(64.5–333.2)	26.8(9.1–72.3)

[a] *M. perslcae* (Sulzer). [b] *H. amygdale* Blanchard.

Fungicidal activity. The fungicidal activity was investigated both *in vitro* and *in vivo*, and the results are summarized in Tables 2 and 3 respectively. No obvious differences in the antifungal activity between the aliphatic and aromatic series were observed. In general, these compounds were highly active against *Botrytis cinerea* and *Physalospora piricola* Nose *in vitro* at 50 μg mL^{-1}. Several compounds displayed a higher activity than azoxystrobin, for example, most of the compounds (**6**) against *B. cinerea* and compounds **6-10** and **6-13** against *P. piricola* Nose. Unfortunately, they didn't display as broad a fungicidal spectrum as azoxystrobin against these phytopathogens, suggesting that they might have a different mode of action to other strobilurin fungicides. We also didn't find an explicit relationship between their structures and fungicidal activities for *B. cinerea* mycelium inhibition.

All of the compounds (**6**) gave poor control *in vivo* except for **6-04**. This compound exhibited 100% control of cucumber anthrax and rice blast at 100 μg mL^{-1}, and also 100% inhibition of the spore germination of vegetable gray mold at 6.25 μg mL^{-1} (Table 3). This revealed that it was both protective and curative, and that it might be suitable to be developed as a new potential agricultural fungicide.

Table 2 *In vitro* fungicidal activity of **6** against the phytopathogens[a]

	Mycelium growth inhibitory rate (%) at 50 μg mL^{-1}						
Compd.	MS	PC	PI	PP	CO	PA	BC
Azoxystrobin	46.2	37.0	62.2	62.5	51.1	61.3	51.1
6-01	4.4	5.8	0.2	30.8	4.1	32.5	62.1
6-02	6.1	6.2	20.0	35.4	17.0	35.7	34.9
6-03	11.8	6.5	30.5	26.1	12.7	26.1	45.2
6-04	13.9	9.0	34.0	41.7	15.0	30.4	62.1
6-05	—	3.0	7.2	30.8	4.9	18.6	58.9
6-06	10.1	3.7	9.8	28.3	4.9	20.2	46.8
6-07	1.3	0.9	10.0	46.7	5.7	33.3	71.8
6-08	—	8.0	37.8	51.7	14.6	27.6	60.8
6-09	17.4	4.3	24.7	39.2	13.8	26.4	23.7
6-10	5.0	5.4	54.1	70.7	18.9	31.5	55.2
6-11	—	6.5	7.7	44.2	14.6	19.3	64.0
6-12	34.0	7.5	22.8	58.3	19.1	28.3	29.0
6-13	—	4.5	28.4	74.3	11.8	26.1	40.3
6-14	17.2	6.0	53.8	31.9	15.2	23.6	66.9
6-15	25.4	15.3	36.8	44.4	20.3	29.8	61.3
6-16	17.0	7.7	54.3	41.7	20.6	30.3	70.2
6-17	—	4.7	—	19.2	5.7	23.3	53.2
6-18	14.5	3.2	26.6	35.0	14.2	37.6	60.9
6-19	18.9	5.6	60.1	48.8	10.3	18.5	58.1
6-20	—	4.5	13.5	33.8	8.9	20.8	53.5
6-21	—	5.6	14.7	51.7	9.7	17.5	52.4
6-22	22.5	6.5	9.1	39.2	12.6	28.3	68.5
6-23	—	3.4	1.4	33.3	6.9	21.4	36.3

[a] MS = *M. Sterillia*; PC = *P. capsici*; PI = *P. infestans* (Mont.) De Bary; PP = *P. piricola* Nose; CO = *C. orbiculare* (Berk. & Ment.); PA = *P. aphanidermatum* (Edson) Fitzpatrick; BC = *B. cinerea*.

3 Experimental

Instruments and materials

^{1}H NMR and ^{13}C NMR spectra were obtained at 300 MHz using a Bruker Avance DPX300 spectrometer in $CDCl_3$ or DMSO-d_6 solution with TMS as the internal standard. Chemical shift values (δ) are given in parts per million. HRMS data were obtained using a Thermo Scientific LTQ Orbitrap Discovery (Bremen, Germany) instrument. The melting points were determined on a Cole-Parmer microscope melting point apparatus and are uncorrected. *N*′-Nitrohydrazinecarboximidamide (**8**) and the intermediates (**9**) were synthesized in our laboratory and the data are given in the ESI.† All the yields were not optimized.

General procedure for the preparation of the title compounds (6)

A mixture of **9** (26.7 mmol), potassium carbonate (2.67 g, 19.34 mmol), a catalytic quantity of cesium carbonate, and acetonitrile (100 mL) was stirred for 1 h. (*E*)-Methyl 2-(2-(bromomethyl) phenyl)-2-(methoxyimino)acetate[19] (12.83 g, 45.0 mmol) was added, and the reaction mixture was heated to reflux for 2.5 h. After cooling, the solid was filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified using silica gel chromatography with petroleum ether/ethyl acetate (v/v = 1 : 1) as the eluent to give the title compound **6**.

Table 3 *In vivo* fungicidal activity of **6-04** against the phytopathogens

Compd.	Inhibitory rate (%) at 100 μg mL^{-1}		Spore germination inhibitory rate (%) at 6.25 μg mL^{-1}
	Cucumber anthrax	Rice blast	Vegetable gray mold
6-04	100	100	100
Prochloraz	100	—	—
Isoprothiolane	—	100	—
SYP-Z048[a]	—	—	100

[a] Used at 2.8 mg L^{-1}.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((2-butylidene-1-(*N*-nitrocarbamimidoyl)hydrazinyl)methyl)phenyl)acetate (6-01). Yield 21%; yellowish solid; mp 160–162 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.75 (t, J = 7.4 Hz, 3H), 1.46–1.32 (m, 2H), 2.27–2.21 (m, 2H), 3.81 (s, 3H), 4.02 (s, 3H), 4.99 (s, 2H), 7.08–6.87 (m, 2H), 7.26–7.21 (m, 1H), 7.48–7.33 (m, 2H), 8.57 (s, 1H), 9.03 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.4, 19.5, 34.3, 44.3, 53.0, 63.8, 125.6, 127.5, 128.6, 129.2, 132.7, 148.6, 149.2, 158.3, 162.8. HRMS (ESI) m/z calcd for $C_{16}H_{22}N_6O_5$ (M + H)$^+$ 379.1724, found 379.1724.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((2-(2-methylpentylidene)-1-(*N*-nitrocarbamimidoyl)hydrazinyl)methyl)phenyl)acetate (6-02). Yield 15%; white solid; mp 103–105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (t, J = 7.2 Hz, 3H), 0.95 (d, J = 6.81 Hz, 3H), 0.98–1.30 (m, 4H), 2.28–2.42 (m, 1H), 3.91 (s, 3H), 4.10 (s, 3H), 5.01–5.10 (br s, 2H), 6.90 (d, J = 6.09 Hz, 1H), 6.97–7.38 (m, 4H), 7.60 (s, 1H), 9.16 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 17.2, 19.7, 36.2, 36.9, 44.4, 52.9, 63.8, 125.5, 127.2, 128.5, 128.6, 129.6, 132.0, 148.4, 153.9, 158.7, 163.0. HRMS (ESI) m/z calcd for $C_{18}H_{26}N_6O_5$ (M + H)$^+$ 407.2037, found 407.2034.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((2-(2-ethylbutylidene)-1-(*N*-nitrocarbamimidoyl)hydrazinyl)methyl)phenyl)acetate (6-03). Yield 26%; yellowish solid; mp 139–141 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.62 (t, J = 7.40 Hz, 6H), 1.19–1.41 (m, 4H), 2.07–2.13 (m, 1H), 3.79 (s, 3H), 4.00 (s, 3H), 5.00 (s, 2H), 6.76 (d, J = 7.15 Hz, 1H), 6.92–7.42 (m, 4H), 8.46 (s, 1H), 9.10 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 11.3, 25.1, 44.1, 45.6, 53.0, 63.8, 125.6, 127.5, 129.0, 129.3, 129.7, 132.6, 148.5, 152.9, 158.3, 162.9. HRMS (ESI) m/z calcd for $C_{18}H_{26}N_6O_5$ (M + H)$^+$ 407.2037, found 407.2031.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((2-heptylidene-1-(*N*-nitrocarbamimidoyl)hydrazinyl)methyl)phenyl)acetate (6-04). Yield 21%; white solid; mp 97–99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J = 6.70 Hz, 3H), 1.13–1.28 (m, 6H), 1.34–1.43 (m, 2H), 2.19–2.25 (m, 2H), 3.91 (s, 3H), 4.10 (s, 3H), 5.06 (s, 2H), 6.98–7.06 (m, 2H), 7.12–7.15 (m, 1H), 7.29 - 7.39 (m, 2H), 7.61 (s, 1H), 9.15 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.0, 22.1, 26.1, 28.1, 31.2, 32.4, 52.9, 63.5, 72.5, 125.6, 127.4, 128.6, 128.9, 129.2, 129.8, 132.8, 148.6, 158.4, 162.8. HRMS (ESI) m/z calcd for $C_{19}H_{28}N_6O_5$ (M + H)$^+$ 421.2194, found 421.2193.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((1-(*N*-nitrocarbamimidoyl)-2-(propan-2-ylidene)hydrazinyl)methyl)phenyl)acetate (6-05). Yield 24%; yellowish solid; mp 137–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 6H), 3.89 (s, 3H), 4.09 (s, 3H), 4.19 (s, 1H), 4.59 (s, 2H), 7.13–7.46 (m, 4H), 8.22 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 25.1, 48.4, 52.7, 63.5, 76.2, 127.6, 128.7, 128.9, 129.5, 129.9, 134.6, 148.8, 157.3, 159.1, 163.0. HRMS (ESI) m/z calcd for $C_{15}H_{20}N_6O_5$ (M + H)$^+$ 365.1568, found 365.1568.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((1-(*N*-nitrocarbamimidoyl)-2-(pentan-3-ylidene)hydrazinyl)methyl)phenyl)acetate (6-06). Yield 19%; yellowish solid; mp 130–132 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.78 (t, J = 7.35 Hz, 6H), 1.59 (q, J = 7.41 Hz, 4H), 3.75 (s, 3H), 3.96 (s, 3H), 4.34 (s, 2H), 5.32 (s, 1H), 6.99 (d, J = 7.29 Hz, 1H), 7.34–7.46 (m, 3H), 9.39 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.7, 29.1, 48.6, 52.8, 63.5, 81.4, 127.6, 128.7, 128.8, 129.5, 130.0, 134.4, 148.8, 158.4, 163.0. HRMS (ESI) m/z calcd for $C_{17}H_{24}N_6O_5$ (M + H)$^+$ 393.1881, found 393.1872.

Data for (*E*)-methyl 2-(2-((2-(furan-2-ylmethylene)-1-(*N*-nitrocarbamimidoyl)hydrazinyl) methyl)phenyl)-2-(methoxyimino) acetate (6-07). Yield 26%; yellowish solid; mp 217–219 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 3H), 4.04 (s, 3H), 5.12 (s, 2H), 6.62–7.82 (m, 7H), 7.55 (s, 1H), 8.65–9.12 (br s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 44.7, 53.1, 63.8, 112.7, 113.4, 127.7, 129.0, 129.4, 130.1, 132.4, 134.1, 145.7, 148.6, 149.5, 158.2, 162.9. HRMS (ESI) m/z calcd for $C_{17}H_{18}N_6O_6$ (M + H)$^+$ 403.1361, found 403.1360.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((2-benzylidene-1-(*N*-nitrocarbamimidoyl)hydrazinyl)methyl)phenyl)acetate (6-08). Yield 18%; yellowish solid; mp 214–216 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.84 (s, 3H), 4.03 (s, 3H), 5.17 (s, 2H), 7.02–7.82 (m, 9H), 7.70 (s, 1H), 9.05 (br s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 44.7, 53.1, 63.9, 125.6, 127.6, 128.0, 129.0, 129.3, 130.0, 130.7, 132.8, 133.7, 144.4, 148.6, 158.4, 163.1. HRMS (ESI) m/z calcd for $C_{19}H_{20}N_6O_5$ (M + H)$^+$ 413.1568, found 413.1566.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((2-(4-cyanobenzylidene)-1-(*N*-nitrocarbamimidoyl)hydrazinyl)methyl)phenyl)acetate (6-09). Yield 43%; white solid; mp 207–209 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.84 (s, 3H), 4.04 (s, 3H), 5.18 (s, 2H), 7.05 (d, J = 8.33 Hz, 1H), 7.24 (dd, J_1 = 1.06 Hz, J_2 = 7.13 Hz, 1H), 7.32–7.42 (m, 2H), 7.70 (s, 1H), 7.88 (d, J = 8.36 Hz, 2H), 8.01 (d, J = 8.33 Hz, 2H), 9.15 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 45.0, 53.1, 63.9, 112.5, 118.8, 125.7, 127.7, 128.5, 129.0, 129.4, 130.1, 132.5, 132.8, 138.0, 142.3, 148.5, 158.4, 163.2. HRMS (ESI) m/z calcd for $C_{20}H_{19}N_7O_5$ (M + H)$^+$ 438.1520, found 438.1523.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((2-(4-chlorobenzylidene)-1-(*N*-nitrocarbamimidoyl)hydrazinyl)methyl)phenyl)acetate (6-10). Yield 18%; white solid; mp 223–225 °C;

^{1}H NMR (300 MHz, DMSO-d_6) δ 3.84 (s, 3H), 4.04 (s, 3H), 5.16 (s, 2H), 7.02–7.86 (m, 8H), 7.66 (s, 1H), 9.10 (br s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 44.8, 53.1, 63.9, 125.7, 127.6, 129.0, 129.3, 129.7, 130.0, 132.6, 132.7, 136.3, 143.0, 148.5, 158.4, 163.1. HRMS (ESI) m/z calcd for $C_{19}H_{19}ClN_6O_5$ $(M + H)^+$ 447.1178, found 447.1174.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((2-(2-chlorobenzylidene)-1-(*N*-nitrocarbamimidoyl)hydrazinyl)methyl) phenyl)acetate (6-11). Yield 22%; yellowish solid; mp 195–197 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.77 (s, 3H), 3.98 (s, 3H), 5.24 (s, 2H), 7.06–8.41 (m, 8H), 7.95 (s, 1H), 9.09 (br s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 45.5, 52.9, 63.8, 126.1, 127.5, 127.6, 128.5, 129.2, 129.3, 129.9, 129.9, 131.0, 132.0, 132.2, 133.6, 140.3, 148.4, 158.3, 162.6. HRMS (ESI) m/z calcd for $C_{19}H_{19}ClN_6O_5$ $(M + H)^+$ 447.1178, found 447.1172.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((2-(2,4-dichlorobenzylidene)-1-(*N*-nitrocarbamimidoyl)hydrazinyl)methyl) phenyl)acetate (6-12). Yield 47%; grey solid; mp 184–186 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.76 (s, 3H), 3.97 (s, 3H), 5.24 (s, 2H), 7.07 (d, J = 7.41, 1H), 7.23 (dd, J_1 = 1.32, J_2 = 7.38, 1H), 7.33–7.50 (m, 3H), 7.63 (d, J = 2.07, 1H), 7.87 (s, 1H), 8.46 (d, J = 8.64, 1H), 9.13 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 45.6, 52.9, 63.8, 126.1, 127.6, 127.9, 129.2, 129.3, 129.7, 129.8, 130.1, 132.1, 134.3, 135.8, 139.2, 148.4, 158.3, 162.6. HRMS (ESI) m/z calcd for $C_{19}H_{18}Cl_2N_6O_5$ $(M + H)^+$ 481.0789, found 481.0784.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((2-(4-nitrobenzylidene)-1-(*N*-nitrocarbamimidoyl)hydrazinyl)methyl) phenyl)acetate (6-13). Yield 20%; yellow solid; mp 212–214 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.85 (s, 3H), 4.05 (s, 3H), 5.20 (s, 2H), 7.05–8.26 (m, 8H), 7.76 (s, 1H), 9.20 (br s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 45.0, 53.1, 63.9, 124.1, 125.7, 127.7, 128.9, 129.1, 129.4, 130.1, 132.5, 139.8, 141.8, 148.2, 148.5, 158.4, 163.1. HRMS (ESI) m/z calcd for $C_{19}H_{19}N_7O_7$ $(M + H)^+$ 458.1419, found 458.1416.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((2-(3-nitrobenzylidene)-1-(*N*-nitrocarbamimidoyl)hydrazinyl)methyl) phenyl)acetate (6-14). Yield 30%; yellowish solid; mp 118–120 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.86 (s, 3H), 4.04 (s, 3H), 5.19 (s, 2H), 7.06–8.58 (m, 8H), 7.79 (s, 1H), 9.22 (br s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 44.9, 53.0, 59.9, 63.8, 122.5, 124.8, 125.8, 127.7, 129.0, 129.4, 130.0, 130.4, 132.6, 133.7, 135.4, 142.1, 148.5, 158.4, 163.2. HRMS (ESI) m/z calcd for $C_{19}H_{19}N_7O_7$ $(M + H)^+$ 458.1419, found 458.1415.

Data for (*E*)-methyl 2-(2-(((*E*)-2-(4-(*tert*-butyl)benzylidene)-1-(*N*-nitrocarbamimidoyl)hydrazinyl)methyl)phenyl)-2-(methoxyimino)acetate (6-15). Yield 25%; yellowish solid; mp 205–207 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (s, 9H), 3.84 (s, 3H), 4.05 (s, 3H), 5.16 (s, 2H), 7.02 (d, J = 7.68, 1H), 7.24 (dd, J_1 = 1.38, J_2 = 7.17, 1H), 7.31–7.44 (m, 4H), 7.64 (s, 1H), 7.71 (d, J = 8.40, 2H), 9.03 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 31.1, 34.8, 44.6, 53.1, 63.9, 125.6, 125.7, 127.6, 127.9, 129.0, 129.3, 130.0, 131.0, 132.7, 144.5, 148.6, 153.6, 158.4, 163.1. HRMS (ESI) m/z calcd for $C_{23}H_{28}N_6O_5$ $(M + H)^+$ 469.2194, found 469.2193.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((2-(4-methylbenzylidene)-1-(*N*-nitrocarbamimidoyl)hydrazinyl)methyl) phenyl)acetate (6-16). Yield 35%; white solid; mp 211–213 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.84 (s, 3H), 4.03 (s, 3H), 5.17 (s, 2H), 7.02–7.82 (m, 9H), 7.70 (s, 1H), 9.02 (br s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.3, 53.1, 63.9, 125.6, 127.6, 128.0, 129.0, 129.2, 129.5, 130.0, 131.0, 132.8, 140.7, 144.4, 148.5, 158.4, 163.1. HRMS (ESI) m/z calcd for $C_{20}H_{22}N_6O_5$ $(M + H)^+$ 427.1724, found 427.1722.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((2-((2-(4-methoxybenzylidene)-1-(*N*-nitrocarbamimidoyl)hydrazinyl)methyl) phenyl)acetate (6-17). Yield 28%; white solid; mp 213–215 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.78 (s, 3H), 3.84 (s, 3H), 4.04 (s, 3H), 5.14 (s, 2H), 6.95–7.76 (m, 8H), 7.62 (s, 1H), 9.02 (br s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 44.6, 53.1, 55.6, 63.9, 114.4, 126.3, 127.6, 129.0, 129.2, 129.8, 130.0, 132.9, 144.3, 148.5, 158.3, 161.4, 163.1. HRMS (ESI) m/z calcd for $C_{20}H_{22}N_6O_6$ $(M + H)^+$ 443.1674, found 443.1671.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((2-((2-(3-methoxybenzylidene)-1-(*N*-nitrocarbamimidoyl)hydrazinyl)methyl) phenyl)acetate (6-18). Yield 33%; pink solid; mp 214–216 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.79 (s, 3H), 3.84 (s, 3H), 4.05 (s, 3H), 5.15 (s, 2H), 6.97–7.44 (m, 8H), 7.64 (s, 1H), 9.06 (br s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 44.7, 53.1, 55.5, 63.9, 112.4, 116.7, 121.1, 125.6, 127.6, 129.0, 129.3, 130.0, 132.8, 135.0, 144.4, 148.5, 158.4, 159.8, 163.2. HRMS (ESI) m/z calcd for $C_{20}H_{22}N_6O_6$ $(M + H)^+$ 443.1674, found 443.1668.

Data for (*E*)-methyl 2-(2-((2-(2-methoxybenzylidene)-1-(*N*-nitrocarb-amimidoyl)hydrazinyl)methyl)phenyl)-2-(methoxyimino) acetate (6-19). Yield 29%; yellowish solid; mp 186–188 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.89 (s, 3H), 4.11 (s, 3H), 5.25 (s, 2H), 6.86–6.89 (m, 1H), 6.98–7.06 (m, 2H), 7.18–7.20 (m, 1H), 7.32–7.40 (m, 3H), 7.69–7.73 (dd, J_1 = 1.68, J_2 = 7.74, 1H), 7.73 (s, 1H), 8.06 (s, 1H), 9.22 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 45.0, 52.9, 56.0, 63.8, 112.0, 120.8, 121.8, 125.8, 127.1, 127.4, 129.2, 129.8, 132.6, 148.5, 158.1, 158.3, 162.7. HRMS (ESI) m/z calcd for $C_{20}H_{22}N_6O_6$ $(M + H)^+$ 443.1674, found 443.1672.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((2-(benzo[*d*][1,3]dioxol-5-ylmethylene)-1-(*N*-nitrocarbamimidoyl)hydrazinyl) methyl)phenyl)acetate (6-20). Yield 26%; white solid; mp 208–210 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.84 (s, 3H), 4.04 (s, 3H), 5.13 (s, 2H), 6.03 (s, 2H), 6.90–7.81 (m, 7H), 7.57 (s, 1H), 9.05 (br s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 44.6, 53.1, 63.9, 101.8, 105.9, 108.4, 125.7, 127.6, 128.3, 129.0, 129.2, 130.0, 132.9, 144.2, 148.4, 148.5, 149.6, 158.3, 163.1. HRMS (ESI) m/z calcd for $C_{20}H_{20}N_6O_7$ $(M + H)^+$ 457.1466, found 457.1461.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((1-(*N*-nitrocarbamimidoyl)-2-(3-phenoxy benzylidene)hydrazinyl)methyl)phenyl) acetate (6-21). Yield 38%; white solid; mp 189–191 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.77 (s, 3H), 3.99 (s, 3H), 5.15 (s, 2H), 6.98–7.64 (m, 13H), 7.52 (s, 1H), 9.07 (br s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 44.7, 53.0, 63.8, 118.0, 118.6, 121.0, 123.7, 123.7, 125.7, 127.6, 129.0, 129.3, 130.0, 130.3, 130.6, 132.7, 135.8, 143.7, 148.5, 156.9, 157.1, 158.4, 163.1. HRMS (ESI) m/z calcd for $C_{25}H_{24}N_6O_6$ $(M + H)^+$ 505.1830, found 505.1822.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((2-(3-hydroxybenzylidene)-1-(*N*-nitrocarbamimidoyl)hydrazinyl)methyl) phenyl)acetate (6-22). Yield 14%; white solid; mp 202–204 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.84 (s, 3H), 4.04 (s, 3H), 5.15 (s, 2H), 6.80–7.42 (m, 8H), 7.57 (s, 1H), 9.03 (br s, 2H), 9.59 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 44.7, 53.0, 63.9, 114.4, 117.9,

119.0, 125.6, 127.5, 129.0, 129.2, 129.9, 130.0, 132.7, 134.9, 144.6, 148.5, 157.8, 158.4, 163.0. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{20}N_6O_6$ $(M + H)^+$ 429.1517, found 429.1515.

Data for (*E*)-methyl 2-(methoxyimino)-2-(2-((2-(2-hydroxybenzylidene)-1-(*N*-nitrocarbamimidoyl)hydrazinyl)methyl)phenyl)acetate (6-23). Yield 36%; white solid; mp 184–186 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.82 (s, 3H), 4.02 (s, 3H), 5.14 (s, 2H), 6.80–8.12 (m, 8H), 7.97 (s, 1H), 8.96 (br s, 2H), 9.93 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 44.8, 53.0, 63.8, 116.3, 119.4, 120.2, 125.5, 127.3, 127.4, 129.1, 129.8, 132.1, 132.6, 140.6, 148.5, 156.8, 158.3, 162.7. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{20}N_6O_6$ $(M + Na)^+$ 451.1337, found 451.1340.

Biological assays

Insecticidal activity. All the insecticidal bioassays were performed using representative test organisms prepared in the laboratory. The bioassay was performed at 25 ± 1 °C. All the compounds were dissolved in DMF and diluted with 0.05% Triton X-100 to obtain a series of concentrations. The insecticidal activities of the compounds against *M. persicae* (Sulzer) and *H. amygdale* (Blanchard) were performed according to previously reported procedures. Each administration was repeated three times. The LC_{50} values were determined based on standard probit analysis[20] and the results are summarized in Table 1. Imidacloprid (95%) purchased from Jiangsu Changlong Chemicals Co. was used as a control, treating it in the same way.

Fungicidal activity. The fungicidal activity of the target compounds against *M. Sterillia*, *P. capsici*, *P. infestans* (Mont.) De Bary, *P. piricola* Nose, *C. orbiculare* (Berk. & Ment.), *P. aphanidermatum* (Edson) Fitzpatrick and *B. cinerea* was evaluated using a mycelium growth rate test.[21] Azoxystrobin, a gift from Jiangsu Frey Chemicals Co. was used as a control. The relative inhibition ratio (%) was calculated using the following equation:

$$\frac{(\text{Colony diameter of control} - \text{colony diameter of treated})}{(\text{colony diameter of control} - \text{mycelial disk diameter})} \times 100\%.$$

The experiment was conducted twice with three replicates. The fungicidal activities are listed in Table 2.

4 Conclusions

We have designed and synthesized a novel series of the title compounds based on the principle of combining the active substructures of known compounds. Some of these compounds displayed excellent insecticidal and fungicidal activities, suggesting that they have potential to be used as bifunctional agrochemicals. The results of structure–activity relationship (SAR) studies were presented and discussed. Overall, our results reconfirmed the fact that the strategy of combining the active sub-structures of known compounds is effective for new drug design and development. At present, our efforts are devoted to addressing problems like increasing the reaction yield and avoiding side reactions.

Conflict of interest

The authors declare no competing financial interest.

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