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Design, synthesis, and insecticidal activity of novel 1-alkoxy-2-nitroguanidines†

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In searching for new insecticidal lead compounds, a series of novel 1-alkoxy-2-nitroguanidine, guadipyr analogues bearing alkoxy groups were designed, synthesized and confirmed by ^{1}H NMR, ^{13}C NMR, high-resolution mass spectrometry and X-ray diffraction. The primary bioassays showed that most of these compounds exhibited moderate to good insecticidal activity against *Myzus persicae* and *Aphis gossypii*. Especially, the precise insecticidal assay showed that compounds **4-02**, **4-07** and **4-08** displayed excellent *in vitro* activity with IC_{50} values lower than 10 μg mL^{-1} to *M. persicae* which is comparable to guadipyr. On the other hand, the toxicity of compound **4-07** and guadipyr against honey bees was much lower than imidacloprid. The results indicated that the flexible chain on the nitrogen atom was the most crucial factor on honey bee toxicity, which existed in both neonicotinoids and guadipyr series.

1 Introduction

In the last three decades, neonicotinoids have made a significant contribution to the protection of crops from insect pests.[1–3] Neonicotinoids, which target nicotinic acetylcholine receptors (nAChRs), almost have no cross-resistance to conventional insecticides,[4] such as organophosphates, carbamates, and synthetic pyrethroids. However, with the wide and long term use of neonicotinoid insecticides, problems for resistant development and bee safety have thrown neonicotinoids on the cusp.[5,6] The development of new varieties of high-activity and multi-site action insecticides is essential in solving these problems. New insecticides, such as sulfoxaflor, flupyradifurone (FPF) and triflumezopyrim (TFM) (see Fig. 1), with novel modes of action and favorable environmental profiles emerge continually. Sulfoxaflor, which belongs to sulfoximine-class insecticide, targets sap-feeding insect pests probably *via* acting on the insect nicotinic acetylcholine receptor (nAChR) in a distinct manner relative to neonicotinoids.[7–9] Flupyradifurone is a novel butenolide-class insecticide possessing a butenolide ring which has been developed and commercialized by Bayer CropScience.[10,11] It shows unique properties, highly effective insecticidal activities and favorable ecotoxicological profiles. Triflumezopyrim was invented by DuPont Crop Protection, possessing a pyridopyrimidinedione core.[12–14] It is belonging to the novel class of mesoionic insecticides, and targets at nAChR but binds to the orthosteric site of the nAChR. These products provide outstanding control of insects, including the aphids, whiteflies, leafhoppers, and are also effective against some insects which even display strong resistance to imidacloprid (IMI).

As a part of continual efforts for developing novel, effective and bee-safety insecticides, guadipyr was designed by the combination of the pharmacophores of neonicotinoid and semicarbazone.[15] It has a five-carbon alkyl chain containing imine substituent, which is distinct from the short alkyl chain of neonicotinoids, and targets the nicotinic acetylcholine receptor. The insecticidal activity of guadipyr was measured against aphids in laboratory (*Myzus persicae*) and field trials (*Myzus persicae* and *Brevicoryne brassicae* Linnaeus). The influence of length and flexibility of the straight alkyl chain on the bioactivity was investigated. Interestingly, the long carbon-

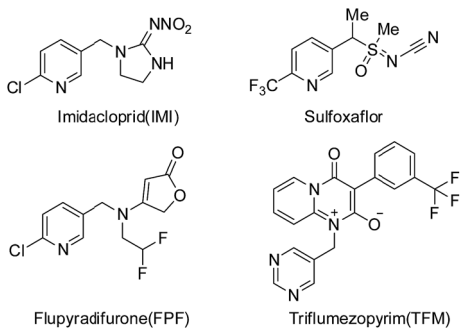

Fig. 1 Chemical structure of imidacloprid, sulfoxaflor, flupyradifurone and triflumezopyrim.

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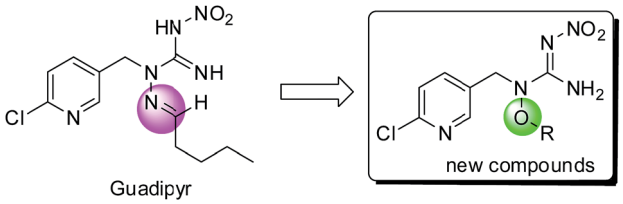
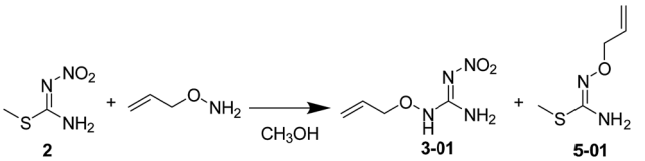


Scheme 1 Design of the target compounds.



Scheme 3 Side reactions in the amination.

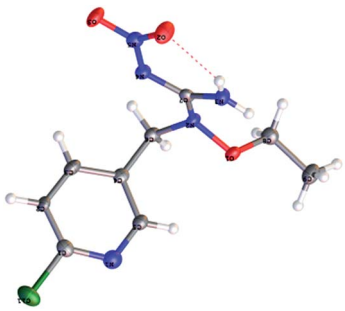


Fig. 2 X-ray crystal structure of compound **4-02** (CCDC number: 1518112).

chain associated analogues showed better peach aphid activity than the short carbon-chain contained analogues.[15,16] Guadipyr is also effective against sap-feeding insects that are resistant to imidacloprid.

In our investigation process, an interesting question has always attracted us, and that is whether the compounds would also show the same excellent biological characteristics when the hydrazinecarboximidamide system was destroyed. So in this work, an oxygen contained side-chain was introduced instead of nitrogen contained side-chain, and a series of alkoxynitroguanidine compounds were designed and synthesized by replacing the imine moiety with more flexible alkoxyl group (see Scheme 1).

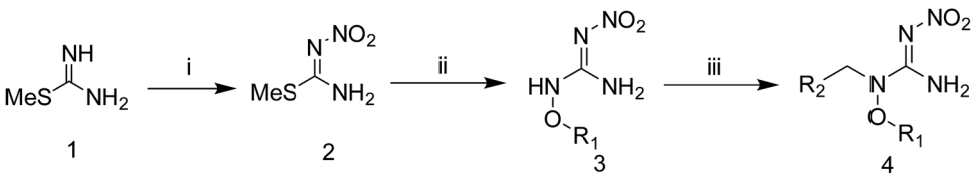
All of the title compounds were identified by ^{1}H NMR, ^{13}C NMR and HRMS. The insecticidal activities of these compounds were evaluated against *Aphis gossypii*, *Myzus persicae* and *Plutella xylostella*. Furthermore, the toxicity and safety evaluation of compound **4-07** to honey bees (*Apis melliferal*) were also investigated.

2 Results and discussion

Synthesis

The synthetic procedures for the title compounds are depicted in Scheme 2. The nitration of *S*-methyl-isothiourea was conducted under concentrated nitric acid and sulfuric acid at −15 °C to produce the key intermediate **2**. R_1ONH_2 was then reacted with intermediate **2** *via* a directly amination under room temperature gave the compound **3**. The synthetic yields of compounds **3** were only between 34% and 44%, the reason is that compound **2** was underwent addition–elimination reaction (Scheme 3), resulting in byproduct (**5**). For instance, compound **2** reacted with *O*-allylhydroxylamine, not only giving compound **3** but also byproduct **5-01**.

Compound **3** was reacted with halides in DMF in the presence of NaH to afford target compound **4**. Most of compounds **4** were obtained in moderate to good yields. In addition, the structure of **4-02** was further identified by X-ray diffraction studies (see Fig. 2). To further verify the structure of the title compound, the compound **4-02** was recrystallized by a slow evaporation from a dichloromethane/*n*-hexane (v/v = 1 : 5) solution. The molecular structure of compound **4-02** is shown in Fig. 2. The double C=NNO_2 bond in compound **4-02** (as well as in other nitroimines for which X-ray diffraction data are available[17]) appears to be a double bond which consists with



i. HNO_3,H_2SO_4, -15°C; ii. R_1ONH_2, MeOH, 6-8h; iii.R_2CH_2X , NaH, KI, DMF, 0°C-rt,22h

3-01 R_1=allyl 3-02 R_1=Et 3-03 R_1=*n*-Pr 3-04 R_1=*n*-Bu 3-05 R_1=*n*-Pentyl

4-01 R_1=allyl, R_2=2-Cl-Pyridin-5-yl
4-02 R_1=Et, R_2=2-Cl-Pyridin-5-yl
4-03 R_1=*n*-Pr, R_2=2-Cl-Pyridin-5-yl
4-04 R_1=*n*-Bu, R_2=2-Cl-Pyridin-5-yl
4-05 R_1=*n*-Pentyl, R_2=2-Cl-Pyridin-5-yl
4-06 R_1=allyl, R_2=2-Cl-thiazol-5-yl
4-07 R_1=Et, R_2=2-Cl-thiazol-5-yl
4-08 R_1=*n*-Pr, R_2=2-Cl-thiazol-5-yl
4-09 R_1=*n*-Bu, R_2=2-Cl-thiazol-5-yl
4-10 R_1=*n*-Pentyl, R_2=2-Cl-thiazol-5-yl
4-11 R_1=allyl, R_2=4-ClC_6H_4
4-12 R_1=Et, R_2=4-ClC_6H_4
4-13 R_1=*n*-Pr, R_2=4-ClC_6H_4
4-14 R_1=*n*-Bu, R_2=4-ClC_6H_4
4-15 R_1=*n*-Pentyl, R_2=4-ClC_6H_4
4-16 R_1=allyl, R_2=4-$NO_2C_6H_4$
4-17 R_1=Et, R_2=4-$NO_2C_6H_4$
4-18 R_1=*n*-Pr, R_2=4-$NO_2C_6H_4$
4-19 R_1=*n*-Bu, R_2=4-$NO_2C_6H_4$
4-20 R_1=*n*-Pentyl, R_2=4-$NO_2C_6H_4$
4-21 R_1=allyl, R_2=4-CNC_6H_4
4-22 R_1=Et, R_2=4-CNC_6H_4
4-23 R_1=*n*-Pr, R_2=4-CNC_6H_4
4-24 R_1=*n*-Bu, R_2=4-CNC_6H_4
4-25 R_1=*n*-Pentyl, R_2=4-CNC_6H_4

Scheme 2 Preparation of title compounds.

precursor **1–3** but differs from guadipyr. In addition, there is intramolecular hydrogen bond present in compound **4-02**. The intramolecular hydrogen bond between the hydrogen atom in NH_2 and the oxygen atoms of the nitro group forms a six-numbered ring. The hydrogen bond makes an important contribution to enhancing the robustness of the compound.

Structure–activity relationship (SAR)

Insecticidal Activity. The insecticidal activities of these compounds were evaluated against *A. gossypii*, *M. persicae* and *P. xylostella*. The initial insecticidal activities were calculated for each compound and the results were summarized in Tables 1–3. The LC_{50}s were calculated for elected compounds and the results were summarized in Table 4. The preliminary bioassay showed that most of the designed compounds exhibited good insecticidal activities against *M. persicae* and *A. gossypii* (see Tables 1 and 2). The results also provide us important structure–activity relationship informations for this class of compounds. At first, the structure of R_2 might be the most crucial factor for their aphid toxicities, an electron-deficient group, especially a heterocyclic ring might be appreciated.

Table 1 The insecticidal activity of title compounds against *A. gossypii* (Glover)[a]

	100 mg L^{-1}			25 mg L^{-1}		
Compd	Total worm number	Death number	Mortality (%)	Total worm number	Death number	Mortality (%)
4-01	184	138	75.00	200	142	71.00
4-02	214	199	92.99	252	227	90.08
4-03	180	116	64.44	165	94	56.97
4-04	186	118	63.44	120	47	39.17
4-05	139	84	60.43	102	41	40.20
4-06	191	182	95.29	122	84	68.85
4-07	109	104	95.41	113	106	93.81
4-08	140	86	61.43	94	48	51.06
4-09	202	98	48.51	160	82	51.25
4-10	112	64	57.14	82	29	35.37
4-11	91	70	76.92	108	54	50.00
4-12	116	14	12.07	96	4	4.17
4-13	152	34	22.37	104	6	5.77
4-14	118	10	8.47	108	2	1.85
4-15	186	126	67.74	54	24	44.44
4-16	104	28	26.92	57	11	19.30
4-17	80	73	91.25	133	109	81.95
4-18	102	93	91.18	74	55	74.32
4-19	109	31	28.44	87	13	14.94
4-20	130	76	58.46	64	37	57.81
4-21	102	87	85.29	100	70	70.00
4-22	74	64	86.49	72	41	56.94
4-23	196	122	62.24	108	43	39.81
4-24	112	80	71.43	189	57	30.16
4-25	85	66	77.65	138	92	66.67
Guadipyr	79	77	97.47	79	74	93.67
IMI	102	100	98.04	92	87	94.57

[a] The lethal rate of CK was 3.98%. When IMI was used at 6.25 μg mL^{-1}, the lethal rate of IMI was 93.75%.

Secondly, R_1 is another key factor affecting the activity. Interestingly, a short chain, for example, ethyl is the best one in the series. This is quite different from guadipyr and its structural isomer series, in which a long linear chain is beneficial to insecticidal activities.[15,16] The two structure requirements made **4-07** as the best candidate for further development. Thirdly, these compounds were nearly ineffective against *Plutella xylostella* at 100 mg L^{-1} (Table 3), and this is agreed with the selectivity of neonicotinoids.

Honey bee toxicity. The honey bee toxicity of compound **4-02**, **4-03**, **4-07** and **4-08** was tested on *Apis melliferal* and compared to imidacloprid and guadipyr (Table 5). Surprisingly, compound **4-02**, **4-03** and **4-08** showed no activity against honey bee at the concentration 1000 μg mL^{-1}, and the LD_{50} of compound **4-07** (5.56 μg bee^{-1}) and Guadipyr (5.19 μg bee^{-1}) were significantly higher than those of commercial insecticides (3.25×10^{-2} μg bee^{-1} of imidacloprid, 1.2 μg bee^{-1} of FPF and 0.51 μg bee^{-1} of TFM, respectively), suggesting the lower toxicity to honey bee for these two compounds. Therefore, compound **4-07** and guadipyr showed selectivity in their effects against the honey bee and aphid. Contrast to traditional acyclic neonicotinoid insecticides, the high effect and low toxicity of guadipyr and **4-07** may attribute to their flexible side-chain.

3 Experimental

Instruments and materials

Melting points (mp) were recorded on a Cole-Parmer microscope melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DPX300 spectrometer with $CDCl_3$ or DMSO-d_6 as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. High resolution mass spectrometry data were obtained with an Accurate-Mass-Q-TOF MS 6520 system equipped with an electrospray ionization (ESI) source. The single crystal structure analysis was performed using X-ray diffraction on Thermo Fisher ESCALAB 250 diffractometer. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F254), and spots were visualized with ultraviolet (UV) light.

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Precursor 2 and R_1ONH_2 were synthesized as literature report.[18–20] All of the yields were not optimized.

General procedure for the preparation of compound (3-01). To the solution of R_1ONH_2 (10 mmol) in methanol (10 mL) was added methyl (*E*)-*N*′-nitrocarbamimidothioate 8 mmol (intermediate 2). The mixture was stirred at room temperature for 4 h. After completion, concentrated the mixture to oil under reduced pressure, and purified by column chromatography with ethyl acetate and petroleum ether, yield compound **3-01** and byproduct **5-01** 38% and 37%, respectively.

*Data for **3-01**.* Yield 38%; light yellow solid; mp 52–53 °C; ^1H NMR (300 MHz, DMSO) δ 11.27 (s, 1H), 8.31 (s, 2H), 6.01 (ddt, J = 16.7, 10.3, 6.3 Hz, 1H), 5.55–5.17 (m, 2H), 4.34 (d, J = 6.3 Hz, 2H).

Table 2 The insecticidal activity of title compounds against *M. persicae* at the concentration of 50 μg mL^{-1}

Compd	Total worm number	Death number	Corrected mortality (%)	Compd	Total worm number	Death number	Corrected mortality (%)
4-01	87	51	55.8	**4-13**	78	36	42.4
4-02	94	68	70.4	**4-14**	88	46	49.0
4-03	86	65	73.9	**4-15**	70	48	66.4
4-04	95	57	57.2	**4-16**	106	61	54.6
4-05	113	63	52.7	**4-17**	49	14	23.6
4-06	50	38	74.3	**4-18**	63	15	18.6
4-07	88	78	87.9	**4-19**	77	20	22.8
4-08	82	63	76.8	**4-20**	98	79	79.3
4-09	67	48	69.7	**4-21**	71	37	48.8
4-10	73	51	67.8	**4-22**	49	14	23.6
4-11	78	45	54.8	**4-23**	65	50	75.3
4-12	55	38	66.9	**4-24**	47	27	54.5
IMI[a]	84	82	97.5	**4-25**	170	120	68.6
Guadipyr	78	73	93.2				

[a] Imidacloprid was used at 20 μg mL^{-1}. The lethal rate of CK was 6.5%.

Table 3 The insecticidal activity of title compounds against *Plutella xylostella* (Linnaeus) at the concentration of 100 μg mL^{-1}

Compd	Total worm number	Death number	Corrected mortality (%)	Compd	Total worm number	Death number	Corrected mortality (%)
CK	56	1	1.79	**4-13**	33	1	3.03
4-01	34	4	11.76	**4-14**	30	0	0.00
4-02	36	2	5.56	**4-15**	35	3	8.57
4-03	32	2	6.25	**4-16**	35	3	8.57
4-04	32	9	28.13	**4-17**	30	1	3.33
4-05	32	7	21.88	**4-18**	30	4	13.33
4-06	30	0	0.00	**4-19**	30	0	0.00
4-07	43	14	32.56	**4-20**	32	1	3.13
4-08	36	8	22.22	**4-21**	30	0	0.00
4-09	30	0	0.00	**4-22**	35	1	2.86
4-10	36	5	13.89	**4-23**	30	0	0.00
4-11	34	1	2.94	**4-24**	30	2	6.67
4-12	30	0	0.00	**4-25**	30	0	0.00
IMI	30	2	6.67	Guadipyr	30	2	6.67
Spinosad[a]	34	23	67.65	Indoxacarb[a]	30	27	90.00

[a] Spinosad and indoxacarb were used at 25 μg mL^{-1}.

*Data for **5-01**.* Yield 37%; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (ddd, J = 16.2, 11.0, 5.8 Hz, 1H), 5.29–5.01 (m, 2H), 4.89 (s, 2H), 4.37 (d, J = 5.8 Hz, 2H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.55, 134.19, 116.87, 73.92, 13.34. HRMS (ESI) m/z calcd for $C_5H_{11}N_2O_S$ $(M + H)^+$ 147.0587, found 147.0586.

Table 4 The precise insecticidal assay of six compounds against *M. persicae*

Compd	LC_{50} (μg mL^{-1})	95% FL
Imidacloprid	0.16	0.12–0.22
Guadipyr	0.70	0.45–1.01
4-02	1.80	0.73–3.78
4-03	12.16	8.29–19.33
4-06	13.13	6.57–29.14
4-07	0.38	0.05–2.01
4-08	4.84	2.28–9.47
4-20	17.21	7.89–33.62

*Data for **3-02**.* Yield 34%; white solid; mp 66–67 °C; ^{1}H NMR (300 MHz, DMSO) δ 11.29 (s, 1H), 8.31 (s, 2H), 3.88 (q, J = 7.0 Hz, 2H), 1.22 (t, J = 7.0 Hz, 3H).

*Data for **3-03**.* Yield 44%; white solid; mp 64–65 °C; ^{1}H NMR (300 MHz, DMSO) δ 11.29 (s, 1H), 8.26 (s, 2H), 3.77 (t, J = 6.8 Hz, 2H), 1.82–1.55 (m, 2H), 1.01–0.83 (m, 3H).

*Data for **3-04**.* Yield 41%; white solid; mp 73–74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.25–10.58 (m, 1H), 9.16–8.06 (m, 1H),

Table 5 The toxicities of commercial insecticides and compound **4-07** against honey bee

Compd	IMI	FPF[a]	TFM[b]	Guadipyr	**4-07**
LD_{50} (μg bee^{-1})	3.25×10^{-2}	1.20	0.51	5.19	5.56

[a] The data was calculated in 72 h and cited from ref. 10. [b] The data was cited from ref. 14.

6.84–5.96 (m, 1H), 4.02 (t, J = 6.7 Hz, 2H), 1.79–1.57 (m, 2H), 1.42 (dd, J = 15.1, 7.4 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H).

*Data for **3-05**.* Yield 40%; white solid; mp 62–63 °C; ^{1}H NMR (300 MHz, DMSO) δ 11.26 (s, 1H), 8.25 (s, 2H), 3.81 (t, J = 6.9 Hz, 2H), 1.75–1.49 (m, 2H), 1.44–1.20 (m, 4H), 0.87 (dd, J = 8.3, 5.5 Hz, 3H).

General procedure for the preparation of title compounds (4). To an ice-cooled solution of 3 (4.8 mmol) in DMF (10 mL) was added sodium hydride (60% oil dispersion; 0.288 g (7.2 mmol)) in portions. The mixture was stirred below 10 °C for 1 h in an ice-water bath followed by adding a solution of halide (5.2 mmol in 10 mL DMF) slowly. Subsequently, the ice-water bath was removed, and the mixture was stirred at room temperature for 22 h. After completion, 30 mL of water was added slowly to the solution and then the product was precipitated. The precipitates were filtered, dried and recrystallized from ethyl acetate. If it did not precipitate, extracted the solution with ethyl acetate (3 × 30 mL) and concentrated the organic layer to oil under reduced pressure, and purified by column chromatography with ethyl acetate and petroleum ether.

*Data for **(4-01)**.* Yield 72%; white solid; mp 83–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.35 (d, J = 2.1 Hz, 1H), 7.71 (dd, J = 8.2, 2.5 Hz, 1H), 7.46–7.27 (m, 1H), 7.09 (s, 1H), 5.93 (ddt, J = 16.6, 10.0, 6.6 Hz, 1H), 5.53–5.21 (m, 2H), 4.84 (s, 2H), 4.39 (d, J = 6.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.12, 151.02, 149.59, 139.25, 129.68, 129.15, 124.04, 122.56, 75.86, 49.78. HRMS (ESI) m/z calcd for $C_{10}H_{13}ClN_5O_3$ $(M + H)^+$ 286.0701, found 286.0704.

*Data for **(4-02)**.* Yield 78%; white solid; mp 71–72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.36 (d, J = 2.3 Hz, 1H), 7.72 (dd, J = 8.2, 2.5 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.01 (s, 1H), 4.84 (s, 2H), 3.99 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.98, 151.05, 149.56, 139.19, 129.18, 124.05, 70.59, 49.40, 12.97. HRMS (ESI) m/z calcd for $C_9H_{13}ClN_5O_3$ $(M + H)^+$ 274.0701, found 274.0704.

*Data for **(4-03)**.* Yield 59%; white solid; mp 101–102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50–8.79 (m, 1H), 8.40 (d, J = 2.4 Hz, 1H), 7.76 (dd, J = 8.2, 2.5 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.00–6.23 (m, 1H), 4.87 (s, 2H), 3.90 (t, J = 6.7 Hz, 2H), 1.73 (dd, J = 14.3, 7.0 Hz, 2H), 1.01 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.94, 151.26, 149.67, 139.19, 129.02, 124.08, 76.54, 49.41, 20.92, 10.04. HRMS (ESI) m/z calcd for $C_{10}H_{15}ClN_5O_3$ $(M + H)^+$ 288.0858, found 288.0858.

*Data for **(4-04)**.* Yield 60%; white solid; mp 68–69 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.38–8.80 (m, 1H), 8.37 (s, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 6.87–6.24 (m, 1H), 4.84 (s, 2H), 3.91 (t, J = 6.6 Hz, 2H), 1.63 (d, J = 8.0 Hz, 2H), 1.39 (d, J = 7.6 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.09, 151.45, 149.84, 139.34, 129.14, 124.24, 75.03, 49.56, 29.70, 19.01. HRMS (ESI) m/z calcd for $C_{11}H_{17}ClN_5O_3$ $(M + H)^+$ 302.1014, found 302.1018.

*Data for **(4-05)**.* Yield 57%; white solid; mp 67–68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.25 (d, J = 2.4 Hz, 1H), 7.62 (dd, J = 8.2, 2.4 Hz, 1H), 7.23 (t, J = 17.1 Hz, 2H), 4.74 (s, 2H), 3.82 (t, J = 6.8 Hz, 2H), 1.67–1.38 (m, 2H), 1.17 (dd, J = 8.8, 5.3 Hz, 4H), 0.73 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.60, 150.69, 149.37, 139.11, 129.41, 123.92, 74.93, 49.02, 27.39, 26.93, 21.85, 13.37. HRMS (ESI) m/z calcd for $C_{12}H_{19}ClN_5O_3$ $(M + H)^+$ 316.1171, found 316.1173.

*Data for **(4-06)**.* Yield 64%; yellow solid; mp 78–79 °C; ^{1}H NMR (300 MHz,$CDCl_3$) δ 9.09 (s, 1H), 7.50 (s, 1H), 7.11 (s, 1H), 5.98 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.61–5.27 (m, 2H), 4.90 (s, 2H), 4.45 (d, J = 6.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.15, 152.84, 141.34, 132.16, 129.78, 122.70, 76.00, 45.81. HRMS (ESI) m/z calcd for $C_8H_{11}ClN_5O_3S$ $(M + H)^+$ 292.0266, found 292.0271.

*Data for **(4-07)**.* Yield 53%; white solid; mp 67–68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.51 (s, 1H), 7.01 (s, 1H), 4.91 (s, 2H), 4.06 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.08, 152.86, 141.29, 132.20, 70.74, 45.44, 13.06. HRMS (ESI) m/z calcd for $C_7H_{11}ClN_5O_3S$ $(M + H)^+$ 280.0266, found 280.0265.

*Data for **(4-08)**.* Yield 61%; white solid; mp 47–48 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.51 (s, 1H), 6.85 (s, 1H), 4.91 (s, 2H), 3.96 (t, J = 6.7 Hz, 2H), 1.89–1.57 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.98, 152.89, 141.33, 132.14, 76.69, 45.32, 20.92, 10.04. HRMS (ESI) m/z calcd for $C_8H_{13}ClN_5O_3S$ $(M + H)^+$ 294.0422, found 294.0424.

*Data for **(4-09)**.* Yield 62%; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36–8.60 (m, 1H), 7.42 (s, 1H), 7.19–6.78 (m, 1H), 4.82 (s, 2H), 3.91 (t, J = 6.7 Hz, 2H), 1.69–1.47 (m, 2H), 1.33 (dd, J = 15.1, 7.4 Hz, 2H), 0.86 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.88, 152.78, 141.25, 132.26, 74.98, 45.24, 29.45, 18.77, 13.39. HRMS (ESI) m/z calcd for $C_9H_{15}ClN_5O_3S$ $(M + H)^+$ 308.0579, found 308.0581.

*Data for **(4-10)**.* Yield 43%; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.43 (s, 1H), 7.11 (s, 1H), 4.83 (s, 2H), 3.91 (t, J = 6.8 Hz, 2H), 1.61 (dd, J = 13.9, 6.9 Hz, 2H), 1.40–1.16 (m, 4H), 0.82 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.75, 152.63, 141.16, 132.41, 75.17, 45.13, 27.48, 27.04, 21.93, 13.45. HRMS (ESI) m/z calcd for $C_{10}H_{17}ClN_5O_3S$ $(M + H)^+$ 322.0735, found 322.0740.

*Data for **(4-11)**.* Yield 64%; white solid; mp 80–81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.09 (s, 1H), 7.50 (s, 1H), 7.11 (s, 1H), 5.98 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.61–5.27 (m, 2H), 4.90 (s, 2H), 4.45 (d, J = 6.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.09, 133.82, 132.92, 129.92, 129.86, 128.46, 122.26, 75.79, 52.29. HRMS (ESI) m/z calcd for $C_{11}H_{13}ClN_4NaO_3$ $(M + Na)^+$ 307.0568, found 307.0571.

*Data for **(4-12)**.* Yield 63%; white solid; mp 73–74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.39–7.20 (m, 4H), 6.87 (s, 1H), 4.82 (s, 2H), 3.93 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.94, 133.82, 132.98, 129.85, 128.47, 70.47, 51.94, 12.96. HRMS (ESI) m/z calcd for $C_{10}H_{13}ClN_4NaO_3$ $(M + Na)^+$ 295.0568, found 295.0572.

*Data for **(4-13)**.* Yield 45%; white solid; mp 106–107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48–8.69 (brs, 1H), 7.41–7.23 (m, 4H), 6.92–6.38 (brs, 1H), 4.84 (s, 2H), 3.84 (t, J = 6.7 Hz, 2H), 1.76–1.59 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.87, 133.90, 132.92, 129.91, 128.49, 76.31, 51.90, 20.89, 10.04. HRMS (ESI) m/z calcd for $C_{11}H_{15}ClN_4NaO_3$ $(M + Na)^+$ 309.0725, found 309.0729.

*Data for **(4-14)**.* Yield 65%; white solid; mp 92–93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.33–7.27 (m, 4H), 6.68 (s, 1H),

4.82 (s, 2H), 3.87 (d, J = 6.7 Hz, 2H), 1.62 (dt, J = 14.7, 6.8 Hz, 2H), 1.38 (dt, J = 14.9, 7.4 Hz, 2H), 1.02–0.85 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.78, 133.82, 132.99, 129.86, 128.45, 74.66, 51.81, 29.47, 18.77, 13.38. HRMS (ESI) m/z calcd for $C_{12}H_{18}ClN_4O_3$ $(M + H)^+$ 301.1062, found 301.1064.

*Data for **(4-15)**.* Yield 58%; white solid; mp 78–79 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.41–7.22 (m, 4H), 6.74 (s, 1H), 4.82 (s, 2H), 3.85 (t, J = 6.7 Hz, 2H), 1.62 (dd, J = 14.0, 6.9 Hz, 2H), 1.31 (dd, J = 9.2, 5.3 Hz, 4H), 0.90 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.81, 133.83, 132.98, 129.87, 128.45, 74.94, 51.85, 27.60, 27.15, 21.96, 13.47. HRMS (ESI) m/z calcd for $C_{13}H_{20}ClN_4O_3$ $(M + H)^+$ 315.1218, found 315.1220.

*Data for **(4-16)**.* Yield 56%; white solid; mp 76–77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.13 (t, J = 5.5 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 7.09 (s, 1H), 6.04–5.80 (m, 1H), 5.38 (dd, J = 12.3, 5.7 Hz, 2H), 4.97 (s, 2H), 4.39 (d, J = 6.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.99, 147.30, 141.98, 129.74, 129.03, 123.43, 122.52, 75.90, 52.10. HRMS (ESI) m/z calcd for $C_{11}H_{13}N_5NaO_5$ $(M + Na)^+$ 318.0809, found 318.0813.

*Data for **(4-17)**.* Yield 64%; white solid; mp 76–77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.20 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.6 Hz, 2H), 6.86 (s, 1H), 4.98 (s, 2H), 4.00 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.92, 147.42, 141.88, 129.05, 123.50, 70.67, 51.89, 12.99. HRMS (ESI) m/z calcd for $C_{10}H_{13}N_5NaO_5$ $(M + H)^+$ 306.0809, found 306.0812.

*Data for **(4-18)**.* Yield 48%; yellow solid; mp 74–75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.34–8.12 (m, 2H), 7.54 (d, J = 8.8 Hz, 2H), 6.77 (s, 1H), 4.99 (s, 2H), 3.90 (t, J = 6.7 Hz, 2H), 1.80–1.62 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.79, 147.44, 141.85, 129.06, 123.50, 76.55, 51.77, 20.87, 9.99. HRMS (ESI) m/z calcd for $C_{11}H_{15}N_5NaO_5$ $(M + Na)^+$ 320.0965, found 320.0971.

*Data for **(4-19)**.* Yield 69%; white solid; mp 93–94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.19 (d, J = 8.7 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 6.79 (s, 1H), 4.98 (s, 2H), 3.93 (t, J = 6.7 Hz, 2H), 1.79–1.53 (m, 2H), 1.38 (dq, J = 14.5, 7.3 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.74, 147.40, 141.92, 129.02, 123.48, 74.88, 51.71, 29.45, 18.76, 13.35. HRMS (ESI) m/z calcd for $C_{12}H_{18}N_5O_5$ $(M + H)^+$ 312.1302, found 312.1306.

*Data for **(4-20)**.* Yield 57%; white solid; mp 88–89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.19 (d, J = 8.7 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 6.80 (s, 1H), 4.98 (s, 2H), 3.92 (t, J = 6.7 Hz, 2H), 1.83–1.49 (m, 2H), 1.49–1.12 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.74, 147.39, 141.93, 129.02, 123.48, 75.15, 51.72, 27.57, 27.13, 21.95, 13.45. HRMS (ESI) m/z calcd for $C_{13}H_{20}N_5O_5$ $(M + H)^+$ 326.1459, found 326.1463.

*Data for **(4-21)**.* Yield 52%; white solid; mp 91–92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.60 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.07 (s, 1H), 5.93 (ddt, J = 16.7, 10.1, 6.6 Hz, 1H), 5.56–5.18 (m, 2H), 4.91 (s, 2H), 4.36 (d, J = 6.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.98, 139.97, 132.07, 129.76, 128.90, 122.49, 118.17, 111.55, 75.85, 52.36. HRMS (ESI) m/z calcd for $C_{12}H_{13}N_5NaO_3$ $(M + H)^+$ 298.0911, found 298.0915.

*Data for **(4-22)**.* Yield 45%; white solid; mp 111–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57–8.76 (m, 1H), 7.66 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 8.1 Hz, 2H), 7.15–6.36 (m, 1H), 4.94 (s, 2H), 3.98 (q, J = 7.0 Hz, 2H), 1.31 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.95, 139.85, 132.12, 128.92, 118.09, 111.83, 70.62, 52.19, 13.01. HRMS (ESI) m/z calcd for $C_{11}H_{13}N_5NaO_3$ $(M + Na)^+$ 286.0911, found 286.0915.

*Data for **(4-23)**.* Yield 59%; white solid; mp 64–65 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.65 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.3 Hz, 2H), 7.14–6.32 (m, 1H), 4.94 (s, 2H), 3.87 (t, J = 6.7 Hz, 2H), 1.78–1.60 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.79, 139.87, 132.10, 128.92, 118.10, 111.80, 76.49, 52.03, 20.86, 9.99. HRMS (ESI) m/z calcd for $C_{12}H_{16}N_5O_3$ $(M + H)^+$ 278.1248, found 278.1250.

*Data for **(4-24)**.* Yield 52%; white crystal; mp 88–89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.75–7.58 (m, 2H), 7.46 (d, J = 8.4 Hz, 2H), 6.79 (s, 1H), 4.92 (s, 2H), 3.90 (t, J = 6.7 Hz, 2H), 1.64 (dt, J = 14.7, 6.9 Hz, 2H), 1.38 (dt, J = 14.9, 7.3 Hz, 2H), 0.94 (dt, J = 14.7, 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.73, 139.95, 132.09, 128.87, 118.12, 111.70, 74.81, 51.97, 29.44, 18.75, 13.35. HRMS (ESI) m/z calcd for $C_{13}H_{18}N_5O_3$ $(M + H)^+$ 292.1404, found 292.1406.

*Data for **(4-25)**.* Yield 62%; white solid; mp 70–71 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62–8.61 (m, 1H), 7.79–7.59 (m, 2H), 7.48 (d, J = 8.2 Hz, 2H), 7.08–6.41 (m, 1H), 4.94 (s, 2H), 3.90 (t, J = 6.7 Hz, 2H), 1.73–1.58 (m, 2H), 1.32 (dd, J = 9.2, 5.3 Hz, 4H), 0.91 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.78, 139.87, 132.11, 128.92, 118.09, 111.82, 75.11, 52.05, 27.59, 27.16, 21.95, 13.47. HRMS (ESI) m/z calcd for $C_{14}H_{20}N_5O_3$ $(M + H)^+$ 306.1561, found 306.1565.

X-ray diffraction

Compound **4-02** was recrystallized by a slow evaporation from a dichloromethane/*n*-hexane (v/v = 1 : 5) solution to afford a single crystal suitable for X-ray crystallography and mounted in inert oil and transferred to the cold gas stream of the diffractometer. Cell dimensions and intensities were measured using a Thermo Fisher ESCALAB 250 diffractometer with graphite monochromated Mo Kα radiation. A total of 4458 reflections were measured, of which 2357 were unique (R_{int} = 0.0201) in the range of $6.32 < 2\theta < 51.98°$ ($-14 \le h \le 14$, $-11 \le k \le 6$, $-7 \le l \le 14$), and 2357 observed reflections with $I > 2\sigma(I)$ were used in the refinement on F_2. The structure was solved by direct method with the SHELXTL-97 program. All of the non-H atoms were refined anisotropically by fullmatrix least-squares to give the final w$R(F_2)$ = 0.1039. The atomic coordinates for **4-02** have been deposited at the Cambridge Crystallographic Data Centre.† CCDC-1518112 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* CCDC CIF Depository Request Crystallographic data in CIF format are in the ESI.†

Biological assays

Insecticidal activity. Insecticidal bioassays were performed on representative test organisms prepared in the laboratory. The bioassay was repeated at 25 ± 1 °C. All compounds were dissolved in *N*,*N*-dimethylformamide and diluted with 0.05% Triton X-100 to obtain a series of concentrations for bioassays. For comparative purposes, imidacloprid was tested under the

same conditions. The preliminary bioassay of compounds against *A. gossypii* (Glover) was tested by leaf-dipping method and *M. persicae* (Sulzer) was tested by spray-method and according to previously reported procedures and the results were summarized in Tables 1 and 2.[21–23] The precise insecticidal assay was also tested by spray-method. Imidacloprid (95%) purchased from Jiangsu Changlong Chemicals Co. was used as control treating in the same way. *Plutella xylostella* was tested by leaf-dipping method which was recommended by Insecticide Resistance Action Committee (IRAC).[24] *A. mellifera* was provided by Institute of Apicultural Research, Chinese Academy of Agricultural Sciences in July 2016, and a bioassay was performed following the Organisation for Economic Cooperation and Development (OECD) method for the acute oral toxicity test on honey bees.[25,26] The mortality was recorded in 48 h. The data obtained were analyzed using IBM SPSS Statistics 20 to determine LD_{50} or LC_{50} values based on the bioassay methods.

4 Conclusions

In summary, by replacing the iconic imine chain with alkoxyl group, the hydrazine-carboximidamide system which assigned to the sodium ion channel inhibiting activity in guadipyr and its structural isomers was destroyed, and a novel series of standard neonicotinoid compounds, alkoxynitroguanidine compounds were designed and synthesized. Most of these compounds exhibited good insecticidal activity against *M. persicae* and *A. gossypii* (Glover), and compound **4-07** was the best. Its high insecticidal activity and low toxicity to honey bees made it a good candidate for further development. The structure–activity relationship (SAR) analysis also points us the optimal path for further development of this kind of neonicotinoids, and this is undergoing in our lab.

Conflicts of interest

The authors declare no competing financial interest.

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