JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Article

pubs.acs.org/JAFC

N′-Nitro-2-hydrocarbylidenehydrazinecarboximidamides: Design, Synthesis, Crystal Structure, Insecticidal Activity, and Structure–Activity Relationships

Wangcang Su,[†] Yihui Zhou,[†] Yongqiang Ma,*[,†] Lei Wang,[†] Zheng Zhang,[†] Changhui Rui,[‡] Hongxia Duan,[†] and Zhaohai Qin*[,†]

[†]Department of Applied Chemistry, College of Science, China Agricultural University, Beijing 100193, China

[‡]Institute of Plant Protection, Chinese Academy of Agricultural Sciences, Beijing 100193, China

Supporting Information

ABSTRACT: A novel series of acyclic imine-substituted nitenpyram analogues were designed and synthesized from nitroaminoguanidine, and their structures were confirmed using X-ray diffraction crystallography. Preliminary bioassays showed that the target molecules exhibited good activities against aphids in laboratory (*Myzus persicae* Sulzer) and field trials (*M. persicae* Sulzer and *Brevicoryne brassicae* Linnaeus). Comparative molecular field analysis and comparative molecular similarity indices analysis were employed to develop a three-dimensional quantitative structure–activity relationship model that describes the insecticidal activity of 21 neonicotinoid derivatives. Simple synthesis, low cost, and good insecticidal activity have made this series of compounds become very promising candidates for future commercial pesticides.

KEYWORDS: *nitroaminoguanidine, acyclic neonicotinoid, insecticide activity, QSAR*

INTRODUCTION

The current neonicotinoids insecticides have been used extensively against a broad spectrum of pests in modern crop protection since 1991, accounting for about one-fifth of the current global insecticide market.[1−7] Imidacloprid, for example, is the top-selling insecticide today. Neonicotinoids as agonists of nicotinic acetylcholine receptors (nAChRs) show high selectivity for insects over vertebrates. High activity and target specificity play important roles in their application.[8−12] Resistance, however, has already reduced their effectiveness for many of the early uses. The discovery and commercialization of new insecticide molecules are currently active areas of research.[13−16]

Many research papers that discuss the structure optimization of neonicotinoid insecticides (NNs) are based on cyclic NNs, such as imidacloprid. Few studies have focused on the structural modification of acyclic NNs, such as nitenpyram.[16−18] However, of the seven commercial neonicotinoids[7,19−25] on the market, four are open-chain compounds, that is, nitenpyram, clothianidin, dinotefuran, and acetamiprid, while three are cyclic compounds, that is, imidacloprid, thiamethoxam, and thiacloprid. Although cyclic and acyclic neonicotinoids bind in a similar manner to the nAChR recognition site, there are important differences between them. Nitenpyram, for example, is characterized by a much lower toxicity in mammals, birds, and aquatic organisms than imidacloprid.[16] Open-chain neonicotinoids, as super agonists, show a greater maximum response to the nAChRs and are less lipophilic than the corresponding cyclic compounds.[1] Although strategies for designing and synthesizing acyclic neonicotinoids molecules are emerging, further studies on structure optimization of acyclic NNs are still an attractive area of research. In addition, a trivial change in the structure of a pesticide may lead to great changes in the chemical properties and activities.[17] Inspired by these findings, this work focused on the design and synthesis of a series of novel *N*′-nitro-2-hydrocarbylidenehydrazinecarboximidamides, imine-substituted nitenpyram analogues. The insecticidal activities of these compounds were measured against aphid in laboratory and field trials, and a quantitative structure–activity relationship (QSAR) model was developed based on the results.

MATERIALS AND METHODS

Instrumentation and Chemicals. For all reactions, solvents and chemical reagents were of analytical or synthetic grade obtained from Sinopharm Chemical Reagent Beijing Co., Ltd., and were used without purification. Column chromatography purification was performed using silica gel. Melting points of all compounds were determined using a B-III microscope (Beijing Technical Instrument Co., China), and the thermometer was not corrected. NMR spectra were obtained using a Bruker Avance DPX300 spectrometer with tetramethylsilane as the internal standard. Elemental analyses were performed on a Yanaca CHN Corder MT-3 elemental analyzer. IR was recorded on a Bruker Vector 22 FT-IR spectrometer using pressed KBr pellets. The single crystal structure analysis was performed using X-ray diffraction on a Rigaku Saturn 724 CCD diffractometer. Mass spectra were obtained with an Agilent 1100 LC-MSD-Trap mass spectrometer equipped with standard electrospray ionization (ESI) apparatus.

Synthetic Procedures. *General Synthesis Procedure for Intermediate (II).* In a 250 mL flask, nitroaminoguanidine (**I**) (2.0 g, 17 mmol) and glacial acetic acid (0.2 mL) were dissolved in menthol (100 mL), the mixture was heated at 50 °C, aldehyde (20 mmol) was added dropwise to the mixture, and the reaction was refluxed for 1 h.

Received: February 14, 2012
Revised: April 25, 2012
Accepted: April 30, 2012
Published: April 30, 2012

After completion, the solvent was removed under reduced pressure, and the resulting crude material was recrystallized using ethanol and petroleum ether (v/v, 3:1).

General Synthetic Procedure for Compound (III). Intermediate **II** (8 mmol) was dissolved in DMF (30 mL), and a catalytic amount of KI was added to the mixture, followed by the addition of 70% NaH (0.48 g, 14 mmol) at 10 °C. The reaction was allowed to stir for 1 h at this temperature. A solution of halides (16 mmol) in 10 mL of DMF was then added dropwise to the mixture, and the progress of the reaction was monitored by thin-layer chromatography. Upon completion, the precipitate was filtrated and washed with water, and the crude product was recrystallized from an ethanol and petroleum ether (v/v, 1:2) solution to afford the corresponding compound.

Data for ***1***. White crystal; yield, 66%; mp: 159−160 °C. ^{1}H NMR ($CDCl_3$): δ 1.06 (d, J = 6.87 Hz, 6H), 2.52−2.62 (m, 1H), 5.24 (s, 2H), 7.07 (t, J = 4.83 Hz, 1H), 7.31 (d, J = 8.25 Hz, 1H), 7.49 (dd, J = 2.58, 8.25 Hz, 1H), 7.56 (brs, 1H), 8.21 (d, J = 2.58 Hz, 1H), 9.15 (brs, 1H). IR (KBr, cm^{-1}) ν: 3400, 3319, 2967, 2870, 2357, 1600, 1476, 1245, 1052, 939. Anal. calcd for $C_{11}H_{15}ClN_6O_2$: C, 44.23; H, 5.06; N, 28.13. Found: C, 44.27; H, 5.07; N, 27.70

Data for ***2***. White needle crystal; yield, 49%; mp: 35 °C. ^{1}H NMR ($CDCl_3$): δ 1.18 (t, J = 7.25 Hz, 3H), 1.24 (t, J = 7.22 Hz, 3H), 2.40−2.50 (m, 2H), 4.03 (q, J = 7.56 Hz, 2H), 7.27 (t, J = 4.98 Hz, 1H), 7.41 (brs, 1H), 9.03 (brs, 1H). IR (KBr, cm^{-1}) ν: 3405, 3253, 2981, 2883, 2356, 1590, 1263, 1080. MS (ESI) m/z: 188.2 $(M+H)^+$.

Data for ***3***. White needle crystal; yield, 50%; mp: 95−96 °C. ^{1}H NMR ($CDCl_3$): δ 0.93(t, J = 7.34 Hz, 3H), 1.17 (t, J = 7.27 Hz, 3H), 1.49−1.62(m, 2H), 2.40−2.49(m, 2H), 3.90(t, J = 7.68 Hz, 2H), 7.27(t, J = 5.99 Hz, 1H), 7.41(brs, 1H), 9.03(brs, 1H). IR (KBr, cm^{-1})ν: 3424, 3305, 2953, 2873, 2358, 1594, 1244, 1045. Anal. calcd for $C_7H_{15}N_5O_2$: C, 41.78; H, 7.51; N, 34.80. Found: C, 41.86; H, 7.53; N, 34.90.

Data for ***4***. White crystal; yield, 46%; mp: 52−53 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 (t, J = 7.55 Hz, 3H), 1.00 (t, J = 6.99 Hz, 3H), 1.31−1.36 (m, 2H), 1.46−1.52 (m, 2H), 1.59−1.66 (m, 2H), 2.35−2.42 (m, 2H), 3.94 (t, J = 7.33 Hz, 2H), 7.59 (brs, 1H), 7.24 (t, J = 5.13 Hz, 1H), 7.42 (brs, 1H), 9.03 (brs, 1H). IR (KBr, cm^{-1}) ν: 3400, 3350, 2950, 2869, 2359, 1594, 1245, 1019. Anal. calcd for $C_9H_{19}N_5O_2$: C, 41.75; H, 8.35; N, 30.55. Found: C, 46.63; H, 7.96; N, 30.31.

Data for ***5***. White flake crystal; yield, 68%; mp: 136−137 °C. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J = 7.32 Hz, 3H), 1.44−1.56 (m, 2H), 2.26−2.33 (m, 2H), 5.24 (s, 2H), 7.12 (t, J = 4.89 Hz, 1H), 7.32 (d, J = 8.25 Hz, 1H), 7.48 (dd, J = 2.55, 8.28 Hz, 1H), 7.59 (brs, 1H), 8.21 (d, J = 2.52 Hz, 1H), 9.15 (brs, 1H). IR (KBr, cm^{-1}) ν: 3422, 3307, 2960, 2871, 2357, 1610, 1491, 1250, 1060, 941. Anal. calcd for $C_{11}H_{15}ClN_6O_2$: C, 44.23; H, 5.06; N, 28.13. Found: C, 44.15; H, 5.04; N, 27.95.

Data for ***6***. Pale yellow crystal; yield, 43%; mp: 99−100 °C. ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.55 Hz, 3H), 1.31−1.42 (m, 2H), 1.49−1.57 (m, 2H), 4.00 (t, J = 7.88 Hz, 1H), 5.71−5.77 (m, 2H), 6.50−6.62 (m, 1H), 7.42 (brs, 1H), 7.52 (d, J = 9.56 Hz, 1H), 9.07 (brs, 1H). IR (KBr, cm^{-1}) ν: 3420, 3300, 2958, 2870, 2359, 1600, 1233, 1050, 985. Anal. calcd for $C_8H_{15}N_5O_2$: C, 45.06; H, 7.09; N, 32.84. Found: C, 45.10; H, 7.05; N, 32.66.

Data for ***7***. White flake crystal; yield, 65%; mp: 97−98 °C. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J = 7.67 Hz, 3H), 1.20−1.28 (m, 6H), 1.40−1.47 (m, 2H), 2.28−2.34 (m, 2H), 5.24 (s, 2H), 7.11 (t, J = 6.06 Hz, 1H), 7.31 (d, J = 8.25 Hz, 1H), 7.48 (dd, J = 2.58, 8.28 Hz, 1H), 7.57 (brs, 1H), 8.21 (d, J =2.55 Hz, 1H), 9.14 (brs, 1H). IR (KBr, cm^{-1}) ν: 3410, 3320, 2927, 2858, 2355, 1609, 1479, 1260, 1070, 984. Anal. calcd for $C_{14}H_{21}ClN_6O_2$: C, 47.78; H, 5.86; N, 25.72. Found: C, 49.08; H, 6.15; N, 24.56.

Data for ***8***. Pale yellow crystal; yield, 60%; mp: 44−45 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 (t, J = 7.26 Hz, 3H), 1.30−1.38 (m, 2H), 1.50−1.58 (m, 2H), 2.33−2.40 (m, 2H), 4.63 (d, 2H), 4.98−5.05 (m, 1H), 5.19−5.24 (m, 1H), 5.64−5.74 (m, 1H), 7.19 (t, J = 5.97 Hz, 1H), 7.48 (brs, 1H), 9.07 (brs, 1H). IR (KBr, cm^{-1}) ν: 3439, 3322, 2935, 2866, 2355, 1595, 1250, 1060, 980. Anal. calcd for $C_9H_{17}N_5O_2$: C, 47.56; H, 7.54; N, 30.82. Found: C, 47.43; H, 7.37; N, 30.88.

Data for ***9***. White crystal; yield, 70%; mp: 113−114 °C. ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.47 Hz, 3H), 1.22−1.27 (m, 2H), 1.39−1.49 (m, 2H), 2.28−2.35 (m, 2H), 5.24 (s, 2H), 7.12 (t, J = 5.66 Hz, 1H), 7.31 (d, J = 8.25 Hz, 1H), 7.48 (dd, J = 2.49, 8.19 Hz, 1H), 7.57 (brs, 1H), 8.20 (d, J = 2.55 Hz, 1H), 9.14 (brs, 1H). IR (KBr, cm^{-1}) ν: 3420, 3333, 2951, 2865, 2357, 1610, 1499, 1250, 1023, 954. Anal. calcd for $C_{12}H_{17}ClN_6O_2$: C, 46.08; H, 5.48; N, 26.87. Found: C, 46.08; H, 5.44; N, 26.77.

Data for ***10***. White powder; yield, 68%; mp: 176−177 °C. ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.11 Hz, 3H), 2.42 (s, 3H), 4.19 (q, J = 7.12 Hz, 2H), 7.26 (t, J = 3.93 Hz, 2H), 7.58 (d, J = 8.25 Hz, 2H), 7.86 (s, 1H), 9.11 (brs, 2H). IR (KBr, cm^{-1}) ν: 3438, 3327, 2969, 1607, 1522, 1485, 1413, 1368, 1316, 1246, 1185, 1017. Anal. calcd for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.07; N, 28.09. Found: C, 52.81; H, 6.03; N, 27.95.

Data for ***11***. White crystal, 77%; mp: 173−174 °C. ^{1}H NMR (DMSO-d_6): δ 0.97 (t, J = 7.26 Hz, 3H), 1.35−1.48 (m, 2H), 1.56−1.66 (m, 2H), 2.41 (s, 3H), 4.11 (t, J = 7.61 Hz, 2H), 7.26 (t, J = 3.96 Hz, 2H), 7.57 (t, J = 9.29 Hz, 3H), 7.84 (s, 1H), 9.09 (brs, 2H). IR (KBr, cm^{-1}) ν: 3416, 3310, 2959, 2865, 1597, 1459, 1041, 931, 818. Anal. calcd for $C_{13}H_{19}N_5O_2$: C, 56.30; H, 6.91; N, 25.25. Found: C, 56.39; H, 6.87; N, 25.53.

Data for ***12***. White crystal; yield, 83%; mp: 169−170 °C. ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 3H), 4.78−4.81 (m, 2H), 5.09−5.16 (m, 1H), 5.24−5.29 (m, 1H), 5.74−5.85 (m, 1H), 7.25 (d, J = 8.71 Hz, 2H), 7.56 (q, J = 6.58 Hz, 2H), 7.81 (s, 1H), 9.17 (brs, 2H). IR (KBr, cm^{-1}) ν: 3424, 3314, 1613, 1524, 1470, 1360, 1188, 1050, 936. Anal. calcd for $C_{12}H_{15}N_5O_2$: C, 55.16; H, 5.79; N, 26.80. Found: C, 54.92; H, 5.72; N, 26.97

Data for ***13***. White powder; yield, 77%; mp: 177−178 °C. ^{1}H NMR (DMSO-d_6): δ 3.72 (s, 3H), 5.37 (s, 2H), 6.96−7.05 (m, 3H), 7.23−7.30 (m, 3H), 7.32−7.43 (m, 3H), 8.22 (s, 1H), 8.99 (brs, 2H). IR (KBr, cm^{-1}) ν: 3424, 3310, 2958, 2835, 1601, 1520, 1044, 936, 745. Anal. calcd for $C_{16}H_{17}N_5O_3$: C, 58.71; H, 5.23; N, 21.39. Found: C, 58.75; H, 5.18; N, 21.37.

Data for ***14***. Pale yellow crystal; yield, 65%; mp: 141−142 °C. ^{1}H NMR (DMSO-d_6): δ 0.92 (t, J = 7.25 Hz, 3H), 1.27−1.39 (m, 2H), 1.46−1.56 (m, 2H), 3.83 (s, 3H), 4.06 (t, J = 7.40 Hz, 2H), 7.00−7.04 (m, 1H), 7.37 (t, J = 7.89 Hz, 1H), 7.54−7.60 (m, 2H), 8.16 (s, 1H), 8.80 (brs, 2H). IR (KBr, cm^{-1}) ν: 3413, 3310, 2955, 2871, 1584, 1524, 1041, 938, 800, 685. Anal. calcd for $C_{13}H_{19}N_5O_3$: C, 53.23; H, 6.53; N, 23.88. Found: C, 53.24; H, 6.55; N, 23.88.

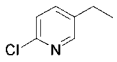
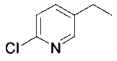
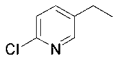
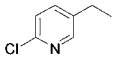
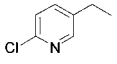
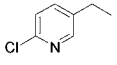
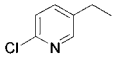
Data for ***15***. White powder; yield, 75%; mp: 197−198 °C. ^{1}H NMR (DMSO-d_6): δ 0.92 (t, J = 7.26 Hz, 3H), 1.27−1.40 (m, 2H), 1.47−1.57 (m, 2H), 4.07 (t, J = 7.41 Hz, 2H), 7.43−7.48 (m, 3H), 7.98−8.03 (m, 2H), 8.19 (s, 1H), 8.78 (brs, 2H). IR (KBr, cm^{-1}) ν: 3422, 3300, 2930, 2864, 1594, 1527, 1450, 1411, 1376, 1243, 1036, 975, 760. Anal. calcd for $C_{12}H_{17}N_5O_2$: C, 54.74; H, 6.51; N, 26.60. Found: C, 54.75; H, 6.37; N, 26.58.

Data for ***16***. White powder; yield, 73%; mp: 184−185 °C. ^{1}H NMR (DMSO-d_6): δ 4.80 (t, J = 2.44 Hz, 2H), 5.09 (q, J = 6.18 Hz, 1H), 5.26 (q, J = 3.90 Hz, 1H), 5.76−5.88 (m, 1H), 7.40−7.55 (m, 3H), 8.20 (s, 1H), 8.43 (q, J = 3.16 Hz, 1H), 8.96 (brs, 2H). IR (KBr, cm^{-1}) ν: 3441, 3324, 1593, 1524, 1477, 1413, 1365, 1245, 1042, 939, 760. Anal. calcd for $C_{11}H_{12}N_5O_2Cl$: C, 46.90; H, 4.29; N, 24.86. Found: C, 46.91; H, 4.39; N, 24.92

Data for ***17***. White powder; yield, 79%; mp: 195−196 °C. ^{1}H NMR (DMSO-d_6): δ 1.51 (t, J = 7.00 Hz, 3H), 3.55 (s, 3H), 3.95 (s, 3H), 4.16 (q, J = 7.00 Hz, 2H), 6.92 (q, J = 8.29 Hz, 1H), 7.19 (q, J = 3.42 Hz, 1H), 7.25 (t, J = 3.08 Hz, 1H), 7.55 (brs, 1H), 7.81 (s, 1H), 9.15 (brs, 1H). IR (KBr, cm^{-1}) ν: 3407, 3268, 2977, 2874, 1600, 1512, 1477, 1406, 1258, 1218, 1139, 1003. Anal. calcd for $C_{12}H_{15}N_5O_4$:C, 48.81; H, 5.80; N, 23.72. Found: C, 48.78; H, 5.74; N, 23.86.

Data for ***18***. Pale green powder; yield, 74%; mp: 190−191 °C. ^{1}H NMR (DMSO-d_6): δ 0.91 (t, J = 7.38 Hz 3H), 1.50−1.58 (m, 2H), 1.35 (t, J = 6.95 Hz, 3H), 3.85 (s, 3H), 3.98−4.10 (m, 4H), 7.01 (d, J = 8.40 Hz, 1H), 7.43−7.47 (m, 1H), 7.62 (s, 1H), 8.13 (s, 1H), 8.89 (brs, 2H). IR (KBr, cm^{-1}) ν: 3400, 3300, 2938, 1594, 1425, 1238, 1143, 1027, 944, 799. Anal. calcd for $C_{14}H_{21}N_5O_4$: C, 52.00; H, 6.55; N, 21.66. Found: C, 51.97; H, 6.55; N, 21.78.

Table 1. Insecticidal Activities and Predicted pLD_{50} of Compounds 1−21 against *M. persicae* (Sulzer)

No.	R	R′	LD_{50} (μg/mL)	pLD_{50}	Predicted pLD_{50}	
					CoMFA	ComSIA
1		i-Pr	92.52	4.03	4.25	4.40
2	Et	Et	522.92	3.28	3.50	3.44
3	n-Pr	Et	283.29	3.55	3.52	3.44
4	n-Bu	n-Pr	367.08	3.44	3.58	3.49
5		n-Pr	20.99	4.68	4.33	4.48
6	n-Bu	vinyl	327.90	3.48	3.48	3.38
7		$CH_3(CH_2)_5$	25.47	4.59	4.48	4.59
8	Allyl	n-Bu	400.38	3.40	3.62	3.53
9		n-Bu	25.32	4.60	4.41	4.53
10	Et	p-$CH_3C_6H_4$	1024.18	2.99	2.77	2.92
11	n-Bu	p-$CH_3C_6H_4$	1076.12	2.97	2.79	2.93
12	Allyl	p-$CH_3C_6H_4$	744.27	3.13	2.81	2.91
13	Benzyl	o-$MeOC_6H_4$	3840.13	2.42	3.16	3.00
14	n-Bu	m-$MeOC_6H_4$	1797.06	2.75	2.80	2.81
15	n-Bu	phenyl	1796.44	2.75	2.86	2.91
16	Allyl	o-ClC_6H_4	362.37	3.44	2.90	3.10
17	Me	3, 4-$(MeO)_2C_6H_3$	1343.48	2.87	2.75	2.81
18	n-Pr	3, 4-$(MeO)_2C_6H_3$	3232.63	2.49	2.77	2.75
19		o-$NO_2C_6H_4$	357.39	3.45	3.62	3.13
20		4-FC_6H_4	1448.50	2.84	3.01	2.92
21		2-furanyl	345.22	3.46	3.25	3.15
Imidacloprid			24.20			

Data for ***19***. Yellow crystal; yield, 73%; mp: 228−229 °C. ^{1}H NMR (DMSO-d_6): δ 5.38 (s, 2H), 7.54 (d, J = 8.25 Hz, 1H), 7.65−7.73 (m, 2H), 7.79 (t, J = 7.08 Hz, 1H), 8.03 (dd, J = 1.08, 8.13 Hz, 1H), 8.31 (s, 1H), 8.34 (d, J = 2.34 Hz, 1H), 8.44(dd, J = 1.15, 7.84 Hz, 1H), 9.07 (s, 2H). IR (KBr, cm^{-1}) ν: 3400, 3300, 1605, 1520, 1490, 1420, 1350, 1260, 1060, 970, 930, 870, 750. Anal. calcd for $C_{14}H_{12}N_7O_4Cl$: C, 44.51; H, 3.18; N, 25.94. Found: C, 44.63; H, 3.37; N, 25.46.

Data for ***20***. White powder; yield, 86%; mp: 202−203 °C. ^{1}H NMR (DMSO-d_6): δ 5.40 (s, 2H), 7.27 (t, J = 8.88 Hz, 2H), 7.51 (d, 1H, J = 8.22 Hz), 7.69 (dd, J = 2.55, 8.28 Hz, 1H), 8.01−8.05 (m, 2H), 8.12 (s, 1H), 8.39 (d, J = 2.25 Hz, 1H), 9.07 (s, 2H). IR (KBr, cm^{-1}) ν: 3400, 3300, 1700, 1600, 1510, 1470, 1420, 1370, 1240, 1070, 960, 840. Anal. calcd for $C_{14}H_{12}N_6O_2ClF$: C, 47.94; H, 3.24; N, 23.95. Found: C, 47.38; H, 3.37; N, 23.31.

Data for ***21***. Brown crystal; yield, 72%; mp: 222−223 °C. ^{1}H NMR (DMSO-d_6): δ 5.37 (s, 2H), 6.64 (dd, J = 1.78, 3.46 Hz, 1H), 7.12 (dd, J = 0.58, 3.46 Hz, 1H), 7.51 (d, J = 7.71 Hz, 1H), 7.66 (dd, J = 2.58, 8.31 Hz, 1H), 7.85 (dd, J = 0.72, 1.74 Hz, 1H), 7.99(s, 1H), 8.35

dx.doi.org/10.1021/jf300616x | J. Agric. Food Chem. 2012, 60, 5028−5034

(d, J = 2.55 Hz, 1H), 9.00 (br, 2H). IR (KBr, cm^{-1}) ν: 3400, 3300, 1605, 1520, 1485, 1410, 1350, 1250, 1070, 970, 880. Anal. calcd for $C_{12}H_{11}N_6O_3Cl$: C, 44.66; H, 3.41; N, 26.03. Found: C, 44.75; H, 3.50; N, 25.68.

X-ray Diffraction. Compound **1** was recrystallized by a slow evaporation from an acetone/petroleum ether (v/v = 1:5) solution to afford a single crystal suitable for X-ray crystallography. Colorless pieces of **1** were mounted on a quartz fiber. Cell dimensions and intensities were measured using a Rigaku Saturn 724 CCD diffractometer with graphite monochromated Mo Ka radiation. The structure was resolved by direct methods with SHELXS-97. Hydrogen atoms were observed and refined at a fixed value of their isotropic displacement parameter. Crystallographic data in CIF format are in the Supporting Information.[27]

Biological Assay. All bioassays were performed on representative test organisms prepared in the laboratory. The bioassay was repeated at 25 ± 1 °C. All compounds were dissolved in DMF and diluted with distilled water containing Triton X-100 to obtain a series of concentrations. The activities of the insecticidal compounds against *Myzus persicae* (Sulzer) were tested according to a previously reported procedure. The LD_{50} values were determined based on standard probit analysis.[28]

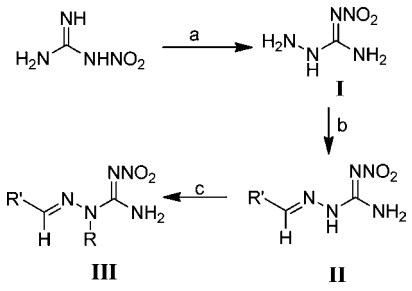
QSAR Analyses. Three-dimensional QSAR analyses were performed to predict the favorable and unfavorable moieties for improved bioactivity using the CoMFA (comparative molecular field analysis) and the ComSIA (comparative molecular similarity indices analysis) models in the SYBYL7.3 program.[29,30] CoMFA models were generated using the Sybyl7.3 package on a Linux system. In total, 21 compounds obtained from synthesis were used to create a data set in which the bioactivity of all compounds was determined (Table 1) against *M. persicae* (Sulzer). The pLD_{50} values were used for constructing the models. Three-dimensional molecular structures were built using the SKETCH module in Sybyl 7.3, while structural energy minimization was performed with the Tripos force field until a gradient convergence of 0.05 kcal/(mol A) was achieved. Gasteiger–Hückel charges were calculated and used to construct the CoMFA models.

Field Trials. The experiments were carried out in the Haidian district in Beijing (North China), Wuhan City in Hubei and Hefei City in Anhui (Middle China), and Nanchang city in Jiangxi, Nanning City in Guangxi, and Xianyou City in Fujian (South China) during 2009 and 2010. The experimental design was a randomized complete block with five treatments. The untreated cabbages or rice served as a control. The formulation of imidacloprid (10% WP) was obtained from Bayer Crop Science (Beijing, China). The tested pesticides were sprayed using No. 20B handed-spray of Shantou Yongsheng Atomizer Factory (Shantou, Guangdong).

RESULTS AND DISCUSSION

Synthesis. The target molecules III were synthesized from nitroguanidine, as shown in Scheme 1. Several bases were tested, and it was found that NaH resulted in a smooth reaction between compound II and an alkyl halide. Upon treatment of II with the corresponding alkyl or aryl halide at room temperature, a solid powder was obtained after recrystallization. On the basis of the spectral and analytical data, it was found that in the product, the alkyl or aryl groups were connected to the secondary amine (−NH−) rather than the less sterically hindered primary amine ($-NH_2$).[26] A simple calculation was used to determine the heat of anion formation. The values of 178.7860 kcal/mol for the sodium salt of a secondary amine and 360.2869 kcal/mol for a primary amine demonstrate that the reaction is endothermic, meaning that energy is necessary for the formation of the former product. This is consistent with the X-ray crystallography diffraction analysis. The structures of the compounds were characterized by proton nuclear magnetic resonance (^{1}H NMR), mass, IR, and elemental analysis.

Scheme 1[a]



[a]Reagents and conditions: (a) NH_2-NH_2, H_2O, 60 °C. (b) Various substituent aldehydes, CH_3OH, CH_3CO_2H, refluxing. (c) Various alkyl or arylmethylene halide, NaH, DMF, 10 °C.

Crystal Structure Analysis. To further verify the structure of **1**, the compound was recrystallized by slow evaporation from an acetone/petroleum ether (v/v = 1:5) solution. The molecular structure of compound **1** is shown in Figure 1, with omitted hydrogen atoms. The formal double C═NNO2 bond in compound **1** and presumably in compounds **2**–**21** (as well as in other nitroimines for which X-ray diffraction data are available[31]) does not appear to be a double bond nor even the shortest bond among all other C−N bonds in the molecule. Nevertheless, the C5−N3, C5−N4, N4−N5, and N−O bond lengths are of intermediate length between those typical of a single and a double bond; that is, the unique nature of the bonding allows for the partial delocalization of the π-electron density over N3−C5−N4−NO2. In addition, there are intramolecular and intermolecular hydrogen bonds present in compound **1**. The intramolecular hydrogen bonds between the nitrogen atom in NH_2 and the oxygen atoms of the nitro group (N3−H3···O1) form a six-numbered ring, and two intermolecular hydrogen bonds (N3−H3−O2; N3−H3−Cl) are found between the molecules. All of these hydrogen bonds make an important contribution to enhancing the robustness of the compound and extending the structure into a 3D supramolecular array, as shown in Figure 1.

Insecticidal Activities in Laboratory. The insecticide activity of the target compounds was evaluated against *M. persicae* (Sulzer) (Table 1). The acyclic neonicotinoids with alkyl −N═C−R′ substituents displayed higher activities than those with aryl groups (compounds **10**–**21**) on the whole. We also investigated the influence of length and flexibility of the straight alkyl chain on the bioactivity. *N*-Alkyl moieties may be important for the steric interaction between the R′ group and the receptor-binding site. Compounds **5**, **7**, and **9** indicate better insecticidal activity (LD_{50}, 21–25 μg/mL) than other compounds in Table 1. All of these compounds have a 2-Cl-pyridine moiety in the R position. Compound **5** has marginally higher activity than compounds **7** and **9** and has similar activity as imidacloprid (see Table 1). For this reason, compound **5** will be selected as the lead insecticide for further modification.

QSAR Analyses. During biological screening, models of the new compounds were constructed using CoMFA and ComSIA with Sybyl 7.3 to find some relationship about structure–activity in theory. Compound **5** was the template molecule during constructing models. Some important parameters of the models are as follows: q^2 = 0.734, r^2 = 0.838, standard deviation = 0.27, F = 98.353. In the three-dimensional contour maps of the CoMFA electrostatic field (Figure 2, 1), R′ with more positive charge compounds showed enhanced bioactivity in the

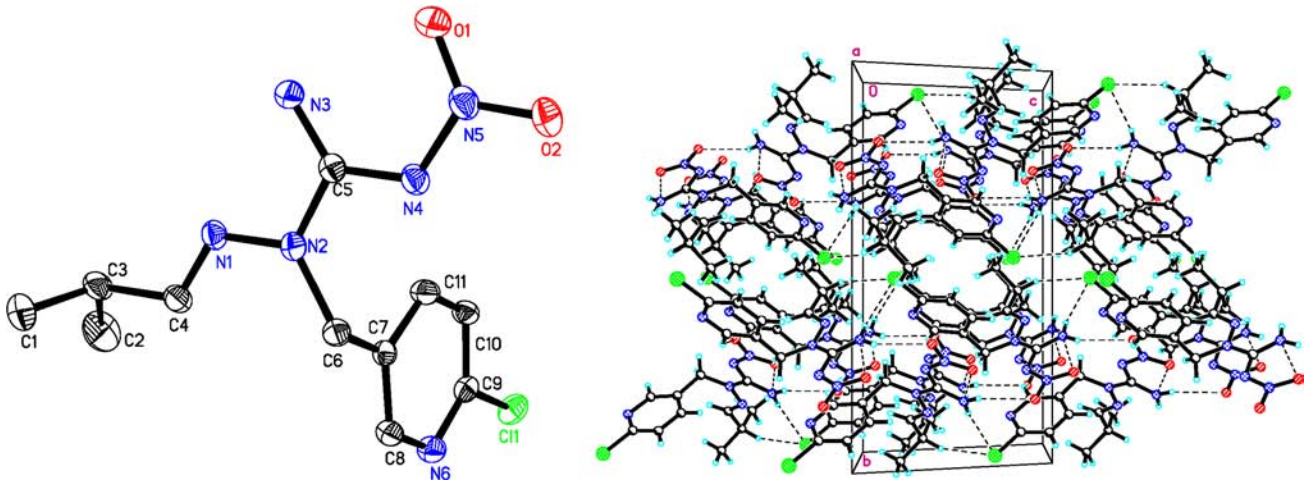


Figure 1. ORTEP drawing with thermal ellipsoids drawn at 30% probability for compound **1** and the packing representation (CCDC number 819437).

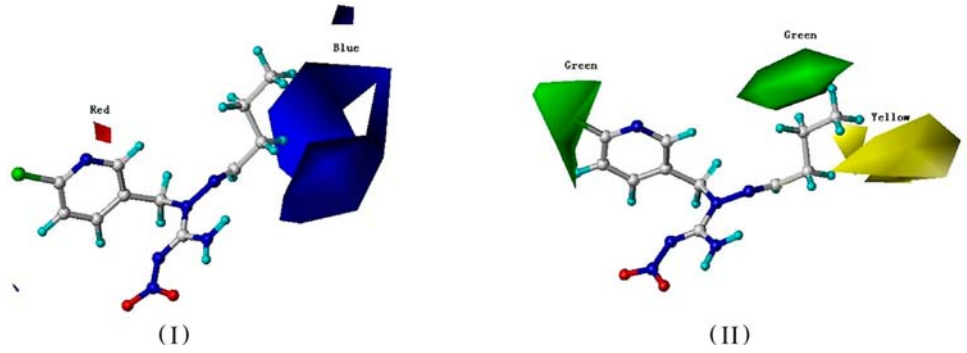


Figure 2. Dimensional contour maps of CoMFA electrostatic field (1) and CoMFA steric field (2).

order **5** > **9** > **7** > **1** > **21** > **19** > **20** (R is same substituent group). In other words, the results of both CoMFA and the insecticide activity in laboratory indicated the introduction of alkyl group (**1**, **5**, **7**, and **9**) in the R′ position is more benefit than aromatic group (**19**–**21**). At the same time, the R group with increasing steric hindrance with larger substituent exhibits stronger bioactivities in the map of the CoMFA steric field (Figure 2, 2). In addition, when R is chloropyridine show improved bioactivity, as visualized with the three-dimensional contours map of the ComSIA electrostatic field (Figure 3) and the map of the CoMFA electrostatic field. In the hydrogen acceptor field (Figure 3), the results showed that more hydrogen bonds facilitated the improvement of biological activity. When R is a pyridine group, a hydrogen acceptor is helpful to form hydrogen bonds. So, compounds containing pyridine showed better insecticidal activity in Table 1. The predicted pLD_{50} with CoMFA and ComSIA model is in agreement with the results of laboratory on the whole (Table 1). These above discussions about SARs are conducive to further structure optimization of this series of compounds.

Field Trials. Because compound **9** (named Guadipyr) showed excellent insecticidal activity in laboratory, 10% WP and 20% SC of compound **9** were evaluated for the control of aphids in the north, middle, and south of China in the field. Their efficacy was compared with the neonicotinoid imidacloprid and an untreated control. The experiment was replicated for 2 years (2009 and 2010). Table 2 presents part of the results of field trials in Beijing (North China), Hubei and

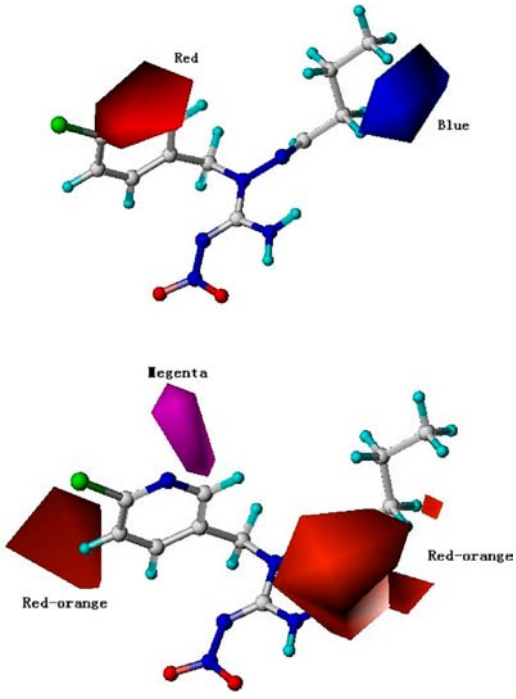


Figure 3. ComSIA electrostatic field (1) and H-acceptor field (2).

Anhui (Middle China), and Jiangxi, Guangxi, and Fujian (South China). Guadipyr showed good control with average Abbott's

dx.doi.org/10.1021/jf300616x | J. Agric. Food Chem. 2012, 60, 5028–5034

Table 2. Results of Insecticidal Activities of Field Trial against Aphids in 2009 or 2010 after 14 Days of Application of Guadipyr and Imidacloprid[a]

		Guadipyr		imidacloprid	
treatment distract (year)	target	g/ha	% Abbott's efficiency	g/ha	% Abbott's efficiency
Haidian, Beijing (2009)	*M. persicae* (Sulzer)	22.5 (WP)	98.10	22.5 (WP)	93.30
Haidian, Beijing (2010)	*M. persicae* (Sulzer)	22.5 (WP)	95.4a	22.5 (WP)	98.7a
Xianyou, Fujian Province (2009)	*M. persicae* (Sulzer)	20 (WP)	83.35	30 (WP)	80.64
Wuhai, Hubei Province (2009)	*B. brassicae* (Linnaeus)	22.5 (WP)	75.11	22.5 (WP)	72.63
Nanchang, Jiangxi Province (2009)	*M. persicae* (Sulzer)	450 (WP)	68.37	450 (WP)	69.80
Nanning, Guangxi Province (2010)	*B. brassicae*	15 (SC)	96.81	22.5 (WP)	97.59
Hefei, Anhui Province (2010)	*B. brassicae* (Linnaeus)	60 (SC)	83.51	112.5 (WP)	81.23

[a]WP, wettable powder; SC, suspension concentrates.

efficiency ranging from 68 to 98% as compared with the untreated control. The results of field trials exhibited the insecticidal activity of Guadipyr equal to commercial imidacloprid in both years, and this is also in agreement with the results in the laboratory. In addition, the SC of compound **9** showed better activity than WP. The results showed that the series of compounds and especially Guadipyr are promising for aphid control.

In conclusion, a series of acyclic neonicotinoids were designed and synthesized by incorporating an imine substituent into nitroamine analogues of nitenpyram. Bioassays showed that all of the target molecules exhibited good insecticidal activity against *M. persicae* (Sulzer) in the laboratory and *M. persicae* (Sulzer) and *Brevicoryne brassicae* (Linnaeus) in field trials. From the crystal structure of compound **1**, the R and R′ substituent positions were confirmed. In addition, CoMFA and ComSIA were employed to develop a 3D QSAR model on the insecticidal activity of target molecules. Easy synthesis and good insecticidal activity make this series of compounds very promising candidates for future commercial pesticides. Acute toxicity, field residues, and their inhibitory activities against resistant insect species are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystallographic data of compound **1** in CIF format and some data of acute toxicity and selectivity of compound **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +86 10 62732958. Fax: +86 10 62733620. E-mail: mayongqiang@cau.edu.cn (Y.Q.M) or qinzhaohai@263.net (Z.H.Q.).

Funding

This work was supported by the National Scientific and Technology Supporting Program of China (2011BAE06B05-5, 2006BAE01A01-11), Special Fund for Agro-scientific Research in the Public Interest (201203022), and the Innovation Fund for Graduate Students of China Agricultural University.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Jeschke, P.; Nauen, R. Neonicotinoids-from zero to hero in insecticide chemistry. *Pest Manage. Sci.* **2008**, *64*, 1084−1098.

(2) Casida, J. E. Neonicotinoid metabolism: compounds, substituents, pathways, enzymes, organisms, and relevance. *J. Agric. Food Chem.* **2011**, *59*, 2923−2931.

(3) Yamamoto, I., Casida, J. E., Eds. *Nicotinoid Insecticides and the Nicotinic Acetylcholine Receptor*; Springer-Verlag: Tokyo, Japan, 1999; 300 pp.

(4) Tomizawa, M.; Casida, J. E. Neonicotinoid insecticides: Highlights of a symposium on strategic molecular designs. *J. Agric. Food Chem.* **2011**, *59*, 2883−2886.

(5) Kagabu, S. Discovery of imidacloprid and further development s from strategic molecular designs. *J. Agric. Food Chem.* **2011**, *59*, 2887−2896.

(6) Tomizawa, M.; Casida, J. E. Molecular recognition of neonicotinoid insecticides: The determinants of life or death. *Acc. Chem. Res.* **2009**, *42*, 260−269.

(7) Casida, J. E.; Quistad, G. B. Golden age of insecticide research: Past, present, or future. *Annu. Rev. Entomol.* **1998**, *43*, 1−16.

(8) Chao, S. L.; Dennehy, T. J.; Casida, J. E. Whitefly (Hemiptera: Aleyrodidae) binding site for imidacloprid and related insecticides: A putative nicotinic acetylcholine receptor. *J. Econ. Entomol.* **1997**, *90*, 879−882.

(9) Bai, D.; Lummis, S.; Leicht, W.; Breer, H.; Sattelle, D. Actions of imidacloprid and a related nitromethylene on cholinergic receptors of an identified insect motor-neuron. *Pestic. Sci.* **1991**, *33*, 197−204.

(10) Zhang, A.; Kayser, H.; Maienfisch, P.; Casida, J. E. Insect nicotinic acetylcholine receptor: conserved neonicotinoid specificity of [H-3]imidacloprid binding site. *J. Neurochem.* **2000**, *75*, 1294−1303.

(11) Matsuo, H.; Tomizawa, M.; Yamamoto, I. Structure-activity relationships of acyclic nicotinoids and neonicotinoids for insect nicotinic acetylcholine receptor/ion channel complex. *Arch. Insect Biochem. Physiol.* **1998**, *37*, 17−23.

(12) Kashiwada, Y. Bestguard (nitenpyram, TI-304) − a new systemic insecticide. *Agrochem. Jpn.* **1996**, *68*, 18−19.

(13) Shao, X. S.; Li, Z.; Qian, X. H.; Xu, X. Y. Design, Synthesis, and insecticidal activities of novel analogues of neonicotinoids: Replacement of nitromethylene with nitroconjugated system. *J. Agric. Food Chem.* **2009**, *57*, 951−957.

(14) Shao, X. S.; Philip, W. L.; Liu, Z. W.; Xu, X. Y.; Li, Z.; Qian, X. H. Cis-configuration: A new tactic/rationale for neonicotinoid molecular design. *J. Agric. Food Chem.* **2011**, *59*, 2943−2949.

(15) Kagabu, S. Discovery of the chloronicotinyl insecticides. 214th American Chemical Society national meeting. *Abstr. Pap. Am. Chem. Soc.* **1997**, *214*, 1−2.

(16) Okazawa, A.; Akamatsu, M.; Nishiwaki, H.; Nakagawa, Y.; Miyagawa, H.; Nishimura, K.; Ueno, T. Three-dimensional quantitative structure−activity relationship analysis of acyclic and cyclic chloronicotinyl insecticides. *Pest Manage. Sci.* **2000**, *56*, 509−515.

(17) Sun, C. W.; Jin, J.; Zhu, J.; Wang, H. F.; Yang, D. G.; Xing, J. H. Discovery of bis-aromatic ring neonicotinoid analogues fixed as cis-configuration: Synthesis, insecticidal activities, and molecular docking studies. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3301−3305.

(18) Minamida, I.; Iwanaga, K.; Tabuchi, T.; Aoki, I.; Fusaka, T.; Ishizuka, H.; Okauchi, T. Synthesis and insecticidal activity of acyclic

nitroethene compounds containing a heteroarylmethylamino group. *J. Pestic. Sci.* **1993**, *18*, 41−48.
(19) Kollmeyer, W. D.; Flattum, R. F.; Foster, J. P.; Powell, J. E.; Schroeder, M. E.; Soloway, S. *Neoicotinoid Insecticides and the Nicotinic Acetylcholine Receptor*; Springer: New York, 1999.
(20) Takahashi, H.; Mitsui, J.; Takakusa, N.; Matsuda, M.; Yoneda, H.; Suzuki, J.; Ishimitsu, K.; Kishimoto, T. NI-25, a new type of systemic and broad spectrum insecticide. *Proc. Brighton Crop Prot. Conf. Pests and Diseases*; BCPC: Farnham, Surrey, United Kingdom, 1992; pp 89−96.
(21) Ohkawara, Y.; Akayama, A.; Matsuda, K.; Andersch, W. Clothianidin: A novel broad spectrum neonicotinoid insecticide. *Proc. Brighton Crop Prot. Conf. Pests and Diseases*; BCPC: Farnham, Surrey, United Kingdom, 2002; pp 51−58.
(22) Jeschke, P.; Uneme, H.; Benet-Buchholz, J.; Stolting, J.; Sirges, W.; Beck, M. E. Clothianidin (TI-435) - the third member of the chloronicotinyl insecticide (CNI^{TM}) family. *Pflanzenschutz-Nachrichten Bayer* **2003**, *56*, 5−25.
(23) Kodaka, K.; Kinoshita, K.; Wakita, T.; Kawahara, N.; Yasui, N. MTI-446: A novel systemic insect control compound. *Proc. Brighton Crop Prot. Conf. Pests and Diseases*; BCPC: Farnham, Surrey, United Kingdom, 1998; pp 21−26.
(24) Wakita, T.; Yasui, N.; Yamada, E.; Kishi, D. Development of a novel insecticide, dinotefuran. *J. Pestic. Sci.* **2005**, *30*, 122−123.
(25) Wakita, T.; Yasui, N.; Yamada, E.; Kishi, D. Development of a novel insecticide, dinotefuran. *J. Pestic. Sci.* **2005**, *30*, 133−138.
(26) Henry, R. A.; Devries, J. E.; Boscha, R. H. The acidity of nitroguanylhydrazones. *J. Am. Chem. Soc.* **1955**, *77*, 5693−5695.
(27) The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre with deposition Number CCDC 819437. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, United Kingdom; e-mail: deposit@ccdc.cam.ac.uk.
(28) Raymond, M. Log-probit analysis basic program for micro-computer. *Cah. ORSTOM Ser. Entomol. Med. Parasitol.* **1985**, *23*, 117−121.
(29) Duan, H. X.; Liang, D. S.; Yang, X. L. 3D quantitative structure-property relationship study on *cis*-neonicotinoid derivatives. *Acta Chim. Sin.* **2010**, *68*, 595−602.
(30) Cramer, R. D., III; Patterson, D. E.; Bunce, J. D. Comparative molecular-field analysis (COMFA) 1. effectt of shape on binding of steroids to carrier proteins. *J. Am. Chem. Soc.* **1988**, *110*, 5959−5967.
(31) Astakhov, A. M.; Vasilev, A. D.; Molokeev, M. S.; Revenko, V. A.; Stepanov, R. S. Nitroimines: II. Structure of nitroamino-1,2,4-triazoles. *Russ. J. Org. Chem.* **2005**, *41*, 910−915.