JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

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Design, Synthesis, and Insecticidal Activity of Novel Pyrazole Derivatives Containing α-Hydroxymethyl-*N*-benzyl Carboxamide, α-Chloromethyl-*N*-benzyl Carboxamide, and 4,5-Dihydrooxazole Moieties

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ABSTRACT: On the basis of commercial insecticides tebufenpyrad and tolfenpyrad, two series of novel pyrazole-5-carboxamides containing α-hydroxymethyl-*N*-benzyl or α-chloromethyl-*N*-benzyl and pyrazoles containing 4,5-dihydrooxazole moieties were designed and synthesized via the key intermediate 2-amino-1-(4-substituted) phenyl ethanol. The structures of target compounds were confirmed by ^{1}H NMR and elemental analysis or high-resolution mass spectrum (HRMS), and their activities against cotton bollworm (*Helicoverpa armigera*), diamondback moth (*Plutella xylostella*), bean aphid (*Aphis craccivora*), mosquito (*Culex pipiens pallens*), and spider mite (*Tetranychus cinnabarinus*) were tested. The results of bioassays indicated that compounds containing α-chloromethyl-*N*-benzyl and compounds containing 4,5-dihydrooxazole showed high insecticidal activity against cotton bollworm. Especially, stomach activities of compounds **Ij**, **Il**, and **IIe** were 60% at 5 mg kg^{-1}. Moreover, the target compounds exhibited high selectivity between cotton bollworm and diamondback moth, although both of them belong to the order *Lepidoptera*. Although the activities against diamondback moth were at a low level, some of the target compounds exhibited antifeedant activity. The compounds also had good activities against bean aphid, mosquito, and spider mite. The foliar contact activity of compounds **Ic**, **Id**, **Ie**, and **IIf** against bean aphid were 95, 95, 100, and 95%, respectively, at 200 mg kg^{-1}. The miticidal and ovicidal activities of compound **IIi** against spider mite were both 95% at 200 mg kg^{-1}. Furthermore, a trivial change at 4-position of pyrazole ring would lead to great changes in properties and activities, which can easily be deduced by comparing the activities of compounds in series **I** (4-chloro-pyrazole compounds) with corresponding compounds in series **II** (4-hydro-pyrazole compounds), especially from the miticidal and ovicidal activities of **Ii** and **IIi** against spider mite.

KEYWORDS: *pyrazole-5-carboxamide, α-hydroxymethyl-N-benzyl, α-chloromethyl-N-benzyl, 4,5-dihydrooxazole, insecticidal activity, antifeedant activity*

INTRODUCTION

Synthetic pyrazole-5-carboxamide derivatives such as tebufenpyrad and tolfenpyrad (Figure 1) belong to an important kind mitochondrial respiration inhibitors, and they interrupt the mitochondrial electron transport by inhibition of NADH: ubiquinone oxidoreductase (complex I).[1] Tebufenpyrad, discovered by Mitsubishi Kasei Co., Ltd., in 1987, shows an excellent acaricidal activity against phytophagous mites and *Homoptera* pests.[2] Tolfenpyrad, discovered by Mitsubishi Chemical Corp. (now Nihon Nohyaku Co., Ltd.), is one of the most important insecticides for control pests that are difficult to control, such as *Hemiptera*, *Coleoptera*, *Diptera*, *Lepidoptera*, *Thysanoptera*, and *Acarina*. It mainly provides contact activity against target pests on egg, larva, nymph, and adult stages.[3]

Because of their outstanding performance in controlling agricultural pests, pyrazole-5-carboxamide derivatives have attracted considerable attention for decades.[4] Most of the work was based on the structures of the two commercial varieties, and the studies focused on two aspects: the changes of substituents on the pyrazole ring and the modification of the benzene ring. However, there were little studies on the bridge between the pyrazole and the benzene ring. Although there is significant progress in the study of the mechanism of pyrazole insecticides in recent years,[5] until now, it is unknown about the specific interaction between the pyrazole derivatives and the receptor. Okada et al.[2c] gave a proposed model about the interaction between tebufenpyrad and complex I, a model in which the hydrogen of the amide in the bridge binds with the acceptor as a hydrogen donor. In addition, some research showed that the miticidal activity was significantly decreased when the methylene in the bridge was substituted by a methyl group,[6] whereas the compounds still exhibited excellent activities against a broad spectrum of insects when the cyano group was introduced to the methylene.[7] That is to say, the substituent on the methylene also plays an important role in the activities.

On the basis of the above consideration, hydroxymethyl and chloromethyl were introduced to the methylene of the bridge, which means α-hydroxymethyl-*N*-benzyl and α-chloromethyl-*N*-benzyl pyrazole-5-carboxamides (**Ia−h** and **IIa−h**) were designed and synthesized. To further study the role of the bridge moiety played in the biological activities, compounds containing 4,5-dihydrooxazole moieties (**Ii−l** and **IIi−l**) were

Received: November 21, 2011
Revised: January 15, 2012
Accepted: January 20, 2012
Published: February 3, 2012

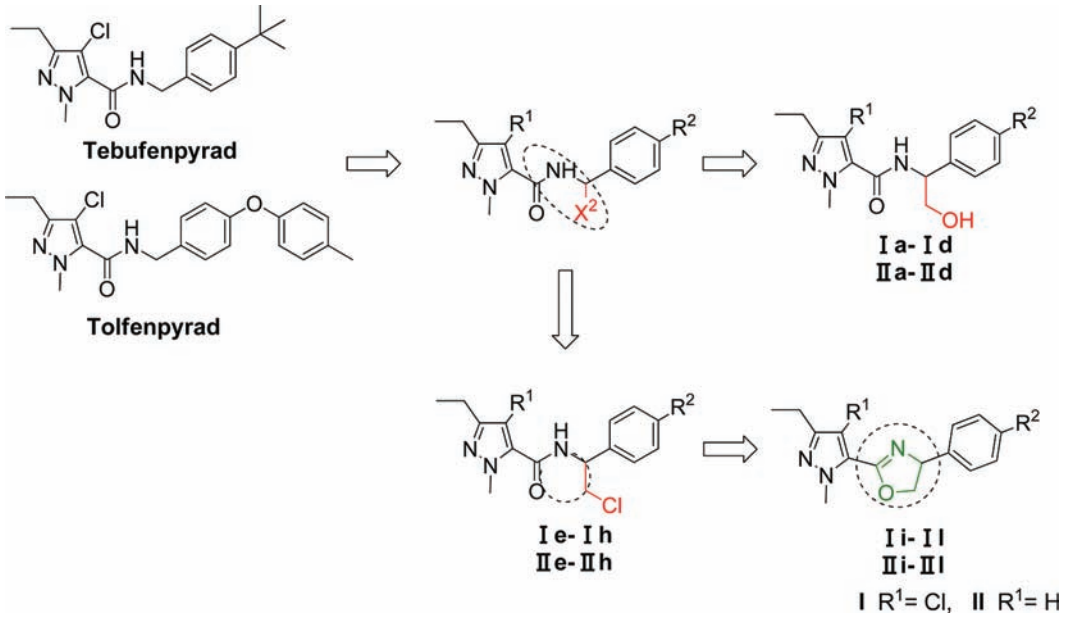
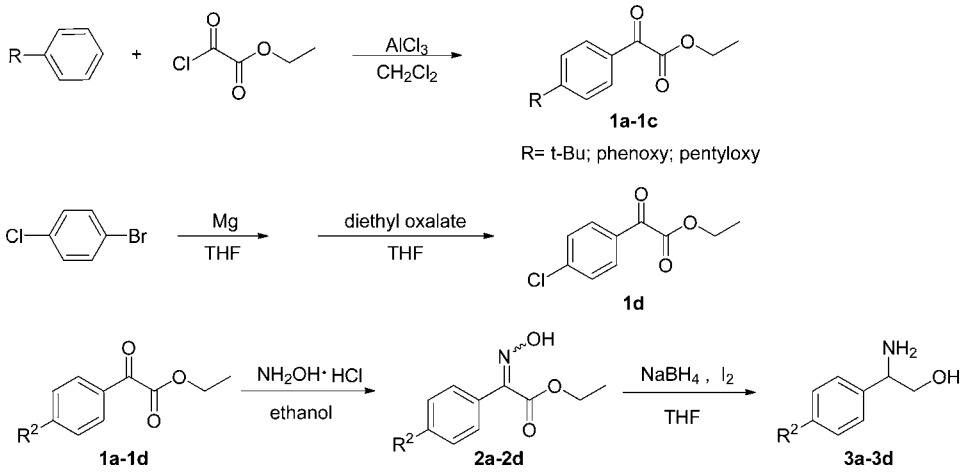


Figure 1. Design of target compounds (**Ia–l** and **IIa–l**).

Scheme 1. General Synthetic Route for Key Intermediate 2-Amino-2-(4-substitudedphenyl) Ethanol



also synthesized. To better compare the activities, four representative substituents (*t*-butyl, phenoxy, pentyloxy, and Cl) were selected to be introduced into the para position of the benzene ring. Moreover, the changes on 4-position of pyrazoles were also reported to have an important impact on the biological activity of the compounds.[8] Therefore, both of the compounds that were chlorinated or not chlorinated at the 4-position of pyrazole were synthesized and classified as series **I** and **II**, respectively. The insecticidal and acaricidal activities of the target compounds (**Ia–l** and **IIa–l**) against cotton bollworm (*Helicoverpa armigera*), diamondback moth (*Plutella xylostella*), spider mite (*Tetranychus cinnabarinus*), bean aphid (*Aphis craccivora*), and mosquito (*Culex pipiens pallens*) were tested and discussed.

MATERIALS AND METHODS

Instruments. ^{1}H NMR spectra were obtained at 400 MHz using a Bruker AV400 spectrometer in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane as the internal standard. Chemical shift values (δ) are given in parts per million. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. High-resolution mass spectrometry (HRMS) data were obtained on an FTICR-MS instrument (Ionspec 7.0 T). The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and are uncorrected. Yields were not optimized.

General Synthesis. All anhydrous solvents were dried and purified by standard techniques just before use. 4-Chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid (**I**) was synthesized according to reported method.[2b] The synthetic route is given in Schemes 1 and 2.

Synthesis of Ethyl 2-(4-(*tert*-Butyl)phenyl)-2-oxoacetate (1a). Anhydrous $AlCl_3$ (2.67 g, 20.0 mmol) and ethyloxalyl monochloride (2.72 g, 20.0 mmol) were added to anhydrous dichloromethane (20 mL) under nitrogen. The mixture was stirred at room temperature until $AlCl_3$ was dissolved completely. After the mixture was cooled to 5 °C, *tert*-butyl benzene (2.24 g, 16.7 mmol) in dichloromethane (5 mL) was added dropwise. After the mixture was stirred for 2 h at room temperature, the mixture was poured into ice water (20 mL), and concentrated HCl (10 mL) was added. After separation, the water phase was extracted by dichloromethane (10 mL × 3). The combined organic phase was washed with water (10 mL × 2) and brine (10 mL × 2) successively, dried over anhydrous Na_2SO_4, and concentrated to give **1a** as a yellow liquid (3.10 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar–H), 7.53 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar–H), 4.44 (q, $^3J_{HH}$ = 7.2 Hz, 2H, CH_2CH_3), 1.42 (t, $^3J_{HH}$ = 7.2 Hz, 3H,

dx.doi.org/10.1021/jf204778v | J. Agric.Food Chem. 2012, 60, 1470–1479

Scheme 2. General Synthetic Route for Target Compounds

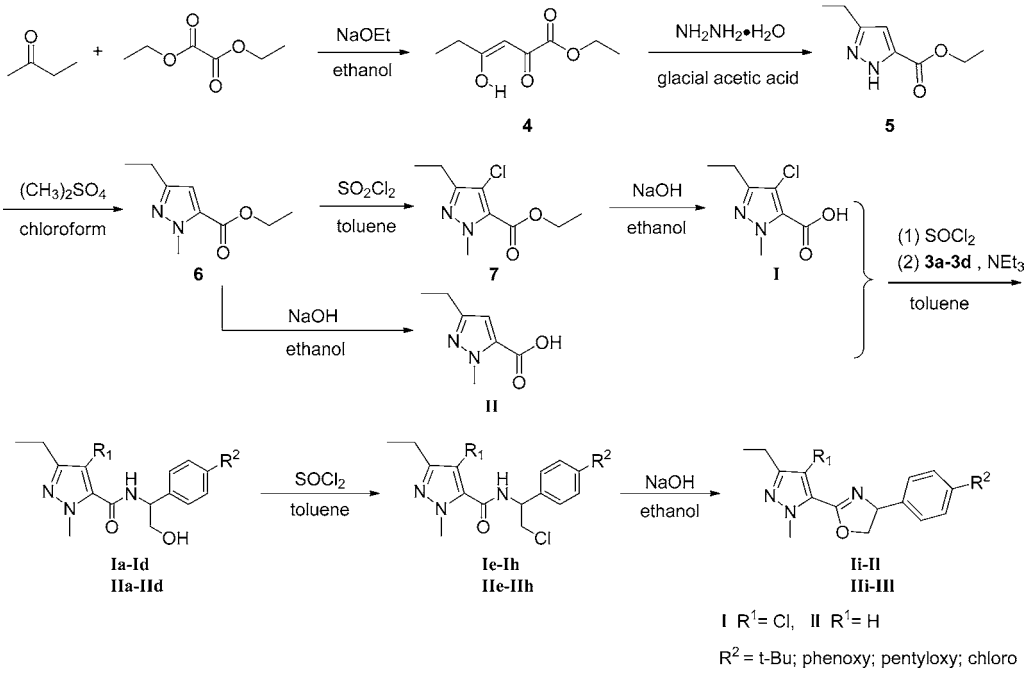


Table 1. Physical Properties and Elemental Analyses or HRMS of Compounds Ia−l and IIa−l

					elemental anal (%) (calcd) or HRMS (calcd)		
compd	R^1	R^2	mp (°C)	yield (%)	C	H	N
Ia	Cl	$C(CH_3)_3$		90	386.1601 (386.1606) (m + Na)$^+$		
Ib	Cl	C_6H_5O	122−123	89	62.89 (63.08)	5.85 (5.55)	10.43 (10.51)
Ic	Cl	$C_5H_{11}O$	98−99	63	60.90 (60.98)	7.31 (7.16)	10.61 (10.67)
Id	Cl	Cl	124−125	94	52.43 (52.64)	5.24 (5.01)	12.10 (12.28)
Ie	Cl	$C(CH_3)_3$		74	404.1266 (404.1267) (m + Na)$^+$		
If	Cl	C_6H_5O	111−112	95	60.15 (60.30)	5.26 (5.06)	10.01 (10.05)
Ig	Cl	$C_5H_{11}O$	93−94	87	57.95 (58.25)	6.59 (6.60)	9.98 (10.19)
Ih	Cl	Cl	118−119	90	49.66 (49.95)	4.58 (4.47)	11.48 (11.65)
Ii	Cl	$C(CH_3)_3$		95	346.1677 (346.1681) (m + H)$^+$		
Ij	Cl	C_6H_5O		93	382.1313 (382.1317) (m + H)$^+$		
Ik	Cl	$C_5H_{11}O$	26−27	89	376.1788 (376.1786) (m + H)$^+$		
Il	Cl	Cl	49−50	94	324.0673 (324.0665) (m + H)$^+$		
IIa	H	$C(CH_3)_3$	147−149	92	69.34 (69.27)	8.20 (8.26)	12.68 (12.76)
IIb	H	C_6H_5O	120−123	63	68.84 (69.02)	6.62 (6.34)	11.42 (11.50)
IIc	H	$C_5H_{11}O$	73−74	71	66.70 (66.83)	8.28 (8.13)	11.63 (11.69)
IId	H	Cl	171−173	57	58.35 (58.54)	6.08 (5.89)	13.47 (13.65)
IIe	H	$C(CH_3)_3$	147−148	95	65.78 (65.60)	7.48 (7.53)	11.99 (12.08)
IIf	H	C_6H_5O	115−116	91	65.45 (65.71)	6.00 (5.78)	10.83 (10.95)
IIg	H	$C_5H_{11}O$	92−93	87	63.29 (63.56)	7.49 (7.47)	11.01 (11.12)
IIh	H	Cl	145−147	93	54.94 (55.23)	5.36 (5.25)	12.79 (12.88)
IIi	H	$C(CH_3)_3$	61−62	87	73.52 (73.28)	7.85 (8.09)	13.60 (13.49)
IIj	H	C_6H_5O		92	348.1707 (348.1707) (m + H)$^+$		
IIk	H	$C_5H_{11}O$		89	342.2176 (324.2174) (m + H)$^+$		
IIl	H	Cl		85	290.1061 (290.1055) (m + H)$^+$		

CH_2CH_3), 1.34 (s, 9H, t-Bu). Compounds **1b** and **1c** were prepared using the same procedure as **1a.**

*Data for Ethyl 2-Oxo-2-(4-phenoxyphenyl)acetate (**1b**).* Yellow liquid. Yield: 51%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 7.41 (t, $^3J_{HH}$ = 7.6 Hz, 2H, Ar−H), 7.22 (t, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 7.08 (d, $^3J_{HH}$ = 7.6 Hz, 2H, Ar−H), 7.01 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar−H), 4.42 (q, $^3J_{HH}$ = 7.2 Hz, 2H, OCH_2CH_3), 1.40 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_2CH_3).

*Data for Ethyl 2-Oxo-2-(4-(pentyloxy)phenyl)acetate (**1c**).* Pale yellow liquid. Yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar−H), 6.95 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar−H), 4.43 (q, $^3J_{HH}$ = 7.2 Hz, 2H, OCH_2CH_3), 4.04 (t, $^3J_{HH}$ = 6.8 Hz, 2H, $OCH_2C_4H_9$), 1.78−1.84 (m, 2H, $OCH_2CH_2C_3H_7$), 1.34−1.48 (m, 7H, OCH_2CH_3 and $OCH_2CH_2(CH_2)_2CH_3$), 0.93 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $CH_2CH_2CH_3$).

Synthesis of Ethyl 2-(4-Chlorophenyl)-2-oxoacetate (1d).[9] To magnesium (0.63 g, 26.1 mmol) in ether (15 mL) was added

dx.doi.org/10.1021/jf204778v | J. Agric.Food Chem. 2012, 60, 1470−1479

Table 2. ^{1}H NMR of Compounds Ia−l and IIa−l

compd	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm)
Ia	7.53 (d, $^3J_{HH}$ = 7.2 Hz, 1H, NH), 7.40 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 7.29 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar−H), 5.22−5.26 (m, 1H, NHC**H**), 4.10 (s, 3H, pyrazole-Me), 3.96 (br, 2H, C**H$_2$**OH), 2.64 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.31 (s, 9H, t-Bu), 1.24 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**)
Ib	7.53 (d, $^3J_{HH}$ = 6.8 Hz, 1H, NH), 7.32−7.36 (m, 4H, Ar−H), 7.11 (t, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 6.99−7.02 (m, 4H, Ar−H), 5.21−5.25 (m, 1H, NHC**H**), 4.10 (s, 3H, pyrazole-Me), 3.93−4.01 (m, 2H, CH$_2$OH), 2.64 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**)
Ic	7.45 (d, $^3J_{HH}$ = 6.8 Hz, 1H, NH), 7.27 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar−H), 6.90 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar−H), 5.17−5.21 (m, 1H, NHC**H**), 4.10 (s, 3H pyrazole-Me), 3.92−3.96 (m, 4H), 2.64 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.74−1.81 (m, 2H, OCH$_2$C**H$_2$**−),1.36−1.45 (m, 4H, −C**H$_2$C H$_2$**−), 1.24 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**), 0.92 (t, $^3J_{HH}$ = 7.2 Hz, 3H, −CH$_2$C**H$_3$**)
Id	7.57 (d, $^3J_{HH}$ = 6.8 Hz, 2H, NH), 7.36 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 7.32 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 5.18−5.22 (m, 1H, C**H**NH), 4.09 (s, 3H, pyrazole-Me), 3.93−4.01 (m, 2H, C**H$_2$**OH), 2.65 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 2.05 (br, 1H, OH), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**)
Ie	7.45 (d, $^3J_{HH}$ = 7.2 Hz, 1H, NH), 7.40 (d, $^3J_{HH}$ = 8 Hz, 2H, Ar−H), 7.30 (d, $^3J_{HH}$ = 8 Hz, 2H, Ar−H), 5.49−5.51 (m, 1H, CHNH), 4.11 (s, 3H, pyrazole-Me), 3.95-3.99 (m, 1H, C**H$_2$**Cl), 3.87−3.91 (m, 1H, CH$_2$Cl), 2.65 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.31 (s, 9H, t-Bu), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**)
If	7.46 (d, $^3J_{HH}$ = 7.2 Hz, 1H, NH), 7.32−7.36 (m, 4H, Ar−H), 7.12 (t, $^3J_{HH}$ = 7.6 Hz, 3H, Ar−H), 7.00−7.03 (m, 4H, Ar−H), 5.48−5.52 (m, 1H, NHC**H**), 4.11 (s, 3H, pyrazole-Me), 3.97 (dd, $^3J_{HH}$ = 4.8 Hz, $^2J_{HH}$ = 11.2 Hz, 1H, C**H$_2$**Cl), 3.89 (dd, $^3J_{HH}$ = 5.2 Hz, $^2J_{HH}$ = 11.2 Hz, 1H, C**H$_2$**Cl), 2.65 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**)
Ig	7.40 (d, $^3J_{HH}$ = 7.2 Hz, 1H, NH), 7.28 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 6.90 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 5.44 (dd, $^3J_{HH}$ = 5.6 Hz, $^2J_{HH}$ = 8.4 Hz, 1H, NHC**H**), 4.11 (s, 3H, pyrazole-Me), 3.92−3.96 (m, 4H, C**H$_2$**Cl and OC**H$_2$**−), 2.65 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.74−1.81 (m, 2H, OCH$_2$C**H$_2$**−), 1.34−1.45 (m, 4H, −C**H$_2$C H$_2$**−), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**), 0.92 (t, $^3J_{HH}$ = 7.2 Hz, 3H, −CH$_2$C**H$_3$**)
Ih	7.49 (d, $^3J_{HH}$ = 6.8 Hz, 1H, NH), 7.37 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 7.32 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 5.47−5.51 (m, 1H, C**H**NH), 4.10 (s, 3H, pyrazole-Me), 3.96 (dd, $^3J_{HH}$ = 4.8 Hz, $^2J_{HH}$ = 11.2 Hz, 1H, C**H$_2$**Cl), 3.87 (dd, $^3J_{HH}$ = 4.8 Hz, $^2J_{HH}$ = 11.2 Hz, 1H, C**H$_2$**Cl), 2.66 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**)
Ii	7.39 (d, 2H, Ar−H), 7.23 (d, $^3J_{HH}$ = 8 Hz, 2H, Ar−H), 5.36−5.41 (m, 1H, C**H$_2$**O), 4.74−4.79 (m, 1H, CH$_2$O), 4.24-4.28 (m, 1H, C**H**N), 4.12 (s, 3H, pyrazole-Me), 2.66 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.31 (s, 9H, t-Bu), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**)
Ij	7.31−7.35 (m, 2H, Ar−H), 7.25−7.27 (m, 2H, Ar−H), 7.10 (t, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 6.99−7.02 (m, 4H, Ar−H), 5.40 (dd, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 10.0 Hz, 1H, OC**H$_2$**), 4.78 (dd, $^3J_{HH}$ = 8.4 Hz, $^2J_{HH}$ = 10.0 Hz, 1H, OC**H$_2$**), 4.24 (t, $^3J_{HH}$ = 8.4 Hz, 1H, NC**H**), 4.12 (s, 3H, pyrazole-Me), 2.66 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**)
Ik	7.19 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar−H), 6.88 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar−H), 5.35 (dd, $^3J_{HH}$ = 8.4 Hz, $^2J_{HH}$ = 10.0 Hz, 1H, OC**H$_2$**), 4.75 (dd, $^3J_{HH}$ = 8.4 Hz, $^2J_{HH}$ = 10.0 Hz, 1H, OC**H$_2$**), 4.22 (t, $^3J_{HH}$ = 8.4 Hz, 1H, NC**H**), 4.11 (s, 3H, pyrazole-Me), 3.94 (t, $^3J_{HH}$ = 6.8 Hz, 2H, OC**H$_2$**−), 2.66 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.74−1.81 (m, 2H, OCH$_2$C**H$_2$**−), 1.34−1.45 (m, −C**H$_2$C H$_2$**−), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**), 0.92 (t, $^3J_{HH}$ = 7.2 Hz, 3H, −CH$_2$C**H$_3$**)
Il	7.34 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar−H), 7.23 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar−H), 5.40 (dd, $^3J_{HH}$ = 8.4 Hz, $^2J_{HH}$ = 10.0 Hz, 1H, OC**H$_2$**), 4.78 (dd, $^3J_{HH}$ = 8.4 Hz, $^2J_{HH}$ = 10.0 Hz, 1H, OC**H$_2$**), 4.20 (t, $^3J_{HH}$ = 8.4 Hz, 1H, NC**H**), 4.12 (s, 3H, pyrazole-Me), 2.66 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.26 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**)
IIa	7.40 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 7.27 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar−H), 6.65 (d, $^3J_{HH}$ = 6.4 Hz, 1H, NH), 6.38 (s, 1H, pyrazole-H), 5.15−5.19 (m, 1H, NHC**H**), 4.09 (s, 3H, pyrazole-Me), 3.96−3.98 (m, 2H, C**H$_2$**OH), 2.63 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.31 (s, 9H, t-Bu), 1.24 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**)
IIb	7.30−7.36 (m, 4H, Ar−H), 7.12 (t, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 6.99−7.02 (m, 4H, Ar−H),6.65 (d, $^3J_{HH}$ = 6.8 Hz, 1H, NH), 6.39 (s, 1H, pyrazole-H), 5.15−5.19 (m, 1H, NHCH), 4.09 (s, 3H, pyrazole-Me), 3.97−3.98 (m, 2H, C**H$_2$**OH), 2.63 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 2.22 (br, 1H, OH), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**)
IIc	7.25 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar−H), 6.90 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar−H), 6.56 (d, $^3J_{HH}$ = 7.2 Hz, 1H, NH), 6.36 (s, 1H, pyrazole-H), 5.11−5.15 (m, 1H, NHC**H**), 4.09 (s, 3H, pyrazole-Me), 3.92−3.97 (m, 4H, C**H$_2$**OH and OC**H$_2$**−), 2.63 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.74−1.81 (m, 2H, OCH$_2$C**H$_2$**−), 1.34−1.45 (m, 4H, −C**H$_2$C H$_2$**−), 1.24 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**), 0.92 (t, $^3J_{HH}$ = 7.2 Hz, 3H, −CH$_2$C**H$_3$**)
IId	7.35 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 7.29 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 6.70 (d, $^3J_{HH}$ = 6.8 Hz, 1H, NH), 6.40 (s, 1H, pyrazole-H), 5.12−5.16 (m, 1H, C**H**NH), 4.08 (s, 3H, pyrazole-Me), 3.91−4.02 (m, 2H, CH$_2$OH), 2.64 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**)
IIe	7.41 (d, $^3J_{HH}$ = 8 Hz, 2H, Ar−H), 7.29 (d, $^3J_{HH}$ = 8 Hz, 2H, Ar−H), 6.47 (d, $^3J_{HH}$ = 7.2 Hz, 1H, NH), 6.38 (s, 1H, pyrazole-4H), 5.40−5.45 (m, 1H, CHNH), 4.10 (s, 3H, pyrazole-Me), 3.90−3.99 (m, 2H, C**H$_2$**Cl), 2.64 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.31 (s, 9H, t-Bu), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**)
IIf	7.30−7.37 (m, 4H, Ar−H), 7.13 (t, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 6.98−7.03 (m, 4H, Ar−H), 6.48 (d, $^3J_{HH}$ = 7.5 Hz, 1H, NH), 5.40−5.46 (m, 1H, NHC**H**), 4.10 (s, 3H, pyrazole-Me), 3.88−3.99 (m, 2H, C**H$_2$**Cl), 2.64 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**)
IIg	7.27 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar−H), 6.90 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar−H), 6.43 (d, $^3J_{HH}$ = 7.2 Hz, 1H, NH), 4.09 (s, 3H, pyrazole-Me), 5.35−5.40 (m, 1H, NHC**H**), 3.87−3.96 (m, 4H, C**H$_2$**OH and OC**H$_2$**−), 2.64 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.74−1.81 (m, 2H, OCH$_2$C**H$_2$**−), 1.34−1.45 (m, 4H, −C**H$_2$C H$_2$**−), 1.24 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H$_3$**), 0.92 (t, $^3J_{HH}$ = 7.2 Hz, 3H, −CH$_2$C**H$_3$**)
IIh	7.37 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 7.30 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 6.50 (d, $^3J_{HH}$ = 6.8 Hz, 1H, NH), 6.40 (s, 1H, pyrazole-H), 5.40−5.45 (m, 1H, C**H**NH), 4.09 (s, 3H, pyrazole-Me), 3.95 (dd, $^3J_{HH}$ = 4.8 Hz, $^2J_{HH}$ = 11.6 Hz, 1H, C**H$_2$**Cl), 3.89 (dd, $^3J_{HH}$ = 4.8 Hz, $^2J_{HH}$ = 11.6 Hz, 1H, C**H$_2$**Cl), 2.65 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.26 (t, $^3J_{HH}$ = 7. 6 Hz, 3H, CH$_2$C**H$_3$**)

dx.doi.org/10.1021/jf204778w | J. Agric.Food Chem. 2012, 60, 1470−1479

Table 2. continued

compd	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm)
IIi	7.38 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar−H), 7.21 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 6.57 (s, 1H, pyrazole-H), 5.37 (t, $^3J_{HH}$ = 9.2 Hz, 1H, CH_2O), 4.69 (t, $^3J_{HH}$ = 9.2 Hz, 1H, CH_2O), 4.19 (t, $^3J_{HH}$ = 8.4 Hz, 1H, CHN), 4.17 (s, 3H, pyrazole-Me), 2.66 (q, $^3J_{HH}$ = 7.6 Hz, 2H, CH_2CH_3), 1.31 (s, 9H, t-Bu), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH_2CH_3)
IIj	7.33 (t, $^3J_{HH}$ = 8.0 Hz, 2H, Ar−H), 7.23−7.26 (m, 2H, Ar−H), 7.10 (t, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 6.99−7.01 (m, 4H, Ar−H), 6.58 (s, 1H, pyrazole-4H), 5.37−5.41 (m, 1H, CHN), 4.69-4.74 (m, 1H, OCH_2), 4.17 (m, 4H, OCH_2 and pyrazole-Me), 2.66 (q, $^3J_{HH}$ = 7.6 Hz, 2H, CH_2CH_3), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH_2CH_3)
IIk	7.18 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar−H), 6.88 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 6.57 (s, 1H, pyrazole-H), 5.34 (dd, $^3J_{HH}$ = 8.4 Hz, $^2J_{HH}$ = 10.0 Hz, 1H, OCH_2), 4.68 (dd, $^3J_{HH}$ = 8.4 Hz, $^2J_{HH}$ = 10.0 Hz, 1H, OCH_2), 4.16 (s, 3H, pyrazole-Me), 4.15 (t, $^3J_{HH}$ = 8.4 Hz, 1H, CH), 3.94 (t, $^3J_{HH}$ = 6.8 Hz, 2H, OCH_2−), 2.66 (q, $^3J_{HH}$ = 7.6 Hz, 2H, CH_2CH_3), 1.74−1.81 (m, 2H, OCH_2CH_2−), 1.33−1.47 (m, 4H, $-CH_2CH_2$−), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH_2CH_3), 0.92 (t, $^3J_{HH}$ = 7. 2 Hz, 3H, $-CH_2CH_3$)
III	7.33 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 7.23 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 6.58 (s, 1H, pyrazole-4H), 5.38 (dd, $^3J_{HH}$ = 8.4 Hz, $^2J_{HH}$ = 10.0 Hz, 1H, OCH_2), 4.47 (dd, $^3J_{HH}$ = 8.4 Hz, $^2J_{HH}$ = 10.0 Hz, 1H, OCH_2), 4.17 (s, 3H, pyrazole-Me), 4.13 (t, $^3J_{HH}$ = 8.4 Hz, 1H, NCH), 2.66 (q, $^3J_{HH}$ = 7.6 Hz, 2H, CH_2CH_3), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH_2CH_3)

1-bromo-4-chlorobenzene (5.00 g, 26.1 mmol) in ether (30 mL), and the mixture was stirred for 1 h at room temperature. The Grignard reagent was added to diethyl oxalate (5.72 g, 39.2 mmol) in ether (60 mL) at −78 °C. The reaction mixture was stirred for 5 h in the temperature range −78 to 0 °C. The reaction was quenched with 50 mL of NH_4Cl (10%, w/w), and the aqueous layer was extracted with ether twice. The combined organic layer was dried and concentrated to give a yellow liquid (2.80 g, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 7.41 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 4.37 (q, $^3J_{HH}$ = 7.2 Hz, 2H, OCH_2CH_3), 1.34 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_2CH_3).

Synthesis of Ethyl 2-(4-(*tert*-Butyl)phenyl)-2-(hydroxyimino)-acetate (2a). To a solution of **1a** (1.50 g, 6.41 mmol) in alcohol was added hydroxylamine hydrochloride (0.53 g, 7.70 mmol), and the mixture was refluxed for 5 h. After most of the alcohol was removed in vacuo, water (20 mL) and ethyl acetate (20 mL) were added. The separated organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude product **2a**, which was used in the next reaction without further purification. Compounds **2b**−**2d** were prepared using the same procedure as **2a.**

Synthesis of 2-Amino-2-(4-(*tert*-butyl)phenyl)ethanol (3a).[10] To a solution of **2a** (0.70 g, 2.80 mmol) in tetrahydrofuran (10 mL) was added $NaBH_4$ (0.32 g, 8.40 mmol) in portions, then iodine (1.07 g, 4.2 mmol) dissolved in tetrahydrofuran (10 mL) was added slowly, and then the mixture was refluxed for 4 h. After the mixture was cooled to room temperature, methanol (10 mL) was added dropwise. Then, the solvent was removed in vacuo. To the residue, NaOH solution (20 mL of 5%, w/w) was added, and then, the mixture was heated at 100 °C for 3 h. After the mixture was cooled to room temperature, the aqueous solution was extracted with dichloromethane (10 mL × 3), and then, the combined organic phase was washed with water (10 mL × 2) and brine (10 mL × 2) successively, dried over anhydrous Na_2SO_4, and concentrated to give white solid (0.37 g, 69%); mp 109−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, $^3J_{HH}$ = 7.6 Hz, 2H, Ar−H), 7.25 (d, $^3J_{HH}$ = 7.6 Hz, 2H, Ar−H), 4.00−4.01 (m, 1H, CH_2OH), 3.71−3.74 (m, 1H, CH_2OH), 3.54 (t, $^3J_{HH}$ = 9.6 Hz, 1H, $CHNH_2$), 2.00 (br, 3H, OH and NH_2), 1.31 (s, 9H, t-Bu). Compounds **3b**−**3d** were prepared using the same procedure as **3a**.

*Data for 2-Amino-2-(4-phenoxyphenyl)ethanol (**3b**).* White solid. Yield: 58%. mp: 90−92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26−7.35 (m, 4H, Ar−H), 7.10 (t, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 6.97−7.01 (m, 4 H, Ar−H), 4.04 (br, 1H, $CHNH_2$), 3.72−3.75 (m, 1H, CH_2OH), 3.55 (t, $^3J_{HH}$ = 9.6 Hz, 1H, CH_2OH), 1.97 (br, 3H, NH_2 and OH).

*Data for 2-Amino-2-(4-(pentyloxy)phenyl)ethanol (**3c**).* Cream yellow solid. Yield: 75%. mp: 79−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 6.87 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 3.97−4.00 (m, 1H, $CHNH_2$), 3.93 (t, $^3J_{HH}$ = 6.8 Hz, 2H, $OCH_2C_4H_9$), 3.69 (dd, $^3J_{HH}$ = 4.4 Hz, $^2J_{HH}$ = 10.4 Hz, 1H, CH_2OH), 3.50−3.54 (m, 1H, CH_2OH), 1.96 (br, 3H, NH_2 and OH), 1.74−1.81 (m, 2H, $OCH_2CH_2C_3H_7$), 1.35−1.45 (m, 4H, $OCH_2CH_2(CH_2)_2CH_3$), 0.92 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $CH_2CH_2CH_3$).

*Data for 2-Amino-2-(4-chlorophenyl)ethanol (**3d**).* Corlorless solid. Yield: 65%. mp: 86−87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32(d, 2 H, $^3J_{HH}$ = 8.4 Hz, Ar−H), 7.28 (d, 2 H, $^3J_{HH}$ = 8.4 Hz, Ar−H), 4.05 (dd, 1 H, $^3J_{HH}$ = 4.4 Hz, $^2J_{HH}$ = 8.0 Hz, $CHNH_2$), 3.71 (dd, 1 H, $^3J_{HH}$ = 8.8 Hz, $^2J_{HH}$ = 10.8 Hz, CH_2OH), 3.52 (dd, 1 H, $^3J_{HH}$ = 8.8 Hz, $^2J_{HH}$ = 10.8 Hz, CH_2OH), 1.97 (br, 3 H, OH and NH_2).

Synthesis of Ethyl 2,4-Dioxohexanoate (4).[11] Metallic sodium (1.90 g, 26.4 mmol) was dissolved in absolute alcohol (20 mL). When the solution had been cooled to −5 °C, a mixture of 2-butanone (1.90 g, 26.4 mmol) and diethyl oxalate (3.85 g, 26.4 mmol) was added dropwise. The reaction mixture was stirred at −5 °C overnight and then concentrated to dryness. The resulting residue was partitioned between water (20 mL) and ethyl acetate (70 mL × 3). The aqueous layer was acidified to pH 2 with dilute H_2SO_4 and then extracted with ethyl acetate (50 mL × 3). The combined organic phase was dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by flash chromatography on silica gel using petroleum ether (60−90 °C) and ethyl acetate (v/v = 10:1) as the eluent to give **4** as yellow oil (3.18 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.40 (br, 1H, OH), 6.38

Table 3. Stomach Activities against Cotton Bollworm (*H. armigera*) and Diamondback Moth (*P. xylostella*) of Compounds Ia–l, IIa–l, and Tolfenpyrad

			larvicidal activity (%) at concn (mg kg^{-1})						
			H. armigera					*P. xylostella*	
compd	R^1	R^2	110	55	22	11	5.5	600	200
Ia	Cl	$C(CH_3)_3$	100	100	40	0		80	40
Ib	Cl	C_6H_5O	100	100	70	40	0	60	20
Ic	Cl	$C_5H_{11}O$	100	100	30	0		90	30
Id	Cl	Cl	100	100	40	0		30	0
Ie	Cl	$C(CH_3)_3$	100	100	100	20	0	90	30
If	Cl	C_6H_5O	100	100	100	80	40	90	60[a]
Ig	Cl	$C_5H_{11}O$	100	100	100	60	10	90	45
Ih	Cl	Cl	100	100	100	70	40	70	60[a]
Ii	Cl	$C(CH_3)_3$	100	100	100	70	40	50	30
Ij	Cl	C_6H_5O	100	100	100	90	60	90	20
Ik	Cl	$C_5H_{11}O$	100	100	100	80	30	70	30[a]
Il	Cl	Cl	100	100	100	90	60	0	
IIa	H	$C(CH_3)_3$	100	100	60	10	0	70	60
IIb	H	C_6H_5O	100	100	30	0		90	45
IIc	H	$C_5H_{11}O$	100	100	60	20	0	45	30
IId	H	Cl	100	100	50	0		100	60
IIe	H	$C(CH_3)_3$	100	100	100	90	60	30	15
IIf	H	C_6H_5O	100	100	40	0		45	30
IIg	H	$C_5H_{11}O$	100	100	40	0		15	0
IIh	H	Cl	100	100	20	0		30	0
IIi	H	$C(CH_3)_3$	100	100	40	0		60	45[a]
IIj	H	C_6H_5O	100	100	40	0		70	45
IIk	H	$C_5H_{11}O$	100	100	30	0		30	0
IIl	H	Cl	100	100	70	40	0	60	15
tolfenpyrad			100	100	100	100	70	100	100

[a]Compounds exhibited obvious antifeedant activities.

(s, 1H, vinyl hydrogen), 4.35 (d, $^3J_{HH}$ = 7.2 Hz, 2H, OC**H**$_2$CH$_3$), 2.54 (d, $^3J_{HH}$ = 7.6 Hz, 2H, C**H**$_2$CH$_3$), 1.38 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH$_2$C**H**$_3$), 1.18 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H**$_3$).

Synthesis of Ethyl 3-Ethyl-1*H*-pyrazole-5-carboxylate (5). To a solution of **4** (1.17 g, 6.80 mmol) in glacial acetic acid (20 mL) was added hydrazine hydrate (0.46 g of 80%, w/w) dropwise. The mixture was heated at 80 °C for 5 h. After the mixture was cooled to room temperature, water (20 mL) was then added, and the aqueous layer was extracted with dicholoromethane (15 mL × 3). The combined organic phase was washed with saturated Na_2CO_3 (10 mL × 2) and brine (10 mL × 2) successively, dried over anhydrous Na_2SO_4, and concentrated to give **5** as pale yellow oil (1.00 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.49 (br, 1H, N**H**), 6.58 (s, 1H, pyrazole-H), 4.35 (q, $^3J_{HH}$ = 7.2 Hz, 2H, OC**H**$_2$CH$_3$), 2.72 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H**$_2$CH$_3$), 1.33 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH$_2$C**H**$_3$), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H**$_3$).

Synthesis of Ethyl 3-Ethyl-1-methyl-1*H*-pyrazole-5-carboxylate (6). To a solution of **5** (5.00 g, 30.0 mmol) in dichloromethane, anhydrous Na_2CO_3 (4.42 g, 41.7 mmol) was added in portion, and after the mixture was heated to 40 °C, dimethyl sulfate (5.25 g, 41.7 mmol) was added dropwise, and then, the mixture was heated at 80 °C for 5 h. After the mixture was cooled to room temperature, water and dichloromethane were added, and the aqueous layer was extracted twice with dichloromethane. The combined organic phase was washed with brine (100 mL × 2), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by flash chromatography on silica gel using petroleum ether (60–90 °C) and ethyl acetate (v/v = 10:1) as eluent to give **6** as yellow oil (3.93 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.60 (s, 1H, pyrazole-H), 4.29 (q, $^3J_{HH}$ = 7.2 Hz, 2H, OC**H**$_2$CH$_3$), 4.08 (s, 3H, pyrazole-CH$_3$), 2.60 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H**$_2$CH$_3$), 1.33 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH$_2$C**H**$_3$), 1.20 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H**$_3$).

Synthesis of Ethyl 4-Chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylate (7). To a solution of **6** (0.55 g, 3.02 mmol) in toluene (10 mL) was added sulfonyl chloride (0.45 g, 3.32 mmol) dropwise. After the mixture was heated at 100 °C for 2 h, the mixture was cooled, water (20 mL) was added, and the aqueous layer was extracted twice with dichloromethane. The combined organic phase was washed with brine (20 mL × 2), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give **7** as orange-yellow oil (0.58 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.37 (q, $^3J_{HH}$ = 7.2 Hz, 2H, OC**H**$_2$CH$_3$), 4.07 (s, 3H, pyrazole-CH$_3$), 2.62 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H**$_2$CH$_3$), 1.39 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH$_2$C**H**$_3$), 1.21 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H**$_3$).

Synthesis of 4-Chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic Acid (I). NaOH (1.03 g, 5.14 mmol) was added to a solution of **7** (0.56 g, 2.57 mmol) in absolute alcohol (30 mL) in portions, and the mixture was heated under reflux for 3 h. The alcohol was removed in vacuo, and the residue was acidified to pH 2 with dilute H_2SO_4. The white slurry was filtered, and the cake was washed with water to afford **I** as a white solid (0.45 g, 84%). mp: 133–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13 (s, 3H, pyrazole-Me), 2.67 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C**H**$_2$CH$_3$), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C**H**$_3$).

Data for 3-Ethyl-1-methyl-1H-pyrazole-5-carboxylic Acid (II). Compound **II** was prepared from **6** using the same synthetic procedure as **I**. White solid. Yield: 95%. mp: 158–159 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77 (s, 1H, pyrazole-H), 4.15 (s, 3H, pyrazole-Me), 2.67 (q, 2H, $^3J_{HH}$ = 7.6 Hz, C**H**$_2$CH$_3$), 1.26 (t, 3H, $^3J_{HH}$ = 7.6 Hz, CH$_2$C**H**$_3$).

Synthesis of *N*-(1-(4-(*tert*-Butyl)phenyl)-2-hydroxyethyl)-4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (Ia). A mixture of **I** (0.20 g, 1.04 mmol) and thionyl chloride (15 mL) was heated under reflux for 1 h. After the mixture had been cooled to room temperature, the excess thionyl chloride was removed under reduced pressure, and the residue was dissolved in toluene (10 mL).

The obtained solution was added dropwise to a toluene (15 mL) solution of **3a** (0.20 g, 1.04 mmol) and triethyamine (0.12 g, 1.14 mmol) at −5 °C. Then, the mixture was stirred at −5 °C for 8 h, then poured into ice water (40 mL), and extracted with toluene (20 mL × 3). The combined organic layer was washed twice with water (40 mL) and dried over anhydrous Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel and eluted with petroleum ether (60−90 °C) and ethyl acetate (v/v = 1:1) to give **Ia** as yellow viscous oil (0.34 g, 90%).

Compounds **Ib−d** and **IIa−d** were synthesized using corresponding acid and substituted benzylamine according to the same procedure as **Ia**. The physical properties and elemental analysis or HRMS of compounds **Ia−d** and **IIa−d** are listed in Table 1, and their ^{1}H NMR data are listed in Table 2.

Synthesis of *N*-(1-(4-(*tert*-Butyl)phenyl)-2-chloroethyl)-4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (Ie). To the solution of **Ia** (0.30 g, 0.83 mmol) in toluene (10 mL), thionyl chloride (0.30 g, 2.52 mmol) was added dropwise, and then, the mixture was heated to 80 °C for 3 h. After it was cooled, the reaction mixture was added a solution of Na_2CO_3 to make pH 8, and then, the organic layer was separated and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel and eluted with petroleum ether (60−90 °C) and ethyl acetate (v/v = 10:1) to give **Ie** as pale yellow viscous oil (0.23 g, 74%).

Compounds **If−h** and **IIe−h** were synthesized from **Ib−d** and **IIa−d**, respectively, according to the same procedure as **Ie**. The physical properties and elemental analysis or HR-MS of compounds of **Ie−h** and **IIe−h** are listed in Table 1, and their ^{1}H NMR data are listed in Table 2.

Synthesis of 4-(4-(*tert*-Butyl)phenyl)-2-(4-chloro-3-ethyl-1-methyl-1*H*-pyrazol-5-yl)-4,5-dihydrooxazole (Ii).[12] Compound **Ie** (0.21 g, 0.55 mmol) was dissolved in alcohol (5 mL) and treated with NaOH (0.44 g, 1.10 mmol). After reflux at 100 °C for 1 h, the reaction mixture was poured into water (10 mL) and extracted with ethyl acetate (10 mL × 3). The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel and eluted with petroleum ether (60−90 °C) and ethyl acetate (v/v = 10:1) to give **Ii** as colorless viscous oil (0.18 g, 95%).

Compounds **Ij−l** and **IIi−l** were synthesized from **If−h** and **IIe−h**, respectively, according to the same procedure as **Ii**. The physical properties and elemental analysis or HRMS of compounds **Ii−l** and **IIi−l** are listed in Table 1, and their ^{1}H NMR data are listed in Table 2.

Biological Assay. All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated in triplicate at 25 ± 1 °C. The error of the experiments was 5%. Assessments were made on a dead/alive basis, and mortality rates were corrected using Abbott's formula.[13] Evaluations were based on a percentage scale of 0−100, where 0 equals no activity and 100 equals total kill. For comparative purposes, tebufenpyrad and tolfenpyrad were tested under the same conditions.

Stomach Activities against Cotton Bollworm (*H. armigera*). The stomach toxicities of the target compounds **Ia−l**, **IIa−l**, and the contrast tolfenpyrad against cotton bollworm were tested by the diet-corporate method.[14] The test samples were dissolved in acetone in appropriate quantities to give the desired final concentrations, and then pipetted 3 mL of the test solution to about 27 g of configured feed, which was mixed evenly and poured into clean 24-well plates. After evaporation of acetone, 24 third-instars cotton bollworm larvae were infested. The diet fed to controls contained an amount of acetone equal to the treatment containing the maximum amount (normally not >5% of total volume). The insects were maintained under normal rearing conditions for development and larvae fed ad lib. Percentage mortalities were evaluated 3 days after treatment.

Stomach Toxicity against Diamondback Moth (*P. xylostella*). The stomach toxicities of the target compounds **Ia−l**, **IIa−l**, and the contrast tolfenpyrad against diamondback moth were tested by the leaf dip method using the reported procedure.[18,19]

Table 4. LC_{50} Value of Ij, IIe, and Tolfenpyrad against Cotton Bollworm

compd	$y = a + bx$	toxic ratio	LC_{50} (mg kg^{-1})	confidence interval (95%)
Ij	$y = 4.15 + 1.91x$	0.88	2.80	2.59−3.03
IIe	$y = 4.00 + 1.90x$	0.74	3.33	2.97−3.74
tolfenpyrad	$y = 4.29 + 1.81x$	1	2.47	2.23−2.73

Acaricidal Activity against Adults, Eggs, and Larvae of Spider Mite (*T. cinnabarinus*). The acaricidal activities of the target compounds **Ia−l**, **IIa−l**, and the contrast compound tebufenpyrad against adults, eggs, and larvae of spider mite were evaluated by the leaf dip method using reported procedure.[20]

Foliar Contact Activity against Bean Aphid (*A. craccivora*). The foliar contact activities of compounds **Ia−l**, **IIa−l**, tebufenpyrad, and tolfenpyrad against bean aphid were tested by the leaf dip method according to a reported procedure.[15−17]

Toxicity against Mosquito (*C. pipiens pallens*). The toxicities of the target compounds **Ia−l**, **IIa−l**, and tebufenpyrad against mosquito were evaluated according to the reported procedure.[16,21]

RESULTS AND DISCUSSION

Synthesis. Ethyl 2-oxo-2-(4-substitutedphenyl) acetate (**1a−c**) was prepared from substituted benzene by Friedel−Crafts acylation in high regioselectivity. However, ethyl 2-(4-chlorophenyl)-2-oxoacetate (**1d**) could not be obtained selectively by Friedel−Crafts acylation, and the ortho and para acylated products were difficult to be separated. Then, Grignard reagent of 1-bromo-4-chlorobenzene was applied in the synthesis of **1d**. Compounds **1a−d** were, respectively, reacted with hydroxylamine hydrochloride and then reduced by $NaBH_4$/iodine system to afford the key intermediate 2-amino-2-(4-substitutedphenyl) ethanol (**3a−3d**). (Scheme 1).

Butan-2-one reacted with diethyl oxalate to give kinetic controlled product ethyl 2,4-dioxohexanoate (**4**) according to the reported method.[11] Further treatment with hydrazine hydrate provided ethyl 3-ethyl-1*H*-pyrazole-5-carboxylate (**5**), and the methylation of **5** by dimethyl sulfate assisted with sodium carbonate afforded *N*-methylated product **6**. Then, the intermediate **6** was chlorinated by sulfonyl chloride to give intermediate **7** and then hydrolyzed by sodium hydroxide to afford acid **I**. Similarly, acid **II** could be obtained by the hydrolysis of intermediate **6**. Both acid **I** and **II** were treated with thionyl chloride to give corresponding carbonyl chloride and then condensed with 2-amino-2-(4-substitutedphenyl) ethanol (**3a−d**) to afford amides **Ia−d** and **IIa−d**, which were converted to **Ie−h** and **IIe−h** by thionyl chloride. Compounds **Ie−h** and **IIe−h** were treated with sodium hydroxide to afford oxazoles **Ii−l** and **IIi−l**, respectively.

It is worth mentioning that when acid **II** was reacted with thionyl chloride, except for the expected 3-ethyl-pyrazole-5-carbonyl chloride, 4-chloro-3-ethyl-pyrazole-5-carbonyl chloride was also formed. To reduce the dichlorated product, the reaction temperature must be controlled under 80 °C, and thionyl chloride must be added no more than 1.5-fold. However, from another aspect, the dichlorated compound could be prepared from acid **II** (instead of acid **I**) by using excess thionyl chloride at a higher temperature, which provided an alternative synthetic procedure.

Bioassays. Stomach Activities against Cotton Bollworm (*H. armigera*) and Diamondback Moth (*P. xylostella*). Table 3 shows the stomach activities of the target compounds and the contrast tolfenpyrad against cotton bollworm and diamondback moth. The results indicated that most of the

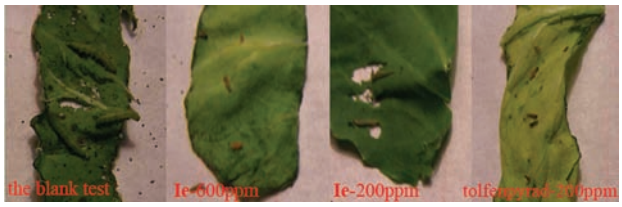


Figure 2. Stomach activities against diamondback moth. The picture above showed the antifeedant effect of compound **Ie** at 600 and 200 mg kg^{-1}. **Ie** had 90% inhibitory effect against diamondback moth at 600 mg kg^{-1}. At 200 mg kg^{-1}, the inhibitory effect was only 30%, but the worms were much smaller as compared with the blank test, because the insects no longer eat after a period of time.

Table 5. Acaricidal Activities against Spider Mite (*T. cinnabarinus Boisduval*) Eggs, Adults, and Larvae of Compounds Ia–l, IIa–l, and Tebufenpyrad

			activity (%) against					
			eggs		adults		larvae	
compd	R^1	R^2	600	200	600	200	600	200
Ia	Cl	$C(CH_3)_3$	40	0	10	0	25	
Ib	Cl	C_6H_5O	15	0	0		30	0
Ic	Cl	$C_5H_{11}O$	30	20	15	0	20	0
Id	Cl	Cl	10	0	0		25	0
Ie	Cl	$C(CH_3)_3$	34	30	0		30	0
If	Cl	C_6H_5O	20	0	0		30	20
Ig	Cl	$C_5H_{11}O$	40	0	0		30	0
Ih	Cl	Cl	10	0	0		0	
Ii	Cl	$C(CH_3)_3$	20	0	30	10	45	30
Ij	Cl	C_6H_5O	0		0		25	0
Ik	Cl	$C_5H_{11}O$	40	20	20	15	15	0
Il	Cl	Cl	40	0	10	0	20	0
IIa	H	$C(CH_3)_3$	50	40	0		0	
IIb	H	C_6H_5O	20	0	30	0	0	
IIc	H	$C_5H_{11}O$	20	0	45	0	20	0
IId	H	Cl	0		25	0	25	0
IIe	H	$C(CH_3)_3$	80	40	30	0	20	0
IIf	H	C_6H_5O	50	40	50	0	40	30
IIg	H	$C_5H_{11}O$	70	50	0		70	40
IIh	H	Cl	30	0	0		20	0
IIi	H	$C(CH_3)_3$	100	95	100	95	90	80
IIj	H	C_6H_5O	90	50	40	10	70	50
IIk	H	$C_5H_{11}O$	50	40	20	0	30	0
IIl	H	Cl	100	80	20	0	40	20
tebufenpyrad			100	100	100	100	100	100

target compounds exhibited excellent activities against cotton bollworm, and all of the compounds had 100% inhibitory effect at 55 mg kg^{-1}. At reduced dosages, the compounds chlorinated at the 4-position of pyrazole (series **I**) were more potent than that of not chlorinated (series **II**). In series **I**, the compounds containing α-chloromethyl-*N*-benzyl and 4,5-dihydrooxazole moieties exhibited higher activities than the compounds containing α-hydroxymethyl-*N*-benzyl moieties. For instance, the activities of **Ie–l** were 100% at 22 mg kg^{-1}, while **Ia–d** had no more than 70% at the same dosage. In particular, the activities of **Ij** and **Il** were 60% at 5.5 mg kg^{-1}, which was near that of tolfenpyrad. It suggested that the hydrogen donor of the bridge was not necessary for the high activity against cotton bollworm. Moreover, the substituent on the benzene ring of the target compounds was also important for the activities. When the substituent on the benzene ring was phenoxyl or chloro, the

Table 6. Foliar Contact Activities against Bean Aphid (*A. craccivora*) of Compounds Ia–l, IIa–l, and Tebufenpyrad

			larvicidal activity (%) at concn (mg kg^{-1})	
compd	R^1	R^2	600	200
Ia	Cl	$C(CH_3)_3$	100	80
Ib	Cl	C_6H_5O	100	50
Ic	Cl	$C_5H_{11}O$	100	95
Id	Cl	Cl	100	95
Ie	Cl	$C(CH_3)_3$	100	100
If	Cl	C_6H_5O	100	80
Ig	Cl	$C_5H_{11}O$	100	45
Ih	Cl	Cl	80	50
Ii	Cl	$C(CH_3)_3$	90	50
Ij	Cl	C_6H_5O	90	60
Ik	Cl	$C_5H_{11}O$	100	90
Il	Cl	Cl	60	35
IIa	H	$C(CH_3)_3$	70	50
IIb	H	C_6H_5O	95	70
IIc	H	$C_5H_{11}O$	100	85
IId	H	Cl	98	75
IIe	H	$C(CH_3)_3$	80	65
IIf	H	C_6H_5O	100	95
IIg	H	$C_5H_{11}O$	100	80
IIh	H	Cl	30	0
IIi	H	$C(CH_3)_3$	98	90
IIj	H	C_6H_5O	50	20
IIk	H	$C_5H_{11}O$	75	20
IIl	H	Cl	100	90
tebufenpyrad			100	100

activities of these compounds were more than those with *t*-butyl or *n*-pentyloxy group. In series **II**, α-hydroxymethyl-*N*-benzyl, α-chloromethyl-*N*-benzyl, and 4,5-dihydrooxazole compounds did not have significant difference at 5.5 mg kg^{-1}, and the substituent on the benzene ring did not have obvious effect on the activity either. Only compound **IIe**, which bears 2-chloro-1-(4-t-butylphenyl) ethyl carboxamide, exhibited 60% at 5.5 mg kg^{-1}, much higher than the others. The LC_{50} values of compounds **Ij** and **IIe** are given in Table 4, which show approximate concentrations as commercial tolfenpyrad.

The stomach toxicity of the target compounds against diamondback moth formed a sharp contrast to the activities against cotton bollworm, although both of the worms are of the order *Lepidoptera*. Although the activities against diamondback moth of the target compounds at a low level compare with commercial insecticides tolfenpyrad, we had been pleasantly surprised to find that **Ie**, **If**, and **Ih** exhibited obvious antifeedant activities. Figure 2 shows the antifeedant effect of compound **Ie**.

Acaricidal Activities against Spider Mite (*T. cinnabarinus Boisduval*) Eggs, Adults, and Larvae. Table 5 shows the acaricidal activities against spider mite eggs, adults, and larvae. The activities of the target compounds were lower than tebufenpyrad, which suggested that the changes on the bridge moiety were detrimental to the acaricidal activity. Nevertheless, there are still some rules that could be found. Generally, the ovicidal activities of the target compounds were a little higher than miticidal and larvicidal activities, especially the compounds containing 4,5-dihydrooxazole moieties in series **II** exhibited excellent activities against spider mite eggs. For instance, the ovicidal activities of **IIi** and **IIl** against spider mite were 95 and

dx.doi.org/10.1021/jf204778v | J. Agric.Food Chem. 2012, 60, 1470–1479

80% at 200 mg kg^{-1}, respectively. We also noticed that compound **IIi** exhibited excellent activities against spider mite eggs, adults, and larvae at 200 mg kg^{-1}, which were 95, 95, and 80%, respectively, whereas the corresponding compound **Ii** were only 0, 10, and 30%, respectively. It indicated that the 4-position in pyrozole was a sensitive site. Therefore, a trivial change at that site would lead to great changes in properties and activities. The substituents on the benzene ring also have a significant effect on acaricidal activities, and the *tert*-butyl substituent is optimal.

Foliar Contact Activities against Bean Aphid (*A. craccivora*). Table 6 shows the foliar contact activities of the target compounds and contrast tebufenpyrad. Among series **I**, the compounds containing α-hydroxymethyl-*N*-benzyl and α-chloromethyl-*N*-benzyl moieties exhibited higher activities against bean aphid than the compounds containing 4,5-dihydrooxazole moieties, which indicated that high polarity of the target compounds and the hydrogen donor of the bridge moiety might be favorable to the foliar contact activities. Series **II** did not give obvious activity relationship with the bridge moiety or the substituents on the benzene ring. Among all of the compounds, the activities against bean aphid of **Ic**, **Id**, **Ie**, and **IIf** were more than 95% at 200 mg kg^{-1}.

Toxicity against Mosquito (*C. pipiens pallens*). Table 7 showed the larvacidal activities of the target compounds and the contrast tebufenpyrad against mosquito. Overall, the compounds chlorinated in 4-position of pyrazole (series **I**) were more potent than that of not chlorinated (series **II**), and the compounds containing α-chloromethyl-*N*-benzyl moieties exhibited a little higher activities than most of the compounds containing α-hydroxymethyl-*N*-benzyl and 4,5-dihydrooxazole moieties. The substituent R^2 on the benzene ring of the target compounds was also important for the activities against mosquito. When the R^2 group was fixed as phenoxy, the activities of the target compounds were the highest whatever in series **I** or **II**. The phenoxy on benzene ring of the target compounds is beneficial to the activity against mosquito larvae. Especially, the activity of **IIf** was 60% at 0.5 mg kg^{-1}, which was higher than tebufenpyrad. Then, their LC_{50} values were tested and are given in Table 8, which showed **IIf** was nearly two times better than tebufenpyrad.

Table 7. Larvacidal Activities against Mosquito (*C. pipiens pallens*) of Compounds Ia–l, IIa–l, and Tebufenpyrad

			larvicidal activity (%) at concn (mg kg^{-1})			
compd	R^1	R^2	5	2	1	0.5
Ia	Cl	$C(CH_3)_3$	20	0		
Ib	Cl	C_6H_5O	100	100	40	0
Ic	Cl	$C_5H_{11}O$	20	0		
Id	Cl	Cl	30	0		
Ie	Cl	$C(CH_3)_3$	100	100	40	0
If	Cl	C_6H_5O	100	100	60	0
Ig	Cl	$C_5H_{11}O$	100	70	0	
Ih	Cl	Cl	100	100	50	0
Ii	Cl	$C(CH_3)_3$	100	100	50	0
Ij	Cl	C_6H_5O	100	60	0	
Ik	Cl	$C_5H_{11}O$	100	50	0	
Il	Cl	Cl	100	50	0	
IIa	H	$C(CH_3)_3$	10	0		
IIb	H	C_6H_5O	30	0		
IIc	H	$C_5H_{11}O$	20	0		
IId	H	Cl	20	0		
IIe	H	$C(CH_3)_3$	60	0		
IIf	H	C_6H_5O	100	100	100	60
IIg	H	$C_5H_{11}O$	100	60	0	
IIh	H	Cl	10	0		
IIi	H	$C(CH_3)_3$	100	60	0	
IIj	H	C_6H_5O	30	0		
IIk	H	$C_5H_{11}O$	30	0		
IIl	H	Cl	10	0		
tebufenpyrad			100	100	70	0

Table 8. LC_{50} Value of IIf and Tebufenpyrad against Mosquito

compd	$y = a + bx$	toxic ratio	LC_{50} (mg kg^{-1})	confidence interval (95%)
IIf	$y = 5.88 + 1.91x$	1.7	0.35	0.32–0.38
tebufenpyrad	$y = 5.41 + 1.87x$	1	0.61	0.53–0.69

In summary, a series of novel pyrazoles containing α-hydroxymethyl-*N*-benzyl carboxamide, α-chloromethyl-*N*-benzyl carboxamide, and 4, 5-dihydrooxazole moieties were designed and synthesized via the key intermediate 2-amino-2-(4-substitutedphenyl) ethanol. The results of bioassays indicated that the target compounds possessed good to excellent activities against a broad spectrum of insects such as cotton bollworm (*H. armigera*), bean aphid (*A. craccivora*), mosquito (*C. pipiens pallens*), and spider mite (*T. cinnabarinus*). Although the acaricidal activity of these compounds was reduced significantly as compared with commercial insecticide tebufenpyrad, compounds containing α-chloromethyl-*N*-benzyl carboxamide and compounds containing 4,5-dihydrooxazole showed the high insecticidal activity against cotton bollworm. Especially, stomach activities against cotton bollworm of compounds **Ij**, **Il**, and **IIe** were 60% at 5.5 mg kg^{-1}, which was near to the activity of contrast tolfenpyrad. Moreover, the target compounds exhibited high selectivity between cotton bollworm and diamondback moth, both of which are of the order *Lepidoptera*. Although the activities against diamondback moth at a low level, it was found that compounds **Ie**, **If**, and **Ih** exhibited antifeedant activities. The foliar contact activity against bean aphid of compounds **Ic**, **Ie**, **Id**, **Ik**, **IIf**, **IIi**, and **Ill** were more than 90% at 200 mg/kg. The miticidal and ovicidal activities against spider mite of compound **IIi** were both 95% at 200 mg kg^{-1}, while compound **Ii** was inactive at 600 mg kg^{-1}. Just as we envisioned, a trivial change at 4-position of pyrazole ring would lead to great changes in activities.

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Funding

This work was supported by the National Key Project for Basic Research (2010CB126106), the National Natural Science Foundation of China (21072109), and the National Key Technology Research and Development Program (2011BAE06B05).

Notes

The authors declare no competing financial interest.

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