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Design, Synthesis, and Insecticidal Evaluation of New Pyrazole Derivatives Containing Imine, Oxime Ether, Oxime Ester, and Dihydroisoxazoline Groups Based on the Inhibitor Binding Pocket of Respiratory Complex I

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ABSTRACT: On the basis of complex I receptor protein binding site and commercial tebufenpyrad and tolfenpyrad, four series of novel pyrazole-5-carboxamides containing imine, oxime ether, oxime ester, and dihydroisoxazoline were designed and synthesized via the key intermediate 4-chloro-3-ethyl-*N*-(4-formylbenzyl)-1-methyl-1*H*-pyrazole-5-carboxamide. The structures of target compounds were confirmed by ^{1}H NMR and high-resolution mass spectrum (HRMS). The results of bioassays indicated that the target compounds possessed good-to-excellent activities against a broad spectrum of insects such as cotton bollworm (*Helicoverpa armigera*), spider mite (*Tetranychus cinnabarinus*), bean aphid (*Aphis craccivora*), and mosquito (*Culex pipiens pallens*), but gave different structure−activity relationships for each species. Compounds containing imine showed high insecticidal activity against cotton bollworm. Especially, stomach activity of compounds **5-1c** was 60% at 11 mg kg^{-1}. The compounds also had good activities against bean aphid and mosquito. The foliar contact activity of compounds **5-1a**, **5-1b**, **5-1e**, **5-3c**, and **5-3d** against bean aphid were 90, 100, 90, 90, and 90%, respectively, at 200 mg kg^{-1}. The activity of compound containing dihydroisoxazoline moiety (**5-4**) against mosquito was 60% at 1 mg kg^{-1}, which was near that of tebufenpyrad. The introduction of dihydroisoxazoline structure (**5-4**) was advantageous to improve the activity of the compound against adult mites compared with other structures; the miticidal activity of **5-4**− against adult mites was 60% at 50 mg kg^{-1}.

KEYWORDS: *pyrazole-5-carboxamide, complex I, imine, oxime ether, oxime ester, dihydroisoxazoline, insecticidal activity*

INTRODUCTION

Pyrazole-5-carboxamide derivatives such as tebufenpyrad and tolfenpyrad (Figure 1) are important kinds of mitochondrial respiration inhibitors, and they interrupt the mitochondrial electron transport by inhibition of NADH:ubiquinone oxidoreductase (complex I).[1] The difference between the two compounds is the substituent on the para position of the benzene ring, and the substituent plays a great role in regulating their activities. Usually, compounds possessing a large steric alkyl or aryl substituent on the benzene ring mainly exhibit acaricidal activity, whereas alkoxy- or phenoxy-substituted benzene derivatives mainly exhibit insecticidal activity.[2] A similar result was found in our previous work on the study of novel pyrazolecarboxamide derivatives and pyrazole derivatives containing 4,5-dihydrooxazole moieties.[3]

Complex I is the largest enzyme complex of the inner mitochondrial or bacterial plasma membrane. It transfers two electrons from NADH to ubiquinone and translocates four protons across the bioenergetic membrane.[4] The enzyme is L-shaped with a hydrophobic membrane embedded arm and a hydrophilic peripheral arm.[5] Fendel et al.[6] generated a large collection of site-directed mutants in the yeast *Yarrowia lipolytica*, which targeted the proposed inhibitor binding pocket of complex I, in 2008. They found that the various types of complex I inhibitors bind to partially overlapping sites in a single, large pocket. It is a rather wide opening that narrows to a gorge defined by two hydrophobic residues of the 49 kDa subunit and the PSST subunit. Therefore, we speculated that the introduction of a hydrophobic group other than *tert*-butyl and 4-methylphenoxy to the benzene ring was conducive to improving the interaction between molecules and binding pocket, thereby inhibiting the mitochondrial electron transport and increasing the insecticidal or acaricidal activity of the compound.

To verify our speculation, imine (**5-1a−e**), oxime ether (**5-2**), and oxime ester substructure (**5-3a−e**) were introduced to the para position of the benzene rings. These groups were commonly used in pesticide molecules optimizing physicochemical properties and enhancing the biological activity of compounds.[7] To further study the role of the substituents of benzene rings played in the biological activities, a compound containing a dihydroisoxazoline moiety was also synthesized (Scheme 1). The insecticidal and acaricidal activities of the target compounds against cotton bollworm (*Helicoverpa armigera*), spider mite (*Tetranychus cinnabarinus*), bean aphid (*Aphis craccivora*), and mosquito (*Culex pipiens pallens*) were tested, and the structure−activity relationship was 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

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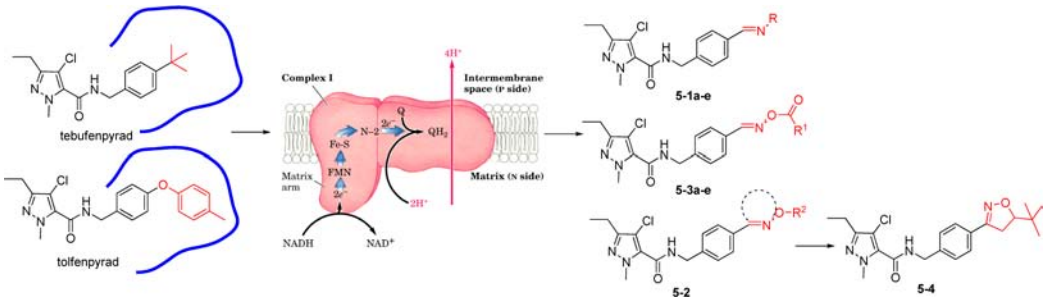
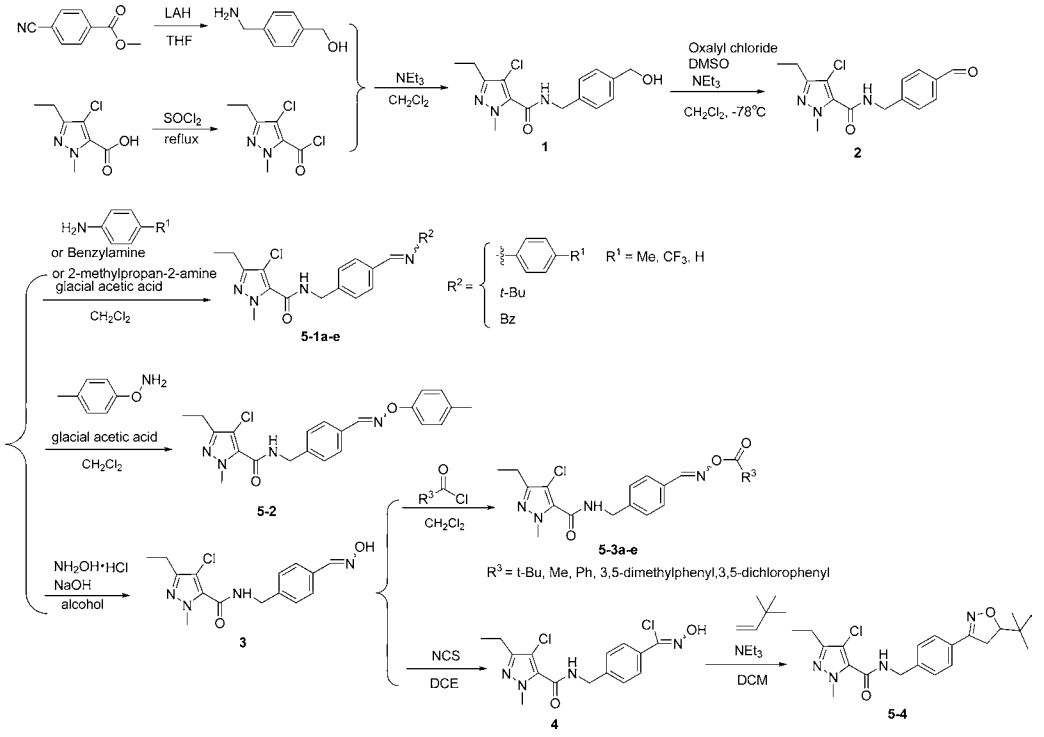


Figure 1. Design of target compounds (**5-1a−e**, **5-2**, **5-3a-e**, and **5-4**).

Scheme 1. General Synthetic Route for Target Compounds



tetramethylsilane as the internal standard. Chemical shift values (δ) are given in parts per million. 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 was synthesized according to a reported method.[3] The synthetic route is given in Scheme 1.

Synthesis of (4-(Aminomethyl)phenyl)methanol.[8] Methyl 4-cyanobenzoate (3.00 g, 18.6 mmol) was dissolved in dry THF (100 mL) and cooled to 0 °C. To the vigorously stirred solution was then slowly added $LiAlH_4$ (1.90 g, 50.0 mmol), leading to a change of color to blue/dark green and the formation of a slurry. The reaction mixture was refluxed for 12 h and then cooled to 0 °C, and H_2O (50 mL) was added slowly to quench unreacted $LiAlH_4$. The mixture was treated with aqueous NaOH (10%, 50 mL) and then extracted by ethyl acetate (40 mL × 5). The combined organic layers were washed twice with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness in vacuo, yielding (4-(aminomethyl)phenyl)methanol as a white solid (1.80 g, 71%): mp = 80−82 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.26 (d, J_{HH} = 8.4 Hz, 2H, Ar−H), 7.23 (d, J_{HH} = 8.0 Hz, 2H, Ar−H), 5.11 (br, 2H, NH_2), 4.46 (s, 2H, CH_2OH), 3.68 (s, 2H, CH_2NH_2), 1.81 (br, 1H, OH).

Synthesis of 4-Chloro-3-ethyl-*N*-(4-(hydroxymethyl)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (1). A mixture of 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid (0.62 g, 3.28 mmol) and thionyl chloride (0.78 g, 6.56 mmol) 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 dichloromethane (10 mL). The obtained solution was added dropwise to a dichloromethane (30 mL) solution of (4-(aminomethyl)phenyl)methanol (0.45 g, 3.28 mmol) and triethylamine (0.50 g, 4.92 mmol) at −5 °C. The mixture was stirred at −5 °C for 8 h, then poured into ice water (40 mL), extracted with dichloromethane (30 mL × 3), and dried over anhydrous Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by recrystallization using ethyl acetate and dichloromethane to give **1** as a pale-yellow solid (0.87 g, 86%): mp = 123−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.39 (m, 4H, Ar−H), 7.03 (br, 1H, NH), 4.71 (d, J_{HH} = 5.6 Hz, 2H, CH_2OH), 4.64 (d, J_{HH} = 5.6 Hz, 2H, CH_2NH), 4.42 (s, 3H, pyrazole-Me), 2.63 (q, J_{HH} = 7.6 Hz, 2H, CH_2CH_3), 1.24 (t, J_{HH} = 7.6 Hz, 3H, CH_2CH_3).

Synthesis of 4-Chloro-3-ethyl-*N*-(4-formylbenzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (2).[9] To the solution of oxalyl chloride (1.56 g, 12.28 mmol) in dichloromethane (20 mL) was added dimethyl sulfoxide (1.60 g, 20.47 mmol) in dichloromethane (10 mL) dropwise under a nitrogen atmosphere at −78 °C. After 0.5 h, **1** (0.63 g, 2.05 mmol) in dichloromethane (20 mL) was added

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dropwise, and after the mixture was stirred for 1 h, triethylamine (2.27 g, 22.52 mmol) was added. The reaction mixture was stirred for 8 h in the temperature range from −78 °C to room temperature, then water (20 mL) was then added, and the aqueous layer was extracted with dichloromethane (40 mL × 2). The combined organic phase was washed with brine (40 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 = 3:1) as eluent to give **2** as white solid (0.54 g, 86%): mp = 128−129 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H, aldehyde−H), 9.05 (t, 1H, J_{HH} = 6.4 Hz, N**H**CH$_2$), 7.90 (d, 2H, J_{HH} = 8.0 Hz, Ar−H), 7.57 (d, 2H, J_{HH} = 8.0 Hz, Ar−H), 4.57 (d, 2H, J_{HH} = 5.6 Hz, C**H**$_2$NH), 3.85 (s, 3H, pyrazole-Me), 2.55 (q, 2H, J_{HH} = 7.6 Hz, C**H**$_2$CH$_3$), 1.17 (t, 3 H, J_{HH} = 7.6 Hz, CH$_2$C**H**$_3$).

Synthesis of 4-Chloro-3-ethyl-1-methyl-*N*-(4-((*p*-tolylimino)-methyl)benzyl)-1*H*-pyrazole-5-carboxamide (5-1a).[10] To a solution of **2** (0.5 g, 1.64 mmol) and glacial acetic acid (0.08 g) in dichloromethane (40 mL) was added *p*-toluidine (0.22 g, 2.06 mmol) in dichloromethane (8 mL) dropwise, and the mixture was stirred at room temperature until TLC indicated the reaction was completed. Water (50 mL) was added, and the aqueous layer was extracted with dichloromethane (30 mL × 3). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo, and the residue was purified by recrystallization using ethanol to give the title compound as a white solid (0.50 g, 77%): mp = 138−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H, CHN), 7.90 (d, J_{HH} = 8.0 Hz, 2H, Ar−H), 7.46 (d, J_{HH} = 8.4 Hz, 2H, Ar−H), 7.20 (d, J_{HH} = 8.0 Hz, 2H, Ar−H), 7.14 (d, J_{HH} = 8.0 Hz, 2H, Ar−H), 7.09 (br, 1H, NH), 4.70 (d, J_{HH} = 6.4 Hz, 2H, C**H**$_2$NH), 4.15 (s, 3H, pyrazole−Me), 2.64 (q, J_{HH} = 7.6 Hz, 2H, C**H**$_2$CH$_3$), 2.37 (s, 3H, Ar−Me), 1.25 (t, J_{HH} = 7.6 Hz, 3H, CH$_2$C**H**$_3$); HRMS (ESI+) *m*/*z* calcd for $C_{22}H_{24}ClN_4O^+$ 395.1633 [M + H] $^+$, found 395.1634.

Compounds **5-1b−e** were synthesized using aldehyde **2** and corresponding substituted amine according to the same procedure as **5-1a**.

*4-Chloro-3-ethyl-1-methyl-N-(4-((4-(trifluoromethyl)-phenylimino)methyl)benzyl)-1H-pyrazole-5-carboxamide (**5-1b**).* This compound was obtained as a white solid in 68% yield: mp = 135−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H, CHN), 7.91 (d, J_{HH} = 8.0 Hz, 2H, Ar−H), 7.65 (d, J_{HH} = 8.0 Hz, 2H, Ar−H), 7.49 (d, J_{HH} = 7.6 Hz, 2H, Ar−H), 7.25 (d, J_{HH} = 8.0 Hz, 2H, Ar−H), 7.13 (br, 1H, NH), 4.72 (d, J_{HH} = 6.4 Hz, 2H, C**H**$_2$NH), 4.16 (s, 3H, pyrazole−Me), 2.65 (q, J_{HH} = 7.6 Hz, 2H, C**H**$_2$CH$_3$), 1.25 (t, J = 7.6 Hz, 3H, CH$_2$C**H**$_3$); HRMS (ESI+) *m*/*z* calcd for $C_{22}H_{21}ClF_3N_4O^+$ 449.1351 [M + H] $^+$, found 449.1354.

*4-Chloro-3-ethyl-1-methyl-N-(4-((phenylimino)methyl)benzyl)-1H-pyrazole-5-carboxamide (**5-1c**).* This compound was obtained as a white solid in 88% yield: mp = 104−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H, CHN), 7.91 (d, J_{HH} = 8.0 Hz, 2H, Ar−H), 7.47 (d, J_{HH} = 8.0 Hz, 2H, Ar−H), 7.40 (t, J_{HH} = 8.0 Hz, 2H, Ar−H), 7.21−7.24 (m, 3H, Ar−H), 7.10 (br, 1H, NH), 4.71 (d, J_{HH} = 6.0 Hz, 2H, C**H**$_2$NH), 4.16 (s, 3H, pyrazole−Me), 2.64 (q, J_{HH} = 7.6 Hz, 2H, C**H**$_2$CH$_3$), 1.25 (t, J_{HH} = 7.6 Hz, 3H, CH$_2$C**H**$_3$); HRMS (ESI+) *m*/*z* calcd for $C_{21}H_{21}ClN_4ONa^+$ 403.1296 [M + Na] $^+$, found 403.1294.

*N-(4-((tert-Butylimino)methyl)benzyl)-4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (**5-1d**).* This compound was obtained as a white solid in 76% yield: mp = 90−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H, CHN), 7.75 (d, J_{HH} = 8.0 Hz, 2H, Ar−H), 7.39 (d, J_{HH} = 8.0 Hz, 2H, Ar−H),7.02 (br, 1H, NH), 4.66 (d, J_{HH} = 6.4 Hz, 2H, C**H**$_2$NH), 4.15 (s, 3H, pyrazole−Me), 2.63 (q, J_{HH} = 7.6 Hz, 2H, C**H**$_2$CH$_3$), 1.29 (s, 9H, t-Bu), 1.24 (t, J_{HH} = 7.6 Hz, 3H, CH$_2$C**H**$_3$); HRMS (ESI+) *m*/*z* calcd for $C_{19}H_{26}ClN_4O^+$ 361.1790 [M + H] $^+$, found 361.1795.

*N-(4-((Benzylimino)methyl)benzyl)-4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (**5-1e**).* This compound was obtained as a white solid in 92% yield: mp = 116−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H, CHN), 7.78 (d, J_{HH} = 8.4 Hz, 2H, Ar−H), 7.40 (d, J_{HH} = 8.0 Hz, 2H, Ar−H), 7.32−7.37 (m, 3H, Ar−H), 7.25−7.28 (m, 2H, Ar−H), 7.06 (br, 1H, NH), 4.83 (s, 2H, CH$_2$Ar), 4.67 (d, J_{HH} = 6.0 Hz, 2H, C**H**$_2$NH), 4.15 (s, 3H, pyrazole−Me), 2.63 (q, J_{HH} = 7.6 Hz, 2H, C**H**$_2$CH$_3$), 1.24 (t, J_{HH} = 7.6 Hz, 3H, CH$_2$C**H**$_3$); HRMS (ESI+) *m*/*z* calcd for $C_{22}H_{24}ClN_4O^+$ 395.1633 [M + H] $^+$, found 395.1635.

Synthesis of 4-Chloro-3-ethyl-1-methyl-*N*-(4-((*p*-tolyloxyimino)methyl)benzyl)-1*H*-pyrazole-5-carboxamide (5-2). To a mixture of **2** (0.5 g, 1.64 mmol) and glacial acetic acid (0.05 g) in dichloromethane was added dropwise *O*-*p*-tolylhydroxylamine (0.24 g, 1.96 mmol), and the mixture was stirred at room temperature until TLC indicated consumption of the substrate. Water (30 mL) was added to the mixture, and the aqueous layer was extracted with dichloromethane (20 mL × 3); the combined organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo, and the residue was purified by flash chromatography on silica gel using petroleum ether (60−90 °C) and ethyl acetate (v/v = 5:1) as eluent to give **5-2** as a white solid (0.27 g, 40%): mp = 121−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 and 8.39 (s, 1H, CHN), 7.71 and 8.00 (d, J_{HH} = 8.4 Hz, 2H, Ar−H), 7.41 and 7.46 (d, J_{HH} = 8.4 Hz, 2H, Ar−H), 7.09−7.19 (m, 5H, Ar−H and NH), 4.68 (d, J_{HH} = 6.0 Hz, 2H, C**H**$_2$NH), 4.15 (s, 3H, pyrazole−Me), 2.64 (q, J_{HH} = 7.6 Hz, 2H, C**H**$_2$CH$_3$), 2.33 (s, 3H, Ar−Me), 1.24 (t, J_{HH} = 7.6 Hz, 3H, CH$_2$C**H**$_3$); HRMS (ESI+) *m*/*z* calcd for $C_{22}H_{23}ClN_4NaO_2^+$ 433.1402 [M + Na] $^+$, found 433.1405.

Synthesis of 4-Chloro-3-ethyl-*N*-(4-((hydroxyimino)methyl)-benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (3).[11] To a solution of **2** (0.52 g, 1.70 mmol) in ethanol was added hydroxyamine hydrochloride (0.14 g, 2.04 mmol), and the mixture was heated under reflux for 4 h and then cooled. The precipitated solid was collected by filtration as **3** to give a white solid (0.49 g, 90%): mp = 178−179 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ11.20 and 11.21(s, 1H, OH), 8.96−8.97 (m, 1H, NH), 8.12 and 8.13 (s, 1H, CHN), 7.57 and 7.58 (d, 2H, J_{HH} = 7.6 Hz, Ar−H), 7.37 and 7.38 (d, 2H, J_{HH} = 7.6 Hz, Ar−H), 4.48−4.50 (m, 2H, C**H**$_2$NH), 3.84 and 3.85 (s, 3H, pyrazole−Me), 2.55 and 2.56 (q, 2H, J_{HH} = 7.6 Hz, C**H**$_2$CH$_3$), 1.17 and 1.18 (t, 3H, J_{HH} = 7.6 Hz, CH$_2$C**H**$_3$).

Synthesis of 4-Chloro-3-ethyl-1-methyl-*N*-(4-((pivaloyloxyimino)methyl)benzyl)-1*H*-pyrazole-5-carboxamide (5-3a).[12] To a mixture of **3** (0.28 g, 0.87 mmol) and triethylamine (0.1 g, 1.05 mmol) in dichloromethane (50 mL) was added pivaloyl chloride (0.11 g, 0.87 mmol) dropwise at 0 °C, and then the reaction mixture was warmed to room temperature and stirred overnight. Water (30 mL) was added to the mixture, and the aqueous layer was extracted with dichloromethane (20 mL × 3). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo, and the residue was purified by flash chromatography on silica gel using petroleum ether (60−90 °C) and ethyl acetate (v/v = 5:1) as eluent to give **5-3a** as a white solid (0.34 g, 97%): mp = 74−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H, CHN), 7.75 (d, J_{HH} = 8.0 Hz, 2H, Ar−H), 7.42 (d, J_{HH} = 8.0 Hz, 2H, Ar−H), 7.11 (t, J_{HH} = 6.0 Hz, 1H, NH), 4.68 (d, J_{HH} = 6.0 Hz, 2H, C**H**$_2$NH), 4.14 (s, 3H, pyrazole−Me), 2.64 (q, J_{HH} = 7.6 Hz, 2H, C**H**$_2$CH$_3$), 1.32 (s, 9H, t-Bu), 1.24 (t, J_{HH} = 7.6 Hz, 3H, CH$_2$C**H**$_3$); HRMS (ESI+) *m*/*z* calcd for $C_{20}H_{25}ClN_4NaO_3^+$ 427.1507 [M + Na] $^+$, found 427.1508.

Compounds **5-3b−e** were synthesized using oxime and the corresponding acyl chloride according to the same procedure as **5-3a**.

*N-(4-((Acetoxyimino)methyl)benzyl)-4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (**5-3b**).* This compound was obtained as a white solid in 78% yield: mp = 126−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H, CHN), 7.76 (d, J_{HH} = 8.0 Hz, 2H, Ar−H), 7.44 (d, J_{HH} = 8.0 Hz, 2H, Ar−H), 7.12 (br, 1H, NH), 4.71 (d, J_{HH} = 5.6 Hz, 2H, C**H**$_2$NH), 4.17 (s, 3H, pyrazole−Me), 2.64 (q, J_{HH} = 7.6 Hz, 2H, C**H**$_2$CH$_3$), 2.26 (s, 3H, CH$_3$), 1.27 (t, J_{HH} = 7.6 Hz, 3H, CH$_2$C**H**$_3$); HRMS (ESI+) *m*/*z* calcd for $C_{17}H_{19}ClN_4NaO_3^+$ 385.1038 [M + Na] $^+$, found 385.1033.

*N-(4-((Benzoyloxyimino)methyl)benzyl)-4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (**5-3c**).* This compound was obtained as a white solid in 90% yield: mp = 148−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H, CHN), 8.14 (d, J_{HH} = 7.6 Hz, 2H, Ar−H), 7.82 (d, J_{HH} = 7.6 Hz, 2H, Ar−H), 7.61−7.64 (m, 1H, Ar−H), 7.44−7.52 (m, 4H, Ar−H), 7.12 (t, J_{HH} = 5.6 Hz, 1H, NH), 4.70 (d, J_{HH} = 6.0 Hz, 2H, C**H**$_2$NH), 4.15 (s, 3H, pyrazole−Me), 2.65 (q, J_{HH} = 7.6 Hz, 2H,

Scheme 2

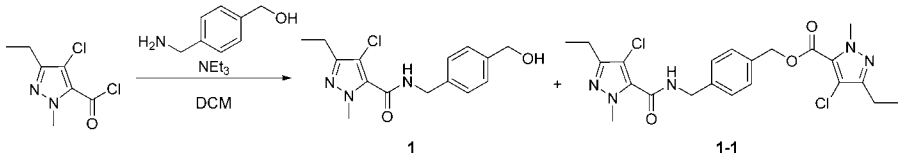

Table 1. Stomach Activities against Cotton Bollworm (*H. armigera*)

	larvicidal activity[a] (%) at concn of				
compd	110 (mg kg^{-1})	55 (mg kg^{-1})	22 (mg kg^{-1})	11 (mg kg^{-1})	5.5 (mg kg^{-1})
tollfenpyrad	100	100	100	100	70
5-1a	100	100	70	30	–
5-1b	100	100	70	10	–
5-1c	100	100	90	60	30
5-1d	100	100	70	10	–
5-1e	100	100	90	40	–
5-2	100	60	–		
5-3a	100	30	–		
5-3b	100	0			
5-3c	100	30	–		
5-3d	100	10	–		
5-3e	100	20	–		
5-4	100	40	–		

[a]–, not tested.

CH_2CH_3), 1.25 (t, J_{HH} = 7.6 Hz, 3H, CH_2CH_3); HRMS (ESI+) *m*/*z* calcd for $C_{22}H_{21}ClN_4NaO_3^+$ 447.1194 [M + Na] $^+$, found 447.1198.

*4-Chloro-N-(4-((3,5-dimethylbenzoyloxyimino)methyl)benzyl)-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (**5-3d**).* This compound was obtained as a white solid in 90% yield: mp = 143−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H, CHN), 7.82 (d, J_{HH} = 8.4 Hz, 2H, Ar−H), 7.75 (s, 2H, Ar−H), 7.45 (d, J_{HH} = 8.4 Hz, 2H, Ar−H), 7.25 (s, 1H, Ar−H), 7.11 (t, J_{HH} = 5.6 Hz, 1H, NH), 4.70 (d, J = 6.0 Hz, 2H, CH_2NH), 4.15 (s, 3H, pyrazole−Me), 2.39 (s, 6H, Ar−Me), 2.65 (q, J_{HH} = 7.6 Hz, 2H, CH_2CH_3), 1.25 (t, J_{HH} = 7.6 Hz, 3H, CH_2CH_3); HRMS (ESI+) *m*/*z* calcd for $C_{24}H_{25}ClN_4NaO_3^+$ 475.1507 [M + Na] $^+$, found 475.1510.

*4-Chloro-N-(4-((3,5-dichlorobenzoyloxyimino)methyl)benzyl)-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (**5-3e**).* This compound was obtained as a white solid in 95% yield: mp = 174−176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59(s, 1H, CHN), 8.03 (d, J_{HH} = 2.0 Hz, 2H, Ar−H), 7.63 (t, J_{HH} = 2.0 Hz, 1H, Ar−H), 7.83 (d, J_{HH} = 8.4 Hz, 2H, Ar−H), 7.48 (d, J_{HH} = 8.4 Hz, 2H, Ar−H), 7.15 (t, J_{HH} = 5.6 Hz, 1H, NH), 4.73 (d, J_{HH} = 5.6 Hz, 2H, CH_2NH), 4.17 (s, 3H, pyrazole−Me), 2.67 (q, J_{HH} = 7.6 Hz, 2H, CH_2CH_3), 1.27 (t, J_{HH} = 7.6 Hz, 3H, CH_2CH_3); HRMS (ESI+) *m*/*z* calcd for $C_{22}H_{19}Cl_3N_4NaO_3^+$ 515.0415 [M + Na] $^+$, found 515.0410.

Synthesis of 4-((4-Chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamido)methyl)-*N*-hydroxybenzimidoyl Chloride (4) and *N*-(4-(5-*tert*-Butyl-4,5-dihydroisoxazol-3-yl)benzyl)-4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (5-4).[7] To a mixture of **3** (0.15 g, 0.47 mmol) and isopropanol (5 mL) in 1,2-dichloroethane was added two drops of pyridine. After 5 min, *N*-bromosuccinimide (0.062 g, 0.47 mmol) was added in portions. The mixture was stirred overnight at room temperature until TLC indicated the end of the reaction and then concentrated in vacuo to give **4** as a white solid (0.19 g, 0.54 mmol), which was used in the next reaction without further purification. To the solution of **4** in dichloromethane (20 mL) was added 3,3-dimethylbut-1-ene (0.05 g, 0.64 mmol), and then a solution of triethylamine (0.07 g, 0.64 mmol) in dichloromethane (50 mL) was added dropwise under −10 °C. The mixture was warmed to room temperature and stirred overnight. At the end of reaction it was successively washed with diluted hydrochloric acid (20 mL of 5%, v/v) and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using petroleum ether (60−90 °C) and ethyl acetate (v/v = 5:1) as eluent to give **5-4** as a white solid (0.073 g, 36%): mp = 74−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J_{HH} = 8.4 Hz, 2H, Ar−H), 7.39 (d, J_{HH} = 8.4 Hz, 2H, Ar−H), 7.09 (br, 1H, NH), 4.66 (d, J_{HH} = 6 Hz, 2H, $NHCH_2$), 4.46 (dd, J_{HH} = 10.8 Hz, J_{HH} = 9.6 Hz, 1H, OCH), 4.14 (s, 3H, pyrazole−Me), 3.22(dd, J_{HH} = 11.2 Hz, J_{HH} = 17.2 Hz, 1H, $NCCH_2$), 3.07 (dd, J_{HH} = 9.2 Hz, J_{HH} = 16.8 Hz, 1H, $NCCH_2$), 2.63 (q, J_{HH} = 7.6 Hz, 2H, CH_2CH_3), 1.24 (t, J_{HH} = 7.6 Hz, 3H, CH_2CH_3), 0.97 (s, 9H, t-Bu); HRMS (ESI+) *m*/*z* calcd for $C_{21}H_{27}ClN_4NaO_2^+$ 425.1715 [M + Na] $^+$, found 425.1718.

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.

The stomach toxicities of the target compounds **5-1a−e**, **5-2**, **5-3a−e**, and **5-4** against cotton bollworm (*H. armigera*) were tested by the diet−corporate method.[14]

The acaricidal activities against adults, eggs, and larvae of spider mite (*T. cinnabarinus* Boisduval)[15] and the foliar contact activity against bean aphid (*A. craccivora*)[16] were both evaluated by the leaf dip method using reported procedures.

Toxicities against mosquito (*C. pipiens pallens*) were evaluated according to the reported procedure.[17]

RESULTS AND DISCUSSION

Synthesis. The key intermediate aldehyde **2** was obtained through Swern oxidation of benzyl alcohol **1**, which was prepared from the amidation of 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carbonyl chloride[3] and (4-(aminomethyl)phenyl)-methanol.[8] **2** reacted with corresponding amines to give imine compounds **5-1a−e** using acetic acid as catalyst. The compound containing oxime ether structure **5-2** was obtained when **2** reacted with a substituted hydroxylamine. **2** reacted with hydroxylamine hydrochloride to give intermediate **3** and

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Table 2. Acaricidal Activities against Spider Mite (*T. cinnabarinus* Boisduval) Eggs, Larvae, and Adults of Compounds and Tebufenpyrad

	activity[a] (%) at concn of									
	eggs			larvae			adults			
compd	600 (mg kg^{-1})	200 (mg kg^{-1})	100 (mg kg^{-1})	600 (mg kg^{-1})	200 (mg kg^{-1})	100 (mg kg^{-1})	600 (mg kg^{-1})	200 (mg kg^{-1})	100 (mg kg^{-1})	50 (mg kg^{-1})
tebufenpyrad	100	100	100	100	100	100	100	100	100	100
5-1a	80	60	40	80	50	–	0			
5-1b	50	10	–	90	60	40	10	–		
5-1c	40	–		70	–		100	100	70	40
5-1d	0			80	60	30	30	–		
5-1e	0			30	–		0			
5-2	70	60	50	50	30		0			
5-3a	60	–		20	–		30	–		
5-3b	60	–		20	–		30	–		
5-3c	20	–		40	20	–	20	–		
5-3d	70	–		0			0			
5-3e	0			0			0			
5-4	100	40	–	100	80	50	100	100	100	60

[a] –, not tested.

then reacted with an acid chloride to give the compounds containing oxime ester structure **5-3a–e**. **3** reacted with *N*-chlorosuccinimide in alkaline condition to give intermediate **4**, which was reacted with an olefin to give compound **5-4** via a [3 + 2] dipolar cyclization (Scheme 1).

In the process of preparing compound **1**, when acyl chloride (1 equiv) reacted with (4-(aminomethyl)phenyl)methanol (1 equiv) at −5 °C for 1 h and then at room temperature overnight, in addition to the target compound, **1**, a byproduct, 4-((4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamido)-methyl)benzyl 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylate (**1-1**), was also obtained (Scheme 2). We assumed that because of the poor solubility of (4-(aminomethyl)-phenyl)methanol in dichloromethane, the acyl chloride was temporarily excess in solution, and then the excess acyl chloride was further reacted with the hydroxyl group in compound **1**. To minimize the formation of byproduct, when we repeated the reaction, the concentration of the reaction solution was lowered, the time of the addition of acyl chloride was extended to 6 h, and the temperature was maintained under 0 °C.

Bioassays. Stomach Activities against Cotton Bollworm (*H. armigera*). Table 1 shows the stomach activities of the target compounds and the contrast tolfenpyrad against lepidopteron cotton bollworm. The results indicated that all of the compounds had 100% inhibitory effect at 110 mg kg^{-1}. At reduced dosages, the compounds containing imine structure (**5-1a–e**) still exhibited good to excellent inhibitory reactivity. The substituents on the imine also had an impact on the activities, as the compound with phenyl (**5-1c**) was better than a substituted phenyl (**5-1a** and **5-1b**) or other substituents (**5-1d** and **5-1e**). When the imine structure was changed to oxime ether (**5-2**) and oxime ester (**5-3a–e** and **5-4**), the activities of these compounds were decreased significantly; these oxime ether (**5-2**) and oxime ester (**5-3a–e** and **5-4**) compounds did not demonstrate 100% inhibitory effect against cotton bollworm at 55 mg kg^{-1}.

Acaricidal Activities against Spider Mite (*T. cinnabarinus*) Eggs, Larvae, and Adults. Table 2 shows the acaricidal activities against spider mite eggs, larvvae, and adults. The activities of the target compounds were lower than that of tebufenpyrad, which suggested that the changes on the para position of the benzene rings were detrimental to the acaricidal activity. Nevertheless, these data provided us with very valuable information. To the imide structure-containing compounds was exhibited better activity against adult mites, 40% at 50 mg kg^{-1}, when the substituents on the nitrogen was phenyl (**5-1c**). Substituted phenyl was adverse to the activity of acaricidal activities (compounds **5-1a** and **5-1b**), but the introduction of a methyl group on the benzene ring (**5-1a**) was advantageous to improve the activity against acaricidal eggs. Compound **5-2** mainly exhibited activity against eggs; the activity of **5-2** against eggs was 50% at 100 mg kg^{-1}. The introduction of dihydroisoxazoline structure (**5-4**) was advantageous to improve the activity of the compound against adult mites compared with other structures. For instance, the activity of **5-4** against adult mites was 60% at 50 mg kg^{-1}, whereas the compounds containing oxime ether structure (**5-2**) had no activity at 600 mg kg^{-1}.

Foliar Contact Activities against Bean Aphid (*A. craccivora*). Table 3 shows the foliar contact activities of the target compounds and contrast tebufenpyrad. All of the

Table 3. Foliar Contact Activities against Bean Aphid (*A. craccivora*) of Compounds

	larvicidal activity[a] (%) at concn		
compd	600 (mg kg^{-1})	200 (mg kg^{-1})	100 (mg kg^{-1})
tebufenpyrad	100	100	100
5-1a	100	90	70
5-1b	100	100	30
5-1c	100	30	–
5-1d	100	85	40
5-1e	100	90	60
5-2	100	75	30
5-3a	100	50	–
5-3b	0		
5-3c	100	90	50
5-3d	100	90	60
5-3e	100	85	40
5-4	100	40	–

[a] –, not tested.

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compounds had 100% inhibitory effect at 600 mg kg^{-1} except compound **5-3b**. In general, the activities of the compounds (**5-1a−e**) containing imine structures were better than those of the compounds containing oxime ether (**5-2**) and oxime ester (**5-3a−e**). The substituents on the imine also had an impact on the activities; the phenyl bearing electron-donating group (**5-1a**) and benzyl (**5-1e**) were more favorable to the insecticidal activities than other substituents. The compounds bearing benzoyl oxime structure (**5-3c**) exhibited 50% activity at 100 mg kg^{-1}, which was higher than the activities of those bearing pivaloyl (**5-3a**) and acetyl (**5-3b**). The substituent on the benzoyl had no obvious effect on the activity (compounds **5-3d** and **5-3e**).

Toxicity against Mosquito (*C. pipiens pallens*). Table 4 shows the larvacidal activities of the target compounds and the

Table 4. Larvacidal Activities against Mosquito (*C. pipiens pallens*) of Compounds

	larvicidal activity[a] (%) at concn of		
compd	5 (mg kg^{-1})	2 (mg kg^{-1})	1 (mg kg^{-1})
tebufenpyrad	100	100	70
5-1a	50	–	
5-1b	20	–	
5-1c	20	–	
5-1d	30	–	
5-1e	60	–	
5-2	50	–	
5-3a	40	–	
5-3b	70	–	
5-3c	80	–	
5-3c	100	100	30
5-3e	100	100	40
5-4	100	100	60

[a]–, not tested.

contrast tebufenpyrad against mosquito. Of the oxime ester compounds, it was advantageous to increase the activity when substituents were introduced on the phenyl ring. For instance, the activities of **5-3d** (containing 3,5-dimethylphenyl) and **5-3e** (containing 3,5-dichlorophenyl) were 30 and 40%, respectively at 1 mg kg^{-1}, whereas **5-3c** (containing phenyl) exhibited no activity at 2 mg kg^{-1}. The compound containing the dihydroisoxazoline moiety (**5-4**) exhibited a higher activity than the compound containing an oxime ester moiety. The activity of **5-4** was 60% at 1 mg kg^{-1}, which was near that of tebufenpyrad. This suggested that the dihydroisoxazoline moiety on the benzene ring was beneficial to the activity against mosquito larvae.

In summary, to adjust the hydrophobicity of molecular and thus improve the interaction with the receptor binding site of complex I, and to inhibit the electron transfer process of respiration, a series of novel pyrazoles containing imine, oxime ether, oxime ester, and dihydroisoxazoline moieties were designed and evaluated for their insecticidal and acaricidal activities. 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*), spider mite (*T. cinnabarinus*), bean aphid (*A. craccivora*), and mosquito (*C. pipiens pallens*), but gave different structure−activity relationships for each species. Although the acaricidal activity of these compounds was reduced significantly as compared with commercial insecticide tebufenpyrad, compounds containing imine showed high insecticidal activity against cotton bollworm. Especially, stomach activity against cotton bollworm of compounds **5-1c** containing phenyl imine moiety was 30% at 5.5 mg kg^{-1}, which was near the activity of contrast tolfenpyrad. The foliar contact activities against bean aphid of imine compounds (**5-1**) and oxime ester compounds (**5-3**) were relatively higher than the others. Compound **5-4**, containing a dihydroisoxazoline moiety, gave 60% inhibition at 50 mg kg^{-1} against spider mite adults. It also exhibited good activities against mosquito (60% at 1 mg kg^{-1}), which was near that of tebufenpyrad (70% at 1 mg kg^{-1}). The experimental data above preliminarily proved the rationality of our speculation and design ideology.

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Notes

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