JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Synthesis and Insecticidal Activity of *N*-Substituted (1,3-Thiazole)alkyl Sulfoximine Derivatives

HAIBO YU, ZHENFANG QIN, HONG DAI, XIN ZHANG, XUE QIN, TINGTING WANG, AND JIANXIN FANG*

State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry and Tianjin Key Laboratory of Pesticide Science, Nankai University, Tianjin 300071, People's Republic of China

The *N*-substituted alkyl sulfoximine derivatives are a new chemical family of neonicotinoid insecticides. We have designed and synthesized 10 (1,3-thiazole)alkyl sulfoximine derivatives. All compounds were identified by ^{1}H and ^{13}C nuclear magnetic resonance (NMR), IR, and elemental analyses. Preliminary bioassays indicated that some title compounds exhibited good insecticidal activities at 10 mg/L against *Myzus persicae*. The relationship between structure and biological activity was also discussed.

KEYWORDS: Sulfoximine derivatives; bioisosterism; synthesis; insecticidal activity; pharmacophore; peach aphid

INTRODUCTION

Since the introduction of midacloprid (**1a**) in the 1980s as an insecticide for crop protection (*1*), neonicotinoid insecticides have been rapidly developed worldwide for controlling insects because of their high potency, low mammalian toxicity, broad insecticidal spectra, and good systemic properties. Neonicotinoids, which interact with nicotinic acetylcholine receptors (nAChR), have a higher affinity for the insect receptor than for the mammalian receptor (*2*−*5*) and are relatively safe toward mammals and aquatic life. Imidacloprid was the first major active ingredient of the neonicotinoid class to reach market. Research on molecules with a similar structure containing the 6-chloro-3-pyridylmethyl moiety led to acetamiprid (**1b**), nitenpyram (**1c**), and thiacloprid (**1d**). The substitution of the chloropyridyl moiety by a chlorothiazolyl group resulted in second-generation neonicotinoid insecticides, including clothianidin (**1e**) and thiamethoxam (**1f**) (**Figure 1**) (*6*).

The development of resistance to insecticide in insect populations is a well-recognized phenomenon, and there are well-documented cases of resistance for the major classes of insecticides. Although the neonicotinoids have proven relatively resilient to the development of resistance, stronger resistance has been confirmed in some populations of the whitefly, *Bemisa tabaci*, and the Colorado potato beetle, *Leptinotarsa decemlineata*. During the late 1990s, resistant species increased in potency, with more recently collected strains of this whitefly exhibiting more than 100-fold resistance to imidacloprid and comparable levels of resistance to thiamethoxam and acetamiprid (*7*−*9*). Historically, the problem of insect resistance to insecticides was tackled by continuously introducing new active ingredients to replace ones lost through resistance. Therefore, new insecticides that lack cross-resistance to currently available insecticides are imminent.

N-Substituted (pyridyl)alkyl sulfoximine derivatives (**2a**−**d**) (**Figure 2**) were described by Dow AgroSciences (*10*−*13*). It has been reported that these compounds lack cross-resistance on insect pests that have developed resistance to one ore more classes of insecticides, including imidacloprid and other neonicotinoids (*14*). The thiazole group can be taken as a bioisostere of the pyridine. Hence, when the thiazolyl group was used to replace pyridyl, a series of novel *N*-substituted (1,3-thiazolyl-5-yl)alkyl sulfoximine derivatives were designed and synthesized. This paper describes the syntheses and bioactivities. The relationship between structure and biological activity was also discussed.

MATERIALS AND METHODS

Synthetic Procedures. Melting points were measured using a RY-1 melting-point apparatus (TaiKe Co.) and are uncorrected. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker-300 (Bruker Co.) spectrometer using tetramethylsilane (TMS) as an internal reference. Chemical-shift values (δ) were given in parts per million (ppm). Infrared spectra were obtained on a Bio-Rad spectrophotometer (Bio-Rad Co.) using potassium bromide pellets or neat oils and are reported as wavenumbers (cm^{-1}). Mass spectra [gas chromatography−mass spectrometry (GC−MS)] were obtained on an Agilent 6890-5973 instrument (Agilent Co.). Elemental analysis was performed on a Yanaco Corder MT-3 (Yanaco Co. Ltd.) elemental analyzer. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F_{254}), and spots were visualized with ultraviolet (UV) light. The reference compound **2a** (98%) was provided by Mrs. Aiying Guan. Cyanamide (98%), iodobenzene diacetate (98%), and 3-chloroperoxy-benzoid acid (85%) were obtained from Sigma (St. Louis, MO). The solvents [dichloromethane (99%), ethanol (99%), and methanol (99%)] were used directly without further purification.

General Procedure for the Preparation of Methyl (1,3-Thiazole-5-yl)methyl Sulfide. To a solution of 5-halomethyl-1,3-thiazole (10

* To whom correspondence should be addressed. E-mail: fjx@nankai.edu.cn.

10.1021/jf802802g CCC: $40.75
Published on Web 11/14/2008

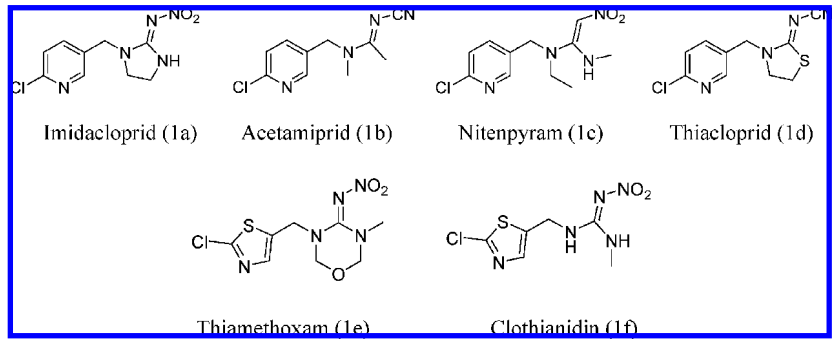


Figure 1. Commercial neonicotinoids.

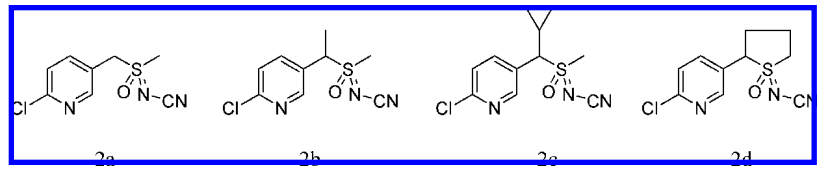
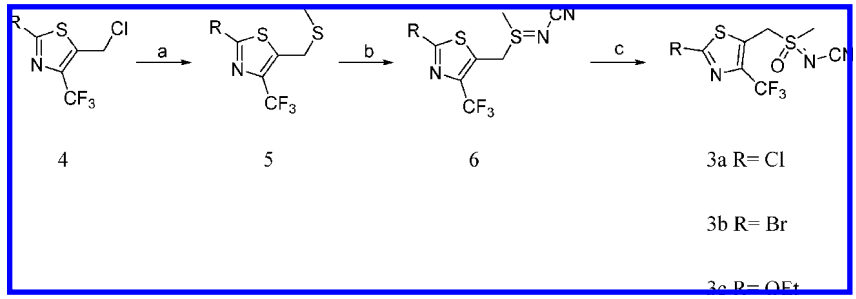


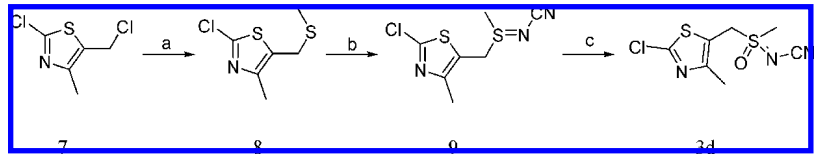
Figure 2. Chemical structure of *N*-substituted (pyridyl)alkyl sulfoximine derivatives.

Scheme 1[a]



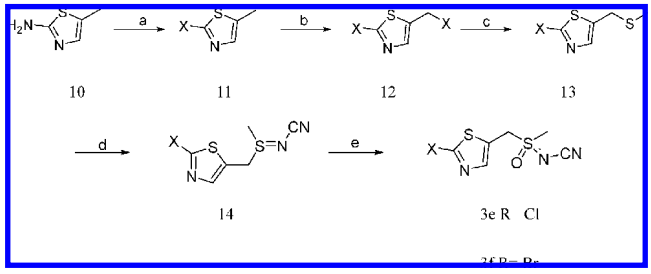
[a] Reagents and conditions: (a) MeSNa/EtOH, room temperature (80−85%); (b) $PhI(OAc)_2$, NH_2CN/CH_2Cl_2, 0 °C (62−70%); (c) *m*-CPBA, K_2CO_3/EtOH (60−65%).

Scheme 2[a]



[a] Reagents and conditions: (a) MeSNa/EtOH, room temperature (90%); (b) $PhI(OAc)_2$, NH_2CN/CH_2Cl_2, 0 °C (90%); (c) *m*-CPBA, K_2CO_3/EtOH (85%).

Scheme 3[a]



[a] Reagents and conditions: (a) HCl or HBr, $NaNO_2$ (60−65%); (b) NCS or NBS, CCl_4 (65−68%); (c) MeSNa/EtOH, room temperature (90−92%) (d) $PhI(OAc)_2$, NH_2CN/CH_2Cl_2, 0 °C (80−85%); (e) *m*-CPBA, K_2CO_3/EtOH, 0 °C (65−70%).

mmol) in ethanol (10 mL) was added in one portion sodium thiomethoxide (1.05 mmol) at room temperature. The reaction was stirred for 2 h, and then the solvent was removed under reduced pressure. The residue was partitioned between dichloromethane (30 mL) and dilute hydrochloric acid (10 mL, 5%), washed with saturated brine (20 mL), and dried over anhydrous Na_2SO_4. The solvent was again removed under reduce pressure, and the residue was purified by silica gel (65 g) column chromatography (1:10 ethyl acetate/petroleum ether) to afford the title compounds as a yellow oil.

2-Chloro-5-(methylthiomethyl)-4-(trifluoromethyl)thiazole (5a). Yield: 85% (2.10 g). ^{1}H NMR ($CDCl_3$, δ): 2.15 (s, 3H, CH_3), 3.92 (s, 2H, CH_2).

2-Bromo-5-(methylthiomethyl)-4-(trifluoromethyl)thiazole (5b). Yield: 83% (2.42 g). ^{1}H NMR ($CDCl_3$, δ): 2.15 (s, 3H, CH_3), 3.93 (s, 2H, CH_2).

2-Ethoxy-5-(methylthiomethyl)-4-(trifluoromethyl)thiazole (5c). Yield: 80% (2.12 g). ^{1}H NMR ($CDCl_3$, δ): 1.44 (t, 3H, J = 7.2 Hz, CH_3), 2.16 (s, 3H, CH_3), 3.94 (s, 2H, CH_2), 4.49 (q, 2H, J = 7.2 Hz, CH_2).

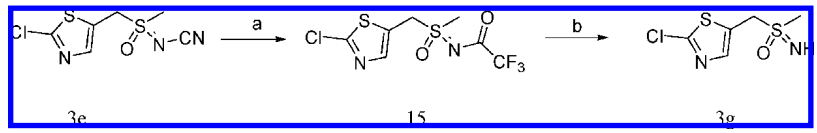
2-Chloro-4-methyl-5-(methylthiomethyl)thiazole (8). Yield: 90% (1.85 g). ^{1}H NMR ($CDCl_3$, δ): 2.09 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.73 (s, 2H, CH_2).

2-Chloro-5-(methylthiomethyl)thiazole (13a). Yield: 90% (1.62 g). ^{1}H NMR ($CDCl_3$, δ): 2.08 (s, 3H, CH_3), 3.79 (s, 2H, CH_2), 7.64 (s, 1H).

2-Bromo-5-(methylthiomethyl)thiazole (13b). Yield: 92% (1.93 g). ^{1}H NMR ($CDCl_3$, δ): 2.08 (s, 3H, CH_3), 3.81 (s, 2H, CH_2), 7.38 (s, 1H).

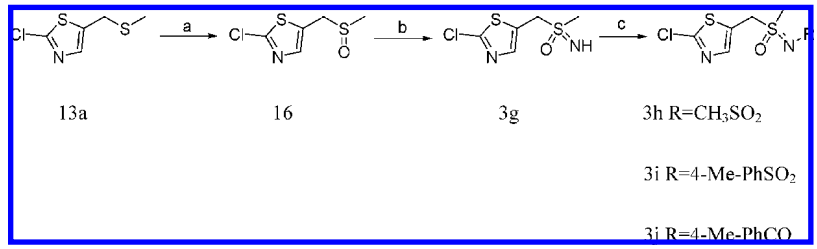
General Procedure for the Preparation of *N*-(Cyano) Sulfilimine. To a solution of sulfide (5 mmol) and cyanamide (10 mmol) in

Scheme 4[a]



[a] Reagents and conditions: (a) TFAA/CH_2Cl_2 (92%); (b) K_2CO_3, MeOH (85%).

Scheme 5[a]



[a] Reagents and conditions: (a) *m*-CPBA/$CHCl_3$, 0 °C (80%); (b) NaN_3, H_2SO_4/$CHCl_3$ (72%); (c) RSO_2Cl or RCOCl, DMAP/CH_2Cl_2 (80−92%).

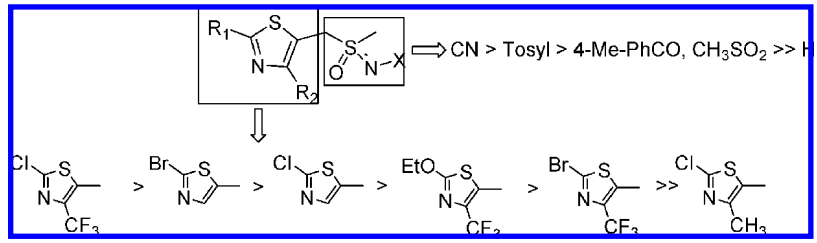


Figure 3. Structure relationships for sulfoximine derivatives.

dichloromethane (10 mL) cooled to 0 °C was added iodobenzene diacetate (7.5 mmol). The mixture was allowed to warm to room temperature over 1 h; the solvent was removed under reduced pressure; and the residue was purified by silica gel (45 g) column chromatography (5:1 ethyl acetate/ethanol) to afford the title compounds.

***N*-(Cyano) Methyl (2-Chloro-1,3-thiazole-4-(trifluoromethyl)-5-yl)methyl Sulfilimine (6a).** Yield: 65% (0.93 g). White crystalline solid. mp: 119−120 °C. ^{1}H NMR ($CDCl_3$, δ): 2.87 (s, 3H, CH_3), 4.57 (s, 2H, CH_2). IR (KBr, cm^{-1}) ν: 2100 (CN).

***N*-(Cyano) Methyl (2-Bromo-1,3-thiazole-4-(trifluoromethyl)-5-yl))methyl Sulfilimine (6b).** Yield: 62% (1.01 g). White crystalline solid. mp: 106−107 °C. ^{1}H NMR ($CDCl_3$, δ): 2.87 (s, 3H, CH_3), 4.53 (s, 2H, CH_2). IR (KBr, cm^{-1}) ν: 2130 (CN).

***N*-(Cyano) Methyl (2-Ethoxy-1,3-thiazole-4-(trifluoromethyl)-5-yl)methyl Sulfilimine (6c).** Yield: 70% (1.04 g). White crystalline solid. mp: 110−111 °C. ^{1}H NMR ($CDCl_3$, δ): 1.45 (t, J = 7.2 Hz, 3H, CH_3), 2.84 (s, 3H, CH_3), 4.45 (q, 2H, J = 6.9 Hz, CH_2), 4.54 (q, 2H, J = 7.2 Hz, CH_2). IR (KBr, cm^{-1}) ν: 2100 (CN).

***N*-(Cyano) Methyl (2-Chloro-1,3-thiazole-4-(methyl)-5-yl)methyl Sulfilimine (9).** Yield: 90% (1.05 g). White crystalline solid. mp: 88−90 °C. ^{1}H NMR ($CDCl_3$, δ): 2.46 (s, 3H, CH_3), 2.84 (s, 3H, CH_3), 4.39 (q, 2H, CH_2). IR (KBr, cm^{-1}) ν: 2120 (CN).

***N*-(Cyano) Methyl (2-Chloro-1,3-thiazole-5-yl)methyl Sulfilimine (14a).** Yield: 80% (0.93 g). White crystalline solid. mp: 105−106 °C. ^{1}H NMR ($CDCl_3$, δ): 2.83 (s, 3H, CH_3), 4.48 (s, 2H, CH_2), 7.64 (s, 1H). IR (KBr, cm^{-1}) ν: 2130 (CN).

***N*-(Cyano) Methyl (2-Bromo-1,3-thiazole-5-yl)methyl Sulfilimine (14b).** Yield: 85% (1.12 g). White crystalline solid. mp: 109−110 °C. ^{1}H NMR ($CDCl_3$, δ): 2.81 (s, 3H, CH_3), 4.72 (q, 2H, CH_2), 7.73 (s, 1H). IR (KBr, cm^{-1}) ν: 2120 (CN).

General Procedure for the Preparation of *N*-(Cyano) Sulfoximines. To a stirred solution 3-chloroperoxy-benzoid acid (0.81 mg, 4 mmol) in ethanol (5 mL) cooled to 0 °C was added a solution of potassium carbonate (0.82 mg, 6 mmol) in water (4 mL). The resulting mixture was stirred at 0 °C for 20 min. Then, the solution of the sulfilimine starting material (2 mmol) in ethanol (4 mL) was added all at once. The resulting mixture was stirred for 40 min at 0 °C, and saturated sodium bisulfite (5 mL) was added to quench the excess peracid. The resulting mixture was extracted with dichloromethane (30 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduce pressure, and the residue was purified by silica gel (25 g) column chromatography (10:1 ethyl acetate/ethanol) to afford the title compounds.

***N*-(Cyano) Methyl (2-Chloro-1,3-thiazole-4-(trifluoromethyl)-5-yl)methyl Sulfoximine (3a).** Yield: 60% (0.36 g). White crystalline solid. mp: 128−131 °C. ^{1}H NMR (DMSO-d_6, δ): 3.65 (s, 3H, CH_3), 5.54 (q, 2H, CH_2). ^{13}C NMR (100 M Hz, DMSO-d_6, δ): 39.95, 51.43, 111.23 (CN), 125.84, 154.49, 161.81, 161.85. IR (KBr, cm^{-1}) ν: 2190 (CN).

Anal. Calcd for $C_7H_5ClF_3N_3OS_2$: C, 27.68; H, 1.66; N, 13.84. Found: C, 27.59; H, 1.69; N, 13.96.

***N*-(Cyano) Methyl (2-Bromo-1,3-thiazole-4-(trifluoromethyl)-5-yl)methyl Sulfoximine (3b).** Yield: 62% (0.45 g). White crystalline solid. mp: 105−106 °C. ^{1}H NMR (DMSO-d_6, δ): 3.64 (s, 3H, CH_3), 5.54 (q, 2H, CH_2). ^{13}C NMR (100 M Hz, DMSO-d_6, δ): 39.99, 51.32, 111.22 (CN), 127.86, 140.52, 161.83, 166.01. IR (KBr, cm^{-1}) ν: 2200 (CN).

Anal. Calcd for $C_7H_5BrF_3N_3OS_2$: C, 24.15; H, 1.45; N, 12.07. Found: C, 24.20; H, 1.49; N, 12.11.

***N*-(Cyano) Methyl (2-Ethoxy-1,3-thiazole-4-(trifluoromethyl)-5-yl)methyl Sulfoximine (3c).** Yield: 65% (0.41 g). White crystalline solid. mp: 112−113 °C. ^{1}H NMR (DMSO-d_6, δ): 1.38 (t, 3H, J = 7.2 Hz, CH_3), 3.59 (s, 3H, CH_3), 4.49 (q, 2H, J = 6.9 Hz, CH_2), 5.36 (q, 2H, J = 7.2 Hz, CH_2). ^{13}C NMR (100 M Hz, DMSO-d_6, δ): 14.01, 39.99, 51.67, 69.03, 111.43 (CN), 127.84, 161.83, 166.02, 174.58. IR (KBr, cm^{-1}) ν: 2190 (CN).

Anal. Calcd for $C_9H_{10}F_3N_3O_2S_2$: C, 34.50; H, 3.22; N, 13.41. Found: C, 34.58; H, 3.18; N, 13.49.

***N*-(Cyano) Methyl (2-Chloro-1,3-thiazole-4-(methyl)-5-yl)methyl Sulfoximine (3d).** Yield: 85% (0.42 g). White crystalline solid. mp: 97−99 °C. ^{1}H NMR (DMSO-d_6, δ): 2.40 (s, 3H, CH_3), 3.50 (s, 3H, CH_3), 5.34 (q, 2H, CH_2). ^{13}C NMR (100 M Hz, DMSO-d_6, δ): 15.21, 38.68, 51.94, 111.79 (CN), 117.89, 150.85, 153.88. IR (KBr, cm^{-1}) ν: 2198 (CN). MS (EI) m/z (%): 250.3 ($[M + 1]^+$, 40), 248.2 ($[M - 1]^+$, 100).

Anal. Calcd for $C_7H_8ClN_3OS_2$: C, 33.66; H, 3.23; N, 16.83. Found: C, 33.68; H, 3.21; N, 16.77.

***N*-(Cyano) Methyl (2-Chloro-1,3-thiazole-5-yl)methyl Sulfoximine (3e).** Yield 65% (0.31 g). White crystalline solid. mp: 109−110 °C. ^{1}H NMR (DMSO-d_6, δ): 3.48 (s, 3H, CH_3), 5.43 (q, 2H, CH_2), 7.80 (s, 1H). ^{13}C NMR (100 M Hz, DMSO-d_6, δ): 38.89, 52.25, 111.71 (CN), 125.29, 114.79, 152.94. IR (KBr, cm^{-1}) ν: 2200 (CN).

Anal. Calcd for $C_6H_6ClN_3OS_2$: C, 30.57; H, 2.57; N, 17.83. Found: C, 30.41; H, 2.61; N, 17.88.

***N*-(Cyano) Methyl (2-Bromo-1,3-thiazole-5-yl)methyl Sulfoximine (3f).** Yield: 70% (0.39 g). White crystalline solid. mp: 99−100 °C. ^{1}H NMR (DMSO-d_6, δ): 4.03 (s, 3H, CH_3), 5.32 (q, 2H, CH_2), 7.77 (s, 1H). ^{13}C NMR (100 M Hz, DMSO-d_6, δ): 38.98, 52.08, 111.72 (CN), 126.74, 138.60, 146.15. IR (KBr, cm^{-1}) ν: 2198 (CN).

Anal. Calcd for $C_6H_6BrN_3OS_2$: C, 25.72; H, 2.16; N, 15.00. Found: C, 25.82; H, 2.17; N, 15.08.

***N*-(Trifluoroacetyl) Methyl (2-Chloro-1,3-thiazole-5-yl)methyl Sulfoximine (15).** To a stirring solution of sulfoximine **3e** (0.24 g, 1.0 mmol) in CH_2Cl_2 (18 mL) at 0 °C, TFAA (417.0 μL, 3.0 mmol) was added. The mixture was allowed to react at room temperature until the starting material was consumed (monitored by TLC). The mixture was poured into water. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by flash silica gel (20 g) column chromatography (1:2 ethyl acetate/petroleum ether) to afford the title compound **3g** (0.28 g, 92% yeild) as a colorless oil. ^{1}H NMR ($CDCl_3$, δ): 3.33 (s, 3H, CH_3), 4.96 (s, CH_2, CH_2), 7.68 (s, 1H). ^{13}C NMR (100 M Hz, DMSO-d_6, δ): 37.93, 52.47, 123.52, 144.47, 155.85, 162.31, 162.35.

Anal. Calcd for $C_7H_6ClF_3N_2O_2S_2$: C, 27.41; H, 1.97; N, 9.13. Found: C, 27.51; H, 1.98; N, 9.19.

2-Chloro-5-(*S*-methylsulfonimidoylmethyl)thiazole (3g). *Method A.* To a stirring solution of **15** (0.31 g, 1.0 mmol) in MeOH (7 mL) was added K_2CO_3 (0.38 g, 3.0 mmol). The mixture was allowed to react at room temperature for 30 min until the starting material was consumed (monitored by TLC). The solvent was removed under reduced pressure, and the residue was purified by flash silica gel (18 g) column chromatography (10:1 ethyl acetate/ethanol) to afford the title compound **3g** (0.18 g, 82% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, δ): 2.99 (s, 3H, CH_3), 4.46 (q, 2H, CH_2), 7.57 (s, 1H).

Anal. Calcd for $C_5H_7ClN_2OS_2$: C, 28.50; H, 3.35; N, 13.30. Found: C, 28.52; H, 3.30; N, 13.29.

Method B. To a solution of 2-chloro-5-(methylthiomethyl)thiazole **13a** (0.90 g, 5 mmol) in $CHCl_3$ (15 mL) at −5 °C was added a solution of *m*-MCPBA (1.00 g, 85%, 5 mmol) in $CHCl_3$ over the course of 3 h. The solution was stirred an additional 1 h, and then it was concentrated and purified by flash silica gel (45 g) chromatography (10:1 ethyl acetate/ethanol) to afford 2-chloro-5-(methylsulfinylmethyl)thiazole **16** (0.78 g, 80% yield) as a white solid. mp: 53−55 °C. ^{1}H NMR ($CDCl_3$, δ): 2.51 (s, 3H, CH_3), 4.00 (d, 1H, J = 14.1 Hz, CH), 4.22 (d, 1H, J = 14.1 Hz, CH), 7.50 (s, 1H).

To a solution of 2-chloro-5-(methylsulfinylmethyl)thiazole **16** (0.98 g, 5 mmol) in $CHCl_3$ (10 mL) at −5 °C was added sodium azide (0.52 g, 8 mmol) and H_2SO_4 (2 mL). The reaction was heated to 60 °C and kept the temperature for 4 h. Then, the liquid was decanted into a separated flask, and residual syrup was dissolved in water (10 mL), basified with K_2CO_3, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, concentrated, and purified by flash silica gel (40 g) column chromatography (10:1 ethyl acetate/ethanol) to afford the title compound **3g** (0.18 g, 72% yield) as a yellow oil.

***N*-(Methylsulfonyl) Methyl (2-Chloro-1,3-thiazole-5-yl)methyl Sulfoximine (3h).** A mixture of **3g** (0.42 g, 2 mmol), DMAP (0.25 g, 2 mmol), and methyl sulfonyl chloride (0.23 g, 2 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 1 h. The reaction mixture were treated with water (10 mL) and extracted with CH_2Cl_2 (2 × 5 mL), and the combined extracts were dried over anhydrous $MgSO_4$. The organic phase were evaporated under reduced pressure, and the crude product were purified by flash silica gel column (30 g) column chromatography (1:2 ethyl acetate/petroleum ether) to afford the tiltle compound (0.52 g, 92% yield) as a white solid. mp: 132−134 °C. ^{1}H NMR ($CDCl_3$, δ): 3.15 (s, 3H, CH_3), 3.21 (s, 1H, CH_3), 4.97 (q, 2H, CH_2), 7.69 (s, 1H). ^{13}C NMR (100 M Hz, DMSO-d_6, δ): 39.78, 45.01, 53.99, 125.04, 144.33, 162.35.

Anal. Calcd for $C_6H_9ClN_2O_3S_3$: C, 24.95; H, 3.14; N, 9.70. Found: C, 24.87; H, 3.15; N, 9.80.

***N*-(Tosyl) Methyl (2-Chloro-1,3-thiazole-5-yl)methyl Sulfoximine (3i).** Following the preparation precudure of **3h**, the reaction of **3g** with 4-methylbenzenesulfonyl chloride gave **3i**. Yield: 80% (0.39 g). White crystalline solid. mp: 137−138 °C. ^{1}H NMR ($CDCl_3$, δ): 2.42 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 4.997 (q, 2H, CH_2), 7.29 (d, 2H, J = 8.4 Hz, Ph), 7.67 (s, 1H), 7.83 (d, 2H, J = 8.4 Hz, Ph). ^{13}C NMR (100 M Hz, DMSO-d_6, δ): 21.53, 39.96, 54.37, 125.20, 126.57, 129.45, 140.08, 143.39, 144.36, 155.37.

Anal. Calcd for $C_{12}H_{13}ClN_2O_3S_3$: C, 39.50; H, 3.59; N, 7.68. Found: C, 39.40; H, 3.55; N, 7.66.

***N*-(4-Methylbenzoyl) Methyl (2-Chloro-1,3-thiazole-5-yl)methyl Sulfoximine (3j).** Following the preparation precudure of **3h**, the reaction of **3g** with 4-methylbenzoyl chloride gave **3j**. Yield: 82% (0.53 g). White crystalline solid. mp: 160−161 °C. ^{1}H NMR ($CDCl_3$, δ): 2.42 (s, 3H, CH_3), 3.27 (s, 3H, CH_3), 4.93 (d, 1H, J = 10.8 Hz, CH), 5.06 (d, 1H, J = 10.8 Hz, CH), 7.24 (d, 2H, J = 6 Hz, Ar−H), 7.62 (s, 1H), 8.01 (d, 2H, J = 6 Hz, Ar−H).

Anal. Calcd for $C_{13}H_{13}ClN_2O_2S_2$: C, 47.48; H, 3.98; N, 8.52; Found: C,47.58; H, 3.89; N, 8.58.

Biology Assay. The bioassay was performed on a representative test organism reared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected using Abbott's formula (*15*). Evaluations are based on a percentage scale of 0−100, in which 0 = no activity and 100 = total kill.

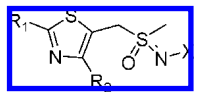
The insecticidal activities of the title compounds were tested against peach aphid (*Myzus persicae*) by foliar application. About 60 aphids were transferred to the shoot with 3−5 fresh leaves of horsebean. The shoot with aphids was cut and dipped into the solution of 10 mg/L of test compound for 2 s, after removing extra solutions on the leaf; the aphids were raised in the shoot at 25 ± 1 °C and 85% relative humidity for 16 h. Each experiment for one compound was triplicated. The revised death rate was calculated by Abbott's formula. The reference compound was compound **2a**.

RESULTS AND DISCUSSION

Synthesis. The *N*-cyano sulfoximine derivatives **3a**−**f** were prepared according to **Schemes 1**−**3**. Methyl (1,3-thiazolyl-5-yl)methyl sulfide derivatives of **5**, **8**, and **13** were prepared starting from 5-halomethyl-1,3-thiazole. 5-Halomethyl-1,3-thiazole were prepared according to the procedures in the literature (*16, 17*). The syntheses of **12a** and **12b** are described in **Scheme 3**. 2-Amine-5-methyl-thiazole was subjected to the Sandmeyer reaction to give 2-halo analogues, which convereted into 5-halomethyl derivatives **12a** and **12b** by side-chain halogeration (*18*). Sulfide is oxidized with iodobenzene diacetate in the presence of cyanamide at 0 °C to give sulfilimine derivatives **6**, **9**, and **14**. The reaction was carried out in a polar aprotic solvent, such as dichloromethane. The sulfilimine was oxidized with 3-chloroperoxy-benzoid acid (*m*-CPBA), and potassium carbonate as a base was employed to neutralize the acidity of *m*-CPBA (**Schemes 1**−**3**) and afforded the *N*-cyano sulfoximines **3a**−**f** in good (60−85%) yields (*12*). Protic polar solvent ethanol and water were used to increase the solubility of sulfilimines starting material.

To synthesize *N*H-free sulfoximine **3g**, two methods were explored (**Schemes 4** and **5**). The *N*-cyano group proved to be easily cleaved upon treatment with TFAA, affording *N*-trifluoroacetyl sulfoximine **15** in 92% yield. Sulfoximine **15** was converted into *N*H-free sulfoximine **3g** by methanolysis of the trifluoroacetyl moiety in 85% yield (**Scheme 4**). In another method, first, oxidation of **13a** with *m*-CPBA afforded the sulfoxide **16** in good (90%) yield. Finally, sulfoxide was imintated with sodium azide in the presence of concentrated

Table 1. Insecticidal Activities against *M. persicae* of Compounds **3a**−**j** and **2a**



compound	R_1	R_2	X	mortality (%) at a concentration of 10 mg/L
3a	Cl	CF_3	CN	100
3b	Br	CF_3	CN	48
3c	OEt	CF_3	CN	68
3d	Cl	CH_3	CN	0
3e	Cl	H	CN	75
3f	Br	H	CN	93
3g	Cl	H	H	0
3h	Cl	H	CH_3SO_2	20
3i	Cl	H	4-CH_3−Ph−SO_2	35
3j	Cl	H	4-CH_3−Ph−CO	20
2a				100

sulfuric acid under heating to provide *N*H-free sulfoximine (**Scheme 5**) (*19*). The title compounds **3h**−**j** were prepared by the reaction of sulfonyl or benzoyl chloride with *N*H-free sulfoximine in dichloromethane, using DMAP as the acid acceptor (**Scheme 5**).

Structure−**Activity Relationship.** Some title compounds exhibited good insecticidal activities at 10 mg/L against *M. persicae*.

The results of insecticidal activities are listed in **Table 1**. The insecticidal activity of compound **3a** is similar to the reference compound **2a** and better than other compounds. The structure−activity relationships for the pharmacophore S(O)═N−X and the heterocyclic group thiazole were elucidated. A summary of results is outlined in **Figure 3**.

We first focused our attention on the influence of the pharmacophore S(O)═N−X. Among the compounds tested, the best activity was observed for the *N*-cyano sulfoximine pharmacophore (S(O)═N−CN). Replacement of the cyano group by a tosyl, 4-methylbenzoyl, or a methylsulfonyl group clearly diminished the activity, while the compounds with X = H were not effective at 10 mg/L.

The structure−activity relationships for the thiazole group were also investigated. 2-Chloro-4-trifluomethyl-5-thiazolyl derivatives gave the best activity, and the 2-bromo-5-thiazolyl compound was somewhat less active. Replacement of the chloro group by ethoxy caused a loss of activity. Adding a methyl group at the 4 position of the thiazole heterocycle led to a significant decrease in activity. These data show that efficacy is strongly influenced by the nature of the substitutes and their position on the thiazolyl ring.

In conclusion, new neonicotinoids were designed and synthesized, and some title compounds exhibited good insecticidal activities against *M. persicae*. The structure−activity relationships can thus be summarized as follows: as pharmacophore, the *N*-cyano sulfoximine (S(O)═N−CN) is the best. 2-Chloro-4-trifluomethyl-5-thiazolyl is the most promising thiazole heterocyclic system.

ACKNOWLEDGMENT

The authors thank Dr. Bin Li for providing us invaluable suggestions. We thank Mr. Hong Zhang and Mrs. Yanmei Luo for the test of biological activities. We thank Mrs. Aiying Guan for providing us compound **2a**.

LITERATURE CITED

(1) Moriya, K.; Shibuya, K.; Hattori, Y.; Tsuboi, S.; Shiokawa, K.; Kagabu, S. 1-(6-Chloronicotinyl)-2-nitroiminoimidazolidines and related compounds as potential new insecticides. *Biosci., Biotechnol., Biochem.* **1992**, *56*, 364–365.

(2) Bai, D.; Lummis, S. C. R.; Leicht, W.; Breer, H.; Sattelle, D. B. Actions of imidacloprid and a related nitromethylene on cholinergic receptors of an identified insect motor neurone. *Pestic. Sci.* **1991**, *33*, 197–204.

(3) Liu, M.; Casida, J. E. High affinity binding of [^{3}H]imidacloprid in the insect acetylcholine receptor. *Pestic. Biochem. Physiol.* **1993**, *46*, 40–46.

(4) Nishimura, K.; Kanda, Y.; Okazawa, A.; Ueno, T. Relationship between insecticidal and neurophysiological activities of imidacloprid and related compounds. *Pestic. Biochem. Physiol.* **1994**, *50*, 51–59.

(5) Mori, K.; Okumoto, T.; Kawahara, N.; Ozoe, Y. Interaction of dinotefuran and its analogues with nicotinic acetylcholine receptors of cockroach nerve cords. *Pest Manage. Sci.* **2001**, *58*, 190–196.

(6) Jeschke, P.; Schindler, M.; Beck, M. Neonicotinoid insecticides: Retrospective consideration and prospects. *Proc. Brighton Crop Prot. Conf.: Pest Dis.* **2002**, *1*, 137–144.

(7) Elbert, A.; Nauen, R. Resistance of *Bemisia tabaci* (Homoptera: Aleyrodidae) to insecticides in southern Spain with special reference to neonicotinoids. *Pest Manage. Sci.* **2000**, *56*, 60–64.

(8) Rauch, N.; Nauen, R. Identification of biochemical markers linked to neonicotinoid cross resistance in *Bemisia tabaci* (Hemiptera: Aleyrodidae). *Arch. Insect Biochem. Physiol.* **2003**, *54*, 165–176.

(9) Nauen, R.; Denholm, I. Resistance of insect pests to neonicotinoid insecticides: Current status and future prospects. *Arch. Insect Biochem. Physiol.* **2005**, *58*, 200–215.

(10) Loso, M. R.; Nugent, B. M.; Huang, J. X.; Rogers, R. B.; Zhu, Y. M.; Renga, J. M.; Hegde, V. B.; Demark, J. J. Insecticidal *N*-substituted (6-haloalkylpyridin-3-yl)alkyl sulfoximines. PCT Int. Appl. WO2007095229, 2007.

(11) Loso, M. R.; Nugent, B. M.; Huang, J. X. Insecticidal *N*-substituted (heteroaryl) cycloalkyl sulfoximines. PCT Int. Appl. WO2008027073, 2008.

(12) Zhu, Y. M.; Loso, M. R.; Nugent, B. M.; Huang, J. X.; Rogers, R. B. Multi-substituted pyridyl sulfoximines and their use as insecticides. PCT. Int. Appl. WO2008057129, 2008.

(13) Loso, M. R.; Nugent, B. M.; Zhu, Y. M.; Rogers, R. B.; Huang, J. X.; Renga, J. M.; Whiteker, G. T.; Breaux, N. T.; Daeuble, J. F. Heteroaryl (substituted) alkyl *N*-substituted sulfoximines as insecticides. PCT. Int. Appl. WO2008057131, 2008.

(14) Huang, J. X.; Rogers, R. B.; Orr, N.; Sparks, T. C.; Gifford, J. M.; Loso, M. R.; Zhu, Y. M.; Meade, T. A method to control insects resistant to common insecticides. PCT. Int. Appl. WO2007149134, 2007.

(15) Abbott, W. S. A method of computing the effectiveness of an insecticide. *J. Econ. Entomol.* **1925**, *18*, 265–267.

(16) Lee, L. F.; Schleppnik, F. M.; Howe, R. K. Syntheses and reaction of 2-halo-5-thiazolecarboxylates. *J. Heterocycl. Chem.* **1985**, *22*, 1621–1630.

(17) Podhorez, D. E.; Hull, J. W.; Brady, C. H. One pot synthesis of 1,2,4-triazole. U.S. Patent 6,096,898, 2000.

(18) Kim, H. J.; Liu, S. Z.; Young, S.; Li, Q. X. Development of an enzyme-linked immunosorbent assay for the insecticide thiamethoxam. *J. Agric. Food Chem.* **1997**, *45*, 276–281.

(19) Mancheno, O. G.; Bistri, O.; Bolm, C. Iodinane- and metal-free synthesis of *N*-cyano sulfilimines: Novel and easy access of *N*H-sulfoximines. *Org. Lett.* **2007**, *9*, 3809–3811.

Received for review September 11, 2008. Revised manuscript received October 24, 2008. Accepted October 27, 2008. We gratefully acknowledge the National Natural Science Foundation of China (NNSFC) (20772068) and the National Key Project of Scientific and Technical Supporting Programs funded by the Ministry of Science and Technology of China (2006BAE01A01-5) for financial support.

JF802802G