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

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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 ¹H and ¹³C 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. ¹H and ¹³C 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 F₂₅₄), 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

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N-Substituted (1,3-Thiazole)alkyl Sulfoximine Derivatives







Acetamiprid (1b) Nitenpyram (1c)

Thiacloprid (1d)



Thiamethoxam (1e)



Clothianidin (1f)

Figure 1. Commercial neonicotinoids.



 2a
 2b
 2c

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

Scheme 1^a



3c R= OEt

2d

^a Reagents and conditions: (a) MeSNa/EtOH, room temperature (80-85%); (b) PhI(OAc)₂, NH₂CN/CH₂Cl₂, 0 °C (62-70%); (c) m-CPBA, K₂CO₃/EtOH (60-65%).

Scheme 2^a



^a Reagents and conditions: (a) MeSNa/EtOH, room temperature (90%); (b) PhI(OAc)₂, NH₂CN/CH₂Cl₂, 0 °C (90%); (c) m-CPBA, K₂CO₃/EtOH (85%).

Scheme 3^a



^a Reagents and conditions: (a) HCl or HBr, NaNO₂ (60–65%); (b) NCS or NBS, CCl₄ (65–68%); (c) MeSNa/EtOH, room temperature (90–92%) (d) PhI(OAc)₂, NH₂CN/CH₂Cl₂, 0 °C (80–85%); (e) *m*-CPBA, K₂CO₃/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 Na₂SO₄. 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). ¹H NMR (CDCl₃, δ): 2.15 (s, 3H, CH₃), 3.92 (s, 2H, CH₂).

2-Bromo-5-(methylthiomethyl)-4-(trifluoromethyl)thiazole (5b). Yield: 83% (2.42 g). ¹H NMR (CDCl₃, δ): 2.15 (s, 3H, CH₃), 3.93 (s, 2H, CH₂).

2-Ethoxy-5-(methylthiomethyl)-4-(trifluoromethyl)thiazole (5c). Yield: 80% (2.12 g). ¹H NMR (CDCl₃, δ): 1.44 (t, 3H, J = 7.2 Hz, CH₃), 2.16 (s, 3H, CH₃), 3.94 (s, 2H, CH₂), 4.49 (q, 2H, J = 7.2 Hz, CH₂).

2-Chloro-4-methyl-5-(methylthiomethyl)thiazole (8). Yield: 90% (1.85 g). ¹H NMR (CDCl₃, δ): 2.09 (s, 3H, CH₃), 2.31 (s, 3H, CH₃), 3.73 (s, 2H, CH₂).

2-Chloro-5-(methylthiomethyl)thiazole (13a). Yield: 90% (1.62 g). ¹H NMR (CDCl₃, δ): 2.08 (s, 3H, CH₃), 3.79 (s, 2H, CH₂), 7.64 (s, 1H).

2-Bromo-5-(methylthiomethyl)thiazole (13b). Yield: 92% (1.93 g). ¹H NMR (CDCl₃, δ): 2.08 (s, 3H, CH₃), 3.81 (s, 2H, CH₂), 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/CH₂Cl₂ (92%); (b) K₂CO₃, MeOH (85%)

Scheme 5^a



3j R=4-Me-PhCO

^a Reagents and conditions: (a) m-CPBA/CHCl₃, 0 °C (80%); (b) NaN₃, H₂SO₄/CHCl₃ (72%); (c) RSO₂Cl or RCOCI, DMAP/CH₂Cl₂ (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)-5yl)methyl Sulfilimine (6a). Yield: 65% (0.93 g). White crystalline solid. mp: 119–120 °C. ¹H NMR (CDCl₃, δ): 2.87 (s, 3H, CH₃), 4.57 (s, 2H, CH₂). IR (KBr, cm⁻¹) ν : 2100 (CN).

N-(Cyano) Methyl (2-Bromo-1,3-thiazole-4-(trifluoromethyl)-5yl))methyl Sulfilimine (6b). Yield: 62% (1.01 g). White crystalline solid. mp: $106-107 \,^{\circ}$ C. ¹H NMR (CDCl₃, δ): 2.87 (s, 3H, CH₃), 4.53 (s, 2H, CH₂). IR (KBr, cm⁻¹) ν : 2130 (CN).

N-(Cyano) Methyl (2-Ethoxy-1,3-thiazole-4-(trifluoromethyl)-5yl)methyl Sulfilimine (6c). Yield: 70% (1.04 g). White crystalline solid. mp: 110–111 °C. ¹H NMR (CDCl₃, δ): 1.45 (t, *J* = 7.2 Hz, 3H, CH₃), 2.84 (s, 3H, CH₃), 4.45 (q, 2H, *J* = 6.9 Hz, CH₂), 4.54 (q, 2H, *J* = 7.2 Hz, CH₂). 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. ¹H NMR (CDCl₃, δ): 2.46 (s, 3H, CH₃), 2.84 (s, 3H, CH₃), 4.39 (q, 2H, CH₂). 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. ¹H NMR (CDCl₃, δ): 2.83 (s, 3H, CH₃), 4.48 (s, 2H, CH₂), 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. ¹H NMR (CDCl₃, δ): 2.81 (s, 3H, CH₃), 4.72 (q, 2H, CH₂), 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)-5yl)methyl Sulfoximine (3a). Yield: 60% (0.36 g). White crystalline solid. mp: 128–131 °C. ¹H NMR (DMSO- d_6 , δ): 3.65 (s, 3H, CH₃), 5.54 (q, 2H, CH₂). ¹³C 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)-5yl)methyl Sulfoximine (3b). Yield: 62% (0.45 g). White crystalline solid. mp: 105–106 °C. ¹H NMR (DMSO- d_6 , δ): 3.64 (s, 3H, CH₃), 5.54 (q, 2H, CH₂). ¹³C 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)-5yl)methyl Sulfoximine (3c). Yield: 65% (0.41 g). White crystalline solid. mp: 112–113 °C. ¹H NMR (DMSO- d_6 , δ): 1.38 (t, 3H, J = 7.2Hz, CH₃), 3.59 (s, 3H, CH₃), 4.49 (q, 2H, J = 6.9 Hz, CH₂), 5.36 (q, 2H, J = 7.2 Hz, CH₂). ¹³C 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) v: 2190 (CN).

Anal. Calcd for C₉H₁₀F₃N₃O₂S₂: 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. ¹H NMR (DMSO- d_6 , δ): 2.40 (s, 3H, CH₃), 3.50 (s, 3H, CH₃), 5.34 (q, 2H, CH₂). ¹³C 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) *mlz* (%): 250.3 ([M + 1]⁺, 40), 248.2 ([M - 1]⁺, 100).

Anal. Calcd for $C_7H_8CIN_3OS_2$: C, 33.66; H, 3.23; N, 16.83. Found: C, 33.68; H, 3.21; N, 16.77.

N-Substituted (1,3-Thiazole)alkyl Sulfoximine Derivatives

Anal. Calcd for $C_6H_6CIN_3OS_2$: 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. ¹H NMR (DMSO- d_6 , δ): 4.03 (s, 3H, CH₃), 5.32 (q, 2H, CH₂), 7.77 (s, 1H). ¹³C 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 C₆H₆BrN₃OS₂: 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 CH₂Cl₂ (18 mL) at 0 °C, TFAA (417.0 μ L, 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 CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried over anhydrous MgSO₄, 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. ¹H NMR (CDCl₃, δ): 3.33 (s, 3H, CH₃), 4.96 (s, CH₂, CH₂), 7.68 (s, 1H). ¹³C 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 K₂CO₃ (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. ¹H NMR (CDCl₃, δ): 2.99 (s, 3H, CH₃), 4.46 (q, 2H, CH₂), 7.57 (s, 1H).

Anal. Calcd for C₅H₇ClN₂OS₂: 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 CHCl₃ (15 mL) at -5 °C was added a solution of *m*-MCPBA (1.00 g, 85%, 5 mmol) in CHCl₃ 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. ¹H NMR (CDCl₃, δ): 2.51 (s, 3H, CH₃), 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 CHCl₃ (10 mL) at -5 °C was added sodium azide (0.52 g, 8 mmol) and H₂SO₄ (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 K₂CO₃, and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried over anhydrous MgSO₄, 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 CH₂Cl₂ (5 mL) was stirred at room temperature for 1 h. The reaction mixture were treated with water (10 mL) and extracted with CH₂Cl₂ (2 × 5 mL), and the combined extracts were dried over anhydrous MgSO₄. 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. ¹H NMR (CDCl₃, δ): 3.15 (s, 3H, CH₃), 3.21 (s, 1H, CH₃), 4.97 (q, 2H,

CH₂), 7.69 (s, 1H). ¹³C NMR (100 M Hz, DMSO- d_6 , δ): 39.78, 45.01, 53.99, 125.04, 144.33, 162.35.

Anal. Calcd for C₆H₉ClN₂O₃S₃: 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. ¹H NMR (CDCl₃, δ): 2.42 (s, 3H, CH₃), 3.20 (s, 3H, CH₃), 4.997 (q, 2H, CH₂), 7.29 (d, 2H, J = 8.4 Hz, Ph), 7.67 (s, 1H), 7.83 (d, 2H, J = 8.4 Hz, Ph). ¹³C 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. ¹H NMR (CDCl₃, δ): 2.42 (s, 3H, CH₃), 3.27 (s, 3H, CH₃), 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 C₁₃H₁₃ClN₂O₂S₂: 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-5yl)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 $\it M.$ persicae of Compounds 3a-j and 2a



compound	R ₁	R_2	Х	mortality (%) at a concentration of 10 mg/L
3a	CI	CF₃	CN	100
3b	Br	CF ₃	CN	48
3c	OEt	CF ₃	CN	68
3d	CI	CH₃	CN	0
3e	CI	Н	CN	75
3f	Br	Н	CN	93
3g	CI	Н	Н	0
3h	CI	Н	CH ₃ SO ₂	20
3i	CI	Н	4-CH ₃ -Ph-SO ₂	35
3j	CI	Н	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.

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