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Article

Synthesis and Fungicidal Activity of *N*-[4-(4-Fluoro)phenyl-2-piperidin-4-yl-thiazol-5-yl]pyrimidin-2-yl-*N*-phenylamines on *Phytophthora capsici*

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The fungicidal activities against phytopathogenic fungi of two aminothiazole compounds of *N*-[4-(4-fluoro)phenyl-2-aminothiazol-5-yl]pyrimidin-2-yl-*N*-subst. phenylamine (V-1, V-2) have been determined and these two compounds were used as the leading compounds in this study as V-1 for *N*-[4-(4-fluoro)phenyl-2-aminothiazol-5-yl]pyrimidin-2-yl-*N*-(3-hydroxymethyl)phenylamine and V-2 for *N*-[4-(4-fluoro)phenyl-2-aminothiazol-5-yl]pyrimidin-2-yl-*N*-3-(1-hydroxyethyl)phenylamine. Further syntheses of these two compounds, V-1 and V-2, were conducted by reacting them with three functional groups, 2-(*N*-ethoxycarbonyl)piperidin-4-yl, 2-piperidin-4-yl, and 2-(*N*-methyl)-piperidin-4-yl-thiazole. From this scheme, 21 compounds were newly synthesized and their structures were confirmed by ^{1}H-NMR-spectrum. The fungicidal activities of all the synthesized compounds against *Phytophthora capsici* were examined using the whole plant method. While the EC_{50} value of the commercial fungicide dimethomorph was 4.26 mM, that of IX-3g on *P. capsici* was 1.03 mM. Among the 21 chemicals, IX-3g showed the most potential antifungal activity *in vivo*. Therefore, IX-3g may be considered as a potential candidate for the control of phytopathogenic diseases characterized by *P. capsici* infection, and further studies will be conducted on the mode of action IX-3g.

Key words: fungicidal activity, *Phytophthora capsici*, *N*-[4-(4-fluoro)phenyl-2-piperidin-4-yl-thiazol-5-yl]pyrimidin-2-yl-*N*-phenylamine derivatives

Many chemicals have been developed and used as pesticides and therapeutic agents not only to improve human health but also to reduce food shortages throughout the world [Horita *et al*., 2009; Sun *et al*., 2009; Yao *et al*., 2009]. Their continued use, however, often breeds resistance to these chemicals in microbes [Zhang *et al*., 2009], plants [Yu *et al*., 2009], and insect pests [Ramoutar *et al*., 2009], which can develop molecular mechanisms that allow them to survive levels of these chemicals that would previously kill them. Fungicide resistance in fungal pathogens refers to poor disease control in plants [Chen and Zhou, 2009]. The development of fungicide resistance becomes common and the mechanisms of resistance to fungal pathogens may rely on the insensitivity of target sites to fungicides and enhanced detoxification by a number of metabolizing enzymes [Kanetis *et al*., 2008; Cabañas *et al*., 2009].

Many species of vegetables including the Solanaceae such as pepper and tomato, and Cucurbitaceae such as melon and cucumbers are attacked by *Phytophthora capsici* [Sujkowski *et al*., 2000]. This infection can be readily found in pepper and tomato plants in South Korea [Rajkumar *et al*., 2005] and the fungus has also been reported in Europe, the Western hemisphere and Asia [Lamour and Hausbeck, 2002; Hurtado-Gozales *et al*., 2008]. The infection takes place during wet weather and leaf blights begin as small water-soaked areas on the undersides of the leaves. The formation of rots can cause the plant to wilt or die and induces the plant to produce mummified fruits. Recently, several reports have demonstrated a method by which this fungus can be

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controlled in the pepper fields by means of rotation with non-susceptible crops, planting with fresh, clean seeds, and the development of cultivars that are resistant to *P. capsici* [Granke *et al*., 2009]. To reduce the failure of fungal disease management by currently used fungicides, new compounds with high efficacy and selectivity against target species are desirable [Huang *et al*., 2007]. A variety of reports regarding studies of the synthesis of thiazole derivatives have been published reflecting growing interest in the chemical and biological significance of these chemicals [Xu *et al*., 2004].

For this report, based on the structural features of thiazole, we designed and synthesized *N*-[4-(4-fluoro)-phenyl-2-piperidin-4-yl-thiazol-5-yl]pyrimidin-2-yl-*N*-phenylamine derivatives and investigated their bioactivities and examined their fungicidal activities in regard to *P. capsici*.

Materials and Methods

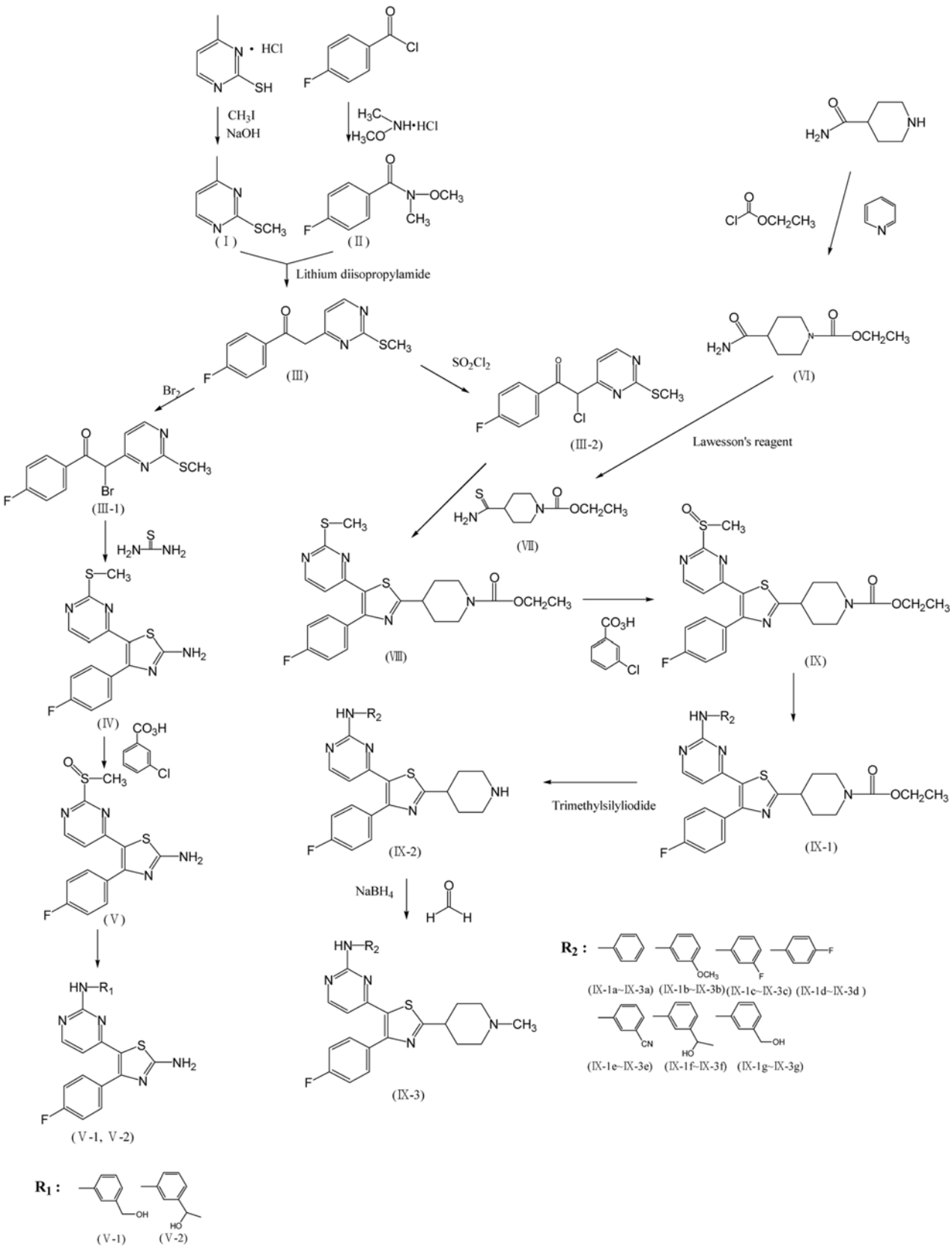
Phytopathogen. *P. capsici* was maintained and supplied by the National Institute of Agricultural Science and Technology (NIAST, Suwon, Korea). This species was subcultured on potato dextrose agar (PDA) slants sterilized to a solution of PDA (3.9 g) in water (100 mL) at 15 atm, 121°C for 15 min and then uniformly sprayed on a petri dish. *P. capsici* was inoculated on the medium at intervals of 5 mm and was then used to test for antifungal activity for 4~7 days at 20~25°C at a humidity as high as 70% in a darkroom.

Chemicals. 2-Mercapto-4-methylpyrimidine hydrochloride (98%), iodomethane (99%), *N,O*-dimethylhydroxylamine hydrochloride (98%), 4-fluorobenzoyl chloride (98%), lithium diisopropylamide (2.0 M), bromine (99.5%), thiourea (99%), sulfuryl chloride (97%), isonipecotamide (97%), lawesson's reagent (97%), 3-chloroperoxybenzoic acid (77%), aniline (99.5%), *m*-anisidine (97%), 3-fluoroaniline (99%), 4-fluoroaniline (99%), 3-amino-benzonitrile (99%), 3-aminobenzyl alcohol (99%), 3-(1-hydroxyethyl)aniline (99%), trimethylsilyliodide (97%), formaldehyde solution (37%) and sodium borohydride (98%) were obtained from Aldrich Chemical (St. Louis, MO). PDA was supplied from Difco (Sparks, MD). Dimethomorph was supplied from Dongbu-hannong Chemical Co (Daejeon, Korea). All other chemicals were of reagent grade.

***In vitro* fungicidal activity.** The *in vitro* test determined the inhibition of mycelium in the agar culture medium caused by the compound under investigation [Li *et al*., 2005]. A bioindicator (Table 1) was established and used in the test. The solutions (suspensions) were prepared at the concentrations needed to obtain 40 mg/L of the studied substance after dilution with the agar culture medium (PDA). Petri scale pans were used, into which the agar culture medium and the studied substance were poured. As the culture medium set, the infectious material of the tested fungus, in the form of agar disks overgrown with mycelium, was placed at three sites on its surface. After 7 days, depending on the mycelium culture, the linear growth of the mycelium colony was measured [Kim *et al*., 2004]. The compound's action was determined by the percentage of mycelium growth inhibition as compared with the control using the equation $J=[(C-T)/C]\times100$ where J is the percentage of colony growth inhibition, C is the zone of fungus colony growth in the control combination (millimeters), and T is the zone of fungus colony growth in the combination with the compound (millimeters). The inhibitory responses were classified as follows: very strong response, ++++, J 81-100%; strong response, +++, J 61-80%; moderate response, ++, J 41-60%; weak response, +, J 21-40%; no response, –, J <20%.

***In vivo* fungicidal activity.** The plant diseases evaluated in this study was phytophthora blight caused by *P. capsici*. The fungi were routinely maintained on PDA slants and V-8 agar slants, and kept for stock at 4°C. The fungicidal activity of the test sample was determined by the whole plant method in a greenhouse, as previously described [Lee *et al*., 2001]. The initial concentration of the test solution was 330 mg/L, and the tests employed a dilution sequence of 40, 20, and 12.5 mg/L. To prepare the test solutions, 330 mg/L of the test sample was dissolved in 10 mL of acetone, followed by dilution with 90 mL of water containing Tween 20 (330 mg/mL). Fifty milliliters of each test sample solution was simultaneously sprayed onto two pots on a turntable. The treated plants were kept in a greenhouse for 1 day, before being inoculated with the pathogen. The controls were sprayed with the Tween 20 solution. All tests were replicated three times. In a test with phytophthora blight caused by *P. capsici*, red pepper plants at the first leaf stage (one plant per pot) were sprayed with each test solution. The red pepper was inoculated by spraying the leaves with conidia (1×10^4 spores/mL) of *P. capsici* incubated on a PDA medium at 23°C for 2 days and was then placed in a chamber (23°C) for 4-5 days. The control effect of the test sample on disease was evaluated with a control value (CV) calculated using the formula $CV\ (\%)=[(A-B)/A]\times100$, where A and B represent the disease area on the untreated and treated plants, respectively.

Statistical analysis. Analysis of variance was performed with the procedure supplied by SAS (SAS Institute, Cary, NC). If $P>F$ was less than 0.01, the means were separated with the least significant difference pest at the $P=0.05$



Scheme 1. Synthesis of *N*-[4-(4-fluoro)phenyl-2-aminothiazol-5-yl]pyrimidin-2-yl-*N*-phenylamine compounds (V-1 and V-2) and further synthesis of *N*-[4-(4-fluoro)phenyl-2-piperidin-4-yl-thiazol-5-yl]pyrimidin-2-yl-*N*-phenylamine derivatives (IX-1a~IX-3g) from V-1 and V-2. IX: V-1 and V-2 containing *N*-ethoxycarbonylpiperidine group, IX-2: V-1 and V-2 containing piperdine group, IX-3: V-1 and V-2 containing *N*-methylpiperidine group.

level.

Synthesis. Synthesis of compounds designated as **IX-1a**~**IX-1g**, **IX-2a**~**IX-2g**, and **IX-3a**~**IX-3g** was shown in Scheme 1. At first, compounds **V-1** and **V-2** were synthesized by the method of Laszlo *et al*. [2004] and I was synthesized by the method of Kenneth *et al*. [2003].

***N*-Methoxy-*N*-methyl 4-fluorobenzamide (II).** Triethylamine (1.27 g, 12.60 mmole) was added dropwise to a solution of *N,O*-dimethylhydroxylamine hydrochloride (0.61 g, 6.30 mmole) in methylene chloride (15 mL) at 5-10°C. To this mixture was added slowly 4-fluorobenzoyl chloride (1 g, 6.30 mmole) at 0°C for 30 min. The reaction mixture was stirred at room temperature for 1 h. Partitioning of the mixture between water and methylene chloride, drying over magnesium sulfate, and the filtering and evaporating of the solvents under reduced pressure gave the desired product (1.09 g, 95.0%) as a yellow oil; ^{1}H-NMR ($CDCl_3$, ppm): 3.38 (s, 3H, -N**C**$\mathbf{H_3}$), 3.55 (s, 3H, -O**C**$\mathbf{H_3}$), 7.07-7.77 (m, 4H, aromatic *J*=7.29 Hz).

1-(4-Fluoro)phenyl-2-[2-(methylthio)pyimidin-4-yl]ethanone (III). To a brown solution of lithium diisopropylamide (0.84 g, 7.84 mmole) in tetrahydrofuran (9 mL), 4-methyl-2-(methylthio)pyrimidine (**I**) (1 g, 7.13 mmole) was added dropwise at −70°C for 10 min with stirring then maintained for 1 h at −70°C. *N*-methoxy-*N*-methyl 4-fluorobenzamide (**II**) (1.3 g, 7.13 mmole) in tetrahydrofuran (1 mL) was added slowly to this mixture at −70°C for 10 min. After the addition was completed, the resulting mixture was stirred at room temperature for 2 h and then 2 mL of saturated ammonium chloride solution and 10 mL of water were added. The organic phase was then separated and dried (magnesium sulfate), and the evaporation of the solvent yielded the crude 1-(4-fluoro)phenyl-2-[2-(methylthio)pyimidin-4-yl]ethanone (**III**) in the form of a solid. This crude was crystallized by the addition of *tert*-butylmethyl ether. Filtering and drying then gave the desired product (0.99 g, 53.0%) as a yellow crystal; ^{1}H-NMR ($CDCl_3$, ppm): 2.47-2.63 (s, 3H, -S**C**$\mathbf{H_3}$), 3.38-3.56 (s, 2H, -CO**C**$\mathbf{H_2}$), 7.02 (d, 1H, -**C**$\mathbf{H}$=CH-N *J*= 2.75 Hz), 7.10-7.87 (m, 4H, aromatic *J*=7.29 Hz), 8.32-8.34 (d, 1H, -CH=**C**$\mathbf{H}$-N *J*=2.71 Hz).

2-Chloro-1-(4-fluoro)phenyl-2-[2-(methylthio)pyrimidin-4-yl]ethanone (III-2). A solution of 1-(4-fluoro)phenyl-2-[2-(methylthio)pyrimidin-4-yl]ethanone (**III**) (1.0 g, 3.81 mmole) in chloroform (20 mL) was refluxed, then a solution of sulfuryl chloride (0.54 g, 4.0 mmole) in chloroform was added and the solution was refluxed for 20 min. The reaction mixture was washed with saturated sodium bicarbonate solution and water. The organic phase was dried (magnesium sulfate) and concentrated to give a yellow oil. Without further purification, the crude product (1.17 g, 96.0%) was used in the next step; ^{1}H-NMR ($CDCl_3$, ppm): 2.28-2.50 (s, 3H, -S**C**$\mathbf{H_3}$), 6.18 (s, 1H, -**C**$\mathbf{H}$Cl), 7.33-7.64 (d, 1H, -**C**$\mathbf{H}$=CH-N *J*=2.75 Hz), 7.05-7.87 (m, 4H, aromatic *J*=7.29 Hz), 8.60-8.75 (d, 1H, -CH=**C**$\mathbf{H}$-N *J*=2.71 Hz).

Ethyl 4-carbamoylpiperidine-1-carboxylate (VI). To a solution of isonipecotamide (1.0 g, 8.32 mmole) and pyridine (1.31 g, 16.64 mmole) in methylene (5 mL), ethyl chloroformate (0.90 g, 8.32 mmole) was added dropwise under 0°C, and the mixture was stirred at room temperature for 1 h. The reaction mixture was washed with water. The organic phase was dried (magnesium sulfate) and concentrated. The residue was recrystallized from methylene chloride and hexane to give the desired product (1.10 g, 71.0%) as a white solid; ^{1}H-NMR ($CDCl_3$, ppm): 1.25-1.30 (t, 3H, -OCH$_2$**C**$\mathbf{H_3}$ *J*=7.5 Hz), 1.62-1.69 (q, 4H, -**C**$\mathbf{H_2}$CH$_2$N- *J*=11.2 Hz), 1.87-2.84 (t, 4H, -CH$_2$**C**$\mathbf{H_2}$N- *J*=10.2 Hz), 2.34 (quin, 1H, -CO**C**$\mathbf{H}$- *J* =2.5 Hz), 4.11-4.20 (q, 2H, -O**C**$\mathbf{H_2}$CH$_3$ *J*=7.5 Hz).

Ethyl 4-carbamothioylpiperidine-1-carboxylate (VII). Compound **VII** was synthesized by the method of James *et al*. [2005].

2-Methylthio-[4-(4-fluoro)phenyl-2-(*N*-ethoxycarbonyl)-piperidin-4-yl-thiazol-5-yl]pyrimidine (VIII). A mixture of 2-chloro-1-(4-fluoro)phenyl-2-[3-(methylthio)pyrimidin-4-yl]ethanone (**III-2**) (1.0 g, 3.36 mmole) and ethyl 4-carbamothioylpiperidine-1-carboxylate (**VII**) (1.45 g, 6.73 mmole) in ethanol (10 mL) was refluxed for 2 h. The reaction mixture was concentrated and partitioned between saturated sodium bicarbonate solution and ethyl acetate. The organic phase was dried (magnesium sulfate) and concentrated. The residue was recrystallized from ethyl acetate and hexane to give the desired product (0.47 g, 31.0%) as a yellow solid; ^{1}H-NMR ($CDCl_3$, ppm): 1.27-1.31 (t, 3H, -OCH$_2$**C**$\mathbf{H_3}$ *J*=7.5 Hz), 1.77-2.20 (q, 4H, -**C**$\mathbf{H_2}$CH$_2$N- *J*=10.5 Hz), 2.56 (s, 3H, -S**C**$\mathbf{H_3}$), 3.18-3.25 (quin, 1H, -**C**$\mathbf{H}$CH$_2$- *J*=11.2 Hz), 2.92-3.00 (t, 4H, -CH$_2$**C**$\mathbf{H_2}$N- *J*=12.0 Hz), 4.13-4.21 (q, 2H, -O**C**$\mathbf{H_2}$CH$_3$ *J*= 7.5 Hz), 7.12-7.5 (m, 4H, aromatic *J*=7.9 Hz), 6.73-6.75 (d, 1H, -CH=**C**$\mathbf{H}$-N *J*=1.5 Hz), 8.28-8.30 (d, 1H, -CH=**C**$\mathbf{H}$-N *J*=1.8 Hz).

2-Methylsulfinyl-[4-(4-fluoro)phenyl-2-(*N*-ethoxycarbonyl)-piperidin-4-yl-thiazol-5-yl]pyrimidine (IX). To a solution of 2-methylthio-[4-(4-fluoro)phenyl-2-(*N*-ethoxy-carbonyl)piperidin-4-yl-thiazol-5-yl]pyrimidine (**VIII**) (1.0 g, 2.18 mmole) in methylene chloride (10 mL), *m*-chloroperoxybenzoic acid (0.41 g, 2.39 mmole) was slowly added at 0°C for 5 min, then the mixture was stirred at room temperature for 30 min. The mixture was then poured into saturated $NaHCO_3$ solution (10 mL) and extracted with methylene chloride. The combined organic phase was dried (magnesium sulfate) and concentrated to give the desired product (1.03 g, 95.0%) as a white solid;

^{1}H-NMR ($CDCl_3$, ppm): 1.27-1.31 (t, 3H, -OCH_2**CH_3** *J*= 7.5 Hz), 1.79-1.87 (q, 4H, -**CH_2**CH_2N- *J*=10.5 Hz), 2.92 (quin, 1H, -**CH**CH_2- *J*=2.5 Hz), 2.99 (s, 3H, -SO**CH_3**), 3.21-3.36 (t, 4H, -CH_2**CH_2**N- *J*=12.0 Hz), 4.13-4.29 (q, 2H, -O**CH_2**CH_3 *J*=2.5 Hz), 7.13-7.14 (d, 1H, -**CH**=CH-N *J*=1.8 Hz), 7.15-7.57 (m, 4H, aromatic *J*=7.7 Hz), 8.63-8.64 (d, 1H, -CH=**CH**-N *J*=1.9 Hz).

***N*-[4-(4-Fluoro)phenyl-2-(*N*-ethoxycarbonyl)piperidin-4-yl-thiazol-5-yl]pyrimidin-2-yl-*N*-phenylamine derivatives (IX-1a, IX-1b).** A mixture of 2-methylsulfinyl-[4-(4-fluoro)-phenyl-2-(*N*-ethoxy-carbonyl)piperidin-4-yl-thiazol-5-yl]pyrimidine (**IX**) (1.0 g, 2.10 mmole) in aniline (1.96 g, 21.07 mmole) and *m*-anisidine (2.59 g, 21.07 mmole) was stirred at 100°C and added to boron trifluoride diethyl etherate (0.3 g, 2.11 mmole), then the mixture was stirred at 150°C for 2 h. The mixture was poured into 5% HCl solution (5 mL) and extracted with ethyl acetate (5 mL). The combined organic phase was dried (magnesium sulfate) and concentrated. The residue was recrystallized from ethyl acetate and hexane to give **IX-1a** (0.51 g, 49.0%) as a dark green solid, **IX-1b** (0.73 g, 66.0%) as a green solid.

IX-1a; ^{1}H-NMR ($CDCl_3$, ppm): 1.27-1.32 (t, 3H, OCH_2**CH_3** *J*=7.5 Hz), 1.81-1.86 (q, 4H, -**CH_2**CH_2N- *J*=10.5 Hz), 2.93-3.23 (t, 4H, -CH_2**CH_2**N- *J*=12.1 Hz), 3.23 (quin, 1H, -**CH**CH_2- *J*=2.5 Hz), 4.14-4.22 (q, 2H, O**CH_2**CH_3 *J*=7.5 Hz), 6.53-6.55 (d, 1H, -**CH**=CH-N *J*=1.6 Hz), 7.08-7.21 (m, 5H, aromatic *J*=8.1 Hz), 7.55-7.62 (m, 4H, aromatic *J*=8.5 Hz), 8.21-8.23 (d, 1H, CH=**CH**-N *J*=1.8 Hz).

IX-1b; ^{1}H-NMR ($CDCl_3$, ppm): 1.27-1.32 (t, 3H, -OCH_2**CH_3** *J*=7.5 Hz), 1.79-1.85 (q, 4H, -**CH_2**CH_2N- *J*=10.5 Hz), 2.97 (t, 4H, -CH_2**CH_2**N- *J*=11.9 Hz), 3.22 (quin, 1H, -**CH**CH_2- *J*=2.5 Hz), 3.88 (s, 3H, -OCH_3), 4.14-4.19 (q, 2H, -O**CH_2**CH_3 *J*=7.5 Hz), 6.63-7.19 (m, 4H, aromatic *J*=7.7 Hz), 6.53-6.55 (d, 1H, -**CH**=CH-N *J*=1.7 Hz), 7.24-7.60 (m, 4H, aromatic *J*=7.9 Hz), 8.21-8.23 (d, 1H, -CH=**CH**-N *J*=1.6 Hz).

***N*-[4-(4-Fluoro)phenyl-2-(*N*-ethoxycarbonyl)piperidin-4-yl-thiazol-5-yl]pyrimidin-2-yl-*N*-phenylamine derivatives (IX-1c~IX-1g).** A mixture of **IX** (1.0 g, 2.10 mmole) in dioxane (25 mL) was added 3-fluoroaniline (0.46 g, 4.21 mmole), 4-fluoroaniline (0.46 g, 4.21 mmole), 3-amino-benzonitrile (0.49 g, 4.21 mmole), 3-(1-hydroxyethyl)-aniline (0.57 g, 4.21 mmole) and 3-aminobenzyl alcohol (0.57 g, 4.21 mmole) and *p*-toluenesulfonic acid (0.35 g, 1.89 mmole). Application of the **IX-1a** method described above then afforded **IX-1c** (0.46 g, 42.4%) as a green solid, **IX-1d** (0.33 g, 29.2%), **IX-1e** (0.15 g, 14.3%), **IX-1f** (0.51 g, 50.0%) and **IX-1g** (0.93 g, 83.3%) as a yellow solid.

IX-1c; ^{1}H-NMR ($CDCl_3$, ppm): 1.20-1.32 (t, 3H, OCH_2**CH_3** *J*=7.5 Hz), 1.78-1.89 (q, 4H, -**CH_2**CH_2N- *J*= 11.3 Hz), 3.23 (quin, 1H -**CH**CH_2- *J*=2.5 Hz), 2.93-2.97 (t, 4H, -CH_2**CH_2**N- *J*=12.0 Hz), 4.14-4.21 (q, 2H, O**CH_2**CH_3 *J*=7.5 Hz), 6.78-7.18 (m, 4H, aromatic *J*=8.0 Hz), 6.58-6.60 (d, 1H, -**CH**=CH-N *J*=1.6 Hz), 7.30-7.60 (m, 4H, aromatic *J*=8.2 Hz), 8.30-8.31 (d, 1H, -CH=**CH**-N *J*=1.8 Hz).

IX-1d; ^{1}H-NMR ($CDCl_3$, ppm): 1.27-1.32 (t, 3H, OCH_2**CH_3** *J*=7.5 Hz), 1.80-1.90 (q, 4H, -**CH_2**CH_2N- *J*=10.8 Hz), 2.97-3.01 (t, 4H, -CH_2**CH_2**N- *J*=11.1 Hz), 3.23 (quin, 1H -**CH**CH_2- *J*=2.5 Hz), 4.14-4.21 (q, 2H, O**CH_2**CH_3 *J*=7.5 Hz), 6.54-6.65 (d, 1H, -**CH**=CH-N *J*=1.5 Hz) , 7.03-7.17 (m, 4H, aromatic *J*=8.1 Hz), 7.52-7.59 (m, 4H, aromatic *J*=8.4 Hz), 8.19-8.21 (d, 1H, CH=**CH**-N *J*=1.7 Hz).

IX-1e; ^{1}H-NMR ($CDCl_3$, ppm): 1.27-1.32 (t, 3H, OCH_2**CH_3** *J*=2.5 Hz), 1.82-1.88 (q, 4H, -**CH_2**CH_2N- *J*=11.3 Hz), 2.98 (t, 4H, -CH_2**CH_2**N- *J*=12.0 Hz), 3.24 (quin, 1H, -**CH**CH_2- *J*=2.4 Hz), 4.14-4.21 (q, 2H, O**CH_2**CH_3 *J*=7.5 Hz), 6.63-6.65 (d, 1H, -**CH**=CH-N *J*=1.6 Hz),7.12-7.19 (m, 4H, aromatic *J*=7.2 Hz), 7.31-7.57 (m, 4H, aromatic *J*=8.4 Hz), 8.25-8.29 (d, 1H, CH=**CH**-N *J*=1.7 Hz).

IX-1f; ^{1}H-NMR ($CDCl_3$, ppm): 1.27-1.32 (t, 3H, OCH_2**CH_3** *J*=7.5 Hz), 1.56-1.58 (d, 3H, -CH(**CH_3**)OH *J*=7.2 Hz), 1.80-1.85 (q, 4H, -**CH_2**CH_2N- *J*=11.6 Hz), 2.97 (t, 4H, -CH_2**CH_2**N- *J*=12.0 Hz), 3.22 (quin, 1H, **CH**CH_2- *J*=2.5 Hz), 4.14-4.19 (q, 2H, -O**CH_2**CH_3 *J*=7.5 Hz), 4.94-4.97 (q, 1H, -**CH**(CH3)OH *J*=7.7 Hz), 6.53-6.55 (d, 1H, -**CH**=CH-N *J*=1.6 Hz), 7.08-7.20 (m, 4H,aromatic *J*=7.7 Hz), 7.32-7.77 (m, 4H, aromatic *J*=8.4 Hz), 8.21-8.23 (d, 1H, -CH=**CH**-N *J*=1.6 Hz).

IX-1g; ^{1}H-NMR ($CDCl_3$, ppm): 1.27-1.32 (t, 3H, OCH_2**CH_3** *J*=7.5 Hz), 1.78-1.85 (q, 4H, -**CH_2**CH_2N- *J*=11.1 Hz), 3.19-3.22 (quin, 1H, -**CH**CH_2- *J*=2.5 Hz), 2.93-3.01 (t, 4H, -CH_2**CH_2**N- *J*=12.0 Hz), 4.14-4.21 (quar, 2H, -O**CH_2**CH_3 *J*=7.5 Hz), 6.54-6.56 (d, 1H, **CH**=CH-N *J*=1.6 Hz), 7.07-7.19 (m, 4H, aromatic *J*=7.7 Hz), 7.32-7.75 (m, 4H, aromatic *J*=8.5 Hz), 8.21-8.23 (d, 1H, -CH=**CH**-N *J*=1.7 Hz).

***N*-[4-(4-Fluoro)phenyl-2-piperidin-4-yl-thiazol-5-yl]-pyrimidin-2-yl-*N*-phenylamine derivatives (IX-2a~IX-2g).** To a solution of **IX-1a** (1.0 g, 1.98 mmole), **IX-1b** (0.91 g, 1.98 mmole), **IX-1c** (1.0 g, 1.98 mmole), **IX-1d** (1.0 g, 1.98 mmole), **IX-1e** (1.04 g, 1.98 mmole), **IX-1f** (1.08 g, 1.98 mmole) and **IX-1g** (1.05 g, 1.98 mmole) in chloroform (10 mL) was added trimethylsilyliodide (1.18 g, 5.94 mmole). After the addition was completed, the resulting mixture was stirred at 60°C for 4 h then 10 mL of 6 M HCl in isopropanol and 10 mL of 2 M NaOH solution were added. The organic phase was then separated, dried (magnesium sulfate) and evaporated to

yield a residue. The residue was recrystallized from methylene chloride and ether to give **IX-2a** (0.27 g, 31.7%), **IX-2b** (0.66 g, 67.0%), **IX-2c** (0.46 g, 52.0%), **IX-2d** (0.48 g, 55.0%), **IX-2e** (0.41 g, 48.0%), **IX-2f** (0.36 g, 42.0%) and **IX-2g** (0.36 g, 42.0%) as a yellow solid.

IX-2a; ^{1}H-NMR ($CDCl_3$, ppm): 1.79-1.85 (q, 4H, **CH_2**CH_2NH *J*=11.3 Hz), 2.77-2.84 (t, 4H, -CH_2**CH_2**NH *J*=12.0 Hz), 3.19-3.27 (quin, 1H, -**CH**CH_2- *J*=2.5 Hz), 6.53-6.55 (d, 1H, -**CH**=CH-N *J*=1.6 Hz), 7.05-7.18 (m, 5H, aromatic *J*=7.8 Hz), 7.33-7.63 (m, 4H, aromatic *J*=8.4 Hz), 8.21 (d, 1H, -CH=**CH**-N *J*=1.6 Hz).

IX-2b; ^{1}H-NMR ($CDCl_3$, ppm): 1.59-1.63 (q, 4H, **CH_2**CH_2NH *J*=11.2 Hz), 2.61 (t, 4H, -CH_2**CH_2**NH *J*=12.0 Hz), 3.77 (s, 3H, -O**CH_3**), 6.5-6.53 (d, 1H, **CH**=CH-N *J*=1.6 Hz), 7.16-8.06 (m, 4H, aromatic *J*=7.9 Hz), 8.10-8.32 (m, 4H, aromatic *J*=8.4 Hz), 9.7 (s, 1H, CH=**CH**-N).

IX-2c; ^{1}H-NMR ($CDCl_3$, ppm): 1.79-1.85 (q, 4H, **CH_2**CH_2NH *J*=11.3 Hz), 2.77-2.84 (t, 4H, -CH_2**CH_2**NH *J*=12.0 Hz), 3.18 (quin, 1H, -**CH**CH_2- *J*=2.5 Hz), 6.56-6.57 (d, 1H, -**CH**=CH-N *J*=1.6 Hz), 7.21-7.30 (m, 4H, aromatic *J*=7.8 Hz), 7.59-7.63 (m, 4H, aromatic *J*=8.4 Hz), 8.27-8.29 (d, 1H, -CH=**CH**-N *J*=1.7 Hz).

IX-2d; ^{1}H-NMR ($CDCl_3$, ppm): 1.84-1.87 (q, 4H, **CH_2**CH_2NH *J*=11.6 Hz), 2.83 (t, 4H, -CH_2**CH_2**NH *J*=12.0 Hz), 3.26 (quin, 1H, -**CH**CH_2- *J*=2.5 Hz), 6.53-6.55 (d, 1H, -**CH**=CH-N *J*=1.5 Hz), 7.03-7.17 (m, 4H, aromatic *J*=9 Hz), 7.52-7.60 (m, 4H, aromatic *J*=8.5 Hz), 8.20-8.21(d, 1H, -CH=**CH**-N *J*=1.8 Hz).

IX-2e; ^{1}H-NMR ($CDCl_3$, ppm): 1.78-1.84 (q, 4H, **CH_2**CH_2NH *J*=11.6 Hz), 2.81-2.84 (t, 4H, -CH_2**CH_2**NH *J*=12.0 Hz), 2.99-3.03 (quin, 1H, -**CH**CH_2- *J*=2.5 Hz), 6.62-6.64 (d, 1H, -**CH**=CH-N *J*=1.6 Hz), 7.12-7.27 (m, 4H, aromatic *J*=7.7 Hz), 7.35-7.60 (m, 4H, aromatic *J*=8.5 Hz), 8.25-8.29 (d, 1H, -CH=**CH**-N *J*=1.9 Hz).

IX-2f; ^{1}H-NMR ($CDCl_3$, ppm): 1.23-1.37 (d, 3H, CH(OH)**CH_3** *J*=7.1 Hz), 1.78-1.84 (q, 4H, -**CH_2**CH_2NH *J*=11.0 Hz), 4.70 (q, 1H ,-**CH**(OH)CH_3 *J*=7.5 Hz), 2.81-2.84 (t, 4H,-CH_2**CH_2**NH *J*=12.0 Hz), 3.01 (quin, 1H, **CH**CH_2- *J*=2.5 Hz), 6.48-6.50 (d, 1H,-**CH**=CH-N *J*=1.6 Hz), 7.20-7.32 (m, 4H, aromatic *J*=7.1 Hz), 7.56-7.82 (m, 4H, aromatic *J*=7.7 Hz), 8.32-8.34 (d, 1H, -CH=**CH**-N *J*=1.8 Hz).

IX-2g; ^{1}H-NMR ($CDCl_3$, ppm): 1.93-1.97 (q, 4H, **CH_2**CH_2NH *J*=10.1 Hz), 2.07-2.20 (t, 4H, -CH_2**CH_2**NH *J*=12.0 Hz), 3.22 (quin, 1H, -**CH**CH_2- *J*=2.5 Hz), 4.51 (s, 2H, -**CH_2**OH), 6.31-6.33 (d, 1H, -**CH**=CH-N *J*=1.5 Hz), 6.88-7.32 (m, 4H, aromatic *J*=8.1 Hz), 7.55-7.62 (m, 4H, aromatic *J*=8.3 Hz), 8.02-8.03 (d, 1H, -CH=**CH**-N *J*=1.5 Hz).

***N*-[4-(4-Fluoro)phenyl-2-(*N*-methyl)piperidin-4-yl-thiazol-5-yl]pyrimidin-2-yl-*N*-phenyl-amine derivatives (IX-3a~IX-3g).** To a solution of **IX-2a** (1.0 g, 2.31 mmole), **IX-2b** (1.06 g, 2.31 mmole), **IX-2c** (1.04 g, 2.31 mmole), **IX-2d** (1.04 g, 2.31 mmole), **IX-2e** (1.05 g, 2.31 mmole), **IX-2f** (1.10 g, 2.31 mmole) and **IX-2g** (1.06 g, 2.31 mmole) in methanol (10 mL) was added formaldehyde (0.13 g, 4.33 mmole) and sodium borohydride (0.16 g, 4.33 mmole). After the addition was completed, the resulting mixture was stirred at room temperature for 30 min and then, 10 mL of water and 10 mL of ethyl acetate were added. The organic phase was then separated, dried (magnesium sulfate), and evaporated to yield a residue. The residue was recrystallized from methylene chloride and ether to give **IX-3a** (0.28 g, 28.0%), **IX-3c** (0.25 g, 49.0%), **IX-3d** (0.46 g, 45.0%), **IX-3e** (0.35 g, 34.0%) as a yellow solid, **IX-3b** (0.28 g, 28.0%) as a green solid, **IX-3f** (0.32 g, 32.0%), **IX-3g** (0.35 g, 34.0%) as a yellow solid.

IX-3a; ^{1}H-NMR($CDCl_3$, ppm): 1.94-1.98 (q, 4H, **CH_2**CH_2NCH_3 *J*=10.3 Hz), 2.09-2.19(t, 4H, -CH_2**CH_2**NCH_3 *J*=12.0 Hz), 2.36 (s, 3H, -N**CH_3**), 2.99-3.04 (quin, 1H, **CH**CH_2- *J*=2.5 Hz), 6.53-6.55 (d, 1H, -**CH**=CH-N *J*=1.5 Hz), 7.08-7.19 (m, 5H, aromatic *J*=7.7 Hz), 7.32-7.34 (m, 4H, aromatic *J*=8.2 Hz), 8.20-8.22(d, 1H, -CH=**CH**-N *J*=1.5 Hz).

IX-3b;^{1}H-NMR($CDCl_3$, ppm): 1.79(q, 4H, -**CH_2**CH_2NCH_3 *J*=10.1 Hz), 2.04-2.07(t, 4H, -CH_2**CH_2**NCH_3 *J*=12.0 Hz), 2.20(s, 3H, -N**CH_3**), 2.99-3.04(quin, 1H, -**CH**CH_2- *J*=2.5 Hz), 3.77(s, 3H, -O**CH_3**), 6.49-6.51(d, 1H, -**CH**=CH-N *J*=1.5 Hz), 7.16-7.32(m, 4H, aromatic *J*=7.7 Hz), 7.35-7.52(m, 4H, aromatic *J*=8.1 Hz), 8.32-8.34(d, 1H, CH=**CH**-N *J*=1.7 Hz).

IX-3c; ^{1}H-NMR($CDCl_3$, ppm): 1.92-2.04(q, 4H, **CH_2**CH_2NCH_3 *J*=10.3 Hz), 2.20-2.36(t, 4H, -CH_2**CH_2**NCH_3 *J*=12.0 Hz), 2.40(s, 3H, -N**CH_3**), 4.91(quin, 1H, **CH**CH_2- *J*=2.5 Hz), 6.52-6.54(d, 1H, -**CH**=CH-N *J*=1.5 Hz), 6.71-7.18(m, 4H, aromatic *J*=7.7 Hz), 7.32-7.61(m, 4H, aromatic *J*=8.3 Hz), 8.23-8.25(d, 1H, -CH=**CH**-N *J*=1.8 Hz).

IX-3d; ^{1}H-NMR($CDCl_3$, ppm): 1.92-1.97(q, 4H, **CH_2**CH_2NCH_3 *J*=10.6 Hz), 2.09-2.23(t, 4H, -CH_2**CH_2**NCH_3 *J*=12.0 Hz), 2.35(s, 3H, -N**CH_3**), 4.91(quin, 1H, **CH**CH_2- *J*=2.5 Hz), 6.53-6.55(d, 1H, -**CH**=CH-N *J*=1.6 Hz), 7.02-7.19(m, 4H, aromatic *J*=7.0 Hz), 7.33-7.60(m, 4H, aromatic *J*=8.4 Hz), 8.19-8.21(d, 1H, -CH=CH-N *J*=1.5 Hz).

IX-3e; ^{1}H-NMR($CDCl_3$, ppm): 1.97-1.99(q, 4H, **CH_2**CH_2NCH_3 *J*=10.3 Hz), 2.09-2.20(t, 4H, -CH_2**CH_2**NCH_3 *J*=12.0 Hz), 2.35(s, 3H, -N**CH_3**), 2.99-3.04(quin, 1H, **CH**CH_2- *J*=2.5 Hz), 6.62-6.64(d, 1H, -**CH**=CH-N *J*=1.5

Hz), 7.14-7.33 (m, 4H, aromatic J=8.2 Hz), 7.35-7.60 (m, 4H, aromatic J=8.4 Hz), 8.23-8.27(d, 1H, -CH=**CH**-N J=1.9 Hz).

IX-3f; ^{1}H-NMR ($CDCl_3$, ppm): 1.23-1.37 (d, 3H, CH(OH)**CH_3** J=7.1 Hz), 1.78-1.84 (q, 4H, -**CH_2**CH_2NCH_3 J=10.2 Hz), 2.33 (s, 3H, -N**CH_3**), 4.70 (q, 1H, **CH**(OH)CH_3 J=7.7 Hz), 2.81-2.84 (t, 4H, -CH_2**CH_2**NH J=12.0 Hz), 3.01 (quin, 1H, -**CH**CH_2- J=2.5 Hz), 6.48-6.50 (d, 1H, -**CH**=CH-N J=1.5 Hz), 7.20-7.56 (m, 4H, aromatic J=8.6 Hz), 7.77-7.82 (m, 4H, aromatic J=8.4 Hz), 8.32-8.34 (d, 1H, -CH=**CH**-N J=1.5 Hz).

IX-3g; ^{1}H-NMR($CDCl_3$, ppm): 1.93-1.97(q, 4H, **CH_2**CH_2NCH_3 J=10.3 Hz), 2.07- 2.20 (t, 4H, -CH_2**CH_2**NCH_3 J=12.0 Hz), 2.33 (s, 3H, -N**CH_3**), 3.22 (quin, 1H, **CH**CH_2- J=2.5 Hz), 4.74 (s, 2H, -**CH_2**OH), 6.51-6.53(d, 1H, -**CH**=CH-N J=1.6 Hz), 7.05-7.34 (m, 4H, aromatic J=9.0 Hz), 7.42-7.82 (m, 4H, aromatic J=8.5 Hz), 8.18-8.20 (d, 1H, -CH=**CH**-N J=2.0 Hz).

Results and Discussion

N-[4-(4-Fluoro)phenyl-2-piperidin-4-yl-thiazol-5-yl]-pyrimidin-2-yl-*N*-phenylamine was reacted with 3-aminobenzyl alcohol and 3-(1-hydroxylethyl)aniline. Two major products were produced and designated as **V-1** for *N*-[4-(4-fluoro)phenyl-2-aminothiazol-5-yl]pyrimidin-2-yl-*N*-(3-hydroxymethyl)phenylamine, and as **V-2** for *N*-[4-(4-fluoro)phenyl-2-aminothiazol-5-yl]pyrimidin-2-yl-*N*-3-(1-hydroxyethyl)phenylamine in good yield. **V-1** and **V-2** were examined for their fungicidal activities against *P. capsici* yielding results that are presented in Table 1. At a concentration of 40 mg/L, **V-1** and **V-2** exerted a strong inhibitory action on the growth of *P. capsici* inhibiting growth in at least 80% of the growth zone. The degree of their fungicidal activity appeared to be similar in the plate experiments. In the whole plant experiments, the EC_{50} values of **V-1** and **V-2** were 3.42 and 2.59, respectively, while that of the commercial fungicide dimethomorph was 4.26 mM. These two compounds thus demonstrated a potent fungicidal effect on *P. capsici*, and thus appear suitable for use as a leading compound for further synthesis.

To obtain new synthesized compounds from **V-1** and **V-2**, three functional groups, 2-(*N*-ethoxycarbonyl)piperidin-4-yl, 2-piperidin-4-yl, and 2-(*N*-methyl)piperidin-4-yl-thiazole were introduced as the leads instead of the 2-aminothiazole group of **V-1** and **V-2** compounds. 21 compounds were newly synthesized using Scheme 1 and their structures were confirmed by ^{1}H-NMR spectroscopy. For instance, *N*-[4-(4-fluoro)phenyl-2-(*N*-methyl)piperidin-4-yl-thiazol-5-yl]pyrimidin-2-yl-(3-hydroxymethyl)-phenylamine, designated as **IX-3g**, was synthesized, and

Table 1. Fungicidal activities of *N*-[4-(4-fluoro)phenyl-2-aminothiazol-5-yl]pyrimidin-2-yl-*N*-phenylamine compounds (V-1 and V-2) and *N*-[4-(4-fluoro)phenyl-2-piperidin-4-yl-thiazol-5-yl]pyrimidin-2-yl-*N*-phenylamine derivatives (IX-1a~IX-3g) against *Phytophthora capsici* using plate culture method

Compounds	Inhibition Zone (Diameter, mm[a])
V-1	+++[b]
V-2	+++
IX-1a~IX-1g	-
IX-2a	-
IX-2b	+
IX-2c	+
IX-2d	-
IX-2e	++
IX-2f	+++
IX-2g	++++
IX-3a	++
IX-3b	++
IX-3c	++
IX-3d	++
IX-3e	++
IX-3f	+++
IX-3g	++++
Dimethomorph	++

[a] $p<0.05$ [b] 40.0 mg/L

in its ^{1}H-NMR analysis, a peak was observed, which was displayed as a doublet at d 8.18 and 8.20 corresponding to CH of -CH=**CH**-N, a multiplet at d 7.05 and 7.82 corresponding to the eight hydrogens of a phenyl group, a doublet at d 6.51 and 6.53 corresponding to CH of -**CH**=CH-N, a singlet at d 4.74 corresponding to CH_2 of -**CH_2**OH, a quintet at d 3.22 corresponding to CH of -**CH**CH_2-, a singlet at d 2.33 corresponding to CH_3 of -N**CH_3**, a triplet at d 2.07 and 2.20 corresponding to CH_2-N of -CH_2**CH_2**NCH_3 and a quartet at d 1.93 and 1.97 corresponding to CH_2 of -**CH_2**CH_2NCH_3. The others were also confirmed using the same method.

A series of new compounds that possessed the benzene ring of the *N*-phenyl groups (**IX-2f** and **IX-2g**, **IX-3f** and **IX-3g**) on the 2-aminothiazole ring of **V-1** and **V-2** compounds showed potent fungicidal effects on *P. capsici* in Table 1. As shown in Table 3, compounds **IX-2f**, **IX-2g**, **IX-3f** and **IX-3g** had the EC_{50} values of 2.32, 1.86, 1.99, and 1.03 mM, respectively. These EC_{50} values were much stronger than that of the commercial fungicide dimethomorph (EC_{50} value, 4.26 mM) and there was a pattern in the activity. The structure-activity relationship in compounds **IX-2f**, **IX-2g**, **IX-3f** and **IX-3g** was observed as: (1) **IX-2g** and **IX-3g** with a *N*-methyl-

Table 2. Fungicidal activities of *N*-[4-(4-fluoro)phenyl-2-aminothiazol-5-yl]pyrimidin-2-yl-*N*-phenylamine compounds (V-1 and V-2) and *N*-[4-(4-fluoro)phenyl-2-piperidin-4-yl-thiazol-5-yl]pyrimidin-2-yl-*N*-phenylamine derivatives (IX-2f, IX-2g, IX-3f and IX-3g) against *Phytophthora capsici* using whole plant experiments

Compounds	Inhibition Activity (%)[a]		
	40.0 mg L^{-1}	20.0 mg L^{-1}	12.5 mg L^{-1}
V-1	80.5 [b]	54.3 [c]	20.4 [d]
V-2	85.3	62.1	28.2
IX-2f	88.5	63.4	30.5
IX-2g	92.1	79.2	48.4
IX-3f	90.3	65.4	31.3
IX-3g	98.1	85.5	59.1
Dimethomorph	75.4[b]	50.2[c]	17.1[d]

[a] $p<0.05$ [b] 40.0 mg/L [c] 20.0 mg/L [d] 12.5 mg/L

Table 3. EC_{50} and EC_{90} values of fungicidal activities of *N*-[4-(4-fluoro)phenyl-2-aminothiazol-5-yl]pyrimidin-2-yl-*N*-phenylamine compounds (V-1 and V-2) and *N*-[4-(4-fluoro)phenyl-2-piperidin-4-yl-thiazol-5-yl]pyrimidin-2-yl-*N*-phenylamine derivatives (IX-2f, IX-2g, IX-3f and IX-3g) against *Phytophthora capsici* using whole plant experiments

Compounds	EC_{50} (mM)	EC_{90} (mM)
V-1	3.42	13.61
V-2	2.59	14.15
IX-2f	2.32	11.68
IX-2g	1.86	9.31
IX-3f	1.99	9.55
IX-3g	1.03	8.26
Dimethomorph	4.26	14.72

carbonylpiperidine displayed potent fungicidal activity, and (2) The replacement of the *N*-(3-hydroxymethyl)-phenylamine (**IX-2g** and **IX-3g**) significantly improved fungicidal activity. Compounds **IX-2f** and **IX-3f** had also improved fungicidal activity against *P. capsici* than that of **V-1** and **V-2**, but less active than **IX-2g** and **IX-3g**. As listed in Tables 2 and 3, the compounds showed a gradual increase in fungicidal activity in the following order: **V-1**, **V-2**, **IX-2f**, **IX-3f**, **IX-2g** and **IX-3g**.

Taken together, all results confirmed our original scheme: thiazole compounds with two polar groups on the ring might increase fungicidal activity. In this research, all the newly synthesized compounds containing two polar groups displayed potent fungicidal activity against *P. capsici*. In regard to structure-activity relationship of newly synthesized compounds **IX-2a** to **IX-2g**, the functional group on the pyrimidine ring of compounds like aminophenyl group may play an important role in the fungicidal activity against *P. capsici*. A dramatic fungicidal effect was found in the compounds that possessed the hydroxymethyl or 1-hydroxyethyl groups on the aminophenyl ring designated as **IX-2f**, **IX-3f**, **IX-2g**, and **IX-3g**.

On the other hand, amine of piperidine groups containing hydrogen or *N*-methyl group among the newly synthesized compounds also showed fungicidal activity on *P. capsici* and **IX-2g** and **IX-3g** containing *m*-1-hydroxyethylaminophenyl group increased fungicidal activities against *P. capsici* as the protection rate of **IX-2g** and **IX-3g** was 79.2% and 85.5% at the concentration of 20 mg/mL, respectively.

This data may be very useful for developing new fungicides from compounds that include an aminothiazole ring. Further study that validates the target site of the newly synthesized compounds displaying this mode of action on *P. capsici* should be conducted with different functional groups.

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