4854 *J. Agric. Food Chem.* **2009,** *57,* 4854–4860
DOI:10.1021/jf900222s

JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY
ARTICLE

Synthesis and Fungicidal Evaluation of 2-Arylphenyl Ether-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol Derivatives

GUAN-PING YU,[‡,§,†] LIANG-ZHONG XU,*,[†] XU YI,[†] WEN-ZHAO BI,[†] QI ZHU,[†] AND ZHI-WEI ZHAI[†]

[†]College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao 266042, China, [‡]Xinjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Urumqi 830011, China, and [§]Graduate School of the Chinese Academy of Sciences, Beijing 100039, China

A series of novel 2-arylphenyl ether-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol derivatives were designed and synthesized as candidate fungicides. The new compounds were identified by ^{1}H NMR spectroscopy and element analysis. Their antifungal activities were evaluated. They exhibited excellent antifungal activities against five common pathogens in comparison with the commercial fungicides tebuconazole and difenoconazole. The antifungal activities of three new triazole alcohol compounds were compared with those of tebuconazole and difenoconazole at a concentration of 1 μg/mL.

KEYWORDS: Triazole alcohol; aryl ether; fungicides; synthesis

INTRODUCTION

Many 1,2,4-triazole derivatives possess potent pesticidal (*1*), herbicidal (*2*), and antifungal (*3*−*5*) activities, such as tebuconazole, flutriafol, hexaconazole and cyproconazole (**Figure 1**) (*6*−*9*) and the structure unit “(1*H*-1,2,4-triazol-1-yl)ethanol” is key to their bioactivities. These compounds represent the most important category of fungicides to date and have long protective and curative activity against a broad spectrum of foliar, root, and seedling diseases caused by many ascomycetes, basidiomycetes, and imperfect fungi (*10*). In addition, the arylphenyl ether group is a highly efficient pharmacophore and is widely used in pesticide and drug molecular design (*11*, *12*). For example, difenoconazole (**Figure 2**) (*12*), discovered by Ciba-Geigy (U.K.) Limited, as fungicide offers a high level of control against soilborne dwarf bunt, for which chemical control was not previously available.

Bioisosterism (*13*) is an effective way to design bioactive compounds. To find some valuable compounds, a series of novel 2-arylphenylether-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol derivatives **V** were designed by introducing the arylphenyl ether group into the pharmacophore (1*H*-1,2,4-triazol-1-yl)ethanol (**Figure 2**). At first, compounds **V1** and **V20**−**V27** (*14*, *15*) (**Figure 3**) were synthesized in our laboratory. The results of preliminary biological tests against *Gibberella zeae*, *Alternaria solani*, *Fusarium oxysporum*, *Physalospora pircola*, and *Cercospora arachidicola* showed that all of these compounds, especially **V1**, possess higher antifungal activities comparable to those of commercial fungicides.

To further amplify the structure−activity relationship (SAR) between R^1 and R^2 of **V** and the resulting activity and to find valuable lead compounds with high antifungal activity, subsequent optimization of **V** was focused on varying the substituents R^1 and R^2 while retaining the arylphenyl ether group. In this paper, we describe the synthesis and antifungal activities of some novel triazole alcohol compounds containing an arylphenyl ether group (**Schemes 1**−**3** and **Table 1**).

*Author to whom correspondence should be addressed [telephone: +86-(0)532-84023177; fax: +86-(0)532-84023177; e-mail: qknhs@yahoo.com.cn].

MATERIALS AND METHODS

Synthetic Procedures. Proton NMR spectra were obtained at 500 MHz using a Bruker AC-500 spectrometer in $CDCl_3$ or DMSO-d_6 solution with TMS as internal standard. Chemical shift values (δ) are given in parts per million. Elemental analyses were determined on a Perkin-Elmer 240 elemental analyzer. Melting points were taken on a Yanaco-MP-500 microscopic melting apparatus and are uncorrected. Yields are not optimized.

General Procedure To Synthesize Intermediate 1-((2-(4-(4-Halogenated phenoxy)-2-chlorophenyl)oxiran-2-yl)methyl)-1*H*-1,2,4-triazole (IV-1). The intermediates **II-1** were prepared according to a literature procedure (*16*). The substituted acetophenones were reacted with bromine in anhydrous diethyl ether. Two intermediates **II-1** were prepared in this manner: **II-1a**, R^1 = Cl, yield 95.8%, mp 65−66 °C (lit. (*17*) yield 89.1%, mp 64−65 °C); and **II-1b**, R^1 = F, yield 90.1%, mp 44−46 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.70−7.77 (m, 7H, Ar−H), 4.54 (s, 2H, $C\underline{H}_2$Br).

To the solution of 2-bromo-1-(2-chloro-4-(4-halogenated phenoxy) phenyl)ethanone (**II-1**) (0.1 mol) and 1*H*-1,2,4-triazole (8.28 g, 0.12 mol) in ethyl acetate (70 mL) was added potassium carbonate (16.56 g, 0.12 mol); the resulting mixture was refluxed for 6 h and filtered, and the filtrate was condensed. The residual was recrystallized with ethyl acetate to give intermediate **III-1**: **III-1a**, R^1 = Cl, yield 67.3%, mp 151−153 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.43 (s, 1H, triazole−H), 8.01 (s, 1H, triazole−H), 6.68−7.69 (m, 7H, Ar−H), 4.89 (s, 2H, $C\underline{H}_2$); **III-1b**, R^1 = F, yield 60.5%, mp 125−126 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.23 (s, 1H, triazole−H), 7.99 (s, 1H, triazole−H). 6.76−7.81 (m, 7H, Ar−H), 4.92 (s, 2H, $C\underline{H}_2$).

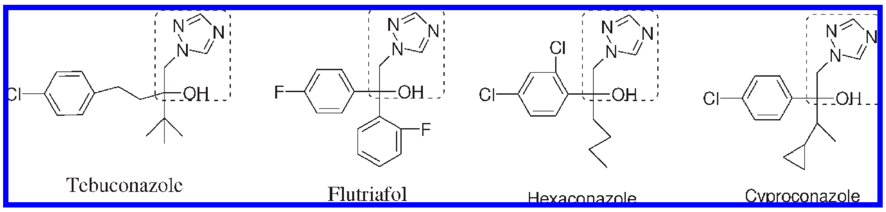


Figure 1. Structures of hexaconazole, cyproconazole, flutriafol, and tebuconazole.

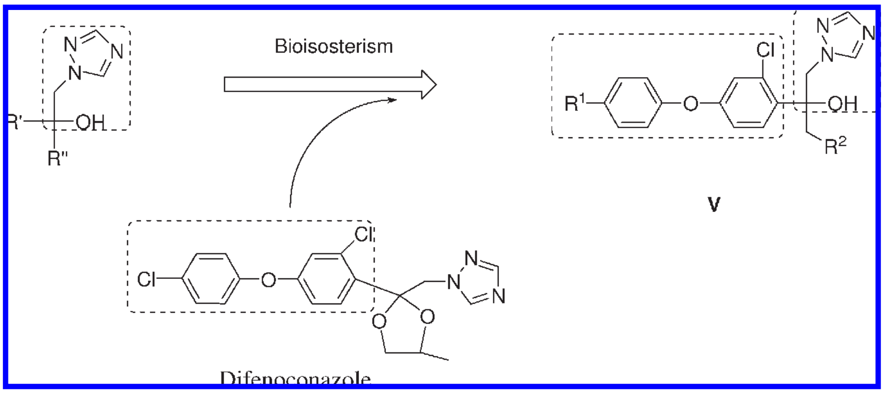


Figure 2. Design strategy of the title compounds.

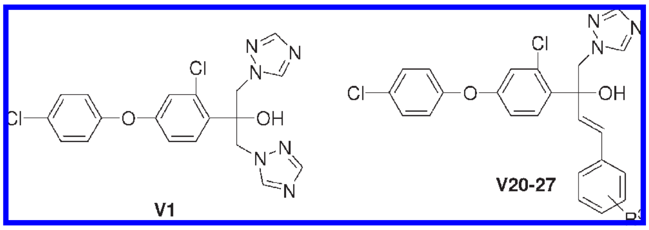


Figure 3. Structures of **V1** and **V20**−**27**.

To the mixture of **III-1** (0.1 mol), trimethylsulfoxonium iodide (26.4 g, 0.12 mol), and triethylbenzylammonium chloride (0.3 g) in 100 mL toluene was added dropwise the aqueous sodium hydroxide (20%, 80 g). After the resulting mixture had been stirred at 60 °C for 3−4 h, the organic phase was separated and condensed. The residual was recrystallized with ethyl acetate to afford intermediate **IV-1**: **IV-1a**, R^1 = Cl, yield 80%, mp 70−71 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89 (s, 1H, triazole−H), 7.65 (s, 1H, triazole−H), 6.55−7.22 (m, 7H, Ar−H), 4.64 (d, 1H, $^2J_{HH}$ = 15 Hz, triazole−C$\underline{H_2}$), 4.63 (d, 1H, $^2J_{HH}$ = 15 Hz, triazole−C$\underline{H_2}$), 2.72 (d, 1H, $^2J_{HH}$ = 4.5 Hz, O−C$\underline{H_2}$), 2.66 (d, 1H, $^2J_{HH}$ = 4.5 Hz, O−C$\underline{H_2}$); **IV-1b**, R^1 = F, yield 75.2%, mp 93−94 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.87 (s, 1H, triazole−H), 7.65 (s, 1H, triazole−H), 6.58−7.42 (m, 7H, Ar−H), 4.63 (d, 1H, $^2J_{HH}$ = 15 Hz, triazole−C$\underline{H_2}$), 4.62 (d, 1H, $^2J_{HH}$ = 15 Hz, triazole−C$\underline{H_2}$), 2.72 (d, 1H, $^2J_{HH}$ =4.5 Hz, O−C$\underline{H_2}$), 2.67 (d, 1H, $^2J_{HH}$ = 4.5 Hz, O−C$\underline{H_2}$).

General Procedure To Synthesize Intermediate 2-(4-(4-Halogenated phenoxy)-2-chlorophenyl)-2-methyloxirane (IV-2). According to the above procedure from **III-1** to **IV-1**, compound **IV-2** was synthesized from **I**: **IV-2a**, R^1 = Cl, yield 86.5%, mp 46−48 °C, ^{1}H NMR (DMSO-d_6, 500 MHz) δ 6.97−7.47 (m, 7H, Ar−H), 3.02 (d, 1H, $^2J_{HH}$ = 5 Hz, O−C$\underline{H_2}$), 2.77 (d, 1H, $^2J_{HH}$ = 5 Hz, O−C$\underline{H_2}$), 1.55 (s, 3H, C$\underline{H_3}$); **IV-2b**, R^1 = F, yield 76.2%, orange liquid, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.95−7.57 (m, 7H, Ar−H), 3.04 (d, 1H, $^2J_{HH}$ = 5 Hz, O−C$\underline{H_2}$), 2.79 (d, 1H, $^2J_{HH}$ = 5 Hz, O−C$\underline{H_2}$), 1.58 (s, 3H, C$\underline{H_3}$).

General Procedure To Synthesize Intermediate IV-3. The intermediates **II-3** were prepared according to the method given in ref (*18*). Intermediate **II-3** (10 mmol) and trimethylsulfonium methylsulfate (2.26 g, 12 mol) were dissolved in 20 mL of ethyl ether; potassium hydroxide (2.24 g, 40 mmol) powder was added to the solution at 0 °C, and then the mixture was heated to boiling (5 h). The mixture was cooled, poured into water, acidified with 30% H_2SO_4 to pH 7−8, and extracted with ethyl ether. The organic extract was washed with water twice, dried with sodium sulfate, and filtered. The solvent was evaporated, and the residue was recrystallized from acetone to give **IV-3**. The melting points and yields of intermediate **II-3** and **IV-3** are listed in **Table 2**, and their ^{1}H NMR data are listed in **Table 3**.

General Procedure for Target Compounds V1−V27. A mixture of epoxide **IV** (5 mmol), potassium carbonate (0.69 g, 5 mmol), and ring cleavage (6 mmol) was refluxed for 5−6 h in 20 mL of DMF. The organic phase was separated and condensed, and the residual was purified by vacuum column chromatography on silica gel to afford the desired compounds **V1**−**V27**.

Data for **V1**: see ref (*14*)

Data for **V2**: yield 71.5%; white solid, mp 85−88 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12 (s, 1H, triazole−H), 7.96 (s, 1H, triazole−H), 6.70−7.49 (m, 10H, Ar−H, imidazole−H), 5.50 (s, 1H, O$\underline{H}$), 5.40 (d, 1H, $^2J_{HH}$ = 14.2 Hz, triazole−C$\underline{H_2}$), 4.64 (d, 1H, $^2J_{HH}$ = 14.1 Hz, imidazole−C$\underline{H_2}$), 4.53 (d, 1H, $^2J_{HH}$ = 14.1 Hz, imidazole−C$\underline{H_2}$), 4.31 (d, 1H, $^2J_{HH}$ = 14.2 Hz, triazole−C$\underline{H_2}$). Anal. Calcd for $C_{20}H_{17}Cl_2N_5O_2$ (M_r = 430.29): C, 55.83; H, 3.98; N, 16.28. Found: C, 55.78; H, 3.90; N, 16.11.

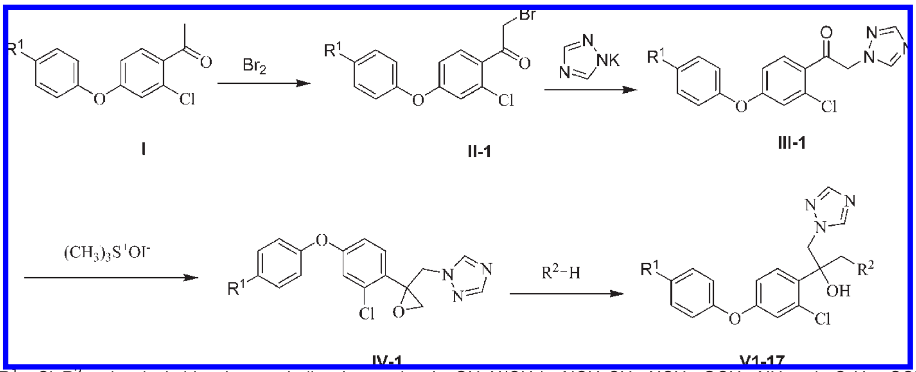
Data for **V3**: yield 51.3%; white solid, mp 100−103 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.08 (s, 1H, triazole−H), 7.98 (s, 1H, triazole−H), 6.87−7.47 (m, 7H, Ar−H), 5.23 (d, 1H, $^2J_{HH}$ = 14.5 Hz, triazole−C$\underline{H_2}$), 4.79 (d, 1H, $^2J_{HH}$ = 14.5 Hz, triazole−C$\underline{H_2}$), 4.52 (d, 1H, $^2J_{HH}$ = 14.1 Hz, morpholine−C$\underline{H_2}$), 4.38 (d, 1H, $^2J_{HH}$ = 14.1 Hz, morpholine−C$\underline{H_2}$), 3.49−4.26 (m, 8H, morpholine−H). Anal. Calcd for $C_{21}H_{22}Cl_2N_4O_3$ (M_r = 449.33): C, 56.13; H, 4.94; N, 12.47. Found: C, 56.01; H, 4.52; N, 12.41.

Data for **V4**: yield 61.6%; canary yellow solid, mp 112−115 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.55 (s, 1H, triazole−H), 8.01 (s, 1H, triazole−H), 6.64−7.85 (m, 11H, Ar−H, aziminobenzene), 5.52 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−C$\underline{H_2}$), 5.36 (d, 1H, aziminobenzene−H, $^2J_{HH}$ = 14.5 Hz), 5.34 (d, 1H, $^2J_{HH}$ = 14.5 Hz, aziminobenzene−H), 4.53 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−C$\underline{H_2}$). Anal. Calcd for $C_{23}H_{18}Cl_2N_6O_2$ (M_r = 481.33): C, 57.39; H, 3.77; N, 17.46. Found: C, 57.33; H, 3.67; N, 17.55.

Data for **V5**: yield 43.5%; white solid, mp 138−140 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.47 (s, 1H, triazole−H), 8.01 (s, 1H, triazole−H), 6.78−7.64 (m, 7H, Ar−H), 5.29 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−C$\underline{H_2}$), 4.88 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−C$\underline{H_2}$), 4.23 (s, 1H, OH), 4.36 (d, 1H, $^2J_{HH}$ = 12 Hz, HO−C$\underline{H_2}$), 3.90 (d, 1H, $^2J_{HH}$ = 14 Hz, HO−C$\underline{H_2}$). Anal. Calcd for $C_{17}H_{15}Cl_2N_3O_3$ (M_r = 380.23): C, 53.70; H, 3.98; N, 11.05. Found: C, 54.01; H, 3.89; N, 11.12.

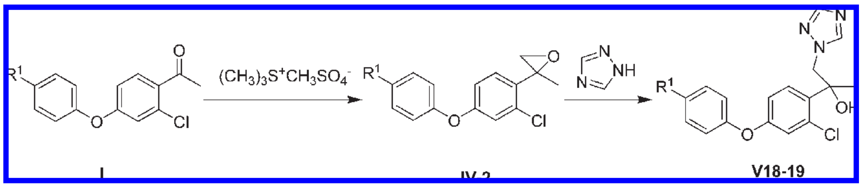
Data for **V6**: yield 86.2%; white solid, mp 119−120 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.18 (s, 1H, triazole−H), 8.01 (s, 1H, triazole−H), 6.78−7.64 (m, 7H, Ar−H), 4.74 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−C$\underline{H_2}$),

Scheme 1. Compounds **V1**−**V17**[a]



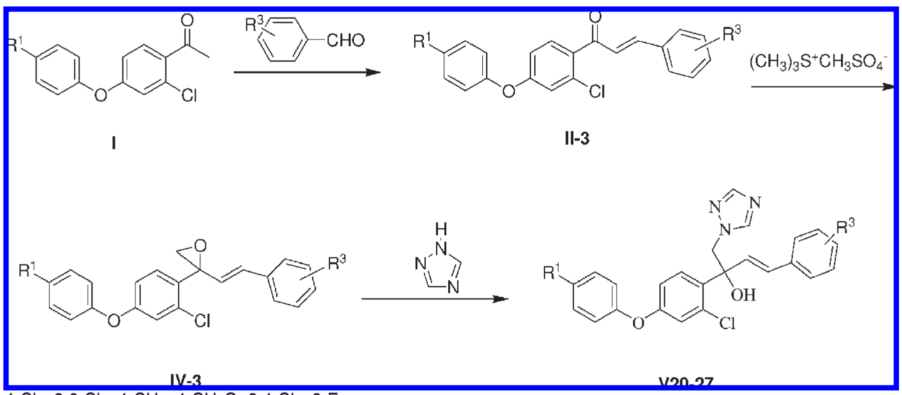
[a] Compounds **V1**−**V13**: R^1 = Cl. R^2 = triazole; imidazole; morpholine; benzotriazole; OH; $N(CH_3)_2$; NCH_2CH_3; NCH_3; OCH_3; NH-cyclo-C_6H_{11}; SCH_3; NCH_2CH_2OH; NCH_2OH. Compounds **V14**−**V17**: R^1 = F. R^2 = OCH_3; NCH_3; imidazole; triazole.

Scheme 2. Compounds **V18** and **V19**[a]



[a] R^1 = Cl; F.

Scheme 3. Compounds **V20**−**V27**[a]



[a] R^1 = Cl. R^3 = H; 4-Cl; 2,4-Cl_2; 2,6-Cl_2; 4-CH_3; 4-CH_3O; 3,4-Cl_2; 2-F.

4.71 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2), 3.41 (d, 1H, $^2J_{HH}$ = 13.5 Hz, $CH_2N(CH_3)_2$), 2.70 (d, 1H, $^2J_{HH}$ = 13.5 Hz, $CH_2N(CH_3)_2$), 2.13 (s, 6H, N$(CH_3)_2$). Anal. Calcd for $C_{19}H_{20}Cl_2N_4O_2$ (M_r = 407.29): C, 56.03; H, 4.95; N, 13.76. Found: C, 55.94; H, 4.90; N, 13.69.

Data for **V7**: yield 80.0%; white solid, mp 109−110 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.15 (s, 1H, triazole−H), 7.84 (s, 1H, triazole−H), 6.82−7.74 (m, 7H, Ar−H), 4.84 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2), 4.74 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2), 3.48 (d, 1H, $^2J_{HH}$ = 12.5 Hz, $CH_2NHC_2H_5$), 2.97 (d, 1H, $^2J_{HH}$ = 12.5 Hz, $CH_2NHC_2H_5$), 2.54 (q, 2H, $^3J_{HH}$ = 7 Hz, $NHCH_2CH_3$), 1.00 (t, 3H, $^3J_{HH}$ = 7 Hz, $NHCH_2CH_3$), 1.62 (s, 1H, $CH_2NHC_2H_5$). Anal. Calcd for $C_{19}H_{20}Cl_2N_4O_2$ (M_r = 407.29): C, 56.03; H, 4.95; N, 13.76. Found: C, 56.13; H, 4.89; N, 13.72.

Data for **V8**: yield 85.3%; white solid, mp 110−112 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.47 (s, 1H, triazole−H), 8.01 (s, 1H, triazole−H), 6.78−7.64 (m, 7H, Ar−H), 5.25 (d, 1H, $^2J_{HH}$ = 14.1 Hz, triazole−CH_2), 4.81 (d, 1H, $^2J_{HH}$ = 14.1 Hz, triazole−CH_2), 3.85 (d, 1H, $^2J_{HH}$ = 10 Hz, CH_2NHCH_3), 3.73 (d, 1H, $^2J_{HH}$ = 10 Hz, CH_2NHCH_3), 3.12 (s, 3H, NH−CH_3), 2.26 (s, 1H, NH−CH_3). Anal. Calcd for $C_{18}H_{18}Cl_2N_4O_2$ (M_r = 393.27): C, 54.97; H, 4.61; N, 14.25. Found: C, 54.89; H, 4.69; N, 14.18.

Data for **V9**: yield 83.4%; white solid, mp 149−150 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.15 (s, 1H, triazole−H), 7.80 (s, 1H, triazole−H), 6.74−7.60 (m, 7H, Ar−H), 5.05 (d, 1H, $^2J_{HH}$ = 14.5 Hz, triazole−CH_2), 4.74 (d, 1H, $^2J_{HH}$ = 14.5 Hz, triazole−CH_2), 3.92 (d, 1H, $^2J_{HH}$ = 9.5 Hz, CH_2OCH_3), 3.80 (d, 1H, $^2J_{HH}$ = 9.5 Hz, CH_2OCH_3), 3.35 (s, 3H, O−CH_3). Anal. Calcd for $C_{18}H_{17}Cl_2N_3O_3$ (M_r = 394.25): C, 54.84; H, 4.35; N, 10.66. Found: C, 54.88; H, 4.29; N, 10.72.

Data for **V10**: yield 82.7%; white solid, mp 106−107 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.16 (s, 1H, triazole−H), 7.85 (s, 1H, triazole−H), 6.82−7.45 (m, 7H, Ar−H), 4.85 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2), 4.67 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2), 3.43 (d, 1H, $^2J_{HH}$ = 12.5 Hz, CH_2NH), 3.04 (d, 1H, $^2J_{HH}$ = 12.5 Hz, CH_2NH), 0.91−2.21 (m, 11H, $CH_2NHC_6H_{11}$). Anal. Calcd for $C_{22}H_{24}Cl_2N_4O_2$ (M_r = 447.36): C, 59.87; H, 5.68; N, 12.14. Found: C, 59.78; H, 5.72; N, 12.20.

Data for **V11**: yield 90.5%; yellowish solid, mp 143−144 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.05 (s, 1H, triazole−H), 7.84 (s, 1H, triazole−H), 6.81−7.67 (m, 7H, Ar−H), 5.07 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2), 4.81 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2), 3.65 (d, 1H, $^2J_{HH}$ = 14 Hz, CH_2SCH_3), 2.97 (d, 1H, $^2J_{HH}$ = 14 Hz, CH_2SCH_3), 1.96 (s, 3H, S−CH_3). Anal. Calcd for $C_{18}H_{17}Cl_2N_3O_2S$ (M_r = 410.32): C, 52.69; H, 4.18; N, 10.24. Found: C, 52.64; H, 4.11; N, 10.32.

Data for **V12**: yield 91.6%; white solid, mp 100−101 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10 (s, 1H, triazole−H), 7.84 (s, 1H, triazole−H), 6.80−7.71 (m, 7H, Ar−H), 5.29 (s, 1H, NH), 4.86 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2), 4.82 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2), 3.60 (t, 2H, $^3J_{HH}$ = 5 Hz, CH_2CH_2OH), 3.50 (d, 1H, $^2J_{HH}$ = 12.5 Hz, $CH_2NHCH_2CH_2$), 3.01 (d, 1H, $^2J_{HH}$ = 12.5 Hz, $CH_2NHCH_2CH_2$),

Table 1. Compounds **V1**−**V27**

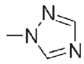
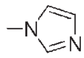
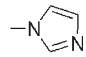
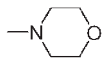
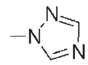
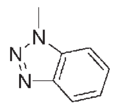
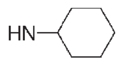
Comp	R[1]	R[2]	R[3]	Comp	R[1]	R[2]	R[3]
V1	Cl		----	**V15**	F	$-NHCH_3$	----
V2	Cl		----	**V16**	F		----
V3	Cl		----	**V17**	F		----
V4	Cl		----	**V18**	Cl	----	----
V5	Cl	OH	----	**V19**	F	----	----
V6	Cl	$-N(CH_3)_2$	----	**V20**	Cl	----	H
V7	Cl	$-NHCH_2CH_3$	----	**V21**	Cl	----	4-Cl
V8	Cl	$-NHCH_3$	----	**V22**	Cl	----	2,4-Cl_2
V9	Cl	$-OCH_3$	----	**V23**	Cl	----	2,6-Cl_2
V10	Cl		----	**V24**	Cl	----	4-CH_3
V11	Cl	$-SCH_3$	----	**V25**	Cl	----	4-OCH_3
V12	Cl	$-NHCH_2CH_2OH$	----	**V26**	Cl	----	3,4-Cl_2
V13	Cl	$-NHOCH_3$	----	**V27**	Cl	----	2-F
V14	F	$-OCH_3$	----				

Table 2. Yields and Melting Points of Intermediates **II-3** and **IV-3**[a]

compd	R[3]	yield (%)	mp (°C)	compd	R[3]	yield (%)	mp (°C)
II-3a	H	90.0	68−69	**IV-3a**	H	94.1	54−55
II-3b	4-Cl	81.2	117−118	**IV-3b**	4-Cl	70.5	118−119
II-3c	2,4-Cl_2	88.5	124−125	**IV-3c**	2,4-Cl_2	79.4	77−79
II-3d	2,6-Cl_2	92.7	79−80	**IV-3d**	2,6-Cl_2	86.0	47−48
II-3e	4-CH_3	73.6	86−87	**IV-3e**	4-CH_3	73.3	84−86
II-3f	4-CH_3O	96.0	91−93	**IV-3f**	4-CH_3O	82.1	78−81
II-3 g	3,4-Cl_2	91.2	107−111	**IV-3 g**	3,4-Cl_2	65.4	62−63
II-3 h	2-F	58.6	103−104	**IV-3 h**	2-F	52.8	81−82

[a] Intermediates **II-3** and **IV-3**: R[1] = Cl.

2.68 (t, 2H, $^3J_{HH}$ = 5 Hz, $NHC\underline{H}_2CH_2OH$), 2.02 (s, 1H, $NHCH_2$-$CH_2O\underline{H}$). Anal. Calcd for $C_{19}H_{20}Cl_2N_4O_3$ (M_r = 423.29): C, 53.91; H, 4.76; N, 13.24. Found: C, 54.02; H, 4.70; N, 13.34.

Data for **V13**: yield 60.5%; white solid, mp 124−125 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.01 (s, 1H, triazole−H), 7.71 (s, 1H, triazole−H), 6.17−7.61 (m, 7H, Ar−H), 5.59 (s, 1H, NH), 4.86 (d, 1H, $^2J_{HH}$ = 14.5 Hz, triazole−$C\underline{H}_2$), 4.72 (d, 1H, $^2J_{HH}$ = 14.5 Hz, triazole−$C\underline{H}_2$), 3.62 (d, 1H, $^2J_{HH}$ = 14.5 Hz, $C\underline{H}_2NHCH_2OH$), 3.38 (d, 1H, $^2J_{HH}$ = 14.5 Hz, $C\underline{H}_2NHCH_2OH$), 3.30 (s, 3H, $NHOC\underline{H}_3$). Anal. Calcd for $C_{18}H_{18}Cl_2N_4O_3$ (M_r = 409.27): C, 52.82; H, 4.43; N, 13.69. Found: C, 52.04; H, 4.39; N, 13.60.

Data for **V14**: yield 61%; white solid, mp 88−89 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10 (s, 1H, triazole−H), 7.82 (s, 1H, triazole−H), 6.65−7.61 (m, 7H, Ar−H), 5.12 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−$C\underline{H}_2$), 4.93 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−$C\underline{H}_2$), 4.10 (s, 1H, OH), 3.92 (d, 1H, $^2J_{HH}$ = 9.5 Hz, $C\underline{H}_2OCH_3$), 3.81 (d, 1H, $^2J_{HH}$ = 9.5 Hz, $C\underline{H}_2OCH_3$), 3.45 (s, 3H, $OC\underline{H}_3$). Anal. Calcd for $C_{18}H_{17}ClFN_3O_3$ (M_r = 377.8): C, 57.22; H, 4.54; N, 11.12. Found: C, 57.13; H, 4.49; N, 11.24.

Data for **V15**: yield 65%; yellowish solid, mp 143−145 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (s, 1H, triazole−H), 8.00 (s, 1H, triazole−H), 6.67−7.55 (m, 7H, Ar−H), 5.25 (d, 1H, $^2J_{HH}$ = 13.5 Hz, triazole−$C\underline{H}_2$), 4.71 (d, 1H, $^2J_{HH}$ = 13.5 Hz, triazole−$C\underline{H}_2$), 3.63 (s, 1H, $O\underline{H}$), 3.55 (d, 1H, $^2J_{HH}$ = 10 Hz, $C\underline{H}_2NHCH_3$), 3.27 (d, 1H, $^2J_{HH}$ = 10 Hz, $C\underline{H}_2NHCH_3$), 3.10 (m, 1H, $N\underline{H}$), 2.25 (s, 3H, $CH_2NHC\underline{H}_3$). Anal. Calcd for $C_{18}H_{18}ClFN_4O_2$ (M_r = 376.81): C, 57.37; H, 4.81; N, 14.87. Found: C, 57.23; H, 4.71; N, 14.70.

Data for **V16**: yield 75%; white solid, mp 167−168 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93 (s, 1H, triazole−H), 7.81 (s, 1H, triazole−H), 6.63−7.52 (m, 10H, Ar−H, imidazole−H), 5.35 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−$C\underline{H}_2$), 4.63 (d, 1H, $^2J_{HH}$ = 14.2 Hz, imidazole−$C\underline{H}_2$), 4.49 (d, 1H, $^2J_{HH}$ = 14.2 Hz, imidazole−$C\underline{H}_2$), 4.29 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−$C\underline{H}_2$), 2.03 (s, 1H, $O\underline{H}$). Anal. Calcd for $C_{20}H_{17}ClFN_5O_2$ (M_r = 413.83): C, 58.05; H, 4.14; N, 16.92. Found: C, 58.25; H, 4.10; N, 16.77.

Data for **V17**: yield 43%; white solid, mp 215−217 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12 (s, 2H, triazole−H), 7.91 (s, 2H, triazole−H), 6.68−7.54 (d, 7H, Ar−H), 5.34 (d, 2H, $^2J_{HH}$ = 14.5 Hz, triazole−$C\underline{H}_2$), 4.60 (d, 2H, $^2J_{HH}$ = 14.5 Hz, triazole−$C\underline{H}_2$), 1.94 (s, 1H, $O\underline{H}$). Anal. Calcd for $C_{19}H_{16}ClFN_6O_2$ (M_r = 414.82): C, 55.01; H, 3.89; N, 20.26. Found: C, 55.31; H, 3.82; N, 20.33.

Data for **V18**: yield 87.5%; white solid, mp 133−136 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97 (s, 1H, triazole−H), 7.87 (s, 1H, triazole−H), 7.66−6.77 (m, 7H, Ar−H), 5.26 (d, 1H, $^2J_{HH}$ = 14.1 Hz, triazole−$C\underline{H}_2$), 4.65 (d, 1H, $^2J_{HH}$ = 14.1 Hz, triazole−$C\underline{H}_2$), 4.74 (s, 1H, O−$\underline{H}$), 1.73

Table 3. ^{1}H NMR Data of Intermediates **II-3** and **IV-3**

compd	δ (500 MHz, DMSO-d_6)
II-3a	7.76 (d, 1H, $^3J_{HH}$ = 3.5 Hz, Ar—CH=CH), 7.66 (d, 1H, $^3J_{HH}$ = 3.5 Hz, Ar—CH=CH), 7.05−7.52 (m, 12H, Ar—H)
II-3b	7.82 (d, 1H, $^3J_{HH}$ = 3.5 Hz, Ar—CH=CH), 7.67 (d, 1H, $^3J_{HH}$ = 3.5 Hz, Ar—CH=CH), 7.06−7.53 (m, 11H, Ar—H)
II-3c	8.16 (d, 1H, $^3J_{HH}$ = 3.0 Hz, Ar−CH=CH), 8.14 (d, 1H, $^3J_{HH}$ = 3.0 Hz, Ar—CH=CH), 7.13−7.82 (m, 10H, Ar—H)
II-3d	7.70 (d, 1H, $^3J_{HH}$ = 4.0 Hz, Ar—CH=CH), 7.57 (d, 1H, $^3J_{HH}$ = 4.0 Hz, Ar—CH=CH), 7.07−7.54 (m, 10H, Ar—H)
II-3e	7.67 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ar—CH=CH), 7.64 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ar—CH=CH), 7.05−7.52 (m, 11H, Ar—H), 2.33 (s, 3H, CH_3)
II-3f	7.71 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ar-CH=CH), 7.65 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ar-CH=CH), 7.03−7.55 (m, 11H, Ar−H), 3.63 (s, 3H, CH_3)
II-3 g	7.88(d, 1H, $^3J_{HH}$ = 3.5 Hz, Ar—CH=CH), 7.69 (d, 1H, $^3J_{HH}$ = 3.5 Hz, Ar—CH=CH), 7.05−7.54 (m, 11H, Ar—H)
II-3 h	7.97 (d, 1H, $^3J_{HH}$ = 4.0 Hz, Ar—CH=CH), 7.94 (d, 1H, $^3J_{HH}$ = 4 Hz, Ar—CH=CH), 7.06−7.71 (m, 11H, Ar—H)
IV-3a	7.01−7.49 (m, 12H, Ar—H), 6.24 (d, 1H, $^3J_{HH}$ = 16 Hz, Ar—CH=CH), 6.16 (d, 1H, $^3J_{HH}$ = 16 Hz, Ar—CH=CH), 3.34 (d, 1H,$^2J_{HH}$ = 5 Hz, O—CH_2), 3.13 (d, 1H, $^2J_{HH}$ = 5 Hz, O—CH_2)
IV-3b	7.03−7.51 (m, 11H, Ar—H), 6.34 (d, 1H, $^3J_{HH}$ = 16.5 Hz, Ar—CH=CH), 6.22 (d, 1H, $^3J_{HH}$ = 16.5 Hz, Ar—CH=CH), 3.33 (d, 1H, $^2J_{HH}$ = 5 Hz, O—CH_2), 3.11 (d, 1H, $^2J_{HH}$ = 5 Hz, O—CH_2)
IV-3c	7.03−7.57 (m, 10H, Ar—H), 6.32 (d, 1H, $^3J_{HH}$ = 16 Hz, Ar—CH=CH), 6.27 (d, 1H, $^3J_{HH}$ = 16 Hz, Ar—CH=CH), 3.35 (d, 1H,$^2J_{HH}$ = 5 Hz, O—CH_2), 3.15 (d, 1H, $^2J_{HH}$ = 5 Hz, O—CH_2)
IV-3d	7.04−7.55 (m, 10H, Ar—H), 6.21 (d, 1H, $^3J_{HH}$ = 16 Hz, Ar—CH=CH), 6.20 (d, 1H, $^3J_{HH}$ = 16 Hz, Ar—CH=CH), 3.35 (d, 1H, $^2J_{HH}$ = 5.5 Hz, O—CH_2), 3.15(d, 1H, $^2J_{HH}$ = 5.5 Hz, O—CH_2)
IV-3e	7.02−7.51 (m, 11H, Ar—H), 6.22 (d, 1H, $^3J_{HH}$ = 16 Hz, Ar—CH=CH), 6.17 (d, 1H, $^3J_{HH}$ = 16 Hz, Ar—CH=CH), 3.32 (d, 1H,$^2J_{HH}$ = 5 Hz, O—CH_2), 3.10 (d, 1H, $^2J_{HH}$ = 5 Hz, O—CH_2), 2.25 (s, 3H, CH_3)
IV-3f	7.03−7.54 (m, 11H, Ar—H), 6.26 (d, 1H, $^3J_{HH}$ = 16 Hz, Ar—CH=CH), 6.19 (d, 1H, $^3J_{HH}$ = 16 Hz, Ar—CH=CH), 3.75 (s, 3H, CH_3), 3.35 (d, 1H,$^2J_{HH}$ = 5 Hz, O—CH_2), 3.13 (d, 1H,$^2J_{HH}$ = 5 Hz, O—CH_2)
IV-3 g	7.03−7.68 (m, 10H, Ar—H), 6.31 (d, 1H, $^3J_{HH}$ = 16 Hz, Ar—CH=CH), 6.23 (d, 1H, $^3J_{HH}$ = 16 Hz, Ar—CH=CH), 3.33 (d, 1H, $^2J_{HH}$ = 5 Hz, O—CH_2) 3.16 (d, 1H, $^2J_{HH}$ = 5 Hz, O—CH_2)
IV-3 h	7.04−7.65 (m, 11H, Ar—H), 6.41 (d, 1H, $^3J_{HH}$ = 16.5 Hz, Ar—CH=CH), 6.33 (d, 1H, $^3J_{HH}$ = 16.5 Hz, Ar—CH=CH), 3.35 (d, 1H, $^2J_{HH}$ = 5 Hz, O—CH_2) 3.15 (d, 1H, $^2J_{HH}$ = 5 Hz, O—CH_2)

(s, 3H, CH_3). Anal. Calcd for $C_{17}H_{15}Cl_2N_3O_2$ (M_r = 364.23): C, 56.06; H, 4.15; N, 11.54. Found: C, 56.21; H, 4.10; N, 11.66.

Data for **V19**: yield 85%; white solid, mp 125−127 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97 (s, 1H, triazole−H), 7.86 (s, 1H, triazole−H), 6.75−7.63 (m, 7H, Ar−H), 5.28 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2), 4.73 (s, 1H, OH), 4.52 (d, 1H, $^2J_{HH}$ = 14.1 Hz, triazole−CH_2), 1.73 (s, 3H, CH_3). Anal. Calcd for $C_{17}H_{15}ClFN_3O_2$ (M_r = 347.77): C, 58.71; H, 4.35; N, 12.08. Found: C, 58.66; H, 4.45; N, 12.28.

Data for **V20**: yield 68.9%; yellow solid, mp 142−145 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.04 (s, 1H, triazole−H), 7.87 (s, 1H, triazole−H), 6.93−7.74 (m, 12H, Ar−H), 6.76−6.83 (q, 2H, CH=CH), 5.20 (d, 1H, $^2J_{HH}$ = 14.5 Hz, triazole−CH_2), 4.76 (d, 1H, $^2J_{HH}$ = 14.5 Hz, triazole−CH_2). Elemental Anal. Calcd for $C_{24}H_{19}Cl_2N_3O_2$: C, 63.73; H, 4.23; N, 9.29. Found: C, 63.72; H, 4.28; N, 9.26.

Data for **V21**: yield 81.5%; yellowish solid, mp 116−119 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.23 (s, 1H, triazole−H), 7.91 (s, 1H, triazole−H), 6.96−7.74 (m, 11H, Ar−H), 6.79−6.85 (q, 2H, CH=CH), 5.26 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2), 4.77 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2). Elemental Anal. Calcd for $C_{24}H_{18}Cl_3N_3O_2$: C, 59.22; H, 3.73; N, 8.63. Found: C, 59.28; H, 3.71; N, 8.67.

Data for **V22**: yield 75.4%; white solid, mp 128−130 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.18 (s, 1H, triazole−H), 7.91 (s, 1H, triazole−H), 6.99−7.77 (m, 10H, Ar−H), 6.79−6.85 (q, 2H, CH=CH), 5.24 (d, 1H, $^2J_{HH}$ = 14.1 Hz, triazole−CH_2), 4.78 (d, 1H, $^2J_{HH}$ = 14.1 Hz, triazole−CH_2), 1.77 (s, 1H, OH). Elemental Anal. Calcd for $C_{24}H_{17}Cl_4N_3O_2$: C, 55.30; H, 3.29; N, 8.06. Found: C, 55.33; H, 3.35; N, 8.02.

Data for **V23**: yield 80.6%; yellowish solid, mp 128−130 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.38 (s, 1H, triazole−H), 7.98 (s, 1H, triazole−H), 6.93−7.81 (m, 10H, Ar−H), 6.82−6.87 (q, 2H, CH=CH), 5.24 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2), 4.92 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2). Elemental Anal. Calcd for $C_{24}H_{17}Cl_4N_3O_2$: C, 55.30; H, 3.29; N, 8.06. Found: C, 55.28; H, 3.31; N, 8.09.

Data for **V24**: yield 53%; yellow viscous fluid; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12 (s, 1H, triazole−H), 7.98 (s, 1H, triazole−H), 6.89−7.82 (m, 11H, Ar−H), 6.75−6.79 (q, 2H, CH=CH), 5.16 (d, 1H, $^2J_{HH}$ = 14.5 Hz, triazole−CH_2), 4.78 (d, 1H, $^2J_{HH}$ = 14.5 Hz, triazole−CH_2), 2.81 (s, 3H, CH_3). Elemental Anal. Calcd for $C_{25}H_{21}Cl_2N_3O_2$: C, 64.39; H, 4.54; N, 9.01. Found: C, 64.38; H, 4.58; N, 8.87.

Data for **V25**: yield 61.8%; yellow solid, mp 121−124 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.31 (s, 1H, triazole−H), 7.92 (s, 1H, triazole−H), 6.82−7.73 (m, 11H, Ar−H), 6.66−6.74 (q, 2H, CH=CH), 5.26 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2), 4.78 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2), 3.85 (s, 3H, O−CH_3). Elemental Anal. Calcd for $C_{25}H_{21}Cl_2N_3O_3$: C, 62.25; H, 4.39; N, 8.71. Found: C, 62.21; H, 4.42; N, 8.75.

Data for **V26**: yield 52.2%; yellowish solid, mp 117−120 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.29 (s, 1H, triazole−H), 7.89 (s, 1H, triazole−H), 6.78−7.69 (m, 10H, Ar−H), 6.67−6.69 (q, 2H, CH=CH), 5.27 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2), 4.77 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2). Elemental Anal. Calcd for $C_{24}H_{17}Cl_4N_3O_2$: C, 55.30; H, 3.29; N, 8.06. Found: C, 55.31; H, 3.28; N, 8.11.

Data for **V27**: yield 50.3%; white solid, mp 105−107 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10 (s, 1H, triazole−H), 7.91 (s, 1H, triazole−H), 6.96−7.76 (m, 11H, Ar−H), 6.83−6.85 (q, 2H, CH=CH), 5.27 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2), 4.77 (d, 1H, $^2J_{HH}$ = 14 Hz, triazole−CH_2). Elemental Anal. Calcd for $C_{24}H_{18}Cl_2FN_3O_2$: C, 61.29; H, 3.86; N, 8.93. Found: C, 61.27; H, 3.88; N, 8.96.

Bioassays. For comparison, the antifungal activities of the title compounds (**V1**−**V27**) and the commercial fungicides (tebuconazole, difenoconazole) were evaluated according to a procedure described in our previous work (*14*, *15*). A mixture of the same amount of water, *N*-dimethylformamide, and Tween 20 was used as a negative control. The inhibition rates (%) of **V1**−**V27** are summarized in **Table 4**.

RESULTS AND DISCUSSION

Preparations. The target compounds **V1**−**V27** were synthesized from 1-(4-(4-halogenated phenoxy)-2-chlorophenyl)ethanone (**I**) as shown in **Schemes 1**−**3**. The substituted acetophenones (**I**) were reacted with bromine in anhydrous diethyl ether to give intermediate **II-1** according to a reported procedure (*16*), and subsequent reaction with 1*H*-1,2,4-triazole yielded compounds **III-1**; further epoxidation reaction using trimethylsulfoxonium iodide provided epoxide **IV-1** (**Scheme 1**). Intermediates **IV-2** were prepared by epoxidized compound **I** with trimethylsulfonium methylsulfate as shown in **Scheme 2**. To obtain intermediate **IV-3**, we synthesized **II-3** according to method given in ref (*18*) and then epoxidized **II-3** using trimethylsulfonium methylsulfate (**Scheme 3**). The epoxide **IV**, in base-catalyzed ring-opening, was attacked by the 1*H*-1,2,4-triazole and other ring cleavages at the less sustituted carbon atom to afford target compounds **V1**−**27**. Intermediates **IV-2** and **IV-3** can be epoxidized **I** and **II-3** by trimethylsulfoxonium iodide or

Table 4. Fungicidal Activities of Compounds **V1**−**V27**

compd	concn (μg/mL)	fungicidal activities (inhibition %)				
		G. zeae	*A. solani*	*C. arachidicoa*	*P. pircola*	*F. oxysporum*
V1[a]	50	100	99.0	100	100	99.0
	5	100	84.2	100	91.0	80.9
	1	82.6	58.6	88.1	90.3	62.5
V2	50	71.4	99.0	100.0	99.0	95.0
V3	50	78.3	55.2	60.0	65.2	34.4
V4	50	45.4	53.3	62.7	55.6	48.7
V5	50	99.0	99.0	100.0	99.0	77.1
V6	50	96.9	99.1	97.2	100	100
	1	4.2	18.6	0	27.7	0
V7	50	56.8	63.8	61.4	75.4	86.9
V8	50	98	99	99	100	100
	1	72.5	50.3	57.2	96	0
V9	50	98.7	100	99.1	100	100
	1	63.2	98.7	78.6	99.2	89.9
V10	50	47.5	87.3	75.2	100	78.9
V11	50	37.2	83.7	82.4	100	78.9
V12	50	37.3	98.5	72.2	97.7	100
V13	50	97.3	100	98.4	100	100
	1	18.2	61.3	55.3	84.2	0
V14	50	100	100	100	100	100
	1	57.2	96.9	76.2	89.5	82.7
V15	50	100	100	100	100	100
	1	67.2	86.7	72.1	74.6	68.7
V16	50	84.3	73.2	100.0	87.9	57.1
V17	50	95	97.5	100	95.9	100
	1	21.8	75.0	39.5	49.3	90.0
V18	50	100.0	78.2	100.0	100.0	85.3
V19	50	98	100	99	100	99
	1	0	20.0	37.5	48.7	17.9
V20[a]	50	64.3	81.2	100	67.9	68.7
V21[a]	50	77.2	76.8	95.0	64.1	57.1
V22[a]	50	37.2	54.4	97.8	58.7	50.9
V23[a]	50	50.3	60.7	92.4	79.3	51.8
V24[a]	50	51.8	63.2	95.0	59.3	60.2
V25[a]	50	61.4	55.0	91.3	64.5	55.4
V26[a]	50	53.6	66.7	100.0	64.6	57.1
V27[a]	50	61.4	55.0	99.3	52.1	65.9
difenoconazole	50	100	99.2	100	100	99.9
	1	73.9	95	56.7	69.7	53.1
tebuconazole	50	100	100	100	100.0	100.0
	1	86.9	65.5	91.0	68.2	65.6

[a] These compounds and their antifungal activities had been reported in refs (*14*) and (*15*).

trimethylsulfonium methylsulfate. We preferred the latter agent for its cheapness and greater convenience.

The structures of all of the target compounds were characterized by ^{1}H NMR and elemental analyses. In the ^{1}H NMR spectra of compounds **V** the signals of the two protons of the CH_2 group connecting the triazoles appear as two doublets at around 5.2 and 4.7 ppm. It is believed that this is due to the fact they are attached to an asymmetrical carbon atom, which makes the magnetic environments of the two CH_2 group protons different.

Structure−Activity Relationship. The antifungal activities for compound **V** were tested, and the results are listed in **Table 4**.

The 1*H*-1,2,4-triazole compounds' mode of action is the arrest of sterol biosynthesis by inhibiting 14α-demethylase (**14α-DM**), a specific cytochrome P450. Evidence that sterol biosynthesis inhibition is linked to the binding of nucleophilic N_4 of 1,2,4-triazole to iron in the ferric state of the heme is an essential feature of the inhibition action (*19*). The N_1 substituent, which generally bears one or more hydrophobic groups, binds to a region normally occupied by the natural sterol substrate. Structural limitations to binding have been analyzed with computer graphic approaches (*19*). As shown in **Table 4**, all title compounds had a high inhibition rate at 50 μg/mL concentration; **V**, with a small size of R^2, favorably inhibited the oxidative removal of sterol C(*14*) methyl groups by the cytochrome P450 enzyme, which increased the antifungal activity, especially when the substituents of R^2 were smaller alkylamino/alkoxy groups (such as methylamino, methoxy) or a triazole group (compounds **V1**, **V8**, **V9**, **V14**, **V15**, **V17**). It was also found that when the R^2 was modified by a substituted benzyl group, the target molecules **V20**−**V27** showed excellent inhibitory activities to *C. arachidicoa*. When R^2 was not changed, the antifungal acitvities for R^1 (Cl, F) were in the same level as the similar hydrophobic parameter of Cl (0.71) and F (0.14) (*20*).

Compounds (**V1**, **V6**, **V8**, **V9**, **V13**−**V15**, **V17**, **V19**) with higher inhibition rates (>90% for all five fungi at 50 μg/mL concentration) were further bioassayed at a concentration of 1 μg/mL. The bioassay result showed that compounds **V1**, **V9**, and **V15** possess higher antifungal activities comparable to those of commercial fungicides tebuconazole and difenoconazole.

In conclusion, by introducing the arylphenyl ether group in triazole alcohol compounds, a new type of fungicidal candidate was synthesized and explored. When the substituents R^2 were smaller alkylamino/alkoxy groups (such as methylamino, methoxy) or a triazole group, the new target compounds showed higher antifungal activities comparable to those of commercial fungicides tebuconazole and difenoconazole.

LITERATURE CITED

(1) Parsons, J. H.; West, P. J. Pesticidal 1,2,4-triazole compounds. U.S. Patent 4414221, 1981.

(2) Ma, Y. M.; Liu, R. H.; Gong, X. Y.; Li, Z.; Huang, Q. C.; Wang, H. S.; Song, G. H. Synthesis and herbicidal activity of *N*,*N*-diethyl-3-(arylselenonyl)-1*H*-1,2,4-triazole-1-carboxamide. *J. Agric. Food Chem.* **2006**, *54*, 7724–7728.

(3) Arnoldi, A.; Carzaniga, R.; Morini, G.; Merlini, L.; Farina, G. Synthesis, fungicidal activity, and QSAR of a series of 2-dichlorophenyl-3-triazolylpropyl ethers. *J. Agric. Food Chem.* **2000**, *48*, 2547–2555.

(4) Mares, D.; Romagnoli, C.; Andreotti, E.; Manfrini, M.; Vicentini, C. B. Synthesis and antifungal action of new tricyclazole analogues. *J. Agric. Food Chem.* **2004**, *52*, 2003–2009.

(5) Arnoldi, A.; Dallavalle, S.; Merlini, L.; Musso, L.; Farina, G.; Moretti, M.; Jayasinghe, L. Synthesis and antifungal activity of a series of N-substituted [2-(2,4-dichlorophenyl)-3-(1,2,4-triazol-1-yl)]propylamines. *J. Agric. Food Chem.* **2007**, *55*, 8187–8192.

(6) Worthington, P. A. Synthesis of 1,2,4-triazole compounds related to the fungicides flutriafol and hexaconazole. *Pestic. Sci.* **1991**, *31*, 457–498.

(7) Reinhard, S. Bayer fungicides of the triazole group. *Zesz. Probl. Postepow Nauk Roln.* **1988**, *371*, 33–46.

(8) Ferreira, E. M.; Alfenas, A. C.; Maffia, L. A.; Mafia, R. G.; Mounteer, A. H. Effectiveness of systemic fungicides in the control of *Quambalaria eucalypti* and their effects on production of eucalypt mini-cuttings for rooting. *Crop Prot*. **2008**, *27*, 161–170.
(9) Klopman1, G.; Ptchelintsev1, D. Antifungal triazole alcohols: a comparative analysis of structure-activity, structure-teratogenicity and structure-therapeutic index relationships using the Multiple Computer-Automated Structure Evaluation (Multi-CASE) methodology. *J. Comput. Aid. Mol. Des*. **1993**, *7*, 349–362.
(10) Berg, D. Biochemical mode of action of fungicides. Ergosterol biosynthesis inhibitors. In *Fungicide Chemistry: Advances and Practical Applications*; Green, M. B., Spilker, D. A., Eds.; ACS Symposium Series 304; American Chemical Society: Washington, DC, 1986; pp 25−51.
(11) Hubele, A.; Riebli, P. Arylphenyl ether derivatives, compositions containing these compounds and use thereof. U.S. Patent 5266585, 1993.
(12) Hubele, A.; Riebli, P. Novel microbicidal arylphenyl ether derivatives. GB 2098607, 1982.
(13) Lima, L. M. A.; Barreiro, E. J. Bioisosterism: a useful strategy for molecular modification and drug design. *Curr. Med. Chem*. **2005**, *12*, 23–49.
(14) Xu, L. Z.; Wu, H. L.; Hu, Z. Q.; Zhu, Q.; Yu, G. P.; Bi, W. Z. Synthesis ditriazole compounds containing aromatic ether group and use. CN 1923819, 2006.
(15) Jian, F. F.; Xu, L. Z.; Hu, Z. Q.; Zhu, Q.; Yu, G. P. Synthese and biological activities of novel triazole compounds containing a aromatic ether group. CN 101225074, 2007.
(16) Cowper, R. M.; Davidson, L. H. Phenacyl bromide. *Org. Synth. Collect*. **1943**, *2*, 480.
(17) Li, H. H.; Liao, F. G.; Wang, P.; Gao, Y. X. Preparation of fungicide difenoconazol. *Trans. Beijing Inst. Technol*. **2006**, *26*, 365−368 (in Chinese).
(18) Kohler, E. P.; Chadewell, H. M. Benzalacetophenone. *Org. Synth. Collect*. **1922**, *2*, 1.
(19) Gozzo, F.; Carelli, A.; Carzaniga, R.; Farina, G.; Arnoldi, A.; Lamb, D.; Kelly, S. L. Stereoselective interaction of tetraconazole with 14α-demethylase in fungi. *Pestic. Biochem. Physiol*. **1995**, *53*, 10–22.
(20) Hansch, C.; Leo, A.; Hoekman, D. *Exploring QSAR*; ACS Professional Reference Book; American Chemical Society: Washington, DC, 1995.

Received January 20, 2009. Revised manuscript received April 16, 2009.