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Synthesis and Fungicidal Activity of Some Novel Thiazole Schiff Bases Derived from Benzo[*d*][1,3]dioxole

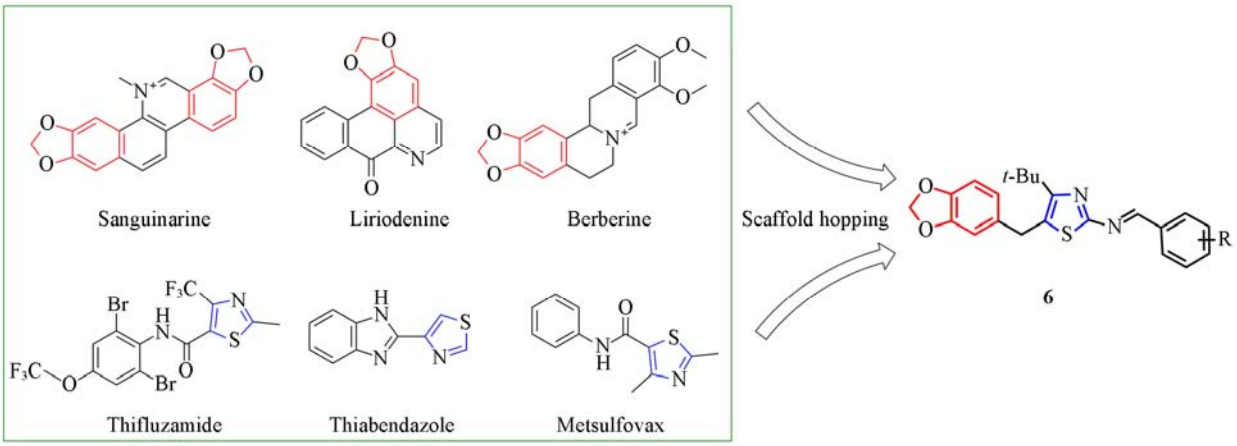
WU Zhilin, DING Na, LIN Ding, HU Aixi*, YE Jiao and LI Guoxi
College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, P. R. China

Abstract A series of novel thiazole Schiff base derivatives containing benzo[*d*][1,3]dioxole moiety was designed, synthesized and screened for their fungicidal activities. The preliminary results demonstrated that compounds **6**p, **6**q and **6**r possessed potent activities against *Phytophthora infestans*, *Pyricularia oryzae* and *Septoria tritici in vitro*. Compounds **6**d and **6**r exhibited remarkable activities against *Botrytis cinerea*(whole plant) and *Phytophthora infestans*(leaf disk) respectively *in vivo*, which were identified as the most promising candidates for further study and could be used as possible lead compounds for developing new fungicides.

Keywords Thiazole; Schiff base; Benzo[*d*][1,3]dioxole; Fungicidal activity

1 Introduction

Broad-spectrum fungicides play a significant role in maintaining high yields and quality of crops. However, resistance to fungicides, especially the single-target site pesticides, has emerged in many plant pathogens[1]. Therefore, it is important to develop and formulate more effective and safe agricultural fungicides, which can be effectively used in various medical conditions and are friendly to the environment. Benzo[*d*][1,3]dioxole exists widely in many natural plant alkaloids, such as Sanguinarine[2], Liriodenine[3] and Berberine, which exhibits broad-spectrum activity in both medicine and pesticide fields[4]. The thiazole moiety is a very important heterocycle and plays vital roles in many fungicides structures, such as thifluzamide, thiabendazole, and metsulfovax[5]. Various bioactivities make thiazole one of the most extensively studied heterocycles at present[6]. An increasing number of novel compounds based on thiazole moiety has been designed and synthesized as antitumor[7], insecticidal[8] and fungicidal[9—11] agents in the past few years. Schiff bases, which contain azomethine group(—C═N—) in the structure, are well known for their pharmacological properties as antibacterial, antifungal, anticancer and antiviral agents[12]. In recent years, a lot of novel Schiff base derivatives possessing potent antifungal activity were reported[13—16]. In view of all these facts, and according to scaffold hopping approach[17—19], a series of novel 5-(benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*-benzyl-idene-4-(*tert*-butyl)thiazol-2-amine derivatives was rationally designed(Scheme 1), synthesized and screened for their fungicidal activities in BASF SE(Ludwigshafen, Germany). The preliminary results demonstrated that some of the tested compounds exhibited potent fungicidal activities.



Scheme 1 Design strategy of the title compounds

*Corresponding author. E-mail: axhu@hnu.edu.cn
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2 Experimental

2.1 Reagents and Instruments

All the reagents were of analytical grade and were used without further purification. Melting points were measured on an X-4 electrothermal digital melting point apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400(USA) spectrometer with tetramethylsilane (TMS) as internal standard. Elemental analyses were performed on a Vario EL III(Germany) instrument.

2.2 Synthesis

*2.2.1 Synthesis of Compounds **1—3***

Compound **1** was prepared according to a classical method[20] and was obtained as a white solid. Yield 51%, m. p. 37—39 °C(literature value[21]: 35—37 °C). Compounds **2** and **3** were synthesized according to the reported methods[22]. Compound **2** was obtained as a light yellow solid. Yield 92%, m. p. 95.5—97.5 °C(literature value[23]: 93—94 °C). Compound **3** was obtained as colorless liquid, yield 95%.

*2.2.2 Synthesis of Compound **4***

A mixture of 11.7 g(50 mmol) of compound **3**, 100 mL of chloroform, 100 mL of ethyl acetate and 22.5 g(0.1 mol) of $CuBr_2$ was heated for 4 h under reflux and then filtered immediately. The filtrate was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to remove the solvent. Compound **4**(13.77 g, yield 88%) was obtained as colorless liquid and was used directly in the next step without further purification. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 6.71(d, J=7.6 Hz, 1H), 6.65(s, 1H), 6.61(d, J=7.6 Hz, 1H), 5.93(s, 2H), 4.72—4.68(m, 1H), 3.62—3.07(m, 2H), 1.02(s, 9H).

*2.2.3 Synthesis of Compound **5***

A mixture of 15.65 g(50 mmol) of compound **4** and 3.80 g (50 mmol) of thiourea in 200 mL of ethanol was stirred for 2 h under reflux. When cooled to room temperature, aqueous ammonia was added to adjust pH=7—8. The suspension was filtered to afford 13.20 g of compound **5** as a yellow solid. Yield 91%, m. p. 124.5—126.5 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 6.74(d, J=8.0 Hz, 1H), 6.69(s, 1H), 6.65(d, J=8.0 Hz, 1H), 5.94(s, 2H), 4.68(s, 2H), 4.05(s, 2H), 1.34(s, 9H).

*2.2.4 Synthesis of Compounds **6***

Target compounds **6** were synthesized according to the following general method: a mixture of compound **5**(2 mmol), substituted benzaldehyde(2 mmol) and triethylamine(0.15 mL) was heated for 1—4 h in 20 mL of toluene at 80 °C. The mixture was concentrated under reduced pressure to remove the solvent. The residue was recrystallized from ethanol to afford compounds **6** as a single *E* isomer[24].

(*E*)-5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*-benzylidene-4-(*tert*-butyl)thiazol-2-amine(**6**a): a yellow solid, yield 56%, m. p. 88—90 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.74(s, 1H), 7.93(d, J=7.6 Hz, 2H), 7.50—7.43(m, 3H), 6.77(d, J=8.0 Hz, 1H), 6.71(s, 1H), 6.69(d, J=8.0 Hz, 1H), 5.95(s, 2H), 4.21(s, 2H), 1.46(s, 9H). ^{13}C NMR(101 MHz, $CDCl_3$), δ: 166.90, 162.23, 157.74, 147.50, 145.98, 134.75, 133.96, 131.93, 129.71, 129.31, 128.40, 121.01, 108.56, 107.91, 100.66, 76.99, 76.68, 76.36. Elemental anal.(%) calcd.: C 69.81, H 5.86, N 7.40, S 8.47; found: C 69.84, H 5.88, N 7.39, S 8.45.

(*E*)-5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(*tert*-butyl)-*N*-(4-fluorobenzylidene)thiazol-2-amine(**6**b): a yellow solid, yield 69%, m. p. 90—92 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.68(s, 1H), 7.83(d, J=8.0 Hz, 2H), 7.26(d, J=8.0 Hz, 2H), 6.76(d, J=8.0 Hz, 1H), 6.71(s, 1H), 6.69(d, J=8.0 Hz, 1H), 5.95(s, 2H), 4.21(s, 2H), 1.46(s, 9H). ^{13}C NMR(101 MHz, $CDCl_3$), δ: 167.01, 166.48, 163.96, 160.90, 158.06, 147.84, 146.32, 134.26, 131.75, 131.66, 131.45, 130.16, 121.33, 116.15, 115.93, 108.89, 108.24, 100.99, 77.29, 76.98, 76.66, 36.15, 33.55, 31.02. Elemental anal.(%) calcd.: C 66.65, H 5.34, N 7.07, S 8.09; found: C 66.67, H 5.37, N 7.04, S 8.06.

(*E*)-5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(*tert*-butyl)-*N*-(2-chlorobenzylidene)thiazol-2-amine(**6**c): a yellow solid, yield 78%, m. p. 103—105 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 9.18(s, 1H), 8.32(d, J=8.0 Hz), 7.41(d, J=4.0 Hz, 2H), 7.36—7.31(m, 1H), 6.77(d, J=8.0 Hz, 1H), 6.71(s, 1H), 6.69(d, J=8.0 Hz, 1H), 5.96(s, 2H), 4.22(s, 2H), 1.47(s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$), δ: 162.04, 154.01, 153.48, 142.92, 141.42, 131.79, 129.21, 128.06, 127.29, 125.89, 125.04, 124.28, 122.11, 116.41, 103.94, 103.34, 96.07, 72.37, 72.05, 71.73, 31.22, 28.66, 26.09. Elemental anal.(%) calcd.: C 63.99, H 5.13, N 6.78, S 7.77; found: C 64.02, H 5.16, N 6.77, S 7.76.

(*E*)-5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(*tert*-butyl)-*N*-(4-chlorobenzylidene)thiazol-2-amine(**6**d): a yellow solid, yield 78%, m. p. 116—118 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.71(s, 1H), 7.87(d, J=8.4 Hz, 2H), 7.43(d, J=8.4 Hz, 2H), 6.76(d, J=8.0 Hz, 1H), 6.71(s, 1H), 6.69(d, J=8.0 Hz, 1H), 5.96(s, 2H), 4.21(s, 2H), 1.46(s, 9H). ^{13}C NMR(101 MHz, $CDCl_3$), δ: 166.49, 160.46, 157.85, 147.51, 146.01, 138.02, 133.88, 133.26, 130.35, 130.25, 128.79, 121.01, 108.55, 107.91, 100.67, 76.98, 76.66, 76.34, 35.83, 33.24, 30.68. Elemental anal.(%) calcd.: C 63.99, H 5.13, N 6.78, S 7.77; found: C 64.01, H 5.15, N 6.76, S 7.75.

(*E*)-5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(*tert*-butyl)-*N*-(2-nitrobenzylidene)thiazol-2-amine(**6**e): a yellow solid, yield 60%, 133—135 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 9.25(s, 1H), 8.40(d, J=8.0 Hz, 1H), 8.06(d, J=8.0 Hz, 1H), 7.71(d, J=7.6 Hz, 1H), 7.63(t, J=7.6 Hz, 1H), 6.77(d, J=8.0 Hz, 1H), 6.71(s, 1H), 6.69(d, J=8.0 Hz, 1H), 5.96(s, 2H), 4.23(s, 2H), 1.46(s, 9H). ^{13}C NMR(101 MHz, $CDCl_3$), δ: 161.15, 153.69, 152.32, 144.66, 142.96, 141.49, 129.04, 128.46, 127.31, 126.94, 125.01, 124.91, 119.69, 116.45, 103.94, 103.37, 96.08, 72.35, 72.03, 71.71, 31.24, 28.72, 26.05. Elemental anal.(%) calcd.: C 62.40, H 5.00, N 9.92, S 7.57; found: C 62.41, H 5.02, N 9.91, S 7.58.

(*E*)-5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(*tert*-butyl)-*N*-(3-nitrobenzylidene)thiazol-2-amine(**6**f): a brown yellow solid, yield 55%, m. p. 117—119 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.89(s, 1H), 8.77(s, 1H), 8.29(d, J=8.0 Hz, 1H), 7.65(t, J=8.0 Hz, 1H), 6.78(d, J=8.0 Hz, 1H), 6.71(s, 1H), 6.70(d, J=8.0 Hz, 1H), 5.97(s, 2H), 4.23(s, 2H), 1.47(s, 9H). ^{13}C NMR(101 MHz, $CDCl_3$), δ: 165.91, 158.79, 158.50, 148.66, 147.88, 146.42, 136.87, 134.51, 134.05, 132.13, 129.81, 126.20, 124.11, 121.39,

108.89, 108.29, 101.03, 77.30, 76.98, 76.66, 36.20, 33.63, 30.98. Elemental anal.(%) calcd.: C 62.40, H 5.00, N 9.92, S 7.57; found: C 62.43, H 5.02, N 9.96, S 7.52.

(*E*)-5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(*tert*-butyl)-*N*-(4-nitrobenzylidene)thiazol-2-amine(**6g**): a yellow solid, yield 62%, m. p. 127—129 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.89(s, 1H), 8.31(d, *J*=8.4 Hz, 2H), 8.10(d, *J*=8.4 Hz, 2H), 6.78(d, *J*=8.0 Hz, 1H), 6.71(s, 1H), 6.69(d, *J*=8.0 Hz, 1H), 5.96(s, 2H), 4.23(s, 2H), 1.47(s, 9H). ^{13}C NMR(101 MHz, $CDCl_3$), δ: 165.90, 158.69, 149.59, 147.89, 146.44, 140.59, 134.00, 132.65, 130.42, 130.01, 124.27, 123.96, 121.40, 108.89, 108.30, 101.04, 77.29, 76.97, 76.65, 36.21, 33.68, 30.97. Elemental anal.(%) calcd.: C 62.40, H 5.00, N 9.92, S 7.57; found: C 62.43, H 5.02, N 9.91, S 7.55.

(*E*)-5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(*tert*-butyl)-*N*-(2-methoxybenzylidene)thiazol-2-amine(**6h**): a yellow solid, yield 70%, m. p. 142—143 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 9.13(s, 1H), 8.25(d, *J*=7.6 Hz, 1H), 7.43(t, *J*=6.8 Hz, 1H), 7.00(t, *J*=8.0 Hz, 1H), 6.92(d, *J*=8.0 Hz, 1H), 6.77(d, *J*=8.0 Hz, 1H), 6.72(s, 1H), 6.69(d, *J*=8.0 Hz, 1H), 5.95(s, 2H), 4.21(s, 2H), 3.89(s, 3H), 1.46(s, 9H). ^{13}C NMR(101 MHz, $CDCl_3$), δ: 168.20, 160.01, 158.91, 158.01, 147.81, 146.26, 134.40, 133.83, 129.16, 128.43, 123.55, 121.31, 120.78, 111.00, 108.89, 108.21, 100.97, 77.31, 76.99, 76.67, 55.54, 36.11, 33.56, 31.07. Elemental anal.(%) calcd.: C 67.62, H 5.92, N 6.86, S 7.85; found: C 67.65, H 5.94, N 6.85, S 7.83.

(*E*)-5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(*tert*-butyl)-*N*-(4-methylbenzylidene)thiazol-2-amine(**6i**): a yellow solid, yield 96%, m. p. 103—105 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.68(s, 1H), 7.83(d, *J*=8.0 Hz, 2H), 7.26(d, *J*=8.0 Hz, 2H), 6.76(d, *J*=8.0 Hz, 1H), 6.71(s, 1H), 6.69(d, *J*=8.0 Hz, 1H), 5.95(s, 2H), 4.21(s, 2H), 2.41(s, 3H), 1.46(s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$), δ: 167.18, 162.28, 157.63, 147.49, 145.95, 142.74, 134.02, 132.19, 129.37, 129.19, 120.99, 108.56, 107.88, 100.64, 76.96, 76.65, 76.33, 35.81, 33.21, 30.71, 21.39. Elemental anal.(%) calcd.: C 70.38, H 6.16, N 7.14, S 8.17; found: C 70.41, H 6.19, N 7.12, S 8.15.

(*E*)-5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(*tert*-butyl)-*N*-(2,4-dichlorobenzylidene)thiazol-2-amine(**6j**): a yellow solid, yield 52%, m. p. 101—102.5 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 9.10(s, 1H), 8.27(d, *J*=8.8 Hz, 1H), 7.44(d, *J*=1.2 Hz, 1H), 7.32(dd, *J*=8.8, 1.2 Hz, 1H), 6.77(d, *J*=8.0 Hz, 1H), 6.71(s, 1H), 6.69(d, *J*=8.0 Hz, 1H), 5.96(s, 2H), 4.22(s, 2H), 1.46(s, 9H). ^{13}C NMR(101 MHz, $CDCl_3$), δ: 166.61, 158.54, 157.46, 147.87, 146.38, 138.56, 137.13, 134.08, 131.33, 130.89, 130.02, 129.80, 127.68, 121.35, 108.87, 108.28, 101.01, 77.29, 76.98, 76.66, 36.15, 33.62, 31.01. Elemental anal.(%) calcd.: C 59.06, H 4.51, N 6.26, S 7.17; found: C 59.09, H 4.53, N 6.25, S 7.15.

(*E*)-2-({[5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(*tert*-butyl)-thiazol-2-yl]imino}methyl)phenol(**6k**): a yellow solid, yield 51%, m. p. 90—91 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 12.35(s, 1H), 9.04(s, 1H), 7.44(d, *J*=7.6 Hz, 1H), 7.40(t, *J*=7.6 Hz, 1H), 7.00(d, *J*=8.4 Hz, 1H), 6.95(t, *J*=7.2 Hz, 1H), 6.77(d, *J*=8.0 Hz, 1H), 6.71(s, 1H), 6.69(d, *J*=8.0 Hz, 1H), 5.96(s, 2H), 4.21(s, 2H), 1.45(s, 9H). ^{13}C NMR(101 MHz, $CDCl_3$), δ: 164.13, 163.28, 161.33, 157.92, 147.87, 146.39, 134.14, 134.04, 133.29, 131.43, 121.35, 119.38, 118.62, 117.33, 108.87, 108.28, 101.02, 77.30, 76.98, 76.66, 36.21, 33.51, 30.99. Elemental anal.(%) calcd.: C 66.98, H 5.62, N 7.10, S 8.13; found: C 66.97, H 5.63, N 7.08, S 8.10.

(*E*)-2-({[5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(*tert*-butyl)-thiazol-2-yl]imino}methyl)-4-chlorophenol(**6l**): a yellow solid, yield 84%, m. p. 129—131 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 12.30(s, 1H), 9.01(s, 1H), 7.43(d, *J*=2.0 Hz, 1H), 7.33(dd, *J*=8.8, 2 Hz, 1H), 6.95(d, *J*=8.8 Hz, 1H), 6.77(d, *J*=7.6 Hz, 1H), 6.70(s, 1H), 6.68(d, *J*=7.6 Hz, 1H), 5.96(s, 2H), 4.21(s, 2H), 1.45(s, 9H). ^{13}C NMR(101 MHz, $CDCl_3$), δ: 163.11, 161.37, 159.46, 157.81, 147.57, 146.11, 133.68, 133.39, 132.04, 131.70, 123.68, 121.04, 119.09, 118.56, 108.53, 107.97, 100.71, 76.96, 76.64, 76.33, 35.90, 33.21, 30.62. Elemental anal.(%) calcd.: C 61.60, H 4.93, N 6.53, S 7.48; found: C 61.61, H 4.95, N 6.54, S 7.49.

(*E*)-2-({[5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(*tert*-butyl)-thiazol-2-yl]imino}methyl)-4-bromophenol(**6m**): a yellow solid, yield 74%, m. p. 153—154 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 12.30(s, 1H), 9.01(s, 1H), 7.57(d, *J*=2.4 Hz, 1H), 7.46(dd, *J*=8.8, 2.4 Hz, 1H), 6.90(d, *J*=8.8 Hz, 1H), 6.77(d, *J*=8.0 Hz, 1H), 6.70(s, 1H), 6.68(d, *J*=8.0 Hz, 1H), 5.96(s, 2H), 4.21(s, 2H), 1.45(s, 9H). ^{13}C NMR(101 MHz, $CDCl_3$), δ: 163.08, 161.26, 159.91, 157.81, 147.57, 146.11, 136.15, 134.73, 133.68, 132.06, 121.04, 119.73, 118.97, 110.51, 108.53, 107.97, 100.70, 76.96, 76.64, 76.32, 35.90, 33.21, 30.61. Elemental anal.(%) calcd.: C 55.82, H 4.47, N 5.92, S 6.77; found: C 55.83, H 4.49, N 5.92, S 6.78.

(*E*)-2-({[5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(*tert*-butyl)-thiazol-2-yl]imino}methyl)-6-nitrophenol(**6n**): a brown yellow solid, yield 82%, m. p. 163—165 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 13.52(s, 1H), 9.21(s, 1H), 8.14(dd, *J*=8.0, 1.2 Hz, 1H), 7.94(d, *J*=6.8 Hz, 1H), 7.05(t, *J*=8.0 Hz, 1H), 6.77(d, *J*=8.0 Hz, 1H), 6.69(s, 1H), 6.68(d, *J*=8.0 Hz, 1H), 5.97(s, 2H), 4.22(s, 2H), 1.45(s, 9H). ^{13}C NMR(101 MHz, $CDCl_3$), δ: 159.13, 158.17, 155.36, 147.59, 146.15, 137.28, 136.74, 133.51, 132.74, 129.07, 121.95, 121.03, 118.45, 108.49, 108.00, 100.72, 76.96, 76.64, 76.33, 35.91, 33.21, 30.61. Elemental anal.(%) calcd.: C 60.12, H 4.82, N 9.56, S 7.30; found: C 60.13, H 4.85, N 9.53, S 7.28.

(*E*)-2-({[5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(*tert*-butyl)-thiazol-2-yl)imino]methyl}-4-nitrophenol(**6o**): a yellow solid, yield 85%, m. p. 152—154 °C. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 13.26(s, 1H), 9.18(s, 1H), 8.45(d, *J*=2.8 Hz, 1H), 8.27(dd, *J*=9.2, 2.8 Hz, 1H), 7.09(d, *J*=9.2 Hz, 1H), 6.78(d, *J*=7.6 Hz, 1H), 6.70(s, 1H), 6.69(d, *J*=7.6 Hz, 1H), 5.97(s, 2H), 4.22(s, 2H), 1.46(s, 9H). ^{13}C NMR(101 MHz, $CDCl_3$), δ: 165.86, 161.97, 160.49, 158.16, 147.62, 146.21, 140.03, 133.51, 133.35, 128.77, 128.45, 121.09, 117.91, 117.55, 108.53, 108.01, 100.74, 76.95, 76.64, 76.32, 35.95, 33.30, 30.58. Elemental anal.(%) calcd.: C 60.12, H 4.82, N 9.56, S 7.30; found: C 60.11, H 4.85, N 9.54, S 7.28.

(*E*)-2-({[5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(*tert*-butyl)-thiazol-2-yl]imino}methyl)-4,6-dichlorophenol(**6p**): a yellow solid, yield 83%, m. p. 146—148 °C. ^{1}H NMR(400 MHz, DMSO-d_6), δ: 12.88(s, 1H), 9.10(s, 1H), 7.88(d, *J*=2.4 Hz, 1H), 7.80(d, *J*=2.4 Hz, 1H), 6.89(d, *J*=8.0 Hz, 1H), 6.85(s, 1H), 6.74(d, *J*=8.0 Hz, 1H), 6.01(s, 2H), 4.25(s, 2H), 1.41(s, 9H).

^{13}C NMR(101 MHz, $CDCl_3$), δ: 162.50, 160.59, 158.44, 155.66, 147.94, 146.50, 133.87, 133.34, 130.58, 123.84, 122.85, 121.38, 119.93, 108.84, 108.35, 101.07, 77.31, 76.99, 76.67, 36.28, 33.55, 30.94. Elemental anal.(%) calcd.: C 57.02, H 4.35, N 6.05, S 6.92; found: C 57.04, H 4.39, N 6.04, S 6.90.

(*E*)-2-({[5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(*tert*-butyl)-thiazol-2-yl]imino}methyl)-4,6-dibromophenol(**6q**): a yellow solid, yield 91%, m. p. 166—168 °C. ^{1}H NMR(400 MHz, DMSO-d_6), δ: 13.10(s, 1H), 9.08(s, 1H), 8.04(d, J=2.4 Hz, 1H), 7.99(d, J=2.4 Hz, 1H), 6.89(d, J=8.0 Hz, 1H), 6.85(d, J=1.6 Hz, 1H), 6.74(dd, J=8.0, 1.6 Hz, 1H), 6.01(s, 2H), 4.25(s, 2H), 1.41(s, 9H). ^{13}C NMR(101 MHz, $CDCl_3$), δ: 162.04, 159.98, 158.11, 156.63, 147.59, 146.15, 138.39, 133.94, 133.52, 132.97, 121.02, 120.07, 111.73, 110.39, 108.48, 108.00, 100.72, 76.96, 76.64, 76.32, 35.93, 33.18, 30.59. Elemental anal.(%) calcd.: C 47.84, H 3.65, N 5.07, S 5.81; found: C 47.85, H 3.67, N 5.06, S 5.80.

(*E*)-2-({[5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(*tert*-butyl)-thiazol-2-yl]imino}methyl)-4,6-diiodophenol(**6r**): a yellow solid, yield 86%, m. p. 203—204.5 °C. ^{1}H NMR(400 MHz, DMSO-d_6), δ: 13.32(s, 1H), 8.99(s, 1H), 8.19(d, J=2.0 Hz, 1H), 8.14(d, J=2.0 Hz, 1H), 6.89(d, J=8.0 Hz, 1H), 6.85(d, J=1.2 Hz, 1H), 6.74(dd, J=8.0, 2.0 Hz, 1H), 6.01(s, 2H), 4.25(s, 2H), 1.41(s, 9H). ^{13}C NMR(101 MHz, $CDCl_3$), δ: 162.34, 160.02, 159.88, 158.45, 149.71, 147.93, 146.48, 141.33, 133.88, 133.15, 121.36, 120.34, 108.82, 108.33, 101.06, 86.99, 80.44, 77.30, 76.98, 76.66, 36.28, 33.51, 30.93. Elemental anal.(%) calcd.: C 40.89, H 3.12, N 4.33, S 4.96; found: C 40.88, H 3.14, N 4.32, S 4.94.

2.3 Fungicidal Activity Assay

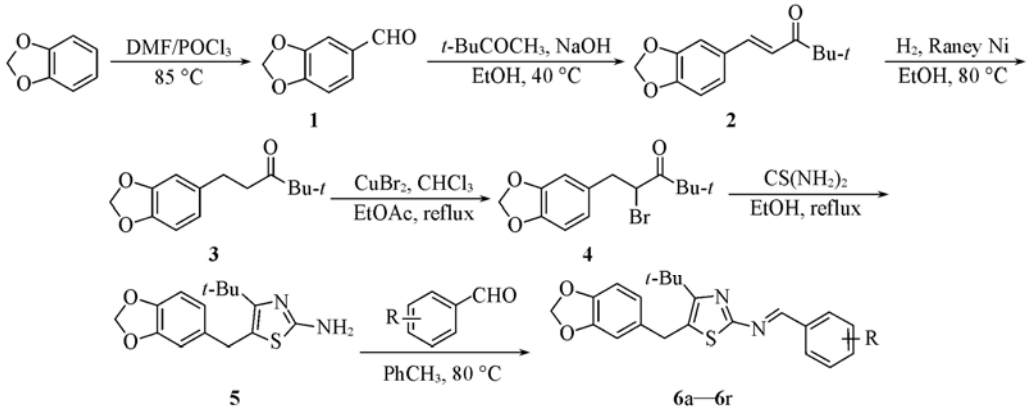
The *in vitro* toxicities of target compounds **6** against *Botrytis cinerea*(BOT), *Phytophthora infestans*(PHY), *Pyricularia oryzae*(PYR) and *Septoria tritici*(SEP) were tested according to the following procedure[25]: the stock solution was prepared as follows: 0.84 mL of a mixture of cyclohexanone and dimethylsulfoxide(1:1, volume ratio) was added to 16.8 mg of active ingredient; then, 27.16 mL of a mixture of water, acetone(10%, volume ratio), the emulsifier Wettol(0.1%, volume ratio) and the wetting agent Silwet(0.05%, volume ratio) was added to the mixture. This stock solution was then further diluted with the above described solvent-emulsifier-water mixture to desired concentrations. The stock solutions were mixed according to the ratio, pipetted onto a micro titer plate(MTP) and diluted with water to the stated concentrations. A spore suspension of fungus(*Botrytis cinerea*, *Pyricularia oryzae* and *Septoria tritici*) in an aqueous biomalt, or yeast-bactopeptone-sodium acetate solution or a spore suspension of fungus (*Phytophtora infestans*) containing a pea juice-based aqueous nutrient medium or dopamine decarboxylase(DDC) medium was then added. The plates were placed in a water vapor-saturated chamber at a temperature of 18 °C. The MTPs were measured at 405 nm using an absorption photometer 7 d after the inoculation.

The *in vivo* fungicidal activities of target compounds **6** against *Botrytis cinerea*, *Erysiphegraminis f. sp. Tritici*(ERY), *Phakopsora pachyrhizi*(PHA), *Phytophthora infestans*, *Puccinia recondita*(PUC) and *Septoria tritici* were tested according to the procedure described in the patent[26].

3 Results and Discussion

3.1 Chemistry

The general synthetic process for all the intermediates and target compounds are depicted in Scheme 2. Compound **1** was synthesized from benzo[*d*][1,3]dioxole *via* Vilsmeier-Haack reaction using $POCl_3$/DMF as Vilsmeier reagent. Compound **2** was synthesized through aldol condensation of compound **1** and pinacolone in alcohol catalyzed by sodium hydroxide. The hydrogenation reaction of compound **2** catalyzed by Raney Ni generated compound **3**. The α-bromination reaction(using $CuBr_2$ as brominating reagent) of compound **3** produced the intermediate 1-(benzo[*d*][1,3]dioxol-5-yl)-2-bromo-4,4-di-methyl-pentan-3-one(**4**). The main intermediate 5-(benzo-[*d*][1,3]-dioxol-5-ylmethyl)-4-(*tert*-butyl)thiazol-2-amine(**5**) was prepared by reacting compound **4** with thiourea in alcohol and neutralized with aqueous ammonia[27]. The target compounds **6** were obtained as yellow to brown solids by reaction of compound **5** with different substituted benzaldehydes. The reactions between compound **5** with salicylaldehyde derivatives tend to possess faster rates and higher yields than other benzaldehydes, because a hydrogen bond was formed between the phenolic



R: a. H; b. 4-F; c. 2-Cl; d. 4-Cl; e. 2-NO_2; f. 3-NO_2; g. 4-NO_2; h. 2-OCH_3; i. 4-CH_3; j. 2,4-2Cl; k. 2-OH; l. 5-Cl-2-OH; m. 5-Br-2-OH; n. 3-NO_2-2-OH; o. 5-NO_2-2-OH; p. 3,5-2Cl-2-OH; q. 3,5-2Br-2-OH; r. 3,5-2I-2-OH

Scheme 2 General synthetic routes for compounds 6a—6r

hydroxyl group and the N of azomethine group, which could make the structure more stable.

3.2 Fungical Activities

The *in vitro* fungicidal activity results of target compounds **6** are listed in Table 1. To make a judgement concerning the fungicidal potency of the target compounds, the 50% effective dose(ED_{50}) values of some commercial fungicides were listed in the table as standards. The preliminary bioassay results indicated that most of the compounds **6** showed potent toxicities against the tested fungi. Of all the tested compounds, phenol derivatives(**6**l—**6**r) exhibited excellent activities against most of the tested fungi, the ED_{50} values of which were comparable to those of commercial fungicides. Especially, dihalide phenol derivatives(**6**p—**6**r) showed excellent toxicities against all of the tested fungi. For *Phytophthora infestans*, the ED_{50} values of compounds **6**p, **6**q and **6**r were (0.775±2.2), (0.723±1.9) and (0.601±0.9) mg/L respectively, much lower than that of metalaxyl(ED_{50}=2.0 mg/L). For *Pyricularia oryzae*, compounds **6**p[ED_{50}=(5.66±1.4) mg/L], **6**q[ED_{50}=(2.35±2.8) mg/L] and **6**r[ED_{50}=(1.75±0.7) mg/L] also displayed better fungicidal activities than commercial fungicide edifenphos (ED_{50}=7.0 mg/L). For *Septoria tritici*, the ED_{50} value of compound **6**r[ED_{50}=(0.975±0.6) mg/L] was lower than that of azoxystrobin(ED_{50}=0.98 mg/L), a known commercial fungicide. Other two compounds **6**m and **6**q also showed good ED_{50} values[(1.8±0.4) and (2.18±1.2) mg/L], which were approximate to the standard. The reason why the compounds with —OH showed better fungicidal activities might be as follows: first, —OH increased the water solubility of the compound, thus improving the bioavailability; second, —OH provided donator and receptor of hydrogen bond when the compound was absorbed by fungus and bound to the binding sites.

The *in vivo* fungicidal activities of target compounds **6**

Table 1 ED_{50} values of target compounds 6a—6r(mg/L, *in vitro*)

Compd.	BOT	PHY	PYR	SEP
6a	20.8±1.8	4.57±1.6	11.4±2.5	5.84±1.0
6b	23.3±2.5	8.94±2.8	13.4±3.0	5.20±0.8
6c	21.6±2.0	8.35±2.1	11.7±2.4	5.63±0.3
6d	17.9±2.7	5.96±2.2	8.17±1.6	7.75±1.7
6e	>31.0	7.76±1.3	9.44±2.3	3.19±0.3
6f	6±0.6	10.7±1.3	7.08±1.1	5.06±0.3
6g	>31.0	9.37±1.7	11.7±2.6	12.6±0.2
6h	19.1±2.4	8.61±1.9	11.7±2.5	4.38±0.3
6i	20.8±4.2	13.8±3.3	14.5±3.8	6.18±0.9
6j	>31.0	9.85±2.1	12.8±2.3	30.5±0.1
6k	23.6±2.1	5.94±1.2	12.4±2.3	2.81±0.3
6l	14.8±3.0	8.09±1.3	7.89±1.4	9.06±1.7
6m	24.7±1.4	6.79±1.7	11.5±1.3	1.80±0.4
6n	15.0±3.6	2.33±2.0	10.5±2.9	9.40±1.8
6o	15.8±5.5	5.93±2.1	12.4±3.8	7.29±1.1
6p	15.4±2.1	0.775±2.2	5.66±1.4	3.79±4.9
6q	14.3±1.3	0.723±1.9	2.35±2.8	2.18±1.2
6r	3.55±0.6	0.601±0.9	1.75±0.7	0.975±0.6
Positive control	0.1(Carbendazim[28])	2.0(Metalaxyl[29])	7.0(Edifenphos[29])	0.98(Azoxystrobin[30])

Table 2 Fungicidal activities of target compounds 6a—6r(*in vivo*)

Compd.	Diseased area(%)										
	Leaf disk(100 mg/L)					Whole plant(600 mg/L)					
	BOT	ERY	PHA	PHY	PUC	BOT	ERY	PHA	PHY	PUC	SEP
6a	100	100	100	100	100	90	90	90	90	70	70
6b	67	100	100	100	100	90	90	90	90	90	90
6c	100	100	83	67	—	90	90	90	90	90	90
6d	100	100	100	100	100	10	90	90	90	90	90
6e	100	83	100	100	100	90	90	90	90	90	80
6f	100	100	100	100	100	90	90	90	90	70	90
6g	100	100	100	100	100	90	90	90	90	90	90
6h	67	100	100	100	50	90	90	90	90	90	90
6i	100	100	100	100	100	—	—	—	—	—	—
6j	100	100	100	100	100	—	—	—	—	—	—
6k	67	100	100	100	100	70	90	90	90	70	80
6l	100	100	100	100	100	90	90	90	90	90	90
6m	100	83	100	100	100	90	90	90	90	70	90
6n	100	100	100	100	100	—	—	—	—	—	—
6o	100	100	100	100	—	90	90	90	60	90	90
6p	100	67	100	100	—	90	60	90	60	70	80
6q	100	67	100	100	—	90	60	90	90	60	90
6r	67	83	100	17	100	—	—	—	—	—	—

are listed in Table 2. The test results revealed that most of the compounds showed poor *in vivo* fungicidal activities except compounds **6**r and **6**d. When dealt with compound **6**r, the tomato leaf area infected by *Phytophthora infestans* was 17%(leaf disk) at the concentration of 100 mg/L. The diseased area caused by *Botrytis cinerea* of green pepper dealt with compound **6**d was 10%(whole plant) at the concentration of 600 mg/L. Overall, the fungicidal activities of the tested compounds on whole plant was better than that on leaf disk.

4 Conclusions

A series of 5-(benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*-benzylidene-4-(*tert*-butyl)thiazol-2-amine derivatives(**6**) was designed, synthesized and tested for fungicidal activities. The preliminary results revealed that compounds **6**l—**6**r showed high levels of *in vitro* antifungal activities against all the four kinds of fungi. The ED_{50} values of compounds **6**p, **6**q and **6**r against *Phytophthora infestans* and *Pyricularia oryzae* were lower than published values of commercial fungicides. Compound **6**r also showed an ED_{50} value which is lower than the standard fungicide against *Septoria tritici.* The *in vivo* biological activity evaluation indicated that compound **6**d and **6**r displayed potent antifungal activities against *Botrytis cinerea* (whole plant) and *Phytophthora infestans*(leaf disk) respectively. In conclusion, compound **6**r showed potent toxicity against several tested fungi both *in vitro* and *in vivo*, and could be a good lead compound for the development of new fungicide.

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