Synthesis and Evaluation of Novel *N*-(4'-Arylpyrimidin-2'-yl) Sulfonylurea Derivatives as Potential Antifungal Agents

CHEN Wei[1,2], LI Yuxin[1,2], SHI Yanxia[3], WEI Wei[1,2], CHEN Youwei[1,2], LI Yonghong[1], LIU Jingbo[1,2], LI Baoju[3*] and LI Zhengming[1,2*]

1. State Key Laboratory of Elemento-Organic Chemistry,
2. Collaborative Innovation Center of Chemical Science and Engineering(Tianjin),
Nankai University, Tianjin 300071, P. R. China;
3. Institute of Vegetables and Flowers, Chinese Academy of Agricultural Sciences,
Beijing 100081, P. R. China

Abstract Sulfonylureas(SUs) are potent and selective inhibitors of acetohydroxyacid synthase and has been used as herbicides. Some SUs also displayed other biological activities. In order to discuss the antifungal activity of SUs, a series of novel SUs containing aryl-substituted pyrimidine moieties was designed and synthesized. The preliminary bioassay showed that the title compounds exhibited moderate to favorable fungicidal activities *in vivo*. Especially, compound **9**b exhibited more efficacy than the controls against five fungi at 25 mg/L. These promising results indicate that an aryl group on pyrimidine ring is favorable for antifungal activity and SUs are potential inhibitors for some phytopathogenic fungi.

Keywords Acetohydroxyacid synthase; Sulfonylurea; Fungicidal activity; Substituted pyrimidine

1 Introduction

Acetohydroxyacid synthase(AHAS, also known as acetolactate synthase, EC 2.2.1.6) belongs to a homologous family of thiamin diphosphate(ThDP)-dependent enzymes and participates in the biosynthetic pathway of branched-chain amino acids(BCAA)[1]. The inhibition of AHAS interrupts the catalytic cycle and prevents the synthesis of BCAA, which is essential for the subsistence of plants and microorganisms. In addition, AHAS was found in plants, fungi and bacteria, but not in animals, making it an attractive target for the molecular design of novel agrochemicals[2—4]. Sulfonylureas(SUs) have been one group of the most applied AHAS-inhibitors used as herbicides[5,6]. Given the importance of the BCAA biosynthesis pathway in plants and microbes, it seems plausible that AHAS inhibitors would not only possess herbicidal activity but also have antimicrobial activity. Furthermore, metabolic investigations have also shown that AHAS activity is required for the growth and survival of fungi and bacteria in cell cultures[7—12] and in animal models[13,14]. Obviously, there are reasons to assume that AHAS inhibitors could be developed as antimicrobial agents.

The SUs have previously been shown to be active against *Saccharomyces cerevisiae*(*S. cerevisiae*)[15] and fungal pathogens *Cryptococcus neoformans* and *Candida albicans*[8,9]. Recently, our group has found that some SUs also showed antimicrobial activities against the bacteria-*Mycobacterium tuberculosis*[16,17]. Additionally, crystal structures of *S. cerevisiae* AHAS(as free enzyme and in complex with SUs) have been determined[18—20]. These studies have elucidated the molecular basis for the inhibition of the SUs toward fungal AHAS, and provided us some powerful information about the location and organization of the active site. With this knowledge in hand, it will be helpful for designing new antifungal agents.

As we all know, the structures of SUs can be generally divided into three parts: *ortho*-substituted benzene ring(A), sulfonylurea bridge(B) and heterocyclic ring(Z=CH, N)(C)(Fig.1). Literatures survey revealed that the biological activities of the SU molecules were greatly influenced by different

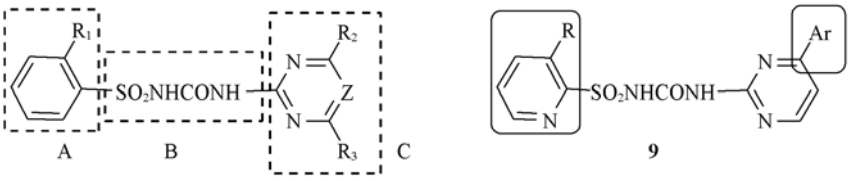


Fig.1 Structures of sulfonylurea herbicides and title compound 9

*Corresponding authors. E-mail: nkzml@vip.163.com; libj@mail.coas.net.cn

Received September 28, 2014; accepted January 22, 2015.

Supported by the National Natural Science Foundation of China(No.21272129) and the National Key Technologies R&D Program of China(No.2011BAE06B05).

heterocycles or substituents on them[16,21,22]. Meanwhile, it was reported that substituted pyrimidine was an important pharmacophore in antifungal agents[23,24], and more attention has been paid to improving antifungal activity based on structural modification of pyrimidine ring. Thus, it was postulated that some modifications at pyrimidine ring might bring SU with some unexpected antifungal activity.

In addition to our investigations on the synthesis of biologically active SU compounds, a series of novel SU derivatives containing aryl-monosubstituted pyrimidine was designed, synthesized and thier *in vivo* fungicidal activities against six phytopathogens were evaluated. The structure-activity relationships were also discussed.

2 Materials and Methods

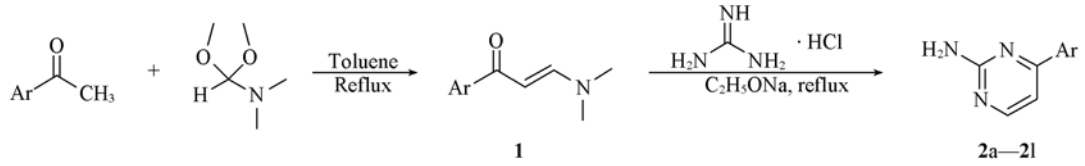
2.1 Instruments and Reagents

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer with tetramethylsilane as internal standard. High-resolution mass spectrometry(HRMS) data were obtained on an Agilent 6520 Q-TOF LC/MS instrument. The melting points were determined on an X-4 binocular microscope melting point apparatus(uncorrected).

The reagents used were all analytical or chemical pure. All the anhydrous solvents were dried and purified by standard methods.

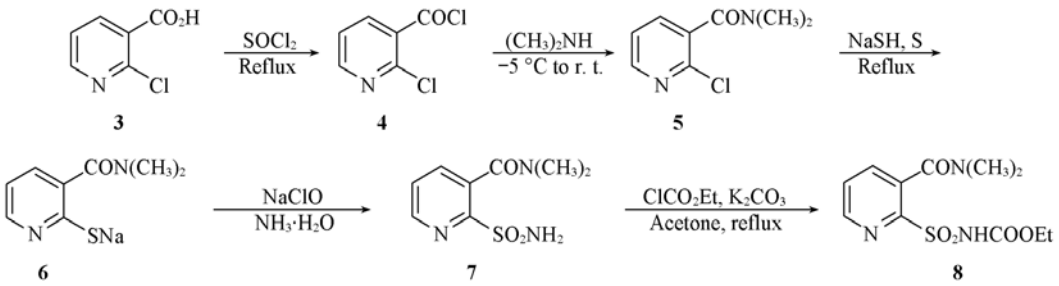
2.2 Syntheses of Title Compounds 9a—9l

Substituted pyrimidines **2**a—**2**l were prepared referring to the literature methods[25,26](Scheme 1), compound **8** was prepared by previously described methods[27,28](Scheme 2). Compounds **9**a—**9**l were synthesized according to ref. [29,30], and the synthetic routes are shown in Scheme 3. A mixture of each of compounds **2**(1.0 mmol) and compound **8**(1.0 mmol) in toluene(20 mL) was refluxed and the lower boiling component was distilled out continuously. The reaction was monitored by thin layer chromatography(TLC). When the reaction was finished, the reaction mixture was cooled and concentrated. The residue was purified by silica gel column with acetone/petroleum ether(1:4, volume ratio) as eluent to give compounds **9**a—**9**l, respectively.

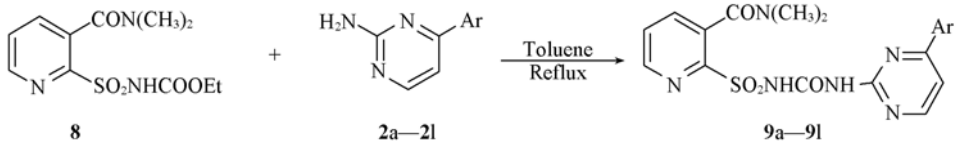


Ar: a. Phenyl; b. 2-furyl; c. 2-thienyl; d. 2-pyridyl; e. 3-pyridyl; f. 4-pyridyl; g. 3-nitrophenyl; h. 4-nitrophenyl; i. 4-fluorophenyl; j. 4-chlorophenyl; k. 4-bromophenyl; l. 4-methylphenyl

Scheme 1 General synthetic routes for compounds 2a—2l



Scheme 2 Synthetic routes for compound 8



Ar: a. Phenyl; b. 2-furyl; c. 2-thienyl; d. 2-pyridyl; e. 3-pyridyl; f. 4-pyridyl; g. 3-nitrophenyl; h. 4-nitrophenyl; i. 4-fluorophenyl; j. 4-chlorophenyl; k. 4-bromophenyl; l. 4-methylphenyl

Scheme 3 General synthetic routes for title compounds 9a—9l

N,*N*-Dimethyl-2-[*N*-(4-phenylpyrimidin-2-ylcarbamoyl)-sulfamoyl]nicotinamide(**9**a): a white solid, yield 71.2%; m. p. 211—213 °C. ^{1}H NMR(400 MHz, DMSO-d$_6$), δ: 12.97(br, 1H, SO_2NH), 10.94(s, 1H, CONH-pyrim), 8.79(d, J=4.6 Hz, 1H, Py-H), 8.25(d, J=4.4 Hz, 1H, pyrim-H), 8.23(d, J=7.8 Hz, 2H, Ph-H), 8.10(d, J=7.6 Hz, 1H, Py-H), 7.86—7.67(m, 5H, Ph-H, Py-H, pyrim-H), 2.81[s, 3H, 1/2N(CH_3)$_2$], 2.72[s, 3H, 1/2 N(CH_3)$_2$]. ^{13}C NMR(101 MHz, DMSO-d$_6$), δ: 169.56, 164.00, 163.38, 158.17, 154.09, 153.20, 152.00, 137.31, 135.93, 133.06, 129.25, 128.43, 127.57, 126.68, 104.96, 38.62, 35.45. HRMS(ESI) calcd. for $C_{19}H_{18}ClN_6O_4S$([M+H]$^+$), *m/z*: 427.1188; found: 427.1179.

2-{*N*-[4-(Furan-2-yl)pyrimidin-2-ylcarbamoyl]sulfamoyl}*N*,*N*-dimethylnicotinamide(**9**b): a pale yellow solid, yield 73.7%; m. p. 217—218 °C. ^{1}H NMR(400 MHz, DMSO-d$_6$), δ: 13.12(br, 1H, SO_2NH), 10.88(s, 1H,

CONH-pyrim), 8.03(d, *J*=7.5 Hz, 1H, pyrim-H), 7.89—7.79(m, 2H, Py-H), 7.52—7.45 (m, 3H, pyrim-H, furan-H), 6.95—6.79(m, 2H, furan-H), 2.96[s, 3H, 1/2N(CH_3)$_2$], 2.85[s, 3H, 1/2N(CH_3)$_2$]. ^{13}C NMR(101 MHz, DMSO-d_6), *δ*: 165.63, 159.46, 156.91, 149.71, 149.34, 147.33, 146.86, 137.17, 132.94, 127.89, 126.69, 114.32, 113.22, 112.98, 104.02, 38.21, 34.27. HRMS(ESI) calcd. for $C_{17}H_{17}N_6O_5S$ ([M+H]$^+$), *m/z*: 417.0981; found: 417.0979.

N,*N*-Dimethyl-2-{*N*-[4-(thiophen-2-yl)pyrimidin-2-ylcarbamoyl]sulfamoyl}nicotinamide(**9c**): a pale yellow solid, yield 71.2%; m. p. 219—220 °C. ^{1}H NMR(400 MHz, DMSO-d_6), *δ*: 12.77(br, 1H, SO_2NH), 10.81(s, 1H, CONH-pyrim), 8.74—8.71(m, 2H, Py-H), 8.03—7.88(m, 3H, Py-H, pyrim-H), 7.30—7.07(m, 3H, thio-H), 2.85[s, 3H, 1/2N(CH_3)$_2$], 2.73[s, 3H, 1/2N(CH_3)$_2$]. ^{13}C NMR(101 MHz, DMSO-d_6), *δ*: 167.13, 166.15, 163.93, 159.16, 150.18, 149.70, 137.26, 132.91, 130.74, 130.39, 128.91, 128.13, 127.18, 110.68, 104.74, 38.72, 34.77. HRMS(ESI) calcd. for $C_{17}H_{17}N_6O_4S_2$ ([M+H]$^+$), *m/z*: 433.0753; found: 433.0753.

N,*N*-Dimethyl-2-{*N*-[4-(pyridin-2-yl)pyrimidin-2-ylcarbamoyl]sulfamoyl}nicotinamide(**9d**): a yellow solid, yield 68.9%; m. p. 216—217 °C. ^{1}H NMR(400 MHz, DMSO-d_6), *δ*: 12.96(br, 1H, SO_2NH), 10.89(s, 1H, CONH-pyrim), 8.82—8.65(m, 2H, Py-H), 8.50—8.24(m, 2H, pyrim-H, Py-H), 8.14—7.62(m, 5H, Py-H, pyrim-H), 2.96[s, 3H, 1/2N(CH_3)$_2$], 2.73[s, 3H, 1/2N(CH_3)$_2$]. ^{13}C NMR(101 MHz, DMSO-d_6), *δ*: 167.14, 164.18, 163.33, 159.94, 155.07, 154.45, 149.90, 149.70, 138.30, 137.77, 137.26, 131.05, 127.18, 125.85, 121.17, 106.32, 38.72, 34.77. HRMS(ESI) calcd. for $C_{18}H_{18}N_7O_4S$([M+H]$^+$), *m/z*: 428.1141; found: 428.1142.

N,*N*-Dimethyl-2-{*N*-[4-(pyridin-3-yl)pyrimidin-2-ylcarbamoyl]sulfamoyl}nicotinamide(**9e**): a yellow solid, yield 71.7%; m. p. 206—208 °C. ^{1}H NMR(400 MHz, DMSO-d_6) *δ*: 10.89(s, 1H, CONH-pyrim), 8.80—8.44(m, 4H, SO_2NH, Py-H), 8.23(d, *J*=5.5 Hz, 1H, pyrim-H), 7.84—7.64(m, 4H, Py-H), 7.38(d, *J*=5.5 Hz, 1H, pyrim-H), 2.96[s, 3H, 1/2N(CH_3)$_2$], 2.85[s, 3H, 1/2N(CH_3)$_2$]. ^{13}C NMR(101 MHz, DMSO-d_6), *δ*: 166.13, 163.42, 161.99, 157.06, 153.75, 150.63, 148.39, 147.28, 136.88, 135.83, 133.28, 132.98, 127.79, 125.07, 112.78, 106.65, 38.72, 34.80. HRMS(ESI) calcd. for $C_{18}H_{18}N_7O_4S$([M+H]$^+$), *m/z*: 428.1141; found: 428.1144.

N,*N*-Dimethyl-2-{*N*-[4-(pyridin-4-yl)pyrimidin-2-ylcarbamoyl]sulfamoyl}nicotinamide(**9f**): a white solid, yield 61.4%; m. p. 225—227 °C. ^{1}H NMR(400 MHz, DMSO-d_6), *δ*: 12.80(br, 1H, SO_2NH), 10.93(s, 1H, CONH-pyrim), 8.95(d, *J*=5.3 Hz, 1H, Py-H), 8.74(d, *J*=7.7 Hz, 2H, Py-H), 8.49(d, *J*=5.2 Hz, 1H, pyrim-H), 8.22(d, *J*=7.7 Hz, 2H, Py-H), 7.98(d, *J*=5.3 Hz, 1H, Py-H), 7.79(dd, *J*=7.8, 4.7 Hz, 1H, Py-H), 7.37(d, *J*=5.2 Hz, 1H, pyrim-H), 2.85[s, 3H, 1/2N(CH_3)$_2$], 2.73[s, 3H, 1/2N(CH_3)$_2$]. ^{13}C NMR(101 MHz, DMSO-d_6), *δ*: 169.52, 164.13, 163.15, 163.93, 158.16, 154.00, 153.18, 149.80, 137.26, 132.91, 128.91, 128.13, 127.18, 104.74, 38.32, 34.25. HRMS(ESI) calcd. for $C_{18}H_{18}N_7O_4S$([M+H]$^+$), *m/z*: 428.1141; found: 428.1138.

N,*N*-Dimethyl-2-{*N*-[4-(3-nitrophenyl)pyrimidin-2-ylcarbamoyl]sulfamoyl}nicotinamide(**9g**): a yellow solid, yield 68.1%; m. p. 183—184 °C. ^{1}H NMR(400 MHz, DMSO-d_6), *δ*: 12.70(br, 1H, SO_2NH), 10.91(s, 1H, CONH-pyrim), 8.99(s, 1H, Ph-H), 8.61(d, *J*=7.0 Hz, 1H, pyrim-H), 8.22(d, *J*=7.4 Hz, 1H, Py-H), 8.08—7.99(m, 2H, Ph-H, Py-H), 7.76—7.69(m, 2H, Py-H, Ph-H), 7.40—7.39(m, 2H, Ph-H, pyrim-H), 2.86[s, 3H, 1/2N(CH_3)$_2$], 2.73[s, 3H, 1/2N(CH_3)$_2$]. ^{13}C NMR(101 MHz, DMSO-d_6), *δ*: 169.56, 164.98, 163.32, 158.10, 153.26, 153.21, 152.95, 148.40, 137.26, 136.85, 129.56, 128.42, 126.18, 124.81, 106.61, 104.91, 103.52, 34.79. HRMS(ESI) calcd. for $C_{19}H_{18}N_7O_6S$([M+H]$^+$), *m/z*: 472.1039; found: 472.1039.

N,*N*-Dimethyl-2-{*N*-[4-(4-nitrophenyl)pyrimidin-2-ylcarbamoyl]sulfamoyl}nicotinamide(**9h**): a yellow solid, yield 65.6%; m. p. 219—221 °C. ^{1}H NMR(400 MHz, DMSO-d_6), *δ*: 12.75(br, 1H, SO_2NH), 10.93(s, 1H, CONH-pyrim), 8.92(d, *J*=5.1 Hz, 1H, pyrim-H), 8.49—8.43(m, 2H, Ph-H, Py-H), 8.08—7.72(m, 4H, Ph-H, Py-H), 7.54—7.32(m, 2H, Ph-H, pyrim-H), 2.97[s, 3H, 1/2N(CH_3)$_2$], 2.86[s, 3H, 1/2N(CH_3)$_2$]. ^{13}C NMR(101 MHz, DMSO-d_6), *δ*: 167.17, 163.18, 162.79, 158.26, 153.74, 149.70, 149.26, 142.95, 137.25, 133.28, 128.72, 127.78, 127.18, 124.37, 107.13, 38.73, 34.78. HRMS(ESI) calcd. for $C_{19}H_{18}N_7O_6S$([M+H]$^+$), *m/z*: 472.1039; found: 472.1033.

2-{*N*-[4-(4-Fluorophenyl)pyrimidin-2-ylcarbamoyl]sulfamoyl}-*N*,*N*-dimethylnicotinamide(**9i**): a white solid, yield 56.5%; m. p. 225—227 °C. ^{1}H NMR(400 MHz, DMSO-d_6), *δ*: 13.02(br, 1H, SO_2NH), 10.86(s, 1H, CONH-pyrim), 8.81(d, *J*=5.4 Hz, 1H, pyrim-H), 8.35(d, *J*=5.5 Hz, 1H, Py-H), 8.20—8.17(m, 1H, Py-H), 7.90(d, *J*=7.7 Hz, 2H, Ph-H), 7.84(d, *J*=5.4 Hz, 1H, Py-H), 7.79(d, *J*=7.7 Hz, 2H, Ph-H), 7.71—7.68(m, 1H, pyrim-H), 2.85[s, 3H, 1/2N(CH_3)$_2$], 2.73[s, 3H, 1/2N(CH_3)$_2$]. ^{13}C NMR(101 MHz, DMSO-d_6), *δ*: 167.16, 164.20, 162.98, 159.57, 155.09, 149.69, 137.26, 133.93, 131.06, 129.55, 129.47, 127.17, 116.18, 115.97, 106.06, 38.72, 34.79. HRMS(ESI) calcd. for $C_{19}H_{18}FN_6O_4S$([M+H]$^+$), *m/z*: 445.1094; found: 445.1097.

2-{*N*-[4-(4-Chlorophenyl)pyrimidin-2-ylcarbamoyl]sulfamoyl}-*N*,*N*-dimethylnicotinamide(**9j**): a white solid, yield 69.7%; m. p. 221—223 °C. ^{1}H NMR(400 MHz, DMSO-d_6), *δ*: 12.95(br, 1H, SO_2NH), 10.86(s, 1H, CONH-pyrim), 8.83(d, *J*=4.6 Hz, 1H, Py-H), 8.33(d, *J*=4.6 Hz, 1H, pyrim-H), 8.21(d, *J*=7.8 Hz, 2H, Ph-H), 8.03(d, *J*=7.6 Hz, 1H, Py-H), 7.86—7.67(m, 4H, pyrim-H, Py-H, Ph-H), 2.82[s, 3H, 1/2N(CH_3)$_2$], 2.73[s, 3H, 1/2N(CH_3)$_2$]. ^{13}C NMR(101 MHz, DMSO-d_6), *δ*: 169.16, 164.20, 163.98, 158.57, 154.09, 153.69, 137.26, 134.93, 133.06, 129.55, 128.47, 127.17, 126.18, 115.97, 106.06, 38.72, 35.49. HRMS(ESI) calcd. for $C_{19}H_{18}ClN_6O_4S$ ([M+H]$^+$), *m/z*: 461.0799; found: 461.0794.

2-{*N*-[4-(4-Bromophenyl)pyrimidin-2-ylcarbamoyl]sulfamoyl}-*N*,*N*-dimethylnicotinamide(**9k**): a white solid, yield 74.7%; m. p. 207—209 °C. ^{1}H NMR(400 MHz, DMSO-d_6), *δ*: 12.94(br, 1H, SO_2NH), 10.87(s, 1H, CONH-pyrim), 8.36(d, *J*=5.4 Hz, 1H, pyrim-H), 8.12(d, *J*=8.6 Hz, 1H, Py-H), 8.05(d, *J*=8.3 Hz, 2H, Ph-H), 7.89(d, *J*=7.7 Hz, 1H, Py-H), 7.80(d, *J*=8.2 Hz, 1H, Py-H), 7.73(d, *J*=8.5 Hz, 2H, Ph-H), 7.23(d, *J*=5.4 Hz, 1H, pyrim-H), 2.96[s, 3H, 1/2N(CH_3)$_2$], 2.76[s, 3H, 1/2N(CH_3)$_2$]. ^{13}C NMR(101 MHz, DMSO-d_6), *δ*: 167.13, 164.15, 162.74, 157.81, 149.70, 137.26, 136.15, 132.66, 132.28, 131.04, 129.71, 129.44, 127.19, 125.18, 106.15, 38.72, 34.77.

HRMS(ESI) calcd. for $C_{19}H_{18}BrN_6O_4S([M+H]^+)$, *m/z*: 505.0294; found: 505.0292.

N,*N*-Dimethyl-2-[*N*-(4-*p*-tolylpyrimidin-2-ylcarbamoyl)-sulfamoyl]nicotinamide(**9**l): a white solid, yield 73.9%; m. p. 228—230 °C. ^{1}H NMR(400 MHz, DMSO-d_6), δ: 13.18(br, 1H, SO_2NH), 10.82(s, 1H, CONH-pyrim), 8.28(d, *J*=5.1 Hz, 1H, pyrim-H), 8.09(d, *J*=7.8 Hz, 2H, Ph-H), 7.98(d, *J*=7.8 Hz, 1H, Py-H), 7.90(d, *J*=7.7 Hz, 1H, Py-H), 7.74—7.67(m, 1H, Py-H), 7.40(d, *J*=7.8 Hz, 2H, Ph-H), 7.10(d, *J*=5.0 Hz, 1H, pyrim-H), 2.96[s, 3H, 1/2N(CH_3)$_2$], 2.73[s, 3H, 1/2N(CH_3)$_2$], 2.41(s, 3H, CH_3). ^{13}C NMR(101 MHz, DMSO-d_6), δ: 164.22, 159.34, 157.59, 150.20, 142.67, 137.65, 137.27, 133.41, 130.28, 129.75, 128.33, 127.68, 127.09, 111.93, 105.95, 38.72, 34.78, 21.48. HRMS(ESI) calcd. for $C_{20}H_{21}N_6O_4S([M+H]^+)$, *m/z*: 441.1345; found: 441.1344.

2.3 Fungicidal Activity Assay

The fungicidal activities of the title compounds **9**a—**9**l were tested *in vivo* against *Rhizoctonia solanii*(*R. solanii*), *Pseudomonas syringae*(*P. syringae*), *Phytophthora capsici*(*P. capsici*), *Corynespora cassiicola*(*C. cassiicola*), *Botrytis cinerea*(*B. cinerea*), *Fusarium oxysporum*(*F. oxysporum*) and their relative inhibitory ratios(%) were determined by the mycelim growth rate method[31]. The corresponding commercialized fungicides(Validamycin, *Bacillus subtilis Cohn*, Chlorothalonil, Dimethomorph, Procymidone and Thiophanate-methyl) were used as controls. The inhibition rate(*I*) was calculated according to the formula: $I=(D_1-D_2)/D_1\times100\%$, where D_1 is the average diameter of mycelia in the blank test, and D_2 is the average diameter of mycelia in the presence of those compounds.

2.4 Herbicidal Activity Assay

The herbicidal activities of target compounds **9**a—**9**l were tested against *Brassica napus*, *Amaranthus retroflexus*, *Echinochloa crusgalli* and *Digitaria sanguinalis* at a dosage of 1500 g/ha(1 ha=1×10^4 m^2) *via* the known procedure[32]. Monosulfuron and Nicosulfuron were selected as positive controls. The herbicidal inhibition was determined by the fresh mass relative to the controls.

3 Results and Discussion

3.1 Chemistry

N,*N*-Dimethylformamide dimethyl acetal was refluxed with arylmethylketones to give the intermediates **1** and this reaction solution was used in the subsequent reaction without further treatment. Compounds **2**a—**2**l were obtained in excellent yields from intermediate **1**, which were purified by crystallization from a mixture of ethanol/hexane. Compared to the previous methods[26,27], this method was much more efficiently and easier to obtain the aryl-monosubstituted pyrimidinamines. In this paper, sodium hypochlorite was used as an oxidant to facilely generate compound **7** instead of poisonous oxidant chlorine. The intermediate **8** was obtained *via* reaction of compound **7** with ethyl chloroformate in acetone in the presence of potassium carbonate. As shown in Scheme 3, the title compounds **9**a—**9**l were synthesized from intermediates **2** with compound **8** in toluene under refluxing and monitored by TLC. The low-boiling component was distilled out continuously to improve the yield.

3.2 Fungical Activities

The *in vivo* fungicidal activities of title compounds **9** are summarized in Table 1. At the dosage of 100 mg/L, most of the target compounds showed moderate to favorable activities in inhibiting the mycelial growth of all of the test fungi, while the commercialized sulfonylurea herbicide-Nicosulfuron almost showed no fungicidal activity. Furthermore, the title compounds also held promising inhibitory activities at a much lower concentration(25 mg/L). Especially, compound **9**b exhibited much higher inhibition activity than the controls against five phytopathogens(*R. solanii*, *P. capsici*, *P. syringae*, *C. cassiicola* and *B. cinerea*). Compounds **9**c, **9**e, **9**j, **9**f and **9**k showed more efficacy than the controls against two fungi. Among all the tested fungi, *R. solanii* was more sensitive to the target compounds compared with the other fungi, revealing that the compounds may have selectivity to the phytopathogens.

The comparison of the fungicidal activities of compounds **9** against six tested fungi to those of controls leads to the following conclusions: (1) the title SUs containing bulky substituted groups(aryl) in pyrimidine moiety possessed obviously much higher antifungal activities than Nicosulfuron(pyrimidine was substituted by methoxyl), indicating that an aryl group on the pyrimidine ring is favorable for antifungal activity. (2) Among the aryl groups, the five-membered aryl-heterocycles and six-membered aromatic rings with electron deficient groups exhibited much higher inhibitory activity than the others. For example, compound **9**b(2-thienyl) displayed much higher fungicidal activities for the tested fungi than the others. (3) For the benzyl series, there is no direct relationships between the substitutents on the phenyl and the inhibitory rate, but it was demonstrated that bromine was a vital factor to increase the fungicidal activity. Compound **9**k(*p*-bromophenyl) held promising efficacy similar to the control against three fungi. (4) In addition, the introduction of pyridyl group(**9**c, **9**d, **9**e) did not lead to a remarkable increase in activity against the tested fungi in comparison with compounds **9**g and **9**h(*m*- or *p*-nitrophenyl).

Table 1 Antifungal activity(%) of title compounds 9a—9l(*in vivo*)*

Compd.	Dosage(mg·L^{-1})	*R. solanii*	*P. syringae*	*P. capsici*	*C. cassiicola*	*B. cinerea*	*F. oxysporum*
9a	100	59.4	28.2	49.6	49.6	62.5	22.2
	25	40.5	11.9	20.2	33.0	44.5	19.7
9b	100	81.7	43.9	67.6	62.0	70.0	38.4
	25	60.4	25.5	36.2	53.4	46.6	19.2

To be continued on the next page.

Compd.	Dosage(mg·L^{-1})	*R. solanii*	*P. syringae*	*P. capsici*	*C. cassiicola*	*B. cinerea*	*F. oxysporum*
9c	100	84.1	38.2	32.7	39.6	30.6	32.9
	25	65.9	21.3	14.4	25.7	24.9	18.1
9d	100	53.4	37.1	31.3	39.9	53.1	53.3
	25	34.1	20.1	17.2	22.3	37.1	33.0
9e	100	76.3	34.5	42.6	40.9	55.0	22.6
	25	59.0	19.1	25.4	28.3	42.3	4.9
9f	100	67.9	50.0	43.8	44.2	39.8	50.8
	25	44.5	26.7	22.9	29.6	30.6	28.4
9g	100	89.3	12.6	23.5	17.2	24.4	39.3
	25	66.7	8.1	11.7	16.6	9.9	12.9
9h	100	60.4	45.0	34.5	30.6	14.0	49.4
	25	47.0	26.2	14.0	21.3	5.2	27.4
9i	100	48.1	31.8	54.4	30.2	45.6	27.7
	25	32.1	18.4	24.6	25.8	27	17.2
9j	100	79.0	46.2	57.9	39.6	62.6	54.4
	25	60.2	26.5	27.1	27.4	36.4	34.7
9k	100	63.3	24.5	75.3	72.7	50.4	22.6
	25	44.1	5.1	41.5	62.5	31.4	11.1
9l	100	58.3	27.8	40.8	59.8	51.8	53.5
	25	42.5	10.5	17.3	44.5	36.7	31.4
Nicosulfuron	100	7.1	25.0	37.3	13.5	26.0	6.5
	25	–4.9	7.2	8.5	0	9.5	–3.2
Validamycin	100	71.6	——	——	——	——	——
	25	57.3	——	——	——	——	——
Bacillus subtilis Cohn	100	——	43.8	——	——	——	——
	25	——	24.2	——	——	——	——
Dimethomor Ph	100	——	——	81.1	——	——	——
	25	——	——	28.5	——	——	——
Chlorothalonil	100	——	——	——	62.1	——	——
	25	——	——	——	49.7	——	——
Procymidone	100	——	——	——	——	70.3	——
	25	——	——	——	——	24.9	——
Thiophanate-methyl	100	——	——	——	——	——	64.1
	25	——	——	——	——	——	36.3

* Nicosulfuron is commercialized sulfonylurea herbicide. Validamycin, *Bacillus subtilis Cohn*, Dimethomorph, Chlorothalonil, Procymidone and Thiophanate-methyl are corresponding commercialized fungicides against *R. solani*, *P. syringae*, *P. capsici*, *C. cassiicola*, *B. cinerea* and *F. Oxysporum*, respectively; "—" means not tested.

3.3 Herbicidal Activities

As shown in Table 2, most of title compounds **9** showed extremely low inhibitory activities against the tested plants, demonstrating that the bulky group——aryl, introduced to the pyrimidine moiety is unfavorable for herbicidal activities and confirming that the herbicidal activity-structure relationships should obey the Levitt's guidelines[18].

Table 2 Herbicidal activities(%) of compounds 9a—9l (1500 g/ha)

Compd.	*Brassica napus*		*Amaranthus retroflexus*		*Echinochloa crusgalli*		*Digitaria sanguinalis*	
	Soil treatment	Foliage spray	Soil treatment	Foliage spray	Soil treatment	Foliage spray	Soil treatment	Foliage spray
9a	0	15.0	47.7	0	0	10.0	0	0
9b	0	15.0	0	54.9	0	5.0	0	35.0
9c	0	15.0	10.0	53.8	0	15.0	0	33.5
9d	0	30.0	0	20.0	0	10.0	0	15.0
9e	0	40.0	0	61.7	0	5.0	0	15.0
9f	0	20.0	10.0	50.9	0	10.0	0	0
9g	0	15.0	0	15.0	0	5.0	0	20.0
9h	5.0	5.0	10.0	15.0	5.0	10.0	5.0	0
9i	0	20.0	46.5	10.0	0	10.0	0	0
9j	15.0	15.0	0	20.0	10.0	15.0	0	0
9k	0	20.0	0	5.0	10.0	15.0	0	15.0
9l	32.2	10.0	0	15.0	10.0	20.0	0	10.0
Monosulfuron	100	100	100	100	99.8	100	100	100
Nicosulfuron	100	100	100	100	100	100	100	100

4 Conclusions

In summary, a series of novel *N*-(4'-arylpyrimidin-2'-yl)sulfonylurea derivatives was designed and synthesized. Their structures were characterized by ^{1}H NMR, ^{13}C NMR and HRMS. The antifungal results indicated that a bulky group(aryl) at the pyrimidine moiety was favorable for antifungal activity and SUs can be considered as potential fungicides. Compounds **9**b and **9**k were promising leading compounds for development of novel antifungal agents. The herbicidal data indicated that the bulky groups on pyrimidine ring were unfavorable for herbicidal activity. Further studies on structural optimization and structure-activity relationships of these compounds are in progress.

References

[1] McCourt J. A., Duggleby R. G., *Amino Acids*, **2006**, *31*, 173

[2] Pue N., Guddat L. W., *Curr. Pharm. Des.*, **2014**, *20*, 740

[3] Liu Z., Pan L., Li Y. H., Wang S. H., Li Z. M., *Chem. Res*. *Chinese Universities*, **2013**, *29*(3), 466

[4] Chipman D., Barak Z. A., Schloss J. V., *Biochim. Biophys. Acta*, **1998**, *1385*, 401

[5] Guo X. H., Jia K. L., Dan W. Y., Li J. F., *Chem. Eng.*, **2012**, *9*, 25

[6] Lafontaine Y., Beauvais C., Cessna A. J., Gagnon P., Hudon C., Poissant L., *Sci. Total Environ.*, **2014**, *479/480*, 1

[7] Grandoni J. A., Marta P. T., Schloss J. V., *J. Antimicrob. Chemother.*, **1998**, *42*, 475

[8] Kingsbury J. M., Yang Z. H., Ganous T. M., Cox G. M., McCusker J. H., *Microbiol.*, **2004**, *150*, 1547

[9] Kingsbury J. M., McCusker J. H., *Microbiol.*, **2010**, *156*, 929

[10] Boigegrain R. A., Liautard J. P., Kohler S., *Antimicrob. Agents Chemother.*, **2005**, *49*, 3922

[11] Bange F. C., Brown A. M., Jacobs Jr. W. R., *Infect. Immun.*, **1996**, *64*, 1794

[12] Kingsbury J. M., Goldstein A. L., McCusker J. H., *Euk. Cell*, **2006**, *5*, 816

[13] Awasthy D., Gaonkar S., Shandil R. K., Yadavr., Bharath S., Marcel N., Subbulakshmi V., Sharma U., *Microbiol.*, **2009**, *155*, 2978

[14] Atkins T., Prior R. G., Mack K., Russell P., Nelson M., Oyston P. C. F., Dougan G., Titball R. W., *Infect. Immun.*, **2002**, *70*, 5290

[15] Duggleby R. G., Pang S. S., Yu H., Guddat L.W., *Eur. J. Biochem.*, **2003**, *270*, 2895

[16] Pan L., Jiang Y., Liu Z., Liu X. H., Liu Z., Wang G., Li Z. M., Wang D., *Eur. J. Med. Chem.*, **2012**, *50*, 18

[17] Wang D., Pan L., Cao G., Lei H., Meng X. H., He J. F., Dong M., Li Z. M., Liu Z., *Inter. J. Antimicrob. Agents*, **2012**, *40*, 463

[18] Pang S. S., Duggleby R. G., Guddat L. W., *J. Mol. Biol.*, **2002**, *317*, 249

[19] Pang S. S., Guddat L. W., Duggleby R. G., *J. Biol. Chem.*, **2003**, *278*, 7639

[20] McCourt J. A., Pang S. S., Duggleby R. G., *Biochem.*, **2005**, *44*, 2330

[21] Levitt G., Baker D., Fenyes J., Moberg W., *Synthesis and Chemistry of Agrochemicals II*, American Chemical Society, Washington D. C., **1991**, 16

[22] Li Z. M., Ma Y., Guddat L., Cheng P. Q., Wang J. G., Pang S. S., Dong Y. H., Lai C. M., Wang L.X., Jia G. F., Li Y. H., Wang S. H., Liu J., Zhao W. G., Wang B. L., *Pest. Manag. Sci.*, **2012**, *68*, 618

[23] Ungureanu M., Moldoveanu C. C., Poeata A., Drochioiu G., Petrovanu M., Mangalagi I. I., *Ann. Pharm. Fr.*, **2006**, *64*, 287

[24] Akbas E., Berber I., Akyazi I., Anil B., Yildiz E., *Lett. Org. Chem.*, **2011**, *8*, 663

[25] McCourt J. A., Pang S. S., King-Scott J., Guddat L. W., Duggleby R. G., *Proc. Natl. Acad. Sci.*, **2006**, *103*, 569

[26] Chen Q. F., Zhang H. D., Gong S. C., *Chin. J. Appl. Chem.*, **2011**, *8*, 382

[27] Zheng Z. Y., Chen J. Y., Liu G. L., Li Y. H., Li Z. M., *Chin. J. Pest. Sci.*, **2012**, *14*, 607

[28] Mayer H., Hamprecht G., Westphalen K. O., Gerber M., Walter H., *(Phenylsulfonylureido)triazine or -Pyrimidine Herbicides*, DE 4238175, **1994**

[29] Pan L., Liu Z., Chen Y. W., Li Y. H., Li Z. M., *Chem. J. Chinese Universities*, **2013**, *34*(6), 1416

[30] Liu Z., Pan L., Yu S. J., Li Z. M., *Chem. J. Chinese Universities*, **2013**, *34*(8), 1868

[31] Chen N. C., *Bioassay of Pesticides*, Beijing Agricultural University Press, Beijing, **1991**, 161

[32] Peng H., Deng X. Y., Gao L., Tan X. S., He H. W., *Chem. Res*. *Chinese Universities*, **2014**, *30*(1), 82