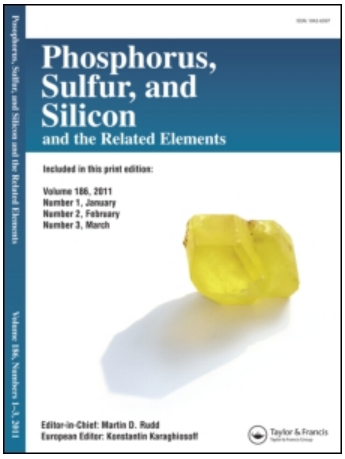

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Synthesis of Some New 4-(2-Chloropyridin-4-yl)-*N*-Aryl-1,3-Thiazol-2-Amine Derivatives as Possible Antifungal and Antibacterial Agents

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Novel 4-(2-chloropyridin-4-yl)-N-aryl-1,3-thiazol-2-amines have been prepared by reacting (4-bromoacetyl)-2-chloropyridine with thiourea and substituted thioureas. The newly synthesized compounds have been characterized by analytical and spectral data. All the compounds have been screened for their antifungal and antibacterial activities. Almost all the compounds were found to possess excellent antifungal and antibacterial activities.

Keywords 2-chloropyridinyl; antibacterial; antifungal; synthesis; thiazole

Pyridine is an important structural unit found in many known therapeutic agents.[1–5] Many pyridinyl thiazoles have been proven to possess a wide range of biological activities, such as cardiotonic,[6] antiasthmatic, and antiinflammatory activities;[7,8] selective inhibitors of cytochrome P-450 2A6;[9] and NPY5 antagonists.[10] Antimicrobial activity of thiazole derivatives has been extensively studied by many researchers.[11] As a continuation of our research to explore potent

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biologically active thiazole-containing molecules,[12–14] we synthesized novel 4-(2-chloropyridin-4-yl)-N-aryl-1,3-thiazol-2-amines and evaluated their antifungal and antibacterial activities.

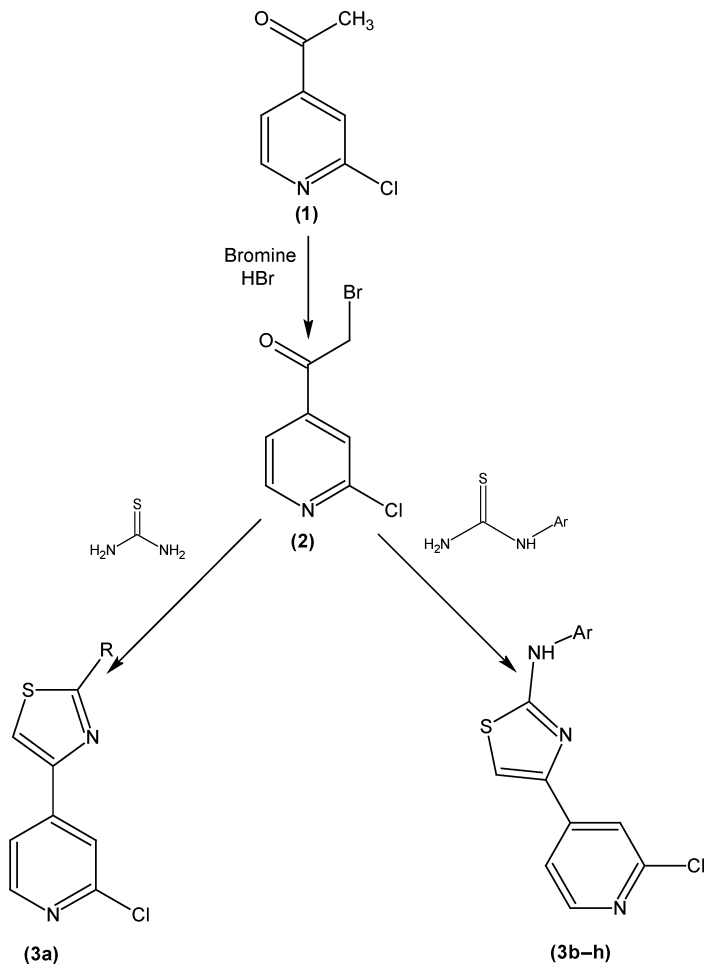
RESULTS AND DISCUSSION

2-Chloro-4-acetylpyridine (**1**) was prepared from 4-cyanopyridine by following a literature procedure.[15] 2-Chloro-4-acetylpyridine then was treated with bromine in the presence of a catalytic amount of HBr and yielded 2-chloro-4-(2-bromoacetyl) pyridine (**2**). 2-Chloro-4-(2-bromoacetyl) pyridine (**2**) was then treated with thiourea and substituted thioureas and yielded 4-(2-chloropyridin-4-yl)-N-aryl-1,3-thiazol-2-amines (**3a–h**) (Scheme 1). All compounds were further purified in a methanol/dimethylformamide mixture and isolated in 60–84% yields. Selected compounds were characterized by IR, ^{1}H NMR, and mass spectral analysis.

The IR spectrum of **3c** showed a band at 3267 cm^{-1} and 2923 cm^{-1} due to —NH and —CH stretches respectively. A band at 1595 cm^{-1} and 1550 cm^{-1} was due to a —C=N stretch. The ^{1}H NMR spectrum (300 MHz) of **3c** showed a singlet at δ 2.33 due to —CH_3 protons. Two singlets at δ 7.20 and δ 7.21 were due to —NH— and the aromatic proton on the thiazole ring, respectively. A doublet of doublets at δ 7.48 (J = 6.12, 8.14 Hz) and a doublet at δ 7.68 (J = 5.93 Hz) were due to aromatic protons. A singlet at δ 7.80 and doublet at δ 8.38 (J = 5.23 Hz), and a singlet at δ 9.86 were due to the protons on the pyridine ring. The FAB-MS of **3c** showed peaks at *m/z* 336 (M^+, 100%) and *m/z* 338 (M+2, 70%) corresponding to the molecular formula $C_{15}H_{11}Cl_2N_3S$. The percentage of nitrogen analysis of **3c** was 12.51, which is in accordance with the theoretical value of 12.50.

ANTIFUNGAL AND ANTIBACTERIAL ACTIVITY

The newly synthesized 4-(2-chloropyridin-4-yl)-N-aryl-1,3-thiazol-2-amines (**3a–h**) were screened for their antibacterial activity against *Escherichia coli* (ATTC-25922), *Staphyllococcus aureus* (ATTC-25923), *Psuedomonus aeruginosa* (ATTC-27853), and *Klebsiella pneumoniae* (recultured) bacterial strains by the disc diffusion method.[16–18] Nitrofurazone was used as a standard drug. Compounds also were screened for their antifungal activity against *Aspergilus flavus* (NCIM No. 524), *Aspergilus fumigatus* (NCIM No. 902), *Candida albicans* (NCIM No. 3100), *Penicillium marneffei* (recultured), and *Trichophyton mentagrophytes* (recultered) in DMSO by the serial plate dilution method.[16–18] The activity of each compound was compared with



SCHEME 1

that of Itraconozole as a standard drug. The results of such studies are given in Tables I and II.

Among the tested compounds, **3d**, bearing a 2-methylphenyl moiety, and **3g**, bearing a 3-chlorophenyl moiety, exhibited maximum antibacterial activity while all other compounds showed excellent antifungal activity except with *P. marneffei* for which the test compounds have exhibited moderate activity. It is interesting to note that all compounds exhibited excellent antibacterial activity against *E. coli*. For the bacteria *P. aeruginosa,* except **3a** and **3h**, all other compounds exhibited excellent antibacterial activity.

TABLE I Antibacterial Activity of Compounds (MIC in μg/mL) 3a–h

Compound	*Escherichia coli*	*Staphyllococcus aureus*	*Psuedomonus aeruginosa*	*Klebsiella pneumoniae*
3a	10	10	—	100
3b	10	—	10	—
3c	10	—	18	—
3d	10	10	10	—
3e	10	—	10	100
3f	10	—	10	—
3g	6.25	10	6.25	100
3h	10	10	—	—
Nitrofurazone	6	12.5	>100	—

The structural activity study included **3g**, which possessed the N-(3-chlorophenyl) moiety. In earlier works with thiazoles that we reported recently, it was found that thiazoles bearing a N-(4-chlorophenyl) moiety exhibited excellent antimicrobial activity.[12–14] A known antifungal agent N-[4-(4-chlorophenyl)-2-thiazolyl salicylamide[19] also contained a 4-chlorophenyl moiety. Hence, we conclude that the higher activity of compound **3g** may be attributed to the N-(3-chorophenyl) moiety, which is structurally similar to N-(4-chlorophenyl) moiety. Since all the tested compounds exhibited excellent antifungal activity, we conclude that antifungal activity is due to the presence of a 2-chloropyridine moiety. The compound **3g**, 4-(2-chloropyridin-4-yl)-N-(3-chlorophenyl)-1, 3-thiazol-2-amine, can be projected as a promising antifungal and antibacterial agent.

TABLE II Antifungal Activity of Compounds (MIC in μg/mL) 3a–h

Compound	*Aspergilus flavus*	*Aspergilus fumigatus*	*Penicillium marneffei*	*Trichophyton mentagrophytes*
3a	10	10	60	10
3b	10	10	60	10
3c	10	10	60	10
3d	10	10	60	10
3e	10	10	60	10
3f	10	10	60	10
3g	6.25	10	60	6.25
3h	10	10	60	10
Itraconazole	<16	<16	<16	<16

EXPERIMENTAL

Melting points were taken in open capillary tubes and were uncorrected. The purity of the compounds was confirmed by TLC using Merck silica gel 60 F_{254} coated aluminium plates. IR spectra were recorded on a Shimadzu-FTIR infrared spectrometer in KBr (ν_{max} in cm^{-1}). ^1H NMR spectra were recorded in $CDCl_3$ and in DMSO-d_6 on a Varian (300 MHz) spectrometer using TMS as the internal standard. ^{13}C NMR spectra were recorded in $CDCl_3$and in DMSO-d_6 on a Varian (75 MHz) spectrometer. FABMS spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer using argon/xenon (6 kv, 10 mA) as the FAB gas.

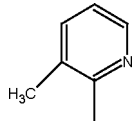
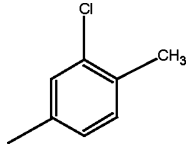
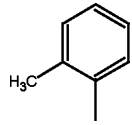
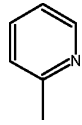
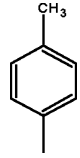
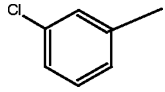
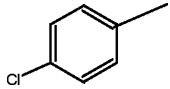
THE SYNTHESIS OF 2-CHLORO-4-ACETYLPYRIDINE (1)

This compound was prepared via the procedure described in the literature.[15] The product was obtained as a light-yellow solid, m.p. 35–37°C (Lit.[15] 36–39°C).

TABLE III Spectral Data and Elemental Analysis of Some Selected Compounds

Compound	Spectra and %N
3c	IR (KBr, ν cm^{-1}) 3267 (—NH), 2923 (—CH), 1595 cm^{-1} and 1550 (—C═N); ^1H NMR (300 MHz) δ 2.33 (s, —CH_3), δ 7.20 (d $_{(J=3.5)}$, 1H, Ar-H), δ 7.21(s, 1H, Ar-H), δ 7.48 (dd $_{(J=2.6,8.41Hz)}$, 1H, Ar-H) δ 7.68 (dd $_{(J=5.93)}$, 1H, Ar-H), δ 7.80 (s, 1H, Ar-H), δ 8.38 (d $_{(J=5.23)}$, 1H, Ar-H), δ 9.86 (s, 1H, —NH); FABMS: m/z 336 (M^+, 100%), m/z 338 (M+2, 70%); % N, Found, 12.51; Calcd., 12.40.
3f	IR (KBr, ν cm^{-1}) 3259 (—NH), 3111 and 2821 (—CH), 1637 and 1589 (—C═N); ^1H NMR (300 MHz) δ 2.41 (s, —CH_3), δ 7.24 (d $_{(J=8.36)}$, 2H, Ar-H), δ 7.33 (d $_{(J=8.42)}$, 2H, Ar-H), δ 7.53 (s, 1H, Ar-H), δ 8.05 (d $_{(J=5.75)}$, 1H, Ar-H), δ 8.23 (s, 1H, Ar-H), δ 8.84 (d $_{(J=5.95)}$, 1H, Ar-H); ^{13}C NMR (75 MHz, ppm) 109.81, 118.49 (2-C), 119.41, 124.89, 128.87(2-C), 139.68, 144.42, 146.36, 150.42, 151.13, 163.25; DEPT-109.84, 118.51, 119.45, 119.82, 128.90, 150.45; FABMS: m/z 303 (M+1, 80%), m/z 289(M—CH_3), 30%); m/z 139 (M-C_7H_6ClN, 44%); N, Found, 13.86; Calcd., 13.82.
3h	IR (KBr, ν cm^{-1}) 3271 (—NH), 3066 (—CH), 1598 & 1552 (—C═N); ^1H NMR (300 MHz) δ 2.33 (s, —CH_3), δ 7.39 (d $_{(J=8.4)}$, 2H, Ar-H), δ 7.72 (d $_{(J=8.7)}$, 2H, Ar-H), δ 7.48 (dd $_{(J=8.1)}$, 2H, Ar-H), δ 8.05 (s, 1H, Ar-H), δ 8.43 (d $_{(J=5.1)}$, 1H, Ar-H), δ 10.53 (s, 1H, —NH); MS: m/z 286 (M-Cl, 17%), m/z 184 (M—NHC_6H_5Cl), 50%); m/z 139 (M-C_7H_6ClN, 44%); N, Found, 12.96; Calcd., 12.69.

TABLE IV Characterization Data of 4-(2-Chloropyridin-4-yl)-N-Aryl-1,3-Thiazol-2-Amines (3a–h)

Compound No.	R, Ar	Yield %	M.P.,°C	Nature of Products
3a	R=NH_2	75	234–236	Light-yellow crystals
3b		82	236–238	Cream crystals
3c		84	196–198	Orange crystals
3d		68	200–202	Beige crystals
3e		69	158–160	Yellow powder
3f		70	160–162	Orange crystals
3g		80	181–183	Dark-orange crystals
3h		60	252–254	Dark-yellow powder

[a]All the yields are on the isolated basis.
[b]All compounds were recrystallised from methanol/DMF.

THE SYNTHESIS OF 2-CHLORO-4-(2-BROMOACETYL)PYRIDINE (2)

Ethyl acetate (37.5 mL) and HBr (0.25 mL) were placed in a flask and cooled to 5–10°C. Then 30.2 g (0.167 mol) of bromine was slowly added at 5–10°C over 0.5 h. In another flask was placed 21.7 g (0.139 mol) of 2-chloro-4-acetylpyridine **1** in 200 mL of ethylacetate, and 0.25 mL of HBr was added. The reaction mixture was cooled to 5–10°C, and

the previously prepared brominating mixture was slowly added over a period of 6 h. The reaction mixture was stirred for an additional 6 h at 5–10°C. The precipitated solid was filtered and washed with hexane. The HBr salt of the product thus obtained was then basified with 25% sodium bicarbonate solution, and the resulting solution was extracted with chloroform. The chloroform layer was then distilled out to yield the 2-chloro-4-(2-bromoacetyl)pyridine (**2**) as a brown yellow solid, yield of 28.2 g (85.9%); m.p. 50°C Lit.[20] 52–55°C); **IR** (KBr, γ_{max} cm^{-1}): 3031 (–CH), 2366 (–C=N), 1720 (–C=O), 1205 (–CH_2Br), 700. (Ar-Cl).

SYNTHESIS OF 4-(2-CHLOROPYRIDIN-4-YL)-N-ARYL-1, 3-THIAZOL-2-AMINES (3A-H)

2-Chloro-4-(2-bromoacetyl)pyridine (**2**), (0.01 mole) and thiourea/N-substituted thioureas (0.01 mole) in absolute alcohol were refluxed for 6 h, and the resulting solution was allowed to stand overnight; a solid separated and was filtered and recrystallized from a mixture of ethanol and dimethylformamide. Yield and melting point data for each compound are given in Table IV and spectral data of selected compounds are given in Table III.

CONCLUSION

Novel 4-(2-chloropyridin-4-yl)-N-phenyl-1,3-thiazol-2-amines were prepared by reacting (4-bromoacetyl)-2-chloropyridine with thiourea and substituted thioureas. All compounds exhibited excellent activity against all the fungal strains tested, and the compound **3g**, bearing a 3-chlorophenyl moiety, was found to be active against all the tested bacterial and fungal strains. Compound **3g** can be projected as a promising antifungal and antibacterial agent.

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