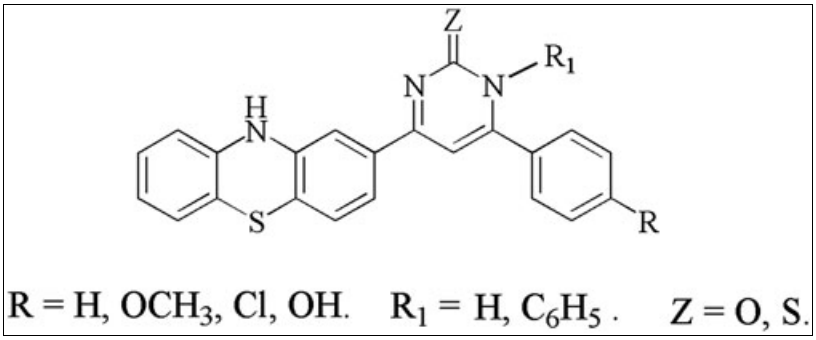
Tanaji N. Bansode[a,b] and Gangadhar A. Meshram[a]*

[a]Department of Chemistry, University of Mumbai, Vidyanagari, Kalina, Santacruz (East), Mumbai 400 098, India
[b]Department of Chemistry, B.N.N.College, Bhiwandi, Thane (M.S.) 421 305, India
*E-mail: meshramga@chem.mu.ac.in

Received April 12, 2010
DOI 10.1002/jhet.704
Published online 29 October 2012 in Wiley Online Library (wileyonlinelibrary.com).



A series of chalcones **3a–d** containing phenothiazine nucleus were prepared by Claisen–Schmidt condensation. The chalcones on treatment with urea, thiourea, phenyl urea, and phenyl thiourea in alcoholic KOH yielded compounds **4a–p**, and the structures of these compounds were confirmed by spectral and elemental analyses. The newly synthesized compounds were evaluated for antimicrobial activity.

J. Heterocyclic Chem., **49**, 1004 (2012).

INTRODUCTION

Heterocyclic compounds particularly five- or six-membered ring compounds have occupied the first place among various classes of organic compounds for their diverse biological activities [1]. Pyrimidine rings have received significant attention owing to their diverse range of biological properties [2,3]. Pyrimidine derivatives are of interest because of their pharmacological properties including antibacterial [4], anticancer [5], antitubercular [6], antifungal [7], antimalerial [8], analgesic [9], antihypertensive [10], and anti-inflammatory activity [11,12].

Phenothiazine and related compounds have shown diverse biological activities including tranquilizers [13], anti-inflammatory [14], antimalarial [15], antipsychotropic [16], antimicrobial [17], antitubercular [18–20], antitumor [21–23] antihistamine [24], and analgesic [25,26] properties. These observations prompted us to synthesize the Phenothiazine derivatives containing pyrimidine ring and evaluate their antimicrobial activities.

RESULT AND DISCUSSION

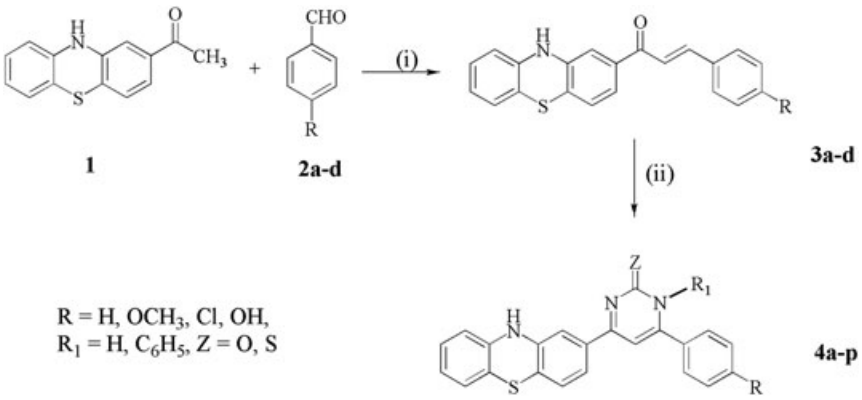
Chalcones **3a–d** were obtained by Claisen–Schmidt reaction, that is, by treating 2-acetylphenothiazine with methanolic KOH (40%) and various aldehydes **2a–d** gave above 90% yield. The cyclization of chalcones **3a–d** with urea, thiourea, pheyl urea, and phenyl thiourea under basic condition led to the formation of new pyrimidine derivatives **4a–p**. The reaction sequences are outlined in Scheme 1.

Formation of substituted (10H-phenothiazin-2-yl) pyrimidin-2(1H)-one/thione derivatives (**4**) was confirmed on the basis of elemental analysis, IR, ^{1}H NMR, and mass. Compounds **4** showed IR absorption bands in the regions 3331–3360 cm^{-1} (NH Streching), 1576–1593 cm^{-1} (C═N streching), and 1463–1469 cm^{-1} (C═C pyrimidine). The ^{1}H NMR spectrum of compounds **4a–p** showed singlet at δ 8.11–8.79 due phenothiazine NH proton. In case of compounds, **4a–d** and **4i–l** showed additional singlet at 8.02–8.08 due to pyrimidine NH protons. It showed multiplets at 7.87–6.66 due to aromatic protons and one singlet at δ 5.68–5.36 due to pyrimidine ring protons in all compounds. The ^{13}C NMR spectrum of **4** showed signals at δ 115.3–144.7 due to aromatic carbons and at δ 104.7–109.8, 157.1–181.4 due to pyrimidine ring carbons. The physical data of compounds **4a–p** are recorded in Table 1.

CONCLUSIONS

In conclusion, we have described a mild, efficient, and convienent method for the synthesis of new 6-(10H-

Scheme 1. Synthetic route of compounds **4a–p**, R = H, OCH_3, Cl, OH, R1 = C_6H_5, Z = O, S. Reaction reagents and conditions (i) 40% methanolic KOH, reflux 70°C, 2–3 h, 90%. (ii) Urea, phenyl urea, thiourea, and phenyl thiourea, reflux in methanolic KOH 70°C, 3–4 h, 67%.



phenothiazine 2-yl)-pyrimidin-2(1H)-one/thione derivatives from corresponding chalcones. All compounds of the series showed moderate to good biological activity. Hence, it is concluded that there is ample scope for further developing this field.

EXPERIMENTAL

General procedures. All chemicals were purchased from Aldrich and Merck chemicals, Mumbai (India) and were used without further purification. Melting points were determined in open capillaries using a Toshniwal melting point apparatus and are uncorrected. Formation of compound was routinely checked by TLC using Silica G, and the spots were exposed to iodine vapor for visualization. The IR spectra in KBr were recorded on a Perkin-Elmer FTIR spectrometer (ν_{max} in cm^{-1}); ^1H NMR and ^{13}C NMR spectra were obtained in DMSO-d_6 on a Brucker 300 MHz instrument using TMS as internal standard (chemical shifts in δ, ppm), mass spectra on LCQ Adavantage Therma Finiger spectrometer. Elemental analysis was performed on Carlo Erba 1108 analyzer.

General Procedure for synthesis of compounds 3a–d. To a solution of 2-acetyl phenothiazine **1** (0.01mol) in absolute methanol (50 mL), benzaldehyde **2a** (0.01 mol) in 40% methanolic KOH (10 mL) was added and refluxed for 2–3 h at 70°C. The reaction mixture was then cooled to room temperature and poured on to crushed ice containing few drops of conc. HCl. The solid, thus, obtained was filtered and recrystallized from methanol to give **3a**.

Similarly, chalcones **3b–d** were synthesized by condensing 2-acetyl phenothiazine with various aldehydes **2b–d**.

(E)-1(10H-Phenothiazin-8-yl)-3-phenyl-2-en-1-one (3a). Yield 90%, m.p.201–203°C, IR (KBr) cm^{-1}:3352 (NH), 3056 (Ar-H), 1653 (C=O), 1606 (C=C); ^1H NMR (DMSO-d_6): δ 8.11 (s, 1H, NH), 7.88 (d, J = 3.8 Hz, 1H, =CH-Ar), 7.56 (d, J = 3.6 Hz, 1H, =COCH=), 7.38–6.69 (m, 12H, Ar-H); ^{13}C NMR (DMSO-d_6): δ 118.5, 119.8, 120.8, 127.1, 127.9, 129.5, 131.9, 132.8, 133.9, 135.2, 136.8, 140.3, 141.6, 143.9, 144.9, 146.1, 147.6 (Ar-*C*, =CH=*C*H=C=O), 151.3 (=*C*H=CH=C; =O), 187.2 (*C*=O); Ms: *m*/*z* (%): 329 (85), 226 (76), 198 (40), 103 (55). Anal. Calcd for $C_{21}H_{15}NOS$: C, 76.57; H, 4.59; N, 4.25. Found: C, 76.42; H, 4.48; N, 4.33%.

(E)-3-(4-Methoxyphenyl)-1-(10H-phenothiazin-8-yl)prop-2-en-1-one (3b). Yield 93%, m.p. 208–210°C, IR (KBr) cm^{-1}:3349 (NH), 3051 (Ar-H), 2963 (C=H), 1658 (C=O), 1609 (C=C); ^1H NMR (DMSO-d_6): δ 8.23 (s, 1H, NH), 7.95 (d, J = 3.8 Hz, 1H, =CH-Ar), 7.55 (d, J = 3.6 Hz, 1H, =COCH=), 7.30–6.66 (m, 11H, Ar-H); ^{13}C NMR (DMSO-d_6): δ 55.1 (O*C*H_3); 117.8, 120.9, 121.3, 122.5, 125.3, 126.2, 129.8, 130.1, 133.6, 139.3, 140.8, 141.2, 141.8, 143.8, 144.1, 145.3 (Ar-*C*, =CH=*C*H=C=O), 149.2 (=*C*H=CH=C=O), 162.3 (Ar-*C*=OCH_3), 188.4 (*C*=O), Ms: *m*/*z* (%): 359 (88), 226 (72), 198 (45), 133 (50). Anal. Calcd for $C_{22}H_{17}NO_2S$: C, 73.51; H, 4.77; N, 3.90. Found: C, 73.39; H, 4.58; N, 3.73%.

(E)-3-(4-Chlorophenyl)-1-(10H-phenothiazin-8-yl)prop-2-en-1-one (3c). Yield 96%, m.p.175–178°C, IR (KBr) cm^{-1}:3346 (NH), 3048 (Ar-H), 1660 (C=O), 1610 (C=C), 740 (C=Cl); ^1H NMR (DMSO-d_6): δ 8.17 (s, 1H, NH), 7.93 (d, J = 3.8 Hz, 1H, =CH-Ar), 7.55 (d, J = 3.6 Hz,1H, =COCH=), 7.26–6.66 (m, 12H, Ar-H); ^{13}C NMR (DMSO-d_6): δ 117.3, 120.1, 120.5, 121.1, 121.9, 124.6, 125.7, 127.9, 128.7, 129.8, 132.9, 138.5, 140.2, 141.3, 143.5, 144.0, 144.8 (Ar-C, =CH=*C*H=C=O), 147.9 (=*C*H=CH=C=O), 189.1 (*C*=O); Ms: *m*/*z* (%): 363 (85), 226 (70), 198 (48), 137 (52).

Table 1

Physical data of compounds **4a–p**.

Compound	R	R_1	Z	m.p. (°C)	Yield (%)
4a	H	H	O	260–262	63
4b	OCH_3	H	O	266–268	68
4c	Cl	H	O	268–270	64
4d	OH	H	O	264–266	71
4e	H	Ph	O	180–182	67
4f	OCH_3	Ph	O	187–189	65
4g	Cl	Ph	O	192–194	64
4h	OH	Ph	O	189–192	72
4i	H	H	S	112–114	67
4j	OCH_3	H	S	123–125	69
4k	Cl	H	S	165–167	68
4l	OH	H	S	178–181	76
4m	H	Ph	S	142–146	68
4n	OCH_3	Ph	S	118–121	66
4o	Cl	Ph	S	128–130	71
4p	OH	Ph	S	136–138	60

Anal. Calcd for $C_{21}H_{14}ClNOS$: C, 69.32; H, 3.88; N, 3.85. Found: C, 69.19; H, 3.64; N, 3.73%.

(E)-3-(4-Hydroxyphenyl)-1-(10H-phenothiazin-8-yl)prop-2-en-1-one (3d). Yield 92%, m.p. 175–178°C, IR (KBr) cm^{-1}:3353 (NH), 3054 (Ar-H), 1660 (C=O), 1611 (C=C); ^1H NMR (DMSO-d_6): δ 8.11 (s, 1H, NH), 7.91 (d, *J* = 3.8 Hz, 1H, =CH-Ar), 7.55 (d, *J* = 3.6 Hz, 1H, =COCH=), 7.18–6.69 (m, 11H, Ar-H), 5.23 (s,1H); ^{13}C NMR (DMSO-d_6): δ 114.3, 116.9, 119.3, 120.4, 120.9, 121.8, 124.9, 125.4, 128.6, 129.7, 132.9, 138.4, 141.2, 142.5, 143.6, 144.1 (Ar-*C*, =CH=*C*H=C=O), 147.3 (=*C*H=CH=C=O), 160.3 (Ar-*C*=OH), 191.1 (*C*=O); Ms: *m/z* (%): 345 (80), 226 (68),198 (50), 119 (48). Anal. Calcd for $C_{21}H_{15}NO_2S$: C, 73.02; H, 4.38; N, 4.06. Found: C, 72.86; H, 4.08; N, 3.93%.

General procedure for synthesis of compounds 4a–p. A mixture of chalcone **3a** (0.01 mol) and urea/phenyl urea/ thiourea/phenyl thiourea (0.03 mol) in methanolic KOH (10 mL) was refluxed for 4 h at 70°C. The solid, thus, obtained was washed with water and recrystallized from methanol to give **4a–d**.

Similarly, **4e–p** were synthesized by using chalcones **3b–d**.

4-(10H-Phenothiazin-2-yl)-6-phenylpyrimidin-2(1H)-one (4a). IR (KBr) cm^{-1}: 3331 (NH), 3056 (Ar-H), 1593 (C=N), 1466 (C=C pyrimidine); ^1H NMR (DMSO-d_6): δ 8.75 (s, 1H, NH, phenothiazine), 8.28 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.06 (s, 1H, NH, pyrimidine), 7.69–6.66 (m, 12H, Ar-H), 5.50 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 118.1, 119.8, 120.6, 120.9, 121.8, 127.1, 128.2, 128.9, 130.6, 134.6, 134.9, 135.3, 136.4, 137.1, 144.9, 145.1 (Ar-*C*), 109.2, 154.3, 166.4, 166.9 (pyrimidine-*C*); MS: *m/z* (%): 368 [M^+-1] (98), 340 (74), 312 (46), and 238 (32). Anal. Calcd for $C_{22}H_{15}N_3OS$: C, 71.52; H, 4.09; N, 11.37. Found: C, 71.37; H, 4.01; N, 11.29%.

6-(4-Methoxyphenyl)-4-(10H-phenothiazin-2-yl)pyrimidin-2 (1H)-one (4b). IR (KBr) cm^{-1}: 3341 (NH), 3056 (Ar-H), 1577 (C=N), 1468 (C=C pyrimidine); ^1H NMR (DMSO-d_6): δ 8.79 (s, 1H, NH, phenothiazine), 8.28 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.02 (s, 1H, NH, pyrimidine), 7.71 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.63–6.67 (m, 7H, Ar-H), 5.61 (s,1H), 3.68 (s,3H); ^{13}C NMR (DMSO-d_6): δ 55.8 (O*C*H$_3$), 115.4, 118.1, 119.3, 120.6, 121.2, 122.6, 127.1, 127.8, 128.5, 129.6, 130.1, 130.3, 139.4, 140.1, 142.7 (Ar-*C*), 105.4, 162.3, 163.6, 165.4, 166.2 (pyrimidine-*C*, Ar-*C*=OCH$_3$), MS: *m/z* (%): 398 [M^+-1] (99), 370 (78), 328 (15),300 (50), and 240 (48); Anal. Calcd for $C_{23}H_{17}N_3O_2S$: C, 69.15; H, 4.29; N, 10.52. Found: C, 69.01; H, 4.11; N, 10.40%.

6-(4-Chlorophenyl)-4-(10H-phenothiazin-2-yl)pyrimidin-2 (1H)-one (4c). IR (KBr) cm^{-1}: 3339 (NH), 3056 (Ar-H), 1583 (C=N), 1466 (C=C pyrimidine); ^1H NMR (DMSO-d_6): δ 8.77 (s, 1H, NH, phenothiazine), 8.29 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.04 (s, 1H, NH, pyrimidine), 7.74 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.23–6.89 (m, 7H, Ar-H), 5.68 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 118.2, 120.2, 120.8, 121.3, 122.5, 123.1, 128.5, 128.8, 129.6, 133.8, 134.3, 135.3, 135.8, 136.1, 141.6, 141.9 (Ar-C), 107.7, 157.1, 166.8, 167.5 (pyrimidine-*C*); MS: *m/z* (%): 402 [M^+-1] (100), 374 (60), 344 (38), 314 (52) and 238 (28); Anal. Calcd for $C_{22}H_{14}N_3SOCl$: C, 65.45; H, 3.49; N, 10.40. Found: C, 65.59; H, 3.31; N, 10.22%.

6-(4-Hydroxyphenyl)-4-(10H-phenothiazin-2-yl) pyrimidin-2 (1H)-one (4d). IR (KBr) cm^{-1}: 3340 (NH), 3048 (Ar-H), 1575 (C=N), 1466 (C=C pyrimidine); ^1H NMR (DMSO-d_6): δ 8.71 (s, 1H, NH, phenothiazine), 8.26 (d, *J* = 8.3 Hz, 2H, Ar-H), 8.05 (s, 1H, NH, pyrimidine), 7.73 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.33–6.69 (m, 7H, Ar-H), 5.61 (s,1H), 5.56 (s,1H); ^{13}C NMR (DMSO-d_6): δ 116.8, 119.5, 120.3, 121.6, 122.1, 122.8, 123.5, 124.8, 128.3, 128.9, 129.4, 130.8, 131.3, 139.8, 140.4, (Ar-*C*), 108.7, 158.1, 159.7, 167.6, 168.5 (pyrimidine-*C*, Ar-*C*=OH); MS: *m/z* (%): 384 [M^+-1] (98), 356 (66), 330 (40), and 328 (28); Anal. Calcd for $C_{22}H_{15}N_3O_2S$: C, 68.55; H, 3.92; H, 10.90. Found: C, 68.48; H, 3.82; N, 10.99%.

4-(10H-Phenothiazin-2-yl)-1,6-diphenylpyrimidin-2(1H)-one (4e). IR (KBr) cm^{-1}: 3343 (NH), 3050 (Ar-H), 1591 (C=N), 1467 (C=C pyrimidine); ^1H NMR (DMSO-d_6): δ 8.35 (s, 1H, NH, phenothiazine), 7.87–6.69 (m, 17H, Ar-H), 5.39 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 117.8, 118.5, 119.6, 120.4, 120.8, 121.6, 122.1, 125.3, 127.4, 128.1, 129.3, 129.8, 130.6, 132.4, 134.1, 134.9, 135.3, 136.2, 142.1, 142.8 (Ar-C), 103.2, 153.1, 156.2, 162.5 (pyrimidine-*C*); MS: *m/z* (%): 444 [M^+-1] (88), 416 (60), 326 (48), 312 (20), and 238 (38); Anal. Calcd for $C_{28}H_{19}N_3OS$: C, 75.48; H, 4.30; N, 9.43. Found: C, 75.57; H, 4.51; N, 9.32%.

6-(4-Methoxyphenyl)-4-(10H-phenothiazin-2-yl)-1-phenylpyrimidin-2(1H)-one (4f). IR (KBr) cm^{-1}: 3336 (NH), 3048 (Ar-H), 1593 (C=N), 1469 (C=C pyrimidine); ^1H NMR (DMSO-d_6): δ 8.11 (s, 1H, NH, phenothiazine), 7.78 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.46 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.35–6.69 (m, 12H, Ar-H), 5.37 (s, 1H), 3.73 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 56.7 (O*C*H$_3$), 116.3, 118.6, 119.6, 120.8, 121.5, 122.3, 123.1, 124.3, 126.1, 128.3, 129.7, 130.3, 131.8, 134.4, 134.9, 135.5, 136.3, 143.8, 144.2 (Ar-*C*), 104.7, 158.1, 161.6, 168.3 (pyrimidine-*C*, Ar-*C*=OCH$_3$); MS: *m/z* (%): 474 [M^+-1] (96), 446 (70), 356 (54), 342(30), and 238 (42); Anal. Calcd for $C_{29}H2_1N_3OS$: C, 73.14; H, 4.55; N, 8.84. Found: C, 73.27; H, 4.41; N, 8.89%.

6-(4-Methoxyphenyl)-4-(10H-phenothiazin-2-yl)pyrimidine-2(1H)-thione (4j). IR (KBr) cm^{-1}: 3349 (NH), 3056 (Ar-H), 1577 (C=N), 1468 (C=C pyrimidine), 1270 (C=S); ^1H NMR (DMSO-d_6): δ 8.59 (s, 1H, NH, phenothiazine), 8.08 (d, *J* = 8.1 Hz, 2H, Ar-H), 8.02 (s, 1H, NH, pyrimidine), 7.86 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.47–6.60 (m, 7H, Ar-H), 5.38 (s, 1H), 3.65 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 56.2 (O*C*H$_3$), 115.3, 118.2, 119.4, 120.7, 121.4, 122.8, 123.6, 127.4, 128.6, 129.5, 134.5, 135.6, 136.4, 144.4, 144.7 (Ar-*C*), 104.9, 160.3, 165.8, 178.6, 181.2 (pyrimidine-*C*, Ar-*C*=OCH$_3$), MS: *m/z* (%): 415 [M^+] (100), 371 (70), 342 (40) and 238 (22); Anal. Calcd for $C_{23}H_{17}N_3OS_2$: C, 66.48; H, 4.12; N, 10.11. Found: C, 66.59; H, 3.90; N, 10.19%.

6-(4-Chlorophenyl)-4-(10H-phenothiazin-2-yl)pyrimidine-2(1H)-thione (4k). IR (KBr) cm^{-1}: 3347 (NH), 3050 (Ar-H), 1576 (C=N), 1465 (C=C pyrimidine), 1273 (C=S); ^1H NMR (DMSO-d_6): δ 8.52 (s, 1H, NH, phenothiazine), 8.18 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.93 (s, 1H, NH, pyrimidine), 7.86 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.26–6.63 (m, 7H, Ar-H), 5.36 (s,1H); ^{13}C NMR (DMSO-d_6): δ 118.3, 120.4, 121.3, 121.9, 122.6, 123.3, 128.3, 128.8, 129.7, 133.5, 134., 135.6, 135.5, 136.2, 143.6, 143.8 (Ar-*C*), 105.7, 166.3, 178.5, 181.4 (pyrimidine-*C*); MS: *m/z* (%): 419 [M^+] (96), 375 (78), 346 (24), and 238 (28); Anal. Calcd for $C_{23}H_{14}N_3S_2Cl$: C, 62.92; H, 3.36; N, 10.01. Found: C, 63.04; H, 3.49; N, 9.89%.

6-(4-Chlorophenyl)-4-(10H-phenothiazin-2-yl)-1-phenylpyrimidine-2(1H)-thione (4o). IR (KBr) cm^{-1}: 3366 (NH), 3048 (Ar-H), 1591 (C=N), 1463 (C=C pyrimidine), 1272(C=S); ^1H NMR (DMSO-d_6): δ 8.19 (s, 1H, NH, phenothiazine), 8.08 (d,

Table 2

Antibacterial activity of the compounds **4a**–**p**.

	Antibacterial activity			
Compound	*Bacillus subtilis*	*Escherichia coli*	*Staphylococcus aureus*	*Pseudomonas aeruginosa*
4a	10(25)	18(10)	12(5)	12(25)
4b	14(5)	16(5)	12(25)	12(25)
4c	12(25)	18(5)	12(5)	22(5)
4d	18(25)	19(10)	17(15)	20(25)
4e	16(20)	20(15)	18(10)	21(20)
4f	17(15)	22(15)	16(20)	15(20)
4g	15(20)	21(10)	20(20)	17(25)
4h	20(15)	20(15)	21(15)	19(25)
4i	13(5)	19(5)	15(5)	10(10)
4j	16(25)	20(5)	15(5)	8(10)
4k	17(25)	24(5)	12(25)	10(25)
4l	18(15)	24(10)	14(20)	11(15)
4m	17(15)	26(15)	19(20)	14(10)
4n	14(20)	25(20)	20(15)	17(15)
4o	11(20)	24(20)	21(10)	14(15)
4p	12(15)	21(20)	22(20)	10(20)
Ampicillin	24(5)	26(5)	24(5)	23(5)

MIC values are given in brackets; MIC (μg/mL) = minimum inhibitory concentration, that is, lowest concentration to completely inhibit bacterial growth; zone of inhibition is expressed in mm.

J = 8.2 Hz, 2H, Ar-H), 7.66 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.25–6.66 (m, 12H, Ar-H), 5.37 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 117.9, 119.6, 120.5, 120.9, 121.7, 122.3, 125.6, 127.6, 128.3, 129.2, 130.2, 130.7, 133.5, 134.2, 134.4, 135.3, 136.2, 137.4, 142.1, 142.8 (Ar-*C*), 104.6, 157.3, 168.5, 181.2 (pyrimidine-*C*); MS: *m/z* (%): 495 [M^+] (99), 451 (66), 360 (36), 347 (52), and 238 (22); Anal. Calcd for $C_{28}H_{18}N_3S_2Cl$: C, 67.80; H, 3.66; N, 8.47. Found: C, 67.97; H, 3.51; N, 8.29%.

6-(4-Hydroxyphenyl)-4-(10H-phenothiazin-2-yl)-1-phenylpyrimidine-2(1H)-thione (4p). IR (KBr) cm^{-1}: 3360 (NH), 3052 (Ar-H), 1578 (C═N), 1465 (C═C pyrimidine); 1272 (C═S); ^{1}H NMR (DMSO-d_6): δ 8.13 (s, 1H, NH, phenothiazine), 8.04 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.69 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.28–6.67 (m, 12H, Ar-H), 5.57 (s, 1H), 5.37 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 116.6, 118.6, 120.8, 121.5, 122.3, 123.1, 124.4, 127.9, 128.8, 129.7, 131.3, 132.2, 133.7, 134.5, 135.8, 136.3,

Table 3

Antifungal activity of the compounds **4a**–**p**.

	Antifungal activity			
Compound	*Aspergillus niger*	*Aspergillus fumigatus*	*Aspergillus flavus*.	*Candida albicans*
4a	17(5)	18(5)	14(15)	10(15)
4b	18(5)	18(5)	16(15)	13(15)
4c	12(5)	18(5)	20(15)	10(15)
4d	17(10)	22(10)	13(10)	13(15)
4e	16(15)	22(10)	17(15)	12(10)
4f	15(10)	19(10)	13(15)	20(20)
4g	18(20)	16(10)	19(10)	21(20)
4h	17(20)	20(25)	17(15)	20(25)
4i	14(15)	18(5)	21(5)	12(20)
4j	12(15)	18(5)	18(5)	12(20)
4k	12(15)	10(5)	10(5)	12(20)
4l	23(10)	18(10)	20(10)	14(15)
4m	25(20)	19(15)	25(15)	12(15)
4n	24(20)	21(20)	26(15)	14(20)
4o	25(20)	20(20)	22(15)	13(20)
4p	22(20)	19(15)	24(20)	14(20)
Fluconazole	24(5)	22(5)	16(5)	19(5)

MIC values are given in brackets, MIC (μg/mL) = minimum inhibitory concentration, that is, lowest concentration to completely inhibit fungal growth; zone of inhibition is expressed in mm.

137.6, 143.8, 144.2 (Ar-*C*), 104.1, 158.2, 165.6, 181.3 (pyrimidine-*C*, Ar-*C*═OH); MS: *m/z* (%): 477 [M^+] (96), 433 (74), 342 (28), 329 (40), and 238 (28); Anal. Calcd for $C_{28}H_{19}N_3S_2O$: C, 70.41; H, 4.01; N, 8.80. Found: C, 70.59; H, 4.06; N, 8.90%.

BIOLOGICAL ACTIVITY

Antibacterial activity. The newly synthesized compounds were screened for their antibacterial activity against *Bacillus subtillis* (ATCC-11774), *Escherichia coli* (ATCC-25922), *Staphylococcus aureus* (ATCC-25923), and *Pseudomonas aeruginosa* (ATCC-27853) bacterial strains by disc diffusion method [27, 28]. The test compounds were prepared with different concentrations using dimethylsuphoxide. The discs of each concentration were placed in triplicate in nutrient agar medium seeded with fresh bacteria separately. The incubation was carried out at 37°C for 24 h. Ampicillin was used as a standard drug. Solvent and growth controls were prepared and kept. Zones of inhibition and minimum inhibitory concentrations (MICs) were noted. The results of antibacterial studies are given in Table 2.

Antifungal activity. Newly prepared compounds were screened for their antifungal activity against *Aspergillus niger* (NCIM no. 617), *Aspergillus flavus* (NCIM no. 524), *Aspergillus fumigatus* (NCIM no. 902), and *Candida albicans* (NCIM no. 300) in DMSO by serial plate dilution method [29, 30]. Sabouraud agar media were prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 mL) and adjusting pH to 5.7. A particular fungal strain was transferred to 3-mL saline to get a suspension of corresponding species. Agar media (20 mL) were poured into each Petri dish. The plates were dried by placing in an incubator at 37°C for 1 h. Using an agar punch, wells were made and each well was labeled. A control was also prepared in triplicate and maintained at 37°C for 2 to 3 days. Zone of inhibition and MIC were noted. The activity of each compound was compared with fluconazole as the standard drug. The results of antifungal studies are given in Table 3.

REFERENCES AND NOTES

[1] Virtonean, A. I.; Hietala, P. K. Acta Chem Scand 1960, 14, 499.

[2] Foroughifar, N.; Mobini, A.; Khaledi, A.; Shariatzadesh, S. M.; Masoudnia, M. Asian J Chem 2002, 14, 782.

[3] Baddiley, J.; Lythgoe, B.; Todd, A. R. J Chem Soc 1944, 318.

[4] Garg, G. H.; Prakash, C. J Med Chem 1971, 14, 175.

[5] (a)Xie, W.; Jin, Y.; Wang, P. G. Chemtech 1999, 2, 23; (b) Kappe, C. O.; Falsone, F. S. Synlett 1998, 718. (c) Grover, G. J.; Dzwonczyk, S.; Normadinam, C. S.; Sleph, P. G.; Moreland, S. J. Cardiovasc Pharmacol 1995, 26, 289.

[6] Safonova, T. V.; Keremov, A. F.; Ershova, A. Khim Farm Zn 1998, 12, 32 (Eng); Chem Abstr 1999, 131, 18975e.

[7] Jani, M. K.; Shah, B. R.; Undavia, N. K.; Trivedi, P. B. Chem Abstr 1994, 121, 35513p.

[8] (a) Fathalla, O. A.; Awad, S. M.; Mohamed, M. S. Arch Pharm Res 2005, 28, 1205; (b) Lalezari, I.; Shafiee, A.; Yasdany, S. J Pharm Sci 1974, 63, 628.

[9] (a) Tokutake, N. Brit. Pat. 146836B, 1977; (b) Tokutake, N. Chem Abstr 1977, 87, 102370.

[10] (a) Gauthier, B. Ann Pharm Fr 1963, 21, 655; (b) Takeda, U.S. Pat. 3,016,380, 1962.

[11] (a) Koshy, M. M.; Mickey, D. Circulation 1977, 55, 533; (b) Hara, H.; Ichikawa, M.; Oku, H.; Shimazawa, M.; Araie, M. Cardiovasc Drug Rev 2005, 23, 43; (c) Meredith, P. A.; Scott, P. J.; Kelman, A. W.; Hughes, D. M.; Reid, J. L. Am J Ther 1995, 2, 541; (d) Ganzevoort, W.; Rep, A.; Bonsel, G. J.; de Vries, J. I.; Wolf, H. Hypertension 2004, 22, 1235; (e) Wong, W. M. Ann Pharmacother 1994, 28, 290; (f) Jargon, A. Lancet 1991, 337, 1457.

[12] Machon, Z.; Krystyna, U. Acta Pol Chem B 1985, 42, 516.

[13] Shishoo, J. C.; Pathak, S. U.; Rathod, S. I.; Jain, S. K. Indian J Chem B 1999, 38, 684.

[14] El-Said, M. K. Pharmazie 1981, 36, 678.

[15] Tilak, R.; Tyagi, R.; Goel, B.; Saxena, K. K.; Srivastava, V. K.; Kumar, A. Indian Drugs 1998, 35, 216.

[16] Dominguez, J. N.; Lopez, S.; Charris, J.; Iarruso, L.; Lobo, G.; Semenow, A.; Olson, J. E.; Rosenthal, P. J. J Med Chem 1997, 40, 2726.

[17] Lin, G.; Midha, K. K.; Hawes, E. M. J Heterocycl Chem 1991, 28, 215.

[18] (a) Bansode, T. N.; Shelke, J. V.; Dongre, V. G. Eur J Med Chem 2009, 44, 5094; (b) Bansode, T. N.; Dongre, P. M.; Dongre, V. G. Pharm Chem J 2009, 43, 311.

[19] Viveros, M.; Amaral, L. Int J Antimicrob Agents 2001, 17, 225.

[20] Amaral, L.; Kristiansen, J. E. Int J Antimicrob Agents 2000, 14, 173.

[21] Trivedi, A.; Siddiqui, A.; Shah, V. ARKIVOC 2008, ii, 210.

[22] Motohashi, N.; Kawase, M.; Saito, S.; Sakagami, H. Curr Drug Targets 2000, 1, 237.

[23] Motohashi, N.; Kurihara, T.; Satoh, K.; Sakagami, H.; Mucsi, I.; Pusztai, R.; Molnar, J. Anticancer Res 1999, 19, 1837.

[24] Kurihara, T.; Motohashi, N.; Pang, G. L.; Higno, M.; Kiguchi, K.; Molnar, J. Anticancer Res 1996, 16, 2757.

[25] Ledincer, D.; Mitscher, L. A. Org Chem Drug Syn 1976, 1, 372.

[26] Borbely, A. A.; Loepfe-Hinkkanen, M. Mod Phamacol-Toxicol 1979, 16, 403.

[27] Cruickshank, R.; Duguid, J. P.; Marion, B.P.; Swain, R. H. A. Medicinal Microbiology, 12 ed.; Churchil Livingstone: London, 1975; Vol. II, p 196.

[28] Collins A. H., Ed. Microbiological Methods, 2nd ed., Butterworth: London, 1976.

[29] Khan, Z. K. In vitro and vivo screening techniques for bioactivity screening and evaluation, In: ProceedingS of the International Workshop on UNIDO-CDRI, 1997; p 210.

[30] Varma, R. S., Eds., Antifungal Agents: Past, Present and Future Prospects. National Academy of Chemistry & Biology: India, Lucknow, 1998.