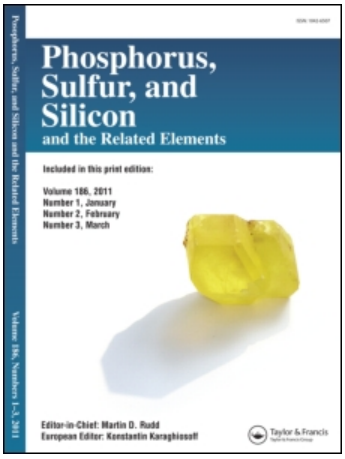

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Convenient Synthesis of Some 4'-Methtylthio-Containing Aryl and Arylfuryl Pyrazolines and Their Antimicrobial Activity Studies

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*The condensation of 4-acetylthioanisole with different aryl and aryfuryl aldehydes under aldol conditions affords α, β-unsaturated ketones (propenones), which undergo a facile and clean cyclization with hydrazines to give pyrazolines (**4–6**) in quantitative yields. The structures of newly synthesized compounds have been confirmed on the basis of spectral studies. All newly synthesized compounds were tested for their antibacterial and antifungal activity.*

Keywords 4-Acetylthioanisole; aryfuryl aldehydes; antimcrobial; propenones; pyrazolines

INTRODUCTION

Pyrazolines have been reported to show a broad spectrum of biological activities, including antibacterial,[1] antifungal,[2] anti-inflammatory,[3] antidepressant,[4] and antiviral[5] agents. Some these compounds have also shown antidiabetic,[6] anaesthetic,[7] and analgesic properties.[8] The pyrazoline function is quite stable and has inspired chemists to utilize this stable fragment in bioactive moieties to synthesize new compounds

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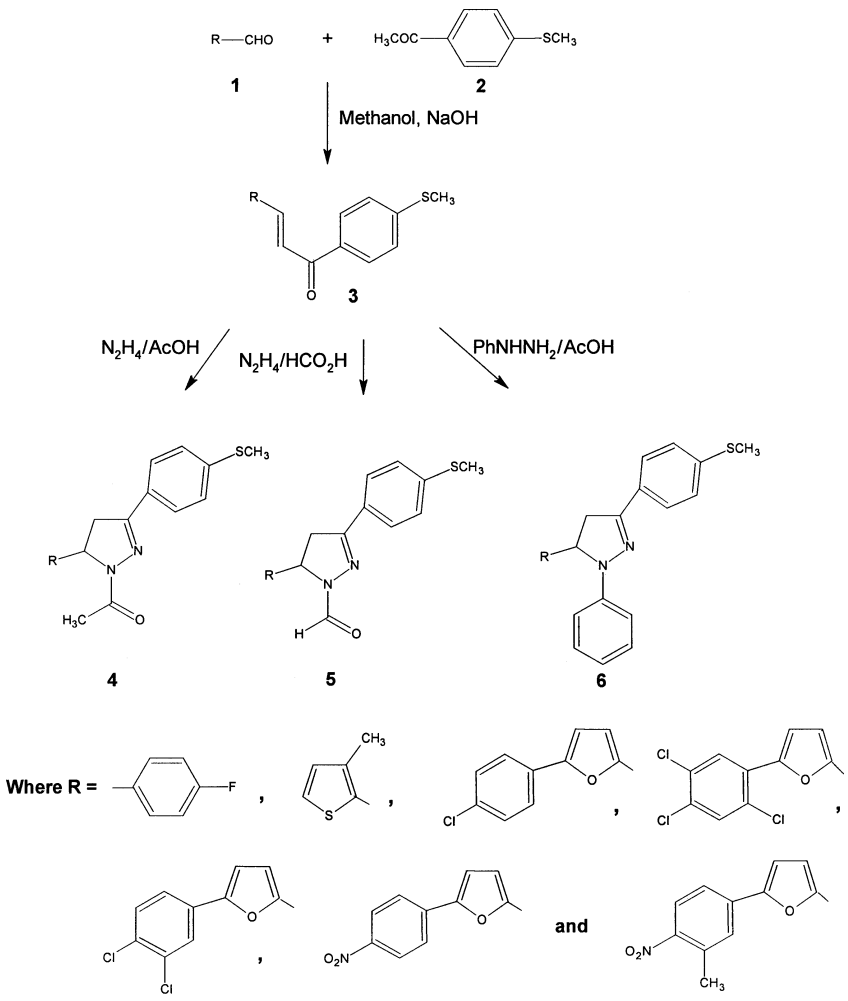
possessing biological activities, and the presence of $-SCH_3$ group in molecules at strategic positions alters the activity. This prompted us to synthesize various substituted pyrazoline derivatives. A classical synthesis of these compounds involves the base-catalyzed aldol condensation reaction of aromatic ketones and aldehydes to give α, β-unsaturated ketones (propenones), which undergo a subsequent cyclization reaction with hydrazines affording pyrazolines. In this method, hydrazones are formed as intermediates, which can be subsequently cyclized to 2-pyrazolines in the presence of suitable cyclizing reagents.

RESULTS AND DISCUSSION

The newly prepared propenones were confirmed on the basis of IR, proton NMR, and mass spectral data. They show a characteristic IR absorption peak at $\nu = 1700–1660\ cm^{-1}$, indicating the presence of a conjugated carbonyl group. As their NMR spectra suggests, the $-CH=CH-$ are considerably shifted down field to the extent that they appear in the aromatic region δ 6.5–8.5. As a result, these protons can hardly be distinguished from those of the aromatic rings. In the 400 MHz ^1H NMR spectrum of compounds **4–6**, the pyrazolines, the CH_2 protons of the pyrazoline ring **6a**, resonated as a pair of doublet of doublets in the region δ 3.03–3.11 (J = 7.2 Hz, 7.5 Hz) and δ 3.75–3.85 (J = 12.2 Hz, 12.2 Hz), respectively, due to geminal and vicinal coupling. The CH proton appeared as a doublet of doublets at δ 5.21–5.28 (J = 7.1 Hz, 7.1 Hz) due to vicinal coupling with the two magnetically nonequivalent protons of the methylene group at position 4 of the pyrazoline ring. The reaction probably involved the intermediate formation of hydrazones and subsequent addition of NH on the carbon-carbon double bond of the propenone moiety.

As a result of our studies related to the development of the heterocyclic compounds, we report a synthesis of some new heterocyclic compounds, which are found to be biologically active towards test organisms. We report in this article some aldol condensation reactions between *p*-acetylthioanisole (**2**) with different aryl and arylfuryl aldehydes (**1**) in the presence of sodium hydroxide/methanol to give intermediate chalcones (**3**), which undergo a rapid cyclization with hydrazines. The starting material 4-acetylthioanisole was prepared by Methods A and B, and all arylfurfuraldehydes were synthesized through a Meerwin reaction.[9]

3a: IR (KBr, cm^{-1}): 3030, 2914.2 (Ar-H), 1649 (C=O), 1127 (C–F). ^1H-NMR (DMSO-d_6) δ: 2.50 (s, 3H, SCH_3), 6.99–6.96 (d, 2H, J = 8.84 Hz, 4-methylthiolphenyl), 7.11–7.06 (d, 2H, J = 8.6 Hz, 4-methylthiophenyl),



SCHEME 1 Synthesis of substituted pyrazolines (4), (5), and (6).

7.44–7.40 and 7.77–7.73 (2d, 2H, J = 16 Hz, —CH=CH—), 7.61–7.60 (t, 2H, J = 5.4Hz, 4-fluorophenyl), 8.04–8.01 (d, 2H, J = 8.8 Hz, 4-fluorophenyl). MS: (M^+, %); (272, 100), 225(35), 178(90), 152(20), 102(20), 69(38), 55(25). **3c**: IR (KBr, cm^{-1}): 3029, 2915 (Ar-H), 1665 (C=O), 820 (C—Cl), 1025 (C—F). ^{1}H-NMR (DMSO-d_6): 2.55 (s, 3H, SCH_3), 6.77–6.76 (d, 1H, J = 3.5 Hz, furanyl), 6.81–6.79 (d, 1H, J = 3.5 Hz, furanyl), 7.33–7.31 (d, 2H, J = 8.4 Hz, 4-methylthiophenyl), 7.42–7.39 (2H, J = 8.5 Hz, 4-methylthiophenyl), 7.63–7.46 (2d, 2H, J = 15.3 Hz, CH=CH), 7.71–7.69 (d, 2H, J = 8.5 Hz, *p*-chlorophenyl),

8.00–7.98 (d, 2H, J = 8.3 Hz, 4-chlorophenyl). MS: (M^+, %); (354, 100), 307 (22), 243 (20), 215 (20), 151 (30), 139 (50), 111 (12), 79(20), 57(10). **3d**: IR (KBr, cm^{-1}): 3032, 2930 (Ar-H), 1680 (C═O), 815, 820, 822 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 2.55 (s, 3H, SCH_3), 6.84–6.62 (d, 1H, J = 3.6 Hz, furanyl), 7.27–7.26 (d, 2H, J = 3.6 Hz, furanyl), 7.27 (s, 1H, 2,4,5-trichlorophenyl), 7.34–7.32 (d, 2H, J = 8.4Hz, 4-methylthiophenyl), 7.63–7.48 (2d, 2H, J = 15.3 Hz, CH═CH), 8.00–7.93 (d, 2H, J = 8.5 Hz, 4-methylthiophenyl), 8.03 (s, 1H, 2,4,5-trichlorophenyl).

4a: IR (KBr, cm^{-1}): 3036, 2928 (Ar-H), 1016 (C—F). ^{1}H-NMR (DMSO-d_6) δ: 2.39 (s, 3H, $COCH_3$), 2.51 (s, 3H, SCH_3), 3.13–3.06 (dd, 1H, J = 4.5Hz, CH2), 3.76–3.66 (dd, 1H, J = 11.7 Hz, CH_2), 5.58–5.52 (dd, 1H , J = 4.6 Hz, CH), 7.65–6.96 (m, 8H, Ar-H). MS: (M^+, %); (328, 65), 286(100), 269(8), 245(10), 225(22), 210(18), 191(10), 165(23), 149(30), 109(35), 77(36), 55(16). **4c**: IR (KBr, cm^{-1}): 3030, 2925 (Ar-H), 816 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ:^{1}H-NMR (DMSO-d_6) δ: 2.35 (s, 3H, $COCH_3$), 2.51 (s, 3H, SCH_3), 3.47–3.35 (dd, 1H, J = 6.4 Hz, CH_2), 3.75–3.67 (dd, 1H, J = 12.1 Hz, CH_2), 5.41-5.34 (dd, 1H, J = 6.9 Hz, CH), 7.67–6.20 (m, 8H, Ar-H). **5a**: IR (KBr, cm^{-1}): 3030, 2925 (Ar-H), 1734 (C═O). ^{1}H-NMR (DMSO-d_6) δ: 2.32 (s, 3H, CH_3), 2.51 (s, 3H, SCH_3), 3.29–3.22 (dd, 1H, J = 4.9 Hz, CH_2), 3.79–3.70 (dd, 1H, J = 11.7 Hz, CH_2), 5.81–5.75 (dd, 1H, J = 4.7 Hz, CH), 6.76–6.74 (d, 1H, J = 5.0 Hz, thiophene ring), 7.08–7.06 (d, 1H, J = 5.0 Hz, thiophene ring), 7.28–7.25 (d, 2H, J = 6.7 Hz, 4-methylthiophenyl), 7.66–7.63 (d, 2H, J = 6.8 Hz, 4-methylthiophenyl), 8.88 (s, 1H, CHO). **6a**: IR (KBr, cm^{-1}): 3035, 2940 (Ar-H), 1026 (C—F).^{1}H-NMR (DMSO-d_6) δ: 2.50 (s, 3H, SCH_3), 3.11–3.03 (dd, 1H, J = 7.2 Hz, CH_2), 3.85–3.75 (dd, 1H, J = 12.2 Hz, CH_2), 5.28–5.21 (dd, 1H, J = 7.1 Hz, CH), 7.64–6.76 (m, 13H, Ar-H). MS: (M^+, %); (362, 20), 149 (10), 122 (10), 109 (20), 91 (100), 77 (65), 58 (45). **6c**: IR (KBr, cm^{-1}): 3030, 2928 (Ar-H), 816 (C—Cl).^{1}H-NMR (DMSO-d_6) δ: 2.51 (s, 3H, SCH_3), 3.45–3.37 (dd, 1H, J = 6.5 Hz, CH_2), 3.78–3.68 (dd, 1H, J = 12.0 Hz, CH_2), 5.41-5.34 (dd, 1H, J = 6.8 Hz, CH), 7.68–6.21 (m, 13H, Ar-H). MS: (M^+, %); (444, 10), 354 (10), 305 (8), 266 (20), 178 (25), 151 (15), 149 (25), 115 (43), 77 (70), 57 (100). **6d**: IR (KBr, cm^{-1}): 3030, 2925 (Ar-H), 816, 820, 822 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 2.53 (s, 3H, SCH_3), 3.43–3.37 (dd, 1H, J = 6.8 Hz, CH_2), 3.79–3.71 (dd, 1H, J = 12.0 Hz, CH_2), 5.43–5.38 (dd, 1H, J = 6.4 Hz, CH), 7.53–6.85 (m, 11H, Ar-H).

BIOLOGICAL ACTIVITY

Antibacterial Studies

The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli* (ATTC-25922), *Staphylococcus*

TABLE I Antibacterial Activity of Compounds 4–6

	Antibacterial activity (Zone of Inhibition in mm)			
Compound no.	*E. coli*	*S. aureus*	*P. aeruginosa*	*K. pneumoniae*
4a	14	9	19	13
4b	10	15	12	16
4c	19	18	19	19
4d	22	26	22	23
4e	20	18	23	20
4f	20	19	17	22
4g	18	19	17	14
5a	12	8	11	15
5b	17	12	19	14
5c	18	19	12	11
5d	20	22	12	19
5e	12	13	12	11
5f	14	12	14	8
6a	17	12	21	9
6b	13	16	18	11
6c	19	20	21	15
6d	22	17	19	18
6e	22	18	25	26
6f	24	18	15	19
6g	22	23	22	26
Ampicillin	20	23	24	24

aureus (ATTC-25923), *Psuedomonus aeruginosa* (ATTC-27853), and *Klebsiella pneumoniae* (recultured) bacterial stains by the disc diffusion method.[10,11] The discs measuring 6.25 mm in diameter were punched from Whatman no. 1 filter paper. Batches of 100 discs were dispensed to each screw-capped bottle and sterilized by dry heat at 140°C for 1 h. Test compounds were prepared with different concentrations using dimethylformamide. Exactly 1 mL containing 100 times the amount of chemical in each disc was added to each bottle, which contains 100 discs. The discs of each concentration were placed in triplicate in a nutrient agar medium separately seeded with fresh bacteria. The incubation was carried out at 37°C for 24 h. Ampicillin was used as a standard drug. Solvent and growth controls were kept, and zones of inhibition were noted. The results of such studies are given in the Table I. Among the tested compounds, **4d**, **6e**, and **6g** emerged as most active against the tested organisms at a 10 μg concentration. It was interesting to note that there was a drastic increase in the bacteriostatic activity in the pyrazolines of arylfuraldehydes compared to the pyrazolines of aryl aldehydes.

Antifungal Studies

Newly prepared compounds were screened for their antifungal activity against *Aspergilus flavus* (NICM No. 524), *Aspergilus fumigatus* (NCIM No. 902), *Candida albicans* (NCIM No.300), and *Penicillium marneffei* (recultured) in DMSO by the serial plate dilution method.[14,15] Sabourands agar media was prepared by dissolving peptone (1 g), D-glucose (4 g), and agar (2 g) in distilled water (100 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of a spore of a fungal strain for inoculating. A loopful of particular fungal strain was transferred to 3 mL of saline to get a suspension of the corresponding species. Then 20 mL of agar media was poured into each petri dish. Excess suspension was decanted, and plates were dried by placement in an incubator at 37°C for 1 h. Using an agar punch, wells were made into each and were well labeled. A control was also prepared in triplicate and maintained at 37°C for 3–4 days. Antifungal activity was determined by measuring the diameter of the inhibition zone (Table II). The activity of each compound was compared with Flucanazole as the standard. Results of the antifungal activity study reveals that the compound **4d** was

TABLE II Antifungal Activity of Compounds 4–6

	Antifungal activity (Zone of Inhibition in mm)			
Compound no.	*A. flavus*	*A. fumigatus*	*C. albicans*	*P. marneffei*
4a	20	18	22	17
4b	18	22	12	21
4c	12	23	17	21
4d	22	18	23	18
4e	23	26	22	16
4f	20	21	17	18
4g	22	15	16	21
5a	16	13	13	17
5b	23	20	18	16
5c	12	16	19	12
5d	18	22	13	18
5e	14	18	19	22
5f	22	19	12	18
6a	13	17	13	18
6b	9	12	18	12
6c	17	17	15	9
6d	22	20	19	12
6e	18	12	18	13
6f	18	18	20	15
6g	20	20	13	20
Flucanazole	21	18	21	22

active against *Aspergilus flavus* and *Candida albicans*. Compound **4e** was active against *Aspergilus flavus, Aspergilus fumigatus*, and *Candida albicans*. Compound **6d** was active against *Aspergilus flavus* and *Aspergilus fumigatus*.

Conclusions

It appears that antimicrobial activity is enhanced by the presence of a $-SCH_3$ group as a substituent on the benzene ring. Furthermore, it can be concluded that compounds containing Cl and F groups in combination with a $-SCH_3$ group as substituent on benzene rings can act as very effective antimicrobial agents. Antibacterial and antifungal screening results also indicate that pyrazolines of arylfuraldehydes are more active than pyrazolines of aryl aldehydes.

EXPERIMENTAL

Melting points were determined by an open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. PMR spectra were recorded either on a Perkin-Elmer EM-390 (90 MHz) or on a Bruker WH-200 (270 MHz) spectrometer using TMS as an internal standard. Mass spectra were recorded on a Jeol JMS-D 300 spectrometer operating at 70 Ev. The purity of the compounds was checked by TLC on silica gel plates.

4-Acetyl Thioanisole

Method A

To a solution of thioanisole (100 g, 0.80 mol) in anhydrous chlorobenzene (500 mL) anhydrous aluminium chloride (107.5 g, 0.80 mol) was added under a nitrogen atmosphere. After cooling to $-10^{\circ}C$ using an ice-salt mixture, acetic anhydride (82.3 g, 0.80 mol) was added between -10–$5^{\circ}C$. After completion of the addition, the temperature was raised to 20–25°C over a period of 30 min. The mixture was then quenched with 2 L of ice cold water. The lower organic layer was separated and washed with water to neutral. The organic solution was dried (Na_2SO_4). The chlorobenzene was completely removed under reduced pressure. The crude product was recrystallized from n-hexane white to a crystalline solid, yield 78 g, (58.3%), m.p. 81°C (lit. 80–82°C, Beil., 8(3), 296).

TABLE III Characterization Data of Propenones 3a–g

Compound no.	R	Molecular formula	Yield (%)	M.P.(°C)
3a	4-fluorophenyl	$C_{16}H_{13}FOS$	80	112–113
3b	3-methylthienyl	$C_{15}H_{14}OS_2$	82	132–133
3c	4-chlorophenylfuryl	$C_{20}H_{15}ClO_2S$	83	195–197
3d	2,4,5-trichlorophenylfuryl	$C_{20}H_{13}Cl_3O_2S$	81	188–189
3e	3,4-dichlorophenylfuryl	$C_{20}H_{14}Cl_3O_2S$	80	185–186
3f	4-nitrophenylfuryl	$C_{20}H_{15}NO_4S$	85	194–196
3g	3-methyl-4-nitrophenylfuryl	$C_{21}H_{17}NO_4S$	82	165–167

Method B

Phosphoryl chloride (123.4 g, 0.80 mol) was added dropwise to the mixture containing N,N-dimethylacetamide (76.5 g, 0.96 mol) and thioanisole (100 g, 0.80 mol) in dry chlorobenzene (300 mL) at 0–10°C with stirring. The mixture was kept at 80°C for 2 hr, and then it was poured into crushed ice and neutralized with sodium acetate. The organic phase was washed with sodium chloride solution, followed by water. After concentrating under reduced pressure, the residue was extracted in n-hexane to obtain a white crystalline solid, yield 75 g, (56%), m.p. 81°C.

General Procedure for the Preparation of Propenones 3a–g

The method was reported in the literature.[16] Characterization data are given in Table III.

General Procedure for the Preparation of Pyrazolines 4a–g

A mixture of **3** (0.01 mol) and a molar equivalent of hydrazine hydrate (80%) in glacial acetic acid (15 mL) was heated on a water bath at 90–95°C for 5–6 h. The reaction mass then was poured into ice cold water. The solid obtained was filtered, washed with water, dried, and crystallized from ethanol to give **4a–g**. Characterization data are given in Table IV.

General Procedure for the Preparation of Pyrazolines 5a–f

A mixture of **3** (0.01 mol) and a molar equivalent of hydrazine hydrate (80%) in formic acid (15 mL) was heated on a water bath at 100°C for 3–5 h. The reaction mass was then poured into ice cold water and neutralized with diluted sodium bicarbonate solution. The solid obtained was filtered, washed with water, dried, and crystallized from ethanol to give **5a–f**. Characterization data are given in Table IV.

TABLE IV Characterization Data of Compounds 4–6

Compound no.	R	Molecular formula	Yield (%)	M.P. (°C)	% Analysis found (calculated) C	H	N
4a	4-fluorophenyl	$C_{18}H_{17}FN_2OS$	60	140–141	65.80 (65.83)	5.20 (5.21)	8.52 (8.53)
4b	3-methylthienyl	$C_{17}H_{18}N_2OS_2$	65	118–120	61.70 (61.78)	5.48 (5.48)	8.40 (8.47)
4c	4-chlorophenylfuryl	$C_{22}H_{19}ClN_2O_2S$	63	177–179	64.24 (64.30)	4.65 (4.66)	6.77 (6.81)
4d	2,4,5-trichlorophenylfuryl	$C_{22}H_{17}Cl_3N_2O_2S$	65	170–171	55.10 (55.07)	3.51 (3.57)	5.82 (5.83)
4e	3,4-dichlorophenylfuryl	$C_{22}H_{18}Cl_2N_2O_2S$	75	167–169	59.29 (59.33)	4.00 (4.07)	6.29 (6.29)
4f	4-nitrophenylfuryl	$C_{22}H_{19}N_3O_4S$	67	175–177	63.00 (62.69)	4.55 (4.54)	9.99 (9.96)
4g	3-methyl-4-nitrophenylfuryl	$C_{23}H_{21}N_3O_4S$	69	169–171	63.40 (63.43)	4.85 (4.86)	9.62 (9.64)
5a	3-methylthienyl	$C_{16}H_{16}N_2OS_2$	58	153–154	60.71 (60.72)	5.01 (5.09)	8.86 (8.85)
5b	4-chlorophenylfuryl	$C_{21}H_{17}ClN_2O_2S$	66	170–172	63.11 (63.55)	4.26 (4.31)	7.05 (7.05)
5c	2,4,5-trichlorophenylfuryl	$C_{21}H_{15}Cl_3N_2O_2S$	70	182–184	54.13 (54.15)	3.22 (3.24)	6.02 (6.01)
5d	3,4-dichlorophenylfuryl	$C_{21}H_{16}Cl_2N_2O_2S$	77	174–176	58.44 (58.47)	3.73 (3.73)	6.48 (6.49)
5e	4-nitrophenylfuryl	$C_{21}H_{17}N_3O_4S$	78	180–182	61.88 (61.90)	4.12 (4.20)	10.31 (10.31)
5f	3-methyl-4-nitrophenylfuryl	$C_{22}H_{19}N_3O_4S$	65	176–178	62.66 (62.69)	4.55 (4.54)	9.96 (9.96)
6a	4-fluorophenyl	$C_{22}H_{19}FN_2S$	56	140–142	72.88 (72.90)	5.23 (5.28)	7.74 (7.72)
6b	3-methylthienyl	$C_{21}H_{20}N_2S_2$	70	148–150	69.20 (69.19)	5.50 (5.52)	7.67 (7.68)
6c	4-chlorophenylfuryl	$C_{26}H_{21}ClN_2OS$	64	176–177	70.00 (70.17)	4.75 (4.75)	6.26 (6.29)
6d	2,4,5-trichlorophenylfuryl	$C_{26}H_{19}Cl_3N_2OS$	65	182–184	60.77 (60.77)	3.71 (3.72)	5.44 (5.45)
6e	3,4-dichlorophenylfuryl	$C_{26}H_{20}Cl_2N_2OS$	56	170–172	65.13 (65.13)	4.21 (4.20)	5.81 (5.84)
6f	4-nitrophenylfuryl	$C_{26}H_{21}N_3O_3S$	58	190–192	68.55 (68.55)	4.63 (4.64)	5.21 (5.22)
6g	3-methyl-4-nitrophenylfuryl	$C_{27}H_{23}N_3O_3S$	60	188–190	69.00 (69.06)	4.93 (4.93)	8.91 (8.94)

General Procedure for the Preparation of Pyrazolines 6a–g

A mixture of **3** (0.01 mol) and a molar equivalent of phenylhydrazine in glacial acetic acid (15 mL) was heated on a water bath at 90–95°C for 5–6 h. The reaction mass was then poured into ice cold water. The solid

obtained was filtered, washed with water, dried, and crystallized from ethanol to give **5a–g**. Characterization data are given in Table IV.

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