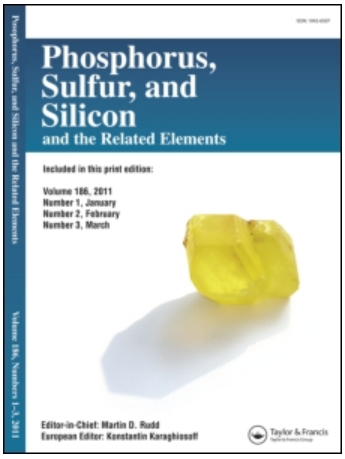

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis and Antimicrobial Activity of Some Thiazolyl-Pyrazoline Derivatives

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*Some 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives (**TP 1–28**) were synthesized by reacting substituted 3-(2-thienyl)-5-aryl-1-thiocarbamoyl-2-pyrazolines (**P 1–7**) with phenacyl bromides in ethanol. Structures of the synthesized compounds were confirmed by elemental analyses and IR, ^{1}H-NMR and MS-FAB$^+$ spectral data. Their antimicrobial activities against* Escherichia coli *(NRRL B-3704),* Staphylococcus aureus *(NRLL B-767),* Salmonella typhimurium *(NRRL B-4420),* Bacillus cereus *(NRRL B-3711),* Listeria monocytogenes *(Ankara University, Faculty of Veterinary, Ankara, Turkey),* Aeromonas hydrophila *(Ankara University, Faculty of Veterinary, Ankara, Turkey),* Candida albicans*, and* Candida glabrata *(isolates obtained from Osmangazi University, Faculty of Medicine, Eskisehir Turkey) were investigated. A significant level of activity was illustrated.*

Keywords 2-Pyrazoline; Antimicrobial activity; thiazole

INTRODUCTION

Antimicrobials are one of our most important weapons in fighting bacterial infections and have greatly benefited the health-related quality of human life since their introduction. However, over the past few decades

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these health benefits have come under threat as many commonly used antibiotics have become less and less effective against certain illnesses, not only because many of them produce toxic reactions but also due to the emergence of drug-resistant bacteria. It is essential to investigate newer drugs with lesser resistance.[1–4]

At the same time, there has been significant increase in the frequency of systematic fungal infection in humans. Patients undergoing organ transplants, anticancer chemotherapy, or long treatment with antimicrobial agents, and patients with AIDS, are immunosuppressed and very susceptible to life-threatening systemic fungal infections like Candidiasis, Cryptococcosis, and Aspergillosis. Reports are available on the developments of resistance to currently available antifungal agents in *Candida* species, as well as clinical failures in the treatment of fungal infections.[5–7]

Development of resistance to existing drugs is a constant growing phenomenon that has concerned researchers throughout the world and now has reached alarming levels for certain infectious diseases. This combined with recent decline in the development of new drugs to combat them can be anticipated to lead to infectious diseases lacking ready treatment regimens.[8]

There are two basic approaches to get a new drug for microbial infection treatment: (i) synthesis of analogues, modifications, or derivatives of existing compounds for shortening and improving microbial infection treatment; and (ii) searching novel structures, which the pathogen organism has never seen before, for treatment of multidrug-resistant bacterial and fungal infections.[9]

To pursue this goal, our research efforts are directed to find new chemical classes of active antimicrobial agents. The methods of investigation of structure-activity relationships enabled us to find some new pharmacophores of the previously mentioned activity. Many studies were carried out on heterocyclic systems bearing thiazole and pyrazoline groups as a pharmacophore.[10–15]

Electron-rich nitrogen heterocycles play an important role in diverse biological activities. Introducing a pyrazolidinone[16–17] ring in place of the β-lactam ring (in penicillins and cephalosporins[18]) results in enhanced activity. A second nitrogen in the five-membered ring like pyrazoline also influences antibacterial or pharmacokinetic properties.[19–25]

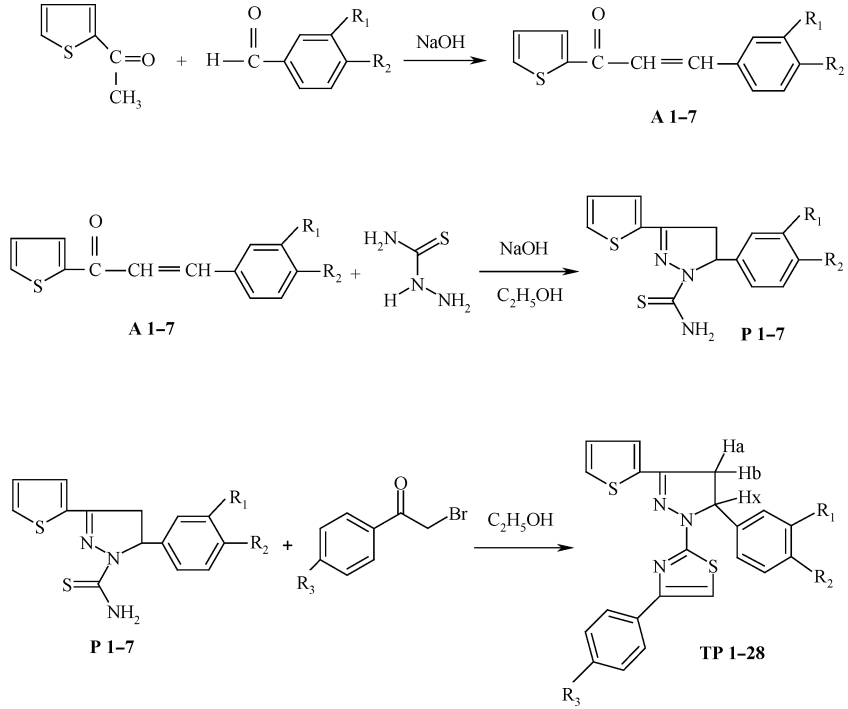
On the other hand, sulfur and/or nitrogen heterocycles that possess pharmaceutical activities widely occur in nature in the form of alkaloids, vitamins, pigments, and as constituents of plant and animal cells. Thiazoles especially exhibit antimicrobial,[26–30] antituberculosis,[31] anti-HIV[32] activities.

Given our interest in the pharmaceutical properties of these heterocyclic compounds, we planned to synthesize a system that combines these two biolabile components, which are pyrazolines and thiazoles, together to give a compact structure like title compounds.

RESULTS AND DISCUSSION

Chemistry

In the present work, 28 new compounds were synthesized (Scheme 1, Table I). First, chalcones (1-(2-thienyl)-3-aryl-2-propen-1-ones) **A 1–7** were synthesized by literature methods as described[33] and treated with thiosemicarbazide to obtain 3-(2-thienyl)-5-aryl-1-thiocarbamoyl-2-pyrazolines **P 1–7** (Scheme 1).



SCHEME 1 Synthetic route of the title compounds.

This reaction probably involved the intermediate formation of hydrazones and subsequent addition of N—H on the olefinic bond of the propenone moiety. Condensation of chalcones with thiosemicarbazide can lead to two different pyrazolines, **P 1–7** or **P′ 1–7**, as shown in

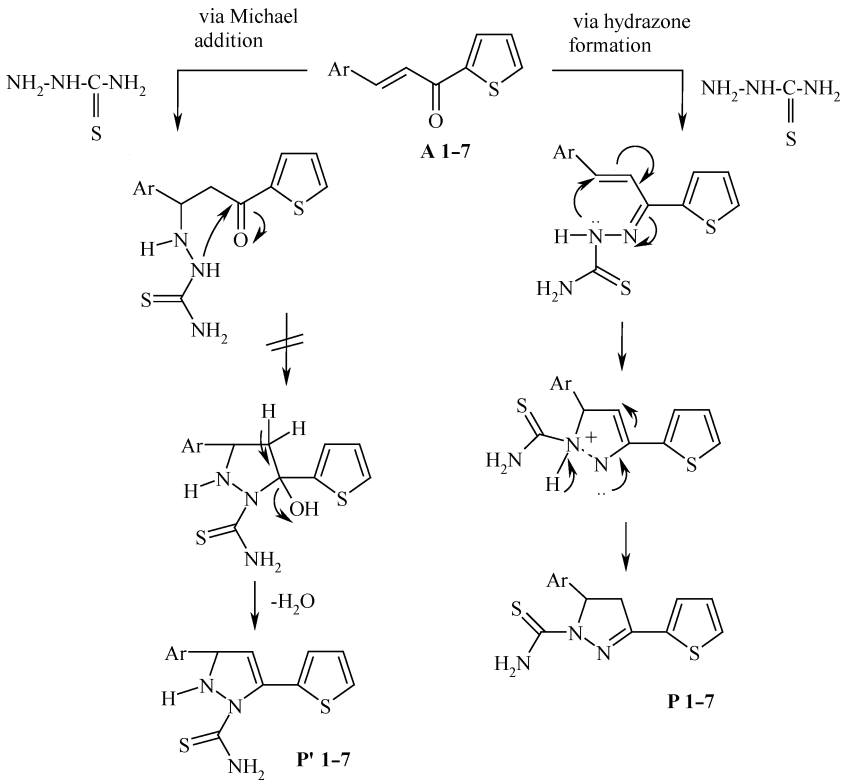
TABLE I Experimental Data for Compounds TP 1-28.

Compound	R_1	R_2	R_3	M.P. (°C)	Yield (%)	Molecular Formula	M.W.
TP 1	H	H	H	176–177	72	$C_{22}H_{17}N_3S_2$	387.53
TP 2	H	H	CH_3	206–208	74	$C_{23}H_{19}N_3S_2$	401.56
TP 3	H	H	OCH_3	209–211	70	$C_{23}H_{19}N_3OS_2$	417.56
TP 4	H	H	Cl	214–216	75	$C_{22}H_{16}ClN_3S_2$	421.97
TP 5	H	Cl	H	190–191	69	$C_{22}H_{16}ClN_3S_2$	421.97
TP 6	H	Cl	CH_3	212–213	73	$C_{23}H_{18}ClN_3S_2$	436.00
TP 7	H	Cl	OCH_3	237–238	70	$C_{23}H_{18}ClN_3OS_2$	452.00
TP 8	H	Cl	Cl	232–234	68	$C_{22}H_{15}Cl_2N_3S_2$	456.42
TP 9	H	OCH_3	H	169–171	66	$C_{23}H_{19}N_3OS_2$	417.56
TP 10	H	OCH_3	CH_3	173–174	63	$C_{24}H_{21}N_3OS_2$	431.58
TP 11	H	OCH_3	OCH_3	198–199	61	$C_{24}H_{21}N_3O_2S_2$	447.58
TP 12	H	OCH_3	Cl	180–182	65	$C_{23}H_{18}ClN_3OS_2$	452.00
TP 13	H	CH_3	H	178–180	69	$C_{23}H_{19}N_3S_2$	401.56
TP 14	H	CH_3	CH_3	195–196	71	$C_{24}H_{21}N_3S_2$	415.58
TP 15	H	CH_3	OCH_3	192–193	73	$C_{24}H_{21}N_3OS_2$	431.58
TP 16	H	CH_3	Cl	186–187	68	$C_{23}H_{18}ClN_3S_2$	436.00
TP 17	H	NO_2	H	197–199	80	$C_{22}H_{16}N_4O_2S_2$	432.53
TP 18	H	NO_2	CH_3	201–203	77	$C_{23}H_{18}N_4O_2S_2$	446.55
TP 19	H	NO_2	OCH_3	188–189	79	$C_{23}H_{18}N_4O_3S_2$	462.55
TP 20	H	NO_2	Cl	194–195	76	$C_{22}H_{15}ClN_4O_2S_2$	466.97
TP 21	O—CH_2-O		H	153–155	65	$C_{23}H_{17}N_3O_2S_2$	431.54
TP 22	O—CH_2-O		CH_3	142–144	62	$C_{24}H_{19}N_3O_2S_2$	445.57
TP 23	O—CH_2-O		OCH_3	165–167	67	$C_{24}H_{19}N_3O_3S_2$	461.57
TP 24	O—CH_2-O		Cl	183–185	63	$C_{23}H_{16}ClN_3O_2S_2$	465.98
TP 25	H	F	H	140–141	68	$C_{22}H_{16}FN_3S_2$	405.52
TP 26	H	F	CH_3	202–204	71	$C_{23}H_{18}FN_3S_2$	419.55
TP 27	H	F	OCH_3	221–223	73	$C_{23}H_{18}FN_3OS_2$	435.55
TP 28	H	F	Cl	218–220	70	$C_{22}H_{15}ClFN_3S_2$	439.96

Scheme 2. According to the currently accepted mechanism,[34] the formation of **P 1–7**, instead of the regioisomer **P′ 1–7**, is favoured via hydrazone or thiosemicarbazone formation.

Compounds **TP 1–28** were obtained by reacting compounds **P 1–7** with phenacyl bromide or its derivatives in ethanol[35] Scheme 1. The substitution on the *para* site of phenacyl bromide played an important role in thiazole formation step.

The structure of compounds **TP 1–28** were confirmed by elemental analyses and IR, ^{1}H-NMR, and MS-FAB$^+$ spectral data. All compounds gave satisfactory elemental analysis. IR spectra of compounds **TP 1–28** showed C=N and C=C stretching bands at 1640–1685 and 1570–1596 cm^{-1} regions, respectively. ^{1}H-NMR and MS-FAB$^+$ spectral data also were consistent with the assigned structures. In the 250-MHz ^{1}H-NMR spectrum of the compounds, the CH_2 protons of the pyrazoline



SCHEME 2 Proposed mechanisms of pyrazoline formation.

ring resonated as a pair of doublets of doublets at δ 3.15–3.50 ppm (Ha) and 3.98–4.07 ppm (Hb). The CH (Hx) proton appeared as a doublet of doublets at δ 5.59–5.70 ppm due to vicinal coupling with the two magnetically non-equivalent protons of the methylene group at position 4 of the pyrazoline ring (J_{AB} = 17.50–18.10 Hz, J_{AX} = 6.00–6.80 Hz, J_{BX} = 11.70–12.10 Hz). All other aromatic and aliphatic protons were observed at the expected regions.

Microbiology

The results of antimicrobial screening of newly prepared compounds **TP 1–28** expressed as the Minimum Inhibitory Concentration (MIC) are summarized in Table II.

The most important part of the results was those that were obtained from antifungal activity screening. Most of the compounds were

TABLE II MIC Values μg/mL of Compounds TP 1–28

Compounds	*E. coli* (NRRL B-3704)	*Staphylococcus aureus* (NRRL B-767)	*Salmonella typhimurium* (NRRL B-4420)	*B. cereus* (NRRL B-3711)	*Listeria monocytogenes* (Ankara Uni. Fac. of Veterinary)	*A. hydrophila* (Ankara Uni. Fac. of Veterinary)	*C. albicans* (isolates obtained from Osmangazi Uni. Fac.of Medicine)	*Candida glabrata* (isolates obtained from Osmangazi Uni. Fac.of Medicine)
TP 1	250	31.25	125	125	250	31.25	62.5	62.5
TP 2	250	31.25	250	250	125	31.25	62.5	62.5
TP 3	250	62.5	250	250	125	125	125	125
TP 4	125	31.25	125	250	125	62.5	125	125
TP 5	250	250	250	250	250	125	250	250
TP 6	125	62.5	250	250	250	125	125	125
TP 7	250	62.5	125	250	125	125	125	125
TP 8	125	31.25	125	250	250	125	125	125
TP 9	125	31.25	125	250	125	62.5	62.5	62.5
TP 10	125	62.5	62.5	250	125	62.5	62.5	62.5
TP 11	125	62.5	125	250	125	62.5	125	125
TP 12	250	62.5	125	250	125	125	125	125
TP 13	500	500	500	500	500	500	500	500
TP 14	250	125	125	250	125	62.5	62.5	125
TP 15	250	250	250	250	250	62.5	125	125
TP 16	250	62.5	125	250	125	62.5	125	125
TP 17	250	125	250	125	125	62.5	125	125
TP 18	250	125	250	250	125	62.5	250	250
TP 19	125	125	125	125	125	62.5	125	125
TP 20	250	125	125	250	125	62.5	125	125
TP 21	250	250	250	250	125	62.5	250	250
TP 22	250	125	125	250	125	62.5	125	125
TP 23	250	125	125	250	125	62.5	250	250
TP 24	250	250	250	250	125	62.5	250	250
TP 25	250	250	250	250	250	125	250	250
TP 26	250	250	250	250	250	62.5	125	125
TP 27	250	125	125	250	125	62.5	125	125
TP 28	250	250	125	250	250	125	125	125
Chloramphenicol	15.60	31.25	31.25	31.25	31.25	125	—	—
Flucanazol	—	—	—	—	—	—	250	250

effective against *Candida albicans* and *Candida glabrata.* When compared with flucanazol, especially **TP 1**, **TP 2**, **TP 3**, **TP 4**, **TP 6**, **TP 7**, **TP 8**, **TP 9**, **TP 10**, **TP 11**, **TP 12**, **TP 14**, **TP 15**, **TP 16**, **TP 17**, **TP 19**, **TP 20**, **TP 22**, **TP 26**, **TP 27**, **TP 28** showed strong activity; **TP 5**, **TP 18**, **TP 21**, **TP 23**, **TP 24**, **TP 25** were similar to the reference agent; and showed **TP 13** moderate activity.

In the case of thiazole derivatives, a potent antifungal activity, comparable with a commercially available compound, was observed, in particular against *C. albicans* and *C. glabrata*.

Antibacterial assessment revealed that the compounds possess only a moderate or slight activity. The MIC values were generally within the range of 31.25–500 μg/mL against all evaluated strains. By comparing their MIC values with chloramphenicol, the compounds were less active against *Escherichia coli, Salmonella typhimurium, Bacillas cereus, and Listeria monocytogenes*. On the other hand, the compounds exhibited comparable or better activities against *Aeromonas hydrophila* and *Saureus aureus* than those of chloramphenicol.

Considering all the results obtained from antifungal and antibacterial tests, in comparision with reference agents, it is possible to say that the tested compounds are mostly active toward fungi then bacteria.

When structure and activity relationships are investigated, we can infer from the results that R_3 substitions seem to be effective on antifungal activity. Especially nonsubstituated and methyl substituated derivatives are more active then other derivatives. For further studies, we are planning to synthesize new compounds bearing methyl substituents at different positions which will also be evaluated against important human pathogenic fungi for their inhibitory activity.

EXPERIMENTAL

Chemistry

All reagents were used as purchased from commercial suppliers without further purification. Melting points were determined by using an Electrothermal 9100 digital melting-point apparatus (Barnstead International, Iowa, USA) and were uncorrected. Compounds were checked for purity by TLC on silica gel 60 F_{254} (Merck, Darmstadt, Germany). Spectroscopic data were recorded on the following instruments: elemental analyses were performed on a Perkin Elmer EAL 240 elemental analyzer (Perkin Elmer, Wellesly, MA, USA); IR (v, cm^{-1}), were recorded on a Shimadzu 435 IR spectrophotometer (Shimadzu, Tokyo, Japan); and ^{1}H-NMR spectra (δ, ppm, Hz) were recorded on a Bruker 250 MHz spectrometer (Bruker, Billerica, MA, USA) in solvent DMSO-d_6 with TMS as an internal standard. MS-FAB$^+$ was recorded, VG Quattro mass spectrometer (Agilent, Minnesota, USA).

General Synthesis Procedure

1-(2-Thienyl)-3-aryl-2-propen-1-ones (chalcones) (A 1–7). A mixture of 2-acetylthiophene (40 mmol, 5.04 g), aromatic aldehyde (40 mmol, benzaldehyde = 4.24 g, 4-chlorobenzaldehyde = 5.62 g, 4-methoxybenzaldehyde = 5.44 g, 4-methylbenzaldehyde = 4.80 g, 4-nitrobenzaldehyde = 6.04 g, 1,3-benzodioxole-4-carbaldehyde = 6.00 g, 4-florobenzaldehyde = 4.96 g) and sodium hydroxide (1.00 g in water [10 ml]) in ethanol (30 mL) was stirred at r. t. for about 3 h. The resulting solid was washed, dried, and crystallized from ethanol.[33]

3-(2-Thienyl)-5-aryl-1-thiocarbamoyl-2-pyrazolines (P 1–7). To a suspension of chalcone derivatives **A 1–7** (10 mmol, A 1 = 2.14 g, A 2 = 2.48 g, A 3 2.44 g, A 4 = 2.28 g, A 5 = 2.59 g, A 6 = 2.58 g, A 7 = 2.32 g) and sodium hydroxide (1.00 g) in ethanol (50 mL), thiosemicarbazide (12 mmol, 1.09 g) was added. The mixture was refluxed for 8 h. The products were poured into crushed ice, and the solid mass that separated out was filtered, dried, and crystallized from ethanol.[35]

1-(4-Aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline (TP 1–28). To a suspension of compound **P 1–7** (10 mmol, P 1 = 2.87 g, P 2 = 3.21 g, P 3 = 3.17 g, P 4 = 3.01 g, P 5 = 3.32 g, P 6 = 3.31 g, P 7 = 3.05 g) in ethanol (15 mL) phenacyl bromide (10 mmol, phenacyl bromide = 1.99 g, 4-methylphenacyl bromide = 2.13 g, 4-methoxyphenacyl bromide = 2.29 g, 4-chloro phenacyl bromide = 2.33 g) was added and heated to reflux for 1 h. After cooling, the precipitate was collected. The product was crystallized from ethanol.

Some characteristics of the synthesized compounds are shown in Table I. Analytical and spectral data (IR, ^{1}HNMR, MS-FAB$^+$) confirmed the structures of the new compounds.

IR spectra of compounds **TP 1–28** showed C=N and C=C stretching bands at 1640–1685 and 1570–1596 cm^{-1} regions respectively.

*1-(4-Phenyl-2-thiazolyl)-3-(2-thienyl)-5-phenyl-2-pyrazoline (***TP 1***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 3.37 (1H, dd, J = 17.7, 6.4 Hz), 4.07 (1H, dd, J = 17.7, 11.7 Hz), 5.70 (1H, dd, J = 11.7, 6.4 Hz), 7.17 (1H, dd, J = 5.1, 3.6 Hz), 7.21–7.44 (9H, m), 7.45 (1H, dd, J = 3.4, 1.1 Hz), 7.70 (2H, d, J = 6.8 Hz), 7.75 (1H, dd, J = 4.9, 1.1 Hz). MS-FAB$^+$: m/z: 387 [M], 388 [M+1]. For $C_{22}H_{17}N_3S_2$, calculated: C, 68.19; H, 4.42; N, 10.84; found: C, 68.61; H, 4.77; N, 10.90%.

*1-[4-(p-Methylphenyl)-2-thiazolyl]-3-(2-thienyl)-5-phenyl-2-pyrazoline (***TP 2***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 2.28 (3H, s), 3.36 (1H, dd, J = 17.5, 6.8 Hz), 4.06 (1H, dd, J = 17.5, 11.9

Hz), 5.69 (1H, dd, $J = 11.9$, 6.8 Hz), 7.11–7.43 (9H, m), 7.44 (1H, dd, $J = 3.8$, 1.1 Hz), 7.60 (2H, d, $J = 8.3$ Hz), 7.74 (1H, dd, $J = 4.9$, 1.1 Hz). MS-FAB$^+$: m/z: 401 [M], 402 [M + 1]. For $C_{23}H_{19}N_3S_2$, calculated: C, 68.80; H, 4.77; N, 10.46; found: C, 68.91; H, 4.65; N, 10.49%.

*1-[4-(p-Methoxyphenyl)-2-thiazolyl]-3-(2-thienyl)-5-phenyl-2-pyrazoline (***TP 3***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 3.20–3.35 (1H, m), 3.66 (3H, s), 3.98 (1H, dd, $J = 17.5$, 11.9 Hz), 5.59 (1H, dd, $J = 11.9$, 6.6 Hz), 6.82 (2H, d, $J = 9.0$ Hz), 7.05 (1H, s), 7.08 (1H, dd, $J = 5.3$, 3.6 Hz), 7.15–7.34 (5H, m), 7.35 (1H, dd, $J = 3.4$, 1.1 Hz), 7.54 (2H, d, $J = 9.0$ Hz), 7.65 (1H, dd, $J = 4.9$, 1.1 Hz). MS-FAB$^+$: m/z: 417 [M], 418 [M+1]. For $C_{23}H_{19}N_3OS_2$ calculated: C, 66.16; H, 4.59; N, 10.06; found: C, 65.97; H, 4.68; N, 10.11%.

1-[4-(p-Chlorophenyl)-2-thiazolyl]-3-(2-thienyl)-5-phenyl-2-pyrazoline (**TP 4**). ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 3.30–3.45 (1H, m), 4.07 (1H, dd, $J = 17.7$, 12.1 Hz), 5.70 (1H, dd, $J = 12.1$, 6.4 Hz), 7.17 (1H, dd, $J = 5.3$, 3.5 Hz), 7.24–7.43 (8H, m), 7.46 (1H, dd, $J = 3.8$, 1.1 Hz), 7.72 (2H, d, $J = 8.7$ Hz), 7.75 (1H, dd, $J = 4.9$, 1.1 Hz). MS-FAB$^+$: m/z: 421 [M], 422 [M+1], 423 [M+2]. For $C_{22}H_{16}ClN_3S_2$ calculated: C, 62.62; H, 3.82; N, 9.96; N; found: C, 62.75; H, 3.94; N, 10.01%.

1-[4-Phenyl-2-thiazolyl]-3-(2-thienyl)-5-(p-chlorophenyl)-2-pyrazoline (**TP 5**). ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 3.25–3.40 (1H, m), 4.01 (1H, dd, $J = 17.7$, 11.9 Hz), 5.68 (1H, dd, $J = 11.9$, 6.5 Hz), 7.15 (1H, dd, $J = 5.3$, 3.8 Hz), 7.26–7.35 (8H, m), 7.44 (1H, dd, $J = 3.8$, 1.1 Hz), 7.70 (2H, d, $J = 8.7$ Hz), 7.74 (1H, dd, $J = 4.9$, 1.1 Hz). MS-FAB$^+$: m/z: 421 [M], 422 [M+1], 423 [M+2]. For $C_{22}H_{16}ClN_3S_2$, calculated: C, 62.62; H, 3.82; N, 9.96; found: C, 62.75; H, 3.94; N, 10.01%.

1-[4-(p-Methylphenyl)-2-thiazolyl]-3-(2-thienyl)-5-(p-chlorophenyl)-2-pyrazoline (**TP 6**). ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 2.29 (3H, s), 3.35–3.45 (1H, m), 4.06 (1H, dd, $J = 17.7$, 11.9 Hz), 5.69 (1H, dd, $J = 11.9$, 6.5 Hz), 7.13–7.19 (3H, m), 7.25 (1H, s), 7.41–7.46 (5H, m), 7.59 (2H, d, $J = 7.8$ Hz), 7.74 (1H, dd, $J = 4.9$, 1.1 Hz). MS-FAB$^+$: m/z: 436 [M], 437 [M+1], 438 [M+2]. For $C_{23}H_{18}ClN_3S_2$, calculated: C, 63.36; H, 4.16; N, 9.64; found: C, 63.06; H, 4.18; N, 9.72%.

*1-[4-(p-Methoxphenyl)-2-thiazolyl]-3-(2-thienyl)-5-(p-chlorophenyl)-2-pyrazoline (***TP 7***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6):

3.35–3.45 (1H, m), 3.72 (3H, s), 4.05 (1H, dd, $J = 17.7$, 11.7 Hz), 5.68 (1H, dd, $J = 11.7$, 6.8 Hz), 6.93 (2H, d, $J = 9.0$ Hz), 7.15–7.22 (4H, m), 7.40–7.48 (3H, m), 7.57 (2H, d, $J = 9.0$ Hz), 7.71 (1H, dd, $J = 4.9$, 1.1 Hz). MS-FAB$^+$: m/z: 452 [M], 453 [M+1], 454 [M+2]. For $C_{23}H_{18}ClN_3OS_2$, calculated: C, 61.12; H, 4.01; N, 9.30; found: C, 61.01; H, 4.08; N, 9.42%.

*1-[4-(p-Chlorophenyl)-2-thiazolyl]-3-(2-thienyl)-5-(p-chlorophenyl)-2-pyrazoline (***TP 8***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 3.20–3.35 (1H, m), 3.98 (1H, dd, $J = 18.1$, 12.1 Hz), 5.62 (1H, dd, $J = 12.1$, 6.4 Hz), 7.09 (1H, dd, $J = 5.3$, 3.8 Hz), 7.31–7.38 (8H, m), 7.63 (2H, d, $J = 8.7$ Hz), 7.66 (1H, dd, $J = 4.9$, 1.1 Hz). MS-FAB$^+$: m/z: 456 [M], 457 [M+1], 458 [M+2]. For $C_{22}H_{15}Cl_2N_3S_2$, calculated: C, 57.90; H, 3.31; N, 9.21; found: C, 57.78; H, 3.45; N, 9.29%.

*1-[4-Phenyl-2-thiazolyl]-3-(2-thienyl)-5-(p-methoxphenyl)-2-pyrazoline (***TP 9***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 3.35–3.50 (1H, m), 3.69 (3H, s), 3.99 (1H, dd, $J = 17.5$, 11.9 Hz), 5.62 (1H, dd, $J = 11.9$, 6.6 Hz), 6.85 (2H, d, $J = 9.0$ Hz), 7.10 (1H, s), 7.14 (1H, dd, $J = 4.9$, 3.8 Hz), 7.18–7.34 (5H, m), 7.40 (1H, dd, $J = 3.8$, 1.1 Hz), 7.60 (2H, d, $J = 9.0$ Hz), 7.69 (1H, dd, $J = 4.9$, 1.1 Hz). MS-FAB$^+$: m/z: 417 [M], 418 [M+1]. For $C_{23}H_{19}N_3OS_2$, calculated: C, 66.16; H, 4.59; N, 10.06; found: C, 65.97; H, 4.68; N, 10.11%.

*1-[4-(p-Methylphenyl)-2-thiazolyl]-3-(2-thienyl)-5-(p-methoxyphenyl)-2-pyrazoline (***TP 10***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 2.23 (3H, s), 3.28 (1H, dd, $J = 17.7$, 6.4 Hz), 3.72 (3H, s), 4.00 (1H, dd, $J = 17.7$, 12.1 Hz), 5.67 (1H, dd, $J = 12.1$, 6.4 Hz), 6.88 (2H, d, $J = 8.7$ Hz), 7.17 (1H, s), 7.19–7.26 (3H, m), 7.33 (2H, d, $J = 8.3$ Hz), 7.46 (1H, dd, $J = 3.8$, 1.1 Hz), 7.71 (2H, d, $J = 8.7$ Hz), 7.77 (1H, dd, $J = 4.9$, 1.1 Hz). MS-FAB$^+$: m/z: 431 [M], 432 [M+1]. For $C_{24}H_{21}N_3OS_2$, calculated: C, 66.79; H, 4.90; N, 9.74; found: C, 66.54; H, 4.75; N, 9.63%.

*1-[4-(p-Methoxyphenyl)-2-thiazolyl]-3-(2-thienyl)-5-(p-methoxphenyl))-2-pyrazoline (***TP 11***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 3.35 (1H, dd, $J = 17.7$, 6.4 Hz), 3.71 (3H, s), 3.76 (3H, s), 4.02 (1H, dd, $J = 17.7$, 11.9 Hz), 5.63 (1H, dd, $J = 11.9$, 6.4 Hz), 6.88–6.95 (4H, m), 7.13 (1H, s), 7.17 (1H, dd, $J = 4.9$, 3.8 Hz), 7.33 (2H, d, $J = 8.7$ Hz), 7.44 (1H, dd, $J = 3.8$, 1.1 Hz), 7.66 (2H, d, $J = 9.0$ Hz), 7.73 (1H, dd, $J = 4.9$, 1.1 Hz). MS-FAB$^+$: m/z: 447 [M], 448 [M+1]. For

$C_{24}H_{21}N_3O_2S_2$, calculated: C, 64.41; H, 4.73; N, 9.39; found: C, 64.04; H, 4.78; N, 9.58%.

*1-[4-(p-Chlorophenyl)-2-thiazolyl]-3-(2-thienyl)-5-(p-methoxyphenyl)-2-pyrazoline (***TP 12***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 3.32–3.47 (1H, m), 3.75 (3H, s), 4.01 (1H, dd, $J = 17.7$, 11.7 Hz), 5.62 (1H, dd, $J = 11.7$, 6.0 Hz), 6.88 (2H, d, $J = 8.7$ Hz), 7.11–7.18 (4H, m), 7.33–7.40 (3H, m), 7.53 (2H, d, $J = 8.7$ Hz), 7.67 (1H, dd, $J = 4.9$, 1.1 Hz). MS-FAB$^+$: m/z: 452 [M], 453 [M+1], 454 [M+2]. For $C_{23}H_{18}ClN_3OS_2$, calculated: C, 61.12; H, 4.01; N, 9.30; found: C, 61.01; H, 4.08; N, 9.42%.

*1-[4-Phenyl-2-thiazolyl]-3-(2-thienyl)-5-(p-methylphenyl)-2-pyrazoline (***TP 13***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 2.25 (3H, s), 3.38 (1H, dd, $J = 17.7$, 6.4 Hz), 4.01 (1H, dd, $J = 17.7$, 12.1 Hz), 5.64 (1H, dd, $J = 12.1$, 6.4 Hz), 7.10–7.41 (9H, m), 7.47 (1H, dd, $J = 3.8$, 1.1 Hz), 7.63 (2H, d, $J = 8.7$ Hz), 7.79 (1H, dd, $J = 4.9$, 1.1 Hz). MS-FAB$^+$: m/z: 401 [M], 402 [M+1]. For $C_{23}H_{19}N_3S_2$, calculated: C, 68.80; H, 4.77; N, 10.46; found: C, 68.95; H, 4.83; N, 10.44%.

*1-[4-(p-Methylphenyl)-2-thiazolyl]-3-(2-thienyl)-5-(p-methylphenyl)-2-pyrazoline (***TP 14***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 2.25 (3H, s), 2.30 (3H, s), 3.37 (1H, dd, $J = 17.5$, 6.6 Hz), 3.99 (1H, dd, $J = 17.5$, 11.9 Hz), 5.61 (1H, dd, $J = 11.9$, 6.6 Hz), 6.85–6.91 (4H, m), 7.08 (1H, s), 7.14 (1H, dd, $J = 5.3$, 3.8 Hz), 7.29 (2H, d, $J = 8.7$ Hz), 7.41 (1H, dd, $J = 3.8$, 1.1 Hz), 7.62 (2H, d, $J = 9.0$ Hz), 7.70 (1H, dd, $J = 5.3$, 1.1 Hz). MS-FAB$^+$: m/z: 415 [M], 416 [M+1]. For $C_{24}H_{21}N_3S_2$, calculated: C, 69.36; H, 5.09; N, 10.11; found: C, 69.53; H, 5.17; N, 10.15%.

*1-[4-(p-Methoxyphenyl)-2-thiazolyl]-3-(2-thienyl)-5-(p-methylphenyl)-2-pyrazoline (***TP 15***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 2.26 (3H, s), 3.33 (1H, dd, $J = 17.7$, 6.4 Hz), 3.76 (3H, s), 4.03 (1H, dd, $J = 17.7$, 12.1 Hz), 5.65 (1H, dd, $J = 12.1$, 6.4 Hz), 6.91 (2H, d, $J = 8.7$ Hz), 7.13 (1H, s), 7.14–7.19 (3H, m), 7.28 (2H, d, $J = 8.3$ Hz), 7.43 (1H, dd, $J = 3.8$, 1.1 Hz), 7.65 (2H, d, $J = 8.7$ Hz), 7.73 (1H, dd, $J = 4.9$, 1.1 Hz). MS-FAB$^+$: m/z: 431 [M], 432 [M+1]. For $C_{24}H_{21}N_3OS_2$, calculated: C, 66.79; H, 4.90; N, 9.74; found: C, 66.54; H, 4.75; N, 9.63%.

*1-[4-(p-Chlorophenyl)-2-thiazolyl]-3-(2-thienyl)-5-(p-methylphenyl)-2-pyrazoline (***TP 16***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 2.26 (3H, s), 3.34 (1H, dd, $J = 17.7$, 6.0 Hz), 4.04 (1H, dd, $J = 17.7$, 12.0 Hz), 5.66 (1H, dd, $J = 12.0$, 6.0 Hz), 7.13–7.19 (3H, m), 7.27 (2H, d, $J = 8.3$ Hz), 7.38 (1H, s), 7.41 (2H, d, $J = 9.0$ Hz), 7.44 (1H, dd, $J =$ 3.8, 1.1 Hz), 7.71–7.77 (3H, m). MS-FAB$^+$: m/z: 436 [M], 437 [M+1], 438 [M+2]. For $C_{23}H_{18}ClN_3S_2$, calculated: C, 63.36; H, 4.16; N, 9.64; found: C, 63.06; H, 4.18; N, 9.72%.

*1-[4-Phenyl-2-thiazolyl]-3-(2-thienyl)-5-(p-nitrophenyl)-2-pyrazoline (***TP 17***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 3.15–3.35 (1H, m), 4.01 (1H, dd, $J = 17.9$, 11.7 Hz), 5.64 (1H, dd, $J = 11.7$, 6.4 Hz), 7.10 (1H, dd, $J = 4.9$, 3.8 Hz), 7.16–7.37 (5H, m), 7.39 (1H, dd, $J = 3.8$, 1.1 Hz), 7.63 (1H, s), 7.68 (1H, dd, $J = 4.9$, 1.1 Hz), 7.87 (2H, d, $J = 9.0$ Hz), 8.14 (2H, d, $J = 9.0$ Hz). MS-FAB$^+$: m/z: 432 [M], 433 [M+1]. For $C_{22}H_{16}N_4O_2S_2$, calculated: C, 61.09; H, 3.73; N, 12.95; found: C, 60.92; H, 3.84; N, 12.82%.

*1-[4-(p-Methylphenyl)-2-thiazolyl]-3-(2-thienyl)-5-(p-nitrophenyl)-2-pyrazoline (***TP 18***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 2.29 (3H, s), 3.35–3.45 (1H, m), 4.05 (1H, dd, $J = 17.8$, 11.7 Hz), 5.67 (1H, dd, $J = 11.7$, 6.3 Hz), 6.94 (2H, d, $J = 9.0$ Hz), 7.18 (1H, dd, $J = 4.9$, 3.8 Hz), 7.36 (2H, d, $J = 8.7$ Hz), 7.48 (1H, dd, $J = 3.8$, 1.1 Hz), 7.70 (1H, s), 7.76 (1H, dd, $J = 4.9$, 1.1 Hz), 7.99 (2H, d, $J = 9.0$ Hz), 8.24 (2H, d, $J = 9.0$ Hz). MS-FAB$^+$: m/z: 446 [M], 447 [M+1]. For $C_{23}H_{18}N_4O_2S_2$, calculated: C, 61.86; H, 4.06; N, 12.55; found: C, 62.09; H, 4.18; N, 12.67%.

*1-[4-(p-Methoxyphenyl)-2-thiazolyl]-3-(2-thienyl)-5-(p-nitrophenyl)-2-pyrazoline (***TP 19***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 3.34 (1H, dd, $J = 17.7$, 6.0 Hz), 3.76 (3H, s), 4.00 (1H, dd, $J = 17.7$, 11.8 Hz), 5.62 (1H, dd, $J = 11.8$, 6.0 Hz), 6.92 (2H, d, $J = 8.7$ Hz), 7.13 (1H, s), 7.17 (1H, dd, $J = 4.9$, 3.8 Hz), 7.30 (2H, d, $J = 8.3$ Hz), 7.44 (1H, dd, $J = 3.8$, 1.1 Hz), 7.48 (1H, d, $J = 9.0$ Hz), 7.68 (2H, d, $J = 8.7$ Hz), 7.73 (1H, dd, $J = 5.3$, 1.1 Hz), 7.77 (1H, d, $J = 8.7$ Hz). MS-FAB$^+$: m/z: 462 [M], 463 [M+1]. For $C_{23}H_{18}N_4O_3S_2$, calculated: C, 59.72; H, 3.92; N, 12.11; found: C, 59.67; H, 4.01; N, 12.00%.

*1-[4-(p-Chlorophenyl)-2-thiazolyl]-3-(2-thienyl)-5-(p-nitrophenyl)-2-pyrazoline (***TP 20***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 3.35 (1H, dd, $J = 17.7$, 6.4 Hz), 4.03 (1H, dd, $J = 17.7$, 11.7 Hz), 5.65 (1H,

dd, $J = 11.7$, 6.4 Hz), 6.79 (2H, d, $J = 8.7$ Hz), 7.17 (1H, dd, $J = 5.3$, 3.8 Hz), 7.30–7.52 (3H, m), 7.72–7.78 (3H, m), 7.86 (2H, d, $J = 8.3$ Hz), 7.93 (1H, s). MS-FAB$^+$: m/z: 466 [M], 467 [M+1], 468 [M+2]. For $C_{22}H_{15}ClN_4O_2S_2$, calculated: C, 56.59; H, 3.24; N, 12.00; found: C, 56.46; H, 3.17; N, 11.89%.

*1-[4-Phenyl-2-thiazolyl]-3-(2-thienyl)-5-(3,4-methylenedioxyphenyl)-2-pyrazoline (***TP 21***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 3.23–3.44 (1H, m), 4.03 (1H, dd, $J = 17.7$, 11.7 Hz), 5.64 (1H, dd, $J = 11.7$, 6.0 Hz), 5.93 (1H, d, $J = 15.7$ Hz), 6.00 (1H, d, $J = 15.7$ Hz), 6.83–6.92 (3H, m), 7.18 (1H, dd, $J = 4.9$, 3.8 Hz), 7.34–7.42 (5H, m), 7.70–7.76 (3H, m). MS-FAB$^+$: m/z: 431 [M], 432 [M+1]. For $C_{23}H_{17}N_3O_2S_2$, calculated: C, 64.02; H, 3.97; N, 9.74; found: C, 64.06; H, 4.01; N, 9.81%.

*1-[4-(p-Methylphenyl)-2-thiazolyl]-3-(2-thienyl)-5-(3,4-methylenedioxyphenyl)-2-pyrazoline (***TP 22***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 2.29 (3H, s), 3.36 (1H, dd, $J = 17.7$, 6.4 Hz), 4.00 (1H, dd, $J = 17.7$, 11.7 Hz), 5.62 (1H, dd, $J = 11.7$, 6.4 Hz), 5.95 (1H, d, $J = 15.5$ Hz), 6.02 (1H, d, $J = 15.5$ Hz), 6.88–6.95 (3H, m), 7.14–7.19 (3H, m), 7.24 (1H, s), 7.44 (1H, dd, $J = 3.8$, 1.1 Hz), 7.63 (2H, d, $J = 8.3$ Hz), 7.73 (1H, dd, $J = 4.9$, 1.1 Hz). MS-FAB$^+$: m/z: 445 [M], 446 [M+1]. For $C_{24}H_{19}N_3O_2S_2$, calculated: C, 64.70; H, 4.30; N, 9.43; N; found: C, 64.68; H, 4.26; N, 9.42%.

*1-[4-(p-Methoxyphenyl)-2-thiazolyl]-3-(2-thienyl)-5-(3,4-methylenedioxyphenyl)-2-pyrazoline (***TP 23***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 3.36 (1H, dd, $J = 17.5$, 6.6 Hz), 3.70 (3H, s), 4.02 (1H, dd, $J = 17.5$, 11.7 Hz), 5.66 (1H, dd, $J = 11.7$, 6.6 Hz), 5.93 (1H, d, $J = 15.5$ Hz), 6.04 (1H, d, $J = 15.5$ Hz), 6.85–6.92 (3H, m), 7.12–7.17 (3H, m), 7.29 (1H, s), 7.40 (1H, dd, $J = 3.8$, 1.1 Hz), 7.61 (2H, d, $J = 8.7$ Hz), 7.69 (1H, dd, $J = 5.3$, 1.1 Hz). MS-FAB$^+$: m/z: 461 [M], 462 [M+1]. For $C_{24}H_{19}N_3O_3S_2$, calculated: C, 62.45; H, 4.15; N, 9.10; found: C, 62.68; H, 4.26; N, 9.15%.

*1-[4-(p-Chlorophenyl)-2-thiazolyl]-3-(2-thienyl)-5-(3,4-methylenedioxyphenyl)-2-pyrazoline (***TP 24***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 3.20–3.42 (1H, m), 4.01 (1H, dd, $J = 17.7$, 11.7 Hz), 5.62 (1H, dd, $J = 11.7$, 6.0 Hz), 5.95 (1H, d, $J = 15.7$ Hz), 6.02 (1H, d, $J = 15.7$ Hz), 6.87–6.95 (3H, m), 7.17 (1H, dd, $J = 4.9$, 3.8 Hz),

7.38–7.47 (4H, m), 7.72–7.78 (3H, m). MS-FAB$^+$: m/z: 465 [M], 466 [M+1], 467 [M+2]. For $C_{23}H_{16}ClN_3O_2S_2$, calculated: C, 59.28; H, 3.46; N, 9.02; found: C, 59.47; H, 3.58; N, 9.12%.

*1-[4-Phenyl-2-thiazolyl]-3-(2-thienyl)-5-(p-fluoro phenyl)-2-pyrazoline (***TP 25***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 3.38 (1H, dd, $J = 17.7$, 6.4 Hz), 4.05 (1H, dd, $J = 17.7$, 12.0 Hz), 5.70 (1H, dd, $J =$ 12.0, 6.4 Hz), 7.15–7.28 (4H, m), 7.31–7.38 (3H, m), 7.43–7.50 (3H, m), 7.70 (2H, d, $J = 8.3$ Hz), 7.74 (1H, dd, $J = 4.9$, 1.1 Hz). MS-FAB$^+$: m/z: 405 [M], 406 [M+1]. For $C_{22}H_{16}FN_3S_2$, calculated: C, 65.16; H, 3.98; N, 10.36; found: C, 65.06; H, 3.93; N, 10.38%.

*1-[4-(p-Methylphenyl)-2-thiazolyl]-3-(2-thienyl)-5-(p-fluorophenyl)-2-pyrazoline (***TP 26***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 2.29 (3H, s), 3.41 (1H, dd, $J = 17.7$, 6.8 Hz), 4.05 (1H, dd, $J = 17.7$, 11.7 Hz), 5.69 (1H, dd, $J = 11.7$, 6.8 Hz), 7.12–7.25 (6H, m), 7.42–7.50 (3H, m), 7.60 (2H, d, $J = 8.3$ Hz), 7.74 (1H, dd, $J = 4.9$, 1.1 Hz). MS-FAB$^+$: m/z: 419 [M], 420 [M+1]. For $C_{23}H_{18}FN_3S_2$, calculated: C, 65.85; H, 4.32; N, 10.02; found: C, 65.85; H, 4.30; N, 10.01%.

*1-[4-(p-Methoxphenyl)-2-thiazolyl]-3-(2-thienyl)-5-(p-fluorophenyl)-2-pyrazoline (***TP 27***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 3.37 (1H, dd, $J = 17.7$, 6.8 Hz), 3.76 (3H, s), 4.05 (1H, dd, $J = 17.7$, 11.7 Hz), 5.68 (1H, dd, $J = 11.7$, 6.8 Hz), 6.91 (2H, d, $J = 9.0$ Hz), 7.13–7.25 (4H, m), 7.42–7.50 (3H, m), 7.60 (2H, d, $J = 9.0$ Hz), 7.74 (1H, dd, $J =$ 5.3, 1.1 Hz). MS-FAB$^+$: m/z: 435 [M], 436 [M+1]. For $C_{23}H_{18}FN_3OS_2$, calculated: C, 63.43; H, 4.17; N, 9.65; found: C, 63.56; H, 4.30; N, 9.74%.

*1-[4-(p-Chlorophenyl)-2-thiazolyl]-3-(2-thienyl)-5-(p-fluorophenyl)-2-pyrazoline (***TP 28***).* ^{1}H-NMR (250 MHz, δ ppm, DMSO-d_6): 3.40 (1H, dd, $J = 17.7$, 6.4 Hz), 3.98 (1H, dd, $J = 17.7$, 12.0 Hz), 5.62 (1H, dd, $J = 12.0$, 6.4 Hz), 7.09 (1H, dd, $J = 5.3$, 3.8 Hz), 7.31–7.38 (8H, m), 7.63 (2H, d, $J = 8.7$ Hz), 7.70 (1H, dd, $J = 4.9$, 1.1 Hz). MS-FAB$^+$: m/z: 439 [M], 440 [M+1], 441 [M+2]. For $C_{22}H_{15}ClFN_3S_2$, calculated: C, 60.06; H, 3.44; N, 9.55; found: C, 60.01; H, 3.53; N, 9.52%.

Microbiology

Antimicrobial activities of compounds were tested using the microbroth dilution method.[36] Tested microorganism strains were; *E. coli* (NRRL

B-3704), *S. aureus* (NRLL B-767), *S. typhimurium* (NRRL B-4420), *B. cereus* (NRRL B-3711), *L. monocytogenes* (Ankara Uni. Fac. of Veterinary), *A. hydrophila* (Ankara Uni. Fac. of Veterinary), *C. albicans*, and *C. glabrata* (isolates obtained from Osmangazi Uni. Fac. of Medicine). Microbroth dilution susceptibility assay was used for antimicrobial evaluation of the compounds. Stock solutions of the samples were prepared in dimethylsulfoxide. Dilution series using sterile distilled water were prepared from 4 mg/mL to 0.007 mg/mL in micro-test tubes that were transferred to 96-well microtiter plates. Overnight grown bacterial and *Candida* suspensions in double-strength Mueller-Hinton broth were standardized to 10^8 Colony Forming Units/mL using McFarland No. 0.5 standard solution. hundred mul of each microorganism suspension then was added into the wells. The last well-chain without a microorganism was used as a negative control. Sterile distilled water and the medium served as a positive growth control. After incubation at 37°C for 18–24 h, the first well without turbidity was determined as the MIC. Chloramphenicol was used as standard antibacterial agent, whereas flucanazol was used as an antifungal agent. The observed data on the antimicrobial activity of the compounds and control drugs are given in Table II.

REFERENCES

[1] A. Sarkar, K. A. Kumar, N. K. Dutta, P. Chakraborty, and S. G. Dastidar, *Indian J. Med. Microbiol.*, **21,** 172 (2003).

[2] H. S. Gold and R. C. Moellering, *N. Engl. J. Med. Chem.,* **335,** 1445 (1996).

[3] H. V. Bossche, P. Marichal, and F. C. Odds, *Trends Microbiol*., **10,** 393 (1994).

[4] M. L. Cohen, *Science*, **257,** 1050 (1992).

[5] F. C. Odd, *J. Antimicrob. Chemother.,* **31,** 463 (1993).

[6] C. A. Hitchock, *Biochem. Soc. Trans.,* **21,** 10 (1993).

[7] E. M. Johnson, D. W. Warnock, J. Luker, and S. R. Porter, *J. Antimicrob. Chemother.,* **35,** 103 (1995).

[8] (a) WHO Web site, http://www.who.int/drugresistance/WHO_Global_Strategy-English.pdf (26 June 2002); (b) NIAID Web site, http://www.niaid.nih.gov/factsheets/tb.htm (12 September 2003).

[9] Ch. Crabb, *Bull World Health Organ*., **80,** 517 (2002).

[10] A. D. Logu, M. Saddi, M. C. Cardia, R. Borgna, C. Sanna, B. Saddi, et al., *J. Antimicrob. Chemother.,* **55,** 692 (2005).

[11] C. L. Liu, Z. M. Li, and B. Zhong, *J. Fluorine Chemistry.*, **125,** 1287 (2004).

[12] R. V. Kumar and K. V. S. R. S. Kumar, *J. Heterocyclic Chem.,* **42,** 1191 (2005).

[13] S. D' Andrea, Z. B. Zheng, K. DenBleyker, J. C. Fung-Tomc, H. Yang, J. Clark, et al., *Bioorganic & Medicinal Chemistry Letters,* **15,** 2834 (2005).

[14] D. Azarifar and M. Shaebanzadeh, *Molecules,* **7,** 885 (2002).

[15] J. Matysiak and A. Niewiadomy, *Bioorganic & Medicinal Chemistry*, **11,** 2285 (2003).

[16] L. N. Jungheim, S. K. Sigmund, and J. W. Fisher, *Tetrahedron Letters*, **28,** 285 (1987).

[17] L. N. Jungheim, S. K. Sigmund, N. D. Jones, and J. K. Swartzendruber, *Tetrahedron Letters*, **28,** 289 (1987).
[18] D. B. Boyd, In *Theoretical and Physicochemical Studies on β- Lactam Antibiotics in β -Lactam Antibiotics Chemistry and Biology*, R. B. Morin and M. Gorman, eds., Vol. 1, p. 437 (Academic Press, New York, 1982).
[19] L. N. Jungheim, R. E. Holmes, J. L. Ott, R. J. Ternansky, S. E. Draheim, D. A. Neel, et al., *Interscience Conference on Antimicrobial Agents and Chemotherapy, Sept. 28–Oct. 1, 1988* (Abstracts of 26th), p. 601, New Orleans, LA.
[20] L. N. Jungheim, R. E. Holmes, R. J. Ternansky, T. A. Stepherd, D. A. Neel, S. E. Draheim, et al., *Interscience Conference on Antimicrobial Agents and Chemotherapy, Oct. 23–26, 1988* (Abstracts of 28th), p. 240. New Orleans, Louisiana, USA.
[21] R. J. Ternansky and S. E. Draheim, *Tetrahedron Letters.*, **31,** 2805 (1990).
[22] D. Nauduri and G. S. Reddy, *Chem. Pharm. Bull.*, **46,** 1254 (1998).
[23] N. Grant, N. Mishriky, F. M. Asaad, and N. G. Fawzy, *Die Pharmazie*, **53,** 543 (1998).
[24] G. Turan-Zitouni, A. Özdemir, and K. Güven, *Arch. Pharm. Pharm. Med. Chem.*, **338,** 96 (2005).
[25] G. Turan-Zitouni, A. Özdemir, Z. A. Kaplancıklı, P. Chevallet, and Y. Tunalı, *Phosphorus, Sulfur, and Silicon,* **180**, 2717 (2005).
[26] H. T. Fhamy, *Pharmazie*, **52,** 750 (1997).
[27] S. N. Pandeya, D. Sriram, and G. Nath, *Eur. J. Pharm. Sci.*, **9,** 25 (1999).
[28] Ö. Ateş, H. Altintas, and G. Ötük, *Arzneim. Forsch.*, **50,** 569 (2000).
[29] Z. A. Kaplancikli, G. Turan-Zitouni, G. Revial, and K. Güven, *Arch. Pharm. Res.*, **27,** 1081 (2004).
[30] G. Turan-Zitouni, Ş. Demirayak, A. Özdemir, Z. A. Kaplancıklı, and M. T. Yıldız, *Eur. J. Med. Chem.*, **39,** 267 (2004).
[31] D. R. Ashtekar, F. Fernandes, B. G. Khadse, and M. V. Shirodkar, *Chemotherapy,* **33,** 22 (1987).
[32] G. Maass, U. Immendoerfer, B. Koenig, U. Leser, B. Mueller, R. Goody, et al., *Antimicrob. Agents Chemother.*, **37,** 2612 (1993).
[33] R. A. Kabli, A. A. Khalaf, M. T. Zimaity, A. M. Khalil, A. M. Kaddah, and H. A. Al-Rifaie, *J. Indian Chem. Soc.,* **68,** 47 (1991).
[34] R. H. Wiley, C. H. Jarboe, F. N. Hayes, E. Hansbury, J. T. Nielsen, P. X. Callahan et al., *J. Org. Chem.,* **23,** 732 (1958).
[35] G. Turan-Zitouni, P. Chevallet, F. S. Kiliç, and K. Erol, *Eur. J. Med. Chem.*, **35,** 635 (2000).
[36] E. W. Koneman, S. D. Allen, and W. C. Winn, *Colour Atlas and Textbook of Diagnostic Microbiology,* p. 86, Lippincott Raven Pub., Philadelphia (1997).