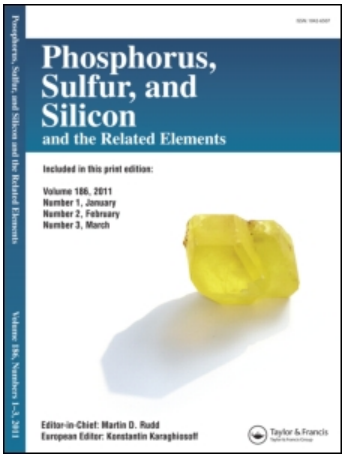


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW PYRAZOLES AND THIEN0[2,3-c]PYRAZOLES

E. A. Bakhite[a]; A. A. Geies[a]; H. S. El-kashef[a]
[a] Chemistry Department, Faculty of Science, Assiut University Assiut, A.R., Egypt

To cite this Article Bakhite, E. A. , Geies, A. A. and El-kashef, H. S.(2000) 'SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW PYRAZOLES AND THIEN0[2,3-c]PYRAZOLES', Phosphorus, Sulfur, and Silicon and the Related Elements, 157: 1, 107 — 122
To link to this Article: DOI: 10.1080/10426500008040516
URL: http://dx.doi.org/10.1080/10426500008040516

Phosphorus, Sulfur and Silicon, 2000, Vol. 157, pp. 107-122
Reprints available directly from the publisher
Photocopying permitted by license only

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW PYRAZOLES AND THIENO[2,3-c]PYRAZOLES

E.A. BAKHITE, A.A. GEIES and H.S. EL-KASHEF*

Chemistry Department, Faculty of Science, Assiut University Assiut 71516, A.R. Egypt

(Received May 07, 1999; In final form September 23, 1999)

Starting with 5-chloro-1,3-diphenyl-1H-pyrazole-4-carboxaldehyde (**1**), both of (4-cyano-1,3-diphenyl-1H-pyrazol-5-ylthio) acethydrazide (**6**) and 1,3-diphenyl-1H-thieno[2,3-c] pyrazole-5-carbohydrazide (**15**) were synthesized. These hydrazides (**6** and **15**) were used as key intermediates in the synthesis of other new pyrazoles **7–12** and thieno[2,3-c]pyrazoles **16–30** respectively. Some of the prepared compounds were screened *in vitro* for their antibacterial and antifungal activity.

Keywords: Pyrazole; thieno [2,3-c] pyrazole; oxadiazole; s-triazole; antimicrobial activity

INTRODUCTION

Many pyrazoles are known to possess significant antibacterial[1,2], antifungal[3,4] and antiinflammatory[5,6] properties. Also, the antiulcer[7], antiamebic[8], antipyretic and analgesic[6] activity of some thienopyrazoles has been reported.

Thus in view of the aforementioned observations and in continuation to our previous work on condensed thiophenes [9–14], we report herein the synthesis of some new 1,3-diphenyl-1H-pyrazole-4-carbonitrile derivatives (**3–12**), and 1,3-diphenyl-5-substituted-1H-thieno[2,3-c]pyrazoles (**14–30**). The evaluation of the antibacterial and antifungal activities of some derivatives is hereby included.

* To whom correspondence should be addressed. E-mail: assiut@frcu.eun.eg

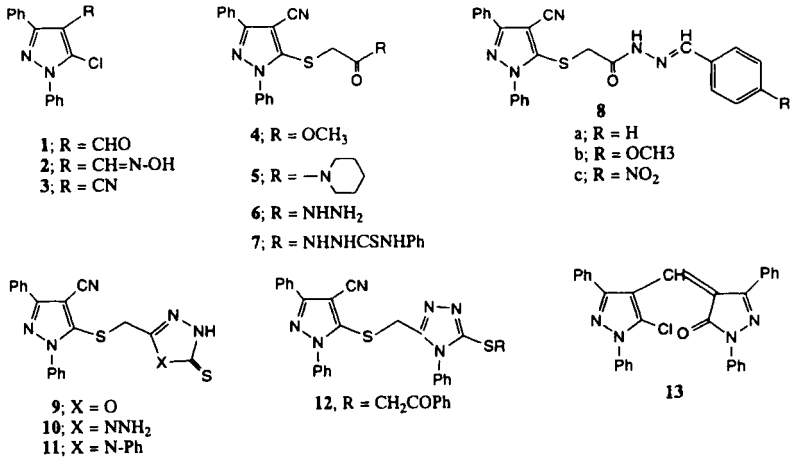
RESULTS AND DISCUSSION

Based on the important synthetic utility of many vicinal heterocyclic chlorocarboxaldehydes[15-18], the 5-chloro-1,3-diphenyl-1H-pyrazole-4-carboxaldehyde (**1**)[17] was used as a starting material in the synthesis of our target heterocycles.

Thus, **1** was allowed to condense with hydroxylamine to afford the aldoxime **2** which was dehydrated by heating in boiling acetic anhydride to give the corresponding pyrazolecarbonitrile **3**. When the latter compound (**3**) was reacted with methyl thioglycolate in methanol containing anhydrous sodium carbonate, the product was the methyl (4-cyano-1,3-diphenyl-1H-pyrazol-5-ylthio) acetate (**4**)which gave the acetamido derivative **5** upon treatment with piperidine. The reaction of the ester **4** with hydrazine hydrate led to the formation of (4-cyano-1,3-diphenyl-1H-pyrazol-5-ylthio) acethydrazide (**6**).

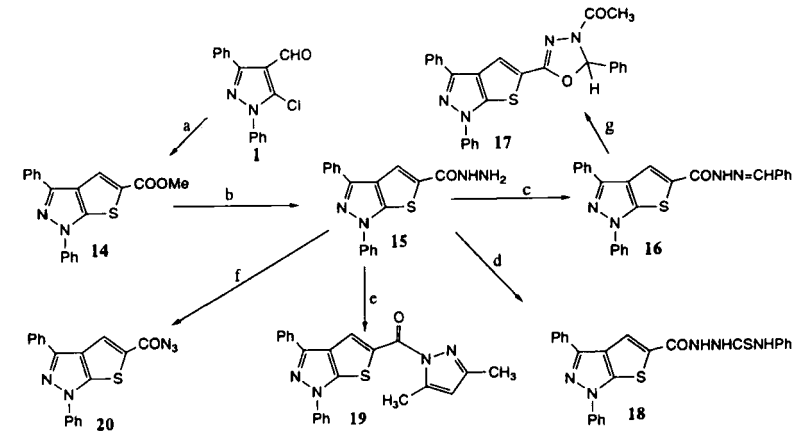
Compound **6** served as a facile point of departure to a variety of S-substituted mercaptopyrazoles **7–12**. Thus, the interaction of the hydrazide **6** with phenyl isothiocyanate, aromatic aldehydes and carbon disulfide gave the corresponding thiosemicarbazide **7**, hydrazones **8a-c** and oxadiazolethione **9** respectively. The thiosemicarbazide **7** was subjected to a cyclization reaction by heating in an ethanolic sodium hydroxide solution to give the s-triazolethione **11**. However, the aminotriazolethione **10** was obtained by treatment of the oxadiazolethione **9** with an excess of hydrazine hydrate. When **11** was allowed to react with phenacyl bromide in boiling ethanol containing sodium acetate, the phenacylthio-s-triazole **12** was obtained (Scheme I). The condensation of **1** with 1,3- diphenyl-2-pyrazolin-5-one afforded the pyrazolinylidenemethylpyrazole **13** in a good yield (Scheme I).

On the other hand, an access to the synthesis of the thieno [2,3-c] pyrazole system involved the reaction of **1** with methyl thioglycolate in ethanol in the presence of anhydrous sodium carbonate which gave the methyl 1,3-diphenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate (**14**). The treatment of **14** with hydrazine hydrate afforded the corresponding hydrazide **15** which was used as a key intermediate in the synthesis of the other thienopyrazoles **16–30** (Scheme 2). Thus, the condensation of **15** with benzaldehyde yielded the hydrazone **16** which was cyclized into oxadiazoline derivative **17** by heating in boiling acetic anhydride. The carbohydrazide **15** was also reacted with phenyl isothiocyanate, acetylacetone and



SCHEME 1

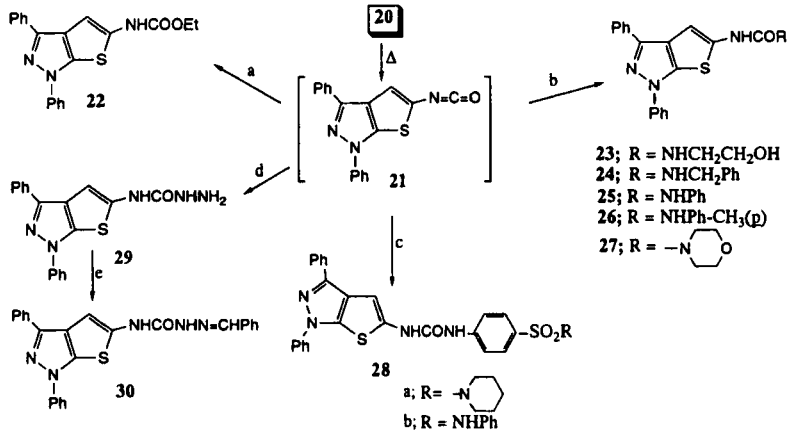
nitrous acid to give the thiosemicarbazide **18**, the dimethylpyrazolyl derivative **19** and the acid azide **20** respectively.



a; $HSCH_2COOMe$ /Na_2CO_3, b; NH_2NH_2, c; PhCHO, d; PhNCS, e; $CH_3COCH_2COCH_3$, f ; $NaNO_2$/AcOH, g; Ac_2O

SCHEME 2

Curtius rearrangement occured when the acid azide **20** was heated in boiling ethanol where the isocyanate intermediate **21** was formed (Scheme 3). The latter intermediate reacted concomitantly with the ethanol, used as a solvent, to give the corresponding ethyl carbamate **22**. When the alcohol was replaced by amines or conducted in dry toluene in the presence of N^1-substituted sulphanilamides, the corresponding urea derivatives **23–27** and **28a, b** were obtained. It is worthy to note that when the acid azide **20** was heated in an excess of hydrazine hydrate, Curtius rearrangement did not occur and the product proved to be the acid hydrazide **15**. However, when **20** was first heated in dry toluene to insure the Curtius rearrangement of **20** into the isocyanate **21** followed by the addition of an excess of hydrazine hydrate, the expected semicarbazide **29** was obtained. The latter compound (**29**) gave the benzylidene derivative **30** on condensation with benzaldehyde.



a, EtOH, b; Amine, c; $RSO_2C_6H_4NH_2$/toluene, d; toluene/NH_2NH_2, e; PhCHO

SCHEME 3

Some of the prepared compounds (**8c, 12, 14, 17, 22, 23, 26** and **28a**) were screened *in vitro* for their antibacterial activity against four different species of bacteria namely; *Pseudomonas aeruginosa, Escherichia coli, Bacillus cereus and Staphylococcus aureus* and for their antifungal activity against five species of fungi namely; *Alternaria alternata, Aspergillus flavus, Fusarium solani, Penicillium citrinum and Trichoderma pesii* using disc-diffusion method[19,20]. It is obvious that all compounds under investi-

gation were inactive against both the two species of Gram negative bacteria and the five species of fungi studied. However, concerning the Gram positive bacteria only four compounds **8c, 14, 17** and **28a** showed growth inhibition activity against *Staphylococcus aureus* (inhibition zones: **10, 25, 13** and **15** mm respectively).

EXPERIMENTAL

All melting points are uncorrected and were measured on a Gallan-Kamp melting point apparatus. IR spectra were run on a Pye-Unicam SP-3–100 Spectrophotometer using KBr disc technique. ^{1}H-NMR spectra were recorded on a Varian EM 390 90 MHz ^{1}H-NMR spectrometer in the suitable deuterated solvent using TMS as an internal standard. The elemental analyses were carried out on a Perkin Elmer 240 C elemental analyzer and the results were within ±0.4% of the calculated values.

5-Chloro-1,3-diphenyl-1H-pyrazole-4-carboxaldehyde (1)

This compound was prepared according to the reported method[17].

5-Chloro-1,3-diphenyl-1H-pyrazole-4-aldoxime (2)

To a mixture of **1** (5.65 g, 0.02 mol) and hydroxylamine hydrochloride (1.39 g, 0.02 mol) in ethanol (50 ml), sodium acetate trihydrate (2.72 g, 0.02 mol) was added. The reaction mixture was stirred at room temperature for 2 hrs. and then it was poured onto an ice-cold water. The product thus obtained was crystallized from ethanol as white crystals, m.p. 137–38°C, yield 82%. IR: υ cm^{-1} 3260 (OH). ^{1}H NMR (CDCl3): δ 8.50 (s, 1H, CH=N), 7.2–8.2 (m, 10H, Ar-H), 2.6 (s, 1H, OH).

Anal. Calcd. for $C_{16}H_{12}ClN_3O$:	C, 64.54; H, 4.06; N, 14.11; Cl, 11.91.
Found:	C, 64.75; H, 4.18; N, 14.37; Cl, 11.60.

5-Chloro-1,3-diphenyl-1H-pyrazole-4-carbonitrile (3)

Compound **2** (2.98 g, 0.01 mol) in redistilled acetic anhydride (50 ml) was heated under reflux for 3 hrs., concentrated and left to cool. The yellow

coloured precipitate was collected and recrystallized from methanol to give compound **3** in the form yellow crystals, m.p. 155–56°C, yield 80%. IR: υ cm^{-1} 2220, (CN). ^1H NMR (CDCl3): δ 7.20 – 8.20 (m, 10H, Ar-H).

Anal. Calcd. for $C_{16}H_{10}ClN_3$:	C, 68.70; H, 3.60; N, 15.02; Cl, 12.67.
Found:	C, 68.55; H, 3.62; N, 15.24; Cl, 13.00.

Methyl (4-cyano-1,3-diphenyl-1H-pyrazol-5-ylthio)acetate (4)

To a suspension of **3** (2.80 g, 0.01 mol) and methyl thioglycolate (1.06 g, 0.01 mol) in methanol (40 ml), anhydrous sodium carbonate (1.59 g, 0.015 mol) was added. The reaction mixture was refluxed for 3 hrs., cooled and then poured onto an ice-cold water. The precipitated solid was collected and recrystallized from diluted ethanol to give **4** in the form of colourless needles, m.p. 160–61°C, 73%. IR: υ cm^{-1} 2220, (CN) and 1730 (C=O). ^1H NMR ($CDCl_3$): δ 7.20 – 8.20 (m, 10H, Ar-H), 4.1 (s, 2H, CH_2), 3.9 (s, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{15}N_3O_2S$:	C, 65.31; H, 4.33; N, 12.03; S, 9.18.
Found:	C, 65.06; H, 4.17; N, 12.33; S, 9.00.

1,3-Diphenyl-5-piperidinocarbonylmethylthio-1H-pyrazole-4-carbonitrile (5)

A mixture of **4** (0.70 g, 0.002 mol) and piperidine (1.0 ml, 0.01 mol) in ethanol (20 ml) was refluxed for 5 hrs., then cooled and poured onto an ice-cold water. The solid thus separated was collected and recrystallized from diluted ethanol as white crystals, m.p. 162–63°C, yield 88%. IR: υ cm^{-1} 2230, (CN), and 1640 (C=O).

Anal. Calcd. for $C_{23}H_{22}N_4OS$:	C, 68.63; H, 5.51; N, 13.92; S, 7.96.
Found:	C, 68.68; H, 5.67; N, 13.77; S, 8.00.

(4-Cyano-1,3-diphenyl-1H-pyrazol-5-ylthio)acethydrazide (6)

A mixture of **4** (3.50 g, 0.01 mol) and hydrazine hydrate 99% (1.0 ml, 0.02 mol) in ethanol (40 ml) was refluxed for 2 hrs., then cooled and diluted with water. The product thus formed was collected and crystallized

from ethanol as colourless needles, m.p. 168–69°C, 90%. IR: υ cm^{-1} 3320–3100, ($NHNH_2$), 2210 (CN) and 1660 (C=O). ^1H NMR (DMSO-d6): δ 9.3 (br, 1H, NH), 7.2–8 2 (m, 10H, Ar-H), 4.3 (br., 2H, NH_2) and 4.0 (s, 2H, CH_2).

Anal. Calcd. for $C_{18}H_{15}N_5OS$:	C, 61.88; H, 4.33; N, 20.04; S, 9.18.
Found:	C, 61.77; H, 4.37; N, 20.30; S, 9.50.

N^1-(4-Cyano-1,3-diphenyl-1H-pyrazol-5-ylthio)acetyl-N^4-phenyl-3-thiosemicarbazide (7)

A mixture of **6** (3.50 g, 0.01 mol) and phenyl isothiocyanate (1.28 ml, 0.01 mol) in ethanol (80 ml) was refluxed for 3 hrs. After cooling, the solid thus formed was collected and recrystallized from ethanol as white needles, m.p. 190–91°C, yield 81%. IR: υ cm^{-1} 3360, 3140 (NH), 2210 (CN) and 1690 (C=O). ^1H NMR (CF_3CO_2D): δ 7.30–8.00 (m, 15H, Ar-H), 3.90 (s, 2H, CH_2).

Anal. Calcd. for $C_{25}H_{20}N_6OS_2$:	C, 61.96; H, 4.16; N, 17.34; S, 13.23.
Found:	C, 62.12; H, 4.18; N, 17.21; S, 13.30.

N-Arylidene-(4-cyano-1,3-diphenyl-1H-pyrazol-5-ylthio) acethydrazides (8a-c). General procedure

To a solution of **6** (0.7 g, 0.002 mol) in ethanol (20 ml), an ethanolic solution of the appropriate aldehyde (0.002 mol) was added. The resulting mixture was refluxed for 2 hrs. After cooling, the solid precipitate was collected and recrystallized from ethanol.

N-Benzylidene-(4-cyano-1,3-diphenyl-1H-pyrazol-5-ylthio) acethydrazide (8a)

White crystals, m.p. 195–96°C, yield 95%. IR: υ cm^{-1} 3180, (NH), 2210 (CN) and 1650 (C=O). ^1H NMR (DMSO-d_6): δ 11.4 (s, 1H, NH), 7.2–8.2 (m, 16H, Ar-H + N=CH), 4.00 (s, 2H, CH_2).

Anal. Calcd. for $C_{25}H_{19}N_5OS$:	C, 68.63; H, 4.38; N, 16.01; S, 7.33.
Found:	C, 68.85; H, 4.41; N, 15.76; S, 7.00.

N-4-Anisylidene-(4-cyano-1,3-diphenyl-1H-pyrazol-5-ylthio) acethydrazide (8b)

White crystals, m.p. 174–75°C, yield 94%. IR: υ cm^{-1} 3200, (NH), 2210 (CN) and 1660 (C=O). ^1H NMR (CF_3CO_2D): δ 8.60 (s, 1H, CH=N), 6.8–8.0 (m, 14H, Ar-H), 3.70–4.10 (m, 5H, SCH_2 + CH_3).

Anal. Calcd. for $C_{26}H_{21}N_5O_2S$:	C, 66.79; H, 4.53; N, 14.98; S, 6.86.
Found:	C, 66.46; H, 4.67; N, 15.23; S, 6.50.

N-4-Nitrobenzylidene-(4-cyano-1,3-diphenyl-1H-pyrazol-5-ylthio) acethydrazide (8c)

Yellow crystals from ethanol, m.p. 219–20°C, yield 93%. IR: υ cm^{-1} 3190, (NH), 2210 (CN) and 1650 (C=O). ^1H NMR (DMSO-d_6): δ 11.6 (s, 1H, NH), 7.3–8.2 (m, 15H, Ar-H + N=CH), 4.00 (s, 2H, CH_2).

Anal. Calcd. for $C_{25}H_{18}N_6O_3S$:	C, 62.23; H, 3.76; N, 17.42; S, 6.64.
Found:	C, 62.07; H, 3.80; N, 17.11; S, 6.80.

(4-Cyano-1,3-diphenyl-1H-pyrazol-5-ylthio)methyl-1,3,4-oxadiazole-5(4H)-thione (9)

To a solution of **6** (2.80 g, 0.008 mol) in pyridine (30 ml), carbon disulfide (3 ml) was added The resulting mixture was heated on a water bath for 7 hrs., then cooled and poured onto ice-cold water. The precipitated product was collected and crystallized from methanol as white needles, m.p. 189–90°C, yield 75%. IR: υ cm^{-1} 3200, (NH), 2220 (CN). ^1H NMR (CF_3CO_2D): δ 7.5–8.0 (m, 10H, Ar-H), 4.0 (s, 2H, CH_2).

Anal. Calcd. for $C_{19}H_{13}N_5OS_2$:	C, 58.30; H, 3.35; N, 17.89; S, 16.38.
Found:	C, 58.51; H, 3.38; N, 17.50; S, 16.20.

4-Amino-3-(4-cyano-1,3-diphenyl-1H-pyrazol-5-ylthio)methyl-s-triazole-5(1H)-thione (10)

A mixture of **9** (0.78 g, 0.002 mol) and hydrazine hydrate 99% (1 ml, 0.02 mol) in ethanol (20 ml) was refluxed for 5 hrs. and left to cool. The precipitated solid was collected and recrystallized from diluted. ethanol as white needles, m.p. 220–21°C, yield 70%. IR: υ cm^{-1} 3320, 3220 (NH_2),

3100 (NH) and 2210 (CN). ^{1}H NMR (DMSO-d_6): δ 13.4 (s, 1H, NH), 7.4–8.0 (m, 10H, Ar-H), 5.2 (s, 2H, NH_2), 4.2 (s, 2H, CH_2).

Anal. Calcd. for $C_{19}H_{15}N_7S_2$:	C, 56.28; H, 3.73; N, 24.18; S, 15.81.
Found:	C, 56.00; H, 3.71; N, 24.47; S, 15.90.

3-(4-Cyano-1,3-diphenyl-1H-pyrazol-5-ylthio)methyl-4-phenyl-s-triazole-5(1H)-thione (11)

Compound **7** (2.42 g, 0.005 mol) in an ethanolic sodium hydroxide solution 8% (20 ml) was heated on a water bath for 4 hrs. The reaction mixture was concentrated, diluted with cold water and neutralized with diluted HCl at 5–10°C. The crude product was filtered off, washed with water and crystallized from ethanol as white crystals, m.p. 172–73°C, yield 70%. IR: υ cm^{-1} 3100 (NH) and 2210 (CN). ^{1}H NMR ($CDCl_3$): δ 13.0 (s, 1H, NH), 7.2–8.2 (m, 15H, Ar-H), 3.9 (s, 2H, SCH_2).

Anal. Calcd. for $C_{25}H_{18}N_6S_2$:	C, 64.36; H, 3.89; N, 18.01; S, 13.74.
Found:	C, 64.07; H, 3.95; N, 18.11; S, 13.90.

3-(4-Cyano-1,3-diphenyl-1H-pyrazol-5-ylthio)methyl-5-phenacylthio-4-phenyl-s-triazole (12)

A mixture of **11** (0.47 g, 0.001 mol), phenacyl bromide (0.2 g, 0.001 mol) and sodium acetate trihydrate (0.27 g, 0.002 mol) in ethanol (15 ml) was refluxed for 2 hrs. The solid thus formed on cooling was filtered, washed with water and recrystallized from methanol as white crystals m.p. 137–38°C, yield 93%. IR: υ cm^{-1} 2220 (CN) and 1680 (C=O). ^{1}H NMR (DMSO-d_6): δ 7.2–8.0 (m, 20H, Ar-H), 4.9 (s, 2H, CH_2CO), 4.2 (s, 2H, SCH_2).

Anal. Calcd. for $C_{33}H_{24}N_6OS_2$:	C, 67.79; H, 4.14; N, 14.37; S, 10.97.
Found:	C, 67.92; H, 4.19; N, 14.19; S, 10.75.

5-Chloro-1,3-diphenyl-4-(1,5-dihydro-1,3-diphenyl-5-oxo-4-pyrazolylidene)methylpyrazole (13)

A mixture of **1** (1.4 g, 0.005 mol) and 1,3-diphenyl-2-pyrazoline-5-one (1.1 g, 0.005 mol) in ethanol (20 ml) was refluxed for one hour. The prod-

uct thus formed was collected and recrystallized from ethanol as orange crystals m.p. 255–56°C, yield 90%. IR: υ cm^{-1} 1620 (C=O). ^1H NMR ($CDCl_3$): δ 6.7–8.0 (m, 20H, Ar-H), 5.0 (s, 1H, CH=C).

Anal. Calcd. for $C_{31}H_{21}ClN_4O$:	C, 74.32; H, 4.23; N, 11.18; Cl, 7.08.
Found:	C, 74.08; H, 4.26; N, 11.07; Cl, 6.80.

Methyl 1,3-diphenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate (14)

To a mixture of **1** (8.50 g, 0.03 mol) and methyl thioglycolate (3.2 g, 0.03 mol) in methanol (150 ml), anhydrous sodium carbonate (5.3 g, 0.05 mol) was added The reaction mixture was heated under reflux for 2 hrs. After cooling the solid precipitate was collected and recrystallized from methanol as white needles, m.p. 185–86°C, yield 66%. IR: υ cm^{-1} 1700 (C=O). ^1H NMR ($CDCl_3$): δ 7.2–8.2 (m, 11H, Ar-H + thoiphene-H), 3.9 (s, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{14}N_2O_2S$:	C, 68.25; H, 4.22; N, 8.38; S, 9.59.
Found:	C, 68.50; H, 4.21; N, 8.63; S, 9.45.

1,3-Diphenyl-1H-thieno[2,3-c]pyrazole-5-carbohydrazide (15)

A mixture of **14** (6.7 g, 0.02 mol) and hydrazine hydrate 99% (2.0 ml, 0.04 mol) in ethanol (100 ml) was heated under refluxed for 3 hrs. and then allowed to cool. The white product thus formed was collected and recrystallized from ethanol as white needles, m.p. 221–22°C, yield 95%. IR: υ cm^{-1} 3340–3190 ($NHNH_2$) and 1640 (C=O). ^1H NMR (DMSO-d_6): δ 9.7 (br, 1H, NH), 7.3–8.3 (m, 11H, Ar-H + thiophene-H), 4.5 (br, 2H, NH_2).

Anal. Calcd. d for $C_{18}H_{14}N_4OS$:	C, 64.65; H, 4.22; N, 16.75; S, 9.59.
Found:	C, 64.61; H, 4.43; N, 16.46; S, 9.50.

N-Benzylidene-1,3-diphenyl-1H-thieno[2,3-c]pyrazole-5-carbohydrazide (16)

A mixture of **15** (1.0 g, 0.003 mol) and benzaldehyde (0.32 g, 0.003 mol) in ethanol (25 ml) was refluxed for 3 hrs. and left to cool. The precipitate which formed on cooling was collected and recrystallized from dioxane as

white needles, m.p. 319–20°C, yield 90%. IR: υ cm^{-1} 3190 (NH) and 1650 (C=O). ^1H NMR (CF_3CO_2D): δ 8.60 (s, 1H, N=CH), 7.3–8.3 (m, 16H, Ar-H + thiophene-H).

Anal. Calcd. for $C_{25}H_{18}N_4OS$:	C, 71.07; H, 4.29; N, 13.26; S, 7.59.
Found:	C, 71.28; H, 4.40; N, 13.17; S, 7.80.

4-Acetyl-4,5-dihydro-2-(1,3-diphenyl-1H-thieno[2,3-c]pyrazol-5-yl)-5-phenyl-1,3,4-oxadiazole (17)

Compound **16** (0.85 g, 0.002 mol) in redistilled acetic anhydride (30 ml) was heated under reflux for 4 hrs. The reaction mixture was cooled, poured onto water and allowed to stand at room temperature for 2 hrs. The solid precipitate was collected and crystallized from ethanol as white crystals, m.p. 170–71°C, yield 70%. IR: υ cm^{-1} 1650 (C=O). ^1H NMR ($CDCl_3$): δ 7.0–8.1 (m, 16H, Ar-H + thiophene-H), 3.0 (s, 1H, oxadiazole), 2.3 (s, 3H, CH_3).

Anal. Calcd. for $C_{27}H_{20}N_4O_2S$:	C, 69.81; H, 4.34; N, 12.06; S, 6.90.
Found:	C, 70.11; H, 4.32; N, 12.33; S, 7.00.

N^1-(1,3-Diphenyl-1H-thieno[2,3-c]pyrazol-5-yl)-N^4-phenyl-3-thiosemicarbazide (18)

A mixture of **15** (0.67 g, 0.002 mol) and phenyl isothiocyanate (0.26 ml, 0.002 mol) in ethanol (15 ml) was refluxed for 4 hrs. and left to cool. The white solid was collected and recrystallized from dioxane in the form of white needles, m.p. 274–275°C, yield 83%. IR: υ cm^{-1} 3330, 3220, 3160 (NH) and 1650 (C=O. ^1H NMR (DMSO-d_6): δ 10.7 (br, 1H, NH), 9.9 (s, 1H, NH), 8.4 (s, 1H, NH), 7.0–8.2 (m, 16H, Ar-H + thiophene-H).

Anal. Calcd. for $C_{25}H_{19}N_5OS_2$:	C, 63.95; H, 4.08; N, 14.91; S, 13.65.
Found:	C, 63.90; H, 4.11; N, 14.78; S, 13.45.

5-(3,5-Dimethylpyrazol-1-ylcarbonyl)-1,3-diphenyl-1H-thieno[2,3-c]pyrazole (19)

A mixture of **15** (0.67 g, 0.002 mol) and acetylacetone (1.0 ml, 0.01 mol) was gently heated under reflux for one hour. The reaction mixture was

then triturated with ethanol (10 ml) and allowed to cool. The solid precipitate was collected by filtration and recrystallized from acetic acid as white crystals, m.p. 218–19°C, yield 78%. IR: υ cm^{-1} 1660 (C=O). ^1H NMR ($CDCl_3$): δ 8.6 (s, 1H, thiophene-H), 7.2–8.1 (m, 10H, Ar-H), 6.0 (s, 1H, pyrazole-H), 2.6 (s, 3H, CH_3), 23 (s, 3H, CH_3).

Anal. Calcd. for $C_{23}H_{18}N_4OS$:	C, 69.33; H, 4.55; N, 14.06; S, 8.05.
Found:	C, 69.39; H, 4.86; N, 14.00; S, 8.15.

1,3-Diphenyl-1H-thieno[2,3-c]pyrazole-5-carboxylic acid azide (20)

To a chilled suspension of **15** (3.34 g, 0.01 mol) in glacial acetic acid (100 ml), a cold solution of sodium nitrite (10 ml, 33%) was added dropwise with stirring. After completion of addition, stirring was continued for one hour. The solid product thus formed was filtered, washed with water, air dried and applied in the next reactions without purification, m.p. 151°C (decomp.), yield 70%. IR: υ cm^1 2150 (N3) and 1670 (C=O). ^1H NMR ($CDCl_3$): δ 7.20 – 8.20 (m, 11H, Ar-H + thiophene-H).

Anal. Calcd. for $C_{18}H_{11}N_5OS$:	C, 62.60; H, 3.21; N, 20.28; S, 9.28.
Found:	C, 62.49; H, 3.27; N, 20.48; S, 9.00.

Ethyl N-(1,3-diphenyl-1H-thieno[2,3-c]pyrazol-5-yl)carbamate (22)

Compound **20** (0.69 g, 0.002 mol) was heated under reflux in ethanol (20 ml) for 2 hrs. The reaction mixture was then concentrated and left to cool. The crystalline solid product was collected and recrystallized from ethanol as pale yellow needles, m.p. 170–71°C, yield 65%. IR: υ cm^{-1} 3340, (NH) and 1705 (C=O). ^1H NMR ($CDCl_3$): δ 7.2–8.2 (m, 12H, Ar-H + NH + thiophene-H), 4.3 (q, 2H, CH_2), 1.4 (t, 3H, CH_3).

Anal. Calcd. for $C_{20}H_{17}N_3O_2S$:	C, 66.10; H, 4.71; N, 11.56; S, 8.82.
Found:	C, 66.26; H, 4.75; N, 11.81; S, 8.70.

Reaction of acid azide 20 with amines: Formation of the derivatives 23, 24, 25, 26 and 27. General procedure

A mixture of **20** (0.69 g, 0.002 mol) and an excess (0.04 mol) of the respective amine (ethanolamine, benzylamine, aniline, p-toluidine or mor-

pholine) was gently heated at 100–120°C for 30 minutes. The reaction mixture was then triturated with ethanol (5 ml) and left to cool. The crystalline precipitate was collected by filtration and recrystallized.

4.22.1. N^1-(1,3-Diphenyl-1H-thieno[2,3-c]pyrazol-5-yl)-N^3-(2-hydroxyethyl) urea (23)

White crystals from aqueous ethanol, m.p. 207–08°C, yield 82%. IR: υ cm^{-1} 3420–3100 (OH, NH) and 1630 (C=O). ^1H NMR (DMSO-d_6): δ 8.5 (s, 1H, NH), 8.3 (s, 1H, NH), 7.2–8.1 (m, 11H, Ar-H + thiophene-H), 3.3–3.8 (m, 5H, $2CH_2$ + OH).

Anal. Calcd. for $C_{20}H_{18}N_4O_2S$:	C, 63.48; H, 4.79; N, 14.80; S, 8.47.
Found:	C, 63.29; H, 4.60; N, 14.71; S, 8.40.

N^1-Benzyl-N^3-(1,3-Diphenyl-1H-thieno[2,3-c]pyrazol-5-yl)urea (24)

White crystals from aqueous ethanol, m.p. 346–47°C, yield 70%. IR: υ cm^{-1} 3370 (NH), 3120 (NH) and 1630 (C=O).

Anal. Calcd. for $C_{25}H_{20}N_4OS$:	C, 70.73; H, 4.75; N, 13.20; S, 7.55.
Found:	C, 70.76; H, 4.65; N, 13.11; S, 7.70.

N^1-(1,3-Diphenyl-1H-thieno[2,3-c]pyrazol-5-yl)-N^3-phenylurea (25)

White crystals from methanol, m.p. 305–06°C, yield 87%. IR: υ cm^{-1} 3250 (NH) and 1630 (C=O). ^1H NMR (DMSO-d_6): δ 9.6 (s, 1H, NH), 8.8 (s, 1H, NH), 6.9–8.0 (m, 16H, Ar-H + thiophene-H).

Anal. Calcd. for $C_{24}H_{18}N_4OS$:	C, 70.22; H, 4.42; N, 13.65; S, 7.81.
Found:	C, 70.08; H, 4.48; N, 13.86; S, 7.70.

N^1-(1,3-Diphenyl-1H-thieno[2,3-c]pyrazol-5-yl)-N^3-p-tolylurea (26)

White crystals, m.p. 301–02°C, yield 90%. IR: υ cm^{-1} 3250 (NH) and 1630 (C=O). ^1H NMR (DMSO-d_6): δ 9.7 (s, 1H, NH), 8.9 (s, 1H, NH), 6.9–8.1 (m, 15H, Ar-H + thiophene-H), 2.3 (s, 3H, CH_3).

Anal. Calcd. for $C_{25}H_{20}N_4OS$:	C, 70.73; H, 4.75; N, 13.20; S, 7.55.
Found:	C, 70.55; H, 4.73; N, 13.51; S, 7.60.

1,3-Diphenyl-5-morpholinocarbonylamino-1H-thieno[2,3-c] pyrazole (27)

White crystals from methanol, m.p. 168–69°C, yield 77%. IR: υ cm^{-1} 3450 (NH) and 1620 (C=O). ^1H NMR ($CDCl_3$): δ 7.2–8.0 (m, 12H, Ar-H + NH + thiophene-H), 3.7–3.8 (m, 8H, $4CH_2$).

Anal. Calcd. for $C_{22}H_{20}N_4O_2S$:	C, 65.33; H, 4.98; N, 13.85; S, 7.93.
Found:	C, 65.67; H, 5.03; N, 13.74; S, 8.15.

Reaction of acid azide 20 with N^1-substituted sulphanilamides; Formation of the urea derivatives (28a, b). General procedure

A mixture of **20** (0.69 g, 0.002 mol) and the respective sulphanilamide derivative (0.002 mol) in dry toluene (15 ml) was heated under reflux for 3 hrs. The precipitate thus formed on cooling was collected and recrystallized from dioxane as fine white needles.

N^1-(1,3-Diphenyl-1H-thieno[2,3-c]pyrazol-5-yl)-N^3-[4-(piperidinosulphonyl)phenyl]urea (28a)

m.p. 263–65°C, yield 78%. IR: υ cm^{-1} 3300 (NH) and 1630 (C=O). ^1H NMR (DMSO-d_6): δ 9.9 (s, 1H, NH), 9.5 (s, 1H, NH), 7.0–8.1 (m, 15H, Ar-H + thiophene-H), 2.9 (t, 4H, $2CH_2$), 1.5 (m, 6H, $3CH_2$).

Anal. Calcd. for $C_{29}H_{27}N_5O_3S_2$:	C, 62.46; H, 4.88; N, 12.56; S, 11.50.
Found:	C, 62.78; H, 4.72; N, 12.30; S, 11.50.

N^1-(1,3-Diphenyl-1H-thieno[2,3-c]pyrazol-5-yl)-N^3-[4-(phenylaminosulphonyl)phenyl]urea (28b)

m.p. 278–79°C, yield 81%. IR: υ cm^{-1} 3300, 3200 (NH) and 1650 (C=O). ^1H NMR (DMSO-d_6): δ 9.8 (s, 1H, NH), 8.9 (br, 2H, 2NH), 6.9–8.2 (m, 20H, Ar-H + thiophene-H).

Anal. Calcd. for $C_{30}H_{23}N_5O_3S_2$:	C, 63.70; H, 4.10; N, 12.38; S, 11.34.
Found:	C, 63.71; H, 4.16; N, 12.01; S, 11.10.

Reaction of 20 with hydrazine hydrate

A mixture of the acid azide **20** (0.69 g, 0.002 mol) and hydrazine hydrate (2 ml, 0.04 mol) was 10 refluxed for 30 minutes. The reaction mixture was then triturated with ethanol (15 ml) and allowed to cool. The precipitate was collected and recrystallized from ethanol as white needles. This compound was identified as 1,3-diphenyl-1H-thieno[2,3-c]pyrazole-5-carbohydrazide (**15**)which was identical to that obtained from the ester **14** in all aspects.

N^4-(1,3-Diphenyl-1H-thieno[2,3-c]pyrazol-5-yl)semicarbazide (29)

Compound **20** (1.38 g, 0.004 mol) in dry toluene (20 ml) was heated under reflux for one hour. After cooling hydrazine hydrate (2 ml; 0.04 mol) was added and the resulting mixture was refluxed for two hrs. The solid precipitate obtained after cooling was collected and recrystallized from ethanol as white crystals, m.p. 231–33°C, yield 70%. IR: υ cm^{-1} 3400–3200 (NH and NH_2) and 1660 (C=O). ^1H NMR (DMSO-d_6): δ 9.8 (s, 1H, NH), 9.5 (s, 1H, NH), 7.0–8.1 (m, 11H, Ar-H + thiophene-H), 4.6 (br, 2H, NH_2).

Anal. Calcd. for $C_{18}H_{15}N_5OS$:	C, 61.88; H, 4.33; N, 20.04; S, 9.18.
Found:	C, 61.80; H, 4.51; N, 20.17; S, 9.00.

N^1-Benzylidene-N^4-(1,3-diphenyl-1H-thieno[2,3-c]pyrazol-5-yl)semicarbazide (30)

A mixture of **29** (1.75 g, 0.005 mol) and benzaldehyde (0.53 g, 0.005 mol) in ethanol (30 ml) was refluxed for 2 hrs. On cooling, the formed precipitate was collected and recrystallized from dioxane to give white crystals, m.p. 278–79°C, yield 86%. IR: υ cm^{-1} 3300 (NH), 3200 (NH) and 1670 (C=O). ^1H NMR (DMSO-d_6): δ 10 (s, 1H, NH), 9.7 (s, 1H, NH), 7.2–8.2 (m, 17H, Ar-H + N=CH + thiphene-H).

Anal. Calcd. for $C_{25}H_{19}N_5OS$:	C, 68.63; H, 4.38; N, 16.01; S, 7.33.
Found:	C, 68.47; H, 4.32; N, 16.26; S, 7.30.

Antimicrobial Testing

The tested compounds were dissolved in DMSO to get a solution of 1% concentration. Filter paper discs (Whatman No. 3 filter paper, 5 mm diameter) were saturated with this former solution. The saturated filter paper discs were placed on the surface of solidified Nutrient agar dishes seeded by the test bacteria and Czapekís Dox agar dishes seeded by the test fungi. The inhibition zones were measured in mm. at the end of an incubation period of 48 hrs. (at 37°C for the bacteria and at 28°C for the fungi).

References

1. V.M. Barot, Asian J. Chem., **8**, 565 (1996).
2. N.S. Habib, G.G. Tawil, **49**, 42 (1981).
3. A.W. Raut, A.G. Doshi, Orient. J. Chem., **12**, 79 (1996).
4. S. Devi, P.Mitro, S.b. Mishra, A. S. Mittra, J. Indian Chem. Soc., **60**, 679 (1983).
5. A.I.Eid, M.A. Kira, H.H. Fahmy, J. Pharm. Belg., **33**, 303 (1978); Chem. Abstr., **90**, 152073 (1979).
6. G. Menozzi, L. Mosti, P.Schenone, M. D'Amico, A. Filippelli, F. Rossi, Farmaco, **47**, 1495 (1992).
7. D. Briel, Pharmazie, **50**, 675 (1995).
8. D. H. Kim, A.A. Santilli, US Pat. 3, 649, 641 (1972); Chem. Abstr., **76**, 140803h (1972).
9. E.A. Bakhite, Collect. Czech. Chem. Commun., **57**, 2359 (1992).
10. E.A. Bakhite, A.A. Geies, A.M. Kamal El-Dean, H.S. El-Kashef, Phosphorus, Sulfur and Silicon, **104**, 143 (1995).
11. A.A. Geies, E.A. Bakhite, H.S. El-Kashef, Pharmazie, **35**, 686 (1998).
12. A.A. Abdel-Hafez, A.M. Kamal El-Dean, A.A.Hassan, H.S. El-Kashef, S. Rault, M. Robba, J. Heterocyclic Chem., **33**, 431 (1996).
13. H. El-Kashef, S.Rault, J.C. Lancelot, M. Robba, J. Heterocyclic Chem., **23**, 161 (1986).
14. Sh. Radwan, M.S. Abbady, H.S. El-Kashef, Phosphorus, Sulfur and Silicon, **89**, 193 (1994).
15. J.Becher, P.L. Jorgensen, K. Pluta, N.J. Karke, B. Fält-Hansen, J. Org. Chem., **57**, 2127 (1992).
16. R.A. Pawar, A.P. Rajput, Indian J. Chem. **28B**, 866 (1989).
17. A. Babaqi, A. El-Shekeil, M. Hassan, S. Shiba, Heterocycles, **27**, 2119 (1988).
18. J. Becher, P.H. Olesen, K. Brondum, Heterocycles, **24**, 2299 (1986).
19. L.P. Carrod, F.D. Grady, Antibiotic and Chemotherapy, 3rd Edition., Churchill Livingston, Edinburgh/London, p. 477 (1972).
20. A. Cremer, Antibiotic sensitivity and assay tests, 4th Edition, Butterworth and Co Ltd-London, p. 521. (1980).