# Thieno[2,3-*c*]pyrazoles and related heterocycles

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5-Chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxaldehyde (**1**) was converted, *via* the oxime **2**, into the chloronitrile **3**. Treatment of compound **3** with methyl thioglycolate gave the novel methyl 4-amino-3-methyl-1-phenyl-1*H*-thieno [2,3-*c*]pyrazole-5-carboxylate (**4**). This with 2,5-dimethoxytetrahydrofuran gave the pyrrolyl ester **5**. Hydrazinolysis of the ester **5** gave the carbohydrazide derivative **6** which was used in the synthesis of substituted heterocycles.

**Keywords:** pyrazoles, pyrroles, 1,2,4-triazoles, 1,3,4-oxadiazoles, fused pyrazoles, thiophenes, hydrazides

Several heterocycles containing the pyrazole nucleus are known to possess biological activity.[1-6] Thieno[3,4-*c*]pyrazoles are a class of biologically active compounds currently employed in the field of medicinal chemistry owing to their remarkable anti-inflammatory,[7,8] analgesic and antithrombotic activities, also for the treatment of cardiovascular or cerebrovascular diseases, and hyperglycemia.[9] Thieno[3,2-*c*]pyrazoles are used in the treatment of hypertension and glaucoma.[10]

Thieno[2,3-*c*]pyrazoles on the other hand, represent a class of heterocyclic compounds which has received very little attention; few references dealing with this heterocyclic system have been reported.[11-17] To the best of our knowledge no reports have appeared in the literature since our last publication on this topic in 2000.[18]

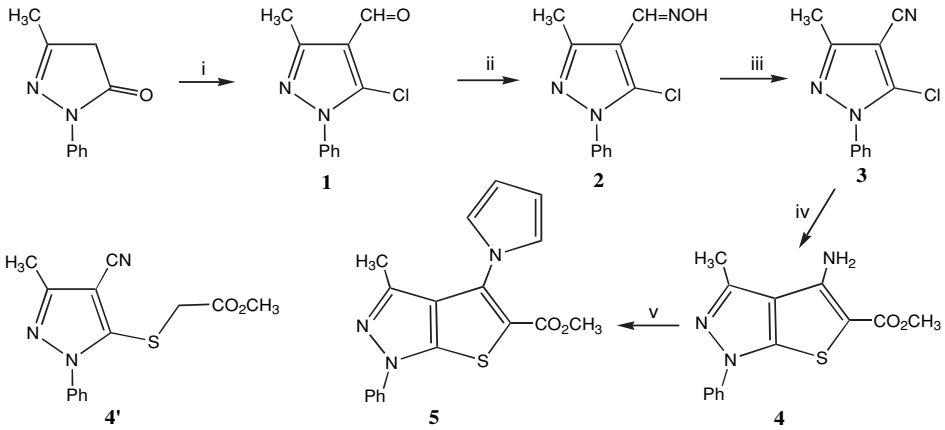
In continuation of our interest in the synthesis of fused thiophenes of biological importance,[7, 18-20] we describe herein the synthesis of the title heterocycles. 5-Chloro-3-methyl-1-phenyl-1*H*-pyrazole-3-carboxaldhyde **1** was prepared by a Vilsmeier–Haack reaction[16, 21-25] and used in the synthesis of our target heterocycles. Thus, when **1** was allowed to interact with hydroxylamine in ethanol at ambient temperature, the corresponding oxime **2** was obtained. The latter compound was subjected to dehydration in boiling acetic anhydride to give the chloro-nitrile **3**. Interaction of compound **3** with methyl thioglycolate in boiling methanol containing fused potassium carbonate afforded methyl 4-amino-3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazole-5-carboxylate (**4**).

Several trials were made to improve the yield of the amino ester **4** by synthesis of the intermediate structure **4'** followed by cyclisation. However, this intermediate could not be obtained under various reaction conditions (the two reactants in boiling methanol using sodium acetate or triethylamine as a base), where the starting materials were recovered unchanged in each trial. The only procedure which gave a positive result was that using anhydrous potassium carbonate as a base in refluxing methanol. This procedure led directly (although in poor yield, 23%) to the amino ester **4**

The amino function of **4** could be easily converted into a pyrrol-1-yl group in a Paal-Knorr reaction on treatment with 2,5-dimethoxytetrahydrofuran in refluxing acetic acid following our previously reported[19] procedure, to give **5** (Scheme 1).

The pyrrolyl ester **5** with hydrazine hydrate afforded the corresponding hydrazide (**6**). Condensation of **6** with some aromatic aldehydes yielded the expected hydrazones (**7a–c**). The carbohydrazide **6** proved to be a versatile compound in the synthesis of several thieno[2,3-*c*]pyrazole derivatives. Thus, the oxadiazolethione **8** was obtained directly by the reaction of **6** with carbon disulfide in the presence of pyridine. The 1,2,4-triazolethione **10**, however, was obtained in two steps *via* the reaction of **6** with phenyl isothiocyanate, followed by heating the resulting aroylthiosemicarbazide (**9**) in aqueous NaOH. The thioamide groups of both **8** and **10** were readily methylated by methyl iodide in the presence of sodium acetate to give the corresponding methylthio derivatives **11** and **12** respectively (Scheme 2).

The interaction of **6** with an equimolar ratio of acetylacetone in refluxing ethanol led to a condensation reaction with the loss of one molecule of water, yielding the 4-oxo-2-penten-2-yl) carbohydrazide (**13**). However, using an excess of neat acetylacetone, two molecules of water were eliminated in a cyclodehydration reaction leading to the dimethylpyrazolyl




*Reagents:* i, $POCl_3$/DMF; ii, $H_2NOH.HCl$/EtOH/AcONa; iii, $Ac_2O$; iv, $HSCH_2CO_2CH_3$ / $K_2CO_3$ / $CH_3OH$; v, DMTHF

**Scheme 1**

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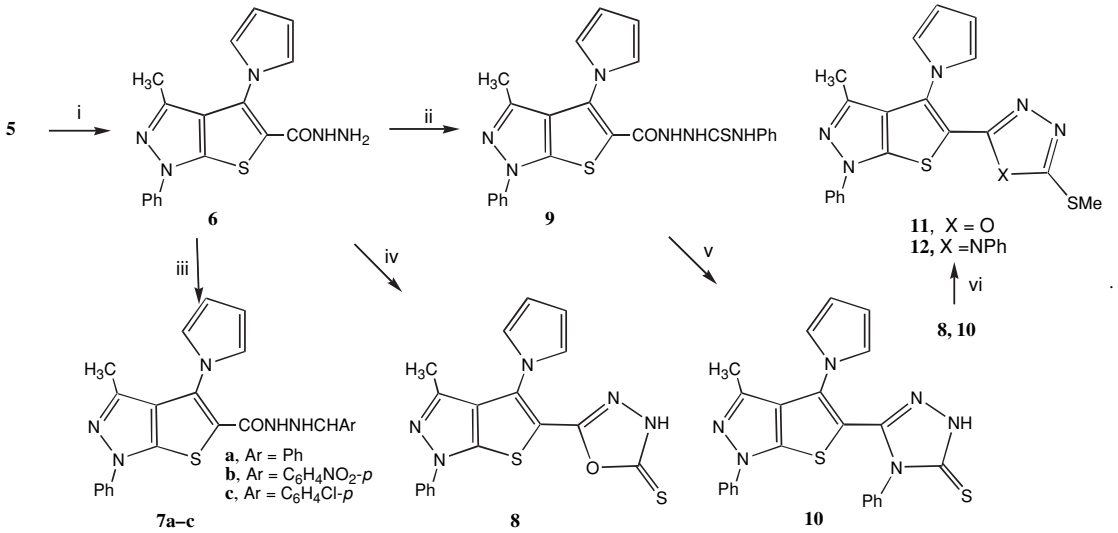



*Reagents:* i, $N_2H_4/H_2O$/EtOH; ii, PhNCS/EtOH; iii, ArCHO/EtOH; iv, $CS_2$/pyridine; v, NaOH; vi, MeI/EtOH/AcONa

**Scheme 2**

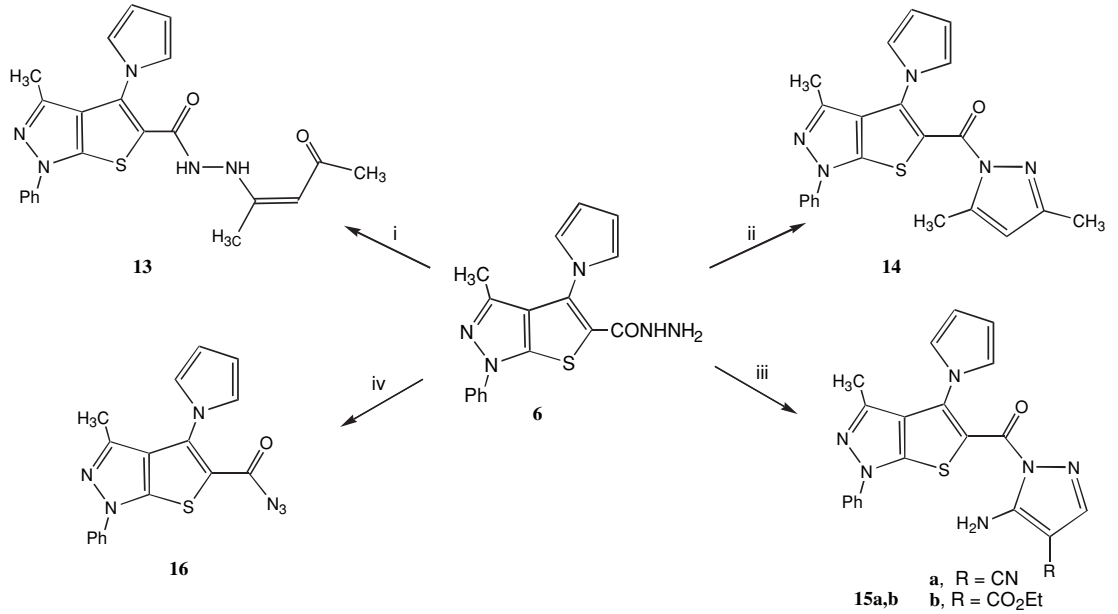
derivative **14.** The reaction of the carbohydrazide **6** with ethoxymethylenemalononitrile, and ethyl ethoxymethylene-cyanoacetate gave the substituted pyrazol-1-ylcarbonyl thieno[2,3-*c*]pyrazoles **15a,b** respectively (Scheme 3). Treatment of **6** with nitrous acid resulted in the formation of 3-methyl-1-phenyl-4-(pyrrol-1-yl)-1*H*-thieno[2,3-*c*]pyrazole-5-carbonyl azide (**16**) in a good yield.

The synthetic utility of the acid azide **16** as a key intermediate in the synthesis of new thienopyrazole derivatives is shown in Scheme 4. Thus, when **16** was heated with various alcohols, Curtius rearrangement occurred to give the isocyanate intermediate **17** which reacted with the alcohols to afford the corresponding urethanes **18a–d**. The symmetric disubstituted urea **19** was obtained when the acid azide **16** was heated in boiling water. The urea derivatives **20a,b** were obtained when the acid azide **16** was heated with aniline and morpholine, again *via* Curtius rearrangement. Attempts to hydrolyse the carbamates **18** to the amino-thienopyrazoles **21** by boiling with aqueous ethanolic sodium hydroxide were unsuccessful; the starting carbamates were recovered unchanged (Scheme 4).

When the acid azide **16** was heated in an inert solvent such as dry benzene and in absence of any other reactant, the Curtius rearrangement was followed by intramolecular ring closure to give the 5,7-dihydro-9-methyl-7-phenyl-4*H*-pyrazolo[4',3':4,5]thieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazin-4-one (**22**) (Scheme 4).

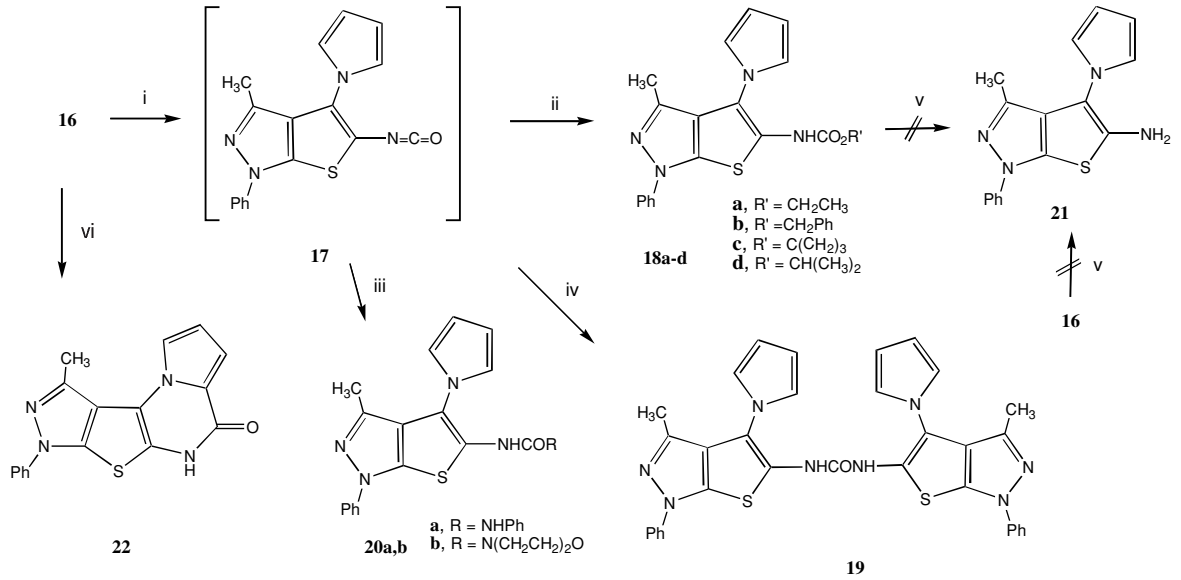
## Experimental

Melting points were measured on a Gallenkamp melting point apparatus. IR spectra were recorded on a Shimadzu 470 IR spectrophotometer using the KBr wafer technique. $^1$H NMR spectra were recorded on a Jeol LA 400 MHz FT NMR, Varian Unity-plus 300 (300 MHz) and Varian EM-390 (90 MHz) spectrometer with TMS as internal standard. Mass spectra were measured in EI mode




*Reagents:* i, $(CH_3CO)_2CH_2$/EtOH; ii, $(CH_3CO)_2CH_2$; iii, EtOCH=C(CN)R/EtOH; iv, $NaNO_2$/AcOH

**Scheme 3**




*Reagents:* i, Δ; ii, alcohols R'OH; iii, amines RH; iv, $H_2O$; v, $NaOH/H_2O$; vi, dry benzene, Δ

**Scheme 4**

on a Jeol JMS-600 mass spectrometer and the elemental analyses were carried out using a Perkin-Elmer 240C microanalyser.

*5-Chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxaldehyde* (**1**): This compound was prepared according to the literature.[16, 21-25]

*5-Chloro-3-methyl-1-phenyl-1H-pyrazole-4-aldoxime* (**2**):[26] To the aldehyde **1** (4.45 g, 0.02 mol) in ethanol (50 ml), hydroxylamine hydrochloride (1.39 g, 0.02 mol) and sodium acetate (2.72 g, 0.02 mol) were added. The reaction mixture was stirred at room temperature for 2 h. After cooling, it was poured into ice-cold water. The solid product which separated was filtered off and recrystallised from methanol/water to give yellow needles (4.1g, 86%), m.p. 139–140 °C. IR: $\nu_{max}$ 3260 (OH) 3080 (CH arom), 2960 (CH aliph), 1640 $cm^{-1}$ (C=N). $^1H$ NMR ($CDCl_3$): δ 2.47 (s, 3H, $CH_3$); 7.44 (m, 5H, Ar–H); 8.07 (s, 1H, CH=N); 8.33 (s, 1H, OH). MS: *m/z* 237 ($M^+$, 28%), 235 ($M^+$, 52%).

*5-Chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbonitrile* (**3**):[26-28] The oxime **2** (0.224 g, 0.001 mol) was heated to reflux in acetic anhydride (5 ml) for 3 h. After cooling, acetic acid (2 ml) was added and the reaction mixture was poured into ice-cold water. The solid product obtained was collected and recrystallised from methanol/water to give buff crystals (0.195 g, 97%), m.p.121–123°C. IR: $\nu_{max}$ 3090 (CH arom), 2910 (CH aliph), 2210 (C≡N), 758 $cm^{-1}$ (C–Cl). $^1H$ NMR ($CDCl_3$): δ 2.44 (s, 3H, $CH_3$); 7.49 (m, 5H, Ar–H). MS: *m/z* 217 ($M^+$, 72 %).

*Methyl 4-amino-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate* (**4**): Compound **3** (5 g, 0.023 mol), methyl thioglycolate (2.44 g, 0.023 mol) and anhydrous potassium carbonate (4.6 g, 0.033 mol) were heated to reflux in ethanol (20 ml) for 6 h. The reaction mixture was cooled and then poured into ice-cold water, followed by recrystallisation of the precipitate formed from ethanol, to give yellow crystals (1.53 g, 23%), m.p.176–177 °C. IR: $\nu_{max}$ 3480, 3310 ($NH_2$), 3050 (CH arom), 2910 (CH aliph), 1650 $cm^{-1}$ (C=O). $^1H$ NMR ($CDCl_3$): δ 2.13 (s, 3H, $CH_3$), 2.54 (s, 2H, $NH_2$), 3.80 (s, 3H, $CO_2C\underline{H}_3$), 7.22 (m, 1H, Ar–H), 7.45 (m, 2H, Ar–H), 7.66 (m, 2H, Ar–H). MS: *m/z* 287 ($M^+$, 100%). Anal. Calcd. for $C_{14}H_{13}N_3O_2S$ (287.34): C, 58.52; H, 4.56; N, 14.62; S, 11.16. Found: C, 58.18; H, 5.18; N, 14.55; S, 11.13 %.

*Methyl3-methyl-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazole-5-carboxylate* (**5**): A mixture of the amino ester **4** (0.29 g, 0.001 mol) and 2,5-dimethoxytetrahydrofuran (0.133 g, 0.001 mol) in acetic acid (1.5 ml) was heated under reflux for 1.5 h. After cooling, the reaction mixture was poured into ice-cold water and neutralised with $NaHCO_3$. The solid product obtained was filtered off and recrystallised from ethanol as deep brown crystals (0.29 g, 85%), m.p.130–133 °C. IR: $\nu_{max}$ 3050 (CH arom), 2920 (CH aliph), 1670 $cm^{-1}$ (C=O). $^1H$ NMR ($CDCl_3$): δ 2.26 (s, 3H, $CH_3$), 3.73 (s, 3H, $CO_2C\underline{H}_3$), 6.25 (m, 2H, $H_{3,4}$ pyrrole), 6.56 (m, 2H, $H_{2,5}$ pyrrole), 7.33 (m, 5H, Ar–H). Anal. Calcd. for $C_{18}H_{15}N_3O_2S$ (337.40): C, 64.08; H, 4.48; N, 12.45; S, 9.50. Found: C, 64.04; H, 4.89; N, 12.24; S, 8.95 %.

*3-Methyl-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazole-5-carbohydrazide* (**6**): The ester **5** (3.81 g, 0.011 mol) in ethanol (20 ml) was heated under reflux with hydrazine hydrate (3.2 ml, 0.065 mol) for 6 h. The reaction mixture was then allowed to cool, and the solid product obtained was collected and recrystallised from ethanol as yellow crystals (3 g, 75%), m.p. 157–160 °C. IR: $\nu_{max}$ 3330–3260 ($NHNH_2$), 3070 (CH arom), 2920 (CH aliph), 1630 $cm^{-1}$ (C=O). $^1H$ NMR (DMSO): δ 2.09 (s, 3H, $CH_3$), 6.35 (m, 2H, $H_{3,4}$ pyrrole), 6.84 (m, 2H, $H_{2,5}$ pyrrole), 7.22 (m, 1H, Ar–H), 7.44 (m, 2H, Ar–H), 7.49 (s, 2H, $NH_2$), 7.63 (m, 2H, Ar–H), 12.18 (s, 1H, NH). Anal. Calcd. for $C_{17}H_{15}N_5OS$ (337.10): C, 60.52; H, 4.48; N, 20.76; S, 9.50. Found: C, 60.32; H, 4.88; N, 20.45; S, 9.21 %.

*N-Arylmethylene-(3-methyl-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazole-5-carbohydrazides* (**7a-c**): *General procedure*

Equimolar amounts of carbohydrazide (0.337 g, 0.001 mol) and the appropriate aromatic aldehyde in ethanol (10 ml) were refluxed for 3 h. After cooling, the solid precipitate was collected by filtration and recrystallised from the appropriate solvent.

*Benzylidene compound* (**7a**): This was obtained as a white powder (0.4 g, 90%), m.p. 235–238 °C, from ethanol/dioxan. IR: $\nu_{max}$ 3180 (NH), 3050 (CH, arom), 2910 (CH, aliph), 1640 (C=O), 1590 $cm^{-1}$ (C=N). $^1H$ NMR (DMSO): δ 2.80 (s, 3H, $CH_3$), 6.69 (m, 2H, $H_{3,4}$ pyrrole), 7.10 (m, 2H, $H_{2,5}$ pyrrole), 7.50 (m, 10H, Ar–H), 7.79 (s, 1H, N=CH), 11.84 (s, 1H, NH) ppm. Anal. calcd. for $C_{24}H_{19}N_5OS$ (425.51): C, 67.74; H, 4.50; N, 16.46; S, 7.54. Found: C, 67.34; H, 4.22; N, 16.03; S, 7.10 %.

*4-Nitrobenzylidene compound* (**7b**): This formed bright yellow crystals (0.25 g, 71%), m.p. 295–298 °C, from ethanol/dioxan. IR: $\nu_{max}$ 3290 (NH), 3100 (CH, arom), 2900 (CH, aliph), 1660 (C=O), 1595 (C=N) $cm^{-1}$. $^1H$ NMR (DMSO): δ 2.29 (s, 3H, $CH_3$); 6.07 (m, 2H, $H_{3,4}$ pyrrole), 7.11 (m, 2H, $H_{2,5}$ pyrrole), 7.38 (m, 1H, Ar–H), 7.66 (m, 2H, Ar–H), 7.78 (m, 2H, Ar–H), 7.89 (d, $J$ = 8.8 Hz, 2H, Ar–H), 8.25 (d, $J$ = 8.8 Hz, 2H, Ar–H), 8.11 (s, 1H, N=CH) ppm. Anal. Calcd. for $C_{24}H_{18}N_6O_3S$ (470. 50): C, 61.27, H, 3.86; N, 17.86; S, 6.82. Found: C, 61.08; H, 3.91; N, 17.27; S, 6.40 %.

*4-Chlorobenzylidene compound* (**7c**): This compound was obtained as white flakes (0.24 g, 70%), m.p. 271–274 °C, from ethanol/dioxan. IR: $\nu_{max}$ 3280 (NH), 3050 (CH, arom), 2900 (CH, aliph), 1640 (C=O), 1595 $cm^{-1}$ (C=N). $^1H$ NMR (DMSO): δ 2.23 (s, 3H, $CH_3$), 6.27 (m, 2H, $H_{3,4}$ pyrrole), 6.94 (m, 2H, $H_{2,5}$ pyrrole), 7.28 (m, 1H, Ar–H), 7.35 (d, $J$ = 8.0 Hz, 2H, Ar–H), 7.53 (s, 2H, Ar–H), 7.60 (m, 2H, Ar–H), 7.69 (d, $J$ = 8.0 Hz, 2H, Ar–H), 7.83 (s, 1H, NH), 8.02 (s, 1H, N=C$\underline{H}$) ppm. Anal. Calcd. for $C_{24}H_{18}ClN_5OS$ (459.95): C, 62.67 ; H, 3.94; N, 15.23; S, 6.97; Cl, 7.71. Found: C, 62.45; H, 3.75; N, 4.92; S, 6.63; Cl, 7.45 %.

*5-[3-Methyl-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazol-5-yl) -1,3,4-oxadiazole-2(3H)-thione* (**8**): The carbohydrazide **6** (0.337 g, 0.001mol) was heated on water bath under reflux for 8 h with carbon disulfide (1 ml) in pyridine (10 ml). The excess of carbon disulfide was then removed under reduced pressure and the residue was poured into

cold water (100 ml). The resulting solution was acidified with dilute hydrochloric acid and the solid precipitate formed was collected and recrystallised from ethanol/water to give yellow crystals (0.62 g), m.p. 180–182 °C, in quantitative yield. IR: $\nu_{max}$ 3400 (NH), 3100 (CH arom), 2900 (CH aliph), 1630 (C=N) $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 2.23 (s, 3H, $CH_3$), 6.34 (s, 2H, $H_{3,4}$ pyrrole), 7.18 (s, 2H, $H_{2,5}$ pyrrole), 7.38 (m, 1H, Ar–H), 7.61 (m, 2H, Ar–H), 7.73 (m, 2H, Ar–H), 10.11 (s, 1H, NH) ppm. Anal. Calcd. for $C_{18}H_{13}N_5OS_2$ (379.46): C, 56.97; H, 3.45; N, 18.46; S, 16.90. Found: C, 56.45; H, 3.25; N, 18.15; S, 16.70 %.

*$N^1$-(3-Methyl-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazole-5-oyl)-$N^4$-phenylthiosemicarbazide* (**9**): The carbohydrazide **6** (0.337 g, 0.001mol) and phenyl isothiocyanate (0.14 g, 0.001mol) were refluxed in ethanol (10 ml) for 4 h. After cooling, the white solid precipitate which formed was filtered off and recrystallised from ethanol/dioxan to give yellow crystals (0.44 g, 93%), m.p.186–189 °C. IR: $\nu_{max}$ 3290, 3230 (NH), 2910 (CH aliph.), 1610 $cm^{-1}$ (C=O). $^1H$ NMR (DMSO-$d_6$): δ 2.22 (s, 3H, $CH_3$), 6.31 (m, 2H, $H_{3,4}$ pyrrole), 7.20 (m, 2H, $H_{2,5}$ pyrrole), 7.41 (m, 5H, Ar–H), 7.68 (m, 5H, Ar–H), 9.49 (s, 1H, NH), 9.81 (s, 1H, NH). One NH was not observed. Anal. Calcd. for $C_{24}H_{20}N_6OS_2$ (472.59): C, 61.00; H, 4.27; N, 17.78; S, 13.57. Found: C, 60.67; H, 3.99; N, 17.62; S, 13.05 %.

*2,4-Dihydro-5-(3-methyl-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazol-5-yl)-4-phenyl-2H-1,2,4-triazole-2-thione* (**10**): Compound **9** (0.21 g, 0. 5 mmol) was heated under reflux in aqueous NaOH (2*N*, 5 ml) for 2 h. The reaction mixture was cooled and acidified with hydrochloric acid (2*N*), whereupon a solid product separated. Filtration and recrystallisation from ethanol gave the thione **10** as buff crystals (0.19 g, 95%), m.p. 323–325 °C. IR: $\nu_{max}$ 3300 (NH), 3100 (CH arom.), 2900 (CH aliph.), 1650 (C=N), 1595 $cm^{-1}$ (C=C). $^1H$ NMR (DMSO-$d_6$): δ 2.22 (s, 3H, $CH_3$), 6.21 (m, 2H, $H_{3,4}$ pyrrole), 6.61 (m, 2H, $H_{2,5}$ pyrrole), 6.88 (m, 2H, Ar–H), 7.30 (m, 4H, Ar–H), 7.62 (m, 4H, Ar–H), 14.37 (s, 1H, NH). Anal. Calcd. for $C_{24}H_{18}N_6S_2$ (454.57): C, 63.41; H, 3.99; N, 18.49; S, 14.11. Found: C, 59.13; H, 3.75; N, 18.20; S, 14.00 %.

*3-Methyl-5-(5-methylthio-1,3,4-oxadiazol-2-yl)-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazole* (**11**): The thione **8** (0.26 g, 0. 7 mmol), methyl iodide (2 ml) and sodium acetate (0.5 g) were heated under reflux in ethanol (10 ml) for 2 h. After cooling, the solid product was collected by filtration, washed with water and recrystallised from ethanol/dioxane to give brown crystals (0.08 g, 27%), m.p. 174–176 °C. IR: $\nu_{max}$ 3100 (CH arom.), 2900 (CH aliph.), 1580 (C=C) $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 2.24 (s, 3H, $CH_3$), 2.60 (s, 3H, $SCH_3$), 6.35 (m, 2H, $H_{3,4}$ pyrrole), 7.20 (m, 2H, $H_{2,5}$ pyrrole), 7.39 (m, 1H, Ar–H), 7.62 (m, 2H, Ar–H), 7.77 (m, 2H, Ar–H). Anal. Calcd. for $C_{19}H_{15}N_5OS_2$ (393.49): C, 58.00; H, 3.84; N, 17.80; S,16.30. Found: C, 57.57; H, 3.71; N, 17.92; S, 16.12 %.

*3-Methyl-5-(5-methylthio-4-phenyl-4H-1,2,4-triazol-3-yl)-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazole* (**12**): The thione **10** (0.22 g, 0.5 mmol), methyl iodide (2 ml) and sodium acetate (0.5 g) in ethanol (10 ml) were heated under reflux in ethanol (10 ml) for 2 h. After cooling, the solid product was filtered off, washed with water, and recrystallised from benzene/ethanol to give brown crystals of **10** (0.2 g, 90%), m.p. 262–263 °C. IR: $\nu_{max}$ 3100 (CH arom.), 2900 (CH aliph.), 1620 (C=N), 1595 $cm^{-1}$ (C=C). $^1H$ NMR ($CDCl_3$): δ 2.16 (s, 3H, $CH_3$), 2.26 (s, 3H, $SCH_3$), 6.44 (m, 2H, $H_{3,4}$ pyrrole), 6.94 (m, 2H, $H_{2,5}$ pyrrole), 7.11 (m, 1H, Ar–H), 7.18 (m, 2H, Ph), 7.29 (m, 3H, Ar–H), 7.53 (m, 2H, Ar–H), 7.72 (m, 2H, Ar–H). Anal. Calcd. for $C_{25}H_{20}N_6S_2$ (468.60): C, 64.08; H,4.30; N, 17.93; S, 13.69. Found: C, 63.88; H, 4.02; N, 17.65; S, 13.16 %.

*$N^1$-(4-Oxo-2-penten-2-yl)-3-methyl-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazole-5-carbohydrazide* (**13**): The carbohydrazide **6** (0.33 g, 10 mmol) and acetylacetone (0.10 ml, 10 mmol) were heated under reflux in ethanol (10 ml) for 4 h. After cooling, the solvent was removed *in vacuo* and the solid residue obtained was recrystallised from methanol to give brown crystals (0.23 g, 56%), m.p. 182–184 °C. IR: $\nu_{max}$ 3420 (NH), 3120 (CH arom.), 2900 (CH aliph.), 1630 $cm^{-1}$ (C=O). $^1H$ NMR ($CDCl_3$): δ 2.15 (s, 3H, $CH_3$), 2.28 (s, 3H, $CH_3$), 2.42 (s, 3H, $CH_3$), 5.94 (s, 1H, CH=C), 6.32 (m, 2H, $H_{3,4}$ pyrrole), 6.85 (m, 2H, $H_{2,5}$ pyrrole), 7.23 (m, 1H, Ar–H), 7.42 (m, 2H, Ar–H), 7.72 (m, 2H, Ar–H). MS: *m/z* 419 ($M^+$, 31%), 306 (100), 77 (21). Anal. Calcd. for $C_{22}H_{21}N_5O_2S$ (419.50): C, 62.99; H, 5.05; N, 16.69; S, 7.64. Found: C, 62.63; H, 4.75; N, 16.24; S, 7.55 %.

*5-(3,5-Dimethylpyrazol-1-ylcarbonyl)-3-methyl-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazole* (**14**): The carbohydrazide **6** (0.15 g, 0. 5 mmol) was heated under reflux with acetylacetone (5 ml, 0.05 mol) for 4 h, then triturated with ethanol (10 ml) and left to cool. The precipitate that formed was collected and recrystallised from ethanol to give brown crystals of the pyrazole **14** (0.06g, 28%), m.p. 130–131 °C. IR: $\nu_{max}$ 3100 (CH arom.), 2900 (CH aliph.), 1670 (C=O), 1595 $cm^{-1}$ (C=C). $^1H$ NMR (DMSO-$d_6$): δ 2.15, 2.21, 2.42 (each s, 3H, $CH_3$), 6.20 (s, 1H, CH pyrazole), 6.22 (m, 2H, $H_{3,4}$ pyrrole), 7.03 (m, 2H, $H_{2,5}$ pyrrole), 7.36 (m, 1H, Ar–H), 7.61 (m, 2H, Ar–H), 7.71 (m, 2H, Ar–H). Anal. Calcd. for $C_{22}H_{19}N_5OS$ (401.49): C, 65.81; H, 4.77; N, 17.44; S, 7.99. Found: C, 65.45; H, 4.62; N, 17.24; S, 7.62 %.

*5-Amino-1-(3-methyl-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazolyl-5-carbonyl)-1H-pyrazole-4-carbonitrile* (**15a**): The carbohydrazide **6** (0.17 g, 0.5 mmol) and ethoxymethylenemalononitrile (0.061 g, 0.5 mmol) were heated in ethanol (10 ml) under reflux for 8 h. After cooling, the solvent was removed *in vacuo* and the solid residue was recrystallised from ethanol to give yellow crystals (0.094 g 47 %), m.p. 187–189 °C. IR: $\nu_{max}$ 3410– 3320 ($NH_2$), 3100 (CH arom.), 2910 (CH aliph.), 2200 (C≡N), 1660 (C=O), 1620 $cm^{-1}$ (C=N). $^1H$ NMR (DMSO-$d_6$): δ 2.19 (s, 3H, $CH_3$), 6.27 (m, 2H, $H_{3,4}$ pyrrole), 7.09 (m, 2H, $H_{2,5}$ pyrrole), 7.34 (s, 2H, $NH_2$), 7.64 (m, 4H, Ar–H), 7.99 (m, 2H, CH pyrazole and 1H, Ar–H). Anal. Calcd. for $C_{21}H_{15}N_7OS$ (413.46): C, 61.00; H, 3.66; N, 23.71; S, 7.76. Found: C, 59.83; H, 3.35; N, 23.43; S, 7.55 %.

*Ethyl 5-amino-1-[3-methyl-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazolyl-5-carbonyl]-1H-pyrazole-4-carboxylate* (**15b**): The carbohydrazide **6** (0.17 g, 0.5 mmol) and ethyl ethoxymethylenecyanoacetate (0.09 g, 0.5 mmol) were heated in absolute ethanol (10 ml) under reflux for 8 h. After cooling, the solvent was removed under reduced pressure and the residue was recrystallised from ethanol to give pale-yellow crystals (0.16g, 69 %), m.p. 194–195 °C. IR: $\nu_{max}$ 3450, 3310 ($NH_2$), 3100 (CH arom.), 2910 (CH aliph.), 1680 (C=O), 1610 $cm^{-1}$ (C=O). $^1H$ NMR (DMSO-$d_6$): δ 1.25 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH}_3$), 2.16 (s, 3H, $CH_3$), 4.19 (q , *J* = 7.1 Hz, 2H,$C\underline{H}_2CH_3$), 6.28 (m, 2H, $H_{3,4}$ pyrrole), 7.08 (m, 2H, $H_{2,5}$ pyrrole), 7.35 (m, 3H,1H Ar–H and 2H $NH_2$), 7.58 (m, 2H, Ar–H), 7.62 (m, 2H, Ar–H), 7.84 (s, 1H, CH pyrazole). Anal. Calcd. for $C_{23}H_{20}N_6O_3S$ (460.51): C, 59.99; H, 4.38; N, 18.25; S, 6.96. Found: C, 59.46; H, 4.09; N, 18.03; S, 6.89 %.

*3-Methyl-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazole-5-carbonyl azide* (**16**): To a solution of the carbohydrazide **6** (1.35 g, 0.004 mol) in glacial acetic acid (15 ml), a cooled solution of sodium nitrite (0.69 g, 0.01 mol in 1.5 ml $H_2O$) was added dropwise with stirring. After completion of the addition, the reaction mixture was stirred at room temperature for 1 h. The solid product formed was filtered off, washed abundantly with cold water and air-dried. to give brown crystals of the azide **16** (1.2g, 83%), m.p. 114–116 °C. It was used without any further purification. IR: $\nu_{max}$ 3110 (CH arom), 2130 ($N_3$), 1680 $cm^{-1}$ (C=O). $^1H$ NMR (DMSO-$d_6$): δ 2.31 (s, 3H, $CH_3$), 6.41 (m, 2H, $H_{3,4}$ pyrrole), 6.95 (m, 2H, $H_{2,5}$ pyrrole), 7.33 (m, 1H, Ar–H), 7.54 (m, 2H, Ar–H), 7.74 (m, 2H, Ar–H). Anal. Calcd. for $C_{17}H_{12}N_6OS$ (348.38): C, 58.61; H, 3.47; N, 24.12; S, 9.50. Found: C, 58.43; H, 3.12; N, 24.03; S, 9.17 %.

*Ethyl N-[3-methyl-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazol-5-yl]carbamate* (**18a**): A mixture of acid azide **16** (0.5 g, 0.0014 mol) in ethanol (8 ml) was heated under reflux for 2 h. The reaction mixture was concentrated and then allowed to cool. The precipitate formed was collected and recrystallised from ethanol to give pale buff crystals (0.49 g, 92%), m.p. 156–157 °C. IR: $\nu_{max}$ 3220 (NH), 3090 (CH arom.), 2910 (CH aliph.), 1680 (C=O), 1595 $cm^{-1}$ (C=C). $^1H$ NMR ($CDCl_3$-$d_6$): δ 1.32 (t, *J* = 7.2 Hz, 3H, $CH_2\underline{CH}_3$), 2.24 (s, 3H, $CH_3$), 4.26 (q, *J* = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 6.41 (m, 2H, $H_{3,4}$ pyrrole), 6.87 (m, 2H, $H_{2,5}$ pyrrole), 7.26 (m, 1H , Ar–H), 7.49 (m, 2H, Ar–H), 7.74 (m, 2H, Ar–H). Anal. Calcd. for $C_{19}H_{18}N_4O_2S$ (366.44): C, 62.28; H, 4.95; N, 15.29; S, 8.75. Found: C, 62.30; H, 4.84; N, 15.08; S, 8.34 %.

*Benzyl N-[3-methyl-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazol-5-yl]carbamate* (**18b**): The acid azide **16** (0.13 g, 0. 35 mmol) was heated under reflux in benzyl alcohol (8 ml) for 2 h. The reaction mixture was concentrated and allowed to cool. The solid precipitate was filtered off and recrystallised from ethanol/dioxan to give pale yellow crystals (0.14 g, 87%), m.p. > 330 °C. IR: $\nu_{max}$ 3150 (NH), 2990 (CH aliph), 1630 (C=O) $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ = 2.78 (s, 3H, $CH_3$), 4.47 (s, 2H, $CH_2$),6.68 (m, 2H, $H_{3,4}$ pyrrole), 7.04 (m, 2H, $H_{2,5}$ pyrrole), 7.31 (m, 2H, Ar–H), 7.56 (m, 3H, Ar–H), 7.62 (m, 2H, Ar–H), 7.76 (m, 2H, Ar–H), 11.72 (s, 1H, NH). Anal. Calcd. for $C_{24}H_{20}N_4O_2S$ (428.51): C, 67.27; H, 4.70; N, 13.07; S, 8.43. Found: C, 67.16; H, 4.61; N, 12.98; S, 8.32 %.

*t-Butyl N-[3-methyl-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazol-5-yl]carbamate* (**18c**): The acid azide **16** (0.34 g, 0.001 mol) and *t*-butyl alcohol (0.074 ml, 0.001 mol) in dry toluene (10 ml) were heated under reflux for 2 h, concentrated and then allowed to cool. The precipitated solid was collected and recrystallised from

ethanol/dioxan to give brown crystals (0.35 g, 90%), m.p. > 300 °C. IR: $\nu_{max}$ 3100 ($NH_2$), 2910 (CH aliph), 1660 $cm^{-1}$ (C=O). $^1H$ NMR (DMSO-$d_6$): δ 2.49 (s, 3H, $CH_3$), 2.78 (s, 9H, $CH_3$), 6.66 (m, 2H, $H_{3,4}$ pyrrole), 7.03 (m, 2H, $H_{2,5}$ pyrrole), 7.30 (m, 1H, Ar–H), 7.52 (m, 2H, Ar–H), 7.61 (m, 2H, Ar–H), 11.72 (s, 1H, NH). Anal. Calcd. for $C_{21}H_{22}N_4O_2S$ (394.49): C, 63.94; H, 5.62; N, 14.20; S, 8.13. Found: C, 63.53; H, 5.33; N, 14.03; S, 8.00 %.

*Isopropyl N-[3-methyl-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c] pyrazol-5-yl]carbamate* (**18d**): A suspension of azide **16** (0.13 g, 0.35 mmol) was heated under reflux in isopropanol (20 ml) for 2 h. The reaction mixture was concentrated, and allowed to cool. The solid precipitate was collected and recrystallised from isopropanol to give buff crystals (0.135 g, 91 %), m.p. 174–175 °C. IR: $\nu_{max}$ 3150 (NH), 2990 (CH aliph.), 1720 (C=O), 1590 $cm^{-1}$ (C=C). $^1H$ NMR ($CDCl_3$): δ 1.30 (d, *J* = 6.1 Hz, 6H, $2CH_3$), 2.23 (s, 3H, $CH_3$), 5.03 (m, 1H, $C\underline{H}(CH_3)_2$), 6.42 (m, 2H, $H_{3,4}$ pyrrole), 6.87 (m, 2H, $H_{2,5}$ pyrrole), 7.26 (m, 1H, Ar–H), 7.48 (m, 2H, Ar–H), 7.73 (m, 2H, Ar–H) ppm. Anal. Calcd. for $C_{20}H_{20}N_4O_2S$ (380.46): C, 63.14; H, 5.30; N, 14.73; S, 8.43. Found: C, 62.95; H, 5.11; N, 14.21; S, 8.10 %.

*N,N'-Bis-[3-methyl-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c] pyrazol-5-yl]urea* (**19**): The acid azide **16** (0.34 g, 0.001 mol) was heated under reflux in water (15 ml) for 2 h. After cooling, the solid product was collected and recrystallised from ethanol/dioxan to give yellow crystals of the urea (0.33 g, 55%), m.p. > 340 °C. IR: $\nu_{max}$ 3250 (two NH), 2930 (CH aliph.), 1630 (C=O), 1590 (C=C) $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 2.82 (s, 6H, $2CH_3$), 6.6.9 (m, 4H, $H_{3,4}$ pyrrole), 7.06 (m, 4H, $H_{2,5}$ pyrrole), 7.33 (m, 2H, Ar–H), 7.58 (m, 4H, Ar–H), 7.67 (m, 4H, Ar–H), 7.81 (s, 2H, 2NH). MS: *m/z* 614 ($M^+$, 5%), 320 (100), 77 (92). Anal. Calcd. for $C_{33}H_{26}N_8OS_2$ (614.74): C, 64.47; H, 4.26; N, 18.23; S, 10.43. Found: C, 64.25; H, 4.00; N, 18.10; S, 10.17 %.

*$N^1$-(3-Methyl-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazol-5-yl)-$N^3$-phenylurea* (**20a**): A mixture of acid azide **16** (0.4 g, 0.001 mol) and an excess of aniline (5 ml) 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 which formed was collected by filtration and recrystallised from ethanol to give buff needles (0.24 g, 51%), m.p. >300 °C. IR: $\nu_{max}$ 3300, 3200 (2NH), 3090 (CH arom), 2900 (CH aliph), 1635 (C=O), 1595 $cm^{-1}$ (C=C). $^1H$ NMR (DMSO-$d_6$): δ 2.08 (s, 3H, $CH_3$), 6.32 (m, 2H, $H_{3,4}$ pyrrole), 7.07 (m, 1H, Ar–H), 7.08 (m, 2H, $H_{2,5}$ pyrrole), 7.02 (m, 2H, Ar–H), 7.43 (m, 2H, Ar–H), 7.58 (m, 2H, Ar–H), 7.7 (m, 2H, Ar–H), 8.99 (s, 1H, NH), 9.27 (s, 1H, NH). Anal. Calcd. for $C_{23}H_{19}N_5OS$ (413.50): C, 66.81; H, 4.63; N, 16.94; S, 7.75. Found: C, 66.13; H, 4.45; N, 16.94; S, 7.61 %.

*3-Methyl-5-morpholinocarbonylamino-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazole* (**20b**): A suspension of acid azide **16** (0.4 g, 0.0011 mol) in an excess of morpholine (5 ml) 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 recrystallised with ethanol to give pale brown crystals (0.24 g, 52%), m.p. 176–177 °C. IR: $\nu_{max}$ 3400 (NH), 3100 (CH arom), 2930 (CH aliph), 1620 (C=O), 1595 $cm^{-1}$ (C=C). $^1H$ NMR (DMSO-$d_6$): δ 2.33 (s, 3H, $CH_3$), 3.39 (s, 8H, morpholine), 6.35 (m, 2H, $H_{3,4}$ pyrrole), 7.05 (m, 2H, $H_{2,5}$ pyrrole), 7.34 (m, 1H, Ar–H), 7.59 (m, 2H, Ar–H), 7.69 (m, 2H, Ar–H). The NH signal was not observed. Anal. Calcd. for $C_{21}H_{21}N_5O_2S$ (407.49): C, 61.90; H, 5.19; N, 17.19; S, 7.87. Found: C, 61.75; H, 4.95; N, 17.00; S, 7.45 %.

*5,7-Dihydro-9-methyl-7-phenyl-4H-pyrazolo[4',3':4,5]thieno[2,3-e]pyrrolo[1,2-a]pyrazin-4-one* (**22**): The acid azide **16** (0.2 g, 0. 5 mmol) in dry benzene (10 ml) was heated under reflux for 1.5 h. After cooling, the solid product was collected and recrystallised from ethanol/dioxan to give buff crystals (0.14 g, 77%), m.p. > 300 °C. IR: $\nu_{max}$ 3450 (NH), 3120 (CH arom.), 2910 (CH aliph.), 1625 (C=O), 1590 $cm^{-1}$ (C=C). $^1H$ NMR (DMSO-$d_6$): δ 3.26 (s, 3H, $CH_3$), 3.81 (s, 1H, NH), 7.12 (m, 1H, $H_6$ pyrrole), 7.44 ( m, 1H, $H_7$ pyrrole), 7.77 (m, 1H, Ar–H), 8.02 (m, 2H, Ar–H), 8.11 (m, 2H, Ar–H), 8.24 (m, 1H, $H_5$ pyrrole). Anal. Calcd. for $C_{17}H_{12}N_4OS$ (320.37): C, 63.73; H, 3.78; N,17.49; S, 10.01. Found: C, 63.33; H, 3.99; N, 17.78; S, 10.45 %.

*Received 3 October 2004; accepted 13 June 2005*
*Paper 04/2795*

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