Synthesis of some heteroaryl pyrazole derivatives and their biological activities

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In order to search for novel fungicides with high activity, a series of heteroaryl pyrazoles were synthesized from 5-pyrazole formhydrazide. The structures of all new compounds were confirmed by spectroscopic methods and microanalyses. Preliminary bioassays indicated that some compounds showed fungicidal activity against *Puccinia tritinia* and PGR activity as well.

Keywords 5-(Substituted-pyrazol-5′-yl)-1,3,4-thiadiazole, 5-(substituted-pyrazol-5′-yl)-1,2,4-triazole, 5-(substituted-pyrazol-5′-yl)-1,3,4-oxadiazole, fungicidal activity, PGR activity

Introduction

Pyrazole derivatives have attracted much attention over the past two decades in pesticide and synthetic organic chemistry due to their diverse biological activities. Some of these compounds exhibit fungicidal, herbicidal, and insecticidal properties. For example, fipronil (MB46030) is a new pyrazole insecticide that provides excellent control of many soil and foliar insects on a wide variety of crops and noncrops.[1] ET-751 is a new 3-phenylpyrazole herbicide, its primary use is for the post-emergence control of the broad-leaved weeds in cereals.[2] In addition, other compounds, such as furametpyr (S-82658),[3] azimsulfuron (DPX-A8947)[4] and vaniliprole (RPA-098231)[5] are being developed and will be used as pesticides.

A wide range of biological activities has been attributed to 1,2,4-triazole,[6] 1,3,4-thiadiazole[7] and 1,3,4-oxadiazole.[8] If these heterocycles are introduced into pyrazole ring, the linked bis-heterocylic compounds may enhance biological activities. As part of our ongoing program aimed at searching for novel agrochemicals, our interest in the bis-heterocyclic compounds containing pyrazole led us to synthesize a number of title compounds.

Results and discussion

Synthesis

The hydrazide **1** reacted with phenylisothiocyanate to give the *N*-phenylthiosemicarbazides **2a—b**. Similarly, **1** was treated with KSCN in the presence of acid to afford corresponding thiosemicarbazides **2c—d**, which underwent cyclization in a basic condition to give the corresponding 5-(substituted-pyrazol-5-yl)-1,2,4-triazole-3-thione **4**. Alkylation of compounds **4** yielded 3-alkylthio-5-(substituted pyrazol-5-yl)-1,2,4-triazole **5**. The treatment of **2a** with concentrated H_2SO_4 yielded 2-anilino-5-(substituted pyrazol-5-yl)-1,3,4-thiadiazole **3**, while treatment of **2a** with I_2/KI solution in a basic condition resulted in the formation of 2-anilino-5-(substituted pyrazol-5-yl)-1,3,4-oxadiazole **6**. Attempt to cyclize **2a** in refluxing acetic acid gave 1-acetyl-2-(substituted pyrazol-5-yl) carbonylhydrazine **7**, which was confirmed by its NMR spectra and by comparison with an authentic sample prepared by acetylating **1a** in refluxing acetic acid (Scheme 1).

5-Pyrazole hydrazide **1** was condensed with carbon disulfide in ethanolic potassium hydroxide at room temperature to afford the corresponding potassium dithiocarbazates **8**, which were cyclized in hydrazine hydrate

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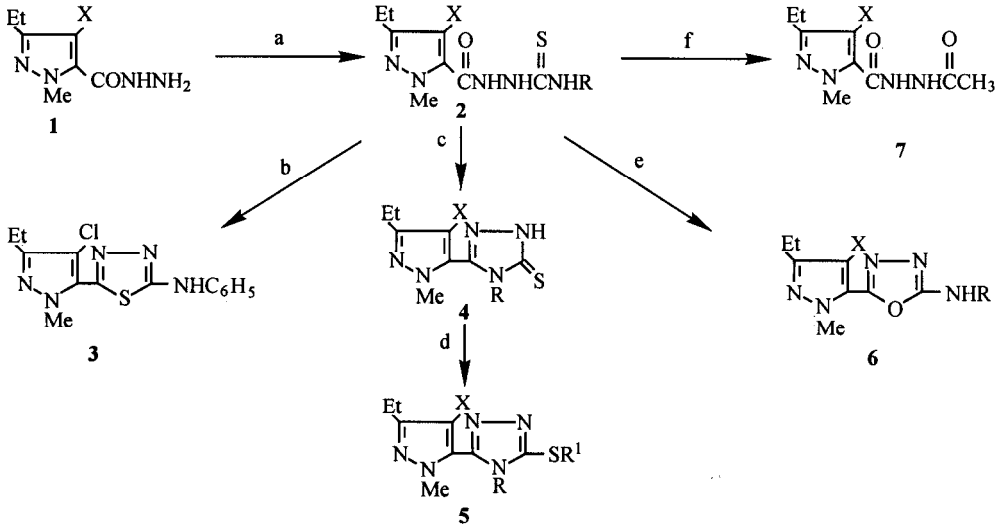
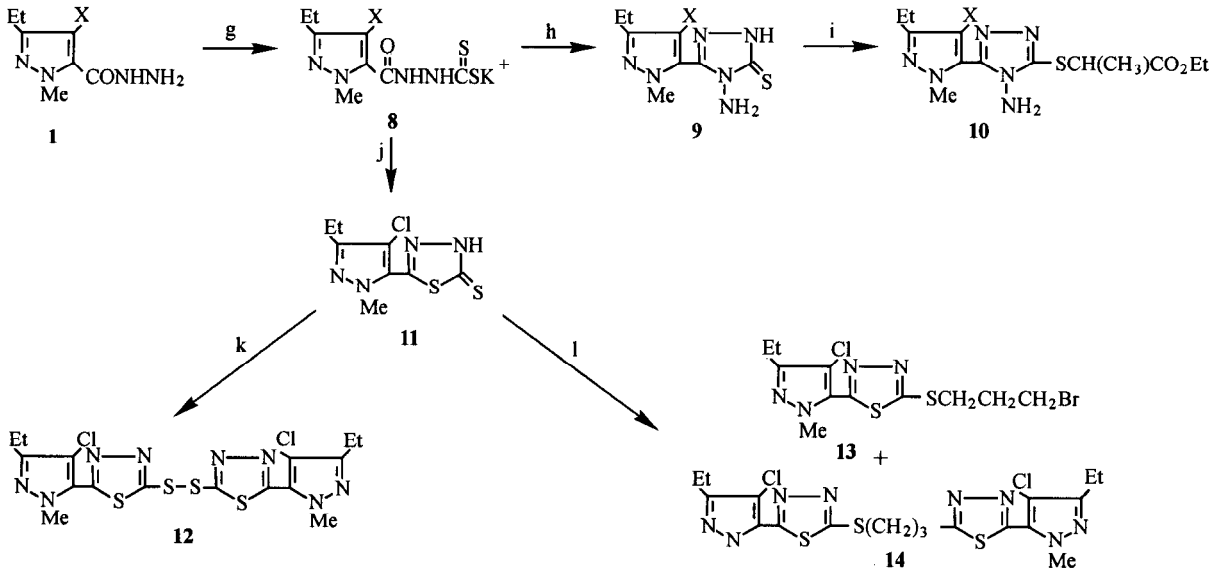
(85%) to form 4-amino-5-(substituted pyrazol-5-yl)-1, 2, 4-triazole-3-thiones **9**, followed by alkylation giving compounds **10**. The treatment of **8a** with concentrated H_2SO_4 yielded 5-(substituted pyrazol-5-yl)-1, 3, 4-thiadiazole-2-thione **11**. When **3** was oxidized by hydrogen peroxide in ethanol, the corresponding disulfide **12** was produced quantitatively. When compound **3** reacted with 1, 3-dibromopropane using a phase transfer catalyst tetrabutylammonium bromide (TBAB), a mixture of 1, 3-bis (5-(substituted pyrazol-5-yl)-1, 3, 4-thiadiazol-2-ylthio)-propane **14** and 2-(3-bromopropyl)thio-5-(substituted pyrazol-5-yl)-1, 3, 4-thiadiazole **13** was obtained (Scheme 2).

Scheme 1



Reagents and conditions a. PhNCS/EtOH or KSCN, HCl/EtOH; b. Conc. H_2SO_4/rt; c. 5% Na_2CO_3/reflux; d. R^1X, OH^-, TBAB/toluene; e. I_2, KI, 4N NaOH/EtOH; f. HOAc/reflux.

Scheme 2

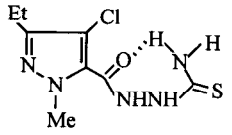


Reagents and conditions g. CS_2, KOH/EtOH, rt; h. $NH_2NH_2 \cdot H_2O$/reflux; i. $BrCH(CH_3)CO_2Et$, TBAB, OH^-/toluene; j. Conc. H_2SO_4, rt; k. H_2O_2/EtOH, rt; l. $Br(CH_2)_3Br$, TBAB, OH^-/toluene.

Spectral properties and structures of products

The structures of all compounds prepared were confirmed by IR, ^1H NMR, ^{13}C NMR spectroscopies and elemental analyses.

In the ^1H NMR spectra of compound **2c**, two protons of NH_2 are magnetically nonequivalent and display two singlet peaks in 7.65 and 7.91 respectively, which is caused by intramolecular hydrogen bond. It can be illustrated as follows:



Compounds **4a—d** and **11** exist predominantly as thione tautomers, which were confirmed by their NMR and IR spectra. Compound **11** was taken as an example to explain it. ^{13}C NMR makes possible the direct observation of functional groups such as thiocarbonyl.[9] The chemical shift of C-2 in compound **11** is 188.59, which should approximate to that of thiocarbonyl group. In IR spectrum of compound **11**, a strong absorption is observed in 1260 cm^{-1}, indicating the existence of thiocarbonyl group. "NH" absorption is also found in 3047 cm^{-1}.

Biological activities

Fungicidal activities of some compounds against *Puccinia tritinia* (*P. t.*), *Botrytis cinerea* (*B. c.*) and *Sclerotinia sclertiorum* (*S. s*) were evaluated *in vivo* at a concentration of 500 ppm by a preventive foliar application in a green house. The test result was shown in Table 1. Preliminary bioassays indicate that compounds **3**, **5c** and **10a** have moderate inhibitory activities against *P. t.* and *S. s.*, respectively.

In addition, some compounds exhibited certain PGR activity at 10 ppm (Table 2). For example, **2a**, **2c**, **4b**, and **10b** have inhibition activity to elongation of wheat coleoptile segments, and **5a** and **5c** have promotion activity to cucumber cotyledom root producing.

Table 1 Fungicidal activities of some compounds

	Inhibition rate (%)														
Compd.	**2a**	**2b**	**2c**	**3**	**4a**	**4b**	**4c**	**4d**	**5a**	**5d**	**5e**	**6**	**7**	**10a**	**10b**
P. t.	20	11	60	50	30	0	20	25	40	60	85	10	0	75	60
B. c.	0	16	47	54	58	19	34	5.6	6.3	26	13	47	0	0	6.3
S. s.	0	0	0	77	25	5.7	0	26	0	29	25	41	0	31	23

Table 2 Plant growth regulator activities of some compounds

	Inhibition or promotion rate (%)								
Compd.	**2a**	**2b**	**2c**	**3**	**4b**	**5a**	**5c**	**7**	**10b**
Elongation of wheat coleoptile segments	−10.6	10.5	−12.5	2.2	−12.4	2.2	0.95	0.73	−12.4
Cucumber cotyledom root producing	−10.0	−25.0	0	30	−3.0	80	66.6	53.5	26.6

Experimental

NMR spectra were taken on a Bruker AC-P200 spectrometer. Tetramethylsilane (TMS) was used as an internal standard. IR spectra were recorded on a Shimadzu-435 spectrometer. Elemental analyses were carried out on a Yanaco MT-3 instrument. Melting points were determined with a model Yanaco MP-500 apparatus and uncorrected.

5-Pyrazole formhydrazides and 5-(substituted pyrazol-5-yl)-1,2,4-triazole-3-thiones were prepared according to the previously published procedures.[10,11]

1-(4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-carbonyl)-4-phenylthiosemicarbazide (**2a**)

To a solution of 5-pyrazole formhydrazide (**1**, 15 mmol) in ethanol (25 mL) was added phenylisothiocyanate (2.2 g, 16 mmol). The reaction mixture was refluxed for 3.5 h, cooled and the separated solid was washed with water and recrystallized from ethanol.

Compound **2b** was prepared in the same method as **2a**.

2a (X = Cl, R = Ph) Yield 93%, mp 144—145℃. δ_H(CDCl$_3$): 1.20(t, J = 7.4 Hz, 3H, CH$_3$), 2.61(q, J = 7.4 Hz, 2H, CH$_2$), 4.03(s, 3H, NCH$_3$), 7.20—7.39(m, 5H, Ph), 8.56, 9.23, 9.93(3s, 3H, 3NH). Anal. $C_{14}H_{16}ClN_5OS$. Calcd: C, 49.72; H, 4.77; N, 20.73. Found: C, 49.47; H, 4.58; N, 20.38.

2b (X = H, R = Ph) Yield 90%, mp 154—155℃. ν_{max}: 3389(NH), 3127, 2951, 1682(C = O), 1595, 1541, 1458, 1397, 1231(C = S), 689 cm^{-1}. δ_H: 1.22(t, J = 7.2Hz, 3H, CH$_3$), 2.60(q, J = 7.2 Hz, 2H, CH$_2$), 4.03(s, 3H, NCH$_3$), 6.51(s, 1H, 4H-pyrazole), 7.20—7.39(m, 5H, Ph), 8.56, 9.23, 9.93(3s, 3H, 3NH). Anal. $C_{14}H_{17}N_5OS$. Calcd: C, 55.53; H, 5.65; N, 23.08. Found: C, 55.31; H, 5.85; N, 22.90.

4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-carbonylthiosemicarbazide (**2c**)

To a solution of 5-pyrazole formhydrazide (**1**, 20 mmol) in ethanol (20 mL) was added potassium thiocyanate (2.1 g, 22 mmol), followed by a few drops of concentrated hydrochloric acid. The mixture was refluxed for 4.5 h, cooledand the separated solid was washed with water and recrystallized from ethanol.

Compound **2d** was prepared in the same method as **2c**.

2c (X = Cl, R = H) Yield 90%, mp 200℃ (dec). δ_H(DMSO): 1.16(t, J = 7.5 Hz, 3H, CH$_3$), 2.50(q, J = 7.5 Hz, 2H, CH$_2$), 3.86(s, 3H, NCH$_3$), 8.02, 7.56(2s, 2H, NH$_2$), 9.55, 10.12 (2s, 2H, NHNH). Anal. $C_8H_{12}ClN_5OS$. Calcd: C, 36.71; H, 4.62; N, 26.76. Found: C, 36.74; H, 4.69; N, 26.82.

2d (X = H, R = H) Yield 64%, mp 204—205℃. δ_H(DMSO): 1.16(t, J = 7.5 Hz, 3H, CH$_3$), 2.50(q, J = 7.5 Hz, 2H, CH$_2$), 3.94(s, 3H, NCH$_3$), 6.88(s, 1H, 4-H-pyrazole), 7.65, 7.91(2s, 2H, NH$_2$), 9.35, 10.25(2s, 2H, NHNH). Anal. $C_8H_{13}N_5OS$. Calcd: C, 42.28; H, 5.76; N, 30.81. Found: C, 42.07; H, 5.54; N, 31.03.

2-Anilino-(4-chloro-3-ethyl-1-methyl-1H-pyrazol-5-yl)-1,3,4-thiadiazole (**3**)

2a (3 mmol) was added in portion to concentrated sulfuric acid (10 mL) at 0℃, the mixture was stirred for 1 h at room temperature and poured into crushed ice with stirring. The separated solid was washed with water and recrystallized from ethanol.

3 (X = Cl, R = Ph) Yield 31%, mp 159—160℃. δ_H(DMSO): 1.19(t, J = 7.5 Hz, 3H, CH$_3$), 2.57(q, J = 7.5 Hz, 2H, CH$_2$), 4.09(s, 3H, NCH$_3$), 7.04—7.68(m, 5H, Ph), 10.68(s, 1H, NH). Anal. $C_{14}H_{14}ClN_5S$. Calcd: C, 52.58; H, 4.41; N, 21.90. Found: C, 52.40; H, 4.32; N, 22.10.

5-(4-Chloro-3-ethyl-1-methyl-1H-pyrozol-5-yl)-4-phenyl-1,2,4-triazole-3-thione (**4a**)

A stirring mixture of compound **2a** (3 mmol) and 5% aqueous sodium carbonate solution (20 mL) was refluxed for 6 h. After being cooled, the solution was acidified with hydrochloric acid and the precipitate was filtered, washed with water and recrystallized from ethanol.

Compounds **4b—d** were prepared in the same method as **4a**.

4a (X = Cl, R = Ph) Yield 94%, mp 232—233℃. δ_H(CDCl$_3$): 1.14(t, J = 7.4 Hz, 3H, CH$_3$), 2.53(q, J = 7.4 Hz, 2H, CH$_2$), 3.70(s, 3H, NCH$_3$), 7.26—7.42(m, 5H, Ph). Anal. $C_{14}H_{14}ClN_5S$. Calcd: C, 52.58; H, 4.41; N, 21.90. Found: C, 52.79; H, 4.63; N, 21.85.

4b (X = H, R = Ph) Yield 76%, mp 270—271℃. ν_{max}: 3089(NH), 2957, 2828, 1599, 1532, 1488, 1433, 1370, 1293(C = S), 973, 630 cm^{-1}. δ_H (DMSO): 0.95(t, J = 7.6 Hz, 3H, CH$_3$), 2.34(q, J = 7.6 Hz, 2H, CH$_2$), 3.89(s, 3H, NCH$_3$), 5.44 (s, 1H, 4-H-pyrazole), 7.41—7.54(m, 5H, Ph). Anal. $C_{14}H_{15}N_5S$. Calcd: C, 58.92; H, 5.30; N, 24.54. Found: C, 59.14; H, 5.61; N, 24.52.

4c (X = Cl, R = H) Yield 67%, mp 254—255℃. ν_{max}: 3078(NH), 2951, 2724, 1595, 1478, 1451, 1380, 1320(C = S), 689cm^{-1}. δ_H(CDCl$_3$): 1.22(t, J = 7.5 Hz, 3H, CH$_3$), 2.61(q, J = 7.5 Hz, 2H, CH$_2$), 3.98(s, 3H, NCH$_3$), 12.33, 12.88

(2s, 2H, 2NH). Anal. $C_8H_{10}ClN_5S$. Calcd: C, 39.42; H, 4.14; N, 28.73. Found: C, 39.60; H, 4.31; N, 28.52.

4d (X = H, R = H) Yield 58%, mp 72—73℃. δ_H(DMSO): 1.15(t, J = 7.6 Hz, 3H, CH_3), 2.52(q, J = 7.6 Hz, 2H, CH_2), 3.97(s, 3H, NCH_3), 6.72(s, 1H, 4-H-pyrazole), 13.83 (s, 1H, NH). Anal. $C_8H_{11}N_5S$. Calcd: C, 45.92; H, 5.30; N, 33.47. Found: C, 46.10; H, 5.46; N, 33.54.

5-(4-*Chloro*-3-*ethyl*-1-*methy*-1H-*pyrazol*-5-*yl*)-3-*methylthio*-4-*phenyl*-1,2,4-*triazole* (**5a**)

To a solution of compound **4a** (2.5 mmol) in 1 mol/L aqueous sodium hydroxide (2.5 mL) was stirred for several minutes, methyl iodide (2.5 mmol) in toluene (20 mL) were added. After stirring for 24 h at room temperature, the organic layer was separated and dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue was subjected to silica gel column chromatography with ethyl acetate/petroleum ether (60—90℃) as an eluent to give the pure product.

Compounds **5b—g** were prepared in the same method as **5a** by using the corresponding alkyl halide instead of methyl iodide.

5a (X = Cl, R = Ph, R^1 = Me) Yield 43%, mp 98—99℃. (H ($CDCl_3$): 1.14(t, J = 7.4 Hz, 3H, CH_3), 2.46(q, J = 7.4 Hz, 2H, CH_2), 2.74 (s, 3H, SCH_3), 3.77(s, 3H, NCH_3), 7.12—7.41 (m, 5H, Ph). Anal. $C_{15}H_{16}ClN_5S$. Calcd: C, 53.97; H, 4.83; N, 20.98. Found: C, 53.73; H, 4.79; N, 20.72.

5b (X = Cl, R = Ph, R^1 = $CH(CH_3)CO_2Et$) Yield 81%, colorless syrup. δ_H($CDCl_3$): 1.07, 1.18 (2t, J_1 = 7.3 Hz, J_2 = 7.3 Hz, 6H, $2CH_3$), 1.60(d, J = 7.1 Hz, 3H, $CHCH_3$), 2.46(q, J_2 = 7.3 Hz, 2H, CH_2), 3.72(s, 3H, NCH_3), 4.11(q, J_1 = 7.3 Hz, 2H, OCH_2), 4.75(q, J = 7.1 Hz, 1H, SCH), 7.12—7.37(m, 5H, Ph). Anal. $C_{19}H_{22}ClN_5O_2S$. Calcd: C, 54.34; H, 5.28; N, 16.68. Found: C, 53.97; H, 5.12; N, 16.39.

5c (X = H, R = Ph, R^1 = $CH(CH_3)CO_2Et$) Yield 78%, mp 74—75℃. δ_H($CDCl_3$): 1.05(t, J = 7.3 Hz, 3H, OCH_2CH_3), 1.24(t, J = 7.3 Hz, 3H, CH_3), 1.63(d, J = 7.3 Hz, 3H, $CHCH_3$), 2.43(q, J = 7.3 Hz, 2H, CH_2), 4.14(s, 3H, NCH_3), 4.16 (q, J = 7.3 Hz, 2H, OCH_2), 4.58(q, J = 7.3 Hz, 1H, SCH), 5.30(s, 1H, H4-pyrazole), 7.20—7.53 (m, 5H, Ph). Anal. $C_{19}H_{23}N_5O_2S$. Calcd: C, 59.20; H, 6.01N, 18.17. Found: C, 59.02; H, 5.95; N, 17.87.

5d (X = Cl, R = H, R^1 = Me) Yield 68%, mp 102—103℃. δ_H($CDCl_3$): 1.25(t, J = 7.7 Hz, 3H, CH_3), 2.66(s, 3H, SCH_3), 2.66(q, J = 7.7 Hz, 2H, CH_2), 4.18(s, 3H, NCH_3), 8.70(s, 1H, NH). Anal. $C_9H_{12}ClN_5S$. Calcd: C, 41.94; H, 4.83; N, 27.17. Found: C, 42.10; H, 4.64; N, 27.47.

5e (X = Cl, R = H, R^1 = Et) Yield 66%, mp 254—255℃. δ_H($CDCl_3$): 1.26(t, J = 7.8 Hz, 3H, CH_2CH_3), 1.43(t, J = 7.3 Hz, 3H, SCH_2CH_3), 2.67(q, J = 7.8 Hz, 2H, CH_2CH_3), 3.21(q, J = 7.3 Hz, 2H, SCH_2), 4.19(s, 3H, NCH_3), 8.70(s, 1H, NH). Anal. $C_{10}H_{14}ClN_5S$. Calcd: C, 44.20; H, 5.19; N, 25.77. Found: C, 44.47; H, 5.06; N, 25.59.

5f (X = Cl, R = H, R^1 = $CH(CH_3)CO_2Et$) Yield 73%, mp 77—78℃. δ_H($CDCl_3$): 1.20—1.28 (m, 6H, $2CH_3$), 1.62 (d, J = 7.3 Hz, 3H, $CHCH_3$), 2.63(q, J = 7.3 Hz, 2H, CH_2), 4.14—4.21(m, 6H, NCH_2, OCH_2 and SCH). Anal. $C_{13}H_{18}ClN_5O_2S$. Calcd: C, 45.41; H, 5.25; N, 20.37. Found: C, 45.13; H, 5.28; N, 20.33.

5g (X = H, R = H, R^1 = $CH(CH_3)CO_2Et$) Yield 68%, mp 59—60℃. ν_{max}: 3398(NH), 3103 (=CH), 2961, 2753, 1742(C=O), 1533, 1498, 1450, 1382, 1323, 1160, 1007, 810, 740 cm^{-1}. δ_H ($CDCl_3$): 1.18—1.25(m, 6H, $2CH_3$), 1.57(d, J = 7.3 Hz, 3H, $CHCH_3$), 2.62 (q, J = 7.4 Hz, 2H, CH_2), 4.17(m, 6H, NCH_2, OCH_2 and SCH), 6.52 (s, 1H, 4-H-pyrazole). Anal. $C_{13}H_{19}N_5O_2S$. Calcd: C, 50.47; H, 6.19; N, 22.64. Found: C, 50.20; H, 5.89; N, 22.58.

2-*Anilino*-(4-*chloro*-3-*ethyl*-1-*methyl*-1*H*-*pyrazol*-5-*yl*)-1,3,4-*oxadiazole* (**6**)

To a solution of compound **2a** (2 mmol) in ethanol (10 mL) were added aqueous sodium hydroxide (4 mol/L, 3 mL) and I_2 in potassium iodide (5% solution) dropwise till a great amount of solid appeared at 0℃. The mixture was refluxed for 40 min and allowed to stand overnight at room temperature, poured over crushed ice

and the precipitated solid was washed with dilute sodium thiosulphate solution followed by washing with water and recrystallized from ethanol.

6 (X = Cl, R = Ph) Yield 25%, mp 200—201℃. δ_H($CDCl_3$): 1.26(t, J = 7.4 Hz, 3H, CH_3), 2.65(q, J = 7.4 Hz, 2H, CH_2), 4.18(s, 3H, NCH_3), 7.08—7.52(m, 5H, Ph), 8.63(s, 3H, NH). Anal. $C_{14}H_{14}ClN_5O$. Calcd: C, 55.36; H, 4.64; N, 23.06. Found: C, 55.35; H, 4.89; N, 22.99.

1-Acetyl-2-(4-chloro-3-ethyl-1-methyl-1H-pyrazol-5-carbonyl) hydrazine (**7**)

Method I: A solution of compound **2a** (2 mmol) in acetic acid (8 mL) was refluxed for 4.5 h and cooled. The separated solid was filtered and recrystallized from ethanol.

Method II: **1a** (X = Cl, 2 mmol) was dissolved in acetic acid (8 mL) and the mixture refluxed for 4 h and cooled. The separated solid was filtered, washed with water, dried and crystallized from ethanol.

7 (X = Cl) Yield 64%, mp 185—186℃. δ_H ($CDCl_3$): 1.20(t, J = 7.5 Hz, 3H, CH_3), 2.11(s, 3H, $COCH_3$), 2.60(q, J = 7.5 Hz, 2H, CH_2), 4.07 (s, 3H, NCH_3), 8.97(s, 1H, NH), 9.26(s, 1H, NH). Anal. $C_9H_{13}ClN_4O_2$. Calcd: C, 44.18; H, 5.36; N, 22.90. Found: C, 44.32; H, 5.31; N, 22.79.

4-Amino-5-(4-chloro-3-ethyl-1-methy-1H-pyrazol-5-yl)-3-(1-ethoxycarbonylethylthio)-1,2,4-triazole (**10a**)

Compounds **10a—b** were prepared in the same method as **5a** using compound **9** and the corresponding alkyl halide instead of **4a** and methyl iodide respectively.

10a (X = Cl) Yield 77%, Colorless Syrup. δ_H($CDCl_3$): 1.09—1.17(m, 6H, $2CH_3$), 1.53(d, J = 7.2 Hz, 3H, $CHCH_3$), 2.53(q, J = 7.6 Hz, 2H, CH_2), 3.71(s, 3H, NCH_3), 4.03(q, J = 7.0 Hz, 2H, OCH_2), 4.33(q, J = 7.2 Hz, 1H, SCH), 5.21 (s, 2H, NH_2). Anal. $C_{13}H_{19}ClN_6O_2S$. Calcd: C, 43.51; H, 5.34; N, 23.42. Found: C, 43.81; H, 5.51; N, 23.12.

10b (X = H) Yield 72%, mp 115—116℃. δ_H($CDCl_3$): 1.17—1.29(m, 6H, $2CH_3$), 1.61(d, J = 7.3 Hz, 3H, $CHCH_3$), 2.64(q, J = 7.4 Hz, 2H, CH_2), 4.15(s, 3H, NCH_3), 4.10—4.17(m, 3H, OCH_2 and SCH), 5.14(s, 2H, NH_2), 6.52(s, 1H, 4-H-pyrazole). Anal. $C_{13}H_{20}N_6O_2S$. Calcd: C, 43.13; H, 6.21; N, 25.91. Found: C, 43.38; H, 6.07; N, 25.94.

5-(4-Chloro-3-ethyl-1-methyl-1H-pyrazol-5-yl)-1, 3, 4-thiadiazole-2-thione (**11**)

Potassium dithiocarbazate **8** (10 mmol) was added in portion to concentrated H_2SO_4 (15 mL) at 0℃ over 40 min. The mixture was stirred for 1 h at room temperature and poured over crushed ice and allowed to stand overnight. The separated solid was dissolved in dilute aqueous sodium hydroxide. The insoluble solid was filtered and the filtrate was acidified with dilute hydrochloric acid. The precipitate was filtered, washed with water, dried, and recrystallized from ethanol.

11 (X = Cl) Yield 64%, mp 182—183℃. ν_{max}: 3047(NH), 2834, 2726, 1513, 1463, 1372, 1260(C=S), 1060, 982, 727 cm^{-1}. δ_H(CD_3COCD_3): 1.20(t, J = 7.5 Hz, 3H, CH_3), 2.59(q, J = 7.5 Hz, 2H, CH_2), 4.06(s, 3H, NCH_3), δ_C: 12.81 (CH_3), 19.59(CH_2), 41.05(NCH_3), 110.50(pyrazole-C3), 128.83(pyrazole-C4), 148.89(pyrazole-C5), 150.43(thiadiazole-C5), 188.59(C=S). Anal. $C_8H_9ClN_4S_2$. Calcd: C, 36.85; H, 3.48; N, 21.49. Found: C, 37.00; H, 3.21; N, 21.78.

Bis[5-(4-chloro-3-ethyl-1-methyl-1H-pyrazol-5-yl)-1,3,4-thiadiazol-2-yl] disulfide (**12**)

To a solution of **8** (2 mmol) in ethanol (10 mL) was added hydrogen peroxide (30%, 2.5 mmol) in ethanol (2 mL). The mixture was stirred for 3 h at room temperature. The solid obtained was recrystallized from ethanol.

12 (X = Cl) Yield 92%, mp 162—163℃. δ_H(DMSO): 1.18(t, J = 7.4 Hz, 6H, $2CH_3$), 2.60 (q, J = 7.4 Hz, 4H, $2CH_2$), 4.15(s, 6H, $2NCH_3$). Anal. $C_{16}H_{16}Cl_2N_8S_4$. Calcd: C, 36.99; H, 3.10; N, 21.57. Found: C, 36.78; H, 3.25; N, 21.32.

2-(3-Bromopropyl) thio-5-(4-chloro-3-ethyl-1-methyl-

1H-pyrazol-5-yl)-1,3,4-*thiadiazole* (**13**) *and* 1,3-*bis*[5-(4-*chloro*-3-*ethyl*-1-*methyl*-1*H*-*pyrazol*-5-*yl*)-1,3,4-*thiadiazolylthio*]*propane* (**14**)

To a solution of compound **11** (2 mmol) in 1 mol/L aqueous sodium hydroxide (2 mL, 2 mmol) was added tetrabutylammonium bromide (0.12 g). The mixture was stirred for several minutes, 1, 3-dibromopropane (1 mmol) in toluene (20 mL) was added. After stirring for 48 h at room temperature, the organic layer was separated and dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue was subjected to silica gel column chromatography with ethyl acetate/petroleum ether (60—90℃) as an eluent to give **13** and **14**.

13 (X = Cl) Yield 39%, mp 49—50℃. δ_H ($CDCl_3$): 1.24(t, J = 7.4Hz, 3H, CH_3), 2.35—2.46(m, 2H, $SCH_2CH_2CH_2Br$), 2.64(q, J = 7.4 Hz, 2H, CH_2), 3.45—3.59(m, 4H, SCH_2 and CH_2Br), 4.22(s, 3H, NCH_3). Anal. $C_{11}H_{14}BrClN_4S_2$. Calcd: C, 34.61; H, 3.70; N, 14.68. Found: C, 34.38; H, 3.57; N, 14.67.

14 (X = Cl) Yield 36%, mp 130—131℃. δ_H($CDCl_3$): 1.25(t, J = 7.4Hz, 6H, $2CH_3$), 2.40—2.49(m, 2H, $CH_2CH_2CH_2$), 2.66(q, J = 7.4 Hz, 4H, $2CH_2CH_3$), 3.56(t, J = 7.0 Hz, 4H, $CH_2CH_2CH_2$), 4.22(s, 6H, $2NCH_3$). Anal. $C_{19}H_{22}Cl_2N_8S_4$. Calcd: C, 40.60; H, 3.95; N, 19.95. Found: C, 40.66; H, 3.98; N, 19.67.

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