Synthesis of some new azoles with antiviral potential[1]

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Abstract
Starting from the pyrazole-4-carboxylic acid hydrazide **3**, a variety of new oxadiazoles **7-9, 11, 13, 17, 18,** triazoles **20, 22-25**, thiadiazole **21** and pyrazole derivatives **26-29** have been synthesized.

Keywords: Pyrazoles, 1,3,4-oxadiazoles, 1,2,4-triazoles 1,3,4-thiadiazole, 1,2,4-triazine

Introduction

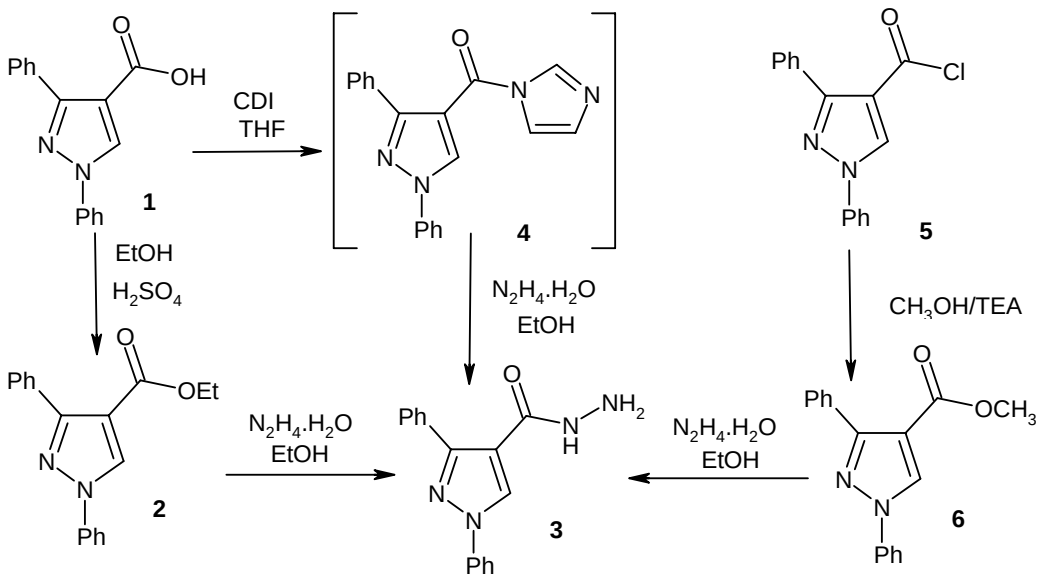
1,3,4-Oxadiazoles are known to have a broad spectrum of biological activities.[2-6] Some C-(β-D-Glucopyranosyl)-1,3,4-oxadiazoles were synthesized as potential glycogen phosphorylase inhibitors.[7] Katritzky *et al.*[8] reported a new route to 2-amino-1,3,4-oxadiazoles. These compounds were shown to possess antidiabetic,[9] antiarthritic and antiinflammatory[10] activities.

On the other hand, 1,2,4-triazoles are associated with diverse pharmacological activities such as analgesic, antiasthmatic, diuretic, antihypertensive, anticholinergic, antibacterial, antifungal and anti-inflammatory activity.[11-14] It was also reported that a large number of compounds containing a triazole ring possess a moderate antiviral activity.[15] Also, it was reported that the pyrazole-4-carboxylic acid hydrazides and its hydrazones possess antimicrobial activity.[16] Recently, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, 1,2,4-triazoles and triazines have attracted particular attention due their anti-inflammatory,[17-19] analgesic, ulcerogenic and lipid peroxidation activities.[17]

Because of our interest in the synthesis of new 1,3,4-oxadiazoles, 1,2,4-triazoles, 1,3,4-thiadiazines and pyrazole derivatives of biological interest,[20-26] we decided to synthesize the title compounds for the future evaluation of their antiviral activity.

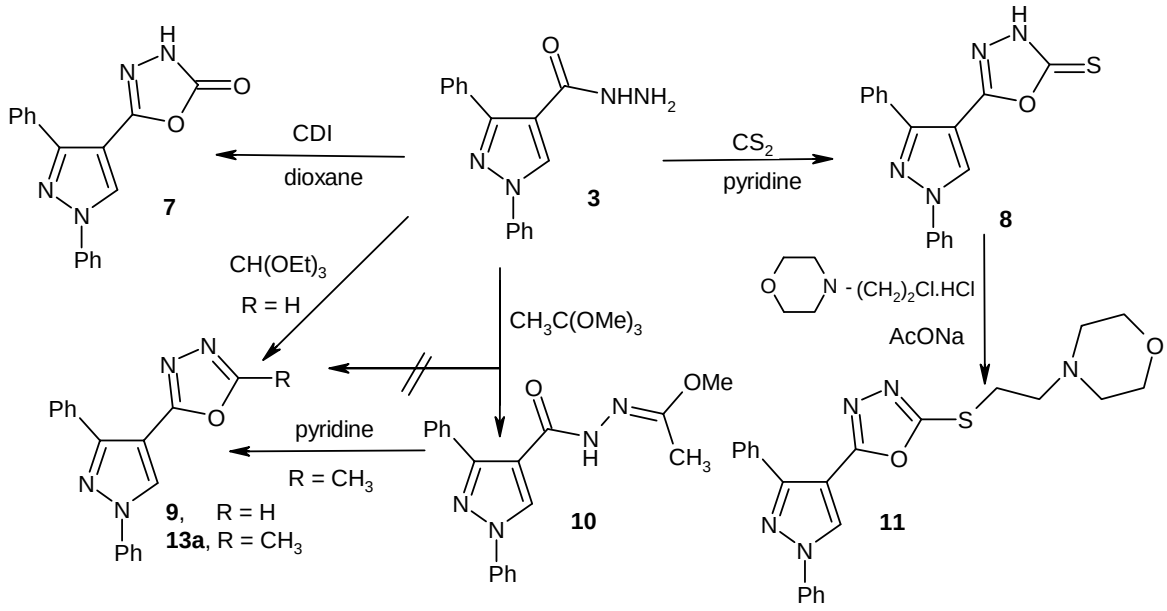
Results and Discussion

The synthesis of the key intermediate **3** was described previously by Chornous *et al*.[16] via the reaction of the pyrazole-4-carboxylic acid chloride **5** with methanol in the presence of an organic base followed by hydrazinolysis with hydrazine hydrate giving **3** in 75 % yield, m.p. 157-58 ºC. In our hands, a better yield (95%) of the hydrazide **3** could be obtained by hydrazinolysis of the pyrazole-4-carboxylic acid ethyl ester **2**. A comparable yield (94%) of **3** was also obtained via an alternative activation of the carboxylic acid function of **1** using 1,1'-carbonyldiimidazole (CDI) in an inert solvent at room temperature, followed by hydrazinolysis of the imidazolyl intermediate **4** to afford the corresponding 1,3-diphenyl-1*H*-pyrazole-4-carbohydrazide **3** (Scheme 1).



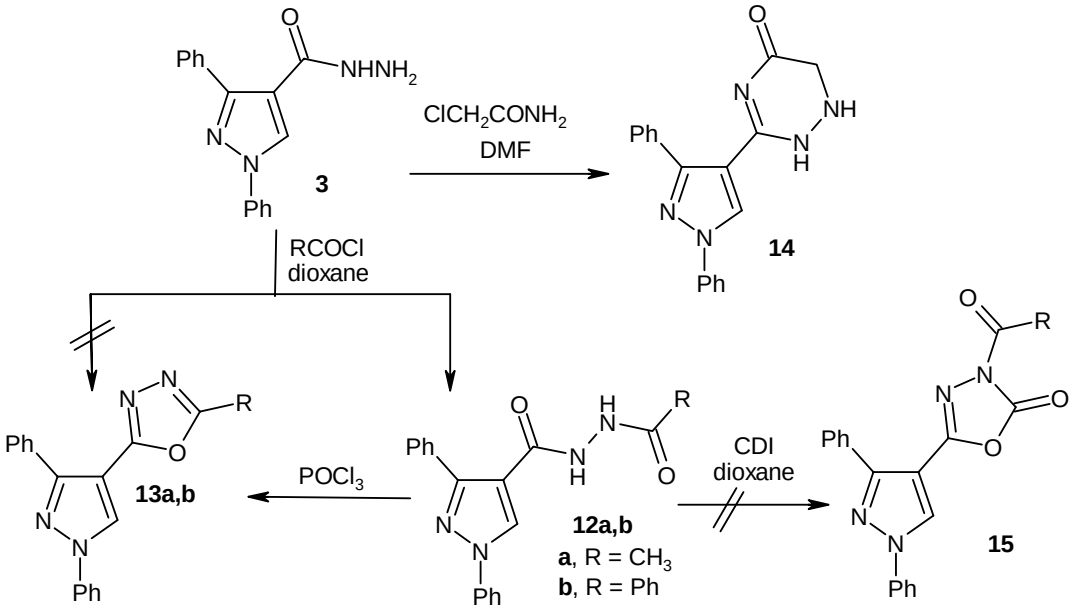
Scheme 1

The latter compound **3** was shown to be a key intermediate for the synthesis of several azoles. Thus, the interaction of **3** with carbon disulfide in boiling pyridine gave the corresponding oxadiazolinethione **8**. The oxadiazolinone **7** was obtained by treatment of the hydrazide **3** with 1,1'-carbonyldiimidazole (CDI) in refluxing dioxane. Another 1,3,4-oxadiazole **9** could be prepared by reaction of **3** with triethyl orthoformate. The thione function of **8** could be alkylated using the bioactive alkylating agent 4-(2-chloroethyl)morpholine hydrochloride in boiling ethanol in the presence of fused sodium acetate giving the corresponding 4-{2-[5-(1,3-diphenyl-1H-pyrazol-4-yl)[1,3,4]oxadiazol-2-ylthio]ethyl}morpho line (**11**). When **3** was allowed to react with trimethyl orthoacetate, the product was not the expected methyl oxadiazole derivative **13a**, it was identified as the hydrazone **10**. This latter compound could be cyclized in boiling pyridine to give **13a** (Scheme 2).



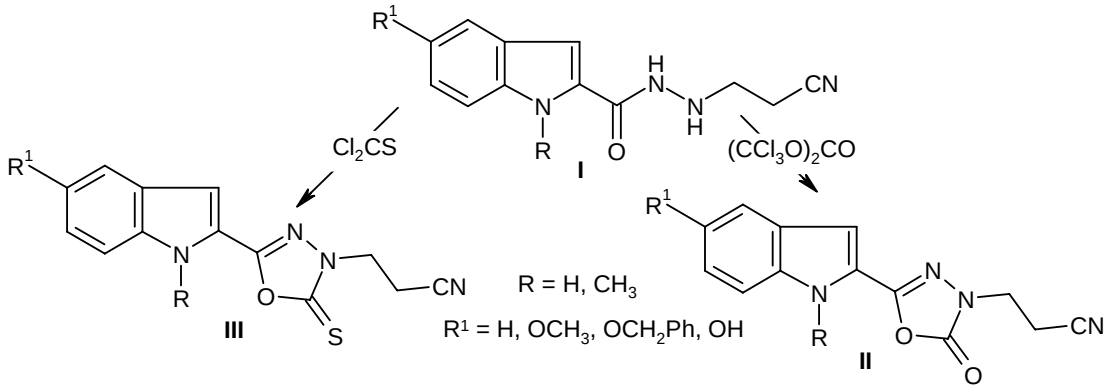
Scheme 2

The interaction of **3** with acid chlorides (acetyl- or benzoyl chloride) in boiling dioxane did not afford the expected 5-methyl or 5-phenyl[1,3,4]oxadiazole derivatives **13a,b**, however the *N*-acetyl or *N*-phenyl carboxylic acid hydrazide **12a**,**b** derivatives were shown to be the reaction products. The latter compounds **12a,b** were subjected to cyclodehydration in boiling phosphorus oxychloride to give the corresponding oxadiazoles **13a,b**. The reaction of **3** with chloroacetamide in *N*,*N*-dimethylformamide gave the triazinone **14** (Scheme 3). An attempt to prepare the 3-substitued[1,3,4]oxadiazol-2-one **15** via cyclization of **12** using 1,1'-carbonyldiimidazole (CDI) in dry dioxane was unsuccessful.



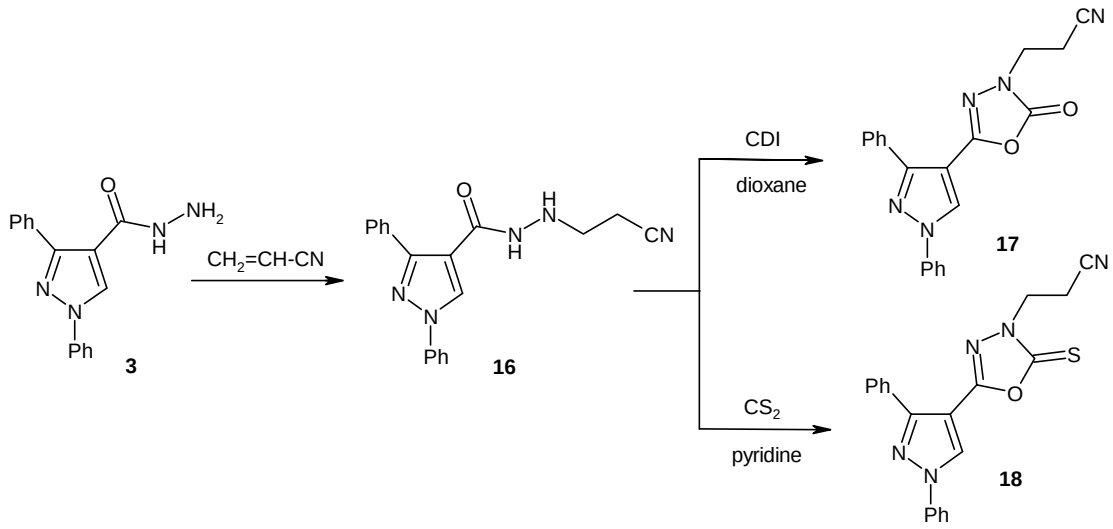
Scheme 3

Cyanoethylation of **3** through Michael addition reaction using neat acrylonitrile under reflux afforded N^2-(2-cyanoethyl)-1,3-diphenyl-1*H*-pyrazole-4-carbo- hydrazide **(16)**. Monge *et al*[27] reported that the N^2-(2-cyanoethyl)-*N*-methylindole–2-carbohydrazide **I** could be transformed into the oxadiazolone **II** and the oxadiazolethione **III** by the reaction with triphosgene and thiophosgene respectively.



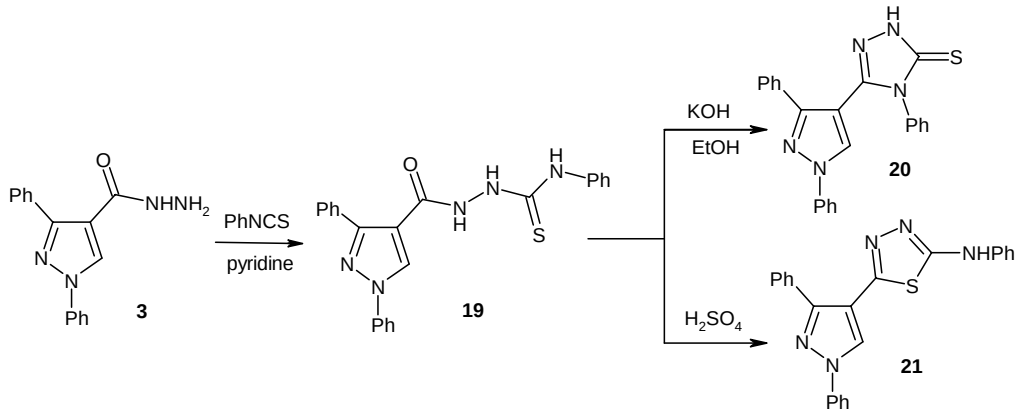
We have modified the reagents used in the above two reactions and carried out similar cyclization reactions on our cyanoethylhydrazide **16** using 1,1'-carbonyldiimidazole (CDI) and CS_2 instead of triphosgene and thiophosgene respectively. Consequently, compound **17** could be obtained by a new unreported method via the treatment of **16** with CDI. Also, the treatment of **16** with carbon disulfide in pyridine afforded the corresponding oxadiazolethione derivative **18**

(Scheme 4). Both IR and ^{1}H NMR spectra showed no signals corresponding to the NH groups thus confirming the structure of compounds **17** and **18**.



Scheme 4

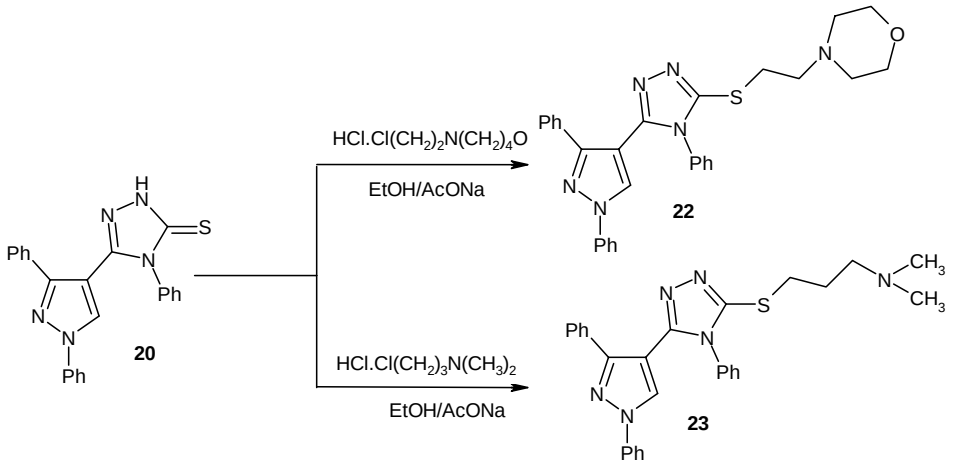
The reaction of **3** with phenyl isothiocyanate in boiling pyridine gave N^1-(1,3-diphenyl-1*H*-pyrazol-4-ylcarbonyl)-N^4-phenylthiosemicarbazide (**19**). The latter compound **19** underwent two different cyclization reactions. Thus, when an ethanolic solution of **19** was treated with a KOH solution under reflux, the product was 1,2,4-triazole-3-thione **20**. Treatment of **19** with cold concentrated H_2SO_4 resulted in dehydrocyclization giving the 2-phenylamino-1,3,4-thiadiazole derivative **21** (Scheme 5).



Scheme 5

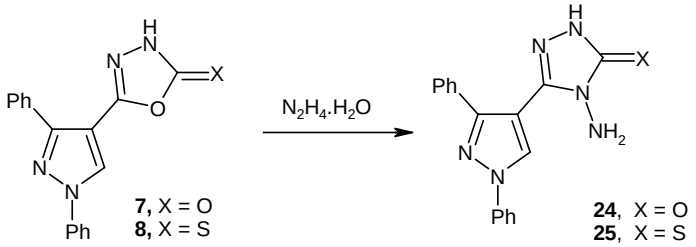
Alkylation of the triazolethione derivative **20** with some alkylating agents such as 4-(2-chloroethyl)morpholine hydrochloride or 2-dimethyaminopropyl chloride hydrochloride in

boiling ethanol in the presence of fused sodium acetate gave the corresponding 4-{2-[5-(1,3-diphenyl-1*H*-pyrazol-4-yl)-4-phenyl-4*H*[1,2,4]triazol-3-ylthio]ethyl}morpholine **22** and {3-[5-(1,3-diphenyl-1*H*-pyrazol-4-yl)-4-phenyl-4*H*-[1,2,4]triazol-3-ylthio]propyl}dimethylamine **23** respectively.



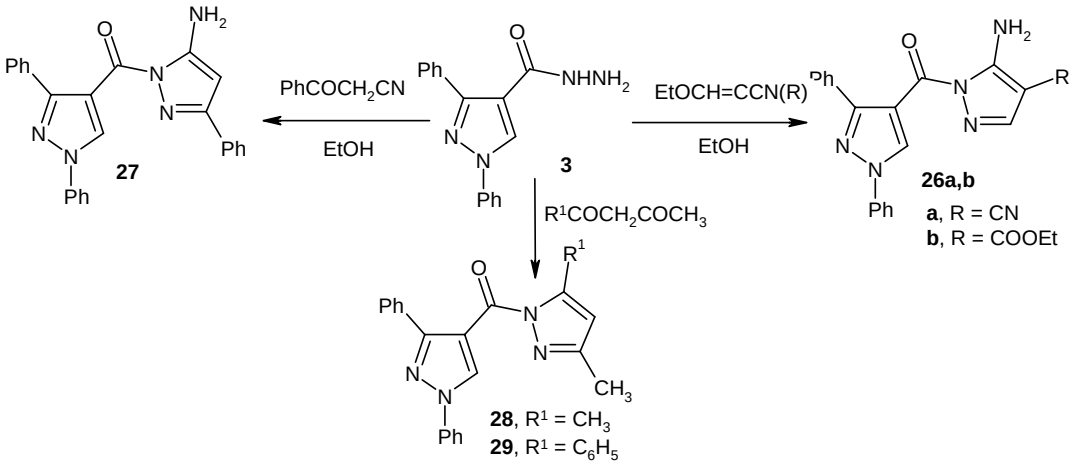
Scheme 6

The oxadiazolinone **7** or its thione analogue **8** when treated with hydrazine hydrate in boiling ethanol afforded the corresponding aminotriazolone **24** or the aminotriazolonethione **25** respectively.



Scheme 7

Finally, the reaction of the hydrazide **3** with ethoxymethylenemalononitrile and/or ethyl (ethoxymethylene)cyanoacetate in boiling ethanol gave the corresponding 5-amino-4-substituted pyrazole derivatives **26a,b**. The 5-amino-3-phenyl pyrazole derivative **27** could be isolated by the reaction of **3** with benzoylacetonitrile. In addition, the interaction of **3** with acetyl- or benzoylacetone in absolute ethanol afforded the corresponding pyrazole derivatives **28** and **29** respectively.



Scheme 8

All the compounds prepared are under evaluation for their antiviral activity and the results will be published later.

Experimental Section

General Procedures. Melting points are uncorrected and were measured on a Kofler melting point apparatus. IR spectra were recorded on a Shimadzu 470 IR-Spectrophotometer (KBr; υ_{max} in cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded on a Jeol LA 400 MHz FT NMR spectrometer and on a Varian EM 390, 90 MHz spectrometer (TMS as internal reference, δ values in ppm). Mass spectra were obtained with a Jeol JMS-600 mass spectrometer. Elemental analyses (C, H, N) were carried out using a Perkin-Elmer 240 C Micro analyzer and sulfur analysis were obtained using oxygen flask method at the Chemistry Department (Microanalytical Laboratory), Assiut University.

1,3-Diphenyl-1*H*-pyrazole-4-carboxylic acid hydrazide (3). Method (a). A mixture of ethyl 1,3-diphenyl-1*H*-pyrazole-4-carboxylate **2** (292 mg, 1 mmol) and hydrazine hydrate (2 mL, 85 %) in ethanol (10 mL) was heated under reflux for 8 h. The reaction mixture was then concentrated and left to cool. The solid product obtained was washed with water and recrystallized from ethanol to give **3** as white crystals (264 mg, 95 %), mp.158-160 ºC (Lit.[16] 75 %, mp. 157-158 ºC).

Method (b). A mixture of 1,3-diphenyl-1*H*-pyrazole-4-carboxylic acid **1** (264 mg, 1 mmol) and *N*,*N*'-carbonyldiimidazole (243 mg, 1.5 mmol) in dry THF was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was heated under reflux with hydrazine hydrate (1 mL, 50 mmol) in ethanol (10 mL) for 12 h. The solvent was removed under reduced pressure and the residue obtained was triturated with water. The solid precipitate

thus obtained was collected by filtration and recrystallized from ethanol to give **3** as white crystals (261 mg, 94 %), mp.158-160 ºC.

5-(1,3-Diphenyl-1*H*-pyrazol-4-yl)[1,3,4]oxadiazole-2(3*H*)-one (7). A mixture of **3** (278 mg, 1 mmol) and *N*,*N*'-carbonyldiimidazole (243 mg, 1.5 mmol) in dioxane (10 mL) was heated under reflux for 8 h. After cooling, the solvent was removed under reduced pressure and the residue was triturated with water. The solid product formed was filtered off and recrystallized from ethanol to give **7** as colorless crystals (220 mg, 72%), mp. 244-246 ºC. ^{1}H NMR (DMSO-d_6) δ 10.83 (s, 1H, NH), 8.90 (s, 1H, pyrazole CH), 7.97-7.80 (m, 4H, Ph), 7.60-7.27 (m, 6H, Ph); IR (KBr): $\bar{\nu}$ 3200 (NH), 3010 (arom. CH), 1690 (C=O), 1640 (C=N) cm^{-1}; Anal. calcd. for $C_{17}H_{12}N_4O_2$ (304.31): C, 67.10; H, 3.97; N, 18.41. Found: C, 67.02; H, 3.84; N, 18.29.

5-(1,3-Diphenyl-1*H*-pyrazol-4-yl)[1,3,4]oxadiazole-2(3*H*)-thione (8). A mixture of **3** (278 mg, 1 mmol) and carbon disulfide (3 mL) in pyridine (10 mL) was heated under reflux on water bath for 6 h. After cooling, the solvent was evaporated under reduced pressure and the residue was triturated with an ice-water mixture and neutralized with diluted HCl. The solid precipitate formed was filtered off and recrystallized from ethanol to afford **8** as pale yellow crystals (318 mg, 99%), mp. 222-224 ºC. ^{1}H NMR (DMSO-d_6) δ 10.80 (s, 1H, NH), 9.23 (s, 1H, pyrazole CH), 8.07-7.77 (m, 4H, Ph), 7.63-7.30 (m, 6H, Ph); IR (KBr): $\bar{\nu}$ 3200 (NH), 3030 (arom. CH), 1640 (C=N), 1210 (C=S) cm^{-1}; Anal. calcd. for $C_{17}H_{12}N_4OS$ (320.38): C, 63.73; H, 3.78; N, 17.49; S, 10.01. Found: C, 63.67; H, 3.63; N, 17.33; S, 9.92.

2-(1,3-Diphenyl-1*H*-pyrazol-4-yl)[1,3,4]oxadiazole (9). A mixture of **3** (278 mg, 1 mmol) and triethylorthoformate (5 mL) was heated under reflux for 12 h. After cooling, the solvent was evaporated under reduced pressure and the solid product obtained was filtered off and recrystallized from ethanol to give compound **9** as colorless crystals (210 mg, 73%), mp.208-210 ºC. ^{1}H NMR (DMSO-d_6) δ 9.10 (s, 1H, pyrazole CH), 8.03-7.67 (m, 4H, Ph), 7.57-7.27 (m, 7H, Ph and oxadiazole CH); IR (KBr): $\bar{\nu}$ 3050 (arom. CH), 1640 (C=N) cm^{-1}; Anal. calcd. for $C_{17}H_{12}N_4O$ (288.30): C, 70.82; H, 4.20; N, 19.43. Found: C, 70.76; H, 4.13; N, 19.35.

***N*^{2}-(1-Methoxyethylidene)-1,3-diphenyl-1*H*-pyrazole-4-carbohydrazide (10).** A mixture **3** (278 mg, 1 mmol) and trimethylorthoacetate (5 mL) was boiled under reflux for 12 h. After cooling, the solvent was removed under reduced pressure and the residue obtained was triturated with ethanol. The solid product obtained was collected by filtration and recrystallized from ethanol to give compound **10** as white flakes (250 mg, 75%), mp.168-170 ºC. ^{1}H NMR (DMSO-d_6) δ 10 57 (s, 1H, NH), 9.13 (s, 1H, pyrazole CH), 8.03-7.80 (m, 4H, Ph), 7.60-7.27 (m, 6H, Ph), 3.32 (s, 3H, OCH_3), 2.52 (s, 3H, CH_3); IR (KBr): $\bar{\nu}$ 3200 (NH), 3030 (arom. CH), 1660 (C=O), 1640 (C=N) cm^{-1}; Anal. calcd. for $C_{19}H_{18}N_4O_2$ (334.37): C, 68.25; H, 5.43; N, 16.76. Found: C, 68.14; H, 5.37; N, 16.63.

4-{2-[5-(1,3-Diphenyl-1*H*-pyrazol-4-yl)[1,3,4]oxadiazol-2-ylthio]ethyl}morpholine (11). A mixture of the oxadiazolethione **8** (320 mg, 1 mmol), sodium acetate (400 mg, 5 mmol) and 4-(2-chloroethyl)morpholine hydrochloride (188 mg, 1 mmol) in ethanol (10 ml) was heated under reflux for 6 h. The solvent was evaporated and the residue was triturated with water. The solid product formed was collected by filtration and recrystallized from ethanol to afford **11** as bright

grey crystals (375 mg, 87%), mp.188-190 ºC. ^{1}H NMR ($CDCl_3$) δ 8.54 (s, 1H, pyrazole CH), 7.92-7.74 (m, 4H, Ph), 7.51-7.38 (m, 6H, Ph), 3.68 (t, *J* = 4.1 Hz, 4H, OCH_2), 3.38 (t, *J* = 6.6 Hz, 2H, SCH_2CH_2N), 2.76 (t, *J* = 6.6 Hz, 2H, SCH_2CH_2N), 2.47 (t, *J* = 4.1 Hz, 4H, NCH_2); ^{13}C NMR ($CDCl_3$) δ 29.65 (SCH_2CH_2N), 53.22 (SCH_2CH_2N), 57.03 ($2CH_2N$), 66.81 ($2CH_2O$), ar-C: [119.39 (2CH), 128.21 (2CH), 128.88 (CH), 128.94 (CH), 129.20 (2CH), 129.54 (2CH), 129.60 (C), 135.20 (C)], 131.57 (pyrazole–C-4), 132.87 (pyrazole-C-2), 139.11 (pyrazole-C-5), 162.41 (oxadiazole-C-2), 165.22 (oxadiazole-C-5); IR (KBr): $\bar{\nu}$ 3080 (arom. CH), 1660 (C=O), 1640 (C=N) cm^{-1}; Anal. calcd. for $C_{23}H_{23}N_5O_2S$ (433.53): C, 63.72; H, 5.35; N, 16.15; S, 7.40. Found: C, 63.61; H, 5.27; N, 16.07; S, 7.26.

***N*^{2}-Acetyl-1,3-diphenyl-1*H*-pyrazole-4-carbohydrazide (12a).** To a solution **3** (278 mg, 1 mmol) in dioxane (10 mL) acetyl chloride (78 mg, 1 mmol) was added. The reaction mixture was refluxed for 4 h., then the solvent was removed under reduced pressure and the residue was triturated with an ice-water mixture. The solid product obtained was filtered off and recrystallized from ethanol to give **12a** as white crystals (290 mg, 90%), mp.190-192 ºC. ^{1}H NMR (DMSO-d_6) δ 10.52 (s, 1H, NH), 10.40 (s, 1H, NH), 8.85 (s, 1H, pyrazole CH), 7.97-7.73 (m, 4H, Ph), 7.60-7.27 (m, 6H, Ph), 1.92 (s, 3H, CH_3); IR (KBr): $\bar{\nu}$ 3200 (NH), 3010 (arom. CH), 1670 (C=O), 1640 (C=N) cm^{-1}; Anal. calcd. for $C_{18}H_{16}N_4O_2$ (320.35): C, 67.49; H, 5.03; N, 17.49. Found: C, 67.37; H, 4.92; N, 17.29.

***N*^{2}-Benzoyl-1,3-diphenyl-1*H*-pyrazole-4-carbohydrazide (12b).** To a solution of **3** (278 mg, 1 mmol) in dioxane (10 mL) benzoyl chloride (88 mg, 1 mmol) was added. The reaction mixture was refluxed for 4 h., then the solvent was removed under reduced pressure and the residue obtained was triturated with an ice-water mixture. The solid product obtained was filtered off and recrystallized from ethanol to give **12b** as white crystals (295 mg, 77%), mp. 206-208 ºC. ^{1}H NMR (DMSO-d_6) δ 10.87 (s, 1H, NH), 10.62 (s, 1H, NH), 8.85 (s, 1H, pyrazole CH), 7.92-7.78 (m, 6H, Ph), 7.60-7.27 (m, 9H, Ph); IR (KBr): $\bar{\nu}$ 3200 (NH), 3010 (arom. CH), 1670 (C=O), 1640 (C=N) cm^{-1}; Anal. calcd. for $C_{23}H_{18}N_4O_2$ (382.41): C, 72.24; H, 4.74; N, 14.65. Found: C, 72.13; H, 4.65; N, 14.51.

General procedure for the synthesis of 2-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-5-substituted[1,3,4]oxadiazoles (13a,b)

A solution of the hydrazide **12a,b** (1 mmol) in phosphorous oxychloride (5 mL) was heated under reflux at 100 ºC for 4 h. After cooling, the solvent was removed *in vacuo* and the residue was poured into an ice-water mixture and neutralized with ammonium hydroxide (20%). The solid product obtained was collected by filtration and recrystallized from ethanol to give **13a,b** .

2-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-5-methyl[1,3,4]oxadiazole (13a). White crystals (240 mg, 79%), mp.100-102 ºC. ^{1}H NMR (DMSO-d_6) δ 9.13 (s, 1H, pyrazole CH), 8.03-7.80 (m, 4H, Ph), 7.60-7.27 (m, 6H, Ph), 2.52 (s, 3H, CH_3); IR (KBr): $\bar{\nu}$ 3200 (NH), 3010 (arom. CH), 1670 (C=O), 1640 (C=N) cm^{-1}; Anal. calcd. for $C_{18}H_{14}N_4O$ (302.33): C, 71.51; H, 4.67; N, 18.53. Found: C, 71.39; H, 4.48; N, 18.43.

2-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-5-phenyl[1,3,4]oxadiazole (13b). White crystals (286 mg, 78%), mp.88-90 ºC. ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H, Pyrazole CH), 7.87-7.70 (m, 4H, Ph), 7.60-

7.27 (m, 11H, Ph); IR (KBr): $\bar{\nu}$ 3010 (arom. CH), 1640 (C=N) cm^{-1}; Anal. calcd. for $C_{23}H_{16}N_4O$ (364.40): C, 75.81; H, 4.43; N, 15.38. Found: C, 75.69; H, 4.35; N, 15.26.

3-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-1,2-dihydro[1,2,4]triazin-5(6*H*)-one (14). A mixture of **3** (278 mg, 1 mmol) and chloroacetamide (93 mg, 1 mmol) in dimethylformamide (10 ml) was heated under reflux for 25 h. The solvent was evaporated under reduced pressure and the residue was triturated with water. The solid thus obtained was filtered, dried and recrystallized from ethanol to afford compound **14** as yellow crystals (254 mg, 79%), mp. 98-100 ºC. ^{1}H NMR ($CDCl_3$) 8.46 (s, 1H, pyrazole CH), 7.66-7.55 (m, 4H, Ph), 7.34-7.16 (m, 6H, Ph), 6.37 (s, 1H, NH), 5.72 (s, 1H, NH), 2.81 (s, 2H, CH_2); IR (KBr): $\bar{\nu}$ 3350 (NH), 3030 (arom. CH), 2900 (aliph.CH), 1660 (C=O), 1640 (C=N) cm^{-1}; Anal. calcd. for $C_{18}H_{15}N_5O$ (317.34): C, 68.13; H, 4.76; N, 22.07. Found: C, 68.05; H, 4.64; N, 21.96.

***N*^{2}-(2-Cyanoethyl)-1,3-diphenyl-1*H*-pyrazole-4-carbohydrazide (16)**. Freshly distilled acrylonitrile (66 mg, 1.25 mmol) was added to a suspension of the carbohydrazide **3** (278 mg, 1 mmol) in ethanol (10 mL). The reaction mixture was heated under reflux for 24 h., then the solvent was removed under reduced pressure. The solid precipitate formed was filtered and recrystallized from ethanol to afford compound **16** as white crystals (301 mg, 91%), mp.144-146 ºC. ^{1}H NMR ($CDCl_3$) 11.53 (s, 1H, NHCO), 11.27 (s, 1H, NH), 8.38 (s, 1H, pyrazole CH), 7.70-7.57 (m, 4H, Ph), 7.47-7.30 (m, 6H, Ph), 3.07 (m, 2H, $NHCH_2CH_2CN$), 2.38 (t, *J* = 7.6 Hz, 2H, $NHCH_2CH_2CN$); IR (KBr): $\bar{\nu}$ 3290 (NH), 3050 (arom. CH), 2220 (C≡N), 1660 (C=O), 1630 (C=N) cm^{-1}; Anal. calcd. for $C_{19}H_{17}N_5O$ (331.37): C, 68.87; H, 5.17; N, 21.13. Found: C, 68.69; H, 5.08; N, 21.02.

3-[5-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-2-oxo[1,3,4]oxadiazol-3-yl]propionitrile (17). A mixture of **16** (278 mg, 1 mmol) and *N,N'*-carbonyldiimidazole (243 mg, 1.5 mmol) in dry dioxane (10 mL) was heated under reflux for 24 h., then it was concentrated and left to cool. The solid product obtained was filtered, washed with water, dried and recrystallized from petroleum ether/benzene (2:1) to give **17** as buff crystals (195 mg, 59%), mp. 88-90 ºC. ^{1}H NMR ($CDCl_3$) δ 9.03 (s, 1H, pyrazole CH), 7.87-7.57 (m, 4H, Ph), 7.50-7.23 (m, 6H, Ph); 3.67 (t, *J* = 5.8 Hz, 2H, NCH_2CH_2CN), 2.46 (t, *J* = 5.8 Hz, 2H, NCH_2CH_2CN); IR (KBr): $\bar{\nu}$ 3030 (arom. CH), 2900 (aliph.CH), 2220 (C≡N), 1770 (C=O), 1640 (C=N) cm^{-1}; Anal. calcd. for $C_{20}H_{15}N_5O_2$ (357.37): C, 67.22; H, 4.23; N, 19.60. Found: C, 67.11; H, 4.13; N, 19.47.

3-[5-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-2-thioxo[1,3,4]oxadiazol-3-yl]propionitrile (18). A suspension of **16** (278 mg, 1 mmol) and carbon disulfide (2 mL) in pyridine (5 mL) was heated under reflux on water bath for 24 h. The solvent was eliminated under reduced pressure and the residue was triturated with an ice-cold water and neutralized with diluted HCl. The solid product obtained was filtered off and recrystallized from petroleum ether/ethyl acetate (2:1) to afford **18** as buff crystals (242 mg, 64%), mp.110-112 ºC. ^{1}H NMR ($CDCl_3$) δ 9.03 (s, 1H, pyrazole CH), 7.87-7.63 (m, 4H, Ph), 7.53-7.23 (m, 6H, Ph); 3.33 (t, *J* = 5.8 Hz, 2H, NCH_2CH_2CN), 2.50 (t, *J* = 5.8 Hz, 2H, NCH_2CH_2CN); IR (KBr): $\bar{\nu}$ 3030 (arom. CH), 2900 (aliph.CH), 2220 (C≡N), 1640 (C=N), 1160 (C=S) cm^{-1}; Anal. calcd. for $C_{20}H_{15}N_5OS$ (373.43): C, 64.33; H, 4.05; N, 18.75; S, 8.59. Found: C, 64.19; H, 3.97; N, 18.64; S, 8.47.

***N*^{1}-(1,3-Diphenyl-1*H*-pyrazol-4-ylcarbonyl)-*N*^{4}-phenylthiosemicarbazide (19).** A suspension of **3** (278 mg, 1 mmol) and phenyl isothiocyanate (135 mg, 1 mmol) in ethanol (10 mL) was heated under reflux on water bath for 6 h. The solvent was concentrated and the solid product thus formed was filtered off and recrystallized from ethanol to afford compound **19** as white crystals (400 mg, 96%), mp.124-126 ºC. ^{1}H NMR (DMSO-d_6) δ 11.30 (s, 1H, NH), 10.60 (s, 1H, NH), 10.10 (s, 1H, NH), 9.10 (s, 1H, pyrazole CH), 8.03-7.80 (m, 5H, Ph), 7.62-7.30 (m, 10H, Ph); IR (KBr): $\bar{\nu}$ 3400 (NH), 3300 (NH), 3200 (NH), 3030 (arom. CH), 1660 (C=O), 1620 (C=N), 1220 (C=S) cm^{-1}; 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, 66.68; H, 4.49; N, 16.82; S, 7.59.

5-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-4-phenyl-2,4-dihydro-1,2,4-triazole-3-thione (20). A suspension of **19** (413 mg, 1 mmol) in ethanol (10 mL) was dissolved in aqueous potassium hydroxide (3 mL, 4 *N*). The reaction mixture was gently refluxed for 3 h., and then it was concentrated to one third of its volume, cooled, filtered and the filtrate was adjusted to pH 5-6 with dilute acetic acid. The white solid formed was filtered off and recrystallized from ethanol to give **20** as fine white crystals (356 mg, 90%), mp. 250-252 ºC. ^{1}H NMR (DMSO-d_6) δ 10.37 (s, 1H, NH), 8.70 (s, 1H, pyrazole CH), 7.92-7.78 (m, 3H, Ph), 7.47-7.30 (m, 8H, Ph), 7.13-6.97 (m, 4H, Ph); IR (KBr): $\bar{\nu}$ 3200 (NH), 3030 (arom. CH), 1620 (C=N), 1210 (C=S) cm^{-1}; Anal. calcd. for $C_{23}H_{17}N_5S$ (395.48): C, 69.85; H, 4.33; N, 17.71; S, 8.11 . Found: C, 69.74; H, 4.13; N, 17.59; S, 7.92.

***N*-Phenyl-[5-(1,3-diphenyl-1*H*-pyrazol-4-yl)-[1,3,4]thiadiazol-2-yl]amine (21)**. The thiosemicarbazide **19** (413 mg, 1 mmol) was added gradually with stirring to an ice-cold concentrated sulphuric acid (5 mL) and the reaction mixture was further stirred for 4 h in an ice bath. It was then poured into crushed ice and the resulting solution was adjusted to pH 7-8 with ammonium hydroxide solution. The grey solid formed was filtered off and recrystallized from ethanol/dioxane (1:1) to give **21** as grey crystals (300 mg, 76%), mp. 256-258 ºC. ^{1}H NMR (DMSO-d_6) δ 9.03 (s, 1H, NH), 8.66 (s, 1H, pyrazole CH), 8.00-7.87 (m, 2H, Ph), 7.63-7.37 (m, 10H, Ph), 7.23-7.96 (m, 3H, Ph); IR (KBr): $\bar{\nu}$ 3200 (NH), 3030 (arom. CH), 1600 (C=N), 1540 cm^{-1}; Anal. calcd. for $C_{23}H_{17}N_5S$ (395.48): C, 69.85; H, 4.33; N, 17.71; S, 8.11 . Found: C, 69.65; H, 4.16; N, 17.56; S, 7.89.

4-{2-[5-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-4-phenyl-4*H*-[1,2,4]triazol-3-ylthio]-ethyl}-morpholine (22). A mixture of the triazolinethione **20** (395 mg, 1 mmol), fused sodium acetate (400 mg, 5 mmol) and 4-(2-chloroethyl) morpholine hydrochloride (188 mg, 1 mmol) in ethanol (10 mL) was refluxed for 8 h. After cooling, the solvent was then removed under reduced pressure and the solid product thus obtained was washed with water, collected by filtration and recrystallized from petroleum ether/ethyl acetate (2:1) to give **22** as white crystals (410 mg, 81%), mp. 82-84 ºC. ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H, pyrazole CH), 7.71-7.69 (m, 3H, Ph), 7.46-7.10 (m, 10H, Ph), 6.70-6.68 (m, 2H, Ph), 3.68 (t, *J* = 4.5 Hz, 4H, OCH_2), 3.46 (t, *J* = 6.8 Hz, 2H, $SC\underline{H_2}CH_2N$), 2.77 (t, *J* = 6.8 Hz, 2H, $SCH_2C\underline{H_2}N$), 2.51 (t, *J* = 4.5 Hz, 4H, NCH_2); ^{13}C NMR ($CDCl_3$) δ 29.65 ($S\underline{C}H_2CH_2N$), 53.24 ($SCH_2\underline{C}H_2N$), 57.34 ($2\underline{C}H_2N$), 66.75 ($2\underline{C}H_2O$), ar-C: [119.37 (2CH), 126.50 (CH), 128.23 (2CH), 128.34 (CH), 128.41 (CH), 128.79 (2CH),

128.92 (2CH), 129.77 (2CH), 130.63 (2CH), 127.66 (C), 131.08 (C), 131.20 (C)], 132.11 (pyrazole–C-4), 132.97 (pyrazole-C-3), 139.33 (pyrazole-C-5), 149.267 (triazole-C-2), 151.82 (triazole-C-5); IR (KBr): $\bar{\nu}$ 3050 (arom. CH), 2920 (aliph.CH), 1640 (C=N), 1600 cm^{-1}; Anal. calcd. for $C_{29}H_{28}N_6OS$ (508.64): C, 68.48; H, 5.55; N, 16.52; S, 6.30. Found: C, 68.23; H, 5.36; N, 16.39; S, 6.12.

{3-[5-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-4-phenyl-4*H*-[1,2,4]triazol-3-ylthio]propyl} dimethyl amine (23). A mixture of the triazolinethione **20** (395 mg, 1 mmol), fused sodium acetate (400 mg, 5 mmol) and 2-diethylaminoethyl chloride hydrochloride (172 mg, 1 mmol) in ethanol (10 mL) was heated under reflux for 7 h. The solvent was eliminated *in vacuo* and the solid obtained was washed with water, filtered off and recrystallized from petroleum ether/benzene (2:1) to give compound **23** as white crystals (158 mg, 33%), mp. 65-67 ºC. ^{1}H NMR ($CDCl_3$) δ 8.13 (s, 1H, pyrazole CH), 7.87-7.57 (m, 3H, Ph), 7.43-7.06 (m, 10H, Ph), 6.73-6.60 (m, 2H, Ph), 3.22 (t, *J* = 7.5 Hz, 2H, SCH_2), 2.52 (t, unresolved, 2H, CH_2N), 2.30 (s, 6H, $N(CH_3)_2$), 2.06-1.83 (m, 2H, $SCH_2C\underline{H}_2CH_2N$); IR (KBr): $\bar{\nu}$ 3050 (arom. CH), 2920 (aliph.CH), 1640 (C=N), 1600 cm^{-1}; Anal. calcd. for $C_{28}H_{28}N_6S$ (480.63): C, 69.97; H, 5.87; N, 17.49; S, 6.67. Found: C, 69.78; H, 5.69; N, 17.31; S, 6.47.

4-Amino-5-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2,4-dihydro[1,2,4]triazole-3-one (24). A mixture of the oxadiazolinone **7** (304 mg, 1 mmol) and hydrazine hydrate (3 mL) in ethanol (10 mL) was heated under reflux for 6 h. After cooling, the solvent was removed *in vacuo* and the residue obtained was triturated with water. The solid precipitate formed was filtered off and recrystallized from ethanol to afford the title compound **24** as white crystals (266 mg, 87%), mp. 210-212 ºC. ^{1}H NMR (DMSO-d_6) δ 10.38 (s, 1H, NH), 8.93 (s, 1H, pyrazole CH), 7.97-7.73 (m, 4H, Ph), 7.62-7.30 (m, 6H, Ph), 3.67 (s, 2H, NH_2); IR (KBr): $\bar{\nu}$ 3350, 3250 (NH_2), 3150 (NH), 3030 (arom. CH), 1690 (C=O), 1640, 1600 (C=N) cm^{-1}; Anal. calcd. for $C_{17}H_{14}N_6O$ (318.33): C, 64.14; H, 4.43; N, 26.40; S, 5.03. Found: C, 63.92; H, 4.25; N, 26.16; S, 4.87.

4-Amino-5-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2,4-dihydro[1,2,4]triazole-3-thione (25). A mixture of the oxadiazolinethione **8** (320 mg, 1 mmol) and hydrazine hydrate (3 mL) in ethanol (10 mL) was heated refluxed 6 h. After cooling, the solvent was removed *in vacuo* and the residue obtained was triturated with water. The solid product formed was filtered off and recrystallized from ethanol to afford compound **25** as white crystals (297 mg, 89%), mp. 208-210 ºC. ^{1}H NMR (DMSO-d_6) δ 10.40 (s, 1H, NH), 8.96 (s, 1H, pyrazole CH), 7.97-7.73 (m, 4H, Ph), 7.73-7.30 (m, 6H, Ph), 5.63 (s, 2H, NH_2); IR (KBr): $\bar{\nu}$ 3350, 3250 (NH_2), 3150 (NH), 3030 (arom. CH), 1640, 1600 (C=N), 1210 (C=S) cm^{-1}; Anal. calcd. for $C_{17}H_{14}N_6S$ (334.40): C, 61.06; H, 4.22; N, 25.13; S, 9.59. Found: C, 60.87; H, 4.10; N, 25.00; S, 9.34.

5-Amino-1-(1,3-diphenyl-1*H*-pyrazol-4-ylcarbonyl)-1*H*-pyrazole-4-carbonitrile (26a). A mixture of **3** (278 mg, 1 mmol) and ethoxymethylene malononitrile (122 mg, 1 mmol) in absolute ethanol (10 ml) was heated under reflux for 8 h. After cooling, the solvent was removed *in vacuo* and the solid residue was recrystallized from ethanol to give **22a** as pale yellow crystals (165 mg, 47%), mp.226-28 ºC. ^{1}H NMR (DMSO-d_6) δ 9.17 (s, 1H, pyrazole CH-5), 8.03-7.80 (m, 5H, Ph), 7.60 (s, 1H, pyrazole CH-3`), 7.73-7.30 (m, 5H, Ph), 6.97 (bs, 2H, NH_2); IR (KBr):

$\bar{\nu}$ 3450, 3350, 3150 (NH_2), 3030 (arom. CH), 2220 (CN), 1690 (C=O), 1630, 1600 (C=N) cm^{-1}; Anal. calcd. for $C_{20}H_{14}N_6O$ (354.37): C, 67.79; H, 3.98; N, 23.72. Found: C, 67.58; H, 3.79; N, 23.62.

Ethyl 5-amino-1-(1,3-diphenyl-1*H*-pyrazol-4-ylcarbonyl)-1*H*-pyrazole-4-carboxylate (26b). A mixture of **3** (278 mg, 1 mmol) and ethyl ethoxymethylene cyanoacetate (169 mg, 1 mmol) in absolute ethanol (10 ml) was heated under reflux for 8 h. After cooling, the solvent was removed *in vacuo* and the solid residue was recrystallized from ethanol to give **26b** as white fluffy crystals (295 mg, 74%), mp.182-83 ºC. ^{1}H NMR ($CDCl_3$) δ 9.18 (s, 1H, pyrazole CH-5), 7.87-7.70 (m, 5H, Ph), 7.76 (s, 1H, pyrazole CH-3`), 7.60-7.27 (m, 5H, Ph), 7.18 (bs, 2H, $NH_2$), 4.30 (q, *J* = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 1.36 (t, *J* = 7.2 Hz, 3H, $CH_2C\underline{H}_3$); $^{13}$C NMR ($CDCl_3$) δ 14.48 (-$OCH_2\underline{CH}_3$), 59.85 (-$O\underline{CH}_2CH_3$), 94.64 (pyrazole-C-4`), 112.81 (pyrazole-C-4), Ar-C: [119.37 (2CH), 127.44 (CH), 127.70 (2CH), 127.99 (CH), 128.93 (2CH), 129.52 (2CH), 132.42 (C), 134.69 (C)], 131.14 (pyrazole-C-5`), 139 (pyrazole-C-3`), 142 (pyrazole-C-5`), 154.51 (pyrazole-C-3), 156.52 (C=O), 164.03 (ester-C=O); IR (KBr): $\bar{\nu}$ 3450, 3350, 3150 (NH_2), 3030 (arom. CH), 2220 (CN), 1700 (C=O), 1630, 1600 (C=N) cm^{-1}; Anal. calcd. for $C_{22}H_{19}N_5O_3$ (401.42): C, 65.83; H, 4.77; N, 17.45. Found: C, 65.67; H, 4.55; N, 17.24.

5-Amino-1-(1,3-diphenyl-1*H*-pyrazol-4-ylcarbonyl)-1*H*-3-phenylpyrazole (27). A mixture of **3** (278 mg, 1 mmol) and benzoyl acetonitrile (145 mg, 1 mmol) in absolute ethanol (10 ml) was refluxed for 5 h. After cooling, the solvent was evaporated and the solid residue was recrystallized from ethanol to give **27** as pale yellow crystals (300 mg, 74%), mp.202-204 ºC. ^{1}H NMR (DMSO-d_6) δ 8.92 (s, 1H, pyrazole CH-5), 8.03-7.80 (m, 5H, Ph), 7.73-7.30 (m, 10H, Ph), 6.73 (bs, 2H, NH_2), 5.73 (s, 1H, pyrazole CH-4`); IR (KBr): $\bar{\nu}$ 3480, 3400, 3200 (NH_2), 3030 (arom. CH), 2220 (CN), 1670 (C=O), 1640 (C=N), 1600 cm^{-1}; Anal. calcd. for $C_{25}H_{19}N_5O$ (405.45): C, 74.06; H, 4.72; N, 17.27. Found: C, 73.92; H, 4.58; N, 17.11.

1-(1,3-Diphenyl-1*H*-pyrazol-4-ylcarbonyl)-1*H*-3,5-dimethylpyrazole (28). A mixture of **3** (278 mg, 1 mmol) and acetyl acetone (1 ml, 10 mmol) in ethanol (5 mL) was gently refluxed for 2 h. After cooling, the excess of solvent was removed *in vacuo*. The residue obtained was recrystallized from methanol/ ethyl acetate (1:1) to give **28** as white crystals (290 mg, 85%), mp.98-100 ºC. ^{1}H NMR ($CDCl_3$) δ 8.83 (s, 1H, pyrazole CH-5), 7.87-7.63 (m, 4H, Ph), 7.47-7.30 (m, 6H, Ph), 5.92 (s, 1H, pyrazole CH-4`), 2.55 (s, 3H, $CH_3$), 2.20 (s, 3H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$) δ 13.45 ($CH_3$), 112.40 (pyazole-C-4), 114.60 (pyrazole-C-4`), Ar-C: [119.39 (2CH), 126.82 (CH), 128.10 (2CH), 128.36 (CH), 128.41 (CH), 128.56 (2CH), 128.77 (2CH), 129.77 (2CH), 130.63 (2CH), 127.64 (C), 135.20 (C), 138.76 (C)], 132.07 (pyrazole–C-5), 146.46 (pyrazole-C-5`), 151.35 (pyrazole-C-3), 154.21 (pyrazole-C-3`), 161.31 (C=O); IR (KBr): $\bar{\nu}$ 3030 (arom. CH), 1690 (C=O), 1610 (C=N), 1600 (C=C) cm^{-1}; Anal. calcd. for $C_{21}H_{18}N_4O$ (342.39): C, 73.67; H, 5.30; N, 16.36. Found: C, 73.48; H, 5.13; N, 16.17.

1-(1,3-Diphenyl-1*H*-pyrazol-4-ylcarbonyl)-1*H*- 3-methyl-5-phenylpyrazole (29). A mixture of **3** (278 mg, 1 mmol) and benzoyl acetone (161 mg, 1 mmol) in ethanol (10 mL) was heated under reflux for 2 h. After cooling, the solvent was evaporated and the residue obtained was collected by filtration and recrystallized from ethanol to afford **29** as white crystals (400 mg,

99%), mp. 268-270 ºC. ^{1}H NMR (DMSO-d_6) δ 9.13 (s, 1H, pyrazole CH-5), 8.00-7.87 (m, 6H, Ph), 7.60-7.27 (m, 9H, Ph), 6.43 (s, 1H, pyrazole CH-4`), 2.20 (s, 3H, CH_3); IR (KBr): $\bar{\nu}$ 3030 (arom. CH), 1695 (C=O), 1610 (C=N), 1600 (C=C) cm^{-1}; Anal. calcd. for $C_{26}H_{20}N_4O$ (404.46): C, 77.21; H, 4.98; N, 13.85. Found: 77.02; H, 4.67; N, 13.61.

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