Synthesis of some new azoles with antiviral potential

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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, thia diazole 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.\textsuperscript{2-6} Some C-(β-D-Glucopyranosyl)-1,3,4-oxadiazoles were synthesized as potential glycogen phosphorylase inhibitors.\textsuperscript{7} Katritzky \textit{et al}.\textsuperscript{8} reported a new route to 2-amino-1,3,4-oxadiazoles. These compounds were shown to possess antidiabetic,\textsuperscript{9} antiarthritic and antiinflammatory\textsuperscript{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.\textsuperscript{11-14} It was also reported that a large number of compounds containing a triazole ring possess a moderate antiviral activity.\textsuperscript{15} Also, it was reported that the pyrazole-4-carboxylic acid hydrazides and its hydrazones possess antimicrobial activity.\textsuperscript{16} Recently, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, 1,2,4-triazoles and triazines have attracted particular attention due their anti-inflammatory,\textsuperscript{17-19} analgesic, ulcerogenic and lipid peroxidation activities.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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 °C. 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-1H-pyrazole-4-carbohydrazide 3 (Scheme 1).

\begin{center}
\includegraphics[width=\textwidth]{Scheme1.png}
\end{center}

\textbf{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-y1)[1,3,4]oxadiazol-2-ylthio]ethyl}morpholine (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-substituted[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 \( N^2-(2\text{-cyanoeethyl})-1,3\text{-diphenyl}-1H\text{-pyrazole}-4\text{-carbohydrazide} \ (16) \). Monge et al\(^2\) reported that the \( N^2-(2\text{-cyanoeethyl})-N\text{-methylindole-2-carbohydrazide} \ I \) 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 \( \text{CS}_2 \) 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](image)

The reaction of 3 with phenyl isothiocyanate in boiling pyridine gave $N'$-(1,3-diphenyl-1$H$-pyrazol-4-ylcarbonyl)-$N''$-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$_2$SO$_4$ resulted in dehydrocyclization giving the 2-phenylamino-1,3,4-thiadiazole derivative 21 (Scheme 5).

![Scheme 5](image)

Alkylation of the triazolethione derivative 20 with some alkylation agents such as 4-(2-chloroethyl)morpholine hydrochloride or 2-dimethylaminopropyl chloride hydrochloride in
boiling ethanol in the presence of fused sodium acetate gave the corresponding 4-{2-[5-(1,3-
diphenyl-1H-pyrazol-4-yl)-4-phenyl-4H[1,2,4]triazol-3-ylthio]ethyl}morpholine 22 and 3-{5-
(1,3-diphenyl-1H-pyrazol-4-yl)-4-phenyl-4H-[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
benzoylacetonitrile in absolute ethanol afforded the corresponding pyrazole derivatives 28 and
29 respectively.
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; v max in cm⁻¹). ¹H NMR and ¹³C 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-1H-pyrazole-4-carboxylic acid hydrazide (3). Method (a).** A mixture of ethyl 1,3-diphenyl-1H-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 °C (Lit.¹⁶ 75 %, mp. 157-158 °C).

**Method (b).** A mixture of 1,3-diphenyl-1H-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 °C.

5-(1,3-Diphenyl-1H-pyrazol-4-yl)[1,3,4]oxadiazole-2(3H)-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 °C. $^1$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): $\nu$ 3200 (NH), 3010 (arom. CH), 1690 (C=O), 1640 (C=N) cm$^{-1}$; Anal. calcd. for C$_{17}$H$_{12}$N$_4$O$_2$ (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-1H-pyrazol-4-yl)[1,3,4]oxadiazole-2(3H)-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 °C. $^1$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): $\nu$ 3200 (NH), 3030 (arom. CH), 1640 (C=N), 1210 (C=S) cm$^{-1}$; Anal. calcd. for C$_{17}$H$_{12}$N$_4$OS (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-1H-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 9 as colorless crystals (210 mg, 73%), mp. 208-210 °C. $^1$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): $\nu$ 3050 (arom. CH), 1640 (C=N) cm$^{-1}$; Anal. calcd. for C$_{17}$H$_{12}$N$_4$O (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-1H-pyrazole-4-carbohydrazide (10). A mixture of 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 °C. $^1$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): $\nu$ 3200 (NH), 3030 (arom. CH), 1660 (C=O), 1640 (C=N) cm$^{-1}$; Anal. calcd. for C$_{19}$H$_{18}$N$_4$O$_2$ (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-1H-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 °C. 1H NMR (CDCl3) 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, OCH2), 3.38 (t, J = 6.6 Hz, 2H, SCH2CH2N), 2.76 (t, J = 6.6 Hz, 2H, SCH2CH3N), 2.47 (t, J = 4.1 Hz, 4H, NCH2); 13C NMR (CDCl3) δ 29.65 (SCH2CH2N), 53.22 (SCH2CH2N), 57.03 (2CH2N), 66.81 (2CH2O), ar-C: [119.39 (2CH), 128.21 (2CH), 128.88 (CH), 128.94 (CH), 129.20 (2CH), 129.35 (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): ν 3080 (arom. CH), 1660 (C=O), 1640 (C=N) cm-1; Anal. calcd. for C23H23N5O2S (433.53): C, 63.72; H, 5.35; N, 16.15; S, 7.40. Found: C, 63.61; H, 5.27; N, 16.15; S, 7.26.

N2-Acetyl-1,3-diphenyl-1H-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 °C. 1H NMR (DMSO-d6) 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, CH3); IR (KBr): ν 3200 (NH), 3010 (arom. CH), 1670 (C=O), 1640 (C=N) cm-1; Anal. calcd. for C18H16N4O2 (320.35): C, 67.49; H, 5.03; N, 17.49. Found: C, 67.37; H, 4.92; N, 17.29.

N2-Benzoyl-1,3-diphenyl-1H-pyrazole-4-carbohydrazide (12b). To a solution of 3 (278 mg, 1 mmol) in dioxane (10 mL) benzoic 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 °C. 1H NMR (DMSO-d6) 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): ν 3200 (NH), 3010 (arom. CH), 1670 (C=O), 1640 (C=N) cm-1; Anal. calcd. for C23H18N4O2 (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-1H-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 °C 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-1H-pyrazol-4-yl)-5-methyl[1,3,4]oxadiazole (13a). White crystals (240 mg, 79%), mp.100-102 °C. 1H NMR (DMSO-d6) 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, CH3); IR (KBr): ν 3200 (NH), 3010 (arom. CH), 1670 (C=N), 1640 (C=N) cm-1; Anal. calcd. for C18H14N4O (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-1H-pyrazol-4-yl)-5-phenyl[1,3,4]oxadiazole (13b). White crystals (286 mg, 78%), mp.88-90 °C. 1H NMR (CDCl3) δ 8.25 (s, 1H, Pyrazole CH), 7.87-7.70 (m, 4H, Ph), 7.60-
7.27 (m, 11H, Ph); IR (KBr): \( \nu \) 3010 (arom. CH), 1640 (C=N) cm\(^{-1}\); Anal. calcd. for C\(_{23}\)H\(_{16}\)N\(_4\)O (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-1H-pyrazol-4-yl)-1,2-dihydro[1,2,4]triazin-5(6H)-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 °C. \( ^1\)H NMR (CDCl\(_3\)) \( \delta \) 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): \( \nu \) 3350 (NH), 3030 (arom. CH), 2900 (aliph.CH), 1660 (C=O), 1640 (C=N) cm\(^{-1}\); Anal. calcd. for C\(_{18}\)H\(_{15}\)N\(_5\)O (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-1H-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 °C. \( ^1\)H NMR (CDCl\(_3\)) \( \delta \) 11.53 (s, 1H, NH\(_{CO}\)), 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\(_2\)CH\(_2\)CN), 2.38 (t, \( J = 7.6 \) Hz, 2H, NHCH\(_2\)CH\(_2\)CN); IR (KBr): \( \nu \) 3290 (NH), 3050 (arom. CH), 2220 (C≡N), 1660 (C=O), 1630 (C=N) cm\(^{-1}\); Anal. calcd. for C\(_{19}\)H\(_{17}\)N\(_5\)O (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-1H-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 (301 mg, 91%), mp. 88-90 °C. \( ^1\)H NMR (CDCl\(_3\)) \( \delta \) 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\(_2\)CH\(_2\)CN), 2.50 (t, \( J = 5.8 \) Hz, 2H, NCH\(_2\)CH\(_2\)CN); IR (KBr): \( \nu \) 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\(_5\)O\(_2\) (357.37): C, 68.69; H, 5.08; N, 19.75. Found: C, 68.19; H, 3.97; N, 19.47.

3-[5-(1,3-Diphenyl-1H-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 °C. \( ^1\)H NMR (CDCl\(_3\)) \( \delta \) 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\(_2\)CH\(_2\) CN), 2.50 (t, \( J = 5.8 \) Hz, 2H, NCH\(_2\)CH\(_2\)CN); IR (KBr): \( \nu \) 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\(_5\)S\(_2\) (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\(^2\)-[(1,3-Diphenyl-1\textit{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 °C. \(^1\)H NMR (DMSO-\textit{d}_6) \(\delta\) 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): \(\nu\) 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\(_5\)OS (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\textit{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\(\text{N}\)). 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 °C. \(^1\)H NMR (DMSO-\textit{d}_6) \(\delta\) 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): \(\nu\) 3200 (NH), 3030 (arom. CH), 1620 (C=N), 1210 (C=S) cm\(^{-1}\); Anal. calcd. for C\(_{23}\)H\(_{17}\)N\(_5\)S (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\textit{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 °C. \(^1\)H NMR (DMSO-\textit{d}_6) \(\delta\) 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): \(\nu\) 3200 (NH), 3030 (arom. CH), 1600 (C=N), 1540 cm\(^{-1}\); Anal. calcd. for C\(_{23}\)H\(_{17}\)N\(_5\)S (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\textit{H}-pyrazol-4-yl)-4-phenyl-4\textit{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 °C. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 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, SCH\(_2\)CH\(_2\)N), 2.77 (t, \(J = 6.8\) Hz, 2H, SCH\(_2\)CH\(_2\)N), 2.51 (t, \(J = 4.5\) Hz, 4H, NCH\(_2\)); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 29.65 (SCH\(_2\)CH\(_2\)N), 53.24 (SCH\(_2\)CH\(_2\)N), 57.34 (2CH\(_2\)N), 66.75 (2CH\(_2\)O), ar-C: [119.37 (2CH), 126.50 (CH), 128.23 (2CH), 128.34 (CH), 128.41 (CH), 128.79 (2CH), 128.23 (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): $\nu$ 3050 (arom. CH), 2920 (aliph.CH), 1640 (C=N), 1600 cm$^{-1}$; Anal. calcd. for C$_{29}$H$_{28}$N$_6$OS (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-1H-pyrazol-4-yl)-4-phenyl-4H-[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$_3$) $\delta$ 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$_2$N), 2.30 (s, 6H, N(CH$_3$)$_2$), 2.06-1.83 (m, 2H, SCH$_2$CH$_2$CH$_2$N); IR (KBr): $\nu$ 3050 (arom. CH), 2920 (aliph.CH), 1640 (C=N), 1600 cm$^{-1}$; Anal. calcd. for C$_{28}$H$_{28}$N$_6$S (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-1H-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$_6$) $\delta$ 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): $\nu$ 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$_6$O (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-1H-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 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 product formed was filtered off and recrystallized from ethanol to afford compound 25 as white crystals (297 mg, 89%), mp. 208-212 ºC. $^1$H NMR (DMSO-d$_6$) $\delta$ 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): $\nu$ 3350, 3250 (NH$_2$), 3150 (NH), 3030 (arom. CH), 1640, 1600 (C=N) cm$^{-1}$; Anal. calcd. for C$_{17}$H$_{14}$N$_6$S (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-1H-pyrazol-4-ylcarbonyl)-1H-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$_6$) $\delta$ 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):
ν 3450, 3350, 3150 (NH₂), 3030 (arom. CH), 2220 (CN), 1690 (C=O), 1630, 1600 (C=N) cm⁻¹; Anal. calcd. for C₂₀H₁₄N₆O (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-1H-pyrazol-4-ylcarbonyl)-1H-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. ¹H NMR (CDCl₃) 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, NH₂), 4.30 (q, J = 7.2 Hz, 2H, CH₂CH₃), 1.36 (t, J = 7.2 Hz, 3H, CH₂CH₃); ¹³C NMR (CDCl₃) δ 14.48 (-OCH₂CH₃), 59.85 (-OCH₂CH₃), 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): ν 3450, 3350, 3150 (NH₂), 3030 (arom. CH), 2220 (CN), 1690 (C=O), 1630, 1600 (C=N) cm⁻¹; Anal. calcd. for C₂₂H₁₉N₅O₃ (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-1H-pyrazol-4-ylcarbonyl)-1H-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. ¹H NMR (DMSO-d₆) 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, NH₂), 5.73 (s, 1H, pyrazole CH-4'); IR (KBr): ν 3480, 3400, 3200 (NH₂), 3030 (arom. CH), 2220 (CN), 1670 (C=O), 1640 (C=N), 1600 cm⁻¹; Anal. calcd. for C₂₅H₁₉N₅O (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-1H-pyrazol-4-ylcarbonyl)-1H-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. ¹H NMR (CDCl₃) δ 8.83 (s, 1H, pyrazole CH-5), 8.03-7.80 (m, 5H, Ph), 7.73-7.30 (m, 10H, Ph), 6.73 (bs, 2H, NH₂), 5.73 (s, 1H, pyrazole CH-4'); ¹³C NMR (DMSO-d₆) δ 13.45 (CH₃), 112.40 (pyrazole-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), 130.63 (2CH), 127.64 (C), 135.20 (C), 138.76 (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): ν 3030 (arom. CH), 1690 (C=O), 1610 (C=N), 1600 cm⁻¹; Anal. calcd. for C₂₁H₁₈N₄O (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-1H-pyrazol-4-ylcarbonyl)-1H- 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 °C. $^1$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): ν 3030 (arom. CH), 1695 (C=O), 1610 (C=N), 1600 (C=C) cm$^{-1}$; Anal. calcd. for C$_{26}$H$_{20}$N$_4$O (404.46): C, 77.21; H, 4.98; N, 13.85. Found: C, 77.02; H, 4.67; N, 13.61.

References

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