Site-Selectivity in the reaction of hydrazine hydrate with 3,4'-*Bis*-(functionalized carbonyl)-4,3'-*bis*(pyrazolyl)ketones. Synthesis of 4-(pyrazol-3-yl)-2*H*-pyrazolo[3,4-*d*]-pyridazines

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Abstract

Reaction of hydrazine hydrate with 3,4-bis-(functionalized carbonyl)-4,3-bis(pyrazolyl)ketones proceeds regioselectively affording the corresponding 4-(pyrazol-3-yl)-2*H*-pyrazolo[3,4-*d*]pyridazine derivatives in high yields. The structures of the products were determined by spectroscopic and elemental analyses and supported by comparison with the possible isomers prepared by an independent route.

Keywords: Hydrazonoyl halides, enaminones, pyrazoles, pyrazolopyridazines

Introduction

We[1] and others[2] have reported that vicinal 3,4-di-(functionalizedcarbonyl)pyrazoles **1** react with hydrazines to give the respective pyrazolo[3,4-*d*]pyridazines **2** (Figure 1). Also, in conjunction with our continued studies on the chemistry of hydrazonoyl halides,[3-13] we reported the synthesis of several 3,4'-bis(functionalized-carbonyl)-4,3'-*bis*(pyrazolyl) ketones of type **3** (Figure 1).[14,15] We have now studied the site-selectivity of the condensation between hydrazine hydrate and functionalized tricarbonyl compounds **3** which theoretically can lead to 4-(pyrazol-3-yl)-2*H*-pyrazolo[3,4-*d*]pyridazines **4** and/or 7-(pyrazol-4-yl)-2*H*-pyrazolo[3,4-*d*]pyridazines **5** (Figure 1). These structures are of possible biological interest since they contain both the pyrazole motif present in pharmaceuticals such as Sildenafil (Viagra),[16] Ionazlac[17] and Difenamizole[18] and since several pyrazolo[3,4-d]pyridazine derivatives exhibit antibacterial and antifungal activities.[19]

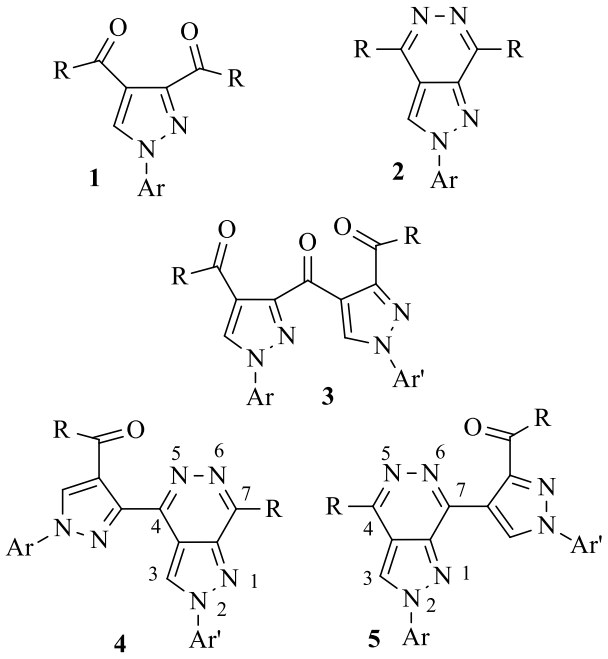
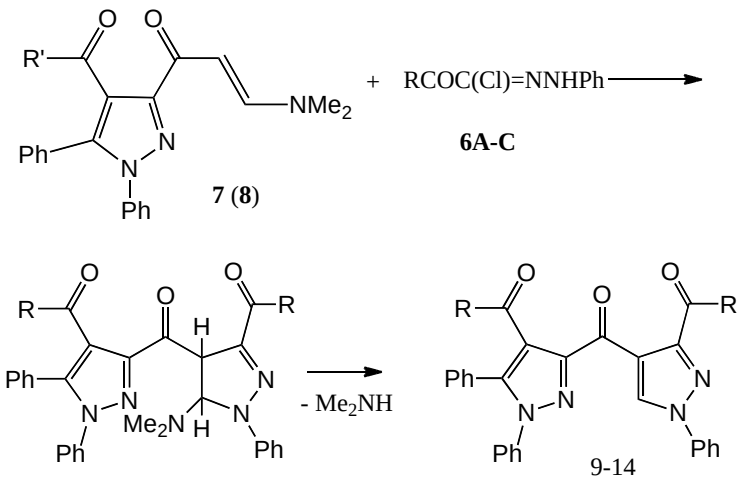


Figure 1

Results and Discussion

The synthetic strategy adopted in this work for synthesis of the target compounds **9-14** is depicted in Scheme 1. The required enaminone precursors **7(8)** were prepared as previously described from our laboratory.[14,20] Reaction of the hydrazonoyl halides **6A-C** with the enaminone **7** in benzene in the presence of triethylamine gave, in each case, one isolable product as evidenced by TLC analysis. Both mass spectra and elemental analysis data of the isolated products from these reactions were consistent with the structures **9-11** (Scheme 1). Similar reactions of the enaminone **8** with each of **6A-C** under the same reaction conditions furnished the products **12-14**, respectively (Scheme 1). The physical properties of the products **9** and **12-14** were consistent with those reported in literature.[14,15] The structures of the new products **10** and **11** were established on the basis of their spectroscopic (IR, MS, ^{1}H-NMR) and elemental analyses (see Experimental). For example, while the IR spectrum of the compound **10** exhibited three CO bands at υ 1726, 1670 and 1640 cm^{-1}, the spectrum of compound **11** revealed an NH band at υ 3430 and three CO bands at υ 1692, 1670 and 1640 cm^{-1}. Also, the ^{1}H NMR spectrum of compound **10** revealed, in addition to the aromatic proton signals, a characteristic singlet signal at δ 9.23 assignable to the pyrazole-CH proton. The ^{1}H NMR spectrum of compound **11** exhibited two characteristic signals at δ 9.28 and 10.6 assignable to the pyrazole-CH and amide NH protons, respectively.



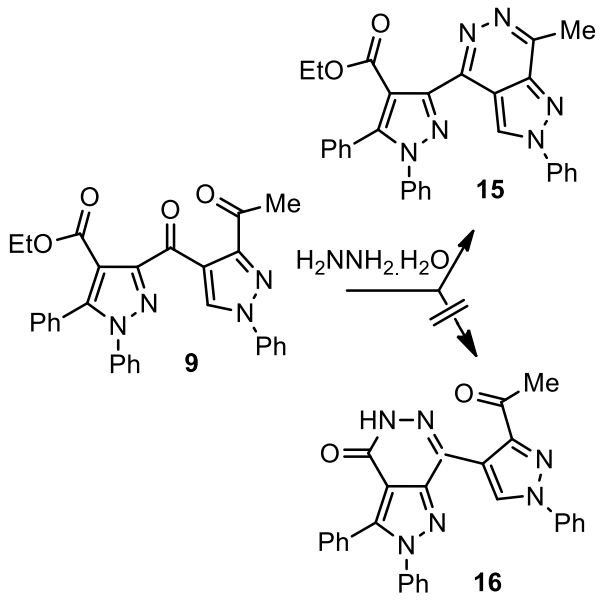
R : **6A**, Me; **6B**, EtO; **6C**, PhNH R' : **7**, EtO; **8**, Ph

R / R' : **9**, Me / EtO; **10**, EtO / EtO; **11**, PhNH / EtO;
12, Me / Ph; **13**, EtO / Ph; **14**, PhNH / Ph

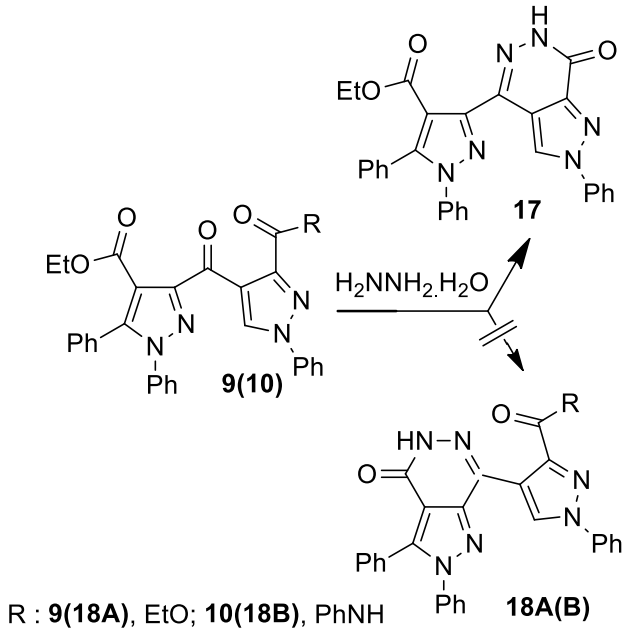
Scheme 1

Reaction of compound **9** with hydrazine hydrate in refluxing EtOH yielded a product the spectroscopic (IR, MS, ^{1}H NMR) and elemental analysis data (see Experimental) for which were consistent with structure **15**. Thus, the mass spectrum showed a molecular ion peak at *m/z* 500 and the IR spectrum displayed one carbonyl absorption band at ν 1712 cm^{-1} attributed to the ester carbonyl group. The ^{1}H NMR spectrum showed, in addition to the aromatic proton signals, signals at δ 1.06 (t), 4.16 (q) and 2.26 (s) revealing the presence of CH_3CH_2OCO and CH_3 groups. Based on these data, the other possible structure **16** was discarded (Scheme 2). This conclusion is further confirmed by our finding that compound **15** was different from a sample of **16** prepared by an independent route as depicted in Scheme 6.

Similar reaction of hydrazine hydrate with each of **10** (R=EtO) and **11** (R=PhNH) was found to give in both cases one and the same product that proved to be **17** (Scheme 3). The assigned structure **17** was consistent with its spectroscopic (IR, Mass and ^{1}H NMR) and elemental analysis data (see Experimental). The other possible structures **18A** (R=EtO) and **18B** (R=PhNH) were thus discarded. This conclusion is also supported by our finding that the isolated compound **17** was different from compound **18A** (R = EtO) which was prepared by an independent route as outlined in Scheme 6 (see Experimental).

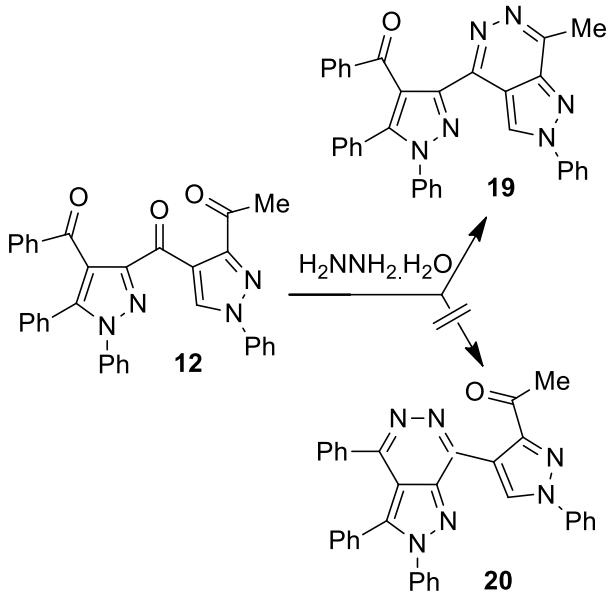


Scheme 2



Scheme 3

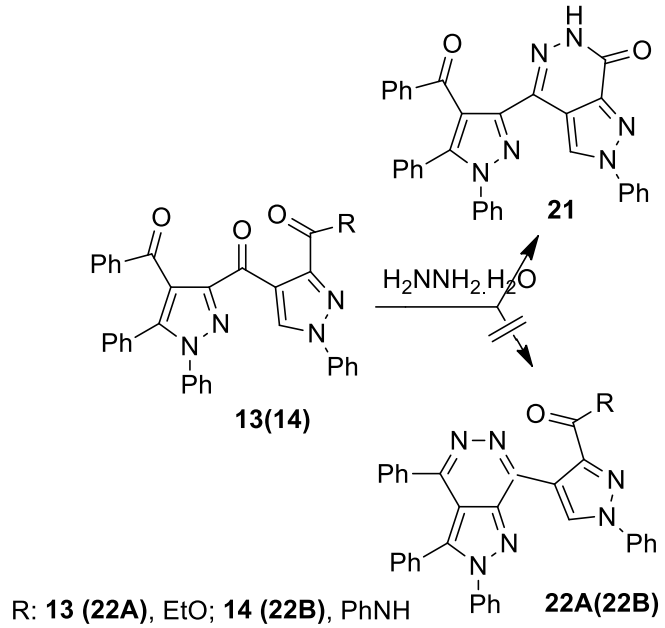
Also, refluxing **12** with hydrazine hydrate in EtOH yielded a single product that was identified, on the basis of its spectroscopic data (IR, MS, and ^{1}H NMR) and elemental analysis, as 4-[(1,5-diphenyl-4-benzoyl-pyrazol-3-yl)]-1-phenyl-7-methylpyrazolo[3,4-*d*]pyridazine **19** (Scheme 4).



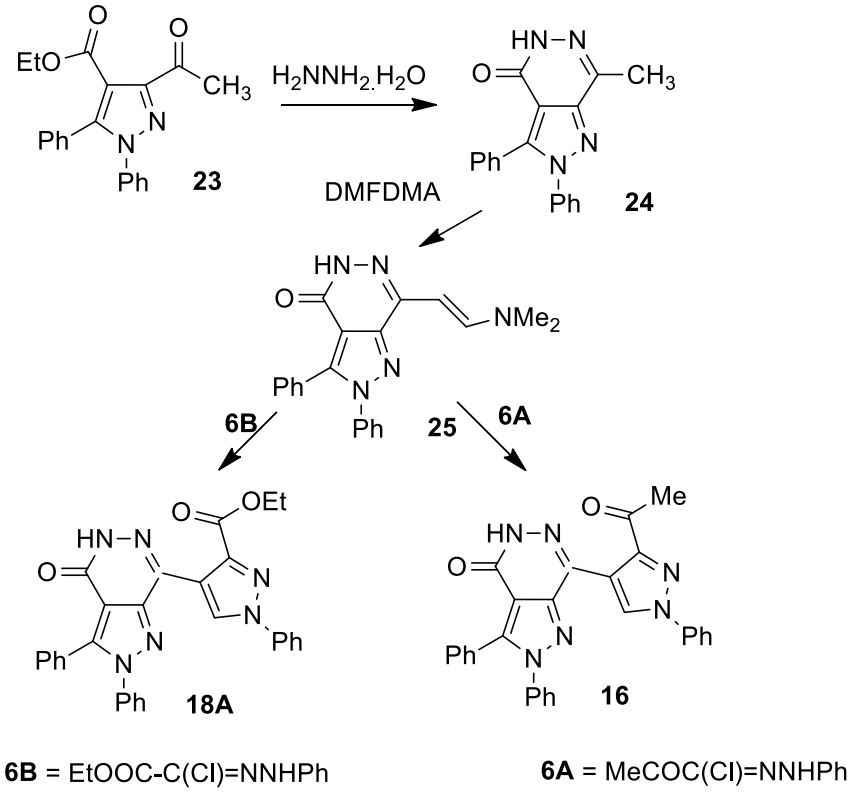
Scheme 4

Similar reaction of each of the compounds **13** (R = EtO) and **14** (PhNH) with hydrazine hydrate under the same conditions gave in both cases one and the same product that was identified as **21** (Scheme 5). For example, its ^{1}H NMR spectrum revealed a broad singlet (D_2O-exchangeable) at δ 12.9 due to the pyridazine-NH proton. This NH group gave an absorption band at 3148 cm^{-1} in the IR spectrum of **21**. The other isomeric structure **22** was thus discarded.

To provide conclusive evidence for the assigned structures for the products isolated from reaction of the pyrazole derivatives **9-14** with hydrazine and in turn the site selectivity in the studied reactions, the two products **15** and **17**, taken as examples of the series prepared, were compared with authentic samples of their isomers, **16** and **18A**, respectively prepared by an unambiguous routes as depicted in Scheme 6. Thus, reaction of hydrazine hydrate with the pyrazole derivative **23** in refluxing EtOH gave a product that was identified as **24** (Scheme 6) on the basis of its spectra (IR, ^{1}H NMR and MS) and elemental analysis (see Experimental). Reaction of **24** with DMFDMA gave the enamine **25**. Treatment of the latter with each of the hydrazonoyl chlorides **6A** and **6B** in refluxing dry dioxane in the presence of triethylamine yielded the two products **16** and **18A**, respectively (Scheme 6), which were found to be different from their respective isomers **15** (Scheme 2) and **17** (Scheme 3).



Scheme 5



Scheme 6

The foregoing results provide unambiguous evidence that the studied reactions are site selective. The observed site-selectivity in the studied reactions can be rationalized in terms of the difference in electrophilicity of the carbonyl groups involved. In general, in a given 3,4-disubstituted pyrazole derivative having two functionalized carbonyl groups at the 3- and 4-positions, the former group is expected to be more electron deficient than the latter. This is because the C=N moiety is more electron-withdrawing than the C=C moiety. On this basis, in the studied reactions, hydrazine is expected to condense preferentially with the two C=O groups at 3 and 3'-sites in the compounds **9-14** to give the products **15**, **17**, **19** and **21** as end products, respectively (Schemes 2 and 3).

Conclusions

Reaction of hydrazine hydrate with various functionalized tricarbonyl heterocycles proved to be site selective. The reaction provides a convenient method for synthesis of various 4-(pyrazol-3-yl)-2*H*-pyrazolo[3,4-*d*]pyridazine derivatives.

Experimental Section

General. All melting points were determined on an electrothermal Gallenkamp apparatus. Solvents were generally distilled and dried by standard literature procedures prior to use. The IR spectra were measured on a Pye-Unicam SP300 instrument in potassium bromide discs. The ^{1}H NMR spectra were recorded on a Varian Mercury VXR-300 MHz spectrometer and the chemical shifts δ downfield from tetramethylsilane (TMS) as an internal standard. The mass spectra were recorded on a GCMS-Q1000-EX Shimadzu and GCMS 5988-A HP spectrometers, the ionizing voltage was 70 eV. Elemental analyses were carried out by the Microanalytical Center of Cairo University, Giza, Egypt. Both the hydrazonoyl chlorides **6A-C** and the enaminones **7** and **8** were prepared as previously described.[14, 20]

Preparation of 4-[1,5-diphenyl-4-substituted-1*H*-pyrazole-3-carbonyl]-1-aryl-3-substituted-1*H*-pyrazoles 9-14. General procedure

To a stirred solution of the appropriate hydrazonoyl halide **6** (5 mmol) and the enaminone **7** (1.94 mmol) in dry benzene (30 mL), was added triethylamine (0.5 ml) and the mixture was refluxed for 20 h. The precipitated triethylamine hydrochloride was filtered off, and the filtrate was evaporated under reduced pressure. The residue was triturated with MeOH. The solid product so formed was filtered off, washed with water, and dried. Recrystallization from EtOH afforded the corresponding 4-[1,5-diphenyl-4-ethoxycarbonyl-1*H*-pyrazole-3-carbonyl]-1-aryl-3-substituted-1*H*-pyrazoles **9-11**.

When the above procedure was repeated using the enaminone **8** *in lieu* of **7**, the respective 4-[1,5-diphenyl-4-benzoyl-1*H*-pyrazole-3-carbonyl]-1-aryl-3-substituted-1*H*-pyrazoles **12-14** were obtained. The products **9-14** together with their physical properties are listed below.

Ethyl 3-(3-acetyl-1-phenyl-1*H*-pyrazole-4-carbonyl)-1,5-diphenyl-pyrazole-4-carboxylate (9). Yellow crystals, (1.89 g, 75% yield), mp 110-12 °C (Lit[14] mp 110 °C).

Ethyl 4-[1,5-Diphenyl-4-ethoxycarbonyl-1*H*-pyrazole-3-carbonyl]-1-phenyl-1*H*-pyrazole-3-carboxylate (10). Yellow crystals, (2.13 g, 80% yield), mp 72-74 °C; IR (KBr) ν_{max} / cm^{-1} 1726, 1670, 1640 (C=O); ^{1}H NMR (DMSO-d_6) δ 1.08 (t, J = 7Hz, 6H, 2 OCH_2CH_3), 4.15 (q, J = 7 Hz, 4H, 2 OCH_2CH_3), 7.24-7.95 (m, 15H, Ar-H), 9.23 (s, 1H, pyrazole); MS *m/z* (%) 534 (M^+, 1), 180 (23), 138 (24), 110 (32), 77 (100). Anal. Calcd. for $C_{31}H_{26}N_4O_5$ (534.56): C, 69.65; H, 4.90; N, 10.48. Found: C, 69.80; H, 4.99 ; N, 14.60%.

4-[1,5-Diphenyl-4-ethoxycarbonyl-1*H*-pyrazole-3-carbonyl]-1-phenyl-1*H*-pyrazole-3-carboxanilide (11). yellow solid, (1.74 g, 60% yield), mp 110 °C; IR (KBr) ν_{max} / cm^{-1} 3430 NH), 1692, 1670, 1640 (C=O); ^{1}H NMR (DMSO-d_6) δ 1.02 (t, J = 7 Hz, 3H, OCH_2CH_3), 4.06 (q, J = 7 Hz, 2H, OCH_2CH_3), 7.11-8.01 (m, 20H, Ar-H), 9.28 (s, 1H, pyrazole), 10.68 (s, 1H, -CONH-); MS *m/z* (%) 579 (M^+, 1), 97 (17), 91 (48), 77 (100), 64 (61). Anal. Calcd. for $C_{35}H_{27}N_5O_4$ (581.62): C, 72.28; H, 4.68; N, 12.04. Found: C, 72.39 ; H, 4.80 ; N, 12.12%.

4-[1,5-Diphenyl-4-benzoyl-1*H*-pyrazole-3-carbonyl]-1-phenyl-3-acetyl-1*H*-pyrazole (**12**). This compound was obtained as pale yellow crystals, (yield 2.01 g, 75%), m.p. 150 °C (Lit[15] mp. 150-152 °C).

Ethyl 4-[1,5-diphenyl-4-benzoyl-1*H*-pyrazole-3-carbonyl]-1-phenyl-1*H*-pyrazole-3-carboxylate (13). This compound was obtained as pale orange crystals, (yield 2.12, 75%), mp 108 °C, (Lit[15] m.p. 105-107 °C).

4-[1,5-diphenyl-4-benzoyl-1*H*-pyrazole-3-carbonyl]-1-phenyl-1*H*-pyrazole-3-carboxanilide (14). This compound was obtained as yellow crystals, (2.29 g, yield 72%), mp. 122 °C (Lit[15] mp. 120-122 °C).

Reaction of hydrazine hydrate with the compounds 9-14. General method

A mixture of the pyrazole derivative **9** (1.0 g, 2 mmol) and hydrazine hydrate (10 ml) in absolute EtOH was heated at reflux for 10 h and the reaction mixture was then cooled. The solid that precipitated was filtered off and crystallized from EtOH to give **15**.

When the above procedure was repeated using **10** or **11** each in place of **9**, it yielded in both cases only one product namely **17**.

Also, reaction of hydrazine with **12** yielded the product **19**. Reaction with hydrazine of either **13** or **14** following the same procedure gave the product **21**, respectively.

Ethyl 3-(2-phenyl-7-methyl-2*H*-pyrazolo[3,4-*d*]pyridazin-4-yl)-1,5-diphenyl-pyrazole-4-carboxylate (15). White solid, 1.5 g (60% yield), mp. 296-298 °C (EtOH/dioxane); IR(KBr) ν_{max} / cm^{-1} 1684 (C=O); ^{1}H NMR (DMSO-d_6): δ 1.04 (t, J = 7 Hz, 3H, CH_3-CH_2O), 2.88 (s, 3H, CH_3), 4.15 (q, J = 7 Hz, 2H, OCH_2CH_3), 7.29-7.53 (m, 15H, ArH), 8.75 (s, 1H, pyrazole-H). MS *m/z* (%) 502 (M^+ +2, 4), 500 (M^+, 0.58), 486 (19), 470 (27), 455 (19), 178 (18), 76 (83), 63 (24),

55 (100); Anal. Calcd. For $C_{30}H_{24}N_6O_2$ (500.55): C, 71.99; H, 4.83; N, 16.79. Found : C, 72.06; H, 4.75; N, 16.80.

Ethyl 3-(2-phenyl-7-oxo-6*H*,7*H*-pyrazolo[3,4-*d*]pyridazin-4-yl)-1,5-diphenyl-pyrazole-4-carboxylate (17). Pale yellow solid, 1.5 g (60% yield), mp. 179-180 ºC (EtOH); IR(KBr) ν_{max} / cm^{-1} 3426 (NH), 1689, 1650 (C=O); ^{1}H NMR (DMSO-d_6): δ 1.26 (t, J = 7 Hz, 3H, CH_3-CH_2O), 4.15 (q, J = 7 Hz, 2H, OCH_2CH_3), 7.33-8.07 (m, 15H, ArH), 9.19 (s, 1H, pyrazole-H), 12.05 (s, 1H, NH). MS *m/z* (%) 502 (M^+ , 3), 176 (29), 149 (19), 135 (100), 119 (53), 111 (11), 107 (37), 94 (12), 91 (73), 82 (24), 77 (53), 69 (19), 63 (38). Anal. Calcd. For $C_{29}H_{22}N_6O_3$ (502.54): C, 69.31; H, 4.41; N, 16.72. Found : C, 69.40; H, 4.53; N, 16.79.

4-(1,5-Diphenyl-4-benzoyl-pyrazol-3-yl)-2-phenyl-7-methyl-2*H*-pyrazolo-[3,4-*d*]pyridazine (19). Pale orange solid, 0.53 g (50% yield), mp. 148-150 °C (EtOH); IR(KBr) ν_{max} / cm^{-1} 1660 (C=O); ^{1}H NMR (DMSO-d_6): δ 2.80 (s, 3H, CH_3), 7.25-7.65 (m, 20H, ArH), 9.45 (s, 1H, pyrazole-H-5). MS *m/z* (%) 532 (M^+, 10), 518 (33), 504 (17), 531 (14), 514 (16), 481 (19), 464 (17), 448 (13), 438 (30), 398 (22), 390 (15), 404 (14), 180 (20), 104 (15), 92 (12), 77 (100), 50 (24); Anal. Calcd. For $C_{34}H_{24}N_6O$ (532.61): C, 76.68; H, 4.54; N, 15.78. Found : C, 76.69; H, 4.65; N, 15.83.

4-(1,5-Diphenyl-4-benzoyl-pyrazol-3-yl)-2-phenyl-7-oxo-2*H*,6*H*-pyrazolo-[3,4-*d*]pyridazine (21). Pale yellow solid, 0.58 g (55% yield), mp. 170-172 °C (EtOH); IR(KBr) ν_{max} / cm^{-1} 3450 (NH), 1689, 1660 (C=O); ^{1}H NMR (DMSO-d_6): δ 7.24-8.07 (m, 20H, ArH), 9.24 (s, 1H, pyrazole-H-5), 12.33 (s, 1H, NH). MS *m/z* (%) 535 (M^+, 51), 506 (14), 458 (11), 104 (27), 77 (100), 51 (21); Anal. Calcd. For $C_{33}H_{22}N_6O_2$ (534.58): C, 74.15; H, 4.15; N, 15.72. Found : C, 74.30; H, 4.32; N, 15.85.

Synthesis of 7-methyl-2,3-diphenyl-4-oxo-2*H*,5*H*-pyrazolo[3,4-*d*]-pyridazine (24). A mixture of compound **23** (1.67 g, 5 mmol) and hydrazine hydrate (5 ml) in absolute EtOH (30 ml) was heated at reflux for 10 h and the mixture was then cooled. The solid that precipitated was filtered off and crystallized from EtOH to compound **24** as white solid, 1.50 g (64% yield), mp. 260 °C (EtOH); IR(KBr) ν_{max} / cm^{-1} 3171 (NH), 1658 (C=O); ^{1}H NMR (DMSO-d_6): δ 2.46 (s, 3H, CH3), 7.35-7.46 (m, 10H, ArH), 11.96 (s, 1H, NH). MS *m/z* (%) 301 (M^+, 1.5), 506 (14), 139 (11), (11), 77 (100). Anal. Calcd. For $C_{18}H_{14}N_4O$ (302.34): C, 71.51; H, 4.67; N, 18.53. Found : C, 71.60; H, 4.70; N, 18.65.

Synthesis of 7-(β-dimethylaminovinyl)-2,3-diphenyl-4-oxo-2*H*,5*H*-pyrazolo[3,4-*d*]pyridazine enamine (25). A mixture of compound **24** (0.66 g, 2.1 mmol) and dimethylformamide dimethyl acetal (2 g) was heated at reflux for 50 h, then left to cool then MeOH was added to the cold mixture. The resulting solid was collected by filtration, washed with MeOH, dried and finally crystallized from EtOH to give the enamine **25** as yellow solid, 1.50 g (80% yield), mp. 158 °C (EtOH); IR(KBr) ν_{max} / cm^{-1} 3428 (NH), 1660 (C=O); ^{1}H NMR (DMSO-d_6): δ 3.31 (s, 6H, $N(CH_3)_2$, 5.66 (d, *J* = 13 Hz, 1H COCH=CH), 7.34-7.44 (m, 10H, ArH), 7.8 (d, J = 13 Hz, -CH=CHN), 11.95 (s, 1H, NH). MS *m/z* (%) 357 (M^+, 0.05), 315 (100), 288 (11), 180 (16), 139 (16), 114 (12), 76 (45). Anal. Calcd. For $C_{21}H_{19}N_5O$ (357.41): C, 70.57; H, 5.36; N, 19.59. Found : C, 70.45; H, 5.42; N, 19.68.

Synthesis of 16 and 18A. General method

To a stirred solution of the enamine **25** (0.36 g, 1 mmol) and the hydrazonoyl chloride **6A** (0.196 g, 1 mol) in dry 1,4-dioxane (20 ml) , triethylamine (0.2 ml) was added and the mixture was heated at reflux for 20 h. The precipitated triethylamine hydrochloride was filtered off, and the filtrate was evaporated under reduced pressure and the residue was triturated with MeOH. The solid product, so formed, was collected by filtration and crystallized from EtOH to give compound **16**.

When the above procedure was repeated using ethyl *N*-phenylhydrazonochloro-acetate **6B** in place of the hydrazonoyl chloride **6A,** the product **18A** was produced. The physical constants of both products **16** and **18A** are given below.

7-(1-Phenyl-3-acetyl-pyrazol-4-yl)-2,3-diphenyl-4-oxo-2*H*,5*H*-pyrazolo[3,4-*d*]pyridazine (16). Pale yellow solid, 0.27 g (78% yield), mp. 244-246 °C (EtOH); IR(KBr) ν_{max} / cm^{-1} 1674, 1663 (C=O); ^{1}H NMR (DMSO-d_6): δ 2.73 (s, 3H, CH_3), 7.31-7.51 (m, 15H, ArH), 8.04 (s, 1H, pyrazole-H), 11.99 (s, 1H, NH). MS *m/z* (%) 472 (M^+, 0.11), 506 (14), 301 (20), 139 (19), 114 (15), 102 (16), 90 (10), 77 (100), 64 (14); Anal. Calcd. For $C_{28}H_{20}N_6O_2$ (472.51): C, 71.18; H, 4.27; N, 17.79. Found : C, 71.30; H, 4.40; N, 17.86.

7-(1-Phenyl-3-ethoxycarbonyl-pyrazol-4-yl)-2,3-diphenyl-4-oxo-2*H*,5*H*-pyrazolo[3,4-*d*]pyridazine (18A). Pale yellow solid, 1.50 g (60% yield), mp. 212-214 °C (EtOH); IR(KBr) ν_{max} / cm^{-1} 3426 (NH), 1710, 1660 (C=O); ^{1}H NMR (DMSO-d_6): δ 1.41 (t, J = 7 Hz, 3H, CH_3-CH_2O), 4.15 (q, J = 7 Hz, 2H, OCH_2CH_3), 7.26-7.46 (m, 15H, ArH), 9.19 (s, 1H, pyrazole-H), 12.05 (s, 1H, NH). MS *m/z* (%) 502 (M^+, 0.66), 301 (29), 458 (11), 179 (23), 139 (17), 118 (30), 140 (66), 91 (33), 76 (75), 56 (100), 45 (57); Anal. Calcd. For $C_{29}H_{22}N_6O_3$ (502.54): C, 69.31; H, 4.41; N, 16.72. Found : C, 69.40; H, 4.50; N, 16.76.

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