A convenient synthesis of pyrazole-substituted heterocycles

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(E)-1-(5-Methyl-1-phenylpyrazol-4-yl)-3-(*N,N*-dimethylamino)-2-propen-1-one reacts with hydrazine, hydroxylamine, guanidine and aminopyrazole derivatives to afford the corresponding 3,4′-bipyrazole, pyrazolylisoxazole, pyrazolylpyrimidine and pyrazolo[1,5-*a*]pyrimidine derivatives**,** respectively. It reacts also with benzoquinone**,** naphthoquinone and *N*-benzoylglycine to give the corresponding benzofuran and pyrazolylpyranone derivatives, respectively.

Keywords: 3,4′-bipyrazole, isoxazole, pyrimidine, pyrazolo[1,5-*a*]pyrimidine, benzofuran, pyranone

The pyrazole ring is a prominent structural motif found in numerous pharmaceutically active compounds. Due to the easy preparation and rich biological activity, the pyrazole framework plays an essential role in many biologically active compounds and therefore represents an interesting template for combinatorial[1–4] as well as medicinal chemistry.[5–7] Indeed, pyrazole-based derivatives have shown several biological activities as seen in COX-2,[5] p38 MAP kinase,[6] and CDK2/ Cyclin A inhibitors.[7] Many of them were tested and/or evaluated in potential drug discovery.[8–11]

Our attention was focused on functionalised pyrazole scaffolds, which produce a variety of heterocyclic compounds. Thus, *(E)*-1-(5-methyl-1-phenylpyrazol-4-yl)-3-(*N,N*-dimethylamino)-2-propen-1-one (**2**) was obtained from the reaction of 4-acetyl-5-methyl-1-phenyl-1*H*-pyrazole (**1**) with *N, N*-dimethylformamide dimethyl acetal (DMF-DMA) and has recently been reported as a useful precursor for the synthesis of many interesting heterocycles.[12]

In continuation of our interest in the synthesis of a variety of pyrazole-based heterocyclic systems for biological evaluation,[13–15] we report here on the behaviour of the versatile enaminone **2** towards some nitrogen nucleophiles, *p*-benzoquinone and 1,4-naphthoquinone, as a facile and convenient route to novel 3,4′**-**bipyrazole, pyrazolylisoxazole, pyrazolylpyrimidine, pyrazolo[1,5-*a*]pyrimidines, pyrazolylbenzo- furan and pyrazolylpyranone derivatives of anticipated biological and pharmaceutical activities.

Results and discussion

Treatment of 1-(5-methyl-1-phenylpyrazol-4-yl)-3-(*N,N*-dimethylamino)-2-propen-1-one **(2)** with hydrazine hydrate and with phenylhydrazine in refluxing ethanol, led to the formation of the novel 5′-methyl-1′-phenyl-1′*H*,2*H*-3,4′-bipyrazole **(3a)** and 5′-methyl-1′,2-diphenyl-1′*H*,2*H*-3,4′-bipyrazole **(3b)**, respectively (Scheme 1).

The IR spectra of the products **3a** and **3b** were free of a carbonyl function**.** In addition, compound **3a** exhibited an absorption band at 3425 cm^{-1} due to a NH function. The ^1H NMR spectrum of the same compound revealed a singlet signal at δ 2.61 due to methyl protons, two doublet signals at δ 6.46 and 7.70 (J = 2.33 Hz) due to pyrazole protons, a singlet signal at δ 8.05 due to pyrazole-3H and D_2O-exchangeable signal at δ 12.81 due to the NH proton, in addition to an aromatic multiplet at δ 7.42–7.55.

Similarly, the enaminone **2** reacts with hydroxylamine, to afford only one isolable product identified as 5-(5-methyl-1-phenyl-*1H*-pyrazol-4-yl)isoxazole (**4**) (Scheme 1). The ^1H NMR spectrum of the latter product exhibited a singlet signal at δ 2.51 due to methyl protons, two doublets at δ 6.68 and 8.61 (J = 1.23 Hz) due to two isoxazole protons, a singlet signal at δ 8.12 due to a pyrazole-3H and an aromatic multiplet at δ 7.50–7.58.

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When compound **2** was treated with guanidine, it afforded an excellent yield of a single product (as examined by TLC). The reaction product was identified as 4-(5-methyl-1-phenyl-*1H*-pyrazol-4-yl)pyrimidin-2-amine (**5**) on the basis of its spectral data (see Experimental). Compounds **3, 4** and **5** are assumed to be formed *via* addition of the amino group of hydrazines, hydroxylamine, and guanidine to the activated ethylenic double bond of enaminone **2** followed by intramolecular cyclisation and elimination of water and dimethylamine.

The behaviour of compound **2** towards some aminopyrazole derivatives, as potential precursors for the interesting biologically active pyrazolo[1,5-*a*]pyrimidines, was also investigated. Thus, when the enaminone **2** was treated with 5-amino-1*H*-pyrazole derivatives **6a–c**, in the presence of piperidine, it afforded the pyrazolo[1,5-*a*]pyrimidine derivatives **8a–c** *via* the non-isolable intermediates **7a–c** (Scheme 2). The structures of compounds **8a–c** were established on the basis of their elemental analyses and spectral data (see Experimental).

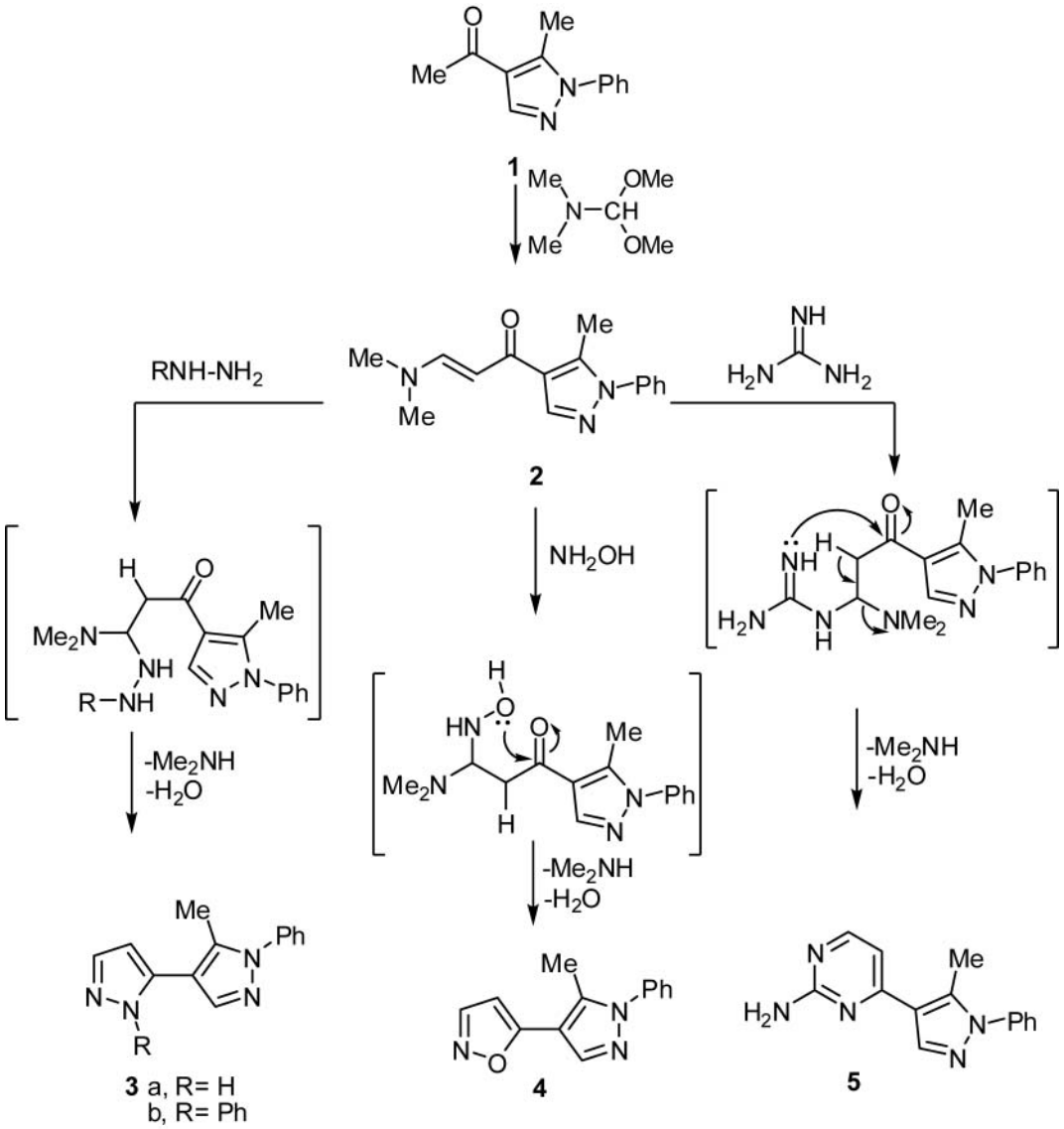
Benzofurans are widely distributed in nature and of established biological activities,[11] therefore, a novel route to biologically interesting 5-hydroxy-3-aroylbenzofurans bearing a substituted pyrazole moiety was investigated. Thus, it was found that the enaminone **2** reacts readily with *p*-benzoquinone in acetic acid at room temperature, yielding a single product which was assigned as (5-hydroxybenzofuran-3-yl)(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)methanone (**10**). The latter product was assumed to be formed *via* initial addition of the electron-rich moiety C2 in the enaminone **2** to the activated electron-poor double bond system in the quinone to afford the product **10** *via* the non-isolable intermediate **9**. In a similar manner, the enaminone **2** reacts with 1,4-naphthoquinone to afford (5-hydroxynaphtho[1,2-*b*]furan-3-yl)(5-methyl-1-phenyl-1*H*-pyrazol-4-yl) methanone **(11)** (Scheme 3).

Treatment of the enaminone **2** with *N*-benzoylglycine **(12)** in refluxing acetic anhydride led to the formation of a product that was assigned as 3-benzoylamino-6-(5-methyl-1-phenylpyrazol-4-yl))-2*H*-pyran-2-one (**15**). The structure of the latter product was established on the basis of its elemental analysis and spectral data (see Experimental). Compound **15** is assumed to be formed *via* the reaction of the intermediate oxazolone **13**, which is formed *in situ*, with the enaminone **2**, yielding the non-isolable intermediate **14**, that further rearranges into the corresponding pyranone derivative **15** (Scheme 4).

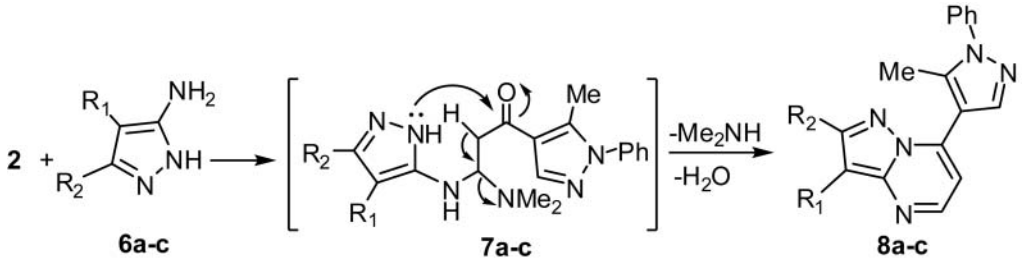
In conclusion, we have investigated the synthetic potential of *(E)*-1-(5-methyl-1-phenylpyrazol-4-yl)-3-(*N,N*-dimethylamino)-2-propen-1-one (**2**) as a versatile, readily accessible building block for the synthesis of new pyrazole-substituted heterocyclic compounds of biological and pharmaceutical importance.

Experimental

All melting points were measured with a Gallenkamp apparatus. The IR spectra were recorded of samples in KBr on a Shimadzu FT-IR 8101 PC IR spectrophotometer. ^1H spectra were run at 300 MHz and

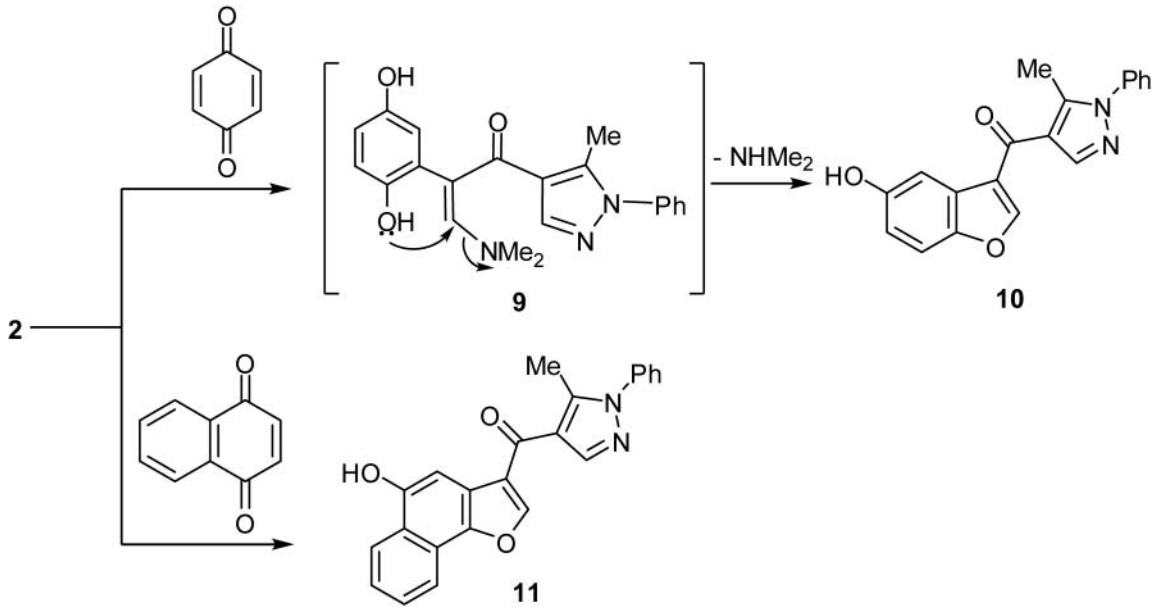


Scheme 1

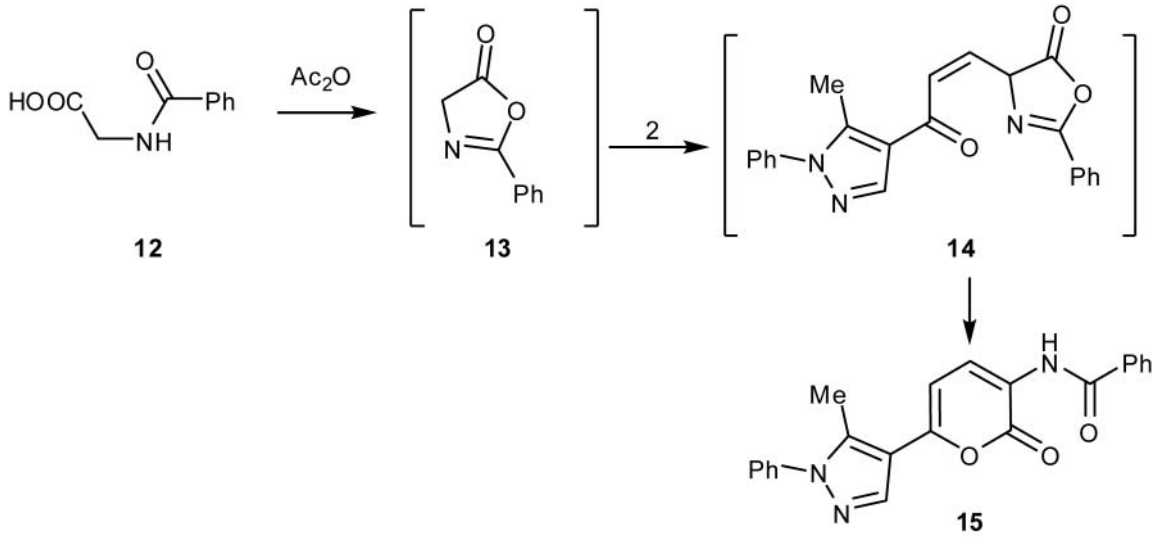


6-8	R_1	R_2
a	H	Ph
b	H	CH_3
c	CH_3	Ph

Scheme 2



Scheme 3



Scheme 4

^{13}C spectra were run at 75.46 MHz in dimethyl sulfoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt.

1-(5-Methyl-1-phenylpyrazol-4-yl)-3-(*N,N*-dimethylamino)-2-propen-1-one (**2**)[12] and aminopyrazoles **7a–c**[16–18] were prepared following the literature procedures.

3,4′-Bipyrazole derivatives **3a, b;** *general procedure*

Hydrazine hydrate (2 mL) or phenylhydrazine (1.5 mL), was added to a stirred solution of the enaminone **2** (2.55g, 10 mmol) dissolved in acetic acid (30 mL). Stirring was continued overnight at room temperature for 12 h. The solid product was filtered off washed with water dried and recrystallised from DMF.

5′-Methyl-1′-phenyl-1′H,2H-3,4′-bipyrazole **(3a):** Yield (78%); m. p. 160–162 °C; IR (KBr) υ_{max}/cm^{-1} 3425 (NH), 1597 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.61 (s, 3H, CH_3), 6.46 (d, 1H, *J* = 2.33 Hz, pyrazole-4-CH), 7.42–7.55 (m, 5H, ArH), 7.70 (d, 1H, *J* = 2.33 Hz, pyrazole-5-CH), 8.05 (s, 1H, pyrazole-3′-CH), 12.81 (s, 1H, NH); MS, *m/z* 224 (M$^+$). Found: C, 69.55 H, 5.44; N, 24.95%. $C_{13}H_{12}N_4$ requires C, 69.62; H, 5.39; N, 24.98%.

5′-Methyl-1′,2-diphenyl-1′H,2H-3,4′-bipyrazole **(3b):** Yield (74%); m.p. 195–197 °C; IR (KBr) υ_{max}/cm^{-1} 1594 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.60 (s, 3H, CH_3), 6.53 (d, 1H, *J* = 2.41 Hz, pyrazole-4-CH), 7.37–7.75 (m, 10H, ArH), 7.92 (d, 1H, *J* = 2.41 Hz, pyrazole-5-CH), 8.23 (s, 1H, pyrazole-3′-CH); MS, *m/z* 300 (M$^+$). Found: C, 75.90; H, 5.41; N, 18.69. $C_{19}H_{16}N_4$ requires C, 75.98; H, 5.37; N, 18.65%.

5-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)isoxazole **(4):** A solution of the enaminone **2** (2.55 g, 10 mmol) in ethanol (50 mL) was treated with hydroxylamine hydrochloride (0.7 g, 10 mmol) in the presence of ammonium acetate (1.5 g). The reaction mixture was heated under reflux for 2 h. then poured into ice-cold water. The resulting solid product was filtered off washed with water dried and recrystallised from DMF. Yield (86%); m.p. 159–161 °C; IR (KBr) υ_{max}/cm^{-1} 1595 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.51(s, 3H, CH_3), 6.68 (d, 1H, *J* = 1.23, isoxazole-4-CH), 7.50–7.58 (m, 5H, ArH), 8.12 (s, 1H, pyrazole-3-CH), 8.61 (d, 1H, *J* = 1.23, isoxazole-3-CH); MS, *m/z* 225 (M$^+$). Found: C, 69.27; H, 4.96; N, 18.61%. $C_{13}H_{16}N_3O$ requires C, 69.32; H, 4.92; N, 18.66%.

4-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)pyrimidin-2-amine **(5):** To a mixture of the enaminone 2 (0.51 g, 2 mmol) and guanidine nitrate (2.3 mmol) in ethanol (30 mL), anhydrous potassium carbonate (0.55 g, 4 mmol) was added. The resulting mixture was refl formed solid products was collected by filtration, washed with water and dried. Recrystallisation from DMF afforded 2-amino-4-(5-methyl-1-phenyl-pyrazol-4-yl)pyrimidine **(6).** Yield (79%); m.p. 220–222°C; IR (KBr) υ_{max}/cm^{-1} 3471, 3286 (NH_2), 1585 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.65 (s, 3H, CH_3), 6.47(s, 2H, NH_2), 6.88 (d, 1H, *J* = 5.4 Hz pyrimidine-5-CH), 7.48–7.56 (m, 5H, ArH), 8.17 (s, 1H, pyrazole-3-CH), 8.20 (d, 1H, *J* = 5.4 Hz pyrimidine-6-CH); ^{13}CNMR δ 9.98, 93.73,104.74, 108.26, 124.12 125.16, 129.33, 139.71, 142.23, 155.48, 161.29, 164.39; MS, *m/z* 251(M$^+$). Found: C, 66;98 H, 5;19 N, 27.79%. $C_{14}H_{23}N_5$ requires: C, 66.92 H, 5.21 N, 27.87%.

Pyrazolo[1,5-a]pyrimidine derivatives **8a–c;** *general procedure*
To a mixture of the enaminone **2** (2.55 g, 10 mmol) and appropriate aminopyrazole derivatives **6a–c** (10 mmol) in absolute ethanol (25 mL) and few drops of piperidine was refluxed for 3 h. The formed solid product was filtered off washed with ethanol,dried and recrystallised from ethanol/DMF to afford pyrazol[1,5-*a*]pyrimidine derivatives **8a–c** in 65-70% yield. The physical and spectra data of compound **8a–c** are listed below.

7-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)-2-phenylpyrazolo[1,5-a] pyrimidine **(8a):** Yield (70%); m.p. 216–218°C; IR (KBr) υ_{max}/cm^{-1} 1596 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.57 (s, 3H, CH_3), 7.14 (s, 1H, pyrazole-3 CH), 7.30–8.57 (m, 13H, ArH); ^{13}C NMR δ 11.98, 88.74, 93.73, 108.10, 122.26, 124.90, 125.25, 126.21, 127.53, 128.16, 129.33, 137.12, 138.90, 140.71, 142.23, 149.3, 152.48, 157.29; MS, *m/z* 351 (M$^+$). Found: C, 75.23; H, 4.81; N, 19.99%. $C_{22}H_{17}N_5$ requires C, 75.19; H, 4.88; N, 19.93%.

2-Methyl-7-(5-methyl-1-phenyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine **(8b):** Yield (76%); m.p. 202–204 °C; IR (KBr) υ_{max}/cm^{-1} 1594 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.61 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 7.01 (s, 1H, pyrazole-4-CH), 7.36–8.61 (m, 7H, ArH), 8.12 (s, 1H, pyrazole-3-CH); MS, *m/z* 289 (M$^+$). Found: C, 70.52; H, 5.20; N, 24.26%. $C_{17}H_{15}N_5$ requires C, 70.57; H, 5.23; N, 24.21%.

3-Methyl-7-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-2-phenylpyrazolo[1,5-a]pyrimidine **(8c):** Yield (68%); m.p. 226–228 °C; IR (KBr) υ_{max}/cm^{-1} 1596 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.05 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 7.21–8.66 (m, 12H, ArH), 8.16 (s, 1H, pyrazole-3-CH); MS, *m/z* 365 (M$^+$). Found: C, 75.53; H, 5.21; N, 19.19%. $C_{23}H_{19}N_5$ requires C, 75.59; H, 5.24; N, 19.16%.

(5-Hydroxybenzo]furan-3-yl)(5-methyl-1-phenyl-1H-pyrazol-4-yl)methanone **(10)** *and (5-Hydroxynaphtho[1,2-b]furan-3-yl) (5-methyl-1-phenyl-1H-pyrazol-4-yl)methanone* **(11)***; general procedure*

To a stirred solution of the enaminone **2** (2.55 g, 10 mmol) in acetic acid (50 mL), each of *p*-benzoquinone or1,4-naphthoquinone (10 mmol) was added and stirring continued at room temperature for 12h. The reaction mixture was evaporated *in vacuo*, and the solid product obtained was triturated with ethanol, filtered off, and recrystallised from DMF to afford (5-hydroxybenzo]furan-3-yl) (5-methyl-1-phenyl-1*H*-pyrazol-4-yl)methanone (**10**) and (5-hydroxynaphtho[1,2-*b*]furan-3-yl)(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)methanone (**11**).

(5-Hydroxybenzo[1,2-a]furan-3-yl)(5-methyl-1-phenyl-1H-pyrazol-4-yl)methanone **(10)**: Yield (72%); m.p. 240–242°C; IR (KBr) υ_{max}/cm^{-1} 3209 (OH), 1627 (C=O), 1596 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.60 (s, 3H, CH_3), 3.31 (s, 1H, OH), 6.87–8.38 (m, 8H, ArH), 8.78 (s, 1H, pyrazole-3-CH), 9.41 (s, 1H, furan-2-CH); MS, *m/z* 318 (M$^+$). Found: C, 71.64; H, 4.46; N, 8.85%. $C_{19}H_{14}N_2O_3$ requires C, 71.69; H, 4.43; N, 8.80%.

(5-Hydroxynaphtho[1,2-b]furan-3-yl)(5-methyl-1-phenyl-1H-pyrazol-4-yl)methanone **(11):** Yield (76%); m.p. 264–266 °C; IR (KBr) υ_{max}/cm^{-1} 3218 (OH), 1624 (C=O), 1594 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.60 (s, 3H, CH_3), 3.39 (s, 1H, OH), 7.54–8.37 (m, 10H, ArH), 8.91 (s, 1H, pyrazole-3-CH), 10.23 (s, 1H, furan-2-CH); MS, *m/z* 368 (M$^+$). Found: C, 74.95; H, 4.36; N, 7.57%. $C_{23}H_{16}N_2O_3$ requires C, 74.99; H, 4.38; N, 7.60%.

N-(6-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-oxo-2H-pyran-3-yl) benzamide **(15):** A solution of the enaminone **2** (2.55 g, 10 mmol) and *N*-benzoylglycine **(12)** (1.7 g, 10 mmol) in acetic anhydride (50mL) was heated under reflux for 2 h. The reaction mixture was concentrated *in vacuo* and the solid product obtained upon cooling was filtered off washed with water and recrystallised from DMF. Yield (85%); m.p. 288–290 °C; IR (KBr) υ_{max}/cm^{-1} 3406 (NH), 1699, 1672 (two C=O), 1561 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.57 (s, 3H, CH_3), 6.70 (d, 1H, *J* = 5.2 Hz, pyran-5-CH), 6.89 (d, 1H, *J* = 5.2 Hz, pyran-4-CH), 7.31–7.94 (m, 10H, ArH), 8.06 (s, 1H, pyrazole-3-CH), 9.69 (s, 1H, NH); ^{13}C NMR δ 12.1, 101.35, 111.43, 113.64, 120.76, 125.22, 126.63, 127.54, 128.49, 129.25, 133.46, 134.99, 138.91, 140.02, 146.96, 151.28, 158.89, 166.30; MS, *m/z* 371 (M$^+$). Found: C, 71.19; H, 4.57; N, 11.26%. $C_{22}H_{17}N_3O_3$ requires C, 71.15; H, 4.61; N, 11.31%.

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