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SIMPLE APPROACH TO SOME *N*-(5-HYDROXY-1-PHENYL-1*H*-PYRAZOL-4-YL)BENZAMIDES[#]

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Abstract – A series of substituted 5-hydroxy-1*H*-pyrazoles (**5**) was prepared by treatment of 4-hydroxymethylidene-2-phenyloxazol-5(4*H*)-one (**1**) with ethanol followed by reaction with phenylhydrazines and subsequent treatment with NaOH. Structures of the pyrazoles (**5p**) and (**5r**) were confirmed by X-ray structure analysis.

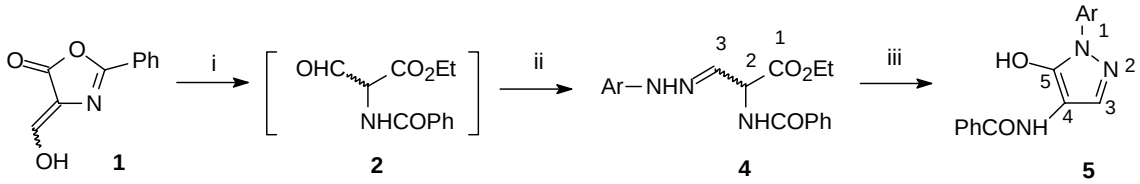
INTRODUCTION

Although the pyrazole system is a rare structural unit in naturally occurring compounds, numerous synthetic pyrazoles have attracted a considerable interest in the last decades owing to their use as pharmaceuticals, agrochemicals, dyes, plastics, and other materials.[1] One of the most used methods for the preparation of pyrazoles is treatment of 1,3-dicarbonyl or related difunctional compounds with hydrazine derivatives. Starting 1,3-difunctional compounds are often easy available acyclic and cyclic α,β-didehydroamino acid derivatives allowing synthesis of numerous highly substituted pyrazoles.[2,3] These examples are mostly dealing with the synthesis of 3- or 5-hydroxypyrazoles,[4] compounds which are also well-known due to prototropic tautomerism studies.[5]

During the course of our investigations on novel approaches to various heterocyclic compounds based on the functionalization of simple amino acid derivatives,[6] the utility of 2-(benzoylamino)-3-chloropropenoic acid and 4-hydroxymethylidene-2-phenyloxazol-5(4*H*)-one in the synthesis of α-heteroarylglycinates and indoles has been studied.[6a,c,g] In principle, regarding their structures, these unsaturated amino acid derivatives should be suitable starting compounds for the synthesis of 3- or/and 5-hydroxypyrazoles. It turned out, that this is not the case with 2-benzoylamino-3-chloropropenoic acid. Reactions of this acid with heteroarylhydrazines took place with decarboxylation resulting in the formation of *N*-(heteroaryl-hydrazonoethyl)benzamides.[6c] On the other hand, treatment of 4-hydroxymethylidene-2-phenyl-

[#] Dedicated to the memory of Professor Ivar Ugi

oxazol-5(4*H*)-one (**1**) with heteroarylhydrazine in ethanol gave a mixture of the corresponding ethyl 2-benzoylamino-3-(heteroarylhydrazono)propanoate and 5-hydroxypyrazole derivative.[6a] Selective transformation of **1** into hydrazones is possible through ethyl formylhippurate (**2**).[6a,g] In this paper we report on an unambiguous synthesis of a series of *N*-(5-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)benzamides (**5**) starting from **1** via the intermediate compounds (**2**) and (**4**) (Scheme 1).



Ar:		
phenyl (**a**)	3-chlorophenyl (**g**)	4-fluorophenyl (**m**)
2-bromophenyl (**b**)	3-fluorophenyl (**h**)	4-methylphenyl (**n**)
2-carboxyphenyl (**c**)	3-methylphenyl (**i**)	4-nitrophenyl (**o**)
2-chlorophenyl (**d**)	3-(trifluoromethylphenyl (**j**)	4-(trifluoromethyl)phenyl (**p**)
2-fluorophenyl (**e**)	4-bromophenyl (**k**)	2,5-difluorophenyl (**q**)
3-bromophenyl (**f**)	4-chlorophenyl (**l**)	2,4,6-trichlorophenyl (**r**)

Scheme 1. Reaction conditions: (i) EtOH, rt; (ii) $ArNHNH_2$ (**3a-r**), rt; (iii) 1) 1M NaOH, rt.

RESULTS AND DISCUSSION

The first part of the preparation of hydrazones (**4**) is *in situ* generation of ethyl 2-formylhippurate (**2**), achieved by simple stirring of 2-phenyl-4-hydroxymethylidene-5(4*H*)-oxazolone (**1**)[7] in ethanol. Condensation of this key compound (**2**) with phenylhydrazines (**3a-r**) gave the corresponding ethyl 2-benzoylamino-3-phenylhydrazonopropanoates (**4**) in 56-90% yield. In order to achieve easy precipitation of sufficiently pure hydrazones (**4**) from reaction mixtures and high yields of products, we carried out reactions with various hydrazine derivatives under slightly different reaction conditions. The best yields with the hydrazine derivatives used as hydrochlorides were obtained when an equivalent amount of $NaHCO_3$ in a mixture of water and ethanol was added to the corresponding hydrazine hydrochloride and the resulting mixture was then poured into a solution of **2** (formation of **4b-g**, **4i**, **4k**, **4l**, and **4n**). Exceptions are reactions with the hydrochlorides of **3h** and **3m** which gave good yields of relatively pure hydrazones (**4h**) and (**4m**) in the absence of $NaHCO_3$. Hydrazine derivatives available as free bases were added without a solvent (formation of **4a**, **4o**, **4p**, and **4r**) or with a small amount of water (formation of **4j** and **4q**). Treatment of hydrazones (**4**) with 1M NaOH resulted in the formation of 5-hydroxypyrazoles (**4**) in 56-99% yield. All reactions were performed at room temperature (Table 1).

Table 1. Reaction conditions for the preparation of hydrazones (**4**) and hydroxypyrazoles (**5**).

Ar-	Synthesis of **4**							Synthesis of **5**		
	Synthesis of **2**[a]		Continuation of reaction after addition of **3**							
	1 (mmol)	EtOH (mL)	**3** (mmol)	H_2O/EtOH (mL)/(mL)	$NaHCO_3$ (mmol)	Time (h)	Yield[c] (%)	**4**/EtOH/1M NaOH (mmol/mL/mL)	Time (h)	Yield[c] (%)
a	2	5	2	-/-	-	24	77	1/2/2	0.5	95[d]
b	1	1	1[b]	1/2	1	3	56	0.5/2/1	2	77[d]
c	1	1	1[b]	1.5/2.5	1	3	89	0.5/2/1	5	56[d]
d	1	1	1[b]	1/2	1	3	89	0.5/2/1	2	88[e]
e	10	7	10[b]	5/5	10	12	71	0.5/2/1	2	94[f]
f	1	1	1[b]	1/1	1	3	61	0.5/2/1	2	99[f]
g	1	1	1[b]	1.5/1.5	1	3	90	0.5/2/1	2	99[g]
h	1	2	1[b]	1/-	-	2	85	0.5/2/1	2	95[d]
i	1	2	1[b]	1.5/2.5	1	5	76	0.5/2/1	1.5	89[d]
j	3	6	3	0.5/-	-	2	86	0.5/2/1	2	96[d]
k	1	1	1[b]	2/2	1	1	85	0.5/2/1	1.5	85[g]
l	1	1	1[b]	2/2	1	1	86	0.5/2/1	1	99[e]
m	1	2	1[b]	1.5/-	-	3.5	66	0.5/2/1	2	84[d]
n	1	1	1[b]	2/2	1	1	76	0.5/2/1	1.5	99[g]
o	1	6	1	-/-	-	10	78	1/5/2	1	88[d]
p	5	12	5	-/-	-	4	85	0.5/2/1	1	92[d]
q	1	2	1	0.5/-	-	24	73	0.5/3/1	2	74[h]
r	1	1.5	1	-/-	-	2	75	0.5/2/1	1.5	67[i]

[a] Reaction time: 1h; [b] Corresponding arylhydrazine hydrochloride was used; [c] Yield of crude product; [d] Filtration at pH = 3; [e] Filtration at pH = 7; [f] Filtration at pH = 2; [g] Filtration at pH = 6; [h] Filtration after acidification to pH = 3, evaporation of solvent, and addition of 2 mL of H_2O; [i] Isolation after acidification to pH = 7 by extraction with $CHCl_3$.

Both types of products, hydrazones (**4**) and pyrazoles (**5**) can exist in several tautomeric forms. The structures of **4** and **5** were established on the basis of NMR spectra, MS, and elemental analyses.

^{1}H NMR spectra of **4** in DMSO-d_6 show doublet of doublet for H-2 in the range of 5.0−5.2 ppm, doublet for H-3 in the range of 7.2−7.8 ppm, and doublet for NHCO around 9.2 ppm indicating −NHN=CHCHNHCO− sequence.

In the cases of ^{1}H NMR spectra of pyrazoles (**5**) in DMSO-d_6 solution a broad singlet around 12 ppm can be most likely ascribed to OH proton. In addition, ^{13}C NMR spectra of **5d** and **5l** in DMSO-d_6 show a signal around 145 ppm which can be ascribed to C-5.

The hydroxypyrazole structure of **5** was also confirmed by X-ray structure analysis of **5p** and **5r** (Figure 1 and 2).

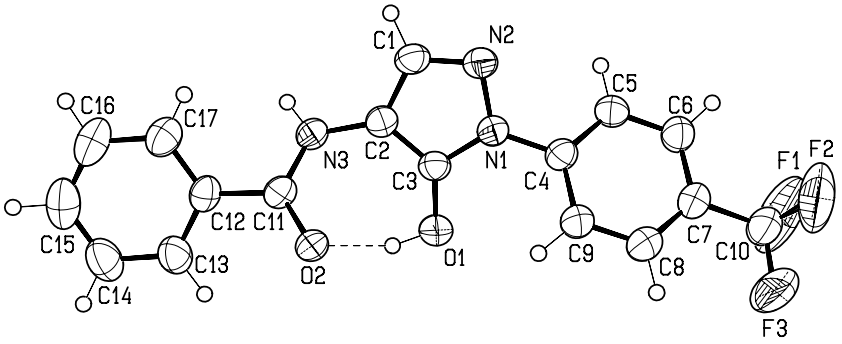


Figure 1. ORTEP view of the asymmetric unit of **5p** with labeling of nonhydrogen atoms. (Ellipsoids are drawn at 50% probability level.)

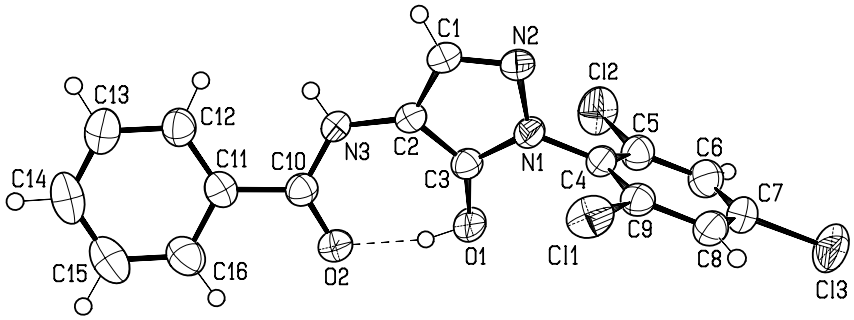


Figure 2. ORTEP view of the asymmetric unit of **5r** with labelling of nonhydrogen atoms. (Ellipsoids are drawn at 50% probability level.)

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. NMR spectra were recorded on a Bruker AVANCE DPX-300 spectrometer (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) in DMSO-d_6 with TMS as an internal standard. Coupling constants (*J*) are given in Hz. MS spectra were obtained on a VG-Analytical AutoSpec Q instrument. Elemental analyses were recorded on Perkin-Elmer CHN Analyzer 2400. 2-Phenyl-4-hydroxymethylidene-5(4*H*)-oxazolone (**1**) was prepared as described in the literature.[7]

General procedure for the synthesis of ethyl 2-benzoylamino-3-(phenylhydrazono)propanoates (4a-r). A mixture of the oxazolone (**1**) and ethanol was stirred for 1 h at rt. A solution of an equivalent amount of arylhydrazine derivative (**3**) in water (or in a mixture of ethanol and water) or hydrazine derivative alone was then added. When arylhydrazine hydrochloride was used, it was in most cases first neutralized by an equivalent amount of $NaHCO_3$ in water/ethanol mixture and this mixture was added to a

solution of **2**. The reaction mixture was then stirred for 1-24 h at rt, cooled, and the precipitated crude product (**4**) was filtered off (Table 1).

Ethyl 2-benzoylamino-3-(phenylhydrazono)propanoate (4a). mp 132-134 °C (EtOH). ^{1}H-NMR δ: 1.22 (t, 3H, *J* = 7.0 Hz, CH_2CH_3), 4.20 (q, 2H, *J* = 7.0 Hz, CH_2CH_3), 5.15 (dd, 1H, *J* = 6.0, 7.0 Hz, 2-H), 6.58−7.68 (m, 9H, 3-H, 3H of Ph, 5H of Ar), 7.84−8.10 (m, 2H, Ph), 9.22 (d, 1H, *J* = 7.0 Hz, N*H*COPh), 10.22 (s, 1H, NNH). MS (EI, *m/z*, %): 325 (M^+, 15). *Anal.* Calcd for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; N, 12.91. Found: C, 66.46; H, 5.85; N, 13.27.

Ethyl 2-benzoylamino-3-[(2-bromophenyl)hydrazono]propanoate (4b). mp 119-121 °C (EtOH). ^{1}H-NMR δ: 1.23 (t, 3H, *J* = 7.2 Hz, CH_2CH_3), 4.19 (q, 2H, *J* = 7.2 Hz, CH_2CH_3), 5.16 (dd, 1H, *J* = 5.6, 7.2 Hz, 2-H), 6.72 (ddd, 1H, *J* = 1.6, 7.0, 7.9 Hz, Ar), 7.24 (ddd, 1H, *J* = 1.4, 7.0, 8.3 Hz, Ar), 7.33 (dd, 1H, *J* = 1.6, 8.3 Hz, Ar), 7.44−7.60 (m, 4H, 3H of Ph, 1H of Ar), 7.78 (d, 1H, *J* = 5.6 Hz, 3-H), 7.90−7.95 (m, 2H, Ph), 9.21 (d, 1H, *J* = 7.2 Hz, N*H*COPh), 9.66 (s, 1H, NNH). MS (EI, *m/z*, %): 403 (M^+, 8). *Anal.* Calcd for $C_{18}H_{18}BrN_3O_3$: C, 53.48; H, 4.49; N, 10.39. Found: C, 53.51; H, 4.52; N, 10.37.

Ethyl 2-benzoylamino-3-[(2-carboxyphenyl)hydrazono]propanoate (4c). mp 192-195 °C (EtOH). ^{1}H-NMR δ: 1.23 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 4.20 (q, 2H, *J* = 7.1 Hz, CH_2CH_3), 5.20 (dd, 1H, *J* = 5.3, 7.1 Hz, 2-H), 6.80 (ddd, 1H, *J* = 1.9, 6.3, 8.0 Hz, Ar), 7.42−7.61 (m, 6H, 3H of Ph, 2H of Ar, 3-H), 7.83 (ddd, 1H, *J* = 0.7, 1.3, 8.0 Hz, Ar), 7.89−7.96 (m, 2H, Ph), 9.19 (d, 1H, *J* = 7.1 Hz, N*H*COPh), 11.13 (s, 1H, NNH), 13.05 (br s, 1H, COOH). MS (EI, *m/z*, %): 369 (M^+, 7). *Anal.* Calcd for $C_{19}H_{19}N_3O_5$: C, 61.78; H, 5.18; N, 11.38. Found: C, 62.02; H, 4.99; N, 11.47.

Ethyl 2-benzoylamino-3-[(2-chlorophenyl)hydrazono]propanoate (4d). mp 127-129 °C (EtOH/H_2O). ^{1}H-NMR δ: 1.23 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 4.19 (q, 2H, *J* = 7.1 Hz, CH_2CH_3), 5.16 (dd, 1H, *J* = 5.5, 7.2 Hz, 2-H), 6.77 (ddd, 1H, *J* = 1.6, 7.3, 8.0 Hz, Ar), 7.16−7.24 (m, 1H, Ar), 7.30 (dd, 1H, *J* = 1.4, 8.0 Hz, Ar), 7.35 (dd, 1H, *J* = 1.4, 8.0 Hz, Ar), 7.46−7.60 (m, 3H, Ph), 7.75 (d, 1H, *J* = 5.5 Hz, 3-H), 7.89−7.96 (m, 2H, Ph), 9.22 (d, 1H, *J* = 7.2 Hz, N*H*COPh), 9.87 (s, 1H, NNH). MS (EI, *m/z*, %): 359 (M^+, 10). *Anal.* Calcd for $C_{18}H_{18}ClN_3O_3$: C, 60.09; H, 5.04; N, 11.68. Found: C, 60.18; H, 5.10; N, 11.66.

Ethyl 2-benzoylamino-3-[(2-fluorophenyl)hydrazono]propanoate (4e). mp 110-112 °C (EtOH). ^{1}H-NMR δ: 1.22 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 4.19 (q, 2H, *J* = 7.1 Hz, CH_2CH_3), 5.17 (dd, 1H, *J* = 5.7, 7.2 Hz, 2-H), 6.70−6.78 (m, 1H, Ar), 7.02−7.16 (m, 2H, Ar), 7.28−7.36 (m, 1H, Ar), 7.46−7.63 (m, 4H, 3H of Ph, 3-H), 7.89−7.96 (m, 2H, Ph), 9.22 (d, 1H, *J* = 7.2 Hz, N*H*COPh), 10.17 (s, 1H, NNH). ^{13}C-NMR δ: 14.09, 55.36, 60.92, 113.70, 115.04, 118.71, 124.81, 127.46, 128.34, 131.63, 133.25, 133.38, 136.10, 148.89, 166.22, 169.39. ^{1}F-NMR δ: -134.08. MS (EI, *m/z*, %): 343 (M^+, 24). *Anal.* Calcd for $C_{18}H_{18}FN_3O_3$: C, 62.97; H, 5.28; N, 12.24. Found: C, 62.73; H, 5.46; N, 12.02.

Ethyl 2-benzoylamino-3-[(3-bromophenyl)hydrazono]propanoate (4f). mp 148-150 °C (EtOH/H_2O). ^{1}H-NMR δ: 1.23 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 4.14−4.23 (m, 2H, CH_2CH_3), 5.14 (dd, 1H, *J* = 5.5, 7.2 Hz, 2-H), 6.83−6.90 (m, 2H, Ar), 7.09−7.16 (m, 2H, Ar), 7.35 (d, 1H, *J* = 5.5 Hz, 3-H), 7.46−7.60 (m, 3H, Ph), 7.88−7.94 (m, 2H, Ph), 9.21 (d, 1H, *J* = 7.2 Hz, N*H*COPh), 10.40 (s, 1H, NNH). MS (EI, *m/z*, %): 403 (M^+, 8). *Anal.* Calcd for $C_{18}H_{18}BrN_3O_3$: C, 53.48; H, 4.49; N, 10.39. Found: C, 53.47; H, 4.53; N, 10.67.

Ethyl 2-benzoylamino-3-[(3-chlorophenyl)hydrazono]propanoate (4g). mp 145-147 °C (EtOH). ^{1}H-NMR δ: 1.22 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 4.14−4.23 (m, 2H, CH_2CH_3), 5.15 (dd, 1H, *J* = 5.6, 7.2 Hz, 2-H), 6.74 (ddd, 1H, *J* = 0.8, 2.1, 8.0 Hz, Ar), 6.82 (ddd, 1H, *J* = 0.9, 2.1, 8.0 Hz, Ar), 6.97 (dd, 1H, *J* = 2.1, 2.1 Hz, Ar), 7.19 (dd, 1H, *J* = 8.0, 8.0 Hz, Ar), 7.36 (d, 1H, *J* = 5.6 Hz, 3-H), 7.46−7.61 (m, 3H, Ph), 7.89−7.94 (m, 2H, Ph), 9.21 (d, 1H, *J* = 7.1 Hz, N*H*COPh), 10.42 (s, 1H, NNH). MS (EI, *m/z*, %): 359 (M^+, 16). *Anal.* Calcd for $C_{18}H_{18}ClN_3O_3$: C, 60.09; H, 5.04; N, 11.68. Found: C, 59.90; H, 4.98; N, 11.58.

Ethyl 2-benzoylamino-3-[(3-fluorophenyl)hydrazono]propanoate (4h). mp 125-127 °C (EtOH/H_2O). ^{1}H-NMR δ: 1.22 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 4.19 (q, 2H, *J* = 7.1 Hz, CH_2CH_3), 5.14 (dd, 1H, *J* = 5.3, 7.2 Hz, 2-H), 6.46−6.54 (m, 1H, Ar), 6.67−6.73 (m, 1H, Ar), 7.15−7.23 (m, 1H, Ar), 7.35 (d, 1H, *J* = 5.3 Hz, 3-H), 7.46−7.60 (m, 3H, Ph), 7.89−7.94 (m, 2H, Ph), 9.21 (d, 1H, *J* = 7.2 Hz, N*H*COPh), 10.43 (s, 1H, NNH). ^{1}F-NMR δ: -113.03. MS (EI, *m/z*, %): 343 (M^+, 24). *Anal.* Calcd for $C_{18}H_{18}FN_3O_3$: C, 62.97; H, 5.28; N, 12.24. Found: C, 62.60; H, 5.30; N, 12.40.

Ethyl 2-benzoylamino-3-[(3-methylphenyl)hydrazono]propanoate (4i). mp 126-128 °C (EtOH). ^{1}H-NMR δ: 1.22 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 2.22 (s 3H, CH_3), 4.14−4.22 (m, 2H, CH_2CH_3), 5.11 (dd, 1H, *J* = 5.6, 7.2 Hz, 2-H), 6.52−6.56 (m, 1H, Ar), 6.68−6.72 (m, 1H, Ar), 6.76−6.78 (m, 1H, Ar), 7.05 (dd, 1H, *J* = 7.7, 7.7 Hz, Ar), 7.30 (d, 1H, *J* = 5.6 Hz, 3-H), 7.46−7.60 (m, 3H, Ph), 7.88−7.94 (m, 2H, Ph), 9.19 (d, 1H, *J* = 7.2 Hz, N*H*COPh), 10.13 (s, 1H, NNH). MS (EI, *m/z*, %): 339 (M^+, 30). *Anal.* Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 66.89; H, 6.53; N, 12.18.

Ethyl 2-benzoylamino-3-{[(3-trifluoromethyl)phenyl]hydrazono}propanoate (4j). mp 149-151 °C (EtOH/H_2O). ^{1}H-NMR δ: 1.22 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 4.14−4.25 (m, 2H, CH_2CH_3), 5.17 (dd, 1H, *J* = 5.4, 7.3 Hz, 2-H), 7.01−7.06 (m, 1H, Ar), 7.10−7.15 (m, 1H, Ar), 7.22−7.25 (m, 1H, Ar), 7.37−7.43 (m, 2H, 1H of Ar, 3-H), 7.46−7.60 (m, 3H, Ph), 7.89−7.94 (m, 2H, Ph), 9.23 (d, 1H, *J* = 7.3 Hz, N*H*COPh), 10.57 (s, 1H, NNH). ^{1}F-NMR δ: -61.96. MS (EI, *m/z*, %): 393 (M^+, 19). *Anal.* Calcd for $C_{19}H_{18}F_3N_3O_3$: C, 58.01; H, 4.61; N, 10.68. Found: C, 57.75; H, 4.48; N, 10.57.

Ethyl 2-benzoylamino-3-[(4-bromophenyl)hydrazono]propanoate (4k). mp 144-146 °C (EtOH). ^{1}H-NMR δ: 1.21 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 4.18 (q, 2H, *J* = 7.1 Hz, CH_2CH_3), 5.12 (dd, 1H, *J* = 5.7, 7.2 Hz, 2-H), 6.85−6.90 (m, 2H, Ar), 7.30−7.36 (m, 3H, 2H of Ar, 3-H), 7.46−7.60 (m, 3H, Ph),

7.88−7.93 (m, 2H, Ph), 9.20 (d, 1H, *J* = 7.2 Hz, N*H*COPh), 10.35 (s, 1H, NNH). MS (EI, *m/z*, %): 403 (M^+, 8). *Anal.* Calcd for $C_{18}H_{18}BrN_3O_3$: C, 53.48; H, 4.49; N, 10.39. Found: C, 53.37; H, 4.38; N, 10.35.

Ethyl 2-benzoylamino-3-[(4-chlorophenyl)hydrazono]propanoate (4l). mp 137-139 °C (EtOH/H_2O). ^{1}H-NMR δ: 1.22 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 4.19 (q, 2H, *J* = 7.1 Hz, CH_2CH_3), 5.14 (dd, 1H, *J* = 5.7, 7.2 Hz, 2-H), 6.91−6.97 (m, 2H, Ar), 7.19−7.24 (m, 2H, Ar), 7.36 (d, 1H, *J* = 5.7 Hz, 3-H), 7.46−7.60 (m, 3H, Ph), 7.90−7.95 (m, 2H, Ph), 9.22 (d, 1H, *J* = 7.2 Hz, N*H*COPh), 10.40 (s, 1H, NNH). ^{13}C-NMR δ: 14.09, 55.27, 60.92, 113.16, 121.98, 127.45, 128.34, 128.84, 131.62, 133.37, 134.14, 144.12, 166.21, 169.42. MS (EI, *m/z*, %): 359 (M^+, 10). *Anal.* Calcd for $C_{18}H_{18}ClN_3O_3$: C, 60.09; H, 5.04; N, 11.68. Found: C, 59.91; H, 4.98; N, 11.73.

Ethyl 2-benzoylamino-3-[(4-fluorophenyl)hydrazono]propanoate (4m). mp 110-112 °C (EtOH/H_2O). ^{1}H-NMR δ: 1.21 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 4.18 (q, 2H, *J* = 7.1 Hz, CH_2CH_3), 5.11 (dd, 1H, *J* = 5.7, 7.1 Hz, 2-H), 6.88−6.94 (m, 2H, Ar), 6.99−7.06 (m, 2H, Ar), 7.30 (d, 1H, *J* = 5.7 Hz, 3-H), 7.45−7.60 (m, 3H, Ph), 7.88−7.95 (m, 2H, Ph), 9.18 (d, 1H, *J* = 7.1 Hz, N*H*COPh), 10.18 (s, 1H, NNH). ^{1}F-NMR δ: -126.56. MS (EI, *m/z*, %): 343 (M^+, 8). *Anal.* Calcd for $C_{18}H_{18}FN_3O_3$: C, 62.97; H, 5.28; N, 12.24. Found: C, 62.76; H, 5.27; N, 12.20.

Ethyl 2-benzoylamino-3-[(4-methylphenyl)hydrazono]propanoate (4n). mp 130-132 °C (EtOH). ^{1}H-NMR δ: 1.21 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 2.18 (s 3H, CH_3), 4.17 (q, 2H, *J* = 7.1 Hz, CH_2CH_3), 5.10 (dd, 1H, *J* = 5.7, 7.1 Hz, 2-H), 6.83 (d, 2H, *J* = 8.3 Hz, Ar), 6.99 (d, 2H, *J* = 8.3 Hz, Ar), 7.27 (d, 1H, *J* = 5.7 Hz, 3-H), 7.45−7.60 (m, 3H, Ph), 7.88−7.95 (m, 2H, Ph), 9.17 (d, 1H, *J* = 7.1 Hz, N*H*COPh), 10.07 (s, 1H, NNH). MS (EI, *m/z*, %): 339 (M^+, 20). *Anal.* Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 66.86; H, 6.45; N, 12.48.

Ethyl 2-benzoylamino-3-[(4-nitrophenyl)hydrazono]propanoate (4o). mp 174-176 °C (EtOH). ^{1}H-NMR δ: 1.22 (t, 3H, *J* = 7.0 Hz, CH_2CH_3), 4.20 (q, 2H, *J* = 7.0 Hz, CH_2CH_3), 5.17 (dd, 1H, *J* = 5.5, 7.0 Hz, 2-H), 7.01 (d, 2H, *J* = 9.5 Hz, Ar), 7.33−7.63 (m, 4H, *J* = 5.7 Hz, 3-H, 3H of Ph), 7.76−8.01 (m, 2H, Ph), 8.10 (d, 2H, *J* = 9.5 Hz, Ar), 9.27 (d, 1H, *J* = 7.0 Hz, N*H*COPh), 11.18 (s, 1H, NNH). MS (EI, *m/z*, %): 370 (M^+, 29). *Anal.* Calcd for $C_{18}H_{18}N_4O_5$: C, 58.37; H, 4.90; N, 15.13. Found: C, 58.48; H, 5.15; N, 15.25.

Ethyl 2-benzoylamino-3-{[(4-trifluoromethyl)phenyl]hydrazono}propanoate (4p). mp 175-178 °C (EtOH). ^{1}H-NMR δ: 1.22 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 4.19 (q, 2H, *J* = 7.1 Hz, CH_2CH_3), 5.15 (dd, 1H, *J* = 5.7, 7.2 Hz, 2-H), 7.05 (d, 2H, *J* = 8.4 Hz, Ar), 7.43 (d, 1H, *J* = 5.7 Hz, 3-H), 7.46−7.60 (m, 5H, 3H of Ph, 2H of Ar), 7.89−7.93 (m, 2H, Ph), 9.24 (d, 1H, *J* = 7.2 Hz, N*H*COPh), 10.68 (s, 1H, NNH). ^{1}F-NMR δ: -59.84. MS (EI, *m/z*, %): 393 (M^+, 24). *Anal.* Calcd for $C_{19}H_{18}F_3N_3O_3$: C, 58.01; H, 4.61; N, 10.68. Found: C, 58.10; H, 4.43; N, 10.70.

Ethyl 2-benzoylamino-3-[(2,5-difluorophenyl)hydrazono]propanoate (4q). mp 122-125 °C (EtOH/H_2O). ^{1}H-NMR δ: 1.22 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 4.15−4.23 (m, 2H, CH_2CH_3), 5.18 (dd, 1H, *J* = 5.4, 7.3 Hz, 2-H), 6.48−6.56 (m, 1H, Ar), 6.97−7.05 (m, 1H, Ar), 7.10−7.20 (m, 1H, Ar), 7.45−7.61 (m, 3H, Ph), 7.64 (d, 1H, *J* = 5.4 Hz, 3-H), 7.89−7.95 (m, 2H, Ph), 9.23 (d, 1H, *J* = 7.3 Hz, NHCOPh), 10.41 (s, 1H, NNH). ^{1}F-NMR δ: -117.82, -139.24. MS (EI, *m/z*, %): 361 (M^+, 27). *Anal.* Calcd for $C_{18}H_{17}F_2N_3O_3$: C, 59.83; H, 4.74; N, 11.63. Found: C, 59.77; H, 4.99; N, 11.48.

Ethyl 2-benzoylamino-3-[(2,4,6-trichlorophenyl)hydrazono]propanoate (4r). mp 112-114 °C (EtOH). ^{1}H-NMR δ: 1.19 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 4.14 (q, 2H, *J* = 7.1 Hz, CH_2CH_3), 5.07 (dd, 1H, *J* = 5.5, 7.2 Hz, 2-H), 7.43−7.66 (m, 6H, 3H of Ph, 2H of Ar, 3-H), 7.86−7.92 (m, 2H, Ph), 9.10 (d, 1H, *J* = 7.2 Hz, NHCOPh), 9.49 (s, 1H, NNH). MS (EI, *m/z*, %): 427 (M^+, 4). *Anal.* Calcd for $C_{18}H_{16}Cl_3N_3O_3$: C, 50.43; H, 3.76; N, 9.80. Found: C, 50.09; H, 3.53; N, 9.59.

General procedure for the synthesis of *N*-(1-phenyl-5-hydroxy-1*H*-pyrazol-4-yl)benzamides (5a-r). To a mixture of **4** and ethanol, 1M NaOH was slowly added. The reaction mixture was then stirred for 0.5−5 h at rt and neutralized or acidified with 7% HCl. After cooling, the precipitate was usually filtered off and washed with water to give crude **5** (Table 1).

***N*-(5-Hydroxy-1-phenyl-1*H*-pyrazol-4-yl)benzamide (5a).** mp 199-202 °C (EtOH)(lit,[7] 204-205 °C). ^{1}H-NMR δ: 7.27−7.33 (m, 1H, Ar), 7.45−7.69 (m, 6H, 3-H, 3H of Ph, 2H of Ar), 7.74−7.79 (m, 2H, Ar), 7.97−8.02 (m, 2H, Ph), 10.13 (br s, 1H, NHCOPh), 11.86 (br s, 1H, OH).

***N*-[1-(2-Bromophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]benzamide (5b).** mp 183-185 °C (CH_2Cl_2). ^{1}H-NMR δ: 7.41−7.64 (m, 7H, 3-H, 3H of Ph, 3H of Ar), 7.81 (ddd, 1H, *J* = 0.5, 1.5, 7.9 Hz, Ar), 7.95−8.00 (m, 2H, Ph), 10.14 (br s, 1H, NHCOPh), 11.51 (br s, 1H, OH). MS (EI, *m/z*, %): 357 (M^+, 22). *Anal.* Calcd for $C_{16}H_{12}BrN_3O_2$: C, 53.65; H, 3.38; N, 11.73. Found: C, 53.68; H, 3.32; N, 11.48.

***N*-[1-(2-Carboxyphenyl)-5-hydroxy-1*H*-pyrazol-4-yl]benzamide (5c).** mp 235-240 °C (EtOH). ^{1}H-NMR δ: 7.47−7.70 (m, 7H, 3-H, 3H of Ph, 3H of Ar), 7.80 (dd, 1H, *J* = 1.5, 7.9 Hz, Ar), 7.95−8.00 (m, 2H, Ph), 10.19 (br s, 1H, NHCOPh), 11.74 (br s, 1H, OH), 12.72 (br s, 1H, COOH). MS (FAB, *m/z*, %): 324 (MH^+, 54). *Anal.* Calcd for $C_{17}H_{13}N_3O_4$: C, 63.16; H, 4.05; N, 13.00. Found: C, 63.29; H, 4.08; N, 12.99.

***N*-[1-(2-Chlorophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]benzamide (5d).** mp 177-180 °C (EtOH/H_2O). ^{1}H-NMR δ: 7.48−7.68 (m, 8H, 3-H, 3H of Ph, 4H of Ar), 7.96−8.01 (m, 2H, Ph), 10.14 (br s, 1H, NHCOPh), 11.52 (br s, 1H, OH). ^{13}C-NMR δ: 102.17, 127.58, 127.87, 128.38, 129.90, 130.00, 130.45, 131.12, 131.65, 133.40, 134.79, 135.64, 144.75, 164.99. MS (EI, *m/z*, %): 313 (M^+, 39). *Anal.* Calcd for $C_{16}H_{12}ClN_3O_2$: C, 61.25; H, 3.86; N, 13.39. Found: C, 61.16; H, 3.88; N, 13.34.

***N*-[1-(2-Fluorophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]benzamide (5e).** mp 135-137 °C (EtOH/H_2O). ^{1}H-NMR δ: 7.32−7.63 (m, 7H, 3H of Ph, 4H of Ar), 7.72 (s, 1H, 3-H), 7.98−8.02 (m, 2H, Ph), 10.11 (s, 1H, N*H*COPh). MS (EI, *m/z*, %): 297 (M^+, 56). *Anal.* Calcd for $C_{16}H_{12}FN_3O_2 \cdot 0.25\ H_2O$: C, 63.68; H, 4.14; N, 13.93. Found: C, 63.56; H, 3.81; N, 14.02.

***N*-[1-(3-Bromophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]benzamide (5f).** mp 154-157 °C (CH_2Cl_2). ^{1}H-NMR δ: 7.42−7.64 (m, 5H, 3H of Ph, 2H of Ar), 7.71 (br s, 1H, 3-H), 7.83 (ddd, 1H, *J* = 1.9, 1.9, 7.4 Hz, Ar), 7.95−8.01 (m, 3H, 2H of Ph, 1H of Ar), 10.08 (br s, 1H, N*H*COPh), 12.05 (br s, 1H, OH). MS (EI, *m/z*, %): 357 (M^+, 19). *Anal.* Calcd for $C_{16}H_{12}BrN_3O_2$: C, 53.65; H, 3.38; N, 11.73. Found: C, 53.49; H, 3.31; N, 11.42.

***N*-[1-(3-Chlorophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]benzamide (5g).** mp 102-104 °C (EtOH/H_2O). ^{1}H-NMR δ: 7.35 (ddd, 1H, *J* = 1.0, 2.0, 8.1 Hz, Ar), 7.48−7.63 (m, 4H, 3H of Ph, 1H of Ar), 7.72 (br s, 1H, 3-H), 7.79 (ddd, 1H, *J* = 1.0, 2.0, 8.1 Hz, Ar), 7.85 (dd, 1H, *J* = 2.0, 2.0 Hz, Ar), 7.96−8.00 (m, 2H, Ph), 10.09 (s, 1H, N*H*COPh), 12.05 (br s, 1H, OH). MS (EI, *m/z*, %): 313 (M^+, 46). *Anal.* Calcd for $C_{16}H_{12}ClN_3O_2 \cdot 0.5\ H_2O$: C, 59.54; H, 4.03; N, 13.02. Found: C, 59.45; H, 4.10; N, 13.05.

***N*-[1-(3-Fluorophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]benzamide (5h).** mp 173-175 °C ($CHCl_3$). ^{1}H-NMR δ: 7.13 (dddd, 1H, *J* = 0.9, 2.6, 8.4, 8.5 Hz, Ar), 7.49−7.77 (m, 7H, 3-H, 3H of Ph, 3H of Ar), 7.96−8.01 (m, 2H, Ph), 10.09 (br s, 1H, N*H*COPh), 12.05 (br s, 1H, OH). MS (EI, *m/z*, %): 297 (M^+, 35). *Anal.* Calcd for $C_{16}H_{12}FN_3O_2$: C, 64.64; H, 4.07; N, 14.13. Found: C, 64.79; H, 4.10; N, 14.31.

***N*-[5-Hydroxy-1-(3-methylphenyl)-1*H*-pyrazol-4-yl]benzamide (5i).** mp 93-95 °C (EtOAc/hexane). ^{1}H-NMR δ: 2.37 (s, 3H, CH_3), 7.12 (br d, 1H, *J* = 7.9 Hz, Ar), 7.36 (dd, 1H, *J* = 7.9, 7.9 Hz, Ar), 7.50−7.71 (m, 6H, 3-H, 3H of Ph, 2H of Ar), 7.96−8.01 (m, 2H, Ph), 10.12 (br s, 1H, N*H*COPh), 11.79 (br s, 1H, OH). MS (EI, *m/z*, %): 293 (M^+, 47). *Anal.* Calcd for $C_{17}H_{15}N_3O_2 \cdot 0.5\ H_2O$: C, 67.55; H, 5.30; N, 13.91. Found: C, 67.43; H, 5.67; N, 13.99.

***N*-{5-Hydroxy-1-[3-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}benzamide (5j).** mp 166-169 °C (CH_2Cl_2/EtOAc). ^{1}H-NMR δ: 7.51−7.68 (m, 4H, 3H of Ph, 1H of Ar), 7.71−7.78 (m, 2H, 3-H, 1H of Ar), 7.96−8.01 (m, 2H, Ph), 8.11−8.16 (m, 2H, Ar), 10.10 (s, 1H, N*H*COPh), 12.25 (br s, 1H, OH). MS (EI, *m/z*, %): 347 (M^+, 40). *Anal.* Calcd for $C_{17}H_{12}F_3N_3O_2$: C, 58.79; H, 3.48; N, 12.10. Found: C, 58.75; H, 3.42; N, 12.25.

***N*-[1-(4-Bromophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]benzamide (5k).** mp 199-202 °C ($CHCl_3$). ^{1}H-NMR δ: 7.50−7.71 (m, 6H, 3-H, 3H of Ph, 2H of Ar), 7.76 (ddd, 1H, *J* = 2.4, 2.4, 9.3 Hz, Ar), 7.96−8.01 (m, 2H, Ph), 10.10 (br s, 1H, N*H*COPh), 12.02 (br s, 1H, OH). MS (EI, *m/z*, %): 357 (M^+, 18). *Anal.* Calcd for $C_{16}H_{12}BrN_3O_2$: C, 53.65; H, 3.38; N, 11.73. Found: C, 53.56; H, 3.46; N, 11.59.

***N*-[1-(4-Chlorophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]benzamide (5l).**[6g]

***N*-[1-(4-Fluorophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]benzamide (5m).** mp 203-205 °C ($CHCl_3$). ^{1}H-NMR δ: 7.28−7.37 (m, 2H, Ar), 7.50−7.68 (m, 4H, 3-H, 3H of Ph), 7.74−7.81 (m, 2H, Ar), 7.95−8.01 (m, 2H, Ph), 10.10 (s, 1H, N*H*COPh), 11.88 (br s, 1H, OH). MS (EI, *m/z*, %): 297 (M^+, 33). *Anal.* Calcd for $C_{16}H_{12}FN_3O_2$: C, 64.64; H, 4.07; N, 14.13. Found: C, 64.73; H, 4.13; N, 14.29.

***N*-[5-Hydroxy-1-(4-methylphenyl)-1*H*-pyrazol-4-yl]benzamide (5n).** mp 200-203 °C ($CHCl_3$). ^{1}H-NMR δ: 2.34 (s, 3H, CH_3), 7.28 (d, 2H, *J* = 7.9 Hz, Ar), 7.50−7.66 (m, 6H, 3-H, 2H of Ar, 3H of Ph), 7.96−8.01 (m, 2H, Ph), 10.12 (br s, 1H, N*H*COPh), 11.80 (br s, 1H, OH). MS (EI, *m/z*, %): 293 (M^+, 49). *Anal.* Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.32; H, 5.18; N, 14.34.

***N*-[5-Hydroxy-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]benzamide (5o).** mp 223-226 °C (DMF/EtOH). ^{1}H-NMR δ: 7.51−7.64 (m, 3H, Ph), 7.84 (br s, 1H, 3-H), 7.97−8.02 (m, 2H, Ph), 8.10−8.16 (m, 2H, Ar), 8.34−8.40 (m, 2H, Ar), 10.08 (s, 1H, N*H*COPh), 12.35 (br s, 1H, OH). MS (EI, *m/z*, %): 324 (M^+, 49). *Anal.* Calcd for $C_{16}H_{12}N_4O_4$: C, 59.26; H, 3.73; N, 17.28. Found: C, 58.99; H, 3.61; N, 17.09.

***N*-{5-Hydroxy-1-[4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}benzamide (5p).** mp 203-204 °C ($CHCl_3$). ^{1}H-NMR δ: 7.50−7.64 (m, 3H of Ph), 7.77 (br s, 1H, 3-H), 7.83-7.89 (m, 2H, Ar), 7.96−8.01 (m, 2H, Ph), 8.03−8.08 (m, 2H, Ar), 10.08 (s, 1H, N*H*COPh), 12.20 (br s, 1H, OH). MS (EI, *m/z*, %): 347 (M^+, 51). *Anal.* Calcd for $C_{17}H_{12}F_3N_3O_2$: C, 58.79; H, 3.48; N, 12.10. Found: C, 59.00; H, 3.33; N, 12.14.

***N*-[1-(2,5-Difluorophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]benzamide (5q).** mp 106-108 °C ($EtOH/H_2O$). ^{1}H-NMR δ: 7.34−7.63 (m, 6H, 3H of Ar, 3H of Ph), 7.73 (s, 1H, 3-H), 7.96−8.01 (m, 2H, Ph), 10.05 (s, 1H, N*H*COPh), 11.83 (br s, 1H, OH). MS (EI, *m/z*, %): 315 (M^+, 39). *Anal.* Calcd for $C_{16}H_{11}F_2N_3O_2 \cdot 0.5\ H_2O$: C, 59.26; H, 3.70; N, 12.96. Found: C, 59.01; H, 3.73; N, 12.97.

***N*-[5-Hydroxy-1-(2,4,6-trichlorophenyl)-1*H*-pyrazol-4-yl]benzamide (5r).** mp 211-213 °C (EtOAc/hexane). ^{1}H-NMR δ: 7.49−7.63 (m, 3H, Ph), 7.69 (br s, 1H, 3-H), 7.93 (s, 2H, Ar), 7.95−8.01 (m, 2H, Ph), 10.10 (br s, 1H, N*H*COPh), 11.69 (br s, 1H, OH). MS (EI, *m/z*, %): 381 (M^+, 11). *Anal.* Calcd for $C_{16}H_{10}Cl_3N_3O_2$: C, 50.22; H, 2.63; N, 10.98. Found: C, 50.07; H, 2.64; N, 10.78.

X-Ray structure analysis of 5p and 5r

Structures were solved by direct methods using SIR92.[8] The XTAL3.4[9] system of crystallographic programs was used for the correlation and reduction of data, structure refinement and interpretation. The crystallographic plots were made with ORTEPII.[10] The crystallographic data for both compounds have been deposited with the Cambridge Crystallographic Data Center as supplementary material with the deposition numbers CCDC 658310 (**5r**) and CCDC 658311 (**5p**). These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk).

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