3-(DIMETHYLAMINO)PROPENOATE-BASED REGIOSELECTIVE SYNTHESIS OF 1,4-DISUBSTITUTED 5-HYDROXY-1H-PYRAZOLES

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Abstract – 1,4-Disubstituted 5-hydroxy-1H-pyrazoles (9), (12), and (13) were prepared in two steps from hydrazines (2a–k) and 3-(dimethylamino)propenoates (1), (4), and (5). First, acid-catalyzed treatment of enaminones (1), (4), and (5) with (hetero)arylhydrazines (2a–k) afforded the corresponding dimethylamine substitution products, hydrazones (3’) and enehydrazines (6) and (7). Under acidic conditions, intermediates (3’), (6), and (7) did not undergo cyclization into the pyrazole derivatives. However, heating 3’, 6, and 7 in a mixture of methanol and triethylamine furnished the desired products in 65–98% yields.

INTRODUCTION

Pyrazole and its derivatives certainly belong among the most important class of heterocyclic systems. Despite its rare occurrence in nature, numerous pyrazole derivatives found use in various applications and a general interest in the chemistry of pyrazoles is still continuing.1 Some examples of important pyrazole derivatives are depicted in Figure 1.

Among various synthetic options for the construction of the pyrazole ring, two classical approaches are most frequently employed. The first one is based on a cyclocondensation reaction between a suitable 1,3-dicarbonyl compound (or its analog) and a hydrazine derivative, while the second one is based on a 1,3-dipolar cycloaddition of a suitable dipolarophile to diazoalkane, nitrile imine, or azomethine imine.1 In the last few decades, a substantial part of our research interest has been devoted to the chemistry of pyrazoles and their fused analogs. Our studies in pyrazole chemistry were especially focused on: (a) regioselective and stereoselective 1,3-dipolar cycloadditions to fused pyrazoline2 and pyrazolidin-3-one derived azomethine imines3,4 and (b) utilization of 3-(dimethylamino)propenoates and related enaminones
in the synthesis of pyrazoles.\textsuperscript{4,5} Within the context of 3-(dimethylamino)propenoate chemistry, we have previously reported several regioselective syntheses of various pyrazole derivatives,\textsuperscript{6–13} including synthesis of functionalized pyrazoles, such as 3-pyrazoylalanines,\textsuperscript{14} 3-pyrazolylpropane-1,2-diols,\textsuperscript{15} \(\beta\)-aminoalcohols and 2-phenylethylamines,\textsuperscript{16} spiro and fused heterocycles containing a dipeptide structural element,\textsuperscript{17–20} and terpene functionalized pyrazoles.\textsuperscript{21}

![Chemical structures](image)

Figure 1. Some examples of important pyrazole derivatives.

In continuation of our work in this field, we now report acid-catalyzed reactions of methyl (\(Z\))-2-acetylamino-3-(dimethylamino)propenoate (1) and dialkyl 2-(dimethylaminomethylidene)malonates (4) and (5) with monosubstituted hydrazines (2) leading to the corresponding hydrazones (3') or/and enehydrazines (6) and (7) and further base-promoted cyclizations of the intermediates (3'), (6), (7) into the 1,4-disubstituted-5-hydroxy-1\(H\)-pyrazoles (9), (12), and (13).

**RESULTS AND DISCUSSION**

Methyl (\(Z\))-2-acetylamino-3-(dimethylamino)propenoate (1),\textsuperscript{22} dimethyl 2-[(dimethylamino)methylidene]malonate (4),\textsuperscript{23} and diethyl 2-[(dimethylamino)methylidene]malonate (5)\textsuperscript{24} were prepared according to the literature procedures. Treatment of the propenoate (1) with hydrazines (2a–e,g–i) hydrochlorides in water at room temperature gave hydrazones (3'a–e,g–i), respectively, in 67–96\% yields. Hydrazones (3'a,b,d,i) were isolated in isomerically pure form, while compounds (3'c,e,g,h) were obtained as mixtures of the major hydrazones (3'c,e,g,h) and the minor enehydrazines (3c,e,g,h). Under the same reaction conditions,
the propenoate (1) was transformed with 2-hydrazinopyridine (2f) hydrochloride directly into 3-acetylamino-5-hydroxy-1-(pyridin-2-yl)-1H-pyrazole (9f), without isolation of the corresponding intermediate (3/3’f). On the other hand, reactions of dialkyl 2-[(dimethylamino)methylidene]malonates (4) and (5) with hydrazine derivatives (2c–k) afforded enehydrazines (6d–g,j,k) and (7c,f–j) in 39–94% yields. Enehydrazines (6d,f,j,k) and (7f–j) were obtained in isomerically pure form, whilst compounds (6e,g) and (7c) were isolated as mixtures of the major enehydrazines (6e,g), (7c) and the minor hydrazones (6’e,g), (7’c). According to general reactivity of 3-(dimethylamino)propenoates towards nitrogen nucleophiles,4,5 these reactions most probably proceed by initial substitution of the dimethyl amino group to give the intermediate enehydrazines (3), (6), (7), which are in equilibrium with the hydrazono tautomeric forms (3’), (6’), (7’) (Scheme 1, Table 1).25–27

Scheme 1. (i) H2O, rt.
All attempts to carry out cyclization of hydrazones (3') and enehydrazines (6), (7) into the corresponding pyrazole derivatives (9), (12), (13) under acidic conditions, e.g. by heating in acetic acid or by heating in ethanol–HCl,\textsuperscript{4,5,21} were unsuccessful. On the other hand, treatment of 1 with 2-hydrazinopyridine (2f) hydrochloride in water at room temperature gave the corresponding 4-acetylamino-5-hydroxy-1-(pyridin-2-yl)-1\textit{H}-pyrazole (9f) in 32\% yield (cf, Scheme 1). Since spontaneous cyclization of the intermediate (3/3'f) under mild conditions might have been due to the basic pyridine residue, we tried to carry out cyclization of the intermediates (3'), (6), and (7) under basic conditions, according to the procedure described previously.\textsuperscript{7} Thus, heating of compounds (3'), (6), and (7) in a mixture of water, methanol, and triethylamine (3:3:1), resulted in smooth conversion into the corresponding 5-hydroxy-1\textit{H}-pyrazoles (9), (12), and (13), respectively. In this manner, 1-substituted 4-acetylamino-5-hydroxy-1\textit{H}-pyrazoles (9a–d,g,h) and 1-substituted alkyl 5-hydroxy-1\textit{H}-pyrazole-4-carboxylates (12d,f,j,k) and (13c,f–h,j) were obtained in 65–98\% yields. Formation of pyrazoles (9), (12), and (13) can be explained according to the literaturely known pathways.\textsuperscript{1,4,5,7,8,11,21} First, intramolecular addition of NH group to the ester group gives the intermediates (8), (10), and (11), from which elimination of methanol takes place to afford the final 1,4-disubstituted 5-hydroxy-1\textit{H}-pyrazoles (9), (12), and (13) (Scheme 2, Table 1).

The structures of compounds (3/3'), (6/6'), (7/7'), (9), (12), and (13) were determined by spectroscopic methods (IR, NMR, and MS) and by elemental analyses for C, H, and N. Compounds (3/3'c), (9c,g), (12k), and (13g) were not obtained in analytically pure form because of including water. The structures of compounds (3/3'c) and (9c,g) were confirmed by \textsuperscript{13}C NMR and/or HRMS, while structures of compounds
(12k) and (13g) were confirmed by HRMS. Data for known compounds (7f,j) and (13f,j)\textsuperscript{28} and (7h)\textsuperscript{29} were in agreement with the literature data.

Table 1. Selected experimental data for compounds (3), (6), (7), (9), (12), and (13).

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<th>Yield (%)</th>
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In conclusion, various 1,4-disubstituted 5-hydroxy-1\textsuperscript{H}-pyrazoles (9), (12), and (13) are available in two steps from the 3-(dimethylamino)propenoates (1), (4), and (5) via acid-catalyzed substitution of the dimethylamino group with monosubstituted hydrazines (2) followed by base-catalyzed heterocyclization of the corresponding hydrazones (3’) or/and enehydrazines (6) and (7). Cyclizations of intermediates (3’), (6), and (7) into the corresponding pyrazoles (9), (12), and (13) had to be carried out in the presence of a base. Acidic reaction conditions, which are usually employed in heterocyclization reactions of 3-(dimethylamino)propenoates with various ambident nucleophiles,\textsuperscript{4,5} were not suitable. The methodology is closely related to the previously reported synthesis of 1-substituted alkyl 5-hydroxy-1\textsuperscript{H}-pyrazole-4-carboxylates from monosubstituted hydrazines and diethyl 2-(ethoxymethylidene)malonate. Interestingly, we did not observe formation of [1,2,4]triazolo[4,3-x]azines, which was reported previously in the reactions of hydrazinoazines with diethyl ethoxymethylidenemalonate.\textsuperscript{28,29}

**EXPERIMENTAL**

Melting points were determined on a Kofler micro hot stage. The NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for \textsuperscript{1}H and at 75.5 MHz for \textsuperscript{13}C nucleus, using DMSO-\textit{d}_6 and
CDCl₃ as solvents and with Me₄Si as the internal standard. Mass spectra were recorded on an AutoSpecQ spectrometer, IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN Analyser 2400 II. Ratio of isomers were determined by ¹H NMR.

Hydrazines (2a–f,i,k) are commercially available (Fluka AG). Methyl (Z)-2-acetylamino-3-(dimethylamino)propenoate (1), dimethyl 2-[(dimethylamino)methylidene]malonate (4), diethyl 2-[(dimethylamino)methylidene]malonate (5), 3-hydrazino-6-phenylpyridazine (2g), 6-chloro-3-hydrazinopyridazine (2h), and 2-hydrazinopyrimidine (2j), were prepared according to the literature procedures.

**General Procedure for the Preparation of Hydrazones (3’) and Enehydrazines (6) and (7).**

Propenoate (1), (4), or (5) (1 mmol) was added to a stirred solution of hydrazine derivative (2) (1 mmol) in a mixture of water (2 mL) and 37% hydrochloric acid (0.1 mL, 1 mmol). In the case of hydrazines hydrochlorides (2a,b,i,k), addition of 37% hydrochloric acid was omitted. The reaction mixture was then stirred at room temperature for 15 min–5 h and the precipitate was collected by filtration to give 3’, 6 or 7.

The following compounds were prepared in this manner:

**Methyl 2-acetamido-3-(2-phenylhydrazono)propanoate (3’a).** Prepared from 1 (0.186 g, 1 mmol) and phenylhydrazine (2a) hydrochloride (0.1445 g, 1 mmol); stirring for 2 h. Yield: 0.220 g (88%); reddish solid; mp 120–123 °C. IR (KBr): 3425, 3260, 3048, 1750 (C=O), 1745 (C=O), 1661, 1602, 1497, 1268, 1208, 1147, 761, 699 cm⁻¹. ¹H NMR (CDCl₃): δ 2.11 (3H, s, MeCO); 3.80 (3H, s, OMe); 5.27 (1H, dd, J = 4.0, 7.2 Hz; 2–H); 6.62 (1H, br d, J = 6.4 Hz, NHCOMe); 6.86–6.91 (1H, m, 1H of Ph); 6.94–6.98 (2H, m, 2H of Ph); 7.14 (1H, br d, J = 4.0 Hz, 3–H); 7.22–7.28 (2H, m, 2H of Ph); 7.62 (1H, s, NHPh). Anal Calcd for C₁₂H₁₅N₃O₃ (249.27): C, 57.82; H, 6.07; N, 16.86. Found: C, 57.67; H, 6.33; N, 16.91.

**Methyl 2-acetamido-3-[2-(4-metoxyphenyl)hydrazono]propanoate (3'b).** Prepared from 1 (0.186 g, 1 mmol) and 4-metoxyphenylhydrazine (2b) hydrochloride (0.138 g, 1 mmol); stirring for 1 h. Yield: 0.229 g (82%); ocre solid; mp 110–115 °C. IR (KBr): 3425, 3260, 3048, 1750 (C=O), 1661, 1600, 1497, 1268, 1208, 1141, 1209, 1034, 834, 521 cm⁻¹. ¹H NMR (DMSO-d₆): δ 1.89 (3H, s, MeCO); 3.66 and 3.67 (6H, 2s, 1:1, 2×OMe); 4.95 (1H, dd, J = 5.3, 7.5 Hz, 2–H); 6.78–6.87 (4H, m, C₆H₄); 7.09 (1H, d, J = 5.3 Hz, 3–H); 8.59 (1H, d, J = 7.5 Hz, NHCOME); 9.91 (1H, s, NHAr). Anal Calcd for C₁₃H₁₇N₃O₄ (279.29): C, 55.91; H, 6.14; N, 15.05. Found: C, 56.26; H, 6.21; N, 15.27.

**Methyl 2-acetamido-3-[2-(4-carboxyphenyl)hydrazono]propanoate (3’c) and methyl 2-acetamido-3-[2-(4-carboxyphenyl)hydrazino]propenoate (3c).** Prepared from 1 (0.186 g, 1 mmol), 4-hydrazinobenzoic acid (2c) (0.152 g, 1 mmol), and 37% hydrochloric acid (0.1 mL, 1 mmol); stirring for 1 h. Yield: 0.282 g (96%); brown solid; 3’c:3c = 89:11; mp 119–122 °C. IR (KBr): 3417, 3357, 30118.
1746 (C=O), 1675 (C=O), 1651, 1605, 1530, 1265, 1224, 1144, 853, 772 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): 

**Major isomer** ($3'$c) δ 1.91 (3H, s, MeCO); 3.69 (3H, s, OMe); 5.01 (1H, dd, $J = 5.3, 7.5$ Hz; 2–H); 6.96 (2H, d, $J = 8.7$ Hz, 2H of C$_6$H$_4$); 7.28 (1H, d, $J = 5.3$ Hz, 3–H); 7.78 (2H, d, $J = 8.7$ Hz, 2H of C$_6$H$_4$); 8.65 (1H, d, $J = 7.2$ Hz, NHCOMe); 10.64 (1H, s, NHAr); 12.27 (1H, br s, COOH); 

**Minor isomer** ($3$c) δ 1.91 (3H, s, MeCO); 3.55 (3H, s, OMe); 6.80 (2H, d, $J = 8.7$ Hz, 2H of C$_6$H$_4$); 7.20 (1H, d, $J = 10.7$ Hz, 3–H); 7.78 (2H, d, $J = 8.7$ Hz, 2H of C$_6$H$_4$); 8.30 (1H, br d, $J = 10.7$ Hz, NHNHAr); 8.53 (1H, s, NHHAr).

$^{13}$C NMR (DMSO-$d_6$): 

**Major isomer** ($3'$c) δ 23.1, 53.1, 55.2, 111.8, 121.4, 132.0, 136.4, 149.5, 168.1, 170.3, 170.7. EI-MS: $m/z$ 293 (M$^+$). HRMS Calcd for C$_{13}$H$_{15}$N$_3$O$_5$ (M$^+$): 293.101171. Found: 293.101320.

**Anal.** Calcd for C$_{13}$H$_{15}$N$_3$O$_5$ (293.28): C, 53.24; H, 5.16; N, 14.33. Calcd for C$_{13}$H$_{15}$N$_3$O$_5$·½H$_2$O: C, 51.65; H, 5.34; N, 13.90. Found: C, 51.79; H, 5.51; N, 13.92.

**Methyl 2-acetamido-3-[2-(4-nitrophenyl)hydrazono]propanoate (3’d).** Prepared from 1 (0.186 g, 1 mmol), 4-nitrophenylhydrazine ($2d$) (0.153 g, 1 mmol), and 37% hydrochloric acid (0.1 mL, 1 mmol); stirring for 180 min. Yield: 0.270 g (92%); yellowish solid; mp 164–168 °C. IR (KBr): 3379, 3233, 3071, 1744 (C=O), 1663, 1595, 1490, 1281, 843, 750 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): δ 1.92 (3H, s, MeCO); 3.70 (3H, s, OMe); 5.06 (1H, dd, $J = 5.3, 7.5$ Hz; 2–H); 7.04 (2H, d, $J = 9.0$ Hz, 2H of C$_6$H$_4$); 7.40 (1H, d, $J = 5.3$ Hz, 3–H); 8.12 (2H, d, $J = 9.3$ Hz, 2H of C$_6$H$_4$); 8.70 (1H, d, $J = 7.5$ Hz, NHCOMe); 11.14 (1H, s, NHAr).

**Anal.** Calcd for C$_{12}$H$_{14}$N$_4$O$_5$ (294.26): C, 48.98; H, 4.80; N, 19.04. Found: C, 49.24; H, 4.93; N, 18.76.

**Methyl 2-acetamido-3-[2-(2,4-dinitrophenyl)hydrazono]propanoate (3’e) and methyl 2-acetamido-3-[2-(2,4-dinitrophenyl)hydrazino]propenoate (3e).** Prepared from 1 (0.186 g, 1 mmol), 2,4-dinitrophenylhydrazine ($2e$) (0.198 g, 1 mmol), and 37% hydrochloric acid (0.1 mL, 1 mmol); stirring for 15 min. Yield: 0.283 g (83%); yellow solid; 3’e:3e = 75:25; mp 148–150 °C. IR (KBr): 3289, 3105, 2955, 1727 (C=O), 1659, 1616, 1514, 1431, 1327, 1218, 1140, 1078, 833, 598 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): δ 1.94 (3H, s, MeCO); 3.73 (3H, s, OMe); 5.18 (1H, dd, $J = 4.9$, 7.9 Hz; 2–H); 7.91 (1H, d, $J = 9.4$ Hz, 1H of C$_6$H$_3$); 8.13 (1H, d, $J = 4.9$ Hz, 3–H); 8.40 (1H, dd, $J = 2.6$, 9.4 Hz, 1H of C$_6$H$_3$); 8.78 (1H, d, $J = 7.6$ Hz, NHCOMe); 8.85 (1H, d, $J = 2.6$ Hz, 1H of C$_6$H$_3$); 11.59 (1H, br s, NHPh); 

**Minor isomer** ($3e$) δ 1.94 (3H, s, MeCO); 3.58 (3H, s, OMe); 7.24 (1H, br s, H–C (3)); 7.54 (1H, d, $J = 9.4$ Hz, 1H of C$_6$H$_3$); 8.36 (1H, d, $J = 2.6$ Hz, 1H of C$_6$H$_3$); 8.70 (1H, br s, NHNPh); 8.85 (1H, d, $J = 2.6$ Hz, 1H of C$_6$H$_3$); 11.59 (1H, br s, NHHAr).

**Anal.** Calcd for C$_{12}$H$_{13}$N$_5$O$_7$ (339.26): C, 49.24; H, 4.93; N, 18.76.

**Methyl 2-acetamido-3-[2-(6-phenylpyridazin-3-yl)hydrazono]propanoate (3’g) and methyl 2-acetamido-3-[2-(6-phenylpyridazin-3-yl)hydrazino]propenoate (3g).** Prepared from 1 (0.186 g, 1
mmol), 6-phenyl-3-hydrazinopyridazine (2g) (0.186 g, 1 mmol), and 37% hydrochloric acid (0.1 mL, 1mmol); stirring for 2 h. Yield: 0.218 g (67%); white solid; 3’g:3g = 90:10; mp 190–194 °C. IR (KBr): 3324, 3202, 2953, 2819, 1752 (C=O), 1651, 1611, 1536, 1420, 1214, 1155, 1033, 339, 743, 660 cm⁻¹. ¹H NMR (DMSO-d₆): Major isomer (3’g) δ 1.93 (3H, s, MeCO); 3.71 (3H, s, OMe); 5.07 (1H, dd, J = 5.2, 7.5 Hz; 2–H); 7.49 (5H, m, 3H of Ph, 4’–H, 5’–H); 8.03 (1H, d, J = 5.2 Hz, 3–H); 7.99–8.10 (2H, m, 2H of Ph); 8.69 (1H, d, J = 7.5 Hz, NHCOMe); 11.51 (1H, s, Het–N₂H); Minor isomer (3g) δ 1.93 (3H, s, MeCO); 3.57 (3H, s, OMe); 7.22 (1H, d, J = 9.7 Hz, 4’–H); 7.26 (1H, d, J = 10.6 Hz, 3–H); 7.49 (3H, m, 3H of Ph); 7.70 (1H, d, J = 9.7 Hz, 5’–H); 7.99–8.10 (2H, m, 2H of Ph); 8.44 (1H, d, J = 10.6 Hz NH/NHHet); 8.61 (1H, br s, NHCOMe); 9.55 (1H, s, Het–NH). Anal. Calcd for C₁₆H₁₇N₅O₃ (327.34): C, 58.71; H, 5.23; N, 21.39. Found: C, 58.42; H, 5.37; N, 21.16.

Methyl 2-acetamido-3-[2-(6-chloropyridazin-3-yl)hydrazono]propanoate (3’h) and methyl 2-acetamido-3-[2-(6-chloropyridazin-3-yl)hydrazino]propanoate (3h). Prepared from 1 (0.186 g, 1 mmol), 6-chloro-3-hydrazinopyridazine (2h) (0.1445 g, 1 mmol), and 37% hydrochloric acid (0.1 mL, 1mmol); stirring for 1 h. Yield: 0.237 g (83%); white solid; 3’h:3h = 88:12; mp 194–196 °C. IR (KBr): 3363, 3228, 3038, 2958, 1743 (C=O), 1674, 1614, 1519, 1414, 1288, 1219, 1079, 843, 743 cm⁻¹. ¹H NMR (DMSO-d₆): Major isomer (3’h) δ 1.91 (3H, s, MeCO); 3.69 (3H, s, OMe); 5.05 (1H, dd, J = 5.3, 7.5 Hz, 2–H); 7.47 (1H, d, J = 9.4 Hz, 4’–H), 7.48 (1H, d, J = 5.3 Hz, 3–H); 7.82 (1H, d, J = 9.4 Hz, 5’–H); 8.67 (1H, d, J = 7.5 Hz, NHCOMe); 11.58 (1H, br s, Het–NH); Minor isomer (3h) δ 1.91 (3H, s, MeCO); 3.56 (3H, s, OMe); 7.18 (1H, d, J = 9.4 Hz, 4’–H); 7.21 (1H, d, J = 10.6 Hz, 3–H); 7.64 (1H, d, J = 9.4 Hz, 5’–H); 8.39 (1H, d, J = 10.6 Hz, NH/NHHet); 8.58 (1H, s, NHCOMe); 9.46 (1H, br s, Het–NH). Anal. Calcd for C₁₀H₁₂ClN₅O₃ (285.69): C, 42.04; H, 4.23; N, 24.51. Found: C, 42.17; H, 4.37; N, 24.38.

Methyl 2-acetamido-3-[2-(phthalazin-1-yl)hydrazono]propanoate (3’i). Prepared from 1 (0.186 g, 1 mmol), 1-hydrazinophthalazine (2i) hydrochloride (0.1965 g, 1 mmol); stirring for 3 h. Yield: 0.280 g (93%); orange solid; mp 161–166 °C. IR (KBr): 3465, 3277, 2949, 1743 (C=O), 1674, 1614, 1519, 1414, 1288, 1219, 1079, 843, 743 cm⁻¹. ¹H NMR (DMSO-d₆): Major isomer (3’i) δ 2.02 (3H, s, MeCO); 3.70 (3H, s, OMe); 5.20 (1H, dd, J = 4.2, 6.4 Hz, 2–H); 7.77 (4H, m, 4’–H, 6’–H, 7’–H, 8’–H); 8.16 (1H, d, J = 9.4 Hz, 5’–H); 8.23 (1H, d, J = 4.2 Hz, 3–H); 8.68 (1H, d, J = 6.4 Hz, NHCOMe); 12.27 (1H, s, Het–NH). Anal. Calcd for C₁₄H₁₃N₅O₃ (301.30): C, 55.81; H, 5.02; N, 24.51. Found: C, 55.82; H, 5.16; N, 23.23.

Dimethyl 2-[(2-(4-nitrophenyl)hydrazinyl)methylidene]malonate (6d). Prepared from 4 (0.187 g, 1 mmol), 4-nitrophenylhydrazine (2d, 0.153 g, 1 mmol), and 37% hydrochloric acid (0.1 mL, 1 mmol); stirring for 15 min. Yield: 0.196 g (66%); yellow solid; mp 135–137 °C (from methanol). IR (KBr): 3328, 1726 (C=O), 1666 (C=O), 1593, 1309, 1279, 1227, 1109, 1076, 843, 797 cm⁻¹. ¹H NMR (CDCl₃): δ 3.74
and 3.85 (6H, 2s, 1:1, OMe); 6.81 (1H, s, NHAr); 6.87 (2H, d, J = 9.0 Hz, 2H of C6H4); 8.15 (1H, d, J = 10.9 Hz, CHNH); 8.17 (2H, d, J = 9.0 Hz, 2H of C6H4); 10.08 (1H, br d, J = 9.8 Hz, CHNH). EI-MS: m/z 295 (M+). HRMS Calcd for C12H13N3O6 (M+): 295.080435. Found: 295.081150. Anal. Calcd for C12H13N3O6 (295.25): C, 48.81; H, 4.44; N, 14.24. Found: C, 49.15; H, 4.56; N, 14.22.

Dimethyl 2-[[2-(2,4-dinitrophenyl)hydrazinyl]methylidene]malonate (6e) and dimethyl 2-[[2-(2,4-dinitrophenyl)hydrazono]methyl]malonate (6’e). Prepared from 4 (0.187 g, 1 mmol), 2,4-nitrophenylhydrazine (2e, 0.198 g, 1 mmol), and 37% hydrochloric acid (0.1 mL, 1 mmol); stirring for 5 h. Yield: 0.320 g (94%); yellow solid; 6e:6’e = 67:33; mp 150–154 °C (from ethanol). IR (KBr): 3450, 1690 (C=O), 1659 (C=O), 1626, 1607, 1519, 1449, 1352, 1284, 798 cm–1. 1H NMR (CDCl3). Major isomer (6e): δ 3.75 and 3.88 (6H, 2s, 1:1, OMe); 7.31 (1H, d, J = 9.4 Hz, 1H of C6H3); 8.07 (1H, s, CHNH); 8.42 (1H, dd, J = 2.3, 9.4 Hz, 1H of C6H3); 9.16 (1H, d, J = 2.6 Hz, 1H of C6H3); 9.86 (1H, s, Ar–NH); 10.11 (1H, s, CHNH). Minor isomer (6’e): δ 3.85 (6H, s, 2×OMe); 4.49 (1H, d, J = 7.2 Hz, 2–H); 7.67 (1H, d, J = 7.2 Hz, CH=N); 7.92 (1H, d, J = 9.8 Hz, 1H of C6H3); 8.35 (1H, dd, J = 2.3, 9.4 Hz, 1H of C6H3); 9.13 (1H, d, J = 2.6 Hz, 1H of C6H3); 11.21 (1H, s, ArNH). EI-MS: m/z 340 (M+). HRMS Calcd for C12H12N4O8 (M+): 340.065514. Found: 340.066120. Anal. Calcd for C12H12N4O8 (340.25): C, 42.36; H, 3.56; N, 16.47. Found: C, 42.50; H, 3.75; N, 16.23.

Dimethyl 2-[[2-(pyridin-2-yl)hydrazinyl]methylidene]malonate (6f). Prepared from 4 (0.187 g, 1 mmol), 2-hydrazinopyridine (2f, 0.109 g, 1 mmol), and 37% hydrochloric acid (0.1 mL, 1 mmol); stirring for 24 h. Yield: 0.113 g (45%); orange solid; mp 142–144 °C (from methanol). IR (KBr): 3264, 1694 (C=O), 1652 (C=O), 1603, 1441, 1408, 1268, 1229, 1074, 1001, 799, 776 cm–1. 1H NMR (CDCl3). δ 3.73 and 3.84 (6H, 2s, 1:1, OMe); 6.73 (1H, d, J = 8.4 Hz, 3’–H); 6.88 (1H, m, 5’–H); 7.12 (1H, s, Het–NH); 7.61 (1H, m, 4’–H); 8.20 (1H, d, J = 11.1 Hz, CHNH); 8.24 (1H, d, 8.4 Hz, 6’–H); 10.12 (1H, br d, J = 11.1 Hz, CHNH). EI-MS: m/z 251 (M+). HRMS Calcd for C11H13N3O4 (M+): 251.090606. Found: 251.090650. Anal. Calcd for C11H13N3O4 (251.24): C, 52.58; H, 5.22; N, 16.73. Found: C, 52.76; H, 5.43; N, 17.03.

Dimethyl 2-[[2-(6-phenylpyridazin-3-yl)hydrazinyl]methylidene]malonate (6g) and dimethyl 2-[[2-(6-phenylpyridazin-3-yl)hydrazono]methyl]malonate (6’g). Prepared from 4 (0.187 g, 1 mmol), 3-hydrazino-6-phenylpyridazine (2g, 0.186 g, 1 mmol), and 37% hydrochloric acid (0.1 mL, 1 mmol); stirring for 5 h. Yield: 0.230 g (70%); yellow solid; 6g:6’g = 89:11; mp 145–147 °C (from ethanol). IR (KBr): 3432, 3289, 1750 (C=O), 1692 (C=O), 1654 (C=O), 1447, 1266, 1234, 1077, 799 cm–1. 1H NMR (CDCl3). Major isomer (6g): δ 3.74 and 3.85 (6H, 2s, 1:1, 2×OMe); 7.07 (1H, d, J = 10.5 Hz, 4’–H); 7.43–7.53 (4H, m, 3H of Ph, Het–NH); 7.78 (1H, br d, J = 10.9 Hz, 5’–H); 7.94–8.02 (2H, m, 2H of Ph); 8.28 (1H, d, J = 10.9 Hz, CHNH); 10.26 (1H, br d, J = 10.2 Hz, CHNH). Minor isomer (6’g): δ 3.81 (6H,
Dimethyl 2-[(2-(pyrimidin-2-yl)hydrazinyl)methylidene]malonate (6j). Prepared from 4 (0.187 g, 1 mmol), 2-hydrazinopyrimidine (2j, 0.110 g, 1 mmol), and 37% hydrochloric acid (0.1 mL, 1 mmol); stirring for 4 h. Yield: 0.234 g (93%); yellow solid; mp 168–171 °C (from methanol). IR (KBr): 3285, 1691 (C=O), 1619, 1583, 1447, 1412, 1272, 1234, 800 cm$^{-1}$. $^{1}$H NMR (CDCl$_3$): $\delta$ 3.72 and 3.83 (6H, 2s, 1:1, 2×OMe); 6.83 (1H, t, $J$ = 4.9 Hz, 5′–H); 8.20 (1H, s, C$_7$H$_6$N); 8.21 (1H, br s, Het–N$_H$); 8.44 (2H, d, $J$ = 4.9 Hz, 4′–H and 6′–H); 10.28 (1H, s, CHN$_H$). EI-MS: $m/z$ 251 (M$^+$). HRMS Calcd for C$_{10}$H$_{12}$N$_4$O$_4$ (M$^+$): 252.085855. Found: 252.086230.

Anal. Calcd for C$_{10}$H$_{12}$N$_4$O$_4$ (252.23): C, 47.61; H, 4.80; N, 22.22. Found: C, 47.59; H, 5.01; N, 22.25.

Dimethyl 2-[(2-(4-fluorophenyl)hydrazinyl)methylidene]malonate (6k). Prepared from 4 (0.187 g, 1 mmol) and 4-fluorophenylhydrazine hydrochloride (2k, 0.163 g, 1 mmol); stirring for 15 min. Yield: 0.145 g (54%); yellow solid; mp 94–97 °C (from methanol). IR (KBr): 3439, 3265, 1682 (C=O), 1657 (C=O), 1609, 1510, 1443, 1402, 1281, 1223, 1072, 792 cm$^{-1}$. $^{1}$H NMR (CDCl$_3$): $\delta$ 3.73 and 3.82 (6H, 2s, 1:1, 2×OMe); 6.22 (1H, s, Ar–N$_H$); 6.78 (2H, dd, $J$ = 4.1, 9.0 Hz, 2H of C$_6$H$_4$); 6.98 (2H, dd, $J$ = 2.3, 8.7 Hz, 2H of C$_6$H$_4$); 8.25 (1H, d, $J$ = 11.3 Hz, C$_7$H$_6$N); 10.04 (1H, d, $J$ = 11.3 Hz, CHN$_H$); 10.04 (1H, d, $J$ = 11.3 Hz, CHNH). EI-MS: $m/z$ 268 (M$^+$). HRMS Calcd for C$_{12}$H$_{13}$N$_2$O$_4$F (M$^+$): 268.085935. Found: 268.086550.

Anal. Calcd for C$_{12}$H$_{13}$N$_2$O$_4$F (268.24): C, 53.73; H, 4.89; N, 10.45. Found: C, 53.71; H, 4.99; N, 9.84.

Diethyl 2-[(2-(4-carboxyphenyl)hydrazinyl)methylidene]malonate (7c) and diethyl 2-[(2-(4-carboxyphenyl)hydrazono)methyl]malonate (7′c). Prepared from 5 (0.215 g, 1 mmol), 4-hydrazinobenzoic acid (2c, 0.152 g, 1 mmol), and 37% hydrochloric acid (0.1 mL, 1 mmol); stirring for 5 h. Yield: 0.254 g (79%); yellowish solid; 7c:7′c = 89:11; mp >350 °C (from ethanol). IR (KBr): 3447, 3273, 1697 (C=O), 1681 (C=O), 1647 (C=O), 1609, 1585, 1425, 1283, 1260, 1175, 793 cm$^{-1}$. $^{1}$H NMR (DMSO-d$_6$). Major isomer (7c): $\delta$ 1.19 and 1.24 (6H, 2t, 1:1, $J$ = 7.2 Hz, OCH$_2$C$_3$H$_7$); 4.07 and 4.19 (4H, 2q, 1:1, $J$ = 7.2 Hz, CH$_2$CH$_3$); 6.76 and 7.83 (4H, 2d, 1:1, $J$ = 8.7 Hz, C$_6$H$_4$); 7.94 (1H, d, $J$ = 12.1 Hz, CHNH); 9.08 (1H, s, Ar–NH); 10.14 (1H, d, $J$ = 12.1 Hz, CHNH); 11.88 (1H, br s, COOH). Minor isomer (7′c): $\delta$ 1.24 (6H, t, $J$ = 7.2 Hz, 2×CH$_2$CH$_3$); 4.19 (4H, q, $J$ = 7.2 Hz, 2×CH$_2$CH$_3$); 4.49 (1H, d, $J$ = 6.0 Hz, 2–H); 6.95 (2H, d, $J$ = 8.7 Hz, 2H of C$_6$H$_4$); 7.36 (1H, d, $J$ = 6.4 Hz, CH=N); 7.69 (2H, d, $J$ = 9.0 Hz, 2H of C$_6$H$_4$); 10.72 (1H, s, Ar–NH); 11.88 (1H, br s, COOH). EI-MS: $m/z$ 322 (M$^+$). HRMS Calcd
for C_{15}H_{18}N_{2}O_{6} (M^+) 322.1164. Found: 322.1171. Anal. Calcd for C_{15}H_{18}N_{2}O_{6} (322.31): C, 55.89; H, 5.63; N, 8.69. Found: C, 56.06; H, 5.72; N, 8.58.

**Diethyl 2-{{2-(pyridin-2-yl)hydrazinyl}methylidene}malonate (7f).** Prepared from 5 (0.215 g, 1 mmol), 2-hydrazinopyridine (2f, 0.109 g, 1 mmol), and 37% hydrochloric acid (0.1 mL, 1 mmol); stirring for 24 h. Yield: 0.157 g (56%); orange solid; mp 95–97 °C (from ethanol) (lit., mp not given). IR (KBr): 3260, 1686 (C=O), 1655 (C=O), 1646 (C=O), 1596, 1420, 1264, 1224, 1072, 1028, 800, 778 cm⁻¹. ¹H NMR (CDCl₃): δ 1.29 and 1.37 (6H, 2t, 1:1, J = 7.2 Hz, 2×CH₂CH₃); 4.21 and 4.30 (4H, 2q, 1:1, J = 7.2 Hz, 2×CH₂CH₃); 6.74 (1H, d, J = 8.3 Hz, 3’–H); 6.88 (1H, deg dt, J = 1.9, 8.3 Hz, 5’–H); 7.16 (1H, s, Het–NH); 7.61 (1H, deg dt, J = 1.9, 8.3 Hz, 4’–H); 8.19 (1H, d, J = 11.3 Hz, CH=NH); 8.21 (1H, d, J = 8.3 Hz, 6’–H); 10.09 (1H, d, J = 11.3 Hz, CHN). EI-MS: m/z 279 (M⁺). HRMS Calcd for C₁₃H₁₇N₃O₄ (M⁺): 279.121906. Found: 279.122040. Anal. Calcd for C₁₃H₁₇N₃O₄ (279.29): C, 55.91; H, 6.14; N, 15.05. Found: C, 55.82; H, 6.33; N, 15.09.

**Diethyl 2-{{2-(6-Phenylpyridazin-3-yl)hydrazinyl}methylidene}malonate (7g).** Prepared from 5 (0.215 g, 1 mmol), 3-hydrazino-6-phenylpyridazine (2g, 0.186 g, 1 mmol), and 37% hydrochloric acid (0.1 mL, 1 mmol); stirring for 4 h. Yield: 0.293 g (82%); yellow solid; mp 139–142 °C (from ethanol). IR (KBr): 3437, 1698 (C=O), 1648 (C=O), 1617, 1458, 1429, 1261, 1231, 1079, 1031, 797 cm⁻¹. ¹H NMR (CDCl₃): δ 1.30 and 1.38 (6H, 2t, 1:1, J = 7.2 Hz, 2×CH₂CH₃); 7.12 (1H, d, J = 9.4 Hz, 4’–H); 7.43–7.55 (4H, m, 3H of Ph, Het–NH); 7.81 (1H, d, J = 9.0 Hz, 5’–H); 7.95–8.03 (2H, m, 2H of Ph); 8.23 (1H, d, J = 10.5 Hz, CH=NH); 10.17 (1H, d, J = 11.3 Hz, CHN). EI-MS: m/z 356 (M⁺). HRMS Calcd for C₁₈H₂₀N₄O₄ (M⁺): 356.148455. Found: 356.149540. Anal. Calcd for C₁₈H₂₀N₄O₄ (356.38): C, 60.66; H, 5.66; N, 15.72. Found: C, 60.01; H, 5.67; N, 15.73.

**Diethyl 2-{{2-(6-Chloropyridazin-3-yl)hydrazinyl}methylidene}malonate (7h).** Prepared from 5 (0.215 g, 1 mmol), 6-chloro-3-hydrazinopyridazine (2h, 0.144 g, 1 mmol), and 37% hydrochloric acid (0.1 mL, 1 mmol); stirring for 4 h. Yield: 0.210 g (67%); yellow solid; mp 153–157 °C (from ethanol) (lit., mp 165 °C (ethanol–water)). IR (KBr): 3432, 3237, 1687 (C=O), 1648 (C=O), 1617, 1458, 1429, 1261, 1231, 1079, 1031, 799 cm⁻¹. ¹H NMR (CDCl₃): δ 1.30 and 1.38 (6H, 2t, 1:1, J = 7.2 Hz, 2×CH₂CH₃); 7.12 (1H, d, J = 9.4 Hz, 4’–H); 7.43–7.55 (4H, m, 3H of Ph, Het–NH); 7.81 (1H, d, J = 9.0 Hz, 5’–H); 7.95–8.03 (2H, m, 2H of Ph); 8.23 (1H, d, J = 10.5 Hz, CH=NH); 10.17 (1H, d, J = 11.3 Hz, CHN). EI-MS: m/z 314 (M⁺). HRMS Calcd for C₁₂H₁₅ClN₄O₄ (M⁺): 314.078183. Found: 314.078850. Anal. Calcd for C₁₂H₁₅ClN₄O₄ (314.72): C, 45.79; H, 4.80; N, 17.81. Found: C, 45.75; H, 4.94; N, 17.88.

**Diethyl 2-{{2-(Phthalazin-1-yl)hydrazinyl}methylidene}malonate (7i).** Prepared from 5 (0.215 g, 1 mmol) and 1-hydrazinophthalazine hydrochloride (2i, 0.215 g, 1 mmol); stirring for 4 h. Yield: 0.220 g (67%); yellow solid; mp 153–156 °C (from ethanol). IR (KBr): 3500, 3260, 1713 (C=O), 1675 (C=O),
1637, 1610, 1598, 1424, 1376, 1279, 1233, 1080, 1035, 788, 770 cm⁻¹. ¹H NMR (CDCl₃): δ 1.31 and 1.38 (6H, 2t, 1:1, J = 7.2 Hz, 2×CH₂C₃H₇); 4.23 and 4.31 (4H, 2q, 1:1, J = 7.2 Hz, 2×C₃H₂CH₃); 7.49–8.27 (4H, m, 5’–H, 6’–H, 7’–H, 8’–H); 7.88 (1H, s, 4’–H); 8.51 (1H, d, J = 11.7 Hz, CHNH); 9.94 (1H, s, Het–NH); 11.34 (1H, d, J = 11.7 Hz, CHN). EI-MS: m/z 330 (M⁺). HRMS Calcd for C₁₆H₁₈N₄O₄ (M⁺): 330.132805. Found: 330.133450.


Diethyl 2-[[pyrimidin-2-yl]hydrazinyl]methylidene]malonate (7j).²⁸ Prepared from 5 (0.215 g, 1 mmol), 2-hydrazinopyrimidine (2j, 0.110 g, 1 mmol), and 37% hydrochloric acid (0.1 mL, 1 mmol); stirring for 3 h. Yield: 0.110 g (39%); yellow solid; mp 126–129 °C (from ethanol) (lit.,²⁸ mp 136–137 °C). IR (KBr): 3275, 3215, 1712 (C=O), 1661 (C =O), 1618, 1582, 1450, 1423, 1260, 1222, 1070, 797 cm –¹. ¹H NMR (CDCl₃): δ 1.28 and 1.36 (6H, 2t, 1:1, J = 7.2 Hz, 2×CH₂C₃H₇); 4.20 and 4.31 (4H, 2q, 1:1, J = 7.2 Hz, 2×C₃H₂CH₃); 6.85 (1H, t, J = 4.9 Hz, 5’–H); 7.35 (1H, s, Het–NH); 8.16 (1H, d, J = 10.2 Hz, CHNH); 8.46 (2H, d, J = 4.9 Hz, 4’–H and 6’–H); 10.18 (1H, br d, J = 10.2 Hz, CHN). EI-MS: m/z 280 (M⁺). HRMS Calcd for C₁₂H₁₆N₄O₄ (M⁺): 280.117155. Found: 280.117530. Anal. Calcd for C₁₂H₁₆N₄O₄ (280.28): C, 51.42; H, 5.75; N, 19.99. Found: C, 51.40; H, 5.90; N, 20.02.

4-Acetamido-5-hydroxy-1-(pyridin-2-yl)-1H-pyrazole (9f). Propenoate (1) (0.093 g, 0.5 mmol) was added to a stirred solution of 2-hydrazinopyridine (2f, 0.055 g, 0.5 mmol) and 37% hydrochloric acid (0.05 mL, 0.5 mmol) in water (1 mL) and the mixture was stirred at room temperature for 48 h. Yield: 0.035 g (32%); white solid; mp 210–214 °C. IR (KBr): 3408, 3258, 3070, 1727 (C=O), 1624, 1604, 1573, 1435, 1380, 1153, 1087, 782, 745 cm –¹. ¹H NMR (DMSO-d₆): δ 2.02 (3H, s, MeCO); 7.28–7.32 (1H, m, 1H of 5’–H); 7.95–8.01 (2H, m, 3’–H, 4’–H); 8.34 (1H, br s, 3–H); 8.45–8.47 (1H, m, 1H of 6’–H); 9.53 (1H, s, NHCOMe); 11.61 (1H, br s, OH). Anal. Calcd for C₁₀H₁₀N₄O₂ (218.21): C, 55.04; H, 4.62; N, 25.68. Found: C, 55.04; H, 4.79; N, 25.86.

General Procedure for the Preparation of 1-Substituted 4-Acetylamino-5-hydroxy-1H-pyrazoles (9a–d,g–i) and Alkyl 5-Hydroxy-1H-pyrazole-4-carboxylates (12d,g,j,k) and (13c,f–h,j). Hydrazone (3’) or enehydrazine (6), (7) (0.5 mmol) was suspended in a mixture of methanol–water–triethylamine (3:3:1, 4 mL) and the mixture was heated under reflux for 2–3 h. Volatile components were evaporated in vacuo and the residue was triturated with 10% aqueous hydrochloric acid (10 mL). The precipitate was collected by filtration and washed with water (5 mL) to give the pyrazole derivative (9), (12), (13).

The following compounds were prepared in this manner:
4-Acetamido-5-hydroxy-1-phenyl-1H-pyrazole (9a). Prepared from 3’a (0.1245 g, 0.5 mmol); reflux for 3 h. Yield: 0.084 g (78%); brownish solid; mp 210–215 °C. IR (KBr): 3439, 3275, 3046, 1680, 1608, 1578, 1378, 1238, 1074, 834, 761 cm⁻¹. ¹H NMR (DMSO-d₆): δ 2.04 (3H, s, MeCO); 7.27 (1H, br t, J = 7.2 Hz, 1H of Ph); 7.35–7.49 (3H, m, 2H of Ph, 3–H); 7.73 (2H, d, J = 7.9 Hz, 2H of Ph); 9.70 (1H, br s, NHCOMe); 12.02 (1H, br s, OH). Anal. Calcd for C₁₁H₁₁N₃O₂ (217.23): C, 60.82; H, 5.10; N, 19.34. Found: C, 60.82; H, 5.29; N, 19.36.

4-Acetamido-5-hydroxy-1-(4-methoxyphenyl)-1H-pyrazole (9b). Prepared from 3’b (0.140 g, 0.5 mmol); reflux for 3 h. Yield: 0.106 g (86%); brown solid; mp 213–215 °C. IR (KBr): 3329, 3042, 2772, 1687 (C=O), 1597, 1580, 1515, 1377, 1246, 1020, 836, 741 cm⁻¹. ¹H NMR (DMSO-d₆): δ 2.03 (3H, s, MeCO); 3.78 (3H, s, OMe); 7.00–7.03 (2H, m, 2H of C₆H₄); 7.48 (1H, br s, 3–H); 7.58–7.61 (2H, m, 2H of C₆H₄); 9.87 (1H, s, NHCOMe); 11.57 (1H, br s, OH). Anal. Calcd for C₁₂H₁₃N₃O₃ (247.25): C, 58.29; H, 5.30; N, 17.00. Found: C, 58.26; H, 5.51; N, 16.76.

4-Acetamido-1-(4-carboxyphenyl)-5-hydroxy-1H-pyrazole (9c). Prepared from 3/3’c (0.149 g, 0.5 mmol); reflux for 3 h. Yield: 0.123 g (94%); brown solid; mp 290–295 °C. IR (KBr): 3478, 3059, 1679 (C=O), 1616, 1601, 1425, 1361, 1281, 1181, 854, 768 cm⁻¹. ¹H NMR (DMSO-d₆): δ 2.05 (3H, s, MeCO); 7.67 (1H, br s, 3–H); 7.90–7.93 and 8.02–8.05 (4H, 2m, 1:1, C₆H₄); 9.90 (1H, s, NHCOMe); 13.00 (1H, br s, OH). ¹³C NMR (DMSO-d₆): δ 23.0, 107.0, 120.1, 128.2, 131.3, 134.0, 142.5, 148.9, 167.7, 170.2. EI-MS: m/z 262 (MH⁺). HRMS Calcd for C₁₂H₁₁N₃O₄ (M⁺): 261.074956. Found: 261.075030. Anal. Calcd for C₁₂H₁₁N₃O₄ (261.24): C, 55.17; H, 4.24; N, 16.09. Calcd for C₁₂H₁₁N₃O₄·½H₂O: C, 54.60; H, 4.42; N, 15.73. Found: C, 54.69; H, 4.37; N, 15.70.

4-Acetamido-5-hydroxy-1-(4-nitrophenyl)-1H-pyrazole (9d). Prepared from 3’d (0.147 g 0.5 mmol); reflux for 3 h. Yield: 0.128 g (97%); brown solid; mp 250–255 °C. IR (KBr): 3265, 3084, 2900, 1647, 1618, 1589, 1334, 1110, 851, 747 cm⁻¹. ¹H NMR (DMSO-d₆): δ 2.03 (3H, s, MeCO); 7.75 (1H, s, 3–H); 8.11 (2H, d, J = 9.4 Hz, 2H of C₆H₄); 8.34 (2H, d, J = 9.4 Hz, 2H of C₆H₄); 9.80 (1H, s, NHCOMe), OH exchanged. Anal. Calcd for C₁₁H₁₀N₄O₄ (262.22): C, 50.38; H, 3.84; N, 21.37. Found: C, 50.45; H, 4.06; N, 21.09.

4-Acetamido-5-hydroxy-1-(6-phenylpyridazin-3-yl)-1H-pyrazole (9g). Prepared from 3’g (0.148 g, 0.5 mmol); reflux for 3 h. Yield: 0.114 g (77%); brownish solid; mp 289–293 °C. IR (KBr): 3325, 3084, 2900, 1647, 1618, 1589, 1334, 1110, 851, 747 cm⁻¹. ¹H NMR (DMSO-d₆): δ 2.04 (3H, s, MeCO); 7.54–7.62 (3H, m, 3H of Ph); 8.12–8.17 (3H, m, 2H of Ph, 3–H); 8.41 (1H, d, J = 9.4 Hz, 5’–H); 8.69 (1H, br s, 4’–H); 9.63 (1H, s, NHCOMe); 12.07 (1H, br s, OH). ¹³C NMR (DMSO-d₆): δ 23.4, 109.3, 118.3, 127.4, 127.6, 129.8, 129.83, 129.9, 130.9, 136.4, 151.7, 157.4, 168.9. EI-MS: m/z 295 (M⁺). HRMS Calcd for C₁₅H₁₃N₅O₂ (M⁺): 295.106925. Found: 295.107050. Anal. Calcd for C₁₅H₁₃N₅O₂
(218.20): C, 61.01; H, 4.44; N, 23.72. Calcd for C_{15}H_{13}N_{5}O_{2}·\frac{1}{8}H_{2}O: C, 60.55; H, 4.49; N, 23.54. Found: C, 60.38; H, 4.48; N, 23.44.

4-Acetamido-1-(6-chloropyridazin-3-yl)-5-hydroxy-1H-pyrazole (9h). Prepared from 3/3‘h (0.143 g, 0.5 mmol); reflux for 3 h. Yield: 0.1165 g (91%); yellowish solid; mp 279–282 °C. IR (KBr): 3276, 3068, 1599, 1543, 1429, 1361, 1230, 1146, 850, 729 cm\(^{-1}\). \(^1\)H NMR (DMSO-\(d_6\)): \(\delta\) 2.03 (3H, s, MeCO); 8.04 (1H , d, \(J = 9.4\) Hz, 5‘–H); 8.12 (1H, s, 3–H); 8.72 (1H, br d, \(J = 7.5\) Hz, 4‘–H); 9.63 (1H, br s, NHCOMe); 12.02 (1H, br s, OH). Anal. Calcd for C_{9}H_{8}N_{5}O_{2}Cl (253.65): C, 42.62; H, 3.18; N, 27.61. Found: C, 42.54; H, 3.33; N, 27.61.

Methyl 5-hydroxy-1-(4-nitrophenyl)-1H-pyrazole-4-carboxylate (12d). Prepared from 6d (0.147 g, 0.5 mmol); reflux for 2 h. Yield: 0.129 g (98%); yellowish solid; mp 246–252 °C (from methanol). IR (KBr): 3268, 1718 (C=O), 1692 (C=O), 1641, 1586, 1517, 1450, 1340, 1232, 1114, 850 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 3.93 (3H, s, OMe); 7.82 (1H, s, 3–H); 8.12 (2H, d, \(J = 9.0\) Hz, 2H of C\(_6\)H\(_4\)); 8.36 (2H, d, 2H, d, \(J = 9.4\) Hz, 2H of C\(_6\)H\(_4\)); 10.03 (1H, br s, OH). EI-MS: \(m/z\) 263 (M\(^+\)). HRMS Calcd for C\(_{11}\)H\(_9\)N\(_3\)O\(_5\) (M\(^+\)): 263.054221. Found: 263.054850.

Methyl 5-hydroxy-1-(pyridin-2-yl)-1H-pyrazole-4-carboxylate (12f). Prepared from 6f (0.125 g, 0.5 mmol); reflux for 3 h. Yield: 0.071 g (65%); yellowish solid; mp 207–208 °C (from ethanol). IR (KBr): 3443, 1688 (C=O), 1651, 1637, 1609, 1547, 1531, 1448, 1238, 1082, 781 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 3.87 (3H, s, OMe); 7.29 (1H, s, 5‘–H); 7.90 (1H, s, 3–H); 7.96 (2H, m, 3’–H and 4’–H); 8.35 (1H, m, 6’–H); 14.05 (1H, s, OH). EI-MS: \(m/z\) 219 (M\(^+\)). HRMS Calcd for C\(_{10}\)H\(_9\)N\(_3\)O\(_3\) (M\(^+\)): 219.064391. Found: 219.064391.

Methyl 5-hydroxy-1-(pyrimidin-2-yl)-1H-pyrazole-4-carboxylate (12j). Prepared from 6j (0.126 g, 0.5 mmol); reflux for 2 h. Yield: 0.087 g (79%); yellowish solid; mp 207–208 °C (from ethanol). IR (KBr): 3473, 1697 (C=O), 1533, 1447, 1391, 1329, 781 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 3.88 (3H, s, OMe); 7.36 (1H, \(t, J = 5.0\) Hz, 5‘–H; 8.00 (1H, s, 3–H); 8.83 (2H, d, \(J = 4.8\) Hz, 4’–H and 6’–H); 12.75 (1H, br s, OH). EI-MS: \(m/z\) 219 (M\(^+\)). HRMS Calcd for C\(_{9}\)H\(_8\)N\(_4\)O\(_3\) (M\(^+\)): 220.059640. Found: 220.060250. Anal. Calcd for C\(_{9}\)H\(_8\)N\(_4\)O\(_3\) (220.18): C, 49.09; H, 3.66; N, 25.45. Found: C, 49.03; H, 3.82; N, 25.80.

Methyl 1-(4-fluorophenyl)-5-hydroxy-1H-pyrazole-4-carboxylate (12k). Prepared from 6k (0.134 g, 0.5 mmol); reflux for 3 h. Yield: 0.103 g (87%); yellowish solid; mp 160–165 °C (from methanol). IR
Ethyl 1-(4-carboxyphenyl)-5-hydroxy-1H-pyrazole-4-carboxylate (13c). Prepared from 7/7′c (0.161 g, 0.5 mmol); reflux for 2 h. Yield: 0.105 g (76%); yellow solid; mp >350 °C (from ethanol). IR (KBr): 3157, 1713 (C=O), 1686 (C=O), 1633, 1605, 1588, 1432, 1342, 1292, 1173, 1063, 764 cm–1. 1H NMR (DMSO-d6): δ 1.29 (3H, t, J = 7.2 Hz, CH2CH3); 4.25 (2H, q, J = 7.2 Hz, CH2CH3); 7.88 (1H, s, 3–H); 7.91 (2H, d, J = 8.3 Hz, 2H of C6H4); 8.08 (2H, d, J = 8.7 Hz, 2H of C6H4); 12.99 (1H, br s, OH). EI-MS: m/z 276 (M+). HRMS Calcd for C13H12N2O5 (M+): 276.074622. Found: 276.075510. Anal. Calcd for C13H12N2O5 (276.24): C, 56.52; H, 4.38; N, 10.14. Found: C, 56.79; H, 4.38; N, 9.97.

Ethyl 5-hydroxy-1-(pyridin-2-yl)-1H-pyrazole-4-carboxylate (13f). Prepared from 7f (0.140 g, 0.5 mmol); reflux for 2 h. Yield: 0.084 g (72%); yellowish solid; mp 146–147 °C (from ethanol) (lit., mp not given). IR (KBr): 3460, 1709 (C =O), 1640, 1619, 1542, 1528, 1409, 1382, 1323, 1164, 1077, 937, 777 cm–1. 1H NMR (CDCl3): δ 1.38 (3H, t, J = 7.2 Hz, CH2CH3); 4.35 (2H, q, J = 7.2 Hz, CH2CH3); 7.23–7.30 (1H, m, 5’–H); 7.88 (1H, s, 3–H); 7.96 (2H, m, 3’–H and 4’–H); 8.34 (1H, m, 6’–H); OH exchanged. EI-MS: m/z 233 (M+). HRMS Calcd for C11H11N3O3 (M+): 233.080041. Found: 233.080730. Anal. Calcd for C11H11N3O3 (233.22): C, 56.65; H, 4.75; N, 18.02. Found: C, 56.61; H, 4.96; N, 18.25.

Ethyl 5-hydroxy-1-(6-phenylpyridazin-3-yl)-1H-pyrazole-4-carboxylate (13g). Prepared from 7g (0.178 g, 0.5 mmol); reflux for 3 h. Yield: 0.127 g (82%); yellow solid; mp 280–283 °C (from ethanol). IR (KBr): 3437, 1717 (C=O), 1645, 1557, 1468, 1452, 1430, 1369, 1341, 1222, 1073, 781 cm–1. 1H NMR (CDCl3): δ 1.39 (3H, t, J = 7.2 Hz, CH2CH3); 4.37 (2H, q, J = 7.2 Hz, CH2CH3); 7.57 (3H, m, 2H of Ph); 7.97 (1H, s, 3–H); 8.05 (2H, m, 2H of Ph); 8.15 (1H, d, J = 9.4 Hz, 4’–H); 8.27 (1H, d, J = 9.0 Hz, 5’–H); 13.04 (1H, br s, OH). EI-MS: m/z 310 (M+). HRMS Calcd for C16H14N4O3 (M+): 310.106591. Found: 310.107250. Anal. Calcd for C16H14N4O3 (310.31): C, 61.92; H, 4.55; N, 18.06. Found: C, 61.46; H, 4.60; N, 18.70.

Ethyl 1-(6-chloropyridazin-3-yl)-5-hydroxy-1H-pyrazole-4-carboxylate (13h). Prepared from 7h (0.157 g, 0.5 mmol); reflux for 3 h. Yield: 0.105 g (78%); yellow solid; mp >350 °C (from ethanol). IR (KBr): 3425, 3137, 1716 (C=O), 1651, 1558, 1465, 1425, 1141, 750 cm–1. 1H NMR (CDCl3): δ 1.26 (3H, t, J = 7.2 Hz, CH2CH3); 4.37 (2H, q, J = 7.2 Hz, CH2CH3); 7.57 (3H, m, 2H of Ph); 7.97 (1H, s, 3–H); 8.05 (2H, m, 2H of Ph); 8.15 (1H, d, J = 9.4 Hz, 4’–H); 8.27 (1H, d, J = 9.0 Hz, 5’–H); 13.04 (1H, br s, OH). EI-MS: m/z 268 (M+). HRMS Calcd for
C\textsubscript{10}H\textsubscript{9}N\textsubscript{4}O\textsubscript{3}Cl (M\textsuperscript{+}): 268.036318. Found: 268.036880. 

**Anal. Calcd for C\textsubscript{10}H\textsubscript{9}N\textsubscript{4}O\textsubscript{3}Cl (268.66): C, 44.70; H, 3.38; N, 20.86. Found: C, 44.51; H, 3.56; N, 21.03.**

**Ethyl 5-hydroxy-1-(pyrimidin-2-yl)-1H-pyrazole-4-carboxylate (13j).** Prepared from 7j (0.140 g, 0.5 mmol); reflux for 2 h. Yield: 0.088 g (75%); yellow solid; mp 154–156 °C (from ethanol) (lit., mp 156 °C). IR (KBr): 3498, 1698 (C=O), 1606, 1526, 1412, 1385, 1327, 1173, 975, 782 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (CDCl\textsubscript{3}): \(\delta\) 1.38 (3H, t, \(J = 7.2\) Hz, \(\text{CH}_2\text{CH}_3\)); 4.36 (2H, q, \(J = 7.2\) Hz, \(\text{CH}_2\text{CH}_3\)); 7.34 (1H, t, \(J = 4.9\) Hz, 5′–H); 8.00 (1H, s, 3–H); 8.83 (2H, d, \(J = 5.0\) Hz, 4′–H and 6′–H); 12.68 (1H, s, OH). EI-MS: \(m/z\) 234 (M\textsuperscript{+}). HRMS Calcd for C\textsubscript{10}H\textsubscript{10}N\textsubscript{4}O\textsubscript{3} (M\textsuperscript{+}): 234.075290. Found: 234.075850. 

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