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

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Abstract – 1,4-Disubstituted 5-hydroxy-1*H*-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 pyrazoline[2] and pyrazolidin-3-one derived azomethine imines[3,4] and (b) utilization of 3-(dimethylamino)propenoates and related enaminones

in the synthesis of pyrazoles.[4,5] Within the context of 3-(dimethylamino)propenoate chemistry, we have previously reported several regioselective syntheses of various pyrazole derivatives,[6–13] including synthesis of functionalized pyrazoles, such as 3-pyrazoylalanines,[14] 3-pyrazolylpropane-1,2-diols,[15] β-aminoalcohols and 2-phenylethylamines,[16] spiro and fused heterocycles containing a dipeptide structural element,[17–20] and terpene functionalized pyrazoles.[21]

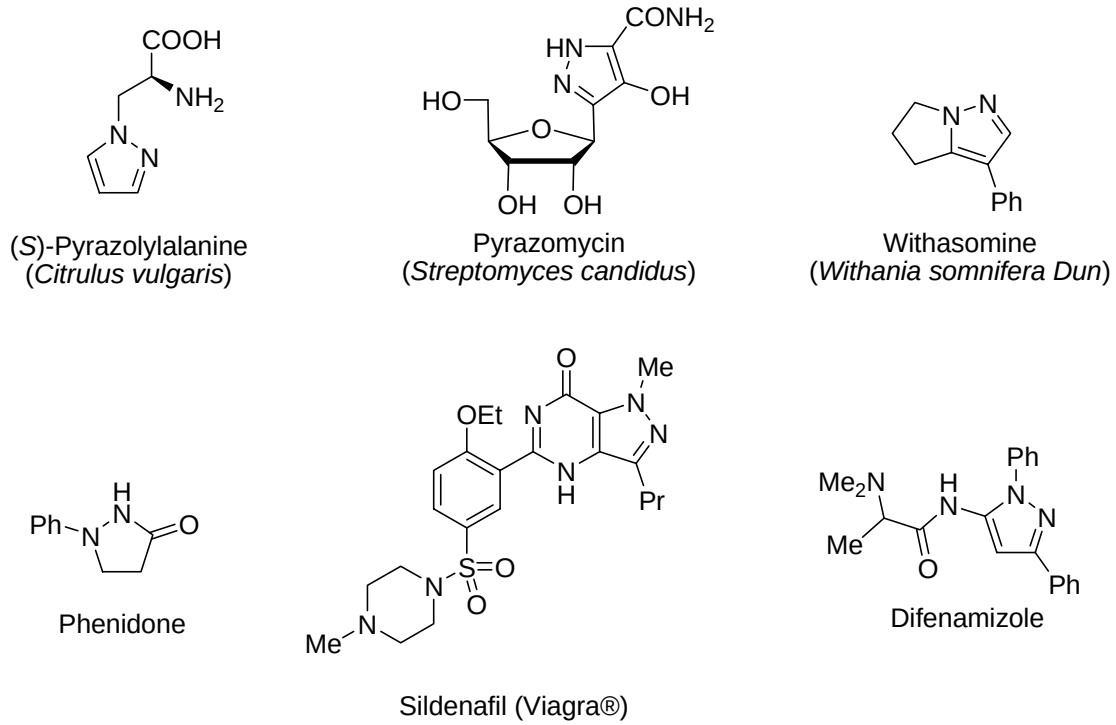


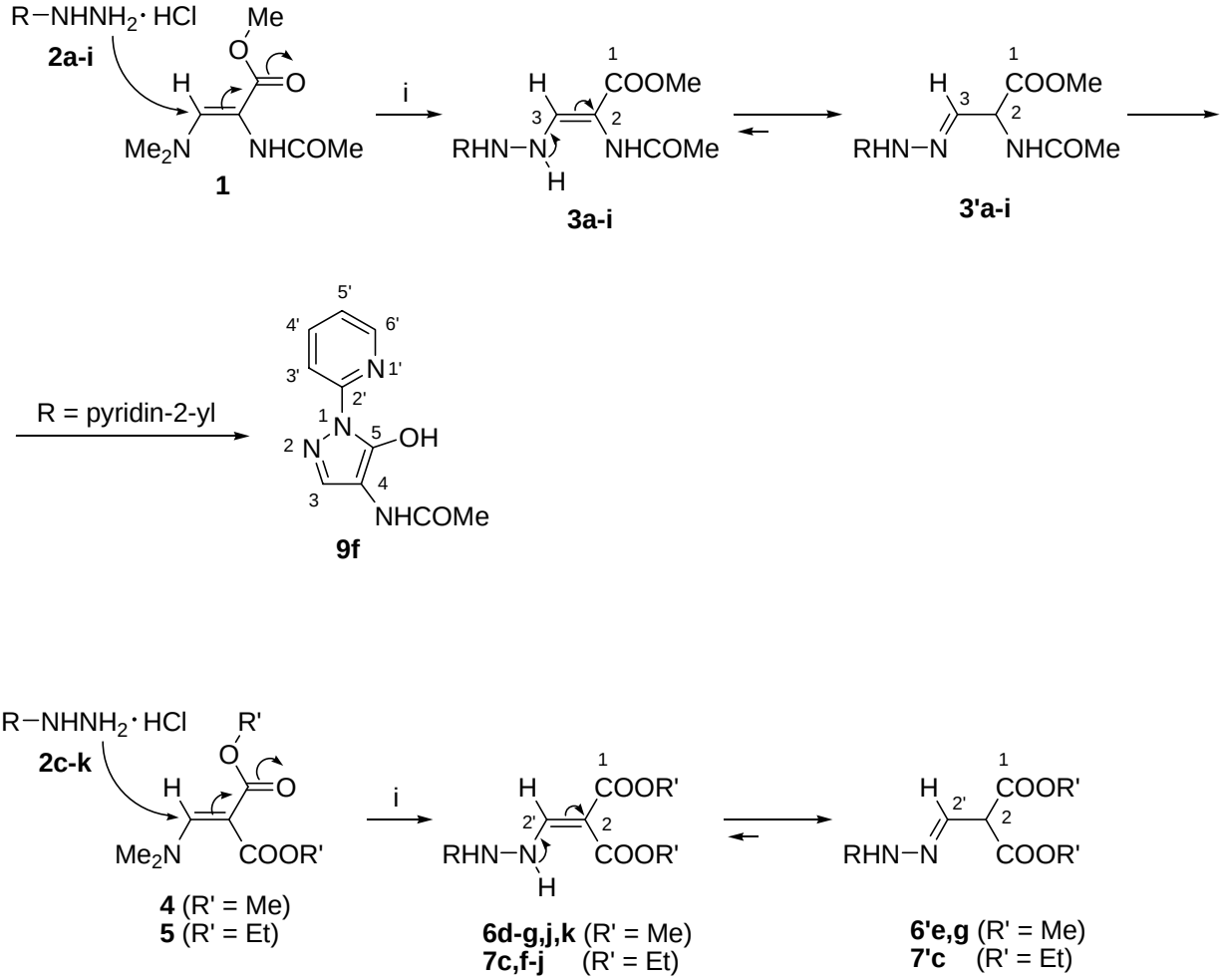
Figure 1. Some examples of important pyrazole derivatives.

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

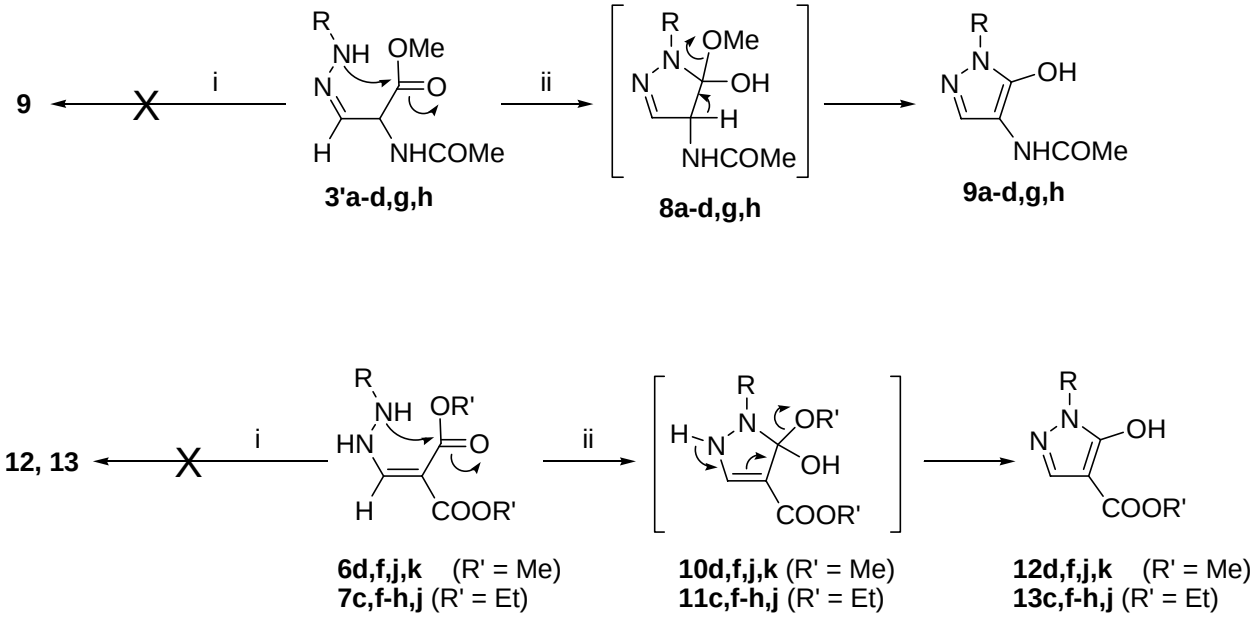
Methyl (*Z*)-2-acetylamino-3-(dimethylamino)propenoate (**1**),[22] dimethyl 2-[(dimethylamino)methylidene]-malonate (**4**),[23] and diethyl 2-[(dimethylamino)methylidene]malonate (**5**)[24] were prepared according to the literature procedures. Treatment of the propenoate (**1**) with hydrazines (**2a–e,g–i**) 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)-1*H*-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 dimethylamino 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) H_2O, 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,[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*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.[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*H*-pyrazoles (**9**), (**12**), and (**13**), respectively. In this manner, 1-substituted 4-acetylamino-5-hydroxy-1*H*-pyrazoles (**9a–d,g,h**) and 1-substituted alkyl 5-hydroxy-1*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.[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*H*-pyrazoles (**9**), (**12**), and (**13**) (Scheme 2, Table 1).



Scheme 2. (i) AcOH or EtOH–HCl, rt→reflux; (ii) MeOH–H_2O–Et_3N (3:3:1), reflux.

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 ^{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**)[28] and (**7h**)[29] were in agreement with the literature data.

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

Compound	R	Yield (%)					
		3	**6**	**7**	**9**	**12**	**13**
2a, **3'a**, **9a**	phenyl	88			78		
2b, **3'b**, **9b**	4-methoxyphenyl	82			86		
2c, **3/3'c**, **7/7'c**, **9c**, **13c**	4-carboxyphenyl	96		79	94		76
2d, **3'd**, **6d**, **9d**, **12d**	4-nitrophenyl	92	66		97	98	
2e, **3/3'e**, **6/6'e**	2,4-dinitrophenyl	83	94				
2f, **6f**, **7f**, **9f**, **12f**, **13f**	pyridin-2-yl		45	56	32	65	72
2g, **3/3'g**, **6/6'g**, **7g**, **9g**, **13g**	6-phenylpyridazin-3-yl	67	70	82	77		82
2h, **3/3'h**, **7h**, **9h**, **13h**	6-chloropyridazin-3-yl	83		67	91		78
2i, **3'i**, **7i**	phthalazin-1-yl	93		67			
2j, **6j**, **7j**, **12j**, **13j**	pyrimidin-2-yl		93	39		79	75
2k, 6k, 12k	4-fluorophenyl		54			87	

In conclusion, various 1,4-disubstituted 5-hydroxy-1*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,[4,5] were not suitable. The methodology is closely related to the previously reported synthesis of 1-substituted alkyl 5-hydroxy-1*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.[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 ^{1}H and at 75.5 MHz for ^{13}C nucleus, using DMSO-d_6 and

$CDCl_3$ as solvents and with Me_4Si 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 ^{1}H NMR.
Hydrazines (**2a–f,i,k**) are commercially available (Fluka AG). Methyl (*Z*)-2-acetylamino-3-(dimethylamino)propenoate (**1**),[22] dimethyl 2-[(dimethylamino)methylidene]malonate (**4**),[23] diethyl 2-[(dimethylamino)methylidene]malonate (**5**),[24] 3-hydrazino-6-phenylpyridazine (**2g**),[30] 6-chloro-3-hydrazinopyridazine (**2h**),[31] and 2-hydrazinopyrimidine (**2j**),[32] 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 2h. 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}. ^{1}H NMR ($CDCl_3$): 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, N*H*COMe); 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, br s, N*H*Ph). *Anal*. Calcd for $C_{12}H_{15}N_3O_3$ (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): 3399, 3256, 3046, 2949 1750 (C=O), 1661, 1600, 1507, 1441, 1241, 1209, 1034, 834, 521 cm^{-1}. ^{1}H NMR (DMSO-d_6): 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, C_6H_4); 7.09 (1H, d, *J* = 5.3 Hz, 3–H); 8.59 (1H, d, *J* = 7.5 Hz, N*H*COMe); 9.91 (1H, s, N*H*Ar). *Anal*. Calcd for $C_{13}H_{17}N_3O_4$ (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, 1mmol); 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}. ^1H 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_6H_4); 7.28 (1H, d, *J* = 5.3 Hz, 3–H); 7.78 (2H, d, *J* = 8.7 Hz, 2H of C_6H_4); 8.65 (1H, d, *J* = 7.2 Hz, N*H*COMe); 10.64 (1H, s, N*H*Ar); 12.27 (1H, br s, COOH); *Minor isomer* (**3c**) δ 1.91 (3H, s, MeCO); 3.55 (3H, s, OMe); 6.80 (2H, d, *J* = 8.7 Hz, 2H of C_6H_4); 7.20 (1H, d, *J* = 10.7 Hz, 3–H); 7.78 (2H, d, *J* = 8.7 Hz, 2H of C_6H_4); 8.30 (1H, br d, *J* = 10.7 Hz, N*H*NHAr); 8.53 (1H, s, NHN*H*Ar). ^{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 $C_{13}H_{15}N_3O_5$ (M^+): 293.101171. Found: 293.101320. *Anal*. Calcd for $C_{13}H_{15}N_3O_5$ (293.28): C, 53.24; H, 5.16; N, 14.33. Calcd for $C_{13}H_{15}N_3O_5 \cdot ½H_2O$: 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, 1mmol); 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, 1109, 843, 750 cm^{-1}. ^1H 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_6H_4); 7.40 (1H, d, *J* = 5.3 Hz, 3–H); 8.12 (2H, d, *J* = 9.3 Hz, 2H of C_6H_4); 8.70 (1H, d, *J* = 7.5 Hz, N*H*COMe); 11.14 (1H, s, N*H*Ar). *Anal*. Calcd for $C_{12}H_{14}N_4O_5$ (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}. ^1H NMR (DMSO-d_6): *Major isomer* (**3'e**) 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_6H_3); 8.13 (1H, d, *J* = 4.9 Hz, 3–H); 8.40 (1H, dd, *J* = 2.6, 9.4 Hz, 1H of C_6H_3); 8.78 (1H, d, *J* = 7.6 Hz, N*H*COMe); 8.85 (1H, d, *J* = 2.6 Hz, 1H of C_6H_3); 11.59 (1H, br s, N*H*Ph); *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_6H_3); 8.36 (1H, d, *J* = 2.6 Hz, 1H of C_6H_3); 8.70 (1H, br s, N*H*NHPh); 8.85 (1H, d, *J* = 2.6 Hz, 1H of C_6H_3); 10.42 (1H, br s, N*H*Ar). *Anal.* Calcd for $C_{12}H_{13}N_5O_7$ (339.26): C, 42.48; H, 3.86; N, 20.64. Found: C, 42.68; H, 4.02; N, 20.53.

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-d_6): *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, N*H*COMe); 11.51 (1H, s, Het–N*H*); *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 N*H*NHHet); 8.61 (1H, br s, N*H*COMe); 9.55 (1H, s, Het–N*H*). *Anal*. Calcd for $C_{16}H_{17}N_5O_3$ (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-hydrazinopyrdazine (**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-d_6): *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, N*H*COMe); 11.58 (1H, br s, Het–N*H*); *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, N*H*NHHet); 8.58 (1H, s, N*H*COMe); 9.46 (1H, br s, Het–N*H*). *Anal*. Calcd for $C_{10}H_{12}ClN_5O_3$ (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**) hydrocloride (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, 1750 (C=O), 1741 (C=O), 1651, 1622, 1584, 1537, 1215, 1154, 1084, 789, 752 cm^{-1}. ^1H NMR (DMSO-d_6): 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, N*H*COMe); 12.27 (1H, s, Het–N*H*). *Anal.* Calcd for $C_{14}H_{15}N_5O_3$ (301.30): C, 55.81; H, 5.02; N, 23.24. Found: C, 55.82; H, 5.16; N, 23.23.

Dimethyl 2-{[2-(4-nitrophenyl)hydrazinyl]methylidene}malonate (6d).[33] 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 ($CDCl_3$): δ 3.74

and 3.85 (6H, 2s, 1:1, OMe); 6.81 (1H, s, N*H*Ar); 6.87 (2H, d, *J* = 9.0 Hz, 2H of C_6H_4); 8.15 (1H, d, *J* = 10.9 Hz, C*H*NH); 8.17 (2H, d, *J* = 9.0 Hz, 2H of C_6H_4); 10.08 (1H, br d, *J* = 9.8 Hz, CHN*H*). EI-MS: *m*/*z* 295 (M^+). HRMS Calcd for $C_{12}H_{13}N_3O_6$ (M^+): 295.080435. Found: 295.081150. *Anal*. Calcd for $C_{12}H_{13}N_3O_6$ (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 ($CDCl_3$). *Major isomer* (**6e**): δ 3.75 and 3.88 (6H, 2s, 1:1, OMe); 7.31 (1H, d, *J* = 9.4 Hz, 1H of C_6H_3); 8.07 (1H, s, C*H*NH); 8.42 (1H, dd, *J* = 2.3, 9.4 Hz, 1H of C_6H_3); 9.16 (1H, d, *J* = 2.6 Hz, 1H of C_6H_3); 9.86 (1H, s, Ar–N*H*); 10.11 (1H, s, CHN*H*). *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, C*H*=N); 7.92 (1H, d, *J* = 9.8 Hz, 1H of C_6H_3); 8.35 (1H, dd, *J* = 2.3, 9.4 Hz, 1H of C_6H_3); 9.13 (1H, d, *J* = 2.6 Hz, 1H of C_6H_3); 11.21 (1H, s, ArN*H*). EI-MS: *m*/*z* 340 (M^+). HRMS Calcd for $C_{12}H_{12}N_4O_8$ (M^+): 340.065514. Found: 340.066120. *Anal*. Calcd for $C_{12}H_{12}N_4O_8$ (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 ($CDCl_3$): 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–N*H*); 7.61 (1H, m, 4'–H); 8.20 (1H, d, *J* = 11.1 Hz, C*H*NH); 8.24 (1H, d, 8.4 Hz, 6'–H); 10.12 (1H, br d, *J* = 11.1 Hz, CHN*H*). EI-MS: *m*/*z* 251 (M^+). HRMS Calcd for $C_{11}H_{13}N_3O_4$ (M^+): 251.090606. Found: 251.090650. *Anal*. Calcd for $C_{11}H_{13}N_3O_4$ (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 ($CDCl_3$). *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–N*H*); 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, C*H*NH); 10.26 (1H, br d, *J* = 10.2 Hz, CHN*H*). *Minor isomer* (**6'g**): δ 3.81 (6H,

s, 2×OMe); 4.44 (1H, d, *J* = 7.2 Hz, 2–H); 7.43–7.56 (3H, m, 3H of Ph); 7.64 (1H, d, *J* = 8.7 Hz, 4'–H); 7.72 (1H, d, *J* = 7.2 Hz, C*H*=N); 7.87 (1H, d, *J* = 8.7 Hz, 5'–H); 7.94–8.02 (2H, m, 2H of Ph); 9.65 (1H, s, Het–N*H*). EI-MS: *m*/*z* 328 (M^+). HRMS Calcd for $C_{16}H_{16}N_4O_4$ (M^+): 328.117155. Found: 328.118050. *Anal*. Calcd for $C_{16}H_{16}N_4O_4$ (328.32): C, 58.53; H, 4.91; N, 17.07. Found: C, 58.22; H, 4.96; N, 16.96.

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}. ^1H NMR ($CDCl_3$): δ 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*H*NH); 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 $C_{10}H_{12}N_4O_4$ (M^+): 252.085855. Found: 252.086230. *Anal*. Calcd for $C_{10}H_{12}N_4O_4$ (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), 1603, 1510, 1443, 1402, 1281, 1223, 1072, 792 cm^{-1}. ^1H NMR ($CDCl_3$): δ 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_6H_4); 6.98 (2H, dd, *J* = 2.3, 8.7 Hz, 2H of C_6H_4); 8.25 (1H, d, *J* = 11.3 Hz, C*H*NH); 10.04 (1H, d, *J* = 11.3 Hz, CHN*H*). EI-MS: *m*/*z* 268 (M^+). HRMS Calcd for $C_{12}H_{13}N_2O_4F$ (M^+): 268.085935. Found: 268.086550. *Anal*. Calcd for $C_{12}H_{13}N_2O_4F$ (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}. ^1H NMR (DMSO-d_6). *Major isomer* (**7c**): δ 1.19 and 1.24 (6H, 2t, 1:1, *J* = 7.2 Hz, OCH_2CH_3); 4.07 and 4.19 (4H, 2q, 1:1, *J* = 7.2 Hz, CH_2CH_3); 6.76 and 7.83 (4H, 2d, 1:1, *J* = 8.7 Hz, C_6H_4); 7.94 (1H, d, *J* = 12.1 Hz, C*H*NH); 9.08 (1H, s, Ar–N*H*); 10.14 (1H, d, *J* = 12.1 Hz, CHN*H*); 11.88 (1H, br s, COOH). *Minor isomer* (**7'c**): δ 1.24 (6H, t, *J* = 7.2 Hz, 2×CH_2CH_3); 4.19 (4H, q, *J* = 7.2 Hz, 2×CH_2CH_3); 4.49 (1H, d, *J* = 6.0 Hz, 2–H); 6.95 (2H, d, *J* = 8.7 Hz, 2H of C_6H_4); 7.36 (1H, d, *J* = 6.4 Hz, C*H*=N); 7.69 (2H, d, *J* = 9.0 Hz, 2H of C_6H_4); 10.72 (1H, s, Ar–N*H*); 11.88 (1H, br s, COOH). EI-MS: *m*/*z* 322 (M^+). HRMS Calcd

for $C_{15}H_{18}N_2O_6$ (M^+): 322.116487. Found: 322.117100. *Anal*. Calcd for $C_{15}H_{18}N_2O_6$ (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.,[28] 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 ($CDCl_3$): δ 1.29 and 1.37 (6H, 2t, 1:1, J = 7.2 Hz, 2×CH_2CH_3); 4.21 and 4.30 (4H, 2q, 1:1, J = 7.2 Hz, 2×CH_2CH_3); 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–N*H*); 7.61 (1H, deg dt, J = 1.9, 8.3 Hz, 4'–H); 8.19 (1H, d, J = 11.3 Hz, C*H*NH); 8.21 (1H, d, J = 8.3 Hz, 6'–H); 10.09 (1H, d, J = 11.3 Hz, CHN*H*). EI-MS: *m*/*z* 279 (M^+). HRMS Calcd for $C_{13}H_{17}N_3O_4$ (M^+): 279.121906. Found: 279.122040. *Anal*. Calcd for $C_{13}H_{17}N_3O_4$ (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 ($CDCl_3$): δ 1.30 and 1.38 (6H, 2t, 1:1, J = 7.2 Hz, 2×CH_2CH_3); 4.23 and 4.31 (4H, 2q, 1:1, J = 7.2 Hz, 2×CH_2CH_3); 7.12 (1H, d, J = 9.4 Hz, 4'–H); 7.43–7.55 (4H, m, 3H of Ph, Het–N*H*); 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, C*H*NH); 10.17 (1H, d, J = 11.3 Hz, CHN*H*). EI-MS: *m*/*z* 356 (M^+). HRMS Calcd for $C_{18}H_{20}N_4O_4$ (M^+): 356.148455. Found: 356.149540. *Anal*. Calcd for $C_{18}H_{20}N_4O_4$ (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).[29] 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.,[29] 165 °C (ethanol–water)). IR (KBr): 3432, 3237, 1687 (C=O), 1655 (C=O), 1616, 1443, 1421, 1266, 1229, 1075, 799 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.29 and 1.36 (6H, 2t, 1:1, J = 7.2 Hz, 2×CH_2CH_3); 4.21 and 4.29 (4H, 2q, 1:1, J = 7.2 Hz, 2×CH_2CH_3); 7.06 (1H, d, J = 9.4 Hz, 4'–H); 7.41 (1H, d, J = 9.1 Hz, 5'–H); 8.13 (1H, br s, Het–N*H*); 8.17 (1H, d, J = 10.5 Hz, C*H*NH); 10.14 (1H, d, J = 11.3 Hz, CHN*H*). EI-MS: *m*/*z* 314 (M^+). HRMS Calcd for $C_{12}H_{15}N_4O_4Cl$ (M^+): 314.078183. Found: 314.078850. *Anal*. Calcd for $C_{12}H_{15}ClN_4O_4$ (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 ($CDCl_3$): δ 1.31 and 1.38 (6H, 2t, 1:1, *J* = 7.2 Hz, 2×CH_2CH_3); 4.23 and 4.31 (4H, 2q, 1:1, *J* = 7.2 Hz, 2×CH_2CH_3); 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, CHNH). EI-MS: *m*/*z* 330 (M^+). HRMS Calcd for $C_{16}H_{18}N_4O_4$ (M^+): 330.132805. Found: 330.133450. *Anal*. Calcd for $C_{16}H_{18}N_4O_4$ (330.34): C, 58.17; H, 5.49; N, 16.96. Found: C, 58.14; H, 5.71; N, 17.06.

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 ($CDCl_3$): δ 1.28 and 1.36 (6H, 2t, 1:1, *J* = 7.2 Hz, 2×CH_2CH_3); 4.20 and 4.31 (4H, 2q, 1:1, *J* = 7.2 Hz, 2×CH_2CH_3); 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, CHNH). EI-MS: *m*/*z* 280 (M^+). HRMS Calcd for $C_{12}H_{16}N_4O_4$ (M^+): 280.117155. Found: 280.117530. *Anal*. Calcd for $C_{12}H_{16}N_4O_4$ (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)-1*H*-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-d_6): 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 $C_{10}H_{10}N_4O_2$ (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-1*H*-pyrazoles (9a–d,g–i) and Alkyl 5-Hydroxy-1*H*-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-1*H*-pyrazole (9a).[34] 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-d_6): 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, N*H*COMe); 12.02 (1H, br s, OH). *Anal*. Calcd for $C_{11}H_{11}N_3O_2$ (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)-1*H*-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-d_6): δ 2.03 (3H, s, MeCO); 3.78 (3H, s, OMe); 7.00–7.03 (2H, m, 2H of C_6H_4); 7.48 (1H, br s, 3–H); 7.58–7.61 (2H, m, 2H of C_6H_4); 9.87 (1H, s, N*H*COMe); 11.57 (1H, br s, OH). *Anal.* Calcd for $C_{12}H_{13}N_3O_3$ (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-1*H*-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-d_6): 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, C_6H_4); 9.90 (1H, s, N*H*COMe); 13.00 (1H, br s, OH). ^{13}C NMR (DMSO-d_6): 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 $C_{12}H_{11}N_3O_4$ (M^+): 261.074956. Found: 261.075030. *Anal.* Calcd for $C_{12}H_{11}N_3O_4$ (261.24): C, 55.17; H, 4.24; N, 16.09. Calcd for $C_{12}H_{11}N_3O_4 \cdot \frac{1}{8}H_2O$: 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)-1*H*-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-d_6): δ 2.03 (3H, s, MeCO); 7.75 (1H, s, 3–H); 8.11 (2H, d, J = 9.4 Hz, 2H of C_6H_4); 8.34 (2H, J = 9.4 Hz, 2H of C_6H_4); 9.80 (1H, s, N*H*COMe), OH exchanged. *Anal*. Calcd for $C_{11}H_{10}N_4O_4$ (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)-1*H*-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): 3329, 3078, 1683 (C=O), 1637, 1607, 1540, 1229, 1083, 863, 783, 745 cm^{-1}. ^1H NMR (DMSO-d_6): 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, N*H*COMe); 12.07 (1H, br s, OH). ^{13}C NMR (DMSO-d_6): 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 $C_{15}H_{13}N_5O_2$ (M^+): 295.106925. Found: 295.107050. *Anal*. Calcd for $C_{15}H_{13}N_5O_2$

(218.20): C, 61.01; H, 4.44; N, 23.72. Calcd for $C_{15}H_{13}N_5O_2 \cdot \frac{1}{8}H_2O$: 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-1*H*-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, 1093, 850, 729 cm^{-1}. ^1H NMR (DMSO-d_6): δ 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, N*H*COMe); 12.02 (1H, br s, OH). *Anal.* Calcd for $C_9H_8N_5O_2Cl$ (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)-1*H*-pyrazole-4-carboxylate (12d).[33] 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}. ^1H NMR ($CDCl_3$): δ 3.93 (3H, s, OMe); 7.82 (1H, s, 3–H); 8.12 (2H, d, J = 9.0 Hz, 2H of C_6H_4); 8.36 (2H, d, 2H, d, J = 9.4 Hz, 2H of C_6H_4); 10.03 (1H, br s, OH). EI-MS: m/z 263 (M^+). HRMS Calcd for $C_{11}H_9N_3O_5$ (M^+): 263.054221. Found: 263.054850. *Anal*. Calcd for $C_{11}H_9N_3O_5$ (263.21): C, 50.19; H, 3.45; N, 15.97. Found: C, 50.47; H, 3.65; N, 15.80.

Methyl 5-hydroxy-1-(pyridin-2-yl)-1*H*-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}. ^1H NMR ($CDCl_3$): δ 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 $C_{10}H_9N_3O_3$ (M^+): 219.064391. Found: 219.064850. *Anal*. Calcd for $C_{10}H_9N_3O_3$ (219.20): C, 54.79; H, 4.14; N, 19.17. Found: C, 54.70; H, 4.30; N, 19.21.

Methyl 5-hydroxy-1-(pyrimidin-2-yl)-1*H*-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}. ^1H NMR ($CDCl_3$): δ 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 $C_9H_8N_4O_3$ (M^+): 220.059640. Found: 220.060250. *Anal*. Calcd for $C_9H_8N_4O_3$ (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-1*H*-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

(KBr): 3434, 1713 (C=O), 1627, 1598, 1555, 1515, 1438, 1356, 1239, 1196, 1073, 828, 753. cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.91 (3H, s, OMe); 7.16 (2H, dd, *J* = 2.2, 9.1 Hz, 2H of C_6H_4); 7.18 (2H, dd, *J* = 2.2, 9.1 Hz, 2H of C_6H_4); 7.75 (1H, s, 3–H); 9.64 (1H, br s, OH). EI-MS: *m*/*z* 236 (M^+). HRMS Calcd for $C_{11}H_9N_2O_3F$ (M^+): 236.059721. Found: 236.060230. *Anal*. Calcd for $C_{11}H_9N_2O_3F$ (236.20): C, 55.93; H, 3.84; N, 11.86. Found: C, 55.70; H, 3.96; N, 11.16.

Ethyl 1-(4-carboxyphenyl)-5-hydroxy-1*H*-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-d_6): δ 1.29 (3H, t, *J* = 7.2 Hz, CH_2CH_3); 4.25 (2H, q, *J* = 7.2 Hz, CH_2CH_3); 7.88 (1H, s, 3–H); 7.91 (2H, d, *J* = 8.3 Hz, 2H of C_6H_4); 8.08 (2H, d, *J* = 8.7 Hz, 2H of C_6H_4); 12.99 (1H, br s, OH). EI-MS: *m*/*z* 276 (M^+). HRMS Calcd for $C_{13}H_{12}N_2O_5$ (M^+): 276.074622. Found: 276.075510. *Anal*. Calcd for $C_{13}H_{12}N_2O_5$ (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)-1*H*-pyrazole-4-carboxylate (13f).[28] 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.,[28] mp not given). IR (KBr): 3460, 1709 (C=O), 1640, 1619, 1542, 1528, 1409, 1382, 1323, 1164, 1077, 937, 777 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.38 (3H, t, *J* = 7.2 Hz, CH_2CH_3); 4.35 (2H, q, *J* = 7.2 Hz, CH_2CH_3); 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 $C_{11}H_{11}N_3O_3$ (M^+): 233.080041. Found: 233.080730. *Anal*. Calcd for $C_{11}H_{11}N_3O_3$ (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)-1*H*-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 ($CDCl_3$): δ 1.39 (3H, t, *J* = 7.2 Hz, CH_2CH_3); 4.37 (2H, q, *J* = 7.2 Hz, CH_2CH_3); 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 $C_{16}H_{14}N_4O_3$ (M^+): 310.106591. Found: 310.107250. *Anal*. Calcd for $C_{16}H_{14}N_4O_3$ (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-1*H*-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 ($CDCl_3$): δ 1.26 (3H, t, *J* = 7.2 Hz, CH_2CH_3); 4.37 (2H, q, *J* = 7.2 Hz, CH_2CH_3); 7.76 (1H, d, *J* = 9.0 Hz, 4'–H); 7.95 (1H, s, 3–H); 8.21 (1H, d, *J* = 9.0 Hz, 5'–H); OH exchanged. EI-MS: *m*/*z* 268 (M^+). HRMS Calcd for

$C_{10}H_9N_4O_3Cl$ (M^+): 268.036318. Found: 268.036880. *Anal*. Calcd for $C_{10}H_9N_4O_3Cl$ (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)-1*H*-pyrazole-4-carboxylate (13j).[28] 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.,[28] mp 156 °C). IR (KBr): 3498, 1698 (C=O), 1606, 1526, 1412, 1385, 1327, 1173, 975, 782 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.38 (3H, t, J = 7.2 Hz, CH_2CH_3); 4.36 (2H, q, J = 7.2 Hz, CH_2CH_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^+). HRMS Calcd for $C_{10}H_{10}N_4O_3$ (M^+): 234.075290. Found: 234.075850. *Anal*. Calcd for $C_{10}H_{10}N_4O_3$ (234.21): C, 51.28; H, 4.30; N, 23.92. Found: C, 51.32; H, 4.44; N, 23.69.

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