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A simple synthesis of 4-(2-aminoethyl)-5-hydroxy-1*H*-pyrazoles

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Abstract—A simple four-step synthesis of 4-(2-aminoethyl)-5-hydroxy-1*H*-pyrazoles **8** (or their 1*H*-pyrazol-3(2*H*)-one tautomers **8′**) as the pyrazole analogues of histamine was developed. First, enamino lactam **3** was prepared as the key intermediate in two steps from 2-pyrrolidinone (**1**). Next, acid-catalysed 'ring switching' transformations of **3** with monosubstituted hydrazines **4** gave *N*-[(1-substituted 5-hydroxy-1*H*-pyrazol-4-yl)ethyl]benzamides **7a–k** and *N*-[2-(2-heteroaryl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)ethyl]benzamides **7′l–o**. Benzamides **7a–k** and **7′l–o** were finally hydrolysed by heating in 6 M hydrochloric acid to furnish 1-substituted 4-(2-aminoethyl)-5-hydroxy-1*H*-pyrazoles **8a–k** and 4-(2-aminoethyl)-2-heteroaryl-1*H*-pyrazol-3(2*H*)-ones **8′l–o** in good overall yields.

1. Introduction

Due to the crucial role of histamine, tyramine, dopamine, tryptamine, serotonine and melatonin (Fig. 1) as chemical messengers in biological processes, the preparation of their novel synthetic analogues represents an important target in medicinal and synthetic organic chemistry.[1–3]

2-Substituted alkyl 3-(dimethylamino)prop-2-enoates and related enaminones are a group of enamino masked alkyl α-formylacetates, which are easily available and versatile reagents in heterocyclic synthesis.[4–6] In addition to their extensive use in the synthesis of various heterocyclic systems, recent applications of enaminones are mostly orientated towards preparation of analogues of natural products,[4–9] such as (+)-camphor and related terpenes,[10–17] tetramic acids,[18] aplysinopsins,[9,19] β-carbolines,[19] meridianines[20,21] and dipodazine.[22] Recently, enaminones were also employed in combinatorial synthesis of dehydroalanines and their cyclic analogues[23,24] and (2*S*,4*S*)-4-aminopyroglutamic acid amides.[25]

A part of our research in the field of functionalised heterocycles has been devoted to the synthesis of pyrazole derivatives via cyclocondensations of enaminones with monosubstituted hydrazines.[4–8,11,26–29] Within this context, we have previously reported several regioselective syntheses of various functionalised pyrazole derivatives containing alanine,[27,30] β-aminoalcohol,[29,31] propane-1,2-diol,[32] 2-phenylethylamine[29] and terpene[11] structural motifs. In continuation of our work in this field we now report a novel application of the enaminone methodology in the synthesis of 4-(2-aminoethyl)-5-hydroxy-1*H*-pyrazoles **8** (or their 1*H*-pyrazol-3(2*H*)-one tautomers **8′**) as the pyrazole analogues of histamine.

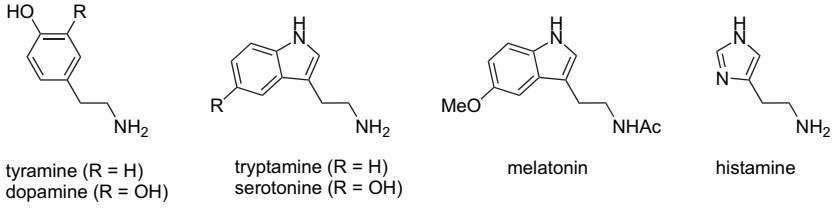

Figure 1.

Keywords: Enaminones; Hydrazines; Cyclisation; Pyrazoles; Histamine analogues.
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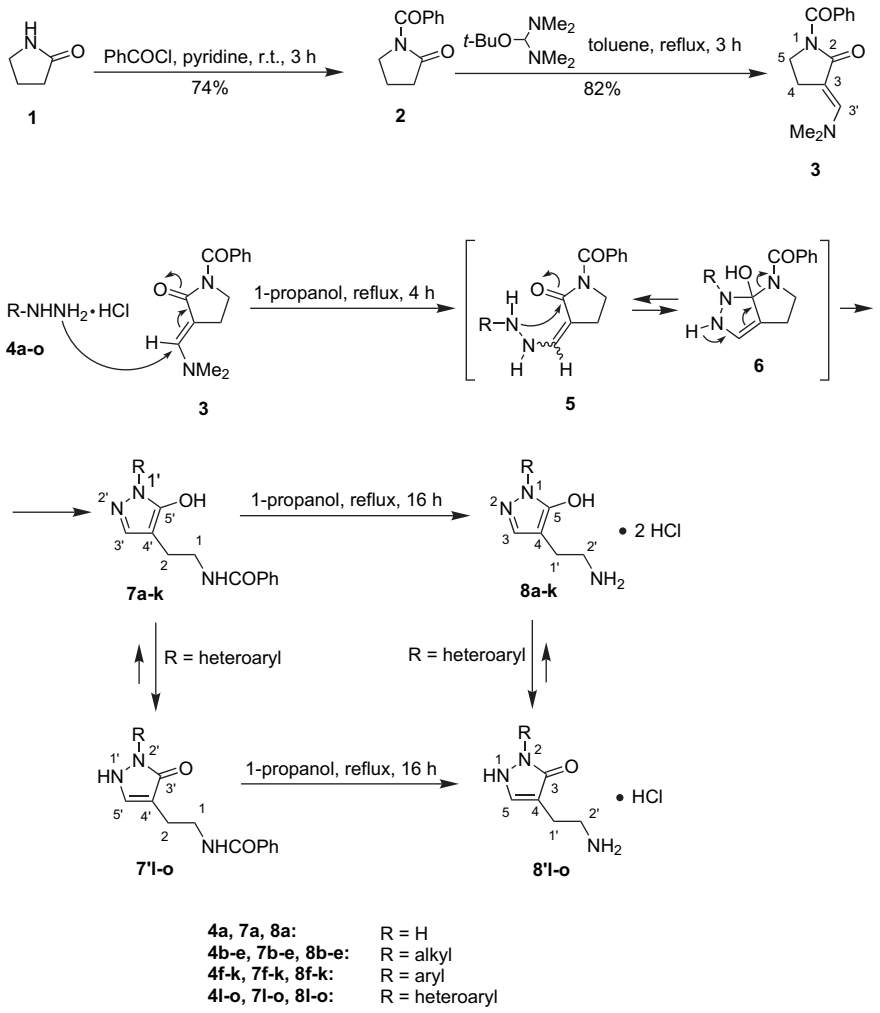

Scheme 1.

2. Results and discussion

The key intermediate **3** was first prepared in two steps from 2-pyrrolidinone (**1**). Treatment of a mixture of **1** and anhydrous pyridine in a molar ratio of 1:1, respectively, with 1 equiv of benzoyl chloride gave *N*-benzoylpyrrolidin-2-one (**2**) in 74% yield upon simple filtration workup. In comparison to the literature procedure for benzoylation of 2-pyrrolidinone (**1**),[33] our simplified version is very convenient for a large-scale preparation of **2**, since it avoids extraction workup and use of excess of noxious reagents. *N*-Benzoylpyrrolidin-2-one (**2**) was then treated with bis(dimethylamino)-*tert*-butoxymethane (TBDMAM, Bredereck's reagent) in refluxing toluene to give (*E*)-1-benzoyl-3-[(dimethylamino)methylidene]pyrrolidin-2-one (**3**) in 82% yield. Heating of the enamino lactam **3** with hydrazine hydrochlorides **4a–o** in *n*-propanol under reflux for 4 h afforded *N*-[(1-substituted 5-hydroxy-1*H*-pyrazol-4-yl)ethyl]benzamides **7a–k** and *N*-[2-(2-heteroaryl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)ethyl]benzamides **7′l–o** as products of the 'ring switching' transformations in 72–100% yields. The reaction mechanism can be explained by initial 1,4-addition of hydrazine **4** to the vinylogous amide **3** followed by elimination of the dimethylamino group to give the enehydrazine intermediate **5**. Addition of the secondary nitrogen atom to the lactone carbonyl group gives the bicyclic intermediate **6**, which then tautomerises into **7** via opening of the pyrrolidine ring.[11,28,30–32,34] Finally, the *N*-benzoyl-2-(pyrazolyl)ethylamines **7a–k** and **7′l–o** were deprotected by heating in 6 M hydrochloric acid for 16 h to furnish 1-substituted 4-(2-aminoethyl)-5-hydroxy-1*H*-pyrazoles **8a–k** and 4-(2-aminoethyl)-2-heteroaryl-1*H*-pyrazol-3(2*H*)-ones

Table 1. Experimental data for compounds **7a–k**, **7′l–o**, **8a–k** and **8′l–o**

Compound	R	Yield (%)	
		7	**8**
7a, **8a**	H	81	100
7b, **8b**	Methyl	86	100
7c, **8c**	2,2,2-Trifluoroethyl	94	92
7d, **8d**	Benzyl	72	62
7e, **8e**	Cyclohexyl	96	100
7f, **8f**	Phenyl	82	50
7g, **8g**	4-Carboxyphenyl	92	87
7h, **8h**	3-Chlorophenyl	97	83
7i, **8i**	4-Chlorophenyl	91	78
7j, **8j**	3-Methoxyphenyl	87	86
7k, **8k**	4-Methoxyphenyl	79	91
7′l, **8′l**	Pyridin-2-yl	84	65
7′m, **8′m**	6-Chloropyridazin-2-yl	72	34
7′n, **8′n**	6-Phenylpyridazin-2-yl	81	51
7′o, **8′o**	Imidazo[1,2-*b*]pyridazin-6-yl	100	79

8′l–o, respectively, in 34–100% yields. Compounds **8a–l** were isolated as dihydrochlorides, while 2-pyridazinyl substituted 4-(2-aminoethyl)-1*H*-pyrazol-3(2*H*)-ones **8m–o** were obtained as monohydrochlorides (Scheme 1, Table 1).

3. Structure determination

The structures of novel compounds **3**, **7a–k**, **7′l–o**, **8a–k** and **8′l–o** were determined by spectroscopic methods (IR, ^{1}H and ^{13}C NMR, NOESY spectroscopy and MS) and by elemental analyses for C, H and N. Compounds **7′o**, **8a**,**c**,**e**,**g** and **8′l–o** were not obtained in analytically pure form. Their identities were confirmed by ^{13}C NMR and/or EI-HRMS.

The (*E*)-configuration around the exocyclic C=C bond in the enamino lactam **3** was determined by NOESY spectroscopy. Absence of NOE between 3′-H and the methylene group at position 4 was in agreement with the (*E*)-configuration. Unfortunately, measurement of NOE between the dimethylamino group and the methylene group at position 4 was not possible due an overlap of these two signals. The (*E*)-configuration of compound **3** is also in agreement with typical configuration around the C=C double bond in related enaminones (Fig. 2).[4–6]

Tautomeric forms of pyrazolone derivatives **7**, **7′**, **8** and **8′** were determined by IR, NMR and X-ray diffraction. First, absence of C=O vibrations in the final products **8a–k** and the C=O absorption at ~1640 cm^{-1} in compounds **8′l–o** indicated that pyrazoles **8a–k** were obtained as the 5-hydroxy-1*H*-pyrazole tautomers (OH tautomers), while 1-heteroaryl substituted pyrazoles **8l–o** were isolated as the 1*H*-pyrazol-3(2*H*)-one tautomers (NH tautomers). Such discrimination was not possible in the case of the *N*-benzoylated compounds **7** and **7′**, due to the benzamide carbonyl absorption at ~1640 cm^{-1}. However, the tautomeric forms of the *N*-benzoylated compounds **7** and **7′** should most probably be the same as the tautomeric forms of the corresponding final products **8** and **8′**. Higher stability of the NH

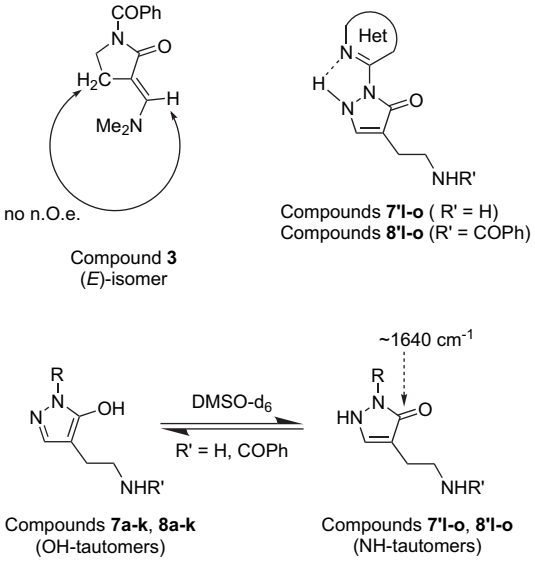

Figure 2. Structural determination by IR and NMR.

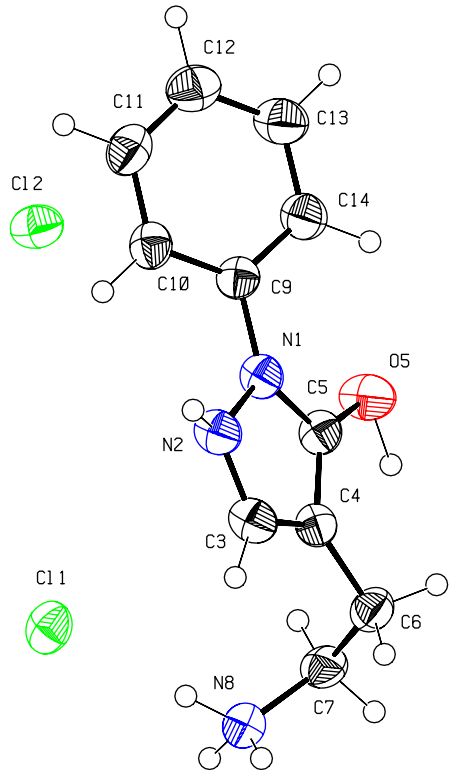

Figure 3. The asymmetric unit of compound **8f**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

tautomeric forms in the case of *N*-heteroaryl substituted pyrazoles **7′l–o** and **8′l–o** could be due to intramolecular N···H bond between the *H*–N(1) and the azine ring nitrogen atom (Fig. 2).[27,35–41]

Next, the ^{1}H and ^{13}C NMR spectra of compounds **7** and **8** usually exhibited broad signals for the heteroaromatic C and H nuclei and for both CH_2 groups. Broadening of these signals can be explained by fast equilibration between the 5-hydroxy-1*H*-pyrazole form (OH tautomers **7** and **8**) and 1*H*-pyrazol-3(2*H*)-one form (NH tautomers **7′** and **8′**) in DMSO-d_6 solution (Fig. 2).[35–41]

Finally, the structure of compound **8f** was determined by X-ray diffraction (Fig. 3). To our surprise, the bond lengths of the pyrazole ring of **8f** were between the typical values for the OH tautomer and the NH tautomer.[35–40] Furthermore, the crystal cell consisted of **8f** and HCl in a ratio of 2:3, respectively, where two molecules of **8f** were connected via the O···H···O bridge with identical O···H distances and identical C–O bond lengths (Fig. 4). Therefore, the structure of **8f** could be regarded as a hybrid between the OH tautomer **8f** and the NH tautomer **8′f** as represented by the structural formula **8″f** (Fig. 5).

4. Conclusion

In summary, we developed a simple and efficient synthesis of 1-substituted 2-(5-hydroxy-1*H*-pyrazol-4-yl)ethylamines **8** (or their 1*H*-pyrazol-3-(2*H*)-one tautomers **8′**) as the pyrazole analogues of histamine. In this manner, 15

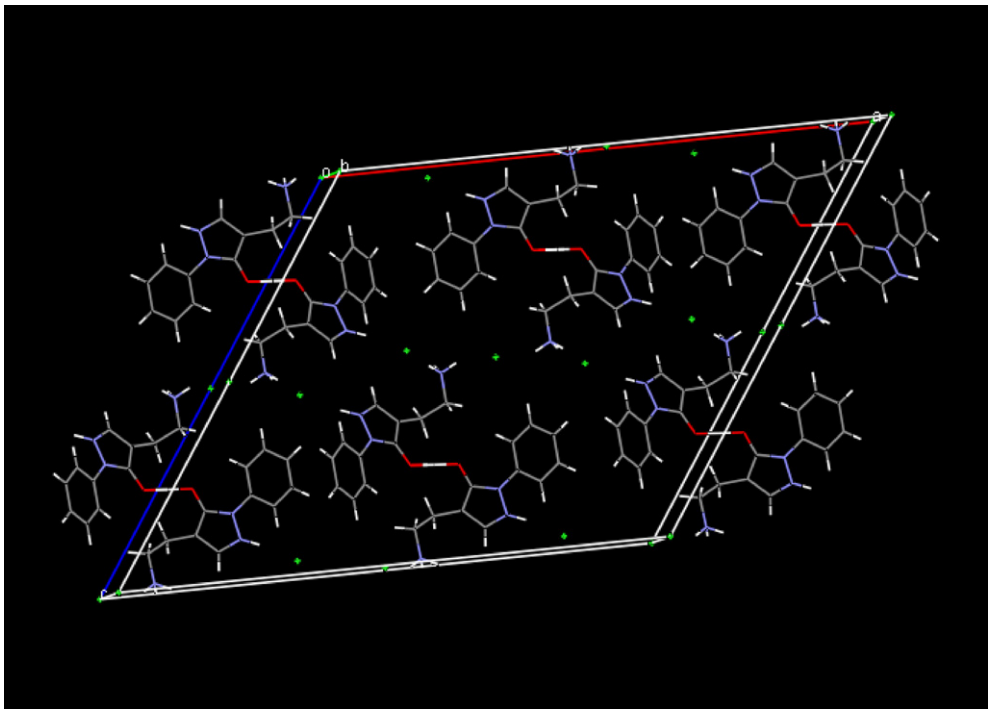

Figure 4. Packing of compound **8f** in the crystal cell.

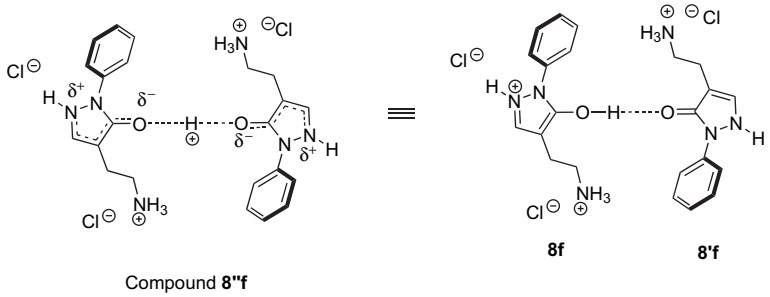

Figure 5.

2-(pyrazolyl)ethylamines **8a–o** with various alkyl, aryl and heteroaryl residues attached at position 1 in the pyrazole ring were synthesised in four steps and in good overall yields from pyrrolidin-2-one (**1**). The key step in this synthesis is the acid-catalysed 'ring switching' transformation of the enamino lactam **3** with hydrazine derivatives **4**. In addition to the Young's 'ring switching' synthesis of heteroarylalanines[42–44] and our enaminone-based syntheses of heteroaryl substituted alanines, β-amino alcohols, ethylamines and terpenes,[4–8,11,26–32] this work represents a novel synthetic application of the enaminone method for the preparation of histamine analogues.

5. Experimental

5.1. General

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 75.5 MHz for ^{13}C nucleus, using DMSO-d_6 and $CDCl_3$ as solvents with TMS 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.

Pyrrolidin-2-one (**1**), bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent), hydrazines **4a–i**,**k**,**l** (Sigma–Aldrich) and 3-methoxyphenylhydrazine hydrochloride (**4j**) (Manchester Chemicals) are commercially available. 6-Chloro-3-hydrazinopyridazine (**4m**),[45] 3-hydrazino-6-phenylpyridazine (**4n**)[46] and 6-hydrazinoimidazo[1,2-*b*]pyridazine (**4o**),[47] were prepared according to the literature procedures.

5.2. 1-Benzoylpyrrolidin-2-one (2)

This compound was prepared according to the modified literature procedure.[33] Benzoyl chloride (46 mL, 0.4 mol) was added to a mixture of pyrrolidin-2-one (**1**) (32 mL, 0.42 mol) and anhydrous pyridine (32.5 mL, 0.4 mol) and the mixture

was stirred at rt for 3 h. To the so formed solid cake water (200 mL) was added, the mixture was heated on water bath until the solid cake melted completely. Then vigorous stirring was started and the so formed emulsion was allowed to cool to rt. The precipitate was collected by filtration and washed with water (3×50 mL). The crude **2** was re-suspended in water (200 mL), heated on water bath until the solid melted completely. The vigorously stirred mixture was then allowed to cool to rt, the precipitate was collected by filtration, washed with water (3×100 mL) and crystallised from acetone–water (2:1, ~200 mL) to give the purified *title compound* **2** (140 g, 74%) as a slightly yellowish solid. Mp and spectral data for compound **2** were in agreement with the literature data.[33]

5.3. (3*E*)-1-Benzoyl-3-(dimethylamino)methylidenepyrrolidin-2-one (3)

A mixture of *N*-acylpyrrolidin-2-one (**2**) (18.9 g, 0.1 mol), anhydrous toluene (100 mL) and Bredereck's reagent (22 mL, 0.11 mol) was heated under reflux for 3 h. The volatile components were evaporated in vacuo and the residue was crystallised from EtOAc to give the *title compound* **3** (20.1 g, 82%) as yellowish crystals; mp 126–128 °C (from EtOAc). δ_H (300 MHz, DMSO-d_6) 2.98 (2H, t, J=7.7 Hz, 4-CH_2), 3.04 (6H, s, NMe_2), 3.72 (2H, t, J=7.7 Hz, 5-CH_2), 6.99 (1H, s, 3′-H), 7.32–7.38 (5H, m, Ph). δ_C NMR (75.5 MHz, DMSO-d_6) 21.9, 42.5, 43.9, 93.6, 128.1, 129.2, 131.3, 137.0, 147.3, 170.1, 170.7. [Found: C, 68.60; H, 6.55; N, 11.82. $C_{14}H_{16}N_2O_2$ requires: C, 68.83; H, 6.60; N, 11.47.] ν_{max} (KBr) 3438, 1695, 1644, 1607, 1337, 1304, 1269, 1236, 1202, 985, 885 cm^{-1}.

5.4. 'Ring switching' reactions of enamino lactam 3 with hydrazine derivatives 4. General procedure for the preparation of *N*-[2-(1-substituted 5-hydroxy-1*H*-pyrazol-4-yl)ethyl]benzamides 7a–k and *N*-[2-(2-heteroaryl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)ethyl]benzamides 7′l–o

Enaminone **3** (4.80 mg, 20 mmol) was added to a stirred mixture of hydrazine derivative **4**·hydrochloride (20 mmol) and 1-propanol (80 mL) or to a stirred mixture of hydrazine derivative **4** (20 mmol), 37% hydrochloric acid (1.8 mL, 20 mmol) and 1-propanol (80 mL). The mixture was refluxed for 4 h, cooled and volatile components were evaporated in vacuo. The residue was triturated with water (80 mL) or ethanol–water (80 mL) and the precipitate was collected by filtration to give **7**.

The following compounds were prepared in this manner.

5.4.1. *N*-[2-(5-Hydroxy-1*H*-pyrazol-4-yl)ethyl]benzamide (7a). Prepared from **3** and hydrazine hydrochloride (**4a**) (1.370 g, 20 mmol), trituration with ethanol–water (1:2). Yield: 3.74 g (81%) of a white solid; mp 182–184 °C. δ_H (300 MHz, DMSO-d_6) 2.51 (2H, br s, 2-CH_2), 3.38 (2H, br dt, J=5.5, 7.9 Hz, 1-CH_2), 7.26 (1H, s, 3′-H), 7.42–7.55 (3H, m, 3H of Ph), 7.80–7.88 (2H, m, 2H of Ph), 8.47 (1H, t, J=5.5 Hz, N*H*CH$_2$), 9.59 (1H, br s, 1′-H), 11.24 (1H, br s, O*H*). ^{1}H NMR (CD$_3$OD): δ 2.62 (2H, t, J=7.0 Hz, 2-CH_2), 3.51 (2H, t, J=7.0 Hz, 1-CH_2), 7.38 (1H, br s, 3′-H), 7.41–7.55 (3H, m, 3H of Ph), 7.80–7.85 (2H, m, 2H of Ph). δ_C NMR (75.5 MHz, DMSO-d_6) 22.5, 40.1, 100.9, 127.2, 128.3, 128.4, 131.1, 134.7, 159.6, 166.4. [Found: C, 62.34; H, 5.81; N, 18.31. $C_{12}H_{13}N_3O_2$ requires: C, 62.33; H, 5.67; N, 18.17.] ν_{max} (KBr) 3422, 3007, 2837, 1686, 1454, 1425, 1327, 1293, 935, 708 cm^{-1}.

5.4.2. *N*-[2-(5-Hydroxy-1-methyl-1*H*-pyrazol-4-yl)ethyl]benzamide (7b). Prepared from **3**, methylhydrazine (**4b**) (920 mg, 20 mmol) and 37% hydrochloric acid; trituration with water. Yield: 4.22 g (86%) of a white solid; mp 192–195 °C. δ_H (300 MHz, DMSO-d_6) 2.51 (2H, t, J=7.3 Hz, 2-CH_2), 3.37 (2H, br td, J=7.3, 5.7 Hz, 1-CH_2), 3.45 (3H, br s, *Me*), 7.26 (1H, br s, 3′-H), 7.42–7.54 (3H, m, 3H of Ph), 7.80–7.87 (2H, m, 2H of Ph), 8.54 (1H, br s, N*H*), 10.02 (1H, br s, O*H*). δ_H (300 MHz, CD$_3$OD) 2.62 (2H, t, J=7.2 Hz, 2-CH_2), 3.48 (3H, s, *Me*), 3.51 (2H, t, J=7.2 Hz, 1-CH_2), 7.38 (1H, br s, 3′-H), 7.42–7.54 (3H, m, 3H of Ph), 7.80–7.84 (2H, m, 2H of Ph). δ_C NMR (75.5 MHz, DMSO-d_6) 22.6, 32.4, 40.2, 99.9, 127.0, 128.1, 130.9, 134.6, 136.1, 152.8, 166.0. [Found: C, 63.39; H, 6.07; N, 16.92. $C_{13}H_{15}N_3O_2$ requires: C, 63.66; H, 6.16; N, 17.13.] ν_{max} (KBr) 3430, 3269, 1638, 1545, 1382, 1312, 1155, 952, 705 cm^{-1}.

5.4.3. *N*-{2-[5-Hydroxy-1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl]ethyl}benzamide (7c). Prepared from **3**, 2,2,2-trifluoroethylhydrazine (**4c**) (70% in water, 3.26 g, 20 mmol) and 37% hydrochloric acid; trituration with water. Yield: 5.89 g (94%) of a white solid; mp 183–186 °C. δ_H (300 MHz, DMSO-d_6) 2.53 (2H, t, J=7.3 Hz, 2-CH_2), 3.36 (2H, br td, J=7.3, 5.7 Hz, 1-CH_2), 4.67 (2H, q, J=8.8 Hz, CH_2CF$_3$), 7.24 (1H, br s, 3′-H), 7.40–7.54 (3H, m, 3H of Ph), 7.79–7.84 (2H, m, 2H of Ph), 8.50 (1H, br s, N*H*), 10.68 (1H, br s, O*H*). δ_C NMR (75.5 MHz, DMSO-d_6) 22.3, 39.8, 46.3, 118.1, 121.8, 125.5, 127.0, 128.1, 130.9, 134.6, 139.3, 166.1. [Found: C, 53.78; H, 4.72; N, 13.37. $C_{14}H_{14}F_3N_3O_2$ requires: C, 53.67; H, 4.50; N, 13.41.] ν_{max} (KBr) 3309, 3068, 2932, 1650, 1615, 1575, 1557, 1252, 1160, 693 cm^{-1}.

5.4.4. *N*-[2-(1-Benzyl-5-hydroxy-1*H*-pyrazol-4-yl)ethyl]benzamide (7d). Prepared from **3** and benzylhydrazine dihydrochloride (**4d**) (3.90 g, 20 mmol); trituration with ethanol–water (1:1). Yield: 4.63 g (72%) of a greyish solid; mp 144–149 °C. EIMS: m/z=321 (M$^+$). δ_H (300 MHz, DMSO-d_6) 2.58 (2H, t, J=7.2 Hz, 2-CH_2), 3.40 (2H, td, J=7.2, 5.7 Hz, 1-CH_2), 5.09 (2H, s, CH_2Ph), 7.14–7.17 (2H, m, 2H of Ph), 7.23–7.34 (3H, m, 3H of Ph), 7.39 (1H, s, 3′-H), 7.42–7.54 (3H, m, 3H of Ph), 7.82–7.87 (2H, m, 2H of Ph), 8.58 (1H, br t, J=5.7 Hz, N*H*), 10.25 (1H, br s, O*H*). δ_C NMR (75.5 MHz, DMSO-d_6) 22.6, 40.1, 48.6, 127.0, 127.0, 128.1, 128.2, 130.9, 134.6, 136.8, 137.7, 166.0. [Found: C, 70.84; H, 5.98; N, 13.32. $C_{19}H_{19}N_3O_2$ requires: C, 71.01; H, 5.96; N, 13.08.] ν_{max} (KBr) 3366, 1630, 1574, 1542, 1492, 1411, 1312, 1268, 699 cm^{-1}. EI-HRMS: m/z=321.146800 (M$^+$); $C_{19}H_{19}N_3O_2$ requires: m/z=321.147727 (M$^+$).

5.4.5. *N*-[2-(1-Cyclohexyl-5-hydroxy-1*H*-pyrazol-4-yl)ethyl]benzamide (7e). Prepared from **3** and cyclohexylhydrazine hydrochloride (**4e**) (3.01 g, 20 mmol); trituration with water. Yield: 6.01 g (96%) of a white solid; mp 208–210 °C. δ_H (300 MHz, DMSO-d_6) 1.06–1.23 (1H, m, 1H

of C_6H_{11}), 1.28–1.45 (2H, m, 2H of C_6H_{11}), 1.57–1.84 (7H, m, 7H of C_6H_{11}), 2.52 (2H, br s, 2-CH_2), 3.36 (2H, br dt, J=5.9, 7.0 Hz, 1-CH_2), 4.03 (1H, br m, 1H of C_6H_{11}), 7.42–7.55 (4H, m, 3H of Ph, 3′-H), 7.81–7.88 (2H, m, 2H of Ph), 8.48 (1H, br s, N*H*), 9.88 (1H, br s, O*H*). δ_H (300 MHz, CD_3OD) 1.25 (1H, qt, J=3.3, 12.8 Hz, 1H of C_6H_{11}), 1.46 (2H, br qt, J=3.2, 12.8 Hz, 2H of C_6H_{11}), 1.61–1.79 (3H, m, 3H of C_6H_{11}), 1.83–1.95 (4H, m, 4H of C_6H_{11}), 2.64 (2H, t, J=7.0 Hz, 2-CH_2), 3.53 (2H, t, J=7.0 Hz, 1-CH_2), 4.26 (1H, tt, J=3.6, 12.0 Hz, 1H of C_6H_{11}), 7.42 (1H, s, 3′-H), 7.43–7.57 (3H, m, 3H of Ph), 7.81–7.87 (2H, m, 2H of Ph). δ_C NMR (75.5 MHz, DMSO-d_6) 22.6, 24.9, 25.1, 31.6, 40.2, 53.7, 98.5, 127.0, 128.1, 130.9, 134.6, 136.0, 148.4, 166.0. [Found: C, 68.79; H, 7.60; N, 13.48. $C_{18}H_{23}N_3O_2$ requires: C, 68.98; H, 7.40; N, 13.41.] ν_{max} (KBr) 3348, 2936, 2853, 1631, 1547, 1296, 804 cm^{-1}.

5.4.6. *N*-[2-(5-Hydroxy-1-phenyl-1*H*-pyrazol-4-yl)ethyl]-benzamide (7f). Prepared from **3** and phenylhydrazine hydrochloride (**4f**) (2.89 g, 20 mmol); trituration with ethanol–water (1:1). Yield: 5.04 g (82%) of a white solid; mp 164–167 °C. δ_H (300 MHz, DMSO-d_6) 2.60 (2H, br s, 2-CH_2), 3.44 (2H, br dt, J=5.7, 7.2 Hz, 1-CH_2), 7.23 (1H, t, J=7.5 Hz, 1H of Ph), 7.42–7.55 (6H, m, 5H of Ph, 3′-H), 7.72 (2H, d, J=7.5 Hz, 2H of Ph), 7.83–7.87 (2H, m, 2H of Ph), 8.58 (1H, br s, N*H*), 10.75 (1H, br s, O*H*). δ_C NMR (75.5 MHz, DMSO-d_6) 22.5, 120.7, 125.2, 127.0, 128.2, 128.8, 130.9, 134.6, 138.9, 166.2. [Found: C, 70.38; H, 5.69; N, 13.73. $C_{18}H_{17}N_3O_2$ requires: C, 70.34; H, 5.58; N, 13.67.] ν_{max} (KBr) 3429, 3304, 1633, 1539, 1500, 1416, 1317, 1097, 754, 692 cm^{-1}.

5.4.7. 4-[4-(2-Benzamidoethyl)-5-hydroxy-1*H*-pyrazol-1-yl]benzoic acid (7g). Prepared from **3**, 4-hydrazinobenzoic acid (**4g**) (3.04 g, 20 mmol) and 37% hydrochloric acid; trituration with ethanol–water (1:1). Yield: 6.46 g (92%) of a greyish solid; mp 260–264 °C. EIMS: m/z=351 (M^+). δ_H (300 MHz, DMSO-d_6) 2.60 (2H, br t, J=7.2 Hz, 2-CH_2), 3.44 (2H, br td, J=7.2, 5.5 Hz, 1-CH_2), 7.43–7.54 (4H, m, 3H of Ph and 3′-H), 7.83–7.86 (2H, m, 2H of Ph), 7.90–7.93 (2H, m, 2H of Ph), 8.00–8.03 (2H, m, 2H of Ph), 8.56 (1H, br t, J=5.5 Hz, N*H*), 11.08 (1H, br s, O*H*), 12.87 (1H, br s, COO*H*). δ_C NMR (75.5 MHz, DMSO-d_6) 22.5, 39.6, 103.6, 119.2, 127.0, 127.2, 128.3, 130.4, 131.1, 134.7, 140.3, 141.9, 155.3, 166.4, 166.9. [Found: C, 63.66; H, 5.17; N, 11.75. $C_{19}H_{17}N_3O_4\cdot\frac{1}{2}H_2O$ requires: C, 63.33; H, 5.03; N, 11.66.] ν_{max} (KBr) 3289, 3060, 1682, 1627, 1585, 1517, 1489, 1431, 1306, 769 cm^{-1}. EI-HRMS: m/z=351.122500 (M^+); $C_{19}H_{17}N_3O_4$ requires: m/z= 351.121906 (M^+).

5.4.8. *N*-{2-[1-(3-Chlorophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]ethyl}benzamide (7h). Prepared from **3** and 3-chlorophenylhydrazine hydrochloride (**4h**) (3.58 g, 20 mmol); trituration with ethanol–water (1:1). Yield: 6.63 g (97%) of a white solid; mp 168–171 °C. δ_H (300 MHz, DMSO-d_6) 2.60 (2H, br t, J=7.1 Hz, 2-CH_2), 3.44 (2H, br td, J=7.1, 5.5 Hz, 1-CH_2), 7.29 (1H, ddd, J=0.7, 1.9, 8.0 Hz, 1H of Ar), 7.43–7.55 (4H, m, 4H of Ar), 7.48 (1H, s, 3′-H), 7.75 (1H, ddd, J=0.9, 2.0, 8.3 Hz, 1H of Ar), 7.83–7.88 (3H, m, 3H of Ar), 8.57 (1H, br t, J=5.5 Hz, N*H*), 11.07 (1H, br s, O*H*). δ_C NMR (75.5 MHz, DMSO-d_6) 23.4, 119.4, 120.4, 125.7, 128.0, 129.1, 131.5, 131.9, 134.1, 135.5, 140.9, 167.1. [Found: C, 63.15; H, 4.99; N, 12.15. $C_{18}H_{16}ClN_3O_2$ requires: C, 63.25; H, 4.72; N, 12.29.] ν_{max} (KBr) 3385, 3295, 3072, 1629, 1589, 1559, 1323, 700 cm^{-1}.

5.4.9. *N*-{2-[1-(4-Chlorophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]ethyl}benzamide (7i). Prepared from **3** and 4-chlorophenylhydrazine hydrochloride (**4i**) (3.58 g, 20 mmol); trituration with ethanol–water (1:2). Yield: 6.22 g (91%) of a white solid; mp 190–193 °C. EIMS: m/z=341 (M^+). δ_H (300 MHz, DMSO-d_6) 2.61 (2H, br t, J=7.0 Hz, 2-CH_2), 3.44 (2H, br td, J=7.0, 5.6 Hz, 1-CH_2), 7.42–7.55 (6H, m, 5H of Ar, 3′-H), 7.78 (2H, d, J=8.9 Hz, 2H of Ar), 7.83–7.88 (2H, m, 2H of Ar), 8.59 (1H, br t, J=5.6 Hz, N*H*), 10.23 (1H, br s, O*H*). δ_C NMR (75.5 MHz, DMSO-d_6) 22.4, 39.6, 102.3, 121.7, 127.1, 128.2, 128.8, 129.2, 131.0, 134.6, 137.3, 139.6, 166.2. [Found: C, 63.23; H, 4.72; N, 12.26. $C_{18}H_{16}ClN_3O_2$ requires: C, 63.25; H, 4.72; N, 12.29.] ν_{max} (KBr) 3311, 1633, 1575, 1490, 1330, 893, 696 cm^{-1}. EI-HRMS: m/z=341.093680 (M^+); $C_{18}H_{16}ClN_3O_2$ requires: m/z=341.093105 (M^+).

5.4.10. *N*-{2-[5-Hydroxy-1-(3-methoxyphenyl)-1*H*-pyrazol-4-yl]ethyl}benzamide (7j). Prepared from **3** and 3-methoxyphenylhydrazine hydrochloride (**4j**) (3.49 g, 20 mmol); trituration with ethanol–water (1:2). Yield: 5.85 g (87%) of a beige solid; mp 69–72 °C. δ_H (300 MHz, DMSO-d_6) 2.60 (2H, br s, 2-CH_2), 3.44 (2H, br dt, J=5.7, 7.1 Hz, 1-CH_2), 3.79 (3H, s, O*Me*), 6.79–6.86 (1H, m, 1H of Ar), 7.34 (1H, br s, 3′-H), 7.32–7.36 (2H, m, 2H of Ar), 7.43–7.55 (4H, m, 3H of Ph, 1H of Ar), 7.78–7.88 (2H, m, 2H of Ph), 8.58 (1H, br s, N*H*), 10.81 (1H, br s, O*H*). δ_C NMR (75.5 MHz, DMSO-d_6) 23.4, 56.1, 107.1, 111.7, 113.3, 128.0, 129.1, 130.6, 131.9, 135.6, 140.0, 140.5, 160.4, 167.1. [Found: C, 67.47; H, 5.82; N, 12.41. $C_{19}H_{19}N_3O_3$ requires: C, 67.64; H, 5.68; N, 12.46.] ν_{max} (KBr) 3333, 1634, 1600, 1541, 1495, 1467, 1403, 1290, 1237, 1100, 994, 865 cm^{-1}.

5.4.11. *N*-{2-[5-Hydroxy-1-(4-methoxyphenyl)-1*H*-pyrazol-4-yl]ethyl}benzamide (7k). Prepared from **3** and 4-methoxyphenylhydrazine hydrochloride (**4k**) (3.49 g, 20 mmol); trituration with ethanol–water (1:2). Yield: 5.33 g (79%) of a grey solid; mp 170–174 °C. δ_H (300 MHz, DMSO-d_6) 2.59 (2H, br t, J=7.1 Hz, 2-CH_2), 3.43 (2H, br dt, J=7.1, 5.7 Hz, 1-CH_2), 3.78 (3H, s, O*Me*), 7.01 (2H, d, J=9.0 Hz, 2H of Ar), 7.40 (1H, br s, 3′-H), 7.42–7.55 (3H, m, 3H of Ph), 7.59 (2H, d, J=9.0 Hz, 2H of Ar), 7.83–7.88 (2H, m, 2H of Ph), 8.60 (1H, br s, N*H*), 10.66 (1H, br s, O*H*). δ_C NMR (75.5 MHz, DMSO-d_6) 22.5, 39.8, 55.2, 113.9, 122.6, 127.1, 128.2, 130.9, 131.9, 134.6, 138.5, 157.0, 166.2. [Found: C, 67.89; H, 5.76; N, 12.48. $C_{19}H_{19}N_3O_3$ requires: C, 67.64; H, 5.68; N, 12.46.] ν_{max} (KBr) 3301, 3067, 1632, 1539, 1512, 1426, 1248, 835 cm^{-1}.

5.4.12. *N*-{2-[3-Oxo-2-(pyridin-2-yl)-2,3-dihydro-1*H*-pyrazol-4-yl]ethyl}benzamide (7′l). Prepared from **3**, 2-hydrazinopyridine (**4l**) (2.18 g, 20 mmol) and 37% hydrochloric acid; trituration with ethanol–water (1:2). Yield: 5.17 g (84%) of a white solid; mp 153–154 °C. δ_H (300 MHz, DMSO-d_6) 2.50 (2H, br s, 2-CH_2), 3.46 (2H, br td, J=7.2, 5.3 Hz, 1-CH_2), 7.28 (1H, br t, J=6.8 Hz,

5″-H), 7.42–7.54 (3H, m, 3H of Ph), 7.61 (1H, br s, 5′-H), 7.83–7.86 (2H, m, 2H of Ph), 7.98 (1H, br t, J=6.8 Hz, 4″-H), 8.23 (1H, broad signal, 3″-H), 8.43 (1H, dd, J=1.1, 4.9 Hz, 6″-H), 8.60 (1H, br t, J=5.3 Hz, N*H*), 12.02 (1H, br s, 1′-H). δ_C NMR (75.5 MHz, DMSO-d_6) 22.4, 39.3, 111.5, 120.4, 127.1, 128.2, 130.9, 134.6, 139.5, 146.9, 166.2. [Found: C, 66.36; H, 5.30; N, 18.18. $C_{17}H_{16}N_4O_2$ requires: C, 66.22; H, 5.23; N, 18.17.] ν_{max} (KBr) 3310, 3198, 2940, 1650, 1631, 1572, 1472, 1434, 1364, 1323, 1295, 774, 704 cm^{-1}.

5.4.13. *N*-{2-[2-(6-Chloropyridazin-3-yl)-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl]ethyl}benzamide (7′m). Prepared from **3**, 6-chloro-3-hydrazinopyridazine (**4m**) (2.89 g, 20 mmol) and 37% hydrochloric acid; trituration with ethanol–water (1:2). Yield: 4.95 g (72%) of a yellowish solid; mp 222–225 °C. δ_H (300 MHz, DMSO-d_6) 2.50 (2H, br s, 2-CH_2), 3.48 (2H, br td, J=7.2, 5.5 Hz, 1-CH_2), 7.43–7.55 (3H, m, 3H of Ph), 7.84–7.87 (3H, m, 2H of Ph and 5′-H), 8.03 (1H, d, J=9.0 Hz, 4″-H), 8.57 (1H, br t, J=5.5 Hz, N*H*), 8.77 (1H, br s, 5″-H), 12.30 (1H, br s, 1′-H). δ_C NMR (75.5 MHz, DMSO-d_6) 22.5, 34.0, 103.8, 119.6, 127.1, 128.1, 130.8, 130.9, 134.5, 139.4, 151.3, 152.2, 163.5, 166.1. [Found: C, 55.67; H, 4.20; N, 20.35. $C_{16}H_{14}ClN_5O_2$ requires: C, 55.90; H, 4.10; N, 20.37.] ν_{max} (KBr) 3314, 3075, 1638, 1578, 1542, 1460, 1424, 1225, 1196, 1142, 854, 693 cm^{-1}.

5.4.14. *N*-{2-[3-Oxo-2-(6-phenylpyridazin-3-yl)-2,3-dihydro-1*H*-pyrazol-4-yl]ethyl}benzamide (7′n). Prepared from **3**, 3-hydrazino-6-phenylpyridazine (**4n**) (3.72 g, 20 mmol) and 37% hydrochloric acid; trituration with ethanol–water (1:2). Yield: 6.24 g (81%) of a pale yellowish solid; mp 234–238 °C. EIMS: m/z=385 (M$^+$). δ_H (300 MHz, DMSO-d_6) 2.50 (2H, br s, 2-CH_2), 3.48 (2H, br td, J=7.2, 5.5 Hz, 1-CH_2), 7.43–7.61 (6H, m, 6H of Ph), 7.84–7.87 (3H, m, 2H of Ph and 5′-H), 8.13–8.17 (2H, m, 1H of Ph and 4″-H), 8.37–8.44 (1H, m, 1H of Ph), 8.61 (1H, br t, J=5.5 Hz, N*H*), 8.76 (1H, br s, 5″-H), 12.39 (1H, br s, 1′-H). δ_C NMR (75.5 MHz, DMSO-d_6) 22.5, 39.0, 103.6, 117.0, 126.4, 126.6, 127.0, 128.1, 128.9, 129.8, 130.9, 131.9, 134.6, 135.4, 138.7, 150.5, 156.0, 166.1. [Found: C, 66.96; H, 4.88; N, 17.73. $C_{22}H_{19}N_5O_2\cdot\frac{1}{2}H_2O$ requires: C, 66.99; H, 5.11; N, 17.76.] ν_{max} (KBr) 3431, 3333, 1635, 1549, 1455, 1427, 1370, 1313, 1203, 1084, 689 cm^{-1}. EI-HRMS: m/z=385.154500 (M$^+$), $C_{22}H_{19}N_5O_2$ requires: m/z=385.153875 (M$^+$).

5.4.15. *N*-{2-[2-(Imidazo[1,2-*b*]pyridazin-6-yl)-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl]ethyl}benzamide (7′o). Prepared from **3**, 6-hydrazinoimidazo[1,2-*b*]pyridazine (**4o**) (2.98 g, 20 mmol) and 37% hydrochloric acid; trituration with ethanol–water (1:2). Yield: 6.95 g (100%) of a pale brownish solid; mp 119–122 °C. EIMS: m/z=348 (M$^+$). δ_H (300 MHz, DMSO-d_6) 2.55 (2H, br s, 2-CH_2), 3.46 (2H, br td, J=7.2, 5.3 Hz, 1-CH_2), 7.43–7.54 (3H, m, 3H of Ph), 7.78 (1H, br s, 5′-H), 7.79 (1H, d, J=1.1 Hz, 3″-H), 7.83–7.86 (2H, m, 2H of Ph), 8.20 (1H, br s, 2″-H), 8.24 (1H, d, J=9.4 Hz, 7″-H), 8.41 (1H, broad signal, 8″-H), 8.58 (1H, br t, J=5.3 Hz, N*H*), 11.61 (1H, br s, 1′-H). δ_C NMR (75.5 MHz, DMSO-d_6) 22.6, 39.0, 103.8, 110.7, 117.1, 127.1, 128.2, 131.0, 133.6, 134.6, 137.1, 139.8, 146.0, 166.2. [Found: C, 60.53; H, 5.05; N, 23.62. $C_{18}H_{16}N_6O_2\cdot\frac{1}{2}H_2O$ requires: C, 60.50; H, 4.79; N, 23.72.] ν_{max} (KBr) 3400, 3155, 1634, 1605, 1542, 1487, 1400, 1306, 1216, 1150, 966, 698 cm^{-1}. EI-HRMS: m/z=348.134050 (M$^+$); $C_{18}H_{16}N_6O_2$ requires: m/z=348.133474 (M$^+$).

5.5. Hydrolytic removal of the benzoyl *N*-protecting group. General procedure for the preparation of 1-substituted 4-(2-aminoethyl)-5-hydroxy-1*H*-pyrazoles 8a–k and 4-(2-aminoethyl)-2-heteroaryl-1*H*-pyrazol-3(2*H*)-ones 8′l–o

A mixture of **7** (10 mmol) and 6 M hydrochloric acid (50 mL) was heated to reflux for 16 h. Volatile components were evaporated in vacuo, anhydrous ethanol (20 mL) was added to the residue and the mixture was evaporated in vacuo again. The semi-solid residue was triturated with anhydrous ethanol (20 mL) until a crystalline precipitate was formed. Then, ethyl acetate (20 mL) was added, the precipitate was collected by filtration and washed with ethanol–ethyl acetate (1:1, 10 mL), ethyl acetate (20 mL) and diethyl ether (20 mL) to give **8**.

The following compounds were prepared in this manner.

5.5.1. 4-(2-Aminoethyl)-5-hydroxy-1*H*-pyrazole dihydrochloride (8a). Prepared from **7a** (2.31 g, 10 mmol). Yield: 2.00 g (100%) of a white solid; mp 161–166 °C. EIMS: m/z=127 (M$^+$). δ_H (300 MHz, DMSO-d_6) 2.73 (2H, br t, J=7.1 Hz, 1′-CH_2), 2.97 (2H, br sextet, J=7.1 Hz, 2′-CH_2), 7.87 (1H, s, 3-H), 8.19 (3H, br s, NH_3^+), OH exchanged. δ_C NMR (75.5 MHz, DMSO-d_6) 19.9, 38.3, 100.3, 133.7, 155.1. [Found: 30.79; H, 5.71; N, 20.94. $C_5H_9N_3O\cdot 1.93HCl$ requires: C, 30.39; H, 5.58; N, 21.26.] ν_{max} (KBr) 3392, 3042, 2971, 1612, 1578, 1484, 1385, 1150, 1067, 878, 703 cm^{-1}. EI-HRMS: m/z=127.074950 (M$^+$); $C_5H_9N_3O$ requires: m/z=127.074562 (M$^+$).

5.5.2. 4-(2-Aminoethyl)-5-hydroxy-1-methyl-1*H*-pyrazole dihydrochloride (8b). Prepared from **7b** (2.45 g, 10 mmol). Yield: 2.14 g (100%) of a white solid; mp 169–174 °C. EIMS: m/z=141 (M$^+$). δ_H (300 MHz, DMSO-d_6) 2.70 (2H, br t, J=7.2 Hz, 1′-CH$_2$), 2.94 (2H, br sextet, J=7.2 Hz, 2′-CH_2), 3.61 (3H, s, *Me*), 7.74 (1H, s, 3-H), 8.13 (3H, br s, NH_3^+), OH exchanged. [Found: C, 33.22; H, 6.40; N, 19.09. $C_6H_{13}Cl_2N_3O\cdot\frac{1}{4}H_2O$ requires: C, 32.97; H, 6.22; N, 19.22.] ν_{max} (KBr) 3593, 3493, 2925, 1610, 1566, 1529, 1438, 1261, 836, 693 cm^{-1}. EI-HRMS: m/z=141.090650 (M$^+$); $C_6H_{11}N_3O$ requires: m/z=141.090212 (M$^+$).

5.5.3. 4-(2-Aminoethyl)-5-hydroxy-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole dihydrochloride (8c). Prepared from **7c** (3.13 g, 10 mmol). Yield: 2.60 g (92%) of a white solid; mp 166–168 °C. EIMS: m/z=209 (M$^+$). δ_H (300 MHz, DMSO-d_6) 2.62 (2H, t, J=7.4 Hz, 1′-CH_2), 2.92 (2H, br sextet, J=7.4 Hz, 2′-CH_2), 4.72 (2H, q, J=9.2 Hz, CH_2CF$_3$), 7.35 (1H, br s, 3-H), 8.07 (3H, br s, NH_3^+), OH exchanged. δ_C NMR (75.5 MHz, DMSO-d_6) 20.7, 46.5, 97.4, 121.7, 125.4, 139.0, 153.0. [Found: C, 30.96; H, 4.59; N, 15.32. $C_7H_{10}F_3N_3O\cdot 1\frac{3}{4}HCl$ requires: C, 30.80; H, 4.34; N, 15.39.] ν_{max} (KBr) 3422, 2967, 1594, 1571, 1389, 1297, 1263, 1179, 1159, 836, 699 cm^{-1}. EI-HRMS: m/z=209.077700 (M$^+$); $C_7H_{10}F_3N_3O$ requires: m/z=209.077597 (M$^+$).

5.5.4. 4-(2-Aminoethyl)-1-benzyl-5-hydroxy-1*H*-pyrazole dihydrochloride (8d). Prepared from **7d** (3.21 g,

10 mmol). Yield: 1.80 g (62%) of a greyish solid; mp 144–149 °C. δ_H (300 MHz, DMSO-d_6) 2.70 (2H, br t, J=7.2 Hz, 1′-CH_2), 2.95 (2H, br sextet, J=7.2 Hz, 2′-CH_2), 5.20 (2H, s, CH_2Ph), 7.22–7.38 (5H, m, Ph), 7.70 (1H, s, 3-H), 8.18 (3H, br s, NH_3^+), OH exchanged. δ_C NMR (75.5 MHz, DMSO-d_6) 20.4, 38.4, 48.7, 100.1, 127.7, 128.0, 128.6, 134.7, 135.1, 153.5. [Found: C, 49.43; H, 6.06; N, 14.41. $C_{12}H_{17}Cl_2N_3O$ requires: C, 49.67; H, 5.90; N, 14.48.] ν_{max} (KBr) 3428, 3102, 2954, 2861, 1606, 1573, 1434, 1237, 729, 693 cm^{-1}.

5.5.5. 4-(2-Aminoethyl)-1-cyclohexyl-5-hydroxy-1*H*-pyrazole dihydrochloride (8e). Prepared from **7e** (3.13 g, 10 mmol). Yield: 2.82 g (100%) of a white solid; mp 133–138 °C. EIMS: m/z=209 (M$^+$). δ_H (300 MHz, DMSO-d_6) 1.12–1.23 (1H, m, 1H of C_6H_{11}), 1.28–1.46 (2H, m, 2H of C_6H_{11}), 1.64 (1H, br d, J=12.3 Hz, 1H of C_6H_{11}), 1.75–1.95 (6H, m, 6H of C_6H_{11}), 2.72 (2H, br t, J=7.2 Hz, 1′-CH_2), 2.98 (2H, br sextet, J=7.2 Hz, 2′-CH_2), 4.22–4.35 (1H, m, 1H of C_6H_{11}), 7.78 (1H, s, 3-H), 8.16 (3H, br s, NH_3^+), OH exchanged. δ_C NMR (75.5 MHz, DMSO-d_6) 21.2, 25.3, 25.8, 31.6, 39.2, 56.5, 101.1, 135.0, 153.4. [Found: C, 46.02; H, 8.19; N, 14.69. $C_{11}H_{21}Cl_2N_3O\cdot\frac{1}{3}H_2O$ requires: C, 45.84; H, 7.58; N, 14.58.] ν_{max} (KBr) 3331, 2949, 1589, 1566, 1498, 1431, 1320, 1109, 896 cm^{-1}. EI-HRMS: m/z=209.153450 (M$^+$); $C_{11}H_{19}N_3O$ requires: m/z=209.152812 (M$^+$).

5.5.6. 4-(2-Aminoethyl)-5-hydroxy-1-phenyl-1*H*-pyrazole dihydrochloride (8f). Prepared from **7f** (3.07 g, 10 mmol). Yield: 1.38 g (50%) of a white solid; mp 210–212 °C. EIMS: m/z=203 (M$^+$). δ_H (300 MHz, DMSO-d_6) 2.68 (2H, br t, J=7.2 Hz, 1′-CH_2), 2.97 (2H, br sextet, J=7.2 Hz, 2′-CH_2), 7.26 (1H, tt, J=1.1, 7.4 Hz, 1H of Ph), 7.40–7.48 (2H, m, 2H of Ph), 7.57 (1H, s, 3-H), 7.68–7.73 (2H, m, 2H of Ph), 8.12 (3H, br s, NH_3^+), OH exchanged. [Found: C, 47.85; H, 5.63; N, 15.19. $C_{11}H_{15}Cl_2N_3O$ requires: C, 47.84; H, 5.47; N, 15.22.] ν_{max} (KBr) 3362, 3001, 1597, 1569, 1503, 1421, 1081, 693 cm^{-1}. EI-HRMS: m/z=203.106000 (M$^+$); $C_{11}H_{13}N_3O$ requires: m/z=203.105862 (M$^+$).

5.5.7. 4-(4-(2-Aminoethyl)-5-hydroxy-1*H*-pyrazol-1-yl)-benzoic acid dihydrochloride (8g). Prepared from **7g** (3.51 g, 10 mmol). Yield: 2.79 g (87%) of a white solid; mp 265–272 °C. EIMS: m/z=247 (M$^+$). δ_H (300 MHz, DMSO-d_6) 2.68 (2H, br t, J=7.3 Hz, 1′-CH_2), 3.00 (2H, br sextet, J=7.3 Hz, 2′-CH_2), 7.63 (1H, s, 3-H), 7.92 (2H, dt, J=1.9, 8.9 Hz, 2H of Ar), 8.02 (2H, dt, J=1.9, 8.9 Hz, 2H of Ar), 8.06 (3H, br s, NH_3^+), OH and COOH exchanged. δ_C NMR (75.5 MHz, DMSO-d_6) 20.7, 38.3, 100.4, 112.2, 121.0, 138.7, 140.0, 146.9, 149.2, 158.4. [Found: C, 46.72; H, 5.05; N, 13.52. $C_{12}H_{13}N_3O_3\cdot 1\frac{2}{3}HCl$ requires: C, 46.79; H, 4.80; N, 13.64.] ν_{max} (KBr) 3422, 3022, 2912, 1716, 1683, 1588, 1419, 1313, 1227, 1117, 767 cm^{-1}. EI-HRMS: m/z 247.096000 (M$^+$); $C_{12}H_{13}N_3O_3$ requires: m/z=247.095691 (M$^+$).

5.5.8. 4-(2-Aminoethyl)-1-(3-chlorophenyl)-5-hydroxy-1*H*-pyrazole dihydrochloride (8h). Prepared from **7h** (3.42 g, 10 mmol). Yield: 2.58 g (83%) of a greyish solid; mp 206–207 °C. EIMS: m/z=237 (M$^+$). δ_H (300 MHz, DMSO-d_6) 2.68 (2H, br t, J=7.3 Hz, 1′-CH_2), 2.99 (2H, br sextet, J=7.3 Hz, 2′-CH_2), 7.31 (1H, ddd, J=0.9, 2.1, 8.1 Hz, 1H of Ar), 7.49 (1H, t, J=8.1 Hz, 1H of Ar), 7.60 (1H, s, 3-H), 7.75 (1H, ddd, J=0.9, 2.1, 8.1 Hz, 1H of Ar), 7.86 (1H, t, J=2.1 Hz, 1H of Ar), 8.01 (3H, br s, NH_3^+), OH exchanged. [Found: C, 42.56; H, 4.66; N, 13.48. $C_{11}H_{14}Cl_3N_3O$ requires: C, 42.54; H, 4.54; N, 13.53.] ν_{max} (KBr) 3057, 2878, 2754, 2632, 1589, 1560, 1477, 1444, 1258, 781, 677 cm^{-1}. EI-HRMS: m/z 237.067000 (M$^+$); $C_{11}H_{12}ClN_3O$ requires: m/z=237.066890 (M$^+$).

5.5.9. 4-(2-Aminoethyl)-1-(4-chlorophenyl)-5-hydroxy-1*H*-pyrazole dihydrochloride (8i). Prepared from **7i** (3.42 g, 10 mmol). Yield: 2.42 g (78%) of a greyish solid; mp 206–210 °C. EIMS: m/z=237 (M$^+$). δ_H (300 MHz, DMSO-d_6) 2.69 (2H, br t, J=7.3 Hz, 1′-CH_2), 2.96 (2H, br sextet, J=7.3 Hz, 2′-CH_2), 7.50 (2H, dt, J=2.6, 9.0 Hz, 2H of Ar), 7.55 (1H, s, 3-H), 7.76 (2H, dt, J=2.6, 9.0 Hz, 2H of Ar), 8.09 (3H, br s, NH_3^+), OH exchanged. δ_C NMR (75.5 MHz, DMSO-d_6) 20.1, 38.8, 100.3, 122.8, 129.0, 130.3, 136.2, 139.0, 153.9. [Found: C, 42.80; H, 4.61; N, 13.33. $C_{11}H_{14}Cl_3N_3O$ requires: C, 42.54; H, 4.54; N, 13.53.] ν_{max} (KBr) 3434, 3078, 2871, 2361, 1594, 1560, 1483, 1425, 1251, 1226, 1090, 669 cm^{-1}. EI-HRMS: m/z=236.058500 (M$^+-1$); $C_{11}H_{11}ClN_3O$ requires: m/z=236.059065 (M$^+-1$).

5.5.10. 4-(2-Aminoethyl)-5-hydroxy-1-(3-methoxyphenyl)-1*H*-pyrazole dihydrochloride (8j). Prepared from **7j** (3.37 g, 10 mmol). Yield: 2.62 g (86%) of a greyish solid; mp 150–154 °C. EIMS: m/z=233 (M$^+$). δ_H (300 MHz, DMSO-d_6) 2.68 (2H, br t, J=7.3 Hz, 1′-CH_2), 2.99 (2H, br sextet, J=6.8 Hz, 2′-CH_2), 3.79 (3H, s, O*Me*), 6.85 (1H, dt, J=2.6, 6.5 Hz, 1H of Ar), 7.32–7.40 (3H, m, 3H of Ar), 7.58 (1H, br s, 3-H), 8.12 (3H, br s, NH_3^+), OH exchanged. δ_C NMR (75.5 MHz, DMSO-d_6) 20.8, 38.7, 55.3, 100.5, 107.1, 111.9, 113.4, 129.8, 138.1, 138.2, 154.2, 159.5. [Found: C, 47.64; H, 5.69; N, 13.79. $C_{12}H_{15}N_3O_2\cdot 1.9HCl$ requires: C, 47.64; H, 5.63; N, 13.89.] ν_{max} (KBr) 3428, 2887, 1607, 1564, 1469, 1266, 1237, 1039, 684 cm^{-1}. EI-HRMS: m/z=233.117500 (M$^+$); $C_{12}H_{15}N_3O_2$ requires: m/z=233.116427 (M$^+$).

5.5.11. 4-(2-Aminoethyl)-5-hydroxy-1-(4-methoxyphenyl)-1*H*-pyrazole dihydrochloride (8k). Prepared from **7k** (3.37 g, 10 mmol). Yield: 2.77 g (91%) of a greyish solid; mp 211–214 °C. δ_H (300 MHz, DMSO-d_6) 2.71 (2H, br t, J=7.3 Hz, 1′-CH_2), 2.99 (2H, br sextet, J=6.6 Hz, 2′-CH_2), 3.79 (3H, s, O*Me*), 7.03 (2H, d, J=9.0 Hz, 2H of Ar), 7.58 (1H, br s, 3-H), 7.59 (2H, d, J=9.0 Hz, 2H of Ar), 8.14 (3H, br s, NH_3^+), OH exchanged. [Found: C, 47.27; H, 5.83; N, 13.43. $C_{12}H_{17}Cl_2N_3O_2$ requires: C, 47.07; H, 5.60; N, 13.72.] ν_{max} (KBr) 3434, 2894, 1558, 1522, 1437, 1273, 1024, 834 cm^{-1}.

5.5.12. 4-(2-Aminoethyl)-1-(pyridin-2-yl)-1*H*-pyrazol-3(2*H*)-one dihydrochloride (8′l). Prepared from **7l** (3.08 g, 10 mmol). Yield: 1.79 g (65%) of a white solid; mp 137–142 °C. EIMS: m/z=204 (M$^+$). δ_H (300 MHz, DMSO-d_6) 2.61 (2H, br t, J=7.1 Hz, 1′-CH_2), 2.98 (2H, br q, J=7.1 Hz, 2′-CH_2), 7.30 (1H, br dt, J=5.4, 6.8 Hz, 5″-H), 7.72 (1H, s, 5-H), 7.99 (1H, br dt, J=1.8, 6.8 Hz, 4″-H), 8.19 (3H, br s, NH_3^+), 8.24 (1H, br d, J=6.8 Hz, 3″-H), 8.45 (1H, br d, J=5.4 Hz, 6″-H), 1-H exchanged. δ_C NMR

(75.5 MHz, DMSO-d_6) 20.7, 38.3, 100.4, 112.2, 121.0, 138.7, 140.0, 146.9, 149.2, 158.4. [Found: C, 40.76; H, 5.51; N, 18.81. $C_{10}H_{14}Cl_2N_4O\cdot H_2O$ requires: C, 40.69; H, 5.46; N, 18.98.] ν_{max} (KBr) 4363, 3037, 3011, 1645, 1629, 1612, 1548, 1479, 1212, 768 cm^{-1}.

5.5.13. 4-(2-Aminoethyl)-1-(6-chloropyridazin-3-yl)-1*H*-pyrazol-3(2*H*)-one hydrochloride (8′m). Prepared from **7m** (3.44 g, 10 mmol). Yield: 1.06 g (34%) of a yellowish solid; mp 258 °C (decomp.). EIMS: m/z=239 (M^+). δ_H (300 MHz, DMSO-d_6) 2.58 (2H, br t, J=7.2 Hz, 1′-CH_2), 2.99 (2H, br sextet, J=7.2 Hz, 2′-CH_2), 7.93 (1H, br s, 5-H), 7.99 (3H, br s, NH_3^+), 8.05 (1H, d, J=9.4 Hz, 5″-H), 8.75 (1H, d, J=9.4 Hz, 4″-H), 12.63 (1H, br s, 1-H). δ_C NMR (75.5 MHz, DMSO-d_6) 20.7, 37.9, 101.3, 119.6, 130.8, 137.4, 139.6, 151.1, 152.3. [Found: C, 39.88; H, 4.28; N, 24.07. $C_9H_{11}Cl_2N_5O$ requires: C, 39.15; H, 4.02; N, 25.36.] ν_{max} (KBr) 3428, 3077, 1638, 1561, 1476, 1423, 1138, 702 cm^{-1}. EI-HRMS: m/z=239.058200 (M^+); $C_9H_{10}ClN_5O$ requires: m/z=239.057388 (M^+).

5.5.14. 4-(2-Aminoethyl)-1-(6-phenylpyridazin-3-yl)-1*H*-pyrazol-3(2*H*)-one hydrochloride (8′n). Prepared from **7n** (3.85 g, 10 mmol). Yield: 1.81 g (51%) of a greyish solid; mp 252–255 °C. EIMS: m/z=281 (M^+). δ_H (300 MHz, DMSO-d_6) 2.60 (2H, br t, J=7.1 Hz, 1′-CH_2), 2.99 (2H, br sextet, J=7.1 Hz, 2′-CH_2), 7.48–7.60 (3H, m, 3H of Ph), 7.90 (1H, br s, 5-H), 8.05–8.16 (5H, m, 2H of Ph and NH_3^+), 8.40 (1H, d, J=9.4 Hz, 5″-H), 8.71 (1H, br s, 4″-H), 12.70 (1H, br s, 1-H). δ_C NMR (75.5 MHz, DMSO-d_6) 21.7, 39.0, 102.1, 117.8, 127.4, 127.7, 129.4, 129.9, 130.8, 132.9, 135.5, 136.3, 157.1. [Found: C, 55.13; H, 4.96; N, 21.59. $C_{15}H_{15}N_5O\cdot 1\frac{1}{4}HCl$ requires: C, 55.11; H, 5.01; N, 21.42.] ν_{max} (KBr) 3392, 3063, 1634, 1591, 1549, 1452, 1369, 1221, 1087, 780, 687 cm^{-1}.

5.5.15. 4-(2-Aminoethyl)-1-(imidazo[1,2-*b*]pyridazin-6-yl)-1*H*-pyrazol-3(2*H*)-one hydrochloride (8′o). Prepared from **7o** (3.48 g, 10 mmol). Yield: 2.51 g (79%) of a pale yellow solid; mp 238–240 °C. EIMS: m/z=244 (M^+). δ_H (300 MHz, DMSO-d_6) 2.63 (2H, br t, J=7.2 Hz, 1′-CH_2), 3.00 (2H, br sextet, J=7.2 Hz, 2′-CH_2), 7.94 (1H, s, 5-H), 8.17 (3H, br s, NH_3^+), 8.24 (1H, d, J=1.8 Hz, 3″-H), 8.49 (1H, br d, J=1.8 Hz, 2″-H), 8.51 (1H, d, J=10.1 Hz, 7″-H), 8.62 (1H, d, J=10.1 Hz, 8″-H), 1-H exchanged. ν_{max} (KBr) 3419, 3087, 2969, 1656, 1639, 1577, 1491, 1369, 1329, 825, 785, 753 cm^{-1}. EI-HRMS: m/z=244.10500 (M^+); $C_{11}H_{12}N_6O$ requires: m/z=244.107259 (M^+).

5.6. X-ray structure analysis for compound 8f

Single crystal X-ray diffraction data of compound **8f** were collected at rt on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[48] DENZO and SCALEPACK[49] were used for indexing and scaling of the data and the structure was solved by means of SIR97.[50] Refinement and plotting were done using Xtal3.4[51] program package. Crystal structure was refined on F values using the full-matrix least-squares procedure. The non-hydrogen atoms were refined anisotropically in all cases, while the positions of hydrogen atoms were geometrically calculated and their positional and isotropic atomic displacement parameters were not refined. Absorption correction was not necessary. Regina[52] weighting scheme was used in all cases.

Crystallographic data (excluding structure factors) for compound **8f** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 643600. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.

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