Synthesis of 3-(2-aminoethyl)-5-hydroxy-1*H*-pyrazole derivatives

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Dedicated to Professor Reiner Beckert, Friedrich Schiller University Jena, on the occasion of his 60th anniversary

Abstract

Treatment of *β*-keto ester **8** with hydrazines **9a–g** gave 1'-substituted *tert*-butyl 2-(5-hydroxy-1*H*-pyrazol-3-yl)ethylcarbamates **10a–e** and 2-(5-oxo-2,5-dihydro-1*H*-pyrazol-3-yl)ethylcarbamates **11f,g**. Acidolytic deprotection of **10b,c** afforded the corresponding 3-(2-aminoethyl)-5-hydroxy-1*H*-pyrazoles **6b,c** in good yields. Acylation of **6** gave either the *N*-acyl compounds **12b,c** and **13c**, or the *N*,*O*-diacyl derivative **14**. Next, three *N*,*N*-dialkyl analogues **15a,b** and **26c** were prepared from dimethyl acetone-1,3-*di*carboxylate **21** via condensation with hydrazines **9a** and **9h** followed by hydrolysis of the esters **22a,b**, amidation of the carboxylic acids **23a,b**, and reduction of the tertiary carboxamides **24a** and **25b,c**.

Keywords: Acetone-1,3-*di*carboxylates, enaminones, hydrazines, pyrazole, histamine analogues

Introduction

Novel 2-(heteroaryl)ethylamine-containing molecules represent important targets in medicinal and synthetic organic chemistry because these compounds are synthetic analogs of histamine **1**, tyramine, dopamine, tryptamine, serotonin, and melatonin, which are involved as chemical messengers in numerous biological processes.[1]

Pyrazoles[2] and imidazoles[3] are important classes of structurally closely related heterocyclic compounds. The ability of 1-unsubstituted derivatives to act as proton acceptor and donor simultaneously is probably the most important common feature of both systems. In contrast to naturally abundant imidazoles, the occurrence of pyrazoles among natural products is rare.

Nevertheless, numerous synthetic pyrazole derivatives found use in various pharmaceutical, agrochemical, and other applications, and a general interest in the chemistry of pyrazoles is still continuing.[2]

Recently, a part of our research has been focused on the synthesis of histamine analogues **2–5** based on aminoethyl functionalized pyrazole scaffold.[4–7] Within this context, syntheses of analogues **2**[4] and **3**[5] have been developed first, followed by synthesis of conformationally constrained histamine analogues **4**[6] and **5**[7]. Next, we focused our attention on 3-(2-aminoethyl)pyrazol-5-ols **6** as novel type of histamine analogues (Figure 1).

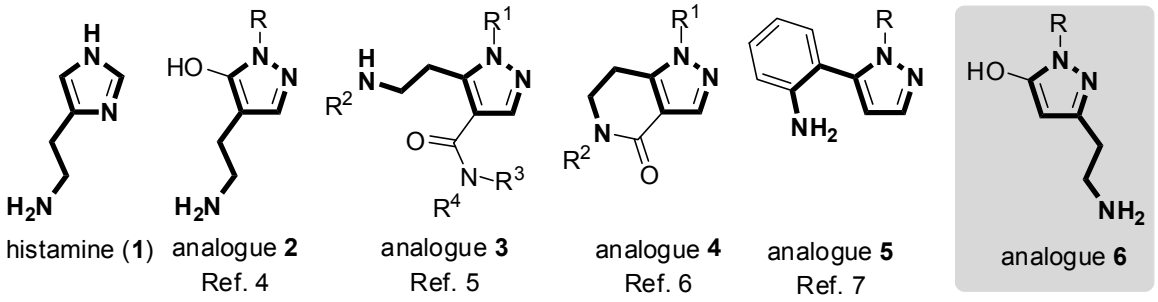


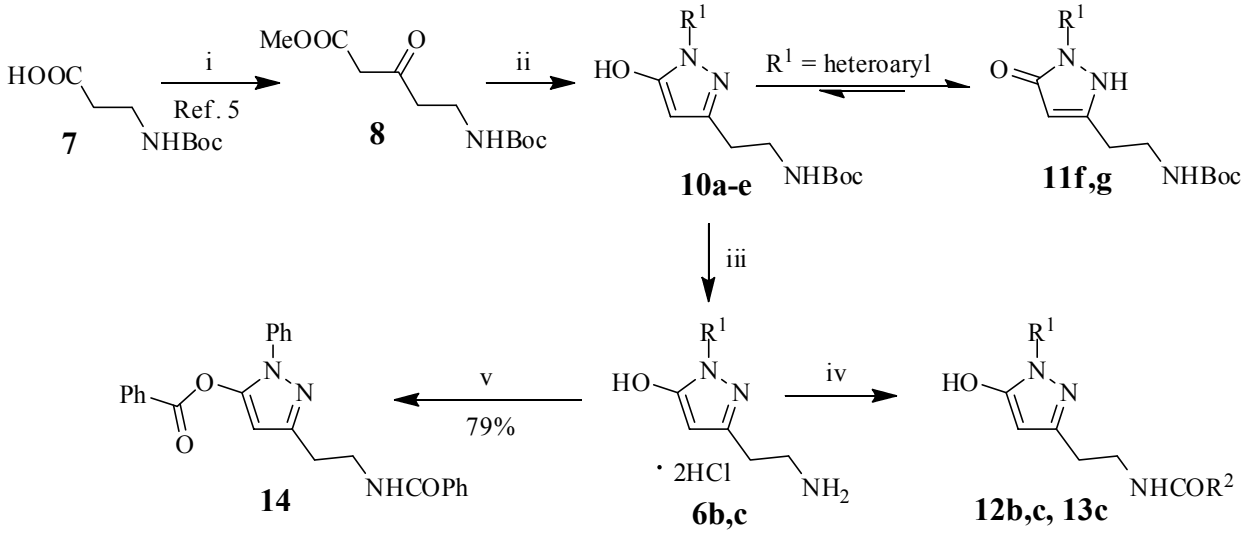
Figure 1. Histamine **1** and its analogues **2**–**6**.

We found pyrazolols **6** interesting because they are structurally closer analogues of histamine **1** than their known regioisomers **2**. Like histamine **1**, compounds **6** have the aminoethyl residue attached at the position adjacent to the ring nitrogen atom. Besides, 3-(2-aminophenyl)pyrazolols could also serve as useful building blocks for further transformations including combinatorial studies. As a result of our research efforts in this field, we now report two simple syntheses of title compounds **6** and their derivatives.

Results and Discussion

First, a simple and straightforward three-step synthesis of 3-(2-aminoethyl)-1*H*-pyrazol-5-ols **6** from *N*-Boc-*β*-alanine **7** was developed. Following literature procedure,[5] *β*-keto ester **8** was prepared from **7** by Masamune-Claisen type condensation.[8] Further treatment of the *β*-keto ester **8** with hydrazine derivatives **9a–g** in refluxing methanol gave 1'-substituted *tert*-butyl 2-(5-hydroxy-1*H*-pyrazol-3-yl)ethylcarbamates **10a–e** and 2-(5-oxo-2,5-dihydro-1*H*-pyrazol-3-yl)ethylcarbamates **11f,g** in 48–83% yields. Subsequent acidolytic deprotection of **10b** and **10c** with HCl–EtOAc furnished the title compounds **6b** and **6c** in 78% and 84% yield, respectively. Treatment of **6b**,**c** with acetic anhydride in methanol produced the N-acetylated compounds **12b,c** in good yields. Similarly, treatment of **6c** with benzoyl chloride in methanol in the presence of triethylamine gave the N-benzoylated compound **13c**, whereas benzoylation in dichloromethane furnished the N,O-dibenzoylated compound **14** in 79% yield. O-Benzoylation

was not really surprising, since pyrazolones are readily O-acylated with acid chlorides and anhydrides (Scheme 1, Table 1).[2]



Scheme 1

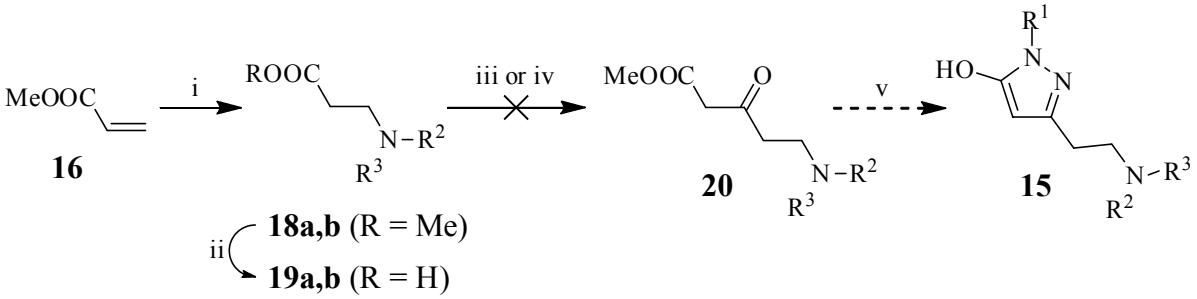
Reagents and conditions: i: CDI, MeCN, r.t., then potassium monomethyl malonate, $MgCl_2$, r.t. ii: R^1NHNH_2 **9a–g**, MeOH, reflux. iii: HCl-EtOAc, r.t. iv: Ac_2O (1 equiv.) or PhCOCl (1 equiv.), MeOH, Et_3N, 0→20 °C. v: PhCOCl (2 equiv.), CH_2Cl_2, Et_3N, r.t.

Table 1. Selected experimental data for compounds **6** and **10–13**

Compound	R^1	R^2	Yield (%)
6b	Me	-	78
6c	Ph	-	84
10a	H	-	48
10b	Me	-	73
10c	Ph	-	83
10d	4-chlorophenyl	-	61
10e	4-carboxyphenyl	-	55
11f	6-phenylpyridazin-3-yl	-	81
11g	imidazo[1,2-*b*]pyridazin-6-yl	-	66
12b	Me	Me	62
12c	Ph	Me	87
13c	Ph	Ph	55

Next, we tried to synthesize the *N,N-d*ialkyl analogues **15** by a similar synthetic pathway. *N,N*-dialkyl-*β*-alanines **19** seemed to be obvious starting materials, since they are available by

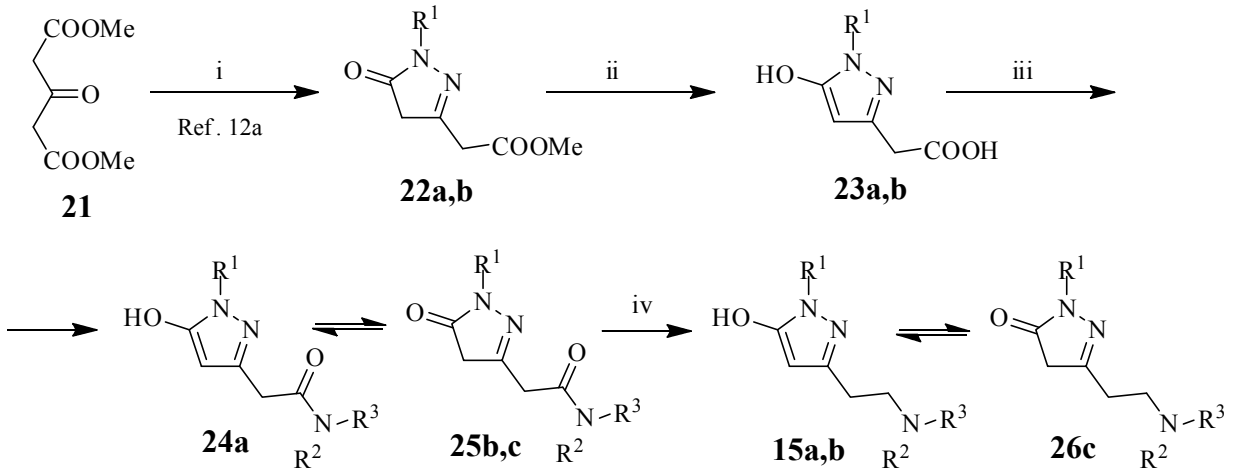
1,4-addition of secondary amines **17** to methyl acrylate **16** followed by hydrolysis of the esters **18**.[9] Indeed, alaninates **18a**[10a] and **18b**[10b,c] were obtained in quantitative yield by addition of benzyl(methyl)amine **17a** and pyrrolidine **17b** to methyl acrylate **16** following a slightly modified literature procedure.[10a] Hydrolysis of the esters **18a,b** in aqueous NaOH, followed by neutralization, and isolation by ion-exchange chromatography gave the crude *β*-amino acids **19a**[11a] and **19b**[11b] in 77% and 80% yield, respectively. Unfortunately, all attempts to prepare the *β*-keto ester **20** by carboxymethylation of the *β*-amino acids **19a,b**, either under Masamune-Claisen conditions, or by condensation with Meldrum's acid followed by methanolysis, failed. Nevertheless, this was not surprising, since changing the NHBoc group of compound **7** (*cf.* Scheme 1) to a strongly basic tertiary amino group of compounds **18** results in zwitterionic structure and, hence, different reactivity (Scheme 2).



Scheme 2

Reagents and conditions: i: Bn(Me)NH **17a** or pyrrolidine **17b**, CH_2Cl_2, r.t. ii: NaOH, H_2O, r.t. iii: CDI, MeCN, r.t., then potassium monomethyl malonate, $MgCl_2$, r.t. (Method A). iv: Meldrum's acid, DMAP, DCC, THF, r.t., then MeOH, reflux (Method B). v: R^1NHNH_2 **9c,h**, MeOH, reflux.

Our alternative strategy for the preparation of the desired products **15** started from (pyrazol-3-yl)acetates **22**, which are easily available from dimethyl acetone-1,3-dicarboxylate **21** and monosubstituted hydrazines **9**.[2,12] First, methyl (pyrazol-3-yl)acetates **22a,b** were prepared from **21** following the literature procedure.[12a] Base-catalyzed hydrolysis of **22a**,**b** gave the acids **23a,b**, which were subsequently amidated with the secondary amines **17a–c** to give the carboxamides **24a** and **25b,c** in 42–79% yields. Reduction of the carboxamides **24a** and **25b,c** with $LiAlH_4$ in refluxing THF furnished the title compounds **15a,b** and **26c** in 50–54% yields (Scheme 3, Table 2).



Scheme 3

Reagents and conditions: i: R^1NHNH_2 **9a**,**h**, MeOH, reflux.[12a] ii: NaOH–H_2O, r.t. iii: CDI, MeCN, r.t., then Bn(Me)NH **17a** or pyrrolidine **17b** or Bn_2NH **17c**, MeCN, r.t. iv: $LiAlH_4$, THF, 60 °C.

Table 2. Selected experimental data for compounds **15** and **22–26**

Compound	R^1	R^2	R^3	Yield (%)
22a	Ph	-	-	62[12a]
22b	4-methoxyphenyl	-	-	43
23a	Ph	-	-	94
23b	4-methoxyphenyl	-	-	79
24a	Ph	Me	CH_2Ph	48
25b	4-methoxyphenyl	$-(CH_2)_4-$		79
25c	Ph	CH_2Ph	CH_2Ph	42
15a	Ph	Me	CH_2Ph	50
15b	4-methoxyphenyl	$-(CH_2)_4-$		54
26c	Ph	CH_2Ph	CH_2Ph	50

The structures of novel compounds **6b**,**c**, **10a–e**, **11f,g**, **12b,c**, **13c**, **14**, **15a,b**, **22b**, **24a**, **25b,c**, and **26c** were determined by spectroscopic methods (IR, ^1H and ^{13}C NMR, NOESY spectroscopy, and MS) and by elemental analyses for C, H, and N. Compounds **23a,b**, **24a**, and **25b,c** were not obtained in analytically pure form. The identities of carboxamides **24a** and **25b,c** were confirmed by ^1H NMR, ^{13}C NMR and HRMS, while the intermediate carboxylic acids **23a,b** were characterized only by ^1H NMR and HRMS. Physical and spectral data for known compounds **18a**,[10a] **18b**,[10b,c] **19a**,[11a] **19b**,[11b] and **22a**[12a] were in agreement with the literature data.

Like related 5-hydroxypyrazoles,[2–4,13] the novel derivatives **6**, **10–13**, **15**, and **22–26** can exist in three tautomeric forms, the fully unsaturated "OH-tautomer" (5-hydroxy-1*H*-pyrazole, **6**, **10, 12–15**, **23**, **24**) and the partially unsaturated "NH-tautomer" (1*H*-pyrazol-3(2*H*)-one, **11**) and "CH-tautomer" (1*H*-pyrazol-5(4*H*)-one, **22**, **25**, **26**). In the solid state, the tautomerism of novel compounds **6**, **10–13**, **15**, and **22–26** was studied by IR. Absence of C=O vibrations indicate that pyrazoles **6b**,**c** and **15a**,**b** exist as the 5-hydroxy-1*H*-pyrazoles (OH-tautomers), whereas absorption at 1700–1750 cm^{-1} is in agreement with the 1*H*-pyrazol-5(4*H*)-one form for compounds **22b**, **25b,c**, and **26c** (CH-tautomers). Unambiguous discrimination between the OH- and the NH-tautomers for the *N*-acylated compounds **10–13** and **24** was not possible, due to carboxamide absorption at ~1640 cm^{-1}. However, the absorption band at ~1690 cm^{-1} (Boc) and absence of C=O vibrations at ~1640 cm^{-1} support the OH-tautomeric form of **10a–e**, while absorption bands at ~1690 cm^{-1} and ~1640 cm^{-1} are in agreement with the NH-tautomeric form of 1-heteroarylpyrazoles **11f,g**. Accordingly, the *N*-acylated 1-methylpyrazole **12b** and 1-phenylpyrazoles **12c**, **13c**, and **24a** exhibiting single C=O absorption bands at ~1640 cm^{-1} most probably exist as the OH-tautomers. In solution, the tautomer equilibrium was solvent-depended. In DMSO-d_6, chemical shifts of 4-H (δ ~ 5.5 ppm) and 5-C (δ ~ 153 ppm) were in agreement with the 1*H*-pyrazol-5-ols **6b**,**c**, **10a–e**, **12b**,**c**, **13c**, **15b**, **22b**, **23a,b**, **24a**, **25b,c**, and **26c**. Broad signals for the 4-H and methylene protons and the corresponding carbon nuclei indicated fast tautomerisation between the OH- and the NH-tautomer in these compounds. In $CDCl_3$, on the other hand, a singlet for the 4-CH_2 group at ~3.5 ppm clearly indicated the 1*H*-pyrazol-5(4*H*)-ones **13c**, **15a**, **22b**, **24a**, **25b,c**, and **26c**. These data are also in agreement with the literature data on tautomerism of related pyrazolones (Figure 2).[2,4,13]

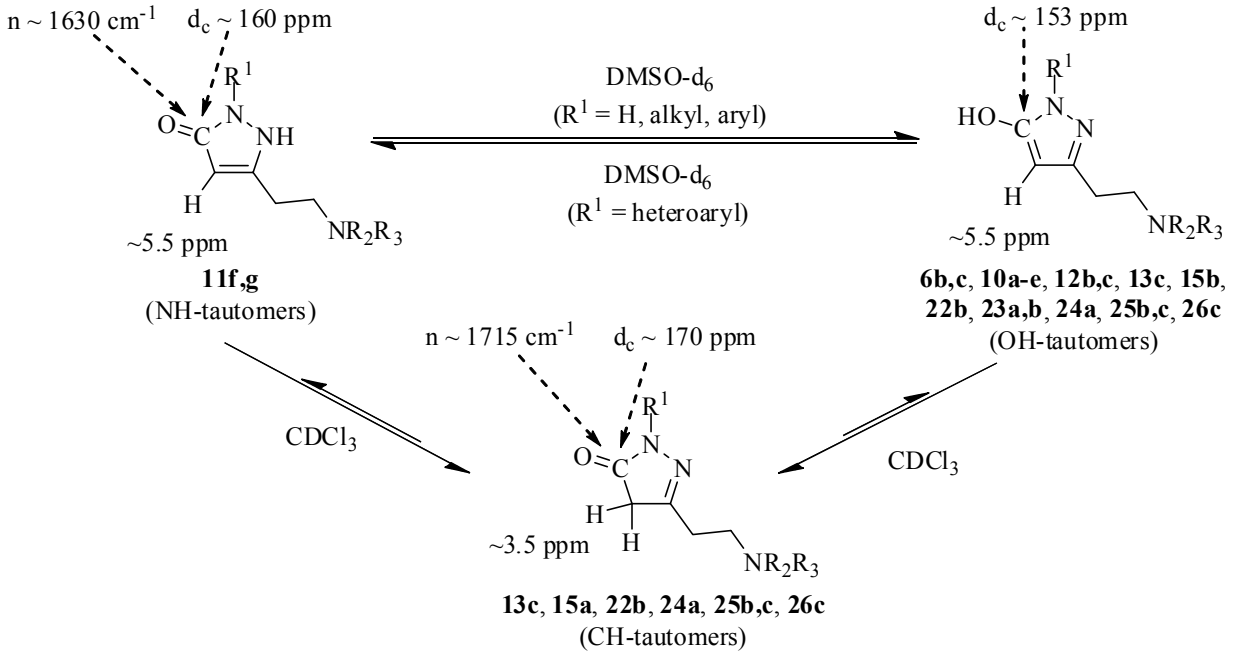


Figure 2. Tautomeric forms of pyrazole derivatives **6**, **10–13**, **15**, and **22–26**.

Conclusions

In summary, two synthetic methods for the preparation of a novel type of pyrazole analogues of histamine **6**, **15**, and **26** were developed. The first method starts from Boc-*β*-alanine **7**, which is transformed in three steps into the title compounds, 1-substituted 3-(2-aminophenyl)-1*H*-pyrazol-5(4*H*)-ones **6**. Further acylation of **6** in methanol produced the *N*-acyl derivatives **12** and **13**, while acylation of **6c** in dichloromethane led to the N,O-diacylated compound **14**. The second method enables access to *N,N*-dialkyl analogues **15**. It comprises cyclisation of dialkyl acetone-1,3-dicarboxylate **21** with monosubstituted hydrazines **9** to give alkyl pyrazolone-3-acetates **22**, followed by a three-step transformation into 3-(2-(dialkylamino)phenyl)-1*H*-pyrazol-5-ols **15** and **26**. These synthetic methods enable easy access to a novel type of histamine analogues as interesting molecules for biological studies.

Experimental Section

General. Melting points were determined on a Kofler micro hot stage and on a Stanford Research Systems MPA100 OptiMelt automated melting point system. 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 and on Bruker Avance III UltraShield 500 plus at 500 MHz for ^{1}H and 126 MHz for ^{13}C nucleus, using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, as solvents. Mass spectra were recorded on an AutoSpecQ spectrometer and Agilent 6224 Accurate Mass TOF LC/MS, IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN Analyzer 2400 II. Column chromatography (CC) and flash chromatography (FC) were performed on silica gel (Fluka, Silica gel 60, particle size: 0.035-0.070 mm).
Boc-*β*-alanine **7**, hydrazines **9a–h**, methyl acrylate **16**, amines **17a–c**, and dimethyl acetone-1,3-*d*icarboxylate **21** are commercially available (Sigma-Aldrich). Methyl 5-(*tert*-butoxycarbonylamino)-3-oxopentanoate **8**[5] and methyl 2-(5-oxo-1-phenyl-4,5-*d*ihydro-1*H*-pyrazol-3-yl)acetate **22a**[12a] were prepared following the literature procedures.

Preparation of 1'-substituted *tert*-butyl 2-(5-hydroxy-1*H*-pyrazol-3-yl)ethylcarbamates 10a–e and *tert*-butyl 2-(5-oxo-2,5-dihydro-1*H*-pyrazol-3-yl)ethylcarbamates 11f,g. A mixture of **8** (245 mg, 1 mmol), methanol (5 mL), and hydrazine derivative **9a–g** (1 mmol)[14] was stirred under reflux for 5 h, and cooled to r.t. Compounds **10a**, **10e**, and **11f** precipitated from the reaction mixtures and were collected by filtration to give **10a,e** and **11f**. Compounds **10b–d** and **11g** did not precipitate from the reaction mixtures, which were evaporated in vacuo and the residues were chromatographed over silica gel (EtOH/EtOAc or EtOAc/hexanes, column dimensions: 1.5×7 cm). Fractions containing the product were combined and evaporated *in vacuo* to give **10b–d** and **11g**.

***tert*-Butyl 2-(5-hydroxy-1*H*-pyrazol-3-yl)ethylcarbamate (10a).** Prepared from **8** (245 mg, 1 mmol) and hydrazine hydrate **9a** (50 μL, 50 mg, 1 mmol). White solid, yield 48%, 108 mg, mp 188–191 °C, IR (ν_{max}, cm^{-1}): 3380, 2982, 1689 (C=O), 1613, 1528, 1460, 1364, 1271, 1246, 1171, 974, 759. ^{1}H NMR (500 MHz, DMSO-d_6), δ_H 1.38 (9H, s, *t*-Bu), 2.56 (2H, t, $^3J_{HH}$ = 7.5 Hz, CH_2CH$_2$NH), 3.10 (2H, br q, $^3J_{HH}$ = 6.9 Hz, CH$_2$CH_2NH), 5.25 (1H, br s, 4-H of pyrazole), 6.86 (1H, br t, $^3J_{HH}$ = 6.3 Hz, N*H*Boc), 9.44 (1H, br s, 1-H), 11.14 (1H, br s, OH). ^{13}C NMR (126 MHz, DMSO-d_6), δ_C 26.5, 28.3, 77.6, 77.8, 88.3, 141.8, 155.5, 160.8. MS, *m/z* = 228 (MH^+), HRMS (ESI), *m/z* = 228.1335 (MH^+), $C_{10}H_{18}N_3O_3$ requires 228.1343. Anal. Calcd for $C_{10}H_{17}N_3O_3$ (227.26): C, 52.85; H, 7.84; N, 18.49%, Found: C, 52.83; H, 7.60; N; 18.46%.

***tert*-Butyl 2-(5-hydroxy-1-methyl-1*H*-pyrazol-3-yl)ethylcarbamate (10b).** Prepared from **8** (245 mg, 1 mmol) and methylhydrazine **9b** (50 μL, 46 mg, 1 mmol), CC (EtOAc/hexanes, 1:1). White solid, yield 73%, 177 mg, mp 160–162 °C, IR (ν_{max}, cm^{-1}): 3376, 2982, 1690 (C=O), 1533, 1459, 1401, 1270, 1173, 1039, 1000, 974, 748, 684. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 1.37 (9H, s, *t*-Bu), 2.45 (2H, bt t, $^3J_{HH}$ = 7.7 Hz, CH_2CH$_2$NH), 3.08 (2H, br m, CH$_2$CH_2NH), 3.41 (3H, s, NMe), 5.16 (1H, br s, 4-H of pyrazole), 6.73 (1H, br s, N*H*Boc), 10.64 (1H, br s, OH). ^{13}C NMR (75.5 MHz, DMSO-d_6), δ_C 28.3, 29.1, 32.5, 77.5, 77.8, 85.2, 147.3, 153.0, 155.5. MS, *m/z* = 242 (MH^+), HRMS (ESI), *m/z* = 242.1494 (MH^+), $C_{11}H_{19}N_3O_3$ requires 242.1499. Anal. Calcd for $C_{11}H_{19}N_3O_3$ (241.29): C, 54.76; H, 7.94; N, 17.41%, Found: C, 54.76; H, 8.05; N; 17.29%.

***tert*-Butyl 2-(5-hydroxy-1-phenyl-1*H*-pyrazol-3-yl)ethylcarbamate (10c).** Prepared from **8** (245 mg, 1 mmol) and phenylhydrazine **9c** (103 μL, 108 mg, 1 mmol), CC (EtOAc/hexanes, 1:2). Beige solid, yield 83%, 250 mg, mp 155–157 °C. IR (ν_{max}, cm^{-1}): 3218, 3050, 2866, 1669 (C=O), 1601, 1560, 1455, 1409, 1365, 1306, 1256, 1160, 1060, 1037, 964, 868, 761, 694, 644. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.41 (9H, s, *t*-Bu), 2.67 (2H, br t, $^3J_{HH}$ = 6.3 Hz, CH_2CH$_2$NH), 3.49 (2H, br s, 4'-CH$_2$), 3.52 (2H, br q, $^3J_{HH}$ = 6.2 Hz, CH$_2$CH_2NH), 4.87 (1H, br s, N*H*Boc), 7.19 (1H, tt, $^4J_{HH}$ = 1.1 Hz, $^3J_{HH}$ = 7.4 Hz, *p*-Ph), 7.36–7.40 (2H, m, *m*-Ph), 7.82–7.88 (2H, m, *o*-Ph). ^{1}H NMR (500 MHz, DMSO-d_6), δ_H 1.38 (9H, s, *t*-Bu), 2.58 (2H, br t, $^3J_{HH}$ = 7.5 Hz, CH_2CH$_2$NH), 3.18 (2H, br q, $^3J_{HH}$ = 6.8 Hz, CH$_2$CH_2NH), 5.40 (1H, br s, 4-H of pyrazole), 6.88 (1H, br s, N*H*Boc), 7.21 (1H, t, $^3J_{HH}$ = 7.4 Hz, *p*-Ph), 7.41 (2H, t, $^3J_{HH}$ = 7.9 Hz, *m*-Ph), 7.68 (2H, d, $^3J_{HH}$ = 7.8 Hz, *o*-Ph), 11.53 (1H, br s, OH). ^{13}C NMR (126 MHz, DMSO-d_6), δ_C 28.2, 28.3, 29.2, 77.6, 87.0, 120.6, 125.1, 128.8, 138.9, 150.0, 153.1, 155.5. MS, *m/z* = 304 (MH^+), HRMS (ESI), *m/z* = 304.1650 (MH^+), $C_{16}H_{22}N_3O_3$ requires 304.1656. Anal. Calcd for $C_{16}H_{21}N_3O_3$ (303.36): C, 63.35; H, 6.98; N, 13.85%, Found: C, 63.24; H, 7.08; N, 13.60%.

***tert*-Butyl 2-(5-hydroxy-1-(4-chlorophenyl)-1*H*-pyrazol-3-yl)ethylcarbamate (10d).** Prepared from **8** (245 mg, 1 mmol) and 4-chlorophenylhydrazine hydrochloride **9d** (179 mg, 1 mmol), CC (EtOAc/hexanes, 1:2). Grayish solid, yield 61%, 206 mg, mp 107–108 °C. IR (ν_{max}, cm^{-1}): 3393, 2980, 2928, 1688 (C=O), 1526, 1493, 1397, 1366, 1274, 1254, 1168, 1092, 1028, 1012, 842, 788, 755, 659. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.39 (9H, s, *t*-Bu), 2.66 (2H, br t, $^3J_{HH}$ = 6.3 Hz, CH_2CH$_2$NH), 3.49 (2H, br s, 4'-CH$_2$), 3.49 (2H, br q, $^3J_{HH}$ = 6.3 Hz, CH$_2$CH_2NH), 4.83 (1H, br s, N*H*Boc), 7.34 and 7.83 (4H, 2dt, 1:1, $^3J_{HH}$ = 2.6, 9.0 Hz, C_6H_4). ^{1}H NMR (500 MHz, DMSO-d_6),

δ_H 1.38 (9H, s, *t*-Bu), 2.58 (2H, br t, $^3J_{HH}$ = 7.2 Hz, C*H*$_2$CH$_2$NH), 3.18 (2H, br q, $^3J_{HH}$ = 6.5 Hz, CH$_2$C*H*$_2$NH), 5.42 (1H, s, 4-H of pyrazole), 6.88 (1H, br s, N*H*Boc), 7.48 and 7.77 (4H, 2dt, 1:1, $^3J_{HH}$ = 2,5, 8.7 Hz, C_6H_4), 11.73 (1H, br s, OH). ^{13}C NMR (126 MHz, DMSO-d_6), δ_C 28.1, 28.3, 29.2, 77.5, 87.1, 121.8, 128.8, 129.0, 137.9, 150.4, 153.2, 155.5. MS, *m/z* = 338 (MH^+), HRMS (ESI), *m/z* = 338.1264 (MH^+), $C_{16}H_{21}ClN_3O_3$ requires 338.1266. Anal. Calcd for $C_{16}H_{20}ClN_3O_3$ (337.80): C, 56.89; H, 5.97; N, 12.44%, Found: C, 56.87; H, 5.80; N, 12.28%.

4-(3-(2-(*tert*-butoxycarbonylamino)ethyl)-5-hydroxy-1*H*-pyrazol-1-yl)benzoic acid (10e). Prepared from **8** (245 mg, 1 mmol) and 4-hydrazinobenzoic acid **9e** (152 mg, 1 mmol). White solid, yield 55%, 192 mg, mp 187–189 °C (decomp.), IR (ν_{max}, cm^{-1}): 3328, 1691 (C=O), 1649 (C=O), 1621, 1604, 1588, 1573, 1539, 1511, 1407, 1366, 1337, 1237, 1186, 1154, 993, 854, 773, 703, 684. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 1.38 (9H, s, *t*-Bu), 2.60 (2H, br t, $^3J_{HH}$ = 7.3 Hz, C*H*$_2$CH$_2$NH), 3.19 (2H, br q, $^3J_{HH}$ = 6.7 Hz, CH$_2$C*H*$_2$NH), 5.46 (1H, br s, 4-H of pyrazole), 6.89 (1H, br s, N*H*Boc), 7.91 and 7.98 (4H, 2 br d, 1:1, $^3J_{HH}$ = 8.7 Hz, C_6H_4), 11.90 and 12.89 (2H, 2 br s, 1:1, OH and COOH). ^{13}C NMR (75.5 MHz, DMSO-d_6), δ_C 28.1, 28.3, 29.3, 77.6, 87.5, 119.4, 126.7, 130.3, 142.5, 151.1, 153.8, 155.5, 166.9. MS, *m/z* = 348 (MH^+), HRMS (ESI), *m/z* = 348.1548 (MH^+), $C_{17}H_{22}N_3O_5$ requires 348.1554. Anal. Calcd for $C_{17}H_{21}N_3O_5$ (347.37): C, 58.78; H, 6.09; N, 12.10%, Found: C, 58.78; H, 6.16; N, 12.06%.

***tert*-Butyl 2-(5-oxo-1-(6-phenylpyridazin-3-yl)-2,5-dihydro-1*H*-pyrazol-3-yl)ethylcarbamate (11f).** Prepared from **8** (245 mg, 1 mmol) and 3-hydrazino-6-phenylpyridazine **9f** (186 mg, 1 mmol). White solid, yield 81%, 310 mg, mp 242–246 °C, IR (ν_{max}, cm^{-1}): 3321, 3076, 1713 (C=O), 1634 (C=O), 1562, 1547, 1455, 1422, 1366, 1296, 1247, 1167, 1131, 784, 690. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 1.38 (9H, s, *t*-Bu), 2.69 (2H, br t, $^3J_{HH}$ = 7.0 Hz, C*H*$_2$CH$_2$NH), 3.25 (2H, br q, $^3J_{HH}$ = 6.8 Hz, CH$_2$C*H*$_2$NH), 5.28 (1H, br s, 4-H of pyrazole), 6.97 (1H, br t, $^3J_{HH}$ = 5.0 Hz, N*H*Boc), 7.49–7.61 (3H, m, *p*-Ph, *m*-Ph), 8.12–8.17 (2H, m, *o*-Ph), 8.36 (1H, d, $^3J_{HH}$ = 9.4 Hz, 4"-H), 8.65 (1H, br s, 5"-H), 12.52 (1H, br s, 2'-H). ^{13}C NMR (126 MHz, DMSO-d_6), δ_C 26.8, 28.3, 38.4, 77.7, 101.7, 116.7, 126.1, 126.4, 129.1, 129.9, 135.6, 153.3, 155.5, 162.7, 167.0, 171.4. MS, *m/z* = 382 (MH^+), HRMS (ESI), *m/z* = 382.1866 (MH^+), $C_{20}H_{24}N_5O_3$ requires 382.1874. Anal. Calcd for $C_{20}H_{23}N_5O_3$ (381.43): C, 62.98; H, 6.08; N, 18.36%, Found: C, 62.85; H, 5.99; N; 18.46%.

***tert*-Butyl 2-(1-(imidazo[1,2-*b*]pyridazin-6-yl)-5-oxo-2,5-dihydro-1*H*-pyrazol-3-yl)ethyl-carbamate (11g).** Prepared from **8** (245 mg, 1 mmol) and 6-hydrazinoimidazo[4,3-*b*]pyridazine **9g** (149 mg, 1 mmol), CC: EtOAc. Yellowish solid, yield 66%, 227 mg, mp 221–225 °C, IR (ν_{max}, cm^{-1}): 3370, 3137, 2978, 1716 (C=O), 1684 (C=O), 1638 (C=O), 1573, 1544, 1522, 1403, 1403, 1366, 1327, 1288, 1250, 1168, 1061, 813, 778. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 1.38 (9H, s, *t*-Bu), 2.64 (2H, br t, $^3J_{HH}$ = 7.1 Hz, C*H*$_2$CH$_2$NH), 3.23 (2H, br q, $^3J_{HH}$ = 7.1 Hz, CH$_2$C*H*$_2$NH), 5.28 (1H, br s, 4-H of pyrazole), 6.94 (1H, br s, N*H*Boc), 7.76–7.78 (1H, m, 3"-H), 8.15–8.28 (3H, m, 2"-H, 7"-H, 8"-H), 11.92 (1H, br s, 2'-H). ^{13}C NMR (126 MHz, DMSO-d_6), δ_C 28.1, 28.3, 38.7, 77.7, 88.0, 92.4, 110.2, 117.2, 127.1, 133.7, 137.1, 146.4, 153.9, 155.6. MS, *m/z* = 345 (MH^+), HRMS (ESI), *m/z* = 345.1669 (MH^+), $C_{16}H_{21}N_6O_3$ requires 345.1670. Anal. Calcd for $C_{16}H_{20}N_6O_3$ (344.37): C, 55.80; H, 5.85; N, 24.40%, Found: C, 55.73; H, 5.87; N; 24.33%.

General procedure for the synthesis of 1-substituted 3-(2-aminoethyl)-5-hydroxy-1*H*-pyrazoles dihydrochlorides (6b,c)

2 M HCl-EtOAc (25 mL, 50 mmol) was added to a stirred suspension of **10** (5 mmol) in anhydrous ethanol (25 mL) and the mixture was stirred at r.t. for 3 h. The precipitate was collected by filtration and washed subsequently with EtOAc (25 mL) and ether (25 mL) to give **6**.

3-(2-Aminoethyl)-5-hydroxy-1-methyl-1*H*-pyrazole dihydrochloride (6b). Prepared from **10b** (1.206 g, 5 mmol). White solid, yield 78%, 832 mg, mp 197–200 °C, IR (ν_{max}, cm^{-1}): 1609, 1539, 1287, 1096, 945, 831, 673. ^{1}H NMR (500 MHz, DMSO-d_6), δ_H 2.90 (2H, br t, $^3J_{HH}$ = 7.2 Hz, CH_2CH$_2$NH$_3^+$), 3.10 (2H, br sextet, $^3J_{HH}$ = 7.2 Hz, CH_2CH$_2$NH$_3^+$), 3.60 (3H, s, CH$_3$), 5.75 (1H, s, 4-H of pyrazole), 8.23 (3H, br s, NH$_3^+$), OH exchanged. ^{13}C NMR (125 MHz, DMSO-d_6), δ_C 24.6, 32.3, 37.3, 88.7, 144.7, 154.8. MS, *m/z* = 142 (MH$^+$), HRMS (ESI), *m/z* = 142.0969 (MH$^+$), $C_6H_{12}N_3O$ requires 142.0975. Anal. Calcd for $C_6H_{11}N_3O{\cdot}2^1/_6HCl$ (220.17): C, 32.73; H, 6.03; N, 19.09%, Found: C, 32.67; H, 6.39; N, 18.90%.

3-(2-Aminoethyl)-5-hydroxy-1-phenyl-1*H*-pyrazole dihydrochloride (6c). Prepared from **10c** (1.515g, 5 mmol). White solid, yield 84%, 1.159 g, mp 192–195 °C, IR (ν_{max}, cm^{-1}): 3381, 1603, 1547, 1497, 1464, 1366, 1310, 1145, 942, 812, 754, 691. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 2.92 (2H, t, $^3J_{HH}$ = 7.5 Hz, CH_2CH$_2$NH$_3^+$), 3.13 (2H, br sextet, $^3J_{HH}$ = 6.3 Hz, CH$_2$CH_2NH$_3^+$), 5.72 (1H, s, 4-H of pyrazole), 7.32 (1H, br t, $^3J_{HH}$ = 7.4 Hz, *p*-Ph), 7.46 (2H, br t, $^3J_{HH}$ = 7.9 Hz, *m*-Ph), 7.71 (2H, br d, $^3J_{HH}$ = 7.7 Hz, *o*-Ph), 8.30 (3H, br s, NH$_3^+$), OH exchanged. ^{13}C NMR (75.5 MHz, DMSO-d_6), δ_C 25.9, 37.7, 88.4, 121.8, 126.5, 129.1, 137.3, 148.0, 154.4. MS, *m/z* = 204 (MH$^+$), HRMS (ESI), *m/z* = 204.1130 (MH$^+$), $C_{11}H_{14}N_3O$ requires 204.1131. Anal. Calcd for $C_{11}H_{13}N_3O{\cdot}2HCl$ (276.16): C, 47.84; H, 5.47; N, 15.22%, Found: C, 47.22; H, 5.69; N, 14.95%.

General procedures for acylation of amines 6b,c. Synthesis of 1-substituted 3-(2-(acylamino)ethyl)-5-hydroxy-1*H*-pyrazoles (12b,c)and (13c)

Acetic anhydride (0.1 mL, 1 mmol) or benzoyl chloride (0.115 μL, 1 mmol) was added to a stirred cold (0 °C) solution of amine **6** (1 mmol) and 4-methylmorpholine (440 μL, 4 mmol) in anhydrous methanol (5 mL) and the mixture was stirred at 0 °C for 1 h and then at r.t. for 12 h. Volatile component were evaporated *in vacuo* and the residue was chromatographed over silica gel (10% EtOH/EtOAc). Fractions containing the product were combined and evaporated in vacuo to give **12b,c** and **13c**.

***N*-(2-(5-Hydroxy-1-methyl-1*H*-pyrazol-3-yl)ethyl)acetamide (12b).** Prepared from **6b** (214 mg, 1 mmol). White solid, yield 62%, 113 mg, mp 129–133 °C, IR (ν_{max}, cm^{-1}): 3255, 3084, 2953, 2884, 1633 (C=O), 1562, 1479, 1424, 1360, 1279, 1199, 1184, 1096, 1062, 1037, 894, 849, 768, 746, 716, 685, 674, 606. ^{1}H NMR (500 MHz, DMSO-d_6), δ_H 1.78 (3H, s, MeCO), 2.46 (2H, br t, $^3J_{HH}$ = 7.5 Hz, CH_2CH$_2$NH), 3.30 (2H, br dt, $^3J_{HH}$ = 5.9, 7.5 Hz, CH$_2$CH_2NH), 3.41 (3H, s, 1'-Me), 5.17 (1H, s, 4-H of pyrazole), 7.83 (3H, br s, NH), 10.66 (1H, br s OH). ^{13}C NMR (126 MHz, DMSO-d_6), δ_C 22.7, 28.8, 32.6, 38.5, 85.0, 147.4, 152.5, 169.1. MS, *m/z* = 184 (MH$^+$), HRMS (ESI), *m/z* = 184.1077 (MH$^+$), $C_8H_{14}N_3O_2$ requires 184.1081. Anal. Calcd for $C_8H_{13}N_3O_2$ (183.21): C, 52.45; H, 7.15; N, 22.94%, Found: C, 52.25; H, 7.38; N, 22.56%.

***N*-(2-(5-Hydroxy-1-phenyl-1*H*-pyrazol-3-yl)ethyl)acetamide (12c).** Prepared from **6c** (276 mg, 5 mmol) and acetic anhydride. Yellowish solid, yield 87%, 213 mg, mp 150–155 °C, IR (ν_{max}, cm^{-1}): 3312, 1640 (C=O), 1577, 1558, 1497, 1398, 1358, 1308, 1202, 1150, 787, 751, 687. ^{1}H NMR (500 MHz, DMSO-d_6), δ_H 1.80 (3H, s, Me), 2.59 (2H, br t, $^3J_{HH}$ = 7.4 Hz, CH_2CH$_2$NH), 3.30 (2H, br q, $^3J_{HH}$ = 7.3 Hz, CH$_2$CH_2NH), 5.41 (1H, br s, 4-H of pyrazole), 7.21 (1H, br t, $^3J_{HH}$ = 7.4 Hz, *p*-Ph), 7.42 (2H, br t, $^3J_{HH}$ = 8.0 Hz, *m*-Ph), 7.72 (2H, br d, $^3J_{HH}$ = 7.8 Hz, *o*-Ph), 7.90 (3H, br s, NH), 11.46 (1H, br s OH). ^{13}C NMR (126 MHz, DMSO-d_6), δ_C 22.7, 28.9, 38.2, 86.9, 120.7, 125.1, 128.8, 138.9, 150.0, 153.0, 169.1. MS, *m/z* = 246 (MH^+), HRMS (ESI), *m/z* = 246.1231 (MH^+), $C_{13}H_{16}N_3O_2$ requires 246.1237. Anal. Calcd for $C_{13}H_{15}N_3O_2$ (245.28): C, 63.66; H, 6.16; N, 17.13%, Found: C, 63.47; H, 6.30; N, 16.91%.

***N*-(2-(5-Hydroxy-1-phenyl-1*H*-pyrazol-3-yl)ethyl)benzamide (13c).** Prepared from **6c** (276 mg, 1 mmol) and benzoyl chloride. Yellowish solid, yield 53%, 163 mg, mp 151–155 °C, IR (ν_{max}, cm^{-1}): 3280, 1638 (C=O), 1543, 1495, 1396, 1312, 1150, 843, 677. ^{1}H NMR (500 MHz, DMSO-d_6), δ_H 2.76 (2H, br t, $^3J_{HH}$ = 7.4 Hz, CH_2CH$_2$NH), 3.54 (2H, br q, $^3J_{HH}$ = 7.3 Hz, CH$_2$CH_2NH), 5.47 (1H, br s, 4-H of pyrazole), 7.22 (1H, br t, $^3J_{HH}$ = 7.4 Hz, *p*-Ph), 7.40–7.49 (4H, m, 2×*m*-Ph), 7.50–7.55 (1H, m, *p*-Ph), 7.73 and 7.86 (4H, 2br d, 1:1, $^3J_{HH}$ = 7.5 Hz, 2×*o*-Ph), 8.60 (1H, br s, NH), 11.55 (1H, br s, OH). ^{1}H NMR (500 MHz, $CDCl_3$), δ_H 2.81 (2H, br t, $^3J_{HH}$ = 6.2 Hz, CH_2CH$_2$NH), 3.51 (2H, br s, 4-CH$_2$ of pyrazole), 3.88 (2H, br q, $^3J_{HH}$ = 6.2 Hz, CH$_2$CH_2NH), 6.75 (1H, br s, NH), 7.19 (1H, br t, $^3J_{HH}$ = 7.4 Hz, *p*-Ph), 7.36–7.44 (4H, m, 2×*m*-Ph), 7.45–7.52 (1H, m, *p*-Ph), 7.72–7.77 and 7.80–7.86 (4H, 2m, 1:1, 2×*o*-Ph). ^{13}C NMR (126 MHz, DMSO-d_6), δ_C 28.8, 39.0, 87.0, 118.0, 120.7, 125.2, 127.2, 128.3, 128.8, 131.1, 134.6, 150.0, 153.0, 166.1. MS, *m/z* = 308 (MH^+), HRMS (ESI), *m/z* = 308.1385 (MH^+), $C_{18}H_{18}N_3O_2$ requires 308.1394. Anal. Calcd for $C_{18}H_{17}N_3O_2$ (307.35): C, 70.34; H, 5.58; N, 13.67%, Found: C, 70.18; H, 5.60; N, 13.35%.

3-(2-(Benzoylamino)ethyl)-1-phenyl-1*H*-pyrazol-5-yl benzoate (14). Benzoyl chloride (0.230 mL, 2 mmol) was added to a stirred suspension of amine **6c** (276 mg, 1 mmol) in a mixture of anhydrous dichloromethane (10 mL) and 4-methylmorpholine (0.66 mL, 6 mmol) and the mixture was stirred at r.t. for 12 h. Volatile component were evaporated *in vacuo* and the residue was chromatographed over silica gel (50% EtOAc/hexanes). Fractions containing the products were combined and evaporated *in vacuo* to give **14**. Yellow solid, yield 79%, 326 mg, mp 109–112 °C, IR (ν_{max}, cm^{-1}): 3289, 1753 (C=O), 1632 (C=O), 1445, 1315, 1247, 1076, 760, 697. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 3.01 (2H, t, $^3J_{HH}$ = 6.3 Hz, CH_2CH$_2$NH), 3.86 (2H, q, $^3J_{HH}$ = 6.0 Hz, CH$_2$CH_2NH), 6.36 (1H, s, 4-H of pyrazole), 7.16 (3H, br s, NH), 7.31–7.53 (8H, m, 8H of Ph), 7.59–7.68 (3H, m, 3H of Ph), 7.78–7.83 (2H, m, 2H of Ph), 8.05–8.11 (2H, m, 2H of Ph). ^{13}C NMR (126 MHz, DMSO-d_6), δ_C 28.7, 38.9, 95.8, 122.7, 127.17, 127.23, 127.3, 128.3, 129.25, 129.30, 130.1, 131.1, 134.6, 134.8, 137.6, 144.0, 150.3, 161.8, 166.2. MS, *m/z* = 412 (MH^+), HRMS (ESI), *m/z* = 412.1649 (MH^+), $C_{25}H_{22}N_3O_3$ requires 412.1656. Anal. Calcd for $C_{25}H_{21}N_3O_3$ (411.45): C, 63.66; H, 6.16; N, 17.13%, Found: C, 63.47; H, 6.30; N, 16.91%.

General procedure for the synthesis of *N*,*N*-dialkyl-*β*-alanines (19a,b)

First, the esters **18a** and **18b** were prepared following slightly modified literature procedure.[10a] Amine **17** (141 mmol) was added to a cooled (0°C) solution of methyl acrylate **16** (12.7 mL, 141 mmol) in dichloromethane (150 mL) and the reaction mixture was stirred at room temperature for 2–24 h. The solvent was evaporated *in vacuo* to yield the *β*-amino ester **18** as a yellowish oil, which was characterized by ^{1}H NMR.

Then, 4.4 M aq. NaOH (100 mL, 440 mmol) was added to the ester **18** (141 mmol) and the mixture was vigorously stirred at r.t. for 2–5 h. Reaction mixture was cooled to 0 °C and neutralized with 6 M aq. HCl (73.3 mL), stirred at r.t. for 15 min, and washed with EtOAc (50 mL) to remove non-polar impurities. The aqueous phase was purified by ion-exchange chromatography over Dowex® 50 W cation exchange resin. The product was eluted from the resin with 4% aq. ammonia (1 L), volatile components were evaporated *in vacuo*, and the residue was re-suspended five times in EtOH (100 mL) to remove H_2O and five times in CH_2Cl_2 (100 mL) to remove EtOH. The residue was dried *in vacuo* (0.01 Torr, 40 °C) to give the *β*-amino acids **19a,b**, which were characterized by NMR.

Methyl 3-(benzyl(methyl)amino)propanoate (18a).[10a] Prepared from **16** (12.7 mL, 141 mmol) and benzyl(methyl)amine **17a** (18.9 mL, 141 mmol), stirring for 24 h. Yellowish oil, yield: 100%, 29.02 g. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.20 (3H, s, NMe), 2.51 (2H, t, J = 7.1 Hz, 2-CH_2), 2.74 (2H, t, J = 7.1 Hz, 2-CH_2), 3.50 (2H, s, CH_2Ph), 3.66 (3H, s, OMe), 7.20–7.35 (5H, m, Ph).

Methyl 3-(pyrrolidin-1-yl)propanoate (18b).[10b,c] Prepared from **16** (12.7 mL, 141 mmol) and pyrrolidine **17a** (11.8 mL, 141 mmol), stirring for 2 h. Yellowish oil, yield: 100%, 22.01 g. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.74–1.82 (4H, m, 3'-CH_2 and 4'-CH_2), 2.47–2.58 (6H, m, 2'-CH_2, 5'-CH_2, and 2-CH_2), 2.74–2.81 (2H, m, 3-CH_2), 3.68 (3H, s, OMe).

3-(Benzyl(methyl)amino)propanoic acid (19a).[11a] Prepared from methyl 3-(benzyl(methyl)amino)propanoate **18a** (29.02 g, 140 mmol), stirring for 5 h. Brownish semi-solid, yield: 77%, 22.12 g. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (3H, s, NMe), 2.45 (2H, t, $^3J_{HH}$ = 7.1 Hz, 2-CH_2), 2.80 (2H, t, $^3J_{HH}$ = 7.1 Hz, 3-CH_2), 3.60 (2H, s, CH_2Ph), 7.15–7.31 (5H, m, Ph), 10.69 (1H, br s, COOH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.7, 40.75, 53.7, 61.1, 127.8, 128.59, 129.9, 136.1, 178.0.

3-(Pyrrolidin-1-yl)propanoic acid (19b).[11b] Prepared from methyl 3-(pyrrolidin-1-yl)propanoate **18b** (22.01 g, 140 mmol), stirring for 2 h. Brownish semi-solid, yield: 80%, 16.19 g. ^{1}H NMR (300 MHz, D_2O): δ 1.90–2.06 (4H, m, 3'-CH_2 and 4'-CH_2), 2.54 (2H, t, $^3J_{HH}$ = 7.3 Hz, 2-CH_2), 3.08–3.24 (6H, m, 3-CH_2, 2'-CH_2, and 5'-CH_2), COOH exchanged. ^{13}C NMR (75 MHz, D_2O): δ 23.1, 34.4, 52.3, 53.9, 178.5.

Synthesis of methyl 2-(1-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)acetate (22b). A mixture of **21** (0.803 mL, 5.28 mmol), (4-methoxyphenyl)hydrazine hydrochloride **9h** (922 mg, 5.28 mmol), toluene (15 mL), and Et_3N (0.736 mL, 5.28 mmol) was stirred at r.t. for 4 h and then at 80 °C for additional 2 h. The reaction mixture was purified directly by CC

(hexanes/EtOAc, 1:1) without the prior removal of volatile components (mainly toluene). Fractions containing the product were combined and evaporated *in vacuo*. The solid residue was re-crystallized from a mixture of EtOAc/*n*-heptane to give **22b**. White solid, yield: 43%, 600 mg, mp 141–142 °C, IR (ν_{max}, cm^{-1}): 3448, 1744 (C=O), 1637 (C=O), 1542, 1516, 1465, 1406, 1314, 1252, 1173, 1150, 1111, 1032, 1005, 840, 756, 630. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.58 and 3.60 (4H, 2s, 1:1, 2-CH_2, 4-CH_2 of pyrazole), 3.77 and 3.81 (6H, 2s, 1:1, 2×OMe), 6.88–6.96 (2H, m, *m*-C_6H_4), 7.67–7.75 (2H, m, *o*-C_6H_4). ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 3.54 (2H, s, CH_2), 3.63 and 3.77 (6H, 2s, 1:1, 2×OMe), 5.47 (1H, s, 4-H of pyrazole), 6.99 and 7.57 (4H, 2td, 1:1, $^4J_{HH}$ = 2.8 Hz, $^3J_{HH}$ = 9.1 Hz, C_6H_4), 11.44 (1H, s, OH). ^{13}C NMR (126 MHz, DMSO-d_6): δ_C 34.6, 51.7, 55.3, 87.4, 114.0, 122.7, 132.0, 144.6, 152.6, 157.0, 170.7. MS, *m/z* = 263 (MH^+), HRMS (ESI), *m/z* = 263.1035 (MH^+), $C_{13}H_{15}N_2O_4$ requires 263.1032. Anal. Calcd for $C_{13}H_{14}N_2O_4$ (262.26): C, 59.54; H, 5.38; N, 10.68%, Found: C, 59.54; H, 5.14; N, 10.61%.

General procedure for the preparation of carboxamides (24a) and (25b,c)

A suspension of the ester **22** (10 mmol) in 1.5 M aq. NaOH (40 mL) was vigorously stirred at r.t. for 24 h. Reaction mixture was neutralized with 3 M aq. HCl (20 mL) and stirred for additional 15 min at r.t. The product was extracted with EtOAc (3×100 mL), the combined organic phase was dried over anh. Na_2SO_4, filtered, and the volatile components were evaporated *in vacuo* to give **23a,b** as sticky resins, which were characterised by ^{1}H NMR and HRMS and then used for further amidation without purification. Under argon, the crude acid **23** (10 mmol) was dissolved in anh. THF (40 mL), 1,1'-carbonyldiimidazole (2.432 g, 15 mmol) was added, and the reaction mixture was stirred at r. t. for 2 h. Then, the corresponding amine **17** (40 mmol) was added and stirring at r.t. was continued for 3 h. Volatile components were evaporated *in vacuo*, the residue was dissolved in EtOAc (200 mL) and the resulting solution was washed with 1 M aq. $NaHSO_4$ (100 mL). The organic phase was dried over anh. Na_2SO_4, filtered, and volatile components were evaporated *in vacuo*. The residue was purified by CC (EtOAc/hexanes). Fractions containing the product were combined and volatile components were evaporated *in vacuo* to give **24** or **25** as a viscous oil.

2-(5-Hydroxy-1-phenyl-1*H*-pyrazol-3-yl)acetic acid (23a). Prepared from **21a** (2.46 g, 10 mmol). Yellow-orange resin, yield 94%, 2.064 g. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 3.45 (2H, s, CH_2), 5.49 (1H, s, 4-H of pyrazole), 7.18–7.28 (1H, m, *p*-Ph), 7.38–7.49 (2H, m, *m*-Ph), 7.68–7.74 (2H, m, *o*-Ph), 11.68 (1H, br s, OH), 12.25 (1H, br s, OH). MS, *m/z* = 219 (MH^+), HRMS (ESI), *m/z* = 219.0766 (MH^+), $C_{11}H_{11}N_2O_3$ requires 219.0770.

2-(5-Hydroxy-1-(4-methoxyphenyl)-1*H*-pyrazol-3-yl)acetic acid (23b). Prepared from **21b** (2.625 g, 10 mmol). Yellow-brown resin, yield 79%, 1.979 g. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 3.42 (2H, s, CH_2), 3.77 (3H, s, OMe), 5.45 (1H, s, 4-H of pyrazole), 6.95–7.03 and 7.52–7.61 (4H, 2m, 1:1, C_6H_4), 11.34 (1H, br s, OH), 12.29 (1H, br s, COOH). MS, *m/z* = 249 (MH^+), HRMS (ESI), *m/z* = 249.0867 (MH^+), $C_{12}H_{13}N_2O_4$ requires 219.0875.

***N*-Benzyl-2-(5-hydroxy-1-phenyl-1*H*-pyrazol-3-yl)-*N*-methylacetamide (24a).** Prepared from **23a** (2.181 g, 10 mmol) and benzyl(methyl)amine **17a** (4.844 g, 40 mmol), CC (EtOAc/hexanes, 2:1). Yellowish oil, yield 48%, 1.561 g, IR (ν_{max}, cm^{-1}): 3490, 1639 (C=O), 1559, 1496, 1453, 1401, 1112, 1020, 804, 759, 731, 692. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 3.01 (3H, s, Me), 3.63–3.72 (4H, m, 2-CH_2 and 4-CH_2 of pyrazole), 4.61 and 4.63 (2H, 2br s, 5:3, CH_2Ph), 7.14–7.22 (2H, m, 2H of Ph), 7.24–7.42 (6H, m, 6H of Ph), 7.77–7.86 (2H, m, 2H of Ph). ^{13}C NMR (300 MHz, $CDCl_3$), δ_C 33.8/34.0, 35.9/36.2, 42.1/42.2, 50.8/50.9, 118.58/118.60, 121.3/121.4, 127.5/127.6, 127.3/127.4, 128.3/128.4, 128.5/128.6, 136.3/136.4, 137.7/137.8, 154.6/154.7, 167.7/167.9, 170.7/170.9. ^{1}H NMR (500 MHz, DMSO-d_6), δ_H 2.79 and 2.98 (3H, 2s, 1:2, Me), 3.62 and 3.67 (2H, 2s, 1:2, 2-CH_2), 4.54 and 4.68 (2H, 2s, 2:1, CH_2Ph), 5.47 and 5.48 (1H, 2s, ~1:2, 4-H of pyrazole), 7.16–7.36 (8H, m, 8H of Ph), 7.38–7.46 (2H, m, 2H of Ph), 7.64–7.67 and 7.72–7.75 (1H, 2m, 1:2, 1H of Ph), 11.63 (1H, br s, OH). ^{13}C NMR (126 MHz, DMSO-d_6), δ_C 33.4/35.3, 34.6/34.8, 50.0/52.8, 87.7, 120.6/120.9, 125.3/125.4, 126.8/127.4, 127.0/127.3, 128.4/128.6, 128.8/128.9, 137.4/137.8, 138.8/138.9, 146.7, 153.2, 169.4/169.5. MS, *m/z* = 322 (MH^+), HRMS (ESI), *m/z* = 322.1549 (MH^+), $C_{19}H_{20}N_3O_2$ requires 322.1556.

1-(4-Methoxyphenyl)-3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-1*H*-pyrazol-5(4*H*)-one (25b). Prepared from **23b** (2.491 g, 10 mmol) and pyrrolidine **17b** (2.840 g, 40 mmol), CC (first EtOAc to elute less polar impurities, then MeOH/EtOAc, 1:9, to elute the product). Yellowish oil, yield 79%, 2.388 g, IR (ν_{max}, cm^{-1}): 3438, 2928, 2877, 1703 (C=O), 1621, 1557, 1511, 1454, 1340, 1298, 1249, 1172, 1024, 913, 833, 730. ^{1}H NMR (500 MHz, $CDCl_3$), δ_H 1.89 and 2.00 (4H, 2 quintets, 1:1, $^3J_{HH}$ = 6.8 Hz, 3"-CH_2, 4"-CH_2), 3.49 and 3.51 (4H, 2t, 1:1, $^3J_{HH}$ = 6.9 Hz, 2"-CH_2, 5"-CH_2), 3.53 and 3.68 (4H, 2s, 1:1, 2'-CH_2, 4-CH_2 of pyrazole), 3.81 (3H, s, OMe), 6.91 and 7.70 (4H, 2br d, 1:1, $^3J_{HH}$ = 9.1 Hz, C_6H_4). ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 1.70–1.93 (4H, m, 3"-CH_2, 4"-CH_2), 3.28 and 3.50 (4H, 2t, $^3J_{HH}$ = 6.9 Hz, 2"-CH_2, 5"-CH_2), 3.46 (2H, s, 1'-CH_2), 3.77 (3H, s, OMe), 5.40 (1H, s, 4-H of pyrazole), 6.95–7.03 and 7.52–7.60 (4H, 2m, 1:1, C_6H_4), 11.31 (1H, br s, OH). ^{13}C NMR (126 MHz, $CDCl_3$), δ_C 24.5, 26.2, 37.8, 42.5, 46.2, 47.1, 55.6, 114.1, 121.1, 131.4, 154.5, 157.2, 166.0, 170.9. MS, *m/z* = 302 (MH^+), HRMS (ESI), *m/z* = 302.1510 (MH^+), $C_{16}H_{20}N_3O_3$ requires 302.1505.

***N,N*-dibenzyl-2-(1-phenyl-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)acetamide (25c).** Prepared from **23a** (2.181 g, 10 mmol) and dibenzylamine **17c** (7.88 g, 40 mmol), CC (EtOAc/hexanes, 1:1). Yellowish semi-solid, yield 42%, 1.675 g, IR (ν_{max}, cm^{-1}): 3480, 1715 (C=O), 1633 (C=O), 1558, 1496, 1452, 1360, 1208, 1168, 1078, 954, 751, 694. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 3.65 (4H, s, 2-CH_2, 4-CH_2 of pyrazole), 4.52 and 4.64 (4H, 2 s, 1:1, 2×CH_2Ph), 7.12–7.42 (13H, m, 13H of Ph), 7.77–7.83 (2H, m, 2H of Ph). ^{1}H NMR (500 MHz, DMSO-d_6), δ_H 3.68 (2H, 2s, 1:2, 2-CH_2), 4.51 and 4.60 (4H, 2s, 1:1, CH_2Ph), 5.51 (1H, s, 4-H of pyrazole), 7.19 (3H, d, $^3J_{HH}$ = 7.1 Hz, 3H of Ph), 7.22–7.30 (6H, m, 6H of Ph), 7.35 (2H, t, $^3J_{HH}$ = 7.4 Hz, 2H of Ph), 7.43 (2H, dd, $^3J_{HH}$ = 7.3, 8.6 Hz, 2H of Ph), 7.70 (2H, dd, $^3J_{HH}$ = 1.4, 8.3 Hz, 2H of Ph), 11.67 (1H, br s, OH). ^{13}C NMR (126 MHz, DMSO-d_6), δ_C 34.8, 47.7, 50.4, 87.7, 120.8, 125.4, 126.7, 127.0, 127.4, 127.5, 128.4, 128.7, 128.8, 137.2, 137.6, 138.8, 146.6, 153.2, 169.9. MS, *m/z* = 398 (MH^+), HRMS (ESI), *m/z* = 398.1859 (MH^+), $C_{25}H_{24}N_3O_2$ requires 398.1869.

General procedure for the reduction of amides (24a) and (25b,c) to amines (15a,b) and (26c)

Under argon, $LiAlH_4$ (1 M in THF, 10 mL, 10 mmol) was added to a cooled (0 °C) solution of amide **24** or **25** (5 mmol) in anhydrous THF (10 mL) and the resulting reaction mixture was stirred at 0 °C for 20 min. and then at 60°C for 5 h. The reaction mixture was cooled to 0 °C and quenched subsequently with aq. sat. $NaHCO_3$ (5 mL) and MeOH (10 mL). The resulting mixture was stirred at room temperature for 10 min. followed by filtration through a short plug of Celite® and washing with EtOAc (200 mL). The filtrate was evaporated *in vacuo* and the residue was purified by CC. Fractions containing the product were collected and volatile components evaporated *in vacuo* to give **15a,b** and **26c**. Compound **15b** was isolated as dihydrochloride in the following way. The partially purified free amine obtained by CC was dissolved in CH_2Cl_2 (5 mL) and, while vigorous stirring at r.t., 2 M HCl–EtOAc (2 mL, 4 mmol) was added. The precipitate was collected by filtration, washed with EtOAc, dried *in vacuo* to give the dihydrochloride of **15b**.

3-(2-(Benzyl(methyl)amino)ethyl)-5-hydroxy-1-phenyl-1*H*-pyrazole (15a). Prepared from **24a** (1.605 g, 5 mmol), CC (MeOH/EtOAc, 1:7). Yellowish-brown semi-solid, yield 50%, 771 mg, IR (ν_{max}, cm^{-1}): 3030, 2951, 2790, 1598, 1564, 1498, 1454, 1362, 1153, 1069, 1023, 907, 757, 698. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.26 (3H, s, NMe), 2.68 (4H, s, 2×CH_2), 3.38 (2H, s, CH_2), 3.52 (2H, s, CH_2), 7.14–7.43 (8H, m, 8H of Ph), 7.86 (2H, d, $^3J_{HH}$ = 8.0 Hz, 2H of Ph). MS, *m/z* = 308 (MH^+), HRMS (ESI), *m/z* = 308.1759 (MH^+), $C_{19}H_{22}N_3O$ requires 308.1763. Anal. Calcd for $C_{19}H_{21}N_3O_3$ (307.39): C, 74.24; H, 6.89; N, 13.67%, Found: C, 73.19; H, 6.88; N, 13.31%.

5-Hydroxy-1-(4-methoxyphenyl)-3-(2-(pyrrolidin-1-yl)ethyl)-1*H*-pyrazole dihydrochloride (15b). Prepared from **25b** (1.506 g, 5 mmol), CC (neutral Al_2O_3, MeOH/CH_2Cl_2, 1:9). White solid, yield 54%, 981 mg, mp 199–201 °C, IR (ν_{max}, cm^{-1}): 3424, 2958, 2841, 2702, 2605, 2514, 2359, 2331, 1592, 1580, 1559, 1535, 1508, 1448, 1420, 1400, 1362, 1303, 1257, 1184, 1172, 1109, 1065, 1034, 1018, 850, 799. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 1.80–2.09 (4H, m, 3"-CH_2, 4"-CH_2), 2.88–2.98 and 2.99–3.10 (4H, 2m, 1:1, CH_2CH_2), 3.35–3.46 and 3.47–3.60 (4H, 2m, 1:1, 2"-CH_2, 5"-CH_2), 3.78 (3H, s, OMe), 5.52 (1H, s, 4-H of pyrazole), 5.93 (2H, br s, NH_2^+), 6.96–7.04 and 7.52–7.61 (4H, 2m, 1:1, C_6H_4), 10.75 (1H, br s, OH). ^{13}C NMR (126 MHz, DMSO-d_6), δ_C 22.8, 24.2, 52.3, 52.8, 55.5, 88.1, 114.2, 124.0, 129.9, 146.8, 154.0, 157.9. MS, *m/z* = 288 (MH^+), HRMS (ESI), *m/z* = 288.1720 (MH^+), $C_{16}H_{22}N_3O_2$ requires 288.1712. Anal. Calcd for $C_{16}H_{23}Cl_2N_3O_2$ (360.28): C, 53.34; H, 6.43; N, 11.66%, Found: C, 52.76; H, 6.41; N, 11.60%.

3-(2-(Dibenzylamino)ethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (26c). Prepared from **25c** (1.985 g, 5 mmol), CC (EtOAc/hexanes, 1:1). Brownish oil, yield 50%, 966 mg, IR (ν_{max}, cm^{-1}): 3060, 3027, 2928, 2800, 2359, 2341, 1714 (C=O), 1597, 1558, 1497, 1453, 1409, 1365, 1337, 1248, 1154, 1128, 1071, 1027, 977, 906, 749, 697. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.61–2.67 and 2.69–2.76 (4H, 2m, 1:1, C*H*$_2$C*H*$_2$), 2.99 (2H, s, 4-CH_2 of pyrazole), 3.57 (4H, s, 2×C*H*$_2$Ph), 7.14–7.43 (13H, m, 13H of Ph), 7.84–7.91 (2H, m, 2H of Ph). ^{1}H NMR (500 MHz, DMSO-d_6),

δ_H 3.07–3.13 and 3.19–3.25 (4H, 2m, 1:1, CH_2CH_2NBn$_2$), 4.39 (4H, s, 2×CH_2Ph), 5.44 (1H, s, 4-H of pyrazole), 7.24 (1H, t, $^3J_{HH}$ = 7.4 Hz, 1H of Ph), 7.41–7.45 (9H, m, 9H of Ph), 7.62–7.65 (2H, m, 2H of Ph), 7.69–7.73 (3H, m, 3H of Ph), 11.55 (1H, br s, OH). ^{13}C NMR (75.5 MHz, DMSO-d_6), δ_C 22.7, 22.7, 50.0, 56.1, 87.4, 121.1, 121.1, 125.8, 128.6, 128.8, 128.9, 129.0, 129.5, 130.1, 130.3, 131.5, 138.2, 147.6, 153.8. MS, *m/z* = 384 (MH^+), HRMS (ESI), *m/z* = 384.2080 (MH^+), $C_{25}H_{25}N_3O$ requires 384.2076. Anal. Calcd for $C_{25}H_{25}N_3O$ (383.49): C, 78.30; H, 6.57; N, 10.96%, Found: C, 79.59; H, 6.74; N, 10.83%.

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14. In the case of hydrazine hydrochloride, one equivalent of Et_3N (0.14 mL, 1 mmol) was added as well.

