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

Uroš Grošelj, a David Kralj, a Jernej Wagger, a Georg Dahmann, b Branko Stanovnik, a and Jurij Svete*a

a Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, P.O. Box 537, 1000 Ljubljana, Slovenia
b Boehringer Ingelheim Pharma GmbH & Co. KG, Medicinal Chemistry, Birkendorfer Strasse 65, 88397 Biberach, Germany
E-mail: jurij.svete@fkkt.uni-lj.si

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

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Abstract
Treatment of β-keto ester 8 with hydrazines 9a–g gave 1'-substituted tert-butyl 2-(5-hydroxy-1H-pyrazol-3-yl)ethylcarbamates 10a–e and 2-(5-oxo-2,5-dihydro-1H-pyrazol-3-yl)ethylcarbamates 11f.g. Acidolytic deprotection of 10b,c afforded the corresponding 3-(2-aminoethyl)-5-hydroxy-1H-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-dicarboxylate 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-dicarboxylates, enaminones, hydrazines, pyrazole, histamine analogues

Introduction

Novel 2-(heteroaryl)ethamine-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

Pyrazoles2 and imidazoles3 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 24 and 35 have been developed first, followed by synthesis of conformationally constrained histamine analogues 46 and 57. 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.](image)

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)-1H-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-1H-pyrazol-3-yl)ethylcarbamates 10a–e and 2-(5-oxo-2,5-dihydro-1H-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-benzyolated 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, MgCl₂, r.t.  ii: R¹NH₂ 9a–g, MeOH, reflux. iii: HCl-EtOAc, r.t.  iv: Ac₂O (1 equiv.) or PhCOCl (1 equiv.), MeOH, Et₃N, 0→20 °C. v: PhCOCl (2 equiv.), CH₂Cl₂, Et₃N, r.t.

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

<table>
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<th>Compound</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
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<tr>
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<tr>
<td>6c</td>
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<td>-</td>
<td>84</td>
</tr>
<tr>
<td>10a</td>
<td>H</td>
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</tr>
<tr>
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<td>Me</td>
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<tr>
<td>10c</td>
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<tr>
<td>10d</td>
<td>4-chlorophenyl</td>
<td>-</td>
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<tr>
<td>10e</td>
<td>4-carboxyphenyl</td>
<td>-</td>
<td>55</td>
</tr>
<tr>
<td>11f</td>
<td>6-phenylpyridazin-3-yl</td>
<td>-</td>
<td>81</td>
</tr>
<tr>
<td>11g</td>
<td>imidazo[1,2-b]pyridazin-6-yl</td>
<td>-</td>
<td>66</td>
</tr>
<tr>
<td>12b</td>
<td>Me</td>
<td>Me</td>
<td>62</td>
</tr>
<tr>
<td>12c</td>
<td>Ph</td>
<td>Me</td>
<td>87</td>
</tr>
<tr>
<td>13c</td>
<td>Ph</td>
<td>Ph</td>
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Next, we tried to synthesize the N,N-dialkyl 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. Indeed, alaninates 18a\textsuperscript{10a} and 18b\textsuperscript{10b,c} were obtained in quantitative yield by addition of benzyl(methyl)amine 17a to methyl acrylate 16 following a slightly modified literature procedure.\textsuperscript{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 19 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](image)

Reagents and conditions: i: Bn(Me)NH 17a or pyrrolidine 17b, CH\textsubscript{2}Cl\textsubscript{2}, r.t. ii: NaOH, H\textsubscript{2}O, r.t. iii: CDI, MeCN, r.t., then potassium monomethyl malonate, MgCl\textsubscript{2}, r.t. (Method A). iv: Meldrum’s acid, DMAP, DCC, THF, r.t., then MeOH, reflux (Method B). v: R\textsuperscript{1}NHNH\textsubscript{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.\textsuperscript{2,12} First, methyl (pyrazol-3-yl)acetates 22a,b were prepared from 21 following the literature procedure.\textsuperscript{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\textsubscript{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: R¹NHNH₂ 9a,h, MeOH, reflux.¹²a ii: NaOH–H₂O, r.t. iii: CDI, MeCN, r.t., then Bn(Me)NH 17a or pyrrolidine 17b or Bn₂NH 17c, MeCN, r.t. iv: LiAlH₄, THF, 60 °C.

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

<table>
<thead>
<tr>
<th>Compound</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Yield (%)</th>
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<td>Ph</td>
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<td>-</td>
<td>62¹²a</td>
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<td>22b</td>
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<td>4-methoxyphenyl</td>
<td>-</td>
<td>(CH₂)₄⁻</td>
<td>79</td>
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<tr>
<td>25c</td>
<td>Ph</td>
<td>CH₂Ph</td>
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<td>4-methoxyphenyl</td>
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<tr>
<td>26c</td>
<td>Ph</td>
<td>CH₂Ph</td>
<td>CH₂Ph</td>
<td>50</td>
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</tbody>
</table>

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 ¹³C 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, ¹³C 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 22a¹²a were in agreement with the literature data.
Like related 5-hydroxy-1H-pyrazoles,\textsuperscript{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-1H-pyrazole, 6, 10, 12–15, 23, 24) and the partially unsaturated “NH-tautomer” (1H-pyrazol-3(2H)-one, 11) and “CH-tautomer” (1H-pyrazol-5(4H)-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-1H-pyrazoles (OH-tautomers), whereas absorption at 1700–1750 cm\textsuperscript{-1} is in agreement with the 1H-pyrazol-5(4H)-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\textsuperscript{-1}. However, the absorption band at \~ 1690 cm\textsuperscript{-1} (Boc) and absence of C=O vibrations at \~ 1640 cm\textsuperscript{-1} support the OH-tautomeric form of 10a–e, while absorption bands at \~ 1690 cm\textsuperscript{-1} and \~ 1640 cm\textsuperscript{-1} are in agreement with the NH-tautomeric form of 1-heteroarylypyrazoles 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\textsuperscript{-1} most probably exist as the OH-tautomers. In solution, the tautomer equilibrium was solvent-depended. In DMSO-\textsubscript{d}6, chemical shifts of 4-H (\~ 5.5 ppm) and 5-C (\~ 153 ppm) were in agreement with the 1H-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\textsubscript{3}, on the other hand, a singlet for the 4-CH\textsubscript{2} group at \~ 3.5 ppm clearly indicated the 1H-pyrazol-5(4H)-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).\textsuperscript{2,4,13}

![Tautomer forms](image-url)

**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)-1H-pyrazol-5(4H)-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)-1H-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 Kofer 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 1H and 75.5 MHz for 13C nucleus and on Bruker Avance III UltraShield 500 plus at 500 MHz for 1H and 126 MHz for 13C nucleus, using DMSO-d6 and CDCl3 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-dicarboxylate 21 are commercially available (Sigma-Aldrich). Methyl 5-(tert-butoxycarbonylamino)-3-oxopentanoate 85 and methyl 2-(5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)acetate 22a12a were prepared following the literature procedures.

Preparation of 1'-substituted tert-butyl 2-(5-hydroxy-1H-pyrazol-3-yl)ethylcarbamates 10a–e and tert-butyl 2-(5-oxo-2,5-dihydro-1H-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-1H-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 ºC, IR (v_max, cm⁻¹): 3380, 2982, 1689 (C=O), 1613, 1528, 1460, 1364, 1271, 1246, 1171, 974, 759. ¹H NMR (500 MHz, DMSO-d₆), δ_H 1.38 (9H, s, t-Bu), 2.56 (2H, t, ³J_HH = 7.5 Hz, CH₂CH₂NH), 3.10 (2H, br q, ³J_HH = 6.9 Hz, CH₂CH₂NH), 5.25 (1H, br s, 4-H of pyrazole), 6.86 (1H, br t, ³J_HH = 6.3 Hz, NHBoc), 9.44 (1H, br s, 1-H), 11.14 (1H, br s, OH). ¹³C NMR (126 MHz, DMSO-d₆), 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 calcd = 228.1335 (MH⁺), C₁₉H₁₉N₃O₃ requires 228.1343. Anal. Calcd for C₁₉H₁₉N₃O₃ (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-1H-pyrazol-3-yl)ethylcarbamate (10b). Prepared from 8 (245 mg, 1 mmol) and methylhydrazine. CCS (EtOAc/hexanes, 1:1). White solid, yield 73%, 177 mg, mp 160–162 ºC, IR (v_max, cm⁻¹): 3376, 2982, 1690 (C=O), 1533, 1459, 1401, 1270, 1173, 1039, 1000, 747, 748, 684. ¹H NMR (300 MHz, DMSO-d₆), δ_H 1.37 (9H, s, t-Bu), 2.45 (2H, br t, ³J_HH = 7.7 Hz, CH₂CH₂NH), 3.08 (2H, br m, CH₂CH₂NH), 3.41 (3H, s, NMe), 5.16 (1H, br s, 4-H of pyrazole), 6.73 (1H, br s, NHBoc), 10.64 (1H, br s, OH). ¹³C NMR (75.5 MHz, DMSO-d₆), 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 calcd = 242.1494 (MH⁺), C₁₁H₁₀N₃O₃ requires 242.1499. Anal. Calcd for C₁₁H₁₀N₃O₃ (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-1H-pyrazol-3-yl)ethylcarbamate (10c). Prepared from 8 (245 mg, 1 mmol) and phenylhydrazine. CCS (EtOAc/hexanes, 1:2). Beige solid, yield 83%, 250 mg, mp 155–157 ºC, IR (v_max, cm⁻¹): 3218, 3050, 2866, 1669 (C=O), 1601, 1560, 1455, 1409, 1365, 1306, 1256, 1160, 1060, 1037, 964, 868, 761, 694, 644. ¹H NMR (300 MHz, CDC1₃), δ_H 1.41 (9H, s, t-Bu), 2.67 (2H, br t, ³J_HH = 6.3 Hz, CH₂CH₂NH), 3.49 (2H, br s, 4'-CH₂), 3.52 (2H, br q, ³J_HH = 6.2 Hz, CH₂CH₂NH), 4.87 (1H, br s, NHBoc), 7.19 (1H, tt, ⁴J_HH = 1.1 Hz, ⁵J_HH = 7.4 Hz, c-Ph), 7.36–7.40 (2H, m, m-Ph), 7.82–7.88 (2H, m, o-Ph). ¹³C NMR (500 MHz, DMSO-d₆), δ_C 1.38 (9H, s, t-Bu), 2.58 (2H, br t, ³J_HH = 7.5 Hz, CH₂CH₂NH), 3.18 (2H, br q, ³J_HH = 6.8 Hz, CH₂CH₂NH), 5.40 (1H, br s, 4-H of pyrazole), 6.88 (1H, br s, NHBoc), 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). ¹³C NMR (126 MHz, DMSO-d₆), 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 calcd = 304.1650 (MH⁺), C₁₀H₁₂N₂O₃ requires 304.1656. Anal. Calcd for C₁₀H₁₂N₂O₃ (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)-1H-pyrazol-3-yl)ethylcarbamate (10d). Prepared from 8 (245 mg, 1 mmol) and 4-chlorophenylhydrazine hydrochloride 9d (179 mg, 1 mmol), CCS (EtOAc/hexanes, 1:2). Grayish solid, yield 61%, 206 mg, mp 107–108 ºC, IR (v_max, cm⁻¹): 3393, 2980, 2928, 1688 (C=O), 1526, 1493, 1397, 1366, 1274, 1254, 1168, 1092, 1028, 1012, 842, 788, 755, 659. ¹H NMR (300 MHz, CDC1₃), δ_H 1.39 (9H, s, t-Bu), 2.66 (2H, br t, ³J_HH = 6.3 Hz, CH₂CH₂NH), 3.49 (2H, br s, 4'-CH₂), 3.49 (2H, br q, ³J_HH = 6.3 Hz, CH₂CH₂NH), 4.83 (1H, br s, NHBoc), 7.34 and 7.83 (4H, 2dt, 1:1, ³J_HH = 2.6, 9.0 Hz, C₆H₄). ¹³C NMR (500 MHz, DMSO-d₆),
\( \delta_H 1.38 \) (9H, s, t-Bu), 2.58 (2H, br t, \( J_{HH} = 7.2 \) Hz, \( CH_H(CH_2)N_H \)), 3.18 (2H, br q, \( J_{HH} = 6.5 \) Hz, \( CH_HCH_2NH \)), 5.42 (1H, s, 4-H of pyrazole), 6.88 (1H, br s, \( NH_Boc \)), 7.48 and 7.77 (4H, 2dt, 1:1, \( J_{HH} = 2.5 \), 8.7 Hz, \( C_HH_4 \)), 11.73 (1H, br s, OH). \(^{13}\)C NMR (126 MHz, DMSO-\( d_6 \)), \( \delta_C 28.1 \), 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\(^+\)), \( C_{16}H_{32}Cl_2N_3O_3 \) requires 338.1266. Anal. Calcd for \( C_{16}H_{20}Cl_2N_3O_3 \) (337.80): C, 56.89; H, 5.97; N, 12.44\%. Found: C, 56.87; H, 5.80; N, 12.28\%.

4-((2-(tert-butoxycarbonylamino)ethyl)-5-hydroxy-1H-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 (\( \nu_{max} \), cm\(^{-1}\))): 3238, 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-\( d_6 \)), \( \delta_H 1.38 \) (9H, s, t-Bu), 2.60 (2H, br t, \( J_{HH} = 7.3 \) Hz, \( CH_HCH_2NH \)), 3.19 (2H, br q, \( J_{HH} = 6.7 \) Hz, \( CH_HCH_2NH \)), 5.46 (1H, br s, 4-H of pyrazole), 6.89 (1H, br s, \( NH_Boc \)), 7.91 and 7.98 (4H, 2br d, 1:1, \( J_{HH} = 8.7 \) Hz, \( C_HH_4 \)), 11.90 and 12.89 (2H, 2 br s, 1:1, OH and COOH). \(^{13}\)C NMR (75.5 MHz, DMSO-\( d_6 \)), \( \delta_C 28.1 \), 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\(^+\)), \( C_{17}H_{22}N_3O_3 \) requires 348.1554. Anal. Calcd for \( C_{17}H_{21}N_3O_3 \) (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-(6-phenylpyrazidin-3-yl)-2,5-dihydro-1H-pyrazol-3-yl)ethylcarbamate (11f).

Prepared from 8 (245 mg, 1 mmol) and 3-hydrazino-6-phenylpyrazidine 9f (186 mg, 1 mmol). White solid, yield 81\%, 310 mg, mp 242–246 °C, IR (\( \nu_{max} \), 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-\( d_6 \)), \( \delta_H 1.38 \) (9H, s, t-Bu), 2.65 (2H, br t, \( J_{HH} = 7.0 \) Hz, \( CH_HCH_2NH \)), 3.25 (2H, br q, \( J_{HH} = 6.8 \) Hz, \( CH_HCH_2NH \)), 5.28 (1H, br s, 4-H of pyrazole), 6.97 (1H, br t, \( J_{HH} = 5.0 \) Hz, \( NH_Boc \)), 7.49–7.61 (3H, m, p-Ph, m-Ph), 8.12–8.17 (2H, m, o-Ph), 8.36 (1H, d, \( J_{HH} = 9.4 \) Hz, 4"-H), 8.65 (1H, br s, 5"-H), 12.52 (1H, br s, 2"-H). \(^{13}\)C NMR (126 MHz, DMSO-\( d_6 \)), \( \delta_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\(^+\)), \( C_{20}H_{22}N_3O_3 \) requires 382.1874. Anal. Calcd for \( C_{20}H_{22}N_3O_3 \) (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]pyrazidin-6-yl)-5-oxo-2,5-dihydro-1H-pyrazol-3-yl)ethylcarbamate (11g).

Prepared from 8 (245 mg, 1 mmol) and 6-hydrazinimidazo[4,3-b]pyridazine 9g (149 mg, 1 mmol), CC: EtOAc. Yellowish solid, yield 66\%, 227 mg, mp 221–225 °C, IR (\( \nu_{max} \), 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-\( d_6 \)), \( \delta_H 1.38 \) (9H, s, t-Bu), 2.64 (2H, br t, \( J_{HH} = 7.1 \) Hz, \( CH_HCH_2NH \)), 3.23 (2H, br q, \( J_{HH} = 7.1 \) Hz, \( CH_HCH_2NH \)), 5.28 (1H, br s, 4-H of pyrazole), 6.94 (1H, br s, \( NH_Boc \)), 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-\( d_6 \)), \( \delta_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\(^+\)), \( C_{16}H_{21}N_3O_3 \) requires 345.1670. Anal. Calcd for \( C_{16}H_{20}N_3O_3 \) (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-1H-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-1H-pyrazole dihydrochloride (6b). Prepared from 10b (1.206 g, 5 mmol). White solid, yield 78%, 832 mg, mp 197–200 °C, IR (vmax, cm⁻¹): 1609, 1539, 1287, 1096, 945, 831, 673. ¹H NMR (500 MHz, DMSO-d₆), δH 2.90 (2H, br t, ³JHH = 7.2 Hz, CH₂CH₂NH₃⁺), 3.10 (2H, br sextet, ³JHH = 7.2 Hz, CH₂CH₂NH₃⁺), 3.60 (3H, s, CH₃), 5.75 (1H, s, 4-H of pyrazole), 8.23 (3H, br s, NH₃⁺), OH exchanged. ¹³C NMR (125 MHz, DMSO-d₆), δC 24.6, 32.3, 37.3, 88.7, 144.7, 154.8. MS, m/z = 142 (MH⁺). HRMS (ESI), m/z = 142.0969 (MH⁺), C₆H₁₂N₃O requires 142.0975. Anal. Calcd for C₆H₁₁N₃O·2½HCl (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-1H-pyrazole dihydrochloride (6c). Prepared from 10c (1.515g, 5 mmol). White solid, yield 84%, 1.159 g, mp 192–195 °C, IR (vmax, cm⁻¹): 3381, 1603, 1547, 1497, 1464, 1366, 1310, 1145, 942, 812, 754, 691. ¹H NMR (300 MHz, DMSO-d₆), δH 2.92 (2H, t, ³JHH = 7.5 Hz, CH₂CH₂NH₃⁺), 3.13 (2H, br sextet, ³JHH = 6.3 Hz, CH₂CH₂NH₃⁺), 5.72 (1H, s, 4-H of pyrazole), 7.32 (1H, br t, ³JHH = 7.4 Hz, p-Ph), 7.46 (2H, br t, ³JHH = 7.9 Hz, m-Ph), 7.71 (2H, br d, ³JHH = 7.7 Hz, o-Ph), 8.30 (3H, br s, NH₃⁺), OH exchanged. ¹³C NMR (75.5 MHz, DMSO-d₆), δC 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⁺), C₁₇H₁₄N₃O requires 204.1131. Anal. Calcd for C₁₁H₁₃N₃O·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-1H-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-1H-pyrazol-3-yl)ethyl)acetamide (12b). Prepared from 6b (214 mg, 1 mmol). White solid, yield 62%, 113 mg, mp 129–133 °C, IR (vmax, 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. ¹H NMR (500 MHz, DMSO-d₆), δH 1.78 (3H, s, MeCO), 2.46 (2H, br t, ³JHH = 7.5 Hz, CH₂CH₂NH), 3.30 (2H, br dt, ³JHH = 5.9, 7.5 Hz, CH₂CH₂NH), 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). ¹³C NMR (126 MHz, DMSO-d₆), δC 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⁺), C₉H₁₄N₂O requires 184.1081. Anal. Calcd for C₈H₁₃N₃O₂ (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-1H-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 (νmax, cm⁻¹): 3312, 1640 (C=O), 1577, 1558, 1497, 1398, 1358, 1308, 1202, 1150, 787, 751, 687. ¹H NMR (500 MHz, DMSO-d₆), δH 1.80 (3H, s, Me), 2.59 (2H, br t, 3JHH = 7.4 Hz, CH₂CH₂NH), 3.30 (2H, br q, 3JHH = 7.3 Hz, CH₂CH₂NH), 5.41 (1H, br s, 4-H of pyrazole), 7.21 (1H, br t, 3JHH = 7.4 Hz, p-Ph), 7.42 (2H, br t, 3JHH = 8.0 Hz, m-Ph), 7.72 (2H, br d, 3JHH = 7.8 Hz, o-Ph), 7.90 (3H, br s, NH), 11.46 (1H, br s OH). ¹³C NMR (126 MHz, DMSO-d₆), δC 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⁺), C₁₃H₁₄N₃O₂ requires 246.1237. Anal. Calcd for C₁₃H₁₄N₃O₂ (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-1H-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 (νmax, cm⁻¹): 3280, 1638 (C=O), 1543, 1495, 1396, 1312, 1150, 843, 677. ¹H NMR (500 MHz, DMSO-d₆), δH 2.76 (2H, br t, 3JHH = 7.4 Hz, CH₂CH₂NH), 3.54 (2H, br q, 3JHH = 7.3 Hz, CH₂CH₂NH), 5.47 (1H, br s, 4-H of pyrazole), 7.22 (1H, br t, 3JHH = 7.4 Hz, p-Ph), 7.40–7.49 (4H, m, 2xm-Ph), 7.50–7.55 (1H, m, p-Ph), 7.73 and 7.86 (4H, 2 br d, 1:1, 3JHH = 7.5 Hz, 2x-Ph), 8.60 (1H, br s, NH). ¹³C NMR (500 MHz, CDCl₃), δC 2.81 (2H, br t, 3JHH = 6.2 Hz, CH₂CH₂NH), 3.51 (2H, br s, 4-CH₂ of pyrazole), 3.88 (2H, br q, 3JHH = 6.2 Hz, CH₂CH₂NH), 6.75 (1H, br s, NH), 7.19 (1H, br t, 3JHH = 7.4 Hz, p-Ph), 7.36–7.44 (4H, m, 2x-Ph), 7.45–7.52 (1H, m, p-Ph), 7.72–7.77 and 7.80–7.86 (4H, 2m, 1:1, 2x-Ph). ¹⁵N NMR (126 MHz, DMSO-d₆), δN 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⁺), C₁₈H₁₄N₃O₂ requires 308.1394. Anal. Calcd for C₁₈H₁₄N₃O₂ (307.35): C, 70.34; H, 5.58; N, 13.67%. Found: C, 70.18; H, 5.60; N, 13.35%.

3-(2-(Benzoylamino)-1-phenyl-1H-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 (νmax, cm⁻¹): 3289, 1753 (C=O), 1632 (C=O), 1445, 1315, 1247, 1076, 760, 697. ¹H NMR (300 MHz, CDCl₃), δH 3.01 (2H, t, 3JHH = 6.3 Hz, CH₂CH₂NH), 3.86 (2H, q, 3JHH = 6.0 Hz, CH₂CH₂NH), 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), 7.78–8.73 (2H, m, 2H of Ph), 8.05–8.11 (2H, m, 2H of Ph). ¹³C NMR (126 MHz, DMSO-d₆), δC 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⁺), C₂₅H₂₂N₃O₃ requires 412.1656. Anal. Calcd for C₂₅H₂₁N₃O₃ (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-\(\beta\)-alanines (19a,b)

First, the esters 18a and 18b were prepared following slightly modified literature procedure. 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 \(\beta\)-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\textsuperscript{®} 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\(_2\)O and five times in CH\(_2\)Cl\(_2\) (100 mL) to remove EtOH. The residue was dried in vacuo (0.01 Torr, 40 °C) to give the \(\beta\)-amino acids 19a,b, which were characterized by NMR.

**Methyl 3-(benzyl(methyl)amino)propanoate (18a).** 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\(_3\)): \(\delta\) 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, C\(\text{H}_2\)Ph), 3.66 (3H, s, OMe), 7.20–7.35 (5H, m, Ph).

**Methyl 3-(pyrrolidin-1-yl)propanoate (18b).** 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\(_3\)): \(\delta\) 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).** 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\(_3\)): \(\delta\) 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, C\(\text{H}_2\)Ph), 7.15–7.31 (5H, m, Ph), 10.69 (1H, br s, COOH). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 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).** 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\(_2\)O): \(\delta\) 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\(_2\)O): \(\delta\) 23.1, 34.4, 52.3, 53.9, 178.5.

**Synthesis of methyl 2-(1-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1H-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\(_2\)N (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<sub>max</sub>, cm<sup>−1</sup>): 3448, 1744 (C=O), 1637 (C=O), 1542, 1516, 1465, 1406, 1314, 1252, 1173, 1150, 1111, 1032, 1005, 840, 756, 630. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 3.58 and 3.60 (4H, 2s, 1:1, 2-CH<sub>2</sub>, 4-CH<sub>2</sub> of pyrazole), 3.77 and 3.81 (6H, 2s, 1:1, 2×OMe), 6.88–6.96 (2H, m, o-C<sub>6</sub>H<sub>4</sub>), 7.67–7.75 (2H, m, o-C<sub>6</sub>H<sub>4</sub>). <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): δ<sub>H</sub> 3.54 (2H, s, CH<sub>2</sub>), 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, 4<sup>J</sup><sub>HH</sub> = 2.8 Hz, 3<sup>J</sup>HH = 9.1 Hz, C<sub>6</sub>H<sub>4</sub>), 11.44 (1H, s, OH). <sup>13</sup>C NMR (126 MHz, DMSO-d<sub>6</sub>): δ<sub>C</sub> 17.07, 21.39, 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<sup>+</sup>), HRMS (ESI), m/z = 263.1035 (MH<sup>+</sup>), C<sub>13</sub>H<sub>13</sub>N<sub>2</sub>O<sub>4</sub> requires 263.1032. Anal. Calcd for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub> (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<sub>2</sub>SO<sub>4</sub>, filtered, and the volatile components were evaporated in vacuo to give 23a,b as sticky resins, which were characterised by <sup>1</sup>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<sub>4</sub> (100 mL). The organic phase was dried over anh. Na<sub>2</sub>SO<sub>4</sub>, 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-1H-pyrazol-3-yl)acetic acid (23a).** Prepared from 21a (2.46 g, 10 mmol). Yellow-orange resin, yield 94%, 2.064 g. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>), δ<sub>H</sub> 3.45 (2H, s, CH<sub>2</sub>), 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<sup>+</sup>), HRMS (ESI), m/z = 219.0766 (MH<sup>+</sup>), C<sub>11</sub>H<sub>11</sub>N<sub>2</sub>O<sub>3</sub> requires 219.0770.

**2-(5-Hydroxy-1-(4-methoxyphenyl)-1H-pyrazol-3-yl)acetic acid (23b).** Prepared from 21b (2.625 g, 10 mmol). Yellow-brown resin, yield 79%, 1.979 g. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>), δ<sub>H</sub> 3.42 (2H, s, CH<sub>2</sub>), 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<sub>6</sub>H<sub>4</sub>), 11.34 (1H, br s, OH), 12.29 (1H, br s, COOH). MS, m/z = 249 (MH<sup>+</sup>), HRMS (ESI), m/z = 249.0867 (MH<sup>+</sup>), C<sub>12</sub>H<sub>13</sub>N<sub>2</sub>O<sub>4</sub> requires 219.0875.
**N-Benzyl-2-(5-hydroxy-1-phenyl-1H-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 (v_{max}, cm^{-1}): 3490, 1639 (C=O), 1559, 1496, 1453, 1401, 1112, 1020, 804, 759, 731, 692. ^1H NMR (300 MHz, CDCl3), δH 3.01 (3H, s, Me), 3.63–3.72 (4H, m, 2-CH2 and 4-CH2 of pyrazole), 4.61 and 4.63 (2H, 2br s, 5.3, CH2Ph), 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). ^13C NMR (300 MHz, CDCl3), δc 33.8/34.0, 35.9/36.2, 42.1/42.2, 50.8/50.9, 118.5/118.6, 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. ^1H NMR (500 MHz, DMSO-d6), δH 2.79 and 2.98 (3H, 2s, 1:2, Me), 3.62 and 3.67 (2H, 2s, 1:2, 2-CH2), 4.54 and 4.68 (2H, 2s, 2:1, CH2Ph), 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). ^13C NMR (126 MHz, DMSO-d6), δc 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^+). C10H22N2O2 requires 322.1556.

1-(4-Methoxyphenyl)-3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-1H-pyrazol-5(4H)-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 (v_{max}, cm^{-1}): 3438, 2928, 2877, 1703 (C=O), 1621, 1557, 1511, 1454, 1340, 1298, 1249, 1172, 1024, 913, 833, 730. ^1H NMR (500 MHz, CDCl3), δH 1.89 and 2.00 (4H, 2 quintets, 1:1, ^3J_{HH} = 6.8 Hz, 3"-CH2, 4"-CH2), 3.49 and 3.51 (4H, 2t, 1:1, ^3J_{HH} = 6.9 Hz, 2"-CH2, 5"-CH2), 3.53 and 3.68 (4H, 2s, 1:1, 2"-CH2, 4"-CH2 of pyrazole), 3.81 (3H, s, OMe), 6.91 and 7.70 (4H, 2br d, 1:1, ^3J_{HH} = 9.1 Hz, C6H4). ^1H NMR (300 MHz, DMSO-d6), δH 1.70–1.93 (4H, m, 3"-CH2, 4"-CH2), 3.28 and 3.50 (4H, 2t, ^3J_{HH} = 6.9 Hz, 2"-CH2, 5"-CH2), 3.46 (2H, s, 1"-CH2), 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, C6H4), 11.31 (1H, br s, OH). ^13C NMR (126 MHz, CDCl3), δc 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^+). C10H10N4O2 requires 302.1505.

**N,N-dibenzyl-2-(1-phenyl-5-oxo-4,5-dihydro-1H-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 (v_{max}, cm^{-1}): 3480, 1715 (C=O), 1633 (C=O), 1558, 1496, 1452, 1360, 1208, 1168, 1078, 954, 751, 694. ^1H NMR (300 MHz, CDCl3), δH 3.65 (4H, s, 2-CH2, 4-CH2 of pyrazole), 4.52 and 4.64 (4H, 2 s, 1:1, 2xCH2Ph), 7.12–7.42 (13H, m, 13H of Ph), 7.77–7.83 (2H, m, 2H of Ph). ^1H NMR (500 MHz, DMSO-d6), δH 3.68 (2H, 2s, 1:2, 2-CH2), 4.51 and 4.60 (4H, 2s, 1:1, CH2Ph), 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). ^13C NMR (126 MHz, DMSO-d6), δc 34.8, 47.7, 50.4, 87.7, 120.8, 125.4, 126.7, 127.0, 127.4, 128.5, 128.4, 128.7, 132.8, 137.2, 137.6, 138.8, 146.6, 153.2, 169.9. MS, m/z = 398 (MH^+), HRMS (ESI), m/z = 398.1859 (MH^+). C25H24N3O2 requires 398.1869.
General procedure for the reduction of amides (24a) and (25b,c) to amines (15a,b) and (26c)

Under argon, LiAlH₄ (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. NaHCO₃ (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 CH₂Cl₂ (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-1H-pyrazole (15a). Prepared from 24a (1.605 g, 5 mmol), CC (MeOH/EtOAc, 1:7). Yellowish-brown semi-solid, yield 50%, 771 mg, IR (νmax, cm⁻¹): 3030, 2951, 2790, 1598, 1564, 1498, 1454, 1362, 1153, 1069, 1023, 907, 757, 698. ¹H NMR (300 MHz, CDCl₃), δH 2.26 (3H, s, NMe₂), 2.68 (4H, s, 2×CH₂), 3.38 (2H, s, CH₂), 3.52 (2H, s, CH₂), 7.14–7.43 (8H, m, 8H of Ph), 7.86 (2H, d, JHH = 8.0 Hz, 2H of Ph). MS, m/z = 308 (MH⁺), HRMS (ESI), m/z = 308.1759 (MH⁺). C₁₉H₂₁N₃O requires 308.1763.

5-Hydroxy-1-(4-methoxyphenyl)-3-(2-(pyrrolidin-1-yl)ethyl)-1H-pyrazole dihydrochloride (15b). Prepared from 25b (1.506 g, 5 mmol), CC (neutral Al₂O₃, MeOH/CH₂Cl₂, 1:9). White solid, yield 54%, 981 mg, mp 199–201 °C, IR (νmax, 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. ¹H NMR (300 MHz, DMSO-d₆), δH 1.80–2.09 (4H, m, 3″-CH₂, 4″-CH₂), 2.88-2.98 and 2.99–3.10 (4H, 2m, 1:1, CH₂CH₂), 3.35–3.46 and 3.47–3.60 (4H, 2m, 1:1, 2″-CH₂, 5″-CH₂), 3.78 (3H, s, OMe), 5.52 (1H, s, 4-H of pyrazole), 5.93 (2H, br s, NH₂⁺), 6.96–7.04 and 7.52–7.61 (4H, 2m, 1:1, C₈H₄), 10.75 (1H, br s, OH). ¹³C NMR (126 MHz, DMSO-d₆), δC 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⁺). C₁₉H₂₂N₃O₂ requires 288.1712. Anal. Calcd for C₁₉H₂₁Cl₂N₃O₂ (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-1H-pyrazol-5(4H)-one (26c). Prepared from 25c (1.985 g, 5 mmol), CC (EtOAc/hexanes, 1:1). Brownish oil, yield 50%, 966 mg, IR (νmax, 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. ¹H NMR (300 MHz, CDCl₃), δH 2.61–2.67 and 2.69–2.76 (4H, 2m, 1:1, CH₂CH₂), 2.99 (2H, s, 4-CH₂ of pyrazole), 3.57 (4H, s, 2×CH₂Ph), 7.14–7.43 (13H, m, 13H of Ph), 7.84–7.91 (2H, m, 2H of Ph). ¹H NMR (500 MHz, DMSO-d₆),
δ_H 3.07–3.13 and 3.19–3.25 (4H, 2m, 1:1, CH_2CH_2NBn_2), 4.39 (4H, s, 2\times\text{CH}_2\text{Ph}), 5.44 (1H, s, 4-H of pyrazole), 7.24 (1H, t, \text{^3}J_{\text{HH}} = 7.4 \text{ Hz}, 1\text{H of Ph}), 7.41–7.45 (9H, m, 9\text{H of Ph}), 7.62–7.65 (2H, m, 2\text{H of Ph}), 7.69–7.73 (3H, m, 3\text{H of Ph}), 11.55 (1H, br s, OH). \text{^13C NMR} (75.5 \text{ MHz, DMSO-d}_6), \delta_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, \text{m/z} = 384 (\text{MH}^+), \text{HRMS (ESI), m/z} = 384.2080 (\text{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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References


14. In the case of hydrazine hydrochloride, one equivalent of Et₃N (0.14 mL, 1 mmol) was added as well.