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A synthesis of 1-substituted 5-[2-(acylamino)ethyl]-1*H*-pyrazole-4-carboxamides

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ABSTRACT

A seven-step synthesis of 1-substituted 5-(2-acylaminoethyl)-1*H*-pyrazole-4-carboxamides **20** as the pyrazole analogues of histamine was developed. The synthesis starts with a three-step preparation of N(1)-substituted methyl 5-(2-*tert*-butoxycarbonylaminoethyl)-1*H*-pyrazole-4-carboxylates **7** from commercially available Boc-β-alanine (**1**). Subsequent four-step transformation of the key-intermediates **7** into the final products **20** was performed following two complementary reaction sequences comprising acidolytic removal of the Boc group, hydrolysis of the COOMe group, amidations of the COOH group, and acylations of the NH_2 group. The structures of pyrazole derivatives were determined by spectroscopic methods and by X-ray diffraction.

1. Introduction

Functionalised heterocycles represent important scaffolds for the preparation of compound libraries for medicinal and pharmaceutical applications, due to their ability to mimic structures of peptides and reversibly bind proteins.[1–4] Because of the crucial role of histamine, tyramine, dopamine, tryptamine, serotonin, and melatonin as chemical messengers in biological processes, the preparation of their novel synthetic analogs based on the 2-(heteroaryl)ethylamine scaffold represents an important target in medicinal and synthetic organic chemistry.[5,6]

Pyrazole and its derivatives certainly are important class of heterocyclic compounds. Despite their rare occurrence in nature, numerous pyrazole derivatives found use in various applications and a general interest in the chemistry of pyrazoles is still continuing.[7] Some examples of important pyrazole derivatives are depicted in Figure 1.

Among numerous synthetic options for the construction of the pyrazole ring, two classical approaches are most frequently employed. The first one is based on a cyclocondensation reaction between a 1,3-dicarbonyl compound (or its analogue) and a hydrazine derivative, whilst the second one is based on a cycloaddition of a C–N–N type 1,3-dipole (diazoalkane, nitrile imine, or azomethine imine) to a C=C multiple bond.[7]

Various β-(dimethylamino)enones are easily available and stable enamino analogues of 1,3-dicarbonyl compounds, which found use as versatile reagents in heterocyclic synthesis.[8–10] Some recent applications also showed, that enaminones are suitable reagents (or key-intermediates) for the combinatorial synthesis of heterocyclic compounds as well.[11]

Recently, a substantial part of our research has been focused on the synthesis of functionalised pyrazoles via (a) 1,3-dipolar cycloadditions of (4*R**,5*R**)-4-benoylamino-5-phenyl-3-pyrazolidinone derived azomethine imines to various dipolarophiles[8c,9a,e,12] and (b) cyclocondensations of functionalised enaminones with monosubstituted hydrazines.[8–10,11a,13–16] In this manner, various pyrazole derivatives having amino acid,[14] dipeptide,[12] β-aminoalcohol,[15] 1,2-diol,[16] 2-phenylethylamine,[15a] and terpene[13] structural motifs have been synthesized. Within this context, we have recently reported a simple enaminone-based synthesis of 4-(2-aminoethyl)-5-hydroxy-1*H*-pyrazoles[10d] and, soon after, a one-pot parallel solution phase synthesis of these histamine analogues.[11a] In continuation, we focused our attention on preparation of another type of histamine analogues, 1-substituted 5-[2-(acylamino)ethyl]-1*H*-pyrazole-4-carboxamides. We found these compounds interesting, because the substituents can easily be varied at three different nitrogen atoms: (a) at the pyrazole ring nitrogen atom, (b) at the 4-carboxamido group, and (c) at the 5-aminoethyl group. As a result of our research efforts in this field, we now report a new enaminone-based synthesis of a novel type of histamine analogues.

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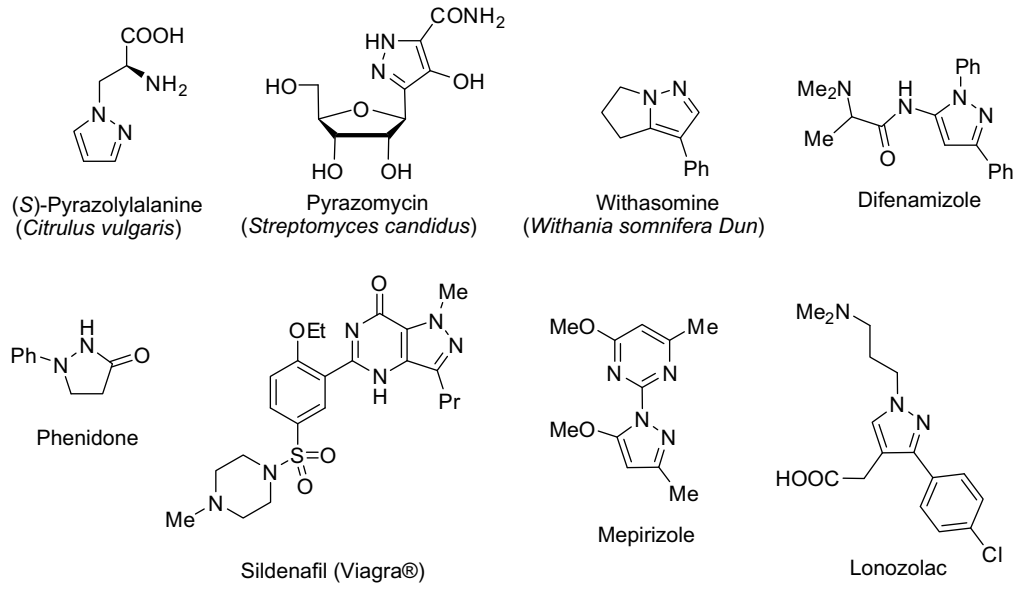


Figure 1.

2. Results and discussion

First, the β-keto ester **3** was prepared from *N*-Boc-β-alanine (**1**) and Meldrum's acid following literature procedures for the preparation of closely related compounds.[14a,17] Accordingly, the starting compound **1** was treated with Meldrum's acid and *N*,*N*-dicyclohexylcarbodiimide (DCC) in the presence of 4-dimethylaminopyridine (DMAP) to give the cyclic intermediate **2**. Heating of the crude **2** in anhydrous methanol followed by chromatographic workup gave the desired β-keto ester **3** in 60% yield over two steps (Scheme 1, Method A). Because the yield and the purity of the β-keto ester **3** obtained by the Method A were only moderate and sometimes non-reproducible as well, we prepared the β-keto ester **3** from **1** by Masamune–Claisen type condensation following slightly modified literature procedure.[18] Activation of *N*-Boc-β-alanine (**1**) with 1,1′-carbonyldiimidazole (CDI) gave the imidazolide **4**, which was subsequently reacted with potassium monomethyl malonate in the presence of magnesium chloride to afford the desired β-keto ester **3** in 90% upon simple extraction workup (Scheme 1, Method B). In our hands, Method B was reproducible and scalable and, hence, suitable for the preparation of **3** on a 200 mmol scale. Further treatment of β-keto ester **3** with DMFDMA in dichloromethane at rt followed by evaporative workup gave the crude oily enaminone **5**, which was subsequently reacted with hydrazine derivatives **6**{*1–13*} to give the 1-substituted methyl 5-[2-(*tert*-butoxycarbonylamino)ethyl]-1*H*-pyrazole-4-carboxylates **7**{*1–13*} in 34–80% yields (Scheme 1, Table 1). It is noteworthy, that the crude enaminone **5** had to be immediately transformed further with hydrazine derivatives **6**, because the enamino ketone **5** slowly cyclised into methyl 4-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (**10**). For example, pyridone **10** was isolated in 48% yield upon standing of the crude **5** at rt for 48 h. Formation of **10** could be explained by intramolecular base-catalysed cyclisation of **5** into the Boc-protected pyridone **8**, followed by addition of dimethylamine to the Boc group and elimination of *tert*-butyl dimethylcarbamate (**9**) to afford **10** (Scheme 1).

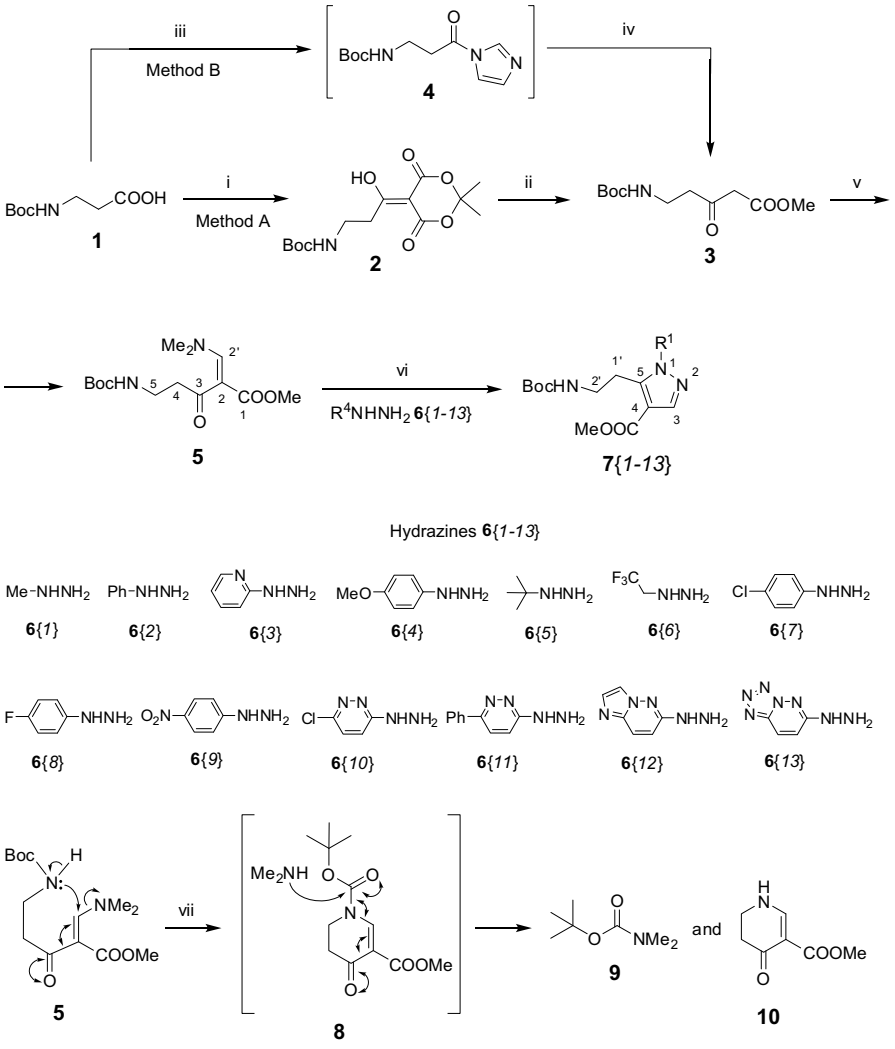
Next, we studied a four-step transformation of the primary key-intermediates **7** into the target compounds **20** by a series of selective deprotection and N-acylation reactions. Two complementary synthetic pathways were employed: (a) transformation of **7** into **20** via the intermediates **14**, **16**, and **18** (Scheme 2, Path A) and (b) transformation of **7** into **20** via the intermediates **15**, **17**, and **19** (Scheme 2, Path B). First, synthetic Path A was explored. Base-catalysed hydrolysis of methyl 5-[2-(*tert*-butoxycarbonylamino)ethyl]-1*H*-pyrazole-4-carboxylates **7**{*1–5*} in a mixture of methanol and 2 M aq sodium hydroxide at 50 °C followed by careful acidification afforded 5-[2-(*tert*-butoxycarbonylamino)ethyl]-1*H*-pyrazole-4-carboxylic acids **14**{*1–5*} in 37–94% yields. Further amidations of the acids **14**{*1,2,4*} with amines **11**{*1–5*} were carried out with bis-(pentafluorophenyl)carbonate (BPC) as coupling reagent and gave the corresponding 5-[2-(*tert*-butoxycarbonylamino)ethyl]-1*H*-pyrazole-4-carboxamides **16**{*1,1*}, **16**{*2; 2–4*}, and **16**{*4; 5*} in 40–80% yields. Acidolytic removal of the Boc group from compounds **16**{*1,1*}, **16**{*2; 2–4*}, and **16**{*4; 5*} afforded the free 5-(2-aminoethyl)-1*H*-pyrazole-4-carboxamides **18**{*1,1*}, **18**{*2; 2–4*}, and **18**{*4; 5*}, respectively, in 67–96% yields. Finally, acylation of the amine **18**{*1; 1*} with acetyl chloride **12**{*1*} and acylations of amines **18**{*2; 2–4*}, and **18**{*4; 5*} with the in situ formed pentafluorophenyl carboxylates **13**′{*2,3*} furnished the final compounds **20**{*1; 1; 1*}, **20**{*2; 2–4; 2*}, and **20**{*4; 5; 3*} in 52–89% yields (Scheme 2, Table 1).

Next, we envisaged the synthetic Path B. Treatment of the key-intermediates **7**{*1–3*} with 2 M HCl/EtOAc at 0–20 °C resulted in selective removal of the Boc group to give methyl 5-(2-aminoethyl)-1*H*-pyrazole-4-carboxyaltes hydrochlorides **15**{*1–3*} in 72–86% yields (Scheme 2, Table 1). N-Benzoylation of the δ-amino ester **15**{*2*} with benzoyl chloride **12**{*2*} then gave the *N*-benzoylated derivative **17**, which was further hydrolysed in a mixture of 2 M aq sodium hydroxide and methanol at 50 °C to afford the δ-benzamido acid **19** in 71% yield over two steps. Activation of the carboxylic acid **19** with BPC followed by treatment with amines **11**{*6–8*} gave the final carboxamides **20**{*2; 6–8; 2*} in very good yields (Scheme 2, Table 1).

3. Structure determination

The structures of novel compounds **5**, **7**, **10**, and **14**–**20** 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 **5**, **7**{*1,6,13*}, **14**{*4*}, **15**{*3*}, **16**{*4; 5*}, **17**, **18**{*4; 5*}, **19**, **20**{*2; 6–8; 2*}, and **20**{*4; 5; 3*} 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 enaminone **5** was determined by HMBC spectroscopy on the basis of long-range coupling constants ($^{3}J_{C-H}$) between the methylidene proton (*H*–C(2′)) and the carbonyl carbon atoms (O=*C*(1) and



Scheme 1. Reaction conditions: (i) Meldrum's acid, DCC, DMAP, CH_2Cl_2, 0 °C; (ii) MeOH, reflux; (iii) CDI, THF, rt; (iv) potassium monomethyl malonate, $MgCl_2$, THF, rt; (v) DMFDMA, CH_2Cl_2, rt; (vi) R^1NHNH_2 **6**{*1–13*}, MeOH or *n*-PrOH, rt or reflux; (vii) standing rt for 48 h.

O═C(3)), measured from the antiphase splitting of cross peaks in the HMBC spectrum. Generally, the magnitude of coupling constant, $^3J_{C-H}$, for nuclei with *cis*-configuration around the C═C double bond are smaller (2–6 Hz) than that for *trans*-oriented nuclei (8–12 Hz).[8–14,19] In compound **5**, the magnitudes of coupling constants, $^3J_{C(1)-H(2')}$=7 Hz (*trans*) and $^3J_{C(3)-H(2')}$=5 Hz (*cis*) showed the (*E*)-configuration around the exocyclic C═C double bond (Fig. 2).

The structure of compound **7**{*10*} was determined by X-ray diffraction (Fig. 3).

4. Conclusion

In summary, a seven-step synthesis of 1-substituted 5-(2-acylaminoethyl)-1*H*-pyrazole-4-carboxamides **20** was developed. The synthesis starts with a three-step one-pot transformation of commercially available Boc-β-alanine (**1**) into 1-substituted methyl 5-[(2-*tert*-butoxycarbonylamino)ethyl]-1*H*-pyrazole-4-carboxylates **7** comprising (a) Masamune–Claisen transformation of *N*-Boc-β-alanine (**1**) into the β-keto ester **3**,[18] (b) condensation of **3** with DMFDMA to give the enaminone **5**, and cyclisation of **5** with monosubstituted hydrazines **6**. Compounds **7** are useful intermediates for further derivatisations, since they can be selectively deprotected, either at the amino, or at the carboxy group. Several 1-substituted methyl 5-[(2-acylamino)ethyl]-1*H*-pyrazole-4-carboxamides **20** were then prepared in good yields over four steps from the key-intermediates **7**, following two complementary deprotection/acylation reaction sequences (synthetic Paths A and B, cf. Scheme 2). In conclusion, this work represents a useful synthetic application of enaminones as versatile reagents in the diversity-oriented synthesis of functionalised heterocycles.

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 ^1H and 75.5 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, IR spectra on a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyser 2400 II.

Boc-β-alanine (**1**), 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid), *N*,*N*′-dicyclohexylcarbodiimide (DCC), 4-dimethylminopyridine (DMAP), di(1*H*-imidazol-1-yl)methanone (1,1′-carbonyldiimidazole), *N*,*N*-dimethylformamide dimethylacetal (DMFDMA), hydrazines **6**{*1–9*}, bis(pentafluorophenyl) carbonate (BPC), amines **11**{*1–9*},

Table 1
Experimental data for compounds **7** and **14**–**20**

Synthesis of the key-intermediates **7**, **14**, and **15**					
Compound	R^1	Yield (%)			
		7	**14**	**15**	
7{*1*}, **14**{*1*}, **15**{*1*}	Methyl	72	59	82	
7{*2*}, **14**{*2*}, **15**{*2*}	Phenyl	65	64	72	
7{*3*}, **14**{*3*}, **15**{*3*}	Pyridin-2-yl	65	88	86	
7{*4*}, **14**{*4*}	4-Methoxyphenyl	77	94	—	
7{*5*}, **14**{*5*}	*tert*-Butyl	69	52	—	
7{*6*}	2,2,2-Trifluoroethyl	58	—	—	
7{*7*}	4-Chlorophenyl	34	—	—	
7{*8*}	4-Fluorophenyl	39	—	—	
7{*9*}	4-Nitrophenyl	55	—	—	
7{*10*}	6-Chloropyridazin-2-yl	47	—	—	
7{*11*}	6-Phenylpyridazin-2-yl	80	—	—	
7{*12*}	Imidazo[1,2-*b*]pyridazin-6-yl	62	—	—	
7{*13*}	Tetrazolo[1,5-*b*]pyridazin-6-yl	68	—	—	

Synthesis of compounds **20** by Path A (**14**→**16**→**18**→**20**)						
Compound	R^1	$-NR^2R^3$	R^4	Yield (%)		
				16	**18**	**20**
16{*1; 1*}, **18**{*1; 1*}, **20**{*1; 1; 1*}	Me	–NHMe	Me	83	67	65
16{*2; 2*}, **18**{*2; 2*}, **20**{*2; 2; 2*}	Ph	$-NHCH_2Ph$	Ph	80	96	78
16{*2; 3*}, **18**{*2; 3*}, **20**{*2; 3; 2*}	Ph	Piperidin-1-yl	Ph	93	91	89
16{*2; 4*}, **18**{*2; 4*}, **20**{*2; 4; 2*}	Ph	$-NH(CH_2)_3NMe_2$	Ph	40	85	52
16{*4; 5*}, **18**{*4; 5*}, **20**{*4; 5; 3*}	4-MeO–C_6H_4	$-NH(CH_2)_2COOEt$	Z-GlyGly[b]	52	85	71

Synthesis of compounds **20** by Path B (**15**→**17**→**19**→**20**)						
Compound	R^1	$-NR^2R^3$	R^4	Yield (%)		
				17	**19**	**20**
17, **19**, **20**{*2; 6; 2*}	Ph	$-NHCH_2Py$[a]	Ph	81	88	91
20{*2; 7; 2*}	Ph	3-(2-Oxopyrrolidin-1-yl)propylamino	Ph			90
20{*2; 8; 2*}	Ph	3-(Diethylcarbamoyl)piperidin-1-yl	Ph			97

[a] Py=pyridin-2-yl.
[b] Z-GlyGly=*N*-[*N*-(benzyloxycarbonyl)aminoacetyl]aminoacetyl.

acid chlorides **12**{*1,2*}, and carboxylic acids **13**{*1–3*} are commercially available (Sigma–Aldrich). 6-Chloro-3-hydrazinopyridazine **6**{*10*},[20] 3-hydrazino-6-phenylpyridazine **6**{*11*},[21] 6-hydrazinoimidazo[1,2–*b*]pyridazine **6**{*12*},[22] and 6-hydrazinotetrazolo[1,5–*b*]pyridazine **6**{*13*},[23] were prepared according to the literature procedures.

5.2. Synthesis of methyl 5-(*tert*-butoxycarbonylamino)-3-oxopentanoate (3)

Method A

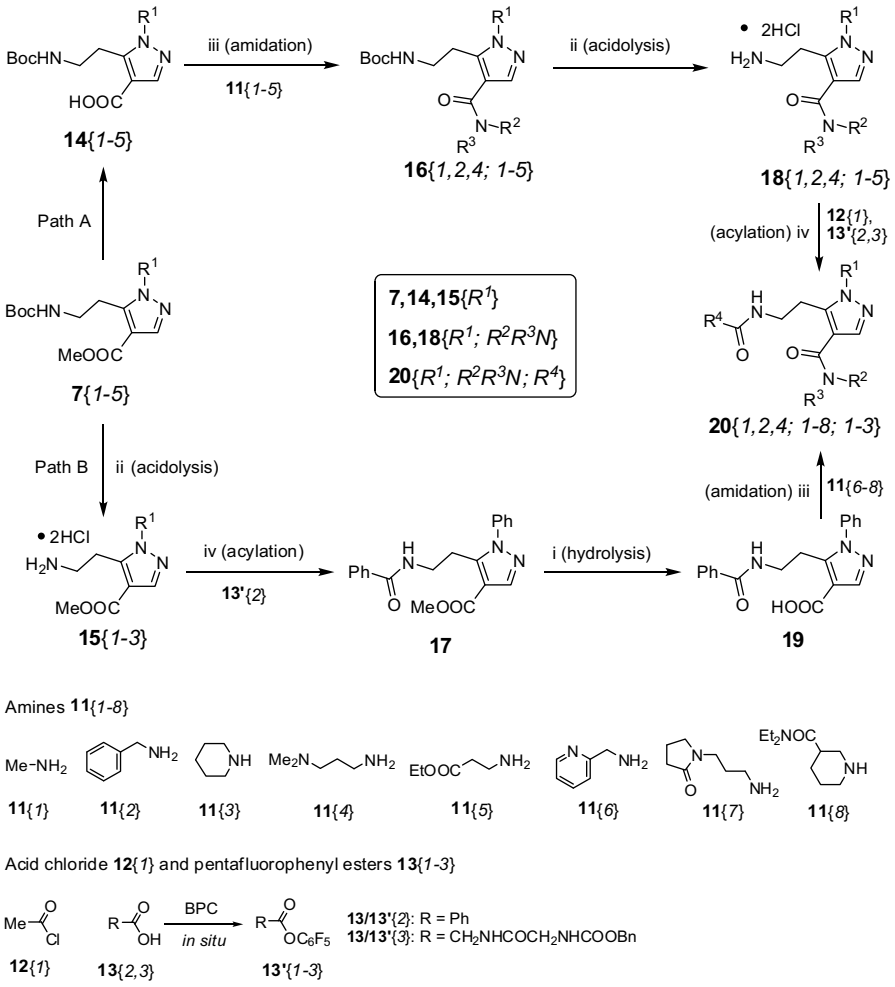
Compound **3** was prepared according to a slightly modified literature procedure for the preparation of a closely related compound.[14a] A solution of DCC (5.674 g, 27.5 mmol) in anhydrous dichloromethane (25 mL) was added slowly to a stirred solution of Meldrum's acid (3.603 g, 25 mmol), Boc-β-alanine (**1**) (4.730 g, 25 mmol), and DMAP (3.360 g, 27.5 mmol) in anhydrous dichloromethane (55 mL) at 0 °C (ice-bath). The reaction mixture was stirred at 0 °C for 16 h and the precipitated *N*,*N*′-dicyclohexylurea (DCU) was removed by filtration and washed with anhydrous dichloromethane (25 mL). The filtrate was washed subsequently with 1 M aq $NaHSO_4$ (2×170 mL) and brine (2×170 mL), dried with anhydrous Na_2SO_4, filtered, and the filtrate was evaporated in vacuo. The residue (crude compound **8**) was dissolved in anhydrous methanol (150 mL) and the solution was refluxed under argon for 5 h. Volatile components were evaporated in vacuo and the residue was purified by column chromatography (silica gel, EtOAc). Fractions containing the product were combined and evaporated in vacuo to give the *title compound* **3**. Yield: 3.65 g (60%) of yellow oil. Spectral data of compound **3** were in agreement with the literature data.[18b,c] The crude compound **3** was used in the next step without any further purification.

Method B

Compound **3** was prepared according to a slightly modified literature procedure.[18c] Under argon, 1,1′-carbonyldiimidazole (38.8 g 244 mmol) was added portion wise (~3–5 min.) to a solution of Boc-β-alanine (**1**) (37.8 g, 200 mmol) in anhydrous THF (700 mL) and the mixture was stirred at rt for 1 h. Then, a well homogenised and powdered solid mixture of $MgCl_2$ (18.4 g, 193 mmol) and potassium hydrogen methyl malonate (47.0 g, 300 mmol) was added and the reaction mixture was stirred at rt for 14 h. Volatile components were evaporated in vacuo, ethyl acetate (600 mL) was added, and the so formed suspension was washed subsequently with 1 M aq $NaHSO_4$ (3×200 mL) and brine (200 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and the filtrate was evaporated in vacuo to give the *title compound* **3**. Yield: 44.2 g (90%) of colourless oil. Spectral data of compound **3** were in agreement with the literature data.[18b,c] Compound **3** was used in the next step without any further purification.

5.3. Synthesis of methyl (*E*)-5-(*tert*-butoxycarbonylamino)-2-[(dimethylamino)methylidene]-3-oxopentanoate (5)

The crude β-keto ester **3** from the previous step (24.5 g, 100 mmol) was dissolved in anhydrous dichloromethane (100 mL), *N*,*N*′-dimethylformamide dimethylacetal (DMFDMA) (18 mL, 130 mmol) was added, the so formed solution was left at rt for 12 h, and volatile components were evaporated in vacuo to give the *title compound* **3**, which was used for further transformations without purification. Yield: 30 g (99%) of yellow oil; R_f (EtOAc) 0.26; ν_{max} (liquid film) 3362, 2977, 2930, 1707, 1642, 1578, 1502, 1426, 1366, 1172, 1113, 1046, 965, 863 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.28 (9H, s, *t-Bu*), 2.59 (2H, t, *J*=7.2 Hz, 4-CH_2), 2.86 (6H, br s, NMe_2), 3.04 (2H,



Scheme 2. Reaction conditions: (i) 2 M aq NaOH, MeOH, 50 °C; (ii) 2 M HCl–EtOAc, 0–20 °C; (iii) BPC, Et_3N, MeCN, rt, then R^2R^3NH **11**{*1–8*}, Et_3N, MeCN, rt; (iv) MeCOCl **12**{*1*}, Et_3N, EtOH, 0–20 °C or $R^4COOC_6F_5$ **13′** (obtained R^4COOH **13**, BPC, and Et_3N), MeCN, Et_3N, rt.

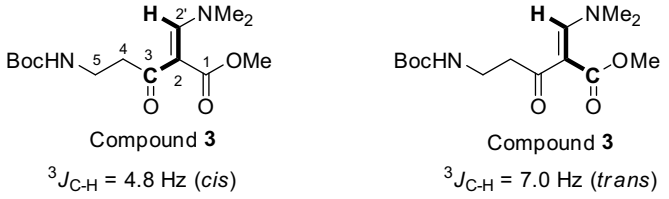


Figure 2.

m, 5-CH_2), 3.55 (3H, s, O*Me*), 6.47 (1H, t, N*H*), 7.56 (1H, 2′-*H*); δ_C (75.5 MHz, DMSO-d_6) 28.2, 32.0, 36.6, 41.1, 50.7, 77.4, 101.4, 155.5, 156.1, 167.9, 194.1; *m*/*z* 301 (77, MH^+), 245 (97), 201 (85), 184 (70), 169 (100), 156 (66), 130 (39%); HRMS (ESI): MH^+, found 301.1749, $C_{14}H_{25}N_2O_5$ requires 301.1763.

*5.3.1. Intramolecular cyclisation of (E)-methyl 5-(tert-butoxycarbonylamino)-2-[(dimethylamino)methyidene]-3-oxopentanoate (**5**) into methyl 4-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (**10**)*

The crude oily enaminone **5** (15 g, 50 mmol) was left to stand at rt for two days. The solid residue was triturated with ethyl acetate (50 mL) and the precipitate was collected by filtration to give the *title compound* **10**. Yield: 3.76 g (48%) of a white solid, mp 230–235 °C; [Found: C, 54.40; H, 5.95; N; 9.04. $C_7H_9NO_3$ requires: C, 54.19; H, 5.85; N, 9.03%]; R_f (17% EtOH/EtOAc) 0.15; ν_{max} (KBr) 3165, 2982, 2944, 1705, 1687, 1591, 1502, 1440, 1388, 1329, 1289, 1221, 1184, 1074, 1032, 784 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 2.29 (2H, t, *J*=7.8 Hz, 5-CH_2), 3.51 (2H, *J*=7.8 Hz, 6-CH_2), 3.55 (3H, s, O*Me*), 8.17 (1H, s, 2-*H*), 8.89 (1H, br s, N*H*); δ_C (75.5 MHz, DMSO-d_6) 36.6, 41.1, 50.9, 99.5, 158.7, 165.8, 187.2; *m*/*z* 156 (100, MH^+), 124 (81%); HRMS (ESI): MH^+, found 156.0662, $C_7H_{10}NO_3$ requires 156.0661.

5.4. Reactions of the enaminone 5 with hydrazine derivatives 6{*1–13*}. General procedures for the preparation of 1-substituted methyl 5-[2-(*tert*-butoxycarbonylamino)ethyl]-1*H*-pyrazole-4-carboxylates 7{*1–13*}

General procedure A

Hydrazine derivative **6** (10 mmol) was added to a stirred solution of the enaminone **5** (3.0 g, 10 mmol) in methanol (20 mL) and the mixture was stirred at rt for 3 h. The precipitate was collected by filtration to give the *title compound* **7**. Compounds **7**{*3,7,8,12*} were prepared in this manner.

General procedure B

Hydrazine derivative **6** (10 mmol) was added to a stirred solution of the enaminone **5** (3.0 g, 10 mmol) in methanol (20 mL) or 1-propanol (20 mL) and the mixture was stirred at rt or under reflux for 3 h. Volatile components were evaporated in vacuo and the residue was triturated with water or ethanol/water. The precipitate was collected by filtration to give the *title compound* **7**. Compounds **7**{*1,2,5,6,9,13*} were prepared in this manner.

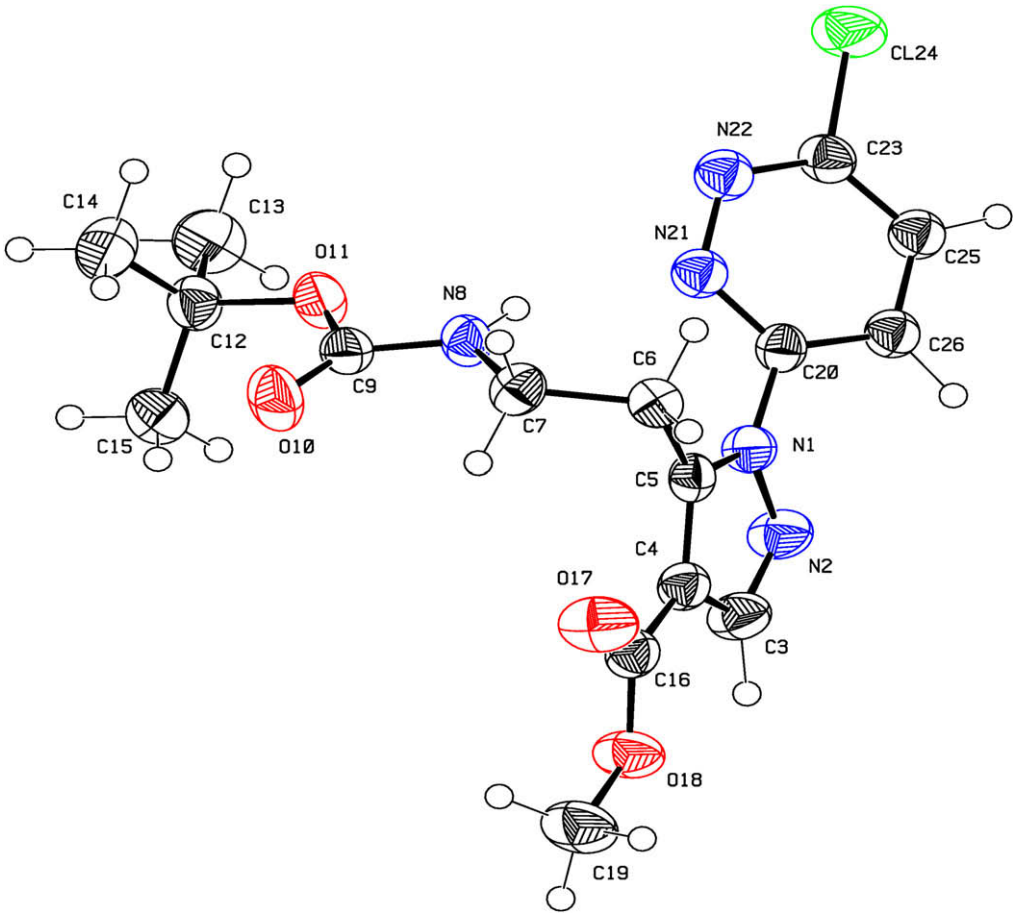


Figure 3. The asymmetric unit of compound **7**{*10*}. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

General procedure C

Hydrazine derivative hydrochloride **6** (10 mmol) was added to a stirred solution of the enaminone **5** (3.0 g, 10 mmol) in methanol (20 mL) or 1-propanol (20 mL) and the mixture was stirred under refluxed for 3 h. Volatile components were evaporated in vacuo and the residue was purified by flash chromatography (FC) over silica gel. Fractions containing the product were combined and evaporated in vacuo to give the *title compound* **7**. Compounds **7**{*4,10,11*} were prepared in this manner.

The following compounds were prepared in this manner:

5.4.1. Methyl 5-[2-(tert-butoxycarbonylamino)ethyl]-1-methyl-1H-pyrazole-4-carboxylate **7***{1}*. Prepared from **5** and methylhydrazine **6**{*1*} (0.46 g, 0.53 mL, 10 mmol) in methanol at rt; General Procedure B; trituration with water. Yield: 2.036 g (72%) of a yellowish solid; mp 80–82 °C; R_f (33% EtOAc/hexanes) 0.28; ν_{max} (KBr) 3370, 2983, 1703, 1684, 1556, 1535, 1498, 1444, 1373, 1281, 1238, 1162, 1086, 1026, 990, 784 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.36 (9H, s, *t-Bu*), 3.02–3.10 (2H, m, 1′-CH_2), 3.11–3.22 (2H, m, 2′-CH_2), 3.74 (3H, s, N*Me*), 3.80 (3H, s, O*Me*), 6.94 (1H, t, *J*=5.7 Hz, N*H*), 7.75 (1H, s, 3-*H*); δ_C (75.5 MHz, DMSO-d_6) 24.9, 28.1, 36.2, 40.7, 50.7, 77.6, 110.8, 139.7, 144.5, 155.5, 163.2; *m*/*z* 284 (35, MH^+), 228 (39), 214 (18), 184 (100%); HRMS (ESI): MH^+, found 284.1621, $C_{13}H_{22}N_3O_4$ requires 284.1610.

5.4.2. Methyl 5-[2-(tert-butoxycarbonylamino)ethyl]-1-phenyl-1H-pyrazole-4-carboxylate **7***{2}*. Prepared from **5** and phenylhydrazine **6**{*2*} (1.08 g, 10 mmol) in methanol at rt; General Procedure B; trituration with ethanol/water (1:2). Yield: 2.238 g (65%) of a yellowish solid; mp 102–105 °C; [Found: C, 62.41; H, 6.91; N; 12.12. $C_{18}H_{23}N_3O_4$ requires C, 62.59; H, 6.71; N, 12.17%]; R_f (33% EtOAc/hexanes) 0.33; ν_{max} (KBr) 3345, 2972, 1720, 1701, 1554, 1510, 1361, 1281, 1255, 1243, 1195, 1009, 759 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.36 (9H, s, *t-Bu*), 3.12 (2H, t, *J*=6.6 Hz, 1′-CH_2), 3.36 (2H, m, 2′-CH_2), 3.87 (3H, s, O*Me*), 4.86 (1H, br s, N*H*), 7.36–7.59 (5H, m, *Ph*), 8.02 (1H, s, 3-*H*); δ_C (75.5 MHz, DMSO-d_6) 25.7, 28.1, 39.5, 51.0, 77.5, 112.2, 126.1, 128.9, 129.3, 138.5, 141.2, 145.1, 155.3, 163.1.

5.4.3. Methyl 5-[2-(tert-butoxycarbonylamino)ethyl]-1-(pyridin-2-yl)-1H-pyrazole-4-carboxylate **7***{3}*. Prepared from **5** and 2-hydrazinopyridine **6**{*3*} (1.090 g, 10 mmol) in methanol at rt; General Procedure A. Yield: 2.263 g (65%) of a yellowish solid; mp 117–121 °C; [Found: C, 58.93; H, 6.49; N; 16.02. $C_{17}H_{22}N_4O_4$ requires C, 58.95; H, 6.40; N, 16.17%]; R_f (EtOAc) 0.60; ν_{max} (KBr) 3393, 2978, 1711, 1699, 1561, 1507, 1436, 1290, 1164, 1099, 787 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.36 (9H, s, *t-Bu*), 3.54–3.65 (4H, m, CH_2CH_2), 3.87 (3H, s, O*Me*), 5.68 (1H, br s, N*H*), 7.28–7.35 (1H, m, 5″-*H*), 7.84–7.92 (2H, m, 4″-*H*, 6″-*H*), 8.03 (1H, s, 3-*H*), 8.50 (1H, dt, *J*=1.2, 4.8 Hz, 3″-*H*); δ_C (75.5 MHz, DMSO-d_6) 25.9, 28.1, 39.5, 51.1, 77.3, 113.7, 118.0, 123.2, 139.4, 141.8, 146.0, 147.9, 152.1, 155.2, 163.0.

5.4.4. Methyl 5-[2-(tert-butoxycarbonylamino)ethyl]-1-(4-methoxyphenyl)-1H-pyrazole-4-carboxylate **7***{4}*. Prepared from **5** and 4-methoxyphenylhydrazine hydrochloride **6**{*4*} (1.74 g, 10 mmol) in methanol under reflux; General Procedure C; FC: EtOAc/hexanes, 1:1. Yield: 2.893 g (77%) of an orange solid; mp 108–110 °C; [Found: C, 60.49; H, 6.81; N; 11.14. $C_{19}H_{25}N_3O_5$ requires C, 60.79; H, 6.71; N, 11.19%]; R_f (33% EtOAc/hexanes) 0.28; ν_{max} (KBr) 3289, 2977, 1714, 1561, 1519, 1288, 1253, 1173, 1094, 990, 848 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.36 (9H, s, *t-Bu*), 3.08 (2H, t, *J*=6.6 Hz, 1′-CH_2), 3.30–3.42 (2H,

m, 2′-CH_2), 3.88 and 3.89 (6H, 2s, 1:1, 2×O*Me*), 4.84 (1H, br s, N*H*), 6.99–7.06 and 7.34–7.41 (4H, 2m, 1:1, C$_6H_4$), 8.01 (1H, s, 3-*H*); δ_C (75.5 MHz, $CDCl_3$) 26.1, 28.7, 40.0, 51.7, 55.9, 79.5, 112.9, 114.9, 128.1, 132.0, 142.0, 145.7, 156.2, 160.4, 164.8; *m*/*z* 375 (58, M^+), 319 (31), 302 (51), 258 (34), 246 (100%); HRMS (EI): M^+, found 375.180320, $C_{19}H_{25}N_3O_5$ requires 375.179421.

5.4.5. Methyl 5-[2-(tert-butoxycarbonylamino)ethyl]-1-(tert-butyl)-1H-pyrazole-4-carboxylate ***7****{5}*. Prepared from **5** and *tert*-butylhydrazine hydrochloride **6**{*5*} (1.246 g, 10 mmol) in 1-propanol under reflux; General Procedure B; trituration with water. Yield: 2.245 g (69%) of a yellowish solid; mp 89–92 °C; [Found: C, 59.19; H, 8.54; N; 12.95. $C_{16}H_{27}N_3O_4$ requires C, 59.06; H, 8.36; N, 12.91%]; R_f (33% EtOAc/hexanes) 0.29; ν_{max} (KBr) 3343, 2978, 1721, 1706, 1550, 1525, 1471, 1394, 1365, 1279, 1241, 1241, 1172, 1006, 940, 780 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.38 (9H, s, *t-Bu*), 1.63 (9H, s, *t-Bu*), 3.11–3.29 (4H, m, CH_2CH_2), 3.74 (3H, s, O*Me*), 7.08 (1H, t, N*H*), 7.74 (1H, s, 3-*H*); δ_C (75.5 MHz, $CDCl_3$) 26.7, 28.2, 30.1, 38.7, 50.8, 61.2, 77.6, 112.5, 138.4, 143.9, 155.5, 163.2.

5.4.6. Methyl 5-[2-(tert-butoxycarbonylamino)ethyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxylate ***7****{6}*. Prepared from **5** and 2,2,2-trifluoroethylhydrazine **6**{*6*} (70% in water, 1.26 mL, 10 mmol) in methanol at rt; General Procedure B; trituration with water. Yield: 2.045 g (58%) of a white solid; mp 127–129 °C; R_f (33% EtOAc/hexanes) 0.66; ν_{max} (KBr) 3406, 2981, 1716, 1687, 1566, 1523, 1268, 1242, 1165, 1092, 1066, 930, 783 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.42 (9H, s, *t-Bu*), 3.25 (2H, t, *J*=6.6 Hz, 1′-CH_2), 3.40 (2H, m, 2′-CH_2), 3.86 (3H, s, O*Me*), 4.83 (3H, q, *J*=8.1 Hz, CH_2CF$_3$ and N*H*), 7.95 (1H, s, 3-*H*); δ_C (75.5 MHz, DMSO-d_6) 24.5, 28.0, 38.8, 49.2, 51.1, 77.8, 111.9, 125.2, 140.6, 141.5, 155.6, 162.8. *m*/*z* 352 (50, MH^+), 296 (58), 252 (100), 225 (33%); HRMS (ESI): MH^+, found 352.1487, $C_{14}H_{21}F_3N_3O_4$ requires 352.1484.

5.4.7. Methyl 5-[2-(tert-butoxycarbonylamino)ethyl]-1-(4-chlorophenyl)-1H-pyrazole-4-carboxylate ***7****{7}*. Prepared from **5** and 4-chlorophenylhydrazine hydrochloride **6**{*7*} (1.79 g, 10 mmol) in methanol under reflux; General Procedure A. Yield: 1.291 g (34%) of a brownish solid; mp 136–137 °C; [Found: C, 56.74; H, 5.90; N; 11.00. $C_{18}H_{22}ClN_3O_4$ requires: C, 56.92; H, 5.84; N, 11.06%]; R_f (EtOAc) 0.72; ν_{max} (KBr) 3412, 3115, 2987, 1722, 1697, 1555, 1504, 1434, 1361, 1280, 1261, 1193, 1094, 996, 837, 782 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.30 (9H, s, *t-Bu*), 2.97–3.14 (4H, m, CH_2CH_2), 3.79 (3H, s, O*Me*), 6.77 (1H, br t, N*H*), 7.48–7.58 and 7.59–7.66 (4H, 2m, 1:1, C$_6H_4$), 8.02 (1H, s, 3-*H*); δ_C (75.5 MHz, DMSO-d_6) 25.6, 28.1, 39.5, 51.1, 77.5, 112.3, 127.9, 129.3, 133.5, 137.4, 141.4, 145.4, 155.3, 163.0.

5.4.8. Methyl 5-[2-(tert-butoxycarbonylamino)ethyl]-1-(4-fluorophenyl)-1H-pyrazole-4-carboxylate ***7****{8}*. Prepared from **5** and 4-fluorophenylhydrazine hydrochloride **6**{*8*} (1.625 g, 10 mmol) in methanol under reflux; General Procedure A. Yield: 1.409 g (39%) of a brownish solid; mp 134–136 °C; [Found: C, 59.48; H, 6.29; N; 11.39. $C_{18}H_{22}FN_3O_4$ requires C, 59.49; H, 6.10; N, 11.56%]; R_f (EtOAc) 0.71; ν_{max} (KBr) 3373, 3114, 2985, 1723, 1698, 1557, 1518, 1476, 1437, 1363, 1281, 1220, 1098, 998, 841, 782 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.30 (9H, s, *t-Bu*), 2.95–3.13 (4H, m, CH_2CH_2), 3.79 (3H, s, O*Me*), 6.77 (1H, br s, N*H*), 7.34–7.44 and 7.48–7.61 (4H, 2m, 1:1, C$_6H_4$), 8.00 (1H, s, 3-*H*); δ_C (75.5 MHz, $CDCl_3$) 25.9, 28.4, 39.7, 51.5, 79.4, 113.0, 116.5, 128.5, 134.9, 142.0, 145.5, 156.0, 161.2, 164.4.

5.4.9. Methyl 5-[2-(tert-butoxycarbonylamino)ethyl]-1-(4-nitrophenyl)-1H-pyrazole-4-carboxylate ***7****{9}*. Prepared from **5** and 4-nitrophenylhydrazine **6**{*9*} (1.531 g, 10 mmol); General Procedure B; trituration with water. Yield: 2.119 g (55%) of a brownish solid; mp 119–123 °C; [Found: C, 55.37; H, 5.76; N, 14.37. $C_{18}H_{22}N_4O_6$ requires C, 55.38; H, 5.68; N; 14.35%]; R_f (EtOAc) 0.72; ν_{max} (KBr) 3383, 3124, 1713, 1702, 1596, 1567, 1523, 1394, 1344, 1266, 1252, 1201, 1162, 967, 953, 937, 854 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.36 (9H, s, *t-Bu*), 3.21 (2H, t, *J*=6.7 Hz, 1′-CH_2), 3.42 (2H, q, *J*=6.7 Hz, 2′-CH_2), 3.89 (3H, s, O*Me*), 4.82 (1H, br s, N*H*), 7.79 and 8.39 (4H, 2d, 1:1, *J*=8.7 Hz, C$_6H_4$), 8.07 (1H, s, 3-*H*); δ_C (75.5 MHz, $CDCl_3$) 26.3, 28.5, 39.7, 51.7, 79.7, 114.2, 125.0, 126.7, 143.0, 143.9, 145.6, 147.6, 156.1, 164.0.

5.4.10. Methyl 5-[2-(tert-butoxycarbonylamino)ethyl]-1-(6-chloropyridazin-3-yl)-1H-pyrazole-4-carboxylate ***7****{10}*. Prepared from **5** and 6-chloro-3-hydrazinopyridazine **6**{*10*} (1.446 g, 10 mmol) in methanol under reflux; General Procedure C; FC: EtOAc/hexanes, 1:2. Yield: 1.783 g (47%) of a brownish solid; mp 146–148 °C; [Found: C, 50.46; H, 5.47; N; 17.99. $C_{16}H_{20}ClN_5O_4$ requires C, 50.33; H, 5.28; N, 18.34%]; R_f (33% EtOAc/hexanes) 0.49; ν_{max} (KBr) 3365, 3062, 2979, 1718, 1702, 1570, 1540, 1484, 1428, 1371, 1284, 1242, 1161, 1095, 1013, 941, 868, 781 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.32 (9H, s, *t-Bu*), 3.55 (2H, q, *J*=6.3 Hz, 2′-CH_2), 3.79 (2H, t, *J*=6.3 Hz, 1′-CH_2), 3.90 (3H, s, O*Me*), 5.00 (1H, br s, N*H*), 7.68 (1H, d, *J*=7.2 Hz, 4″-*H*), 8.08 (1H, s, 3-*H*), 8.17 (1H, d, *J*=7.2 Hz, 5″-*H*); δ_C (75.5 MHz, DMSO-d_6) 25.8, 28.1, 39.5, 51.3, 77.4, 114.7, 126.0, 131.7, 143.1, 147.1, 155.2, 155.3, 155.7, 162.7.

5.4.11. Methyl 5-[2-(tert-butoxycarbonylamino)ethyl]-1-(6-phenylpyridazin-3-yl)-1H-pyrazole-4-carboxylate ***7****{11}*. Prepared from **5** and 3-hydrazino-6-phenylpyridazine **6**{*11*} (1.862 g, 10 mmol) in methanol under reflux; General Procedure C; FC: EtOAc–hexanes, 1:2. Yield: 3.404 g (80%) of a white solid; mp 123–125 °C; [Found: C, 62.11; H, 6.01; N; 16.54. $C_{22}H_{25}N_5O_4$ requires C, 62.40; H, 5.95; N, 16.54%]; R_f (33% EtOAc/hexanes) 0.32; ν_{max} (KBr) 3410, 3315, 2977, 1721, 1710, 1569, 1545, 1453, 1404, 1278, 1260, 1170, 1091, 980, 780 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.33 (9H, s, *t-Bu*), 3.61 (2H, q, *J*=6.3 Hz, 2′-CH_2), 3.87 (2H, t, *J*=6.3 Hz, 1′-CH_2), 3.91 (3H, s, O*Me*), 5.19 (1H, br s, N*H*), 7.50–7.61 (3H, m, 3*H* of *Ph*), 8.05 (1H, d, *J*=9.3 Hz, 4″-*H*), 8.07–8.11 (3H, m, 2*H* of *Ph*, 3-*H*), 8.22 (1H, d, *J*=9.3 Hz, 5″-*H*); δ_C (75.5 MHz, DMSO-d_6) 25.8, 28.1, 39.5, 51.3, 77.3, 114.4, 123.4, 127.0, 127.2, 129.1, 130.4, 135.0, 142.9, 146.8, 155.2, 155.3, 158.1, 162.9.

5.4.12. Methyl 5-[2-(tert-butoxycarbonylamino)ethyl]-1-(imidazo-[1,2-b]pyridazin-3-yl)-1H-pyrazole-4-carboxylate ***7****{12}*. Prepared from **5** and 6-hydrazinoimidazo[1,2-*b*]pyridazine **6**{*12*} (1.492 g, 10 mmol) in methanol at rt; General Procedure A. Yield: 2.380 g (62%) of a white solid; mp 178–180 °C; [Found: C, 56.02; H, 5.82; N; 22.0. $C_{18}H_{22}N_6O_4$ requires C, 55.95; H, 5.74; N, 21.75%]; R_f (33% EtOAc/hexanes) 0.30; ν_{max} (KBr) 3238, 3140, 2981, 1720, 1706, 1424, 1272, 1170, 1130, 979, 815, 781 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.38 (9H, s, *t-Bu*), 3.57–3.69 (4H, m, CH_2CH_2), 3.90 (3H, s, O*Me*), 5.07 (1H, br s, N*H*), 7.74 (1H, d, *J*=9.7 Hz, 7″-*H*), 7.85 (1H, d, *J*=0.9 Hz, 2″-*H*), 8.08 (1H, s, 3-*H*), 8.10 (1H, d, *J*=9.5 Hz, 8″-*H*), 8.16 (1H, br s, 3″-*H*); δ_C (75.5 MHz, DMSO-d_6) 27.1, 29.0, 40.4, 52.2, 78.3, 115.0, 115.2, 118.8, 128.6, 135.6, 143.5, 147.5, 148.8, 156.2, 163.6.

5.4.13. Methyl 5-[2-(tert-butoxycarbonylamino)ethyl]-1-(tetrazolo-[1,5-b]pyridazin-3-yl)-1H-pyrazole-4-carboxylate ***7****{13}*. Prepared from **5** and 6-hydrazinotetrazolo[1,2-*b*]pyridazine **6**{*13*} (1.511 g, 10 mmol) in methanol at rt; General Procedure B; trituration with methanol/water. Yield: 3.633 g (68%) of a brownish solid; mp 130–134 °C; [Found: C, 49.36; H, 5.29; N; 28.34. $C_{16}H_{20}N_8O_4$ requires C, 49.48; H, 5.19; N, 28.85%]; R_f (33% EtOAc/hexanes) 0.20; ν_{max} (KBr) 3391, 3084, 1734, 1624, 1574, 1547, 1417, 1379, 1267, 1245, 1175, 1163, 986, 828 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.27 (9H, s, *t-Bu*), 3.64 (2H, q, *J*=6.3 Hz, 2′-CH_2), 3.87 (2H, t, *J*=6.3 Hz, 1′-CH_2), 3.92 (3H, s, O*Me*), 4.87 (1H, br t, N*H*), 8.12 (1H, s, 3-*H*), 8.44 (1H, d, *J*=9.9 Hz, 7″-*H*), 8.50 (1H, d, *J*=9.9 Hz, 8″-*H*), δ_C (75.5 MHz, DMSO-d_6) 25.6, 28.0, 38.8, 51.5, 77.4, 115.4, 123.1, 127.5, 142.5, 143.8, 147.8, 150.9,

155.2, 162.5; *m*/*z* 389 (41, MH^+), 374 (21), 333 (45), 289 (78), 252 (32), 272 (20), 225 (61), 214 (59), 164 (76), 159 (100%); HRMS (ESI): MH^+, found 389.1688, $C_{16}H_{21}N_8O_4$ requires 389.1686.

5.5. Base-catalysed hydrolysis of the methyl esters 7. General procedure for the preparation of 1-substituted 5-[2-(acylamino)-ethyl]-1*H*-pyrazole-4-carboxylic acids 14{*1–5*}

A mixture of **7** (10 mmol), methanol (30 mL), and 2 M aq NaOH (15 mL, 30 mmol) was stirred at 50 °C for 12 h. Methanol was removed by careful evaporation in vacuo (100 mbar, 40 °C) and the residual aqueous solution was cooled to 0 °C (ice-bath) and acidified, first with 6 M hydrochloric acid (4.5 mL, 27 mmol) and then with 1 M aq $NaHSO_4$ (5 mL, 5 mmol). The precipitate was collected by filtration, and washed with cold water (0 °C, 5 mL) to give the *title compound* **14**.

The following compounds were prepared in this manner:

*5.5.1. 5-[2-(tert-Butoxycarbonylamino)ethyl]-1-methyl-1H-pyrazole-4-carboxylic acid **14**{1}*

Prepared from **7**{*1*} (2.833 g, 10 mmol). Yield: 1.574 g (59%) of a white solid; mp 162–165 °C; [Found: C, 53.38; H, 7.31; N; 15.34. $C_{12}H_{19}N_3O_4$ requires C, 53.52; H, 7.11; N, 15.60%]; R_f (EtOAc) 0.53; ν_{max} (KBr) 3373, 2980, 1682, 1536, 1499, 1446, 1280, 1250, 1163, 780 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.35 (9H, s, *t-Bu*), 3.00–3.20 (4H, m, CH_2CH_2), 3.78 (3H, s, O*Me*), 6.94 (1H, br t, *J*=5.4 Hz, N*H*), 7.70 (1H, s, 3-*H*), 12.17 (1H, br s, COO*H*); δ_C (75.5 MHz, DMSO-d_6) 24.8, 28.2, 36.2, 39.5, 77.7, 111.8, 140.1, 144.3, 155.6, 164.4.

5.5.2. 5-[2-(tert-Butoxycarbonylamino)ethyl]-1-phenyl-1H-pyrazole-4-carboxylic acid 14{2}

Prepared from **7**{*2*} (3.454 g, 10 mmol). Yield: 1.920 g (64%) of a white solid; mp 157–160 °C; [Found: C, 61.38; H, 6.58; N; 12.70. $C_{17}H_{21}N_3O_4$ requires C, 61.62; H, 6.39; N, 12.68%]; R_f (EtOAc) 0.41; ν_{max} (KBr) 3315, 3264, 3102, 2980, 1685, 1656, 1552, 1503, 1405, 1368, 1292, 1271, 1165, 1144, 948, 762 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.30 (9H, s, *t-Bu*), 3.01 (2H, t, *J*=6.5 Hz, 1′-CH_2), 3.11 (2H, q, *J*=6.5 Hz, 2′-CH_2), 6.79 (1H, br t, *J*=5.0 Hz, N*H*), 7.46–7.58 (5H, m, *Ph*), 7.95 (1H, s, 3-*H*), 12.42 (1H, br s, COO*H*); δ_C (75.5 MHz, DMSO-d_6) 25.5, 28.1, 39.5, 77.5, 113.1, 126.1, 128.8, 129.2, 138.7, 141.6, 144.9, 155.3, 164.3.

*5.5.3. 5-[2-(tert-Butoxycarbonylamino)ethyl]-1-(pyridin-2-yl)-1H-pyrazole-4-carboxylic acid **14**{3}*

Prepared from **7**{*3*} (3.464 g, 10 mmol). Yield: 2.923 g (88%) of a white solid; mp 147–150 °C; [Found: C, 57.69; H, 6.20; N; 16.69. $C_{16}H_{20}N_4O_4$ requires: C, 57.82; H, 6.07; N, 16.86%]; R_f (EtOAc) 0.11; ν_{max} (KBr) 3330, 2980, 1721, 1697, 1558, 1477, 1436, 1402, 1294, 1190, 1170, 963, 779, 753 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.28 (9H, s, *t-Bu*), 3.22 (2H, q, *J*=6.1 Hz, 2′-CH_2), 3.51 (2H, t, *J*=6.6 Hz, 1′-CH_2), 6.74 (1H, t, *J*=5.0 Hz, N*H*), 7.49 (1H, ddd, *J*=0.9, 4.9, 7.5 Hz, 5″-*H*), 7.78 (1H, dt, *J*=0.9, 8.2 Hz, 3″-*H*), 8.01 (1H, s, 3-*H*), 8.06 (1H, ddd, *J*=1.9, 7.5, 8.2 Hz, 4″-*H*), 8.54 (1H, ddd, *J*=0.9, 1.9, 4.9 Hz, 6″-*H*), O*H* exchanged; δ_C (75.5 MHz, DMSO-d_6) 25.6, 28.1, 40.3, 77.3, 114.6, 118.0, 123.1, 139.4, 142.2, 145.8, 147.9, 152.2, 155.2, 164.2

*5.5.4. 5-[2-(tert-Butoxycarbonylamino)ethyl]-1-(4-methoxyphenyl)-1H-pyrazole-4-carboxylic acid **14**{4}*

Prepared from **7**{*4*} (3.754 g, 10 mmol). Yield: 3.420 g (94%) of a white solid; mp 190–194 °C; R_f (EtOAc) 0.48; ν_{max} (KBr) 3305, 2984, 2937, 1708, 1678, 1552, 1518, 1279, 1255, 1166, 986, 843 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.38 (9H, s, *t-Bu*), 3.11 (2H, t, *J*=6.6 Hz, 1′-CH_2), 3.30–3.41 (2H, m, 2′-CH_2), 3.86 (3H, s, O*Me*), 4.81 (1H, br s, N*H*), 6.98–7.03 and 7.32–7.42 (4H, 2m, 1:1, C_6H_4), 8.06 (1H, s, 3-*H*), O*H* exchanged; δ_C (75.5 MHz, DMSO-d_6) 25.5, 28.2, 55.4, 77.5, 112.8, 114.3, 127.6, 131.7, 141.3, 145.1, 155.3, 159.3, 161.9, 164.4; *m*/*z* 362 (84, MH^+), 306 (37), 262 (43), 244 (100), 225 (18%); HRMS (ESI): MH^+, found 362.1718, $C_{18}H_{24}N_3O_5$ requires 362.1716.

*5.5.5. 5-[2-(tert-Butoxycarbonylamino)ethyl]-1-tert-butyl-1H-pyrazole-4-carboxylic acid **14**{5}*

Prepared from **7**{*5*} (3.254 g, 10 mmol). Yield: 1.628 g (52%) of a white solid; mp 187–190 °C; [Found: C, 57.46; H, 8.30; N; 13.36. $C_{15}H_{25}N_3O_4$ requires C, 57.86; H, 8.09; N, 13.49%]; R_f (EtOAc) 0.43; ν_{max} (KBr) 3451, 3317, 3258, 3103, 2981, 2940, 1690, 1545, 1475, 1462, 1410, 1368, 1292, 1247, 1139, 984, 748 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.36 (9H, s, *t-Bu*), 1.60 (9H, s, *t-Bu*), 3.11–3.35 (4H, m, CH_2CH_2), 7.04 (1H, br s, N*H*), 7.67 (1H, s, 3-*H*), 12.13 (1H, br s, COO*H*); δ_C (75.5 MHz, DMSO-d_6) 26.4, 28.2, 30.2, 41.3, 61.0, 77.6, 113.4, 138.8, 143.8, 155.6, 164.4.

5.6. Acidolytic removal of the Boc group from *tert*-butyl carbamates 7. General procedure for the preparation of 1-substituted methyl 5-(2-aminoethyl)-1*H*-pyrazole-4-carboxylates 15

HCl/EtOAc (2 M, 30 mL, 60 mmol) was added to a stirred mixture of **7** (10 mmol), anhydrous EtOH (5 mL), and EtOAc (10 mL) at 0 °C and the mixture was stirred at 0 °C for 30 min and then at rt for 2 h. The precipitate was collected by filtration, washed with EtOAc (2×20 mL), and dried in vacuo at rt over NaOH pellets for 12 h to give the *title compound* **15**.

The following compounds were prepared in this manner:

*5.6.1. Methyl 5-(2-aminoethyl)-1-methyl-1H-pyrazole-4-carboxylate hydrochloride **15**{1}*

Prepared from **7**{*1*} (2.833 g, 10 mmol). Yield: 1.663 g (82%) of a white solid; mp 228–231 °C; [Found: C, 43.64; H, 6.64; N; 18.95. $C_8H_{14}ClN_3O_2$ requires C, 43.74; H, 6.42; N, 19.13%]; R_f (EtOAc) 0.0; ν_{max} (KBr) 3392, 3007, 1703, 1567, 1494, 1469, 1437, 1374, 1287, 1237, 1112, 1040, 937, 779 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 2.91–3.05 (2H, m, 2′-CH_2), 3.24–3.34 (2H, m, 1′-CH_2), 3.76 (3H, s, N*Me*), 3.87 (3H, s, O*Me*), 7.80 (1H, s, 3-*H*), 8.29 (3H, br s, NH_3^+); δ_C (75.5 MHz, DMSO-d_6) 22.5, 36.8, 37.2, 51.1, 111.3, 139.9, 142.3, 163.1.

*5.6.2. Methyl 5-(2-aminoethyl)-1-phenyl-1H-pyrazole-4-carboxylate hydrochloride **15**{2}*

Prepared from **7**{*2*} (3.454 g, 10 mmol). Yield: 2.04 g (72%) of a white solid; mp 220–225 °C; [Found: C, 55.43; H, 5.93; N; 14.75. $C_{13}H_{16}ClN_3O_2$ requires C, 55.42; H, 5.72; N, 14.91%]; R_f (EtOAc) 0.0; ν_{max} (KBr) 3416, 2949, 1719, 1612, 1556, 1495, 1271, 1232, 1100, 941, 767 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 2.91–3.01 (2H, m, 2′-CH_2), 3.17–3.26 (2H, m, 1′-CH_2), 3.83 (3H, s, O*Me*), 7.51–7.63 (5H, m, *Ph*), 8.08 (1H, s, 3-*H*), 8.22 (3H, br s, NH_3^+); δ_C (75.5 MHz, DMSO-d_6) 23.3, 37.0, 51.4, 112.5, 126.0, 129.2, 129.6, 138.1, 141.4, 142.8, 163.0.

*5.6.3. Methyl 5-(2-aminoethyl)-1-(pyridin-2-yl)-1H-pyrazole-4-carboxylate hydrochloride **15**{3}*

Prepared from **7**{*3*} (3.464 g, 10 mmol). Yield: 2.42 g (86%) of a white solid; mp 205–210 °C; R_f (EtOAc) 0.0; ν_{max} (KBr) 3416, 2976, 1718, 1591, 1557, 1473, 1435, 1297, 1266, 1233, 1192, 1145, 1102, 994, 932, 785, 715 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.14–3.24 (2H, m, 2′-CH_2), 3.63 (2H, t, *J*=7.5 Hz, 1′-CH_2), 3.84 (3H, s, O*Me*), 7.53 (1H, ddd, *J*=1.1, 4.9, 7.5 Hz, 5″-*H*), 7.86 (1H, ddd, *J*=0.9, 1.1, 8.2 Hz, 3″-*H*), 8.09 (1H, ddd, *J*=1.9, 7.5, 8.2 Hz, 4″-*H*), 8.13 (1H, s, 3-*H*), 8.27 (3H, br s, NH_3^+), 8.62 (1H, ddd, *J*=0.8, 1.9, 4.9 Hz, 6″-*H*); δ_C (75.5 MHz, DMSO-d_6) 24.7, 39.1, 52.8, 115.3, 118.7, 124.8, 141.0, 143.2, 144.3, 149.1, 151.9, 164.5; *m*/*z* 247 (100, MH^+), 230 (96%); HRMS (ESI): MH^+, found 247.1204, $C_{12}H_{15}N_4O_2$ requires 247.1195.

5.7. BPC-mediated amidation of carboxylic acids 14. General procedure for the preparation of 1-substituted 5-[2-(acylamino)ethyl]-1*H*-pyrazole-4-carboxamides 16

Under argon, BPC (197 mg, 0.5 mmol) was added to a stirred mixture of **14** (0.5 mmol), anhydrous acetonitrile (3 mL), and triethylamine (70 μL, 0.5 mmol) and the mixture was stirred at rt for 1 h. Then, the amine **11** (0.5 mmol) and triethylamine (70 μL, 0.5 mmol) were added,[†] and the mixture was at rt for 5 h. The volatile components were evaporated in vacuo and the residue was purified by FC (silica gel, EtOAc/hexanes). Fractions containing the product were combined and evaporated in vacuo to give the *title compound* **16**.

The following compounds were prepared in this manner:

5.7.1. 5-[2-(tert-Butoxycarbonylamino)ethyl]-1-methyl-1H-pyrazole-4-(N-methylcarboxamide) ***16****{1; 1}*

Prepared from **14**{*1*} (135 mg, 0.5 mmol) and methylamine hydrochloride **11**{*1*} (34 mg, 0.5 mmol); FC: EtOAc. Yield: 117 mg (83%) of a white solid; mp 175–178 °C; [Found: C, 55.38; H, 8.02; N, 19.91. $C_{13}H_{22}N_4O_3$ requires C, 55.30; H, 7.85; N; 19.84%]; R_f (EtOAc) 0.16; ν_{max} (KBr) 3369, 3289, 2986, 1684, 1631, 1575, 1537, 1444, 1299, 1278, 1169, 1111, 996, 877, 677 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.35 (9H, s, *t-Bu*), 2.70 (3H, d, *J*=4.6 Hz, *Me*NH), 2.99–3.17 (4H, m, CH_2CH_2), 3.75 (3H, s, N*Me*), 6.96 (1H, br s, N*H*CH_2), 7.80 (1H, s, 3-*H*), 7.92 (1H, q, *J*=4.4 Hz, N*H*Me); δ_C (75.5 MHz, DMSO-d_6) 25.2, 26.2, 29.1, 36.8, 40.1, 78.5, 115.4, 137.9, 143.3, 156.5, 164.2.

5.7.2. 5-[2-(tert-Butoxycarbonylamino)ethyl]-1-phenyl-1H-pyrazole-4-(N-benzylcarboxamide) ***16****{2; 2}*

Prepared from **14**{*2*} (166 mg, 0.5 mmol) and benzylamine **11**{*2*} (54 mg, 0.5 mmol); FC: EtOAc–hexanes, 1:1. Yield: 175 mg (80%) of a white solid; mp 105–107 °C; [Found: C, 68.80; H, 6.99; N; 13.23. $C_{24}H_{28}N_4O_3$ requires C, 68.55; H, 6.71; N, 13.32%]; R_f (50% EtOAc/hexanes) 0.24; ν_{max} (KBr) 3375, 3280, 1686, 1659, 1562, 1525, 1501, 1401, 1288, 1171, 764, 695 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.37 (9H, s, *t*-Bu), 3.16 (2H, t, *J*=6.3 Hz, 1′-CH_2), 3.33 (2H, q, *J*=6.3 Hz, 2′-CH_2), 4.62 (2H, d, *J*=5.8 Hz, CH_2Ph), 5.65 (1H, br s, N*H*Boc), 7.05 (1H, br s, N*H*Bn), 7.25–7.54 (10H, m, 2×*Ph*), 7.93 (1H, s, 3-*H*); δ_C (75.5 MHz, DMSO-d_6) 25.3, 28.1, 39.2, 41.9, 77.4, 115.5, 126.1, 126.6, 127.1, 128.2, 128.6, 129.2, 138.8, 138.9, 139.9, 143.4, 155.4, 162.6.

5.7.3. 5-[2-(tert-Butoxycarbonylamino)ethyl]-1-phenyl-4-[(piperidin-1-yl)carbonyl]-1H-pyrazole ***16****{2; 3}*

Prepared from **14**{*2*} (166 mg, 0.5 mmol) and piperidine **11**{*3*} (42 mg, 0.5 mmol); FC: EtOAc–hexanes, 1:1. Yield: 185 mg (93%) of a white solid; mp 119–122 °C; [Found: C, 66.36; H, 7.78; N; 14.02. $C_{22}H_{30}N_4O_3$ requires C, 66.31; H, 7.59; N, 14.06%]; R_f (50% EtOAc/hexanes) 0.15; ν_{max} (KBr) 3293, 2980, 2932, 1694, 1608, 1524, 1450, 1282, 1177, 1052, 977, 772, 700 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.31 (9H, s, *t-Bu*), 1.49–1.69 (6H, m, 3×CH_2 of piperidine), 2.84–3.03 (4H, m, 2×CH_2), 3.50–3.59 (4H, m, 2×CH_2), 6.86 (1H, br s, N*H*Boc), 7.46–7.59 (5H, m, *Ph*), 7.70 (1H, s, 3-*H*); δ_C (75.5 MHz, DMSO-d_6) 24.1, 25.1, 25.6, 25.7, 28.1, 39.5, 77.5, 116.2, 125.7, 128.5, 129.2, 138.2, 138.9, 141.3, 155.3, 163.3.

5.7.4. 5-[2-(tert-Butoxycarbonylamino)ethyl]-1-phenyl-1H-pyrazole-4-[N-(3-dimethylamino-1-prop-1-yl)carboxamide] ***16****{2; 4}*

Prepared from **14**{*2*} (166 mg, 0.5 mmol) and 3-dimethylamino-1-pyropylamine **11**{*4*} (51 mg, 0.5 mmol); FC: $CHCl_3$–MeOH, 5:1, followed by filtration through Celite®, and evaporation. Yield: 82 mg (40%) of a white solid; mp 116–119 °C; [Found: 63.37; H, 7.89; N; 16.66. $C_{22}H_{33}N_5O_3$ requires C, 63.59; H, 8.00; N, 16.85%]; R_f (17% MeOH/$CHCl_3$) 0.10; ν_{max} (KBr) 3328, 2980, 1689, 1654, 1560, 1523, 1499, 1404, 1367, 1281, 1251, 1165, 1016, 976, 945, 764, 695 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.30 (9H, s, *t-Bu*), 1.75 (2H, p, *J*=7.2 Hz, $CH_2CH_2CH_2NMe_2$), 2.43 (6H, s, NMe_2), 2.64 (2H, t, *J*=7.2 Hz, $CH_2CH_2CH_2NMe_2$), 2.98–3.15 (4H, m, CH_2CH_2), 3.27 (2H, q, *J*=6.9 Hz, $CH_2CH_2CH_2NMe_2$), 6.81 (1H, br s, N*H*Boc), 7.43–7.58 (5H, m, *Ph*), 8.09 (1H, s, 3-*H*), 8.23 (1H, t, *J*=5.7 Hz, N*H*); δ_C (75.5 MHz, DMSO-d_6) 26.1, 27.3, 29.0, 37.5, 40.1, 45.1, 57.1, 78.3, 116.6, 126.9, 129.5, 130.1, 132.4, 139.7, 144.0, 156.3, 163.6; *m*/*z* 415 (54, M^+), 342 (32), 244 (28), 214 (51), 185 (36), 101 (25), 84 (23), 72 (25), 58 (100%); HRMS (EI): M^+, found 415.2595, $C_{22}H_{33}N_5O_3$ requires 415.2583.

5.7.5. 5-[2-(tert-Butoxycarbonylamino)ethyl]-1-(4-methoxyphenyl)-1H-pyrazol-4-{N-[2-(ethoxycarbonyl)ethyl] carboxamide} ***16****{4; 5}*

Prepared from **14**{*4*} (361 mg, 1 mmol) and ethyl β-alaninate hydrochloride **11**{*5*} (77 mg, 0.5 mmol); FC: EtOAc–hexanes, 1:1. Yield: 120 mg (52%) of a yellow oil; R_f (50% EtOAc/hexanes) 0.19; ν_{max} (liquid film) 3335, 2978, 2937, 1730, 1712, 1639, 1611, 1565, 1515, 1464, 1391, 1366, 1293, 1250, 1171, 1026, 969, 837, 779 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.27 (3H, t, *J*=6.3 Hz, CH_3CH_2), 1.37 (9H, s, *t-Bu*), 2.64 (2H, t, *J*=6.2 Hz, CH_2COOEt), 3.08 (2H, t, *J*=6.5 Hz, CH_2CH_2NHBoc), 3.29 (2H, q, *J*=6.2 Hz, CH_2NHBoc), 3.66 (2H, q, *J*=6.2 Hz, CH_2CH_2COOEt), 3.85 (3H, s, O*Me*), 4.17 (2H, q, *J*=7.2 Hz, CH_3CH_2), 5.73 (1H, br t, N*H*), 6.98 and 7.33 (4H, 2d, 1:1, *J*=8.8 Hz, C_6H_4), 7.00 (1H, br s, N*H*), 7.83 (1H, s, 3-*H*); δ_C NMR (75.5 MHz, $CDCl_3$) 14.2, 25.0, 28.4, 34.2, 35.0, 40.2, 55.6, 60.8, 78.9, 114.5, 115.7, 127.8, 131.6, 138.2, 143.8, 156.2, 160.0, 164.0, 172.7; *m*/*z* 461 (61, MH^+), 405 (24), 361 (100), 323 (25), 244 (18), 210 (67%); HRMS (ESI): MH^+, 461.2404, $C_{23}H_{33}N_4O_6$ requires 461.2400.

5.8. Methyl 5-(2-benzamidoethyl)-1-phenyl-1*H*-pyrazole-4-carboxylate (17)

Benzoyl chloride (0.64 mL, 5.5 mmol) was added to a stirred cold (0 °C) solution of the amine hydrochloride **15**{*2*} (1.13 g, 4 mmol) in a mixture of ethanol (20 mL) and Et_3N (1.68 mL, 12 mmol) and the mixture was stirred at 0 °C for 30 min and then at rt for 2 h. Volatile components were evaporated in vacuo and the residue was purified by FC on silica gel (EtOAc). Fractions containing the product were combined and evaporated in vacuo to give the *title compound* **17**. Yield: 1.14 g (81%) of a white solid; mp 120–123 °C; R_f (EtOAc) 0.30; ν_{max} (KBr) 3328, 2950, 1708, 1656, 1599, 1580, 1534, 1499, 1469, 1432, 1388, 1295, 1243, 1200, 1107, 1091, 973, 805, 779 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.18 (2H, t, *J*=6.6 Hz, 1′-CH_2), 3.43 (2H, q, *J*=6.6 Hz, 2′-CH_2), 3.75 (3H, s, O*Me*), 7.38–7.54 and 7.67–7.73 (10H, 2m, 8:2, 2×*Ph*), 8.02 (1H, s, 3-*H*), 8.48 (1H, t, *J*=5.7 Hz, N*H*); δ_C (75.5 MHz, $CDCl_3$) 26.0, 39.0, 51.9, 113.1, 127.0, 128.0, 128.9, 129.8, 130.1, 131.9, 135.1, 139.4, 142.2, 146.1, 164.1, 166.9; *m*/*z* 350 (100, MH^+), 318 (73%); HRMS (ESI): MH^+, found 350.1512, $C_{20}H_{20}N_3O_3$ requires 350.1505.

5.9. Acidic removal of the Boc group from *tert*-butyl carbamates 16. General procedure for the preparation of 1-substituted 5-(2-aminoethyl)-1*H*-pyrazole-4-carboxamides 18

HCl–EtOAc (2 M, 3 mL, 6 mmol) was added to a stirred mixture of **16** (1 mmol) and EtOAc (3 mL) at 0 °C and the mixture was stirred at 0 °C for 30 min and then at rt for 2 h. The precipitate was collected by filtration, washed with EtOAc (2×5 mL), and dried in vacuo at rt over NaOH pellets for 12 h to give the *title compound* **18**.

The following compounds were prepared in this manner:

[†] 2 Equiv of Et_3N (140 μL, 1 mmol) were added, if amine hydrochloride **11** was used.

*5.9.1. 5-(2-Aminoethyl)-1-methyl-1H-pyrazole-4-(N-methylcarboxamide) hydrochloride **18**{1; 1}*

Prepared from **16**{*1; 1*} (282 mg, 1 mmol). Yield: 147 mg (67%) of a white solid; mp 155–161 °C; [Found: C, 39.72; H, 6.77; N; 22.65. $C_8H_{14}N_4O\cdot 1.7HCl$ requires C, 39.35; H, 6.48; N, 22.94%]; R_f (EtOAc) 0.0; ν_{max} (KBr) 3362, 3291, 3220, 1649, 1575, 1475, 1449, 1415, 1350, 1292, 1195, 1103, 888, 818, 537 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 2.72 (3H, br s, NH*Me*), 2.96–3.07 (2H, m, 2′-CH_2), 3.25 (2H, t, J=7.5 Hz, 1′-CH_2), 3.82 (3H, s, N*Me*), 7.88 (1H, s, 3-*H*), 8.18 (3H, br s, NH_3^+), N*H* exchanged; δ_C (75.5 MHz, DMSO-d_6) 22.5, 25.5, 36.4, 37.6, 115.2, 137.4, 140.4, 163.4, *m*/*z* 183 (56, MH^+), 166 (20), 158 (62), 152 (100), 141 (49%); HRMS (ESI): MH^+, found 183.1249, $C_8H_{15}N_4O$ requires 183.1246.

*5.9.2. 5-(2-Aminoethyl)-1-phenyl-1H-pyrazole-4-(N-benzylcarboxamide) hydrochloride **18**{2; 2}*

Prepared from **16**{*2; 2*} (420 mg, 1 mmol). Yield: 343 mg (96%) of a white solid; mp 143–147 °C; [Found: C, 59.17; H, 5.87; N; 14.44. $C_{19}H_{20}N_4O\cdot 1.8HCl$ requires C, 59.12; H, 5.69; N, 14.50%]; R_f (EtOAc) 0.0; ν_{max} (KBr) 3269, 3030, 1630, 1569, 1498, 1294, 770, 697 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 2.93–3.06 (2H, m, 2′-CH_2), 3.14–3.22 (2H, m, 1′-CH_2), 4.48 (2H, d, J=6.0 Hz, CH_2Ph), 7.21–7.38 (5H, m, *Ph*), 7.47–7.63 (5H, m, *Ph*), 8.08 (3H, br s, NH_3^+), 8.28 (1H, s, 3-*H*), 8.99 (1H, t, J=6.0 Hz, N*H*); δ_C (75.5 MHz, DMSO-d_6) 24.2, 38.3, 42.9, 116.8, 127.0, 127.6, 128.1, 129.1, 129.8, 130.4, 139.2, 140.1, 140.6, 142.1, 163.5; *m*/*z* 321 (100, MH^+), 214 (45%); HRMS (ESI): MH^+, found 321.1718, $C_{19}H_{21}N_4O$ requires 321.1715.

*5.9.3. 5-(2-Aminoethyl)-1-phenyl-4-[(piperidin-1-yl)carbonyl]-1H-pyrazole hydrochloride **18**{2; 3}*

Prepared from **16**{*2; 3*} (398 mg, 1 mmol). Yield: 303 mg (91%) of a white solid; mp 127–132 °C; [Found: C, 59.39; H, 7.42; N; 15.67. $C_{17}H_{22}N_4O\cdot HCl$ requires: C, 60.98; H, 6.92; N, 16.73%]; R_f (EtOAc) 0.0; ν_{max} (KBr) 3256, 3029, 1630, 1569, 1498, 1454, 1412, 1294, 770, 697 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.49–1.70 (6H, m, 3×CH_2 of piperidine), 2.80–2.92 (2H, m, 2′-CH_2), 3.02–3.11 (2H, m, 1′-CH_2), 3.53–3.63 (4H, m, 3×CH_2 of piperidine), 7.50–7.62 (5H, m, *Ph*), 7.79 (1H, s, 3-*H*), 8.14 (3H, br s, NH_3^+); δ_C (75.5 MHz, DMSO-d_6) 23.9, 24.9, 26.5, 26.7, 37.9, 117.2, 126.7, 129.7, 130.4, 139.3, 139.4, 140.4, 164.0; *m*/*z* 299 (50, MH^+), 269 (86), 185 (100%); HRMS (ESI): MH^+, found 299.1872, $C_{17}H_{23}N_4O$ requires 299.1872.

*5.9.4. 5-(2-Aminoethyl)-1-phenyl-1H-pyrazole-4-{N-[3-(dimethylamino)prop-1-yl]carboxamide} dihydrochloride **18**{2; 4}*

Prepared from **16**{*2; 4*} (415 mg, 1 mmol). Yield: 300 mg (85%) of a white solid; mp 156–159 °C; [Found: C, 52.26; H, 6.96; N; 17.69. $C_{17}H_{25}N_5O\cdot 2HCl$ requires C, 52.58; H, 7.01; N, 18.03%]; R_f (EtOAc) 0.0; ν_{max} (KBr) 2965, 1630, 1570, 1500, 1411, 1296, 1159, 772, 698 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.87–2.00 (2H, m, $CH_2CH_2CH_2NMe_2$), 2.73 and 2.75 (6H, 2s, 1:1, N*Me*$_2$), 2.95–3.22 (6H, m, 3×CH_2), 3.33 (2H, q, J=6.2 Hz, $CH_2CH_2NH_3^+$), 7.46–7.64 (5H, m, *Ph*), 8.15 (3H, br s, NH_3^+), 8.27 (1H, s, 3-*H*), 8.64 (1H, t, J=5.6 Hz, N*H*), Me_2NH^+ exchanged; δ_C (75.5 MHz, DMSO-d_6) 23.3, 24.3, 35.8, 37.4, 41.9, 56.0, 116.0, 126.1, 129.0, 129.5, 138.3, 139.4, 141.0, 162.8; *m*/*z* 315 (15, M^+), 286 (62), 244 (87), 214 (55), 185 (50), 77 (40), 72 (59), 58 (100%); HRMS (EI): M^+, found 315.2061, $C_{17}H_{25}N_5O$ requires 315.2059.

*5.9.5. 5-(2-Aminoethyl)-1-(4-methoxyphenyl)-1H-pyrazole-4-{N-[2-(ethoxycarbonyl)ethyl]carboxamide} hydrochloride **18**{4; 5}*

Prepared from **16**{*4; 5*} (460 mg, 1 mmol). Yield: 338 mg (85%) of a white solid; mp 135–145 °C; R_f (EtOAc) 0.0; ν_{max} (KBr) 3221, 3049, 2986, 1734, 1610, 1574, 1515, 1268, 1188, 1023, 841 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.19 (3H, t, J=7.1 Hz, CH_2CH_3), 2.58 (2H, t, J=7.0 Hz, CH_2COOEt), 2.89–3.03 (2H, m, 2′-CH_2), 3.05–3.16 (2H, m, 1′-CH_2), 3.48 (2H, q, J=6.8 Hz, CH_2NH), 3.83 (3H, s, O*Me*), 4.08 (2H, q, J=7.1 Hz, CH_2CH_3), 7.05–7.15 and 7.36–7.46 (4H, 2m, 1:1, C_6H_4), 8.07 (3H, s, NH_3^+), 8.14 (1H, s, 3-*H*), 8.49 (1H, t, J=5.5 Hz, N*H*); δ_C (75.5 MHz, DMSO-d_6): δ 14.2, 23.5, 34.0, 35.0, 37.4, 55.6, 60.0, 114.6, 115.6, 127.7, 131.3, 138.8, 141.3, 159.5, 162.9, 171.4. *m*/*z* 361 (100, MH^+), 244 (96%); HRMS (ESI): MH^+, found 361.1873, $C_{18}H_{25}N_4O_4$ requires 361.1876.

5.10. 5-[2-(Benzoylamino)ethyl]-1-phenyl-1*H*-pyrazole-4-carboxylic acid (19)

A mixture of **17** (1.05 g, 3 mmol), methanol (10 mL), and 2 M aq NaOH (5 mL, 10 mmol) was stirred at 50 °C for 12 h. Methanol was removed by careful evaporation in vacuo (100 mbar, 40 °C). The residual aqueous solution was cooled to 0 °C (ice-bath) and acidified, first with 6 M hydrochloric acid (0.45 mL, 2.7 mmol) and then with 1 M aq $NaHSO_4$ (1 mL, 1 mmol). The precipitate was collected by filtration, and washed with cold water (0 °C, 5 mL) to give the *title compound* **19**. Yield: 0.888 g (88%) of a white solid; mp 180–185 °C; R_f (EtOAc) 0.28; ν_{max} (KBr) 3334, 3054, 2934, 1672, 1659, 1546, 1473, 1434, 1291, 1253, 1105, 969, 776, 696 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.19 (2H, t, J=6.6 Hz, 1′-CH_2), 3.45 (2H, q, J=6.6 Hz, 2′-CH_2), 7.38–7.53 and 7.68–7.74 (10H, 2m, 8:2, 2×*Ph*), 7.97 (1H, s, 3-*H*), 8.49 (1H, t, J=5.6 Hz, N*H*), 12.47 (1H, br s, COO*H*); δ_C (75.5 MHz, DMSO-d_6) 25.0, 38.4, 113.2, 126.2, 127.2, 128.1, 128.8, 129.2, 131.0, 134.3, 138.7, 141.7, 145.1, 164.5, 166.1; *m*/*z* 336 (68, MH^+), 318 (100%); HRMS (ESI): MH^+, found 336.1339, $C_{19}H_{18}N_3O_3$ requires 336.1348.

5.11. General procedures for the preparation of 1-substituted 5-[2-(acylamino)ethyl]-1*H*-pyrazole-4-carboxamides 20

*Procedure A. Acylation of amine **18**{1; 1} with acetyl chloride **12**{1}*

Acetyl chloride **12**{*1*} (50 μL, 0.7 mmol) was added to a stirred cold (0 °C) solution of the amine **18**{*1; 1*} (110 mg, 0.5 mmol) in a mixture of ethanol (4 mL) and Et_3N (210 μL, 1.5 mmol) and the mixture was stirred at 0 °C for 30 min and then at rt for 2 h. The volatile components were evaporated in vacuo and the residue was purified by FC on silica gel (EtOAc–EtOH, 20:1). Fractions containing the product were combined and evaporated in vacuo to give *the title compound* **20**. Compound **20**{*1; 1; 1*} was prepared in this manner.

*Procedure B. BPC-mediated acylations of amines **18** with carboxylic acids **13**{2,3}*

Under argon, BPC (131.4 mg, 0.33 mmol) was added to a solution of carboxylic acid **13** (0.33 mmol) in a mixture of DMF (2 mL) and Et_3N (47 μL, 0.33 mmol) and the mixture was stirred at rt for 1 h. Then, amine hydrochloride **18** (0.33 mmol) and Et_3N (94 μL, 0.66 mmol) were added and stirring at rt was continued for 18 h. The volatile components were evaporated in vacuo and the residue was purified by FC on silica gel (EtOAc–hexanes). Fractions containing the product were combined and evaporated in vacuo to give *the title compound* **20**. Compounds **20**{*2; 2; 2*}, **20**{*2; 3; 2*}, **20**{*2; 4; 2*}, and **20**{*4; 5; 3*}, were prepared in this manner.

*Procedure C. BPC-mediated amidations of carboxylic acid **19***

Under argon, BPC (197 mg, 0.5 mmol) was added to a stirred mixture of **19** (168 mg, 0.5 mmol), anhydrous acetonitrile (3 mL), and Et_3N (70 μL, 0.5 mmol) and the mixture was stirred at rt for 1 h. Then, the amine **11** (0.5 mmol) and Et_3N (70 μL, 0.5 mmol) were added,[‡] and the mixture was at rt for 5 h. The volatile components were evaporated in vacuo and the residue was purified by FC (silica gel, EtOAc–hexanes). Fractions containing the

[‡] 2 Equiv of Et_3N (140 μL, 1 mmol) were added, if amine hydrochloride **11** was used.

product were combined and evaporated in vacuo to give *the title compound* **20**. Compounds **20**{*2; 6–8; 2*} were prepared in this manner.

The following compounds were prepared in this manner:

5.11.1. 5-(2-Acetamidoethyl)-1-phenyl-1H-pyrazole-4-(N-methylcarboxamide) ***20****{1; 1; 1}*. Prepared from **18**{*1; 1*} (110 mg, 0.5 mmol) and acetyl chloride **12**{*1*} (0.7 mmol); Procedure A. Yield: 73 mg (65%) of a white solid; mp 153–156 °C; [Found: C, 53.30; H, 7.35; N; 24.87. $C_{10}H_{16}N_4O_2$ requires C, 53.56; H, 7.19; N, 24.98%]; R_f (5% EtOH/EtOAc) 0.18; ν_{max} (KBr) 3274, 3101, 2994, 2951, 1663, 1644, 1569, 1528, 1492, 1455, 1408, 1359, 1299, 1264, 1245, 1100, 986, 957, 885, 814, 777, 605 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.77 (3H, s, *Me*CO), 2.71 (3H, d, *J*=4.4 Hz, *Me*NH), 3.06 (2H, t, *J*=6.6 Hz, 1′-CH_2), 3.21 (2H, q, *J*=6.6 Hz, 2′-CH_2), 3.75 (3H, s, N*Me*), 7.80 (1H, s, 3-*H*), 7.94 (1H, q, *J*=4.4 Hz, N*H*Me), 8.10 (1H, t, *J*=5.2 Hz, N*H*CH_2); δ_C (75.5 MHz, DMSO-d_6) 23.4, 25.0, 26.3, 36.8, 38.9, 115.5, 138.0, 143.2, 164.3, 170.2.

5.11.2. 5-(2-Benzamidoethyl)-1-phenyl-1H-pyrazole-4-(N-benzylcarboxamide) ***20****{2; 2; 2}*. Prepared from **18**{*2; 2*} (119 mg, 0.33 mmol) and benzoic acid **13**{*2*} (40 mg, 0.33 mmol); Procedure B; FC: EtOAc–hexanes, 1:1. Yield: 110 mg (78%) of a white solid; mp 107–109 °C; [Found: C, 73.28; H, 5.75; N; 13.23. $C_{26}H_{24}N_4O_2$ requires C, 73.56; H, 5.70; N, 13.20%]; R_f (50% EtOAc/hexanes) 0.21; ν_{max} (KBr) 3303, 3062, 2930, 1667, 1636, 1565, 1452, 1410, 1293, 1096, 952, 768, 696 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.22 (2H, t, *J*=6.8 Hz, 1′-CH_2), 3.44 (2H, q, *J*=6.8 Hz, 2′-CH_2), 4.48 (2H, d, *J*=6.0 Hz, CH_2Ph), 7.21–7.30 (1H, m, 1H of Ph), 7.32–7.38 (4H, m, 4H of Ph), 7.38–7.43 (2H, m, 2H of Ph), 7.43–7.52 (6H, m, 6H of Ph), 7.70–7.75 (2H, m, 2H of *Ph*), 8.19 (1H, s, 3-*H*), 8.65 (1H, t, *J*=5.1 Hz, N*H*), 8.78 (1H, t, *J*=6.0 Hz, N*H*); δ_C (75.5 MHz, DMSO-d_6) 24.5, 42.0, 54.9, 115.6, 126.1, 126.7, 127.1, 127.2, 128.1, 128.3, 128.7, 129.2, 131.0, 134.2, 138.7, 139.0, 139.8, 143.6, 162.9, 166.0.

5.11.3. 5-(2-Benzamidoethyl)-1-phenyl-4-[N-(piperidin-1-yl)carbonyl]-1H-pyrazole ***20****{2; 3; 2}*. Prepared from **18**{*2; 3*} (119 mg, 0.33 mmol) and benzoic acid **13**{*2*} (40 mg, 0.33 mmol); Procedure B; FC: EtOAc–hexanes, 1:1. Yield: 120 mg (89%) of a white solid; mp 165–167 °C; [Found: C, 71.68; H, 6.83; N; 13.97. $C_{24}H_{26}N_4O_2$ requires C, C, 71.62; H, 6.51; N, 13.92%]; R_f (50% EtOAc/hexanes) 0.20; ν_{max} (KBr) 3228, 3056, 2934, 2850, 1654, 1588, 1545, 1440, 1406, 1359, 1340, 130, 1270, 976, 956, 761, 696, 660 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.44–1.64 (6H, m, 3×CH_2 of piperidine), 3.06 (2H, t, *J*=6.9 Hz, 1′-CH_2), 3.27–3.35 (2H, m, 2′-CH_2), 3.45–3.54 (4H, m, 2×CH_2 of piperidine), 7.38–7.57 (8H, m, 8H of *P*h), 7.72 (1H, s, 3-*H*), 7.73–7.80 (2H, m, 2H of *Ph*), 8.64 (1H, t, *J*=5.2 Hz, N*H*); δ_C (75.5 MHz, DMSO-d_6) 24.1, 24.4, 25.7, 25.8, 38.4, 116.3, 125.8, 127.1, 128.1, 128.5, 129.2, 131.0, 134.1, 138.2, 138.9, 141.6, 163.3, 165.9.

5.11.4. 5-(2-Benzamidoethyl)-1-phenyl-1H-pyrazole-4-{N-[3-(dimethylamino)prop-1-yl]carboxamide} ***20****{2; 4; 2}*. Prepared from **18**{*2; 4*} (119 mg, 0.33 mmol) and benzoic acid **13**{*2*} (40 mg, 0.33 mmol); Procedure B; FC: $CHCl_3$–MeOH, 5:1, followed by filtration through Celite®. Yield: 66 mg (52%) of a yellowish oil; R_f (17% MeOH/$CHCl_3$) 0.14; ν_{max} (liquid film) 3284, 2946, 1638, 1599, 1567, 1539, 1499, 1408, 1296, 1158, 1005, 981, 768, 695 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.63–1.74 (2H, m, $CH_2CH_2CH_2$), 2.25 (6H, s, NMe_2), 2.40 (2H, t, *J*=7.1 Hz, CH_2), 3.16–3.32 (4H, m, 2×CH_2), 3.38–3.47 (2H, m, CH_2), 7.37–7.54 (8H, m, 8H of Ph), 7.70–7.78 (2H, m, 2H of *Ph*), 8.10 (1H, s, 3-H), 8.28 (1H, t, *J*=5.1 Hz, N*H*), 8.67 (1H, br t, N*H*); δ_C (75.5 MHz, DMSO-d_6) 24.3, 24.5, 35.7, 28.9, 54.4, 59.7, 115.6, 126.1, 127.1, 128.1, 128.6, 129.2, 131.0, 134.2, 138.7, 139.2, 143.3, 163.1, 166.0; *m*/*z*=420 (100, MH^+), 375 (20%); HRMS (ESI): MH^+, found 420.2417, $C_{24}H_{30}N_5O_2$ requires 420.2400.

5.11.5. 5-(3,6,9-Trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-yl)-1-(4-methoxyphenyl)-1H-pyrazole-4-{N-[2-(ethoxycarbonyl)ethyl]carboxamide} ***20****{4; 5; 3}*. Prepared from **18**{*4; 5*} (132 mg, 0.33 mmol) and Z-glycylglycine (89 mg, 0.33 mmol); Procedure B; FC: EtOAc–EtOH, first 20:1, then 5:1. Yield: 129 mg (71%) of a white solid; mp 70–75 °C; R_f (5% EtOH/EtOAc) 0.09; ν_{max} (KBr) 3312, 3068, 2938, 1726, 1654, 1550, 1516, 1455, 1409, 1373, 1252, 1183, 1045, 1025, 965, 838, 698 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.18 (3H, t, *J*=7.1 Hz, CH_2CH_3), 2.56 and 2.99 (4H, 2 t, 1:1, *J*=7.0, 7.0 Hz, 2×CH_2), 3.21 (2H, q, *J*=6.7 Hz, CH_2NH), 3.40–3.50 (2H, m, CH_2), 3.58 (2H, d, *J*=5.7 Hz, CH_2 of GlyGly), 3.65 (2H, d, *J*=6.0 Hz, CH_2 of GlyGly), 3.82 (3H, s, O*Me*), 4.07 (2H, q, *J*=7.1 Hz, CH_2CH$_3$), 5.03 (2H, s, CH_2Ph), 7.02–7.09 (2H, m, 2H of C_6H_4), 7.26–7.40 (7H, m, 2H of C_6H_4, 3H of *Ph*, 2×N*H*), 7.45 (1H, br t, *J*=5.9 Hz, N*H*), 7.92–8.02 (2H, m, 2H of *Ph*), 8.04 (1H, s, 3-*H*), 8.23 (1H, t, *J*=5.5 Hz, N*H*); δ_H (300 MHz, $CDCl_3$) 1.23 (3H, t, *J*=7.1 Hz, CH_3CH$_2$), 2.57 (2H, t, *J*=6.0 Hz, CH_2), 3.02 (2H, t, *J*=6.2 Hz, CH_2), 3.30 (2H, q, *J*=5.1 Hz, CH_2NH), 3.60 (2H, q, *J*=6.2 Hz, CH_2NH), 3.80 (3H, s, O*Me*), 3.81 (2H, br s, CH_2 of GlyGly), 3.89 (2H, d, *J*=5.2 Hz, CH_2 of GlyGly), 4.12 (2H, q, *J*=7.1 Hz, CH_2CH$_3$), 5.07 (2H, s, CH_2Ph), 6.26 (1H, t, *J*=5.6 Hz, N*H*), 6.94 (2H, d, *J*=8.9 Hz, 2H of C_6H_4), 7.20–7.36 (9H, m, *Ph*, 2H of C_6H_4, 2×N*H*), 7.81 (1H, s, 3-*H*), 8.17 (1H, br s, N*H*); δ_C (75.5 MHz, $CDCl_3$) 14.5, 24.2, 29.3, 32.2, 34.4, 35.6, 39.9, 42.9, 44.6, 55.9, 67.4, 114.9, 116.4, 128.1, 128.4, 128.5, 128.8, 131.6, 136.6, 138.6, 143.7, 157.2, 160.5, 164.8, 169.6, 172.9; *m*/*z*=609 (100%, MH^+); HRMS (ESI): MH^+, found 609.2670, $C_{30}H_{37}N_6O_8$ requires 609.2673.

5.11.6. 5-(2-Benzamidoethyl)-1-phenyl-1H-pyrazole-4-{N-(pyridin-2-yl)methyl]carboxamide} ***20****{2; 6; 2}*. Prepared from **19** (168 mg, 0.5 mmol) and 2-picolylamine **11**{*6*} (54 mg, 0.5 mmol); Procedure C; FC: EtOAc. Yield: 195 mg (91%) of a white solid; mp 114–118 °C; R_f (EtOAc) 0.14; ν_{max} (KBr) 3321, 3296, 3056, 2951, 1648, 1633, 1590, 1566, 1527, 1472, 1361, 1295, 1206, 1155, 1105, 1077, 990, 965, 774, 755, 646 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.21 (2H, t, *J*=6.7 Hz, 1′-CH_2), 3.43 (2H, q, *J*=6.7 Hz, 2′-CH_2), 4.56 (2H, d, *J*=6.0 Hz, NHCH_2Py), 7.27 (1H, ddd, *J*=1.0, 4.8, 7.5 Hz, 5″-*H*), 7.32–7.41 (3H, m, 3″-H, 2H of *Ph*), 7.45–7.51 (6H, m, 6H of *Ph*), 7.69–7.79 (3H, m, 4″-H and 2H of *Ph*), 8.22 (1H, s, 3-*H*), 8.52 (1H, ddd, *J*=1.0, 1.9, 4.8 Hz, 6″-*H*), 8.62 (1H, t, *J*=5.1 Hz, N*H*), 8.87 (1H, t, *J*=6.0 Hz, N*H*); δ_C (75.5 MHz, $CDCl_3$) 23.3, 40.4, 44.2, 115.8, 121.5, 122.1, 126.1, 127.0, 127.9, 129.1, 129.2, 130.8, 133.8, 136.7, 138.2, 138.3, 143.7, 148.7, 156.6, 164.3, 167.5; *m*/*z*=426 (100%, MH^+); HRMS (ESI): MH^+, found 426.1950, $C_{25}H_{24}N_5O_2$ requires 426.1930.

5.11.7. 5-(2-Benzamidoethyl)-1-phenyl-1H-pyrazole-4-{N-[3-(2-oxopyrrolidin-1-yl)prop-1-yl]carboxamide} ***20****{2; 7; 2}*. Prepared from **19** (168 mg, 0.5 mmol) and 1-(3-aminoprop-1-yl)pyrrolidin-2-one **11**{*7*} (71 mg, 0.5 mmol); Procedure C; FC: EtOAc–EtOH, 20:1. Yield: 206 mg (90%) of a yellow oil; R_f (5% EtOH/EtOAc) 0.16; ν_{max} (liquid film) 3305, 2936, 1650, 1567, 1536, 1515, 1501, 1465, 1434, 1293, 1014, 995, 981, 754 cm^{-1}. δ_H (300 MHz, DMSO-d_6) 1.68 (2H, p, *J*=7.1 Hz, $CH_2CH_2CH_2$), 1.85–1.96 (2H, m, 4″-CH_2), 2.21 (2H, t, *J*=8.1 Hz, 3″-CH_2), 3.15–3.45 (10H, m, 5″-CH_2, CH_2CH$_2$CH_2, and CH_2CH_2), 7.36–7.51 (8H, m, 8H of Ph), 7.70–7.75 (2H, m, 2H of *Ph*),8.08 (1H, s, 3-*H*), 8.18 (1H, t, *J*=5.8 Hz, N*H*), 8.63 (1H, t, *J*=5.2 Hz, N*H*); δ_C (75.5 MHz, $CDCl_3$) 17.7, 23.2, 26.2, 26.3, 30.7, 35.3, 39.5, 40.6, 47.3, 126.3, 127.1, 127.9, 129.1, 129.2, 130.9, 134.0, 138.4, 138.5, 143.4, 164.2, 167.6, 176.1; *m*/*z*=460 (100%, MH^+); HRMS (ESI): MH^+, found 460.2368, $C_{26}H_{30}N_5O_3$ requires 460.2349.

5.11.8. 5-(2-Benzamidoethyl)-4-{N-3-[(N,N-diethylcarboxamido)-piperidin-1-yl]carbonyl}-1-phenyl-1H-pyrazole ***20****{2; 8; 2}*. Prepared from **19** (168 mg, 0.5 mmol) and *N*,*N*-diethylnipecotamide **11**{*8*} (92 mg, 0.5 mmol); Procedure C; FC: EtOAc. Yield: 245 mg (97%) of a yellow oil; R_f (EtOAc) 0.21; ν_{max} (liquid film) 3448, 2936, 1618, 1551, 1501, 1438, 1402, 1307, 1264, 1085, 982, 766, 697 cm^{-1}; δ_H (300 MHz,

DMSO-d_6) 1.04 (6H, t, J=7.0 Hz, 2×CH_3CH_2), 1.42–1.86 (4H, m, 4″-CH_2 and 5″-CH_2), 2.65–2.77 (1H, m, 3″-*H*), 3.04 (2H, t, J=7.0 Hz, 1′-CH_2), 3.24–3.37 (4H, m, 2′-CH_2, 6″-CH_2), 3.43 (4H, q, J=7.0 Hz, 2×CH_2CH_3), 4.18–4.53 (2H, m, 2″-CH_2), 7.36–7.55 (8H, m, 8H of Ph), 7.70–7.78 (2H, m, 2H of *Ph*), 7.74 (1H, s, 3-*H*), 8.62 (1H, t, J=5.2 Hz, N*H*); δ_C (75.5 MHz, $CDCl_3$) 12.8, 14.7, 18.1, 23.3, 39.3, 40.1, 41.7, 57.7, 57.8, 126.0, 127.1, 127.9, 129.1, 129.3, 130.9, 133.8, 138.0, 138.1, 138.4, 143.1, 164.6, 167.5, 171.9. m/z=502 (100%, MH^+); HRMS (ESI): MH^+, found 502.2822, $C_{29}H_{36}N_5O_3$ requires 502.2818.

5.12. X-ray structure analysis for compound 7{*10*}

Single crystal X-ray diffraction data of compound **7**{*10*} were collected at rt on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[24] DENZO and SCALEPACK[25] were used for indexing and scaling of the data and the structure was solved by means of SIR97.[26] Refinement and plotting were done using Xtal3.4[27] 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[28] weighting scheme was used in all cases.

Crystallographic data (excluding structure factors) for compound **7**{*10*} have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 716590. 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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References and notes

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