Synthesis of Novel 3D-Rich α-Amino Acid-Derived 3-Pyrazolidinones

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Dedicated to Professor Emeritus Miha Tišler, University of Ljubljana, on the occasion of his 90th birthday.

Abstract

Synthetic approaches towards novel 3-pyrazolidinone derivatives functionalized at positions N(1) and/or C(5) were studied. 5-Aminoalkyl-3-pyrazolidinones were prepared in four steps from N-protected glycines via Masamune-Claisen homologation, reduction, O-mesylation, and cyclisation with a hydrazine derivative. The free amines were prepared by acidolytic deprotection. Title compound was also prepared by ‘ring switching’ transformation of N-Boc-pyrrolin-2(5H)-one with hydrazine hydrate. Hydrogenolytic deprotection of 5-(N-alkyl-N-Cbz-aminomethyl)pyrazolidine-3-ones followed by cyclisation with 1,1'-carbonyldiimidazole (CDI) gave two novel representatives of perhydroimidazo[1,5-b]pyrazole, which is an almost unexplored heterocyclic system. Amidation of 3-oxopyrazolidine-5-carboxylic acid gave the corresponding carboxamides in moderate yields. Diastereomeric non-racemic carboxamides obtained from (S)-AlaOMe and (S)-ProOMe were separated by MPLC.

Keywords: 3-Pyrazolidinones, amino acids, cyclization, heterocycles, synthesis

1. Introduction

Hetero(bi)cycles are commonly used building blocks for applications in medicinal chemistry, catalysis, and materials science.1,2 In this context, 3-pyrazolidinones and their bicyclic analogues are attractive targets due to their easy availability from α,β-unsaturated esters and because of their applicability and biological activity.3–6 Pyrazolidinone derivatives have been employed as dyes and photographic developers3,5 and as inhibitors of cyclooxygenase, lipooxygenase,7 and γ-aminobutyrate aminotransferase8 exhibiting analgesic, antipyretic, anti-inflammatory, and anorectic activity. Among bicyclic analogues, perhydropyrazolo[1,2-a]pyrazoles belong to azabicycloalkane amino acids, which are U-shaped conformationally constrained heterocyclic analogues of peptides that simulate β-turn structures.9,10 Consequently, bicyclic pyrazolidinones are used as drugs to relieve Alzheimer’s disease11 and as antibacterial (Eli-Lilly’s γ-lactam antibiotics),12 and antitrypanosomal agents.13 Synthetic applications of 3-pyrazolidinones comprise their use as chiral auxiliaries,14–19 as templates in asymmetric Diels-Alder cycloadditions,20–22 and as a new scaffold in organocatalysis.23–30 Typical examples of important 3-pyrazolidinone derivatives are depicted in Figure 1.

However, in spite of easy availability of simple pyrazolidinones from α,β-unsaturated esters and hydrazine derivatives,3–6,31,32 the synthesis of functionalized polysubstituted pyrazolidinones remains challenging. Consequently, a majority of saturated bi- and tricyclic 3-pyrazolidinones are either unknown or unexplored heterocyclic systems.

In the context of our ongoing work on the synthesis of chiral heterocycles with emphasis on pyrazole33,34 and pyrazolidinone derivatives,31,32 we reported the synthesis of tetrahydropyrazolo[1,5-c]pyrimidine-2,7-diones as the first representatives of a novel saturated heterocyclic system,35,36 followed by preparation of closely related tetrahydropyrazolo[1,5-c]pyrimidine-3-carboxamides37 and tetrahydro-1H-imidazo[1,5-b]pyrazole-2,6-diones.38 In ex-
tension, the first representatives of octahydro-2H-2a,2a1-diazacyclopenta[cd]inden-2-one as a novel tricyclic pyrazolidinone-based system were also prepared.\(^{39}\) Crucial for all of the above syntheses was the preparation of a pyrazolidinone key-intermediate with suitably functionalized substituent at position 5 allowing for cyclization to position 1. The 5-substituted pyrazolidinone was obtained by cyclization of the corresponding \(\beta\)-mesyloxy ester, which in turn was obtained in three steps from a suitably functionalized carboxylic acid.\(^{31}\) Pyrazolidinones with 2-hydroxyethyl\(^{36}\) and 2-aminoethyl\(^{35,37}\) functional groups at position 5 were used as key intermediates in the synthesis of novel saturated heterocyclic systems, while 5-[(S)-1-aminalkyl] derivatives prepared from N-protected \(\alpha\)-amino acids were used as scaffolds for potential organocatalysts\(^{38}\) and as key-intermediates in the synthesis of 3-pyrrolinones.\(^{40}\)

In addition to previously published 5-aminoethyl and 5-hydroxymethyl-3-pyrazolidinones, we also tried to prepare the 5-aminomethyl analogues, because they could be useful intermediates in the synthesis of novel saturated heterocycles in the imidazo[1,5-b]pyrazole and pyrazolo[1,5-a]pyrazine series. In this paper, we report the preparation and some follow-up transformations of 5-ami-

**Figure 1.** Examples of important 3-pyrazolidinone derivatives.

**Scheme 1.** Synthesis of the 5-aminomethyl-3-pyrazolidinones 5a, 5b, 5'b, and 7–9. Reaction conditions: i) CDI, THF, r.t. 2 h, then MeO\(_2\)CCH\(_2\)CO\(_2\)K, MgCl\(_2\), r.t.; ii) NaBH\(_4\), MeOH, 0–20 °C; iii) MsCl, pyridine, CH\(_2\)Cl\(_2\), 0 °C; iv) N\(_2\)H\(_4\)·H\(_2\)O, MeOH, r.t.; v) MeNHNH\(_2\), MeOH, r.t., then chromatographic separation (MPLC); vi) HCl-EtOAc, MeOH, r.t.

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nomethyl and 5-carboxy substituted 3-pyrazolidinones available from glycine derivatives and from dimethyl maleate, respectively. These novel pyrazolidinone derivatives are interesting intermediates in the synthesis of chiral saturated pyrazolidine-based heterocyclic systems.

2. Results and Discussion

First, 5-tert-butoxycarbonylaminoethyl-3-pyrazolidinones 5a, 5b, and 5’b were prepared in four steps from commercially available N-Boc-glycine (1a) following a well-established literature protocol.\textsuperscript{35–39} Masamune-Claisen condensation of amino acid 1a, i.e. activation of 1a with 1,1’-carbonyldiimidazole (CDI) followed by treatment of the intermediate imidazolide with a mixture of potassium monomethyl malonate and magnesium chloride gave the corresponding β-keto ester 2a in 93% yield. Reduction of 2a with NaBH\textsubscript{4} in methanol followed by O-mesylation of the so formed alcohol 3a afforded the β-mesyloxy ester 4a in 71% yield over two steps. The mesylate 4a was then cyclized with hydrazine hydrate or methylhydrazine to furnish the N(5’)-protected 5-aminomethyl-3-pyrazolidinones 5a, 5b, and 5’b. Cyclisation of the mesylate 4a with methylhydrazine was regioselective to give a ~5:1 mixture of the major 1-methyl regioisomer 5b and the minor 2-methyl isomer 5’b. Upon chromatographic separation (MPLC), the pure regioisomers 5b and 5’b were obtained in 66% and 14% yields, respectively. To shorten the synthetic procedure for the preparation of 5a, commercially available tert-butyl 2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (6) was treated with hydrazine hydrate in methanol at room temperature to afford the pyrazolidinone 5a in 45% yield. However, in spite of its greater simplicity, the latter procedure was less effective in terms of product yield. Finally, the respective free amines 7–9 were prepared.

![Chemical diagram](image_url)

**Scheme 2.** Reaction conditions: i) TFA, CH\textsubscript{2}Cl\textsubscript{2}, r.t.; ii) 50%aq. glyoxal or (MeO)\textsubscript{2}CH\textsubscript{2}CHO, H\textsubscript{2}, Pd-C, MeOH, r.t.; iii) 50%aq. (MeO)\textsubscript{2}CH\textsubscript{2}CHO, NaBH\textsubscript{3}CN, MeOH, r.t.; iv) CDI, THF, r.t.; v) 50%aq. (MeO)\textsubscript{2}CH\textsubscript{2}CHO, NaB\textsubscript{3}H\textsubscript{3}CN, MeOH, r.t.; vi) NaBH\textsubscript{3}, MeOH, 0–20 °C; vii) MeCl\textsubscript{2}, pyridine, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C; viii) N\textsubscript{2}H\textsubscript{4}·H\textsubscript{2}O, MeOH, r.t.; ix) Boc\textsubscript{2}O, r.t.; x) Mel, DMF, K\textsubscript{2}CO\textsubscript{3}, r.t.; xi) TFA-CH\textsubscript{2}Cl\textsubscript{2}, r.t.; xii) H\textsubscript{2}, Pd-C, MeOH, r.t.; xiii) CDI, DMF, r.t.
by acidolytic N-deprotection of 5a, 5b, and 5b'. Quite unexpectedly, treatment of 5a with HCl–MeOH gave the open-chain diamine 7, which is explainable by acid-catalyzed ring-opening of the initially formed intermediate 7 into methanol (Scheme 1).

Next, cyclisation of the pyrazolidinone 5a was studied. Our initial goal was to prepare hexahydropyrazolo[1,5-a]pyrazin-2(1H)-one (10) by concomitant N-deprotection and reductive alkylation of 5a with glyoxal or with dimethoxyacetaldehyde. Unfortunately, this approach did not work and furnished mixtures of products regardless of the variation of the reaction conditions. Nevertheless, we were able to detect the presence of the desired compound 10 in the crude reaction mixture by HRMS (m/z = 142.0974, MH+). Attempted isolation and purification of this highly polar compound 10 failed. On the other hand, reductive alkylation of 5a with dimethoxyacetaldehyde and NaBH4CN in methanol at room temperature gave the corresponding 1-(2,2-dimethoxyethyl) derivative 11a in 37% yield. In the same way, the Cbz-analogue 11b was prepared in five steps from N-Cbz-glycine (1b). Finally, two novel 1,5-dialkyltetrahydro-1'H-imidazo[1,5-b]pyrazole-2,6-diones 14a and 14b were synthesized. Following the established one-pot protocol (cf. Scheme 1), N-Cbz-sarcosine (1c) and N-benzyl-N-Cbz-glycine (1d) were transformed in four steps into the corresponding pyrazolidinones 5c and 5d. In a subsequent one-pot procedure, compounds 5c and 5d were Boc-protected at N(1), methylated at N(2), and Boc-deprotected to give the N(1)-unsubstituted intermediates 12a and 12b in good yields over seven steps. Somewhat expectedly,18 cyclizations of 12a,b into imidazo[1,5-b]pyrazole derivatives 14a,b proceeded well. Hydrogenolytic deprotection of the pyrazolidinones 12a and 12b followed by cyclisation of the intermediate free amines 13 with CDI furnished the expected 1,5-dimethyltetrahydro-1'H-imidazo[1,5-b]pyrazole-2,6-diones 14a and 14b in 42% and 53% yield, respectively (Scheme 2).

In continuation, the amidation of 5-oxo-1-phenylpyrazolinedione-3-carboxylic acid (17) was studied. Compound 17 was obtained in three steps from dimethyl maleate (15) following the literature procedure. Activation of the carboxylic acid 17 with CDI followed by treatment with primary amines 18a–c gave the corresponding carboxamides 19a–c in moderate yields. Somewhat surprisingly, amidation proceeded equally well with secondary diethylylamines (18d) to afford the tertiary carboxamide 19d in 49% yield. Attempted cyclisation of the glycine derivative 19a into 1-phenyltetrahydropyrazolo[1,5-a]pyrazine-2,4,7(1H)-trione (20) in refluxing toluene failed (Scheme 3).

Finally, amidation of racemic carboxylic acid was also performed with the non-racemic α-amino esters, (S)-AlaOMe (18e) and (S)-ProOMe (18f). These amidations afforded mixtures of non-racemic diastereomers 19e/19f and 19f/19f'. Subsequent separation of diastereomeric mixtures by medium pressure liquid chromatography furnished the non-racemic diastereomically pure carboxamides 19e, 19e', 19f, and 19f' in 13–23% yields. Unfortunately, all products 19e, 19e', 19f, and 19f' were obtained as oils and their absolute configuration could not be determined by X-ray diffraction. Therefore, the configurations of the products 19e, 19e', 19f, and 19f' are arbitrary (Scheme 4).

The structures of novel compounds 5a,b, 5b', 5e, 5f, 7–9, 11a,b, 14a,b, 19a–f, and 19f were determined by spectroscopic methods (1H NMR, 13C NMR, IR, MS, HRMS) and by elemental analyses for C, H, and N. Compounds 5b, 5b', 8, 9, 11a,b, 14a,b, 19е,f, and 19f were not obtained in analytically pure form. Their identities were confirmed by 13C NMR and HRMS.

3. Experimental

3.1. General Methods

Melting points were determined on a Stanford Research Systems MPA100 OptiMelt automated melting...
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3. 2. General Procedure for the Synthesis of N-protected 5-aminomethyl-3-pyrazolidinones 5a, 5b, and 5’b

Method A. Compounds 5a, 5b, and 5’b were prepared in a one-pot procedure following the combined slightly modified general literature procedures for the preparation of analogous compounds.35,38,39

3. 2. 1. Methyl 4-tert-butoxycarbonylamino-3-oxobutanoate (2a)42

Under argon, CDI (1.94 g, 12 mmol) was added to a solution of Boc-glycine (1a) (1.75 g, 10 mmol) in anh. THF (20 mL) and the mixture was stirred at room temperature for 2 h. Then a solid mixture of anh. MgCl2 (0.893 g, 9.5 mmol) and potassium monomethyl malonate (2.184 g, 14 mmol) was added under Ar in one portion via a powder funnel, which was rinsed with anh. THF (5 mL) and the mixture was stirred under Ar at r.t. for 20 h. Volatile components were evaporated in vacuo and the residue was triturated with EtOAc (80 mL). The resulting suspension was washed with 1 M aq. NaHSO4 (2 × 20 mL) and brine (20 mL). The organic phase was dried over anh. Na2SO4, filtered, and the filtrate was evaporated in vacuo to give 2a, which was used in the next step without purification. Yield: 2.15 g (93%) of yellow oil. Spectral data were in agreement with the literature data.42

3. 2. 2. Methyl 4-tert-butoxycarbonylamino-3-hydroxybutanoate (3a)43

Finely powdered NaBH4 (650 mg, 17.2 mmol) was slowly added to a cooled (0 °C) stirred solution of Boc-glycine (1a) (1.75 g, 10 mmol) in anh. THF (20 mL) and the mixture was stirred at room temperature for 2 h. Then a solid mixture of anh. MgCl2 (0.893 g, 9.5 mmol) and potassium mono-methyl malonate (2.184 g, 14 mmol) was added under Ar in one portion via a powder funnel, which was rinsed with anh. THF (5 mL) and the mixture was stirred at r.t. for 20 h. Volatile components were evaporated in vacuo and the residue was triturated with EtOAc (80 mL). The resulting suspension was washed with 1 M aq. NaHSO4 (2 × 20 mL) and brine (20 mL). The organic phase was dried over anh. Na2SO4, filtered, and the filtrate was evaporated in vacuo to give 2a, which was used in the next step without purification. Yield: 2.15 g (93%) of yellow oil. Spectral data were in agreement with the literature data.43

3. 2. 2. Methyl 4-tert-butoxycarbonylamino-3-hydroxybutanoate (3a)44

Finely powdered NaBH4 (650 mg, 17.2 mmol) was slowly added to a cooled (0 °C) stirred solution of β-keto ester 2a (6.94 g, 30 mmol) in MeOH (100 mL) and the resulting mixture was stirred at 0 °C for 1 h and then quenched at 0 °C by the addition of H2O (150 mL) followed by the addition of 1 M aq. HCl (30 mL, 30 mmol). The product was extracted with dichloromethane (3 × 150 mL) and the combined organic phase was washed with brine (150 mL). The organic phase was dried over anh. Na2SO4, filtered, and the filtrate was evaporated in vacuo.
The residue was dissolved in anh. toluene (30 mL) and the solution was evaporated in vacuo at 40 °C/2 mbar to give anhydrous crude 3a, which was used in the next step without further purification. Yield: 5.93 g (84%) of yellowish oil. Spectral data were consistent with the literature data.41

3.2.3. Methyl 4-tert-butoxycarbonylamino-3-mesityloxybutanoate (4a)

MsCl (2.25 ml, 29 mmol) was added to a cooled (0 °C) solution of β-hydroxy ester 3 (5.83 g, 25 mmol) in anhy. pyridine (30 mL) and the resulting mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h. The reaction mixture was poured into cooled (0 °C) toluene (350 mL) and the toluene solution was washed thoroughly with 1 M aq. HCl (200 mL) and brine (2 × 200 mL). The reaction mixture was neutralised with 1 M aq. NaOH (200 mL) and then aqueous 5% HCl in ethyl acetate (10 mL, 20 mmol) was added to a solution of 4a (3 mmol) in CH2Cl2 (25 mL) and the mixture was stirred at room temperature for 24–72 h. Volatile components were evaporated in vacuo and the residue was purified by CC. First, the non-polar impurities and starting material 4a were eluted (EtOAc–hexane, 1:1), followed by elution of the products 5 and 5'. 1H-NMR (500 MHz, DMSO-d6): δ 1.38 (9H, s, t-Bu), 1.95 (1H, dd, J = 5.1, 16.3 Hz, 4-Ha), 2.45 (1H, dd, J = 8.2, 16.2 Hz, 4-Hb), 2.81 (3H, s, 1-Me), 2.86–2.94 (1H, m 3'-Ha); 2.96–3.03 (1H, m, 3'-Ha), 3.41 (1H, br s, 3-H), 5.67 (1H, br s, 2-H), 6.89 (1H, t, J = 5.8 Hz, NHCH3). 13C-NMR (126 MHz, DMSO-d6): δ 28.2, 30.6, 35.2, 42.6, 53.0, 77.8, 155.8, 172.1. m/z (ESI) = 230 (MH+). HRMS–ESI (m/z): [MH+] calcd for C10H20N3O3, 230.1499; found, 230.1499. IR (ATR) ν 3344, 2970, 1692, 1649, 1522, 1445, 1392, 1365, 1277, 1252, 1175, 1124, 1081, 1053, 1000, 964, 901, 874, 782, 732, 638 cm–1.

Tert-Butyl [(2-methyl-5-oxopyrazolidin-3-yl)methyl] carbamate (5b) and tert-butyl [(1-methyl-5-oxopyrazolidin-3-yl)methyl]carbamate (5b').

Prepared from 4a (1.38 g, 4.43 mmol) and methylhydrazine (557 µL, 10.37 mmol), stirring for 72 h. Yield: 70 mg (66%) of yellow oil. 1H-NMR (500 MHz, DMSO-d6); δ 1.38 (9H, s, t-Bu), 2.09 (1H, dd, J = 5.1, 16.3 Hz, 4-Ha), 2.45 (1H, dd, J = 8.2, 16.2 Hz, 4-Hb), 2.81 (3H, s, 1-Me), 2.86–2.94 (1H, m 3'-Ha); 2.96–3.03 (1H, m, 3'-Ha), 3.41 (1H, br s, 3-H), 5.67 (1H, br s, 2-H), 6.89 (1H, t, J = 5.8 Hz, NHCH3). 13C-NMR (126 MHz, DMSO-d6): δ 28.2, 30.6, 35.2, 42.6, 53.0, 77.8, 155.8, 172.1. m/z (ESI) = 230 (MH+). HRMS–ESI (m/z): [MH+] calcd for C10H20N3O3, 230.1499; found, 230.1496. IR (ATR) ν 3332, 2977, 2931, 1692, 1520, 1455, 1392, 1366, 1278, 1253, 1168, 1094, 1044 cm–1.

3.2.4. Preparation of 3-pyrazolidinones 5a, 5b, and 5'b

Method A. Hydrazine monohydrate (0.75 ml, 15 mmol) or methylhydrazine (789 µ, 15 mmol) was added to a solution of the mesylate 4a (3 mmol) in CH2Cl2 (25 mL) and the mixture was stirred at room temperature for 24–72 h. Volatile components were evaporated in vacuo and the residue was purified by CC. First, the non-polar impurities and starting material 4a were eluted (EtOAc–hexane, 1:1), followed by elution of the products 5 and 5'. 1H-NMR (500 MHz, DMSO-d6): δ 1.38 (9H, s, t-Bu), 2.20 (dd, J = 9.0, 15.1 Hz, 1H of CH3), 2.44 (dd, J = 3.8, 15.1 Hz, 1H of CH3), 2.86–2.98 (m, CH3); 3.82–3.90 (m, CH); 4.94 (d, J = 5.6 Hz, OH); 6.77 (t, J = 5.8 Hz, NH). 13C-NMR (126 MHz, DMSO-d6): δ 28.2, 37.0, 37.9, 43.0, 51.7, 77.4, 78.2, 155.8, 169.8.

Method B. Hydrazine hydrate (729 µL, 15 mmol) was added to a solution of 5a (6 mmol) in methanol (15 mL) and the mixture was stirred at r.t. for 48 h. Volatile components were evaporated in vacuo and the residue was purified by CC. 1H-NMR (500 MHz, DMSO-d6): δ 1.38 (9H, s, t-Bu), 2.09 (1H, dd, J = 5.1, 16.3 Hz, 4-Ha), 2.45 (1H, dd, J = 8.2, 16.2 Hz, 4-Hb), 2.81 (3H, s, 1-Me), 2.86–2.94 (1H, m 3'-Ha); 2.96–3.03 (1H, m, 3'-Ha), 3.41 (1H, br s, 3-H), 5.67 (1H, br s, 2-H), 6.89 (1H, t, J = 5.8 Hz, NHCH3). 13C-NMR (126 MHz, DMSO-d6): δ 28.2, 30.6, 35.2, 42.6, 53.0, 77.8, 155.8, 170.5. m/z (ESI) = 230 (MH+). HRMS–ESI (m/z): [MH+] calcd for C10H20N3O3, 230.1499; found, 230.1503. IR (ATR) ν 3332, 2977, 2933, 1694, 1520, 1455, 1394, 1367, 1277, 1253, 1169, 1060, 957 cm–1.

3.3. General Procedure for Acidolytic Deprotection of Compounds 5a, 5b, and 5'b. Synthesis of Free Amines 7–9

2 M HCl in ethyl acetate (10 mL, 20 mmol) was added to a stirred solution of 5a, 5b, or 5'b (4 mmol) in methanol (20 mL) and the mixture was stirred at r.t. for 72 h.
The precipitate was collected by filtration, washed with anh. Et₂O (50 mL) and dried in vacuo to give 7a. Yield: 1.606 g (37%) of white foam. 1H-NMR (500 MHz, DMSO-d₆): δ 1.37 (9H, s, t-Bu), 1.89 (1H, dd, J = 2.3, 16.4 Hz, 4'-Ha), 2.70 (1H, dd, J = 4.5, 12.7 Hz, 1H of NCH₃), 2.75 (1H, dd, J = 8.4, 16.8 Hz, 4'-Hb), 2.78–2.87 (1H, m, 1H of NCH₃), 2.89 (1H, dd, J = 5.9, 12.7 Hz, 1H of NCH₃), 3.00 (1H, m, 1H of NCH₃), 3.25 and 3.26 (6H, 2s, 1:1, 2 × OMe), 3.23–3.29 (1H, m, 3'-H overlapped by the signal for H₂O), 4.40 (1H, dd, J = 4.5, 5.9 Hz, CH(OMe)), 6.82 (1H, t, J = 5.9 Hz, NHCH₂), 9.34 (1H, s, 1'-H). 13C-NMR (126 MHz, DMSO-d₆): δ 32.6, 39.2, 45.2, 62.3, 171.5. m/z (ESI) = 130 (M⁺). HRMS–ESI (m/z): [MH⁺] calcd for C₁₃H₂₅N₃O₅, 304.1867; found, 304.1866. IR (ATR) ν 3336, 3058, 2938, 2836, 2360, 2342, 1698, 1507, 1507, 1452, 1423, 1392, 1367, 1266, 1169, 1132, 1074, 974, 896, 866, 741, 705, 668 cm⁻¹.

3. 5. Benzyl ((2-(2,2-dimethoxyethyl)-5-oxopyrazolidin-3-yl)methyl)carbamate (11b)

The crude pyrazolidinone 5b was prepared in four steps from N-Cbz-glycine (1b) following a one-pot procedure for the preparation of its N-Boc analogue 5a (cf. Section 3.2. and Scheme 1). Reductive alkylation of the intermediate pyrazolidinone 5b (1.246 g, 5 mmol) was performed in the same way as described above for the preparation of 11a. The crude product 11b was additionally purified by MPLC (EtOAc–MeOH, 10:1). Yield: 700 mg (41%) of yellow oil. 1H-NMR (500 MHz, DMSO-d₆): δ 1.91 (1H, dd, J = 2.5, 16.9 Hz, 4'-Ha), 2.71 (1H, dd, J = 4.5, 12.8 Hz, 1H of NCH₃), 2.78 (1H, dd, J = 8.3, 16.8 Hz, 4'-Hb), 2.89 (1H, dd, J = 3.2, 5.9 Hz, 1H of NCH₃), 2.90 (1H, m, 1H of NCH₃), 3.08 (1H, m, 1H of NCH₃), 3.24 and 3.25 (6H, 2s, 1:1, 2 × OMe), 3.29–3.36 (1H, m, 3'-H), 4.40 (1H, dd, J = 4.5, 5.9 Hz, CH(OMe)), 5.02 (2H, d, J = 4.3 Hz, PhCH₂), 7.29–7.39 (6H, m, Ph and NHCH₂), 9.36 (1H, s, 1'-H). 13C-NMR (126 MHz, DMSO-d₆): δ 31.8, 43.4, 53.0, 53.1, 60.8, 61.8, 65.3, 101.8, 127.7, 127.8, 128.3, 137.1, 156.3, 172.9. m/z (ESI) = 338 (M⁺). HRMS–ESI (m/z): [MH⁺] calcd for C₁₆H₂₃N₃O₅, 338.1711; found, 338.1709. IR (ATR) ν 3336, 3058, 2938, 2836, 2360, 2342, 1698, 1519, 1455, 1266, 1134, 1073, 977, 918, 869, 830, 739, 701, 668 cm⁻¹.

3. 6. General Procedure for the Synthesis of 5-alkyl-1-methyltetrahydro-1H-imidazo[1,5-b]pyrazole-2,6-diones 14a,b

Bicyclic compounds 14a and 14b were obtained in nine steps from N-Cbz-sarcosine (1c) and N-benzyl-N-Cbz-glycine (1d). First, 3-pyrazolidinones 5c and 5d were prepared following a one-pot procedure for the preparation of their N-Boc analogue 5a (cf. Section 3.2. and Scheme 1).
3. 6. 1. Preparation of the Free Diamines 12a,b

Boc₂O (2.4 g, 11 mmol) was added to a stirred solution of 5c,d (9 mmol) in a mixture of dioxane (12 mL), water (25 mL), and Na₂CO₃ (1.1 g, 10 mmol) and the mixture was stirred at r.t. for 24 h. Most of the dioxane was removed by evaporation in vacuo at 35°C/50 mbar. EtOAc (50 mL) and brine (25 mL) were added to the aqueous residue, the biphasic system was transferred into a separatory funnel, shaken, and the phases were separated. The organic phase was washed with brine (2 × 20 mL), dried over anh. Na₂SO₄, filtered, and the filtrate was evaporated in vacuo. The residue was purified by CC (EtOAc/hexane, 1:1). Fractions containing the product were combined and evaporated in vacuo. Under argon, the residue was dissolved in anh. DMF (25 mL), K₂CO₃ (691 mg, 5 mmol) and methyl iodide (934 µL, 15 mmol) were added and the mixture was stirred at r.t. for 72 h. Volatile components were evaporated in vacuo, EtOAc (100 mL) was added to the residue, and the mixture was washed with brine (3 × 30 mL). The organic phase was dried over anh. Na₂SO₄, filtered, and the filtrate was evaporated in vacuo. The residue was purified by CC (EtOAc/hexane, 1:1). Fractions containing the product were combined and evaporated in vacuo. Under argon, the residue was dissolved in anh. DMSO (20 mL), TFA (5 mL) was added and the mixture was stirred at r.t. for 5 min and then stirring was stopped and the phases were allowed to separate. The organic phase was washed with brine (2 × 10 mL), dried over anh. Na₂SO₄, filtered, and the filtrate was evaporated in vacuo. The residue was purified by CC (EtOAc/hexane, 1:1). Fractions containing the product were combined and evaporated in vacuo to give 12a,b, which were used in the next step without further purification.

3. 6. 2. Preparation of tetrahydro-1H-imidazo[1,5–b]pyrazole-2,6-diones 14a,b

A mixture of crude 12c,d (1.5 mmol), methanol (20 mL), and 10% Pd–C (80 mg) was hydrogenated under 3 bar of H₂ at room temperature for 1.5 h. The catalyst was removed by filtration through a short pad of Celite®, washed with methanol (3 × 10 mL), and the combined filtrate was evaporated in vacuo. The residue was dissolved in toluene (20 mL) and the solution was evaporated in vacuo again to give anhydrous free diamine 13a,b. The crude diamine 13 (1.5 mmol) was dissolved in anh. DMSO (5 mL), CDI (262 mg, 1.55 mmol) was added, and the mixture was stirred at room temperature for 12 h. Volatile components were evaporated in vacuo and the residue was purified by CC (EtOAc–MeOH, 10:1). Fractions containing the product were combined and evaporated in vacuo. The residue (a mixture of 14 and imidazole) was dissolved in EtOAc (1 mL), 2 M HCl–Et₂O (1 mL), was added and the precipitate (imidazole hydrochloride) was removed by filtration and washed with anh. Et₂O (2 × 2 mL). The filtrate was evaporated in vacuo to give 14a,b.

1,5-Dimethyltetrahydro-1H-imidazo[1,5–b]pyrazole-2,6-dione (14a).

Prepared from 12a (222 mg, 1.55 mmol) and CDI (265 mg, 1.55 mmol). Yield: 110 mg (42%) of yellow oil. ¹H-NMR (500 MHz, DMSO-d₆): δ 2.41 (1H, dd, J = 7.8, 16.0 Hz, 3'-H), 2.70 (1H, dd, J = 11.3, 16.4 Hz, 3'-Hb), 2.75 (3H, s, 5'-Me), 3.13 (3H, s, 1'-Me), 3.35 (1H, dd, J = 1.2, 9.7 Hz, 4'-H), 3.58 (1H, dd, J = 7.35, 9.82 Hz, 4'-H), 3.60 (1H, dtd, J = 11.3, 9.82 Hz, 4'-H), 4.30 (1H, dtd, J = 1.20, 7.65, 7.61, 10.97 Hz, CH). ¹³C-NMR (126 MHz, DMSO-d₆): δ 30.1, 32.3, 35.3, 47.6, 53.4, 162.6, 170.1. m/z (ESI) = 130 (MH⁺). HRMS–ESI (m/z): [MH⁺] calcd for C₁₅H₁₄N₃O₂, 246.1237; found, 246.1237.

5-Benzyl-1-methyltetrahydro-1H-imidazo[1,5–b]pyrazole-2,6-dione (14b).

Prepared from 5c (340 mg, 1.55 mmol) and CDI (265 mg, 1.55 mmol). Yield: 201 mg (53%) of yellow oil. ¹H-NMR (500 MHz, DMSO-d₆): δ 2.44 (1H, dd, J = 16.2, 7.7 Hz, 3'-H), 2.59 (1H, dd, J = 16.3, 11.2, 1.1 Hz, 3'-Hb), 3.16 (1H, dd, J = 9.8, 1.1 Hz, 4'-H), 3.34 (3H, s, 1-Me), 3.50 (1H, dd, J = 9.7, 7.3 Hz, 4'-H), 4.25 (1H, dtd, J = 11.3, 7.5, 1.1 Hz, 3'-H), 4.34 (1H, d, J = 14.8 Hz, 1H of CH₂Ph), 4.46 (1H, d, J = 14.9 Hz, 1H of CH₂Ph), 7.18–7.26 (2H, m, 2H of Ph), 7.27–7.43 (3H, m, 3H of Ph). ¹³C-NMR (126 MHz, DMSO-d₆): δ 32.7, 36.0, 45.4, 47.6, 54.0, 128.1, 128.1, 129.0, 135.2, 162.8, 169.6. m/z (ESI) = 246 (MH⁺). HRMS–ESI (m/z): [MH⁺] calcd for C₁₅H₁₄N₃O₂, 246.1237; found, 246.1237.

3. 7. General Procedure for the Synthesis of 5-oxopyrazolidine-3-carboxamides 19a–d

Under argon, CDI (0.892 g, 5.5 mmol) was added to a stirred suspension of carboxylic acid 17 (1.031 g, 5 mmol) in anh. acetonitrile (20 mL), the mixture was stirred at r.t. for 1.5 h, followed by addition of amine 18 (5 mmol). When amine 18 hydrochloride was used, one equivalent of N-methylmorpholine (NMM, 600 µL, 5 mmol) was added as well. The mixture was stirred at r.t. for 12 h and volatile components were evaporated in vacuo. The residue was added to dichloromethane (30 mL) and the solution was washed with 1 M aq. NaHSO₄ (2 × 20 mL), saturated aq. NaHCO₃ (2 × 20 mL), and brine (2 × 20 mL). The organic phase was dried over anh. Na₂SO₄, filtered, and the filtrate was evaporated in vacuo. Volatile components were evaporated in vacuo and the residue was purified by CC (EtOAc). Fractions containing the product were combined and evaporated in vacuo to give 19a–d.
3. 7. 1. Methyl rac-((5-oxo-1-phenylpyrazolidine-3-carboxy)glycinolate (19a)

Prepared from 17 (1.031 g, 5 mmol), CDI (0.892 g, 5.5 mmol), methyl glycinate hydrochloride (18a) (628 mg, 5 mmol), and NMM (600 µL, 5 mmol). Yield: 653 mg (45%) of red crystals; m.p. 148–152 °C. 1H-NMR (500 MHz, DMSO-d6): δ 2.79 (1H, d, J = 1.3, 16.6 Hz, 4'-Ha), 3.06 (1H, dd, J = 9.3, 16.6 Hz, 4'-Hb), 3.60 (3H, s, OMe), 3.85–3.97 (2H, m, CH2CO2Me), 4.16–4.22 (1H, m, 5'-H), 8.68 (1H, d, J = 6.8 Hz, 1'-H), 7.12 (1H, t, J = 7.4 Hz, 1H of Ph), 7.37 (2H, dd, J = 7.3, 8.6 Hz, 2H of Ph), 7.86 (2H, td, J = 1.2, 7.5 Hz, 2H of Ph), 8.57 (1H, t, J = 6.1 Hz, NHCH3). 13C-NMR (126 MHz, DMSO-d6): δ 36.8, 50.7, 51.7, 54.6, 118.1, 123.7, 128.4, 138.8, 146.1, 1410, 1403, 1358, 1338, 1312, 1281, 1242, 1205, 1160, 1072, 1097, 1065, 1031, 1013, 983, 968, 956, 932, 909, 828, 764, 718, 692, 659, 617 cm⁻¹.

3. 7. 2. Methyl rac-3-((5-oxo-1-phenylpyrazolidine-3-carboxamido)propanoate (19b)

Prepared from 17 (208 mg, 1 mmol), CDI (178 mg, 1.1 mmol), methyl β-alanine hydrochloride (18b) (140 mg, 1 mmol), and NMM (120 µL, 1 mmol). Yield: 131 mg (45%) of pale yellowish crystals; m.p. 88–91 °C. 1H-NMR (500 MHz, DMSO-d6): δ 2.41–2.54 (2H, m, CH2NH), 3.07 (1H, dd, J = 17.2, 9.3 Hz, 4'-Ha), 3.13 (1H, dd, J = 17.2, 3.5 Hz, 4'-Hb), 3.47 (1H, ddt, J = 13.6, 7, 5 Hz, CH2CO2Me), 3.50–3.60 (4H, m, OMe and 1H of CH2CO2Me), 4.09 (1H, d, J = 9.7, 6.6, 3.4 Hz, 5'-H), 5.43 (1H, d, J = 6.6 Hz, 1'-H), 7.14 (1H, t, J = 7.4 Hz, 1H of Ph), 7.37 (2H, dd, J = 8.7, 7.3 Hz, 2H of Ph), 7.78 (1H, s, N̶C(O)₂), 7.82 (2H, d, J = 7.6 Hz, 2H of Ph). 13C-NMR (126 MHz, DMSO-d6): δ 33.7, 34.8, 37.2, 51.8, 55.31, 118.0, 124.7, 128.9, 138.2, 169.5, 170.0, 172.6. m/z (ESI) = 292 (MH+). HRMS–ESI (m/z): [MH+] calcd for C18H20NO9, 371.1350; found, 371.1356.

3. 7. 3. 5-Oxo-N-phenethyl-1-phenylpyrazolidine-3-carboxamide (19c)

Prepared from 17 (208 mg, 1 mmol), CDI (178 mg, 1.1 mmol), and 3-phenylethylamine (18c) (126 µL, 1 mmol). Yield: 154 mg (50%) of white crystals; m.p. 131–133 °C. 1H-NMR (500 MHz, DMSO-d6): δ 2.73 (2H, td, J = 4.5, 6.7, 6.9 Hz, NHCH3), 3.02 (1H, dd, J = 9.6, 17.7 Hz, 4'-Ha), 3.09 (1H, dd, J = 3.3, 17.3 Hz, 4'-Hb), 3.45 (1H, qd, J = 6.4, 13.1 Hz, 1H of CH2Ph), 3.58 (1H, qd, J = 6.5, 13.1 Hz, 1H of CH2Ph), 4.02 (1H, ddd, J = 3.3, 6.6, 9.8 Hz, 5'-H), 5.31 (1H, d, J = 6.7 Hz, 1'-H), 7.01–7.08 (1H, m, 1H of Ph), 7.11–7.24 (5H, m, Ph), 7.30–7.38 (2H, m, 2H of Ph), 7.67 (2H, d, J = 7.8 Hz, 2H of Ph). 13C-NMR (126 MHz, DMSO-d6): δ 35.4, 37.3, 40.4, 55.2, 117.8, 124.7, 126.6, 128.6, 128.7, 129.0, 138.2, 138.3, 169.4, 169.9. m/z (ESI) = 310 (MH+). HRMS–ESI (m/z): [MH+] calcd for C16H19NO4, 292.1292; found, 292.1295. Anal. Calcld for C16H19NO4: C, 64.44; H, 7.20; N, 16.08. Found: C, 64.44; H, 7.20; N, 16.08. Found: C, 64.44; H, 7.20; N, 16.08.

3. 7. 4. N,N-Diethyl-5-oxo-1-phenylpyrazolidine-3-carboxamide (19d)

Prepared from 17 (208 mg, 1 mmol), CDI (178 mg, 1.1 mmol), and diethylamine (18d) (104 µL, 1 mmol). Yield: 128 mg (49%) of pale greyish crystals; m.p. 77–80 °C. 1H-NMR (500 MHz, DMSO-d6): δ 1.05 (3H, t, J = 7.1 Hz, Me), 1.18 (3H, t, J = 7.0 Hz, Me), 2.85 (2H, d, J = 15.7 Hz, 4'-CH2), 3.32 (2H, m, CH2Me), 3.42 (2H, m, CH2Me), 4.55 (1H, m, 5'-H), 6.39 (1H, d, J = 9.37 Hz, 1'-H), 7.07 (1H, t, J = 7.4 Hz, 1H of Ph), 7.33 (2H, t, J = 7.85 Hz, 2H of Ph), 7.77 (2H, d, J = 8.10 Hz, 2H of Ph). 13C-NMR (126 MHz, DMSO-d6): δ 12.7, 14.4, 37.4, 39.6, 40.9, 53.2, 117.7, 123.4, 128.4, 139.1, 168.2, 170.5. m/z (ESI) = 262 (MH+). HRMS–ESI (m/z): [MH+] calcd for C17H19NO4, 262.1550; found, 262.1551. Anal. Calcld for C17H19NO4: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.44; H, 7.20; N, 15.93.

3. 8. General Procedure for the Synthesis of Non-racemic Carboxamides 19e, 19f, and 19' e, f

Mixtures of diastereomeric carboxamides 19e/19' e and 19f/19' f were prepared from racemic carboxylic acid 17 and (S)-amino esters 18e and 18f, respectively, following the general procedure for the preparation of racemic carboxamides 19a–d. Mixtures of diastereomers 19e/19' e and 19f/19' f were separated by MPLC (EtOAc–hexane). Fraction containing the products were combined and evaporated in vacuo to give the non-racemic diastereomerically pure carboxamides 19e, 19' e, and 19f.
mg, 1 mmol), and NMM (120 µL, 1 mmol); MPLC (EtOAc–hexane, 1:1).

Data for the (+)-isomer 19e. Yield: 67 mg (23%) of yellow oil; [α]D=+21.2 (c 0.365, CHCl3), MPLC: R = 67 min. 1H NMR (500 MHz, CDCl3): δ 1.33 (3H, d, J = 7.2 Hz, Me), 3.13 (2H, d, J = 6.4 Hz, 4'-CH2), 3.75 (3H, s, CONMe), 4.16 (1H, q, J = 6.6 Hz, 2-H), 4.54 (1H, m, 5-H), 4.85 (1H, d, J = 6.7 Hz, 3-H), 7.16 (1H, t, J = 7.4 Hz, 1H of Ph), 7.38 (2H, dd, J = 7.4, 8.7 Hz, 2H of Ph), 7.73 (1H, s, 1'-H), 7.83 (2H, dd, J = 1.2, 8.8 Hz, 2H of Ph). 13C NMR (126 MHz, CDCl3): δ 18.25, 37.22, 48.06, 52.65, 53.29, 117.97, 124.84, 129.04, 138.23, 169.39, 169.80, 173.12. m/z (ESI) = 292 (MH+). HMRS–ESI (m/z): [MH]+ calcld for C14H17N3O4, 292.1292; found, 292.1292. IR (ATR) ν 3469, 3367, 3227, 3068, 2992, 2952, 2848, 1739, 1664, 1595, 1518, 1495, 1454, 1352, 1323, 1210, 1154, 1112, 1056, 1030, 979, 932, 894, 847, 827, 754, 691, 670, 629 cm⁻¹.

Data for the (+)-isomer 19f. Yield: 60 mg (21%) of yellow oil; [α]D=+82.2 (c 0.39, CHCl3), MPLC: R = 78 min. 1H NMR (500 MHz, CDCl3): δ 1.43 (3H, d, J = 7.1 Hz, Me), 3.09 (1H, dd, J = 9.3, 17.2 Hz, 4'-Ha), 3.16 (1H, dd, J = 3.5, 17.2 Hz, 4'-Hb), 3.62 (3H, s, CONMe), 4.14 (1H, dd, J = 3.5, 6.6, 9.7 Hz, 2-H), 4.54 (1H, m, 5'-H), 5.44 (1H, d, J = 6.7 Hz, 3-H), 7.16 (1H, t, J = 7.4 Hz, 1H of Ph), 7.38 (2H, dd, J = 7.4, 8.7 Hz, 1H of Ph), 7.81–7.90 (3H, m, 1'-H and 2H of Ph). 13C NMR (126 MHz, CDCl3): δ 18.4, 37.0, 48.2, 52.5, 55.4, 118.42, 124.9, 129.0, 138.2, 169.3, 169.6, 172.6. m/z (ESI) = 291 (MH+). HMRS–ESI (m/z): [MH]+ calcld for C14H16N3O4, 292.1292; found, 292.1292. IR (ATR) ν 3469, 3367, 3226, 3066, 2952, 2925, 2848, 1739, 1665, 1595, 1518, 1495, 1454, 1352, 1323, 1210, 1154, 1112, 1056, 1030, 979, 932, 894, 847, 827, 754, 691, 670, 629 cm⁻¹.

4. Conclusions

1,2-Substituted 5-aminomethyl-3-pyrazolidinones are available in four steps from N-protected glycines and their N-alkylated analogues. Although the alternative one-step ‘ring switching’ synthesis of 5-aminomethyl-3-pyrazolidinones is definitely simpler and shorter, the high price or difficult availability of the starting N-protected pyrrolin-2(5H)-one, as well as lower yield and purity of the so obtained product are disadvantageous. Regioselective reductive alkylation 1,2-substituted pyrazolidinones with dimethoxyacetalddehyde provided the 1-(2,2-dimethoxyethyl) substituted 3-pyrazolidinones, which, unfortunately could not be cyclized into the desired hexahydropyrazolo[1,5-a]pyrazin-2(1H)-ones. On the other hand, a three step selective methylation provided selectively the 2-methyl regioisomers as key-intermediates in the preparation of the novel 1,5-dialkyltetrahydro-1H-imidazo[1,5-b]pyrazole-2,6-diones, as rare representatives of almost unexplored 3D-rich heterocyclic system. The number of synthetic steps in the above preparations may seem disadvantageous, nevertheless, this is compensated by performing up to five subsequent steps via a one-pot procedure. Amidation of easily available 3-oxopyrazolidine-5-carboxylic acid yielded the corresponding carboxamides in moderate yields. Diastereomeric non-racemic carboxamides obtained from (S)-AlaOMe and (S)-ProOMe are separable by MPLC.

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6. References

Povzetek
Študirali smo sintetne pristope za pripravo novih 3-pirazolidinonskih derivatov funkcionaliziranih na položajih N(1) in/ali C(3). 5-aminoalkil-3-pirazolidinone smo pripravili v štirih korakih iz N-zaščitenih glicinov preko Masam-une-Claisenove homologacije, redukcije, O-meziliranja in ciklizacije z derivati hidrazina. Proste amine smo pripravili z odščitvo v kislem. Ciljno spojino smo pripravili tudi z ‘ring switching’ transformacijo N-Boc-pirolin-2(5H)-ona s hidrazinom. S katalitskim hidrogeniranjem smo odščitili 5-(N-alkil-N-Cbz-aminometil)pirezolidine-3-ones in s sledečo ciklizacijo z 1,1’-karbonilditimidazolom (CDI) pripravili dva nova predstavnika perhidroimidazo[1,5-b]pirazola, ki je skoraj popolnoma neraziskan heterociklični system. Pri amidiranju 3-oksopirazolidin-5-karboksilne kisline smo dobili ustrezne karboksamide s srednjimi izkoristki. Diastereomerni neracemni karboksamide, pripravljene iz (S)-AlaOMe in (S)-ProOMe, smo ločili s pomočjo MPLC kromatografske tehnike.