Synthesis of N^{β}-substituted 1,2-diazetidin-3-ones by the Ugi reaction comprising chiral α-hydrazino acids

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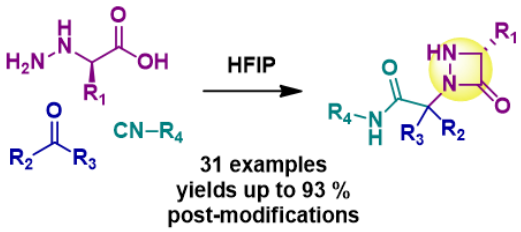
Abstract

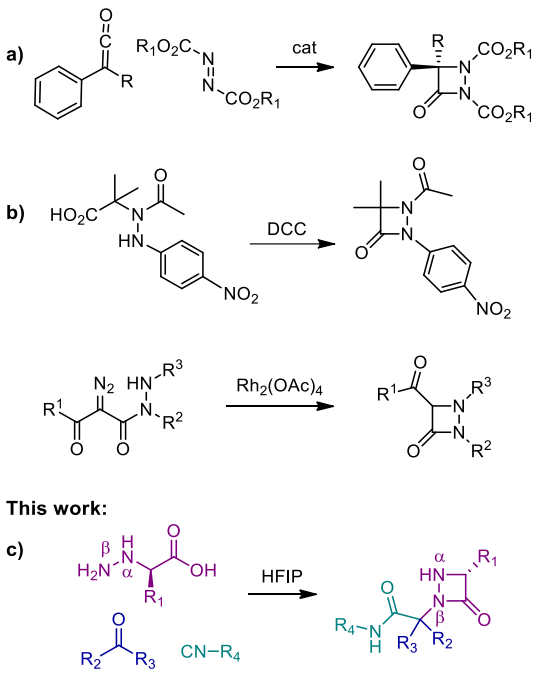
We report the synthesis of a structurally diverse library of chiral N^{β}-substituted 1,2-diazetidin-3-ones by a 4-centre 3-component Ugi reaction comprising unprotected α-hydrazino acids. Various isocyanides and carbonyl compounds, both aldehydes and ketones were utilized. In addition, post-condensation modifications at three different sites have been demonstrated.



Introduction

Heterocyclic compounds are the largest and probably the best studied class of organic compounds, owing to their ubiquity in Nature and myriad of manifested activities. Nitrogen-containing heterocycles account for nearly 60 % of FDA approved small-molecule drugs, with four-membered rings being particularly attractive scaffolds, due to their structural rigidity and ability to adopt a distinct 3D structure.[1] Among nitrogen-containing heterocyclic compounds, 1,2-diazetidin-3-ones (aza-β-lactams) have emerged as pharmaceutically promising motifs, following the discovery that they act as potent inhibitors of serine hydrolase protein phosphatase methylesterase-1.[2,3] Recently, 1,2-diazetidinone was identified as an interesting mechanophore, a force responsive motif with a variety of applications ranging from molecular release to self-healing materials.[4,5]

Available methods for the synthesis of 1,2-diazetidin-3-ones rely on the [2+2] cycloaddition of a ketene with an azo compound,[6] including enantioselective approaches using asymmetric nucleophilic catalysts (Scheme 1a),[7,8] and intramolecular ring cyclization chemistry.[6] Thus, diazetidinones were prepared by cyclodehydratation of azido-acids,[9] while, Moody et al. utilized the intramolecular N-H insertion reaction of rhodium carbene intermediates derived from diazocarbonyl compounds (Scheme 1b).[10] The main shortcoming of these methods are either the narrow substrate scope or the multistep synthesis of cyclization precursor, which limits the availability of structurally diverse libraries of 1,2-diazetidin-3-ones. Moreover, lability of the 4-membered ring hamper the derivatisation and diversification of compounds with this structural motif.[6] Inspired by an elegant multicomponent approach to β-lactams utilizing β-amino acids as bifunctional components in the Ugi reaction,[11] we were keen to examine α-hydrazino acids as key elements to build 1,2-diazetidin-3-one core structure. While Naskar et al. utilized the Petasis Boronic acid–Mannich reaction combined with the Ugi reaction or 1,3-diisopropylcarbodiimide condensation to obtain a small library of racemic diazetidinones,[12] here we used enantiomerically pure unprotected α-hydrazino acids in a 4-centre 3-component Ugi reaction (Scheme 1c). The methodology enables single-pot access to a library of structurally diverse chiral N^{β}-substituted 1,2-diazetidin-3-ones, with N^{α} position available for the last-stage functionalisation. In addition, we optimised the reaction conditions for generally low reactive ketones, previously neglected in multicomponent strategies toward 1,2-diazetidin-3-ones.



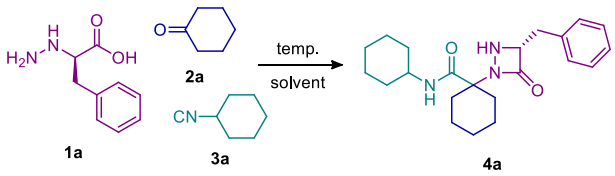
Scheme 1. Synthetic strategies to 1,2-diazetidin-3-ones

Results and duscussion

The unprotected D-α-hydrazino acids **1** used in this work were obtained by the nucleophilic substitution of L-amino acid-derived α-bromo acids with hydrazine hydrate.[13] First, we sought to optimise the reaction conditions on a model reaction with α-hydrazino-D-phenylalanine, cyclohexanone and cyclohexyl isocyanide. We screened solvents and temperature in the reaction performed with 1.1 eq. of α-hydrazino acid and an isocyanide component. Reactions carried out in nonpolar solvents, dichloromethane and tetrahydrofuran failed to give the desired product **4a** (Table 1, Entry 1 and 2). Reactions carried out in methanol at room temperature (Entry 3) and at 60 °C (Entry 4) afforded 1,2-diazetidin-3-one **4a** in 20 % and 24 % yield, respectively. In the reaction carried out in methanol at 60 °C, several additional products appeared which probably originated from the decomposition of the material. Encouraged by these results, we tested the reactions in trifluoroethanol (TFE), and hexafluoroisopropanol (HFIP), which are more acidic and less nucleophilic solvents. Conducting the reaction in TFE at room temperature, gives the product with a slightly better, albeit low yield (32 %, Entry 5). Heating the reaction to 60 °C ended with decomposition of the material. Finally, the Ugi reaction carried out in HFIP at room temperature afforded, after 24 h 1,2-diazetidin-3-one **4a** in high yield (87 %, Entry 7). We were very pleased with this result, becouse it is known the ketones are considerably less reactive in the Ugi reaction than aldehydes. Nevertheless, we tested the Ugi reaction with butyraldehyde in methanol, TFE and

HFIP at room temperature, and found that reaction carried out in HFIP afforded product **4b** in highest yield (76 %, Table 2).

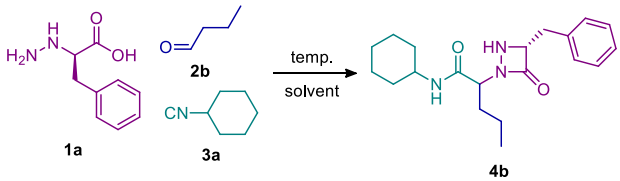
Table 1. Optimisation of the conditions for the formation of 1,2-diazetidin-3-ones with ketones[a]



Entry	Solvent	Temp/°C	Time/h	Yield/%
1	DCM	RT	24	-
2	THF	RT	24	-
3	MeOH	RT	24	20
4	MeOH	60	24	24[b]
5	TFE	RT	24	32
6	TFE	60	24	-
7	**HFIP**	**RT**	**24**	**87**

[a] Reactions were carried out on a 0.2 mmol scale. Yields refer to the isolated product. Oil bath was used for heating reactions. [b] The reaction was accompanied by decomposition of the material.

Table 2. Optimisation of the conditions for the formation of 1,2-diazetidin-3-ones with aldehydes[a]



Entry	Solvent	Temp/°C	Time/h	Yield/%
1	MeOH	RT	24	41
2	TFE	RT	24	53

3	**HFIP**	**RT**	**24**	**76**

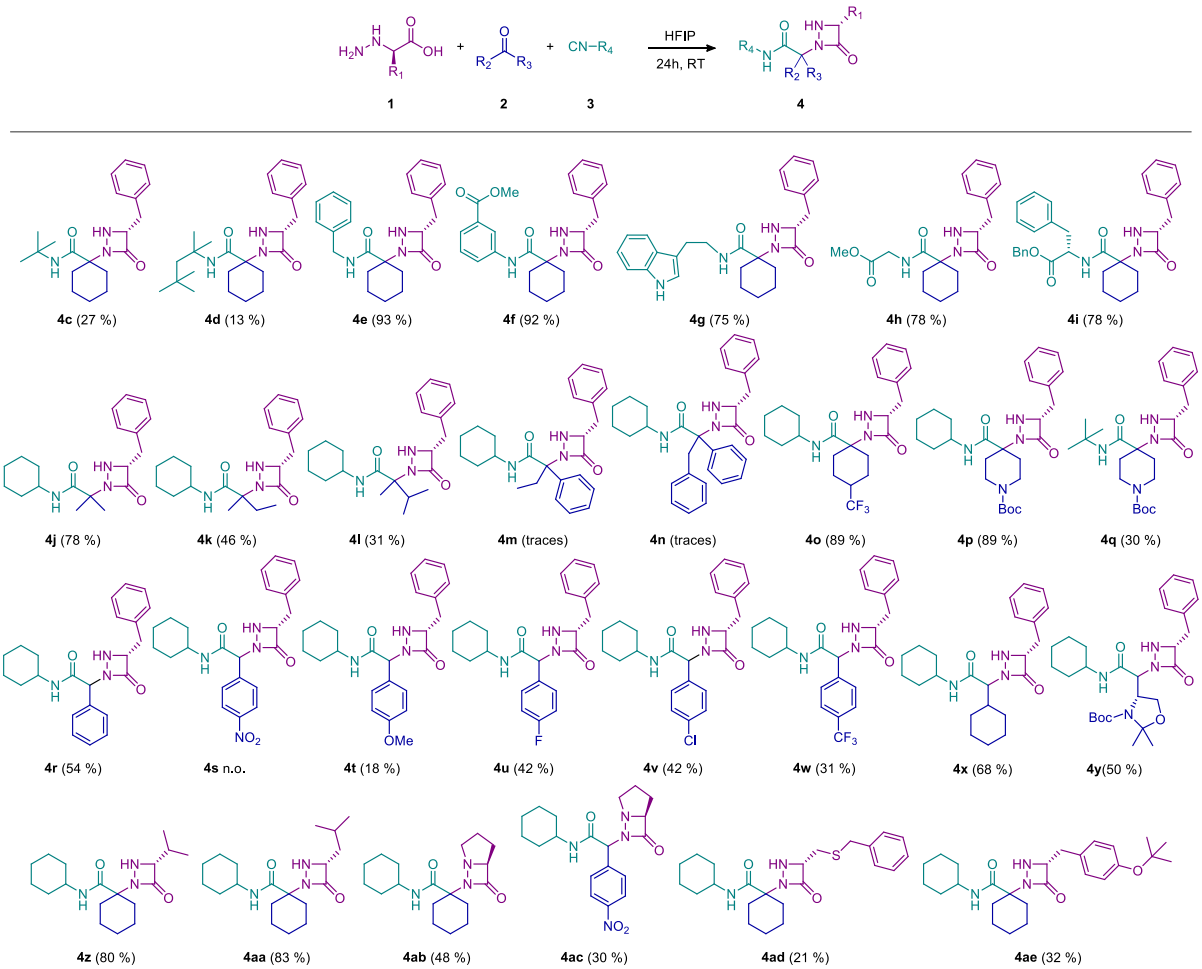
[a] Reactions were carried out on a 0.2 mmol scale. Yields refer to the isolated product.

With the optimised conditions in hand, we set out to test the scope and limitations of this multicomponent methodology. First, we investigated the influence of different isocyanides on the formation of 1,2-diazetidin-3-ones. Compared to **4a**, reactions performed with *tert*-butyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide gave disappointing results; products **4c** and **4d** were isolated in 27 % and 13 % yield, respectively (Figure 1). In contrast, benzyl isocyanide and methyl 3-isocyanobenzoate afforded products **4e** and **4f** in excellent yields (93 % and 92 %). Reaction performed with tryptamine-derived isocyanide gave product **4g** in very good yield (75 %), as did the reaction with glycine- and L-phenylalanine-derived isocyanides (78 % for products **4h** and **4i**). Based on the results obtained, we proceeded with cyclohexyl isocyanide to the next set of reactions where carbonyl component was diversified.

Initially, we performed reactions with di-alkyl ketones, propan-2-one, butan-2-one and 3-methylbutan-2-one and found that the efficiency of the 1,2-diazetidin-3-one formation decreases with increasing steric hindrance of the oxo-component (78 %, 46 % and 31 % for products **4j**-**4l**, respectively). Moreover, reactions conducted with propiophenone and 1,2-diphenylethan-1-one gave only traces of the corresponding products **4m** and **4n** (Figure 1). In contrast, cyclic ketones 1-(trifluoromethyl)piperidin-4-one and *tert*-butyl 4-oxopiperidine-1-carboxylate afforded products **4o** and **4p** in 89 % yield, comparable to the cyclohexanone used in the reaction optimization (87 % for product **4a**, Table 1) . At this point, we again tested the influence of the isocyanide component, and carried out the reaction with *tert*-butyl 4-oxopiperidine-1-carboxylate and *tert*-butyl isocyanide. The product **4q** was isolated in only 30 % yield, compared to 89 % of **4l**, confirming that the bulkiness of the isocyanide component is an important factor for the efficient formation of 1,2-diazetidin-3-ones. The next set of reactions was performed with aldehydes. While benzaldehyde afforded product **4r** in fair yield (54 %), para-substituted derivatives showed reduced reactivity. Thus, a nitro-derivative failed to give expected product **4s**, while a methoxy-derivative afforded only 18 % of product **4t** (Figure 1). para-F and para-Cl benzaldehyde showed increased reactivity (42 % for products **4u** and **4v**), while CF_3-substituted benzaldehyde afforded corresponding 1,2-diazetidin-3-one **4w** in 31 % yield. Finally, the reaction with aliphatic aldehydes was more efficient; cyclohexylcarboxaldehyde and Garner's aldehyde[14] (*tert*-butyl (*S*)-4-formyl-2,2-dimethyloxazolidine-3-carboxylate) gave products **4x** and **4y** in 68 % yield.

Finally, the methodology was evaluated on several α-hydrazino acids. α-hydrazino valine and α-hydrazino leucine afforded the corresponding 1,2-diazetidin-3-ones **4z** and **4aa** in high yields (80 % and 83 %, respectively). The reaction performed with α-hydrazino-L-proline,[15] furnished bicyclic derivative **4ab** in 48 % yield (Figure 1, ccdc number 2024622). Also, reaction with para-NO_2-benzaldehyde gave product **4ac**, albeit in lower yield (30 %). At last, two amino acids with functionalised side-chains were tested. The reaction performed with hydrazino derivative of *S*-benzyl-D-cysteine, afforded the product **4ad** in 21 % yield, while hydrazino derivative of *O-tert*-butyl-D-tyrosine was slightly more reactive and gave the product **4ae** in 32 % yield.

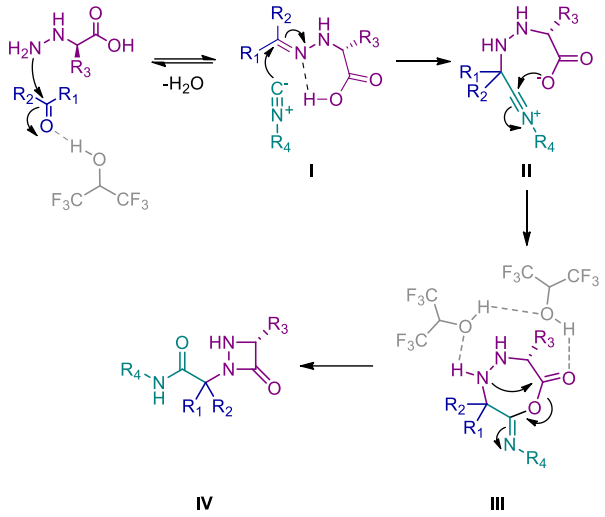
Table 1. Scope of isocyanides, carbonyl components and α-hydrazino acids in the 4-center 3-component Ugi reaction for the formation of 1,2-diazetidin-3-ones (**4**)



This preliminary screening allowed us to draw some conclusions about the scope and limitations of the methodology used for the formation of 1,2-diazetidin-3-ones. Sterically hindered isocyanides, such as *tert*-butyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide are markedly less reactive, but amino acid-derived isocyanides afforded 1,2-diazetidin-3-ones in high yields, opening the possibility of further elongation of peptide backbone or carboxyl group modification. The reactivity of aromatic aldehydes was modest in studied reactions compared with aliphatic aldehydes, while the efficiency of reactions performed with ketones is influenced by their steric hindrance. Interestingly, cyclic ketones exhibit very good reactivity when combined with sterically less demanding isocyanides.

These results are consistent with the general mechanism of the 4-centre 3-component Ugi reaction.[16] Reaction involves *in situ* formation of an imine (**I**), followed by α-addition of the isocyanide to generate a nitrilium **II**, which is trapped by the carboxylate to give the corresponding cyclic imidate intermediate **III** (Scheme 2). Finally, the Mumm rearrangement gives the 1,2-diazetidin-3-one motif **IV**. The presence of sterically demanding components in the close proximity can significantly affect the efficiency of intramolecular reactions leading to the highly strained 4-membered ring A thorough theoretical study by Chéron et al. proposed alternatives to some commonly accepted features of the Ugi reactiom.[17] Thus, the imine formed in the first reaction step is activated by a hydrogen-bonded complex with the acidic substrate rather than by proton transfer (Scheme 2).[17] The role of the solvent has also been studied, particularly in the Mumm rearrangement of the imidate intermediate **III**. In protic polar solvents such as methanol, proton transfer could be mediated by the acid component and the solvent itself. In both cases, the Mumm rearrangement of the imidate was found to proceed through very low barriers, but solvation with methanol dimer was more favourable.[17]

Our reaction optimisation identified HFIP as the best solvent for the 4-center 3-component Ugi reaction. This is due to the fundamental properties of HFIP, namely the high negative inductive effect, which is responsible for the increased acidity and low nucleophilicity, and the hydrogen bonding ability of HFIP, which has been shown to strongly activate carbonyl and epoxide substrates.[18] In addition, HFIP has been used as an acid component in the Passerini reaction providing two-step access to β-amino alcohols.[19] It is therefore reasonable to presume that solvation of imidate intermediate **III** with HFIP lowers the energy barrier for the Mumm rearrangement in the last reaction step (Scheme 2). However, activation of the carbonyl component as well as imine **I** through hydrogen bonding may also contribute to the observed efficiency of the 4-center 3-component Ugi reaction in HFIP.



Scheme 2. Formation of 1,2-diazetidin-3-one by the 4-center 3-component Ugi reaction

All Ugi products derived from aldehydes and unsymmetrical ketones are isolated as an inseparable mixture of diastereoisomers, and inspection of the NMR spectra revealed that there is virtually no diastereoselectivity or is very modest. The best result, 70:30 *d.r.* was obtained for the butyraldehyde-derived Ugi product **4b**. However, the ^{1}H NMR spectra of Ugi products derived from symmetrical ketones show two sets of resonances and we suspected on rotamers arising from the slow *cis/trans* isomerization of the amide bond. Therefore, we selected compound **4o** for detailed NMR analysis. 1D and 2D spectra recorded in DMSO-d_6 at 25 °C revealed two sets of resonances with 80:20 ratio. The largest difference in chemical shifts between two rotamers is observed for the protons marked *a*, *b* and *c* in Figure 1. Variable temperature experiments showed coalescence of these signals, but also most others at 80 °C, supporting the assumption that two sets of resonances belong to two conformational isomers in chemical exchange (Figure 1). This was further confirmed by the exchange peaks between the two rotamers observed in NOESY spectrum (Supporting Information).

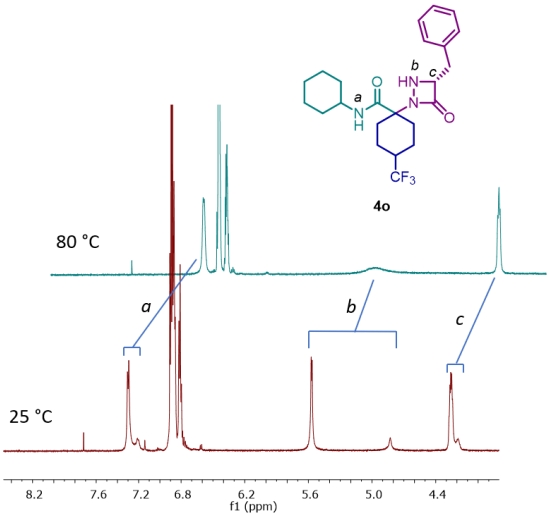
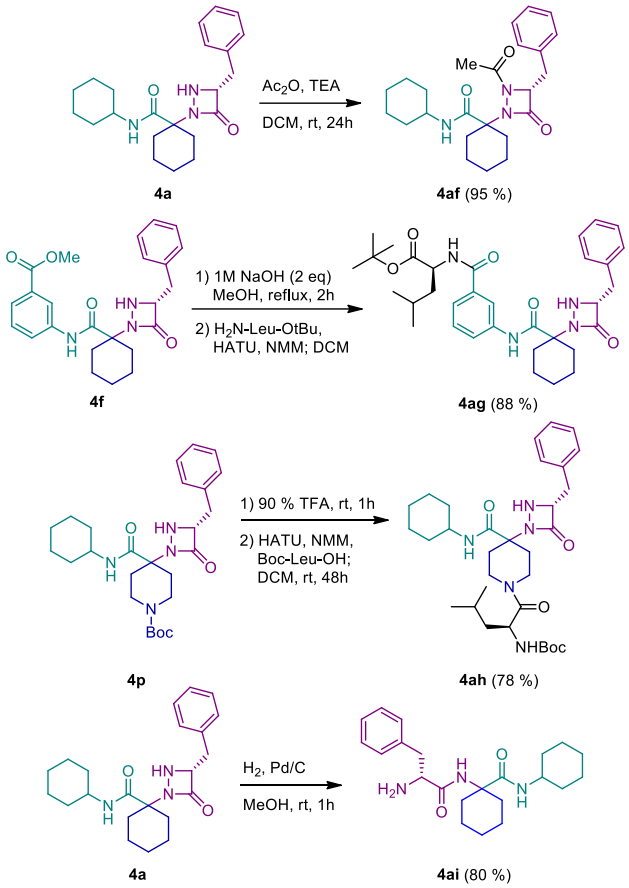


Figure 1. Part of the ^{1}H NMR spectra of **4o** at 25 and 80 °C in DMSO-d_6 showing coalescence of signals with temperature increase

With a general synthetic route to N$^{\beta}$-substituted 1,2-diazetidin-3-ones in hand, we investigated further functionalisation reactions. It is well documented in the literature that 1,2-diazetidin-3-ones are unstable in the presence of weak nucleophiles, bases and acids.[6] Moodey et al. reported problems associated with attempts to cleave acid-labile, and base-labile groups under standard reaction conditions.[10] The advantage of the methodology presented here is that it delivers 1,2-diazetidin-3-ones with unprotected N$^{\alpha}$ position ready for functionalisation. Thus, the acetylation of compound **4a** using acetic anhydride, preceded in a straightforward manner, affording compound **4af** in 95 % yield (Scheme 3). The presence of functional groups at the isocyanide or carbonyl part of the molecule allowed the installation of additional moieties. Compound **4f** was subjected to ester hydrolysis and consecutive coupling with C-terminally protected L-leucine to afford compound **4ag** in 88 % yield over two steps (Scheme 3). Acid-mediated removal of the Boc group from product **4p** and coupling with N-terminally protected L-leucine gave product **4ah** in very good yield (78 %, Scheme 3). No appreciable decomposition of the 1,2-diazetidin-3-one core structure was observed in either the acid- or base-mediated deprotection. Finally, catalytic hydrogenation of diazetidinone **4a** rapidly led to the cleavage of N-N bond resulting in dipeptide amide **4ai** bearing non-natural amino acid.



Scheme 3. Functionalisation of 1,2-diazetidin-3-ones.

Conclusions

In summary, we have prepared a selection of chiral N^{β}-substituted 1,2-diazetidin-3-ones in an efficient one-step procedure by using a bifunctional enantiomerically pure unprotected α-hydrazino acid in the 4-centre 3-component Ugi reaction with various isocyanides and carbonyl components. Depending on the available functional groups, post-condensation functionalisation of three sites of the 1,2-diazetidin-3-one-containing Ugi products was performed.

Experimental section

General Information

All experiments were monitored by analytical thin layer chromatography (TLC) performed on Merck Kieselgel 60 F254 0.25 mm precoated aluminium plates. After elution, plate was visualized under UV illumination at 254 nm for UV active materials. Further visualization was achieved by staining with ammonium molybdate and charring on a hot plate. Ammonium molybdate solution was prepared by dissolving ammonium molybdate (5 g) and ceric sulfate (0.2 g) in 5% aqueous sulfuric acid (100 mL). Flash column chromatography was performed on silica gel (Merck, 40−63 μm particle size) by standard techniques eluting with solvents as indicated.

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 600 MHz equipped with 5 mm diameter BBO probe with z-gradient accessory. Chemical shifts are quoted in ppm, and are referenced to the residual non-deuterated solvent peak. ^{1}H NMR spectra are reported as follows: ^{1}H NMR (spectrometer frequency, solvent): δ chemical shift/ppm (assignment, multiplicity, *J*-coupling constant(s), number of protons). ^{13}C NMR spectra are reported as follows: 13C NMR (spectrometer frequency, solvent): δ chemical shift/ppm (assignment). Peak multiplicities of NMR signals were designated as: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet), etc. and are reported based on appearance rather than interpretation. Compound multiplets are reported in the order of decreasing coupling constant magnitude. Spectra were acquired at 298 K. NOESY spectrum was obtained with the mixing time of 500 ms. Variable temperature spectra were obtained in temperature range from 20 - 80°C.

Mass spectrometry measurements were performed on HPLC system coupled with triple quadrupole mass spectrometer, operating in a positive electrospray ionization (ESI) mode. High resolution mass spectrometry (HRMS) was performed on a 4800 Plus MALDI TOF/TOF Analyzer.

All reactions were carried out in flame-dried reaction tubes under argon atmosphere. Unless otherwise indicated, solvents were used as supplied (analytical or HPLC grade) without further purification. “Petrol” or “petroleum ether” refers to the fraction of petroleum ether boiling in the range 40−60 °C. Where mixtures of solvents are specified, the stated ratios are volume: volume. Unless otherwise indicated, all aqueous solutions used were saturated. Reagents were used directly as supplied by major chemical suppliers.

Where given, systematic compound names are those generated by ChemBioDraw Ultra 12.0 following IUPAC conventions.

General procedure for the Ugi reaction

To a suspension of oxo component (0.15 mmol) and the α-hydrazino acid (0.17 mmol; 1.1 equiv.) in HFIP (1 mL) was added the isocyanide component (0.17 mmol; 1.1 equiv.) and the reaction mixture was stirred at room temperature until the consumption of the oxo component (24-48 h). The reaction mixture was concentrated under the reduced pressure and the residue purified by the flash column chromatography affording final product. Products obtained from aldehydes are isolated as a mixture of diastereoisomers. Moreover, most NMR spectra show two sets of resonance for certain atoms arising from the *cis/trans* isomerization around the amide bond (as confirmed by VT NMR experiments, SI-35).

(*R*)-1-(3-benzyl-4-oxo-1,2-diazetidin-1-yl)-*N*-cyclohexylcyclohexane carboxamide (4a)

Yield: 89 % (49 mg); colorless oil; R_f = 0.63 (petrol ether/ethyl acetate 1:1, v/v). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.58 (d, J = 7.4 Hz, 0.74H), 7.50 (br s, 0.26H), 7.38 – 7.19 (m, 5H), 5.81 (d, J = 5.2 Hz, 0.74 H), 4.99 (bs, 0.22H), 4.62 – 4.50 (m, 1H), 3.56 (br s, 1H), 3.20 – 3.11 (m, 0.5H), 3.02 – 2.91 (m, 1.5H), 2.25 – 2.08 (m, 1H), 1.87 – 1.60 (m, 7H), 1.59 – 1.35 (m, 6H), 1.32 – 1.08 (m, 6H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 172.2, 169.1, 138.0, 129.8, 129.4, 128.7, 126.8, 68.6, 65.9, 48.2, 35.5, 32.8, 32.6, 31.1, 30.6, 25.6, 25.0, 24.9, 24.8, 21.9, 21.7. MS-ESI: *m/z* 368.2 $[M-H]^-$; *m/z* 392,2 $[M+Na]^+$; *m/z* 761,4 $[2M+Na]^+$. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{32}N_3O_2$ 370.2495, found 370.2479.

Scale-up experiment: To a suspension of cyclohexanone (261 µL; 2.52 mmol) and α-hydrazino phenylalanine (500 mg; 2.77 mmol; 1.1 equiv.) in HFIP (17 mL) was added cyclohexyl isocyanide (344 µL; 2.77 mmol; 1.1 equiv.) and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was concentrated under the reduced pressure and the residue purified by the flash column chromatography affording final product as colorless oil (435 mg; 47 %).

2-((*R*)-3-benzyl-4-oxo-1,2-diazetidin-1-yl)-*N*-cyclohexylpentanamide (4b)

Yield: 48 % (25 mg); colorless oil; R_f = 0.47 (petrol ether/ethyl acetate 1:1, v/v); 70:30. d.r. Chemical shits are given for both diastereisomers. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.88 – 7.85 (m, 1H), 7.21 – 7.23 (m, 5H), 5.83 (d, J = 5.4 Hz, 0.22H), 5.44 (d, J = 5.6 Hz, 0.48H), 5.20 (br d, 0.05H), 4.83 (br d, 0.15 H), 4.69 – 4.57 (m, 1H), 4.20 – 4.05 (m, 0.7H), 4.05 – 3.92

(m, 0.3H), 3.63 – 3.41 (m, 1H), 3.15 – 2.88 (m, 2H), 1.81 – 1.59 (m, 7H), 1.34 – 1.06 (m, 7H), 0.90 – 0.83 (m, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO) δ169.1, 137.9, 137.1, 130.0, 129.6, 129.4, 128.8, 128.7, 128.6, 126.7, 69.8, 58.2, 47.9, 35.9, 35.7, 32.7, 32.7, 31.8, 25.6, 24.9, 19.2, 13.9. HRMS (ESI-TOF) m/z $[M + H]^+$: calcd for $C_{20}H_{30}N_3O_2$ 344.2338, found 344.2326.

(*R*)-1-(3-benzyl-4-oxo-1,2-diazetidin-1-yl)-*N*-*tert*-butylcyclohexane carboxamide (4c)

Yield: 27 % (14 mg); colorless oil; R_f = 0.51 (petrol ether/ethyl acetate 1:1, v/v). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.43 (s, 1H), 7.34 – 7.23 (m, 5H), 5.98 (d, *J* = 5.2 Hz, 0.76H), 4.99 (br s, 0.24H), 4.65 – 4.62 (m, 1H), 3.19 – 2.90 (m, 2H), 2.21 (d, *J* = 13.5 Hz, 0.75H), 2.13 (d, *J* = 13.1 Hz, 0.25H), 1.84 – 1.41 (m, 9H), 1.29 – 1.10 (m, 9H). $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6) δ172.7, 168.8, 137.9, 129.3, 128.8, 126.9, 68.6, 65.9, 50.7, 35.3, 31.5, 30.2, 28.9, 24.8, 21.9, 21.7. HRMS (ESI-TOF) m/z $[M + H]^+$: calcd for $C_{20}H_{30}N_3O_2$ 344.2338, found 344.2354.

(*R*)-1-(3-benzyl-4-oxo-1,2-diazetidin-1-yl)-*N*-(2,4,4-trimethylpentan-2-yl)cyclohexanecarboxamide (4d)

Yield: 13 % (8 mg); colorless oil; R_f = 0.58 (petrol ether/ethyl acetate 1:1, v/v). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.42 – 7.17 (m, 6H), 6.00 (d, *J* = 5.4 Hz, 0.72H), 5.00 (br s, 0.28H), 4.68 – 4.51 (m, 1H), 3.00 – 2.97 (m, 2H), 2.28 – 2.06 (m, 2H), 1.82 – 1.42 (m, 10H), 1.40 – 1.30 (m, 6H), 0.93 (s, 9H). $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6) δ 172.3, 168.5, 137.9, 129.2, 128.8, 126.9, 68.6, 66.1, 54.7, 50.9, 37.7, 35.4, 31.7, 31.2, 30.1, 29.8, 29.3, 24.8, 24.5, 22.6, 21.8, 21.7. HRMS (ESI-TOF) m/z $[M + H]^+$: calcd for $C_{24}H_{38}N_3O_2$ 400.2964, found 400.2944.

(*R*)-*N*-benzyl-1-(3-benzyl-4-oxo-1,2-diazetidin-1-yl) cyclohexane carboxamide (4e)

Yield: 93 % (53 mg); colorless oil; R_f = 0.42 (petrol ether/ethyl acetate 1:1, v/v). ^{1}H NMR (600 MHz, DMSO-d_6) δ8.27 (br s, 1H), 7.34 – 7.18 (m, 10H), 5.71 (br s, 0.78H), 4.86 (br s, 0.22H), 4.57 (s, 1H), 4.32 (s, 2H), 3.11 – 2.80 (m, 2H), 2.21 (br s, 1H), 1.94 (br s, 1H), 1.78 (br s, 1H), 1.69 (t, *J* = 11.6 Hz, 1H), 1.60 – 1.29 (m, 5H), 1.26 – 1.14 (m, 1H) $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6) δ 172.9, 169.3, 139.8, 138.1, 129.6, 128.8, 128.6, 127.5, 127.3, 126.8, 68.7, 66.4, 42.8, 35.5, 30.8, 24.8, 21.8. HRMS (ESI-TOF) m/z $[M + Na]^+$: calcd for $C_{23}H_{27}N_3O_2Na$ 400.2001, found 400.1998.

(*R*)-methyl 4-(1-(3-benzyl-4-oxo-1,2-diazetidin-1-yl) cyclohexane carboxamido) benzoate (4f)

Yield: 92 % (58 mg); colorless oil; R_f = 0.47 (petrol ether/ethyl acetate 1:1, v/v). ^{1}H NMR (600 MHz, DMSO-d_6) δ8.27 (br d, 1H), 7.71 – 7.43 (m, 3H), 7.40 –7.17 (m, 6H), 5.84 (d, *J* = 5.5 Hz, 0.76H), 4.97 (br s, 0.24H), 4.73 – 4.57 (m, 1H), 3.86 (s, 3H), 3.26 – 2.94 (m, 2H), 2.32 –

1.68 (m, 4H), 1.60 – 1.27 (m, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 171.5, 169.9, 166.5, 139.4, 138.1, 130.5, 129.8, 129.6, 129.5, 128.7, 127.0, 126.8, 125.3, 124.8, 121.4, 68.71, 67.14, 61.07, 52.65, 35.71, 30.64, 30.49, 24.71, 21.94, 21.83. . HRMS (ESI-TOF) m/z [M + H]$^+$: calcd for $C_{24}H_{28}N_3O_4$ 422.2080, found 422.2085.

(*R*)-N-(2-(1H-indol-3-yl)ethyl)-1-(3-benzyl-4-oxo-1,2-diazetidin-1-yl) cyclohexanecarboxamide (4g)

Yield: 75% (48 mg); colourless oil; R_f = 0.41 (petrol ether/ethyl acetate 1:2, v/v). ^1H NMR (600 MHz, DMSO-d_6) δ 10.81 (s, 1H), 7.83 (br t, 0.7H), 7.71 (br t, 0.3H), 7.56 (d, J = 7.7 Hz, 1H), 7.35 – 6.95 (m, 9H), 5.62 (d, J = 5.3 Hz, 0.6H), 4.79 (bs, 0.4H), 4.62 – 4.35 (m, 1H), 3.48 – 3.35 (m, 2H), 3.03 – 2.73 (m, 4H), 2.19 – 2.06 (m, 1H), 1.97 – 1.81 (m, 1H), 1.77 – 1.58 (m, 2H), 1.55 – 1.40 (m, 4H), 1.25 – 1.10 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6) δ 172.8, 169.0, 138.0, 136.7, 136.4, 129.8, 129.6, 128.6, 127.6, 127.2, 126.7, 123.2, 121.4, 118.7, 112.0, 111.8, 68.6, 66.2, 55.4, 35.5, 35.0, 30.8, 25.6, 24.8, 21.9, 21.7. HRMS (ESI-TOF) m/z [M + H]$^+$: calcd for $C_{26}H_{31}N_4O_2$ 431.2447, found 431.2462.

(*R*)-methyl 2-(1-(3-benzyl-4-oxo-1,2-diazetidin-1-yl) cyclohexane carboxamido) acetate (4h)

Yield: 78% (42 mg); colorless oil; R_f = 0.48 (petrol ether/ethyl acetate 1:1, v/v). ^1H NMR (600 MHz, DMSO-d_6) δ 8.20 (br t, 0.73H), 8.12 (br s, 0.27H), 7.40 – 7.16 (m, 5H), 5.68 (d, J = 5.2 Hz, 1H), 4.62 – 4.56 (m, 1H), 3.89 (s, 2H), 3.63 (s, 3H), 3.07 – 2.95 (m, 2H), 2.14 (d, J = 13.7 Hz, 1H), 1.93 (d, J = 13.3 Hz, 1H), 1.79 (t, J = 11.5 Hz, 1H), 1.60 – 1.33 (m, 6H), 1.30 – 1.20 (m, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 173.4, 170.7, 169.3, 168.9, 138.1, 129.6, 128.8, 128.6, 127.1, 126.7, 68.8, 66.0, 52.2, 41.4, 35.4, 30.9, 30.7, 24.8, 21.8, 21.6. HRMS (ESI-TOF) m/z [M + H]$^+$: calcd for $C_{19}H_{26}N_3O_4$ 360.1923, found 360.1909.

(*S*)-benzyl 2-(1-((*R*)-3-benzyl-4-oxo-1,2-diazetidin-1-yl) cyclohexane carboxamido)-3-phenylpropanoate (4i)

Yield: 78% (61 mg); colourless oil; R_f = 0.35 (petrol ether/ethyl acetate 1:1, v/v). ^1H NMR (600 MHz, DMSO-d_6) δ 8.37 (d, J = 8.0 Hz, 1H), 7.44 – 7.08 (m, 15H), 5.72 (d, J = 5.5 Hz, 0.6H), 5.44 (br d, 0.3H), 5.13 (d, J = 5.3 Hz, 2H), 4.75 – 4.61 (m, 1H), 4.60 – 4.46 (m, 1H), 3.21 – 2.89 (m, 4H), 2.20 – 1.28 (m, 10H). $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 173.1, 171.7, 168.8, 138.2, 137.1, 136.1, 129.6, 129.5, 128.9, 128.7, 128.6, 128.5, 127.1, 126.7, 68.8, 65.7, 53.8, 37.1, 36.7, 35.4, 35.0, 31.2, 31.0, 30.7, 30.5, 30.1, 26.9, 24.7, 21.7, 21.5, 21.2. HRMS (ESI-TOF) m/z [M + H]$^+$: calcd for $C_{32}H_{36}N_3O_4$ 526.2706, found 526.2714.

(*R*)-2-(3-benzyl-4-oxo-1,2-diazetidin-1-yl)-*N*-cyclohexyl-2-methyl propanamide (4j)

Yield: 78% (38 mg); colorless oil; R_f = 0.5 (petrol ether/ethyl acetate 1:1, v/v). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.49 (d, J = 7.5 Hz, 0.8H), 7.41 (d, J = 6.3 Hz, 0.2H), 7.35 – 7.14 (m, 5H), 5.62 (d, J = 5.6 Hz, 0.8H), 5.12 (br s, 0.2H), 4.55 (dt, J = 10.4 Hz, 0.8H), 4.46 (br s, 0.2H), 3.59 – 3.47 (m, 1H), 3.15 – 2.90 (m, 2H), 1.79 – 1.52 (m, 7H), 1.34 (d, J = 19.1 Hz, 6H), 1.30 – 1.08 (m, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 173.8, 172.2, 140.0, 131.8, 130.8, 129.0, 70.9, 65.2, 50.6, 37.6, 34.9, 34.8, 27.9, 27.3, 27.2, 26.2, 25.6. HRMS (ESI-TOF) m/z [M + H]$^+$: calcd for $C_{19}H_{28}N_3O_2$ 330.2182, found 330.2172.

2-((*R*)-3-benzyl-4-oxo-1,2-diazetidin-1-yl)-*N*-cyclohexyl-2-methylbutanamide (4k)

Yield: 46% (24 mg); colorless oil; R_f = 0.45 (petrol ether/ethyl acetate 1:1, v/v).^{1}H NMR (300 MHz, DMSO-d_6) δ 7.64 – 7.39 (m, 1H), 7.34 – 7.18 (m, 5H), 5.69 – 5.58 (m, 1H), 4.67 – 4.53 (m, 1H), 3.54 (bs, 1H), 3.20 – 2.87 (m, 2H), 1.95 – 1.84 (m, 2H), 1.75 – 1.62 (m, 4H), 1.55 (d, J = 11.9 Hz, 1H), 1.39 – 1.15 (m, 8H), 0.86 – 0.73 (m, 3H). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 171.2, 137.9, 129.6, 128.7, 126.8, 66.5, 56.5, 48.3, 35.7, 32.8, 29.9, 28.9, 25.6, 25.1, 20.0, 19.0, 8.6. HRMS (ESI-TOF) m/z [M + H]$^+$: calcd for $C_{20}H_{30}N_3O_2$ 344.2338, found 334.2325.

2-((*R*)-3-benzyl-4-oxo-1,2-diazetidin-1-yl)-*N*-cyclohexyl-2,3-dimethylbutanamide (4l)

Yield: 31% (17 mg); colorless oil; *Rf* = 0.67 (petrol ether/ethyl acetate 1:1, v/v).^{1}H NMR (300 MHz, DMSO-d_6) δ 7.86 (s, 1H), 7.40 – 7.11 (m, 5H), 6.10 – 5.19 (m, 1H), 4.66 – 4.50 (m, 1H), 3.60 (bs, 1H), 3.34 (bs, 2H), 2.98 – 2.87 (m, 1H), 1.85 – 1.46 (m, 5H), 1.41 – 1.13 (m, 8H), 1.03 – 0.88 (m, 3H), 0.79 (d, J = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 171.1, 151.2, 137.8, 129.5, 128.7, 126.9, 87.2, 56.5, 35.6, 32.9, 32.6, 25.6, 25.1, 24.6, 19.0, 17.8, 16.9, 15.8. HRMS (ESI-TOF) m/z [M + H]$^+$: calcd for $C_{21}H_{33}N_3O_2$ 358.2494, found 358.2487.

(*R*)-1-(3-benzyl-4-oxo-1,2-diazetidin-1-yl)-*N*-cyclohexyl-4-(trifluoromethyl)cyclohexanecarboxamide (4o)

Yield: 64% (42 mg); colorless oil; R_f = 0.44 (petrol ether/ethyl acetate 1:1, v/v). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.71 (d, J = 7.7 Hz, 0.8H), 7.62 (d, J = 6.8 Hz, 0.2H), 7.37 – 7.17 (m, 5H), 5.65 (d, J = 5.5 Hz, 0.8H), 5.13 (br s, 0.2H), 4.59 – 4.50 (m, 0.8H), 4.45 (br s, 0.2H), 3.57 (br s, 1H), 3.01 – 2.72 (m, 2H), 2.39 (d, J = 11.0 Hz, 1H), 2.17 (d, J = 13.0 Hz, 1H), 1.78 – 1.48 (m, 11H), 1.45 – 1.01 (m, 5H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 171.7, 169.7, 138.0, 129.5, 129.2, 128.8, 126.9, 68.8, 65.0, 55.4, 48.3, 35.5, 32.8, 32.6, 29.3, 28.8, 25.6, 25.0, 24.9, 20.6, 20.5. HRMS (ESI-TOF) m/z [M + H]$^+$: calcd for $C_{23}H_{31}F_3N_3O_2$ 438.2368, found 438.2378.

(*R*)-*tert*-butyl 4-(3-benzyl-4-oxo-1,2-diazetidin-1-yl)-4-(cyclohexyl carbamoyl) piperidine-1-carboxylate (4p)

Yield: 89% (63 mg); colorless oil; R_f = 0.35 (petrol ether/ethyl acetate 1:1, v/v). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.65 (d, J = 7.6 Hz, 1H), 7.38 - 7.16 (m, 5H), 5.81 (d, J = 5.4 Hz, 0.75H), 5.07 (br s, 0.25H), 4.70 – 4.60 (m, 1H), 3.83 – 3.49 (m, 3H), 3.22 – 2.90 (m, 3H), 2.22 – 1.50 (m, 10H), 1.41 (s, 9H), 1.32 – 1.15 (m, 4H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 170.8, 169.8, 154.3, 137.9, 129.5, 128.7, 126.9, 79.2, 68.8, 64.4, 48.5, 48.2, 35.4, 35.2, 32.7, 32.6, 32.4, 30.2, 28.5, 25.6, 25.1, 24.8. HRMS (ESI-TOF) m/z [M + H]$^+$: calcd for $C_{26}H_{39}N_4O_4$ 471.2971, found 471.2970.

(*R*)-*tert*-butyl 4-(3-benzyl-4-oxo-1,2-diazetidin-1-yl)-4-(*tert*-butyl carbamoyl) piperidine-1-carboxylate (4q)

Yield: 30% (20 mg); colorless oil; R_f = 0.32 (petrol ether/ethyl acetate 1:1, v/v). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.45 (s, 1H), 7.37 – 7.18 (m, 5H), 5.99 (s, 0.78H), 5.15 (s, 0.22H), 4.67 (d, J = 4.6 Hz, 1H), 3.80 – 3.60 (m, 2H), 3.20 – 2.80 (m, 4H), 2.20 – 1.86 (m, 2H), 1.82 – 1.59 (m, 2H), 1.39 (s, 9H), 1.27 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 171.4, 169.5, 154.4, 137.8, 129.8, 129.4, 128.8, 126.9, 79.2, 68.8, 64.4, 51.0, 35.2, 30.6, 29.8, 28.9, 28.5. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{24}H_{37}N_4O_4$ 445.2815, found 445.2809.

2-((*R*)-3-benzyl-4-oxo-1,2-diazetidin-1-yl)-*N*-cyclohexyl-2-phenylacetamide (4r)

Yield: 37% (21 mg); colorless oil; R_f = 0.65 (petrol ether/ethyl acetate 1:1, v/v); 74:26 d.r. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.13 – 7.95 (m, 2H), 7.43 – 7.11 (m, 20H), 5.85 (d, J = 5.5 Hz, 0.13H), 5.66 (d, J = 5.5 Hz, 0.87H), 5.42 (s, 0.87H), 5.24 (s, 0.13H), 4.66 (m, 2H), 3.62 – 3.43 (m, 2H), 3.18 – 2.97 (m, 2H), 2.85 – 2.64 (m, 2H), 1.82 – 1.48 (m, 11H), 1.33 – 1.05 (m, 9H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 169.9, 169.7, 167.1, 167.0, 137.8, 137.5, 136.1, 135.3, 130.1, 129.5, 129.4, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 126.8, 126.7, 70.2, 69.9, 63.8, 62.0, 55.3, 48.2, 35.6, 35.3, 32.6, 32.4, 25.6, 24.9, 24.8. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{23}H_{27}N_3O_2Na$ 400.2001, found 400.2020.

2-((*R*)-3-benzyl-4-oxo-1,2-diazetidin-1-yl)-*N*-cyclohexyl-2-(4-methoxy phenyl)acetamide (4t)

Yield: 43% (26 mg); colourless oil; R_f = 0.23 (petrol ether/ethyl acetate 1:1, v/v); 63:37 d.r. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.01 (d, J = 7.6 Hz, 0.63H), 7.98 (d, J = 7.7 Hz, 0.37H), 7.35 – 7.28 (m, 18H), 5.77 (d, J = 5.5 Hz, 0.63H), 5.62 (d, J = 5.6 Hz, 0.37H), 5.33 (s, 0.63H), 5.16 (s, 0.37H), 4.63 (d, J = 5.1 Hz, 1H), 3.74 (s, 3H), 3.60 – 3.51 (m, 2H), 3.04 – 2.97 (m, 2H), 2.83 – 2.65 (m, 2H), 1.80 – 1.48 (m, 12H), 1.32 – 1.02 (m, 8H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 169.2, 169.2, 168.6, 168.4, 159.5, 159.3, 137.2, 130.1, 130.0, 129.9, 129.5, 129.4, 129.3, 128.8, 128.7, 128.5, 126.8, 114.2, 113.9, 78.1, 75.8, 70.5, 70.2, 55.6, 55.5, 48.2,

47.9, 35.6, 35.3, 32.7, 32.6, 32.4, 31.8, 25.6, 24.9, 24.8. HRMS (ESI-TOF) m/z $[M + H]^+$calcd for $C_{24}H_{30}N_3O_3$ 408.2287, found 408.2287.

2-((*R*)-3-benzyl-4-oxo-1,2-diazetidin-1-yl)-*N*-cyclohexyl-2-(4-fluorophenyl) acetamide (4u)

Yield: 42% (26 mg); colorless oil; R_f = 0.41 (petrol ether/ethyl acetate 1:1, v/v); 61:39 d.r. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.09 (d, *J* = 7.7 Hz, 0.61H), 8.04 (d, *J* = 7.7 Hz, 0.39H), 7.50 – 7.07 (m, 18H), 5.81 (d, *J* = 5.7 Hz, 0.61H), 5.67 (d, *J* = 5.7 Hz, 0.39H), 5.41 (s, 0.61H), 5.24 (s, 0.39H), 4.68 – 4.61 (m, 1H), 3.61 – 3.52 (m, 1H), 3.06 – 2.97 (m, 2H), 2.80 (dd, *J* = 14.4 Hz, 1H), 2.67 (dd, *J* = 14.3 Hz, 1H), 1.81 – 1.47 (m, 15H), 1.31 – 1.06 (m, 5H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 170.1, 169.8, 167.0, 166.8, 161.3, 137.9, 137.8, 132.3, 131.5, 130.8, 130.8, 130.1, 129.5, 129.4, 128.9, 128.7, 128.6, 128.5, 126.8, 126.7, 115.7, 115.5, 115.4, 115.3, 70.2, 69.8, 61.3, 61.2, 48.3, 48.2, 35.6, 35.5, 35.3, 35.2, 32.6, 32.5, 25.5, 24.9, 24.8. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{27}FN_3O_2$ 396.2087, found 396.2090.

2-((*R*)-3-benzyl-4-oxo-1,2-diazetidin-1-yl)-2-(4-chlorophenyl)-*N*-cyclohexylacetamide (4v)

Yield: 42% (26 mg); colorless oil; R_f = 0.39 (petrol ether/ethyl acetate 1:1, v/v); 60:40 d.r. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.10 (d, *J* = 7.7 Hz, 0.6H), 8.02 (d, *J* = 7.8 Hz, 0.4H), 7.48 – 7.10 (m, 18H), 5.81 (d, *J* = 5.7 Hz, 0.6H), 5.68 (d, *J* = 5.7 Hz, 0.4H), 5.41 (s, 0.6H), 5.24 (s, 0.4H), 4.69 – 4.62 (m, 2H), 3.60 – 3.51 (m, 2H), 3.04 – 2.95 (m, 2H), 2.81 (dd, *J* = 14.4 Hz, 0.6H), 2.69 (dd, *J* = 14.3 Hz, 0.4H), 1.80 – 1.48 (m, 14H), 1.32 – 1.10 (m, 6H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 170.2, 169.8, 166.8, 166.5, 137.9, 137.7, 135.0, 134.3, 133.3, 133.0, 130.6, 130.5, 129.5, 129.4, 128.8, 128.7, 128.6, 128.5, 126.8, 126.7, 70.3, 69.8, 63.4, 61.5, 48.3, 48.2, 35.6, 35.3, 32.6, 32.5, 25.6, 24.8, 24.8. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{27}ClN_3O_2$ 412.1792, found 412.1794.

2-((*R*)-3-benzyl-4-oxo-1,2-diazetidin-1-yl)-*N*-cyclohexyl-2-(4-(trifluoromethyl)phenyl)acetamide (4w)

Yield: 42% (26 mg); colorless oil; R_f = 0.42 (petrol ether/ethyl acetate 1:1, v/v); 60:40 d.r. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.14 (m, 1H), 7.65 – 7.12 (m, 18H), 5.86 (d, *J* = 5.7 Hz, 0.6H), 5.73 (d, *J* = 5.7 Hz, 0.4H), 5.51 (s, 0.6H), 5.35 (s, 0.4H), 4.68 (m, 1H), 3.57 (dd, *J* = 9.5 Hz, 1H), 2.86 – 2.66 (m, 2H), 1.83 – 1.03 (m, 20H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 170.3, 169.8, 166.4, 166.1, 140.6, 140.0, 137.9, 137.6, 130.1, 129.9, 129.8, 129.7, 129.6, 129.5, 129.4, 128.9, 128.8, 128.7, 128.6, 128.5, 126.8, 126.7, 126.6, 126.5, 125.7, 125.6, 70.4, 69.9,

63.8, 61.6, 48.4, 48.3, 35.6, 35.2, 32.6, 32.4, 25.6, 24.8. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{27}F_3N_3O_2$ 446.2055, found 446.2036.

2-((*R*)-3-benzyl-4-oxo-1,2-diazetidin-1-yl)-*N*,2-dicyclohexylacetamide (4x)

Yield: 68% (19 mg); colorless oil; R_f = 0.41 (petrol ether/ethyl acetate 1:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 5H), 4.71 (s, 1H), 3.88 (s, 1H), 3.77 (s, 1H), 3.19 – 3.02 (m, 2H), 1.9 – 1.3 (m, 21H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 168.2, 167.2, 137.5, 129.6, 129.0, 128.8, 63.8, 48.2, 33.0, 32.9, 31.9, 29.7, 29.6, 29.4, 26.0, 25.8, 25.7, 25.5, 24.6, 22.7, 14.1. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{34}N_3O_2$ 384.2651, found 384.2650.

(4S)-*tert*-butyl 4-(1-((*R*)-3-benzyl-4-oxo-1,2-diazetidin-1-yl)-2-(cyclohexylamino)-2-oxoethyl)-2,2-dimethyloxazolidine-3-carboxylate (4y)

Yield: 50% (25 mg); colorless oil; R_f = 0.61 (petrol ether/ethyl acetate 1:1, v/v); 40:60 d.r. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.25 (d, J = 7.4 Hz, 0.4H), 8.13 (d, J = 7.4 Hz, 0.6H), 7.40 – 7.13 (m, 5H), 5.69 – 5.54 (m, 1H), 4.98 (d, J = 3.2 Hz, 0.3H), 4.93 – 4.76 (m, 0.7H), 4.65 (d, J = 3.5 Hz, 0.7H), 4.60 – 4.50 (m, 0.7H), 4.35 (bs, 0.3H), 4.26 (bs, 0.3H), 4.06 – 3.84 (m, 2H), 3.50 (bs, 1H), 3.20 – 3.10 (m, 0.6H), 3.00 – 2.90 (m, 1.4H), 1.79 – 1.60 (m, 6H), 1.50 (d, J = 3.2 Hz, 6H), 1.43 (d, J = 5.8 Hz, 9H), 1.27 – 1.15 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6) δ 169.2, 168.9, 166.4, 166.1, 165.4, 137.6, 137.2, 129.4, 129.1, 128.9, 128.8, 127.2, 126.9, 94.0, 93.4, 80.7, 79.9, 71.8, 70.3, 65.1, 64.5, 59.0, 58.7, 48.5, 48.1, 35.6, 35.4, 32.6, 28.6, 28.4, 25.6, 25.2, 24.8, 24.6. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{41}N_4O_5$ 501.3077, found 501.3058.

(*R*)-*N*-cyclohexyl-1-(3-isopropyl-4-oxo-1,2-diazetidin-1-yl)cyclohexane carboxamide (4z)

Yield: 83% (40 mg); colorless oil; R_f = 0.68 (petrol ether/ethyl acetate 1:1, v/v). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (bs, 1H), 4.44 (bs, 0.6H), 4.14 (d, J = 8.0 Hz, 1H), 3.99 (bs, 0.4H), 3.82 – 3.65 (m, 1H), 2.42 (bs, 1H), 2.17 – 1.80 (m, 6H), 1.79 – 1.51 (m, 7H), 1.46 – 1.15 (m, 7H), 1.09 (dd, J = 6.7 Hz, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.6, 66.1, 48.0, 32.9, 29.2, 25.6, 24.8, 24.7, 22.4, 19.2, 18.0. MS-ESI: *m/z* 320,1 $[M-H]^-$; *m/z* 344,1 $[M+Na]^+$; *m/z* 665,4 $[2M+Na]^+$. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{32}N_3O_2$ 322.2495, found 322.2497.

(*R*)-*N*-cyclohexyl-1-(3-isobutyl-4-oxo-1,2-diazetidin-1-yl)cyclohexane carboxamide (4aa)

Yield: 96% (48 mg); colorless oil; R_f = 0.74 (petrol ether/ethyl acetate 1:1, v/v). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (bs, 0.7H), 6.92 (bs, 0.3H), 4.52 (s, 1H), 4.37 (bs, 0.56H), 3.87 (bs, 0.44H),

3.82 – 3.67 (m, 1H), 2.44 (bs, 1H), 2.09 – 1.78 (m, 5H), 1.78 – 1.54 (m, 9H), 1.46 – 1.13 (m, 8H), 0.97 (t, *J* = 6.0 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 172.7, 66.1, 47.9, 38.3, 32.9, 31.5, 30.3, 25.8, 25.6, 24.8, 24.6, 22.8, 22.2, 21.6. MS-ESI: *m/z* 334,1 $[M-H]^-$; *m/z* 693,4 $[2M+Na]^+$. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{34}N_3O_2$ 336.2651, found 336.2649.

(*S*)-*N*-cyclohexyl-1-(6-oxo-1,7-diazabicyclo[3.2.0]heptan-7-yl) cyclohexanecarboxamide (4ab)

Yield: 48% (23 mg); white powder; R_f = 0.65 (petrol ether/ethyl acetate 1:1, v/v); mp = 126 – 127°C. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 7.61 (d, *J* = 7.6 Hz, 1H), 4.60 (d, *J* = 8.9 Hz, 1H), 3.59 – 3.51 (m, 1H), 3.07 (dd, *J* = 13.3 Hz, 1H), 2.17 (d, *J* = 13.4 Hz, 1H), 2.05 – 2.00 (m, 4H), 1.87 – 1.84 (m, 1H), 1.81 – 1.75 (m, 1H), 1.73 – 1.63 (m, 6H), 1.55 – 1.49 (m, 5H), 1.46 – 1.39 (m, 1H), 1.32 – 1.22 (m, 5H), 1.17 – 1.09 (m, 1H). $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6) δ 171.6, 170.8, 76.6, 67.6, 53.9, 48.3, 32.6, 32.5, 31.4, 30.9, 25.6, 25.1, 25.0, 24.9, 24.8, 22.4, 22.3, 22.1. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{30}N_3O_2$ 320.2338, found 320.2344.

(S)-*N*-cyclohexyl-1-(6-oxo-1,7-diazabicyclo[3.2.0]heptan-7-yl) cyclohexane carboxamide (4ac)

Yield: 30% (17 mg); colourless oil; R_f = 0.69 (petrol ether/ethyl acetate 1:1, v/v). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.20 – 8.13 (m, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.74 – 7.62 (m, 3H), 6.05 (d, *J* = 7.1 Hz, 1H), 4.65 – 4.58 (m, 1H), 3.56 – 3.42 (m, 3H), 2.39 – 2.15 (m, 2H), 2.16 – 2.03 (m, 2H), 1.77 – 1.46 (m, 6H), 1.28 – 1.06 (m, 4H). $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6) δ 171.9, 171.8, 166.0, 165.9, 147.99, 147.8, 145.8, 143.9, 143.3, 143.2, 129.7, 128.7, 128.5, 125.7, 124.4, 124.3, 124.1, 123.9, 74.8, 74.7, 64.7, 64.6, 49.3, 48.9, 48.3, 32.6, 32.5, 32.4, 28.4, 28.2, 25.5, 24.8, 24.7, 22.5. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{26}N_4O_4$ 373.4238, found 373.4344.

(*S*)-1-(3-(benzylthiomethyl)-4-oxo-1,2-diazetidin-1-yl)-*N*-cyclohexyl cyclohexanecarboxamide (4ad)

Yield: 21% (13 mg); colorless oil; R_f = 0.56 (petrol ether/ethyl acetate 1:1, v/v). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.51 (d, *J* = 7.5 Hz, 1H), 7.46 – 7.31 (m, 5H), 5.72 (d, *J* = 5.7 Hz, 1H), 4.49 (dd, *J* = 12.0 Hz, 1H), 3.86 (s, 2H), 3.55 – 3.50 (m, 1H), 2.72 (d, *J* = 6.2 Hz, 2H), 1.72 – 1.65 (m, 8H), 1.60 – 1.52 (m, 2H), 1.32 – 1.13 (m, 10H). $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6) δ 171.4, 168.6, 138.8, 129.4, 128.8, 127.3, 68.2, 63.3, 48.5, 36.1, 32.7, 32.6, 30.4, 25.6, 25.1, 23.9, 23.7. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{34}N_3O_2S$ 416.2372, found 416.2380.

(*S*)-1-(3-(4-*tert*-butoxybenzyl)-4-oxo-1,2-diazetidin-1-yl)-*N*-cyclohexylcyclohexanecarboxamide (4ae)

Yield: 32% (21 mg); colorless oil; R_f = 0.59 (petrol ether/ethyl acetate 1:1, v/v). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.58 (d, J = 7.1 Hz, 0.7H), 7.50 (bs, 0.3H), 7.18 (d, J = 7.7 Hz, 2H), 6.90 (d, J = 7.8 Hz, 2H), 5.81 (d, J = 4.8 Hz, 0.7H), 4.85 (bs, 0.3H), 4.57 (s, 1H), 3.54 (s, 1H), 3.12 – 2.85 (m, 2H), 2.15 (d, J = 12.9 Hz, 1H), 1.85 – 1.62 (m, 8H), 1.60 – 1.45 (m, 7H), 1.27 (s, 9H), 1.18 – 1.12 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 172.1, 169.6, 169.1, 154.0, 132.6, 130.5, 129.9, 124.0, 78.1, 69.9, 68.6, 65.9, 55.4, 48.2, 47.9, 34.8, 34.1, 32.8, 32.6, 31.1, 30.6, 28.9, 25.6, 24.9, 24.8, 21.9, 21.7. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{26}H_{40}N_3O_3$ 442.3070, found 442.3050.

Post-modifications

(*R*)-1-(2-acetyl-3-benzyl-4-oxo-1,2-diazetidin-1-yl)-*N*-cyclohexyl cyclohexanecarboxamide (4af)

Compound **4a** (38 mg, 0.10 mmol) was dissolved in dry DCM (5 mL) and solution cooled down to 0 °C. TEA (21 µL, 0.15 mmol; 1.5 eq) and Ac_2O (12 µL, 0.12 mmol; 1.2 eq) were added. Reaction was stirred at room temperature overnight. Solvent was evaporated and the residue purified by the flash column chromatography in petrol ether/EtOAc = 1:1, v/v.

Yield: 95% (41 mg); colorless oil; R_f = 0.55 (petrol ether/ethyl acetate 1:1, v/v). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.31 (m, 5H), 6.86 (d, J = 7.5 Hz, 1H), 4.78 (dd, J = 8.4 Hz, 1H), 3.84 – 3.62 (m, 1H), 3.38 (dd, J = 14.4 Hz, 1H), 3.25 (dd, J = 14.3 Hz, 1H), 2.23 – 2.09 (m, 2H), 2.03 – 1.83 (m, 4H), 1.80 – 1.66 (m, 4H), 1.64 (s, 3H), 1.59 – 1.46 (m, 3H), 1.42 – 1.27 (m, 4H), 1.25 – 1.10 (m, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 178.8, 171.3, 165.8, 135.1, 129.7, 129.1, 127.7, 69.1, 53.4, 48.4, 36.5, 32.8, 32.8, 31.4, 30.8, 25.6, 24.8, 24.7, 22.3, 20.1. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{24}H_{34}N_3O_3$ 412.2600, found 412.2608.

(*R*)-*tert*-butyl 2-(4-(1-((R)-3-benzyl-4-oxo-1,2-diazetidin-1-yl) cyclohexane carboxamido)benzamido)-4-methylpentanoate (4ag)

Compound **4e** (30 mg; 0.074 mmol) was dissolved in 5 mL of methanol and 1 M NaOH (150 µL, 0.15 mmol; 2 eq) was added. The reaction mixture was stirred under reflux for 2 h. The solvent was evaporated, the residue was dissolved in water, acidified to pH 3 by using 10% citric acid and the product was extracted with EtOAc. After solvent evaporation, the residue was dissolved in dry DCM (5 mL), and then NMM (9 µL, 0.081 mmol; 1.1 eq) and HATU (30 mg, 0.081 mmol; 1.1 eq) were added and the reaction mixture was stirred at room temperature. After 15 min a solution of H-Leu-OtBu (13 mg, 0.074 mmol) in 2 mL dry DCM was added. The reaction mixture was stirred at room temperature overnight. The solvent was

evaporated and the residue was purified by the flash column chromatography in petrol ether/EtOAc = 1 : 1, v/v.

Yield: 88% (38 mg); colorless oil; R_f = 0.68 (petrol ether/ethyl acetate 1:1, v/v). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.58 (dd, *J* = 2.8 Hz, 1H), 7.99 (d, *J* = 7.1 Hz, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.41 – 7.30 (m, 4H), 7.26 (t, *J* = 6.8 Hz, 1H), 4.38 – 4.32 (m, 1H), 3.51 – 3.34 (m, 1H), 3.20 (m, 1H), 3.05 – 2.95 (m, 1H), 1.77 – 1.66 (m, 3H), 1.62 – 1.49 (m, 5H), 1.40 (s, 9H), 1.35 – 1.28 (m, 2H), 1.26 – 1.20 (m, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 5.7 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 177.1, 172.5, 172.3, 166.9, 138.3, 135.4, 134.9, 131.3, 129.3, 128.6, 127.6, 123.2, 122.7, 119.4, 80.9, 80.1, 77.1, 61.3, 53.5, 52.1, 44.4, 42.6, 34.2, 33.5, 28.1, 25.2, 25.0, 24.7, 23.3, 22.4, 21.7, 21.5, 21.4. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{33}H_{44}N_4O_5Na$ 599.3209, found 599.3189.

tert-butyl (S)-1-(4-((R)-3-benzyl-4-oxo-1,2-diazetidin-1-yl)-4-(cyclohexyl carbamoyl)piperidin-1-yl)-4-methyl-1-oxopentan-2-ylcarbamate (4ah)

Compound **4p** (63 mg, 0.13 mmol) was dissolved in TFA-H_2O mixture (1 mL, 9:1, v/v) and the reaction was stirred at room temperature for 1 h. The consumption of starting material was monitored by TLC. Solvent was evaporated and the residue was dissolved in in 5 mL of dry DCM. NMM (29 µL, 0.26 mmol; 2 eq) and HATU (54 mg, 0.14 mmol; 1.1 eq) were added. After 15 min solution of Boc-Leu-OH (31 mg, 0.13 mmol) in dry DCM (1 mL) was added. Reaction was stirred at room temperature overnight. Solvent was evaporated and the residue purified by the flash column chromatography in petrol ether/ethyl acetate 1:1, v/v.

Yield: 78% (59 mg); colorless oil; R_f = 0.61 (petrol ether/ethyl acetate 1:1, v/v). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.66 (d, *J* = 7.6 Hz, 1H), 7.41 – 7.21 (m, 5H), 6.93 (d, *J* = 7.2 Hz, 1H), 4.65 (s, 1H), 4.36 (s, 1H), 4.15 – 4.05 (m, 1H), 3.72 (d, *J* = 11.6 Hz, 1H), 3.56 (s, 1H), 3.21 – 3.07 (m, 1H), 3.04 – 2.95 (m, 1H), 2.93 – 2.78 (m, 1H), 2.70 – 2.58 (m, 1H), 2.18 (dd, *J* = 12.2 Hz, 1H), 2.00 – 1.81 (m, 2H), 1.80 – 1.54 (m, 8H), 1.37 (s, 9H), 1.31 – 1.17 (m, 5H), 0.93 – 0.85 (m, 6H). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 171.0, 170.6, 169.6, 155.7, 137.8, 137.3, 129.6, 129.1, 128.7, 128.4, 126.9, 78.4, 78.2, 68.8, 64.5, 49.0, 48.7, 35.3, 32.6, 30.8, 30.0, 28.6, 25.6, 25.0, 24.7, 23.5, 21.9. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{32}H_{49}N_5O_5Na$ 606.3631, found 606.3624.

(*R*)-1-(2-amino-3-phenylpropanamido)-*N*-cyclohexylcyclohexanecarboxamide (4ai)

Compound **4a** (17 mg, 0.05 mmol) was dissolved in 2 mL of dry methanol and 10 % of catalyst Pd/C was added. Reaction was performed under atmosferic pressure using H_2 balloon at room temperature for 1 h. The consumption of starting material was monitored by TLC. Catalyst was

filtered off, solvent evaporated and the residue purified by flash column chromatography in petrol ether/ethyl acetate/triethyl amine = 1:2:0.1, v/v.

Yield: 80% (14 mg); colorless oil; R_f = 0.5 (petrol ether/ethyl acetate/triethyl amine 1:2:0.1, v/v). ^{1}H NMR (600 MHz, MeOD) δ 7.36 – 7.22 (m, 3H), 3.72 – 3.57 (m, 1H), 3.10 – 2.76 (m, 1H), 2.01 (dd, J = 69.1, 13.8 Hz, 1H), 1.85 – 1.46 (m, 6H), 1.41 – 1.09 (m, 5H). ^{13}C{^{1}H} NMR (151 MHz, MeOD) δ 174.5, 137.5, 129.1, 128.3, 126.1, 59.4, 56.2, 48.6, 40.6, 32.4, 32.2, 30.9, 25.2, 24.9, 24.8, 21.0, 20.9. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{33}N_3O_2Na$ 394.2470, found 394.2463.

Conflicts of interest

There are no conflicts to declare.

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra for new compounds, VT ^{1}H NMR experiments, x-ray data.

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References

(1) (a) Vitaku, E.; Smith D. T.; Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257-10274; (b) Heravi, M. M.; Zadsirjan V. Prescribed drugs containing nitrogen heterocycles: an overview. *RSC Adv.* **2020**, *10*, 44247-44311; (c) Mermer, A.; Keles, T.; Sirin Y. Recent studies of nitrogen containing heterocyclic compounds as novel antiviral agents: A review. *Bioorg. Chem.* **2021**, *114*, 105076; (d) Bhutani, P.; Joshi, G.; Raja, N.; Bachhav, N.; Rajanna, P. K.; Bhutani, H.; Paul A. T.; Kumar, R. *J. Med. Chem.* **2021**, *64*, 2339- 2381.

(2) Bachovchin, D. A.; Mohr, J. T.; Speers, A. E.; Wang, C.; Berlin, J. M.; Spicer, T. P.; Fernandez-Vega, V.; Chase, P.; Hodder, P. S.; Schürer, S. C.; Nomura, D. K.; Rosen, H.; Fu, G. C.; Cravatt, B. F. Academic cross-fertilization by public screening yields a remarkable class

of protein phosphatase methylesterase-1 inhibitors. *Proc. Nat. Acad. Sci. USA* **2011**, *108*, 6811-6816.

(3) Zuhl, A. M.; Mohr, J. T.; Bachovchin, D. A.; Niessen, S.; Hsu, K.-L.; Berlin, J. N.; Dochnahl, M.; López-Alberca, M. P.; Fu, G. C.; Cravatt, B. F. Competitive activity-based protein profiling identifies aza-β-lactams as a versatile chemotype for serine hydrolase inhibition *J. Am. Chem. Soc.* **2012**, *134*, 5068-5071.

(4) Lin, Y.; Chang, C.-C.; Craig, S. L. Mechanical generation of isocyanate by mechanically induced retro [2+2] cycloaddition of a 1,2-diazetidinone mechanophore. *Org. Chem. Front*. **2019**, *6*, 1052-1057.

(5) Klein, I. M.; Husic, C. C.; Kovács, D. P.; Choquette N. J., Robb, M. J. Validation of the CoGEF method as a predictive tool for polymer mechanochemistry *J. Am. Chem. Soc*. **2020**, *142*, 16364-16381.

(6) Jungheim, L. N. in *Adv. Heterocycl. Chem.* Vol. 110 (Ed.: A. R. Katritzky), Elsevier, Amsterdam, New York, 2013, pp. 145–174, and references cited therein.

(7) Berlin, J. M. Fu, G. C. Enantioselective nucleophilic catalysis: The synthesis of aza-β-lactams via [2+2] reactions of ketenes with azo compounds. *Angew. Chem. Int. Ed.* **2008**, *47*, 7048-7050.

(8) Huang, X.-L.; Chen, X-Y.; Ye, S. Enantioselective synthesis of aza-β-lactams via NHC-catalyzed [2+2] cycloaddition of ketenes with diazenedicarboxylates. *J. Org. Chem.* **2009**, *74*, 7585-7587.

(9) Downey, C. A.; James, J. P.; Lawler, J.; O'Malley, P.; Wolfe, S. Azoacetates as synthons for the azetidinone and diazetidinone ring systems. *J. Chem. Soc., Chem. Commun.* **1992**, *23*, 454-455.

(10) (a) Santos, M. S.; Nortcliffe, A.; Lewis, W.; Bradsha, T. D.; Moody, C. J. Synthesis of highly substituted 1,2-diazetidin-3-ones, small-ring scaffolds for drug discovery. *Chem. Eur. J.* **2018**, *24*, 8325-8330; (b) Lawton, G.; Moody, C. J.; Pearson, C. J. Rhodium carbenoid mediated cyclisations. Synthesis of 1,2-diazetidinones (aza-β-lactams) *J. Chem. Soc. Perkin Trans. 1* **1987**, 899-902.

(11) Gedey, S.; Van der Eycken, J.; Fülöp, F. Liquid-phase combinatorial synthesis of alicyclic β-lactams via Ugi four-component reaction. *Org. Lett.* **2002**, *4*, 1967-1969.

(12) Naskar, D.; Roy, A.; Seibel, W. L.; West, L.; Portlock, D. E. The synthesis of aza-β-lactams via tandem Petasis–Ugi multi-component condensation and 1,3-diisopropylcarbodiimide (DIC) condensation reaction. *Tetrahedron Lett.* **2003**, *4*, 6297-6300.

(13) (a) Avan, I.; Hall, C. D.; Katritzky, A. R. Peptidomimetics via modifications of amino acids and peptide bond. *Chem. Soc. Rev.* 2014, **43**, 3575-3594; (b) Panda, S. S.; El-Nachef, C.; Bajaj, K.; Katritzky, A. R. Syntheses of hydrazino peptides and conjugates. *Eur. J. Org. Chem.* **2013**, *19*, 4156-4162.

(14) Garner, P. Stereocontrolled addition to a penaldic acid equivalent: an asymmetric of threo-β-hydroxy-L-glutamic acid. *Tetrahedron Lett.* **1984**, *25*, 5855-5858.

(15) Lelais, G.; Seebach, D. Synthesis, CD Spectra, and enzymatic stability of β2-oligoazapeptides prepared from (*S*)-2-hydrazino carboxylic acids carrying the side chains of Val, Ala, and Leu. *Helv. Chim. Acta,* **2003**, *86*, 4152-4168.

(16) (a) Ugi, I. The α-addition of immonium ions and anions to isonitriles accompanied by secondary reactions. *Angew. Chem. Int Ed.* **1962**, *1*, 8-21; (b) Obrecht, R.; Toure, S.; Ugi, I. Recent developments in β-lactam synthesis by four component condensation. *Heterocycles* **1984**, *21*, 271-277.

(17) Chéron, N.; Ramozzi, R.; El Kaïm, L.; Grimaud, L.; Fleurat-Lessard, P. Challenging 50 years of established views on Ugi reaction: a theoretical approach. *J. Org. Chem.* **2012,** *77***,** 1361−1366

(18) Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T. J. Hexafluoroisopropanol as a highly versatile solvent. *Nat. Rev. Chem*. **2017**, *1*, 0088

(19) Saya, J. M.; Berabez, R.; Broersen, P.; Schuringa, I.; Kruithof, A.; Orru, R. V. A.; Ruijter, E. Hexafluoroisopropanol as the acid component in the Passerini reaction: one-pot access to β-amino alcohols. *Org. Lett.* **2018**, *20*, 3988-3991