

Efficient entry into hydrazinopeptide-like structures via sequential Ugi reactions

Ekaterina Bushkova · Vladislav Parchinsky · Mikhail Krasavin

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Abstract Novel types of hydrazinopeptide-like units containing five elements of diversity have been prepared in two steps using sequential Ugi reactions.

Keywords Isocyanide-based multicomponent reactions · Peptidomimetics · Hydrazinopeptides · β -Turn mimics · Sequential Ugi reactions

Introduction

The idea of replacing the primary amine component in the Ugi reaction with monoacylated hydrazine was first reduced to practice over 40 years ago to deliver *N,N'*-bisacylated hydrazines **1** [1] or tetrazoles **2** [2], in the latter case azide anion replacing the traditional carboxylate nucleophile (Scheme 1). However, in subsequent decades this reaction received little attention [3–5], perhaps due to limited room for further chemical manipulation of the products resulting from it.

We reasoned that if the carboxylic acid component in the “hydrazino-Ugi” reaction is chosen such as to allow selective removal of the *N* ^{α} -acyl group, this would provide a facile method to prepare hydrazinopeptide [6] units and also liberate the reactive nitrogen atom for introducing further molecular diversity. Hydrazinopeptides represent a valuable class of mimetic replacements for the natural peptide backbone often leading to analogs of bioactive peptides with preserved biological activity [7] yet enhanced proteolytic stability [8]. Hydrazinopeptide units within short peptide fragments have also been shown [9]

to adopt a unique secondary structure termed a “hydrazino turn” (similar to natural peptide β -turn) due to additional hydrogen bonding via the *sp*³-hybridized nitrogen atom (Fig. 1).

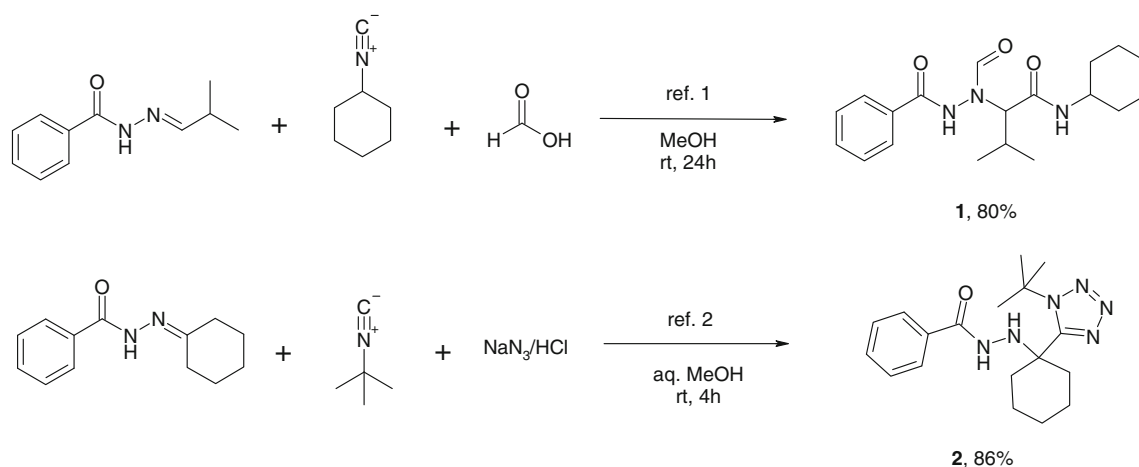
Results and discussion

A series of carboxylic acid hydrazides **3** were reacted with aliphatic aldehydes **4** in methanol to prepare the respective acylhydrazones **5**. Reaction with the isocyanides **6** and TFA was carried out in dioxane as the same reaction in methanol had been found to lead to by-product formation.¹ The expected *N* ^{β} -acyl-*N* ^{α} -trifluoroacetyl hydrazocarboxamides **7** were indeed observed by LC–MS analysis (and isolated in one case—see “Experimental” section) on completion of the reaction. However, upon basic workup, the trifluoroacetyl group was found to partially come off. Therefore, the hydrazo-Ugi reaction with TFA was repeated and on its completion, the trifluoroacetyl group was cleanly removed with aqueous K₂CO₃ solution to provide good to excellent yields of *N* ^{β} -monoacylated hydrazino carboxamides **8a–c** (Scheme 2). The structure of the synthesized compounds was confirmed by ¹H- and ¹³C-NMR spectroscopy. For the compound **8a**, a single-crystal X-ray structure was obtained² to reveal that in the crystalline state,

¹ Detailed investigation of the by-product structure and mechanistic origin is currently underway and will be reported on in a separate publication.

² Crystallographic data (excluding structure factors) for the structure **8a** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 743067. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

E. Bushkova · V. Parchinsky · M. Krasavin (✉)
Chemical Diversity Research Institute, 2a Rabochaya St.,
114401 Khimki, Moscow Region, Russia
e-mail: myk@chemdiv.com



Scheme 1 Earlier examples (see footnotes 1 and 2) of using monoacylated hydrazine in Ugi reaction

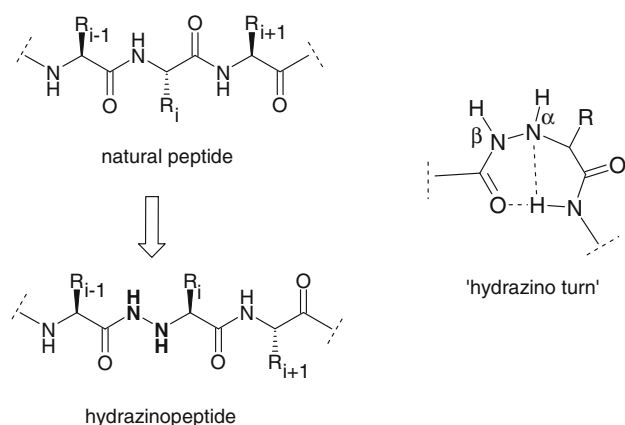


Fig. 1 Hydrazinopeptides and their “hydrazino turn” conformation

this compound adopts a hydrazino turn-like conformation (Fig. 2). NMR studies are currently underway in our laboratories to establish if this conformational bias persists in solution as well.

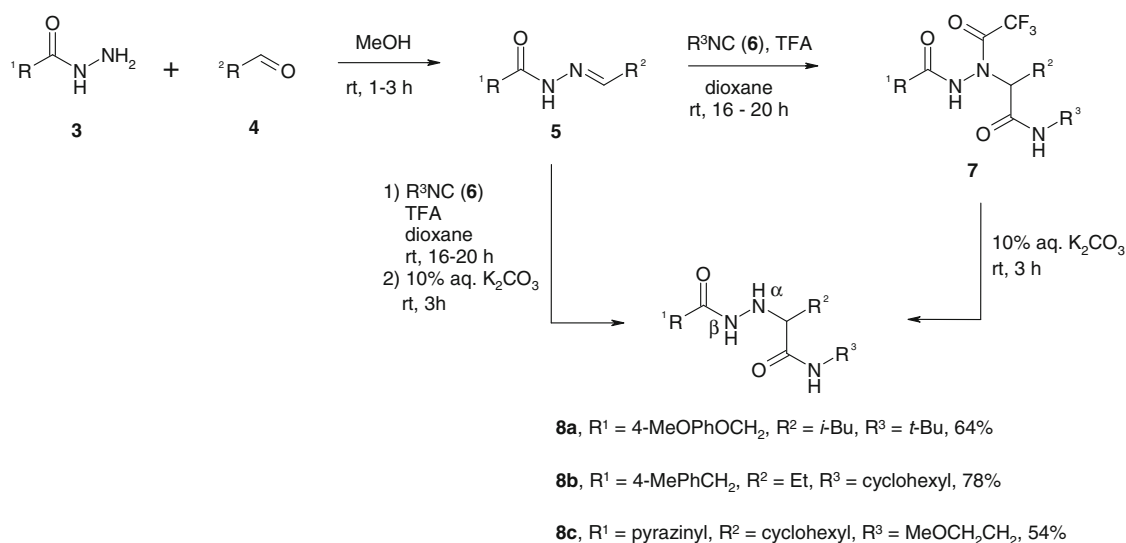
The compounds **8** contain three elements of diversity resulting from the acylhydrazine, the aldehyde, and the isocyanide used. We reasoned that, in principle, these diversely substituted hydrazino carboxamides can be viewed as the starting materials for another Ugi reaction, as the reactive α -nitrogen atom can again serve as a replacement for the amine component in this process. Indeed, when **8b** and **8c** were reacted with an aliphatic aldehyde and an isocyanide in methanol in the presence of TFA, the expected products of the second “hydrazino-Ugi” reaction **9a–c** were obtained in good yields as mixture of diastereomers, with no noticeable diastereomeric control (Scheme 3). In one case (**9a**), we were able to separate the diastereomers

nearly quantitatively by preparative reverse-phase HPLC. Notably, in the NOESY spectrum, only one diastereomer **9a(1)** displayed a through-space interaction between the two methine protons at the chiral carbon atoms, which provided a basis for the assignment of the relative stereochemistry (Fig. 3).

Formation of the difficult-to-separate diastereomeric mixtures in the hydrazo-Ugi reaction of the chiral substrates **8** can be avoided if a non-prochiral carbonyl input is used. Indeed, when **8a** and **8b** were reacted with excess amount of either acetone or paraformaldehyde and an equimolar amount of an isocyanide in methanol in the presence of TFA, the expected products **9d–f** were formed in good yields (Scheme 4).

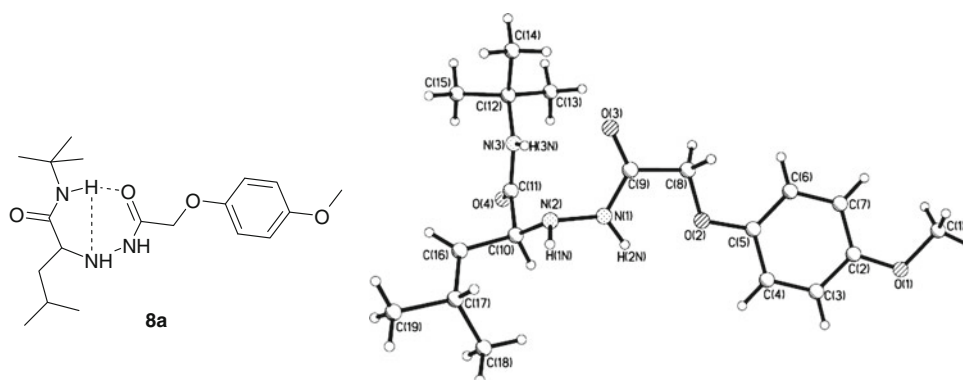
The compounds **9a–f** synthesized via two operationally simple sequential hydrazo-Ugi reactions, remarkably, contain *five* elements of diversity which originate from an acylhydrazine, two carbonyl components, and two isocyanide components and are introduced sequentially, in a regiochemically controlled manner. Trifluoroacetic acid functions as a “silent” carboxylic component in both multi-component reactions. In the first reaction, it is removed upon mildly basic workup to liberate the reactive N^α . In the second reaction, trifluoroacetyl group in the initial four-component adduct **10** cannot undergo the usual Mumm rearrangement [10] (i.e., acyl migration according to the generally accepted mechanism of Ugi reaction) and is cleaved by the nucleophilic solvent molecule (Scheme 5).

Notably, the hydrazinopeptide units **9** represent a conceptually novel class of peptidomimetic structures capable of introducing a “fork” in the polypeptide chain after which the latter may take two alternative ways to continue toward the C-terminus (Fig. 4).

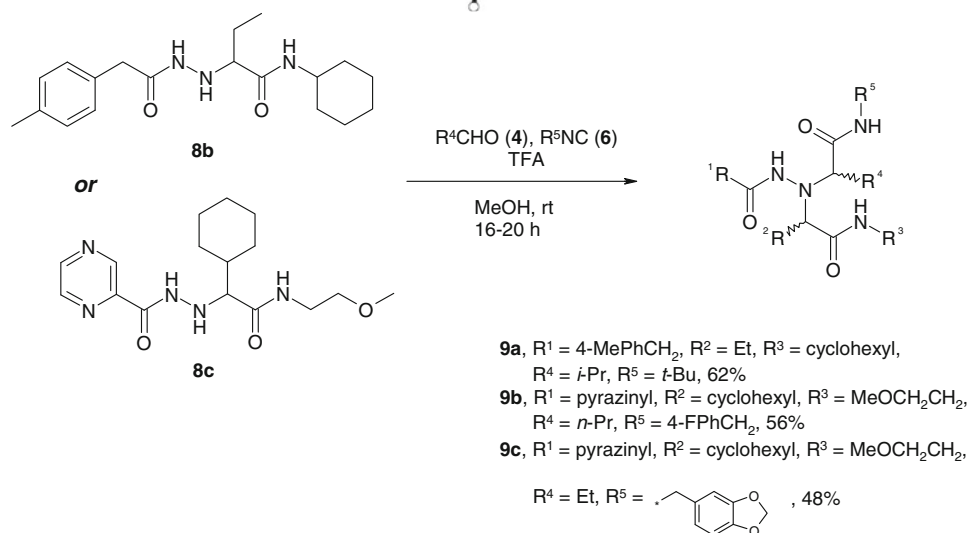


Scheme 2 Synthesis of *N*^β-monoacylated hydrazine carboxamides developed in this work

Fig. 2 X-ray structure of the compound **8a** displaying a hydrazine turn-like conformation



Scheme 3 Second “hydrazo-Ugi” reaction of **8** leading to diastereomeric products

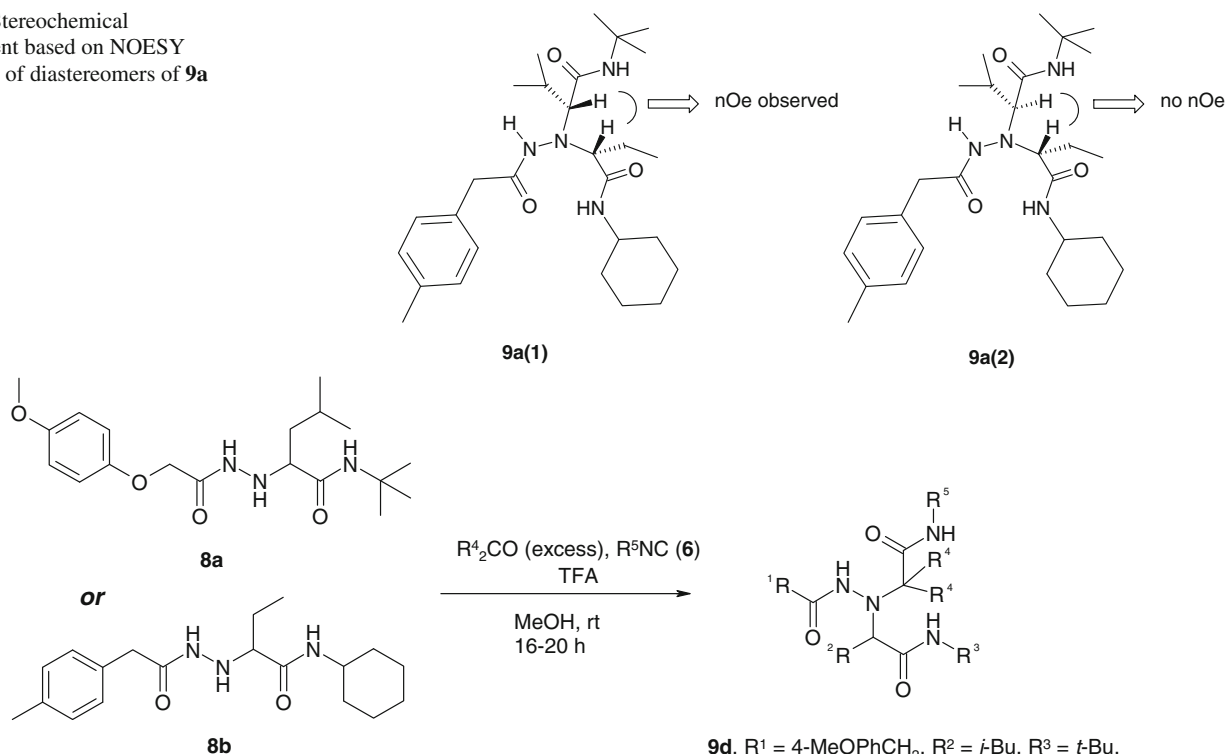


Conclusion

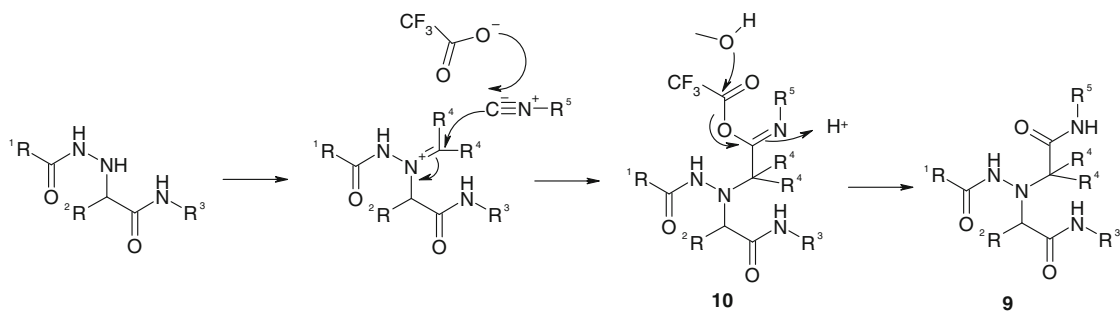
In summary, we have developed an operationally simple method to prepare novel peptidomimetic units containing a hydrazine moiety. Two Ugi reactions starting from acylhydrazide

were coupled in a sequence using a modified protocol with trifluoroacetic acid as removable carboxylic component in each reaction. Efforts are underway in our laboratories to thoroughly characterize the secondary structure of these peptidomimetics in solid state and in solution and to develop

Fig. 3 Stereochemical assignment based on NOESY spectrum of diastereomers of **9a**



Scheme 4 Second “hydrazo-Ugi” reaction with non-prochiral carbonyl inputs



Scheme 5 Mechanism of the second “hydrazo-Ugi” reaction

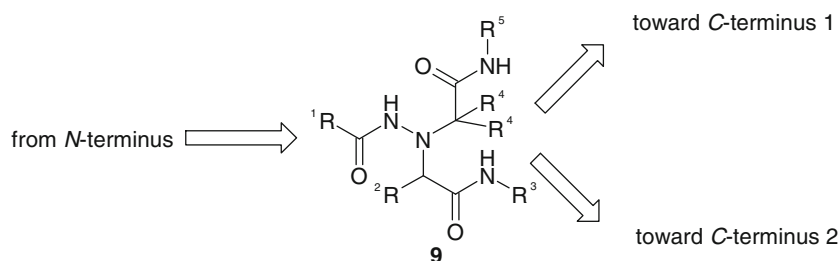
efficient methods of integrating these hydrazine units with the natural peptide chains. The results of these studies will be reported in due course.

Experimental

Melting points were measured with a Buchi B-520 melting point apparatus and were not corrected. Analytical thin layer

chromatography was carried out on EM Separations Technology F₂₅₄ silica gel plates. Compounds were visualized with short-wavelength UV light. ¹H-NMR and ¹³C-NMR spectra were recorded on Bruker DPX-300 spectrometers in DMSO-*d*₆ using TMS as an internal standard. LC–MS analyses were obtained on a PE SCIEX API 150EX mass spectrometer following separation on a Shimadzu LC-10AD liquid chromatography system equipped with Shimadzu SP

Fig. 4 “Forked” peptide chain due to introduction of hydrazino units **9**



D-10A UV–Vis detector (254 nm) and Sedex 75 ELSD detector. Elemental analyses were obtained at Research Institute for Chemical Crop Protection (Moscow, Russia) using Carlo Erba Strumentazione 1106 analyzer. All solvents and reagents were obtained from commercial sources and used without purification.

General procedure 1: synthesis of **8**

The starting acid hydrazide **3** (10 mmol) was dissolved in anhydrous methanol (50 mL) and the aldehyde **4** (10 mmol) was added. The reaction mixture was stirred at room temperature for 1–3 h and the solvent was removed under reduced pressure. The crude product **5** was triturated with dry diethyl ether and filtered off. It was dissolved in anhydrous 1,4-dioxane (50 mL). Isocyanide **6** (1.2 eq.) and trifluoroacetic acid (1.0 eq.) were added. The resulting mixture was stirred at room temperature overnight, the reaction mixture was diluted with 10% aqueous K_2CO_3 (50 mL), stirred for 3 h, and extracted with chloroform (3×50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to provide the crude product. The analytically pure **8** was isolated by column chromatography on silica gel using 5–30% ethyl acetate in hexanes as eluent.

General procedure 2: synthesis of **9**

Compound **8** (1 mmol) was dissolved in anhydrous methanol (3 mL) and treated with the carbonyl compound (3 eq. or excess, as indicated below), the isocyanide (1.2 mmol), and TFA (1 mmol). The reaction mixture was stirred at room temperature overnight, the solvent was removed under reduced pressure and product was isolated by column chromatography using an appropriate gradient of methanol in chloroform as eluent.

N-(*tert*-Butyl)-2-{2-[(4-methoxyphenoxy)acetyl]hydrazino}-4-methylpentanamide (**8a**)

The compound was obtained via the General procedure 1 in 64% yield. White solid, mp = 172–174 °C (decomp). 1H -NMR (DMSO- d_6 , 300 K) δ 0.90 (d, J = 5.9 Hz, 6H), 1.28 (s, 9H), 1.40 (m, 2H), 1.80 (m, 1H), 3.30 (t, J = 6.4 Hz,

1H), 3.72 (s, 3H), 4.44 (bs, 2H), 4.85 (bs, 1H), 6.86 (d, J = 9.3 Hz, 2H), 6.90 (d, J = 9.3 Hz, 2H), 7.32 (bs, 1H), 9.02 (bs, 1H). ^{13}C -NMR (DMSO- d_6 , 300 K) δ 22.3, 23.0, 24.2, 28.4, 40.5, 49.6, 55.9, 62.9, 67.2, 114.5, 115.7, 151.6, 153.9, 166.7, 172.1. LC–MS: m/z = 366 [M+H]. Anal. calcd for $C_{19}H_{31}N_3O_4$: C, 62.44; H, 8.55; N, 11.50. Found: C, 62.50; H, 8.61; N, 11.55.

N-Cyclohexyl-2-{2-[(4-methylphenyl)acetyl]hydrazino}butanamide (**8b**)

The compound was obtained via the General procedure 1 in 78% yield. White solid, mp = 164–166 °C. 1H -NMR (DMSO- d_6 , 300 K) δ 0.83 (t, J = 7.5 Hz, 3H), 0.89–1.28 (m, 5H), 1.44–1.70 (m, 7H), 2.25 (s, 3H), 3.13 (m, 1H), 3.44 (m, 1H), 5.0 (bs, 1H), 7.06 (d, J = 8.2 Hz, 2H), 7.1 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.0 Hz, 1H), 9.34 (d, J = 3.3 Hz, 1H). ^{13}C -NMR (DMSO- d_6 , 300 K) δ 9.8, 20.5, 23.9, 24.4, 25.2, 32.0, 32.3, 47.2, 65.0, 128.6, 128.7, 132.8, 135.3, 169.4, 170.7. LC–MS: m/z = 332 [M+H]. Anal. calcd for $C_{19}H_{29}N_3O_2$: C, 68.85; H, 8.82; N, 12.68. Found: C, 68.79; H, 8.77; N, 12.65.

2-Cyclohexyl-*N*-(2-methoxyethyl)-2-{2-[oxo(pyrazin-2-yl)acetyl]hydrazino}acetamide (**8c**)

The compound was obtained via the General procedure 1 in 54% yield. White solid, mp = 184 °C (decomp). 1H -NMR (DMSO- d_6 , 300 K) δ 1.06–1.30 (m, 5H), 1.53–1.85 (m, 6H), 3.21 (s, 3H), 3.22–3.40 (m, 4H), 5.23 (bs, 1H), 7.73 (bs, 1H), 8.61 (bs, 1H), 8.81 (bs, 1H), 9.12 (bs, 1H), 9.67 (bs, 1H). ^{13}C -NMR (DMSO- d_6 , 300 K): δ 25.9, 28.5, 29.0, 38.0, 38.7, 57.8, 68.0, 70.5, 143.3, 143.4, 144.4, 147.5, 161.1, 171.6. LC–MS: m/z = 364 [M+H]. Anal. calcd for $C_{17}H_{25}N_5O_4$: C, 56.19; H, 6.93; N, 19.27. Found: C, 56.25; H, 7.00; N, 19.25.

N-(*tert*-Butyl)-{1-[1-[(cyclohexylamino)carbonyl]propyl]-2-[(4-methylphenyl)acetyl]hydrazino}-3-methylbutanamide (**9a**)

The compound was obtained via the General procedure 2 (using 3.0 eq. of the aldehyde) as 1:1 mixture of diastereomers in 62% yield. The diastereomers were separated

by preparative reverse-phase HPLC (Reprosil-Pur C18-AQ 10 mm column, gradient elution with 60–100% acetonitrile in water over 17 min, 25 mL/min, 215 nm). **9a(1)**— t_R = 12.4 min. White solid, mp = 162–164 °C. $^1\text{H-NMR}$ (DMSO- d_6 , 363 K) δ 0.86 (m, 6H), 0.99 (d, J = 6.9 Hz, 3H), 1.04–1.32 (m, 5H), 1.27 (s, 9H), 1.47–1.85 (m, 7H), 1.88 (m, 1H), 2.28 (s, 3H), 3.02 (d, J = 7.4 Hz, 1H), 3.26 (t, J = 6.2 Hz, 1H), 3.39 (s, 2H), 3.50 (m, 1H), 7.15 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 7.45 (bs, 1H), 7.67 (d, J = 6.6 Hz, 1H), 9.06 (bs, 1H). Cross peak observed in the NOESY spectrum between d 3.02 (d, J = 7.4 Hz, 1H) and 3.26 (t, J = 6.2 Hz, 1H). $^{13}\text{C-NMR}$ (DMSO- d_6 , 363 K) δ 10.2, 18.1, 20.4, 20.7, 22.4, 24.3, 25.2, 27.6, 28.3, 31.9, 32.3, 47.4, 50.3, 68.1, 70.6, 128.6, 128.9, 132.2, 135.5, 169.8, 170.5, 170.9. LC–MS: m/z = 487 [M+H]. Anal. calcd for $\text{C}_{28}\text{H}_{46}\text{N}_4\text{O}_3$: C, 69.10; H, 9.53; N, 11.51. Found: C, 69.07; H, 9.55; N, 11.46. **9a(2)**— t_R = 14.2 min. White solid, mp = 171–173 °C (decomp). $^1\text{H-NMR}$ (DMSO- d_6 , 363 K) δ 0.81 (m, 6H), 0.95 (d, J = 6.6 Hz, 3H), 1.18–1.57 (m, 8H), 1.30 (s, 9H), 1.64–1.88 (m, 5H), 2.29 (s, 3H), 2.82 (d, J = 8.8 Hz, 1H), 3.09 (t, J = 6.9 Hz, 1H), 3.47 (s, 2H), 3.58 (m, 1H), 7.12 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 7.86 (bs, 1H), 8.53 (d, J = 6.6 Hz, 1H); 8.89 (bs, 1H); $^{13}\text{C-NMR}$ (DMSO- d_6 , 363 K) δ 11.4, 18.8, 20.4, 20.7, 22.4, 24.0, 25.4, 27.8, 28.4, 32.3, 47.0, 50.5, 69.5, 73.0, 128.8, 132.3, 135.6, 171.0, 172.0, 172.3. LC–MS: m/z = 487 [M+H]. Anal. calcd for $\text{C}_{28}\text{H}_{46}\text{N}_4\text{O}_3$: C, 69.10; H, 9.53; N, 11.51. Found: C, 69.12; H, 9.60; N, 11.56.

2-[1-(1-Cyclohexyl-2-[(2-methoxyethyl)amino]-2-oxoethyl)-2-(pyrazin-2-ylcarbonyl)hydrazino]-*N*-(4-fluorobenzyl)pentanamide (**9b**)

The compound was obtained via the General procedure 2 (using 3.0 eq. of the aldehyde) as 2:3 mixture of diastereomers in 56% yield. Grey solid, mp = 184 °C (decomp). $^1\text{H-NMR}$ (DMSO- d_6 , 363 K) δ 0.79 (t, J = 7.0 Hz) and 0.87 (t, J = 7.0 Hz)—3H total, 0.93–1.73 (m, 14H), 2.01 (d, J = 11.9 Hz) and 2.18 (d, J = 11.9 Hz)—1H total, 3.15–3.53 (m, 6H), 3.26 (s) and 3.28 (s)—3H total, 4.27 (d, J = 5.8 Hz) and 4.36 (ddd, J_1 = 27.7 Hz, J_2 = 14.8 Hz, J_3 = 9.6 Hz)—2H total, 7.0 (t, J = 7.0 Hz) and 7.1 (t, J = 7.0 Hz)—2H total, 7.29 (dd, J_1 = 2.5 Hz, J_2 = 5.9 Hz) and 7.37 (dd, J_1 = 2.5 Hz, J_2 = 5.9 Hz)—2H total, 7.93 (bs) and 8.24 (bs)—1H total, 8.14 (bs) and 8.86 (bs)—1H total, 8.68 (s) and 8.73 (s)—1H total, 8.84 (d, J = 2.1 Hz) and 8.88 (d, J = 2.1 Hz)—1H total, 9.10 (s) and 9.20 (s)—1H total, 10.6 (bs, 1H). $^{13}\text{C-NMR}$ (DMSO- d_6 , 363 K) δ 13.6, 13.8, 18.4, 19.6, 25.2, 25.4, 25.9, 26.0, 28.5, 28.9, 30.3, 31.6, 32.0, 36.8, 37.0, 37.9, 38.1, 41.3, 57.8, 67.4, 68.4, 70.4, 114.65 (d, $J_{\text{C-F}}$ = 21.6 Hz), 114.9 (d, $J_{\text{C-F}}$ = 21.6 Hz), 129.4 (d, $J_{\text{C-F}}$ = 8.0 Hz), 129.5 (d, $J_{\text{C-F}}$ = 8.0 Hz), 135.4 (d, $J_{\text{C-F}}$ = 1.2 Hz), 143.4, 145.5, 143.6, 143.7, 147.9, 148.2, 161.0 (d, $J_{\text{C-F}}$ = 242.3 Hz), 161.2 (d, $J_{\text{C-F}}$ =

242.3 Hz), 162.4, 171.2, 171.7, 172.4, 172.4, 172.8. LC–MS: m/z = 543 [M+H]. Anal. calcd for $\text{C}_{28}\text{H}_{39}\text{FN}_6\text{O}_4$: C, 61.97; H, 7.24; N, 15.49. Found: C, 62.03; H, 7.28; N, 15.55.

*N*¹-(1,3-Benzodioxol-4-ylmethyl)-2-[1-(1-cyclohexyl)-2-[(2-methoxyethyl)amino]-2-oxoethyl-2-(2-pyrazinylcarbonyl)hydrazino]butanamide (**9c**)

The compound was obtained via the General procedure 2 (using 3.0 eq. of the aldehyde) as 1:1 mixture of diastereomers in 48% yield. Grey solid, mp = 193 °C (decomp). $^1\text{H-NMR}$ (DMSO- d_6 , 363 K) δ 0.81 (m, 3H), 0.95–1.15 (m, 5H), 1.40–1.68 (m, 6H), 1.76 (m, 1H), 2.02 (d, J = 11.8 Hz) and 2.23 (d, J = 11.8 Hz)—1H total, 3.10–3.50 (m, 9H), 4.19 (d, J = 4.5 Hz) and 4.29 (ddd, J_1 = 33.3 Hz, J_2 = 6.7 Hz, J_3 = 6.2 Hz)—2H total, 5.9 (d, J = 5.9 Hz) and 5.95 (s)—2H total, 6.71 (bs) and 6.72 (bs)—1H total, 6.77 (bs) and 6.88 (bs)—1H total, 6.81 (bs, 1H), 7.98 (bs) and 8.24 (bs)—1H total, 8.09 (bs) and 8.75 (bs)—1H total, 8.68 (dd, J_1 = 0.8 Hz, J_2 = 1.4 Hz) and 8.72 (dd, J_1 = 0.8 Hz, J_2 = 1.4 Hz)—1H total, 8.84 (d, J = 2.4 Hz) and 8.87 (d, J = 2.4 Hz)—1H total, 9.08 (d, J = 1.2 Hz) and 9.20 (d, J = 1.2 Hz)—1H total, 10.62 (bs, 1H). $^{13}\text{C-NMR}$ (DMSO- d_6 , 363 K) δ 9.7, 11.4, 22.7, 23.1, 25.2, 25.4, 25.9, 26.0, 28.5, 28.9, 29.8, 30.3, 36.7, 37.0, 37.9, 38.0, 41.8, 57.8, 63.1, 68.1, 70.4, 72.5, 110.7, 100.8, 107.4, 108.0, 120.6, 120.7, 133.1, 143.4, 143.5, 143.6, 145.9, 146.1, 147.0, 147.2, 147.9, 148.2, 161.3, 162.3, 170.1, 171.8, 172.4. LC–MS: m/z = 555 [M+H]. Anal. calcd for $\text{C}_{28}\text{H}_{38}\text{N}_6\text{O}_6$: C, 60.63; H, 6.91; N, 15.15. Found: C, 60.58; H, 6.86; N, 15.12.

*N*¹-(*tert*-Butyl)-2-1-[2-(*tert*-butylamino)-2-oxoethyl]-2-[2-(4-methoxyphenoxy) acetyl]hydra-zino-4-methylpentanamide (**9d**)

The compound was obtained via the General procedure 2 (using >10-fold excess of paraformaldehyde) in 56% yield. White solid, mp = 157–159 °C. $^1\text{H-NMR}$ DMSO- d_6 , 363 K δ 0.87 (t, J = 8.5 Hz, 6H), 1.29 (d, J = 6.2 Hz, 18H), 1.40 (m, 1H), 1.77 (m, 1H), 3.30 (m, 4H), 3.72 (s, 3H), 4.49 (s, 2H), 6.87 (d, J = 9.3 Hz, 2H), 6.93 (d, J = 9.3 Hz, 2H), 7.45 (bs, 1H), 8.0 (bs, 1H), 9.32 (bs, 1H). $^{13}\text{C-NMR}$ (DMSO- d_6 , 363 K) δ 22.0, 22.7, 24.2, 28.5, 38.6, 49.8, 50.6, 55.8, 60.5, 65.6, 67.9, 115.0, 116.2, 151.9, 154.6, 167.4, 167.9, 172.1. LC–MS: m/z = 479 [M+H]. Anal. calcd for $\text{C}_{25}\text{H}_{42}\text{N}_4\text{O}_5$: C, 62.74; H, 8.84; N, 11.71. Found: C, 62.80; H, 8.88; N, 11.66.

*N*¹-(*tert*-Butyl)-2-(2-[2-(4-methoxyphenoxy)acetyl]-1-2-[(3-methoxypropyl)amino]-1,1-dimethyl-2-oxoethylhydrazino)-4-methylpentanamide (**9e**)

The compound was obtained via the General procedure 2 (using >5-fold excess of acetone) in 68% yield. White solid,

mp = 179–181 °C. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 363 K) δ 0.84 (d, $J = 6.6$ Hz, 6H), 1.18 (s, 3H), 1.28 (bs, 12H), 1.43 (m, 1H), 1.67 (m, 2H), 1.82 (m, 1H), 3.14 (m, 2H), 3.24 (s, 3H), 3.35 (m, 4H), 3.72 (s, 3H), 4.56 (s, 2H), 6.87 ($J = 9.3$ Hz, 2H), 6.91 ($J = 9.3$ Hz, 2H), 7.8 (bs, 2H), 9.56 (bs, 1H). $^{13}\text{C-NMR}$ ($\text{DMSO-}d_6$, 363 K) δ 22.2, 22.6, 23.8, 24.1, 28.3, 29.1, 36.3, 50.0, 55.7, 57.7, 61.0, 66.4, 67.7, 70.0, 115.0, 116.2, 151.9, 154.5, 161.8, 169.0, 175.0. LC–MS: $m/z = 523$ [M+H]. Anal. calcd for $\text{C}_{27}\text{H}_{46}\text{N}_4\text{O}_6$: C, 62.04; H, 8.87; N, 10.72. Found: C, 61.97; H, 8.83; N, 10.79.

2-1-[2-(*tert*-Butylamino)-1,1-dimethyl-2-oxoethyl]-2-[2-(4-methylphenyl)acetyl]hydrazino- N^1 -cyclohexylbutanamide (**9f**)

The compound was obtained via the General procedure 2 (using >5-fold excess of acetone) in 60% yield. White solid, mp = 186 °C (decomp). $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 363 K) δ 0.91 (t, $J = 7.4$ Hz, 3H), 1.12 (s, 3H), 1.16–1.45 (m, 6H), 1.18 (s, 3H), 1.23 (s, 9H), 1.56 (m, 2H), 1.70 (m, 2H), 2.28 (s, 3H), 3.16 (t, $J = 7.1$ Hz, 1H), 3.5 (s, 2H), 3.55 (m, 1H), 7.06 (d, $J = 8.1$ Hz, 2H), 7.1 (d, $J = 8.1$ Hz, 2H), 8.0 (bs, 2H), 9.1 (bs, 1H). $^{13}\text{C-NMR}$ ($\text{DMSO-}d_6$, 363 K) δ 11.4, 20.4, 21.0, 23.4, 24.1, 24.2, 25.2, 28.2, 31.9, 32.0, 47.1, 49.5, 63.7, 67.1, 128.7, 128.9, 132.3, 135.5, 171.8, 174.2. LC–MS: $m/z = 473$ [M+H]. Anal. calcd for $\text{C}_{27}\text{H}_{44}\text{N}_4\text{O}_3$: C, 68.61; H, 9.38; N, 11.85. Found: C, 68.57; H, 9.33; N, 11.91.

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