Hydrazinopeptide Motifs Synthesized via the Ugi Reaction: An Insight into the Secondary Structure

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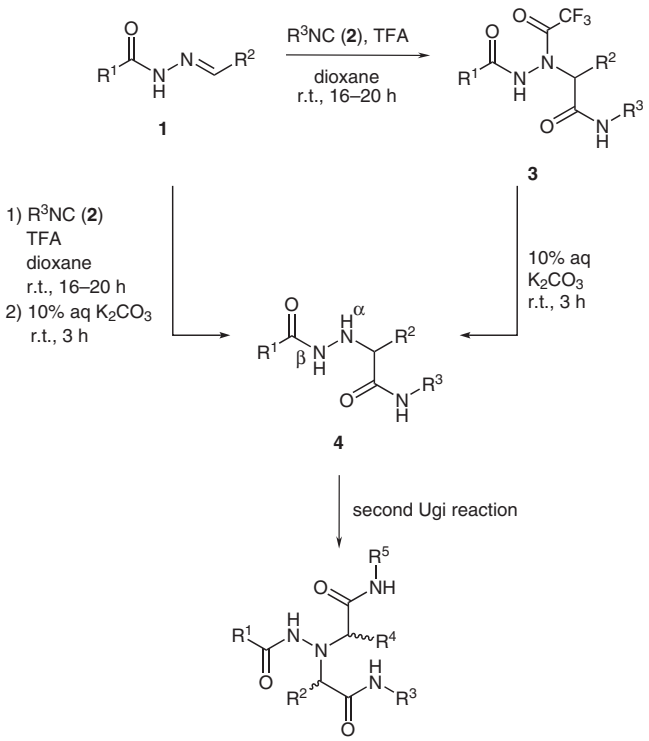
Abstract: A number of N^{α}-alkyl,N^{β}-acylhydrazines have been synthesized via the Ugi reaction of *N*-acylhydrazones with an isocyanide and trifluoroacetic acid. The trifluoroacetic acid acted as a 'silent partner' and becomes removed upon basic workup of the reaction. These compounds have been efficiently modified further via reductive alkylation to produce N^{α},N^{α}-dialkyl,N^{β}-acylhydrazines. The two groups of novel hydrazinopeptide motifs have been shown by simple ^{1}H NMR spectroscopic experiments to display two different secondary structure patterns. These observations were confirmed by X-ray crystallographic analysis. Combining the hydrazone and carboxylic acid moieties in one reaction precursor offers the opportunity for an 'intramolecular' hydrazino-Ugi reaction, which was also demonstrated.

Key words: multicomponent reactions, hydrazones, substituent effects, peptidomimetics, secondary structures

The four-component reaction of an amine, a carbonyl compound, a carboxylic acid, and an isocyanide, known as the Ugi reaction,[1] delivers medicinally relevant[2] dipeptoid compounds in a remarkably efficient, atom-economic manner, the only byproduct being water from the condensation reaction forming the initial imine.

The reaction has gone a long evolutionary path since its discovery in 1959. A common theme in the development of novel isocyanide-based multicomponent reactions has been the replacement of one or more reaction partners in the 'Ugi foursome' with various surrogates. The most-developed strategy to date is the use of noncarboxylate nucleophiles to intercept the isocyanide interacting with the iminium species.[3] However, finding workable surrogates for the iminium component, the formation of which from the amine and carbonyl compounds under acidic catalysis triggers the Ugi reaction, appears more challenging as one finds only a handful of examples of this approach in the literature. Among the examples reported are the successful uses of various hydrazones[4] and oximes,[5] and more recently published methodologies involving *N*-acylazinium[6] and *N*-fluoropyridinium[7] salts as less obvious substitutes for the iminium reaction partner for an isocyanide.

We have recently modified the early methodology by Ugi and Bodesheim[4b] and employed trifluoroacetic acid as the carboxylic acid partner in the reaction of hydrazones **1** with isocyanides **2**. The initially formed 'hydrazino-Ugi' products **3** contain a labile trifluoroacetyl group that is easily removed by mild basic hydrolysis of the isolated products **3** or in situ. The resulting N^{α}-alkyl,N^{β}-acylhydrazines **4** represent hydrazinopeptide-like[8] structures and also contain a reactive α-nitrogen atom that can be used for further derivatization of the newly formed hydrazinopeptide backbone, e.g. through a second Ugi reaction (Scheme 1).[9] Hydrazinopeptides represent a less-studied class of peptidomimetics useful in preparing more proteolytically stable[10] analogues of natural bioactive peptides with preserved biological activity.[11] In addition, these motifs are quite appealing as they are known[12] to adopt a unique secondary structure, a 'hydrazino turn', owing to the bifurcated hydrogen bond involving the sp^3-hydridized α-nitrogen atom (Figure 1), in a similar manner to the natural peptide β-turn.



Scheme 1 Synthesis of N^{α}-alkyl,N^{β}-acylhydrazines **4** for use as starting materials in a second Ugi reaction

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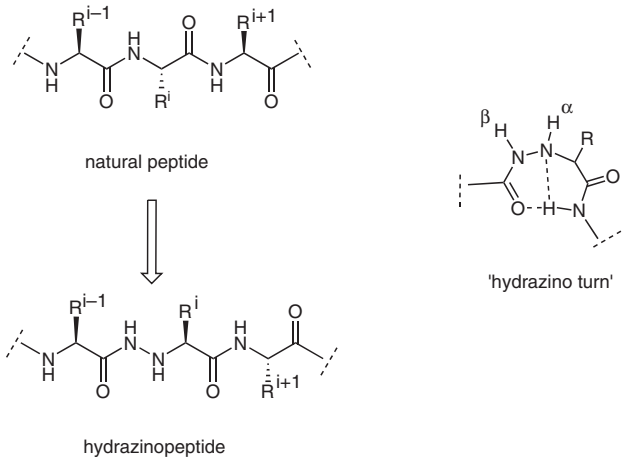


Figure 1 Hydrazinopeptides and their hydrazino turn conformation

Herein, we report on the synthesis of an extended set of hydrazinopeptide units **4** and their modification at the α-nitrogen atom via reductive alkylation. The propensity of such structures to yield intriguing secondary structure patterns also prompted us to investigate the latter modified products using NMR spectroscopy and X-ray crystallography to reveal marked regularity that we disclose in this paper.

Thirteen hydrazinopeptide motifs **4a**–**m** were synthesized according to the above one-pot procedure, with the mild basic workup of the reaction mixture leading to the clean and complete removal of the trifluoroacetyl group (Scheme 1). The isolated yields were moderate to good (Table 1) and the identities of the compounds were consistent with their characterization data. Interestingly, compounds **4j** and **4k** are essentially the racemic *tert*-butoxycarbonyl-protected hydrazine analogues of valine amides.[13]

It should be noted that (trifluoroacetyl)hydrazines **3** are, in principle, stable to isolation, as demonstrated by the isolation and characterization of a representative compound, derivative **3i** (en route to **4i**).

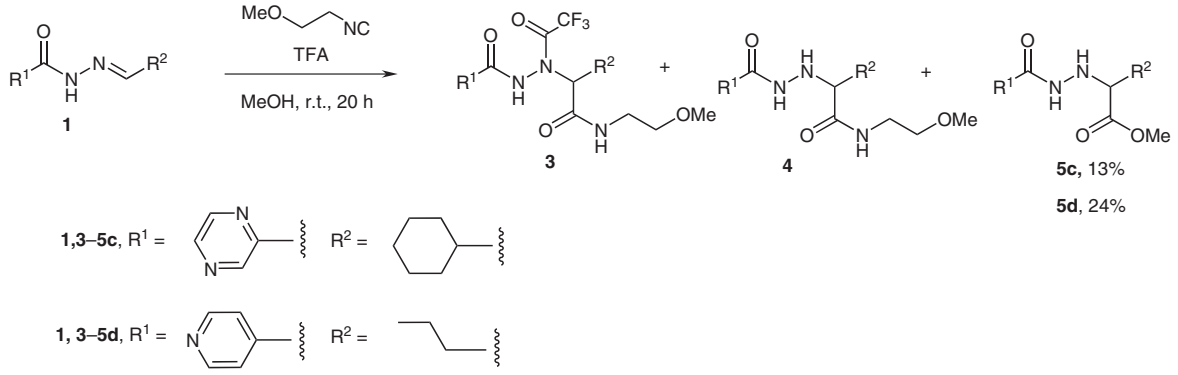
The choice of dioxane as the medium for the hydrazino-Ugi reaction is important; the same reaction carried out in methanol, often the solvent of choice for a number of Ugi reactions,[14] leads to a more-complex mixture of products as shown for the two reactions presented in Scheme 2. Without the basic workup, the reaction mixtures were analyzed by LC-MS to reveal the presence of equal amounts of the expected hydrazino-Ugi product **3** and de-trifluoroacetylated product **4**. In addition, substantial amounts of methyl esters **5** were present; these latter byproducts were isolated chromatographically in the yields indicated and characterized. The formation of products **4** and **5** in methanol can be rationalized by possible interference of the nucleophilic solvent molecule during the course of the reaction, as indicated in Scheme 3.

If two reaction partners for the Ugi process are combined within the structure of a single reactant, a ring-forming process can occur, as has been shown using various oxo- and formyl-substituted acids as substrates for a four-center, three-component Ugi reaction.[15] We designed a precursor, compound **6**, containing both the hydrazone and carboxylic acid moieties which was synthesized in four straightforward chemical operations and involved one purification. Analogous to the previously reported preparation of aza-β-lactams from α-hydrazino acids via the Ugi reaction,[16] compound **6** produced N-monoalkylated tetrahydropyridazine-3,6-dione **7** in good yield upon an

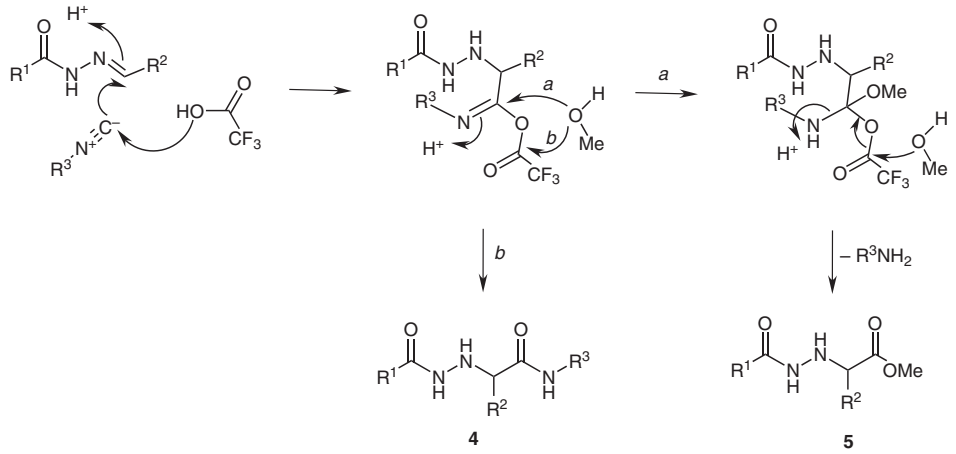
Table 1 Synthesis of N^{α}-Alkyl,N^{β}-acylhydrazines **4**[a]

Compound	R^1	R^2	R^3	Isolated yield (%)	LC-MS (*m*/*z*) [M + H^+]
4a	pyridin-4-yl	*c*-Hex	$MeOCH_2CH_2$	52	335
4b	4-$MeC_6H_4CH_2$	*c*-Hex	$MeOCH_2CH_2$	68	362
4c	pyrazin-2-yl	*c*-Hex	$MeOCH_2CH_2$	54	336
4d	pyridin-4-yl	Pr	$MeOCH_2CH_2$	58	295
4e	pyridin-4-yl	Pr	Bn	44	327
4f	pyrazin-2-yl	*c*-Hex	Bn	44	368
4g	pyridin-4-yl	*c*-Hex	Bn	48	367
4h	4-$MeC_6H_4CH_2$	Et	*c*-Hex	78	332
4i	4-$MeOC_6H_4OCH_2$	*i*-Bu	*t*-Bu	64	366
4j	*t*-BuO	*i*-Pr	*t*-Bu	84	288
4k	*t*-BuO	*i*-Pr	4-$MeOC_6H_4CH_2$	84	352
4l	Me	*c*-Hex	2-$MeOC_6H_4CH_2$	77	334
4m	Ph	*c*-Hex	$MeOCH_2CH_2$	59	334

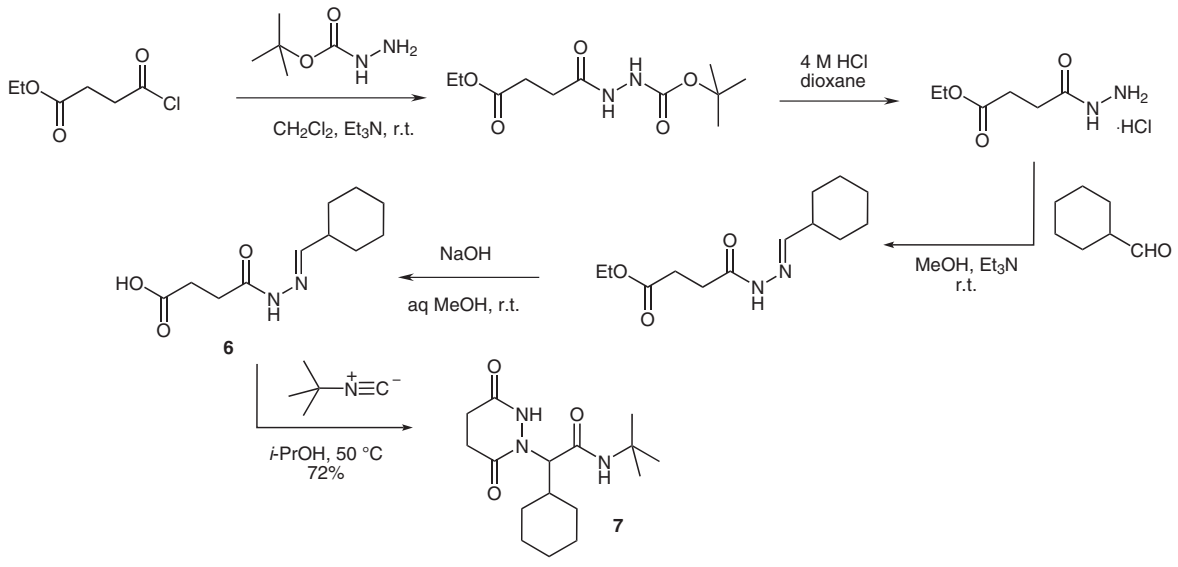
[a] See Scheme 1 for the corresponding reaction conditions and structures.



Scheme 2 Hydrazino-Ugi reaction in methanol



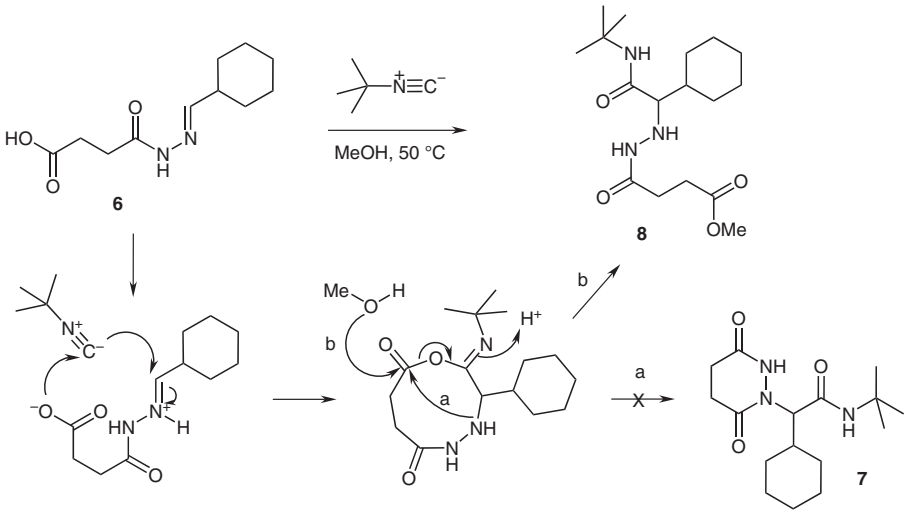
Scheme 3 Possible mechanistic rationale for the formation of byproducts **4** and **5** during the hydrazino-Ugi reaction in methanol



Scheme 4 Preparation of hydrazone **6** and its intramolecular hydrazino-Ugi reaction

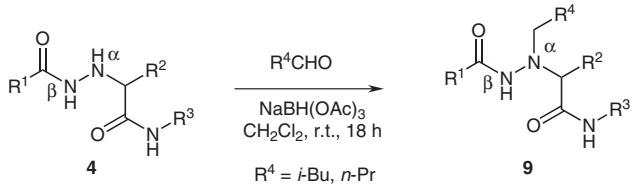
'intramolecular' Ugi reaction with *tert*-butyl isocyanide in isopropyl alcohol (Scheme 4). Notably, when the same reaction was performed in methanol, methyl ester **8** was identified by LC-MS as the main reaction product, though we failed to isolate it from the reaction mixture. Its formation can be rationalized, again, by the interference of methanol, which is more nucleophilic than isopropyl alcohol, during the course of the intramolecular Ugi reaction (Scheme 5).

The α-nitrogen atom of compounds **4** is a potential reactive center and it can be used for the introduction of further diverse functionalities off the hydrazine moiety, as



Scheme 5 Mechanistic rationale for the formation of methyl ester **8** upon reaction of hydrazone **6** with *tert*-butyl isocyanide in methanol

was demonstrated by its participation in the Ugi reaction (Scheme 1).[9] Therefore, we explored its reactivity in reductive alkylation reactions. Although we found reductive alkylation was not feasible with aromatic or heteroaromatic aldehydes, using a range of solvents and temperatures and with various reductants, N^{α},N^{α}-dialkyl,N^{β}-acylhydrazines **9a–k** were successfully prepared in good to excellent yields using isovaleraldehyde and butyraldehyde (Scheme 6 and Table 2).



Scheme 6 Synthesis of N^{α},N^{α}-dialkyl,N^{β}-acylhydrazines **9** via reductive alkylation

Having prepared two sets of hydrazinopeptide fragments, compounds **4** and **9**, we proceeded to study their secondary structures. We compared changes in the ^{1}H NMR

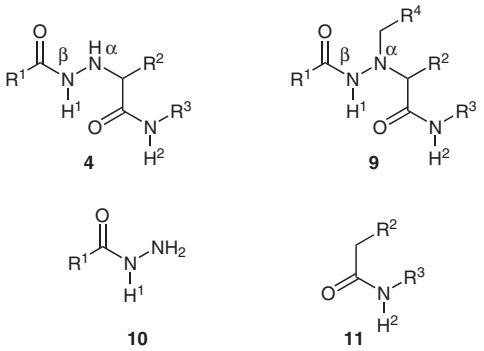


Figure 2 Structures of units **4** and **9** and the reference fragments for the ^{1}H NMR spectroscopic study

Table 2 Synthesis of N^{α},N^{α}-Dialkyl,N^{β}-acylhydrazines **9**[a]

Compound	R^1	R^2	R^3	R^4	Isolated yield (%)	LC-MS (*m*/*z*) [M + H$^+$]
9a	pyridin-4-yl	*c*-Hex	$MeOCH_2CH_2$	*i*-Bu	62	405
9b	4-$MeC_6H_4CH_2$	*c*-Hex	$MeOCH_2CH_2$	*i*-Bu	85	432
9c	pyrazin-2-yl	*c*-Hex	$MeOCH_2CH_2$	Pr	58	392
9d	pyridin-4-yl	Pr	$MeOCH_2CH_2$	*i*-Bu	64	365
9e	pyridin-4-yl	Pr	$MeOCH_2CH_2$	Pr	62	351
9f	pyrazin-2-yl	*c*-Hex	Bn	*i*-Bu	74	438
9g	pyrazin-2-yl	*c*-Hex	Bn	Pr	72	424
9h	pyrazin-4-yl	*c*-Hex	Bn	*i*-Bu	74	438
9i	pyridin-4-yl	*c*-Hex	Bn	Pr	68	423
9j	pyridin-4-yl	Pr	Bn	*i*-Bu	80	397
9k	pyridin-4-yl	Pr	Bn	Pr	59	383

[a] See Scheme 6 for the corresponding reaction conditions and structures.

spectroscopic chemical shifts of the protons in **4** and **9** suspected of participation in intramolecular hydrogen bonding with the same changes in reference fragments **10** and **11** (Figure 2),[17] in which no such bonding is possible. Upon solvent change from deuterated dimethylsulfoxide (DMSO-d_6) to chloroform-*d* ($CDCl_3$), one can pinpoint those protons that are indeed involved in the intramolecular hydrogen bond.[18]

Indeed, as can be seen from Table 3, using DMSO-d_6 as a solvent capable of accepting a hydrogen bond from the solute causes the downfield shift of the acidic, amide-type protons H^1 and H^2 in reference fragments **10** and **11**, respectively (Figure 2).[19] Roughly the same downfield shift of the ^{1}H NMR spectroscopic signals was observed for the N^{β}-H^1 protons of compounds **4** compared to those of **10**, but this was not the case for the terminal amide protons H^2, which were significantly less sensitive to the solvent change than the corresponding H^2 protons in **11**. This can be explained only by the involvement of H^2 in the terminal amide of compounds **4** in an intramolecular hydrogen bond. The situation reverses for compounds **9**, and this observation prompted us to conclude that the introduction of the second alkyl group at the α-nitrogen makes an alternative hydrogen bonding pattern, involving H^1 not H^2 this

Table 3 Changes in the ^{1}H NMR Spectroscopic Chemical Shift Values of the Amide Nitrogen-Bound Protons of Hydrazinopeptide Units **4** and **9** Compared with Those of Reference Fragments **10** and **11** upon Solvent Change[a,b]

Compound	Δδ (DMSO-d_6 → $CDCl_3$) for H^1			Δδ (DMSO-d_6 → $CDCl_3$) for H^2		
	4(**9**)	**10**	Difference [$\Delta\delta_{\mathbf{10}} - \Delta\delta_{\mathbf{4(9)}}$]	**4**(**9**)	**11**	Difference [$\Delta\delta_{\mathbf{11}} - \Delta\delta_{\mathbf{4(9)}}$]
4a	2.43	2.47	0.04	0.73	2.00	1.27
4b	2.21	2.39	0.18	0.95	2.00	1.05
4c	1.56	1.29	–0.27	0.49	2.00	1.51
4d	2.40	2.47	0.07	0.74	2.00	1.26
4e	1.77	2.47	0.70	0.99	2.49	1.50
4f	0.87	1.29	0.42	0.88	2.69	1.81
4g	2.17	2.47	0.30	0.99	2.69	1.70
4h	2.53	2.39	–0.14	1.02	2.09	1.07
4i	1.08	1.49	0.41	0.50	1.99	1.49
4j	2.09	1.79	–0.30	0.51	2.04	1.53
4k	2.12	1.79	–0.33	0.71	2.30	1.59
4l	1.65	1.51	–0.14	0.71	2.09	1.38
4m	1.50	2.09	0.59	0.58	2.00	1.42
9a	0.24	2.47	2.23	2.48	2.00	–0.48
9b	0.89	2.39	1.50	1.98	2.00	0.02
9c	0.05	1.29	1.24	1.82	2.00	0.18
9d	0.42	2.47	2.05	1.81	2.00	0.19
9e	0.40	2.47	2.07	1.73	2.00	0.27
9f	0.28	1.29	1.01	2.28	2.69	0.41
9g	0.10	1.29	1.19	2.29	2.69	0.40
9h	–0.02	2.47	2.49	2.39	2.69	0.30
9i	0.08	2.47	2.39	2.38	2.69	0.31
9j	0.24	2.47	2.23	2.17	2.49	0.32
9k	0.54	2.47	1.93	1.89	2.49	0.60

[a] The ^{1}H NMR spectra of samples containing compounds **4**, **9**, **10**, or **11** (15 μmol) in the solvent (0.6 mL) were recorded at a temperature of 273 K.
[b] See Figure 2 and Tables 1 and 2 for the corresponding structures.

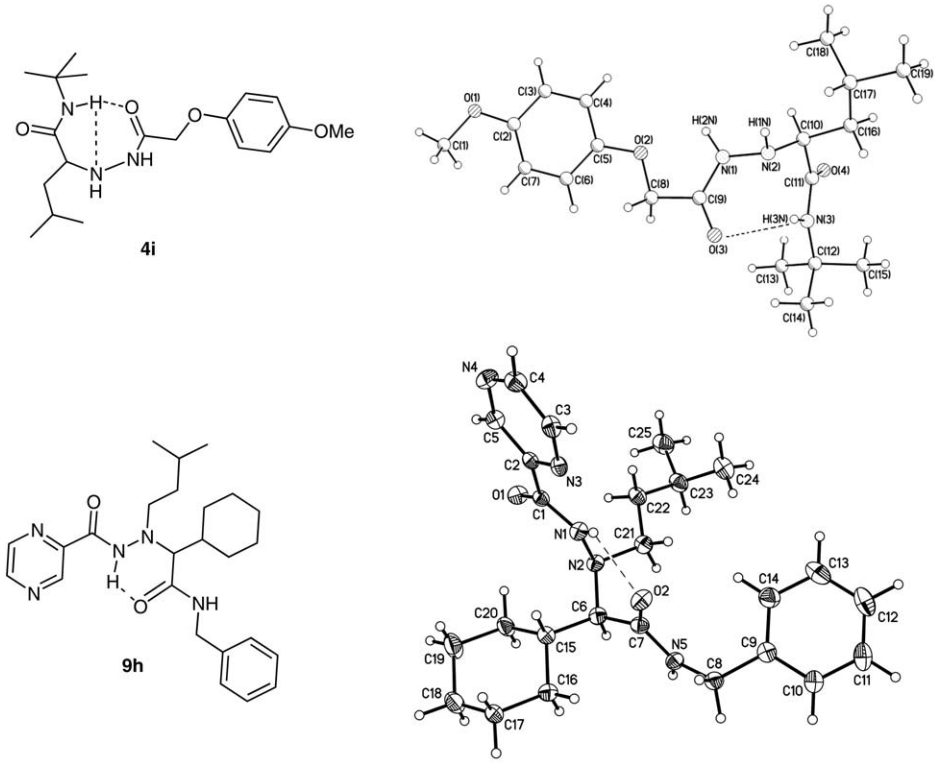


Figure 3 Markedly different secondary structure patterns observed for compounds **4i** and **9h** confirmed by X-ray crystallographic analysis

time, more favorable. To our delight, the above conclusions were fully confirmed by the single-crystal X-ray analysis[20] of compounds **4i** and **9h**, representative of each set of the hydrazinopeptide units studied. Indeed, compound **4i** adopted the typical hydrazino turn secondary structure, while for the N^{α},N^{α}-dialkyl derivative **9h** this structural bias was not observed (Figure 3).[21] These observations are expected to be of importance in the selection of appropriate hydrazinopeptide inserts for natural peptide analogue design.

In conclusion, we have reported on the application of the Ugi reaction of hydrazones toward the simple and efficient preparation of racemic hydrazinopeptide units **4**. An intramolecular version of the same reaction was developed using hydrazone **6** containing a carboxylic acid side chain. The modification of units **4** at the α-nitrogen via reductive alkylation with aliphatic aldehydes produced compounds **9**. As demonstrated by simple ^{1}H NMR spectroscopic experiments in solvents with different hydrogen bond accepting abilities and confirmed by X-ray crystallographic analysis, compounds **4** and **9** consistently displayed two different secondary structure patterns.

All reactions were run in oven-dried glassware under an atmosphere of nitrogen. Melting points were measured with a Buchi B-520 melting point apparatus and are uncorrected. Analytical TLC was carried out on EM Separations Technology F_{254} silica gel plates; compounds were visualized with short-wavelength UV light. ^{1}H and ^{13}C 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 SPD-10A UV-vis (254 nm) and Sedex 75 ELSD detectors. Elemental analyses were obtained at the Research Institute for Chemical Crop Protection, Moscow, using a Carlo Erba Strumentazione 1106 analyzer. All solvents and reagents were obtained from commercial sources and were used without purification.

2-Cyclohexyl-2-(2-isonicotinoylhydrazino)-*N*-(2-methoxyethyl)acetamide (4a); Typical Procedure

N′-(Cyclohexylmethylene)isonicotinohydrazide (600 mg, 2.6 mmol) was dissolved in anhyd dioxane (10 mL) and then 2-methoxyethyl isocyanide (320 mL, 3.9 mmol) was added, followed by TFA (193 mL, 2.6 mmol). The mixture was stirred at r.t. overnight and then was diluted with 10% aq K_2CO_3 (25 mL) and stirred for 3 h. The solution was extracted with $CHCl_3$ (3 × 50 mL), and the extracts were dried (anhyd $MgSO_4$), filtered, and concentrated under reduced pressure. Chromatography on silica gel (10–65% EtOAc in hexanes) provided **4a** as a white solid. Yield: 450 mg (52%); mp 132–134 °C.

^{1}H NMR (DMSO-d_6, 300 K): δ = 0.98–1.34 (m, 5 H), 1.50–1.85 (m, 6 H), 2.93 (d, *J* = 2.8 Hz, 1 H), 3.14–3.43 (m, 7 H), 5.24 (br s, 1 H), 7.62 (m, 3 H), 8.66 (d, *J* = 1.8 Hz, 2 H), 9.77 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 300 K): δ = 25.8, 28.6, 28.9, 38.1, 38.6, 57.8, 68.6, 70.5, 121.1, 140.2, 150.1, 163.5, 171.4.

Anal. Calcd for $C_{17}H_{26}N_4O_3$: C, 61.06; H, 7.84; N, 16.75. Found: C, 61.16; H, 7.92; N, 16.77.

2-Cyclohexyl-*N*-(2-methoxyethyl)-2-{2-[2-(4-tolyl)acetyl]hydrazino}acetamide (4b)

White solid; mp 108–110 °C.

^{1}H NMR (DMSO-d_6, 300 K): δ = 0.99–1.19 (m, 5 H), 1.48–1.71 (m, 6 H), 2.25 (s, 3 H), 3.03 (d, *J* = 2.9 Hz, 1 H), 3.10–3.27 (m, 9 H), 4.98 (br s, 1 H), 7.08 (m, 4 H), 7.86 (br s, 1 H), 9.33 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 300 K): δ = 20.5, 25.8, 28.4, 28.9, 38.0, 39.3, 57.8, 69.0, 70.4, 128.7, 132.9, 135.3, 169.2, 171.4.

Anal. Calcd for $C_{20}H_{31}N_3O_3$: C, 66.45; H, 8.64; N, 11.62. Found: C, 66.51; H, 8.67; N, 11.77.

2-Cyclohexyl-*N*-(2-methoxyethyl)-2-[2-(pyrazin-2-ylcarbonyl)hydrazino]acetamide (4c)
White solid; mp 108–110 °C.

^{1}H NMR (DMSO-d_6, 300 K): δ = 1.06–1.30 (m, 5 H), 1.53–1.85 (m, 6 H), 3.21 (s, 3 H), 3.22–3.40 (m, 5 H), 5.23 (br s, 1 H), 7.73 (br s, 1 H), 8.61 (br s, 1 H), 8.81 (br s, 1 H), 9.12 (br s, 1 H), 9.67 (br s, 1 H).

^{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.

Anal. Calcd for $C_{16}H_{25}N_5O_3$: C, 57.30; H, 7.51; N, 20.88. Found: C, 57.39; H, 7.64; N, 21.06.

2-(2-Isonicotinoylhydrazino)-*N*-(2-methoxyethyl)pentanamide (4d)
White solid; mp 123–125 °C.

^{1}H NMR (DMSO-d_6, 300 K): δ = 0.90 (t, *J* = 2.3 Hz, 3 H), 1.40 (m, 2 H), 1.58 (m, 2 H), 2.98 (br s, 1 H), 3.18–3.49 (m, 7 H), 5.46 (br s, 1 H), 7.65 (d, *J* = 1.8 Hz, 2 H), 7.78 (br s, 1 H), 8.68 (d, *J* = 1.8 Hz, 2 H), 9.83 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 300 K): δ = 13.9, 18.4, 33.1, 26.4, 57.8, 63.3, 70.5, 121.2, 140.4, 149.9, 163.7, 172.2.

Anal. Calcd for $C_{14}H_{22}N_4O_3$: C, 57.13; H, 7.53; N, 19.03. Found: C, 57.33; H, 7.50; N, 18.96.

***N*-Benzyl-2-(2-isonicotinoylhydrazino)pentanamide (4e)**
Beige solid; mp 147–149 °C.

^{1}H NMR (DMSO-d_6, 300 K): δ = 0.91 (t, *J* = 6.7 Hz, 3 H), 1.42 (m, 2 H), 1.63 (m, 2 H), 3.52 (t, *J* = 3.5 Hz, 1 H), 4.32 (ddd, J_1 = 13.9 Hz, J_2 = 5.2 Hz, J_3 = 4.0 Hz, 2 H), 5.23 (br s, 1 H), 7.15–7.30 (m, 5 H), 7.63 (d, *J* = 3.4 Hz, 2 H), 8.15 (br s, 1 H), 8.68 (d, *J* = 3.4 Hz, 2 H), 9.89 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 300 K): δ = 13.9, 18.5, 33.9, 14.9, 63.3, 121.0, 126.6, 127.0, 128.1, 139.3, 140.0, 150.0, 163.7, 172.2.

Anal. Calcd for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.16. Found: C, 66.07; H, 6.88; N, 17.27.

***N*-Benzyl-2-cyclohexyl-2-[2-(pyrazin-2-ylcarbonyl)hydrazino]acetamide (4f)**
Gray solid; mp 163–166 °C.

^{1}H NMR (DMSO-d_6, 300 K): δ = 1.03–1.33 (m, 5 H), 1.55–1.88 (m, 6 H), 3.41 (d, *J* = 5.1 Hz, 1 H), 4.32 (ddd, J_1 = 18.7 Hz, J_2 = 6.0 Hz, J_3 = 5.2 Hz, 2 H), 5.29 (br s, 1 H), 7.12–7.28 (m, 5 H), 8.19 (br s, 1 H), 8.65 (d, *J* = 1.8 Hz, 1 H), 8.82 (d, *J* = 1.8 Hz, 1 H), 9.10 (s, 1 H), 9.79 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 300 K): δ = 25.8, 25.9, 28.6, 29.1, 41.9, 68.0, 126.5, 127.1, 127.9, 139.4, 143.2, 143.3, 144.3, 147.5, 160.9, 171.7.

Anal. Calcd for $C_{20}H_{25}N_5O_2$: C, 65.37; H, 6.86; N, 19.06. Found: C, 65.33; H, 6.91; N, 18.92.

***N*-Benzyl-2-cyclohexyl-2-(2-isonicotinoylhydrazino)acetamide (4g)**
Gray solid; mp 115–116 °C.

^{1}H NMR (DMSO-d_6, 300 K): δ = 1.09–1.30 (m, 5 H), 1.55–1.87 (m, 6 H), 3.34 (d, *J* = 3.9 Hz, 1 H), 4.32 (ddd, J_1 = 22.1 Hz, J_2 = 6.6 Hz, J_3 = 5.8 Hz, 2 H), 5.30 (br s, 1 H), 7.24 (m, 5 H), 7.62 (d, *J* = 2.6 Hz, 2 H), 8.10 (br s, 1 H), 8.67 (d, *J* = 2.6 Hz, 2 H), 9.84 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 300 K): δ = 25.7, 27.4, 28.9, 29.1, 41.9, 68.6, 121.1, 126.6, 127.1, 128.0, 139.4, 140.0, 150.1, 163.3, 171.5.

Anal. Calcd for $C_{21}H_{26}N_4O_2$: C, 68.83; H, 7.15; N, 15.29. Found: C, 68.80; H, 7.25; N, 15.38.

***N*-Cyclohexyl-2-{2-[2-(4-tolyl)acetyl]hydrazino}butanamide (4h)**
White solid; mp 150–152 °C.

^{1}H NMR (DMSO-d_6, 300 K): δ = 0.83 (t, *J* = 7.5 Hz, 3 H), 0.89–1.28 (m, 5 H), 1.44–1.70 (m, 7 H), 2.25 (s, 3 H), 3.13 (m, 1 H), 3.35 (s, 2 H), 3.44 (m, 1 H), 5.00 (br s, 1 H), 7.06 (d, *J* = 8.2 Hz, 2 H), 7.10 (d, *J* = 8.2 Hz, 2 H), 7.76 (d, *J* = 8.0 Hz, 1 H), 9.34 (d, *J* = 3.3 Hz, 1 H).

^{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.

Anal. Calcd for $C_{19}H_{29}N_3O_2$: C, 68.85; H, 8.82; N, 12.68. Found: C, 68.95; H, 8.91; N, 12.74.

***N*-(*tert*-Butyl)-2-{2-[2-(4-methoxyphenoxy)acetyl]hydrazino}-4-methylpentanamide (4i)**
White solid; mp 173 °C (dec.).

^{1}H NMR (DMSO-d_6, 300 K): δ = 0.90 (d, *J* = 5.9 Hz, 6 H), 1.28 (s, 9 H), 1.40 (m, 2 H), 1.80 (m, 1 H), 3.30 (t, *J* = 6.4 Hz, 1 H), 3.72 (s, 3 H), 4.44 (br s, 2 H), 4.85 (br s, 1 H), 6.86 (d, *J* = 9.3 Hz, 2 H), 6.90 (d, *J* = 9.3 Hz, 2 H), 7.32 (br s, 1 H), 9.02 (br s, 1 H).

^{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.

Anal. Calcd for $C_{19}H_{31}N_3O_4$: C, 62.44; H, 8.55; N, 11.50. Found: C, 62.49; H, 8.64; N, 11.30.

***N*-(*tert*-Butyl)-2-{2-[2-(4-methoxyphenoxy)acetyl]-1-(2,2,2-trifluoroacetyl)hydrazino}-4-methylpentanamide (3i)**
The compound was prepared according to the same procedure as for de-trifluoroacetylated product **4i**, but the basic workup was omitted.

Off-white solid; mp 148 °C (dec.).

^{1}H NMR (DMSO-d_6, 363 K): δ = 0.88 (d, *J* = 6.4 Hz, 6 H), 1.27 (s, 9 H), 1.47–1.74 (m, 3 H), 3.72 (s, 3 H), 4.48 (t, *J* = 7.1 Hz, 1 H), 4.64 (s, 2 H), 6.87 (d, *J* = 9.2 Hz, 2 H), 6.94 (d, *J* = 9.2 Hz, 2 H), 7.75 (br s, 1 H), 10.4 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 363 K): δ = 22.1, 22.3, 24.2, 28.2, 37.1, 50.4, 55.8, 62.1, 67.0, 115.0, 115.5 (*J* = 288.5 Hz), 116.2, 152.0, 154.5, 157.4 (*J* = 35.8 Hz), 167.8, 169.0.

Anal. Calcd for $C_{21}H_{30}F_3N_3O_5$: C, 54.66; H, 6.55; N, 9.11. Found C, 54.60; H, 6.43; N, 8.97.

***tert*-Butyl 2-[1-(*tert*-Butylcarbamoyl)-2-methylpropyl]hydrazine-1-carboxylate (4j)**
White solid; mp 172–174 °C.

^{1}H NMR (DMSO-d_6, 300 K): δ = 0.84 (d, *J* = 7.0 Hz, 3 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 1.25 (s, 9 H), 1.39 (s, 9 H), 1.86 (m, 1 H), 2.92 (d, *J* = 3.8 Hz, 1 H), 4.73 (s, 1 H), 7.63 (br s, 1 H), 8.20 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 300 K): δ = 18.2, 18.9, 28.2, 28.3, 29.5, 49.6, 70.1, 78.3, 156.2, 170.8.

Anal. Calcd for $C_{14}H_{29}N_3O_3$: C, 58.51; H, 10.17; N, 14.62. Found: C, 58.43; H, 10.07; N, 14.77.

***tert*-Butyl 2-{1-[(4-Methoxybenzyl)carbamoyl]-2-methylpropyl}hydrazine-1-carboxylate (4k)**
White solid; mp 180 °C (dec.).

^{1}H NMR (DMSO-d_6, 300 K): δ = 0.92 (d, *J* = 6.8 Hz, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 1.40 (s, 9 H), 1.95 (m, 1 H), 3.14 (br s, 1 H), 3.75 (s, 3 H), 4.25 (ddd, J_1 = 36.5 Hz, J_2 = 5.0 Hz, J_3 = 5.3 Hz, 2 H), 4.50

(s, 1 H), 6.86 (d, *J* = 8.2 Hz, 2 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 8.11 (br s, 1 H), 8.22 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 300 K): δ = 18.3, 18.9, 28.2, 29.7, 41.7, 55.2, 69.8, 78.7, 113.9, 128.5, 131.6, 156.2, 158.4, 171.6.

Anal. Calcd for $C_{18}H_{29}N_3O_4$: C, 61.52; H, 8.32; N, 11.96. Found C, 61.57; H, 8.02; N, 12.13.

2-(2-Acetylhydrazino)-2-cyclohexyl-*N*-(2-methoxybenzyl)acetamide (4l)

White solid; mp 166–168 °C.

^{1}H NMR (DMSO-d_6, 300 K): δ = 1.03–1.29 (m, 5 H), 1.53–1.92 (m, 9 H), 3.14 (d, *J* = 1.6 Hz, 1 H), 3.81 (s, 3 H), 4.30 (m, 2 H), 4.87 (s, 1 H), 6.88 (t, *J* = 6.4 Hz, 1 H), 6.96 (d, *J* = 8.2 Hz, 1 H), 7.20 (m, 2 H), 7.89 (br s, 1 H), 8.93 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 300 K): δ = 20.6, 25.9, 26.0, 28.8, 29.2, 37.4, 55.6, 69.5, 111.0, 120.2, 127.2, 128.0, 128.3, 157.1, 168.2, 171.7.

Anal. Calcd for $C_{18}H_{27}N_3O_3$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.86; H, 8.26; N, 12.80.

2-(2-Benzoylhydrazino)-2-cyclohexyl-*N*-(2-methoxyethyl)acetamide (4m)

Yellowish solid; mp 144–145 °C.

^{1}H NMR (DMSO-d_6, 300 K): δ = 1.07–1.30 (m, 5 H), 1.56–1.84 (m, 6 H), 2.97–3.45 (m, 8 H), 5.20 (br s, 1 H), 7.38–7.54 (m, 3 H), 7.69 (br s, 1 H), 7.77 (d, *J* = 7.0 Hz, 2 H), 9.53 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 300 K): δ = 25.9, 28.9, 29.2, 38.3, 39.7, 57.8, 69.2, 70.8, 127.1, 128.2, 131.1, 133.6, 165.8, 171.6.

Anal. Calcd for $C_{18}H_{27}N_3O_3$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.84; H, 8.10; N, 12.46.

Methyl 2-Cyclohexyl-2-[2-(pyrazin-2-ylcarbonyl)hydrazino]acetate (5c)

The compound was prepared using the same procedure as for compound **4c** except MeOH (10 mL) was used as the solvent. The title compound was isolated from the mixture by column chromatography on silica gel (35–70% EtOAc in hexanes) as a sticky colorless solid. Yield: 0.21 g (13%).

^{1}H NMR (DMSO-d_6, 300 K): δ = 1.06–1.32 (m, 5 H), 1.57–1.82 (m, 5 H), 1.84 (m, 1 H), 3.26 (br s, 1 H), 3.51 (d, *J* = 6.2 Hz, 1 H), 3.66 (s, 3 H), 8.66 (s, 1 H), 8.80 (s, 1 H), 9.11 (s, 1 H), 9.85 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 300 K): δ = 25.5, 25.8, 28.9, 38.7, 51.4, 67.3, 143.2, 143.4, 144.3, 147.5, 160.6, 172.8.

LC-MS: *m*/*z* = 293 [M + H$^+$].

Anal. Calcd for $C_{14}H_{20}N_4O_3$: C, 57.52; H, 6.90; N, 19.16. Found: C, 57.68; H, 7.04; N, 19.36.

Methyl 2-(2-Isonicotinoylhydrazino)pentanoate (5d)

The compound was prepared using the same procedure as for compound **4d** except MeOH (10 mL) was used as the solvent. The title compound was isolated from the mixture by column chromatography on silica gel (35–50% EtOAc in hexanes) as a sticky colorless solid. Yield: 0.33 g (24%).

^{1}H NMR (DMSO-d_6, 300 K): δ = 0.91 (t, *J* = 7.3 Hz, 3 H), 1.40 (m, 2 H), 1.66 (q, *J* = 7.3 Hz, 2 H), 3.63 (t, *J* = 7.1 Hz, 1 H), 3.66 (s, 3 H), 4.95 (br s, 1 H), 7.70 (d, *J* = 4.9 Hz, 2 H), 8.70 (d, *J* = 4.9 Hz, 2 H), 10.00 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 300 K): δ = 13.6, 18.3, 32.3, 51.6, 62.0, 121.6, 141.1, 149.0, 163.3, 172.8.

LC-MS: m/z = 252 [M + H$^+$].

Anal. Calcd for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.50; H, 6.94; N, 16.67.

4-[2-(Cyclohexylmethylene)hydrazino]-4-oxobutanoic Acid (6)

tert-Butyl carbazate (1320 mg, 10 mmol) was dissolved in CH_2Cl_2 (50 mL) and the solution was cooled to 5 °C. Ethyl 4-chloro-4-oxobutanoate (2.15 g, 13 mmol) was added dropwise to maintain the temperature of the mixture below 10 °C. The mixture was warmed to r.t. and stirred for 1 h. Then, the mixture was washed with 10% aq Na_2CO_3 (100 mL) and H_2O (100 mL), dried (anhyd $MgSO_4$), and concentrated in vacuo. The residue was dissolved in dioxane (10 mL) and treated with 4 M HCl in dioxane (10 mL). The mixture was stirred at r.t. overnight and the resulting precipitate was collected by filtration and dissolved in MeOH (20 mL). Cyclohexanecarbaldehyde (1.2 mL, 10 mmol) and Et_3N (1.4 mL, 10 mmol) were added and the resulting mixture was stirred at r.t. for 2 h. Then, the solvent was removed in vacuo, the residue was dispersed in H_2O and collected by filtration, and the filter cake was washed with hexane (3 × 50 mL). The solid product was dissolved in MeOH (10 mL), and NaOH (400 mg, 10 mmol) in H_2O (5 mL) was added. The resulting mixture was stirred at r.t. for 3 h and the solvent was removed under reduced pressure. The residue was dissolved in H_2O (30 mL), the mixture was filtered, and the filtrate was carefully neutralized with 5% aq HCl (ca. 15 mL). The resulting precipitate was collected by filtration. Additional crystallization (MeOH) provided **6** as an amber solid. Yield: 720 mg (32%); mp 147–149 °C.

^{1}H NMR (DMSO-d_6, 363 K): δ = 1.19–1.42 (m, 5 H), 1.59–1.85 (m, 5 H), 2.21 (m, 1 H), 2.41–2.76 (m, 4 H), 5.17 (br s, 1 H), 7.31 (br s, 1 H), 10.28 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 363 K): δ = 24.8, 25.5, 28.3, 28.9, 39.7, 151.3, 172.1, 173.4.

***N*-*tert*-Butyl-2-cyclohexyl-2-(3,6-dioxotetrahydropyridazin-1-yl)acetamide (7)**

Compound **6** (340 mg, 1.5 mmol) was dissolved in *i*-PrOH (5 mL), and *t*-BuNC (200 mL, 2.1 mmol) was added. The mixture was stirred at 50 °C overnight. Then, the solvent was removed under reduced pressure and the product was purified by column chromatography on silica gel (0–2.5% MeOH in $CHCl_3$) to provide **7** as a white solid. Yield: 334 mg (72%); mp 129–131 °C.

^{1}H NMR (DMSO-d_6, 300 K): δ = 1.08–1.32 (m, 14 H), 1.59–1.79 (m, 6 H), 2.53–2.66 (m, 4 H), 3.16 (d, *J* = 7.2 Hz, 1 H), 5.46 (d, *J* = 1.5 Hz, 1 H), 7.58 (s, 1 H).

^{13}C NMR (DMSO-d_6, 300 K): δ = 25.8, 26.1, 28.2, 28.4, 28.9, 39.6, 49.8, 67.1, 95.5, 164.2, 170.0, 175.3.

LC-MS: *m*/*z* = 310 [M + H$^+$].

Anal. Calcd for $C_{16}H_{27}N_3O_3$: C, 56.44; H, 8.35; N, 11.52. Found: C, 56.11; H, 8.27; N, 11.48.

2-Cyclohexyl-2-[2-isonicotinoyl-1-(3-methylbutyl)hydrazino]-*N*-(2-methoxyethyl)acetamide (9a); Typical Procedure

Compound **4a** (335 mg, 1 mmol) was dissolved in CH_2Cl_2 (5 mL). Isovaleraldehyde (165 mL, 1.5 mmol) was added, followed by $NaBH(OAc)_3$ (380 mg, 2 mmol). The resulting mixture was stirred at r.t. overnight and then was diluted with CH_2Cl_2 (25 mL), washed with H_2O (3 × 25 mL), dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo to provide the crude product. The compound was purified by column chromatography on silica gel (0–5% MeOH in $CHCl_3$) to provide **9a** as a white solid. Yield: 250 mg (62%); mp 99–101 °C.

^{1}H NMR (DMSO-d_6, 363 K): δ = 0.88 (d, *J* = 6.6 Hz, 6 H), 0.96–1.20 (m, 5 H), 1.38 (m, 2 H), 1.46–1.82 (m, 6 H), 2.20 (m, 1 H), 2.73 (m, 2 H), 3.18 (d, *J* = 9.5 Hz, 1 H), 3.27 (s, 3 H), 3.33 (t, *J* = 5.2 Hz, 2 H), 3.41 (t, *J* = 5.2 Hz, 2 H), 7.60 (d, *J* = 5.4 Hz, 2 H), 8.10 (br s, 1 H), 8.71 (d, *J* = 5.4 Hz, 2 H), 9.40 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 363 K): δ = 22.3, 25.4, 26.1, 29.0, 29.9, 35.6, 37.2, 38.1, 54.3, 57.8, 70.6, 70.7, 120.6, 141.4, 150.3, 162.8, 172.3.

Anal. Calcd for $C_{22}H_{36}N_4O_3$: C, 65.32; H, 8.97; N, 13.85. Found: C, 65.40; H, 9.04; N, 13.90.

2-Cyclohexyl-*N*-(2-methoxyethyl)-2-{1-(3-methylbutyl)-2-[2-(4-tolyl)acetyl]hydrazino}acetamide (9b)
White solid; mp 126–128 °C.

^{1}H NMR (DMSO-d_6, 363 K): δ = 0.68–0.91 (m, 8 H), 0.93–1.69 (m, 11 H), 2.04 (m, 1 H), 2.25 (s, 3 H), 2.56 (m, 2 H), 2.94 (d, J = 9.5 Hz, 1 H), 3.17–3.41 (m, 9 H), 7.08 (d, J = 8.2 Hz, 2 H), 7.14 (d, J = 8.2 Hz, 2 H), 8.18 (br s, 1 H), 8.50 (s, 1 H).

^{13}C NMR (DMSO-d_6, 363 K): δ = 20.6, 22.4, 25.2, 26.2, 28.8, 29.8, 35.5, 36.6, 37.8, 41.1, 54.1, 57.8, 70.5, 71.0, 128.7, 128.8, 133.1, 135.4, 168.5, 172.1.

Anal. Calcd for $C_{25}H_{41}N_3O_2$: C, 69.57; H, 9.57; N, 9.74. Found: C, 69.66; H, 9.61; N, 9.88.

2-[1-Butyl-2-(pyrazin-2-ylcarbonyl)hydrazino]-2-cyclohexyl-*N*-(2-methoxyethyl)acetamide (9c)
Gray solid; mp 137–139 °C.

^{1}H NMR (DMSO-d_6, 363 K): δ = 0.88 (t, J = 6.6 Hz, 3 H), 0.94–1.18 (m, 5 H), 1.33–1.71 (m, 9 H), 2.25 (m, 1 H), 2.73 (m, 2 H), 3.18 (d, J = 9.5 Hz, 1 H), 3.27 (s, 3 H), 3.33 (t, J = 5.2 Hz, 2 H), 3.41 (t, J = 5.2 Hz, 2 H), 8.05 (br s, 1 H), 8.68 (s, 1 H), 8.82 (s, 1 H), 9.17 (s, 1 H), 10.14 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 363 K): δ = 13.7, 19.6, 25.2, 26.1, 28.8, 29.6, 36.7, 37.9, 56.2, 57.8, 69.7 70.6, 143.3, 143.4, 144.4, 147.7, 160.0, 172.6.

Anal. Calcd for $C_{20}H_{33}N_5O_3$: C, 61.36; H, 8.50; N, 17.89. Found: C, 61.43; H, 8.60; N, 17.95.

2-[2-Isonicotinoyl-1-(3-methylbutyl)hydrazino]-*N*-(2-methoxyethyl)pentanamide (9d)
Beige solid; mp 148 °C (dec.).

^{1}H NMR (DMSO-d_6, 363 K): δ = 0.86 (m, 9 H), 1.25–1.47 (m, 4 H), 1.50–1.79 (m, 3 H), 2.81 (m, 2 H), 3.26 (s, 3 H), 3.29 (m, 2 H), 3.35–3.47 (m, 3 H), 7.62 (d, J = 3.7 Hz, 2 H), 8.00 (br s, 1 H), 8.70 (d, J = 3.7 Hz, 2 H), 9.30 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 363 K): δ = 13.7, 18.8, 22.3, 25.3, 31.7, 36.0, 38.2, 39.2, 53.3, 57.7, 66.8, 70.6, 120.9, 141.2, 150.2, 163.9, 172.8.

Anal. Calcd for $C_{19}H_{32}N_4O_3$: C, 62.61; H, 8.85; N, 15.37. Found: C, 62.55; H, 8.92; N, 15.38.

2-(1-Butyl-2-isonicotinoylhydrazino)-*N*-(2-methoxyethyl)pentanamide (9e)
Yellow solid; mp 128–130 °C.

^{1}H NMR (DMSO-d_6, 363 K): δ = 0.86 (m, 6 H), 1.30–1.50 (m, 6 H), 1.60 (m, 2 H), 2.80 (m, 2 H), 3.21–3.24 (m, 5 H), 3.35–3.47 (m, 3 H), 7.63 (d, J = 3.8 Hz, 2 H), 7.97 (br s, 1 H), 8.71 (d, J = 3.8 Hz, 2 H), 9.30 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 363 K): δ = 13.5, 13.6, 18.8, 19.6, 29.1, 31.7, 38.2, 54.7, 57.8, 66.9, 70.6, 120.9, 141.2, 150.1, 163.9, 172.8.

Anal. Calcd for $C_{18}H_{30}N_4O_3$: C, 61.69; H, 8.63; N, 15.99. Found: C, 61.56; H, 8.71; N, 16.07.

***N*-Benzyl-2-cyclohexyl-2-[1-(3-methylbutyl)-2-(pyrazin-2-ylcarbonyl)hydrazino]acetamide (9f)**
Colorless foam; mp 118–120 °C.

^{1}H NMR (DMSO-d_6, 363 K): δ = 0.86 (dd, J_1 = 6.9 Hz, J_2 = 2.7 Hz, 6 H), 0.94–1.19 (m, 5 H), 1.27–1.78 (m, 8 H), 2.24 (m, 1 H), 2.78 (m, 2 H), 3.24 (d, J = 9.9 Hz, 1 H), 4.37 (ddd, J_1 = 19.2 Hz, J_2 = 5.6 Hz, J_3 = 5.6 Hz, 2 H), 7.20–7.35 (m, 5 H), 8.58 (br s, 1 H), 8.68 (s, 1 H), 8.83 (d, J = 1.9 Hz, 1 H), 9.17 (s, 1 H), 10.18 (s, 1 H).

^{13}C NMR (DMSO-d_6, 363 K): δ = 22.4, 25.3, 26.1, 29.2, 29.6, 35.6, 36.8, 41.8, 54.9, 69.6, 126.9, 127.4, 128.2, 139.0, 143.4, 143.4, 144.4, 147.7, 160.0, 172.5.

Anal. Calcd for $C_{25}H_{35}N_5O_2$: C, 68.62; H, 8.06; N, 16.00. Found: C, 68.70; H, 8.18; N, 15.77.

***N*-Benzyl-2-[1-butyl-2-(pyrazin-2-ylcarbonyl)hydrazino]-2-cyclohexylacetamide (9g)**
Gray solid; mp 129–131 °C.

^{1}H NMR (DMSO-d_6, 363 K): δ = 0.86 (t, J = 7.0 Hz, 3 H), 0.93–1.20 (m, 5 H), 1.28–1.72 (m, 9 H), 2.24 (m, 1 H), 2.75 (m, 2 H), 3.23 (d, J = 9.1 Hz, 1 H), 4.40 (ddd, J_1 = 9.6 Hz, J_2 = 4.8 Hz, J_3 = 4.8 Hz, 2 H), 7.18–7.37 (m, 5 H), 8.54 (br s, 1 H), 8.68 (s, 1 H), 8.83 (s, 1 H), 9.16 (s, 1 H), 10.15 (s, 1 H).

^{13}C NMR (DMSO-d_6, 363 K): δ = 13.7, 19.6, 25.2, 26.0, 28.8, 36.8, 41.8, 56.3, 69.7, 126.9, 127.4, 128.3, 139.0, 143.4, 144.4, 147.7, 160.0, 172.5.

Anal. Calcd for $C_{24}H_{33}N_5O_2$: C, 68.06; H, 7.85; N, 16.53. Found: C, 68.01; H, 7.73; N, 16.64.

***N*-Benzyl-2-cyclohexyl-2-[1-(3-methylbutyl)-2-(pyrazin-2-ylcarbonyl)hydrazino]acetamide (9h)**
White solid; mp 154–156 °C.

^{1}H NMR (DMSO-d_6, 363 K): δ = 0.86 (dd, J_1 = 6.9 Hz, J_2 = 2.7 Hz, 6 H), 0.94–1.19 (m, 5 H), 1.27–1.78 (m, 8 H), 2.24 (m, 1 H), 2.78 (m, 2 H), 3.24 (d, J = 9.9 Hz, 1 H), 4.37 (ddd, J_1 = 19.2 Hz, J_2 = 5.6 Hz, J_3 = 5.6 Hz, 2 H), 7.20–7.35 (m, 5 H), 8.58 (br s, 1 H), 8.68 (s, 1 H), 8.83 (d, J = 1.9 Hz, 1 H), 9.17 (s, 1 H), 10.18 (s, 1 H).

^{13}C NMR (DMSO-d_6, 363 K): δ = 22.4, 25.3, 26.1, 29.2, 29.6, 35.6, 36.8, 41.8, 54.9, 69.6, 126.9, 127.4, 128.2, 139.0, 143.4, 143.4, 144.4, 147.7, 160.0, 172.5.

Anal. Calcd for $C_{25}H_{35}N_5O_2$: C, 68.62; H, 8.06; N, 16.00. Found: C, 68.71; H, 8.11; N, 15.93.

***N*-Benzyl-2-(1-butyl-2-isonicotinoylhydrazino)-2-cyclohexylacetamide (9i)**
White solid; mp 157 °C (dec.).

^{1}H NMR (DMSO-d_6, 363 K): δ = 0.87 (t, J = 7.0 Hz, 3 H), 0.96–1.22 (m, 5 H), 1.34–1.76 (m, 9 H), 2.20 (m, 1 H), 2.80 (m, 2 H), 3.24 (d, J = 9.2 Hz, 1 H), 4.40 (ddd, J_1 = 7.0 Hz, J_2 = 5.5 Hz, J_3 = 5.5 Hz, 2 H), 7.20–7.34 (m, 5 H), 7.63 (d, J = 7.3 Hz, 2 H), 8.50 (br s, 1 H), 8.73 (d, J = 4.8 Hz, 2 H), 9.40 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 363 K): δ = 13.5, 19.5, 25.3, 26.0, 29.0, 29.9, 37.4, 42.2, 55.7, 70.8, 120.8, 126.8, 127.5, 128.1, 138.9, 141.8, 149.9, 162.8, 172.2.

Anal. Calcd for $C_{25}H_{34}N_4O_2$: C, 71.06; H, 8.11; N, 13.26. Found: C, 70.99; H, 8.03; N, 13.34.

***N*-Benzyl-2-[2-isonicotinoyl-1-(3-methylbutyl)hydrazino]pentanamide (9j)**
Beige solid; mp 133–134 °C.

^{1}H NMR (DMSO-d_6, 363 K): δ = 0.81–0.91 (m, 9 H), 1.29–1.49 (m, 4 H), 1.54–1.74 (m, 3 H), 2.85 (m, 2 H), 3.51 (t, J = 6.0 Hz, 1 H), 4.34 (ddd, J_1 = 5.5 Hz, J_2 = 4.1 Hz, J_3 = 4.8 Hz, 2 H), 7.19–7.23 (m, 5 H), 7.64 (d, J = 5.8 Hz, 2 H), 8.45 (br s, 1 H), 8.72 (d, J = 5.8 Hz, 2 H), 9.34 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 363 K): δ = 13.6, 18.8, 22.3, 25.3, 31.7, 36.0, 42.2, 53.4, 66.8, 121.1, 126.7, 127.3, 128.1, 139.1, 141.5, 149.8, 163.8, 172.8.

Anal. Calcd for $C_{23}H_{32}N_4O_2$: C, 69.67; H, 8.13; N, 14.13. Found: C, 69.55; H, 8.07; N, 14.19.

***N*-Benzyl-2-(1-butyl-2-isonicotinoylhydrazino)pentanamide (9k)**

Yellowish solid; mp 150 °C (dec.).

^{1}H NMR (DMSO-d_6, 363 K): δ = 0.87 (m, 6 H), 1.28–1.51 (m, 6 H), 1.65 (m, 2 H), 2.82 (m, 2 H), 3.50 (t, *J* = 6.3 Hz, 1 H), 4.35 (d, *J* = 5.8 Hz, 2 H), 7.17–7.33 (m, 5 H), 7.63 (d, *J* = 4.4 Hz, 2 H), 8.43 (br s, 1 H), 8.70 (d, *J* = 4.4 Hz, 2 H), 9.34 (br s, 1 H).

^{13}C NMR (DMSO-d_6, 363 K): δ = 13.5, 13.6, 18.8, 19.6, 29.1, 31.7, 42.2, 54.8, 66.8, 121.0, 126.7, 127.3, 128.1, 139.1, 141.4, 150.0, 164.0, 172.3.

Anal. Calcd for $C_{22}H_{30}N_4O_2$: C, 69.08; H, 7.91; N, 14.65. Found: C, 68.93; H, 8.00; N, 14.52.

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(21) Molecular mechanics (MM2) calculations performed using ChemBio3D (Ultra) v11.0 demonstrated that the observed conformations for compounds **4i** and **9h** displayed minimized energies of 6.48 and 7.62 kcal/mol, respectively. Alternative hydrogen-bonded conformations displayed significantly higher minimized energies (14.1 and 14.0 kcal/mol, respectively).