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Synthesis of 5*H*-Pyrrolo[3,4-*b*]pyrazine-Based Peptidomimetics

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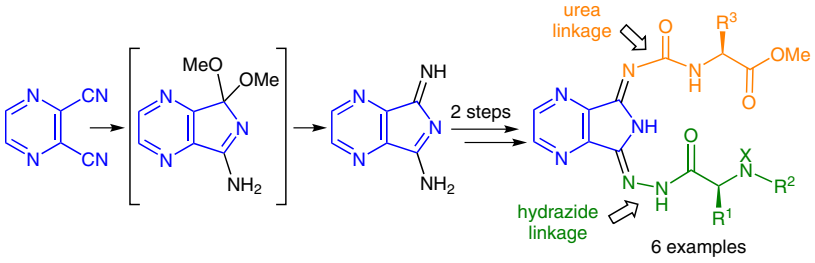
Dedicated to Professor Mykhailo Yu. Kornilov on the occasion of his retirement



Received: 28.05.2015
Accepted after revision: 30.07.2015
Published online: 16.09.2015
DOI: 10.1055/s-0035-1560184; Art ID: ss-2015-z0339-op

Abstract A range of 5*H*-pyrrolo[3,4-*b*]pyrazine-based peptidomimetics were designed, and their efficient synthesis starting from 5-imino-5*H*-pyrrolo[3,4-*b*]pyrazin-7-amine by subsequent interaction with N-protected amino acid hydrazides and amino acid esters with *N*,*N*-carbonyldiimidazole as the coupling agent was elaborated.

Key words amino acids, peptidomimetics, nitrogen heterocycles, coupling, hydrazones, ureas

Peptidomimetics are small organic molecules that are chemically designed to mimic natural peptides. They interact with various receptors in a manner similar to those of the natural peptides, and often exhibit the same biological activities.[1] The design of novel peptidomimetics and structural modifications of natural peptides has generated substantial interest in the scientific community, particularly in the area of synthesis and development of new drug-like molecules.[2] Various synthetic approaches have been developed to generate molecules with the desired ADME properties that mimic natural peptides.[3] The design principles involve side-chain modifications, isosteric replacement of peptide bonds, transition-state mimics, and constrained mimics for amino acids or peptides, peptoids, cyclic peptides, and privileged substructures.[4] Another strategy is the creation of hybrid peptides by combining small organic fragments such as aromatic rings or heterocycles with a peptide motif. These fragments could be introduced at the C-terminus[5] or the N-terminus[6] as well as into the peptide chains.[7] The insertion of a non-peptidic fragment that can conformationally constrain the peptide backbone could stabilize a biologically active conformation, thus increasing the selectivity of biological action and decreasing toxicity. Moreover, metabolic stability and biological activity are known to be higher in peptidomimetics that contain heterocyclic cores as non-peptidic fragments. Peptidomimetics of this type have been studied extensively.[8] Recently,[9] we described a convenient preparation of a new range of peptidomimetics **1**, bearing a 1*H*-isoindole fragment as an amino acid unit surrogate in a peptide chain (Figure 1).

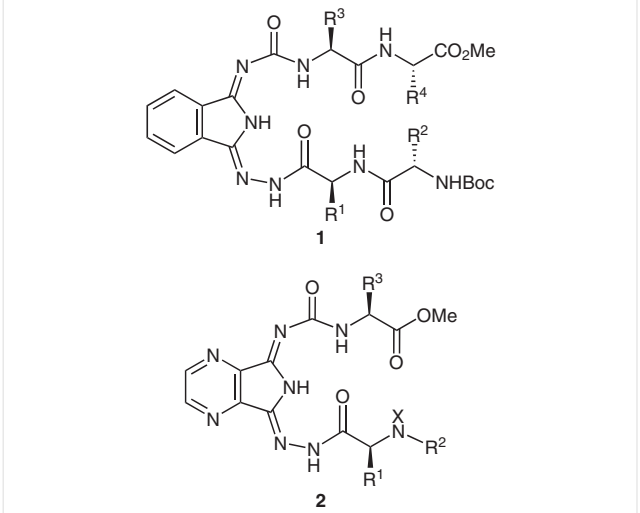
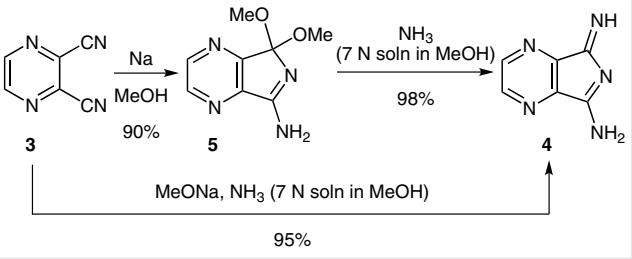


Figure 1 General structure of peptidomimetics **1** and **2**

In a continuation of our research on the synthesis of heterocycle–peptide hybrid molecules, we developed in this work the synthesis of peptidomimetics **2**, which contain the 5*H*-pyrrolo[3,4-*b*]pyrazine moiety incorporated into a peptide backbone (Figure 1). Previously, a range of biological activities have been observed for 5*H*-pyrrolo[3,4-*b*]pyrazine-based compounds.[10a–c] Nitrogen atoms of the pyrazine heterocycle have the potential to be involved in intermolecular hydrogen-bond networks leading to additional structural motifs.[10d]

The initial part of our work focused on synthetic approaches that allowed the amino acid residues to be combined with the 5*H*-pyrrolo[3,4-*b*]pyrazine heterocycle in one molecule. The protocol that was developed previously to prepare compounds **1** could be applied to introduce the amino acid residues into the molecule by reaction of N-protected amino acid hydrazides with pyrazine-2,3-dicarbonitrile (**3**) or 5-imino-5*H*-pyrrolo[3,4-*b*]pyrazin-7-amine (**4**).

Compound **4** was reported to act as an oxidizing-agent-free dye precursor in dyeing human keratin fibers.[11] It was obtained in 96.5% yield by reaction of gaseous anhydrous ammonia with a methanolic solution of dinitrile **3** (1 h, r.t.); reflux of the reaction mixture (3 h) in the presence of a catalytic amount of MeONa accomplished the synthesis.[12] We found that amine **4** could be obtained more easily in 95% yield by stirring a mixture of dinitrile **3** and a catalytic amount of MeONa in 7N ammonia solution in methanol for one hour at room temperature (Scheme 1). We observed that 5,5-dimethoxy-5*H*-pyrrolo[3,4-*b*]pyrazin-7-amine (**5**) was formed as an intermediate in this reaction, which was characterized for the first time.



Scheme 1 Synthesis of **4**

Compound **5** has rarely been used as a precursor for the synthesis of bispyrrolopyrazine dyes, despite its great potential.[13] According to our X-ray diffraction study, dimethoxy derivative **5** exists in the crystal in the tautomeric amino form (Figure 2).

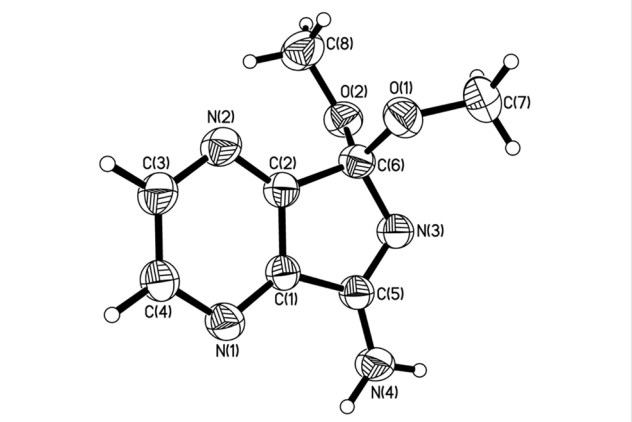
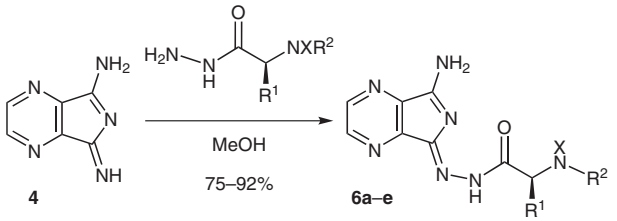


Figure 2 Molecular structure of **5** according to the X-ray diffraction data

By following a previously published procedure,[9] a set of dipeptides **6a**–**e** was synthesized by reacting pyrrolopyrazine **4** with the corresponding N-protected hydrazides. A selection of amino acids either with or without a functionalized side chain (glycine, L-alanine, L-methionine, L-serine(OBn), and Cbz-L-proline) was used (Table 1).

Table 1 Synthesis of **6**



Entry	6	R^1	R^2	X	Yield (%)	*Z*/*E* in $CDCl_3$
1	**6a**	H	H	Boc	92	1:0.75
2	**6b**	Me	H	Boc	85	1:0.55
3	**6c**	$(CH_2)_2SMe$	H	Boc	75	1:0.40
4	**6d**	CH_2OBn	H	Boc	89	1:0.30
5	**6e**	$(CH_2)_3$	–	Cbz	90	1:0.60

Vigorous stirring of equimolar methanolic mixtures of starting compounds for three hours at 50 °C or overnight at room temperature led to the formation of the desired products **6a**–**e** in high yields. Notably, side-chain steric hindrance had no influence on the yields of the couplings.

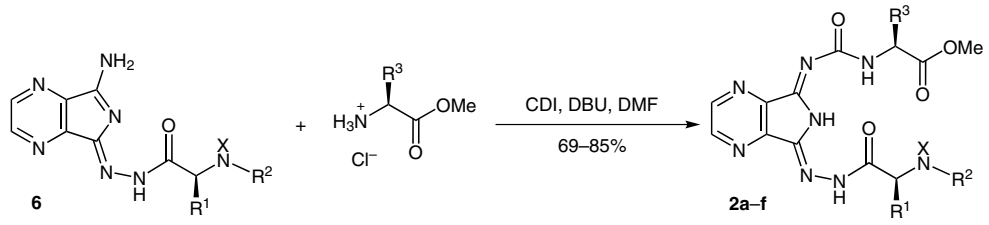
It should be mentioned that both nitrile **3**[14] and dimethoxypyrrolopyrazine **5** could be used as starting materials for the preparation of peptidomimetics **6a**–**e**. However, these routes afforded lower yields than those starting from **4**.

The NMR spectra of all peptidomimetics **6** revealed two sets of signals for most of the atoms. This indicated that compounds exist as mixtures of *Z* and *E* amide isomers (Table 1) because of restricted rotation about the C(O)–N bond at the hydrazide residue, similar to those found in pyrazine-based carboxylic acid derivatives[14] and isoindole carbohydrazides.[9,15]

Previous work in our research group[9] resulted in the development of a general procedure for introducing the second amino acid residue into benzo analogues of **6** by applying the methodology of the present amino group transformation using highly reactive amino acid ester isocyanates. Isoindole analogues of tripeptides **2** were synthesized in high yields through coupling of the corresponding hydrazide derivatives with amino acid methyl ester isocyanates generated in situ from amino acid esters and triphosgene.

However, an attempt to apply the developed reaction protocol to the pyrazine series was unsuccessful; in this case, the conversion of **6** into the products **2** did not exceed 10%. This could be attributed to the significantly lower sol-

Table 2 Synthesis of Peptidomimetics **2**



Entry	2	R^1	R^2	R^3	X	Yield (%)
1	**2a**	H	H	Me	Boc	85
2	**2b**	H	H	$(CH_2)_2SMe$	Boc	69
3	**2c**	CH_2OBn	H	Me	Boc	80
4	**2d**	CH_2OBn	H	$(CH_2)_2SMe$	Boc	71
5	**2e**	$(CH_2)_3$		Me	Cbz	78
6	**2f**	$(CH_2)_3$		CH_2OBn	Cbz	82

ubility of **6** compared with their benzo analogues. Solubility tests revealed that *N*,*N*-dimethylformamide (DMF) was the best solvent for dipeptides **6**. However, the formation of Vilsmeier type intermediates in the reaction of triphosgene with DMF[16] prevented the use of this solvent for the synthesis of the target compounds **2**.

The results described above prompted us to elaborate an alternative protocol for the preparation of urea-tethered peptidomimetics **2** by employing *N*,*N*-carbonyldiimidazole (CDI), which is a widely used coupling reagent for urea dipeptide synthesis.[17] Similar to the published one-pot protocol,[18] compounds **6** were coupled with a set of amino acid methyl esters with CDI in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF at 0 °C with stirring overnight from 0 °C to room temperature (Table 2). Peptidomimetics **2a**–**f** were isolated in good yields (69–85%) after purification by flash column chromatography on silica.

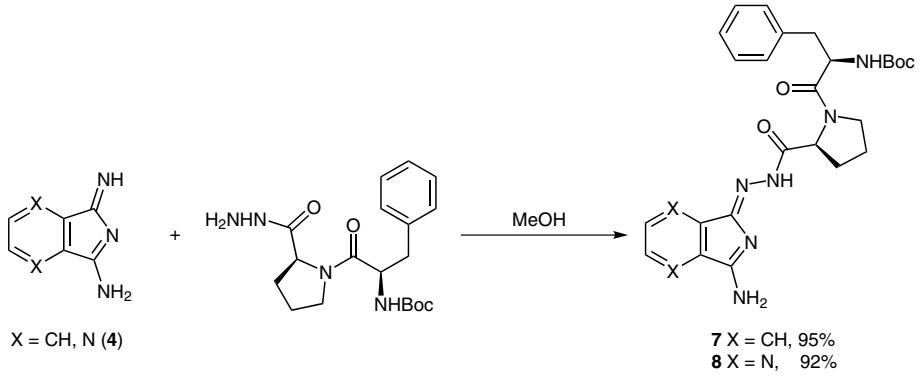
As in the case of **6**, the NMR spectra of all peptidomimetics **2** presented two sets of signals for most of the atoms, corresponding to *Z* and *E* amide isomers. The assignment of signals by means of 1D and 2D NMR spectroscopy was challenging because of the overlap of the signals of isomeric forms and because of the structural features of peptides **2**. Molecules **2** contain three isolated spin systems (protons of pyrazine cycle, hydrazide, and urea residues), which does not allow the correlations needed for assignment of signals in the NMR spectra to be observed.

The ^{1}H NMR spectrum of **2a** in $CDCl_3$ revealed eight NH proton signals of two amide conformers with a ratio of 1:0.2. The resonances at δ = 9.98 and 10.54 ppm were assigned to the Ala NH group, because this proton exhibited a splitting of the NMR signal into a doublet. The resonance of the BocNH group was observed as two broad singlets at δ = 5.34 and 5.64 ppm. The substantial downfield shift of Ala NH resonance indicates a high degree of hydrogen bonding, whereas the low chemical shift value of BocNH is characteristic of a non-hydrogen-bonded amide proton.[19] Four other broad singlets correspond to hydrazide NH and endocyclic NH of two amide conformers.

To obtain preliminary information on the H-bonds in **2**, a hydrogen–deuterium exchange experiment was carried out for peptide **2a** in $CDCl_3$ (in this solvent we observed best resolution of NH signals). A small aliquot of D_2O was added to a sample of **2a** to give an approximately 5% v/v mixture with $CDCl_3$. Monitoring the rate of H/D exchange of NH protons in the ^{1}H NMR spectrum after D_2O addition revealed that Ala NH resonances exchanged relatively slowly compared with the other NH resonances. It could be suggested that they correspond to the NH groups that participate in intramolecular H-bonds to the C=O group of the hydrazide fragment.

To evaluate the possibility of peptide aggregation in $CDCl_3$, the concentration dependence of the NH chemical shifts for **2a** was determined. Studies were conducted over the concentration range of 2 to 50 mM. Three NH groups of the major isomeric form (including Ala NH and BocNH) were insensitive to concentration change. One could conclude that these protons may either be involved in intramolecular interactions or remain as solvent-exposed NH groups. The fourth NH proton signal moved downfield with increasing concentration, indicating that this group participates in the formation of intermolecular hydrogen bonds.[20] This fact promoted us to assign this singlet to hydrazide NH.

We also carried out temperature dependence studies of the ^{1}H NMR chemical shifts of NH protons, which also reflects their state of hydrogen bonding. The temperature dependence of the NH Ala proton chemical shift for peptide **2a** falls within the range of values typical for intramolecularly hydrogen-bonded protons $\Delta\delta(NH)/\Delta T = -4.2$ ppb/K. At the same time, hydrazide NH proton shows a relatively



Scheme 2

large temperature dependence $\Delta\delta(NH)/\Delta T$ = –19.8 ppb/K, suggesting that it is in equilibrium between intermolecular hydrogen-bonded and non-hydrogen-bonded states.[21]

As shown earlier,[9] dipeptide hydrazides could also be used effectively as starting materials in the reaction with 1-imino-1*H*-isoindol-3-amine, which is a benzo analogue of **4**. Given the success of this reaction protocol for the synthesis of linear tripeptides, we became interested in its application to the formation of analogues of the D-Phe-Pro-Arg thrombin inhibitor due to the presence of the NCN amidine triad in **6** and their benzo analogues. Structure optimization of the D-Phe-Pro-Arg tripeptide led to the discovery of a new generation of noncovalent thrombin inhibitors in which arginine residue was effectively replaced by amidine containing groups.[22] A number of inhibitors have been reported that utilize nitrogen-containing heterocycles possessing a cyclic amidine, in particular, 2-aminopyridine[22a] and 2-aminoquinazoline[23] derivatives, as arginine surrogates in the inhibitor templates. Thereby, compounds **7** and **8**, containing substituted 1*H*-isoindole and 5*H*-pyrrolo[3,4-*b*]pyrazine moieties, were easily prepared from the hydrazide of Boc-D-Phe-Pro and corresponding amines in high yields (Scheme 2).

Starting dipeptide Boc-D-Phe-Pro-OMe was prepared by following a standard protocol[24] in high yield (90%) and then further transformed into the corresponding hydrazide in excellent yield (98%).

In summary, we have reported the design and synthetic strategies that can be used to generate new peptidomimetics containing the pyrrolo[3,4-*b*]pyrazine template. CDI was found to be the reagent of choice for the coupling reaction of dipeptide analogues with amino acid esters. The obtained tripeptide analogues possess two strands derived from an amino acid hydrazide and a urea scaffold linked through a pyrrolopyrazine unit, which are designed to allow further incorporation into longer strands through their protected NH_2 and COOH groups. The rigid scaffold of the pyrrolo[3,4-*b*]pyrazine described here can serve as a conformationally constrained template that may find useful application in the development of novel peptidomimetics with promising structures and properties.

Melting points were determined with a Boetius microscope hot-plate apparatus. Elemental analyses (C, H, N) were conducted with a Vario Micro Cube. Mass spectra were recorded with an Agilent 1100 LCMSD SL instrument by chemical ionization (CI). NMR spectra were measured with a Bruker Avance 500 spectrometer (at 500 MHz, ^{1}H and 125 MHz, for ^{13}C) and a Mercury (Varian) 400 spectrometer (400 MHz, ^{1}H and 100 MHz, for ^{13}C) with tetramethylsilane as a standard. For compounds **2** and **6**–**8**, signals of both *Z* and *E* amide conformers are given. Preparative column chromatography was carried out with silica gel 60 (40–63 μm). Boc-protected amino acid hydrazides and Boc-D-Phe-Pro hydrazide were obtained from the corresponding methyl esters and excess hydrazine monohydrate in MeOH by stirring the reaction mixture overnight at r.t., and then evaporation to dryness (yields 95–99%), similar to a reported procedure.[25]

X-ray Diffraction Study of 5

The anti-arrangement of methoxy substituents at the C(6) atom [C(2)–C(6)–O–C torsion angles are 168.6(1)° for O(1)–C(7) and 61.3(2)° for O(2)–C(8) groups] is stabilized by weak attractive intramolecular contacts C–H···N [C(7)–H(7A)···N(3) of 2.58 Å and C(8)–H(8C)···N(2) of 2.56 Å compared with the van der Waals radii sum[26] of 2.67 Å]. The C(1)–C(5) bond length of 1.485(2) Å does not reveal extra conjugation of the C(5)–N(3) bond with aromatic pyrazine ring, despite their coplanar arrangement. The C(5)–N(4) bond of 1.324(3) Å is slightly shorter than the mean value[27] 1.336 Å, but the C(5)=N(3) double bond of 1.300(2) Å is also shortened slightly (1.313 Å), which indicates a lack of conjugation between the double bond and the amino group. Thus, the planar configuration of the N(4) atom (sum of valence angles centered on N(4) is 359°) should not be referred to as intramolecular π-interactions but rather to the formation of intermolecular hydrogen bonds N(4)–H(4A)···N(3)′ (H···N′ 2.11 Å, N–H···N′ 163°) and N(4)–H(4B)···N(1)′ (H···N′ 2.17 Å, N–H···N′ 173°). These hydrogen bonds organize molecules in the crystal into chains along the (010) crystallographic direction.

Crystals of **5** ($C_8H_{10}N_4O_2$, M_r = 194.20) are monoclinic; $P2_1/c$; a = 8.4609(6), b = 8.4049(5), c = 13.0466(8) Å, β = 98.931(6)°; V = 916.54(9) Å^3; Z = 4; d_{calc} = 1.407 g·sm^{-1}; μ = 0.105 mm^{-1}; F(000) = 408. 4308 reflections (2331 independent, R_{int} = 0.024) were collected with

an Xcalibur-3 diffractometer (Mo-K_α radiation, CCD-detector, graphite monochromator, ω-scanning, $2\theta_{max}$= 55°). The structure was solved by direct methods and refined against F^2 within anisotropic approximation for all non-hydrogen atoms by full-matrix least squares procedure using the OLEX2 program package[28] with SHELXS and SHELXL modules.[29] All hydrogen atoms were located from the differential density map and refined using isotropic approximation, except for H atoms of the methyl groups, which were placed in idealized positions (C–H = 0.96 Å) and constrained to ride on their parent atoms with U_{iso} = 1.5U_{equiv}. Final refinement was converged at wR_2 = 0.119 for all 2094 reflections (R_1 = 0.045 for 1452 reflections with F>4σ(F), S = 1.03).

Atom coordinates and crystallographic parameters have been deposited to the Cambridge Crystallographic Data Centre (CCDC 1061021). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

5-Imino-5*H*-pyrrolo[3,4-*b*]pyrazin-7-amine (4)

Sodium methylate (0.108 g, 2 mmol) was added to a solution of ammonia (7 N in MeOH, 30 mL). The resulting mixture was cooled on an ice-water bath and dinitrile **3** (2.60 g, 20 mmol) was added in one portion with vigorous stirring. The solution became yellow and then orange-brown. In 5 min the dimethoxy derivative **5** precipitated as a white solid. After stirring for 1 h, compound **5** dissolved and precipitation of product **4** was observed in a few minutes. The precipitate formed was filtered off, washed with MeOH (10 mL) and dried in vacuo to give the desired product.

Yield: 2.79 g (95%); beige solid; mp 240 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.77 (s, 2 H, 2 × H_{Pyraz}), 8.90 (br s, 3 H, 3 × NH).

^{13}C NMR (100 MHz, CF_3CO_2D): δ = 150.9 (2 × C), 153.3 (2 × CH), 174.7 (2 × C).

Anal. Calcd for $C_6H_5N_5$: C, 48.98; H, 3.43; N, 47.60. Found: C, 49.07; H, 3.55; N, 47.78.

LC/MS (CI): m/z = 148 $[M + H]^+$.

5,5-Dimethoxy-5*H*-pyrrolo[3,4-*b*]pyrazin-7-amine (5)

Sodium methylate (108 mg, 2 mmol) was dissolved in MeOH (30 mL), and dinitrile **3** (2.60 g, 20 mmol) was added in one portion with vigorous stirring. Compound **3** dissolved within a few seconds and the solution became yellow and then orange-brown. After 15 min stirring at r.t., the title compound **5** precipitated. The precipitate formed was filtered off, washed with cold MeOH (10 mL) and dried in vacuo to give the desired product **5** (2.90 g, 75%) as a white solid. An additional portion of pure product **5** (0.58 g, 15%; mp 157–159 °C) was obtained by concentration at r.t. of the methanolic solution under reduced pressure.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.38 (s, 6 H, 2 × OCH_3), 7.46 (br s, 2 H, NH_2), 8.61 (d, J = 2.8 Hz, 1 H, H_{Pyraz}), 8.66 (d, J = 2.8 Hz, 1 H, H_{Pyraz}).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.7 (2 × OMe), 112.7 [C(OMe)$_2$], 143.8 (CH), 144.8 (CH), 146.3 (C), 159.8 (C), 161.6 (C).

Anal. Calcd for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.54; H, 5.07; N, 28.69.

LC/MS (CI): m/z = 195 $[M + H]^+$.

Synthesis of 6a–e; General Procedure

A suspension of pyrrolopyrazine **4** (0.294 g, 2 mmol) and the corresponding N-protected amino acid hydrazide (2.1 mmol) in methanol (25 mL) was stirred for 3 h at 50 °C or overnight at r.t. After cooling, the precipitate was filtered off, washed with cold MeOH (10 mL) and dried in vacuo.

(*Z*)-*tert*-Butyl 2-[2-(7-Amino-5*H*-pyrrolo[3,4-*b*]pyrazin-5-ylidene)hydrazinyl]-2-oxoethylcarbamate (6a)

Yield: 0.59 g (92%); yellow solid; mp 205 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.41 (br s, 9 H, Boc), 3.73 and 4.12 (2 × br s, 2 H, CH_2), 6.82 and 7.24 (2 × br s, 1 H, N*H*Boc), 8.66 and 8.71 (2 × br s, 2 H, 2 × H_{Pyraz}).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 28.0 [C(CH_3)$_3$], 41.5 and 43.1 (CH_2), 78.0 [C(CH_3)$_3$], 143.6, 144.0, 145.2, 147.9, 151.0, 152.0, 155.7, 163.9, 165.9.

Anal. Calcd for $C_{13}H_{17}N_7O_3$: C, 48.90; H, 5.37; N, 30.70. Found: C, 48.81; H, 5.32; N, 30.79.

LC/MS (CI): m/z = 320.3 $[M + H]^+$.

(*S*,*Z*)-*tert*-Butyl 1-[2-(7-Amino-5*H*-pyrrolo[3,4-*b*]pyrazin-5-ylidene)hydrazinyl]-1-oxopropan-2-ylcarbamate (6b)

Yield: 0.57 g (85%); yellow solid; mp 186–187 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.25–1.39 (m, 12 H, Boc + CH_3), 4.15–4.23 and 4.90–4.95 (2 × m, 1 H, CH), 7.07 and 7.33 (2 × br s, 1 H, N*H*Boc), 8.58–8.81 (m, 4 H, 2 × H_{Pyraz} + NH_2), 9.82 and 10.63 (2 × br s, 1 H, NH_{Hydraz}).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 17.2 and 17.9 (Me), 28.5 and 28.6 [C(CH_3)$_3$], 47.0 and 49.8 (CH), 78.3 and 78.8 [C(CH_3)$_3$], 144.4 (CH), 146.2 (CH), 148.1, 151.8, 155.7, 163.9, 164.0, 169.6, 174.1.

Anal. Calcd for $C_{14}H_{19}N_7O_3$: C, 50.44; H, 5.75; N, 29.41. Found: C, 50.59; H, 5.84; N, 29.57.

LC/MS (CI): m/z = 334.4 $[M + H]^+$.

(*S*,*Z*)-*tert*-Butyl 1-[2-(7-Amino-5*H*-pyrrolo[3,4-*b*]pyrazin-5-ylidene)hydrazinyl]-4-(methylthio)-1-oxobutan-2-ylcarbamate (6c)

Yield: 0.59 g (75%); yellow solid; mp 130–131 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.37 and 1.39 (2 × br s, 9 H, Boc), 1.82–2.06 (m, 5 H, SMe + CH_2), 2.53–2.59 (m, 2 H, CH_2), 4.21–4.25 and 5.02–5.06 (2 × br m, 1 H, CH), 7.11 and 7.42 (2 × br d, 1 H, N*H*Boc), 8.59–8.78 (m, 4 H, 2 × H_{Pyraz} + NH_2), 9.84 and 10.66 (2 × br s, 1 H, NH_{Hydraz}).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.9 and 15.0 (SMe), 28.5 [C(CH_3)$_3$], 30.2 (CH_2), 31.4 (CH_2), 52.8 and 54.4 (CH), 78.9 [C(CH_3)$_3$], 144.4, 146.2, 148.1, 149.5, 150.6, 151.8, 152.1, 155.0, 155.4, 156.0, 164.0, 168.6, 173.3.

Anal. Calcd for $C_{16}H_{23}N_7O_3S$: C, C, 48.84; H, 5.89; N, 24.92. Found: C, 48.95; H, 5.98; N, 25.03.

LC/MS (CI): m/z = 394 $[M + H]^+$.

(*S*,*Z*)-*tert*-Butyl 1-[2-(7-Amino-5*H*-pyrrolo[3,4-*b*]pyrazin-5-ylidene)hydrazinyl]-3-(benzyloxy)-1-oxopropan-2-ylcarbamate (6d)

Yield: 0.78 g (89%); pale-yellow solid; mp 185 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.39 and 1.40 (2 × s, 9 H, Boc), 3.65–3.73 (m, 2 H, CH_2OCH_2Ph), 4.42–4.46 and 5.29–5.33 (2 × m, 1 H, CH), 4.50–4.55 (m, 2 H, OCH_2Ph), 6.99–7.33 (m, 6 H, Ph + N*H*Boc), 8.71–8.79 (m, 4 H, 2 × H_{Pyraz} + NH_2), 10.70 (br s, 1 H, NH_{Hydraz}).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 28.2 [C(*C*H$_3$)$_3$], 54.1, 57.2, 69.1, 69.4, 71.9, 72.2, 78.8 [*C*(CH$_3$)$_3$], 127.3, 127.4, 127.5, 127.6, 128.1, 128.3, 138.2, 144.2, 145.9, 146.0, 151.2, 151.6, 152.0, 155.5, 155.6, 163.7, 166.6.

Anal. Calcd for $C_{21}H_{25}N_7O_4$: C, 57.39; H, 5.73; N, 22.31. Found: C, 57.24; H, 5.85; N, 22.27.

LC/MS (CI): *m*/*z* = 440 [M + H]$^+$.

(*S*,*Z*)-Benzyl 2-[2-(7-Amino-5*H*-pyrrolo[3,4-*b*]pyrazin-5-ylidene)hydrazinecarbonyl]pyrrolidine-1-carboxylate (6e)

Yield: 0.71 g (90%); pale-yellow solid; mp 133–134 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.87–1.95 (m, 3 H, 3 × H_{Pro}), 2.15–2.39 (m, 1 H, H_{Pro}), 3.47–3.52 (m, 2 H, 2 × H_{Pro}), 4.56–5.25 (m, 3 H, H_{Pro} + CH_2Ph), 7.15–7.36 (m, 5 H, Ph), 8.53–8.78 (m, 4 H, 2 × H_{Pyraz} + NH_2), 9.90 and 10.83 (2 × br s, 1 H, NH_{Hydraz}).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.1, 23.4, 23.9, 24.3, 29.5, 29.9, 30.5, 31.4, 46.6, 46.7, 47.2, 47.4, 56.6, 57.3, 58.8, 59.2, 65.8, 65.9, 66.2, 126.9, 127.1, 127.4, 127.5, 127.6, 127.8, 127.9, 128.2, 128.5, 136.9, 137.0, 137.1, 144.2, 145.8, 146.0, 147.8, 147.9, 151.1, 151.6, 153.9, 163.6, 163.8, 168.6, 168.9, 172.5.

Anal. Calcd for $C_{19}H_{19}N_7O_3$: C, 58.01; H, 4.87; N, 24.92. Found: C, 57.92; H, 4.77; N, 24.88.

LC/MS (CI): *m*/*z* = 394 [M + H]$^+$.

Synthesis of 2a–f; General Procedure

To an ice-cold solution of amino acid methyl ester hydrochloride (1 mmol) in DMF (5 mL) were added DBU (1 mmol, 0.152 g, 0.15 mL) and CDI (1.1 mmol, 0.178 g). The mixture was stirred for 30 min at 0 °C and hydrazide derivative **6a**–**e** (0.9 mmol) was added in one portion followed by DBU (0.2 mmol, 0.030 g, 0.03 mL). Stirring was continued overnight from 0 °C to r.t., then the DMF was removed at reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL), washed with a saturated solution of citric acid (25 mL) and brine (25 mL), dried with $MgSO_4$, and evaporated to dryness. The title compounds were isolated by flash chromatography using EtOAc as eluent.

(*S*)-Methyl 2-[(*Z*)-3-((*Z*)-7-{2-[2-(*tert*-Butoxycarbonylamino)acetyl]hydrazono}-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-ylidene)ureido]propanoate (2a)

Yield: 0.34 g (85%); yellow solid; mp 136–138 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 and 1.45 (2 × s, 9 H, Boc), 1.58–1.63 (m, 3 H, Me), 3.87 and 3.93 (2 × s, 3 H, OCH_3), 4.16–4.65 (m, 3 H, CH + CH_2), 5.34 and 5.64 (2 × br s, 1 H, N*H*Boc), 8.64 and 8.76 (2 × s, 2 H, 2 × H_{Pyraz}), 9.21, 9.39, 9.98, 10.14, 10.54 and 10.68 (6 × br s, 3 H, 3 × NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.5 (Me), 28.2 [C(*C*H$_3$)$_3$], 42.4 (CH_2), 50.0 (CH), 53.0 (OMe), 79.6 [*C*(CH$_3$)$_3$], 144.2 (CH), 144.8, 146.3, 146.8 (CH), 150.3, 151.4, 155.8, 158.7, 171.2, 173.1.

Anal. Calcd for $C_{18}H_{24}N_8O_6$: C, 48.21; H, 5.39; N, 24.99. Found: C, 48.13; H, 5.46; N, 25.02.

LC/MS (CI): *m*/*z* = 449 [M + H]$^+$.

(*S*)-Methyl 2-[(*Z*)-3-((*Z*)-7-{2-[2-(*tert*-Butoxycarbonylamino)acetyl]hydrazono}-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-ylidene)ureido]-4-(methylthio)butanoate (2b)

Yield: 0.32 g (69%); yellow solid; mp 126–127 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.43 and 1.45 (2 × s, 9 H, Boc), 2.09–2.38 (m, 5 H, $CH_{2(Met)}$ + SMe), 2.53–2.65 (m, 2 H, $CH_{2(Met)}$), 3.87 and 3.93 (2 × s, 3 H, OCH_3), 4.14–4.80 (m, 3 H, CH + $CH_{2(Gly)}$), 5.31 and 5.58 (2 × br s, 1 H, N*H*Boc), 8.66 and 8.78 (2 × br s, 2 H, 2 × H_{Pyraz}), 9.16, 9.36, 9.92, 10.16, 10.52 and 10.69 (6 × br s, 3 H, 3 × NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.5 (SMe), 28.2 [C(*C*H$_3$)$_3$], 29.7 (CH_2), 31.5 (CH_2), 42.5 (CH_2), 53.0 (CH), 53.2 (OMe), 79.6 [*C*(CH$_3$)$_3$], 144.3 (CH), 144.7, 146.3, 146.7 (CH), 150.3, 151.8, 155.8, 158.7, 171.2, 172.0.

Anal. Calcd for $C_{20}H_{28}N_8O_6S$: C, 47.23; H, 5.55; N, 22.03. Found: C, 47.38; H, 5.64; N, 22.14.

LC/MS (CI): *m*/*z* = 509 [M + H]$^+$.

(*S*)-Methyl 2-[(*Z*)-3-((*Z*)-7-{2-[(*S*)-3-(Benzyloxy)-2-(*tert*-butoxycarbonylamino)propanoyl]hydrazono}-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-ylidene)ureido]propanoate (2c)

Yield: 0.41 mg (80%); pale-yellow solid; mp 115–116 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 and 1.46 (2 × s, 9 H, Boc), 1.57–1.62 (m, 3 H, CH_3), 3.70–4.06 (m, 5 H, OCH_3 + CH_{Ser} + CH_{Ala}), 4.54–4.82 (m, 4 H, $CH_{2(Ser)}$ + $CH_{2(Bn)}$), 5.51 and 5.71 (2 × br s, 1 H, N*H*Boc), 7.14–7.28 (m, 5 H, Ph), 8.63, 8.76, 8.79 and 8.88 (4 × s, 3 H, 2 × H_{Pyraz} + NH), 9.92, 10.06, 10.21 and 10.71 (4 × br s, 2 H, 2 × NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.3 and 18.6 (Me), 28.2 [C(*C*H$_3$)$_3$], 49.9 and 50.0 (CH), 52.1, 53.0, 53.3, 54.0, 69.9 and 70.2 (CH_2), 73.0 and 73.3 (CH_2), 79.7 [*C*(CH$_3$)$_3$], 127.4 (CH), 127.5 (CH), 128.0 and 128.2 (CH), 137.4 and 137.7, 144.2 (CH), 144.4, 146.2 and 146.3, 146.8 and 146.9 (CH), 147.7, 150.3, 150.7, 151.2, 151.3, 155.3, 158.5, 158.7, 167.4, 171.6, 172.8.

Anal. Calcd for $C_{26}H_{32}N_8O_7$: C, 54.92; H, 5.67; N, 19.71. Found: C, 54.80; H, 5.59; N, 19.78.

LC/MS (CI): *m*/*z* = 569.6 [M + H]$^+$.

(*S*)-Methyl 2-[(*Z*)-3-((*Z*)-7-{2-[(*S*)-3-(Benzyloxy)-2-(*tert*-butoxycarbonylamino)propanoyl]hydrazono}-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-ylidene)ureido]-4-(methylthio)butanoate (2d)

Yield: 0.40 g (71%); pale-yellow solid; mp 100–102 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 and 1.45 (2 × s, 9 H, Boc), 2.07–2.66 (m, 7 H, 2 × $CH_{2(Met)}$ + SCH_3), 3.67–4.07 (m, 5 H, OCH_3 + CH_{Ser} + CH_{Met}), 4.54–4.80 (m, 4 H, $CH_{2(Ser)}$ + $CH_{2(Bn)}$), 5.51 and 5.70 (2 × br s, 1 H, N*H*Boc), 7.12–7.28 (m, 5 H, Ph), 8.65–8.98 (m, 3 H, 2 × H_{Pyraz} + NH), 9.90, 10.08, 10.19 and 10.69 (4 × br s, 2 H, 2 × NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.3 and 15.5 (SMe), 28.2 [C(*C*H$_3$)$_3$], 29.4 and 29.8 (CH_2), 31.3 and 31.6 (CH_2), 52.1, 53.1, 53.3, 69.9 and 70.2 (CH_2), 73.0 and 73.3 (CH_2), 79.7 [*C*(CH$_3$)$_3$], 127.4 (CH), 127.6 (CH), 128.0 (CH), 128.2 (CH), 137.4 and 137.7, 144.2, 144.3, 144.4, 146.1, 146.2, 146.8, 147.0, 147.7, 150.3, 150.7, 151.5, 151.7, 155.3, 158.5, 158.8, 167.4, 171.6, 171.7, 172.7.

Anal. Calcd for $C_{28}H_{36}N_8O_7S$: C, 53.49; H, 5.77; N, 17.82. Found: C, 53.55; H, 5.81; N, 17.89

LC/MS (CI): *m*/*z* = 629 [M + H]$^+$.

(*S*)-Benzyl 2-((*Z*)-2-{(*Z*)-7-[(*S*)-3-Methoxy-3-oxopropan-2-ylcarbamoylimino]-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-ylidene}hydrazinecarbonyl)pyrrolidine-1-carboxylate (2e)

Yield: 0.37 g (78%); pale-yellow solid; mp 132–133 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.58–1.67 (m, 3 H, CH_3), 1.95–2.48 (br m, 4 H, 2 × $CH_{2(Pro)}$), 3.48–3.87 (m, 5 H, OCH_3 + $CH_{2(Pro)}$), 4.62–5.47 (m, 4 H, $CH_{2(Cbz)}$ + CH_{Ala} + CH_{Pro}), 7.04–7.38 (m, 5 H, Ph), 8.61, 8.65, 8.75, 8.91, 8.99 and 9.02 (6 × br s, 3 H, 2 × H_{Pyraz} + NH), 9.84, 9.98, 10.02, 10.10 and 10.36 (5 × br s, 2 H, 2 × NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.6 and 18.3 (Me), 23.3 and 24.0 and 24.4 ($CH_{2(Pro)}$), 29.7 and 30.6 ($CH_{2(Pro)}$), 46.5 and 47.0 ($CH_{2(Pro)}$), 49.6 (CH), 52.8 (OMe), 56.2 and 57.0 (CH), 66.5 and 67.0 ($CH_{2(Cbz)}$), 127.0, 127.2, 127.3, 127.5, 127.7, 128.0, 135.9, 136.3, 136.4, 143.9, 146.0, 146.3, 146.4, 146.6, 150.0, 151.1, 154.0, 154.5, 155.7, 158.1, 172.6, 172.7, 173.3, 173.7.

Anal. Calcd for $C_{24}H_{26}N_8O_6$: C, 55.17; H, 5.02; N, 21.45. Found: C, 55.09; H, 4.97; N, 21.40.

LC/MS (CI): *m*/*z* = 523 $[M + H]^+$.

(*S*)-Benzyl 2-((*Z*)-2-{(*Z*)-7-[(*S*)-1-(Benzyloxy)-3-methoxy-3-oxopropan-2-ylcarbamoylimino]-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-ylidene}hydrazinecarbonyl)pyrrolidine-1-carboxylate (2f)

Yield: 0.46 g (82%); pale-yellow solid; mp 103–104 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.94–2.06 (br m, 4 H, 2 × $CH_{2(Pro)}$), 3.61–4.07 (m, 6 H, OCH_3 + CH_{Ser} + $CH_{2(Pro)}$), 4.44–5.47 (m, 7 H, $CH_{2(Cbz)}$ + $CH_{2(Ser)}$ + $CH_{2(Bn)}$ + CH_{Pro}), 7.05–7.36 (m, 10 H, Ph_{Cbz} + Ph_{Bn}), 8.63 and 8.75 (2 × br s, 2 H, 2 × H_{Pyraz}), 8.96 (br s, 1 H, NH), 9.85–10.01 (br m, 2 H, 2 × NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.6 and 24.3 ($CH_{2(Pro)}$), 29.9 and 30.9 ($CH_{2(Pro)}$), 46.8 and 47.2 ($CH_{2(Pro)}$), 52.8 and 52.9 (CH), 54.3 (OMe), 56.5 and 57.3 (CH), 66.9 (CH_2), 68.3 and 69.2 (CH_2), 73.2 (CH_2), 127.3, 127.6, 127.7, 127.8, 128.0, 128.2, 128.9, 136.5, 136.7, 137.3, 137.4, 144.0, 144.1, 144.2, 146.3, 146.6, 146.7, 150.2, 150.3, 152.0, 154.2, 154.7, 158.3, 170.0, 170.1, 173.3, 173.7.

Anal. Calcd for $C_{31}H_{32}N_8O_7$: C, 59.23; H, 5.13; N, 17.82. Found: C, 59.31; H, 5.18; N, 17.77.

LC/MS (CI): *m*/*z* = 629 $[M + H]^+$.

Synthesis of 7 and 8; General Procedure

The 1-imino-1*H*-isoindol-3-amine (0.290 g, 2 mmol) or pyrrolopyrazine **4** (0.294 g, 2 mmol) was reacted in MeOH (25–30 mL) with the hydrazide of Boc-D-Phe-Pro (0.772 g, 2.05 mmol) at r.t. under stirring overnight. The mixture was then evaporated to dryness. The title compounds were isolated by flash chromatography (CH_2Cl_2–MeOH, 90:10).

***tert*-Butyl (*R*)-1-{(*S*)-2-[(*Z*)-2-(3-Amino-1*H*-isoindol-1-ylidene)hydrazinecarbonyl]pyrrolidin-1-yl}-1-oxo-3-phenylpropan-2-ylcarbamate (7)**

Yield: 0.96 g (95%); yellow solid; mp 157–158 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.15–1.32 (m, 9 H, Boc), 1.67–2.28 (m, 4 H, 2 × $CH_{2(Pro)}$), 2.63–3.32 (m, 3 H, $CH_{2(Pro)}$ + CH), 3.51–3.64 (m, 2 H, C*H*$_2$Ph), 3.99–4.53, 5.02–5.21 and 5.51–5.68 (3 × m, 2 H, CH + N*H*Boc), 6.87–7.24 (m, 5 H, Ph), 7.46–7.96 (m, 4 H, 4 × H_{Isoind}) 8.21–8.62 (m, 2 H, NH_2), 9.55, 9.96, 10.64, 11.11 and 11.29 (5 × br s, 1 H, NH_{Hydraz}).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.2, 22.4, 24.2, 24.5, 27.6, 28.1, 28.2, 28.4, 28.7, 31.4, 32.4, 36.3, 37.5, 46.6, 47.1, 53.4, 53.5, 54.3, 54.8, 56.8, 57.4, 58.7, 78.1 and 78.8 [*C*$(CH_3)_3$], 120.2, 120.3, 120.5, 121.3, 121.4, 126.0, 126.5, 127.6, 128.1, 129.2, 129.4, 129.6, 130.8, 131.0, 134.8, 137.5, 137.7, 137.9, 138.4, 138.5, 154.4, 154.8, 155.0, 155.5, 156.8, 157.8, 166.8, 167.2, 167.3, 167.5, 167.7, 168.3, 169.4, 170.5, 170.9, 171.1, 171.6.

Anal. Calcd for $C_{27}H_{32}N_6O_4$: C, 64.27; H, 6.39; N, 16.66. Found: C, 64.41; H, 6.47; N, 16.69.

LC/MS (CI): *m*/*z* = 505 $[M + H]^+$.

***tert*-Butyl (*R*)-1-{(*S*)-2-[(*Z*)-2-(7-Amino-5*H*-pyrrolo[3,4-*b*]pyrazin-5-ylidene)hydrazinecarbonyl]pyrrolidin-1-yl}-1-oxo-3-phenylpropan-2-ylcarbamate (8)**

Yield: 0.93 g (92%); pale-yellow solid; mp 172–173 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.19–1.31 (m, 9 H, Boc), 1.68–2.30 (m, 4 H, 2 × $CH_{2(Pro)}$), 2.69–3.26 (m, 3 H, $CH_{2(Pro)}$ + CH), 3.51–3.63 (m, 2 H, C*H*$_2$Ph), 3.93–4.56, 5.10–5.22 and 5.56–5.61 (3 × m, 2 H, CH + N*H*Boc), 6.74–7.26 (m, 5 H, Ph), 8.57–8.88 (m, 4 H, 2 × H_{Pyraz} + NH_2), 9.83, 10.35, 10.44, 10.95, 11.49 and 11.63 (6 × br s, 1 H, NH_{Hydraz}).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.8, 23.0, 24.9, 25.1, 28.3, 28.4, 28.6, 28.8, 29.3, 32.1, 33.0, 36.9, 38.0, 38.5, 47.2, 47.4, 47.7, 54.0, 54.2, 54.9, 55.6, 57.2, 59.2, 59.5, 78.7 and 79.3 [*C*$(CH_3)_3$], 126.6, 127.1, 128.3, 128.7, 130.0, 130.1, 138.1, 138.2, 139.0, 139.2, 144.6, 144.9, 146.4, 146.6, 148.3, 148.6, 149.8, 150.8, 151.7, 152.0, 152.2, 152.3, 152.9, 154.9, 155.4, 155.6, 156.1, 164.1, 164.3, 164.5, 164.7, 168.2, 168.5, 169.8, 170.1, 171.2, 172.0, 172.3, 172.9.

Anal. Calcd for $C_{25}H_{30}N_8O_4$: C, 59.28; H, 5.97; N, 22.12. Found: C, 59.18; H, 6.04; N, 22.05.

LC/MS (CI): *m*/*z* = 507 $[M + H]^+$.

Acknowledgment

The authors thank the French-Ukrainian programs DNIPRO and Egide for financial support of part of this work. A.V.B. thanks LCPM for a post-doctoral fellowship.

Supporting Information

for this article that contains the copies of NMR spectra of all compounds and the details of H/D exchange, concentration and temperature dependence studies is available online at http://dx.doi.org/10.1055/s-0035-1560184.

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