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Hydrazides of 4-Aryl(hetaryl)-2-oxopyrrolidine-3-carboxylic Acids: Synthesis and Structure

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Abstract—Proceeding from reactions of methyl 4-aryl(hetaryl)-2-oxopyrrolidine-3-caroxylates with hydrazine and phenylhydrazine a series of hydrazides of the corresponding 2-oxopyrrolidine-3-carboxylic acids was obtained combining in the molecule a lactam ring and carbohydrazide groups. Phenylhydrazides of 2-oxopyrrolidine-3-carboxylic acids possess the Z-configuration.

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The great interest attracted by derivatives of 2-oxopyrrolidine is due to their considerable applied importance. The lactam ring is known to be the key pharmacophore group in the structure of nootropic drugs used in the medical practice, racetams (piracetam, carphedon, oxiracetam, levetiracetam, etc.) [1–9]. At the same time the replacement of the carbamoyl residue for a carbohydrazide group in the carphedon molecule (phenyl analog of piracetam) supplies it with pronounced antidepressant, anxiolytic, and nootropic properties [10,1 1].

Therefore the substituted 2-oxopyrrolidines containing at the C^3 atom of the lactam ring the carbohydrazide groups are of definite interest as promising biologically active compounds. 2-Oxopyrrolidine-3-caroxylates may be regarded as convenient precursors in the synthesis of such substances since their hydrazinolysis is a targeted way to the preparation of new piracetam analogs.

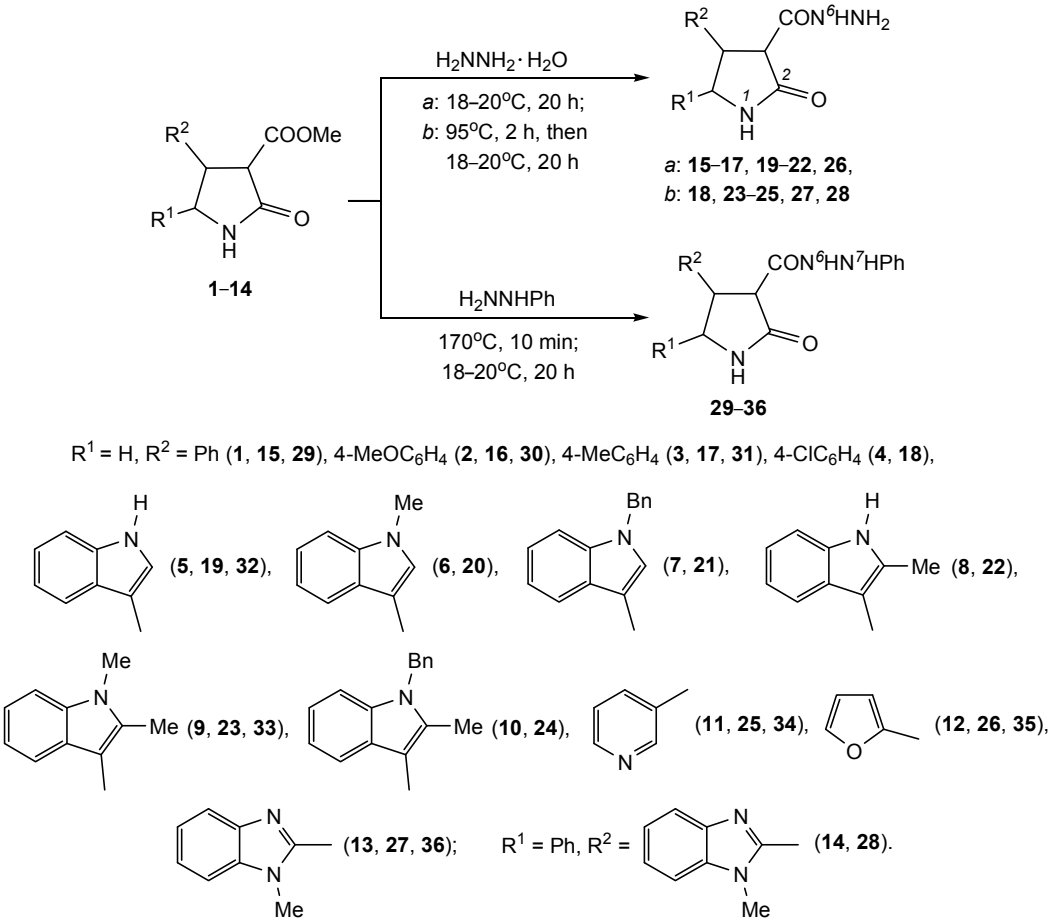
We examined the chemical behavior of 4-aryl-(hetaryl)-2-oxopyrrolidine-3-caroxylates **1–14** in the reactions with hydrazine and phenylhydrazine. Initial esters **1–14** were synthesized along procedures [12–15].

The successful outcome of these reactions essentially depends on their conditions. For instance, esters **1–3**, **5–8**, and **12** react with hydrazine hydrate in relatively mild conditions: At 18–20°C over 20 h they relatively readily form the corresponding hydrazides **15–17**, **19–22**, and **26** in good yields (up to 77%). Hydrazide **15** was obtained before in reaction of ester **1** with hydrazine hydrate, but under other conditions, namely, in ethanol solution under microwave irradiation [16, 17].

Yet the formation of hydrazides **18**, **23–25**, **27**, and **28** in the reaction of esters **4**, **9–11**, **13**, and **14** with hydrazine hydrate required more rigid conditions: Two hour heating of the reaction mixture at 95°C with subsequent keeping for 20 h at 18–20°C. Compounds **18**, **23–25**, **27**, and **28** were isolated in yields up to 74%.

The differences in the chemical behavior of esters **1–14** were observed as well in the reactions with phenylhydrazine. For instance, phenylhydrazides **29–35** were successfully obtained in the reaction of esters **1–3**, **5**, **9**, and **11–13** with phenylhydrazine after 10 min heating of the reagents mixture at 170°C followed by keeping at 18–20°C for 20 h. However we failed to bring into the reaction with phenylhydrazine indole-containing 2-oxopyrrolidinecaroxylates **6–8** and **10** evidently due to the high sterical loading of the molecules.

The structure of all synthesized compounds **15–36** was confirmed by combination of the methods of IR and ^1H, ^{13}C $\{^1H\}$ NMR spectroscopy and X-ray diffraction (XRD) analysis (by an example of hydrazide **36**).



IR spectra of hydrazides **15–28** and phenylhydrazides **29–36** are alike. For instance, in the IR spectrum of compound **36** in the region of carbonyl absorption strong broadened bands are observed with the frequencies 1712 and 1662 cm^{-1} belonging to the stretching vibrations of lactam and hydrazide C=O groups respectively. In the high frequency region a broadened band appears (3270–3185 cm^{-1}) resulting

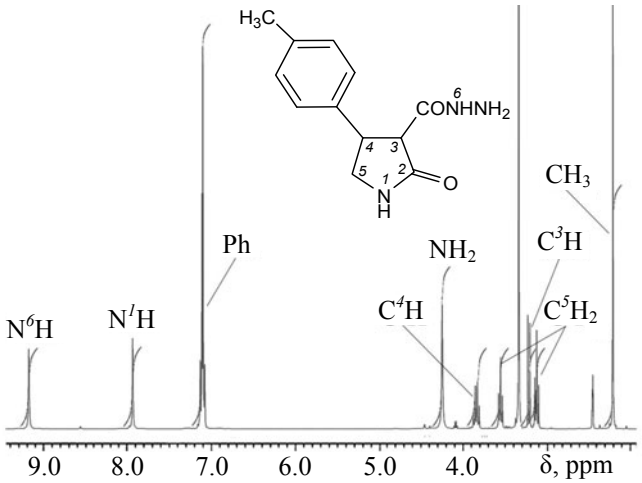


Fig. 1. ^1H NMR spectrum of 4-(4-methylphenyl)-2-oxopyrrolidine-3-carboxylic acid hydrazide **17** in DMSO-d_6.

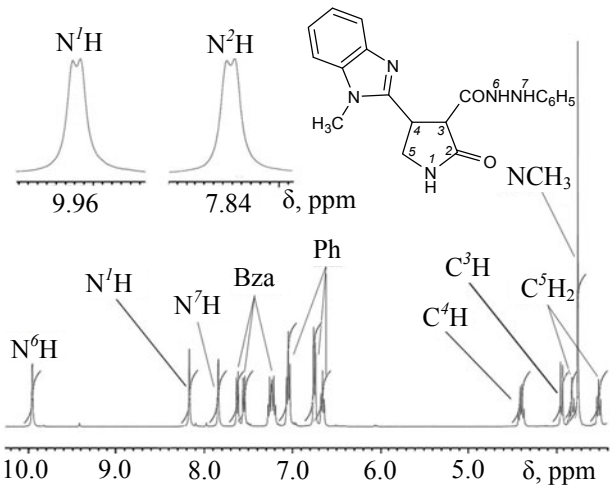


Fig. 2. ^1H NMR spectrum of 4-(1-methylbenzimidazol-2-yl)-2-oxopyrrolidine-3-carboxylic acid phenylhydrazide **36** in DMSO-d_6.

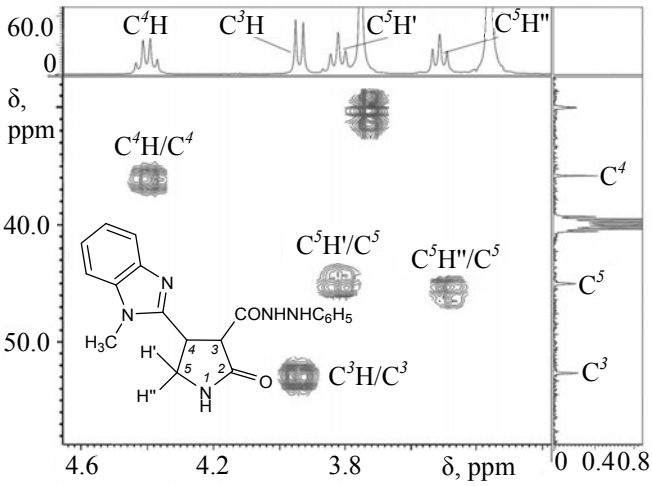


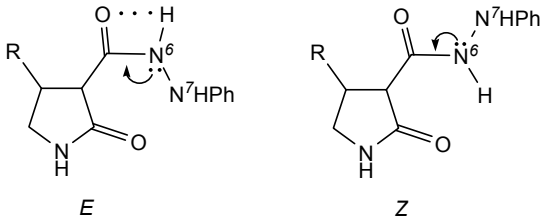
Fig. 3. Fragment of ^{1}H-^{13}C HMQC spectrum of hydrazide **36** in DMSO-d_6.

from superposition of the stretching vibrations of NH groups of the lactam and the hydrazide function.

^{1}H NMR spectrum of each specimen of the hydrazides series **15–28** and phenylhydrazides **29–36** contains a single set of proton signals corresponding to structural fragments thus indicating their diastereo uniformity (Figs. 1, 2). For example, in the ^{1}H NMR spectrum of hydrazide **17** according to the signals multiplicity the doublet at 3.22 ppm ($^{3}J_{3,4}$ 10.4 Hz) belongs to the methine proton H^{3}, and the proton H^{4} gives rise to the quartet at 3.84 ppm ($^{3}J_{3,4}$ 10.4, $^{3}J_{4,5'}$ 9.3, $^{3}J_{4,5''}$ 8.4 Hz). Methylene protons appear as two triplets: H$^{5'}$ at 3.13 ppm ($^{3}J_{4,5'}$ 9.3, $^{2}J_{5',5''}$ 9.3 Hz) and H$^{5''}$ at 3.56 ppm ($^{3}J_{4,5''}$ 8.4, $^{2}J_{5',5''}$ 9.3 Hz). In the weak field of this spectrum signals of proton H^{1} of the pyrrolidine ring (7.92 ppm) and of the phenyl substituent (7.07–7.12 ppm) are present. The protons of the hydrazide fragment appear as singlets: NH_2 group at 4.25 ppm, NH more downfield (9.18 ppm).

In the ^{1}H NMR spectra of phenylhydrazides **29–36** differences in the signals of the protons of the hydrazide function are regularly observed. For instance, in the spectrum of phenylhydrazide **36** (Fig. 2) a doublet is present from the proton H^{3} (3.94 ppm, $^{3}J_{3,4}$ 9.2 Hz) and a quartet from the proton H^{4} (4.40 ppm, $^{3}J_{3,4}$ 9.2, $^{3}J_{4,5'}$ 8.8, $^{3}J_{4,5''}$ 8.8 Hz). Methylene protons are present as two triplets: H$^{5'}$ at 3.52 ppm ($^{3}J_{4,5'}$ 8.8, $^{2}J_{5',5''}$ 9.1 Hz), H$^{5''}$ at 3.83 ppm ($^{3}J_{4,5''}$ 8.8, $^{2}J_{5',5''}$ 8.8 Hz). The downfield part of the spec-trum contains the signals of the H^{1} of the lactam ring (8.17 ppm) and multiplets belonging to protons of phe-nyl (6.61–7.09 ppm) and benzimidazole (7.24–7.63 ppm) substituents. The singlet from the methyl protons of the benzimidazole ring is observed upfield (3.76 ppm). The protons of the carbohydrazide fragment are present downfield as two doublets: 9.96 (N^{6}H, ^{3}J 2.1 Hz), 7.84 ppm (N^{7}H, ^{3}J 2.1 Hz).

Such substituted hydrazides are known to exist as *Z*- or *E*-conformers [18, 19], since in the amide group C(=O)NH due to its ability to form mesomeric structures certain barrier appears against the rotation around the nitrogen-carbon bond.



The chemical shifts of the NH proton of the carbohydrazide function (9.96 ppm) and of the carbonyl carbon atom (168.43 ppm) evidence the *Z*-conformation of compound **36**, namely, the oxygen atom of the carbonyl group and the NHPh fragment are located in the *cis*-position with respect to the C–N bond. This conclusion is based on the close data for structures containing analogous blocks with *trans* (*E*) and *cis* (*Z*) conformations [20, 21]. In particular, carbon signals of the carbonyl group are observed at ~168 (*Z*) and ~173 (*E*) ppm; the downfield shift of the latter is due to the possibility of the formation of intramolecular hydrogen bond between the oxygen and hydrogen atoms of the hydrazide group [20]. Since the data of ^{1}H and ^{13}C NMR spectra of substance **36** are well consistent with those of all phenylhydrazides **29–35** it is possible to conclude with a high probability that the result obtained for compound **36** is valid for all the series of substances.

The analysis of ^{1}H NMR spectra of hydrazides **15–28** and phenylhydrazides **29–36** shows that the values $^{3}J_{3,4}$ 8.9–10.7 Hz of protons H^{3,4} of 2-oxopyrrolidine ring indicate their *trans*-position and are in a good agreement with the data published on *trans*-2-oxopyrrolidinecarboxylic esters [22].

To prove the validity of assignment of signals in ^{1}H and ^{13}C NMR spectra of compounds **15–36** we registered 2D heteronuclear correlation NMR spectra ^{1}H-^{13}C HMQC and HMBC for hydrazides **17** and **20** and phenylhydrazides **32** and **36**. For example, in the correlation spectrum ^{1}H-^{13}C HMQC of phenylhydrazide **36** (Fig. 3) a coupling is observed between the

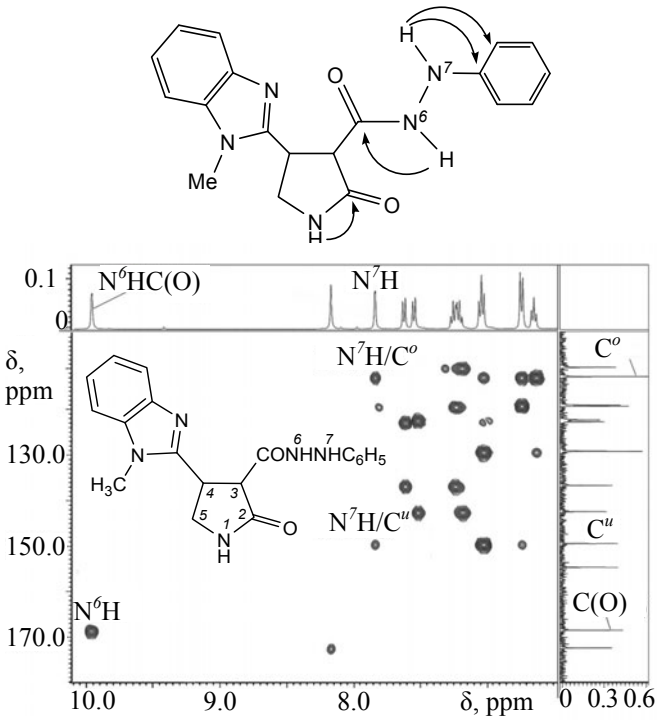


Fig. 4. Fragment of ^{1}H-^{13}C HMBC spectrum of hydrazide **36** in DMSO-d_6.

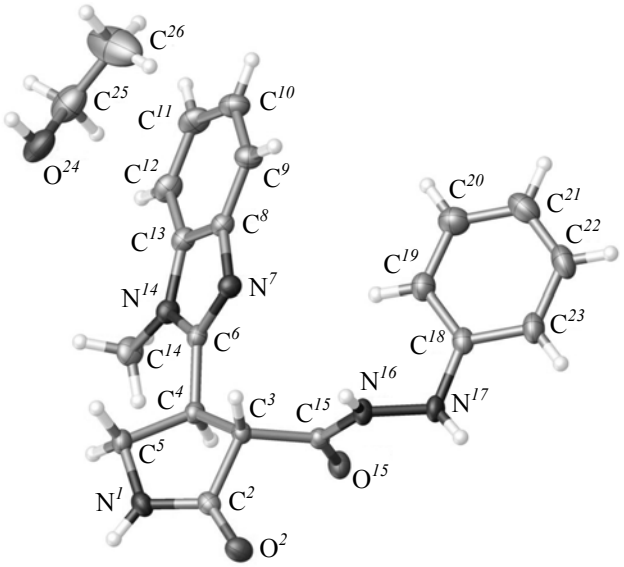


Fig. 5. General arrangement of hydrazide **36** molecule with a solvate ethanol in the crystal represented with thermal ellipsoids of 50% probability.

proton H^3 (3.94 ppm) and the atom C^3 (52.16 ppm), between the proton H^4 (4.40 ppm) and atom C^4 (35.92 ppm), protons $H^{5',5''}$ (3.52 and 3.83 ppm) and atom C^5 (45.06 ppm). Similar correlations appear also in the spectra ^{1}H-^{13}C HMQC of compounds **17**, **20**, and **32**. The application of the 2D heteronuclear correlation NMR spectroscopy ^{1}H-^{13}C HMQC to compounds **17**, **20**, **32**, and **36** made it possible to assign all the signals of protons bound to atoms C^{3-5} of the 2-oxopyrrolidine ring for the total series of obtained hydrazides **15**–**36**.

The validity of the signals assignment of the carbonyl carbon atoms and the protons of NH group of

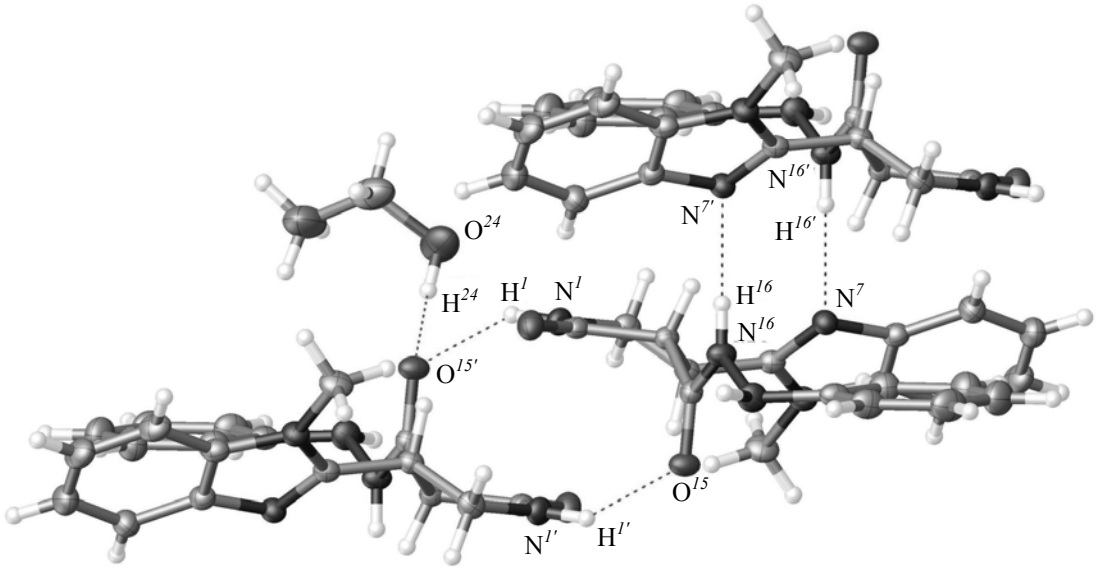


Fig. 6. Fragment of hydrazide **36** structure. Combination into a three-dimentional scaffold occurs due to H-bonds (dotted lines) between contiguous molecules of hydrazide **36** and ethanol molecule.

2-oxopyrrolidine rings and the hydrazide function of compounds **15–36** was proved by registering ^{1}H-^{13}C {^{1}H} HMBC spectra for derivatives **17**, **20**, **32**, and **36**. For example, in the ^{1}H-^{13}C {^{1}H} HMBC spectrum of phenylhydrazide **36** (Fig. 4) a correlation was observed between the proton of the N^{1}H group (8.17 ppm) of lactam and the atom C^{2} (172.36 ppm) of the 2-oxopyrrolidine ring, of the proton N^{6}H (9.96 ppm) and the carbon atom (169.44 ppm) of the hydrazide function, of the proton N^{7}H (7.84 ppm) of the hydrazide function and the *ipso*- (149.39 ppm) and *ortho*- (112.69 ppm) carbon atoms of the benzene ring.

Thus the similar character of spectra of the total series of synthesized hydrazides as well as the phenylhydrazides series, and also the analysis of the ^{1}H-^{13}C {^{1}H} HMQC and HMBC spectra of compounds **17**, **20**, **32**, and **36** made it possible to reliably interpret the ^{1}H and C^{13}{^{1}H} NMR spectra of the whole series of prepared hydrazides **15–28** and phenylhydrazides **29–36** and to show authentically that in their molecules the substituents at the atoms C^{3,4} are located in the *trans*-position.

The spatial arrangement of obtained substances **15–36** was subjected to XRD analysis by an example of hydrazide **36** (Figs. 5, 6). Compound **36** crystallized as racemate. Two asymmetric centers (atoms C^{3,4}) possess relative configurations 3*R* and 4*S*. The five-membered ring possesses an *envelope* conformation, in the molecule **36** the fragment C^{5}N^{1}C^{2}C^{3} is planar within 0.004 Å, the deviation of the atom C^{4} from this plane is 0.561(2) Å. The distribution of bond lengths at the atoms N^{1} and N^{16} indicates the conjugation of the unshared electron pairs on nitrogen atoms and the C=O bonds: bonds N^{1}–C^{2} [1.3420(12) Å] and C^{15}–N^{16} [1.3331(11) Å] are notably shortened as compared with those in the acetanilide PhNHCOMe molecule [1.43(1) Å] [23]. The substituents at the atoms C^{3,4} are located on different sides of the plane of the lactam ring: torsion angle C^{15}C^{3}C^{4}C^{6} 77.5(1)°, respectively, protons at these atoms have a transoid location. The carbonyl oxygen atom and the substituent NHC$_6$H$_5$ of the hydrazide fragment are situated practically in the same plane with respect to the amide bond C^{15}–N^{16}: torsion angle is O^{15}C^{15}N^{16}N^{17} 4.05(14)° corresponding to the *Z*-conformation. The crystals of compound **36** are stabilized with intermolecular hydrogen bonds N^{1}H···O^{15}, N^{16}H···N^{7} forming a three-dimensional scaffold. A solvate molecule of ethanol is present in the crystal and forms a hydrogen bond C$_2$H$_5$OH···O^{15} (Fig. 6).

Compounds synthesized present an independent interest as promising biologically active compounds; they also may be regarded as initial reagents for the synthesis of new derivatives of 2-oxopyrrolidine.

EXPERIMENTAL

Spectral characteristics and elemental analysis data of synthesized compounds were measured using the equipment of the Center of joint usage of the chemical faculty of the Herzen State Pedagogical University. XRD analysis was performed using the equipment of the Resource Center of Saint-Petersburg State University "X-ray diffraction investigation methods."

^{1}H, ^{1}H-^{13}C {^{1}H} HMQC and HMBC NMR spectra were registered on a spectrometer Jeol ECX400A at operating frequencies 399.78 (^{1}H) and 100.52 (^{13}C) MHz in dimethyl sulfoxide-d_6 using the residual signal of the nondeuterated solvent as an internal reference. IR spectra were taken on a Fourier spectrophotometer Shimadzu IRPrestige-21 from pellets with KBr. Elemental analysis of substances synthesized was carried out on an analyzer EuroVector EA 3000 (CHN Dual mode). Melting points were measured on a device PTP(M).

The XRD experiment for compound **36** was performed on a diffractometer Bruker Kappa Apex II Duo (MoK_α, λ 0.71073 Å) using programs of data collection and processing APEX2 [24]. The extinction was taken into consideration applying the program package SADABS [25]. The solving and refining of the structure using the least squares method was carried out by SHELXS program [26] implemented in OLEX2 software [27]. The positions and thermal parameters of nonhydrogen atoms were refined in an anisotropic approximation. The positions of hydrogen atoms were revealed from the difference electron density, the thermal parameters of hydrogen atom were refined in the *rider* model. The crystallographic parameters of the structure refinement of compound **36** at 150(2) K are as follows: $C_{19}H_{19}N_5O_2 \cdot C_2H_5OH$, crystal size 0.24 × 0.17 × 0.11 mm^3, *M* 395.46, triclinic crystal system, space group *P*1, *a* 9.9831(18), *b* 10.7902(19), *c* 11.233(2) Å; β 63.943(3), γ 69.852(4)°; *V* 1012.8(3) Å^3, Z 2, d_{calc} 1.297 g/cm^3, μ 0.089 mm^{-1}. Measured reflections 19065, independent reflections 5798 (R_{int} 0.0598), observed reflections with $|F_o| \geq 4\sigma_F$ 5037, R_1 0.0401, wR_2 0.1121, parameter of refinement 1.055. Maximum unaccounted electron density –0.230, 0.382 e/Å^3. The complete information on the studied

structure is deposited in the Cambridge Crystallographic Data Center (CCDC 1476906).

2-Oxo-4-phenylpyrrolidine-3-carbocylic acid hydrazide (15). A solution of 1.2 g (6 mmol) of ester **1** in 2.33 mL of hydrazine hydrate was stirred for 20 h at 18–20°C. The separated crystalline precipitate was filtered off and dried. Yield 1.09 g (83%), mp 114–116°C (from methanol) {120°C (from methanol) [16]}. IR spectrum, ν, cm^{-1}: 3480–3258 (NH, NH_2), 1708, 1670 (C=O, CON). ^1H NMR spectrum, δ, ppm: 3.16 t (1H, $H^{5'}$, $^3J_{4,5'}$ 9.1, $^2J_{5',5''}$ 9.1 Hz), 3.26 d (1H, H^3, $^3J_{3,4}$ 10.4 Hz), 3.59 t (1H, $H^{5''}$, $^3J_{4,5''}$ 9.1, $^2J_{5',5''}$ 9.1 Hz), 3.89 q (1H, H^4, $^3J_{3,4}$ 10.4, $^3J_{4,5'}$ 9.1, $^3J_{4,5''}$ 9.1 Hz), 4.26 s (2H, NH_2), 7.18–7.30 m ($5H_{arom}$), 7.96 s (1H, N^1H), 9.18 s (1H, N^6H). Found, %: N 19.41, 19.42. $C_{11}H_{13}N_3O_2$. Calculated, %: N 19.17.

Esters **16**, **17**, **19–22**, and **26** were obtained similarly.

4-(4-Methoxyphenyl)-2-oxopyrrolidine-3-carboxylic acid hydrazide (16). Yield 71%, mp 174–176°C (from methanol). IR spectrum, ν, cm^{-1}: 3332–3119 (NH, NH_2), 1715, 1656 (C=O, CON). ^1H NMR spectrum, δ, ppm: 3.11 t (1H, $H^{5'}$, $^3J_{4,5'}$ 9.3, $^2J_{5',5''}$ 9.3 Hz), 3.20 d (1H, H^3, $^3J_{3,4}$ 10.4 Hz), 3.52 t (1H, $H^{5''}$, $^3J_{4,5''}$ 8.5, $^2J_{5',5''}$ 9.3 Hz), 3.68 s (3H, OCH_3), 3.83 q (1H, H^4, $^3J_{3,4}$ 10.4, $^3J_{4,5'}$ 9.3, $^3J_{4,5''}$ 8.5 Hz), 4.25 s (2H, NH_2), 6.84–7.15 m ($4H_{arom}$), 7.92 s (1H, N^1H), 9.15 s (1H, N^6H). Found, %: C 57.88, 57.90; H 5.93, 5.96; N 17.00, 17.02. $C_{12}H_{15}N_3O_3$. Calculated, %: C 57.82; H 6.07; N 16.86.

4-(4-Methylphenyl)-2-oxopyrrolidine-3-carboxylic acid hydrazide (17). Yield 84%, mp 185–187°C (from methanol). IR spectrum, ν, cm^{-1}: 3448–3149 (NH, NH_2), 1710, 1666 (C=O, CON). ^1H NMR spectrum, δ, ppm: 2.22 s (3H, CH_3), 3.13 t (1H, $H^{5'}$, $^3J_{4,5'}$ 9.3, $^2J_{5',5''}$ 9.3 Hz), 3.22 d (1H, H^3, $^3J_{3,4}$ 10.4 Hz), 3.56 t (1H, $H^{5''}$, $^3J_{4,5''}$ 8.4, $^2J_{5',5''}$ 9.3 Hz), 3.84 q (1H, H^4, $^3J_{3,4}$ 10.4, $^3J_{4,5'}$ 9.3, $^3J_{4,5''}$ 8.4 Hz), 4.25 s (2H, NH_2), 7.07–7.12 m ($4H_{arom}$), 7.92 s (1H, N^1H), 9.18 s (1H, N^6H). $^{13}C\{^1H\}$ NMR spectrum, δ, ppm: 21.12 (CH_3), 43.66 (C^4), 47.40 (C^5), 54.13 (C^3), 168.26 (C^6), 173.39 (C^2); 127.61, 129.63, 136.53, 138.15 (C_{arom}). Found, %: C 57.44, 57.46; H 6.56, 6.55; N 16.64, 16.32. $C_{12}H_{15}N_3O_2 \cdot H_2O$. Calculated, %: C 57.36; H 6.82; N 16.72.

4-(Indol-3-yl)-2-oxopyrrolidine-3-carboxylic acid hydrazide (19). Yield 61%, mp 87–89°C (from methanol). IR spectrum, ν, cm^{-1}: 3391–3118 (NH, NH_2), 1693, 1664 (C=O, CON). ^1H NMR spectrum, δ, ppm: 3.24 t (1H, $H^{5'}$, $^3J_{4,5'}$ 9.2, $^2J_{5',5''}$ 9.2 Hz), 3.30 d (1H, H^3, $^3J_{3,4}$ 10.1 Hz), 3.69 t (1H, $H^{5''}$, $^3J_{4,5''}$ 8.6, $^2J_{5',5''}$ 9.2 Hz), 4.11 q (1H, H^4, $^3J_{3,4}$ 10.1, $^3J_{4,5'}$ 9.2, $^3J_{4,5''}$ 8.6 Hz), 4.24 d (2H, NH_2, $^3J_{NH-NH}$ 3.4 Hz), 6.94–7.46 m ($5H_{indole}$), 7.95 s (1H, N^1H), 9.18 d (1H, N^6H, $^3J_{NH-NH}$ 3.4 Hz), 10.90 s (1H, NH_{indole}). Found, %: N 21.96, 21.80. $C_{13}H_{14}N_4O_2$. Calculated, %: N 21.69.

4-(1-Methylindol-3-yl)-2-oxopyrrolidine-3-carboxylic acid hydrazide (20). Yield 83%, mp 190–192°C (from methanol). IR spectrum, ν, cm^{-1}: 3447–3131 (NH, NH_2), 1712, 1662 (C=O, CON). ^1H NMR spectrum, δ, ppm: 3.24 t (1H, $H^{5'}$, $^3J_{4,5'}$ 9.1, $^2J_{5',5''}$ 9.1 Hz), 3.26 d (1H, H^3, $^3J_{3,4}$ 10.4 Hz), 3.66 t (1H, $H^{5''}$, $^3J_{4,5''}$ 9.1, $^2J_{5',5''}$ 9.1 Hz), 3.69 s (NCH_3), 4.11 q (1H, H^4, $^3J_{3,4}$ 10.4, $^3J_{4,5'}$ 9.1, $^3J_{4,5''}$ 9.1 Hz), 4.23 s (2H, NH_2), 6.98–7.47 m ($5H_{indole}$), 7.95 s (1H, N^1H), 9.15 s (1H, N^6H). $^{13}C\{^1H\}$ NMR spectrum, δ, ppm: 32.87 (CH_3), 36.00 (C^4), 46.81 (C^5), 54.15 (C^3), 168.72 (C^6), 173.66 (C^2); 110.27, 114.03, 119.29, 119.50, 121.89, 126.77, 127.11, 137.43 (C_{arom}). Found, %: N 18.31, 18.28. $C_{14}H_{16}N_4O_2 \cdot 2H_2O$. Calculated, %: N 18.17.

4-(1-Benzylindol-3-yl)-2-oxopyrrolidine-3-carboxylic acid hydrazide (21). Yield 69%, mp 233–235°C (from methanol). IR spectrum, ν, cm^{-1}: 3333–3126 (NH, NH_2), 1706, 1664 (C=O, CON). ^1H NMR spectrum, δ, ppm: 3.29 t (1H, $H^{5'}$, $^3J_{4,5'}$ 9.1, $^2J_{5',5''}$ 9.1 Hz), 3.27 d (1H, H^3, $^3J_{3,4}$ 10.0 Hz), 3.69 t (1H, $H^{5''}$, $^3J_{4,5''}$ 9.1, $^2J_{5',5''}$ 9.1 Hz), 4.13 q (1H, H^4, $^3J_{3,4}$ 10.0, $^3J_{4,5'}$ 9.1, $^3J_{4,5''}$ 9.1 Hz), 4.25 s (2H, NH_2), 5.29 d (1H, CH_2, ^2J 16.8 Hz), 5.35 d (1H, CH_2, ^2J 16.8 Hz), 6.95–7.52 m ($5H_{indole}$), 7.97 s (1H, N^1H), 9.16 s (1H, N^6H). Found, %: C 69.11, 69.02; H 5.64, 5.68; N 15.93, 15.96. $C_{20}H_{22}N_4O_2$. Calculated, %: C 68.95; H 5.79; N 16.08.

4-(2-Methylindol-3-yl)-2-oxopyrrolidine-3-carboxylic acid hydrazide (22). Yield 63%, mp 99–101°C (from methanol). IR spectrum, ν, cm^{-1}: 3354–3114 (NH, NH_2), 1699, 1673 (C=O, CON). ^1H NMR spectrum, δ, ppm: 2.26 s (3H, CH_3), 3.31 m (1H, $H^{5'}$), 3.42 d (1H, H^3, $^3J_{3,4}$ 10.1 Hz), 3.46 m (1H, $H^{5''}$), 4.15 m (1H, H^4, $^3J_{3,4}$ 10.1 Hz), 4.18 s (2H, NH_2), 6.89–7.41 m ($4H_{indole}$), 8.00 s (1H, N^1H), 9.03 s (1H, N^6H), 10.79 s (1H, NH_{indole}). Found, %: C 61.25, 61.18; H 5.71, 5.75; N 20.31, 20.19. $C_{14}H_{16}N_4O_2$. Calculated, %: C 61.75; H 5.92; N 20.58.

2-Oxo-4-(furan-2-yl)pyrrolidine-3-carboxylic acid hydrazide (26). Yield 70%, mp 146–148°C (from methanol). IR spectrum, ν, cm^{-1}: 3328–3289 (NH, NH_2), 1695, 1658 (C=O, CON). ^1H NMR spectrum, δ,

ppm: 3.26 t (1H, $H^{5'}$, $^3J_{4,5'}$ 9.1, $^2J_{5',5''}$ 9.1 Hz), 3.36 d (1H, H^3, $^3J_{3,4}$ 9.6 Hz), 3.61 t (1H, $H^{5''}$, $^3J_{4,5''}$ 8.6, $^2J_{5',5''}$ 9.1 Hz), 3.98 q (1H, H^4, $^3J_{3,4}$ 9.6, $^3J_{4,5'}$ 9.1, $^3J_{4,5''}$ 8.6 Hz), 4.33 s (2H, NH_2), 6.24 m ($1H_{Fu}$), 6.39 m ($1H_{Fu}$), 7.58 m ($1H_{Fu}$), 8.01 s (1H, N^1H), 9.27 s (1H, N^6H). Found, %: C 51.63, 51.76; H 5.29, 5.34; N 20.21, 20.19. $C_9H_{11}N_4O_3$. Calculated, %: C 51.68; H 5.26; N 20.10.

2-Oxo-4-(4-chlorophenyl)pyrrolidine-3-carboxylic acid hydrazide (18). A solution of 1.52 g (6 mmol) of reagent **4** in 2.33 mL of hydrazine hydrate was stirred for 2 h at 95°C and 20 h at 18–20°C. The separated crystals were filtered off and dried. Yield 0.94 g (62%), mp 193–196°C (from methanol). IR spectrum, ν, cm^{-1}: 3349–3243 (NH, NH_2), 1731, 1657 (C=O, CON). ^1H NMR spectrum, δ, ppm: 3.15 t (1H, $H^{5'}$, $^3J_{4,5'}$ 9.3, $^2J_{5',5''}$ 9.3 Hz), 3.23 d (1H, H^3, $^3J_{3,4}$ 10.4 Hz), 3.58 t (1H, $H^{5''}$, $^3J_{4,5''}$ 8.5, $^2J_{5',5''}$ 9.3 Hz), 3.89 q (1H, H^4, $^3J_{3,4}$ 10.4, $^3J_{4,5'}$ 9.3, $^3J_{4,5''}$ 8.5 Hz), 4.26 s (2H, NH_2), 7.27–7.35 m ($4H_{arom}$), 7.96 s (1H, N^1H), 9.16 s (1H, N^6H). Found, %: C 52.23, 52.11; H 4.59, 4.66; N 16.76, 16.63. $C_{11}H_{12}ClN_3O_2$. Calculated, %: C 52.08; H 4.77; N 16.56.

Hydrazides **23–25**, **27**, and **28** were obtained similarly.

4-(1,2-Dimethylindole-3-yl)-*2*-oxo-pyrrolidine-3-carboxylic acid hydrazide (23). Yield 68%, mp 215–219°C (from methanol). IR spectrum, ν, cm^{-1}: 3427–3121 (NH, NH_2), 1692, 1660 (C=O, CON). ^1H NMR spectrum, δ, ppm: 2.29 s (3H, CH_3), 3.45 m (1H, $H^{5'}$), 3.47 d (1H, H^3, $^3J_{3,4}$ 9.2 Hz), 3.47 m (1H, $H^{5''}$), 3.59 s (NCH_3), 4.22 m (1H, H^4, $^3J_{3,4}$ 9.2 Hz), 4.19 s (2H, NH_2), 6.95–7.39 m ($4H_{indole}$), 8.01 s (1H, N^1H), 9.03 s (1H, N^6H). Found, %: C 62.58, 62.83; H 6.17, 6.23; N 19.71, 19.83. $C_{15}H_{18}N_4O_2$. Calculated, %: C 62.92; H 6.34; N 19.57.

4-(1-Benzyl-2-methylindole-3-yl)-2-oxopyrrolidine-3-carboxylic acid hydrazide (24). Yield 74%, mp 199–204°C (from methanol). IR spectrum, ν, cm^{-1}: 3322–3241 (NH, NH_2), 1704, 1650 (C=O, CON). ^1H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 3.50 m (1H, $H^{5'}$), 3.46 d (1H, H^3, $^3J_{3,4}$ 9.8 Hz), 3.50 m (1H, $H^{5''}$), 4.22 m (1H, H^4, $^3J_{3,4}$ 9.8 Hz), 4.19 d (2H, NH_2, $^3J_{NH-NH}$ 2.6 Hz), 5.32 d (1H, CH_2, ^2J 17.1 Hz), 5.38 d (1H, CH_2, ^2J 17.1 Hz), 6.94–7.43 m ($4H_{indole.}$), 8.02 s (1H, N^1H), 9.04 d (1H, N^6H, $^3J_{NH-NH}$ 2.6 Hz). Found, %: C 69.70, 69.78; H 6.14, 6.13; N 15.31, 15.36. $C_{21}H_{22}N_4O_2$. Calculated, %: C 69.61; H 6.08; N 15.47.

2-Oxo-4-(pyridin-3-yl)pyrrolidine-3-carboxylic acid hydrazide (25). Yield 60%, mp 154–156°C (from methanol). IR spectrum, ν, cm^{-1}: 3205–3133 (NH, NH_2), 1707, 1671 (C=O, CON). ^1H NMR spectrum, δ, ppm: 3.20 t (1H, $H^{5'}$, $^3J_{4,5'}$ 9.3, $^2J_{5',5''}$ 9.3 Hz), 3.30 d (1H, H^3, $^3J_{3,4}$ 10.4 Hz), 3.63 t (1H, $H^{5''}$, $^3J_{4,5''}$ 8.4, $^2J_{5',5''}$ 9.3 Hz), 3.94 q (1H, H^4, $^3J_{3,4}$ 10.4, $^3J_{4,5'}$ 9.3, $^3J_{4,5''}$ 8.4 Hz), 4.32 s (2H, NH_2), 7.22–7.34 m ($4H_{Py}$), 7.99 s (1H, N^1H), 9.21 s (1H, N^6H). Found, %: N 25.28, 25.19. $C_{10}H_{12}N_4O_2$. Calculated, %: N 25.46.

4-(1-Methylbenzimidazol-2-yl)-2-oxopyrrolidine-3-carboxylic acid hydrazide (27). Yield 61%, mp 223–225°C (from methanol). IR spectrum, ν, cm^{-1}: 3360–3315 (NH, NH_2), 1702, 1644 (C=O, CON). ^1H NMR spectrum, δ, ppm: 3.38 t (1H, $H^{5'}$, $^3J_{4,5'}$ 9.0, $^2J_{5',5''}$ 9.0 Hz), 3.69 d (1H, H^3, $^3J_{3,4}$ 8.9 Hz), 3.53 t (1H, $H^{5''}$, $^3J_{4,5''}$ 9.0, $^2J_{5',5''}$ 9.0 Hz), 3.75 s (3H, NCH_3), 4.37 q (1H, H^4, $^3J_{3,4}$ 8.9, $^3J_{4,5'}$ 9.0, $^3J_{4,5''}$ 9.0 Hz), 4.36 s (2H, NH_2), 7.21–7.59 m (4H, $H_{benzimidazole}$), 7.92 s (1H, N^1H), 9.34 s (1H, N^6H). Found, %: C 57.01, 56.91; H 5.61, 5.58; N 25.60, 25.53. $C_{13}H_{15}N_5O_2$. Calculated, %: C 57.14; H 5.50; N 25.64.

4-(1-Methylbenzimidazol-2-yl)-2-oxo-5-phenylpyrrolidine-3-carboxylic acid hydrazide (28). Yield 59%, mp 230–232°C (from methanol). IR spectrum, ν, cm^{-1}: 3325–3237 (NH, NH_2), 1703, 1644 (C=O, CON). ^1H NMR spectrum, δ, ppm: 5.31 d (1H, $H^{5'}$, $^3J_{4,5'}$ 8.6 Hz), 4.31 d (1H, H^3, $^3J_{3,4}$ 9.1 Hz), 3.70 s (3H, NCH_3), 4.70 t (1H, H^4, $^3J_{3,4}$ 9.1, $^3J_{4,5'}$ 8.6 Hz), 4.95 s (2H, NH_2), 6.97–7.02 ($5H_{arom}$), 7.08–7.35 m ($4H_{benzimidazole}$), 8.59 s (1H, N^1H), 9.63 s (1H, N^6H). Found, %: C 65.07, 65.11; H 5.51, 5.51; N 20.15, 20.21. $C_{19}H_{19}N_5O_2$. Calculated, %: C 65.33; H 5.44; N 20.06.

2-Oxo-4-phenylpyrrolidine-3-carboxylic acid phenylhydrazide (29). A solution of 1.2 g (6 mmol) of ester **1** in 4.72 mL of freshly distilled phenylhydrazine was stirred for 10 min at heating on a glycerol bath (170°C), cooled to 18–20°C, and was stirred for 20 h. The separated crystals were filtered off and dried. Yield 0.96 g (54%), mp 200–202°C (from methanol). IR spectrum, ν, cm^{-1}: 3301–3136 (NH, NH_2), 1701, 1663 (C=O, CON). ^1H NMR spectrum, δ, ppm: 3.26 t (1H, $H^{5'}$, $^3J_{4,5'}$ 10.3, $^2J_{5',5''}$ 10.3 Hz), 3.45 d (1H, H^3, $^3J_{3,4}$ 10.7 Hz), 3.61 t (1H, $H^{5''}$, $^3J_{4,5''}$ 8.4, $^2J_{5',5''}$ 10.3 Hz), 3.93 q (1H, H^4, $^3J_{3,4}$ 10.7, $^3J_{4,5'}$ 10.3, $^3J_{4,5''}$ 8.4 Hz), 6.61–7.04 m ($5H_{arom}$), 7.25–7.35 m ($5H_{arom}$), 7.80 d (1H, N^7H, $^3J_{NH-NH}$ 2.6 Hz), 8.03 s (1H, N^1H), 9.77 d (1H, N^6H, $^3J_{NH-NH}$ 2.6 Hz). Found, %: C 68.98,

69.03; H 5.59, 5.61; N 14.36, 14.39. $C_{17}H_{17}N_3O_2$. Calculated, %: C 69.14; H 5.80; N 14.23.

Hydrazides **30–36** were obtained similarly.

4-(4-Methoxyphenyl)-2-oxopyrrolidine-3-carboxylic acid phenylhydrazide (30). Yield 70%, mp 210°C (from methanol). IR spectrum, ν, cm^{-1}: 3301–3136 (NH, NH_2), 1701, 1663 (C=O, CON). ^1H NMR spectrum, δ, ppm: 3.22 t (1H, $H^{5'}$, $^3J_{4,5'}$ 9.3, $^2J_{5',5''}$ 9.3 Hz), 3.38 d (1H, H^3, $^3J_{3,4}$ 10.7 Hz), 3.56 t (1H, $H^{5''}$, $^3J_{4,5''}$ 8.4, $^2J_{5',5''}$ 9.3 Hz), 3.71 s (3H, OCH_3), 3.86 q (1H, H^4, $^3J_{3,4}$ 10.7, $^3J_{4,5'}$ 9.3, $^3J_{4,5''}$ 8.4 Hz), 6.60–6.90 m ($5H_{arom}$), 7.03–7.20 m ($4H_{arom}$), 7.79 d (1H, N^7H, $^3J_{NH–NH}$ 2.4 Hz), 7.99 s(1H, N^1H), 9.73 d (1H, N^6H, $^3J_{NH–NH}$ 2.4 Hz). Found, %: C 66.77, 66.25; H 5.73, 5.68; N 13.12, 13.05. $C_{18}H_{19}N_3O_3$. Calculated, %: C 66.45; H 5.89; N 12.91.

4-(4-Methylphenyl)-2-oxopyrrolidine-3-carboxylic acid phenylhydrazide (31). Yield 77%, mp 240°C (from methanol). IR spectrum, ν, cm^{-1}: 3354–3130 (NH, NH_2), 1700, 1658 (C=O, CON). ^1H NMR spectrum, δ, ppm: 2.26 s (3H, CH_3), 3.23 t (1H, $H^{5'}$, $^3J_{4,5'}$ 9.3, $^2J_{5',5''}$ 9.3 Hz), 3.40 d (1H, H^3, $^3J_{3,4}$ 10.7 Hz), 3.58 t (1H, $H^{5''}$, $^3J_{4,5''}$ 8.4, $^2J_{5',5''}$ 9.3 Hz), 3.88 q (1H, H^4, $^3J_{3,4}$ 10.7, $^3J_{4,5'}$ 9.3, $^3J_{4,5''}$ 8.4 Hz), 6.61–7.04 m ($5H_{arom}$), 7.12–7.18 m ($4H_{arom}$), 7.79 d (1H, N^7H, $^3J_{NH–NH}$ 2.4 Hz), 8.01 s (1H, N^1H), 9.75 d (1H, N^6H, $^3J_{NH–NH}$ 2.4 Hz). Found, %: C 70.06, 69.93; H 5.63, 5.96; N 13.77, 13.78. $C_{18}H_{19}N_3O_2$. Calculated, %: C 69.88; H 6.19; N 13.58.

4-(Indol-3-yl)-2-oxopyrrolidine-3-carboxylic acid phenylhydrazide (32). Yield 36%, mp 241–242°C (from methanol). IR spectrum, ν, cm^{-1}: 3424–3205 (NH, NH_2), 1719, 1651 (C=O, CON). ^1H NMR spectrum, δ, ppm: 3.33 t (1H, $H^{5'}$, $^3J_{4,5'}$ 9.1, $^2J_{5',5''}$ 9.1 Hz), 3.48 d (1H, H^3, $^3J_{3,4}$ 10.2 Hz), 3.69 t (1H, $H^{5''}$, $^3J_{4,5''}$ 9.1, $^2J_{5',5''}$ 9.1 Hz), 4.16 q (1H, H^4, $^3J_{3,4}$ 10.2, $^3J_{4,5'}$ 9.1, $^3J_{4,5''}$ 9.1 Hz), 6.61–6.99 m ($5H_{arom}$), 6.97–7.51 m (5H, H_{indole}), 7.77 d (1H, N^7H, $^3J_{NH–NH}$ 1.8 Hz), 8.02 s (1H, N^1H), 9.74 d (1H, N^6H, $^3J_{NH–NH}$ 1.8 Hz), 10.96 s (1H, NH_{indole}). $^{13}C\{^1H\}$ NMR spectrum, δ, ppm: 36.00 (C^4), 46.87 (C^5), 54.32 (C^3), 169.44 (C^6), 173.49 (C^2); 112.07, 112.70, 114.66, 118.82, 119.10, 119.39, 121.81, 122.52, 126.81, 129.02, 137.08, 149.37 (C_{arom}). Found, %: C 68.11, 68.09; H 5.23, 5.24; N 16.73, 16.81. $C_{19}H_{18}N_4O_2$. Calculated, %: C 68.25; H 5.43; N 16.76.

4-(1,2-Dimethylindol-3-yl)-2-oxopyrrolidine-3-carboxylic acid phenylhydrazide (33). Yield 32%, mp 220–224°C (from methanol). IR spectrum, ν, cm^{-1}: 3309–3264 (NH, NH_2), 1690, 1660 (C=O, CON). ^1H NMR spectrum, δ, ppm: 2.28 s (3H, CH_3), 3.49 m (1H, $H^{5'}$), 3.63 d (1H, H^3, $^3J_{3,4}$ 9.8 Hz), 3.51 m (1H, $H^{5''}$), 3.63 s (3H, NCH_3), 4.21 q (1H, H^4, $^3J_{3,4}$ 9.8 Hz), 6.63–7.05 m ($5H_{arom}$), 6.98–7.44 m ($4H_{indole}$), 7.71 d (1H, N^7H, $^3J_{NH–NH}$ 2.1 Hz), 8.08 s (1H, N^1H), 9.61 d (1H, N^6H, $^3J_{NH–NH}$ 2.1 Hz). Found, %: C 69.51, 69.38; H 5.98, 5.95; N 15.46, 15.36. $C_{21}H_{22}N_4O_2$. Calculated, %: C 69.59; H 6.12; N 15.46.

4-(Pyridin-3-yl)-2-oxopyrrolidine-3-carboxylic acid phenylhydrazide (34). Yield 43%, mp 188–190°C (from methanol). IR spectrum, ν, cm^{-1}: 3301–3134 (NH, NH_2), 1700, 1663 (C=O, CON). ^1H NMR spectrum, δ, ppm: 3.30 t (1H, $H^{5'}$, $^3J_{4,5'}$ 9.3, $^2J_{5',5''}$ 9.3 Hz), 3.48 d (1H, H^3, $^3J_{3,4}$ 10.7 Hz), 3.65 t (1H, $H^{5''}$, $^3J_{4,5''}$ 8.5, $^2J_{5',5''}$ 9.3 Hz), 3.97 q (1H, H^4, $^3J_{3,4}$ 10.7, $^3J_{4,5'}$ 9.3, $^3J_{4,5''}$ 8.5 Hz), 6.61–7.08 m ($5H_{arom}$), 7.26–7.38 m ($4H_{Py}$), 7.84 d (1H, N^7H, $^3J_{NH–NH}$ 2.2 Hz), 8.08 s (1H, N^1H), 9.81 d (1H, N^6H, $^3J_{NH–NH}$ 2.2 Hz). $^{13}C\{^1H\}$ NMR spectrum, δ, ppm: 44.15 (C^4), 47.10 (C^5), 54.36 (C^3), 168.90 (C^6), 173.02 (C^2); 112.07, 112.70, 114.66, 118.82, 119.10, 119.39, 121.81, 122.52, 126.81, 129.02, 137.08, 149.37 (C_{arom}). Found, %: C 64.91, 64.89; H 5.42. $C_{16}H_{16}N_4O_2$. Calculated, %: C 64.87; H 5.41.

2-Oxo-4-(furan-2-yl)pyrrolidine-3-carboxylic acid phenylhydrazide (35). Yield 70%, mp 174–175°C (from methanol). IR spectrum, ν, cm^{-1}: 3235–3114 (NH, NH_2), 1718, 1655 (C=O, CON). ^1H NMR spectrum, δ, ppm: 3.31 t (1H, $H^{5'}$, $^3J_{4,5'}$ 9.2, $^2J_{5',5''}$ 9.2 Hz), 3.45 d (1H, H^3, $^3J_{3,4}$ 10.0 Hz), 3.63 t (1H, $H^{5''}$, $^3J_{4,5''}$ 8.7, $^2J_{5',5''}$ 9.2 Hz), 4.03 q (1H, H^4, $^3J_{3,4}$ 10.0, $^3J_{4,5'}$ 9.2, $^3J_{4,5''}$ 8.7 Hz), 6.64–7.15 m ($5H_{arom}$), 6.30 m ($1H_{Fu}$), 6.44 m ($1H_{Fu}$), 7.63 m ($1H_{Fu}$), 7.90 d (1H, N^7H, $^3J_{NH–NH}$ 2.4 Hz), 8.10 s (1H, N^1H), 9.89 d (1H, N^6H, $^3J_{NH–NH}$ 2.4 Hz). Found, %: C 63.04, 63.28; H 5.34, 5.37; N 14.70, 14.82. $C_{15}H_{15}N_3O_3$. Calculated, %: C 63.16; H 5.26; N 14.74.

4-(1-Methylbenzimidazol-2-yl)-2-oxopyrrolidine-3-carboxylic acid phenylhydrazide (36). Yield 62%, mp 242–244°C (from ethanol). IR spectrum, ν, cm^{-1}: 3270–3185 (NH, NH_2), 1712, 1662 (C=O, CON). ^1H NMR spectrum, δ, ppm: 3.52 t (1H, $H^{5'}$, $^3J_{4,5'}$ 8.8, $^2J_{5',5''}$ 8.8 Hz), 3.76 s (3H, CH_3), 3.94 d (1H, H^3, $^3J_{3,4}$ 9.2 Hz), 3.83 t (1H, $H^{5''}$, $^3J_{4,5''}$ 8.8, $^2J_{5',5''}$ 8.8 Hz), 4.40 q (1H, H^4, $^3J_{3,4}$ 9.2, $^3J_{4,5'}$ 8.8, $^3J_{4,5''}$ 8.8 Hz), 6.61–7.09 m ($5H_{arom}$), 7.24–7.63 m (4H, $H_{benzimidazole}$), 7.84 d (1H, N^7H, $^3J_{NH–NH}$ 2.1 Hz), 8.17 s (1H, N^1H), 9.96 d (1H,

N^6H, $^3J_{NH–NH}$ 2.1 Hz). $^{13}C\{^1H\}$ NMR spectrum, δ, ppm: 30.15 (CH_3), 35.92 (C^4), 45.06 (C^5), 52.62 (C^3), 168.43 (C^6), 172.36 (C^2); 110.66, 112.69, 118.96, 119.16, 122.20, 122.63, 129.11, 136.62, 142.38, 149.39, 154.62 (C_{arom}). Found, %: C 65.24, 65.09; H 5.52, 5.51; N 19.98, 19.93. $C_{19}H_{19}N_5O_2$. Calculated, %: C 65.33; H 5.44; N 20.06.

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