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SYNTHESIS AND CHARACTERIZATION OF 4-SUBSTITUTED 1-(4-HALOGENOPHENYL)PYRROLIDIN-2-ONES WITH AZOLE AND AZINE MOIETIES

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Abstract – 4-Substituted 1-(4-fluoro- and 4-chlorophenyl)pyrrolidin-2-ones containing azole, oxadiazole, triazole, and triazine fragments have been synthesized, and the characterization of the obtained products is presented. The study compounds have been analyzed by elemental analysis, and the NMR, IR, MS techniques. The $^{1}H/^{13}C$ 2D (HETCOR), APT (^{13}C) NMR methods, and molecular modeling (MM2) were used for structure elucidation in more complicated cases.

INTRODUCTION

Many azoles containing one or several heteroatoms in the molecule are known as biologically active compounds with a lot of practical properties: they are anti-tumour CDK inhibitors,[1] show antituberculous,[2] antifungal,[3-5] antimicrobial and antifungal,[4] antifungal and antiparasitic,[5] antibacterial[6] effects may be used as crop protectors,[7] dyes[8] and in other fields of industry *e.g.*, as catalysts of the polymerization process,[9] corrosion inhibitors.[10] A number of 1,3,4-oxadiazoles have been described in numerous publications in relation to their practical application. The 1,3,4-oxadiazole core is an important pharmacophore in agricultural science, and compounds bearing this moiety often display antifungal, herbicidal,[11] anticandidal,[12] insecticidal[13,14] effects. Some material applications of 1,3,4-oxadiazole derivatives lie in the fields of photosensitizers[15] and liquid crystals.[16,17] 1,2,4-Triazoles and triazines have attracted particular attention due to the wide range of their biological properties such as antibacterial,

antifungal,[18-20] anticancer–antitumour,[21] cyclooxygenase and 5-lipoxygenase inhibiting,[22] antidepressant[23] effects and as agrochemicals[24,25] which treat and control various diseases.

As a continuation of our interest in the synthesis of new azole derivatives,[26-29] we decided to synthesize the title compounds for the future evaluation of their biological activity. Therefore efforts have been made to investigate the structural features[30-43] of compounds containing heteroatoms.

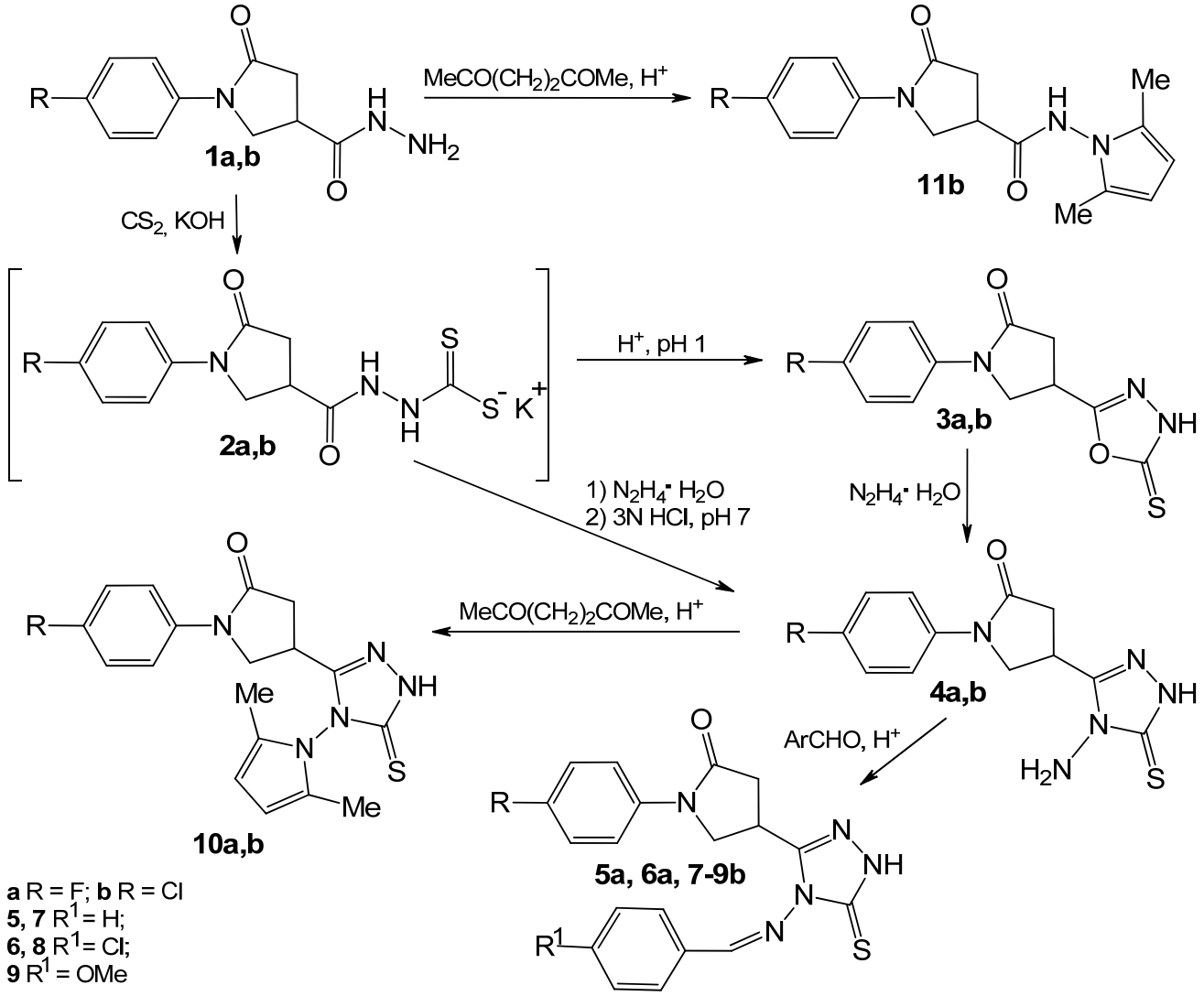
RESULTS AND DISCUSSION

The pathway of synthesis of the new 1,4-disubstituted pyrrolidinone derivatives possesing numerous prominent pharmacologically active structural fragments is shown in Scheme 1 (**3–11**) and in Scheme 2 (**12–16**).

The structure of all newly synthesized compounds has been confirmed by elemental analysis, mass spectrometry, IR, and investigated in detail by ^{1}H, ^{13}C NMR spectroscopy. The ^{1}H and ^{13}C NMR spectral data are presented in the Experimental section. Carbon atoms of the pyrrolidinone ring are marked arbitrarily according to the numbering given in Scheme 1.

For the synthesis of oxadiazole and triazole derivatives, the hydrazides **1a,b**, obtained by the method described in,[44] were heated with carbon disulfide in 2-propanol in the presence of potassium hydroxide. Upon refluxing, the formed potassium dithiocarbazates **2a,b** were dissolved in water, and acidifying the reaction mixture with diluted hydrochloric acid to pH 1 gave 1-(4-halogenophenyl)-4-(4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)pyrrolidin-2-ones **3a,b**. The formation of the oxadiazolethione ring in compounds **3a,b** was proven by signals at ~164 ppm (O-C=N) and ~178 ppm (C=S) in ^{13}C NMR spectra, and by the broad singlet, centered at ~14 ppm (NH) in ^{1}H NMR spectra. A characteristic absorption band of the NH group of compound **3a** was observed at 3106 cm^{-1} in the IR spectrum. The absorption bands at 1683 cm^{-1}, 1482 cm^{-1} and 1329 cm^{-1} were ascribed to the C=O group of the pyrrolidinone ring, the C=N group of the oxadiazole cycle and the C=S group, respectively.

It should be noted that such compounds as **3–10** in DMSO-d_6 solutions can exist in thiole and thione tautomeric forms.[36-41] In the light of the above-mentioned works, the simultaneous presence of thione and thiole tautomers in the DMSO-d_6 solution may be assumed. The theoretical chemical shift for hydrogen bonded to N is 14.35 ppm, the thiole tautomer SH proton chemical shift being 4.12 ppm, and these data were in satisfactory agreement with experimental data: 14.05 ppm (NH) and 3.37 ppm (SH).[39] The observed value (~14 ppm) of the chemical shift of the NH/SH proton for the study compounds **3–10** represents the averaged value of all existing NH/SH proton states. Considering the above-mentioned chemical shift values, the thione form may be concluded to be dominant.



Scheme 1. Synthesis of 4-substituted 1-(4-halogenophenyl)pyrrolidin-2-ones **3–11**

The corresponding aminotriazoles **4a,b** were obtained by heating potassium dithiocarbazates **2a,b** with hydrazine hydrate. Another way of synthesizing aminotriazoles **4a,b** is heating the corresponding 1,3,4-oxadiazoles **3a,b** with hydrazine hydrate in ethanol.[45]

The resonances at ~152.5 ppm (N-C=N) and at ~167 ppm (C=S) in ^{13}C NMR spectra as well as the resonances at ~5.5 ppm (NH_2) and at ~13.6 ppm (NH/SH) in ^{1}H NMR spectra revealed the formation of 5-membered triazole derivatives **4a,b**. The existence of a 5-membered heterocycle, containing three nitrogen atoms, also confirmed by absorption bands in the interval of 3279–2941, and at about 1680, 1495 and 1315 cm^{-1}, were attributed to the NH, NH_2, C=O, C=N and C=S, respectively, in IR spectra.

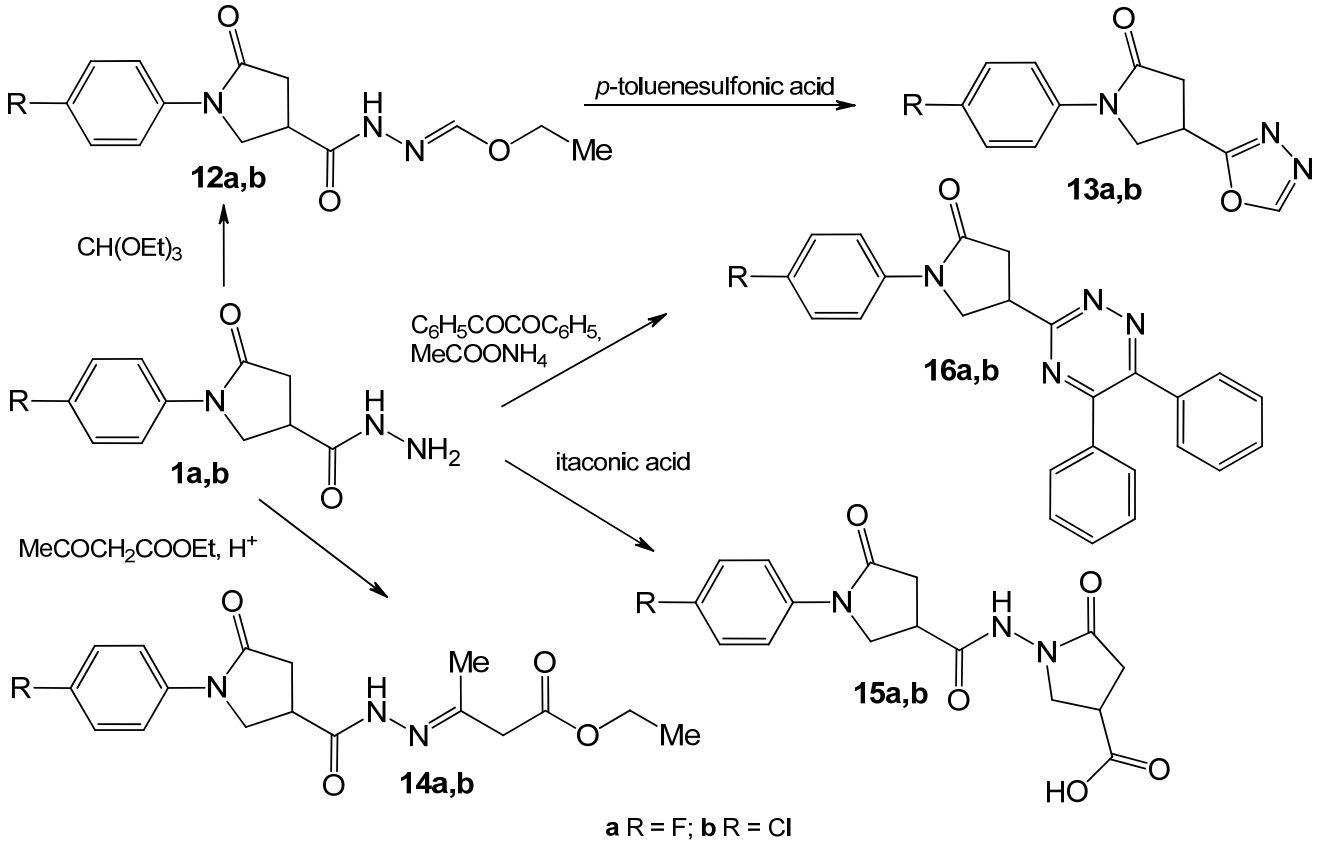
The condensation of aminotriazoles **4a,b** with aromatic aldehydes (benzaldehyde, 4-chlorobenzaldehyde, and 4-methoxybenzaldehyde) were carried out, and the corresponding Schiff bases **5a**, **6a** and **7–9b** were obtained. Due to the above-mentioned condensation reaction, the resonances of protons of the NH_2 group (~5.5 ppm) disappeared in ^{1}H NMR spectra of compounds **5a**, **6a** and **7–9b**. Characteristic changes of the

chemical shift of the resonances of the 5-membered heterocycle moiety were observed because of the changed influence of the substituent at C-N-CS. In this case, the C=S atom resonated at ~162 ppm, and the N-C=N atom at ~151 ppm in ^{13}C NMR spectra. Additional spectral lines were observed in the aromatic region and were assigned to the carbon atoms of the other benzene ring and azomethine group. The value of the latter chemical shifts depends on the nature of the substituent in the benzene ring and was manifested in the range ~160–163 ppm. The ^{1}H NMR spectra of compounds **5a**, **6a** and **7–9b** showed characteristic resonances at ~14 ppm (NH/SH), at ~10 ppm attributed to the azomethine group proton and the multiplet of the benzene ring, integrated for 8 (**6a**, **8b**, **9b**) or 9 (**5a**, **7b**) protons. The NMR spectra of mentioned compounds revealed the absence of geometric isomers. Considering all the above facts, the structure of compounds **5a**, **6a** and **7–9b** certainly exists.

During reactions of 4-amino-1,2,4-triazoles **4a,b** with 2,5-hexanedione, performed in the refluxing 2-propanol in the presence of a catalytic amount of hydrochloric acid, the *N*-substituted pyrrole derivatives **10a,b** were synthesized. The formation of a 2,5-dimethylpyrrole ring included into the **10a,b** composition is displayed by the double intensity resonances of CH at ~106 ppm, =C at 127.5 ppm, and CH_3 at ~11 ppm in ^{13}C NMR spectra, and singlets at ~2 ppm (CH_3), 6 ppm (=CH), ~14 ppm (NH) in ^{1}H NMR spectra. The NCSNH and NC=N carbons of the 1,2,4-triazole ring in comparison with compounds **4a,b** are found to be ~0.5 ppm deshielded and shielded, respectively, in ^{13}C NMR spectra.

The 1-(4-chlorophenyl)-*N*-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-oxopyrrolidine-3-carboxamide (**11b**) was obtained by condensation of hydrazide **1b** with 2,5-hexanedione in refluxing ethanol in the presence of a catalytic amount of glacial acetic acid. The ^{1}H and ^{13}C NMR spectral patterns of the 2,5-dimethylpyrrole ring moiety of compound **11b** are similar to this of compound **10b**. No rotamers were observed in the NMR spectra of compound **11b** in DMSO-d_6 solution despite the fact that the presence of the amide group caused isomer formation. Characteristic absorption band at 3275 cm^{-1} (NH) and sharp band at 1685 cm^{-1} (C=O) in the IR spectrum of derivative **11b** also confirm its structure.

Refluxing of above-mentioned hydrazides **1a,b** in the excess of triethyl orthoformate, in the presence of *p*-toluenesulfonic acid, gave 2-substituted oxadiazoles **13a,b**. The observed resonances at ~155 ppm (O-CH=N), at ~166.5 ppm (O-C=N) in ^{13}C NMR spectra and at ~9.2 ppm (O-CH=N) in ^{1}H NMR spectra, confirmed the successful formation of a oxadiazole ring. The shortening of the reaction time to 5 minutes allowed us to isolate the hydrazone-type intermediates **12a,b** containing amide, azomethine, and ether fragments. The presence of the mentioned above fragments determine the specific features of compounds **12a,b**. The NMR spectra of compounds **12a,b** exhibited four sets of resonances, therefore four different spatial states may exist in the DMSO-d_6 solution.[27]



Scheme 2. Synthesis of 4-substituted 1-(4-halogenophenyl)pyrrolidin-2-ones **12–16**

Condensation of hydrazides **1a,b** with ethyl acetoacetate gave 3-[2-[[5-oxo-1-phenylpyrrolidin-3-yl]carbonyl]hydrazinylidene]butanoates **14a,b**. The NMR spectra of compounds **14a,b** are complicated due to additional sets of resonances. The origin of such resonances is determined by isomers of different spatial structure. This fact was revealed from the optimized molecular models of each isomer. It should be noted that the molecules of the study compounds in the solutions apparently were in the dynamic equilibrium characterized by the equilibrium portion of each structure.

NMR did not provide conclusive information about separate conformations of the molecules studied, but gave a time averaged spectral view from all of the structures existing in the solution. Two sets of resonances observed in ^{13}C NMR spectra may be attributed to *E* (7.15 kJ/mol)/*Z* (9.46 kJ/mol) rotamers. More sensitive ^{1}H NMR spectra showed two intensively and four less intensively resolved resonances in the CH_3 and NH spectral regions. The analysis of isomer composition was not the aim of the present study. Taking into account the facts mentioned above, we may conclude that compounds **14a,b** were synthesized.

Investigation of the reactions of hydrazides **1a,b** with itaconic acid has revealed that they as primary amines form compounds containing a fragment of *γ*-amino acid, which undergoes a closure of 5-membered pyrrolidinone cycle already during the reaction, and compounds with two pyrrolidine rings

15a,b were obtained. The presence of two pyrrolidinone rings and four carbonyl groups in the molecules of the study compounds made the NMR spectra of **15a,b** intricate for interpretation. Nevertheless the NMR spectra of compounds **15a,b** were elucidated and their resonances were unambiguously assigned on the basis of general considerations of NMR properties, spectral data of structurally related compounds, and the computer molecular modeling. Molecules of **15a,b** compounds can exist as a mixture of *E/Z* rotamers through the amide bond. Experimental NMR data exhibited only one isomer in the DMSO-d_6 solution. The information derived from MM2 calculations allowed us to conclude that **15a** compound existed as *Z* rotamer (total sterical energy for rotamer – *E* (31.31 kJ/mol) and for *Z* one (17.92 kJ/mol)).

The chemical shift values of resonances of pyrrolidinone rings and carbonyl group carbons have been paralleled with the Extended Hückel partial charges computed for each atom of *Z* isomer of compounds **15a,b**. The carbons of the pyrrolidinone ring II were found to be more shielded than those of the ring I, whereas, in the sequence of carbonyl group carbons, the CONH group carbon was the most shielded and COOH carbon – the least shielded. Compound **15b** was used in agriculture technology investigating the influence on the yield and quality of oilseed rape (*Brassica napus* L.).[46] It was established that 1-(4-chlorophenyl)-5-oxopyrrolidine-3-carboxylic acid (**15b**) increased the average seed yield, but this compound could be more suitable in *B. napus* cultivation for specifical technical (non-food) purposes because it deteriorated all characteristics which are important for *B. napus* suitability for food industry: the level of linolenic acid exceeded that of linoleic acid, and the levels of erucic acid and glucosinolates were strongly increased. Compound **15b** also increased the fibre level in the seeds.

In the final stage of this work, the 4-(5,6-diphenyl-1,2,4-triazin-3-yl)-1-phenylpyrrolidin-2-ones **16a,b** were synthesized from carbohydrazides **1a,b** by three-component reaction. The expected structure of compounds **16a,b** indicated resonances at ~167 ppm (N=C-N) and ~156 ppm (N-C=C-N); additional resonances of two benzene rings in ^{13}C NMR spectra and the aromatic multiplets integrated to 14 protons in ^{1}H NMR spectra confirmed the formation of compounds **16a,b**.

The study compounds **3–16** have a fluorine atom (compounds **a**) and a chlorine atom (compounds **b**) at the *p*-position of the benzene ring. Because of the specific magnetic properties of the fluorine atom, a spin–spin coupling was observed in the ^{1}H and ^{13}C NMR spectra.[26] The doublets of the aromatic resonances in the ^{1}H NMR spectra overlapped and were insufficiently informative, whereas F-^{13}C coupling doublets were resolved properly in the ^{13}C NMR spectra.

CONCLUSIONS

A variety of 4-substituted 1-(4-halogenophenyl)pyrrolidin-2-ones containing azole and azine fragments can be synthesized from 1-(4-halogenophenyl)-5-oxopyrrolidine-3-carbohydrazides by the condensation reactions or by modification of the obtained compounds. All structures of the new compounds desribed

here were in agreement with the synthetic, analytical, and spectroscopic values. The molecular modeling provided further comprehension of structural features of compounds **14a**,**b** and **15a**,**b**.

EXPERIMENTAL

The starting materials and solvents were obtained from Sigma-Aldrich Chemie GmbH (Germany) and Fluka (Switzerland) and were used without further purification. The methods used to follow the reactions were TLC and NMR. The NMR spectra were recorded on a Varian Unity Inova (300 MHz) spectrometer (Varian, Inc., USA)**.** Samples were prepared using DMSO-d_6 as a solvent. Chemical shifts are expressed as δ, ppm relative to TMS. IR spectra (ν, cm^{-1}) were recorded on a Perkin Elmer BX FT–IR spectrometer (Perkin Elmer Inc., USA) using KBr tablets. Mass spectra were obtained on a Waters ZQ 2000 spectrometer (Waters, Germany) using the atmospheric pressure chemical ionization (APCI) mode and operating at 25 V. Elemental analyses were performed on a CE-440 elemental analyzer (Exeter Analytical Inc., USA). Melting points were determined on a B-540 Melting Point Analyzer (Büchi Corporation, USA) and are uncorrected. TLC was performed using Merck, Silica gel 60 F_{254} (Kieselgel 60 F_{254}) silica gel plates.

The molecular modeling of the study compounds was carried out using Chem3D Ultra 9.0 (Licence Cambridge Software Package, Serial number: 031 406391 4800).

1-(4-Fluorophenyl)-4-(4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (3a): A mixture of the hydrazide **1a** (5 mmol), potassium hydroxide (0.67 g, 12 mmol), carbon disulfide (0.57 g, 7.5 mmol) and 2-propanol (30 mL) was refluxed for 8 h, cooled down to room temperature, diluted with water (20 mL) and acidified with diluted hydrochloric acid (1 : 1) to pH 1. The precipitate was filtered off, washed with water, dried and crystallized from iPrOH to give **3a** (1.16 g, 83%); a white solid; mp 162–163 °C (iPrOH); IR 3106, 2958 (NH), 1683 (C=O), 1512, 1482 (C=N), 1329 (C=S) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.79–3.02 (2H, m, CH_2CO), 3.92–4.00 (1H, m, CH), 4.05–4.24 (2H, m, CH_2N), 7.18–7.27 ($2H_{arom}$, m, 3,5-CH), 7.63–7.70 ($2H_{arom}$, m, 2,6-CH), 14.43 (1H, br. s, NNHCS); ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.9 (C-4′), 34.9 (C-3′), 50.1 (C-5′), 115.3 ($^2J_{C\text{-}F}$ = 22.2 Hz, d, C-3,5), 121.7 ($^3J_{C\text{-}F}$ = 7.9 Hz, d, C-2,6), 135.3 (C-1), 158.7 ($^1J_{C\text{-}F}$ = 241.5 Hz, d, C-4), 163.9 (O-C=N), 170.9 (C-2′), 178.0 (O-CS-N). MS *m/z* 280 ($[M+H]^+$ 100). Anal. Calcd for $C_{12}H_{10}FN_3O_2S$: C, 51.61; H, 3.61; N, 15.05. Found: C, 51.71; H, 3.47; N, 15.16.

1-(4-Chlorophenyl)-4-(4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (3b): (1.14 g, 77%); a white solid. The melting point and spectral data correspond to those given in ref.[47]

General Procedure for the Synthesis of 4-(4-Amino-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl)-1-phenylpyrrolidin-2-ones 4a,b. Method A. A mixture of the corresponding hydrazide **1** (30 mmol),

potassium hydroxide (4.04 g, 72 mmol), carbon disulfide (3.42 g, 45 mmol) and 2-propanol (65 mL) was refluxed for 5 h, cooled down to 15 °C, and diethyl ether (45 mL) was poured into the reaction mixture. The precipitate was filtered off, washed with diethyl ether (3 x 50 mL) and dried. A mixture of the obtained dry solid, hydrazine hydrate (4.38 mL, 90 mmol) and water (10 mL) was refluxed for 5 h (until the orange colour of the mixture turned to green), then the mixture was cooled down to room temperature, diluted with water (25 mL) and neutralized with 3N hydrochloric acid to pH 7. The precipitate of the obtained compound was filtered off, washed with water, dried, and crystallized from EtOH to give **4a** (4.84 g, 55%) and **4b** (4.37 g, 47%).

4-(4-Amino-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl)-1-(4-fluorophenyl)pyrrolidin-2-one (4a): a white solid; mp 220–221 °C (EtOH); IR 3279, 3120 (NH, NH_2), 1689 (C=O), 1510, 1492 (C=N), 1319 (C=S) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.81–3.01 (2H, m, CH_2CO), 3.82–3.94 (1H, m, CH), 4.05–4.24 (2H, m, CH_2N), 5.57 (2H, s, NH_2), 7.19–7.26 ($2H_{arom}$, m, 3,5-CH), 7.62–7.67 ($2H_{arom}$, m, 2,6-CH), 13.63 (1H, br. s, NNHCS); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.3 (C-4′), 35.1 (C-3′), 50.6 (C-5′), 115.3 ($^2J_{C\text{-}F}$ = 22.2 Hz, d, C-3,5), 121.6 ($^3J_{C\text{-}F}$ = 8.1 Hz, d, C-2,6), 135.5 (C-1), 152.6 (N-C=N), 158.5 ($^1J_{C\text{-}F}$ = 241.2 Hz, d, C-4), 167.3 (N-CS-N), 171.6 (C-2′); MS *m/z* (%): 294 ($[M+H]^+$ 100). Anal. Calcd for $C_{12}H_{12}FN_5OS$: C, 49.14; H, 4.12; N, 23.88. Found: C, 49.26; H, 4.24; N, 23.64.

4-(4-Amino-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl)-1-(4-chlorophenyl)pyrrolidin-2-one (4b): a white solid; mp 255–256 °C (EtOH); IR 3104, 3046 (NH, NH_2), 1670 (C=O), 1497 (C=N), 1314 (C=S) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.77–3.01 (2H, m, CH_2CO), 3.80–3.90 (1H, m, CH), 4.04–4.24 (2H, m, CH_2N), 5.57 (2H, s, NH_2), 7.40–7.71 ($4H_{arom}$, m, 4CH), 13.63 (1H, br. s, NNHCS); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.1 (C-4′), 35.2 (C-3′), 50.3 (C-5′), 120.9 (C-2,6), 127.8 (C-4), 128.5 (C-3,5), 137.9 (C-1), 152.4 (N-C=N), 167.2 (N-CS-N), 171.5 (C-2′); MS *m/z* 310 ($[M+H]^+$ 100), 312 ($[M+2+H]^+$ 40). Anal. Calcd for $C_{12}H_{12}ClN_5OS$: C, 46.53; H, 3.90; N, 22.61. Found: C, 46.63; H, 3.91; N, 22.65.

Method B. Compounds **4a,b** were synthesized by the method described in ref.[45]

4-(4-Amino-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl)-1-(4-fluorophenyl)pyrrolidin-2-one (4a): (4.58 g, 52%); a white solid. The melting point and spectral data correspond to those given in Method A.

4-(4-Amino-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl)-1-(4-chlorophenyl)pyrrolidin-2-one (4b): (3.90 g, 42%); a white powder. The melting point and spectral data correspond to those given in Method A.

General Procedure for the Synthesis of 1-(4-Halogenophenyl)-4-[4-[(phenylmethylidene)amino]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]pyrrolidin-2-ones 5–9. A mixture of the corresponding aminotriazole **4** (2 mmol), benzaldehyde, 4-chlorobenzaldehyde or 4-methoxybenzaldehyde (4 mmol), EtOH (8 mL) and hydrochloric acid (2 drops) was refluxed for 8 h, and then cooled down. The precipitate of the obtained compounds was filtered off, washed with EtOH, dried and crystallized from iPrOH (**5a,**

6a) and a mixture of 1,4-dioxane and water (**7–9b**) to give **5a** (0.42 g, 55%), **6a** (0.72 g, 86%), **7b** (0.60 g, 75%), **8b** (0.72 g, 83%), and **9b** (0.84 g, 98%).

1-(4-Fluorophenyl)-4-[4-[(phenylmethylidene)amino]-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]pyrrolidin-2-one (5a): a white solid; mp 219–220 °C (iPrOH); IR 3128 (NH), 1672 (C=O), 1510, 1496 (C=N), 1273 (C=S) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.85–3.04 (2H, m, CH_2CO), 3.99–4.26 (3H, m, CH + CH_2N), 7.17–7.90 ($9H_{arom}$, m, 9CH), 10.12 (1H, s, CH=N), 13.93 (1H, s, NNHCS); ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.3 (C-4′), 35.2 (C-3′), 50.5 (C-5′), 115.3 ($^2J_{C\text{-}F}$ = 22.2 Hz, d, C-3,5), 121.7 ($^3J_{C\text{-}F}$ = 7.8 Hz, d, C-2,6), 128.6 (C-3″,5″), 129.1 (C-2″,6″), 132.1 (C-1″), 132.7 (C-4″), 135.4 (C-1), 151.4 (N-C=N), 158.6 ($^1J_{C\text{-}F}$ = 241.9 Hz, d, C-4), 162.0, (N-CS-N), 162.8 (N=CH), 171.4 (C-2′); MS *m/z* 382 ($[M+H]^+$ 100). Anal. Calcd for $C_{19}H_{16}FN_5OS$: C, 59.83; H, 4.23; N, 18.36. Found: C, 59.86; H, 4.49; N, 18.21.

4-[4-[[(4-Chlorophenyl)methylidene]amino]-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-1-(4-fluorophenyl)pyrrolidin-2-one (6a): a yellow solid; mp 234–235 °C (iPrOH); IR 3160 (NH), 1669 (C=O), 1509, 1491 (C=N), 1275 (C=S) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.84–3.04 (2H, m, CH_2CO), 3.99–4.26 (m, 3H, CH + CH_2N), 7.17–7.93 ($8H_{arom}$, m, 8CH), 10.19 (1H, s, CH=N), 13.96 (1H, s, NNHCS); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.3 (C-4′), 35.2 (C-3′), 50.5 (C-5′), 115.3 (d, $^2J_{C\text{-}F}$ = 22.2 Hz, C-3,5), 121.7 (d, $^3J_{C\text{-}F}$ = 7.8 Hz, C-2,6), 129.3 (C-3″,5″), 130.2 (C-2″,6″), 131.0 (C-1″), 135.4 (C-1), 137.3 (C-4″), 151.5 (N-C=N), 158.6 (d, $^1J_{C\text{-}F}$ = 241.6 Hz, C-4), 161.1 (N=CH), 162,0 (N-CS-N), 171.4 (C-2′); MS *m/z* 417 ($[M+H]^+$ 100), 419 ($[M+2+H]^+$ 40). Anal. Calcd for $C_{19}H_{15}ClFN_5OS$: C, 54.87; H, 3.64; N, 16.84. Found: C, 55.01; H, 3.82; N, 16.77.

1-(4-Chlorophenyl)-4-[4-[[phenylmethylidene]amino]-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]pyrrolidin-2-one (7b): a white solid; mp 212–213 °C (1,4-dioxane and water); IR 3103 (NH), 1662 (C=O), 1500, 1473 (2C=N), 1274 (C=S) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.87–3.05 (2H, m, CH_2CO), 4.00–4.10 (1H, m, CH), 4.08–4.27 (2H, m, CH_2N), 7.40–7.90 ($9H_{arom}$, m, 9CH), 10.12 (1H, s, CH=N), 13.96 (1H, s, NNHCS); ^{13}C NMR (75 MHz, DMSO-d_6) δ 26.8 (C-4′), 35.0 (C-3′), 49.9 (C-5′), 120.7 (C-2,6), 127.5 (C-4), 128.2 (C-2″,6″), 128.3 (C-3,5), 128.8 (C-3″,5″), 131.8 (C-1″), 132.3 (C-4″), 138.1 (C-1), 151.0 (N-C=N), 162.4 (N-CS-N + N=CH), 171.4 (C-2′); MS *m/z* 398 ($[M+H]^+$ 100), 400 ($[M+2+H]^+$ 40). Anal. Calcd for $C_{19}H_{16}ClN_5OS$: C, 57.35; H, 4.05; N, 17.60. Found: C, 57.40; H, 4.06; N, 17.53.

4-[4-[[(4-Chlorophenyl)methylidene]amino]-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-1-(4-chlorophenyl)pyrrolidin-2-one (8b): a white solid; mp 218–219 °C (1,4-dioxane and water); IR 3114 (NH), 1662 (C=O), 1500, 1489 (2C=N), 1309 (C=S) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.85–3.05 (2H, m, CH_2CO), 4.00–4.11 (1H, m, CH), 4.07–4.26 (2H, m, CH_2N), 7.00–7.90 ($8H_{arom}$, m, 8CH), 10.19 (1H, s, CH=N), 13.99 (1H, s, NNHCS); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.1 (C-4′), 35.3 (C-3′), 50.1 (C-5′), 121.0 (C-2,6), 127.7 (C-4), 128.4 (C-3,5), 129.2 (C-3″,5″), 130.2 (C-1″), 131.0 (C-2″,6″), 137.2 (C-4″),

137.8 (C-1), 151.3 (N-C=N), 161.0 (N=CH), 162.0 (N-CS-N), 171.7 (C-2′); MS *m/z* 432 ($[M+H]^+$ 70), 434 ($[M+2+H]^+$ 40). Anal. Calcd for $C_{19}H_{15}Cl_2N_5OS$: C, 52.78; H, 3.50; N, 16.20. Found: C, 52.59; H, 3.52; N, 16.17.

1-(4-Chlorophenyl)-4-[4-[[(4-methoxyphenyl)methylidene]amino]-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]pyrrolidin-2-one (9b): a white solid; mp 217–218 °C (1,4-dioxane and water); IR 3094 (NH), 1657 (C=O), 1497, 1467 (2C=N), 1325 (C=S) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.85–3.02 (2H, m, CH_2CO), 3.80 (3H, s, OCH_3), 3.99–4.09 (1H, m, CH), 4.07–4.28 (2H, m, CH_2N), 7.09–7.99 ($8H_{arom}$, m, 8CH), 9.88 (1H, s, N=CH). 13.90 (1H, br. s, NNHCS); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.2 (C-4′), 35.2 (C-3′), 50.1 (C-5′), 55.5 (CH_3), 114.6 (C-3″,5″), 121.0 (C-2,6), 124.4 (C-1″), 127.8 (C-4), 128.5 (C-3,5), 130.6 (C-2″,6″), 137.8 (C-1), 151.1 (N-C=N), 161.9 (N-CS-N) 162.8 (N=CH), 163.2 (C-4″), 171.7 (C-2′); MS *m/z* 428 ($[M+H]^+$ 100), 430 ($[M+2+H]^+$ 40). Anal. Calcd for $C_{20}H_{18}ClN_5O_2S$: C, 56.14; H, 4.24; N, 16.37. Found: C, 55.98; H, 4.25; N, 16.31.

General Procedure for the Synthesis of 4-[4-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-1-phenylpyrrolidin-2-ones 10a,b. A mixture of the corresponding aminotriazole **4** (1.5 mmol), 2,5-hexanedione (0.26 g, 2.25 mmol), concentrated hydrochloric acid (6 drops) and iPrOH (50 mL) was refluxed for 7 h, the solvent was separated under reduced pressure, and the residue diluted with water (30 mL). The precipitate was filtered off, washed with water, dried, and crystallized from iPrOH (**10a**) or 1,4-dioxane (**10b**) to give **10a** (0.48 g, 87%) and **10b** (0.52 g, 89%).

1-(4-Fluorophenyl)-4-[4-(2,5-dimethyl-1*H*-pyrrol-1-yl)-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]pyrrolidin-2-one (10a): a white solid; mp 215–216 °C (iPrOH); IR 3122 (NH), 1671 (C=O), 1509, 1474 (C=N), 1324 (C=S) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.98 (6H, s, C$\underline{CH_3}$), 2.47–2.55 (0.5(1H), m, CH_2CO), 2.75–2.83 (0.5(1H), m, CH_2CO), 3.47–3.58 (1H, m, CH), 3.85–3.88 (0.5(1H), m, CH_2N), 4.06–4.11 (0.5(1H), m, CH_2N), 5.92 (2H, s, CH=), 7.18–7.24 ($2H_{arom}$, m, 3,5-CH), 7.56–7.61 ($4H_{arom}$, m, 2,6-CH), 14.23 (1H, s, NNHCS); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.9, 11.0 (C$\underline{CH_3}$), 27.4 (C-4′), 35.2 (C-3′), 50.1 (C-5′), 105.8 (CH=), 115.4 ($^2J_{C\text{-}F}$ = 22.3 Hz, d, C-3,5), 121.8 ($^3J_{C\text{-}F}$ = 7.8 Hz, d, C-2,6), 127.4, 127.5 ($\underline{C}CH_3$), 135.2 (C-1), 151.9 (N-C=N), 158.7 ($^1J_{C\text{-}F}$ = 241.6 Hz, d, C-4), 167.7 (N-CS-N), 170.67 (C-2′); MS *m/z* 372 ($[M+H]^+$ 100). Anal. Calcd for $C_{18}H_{18}FN_5OS$: C, 58.21; H, 4.88; N, 18.85. Found: C, 57.99; H, 5.05; N, 18.75.

1-(4-Chlorophenyl)-4-[4-(2,5-dimethyl-1*H*-pyrrol-1-yl)-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]pyrrolidin-2-one (10b): a white solid; mp 177–178 °C (1,4-dioxane); IR 3106 (NH), 1708 (C=O), 1495 (C=N), 1322 (C=S) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.97 (6H, s, C$\underline{CH_3}$), 2.50–2.83 (2H, m, CH_2CO), 3.50–3.59 (1H, m, CH), 3.87–4.12 (2H, m, CH_2N), 5.92 (2H, s, CH=), 7.40-7.64 ($4H_{arom}$, m, 4CH), 14.25 (1H, s, NNHCS); ^{13}C NMR (75 MHz, DMSO-d_6) δ 11.2 (C$\underline{CH_3}$), 27.6 (C-4′), 35.6 (C-3′),

50.0 (C-5′), 106.0 (CH=), 121.3 (C-2,6), 127.6 ($\underline{C}CH_3$), 127.7 (C-4), 128.8 (C-3,5), 137.9 (C-1), 152.0 (N-C=N), 167.9 (N-CS-N), 171.1 (C-2′); MS *m/z* 388 ($[M+H]^+$ 50), 410 ($[M+Na]^+$ 100). Anal. Calcd for $C_{18}H_{18}ClN_5OS$: C, 55.74; H, 4.68; N, 18.06. Found: C, 55.94; H, 4.68; N, 18.13.

1-(4-Chlorophenyl)-*N*-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-oxopyrrolidine-3-carboxamide (11b). A mixture of the hydrazide **1b** (1.19 g, 5 mmol), 2,5-hexanedione (0.86 g, 7.5 mmol), glacial acetic acid (1 mL) and EtOH (35 mL) was refluxed for 16 h, the solvent was separated under reduced pressure, the residue diluted with water (50 mL), and the solution was heated to a gentle boil. Upon cooling of the reaction mixture, the precipitate was filtered off, washed with water, dried and crystallized from EtOH to give **11b** (1.54 g, 93%). A white solid; mp 161–162 °C (EtOH); IR 3275 (NH), 1705, 1685 (2C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.03 (6H, s, $C\underline{C}H_3$), 2.75–2.97 (2H, m, CH_2CO), 3.50–3.63 (1H, m, CH), 3.97–4.20 (2H, m, CH_2N), 5.68 (2H, s, CH=), 7.42–7.79 ($4H_{arom}$, m, 4CH), 10.95 (1H, s, CONH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 11.4 ($C\underline{C}H_3$), 34.47 (C-4′), 36.1 (C-3′), 50.8 (C-5′), 103.6 (CH=), 121.4 (C-2,6), 127.2 ($\underline{C}CH_3$), 128.4 (C-4), 129.1 (C-3,5), 138.4 (C-1), 172.2, 172.1 (C-2′ + CONH); MS *m/z* 332 ($[M+H]^+$ 100), 334 ($[M+2+H]^+$ 40). Anal. Calcd for $C_{17}H_{18}ClN_3O_2$: C, 61.54; H, 5.47; N, 12,66. Found: C, 61.66; H, 5.40; N, 12.62.

General Procedure for the Synthesis of Ethyl [(5-oxo-1-phenylpyrrolidin-3-yl)carbonyl]-hydrazonoformates 12a,b. A mixture of the corresponding hydrazide **1** (5 mmol) and triethyl orthoformate (10 mL) was heated to boiling, and then cooled down. The precipitate was filtered off, washed with ether, dried, and crystallized from iPrOH to give **12a** (1.07 g, 73%) and **12b** (1.28 g, 83%).

Ethyl [[1-(4-fluorophenyl)-5-oxopyrrolidin-3-yl]carbonyl]hydrazonoformate (12a): a white solid; mp 153–154 °C (iPrOH); IR 3201 (NH), 1695, 1664, 1617 (C=O), 1510, 1478, 1460 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.24, 1.26, 1.29 (3H, J = 7.1 Hz, 3t, CH_3), 2.57–2.80 (2H, m, CH_2CO), 3.16–4.21 (5H, m, CH + $O\underline{C}H_2CH_3$ + CH_2N), 6.86, 6.91 ((0.6)1H, 2s, CH=N), 7.17–7.23 ($2H_{arom}$, m, 3,5-CH), 7.65–7.69 ($2H_{arom}$, m, 2,6-CH), 7.94, 8.22 ((0.4) 1H, 2s, CH=N), 10.06, 10.55, 10.76, 10.79 ((0.20 : 0.48 : 0.10 : 0.22)1H, 4s, CONH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.1, 15.3, 15.5 ($OCH_2\underline{C}H_3$), 32.5, 34.1, 34.6, 34.6, 34.8, 35.6, 35.7 (C-4′,3′), 50.1, 50.3, 50.8, 51.0 (C-5‘), 62.5, 62.5, 67.1 ($O\underline{C}H_2CH_3$), 115.3 ($^2J_{C\text{-}F}$ = 22.3 Hz, d, C-3,5), 121.3 ($^3J_{C\text{-}F}$ = 7.8 Hz, d, C-2,6), 135.6 (C-1), 143.2, 145.4, 155.4 (CH=N), 158.4 ($^1J_{C\text{-}F}$ = 240.8 Hz, d, C-4), 167.9, 168.4, 171.9, 172.0, 172.0, 172.5 (CONH + C-2′); MS *m/z* 294 ($[M+H]^+$ 100). Anal. Calcd for $C_{14}H_{16}FN_3O_3$: C, 57.33; H, 5.50; N, 14.33. Found: C, 57.54; H, 5.66; N, 14.18.

Ethyl [(1-(4-chlorophenyl)-5-oxopyrrolidin-3-yl)carbonyl]hydrazonoformate (12b): a white solid; mp 167–168 °C (iPrOH); IR 3211 (NH), 1696, 1664 (2C=O), 1495 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.24, 1.26, 1.29 (3H, J = 7.1 Hz, 3t, CH_3), 2.58–2.82 (2H, m, CH_2CO), 3.15–4.21 (5H, m,

CH + CH_2N + O$\underline{CH_2}CH_3$), 6.86, 6.91 ((0.6)1H, 2s, CH=N), 7.39–7.45 ($2H_{arom}$, m, 3,5-CH), 7.67–7.73 (2H, m, 2,6-CH), 7.94, 8.22 (2s, (0.4) 1H, CH=N), 10.07, 10.56, 10.77, 10.80 ((0.18 : 0.46 : 0.13 : 0.23)1H, 4s, CONH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.2, 15.3, 15.5 (O$CH_2\underline{CH_3}$), 32.4, 34.0, 34.6, 34.7, 34.9, 35.7, 35.8 (C-4′,3′), 49.9, 50.1, 50.6, 50.7 (C-5′), 62.5, 62.5, 67.2, 67.1 (O$\underline{CH_2}CH_3$), 120.8 (C-2,6), 127.7 (C-4), 128.5 (C-3,5), 138.1 (C-1), 143.2, 145.5, 149.6, 155.4 (CH=N), 167.8, 168.4, 172.0, 172.2, 172.3, 172.4, 172.5 (CONH + C-2′); MS *m/z* 310 ($[M+H]^+$ 40), 332 ($[M+Na]^+$ 100). Anal. Calcd for $C_{14}H_{16}ClN_3O_3$: C, 54.29; H, 5.21; N, 13.57. Found: C, 54.09; H, 5.20; N, 13.53.

General Procedure for the Synthesis of 4-(1,3,4-Oxadiazol-2-yl)-1-phenylpyrrolidin-2-ones 13a,b. A mixture of the corresponding hydrazide **1** (5 mmol), triethyl orthoformate (5.93 g, 40 mmol) and *p*-toluenesulfonic acid (0.19 g, 1 mmol) was refluxed for 20 h, cooled down, the precipitate was filtered off, washed with hexane, dried, and crystallized from iPrOH to give **13a** (0.52 g, 42%) and **13b** (0.62 g, 47%).

1-(4-Fluorophenyl)-4-(1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (13a): a white solid; mp 158–159 °C (iPrOH); IR 1705 (C=O), 1603, 1588 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.84–3.10 (2H, m, CH_2CO), 4.09–4.33 (3H, m, CH + CH_2N), 7.19–7.27 ($2H_{arom}$, m, 3,5-CH), 7.64–7.71 (2H, m, 2,6-CH), 9.24 (1H, s, O-CH=N); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.6 (C-4′), 35.8 (C-3′), 50.8 (C-5′), 115.3 ($^2J_{C\text{-}F}$ = 22.3 Hz, d, C-3,5), 121.7 ($^3J_{C\text{-}F}$ = 7.9 Hz, d, C-2,6), 135.1 (C-1), 154.9 (O-CH=N), 158.6 ($^1J_{C\text{-}F}$ = 241.4 Hz, d, C-4), 166.4 (OC=N-N), 171.1 (C-2′); MS *m/z* 248 ($[M+H]^+$ 100). Anal. Calcd for $C_{12}H_{10}FN_3O_2$: C, 58.30; H, 4.08; N, 17.00. Found: C, 58.55; H, 4.24; N, 16.84.

1-(4-Chlorophenyl)-4-(1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (13b). White powder, mp 106–107 °C (iPrOH). IR 1703 (C=O), 1494, 1484 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.90–3.10 (2H, m, CH_2CO), 4.00–4.21 (2H, m, CH_2N), 4.23–4.37 (1H, m, CH), 7.40–7.71 ($4H_{arom}$, m, 4CH), 9.24 (1H, s, O-CH=N). ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.8 (C-4′), 36.1 (C-3′), 50.8 (C-5′), 121.3 (C-2,6), 128.3 (C-4), 128.8 (C-3,5), 138.0 (C-1), 155.1 (O-CH=N), 166.5 (OC=N-N), 171.6 (C-2′). MS m/z (*I,* %): 265 ($[M+H]^+$ 100), 267 ($[M+2+H]^+$ 35). Anal. Calcd for $C_{12}H_{10}ClN_3O_2$: C, 54.66; H, 3.82; N, 15.94%. Found: C, 54.89; H, 3.83; N, 15.99.

General Procedure for the Synthesis of Ethyl 3-[2-[[5-oxo-1-phenylpyrrolidin-3-yl]carbonyl]hydrazinylidene]butanoates 14a,b. A mixture of the corresponding hydrazide **1** (5 mmol), EAA (1.11 g, 8.5 mmol), EtOH (20 mL) and glacial acetic acid (1 mL) was refluxed for 4 h, cooled down, the precipitate was filtered off, washed with EtOH, dried and crystallized from EtOH to give **14a** (1.00 g, 57%) and **14b** (1.04 g, 57%).

Ethyl 3-[2-[[1-(4-fluorophenyl)-5-oxopyrrolidin-3-yl]carbonyl]hydrazinylidene]butanoate (14a): a white solid; mp 136–137 °C (EtOH); IR 3188 (NH), 1735, 1693, 1662 (3C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.10–1.23 (2H, m, O$CH_2\underline{CH_3}$), 1.80, 1.92, 1.95, 1.96, 1.97, 2.16 (2H, 6s, =CCH_3), 2.57–2.86

(2H, m, CH_2CO), 3.24–3.53 (2H, m, =CCH_2-C + H_2O), 3.81–4.15 (5H, m, CH_2N + CH + O$\underline{CH_2}CH_3$), 7.18–7.25 (2H_{arom}, m, 3,5-H), 7.63–7.71 (2H_{arom}, m, 2,6-CH), 10.05, 10.20, 10.40, 10.49, 10.58, 10.66 (1H, 6s, CONH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.0 ($OCH_2\underline{CH_3}$), 16.4, 16.8 ($\underline{CH_3}C$=), 33.3, 34.3, 34.7, 35.6 (C-4′ + C-3′), 43.9, 44.0 (=C$\underline{CH_2}$CO), 50.2, 50.9 (C-5′), 60.4, 60,5 (O$\underline{CH_2}CH_3$), 115.3 ($^2J_{C\text{-}F}$ = 22.4 Hz, d, C-3,5), 121.4, 121.5 ($^3J_{C\text{-}F}$ = 8.3 Hz, $^3J_{C\text{-}F}$ = 10.5 Hz, d, C-2,6), 135.6 (C-1), 147.8, 151.8 (N=$\underline{C}CH_3$), 158.5 ($^1J_{C\text{-}F}$ = 241.5 Hz, d, C-4), 162.2 ($CH_2\underline{C}OOCH_2CH_3$), 168.0, 169.0, 169.5, 169.6, 172.0, 173.7 (CONH + C-2′); MS *m/z* 350 ($[M+H]^+$ 100). Anal. Calcd for $C_{17}H_{20}FN_3O_4$: C, 58.45; H, 5.77; N, 12.03. Found: C, 58.46; H, 5.90; N, 11.91.

Ethyl 3-[2-[[1-(4-chlorophenyl)-5-oxopyrrolidin-3-yl]carbonyl]hydrazinylidene]butanoate (14b): a white solid; mp 138–139 °C (EtOH); IR 3205 (NH), 1733, 1706, 1674 (3C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.10–1.23 (2H, m, $OCH_2\underline{CH_3}$), 1.80, 1.92, 1.95, 1.96, 1.97, 2.15 (2H, 6s, =CCH_3), 2.63–2.88 (2H, m, CH_2CO), 3.25–3.53 (2H, m, =CCH_2-C + H_2O), 3.81–4.15 (5H, m, CH_2N + CH + O$\underline{CH_2}CH_3$), 7.41–7.44 (2H_{arom}, m, 3,5-CH), 7.67–7.72 (2H_{arom}, m, 2,6-CH), 10.05, 10.22, 10.40, 10.49, 10.58, 10.66 (1H, 6s, CONH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.0 ($OCH_2\underline{CH_3}$), 16.5, 16.8 ($\underline{CH_3}C$=), 33.2, 33.7, 34.2, 34.8, 35.6, 35.8 (C-4′ + C-3′), 43.9, 44.0 (=C$\underline{CH_2}$CO), 49.9, 50.4, 50.7 (C-5′), 60.4, 60.8 (O$\underline{CH_2}CH_3$), 120.9, 120.9 (C-2,6), 127.7, 127.9 (C-4), 128.6 (C-3,5), 138.0, 138.01 (C-1), 147.8, 151.9 (N=$\underline{C}CH_3$), 162.2 ($CH_2\underline{C}OOCH_2CH_3$), 167.6, 168.0, 168.01, 169.5, 169.6, 171.4, 172.0, 172.3, 172.3, 173.7 (CONH + C-2′); MS *m/z* 367 ($[M+H]^+$ 100), 369 ($[M+2+H]^+$ 40). Anal. Calcd for $C_{17}H_{20}ClN_3O_4$: C, 55.82; H, 5.51; N, 11.49. Found: C, 55.75; H, 5.73; N, 11.32.

General Procedure for the Synthesis of 5-Oxo-1-[[(5-oxo-1-phenylpyrrolidin-3-yl)carbonyl]amino]pyrrolidine-3-carboxylic acids 15a,b. A mixture of corresponding hydrazide **1** (5 mmol), itaconic acid (0.78 g, 6 mmol) and 10 mL of water was refluxed for 12 h, cooled down, the precipitate was filtered off, washed with water, dried, and crystallized from iPrOH (**15a**) or water (**15b**) to give **15a** (1.20 g, 69%).

1-[[[1-(4-Fluorophenyl)-5-oxopyrrolidin-3-yl]carbonyl]amino]-5-oxopyrrolidine-3-carboxylic acid (15a): a white solid; mp 210–211 °C (iPrOH); IR 3273 (NH), 3027 (OH), 1729, 1702, 1677, 1601 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.45–2.84 (4H, m, CH_2CO (II) + CH_2CO (I)), 3.24–3.34 (2H, m, CH (II) + CH (I)), 3.57–3.72 (2H, m, CH_2N (II)), 3.84–4.07 (2H, m, CH_2N (I)), 7.19–7.24 (2H_{arom}, m, 3,5-CH), 7.64–7.68 (2H_{arom}, m, 2,6-CH), 10.38 (1H, s, CONH), 11.99 (1H, br. s, COOH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 31.3 (C-4″ (II)), 33.6 (C-4′ (I)), 34.1 (C-3″(II)), 35.2 (C-3′(I)), 49.6 (C-5″(II)), 50.5 (C-5′ (I), 115.3 ($^2J_{C\text{-}F}$ = 22.2 Hz, d, C-3,5), 121.6 ($^3J_{C\text{-}F}$ = 8.0 Hz, d, C-2,6), 135.5 (C-1), 158.5 ($^1J_{C\text{-}F}$ = 240.9 Hz, d, C-4), 170.9 (CONH), 171.4 (C-2″ (II)), 171.6 (C-2′ (I)), 174.0 (COOH); MS *m/z* 350 ($[M+H]^+$ 100). Anal. Calcd for $C_{16}H_{16}FN_3O_5$: C, 55.01; H, 4.62; N, 12.03. Found: C, 55.22; H, 4.72; N,

11.91.

1-[[[1-(4-Chlorophenyl)-5-oxopyrrolidin-3-yl]carbonyl]amino]-5-oxopyrrolidine-3-carboxylic acid (15b): a white powder; yield 1.39 g (76%); mp 150–151 °C (water). Melting point and spectral data correspond to those given in ref.[42]

General Procedure for the Synthesis of 4-(5,6-diphenyl-1,2,4-triazin-3-yl)-1-phenylpyrrolidin-2-ones 16a,b. A mixture of corresponding hydrazide **1** (5 mmol), 1,2-diphenylethane-1,2-dione (1.05 g, 5 mmol), ammonium acetate (3.85 g, 50 mmol) and 20 mL of glacial acetic acid was refluxed for 9 h, cooled down and diluted with water (30 mL). The formed crystalline-oily precipitate was washed with hot water (2 × 20 mL), the residue was dissolved in 15 mL of iPrOH, the solution was filtered off, and the solvent was separated under reduced pressure. The residue of formed crystalline substance after the cooling was recrystallized from iPrOH to give **16a** (1.25 g, 61%) and **16b** (1.39 g, 65%).

4-(5,6-Diphenyl-1,2,4-triazin-3-yl)-1-(4-fluorophenyl)pyrrolidin-2-one (16a): a yellow solid; mp 175–176 °C (iPrOH); IR 1695 (C=O), 1509, 1479 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.05–3.20 (2H, m, CH_2CO), 4.24–4.46 (3H, m, CH_2N + CH), 7.19–7.27 ($2H_{arom}$, m, 3,5-CH), 7.35–7.53 ($10H_{arom}$, m, (2″- 6″) + (2‴- 6‴)CH), 7.71 –7.77 ($2H_{arom}$, m, 2,6-CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.9 (C-4′), 37.1 (C-3′), 52.4 (C-5′), 115.3 ($^2J_{C\text{-}F}$ = 22.2 Hz, d, C-3,5), 121.6 ($^3J_{C\text{-}F}$ = 8.0 Hz, d, C-2,6), 128.4, 128.5 (C-3″, 5″+ C-3‴,5‴), 129.3 (C-2″,6″ or C-2‴,6‴), 129.5 (C-4″ or C-4‴), 129.7 (C-2‴,6‴ or C-2″,6″), 130.7 (C-4‴ or C-4″), 135.3, 135.4 (C-1″ + C-1‴), 135.7 (C-1), 156.0, 156.1 (N-C=C-N), 158.5 ($^1J_{C\text{-}F}$ = 240.9 Hz, d, C-4), 166.8 (N=C-N), 172.1 (C-2′); MS *m/z* 411 ($[M+H]^+$ 100). Anal. Calcd for $C_{25}H_{19}FN_4O$: C, 73.16; H, 4.67; N, 13.65. Found: C, 72.95; H, 4.79; N, 13.66.

4-(5,6-Diphenyl-1,2,4-triazin-3-yl)-1-(4-chlorophenyl)pyrrolidin-2-one (16b): a yellow solid; mp 203–204 °C (iPrOH); IR 1698 (C=O), 1491, 1478 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.09–3.16 (2H, br. m, CH_2CO), 4.24–4.46 (3H, br. m, + CH_2N + CH), 7.34–7.77 ($14H_{arom}$, m, 14CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.8 (C-4′), 37.2 (C-3′), 52.1 (C-5′), 121.0 (C-2,6), 127.8 (C-4), 128.4 (C-3,5), 128.5, 128.6 (C-3″,5″ or C-3‴,5‴), 129.3 (C-2″,6″ or C-2‴,6‴), 129.5 (C-4″ or C-4‴), 129.7 (C-2‴,6‴ or C-2″,6″), 130.7 (C-4‴ or C-4″), 135.3, 135.4 (C-1″ + C-1‴), 138.2 (C-1), 155.9, 156.1 (N-C=C-N), 166.7 (N=C-N), 172.4 (C-2′); MS *m/z* 428$[M+H]^+$ 100), 430($[M+2H]^+$ 35. Anal. Calcd for $C_{25}H_{19}ClN_4O$: C, 70.34; H, 4.49; N, 13.12. Found: C, 70.65; H, 4.58; N, 13.21.

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