Synthesis, Characterization and Bioassay of Novel Substituted 1-(3-(1,3-Thiazol-2-yl)phenyl)-5-oxopyrrolidines

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Abstract: Thiazole derivatives attract the attention of scientists both in the field of organic synthesis and bioactivity research due to their high biological activity. In the present study, thiazole ring was obtained by the interaction of 1-(4-(bromoacetyl)phenyl)-5-oxopyrrolidine-3-carboxylic acid with thiocarbamide or benzenecarbothioamide, as well as tioureido acid. A series of substituted 1-(3-(1,3-thiazol-2-yl)phenyl)-5-oxopyrrolidines with pyrrolidinone, thiazole, pyrrole, 1,2,4-triazole, oxadiazole and benzimidazole heterocyclic fragments were synthesized and their antibacterial properties were evaluated against Gram-positive strains of Staphylococcus aureus, Bacillus cereus, Listeria monocytogenes and Gram-negative Pseudomonas aeruginosa, Escherichia coli and Salmonella enterica enteritidis. The vast majority of compounds exhibited between twofold and 16-fold increased antibacterial effect against the test-cultures when compared with Oxytetracycline.

Keywords: biological activity; heterocycles; thiazoles; pyrrolidinones; triazoles

1. Introduction

Heterocyclic compounds are one of the main groups of organic compounds possessing a wide range of applications in various areas of science and high technologies. Recently, greater attention has been paid to heterocyclic compounds such as azoles. The nitrogen-containing five-membered heterocycles—pyrrole, diazole, triazole, thiazole, thiadiazole, benzimidazole demonstrate a wide diversity of biological properties. Thiazoles are commonly reported as active antimicrobial [1–8], anti-tuberculous [9–12], anti-HIV [13], antiviral [14,15], antihistamine [16,17], antipyretic [18], antitumor [3,19], antidepressant [20], fungicidal [21,22] property bearing compounds. 2-Aminothiazoles has found application in agriculture as herbicides and fungicides [23,24]. Pyrrole nucleus has been incorporated into a wide variety of therapeutically important medication candidates. For example, the pyrrole ring is present in the structure of the anti-cancerous drug Sunitinib [25,26], which is used for the treatment of several types of cancer. Compounds with a pyrrolidinone moiety in the structure show inhibition of human carbonic anhydrase [27,28]. Compounds containing a 1,2,4-triazole scaffold demonstrate different pharmacological actions such as analgesic [29,30], antiviral [31], anti-inflammatory [32], anticonvulsant [33,34], anticancer [35], antidepressant [36], antibacterial [37,38], antifungal [37,39], and are used as various pharmaceuticals. They have been approved as drugs such as AnastraZole, Letrozole, Rizatriptan, Ribavirin, Alprazolam, Fluconazole.
and Posaconazole (Figure 1). Therefore, many researchers looking for new medicines are still focused on the synthesis of 1,2,4-triazole derivatives. Benzimidazole is an important heterocyclic compound with the fused-ring system in the structure. Because of its similarity to the structure of purine bases, benzimidazole derivatives can compete with them in the course of bacterial membrane biosynthesis, thereby stimulating the death of bacteria [40,41].

![Figure 1. Pharmaceuticals with 1,2,4-triazole scaffold in the molecule.](image)

This study focused on the synthesis of new, potentially biologically active 1,3-disubstituted 5-oxopyrrolidines with pyrrolidinone, thiazole, pyrrole, 1,2,4-triazole, oxadiazole, benzimidazole and quinoxaline heterocyclic fragments in the structure, and resulted in the discovery of compounds with significantly increased antibacterial activity.

2. Results and Discussion

2.1. Chemistry

In this work, the initial compound 1 was prepared from 4-aminoacetophenone and itaconic acid by a known method [42]. In order to obtain 2,5-disubstituted thiazole derivatives 3a–c, compound 1 was brominated with Br₂ in acetic acid at room temperature (Scheme 1), and then used in the reactions with thiocarbonyl compounds. The bromination reaction resulted in the formation of α-bromocarbonyl compound 1-(4-(2-bromoacetyl)phenyl)-5-oxopyrrolidine-3-carboxylic acid (2). Cyclocondensation of α-bromoacyl derivative 2 with the corresponding thioamide, i.e., thiocarbamide, benzenecarbothioamide or thioureido acid, under different conditions was carried out to obtain the desired outcomes 3a–c. The a reaction was performed in acetic acid at 60 °C; in the cases of b and c, the reaction was carried out in refluxing acetone. A comparison of the 1H and 13C-NMR spectra
of compounds 3a–c revealed the characteristic signals of the formed substituted thiazole moieties. In the spectra of compound 3a, the singlets at 6.96 (S–C=CH) and 7.07 (NH$_2$, $^1$H-NMR) ppm, and the resonance lines at 100.9 (C=S), 138.1 (S–C=CH), 168.2 (C=N, $^{13}$C-NMR) ppm prove the presence of thiazole heterocycle in the molecule. The characteristic signals in the $^1$H (8.20 ppm, S–C=CH) and $^{13}$C (114.0, 154.7, 166.9 ppm, C=S, S–C=CH, C=N) NMR, as well as additional resonances in the aromatic field of the corresponding spectrum of 3b, provide the evidence of new 2-phenyl thiazole fragment. The formation of the 2-carboxyethyl-4-methylanilino moiety in compound 3c was confirmed by the presence of triplets at 2.40 ($J = 7.9$ Hz, NCH$_3$CH$_2$CO) and 4.10 ($J = 7.9$ Hz, NCH$_3$CH$_2$) ppm in the $^1$H-NMR spectrum. The signals of protons of the $p$-substituted benzene cycle resonated as two doublets at 7.26 and 7.32 ppm and the signal arising at 2.32 ppm indicated the presence of the methyl group. All NMR spectra of the synthesized compounds are given in Supplementary Materials.

Compounds 5a,b were prepared following the standard synthesis route, i.e., 5-oxopyrrolidine-3-carboxylic acids 3a,b were esterified with methanol in the presence of a catalytic amount of sulfuric acid to obtain esters 4a,b. The prepared esters were easily converted to the corresponding acid hydrazides 5a,b, when treated with hydrazine hydrate in refluxing propan-2-ol.

The condensation of acid hydrazides 5a,b with aromatic aldehydes in dimethylformamide or 1,4-dioxane afforded hydrazone-type compounds (6–8)a,b, and (9–12)b in good to excellent yield (62–99%, Scheme 2; the yields of all synthesized compounds are given in Table 1).
Table 1. The yields of the synthesized compounds 2–23.

| Compound | Yield, % | Compound | Yield, % | Compound | Yield, % |
|----------|---------|----------|---------|----------|---------|
| 1        | 86      | 7a       | 90      | 14b      | 54      |
| 2        | 95      | 7b       | 69      | 15b      | 86      |
| 3a       | 62      | 8a       | 62      | 16b      | 90      |
| 3b       | 43      | 8b       | 89      | 17b      | 76      |
| 3c       | 82      | 9b       | 82      | 18b      | 67      |
| 4a       | 62      | 10b      | 75      | 19b      | 88      |
| 4b       | 71      | 11b      | 99      | 20       | 82      |
| 5a       | 81      | 12b      | 96      | 21       | 81      |
| 5b       | 65      | 13a      | 57      | 22       | 92      |
| 6a       | 90      | 13b      | 92      | 23       | 88      |
| 6b       | 92      |          |         |          |         |

Scheme 2. Synthesis of compounds 6–19.

The synthesized hydrazones in DMSO-$d_6$ solution, due to the restricted rotation around the CO-NH bond, exist as a mixtures of $E/Z$-amide conformers with the prevailing $Z$ conformational structure [43–45]. However, geometric isomers are also possible due to the presence of the N=C double
bond. The academic literature indicates that hydrazones obtained from acid hydrazides and aromatic aldehydes favour the sterically less-hindered and more stable geometric E-geometrical isomer [46–48].

The reaction of acid hydrazides 5a,b with hexane-2,5-dione (2,5-HD) resulted in the formation of 2,5-dimethylpyrrole derivatives 13a,b, as expected. Using the method of the formation of pyrrolidinone ring from aromatic amines and itaconic acid, hydrazide 5b as an amino group-containing compound was reacted with this dicarboxylic acid. The reaction was performed in toluene at reflux, and the synthesized compound 14b containing two pyrrolidinone rings connected by the amide bond was proved by double sets of the protons (1H-NMR) of the 2COCH₂, 2CH and 2NCH groups, which gave rise in the ranges of 2.54–2.88, 3.25–3.42 and 3.55–4.16 ppm, respectively. In the 13C-NMR spectrum of 14b spectral lines at 31.3, 33.6, 34.2, 35.5, 49.7 and 50.3 ppm have been attributed to the COCH₂, CH and NCH₂ groups of two pyrrolidinone rings, and resonances at 170.9, 171.4, 171.8 and 174.6 ppm approve the presence of four carbonyl groups in this structure. NMR spectral data of compound 14b showed the presence of only one isomer in the DMSO-d₆ solution. Unfortunately, attempts to grow single crystals suitable for stereochemical assignment by X-ray structural analysis were unsuccessful.

Thiosemicarbazide 15b was synthesized by treatment of acid hydrazide 5b with phenyl isothiocyanate in methanol. Singlets at 9.58, 9.68, 9.88, 10.12 and 10.22 ppm in the 1H-NMR spectrum of the compound are characteristic of the 3NH of the thiosemicarbazide moiety, and six additional resonance lines of the newly attached phenyl fragment in the 13C-NMR spectrum of 15b provide clear evidence of the compound structure. 2-(5-Oxo-1-(4-(2-phenylthiazol-5-yl)phenyl)pyrrolidine-3-carbonyl)-N-phenylhydrazine-1-carbothioamide (15b) was then converted to 1,2,4-triazole 16b by a base catalyzed intramolecular dehydrative cyclization reaction.

The reaction of hydrazide 5b with carbon disulfide in methanol under basic conditions (KOH/methanol) gave the intermediate, the potassium dithiocarbazate salt, which under the action of concentrated hydrochloric acid was cyclized to 5-thioxo-1,3,4-oxadiazole 17b. The treatment of potassium carbodithioate with hydrazine monohydrate afforded 4-aminotriazole 18b. The condensation of one equivalent of compound 18b containing free amino group with two equivalents of benzene carbalddehyde in refluxing ethanol containing a catalytic amount of concentrated hydrochloric acid yielded the Schiff base 19b. The characteristic changes in the chemical shift of the resonances of the triazole moiety were observed because of the changed influence of the substituent at the nitrogen atom of the C–N–C=S fragment. In the case of 19b, the carbon atom of the C=S group resonated at 162.9 ppm, and the C=N–NH carbon atom peaked at 162.0 ppm in 13C-NMR spectrum. Additional spectral lines were observed in the aromatic region and were assigned to the carbon atoms of the newly incorporated benzene ring and formed azomethine group. The 1H-NMR spectrum of 1,2,4-triazole derivative 19b showed characteristic singlets at 10.14 ppm (N=CH) and 13.97 (NH), and the multiplet of the benzene rings integrated for 14 protons.

In the next stage of the work, the reactivity of acyl- 1 and α-bromo acyl 2 derivatives was investigated by reacting them with benzene-1,2-diamine (Scheme 3). The reactions were performed in different solvents. The reaction of the derivative 1 with diamine in ethanol yielded the condensation product 1-(4-(1-(2-aminophenyl)iminocarbonyl)phenyl)-5-oxopyrrolidine-3-carboxylic acid (20), while the bromoacyl derivative 2 under the same conditions afforded the compound 21 containing the quinoxaline moiety. The condensation in the compound 1 occurred in the acyl moiety. This resulted in a conjugated system with double bonds in the chain of the benzene ring-iminoethyl fragment-benzene ring, which gave the brightly brown-orange crystalline compound 20. The obtained compound 20 was easily identified by the data of the NMR spectra. In the 1H and 13C-NMR spectra of compound 21, the increased number of spectral lines in the aromatic regions of the respective spectra, the HRMS (High-resolution mass spectrometry) data, and the elemental analysis approved the formation of quinoxaline moiety. The second step of the investigation was to find out the products of the same reaction in refluxing 4 M hydrochloric acid. The reaction of compound 1, having an acyl group on the benzene ring with benzene-1,2-diamine in refluxing 4 M hydrochloric acid, afforded the benzimidazole derivative 22 [49]. Resynthesis was carried out according to a well-known Philips method (the heating...
of reagents in a 4 M HCl); however, extending it to 16 h and neutralizing the mixture with aqueous ammonium hydroxide to pH 7. This resulted in the increased yield of the desired product 22 (from 40 to 92%). The condensation of brominated compound 2 with diamine under the same conditions led to the formation of the complex mixture, and product separation was unsuccessful.

For more extensive analysis of biological properties of the compounds resynthesized benzimidazole 22 [49] was alkylated with iodoethane at solvent-free conditions and in the presence of potassium hydroxide and sodium carbonate.

Scheme 3. Synthesis of compounds 20–23.

The reaction provided N-alkylated compound 1-(4-acetylphenyl)-3-(1-ethyl-1H-benzimidazol-2-yl)-5-oxopyrrolidine (23).

2.2. Biological Activity

All synthesized compounds 2–19 and 21–23 were tested against Gram-positive bacteria strains of Staphylococcus aureus (ATCC 25923), Bacillus cereus (ATCC 10231), Listeria monocytogenes (ATCC 19111) as well as Gram-negative Pseudomonas aeruginosa (ATCC 10145), Escherichia coli (ATCC 8739) and Salmonella enterica enteritidis (ATCC 13076) bacteria for their in vitro antibacterial activity by broth dilution and spread-plate techniques [50–52]. Oxytetracycline was used as a control (C) for antibacterial activity screening. The determined values of the minimum inhibition (MIC, µg/mL) and the minimum bactericidal (MBC, µg/mL) concentrations are presented in Table 2. The investigations demonstrated that the synthesized compounds possessed higher antibacterial properties than those of the known antibiotic Oxytetracycline.

The in vitro evaluation of the above-mentioned compounds revealed the excellent antibacterial activity of compounds 3c, 5b, 15b and 16b. Their effect on Gram-positive bacteria strains (MIC 7.8 µg/mL and MBC 15.6 µg/mL) was 8 times higher, and against Gram-negative 16-fold higher, than those of the control Oxytetracycline.

It should also be noted that among the thiazoles 3a–c the amino thiazole 3c, containing the β-alanine moiety, displayed the best antibacterial results against all the tested bacteria strains.

Among all the tested compounds, methyl ester 4b, hydrazine 6b and oxadiazole derivative 17b should be distinguished. They demonstrated four times stronger inhibition effects against Gram-positive bacteria strains and showed 8-fold higher inhibition against Gram-negative bacteria in comparison with the control. Hydrazones 6a and (7–12)b in most cases displayed good to very good action against the tested bacteria species. However, the best activity showed hydrazone 9b with 4-fluorophenyl moiety in the molecule.
Table 2. The determined MIC and MBC of the synthesized compounds (only the data for compounds that gave positive results in at least one case are included in the table).

| Compound | Gram-Positive Bacteria Strains | Gram-Negative Bacteria Strains |
|----------|--------------------------------|--------------------------------|
|          | S. aureus  | B. cereus | L. monocytogenes | P. aeruginosa | E. coli | S. enterica enteritidis |
|          | MIC (µg/mL) | MBC (µg/mL) | MIC (µg/mL) | MBC (µg/mL) | MIC (µg/mL) | MBC (µg/mL) | MIC (µg/mL) | MBC (µg/mL) | MIC (µg/mL) | MBC (µg/mL) |
| 3a       | 15.6       | 31.25     | 31.25       | 62.5        | 31.25      | 62.5        | 31.25       | 62.5        | 31.25       | 62.5        |
| 3b       | 31.25      | 62.5      | 15.6        | 31.25       | 15.6       | 31.25       | 62.5        | 125         | 15.6        | 31.25       |
| 3c       | 7.8        | 15.6      | 7.8         | 15.6        | 7.8        | 15.6        | 7.8         | 15.6        | 7.8         | 15.6        |
| 4a       | 62.5       | 125       | 31.25       | 62.5        | 31.25      | 62.5        | 31.25       | 62.5        | 31.25       | 62.5        |
| 4b       | 15.6       | 31.25     | 15.6        | 31.25       | 15.6       | 31.25       | 15.6        | 31.25       | 15.6        | 31.25       |
| 5a       | 31.25      | 62.5      | 31.25       | 62.5        | 31.25      | 62.5        | 31.25       | 62.5        | 31.25       | 62.5        |
| 5b       | 7.8        | 15.6      | 7.8         | 15.6        | 7.8        | 15.6        | 7.8         | 15.6        | 7.8         | 15.6        |
| 6a       | 31.25      | 62.5      | 31.25       | 62.5        | 31.25      | 62.5        | 31.25       | 62.5        | 31.25       | 62.5        |
| 6b       | 15.6       | 31.25     | 15.6        | 31.25       | 15.6       | 31.25       | 15.6        | 31.25       | 15.6        | 31.25       |
| 7b       | +          | -         | +           | -           | -          | -           | -           | -           | +           | -           |
| 8b       | 31.25      | 62.5      | 31.25       | 62.5        | 31.25      | 62.5        | 31.25       | 62.5        | 31.25       | 62.5        |
| 9b       | 7.8        | 15.6      | 7.8         | 15.6        | 7.8        | 15.6        | 7.8         | 15.6        | 7.8         | 15.6        |
| 11b      | 62.5       | 125       | +           | -           | 15.6       | 31.25       | 15.6        | 31.25       | 15.6        | 31.25       |
| 12b      | 31.25      | 62.5      | 31.25       | 62.5        | 31.25      | 62.5        | 31.25       | 62.5        | 31.25       | 62.5        |
| 13a      | 31.25      | 62.5      | 31.25       | 62.5        | 31.25      | 62.5        | 31.25       | 62.5        | 31.25       | 62.5        |
| 13b      | 31.25      | 62.5      | 31.25       | 62.5        | 31.25      | 62.5        | 31.25       | 62.5        | 31.25       | 62.5        |
| 14b      | 7.8        | 15.6      | 7.8         | 15.6        | 7.8        | 15.6        | 7.8         | 15.6        | 7.8         | 15.6        |
| 15b      | 7.8        | 15.6      | 7.8         | 15.6        | 7.8        | 15.6        | 7.8         | 15.6        | 7.8         | 15.6        |
| 16b      | 7.8        | 15.6      | 7.8         | 15.6        | 7.8        | 15.6        | 7.8         | 15.6        | 7.8         | 15.6        |
| 17b      | 15.6       | 31.25     | 15.6        | 31.25       | 15.6       | 31.25       | 15.6        | 31.25       | 15.6        | 31.25       |
| 21       | 62.5       | 125       | 31.25       | 62.5        | -          | -           | -           | -           | 125         | 125         |
| 22       | 31.25      | 31.25     | 62.5        | -           | -          | -           | 62.5        | -           | -           | -           |
| 23       | 15.6       | 31.25     | 62.5        | -           | -          | -           | -           | -           | -           | -           |
| C        | 62.5       | -         | -           | -           | -          | -           | -           | -           | -           | -           |

+, the growth of microorganisms; -, the absence of growth inhibition and bactericidal action; C, control antibiotic Oxytetracycline.

The comparison of the antibacterial activity of both benzimidazoles showed that the alkylated derivative 22 was more potent only against the strain of S. aureus. In all other cases, the effect of benzimidazole 20 and its derivative 22 on test-bacteria strains was completely the same. It is also noteworthy that S. aureus and E. coli were the most sensitive to the action of benzimidazoles 20 and 22. The minimum inhibition and minimum bactericidal concentrations of 31.25 µg/mL (MIC 15.6 µg/mL for S. aureus in case of 22) were sufficient in comparison with 62.5 and 125 µg/mL of Oxytetracycline for the inhibition of the growth and bactericidal action of the indicated test-cultures.

The quinoxaline fragment containing derivative 21 exhibited a more marked effect than the control Oxytetracycline only against B. cereus, L. monocytogenes and S. enterica enteritidis. In other cases, resistance of the test-bacteria was found to be the same as that of the used control antibiotic (except for MIC in the case of L. monocytogenes).

Comparing the data of the biological activity of the compounds containing different substituents (amino (a) or phenyl (b)) at the 2-position of thiazole ring, it can be asserted that derivatives with 2-phenylthiazol-5-yl moiety (3–6 and 13b), show stronger inhibition and bactericidal effects than the derivatives with 2-aminothiazol-5-yl fragment (3–6 and 13a). The MIC of compounds with phenyl group changes in range of 7.8–62.5 µg/mL, with prevailing MIC of 15.6 µg/mL, and the MBC vary from 15.6 to 125 µg/mL, with the prevailing value of 31.25 µg/mL. Accordingly, the data of compounds with amino group are as follows: the MIC vary from 15.6 to 62.5 µg/mL, with the prevailing value of 31.25 µg/mL; and the MBC changes in range of 31.25–125 µg/mL, with the prevailing concentration of 62.5 µg/mL. It should be noted that, among the compounds of group a, the 2-aminothiazole derivative 3a exhibited stronger activity only against S. aureus and E. coli in comparison with its analogue 3b.
3. Materials and Methods

3.1. Synthesis

Reagents and solvents were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used without further purification. The reaction course and purity of the synthesized compounds were monitored by TLC (Thin layer chromatography) using aluminum plates pre-coated with Silica gel with F254 nm (Merck KGaA, Darmstadt, Germany). Melting points were determined with a Melt-Temp Melting Point Analyzer (Electrothermal, Bibby Scientific Company, Burlington, NJ, USA) and were uncorrected. NMR spectra were recorded on a Varian Unity Inova (300, 75 MHz) and Bruker BioSpin GmbH (400, 101 and 700, 175 MHz) spectrometers. Chemical shifts were reported in δ ppm relative to tetramethylsilane (TMS) with the residual solvent as internal reference ([D6]DMSO, δ = 2.50 ppm for 1H and δ = 39.5 ppm for 13C). The data are reported as follows: chemical shift, multiplicity, coupling constant [Hz], integration and assignment. IR spectra (ν, cm⁻¹) were recorded on a Bruker TENSOR 27 spectrometer using KBr pellets. Mass spectra were measured on a Waters (Micromas) ZQ 2000 mass spectrometer (ESI 20 eV). Elemental analyses (C, H, N) were conducted using the Elemental Analyzer CE-440 (Exeter Analytical, Inc., North Chelmsford, MA, USA); their results were found to be in good agreement (± 0.3%) with the calculated values.

1-(4-Acetylphenyl)-5-oxopyrrolidine-3-carboxylic acid (1): White solid, yield 62.9 g, 86%, m. p. 170–171 °C (2-propanol) [42]. The 1H and 13C-NMR spectra agreed with that given in the study [42].

1-(4-(2-Bromoacetyl)phenyl)-5-oxopyrrolidine-3-carboxylic acid (2): To a stirred mixture of carboxylic acid 1 (2.47 g, 10 mmol) and acetic acid (5.5 mL) a solution of bromine (9.59 g, 60 mmol) and acetic acid (350 mL). The residual bromine was removed by adding a few milliliters of 20% sodium thiosulfate (15 mL) was slowly added dropwise at room temperature, and then the resulting reaction mixture further was stirred for 4 h. Afterwards, the reaction mixture was poured into the ice/water mixture (350 mL). The residual bromine was removed by adding a few milliliters of 20% sodium thiosulfate solution. The obtained precipitate was filtered off, washed with plenty of water and recrystallized from water to give the title compound 2 (white solid, yield 2.0 g, 62%, m. p. 170–171 °C (water). 1H-NMR (400 MHz, DMSO-d6): δ = 2.67–2.92 (m, 2H, COCH₃), 3.32–3.46 (m, 1H, CH), 3.94–4.20 (m, 2H, NCH₂), 4.76, 4.89 (2s, 2H, CH₂Br), 7.76–8.14 (m, 4H, H₆Ar), 10.52 (br s, 1H, OH) ppm. 13C-NMR (101 MHz, DMSO-d₆): δ = 33.9 (CH₂Br), 35.0 (COCH₃), 35.4 (CH₃), 49.8 (NCH₂), 118.5, 128.6, 129.9, 143.7 (C₆Ar), 172.8 (N=C=O), 174.1 (COOH), 190.6 (C=O) ppm. IR (KBr): νmax = 1738, 1691, 1660 cm⁻¹. MS (ESI), m/z, % [M]+ = 326 (100), [M + 2]+ = 328 (98). Calcd. for C₁₃H₁₂BrNO₄, %: C 47.87; H 3.71; N 4.29. Found, %: 47.78; H 3.68; N 4.29.

1-(4-(2-Aminoazol-5-yl)phenyl)-5-oxopyrrolidine-3-carboxylic acid (3a): A mixture of carboxylic acid 2 (3.26 g, 10 mol), thiourea (1.52 g, 20 mol) and acetic acid (20 mL) was heated at 60 °C for 16 h, then the reaction mixture was diluted with water and the formed precipitate was filtered off, washed with water and hexane, and recrystallized from dimethylformamide/water (2:1) mixture to give the title compound 3a (white solid, yield 2.0 g, 62%, m. p. 271–272 °C (DMF/water). 1H-NMR (400 MHz, DMSO-d₆): δ = 2.69–2.82 (m, 2H, COCH₃), 4.68–4.89 (2s, 2H, CH₂Br), 6.96 (s, 1H, CH=N), 7.07 (s, 2H, NH₂), 7.66 (d, J = 8.8 Hz, 2H, H₆Ar), 7.79 (d, J = 8.8 Hz, 2H, H₆Ar), 12.81 (br s, 1H, OH) ppm. 13C-NMR (101 MHz, DMSO-d₆): δ = 35.2 (COCH₃), 35.3 (CH₃), 50.0 (NCH₂), 100.9 (C=S), 119.3, 125.9, 130.8, 138.2, 149.4 (CH=C, C₆Ar), 168.2 (C=O), 171.8 (COOH), 174.3 (COOCH₃) ppm. IR (KBr): νmax = 3240 (NH₂), 1684, 1664 (2C=O). Calcd. for C₁₄H₁₃N₂O₄S, %: C 55.43; H 4.32; N 13.85. Found, %: C 55.39; H 4.29; N 13.77.

5-Oxo-1-(4-(2-phenylthiazol-5-yl)phenyl)pyrrolidine-3-carboxylic acid (3b): A mixture of compound 2 (0.4 g, 0.123 mmol) and benzencarbothioamide (0.17 g, 0.123 mmol) was refluxed in acetonitrile (5 mL) for 6 h, then cooled down, the formed crystalline precipitate was filtered off, washed with acetone, and recrystallized from methanol to give the title compound 3b (white solid, yield 0.19 g, 43%, m. p.
221–222 °C (methanol). \(^{1}\)H-NMR (400 MHz, DMSO-d\(_6\)): \(\delta = 2.65–2.82\) (m, 2H, COCH\(_2\)), 3.28–3.41 (m, 1H, CH), 4.00–4.18 (m, 2H, NCH\(_2\)), 7.51–7.61 (m, 3H, H\(_{Ar}\)), 7.75–7.86 (m, 2H, H\(_{Ar}\)), 8.01–8.18 (m, 4H, H\(_{Ar}\)), 8.20 (s, 1H, CH=C), 12.82 (s, 1H, OH) ppm. \(^{13}\)C-NMR (101 MHz, DMSO-d\(_6\)): \(\delta = 35.1\) (COCH\(_2\)), 35.3 (CH), 49.9 (NCH\(_2\)), 114.0 (C–S), 119.4, 126.2, 126.5, 129.3, 129.7, 130.4, 133.0, 139.0 (C\(_{Ar}\)), 154.7 (CH=C), 166.9 (C=N), 172.0 (N–C=O), 174.2 (COOH) ppm. IR (KBr): \(v_{\text{max}} = 3446\) (OH), 1727, 1651 (2C=O), MS (ESI), m/z, %: [M + H]\(^{+}\) = 365 (100). Calcd. for C\(_{20}\)H\(_{15}\)N\(_3\)O\(_3\)S, %: C 65.92; H 4.43; N 7.69. Found, %: C 65.82; H 4.35; N 7.62.

1-(4-((2-carboxyethyl)-4-methylanilino)-1,3-thiazol-5-yl)phenyl)-5-oxopyrrolidine-3-carboxylic acid (3c): To a solution of 3-(1-(p-tolyl)thiourea)propanoic acid (0.24 g, 1 mmol) in acetone (5 mL), compound 2 (0.42 g, 1.3 mmol) was added and the mixture was heated at reflux for 8 h. After the completion of the reaction, the mixture was cooled down, the formed crystalline solid was filtered off, washed with acetone, and dissolved in 10% aqueous sodium acetate solution (25 mL) by boiling, and then cooled down. The formed precipitate was filtered off, washed with water, and recrystallized from methanol to give the title compound 3 c (light yellow solid, yield 0.38 g, 82%, m. p. 196–197 °C (methanol)). \(^{1}\)H-NMR (400 MHz, DMSO-d\(_6\)): \(\delta = 2.32\) (s, 3H, CH\(_3\)), 2.40 (t, \(J = 7.9\) Hz, 2H, CH\(_2\)COO), 2.51–2.98 (m, 3H, COCH\(_2\) + CH\(_3\)), 3.88–4.05 (m, 2H, NCH\(_2\)), 4.10 (t, \(J = 7.9\) Hz, 2H, NCH\(_2\)CH\(_2\)), 6.99 (s, 1H, CH=CH), 7.26 (d, \(J = 8.4\) Hz, 2H, H\(_{Ar}; s^1\)), 7.32 (d, \(J = 8.3\) Hz, 2H, H\(_{Ar}; s^1\)), 7.67 (d, \(J = 8.8\) Hz, 2H, H\(_{Ar}; s^2\)), 7.82 (d, \(J = 8.7\) Hz, 2H, H\(_{Ar}; s^3\)) ppm. \(^{13}\)C-NMR (101 MHz, DMSO-d\(_6\)): \(\delta = 20.7\) (CH\(_3\)), 35.0 (COCH\(_2\)), 37.1 (CH), 37.5 (CH\(_2\)), 50.2 (NCH\(_2\)), 51.9 (CH\(_3\)), 101.2 (C–S), 118.9, 125.9, 126.7, 130.1, 130.4, 136.5, 139.0, 142.2, 150.0 (CH=C, C\(_{Ar}\)), 169.1 (C=N), 173.7 (C=O), 174.5 (COOH), 176.0 (COOH) ppm. IR (KBr): \(v_{\text{max}} = 1683, 1605, 1575\) (3C=O), MS (ESI), m/z, %: [M + H]\(^{+}\) = 466 (100). Calcd. for C\(_{24}\)H\(_{23}\)N\(_3\)O\(_5\)S, %: C 61.92; H 4.98; N 9.03. Found, %: C 61.68; H 4.62; N 8.91.

3.1.1. General Procedure for the Preparation of Esters 4a,b

To a solution of the corresponding carboxylic acid 3 (2.75 mmol) in methanol, concentrated sulfuric acid (1 mL) was added dropwise and the mixture was heated at reflux for 5 h. Then the solvent was evaporated under reduced pressure, and the residue neutralized with 7% (a) or 10% (b) sodium carbonate solution to pH 7. The obtained solid was filtered off, washed with plenty of water, and recrystallized from methanol to give the title compound 4a (light yellow solid, yield 0.54 g, 62%, m. p. 271–272 °C (methanol)) and 4b (light yellow solid, yield 0.71 g, 71%, m. p. 139–140 °C (methanol)).

Methyl 1-(4-aminothiazol-5-yl)phenyl)-5-oxopyrrolidine-3-carboxylate (4a): \(^{1}\)H-NMR (400 MHz, DMSO-d\(_6\)): \(\delta = 2.64–2.89\) (m, 2H, COCH\(_2\)), 3.43–3.52 (m, 1H, CH), 3.68 (s, 3H, OCH\(_3\)), 3.94–4.15 (m, 2H, NCH\(_2\)), 6.95 (s, 1H, CH=C), 7.05 (s, 2H, NH\(_2\)), 7.65 (d, \(J = 8.8\) Hz, 2H, H\(_{Ar}\)), 7.79 (d, \(J = 8.8\) Hz, 2H, H\(_{Ar}\)) ppm. \(^{13}\)C-NMR (101 MHz, DMSO-d\(_6\)): \(\delta = 34.9\) (COCH\(_2\)), 35.1 (CH), 49.7 (NCH\(_2\)), 52.2 (OCH\(_3\)), 100.9 (C–S), 119.2, 125.8, 130.8, 138.0, 149.3 (CH=C, C\(_{Ar}\)), 168.2 (C=N), 171.5 (C=O), 173.1 (COO) ppm. IR (KBr): \(v_{\text{max}} = 3430\) (NH\(_2\)), 1692, 1639 (2C=O), MS (ESI), m/z, %: [M + H]\(^{+}\) = 318 (100). Calcd. for C\(_{15}\)H\(_{15}\)N\(_3\)O\(_3\)S, %: C 56.77; H 4.76; N 13.24. Found, %: C 56.66; H 4.75; N 13.40.

Methyl 5-oxo-1-(4-(2-phenylthiazol-5-yl)phenyl)pyrrolidine-3-carboxylate (4b): \(^{1}\)H-NMR (400 MHz, DMSO-d\(_6\)): \(\delta = 2.71–2.80\) (m, 2H, COCH\(_2\)), 3.45–3.55 (m, 1H, CH), 3.70 (s, 3H, OCH\(_3\)), 3.99–4.18 (m, 2H, NCH\(_2\)), 7.44–7.62 (m, 3H, H\(_{Ar}\)), 7.77 (d, \(J = 8.8\) Hz, 2H, H\(_{Ar}\)), 7.96–8.12 (m, 4H, A\(_{Ar}\)), 8.13 (s, 1H, CH=C) ppm. \(^{13}\)C-NMR (101 MHz, DMSO-d\(_6\)): \(\delta = 34.9\) (COCH\(_2\)), 35.1 (CH), 49.7 (NCH\(_2\)), 52.2 (OCH\(_3\)), 114.0 (C–S), 119.4, 126.2, 126.5, 129.3, 130.4, 133.0, 138.9, (C\(_{Ar}\)), 154.7 (CH=C), 166.9 (C=N), 171.7 (N–C=O), 173.1 (COO) ppm. IR (KBr): \(v_{\text{max}} = 1738, 1699\) (2C=O), MS (ESI), m/z, %: [M + H]\(^{+}\) = 379 (100). Calcd. for C\(_{22}\)H\(_{18}\)N\(_2\)O\(_3\)S, %: C 66.65; H 4.79; N 7.40. Found, %: C 66.54; H 4.82; N 7.32.
3.1.2. General Procedure for the Preparation of Hydrazides 5a,b

A mixture of the corresponding methyl ester 4 (10 mmol), hydrazine monohydrate (2.5 g, 2.45 mL, 50 mmol) and propan-2-ol (30 mL) was heated at reflux for 10 h. After completion of the reaction (TLC), the mixture was cooled to room temperature, the formed precipitate filtered off, washed with water, and recrystallized from methanol to give the title compound 5a (white solid, yield 2.7 g, 81.4%, m. p. 248–249 °C) and 5b (white solid, yield 2.46 g, 65%, m. p. 231–232 °C).

1-(4-(2-Aminothiazol-5-yl)phenyl)-5-oxopyrrolidine-3-carbohydrazide (5a): ¹H-NMR (400 MHz, DMSO-d₆): δ = 2.53–2.81 (m, 2H, COCH₂), 3.10–3.23 (m, 1H, CH), 3.88–4.08 (m, 2H, NCH₂), 4.30 (s, 2H, NNNH₂), 6.94 (s, 1H, CH=CH₂), 7.04 (s, 2H, NH₂), 7.65 (d, J = 8.4 Hz, 2H, Hₐ₂), 7.78 (d, J = 8.4 Hz, 2H, Hₐ₂), 9.28 (s, 1H, NH) ppm. ¹³C-NMR (101 MHz, DMSO-d₆): δ = 34.1 (COCH₂), 38.5 (CH), 50.7 (NCH₂), 100.8 (C-S), 119.1, 125.8, 130.7, 138.2, 149.4 (CH=C, CAr), 168.2 (C=N), 171.6, 172.1 (2C=O) ppm. IR (KBBr): νmax = 3391, 3316 (NH, NH₂), 1674, 1643 (2C=O). MS (ESI), m/z, %: [M + H]⁺ = 317 (100).

5-Oxo-1-(4-(2-phenylthiazol-5-yl)phenyl)pyrrolidine-3-carboxylic acid (5b): ¹H-NMR (400 MHz, DMSO-d₆): δ = 2.62–2.80 (m, 2H, COCH₂), 3.12–3.28 (m, 1H, CH), 3.86–4.08 (m, 2H, NCH₂), 4.31 (s, 2H, NNNH₂), 7.48–7.56 (m, 3H, HAr), 7.77 (d, J = 8.8 Hz, 2H, Hₐ₂), 7.98–8.09 (m, 4H, Hₐ₂), 8.12 (s, 1H, CH=CH₂), 9.31 (s, 1H, NH) ppm. ¹³C-NMR (101 MHz, DMSO-d₆): δ = 34.0 (COCH₂), 35.8 (CH), 50.7 (NCH₂), 113.9 (C-S), 119.3, 126.2, 126.5, 129.3, 129.6, 130.4, 133.0, 139.1 (CAr), 154.8 (CH=C), 166.9 (C=N), 171.5, 172.2 (2C=O) ppm. IR (KBBr): νmax = 3318, 3281 (NH, NH₂), 1682, 1638 (2C=O). MS (ESI), m/z, %: [M + H⁺] = 379 (100). Calcd. for C₂₉H₁₈N₄O₂S, %: C 63.47; H 4.79; N 14.80. Found, %: C 63.37; H 4.72; N 14.71.

3.1.3. General Procedure for the Preparation of Hydrazones 6–12

A mixture of the corresponding hydrazide 5a,b (10 mmol), benzenecarbaldehyde (11 mmol) or thioephene-2-carboxaldehyde (2.24 g, 20 mmol) and dimethylformamide (30 mL) was refluxed for 1–3 h. Afterwards, the reaction mixture was cooled down, diluted with water (50 mL), the obtained product was filtered off, washed with water and ether, and recrystallized from the indicated solvent.

1-(4-(2-Aminothiazol-5-yl)phenyl)-3-(benzylidenehydrazinocarbonyl)-5-oxopyrrolidine (6a): light yellow solid, yield 3.65 g, 90.2%, m. p. 239–240 °C (methanol). ¹H-NMR (400 MHz, DMSO-d₆): δ = Z/E 2.68–2.94 (m, 2H, COCH₂), 3.36–3.41 (m, 0.35H, CH), 3.93–4.25 (m, 0.65H, CH + 2H, NCH₂), 6.94, 6.95 (2s, 1H, CH=CH₂), 7.05 (s, 2H, NH₂), 7.24–7.90 (m, 9H, HAr), 8.05 (s, 0.65H, N=CH), 8.23 (s, 0.35H, N=CH), 11.58 (s, 0.65H, NH), 11.65 (s, 0.35H, NH) ppm. IR (KBBr): νmax = 3398 (NH), 1681, 1668 (2C=O). MS (ESI), m/z, %: [M + H⁺] = 406 (100). Calcd. for C₂₁H₉₁N₅O₂S, %: C 62.21; H 4.72; N 17.27. Found, %: C 62.16; H 4.69; N 17.23.

3-(Benzylidenehydrazinocarbonyl)-1-(4-phenylthiazol-5-yl)phenyl)-5-oxopyrrolidine (6b): light yellow solid, yield 4.05 g, 92%, m. p. 214–215 °C (methanol). ¹H-NMR (400 MHz, DMSO-d₆): δ = Z/E 2.73–2.95 (m, 2H, COCH₂), 3.35–3.47 (m, 0.35H, CH); 3.95–4.31 (m, 0.65H, CH + 2H, NCH₂); 7.38–7.61 (m, 6H, HAr), 7.66–7.78 (m, 2H, HAr), 7.81 (d, J = 8.6 Hz, 2H, Hₐ₂), 7.96–8.28 (m, 6H, Hₐ₂ + CH=C + N=CH), 11.61 (s, 0.65H, NH), 11.68 (s, 0.35H, NH) ppm. IR (KBBr): νmax = 3178 (NH₂), 1700, 1668 (2C=O). MS (ESI), m/z, %: [M + H⁺] = 447 (100). Calcd. for C₂₁H₂₁N₃O₂S, %: C 69.51; H 4.75; N 12.01. Found, %: C 69.61; H 4.86; N 11.94.

1-(4-(2-Aminothiazol-5-yl)phenyl)-3-(4-chlorobenzylidenehydrazinocarbonyl)-5-oxopyrrolidine (7a): light yellow solid, yield 3.93 g, 89.5%, m. p. 254 °C (methanol). ¹H-NMR (400 MHz, DMSO-d₆): δ = Z/E 2.69–2.89 (m, 2H, COCH₂), 3.34–3.38 (m, 0.4H, CH), 3.94–4.22 (m, 0.6H, CH + 2H, NCH₂), 6.95 (s, 1H, CH=CH₂), 7.04 (s, 2H, NH₂), 7.48–7.82 (m, 8H, HAr), 8.03 (s, 0.65H, N=CH), 8.22 (s, 0.35H, N=CH), 11.64 (s, 0.65H, NH), 11.71 (s, 0.35H, NH) ppm. IR (KBBr): νmax = 3252 (NH₂), 1673, 1656 (2C=O). MS
3-(3-Chlorobenzylidenehydrazinocarbonyl)-1-(4-(2-phenylthiazol-5-yl)phenyl)-5-oxopyrrolidine (7b): yellow solid, yield 3.45 g, 69%, m. p. 141–142 °C (methanol). 1H-NMR (400 MHz, DMSO-d$_6$): $\delta$ = Z/E 2.67–2.96 (m, 2H, COCH$_2$), 3.35–3.48 (m, 0.4H, CH), 4.01–4.27 (m, 0.6H, CH + 2H, NCH$_2$), 7.50–8.41 (m, 9H, H$_A$ + CH=C + N=CH), 11.87–11.94 (s, 0.65H, NH) ppm. IR (KBr): $\nu_{\text{max}}$ = 3265 (NH), 1673, 1610 (2C=O), 1649, 1630 (C=O), 1610 (C=O). MS (ESI), $m/z$, %: [M + H]$^+$ = 451 (100). Calcd. for C$_{21}$H$_{18}$ClN$_5$O$_2$S, %: C 63.39; H 4.14; N 13.69. Found, %: C 63.42; H 4.15; N 13.29.

1-(4-(2-Aminothiazol-5-yl)phenyl)-3-(3-Chlorobenzylidenehydrazinocarbonyl)-5-oxopyrrolidine (8a): light yellow solid, yield 2.79 g, 62%, m. p. 234–236 °C (ethanol). 1H-NMR (400 MHz, DMSO-d$_6$): $\delta$ = Z/E 2.69–2.96 (m, 2H, COCH$_2$), 3.35–3.44 (m, 0.35H, CH), 3.91–4.28 (m, 0.6H, CH + 2H, NCH$_2$), 6.95 (s, 1H, CH=C), 7.04 (s, 2H, NH$_2$), 7.50–8.41 (m, 9H, H$_A$ + CH=C + N=CH), 11.76 (s, 0.65H, NH), 11.90 (s, 0.35H, NH) ppm. IR (KBr): $\nu_{\text{max}}$ = 3273 (NH$_2$), 3245 (NH), 1675, 1649, 1610 (2C=O). MS (ESI), $m/z$, %: [M + H]$^+$ = 3435 (NH$_2$), 3245 (NH), 1681, 1656 (2C=O). Found, %: C 59.56; H 4.10; N 11.85.

3-(4-Nitrobenzylidenehydrazinocarbonyl)-1-(4-(2-phenylthiazol-5-yl)phenyl)-5-oxopyrrolidine (8b): yellow solid, yield 4.55 g, 89%, m. p. 150–151 °C (methanol). 1H-NMR (400 MHz, DMSO-d$_6$): $\delta$ = Z/E 2.77–2.91 (m, 2H, COCH$_2$), 3.36–3.48 (m, 0.4H, CH), 4.01–4.27 (m, 0.6H, CH + 2H, NCH$_2$), 7.45–8.38 (m, 15H, H$_A$ + CH=C + N=CH), 11.90 (s, 0.65H, NH), 11.97 (s, 0.35H, NH) ppm. IR (KBr): $\nu_{\text{max}}$ = 3221 (NH), 1674, 1612 (2C=O). Calcd. for C$_{27}$H$_{21}$N$_5$O$_5$S, %: C 63.39; H 4.14; N 13.69. Found, %: C 63.42; H 4.15; N 13.29.

3-(4-Fluorobenzylidenehydrazinocarbonyl)-1-(4-(2-phenylthiazol-5-yl)phenyl)-5-oxopyrrolidine (9b): light yellow solid, yield 3.97 g, 82%, m. p. 216–217 °C (methanol). 1H-NMR (400 MHz, DMSO-d$_6$): $\delta$ = Z/E 2.77–2.91 (m, 2H, COCH$_2$), 3.35–3.41 (m, 0.4H, CH), 4.01–4.24 (m, 0.6H, CH + 2H, NCH$_2$), 7.22–8.26 (m, 15H, H$_A$ + CH=C + N=CH), 11.61 (s, 0.65H, NH), 11.68 (s, 0.35H, NH) ppm. IR (KBr): $\nu_{\text{max}}$ = 3265 (NH), 1684, 1604 (2C=O). Calcd. for C$_{27}$H$_{21}$FN$_4$O$_5$S, %: C 66.93; H 4.37; N 11.56. Found, %: C 66.72; H 4.25; N 11.49.

5-Oxo-1-(4-(2-phenylthiazol-5-yl)phenyl)-N’-(thiophen-2-ylmethylene)pyrrolidine-3-carbohydrazide (10b): light yellow solid, yield 3.54 g, 75%, m. p. 198–200 °C (methanol). 1H-NMR (400 MHz, DMSO-d$_6$): $\delta$ = Z/E 2.72–2.90 (m, 2H, COCH$_2$), 3.34–3.40 (m, 0.4H, CH), 3.82–4.30 (m, 0.6H, CH + 2H, NCH$_2$), 7.08–8.18 (m, 13H, H$_A$ + CH=C), 8.23 (s, 0.6H, N=CH), 8.45 (s, 0.4H, N=CH), 11.59 (s, 0.6H, NH), 11.62 (s, 0.35H, NH) ppm. IR (KBr): $\nu_{\text{max}}$ = 3265 (NH), 1673, 1610 (2C=O). Calcd. for C$_{25}$H$_{20}$N$_4$O$_2$S$_2$, %: C 66.54; H 4.27; N 11.86. Found, %: C 66.50; H 4.24; N 11.89.

3.1.4. General Procedure for the Preparation of Hydrazones 11b, 12b

A mixture of hydrazide 5b (1 g, 2.64 mmol) and dimethylformamide (11b) or 1,4-dioxane (12b) (10 mL) was heated to its boiling point and 3- or 4-pyridinecarbaldehyde (5.28 mmol) was added dropwise. The mixture was refluxed for 1 h, diluted with water (20 mL) (11b) or the solvent was evaporated under reduced pressure, the resin mass was poured with diethyl ether (10 mL), stirred and left in refrigerator (12b). The obtained precipitate was filtered off, washed with water and ether, and recrystallized 2-propanol to give the title compound 11b (yellow solid, yield 1.22 g, 99%, m. p. 203–204 °C (propan-2-ol) or 12b (yellow solid, yield 1.19 g, 96.5%, m. p. 236–237 °C (propan-2-ol).
5-Oxo-1-(4-(2-phenylthiazol-5-yl)phenyl)-N′-(pyridin-4-ylmethylene)pyrrolidine-3-carboxamide (12b): 1H-NMR (400 MHz, DMSO-d$_6$): $\delta$ = 2.00 (s, 6H, 2CH$_3$), 2.70–2.94 (m, 2H, COCH$_2$), 3.43–3.52 (m, 1H, CH), 3.96–4.20 (m, 2H, NCH$_2$), 5.65 (s, 2H, 2CH), 6.96 (s, 1H, CH= C), 7.05 (s, 2H, NH$_2$), 7.68 (d, J = 8.8 Hz, 2H, H$_2$A$_r$), 7.80 d, J = 8.8 Hz, 2H, H$_2$A$_r$), 10.91 (s, 1H, NH) ppm. 13C-NMR (101 MHz, DMSO-d$_6$): $\delta$ = 10.9, 11.0 (2CH$_3$), 34.1 (COCH$_3$), 35.7 (CH), 50.3 (NCH$_3$), 100.9, 103.1, 119.3, 125.8, 126.7, 130.8, 138.1, 149.4 (CH=C, C$_r$A$_r$, C$_{Pyr}$), 168.2 (C=N), 171.6, 171.9 (2C=O) ppm. IR (KBr): $\nu_{max}$ = 3403 (NH$_2$), 3325 (NH), 1693, 1678 (2C=O). MS (ESI), m/z, %: [M + H]$^+$ = 396 (100). Calcd. for C$_{25}$H$_{22}$N$_3$N$_2$O$_2$S; %: C 60.74; H 5.31; N 17.69.

5-Oxo-1-(5-oxo-1-(4-(2-phenylthiazol-5-yl)phenyl)pyrrolidine-3-carboxamide)pyrrolidine-3-carboxylic acid (14b): A mixture of acid hydrazide 5b (1 g, 2.64 mmol), itaconic acid (1.2 g, 9.23 mmol) and toluene (30 mL) was heated at reflux for 11 h, then cooled down, the obtained crystalline solid was filtered off, washed with water, and recrystallized from methanol to give the title compound 14b (light yellow solid, yield 0.70 g, 54%, m. p. 170–171 °C (methanol)). 1H-NMR (400 MHz, DMSO-d$_6$): $\delta$ = 2.51–2.88 (m, 4H, 2COCH$_2$), 3.25–3.42 (m, 2H, 2CH), 3.55–4.16 (m, 4H, 2NCH$_2$), 7.50–7.56 (m, 3H, H$_2$A$_r$), 7.75–7.80 (m, 2H, H$_2$A$_r$), 8.03–8.11 (m, 4H, H$_2$A$_r$), 8.13 (s, 1H, CH=C), 10.40 (s, 1H, NH), 12.84 (br s, 1H, OH) ppm. 13C-NMR (101 MHz, DMSO-d$_6$): $\delta$ = 31.3, 33.6 (2COCH$_2$), 34.2, 35.5 (2CH), 49.7, 50.3 (2NCH$_2$), 114.0, 119.4, 126.2, 126.5, 129.3, 129.7, 130.4, 133.0, 139.0 (C$_r$A$_r$), 154.7 (CH=C), 167.0 (C=N), 170.9, 171.4, 171.8, 174.1 (4C=O) ppm. IR (KBr): $\nu_{max}$ = 3421 (OH), 3274 (NH), 1726, 1717, 1699, 1682 (4C=O). Calcd. for C$_{25}$H$_{22}$N$_3$N$_2$O$_2$S; %: C 61.21; H 4.52; N 11.42. Found, %: 61.28; H 4.62; N 11.50.

2-(5-Oxo-1-(4-(2-phenylthiazol-5-yl)phenyl)pyrrolidine-3-carboxyl)-N-phenylhydrazine-1-carbothioamide (15b): To a solution of hydrazide 5b (1 g, 2.64 mmol) in methanol (10 mL), phenyl isothiocyanate (0.714 g, 0.63 mL, 5.28 mmol) was added dropwise and the mixture was heated at reflux for 3 h. After completion of the reaction the mixture was cooled down, the obtained crystalline solid filtered off,
washed with methanol and recrystallized from methanol to give the title compound 15b (white solid, yield 1.17 g, 86.5% m. p. 209–210 °C (methanol)). 1H-NMR (400 MHz, DMSO-d6): δ = 2.70–2.93 (m, 2H, COCH2), 3.31–3.42 (m, 1H, CH), 3.96–4.22 (m, 2H, NCH2), 7.08–7.22 (m, 1H, HAa), 7.31–7.59 (m, 8H, HAa), 7.69–7.83 (m, 2H, HAa), 7.92–8.10 (m, 3H, HAa), 8.13 (s, 1H, CH=N), 9.58 (s, 1H, NH), 9.68, 9.88 (2br s, 1H, NH), 10.12, 10.22 (2s, 1H, NH) ppm. 13C-NMR (101 MHz, DMSO-d6): δ = 27.3 (COCH2), 35.4 (CH), 50.4 (NCH2), 114.1 (C–N), 119.6, 126.2, 126.5, 128.1, 128.2, 129.3, 129.7, 130.4, 133.0, 139.1, 139.2 (CAr), 154.7 (CH=), 166.9 (C=N), 167.8, 168.5, 172.1 (C=S, 2C=O) ppm. IR (KBr): νmax = 3163–3059 (NH), 1715, 1681 (C=O). Calcd. for C27H23N5O2S2, %: C 63.14; H 4.57; N 13.63. Found, %: C 63.26; H 4.57; N 13.81.

3-(4-Phenyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-1-(4-(2-phenylthiazol-5-yl)phenyl)-5-oxopyrrolidine (16b): A mixture of thiosemicarbazide 15b (1 g, 1.94 mmol) and 4% sodium hydroxide solution was refluxed for 6 h. Then, the reaction mixture was cooled down, acidified with diluted hydrochloric acid to pH 1, refluxed for 15 min, afterwards cooled down and neutralized with 10% sodium carbonate solution to pH 7. The formed solid was filtered off, washed with water, and recrystallized from methanol to give the title compound 16b (yellow solid, yield 0.86 g, 89.5%, m. p. 191–192 °C (methanol)). 1H-NMR (400 MHz, DMSO-d6): δ = 2.55–2.86 (m, 2H, COCH2), 3.42–3.76 (m, 1H, CH), 3.87–4.14 (m, 2H, NCH2), 7.25–8.11 (m, 1H, CH=), 8.13 (s, 1H, CH=N), 13.89 (s, 1H, NH) ppm. 13C-NMR (101 MHz, DMSO-d6): δ = 27.8 (COCH2), 36.2 (CH), 50.5 (NCH2), 114.0, 119.6, 126.2, 126.4, 128.6, 129.3, 129.6, 129.8, 130.4, 133.0, 133.5, 138.8, 152.9 (CAr), 154.7 (CH=), 166.9, 168.4 (C=S, C=N), 171.3 C=O) ppm. IR (KBr): νmax = 3406 (NH), 1685 (C=O). Calcd. for C27H21N5OS2, %: C 65.43; H 4.27; N 14.13. Found, %: C 65.39; H 4.14; N 14.11.

3-(5-Thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-1-(4-(2-phenylthiazol-5-yl)phenyl)-5-oxopyrrolidine (17b): To a solution of potassium hydroxide (0.56 g, 10 mmol) in methanol (25 mL), carbon disulfide (0.76 g, 10 mmol) was added dropwise. The obtained mixture was stirred at room temperature for 15 min, and then methanolic solution of acid hydrazide 5b (1.89 g, 5 mmol/50 mL) poured over. The reaction mixture was refluxed for 15 h. After completion of the reaction (TLC), the solvent was evaporated under reduced pressure, the residue was poured with water (30 mL) and the mixture was acidified with diluted hydrochloric acid (1:1) to pH 1. The crystalline solid was filtered off, washed with plenty of water and recrystallized from methanol to give the title compound 17b (white solid, yield 3.21 g, 76.5%, m. p. 254–255 °C (methanol)). H-NMR (400 MHz, DMSO-d6): δ = 2.82–3.07 (m, 2H, COCH2), 3.94–4.04 (m, 1H, CH), 4.10–4.35 (m, 2H, NCH2), 7.49–7.58 (m, 3H, HAa), 7.78 (d, J = 8.8 Hz, 2H, HAa), 7.99–8.11 (m, 4H, HAa), 8.15 (s, 1H, CH=C), 14.42 (br s, 1H, NH) ppm. 13C-NMR (101 MHz, DMSO-d6): δ = 27.9 (COCH2), 35.2 (CH), 49.8 (NCH2), 114.1, 119.6, 126.2, 126.5, 129.3, 129.9, 130.4, 133.0, 138.8, 154.7, 163.9 (CH=C, CAr), 167.0 (C=N), 171.1, 178.0 (C=O, C=S) ppm. IR (KBr): νmax = 3110 (NH), 1658 (C=O). Calcd. for C21H14N4O2S2, %: C 59.98; H 3.84; N 13.32. Found, %: C 59.85; H 3.80; N 13.25.
154.7, 158.4 (C=Ar), 166.9, 167.2, 172.2 (C=S, N=C=N, C=O) ppm. Calcd. for C_{21}H_{18}N_{6}OS_{2}, %: C 58.04; H 4.18; N 19.34. Found, %: C 57.95; H 4.05; N 19.27.

3-(4-(Benzyldieneamino)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-1-(4-(2-phenylthiazol-5-yl)phenyl)-5-oxopyrrolidine (19b): To a mixture of compound 18b (1 g, 2.3 mmol), benzenecarbaldehyde (0.49 g; 4.07 mL, 4.6 mmol) and ethanol (50 mL) catalytic amount of concentrated hydrochloric acid was added (0.5 mL) and the mixture was refluxed for 5 h, then cooled down. The formed crystalline solid was filtered off, washed with water, and recrystallized from methanol to give the title compound 19b (light yellow solid, yield 1.17 g, 92%, m. p. 189–190 °C (methanol)). 1H-NMR (400 MHz, DMSO-d$_6$): δ = 2.90–3.08 (m, 2H, COCH$_3$), 4.04–4.17 (m, 2H, NCH$_3$), 4.18; 4.25–4.38 (m, 2H, H$_{Ar}$), 7.49–7.55 (m, 2H, H$_{Ar}$), 7.85 (d, J = 8.7 Hz, 2H, H$_{Ar}$), 7.99 (d, J = 8.7 Hz, 2H, H$_{Ar}$) ppm. IR (KBr): ν$_{max}$ = 3415 (OH), 3193 (NH), 1732, 1652 (2C=O) ppm. 13C-NMR (101 MHz, DMSO-d$_6$): δ = 26.5 (CH$_3$), 35.1 (COCH$_3$), 35.4 (CH), 49.8 (NCH$_2$), 114.6, 117.4, 118.4, 129.2, 132.1, 134.9, 143.1 (C$_{Ar}$), 172.6, 174.1 (2C=O), 196.7 (H$_3$C=C=N) ppm. Calcd. for C$_{28}$H$_{22}$N$_{6}$OS$_2$, %: C 64.35; H 4.24; N 16.08. Found, %: C 64.24; H 4.22; N 15.96.

1-(4-(1-(2-aminophenyl)iminomethyl)phenyl)-5-oxopyrrolidine-3-carboxylic acid (20): A mixture of acid 1 (2.47 g, 0.01 mol) and benzene-1,2-diamine (2.16 g, 0.02 mol) in ethanol (25 mL) was refluxed for 20 h, then cooled down, the formed crystalline solid was filtered off, washed with ethanol, and recrystallized from water (twice) to give the title compound 20 (brown-orange solid, yield 2.76 g, 82%, m. p. 139–140 °C (water)). 1H-NMR (400 MHz, DMSO-d$_6$): δ = 2.55 (s, 3H, CH$_3$), 2.70–2.88 (m, 2H, COCH$_3$), 3.29–3.45 (m, 1H, CH), 3.95–4.16 (m, 2H, NCH$_3$) ppm. 13C-NMR (101 MHz, DMSO-d$_6$): δ = 27.3 (COCH$_3$), 35.5 (CH), 50.3 (NCH$_2$), 114.0, 119.6, 126.2, 126.4, 128.6, 129.2, 129.3, 132.1, 133.0, 138.9, 151.5 (CH=N, C$_{Th}$, C$_{Ar}$), 154.7 (CH=C), 162.0 (C=NNH), 162.9 (C=S), 166.9 (C=N), 171.7 (C=O) ppm. IR (KBr): ν$_{max}$ = 3278 (NH), 1681 (C=O), 1482 (C=N), 1134 (C=S). Calcd. for C$_{28}$H$_{12}$N$_{6}$OS$_2$, %: C 67.64; H 5.68; N 12.46. Found, %: C 67.76; H 5.61; N 12.42.

5-Oxo-1-(4-(quinoxalin-2-yl)phenyl)pyrrolidine-3-carboxylic acid (21): A mixture of compound 2 (1 g, 3.08 mmol) and benzene-1,2-diamine (0.3 g, 2.77 mmol) in ethanol (12 mL) was refluxed for 5 h, then cooled down, the formed crystalline solid was filtered off, washed with methanol, and recrystallized from propan-2-ol to give the title compound 21 (brown solid, yield 0.72 g, 81%, m. p. 277–278 °C (propan-2-ol)). 1H-NMR (400 MHz, DMSO-d$_6$): δ = 2.72–2.92 (m, 2H, COCH$_3$), 3.36–3.45 (m, 1H, CH), 4.04–4.17 (m, 2H, NCH$_2$), 7.78–7.92 (m, 4H, H$_{Ar}$), 8.04–8.15 (m, 2H, H$_{Ar}$), 8.36 (d, J = 8.9 Hz, 2H, H$_{Ar}$), 9.56 (s, 1H, CH), 12.85 (s, 1H, OH) ppm. 13C-NMR (101 MHz, DMSO-d$_6$): δ = 35.1 (COCH$_3$), 36.4 (CH), 49.9 (NCH$_2$), 119.3, 127.9, 128.8, 129.1, 129.6, 130.6, 131.2, 140.9, 141.1, 141.4, 143.5, 150.3 (C$_{Ar}$), 172.3 (C=O), 174.1 (COOH) ppm. IR (KBr): ν$_{max}$ = 3415 (OH), 3193 (OH), 1732, 1652 (2C=O). Anal Calcd for C$_{19}$H$_{15}$N$_{3}$O$_3$ m/z: 334.1191 [M + H]$^+$, found HRMS (ESI), m/z: 334.1193 [M + H]$^+$ (100%). Calcd. for C$_{19}$H$_{15}$N$_{3}$O$_3$, %: C 68.46; H 4.54; N 12.61. Found, %: 68.41; H 4.64; N 12.72.

1-(4-Acetylphenyl)-3-(1H-benzimidazol-2-yl)-5-oxopyrrolidine (22): A mixture of compound 1 (1 g, 4 mmol), 1,2-benzenediamine (0.86 g, 8 mmol) and 4N hydrochloric acid (15 mL) was heated at reflux for 16 h. After completion of the reaction (TLC), the reaction mixture was filtered off, the solvent was evaporated under reduced pressure, and the residue was neutralized with 25% aqueous ammonia to pH 7. Then, a liquid layer was decanted, the precipitate was poured over with 5% aqueous sodium carbonate solution (20 mL) and afterward boiled and filtered off until hot. The obtained crystalline solid was washed with plenty of water and recrystallized from methanol to give the title compound 22 (yellow solid, yield 1.17 g, 92%, m. p. 222–223 °C). 1H-NMR (400 MHz, DMSO-d$_6$): δ = 2.55 (s, 3H, CH$_3$), 2.99–3.14 (m, 2H, COCH$_3$), 3.98–4.08 (m, 1H, CH), 4.25–4.38 (m, 2H, NCH$_2$), 7.13–7.18 (m, 2H, H$_{Ar}$), 7.49–7.55 (m, 2H, H$_{Ar}$), 7.85 (d, J = 8.7 Hz, 2H, H$_{Ar}$), 7.99 (d, J = 8.7 Hz, 2H, H$_{Ar}$) ppm. 13C-NMR (101 MHz, DMSO-d$_6$): δ = 26.5 (CH$_3$), 30.6 (COCH$_3$), 37.7 (CH), 52.0 (NCH$_2$), 114.8 118.4, 121.5, 129.2,
1-(4-Acetylphenyl)-3-(1-ethyl-1H-benzimidazol-2-yl)-5-oxopyrrolidine (23): A mixture of benzimidazole 22 (1 g, 3 mmol), potassium hydroxide (0.36 g, 6.4 mmol), sodium carbonate (0.21 g, 2 mmol) and ethyl iodide (10 mL) was stirred at room temperature for 48 h. After completion of the reaction (TLC), a mixture was poured over with dry acetone and filtered off. The filtrate was evaporated under reduced pressure to dryness, and then the obtained oily mass was poured over with diethyl ether and left in refrigerator for several hours. The formed crystalline solid was filtered off, washed with diethyl ether, and recrystallized from methanol to give the title compound 23 (light yellow solid, yield 0.96 g, 88%, m. p. 175–176 °C). 1H-NMR (400 MHz, DMSO-d6): δ = 1.30 (t, J = 7.1 Hz, 3H, CH3), 2.96–3.18 (m, 2H, COCH), 4.13–4.45 (m, 5H, CH + NCH2 + CH3CH2), 7.11–7.291 (m, 2H, HAr), 7.50–7.66 (m, 2H, HAr), 7.82 (d, J = 8.8 Hz, 2H, HAr), 7.94 (d, J = 8.8 Hz, 2H, HAr) ppm. 13C-NMR (101 MHz, DMSO-d6): δ = 15.2 (CH3), 26.5 (CH3), 28.4 (COCH2), 37.9 (CH + CH3CH2), 52.0 (NCH2), 110.2, 118.5, 118.8, 121.5, 122.0, 129.2, 132.1, 135.0, 142.0, 143.2 (CAr), 154.4 (N-C=N), 172.7 (N=C=O), 196.6 (H3C–C=O) ppm. IR (KBr): ʋmax = 1707, 1670 (2C=O). Calcd. for C21H21N3O2, %: C 72.60; H 6.09; N 12.10. Found, %: C 71.72; H 5.92; N 12.04.

3.2. Biological Activity

The determination of the antibacterial and antifungal activity by diffusion method in agar was carried out by diffusion in agar on a solid nutrient medium (beef-extract agar for bacteria, wort agar for fungi). Petri plates containing 20 mL of nutrient medium were used for all the tested microorganisms. The inoculum (the microbial loading 109 cells (spores)/1 mL) was spread on the surface of the solidified media and Whatman no. 1 filter paper discs (6 mm in diameter) impregnated with the test compound (0.1 and 0.5%) were placed on the plates. The duration of bacteria incubation was 24 h at 35 °C and that of fungi incubation was 48–72 h at 28–30 °C. The antimicrobial effect and degree of activity of the tested compounds were evaluated by measuring the inhibition zone diameters and the results were compared with the data for the well-known antibacterial/antifungal agent. Each experiment was repeated three times. The determination of minimal inhibitory (MIC) concentrations was achieved using the serial dilution method. The tested compounds were added to the nutrient medium (beef-extract broth for bacteria and wort for fungi) as solutions in dimethyl sulfoxide (DMSO) for ensuring the needed concentration (0.9–500.0 μg/mL). Bacteria and fungi inoculum were inoculated into nutrient medium (the microbial loading was 106 cells (spores)/1 mL). The duration of bacteria incubation was 24 h at 35 °C and that of fungi incubation was 48–72 h at 28–30 °C. The results were estimated by the microorganism growth measured by degree of microbial turbidity in nutrient medium. The MIC of any compound was defined as the lowest concentration, which completely inhibits visible growth (turbidity on liquid nutrient medium).

4. Conclusions

In this study, the condensation of 1-(4-(2-bromoacetyl)phenyl)-5-oxopyrrolidine-3-carboxylic acid with thiourea, benzenecarbothioamide and thioureido acid novel disubstituted thiazole derivatives were obtained. Some transformations of these compounds were carried out; compounds with pyrrolidine, pyrrole, triazole, oxadiazole fragments were synthesized; and their antibacterial properties were investigated. The antibacterial assay revealed that in most cases substituted phenylthiazole derivatives had stronger inhibition and bactericidal properties against the test-cultures Staphylococcus aureus (ATCC 25923), Bacillus cereus (ATCC 10231), Listeria monocytogenes (ATCC 19111), Pseudomonas aeruginosa (ATCC 10145), Escherichia coli (ATCC 8739) and Salmonella enterica enteritidis when compared with the corresponding aminothiazoles. Compounds 3c, 5b, 15b and 16 b were found to have an exceptional antibacterial potency against all tested bacteria strains. The MIC of these compounds was observed...
at 7.8 μg/mL, and MBC – at 15.6 μg/mL, while the minimum inhibitory and minimum bactericidal concentrations of Oxytetracycline for Gram-positive bacteria strains was determined to be 62.5 μg/mL, and 125 μg/mL for Gram-negative ones.

**Supplementary Materials:** The following are available online. Figure S1: 1H-NMR of compound 2, Figure S2: 13C-NMR of compound 2, Figure S3: 1H-NMR of compound 3 a, Figure S4: 13C-NMR of compound 3 a, Figure S5: 1H-NMR of compound 3 b, Figure S6: 13C-NMR of compound 3 b, Figure S7: 1H-NMR of compound 3 c, Figure S8: 13C-NMR of compound 3 c, Figure S9: 1H-NMR of compound 4 a, Figure S10: 13C-NMR of compound 4 a, Figure S11: 1H-NMR of compound 4 b, Figure S12: 13C-NMR of compound 4 b, Figure S13: 1H-NMR of compound 5 a, Figure S14: 13C-NMR of compound 5 a, Figure S15: 1H-NMR of compound 5 b, Figure S16: 13C-NMR of compound 5 b, Figure S17: 1H-NMR of compound 6 a, Figure S18: 1H-NMR of compound 6 b, Figure S19: 1H-NMR of compound 7 a, Figure S20: 1H-NMR of compound 7 b, Figure S21: 1H-NMR of compound 8 a, Figure S22: 1H-NMR of compound 8 b, Figure S23: 1H-NMR of compound 9 b, Figure S24: 1H-NMR of compound 10 b, Figure S25: 1H-NMR of compound 11 b, Figure S26: 1H-NMR of compound 12 b, Figure S27: 1H-NMR of compound 13 a, Figure S28: 13C-NMR of compound 13 a, Figure S29: 1H-NMR of compound 13 b, Figure S30: 13C-NMR of compound 14 b, Figure S31: 1H-NMR of compound 14 b, Figure S32: 13C-NMR of compound 14 b, Figure S33: 1H-NMR of compound 15 b, Figure S34: 13C-NMR of compound 15 b, Figure S35: 1H-NMR of compound 16 b, Figure S36: 13C-NMR of compound 16 b, Figure S37: 1H-NMR of compound 17 b, Figure S38: 13C-NMR of compound 17 b, Figure S39: 1H-NMR of compound 18 b, Figure S40: 13C-NMR of compound 18 b, Figure S41: 1H-NMR of compound 19 b, Figure S42: 13C-NMR of compound 19 b, Figure S43: 1H-NMR of compound 20, Figure S44: 13C-NMR of compound 20, Figure S45: 1H-NMR of compound 21, Figure S46: 13C-NMR of compound 21, Figure S47: 1H-NMR of compound 22, Figure S48: 13C-NMR of compound 22.

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